Substituent Effects in the Radical Reactions of Amino Acid Derivatives and their Analogues

by

Anna Kristina Croft B.Sc.(Hons) *Adel.*

Research School of Chemistry

Australian National University

A thesis submitted for the degree of

Doctor of Philosophy

of the Australian National University

Statement

This work contains no material which has been accepted for the award of any other degree or diploma in any other university or other institution, and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan or photocopying.

Anna Kristina Croft (B.Sc. Hons.) November 27th, 1998

Acknowledgments

I would like to thank both my supervisors, Chris Easton and Leo Radom, for their valuable advice, encouragement, guidance and support that they have provided me with in the time that I have been associated with them.

I would also like to acknowledge that which has been provided me by my colleagues in the way of technical assistance, inspiring scientific discussion and proofreading of this thesis. Particularly, I would like to thank Jason Harper, Andrew Ivory, James Kelly, James Proctor, Danne Rasmussen, Pasquale Razzino, David Smith and Eng Wui Tan for their various contributions.

The receipt of an Australian Postgraduate Award is gratefully acknowledged.

Abstract

Theoretical calculations at the RMP2/6-31G(d)//B3-LYP/6-31G(d) level of theory have been used in conjunction with bromination and chlorination experiments on a variety of amino acid derivatives to elucidate the factors affecting rate of formation and stability of amino acid radicals. Particularly, the effect of protecting groups in reactions involving both α-centred and side chain radicals has been examined.

The effect of acyl protection on the stability of amino acid radicals has been studied by theoretical calculation of the radical stabilisation energies (RSEs) for a selection of free and acetyl-protected amino acid radicals. Examination of their structures has led to the observation that non-bonding interactions of the side chains of these amino acids with the protecting group are an integral factor in the radical stabilisation energies observed. The relative RSEs of the *N*-acetyl-protected amino acids are well reflected in the corresponding relative rates of radical bromination of *N*-benzoyl-protected amino acids. This is evidence that radical stability is the foremost factor in the experimentally observed selectivity for glycine residues in hydrogen abstraction reactions.

The non-bonding interactions between the side chain of an amino acid and its protecting group have been exacerbated by examining sterically bulky and fluorinated derivatives. The *N*-acetyl-protected derivatives examined gave very low RSEs. The *N*-benzoyl-protected derivatives studied showed extremely low rates of reaction in their reactions with *N*-bromosuccinimide (NBS).

The electronic effect of *N*-acyl and *N*-sulfonyl protection on the stability of the corresponding α-centred glycyl radicals has been examined both experimentally and theoretically. The RSEs of these radicals has been shown to exhibit a correlation with the pK_as of the acids corresponding to the *N*-acyl or *N*-sulfonyl protecting groups. This

is reflected to some extent in the relative rates of reaction of *N*-acyl- and *N*-sulfonyl-protected glycines, however, the differing electronic natures of acyl and sulfonyl groups is highlighted.

The factors affecting the stability and rate of formation of radicals adjacent to a phthaloyl protecting group have been investigated theoretically, and compared with existing literature. The contributions from electronic factors have been delineated by the examination of *N*-protected methylamine derivatives. The counteractive nature of phthaloyl protecting groups and carbomethoxy groups in maleyl-protected glycyl and -[illegible]nyl radicals has been clearly demonstrated. Maleyl-protected compounds have also been used as models for $N^{\alpha},N^{\varepsilon}$-diphthaloyllysine and comparison of the selectivity of radical formation with the stabilities of the appropriate radicals suggest that the carbomethoxy and phthalimido substituents interact counteractively in the transition state of radical bromination reactions.

A series of triflyl-protected amino acids have been prepared and their reactions with NBS and sulfuryl chloride have been exploited to manipulate the regioselectivity of radical formation. The regioselectivities observed contrast with those seen in the reaction of *N*-acyl-protected amino acids. The differing effects of phthaloyl and triflyl groups on radical formation have been studied in protected alkylamines and it is found that there is a twofold difference in the rates of radical formation at the α-position, but very little difference in those of radicals remote from the protecting groups.

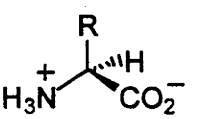
Electron demand in the radical reactions of protected arylalanines has been probed in order to test for neighbouring group effects in these systems. Radical stability has been demonstrated as having little influence on the rates of reaction of arylalanine derivatives, with polar effects in the transition state being dominant. Decreased ratios of the relative rates of reactions of ester and amide derivatives are seen with increasingly electron donating aryl substituents. This is found to be consistent with anchimeric assistance in the radical bromination reactions of arylalanines.

Remote anchimeric assistance in the radical bromination reactions of phenylalkylamine derivatives have also been discovered. The rates of formation of the benzylic radicals of a series of phenylethyl derivatives were shown to be slowed when perfluorinated protecting groups were used. This effect was shown to be consistent with a neighbouring group effect induced by the amine protecting group and not with inductive effects. This neighbouring group effect was shown to persist in the reactions of similarly protected phenylpropyl- and phenylbutyl-amines.

Contents

Introduction

Amino acids exhibit some of the most variant biochemistry of all the classes of biological molecules. This stems from the fact that the most common class of amino acid, the α-amino acid **1**, can exist with a diverse range of side groups each imparting different properties. Despite these differences, α-amino acids each retain the characteristic properties of the class, such as their amphoteric nature, their ability to form peptides and proteins, and their chirality. Amino acids also form important primary and secondary metabolites, many of which are essential to life. At least 700 amino acids and closely related derivatives have been isolated from natural sources,[1] despite only around twenty of these being commonly found in proteins.[2–4] The variety in α-amino acid side chains generally occurs in nature through selective functionalisation of the more common amino acids.[1]



1

Interest in amino acid radicals has been steadily growing due to their synthetic utility,[5–16] pathological significance[17–27] and implied presence in some mechanisms of enzyme catalysed reactions.[28–37] Novel amino acids can be formed *via* radical reactions in reasonable yields, whereas they may be more difficult to form using more common synthetic techniques.[7–11,13,38] Side chain functionalisation of α-amino acid derivatives

using, for instance, radical bromination reactions has been shown to occur without loss of chirality at the α-centre.[8–11,38] This provides a useful route for the preparation of chiral amino acid derivatives which can be utilised either in the synthesis of peptides and antibiotics,[10,39–44] or as probes of the mechanisms of enzyme catalysed reactions.[45,46]

The study of the effect of free radicals on natural peptides is an important area of research, as free radicals have been implicated in several diseases, such as aging,[20,21] Alzheimer's disease[25] and arteriosclerosis.[26] It is believed that prolonged attack on cellular constituents by free radicals results in a toxic build up of oxidised, cross-linked otherwise damaged proteins[17–20] which may be a contributing factor in such diseases,[21] as well as accounting for the toxic action of substances such as carbon tetrachloride[22] and cigarette smoke.[27]

Experiments where radicals have been generated in the presence of amino acid derivatives and peptides commonly give discreet products. Often these products are the result of backbone attack to form α-centred radicals, which then react further to undergo either formation of cross-linked derivatives,[6,18,19,29,47] and unusually substituted derivatives[18,19,29] or result in protein cleavage.[17–19,29] It has been noted that in proteins these cleavages are selective and result in non-random fragments, indicating either a common target or targets for radical attack.[17]

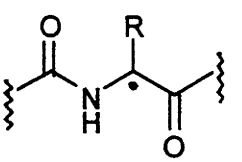


Figure i.1. Peptides and other amino acid derivatives often form α-centred radicals.

α-Centred amino acid radicals (Figure i.1) form readily in peptides and related amino acid derivatives because they are relatively stable.[48] This stability involves extensive delocalisation of the unpaired electron over the amide and carbonyl groups. For these amino acid based systems, many resonance contributors can be drawn, each of which contributes to the delocalisation and stabilisation of the radical (Figure i.2). The radical reactions of such peptides and amino acid derivatives are the only amino acid systems that are readily accessible experimentally. In comparison to their protected counterparts, the α-centred radicals of free amino acids in solution are much less stable under acidic or neutral conditions, because the nitrogen is protonated. Protonation makes the nitrogen lone pair of electrons unavailable to contribute to the resonance delocalisation of the radical, which in turn diminishes the radical stability. In neutral solution, free amino acids do not exist as the uncharged species, but rather as the zwitterions. Uncharged free amino acids and amino acid anions, which can achieve delocalisation of an α-centred radical by using the nitrogen lone pair, only exist either in the gas phase or basic solution, where they are difficult to study. This is due to the incompatibility of many radical reactions with such conditions.

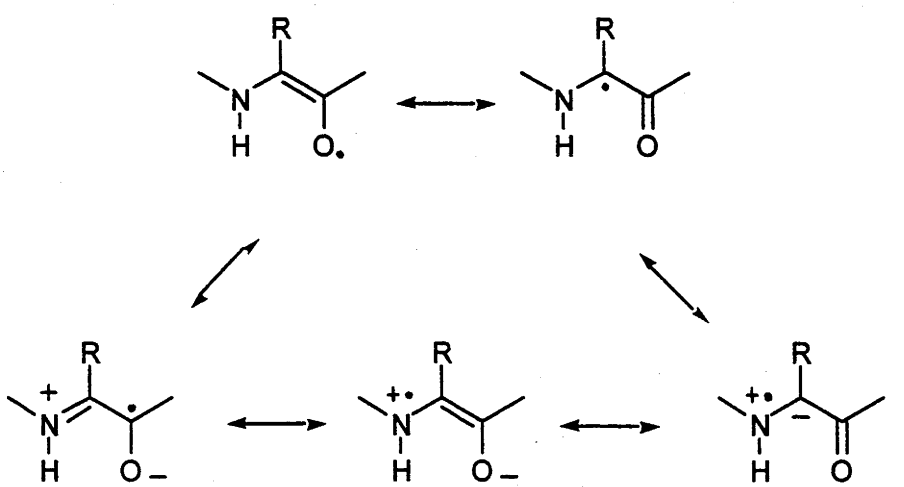


Figure i.2. Resonance contributors that illustrate the delocalisation that stabilises α-centred amino acid radicals.

α-Centred amino acid radicals have also attracted interest for reasons other than their biological importance. In 1952, Dewar first proposed the concept that free radicals stabilised by both an electron donating and an electron withdrawing substituent, such as α-centred amino acid radicals, would be delocalised throughout the system, providing an extra stabilisation when compared to that provided by the two isolated substituents.[49] In effect, the conjunction of the two systems provides extra resonance contributors which can be equated to additional stabilisation, when compared with the total contributors that each single substituent can furnish (compare Figure i.3 and Figure i.2). This effect was later termed "push-pull" stabilisation,[50–53] "merostabilization"[54–56] and the "capto-dative effect".[57] The α-centred amino acid radicals of both free neutral amino acids and peptides are, by definition, captodatively stabilised with the carbonyl group providing capto stabilisation and the amino group providing dative stabilisation (Figure i.2)

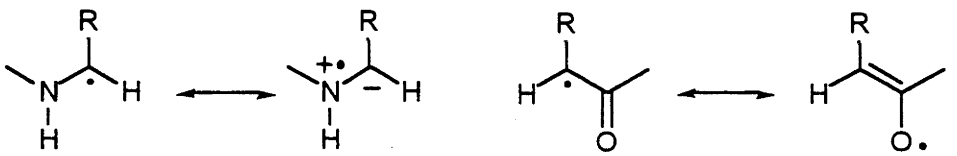
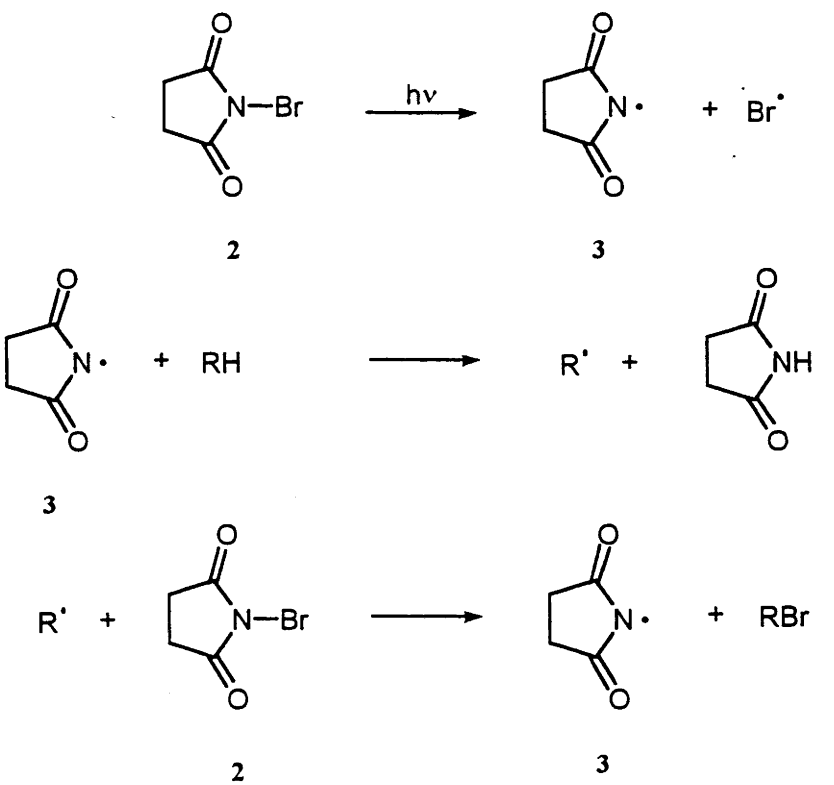


Figure i.3. The corresponding amino and carboxy groups, when isolated, provide less delocalisation (due to less total resonance contributors) of the α-centred radical, than when conjoined (Figure i.2).

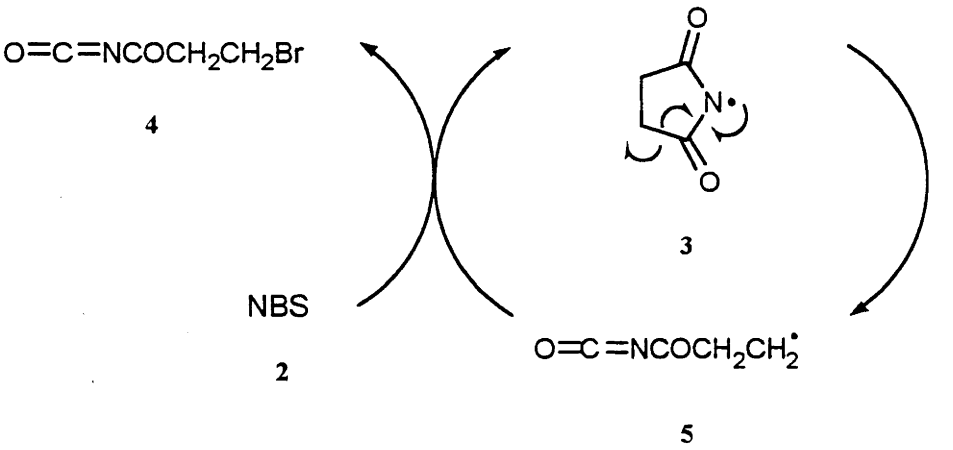
There has been some contention[58–63] as to the magnitude of the synergistic stabilisation predicted by Dewar's proposal[49] and other theoretical models.[55–57,64] However, there is no dispute that the α-centred radicals of amino acid derivatives and peptide residues are often formed preferentially to side chain alkyl and benzylic radicals under bromination[65–68] and some other hydrogen abstracting conditions.[69–72]

In studying the formation of α-centred amino acid radicals from small peptides and other amino acid derivatives, bromination has been used extensively as a tool.[5,7–11,38,48,65–68,73–75] In this thesis, the majority of reactions discussed were carried out using *N*-bromosuccinimide (NBS) **2**. The mechanism of the hydrogen abstraction reaction involving NBS **2** has been extensively studied, due to early ambiguity over the hydrogen abstracting species.[76–84] After the discovery in 1942 that NBS **2** was an excellent radical brominating agent,[85] two different mechanisms appeared to explain its action.[86,87] The first to appear was the Bloomfield mechanism in which the succinimidyl radical **3** was invoked as the radical chain carrier (Scheme i.1).[86]



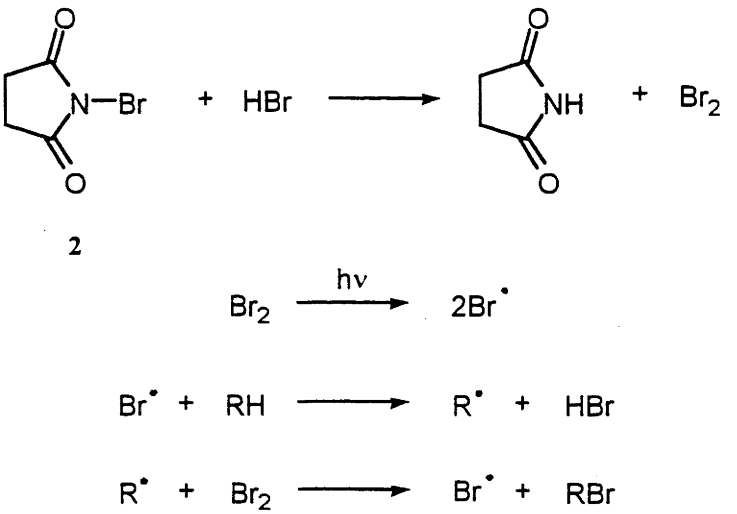
Scheme i.1. The Bloomfield mechanism of radical bromination by NBS **2**.[86]

The Bloomfield mechanism is observable during both the photodecomposition of NBS **2** and the reaction of NBS with compounds of low reactivity toward hydrogen abstraction, particularly in the presence of radical chain inhibiting olefins.[77,82,84] This mechanism occurs with simultaneous formation of β-bromopropionyl isocyanate **4** from the decomposition of the succinimidyl radical **3** by ring opening (Scheme i.2).[77]



Scheme i.2. Photolytic decomposition of the succinimidyl radical **3** with concurrent formation of β-bromopropionyl isocyanate **4** from the ring-opened radical **5**.

In 1953, prompted by earlier work on the induction period required for reaction of *N*-haloamides, a revised mechanism for radical bromination with NBS **2** was published by Goldfinger *et al.*,[87] which included bromine atom as the radical carrier (Scheme i.3). A substantial amount of evidence has since been amassed which provides strong support for bromine atom as the chain carrying species in alkyl and benzylic hydrogen abstraction reactions with NBS.[76–79]



2

Scheme i.3. The Goldfinger mechanism of radical bromination which includes bromine as a radical chain carrier.

The Goldfinger mechanism of radical bromination involves NBS **2** as a provider of a small steady-state concentration of molecular bromine.[77] Subsequent photolysis then produces a smaller steady-state amount of bromine atom which acts as the hydrogen abstracting species. Subsequent halogen abstraction from molecular bromine by the substrate radical thus formed affords the product bromide and a bromine atom, which continues the chain reaction.

Rates of reaction often give information about the steric, polar and resonance effects involved in free radical processes and provide information that can be utilised, for example, in the design of oxidation resistant peptides, enzyme inhibitors and synthetic schemes. It is often difficult to measure absolute reaction rate constants, so competitive methods are commonly employed to obtain relative rate constants. Where possible, a direct competitive approach is highly desirable, as the conditions of the reaction are then kept identical for both the species under examination. This is particularly important in photolytically initiated reactions where the rate of photolysis and, hence, the rate of reaction is highly dependent on the amount of incident light.[88]

Only the hydrogen atom abstraction reaction shown above (Scheme i.3) needs to be considered in order to measure the relative rates of bromination. This is because the abstraction of the hydrogen atom is the rate limiting step at which the substrate becomes involved in the radical chain process. Consider two compounds, AH and EH. The rate of consumption of each from the starting mixture can be written as:

$$\frac{-d[\mathrm{AH}]}{dt} = k_{\mathrm{AH}}[\mathrm{Br}^{\bullet}][\mathrm{AH}] \qquad (1)$$

and

$$\frac{-d[\mathrm{EH}]}{dt} = k_{\mathrm{EH}}[\mathrm{Br}^{\bullet}][\mathrm{EH}] \qquad (2)$$

Equations (1) and (2) can then be combined to provide the following expression:

$$\frac{d[\mathrm{AH}]}{d[\mathrm{EH}]} = \frac{k_{AH}[\mathrm{AH}]}{k_{EH}[\mathrm{EH}]} \qquad (3)$$

Finally expression (3) can be integrated over the limits of the initial (*o*) and final (*f*) concentrations of AH and EH to obtain equation (4), used in this thesis to calculate all relative rates.[89]

$$\frac{k_{AH}}{k_{EH}} = \frac{\ln([\mathrm{AH}]_o/[\mathrm{AH}]_f)}{\ln([\mathrm{EH}]_o/[\mathrm{EH}]_f)} \qquad (4)$$

Direct methods of relative rate determination are sometimes not possible, due to difficulties quantifying starting materials and products by normal chemical and spectroscopic methods. Problems of this nature include either starting materials or products having very similar chemical shifts, or difficulty in separating the compounds by chromatographic means. Under these circumstances, indirect competitive methods

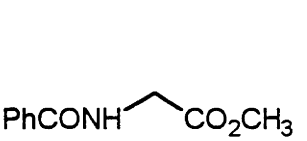
can be used, whereby two sets of directly measured relative rates can be compared. That is, a third component, FH, is used and the relative rates:

$$\frac{k_{AH}}{k_{FH}} \text{ and } \frac{k_{EH}}{k_{FH}}$$

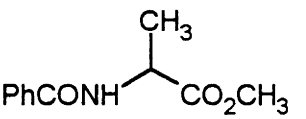
can be compared under identical conditions of concentration[89] and temperature such that:

$$\frac{k_{AH}}{k_{EH}} = \frac{k_{AH}}{k_{FH}} \times \frac{k_{FH}}{k_{EH}}$$

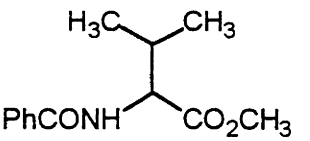
Relative rates of bromination reactions provide information about the relative stabilities of the radicals formed by hydrogen atom abstraction. In the transition state of the reaction there exists a large degree of bond homolysis and therefore the transition state possesses substantial radical character. In these circumstances, the relative rates of radical formation tend to reflect the relative stabilities of the radicals being formed. Under bromination conditions therefore, generally the α-centred radicals of amino acid derivatives are the major reaction products, due to their greater stability when compared with most other types of amino acid radicals. It is found that not all α-centred radicals are equally stable. Selectivity for a particular type of α-centre had been previously characterised in several small peptides.[13,36,73,90] Variation in the nature of the α-substitution (the side chain) had an effect on the relative rates of formation of the α-centred radicals. A detailed examination of this effect was carried out where the relative rates of reaction for the amino acid derivatives **6–8** were examined.[67,68] The results are reproduced in Table i.1.



6



7



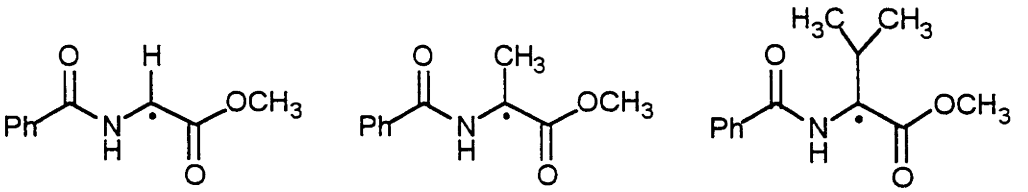
8

Table i.1. Relative rates of bromination of the *N*-benzoyl methyl esters of glycine, alanine and valine **6–8**.

Compound	Relative Rate of Bromination[67,68]
6	23
7	7.7
8	1[†]

[†]Assigned as unity

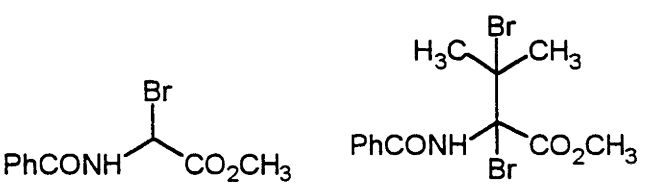
The competitive reactions of the benzoyl amino acid methyl esters **6–8** exhibited a pattern of reactivity that was contrary to that which is usually expected. There was a noticeable selectivity for secondary radical formation at the glycyl α-centre. Also, as the side chains of the amino acid derivatives became progressively more bulky, the reactivity of the α-centre of the derivatives **6–8** toward hydrogen abstraction diminished. This trend has also been observed in other, similar reactions of amino acid derivatives[67–69] as well as in reactions within dipeptides.[11,13,36,73,90]



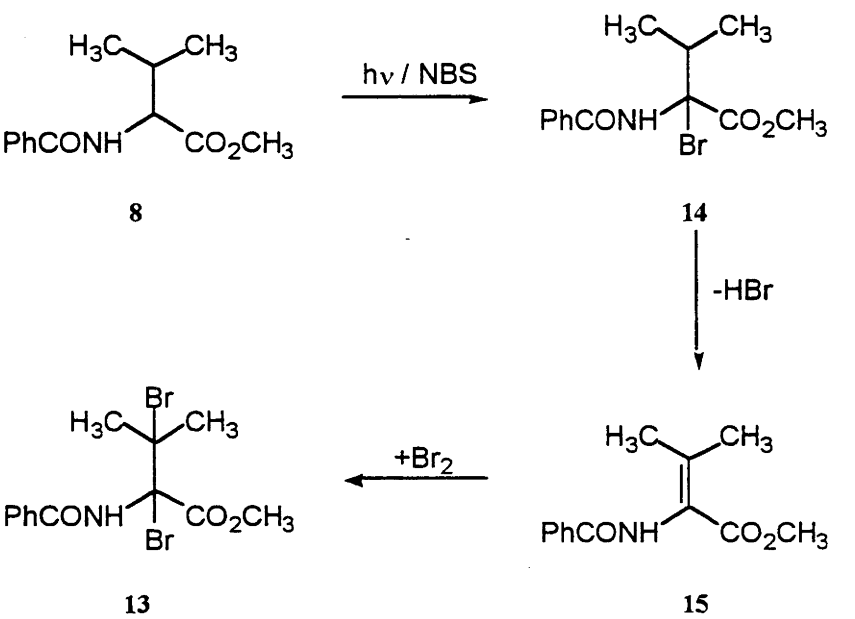
9 10 11

Figure i.4. The α-centred radicals **9–11** of the benzoylamino acid derivatives **6–8**, respectively.

An alternative to bromination reactions for the generation of α-centred radicals in glycine and valine derivatives was achieved by the treatment of the α-bromides **12** and **13** with tributyltin hydride.[67] Note that the product of radical bromination of the valine derivative **8** is actually the dibromide **13**. The dibromide **13** was postulated as arising from initial α-bromination of the valine derivative **8** to give the bromide **14**, followed by elimination of hydrogen bromide to give the alkene **15** and subsequent bromine addition to yield the dibromide **13** (Scheme i.4).[66] Treatment of this dibromide **13** in isolation with one equivalent of tributyltin hydride affords the corresponding β-monobromide **16** (Scheme i.5).

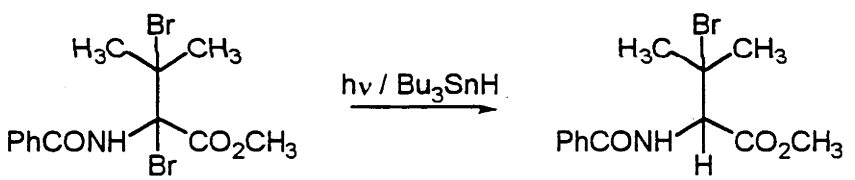


12 13



8 14 13 15

Scheme i.4. Postulated pathway for reaction of *N*-benzoylvaline methyl ester **8** to give the dibromide **13**.

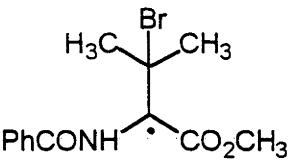


13 16

Scheme i.5. Treatment with tributyltin hydride of the valyl dibromide **13** affords the corresponding monobromide **16**.

Treatment of an equimolar mixture of the bromides **12** and **13** with one equivalent of tributyltin hydride proceeded with exclusive consumption of the glycyl bromide **12** and no visible conversion of the valyl dibromide **13** to the corresponding β-monobromide **16**.[67] The predominant factor in determining the relative rate of halogen atom abstraction is the stability of the radical in question, as is also observed in the bromination reactions. The halogen abstraction and bromination reactions proceed with

reaction of the glycine derivatives **12** and **6** almost to the exclusion of the valine derivatives **13** and **8**, respectively. This pattern of reactivity implies that the glycyl α-centred radical **9** is more stable than either of the corresponding valyl α-centred radicals **11** or **17**.



17

In typical radical bromination reactions, tertiary radicals ($R_3C^{\bullet}$) are more stable, and more easily formed, than secondary radicals ($R_2CH^{\bullet}$),[91] the opposite of what was observed in the reactions of the amino acid derivatives **6–8**, **12** and **13**. The usual selectivity for formation of tertiary radicals is due, in part, to the energy gained from relief of steric compression. When the radical is formed, the hybridisation at the radical centre changes from sp^3 to sp^2, which allows separation of the alkyl substituents and this diminishes any unfavourable interactions between them. Steric compression increases with the number of alkyl substituents, so the energy gained from relief of this steric interaction also increases with the number of alkyl substituents.

The increase in radical stability, with increasing substitution at the radical centre, has also been ascribed to a phenomenon known as hyperconjugation. Stabilisation by hyperconjugation is due to the delocalisation of the unpaired spin density into the σ orbitals attached to the centre adjacent to the radical.[91] This explains why, as more alkyl groups are added, the radicals become more stable due to overlap with more σ orbitals. This overlap increases the spin delocalisation away from the radical centre and onto the

adjacent centres, which can be detected as a distribution of spin density in the electron spin resonance (ESR) spectra of substituted radicals.[92]

The slower rate of formation, and hence, diminished stability of the α-centred radicals **10**, **11** and **17** of the substituted amino acid derivatives **7**, **8** and **13**, with respect to the rate of formation of the α-centred glycyl radical **9**, was attributed to steric interactions. In the planar conformations of the α-centred radicals **9–11** and **17**, bulkier side chains were suggested as interacting more severely with the carbonyl of the amide protecting group *via* non-bonding steric interactions. The more severe these interactions, the less favourable was formation of the corresponding radicals **9–11** and **17**, despite the potential for extra stabilisation through hyperconjugation in those amino acid derivatives **10**, **11** and **17** with side chains (Figure i.5).[48,67,68] Deviation from planarity, which relieves steric interactions, has been used to explain diminished radical stability in some captodatively stabilised radicals[93] because planar conformations provide maximal orbital overlap, and are thus, *a priori*, the preferred form of the radical.

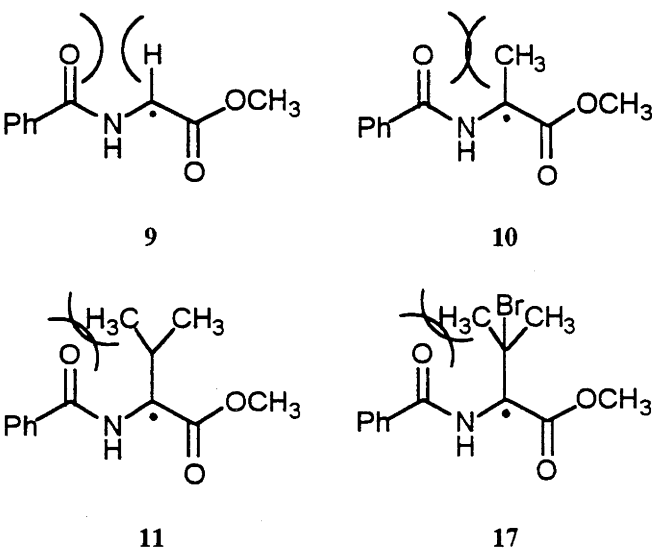
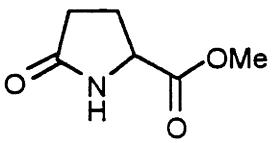
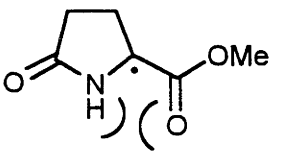


Figure i.5. Potential unfavourable non-bonding interactions in the planar conformations of the α-centred glycyl, alanyl and valyl radicals **9–11** and **17**.

The effect of non-bonding interactions on α-centred radical stability was further investigated by measurement of the relative rate of bromination of methyl pyroglutamate **18**, with respect to *N*-benzoylglycine methyl ester **6**. Methyl pyroglutamate **18** was found to brominate around three times faster than the glycine derivative **6**.[68] Conversion of the unfavourable nonbonding interactions found in the planar conformations of either the protected alanyl radical **10** or protected valyl analogue **11** (Figure i.5), to bonding interactions in the methyl pyroglutamate radical **19** was postulated as one of the reasons for the increased reactivity observed.[68]



18



19

The steric effects, which are postulated to account for the selectivities observed in the formation of the amino radicals **9–11** and **19** under bromination conditions, should be reflected in the structures of either the radicals **9–11** and **19**, or their parent amino acid derivatives **6–8** and **18**. This is very difficult to examine experimentally, particularly for reactive intermediates. Theoretical calculations, however, provide an excellent means of probing the structure and properties of reactive intermediates.

To gain understanding about the nature of factors affecting free radical formation, relative rates of reaction are often compared. A rate of reaction, however, only provides information about the ease of formation of a particular radical, as distinct from the stability of the radical. Such rates are a measure of the activation energy ($\Delta G^{\ddagger}$) and take into account factors present in the transition state, which may not exist in the radical. The thermodynamic stability of a radical is defined by the value of ΔG. Direct

information about the stability of the radical is difficult to obtain experimentally, except in very simple systems. Therefore, it is necessary to employ a different approach if we are to examine the differences that might exist between ΔG and $\Delta G^{\ddagger}$.

Bromination reactions may exhibit major differences between ΔG and $\Delta G^{\ddagger}$. This is because these reactions, particularly in amino acid derivatives, are believed to occur *via* a polarised transition state (Figure i.6). Factors that influence a polar transition state may not be the same as those affecting the radical stability. Thus, a difference in the relative rates of reaction and relative radical stabilities would be observed.

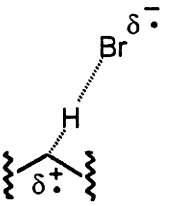


Figure i.6. Bromination reactions pass through a polarised transition state.

Advances in computer technology in the last two decades have made moderate level *ab initio* calculations accessible for the calculation of the properties of medium sized molecules, such as protected amino acids. Therefore, the amount of work on single residues and small peptides has increased significantly in the last few years. Many studies have focussed on the conformational details of neutral and zwitterionic amino acids and peptides, and how the preferred conformations relate to protein folding and structure.[94–112] Neutral amino acids are of interest because they only exist in the gas phase, where they are the preferred configuration both for glycine[109,110] and other amino acids.[100–105,113] Theoretical methods are another way of accessing these molecules,

whilst avoiding the difficulties associated with both zwitterionic structures and solvent effects.

More recently, with better calculation techniques that provide increasingly reliable results for open shell systems, interest in the stability of amino acid radicals has risen. Theoretical calculations allow us to examine these reactive intermediates in detail and offer a direct approach to the measurement of radical stabilisation (or bond dissociation) energies (ΔG) without complications from the transition state effects present in experimental relative rates ($\Delta G^{\ddagger}$). Calculations on amino acid radicals can now be performed at a high enough level to provide reliable absolute values of these stabilisation energies.

Work within the amino acid radical area has, however, been mainly limited to examining the stability of glycyl radicals[31,114–122] with little effort being directed toward the rationalisation of selective glycyl radical formation in peptides. An examination of the bond dissociation energies of glycine, alanine, serine and threonine and their peptide-like derivatives has previously been made.[123] The aim of this study was to obtain information about the factors affecting the susceptibility of particular α-amino acids toward protein damage and repair. Emphasis was placed on the effect of varying both the side chain and the conformations on the bond dissociation energies relative to either the stabilities or reactivities of the species involved in either protein damage or repair. This study made a brief comment on a 'repulsive interaction' between the amido-carbonyl and β-hydrogen moieties in the peptide model of alanine in the discussion. However, this observation of interactions with the amide protecting group has not been elaborated on in either this[123] or any other theoretical studies to date.

Ab initio work has been carried out previously which shows the effect of non-bonding interactions in the radicals of sarcosine derived dipeptides.[90] The low stability of the sarcosyl radicals was rationalised by way of unfavourable interactions of the *N*-methyl substituent with the adjacent α-carbonyl in the planar conformation of the radical,

resulting in significant deviation from planarity. The arrangement of the groups in the planar radical of sarcosine is similar to that which would be expected in a protected alanyl radical (Figure i.7).

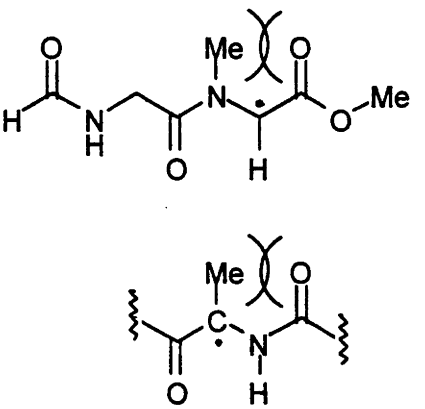


Figure i.7. The sarcosylglycyl radical (top) and an alanyl radical (bottom) show similar non-bonding interactions. The sarcosyl radical is known to undergo geometric distortion to avoid unfavourable non-bonding interactions.[90]

The unusual selectivity for the formation of glycyl radicals in peptides is clearly worth investigating further. If these effects are caused by unfavourable interactions of the side chain with the amido-carbonyl of the protecting group, then this will be revealed by a comparison of amino acids with and without this protecting group. Free neutral amino acids and their α-centred radical derivatives are ideal systems with no possible interactions of this type. The radical stabilisation energies (ΔG) and optimised structures of these radicals are also readily accessible theoretically. Acetyl-protected amino acids are good models for peptide fragments and present us with a system that is both experimentally and theoretically accessible. By comparing the radical stabilisation energies of the protected amino acids, where the interaction with the amido-carbonyl is possible, with those of the unprotected amino acids, where is it not, a test of the

postulated steric effect is possible. Theoretical calculations were performed to elucidate the effects on the common structural elements, and the stability of the appropriate radical species, when the side chain bulk is increased both in a selection of protected and non-protected amino acids. The findings arising from the structural and energetic comparisons of these molecules are presented in Chapter One of this thesis.

Exacerbation of these steric effects in new systems has also been explored, both theoretically and experimentally. Additional to steric effects, the effect of electrostatic interactions has been examined. The results of this inquiry are presented in Chapter Two of this thesis.

The stability of α-centred radicals of amino acids and their derivatives is not only affected by the side-chain they bear. The specific protecting group employed can have a significant impact on the reactivity of a particular α-centre toward hydrogen abstraction, affecting both the rate and regioselectivity of radical formation. It is relatively easy to design model systems to study the effects of protecting groups by employing the amide functionality. *N*-Acyl-protected amino acids combine the major structural features of a single residue of a peptide.

The stability of an α-centred amino acid radical is quite different when the amino acid in question is protected as an amide, compared to the free uncharged form. Replacement of the amino group by an amido group decreases the observed radical stability markedly.[62] ESR measurements also detect a reduction in the delocalisation of the radical and this provides support for the lower radical stability of acylated amino acids.[124] The reduced delocalisation of the radical is a result of the electron density on the amide nitrogen being less able than that of a free amine to datively stabilise the radical. This reduced electron density at the amide nitrogen is due to the competitive delocalisation of the nitrogen lone pair by the carbonyl of the amide, as shown in Figure i.8.

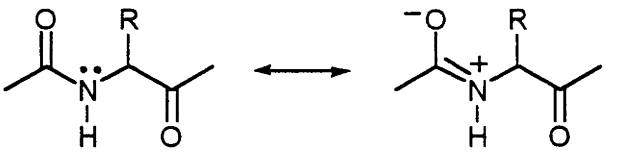


Figure i.8. Delocalisation of the lone electron pair on nitrogen, affecting the ability to stabilise an α-centred radical.

The importance of being able to manipulate the reactivity of glycine residues in radical reactions is many fold. It provides a useful way to control the outcome of synthetic pathways.[38,74] It also shows potential to provide inhibitors of enzymes which act *via* a radical mechanism. One such enzyme where glycine radicals are thought to be important is peptidylglycine α-amidating monooxygenase (PAM). The PAM enzyme acts to oxidise the terminal glycine of the biosynthetic precursors to peptide hormones and neuropeptides through a suspected radical mechanism.[36,125,126] Previous work has shown that the rate of this cleavage can be modified by changing the acyl protecting group on glycyl substrates.[37]

As an extension of the study of the mechanism of reaction of the PAM enzyme, the radical bromination reactions of a variety of glycine derivatives were studied.[37] On varying the amino protecting group of these glycine derivatives, it was shown that the rate of radical bromination of such derivatives also varied. The degree to which the rate of bromination of the glycine derivatives was affected appeared to be directly related to the electron-donating ability of the amide nitrogen. This was ascertained by correlation of the relative rates of reaction of the glycine derivatives with the pK_a values of the carboxylic acids that correspond to the *N*-acyl substituents (Table i.2).

Table i.2. The relative rates of bromination of different *N*-acylated glycines compared with the pK_as of the carboxylic acids corresponding to the acyl moieties.

R	k_{rel} of R-NHCH$_2$CO$_2$CH$_3$[37]	ROH	pK_a[127,128]
$(CH_3)_3COC(O)$-	2.6	$(CH_3)_3COCO_2H$	6-7‡
$CH_3C(O)$-	1.2	CH_3CO_2H	4.76
PhC(O)-	1.0†	$PhCO_2H$	4.20
p-FPhC(O)-	0.86	*p*-$FPhCO_2H$	4.15
$C_6F_5C(O)$-	0.25	$C_6F_5CO_2H$	1.75
$CF_3C(O)$-	0.05	CF_3CO_2H	0.52

† Assigned as unity. ‡ Estimation based on the pK_a of carbonic acid.[37]

The pK_a of a carboxylic acid reflects the ability of the corresponding acyl substituent to stabilise a negative charge. When such an acyl substituent is employed as an amino protecting group it has a similar influence on the delocalisation of the electron density from the nitrogen. The effect of this delocalisation in acyl-protected amino acid derivatives is to make the nitrogen electrons less available for the dative stabilisation of either the radical or the transition state leading to the radical (Figure i.9). Consequently, the observed rate of bromination of an acyl-protected amino acid derivative decreases with the increasing acidity of the carboxylic acid that corresponds to the acyl protecting group.

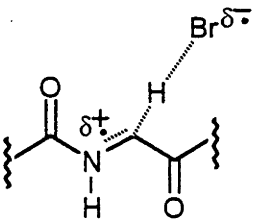


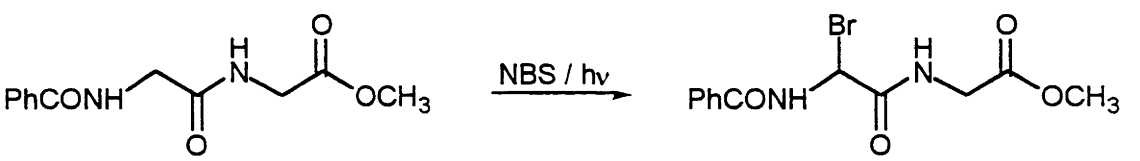
Figure i.9. Delocalisation of the nitrogen electrons by the carbonyl substituent means that they are less available for dative stabilisation of the polarised transition state shown.

In the previous work,[37] the effect on the transition state of radical formation was emphasised because of the possibility of significant polarisation. Thus, the dative effect of the nitrogen being less able to delocalise a partial positive charge, rather than a neutral radical, could be significant. Whether or not this is the case is easily discernible by comparing theoretical calculations of the radical stability with the experimentally determined relative rates. This gives a comparison of ΔG and $\Delta G^{\ddagger}$ between the series of protected amino acids which should reflect how important polarisation is in the transition state, when compared with radical stability. For this reason, a theoretical survey of a selection of protected amino acids and comparison with available relative rates of bromination is presented in Chapter Three of this thesis.

It would be of interest to extend the scope of this electronic mode of radical destabilisation to potentially prevent formation of α-centred amino acid radicals in hydrogen abstraction reactions. For instance, a protected glycine derivative that is inert to α-centred radical formation under normal conditions, and which could bind to the active site of certain enzymes that act through radical mechanisms, may act as an effective inhibitor. Based on the patterns of reactivity observed and their correlation with acidities already discussed, an obvious choice would be to find a protecting group which has a highly acidic analogue.

The class of sulfonic acids contains some of the strongest monoprotic acids yet discovered. One of the most powerful acids known is trifluoromethanesulfonic acid,[129-132] trivially known as triflic acid. Its pK_a has been estimated as being around –5.5 in aqueous solution[132] and quoted as 3.1 in H_2SO_4.[133] As such, the corresponding triflamide protecting group seemed an ideal candidate to investigate the effects of protecting groups on α-centred radical formation under extreme conditions. The use of the triflamide protecting group to affect α-centred radical formation in glycine derivatives was thus examined both experimentally and theoretically and the results are presented in Chapter Three.

The effect that different protecting groups can have on the selectivity of α-centred amino acid radical formation has been illustrated with the bromination reactions of glycylglycine derivatives. *N*-Benzoylglycylglycine methyl ester **20** affords, upon irradiation with NBS, solely the α-bromide **21** from reaction of the *N*-terminal amino acid residue (Scheme i.6).[73] When the benzoyl protecting group was replaced by a phthaloyl protecting group, to give the phthaloylglycylglycine **22**, the regioselectivity of the reaction was altered such that bromination only occured at the *C*-terminal amino acid residue to give the bromide **23** (Scheme i.7).[38,74]



20 **21**

Scheme i.6. Bromination of the benzoyl-protected glycylglycine **20**.

22 23

Scheme i.7. Bromination of the phthaloyl-protected glycylglycine **22**.

The effect of the phthaloyl substituent on radical formation at an adjacent α-centre in amino acid derivatives has been explained as being the result of a combination of factors, both steric[38] and electronic[38,74] in nature. The steric effects are postulated as arising in two different ways. It has been suggested that there is an effect whereby the phthalimido and α-carbonyl substituents interact with the hydrogen abstracting species as it approaches the reaction centre, thus hindering its approach and slowing the rate of hydrogen abstraction. There is also an effect of the interactions between the phthalimido and α-carbonyl substituents, which prevents the radical from adopting a planar conformation in which there is maximal delocalisation of the unpaired spin density (Figure i.10).

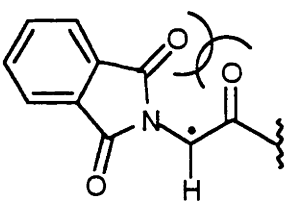


Figure i.10. Nonbonding interactions associated with the planar conformations of the α-centred phthaloylglycyl radical fragment.

Evidence for such non-bonding interactions acting to destabilise α-centred radicals came from the bromination reaction of N^{α},N^{ε}-diphthaloyllysine methyl ester **24**. Bromination occurred selectively at the ε-position to give the bromide **25** (Scheme i.8).[134] This suggested that the *N*-phthaloyl moiety was behaving as an activating substituent in isolation, but resulting in deactivation of the adjacent centre to radical formation when in combination with the methoxycarbonyl group.

24 **25**

Scheme i.8. The N^{α},N^{ε}-diphthaloyllysine **24** brominates exclusively at the ε-position, indicating that the phthaloyl group is activating in isolation, but deactivating in combination with the methoxycarbonyl substituent.

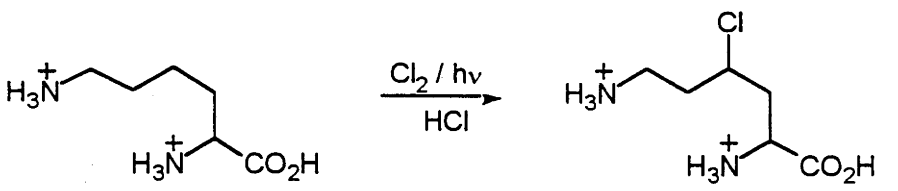
The part of the deactivation suggested in the phthaloyl system **22** that was ascribed to electronic factors was described as being due to the competitive delocalisation of the nitrogen electrons onto the two adjoining carbonyl moieties. This makes the phthalimido nitrogen less able to delocalise the spin density of the radical in comparison with a benzoyl protecting group, which has only one carbonyl group attached to the nitrogen.

A theoretical investigation of the factors affecting α-centred radical formation in phthaloyl-protected amino acid derivatives is presented in Chapter Three. The aim of this investigation was to delineate the exact nature and relative contributions of the steric, electronic and any additional factors which might be involved in making the phthaloyl group a protecting group which is able to prevent α-centred radical formation.

Electronic factors were examined by assessing the effects of amino, amido and imido substitution adjacent to a radical centre free of steric interactions. Comparison of the stabilities of these radicals with the corresponding glycyl radicals allowed determination of the extent of steric factors that affect the radical stability. Finally, comparison of the patterns of radical stabilities with experimentally determined rates of reaction were able to separate those factors which affect solely the transition state from those which also reflect the stability of the radical.

Being able to affect the reactivity of the α-centre of glycine derivatives toward hydrogen abstraction has further implications. Modification of centres other than the α-centre of amino acids such as valine and phenylalanine allows a direct route to non-proteinogenic and otherwise elaborated derivatives. If no reaction occurs at the α-centre, then these derivatives will retain the chirality of the parent amino acid, providing a simple route to chirally pure compounds. The phthaloyl group has been utilised successfully as a protecting group in this manner.[8,9,38,74]

Selectivity on the side chain can be influenced by polar factors, as well as steric factors exerted by the protecting groups used. For example, Kollonitsch *et al.*[135,136] chlorinated lysine **26** in concentrated hydrochloric acid solution to give the γ-chloride **27** (Scheme i.9).



26 **27**

Scheme i.9. Chlorination of lysine **26** under highly acidic conditions yields specifically the γ-chloride **27**.

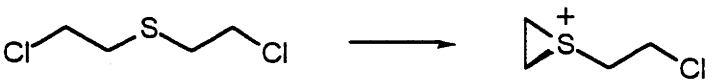
The protonation at the α- and ε-amino groups influences side chain functionalisation by exerting an inductive effect. This inductive effect is so strong that not only are the adjacent centres deactivated, but the chlorine atom prefers also to abstract a hydrogen atom from the carbon furthest from the protonated amines. In the case of lysine **26**, this is at the γ-position, halfway between the protonated α- and ε-amino substituents.

This regioselectivity is different from the case of the N^{α},N^{ε}-diphthaloyllysine **24** where the phthaloyl protecting groups were seen to be activating at one centre and deactivating at the other, to give the ε-bromide **25**. Clearly, the choice of protecting group can have effects that extend beyond the centre adjacent to it. The triflyl group is shown in Chapter Three to have a powerful effect on the formation of α-centred glycyl radicals. These observations are extended in Chapter Four to an examination of how the properties of the triflyl group affect the regioselectivity of the radical bromination reactions of triflyl protected amino acid derivatives and peptides. A comparison of the effects of the triflyl group and the phthaloyl group on such regioselectivity is also presented in this chapter.

Reactions of the side chains of amino acids are of synthetic interest, as mentioned above. Reactivity at these centres can be governed by a variety of factors, such as steric, resonance and inductive effects, and by remote neighbouring group participation. Neighbouring group participation is characterised by a remote functional group having an effect on a reaction by direct interaction with the reaction centre in either a transition state or a reaction intermediate. This is observed as either a change in the stereochemical outcome of a reaction,[137,138] or other changes in the product distribution, or an enhancement of the rate of a reaction.[139] The latter is categorised specifically as anchimeric assistance and manifests itself when the stabilisation afforded to the transition state occurs at a rate determining step.[140]

Neighbouring group participation has attracted interest in its contribution to the mechanisms of many reactions, particularly those involving either physiologically active

or biologically significant compounds.[8,10,75,141–149] Neighbouring group effects have also been utilised in models of enzymatic activity.[139,150] Participation by acetoxy and amido protecting groups in the synthesis of pyranoses provides stereoselective routes to a variety of sugar derivatives.[144,145] It is also well known that the reactive centre of the potent toxin, mustard gas **28**, is activated toward nucleophilic attack *via* 1,3-neighbouring group displacement (Scheme i.10).[151]



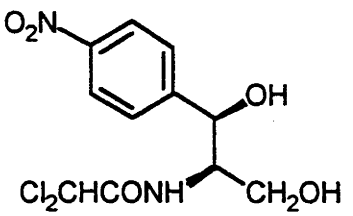
28 **29**

Scheme i.10. Mustard gas **28** is activated by a 1,3-neighbouring group attack to form the highly reactive cation **29**.

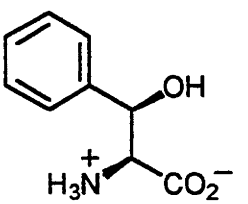
Of particular interest in the present work is the nature of neighbouring group effects in reactions of α-amino acid derivatives and peptides. Several instances have been reported,[8–10,141–143,146] including the well known Edman degradation.[146] The interaction of neighbouring groups has also been used more than once as a tool for the preparation of stereochemically pure chloramphenicol **30**, a widely used antibiotic.[10,147] The most recent of these procedures[10] stemmed from methods for the stereocontrolled syntheses of the β-hydroxyphenylalanine **31** and the β-hydroxytyrosine **32**,[8,9] both of which are important constituents of several biologically active compounds including the cyclic peptides vancomycin,[39] lysobactin,[40,41] phomopsin A[42,43] and bouvardin.[44]

It was discovered that the β-hydroxy amino acids **31** and **32**, as well as several other related derivatives, could be produced with relatively good stereochemical purity when compared with their preparation *via* existing methodologies.[8,9] Initial free radical bromination of the *N*-phthaloyl amino acid methyl esters **33** and **34** gave 1:1 mixtures of the protected β-bromide diastereomers **35** and **36**, respectively. Subsequent hydrolysis

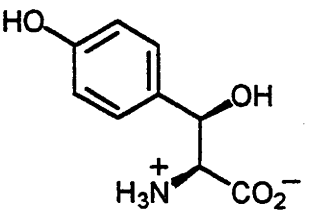
of these bromides, by treatment with silver nitrate in water, afforded 5:1 diastereomeric ratios of the corresponding β-hydroxy amino acids **37a** and **37b**, and **38a** and **38b**.[8,9]



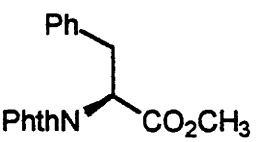
30



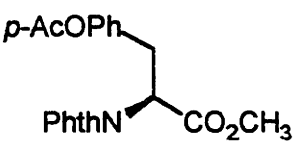
31



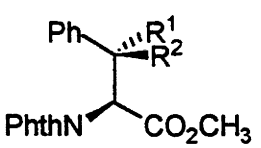
32



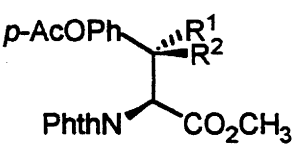
33



34



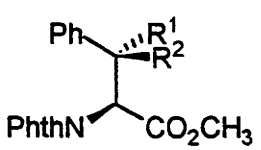
35



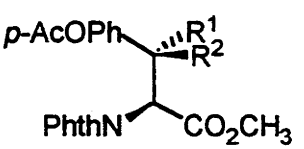
36

a. $R^1 = H$, $R^2 = Br$

b. $R^1 = Br$, $R^2 = H$



37

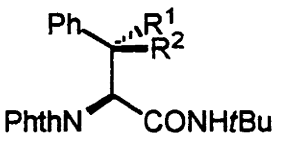


38

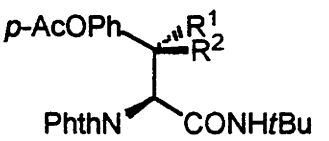
a. $R^1 = H$, $R^2 = OH$

b. $R^1 = OH$, $R^2 = H$

Treatment of the *N*-phthaloyl-β-bromo amino acid *tert*-butyl amides **39** and **40** in a similar fashion, however, gave exclusively the (2*S*,3*R*)-alcohol diastereomers **41a** and **42a**, respectively.[9]



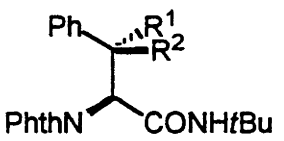
39



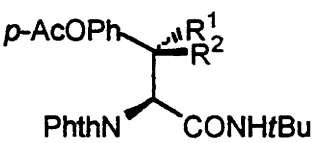
40

a. $R^1 = H$, $R^2 = Br$

b. $R^1 = Br$, $R^2 = H$



41



42

a. $R^1 = H$, $R^2 = OH$

b. $R^1 = OH$, $R^2 = H$

The increase in the stereoselectivity of the hydrolysis reactions of the bromoamides **39** and **40**, over that of the reactions of the corresponding bromoesters **35** and **36**, was attributed to a 1,4-neighbouring group effect. This neighbouring group effect was described as arising from stabilisation of intermediate carbocations in the hydrolysis reactions of the bromides **35**, **36**, **39** and **40**. This proposed stabilisation effectively blocks one face of the carbocations, resulting in face selective attack of water to form the corresponding alcohols **37**, **38**, **41** and **42**. Increased stereoselectivity of product formation in the hydrolysis of the bromoamides **39** and **40** implied increased stabilisation of the relevant carbocation intermediates. This increased stabilisation was ascribed to the enhanced ability of an amide substituent to provide electron density to the electron deficient reactive centre (Figure i.11), when compared with the ability of the corresponding ester substituent.

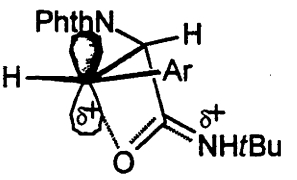
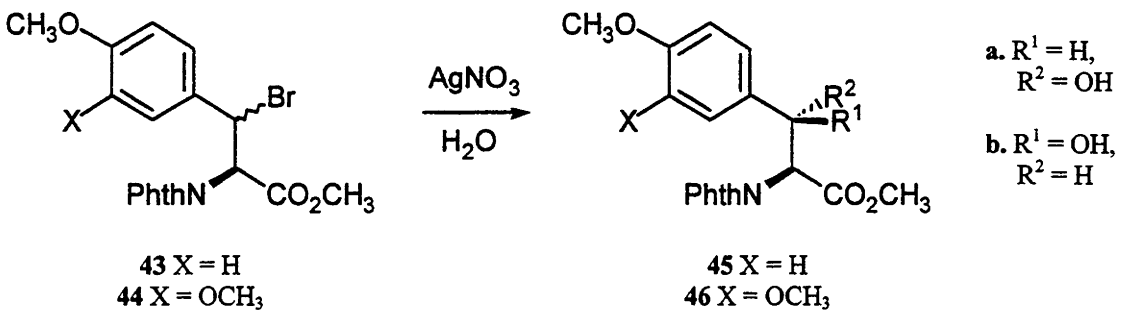


Figure i.11. Stabilisation, by means of 1,4-carbonyl participation of the amido substituent, of the intermediate carbocations formed during the hydrolysis of the bromides **39** and **40**.

It is well known that amides are stronger bases than esters, by about six orders of magnitude.[91] Amides also have been shown to have greater rates of complexation to electron deficient moieties than esters, for example when acting as proton acceptors in the formation of complexes with 4-fluorophenol.[152,153] Overall, amides are much better at donating electron density to electron deficient transition states than the corresponding esters and this is reflected by the increase in stereoselectivity in the formation of the (*2S,3R*)-alcohols **41a** and **42a**, compared with that of the corresponding reaction of the ester bromides **35** and **36**. This is because the amide can more effectively block one face of the intermediate carbocation by binding in a tighter fashion.

The existence of 1,4-carbonyl anchimeric assistance in the phenylalanine systems is unusual, with only a few other examples of 1,4-assistance having been reported.[154,155] The lack of 1,4-neighbouring group effects, compared with the multitude of 1,3- and 1,5-effects is presumably due to ring strain factors. The rarity of 1,4-neighbouring group participation prompted a closer examination of the phenylalanine system. To investigate other factors which may affect stereoselectivity in the hydrolysis reactions of phenylalanines, the reactions of a variety of β-bromides of protected arylalanines, including the *O*-methyltyrosine bromide **43** and the dimethoxyphenylalanine bromide **44**, with silver nitrate in water were analysed.[156]



43 X = H
44 X = OCH_3

45 X = H
46 X = OCH_3

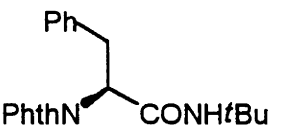
Scheme i.11. Hydrolysis of the *O*-methyltyrosine derivative **43** and the DOPA derivative **44**.

Whereas the hydrolysis of the phenylalanine bromoester **35** gave a 5:1 diastereomeric ratio of the alcohols **37a** and **37b**, the diastereomeric ratio afforded in the reaction of the *O*-methylphenylalanyl derivative **43** was much lower, being only a 1.7:1 mixture of the alcohols **45a** and **45b**. The reaction of the DOPA derivative **44** showed no diastereoselectivity.[156] Steric effects were excluded as the reason for this observed reduction in stereoselectivity, since the only differences between the compounds examined were of sufficient distance from the reactive centre to have no steric effect on either abstraction of the bromine by silver ion or on the approach of water.

The principle of electron demand explains the selectivity observed in the reactions of the arylalanine derivatives **35**, **43** and **44** in terms of electronic effects. When a methoxy substituent is added to the aryl ring, this ring becomes more electron rich. A more electron rich aryl ring is better able to stabilise the adjacent benzylic carbocation that is formed as an intermediate during the hydrolysis reaction. The requirement for this carbocation to be stabilised by the neighbouring group then diminishes. Decreased stabilisation by the neighbouring group results in less effective blocking of a single face of the intermediate carbocation, causing a reduction in the observed diastereoselectivity. An increase in the stereoselectivity of the hydrolysis reactions was observed when electron withdrawing groups were substituted onto the aryl ring.[156] In this case the intermediate carbocation is less able to be stabilised by the aryl ring and the requirement

for the neighbouring group to satisfy this demand for electron density increases. This results in the neighbouring group more effectively blocking a single face, leading to increased stereoselectivity of the hydrolysis. The stereoselectivity observed in these reactions provides strong evidence that the effect observed is indeed caused by a neighbouring group effect.

Most of the examples of neighbouring group effects found in the literature are ionic in nature. Anchimeric assistance is more rarely observed in radical reactions.[75,157–159] In fact, no examples of remote anchimeric assistance for radical reactions had existed in the literature until an unusual example, in an α-amino acid, was reported recently.[75] A fivefold increase in the rate of radical bromination was observed when comparing reaction at the β-position of the amide derivative **47** with the corresponding reaction of the ester derivative **33**. This was the first reported observation of 1,4-anchimeric assistance in a radical reaction and has important implications for free radical chemistry in peptide and protein systems.



47

The anchimeric assistance reported in the radical bromination of the phenylalanine derivatives **33** and **47** is directly analogous to the neighbouring group effects described in the corresponding ionic systems. However, in this case it is the stabilisation of a polar transition state that leads to the observed anchimeric assistance (Figure i.12).

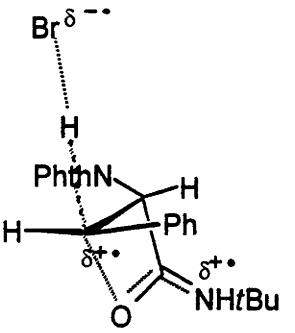
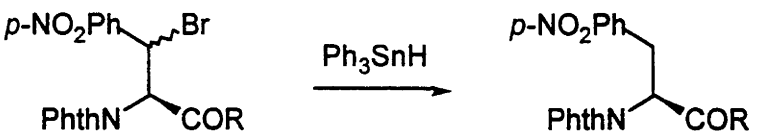


Figure i.12. Anchimeric assistance, as proposed by Easton and Merrett.[75] The carboxyl protecting group of the phenylalanine derivative **47** helps stabilise the transition state during hydrogen abstraction.

Evidence for a polar transition state comes from the comparison of the rates of two different reactions which both form the same radical, but *via* different polarities of the transition state leading to that radical. Two such reactions were the radical reductions of the phenylalanine bromides **35** and **39**, and the nitrophenylalanine bromides **48** and **49** with triphenyltin hydride (Scheme i.12), and the bromination reactions of the corresponding phenylalanine derivatives **33** and **47**, and the nitrophenylalanine derivatives **50** and **51** with NBS.[75]

The relative rates of reduction of the bromoesters **35** and **48**, and also of the bromoamides **39** and **49**, showed that the nitrophenylalanine derivatives **48** and **49** reacted approximately four times faster than their phenylalanine counterparts **35** and **39**. As the nitro group is known to stabilise electron rich transition states, this evidence is consistent with such a transition state. This result is in direct contrast to that obtained for the bromination reactions of the nitrophenylalanine derivatives **50** and **51**. These derivatives reacted eight times slower than the corresponding phenylalanine derivatives **33** and **47**, respectively. This behaviour is consistent with an electron deficient transition state.



48 R=OCH_3
49 R=NH*t*Bu

50 R=OCH_3
51 R=NH*t*Bu

Scheme i.12. Reduction of the *p*-nitrophenylalanine derivatives **48** and **49** by treatment with triphenyltin hydride.

The relative rates of bromine atom abstraction also revealed no difference in the rate of reaction between the ester-amide pairs **35** and **39**, and **48** and **49**, implying no anchimeric assistance, unlike that seen in the bromination reactions. This is consistent with the carbonyl functionality of either the ester or the amide only providing anchimeric assistance to an electron deficient transition state, rather than the electron rich transition state formed by stannane abstraction of bromine atom (Figure i.13).[160]

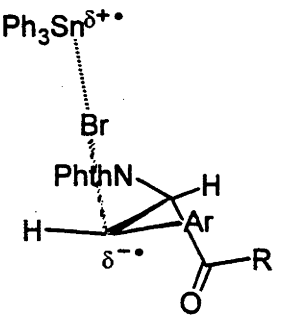


Figure i.13. Transition state for the abstraction by triphenyltin radical of bromine atom. There is no driving force for the electron donating carbonyl to provide anchimeric assistance.

No diastereomeric excess was observed in the formation of the bromides **35** and **39**, in contrast to their hydrolysis. This is also consistent with the neighbouring group providing stabilisation only in the transition state leading to radical formation rather than to the radical itself. Subsequent bromine atom abstraction by the β-centred phenylalanyl radical is then not face selective, as neither face of the radical is shielded by the neighbouring group.

Previous theoretical studies on the radicals of ring substituted toluenes have shown that there is little correlation of the stabilities of these radicals with the Hammett parameters of their ring substituents.[161,162] Hyperfine splitting constants obtained from ESR studies are indicative of the stability of radicals, and these show increased delocalisation of spin from the benzylic position of almost all *para*-substituted benzylic radicals, regardless of the electron withdrawing or electron donating properties of the *para* substituent, when compared with the hyperfine splitting constants of the unsubstituted benzylic radical.[163] This lack of correlation of the stabilities of such a wide variety of benzylic radicals, with either the electron withdrawing or electron donating ability of their *para* substituents, implies that the rate accelerations and decelerations observed in the radical reactions of the phenylalanine derivatives previously studied,[75] cannot be attributed to radical stability. This is consistent with polar effects affecting only the stability of the transition state in these reactions.

The theoretical procedures used previously to determine the radical stabilisation energies of substituted benzylic radicals[161,162] are not thought to be as reliable for calculating these values as the recommended[164] procedure assessed in Chapter One of this thesis. In order to ascertain the accuracy of these previous theoretical calculations, a comparison of the previously calculated RSEs with RSEs calculated at the higher and more reliable level of theory is made in Chapter Five of this thesis.

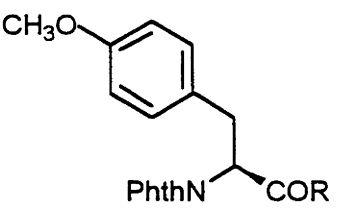
The highly unusual nature of the 1,4-anchimeric assistance seen in the radical reactions of phenylalanine derivatives warrants further investigation. The effect of electron

demand on the radical bromination reactions of a variety of substituted arylalanine derivatives, in a similar fashion to that detailed above for the study of ionic neighbouring group effects,[156] appeared to be a viable method by which to further investigate anchimeric assistance.

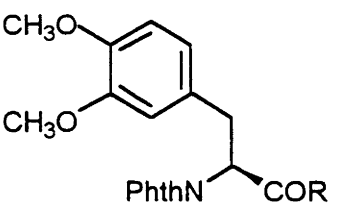
The relative rates of bromination of the nitrophenylalanine ester and amide derivatives, **50** and **51**, examined by Merrett,[165] should give a preliminary indication of the effect of electron demand, when compared with the relative rates of bromination for the corresponding phenylalanines **33** and **47**. By analogy with the ionic reactions of the bromoesters **35** and **48**, withdrawal of electron density by the nitro substituent would lead to a greater requirement for stabilisation from a neighbouring group and, therefore, a more significant neighbouring group effect. The increase in electron demand in the reactions of the nitrophenylalanine derivatives **50** and **51**, when compared with that in the reactions of the corresponding phenylalanine derivatives **33** and **47**, however, does not seem, at first sight, to be reflected in the degree of anchimeric assistance observed. The ratio of the relative rates of reaction reported in the literature for the nitrophenylalanine derivatives **50** and **51** was 1:5,[75] which is the same as that reported for the phenylalanine derivatives **33** and **47**.[75] A closer examination of the raw data, however, reveals that the bromination reactions of the nitrophenylalanine derivatives **50** and **51** were complicated by decomposition.[165] Additionally, whilst the relative rates obtained were within experimental error of the fivefold figure quoted, the relative rate of reaction of the amide, when compared with that of the ester, seems marginally faster for the nitrophenylalanine derivatives **50** and **51** (5.3 : 1),[165] when compared with that of the phenylalanine derivatives **33** and **47** (4.9 : 1).[165] However, any apparent differences, being within experimental error, are not large enough to make valid conclusions. Clearly, other substituents on the aryl ring must be examined to determine if electron demand is having an effect in these systems.

The bromination reactions of the *O*-methyltyrosine derivatives **52** and **53** and the dimethoxyphenylalanine derivatives **54** and **55** provide a means of investigating electron

demand in radical systems, in an analogous fashion to the examination in ionic systems.[156] The ratio of the relative rates of reaction of the phenylalanine amide and ester **47** and **33** is 5 : 1. A decrease from this ratio of amide to ester reactivity in the reactions of systems with decreased electron demand is evidence for anchimeric assistance. Conversely, no change in the ratio of amide to ester reactivity is evidence that the effect in radical reactions is caused by something other than neighbouring group participation. How the ring substituents of the derivatives **52–55** affect the magnitude of anchimeric assistance observed in radical bromination reactions is discussed in Chapter Five.



52 R = OCH_3
53 R = NH*t*Bu



54 R = OCH_3
55 R = NH*t*Bu

As has been previously highlighted, 1,4-carbonyl participation in radical reactions was, until recently,[75] unprecedented in the literature. Four membered transition states are considered much less favourable than larger sized transition states, because of the strain involved in the small four membered ring. A more favourable, and hence less strained, transition state is more likely to lead to increased neighbouring group participation and this is consistent with 1,5-participation having been shown, in ionic reactions, to be considerably more favourable than 1,4-participation, resulting in greater anchimeric assistance.[140] The possibility arises that increased anchimeric assistance in radical reactions, therefore, may be seen in systems which are able to interact *via* 1,5-neighbouring group effects. Peptides and protected amino acids have the potential

for stabilisation of the transition states leading to β-centred radical formation by either 1,4- or 1,5-carbonyl participation (Figure i.14).

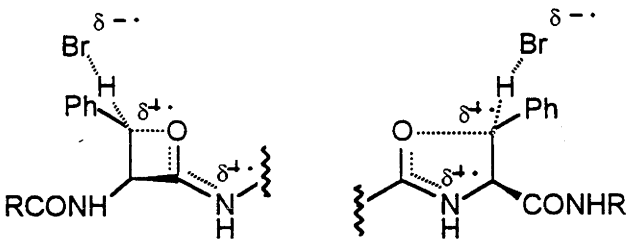


Figure i.14. The possibilities for anchimeric assistance at the β-position in the radical reactions of amino acid residues in peptides: 1,4- and 1,5-neighbouring group participation.

Because the transition state is apparently less strained, 1,5-neighbouring group participation by the amine protecting group would be expected to be more significant in influencing the rate of hydrogen abstraction than the corresponding 1,4-effect of the α-carbonyl. 1,5-Participation in radical reactions of amino acid derivatives has not been examined in previous work. Therefore, in order to investigate the effect that 1,5-participation may have on the formation of benzylic radicals, a selection of phenylethyl derivatives was chosen for examination of their relative rates of reaction. *N*-Phenylethylamides make excellent model compounds for the amide portion of phenylalanine derivatives, but unlike phenylalanines, they lack a captodatively stabilised α-centre, which may compete with the benzylic position in hydrogen abstraction reactions. The amide protecting group of a phenylethylamide can also be varied easily and systematically to test for anchimeric assistance.

In addition to examining the possibility of 1,5-anchimeric assistance, the possibility of 1,6- and 1,7-effects is also intriguing. It is a common assumption that six-membered transition states are favourable. Additionally, several workers have shown that seven-

membered transition state structures may be favoured in both hydrogen atom abstraction[166,167] and halogen transfer reactions.[168] For these reasons, it is of interest to observe the effect that differing ring sizes, in the transition state leading to the radical, can have on possible neighbouring group effects. Consequently, a selection of *N*-phenylalkylamide derivatives was chosen for study to see if their bromination reactions exhibited anchimeric assistance. The results of this inquiry are presented in Chapter Six.

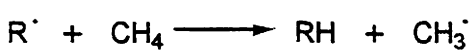
1

A Theoretical Study of Non–bonding Interactions of the Side Chains of Protected Amino Acids with the Amide Carbonyl of Their Protecting Groups

It is important to have a basic understanding of the factors affecting reactions in biochemical systems. Of particular importance in the present work is the study of the factors affecting the formation of α-centred radicals of amino acids, due to their significance in a variety of pathologies, mechanisms of enzyme catalysed reactions and synthetic applications. As has been discussed in the introduction, there exists a particular selectivity for the formation of the α-centred radicals of glycine, when compared with other amino acids. This chapter aims to provide a detailed examination of the factors influencing the selectivity of formation of α-centred glycyl radicals under experimental conditions.[67,68]

Results

Standard *ab initio* molecular orbital theory and density functional theory (DFT) calculations were performed with GAUSSIAN 94[169] and MOLPRO 96.[170] Some preliminary conformational work was carried out at AM1 for the larger amino acids using the Spartan and MacSpartan Plus programs, in order to select the most appropriate conformations to be examined using *ab initio* methods. Radical stabilisation energies (RSEs) were calculated using the isodesmic reaction (Scheme 1.1) shown below:



Scheme 1.1

The RSEs calculated from this isodesmic reaction represent the differences in the bond dissociation energies (BDEs) of the radical ($R^{\bullet}$) and methane. These calculations thus yield positive values for radicals more stable than the methyl radical and negative values for those radicals less stable than the methyl radical. The larger the positive value, the more stable the radical. This is in contrast to typical methods in the literature[114,124,161,162,171–177] for calculation of radical stability which examine the BDE directly (Scheme 1.2). Such calculations yield a larger positive value for less stable radicals.

$$RH \longrightarrow R^{\bullet} + H^{\bullet}$$ **Scheme 1.2**

The isodesmic procedure (Scheme 1.1) involving methane is the recommended procedure employed by Radom *et al.*[164,178] for the comparison of radical stabilisation energies. Rauk *et al.*[123] used a more complicated procedure in their predictions of the absolute stabilities of glycine, alanine, serine and threonine radicals in both neutral amino acids and peptide models. This complex approach, however, is not required in the present study, as only the relative differences between the radicals under examination are of relevance to the work presented in this thesis.

For a preliminary assessment of method reliability, the geometries of a series of model compounds were optimised using the RMP2 and B3-LYP procedures, both in conjunction with the 6-31G(d) basis set. Vibrational frequencies were calculated for the B3-LYP method, as analytical second derivatives of the energy with respect to nuclear displacement are readily available. These frequencies were used in conjunction with the appropriate scaling factor for the calculation of frequency-dependent quantities.[179] Subsequent geometry optimisations, vibrational frequencies and zero point energies (ZPEs) of non-model compounds were calculated using the B3-LYP method with the 6-31G(d) basis set with single point energies obtained with the use of RMP2/6-31G(d).

Improved relative energies for the model compounds studied were obtained from single-point calculations using the RMP2, URCCSD(T) and B3-LYP techniques with basis sets of increasing accuracy: 6-311+G(d,p) and 6-311+G(2df,p). Full URCCSD(T)/6-311+G(2df,p) calculations were not possible, due to limited computer resources, so an approximation to URCCSD(T)/6-311+G(2df,p) was obtained by using a slightly modified version of the G2(MP2, SVP)-RAD methodology,[178] denoted G1(MP2, SVP)-RAD. Using this method, the basis set extension applied to the URCCSD(T)/6-31G(d) calculations was obtained from the RMP2/6-31G(d) and RMP2/6-311+G(2df,p) calculations. The results for this method assessment are presented in Table 1.1 and Table 1.2. The RSEs calculated for all other compounds are presented in Table 1.3, Table 1.4 and Table 1.5. RSEs include the scaled (0.9806)[179] ZPE obtained with B3-LYP/6-31G(d). Temperature corrections are not included because many of the amino acids and their derivatives exhibit either one or more low frequencies ($<260\ cm^{-1}$). Low frequencies are often caused by torsions and other non-harmonic motions which cannot be described in terms of harmonic oscillators and should be treated by solving the Schrödinger equation for the true potential energy of the mode.[180] These frequencies contribute significantly more to the temperature correction than higher frequencies[179] so the treatment required to obtain these values accurately is non-linear and quite complex. It is envisaged that the direct comparison of RSEs will not be overtly affected by the neglect of temperature correction, as the molecules being compared are very similar in structure. This should result in either cancelling of these adjustments or imperceptible deviations from the relative values. The similarity of temperature corrections for amino acid derivatives has been noted by Rauk *et al.*[122] in their examination of protected glycines.

Conformational information from the calculated minimum energy structures was also examined in order to identify modes of interaction of the side chains of the amino acids and their α-centred radicals with the backbone amino acid structure and protecting groups. Details are presented in the text of the discussion and in accompanying diagrams. Bond distances are given to 0.001Å and bond angles are given to 0.1°. The

minimum energy conformers of all molecules examined have C_1 symmetry, unless otherwise noted in the text.

Table 1.1. Radical stabilisation energies for a variety of model radicals with RMP2/6-31G(d) optimised geometries. ZPE corrections have not been included.

		$XCH_2Y + CH_4 \rightarrow XCH_2Y + CH_3^{\bullet}$				
Level of Theory	Basis set	Ethane X=CH_3 Y=H	1,1,1-Trifluoroethane X=CF_3 Y=H	Methylamine X=NH_2 Y=H	Acetic Acid X=CO_2H Y=H	Glycine X=NH_2 Y=CO_2H
		RSEs using RMP2/6-31G(d) geometries (kJ mol^{-1})				
RMP2	6-31G(d)	12.8	–6.6	48.5	25.3	101.8
	6-311+G(d,p)	11.3	–8.8	48.0	22.0	98.8
	6-311+G(2df,p)	13.3	–7.3	49.6	24.8	107.6
URCCSD(T)	6-31G(d)	13.6	–5.7	47.2	26.8	95.1
G1(MP2, SVP)-RAD [†]		14.1	–6.4	48.3	26.3	100.9

[†] G1(MP2, SVP)-RAD approximates the RSE calculated at URCCSD(T)/6-311+G(2df,p), and is calculated using a methodology analogous to G2(MP2, SVP)-RAD[178]—see text.

Table 1.2. Radical stabilisation energies for a variety of model radicals with B3LYP/6-31G(d) optimised geometries. ZPE corrections have not been included.

Level of Theory	Basis set	$XCH^{\bullet}Y + CH_4 \rightarrow XCH_2Y + CH_3^{\bullet}$				
		Ethane X=CH_3 Y=H	1,1,1-Trifluoroethane X=CF_3 Y=H	Methylamine X=NH_2 Y=H	Acetic Acid X=CO_2H Y=H	Glycine X=NH_2 Y=CO_2H
		RSEs using B3-LYP/6-31G(d) geometries (kJ mol^{-1})				
B3-LYP	6-31G(d)	19.8	3.3	59.1	39.3	123.5
	6-311+G(d,p)	19.1	–0.3	59.2	33.9	122.6
	6-311+G(2df,p)	19.4	0.0	59.2	34.3	124.4
RMP2	6-31G(d)	12.7	–6.5	48.6	25.5	102.0
	6-311+G(d,p)	11.1	–8.7	48.1	21.7	98.6
	6-311+G(2df,p)	13.2	–7.2	49.6	24.6	107.1
URCCSD(T)	6-31G(d)	13.6	–5.6	47.2	26.8	95.4
ZPE correction	(B3-LYP/6-31G(d))	0.5	–1.0	–3.9	–4.5	–6.1

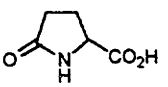
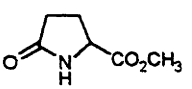
Table 1.3. RSEs of non amino acid radical species calculated at RMP2/6-31G(d)//B3-LYP/6-31G(d).

$XC^{\bullet}RY + CH_4 \rightarrow XCHRY + CH_3^{\bullet}$					Energies (kJ mol^{-1})		
XCHRY	$XC^{\bullet}RY$	X	Y	R	RSE	ZPE correction	RSE(0 K)
56	**57**	NH_2	H	CH_3	53.3	–3.3	50.0
58	**59**	H	CO_2H	CH_3	46.2	–4.0	42.2
60	**61**	H	CO_2CH_3	H	26.2	–4.6	21.6
62	**63**	AcNH	H	H	39.7	–2.3	37.4

Table 1.4. RSEs of amino acid radicals under investigation (RMP2/6-31G(d)//B3-LYP/6-31G(d)).

$H_2NC^{\bullet}RCO_2Y + CH_4 \rightarrow H_2NCHRCO_2Y + CH_3^{\bullet}$				Energies (kJ mol^{-1})		
$H_2NCHRCO_2Y$	$H_2NC^{\bullet}RCO_2Y$	R	Y	RSE	ZPE correction	RSE(0 K)
64	**65**	H	H	102.0	–6.1	95.9
66	**66**	H	CH_3	100.2	–6.2	94.0
67	**68**	CH_3	H	109.5	–6.1	103.4
69	**70**	$CH(CH_3)_2$	H	104.6	–6.1	98.5

Table 1.5. RSEs of the acetyl-protected amino acid radicals under investigation (RMP2/6-31G(d)//B3-LYP/6-31G(d)).

$AcNHC^{\bullet}RCO_2Y + CH_4 \rightarrow AcNHCHRCO_2Y + CH_3^{\bullet}$				Energies (kJ mol^{-1})		
$AcNHCHRCO_2Y$	$AcNHC^{\bullet}RCO_2Y$	R	Y	RSE	ZPE correction	RSE(0 K)
71	**71**	H	H	91.1	–7.6	83.5
72	**73**	H	CH_3	89.7	–7.5	82.2
74	**75**	CH_3	CH_3	87.6	–7.0	80.6
76	**77**	$CH(CH_3)_2$	CH_3	81.6	–8.6	73.0
78	**79**			101.2	–6.1	95.1
18	**19**			99.2	–5.9	93.3

Discussion

Selection of the appropriate theoretical method for the calculation of any molecular property is important. It is generally the case that higher levels of theory and larger basis sets provide results in better agreement with experimental values due to the better description of the molecule in question. However, limited computational resources make it necessary to choose lower levels of theoretical description, particularly as the molecular size, and hence the number of electrons, increases. Medium sized molecules, such as amino acids, can quite easily use up a large amount of computational resources, so an assessment study was undertaken to determine the best level of theory at which to

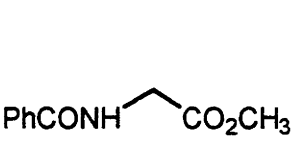
perform calculations. The unrestricted coupled cluster calculations with triples (URCCSD(T)) represent a high level method which provides a good estimation of the actual RSEs.[164,178] However, such calculations are computationally very expensive which is why they are only presented here for a limited range of molecules. Additionally, the cost of these calculations means only a small basis set was used. The G1(MP2, SVP)-RAD method approximates the coupled cluster calculations with a larger basis set and is the best estimate of the true RSEs that is presented in this thesis.

Two main levels of theory were trialed in order to find a cheap alternative to the URCCSD(T) calculations; the B3-LYP density functional theoretical method and restricted MP2 (RMP2). The B3-LYP method was chosen based on growing literature supporting its use as an *ab initio* method to provide accurate predictions of a variety of properties for many closed shell systems.[181] The computational cost of B3-LYP calculations is comparable, for molecules such as the ones under examination, with Hartree-Fock and this makes it a particularly attractive method for this study.[181] However, the utility of the B3-LYP density functional theory alone, for the calculation of stability constants of radicals, has been questioned. Recent studies have shown that, particularly for highly spin contaminated radicals, the theory overestimates stabilisation energies when compared with a suitable benchmark.[164,178] Restricted MO methods appeared to perform much better. In particular, RMP2 provided results which were quoted as being accurate to within 5 kJ mol^{-1} of absolute RSEs,[164] for a medium computational cost. This cost can be significantly lowered by performing RMP2 single point energy calculations on B3-LYP geometries. It has been noted previously that this technique provides near identical relative energies to RMP2 energies calculated on RMP2 geometries.[164,182] This is also reflected in the results presented in Table 1.1 (p. 44) and Table 1.2 (p. 45) for all basis sets tested, and implies that either RMP2 or B3-LYP is adequate for the calculation of geometric parameters. This method should therefore provide satisfactory results for the amino acid radicals under investigation. Additionally, the accuracy of the obtained values should be high, based on previous

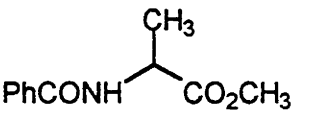
estimates[164] and the fact that the systems under examination are all similar, so any residual errors are likely to cancel when comparing relative energies.

The RSEs calculated using the RMP2/6-31G(d)//RMP2/6-31G(d) method are in good agreement with those obtained from the G1(MP2, SVP)-RAD calculations with the maximum difference being only 1.3 kJ mol^{-1} (Table 1.1, p. 44). This establishes the reliability of the RMP2 method with a small basis set. The B3-LYP density functional method is seen to overestimate the stability of the radical in each case (Table 1.2, p. 45), as has been previously noted.[164,178] This appears to be general for all the basis sets trialed. The RMP2/6-31G(d) stabilisation energies generally appear to give results which are more consistent with the G1(MP2, SVP)-RAD values, than those calculated using the B3-LYP method. Therefore, these RMP2 stabilisation energies are taken as reasonable approximations of the actual RSEs, for a comparatively low computational cost. This use of RMP2 energies to obtain good results for low computational cost is in accordance with the previous method assessments.[164,182] Subsequent discussion in this thesis relates only to the RSEs obtained at the RMP2/6-31G(d)//B3-LYP/6-31G(d) level of theory, unless otherwise specified.

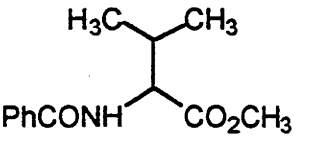
The relative rates of reaction of the *N*-benzoyl-protected glycine, alanine and valine derivatives **6–8** are known, and the selectivity observed has been attributed to steric interactions with the protecting group. It is therefore interesting to examine possible steric effects, or lack thereof, in the radicals of the same amino acids without protecting groups. This is difficult to do experimentally, as free amino acids in solution exist as their zwitterions, not as the neutral species. However, the lowest energy tautomers in the gas phase are the neutral amino acids and their structures are computationally accessible.[100–105,109,110,113]



6

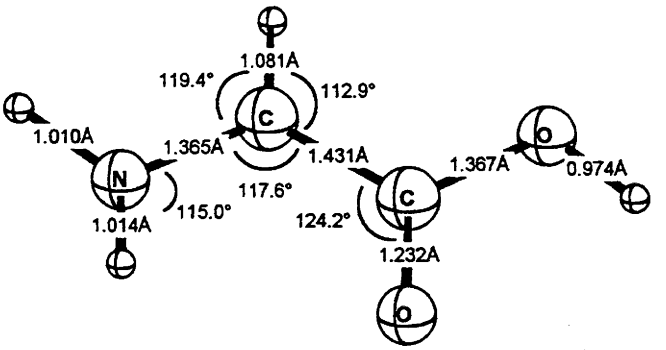


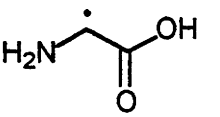
7



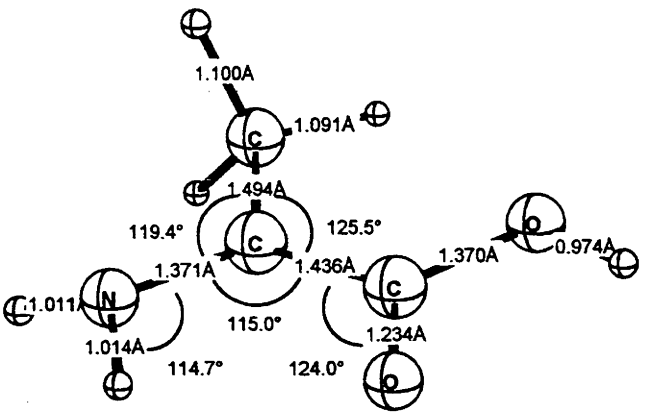
8

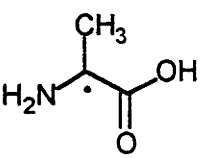
The RSEs calculated for the neutral free amino acid radicals were found to be 95.9 kJ mol^{-1} for the glycyl radical **65**, 103.4 kJ mol^{-1} for the alanyl radical **68** and 98.5 kJ mol^{-1} for the valyl radical **70** (Table 1.4). The increased stabilisation of the alanyl radical **68**, of 7.5 kJ mol^{-1}, over that of the glycyl radical **65**, is consistent with increased stabilisation by substitution. Additional substitution should result in greater steric release on radical formation and additional hyperconjugation, resulting in a comparatively more stable radical. The value of 7.5 kJ mol^{-1} is comparable in magnitude to the increased stabilisation energy of ethane, compared with methane, of 13.2 kJ mol^{-1}. The relative difference between the RSEs of the glycyl radical **65** and the alanyl radical **68** is the same as that quoted by Rauk *et al.*[123] between the BDEs of the same molecules calculated at B3-LYP/6-31G(d). The lower relative stabilisation of the valyl radical **70**, compared with that of the alanyl radical **68**, of 4.9 kJ mol^{-1} is neither consistent with increased stabilisation by hyperconjugation, nor relief of steric compression. The reason for this becomes apparent by considering the structures of the glycyl, alanyl and valyl radicals **65, 68, 70**.



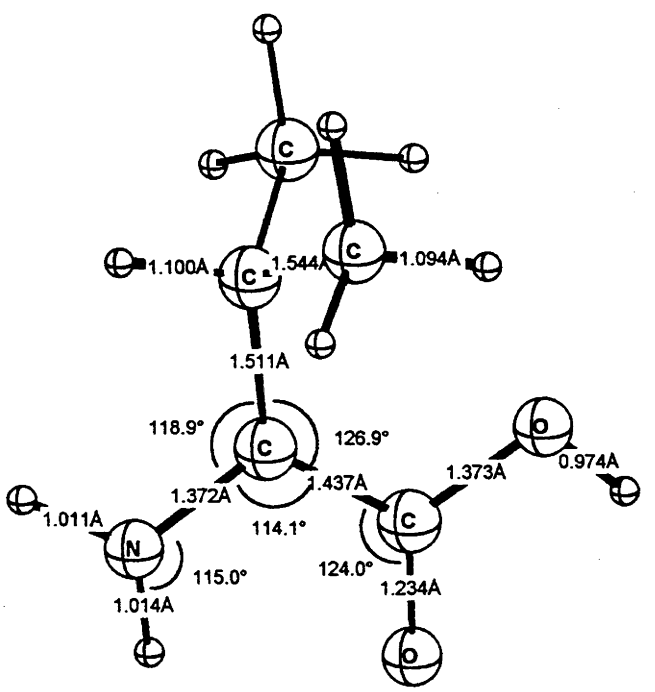


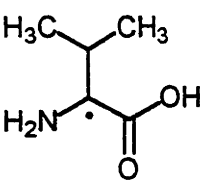
65





68





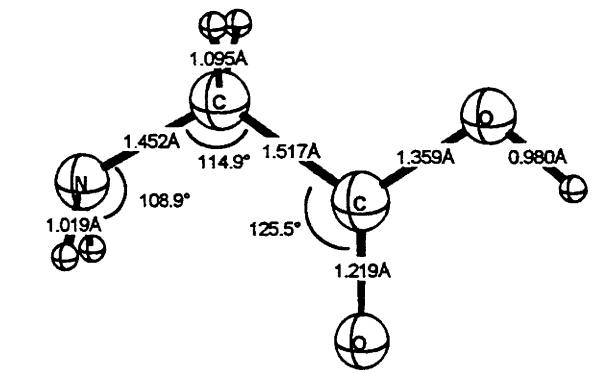
70

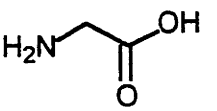
Figure 1.1. From the top, the optimised structures of the glycyl, alanyl and valyl radicals **65, 68, 70**.

The stability and properties of glycine **64** and the glycine radical **65** have been explored in great detail using a variety of theoretical models.[94,100,107,109,110,114,116–123,183–186] It is interesting to observe that the α-centred radical of glycine **65**, unlike the free amino acid **64**, does not prefer to be in the zwitterionic form in solution. Lack of dative stabilisation from the protonated nitrogen causes the zwitterionic structure to be much less stable.[72,116,121,187] In fact, even in highly acidic solutions only the neutral form exists, in preference to the fully protonated glycyl radical.[72] Selection of the gas phase theoretical model avoids inconsistencies arising from considering both a neutral radical structure and a charged ground state structure and subsequent comparison of the two disparate tems. The gas phase structure of the glycine radical **65** obtained in this study (Figure 1.1) shows little difference to the optimal conformation described by Barone *et al.*[117] for the B3-LYP optimised structure of the glycyl radical **65** using the 6-31G(d,p) basis set.

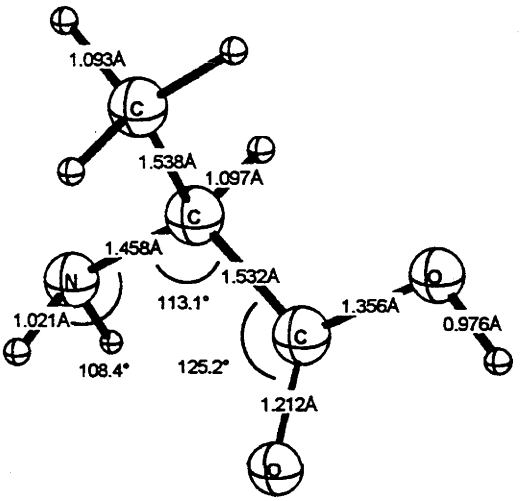
The alanyl radical **68** is very similar to the glycyl radical **65**. The backbone structure is essentially the same, with only a few differences, namely compression of the N-C^{α}-C(O) bond angle and a resultant widening of the C(O)-C^{α}-R bond angle by 3° to accommodate the larger methyl group (R=H for the glycyl radical, R=CH_3 for the alanyl radical). Similar structural differences are also seen in the valyl radical **70** where the N-C^{α}-C(O) bond angle is compressed by another degree with respect to the alanyl radical **68**. Concomitantly the C(O)-C^{α}-C^{β} bond angle increases by one and a half degrees. This is consistent with an unfavourable steric interaction between the methyl groups of the isopropyl side chain with the carboxyl group. The increase over the same angle in the alanyl radical **68** indicates that these interactions with the side chain are more severe for the valyl radical **70**.

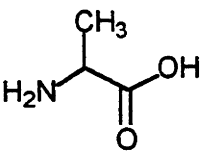
The lowest energy alignment of the isopropyl group in the radical **70** is with both methyl groups staggered over the C^{α}-C(O) bond. This arrangement allows minimal interaction of the isopropyl side chain with the amino hydrogen proximal to the side chain. The



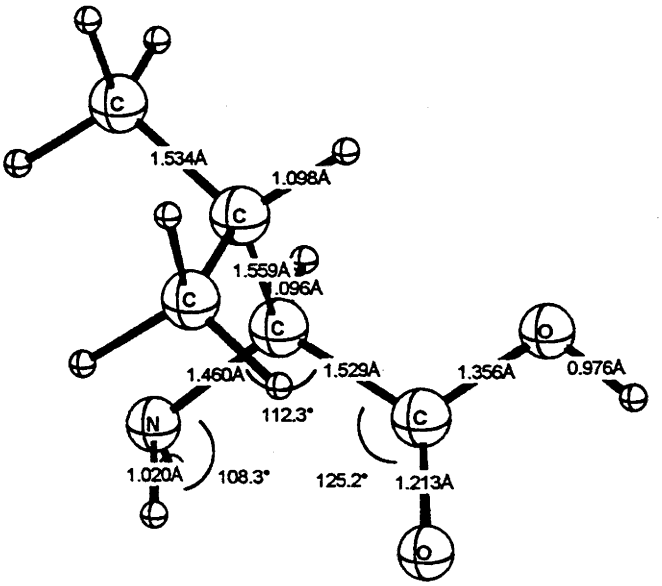


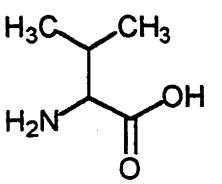
64





67





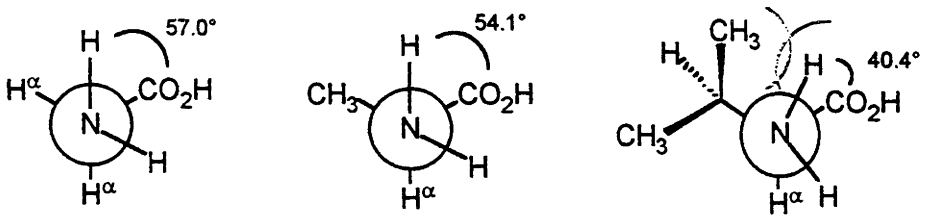
69

Figure 1.2. The optimised structures of the neutral amino acids glycine **64** (top), alanine **67** (middle) and valine **69** (bottom).

N-C^{α}-C^{β} bond angle is seen to compress by almost a half of a degree, compared with the corresponding N-C^{α}-R bond angle in both the glycyl and alanyl radicals **65** and **68**. This decreased bond angle is probably forced as a result of the more severe interaction of the methyl groups with the carboxyl group. This causes interactions of the amino hydrogen with the hydrogen of the side chain which are likely to be unfavourable, but unavoidable.

Comparison of the structures of glycine **64**, alanine **67** and valine **69** shows bond angle and dihedral angle changes consistent with steric compression, when the side chain bulk increases. This is particularly noticeable when the (H)O-C-C^{α}-R dihedral angles in glycine **64** and both alanine **67** and valine **69** are compared. This dihedral angle is only 56.8° in glycine **64** and increases to 69.9° in alanine **67** and 71.5° in valine **69**. Also, evidence for steric compression comes from examination of one of the H-N-C^{α}-C(O) dihedral angles, which is 57.0° in glycine **64** and 54.1° in alanine **67**, and decreases dramatically in valine **69** to only 40.4° (Figure 1.3). This steric compression is released on radical formation. As the steric compression increases in the series of glycine **64**, alanine **67** and valine **69**, the implication is that the valyl radical **70** should be more stable than the corresponding alanyl radical **68**, which should in turn be more stable than the glycyl radical **65**. Whilst this is consistent with the relative RSEs calculated for the glycyl and alanyl radicals **65** and **68**, it is the reverse of the calculated relative stabilities of the alanyl and valyl radicals **68** and **70**.

The major structural changes common to the formation of α-centred radicals in amino acids are easily visible through comparison of the structures of glycine **64** and the glycyl radical **65**. The N-C^{α} bond distance shortens from the typical single bond distance[188] of 1.452 Å to 1.365 Å, approaching the value quoted for a partial double bond.[188] Also the C^{α}-C(O) bond shortens from 1.517 Å to 1.431 Å, with development of partial double bond character[188] and there is a slight lengthening of both of the C-O bonds.



64 67 69

Figure 1.3. A depiction of the steric effects exerted on the amino group by interaction with the side chain in the free amino acids **64**, **67** and **69**.

Formation of the alanyl radical **68** from alanine **67** entails near identical structural changes to formation of the glycyl radical **65** from glycine **64**. There is slightly more steric compression, as noted above, in the alanine **67** than in the glycine **64** and its release is consistent with the increased RSE of the alanyl radical **68** over the glycyl radical **65**. Despite valine **69** showing more signs of steric compression than alanine **67**, the RSE of the valyl radical **70** is lower than that of the alanyl radical **68**. This is not consistent with the higher RSE that would be expected, based on release of this additional steric compression.

The most stable conformer of valine **69**, as found in this and other studies,[102,105] is different from that of the radical **70**, with regards to the orientation of the isopropyl group. In the free amino acid **69**, the amino group hydrogens are positioned away from the side chain, minimising the possibility of interactions. Thus, to reduce interactions with the carboxyl group, the isopropyl methyl substituents prefer to orient themselves over the amino group, where the interactions with the backbone are the least severe. Upon formation of the radical **70**, the amino group must rotate in order to obtain maximal overlap of the nitrogen lone pair orbital with that of the radical centre. This brings the amino hydrogens coplanar with the C^{α}-C^{β} bond. Consequently, one of these amino hydrogens is forced into closer proximity to the isopropyl group. Presumably, unfavourable interactions of this hydrogen with the isopropyl methyl groups cause the

isopropyl group to rotate to the more stable configuration, but steric interactions between the isopropyl group and the carboxyl substituent in the radical **70** will then be more severe than in the free amino acid **69**. In addition, there are steric interactions between the hydrogen of the isopropyl group and the amino group. Such unfavourable interactions will lower the stability of the valyl radical **70** relative to the alanyl radical **68**, where no such interactions are present. The rotation of the isopropyl group is thus an indicator that steric effects are playing an important role in the stability of the radical **70** and explains the relative RSEs obtained for the glycyl, alanyl and valyl radicals **65, 68, 70**.

As models of amino acid residues in peptides, *N*-acetyl methyl ester derivatives were chosen for theoretical study. Methylation of the carboxylic acid caused little difference in the stabilisation energy of the radical. This is observed by comparison of the RSEs of the radicals of the acids **64**, **71** and **78** with those of the radicals of the corresponding esters **66**, **72** and **18**, respectively (Table 1.4, p. 46 and Table 1.5, p. 47). The effect of acetamide formation on the RSEs of α-centred radicals, though, was much more significant. This is reflected in the comparison of the RSEs of the radicals of the amines **64** and **66** with the corresponding RSEs of the radicals of the acetamides **71** and **72**. The difference in stabilisation energy between the α-centred radical of glycine methyl ester **66** and that of the acetylglycine **72** is 11.8 kJ mol^{-1}. For the radicals of the unmethylated derivatives **64** and **71** this difference is 12.4 kJ mol^{-1}. The acetyl substituent lowers the dative stabilisation that the nitrogen can provide to the radical, by a competitive delocalisation mechanism. The electrons on the nitrogen experience delocalisation by the amide carbonyl, which makes them less available for delocalisation of the radical, as discussed in the introduction. The magnitude of the effect of acetyl protection on the stability of the α-centred radicals of glycine derivatives, above, is in accordance with that seen by Rauk *et al.*[122] for these and related glycyl systems.

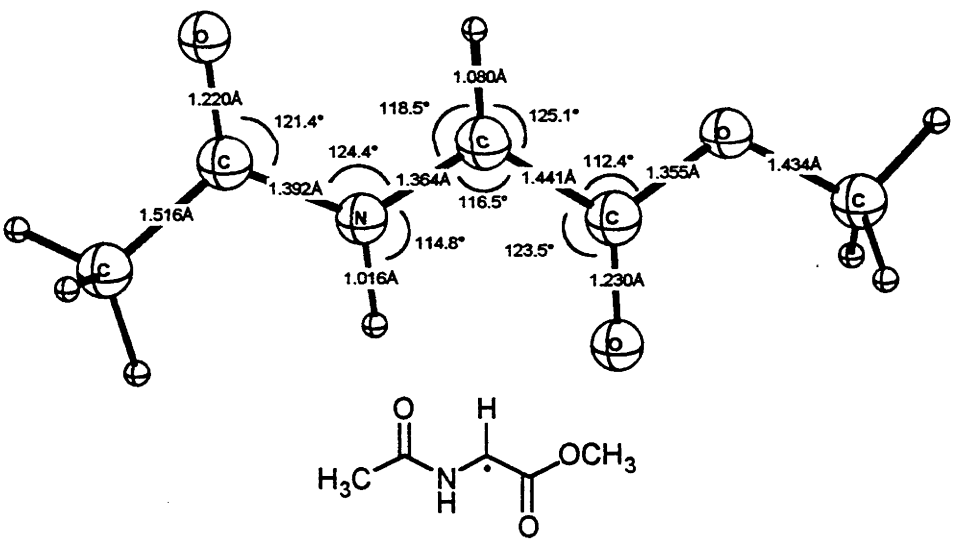
The RSEs calculated for protected amino acid radicals were found to be 82.2 kJ mol^{-1} for the acetylglycyl radical **73**, 80.6 kJ mol^{-1} for the acetylalanyl radical **75**, and

73.0 kJ mol^{-1} for the acetylvalyl radical **77** (Table 1.5). It is observed in this case that the alanyl radical **75** is of comparable stability to the corresponding glycyl radical **73**, being only 1.6 kJ mol^{-1} less stable. The valyl radical **77** is less stable than both the alanyl and glycyl radicals **75** and **73** by around 8 kJ mol^{-1}.

The magnitude of the effect of the amino acid protecting groups on the stability of the radicals **73, 75, 77** can best be determined by a comparison of their RSEs with those of the non-protected amino acid radicals **65, 68, 70**. The difference between the stability of the glycyl radical **65** and the acetylglycyl radical **73** is 13.7 kJ mol^{-1}. This can reasonably be attributed to electronic deactivation of the radical **73** by the protecting groups. The difference between the RSEs of the alanyl radical **68** and the acetylalanyl radical **75** increases to 22.8 kJ mol^{-1}. This is a much larger difference than that observed between the glycyl radicals **65** and **73**, and indicates a much more significant effect of the protecting groups on the RSE of the alanyl radical **75**. Similarly, the difference in stabilisation between the valyl radical **70** and the acetylvalyl radical **77** is 25.5 kJ mol^{-1}, slightly greater than the difference observed between the alanyl radicals **68** and **75**. The implication is that the protecting groups have only a slightly greater effect on the stability of the valyl radical **77** than they do on the stability of the alanyl radical **75**. An electronic effect exerted by the protecting groups would be consistent within a series of amino acids, when comparing the RSEs of the non-protected and protected amino acid radicals. This effect is known from the comparison of the RSEs of the glycyl radicals **65** and **73** to contribute a maximum of 13.7 kJ mol^{-1}. Therefore, the larger apparent deactivating effect of the amino acid protecting groups on the stability of the alanyl and valyl radicals **75** and **77** must be due to other factors.

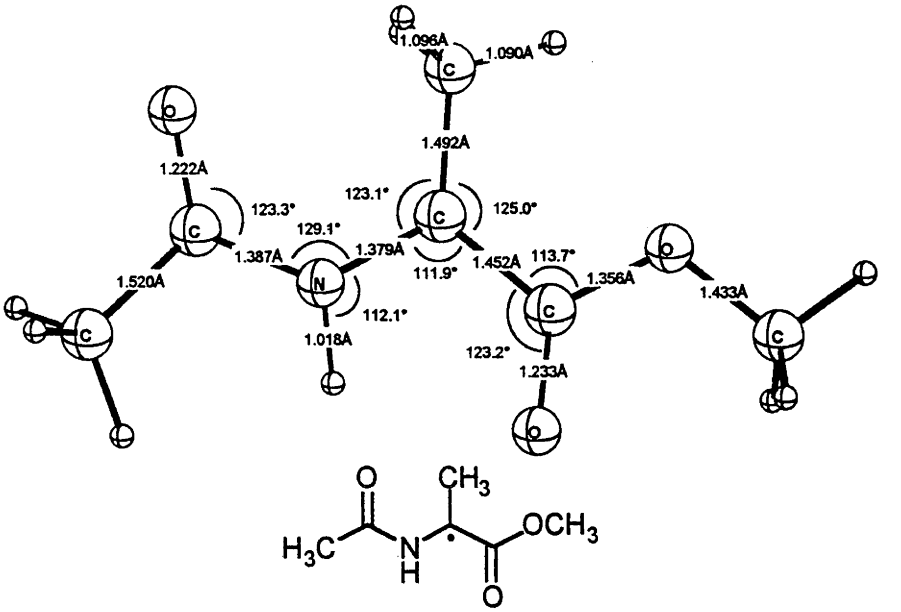
Optimal orbital overlap, to effect maximum delocalisation of a radical, often requires coplanarity of the nuclei whose orbitals are involved in the spin delocalisation. Deviations from planarity have been used to account for the diminished stability of some captodatively stabilised radicals.[93] The minimum energy conformations of the protected glycyl radical **73** (Figure 1.4), and alanyl radical **75** and valyl radical **77** (Figure 1.5)

each exhibit planarity of their backbone structure, as illustrated in Figure 1.6. Any non-bonding interactions in the radicals **73, 75, 77** are clearly not strong enough to distort the molecule from achieving coplanarity of the relevant nuclei required for optimal delocalisation of the radical. However, while there is no disruption of the planarity of the radicals, there are indications that non-bonding interactions are having an effect. The major differences between structures are in the backbone bond angles. A summary of the trends is shown in Table 1.6.

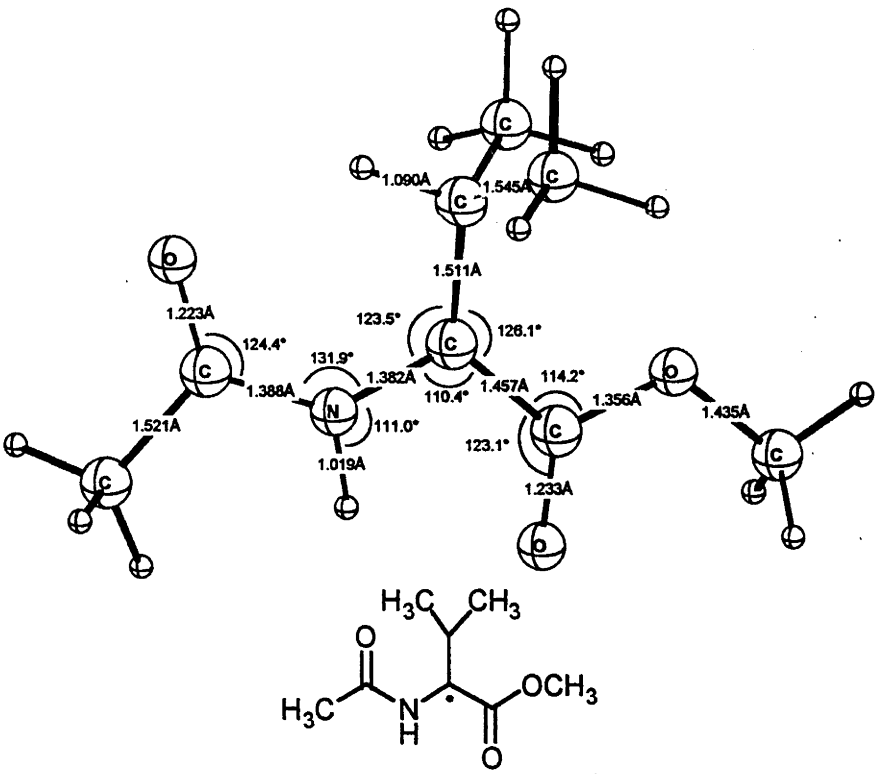


73

Figure 1.4. The minimum energy conformation of the protected glycyl radical **73**.



75



77

Figure 1.5. The minimum energy conformations of the protected alanyl radical 75 (top) and the protected valyl radical 77(bottom).

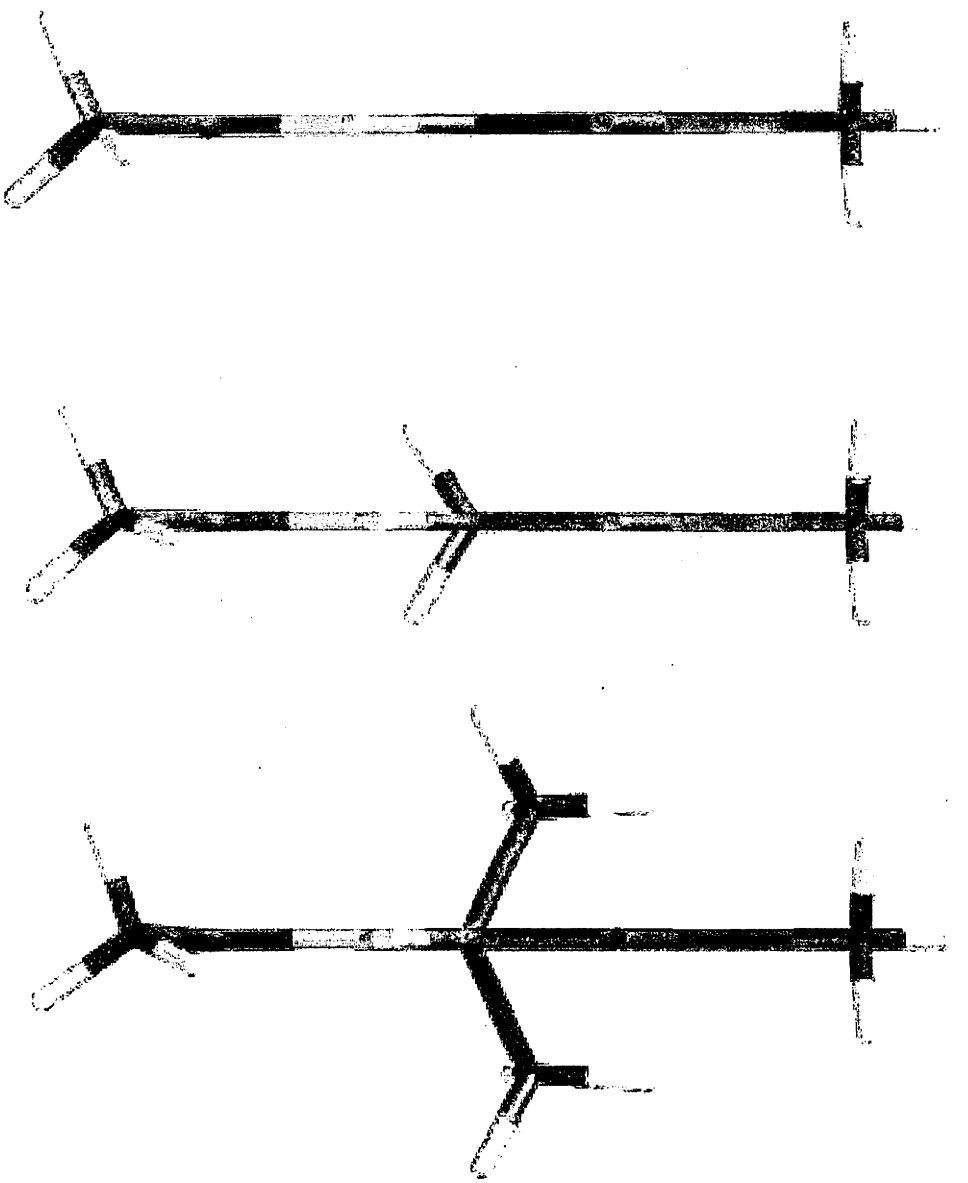


Figure 1.6. An illustration of the planarity in the backbone of the protected amino acid radicals **73** (top), **75** (centre) and **77** (bottom).

Table 1.6. The variation in bond angles of the protected glycyl, alanyl and valyl radicals **73, 75, 77**.

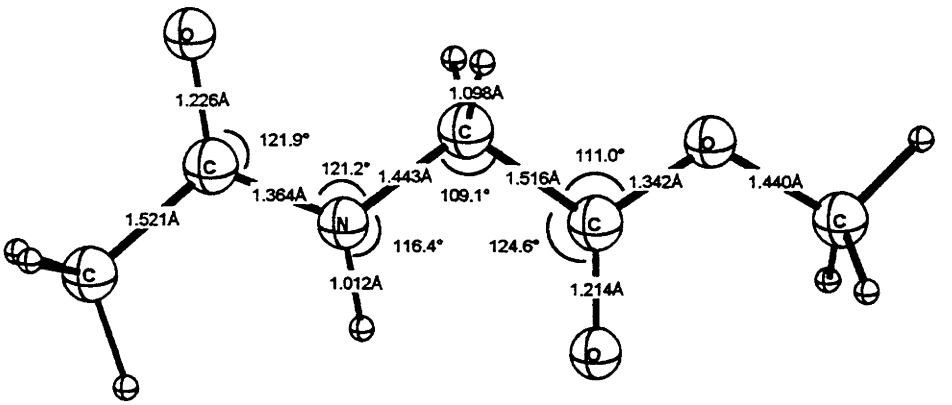
$AcNHC^{\alpha}HRCO_2CH_3$		Bond Angles (°)					
Radical	R	O-C-N	C(O)-N-C^{α}	H-N-C^{α}	N-C^{α}-C(O)	C^{α}-C=O	C^{α}-C-O(CH_3)
73	H	121.4	124.4	114.8	116.5	123.5	112.4
75	CH_3	123.3	129.1	112.1	111.9	123.2	113.7
77	$CH(CH_3)_2$	124.4	131.9	111.0	110.4	123.1	114.2

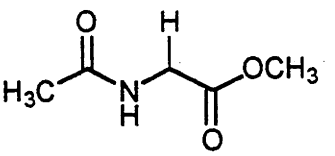
It is observed that on increasing the steric bulk of the α-substituent, the protecting groups are pushed back, away from the side chain. As a consequence, the O-C-N, C(O)-N-C^{α} and C^{α}-C-O(CH_3) bond angles all expand to accommodate the larger alkyl groups (highlighted by Table 1.6). The most significant of these changes is the C(O)-N-C^{α} bond angle which is seen to expand from the 124.4° seen in the glycyl radical **73** to 129.1° in the alanyl radical **75**. This is likely due to unfavourable interactions of the amide carbonyl with the methyl side chain of the alanyl radical **75**. The hydrogens of the methyl are symmetrically disposed to this carbonyl, which presumably results in the minimal possible interaction.

In order for the isopropyl group of the valyl radical **77** to obtain minimal interaction with the amino acid backbone in the planar form, its two methyl substituents must stagger the plane of the radical. Further, the lower energy interaction is with these groups pointing away from the amide carbonyl group. However, the methine hydrogen of the isopropyl group is now forced into the same plane as the amide carbonyl and is likely to interact with it. This is reflected in the expansion of the O-C-N and C(O)-N-C^{α} bond angles of the valyl radical **77** by 1.2° and 2.7°, respectively, compared with the same angles in the alanyl radical **75**.

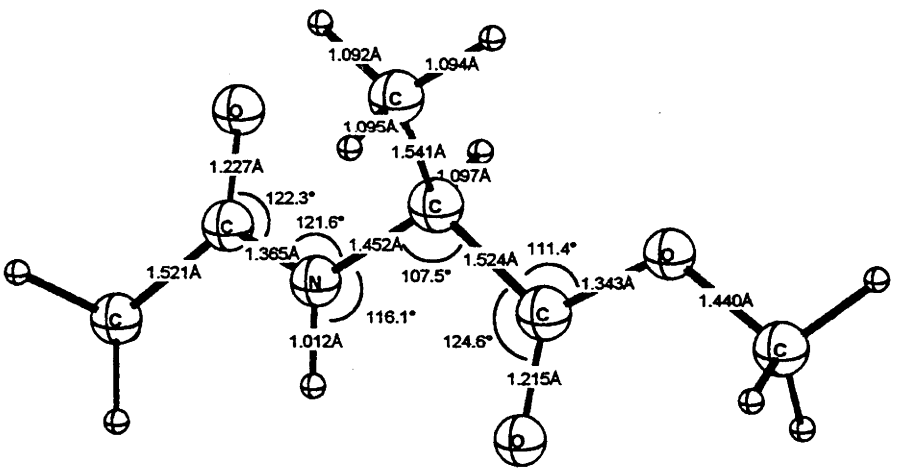
Concurrent with the expansions observed in the O-C-N, C(O)-N-C^{α} and C^{α}-C-O(CH_3) bond angles, is a contraction in the α-centred bond angles; H-N-C^{α}, N-C^{α}-C(O) and C^{α}-C=O. The N-C^{α}-C(O) bond angle of the alanyl radical **75** is almost 5° smaller than the corresponding angle in the glycyl radical **73**, a change which indicates significant interaction of the backbone of the amino acid with the methyl side chain of the alanyl radical **75**. A similar contraction on comparing the valyl radical **77** with the alanyl radical **75** is also noted, though the magnitude of the difference is smaller, indicating a less dramatic difference between the steric effects exerted by the methyl and isopropyl groups with the amino acid backbone.

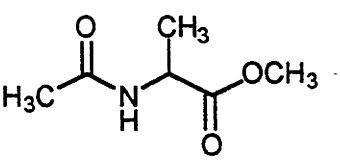
In combination with these bond angle changes, it can be seen that the amount of stabilisation afforded the radical by the resonance contributors is decreased, as indicated by the longer C^{α}-N and C^{α}-C(O) bond lengths observed, on increasing the steric bulk of the α-substituent. As the contribution of the amide substituent toward stabilisation of the radical decreases, the C(O)-N bond length contracts slightly which is suggestive of increased delocalisation of the electrons of the amide nitrogen onto the amide carbonyl.





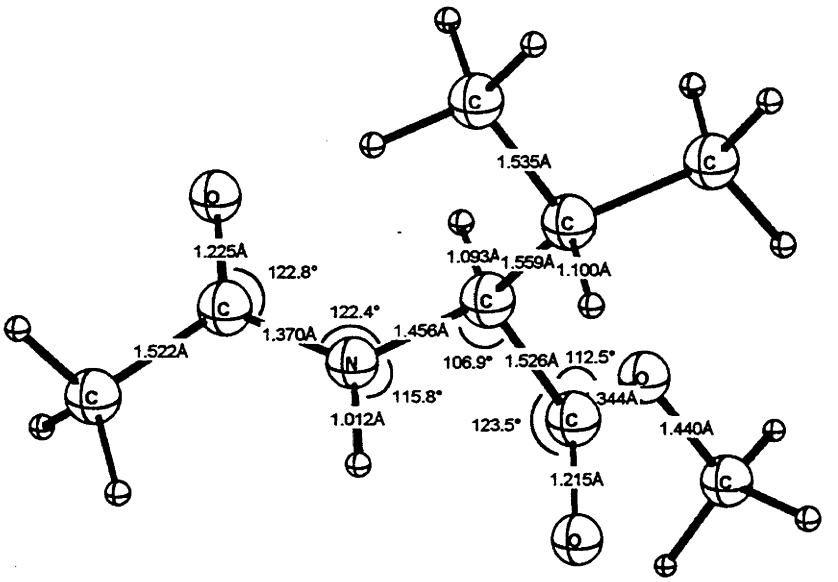
72

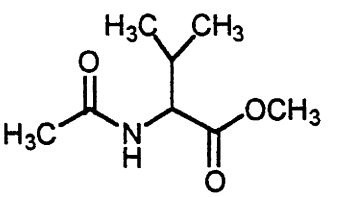




74

Figure 1.7. Optimised structures of the protected glycine derivative **72** (C_s symmetric) (top) and alanine derivative **74** (bottom).





76

Figure 1.8. Optimised structure of the protected valine derivative **76**.

Examination of the protected amino acids **72, 74, 76** does not reveal the same changes in the O-C-N and C(O)-N-C^{α} bond angles that were observed in the corresponding radicals **73, 75, 77**, with increasing side chain bulk. The lack of these changes is a strong indicator that the unfavourable interactions between the amino acid side chains and the amide carbonyl are restricted to the radical structures. The basic structural features of the protected amino acids **72, 74, 76** are consistent with the conclusions of several theoretical calculations done on similarly protected amino acid models,[107,120,122,123,185,189–191] with the protected amino acids **72, 74, 76** exhibiting increased steric compression with increased steric bulk. This is consistent with what is

seen in the free amino acids **64**, **67** and **69**. The subsequent increase in stabilisation energy, with increasing side chain bulk, expected on release of this steric compression is again contrary to the trend in the stabilisation energies observed. Clearly the interaction of the side chain of an amino acid radical with the amide carbonyl of the acyl protecting group is the integral factor in determining the magnitude of the RSE of that amino acid radical.

Experimentally it has been observed that methyl pyroglutamate **18** is one of the few amino acid derivatives to undergo α-centred bromination faster than the glycine derivative **6**.[68] This has been rationalised on the basis of a lack of unfavourable non-bonding interactions between the side chain and the amide carbonyl, which would otherwise cause the radical to be less stable.[68] Theoretical techniques allow a direct examination of the minimum energy conformer and RSE of the pyroglutamyl radical **19**. The calculated RSE for the pyroglutamyl radical **19** is 93.3 kJ mol^{-1}, which is much higher than that of the corresponding acetylglycyl radical **73**.

The methyl pyroglutamyl radical **19** has a planar C_s structure, which is conducive to maximal delocalisation of the unpaired spin density. There is little strain observed in the bond angles around the α-centre, except the N-C^{α}-C^{β} angle which is 109.5°, a typical bond angle for an sp^3 hybridised centre rather than an sp^2 radical centre. To compensate for this, the C-C^{α}-C^{β} bond angle is expanded to 130.8° but, contrary to the expansions of C-C^{α}-C^{β} bond angles seen in the other protected amino acids, this does not appear to be due to unfavourable interactions with the side chain. It is merely a consequence of the ring strain.

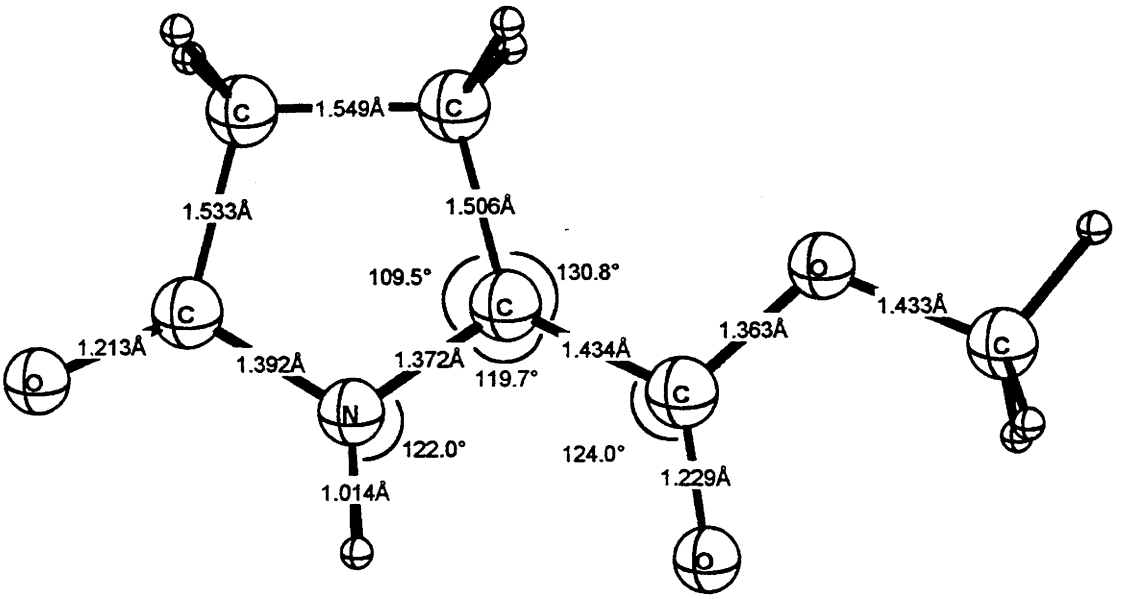


Figure 1.9. The methyl pyroglutamate α-centred radical **19** exhibits C_s symmetry.

Methyl pyroglutamate **18** can exist in more than one ring puckered state. During the optimisation process, two minimum energy structures were found. The differences in the energies were of the order of 1 kJ mol^{-1}, and the lowest energy structure was chosen for structural evaluation. The occurrence of two energy minima suggests that the structure of methyl pyroglutamate **18** is likely to be conformationally labile and, at room temperature, population of multiple low lying conformers means that few general trends about the structure can be drawn. The N-C^{α}-C^{β} bond angle is very small, being only 102.4°. This suggests that the 109.5° N-C^{α}-C^{β} bond angle in the radical **19** is not evidence of gross unfavourable steric interactions, since the corresponding angle in methyl pyroglutamate **18** compensates by also being unusually small.

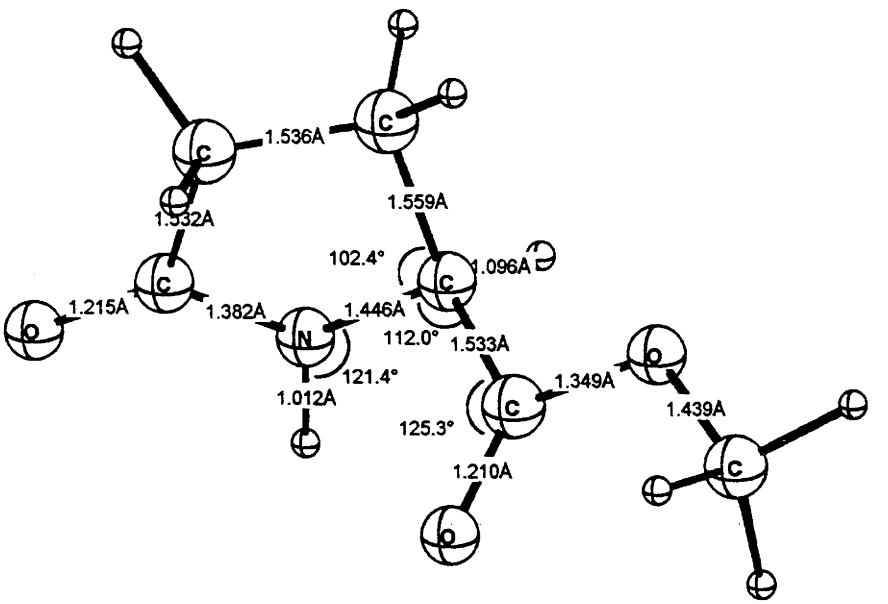


Figure 1.10. The optimised structure of the lower energy conformation of methyl pyroglutamate **18**.

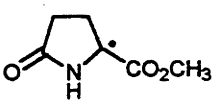
The extra stability afforded the pyroglutamyl radical **19** over the glycyl radical does not appear to be due to any particular structural features, other than the lack of unfavourable non-bonding interactions of the side chain of the pyroglutamyl radical **19** with the amide carbonyl. In fact, the magnitude of the RSE observed for this radical **19** is consistent with the increase in stabilisation afforded by α-alkyl substitution. The pyroglutamyl radical **19** is 11.1 kJ mol^{-1} more stable than the protected glycyl radical **73**. This is comparable to the increase in the RSE of ethyl radical over methyl radical of 13.2 kJ mol^{-1}, as derived from Table 1.2 (p. 45).

It is possible to predict relative rates of bromination, by using relative differences in the RSEs of protected amino acid radicals in calculations involving equation **(5)** (Table 1.7). The comparison of these theoretical values with experiment allows us to gain an idea of how much radical character is reflected in the reaction transition state. The calculations based on these relative RSE differences assume that the Arrhenius pre-exponential factors (A) are similar for the formation of like radicals under the same experimental

conditions. This is a reasonable approximation based on the comparisons of sets of Arrhenius parameters which are available in the literature.[160] The degree to which they mimic experimental relative rates of reaction depends on the transition state having high radical character and, therefore, that the differences in the RSEs are good approximations of differences in activation energy. This is generally thought to be the case for bromination reactions.[192] A comparison of these theoretically calculated rates with those observed experimentally shows that they are generally of the correct magnitude, though the extraordinary reactivity predicted for the pyroglutamate **18** appears anomalous.

$$k = Ae^{\frac{-E_a}{RT}} \qquad (5)$$

Table 1.7. Comparison of the theoretical relative rates of reaction of acetyl protected amino acids, calculated from the RSEs of acetyl protected amino acid radicals, with the corresponding experimental relative rates of bromination determined for the corresponding benzoyl amino acids.

R	$AcNHC^{\cdot}RCO_2CH_3$			$BzNHC^{\cdot}RCO_2CH_3$	
	Radical	RSE (kJ mol^{-1}) (0 K)	Predicted relative rate of formation [a]	Radical	Relative rate of formation [b]
H	**73**	82.2	1[†]	**9**	1[†]
CH_3	75	80.6	0.58	**10**	0.33
$CH(CH_3)_2$	77	73.0	0.044	**11**	0.04
	**19**	93.3	44	**19**	3.1

[†] Assigned as unity. [a] Calculated from equation (5). [b] Taken from Burgess *et al.*[68]

The difference between the RSEs of the alanyl radical **75** and the glycyl radical **73** correspond to an almost twofold decrease in the rate of reaction of the alanine **74**, compared with that of the glycine **72**. Similarly, the difference between the RSEs of the valyl radical **77** and the glycyl radical **73** correspond to an approximate 20-fold decrease in the rate of reaction of the valine **76**, compared with that of the glycine **72**. These predictions are in fairly good agreement with the observed decrease in the relative rates of bromination of the corresponding benzoyl-protected compounds.[68] The difference between the RSEs of the methyl pyroglutamyl radical **19** and the glycyl radical **73**, however, yields a predicted relative rate which is an order of magnitude greater than the experimental relative rate.[68]

An examination of the deuterium isotope effects in the reactions of the deuterated derivatives of both the benzoyl amino acids **6–8** and methyl pyroglutamate **18** gives information about the transition states of the corresponding bromination reactions.[68] Deuterium isotope effects reflect the degree of bond homolysis and relate to the amount of radical character in the transition state. For the bromination reactions of the benzoyl amino acid derivatives **6–8** and methyl pyroglutamate **18**, the deuterium isotope effects are around 3, 1.8, 4 and 1.5, respectively.[68] This indicates that the bromination reactions pass through different types of transition states. So, whilst the calculated relative rates have been shown to generally provide reasonable correlation with the observed relative rates, greater accuracy cannot be expected.

The theoretical investigation presented in this chapter supports the previously held belief that non-bonding interactions in the planar conformations of acyl-protected α-amino acid radicals are responsible for the experimentally observed selectivities of α-hydrogen abstraction. The range of reactivities of a selection of *N*-benzoylamino acid derivatives in radical bromination reactions[68] has been reproduced, both quantitatively and qualitatively, by theoretical calculations of the RSEs for the corresponding acetyl derivatives. The role of non-bonding interactions has been explored from a geometric perspective and it is clear these effects are important in defining the relative stabilities of

the product radicals. Particularly, the unfavourable interactions between the amide carbonyl group of a protected amino acid with the amino acid side chain are integral to the selectivity for hydrogen abstraction from protected glycine observed experimentally, and the diminished stability of α-centred radicals of other protected amino acids with increased side chain bulk.

2

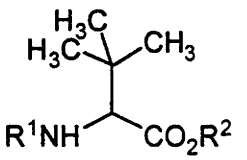
Exacerbation of the Interactions of the Side Chains of Protected Amino Acids with the Amide Carbonyl of Their Protecting Groups

In the previous chapter, the existence of non-bonding interactions in the planar conformations of various amino acid radicals was examined. The results indicated that there are unfavourable interactions of the amino acid side chain with the acyl protecting groups in the radicals **75** and **77**. These interactions led to the tertiary radicals **75** and **77** being less stable than the corresponding secondary glycyl radical **73**. Non-bonding steric interactions were found to be much less important in the corresponding free amino acid radicals **65**, **68** and **70**, where no interaction with an amide carbonyl is possible.

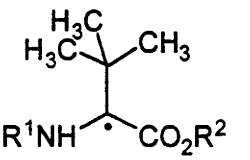
The differences in the RSEs of the protected amino acid radicals border on the quoted limits of accuracy of the theoretical methods used.[164] Thus, a more convincing example of the effect of steric interactions of the side chain with the acyl protecting group of an amino acid is desirable to establish definitively that this is the mechanism by which the α-centred radicals are destabilised. The work presented in this chapter was aimed at designing a system whereby such a result could be obtained.

As discussed in Chapter One, it was observed that the minimum energy conformation of the protected valyl radical **77** had the methyl groups of the isopropyl side chain aligned in such a way as to minimise their interaction with the amide carbonyl of the protecting group. This resulted in the hydrogen of the isopropyl group being in closest proximity to this amide carbonyl. It was envisaged that non-bonding interactions with the amide carbonyl could be exacerbated by replacing this hydrogen of the isopropyl group with a methyl group. The methyl groups of such a *tert*-butyl substituent would not be able to

avoid interacting with the amide carbonyl of the protecting group in the same way as was observed with the methyl groups of the isopropyl substituent of the valyl radical **77**. To probe this theory, *tert*-leucine **80** and its protected counterpart **81** were chosen for theoretical examination. It was expected that the difference in the RSEs of the *tert*-leucyl radical **82** and protected *tert*-leucyl radical **83**, which reflects the severity of the non-bonding interactions in the radical **83**, would be much larger than the difference between the RSEs of the valyl radicals **70** and **77**.

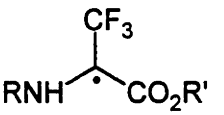


80 $R^1 = R^2 = H$
81 $R^1 = CH_3CO$, $R^2 = CH_3$



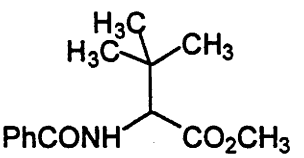
82 $R^1 = R^2 = H$
83 $R^1 = CH_3CO$, $R^2 = CH_3$

It was anticipated that the fluorines of a trifluoromethyl group would also show a significant interaction with the amide carbonyl of a protecting group, more so than the interaction of the hydrogens of the methyl group of the alanyl radical **75**, previously examined. The difference in the RSEs of the trifluoroalanine **84** and protected trifluoroalanyl radical **85**, which reflects the extent of the non-bonding interactions, was thus expected to be larger than that between the RSEs of the alanyl radicals **68** and **75**. To explore how a trifluoromethyl group interacts with an acyl protecting group, the RSEs of the radicals **84** and **85** have been calculated and their significance is discussed in this chapter.

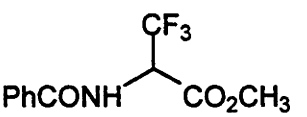


84 R = H, R' = H
85 R = CH_3CO, R' = CH_3

More severe non-bonding interactions in the radicals of the amino acid derivatives **86** and **87**, than in other benzoylamino acid radicals, were expected to lead to lower relative stabilities. Therefore the rates of bromination, which reflect these radical stabilities, of the benzoylamino acids **86** and **87** were anticipated to be slower. The relative rates of bromination of the benzoylamino acids **86** and **87** have been examined to determine the extent to which the proposed non-bonding interactions affect the reactivity at the α-centre and this is discussed in this chapter.



86



87

Results

In a similar fashion to the work presented in the previous chapter, standard *ab initio* molecular orbital theory and DFT calculations were performed with GAUSSIAN 94.[169] Some preliminary conformational work was carried out at AM1 using the Spartan and MacSpartan Plus programs, in order to select the most appropriate conformations to be examined using *ab initio* methods. RSEs were calculated using the isodesmic reaction with methane. Calculation of minimum energy conformations was carried out using the

density functional method B3-LYP/6-31G(d) with subsequent calculation of the single point energies at RMP2/6-31G(d). The results of these calculations are presented in Table 2.1. For more convenient comparison with the calculations introduced in this chapter, a selection of results has been reproduced from Chapter One and are presented in Table 2.2.

Table 2.1. RSEs of trifluoroalanyl, *tert*-leucyl and related radicals calculated at RMP2/6-31G(d)//B3-LYP/6-31G(d).

$XC^{\bullet}RY + CH_4 \rightarrow XCHRY + CH_3^{\bullet}$					Energies (kJ mol^{-1})		
XCHRY	$XC^{\bullet}RY$	X	Y	R	RSE	ZPE correction	RSE(0 K)
88	**89**	H	H	CH_3	12.7	0.5	13.2
90	**91**	H	H	CF_3	-6.5	–1.0	-7.5
56	**57**	NH_2	H	CH_3	52.4	–3.3	49.1
92	**93**	NH_2	H	CF_3	45.9	–4.3	41.6
58	**59**	H	CO_2H	CH_3	46.2	–4.0	42.2
94	**95**	H	CO_2H	CF_3	18.3	–4.1	14.2
80	**82**	NH_2	CO_2H	$C(CH_3)_3$	102.3	–7.0	95.3
96	**84**	NH_2	CO_2H	CF_3	104.6	–6.3	98.3
81	**83**	CH_3CONH	CO_2CH_3	$C(CH_3)_3$	53.6	–8.1	45.5
97	**85**	CH_3CONH	CO_2CH_3	CF_3	50.5	–6.8	43.7

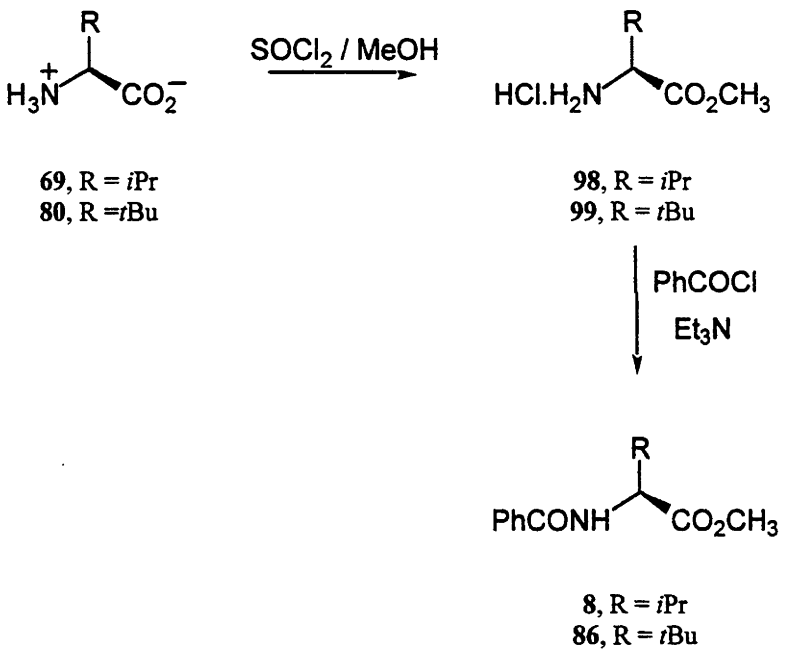
Table 2.2. RSEs of a selection of non-protected and protected amino acid radicals.[†]

$XNHC^{\bullet}RCO_2Y + CH_4 \rightarrow XNHCHRCO_2Y + CH_3^{\bullet}$					Energies (kJ mol^{-1})		
$XNHCHRCO_2Y$	$XNHC^{\bullet}RCO_2Y$	X	Y	R	RSE	ZPE correction	RSE(0 K)
64	**65**	H	H	H	102.0	–6.1	95.9
67	**68**	H	H	CH_3	109.5	–6.1	103.4
69	**70**	H	H	$CH(CH_3)_2$	104.6	–6.1	98.5
72	**73**	CH_3CO	CH_3	H	89.7	–7.5	82.2
74	**75**	CH_3CO	CH_3	CH_3	87.6	–7.0	80.6
76	**77**	CH_3CO	CH_3	$CH(CH_3)_2$	81.6	–8.6	73.0

[†] Results reproduced from Chapter One.

The valine derivative **8** was synthesised for use as a reactive standard to allow the relative rates of reaction of the *tert*-leucine **86** and the trifluoroalanine **87** to be compared on the same scale as existing experimental relative rates of bromination for other benzoyl amino acids.[68] Preparation of the valine **8**, using standard methods, was achieved by initial treatment of valine **69** with methanol, which had been pretreated with thionyl chloride. This yielded the valine methyl ester hydrochloride salt **98**, after removal of the solvent. The crude product was then suspended in a solution of two equivalents of triethylamine in dichloromethane, and benzoyl chloride was added dropwise. *N*-Benzoylvaline methyl ester **8** was thus obtained as a colourless powder upon recrystallisation from ethyl acetate/hexane. The same method was used to obtain *N*-benzoyl-*tert*-leucine methyl ester **86** from the corresponding free amino acid **80** *via*

the hydrochloride **99** (Scheme 2.1). Both products **8** and **86** were identified by comparison of their properties with literature data,[193,194] and by the characteristic ^{1}H NMR spectra produced for *N*-benzoylamino acid methyl esters. These spectra showed signals for five protons in the aromatic region diagnostic of *N*-benzoyl protection, a broadened peak around δ6-7 characteristic of the amide proton, a single proton signal around δ4.5-5 for the α-proton and a singlet with three proton intensity around δ3.7-3.8 for the methyl ester. Side chain signals appear further upfield and are dependent on the specific amino acid.



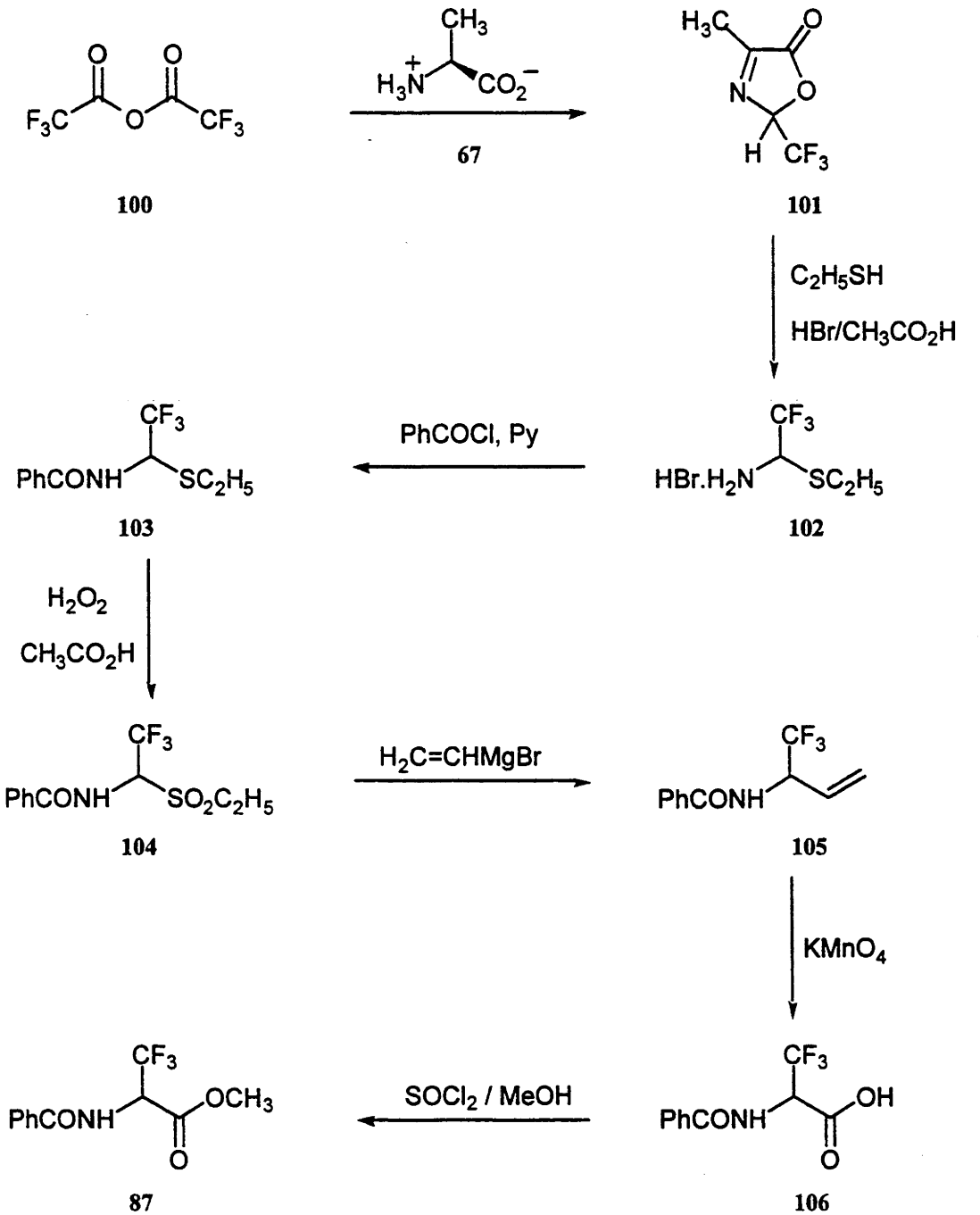
69, R = *i*Pr
80, R = *t*Bu

98, R = *i*Pr
99, R = *t*Bu

8, R = *i*Pr
86, R = *t*Bu

Scheme 2.1. Synthesis of *N*-benzoylamino acid methyl esters.

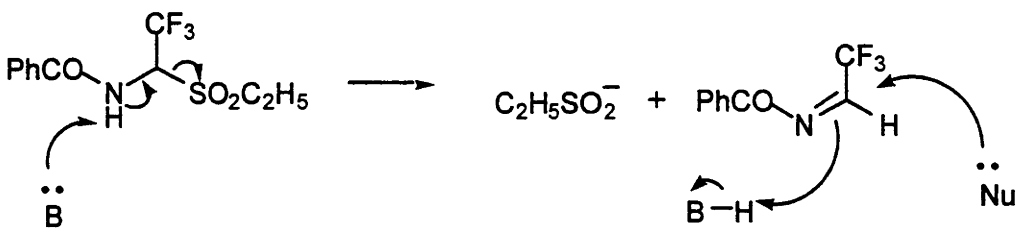
Synthesis of the trifluoroalanine derivative **87** was achieved using a composite of the methods for synthesising perfluorinated amino acids published by Weygand *et al.*[195–201] A summary is shown in Scheme 2.2.



Scheme 2.2. Synthesis of *N*-benzoyl-3,3,3-trifluoroalanine methyl ester **87**.

Alanine **67** was treated with trifluoroacetic anhydride **100** and this mixture was heated to afford the corresponding 2-trifluoromethyl-4-methyloxazolone **101**. After removing the excess anhydride and corresponding acid, the oxazolone **101** was treated with ethanethiol to effect ring opening and produce the α-aminothioether hydrobromide salt **102**. This crude salt was then dissolved in dichloromethane and pyridine, then benzoyl chloride was added to produce the *N*-benzoylated thioether **103**, in 73% yield from alanine **67**.

In order to make the ethanethiyl moiety of the thioether **103** a better leaving group, it was necessary to oxidise it to the corresponding sulfone **104**. Aliphatic sulfones are usually stable in the presence of nucleophiles, however, those with an activated β-hydrogen, and especially those with an additional electron-withdrawing α-substituent, undergo replacement of the sulfonyl moiety *via* initial elimination of a sulfinic acid and formation of an imine intermediate (Scheme 2.3).[196] Oxidation was achieved with acidified hydrogen peroxide and gave the sulfone **104** as white crystals from water, in 75% yield.



Scheme 2.3. Elimination of a sulfinic acid to give a reactive imine is proposed as the reason for facile replacement of the sulfonyl group of the sulfone **104**.[196]

Initially, it was not clear whether the sulfone **104** had been obtained since the melting point of the isolated compound was found to be 150 °C, much lower than the literature

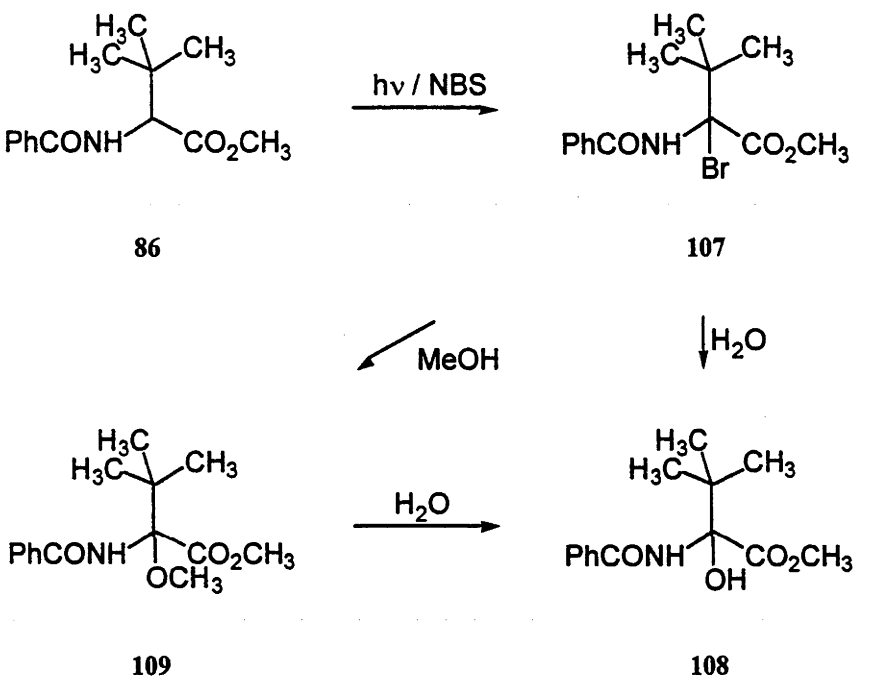
value of 171 °C.[196] This was despite careful drying of the apparently clean sample. Comparison of the ^{1}H NMR spectral data of compound **104** with the data provided in the literature[196] revealed deviations in the proton signals of 0.1-0.2 ppm from those reported, as well as differences in the coupling constants by up to 1 Hz, though these differences were consistent with the use of a different solvent system. Microanalysis of the sample, however, revealed that its composition was consistent with the calculated molecular formula and, thus, the sulfone **104** was used in the subsequent reactions required for the preparation of the trifluoroalanine **87**.

Originally the literature preparation[196] of the alkene **105**, from the sulfone **104**, was adhered to, but the yields obtained were very poor and the reaction produced many unisolated by-products. This preparation was therefore modified to carry out the reaction under much more stringent, inert conditions and with monitoring of the product **105** formation by thin layer chromatography (TLC). Excess vinylmagnesium bromide was added to the reaction mixture as required, instead of addition of the sulfone **104** dropwise to the vinylmagnesium bromide as reported.[196] This produced an apparently clean sample of the alkene **105**, without the necessity for subsequent complicated chromatographic purification, as determined by observation of the ^{1}H NMR spectrum of the compound after workup. Identification of the alkene **105** from the ^{1}H NMR spectrum was readily achieved by the observation of three clear resonances at δ5.48, 5.51 and 5.57, and a multiplet around δ5.98, which are indicative of the terminal vinyl substituent. The crude alkene **105** was used directly in the subsequent oxidation to produce the acid **106**. The original literature report[196] suggested that oxidation of the alkene **105** with excess potassium permanganate proceeded in only 15 minutes to give a moderate yield (23%) of the corresponding acid **106**. When this method was attempted, only trace amounts of product were isolated. In a later publication on higher perfluorinated homologues, the oxidation was allowed to proceed for around two days.[200] Adoption of this procedure resulted in increased yields, reflected in the yields obtained for the esterification of the crude acid **106**. This esterification was effected by treatment of the crude product **106**, obtained from the workup of the potassium

permanganate oxidation, with acidified methanol. The fully protected trifluoroalanine **87** was produced as colourless crystals in 45% yield from the sulfone **104**. Its physical properties were found to be consistent with those found in the literature[196] and the ^{1}H NMR spectrum showed the characteristics of an *N*-benzoylamino acid methyl ester, as discussed previously (p. 76), except that the shift of the signal for the methyl group was downfield due to the electron withdrawing nature of the trifluoromethyl substituent. The trifluoroalanine **87** also exhibited a unique and diagnostic apparent quintet at δ5.59 for the α-proton in the ^{1}H NMR spectrum, the splitting of which was caused by coupling of the α-proton to the β-fluorines and the adjacent amide proton.

Carbon tetrachloride solutions of each of the amino acid derivatives **86** and **87** were placed in a quartz tube with one equivalent of NBS **2** and an aliquot of *N-tert*-butylbenzamide as an internal standard. These mixtures were heated to reflux and irradiated for 6 hours with a 300W sunlamp. The trifluoroalanine derivative **87** was recovered unchanged after this time, with no consumption observed by ^{1}H NMR spectroscopy, when compared against the internal standard. The *tert*-leucine derivative **86** underwent 60% conversion to the corresponding bromide **107**. The formation of this bromide **107** was confirmed through its subsequent preparation, by irradiation of the *tert*-leucine **86** with 1.5 equivalents of NBS **2**. Disappearance of the α-proton signal in the ^{1}H NMR spectrum, as well as shifts of the methyl and *tert*-butyl signals from δ3.75 and δ1.06 to δ3.68 and δ1.37, respectively, were evidence of the formation of the α-bromide **107**. This bromide **107** was very unstable and exchange of the bromine when treated with water, to give the corresponding alcohol **108** was very rapid. Consequently, characterisation of the reaction product was attempted by preparing the methoxide **109** through addition of a small amount of methanol to a filtered, but crude, reaction mixture. The methoxide **109** was identified from a distinct methyl resonance in the ^{1}H NMR spectrum at δ3.44 integrating to three protons. The presence of this compound was confirmed by a peak in the mass spectrum at 222 mass units. This peak corresponds to loss of the *tert*-butyl unit from the methoxide **109** and its composition was confirmed by high resolution mass spectroscopy. Attempted chromatography, however, resulted in

conversion to the corresponding alcohol **108**, as identified from the ^{1}H NMR spectrum. Atempted recrystallisation of this alcohol **108** resulted only in further decomposition and no isolable products.



86 **107**

109 **108**

Scheme 2.4. Bromination of the *tert*-leucine derivative **86**. Treatment with water results in formation of the corresponding alcohol **108** from both the bromide **107** and the methoxide **109**.

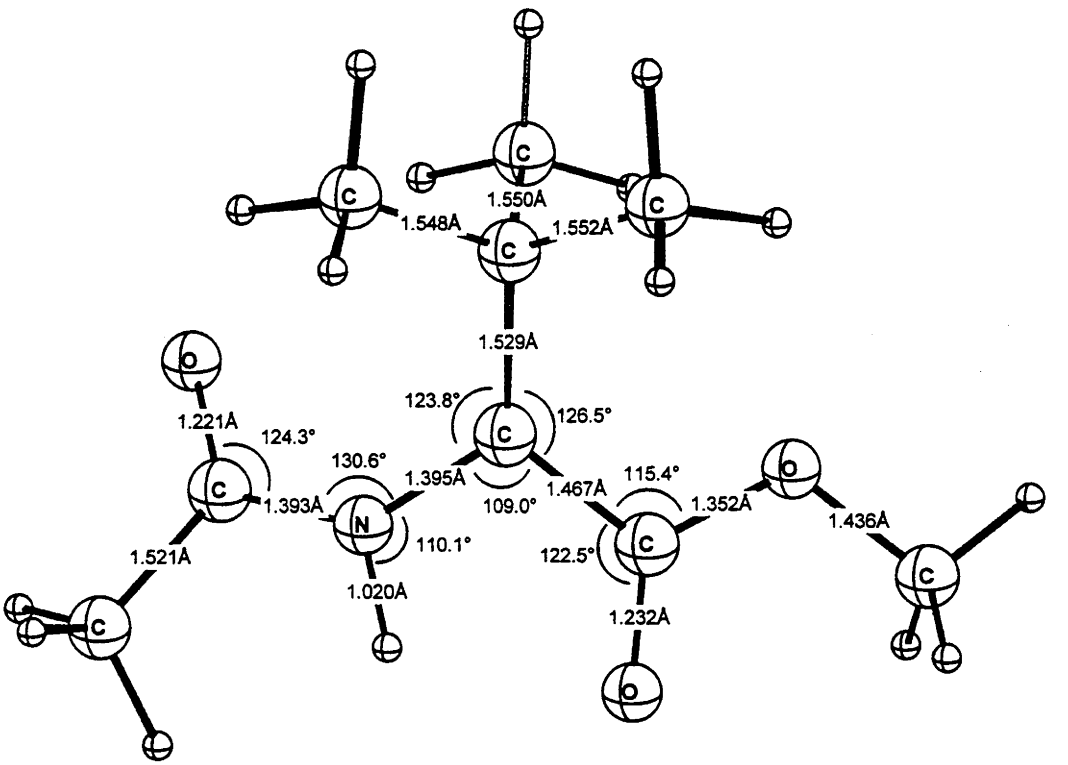
One possibility for the lack of reaction observed for the trifluoroalanine derivative **87** was that there was an inhibiting contaminant present. To check whether this was the case, a competitive reaction with the valine **8** was carried out. An equimolar mixture of the trifluoroalanine **87** and the valine derivative **8** was combined with two equivalents of NBS **2** in carbon tetrachloride. The solution was heated at reflux, whilst irradiating with a 300W sunlamp. *N-tert*-Butylbenzamide was used as the internal standard. ^{1}H NMR spectra were obtained of both the starting and final reaction mixtures and compared to

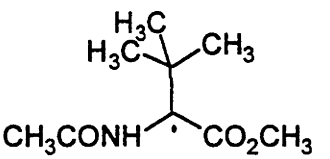
determine the relative rates of reaction. The benzoylvaline **8** was seen to have reacted completely to form the dibromide **13**, as identified by comparison to the literature ^{1}H NMR spectral data for this compound.[66] This shows that there was no inhibiting contaminant. When compared to the internal standard, no consumption of the trifluoroalanine derivative **87** was observed, nor were any products observed which might have arisen from this compound. The relative rate of reaction for the trifluoroalanine derivative **87** must therefore be very slow.

Competitive bromination reactions of the *tert*-leucine **86** and the valine **8** were carried out to determine the relative rate of bromination of these two compounds. The reactions were performed in an identical manner to the competitive reaction of the trifluoroalanine derivative **87** and the valine **8** with NBS. The valine derivative **8** was seen to react to the exclusion of the *tert*-leucine **86**. As a conservative estimate, it was concluded that the bromination reaction of the *tert*-leucine **86** must proceed at least 10 times more slowly than the reaction of the benzoylvaline **8**. This estimate was based on the accuracy of the ^{1}H NMR spectral integrations, from which measurements of the relative amounts of starting materials and products were obtained.

Discussion

Interaction of the side chain of an amino acid with the amide carbonyl of an acyl-protecting group is important in determining the stability of the corresponding protected amino acid radical. *tert*-Leucine **80** was chosen for examination of this effect, because the *tert*-butyl side chain was expected to interact severely with the amide carbonyl in the α-centred radical **83**. The effect of the protecting groups in the destabilisation of the α-centred radical **83** is measured by comparison of the RSE of this derivative with the RSE of the non-protected radical **82**. The RSE of the free amino acid radical **82** is 95.3 kJ mol^{-1} and that of the protected derivative **83** is 45.5 kJ mol^{-1}. The destabilising effect of the protecting groups is thus 49.8 kJ mol^{-1}. This is a large effect, particularly when compared with the effect of protection on other amino acids. Addition of protecting groups to the glycyl radical **65** results in a comparative reduction in stability of the protected radical **73** of 13.7 kJ mol^{-1}, which can be accounted for by way of electronic effects. The effect of protection on the valyl radical **70** is much more severe, with the protected amino acid radical **77** being 25.5 kJ mol^{-1} less stable. This increase in destabilisation over that seen in the glycyl radical **73** has been shown in the previous chapter to be caused by non-bonding interactions of the amide carbonyl of the protecting group with the isopropyl side chain. By extrapolation, the destabilisation of 49.8 kJ mol^{-1} experienced by the *tert*-leucyl radical **83** is likely to reflect a very severe interaction of the *tert*-butyl side chain with the amide carbonyl of the protecting group. This is what is seen by examination of the structure of the radical **83** (Figure 2.1).





83

Figure 2.1. The bond angles of the protected *tert*-leucyl radical **83** exhibit strain. More importantly, this radical is distorted from the planar structure favoured by other α-centred amino acid radicals.

The protected *tert*-leucyl radical **83** is unable to adopt a conformation whereby the methyl groups do not interact severely with the amide carbonyl. The magnitude of these unfavourable non-bonding interactions is most clearly demonstrated in the lack of planarity of the backbone of the minimum energy conformer of **83** (Figure 2.2). This distortion of the radical **83** directly contrasts with the planar backbones of the minimum energy conformers of the radicals **73, 75, 77**, discussed in Chapter One. The degree of twist of the amide from the planar conformation is notable, with the C(O)-N-C^{α}-C^{β}

dihedral angle being 45°. The effect is less severe on the carbomethoxy group of the amino acid, with only a 15° deviation from planarity, as measured by the $(CH_3)O\text{-}C\text{-}C^{\alpha}\text{-}C^{\beta}$ dihedral angle.

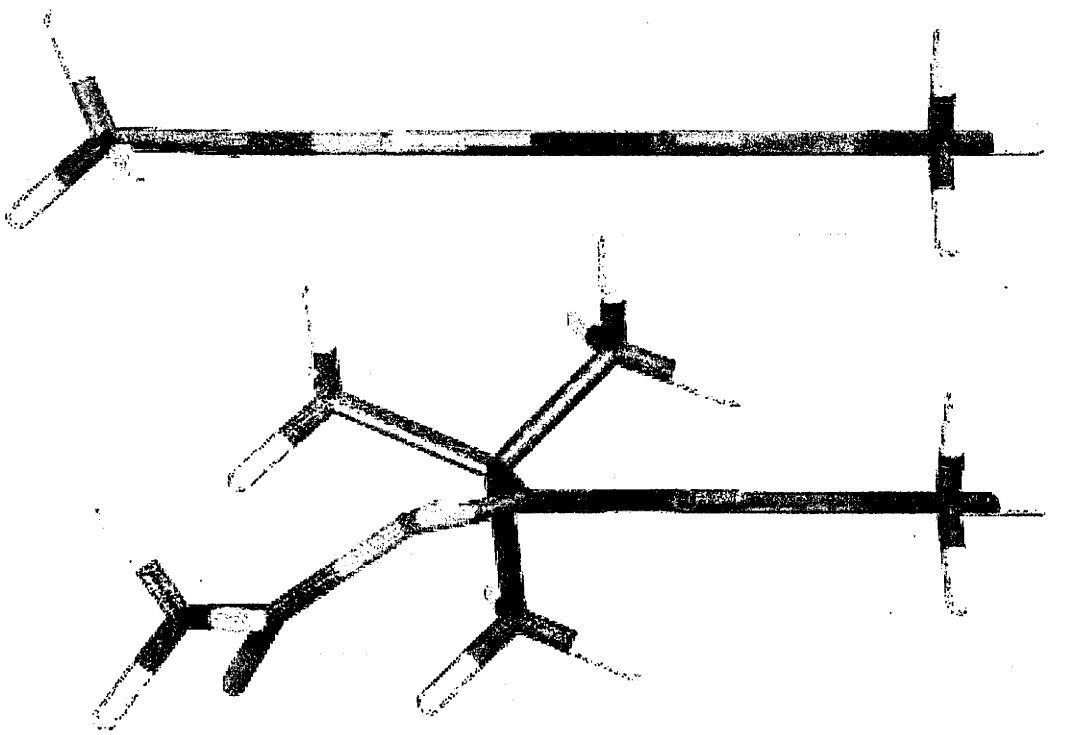


Figure 2.2. There is a significant twisting of the amino acid backbone from planarity in the lowest energy conformer of the protected *tert*-leucyl radical **83** (bottom) compared with that of the protected glycyl radical **73** (top).

A detailed examination of the partially optimised conformations of the protected *tert*-leucyl radical **83** provides an insight into the importance of planarity in the stabilisation of amino acid α-centred radicals. A plot of the initial steps in the geometry optimisation *versus* the stabilisation energy obtained at B3-LYP/6-31G(d) is shown

below (Figure 2.3). This is compared directly with the C(O)-N-C^{α}-C^{β} dihedral angle and also the C(O)-N-C^{α} bond angle at each step.

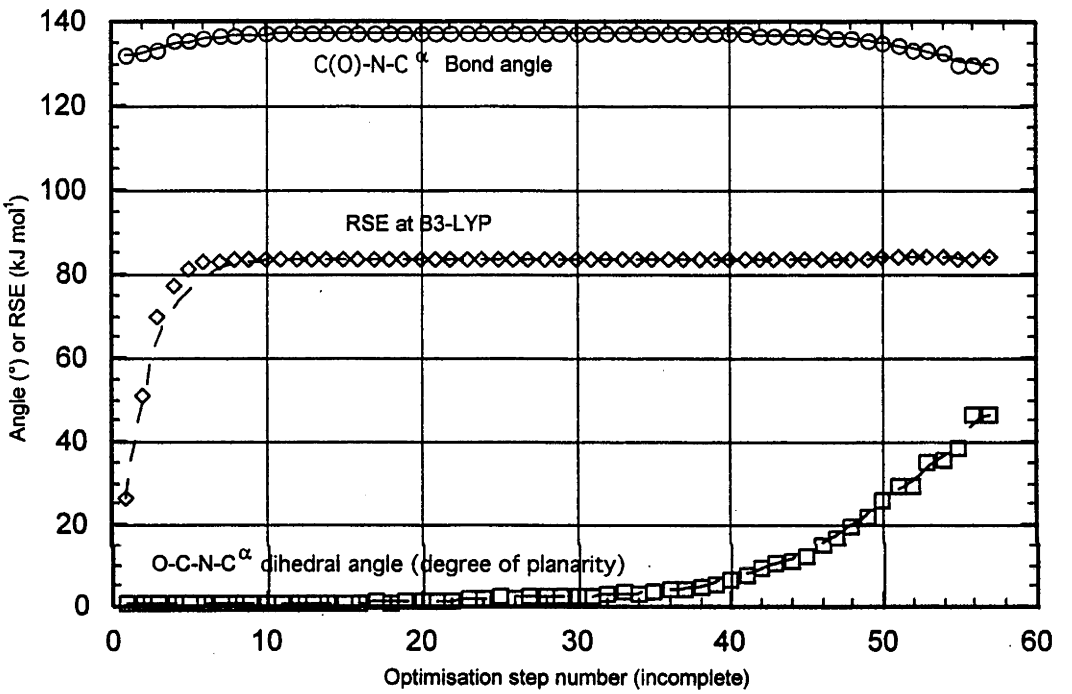


Figure 2.3. Various parameters for the *tert*-leucyl radical **83**, compared with the progression of geometry optimisation.

After approximately ten optimisation steps, the RSE of the radical **83** is within 3 kJ mol^{-1} of the energy of the fully optimised structure (Figure 2.3). At this point the C(O)-N-C^{α} bond angle is a very strained 137°, whereas the C(O)-N-C^{α}-C^{β} dihedral angle, which is an indicator of planarity of the π-system, is still close to zero. Based on these observations, a partial optimisation of the protected *tert*-leucyl radical **83**, with the atoms

in the anino acid backbone constrained to be coplanar, was examined. The structure of this plaiar radical **83** is shown in Figure 2.4.

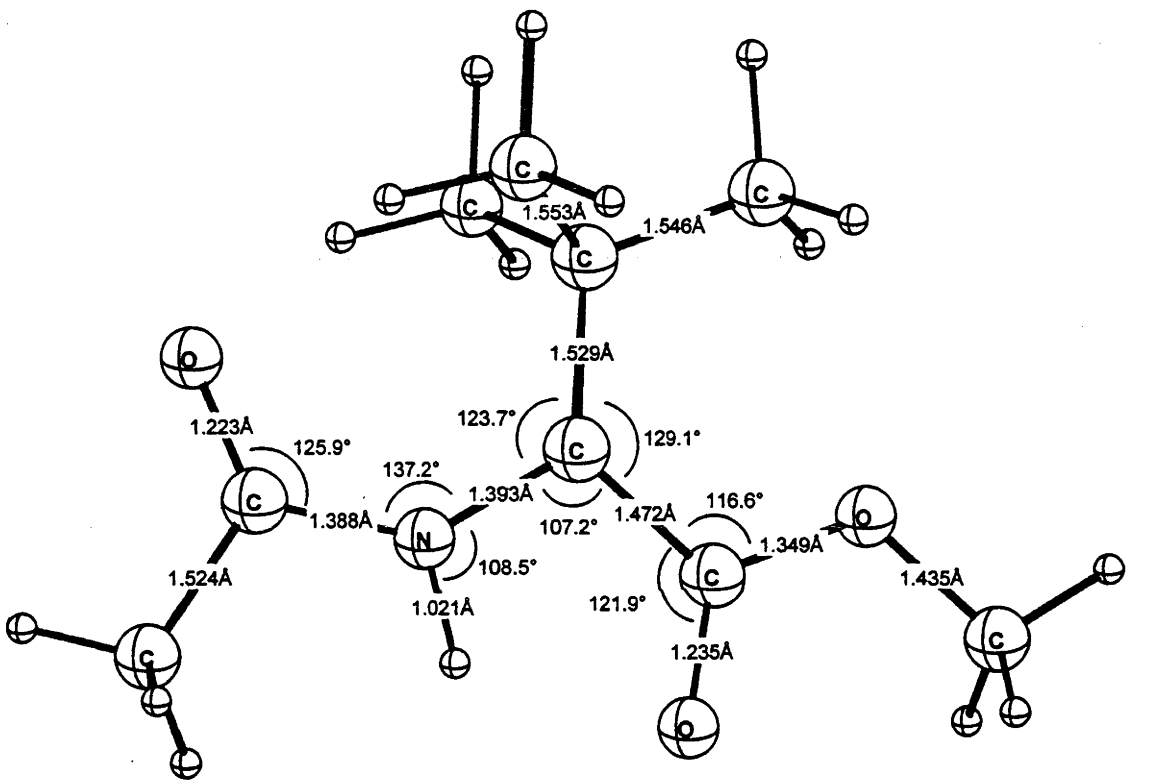


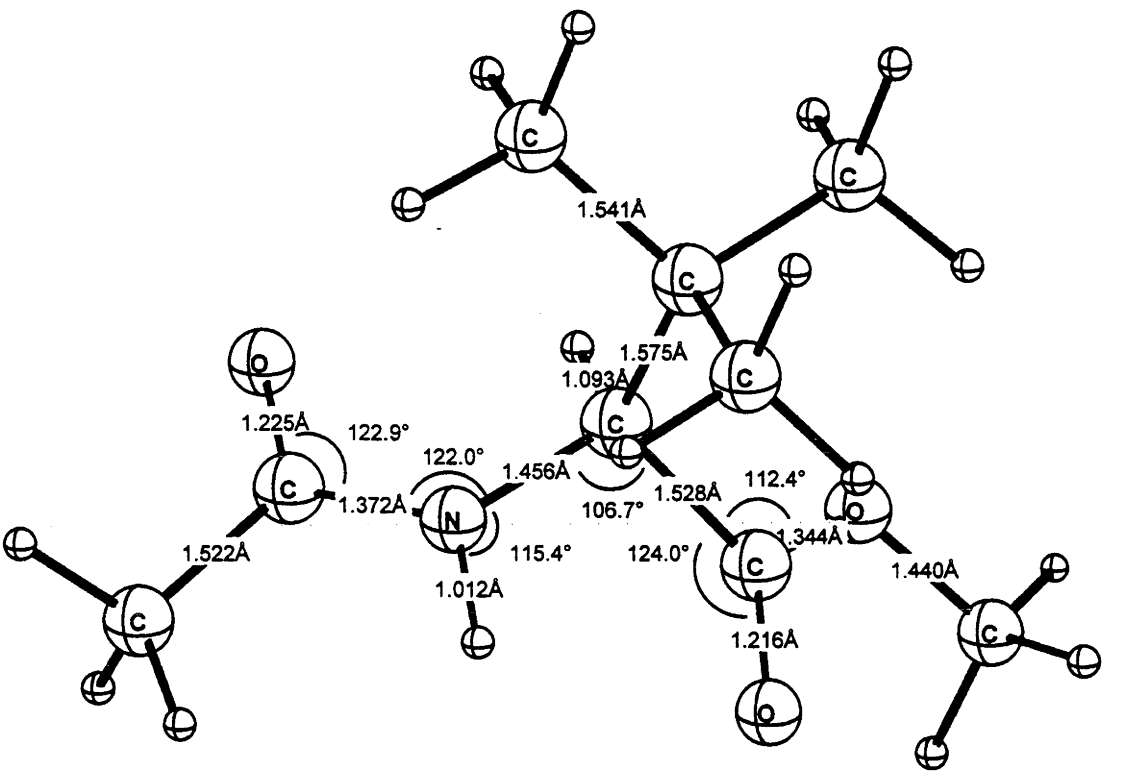
Figure 24. The partially optimised protected *tert*-leucyl radical **83** with the amino acid backbone constrained to be planar.

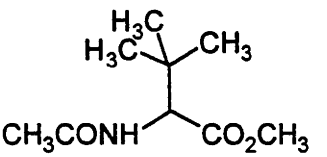
When the amino acid backbone is constrained to be planar, the resultant partially optimised structure of the radical **83** has an RSE of 48.8 kJ mol^{-1} at RMP2, compared with that of the fully optimised structure which is 53.6 kJ mol^{-1} (ZPE correction not included). The C(O)-N-C^{α} bond angle is 137.2° and this is consistent with very severe interactons between the amide carbonyl and the side chain in the planar form of the radical (Figure 2.4). The expansion in this bond angle, relative to the corresponding

124.4° angle in the protected glycyl radical **73**, is reminiscent of that seen in the alanyl and valyl radicals **75** and **77**, where C(O)-N-C^{α} bond angle expansion is a response to increased unfavourable non-bonding interactions in these planar radicals.

Relief of the severe steric strain seen in the planar structure of the radical **83** by distortion from planarity has little effect on the overall stability, in this case, causing a difference in the stabilisation energy of only 4.8 kJ mol^{-1}. Clearly, the stabilisation lost in the distortion of the π-system is balanced, more or less, by the stabilisation obtained by relief of steric strain. The C(O)-N-C^{α} bond angle is seen to decrease from the highly ained 137.2° in the planar conformation, to its final value in the distorted optimised conformation of 130.6° (Figure 2.1). This bond angle is still fairly strained, and comparable to the equivalent bond angle in the valyl radical **77**. Additionally, the distortion from planarity results in pyramidalisation of the nitrogen. This presumably frees the nitrogen electrons from amide conjugation to stabilise the radical, but at the cost of the stability gained from delocalisation of these electrons with the amide carbonyl. There appears to be a fine balance between keeping the π-system of the radical intact, and distorting it to avoid unfavourable non-bonding interactions.

The structure of the protected *tert*-leucine **81** (Figure 2.5), in contrast to that of the radical **83**, shows no evidence of interaction of the *tert*-butyl side chain with the amide carbonyl. This is evidenced by the (O)C-N-C^{α} bond angle of 122.0°, which is comparable to those seen in the protected amino acids **72, 74, 76** in Chapter One. This angle is also much smaller than that seen in the radical **83**, indicating less unfavourable non-bonding interactions. This is despite alleviation of some of the non-bonding interactions in the radical **83** through distortion from planarity. Some steric compression is observed in the *tert*-leucine **81** with the increased bulk of the side chain. However, overall there is nothing apparent from the structure that would counteract the destabilisation observed in the protected *tert*-leucyl radical **83**.



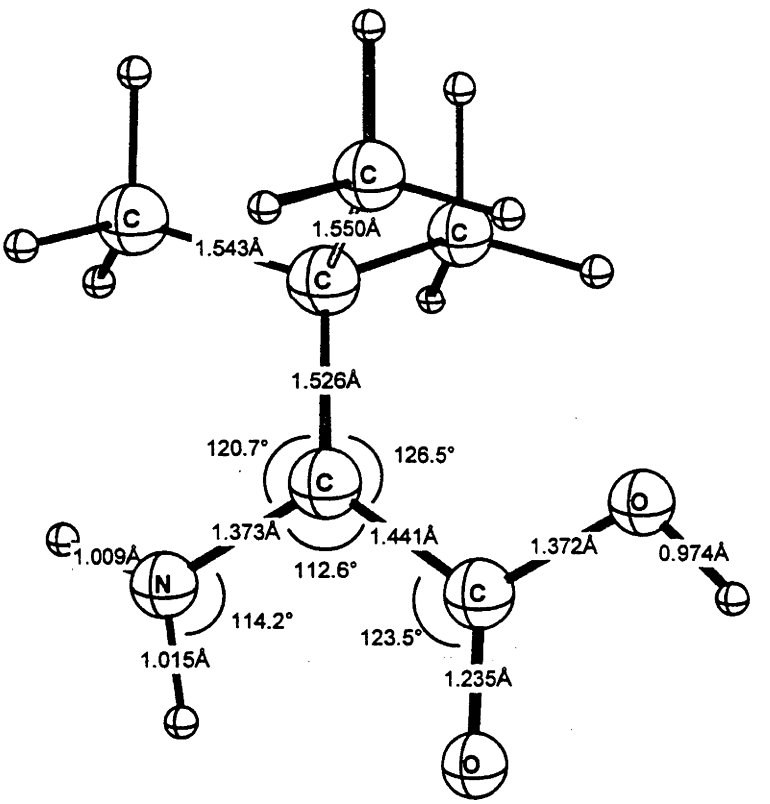


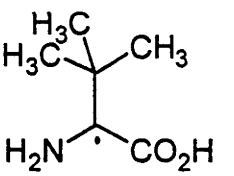
81

Figure 2.5. The interaction of the amide carbonyl with the side chain, seen in the radical **83**, is not visible in the *tert*-leucine derivative **81**.

The 49.8 kJ mol^{-1} difference in the RSEs of the protected radical **83** and the non-protected radical **82** is consistent with the severe interactions seen between the side chain with the amide carbonyl of the protecting group in the protected radical **83**. No such severe interactions are seen in the free amino acid radical **82** between the *tert*-leucyl side chain and the amino acid backbone (Figure 2.6). This is consistent with this effect being caused specifically by interaction of the amide carbonyl with the side chain in the protected species **83**. Some non-bonding interactions of the side chain with

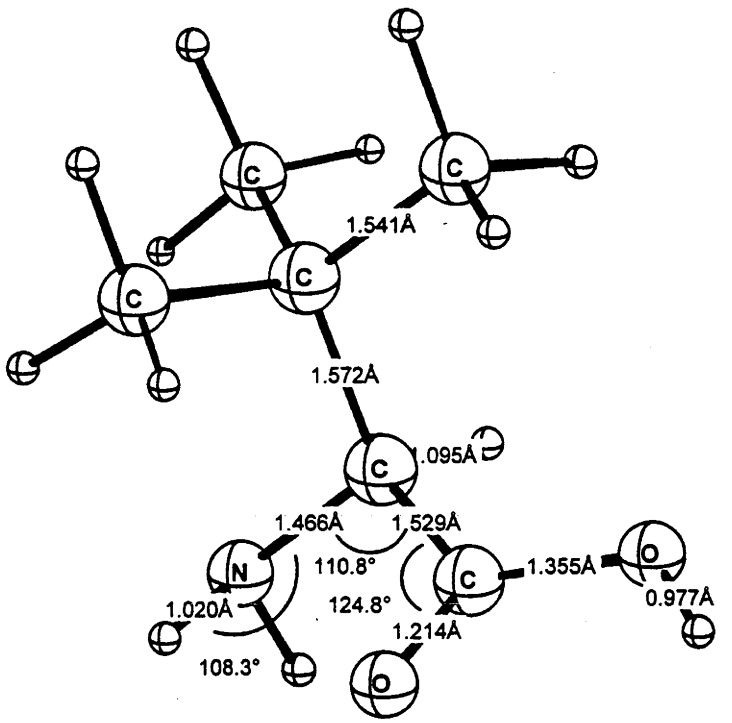
the backbone in the *tert*-leucyl radical **82** are present and these are more pronounced than those seen in the valyl radical **70**. However, as reflected by the 3.2 kJ mol^{-1} lowering of the RSE of the *tert*-leucyl radical **82** compared with the valyl radical **70**, these interactions are trivial compared with those interactions observed in the protected species **83**. This further indicates that interaction of the *tert*-butyl side chain with the acyl protecting group is the cause of the large destabilisation of the protected *tert*-leucyl radical **83**, when compared with other protected amino acids.

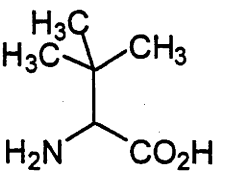




82

Figure 2.6. The *tert*-leucyl radical **82**.





80

Figure 2.7. *tert*-Leucine **80**.

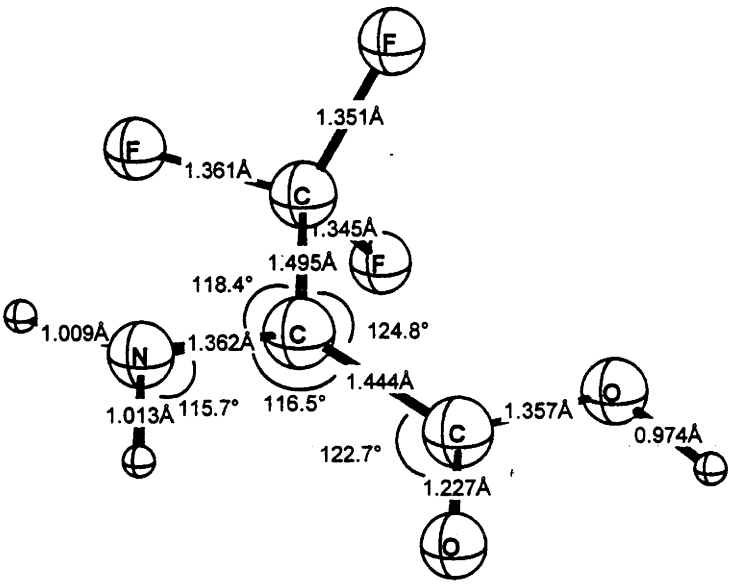
The steric interactions of the side chain with the acyl protecting group in the protected *tert*-leucyl radical **83** are unambiguously important in determining the stability of that radical. The severity of these interactions is reflected in the 49.8 kJ mol^{-1} decrease in stabilisation caused by protection, and is reinforced by the distortion from planarity observed in the minimum energy conformer. This distortion from planarity is a result of the radical **83** being unable to tolerate the extreme non-bonding interactions in the planar conformation of the radical **83**.

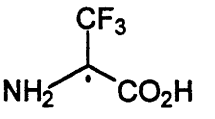
Fluorine has attracted considerable attention as having novel substituent effects. For this reason, it is being used more frequently as a component of physiologically active compounds.[202–207] Fluorine is often thought to have a steric bulk similar to that of hydrogen, with the van der Waals radii being initially reported as 1.35 Å[208] and 1.29 Å,[209] respectively. More recent figures, however, put these distances at 1.47 Å[210]

and 1.20 Å,[208,210] respectively. This radius for fluorine is still smaller than that of all of the other elements in the first-period and significantly smaller than the radius reported for methyl groups, which is estimated at closer to 2.0 Å.[208] The actual 'bulk' of fluorine substituents, as measured by experimental means, is somewhat contentious. Steric parameters in the literature suggest that, whilst a fluoro substituent lies somewhere in size between hydrogen and methyl, a trifluoromethyl group is at least twice as large as a methyl group and not much smaller than a *tert*-butyl group.[207] However, other studies seem to suggest that fluorine substituted compounds interact biochemically more like their hydrogen containing counterparts than their methyl derivatives.[207]

Regardless of steric considerations, fluorine is much more electronegative than hydrogen. A trifluoromethyl group thus has a higher exposed electron density than does a methyl group and this results in unfavourable electrostatic interactions with other electronegative moieties, such as the amide carbonyl of an acyl protecting group. On this basis, it was anticipated that the protected α-centred radical of trifluoroalanine **85** would be much less stable than its unprotected counterpart **84** due to unfavourable interactions of the trifluoromethyl group with the amide carbonyl of the protecting group. This expectation was borne out by the results of theoretical studies.

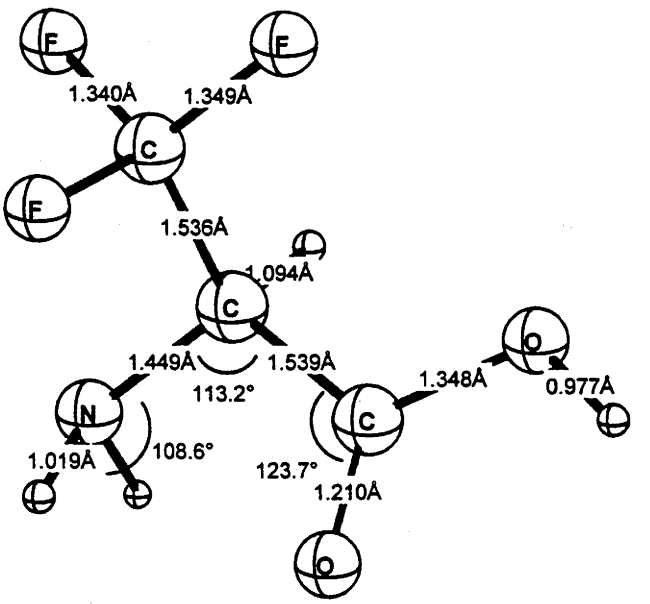
The trifluoroalanyl radical **84** has an RSE of 98.3 kJ mol^{-1} compared with the 103.4 kJ mol^{-1} of the alanyl radical **68**. This equates to 5.1 kJ mol^{-1} of destabilisation and is consistent with the electron withdrawing nature of the trifluoromethyl group. However, the magnitude of this destabilisation is much smaller than the 20.7 kJ mol^{-1} difference between the RSEs of the ethyl and trifluoroethyl radicals **89** and **91**. Conformationally, there is little difference between the trifluoroalanyl radical **84** (Figure 2.8) and the alanyl radical **68**. This suggests that there is little significant steric interaction of the trifluoromethyl group with the amino acid backbone. Examination of the structure of the free amino acid **96** (Figure 2.9) shows some interactions resulting from steric compression, which are consistent with the higher than expected RSE.

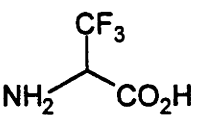




84

Figure 2.8. The trifluoroalanyl radical **84** has a similar geometry to that of the alanyl radical **68**.





96

Figure 2.9. The neutral trifluoroalanine **96**. Overall, most structural features are similar to those of alanine **67**.

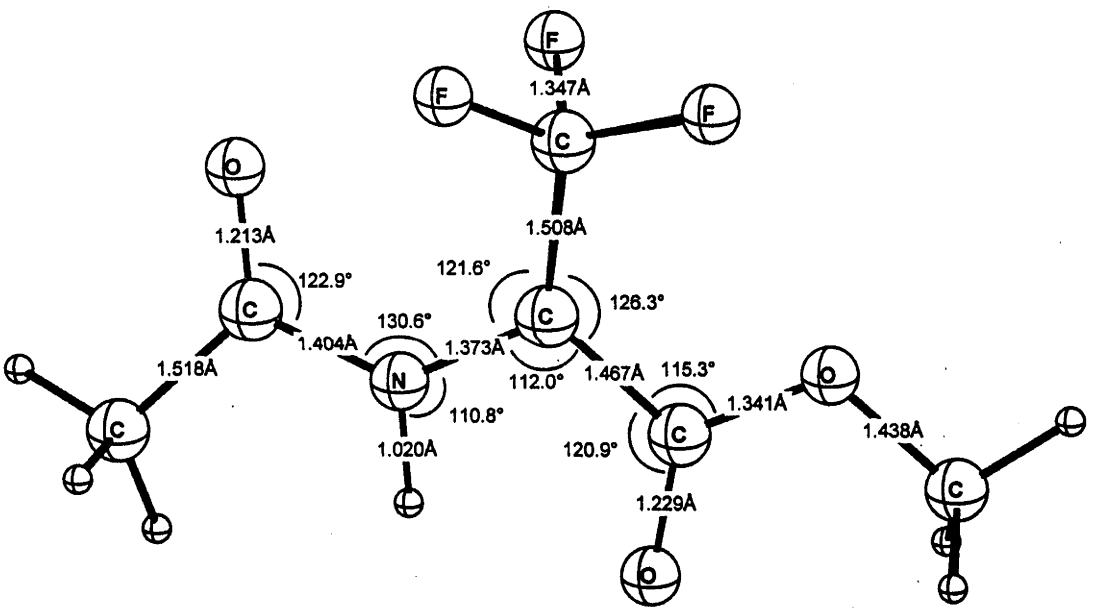
The electronic effect of trifluoro substitution adjacent to a radical centre was examined by comparing the RSEs of a selection of small molecules with their non-fluorinated counterparts. Ethane **88** and trifluoroethane **90** constitute the simplest system examined and a comparison of the RSEs of their corresponding radicals **89** and **91** shows that there is a destabilisation of 20.7 kJ mol^{-1}. This is consistent with the inductive withdrawal of electron density from the radical centre by the highly electronegative fluorines, which is known to have a destabilising influence.[211] It is noted that the absolute B3-LYP energy values for the ethanes **88** and **90**, and their radicals **89** and **91**, are in accordance with a previous study at the same level of theory.[212]

When the RSEs of the propionic acid radical **59** and trifluoropropionate radical **95** are compared, the difference in stability is 28.0 kJ mol^{-1}. This is similar to the effect of trifluoro substitution on the RSEs of the ethyl and trifluoroethyl radicals **89** and **91** and is consistent with the increase in destabilisation due to two electron withdrawing groups attached to the same radical centre observed in the literature.[213]

The influence of the amino substituent is to temper the destabilising influence of the trifluoromethyl group on the radical. The RSE difference between the aminoethyl radical **57** and the trifluoroaminoethyl radical **93** is only 7.5 kJ mol^{-1}. The electron donating ability of the amino substituent helps to compensate for the electron-withdrawing nature of the trifluoromethyl substituent. Consequently, this type of compensatory effect by the amino group of the trifluoroalanyl radical **93** is the likely reason that the RSE of this radical is only 5.1 kJ mol^{-1}, and not 20 kJ mol^{-1}, less than that of the alanyl radical **68**.

Comparison of the RSEs obtained for the free trifluoroalanyl radical **84** and the corresponding protected radical **85** gives strong evidence that the trifluoroalanine side chain does interact significantly with the amide carbonyl of an acyl protecting group. The RSE of the trifluoroalanyl radical **84** is 98.3 kJ mol^{-1} and that of the protected radical **85** is 43.7 kJ mol^{-1} meaning that the effect of protection on the trifluoroalanyl

radical is 54.6 kJ mol^{-1}. This is much larger than the effect of protection on the glycyl radical **65** of 13.7 kJ mol^{-1}, which was attributed to electronic destabilisation of the α-centred radical. It is also much larger than the effect of protection on the alanyl radical **68** of 22.8 kJ mol^{-1}, which also takes into account the non-bonding interactions of the methyl side chain. This large difference cannot be accounted for in terms of the inductive electronic effect of the trifluoromethyl group on the stability of an α-centred amino acid radical, which has been examined above.



85

Figure 2.10. The protected trifluoroalanyl radical **85** experiences significant distortions from planarity and consequently has a very low RSE.

The severe interaction of the protecting group with the side chain of the amino acid radical, indicated by the large difference in RSE of the protected and non-protected species, is visible in the minimum energy conformation of the protected radical **85** (Figure 2.10). This radical, like the protected *tert*-leucyl radical **83**, shows a severe distortion from planarity of the amino acid backbone (Figure 2.11), which is indicative of exceedingly unfavourable interactions of the side chain with the amide carbonyl of the acyl protecting group. The amide group is twisted 21° from the plane of the radical **85**, as measured by the C(O)-N-C^{α}-C^{β} dihedral angle. This is accompanied by a slight pyramidalisation of the amide nitrogen, as was also seen in the protected *tert*-leucyl radical **83**. Twist of the backbone is also evident from the (CH_3)O-C-C^{α}-C^{β} dihedral

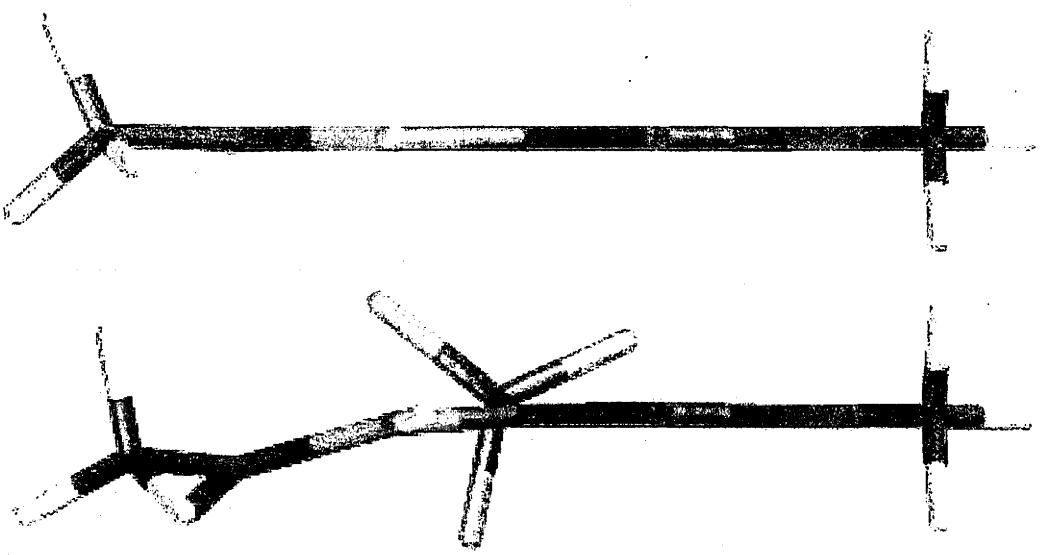
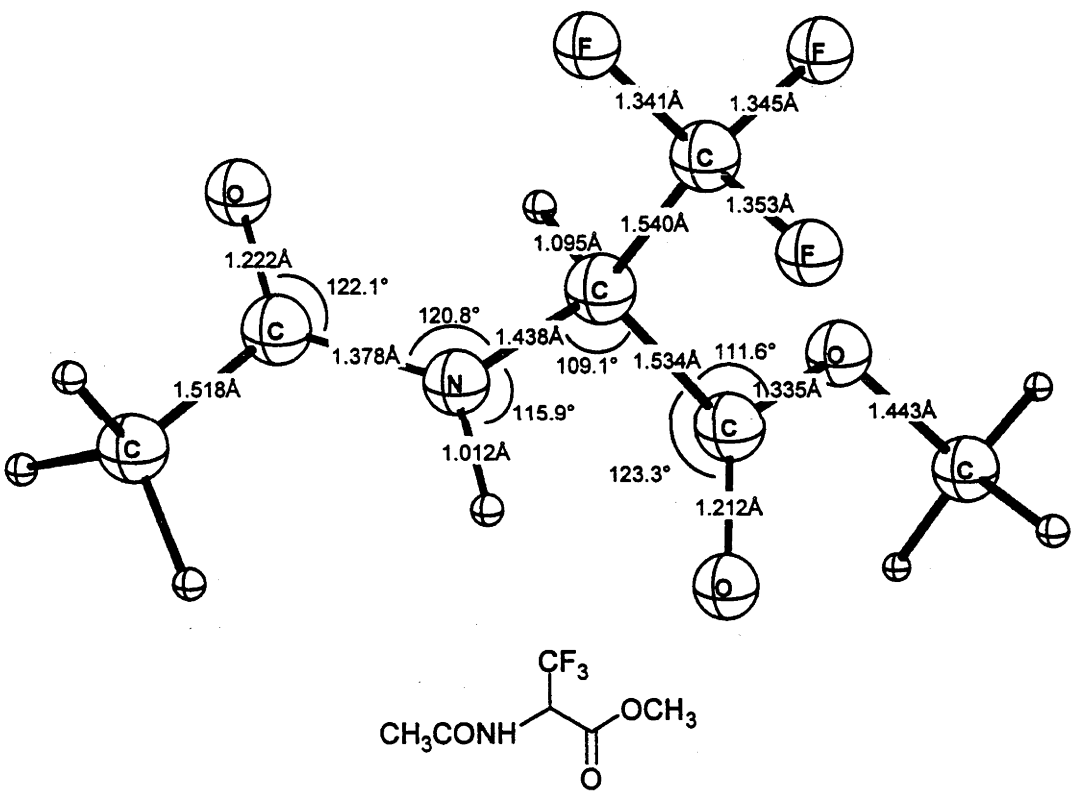


Figure 2.11. The protected trifluoroalanyl radical **85** (bottom) exhibits distortion of the amino acid backbone from planarity, compared with the glycine derivative **73** (top), due to unfavourable interactions with the trifluoro moiety.

angle of –7.5°. Despite the presumed alleviation of some of the unfavourable interactions experienced by the radical **85** in the planar conformation, by the distortion from this planarity, the C(O)-N-C^{α} bond angle is fairly large, being 130.6°. This large bond angle is indicative of unfavourable interactions persisting in the minimum energy conformer.



CF_3

CH_3CONH OCH_3

O

97

Figure 2.12. The protected trifluoroalanine **97** is geometrically similar to its alanine counterpart **74**.

The protected trifluoroalanine **97** (Figure 2.12) is geometrically similar to its alanine counterpart **74**. However, some increase in steric compression is present, as evidenced

by changes in the some of the dihedral angles. It is noted that the C(O)-N-C^{α} bond angle is more consistent with that of an amide, being 120.8°, rather than the highly strained 130.6° seen in the radical **85**.

It is clear that there are severe non-bonding interactions present in the protected trifluoroalanyl radical **85** which are not present in the non-protected radical **84**, and that these interactions are those of the trifluoromethyl group with the amide carbonyl of the acetyl protecting group. The magnitude of these interactions is adequately reflected in the comparatively low RSE of the protected trifluoroalanyl radical **85**.

The RSEs for both the *tert*-leucyl and trifluoroalanyl radicals **83** and **85** are significantly lower than that of the corresponding valyl radical **77**. The rates of the radical bromination reactions of benzoyl-protected amino acids, which proceed *via* the α-centred radicals, tend to reflect the stability of these radicals. As a result, it was expected that the benzoylamino acids **86** and **87**, which are likely to show interactions of the protecting group with the side chain in the intermediate radicals similar to those seen in the acetyl-protected radicals **83** and **85**, would brominate much more slowly than the benzoylvaline **8**. Competitive bromination reactions of the benzoyl-*tert*-leucine **86** and the benzoyltrifluoroalanine **87** with the corresponding benzoylvaline **8** resulted in the benzoylvaline **8** reacting to the exclusion of the *tert*-leucine **86** and the trifluoroalanine **87**. This implies a greater than tenfold selectivity for the formation of the α-centred valyl radical **11**, when compared with the formation of those of *tert*-leucine **86** and trifluoroalanine **87** which is consistent with that which would have been expected from the theoretical calculations. More importantly, the introduction of the *tert*-butyl and trifluoromethyl side chains has decreased the rate of reaction, when compared with that of the *N*-benzoylglycine **6**, by more than two hundred times. This 200-fold selectivity for glycyl radical formation emphasises the significant effect that the interaction of the side chain with the protecting group has on the formation of α-centred radicals in protected amino acid derivatives and peptides.

In general, the correlation that rate of reaction has with the calculated radical stability has been shown to be fairly consistent. Based on this correlation, it would be expected that the rates of bromination of the trifluoroalanine **87** and *tert*-leucine **86** would be similar, since the difference in the RSEs of the trifluoroalanyl radical **85** and *tert*-leucyl radical **83** is only 1.8 kJ mol^{-1}. Yet, when each of the benzoylamino acids **86** and **87** was allowed to react separately, the *tert*-leucine derivative **86** brominated cleanly to give the corresponding bromide **107** whilst, under the same conditions, the trifluoroalanine derivative **87** did not show any signs of having reacted after 9 hours. This suggests that the reactivity difference is greater than the twofold difference that would be predicted by the theoretical calculations. This difference in reactivity indicates that there are peculiar factors which appear to affect the rate of reaction of the trifluoroalanine **87**.

A rationalisation of the slow rate of reaction of the trifluoroalanine **87** is possible through consideration of the transition state of the bromination reaction. As hydrogen is being abstracted from the α-centre, this centre becomes polarised (Figure 2.13). The build up of positive charge is highly disfavoured by the strongly electron withdrawing trifluoromethyl substituent and this increases the activation energy of the reaction by significant amounts. These polar effects are no longer present in the uncharged radical, and so are not reflected by the calculated RSE.

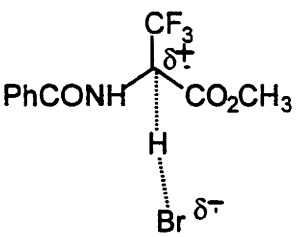


Figure 2.13. This transition state is disfavoured, compared to those of other similar derivatives, by the highly electron withdrawing trifluoromethyl substituent.

An additional explanation, also incorporating transition state effects, may be that the negatively charged fluorines exert a sufficient electrostatic effect to repel the also negatively charged bromine atom. This will hinder close approach of the bromine to the reaction centre and raise the activation energy required for the reaction to proceed.

The results from Chapter One indicate that there are unfavourable interactions between the side chain and the protecting group of protected amino acid radicals that result in diminished stability of these radicals. The exacerbation of this effect, as presented in this chapter, has led to unambiguous evidence for the importance of such interactions with differences in the stabilities of the non-protected radicals **82** and **84** and the protected radicals **83** and **85** of around 50 kJ mol^{-1}. These effects were shown to be severe enough to distort the minimum energy conformations of the protected radicals **83** and **85** from the preferred planar orientations seen in the minimum energy conformers of the radicals **73, 75, 77**, which are less affected by unfavourable non-bonding interactions. Yet, despite these distortions in the radicals **83** and **85** to avoid these unfavourable interactions, persistence of some of these steric effects is still reflected in the large 130° (O)C-N-C^{α} bond angles in the radicals **83** and **85**, compared with the 120° bond angle in the corresponding protected amino acids **81** and **97**. These severe non-bonding interactions seen theoretically are also reflected in the experimental rates of reaction of the corresponding benzoylamino acids **86** and **87**, which react at least ten times slower than the benzoylvaline **8**, and at least 200 times slower than the *N*-benzoylglycine **6**.

3

Effects of Different *N*–Protecting Groups on the Stability of Protected Glycyl Radicals—A Theoretical and Experimental Examination

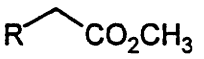
The results presented in Chapters One and Two show how an amino acid *N*-protecting group can have through space interactions with the side chain of the amino acid residue which destabilise the α-centred radical. In this chapter the effect of through bond interactions of the amide protecting group of an amino acid on the α-centred radical stability is explored. Particularly, how the stability of acyl-protected glycyl radicals correlates with the pK_a of the carboxylic acids that correspond to the acyl protecting groups is examined in detail, and also how this extrapolates to sulfonic acids and their corresponding sulfonamides. Amides and sulfonamides are examined both theoretically and experimentally, to delineate the important factors affecting the stability of acyl- and sulfonyl-protected glycyl radicals.

In addition, the α-centred radicals of phthaloyl-protected amino acids have been shown experimentally to be relatively unstable, compared with those of acyl-substituted amino acids.[8,9,11,38,48,74] A comparison of the stability of phthaloylglycyl radicals with acyl- and sulfonyl- protected glycyl radicals is presented as part of this chapter, along with a detailed theoretical examination of the ways in which a phthaloyl protecting group affects the stability of a radical at the adjacent centre.

Results

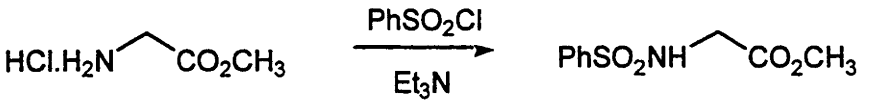
To examine the relative rates of reaction of acyl- and sulfonyl-protected glycines, the compounds **6** and **110–112** were prepared and their reactions with NBS were

investigated. The phthaloylglycine derivative **113** was available as a generous gift[134] and its reaction with NBS was also investigated.



6 R = PhCONH
110 R = CF_3CONH
111 R = $PhSO_2NH$
112 R = CF_3SO_2NH
113 R = $C_6H_4(CO)_2N$

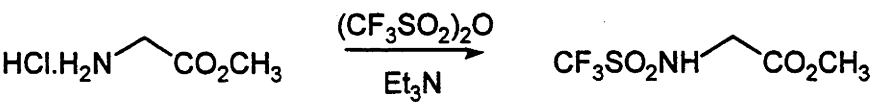
Treatment of glycine methyl ester hydrochloride salt **114**, suspended in dichloromethane, with benzenesulfonyl chloride and triethylamine afforded the benzenesulfonylglycine **111** as colourless needles. Its identity was confirmed by comparison with literature data[214] and the benzenesulfonyl moiety was readilyapparent from the presence of peaks at δ7.50–7.63 and δ7.85–7.88 in the ^1H NMR spectrum corresponding to the phenyl group.



114 **111**

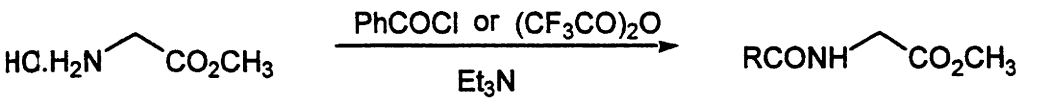
The triflylglycine **112** was prepared by treatment of the hydrochloride salt of glycine methyl ester **114** with triethylamine and then triflic anhydride. The product was isolated as yellow grains, which were fully characterised and showed spectral data consistent with triflamide protection, such as a quartet in the ^{13}C NMR spectrum at δ120.0, attributable to the trifluoromethyl carbon, split by coupling to the attached flucines. As

the triflylglycine **112** does not contain a chromophore, it was initially difficult to monitorthe reaction by TLC. However, it was discovered that a basic, aqueous dip containing potassium permanganate[215] gave excellent visualisation of all triflyl derivatives presented in this thesis.



114 **112**

To carry out competitive bromination reactions, samples of *N*-benzoylglycine methyl ester **6** and *N*-trifluoroacetylglycine methyl ester **110** were required to provide comparisons with the earlier work.[37] These compounds were both prepared using standard methods, namely through treatment of the hydrochloride salt of glycine methyl ester **114** under basic conditions with either benzoyl chloride or trifluoroacetic anhydride to afford the corresponding protected derivatives **6** and **110**, respectively. These were identified by comparison with literature data.[37,216]

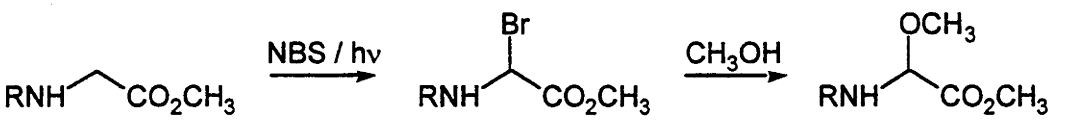


114

6 R = Ph
110 R = CF_3

Treatment of each of the glycine derivatives **6**, **110** and **111** with NBS, and irradiation with a 300W sunlamp, afforded the corresponding bromides **12**, **115** and **116**. Bromination times varied from 10 minutes for reaction of the benzoylglycine **6** to 1 hour

for complete bromination of the trifluoroacetylglycine **110**. The benzenesulfonylglycine **111** began to decompose if left to react for longer than around 15 minutes. The bromides **12, 115** and **116** were each identified from the crude reaction mixtures by characteristic doublets, attributable to the α-protons, at around δ6.3–6.7 in their ^{1}H NMR spectra. However, all were unstable and were converted to the corresponding α-methoxides **117–119** for characterisation. This was achieved by treatment of the crude bromination mixtures with methanol and allowing the mixtures to stir for 2 hours.



6 R = PhCO
110 R = CF_3CO
111 R = $PhSO_2$

12 R = PhCO
115 R = CF_3CO
116 R = $PhSO_2$

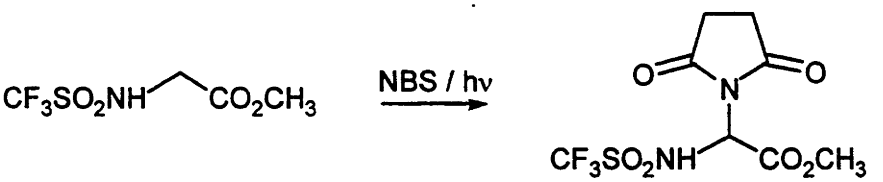
117 R = PhCO
118 R = CF_3CO
119 R = $PhSO_2$

The melting point of the *N*-benzoyl-α-methoxyglycine derivative **117** varied by more than 10 °C from the literature value.[216] However, the ^{1}H NMR spectral data were consistent with the α-methoxide **117**, showing a characteristic methyl signal for the α-methoxy moiety at δ3.56. Elemental composition was confirmed through microanalysis.

The benzenesulfonyl-α-methoxyglycine **119** was difficult to characterise due to rapid decomposition. However, the ^{1}H NMR spectrum of the crude methoxide **119** showed that it had been produced in 85% yield by comparison of the integration of the characteristic methoxy peak at δ3.30 with the integration of the signal from an internal standard. High resolution mass spectrometry confirmed the composition of two ions, one of which corresponds to loss of a single methoxy group ($M^{+\bullet}$–31, 228) and the other of which corresponds to loss of the entire methoxycarbonyl group ($M^{+\bullet}$–59, 200). The latter fragment confirms that the compound isolated is indeed the benzenesulfonyl-

α-methoxyglycine **119**. The trifluoroacetyl-α-methoxyglycine **118** had identical physical and spectroscopic properties to those reported in the literature.[37]

Treatment of the triflylglycine **112** with NBS, and irradiation with a 300W sunlamp, required more than 24 hours for the compound **112** to be completely consumed. At the end of this time the reaction was a dark brown colour, indicating the presence of bromine. The ^{1}H NMR spectrum of the crude reaction mixture was uncomplicated by decomposition products and showed a distinct doublet at δ6.08. Treatment of this crude mixture with methanol indicated no apparent reaction. Chromatography of this mixture lead to isolation of the α-succinimide **120**. This derivative gave a ^{1}H NMR spectrum containing the doublet at δ6.08, but additionally contained a singlet of four proton intensity at δ2.83, indicative of a succinimido substituent. This was confirmed as part of the molecule by the presence of the appropriate parent ion in both the positive and the negative ion electrospray mass spectra.



112 **120**

Relative rates of reaction were obtained by treating equimolar mixtures of pairs of the glycine derivatives **6** and **110–113** with one equivalent of NBS in carbon tetrachloride. Approximately half an equivalent of *N-tert*-butylbenzamide was used as an internal standard. Each mixture was heated to reflux and irradiated with a 300W sunlamp. ^{1}H NMR spectra of the initial and final reaction mixtures were compared. The relative amounts of starting material consumed and product formed were determined by measuring the integrations of a distinctive signal for each compound, relative to that of

the internal standard. Calculation of the relative rates was achieved by using Equation 4 (p. 8). Each experiment was done in triplicate and the results varied by less than 20% each time with a mass balance of over 80%. The largest source of error is thought to be the accuracy of the integration measurements of the signals in the ^{1}H NMR spectra. The relative rates of reaction of the glycine derivatives **6** and **110–113** are shown below (Table 3.1).

Table 3.1. Relative rates of reaction of a variety of glycine derivatives with NBS.

$RCH_2CO_2CH_3$		Relative Rate of Reaction with NBS
Compound	R	
6	PhCONH	1[†]
111	$PhSO_2NH$	0.6
110	CF_3CONH	0.05[‡]
112	CF_3SO_2NH	< 0.005
113	PhthN	< 0.0005

[†] Assigned as unity. [‡] Previous work.[37]

The benzenesulfonylglycine **111** reacted around half as fast as the corresponding benzoylglycine **6** in competitive experiments. The triflamide **112** did not react at all when compared with the benzamide **6**. When compared with the trifluoroacetylglycine **110**, the least reactive of the glycine derivatives already investigated,[37] the triflamide **112** did not react either. Thus, it was concluded that the rate of reaction of the triflamide **112** must be, conservatively, at least ten times slower than that of the trifluoroacetamide

110. In contrast, the triflylglycine **112** reacted to the exclusion of the phthaloylglycine **113** in competitive studies, indicating that the phthaloylglycine **113** must react at least ten times slower again than the triflamide **112**.

Computations on the *N*-methylamides **121**, **62** and **122**, *N*-methylimides **123** and **124** and *N*-methylsulfonamides **125–127** and their corresponding glycine methyl ester derivatives **72**, **110**, **128–131** and **112**, and the α-carbon centred radicals derived from all these molecules, were carried out to yield both structural information and radical stabilisation energies. Additionally, *N*-ethylmaleimide **132** and *N*-maleylalanine methyl ester **133** were also examined theoretically. Calculation of minimum energy conformations was carried out using the density functional method B3-LYP/6-31G(d) with subsequent calculation of the single point energies at RMP2/6-31G(d), as described in Chapter One (p. 41). The results of these calculations are shown below (Table 3.2, Table 3.3 and Table 3.4).

Table 3.2. Stabilisation energies for the glycyl methyl ester radical **134** and the α-centred radicals of the *N*-acyl- and *N*-sulfonyl-glycine methyl esters **128**, **72**, **110**, **130**, **131** and **112**.

$RC^{\bullet}HCO_2CH_3 + CH_4 \rightarrow RCH_2CO_2CH_3 + {}^{\bullet}CH_3$			Energies (kJ mol^{-1})		
$RCH_2CO_2CH_3$	$RC^{\bullet}HCO_2CH_3$	R	RSE	ZPE correction	RSE(0 K)
66[†]	**134**	NH_2	100.2	–6.2	94.0
128	**135**	HCONH	87.2	–7.6	79.6
72[†]	**73**	CH_3CONH	89.7	–7.5	82.2
110	**136**	CF_3CONH	79.8	–7.0	72.8
130	**137**	HSO_2NH	77.3	–4.8	72.5
131	**138**	CH_3SO_2NH	79.2	–5.2	74.0
112	**139**	CF_3SO_2NH	71.3	–5.3	66.0

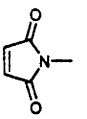
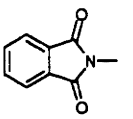
[†]Results reproduced from Chapter One.

Table 3.3. Stabilisation energies for aminomethyl radical **140** and the *N*-acyl- and *N*-sulfonyl-aminomethyl radicals **63** and **141–145**.

$RC^{\bullet}H_2 + CH_4 \rightarrow RCH_3 + {}^{\bullet}CH_3$			Energies (kJ mol^{-1})		
RCH_3	$RCH_2^{\bullet}$	R	RSE	ZPE correction	RSE(0 K)
146	**140**	NH_2	48.6	–3.9	44.7
121	**141**	HCONH	39.2	–2.3	36.9
62	**63**	CH_3CONH	39.7	–2.3	37.4
122	**142**	CF_3CONH	37.0	–3.3	33.7
125	**143**	HSO_2NH	30.9	–2.2	28.7
126	**144**	CH_3SO_2NH	30.7	–2.7	28.0
127	**145**	CF_3SO_2NH	27.4	–2.0	25.4

Table 3.4. Stabilisation energies of a variety of imido protected radicals.

	$XC^{\bullet}RY + CH_4 \rightarrow XCHRY + CH_3^{\bullet}$				Energies (kJ mol^{-1})		
XCHRY	$XC^{\bullet}RY$	X	Y	R	RSE	ZPE	RSE(0 K)
123	**147**	Maleyl	H	H	30.1	–1.6	28.5
124	**148**	Phthaloyl	H	H	31.3	–2.0	28.8
132	**149**	Maleyl	H	CH_3	28.2	–0.8	27.4
129	**150**	Maleyl	CO_2CH_3	H	37.8	–4.6	33.2
133	**151**	Maleyl	CO_2CH_3	CH_3	49.6	–3.6	46.0

Maleyl =  Phthaloyl = 

Discussion

The magnitude of a pK_a of a carboxylic acid is intimately related to the electron-withdrawing or electron-donating nature of the acyl portion, as is the electronic effect exerted by an acyl-protecting group of an amino acid. This electronic effect has been shown specifically to correlate with the rate of formation of α-centred amino acid radicals.[37] By examining the RSEs of α-centred radicals, the influence that an acyl protecting group has on the radical stability can be ascertained. The RSEs of three acyl-protected glycyl radicals were examined, namely those of the formyl-, acetyl- and trifluoroacetyl-glycyl radicals **135**, **73** and **136**, which were 79.6 kJ mol^{-1}, 82.2 kJ mol^{-1} and 72.8 kJ mol^{-1}, respectively. By comparing with the pK_as of the corresponding carboxylic acids, it can be seen that there is a correlation of the pK_a of the acid and the RSE of an acyl-protected glycine (Table 3.5) such that an increased pK_a value entails a higher RSE.

Table 3.5. Comparison of the RSEs calculated for the acyl-protected glycyl radicals **73**, **135** and **136** with the pK_as of the corresponding carboxylic acids.

	RCONHC$^{\bullet}$HCO$_2$CH$_3$		
R	Radical	RSE	pK_a of RCO$_2$H
CH_3	**73**	82.2	4.8
H	**135**	79.6	3.7
CF_3	**136**	72.8	0.5

To further investigate the extent of this correlation, the sulfonyl-protected glycines **138**, **137** and **139** were examined. Sulfonic acids are much more acidic than the corresponding carboxylic acids with comparable substituents. By examining the RSEs of the sulfonamide-protected glycyl radicals **138** and **139** it can be seen that a correlation of RSE with the pK_a of the corresponding sulfonic acid exists (Table 3.6). The hydrogensulfonamide **137** does not have a corresponding sulfonic acid. However, the electronic effect of hydrogen is likely to be quite similar to that of the methyl group, suggesting that the pK_a of hydrogensulfonic acid would be similar to that of methanesulfonic acid. The similar RSEs of the glycyl radicals **138** and **137** are inconsistent with this.

Table 3.6. Comparison of the RSEs of the sulfonylglycyl radicals **138**, **137** and **139** with the pK_as of the corresponding sulfonic acids.

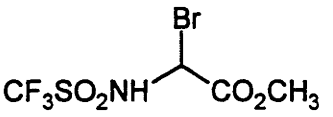
$RSO_2NHC^{\cdot}HCO_2CH_3$			
R	Radical	RSE	pK_a of RSO_3H
CH_3	**138**	74.0	–1.9
H	**137**	72.5	n/a
CF_3	**139**	66.0	–5.5

Despite the good correlations with pK_a within the series of RSEs of acyl-protected and sulfonyl-protected glycyl radicals, a direct cross-correlation between the RSEs of the carbonyl and sulfonyl protected derivatives and their pK_as does not appear to exist. For instance, the RSE of the methanesulfonamide **138** is almost the same as that of the trifluoroacetamide **136**, whereas the corresponding pK_as of methanesulfonic acid and trifluoroacetic acid are different by almost 2.5 units. The reason for this discrepancy is

likely to be that the factors which affect the RSEs of amides and sulfonamides are different to those which affect carboxylate and sulfonate formation. In particular, greater charge delocalisation in sulfonates, relative to carboxylates, is likely to be a factor that is reflected in the pK_as of the corresponding acids but not in the RSEs of the corresponding radicals.

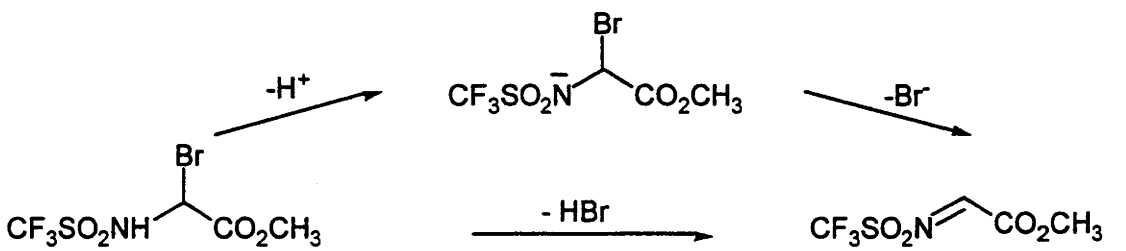
By examining the RSEs of the *N*-protected aminomethyl radicals **63** and **141–145**, it can be seen that these generally follow a similar pattern of stabilities to those of the corresponding glycyl radicals **73** and **135–139**, except that the effects of *N*-acyl- and *N*-sulfonyl-protection on the adjacent radicals are not as large as when the carboxymethyl group is present. For instance, whereas the difference between the RSEs of the acetyl-protected glycyl radical **73** and the trifluoroacetyl-protected glycyl radical **136** is 9.4 kJ mol^{-1}, the difference in RSEs between the *N*-methylacetamide radical **63** and *N*-methyltrifluoroacetamide radical **142** is less than half that. The indication is that the electronic effect of the protecting group becomes more important when greater dative stabilisation is required, because of the presence of the electron-withdrawing methoxycarbonyl group. This is consistent with the observations made in Chapter Two (p. 94) regarding the increased dative contribution required from the nitrogen of the trifluoromethylamine radical **93** or that of the trifluoroalanyl radical **84** to stabilise these radicals, due to the presence of the electron-withdrawing trifluoromethyl substituent.

Relative rates of reaction were measured for the reactions with NBS of the protected glycines **6** and **110–112**. The glycine derivatives **6**, **110** and **111** gave the corresponding bromides **12**, **115** and **116**. The triflylglycine **112** afforded the α-succinimide **120**, in place of the α-bromide **152**. As the other compounds brominated, it can be presumed that the succinimide **120** is formed *via* the α-bromide **152**.



152

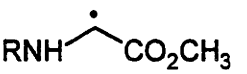
The replacement of the bromine of the glycine **152** with succinimide is unusual. The mechanism of this replacement is unlikely to be nucleophilic substitution, as this would involve an electron deficient α-carbon centre in the intermediate or transition state. This is less likely to occur with the triflamide **152** than with any other of the protected amino acids **12**, **115** and **116**. However, deprotonation of the amide **152**, either in a concerted or stepwise manner with elimination of bromide ion (Scheme 3.1), is likely to be facile as the pK_a of triflamides is known to be low.[130,217–219] Subsequent addition of succinimide to the product imine **153** will result in formation of the succinimidylglycine **120**. Such an imine intermediate **153** is very similar to that described in Chapter Two in the formation of the alkene **105** from the sulfone **104** (p. 78).



152 153

Scheme 3.1. The mechanism of formation of the sulfonylimine **153** (right) can be envisaged as proceeding though either a stepwise or concerted elimination of HBr. The succinimide derivative **120** would then be produced by addition of succinimide to the sulfonylimine **153**.

Formation of the bromides **12**, **115** and **116** indicates that the reactions with NBS of the protected glycines **6** and **110–112** proceed *via* the corresponding α-centred radicals **9**, **154**, **136** and **139**. By comparing the RSEs of these α-centred radicals **9**, **154**, **136** and **139** with the relative rates of reaction of the glycines **6** and **110–112** the degree to which radical stability affects these rates can be delineated.



9 R = PhCO
154 R = $PhSO_2$
136 R = CF_3CO
139 R = CF_3SO_2

RSEs of the benzoylglycyl radical **9** and the benzenesulfonylglycyl radical **154** are not known. However, the pK_as of benzoic acid and acetic acid are similar, as are the pK_as of benzenesulfonic acid and methanesulfonic acid, and the correlation between the pK_a and RSE within a series has already been established. Therefore, it is assumed that the RSEs of the glycyl radicals **9** and **154** are quite similar to those of the acetylglycyl radical **73** and the methanesulfonylglycyl radical **138**.

The relative rates of reaction of the benzoylglycine **6** and the trifluoroacetylglycine **110** seem to correlate well with the RSEs of the acetylglycyl radical **73** and the trifluoroacetylglycyl radical **136**. Similarly, the relative rates of reaction of the benzenesulfonylglycine **111** and the triflylglycine **112** correlate with the RSEs of the methanesulfonylglycyl radical **138** and the triflylglycyl radical **139**. These results suggest a reasonable correlation of RSEs with rates of reaction.

Table 3.7. Variation of the relative rates of reaction, with the pK_as of the corresponding acids.

$RNHCH_2CO_2CH_3$	R	X	Relative Rate of Reaction of $RNHCH_2CO_2CH_3$	RSE of $XNHC^{\cdot}HCO_2CH_3$	pK_a	
					ROH	XOH
6	PhCO	CH_3CO	1[†]	82.2	4.20	4.76
111	$PhSO_2$	CH_3SO_2	0.6	74.0	–2.8	–1.9
110	CF_3CO	CF_3CO	0.05[‡]	72.9	0.52	0.52
112	CF_3SO_2	CF_3SO_2	<0.005	66.0	–5.5	–5.5

[†] Assigned as unity. [‡] From previous work.[37]

A closer inspection of the correlation of RSEs with relative rates of reaction reveals an inconsistency between the relative rates of reaction of the acylglycines **6** and **110** and the sulfonylglycines **111** and **112**. The differences in the relative rates of reaction of the benzenesulfonylglycine **111** and the trifluoroacetylglycine **110** are over an order of magnitude different, whereas the RSEs of the methanesulfonylglycyl radical **138** and the trifluoroacetylglycyl radical **136** are comparable. This suggests a transition state effect in the reactions of the sulfonamides **111** and **112** which differs from that in the reactions of the amides **6** and **110**. The concept of differing transition state effects is reasonable since the electronic distribution in a sulfonamide is very different from that in an amide. The hydrogen abstraction step of bromination reactions is known to have a polarised transition state. Therefore, the differing electronic distributions in the amides and sulfonamides will result in different extents of polarisation, which are likely to have significant effects on the relative rates of reaction.

There appear to be two mechanisms that govern the relative stabilities of α-centred radicals in glycine derivatives. The first is the competitive conjugation of the nitrogen

electrons, which has been noted in the Introduction (p. 20) and Chapter One (p. 56). This has been shown to be a major factor in explaining the lowered stability of α-centred-α-amido radicals with respect to α-centred-α-amino radicals. The second is the absence or presence of an electron deficient centre adjacent to the nitrogen. Both of these mechanisms work *via* the electronic framework of the molecule. It can be seen that such effects are important in determining the stability of α-centred amino acid radicals. The variance of the substituent can also have a significant influence on the stability of the adjacent radical and the magnitude of the effect, within a series, is reflected in the pK_a of the acid corresponding to the protecting group.

Phthaloyl protecting groups have been described in the literature as making an adjacent centre less susceptible to radical formation, through steric interactions and electronic effects.[38,74] Theoretical methods allow us to delineate some of these effects and understand their relative contributions to the stability of adjacent radical centres.

The contribution to radical stability that electronic effects have can best be examined in systems that are free from steric interactions, such as the *N*-methylamine **146**, the *N*-methylamide **62** and the *N*-methylimides **123** and **124**. An examination of the RSEs of the imide radicals **147** and **148** (Table 3.8) reveals that the effect on the radical stabilisation by the maleyl and phthaloyl substituents is computationally indistinguishable. This implies that the maleyl substituent is a good theoretical model for the electronic nature of the phthaloyl substituent. This is fortuitous since the phthaloyl group provides a challenge to current computational resources due to its size. The maleyl substituent is much more manageable in this regard and allows calculation of more complex molecules for considerably less computational cost.

The results reproduced in Table 3.8 also allow delineation of the effect of increasing acyl substitution on the nitrogen adjacent to the radical centre on the RSEs. Acyl protection of the aminomethyl radical **140** to form the methylacetamide radical **63** results in a decrease in the stabilisation afforded the radical by 7.3 kJ mol^{-1}. Similarly,

on comparing the RSEs of the methylacetamide radical **63** and the *N*-methylmaleimide radical **147**, the additional acyl protecting group is seen to cause a decrease in stabilisation of the adjacent radical centre of 8.9 kJ mol^{-1}. These decreases in relative RSEs in the series **140**, **63** and **147** are consistent with the nitrogen electrons being increasingly delocalised over the acyl substituents and therefore less available to provide dative stabilisation to the radical centres.

Table 3.8. The electronic effect of acyl substitution on the stabilisation of the adjacent radical.

$RC^{\bullet}H_2 + CH_4 \rightarrow RCH_3 + {}^{\bullet}CH_3$			RSE (kJ mol^{-1})
RCH_3	$RC^{\bullet}H_2$	R	
146	**140**	NH_2	44.7
62	**63**	CH_3CONH	37.4
123	**147**	Maleyl	28.5
124	**148**	Phthaloyl	28.8

When the RSEs of the protected glycyl derivatives **134**, **73** and **150** are compared, decreased stability with increased acyl substitution is seen, as it was for the corresponding *N*-methylamine radical **140**, *N*-methylamide radical **63** and *N*-methylimide radical **147**. On going from no acyl protection in the free amine **134** to one acyl substituent in the glycine **73**, the stability of the α-centred radical **134** is diminished by 12.1 kJ mol^{-1}. The magnitude of this diminished stability is increased with respect to the corresponding *N*-methylamine radical **140** and *N*-methylimide radical **63**, where it was only 7.3 kJ mol^{-1}. This is consistent with the increased significance of the electronic nature of the amide protecting group on the stability of radicals, seen

earlier in this chapter (p. 113), on going from *N*-methyl radicals **63** and **141–145** to the corresponding glycyl radicals **73** and **135–139**.

Table 3.9. The electronic effect of acyl substitution on the stabilisation of α-centred glycyl radicals.

$RC^{\bullet}HCO_2CH_3 + CH_4 \rightarrow RCH_2CO_2CH_3 + {}^{\bullet}CH_3$			RSE (kJ mol^{-1})
$RCH_2CO_2CH_3$	$RC^{\bullet}HCO_2CH_3$	R	
66	**134**	NH_2	94.0
72	**73**	CH_3CONH	82.2
129	**150**	Maleyl	33.2

The RSEs calculated for the radicals derived from maleylglycine **129** and acetylglycine **72** show that there is a very large difference in the stabilisation afforded the α-centred radicals **150** and **73** of almost 50 kJ mol^{-1}. This is unlikely to be due solely to electronic effects, based on the radical stabilities of the corresponding *N*-methylimide radical **147** and *N*-methylamide radical **63**. The reason for the extreme effect on α-centred radical stability of protection by the maleyl substituent in the *N*-maleylglycine **129** is readily apparent upon examination of the lowest energy conformer of the radical **150**. This structure shows that the plane of the maleimide ring of the maleylglycyl radical **150** is twisted at a 39.4° angle from the plane of the amino acid backbone.

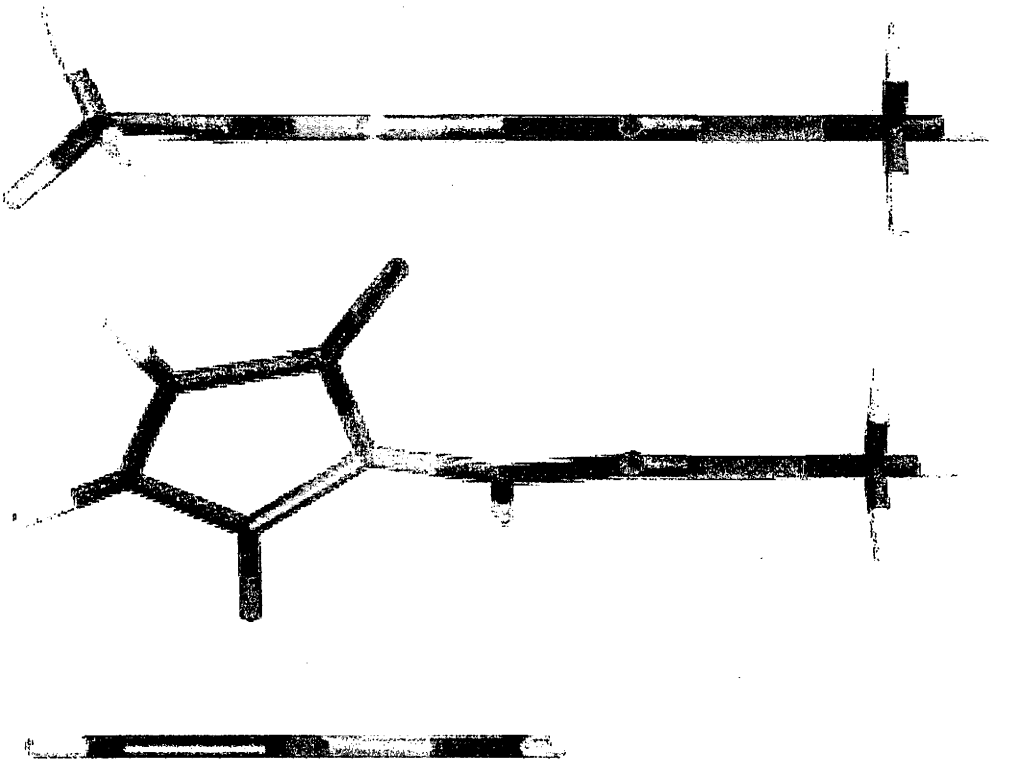


Figure 3.1. The imide moiety of **150** (centre) is seen to twist out of the plane of the radical due to interactions with the ester carbonyl. This behaviour is not observed in either the acetylglycyl radical **73** (top) or the *N*-methylmaleimide radical **147** (bottom).

The twist in the backbone is readily apparent when the structure of the maleylglycyl radical **150** is compared with that of the acetylglycyl radical **73** (Figure 3.1). It suggests that there are significant unfavourable non-bonding interactions in the maleylglycyl radical **150** between the maleimide and the carboxymethyl groups. This is supported by examining the structure of the *N*-methylmaleimide **147**. The preferred geometry of *N*-methylmaleimide **147** is the C_{2v} structure which is planar, allowing the imide π-orbitals to achieve maximum overlap with that of the radical (Figure 3.2). This indicates that the non-planar structure seen in the maleylglycyl radical **150** is likely to be less stable.

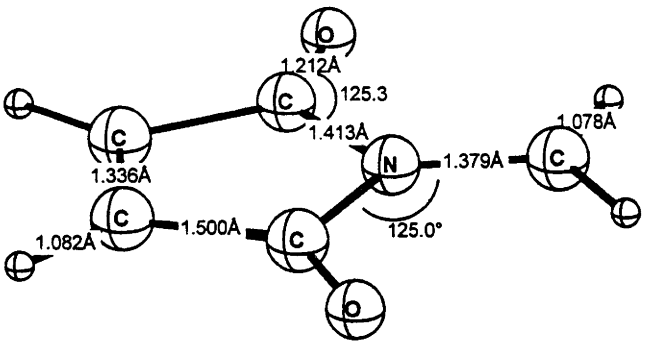


Figure 3.2. The minimum energy (C_{2v}) conformer of the *N*-methylmaleimide radical **147**.

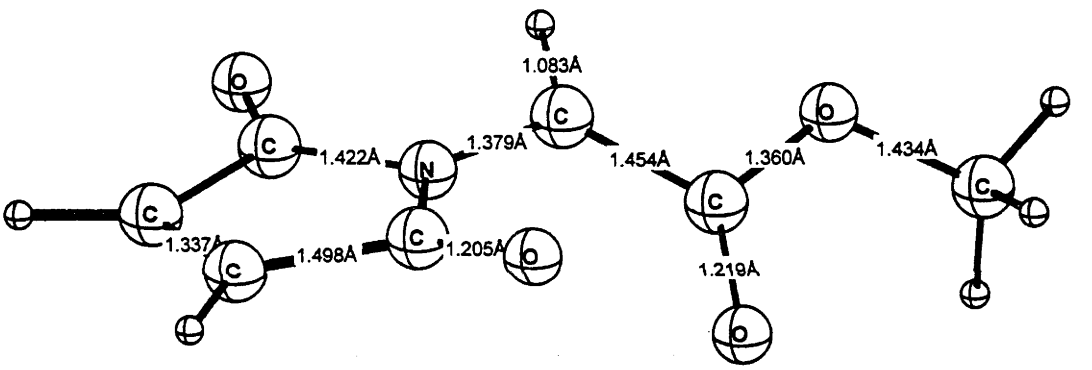


Figure 3.3. The optimised structure of the maleylglycyl radical **150**.

The twist in the backbone of the maleylglycyl radical **150** is similar to that seen in the similarly unstable protected *tert*-leucyl and trifluoroalanyl radicals **83** and **85** (Chapter Two). The lower RSE of the maleylglycyl radical **150** relative to that of the acetylglycyl radical **73**, than could be accounted for by way of electronic effects, is consistent with destabilisation from steric interactions, as seen in the radicals **83** and **85**.

Interactions of amino acid side chains with the amide protecting group have already been shown to cause a destabilising influence on the corresponding α-centred amino acid

radicals in Chapters One and Two. Clearly, interactions of the maleyl protecting group with the carboxymethyl in the maleylglycyl radical **150** are important in affecting the stability of this radical. To examine the possible effects on RSE of a side chain interaction with the maleyl protecting group, the maleylalanine **133** and the *N*-ethylmaleimide **132** were also examined.

When the RSE of the *N*-ethylmaleimide radical **149** is compared with that of the *N*-methylmaleimide radical **147**, it is observed that there is very little difference. The *N*-ethylmaleimide radical **149** is 1.1 kJ mol^{-1} less stable than the *N*-methylmaleimide radical **147**. This is contrary to the increase of around 13 kJ mol^{-1} that would be expected from the addition of a methyl substituent, based on the difference in the RSEs of the ethyl radical **89** and methyl radical, of 13.2 kJ mol^{-1}. This disparity is therefore likely to be attributable to unfavourable non-bonding interactions. An examination of the lowest energy conformer of the *N*-ethylmaleimide radical **149** shows that there are indeed steric interactions of the ethyl side chain with the maleimide (Figure 3.4).

To obtain maximal orbital overlap, the substituents around the radical centre should be coplanar, as for the *N*-methylmaleimide radical **147**. This is not the case in the corresponding ethyl radical **149** and the minimal energy conformer is one in which the methyl group attached to the radical centre is slightly out of the plane by 6.6°. This is presumably due to unavoidable steric interactions in the planar form of the radical. These unfavourable interactions are reflected in the bond angles around the imide bonds. The methyl group is seen to exert a repulsive force such that the C^{α}-N-C(O) and N-C=O bond angles are much larger where they are proximal to the methyl group, rather than to the hydrogen.

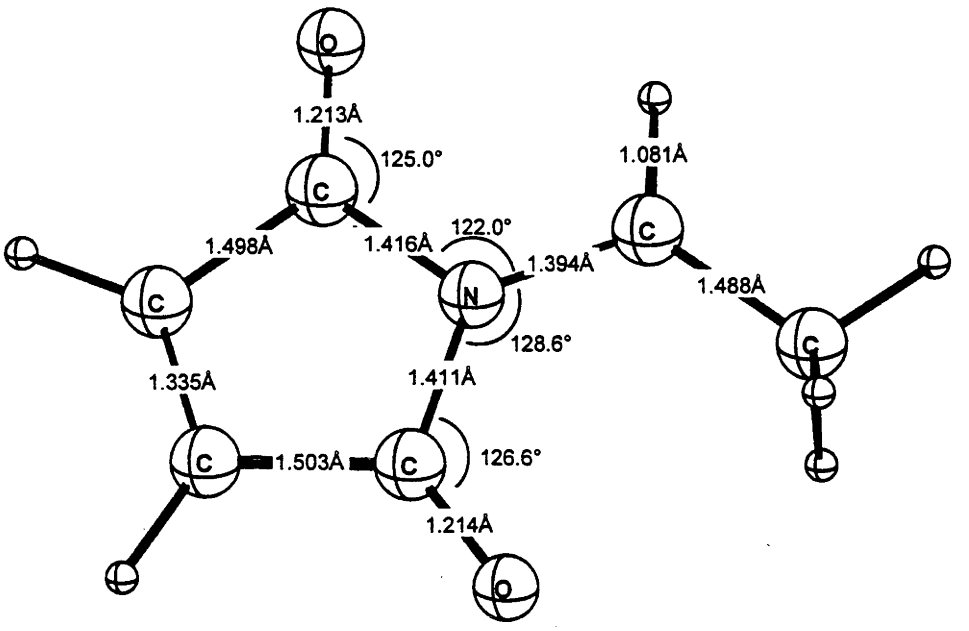


Figure 3.4. The optimised structure of the *N*-ethylmaleimide radical **149**.

The maleylalanyl radical **151** has a higher RSE than the corresponding glycyl radical **150**, by 12.8 kJ mol^{-1}. This is the expected difference in the stabilisation energy when a methyl substituent replaces a hydrogen in a radical, as reflected in the difference between the stabilisation energy of ethyl radical **89** compared with that of methyl radical, which is 13.2 kJ mol^{-1}. The structure of the maleylalanyl radical **151** indicates why this may be so (Figure 3.5).

There is a steric distortion, similar to that seen in the maleylglycyl derivative **150**, which presumably also accounts for the low stability of the maleylalanyl radical **151** compared with that of the acetyl-protected glycine **73**. The angle that the maleimide makes with the methyl and methoxycarbonyl plane is 50°. Once the maleimide has been twisted from the plane it is free to avoid steric interactions with the methyl group, without the penalty of distorting the π-orbital interactions any further. In this fashion, maximal

stabilisation, which now includes the methyl group, is possible, as reflected by the near planar alignment of the methyl group and the methoxycarbonyl group.

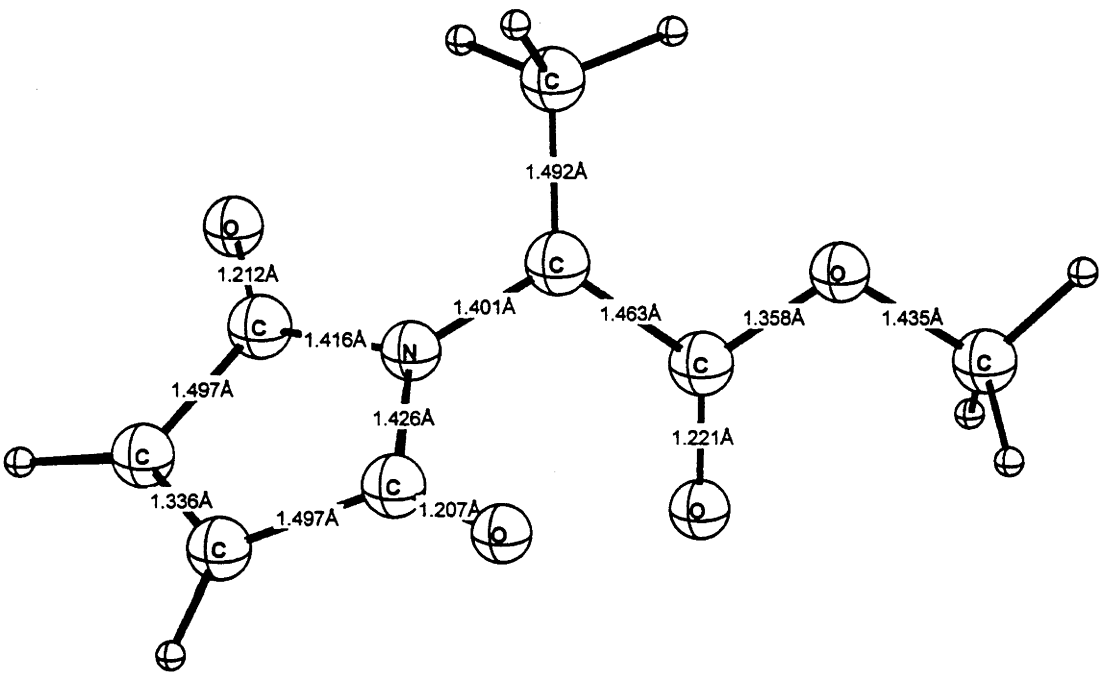
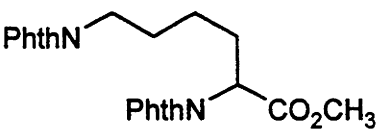


Figure 3.5. The maleylalanyl radical **151** shows the methyl and methoxycarbonyl substituents almost in plane with one another, however, the maleimide exhibits a 50° twist.

The RSE of the maleylglycyl radical **150** is much lower than that of the triflylglycyl radical **139**. Reactions of protected glycines with NBS proceed *via* the corresponding α-centred glycyl radicals and the degree to which radical stability affects these reactions can be gauged by examining the relative rates of reaction. In a competitive study under radical bromination conditions, the triflylglycine **112** reacted to the exclusion of the phthaloylglycine **113**. This is consistent with the rate of formation of the α-centred radicals **139** and **155** correlating with the corresponding RSEs of the glycyl radicals **139** and **150**.

This correlation of rate of reaction with RSE breaks down when the bromination reaction of the N^{α},N^{ε}-diphthaloyllysine **24** is examined. The lysine **24** brominates at the ε-position, as opposed to the α-centre.[134] The *N*-ethylmaleimide radical **149** is a good model of a side chain radical and its RSE can be compared against that of the maleylalanyl radical **151**, which is an appropriate model for an α-substituted amino acid centre, to determine the relative stabilities. The RSE of the *N*-ethylmaleimide radical **149** is only 27.4 kJ mol^{-1}, whereas that of the maleylalanyl radical **151** is 46.0 kJ mol^{-1}. This implies that a side chain radical adjacent to a phthaloyl protecting group would be less stable than the α-centred radical and this is inconsistent with the rates of formation observed experimentally.[134] This discrepancy has already been accounted for in the literature by the suggestion that the approaching hydrogen abstracting species interacts unfavourably with both the methoxycarbonyl substituent and the phthalimide, whereas there is much less interaction of the approaching abstracting species with only the phthalimido substituent.[38,74]



24

It has been shown, by the comparisons of the RSEs of a variety of related systems, that the factors which are involved in the very low reactivity of phthaloyl-protected amino acids are varied. Comparison of the RSEs of the *N*-methylamine radical **140**, *N*-methylamide radical **63** and the *N*-methylimide radical **147** showed that there is an electronic component of the radical stability due to the competing delocalisation of the nitrogen electrons with each addition of an *N*-acyl substituent. The large difference in RSEs between the *N*-acetyl and *N*-maleyl-glycyl radicals **73** and **150**, which cannot be accounted for by the electronic factors, is seen to be an effect of unfavourable non-

bonding interactions in the radical. These interactions result in distortion from the planar structure of the radical that would allow maximum π-orbital overlap. Finally, comparison of the RSEs of the *N*-ethylmaleimide radical **149** and the *N*-maleylalanine radical **151** with experimental observations of the reactivities of analogous centres in N^{α},N^{ε}-diphthaloyllysine **24** was made. The higher RSE of the α-alanyl centred radical **151**, compared to the derivative without the methoxycarbonyl substituent **149**, predicts the reverse reaction to that which was observed in literature bromination reactions.[134] This suggests that a transition state steric effect, such as that involving interaction with the approaching hydrogen abstracting species,[38] is another factor involved in the low reactivity of phthaloyl-protected amino acids.

4

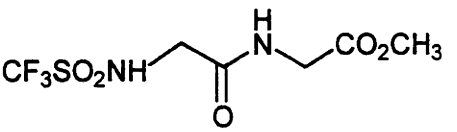
Exploitation of the Triflamide Protecting Group in the Manipulation of Regioselectivity of Radical Formation in Amino Acids and a Comparison with the Effect of the Phthaloyl Protecting Group

In Chapter Three, the triflyl protecting group was demonstrated to have a powerful effect on the stability of an adjacent α-centred glycyl radical. This was highlighted by the particularly low reactivity of the triflyl-protected glycine **112** when treated with NBS, when compared with that of most other protected glycines previously examined (p. 116). It was envisaged that this low stability of radicals adjacent to a triflyl protecting group could be exploited in the formation of regioselectively modified amino acid derivatives and peptides. Such transformations have been examined in this chapter by the preparation of a selection of *N*-triflylamino acid derivatives and investigation of their subsequent reaction with NBS.

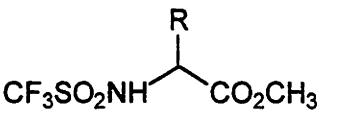
The way in which a triflyl protecting group affects the stability of an adjacent radical has been shown in the previous chapter to involve different factors from those exerted by a phthaloyl group. To examine these differences experimentally, phthaloyl and triflyl protected derivatives have been prepared and their reactions with NBS are compared. Finally, the possibility of polar effects exerted by the triflamide protecting group is investigated by means of radical chlorination of an amino acid derivative.

Results

To investigate the effect of the triflamide protecting group on regioselective functionalisation of peptides and amino acid side chains, the amino acid derivatives **156**, **157** and **158** were prepared and their reactions with NBS were investigated.

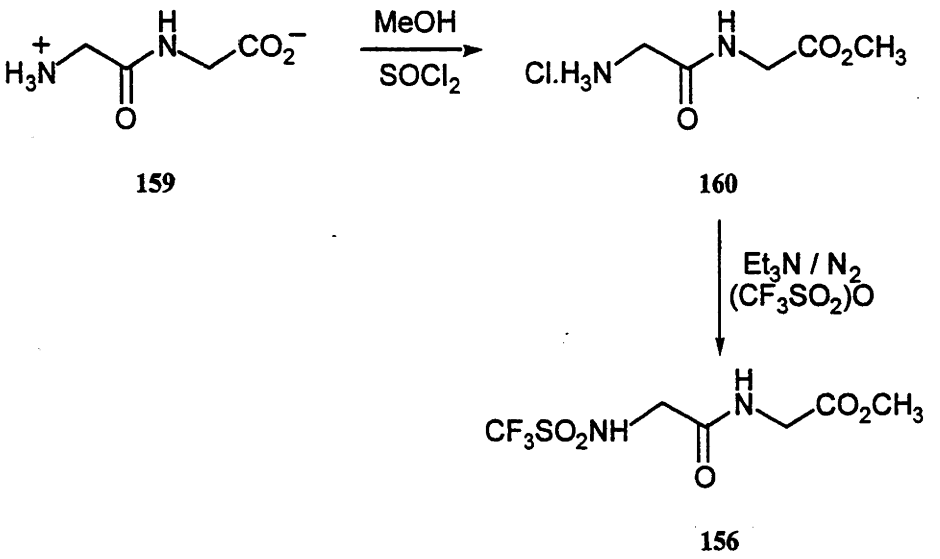


156



157 R = $CH(CH_3)_2$
158 R = CH_2Ph

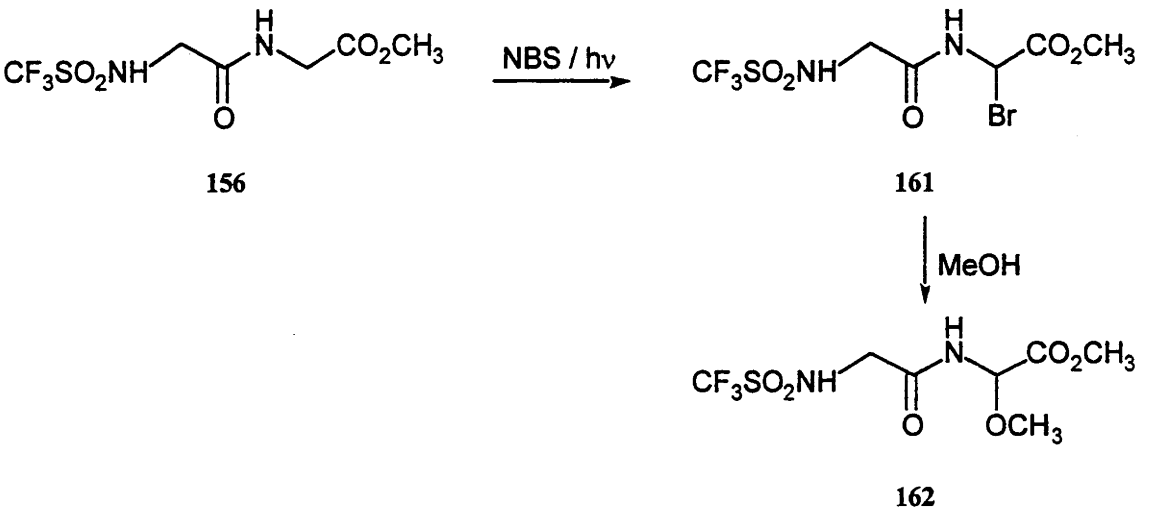
Glycylglycine **159** was treated with methanolic hydrogen chloride for two hours to obtain the glycylglycine methyl ester hydrochloride salt **160**. Subsequent treatment of this salt with triethylamine and triflic anhydride, followed by purification, afforded the *N*-triflylglycylglycine methyl ester **156** (Scheme 4.1), whose structure was confirmed by spectral analysis. A distinctive singlet at δ3.80 in the ^{1}H NMR spectrum indicated that esterification had been successful, and a quartet at δ119.8 in the ^{13}C NMR spectrum was diagnostic of the ^{1}H NMR silent trifluoromethyl substituent. The observed quartet splitting is a result of the coupling of the carbon of the trifluoromethyl group to the three adjacent ^{19}F nuclei. Full characterisation was consistent with the structure and composition of the glycylglycine derivative **156**.



159 160 156

Scheme 4.1. Reaction of glycylglycine **159** to give the fully protected derivative **156**.

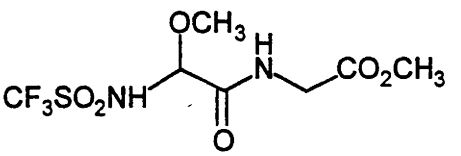
Bromination of the triflylglycylglycine derivative **156** was achieved by treatment with one equivalent of NBS (Scheme 4.2). It was found that reaction in refluxing CCl_4 gave partial decomposition of the product bromide **161**. This was avoided by reaction of the triflamide **156** in refluxing dichloromethane, which has a much lower boiling point. Bromination was characterised by disappearance of one of the α-doublets around δ4.1 and appearance of a new doublet at δ6.4. The bromide **161** was unstable and so was characterised as the methoxy derivative **162**, which was obtained by treatment of the crude bromide **161** with methanol. Only a single regioisomer was seen in both cases. The methoxy compound **162** was identified by the shift of the doublet at δ6.42 of the bromide **161** to δ5.54 and appearance of a three proton singlet at δ3.49.



156 161 162

Scheme 4.2. Reaction of the triflylglycylglycine **156** with NBS to form the bromide **161** and subsequent isolation as the methoxide **162** for characterisation.

The regiochemistry of bromination and methoxylation are the same by virtue of the conversion from the bromide **161** to the methoxide **162** occurring *via* simple substitution. Thus, structural information obtained about the methoxide **162** is valid for the bromide **161**. It was difficult to ascertain from the 1D NMR spectrum whether bromination had occurred at either the *C*- or *N*-terminal glycyl residue, because the shifts of the *C*- and *N*-terminal α-carbons and the attached protons are very similar and not diagnostic of either residue. Evidence for reaction at the *C*-terminal residue came from mass spectral data.



163

Figure 4.1. The alternative methoxy derivative **163** obtainable from initial bromination at the *N*-terminal residue.

Diagnostic fragments were identified in the EI mass spectrum of the methoxide **162**, which could have only originated from the *C*-terminal isomer, and not the *N*-terminal derivative **163** (Figure 4.1). The definitive fragmentation was of mass 103 and indicated cleavage of the *C*-terminal α-carbon-nitrogen bond, to give a fragment carrying both the carboxymethyl group and the methoxy substituent (Figure 4.2). Elemental composition of this fragment was confirmed by high resolution mass spectrometry. Such a fragment could not arise from the triflamide **163**, substituted at the *N*-terminal residue.

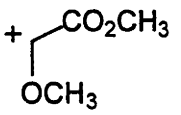
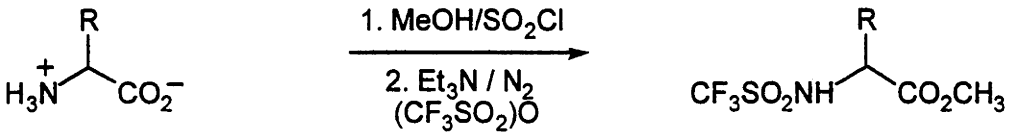


Figure 4.2. The fragment at *m/z* 103 corresponds to a fragment bearing both the carboxymethyl and the methoxy substituents. Such a fragment could not arise from the *N*-terminal substituted derivative **163**.

Valine **69** and phenylalanine **164** were treated in a similar fashion to the glycylglycine **159**. Methylation of each free amino acid in acidified methanol, followed by workup to obtain the crude methyl esters and then treatment with triflic anhydride, afforded the two *N*-triflyl derivatives **157** and **158** (Scheme 4.3). The triflylvaline **157** showed a characteristic singlet in the ^{1}H NMR spectrum attributable to the methyl ester at δ3.81. Esterification of the phenylalanine **158** was evident due to a singlet at δ3.77. Both the valine **157** and the phenylalanine **158** also showed evidence of the trifluoromethyl protecting group by the presence of a quartet in each ^{13}C spectrum, at δ120.0 and δ115.6, respectively. The splittings of these signals were again caused by coupling of the carbon of the triflyl group to the three adjacent ^{19}F nuclei. The data for the valine **157** is consistent with that already obtained by previous workers,[220] whilst the phenylalanine **158** was fully characterised.

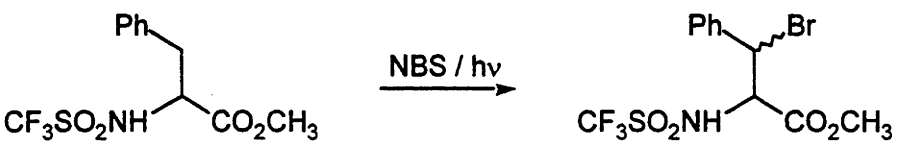


69 R = $CH(CH_3)_2$
164 R = CH_2Ph

157 R = $CH(CH_3)_2$
158 R = CH2Ph

Scheme 4.3. Reaction of the amino acids **69** and **164** to give the corresponding triflyl-protected derivatives **157** and **158**, respectively.

Bromination of the phenylalanine **158** with NBS afforded the β-bromide **165** as a 1 : 1 mixture of diastereomers. The ^{1}H NMR spectrum showed a downfield shift of the signal for the α-proton from δ4.50 to δ5.31 for one diastereomer and δ5.52 for the other. The signals for the β-protons were also shifted downfield from δ3.12 and δ3.18 to δ4.51 for one diastereomer and δ4.71 for the other. The splitting of these signals is consistent with β-bromination, as determined from the data reported for similarly protected β-bromo-phenylalanine derivatives.[38] Monobromination was confirmed by microanalysis. The spectral identity of each of the diastereomers of **165** was achieved by their separation using HPLC, which afforded one of the diastereomers in pure form.

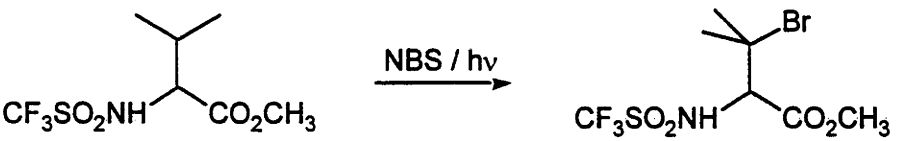


158 **165**

Scheme 4.4. Bromination of the phenylalanine derivative **158** to afford the corresponding β-bromide **165**.

The triflylvaline **157** was also brominated with NBS and afforded the corresponding β-bromide **166**. Formation of this bromide was evidenced by loss of the signal for the β-proton from the ^{1}H NMR spectrum. Additionally, the signal for the α-proton

decreased in multiplicity from a doublet of doublets in the unbrominated derivative **157** to a doublet in the bromide **166**. The methyl protons were also shifted downfield from two doublets at δ0.92 and δ1.04 to two singlets at δ1.91 and δ1.93. The spectral data are consistent with that in the literature for other protected β-bromovaline derivatives.[66] Microanalysis gave the correct composition for the monobromide **166**.

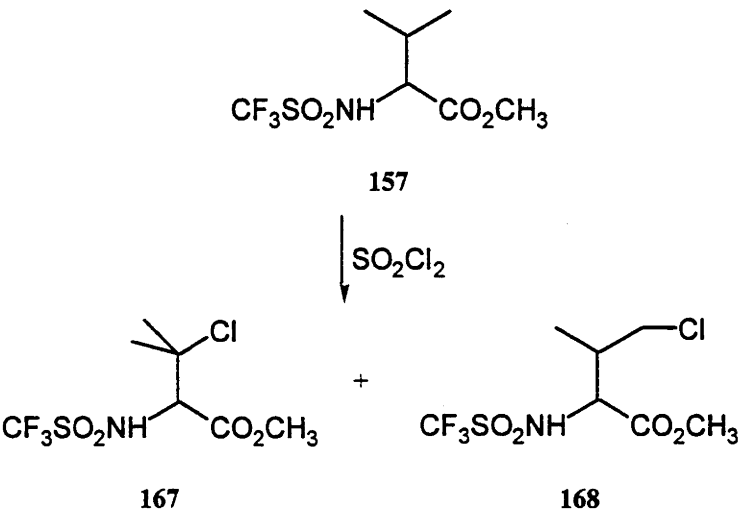


157 **166**

Scheme 4.5. Bromination of the triflylvaline **157** to afford the corresponding β-bromide **166**.

Chlorination of the triflylvaline **157** was carried out by treatment of a solution of the valine **157** with sulfuryl chloride. The reaction was conducted in both carbon tetrachloride and benzene as solvents and was not allowed to proceed to completion, so as to avoid decomposition of the primary products. Chlorination afforded a mixture of regioisomers, namely the β- and γ-chlorides, **167** and **168**, respectively. The β-chloride **167** was characterised by the ^{1}H NMR signal for the α-proton being only a doublet or broad singlet, compared with the doublet of doublets observed for compounds which still retain the β-proton, such as the parent triflamide **157** or the γ-chloride **168**. The methyl peaks of the β-chloride **167** were also shifted downfield and collapsed to singlets, when compared with the methyl peaks in the precursor **157**. The γ-chloride **168** was isolated as a 1 : 1 mixture of diastereomers each characterised by a downfield shift in the ^{1}H NMR spectrum of the α-proton. Additionally, one of the methyl singlets near δ1 had disappeared, when compared with the parent **157**, and was replaced by doubled doublets around δ3.5. This splitting and shift is consistent with diastereotopic hydrogens attached to the same carbon as the chlorine. Separation of the products of the chlorination

reaction was achieved by HPLC and each of the chlorides **167** and **168** gave data consistent with monochlorination.

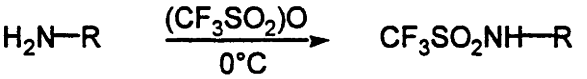


Scheme 4.6. Chlorination of the triflylvaline **157** using sulfuryl chloride affords a mixture of both the β- and γ-chlorides **167** and **168**.

Each solvent in which the chlorination was performed afforded a different ratio of the β-chloride **167** to the γ-chloride **168**. Chlorination in carbon tetrachloride afforded a 0.65 : 1 ratio of β-chloride **167** to γ-chloride **168**, as measured by integration of the distinctive α-protons in the ^{1}H NMR spectrum. In a similar fashion, chlorination in benzene afforded a contrasting ratio of 1.05 : 1 of the β-chloride **167** and the γ-chloride **168**.

To compare the effects of phthaloyl and triflyl substituents on the formation of carbon centred radicals, the triflamides **169** and **170** and the corresponding phthalimides **171** and **172** were prepared and their reactions with NBS investigated.

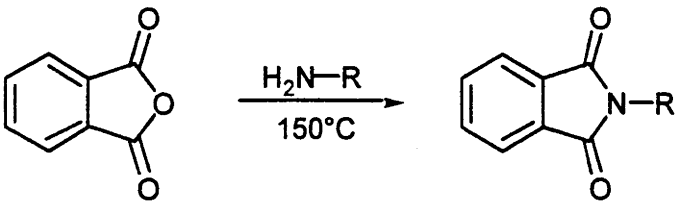
The isobutyltriflamide **169** was synthesised by treatment of two equivalents of isobutylamine in dichloromethane with triflic anhydride. The mixture was then filtered and chromatographed on silica to give the triflamide **169** as a colourless oil, whose characteristics matched the literature data.[221] Similarly, isopropyl triflamide **170** was formed from the reaction of isopropylamine with triflic anhydride. The isopropyl compound **170** was not known in the literature and so was fully characterised. The ^{1}H NMR spectrum showed a similar splitting pattern to the parent isopropylamine, though shifted downfield due to the powerful electron withdrawing nature of the triflyl group. Trifluoromethanesulfonyl substitution was confirmed by the characteristic quartet at δ120.63 in the ^{13}C NMR spectrum, as previously explained.



169 R = $CH_2CH(CH_3)_2$
170 R = $CH(CH_3)_2$

Scheme 4.7. Formation of the triflamides **169** and **170** by treatment of the parent amines with triflic anhydride.

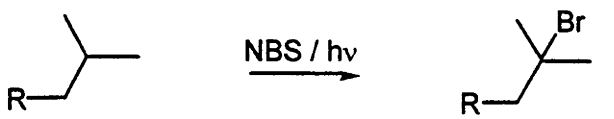
The isobutylphthalimide **171** was formed by heating a slurry of two equivalents of isobutylamine and freshly ground phthalic anhydride to 150 °C, followed by recrystallisation. Isopropylphthalimide **172** was produced in an analogous fashion. However, use of excess isopropylamine resulted in lower yields due to an insoluble by-product being formed. The desired phthalimide **172**, in this case, was isolated by filtration through silica to remove this byproduct. Both the phthalimides **171** and **172** are known compounds and their physical and spectral data are consistent with those found in the literature.[222]



171 R = $CH_2CH(CH_3)_2$
172 R = $CH(CH_3)_2$

Scheme 4.8. Formation of the phthalimides **171** and **172**.

The isobutyltriflamide **169** and isobutylphthalimide **171** were both brominated with NBS to yield the corresponding β-bromides **173** and **174**. Both bromides were identified by loss of the signal due to the β-proton in the ^{1}H NMR spectrum. The methyl signals in the ^{1}H NMR spectra for the each of the bromides **173** and **174** collapsed to singlets from the doublets observed in the spectra of the unbrominated compounds **169** and **171**. This was accompanied by a downfield shift of these methyl peaks from δ0.93 to δ1.81 in each case. The data obtained for the phthaloyl derivative **174** is consistent with the literature values.[223] The triflyl derivative **173** was characterised fully, with the microanalysis consistent with monobromination.



169 R = CF_3SO_2NH
171 R = PhthN

173 R = CF_3SO_2NH
174 R = PhthN

Scheme 4.9. Radical bromination of the isobutylamides **169** and **171**.

The reactions with NBS of both the isopropyl derivatives **170** and **172** did not afford discreet products. Only the starting material consumption was therefore measured. No

depletion of starting material was observed when the reagents were placed with NBS at reflux temperatures for four hours if the mixture was not exposed to UV radiation. Additionally, with NBS absent, neither of the compounds reacted on exposure to UV radiation and only starting material was recovered. Thus, under the bromination conditions used, it can be assumed that the only depletion in the starting materials **170** and **172** is due to radical reaction of these compounds with NBS.

Competitive bromination reactions with NBS were carried out between the triflyl derivatives **169** and **170**, and their phthalimido counterparts **171** and **172** in order to determine their relative rates of reaction. The initial and final reaction mixtures were analysed by ^{1}H NMR spectroscopy. The amount of consumption of starting materials was determined by measurement of the integration of distinctive peaks in the spectrum and comparison of these integrations with that of an internal standard. The signals for the protons of the product bromides **173** and **174**, in the competitive bromination between the isobutyl derivatives **169** and **171**, were unable to be sufficiently resolved from the starting material signals at 300 MHz. Hence, final reaction mixtures were necessarily run on a 600 MHz NMR instrument in order to obtain accurate integrations and, therefore, relative rates.

From these experiments, it was shown that the isobutylphthalimide **171** reacts 5–10% faster than the corresponding triflamide **173**. The triflyl isopropyl derivative **170** reacts twice as fast as the corresponding phthalimide **172**.

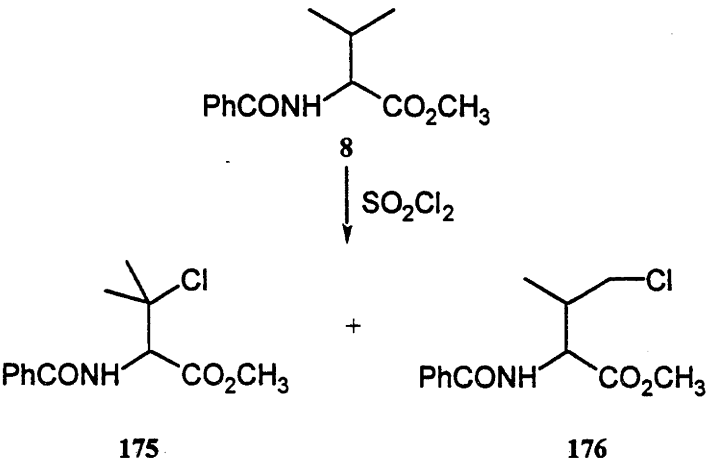
Discussion

By selectively manipulating the stability of radical centres within an amino acid derivative or a peptide , it is possible to control the regioselectivity of radical formation. The triflyl protecting group has been shown in the previous chapter to decrease the stability of an adjacent radical centre, relative to an acyl-protecting group. Treatment of the triflylglycylglycine **156** with NBS gave regioselective bromination of the *C*-terminal

glycine residue. This selectivity contrasts with reaction of the *N*-benzoylglycylglcyine **20**, where bromination occurs at the *N*-terminal residue.[74] This difference in the regioselectivity of bromination indicates that the α-position of an *N*-triflyl-substituted amino acid derivative is less reactive than that of an *N*-acylamino acid derivative toward reaction with NBS. This is consistent with the relative stabilities of the corresponding α-centred glycyl radicals **139** and **73**.

The bromination reactions of the triflylphenylalanine **158** and the triflylvaline **157** again emphasise the extent to which the triflyl protecting group can disfavour radical formation at an adjacent carbon. Both these compounds **158** and **157** are regioselectively brominated on the side chain, at the most stable site for radical formation, namely the tertiary β-centre in the valine **157** and the benzylic β-centre in the phenylalanine **158**. These reactions establish that the triflyl group can diminish the rate of formation of an α-centred radical to a significant enough extent to allow hydrogen abstraction from other sites in the molecule. The regioselectivity of these bromination reactions is contrary to the reactions of the corresponding *N*-acylamino acid derivatives, where reaction occurs at the α-centre.[66] Similar regioselective side chain functionalisation in bromination reactions had only previously been obtained using the phthaloyl protecting group.[74] The triflyl protecting group provides a viable synthetic alternative to this phthaloyl moiety.

These products from the bromination reactions of the phenylalanine **158**, valine **157** and glycylglycine **156** adequately demonstrate the effect that the triflyl group can have on the reactivity of the centre adjacent to the protecting group toward hydrogen abstraction. The reactivity at more remote centres, however, could be influenced by the strong electron withdrawing nature of the triflyl group, resulting in the manifestation of an inductive effect. Chlorination reactions are quite susceptible to polar effects in the transition state and therefore highlight the effect of inductive electron withdrawal. This is demonstrated in the radical chlorination reaction of the benzoylvaline **8**.[5]



175 176

In the chlorination reaction of the benzoylvaline **8**, β- and γ-centred radicals are formed in preference to α-centred radicals to afford the β- and γ-chlorides **175** and **176**, respectively. The formation of α-centred radicals in chlorination reactions is disfavoured by the inductive electron withdrawing nature of the α-substituents, which lowers the stability of the transition state leading to the radical.

When the product distributions of the chlorination reactions of the triflylvaline **157** and the benzoylvaline **8** are compared, the inductive effect of the triflyl protecting group becomes evident. When the reactions are carried out in carbon tetrachloride, the reported ratio of the β-chloride **175** to the γ-chloride diastereomers **176**, from reaction of the *N*-benzoylvaline derivative **8**, was 2 : 1 : 1. This equates to a sixfold selectivity for the abstraction of the β-hydrogen compared with the γ-hydrogens. Chlorination of the triflyl derivative **157** leads to a ratio of β-chloride to γ-chloride diastereomers **167** and **168** of 1.3 : 1 : 1. This equates to only a fourfold selectivity for hydrogen abstraction from the β-position. Similarly, when these reactions are carried out in benzene, the ratio for the formation of the β-chloride to γ-chloride diastereomers **175** and **176** is 3.2 : 1 : 1. This ratio of β- to γ-diastereomers drops to 2.1 : 1 : 1 when the triflylvaline **157** is chlorinated in benzene. The increased selectivity for γ-centred radical formation in the

reactions of the triflylvaline **157** is consistent with an inductive electron-withdrawing effect of the triflyl protecting group. This effect decreases the relative stability of nearer centres, such as the β-centre, resulting in the increased formation of the γ-chloride **168**, relative to the reactions of the benzoylvaline **8**.

The regioselectivity of radical formation in the bromination reactions of the amino acid derivatives **158**, **157** and **156**, induced by the triflyl protecting group, is similar to that induced by the phthaloyl protecting group in the corresponding reactions of phthaloyl protected amino acids. The modes of action by which these two protecting groups deter ical formation at an adjacent centre are quite different, however. The triflamide acts *via* mainly electronic effects, whereas the phthaloyl group acts through both electronic and steric effects. To examine the differences in regioselectivity and rate that the reactions of triflyl- and phthaloyl-protected derivatives may exhibit, the reactions of the isopropyl derivatives **170** and **172** and the isobutyl derivatives **171** and **169** were investigated.

The influence on the rate of formation of α-centred radicals was determined by comparison of the rates of reaction of the isopropyl derivatives **170** and **172**. These showed that the triflamide **170** reacted twice as fast as the phthalimide **172**. This difference in rate does not correlate with the stabilities of the corresponding *N*-methyl radicals **145** and **148** of 25.4 kJ mol^{-1} and 28.8 kJ mol^{-1}, respectively, calculated in Chapter Three (p. 110). Based on these RSEs, it would be expected that the phthalimide **172** would react faster than the triflamide **170**. It was seen, however that the stability of the *N*-ethylmaleimide radical **149** was diminished compared with that of the *N*-methylmaleimide radical **147** due to steric interactions with the ethyl side chain. Presumably, the slower rate of reaction of the phthalimide **172** compared with that of the triflamide **170** can be attributed to non-bonding interactions of the phthalimido substituent with the methyl groups of the isopropyl side chain.

To examine whether slower rates of reaction of phthalimide protected derivatives in comparison with those of triflyl protected derivatives are restricted to the α-centre, the bromination reactions of the isobutyl compounds **171** and **169** were investigated. Both derivatives brominated at the β-position, the *N*-protecting groups showing no difference in their effect on regioselectivity of radical formation. The rate of bromination of the triflamide **169** was reproducibly slower than that of the phthalimide **171**, with the ratio of relative rates being 1 : 1.06. However, this difference in rate is not very significant, nor enough to be synthetically useful. This suggests that beyond the adjacent centre, the phthaloyl and triflyl protecting groups show little difference in their effect on the rate of radical formation.

The deactivating effect of the triflyl protecting group on adjacent radical centres has been exploited in the regioselective bromination of the triflylamino acids **156**, **157** and **158**. The selectivities of radical formation in each case contrast those which are seen in the bromination reactions of the corresponding *N*-acylamino acids. These selectivities of formation are consistent with the relative stabilities of the *N*-triflyl- and *N*-acyl-protected glycyl radicals **139** and **73**. The inductive electron withdrawing nature of the triflyl protecting group has been demonstrated in the chlorination reaction of the triflylvaline **157**, where the apparent formation of γ-centred radicals was enhanced, relative to the reaction of the corresponding benzoyl-protected derivative **8**. The differences in the effects of the phthaloyl and triflyl protecting groups on the formation of adjacent and remote radicals was also examined by comparing the relative rates of the isopropyl and isobutyl derivatives **169–172**. It was found that while there is a difference in the rate of formation of radicals adjacent to the protecting group, there was no difference at more remote centres. Overall, the triflyl protecting group provides a reasonable alternative to the phthaloyl protecting group where regioselective functionalisation of either peptide residues or the side chains of amino acid derivatives is desired, but it does not appear to convey significant synthetic advantages.

5

Investigation of the Effect of Electron Demand in the Radical Reactions of Phenylalanine Derivatives

Examination of the rates of reaction of systems that can satisfy or exacerbate the electron demand of a charged transition state can reveal the existence and extent of anchimeric assistance. Due to the unusual nature of the neighbouring group effect observed in the radical reactions of phenylalanine derivatives[75] described in the Introduction to this thesis, a study of the effect of electron demand on the rates of radical bromination in such derivatives was undertaken.

Previous work did not indicate clearly whether there was a difference in neighbouring group effect between the nitrophenylalanine ester **50** and the corresponding amide **51** as a result of the electron demand in their radical bromination reactions, when compared with the reactions of the phenylalanines **33** and **47**. Closer inspection of the relevant ^{1}H NMR spectra, however, revealed that the reactions of the phenylalanines **50** and **51** were complicated by partial decomposition of the product bromides **48** and **49**. This may have obscured any effect of electron demand on the observed anchimeric assistance. The work presented in this chapter was aimed to clarify these ambiguities by examining the relative rates of bromination of electron rich arylalanine derivatives. Preparation of the 4-methoxy- and 3,4-dimethoxy-phenylalanine derivatives **52**–**55** and their reactions with NBS are described.

Additionally, theoretical calculations on the benzylic radical and *para*-substituted benzylic radicals are described, with the aim of understanding the contributions of

radical stabilisation and the polarisation of the transition state toward the reactivity of phenylalanine derivatives in radical reactions.

Results

Standard *ab initio* molecular orbital theory and DFT calculations were performed with GAUSSIAN 94.[169] RSEs were calculated using the isodesmic reaction with methane (p. 41). Calculation of minimum energy conformations was carried out using the density functional method B3-LYP/6-31G(d) with subsequent calculation of the single point energies at RMP2/6-31G(d). Frequencies were calculated at B3-LYP/6-31G(d), as were the ZPEs. The results are summarised in Table 5.1.

Table 5.1. RSEs of the benzylic radicals of substituted toluenes and ethylbenzenes.

p-X-C_6H_4-C$^{\bullet}$HR + CH_4 → *p*-X-C_6H_4-CH_2R + $CH_3^{\bullet}$				Radical Stabilisation Energy +ZPE correction (kJ mol^{-1})	
R	X	*p*-X-C_6H_4-CH_2R	*p*-X-C_6H_4-C$^{\bullet}$HR	RMP2/6-31G(d)	B3-LYP/6-31G(d)
H	H	**177**	**178**	46.1	69.9
H	NO_2	**179**	**180**	45.0	71.9
H	OCH_3	**181**	**182**	47.8	72.4
CH_3	H	**183**	**184**	57.2	84.1
CH_3	NO_2	**185**	**186**	59.2	89.7
CH_3	OCH_3	**187**	**188**	58.4	85.4

The *N*-phthaloyl-dihydroxyphenylalanine methyl ester **189** had been previously prepared by the treatment of dihydroxyphenylalanine (DOPA) **190** with *N*-carboethoxy-phthalimide followed by treatment with acidic methanol.[224] This procedure gave only moderate yields and an alternate preparation of the ester **189** was accomplished by initial treatment of a solution of the free amino acid **190**, heated to reflux in DMF, with freshly ground phthalic anhydride. It proved important to keep the DMF solution under a nitrogen atmosphere to prevent oxidation of the catechol **190**. Such phenolic derivatives of **190** are readily oxidised to the corresponding quinones (Figure 5.1).

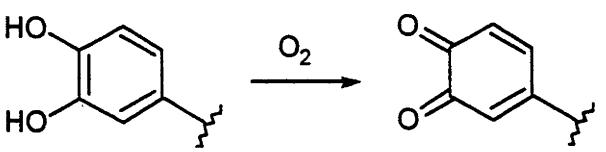
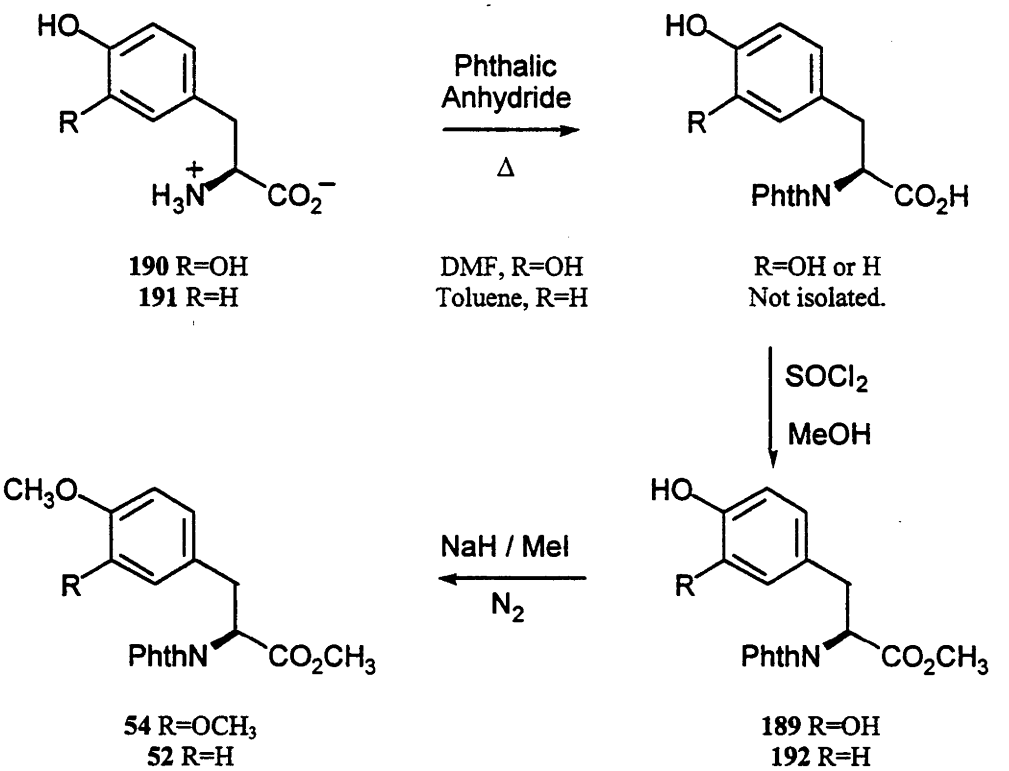


Figure 5.1. Oxidation of dihydroxy compounds to the corresponding quinones is quite facile.

The phthaloylation was then followed by esterification in acidic methanol, produced by pretreatment of the methanol with thionyl chloride, which gave the DOPA derivative **189** in 90% overall yield over 2 steps. *O*-Methylation to form the fully protected ester **54** was accomplished by treatment, under an atmosphere of nitrogen, of the DOPA derivative **189** with sodium hydride in THF followed by dropwise addition of excess methyl iodide (Scheme 5.1). Preliminary examination of the reaction mixture by TLC revealed a significant amount of baseline material. The target compound **54** was recovered in only 50% yield after chromatography on silica. The TLC results, in combination with the low yield, indicate decomposition. This decomposition is likely to be of the phthaloyl protecting group because it is known to be unstable to basic conditions.[225] The NMR spectral data of the product **54** are consistent with those previously reported[224] and were characterised by three singlet resonances attributable to

the methyl ethers and the methyl ester at δ3.66, δ3.73 and δ3.75, as well as the characteristic multiplets at δ7.66 and δ7.74 attributable to the phthaloyl group.



190 R=OH
191 R=H

DMF, R=OH
Toluene, R=H

R=OH or H
Not isolated.

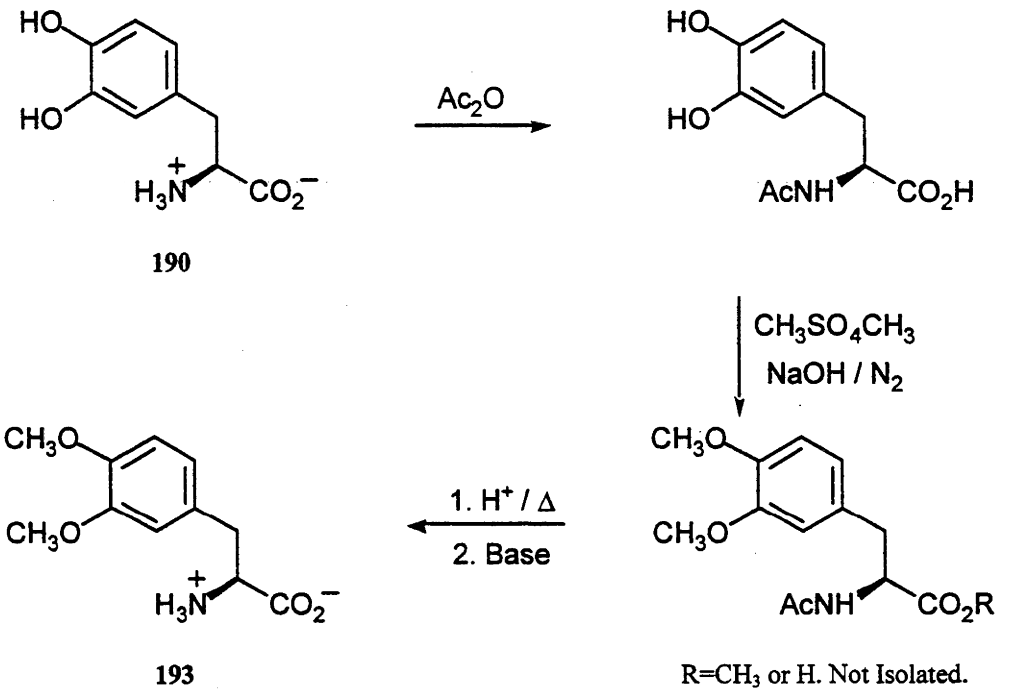
54 R=OCH_3
52 R=H

189 R=OH
192 R=H

Scheme 5.1. Synthesis of the esters **54** and **52**.

In order to produce the *N-tert*-butylamide derivative **55** a modified version of the procedure used by Gensler and Bluhm[226] was used to first synthesise the *O*-methylated free amino acid **193**. The free amino acid **190** was heated in acetic anhydride to form *N*-acetyl-3,4-dihydroxyphenylalanine. Removal of the excess acetic anhydride, followed by treatment of the crude solution with dimethyl sulfate under basic conditions and under an atmosphere of nitrogen, afforded the methylated amino acid. This compound was not isolated so the full extent of methylation was not known. However, the products of subsequent reactions tended to suggest that full aryl *O*-methylation, at

least, was achieved as no unmethylated or partially methylated products were apparent by TLC or NMR analysis. The residue of the methylated amino acid was then heated at reflux for 3 days in concentrated sulfuric acid as specified in the original procedure[226] to ensure full *N*-deprotection to give the amino acid **193**.

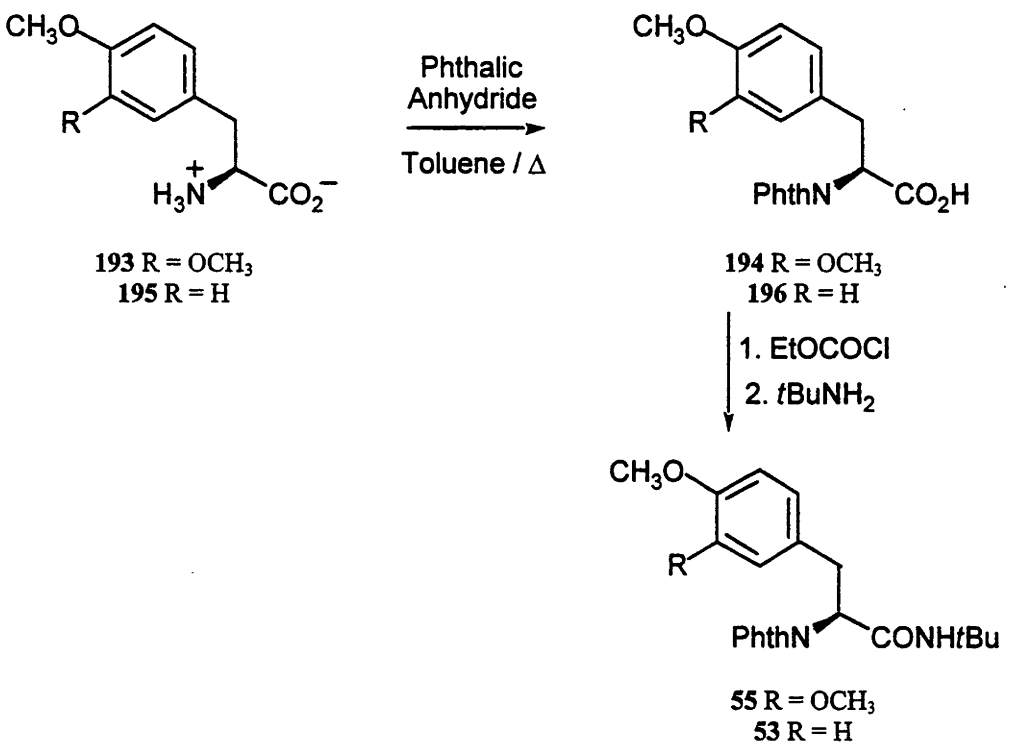


190 **193** R=CH_3 or H. Not Isolated.

Scheme 5.2. Formation of the methylated amino acid **193** by a modification of the procedure used by Gensler and Bluhm.[226]

Gensler and Bluhm[226] had utilised barium salts to neutralise the hydrolysate, which facilitates the purification of the amino acid by producing insoluble barium sulfate. When their original procedure was attempted, the barium salts formed a very fine precipitate that was difficult to filter efficiently, even under vacuum. For this reason, sodium salts were used in the modified procedure. This meant that subsequent phthaloylation of **193** was performed on the crude product, which was contaminated with inorganic salt, possibly leading to a lower than expected yield of **194**. The amide

55 was obtained by the treatment of **194** with ethyl chloroformate and *tert*-butylamine under standard conditions[165,227] (Scheme 5.3.) and was readily identified by spectral comparison with the NMR data of the phenylalanine equivalent **47**. The spectrum was similar except in the aromatic region where only 3 aryl proton resonances were observed, consistent with 3,4-substitution on the ring, as with the starting material. Additionally, two methyl singlet resonances at δ3.68 and δ3.74 were present, corresponding to three protons each, confirming *O*-methylation on the aromatic ring. Despite extensive freeze drying, the NMR spectrum of the amide **55** still showed evidence of one water molecule of crystallisation, which was confirmed by microanalysis.



193 R = OCH_3
195 R = H

194 R = OCH_3
196 R = H

55 R = OCH_3
53 R = H

Scheme 5.3. Formation of the amides **55** and **53** by phthaloylation and subsequent amidation of the methylated amino acids **193** and **195**.

An unusual feature in the ^{13}C NMR spectrum of compound **55** was noted in that there were four signals for the two methoxy carbons around δ56.1 (300 MHz) (Figure 5.2). This reproducible phenomenon was observed consistently with spectra taken at different times, samples prepared at different times and from starting materials prepared on different days. This extra multiplicity is not reflected in the ^{1}H NMR spectrum, which shows only sharp singlet resonances for the methyl protons. Therefore, a conformational effect must be present, which is too fast for the ^{1}H NMR time scale and only barely visible on the ^{13}C NMR time scale. It was noted in conjunction with this that the acid precursor **194** had a broadened singlet for the methoxy groups on the aryl ring in the ^{13}C NMR spectrum. This is consistent with less conformational restriction due to lack of the *tert*-butylamide protecting group. Similarly, Hutton[224] reported two closely neighbouring signals (δ 55.4 and δ 55.5) in the ^{13}C NMR spectrum of **54**, which can be attributed to the aryl methoxy groups. Presumably the methyl ester protecting group, being less bulky than a *tert*-butylamide, provides more steric bulk to slow any rotation than that of the free acid **194**, but less than that of the amide **55**, thus giving rise to two (but not four) peaks.

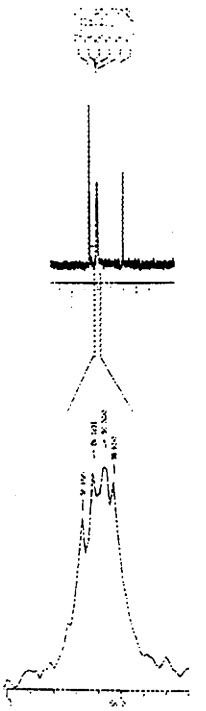
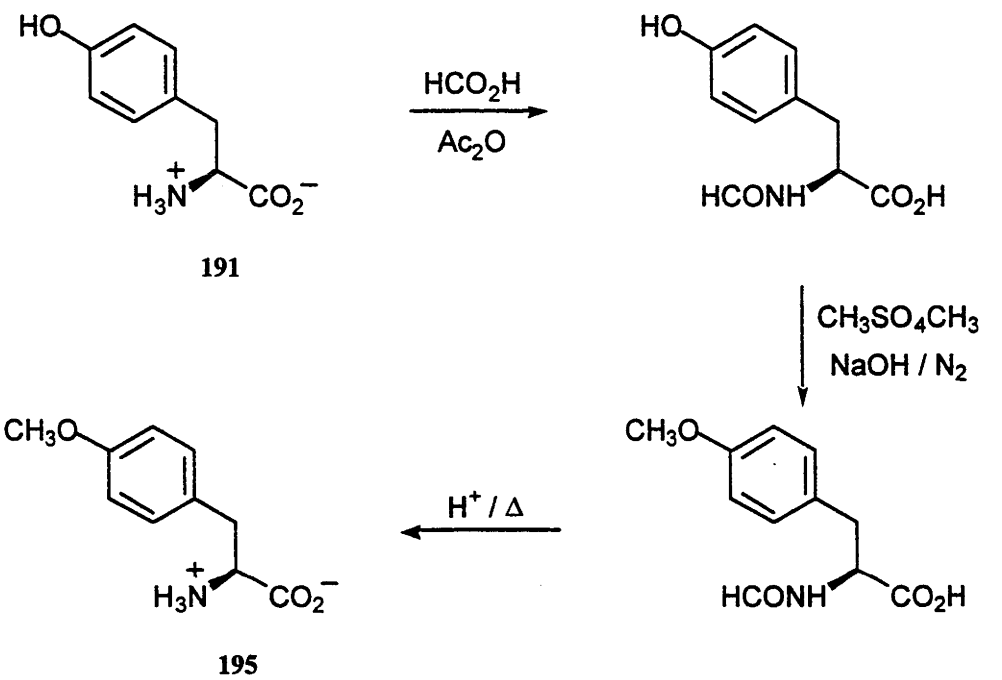


Figure 5.2. The unusual multiplet seen in the ^{13}C NMR spectrum of the amide **55**.

The *O*-methyltyrosine derivatives **52** and **53** were prepared in an analogous fashion to the DOPA derivatives **54** and **55**, respectively. Phthaloylation of tyrosine **191** by standard methods[165] and subsequent esterification using methanolic hydrochloric acid gave the *N*-phthaloyltyrosine methyl ester **192** in 84% overall yield over 2 steps. Treatment of the crude residue **192** with sodium hydride and then methyl iodide, under an atmosphere of nitrogen, gave the *O*-methyl derivative **52** in 64% yield (Scheme 5.1, p. 146). This moderate yield was again accounted for by the probable decomposition of the phthalimido group under the highly basic conditions. The spectral data, again, are consistent with those already reported,[224] this time showing only two methyl singlet resonances at δ3.70 and δ3.78, one due to the methyl ester and the other the methyl ether.

O-Methyltyrosine **195** was produced in a similar fashion to the corresponding DOPA derivative **193** (Scheme 5.2, p 147), by using a modification of the method detailed by

Izumuya and Nagamatsu[228] (Scheme 5.4). Protocols for recrystallisation provided by the authors allowed for the methylated free amino acid **195** to be isolated without inorganic salt contamination.

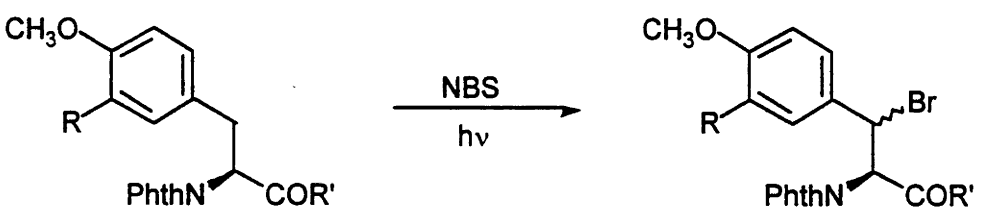


Scheme 5.4. Reaction of tyrosine **191** *via* a modification of the method used by Izumuya and Nagamatsu[228] to produce the methylated tyrosine derivative **195**.

Subsequent phthaloylation gave the *N*-phthaloylated acid **196** in a good yield of 87%. Treatment, as for the DOPA derivative **194**, with ethyl chloroformate and then *tert*-butylamine gave the amide **53** in 81% yield (Scheme 5.3, p 148). The product was identified by comparison with the NMR spectra of the corresponding phenylalanine derivative **47** and DOPA derivative **55**, which showed similar chemical shift and splitting patterns. The aromatic ^1H resonances for the tyrosine derivative **53** were different, however, showing two doublet resonances, each of two protons in intensity, coupled to one another at δ6.73 and δ7.02 corresponding to *para*-ring substitution.

Additionally a singlet at δ3.70 was consistent with methylation of the aromatic hydroxyl moiety.

The protected derivatives **53** and **55** were brominated by heating a CCl_4 solution of each compound with one equivalent of NBS in a quartz tube, whilst irradiating with a 300W sunlamp (Scheme 5.5). These reactions gave the product bromides **197** and **198** as inseparable 1:1 mixtures of diastereomers all in quantitative yield. The spectra for both of the bromides **197** and **198** were consistent with those previously observed for bromination of a variety of other phenylalaninamide derivatives,[165,227] and were characterised by a downfield shift of the α-proton signal, from around δ4.95, to a doublet at δ5.2 and one at δ5.3 from each of the diastereomers of **197** and **198**. Similarly bromination of the ester derivatives **52** and **54** afforded the corresponding ester bromides **43** and **44**. These bromides **43** and **44** also showed distinctive α-proton doublet resonances at both δ5.5 and δ5.6, consistent with the spectral data previously reported.[224] Shifts of the β-proton signals, from around δ3.4-3.5 to pairs of doublet resonances past δ6, were also observed, and were indicative of bromination at the β-position.



52 R=H, R'=OCH_3
53 R=H, R'=NH*t*Bu
54 R=OCH_3, R'=OCH_3
55 R=OCH_3, R'=NH*t*Bu

43 R=H, R'=OCH_3
197 R=H, R'=NH*t*Bu
44 R=OCH_3, R'=OCH_3
198 R=OCH_3, R'=NH*t*Bu

Scheme 5.5. Free radical bromination of arylalanine derivatives to produce β-bromides.

Relative rates of reaction were calculated from bromination experiments, carried out competitively by treatment of equimolar ratios of pairs of substrates **52–55** and **47**, with one equivalent of NBS and irradiation with a 300W sunlamp. *N-tert*-Butylbenzamide was used as the internal standard. The relative rates of reaction were calculated by monitoring the consumption of each substrate by ^{1}H NMR spectroscopy as previously described in Chapter Three (p. 105) and are summarised in Table 5.2. In duplicate experiments, the relative rates of reaction varied by less than 20%, and the mass balance was over 80%. The variations associated with the calculations means that errors in the relative rates of reaction are assumed to be around 20%. Detailed data can be found in Appendix Q, p. 276.

Table 5.2. Relative reactivities of **50–55, 47**and **33**.

PhthNCH(CH_2**Ar**)**COR** + NBS → PhthNCH(CHBr**Ar**)**COR**			
Substrate	**Ar**	**R**	k_{rel}(NBS)
55	3,4-$(MeO)_2$Ph	NH*t*Bu	49
54	3,4-$(MeO)_2$Ph	OCH_3	18
53	*p*-MeOPh	NH*t*Bu	33
52	*p*-MeOPh	OCH_3	10
47	Ph	NH*t*Bu	5‡
33	Ph	OCH_3	1†
50	*p*-NO_2Ph	NH*t*Bu	0.63‡
51	*p*-NO_2Ph	OCH_3	0.13‡

† Assigned as unity within the column and included only for comparative purposes. ‡ Value obtained from literature.[75]

Discussion

Theoretical calculations allow examination of the relationship between the stability of a radical and its rate of formation by comparison of calculated RSEs with experimentally determined relative rates of reaction. Therefore, to probe the nature of electronic effects on benzylic radical formation in ring-substituted phenylalanine derivatives, the RSEs of the *para*-substituted benzylic radicals **182**, **180**, **188** and **186** and the benzylic radicals **178** and **184** were calculated (Table 5.1, p. 144).

It is noted that the variation in the stabilisation energies of substituted and unsubstituted benzylic radicals is quite small. These conclusions are supported by the previous theoretical calculations on benzylic radicals, at lower levels of theory.[161,162] Particularly, the relative differences in RSEs calculated from the supplementary data supplied by Wu and coworkers[162] at the BLYP level of theory are consistent with those presented in this chapter, which were calculated using the B3-LYP functional (Table 5.3). The slight increase in stabilities seen in the density functional calculations for the *para*-substituted tolyl radicals **180** and **182**, over the tolyl radical **178**, is consistent with the increased delocalisation by *para*-substituents reported experimentally.[163] The results of the RMP2 calculations are less clear about this trend for the tolyl radicals **178**, **180** and **182** (Table 5.1, p. 144). However, the differences in RSE are consistently small, indicating very similar stabilities.

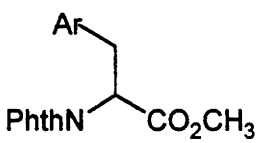
Table 5.3. Radical stabilisation energies of *para*-substituted benzyl radicals, calculated using the density functional methods B3-LYP and BLYP. The ZPE correction has not been included in either set of data because it was not provided in the literature for the BLYP calculations.

p-X-C_6H_4-$C^{\bullet}$HR			Radical Stabilisation Energy (kJ mol^{-1})	
Radical	X	R	B3-LYP/6-31G(d)	BLYP/6-31G(d) [†]
178	H	H	75.1	80.8
180	NO_2	H	77.6	85.1
182	OCH_3	H	78.0	85.3

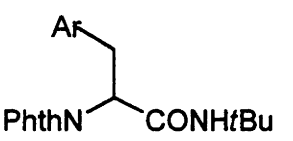
[†]RSE values calculated from the supplementary data supplied by Wu *et al.*[162]

The RSEs of the ethylbenzenes **184**, **186** and **188** indicate slightly increased stabilisation of the resultant benzylic radicals with *para*-substitution at both levels of theory (Table 5.1, p. 144). This is in agreement with the experimental observations.[163] The differences in the RSEs, however, are still very small. The RSEs of both the tolyl radicals **178**, **180** and **182** and ethylbenzenes **184**, **186** and **188** suggest that if the formation of benzylic radicals were dependent solely on radical stability, *para*-substituted derivatives would react faster than unsubstituted derivatives and that this increase in relative rate would be very small, around twofold.

Examination of the relative rates of reaction of the phenylalanine esters **50**, **33**, **52** and **54**, and also of the amide derivatives **51**, **47**, **53** and **55** shows, instead, a large variation (Table 5.2, p. 154). These relative rates also increase with increasingly electron donating substituents on the aromatic ring. These observations support the hypothesis that the reaction proceeds through an electron deficient transition state. This is supported by the plot of relative rates of the bromination reactions of the esters **50**, **33**, **52** and **54** against the σ^+ Hammett substituent parameters (Figure 5.3). The plot gives an excellent correlation coefficient (R^2=0.9975), with the negative ρ value of –1.25 indicating a positively charged transition state or intermediate.



33 Ar = Ph
50 Ar = *p*-NO_2Ph
52 Ar = *p*-MeOPh
54 Ar = 3,4-$(MeO)_2$Ph



47 Ar = Ph
51 Ar = *p*-NO_2Ph
53 Ar = *p*-MeOPh
55 Ar = 3,4-$(MeO)_2$Ph

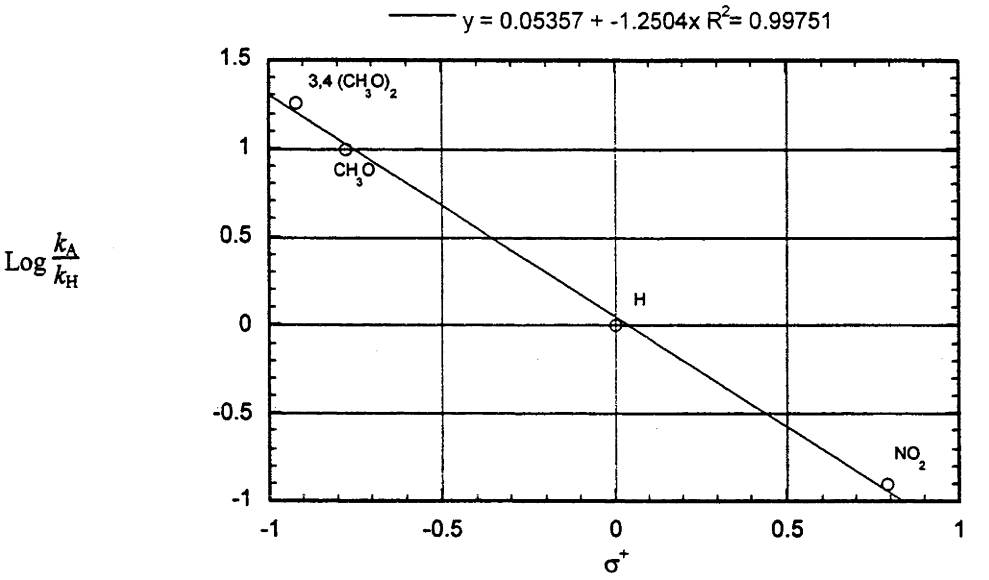


Figure 5.3. Plot of the log of the relative rates of bromination of the aryl substituted phenylalanine esters **50**, **33**, **52** and **54** against σ^{+}.[229,230] ρ = -1.25, indicating a positively charged transition state or intermediate.

The increase in the relative rate of reaction on going from the nitrophenylalanine **50** to the *O*-methyltyrosine **52** is around 80-fold. This is not consistent with the near identical RSEs for the *para*-nitrobenzylic radicals **180** and **186** and the *para*-methoxybenzylic radicals **182** and **188**, calculated theoretically. It is, instead, convincing evidence that the relative rates of reaction of the phenylalanines are governed by polarity in the transition states and not by the stability of the intermediate radicals.

To examine the relative neighbouring group effect of an ester *versus* an amide in the radical bromination reactions of substituted phenylalanines, the relative rates of reaction of the ring-methoxylated phenylalanine derivatives **52–55** were examined.

The amides **53** and **55** react faster than the corresponding ester derivates **52** and **54** (Table 5.2, p. 154). This is consistent with the faster rate of reaction of the phenylalaninamide **47** over that of the corresponding ester **33**, attributed to anchimeric assistance.[75] The ratios of the relative rates of reaction of the amides **47**, **53** and **55** to the rates of reaction of the corresponding esters **33**, **52** and **54** are presented in Table 5.4. It can be seen that as the electron donating ability of the aryl substituents increases, the ratio of these relative rates decreases. This is consistent with the electron demand of the transition state being increasingly satisfied by the aryl ring-substituents and anchimeric assistance thus contributing a proportionately smaller stabilising influence.

Table 5.4. Relative rates of reaction of the amide derivatives **47**, **53** and **55** *versus* those of the corresponding ester derivatives **33**, **52** and **54**.

Aryl substituents	Amide	Ester	k_{rel} (NBS) Amide : Ester
H	**47**	**33**	5[†] : 1
p-CH_3O	**53**	**52**	3.3 : 1
3,4-$(CH_3O)_2$	**55**	**54**	2.7 : 1

[†] Value obtained from literature.[75]

The drop in the ratio from that for the phenylalanine derivatives **47** and **33** of 5 : 1, to that of the methyltyrosines **53** and **52** of 3.3 : 1, is significant in providing evidence that anchimeric assistance in these phenylalanine systems is the cause of the different reactivities of the amide and ester protected derivatives. The difference between the ratio of the rates of reaction of the methyltyrosines **53** and **52** of 3.3 : 1 and that of the DOPA derivatives **55** and **54** of 2.7 : 1 is smaller, but also fits this trend. The small difference between these two ratios can be accounted for because the difference in the electron donating character of *p*-methoxy and 3,4-dimethoxy substituents is small, as indicated by the similar Hammett σ^+ parameters.

It has been shown in this chapter that the stability of *para*-substituted benzylic radicals tends to be slightly higher than the stability of unsubstituted benzylic radicals. Having established this, it was shown that the dominant effect in the magnitude of the relative rates of bromination of substituted phenylalanines must be polarisation in the transition state. This polar transition state has then been exploited in probing anchimeric assistance in these reactions by examining the effect of electron demand on the relative rates of bromination. The ratios of the relative rates of reaction of the amides **47**, **53** and **55** to the rates of reaction of the corresponding esters **33**, **52** and **54** were seen to decrease with increasing electron rich substituents. Such behaviour is consistent with anchimeric assistance in the reactions of these phenylalanine derivatives.

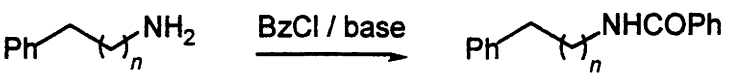
6

Anchimeric Assistance in Radical Reactions of Phenylalkylamine Derivatives

As has been described in the Introduction, anchimeric assistance in the radical reactions of peptides may not be restricted solely to the 1,4-neighbouring group effect presented in the literature.[75] In order to probe the possibility of anchimeric assistance in radical reactions that may proceed *via* a five-membered or larger transition state, a series of phenylalkyl derivatives has been prepared and their reactions with NBS investigated. More particularly the reactions of phenylethylamine derivatives have been chosen as a model for radical formation in peptides that is likely to incur stabilisation *via* a five-membered transition state. The possibility of observed effects being caused by an inductive through-bond effect has also been examined. Finally, phenylpropyl and phenylbutyl derivatives have been prepared and their reactions examined to probe for stabilisation of incipient benzylic radicals by more remote substituents.

Results

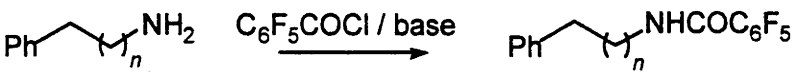
The *N*-benzoylphenylalkylamides **199–201** were prepared using two main methods, both of which gave similar yields. The first method involved treatment of a biphasic mixture of the appropriate amine in ethyl acetate and saturated aqueous sodium bicarbonate with benzoyl chloride followed by standard workup. In a similar fashion, the *N*-benzoyl derivatives **199–201** were prepared by treatment of an homogenous solution of amine in ethyl acetate with benzoyl chloride. The crude derivatives were recrystallised to obtain the pure compounds **199–201**, each as a colourless crystalline solid.



199 n=1
200 n=2
201 n=3

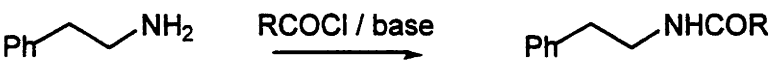
Each of the compounds **199–201** had physical and spectral data which are consistent with that reported in the literature.[231,232] The ethylamide **199** was distinguished by a characteristic splitting in the ^{1}H NMR spectrum of a triplet for the benzylic protons at δ4.94 and an apparent quartet for the α-protons at δ3.73. Similarly, the ^{1}H NMR spectrum for the propylamide **200** also gave a triplet for the benzylic proton at δ2.73 and a doublet of triplets for the α-protons at δ3.50, but it showed an additional quintet due to the β-protons at δ1.97. Finally, the ^{1}H NMR spectrum of the butylamide **201** also showed the same characteristic splittings for the benzylic and α-protons at δ2.68 and δ3.48, respectively, with another 4 proton multiplet at δ1.60-1.78 corresponding to the β- and γ-protons.

The pentafluorobenzamides **202–204** were prepared in an identical fashion to the corresponding *N*-benzamides **199–201** by treatment of the appropriate amine with base and pentafluorobenzoyl chloride. The ^{1}H NMR spectra of the fluorinated compounds **202–204** exhibited very similar proton splitting patterns to the corresponding *N*-benzamides **199–201** and were distinguished mainly by the presence of only a five proton multiplet in the aromatic region, compared with the ten proton multiplet of the benzamides **199–201**.



202 n=1
203 n=2
204 n=3

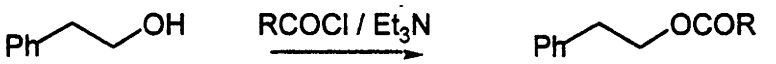
The phenylethylacetamide **205** and phenylethyltrifluoroacetamide **206** were prepared in an analogous fashion to the benzamides **199–201** by the substitution of acetyl or trifluoroacetyl chloride in place of benzoyl chloride, as appropriate. The ^{1}H NMR spectrum of the acetamide **205** gave a triplet for the benzylic protons at δ2.82 and an apparent quartet ascribed to the α-protons at δ3.51. Acetylation was confirmed by the presence of a singlet of three proton intensity at δ1.94. In contrast to the pentafluorobenzamides **202–204**, the trifluoroacetamide **206** did not give similar proton shifts to its unfluorinated analogue **205**, with the benzylic protons appearing in the ^{1}H NMR spectrum at δ2.90 and the α-protons at δ3.63. The splitting pattern observed, however, was the same, with the absence of the methyl peak due to trifluoro substitution. The physical and spectral data of the acetamides **205** and **206** are consistent with that available in the literature.[233,234]



205 R=CH_3
206 R=CF_3

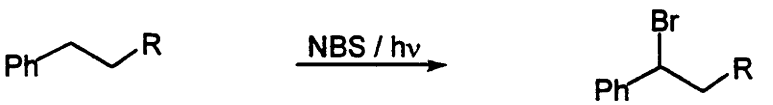
Benzoate analogues of the *N*-benzoylamides **199–201** were prepared by treating 2-phenylethanol and triethylamine in either ethyl acetate or dichloromethane, followed with either benzoyl chloride or pentafluorobenzoyl chloride to afford either the benzoate **207** or the pentafluorobenzoate **208**, respectively. Both gave two triplets in the ^{1}H NMR spectrum for each of the sets of benzylic and α-protons, at δ3.1 and δ4.6. The physical and spectral data of the benzoate **207** are consistent with those reported in the

literature,[235] whereas the pentafluorobenzoate **208**, being a new compound, was fully characterised.



207 R=C_6H_5
208 R=C_6F_5

The bromides **209–218** were obtained by treatment of the starting materials **199–208**, respectively, with one equivalent of NBS. Each mixture was placed in a quartz tube and dissolved in carbon tetrachloride, then heated to reflux whilst irradiating with a 300W sunlamp. The crude bromides were readily identified by their ^{1}H NMR spectra, which showed a downfield shift of the benzylic proton signals in each case to a doublet of doublets around δ5.0-δ5.2 and increased multiplicity of the α-protons, also with a downfield shift.

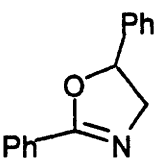


207 R=$OCOC_6H_5$
208 R=$OCOC_6F_5$
205 R=$NHCOCH_3$
206 R=$NHCOCF_3$
199 R=$NHCOC_6H_5$
202 R=$NHCOC_6F_5$
200 R=$CH_2NHCOC_6H_5$
203 R=$CH_2NHCOC_6F_5$
201 R=$(CH_2)_2NHCOC_6H_5$
204 R=$(CH_2)_2NHCOC_6F_5$

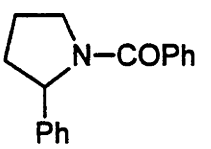
213 R=$OCOC_6H_5$
214 R=$OCOC_6F_5$
211 R=$NHCOCH_3$
212 R=$NHCOCF_3$
209 R=$NHCOC_6H_5$
210 R=$NHCOC_6F_5$
215 R=$CH_2NHCOC_6H_5$
216 R=$CH_2NHCOC_6F_5$
217 R=$(CH_2)_2NHCOC_6H_5$
218 R=$(CH_2)_2NHCOC_6F_5$

Where it was possible to isolate the bromides, the solution was washed with water, to remove the succinimide formed during the reaction, the solvent evaporated and the residue recrystallised. This afforded the bromides **212–214**, **210**, **216** and **218**, which were each characterised using spectroscopic and other physical data. Each of the bromides **212–214**, **210**, **216** and **218** had data consistent with monobromination at the benzylic position.

The bromides **211**, **209**, **215** and **217** were unable to be isolated cleanly, decomposing when subjected to silica chromatography. Each of the bromides **211**, **209**, **215** and **217** was readily identified in the crude reaction mixture by the characteristic doublet of doublets at *ca.* δ5.1 in the ^{1}H NMR spectrum. The presence of the bromides **211** and **215** in the crude reaction mixtures was also determined by high resolution mass spectrometry. The bromides **209** and **217** exhibited formation of isolable byproducts either if left in solution for any period of time or if treated with water. The rate of formation was increased if the reaction was carried out in dichloromethane rather than carbon tetrachloride. These byproducts were isolated as the cyclised derivatives **219** and **220**.



219



220

The formation of the oxazoline **219** was confirmed by comparison of the ^{1}H NMR spectrum with the spectral data previously reported in the literature.[236–239] The physical characteristics are also the same as those reported in the literature.

The *N*-benzoylphenylpyrrolidine **220** was isolated in 55% yield after chromatography of the phenylbutylbromide **217**. The ^{1}H and ^{13}C NMR spectra each showed two sets of signals, suggestive of two products. HPLC chromatography and mass spectral data, however, indicated only one product. The duplicity of the signals in the NMR spectrum was rationalised as being due to two separate conformers existing in solution. This was supported by the change in the ratios of these sets of signals with changing solvent and additionally by performing a variable temperature NMR experiment, where a solution of the pyrrolidine **220** was dissolved in D_6-DMSO and heated in 10 °C increments from room temperature to 105 °C (Figure 6.1). The gradual merging of the signals with increasing temperature indicates that, when conformational restrictions are removed, both sets of signals belong to the same compound.

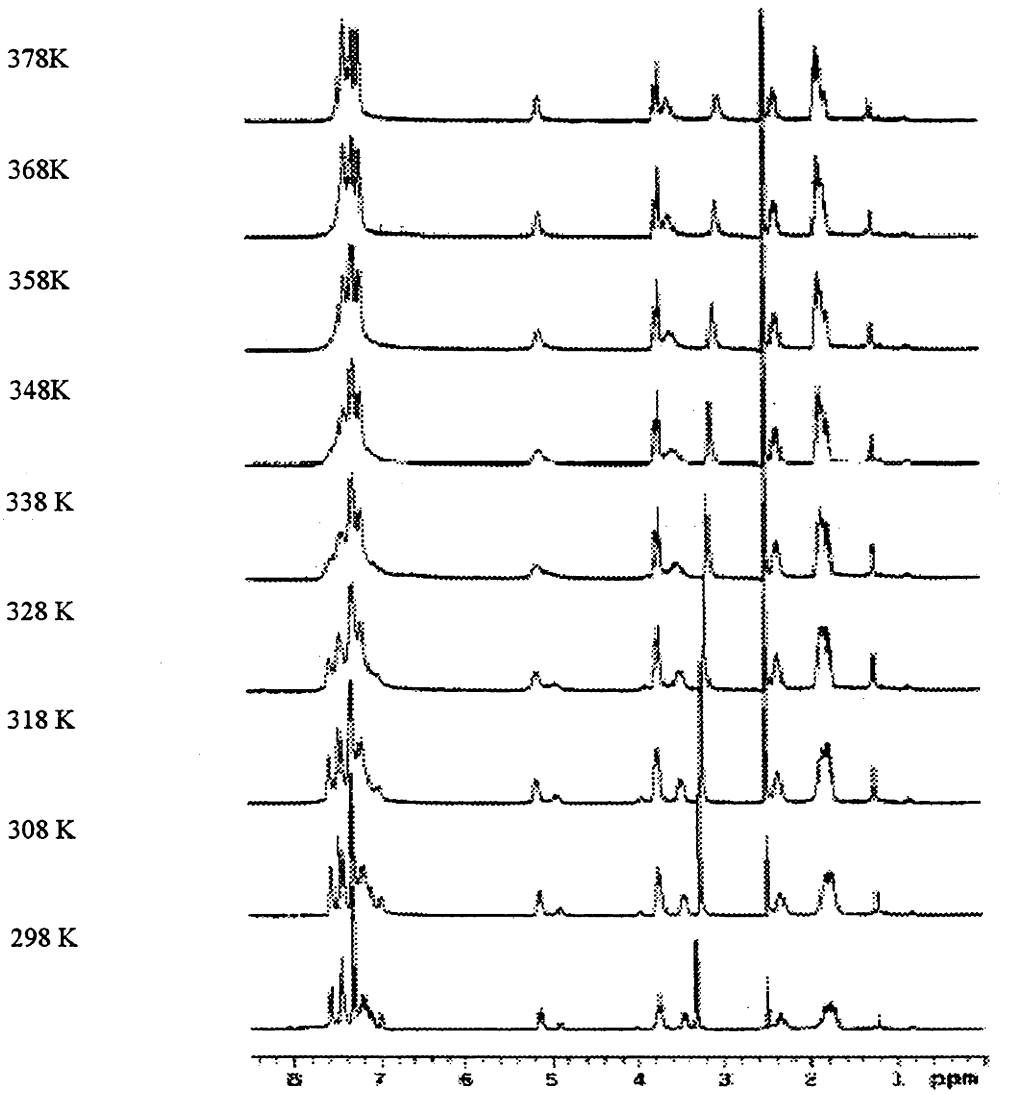


Figure 6.1. Variation in the ^{1}H NMR spectrum of the pyrrolidine **220** with temperature.

Equimolar mixtures of pairs of the phenylethyl derivatives **199**, **202** and **205–208**, with one equivalent of NBS and an aliquot of the internal standard *N-tert*-butylbenzamide, were placed in quartz NMR tubes and dissolved in deuterated dichloromethane. A ^{1}H NMR spectrum was obtained at this point to calculate the initial relative concentrations of the substrates. The NMR tube was placed in a rayonette reactor and the mixture irradiated at 254 nm for 45 minutes. Another ^{1}H NMR spectrum was obtained to

determine the final relative concentrations of substrates and products and these concentrations were then used to calculate the relative rates of bromination. The relative rates of bromination of the phenylalkylamides **199–201**, **203** and **204** were obtained in the same fashion. The use of dichloromethane as a solvent is contrary to previous relative rate experiments described in this thesis. The reason it was used was because it improved the solubility of some of the phenylalkyl derivatives. Comparison with certain experiments performed in carbon tetrachloride produced no difference in the relative rate observed, so it was concluded that the change of solvent did not have a significant effect on the relative rates of reaction. Relative rates of bromination could not be obtained directly for the fluorinated compounds **202–204**, and **208** and their non-fluorinated counterparts **199–201** and **207** respectively, because of the overlap in the signals of the ^{1}H NMR spectra obtained at 300 MHz. In these cases, indirect comparisons were obtained through inclusion of a reactive standard. This standard was one of the other compounds under examination that did not have overlapping signals in the ^{1}H NMR spectrum, and had a comparable relative rate of reaction. The results of these relative rate determinations are summarised in the table below.

Table 6.1. Relative rates of reaction of a variety of phenylalkyl derivatives.

R	Molecule	Relative Rate*
$C_6F_5CO_2$	**208**	0.20
$C_6H_5CO_2$	**207**	0.36
CF_3CONH	**206**	0.34
CH_3CONH	**205**	0.80
C_6F_5CONH	**202**	0.60
C_6H_5CONH	**199**	1†
$C_6F_5CONHCH_2$	**203**	2.9
$C_6H_5CONHCH_2$	**200**	4.5
$C_6F_5CONH(CH_2)_2$	**204**	3.8
$C_6H_5CONH(CH_2)_2$	**201**	6.1

*Determination of the relative rates of reaction in duplicate experiments varied by less than 20%.

† Assigned as unity for comparative purposes.

Discussion

Anchimeric assistance in radical reactions has previously been restricted in the literature to examples of 1,3 participation[157–159] and one example of 1,4 participation.[75] To examine the possibility of anchimeric assistance *via* larger transition states, particularly with relevance to peptide and other biological systems, the bromination reactions of a variety of phenylalkyl derivatives were examined. In these examples, the remote action of a pentafluorobenzoyl substituent was compared with its unfluorinated counterpart.

The action of the pentafluorobenzoyl group, when compared to that of benzoyl protection, should be to diminish the electron density of the amide group. This lower electron density results in less nucleophilicity of the amide and thus diminishes its ability to provide stabilisation of the transition state. As a result, a lower relative rate of reaction is expected for the fluorinated derivatives over the unfluorinated derivatives.

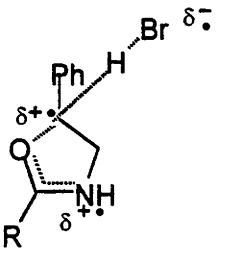


Figure 6.2. As R becomes more electron withdrawing, the amido group will be less able to stabilise the putative transition state, shown above.

Examination of the simplest derivatives, the *N*-pentafluorobenzoyl-phenylethylamide **202** and the *N*-benzoyl-phenylethylamide **199**, revealed a twofold difference in the rate of bromination at the benzylic position. This type of action by a remote substituent is consistent with anchimeric assistance.

The effect on a molecule of the substitution of hydrogens by fluorines is generally acknowledged not to cause any notable steric consequences.[205] Particularly at such a remote site from the reactive centre, any steric effects are expected to be negligible. Fluorine substitution instead produces significant changes in the electronic structure of a molecule. This can take the form of either through-bond or through-space effects, which may not be related to anchimeric assistance. To examine these possibilities, the relative

rates of bromination of the phenylethylamides **205** and **206** and the esters **207** and **208** were examined.

The benzoyl phenylethylamides **199** and **202** have the possibility of intramolecular π-stacking effects. If they exist, these effects are likely to be quite different for the fluorinated and non-fluorinated derivatives due to the difference in π-stacking interactions between benzene rings and perfluorinated benzene rings. These differences arise because of the reversed quadrupoles of the perfluoroaryl unit compared with those of an unsubstituted arene.[240–242] Therefore, if these π-interactions are present, they would give rise to different conformations as a result of the differences in interactions, as exemplified in the crystal packing of a variety of arenes.[243,244] Such conformational differences could account for the differences in the observed reactivities of the phenylethylamides **199** and **202**.

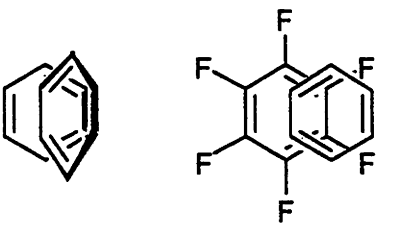


Figure 6.3. Benzene is known to adopt an edge to face stacking in the solid state whereas the mixture of hexafluorobenzene/benzene shows staggered face to face stacking.[243]

The acetamides **205** and **206** cannot exhibit intramolecular π-stacking. The relative rates of reaction of these two derivatives **205** and **206** with respect to one another still show an almost twofold difference. Therefore, alternate conformations that may be induced by having either benzoyl or pentafluorobenzoyl protecting groups are not the reason for the differences in the rates of bromination observed.

Inductive effects work through the sigma framework of a molecule to redistribute electron density. These effects tend to act only over very short distances. However, the possible presence of induction was examined by comparison of the relative rates of reaction of the amides **199, 202, 205** and **206** with the relative rates of bromination of the esters **207** and **208**. These two derivatives **207** and **208** exhibit a marked inductive effect, when compared with the corresponding amides **199** and **202,** as is evidenced by the downfield shift of the α and benzylic protons in their ^{1}H NMR spectra. This shift is most dramatic for the α-proton, being almost 0.9 ppm. The differences between the rates of reaction of the esters **207** and **208** are again around twofold. This shows that perfluorination has a similar effect on the rate of bromination to that seen in the amides **199, 202, 205** and **206.**

Evidence for the relative rates of reaction not being governed by an inductive effect comes from the comparison of inductive field parameters (σ_i). The inductive field parameters are a measure of the inductive effect exerted by various substituents.[229] Comparison of the inductive field parameters available for the amide and ester substituents examined show that there is no correlation between the inductive effect and the relative rate of bromination (Table 6.2).

Table 6.2. Comparison of relative rate with the inductive field parameters σ_i.

Compound[†]	Relative Rate	Substituent	σ_i
199	1.0[‡]	-NHCOPh	0.13
205	0.8	$-NHCOCH_3$	0.31
207	0.6	-OCOPh	0.26
206	0.33	$-NHCOCF_3$	0.38

[†]No σ_i value for the substituents of either **202** or **208** were available, so they have not been included in this table. [‡]Assigned as unity.

It can be seen that the acetamide substituent has a much higher inductive field parameter than the corresponding benzoyl ester. This would imply that the rate of reaction of the benzoyl ester **207** should be faster than the rate of reaction of the acetamide **205**. This is not the case so inductive effects can be discounted as the reason behind the relative rate differences between the phenylethyl derivatives examined.

The above differences in relative rate, with increasing electron withdrawing ability of the amide or ester substituent, are consistent with the effect that would be observed with anchimeric assistance, and not consistent with the other conformational or through bond interactions examined.

In the phenylalanine systems **33** and **47**, discussed in the Introduction, it was observed that the relative rate of bromination of the amide **47** was five times faster than the relative rate of reaction of the ester **33**.[75] The phenylethylamines **199** and **202** react only around twice as fast as their corresponding esters **207** and **208**. This is despite the usual increase in anchimeric assistance seen in comparable ionic systems on going from a less

stable four-membered ring to a more stable five-membered ring in the proposed transition state.

The major difference between the two systems is that the phenylalanines **47** and **33** are much more conformationally rigid than the phenylethylamines **199**, **202**, **207** and **208**. This comparative conformational restriction results in a kind of local concentration effect, with the carbonyl spending more time localised to where it can provide transition state stabilisation in the phenylalanines **47** and **33**. Therefore, any electronic changes in the protecting groups that result in diminished stabilisation of the benzylic radical will appear more significant in the phenylalanyl case. This hypothesis is supported by X-ray crystallographic data for the closely related phenylalanine bromide, (2*S*, 3*S*)-3-bromo-*N*-phthaloyl-*p*-nitrophenylalanine methyl ester, which shows that the ester carbonyl is situated in the correct orientation to provide anchimeric assistance.[227] Significant rotation about the α-carbon-carbonyl bond in the phenylalanine systems **47** and **33** would additionally be disfavoured, compared with the corresponding α-carbon-amido bond in phenylethylamide systems, by steric interactions of the ester carbonyl group with the bulky phthaloyl moiety.

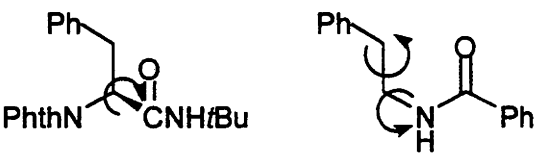
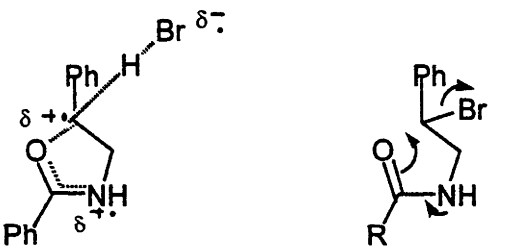


Figure 6.4. Phenylethylamines have more degrees of freedom and so the carbonyl group may be less likely to participate in neighbouring group stabilisation.

Anchimeric assistance in radical reactions *via* 1,4 neighbouring group participation is known to be highly unusual. The above examples also provide support for such an

effect in a system that would proceed *via* 1,5 neighbouring group participation of the carbonyl group. An alternative in this particular example, however, is that the assistance is proceeding *via* 1,3 assistance by the α-nitrogen. Evidence that this is unlikely to be the case comes from the decomposition reaction observed, whereby cyclisation of the bromo-phenylethylamide **209** proceeds spontaneously to give the oxazoline **219**. The formation of the oxazoline **219** is indicative of a five-membered transition state for the polar cyclisation reaction. Since the transition state of the hydrogen abstraction reaction is also polar, it is likely that this radical reaction will also proceed through a 5-membered transition state.



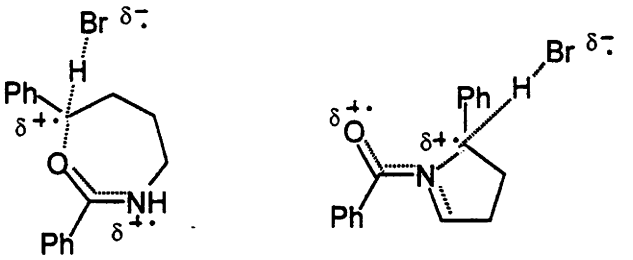
Radical reaction Polar cyclisation reaction

Figure 6.5. Proposed transition states for both the radical anchimeric assistance and the cyclisation reactions.

To examine the effects of increasing the ring size required to afford stabilisation in the transition state, the relative rates of bromination of the phenylpropyl derivatives **200** and **203**, and the phenylbutyl derivatives **201** and **204** were examined. Reactions at the benzylic positions were observed and in each case. The rates of bromination of the fluorinated derivatives **203** and **204** were notably slower than those of the corresponding benzoyl derivatives **200** and **201**. This is suggestive of anchimeric assistance in both of these systems.

The difference between the relative rates of reaction of the phenylethyl derivatives **199** and **202** was approximately twofold. With the addition of one extra carbon in the alkyl chain, the difference between the relative rates of bromination of the phenylpropyl derivatives **200** and **203** drops to just over 1.5. The rate difference between the fluorinated derivative and its unfluorinated counterpart is suggestive of 1,6-anchimeric assistance. The absolute rate of reaction, however, increases notably in comparison to the phenylethyl derivatives. The phenylpropyl derivative **200** reacts approximately 4.5 times faster than the corresponding phenylethyl derivative **199**. A less dramatic increase is also seen when the phenylpropyl and phenylbutyl derivatives are compared, with the addition of the extra carbon atom to the alkyl chain affording an increase in absolute rate of around one and a half times. These increases in absolute rate of reaction with increasing alkyl chain length are likely to be involved with steric approach to the reaction site. The effect of this steric congestion should decrease with each subsequent carbon atom addition.

The rate difference between the reactions of the phenylbutyl derivatives **201** and **204** is again around 1.5. The distance of the reactive centre from the amido protecting group in this case is several atoms. This result is therefore suggestive of anchimeric assistance and also is convincing evidence that the difference between the rates of reaction of the phenylethylamides **199** and **202** cannot be dismissed as being due to an inductive effect. 1,7-Neighbouring group participation is likely to be very unusual. However, on examination of pyrrolidine **220**, the product of decomposition of the benzoyl-phenylbutyl bromide **217**, it is apparent that 1,7-carbonyl participation is not necessary for the reaction and is, in actual fact, unlikely. A more plausible explanation is a switch to a 1,5-neighbouring group effect. This explanation is supported by the likely mechanism of formation of the pyrrolidine **220** from the bromide **217**.



1,7-carbonyl participation 1,5-neighbouring group participation

Figure 6.6. Pyrrolidinone formation from the bromide **217** supports the 5-membered transition state intermediate (right) rather than the more contrived 7 membered transition state (left).

Inductive through bond and π-stacking effects have been discounted as the cause of the observed difference in the rates of reaction of a variety of benzoylated and pentafluorobenzoylated phenylalkyl compounds. Thus, it appears that anchimeric assistance *via* a five membered or larger transition state is possible in radical reactions. This is a novel neighbouring group effect, which has not previously been reported in the literature. However, this assistance is quite small, giving rise to rate enhancements of only a factor of two, and slightly less for the larger systems examined. This effect is much smaller in magnitude than the 1,4 anchimeric assistance observed in the phenylalanyl systems previously studied.[165] This was attributed to a lack of conformational rigidity in the phenylalkyl derivatives when compared with the phenylalanyl derivatives, diminishing the ability of the neighbouring carbonyl group to stabilise the incipient radical. The observation of this effect is of interest as a potential contributing factor to the stabilisation of β-centred radicals in the amino acid residues of peptides.

Conclusion

The work described in this thesis has involved experimental and theoretical investigations of some ways in which protecting groups can influence the stability and rate of formation of amino acid radicals.

The unusual selectivity for the oxidation of glycine residues in biological systems has been examined theoretically. It has been demonstrated that non-bonding interactions or the side chains of amino acids with *N*-acetyl-protecting groups have a dramatic influence on the observed relative RSEs of the corresponding amino acid radicals. These relative RSEs also correlate well with the relative rates of reactions of the corresponding *N*-benzoyl protected amino acids, indicating that radical stability is one of the major factors in determining selectivity of hydrogen abstraction in amino acid derivatives. Thus, the reason for the preferential reactivity of glycine residues, at least in *vitro* has been elucidated.

By understanding the interactions in the radicals of protected amino acid derivatives, it was possible to design systems whereby the reactivity of the α-centre toward hydrogen abstraction was negligible. The low reactivity of such systems may find application as enzyme inhibitors or the design of oxidation resistant peptides.

The influence of electronic effects exerted by a protecting group on adjacent radical centres has also been explored. Both acyl and sulfonyl protecting groups were examined theoretically and experimentally. From the results obtained it was determined that there exists a correlation between the RSE of a protected α-centred glycyl radical and the pK_a of the acid that corresponds to the protecting group. This correlation is fairly good within either the acyl or sulfonyl series, but breaks down when these disparate protecting

groups are compared. It is envisaged, however, that this correlation will provide a rough measure of glycyl radical reactivity such that protecting groups can be chosen which will allow selective reaction of certain glycine residues.

From an examination of the factors governing the stability of radicals adjacent to a phthaloyl protecting group it has been seen that steric, electronic and transition state factors all contribute to the selectivity of formation of these radicals.

The very low stability of radicals adjacent to a triflamide protecting group has been exploited in the regioselective radical bromination and chlorination of a selection of amino acids. This protecting group appears to be a viable alternative to the phthaloyl group for the selective functionalisation of small peptides and amino acid side chains.

Polarity of the transition state has been found to be the dominant factor in determining relative reactivity of benzylic radicals, as opposed to radical stability. This has been used to look at the effect of electron demand on the rates of reaction of a selection of arylalanines to probe the 1,4-anchimeric assistance reported in the reactions of these derivatives. The results have been shown to be consistent with anchimeric assistance.

Anchimeric assistance has also been discovered in the radical reactions of phenylalkylamides. This implies that neighbouring group effects in the radical reactions of amino acid derivatives may be more widespread than previously thought. It is does not appear to be important whether this neighbouring group effect acts *via* the amide carbonyl or the nitrogen. In view of this, it may be envisaged that stabilisation of the transition state leading to benzylic radicals simply requires complexation to the π-system of the amide. This would help to explain the unusual nature of the 1,4-interaction reported in the literature, because stabilisation may not be *via* a four-membered transition state, but rather complexation to the π-system through a more usual three membered transition state. Further work in this area is required to understand the exact nature of this neighbouring group effect.

Experimental

General

Melting points were determined on a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected.

Elemental analyses were carried out by the Research School of Chemistry Microanalytical Service at the Australian National University, Canberra, Australia.

Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR spectrophotometer either as nujol mulls or neat liquids between sodium chloride plates unless otherwise specified.

Nuclear Magnetic Resonance (NMR) spectra were recorded on either a Gemini 300 or Varian VXR 500S spectrometer. Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded at 300 MHz, unless otherwise specified, and carbon nuclear magnetic resonance (^{13}C n.m.r.) spectra were recorded at 75.5 MHz. Spectra were either recorded in deuteriochloroform or in methylene chloride-d_2 using chloroform δ_H 7.26 ppm and dichloromethane δ_H 5.29 ppm as the internal standards, respectively. Coupling constant values J between either protons or carbon and fluorine atoms are given in hertz. Multiplicities are abbreviated to; s, singlet; d, doublet; t, triplet; q, quartet; qu, quintet; se, sextet; non, nonet; m, multiplet; br, broad.

Electron impact (EI) mass spectra were recorded with either a VG Autospec double focussing trisector mass spectrometer operating at 70eV or on a Vacuum Generators ZAB2-SEQ mass spectrometer. Electrospray (ES) mass spectra were recorded on a VG

Quatro 2 triple quadrupole mass spectrometer.

Analytical thin layer chromatography was performed using Merck Kieselgel 60 F_{254} silica on aluminium backed plates. Preparative chromatography was performed either using dry flash column chromatography[245] or radial chromatography on a Harrison research model 7924T chromatotron, with Merck Kieselgel 60 PF_{254} containing gypsum.

High performance liquid chromatography (HPLC) was carried out using a Waters 510 solvent pump, a Rheodyne 200 μl injector, a Waters model 486 tunable absorbence detector and a Waters model 410 differential refractometer, in conjunction with a Digital Electronics Corporation Data Station running Millennium chromatography manager. Analyses were performed using an Alltech econosphere CN 5μ column (4.6 x 250 mm) eluting with various mixtures of ethyl acetate/hexane at 1.5 ml/min. Semi-Preparative HPLC chromatography was performed using an Alltech econosphere CN 10μ column (22 x 250 mm) eluting with various mixtures of ethyl acetate/hexane at 9 ml/min.

All solvents and reagents used were purified using standard methods.[246] Organic extracts were dried by the addition of anhydrous magnesium sulfate, unless otherwise specified.

An OSRAM ULTRA-VITALUX® 300 W (240 V, E 27) sunlamp was used as the light source to initiate radical reactions in carbon tetrachloride, at a distance of between 5–10 cm from the reaction vessel. Reactions in methylene chloride-d_2 were performed in Wilmad Quartz NMR tubes, initiated with a Clemco ultraviolet Oliphant reactor at 300 nm, at a distance of 10 cm from the light source.

N-Benzoylalanine methyl ester, *N*-phthaloylglycine methyl ester, *N*-phthaloylphenylalanine methyl ester, *N-tert*-butyl-N^{α}-phthaloylphenylalaninamide and *N-tert*-butylbenzamide were available for use.

Competitive Reactions with NBS

Relative rates of reaction were determined by treating various mixtures of substrates in carbon tetrachloride with NBS (*ca.* 1.0 equiv.) at reflux under nitrogen and in the presence of *tert*-butylbenzamide (0.1-0.5 equiv.) as an internal standard, whilst being irradiated with a 300 W sunlamp. After being allowed to cool to room temperature, the mixtures were concentrated under reduced pressure and then analysed using ^{1}H NMR spectroscopy. The data obtained from these experiments are summarised in the Appendices.

N–Benzoylglycine Methyl Ester (6)

To a suspension of glycine methyl ester hydrochloride (5.0 g, 40 mmol) and benzoyl chloride (5.8 g, 41 mmol) in dichloromethane (50 ml) was added triethylamine (8.38 g, 83 mmol) dropwise with stirring. A precipitate formed and the mixture was stirred overnight. The mixture was washed with 10% HCl (2 x 50 ml) and then saturated sodium bicarbonate solution (2 x 50 ml). The organic layer was then dried, filtered and evaporated under reduced pressure to obtain the crude product which was then recrystallised to give the *title compound* **6** as colourless needles (5.31 g, 28 mmol, 70%), mp 82 °C from ethyl acetate/hexane (lit.,[247] 83–84 °C); δ_H 3.81 (3H, s), 4.27 (2H, d, *J* 5.0), 6.64 (1H, br s), 7.43–7.53 (3H, m) and 7.80–7.83 (2H, m).

N–Benzoylvaline Methyl Ester (8)

L-Valine (1.0 g, 8.5 mmol) was added to methanol (100 ml), which had been pretreated with thionyl chloride (1.2 g, 10.3 mmol), and allowed to stir overnight. The solution was evaporated under reduced pressure to yield a white powder, which was redissolved in methanol and evaporated under reduced pressure twice to remove excess hydrochloric

acid. The resultant colourless hydrochloride salt was dissolved in dichloromethane (50 ml) by the addition of triethylamine (1.7 g, 17.1 mmol), and benzoyl chloride (1.2 g, 8.5 mmol) was added dropwise with stirring. A precipitate formed and the mixture was stirred overnight. The mixture was washed with 10% HCl (2 x 50 ml) and then saturated sodium bicarbonate solution (2 x 50 ml). The organic layer was then dried, filtered and evaporated under reduced pressure to obtain the crude product which was then recrystallised to give the *title compound* **8** as colourless needles (1.05 g, 4.5 mmol, 53%), mp 86 °C from ethyl acetate/hexane (lit.,[193] 86 °C); δ_H 0.99 (3H, d, *J* 7.4), 1.01 (3H, d, *J* 7.0), 2.29 (1H, m), 3.79 (3H, s), 4.80 (1H, dd, *J* 4.8, 8.7), 6.64 (1H, br d), 7.43–7 53 (3H, m) and 7.80–7.83 (2H, m).

2–Bromo–*N*–benzoylglycine Methyl Ester (12)

To a solution of *N*-Benzoylglycine methyl ester **6** (100 mg, 0.52 mmol) in carbon tetrachloride (50 ml) was added NBS (93 mg, 0.52 mmol). The mixture was irradiated with a 300W UV lamp, and heated at reflux under nitrogen for 10 minutes.[67] This afforded the corresponding 2-bromoglycine derivative **12**. δ_H 3.91 (3H, s), 6.68 (1H, d, *J* 10.2), 7.42–7.60 (3H, m) and 7.81–7.85 (2H, m).

***N*–Phthaloyl–*O*–methyltyrosine Methyl Ester (52)**

The *title compound* was prepared *via* the method of Barton and Brown.[248] *N*-Phthaloyltyrosine methyl ester **192** (500 mg, 1.6 mmol) with sodium hydride (62 mg of 60% dispersion in oil, 1.6 mmol) and methyl iodide (220 mg, 1.6 mmol) afforded, after chromatography on silica, the *title compound* as a colourless powder (335 mg, 1.0 mmol, 64%) mp 143–154 °C; δ_H 3.50 (2H, m), 3.70 (3H, s), 3.78 (3H, s), 5.11 (1H, dd, *J* 5.8, 10.6), 6.71 (2H, d, *J* 8.6), 7.07 (2H, d, *J*, 8.6), 7.68–7.70 (2H, m) and 7.77–

7.80 (2H, m); *m/z* 340 (M^++H, 17%), 339 (M^+, 29), 280 (21), 193 (43), 192 (100), 161 (27), 122 (33), 121 (78) and 104 (25). ^{1}H NMR spectral characteristics are consistent with those previously reported.[224]

N–*tert*–Butyl–N^{α}–phthaloyl–*O*–methyltyrosinamide (53)

To a solution of *N*-phthaloyl-*O*-methyltyrosine **196** (410 mg, 1.3 mmol) and triethylamine (130 mg, 1.3 mmol) in dichloromethane (30 ml) was added ethyl chloroformate (140 mg, 1.3 mmol). The mixture was stirred for 10 minutes, then was cooled to 0 °C. *tert*-Butylamine (92 mg, 1.3 mmol) was added, and the mixture was stirred at 0 °C for 15 minutes. The mixture was allowed to warm to room temperature, then was stirred for a further 30 minutes. The mixture was filtered and the filtrate was washed with water and then dried. The solvent was removed under reduced pressure to afford the *title compound* **53** as a white foam (390 mg, 1.0 mmol, 81%) mp 138–143 °C from ether/dichloromethane/hexane (Found: C, 69.41 H, 6.33 N, 7.09. $C_{22}H_{24}N_2O_4$ requires C, 69.46; H, 6.36; N, 7.36%.); ν_{max} cm^{-1} 3311, 1775, 1755, 1716, 1658, 1610, 1552, 1513, 1302, 1252, 1222, 1174, 1118, 1088, 1036, 1014, 953, 873, 836 and 764; δ_H 1.31 (9H, s), 3.44 (1H, d, *J* 10.0), 3.47 (1H, d, *J* 6.8), 3.70 (3H, s), 4.95 (1H, dd, *J* 6.8, 10.0), 5.89 (1H, br s), 6.73 (2H, d, *J* 8.5), 7.09 (2H, d, *J* 8.5), 7.68–7.71 (2H, m) and 7.78–7.80 (2H, m); δ_C 32.18, 34.92, 52.20, 55.69, 57.43, 114.52, 121.78, 124.05, 128.37, 130.50, 132.07, 134.84, 159.02, 168.06 and 168.68; *m/z* 380 (M^+, 36%), 280 (49), 262 (21), 234 (40), 233 (100), 177 (43), 176 (69), 163 (31), 161 (67), 148 (15), 133 (36), 121 (83), 108 (59) and 104 (33).

N–Phthaloyl–3,4–dimethoxyphenylalanine Methyl Ester (54)

The *title compound* was prepared *via* the method of Barton and Brown.[248] *N*-Phthaloyl-3,4-dihyroxyphenylalanine methyl ester **189** (500 mg, 1.5 mmol) with sodium hydride (200 mg of 60% dispersion in oil, 5.0 mmol) and methyl iodide (430 mg, 3.0 mmol) afforded, after chromatography on silica, the *title compound* as a pale yellow foam (280 mg, 0.8 mmol, 50%) mp 96–98 °C (Found: C, 64.96; H, 4.98; N, 4.02. $C_{20}H_{19}NO_6$ requires C, 65.03; H, 5.18; N, 3.79%.); δ_H 3.49 (2H, m), 3.66 (3H, s), 3.73 (3H, s), 3.75 (3H, s), 5.12 (1H, dd, *J* 6.1, 10.7) 6.61–6.67 (3H, m), 7.64–7.68 (2H, m) and 7.72–7.76 (2H, m); *m/z* 369 (M^+, 40), 223 (31), 222 (100), 163 (47) and 151 (91). ^{1}H NMR spectral characteristics are consistent with those previously reported.[224]

N–*tert*–Butyl–N^{α}–phthaloyl–3,4–dimethoxyphenylalaninamide (55)

To a solution of *N*-phthaloyl-3,4-dimethoxyphenylalanine **194** (900 mg, 2.5 mmol) and triethylamine (290 mg, 2.9 mmol) in dichloromethane (30 ml) was added ethyl chloroformate (300 mg, 2.8 mmol). The mixture was stirred for 10 minutes, then was cooled to 0 °C. *tert*-Butylamine (200 mg, 2.8 mmol) was added, and the mixture was stirred at 0 °C for 15 minutes. The mixture was allowed to warm to room temperature, then was stirred for a further 30 minutes. The mixture was filtered and the filtrate was washed with water and then dried. The solvent was removed under reduced pressure to afford the *title compound* **55** as a white foam (580 mg, 1.4 mmol, 55%) mp 81–82 °C from dichloromethane/hexane (Found: C, 64.61 H, 6.39 N, 6.28. $C_{23}H_{53}N_2O_4.H_2O$ requires C, 64.47; H, 6.59; N, 6.54%.); ν_{max} cm^{-1} 3296, 1774, 1712, 1654, 1608, 1590, 1541, 1514, 1419, 1260, 1157, 1139, 1105, 1026, 964, 935, 885, 874, 795 and 766; δ_H 1.29 (9H, s), 1.61 (2H, s, H_2O of crystallisation), 3.44 (2H, m), 3.68 (3H, s), 3.74 (3H, s), 4.96 (1H, dd, *J* 6.7, 10.1), 5.99 (1H, s), 6.64 (1H, s), 6.67 (1H, s), 6.68 (1H, s), 7.65–7.69 (2H, m) and 7.73–7.77 (2H, m); δ_C 29.02, 35.12, 52.08, 56.10 (dd *J* 3, 6.7), 57.23,

111.63, 112.18, 121.46, 123.88, 129.69, 131.88, 134.66, 148.20, 149.22, 167.95 and 168.54; *m/z* 410 (M^+, 41%), 310 (20), 264 (40), 263 (100), 206 (47), 191 (49), 151 (53), 138 (29) and 58 (31).

N–Benzoyl–*tert*–Leucine Methyl Ester (86)

L-*tert*-Leucine (0.6 g, 4.6 mmol) was added to methanol (50 ml), which had been pretreated with thionyl chloride (0.60 g, 5.1 mmol), and allowed to stir overnight. The solution was evaporated under reduced pressure to yield a colourless powder, which was redissolved in methanol and evaporated under reduced pressure twice to remove excess hydrochloric acid. The resultant colourless hydrochloride salt was dissolved in dichloromethane (25 ml), effected by triethylamine (0.93 g, 9.2 mmol), and benzoyl chloride (0.65 g, 4.6 mmol) was added dropwise with stirring. A precipitate formed and the mixture was stirred overnight. The mixture was washed with 10% HCl (2 x 10 ml) and then saturated sodium bicarbonate solution (2 x 10 ml). The organic layer was then dried, filtered and evaporated under reduced pressure to obtain the crude product which was then recrystallised to give the *title compound* **86** as colourless needles (0.48 g, 1.9 mmol, 42%), mp 68–69 °C from hexane (lit.,[194] 65 °C); δ_H 1.06 (9H, s), 3.75 (3H, s), 4.72 (1H, d, *J* 9.5), 6.67 (1H, br d, *J* 9.5), 7.43–7.53 (3H, m) and 7.80–7.83 (2H, m). The spectral characteristics were consistent with those previously reported.[194]

Treatment of *N*–Benzoyl–*tert*–Leucine Methyl Ester (86) with NBS

A mixture of *N*-benzoyl-*tert*-leucine methyl ester **86** (50 mg, 0.20 mmol) and excess NBS (50 mg, 28 mmol) in carbon tetrachloride (5 ml) was heated at reflux for 9 h under nitrogen whilst being irradiated with a 300 W sunlamp. The mixture was cooled to room temperature, filtered and the solvent evaporated under reduced pressure to yield

the crude bromide **107** (95% by internal standard); δ_H 1.37 (9H, s), 3.68 (3H, s), 7.43–7.57 (3H, m), 7.86–7.90 (2H, m). Attempted isolation of this bromide by washing with 5% sodium metabisulfite solution and water, and subsequent recrystallisation from dichloromethane/hexane, instead afforded the *N*-benzoyl-α-hydroxy-*tert*-leucine methyl ester **108** δ_H 1.25 (9H, s), 3.84 (3H, s), 6.95 (1H, br s), 7.41–7.47 (2H, m), 7.52–7.54 (1H, m), 7.83–7.86 (1H, m). Treatment of the crude reaction bromination mixture with methanol instead afforded the α-methoxy-*tert*-leucine methyl ester **86** (Found *m/z* 222.07608. $C_{11}H_{12}NO_4$ requires *m/z* 222.07663. Found *m/z* 121.05272. C_7H_7NO requires *m/z* 121.05276.); δ_H 1.13 (9H, s), 3.51 (3H, s), 3.83 (3H, s), 5.57 (1H, br s) 7 43–7.55 (3H, m) and 7.73–7.78 (2H, m).

N–Benzoyl 3,3,3–Trifluoroalanine Methyl Ester (87)

The *title compound* was prepared *via* modifications of the methods of Weygand, Steglich and Tanner[195]; Weygand and Steglich[196]; and Weygand, Steglich and Oettmeier[200]. Trifluoroacetic anhydride (48.3 g, 0.23 mol) was carefully added to alanine (8.9 g, 0.10 mol) and the mixture warmed until the alanine had dissolved. The mixture was then refluxed for 20 minutes at 80 °C and subsequently for 20 minutes at 140 °C. The excess anhydride was removed under reduced pressure and the residue suspended in ether and then washed with chilled saturated sodium bicarbonate. The organic layer was dried and the ether removed. The residue was cooled and over a period of 10 minutes a mixture of ethanethiol (33.6 g, 0.54 mol) and 45% HBr/Acetic Acid (24 ml) was added dropwise. The mixture was allowed to stand overnight at room temperature whilst a precipitate formed. The volatile components were then removed under reduced pressure and the residue dissolved in ether. After refrigeration, the precipitate **103** was collected and washed with a little cold ether and then dissolved in dichloromethane (75 ml) and pyridine (22 ml). The mixture was cooled to 0 °C and stirred for one hour, over which time benzoyl chloride (15.7 g, 0.11 mol) was added. The mixture was then stirred for

another 4 hours at 0 °C and then allowed to stir at room temperature overnight. The solvent was removed and the crude solid recrystallised from carbon tetrachloride/hexane (100 ml of each) to afford 2,2,2-trifluoro-1-ethylmercapto-*N*-benzoylethylamine **102** as colourless crystals (19.1 g, 0.073 mol, 73%). This compound was dissolved in acetic acid (120 ml) and a mixture of acetic anhydride (40 ml) and 6% hydrogen peroxide (150 ml). After 4 hours in an icebath, the mixture was allowed to warm to room temperature and left for 2 days. The solution was filtered to obtain 2,2,2-trifluoro-1-ethylsulfone-*N*-benzoylethylamine **104** as a colourless solid (6.1g, 0.02 mol, 28%) and evaporation of the filtrate under reduced pressure afforded a further 10 g (0.03 mol, 47%) to bring the total yield to 16.1 g (0.05 mol, 75%) mp 150 °C (subl.) (lit.,[196] 171 °C) (Found: C, 44.70; H, 4.17; N, 4.99. $C_{11}H_{12}NO_3SF_3$ requires C, 44.74; H, 4.10; N, 4.74%.); δ_H 1.48 (3H, t, *J* 7.5), 3.15 (2H, m), 6.03 (1H, m), 7.15 (1H, br dd, *J* 1.5, 10.4), 7.45–7.66 (2H, m), 7.80–7.89 (1H, m) and 8.09–8.12 (2H, m); *m/z* 240 (4%), 212 (18), 105(26), 97(43) and 75(82).

The *N*-benzoylsulfone **104** (0.5 g, 1.7 mmol) was placed in a flame dried two necked flask. The flask was then both evacuated and purged with nitrogen 5–10 times before the addition of freshly distilled THF (25 ml). The solution was then cooled to –40 °C, whilst being kept under nitrogen, and excess vinyl magnesium bromide (Aldrich, 1.0 M THF solution) was added in aliquots dropwise with stirring until the reaction was seen to have completed by TLC analysis (R_f = 0.43, 20% EtAc/Hex). The excess Grignard reagent remaining was neutralised by the careful addition of 15 ml of 30% acetic acid. The THF was then removed under reduced pressure and the residue obtained was acidified with 2N hydrochloric acid. This mixture was then extracted with ethyl acetate and the organic layer was washed with saturated sodium bicarbonate solution and then evaporated to dryness to obtain the crude vinyl amide **105**. This vinyl amide **105** was then redissolved in acetone (20 ml) and was mixed with 3N sulfuric acid (3.6 ml). The solution was cooled to 0 °C and was stirred gently whilst an aqueous solution of potassium permanganate (1.8 g, 11.7 mmol in 60 ml) was added. The mixture was allowed to stir for a further one hour at 0 °C before being allowed to warm to room

temperature for 24 hours. Subsequently, a further 5.6 ml 3N sulfuric acid was added and then the excess potassium permanganate reduced with sodium metabisulfite. The solution was then concentrated under reduced pressure and extracted three times with ethyl acetate. The organic layer was then dried and the solvent removed under reduced pressure to obtain the crude acid **106**. This was then added to methanol (10 ml) which had been pretreated with excess thionyl chloride and the solution was left to stir for two hours. The methanol was removed under reduced pressure to yield a colourless solid, which was redissolved in methanol and evaporated under reduced pressure twice to remove residual hydrochloric acid. Recrystallisation from ethyl acetate/hexane afforded the *title compound* **87** as a colourless powder (200 mg, 0.8 mmol, 45%), mp 107 °C (subl.) (lit.,[196] 109–110 °C); δ_H 3.91 (3H, s), 5.59 (1H, qu, *J* 7.6), 6.85 (1H, br d), 7.46–7.51 (2H, m), 7.55–7.61 (1H, m) and 7.81–7.86 (2H, m).

_N_–Benzenesulfonylglycine Methyl Ester (111)

To a suspension of glycine methyl ester hydrochloride (5.0 g, 40 mmol) and benzenesulfonyl chloride (7.0 g, 40 mmol) in dichloromethane (50 ml) was added triethylamine (8.1 g, 80 mmol) dropwise with stirring. A precipitate formed and the mixture was stirred overnight. The mixture was washed with 10% HCl (2 x 50 ml) and then saturated sodium bicarbonate solution (2 x 50 ml). The organic layer was then dried, filtered and evaporated under reduced pressure to obtain crude product which was then recrystallised from water to give the *title compound* **111** as colourless needles (6.5 g, 28 mmol, 71%) mp 68 °C (lit.,[214] 69–70 °C); δ_H 3.63 (3H, s), 3.81 (2H, d, *J* 5.7), 5.06 (1H, br s), 7.50–7.63 (3H, m) and 7.85–7.88 (2H, m).

N–Trifluoroacetylglycine Methyl Ester (110)

To a suspension of glycine methyl ester hydrochloride (5.0 g, 40 mmol) and trifluoroacetic anhydride (8.4 g, 40 mmol) in dichloromethane (100 ml) was added triethylamine (8.1 g, 80 mmol) dropwise with stirring and left under nitrogen to stir overnight. The resulting mixture was washed with 10% hydrochloric acid (2 x 50 ml) and saturated sodium bicarbonate (2 x 50 ml), dried over magnesium sulfate and evaporated under reduced pressure to yield the *title compound* **110** as a yellow oil (6.3 g, 34 mmol, 85%); δ_H 3.80 (3H, s) and 4.13 (2H, d, *J* 5.3). The spectral characteristics were consistent with those previously reported.[37]

N–Trifluoromethanesulfonylglycine Methyl Ester (112)

Triethylamine (3.21 g, 31.9 mmol) was added to a suspension of glycine methyl ester hydrochloride (2.01 g, 15.8 mmol) in dry dichloromethane (150 ml). The resulting solution was placed under a blanket of nitrogen and cooled to –78 °C whilst stirring. A solution of trifluoromethanesulfonic anhydride (4.53 g, 16 mmol) in dry dichloromethane (30 ml) was added dropwise over 10 minutes and the mixture allowed to warm to room temperature overnight. The solution was then filtered to give a clear yellow solution and washed with 10% hydrochloric acid (2 x 50 ml) followed by saturated sodium chloride (2 x 50 ml). The organic layer was dried over magnesium sulphate, filtered and evaporated under reduced pressure to give a pale yellow powder (2.64 g, 11.9 mmol, 76%). Recrystallisation from ethyl acetate/hexane gave the *title compound* **112** as pale yellow grains (1.80 g, 8.1 mmol, 52%) mp 96–97 °C; (Found: C, 22.07; H, 2.45; N, 6.59. $C_4H_6F_3NO_4S$ requires C, 21.72; H, 2.73; N, 6.33%); ν_{max} cm^{-1} 3230, 1734 and 1186; δ_H 3.83 (3H, s), 4.07 (2H, d, *J* 5.3) and 5.43 (1H, br s); δ_C 45.1, 53.7, 120.0 (q, *J* 319) and 169.4; *m/z* 222 (M^+, 13%), 162 (100), 133 (15.5), 124 (27), 78 (25), 69 (33) and 59 (21).

2–Bromo–*N*–trifluoroacetylglycine Methyl Ester (115)

To a solution of *N*-trifluoroacetylglycine methyl ester **110** (0.1g, 0.54 mmol) in carbon tetrachloride (5 ml) was added NBS (0.097g, 0.54 mmol). The mixture was irradiated with a 300W UV lamp and heated at reflux under nitrogen for 2.5 hours.[67] This afforded the corresponding 2-bromoglycine derivative **115**, δ_H 3.92 (3H, s) and 6.33 (1H, d, *J* 9.5). The spectral characteristics were consistent with those previously reported.[37]

2–Bromo–*N*–benzenesulfonylglycine Methyl Ester (116)

To a solution of *N*-benzenesulfonylglycine methyl ester **111** (200 mg, 0.87 mmol) in carbon tetrachloride (50 ml) was added NBS (160 mg, 0.90 mmol). The mixture was irradiated with a 300W UV lamp, and heated at reflux under nitrogen for 12.5 minutes.[67] This afforded the corresponding 2-bromoglycine derivative **116** (96% by internal standard); δ_H 3.83 (3H, s), 6.18 (1H, d, *J* 11.3), 6.61 (1H, d, *J* 11.1), 7.48–7.66 (3H, m) and 7.91–7.96 (2H, m).

2–Methoxy–*N*–benzoylglycine Methyl Ester (117)

The 2-methoxyglycine derivative **117** was prepared for characterisation by allowing the corresponding crude bromide **12** to stir with methanol (1 ml) overnight. After concentration under reduced pressure and chromatography on silica, crude 2-methoxy-*N*-benzoylglycine methyl ester **117** was obtained (98 mg, 0.44 mmol, 85%). This was further purified by recrystallisation from ethyl acetate/hexane to yield a white solid (68 mg, 0.30 mmol, 59%) mp 72–73 °C (lit.,[216] 86–87 °C); (Found: C, 59.23; H, 5.98;

N, 6.51. $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27%); ν_{max} cm^{-1} 3310, 1763, 1647, 1521, 1341, 1287, 1227, 1201 and 1109; δ_H 3.56 (3H, s), 3.87 (3H, s), 5.78 (1H, d, *J* 9.1), 7.12 (1H, br d, *J* 8.2), 7.44–7.59 (3H, m) and 7.83–7.86 (2H, m); *m/z* 223 (0.6%), 164 (45), 105 (100) and 77 (40).

2–Methoxy–*N*–trifluoroacetylglycine Methyl Ester (118)

The corresponding 2-methoxyglycine derivative **118** was prepared for characterisation by allowing the filtered extract of the crude bromide **115** to stir with methanol (1 ml) for 2 hours. After concentration under reduced pressure, and recrystallisation from ethyl acetate/hexane, the *title compound* **118** was isolated as colourless crystals (0.097 g, 0.45 mmol, 83%) mp 96–98 °C (lit.,[37] 96–99 °C); δ_H 3.52 (3H, s), 3.86 (3H, s) and 5.49 (1H, d, *J* 8.9). The physical and spectral characteristics of this compound were consistent with those previously reported.[37]

2–Methoxy–*N*–benzenesulfonylglycine Methyl Ester (119)

The corresponding 2-methoxyglycine derivative **119** was prepared for characterisation by allowing the filtered extract of the crude bromide **116** to stir with methanol (1 ml) overnight. After concentration under reduced pressure and chromatography on silica, 2-methoxy-*N* benzenesulfonyl-glycine methyl ester **119** was obtained as a white powder (0.095 g, 0.37 mmol, 42%); (Found *m/z* 228.0328. $C_9H_{10}NO_4S$ (M^+) requires *m/z* 228.0331; Found *m/z* 200.0376. $C_8H_{10}NO_3S$ (M^+) requires *m/z* 200.0381); ν_{max} cm^{-1} 3366, 2866, 1750, 1450, 1350, 1294, 1227, 1166, 1100 and 1077; δ_H 3.30 (3H, s), 3.70 (3H, s), 5.06 (1H, d, *J* 9.1), 5.83 (1H, br d, *J* 8.8), 7.48–7.62 (3H, m) and 7.85–7.95 (2H, m); δ_C 53.7, 55.9, 63.1, 127.4, 129.7, 133.5, 141.4 and 168.0; *m/z* 228 (11%), 214 (10),

200 (59), 141 (75), 77 (100) and 59 (12).

2–Succinimido–*N*–trifluoromethanesulfonylglycine Methyl Ester (120)

To a solution of protected amino acid **112** (0.1 g, 0.45 mmol) in carbon tetrachloride (15 ml) under a nitrogen atmosphere was added NBS (0.081g, 0.45 mmol) and the resultant mixture was heated at reflux for 24 hours with irradiation from a 300W UV lamp. The mixture was cooled to room temperature to afford a mixture of starting material (38% by NMR) and the crude succinimide adduct (61% by NMR); (Found *m/z* 259.0000 $C_8H_9F_3N_2O_6S$ (M^+) requires *m/z* 258.9999); δ_H 2.83 (4H, s), 3.85 (3H, s), 6.08 (1H, d, *J* 9.0) and 7.75 (1H, br d, *J* 8.8); δ_C 28.03, 54.53, 58.28, 119.77 (q, *J* 319), 164.83 and 175.09; *m/z* (EI) 261 (15%), 260 (18), 259 (100), 221 (12), 162 (12) and 69 (24); (ES, MeOH) [M^++H], 319 (22%); (ES, MeOH) [M^-–H], 317 (92%).

***N*–Trifluoromethanesulfonylglycylglycine Methyl Ester (156)**

Glycylglycine (0.8 g, 6 mmol) was added to methanol (20 ml), which had been pretreated with thionyl chloride (0.85 g, 7 mmol), and allowed to stir overnight. The solution was evaporated under reduced pressure to yield a white powder, which was redissolved in methanol and evaporated under reduced pressure twice to remove excess hydrochloric acid. This solid was suspended in freshly distilled dichloromethane (20 ml) under nitrogen and triethylamine (1.26 g, 12.5 mmol) added with stirring. The suspension was cooled to –78 °C and trifluoromethanesulfonic anhydride (1.67 g, 6 mmol) in dichloromethane (10 ml) added dropwise. The mixture was allowed to warm to room temperature overnight. The solution was washed with 10% hydrochloric acid (2 x 10 ml) and saturated sodium chloride (2 x 10 ml) and the organic layer dried over magnesium sulfate. After filtration and evaporation under reduced pressure, the *title*

compound **156** was obtained as a pale yellow powder (0.290 g, 1.0 mmol, 18%) mp 121 °C; (Found: C, 25.96; H, 3.22; N, 10.08. $C_4H_6F_3NO_4S$ requires C, 25.90; H, 3.26; N, 10.07%); ν_{max} cm^{-1} 3297, 3226, 1725, 1660, 1565, 1231 and 1182; δ_H 3.80 (3H, s), 4.02 (2H, d, *J* 5.2), 4.11 (2H, d, *J* 5.1), 6.17 (1H, br t) and 6.32 (1H, br t); δ_C 41.0, 45.7, 52.1, 119.6 (q, *J* 320), 167.8 and 170.0; *m/z* 279 (M^++H 11%), 219 (100), 209 (29), 191 (11), 162 (60), 133 (17), 116 (72) and 88 (99);

N–Trifluoromethanesulfonylvaline Methyl Ester (157)

L-Valine (1.0 g, 8.5 mmol) was added to methanol (100 ml), which had been pretreated with thionyl chloride (1.2 g, 10.3 mmol), and allowed to stir overnight. The solvent was evaporated under reduced pressure to yield a white powder, which was redissolved in methanol and evaporated under reduced pressure twice to remove excess hydrochloric acid. This solid was suspended in freshly distilled dichloromethane (80 ml) under nitrogen and triethylamine (1.8 g, 17.1 mmol) added with stirring. The suspension was cooled to –78 °C and trifluoromethanesulfonic anhydride (2.4 g, 8.6 mmol) in dichloromethane (30 ml) added dropwise. The mixture was allowed to warm to room temperature overnight. The solution was washed with 10% hydrochloric acid (2 x 100 ml) and then saturated aqueous sodium chloride (2 x 100 ml) and the organic layer dried over magnesium sulfate. After filtration and evaporation under reduced pressure, the *title compound* **157** was obtained as colourless crystals (1.2 g, 4.6 mmol, 54%) mp 43–45 °C (lit.,[220] 44–46 °C); δ_H 0.92 (3H, d, *J* 6.8), 1.04 (3H, d, *J* 6.8), 2.21 (1H, m), 3.81 (3H, s), 4.07 (1H, dd, *J* 4.7, 9.7) and 5.48 (1H, br d, *J* 9.5); δ_C 17.50, 19.23, 32.03, 53.45, 62.94, 119.99 (q, *J* 320) and 171.65; *m/z* 204 (100%), 88 (28) and 69 (14). The physical and spectral characteristics were consistent with those previously reported.[220]

N–Trifluoromethanesulfonyl–phenylalanine Methyl Ester (158)

Phenylalanine (0.98 g, 5.94 mmol) was added to methanol (100 ml), which had been pretreated with thionyl chloride (1.2 g, 10.3 mmol), and allowed to stir overnight. The solution was evaporated under reduced pressure to yield a white powder, which was redissolved in methanol and evaporated under reduced pressure twice to remove excess hydrochloric acid. This solid was suspended in freshly distilled dichloromethane (80 ml) under nitrogen and triethylamine (1.2 g, 11.9 mmol) added with stirring. The suspension was cooled to –78 °C and trifluoromethanesulfonic anhydride (1.7 g, 5.94 mmol) in dichloromethane (30 ml) added dropwise. The mixture was allowed to warm to room temperature overnight. The solution was filtered and evaporated to dryness and then chromatographed using 5% ethyl acetate/hexane to give the *title compound* **158** as a colourless powder (350 mg, 1.12 mmol, 19%), mp 45–46 °C from hexane (Found: C, 42.73; H, 3.68; N, 4.45. $C_{11}H_{12}NO_4SF_3$ requires C, 42.45; H, 3.89; N, 4.50%.); ν_{max} cm^{-1} 3258, 1738, 1437, 1382, 1198 and 1147; δ_H 3.12 (1H, dd, *J* 6.0, 13.7), 3.18 (1H, dd, *J* 6.0, 13.7), 3.77 (3H, s), 4.50 (1H, t, *J* 6.0); 5.77 (1H, br s), 7.12–7.15 (2H, m) and 7.29–7.34 (3H, m); δ_C 40.01, 53.50, 58.31, 115.58 (q *J* 320), 128.25, 129.38, 129.88, 134.40 and 170.85; *m/z* 311 (M^+, 6%), 252 (61), 182 (19), 163 (38), 162 (100), 131 (41), 119 (61), 118 (73), 103 (22), 92 (52), 91(55), 77 (15), 69 (56) and 65 (68).

N–Trifluoromethanesulfonyl–glycyl–bromoglycine Methyl Ester (161)

A mixture of *N*-trifluoromethanesulfonyl-glycylglycine methyl ester **156** (50 mg, 0.18 mmol) and NBS (35 mg, 0.20 mmol) in carbon tetrachloride and dichloromethane (1:3, 5 ml) was heated at reflux for 4 h under nitrogen in a quartz tube whilst being irradiated with a 300 W sunlamp. The mixture was allowed to cool to room temperature to afforded the crude bromide **161** (95% by internal standard); δ_H 3.89 (3H, s), 4.09 (2H,

d, *J* 5.3), 6.42 (1H, d, *J* 9.8), 6.75 (1H, br t) and 7.79 (1H, d, *J* 9.8).

N–Trifluoromethanesulfonyl–glycyl–methoxyglycine Methyl Ester (162)

To a solution of crude bromide **161** in carbon tetrachloride and dichloromethane (1:3, 5 ml) was added methanol (1 ml) and the mixture allowed to stir overnight. The crude methoxide **162** was obtained in 90% overall yield from **156** by comparison with an internal standard. This was further purified by chromatography to afford the *title compound* **156** as colourless needles (20 mg, 6.5 mmol, 36%) mp 94–95 °C from ethyl acetate/hexane (Found: *m/z* 277.0108. $C_6H_8N_2O_5F_3S$ (M^+) requires *m/z* 277.0106; Found: *m/z* 103.0396. $C_4H_7O_3$ (M^+) requires *m/z* 103.0395); ν_{max} cm^{-1} 3226, 1733, 1445, 1251, 1229, 1186, 1150 and 1111; δ_H 3.49 (3H, s), 3.85 (3H, s), 4.05 (2H, d, *J* 4.9), 5.54 (2H, d, *J* 9.0), 6.04 (1H, br t) and 6.82 (1H, br d, *J* 9.0); δ_C 46.24, 53.86, 57.82, 120.00 (q, *J* 320), 167.52 and 168.48; *m/z* (EI) 293 (12%), 279 (23), 278 (50), 277 (64), 250 (11), 249 (83), 162 (22), 104 (14) and 103 (54); (ES, MeOH) [M^++H], 309 (6%), [M^+], 308 (9%).

N–Trifluoromethanesulfonyl–3–bromophenylalanine Methyl Ester (165)

To a solution of *N*-trifluoromethanesulfonyl-phenylalanine methyl ester **158** (100 mg, 0.32 mmol) in carbon tetrachloride (10 ml) was added NBS (64 mg, 0.35 mmol). The mixture was heated at reflux for 6 h under nitrogen whilst being irradiated with a 300 W sunlamp and then allowed to cool to room temperature. Purification by chromatography afforded the *title compound* **165** as a colourless 1:1 mixture of diastereomers (85 mg, 0.22 mmol, 68%) mp 113–126 °C (Found: C, 33.98; H, 2.60; N, 3.38. $C_{11}H_{11}NO_4SF_3Br$ requires C, 33.86; H, 2.84; N, 3.59%.); ν_{max} cm^{-1} 3242, 2959, 2852, 1719, 1316, 1240,

1188 and 1147; δ_H 3.79 (3H, s), 3.86 (3H, s), 4.51 (1H, dd, *J* 3.4, 10.0), 4.71 (1H, dd, *J* 5.5, 10.0), 5.31 (1H, d, *J* 5.5), 5.52 (1H, d, *J* 3.4), 5.83 (1H, br d, *J* 10.0), 5.97 (1H, br d, *J* 10.0) and 7.37–7.47 (10H, m); δ_C 51.67, 53.95, 54.38, 63.69, 64.19, 119.69 (q, *J* 320), 119.84 (q, *J* 320), 128.76, 128.87, 129.37, 129.55, 130.07, 130.22, 135.68, 136.33, 168.58 and 168.83; *m/z* 391(M^+, ^{81}Br, 2%), 389(M^+, ^{79}Br, 2), 332(4), 330(4), 310(10), 251(10), 250(13), 242(8), 240(8), 192(6), 171(97), 169(100), 118(62), 117(42), 105(36), 91(71) and 77(22). Further purification by HPLC afforded the diastereomer **165b** in high purity (23 mg, 0.06 mmol, 54%) mp 123–123.5 °C; δ_H 3.86 (3H, s), 4.51 (1H, dd, *J* 3.4, 10.0), 5.52 (1H, d, *J* 3.4), 5.83 (1H, br d, *J* 10.0) and 7.37–7.47 (5H, m).

N–Trifluoromethanesulfonyl–3–bromovaline Methyl Ester (166)

A mixture of *N*-trifluoromethanesulfonylvaline methyl ester **157** (200 mg, 0.76 mmol) and NBS (135 mg, 0.76 mmol) in carbon tetrachloride (5 ml) was heated at reflux for 5 h under nitrogen whilst being irradiated with a 300 W sunlamp. The mixture was allowed to cool to room temperature and was purified by chromatography to give the *title compound* **166** as colourless crystals (180 mg, 0.53 mmol, 69%) mp 47.5–48 °C from hexane (Found: C, 24.62; H, 3.08; N, 4.20. $C_7H_{11}NO_4SF_3Br$ requires C, 24.57; H, 3.24; N, 4.09%.); ν_{max} cm^{-1} 3263, 1747, 1324, 1240, 1196, 1146, 1123, 1101 and 1023; δ_H 1.91 (3H, s), 1.93 (3H, s), 3.87 (3H, s), 4.05 (1H, d, *J* 10.0) and 5.94 (1H, d, *J* 10.0); δ_C 32.32, 32.92, 53.67, 62.71, 66.72, 119.86 (q, *J* 320) and 168.50; *m/z* 342(M^+, ^{81}Br, 7%), 340(M^+, ^{79}Br, 7), 284(49), 282(62), 262(37), 221(67), 220(33), 202(100), 149(23), 123(37), 121(40), 88(52) and 69(40).

Treatment of *N*–Trifluoromethanesulfonylvaline Methyl Ester (157) with Sulfuryl Chloride

To a solution of *N*-trifluoromethanesulfonylvaline methyl ester **157** (100 mg, 0.38 mmol) in carbon tetrachloride (5 ml) was added sulfuryl chloride (51 mg, 0.38 mmol) and a trace amount of benzoyl peroxide. The resulting solution was heated at reflux for 5 h under nitrogen whilst being irradiated with a 300 W sunlamp. The crude reaction mixture was cooled, filtered through silica and separated by semi-preparative HPLC to give starting material, **157** (24 mg, 0.09 mmol, 24%), *N*-trifluoromethanesulfonyl-3-chlorovaline methyl ester **167** (31 mg, 0.10 mmol, 27%) mp 64–65 °C (Found: C, 28.50; H, 3.83; N, 4.89. $C_7H_{11}NO_4SF_3Cl$ requires C, 28.24; H, 3.72; N, 4.71%.); ν_{max} cm^{-1} 3279, 1745, 1324, 1240, 1193, 1151, 1104, 1028, 995 and 914; δ_H 1.73 (3H, s), 1.74 (3H, s), 3.85 (3H, s), 4.16 (1H, br s) and 5.95 (1H, br s); δ_C 30.71, 31.26, 53.69, 66.11, 68.61, 119.96 (q *J* 320) and 168.39; *m/z* 240 (5%), 238 (14), 202 (29), 149 (17), 79 (20) and 77 (44); and *N*-trifluoromethanesulfonyl-4-chlorovaline methyl ester **168** as a 1 : 1 mixture of diastereomers (46 mg, 0.15 mmol, 41%) mp 52–71 °C (Found: C, 28.20; H, 3.74; N, 4.56. $C_7H_{11}NO_4SF_3Cl$ requires C, 28.24; H, 3.72; N, 4.71%.); ν_{max} cm^{-1} 3264, 1736, 1438, 1383, 1311, 1281, 1235, 1198, 1146, 1098, 1024 and 941; δ_H **168a** : 1.12 (3H, d, *J* 7.0), 2.49 (1H, m), 3.55 (2H, dd, *J* 3.7, 6.6), 3.84 (3H, s), 4.33 (1H, d, *J* 4.5) and 5.82 (1H, br s); **168b** : 1.00 (3H, d, *J* 7.0), 2.46 (1H, m), 3.46 (1H, dd, *J* 5.8, 11.4), 3.56 (1H, dd, *J* 7.9, 11.4), 3.85 (3H, s), 4.52 (1H, br d, *J* 2.2) and 5.60 (1H, br s); δ_C **168a** : 14.61, 39.27, 45.69, 53.25, 59.28, 119.28 (q, *J* 320) and 170.06; **168b** : 12.64, 39.36, 45.57, 53.46, 58.21, 119.45 (q, *J* 320) and 170.45; *m/z* 300 (M^++H, ^{37}Cl, 0.3%), 298 (M^++H, ^{35}Cl, 0.8), 274 (3), 272 (5), 240 (49), 238 (100), 220 (30), 202 (49) and 162 (51).

N–(2–Methylpropyl)trifluoromethanesulfonamide (169)

To a solution of isobutylamine (1.0 g, 14.2 mmol) in dichloromethane (20 ml) under a nitrogen atmosphere was added trifluoromethanesulfonic anhydride (2.0 g, 7.1 mmol). The resulting solution was stirred overnight, filtered and then the solvent evaporated under reduced pressure. Chromatography on silica afforded the *title compound* **169** as a clear and colourless oil (1.3 g, 6.4 mmol, 90%); δ_H 0.93 (6H, d, *J* 6.5), 1.83 (1H, non, *J* 6.5), 3.09 (2H, t, *J* 6.5) and 5.41 (1H, br t). The physical characteristics were consistent with those reported in the literature.[221]

N–(1–Methylethyl)trifluoromethanesulfonamide (170)

To a solution of isopropylamine (1.4 g, 23.1 mmol) in dichloromethane (20 ml) under a nitrogen atmosphere was added trifluoromethanesulfonic anhydride (3.3 g, 11.5 mmol). The resulting solution was stirred overnight, filtered and then the solvent evaporated under reduced pressure to afforded the *title compound* as a clear, pale yellow oil (1.7 g, 8.9 mmol, 77%), (Found: C, 25.37; H, 4.32; N, 7.54. $C_4H_8NO_2SF_3$ requires C, 25.13; H, 4.22; N, 7.33%); ν_{max} cm^{-1} (neat) 3636, 3565, 3300, 2984, 2941, 2881, 2361, 1622, 1548, 1468, 1436, 1370, 1332, 1230, 1190, 1153, 1017, 902, 829, 762; δ_H 1.30 (6H, d, *J* 6.6), 3.82 (1H, oct, *J* 6.6) and 4.94 (1H, br s); δ_C 25.02 49.63 120.63 (q, *J* 320); *m/z* 191 (M^+, 10%), 190 (66), 149 (21), 148 (100), 144 (72), 130 (45) and 129 (31).

N–(2–methylpropyl)–phthalimide (171)

To phthalic anhydride (5.0 g, 34 mmol) was added isobutylamine (2.5 g, 34 mmol) and the resulting mixture was heated at 150 °C for an hour. The mixture was allowed to cool and the resulting solid recrystallised from ethyl acetate/hexane to give the *title*

compound **171** as colourless crystals (4.7 g, 23 mmol, 68%) mp 93 °C (lit.,[222] 93 °C); δ_H 0.94 (6H, d, *J* 7.0), 2.12 (1H, non, *J* 7.0), 3.50 (2H, d, *J* 7.0), 7.69–7.72 (2H, m) and 7.83–7.85 (2H m).

N–(1–Methylethyl)phthalimide (172)

To phthalic anhydride (5 g, 34 mmol) was added excess isopropylamine and the resulting mixture was heated at 150 °C for an hour. The mixture was allowed to cool and the resulting solid was suspended in ethyl acetate and filtered through silica. Subsequent recrystallisation from ethyl acetate/hexane gave the *title compound* as colourless crystals (2.1 g, 11 mmol, 33%) mp 84–85 °C (lit.,[222] 86 °C); δ_H 1.50 (6H, d, *J* 6.9), 4.54 (1H, sept, *J* 6.9), 7.68–7.72 (2H, m) and 7.78–7.83 (2H, m).

N–(2–Bromo–2–methylpropyl)trifluoromethanesulfonamide (173)

To a solution of *N*-(2-methylpropyl)trifluoromethanesulfonamide **169** (200 mg, 0.98 mmol) in carbon tetrachloride (5 ml) was added NBS (174 mg, 0.98 mmol) and the resulting mixture was refluxed for 3 hours. The solvent was removed *in vacuo* and the residue chromatographed on silica to yield the *title compound* as colourless needles (225 mg, 0.79 mmol, 81%) mp 90–90.5 °C (Found: C, 21.14; H, 3.16; N, 4.96. $C_5H_9NO_2SF_3Br$ requires C, 21.14; H, 3.19; N, 4.93%); ν_{max} cm^{-1} 3291, 1279, 1232, 1213, 1182, 1150, 1125, 1080 and 875; δ_H 1.81 (6H, s), 3.47 (2H, d, *J* 6.5) and 5.41 (1H, br t); δ_C 31.13, 56.94, 65.24, 120.20 (q, *J* 310); *m/z* 284(M^+-H, ^{81}Br, 5%), 282 (M^+-H, ^{79}Br, 5), 216 (65), 214 (65), 204 (100), 162 (47), 123 (52) and 121 (52).

N–(2–Bromo–2–methylpropyl)phthalimide (174)

To a solution of *N*-(2-methylpropyl)phthalimide **171** (100 mg, 0.49 mmol) in carbon tetrachloride (5 ml) was added NBS (88 mg, 0.49 mmol). The mixture was refluxed for 3 hours, allowed to cool and then washed with water. The organic layer was dried and then the solvent removed *in vacuo*. The mixture was chromatographed with ethyl acetate/hexane as the eluent to afford the *title compound* **174** as white plates (80 mg, 0.28 mmol, 58%) mp 95–96 °C (lit.,[223] 97 °C); δ_H 1.81 (6H, s), 4.09 (2H, s), 7.74–7.77 (2H, m) and 7.87–7.90 (2H, m).

N–Phthaloyl–3,4–dihydroxyphenylalanine Methyl Ester (189)

To a solution of L-3,4-dihydroxyphenylalanine **190** (DOPA) (2.0g, 10 mmol) in refluxing DMF (5 ml) was added freshly ground phthalic anhydride (1.5 g, 10 mmol) under an atmosphere of nitrogen. The mixture was allowed to reflux for 20 minutes, until the DOPA had all dissolved, and was then allowed to cool to room temperature. The solvent was removed under reduced pressure to give the crude *N*-phthaloyl-3,4-dihydroxyphenylalanine as a pale yellow foam δ_H 3.43 (2H, d, *J* 9.3), 5.05 (1H, t, *J* 9.3), 6.47 (1H, d, *J* 8.1), 6.60 (1H, d, *J* 8.1), 6.67 (1H, s), 7.59–7.62 (2H, m) and 7.67–7.71 (2H, m). Further treatment under an atmosphere of nitrogen with methanol which had been pretreated with excess thionyl chloride (10 ml), followed by chromatography on silica, afforded the *title compound* as an air sensitive yellow foam (3.1 g, 0.91 mmol, 90%); δ_H 3.43 (2H, m), 3.76 (3H, s), 5.10 (1H, dd, *J* 5.3, 11), 6.54 (1H, dd, *J* 8.0, 1.9), 6.64 (1H, dd, *J* 8.0, 1.9), 6.68 (1H, d, *J* 1.9), 7.64–7.70 (2H, m) and 7.72–7.78 (2H, m). The spectral characteristics are consistent with those previously reported.[224]

N–Phthaloyltyrosine Methyl Ester (192)

Tyrosine (1.0 g, 5.5 mmol) was suspended in toluene (200 ml) to which was added triethylamine (0.6 g, 5.5 mmol) and phthalic anhydride (0.8 g, 5.5 mmol) and the resulting mixture allowed to reflux for 3 hours. After cooling, the solvent was removed under reduced pressure and the residue taken up in dichloromethane, washed with dilute hydrochloric acid and dried. The dichloromethane was removed under reduced pressure and methanol (50 ml) which had been pretreated with excess thionyl chloride (5 ml) was added and the mixture was allowed to stir overnight. The methanol was removed under reduced pressure to obtain the *title compound* **192** as a white powder (1.5 g, 4.6 mmol, 84%) mp 102–104 °C (lit., 101–104 °C); δ_H 3.48 (2H, m), 3.76 (3H, s), 5.09 (1H, dd, *J* 5.8, 10.7), 6.61 (2H, d, *J* 8.6), 7.00 (2H, d, *J* 8.6) 7.67–7.72 (2H, m) and 7.76–7.79 (2H, m).

N–Phthaloyl–3,4–dimethoxyphenylalanine (194)

The *title compound* was prepared using a modification of the method of Gensler and Bluhm[226] followed by phthaloylation of the crude residue. To a suspension of 3,4-dihydroxyphenylalanine (2.0 g, 10 mmol) in water (20 ml) was added excess acetic anhydride (8 ml) in 8 portions over 15 minutes. The mixture was refluxed for a further 30 minutes until all of the suspension had dissolved and was then evaporated under reduced pressure until no further distillate was observed. The residue was neutralised with sodium carbonate and then sodium hydroxide (1.0 g, 25 mmol) was added under a nitrogen atmosphere. The mixture was treated slowly with dimethyl sulfate (5.3 g, 42 mmol) with intermittent cooling to keep the temperature below 40 °C. The mixture was stirred for 2 hours and concentrated sulfuric acid (3 ml) in water (15 ml) was added, followed by keeping the mixture at reflux for 66 hours. The solution was then adjusted to pH 2 by the addition of sodium carbonate and the mixture evaporated to dryness and

then freeze dried. The residue was suspended in toluene and phthalic anhydride (1.5 g, 10 mmol) and triethylamine (1.0 g, 10 mmol) was added and the mixture refluxed for 3 hours. The mixture was cooled and the toluene removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with 10% hydrochloric acid. The organic layer was then dried and solvent removed to give the *title compound* as a colourless foam (1.4 g, 4.0 mmol, 40%); δ_H 3.53 (2H, d, *J* 8.4), 3.69 (3H, s), 3.76 (3H, s), 5.20 (1H, t, 8.4), 6.64–6.70 (3H, m), 7.67–7.71 (2H, m) and 7.77–7.81 (2H, m); δ_C 34.25, 53.42, 55.98, 111.53, 112.05, 121.34, 123.84, 129.29, 131.74, 134.58, 148.00, 148.97, 167.93 and 173.42; *m/z* 355 (M^+, 44%) 208 (96), 194 (32), 151 (100) and 137 (26).

N–Phthaloyl–O–methyltyrosine (196)

The *title compound* was prepared using a modification of the method of Izumuya and Nagamatsu[228] followed by phthaloylation of the recrystallised *O*-methyltyrosine. Tyrosine (20.0 g, 0.11 mol) was treated with formic acid (99%, 200 ml) and acetic anhydride (65 ml). The mixture was allowed to stir overnight and then the solvent was removed under reduced pressure. Ice cold 1N hydrochloric acid was added and the solvent was removed again. This was followed by addition of more cold hydrochloric acid, after which the crude *N*-formyl tyrosine was collected by filtration. Recrystallisation from water afforded *N*-formyl tyrosine as a colourless powder (12.6 g, 0.06 mol, 55%); δ_H 2.96 (1H, dd, *J* 7.9, 14.1), 3.12 (1H, dd, *J* 5.5, 14.1), 4.67 (1H, dd, *J* 5.5, 7.9), 6.82 (2H, d, *J* 8.5), 7.13 (2H, d, *J* 8.5) and 7.99 (1H, s). The *N*-formyl tyrosine (5.2 g, 24 mmol) was dissolved in 4N sodium hydroxide (12.5 ml) under an atmosphere of nitrogen. The solution was treated alternately with 4N sodium hydroxide (2.5 ml) and dimethyl sulfate (1.6 g, 13 mmol) whilst keeping the temperature between 25 and 40 °C. The addition was repeated four times in total and the mixture was then allowed to stir for 2 hours at room temperature. The solution was acidified slowly to pH 7 with 8N nitric

acid. The resulting precipitate was collected by filtration and then recrystallised from water to yield *N*-formyl-*O*-methyltyrosine as a colourless powder (2.5 g, 11 mmol, 47%); δ_H 2.99 (1H, dd, *J* 8.1, 14.0), 3.16 (1H, dd, *J* 5.5, 14.0), 3.79 (3H, s), 4.69 (1H, dd, *J* 5.5, 8.1), 6.94 (2H, d, *J* 8.5), 7.21 (2H, d, *J* 8.5) and 7.99 (1H, s). The *N*-formyl-*O*-methyltyrosine (2.5 g, 11 mmol) was suspended in 3N hydrochloric acid and the mixture was refluxed for 2 hours. The solution was then evaporated under reduced pressure and concentrated again, subsequent to the addition of water. The resultant residue was dissolved in a minimal amount of water and the solution neutralised to pH 7 with ammonia to give the crude *O*-methyltyrosine as a colourless powder (1.56 g, 8 mmol, 73%); δ_H 3.09 (1H, dd, *J* 7.7, 14.5), 3.24 (1H, dd, *J* 5.5, 14.5), 3.84 (3H, s), 3.98 (1H, dd, *J* 5.5, 7.7), 7.01 (2H, d, *J* 7.6) and 7.26 (2H, d, *J* 7.6). To a solution of *O*-methyltyrosine (1.0 g, 5 mmol) in toluene (25 ml) was added triethylamine (0.5 g, 5 mmol) and freshly ground phthalic anhydride (0.8 g, 5 mmol). The mixture was allowed to reflux for 3 hours and was then cooled and the solvent removed under reduced pressure. The resultant residue was taken up in ethyl acetate and then washed with water and the organic layer was dried. Filtration, followed by evaporation under reduced pressure afforded the *title compound* as a colourless powder (1.4 g, 4.4 mmol, 87%); δ_H 3.49 (2H, d, *J* 8.4), 3.68 (3H, s), 5.13 (1H, t, *J* 8.4), 6.69 (2H, d, *J* 8.5), 7.05 (2H, d, *J* 8.5), 7.64–7.68 (2H, m) and 7.72–7.76 (2H, m).

General Procedure for Bromination

To a solution of substrate in carbon tetrachloride was added *N*-bromosuccinimide (1 equivalent). The mixture was heated to reflux under an atmosphere of nitrogen and irradiated with a 300W UV lamp for one hour to afford the corresponding crude bromide. This was then washed with 5% sodium metabisulfite with added ammonia followed by water. The organic layer was then dried and evaporated under reduced pressure to afford the *title compound* in each case.

3–Bromo–*N*–*tert*–Butyl–N^{α}–phthaloyl–*O*–methyltyrosinamide (197)

N-*tert*-Butyl-N^{α}-phthaloyl-*O*-methyltyrosinamide **53** (50 mg, 0.13 mmol) afforded the *title compound* **197** (1 : 1 mixture of diastereomers) as colourless crystals in quantitative yield (60 mg, 0.13 mmol) mp 124–137 °C (Found: C, 57.64; H, 5.34; N 5.80. $C_{22}H_{23}BrN_2O_4$ requires C, 57.35; H, 5.05; N, 6.10%.); ν_{max} cm^{-1} 3346, 1775, 1718, 1682, 1606, 1513, 1300, 1251, 1227, 1176, 1112, 1077, 1032, 880, 835 and 794; δ_H 1.04 (9H, s), 1.38 (9H, s), 3.66 (3H, s), 3.81 (3H, s), 5.21 (1H, d, *J* 11.9), 5.30 (1H, d, *J* 11.5), 5.94 (1H, br s), 6.05 (1H, d, *J* 11.5), 6.15 (1H, d, *J* 11.9), 6.41 (1H, br s), 6.71 (2H, d, *J* 8.8), 6.92 (2H, d, *J* 8.7), 7.28 (2H, d, *J* 8.8), 7.52 (2H, d, *J* 8.7), 7.61–7.71 (4H, m), 7.75–7.79 (2H, m) and 7.89–7.93 (2H, m); δ_C 28.69, 29.04, 49.30, 51.48, 52.04, 52.54, 55.64, 55.89, 61.34, 63.48, 114.61, 114.87, 124.05, 124.32, 129.58, 130.10, 130.18, 130.28, 130.96, 131.47, 131.99, 134.74, 134.90, 160.20, 160.84, 164.09, 165.68, 167.61 and 168.48; *m/z* 460 (M^+, ^{81}Br, 0.9%), 458 (M^+, ^{79}Br, 0.9), 379 (27), 378 (94), 321 (100), 306 (53), 280 (87), 279 (74), 278 (88), 264 (26), 260 (21), 233 (33) and 104 (62).

3–Bromo–*N*–*tert*–butyl–N^{α}–phthaloyl–3,4–dimethoxyphenylalaninamide (198)

N-*tert*-Butyl-N^{α}-phthaloyl-3,4-dimethoxyphenylalaninamide **55** (50 mg, 0.12 mmol) afforded the *title compound* **198** (1 : 1 mixture of diastereomers) as pale orange crystals in quantitative yield (59 mg, 0.12 mmol) mp 69–75 °C (Found: *m/z* 490.09264. $C_{23}H_{25}{}^{81}Br\ N_2O_5$ requires *m/z* 490.09264. Found: *m/z* 488.09240. $C_{23}H_{25}{}^{79}BrN_2O_5$ requires *m/z* 488.09468.); ν_{max} cm^{-1} 3354, 1775, 1717, 1604, 1516, 1263, 1142, 1101, 1025 and 876; δ_H 1.04 (9H, s), 1.38 (9H, s), 3.48 (3H, s), 3.78 (3H, s), 3.87 (3H, s), 3.93 (3H, s), 5.21 (1H, d, *J* 11.9), 5.32 (1H, d, *J* 11.4), 5.89 (1H, s), 5.99 (1H, d, *J* 11.4), 6.15

(1H, d, *J* 11.9), 6.48 (1H, s), 6.63 (1H, d, *J* 8.1), 6.86–6.91 (3H, m), 7.08 (1H, d, *J* 2.0), 7.16 (1H, dd, *J* 2.0, 8.2), 7.61–7.78 (6H, m) and 7.87–7.92 (2H, m); δ_C 29.23, 29.75, 50.20, 52.38, 52.64, 53.13, 56.76, 56.89, 57.06, 57.18, 61.88, 63.98, 111.06, 111.87, 112.18, 121.76, 122.11, 124.52, 125.05, 130.86, 131.21, 132.01, 132.55, 136.83, 149.88, 150.31, 150.97, 164.66, 166.18 and 168.26; *m/z* 490 (M^+, ^{81}Br, 1.2%), 488 (M^+, ^{79}Br, 1.3), 408 (80), 351 (77), 336 (43), 318 (43), 316 (77), 263 (31), 176 (34), 162 (63) and 104 (70).

General Procedures for the preparation of the amides 199–204

A. To a solution of the appropriate amine (1 equiv.) in ethyl acetate was added, with stirring, a saturated solution of sodium hydrogen carbonate. Either benzoyl chloride or pentafluorobenzoyl chloride (as required) (1 equiv.) was added dropwise and the resulting mixture stirred at room temperature overnight. Extraction with ethyl acetate, followed by washing firstly with 10% hydrochloric acid (3 times) and then saturated sodium bicarbonate (3 times), then drying and evaporation of the solvent under reduced pressure afforded the product which was purified by recrystallisation.

B. To a solution of the appropriate amine (2 equiv.) in ethyl acetate was added dropwise either benzoyl chloride or pentafluorobenzoyl chloride (as required) (1 equiv.) and the resulting mixture stirred at room temperature overnight. The mixture was filtered and the filtrate evaporated under reduced pressure to give the crude product, which was purified by recrystallisation.

N–(2–Phenylethyl) Benzamide (199)

2-Phenylethylamine (5.0 g, 41 mmol) afforded the product **199** as colourless platelets (6.9 g, 31 mmol, 74%), mp 118–118.5 °C from ethyl acetate/hexane (lit.,[231] 117–118 °C); δ_H 2.94 (2H, t, *J* 6.9), 3.73 (2H, apparent quartet, *J* 6.9), 6.21 (1H, br s), 7.24–7.28 (2H, m), 7.32–7.51 (6H, m) and 7.68–7.71 (2H, m).

2,3,4,5,6–Pentafluoro–*N*–(2–phenylethyl) Benzamide (202)

2-Phenylethylamine (0.26 g, 2.2 mmol) afforded the product **202** as a colourless powder (0.45 g, 1.4 mmol, 66%), mp 115–116 °C from ethyl acetate/hexane (lit.,[249] 109–111 °C); (Found: C, 57.18; H, 3.18; N, 4.35. $C_{15}H_{10}NOF_5$ requires C, 57.15; H, 3.20; N, 4.44%); ν_{max} cm^{-1} 3295, 1655, 1556, 1527, 1338, 1264, 1196, 1125, 1058, 986 and 931; δ_H 2.88 (2H, t, *J* 6.8), 3.68 (2H, apparent q, *J* 6.8), 5.84 (1H, br s) and 7.16–7.30 (5H, m); *m/z* 315 (M^+, 6%), 195 (81), 167 (23), 105 (20), 104 (100) and 91 (43).

N–(3–Phenylpropyl) Benzamide (200)

3-Phenylpropylamine (2.08 g, 15.4 mmol) afforded the product **200** as colourless needles (1.78 g, 7.4 mmol, 97%), mp 60–62 °C from ethyl acetate/hexane (lit.,[231] 60 °C); δ_H 1.97 (2H, qu, *J* 7.3), 2.73 (2H, t, *J* 7.3), 3.50 (2H, dt, *J* 6.5, 7.3), 6.22 (1H, br s) and 7.18–7.69 (10H, m).

2,3,4,5,6–Pentafluoro–*N*–(3–phenylpropyl) Benzamide (203)

3-Phenylpropylamine (0.30 g, 2.2 mmol) afforded the product **203** as a colourless powder (0.34 g, 1.0 mmol, 47%), mp 76–77 °C from ethyl acetate/hexane (Found: C, 58.30; H, 3.56; N, 4.12. $C_{16}H_{12}NOF_5$ requires C, 58.36; H, 3.67; N, 4.25%); ν_{max} cm^{-1} 3297, 1655, 1556, 1519, 1121, 1055 and 990; δ_H 1.97 (2H, tt, *J* 7.0, 7.6), 2.73 (2H, t, *J* 7.6), 3.51 (2H, dt, *J* 6.0, 7.0), 5.87 (1H, br s) and 7.19–7.33 (5H, m); *m/z* 330(M^++H, 15%), 329(M^+, 43), 226 (22), 225 (100), 207 (18), 206 (77), 196 (20), 195 (93), 177 (36), 167 (42), 118 (50), 117 (59), 105 (28), 104 (23), 103 (20), 92 (21) and 91 (54).

N–(4–Phenylbutyl) Benzamide (201)

4-Phenylbutylamine (1.00 g, 6.7 mmol) afforded the product **201** as a colourless powder (1.27 g, 5.0 mmol, 75%), mp 83–84 °C from ethyl acetate/hexane (lit.,[232] 83.5 °C); δ_H 1.60–1.78 (4H, m), 2.68 (2H, t, *J* 7.0), 3.48 (2H, dt, *J* 6.3, 7.0), 6.09 (1H, br s), 7.17–7.52 (8H, m) and 7.73–7.76 (2H, m).

2,3,4,5,6–Pentafluoro–*N*–(4–phenylbutyl) Benzamide (204)

4-Phenylbutylamine (0.33 g, 2.2 mmol) afforded the product **204** as a colourless powder (0.67 g, 2.0 mmol, 90%), mp 90–90.5 °C from ethyl acetate/hexane (Found: C, 59.55; H, 3.90; N, 3.97. $C_{17}H_{14}NOF_5$ requires C, 59.48; H, 4.11; N, 4.08%); ν_{max} cm^{-1} 3239, 3065, 1678, 1647, 1570, 1516, 1504, 1339, 1271, 1116, 1066 and 992; δ_H 1.57–1.78 (4H, m), 2.67 (2H, t, *J* 7.2), 3.49 (2H, dt, *J* 6.4, 6.6), 5.90 (1H, br s) and 7.17–7.32 (5H, m); *m/z* 343 (M^+, 50%), 252 (33), 239 (20), 225 (37), 224 (20), 220 (30), 206 (28), 204 (21), 195 (100), 167 (30), 132 (39), 117 (32), 104 (35) and 91 (66).

N–(2–Phenylethyl) Acetamide (205)

To a solution of 2-phenylethylamine (3.00 g, 24.8 mmol) in dichloromethane (50 ml) was added acetyl chloride (1.00 g, 12.7 mmol) dropwise and the mixture allowed to stir overnight. The mixture was filtered and the filtrate evaporated under reduced pressure and dried on an oil pump to give the*title compound* **205** as a pale yellow powder (1.98 g, 12.1 mmol, 98%), mp 56 °C (lit.,[233] 55–56 °C); δ_H 1.94 (3H, s), 2.82 (2H, t, *J* 6.7), 3.51 (2H, q, *J* 6.7), 5.79 (1H, br s) and 7.18–7.34 (5H, m).

1,1,1–Trifluoro–*N*–(2–phenylethyl) Acetamide (206)

To a stirring biphasic solution of saturated sodium bicarbonate and 2-phenylethylamine (1.00 g, 8.3 mmol) in ethyl acetate (15 ml) was added trifluoroacetic anhydride (1.75 g, 8.3 mmol) dropwise. The solution was allowed to stir overnight and the organic layer was extracted and washed with 10% hydrochloric acid (3 x 5 ml) and then saturated sodium bicarbonate (3 x 5 ml), dried and evaporated under reduced pressure to give the crude product which was recrystallised from ethyl acetate/hexane to give the *title compound* **206** as colourless platelets (0.98 g, 4.6 mmol, 55%), mp 56–57 °C (lit.,[234] 56–57 °C); δ_H 2.90 (2H, t, *J* 7.0), 3.63 (2H, q, *J* 7.0), 6.29 (1H, br s) and 7.19–7.37 (5H, m).

Benzoic Acid (2–phenylethyl) Ester (207)

To a solution of 2-phenethanol (5.00 g, 41 mmol) in ethyl acetate (25 ml) was added triethylamine (4.10 g, 41 mmol). Benzoyl chloride (5.76 g, 41 mmol) was added dropwise and the mixture allowed to stir overnight. The resulting solution was washed

with 10% hydrochloric acid (3 x 15 ml) and then saturated sodium bicarbonate (3 x 15 ml), dried and evaporated under reduced pressure to give the crude product which was then purified on silica to give the *title compound* **207** as a pale yellow oil (5.40 g, 24 mmol, 59%); δ_H 3.12 (2H, t, *J* 7.0), 4.58 (2H, t, *J* 7.0), 7.28–7.58 (9H, m) and 8.05–8.09 (1H, m). The physical characteristics were consistent with those reported in the literature.[235]

2,3,4,5,6–Pentafluorobenzoic Acid (2–phenylethyl) Ester (208)

To a solution of 2-phenethanol (0.27 g, 2.2 mmol) in dichloromethane (15 ml) was added triethylamine (0.22 g, 2.2 mmol). Pentafluorobenzoyl chloride (0.50 g, 2.2 mmol) was added dropwise and the mixture allowed to stir overnight. The resulting solution was washed with 10% hydrochloric acid (3 x 10 ml) and then saturated sodium bicarbonate (3 x 10 ml), dried and evaporated under reduced pressure to give the crude product which was then recrystallised from ethyl acetate/hexane to yield the *title compound* **208** as colourless plates (0.62 g, 2.0 mmol, 90%), mp 59–60 °C (Found: C, 57.01; H, 2.90. $C_{15}H_9O_2F_5$ requires C, 56.97; H, 2.87%); ν_{max} cm^{-1} 1736, 1654, 1524, 1329, 1232, 1216, 1105 and 975; δ_H 3.08 (2H, t, *J* 6.9), 4.60 (2H, t, *J* 6.9) and 7.23–7.36 (5H, m); *m/z* 195 (34%), 167 (18), 117 (13), 104 (100) and 91 (38).

General Procedure for the synthesis of the bromides 210, 212–214, 216, 218

A mixture of the substrates **202–204, 206–208** (ca 50–100 mg) and NBS (1 equiv.) in carbon tetrachloride (8 ml) was heated at reflux for 2–4 h under nitrogen whilst being irradiated with a 300 W sunlamp. The mixture was allowed to cool to room temperature, then washed with water, separated, and the organic layer dried.

Evaporation of the resultant solution under reduced pressure afforded the crude bromides, which were then purified by recrystallisation.

2,3,4,5,6–Pentafluoro–*N*–(2–bromo–2–phenylethyl) Benzamide (210)

2,3,4,5,6-Pentafluoro-*N*-(2-phenylethyl) benzamide **202** (100 mg, 0.32 mmol) afforded the product **210** as colourless needles (92 mg, 0.23 mmol, 73%), mp 138–139 °C from ethyl acetate/hexane (Found: C, 45.90; H, 2.44; N, 3.85. $C_{15}H_9NOF_5Br$ requires C, 45.71; H, 2.30; N, 3.55%); ν_{max} cm^{-1} 3289, 1664, 1559, 1526, 1342, 1264, 1201, 1128, 1056, 992 and 914; δ_H 3.80–3.97 (2H, m), 5.15 (1H, dd, *J* 6.5, 8.2), 5.92 (1H, br t) and 7.29–7.39 (5H, m); δ_C 47.43, 53.41, 128.74, 129.02, 129.19, 138.39 and 157.41; *m/z* 395 (M^+-H, ^{81}Br, 0.5%), 394 (M^+-H, ^{79}Br, 0.6), 393 (1), 392 (0.5), 391 (0.6), 315 (18), 314 (72), 313 (20), 224 (20), 207 (72), 195 (100), 184 (12), 182 (12), 167 (23) and 104 (20).

1,1,1–Trifluoro–*N*–(2–bromo–2–phenylethyl) Acetamide (212)

1,1,1-Trifluoro-*N*-(2-phenylethyl) acetamide **206** (50 mg, 0.23 mmol) afforded the product **212** as a colourless powder (58 mg, 0.20 mmol, 85%), mp 87–88 °C (subl.) from ethyl acetate/hexane (Found: C, 40.39; H, 2.85; N, 4.45. $C_{10}H_9NOF_3Br$ requires C, 40.57; H, 3.06; N 4.73%); ν_{max} cm^{-1} 3311, 2722, 1702, 1562, 1208, 1168, 1054, 954 and 764; δ_H 3.85–4.06 (2H, m), 5.08 (1H, dd, *J* 5.7, 8.8), 6.79 (1H, br d) and 7.32–7.42 (5H, m); δ_C 46.86, 51.73, 115.60 (q *J* 288), 127.45, 129.11, 129.38, 137.89 and 157.18 (q *J* 38); *m/z* 296 (M^+-H, ^{81}Br, 0.8%), 294 (M^+-H, ^{79}Br, 0.8), 216 (100), 198 (16), 184 (36), 182 (36), 171 (47), 169 (45), 119 (21), 104 (35), 103 (56) and 77 (22).

Benzoic Acid (2–bromo–2–phenylethyl) Ester (213)

Benzoic acid (2-phenylethyl) ester **207** (100 mg, 0.44 mmol) afforded the product **213** as colourless plates (78 mg, 0.26 mmol, 58%), mp 33–35 °C (Found: C, 59.04; H, 4.43. $C_{15}H_{13}O_2Br$ requires C, 59.04; H, 4.29%); ν_{max} cm^{-1} (neat) 3063, 3037, 1722, 1601, 1582, 1493, 1451, 1382, 1352, 1315, 1269, 1205, 1176, 1109, 1070, 1026, 967, 762 and 710; δ_H 4.76 (1H, dd, *J* 6.7, 11.8), 4.85 (1H, dd, *J* 7.6, 11.8), 5.29 (1H, dd, *J* 6.7, 7.6), 7.31–7.60 (8H, m) and 7.99–8.02 (2H, m); δ_C 49.98, 67.87, 127.78, 128.38, 128.82, 128.96, 129.66, 133.21, 138.03 and 165.81; *m/z* 305 (M^+-H, ^{81}Br, 2%), 303 (M^+-H, ^{79}Br, 2), 225 (39), 184 (17), 182 (17), 105 (100), 104 (32), 103 (32) and 77 (41).

2,3,4,5,6–Pentafluorobenzoic Acid (2–bromo–2–phenylethyl) Ester (214)

2,3,4,5,6-Pentafluorobenzoic acid phenethyl ester **208** (50 mg, 0.16 mmol) afforded the product **214** as a pale yellow solid (52 mg, 0.13 mmol, 82%), mp 64–65 °C from hexane (Found: C, 45.36; H, 1.88%. $C_{15}H_8O_2F_5Br$ requires C, 45.60; H, 2.04%); ν_{max} cm^{-1} 1749, 1716, 1649, 1525, 1499, 1325, 1218, 1009 and 974; δ_H 4.81 (1H, dd, *J* 7.4, 11.9), 4.89 (1H, dd, *J* 7.4, 11.8), 5.21 (1H, t, *J* 7.4) and 7.33–7.46 (5H, m); δ_C 48.70, 69.22, 127.24, 127.87, 128.49, 129.00, 129.48, 129.81, 137.44, 140.85 and 158.43; *m/z* 395 (M^+-H, ^{81}Br, 0.8%), 393 (M^+-H, ^{79}Br, 0.8), 315(35), 195 (100), 184 (12), 182 (12), 169 (16), 168 (16), 104 (40), 103 (38) and 77 (16).

2,3,4,5,6–Pentafluoro–*N*–(3–bromo–3–phenylpropyl) Benzamide (216)

2,3,4,5,6-Pentafluoro-*N*-(3-phenylpropyl) benzamide **203** (100 mg, 0.30 mmol) afforded the product **216** as colourless needles (101 mg, 0.25 mmol, 81%), mp 112–113 °C from

carbon tetrachloride/hexane (Found: C, 47.44; H, 2.55; N, 3.73. $C_{16}H_{11}NOF_5Br$ requires C, 47.08; H 2.72; N, 3.43%); ν_{max} cm^{-1} 3317, 1664, 1547, 1519, 1329, 1247, 1230, 1116, 1092, 1067, 1040, 984, 794, 762 and 694; δ_H 2.48 (2H, dt, *J* 6.9, 6.6), 3.53 (1H, m), 3.65 (1H, m), 5.02 (1H, t, *J* 7.5), 6.65 (1H, br t) and 7.29–7.40 (5H, m); δ_C 39.42, 39.87, 52.81, 127.74, 129.34, 129.50, 141.68 and 158.10; *m/z* 327 (35%), 236 (46), 195 (92), 167 (39), 118 (26), 117 (32), 116 (43), 115 (34), 105 (49), 104 (100), 103 (29), 78 (25) and 77 (34).

2,3,4,5,6–Pentafluoro–*N*–(4–bromo–4–phenylbutyl) Benzamide (218)

2,3,4,5,6-Pentafluoro-*N*-(4-phenylbutyl) benzamide **204** (100 mg, 0.29 mmol) afforded the product **218** as an orange oil (106 mg, 0.25 mmol, 86%), (Found *m/z* 421.00939. $C_{17}H_{13}NOF_5{}^{79}Br$ requires *m/z* 421.00892. Found *m/z* 423.00809. $C_{17}H_{13}NOF_5{}^{79}Br$ requires *m/z* 423.00802.); δ_H 1.60–1.67 (1H, m), 1.70–1.87 (1H, m), 2.14–2.23 (1H, m), 2.25–2.37 (1H, m), 3.40–3.50 (2H, m), 4.98 (1H, dd, *J* 6.4, 8.4), 6.41 (1H, br t) and 7.29–7.40 (5H, m); *m/z* 423 (M^+, ^{81}Br, 1.2%), 421 (M^-, ^{79}Br, 1.3), 343 (30), 342 (63), 341 (33), 294 (16), 224 (23), 196 (21) 195 (100), 167 (36), 132 (23), 131 (58), 130 (53), 129 (30), 118 (20), 117 (42), 116 (21), 115 (33), 104 (36) and 91 (49).

Treatment of *N*–(2–Phenylethyl) Benzamide (199) with NBS

A mixture of *N*-(2-Phenylethyl) benzamide **199** (100 mg, 0.44 mmol) and NBS (1 equiv.) in carbon tetrachloride (8 ml) was heated at reflux for 2–4 h under nitrogen whilst being irradiated with a 300 W sunlamp. The mixture was allowed to cool to room temperature, filtered and the solvent evaporated under reduced pressure to yield the crude bromide **209** (84% by internal standard at 37% consumption of **199**); δ_H 3.87–3.98

(1H, m), 4.09–4.16 (1H, m), 5.23 (1H, dd, *J* 5.6, 8.9), 6.22 (1H, brt), 7.12–7.52 (8H, m), 7.66–7.78 (2H, m). Attempted isolation of this bromide by silica chromatography (ethyl acetate/hexane) instead afforded the cyclised adduct, 2,5-diphenyl-Δ^2-1,3-oxazoline **219** as a colourless oil (23 mg, 0.10 mmol, 75 % from **209**); δ_H 4.00 (1H, dd, *J* 8, 15), 4.49 (1H, dd, *J* 10, 15), 5.68 (1H, dd, *J* 8, 10), 6.47 (1H, br t) 7.23–7.54 (8H, m), 8.02–8.08 (2H, m); *m/z* 223 (M^+, 15%), 118 (19), 117 (100), 105 (25), 77 (27). The physical and spectral characteristics were consistent with those found in the literature.[236–239]

Treatment of *N*–(2–Phenylethyl) Acetamide (205) with NBS

A mixture of *N*-(2-Phenylethyl) acetamide **205** (100 mg, 0.61 mmol) and NBS (1 equiv.) in carbon tetrachloride (8 ml) was heated at reflux for 2–4 h under nitrogen whilst being irradiated with a 300 W sunlamp. The mixture was allowed to cool to room temperature, filtered and the solvent evaporated under reduced pressure to yield the crude bromide **211** (81% by internal standard at 64% consumption of **205**) (Found *m/z* 243.008379. $C_{10}H_{12}NO^{81}Br$ requires *m/z* 243.008279. Found *m/z* 241.009941. $C_{10}H_{12}NO^{79}Br$ requires *m/z* 241.010225); δ_H 1.99 (3H, s), 3.74–3.83 (1H, m), 3.87–3.97 (1H, m), 5.09 (1H, dd, *J* 5.9, 8.7), 6.17 (1H, br s) and 7.16–7.51 (5H, m); *m/z* 243 (M^+, ^{81}Br, 21%), 241 (M^+, ^{79}Br, 27), 163 (65), 121 (50), 119 (91), 117 (92) 104 (100) and 91 (51)..

Treatment of *N*–(3–Phenylpropyl) Benzamide (200) with NBS

A mixture of *N*-(3-Phenylpropyl) benzamide **200** (100 mg, 0.42 mmol) and NBS (1 equiv.) in carbon tetrachloride (8 ml) was heated at reflux for 2–4 h under nitrogen whilst being irradiated with a 300 W sunlamp. The mixture was allowed to cool to room temperature, filtered and the solvent evaporated under reduced pressure to yield the crude bromide **215** (86% by internal standard at 57% consumption of **200**) (Found *m/z* 319.03996. $C_{16}H_{16}NO^{81}Br$ requires *m/z* 319.03948); δ_H 2.54 (2H, apparent q, *J* 7.0),

3.50–3.75 (2H, m), 5.07 (1H, apparent t, *J* 7.4), 6.53 (1H, br s), 7.29–7.50 (8H, m) and 7.69–7.72 (2H, m); *m/z* 319 (M^+, ^{81}Br, 1.6%), 317 (M^+, ^{79}Br, 1.6), 238 (32), 237 (42), 146 (30), 105 (100) 104 (66) and 77 (61). Attempted isolation of this bromide only resulted in a variety of unisolated decomposition products.

Treatment of *N*–(4–Phenylbutyl) Benzamide (201) with NBS

A mixture of *N*-(4-Phenylbutyl) benzamide **201** (250 mg, 1.0 mmol) and NBS (193 mg, 1.1 mmol) in carbon tetrachloride (8 ml) was heated at reflux for 5 h under nitrogen whilst being irradiated with a 300 W sunlamp. The mixture was allowed to cool to room temperature, filtered and the solvent evaporated under reduced pressure to yield the crude bromide **217** (84% by internal standard at 62% consumption of **201**); δ_H 1.58–1.72 (1H, m), 1.76–1.91 (1H, m), 2.14–2.27 (1H, m), 2.29–2.41 (1H, m), 3.42–3.53 (2H, m), 5.00 (1H, apparent t, *J*7.4), 6.41 (1H, br s), 7.29–7.40 (8H, m) and 7.70–7.78 (2H, m). Attempted isolation of this bromide by silica chromatography (ethyl acetate/hexane) instead afforded the cyclised adduct, 1-benzoyl-2-phenylpyrrolidine **220** as a pale yellow oil (137 mg, 0.55 mmol, 55 %), (Found: *m/z* 251.1309. $C_{17}H_{17}NO$ requires *m/z* 251.1310.). The NMR spectra indicated the presence of two conformers as determined from the duplicity of the signals observed. By increasing the temperature of a sample of the pyrrolidine **220** in D_6-DMSO to 110 °C, these signals were seen to merge. The spectra at room temperature in $CDCl_3$ showed both conformers existing as a 1 : 1 mixture. δ_H 1.81–2.03 (4H, m), 2.23–2.32 (2H, m), 2.41–2.47 (2H, m), 3.59–3.67 (1H, m), 3.72–3.80 (1H, m), 3.83–3.91 (1H, m), 3.95–4.01 (1H, m), 4.88(1H, apparent br d, *J* 6.0), 5.35 (1H, apparent br t, *J* 6.5), 7.01–7.04 (2H, m), 7.15–7.43 (16H, m) and 7.59–7.61 (2H, m); δ_C 22.73, 26.27, 35.86, 36.84, 48.19, 52.16, 62.02, 64.52, 126.63, 126.69, 127.66, 127.87, 128.02, 128.48, 128.95, 129.30, 129.56, 130.47, 131.15, 144.02, 144.76, 170.88 and 172.05; *m/z* 251 (M^+, 93%), 222 (91), 146 (41), 105 (100) and 77 (56). The physical properties were consistent with those reported in the literature.[250]

References

1. S. Hunt, in *Chemistry and Biochemistry of the Amino Acids*, ed. G. C. Barrett, New York, 1985, p. 55.
2. P. M. Hardy, in *Chemistry and Biochemistry of the Amino Acids*, ed. G. C. Barrett, New York, 1985, p. 6.
3. *Amino Acids. Chemistry, Biology and Medicine*, ed. G. Lubec and G. A. Rosenthal, ESCOM Science Publishers B. V., 1990.
4. J. P. Greenstein and M. Winitz, *Chemistry of the Amino Acids*, John Wiley & Sons, Inc, 1961.
5. C. J. Easton, N. J. Bowmann, M. P. Hay, and S. G. Love, *J. Chem. Soc., Perkin Trans. 1*, 1988, 259.
6. C. J. Easton and S. C. Peters, *Aust. J. Chem.*, 1990, **43**, 87.
7. C. J. Easton, E. W. Tan, and C. M. Ward, *Aust. J. Chem.*, 1992, **45**, 395.
8. C. J. Easton, C. A. Hutton, E. W. Tan, and E. R. T. Tiekink, *Tetrahedron Lett.*, 1990, **31**, 7059.
9. C. J. Easton, C. A. Hutton, P. D. Roselt, and E. R. T. Tiekink, *Tetrahedron*, 1994, **50**, 7327.
10. C. J. Easton, C. A. Hutton, M. C. Merrett, and E. R. T. Tiekink, *Tetrahedron*, 1996, **52**, 7025.
11. C. J. Easton, *Pure Appl. Chem.*, 1997, **69**, 489.
12. C. J. Easton, *Chem. Rev.*, 1997, **97**, 53.
13. D. Elad, M. Schwarzberg, and J. Sperling, *J. Am. Chem. Soc.*, 1973, **95**, 6418.
14. A. F. Parsons and K. Goodall, *Tetrahedron Lett.*, 1997, **38**, 491.
15. P. Renaud and L. Giraud, *Synthesis*, 1996, 913.
16. R. M. Williams, P. J. Sinclair, D. Zhai, and D. Chen, *J. Am. Chem. Soc.*, 1988, **110**, 1547.

17. S. P. Wolff and R. T. Dean, *Biochem. J.*, 1986, **234**, 399.
18. S. P. Wolff, A. Garner, and R. T. Dean, *Trends Biochem. Sci.*, 1986, **11**, 27.
19. K. J. A. Davies, *J. Biol. Chem.*, 1987, **262**, 9895.
20. E. R. Stadtman, *Science*, 1992, **257**, 1220.
21. M. J. Davies, R. T. Dean, and S. Gieseg, *Trends Biochem. Sci.*, 1993, **18**, 437.
22. W. J. Brattin, E. A. Glende, and R. O. Recknagel, *J. Free Radicals Biol. Med.*, 1985, **1**, 27.
23. B. N. Ames, R. Kohen, Y. Yamamoto, and K. C. Cundy, *Proc. Natl. Acad. Sci. USA*, 1988, **85**, 3175.
24. T. Henriksen, T. B. Melo, and G. Saxebol, in *Free Radicals in Biology*, ed. W. A. Pryor, New York, p. 213.
25. W. R. Markesbery, *Free Radical Biol. Med.*, 1997, **23**, 134.
26. C. Y. Yang, Z. W. Gu, H. X. Yang, M. Yang, A. M. Gotto, and C. V. Smith, *Free Radical Biol. Med.*, 1997, **23**, 82.
27. W. A. Pryor, M. M. Dooley, and D. F. Church, *Adv. Free Radical Biol. Med.*, 1986, **2**, 161.
28. J. Stubbe and W. A. van der Donk, *Chem. Rev.*, 1998, **98**, 705.
29. E. R. Stadtman and B. S. Berlett, *J. Biol. Chem.*, 1991, **266**, 17201.
30. D. M. Dooley, C. E. Ruggiero, J. A. Smith, and K. Tanizawa, *Biochemistry*, 1997, **36**, 1953.
31. L. A. Eriksson and F. Himo, *J. Chem. Soc., Perkin Trans. 2*, 1998, 305.
32. P. A. Frey, *Chem. Rev.*, 1990, **90**, 1343.
33. J. P. Jones, J. I. Manchester, J. P. Dinnocenzo, and L. Higgins, *J. Am. Chem. Soc.*, 1997, **119**, 5069.
34. J. P. Klinman and S. M. Miller, *Biochemistry*, 1985, **24**, 2114.
35. D. Mansuy and P. Battioni, in *Activation and Functionalization of Alkanes*, ed. C. L. Hill, New York, 1989, p. 195.
36. C. J. Easton, S. K. Eichinger, and M. J. Pitt, *Tetrahedron*, 1997, **53**, 5609.
37. K. Kociuba, Ph. D. Thesis, University of Adelaide, Adelaide, 1996.

38. C. J. Easton, C. A. Hutton, G. Rositano, and E. W. Tan, *J. Org. Chem.*, 1991, **56**, 5614.

39. D. H. Williams, *Acc. Chem. Res.*, 1984, **17**, 364 and references cited therein.

40. A. A. Tymiak, J. O'Sullivan, J. E. McCullogh, D. R. Kirsch, W. H. Trejo, and P. A. Principe, *J. Antibiot.*, 1988, **41**, 1740.

41. A. A. Tymiak, T. J. McCormick, and S. E. Unger, *J. Org. Chem.*, 1989, **54**, 1149.

42. C. C. J. Culvenor, P. A. Cockrum, J. A. Edgar, J. L. Frahn, C. P. Gorst–Allman, A. J. Jones, W. F. O. Marasas, K. E. Murray, L. W. Smith, P. S. Steyn, R. Vleggaar, and P. L. Wessels, *J. Chem. Soc., Chem. Commun.*, 1983, 1259.

43. C. C. J. Culvenor, M. F. Mackay, and A. Van Donkelaar, *J. Chem. Soc., Chem. Commun.*, 1986, 1219.

44. S. D. Jolad, H. J. Hoffmann, S. J. Torrance, R. M. Wiedhopf, J. R. Cole, S. K. Arora, R. B. Bates, R. L. Gargiulo, and G. R. Kriek, *J. Am. Chem. Soc.*, 1977, **99**, 8040.

45. C. Walsh, *Tetrahedron*, 1982, **38**, 871.

46. R. H. Abeles and A. L. Maycock, *Acc. Chem. Res.*, 1976, **9**, 313.

47. C. J. Easton, V. A. Burgess, M. P. Hay, and P. J. Steel, *Aust. J. Chem.*, 1988, **41**, 701.

48. C. J. Easton, *Adv. Detailed React. Mech.*, 1991, **1**, 83.

49. M. J. S. Dewar, *J. Am. Chem. Soc.*, 1952, **74**, 3353.

50. A. T. Balaban, *Rev. Roum. Chim.*, 1971, **16**, 725.

51. A. T. Balaban, N. Negoiţă, and R. Baican, *Tetrahedron Lett.*, 1973, **21**, 1877.

52. A. T. Balaban and R. Istrăţoiu, *Tetrahedron Lett.*, 1973, **21**, 1879.

53. A. T. Balaban, M. T. Căproiu, N. Negoiţă, and R. Baican, *Tetrahedron*, 1977, **33**, 2249.

54. A. R. Katritzky and F. Soti, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1427.

55. A. R. Katritzky, F. Soti, R. W. Baldock, and P. Hudson, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1422.

56. A. R. Katritzky, R. W. Baldock, P. Hudson, and F. Soti, *Heterocycles*, 1973, **1**, 67.

57. H. G. Viehe, R. Merényi, L. Stella, and Z. Janousek, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 917.
58. H.–G. Korth and W. Sicking, *J. Chem. Soc., Perkin Trans. 2*, 1997, 715.
59. C. Rüchardt, H. D. Beckhaus, H. Birkhofer, and J. Hadrich, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 573.
60. D. J. Pasto, R. Kranansky, and C. Zercher, *J. Org. Chem.*, 1987, **52**, 3062.
61. D. J. Pasto, *J. Am. Chem. Soc.*, 1988, **110**, 8164.
62. C. Rüchardt, J. J. Brocks, F. M. Welle, and H. D. Beckhaus, *Tetrahedron Lett.*, 1997, **38**, 7721.
63. C. Rüchardt, F. M. Welle, and H. D. Beckhaus, *J. Org. Chem.*, 1997, **62**, 552.
64. G. Leroy, J. P. Dewispelaere, H. Benkadour, D. R. Temsamani, and C. Wilante, *Bull. Soc. Chim. Belg.*, 1994, **103**, 367.
65. C. J. Easton and M. P. Hay, *J. Chem. Soc., Chem. Commun.*, 1985, 425.
66. C. J. Easton, M. P. Hay, and S. G. Love, *J. Chem. Soc., Perkin Trans. 1*, 1988, 265.
67. C. J. Easton and M. P. Hay, *J. Chem. Soc., Chem. Commun.*, 1986, 55.
68. C. J. Easton, V. A. Burgess, and M. P. Hay, *J. Am. Chem. Soc.*, 1989, **111**, 1047.
69. Y. Nakatani, E. Deseke, and G. Ourisson, *Eur. J. Org. Chem.*, 1998, 243.
70. M. Adinarayana, B. Kawle, and M. Thirupathi Rao, *Indian J. Chem., Sect. A*, 1996, **35**, 667.
71. H. Taniguchi, H. Hatano, H. Hasegawa, and T. Maruyama, *J. Phys. Chem.*, 1970, **74**, 3063.
72. R. W. Fessenden and P. Neta, *J. Phys. Chem.*, 1971, **75**, 738.
73. C. J. Easton, I. M. Scharfbillig, and E. W. Tan, *Tetrahedron Lett.*, 1988, **29**, 1565.
74. C. J. Easton, E. W. Tan, and M. P. Hay, *J. Chem. Soc., Chem. Commun.*, 1989, 385.
75. C. J. Easton and M. C. Merrett, *J. Am. Chem. Soc.*, 1996, **118**, 3035.
76. G. A. Russell and K. M. Desmond, *J. Am. Chem. Soc.*, 1963, **85**, 3139.
77. C. Walling, *J. Am. Chem. Soc.*, 1983, **105**, 5119.
78. C. Walling, A. L. Rieger, and D. D. Tanner, *J. Am. Chem. Soc.*, 1963, **85**, 3129.
79. J. C. Martin and R. E. Pearson, *J. Am. Chem. Soc.*, 1963, **89**, 3142.
80. P. S. Skell and J. C. Day, *Acc. Chem. Res.*, 1978, **11**, 381.

81. A. G. Davies and B. P. Roberts, in *Free Radicals*, ed. J. K. Kochi, New York, 1973, p. 547.

82. M. Klobukowski, J. L. Gainsforth, and D. D. Tanner, *J. Am. Chem. Soc.*, 1997, **119**, 3339.

83. Y. L. Chow and D.–C. Zhao, *J. Org. Chem.*, 1987, **52**, 1931.

84. Y. L. Chow and D.–C. Zhao, *J. Org. Chem.*, 1989, **54**, 530.

85. K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, *Liebigs Ann. Chem.*, 1942, **551**, 80.

86. G. F. Bloomfield, *J. Chem. Soc.*, 1944, 114.

87. P. Goldfinger, J. Adam, and P. Gosselain, *Nature (London)*, 1953, **171**, 704.

88. P. Sykes, *A Guidebook to Mechanism in Organic Chemistry*, Longmans, 1961.

89. M. L. Poutsma, in *Free Radicals*, ed. J. K. Kochi, New York, 1973, p. 113.

90. B. Giese, C. Wyss, R. Batra, C. Lehmann, and S. Sauer, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2529.

91. J. March, *Advanced Organic Chemistry*, John Wiley and Sons, 1992.

92. H. Fischer, in *Free Radicals*, ed. J. K. Kochi, New York, 1973, p. 435.

93. A. L. J. Beckwith and S. Brumby, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1801.

94. V. Barone, C. Adamo, and F. Lelj, *Chem. Phys. Lett.*, 1994, **230**, 189.

95. V. Barone, C. Adamo, and V. Dillet, *Chem. Phys. Lett.*, 1996, **263**, 113.

96. L. A. E. Batista de Carvalho and J. J. C. Teixeira–Dias, *Theochem (J. Mol. Struct.)*, 1993, **101**, 211.

97. D. Chakraborty and S. Manogaran, *J. Phys. Chem. A*, 1997, **101**, 6964.

98. A. G. Császár, I. G. Csizmadia, Ö. Farkas, and A. Perczel, *Can. J. Chem.*, 1997, **75**, 1120.

99. R. A. Friesner and K. Kim, *J. Am. Chem. Soc.*, 1997, **119**, 12952.

100. A. G. Császár, *J. Mol. Stuct.*, 1995, **346**, 141.

101. S. Gronert and R. A. J. O'Hair, *J. Am. Chem. Soc.*, 1995, **117**, 2071.

102. S. Gronert and S. Shirazian, *Theochem (J. Mol. Struct.)*, 1997, **397**, 107.

103. V. J. Klimkowski, K. Siam, J. D. Ewbank, C. van Alsenoy, and L. Schäfer, *Theochem (J. Mol. Struct.)*, 1984, **110**, 171.

104. V. J. Klimkowski, J. D. Ewbank, K. Siam, and L. Schäfer, *J. Mol. Stuct.*, 1987, **160**, 275.

105. V. J. Klimkowski, L. Schäfer, S. Q. Kulp–Newton, K. Siam, and C. van Alsenoy, *Theochem (J. Mol. Struct.)*, 1990, **209**, 373.

106. V. J. Klimkowski, J. D. Ewbank, J. N. Scarsdale, L. Schäfer, and C. van Alsenoy, *Theochem (J. Mol. Struct.)*, 1985, **124**, 175.

107. A. Perczel, J. G. Angyán, M. Kajtár, W. Vivani, J. L. Rivail, J. F. Marcoccia, and I. G. Csizmadia, *J. Am. Chem. Soc.*, 1991, **113**, 6256.

108. D. Peters and J. Peters, *Theochem (J. Mol. Struct.)*, 1982, **5**, 157.

109. V. Barone, C. Adamo, and F. Lelj, *J. Chem. Phys.*, 1995, **102**, 364.

110. A. Rauk, D. Armstrong, and D. Yu, *Can. J. Chem.*, 1992, **70**, 1762.

111. A. Sutjianto, J. Ladik, and P. Otto, *Theochem (J. Mol. Struct.)*, 1991, **228**, 271.

112. C. van Alsenoy, J. N. Scarsdale, and L. Schäfer, *Theochem (J. Mol. Struct.)*, 1982, **90**, 297.

113. A. G. Császár, *J. Phys. Chem.*, 1996, **100**, 3541.

114. A. Rauk, D. A. Armstrong, and D. Yu, *J. Am. Chem. Soc.*, 1995, **117**, 1789.

115. A. Rauk, D. Yu, and D. A. Armstrong, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2207.

116. V. Barone, M. Cossi, and N. Rega, *J. Am. Chem. Soc.*, 1998, **120**, 5723.

117. V. Barone, M. Cossi, and N. Rega, *J. Am. Chem. Soc.*, 1997, **119**, 12962.

118. V. Barone, C. Adamo, A. Grand, and R. Subra, *Chem. Phys. Lett.*, 1995, **242**, 351.

119. V. Barone, C. Adamo, A. Grand, F. Jolibois, Y. Brunel, and R. Subra, *J. Am. Chem. Soc.*, 1995, **117**, 12618.

120. V. Barone, C. Adamo, A. Grand, Y. Brunel, M. Fontecave, and R. Subra, *J. Am. Chem. Soc.*, 1995, **117**, 1083.

121. A. Rauk, D. A. Armstrong, and D. Yu, *J. Chem. Soc., Perkin Trans. 2*, 1995, 553.

122. A. Rauk, D. A. Armstrong, and D. Yu, *Can. J. Chem.*, 1996, **74**, 1192.

123. A. Rauk, D. Yu, and D. A. Armstrong, *J. Am. Chem. Soc.*, 1997, **119**, 208.

124. C. Rüchardt, J. J. Brocks, H. D. Beckhaus, and A. L. J. Beckwith, *J. Org. Chem.*, 1998, **63**, 1935.

125. C. J. Easton, S. K. Eichinger, and M. J. Pitt, *J. Chem. Soc., Chem. Commun.*, 1992, 1295.

126. J. S. Kizer, R. C. Bateman, C. R. Miller, J. Humm, W. H. Busby, and W. W. Youngblood, *Endocrinology*, 1986, **118**, 2262.

127. G. F. A. Kortum, *Dissociation Constants of Organic Acids in Aqueous Solution*, Butterworths, 1961.

128. E. P. Serjeant and B. Dempsey, *Ionisation Constants of Organic Acids in Aqueous Solution*, Pergamon Press, 1979.

129. R. D. Howells and J. D. McCown, *Chem. Rev.*, 1977, 77, 69.

130. J. F. King, in *The Chemistry of Sulfonic Acids and Their Derivatives*, ed. S. Patai and Z. Rappoport, 1991, p. 249.

131. T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 1957, 4069.

132. R. Stewart, *The Proton : Applications to Organic Chemistry*, ed. H. H. Wasserman, Academic Press, 1985 and references cited therein.

133. *Dictionary of Organic Compounds*, ed. J. Buckingham, Chapman and Hall, 1982.

134. E. W. Tan, Ph. D. Thesis, Adelaide University, Adelaide, 1990.

135. J. Kollonitsch, Y. Fujita, and B. Witkop, *J. Am. Chem. Soc.*, 1965, **87**, 2030.

136. J. Kollonitsch, A. Rosegay, and G. Doldouras, *J. Am. Chem. Soc.*, 1964, **86**, 1857.

137. S. Winstein, *J. Am. Chem. Soc.*, 1942, **64**, 2791.

138. S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, 1942, **64**, 2780.

139. M. L. Bender, *J. Am. Chem. Soc.*, 1957, **79**, 1258.

140. B. Capon, *Q. Rev., Chem. Soc.*, 1964, **18**, 45 and references cited therein.

141. W. B. Lawson, E. Gross, and B. Witkop, *J. Am. Chem. Soc.*, 1962, **84**, 1715.

142. B. Witkop and L. A. Cohen, *Angew. Chem.*, 1961, **73**, 253.

143. S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, 1962, **84**, 2421.

144. R. U. Lemieux and C. Brice, *Can. J. Chem.*, 1955, **33**, 109.

145. D. H. Buss, L. Hough, and A. C. Richardson, *J. Chem. Soc.*, 1963, 5295.

146. P. Edman, *Acta. Chem. Scand.*, 1950, **4**, 283.

147. S.–i. Yamada, K. Koga, and H. Matsuo, *Chem. Pharm. Bull.*, 1963, **11**, 1140.

148. L. H. Welsh, *J. Am. Chem. Soc.*, 1947, **69**, 128.

149. L. H. Welsh, *J. Am. Chem. Soc.*, 1949, **71**, 3500.

150. A. J. Kirby, *Acc. Chem. Res.*, 1997, **30**, 290 and references cited therein.

151. A. Streitwieser, *Chem. Rev.*, 1956, **56**, 571 and references cited therein.

152. F. Besseau, C. Laurence, and M. Berthelot, *J. Chem. Soc., Perkin Trans. 2*, 1992, 2091.

153. F. Besseau, C. Laurence, and M. Berthelot, *J. Chem. Soc., Perkin Trans. 2*, 1994, 485.

154. S. Warren and P. Hodgson, *J. Chem. Soc., Chem. Commun.*, 1973, 756.

155. S. Warren and P. K. G. Hodgson, *J. Chem. Soc., Perkin Trans. 2*, 1975, 372.

156. C. A. Hutton, *Tetrahedron Lett.*, 1997, **38**, 5899.

157. J. C. Martin and W. G. Bentrude, *J. Am. Chem. Soc.*, 1962, **84**, 1561.

158. J. C. Martin, W. G. Bentrude, and D. L. Tuleen, *J. Am. Chem. Soc.*, 1963, **85**, 1938.

159. R. A. Wheeler and S. E. Walden, *J. Am. Chem. Soc.*, 1997, **119**, 3175.

160. *Free Radicals*, ed. J. K. Kochi, John Wiley & Sons, 1973.

161. R. D. Gilliom, *Theochem (J. Mol. Struct.)*, 1986, **138**, 157.

162. Y. D. Wu, C. L. Wong, K. W. K. Chan, G. Z. Ji, and X. K. Jiang, *J. Org. Chem.*, 1996, **61**, 746.

163. D. R. Arnold and J. M. Dust, *J. Am. Chem. Soc.*, 1983, **105**, 1221.

164. L. Radom, C. J. Parkinson, and P. M. Mayer, *in Manuscript*.

165. M. C. Merrett, Ph. D. Thesis, Australian National University, Canberra, 1997.

166. J. J. Dannenberg and X. L. Huang, *J. Org. Chem.*, 1991, **56**, 5421.

167. K. N. Houk and A. E. Dorigo, *J. Am. Chem. Soc.*, 1987, **109**, 2195.

168. C. H. Schiesser and L. M. Wild, *J. Org. Chem.*, 1998, **63**, 670.

169. M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al–Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head–

Gordon, C. Gonzalez, and J. A. Pople, *Gaussian 94, Revision E.2*, Pittsburgh PA, 1995.

170. MOLPRO 96 is a package of *ab initio* programs written by H. –J. Werner and P. J. Knowles with contributions from J. Almlof, R. D. Amos, M. J. O. Deegan, S. T. Elbert, C. Hampel, W. Meyer, K. Peterson, R. Pitzer, A. J. Stone, P. R. Taylor and R. Lindh, 1996.
171. A. Rauk, D. D. M. Wayner, K. B. Clark, D. Yu, and D. A. Armstrong, *J. Am. Chem. Soc.*, 1997, **119**, 8925.
172. J. D. Goddard, *Can. J. Chem.*, 1982, **60**, 1250.
173. W. M. Nau, *J. Phys. Org. Chem.*, 1997, **10**, 445.
174. C. Rüchardt, F. Welle, S. P. Verevkin, M. Keller, and H. D. Beckhaus, *Chem. Ber.*, 1994, **127**, 697.
175. J. S. Wright, D. J. Carpenter, D. J. McKay, and K. U. Ingold, *J. Am. Chem. Soc.*, 1997, **119**, 4245.
176. X. M. Zhang, *J. Org. Chem.*, 1998, **63**, 3590.
177. T. Brinck, M. Haeberlein, and M. Jonsson, *J. Am. Chem. Soc.*, 1997, **119**, 4239.
178. L. Radom, C. J. Parkinson, and P. M. Mayer, *Theor. Chem. Acc.*, 1998, *Submitted for publication.*
179. L. Radom and A. P. Scott, *J. Phys. Chem.*, 1996, **100**, 16502.
180. J. P. A. Heuts, Ph. D., University of Sydney, Sydney, 1996.
181. J. B. Foresman and Æ. Frisch, *Exploring Chemistry with Electronic Structure Methods*, Gaussian, Inc., 1996.
182. M. Lozynski, H.–G. Mack, and D. Rusinska–Roszak, *J. Phys. Chem. A*, 1998, **102**, 2899.
183. V. Barone, *Theor. Chim. Acta*, 1995, **91**, 113.
184. V. Barone, M. Cossi, and J. Tomasi, *J. Comput. Chem.*, 1998, **19**, 404.
185. V. Barone, G. Capecchi, Y. Brunel, M.–L. D. Andriés, and R. Subra, *J. Comput. Chem.*, 1997, **18**, 1720.
186. L. Adamowicz, S. G. Stepanian, I. D. Reva, E. D. Radchenko, M. T. S. Rosado, M. Duarte, and R. Fausto, *J. Phys. Chem.*, 1998, **102**, 1041.

187. H. Fischer and H. Paul, *Helv. Chim. Acta*, 1971, **54**, 485.

188. *International Tables for X–ray Crystallography*, ed. K. Lonsdale, C. M. Macgillaury, and G. D. Rieck, D.Reidel Publishing Company, 1983.

189. M. A. McAllister, A. Perczel, P. Csaszar, W. Viviani, J. L. Rivail, and I. G. Csizmadia, *Theochem (J. Mol. Struct.)*, 1993, **107**, 161.

190. M. A. McAllister, A. Perczel, P. Csaszar, and I. G. Csizmadia, *Theochem (J. Mol. Struct.)*, 1993, **107**, 181.

191. G. Endredi, A. Perczel, O. Farkas, M. A. McAllister, G. I. Csonka, J. Ladik, and I. G. Csizmadia, *Theochem (J. Mol. Struct.)*, 1997, **391**, 15.

192. M. L. Poutsma, in *Free Radicals*, ed. J. K. Kochi, New York, 1973, p. 159.

193. J.–i. Oh Hashi and K. Harada, *Bull. Chem. Soc. Jpn.*, 1966, **39**, 2287.

194. W. Steglich, T. Bretschneider, W. Miltz, and P. Münster, *Tetrahedron*, 1988, **44**, 5403.

195. F. Weygand, W. Steglich, and H. Tanner, *Liebigs Ann. Chem.*, 1962, **658**, 128.

196. F. Weygand and W. Steglich, *Chem. Ber.*, 1965, **98**, 487.

197. F. Weygand, W. Steglich, I. Lengyel, F. Fraunberger, A. Maierhofer, and W. Oettmeier, *Chem. Ber.*, 1966, **99**, 1944.

198. F. Weygand, W. Steglich, A. Maierhofer, W. Oettmeier, and R. S. Loy, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 600.

199. F. Weygand, W. Steglich, H.–U. Heininger, and H. Dworschak, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 807.

200. F. Weygand, W. Steglich, and W. Oettmeier, *Chem. Ber.*, 1970, **103**, 818.

201. F. Weygand, W. Steglich, and W. Oettmeier, *Chem. Ber.*, 1970, **103**, 1655.

202. K. L. Kirk and J.–Y. Nie, in *Biomedical Frontiers of Fluorine Chemistry*, ed. I. Ojima, J. R. McCarthy, and J. T. Welch, Washington, DC, 1996, p. 312.

203. B. Koksch, N. Sewald, H.–D. Jakubke, and K. Burger, in *Biomedical Frontiers of Fluorine Chemistry*, ed. I. Ojima, J. R. McCarthy, and J. T. Welch, Washington, DC, 1996, p. 42.

204. D. Schirlin, S. Baltzar, J. M. Altenburger, C. Tarnus, and J. M. Remy, *Tetrahedron*, 1996, **52**, 5305.

205. M. Schlosser, *Tetrahedron*, 1978, **34**, 3.

206. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.

207. M. Schlosser, D. Michel, *Tetrahedron*, 1996, **52**, 99 and references cited therein.

208. L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, 1960.

209. E. Mack, *J. Am. Chem. Soc.*, 1932, **54**, 2141.

210. A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441.

211. G. A. Russell, in *Free Radicals*, ed. J. K. Kochi, New York, 1973, p. 275.

212. K. U. Ingold, M. D. Bartberger, W. R. Dolbier, and J. Lusztyk, *Tetrahedron*, 1997, **53**, 9857.

213. C. Rüchardt, H. D. Beckhaus, B. Dogan, and S. Verevkin, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 674.

214. S. Grundziński, *Roczniki Chem.*, 1958, **32**, 533.

215. J. Leonard, B. Lygo, and G. Proctor, *Advanced Practical Organic Chemistry*, Blackie Academic and Professional, 1995.

216. M. M. Chemiakine, E. S. Tchaman, L. I. Denisova, G. A. Raudel, and W. J. Rodionow, *Bull. Soc. Chim. Fr.*, 1959, 530.

217. J. B. Hendrickson and R. Bergeron, *Tetrahedron Lett.*, 1973, **46**, 4607.

218. J. B. Hendrickson, R. Bergeron, A. Giga, and D. Sternbach, *J. Am. Chem. Soc.*, 1973, **95**, 3412.

219. J. B. Hendrickson, K. W. Bair, R. Bergeron, A. Giga, P. L. Skipper, D. D. Sternbach, and J. A. Wareing, *Org. Prep. Proceed. Int.*, 1977, **9**, 173.

220. G. Helmchen, personal communication.

221. R. S. Glass and R. J. Swedo, *J. Org. Chem.*, 1978, **43**, 1978.

222. G. Vanags, *Acta. Univ. Latviensis, Kim. Fakultat.*, 1939, **4**, 405.

223. H. Dersin, *Chem. Ber.*, 1921, **54**, 31558.

224. C. A. Hutton, personal communication.

225. S. Wolfe and S. K. Hasan, *Can. J. Chem.*, 1970, **48**, 3572.

226. W. J. Gensler and A. L. Bluhm, *J. Org. Chem.*, 1956, **21**, 336.

227. C. A. Hutton, Ph. D. Thesis, University of Adelaide, Adelaide, 1993.

228. N. Izumuya and A. Nagamatsu, *Bull. Chem. Soc. Jpn.*, 1952, **25**, 265.

229. R. W. Taft, C. Hansch, and A. Leo, *Chem. Rev.*, 1991, **91**, 165.

230. S. V. Jovanovic, M. Tosic, and M. G. Simic, *J. Phys. Chem.*, 1991, **95**, 10824.

231. K. Kindler, B. Hedemann, and E. Schärfe, *Liebigs Ann. Chem.*, 1948, **560**, 215.

232. J. v. Braun, *Chem. Ber.*, 1910, **43**, 2837.

233. M. E. Smith and H. Adkins, *J. Am. Chem. Soc.*, 1938, **60**, 657.

234. M. M. Joullié and A. R. Day, *J. Am. Chem. Soc.*, 1954, **76**, 2990.

235. E. White, *Org. Synth.*, 1967, **47**, 44.

236. L. N. Pridgen, L. B. Kilmer, and R. L. Webb, *J. Org. Chem.*, 1982, **47**, 1985.

237. H. Stamm and R. Flakenstein, *Chem. Ber.*, 1990, **123**, 2227.

238. O. Tsuge, S. Kanemasa, and K. Matsuda, *J. Org. Chem.*, 1986, **51**, 1997.

239. H. Vorbrüggen and K. Krolikiewicz, *Tetrahedron*, 1993, **49**, 9353.

240. J. H. Williams, *Acc. Chem. Res.*, 1993, **26**, 593.

241. C. A. Hunter, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1584.

242. F. Cozzi, J. S. Siegel, F. Ponzini, R. Annunziata, and M. Cinquini, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1019.

243. D. A. Dougherty, R. H. Grubbs, G. W. Coates, A. R. Dunn, and L. M. Henling, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 248.

244. T. Dahl, *Acta. Chem. Scand.*, 1994, **48**, 95 and references cited therein.

245. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

246. W. L. F. Armarego and D. D. Perrin, *Purification of laboratory chemicals*, Butterworth–Heinemann, 1996.

247. C. Niemann, T. H. Applewhite, and R. B. Martin, *J. Am. Chem. Soc.*, 1958, **80**, 1457.

248. C. A. Brown and D. Barton, *Synthesis*, 1974, 434.

249. S. B. Matin and M. Rowland, *J. Pharm. Sci.*, 1972, **61**, 1235.

250. T. Mizoguchi, *Chem. Pharm. Bull.*, 1961, **9**, 818.

Appendices

Appendix A. GAUSSIAN 94 Archive entries for Ethane (**88**).

RMP2//RMP2/6–31G*

```
1\1\GINC-RSCQC9\FOpt\RMP2-FC\6-31G(d)\C2H6\ANNA\03-Mar-1995\0\\# RMP2/
6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\CH3CH3 RMP2 6-31G* opt
imization - test to compare results\\0,1\C,-0.0000169091,0.0000066322,
-0.7629696838\C,0.0000169118,-0.000001473,0.7629696827\H,1.0193205773,
0.0001088803,1.1581243273\H,-1.0193204431,-0.0001328544,-1.1581239941\
H,0.5097395162,-0.8826678816,-1.1581431009\H,0.5095075422,0.8828038778
,-1.1581766015\H,-0.5095192769,-0.8828074781,1.1581334072\H,-0.5097279
316,0.8826645004,1.1581859686\\Version=IBM-RS6000-G94RevE.1\HF=-79.228
5204\MP2=-79.494742\RMSD=3.274e-09\RMSF=1.743e-05\Dipole=0.,-0.0000062
,0.\PG=C01 [X(C2H6)]\\@

1\1\GINC-RSCQC9\SP\RMP2-FC\6-311+G(d,p)\C2H6\ANNA\03-Mar-1995\0\\# RMP
2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=10485760
00\\CH3CH3 RMP2/6-311+G(d,p) single point -test\\0,1\C,-0.0000169091,0
.0000066322,-0.7629696838\C,0.0000169118,-0.000001473,0.7629696827\H,1
.0193205773,0.0001088803,1.1581243273\H,-1.0193204431,-0.0001328544,-1
.1581239941\H,0.5097395162,-0.8826678816,-1.1581431009\H,0.5095075422,
0.8828038778,-1.1581766015\H,-0.5095192769,-0.8828074781,1.1581334072\
H,-0.5097279316,0.8826645004,1.1581859686\\Version=IBM-RS6000-G94RevE.
1\HF=-79.2516746\MP2=-79.5714739\RMSD=1.206e-09\PG=C01 [X(C2H6)]\\@

1\1\GINC-RSCQC9\SP\RMP2-FC\6-311+G(2df,p)\C2H6\ANNA\03-Mar-1995\0\\# R
MP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1048
576000\\CH3CH3 RMP2/6-311+G(2df,p) single point -test\\0,1\C,-0.000016
9091,0.0000066322,-0.7629696838\C,0.0000169118,-0.000001473,0.76296968
27\H,1.0193205773,0.0001088803,1.1581243273\H,-1.0193204431,-0.0001328
544,-1.1581239941\H,0.5097395162,-0.8826678816,-1.1581431009\H,0.50950
75422,0.8828038778,-1.1581766015\H,-0.5095192769,-0.8828074781,1.15813
34072\H,-0.5097279316,0.8826645004,1.1581859686\\Version=IBM-RS6000-G9
4RevE.1\HF=-79.2548853\MP2=-79.6079953\RMSD=2.960e-09\PG=C01 [X(C2H6)]
\\@
```

B3LYP//B3LYP/6–31G*

```
1\1\GINC-RSCQC8\FOpt\RB3LYP\6-31G(d)\C2H6\ANNA\02-Oct-1997\0\\# B3LYP/
6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\CH3CH3 B3LYP 6-31G* op
timization - test to compare results\\0,1\C,-0.1302753963,-0.000001533
8,-0.7542421165\C,0.130273539,0.0000466156,0.7542414016\H,1.2041276446
,-0.0000796545,0.9734542083\H,-1.2041400825,-0.0001216401,-0.973448194
7\H,0.3052343215,-0.8840728186,-1.2340134366\H,0.3044514078,0.88396450
1,-1.2345409509\H,-0.3052372227,-0.883998859,1.2340535388\H,-0.3044249
249,0.8840379804,1.2344991243\\Version=IBM-RS6000-G94RevE.1\HF=-79.830
4166\RMSD=1.714e-09\RMSF=8.970e-05\Dipole=0.0000039,0.0000915,0.000003
5\PG=C01 [X(C2H6)]\\@

1\1\GINC-RSCQC9\SP\RB3LYP\6-311+G(d,p)\C2H6\ANNA\04-Mar-1995\0\\# B3LY
P/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=10485760
00\\CH3CH3 B3LYP/6-311+G(d,p) single point -test\\0,1\C,-0.1302753963,
-0.0000015338,-0.7542421165\C,0.130273539,0.0000466156,0.7542414016\H,
1.2041276446,-0.0000796545,0.9734542083\H,-1.2041400825,-0.0001216401,
-0.9734481947\H,0.3052343215,-0.8840728186,-1.2340134366\H,0.304451407
8,0.883964501,-1.2345409509\H,-0.3052372227,-0.883998859,1.2340535388\
H,-0.3044249249,0.8840379804,1.2344991243\\Version=IBM-RS6000-G94RevE.
1\HF=-79.8565086\RMSD=3.355e-05\Dipole=0.0000045,0.0001171,0.000004\PG
=C01 [X(C2H6)]\\@

1\1\GINC-RSCQC9\SP\RB3LYP\6-311+G(2df,p)\C2H6\ANNA\07-Mar-1995\0\\# B3
LYP/6-311+G(2DF,P) SCF=DIRECT TEST MAXDISK=1048576000\\CH3CH3 B3LYP/6-
311+G(2df,p) single point\\0,1\C,0,-0.1302753963,-0.0000015338,-0.7542
```

421165\C,0,0.130273539,0.0000466156,0.7542414016\H,0,1.2041276446,-0.0
000796545,0.9734542083\H,0,-1.2041400825,-0.0001216401,-0.9734481947\H
,0,0.3052343215,-0.8840728186,-1.2340134366\H,0,0.3044514078,0.8839645
01,-1.2345409509\H,0,-0.3052372227,-0.883998859,1.2340535388\H,0,-0.30
44249249,0.8840379804,1.2344991243\\Version=IBM-RS6000-G94RevE.1\HF=-7
9.8592858\RMSD=4.294e-06\Dipole=0.0000043,0.0001129,0.000004\PG=C01 [X
(C2H6)]\\@

RMP2//B3LYP/6–31G*

1\1\GINC-RSCQC8\SP\RMP2-FC\6-31G(d)\C2H6\ANNA\08-Oct-1997\0\\# RMP2/6-
31G* SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1048576000\\CH3CH3
RMP2/6-31G* single point // B3LYP/6-31G*\\0,1\C,-0.0058442021,0.76538
79383,-0.0000008488\C,0.0057991146,-0.7653872619,-0.0000008677\H,0.008
789439,-1.1641627639,1.0208742851\H,-0.0085881184,1.1641604924,-1.0208
875288\H,0.8750657826,1.1707739193,0.5109698641\H,-0.8929248112,1.1579
237854,0.5099735875\H,0.8929546009,-1.1573094917,-0.5106649712\H,-0.87
50263679,-1.1713899998,-0.510254938\\Version=IBM-RS6000-G94RevE.1\HF=-
79.228306\MP2=-79.4946874\RMSD=1.847e-09\PG=C01 [X(C2H6)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(d,p)\C2H6\ANNA\08-Oct-1997\0\\# RMP
2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=10485760
00\\CH3CH3 RMP2/6-311+G(d,p) single point //B3LYP/6-31G*\\0,1\C,-0.005
8442021,0.7653879383,-0.0000008488\C,0.0057991146,-0.7653872619,-0.000
0008677\H,0.008789439,-1.1641627639,1.0208742851\H,-0.0085881184,1.164
1604924,-1.0208875288\H,0.8750657826,1.1707739193,0.5109698641\H,-0.89
29248112,1.1579237854,0.5099735875\H,0.8929546009,-1.1573094917,-0.510
6649712\H,-0.8750263679,-1.1713899998,-0.510254938\\Version=IBM-RS6000
-G94RevE.1\HF=-79.251476\MP2=-79.5714402\RMSD=1.200e-09\PG=C01 [X(C2H6
)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(2df,p)\C2H6\ANNA\08-Oct-1997\0\\# R
MP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1048
576000\\CH3CH3 RMP2/6-311+G(2df,p) single point //B3LYP/6-31G*\\0,1\C,
-0.0058442021,0.7653879383,-0.0000008488\C,0.0057991146,-0.7653872619,
-0.0000008677\H,0.008789439,-1.1641627639,1.0208742851\H,-0.0085881184
,1.1641604924,-1.0208875288\H,0.8750657826,1.1707739193,0.5109698641\H
,-0.8929248112,1.1579237854,0.5099735875\H,0.8929546009,-1.1573094917,
-0.5106649712\H,-0.8750263679,-1.1713899998,-0.510254938\\Version=IBM-
RS6000-G94RevE.1\HF=-79.2546465\MP2=-79.6078966\RMSD=2.959e-09\PG=C01
[X(C2H6)]\\@

Appendix B. GAUSSIAN 94 Archive entries for Ethyl Radical (**89**).

ROMP2//ROMP2/6–31G*

```
1\1\GINC-RSCQC9\FOpt\ROMP2-FC\6-31G(d)\C2H5(2)\ANNA\03-Mar-1995\1\\# R
OMP2/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\CH2(.)CH3 ROMP2 6
-31G* optimization (radical) from B3LYP opt - test\\0,2\C\C,1,B1\H,2,B
2,1,A1\H,1,B3,2,A2,3,D1,0\H,1,B4,2,A3,4,D2,0\H,2,B6,1,A5,3,D4,0\H,2,B7
,1,A6,3,D5,0\\B1=1.49040234\B2=1.09348508\B3=1.08209316\B4=1.08209385\
B6=1.09347189\B7=1.09970434\A1=111.37200417\A2=120.72220925\A3=120.719
43694\A5=111.3851538\A6=111.85101843\D1=156.96986147\D2=166.90528295\D
4=-120.78879503\D5=119.60131032\\Version=IBM-RS6000-G94RevE.1\HF=-78.5
923898\MP2=-78.8355954\RMSD=1.771e-09\RMSF=1.384e-05\PG=C01 [X(C2H5)]\
\@

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-311+G(d,p)\C2H5(2)\ANNA\03-Mar-1995\0\\#
 ROMP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=104
8576000\\CH3CH2. ROMP2/6-311+G(d,p) single point from ROMP2/6-31G* opt
\\0,2\C\C,1,1.4904023363\H,2,1.0934850751,1,111.37200417\H,1,1.0820931
575,2,120.72220925,3,156.96986147,0\H,1,1.0820938476,2,120.71943694,4,
166.90528295,0\H,2,1.0934718857,1,111.3851538,3,-120.78879503,0\H,2,1.
0997043419,1,111.85101843,3,119.60131032,0\\Version=IBM-RS6000-G94RevE
.1\HF=-78.6157805\MP2=-78.9048869\RMSD=1.233e-09\PG=C01 [X(C2H5)]\\@

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-311+G(2df,p)\C2H5(2)\ANNA\03-Mar-1995\0\
\# ROMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK
=1048576000\\CH3CH2. ROMP2/6-311+G(2df,p) single point from ROMP2/6-31
G* opt\\0,2\C\C,1,1.4904023363\H,2,1.0934850751,1,111.37200417\H,1,1.0
820931575,2,120.72220925,3,156.96986147,0\H,1,1.0820938476,2,120.71943
694,4,166.90528295,0\H,2,1.0934718857,1,111.3851538,3,-120.78879503,0\
H,2,1.0997043419,1,111.85101843,3,119.60131032,0\\Version=IBM-RS6000-G
94RevE.1\HF=-78.6188856\MP2=-78.9407887\RMSD=9.432e-09\PG=C01 [X(C2H5)
]\\@
```

B3LYP//B3LYP/6–31G*

```
1\1\GINC-RSCQC9\FOpt\UB3LYP\6-31G(d)\C2H5(2)\ANNA\03-Mar-1995\0\\# B3L
YP/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\CH2(.)CH3 B3LYP 6-3
1G* optimization (radical) from RMP2 opt - test\\0,2\C,-0.0599796481,-
0.0186233399,-0.7929905604\C,0.0550664405,-0.0045419924,0.692071324\H,
1.0286893011,-0.3812126564,1.0290465127\H,-1.0306197817,-0.0615959146,
-1.276983911\H,0.8030967583,0.1776719492,-1.4213255749\H,-0.7263088091
,-0.6104695383,1.1671624188\H,-0.0453782233,1.0145981539,1.1076159726\
\Version=IBM-RS6000-G94RevE.1\HF=-79.1578673\S2=0.754\S2-1=0.\S2A=0.75
\RMSD=3.015e-09\RMSF=3.701e-06\Dipole=-0.0001196,0.0521963,0.085047\PG
=C01 [X(C2H5)]\\@

1\1\GINC-RSCQC9\SP\UB3LYP\6-311+G(d,p)\C2H5(2)\ANNA\03-Mar-1995\0\\# B
3LYP/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=10485
76000\\CH3CH2. B3LYP/6-311+G(d,p) single point from B3LYP/6-31G* opt\\
0,2\C,-0.0599796481,-0.0186233399,-0.7929905604\C,0.0550664405,-0.0045
419924,0.692071324\H,1.0286893011,-0.3812126564,1.0290465127\H,-1.0306
197817,-0.0615959146,-1.276983911\H,0.8030967583,0.1776719492,-1.42132
55749\H,-0.7263088091,-0.6104695383,1.1671624188\H,-0.0453782233,1.014
5981539,1.1076159726\\Version=IBM-RS6000-G94RevE.1\HF=-79.1849717\S2=0
.754\S2-1=0.\S2A=0.75\RMSD=3.957e-05\Dipole=0.0012287,0.0641992,0.1221
112\PG=C01 [X(C2H5)]\\@

1\1\GINC-RSCQC9\SP\UB3LYP\6-311+G(2df,p)\C2H5(2)\ANNA\03-Mar-1995\0\\#
 B3LYP/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1
048576000\\CH3CH2. B3LYP/6-311+G(2df,p) single point from B3LYP/6-31G*
 opt\\0,2\C,-0.0599796481,-0.0186233399,-0.7929905604\C,0.0550664405,-
0.0045419924,0.692071324\H,1.0286893011,-0.3812126564,1.0290465127\H,-
```

1.0306197817,-0.0615959146,-1.276983911\H,0.8030967583,0.1776719492,-1
.4213255749\H,-0.7263088091,-0.6104695383,1.1671624188\H,-0.0453782233
,1.0145981539,1.1076159726\\Version=IBM-RS6000-G94RevE.1\HF=-79.187952
5\S2=0.754\S2-1=0.\S2A=0.75\RMSD=1.601e-05\Dipole=0.0016931,0.0602864,
0.1215229\PG=C01 [X(C2H5)]\\@

ROMP2//B3LYP/6–31G*

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-31G(d)\C2H5(2)\ANNA\08-Mar-1995\0\\# ROM
P2/6-31G(D) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1048576000\
\CH3CH2. ROMP2/6-31G(d) single point //B3LYP/6-31G* opt\\0,2\C,0.38137
48527,-0.698061523,-0.0064610338\C,-0.3487008741,0.6001414801,0.015923
6345\H,-0.5409712842,0.9420237682,1.0403859925\H,0.3150859228,-1.36070
22936,-0.8636370611\H,1.1195011413,-0.9362132048,0.7529411594\H,-1.311
0475322,0.5356104538,-0.506696382\H,0.221387881,1.4068015338,-0.479769
313\\Version=IBM-RS6000-G94RevE.1\HF=-78.591994\MP2=-78.8355129\RMSD=5
.257e-09\PG=C01 [X(C2H5)]\\@

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-311+G(d,p)\C2H5(2)\ANNA\08-Mar-1995\0\\#
 ROMP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=104
8576000\\CH3CH2. ROMP2/6-311+G(d,p) single point //B3LYP/6-31G* opt\\0
,2\C,0.3813748527,-0.698061523,-0.0064610338\C,-0.3487008741,0.6001414
801,0.0159236345\H,-0.5409712842,0.9420237682,1.0403859925\H,0.3150859
228,-1.3607022936,-0.8636370611\H,1.1195011413,-0.9362132048,0.7529411
594\H,-1.3110475322,0.5356104538,-0.506696382\H,0.221387881,1.40680153
38,-0.479769313\\Version=IBM-RS6000-G94RevE.1\HF=-78.6154192\MP2=-78.9
048254\RMSD=2.022e-09\PG=C01 [X(C2H5)]\\@

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-311+G(2df,p)\C2H5(2)\ANNA\08-Mar-1995\0\
\# ROMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK
=1048576000\\CH3CH2. ROMP2/6-311+G(2df,p) single point //B3LYP/6-31G*
opt\\0,2\C,0.3813748527,-0.698061523,-0.0064610338\C,-0.3487008741,0.6
001414801,0.0159236345\H,-0.5409712842,0.9420237682,1.0403859925\H,0.3
150859228,-1.3607022936,-0.8636370611\H,1.1195011413,-0.9362132048,0.7
529411594\H,-1.3110475322,0.5356104538,-0.506696382\H,0.221387881,1.40
68015338,-0.479769313\\Version=IBM-RS6000-G94RevE.1\HF=-78.6184921\MP2
=-78.9407233\RMSD=5.422e-09\PG=C01 [X(C2H5)]\\@

Appendix C. GAUSSIAN 94 Archive entries for Trifluoroethane (**90**).

RMP2//RMP2/6–31G*

```
1\1\GINC-RSCQC8\FOpt\RMP2-FC\6-31G(d)\C2H3F3\ANNA\02-Oct-1997\0\\# RMP
2/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\CH3CF3 RMP2 6-31G* o
ptimization from CH3CH3 file - test\\0,1\C,-0.2240163272,0.0166297459,
-1.4543301434\C,0.0039129475,-0.0003012469,0.0251314472\F,1.3199135067
,-0.1029529997,0.3264869887\H,-1.2928840404,0.0992520861,-1.6514394856
\H,0.1599017839,-0.9073651085,-1.8870975128\H,0.2971312196,0.870386708
6,-1.88772375\F,-0.624959029,-1.0441123663,0.6153926139\F,-0.455346553
8,1.1292604016,0.6138373892\\Version=IBM-RS6000-G94RevE.1\HF=-375.8176
275\MP2=-376.5873062\RMSD=5.260e-09\RMSF=3.474e-05\Dipole=-0.1283126,0
.0096069,-0.8339382\PG=C01 [X(C2H3F3)]\\@

1\1\GINC-RSCQC9\SP\RMP2-FC\6-311+G(d,p)\C2H3F3\ANNA\03-Mar-1995\0\\# R
MP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=104857
6000\\CH3CF3 RMP2/6-311+G(2df,p) single point from RMP2/6-31G* opt\\0,
1\C,-0.2240163272,0.0166297459,-1.4543301434\C,0.0039129475,-0.0003012
469,0.0251314472\F,1.3199135067,-0.1029529997,0.3264869887\H,-1.292884
0404,0.0992520861,-1.6514394856\H,0.1599017839,-0.9073651085,-1.887097
5128\H,0.2971312196,0.8703867086,-1.88772375\F,-0.624959029,-1.0441123
663,0.6153926139\F,-0.4553465538,1.1292604016,0.6138373892\\Version=IB
M-RS6000-G94RevE.1\HF=-375.9284321\MP2=-376.8384297\RMSD=5.325e-09\PG=
C01 [X(C2H3F3)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(2df,p)\C2H3F3\ANNA\02-Oct-1997\0\\#
 RMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=10
48576000\\CH3CF3 RMP2/6-311+G(2df,p) single point from RMP2/6-31G* opt
\\0,1\C,-0.2240163272,0.0166297459,-1.4543301434\C,0.0039129475,-0.000
3012469,0.0251314472\F,1.3199135067,-0.1029529997,0.3264869887\H,-1.29
28840404,0.0992520861,-1.6514394856\H,0.1599017839,-0.9073651085,-1.88
70975128\H,0.2971312196,0.8703867086,-1.88772375\F,-0.624959029,-1.044
1123663,0.6153926139\F,-0.4553465538,1.1292604016,0.6138373892\\Versio
n=IBM-RS6000-G94RevE.1\HF=-375.9503685\MP2=-377.0218628\RMSD=2.917e-09
\PG=C01 [X(C2H3F3)]\\@
```

B3LYP//B3LYP/6–31G*

```
1\1\GINC-RSCQC9\FOpt\RB3LYP\6-31G(d)\C2H3F3\ANNA\02-Mar-1995\0\\# B3LY
P/6-31G* FOPT GUESS=CHECK GEOM=CHECK SCF=DIRECT TEST MAXDISK=104857600
0\\CH3CF3 B3LYP 6-31G* optimization from RMP2 optimisation - test\\0,1
\C,-0.2249008699,0.0168278948,-1.4592673576\C,0.004418289,-0.000325344
4,0.0291648593\F,1.3190801166,-0.1023374675,0.3280861019\H,-1.29480155
66,0.0997632964,-1.6638313919\H,0.1572973193,-0.9073044414,-1.89891114
1\H,0.2960845799,0.8699264333,-1.899987273\F,-0.623556971,-1.043618930
5,0.6166795265\F,-0.4550436853,1.1280229991,0.6156060156\\Version=IBM-
RS6000-G94RevE.1\HF=-377.5549188\RMSD=2.339e-09\RMSF=6.653e-05\Dipole=
-0.1222641,0.0089902,-0.7928288\PG=C01 [X(C2H3F3)]\\@

1\1\GINC-RSCQC9\SP\RB3LYP\6-311+G(d,p)\C2H3F3\ANNA\02-Mar-1995\0\\# B3
LYP/6-311+G(D,P) GUESS=CHECK GEOM=CHECK SCF=DIRECT TEST MAXDISK=104857
6000\\CH3CF3 B3LYP 6-31+G(d,p) singlepoint - test\\0,1\C,-0.2249008699
,0.0168278948,-1.4592673576\C,0.004418289,-0.0003253444,0.0291648593\F
,1.3190801166,-0.1023374675,0.3280861019\H,-1.2948015566,0.0997632964,
-1.6638313919\H,0.1572973193,-0.9073044414,-1.898911141\H,0.2960845799
,0.8699264333,-1.899987273\F,-0.623556971,-1.0436189305,0.6166795265\F
,-0.4550436853,1.1280229991,0.6156060156\\Version=IBM-RS6000-G94RevE.1
\HF=-377.6864031\RMSD=1.521e-05\Dipole=-0.1506923,0.0110791,-0.9770073
\PG=C01 [X(C2H3F3)]\\@

1\1\GINC-RSCQC9\SP\RB3LYP\6-311+G(2df,p)\C2H3F3\ANNA\03-Mar-1995\0\\#
B3LYP/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=10
```

48576000\\CH3CF3 B3LYP/6-311+G(2df,p) single point -test\\0,1\C,-0.224
9008699,0.0168278948,-1.4592673576\C,0.004418289,-0.0003253444,0.02916
48593\F,1.3190801166,-0.1023374675,0.3280861019\H,-1.2948015566,0.0997
632964,-1.6638313919\H,0.1572973193,-0.9073044414,-1.898911141\H,0.296
0845799,0.8699264333,-1.899987273\F,-0.623556971,-1.0436189305,0.61667
95265\F,-0.4550436853,1.1280229991,0.6156060156\\Version=IBM-RS6000-G9
4RevE.1\HF=-377.7042443\RMSD=6.434e-05\Dipole=-0.1450642,0.0106653,-0.
9404401\PG=C01 [X(C2H3F3)]\\@

RMP2//B3LYP/6–31G*

1\1\GINC-RSCQC8\SP\RMP2-FC\6-31G(d)\C2H3F3\ANNA\08-Oct-1997\0\\# RMP2/
6-31G* GUESS=CHECK GEOM=CHECK SCF=DIRECT TEST MAXDISK=1048576000\\CH3C
F3 RMP2 6-31G* //b3lyp/6-31G*\\0,1\C,-0.2457294691,0.0002682192,-1.455
9812771\C,0.0051052486,-0.0000714739,0.0289889876\F,1.3249489364,-0.08
23444668,0.3101530976\H,-1.3190064148,0.0765193149,-1.6451050779\H,0.1
344823165,-0.9262385042,-1.8919215096\H,0.2632435587,0.8519256155,-1.9
127614205\F,-0.6008808211,-1.0455688628,0.6352930526\F,-0.461287464,1.
1275370076,0.6114140437\\Version=IBM-RS6000-G94RevE.1\HF=-375.8177578\
MP2=-376.58722\RMSD=8.931e-10\PG=C01 [X(C2H3F3)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(d,p)\C2H3F3\ANNA\09-Oct-1997\0\\# R
MP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=104857
6000\\CH3CF3 RMP2/6-311+G(d,p) single point from B3LYP/6-31G* opt\\0,1
\C,-0.2457294691,0.0002682192,-1.4559812771\C,0.0051052486,-0.00007147
39,0.0289889876\F,1.3249489364,-0.0823444668,0.3101530976\H,-1.3190064
148,0.0765193149,-1.6451050779\H,0.1344823165,-0.9262385042,-1.8919215
096\H,0.2632435587,0.8519256155,-1.9127614205\F,-0.6008808211,-1.04556
88628,0.6352930526\F,-0.461287464,1.1275370076,0.6114140437\\Version=I
BM-RS6000-G94RevE.1\HF=-375.9285551\MP2=-376.8384056\RMSD=8.152e-09\PG
=C01 [X(C2H3F3)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(2df,p)\C2H3F3\ANNA\09-Oct-1997\0\\#
 RMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=10
48576000\\CH3CF3 RMP2/6-311+G(2df,p) single point from B3LYP/6-31G* op
t\\0,1\C,-0.2457294691,0.0002682192,-1.4559812771\C,0.0051052486,-0.00
00714739,0.0289889876\F,1.3249489364,-0.0823444668,0.3101530976\H,-1.3
190064148,0.0765193149,-1.6451050779\H,0.1344823165,-0.9262385042,-1.8
919215096\H,0.2632435587,0.8519256155,-1.9127614205\F,-0.6008808211,-1
.0455688628,0.6352930526\F,-0.461287464,1.1275370076,0.6114140437\\Ver
sion=IBM-RS6000-G94RevE.1\HF=-375.9505268\MP2=-377.0218291\RMSD=3.267e
-09\PG=C01 [X(C2H3F3)]\\@

Appendix D. GAUSSIAN 94 Archive entries for Trifluoroethyl Radical (**91**).

ROMP2//ROMP2/6–31G*

1\1\GINC-RSCQC8\FOpt\ROMP2-FC\6-31G(d)\C2H2F3(2)\ANNA\05-Oct-1997\1\\#
ROMP2/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\CH2(.)CF3 ROMP2
6-31G* optimization (radical) from CH3CH3 file - test\\0,2\C\C,1,B1\F
,2,B2,1,A1\H,1,B3,2,A2,3,D1,0\H,1,B4,2,A3,4,D2,0\F,2,B6,1,A5,3,D4,0\F,
2,B7,1,A6,3,D5,0\\B1=1.47817186\B2=1.35946719\B3=1.07924512\B4=1.07931
185\B6=1.35297153\B7=1.35290718\A1=112.24312117\A2=118.87334361\A3=118
.86391267\A5=111.40791332\A6=111.4762406\D1=-276.55893161\D2=193.54606
498\D4=-119.67456862\D5=119.85375385\\Version=IBM-RS6000-G94RevE.1\HF=
-375.1757328\MP2=-375.9207703\RMSD=7.288e-09\RMSF=9.371e-05\PG=C01 [X(
C2H2F3)]\\@

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-311+G(d,p)\C2H2F3(2)\ANNA\05-Oct-1997\0\
\# ROMP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1
048576000\\CF3CH2. ROMP2/6-311+G(d,p) single point from RMP2/6-31G* op
t\\0,2\C\C,1,1.4781718621\F,2,1.3594671866,1,112.24312117\H,1,1.079245
1247,2,118.87334361,3,-276.55893161,0\H,1,1.079311846,2,118.86391267,4
,193.54606498,0\F,2,1.3529715268,1,111.40791332,3,-119.67456862,0\F,2,
1.3529071823,1,111.4762406,3,119.85375385,0\\Version=IBM-RS6000-G94Rev
E.1\HF=-375.2853517\MP2=-376.1641912\RMSD=4.098e-09\PG=C01 [X(C2H2F3)]
\\@

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-311+G(2df,p)\C2H2F3(2)\ANNA\05-Oct-1997\
0\\# ROMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDI
SK=1048576000\\CF3CH2. ROMP2/6-311+G(d,p) single point from RMP2/6-31G
* opt\\0,2\C\C,1,1.4781718621\F,2,1.3594671866,1,112.24312117\H,1,1.07
92451247,2,118.87334361,3,-276.55893161,0\H,1,1.079311846,2,118.863912
67,4,193.54606498,0\F,2,1.3529715268,1,111.40791332,3,-119.67456862,0\
F,2,1.3529071823,1,111.4762406,3,119.85375385,0\\Version=IBM-RS6000-G9
4RevE.1\HF=-375.3072979\MP2=-376.3468134\RMSD=8.912e-09\PG=C01 [X(C2H2
F3)]\\@

B3LYP//B3LYP/6–31G*

1\1\GINC-RSCQC9\FOpt\UB3LYP\6-31G(d)\C2H2F3(2)\ANNA\03-Mar-1995\0\\# B
3LYP/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\CH2(.)CF3 B3LYP 6
-31G* optimization (radical) from RMP2 opt - test\\0,2\C,0.0069508866,
-0.0123430219,-1.4953795827\C,0.0042406475,-0.007535421,-0.0151256943\
F,1.2600223001,-0.0113421908,0.4835590568\H,-0.8574088581,-0.394466013
1,-2.0224478649\H,0.7824709408,0.5277527408,-2.0224482495\F,-0.6445034
68,-1.082778245,0.4835511611\F,-0.6146534195,1.0925630947,0.4893262018
\\Version=IBM-RS6000-G94RevE.1\HF=-376.8760927\S2=0.754\S2-1=0.\S2A=0.
75\RMSD=7.865e-09\RMSF=6.646e-05\Dipole=-0.0183691,0.032687,-0.7939961
\PG=C01 [X(C2H2F3)]\\@

1\1\GINC-RSCQC9\SP\UB3LYP\6-311+G(d,p)\C2H2F3(2)\ANNA\03-Mar-1995\0\\#
B3LYP/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=104
8576000\\CF3CH2. B3LYP/6-311+G(d,p) single point from B3LYP/6-31G* opt
\\0,2\C,0.0069508866,-0.0123430219,-1.4953795827\C,0.0042406475,-0.007
535421,-0.0151256943\F,1.2600223001,-0.0113421908,0.4835590568\H,-0.85
74088581,-0.3944660131,-2.0224478649\H,0.7824709408,0.5277527408,-2.02
24482495\F,-0.644503468,-1.082778245,0.4835511611\F,-0.6146534195,1.09
25630947,0.4893262018\\Version=IBM-RS6000-G94RevE.1\HF=-377.0074853\S2
=0.753\S2-1=0.\S2A=0.75\RMSD=1.743e-05\Dipole=-0.020833,0.0370665,-0.9
536769\PG=C01 [X(C2H2F3)]\\@

1\1\GINC-RSCQC9\SP\UB3LYP\6-311+G(2df,p)\C2H2F3(2)\ANNA\03-Mar-1995\0\
\# B3LYP/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK
=1048576000\\CF3CH2. B3LYP/6-311+G(d,p) single point from B3LYP/6-31G*

opt\\0,2\C,0.0069508866,-0.0123430219,-1.4953795827\C,0.0042406475,-0
.007535421,-0.0151256943\F,1.2600223001,-0.0113421908,0.4835590568\H,-
0.8574088581,-0.3944660131,-2.0224478649\H,0.7824709408,0.5277527408,-
2.0224482495\F,-0.644503468,-1.082778245,0.4835511611\F,-0.6146534195,
1.0925630947,0.4893262018\\Version=IBM-RS6000-G94RevE.1\HF=-377.025529
8\S2=0.754\S2-1=0.\S2A=0.75\RMSD=6.745e-05\Dipole=-0.0200604,0.0356922
,-0.9153404\PG=C01 [X(C2H2F3)]\\@

ROMP2//B3LYP/6–31G*

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-31G(d)\C2H2F3(2)\ANNA\09-Mar-1995\0\\# R
OMP2/6-31G(D) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=104857600
0\\CF3CH2. ROMP2/6-31G(d) single point //B3LYP/6-31G* opt\\0,2\C,-0.13
21457057,0.0351513326,-1.4889528084\C,-0.0001267344,-0.008116057,-0.01
53810423\F,1.1900914895,-0.5241487275,0.361583266\H,-1.1203272641,0.03
40125406,-1.9299814193\H,0.7424607206,0.246161902,-2.0902924005\F,-0.9
746400247,-0.7552120173,0.5482030059\F,-0.0852846666,1.2302067341,0.53
98000529\\Version=IBM-RS6000-G94RevE.1\HF=-375.1757489\MP2=-375.920733
\RMSD=6.407e-09\PG=C01 [X(C2H2F3)]\\@

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-311+G(d,p)\C2H2F3(2)\ANNA\09-Mar-1995\0\
\# ROMP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1
048576000\\CF3CH2. ROMP2/6-311+G(d,p) single point //B3LYP/6-31G* opt\
\0,2\C,-0.1321457057,0.0351513326,-1.4889528084\C,-0.0001267344,-0.008
116057,-0.0153810423\F,1.1900914895,-0.5241487275,0.361583266\H,-1.120
3272641,0.0340125406,-1.9299814193\H,0.7424607206,0.246161902,-2.09029
24005\F,-0.9746400247,-0.7552120173,0.5482030059\F,-0.0852846666,1.230
2067341,0.5398000529\\Version=IBM-RS6000-G94RevE.1\HF=-375.285391\MP2=
-376.164224\RMSD=2.444e-09\PG=C01 [X(C2H2F3)]\\@

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-311+G(2df,p)\C2H2F3(2)\ANNA\09-Mar-1995\
0\\# ROMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDI
SK=1048576000\\CF3CH2. ROMP2/6-311+G(2df,p) single point //B3LYP/6-31G
* opt\\0,2\C,-0.1321457057,0.0351513326,-1.4889528084\C,-0.0001267344,
-0.008116057,-0.0153810423\F,1.1900914895,-0.5241487275,0.361583266\H,
-1.1203272641,0.0340125406,-1.9299814193\H,0.7424607206,0.246161902,-2
.0902924005\F,-0.9746400247,-0.7552120173,0.5482030059\F,-0.0852846666
,1.2302067341,0.5398000529\\Version=IBM-RS6000-G94RevE.1\HF=-375.30735
96\MP2=-376.346882\RMSD=7.893e-09\PG=C01 [X(C2H2F3)]\\@

Appendix E. GAUSSIAN 94 Archive entries for Methylamine (**146**).

RMP2//RMP2/6–31G*

```
1\1\GINC-RSCQC6\FOpt\RMP2-FC\6-31G(d)\C1H5N1\ANNA\09-Mar-1998\0\\# RMP
2/6-31G* FOPT SCF=DIRECT TEST MAXDISK=471859200\\Methylamine opt RMP2/
6-31G*\\0,1\C,-0.497380948,-0.3688039075,-0.3409677786\N,0.5385922062,
0.3154300667,0.4369939758\H,-0.8508608605,0.1700401849,-1.2327527712\H
,-1.3585482656,-0.5541766158,0.3051131815\H,-0.1129466911,-1.339365648
,-0.6628006105\H,1.342610976,0.5030001798,-0.1582185013\H,0.1938850861
,1.2253148773,0.7355075423\\Version=IBM-RS6000-G94RevD.1\HF=-95.209079
5\MP2=-95.5065308\RMSD=7.238e-09\RMSF=4.523e-05\Dipole=-0.1307975,0.37
54682,-0.4713454\PG=C01 [X(C1H5N1)]\\@

1\1\GINC-RSCQC6\SP\RMP2-FC\6-311+G(d,p)\C1H5N1\ANNA\09-Mar-1998\0\\# R
MP2/6-311+G(D,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=471859
200\\Methylamine sp RMP2/6-311+G(d,p)//RMP2/6-31G*\\0,1\C,-0.497380948
,-0.3688039075,-0.3409677786\N,0.5385922062,0.3154300667,0.4369939758\
H,-0.8508608605,0.1700401849,-1.2327527712\H,-1.3585482656,-0.55417661
58,0.3051131815\H,-0.1129466911,-1.339365648,-0.6628006105\H,1.3426109
76,0.5030001798,-0.1582185013\H,0.1938850861,1.2253148773,0.7355075423
\\Version=IBM-RS6000-G94RevD.1\HF=-95.2451422\MP2=-95.5936175\RMSD=5.5
26e-09\PG=C01 [X(C1H5N1)]\\@

1\1\GINC-RSCQC6\SP\RMP2-FC\6-311+G(2df,p)\C1H5N1\ANNA\09-Mar-1998\0\\#
 RMP2/6-311+G(2DF,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=47
1859200\\Methylamine sp RMP2/6-311+G(2df,p)//RMP2/6-31G*\\0,1\C,-0.497
380948,-0.3688039075,-0.3409677786\N,0.5385922062,0.3154300667,0.43699
39758\H,-0.8508608605,0.1700401849,-1.2327527712\H,-1.3585482656,-0.55
41766158,0.3051131815\H,-0.1129466911,-1.339365648,-0.6628006105\H,1.3
42610976,0.5030001798,-0.1582185013\H,0.1938850861,1.2253148773,0.7355
075423\\Version=IBM-RS6000-G94RevD.1\HF=-95.2488224\MP2=-95.6389244\RM
SD=2.837e-09\PG=C01 [X(C1H5N1)]\\@
```

B3LYP//B3LYP/6–31G*

```
1\1\GINC-RSCQC8\FOpt\RB3LYP\6-31G(d)\C1H5N1\ANNA\09-Oct-1997\0\\# B3LY
P/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\Methylamine opt B3LY
P/6-31G*\\0,1\C,-0.4967426872,-0.3681884444,-0.3404819732\N,0.53921553
4,0.3157209858,0.4374098485\H,-0.8564462518,0.1674530626,-1.2369848018
\H,-1.3623706051,-0.5573953335,0.3038495143\H,-0.1158746067,-1.3427150
958,-0.6652613085\H,1.3444992724,0.5047447079,-0.1571653349\H,0.196139
5759,1.2269964246,0.7365848309\\Version=IBM-RS6000-G94RevE.1\HF=-95.85
32044\RMSD=5.452e-09\RMSF=4.199e-05\Dipole=-0.1073489,0.3671836,-0.434
4894\PG=C01 [X(C1H5N1)]\\@

1\1\GINC-RSCQC8\SP\RB3LYP\6-311+G(d,p)\C1H5N1\ANNA\09-Oct-1997\0\\# B3
LYP/6-311+G(D,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=104857
6000\\Methylamine sp B3LYP/6-311+G(d,p)//B3LYP/6-31G*\\0,1\C,-0.496742
6872,-0.3681884444,-0.3404819732\N,0.539215534,0.3157209858,0.43740984
85\H,-0.8564462518,0.1674530626,-1.2369848018\H,-1.3623706051,-0.55739
53335,0.3038495143\H,-0.1158746067,-1.3427150958,-0.6652613085\H,1.344
4992724,0.5047447079,-0.1571653349\H,0.1961395759,1.2269964246,0.73658
48309\\Version=IBM-RS6000-G94RevE.1\HF=-95.8936317\RMSD=8.960e-06\Dipo
le=-0.144589,0.339453,-0.4599415\PG=C01 [X(C1H5N1)]\\@

1\1\GINC-RSCQC8\SP\RB3LYP\6-311+G(2df,p)\C1H5N1\ANNA\09-Oct-1997\0\\#
B3LYP/6-311+G(2DF,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=10
48576000\\Methylamine sp B3LYP/6-311+G(2df,p)//B3LYP/6-31G*\\0,1\C,-0.
4967426872,-0.3681884444,-0.3404819732\N,0.539215534,0.3157209858,0.43
74098485\H,-0.8564462518,0.1674530626,-1.2369848018\H,-1.3623706051,-0
.5573953335,0.3038495143\H,-0.1158746067,-1.3427150958,-0.6652613085\H
```

,1.3444992724,0.5047447079,-0.1571653349\H,0.1961395759,1.2269964246,0
.7365848309\\Version=IBM-RS6000-G94RevE.1\HF=-95.8970532\RMSD=3.184e-0
5\Dipole=-0.1286022,0.333266,-0.4344167\PG=C01 [X(C1H5N1)]\\@

RMP2//B3LYP/6–31G*

1\1\GINC-RSCQC8\SP\RMP2-FC\6-31G(d)\C1H5N1\ANNA\09-Oct-1997\0\\# RMP2/
6-31G* GEOM=CHECK GUESS=CHECK SCF=DIRECT TEST MAXDISK=1048576000\\Meth
ylamine sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.6394207166,-0.1391222961
,0.2646320763\N,-0.6408636639,0.1621553077,-0.3804732961\H,0.593923112
,-0.3476359464,1.3483607442\H,1.3226272036,0.7043986507,0.1163913487\H
,1.0900944273,-1.010266605,-0.2234715042\H,-1.2860704983,-0.6133189828
,-0.2387666876\H,-1.0710528972,0.9664695066,0.0730067138\\Version=IBM-
RS6000-G94RevE.1\HF=-95.2088618\MP2=-95.5064929\RMSD=2.273e-09\PG=C01
[X(C1H5N1)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(d,p)\C1H5N1\ANNA\09-Oct-1997\0\\# R
MP2/6-311+G(D,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=104857
6000\\Methylamine sp RMP2/6-311+G(d,p)//B3LYP/6-31G*\\0,1\C,0.63942071
66,-0.1391222961,0.2646320763\N,-0.6408636639,0.1621553077,-0.38047329
61\H,0.593923112,-0.3476359464,1.3483607442\H,1.3226272036,0.704398650
7,0.1163913487\H,1.0900944273,-1.010266605,-0.2234715042\H,-1.28607049
83,-0.6133189828,-0.2387666876\H,-1.0710528972,0.9664695066,0.07300671
38\\Version=IBM-RS6000-G94RevE.1\HF=-95.2449294\MP2=-95.593563\RMSD=5.
514e-09\PG=C01 [X(C1H5N1)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(2df,p)\C1H5N1\ANNA\09-Oct-1997\0\\#
 RMP2/6-311+G(2DF,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=10
48576000\\Methylamine sp RMP2/6-311+G(2df,p)//B3LYP/6-31G*\\0,1\C,0.63
94207166,-0.1391222961,0.2646320763\N,-0.6408636639,0.1621553077,-0.38
04732961\H,0.593923112,-0.3476359464,1.3483607442\H,1.3226272036,0.704
3986507,0.1163913487\H,1.0900944273,-1.010266605,-0.2234715042\H,-1.28
60704983,-0.6133189828,-0.2387666876\H,-1.0710528972,0.9664695066,0.07
30067138\\Version=IBM-RS6000-G94RevE.1\HF=-95.2485929\MP2=-95.6388478\
RMSD=2.827e-09\PG=C01 [X(C1H5N1)]\\@

Appendix F. GAUSSIAN 94 Archive entries for Aminoethyl Radical (**140**).

ROMP2//ROMP2/6–31G*

```
1\1\GINC-RSCQC9\FOpt\ROMP2-FC\6-31G(d)\C1H4N1(2)\ANNA\09-Mar-1995\1\\#
 ROMP2/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\Methylamino rad
ical opt RMP2/6-31G*\\0,2\C\N,1,B1\H,2,B2,1,A1\H,2,B3,1,A2,3,D1,0\H,1,
B4,2,A3,3,D2,0\H,1,B5,2,A4,5,D3,0\\B1=1.40055847\B2=1.01384751\B3=1.01
382209\B4=1.08330483\B5=1.08329968\A1=113.73313795\A2=113.73216724\A3=
115.50011837\A4=115.50047122\D1=126.86739868\D2=45.37926671\D3=142.372
23814\\Version=IBM-RS6000-G94RevE.1\HF=-94.5822433\MP2=-94.8610055\RMS
D=6.548e-09\RMSF=5.106e-05\PG=C01 [X(C1H4N1)]\\@

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-311+G(d,p)\C1H4N1(2)\ANNA\09-Mar-1995\0\
\# ROMP2/6-311+G(D,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=1
048576000\\Methylamino radical sp RMP2/6-311+G(d,p)//RMP2/6-31G*\\0,2\
C\N,1,1.400558467\H,2,1.0138475073,1,113.73313795\H,2,1.0138220933,1,1
13.73216724,3,126.86739868,0\H,1,1.0833048254,2,115.50011837,3,45.3792
6671,0\H,1,1.0832996813,2,115.50047122,5,142.37223814,0\\Version=IBM-R
S6000-G94RevE.1\HF=-94.6187715\MP2=-94.9410293\RMSD=6.547e-09\PG=C01 [
X(C1H4N1)]\\@

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-311+G(2df,p)\C1H4N1(2)\ANNA\09-Mar-1995\
0\\# ROMP2/6-311+G(2DF,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDI
SK=1048576000\\Methylamino radical sp RMP2/6-311+G(2df,p)//RMP2/6-31G*
\\0,2\C\N,1,1.400558467\H,2,1.0138475073,1,113.73313795\H,2,1.01382209
33,1,113.73216724,3,126.86739868,0\H,1,1.0833048254,2,115.50011837,3,4
5.37926671,0\H,1,1.0832996813,2,115.50047122,5,142.37223814,0\\Version
=IBM-RS6000-G94RevE.1\HF=-94.6225052\MP2=-94.9855373\RMSD=5.427e-09\PG
=C01 [X(C1H4N1)]\\@
```

B3LYP//B3LYP/6–31G*

```
1\1\GINC-RSCQC9\FOpt\UB3LYP\6-31G(d)\C1H4N1(2)\ANNA\09-Mar-1995\0\\# B
3LYP/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\Methylamino radic
al opt B3LYP/6-31G*\\0,2\C,0.0360177674,0.0623462793,-0.7323386778\N,-
0.0431630602,-0.0747344822,0.6603691063\H,0.8561729629,-0.1772701497,1
.1197616157\H,-0.5820373606,0.6525914482,1.1196796032\H,0.7093488094,-
0.6266965725,-1.233944553\H,-0.8974495951,0.3004389735,-1.2340483431\\
Version=IBM-RS6000-G94RevE.1\HF=-95.1956106\S2=0.753\S2-1=0.\S2A=0.75\
RMSD=5.682e-09\RMSF=3.731e-05\Dipole=0.1307127,0.2265729,0.3934759\PG=
C01 [X(C1H4N1)]\\@

1\1\GINC-RSCQC9\SP\UB3LYP\6-311+G(d,p)\C1H4N1(2)\ANNA\09-Mar-1995\0\\#
 B3LYP/6-311+G(D,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=104
8576000\\Methylamino radical sp B3LYP/6-311+G(d,p)//B3LYP/6-31G*\\0,2\
C,0.0360177674,0.0623462793,-0.7323386778\N,-0.0431630602,-0.074734482
2,0.6603691063\H,0.8561729629,-0.1772701497,1.1197616157\H,-0.58203736
06,0.6525914482,1.1196796032\H,0.7093488094,-0.6266965725,-1.233944553
\H,-0.8974495951,0.3004389735,-1.2340483431\\Version=IBM-RS6000-G94Rev
E.1\HF=-95.237391\S2=0.754\S2-1=0.\S2A=0.75\RMSD=2.408e-05\Dipole=0.10
32099,0.178909,0.4000274\PG=C01 [X(C1H4N1)]\\@

1\1\GINC-RSCQC8\SP\UB3LYP\6-311+G(2df,p)\C1H4N1(2)\ANNA\09-Oct-1997\0\
\# B3LYP/6-311+G(2DF,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK
=1048576000\\Methylamino radical sp B3LYP/6-311+G(2df,p)//B3LYP/6-31G*
\\0,2\C,0.0360177674,0.0623462793,-0.7323386778\N,-0.0431630602,-0.074
7344822,0.6603691063\H,0.8561729629,-0.1772701497,1.1197616157\H,-0.58
20373606,0.6525914482,1.1196796032\H,0.7093488094,-0.6266965725,-1.233
944553\H,-0.8974495951,0.3004389735,-1.2340483431\\Version=IBM-RS6000-
G94RevE.1\HF=-95.2408678\S2=0.754\S2-1=0.\S2A=0.75\RMSD=2.708e-05\Dipo
```

le=0.0988718,0.1713913,0.4057835\PG=C01 [X(C1H4N1)]\\@

ROMP2//B3LYP/6–31G*

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-31G(d)\C1H4N1(2)\ANNA\09-Mar-1995\0\\# R
OMP2/6-31G* GEOM=CHECK GUESS=CHECK SCF=DIRECT TEST MAXDISK=1048576000\
\Aminomethyl radical sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,0.0360177674,
0.0623462793,-0.7323386778\N,-0.0431630602,-0.0747344822,0.6603691063\
H,0.8561729629,-0.1772701497,1.1197616157\H,-0.5820373606,0.6525914482
,1.1196796032\H,0.7093488094,-0.6266965725,-1.233944553\H,-0.897449595
1,0.3004389735,-1.2340483431\\Version=IBM-RS6000-G94RevE.1\HF=-94.5820
591\MP2=-94.8609769\RMSD=1.618e-09\PG=C01 [X(C1H4N1)]\\@

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-311+G(d,p)\C1H4N1(2)\ANNA\09-Mar-1995\0\
\# ROMP2/6-311+G(D,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=1
048576000\\Aminomethyl radical sp RMP2/6-311+G(d,p)//B3LYP/6-31G*\\0,2
\C,0.0360177674,0.0623462793,-0.7323386778\N,-0.0431630602,-0.07473448
22,0.6603691063\H,0.8561729629,-0.1772701497,1.1197616157\H,-0.5820373
606,0.6525914482,1.1196796032\H,0.7093488094,-0.6266965725,-1.23394455
3\H,-0.8974495951,0.3004389735,-1.2340483431\\Version=IBM-RS6000-G94Re
vE.1\HF=-94.6186235\MP2=-94.9410222\RMSD=6.707e-09\PG=C01 [X(C1H4N1)]\
\@

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-311+G(2df,p)\C1H4N1(2)\ANNA\09-Mar-1995\
0\\# ROMP2/6-311+G(2DF,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDI
SK=1048576000\\Aminomethyl radical sp RMP2/6-311+G(2df,p)//B3LYP/6-31G
*\\0,2\C,0.0360177674,0.0623462793,-0.7323386778\N,-0.0431630602,-0.07
47344822,0.6603691063\H,0.8561729629,-0.1772701497,1.1197616157\H,-0.5
820373606,0.6525914482,1.1196796032\H,0.7093488094,-0.6266965725,-1.23
3944553\H,-0.8974495951,0.3004389735,-1.2340483431\\Version=IBM-RS6000
-G94RevE.1\HF=-94.6223425\MP2=-94.9855198\RMSD=5.424e-09\PG=C01 [X(C1H
4N1)]\\@

Appendix G. GAUSSIAN 94 Archive entries for Acetic Acid (**221**).

RMP2//RMP2/6–31G*

1\1\GINC-RSCQC9\FOpt\RMP2-FC\6-31G(d)\C2H4O2\ANNA\09-Mar-1995\0\\# RMP
2/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\CH3CO2H RMP2 6-31G*
optimization\\0,1\C,-1.3962868262,0.042459898,0.0590874892\C,0.1021223
849,0.1157895268,-0.0099714453\O,0.7740414373,1.1286672289,-0.08754091
58\O,0.6540803486,-1.1295894248,0.0251186022\H,-1.8069375512,1.0502068
451,0.0300543167\H,-1.7757656123,-0.5436298307,-0.7810028872\H,-1.6988
847078,-0.4620411373,0.9795503985\H,1.6216002319,-0.986654858,-0.02391
95828\\Version=IBM-RS6000-G94RevE.1\HF=-227.8068333\MP2=-228.4189373\R
MSD=2.633e-09\RMSF=2.998e-05\Dipole=-0.2675751,-0.5016566,0.0354985\PG
=C01 [X(C2H4O2)]\\@

1\1\GINC-RSCQC9\SP\RMP2-FC\6-311+G(d,p)\C2H4O2\ANNA\09-Mar-1995\0\\# R
MP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=104857
6000\\CH3CO2H RMP2/6-311+G(d,p) single point//RMP2/6-31G*\\0,1\C,-1.39
62868262,0.042459898,0.0590874892\C,0.1021223849,0.1157895268,-0.00997
14453\O,0.7740414373,1.1286672289,-0.0875409158\O,0.6540803486,-1.1295
894248,0.0251186022\H,-1.8069375512,1.0502068451,0.0300543167\H,-1.775
7656123,-0.5436298307,-0.7810028872\H,-1.6988847078,-0.4620411373,0.97
95503985\H,1.6216002319,-0.986654858,-0.0239195828\\Version=IBM-RS6000
-G94RevE.1\HF=-227.8785498\MP2=-228.5677497\RMSD=2.929e-09\PG=C01 [X(C
2H4O2)]\\@

1\1\GINC-RSCQC9\SP\RMP2-FC\6-311+G(2df,p)\C2H4O2\ANNA\09-Mar-1995\0\\#
 RMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=10
48576000\\CH3CF3 RMP2/6-311+G(2df,p) single point//RMP2/6-31G*\\0,1\C,
-1.3962868262,0.042459898,0.0590874892\C,0.1021223849,0.1157895268,-0.
0099714453\O,0.7740414373,1.1286672289,-0.0875409158\O,0.6540803486,-1
.1295894248,0.0251186022\H,-1.8069375512,1.0502068451,0.0300543167\H,-
1.7757656123,-0.5436298307,-0.7810028872\H,-1.6988847078,-0.4620411373
,0.9795503985\H,1.6216002319,-0.986654858,-0.0239195828\\Version=IBM-R
S6000-G94RevE.1\HF=-227.8923984\MP2=-228.6820139\RMSD=6.345e-09\PG=C01
 [X(C2H4O2)]\\@

B3LYP//B3LYP/6–31G*

1\1\GINC-RSCQC8\FOpt\RB3LYP\6-31G(d)\C2H4O2\ANNA\09-Oct-1997\0\\# B3LY
P/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\CH3CO2H B3LYP 6-31G*
 optimization\\0,1\C,-1.3996431853,0.0447945754,0.0592155645\C,0.10528
18427,0.1148198587,-0.0100254756\O,0.7709630672,1.1223999267,-0.086742
0674\O,0.6602252828,-1.1250667886,0.0241568044\H,-1.8127661661,1.05315
38721,0.0298685461\H,-1.7863012094,-0.5426115867,-0.7800609383\H,-1.70
91695052,-0.4597853826,0.9803698654\H,1.6248981367,-0.9871086124,-0.02
46359028\\Version=IBM-RS6000-G94RevE.1\HF=-229.0817855\RMSD=8.465e-09\
RMSF=8.718e-07\Dipole=-0.2887584,-0.5485987,0.0385208\PG=C01 [X(C2H4O2
)]\\@

1\1\GINC-RSCQC8\SP\RB3LYP\6-311+G(d,p)\C2H4O2\ANNA\09-Oct-1997\0\\# B3
LYP/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=104857
6000\\CH3CO2H B3LYP/6-311+G(d,p) single point//B3LYP/6-31G*\\0,1\C,-1.
3996431853,0.0447945754,0.0592155645\C,0.1052818427,0.1148198587,-0.01
00254756\O,0.7709630672,1.1223999267,-0.0867420674\O,0.6602252828,-1.1
250667886,0.0241568044\H,-1.8127661661,1.0531538721,0.0298685461\H,-1.
7863012094,-0.5426115867,-0.7800609383\H,-1.7091695052,-0.4597853826,0
.9803698654\H,1.6248981367,-0.9871086124,-0.0246359028\\Version=IBM-RS
6000-G94RevE.1\HF=-229.1645784\RMSD=2.613e-05\Dipole=-0.380862,-0.5710
37,0.0436197\PG=C01 [X(C2H4O2)]\\@

1\1\GINC-RSCQC8\SP\RB3LYP\6-311+G(2df,p)\C2H4O2\ANNA\09-Oct-1997\0\\#

B3LYP/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=10
48576000\\CH3CF3 B3LYP/6-311+G(2df,p) single point//B3LYP/6-31G*\\0,1\
C,-1.3996431853,0.0447945754,0.0592155645\C,0.1052818427,0.1148198587,
-0.0100254756\O,0.7709630672,1.1223999267,-0.0867420674\O,0.6602252828
,-1.1250667886,0.0241568044\H,-1.8127661661,1.0531538721,0.0298685461\
H,-1.7863012094,-0.5426115867,-0.7800609383\H,-1.7091695052,-0.4597853
826,0.9803698654\H,1.6248981367,-0.9871086124,-0.0246359028\\Version=I
BM-RS6000-G94RevE.1\HF=-229.1754395\RMSD=4.014e-05\Dipole=-0.3816872,-
0.5766778,0.0439234\PG=C01 [X(C2H4O2)]\\@

RMP2//B3LYP/6–31G*

1\1\GINC-RSCQC8\SP\RMP2-FC\6-31G(d)\C2H4O2\ANNA\09-Oct-1997\0\\# RMP2/
6-31G* SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1048576000\\CH3C
O2H RMP2 6-31G* sp//B3LYP/6-31G*\\0,1\C,-1.3996431853,0.0447945754,0.0
592155645\C,0.1052818427,0.1148198587,-0.0100254756\O,0.7709630672,1.1
223999267,-0.0867420674\O,0.6602252828,-1.1250667886,0.0241568044\H,-1
.8127661661,1.0531538721,0.0298685461\H,-1.7863012094,-0.5426115867,-0
.7800609383\H,-1.7091695052,-0.4597853826,0.9803698654\H,1.6248981367,
-0.9871086124,-0.0246359028\\Version=IBM-RS6000-G94RevE.1\HF=-227.8079
516\MP2=-228.4187545\RMSD=6.449e-09\PG=C01 [X(C2H4O2)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(d,p)\C2H4O2\ANNA\09-Oct-1997\0\\# R
MP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=104857
6000\\CH3CO2H RMP2/6-311+G(d,p) single point//B3LYP/6-31G*\\0,1\C,-1.3
996431853,0.0447945754,0.0592155645\C,0.1052818427,0.1148198587,-0.010
0254756\O,0.7709630672,1.1223999267,-0.0867420674\O,0.6602252828,-1.12
50667886,0.0241568044\H,-1.8127661661,1.0531538721,0.0298685461\H,-1.7
863012094,-0.5426115867,-0.7800609383\H,-1.7091695052,-0.4597853826,0.
9803698654\H,1.6248981367,-0.9871086124,-0.0246359028\\Version=IBM-RS6
000-G94RevE.1\HF=-227.8798138\MP2=-228.5678694\RMSD=2.788e-09\PG=C01 [
X(C2H4O2)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(2df,p)\C2H4O2\ANNA\09-Oct-1997\0\\#
 RMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=10
48576000\\CH3CO2H RMP2/6-311+G(2df,p) single point//B3LYP/6-31G*\\0,1\C
,-1.3996431853,0.0447945754,0.0592155645\C,0.1052818427,0.1148198587,-
0.0100254756\O,0.7709630672,1.1223999267,-0.0867420674\O,0.6602252828,
-1.1250667886,0.0241568044\H,-1.8127661661,1.0531538721,0.0298685461\H
,-1.7863012094,-0.5426115867,-0.7800609383\H,-1.7091695052,-0.45978538
26,0.9803698654\H,1.6248981367,-0.9871086124,-0.0246359028\\Version=IB
M-RS6000-G94RevE.1\HF=-227.8936995\MP2=-228.6821582\RMSD=5.998e-09\PG=
C01 [X(C2H4O2)]\\@

Appendix H. GAUSSIAN 94 Archive entries for Acetyl Radical (**222**).

ROMP2//ROMP2/6–31G*

1\1\GINC-RSCQC8\FOpt\ROMP2-FC\6-31G(d)\C2H3O2(2)\ANNA\11-Oct-1997\1\\#
ROMP2/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\ROMP2/6-31G* op
timisation of planar acetyl radical\\0,2\C\C,1,B1\O,2,B2,1,A1\O,2,B3,1
,A2,3,-180.,0\H,1,B4,2,A3,3,180.,0\H,1,B5,2,A4,5,-180.,0\H,4,B6,2,A5,1
,180.,0\\B1=1.45299085\B2=1.22521115\B3=1.36534347\B4=1.08037934\B5=1.
07978633\B6=0.97856463\A1=125.16517391\A2=112.00612657\A3=120.96223502
\A4=118.31951404\A5=105.28336124\\Version=IBM-RS6000-G94RevE.1\State=2
-A"\HF=-227.1751033\MP2=-227.7645591\RMSD=4.549e-09\RMSF=9.522e-05\PG=
CS [SG(C2H3O2)]\\@

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-311+G(d,p)\C2H3O2(2)\ANNA\11-Oct-1997\0\
\# ROMP2/6-311+G(D,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=1
048576000\\planar Acetyl radical sp RMP2/6-311+G(d,p)//RMP2/6-31G*\\0,
2\C\C,1,1.4529908452\O,2,1.2252111499,1,125.16517391\O,2,1.3653434716,
1,112.00612657,3,-180.,0\H,1,1.0803793385,2,120.96223502,3,180.,0\H,1,
1.0797863338,2,118.31951404,5,-180.,0\H,4,0.9785646288,2,105.28336124,
1,180.,0\\Version=IBM-RS6000-G94RevE.1\State=2-A"\HF=-227.2457708\MP2=
-227.905244\RMSD=3.771e-09\PG=CS [SG(C2H3O2)]\\@

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-311+G(2df,p)\C2H3O2(2)\ANNA\11-Oct-1997\
0\\# ROMP2/6-311+G(2DF,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDI
SK=1048576000\\Acetyl radical sp RMP2/6-311+G(2df,p)//RMP2/6-31G*\\0,2
\C\C,1,1.4529908452\O,2,1.2252111499,1,125.16517391\O,2,1.3653434716,1
,112.00612657,3,-180.,0\H,1,1.0803793385,2,120.96223502,3,180.,0\H,1,1
.0797863338,2,118.31951404,5,-180.,0\H,4,0.9785646288,2,105.28336124,1
,180.,0\\Version=IBM-RS6000-G94RevE.1\State=2-A"\HF=-227.2597142\MP2=-
228.0191774\RMSD=5.194e-09\PG=CS [SG(C2H3O2)]\\@

B3LYP//B3LYP/6–31G*

1\1\GINC-RSCQC8\FOpt\UB3LYP\6-31G(d)\C2H3O2(2)\ANNA\12-Oct-1997\0\\# B
3LYP/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\B3LYP/6-31G* opti
misation of planar acetyl radical\\0,2\C,0.0993133976,0.,-1.4033883755
\C,0.1013552985,0.,0.0427277938\O,1.105929872,0.,0.7400997046\O,-1.155
104481,0.,0.572988312\H,-0.8276281301,0.,-1.9639121669\H,1.0518232766,
0.,-1.9169547746\H,-1.034810451,0.,1.5401262987\\Version=IBM-RS6000-G9
4RevE.1\State=2-A"\HF=-228.4166638\S2=0.758\S2-1=0.\S2A=0.75\RMSD=8.18
9e-09\RMSF=1.178e-04\Dipole=-0.4966867,0.,-0.3770086\PG=CS [SG(C2H3O2)
]\\@

1\1\GINC-RSCQC8\SP\UB3LYP\6-311+G(d,p)\C2H3O2(2)\ANNA\12-Oct-1997\0\\#
B3LYP/6-311+G(D,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=104
8576000\\planar Acetyl radical sp B3LYP/6-311+G(d,p)//B3LYP/6-31G*\\0,
2\C,0.0993133976,0.,-1.4033883755\C,0.1013552985,0.,0.0427277938\O,1.1
05929872,0.,0.7400997046\O,-1.155104481,0.,0.572988312\H,-0.8276281301
,0.,-1.9639121669\H,1.0518232766,0.,-1.9169547746\H,-1.034810451,0.,1.
5401262987\\Version=IBM-RS6000-G94RevE.1\State=2-A"\HF=-228.4986848\S2
=0.758\S2-1=0.\S2A=0.75\RMSD=2.758e-05\Dipole=-0.5245211,0.,-0.467553\
PG=CS [SG(C2H3O2)]\\@

1\1\GINC-RSCQC8\SP\UB3LYP\6-311+G(2df,p)\C2H3O2(2)\ANNA\12-Oct-1997\0\
\# B3LYP/6-311+G(2DF,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK
=1048576000\\planar Acetyl radical sp B3LYP/6-311+G(2df,p)//B3LYP/6-31
G*\\0,2\C,0.0993133976,0.,-1.4033883755\C,0.1013552985,0.,0.0427277938
\O,1.105929872,0.,0.7400997046\O,-1.155104481,0.,0.572988312\H,-0.8276
281301,0.,-1.9639121669\H,1.0518232766,0.,-1.9169547746\H,-1.034810451
,0.,1.5401262987\\Version=IBM-RS6000-G94RevE.1\State=2-A"\HF=-228.5098
1\S2=0.758\S2-1=0.\S2A=0.75\RMSD=4.377e-05\Dipole=-0.5343284,0.,-0.463

9548\PG=CS [SG(C2H3O2)]\\@

ROMP2//B3LYP/6–31G*

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-31G(d)\C2H3O2(2)\ANNA\09-Oct-1997\0\\# R
OMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=1048576000\
\ROMP2/6-31G* sp of acetyl radical//B3LYP/6-31G*\\0,2\C,0.0816190521,-
0.0011930736,-1.4041388615\C,0.1020175074,-0.0005789806,0.041681884\O,
1.1152412668,-0.0070433797,0.7263308016\O,-1.1479403575,0.0078723417,0
.5868580262\H,-0.8522675829,0.0042227607,-1.9530269998\H,1.0272648508,
-0.0075727208,-1.9302880257\H,-1.0152238992,0.0073505896,1.5525462677\
\Version=IBM-RS6000-G94RevE.1\HF=-227.1756332\MP2=-227.7644582\RMSD=5.
161e-09\PG=C01 [X(C2H3O2)]\\@

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-311+G(d,p)\C2H3O2(2)\ANNA\09-Oct-1997\0\
\# ROMP2/6-311+G(D,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=1
048576000\\Acetyl radical sp RMP2/6-311+G(d,p)//B3LYP/6-31G*\\0,2\C,0.
0816190521,-0.0011930736,-1.4041388615\C,0.1020175074,-0.0005789806,0.
041681884\O,1.1152412668,-0.0070433797,0.7263308016\O,-1.1479403575,0.
0078723417,0.5868580262\H,-0.8522675829,0.0042227607,-1.9530269998\H,1
.0272648508,-0.0075727208,-1.9302880257\H,-1.0152238992,0.0073505896,1
.5525462677\\Version=IBM-RS6000-G94RevE.1\HF=-227.246422\MP2=-227.9052
844\RMSD=4.821e-09\PG=C01 [X(C2H3O2)]\\@

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-311+G(2df,p)\C2H3O2(2)\ANNA\09-Oct-1997\
0\\# ROMP2/6-311+G(2DF,P) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDI
SK=1048576000\\Acetyl radical sp RMP2/6-311+G(2df,p)//B3LYP/6-31G*\\0,
2\C,0.0816190521,-0.0011930736,-1.4041388615\C,0.1020175074,-0.0005789
806,0.041681884\O,1.1152412668,-0.0070433797,0.7263308016\O,-1.1479403
575,0.0078723417,0.5868580262\H,-0.8522675829,0.0042227607,-1.95302699
98\H,1.0272648508,-0.0075727208,-1.9302880257\H,-1.0152238992,0.007350
5896,1.5525462677\\Version=IBM-RS6000-G94RevE.1\HF=-227.2604023\MP2=-2
28.0193102\RMSD=5.135e-09\PG=C01 [X(C2H3O2)]\\@

Appendix I. GAUSSIAN 94 Archive entries for Glycine (**64**).

RMP2//RMP2/6–31G*

```
1\1\GINC-RSCQC8\FOpt\RMP2-FC\6-31G(d)\C2H5N1O2\ANNA\13-Oct-1997\0\\# R
MP2/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\H2NCH2CO2H RMP2 6-
31G* optimization\\0,1\C,-0.2081011582,0.,-0.5059087365\C,-0.214120883
2,0.,1.0113995479\N,1.1005759574,0.,1.6277063724\O,-1.4721804365,0.,-1
.006202176\O,0.7876464988,0.,-1.2090055914\H,-1.3732031587,0.,-1.98108
01893\H,-0.7825184228,0.8740105878,1.3467390807\H,-0.7825184228,-0.874
0105878,1.3467390807\H,1.6219060259,0.8081817362,1.2911873455\H,1.6219
060259,-0.8081817362,1.2911873455\\Version=IBM-RS6000-G94RevE.1\State=
1-A'\HF=-282.8266038\MP2=-283.6006276\RMSD=9.836e-09\RMSF=1.281e-04\Di
pole=-0.3638555,0.,-0.3632345\PG=CS [SG(C2H1N1O2),X(H4)]\\@

1\1\GINC-RSCQC9\SP\RMP2-FC\6-311+G(d,p)\C2H5N1O2\ANNA\14-Mar-1995\0\\#
 RMP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1048
576000\\H2NCH2CO2H RMP2/6-311+G(d,p) single point//RMP2/6-31G*\\0,1\C,
-0.2081011582,0.,-0.5059087365\C,-0.2141208832,0.,1.0113995479\N,1.100
5759574,0.,1.6277063724\O,-1.4721804365,0.,-1.006202176\O,0.7876464988
,0.,-1.2090055914\H,-1.3732031587,0.,-1.9810801893\H,-0.7825184228,0.8
740105878,1.3467390807\H,-0.7825184228,-0.8740105878,1.3467390807\H,1.
6219060259,0.8081817362,1.2911873455\H,1.6219060259,-0.8081817362,1.29
11873455\\Version=IBM-RS6000-G94RevE.1\State=1-A'\HF=-282.9189561\MP2=
-283.7876557\RMSD=3.924e-09\PG=CS [SG(C2H1N1O2),X(H4)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(2df,p)\C2H5N1O2\ANNA\13-Oct-1997\0\
\# RMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=
1048576000\\H2NCH2CO2H RMP2/6-311+G(2df,p) single point//RMP2/6-31G*\\
0,1\C,-0.2081011582,0.,-0.5059087365\C,-0.2141208832,0.,1.0113995479\N
,1.1005759574,0.,1.6277063724\O,-1.4721804365,0.,-1.006202176\O,0.7876
464988,0.,-1.2090055914\H,-1.3732031587,0.,-1.9810801893\H,-0.78251842
28,0.8740105878,1.3467390807\H,-0.7825184228,-0.8740105878,1.346739080
7\H,1.6219060259,0.8081817362,1.2911873455\H,1.6219060259,-0.808181736
2,1.2911873455\\Version=IBM-RS6000-G94RevE.1\State=1-A'\HF=-282.935118
1\MP2=-283.9293039\RMSD=9.967e-09\PG=CS [SG(C2H1N1O2),X(H4)]\\@
```

B3LYP//B3LYP/6–31G*

```
1\1\GINC-RSCQC8\FOpt\RB3LYP\6-31G(d)\C2H5N1O2\ANNA\13-Oct-1997\0\\# B3
LYP/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\neutral gly B3LYP
6-31G* optimization\\0,1\C,-0.2090247732,0.,-0.5108901572\C,-0.2111022
889,0.,1.014827257\N,1.1016949332,0.,1.6338885249\O,-1.4682214327,0.,-
1.0135865214\O,0.7804440063,0.,-1.208797963\H,-1.3757125174,0.,-1.9853
416437\H,-0.7831143492,0.8737218705,1.351186708\H,-0.7831143492,-0.873
7218705,1.351186708\H,1.6265292337,0.8075465253,1.3006009152\H,1.62652
92337,-0.8075465253,1.3006009152\\Version=IBM-RS6000-G94RevE.1\State=1
-A'\HF=-284.4234511\RMSD=8.634e-09\RMSF=1.642e-04\Dipole=-0.3944412,0.
,-0.297289\PG=CS [SG(C2H1N1O2),X(H4)]\\@

1\1\GINC-RSCQC8\SP\RB3LYP\6-311+G(d,p)\C2H5N1O2\ANNA\13-Oct-1997\0\\#
B3LYP/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1048
576000\\neutral gly B3LYP/6-311+G(d,p) single point//B3LYP/6-31G*\\0,1
\C,-0.2090247732,0.,-0.5108901572\C,-0.2111022889,0.,1.014827257\N,1.1
016949332,0.,1.6338885249\O,-1.4682214327,0.,-1.0135865214\O,0.7804440
063,0.,-1.208797963\H,-1.3757125174,0.,-1.9853416437\H,-0.7831143492,0
.8737218705,1.351186708\H,-0.7831143492,-0.8737218705,1.351186708\H,1.
6265292337,0.8075465253,1.3006009152\H,1.6265292337,-0.8075465253,1.30
06009152\\Version=IBM-RS6000-G94RevE.1\State=1-A'\HF=-284.5290635\RMSD
=3.114e-05\Dipole=-0.4546574,0.,-0.239107\PG=CS [SG(C2H1N1O2),X(H4)]\\
@
```

1\1\GINC-RSCQC8\SP\RB3LYP\6-311+G(2df,p)\C2H5N1O2\ANNA\13-Oct-1997\0\\
B3LYP/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=
1048576000\\neutral gly B3LYP/6-311+G(2df,p) single point//B3LYP/6-31G
*\\0,1\C,-0.2090247732,0.,-0.5108901572\C,-0.2111022889,0.,1.014827257
\N,1.1016949332,0.,1.6338885249\O,-1.4682214327,0.,-1.0135865214\O,0.7
804440063,0.,-1.208797963\H,-1.3757125174,0.,-1.9853416437\H,-0.783114
3492,0.8737218705,1.351186708\H,-0.7831143492,-0.8737218705,1.35118670
8\H,1.6265292337,0.8075465253,1.3006009152\H,1.6265292337,-0.807546525
3,1.3006009152\\Version=IBM-RS6000-G94RevE.1\State=1-A'\HF=-284.541938
5\RMSD=3.919e-05\Dipole=-0.4520211,0.,-0.2165197\PG=CS [SG(C2H1N1O2),X
(H4)]\\@

RMP2//B3LYP/6–31G*

1\1\GINC-RSCQC9\SP\RMP2-FC\6-31G(d)\C2H5N1O2\ANNA\14-Mar-1995\0\\# RMP
2/6-31G* GEOM=CHECK GUESS=CHECK SCF=DIRECT TEST MAXDISK=39321600\\H2NC
H2CO2H sp RMP2 6-31G*//B3LYP/6-31G*\\0,1\C,-0.2090247732,0.,-0.5108901
572\C,-0.2111022889,0.,1.014827257\N,1.1016949332,0.,1.6338885249\O,-1
.4682214327,0.,-1.0135865214\O,0.7804440063,0.,-1.208797963\H,-1.37571
25174,0.,-1.9853416437\H,-0.7831143492,0.8737218705,1.351186708\H,-0.7
831143492,-0.8737218705,1.351186708\H,1.6265292337,0.8075465253,1.3006
009152\H,1.6265292337,-0.8075465253,1.3006009152\\Version=IBM-RS6000-G
94RevE.1\State=1-A'\HF=-282.8277212\MP2=-283.6004318\RMSD=7.070e-09\PG
=CS [SG(C2H1N1O2),X(H4)]\\@

1\1\GINC-RSCQC9\SP\RMP2-FC\6-311+G(d,p)\C2H5N1O2\ANNA\14-Mar-1995\0\\#
 RMP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=3932
1600\\H2NCH2CO2H RMP2/6-311+G(d,p) single point//B3LYP/6-31G*\\0,1\C,-
0.2090247732,0.,-0.5108901572\C,-0.2111022889,0.,1.014827257\N,1.10169
49332,0.,1.6338885249\O,-1.4682214327,0.,-1.0135865214\O,0.7804440063,
0.,-1.208797963\H,-1.3757125174,0.,-1.9853416437\H,-0.7831143492,0.873
7218705,1.351186708\H,-0.7831143492,-0.8737218705,1.351186708\H,1.6265
292337,0.8075465253,1.3006009152\H,1.6265292337,-0.8075465253,1.300600
9152\\Version=IBM-RS6000-G94RevE.1\State=1-A'\HF=-282.9202763\MP2=-283
.7878087\RMSD=7.927e-09\PG=CS [SG(C2H1N1O2),X(H4)]\\@

1\1\GINC-RSCQC8\SP\RMP2-FC\6-311+G(2df,p)\C2H5N1O2\ANNA\14-Oct-1997\0\
\# RMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=
1048576000\\H2NCH2CO2H RMP2/6-311+G(2df,p) single point//B3LYP/6-31G*\
\0,1\C,-0.2090247732,0.,-0.5108901572\C,-0.2111022889,0.,1.014827257\N
,1.1016949332,0.,1.6338885249\O,-1.4682214327,0.,-1.0135865214\O,0.780
4440063,0.,-1.208797963\H,-1.3757125174,0.,-1.9853416437\H,-0.78311434
92,0.8737218705,1.351186708\H,-0.7831143492,-0.8737218705,1.351186708\
H,1.6265292337,0.8075465253,1.3006009152\H,1.6265292337,-0.8075465253,
1.3006009152\\Version=IBM-RS6000-G94RevE.1\State=1-A'\HF=-282.9364684\
MP2=-283.9294736\RMSD=5.428e-09\PG=CS [SG(C2H1N1O2),X(H4)]\\@

Appendix J. GAUSSIAN 94 Archive entries for Glycine Radical (65).

ROMP2//ROMP2/6–31G*

1\1\GINC-RSCQC8\FOpt\ROMP2-FC\6-31G(d)\C2H4N1O2(2)\ANNA\15-Oct-1997\1\
\# ROMP2/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\H2NCH.CO2H RM
P2 6-31G* optimization\\0,2\C\C,1,B1\N,1,B2,2,A1\O,2,B3,1,A2,3,D1,0\O,
2,B4,1,A3,4,D2,0\H,3,B5,1,A4,2,D3,0\H,3,B6,1,A5,6,D4,0\H,1,B7,2,A6,3,D
5,0\H,4,B8,2,A7,1,D6,0\\B1=1.42718756\B2=1.3561105\B3=1.37100717\B4=1.
23738781\B5=1.01201028\B6=1.00650543\B7=1.08023731\B8=0.97751107\A1=11
6.79114656\A2=113.07258168\A3=124.39877317\A4=117.74796089\A5=122.5609
0584\A6=123.38885763\A7=104.53530973\D1=180.06571361\D2=-179.98321593\
D3=-0.03161452\D4=180.08612058\D5=180.01714426\D6=180.06001862\\Versio
n=IBM-RS6000-G94RevE.1\HF=-282.2115079\MP2=-282.974963\RMSD=4.641e-09\
RMSF=8.073e-05\PG=C01 [X(C2H4N1O2)]\\@

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-311+G(d,p)\C2H4N1O2(2)\ANNA\15-Oct-1997\
0\\# ROMP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK
=1048576000\\H2NCH.CO2H RMP2/6-311+G(d,p) single point//RMP2/6-31G*\\0
,2\C\C,1,1.4271875647\N,1,1.356110496,2,116.79114656\O,2,1.3710071749,
1,113.07258168,3,180.06571361,0\O,2,1.2373878075,1,124.39877317,4,-179
.98321593,0\H,3,1.0120102781,1,117.74796089,2,-0.03161452,0\H,3,1.0065
054333,1,122.56090584,6,180.08612058,0\H,1,1.0802373131,2,123.38885763
,3,180.01714426,0\H,4,0.9775110726,2,104.53530973,1,180.06001862,0\\Ve
rsion=IBM-RS6000-G94RevE.1\HF=-282.3043552\MP2=-283.1537463\RMSD=7.148
e-09\PG=C01 [X(C2H4N1O2)]\\@

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-311+G(2df,p)\C2H4N1O2(2)\ANNA\15-Oct-199
7\0\\# ROMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAX
DISK=1048576000\\H2NCH.CO2H RMP2/6-311+G(2df,p) single point//RMP2/6-3
1G*\\0,2\C\C,1,1.4271875647\N,1,1.356110496,2,116.79114656\O,2,1.37100
71749,1,113.07258168,3,180.06571361,0\O,2,1.2373878075,1,124.39877317,
4,-179.98321593,0\H,3,1.0120102781,1,117.74796089,2,-0.03161452,0\H,3,
1.0065054333,1,122.56090584,6,180.08612058,0\H,1,1.0802373131,2,123.38
885763,3,180.01714426,0\H,4,0.9775110726,2,104.53530973,1,180.06001862
,0\\Version=IBM-RS6000-G94RevE.1\HF=-282.321524\MP2=-283.2981283\RMSD=
9.567e-09\PG=C01 [X(C2H4N1O2)]\\@

B3LYP//B3LYP/6–31G*

1\1\GINC-RSCQC9\FOpt\UB3LYP\6-31G(d)\C2H4N1O2(2)\ANNA\18-Mar-1995\0\\#
 B3LYP/6-31G* FOPT SCF=DIRECT TEST MAXDISK=1048576000\\neutral gly rad
ical B3LYP 6-31G* optimization\\0,2\C,-0.1927410887,0.005366153,-0.967
6369825\C,-0.2054158517,0.0104341569,0.4632170214\N,1.022527014,-0.001
5943938,-1.5886736365\O,-1.4613880859,0.1037300337,0.9955421042\O,0.80
44927688,-0.0700172823,1.1640989389\H,1.8130368011,-0.1931295742,-0.98
23453587\H,1.095812293,-0.3185539084,-2.5445596659\H,-1.0927755973,0.0
730634547,-1.563278827\H,-1.329658415,0.0852769132,1.9602907294\\Versi
on=IBM-RS6000-G94RevE.1\HF=-283.7903884\S2=0.754\S2-1=0.\S2A=0.75\RMSD
=2.914e-09\RMSF=1.011e-05\Dipole=-0.0191976,-0.269994,-0.9474735\PG=C0
1 [X(C2H4N1O2)]\\@

1\1\GINC-RSCQC8\SP\UB3LYP\6-311+G(d,p)\C2H4N1O2(2)\ANNA\19-Oct-1997\0\
\# B3LYP/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK=1
048576000\\neutral gly radical B3LYP/6-311+G(d,p) single point//B3LYP/
6-31G*\\0,2\C,-0.1927410887,0.005366153,-0.9676369825\C,-0.2054158517,
0.0104341569,0.4632170214\N,1.022527014,-0.0015943938,-1.5886736365\O,
-1.4613880859,0.1037300337,0.9955421042\O,0.8044927688,-0.0700172823,1
.1640989389\H,1.8130368011,-0.1931295742,-0.9823453587\H,1.095812293,-
0.3185539084,-2.5445596659\H,-1.0927755973,0.0730634547,-1.563278827\H
,-1.329658415,0.0852769132,1.9602907294\\Version=IBM-RS6000-G94RevE.1\

HF=-283.8969745\S2=0.754\S2-1=0.\S2A=0.75\RMSD=1.444e-05\Dipole=-0.052
3904,-0.2441101,-1.0413852\PG=C01 [X(C2H4N1O2)]\\@

1\1\GINC-RSCQC8\SP\UB3LYP\6-311+G(2df,p)\C2H4N1O2(2)\ANNA\19-Oct-1997\
0\\# B3LYP/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDI
SK=1048576000\\neutral gly radical B3LYP/6-311+G(2df,p) single point//
B3LYP/6-31G*\\0,2\C,-0.1927410887,0.005366153,-0.9676369825\C,-0.20541
58517,0.0104341569,0.4632170214\N,1.022527014,-0.0015943938,-1.5886736
365\O,-1.4613880859,0.1037300337,0.9955421042\O,0.8044927688,-0.070017
2823,1.1640989389\H,1.8130368011,-0.1931295742,-0.9823453587\H,1.09581
2293,-0.3185539084,-2.5445596659\H,-1.0927755973,0.0730634547,-1.56327
8827\H,-1.329658415,0.0852769132,1.9602907294\\Version=IBM-RS6000-G94R
evE.1\HF=-283.9105974\S2=0.754\S2-1=0.\S2A=0.75\RMSD=1.605e-05\Dipole=
-0.0598629,-0.2320793,-1.0364505\PG=C01 [X(C2H4N1O2)]\\@

ROMP2//B3LYP/6–31G*

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-31G(d)\C2H4N1O2(2)\ANNA\19-Oct-1997\0\\#
ROMP2/6-31G* GEOM=CHECK GUESS=CHECK SCF=DIRECT TEST MAXDISK=104857600
0\\H2NCH.CO2H RMP2 6-31G* sp //B3LYP/6-31G*\\0,2\C,-0.1927410887,0.005
366153,-0.9676369825\C,-0.2054158517,0.0104341569,0.4632170214\N,1.022
527014,-0.0015943938,-1.5886736365\O,-1.4613880859,0.1037300337,0.9955
421042\O,0.8044927688,-0.0700172823,1.1640989389\H,1.8130368011,-0.193
1295742,-0.9823453587\H,1.095812293,-0.3185539084,-2.5445596659\H,-1.0
927755973,0.0730634547,-1.563278827\H,-1.329658415,0.0852769132,1.9602
907294\\Version=IBM-RS6000-G94RevE.1\HF=-282.2132453\MP2=-282.9752782\
RMSD=2.492e-09\PG=C01 [X(C2H4N1O2)]\\@

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-311+G(d,p)\C2H4N1O2(2)\ANNA\19-Oct-1997\
0\\# ROMP2/6-311+G(D,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAXDISK
=1048576000\\H2NCH.CO2H RMP2/6-311+G(d,p) single point//B3LYP/6-31G*\\
0,2\C,-0.1927410887,0.005366153,-0.9676369825\C,-0.2054158517,0.010434
1569,0.4632170214\N,1.022527014,-0.0015943938,-1.5886736365\O,-1.46138
80859,0.1037300337,0.9955421042\O,0.8044927688,-0.0700172823,1.1640989
389\H,1.8130368011,-0.1931295742,-0.9823453587\H,1.095812293,-0.318553
9084,-2.5445596659\H,-1.0927755973,0.0730634547,-1.563278827\H,-1.3296
58415,0.0852769132,1.9602907294\\Version=IBM-RS6000-G94RevE.1\HF=-282.
3058566\MP2=-283.1545006\RMSD=8.002e-09\PG=C01 [X(C2H4N1O2)]\\@

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-311+G(2df,p)\C2H4N1O2(2)\ANNA\19-Oct-199
7\0\\# ROMP2/6-311+G(2DF,P) SCF=DIRECT GEOM=CHECK GUESS=CHECK TEST MAX
DISK=1048576000\\H2NCH.CO2H RMP2/6-311+G(2df,p) single point//B3LYP/6-
31G*\\0,2\C,-0.1927410887,0.005366153,-0.9676369825\C,-0.2054158517,0.
0104341569,0.4632170214\N,1.022527014,-0.0015943938,-1.5886736365\O,-1
.4613880859,0.1037300337,0.9955421042\O,0.8044927688,-0.0700172823,1.1
640989389\H,1.8130368011,-0.1931295742,-0.9823453587\H,1.095812293,-0.
3185539084,-2.5445596659\H,-1.0927755973,0.0730634547,-1.563278827\H,-
1.329658415,0.0852769132,1.9602907294\\Version=IBM-RS6000-G94RevE.1\HF
=-282.3229786\MP2=-283.2980415\RMSD=9.984e-09\PG=C01 [X(C2H4N1O2)]\\@

Appendix K. GAUSSIAN 94 Archive entries for other RMP2/6-31G*//B3LYP/6-31G* calculations from Chapter One.

$NH_2CH_2CH_3$ (56)

```
1\1\GINC-RSCQC8\SP\RMP2-FC\6-31G(d)\C2H7N1\ANNA\11-Nov-1998\0\\# RMP2/
 6-31G(D) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=39321600\\ethy
 lamine sp RMP2/6-31G(d)//B3LYP/6-31G*\\0,1\C,-0.2478375757,-0.34994564
 47,0.3821247401\C,-0.2478370641,1.1845181353,0.3821246153\N,0.46966905
 41,-0.9935335853,-0.7241526499\H,0.190483494,-0.718676296,1.3181803373
 \H,0.0766210759,-0.6787877699,-1.6113014121\H,1.4399837916,-0.67878823
 81,-0.7270555318\H,-0.80348898,1.5865865086,1.2388439367\H,0.775648325
 1,1.5778206144,0.4329371275\H,-0.7116130688,1.5778211252,-0.5316666022
 \H,-1.2812701783,-0.7186757905,0.3636345611\\Version=IBM-RS6000-G94Rev
 E.1\HF=-134.2464727\MP2=-134.6754554\RMSD=1.528e-09\PG=C01 [X(C2H7N1)]
 \\@
```

$NH_2C^{\bullet}HCH_3$ (57)

```
 1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C2H6N1(2)\AKC501\29-Mar-1998\0\\#P RO
 MP2/6-31G(D) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000
 \\ethylamino radical sp ROMP2/6-31G(d)//B3LYP/6-31G*\\0,2\C,-0.4406968
 003,0.0317285829,-0.3103890006\C,-0.4417153387,0.0912958288,1.18244668
 52\N,0.8054546674,-0.0890758703,-0.9531544765\H,-1.1622521422,0.634619
 71,-0.8582074238\H,1.4154554937,-0.7805876443,-0.5239467888\H,0.734270
 8863,-0.2739087434,-1.9491573168\H,0.0797906257,-0.7731023511,1.621383
 1303\H,0.0555891673,0.9943754832,1.5812935651\H,-1.4665638689,0.083988
 167,1.5683700622\\Version=SGI-G94RevE.2\HF=-133.6219279\MP2=-134.03138
 21\RMSD=4.031e-09\PG=C01 [X(C2H6N1)]\\@
```

$CH_3CH_2CO_2H$ (58)

```
 1\1\GINC-VPP07\SP\RMP2-FC\6-31G(d)\C3H6O2\AKC501\26-Mar-1998\0\\# RMP2
 /6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=13107200\\HO2CC
 H2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.2523705776,-0.0007755083,
 -0.9822412859\C,-0.2150499146,0.0000078531,0.531018381\C,1.1399780434,
 0.0004601115,-1.6097184887\H,-0.8381894991,0.8715325526,-1.2998847882\
 O,0.7798485233,0.0009693811,1.221331849\O,-1.4669055758,-0.0006186463,
 1.0588225278\H,-1.3490785418,-0.0001344461,2.0273626825\H,1.7076349576
 ,0.8836816304,-1.3024323901\H,1.7104161696,-0.8799740206,-1.2996201823
 \H,1.0665599706,-0.0013626449,-2.701977057\H,-0.8362319444,-0.87470368
 74,-1.2990349168\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-266.843684\MP2
 =-267.5851371\RMSD=6.074e-09\PG=C01 [X(C3H6O2)]\\@
```

$CH_3C^{\bullet}HCO_2H$ (59)

```
 1\1\GINC-VPP10\SP\ROMP2-FC\6-31G(d)\C3H5O2(2)\AKC501\26-Mar-1998\0\\#
 ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=13107200\\
 HO2CCH'CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.3335642996,-0.133381
 9703,-0.8904025068\C,-0.1351217088,0.0297462724,0.5348393135\C,0.80078
 82414,-0.0522463118,-1.8437210666\H,-1.3429232162,-0.3181951342,-1.245
 558249\O,0.9393524492,0.2422989439,1.0822249389\O,-1.2988914449,-0.078
 9672379,1.2406712496\H,-1.0511931191,0.0456306714,2.1749555472\H,0.900
 4395994,-0.9837823997,-2.4205314687\H,0.6404958027,0.7470418497,-2.582
 5342715\H,1.7368795006,0.1379434225,-1.3137955064\\Version=Fujitsu-VP-
 Unix-G94RevE.2\HF=-266.2172514\MP2=-266.9387019\RMSD=4.610e-09\PG=C01
 [X(C3H5O2)]\\@
```

$CH_3CO_2CH_3$ (60)

```
 1\1\GINC-VPP05\SP\RMP2-FC\6-31G(d)\C3H6O2\AKC501\26-Mar-1998\0\\#P RMP
 2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=13107200\\CH3C
 O2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.2212856658,-0.0973584796,-
 1.8587996548\C,0.3287109336,0.0725567114,-0.3613035619\O,1.3126896576,
```

0.4420632821,0.2403021825\O,-0.8400241183,-0.2469267881,0.2436037083\H
,-0.5751687574,0.5413284763,-2.2546097728\H,1.1724832302,0.1652897034,
-2.3226990339\H,-0.0391169908,-1.132451222,-2.1031389676\C,-0.84445499
1,-0.1188676286,1.6743586117\H,-1.8461043269,-0.4108590281,1.991596922
5\H,-0.0931949026,-0.7749251832,2.1223899927\H,-0.6334722165,0.9125416
824,1.9696813628\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-266.8339999\MP
2=-267.5729805\RMSD=5.803e-09\PG=C01 [X(C3H6O2)]\\@

$^{\bullet}CH_2CO_2CH_3$ (61)

1\1\GINC-VPP02\SP\ROMP2-FC\6-31G(d)\C3H5O2(2)\AKC501\26-Mar-1998\0\\#
ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\C
H3O2CCH2' sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,0.2071470377,0.002180820
8,-1.8685651181\C,0.3290414714,0.0000157645,-0.4263651856\O,1.38922623
24,-0.0025948828,0.1835938839\O,-0.8867676107,0.0012490407,0.185238651
3\H,1.1134817618,0.0014546887,-2.4602912895\H,-0.762979298,0.004460453
1,-2.3506640907\C,-0.8425929966,-0.0007654489,1.6179012621\H,-1.883329
9362,0.0005494168,1.9438341841\H,-0.3257063198,-0.8909894893,1.9881144
167\H,-0.3227082568,0.8867048491,1.9905207477\\Version=Fujitsu-VP-Unix
-G94RevE.2\HF=-266.2018015\MP2=-266.9189312\RMSD=4.321e-09\PG=C01 [X(C
3H5O2)]\\@

$CH_3CONHCH_3$ (62)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C3H7N1O1\AKC501\28-Mar-1998\0\\#P RMP2
/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\CH3
CONHCH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.7944747068,0.0616285657,
-1.810594557\N,0.8088033958,0.1017875152,-0.3602150467\H,1.4063939695,
-0.7643157233,-2.1931169897\H,1.1628474399,1.0014137784,-2.2396578173\
H,1.6906056911,0.235514491,0.11165921\C,-0.326571021,-0.0345813892,0.3
925351862\O,-1.4367890235,-0.2001712965,-0.0971357051\C,-0.1179825742,
0.0337251701,1.8994359793\H,-0.2415675983,-0.0892769283,-2.1173225817\
H,-0.7244042483,0.8509667139,2.30178116\H,-0.4849697312,-0.8946617029,
2.3476796159\H,0.9242562248,0.1845830572,2.199308719\\Version=SGI-G94R
evE.2\HF=-247.003602\MP2=-247.7293343\RMSD=8.734e-09\PG=C01 [X(C3H7N1O
1)]\\@

$CH_3CONHCH_2^{\bullet}$ (63)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C3H6N1O1(2)\AKC501\27-Mar-1998\0\\# R
OMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\
\CH3CONHCH2' sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-1.3619078695,0.08856
20543,1.4472936347\H,-1.4871950607,0.2342857181,2.5090784939\N,-0.0894
128678,0.1285737105,0.9234829017\C,0.1958624659,-0.0444150149,-0.42194
46088\O,-0.6873404033,-0.2479009842,-1.2442079963\H,0.6836277725,0.293
4283762,1.5537392668\C,1.6664704878,0.0367561611,-0.7915852526\H,-2.17
57396023,-0.0881346035,0.7626479598\H,1.9663064308,-0.9010063354,-1.27
06425244\H,1.8058163097,0.8349927463,-1.5279247709\H,2.3292469457,0.22
42067954,0.0598025935\\Version=SGI-G94RevE.2\HF=-246.3722933\MP2=-247.
0804408\RMSD=4.793e-09\PG=C01 [X(C3H6N1O1)]\\@

$NH_2CH_2CO_2CH_3$ (66)

1\1\GINC-RSCQC6\SP\RMP2-FC\6-31G(d)\C3H7N1O2\ANNA\01-May-1998\0\\#P RM
P2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=471859200\\H2
NCH2CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-1.3392939735,-0.000557
0537,0.5606914004\N,-1.4559227733,-0.0042141408,2.008958742\C,0.092892
8498,-0.0003080005,0.0274119242\H,-1.8563755111,0.8749647541,0.1490693
271\O,1.0889620401,-0.0034646233,0.7182608701\O,0.110895134,0.00390992
78,-1.3225846606\C,1.4163493061,0.0043617789,-1.9256107515\H,-0.954976
0287,-0.8117237552,2.3775364795\H,-0.955037928,0.8014294593,2.38166665
61\H,-1.8575965087,-0.8732546256,0.1445848679\H,1.2424482056,0.0078531
892,-3.00202177\H,1.9781799884,0.8924960218,-1.6242263004\H,1.97627070
84,-0.8868088417,-1.6296855682\\Version=IBM-RS6000-G94RevD.1\HF=-321.8
539484\MP2=-322.7548648\RMSD=6.851e-09\PG=C01 [X(C3H7N1O2)]\\@

$NH_2CH^{\bullet}CO_2CH_3$ (134)

1\1\GINC-RSCQC6\SP\ROMP2-FC\6-31G(d)\C3H6N1O2(2)\ANNA\02-May-1998\0\\#
P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=47185920
0\\H2NCHCO2CH3 sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-1.2193725619,0.02
37532304,0.7029035335\N,-1.2256527581,0.0051086235,2.0688421059\C,0.05
31103655,0.005526864,0.0442231584\H,-2.1579410729,-0.0199355457,0.1674
090731\O,1.1330262563,0.0587409648,0.634455802\O,-0.0629426243,-0.0666
288145,-1.3136246568\C,1.1797476736,-0.0717135555,-2.021888961\H,-0.32
33890456,0.1783313847,2.4995147723\H,-2.0353519091,0.3450608876,2.5677
805584\H,0.9156223565,-0.1289189249,-3.0790998253\H,1.7491294023,0.840
9534659,-1.8206742543\H,1.7899176561,-0.9335480687,-1.7349006131\\Vers
ion=IBM-RS6000-G94RevD.1\HF=-321.238884\MP2=-322.1290204\RMSD=3.264e-0
9\PG=C01 [X(C3H6N1O2)]\\@

$CH_3CONHCH_2CO_2H$ (71)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C4H7N1O3\AKC501\24-Jun-1998\0\\#P RMP2
/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\CH3
CONHCH2CO2H sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.7824832063,-0.04354
14057,-1.7040102543\C,-0.8355792679,0.0037094431,-0.1931500923\C,0.738
1908186,0.042860224,1.6750647821\C,2.2004821902,0.0416350404,2.0929167
287\H,-1.3948474448,0.8947910238,0.1214728575\H,-1.4108019867,-0.85573
94301,0.1759078841\H,1.258469878,-0.0188567414,-0.3474870607\H,-1.9010
633155,-0.079369849,-3.2098257227\H,2.3976100078,0.9376435183,2.689481
6537\H,2.3827953885,-0.8246618891,2.7362776664\H,2.8990986435,0.013378
587,1.2509591136\N,0.5083285205,0.0074287912,0.3304939682\O,-2.0183678
184,-0.0482799013,-2.2414811775\O,0.2344064907,-0.0736308301,-2.364024
1751\O,-0.1801916751,0.0735149102,2.4861089582\\Version=SGI-G94RevE.2\
HF=-434.6213177\MP2=-435.8215161\RMSD=6.200e-09\PG=C01 [X(C4H7N1O3)]\\
@

$CH_3CONHC^{\bullet}HCO_2H$ (223)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C4H6N1O3(2)\AKC501\24-Jun-1998\0\\#P
ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000
\\CH3CONHCH-CO2H sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.089253678,-0.0
060128266,-0.7931322629\N,-0.0849320151,-0.0057783825,0.570448591\C,1.
1959774265,-0.0055907855,-1.4386388741\H,-1.0405064805,-0.0070316788,-
1.3037728761\O,2.2655799664,-0.0044776562,-0.8319438381\O,1.1156567832
,-0.0059239973,-2.7952168483\H,2.0363387769,-0.0053394247,-3.114481666
4\H,0.8375627224,-0.0019424311,0.9971604495\C,-1.2343398291,-0.0064649
353,1.358770475\O,-2.3457375736,-0.0172382986,0.8577780875\C,-0.986047
0761,0.0357694232,2.8534152939\H,-1.1831905448,1.0489871198,3.22252834
98\H,-1.6925625472,-0.6368915151,3.3457989329\H,0.0348677117,-0.242419
0303,3.1321996727\\Version=SGI-G94RevE.2\HF=-434.0046548\MP2=-435.1921
757\RMSD=7.007e-09\PG=C01 [X(C4H6N1O3)]\\@

$CH_3CONHCH_2CO_2CH_3$ (72)

1\1\GINC-VPP05\SP\RMP2-FC\6-31G(d)\C5H9N1O3\AKC501\28-Mar-1998\0\\# RM
P2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=12582912\\CH3
O2CCH2NHCOCH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.453984955,0.04227
64497,-0.4610673375\N,-0.434416958,-0.0062114363,0.9807989618\C,0.9689
096865,-0.0262498517,-0.9801271891\H,-0.9312052348,0.9609457186,-0.826
7029336\O,1.9556376518,-0.1077624508,-0.2773614955\O,0.9935745096,0.01
52606135,-2.320978703\C,2.3010407694,-0.0435036938,-2.9216242995\H,0.4
761138148,-0.0746290799,1.416180349\C,-1.5895703494,0.0400642778,1.704
2057359\O,-2.6876253658,0.1238515692,1.1654906135\C,-1.4223696652,-0.0
190545532,3.2149807124\H,-1.0363983067,-0.7867185427,-0.8840263162\H,2
.1281952796,0.0013801949,-3.9966976274\H,2.910140692,0.8022221855,-2.5
927965776\H,2.8040095293,-0.9749485721,-2.6499338831\H,-1.8698201152,0
.8775364171,3.6549097459\H,-1.9769883646,-0.8812328872,3.5979267627\H,
-0.3799758713,-0.0930690085,3.5401386944\\Version=Fujitsu-VP-Unix-G94R

evE.2\HF=-473.6480592\MP2=-474.9764903\RMSD=7.422e-09\PG=C01 [X(C5H9N1
O3)]\\@

$CH_3CONHC^{\bullet}HCO_2CH_3$ (73)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C5H8N1O3(2)\AKC501\30-Mar-1998\0\\# R
OMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\
\CH3O2CCH'NHCOCH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.3824700669,0.
0186723638,-0.37315618\N,-0.3645322925,-0.016000121,0.9905755085\C,0.8
977685159,-0.0135309135,-1.0327292927\H,-1.3377465782,0.0669329941,-0.
8738388169\O,1.9695412086,-0.0685718101,-0.4319076048\O,0.7849387732,0
.024138858,-2.3825116347\C,2.027964724,-0.0050705725,-3.0966484405\H,0
.5628675966,-0.0582000695,1.4044760017\C,-1.5024970986,0.0069307292,1.
7927967609\O,-2.6205637825,0.0512664451,1.3074769728\C,-1.2345521427,0
.0015144636,3.2849788804\H,1.7584939546,0.0303513968,-4.1527005464\H,2
.6479499822,0.8557621457,-2.8302527423\H,2.581666637,-0.921421798,-2.8
728909291\H,-1.3905122245,1.0110838402,3.6827324222\H,-1.9586461144,-0
.6581416589,3.7694459459\H,-0.2209603906,-0.320130371,3.5430878703\\Ve
rsion=SGI-G94RevE.2\HF=-473.0308985\MP2=-474.3466163\RMSD=7.089e-09\PG
=C01 [X(C5H8N1O3)]\\@

$NH_2CH(CH_3)CO_2H$ (67)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C3H7N1O2\AKC501\17-Jun-1998\0\\#P RMP2
/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\H2N
CHCH3CO2H sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.0592907487,-0.1655734
94,-0.7792566982\C,-0.039172236,-0.2507758663,0.7497422524\N,1.3057512
685,-0.3823720956,1.2964624402\O,-1.3062310704,-0.3352234104,-1.285614
2497\O,0.9073266039,0.0418805131,-1.480222016\H,-1.2228607245,-0.24280
87375,-2.253845927\C,-0.7380807172,0.9816250451,1.3481264381\H,-0.6145
181851,-1.1416728807,1.0304586188\H,1.7383335166,-1.2282245411,0.92646
04263\H,1.8770836809,0.3813572383,0.9333256162\H,-0.7342612677,0.90063
98201,2.4383199836\H,-0.2043377714,1.8991280007,1.0717317241\H,-1.7692
001848,1.0632748398,0.9933306484\\Version=SGI-G94RevE.2\HF=-321.864390
6\MP2=-322.7704397\RMSD=6.450e-09\PG=C01 [X(C3H7N1O2)]\\@

$NH_2C^{\bullet}(CH_3)CO_2H$ (68)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C3H6N1O2(2)\AKC501\02-Apr-1998\0\\#P
ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000
\\H2NCHCH3CO2H sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.0157560178,-0.31
28072874,-0.7233267412\C,0.1014862465,0.2010921114,0.6129604378\N,1.27
3150559,-0.1110055598,1.2538028043\O,-1.1494084439,0.0827190988,-1.383
7168223\O,0.8162120867,-1.0549612098,-1.2514460075\H,-1.0917085224,-0.
3492631178,-2.2543296012\C,-0.8903880959,1.089257237,1.2905142909\H,1.
2896326834,-0.1153053184,2.2648927252\H,1.8330194635,-0.8195398357,0.7
916395321\H,-1.1692204824,0.6956256888,2.27935609\H,-0.4828760347,2.09
82572699,1.4503485643\H,-1.7973829597,1.1799487537,0.6918877719\\Versi
on=SGI-G94RevE.2\HF=-321.253052\MP2=-322.1481303\RMSD=2.491e-09\PG=C01
[X(C3H6N1O2)]\\@

$CH_3CONHCH(CH_3)CO_2CH_3$ (74)

1\1\GINC-VPP09\SP\RMP2-FC\6-31G(d)\C6H11N1O3\AKC501\11-Apr-1998\0\\#P
RMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\CH
3CONHCHCH3CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.3667196064,0.0
716605373,-0.3851585219\N,-0.3593680447,0.0963142476,1.0662887614\C,1.
0808071321,-0.0362817008,-0.8478985426\C,-1.0607758274,1.3046628996,-0
.9963952232\O,2.047717929,0.0659179095,-0.1192160876\O,1.1571717024,-0
.2400960536,-2.1728676547\C,2.4886121862,-0.3267202763,-2.7137908888\H
,0.5434545641,0.228654278,1.5041432191\C,-1.4575634565,-0.2628307173,1
.7925221727\O,-2.5283687226,-0.5461233351,1.2645759074\C,-1.2684929532
,-0.2814737137,3.3020748009\H,-0.9069982581,-0.8224565988,-0.719161712
9\H,2.3570402115,-0.4890759774,-3.7834480917\H,3.0372535682,0.60010011
38,-2.5282311505\H,3.0305041193,-1.1605195365,-2.2604873559\H,-2.00231
39405,0.3902365471,3.7578402678\H,-1.4776976635,-1.290486048,3.6711097

592\H,-0.2656671869,0.0155870786,3.6240466441\H,-1.0674609133,1.240711
5494,-2.0882017136\H,-2.0907213239,1.3360728689,-0.6339984271\H,-0.549
1889821,2.2252856527,-0.6956928717\\Version=Fujitsu-VP-Unix-G94RevE.2\
HF=-512.6847518\MP2=-514.148391\RMSD=3.895e-09\PG=C01 [X(C6H11N1O3)]\\
@

$CH3CONHC^{\bullet}(CH_3)CO_2CH_3$ (75)

1\1\GINC-VPP05\SP\ROMP2-FC\6-31G(d)\C6H10N1O3(2)\AKC501\11-Apr-1998\0\
\#P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=838860
8\\CH3NHCHCH3CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.2895558464,
-0.0043989742,-0.3447847739\N,-0.261035049,-0.00380632,1.0337444984\C,
1.0459793091,-0.0080072949,-0.9133489793\C,-1.5555484454,-0.0019046287
,-1.1334105164\O,2.0703765082,-0.0099457488,-0.2278632137\O,1.06017805
82,-0.0083980237,-2.2693401626\C,2.3656961084,-0.010978545,-2.86125717
35\H,0.6895533317,-0.0037459104,1.397201705\C,-1.3186104852,0.00137714
21,1.9309312246\O,-2.4906766582,-0.0027993748,1.5852484563\C,-0.899028
5425,0.0366449658,3.3913756635\H,2.1969269553,-0.0113514078,-3.9387266
398\H,2.9284077197,0.8775909206,-2.561443442\H,2.9254200114,-0.9010402
776,-2.560325528\H,-1.1186872703,1.0287940524,3.8018044423\H,-1.503041
5606,-0.6867679405,3.9454182319\H,0.1612567473,-0.1801581586,3.5520032
749\H,-1.3199753637,-0.0000957147,-2.1980861497\H,-2.1732518732,-0.876
3872315,-0.8994100382\H,-2.171979208,0.8725550952,-0.8960406551\\Versi
on=Fujitsu-VP-Unix-G94RevE.2\HF=-512.0662576\MP2=-513.517739\RMSD=5.39
9e-09\PG=C01 [X(C6H10N1O3)]\\@

$NH_2CH(CH(CH_3)_2)CO_2H$ (69)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C5H11N1O2\AKC501\17-Jun-1998\0\\#P RMP
2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\H2
NCH(CH(CH3)2)CO2H sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,1.3696715138,0.0
765334847,0.3243176488\C,0.0598997699,0.6525514709,-0.2155108907\N,0.0
245667209,0.6756329916,-1.6752275496\O,1.5627803808,0.3709352656,1.633
6809477\O,2.1551321685,-0.5909863848,-0.3150401977\H,2.3983183384,-0.0
635907006,1.8910609239\C,-1.1511438122,-0.132242318,0.3750634012\H,-0.
0148404671,1.683257097,0.1510387185\H,0.6346585946,1.4165892968,-2.016
1804995\H,0.4404685541,-0.1892478104,-2.019917811\H,-1.0046040808,-0.1
581317934,1.4629581202\C,-2.4589524725,0.6123312159,0.0779568331\C,-1.
2048744849,-1.5780462973,-0.1414900627\H,-2.0205121462,-2.1255403428,0
.3437619506\H,-1.3900874627,-1.5988234503,-1.2215592723\H,-0.273791131
2,-2.1226639126,0.0543295217\H,-3.316275826,0.0663544434,0.4886646637\
H,-2.4561158279,1.6149636711,0.5229506104\H,-2.6000890705,0.7210461776
,-1.001661657\\Version=SGI-G94RevE.2\HF=-399.9319237\MP2=-401.1050405\
RMSD=5.407e-09\PG=C01 [X(C5H11N1O2)]\\@

$NH_2C^{\bullet}(CH(CH_3)_2)CO_2H$ (70)

1\1\GINC-VPP01\SP\ROMP2-FC\6-31G(d)\C5H10N1O2(2)\AKC501\20-May-1998\0\
\#P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=838860
8\\H2NC(CH(CH3)2)CO2H sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\N,0.01426596,
-0.0765929797,-2.0313056829\C,-0.0164214244,0.0100041133,-0.6621396384
\C,1.2815413837,0.0165689936,-0.0448093199\O,2.3437293207,0.0358087337
,-0.6730680893\H,-0.7808848708,0.251654386,-2.5617635683\O,1.268248098
8,0.0028743811,1.3279494448\H,0.9286951876,0.0592695732,-2.4491080587\
H,2.2085459596,0.0163393272,1.5820906346\C,-1.3544984913,0.0048796472,
0.0406385323\H,-2.1161106716,0.0246851684,-0.7533633864\C,-1.568685577
,1.2574861078,0.9146014355\C,-1.5809280211,-1.2893246202,0.8507448689\
H,-0.8535385341,-1.3686544083,1.6635423787\H,-1.4815987715,-2.17403196
59,0.2125904972\H,-2.5872497571,-1.2930079237,1.2865746844\H,-0.841796
181,1.2899628473,1.730545958\H,-2.5750934586,1.2474659847,1.3495490023
\H,-1.4626971974,2.1753175012,0.3252155246\\Version=Fujitsu-VP-Unix-G9
4RevE.2\HF=-399.3185485\MP2=-400.4808532\RMSD=2.105e-09\PG=C01 [X(C5H1
0N1O2)]\\@

$CH_3CONHCH(CH(CH_3)_2)CO_2CH_3$ (76)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C8H15N1O3\AKC501\16-Nov-1998\0\\#P RMP
2/6-31G* SCF=DIRECT TEST MAXDISK=5242880000\\CH3COHNCH(CH(CH3)2)CO2CH3
sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\N\C,1,1.45582\C,2,1.52623,1,106.849
7\O,3,1.2153,2,123.5307,1,-37.9818,0\H,1,1.01187,2,115.7499,3,35.8602,
0\O,3,1.3437,2,112.528,4,-179.28,0\C,1,1.37016,2,122.3936,5,-164.5035,
0\H,2,1.09293,1,107.2733,3,117.9441,0\C,2,1.55862,1,112.4377,3,-121.87
58,0\H,9,1.09996,2,106.6144,1,59.9765,0\C,9,1.53468,2,110.5,10,-117.73
49,0\C,9,1.53662,2,111.9643,10,118.3982,0\H,12,1.0969,9,110.9956,2,58.
8867,0\H,12,1.09459,9,112.6104,13,-120.7806,0\H,12,1.09556,9,110.0317,
13,119.1567,0\H,11,1.09606,9,111.0504,2,-61.7298,0\H,11,1.09605,9,110.
1265,16,-119.7861,0\H,11,1.09335,9,111.6018,16,120.2401,0\C,6,1.44044,
3,115.523,2,178.3507,0\H,19,1.09273,6,110.3304,3,60.0916,0\H,19,1.0930
2,6,110.498,20,-120.7141,0\H,19,1.08988,6,105.4406,20,119.6051,0\O,7,1
.22503,1,122.8138,2,-7.5196,0\C,7,1.52184,1,115.1643,23,-179.2576,0\H,
24,1.09403,7,108.752,1,124.2635,0\H,24,1.09436,7,113.8128,25,-121.7564
,0\H,24,1.09471,7,108.7698,25,116.5416,0\\Version=SGI-G94RevE.2\HF=-59
0.7493804\MP2=-592.4814275\RMSD=5.577e-09\PG=C01 [X(C8H15N1O3)]\\@

$CH3CONHC^{\bullet}(CH(CH_3)_2)CO_2CH_3$ (77)

1\1\GINC-VPP06\SP\ROMP2-FC\6-31G(d)\C8H14N1O3(2)\AKC501\25-May-1998\0\
\#P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=838860
8\\CH3COHNC(CH(CH3)2)CO2CH3 sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\N,1.188
7180136,-0.6761028784,0.0114263921\C,-0.0003028205,0.0285423562,0.0018
723124\C,-1.1339987225,-0.8872921424,-0.0091523912\O,-1.0085409831,-2.
1135273756,-0.0117937075\H,1.0184771026,-1.680407962,0.0001678437\O,-2
.343795173,-0.274870856,-0.0165939203\C,2.512825985,-0.2587719041,0.03
35559197\C,-3.4730182839,-1.1602413446,-0.0273011972\C,-0.0745266233,1
.5374563522,0.0001019306\H,0.9565724581,1.8911824293,0.0046191874\C,-0
.7592669713,2.0813941422,1.2734932853\C,-0.7494215543,2.0797458052,-1.
2792629492\H,-1.7951995253,1.7676875077,-1.3466664962\H,-0.2261200132,
1.7338870342,-2.1776547421\H,-0.7169111242,3.175490249,-1.2738531911\H
,-1.8038945498,1.7641623672,1.3356183288\H,-0.7322188043,3.1772553687,
1.2645324061\H,-0.2392254789,1.7410054142,2.175753915\H,-3.4719094903,
-1.7985330441,0.8604711207\H,-3.4587839415,-1.7938595991,-0.918301498\
H,-4.3497040694,-0.5117755002,-0.0320442654\O,2.8682584518,0.910792628
9,0.0635098916\C,3.5140862993,-1.4027928648,-0.0159059878\H,3.89763497
71,-1.5016596196,-1.0383659191\H,3.0957497193,-2.366531077,0.290260199
9\H,4.3588644286,-1.1525809978,0.6300947208\\Version=Fujitsu-VP-Unix-G
94RevE.2\HF=-590.1286727\MP2=-591.8484729\RMSD=5.678e-09\PG=C01 [X(C8H
14N1O3)]\\@

$(NHCOCH_2CH_2)CHCO_2H$ (78)

1\1\GINC-VPP03\SP\RMP2-FC\6-31G(d)\C5H7N1O3\AKC501\19-May-1998\0\\#P R
MP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\H(N
HC(O)CH2CH2CH)CO2H sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.574839104,0.
4886408088,-0.5621147719\N,-0.6923981586,0.6034867538,0.8735027526\C,0
.515913676,0.6205880175,1.5443831989\C,1.6141615995,0.7298985362,0.481
3071668\C,0.8649970283,1.0264605276,-0.8264788471\H,-1.5083306562,0.26
15082075,1.3651979487\O,0.6562698108,0.5526109259,2.7488604596\H,2.345
2371606,1.4926468639,0.7597047071\H,2.1390998346,-0.2327065391,0.45046
3594\H,1.3112671534,0.5701044647,-1.7124967259\H,0.8050813266,2.105155
3282,-0.9988002278\H,-1.3174544303,1.1032112,-1.0843643415\C,-0.760060
347,-0.9519576507,-1.0417579412\O,-0.8961525328,-1.921307981,-0.332646
8768\O,-0.7613593976,-1.0129251066,-2.3957897974\H,-0.8792134383,-1.95
31309443,-2.6296473394\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-472.4906
286\MP2=-473.8176031\RMSD=4.297e-09\PG=C01 [X(C5H7N1O3)]\\@

$(NHCOCH_2CH_2)C^{\bullet}CO_2H$ (79)

1\1\GINC-RSCQC6\SP\ROMP2-FC\6-31G(d)\C5H6N1O3(2)\ANNA\20-May-1998\0\\#
P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=47185920
0\\H(NHC(O)CH2CH2C)CO2H sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.183576
2572,0.,-0.3779650158\N,-0.2211518509,0.,0.9927908877\C,1.0291620259,0
.,1.606666345\C,2.0621328524,0.,0.4742992697\C,1.2481617526,0.,-0.8435

177073\H,-1.094920727,0.,1.5073989504\O,1.2197183024,0.,2.803964324\H,
2.7044507278,0.8791662253,0.583703315\H,2.7044507278,-0.8791662253,0.5
83703315\H,1.4587252162,0.876903509,-1.4672893585\H,1.4587252162,-0.87
6903509,-1.4672893585\C,-1.4067176473,0.,-1.1211813233\O,-2.5259985503
,0.,-0.6129426877\O,-1.2042007122,0.,-2.472451976\H,-2.0944968822,0.,-
2.8681297697\\Version=IBM-RS6000-G94RevD.1\State=2-A"\HF=-471.8785969\
MP2=-473.1921222\RMSD=7.256e-09\PG=CS [SG(C5H2N1O3),X(H4)]\\@

$(NHCOCH_2CH_2)CHCO_2CH_3$ (18)

1\1\GINC-VPP02\SP\RMP2-FC\6-31G(d)\C6H9N1O3\AKC501\21-May-1998\0\\#P R
MP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\H(N
HC(O)CH2CH2CH)CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.4710086303
,0.7314056035,-0.3050674138\N,-0.7126372707,0.8840479261,1.11264329\C,
0.4347095353,0.94571401,1.8804032268\C,1.6153255969,1.0611972956,0.910
2854508\C,0.9704961787,1.3028893972,-0.4628312276\H,-1.5542384236,0.52
22751277,1.5432661669\O,0.4764239354,0.9071961537,3.0939373491\H,2.298
9879623,1.8521312867,1.2280331591\H,2.1677941192,0.1144426419,0.950194
9789\H,0.898591003,2.3750577744,-0.6687551675\H,1.5000869043,0.8365208
206,-1.2960853779\H,-1.1823759888,1.3115945123,-0.9043076842\C,-0.5829
875089,-0.730364631,-0.7524819758\O,-0.7724100686,-1.6739344438,-0.018
9150931\O,-0.4521751952,-0.8229004011,-2.092253776\C,-0.5434991659,-2.
1539060007,-2.6327735116\H,0.2437130353,-2.7894314418,-2.2191305374\H,
-0.4209028219,-2.0411114273,-3.7100589208\H,-1.5161203024,-2.594319294
8,-2.3990147803\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-511.517228\MP2=
-512.9727287\RMSD=5.562e-09\PG=C01 [X(C6H9N1O3)]\\@

$(NHCOCH_2CH_2)C^{\bullet}CO_2CH_3$ (19)

1\1\GINC-RSCQC6\SP\ROMP2-FC\6-31G(d)\C6H8N1O3(2)\ANNA\21-May-1998\0\\#
P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=47185920
0\\H(NHC(O)CH2CH2C)CO2CH3 sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\C,0.08413
05497,0.,-0.0161734458\N,0.0245998254,0.,1.3546157778\C,1.2631866462,0
.,1.9893626727\C,2.3154012795,0.,0.8745528269\C,1.523804031,0.,-0.4570
490657\H,-0.8579069519,0.,1.8539013306\O,1.4345983103,0.,3.1900701776\
H,2.9558273594,-0.8791526792,0.9951021528\H,2.9558273594,0.8791526792,
0.9951021528\H,1.7449374834,-0.8769890839,-1.0770547017\H,1.7449374834
,0.8769890839,-1.0770547017\C,-1.1296849718,0.,-0.7792678107\O,-2.2539
987344,0.,-0.2819053829\O,-0.8878545198,0.,-2.1203631944\C,-2.06075171
06,0.,-2.9440021694\H,-1.6964912638,0.,-3.9721240036\H,-2.66890282,0.8
890525329,-2.7535667625\H,-2.66890282,-0.8890525329,-2.7535667625\\Ver
sion=IBM-RS6000-G94RevD.1\State=2-A"\HF=-510.9047154\MP2=-512.3465016\
RMSD=7.456e-09\PG=CS [SG(C6H2N1O3),X(H6)]\\@

Appendix L. GAUSSIAN 94 Archive entries for other RMP2/6-31G*//B3LYP/6-31G* calculations from Chapter Two.

$NH_2CH(C(CH_3)_3)CO_2H$ (80)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C6H13N1O2\AKC501\18-Jun-1998\0\\#P RMP
2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\H2
NCH(CH3)3CO2H sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.2322971666,-0.6554
443242,-1.3280503005\C,0.3451692859,-0.6729284737,0.1969977395\N,1.749
7579968,-0.7131707073,0.6150142816\O,-0.8041562412,-1.3950649858,-1.79
25189314\O,0.9875709488,-0.0628756131,-2.0715723487\H,-0.7902270542,-1
.3026886407,-2.7649788271\C,-0.4058210922,0.5398152476,0.8565153545\H,
-0.14517888,-1.5853991741,0.5524588847\H,2.1326438148,-1.6384722468,0.
4271586604\H,2.2781375424,-0.0717464242,0.02407822\C,-0.4160246351,0.3
058422063,2.3792406282\C,0.3181790003,1.8635879741,0.5447182412\C,-1.8
585142665,0.6146309272,0.3481540124\H,-2.4067137623,1.384993211,0.9027
922445\H,-1.9142662921,0.873252161,-0.7151069041\H,-2.3844571371,-0.33
72559644,0.487278821\H,-0.2300253239,2.7025355764,0.9891175205\H,1.328
8988619,1.8702800692,0.9661727485\H,0.3939204266,2.0420147048,-0.53326
39626\H,-0.8738917494,1.1601813342,2.8920126075\H,-0.9973529365,-0.588
4968474,2.6375909757\H,0.6011760981,0.1735006388,2.7568652293\\Version
=SGI-G94RevE.2\HF=-438.96224\MP2=-440.2735751\RMSD=5.512e-09\PG=C01 [X
(C6H13N1O2)]\\@

$NH_2C^{\bullet}(C(CH_3)_3)CO_2H$ (82)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C6H12N1O2(2)\AKC501\19-Jun-1998\0\\#P
ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=524288000
0\\H2NCH(CH3)3CO2H sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,0.6439585007,-0
.2865341411,-1.3908637059\C,0.6051480553,0.0990011252,-0.0026801426\N,
1.8164664193,0.5584788364,0.4520718905\O,-0.5575615021,-0.6500087234,-
1.9451128078\O,1.6780490727,-0.3000426168,-2.066566242\H,-0.3385778968
,-0.8790906515,-2.8663895924\C,-0.6276353855,0.1306042026,0.8960282018
\H,2.0262971812,0.5271081313,1.4384509833\H,2.5885612022,0.3946584954,
-0.1856149032\C,-1.2811727483,-1.2714547084,0.9625824273\C,-0.25270882
3,0.5547464961,2.3318945332\C,-1.6498617787,1.1557348691,0.3419081381\
H,-2.5372569228,1.1875629726,0.9865287348\H,-1.2146477972,2.1612249986
,0.3129075989\H,-1.9677337721,0.8890363664,-0.6685873643\H,-2.16851356
94,-1.2395994233,1.6067175422\H,-1.5865929425,-1.614594999,-0.02779683
61\H,-0.5853785106,-2.0074938257,1.3825863326\H,-1.1557223735,0.582363
4269,2.9507546153\H,0.4371078316,-0.156538692,2.8051687945\H,0.1969251
472,1.5538350057,2.3609865472\\Version=SGI-G94RevE.2\HF=-438.3483213\M
P2=-439.6485164\RMSD=1.989e-09\PG=C01 [X(C6H12N1O2)]\\@

$CH_3CONHCH(C(CH_3)_3)CO_2CH_3$ (81)

1\1\ MHPCC-FR31N09\SP\RMP2-FC\6-31G(d)\C9H17N1O3\DANNE\27-Jun-1998\0\\
#P RMP2=(FULLDIRECT)/6-31G* SCF=(RESTART) GEOM=CHECK TEST\\CH3CONHCH(C
H3)3CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.0054735411,0.0571457
527,-0.2326867242\C,-0.271815419,1.5737161023,0.0969661941\C,-1.506701
3545,2.0711891401,-0.6790023067\C,0.9587219168,2.3823817031,-0.3579748
783\C,-0.4879922951,1.7776650352,1.607956367\H,-0.6417933424,2.8411732
801,1.8244112998\H,-1.3618381641,1.2300608529,1.9775169085\H,0.3849560
722,1.4463346453,2.1812710097\H,-1.630686186,3.1492490677,-0.524821729
6\H,-2.4290841242,1.5806940519,-0.3528817898\H,-1.3991659382,1.8968461
581,-1.7560002327\H,0.7889221832,3.4503786479,-0.1764643173\H,1.159389
6651,2.2416291482,-1.4251702501\H,1.8568349405,2.0856368295,0.19145328
8\H,0.1533989673,-0.0298426435,-1.3107469169\N,1.1862770517,-0.4678439
836,0.4188722901\H,1.0335395546,-0.8988501382,1.3217442774\C,2.3262730
186,-0.7654204354,-0.2835243175\O,2.483366564,-0.4545043428,-1.4578741
187\C,3.4012781918,-1.4961879372,0.5075327789\H,3.1519070211,-1.638214
9838,1.5634980597\H,3.5742595216,-2.4745674132,0.0475529817\H,4.335923
3359,-0.9325428847,0.4340085911\C,-1.164219953,-0.850845984,0.17523947
19\O,-1.2360035594,-1.4201672947,1.2471405168\O,-2.0985173268,-0.95170
50474,-0.7855589245\C,-3.2362582339,-1.7738994424,-0.4628436678\H,-3.8

755738541,-1.7433313038,-1.3449978218\H,-2.9174869439,-2.7974777622,-0
.2513855524\H,-3.761081477,-1.3757177938,0.4092688713\\Version=IBM-RS6
000-G94RevE.2\HF=-629.7816858\MP2=-631.6522132\RMSD=1.841e-09\PG=C01 [
X(C9H17N1O3)]\\@

$CH_3CONHC^{\bullet}(C(CH_3)_3)CO_2CH_3$ (83)—Full Optimisation

1\1\ MHPCC-FR5N03\SP\ROMP2-FC\6-31G(d)\C9H16N1O3(2)\DANNE\01-Jul-1998\
0\\#P ROMP2=(FULLDIRECT)/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST
\\CH3CONHC(C(CH3)3)CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\N,1.052882
4882,-0.8126975465,-0.3556328842\C,-0.0976534219,-0.0473340514,-0.1623
609008\C,-1.2605387844,-0.9404294775,-0.1063941569\O,-1.1849905985,-2.
1414150733,-0.3699973762\H,0.801771112,-1.7532463338,-0.6588256502\O,-
2.4168861177,-0.3635581182,0.290409881\C,2.3204390231,-0.7013549456,0.
2101412128\C,-3.5474759745,-1.2462031449,0.3567914214\C,-0.1081562995,
1.4811203065,-0.1321805477\C,-1.3794809186,2.0458680283,-0.8204978006\
C,1.0981626824,2.0531151188,-0.9150026527\C,-0.0676632572,1.9778887291
,1.3359302713\H,0.845953,1.6391278,1.8297355345\H,-0.9345072099,1.6079
843219,1.8943060005\H,-0.0922920442,3.0745729378,1.3563963269\H,2.0489
45092,1.8142109342,-0.4402272422\H,1.0062630917,3.1441802015,-0.954928
2009\H,1.1088752483,1.6825167253,-1.9469269915\H,-3.3609782615,-2.0580
340594,1.0647407945\H,-3.7610404421,-1.6752643152,-0.625865032\H,-4.37
84691121,-0.6257795846,0.6938287948\O,2.6674037967,0.2072557918,0.9478
661919\C,3.2658715564,-1.8140622045,-0.2151505631\H,3.6850749463,-1.58
53988693,-1.2025358253\H,2.7695789711,-2.7884213172,-0.28043045\H,4.08
4581928,-1.8686949591,0.5038795654\H,-1.2819221275,3.1351921621,-0.887
4960625\H,-1.4864539431,1.6580727189,-1.8406371\H,-2.2908019466,1.8179
535066,-0.2694715482\\Version=IBM-RS6000-G94RevE.2\HF=-629.1515143\MP2
=-631.0086085\RMSD=1.634e-09\PG=C01 [X(C9H16N1O3)]\\@

$CH_3CONHC^{\bullet}(C(CH_3)_3)CO_2CH_3$ (83)—Partial Optimisation with Planar Amino Acid Backbone

1\1\ MHPCC-FR28N09\SP\ROMP2-FC\6-31G(d)\C9H16N1O3(2)\DANNE\18-Nov-1998
\0\\#P ROMP2=(FULLDIRECT)/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TES
T\\CH3CONHC(C(CH3)3)CO2CH3 planar backbone sp RMP2/6-31G*//B3LYP/6-31G
*\\0,2\C,-0.115732063,0.0030225363,-0.0876428636\N,-0.1138118398,0.041
5119307,1.3046514732\C,0.8309603689,0.0654496623,2.3214821807\O,2.0444
569421,0.0730279989,2.1728859695\C,0.1930007317,0.0495732212,3.7054291
966\C,-1.5225036059,-0.0192688222,-0.5206493488\O,-2.4556021359,-0.001
7671641,0.2884430263\O,-1.7438054235,-0.0613956989,-1.8504346169\C,-3.
1259525735,-0.0829640524,-2.2367136644\H,-1.08215425,0.0414715487,1.62
97443166\C,1.155581462,-0.007455014,-0.9368611795\C,0.8885246846,-0.04
51982068,-2.4591890581\C,1.9751223766,1.2817095823,-0.6583734175\C,1.9
958088906,-1.2685354912,-0.5981890329\H,2.2823691094,1.3524539378,0.38
47590706\H,1.3939179418,2.171972593,-0.9264206675\H,2.8788743002,1.272
3389452,-1.2793133378\H,2.3069230654,-1.2831454944,0.4461193039\H,2.89
78111434,-1.2754659894,-1.2216868844\H,1.4281337478,-2.1798772481,-0.8
205187878\H,-3.640345583,0.8142590348,-1.8824195939\H,-3.6280147732,-0
.9635237607,-1.8272369224\H,-3.1184313036,-0.1167141199,-3.3266994727\
H,-0.1102954973,-0.9718676389,3.9669167144\H,-0.6935868034,0.689705160
2,3.768128923\H,0.9358602576,0.3842716673,4.4307090851\H,1.8609705563,
-0.0470139865,-2.9643347379\H,0.3465193938,-0.9424640402,-2.766322062\
H,0.3288748794,0.8260942967,-2.8068971658\\Version=IBM-RS6000-G94RevE.
2\HF=-629.1474139\MP2=-631.0067673\RMSD=5.301e-09\PG=C01 [X(C9H16N1O3)
]\\@

$NH_2CH_2CF_3$ (92)

1\1\GINC-RSCQC9\SP\RMP2-FC\6-31G(d)\C2H4F3N1\ANNA\23-Mar-1995\0\\# RMP
2/6-31G* GEOM=CHECK GUESS=CHECK SCF=DIRECT TEST MAXDISK=39321600\\trif
luoro ethylamine RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.1947933493,0.0003
410903,-1.1682056351\C,-0.253095746,-0.0000314769,0.3521680449\N,1.145
721417,0.000173693,-1.7293956905\H,-0.740250023,-0.8823266594,-1.51762
4684\H,1.6580225385,0.8168059715,-1.4010418275\H,1.6576979079,-0.81677
95645,-1.4013346408\F,-1.525823081,0.0000844754,0.8011850136\F,0.36447

23838,-1.0893364556,0.8679744977\F,0.3648669573,1.0887833012,0.8685259
963\H,-0.7398321115,0.8834448323,-1.5171730414\\Version=IBM-RS6000-G94
RevE.1\HF=-430.8366186\MP2=-431.7684629\RMSD=2.986e-09\PG=C01 [X(C2H4F
3N1)]\\@

$NH_2C^{\bullet}HCF_3$ (93)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C2H3F3N1(2)\AKC501\31-Mar-1998\0\\# R
OMP2/6-31G(D) SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=524288000
0\\ethylamino radical sp ROMP2/6-31G(d)//B3LYP/6-31G*\\0,2\C,-0.674185
7722,0.8884856861,0.3135856163\N,-0.9627551473,0.7065723015,1.65752954
31\H,-0.1969114954,0.3348204602,2.2093226931\H,-1.4190316071,1.4871556
996,2.1136938472\C,0.1714002725,-0.123901062,-0.348660706\H,-1.4063982
833,1.4052616299,-0.2944745963\F,1.2167602468,-0.477068994,0.451653756
7\F,-0.4680155326,-1.2897184265,-0.6541764671\F,0.6710708874,0.3489261
267,-1.5108993127\\Version=SGI-G94RevE.2\HF=-430.2065372\MP2=-431.1219
363\RMSD=4.650e-09\PG=C01 [X(C2H3F3N1)]\\@

$CF_3CH_2CO_2H$ (94)

1\1\GINC-VPP03\SP\RMP2-FC\6-31G(d)\C3H3F3O2\AKC501\27-Mar-1998\0\\# RM
P2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\HO2C
CH2CF3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.8224774816,-0.0002510065
,-0.2982593453\C,-0.8279356287,0.0002095613,1.2191140288\C,0.565312821
4,-0.0001611666,-0.907985173\H,-1.3648921024,0.8786190778,-0.660670957
\O,0.1372063513,0.0004838576,1.9428487947\O,-2.1038654944,0.0001894194
,1.6733163912\H,-2.0468223259,0.0004514062,2.6477782789\F,1.2698333889
,1.0899217977,-0.5563649937\F,1.270269881,-1.0897492664,-0.5557196252\
F,0.4621325874,-0.0005804819,-2.2583067261\H,-1.3645334094,-0.87956947
29,-0.6601237673\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-563.4233779\MP
2=-564.6688476\RMSD=6.358e-09\PG=C01 [X(C3H3F3O2)]\\@

$CF_3C^{\bullet}HCO_2H$ (95)

1\1\GINC-VPP12\SP\ROMP2-FC\6-31G(d)\C3H2F3O2(2)\AKC501\27-Mar-1998\0\\
ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\
\HO2CCH'CF3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.8442018937,0.131679
7697,-0.0751204102\C,-0.7575691671,-0.0071964356,1.3707304342\C,0.3249
652684,0.0393330107,-1.0037915195\H,-1.8234894138,0.3137190583,-0.4984
198335\O,-1.7308866011,0.0732914187,2.1023266519\O,0.4986812277,-0.232
7846411,1.8226160146\H,0.4313336168,-0.3073627628,2.7926612203\F,0.932
2901249,-1.162056432,-0.923377935\F,-0.0814116997,0.2107223396,-2.2785
849053\F,1.2503030791,0.983188694,-0.7363364647\\Version=Fujitsu-VP-Un
ix-G94RevE.2\HF=-562.78831\MP2=-564.011781\RMSD=4.233e-09\PG=C01 [X(C3
H2F3O2)]\\@

$NH_2CH(CF_3)CO_2H$ (96)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C3H4F3N1O2\AKC501\17-Jun-1998\0\\#P RM
P2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\H
2NCHCF3CO2H sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.2889622964,-0.648131
4155,-1.2811845558\C,0.2976059082,-0.6816150356,0.2578477007\N,1.63261
39894,-0.7130826764,0.8213284653\O,-0.8665036199,-1.1094302023,-1.7993
00366\O,1.2247515292,-0.2735424924,-1.9496958577\H,-0.7886002448,-1.03
7103405,-2.7702919462\C,-0.4466870654,0.5404481951,0.8170457117\H,-0.2
698459436,-1.5563289695,0.5887163023\H,2.2138428431,-0.0445665506,0.31
74176389\H,2.0475167853,-1.6290454866,0.6685028556\F,-0.5918427431,0.4
526592859,2.1467532141\F,0.2305220842,1.6759683595,0.5431977446\F,-1.6
760661718,0.655616159,0.2740571015\\Version=SGI-G94RevE.2\HF=-618.4419
619\MP2=-619.8526824\RMSD=5.878e-09\PG=C01 [X(C3H4F3N1O2)]\\@

$NH_2C^{\bullet}(CF_3)CO_2H$ (84)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C3H3F3N1O2(2)\AKC501\03-Apr-1998\0\\#
P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=52428800
00\\H2NCHCF3CO2H sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,0.4103521654,-0.7

607562884,-1.2636964216\C,0.4758900143,-0.3389038782,0.1161881393\N,1.
5678427092,-0.7424788463,0.822795938\O,-0.6380929342,-0.245206004,-1.9
542389591\O,1.2310424416,-1.5253582003,-1.7619885896\H,-0.5647730961,-
0.6111808647,-2.8543914956\C,-0.4792580607,0.612203377,0.7633155252\H,
1.5614993561,-0.6831421494,1.8304195603\H,2.1429417673,-1.4474969253,0
.3765870175\F,-0.2418778,0.6634200271,2.1026946983\F,-0.3627111108,1.8
734933158,0.2942099345\F,-1.7620852855,0.2440229055,0.5945165099\\Vers
ion=SGI-G94RevE.2\HF=-617.8278752\MP2=-619.2285188\RMSD=3.671e-09\PG=C
01 [X(C3H3F3N1O2)]\\@

$CH_3CONHCH(CF_3)CO_2CH_3$ (97)

1\1\GINC-VPP12\SP\RMP2-FC\6-31G(d)\C6H8F3N1O3\AKC501\11-Apr-1998\0\\#P
RMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\C
H3CONHCHCF3CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.1237425494,-0
.220071209,-0.0947540658\N,-0.1678951773,-0.1391120853,1.3405000115\C,
1.3343927845,-0.3751654247,-0.5438232934\C,-0.7617972929,1.0234156882,
-0.7420080402\O,2.2792494259,-0.2152826768,0.1979739981\O,1.4189674152
,-0.7002848818,-1.8363420798\C,2.7563475787,-0.8303420316,-2.361706975
9\H,0.668114359,0.2132730801,1.7887705984\C,-1.0942468297,-0.862503460
3,2.0590453619\O,-1.9792366336,-1.5065889996,1.515873719\C,-0.95425750
46,-0.7672556418,3.5678287658\H,-0.7198738183,-1.0805731516,-0.4145561
034\H,2.6284470039,-1.0822901815,-3.4137805414\H,3.299081165,0.1112655
97,-2.2508224597\H,3.2933125382,-1.6225617573,-1.8346980929\H,-1.75591
80721,-0.1301637226,3.9569721291\H,-1.0872485868,-1.7637958509,3.99620
06613\H,0.0059086436,-0.3547992117,3.8923278459\F,-0.911577914,0.86290
11352,-2.0692934724\F,-1.9694376606,1.2697230111,-0.2136022226\F,0.008
9516,2.1176219355,-0.5428209418\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=
-809.2618018\MP2=-811.2302294\RMSD=3.870e-09\PG=C01 [X(C6H8F3N1O3)]\\@

$CH3CONHC^{\bullet}(CF_3)CO_2CH_3$ (85)

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-31G(d)\C6H7F3N1O3(2)\ANNA\12-Apr-1998\0\
\#P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=104857
6000\\CH3NHCHCF3CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,0.160722190
5,0.0684243528,-0.0353213098\N,0.1799096045,0.11754959,1.336227542\C,1
.5127571483,0.0569882134,-0.6042871416\C,-1.1341264452,0.0967216506,-0
.8087105972\O,2.5018381029,0.1552174293,0.1180458296\O,1.5736052814,-0
.0843922088,-1.9361278716\C,2.9010999862,-0.1064013438,-2.4887703515\H
,1.1300954198,0.2536042645,1.6806307261\C,-0.8178013572,-0.1890432513,
2.2757772795\O,-1.917907999,-0.5926556395,1.961795361\C,-0.3757300626,
0.0540299032,3.707287534\H,2.7610646082,-0.228101642,-3.5626002588\H,3
.4222748581,0.829100819,-2.2699130732\H,3.4742219857,-0.9405120556,-2.
0757846214\H,-0.3233451303,1.1305599346,3.9098208729\H,-1.1098174719,-
0.3952417788,4.3769043043\H,0.612821927,-0.373394036,3.9105257879\F,-0
.9346821418,0.4930644569,-2.07973342\F,-1.7296974294,-1.1105689115,-0.
8572678478\F,-1.99878657,0.9721115178,-0.2573026838\\Version=IBM-RS600
0-G94RevE.1\HF=-808.6289105\MP2=-810.585426\RMSD=8.969e-09\PG=C01 [X(C
6H7F3N1O3)]\\@

Appendix M. GAUSSIAN 94 Archive entries for other RMP2/6-31G*//B3LYP/6-31G* calculations from Chapter Three.

$HCONHCH_3$ (121)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C2H5N1O1\AKC501\12-May-1998\0\\# RMP2/
6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\HCON
HCH3 cis sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.7402848904,0.6804831785
,1.1328130645\H,0.2523390095,0.9934133584,2.063420248\H,1.808921578,0.
5298838607,1.3261367062\N,0.1280280187,-0.5221838608,0.5952038767\C,-0
.467384001,-0.567596921,-0.6293844722\O,-0.5603525357,0.3665443119,-1.
4070987924\H,0.1392509634,-1.368690626,1.1467168057\H,-0.871614276,-1.
5752775105,-0.8522328598\H,0.6203215434,1.4662859035,0.385750748\\Vers
ion=SGI-G94RevE.2\HF=-207.959093\MP2=-208.554871\RMSD=2.997e-09\PG=C01
[X(C2H5N1O1)]\\@

$HCONHCH_2^{\bullet}$ (141)

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-31G(d)\C2H4N1O1(2)\ANNA\25-Mar-1995\0\\#
ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=39321600\
\HCONHCH2' sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,1.5238061056,0.,-0.1396
970212\H,1.5411532003,0.,0.9383310904\H,2.4099857161,0.,-0.7549952429\
N,0.2932255142,0.,-0.7563899527\C,-0.9123634308,0.,-0.0868103587\O,-1.
0196637646,0.,1.1275218806\H,0.2567626938,0.,-1.768181915\H,-1.7718261
419,0.,-0.7815550291\\Version=IBM-RS6000-G94RevE.1\State=2-A"\HF=-207.
3274255\MP2=-207.905772\RMSD=6.590e-09\PG=CS [SG(C2H4N1O1)]\\@

$HCONHCH_2CO_2CH_3$ (128)

1\1\GINC-VPP12\SP\RMP2-FC\6-31G(d)\C4H7N1O3\AKC501\27-Mar-1998\0\\# RM
P2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\CH3O
2CCH2NHCHO sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.6321072852,-0.004357
6026,-0.0994318358\N,-0.7611728874,0.003708787,1.3391017181\C,0.839798
2172,-0.000506548,-0.464778683\H,-1.122123968,0.8676767867,-0.55130599
21\O,1.7475790737,0.0023383962,0.341023283\O,1.0031423637,-0.001572395
,-1.7957530488\C,2.3681687151,0.0002638443,-2.2561592244\H,0.099332134
8,0.0063884327,1.8735105744\C,-1.975270072,0.0031472666,1.945705451\O,
-3.0420986598,-0.0027258011,1.3527508549\H,-1.8950005055,0.008548694,3
.0500911389\H,-1.1141740047,-0.8862732818,-0.5409138583\H,2.3065417834
,-0.0010342326,-3.3441311101\H,2.8890040732,0.8923176991,-1.8995488851
\H,2.8921110269,-0.8891889687,-1.8975968539\\Version=Fujitsu-VP-Unix-G
94RevE.2\HF=-434.6029378\MP2=-435.80147\RMSD=6.430e-09\PG=C01 [X(C4H7N
1O3)]\\@

$HCONHC^{\bullet}HCO_2CH_3$ (135)

1\1\GINC-VPP05\SP\ROMP2-FC\6-31G(d)\C4H6N1O3(2)\AKC501\28-Mar-1998\0\\
ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\
\CH3O2CCH'NHCHO sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.5441015687,0.04
86621245,0.0599097503\N,-0.5650547956,-0.0629953759,1.4203267441\C,0.7
51693416,-0.0266111489,-0.5686274526\H,-1.4793977171,0.1845480496,-0.4
619800329\O,1.7980951916,-0.1821317218,0.0570504632\O,0.679364263,0.09
30507414,-1.9146951291\C,1.9381531923,0.0261592242,-2.5999269582\H,0.3
453433429,-0.1893416817,1.8574868357\C,-1.7061346722,-0.0156423946,2.2
002978437\O,-2.8272882787,0.132155213,1.7552024233\H,-1.4782601779,-0.
127900387,3.2742908124\H,2.4273087631,-0.9345301365,-2.4159696051\H,1.
6999958821,0.138078534,-3.6580067006\H,2.6013618644,0.8301125614,-2.26
84896777\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-433.9852256\MP2=-435.1
706672\RMSD=9.329e-09\PG=C01 [X(C4H6N1O3)]\\@

$CF_3CONHCH_3$ (122)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C3H4F3N1O1\AKC501\01-Apr-1998\0\\#P RM
P2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\C
H3NHCOCF3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.8585108985,-0.15130991
27,-2.6935770534\N,0.8237541261,-0.2010055405,-1.24106312\H,1.61004358
44,0.5660167729,-3.0409782076\H,-0.1270439579,0.16620346,-3.0360282349
\H,1.6512325101,-0.4756833078,-0.7318313303\C,-0.2884922538,0.11067058
38,-0.5343878694\O,-1.3636824197,0.4592688346,-0.9897812864\C,-0.11803
3201,-0.0053449104,0.9994509792\H,1.0857555679,-1.1379509139,-3.111848
0403\F,-0.9843863373,-0.8987974126,1.495996028\F,1.1336071507,-0.40350
01357,1.3546014701\F,-0.347967468,1.178987274,1.5824537915\\Version=SG
I-G94RevE.2\HF=-543.5735863\MP2=-544.8062264\RMSD=9.282e-09\PG=C01 [X(
C3H4F3N1O1)]\\@

$CF_3CONHCH_2^{\bullet}$ (142)

1\1\GINC-VPP02\SP\ROMP2-FC\6-31G(d)\C3H3F3N1O1(2)\AKC501\26-Mar-1998\0
\\# ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=131072
00\\CF3CONHCH2' sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-2.1622371945,0.09
73561422,1.805750309\H,-2.2716751538,0.2817272952,2.8630298581\N,-0.90
41216049,0.1353402689,1.2644248092\C,-0.6449659216,-0.0833338333,-0.06
62683779\O,-1.4914274868,-0.3331622934,-0.9092633853\H,-0.1123963508,0
.3337271434,1.8629363794\C,0.8426549758,0.0099162074,-0.4461202734\H,-
2.9863281574,-0.116430118,1.1435337594\F,1.2711482854,-1.150160806,-0.
9629091307\F,1.0372965541,0.9732592571,-1.3574601263\F,1.6268840085,0.
2963749985,0.6307540875\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-542.940
2561\MP2=-544.1563043\RMSD=8.457e-09\PG=C01 [X(C3H3F3N1O1)]\\@

$CF_3CONHCH_2CO_2CH_3$ (110)

1\1\GINC-VPP12\SP\RMP2-FC\6-31G(d)\C5H6F3N1O3\AKC501\30-Mar-1998\0\\#P
 RMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=16777216\\
CH3O2CCH2NHCOCF3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.1181919832,0.0
841375092,-1.4238662227\N,-0.1112523041,-0.0235072653,0.0173413534\C,1
.3054959812,-0.0684386068,-1.9275784705\H,-0.5250128598,1.0501698584,-
1.7471419266\O,2.2636369689,-0.2659424489,-1.2097545595\O,1.3556135739
,0.0421832917,-3.2605081494\C,2.665695439,-0.0884190896,-3.8489821764\
H,0.7817874637,-0.2036357959,0.4611124665\C,-1.2481037278,0.1143135332
,0.7319476218\O,-2.3550789652,0.3257799471,0.2661143162\C,-1.058483487
2,0.0036246585,2.262574948\H,-0.7540995607,-0.6856094921,-1.8793567627
\H,2.5127810385,0.0260708601,-4.921634464\H,3.331760262,0.6891309453,-
3.4674456088\H,3.0881774379,-1.0697315663,-3.6203008801\F,-1.889926550
4,-0.915714177,2.7690911045\F,0.2080573428,-0.3483005911,2.598668354\F
,-1.3235167486,1.1829794016,2.8457950573\\Version=Fujitsu-VP-Unix-G94R
evE.2\HF=-770.2166162\MP2=-772.0522848\RMSD=7.381e-09\PG=C01 [X(C5H6F3
N1O3)]\\@

$CF_3CONHC^{\bullet}HCO_2CH_3$ (136)

1\1\GINC-VPP05\SP\ROMP2-FC\6-31G(d)\C5H5F3N1O3(2)\AKC501\31-Mar-1998\0
\\#P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=20971
520\\CH3O2CCH'NHCOCF3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.102352627
3,0.,-1.3569836426\N,-0.0842256548,0.,0.0067974199\C,1.1898975766,0.,-
2.0062066926\H,-1.0554562355,0.,-1.8646204514\O,2.2495779074,0.,-1.387
1076531\O,1.0872547885,0.,-3.3518848058\C,2.3375145272,0.,-4.059625881
7\H,0.8390677026,0.,0.4356720212\C,-1.2120204268,0.,0.792973712\O,-2.3
525400784,0.,0.3711063384\C,-0.9271791873,0.,2.3089771847\H,2.07239372
46,0.,-5.1169039161\H,2.9208713526,0.8900860002,-3.8087645456\H,2.9208
713526,-0.8900860002,-3.8087645456\F,0.4032178667,0.,2.5732111592\F,-1

.4625905127,1.0871477471,2.879176664\F,-1.4625905127,-1.0871477471,2.8
79176664\\Version=Fujitsu-VP-Unix-G94RevE.2\State=2-A"\HF=-769.5962938
\MP2=-771.4186474\RMSD=4.485e-09\PG=CS [SG(C5H3F1N1O3),X(H2F2)]\\@

HSO_2NHCH_3 (125)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C1H5N1O2S1\AKC501\29-Apr-1998\0\\#P RM
P2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\H
SO2NHCH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\S,0.4010585194,-0.400816896
3,0.2927214098\H,0.4023396286,-0.4213610695,1.6528821682\O,1.792346098
7,-0.378603001,-0.1520419322\O,-0.5578662858,-1.4143021885,-0.13944547
49\N,-0.2084480483,1.1408016099,0.0197812233\H,0.4437208333,1.62781140
03,-0.5910784175\C,-1.6204634154,1.2687139019,-0.3681211443\H,-1.85219
48644,2.3358948459,-0.415699929\H,-1.8545256273,0.7981129072,-1.329415
0899\H,-2.250197953,0.8179590916,0.401926271\\Version=SGI-G94RevE.2\HF
=-642.3577545\MP2=-643.1556857\RMSD=3.629e-09\PG=C01 [X(C1H5N1O2S1)]\\
@

$HSO_2NHCH_2^{\bullet}$ (143)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C1H4N1O2S1(2)\AKC501\29-Apr-1998\0\\#
P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=52428800
00\\HSO2NHCH2 sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\S,0.3488960856,-0.403
6045577,0.2184690072\H,0.2496599814,-0.3786901044,1.5838402548\O,1.762
9393433,-0.3698198217,-0.1303367542\O,-0.5831811807,-1.420279397,-0.24
3981977\N,-0.2691505158,1.0930248112,-0.2418527569\H,0.4321571232,1.82
6364019,-0.2003086153\C,-1.603248941,1.4265157632,0.0124692464\H,-2.33
57899104,0.6499959608,-0.1648176725\H,-1.8628826075,2.4705285395,-0.10
15144127\\Version=SGI-G94RevE.2\HF=-641.7252196\MP2=-642.5034498\RMSD=
6.643e-09\PG=C01 [X(C1H4N1O2S1)]\\@

$HSO_2NHCH_2CO_2CH_3$ (130)

1\1\GINC-VPP09\SP\RMP2-FC\6-31G(d)\C3H7N1O4S1\AKC501\30-Apr-1998\0\\#P
 RMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\H
SO2NHCH2CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\S,1.1594143281,-1.311
1440596,1.27476902\H,1.1762031194,-1.394133267,2.6310901391\O,2.545830
2173,-1.2771691782,0.8219929532\O,0.190467486,-2.3025038812,0.80924303
33\N,0.5395532409,0.2403616844,1.0769413642\H,1.2053436782,0.785164375
7,0.5241470159\C,-0.8233625002,0.3992729351,0.5741483243\H,-1.42389962
18,1.003273865,1.2657170182\C,-0.8036704697,1.097185317,-0.779526099\H
,-1.3137875438,-0.5732687376,0.4735459001\O,0.2016593117,1.5183163844,
-1.3107020484\O,-2.0406740167,1.2056346105,-1.2804952154\C,-2.14177472
25,1.873637122,-2.5547111815\H,-3.2034706538,1.8693801784,-2.799823481
5\H,-1.7657153472,2.8967256417,-2.4779699759\H,-1.5675933985,1.3338353
768,-3.3113765299\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-868.9976328\M
P2=-870.4011917\RMSD=4.933e-09\PG=C01 [X(C3H7N1O4S1)]\\@

$HSO_2NHC^{\bullet}HCO_2CH_3$ (137)

1\1\GINC-VPP10\SP\ROMP2-FC\6-31G(d)\C3H6N1O4S1(2)\AKC501\30-Apr-1998\0
\\# ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=838860
8\\CH3O2CCH2NHSO2H sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\S,1.3293249502,1
.8000691474,0.3053464888\H,1.2969796059,1.7985419328,1.6705383625\O,2.
7245436447,1.78264928,-0.1015446217\O,0.3492905054,2.7771485011,-0.141
5044667\N,0.7201861666,0.2808499485,-0.0793448135\H,1.369672986,-0.505
3567801,-0.0475040468\C,-0.6191320974,-0.0351687856,-0.0859499682\H,-1
.3460723638,0.7612792625,-0.1512629154\C,-0.9343677007,-1.4417495183,-
0.0825051582\O,-0.0797863153,-2.3223522635,-0.0220114873\O,-2.26608298
45,-1.6698112294,-0.1537710831\C,-2.6460386653,-3.0541872668,-0.159303
2182\H,-3.7344680429,-3.0566531056,-0.2216353091\H,-2.2106493314,-3.56

96148934,-1.0198208372\H,-2.3124532433,-3.5496932965,0.7567579573\\Ver
sion=Fujitsu-VP-Unix-G94RevE.2\HF=-868.378144\MP2=-869.7666026\RMSD=8.
293e-09\PG=C01 [X(C3H6N1O4S1)]\\@

$CH_3SO_2NHCH_3$ (126)

1\1\GINC-VPP03\SP\RMP2-FC\6-31G(d)\C2H7N1O2S1\AKC501\28-Apr-1998\0\\#P
RMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\C
H3SO2NHCH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\S,0.3479980357,-0.3346587
084,0.001737572\C,0.3093237525,-0.3714375544,1.8017741515\O,1.74829413
8,-0.3080041975,-0.4320049937\O,-0.5832128678,-1.3607962736,-0.4797522
612\N,-0.261868537,1.2149437378,-0.3295097538\H,0.3724223595,1.6342022
347,-1.0069373605\C,-1.6773254463,1.314296547,-0.7135182588\H,-0.71928
17689,-0.2322569135,2.1404221955\H,0.675057014,-1.3540258346,2.1084381
517\H,0.9565074181,0.4196153516,2.1820234527\H,-1.894339886,2.37040171
62,-0.8957858634\H,-1.9334572084,0.7258375772,-1.6015506261\H,-2.30443
67392,0.9794088506,0.1166798565\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=
-681.4105937\MP2=-682.3412989\RMSD=3.088e-09\PG=C01 [X(C2H7N1O2S1)]\\@

$CH_3SO_2NHCH_2^{\bullet}$ (144)

1\1\GINC-VPP04\SP\ROMP2-FC\6-31G(d)\C2H6N1O2S1(2)\AKC501\28-Apr-1998\0
\\#P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=83886
08\\CH3SO2NHCH2 sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\S,0.3227194508,-0.3
440056649,-0.0708791768\C,0.2582002594,-0.3154050099,1.7363552562\O,1.
7229875742,-0.2958946044,-0.4872513802\O,-0.6019793143,-1.3796344631,-
0.5234866469\N,-0.3355987151,1.1439631474,-0.5589636791\H,0.3479421311
,1.8939320454,-0.5279523237\C,-1.678876333,1.4527479056,-0.330662171\H
,-0.7702239384,-0.1158560235,2.0433639149\H,0.5769615766,-1.3004570988
,2.0844033167\H,0.9364370236,0.4561136922,2.105524784\H,-2.3890356165,
0.6568996876,-0.5169542064\H,-1.9604110208,2.4858914703,-0.4898271984\
\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-680.7778895\MP2=-681.6889525\RM
SD=5.562e-09\PG=C01 [X(C2H6N1O2S1)]\\@

$CH_3SO_2NHCH_2CO_2CH_3$ (131)

1\1\GINC-VPP07\SP\RMP2-FC\6-31G(d)\C4H9N1O4S1\AKC501\29-Apr-1998\0\\#P
RMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\C
H3SO2NHCH2CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\S,1.1028525174,-1.2
884223791,0.864186992\C,1.2106984782,-1.4618633675,2.652807762\O,2.464
3981351,-1.2592611259,0.3259301055\O,0.1082092419,-2.2592014463,0.3903
06927\N,0.4918793792,0.2853082536,0.6942358787\H,1.1201021378,0.801265
5518,0.0737564136\C,-0.8999771035,0.4541110833,0.2825180825\H,0.212284
1228,-1.354860166,3.0810633896\H,1.6041348298,-2.4607336808,2.85506729
51\H,1.8851760511,-0.6961578908,3.0380619707\H,-1.4913933088,0.9348252
306,1.0719188239\C,-0.9643914156,1.32466525,-0.9640028461\H,-1.3657981
372,-0.5130653751,0.0631519741\O,0.007126479,1.7808774832,-1.528324885
5\O,-2.2344055328,1.5280186665,-1.3395990575\C,-2.4138807003,2.3436285
671,-2.5146923697\H,-3.4912130169,2.3925119596,-2.6710286226\H,-2.0008
012973,3.3420121434,-2.3510489458\H,-1.9186094532,1.8850847,-3.3738738
082\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-908.050711\MP2=-909.5868693
\RMSD=5.279e-09\PG=C01 [X(C4H9N1O4S1)]\\@

$CH_3SO_2NHC^{\bullet}HCO_2CH_3$ (138)

1\1\GINC-VPP05\SP\ROMP2-FC\6-31G(d)\C4H8N1O4S1(2)\AKC501\29-Apr-1998\0
\\# ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=838860
8\\CH3O2CCH2NHSO2CH3 sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\S,1.2101807439
,1.6382268839,0.1329004082\C,1.2044107164,1.6195349134,1.9389343826\O,
2.5952471892,1.6435682818,-0.3237703296\O,0.220278067,2.6151041605,-0.
3102544349\N,0.5996110658,0.1128578832,-0.2992387474\H,1.2500931851,-0
.6720101136,-0.272042368\C,-0.7358951897,-0.2070522522,-0.3136293562\H

,0.18453546,1.4452408146,2.2866990688\H,1.5555555328,2.6007708234,2.26
74037083\H,1.8813998897,0.8379096077,2.2883774786\H,-1.462713154,0.589
0862075,-0.3876106596\C,-1.0540974408,-1.6118149832,-0.3169217014\O,-0
.2047753326,-2.4977155147,-0.247229837\O,-2.3873500009,-1.8371993116,-
0.4047042166\C,-2.7689889252,-3.2201383584,-0.418228733\H,-3.856474709
,-3.2213593554,-0.4976014388\H,-2.3212370365,-3.7359249938,-1.27224971
09\H,-2.4511028782,-3.7185851617,0.5020316144\\Version=Fujitsu-VP-Unix
-G94RevE.2\HF=-907.4312788\MP2=-908.9530094\RMSD=8.592e-09\PG=C01 [X(C
4H8N1O4S1)]\\@

$CF_3SO_2NHCH_3$ (127)

1\1\GINC-VPP12\SP\RMP2-FC\6-31G(d)\C2H4F3N1O2S1\AKC501\02-Apr-1998\0\\
#P RMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=16777216
\\CF3SO2NHCH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\S,0.366753925,-0.18785
10321,-0.6650837757\C,0.0547410843,-0.3036665363,1.1733214694\O,1.8152
501301,-0.1376648746,-0.8412242684\O,-0.4807330175,-1.2129464834,-1.26
69596942\N,-0.2314394901,1.3360210333,-0.9836627995\H,0.5089346498,1.9
082578848,-1.3805399752\C,-1.5614791657,1.4777902133,-1.5939386983\F,-
1.2492159169,-0.1197266554,1.4132133205\F,0.4159524886,-1.5137289161,1
.5975422986\F,0.757569025,0.6244031857,1.8208172987\H,-1.7952796538,2.
5449634896,-1.6197183405\H,-1.6177122509,1.0622853881,-2.6054753719\H,
-2.298387897,0.9795827915,-0.9622674912\\Version=Fujitsu-VP-Unix-G94Re
vE.2\HF=-977.9634753\MP2=-979.4037732\RMSD=4.298e-09\PG=C01 [X(C2H4F3N
1O2S1)]\\@

$CF_3SO_2NHCH_2^{\bullet}$ (145)

1\1\GINC-VPP08\SP\ROMP2-FC\6-31G(d)\C2H3F3N1O2S1(2)\AKC501\03-Apr-1998
\0\\#P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=838
8608\\CF3SO2NHCH2 sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\S,0.2236695073,-0
.3752706162,-0.7039925137\C,0.2131954055,-0.0285727869,1.1430855142\O,
1.6256318196,-0.4170268371,-1.0961783232\O,-0.7205353289,-1.4621757498
,-0.9150721977\N,-0.4209257948,1.0108792212,-1.3875618541\H,0.25763378
22,1.7627222482,-1.4615304686\C,-1.784515486,1.3281895362,-1.315593461
\F,-1.0412943925,0.0860254474,1.5793930131\F,0.8221773485,-1.024529211
8,1.7814114366\F,0.866912832,1.116270235,1.3729589744\H,-2.4743371649,
0.4963862258,-1.3505451712\H,-2.0585417062,2.3050888013,-1.6899301304\
\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-977.329505\MP2=-978.7501941\RMS
D=4.068e-09\PG=C01 [X(C2H3F3N1O2S1)]\\@

$CF_3SO_2NHCH_2CO_2CH_3$ (112)

1\1\GINC-VPP06\SP\RMP2-FC\6-31G(d)\C4H6F3N1O4S1\AKC501\09-Apr-1998\0\\
#P RMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\
\CF3SO2NHCH2CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\S,0.9427285886,-1
.0006771662,0.0553349594\C,0.947413067,-1.190197385,1.9126840015\O,2.3
349894606,-0.890956594,-0.3637714664\O,0.0378556444,-2.0387798328,-0.4
339845736\N,0.2492225598,0.5046156785,-0.0902876024\H,0.8510806593,1.1
38508269,-0.6191211567\C,-1.1655372185,0.6397422576,-0.4276423712\F,-0
.2999145024,-1.0294894662,2.372395099\F,1.3808742852,-2.4103495675,2.2
245901938\F,1.7431881456,-0.2785607571,2.4678282363\H,-1.7537819622,0.
9283912878,0.4508970306\C,-1.308160765,1.7132190212,-1.4966405836\H,-1
.5751783428,-0.3031233078,-0.8056886547\O,-0.3727699644,2.3111849187,-
1.9850577878\O,-2.5936736978,1.9070833381,-1.8081789824\C,-2.848742976
6,2.9086508042,-2.8154788511\H,-3.9310748273,2.9240121064,-2.938773396
2\H,-2.4821819867,3.8822919009,-2.4818958274\H,-2.3554544169,2.6372999
429,-3.7516765838\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-1204.6039613\
MP2=-1206.6495106\RMSD=5.407e-09\PG=C01 [X(C4H6F3N1O4S1)]\\@

$CF_3SO_2NHC^{\bullet}HCO_2CH_3$ (139)

1\1\GINC-VPP09\SP\ROMP2-FC\6-31G(d)\C4H5F3N1O4S1(2)\AKC501\08-Apr-1998
\0\\# ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388
608\\CH3O2CCH2NHSO2CF3 sp ROMP2/6-31G*//B3LYP/6-31G*\\0,2\S,0.91993168
66,1.3109915776,-0.3916397164\C,0.9816142155,1.2073685442,1.4824675714
\O,2.2986969815,1.3497818121,-0.8505911076\O,-0.0856090727,2.311630890
4,-0.7143122842\N,0.3051753161,-0.1868852018,-0.8273414071\H,0.9579799
608,-0.9719491943,-0.8464177089\C,-1.0347648587,-0.5141158898,-0.82485
66335\F,-0.2507161237,1.0118839274,1.9553090101\F,1.4766475784,2.34185
47029,1.9666519612\F,1.7606644792,0.1844390987,1.8379706283\H,-1.76983
00417,0.2771058874,-0.8181723484\C,-1.3285755741,-1.9245061192,-0.8979
338179\O,-0.4559491337,-2.7888129307,-0.9120993185\O,-2.6557910234,-2.
1704379869,-0.949142403\C,-3.01548514,-3.5592048644,-1.0233941806\H,-4
.1049057029,-3.5750662585,-1.0573609843\H,-2.5955090063,-4.0173124224,
-1.9229503097\H,-2.6497466836,-4.0985907052,-0.1453944623\\Version=Fuj
itsu-VP-Unix-G94RevE.2\HF=-1203.9815569\MP2=-1206.012663\RMSD=6.797e-0
9\PG=C01 [X(C4H5F3N1O4S1)]\\@

$(CHCO)_2NCH_3$ (123)

1\1\GINC-RSCQC9\SP\RMP2-FC\6-31G(d)\C5H5N1O2\ANNA\03-Apr-1995\0\\#P RM
P2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=1048576000\\C
4H2NO2-CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\N,-0.4774340797,0.0002972
586,-0.3497656701\C,-0.5161573557,0.0457493479,1.0456214803\C,0.917020
8131,0.025857012,1.5012847085\C,1.7068569107,-0.0274598774,0.424879116
5\C,0.8439820908,-0.0460120325,-0.8064751432\O,-1.5222084157,0.0915495
132,1.7233026552\O,1.1954680687,-0.0914861746,-1.9673918621\C,-1.65046
38529,0.0012542684,-1.2045447381\H,2.7872253647,-0.0553948857,0.362965
9344\H,1.1825847425,0.0529419425,2.550351985\H,-2.2381676039,0.9104884
292,-1.0480086178\H,-1.3020296684,-0.0402497516,-2.2377484661\H,-2.281
0831368,-0.8667055649,-0.9910800333\\Version=IBM-RS6000-G94RevE.1\HF=-
396.4378658\MP2=-397.5748351\RMSD=6.415e-09\PG=C01 [X(C5H5N1O2)]\\@

$(CHCO)_2NCH_2^{\bullet}$ (147)

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-31G(d)\C5H4N1O2(2)\ANNA\07-Apr-1998\0\\#
P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=10485760
00\\C4H2NO2-CH2 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\N,-0.5372035584,0.,-
0.3647263061\C,-0.5160022192,0.,1.0476391786\C,0.9319725054,0.,1.44037
65434\C,1.6826170124,0.,0.3346847366\C,0.7832701312,0.,-0.8661716957\O
,-1.4953544594,0.,1.7614971888\O,1.0853999482,0.,-2.0398291582\C,-1.67
8441069,0.,-1.1394990077\H,2.7604623396,0.,0.2358193588\H,1.237785953,
0.,2.4786468981\H,-1.5516979711,0.,-2.2104091363\H,-2.6269874873,0.,-0
.6264957532\\Version=IBM-RS6000-G94RevE.1\State=2-A"\HF=-395.8038734\M
P2=-396.9222784\RMSD=7.294e-09\PG=CS [SG(C5H4N1O2)]\\@

$C_6H_4(CO)_2NCH_3$ (124)

1\1\GINC-VPP01\SP\RMP2-FC\6-31G(d)\C9H7N1O2\AKC501\21-Apr-1998\0\\#P R
MP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=8388608\\C6H
4C2O2N-CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\N,-1.3355289983,-0.000000
932,-1.0086250945\C,-1.4146178828,0.000017373,0.3919561908\C,-0.000793
627,0.0000007937,0.8747508569\C,0.8407957166,0.0000089286,-0.239544249
\C,-0.0078604706,-0.0000197518,-1.4689202383\O,-2.4465115046,0.0000646
443,1.0331185859\O,0.3351241744,-0.0000846065,-2.6342816254\C,-2.49774
61026,0.0000058299,-1.8778178366\H,-3.109484594,0.888803533,-1.6971415
821\H,-2.1371169511,-0.0001338101,-2.9074994648\H,-3.109628369,-0.8886
508631,-1.696942809\C,0.5054638861,-0.0000154826,2.1658467985\C,1.8992
797492,-0.0000133525,2.312061681\C,2.7433741592,0.0000099219,1.1943232
82\C,2.2212415692,0.0000289956,-0.1062169503\H,-0.1583319756,-0.000024
7525,3.0249089273\H,2.3339203751,-0.0000245214,3.3076842468\H,3.819923
6585,0.0000146222,1.3398907616\H,2.8656975018,0.0000424795,-0.97985731
12\\Version=Fujitsu-VP-Unix-G94RevE.2\HF=-549.1104196\MP2=-550.7537262

\RMSD=4.115e-09\PG=C01 [X(C9H7N1O2)]\\@

$C_6H_4(CO)_2NCH_2^{\bullet}$ (148)

1\1\GINC-RSCQC8\SP\ROMP2-FC\6-31G(d)\C9H6N1O2(2)\ANNA\24-Apr-1998\0\\#
P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=10485760
00\\C6H4C2O2N-CH2 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\N,-1.4275982845,-0
.9789456279,0.\C,-0.1021923195,-1.4947574168,0.\C,0.7909453567,-0.3055
327627,0.\C,0.,0.8479033348,0.\C,-1.4311719269,0.4432942262,0.\O,0.175
9592552,-2.6756336857,0.\O,-2.4324975787,1.1282647176,0.\C,-2.55837005
68,-1.7543364254,0.\H,-3.5099860572,-1.2464501903,0.\H,-2.4275384059,-
2.825034524,0.\C,2.1754140053,-0.2342962814,0.\C,2.7571987712,1.042332
1925,0.\C,1.9658412417,2.1963746264,0.\C,0.5653332889,2.113698538,0.\H
,2.7793970885,-1.1361854943,0.\H,3.8392429506,1.1376899398,0.\H,2.4446
99187,3.1713651521,0.\H,-0.0583103473,3.0021060674,0.\\Version=IBM-RS6
000-G94RevE.1\State=2-A"\HF=-548.4761456\MP2=-550.1016181\RMSD=7.012e-
09\PG=CS [SG(C9H6N1O2)]\\@

$(CHCO)_2NCH_2CH_3$ (132)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C6H7N1O2\AKC501\19-Jun-1998\0\\#P RMP2
/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\C4H
2NO2-CH2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\N,-0.2192545534,-0.20216
903,-0.1487826452\C,-0.2201700464,-0.1990216574,1.2489459399\C,1.22514
79548,-0.2007186369,1.6654211557\C,1.9864067287,-0.1976647852,0.567219
9653\C,1.0891511006,-0.1936738712,-0.6400082498\O,-1.2055960298,-0.200
2753574,1.9585564732\O,1.4075462598,-0.1895521375,-1.8118914724\C,-1.4
185419342,-0.1792972368,-0.980246379\H,3.0650877579,-0.1990532521,0.47
59437352\H,1.5181529752,-0.2053088928,2.707541278\C,-1.8772163818,1.23
95686956,-1.3219956867\H,-1.1859063252,-0.740535998,-1.8894255954\H,-2
.1954929452,-0.7155916622,-0.4286556987\H,-2.7772645281,1.2022620718,-
1.9456589538\H,-2.114257685,1.8007486076,-0.412467158\H,-1.0998037454,
1.7761272456,-1.8751395686\\Version=SGI-G94RevE.2\HF=-435.4757262\MP2=
-436.7447802\RMSD=4.509e-09\PG=C01 [X(C6H7N1O2)]\\@

$(CHCO)_2NC^{\bullet}HCH_3$ (149)

1\1\GINC-RSCQC2\SP\ROMP2-FC\6-31G(d)\C6H6N1O2(2)\ANNA\28-Jun-1998\0\\#
P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=78643200
0\\C4H2NO2-CHCH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\N,-0.1471121084,-0.
0276877822,-0.2771346085\C,-0.1415079185,0.0350725601,1.132110252\C,1.
3026943799,0.0842225928,1.5442897817\C,2.07106259,0.0460931098,0.45331
99436\C,1.186912937,-0.0277433173,-0.7532769141\O,-1.1131737022,0.0449
046979,1.8595433328\O,1.5086413532,-0.0787593547,-1.9212591736\C,-1.23
982059,-0.1044823153,-1.1397081199\H,3.1498435876,0.0623785094,0.36688
79618\H,1.5870315618,0.1391992103,2.5872003935\H,-0.953935471,-0.13028
03339,-2.1820896837\C,-2.6495579091,0.0106567656,-0.678818933\H,-2.863
175392,0.9794019593,-0.2024751417\H,-3.3133635639,-0.0934563468,-1.542
0330666\H,-2.9190581073,-0.755507643,0.0586824605\\Version=IBM-RS6000-
G94RevE.1\HF=-434.8402264\MP2=-436.0915096\RMSD=8.923e-09\PG=C01 [X(C6
H6N1O2)]\\@

$(CHCO)_2NCH_2CO_2CH_3$ (129)

1\1\GINC-RSCQC9\SP\RMP2-FC\6-31G(d)\C7H7N1O4\ANNA\13-Apr-1998\0\\#P RM
P2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=1048576000\\C
4H2NO2-CH2CO2CH3 sp nonplanar RMP2/6-31G*//B3LYP/6-31G*\\0,1\N,0.85619
60542,-0.4674124726,-0.1754069042\C,1.19912256,-1.016957961,1.06642937
18\C,2.4558822915,-0.3137431163,1.4913769126\C,2.7682785738,0.60392949
13,0.570881623\C,1.737646112,0.5649681934,-0.5203627549\O,0.5889124198
,-1.8929657336,1.6415772002\O,1.660244844,1.2541015679,-1.5151717385\C
,-0.387582365,-0.7230193883,-0.852341793\H,3.6010723783,1.2947978056,0
.5438098822\H,2.9673436778,-0.5667973635,2.4111313682\C,-1.5070421117,
0.1795782411,-0.3324271367\H,-0.2543744866,-0.5499651802,-1.9237007653

\H,-0.6692404624,-1.768652323,-0.7012699223\O,-1.3831569806,1.00952131
05,0.5370176592\O,-2.6502684382,-0.0883283829,-0.9874979669\C,-3.78981
92529,0.6977060862,-0.5906101415\H,-4.6136356195,0.3519580936,-1.21492
95746\H,-4.0128089341,0.5371404102,0.4671445755\H,-3.5964985392,1.7600
064919,-0.7594149546\\Version=IBM-RS6000-G94RevE.1\HF=-623.0788649\MP2
=-624.819875\RMSD=7.934e-09\PG=C01 [X(C7H7N1O4)]\\@

$(CHCO)_2NCH^{\bullet}CO_2CH_3$ (150)

1\1\GINC-VPP05\SP\ROMP2-FC\6-31G(d)\C7H6N1O4(2)\AKC501\16-Apr-1998\0\\
#P ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=1258291
2\\C4H2NO2-CHCO2CH3 orthish sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\N,0.8327
54255,-0.07508504,-0.0038505114\C,0.9073798446,0.0261185148,1.42044397
54\C,2.3139779991,0.4494398232,1.7158140479\C,3.0173783686,0.492072231
,0.5799859665\C,2.1229688018,0.1360785122,-0.5619990883\O,0.0364888789
,-0.252036732,2.2049428912\O,2.394387076,0.0331156043,-1.7366178668\C,
-0.2468446645,-0.4522364271,-0.7738195658\H,4.0622046398,0.7304655436,
0.4278791861\H,2.6403349374,0.6350796246,2.7310452263\H,-0.009506841,-
0.9007261202,-1.7300764492\C,-1.6042369079,-0.0360957615,-0.4586025649
\O,-1.9255059103,0.8077941022,0.3596866944\O,-2.4845944223,-0.70186648
45,-1.2525553407\C,-3.8580854301,-0.3308306238,-1.0715486063\H,-4.4224
096545,-0.9506987301,-1.7690106379\H,-4.1762673971,-0.5216358839,-0.04
28530801\H,-4.0050685158,0.7297813131,-1.2953266759\\Version=Fujitsu-V
P-Unix-G94RevE.2\HF=-622.4433839\MP2=-624.170242\RMSD=9.108e-09\PG=C01
[X(C7H6N1O4)]\\@

$(CHCO)_2NCH(CH_3)CO_2CH_3$ (133)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C8H9N1O4\AKC501\21-Jun-1998\0\\#P RMP2
/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\C4H
2NO2-CH(CH3)CO2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\N,0.3524486139,-0
.712406331,0.537978241\C,0.3528437179,-0.7103349697,1.9397652785\C,1.7
93976094,-0.7080547997,2.3564368238\C,2.555220213,-0.6563367009,1.2595
985177\C,1.6638478195,-0.6243135157,0.0509223229\O,-0.6347296258,-0.71
617585,2.64521353\O,1.9908321427,-0.5518839415,-1.1151396306\C,-0.8526
212796,-0.5299081709,-0.2531874048\H,3.6337246808,-0.6350668461,1.1699
201739\H,2.086361138,-0.7404921252,3.3981128256\C,-0.9120747142,0.9227
797375,-0.7518279176\C,-1.0036701593,-1.5797845838,-1.3630463478\H,-1.
677530983,-0.6401321046,0.461649724\O,-0.1900292283,1.8144835715,-0.37
00564244\O,-1.9144826868,1.083912961,-1.6357200515\C,-2.0909021683,2.4
253917995,-2.1279804355\H,-2.9329151495,2.3735669136,-2.8182915115\H,-
2.3084597181,3.1085247123,-1.303029651\H,-1.1882104061,2.7624537498,-2
.6433105322\H,-1.9576692833,-1.4420367622,-1.876435899\H,-0.192782216,
-1.4978113218,-2.0897275356\H,-0.9821003117,-2.5814886051,-0.923199692
1\\Version=SGI-G94RevE.2\HF=-662.112228\MP2=-663.98942\RMSD=8.607e-09\
PG=C01 [X(C8H9N1O4)]\\@

$(CHCO)_2NC^{\bullet}(CH_3)CO_2CH_3$ (151)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C8H8N1O4(2)\AKC501\24-Jun-1998\0\\#P
ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000
\\C4H2NO2-C(CH3)CO2CH3 C1 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\N,0.797409
8559,-0.3035314301,0.1488681665\C,0.6848805624,-0.4743103782,1.5598366
407\C,2.0623485606,-0.2653313007,2.1073981242\C,2.9070213434,-0.040346
499,1.097479578\C,2.1480338057,-0.0533535336,-0.1932340652\O,-0.313819
1204,-0.7934601618,2.1568762282\O,2.5830804461,0.1240150521,-1.3101533
863\C,-0.2793478084,-0.3385266361,-0.7461998084\H,3.9747645047,0.13633
85816,1.1192751573\H,2.2624975248,-0.3315797672,3.169121636\C,-0.16755
54911,-1.1578116424,-1.9876320192\C,-1.4255606971,0.5039209761,-0.4026
723202\O,-1.4133908493,1.3716936352,0.4556971563\O,-2.5070637554,0.227
6881408,-1.1758029492\C,-3.6582916183,1.0423418821,-0.9129147968\H,-4.
4281797967,0.6897262918,-1.6000658005\H,-3.9835545661,0.9238350875,0.1
241466572\H,-3.4346717577,2.0973597031,-1.0948503231\H,-1.0587870995,-
1.0396113516,-2.6036714685\H,0.7184684784,-0.8679234195,-2.5651087629\
H,-0.052031991,-2.2224156545,-1.736228651\\Version=SGI-G94RevE.2\HF=-6
61.483941\MP2=-663.3443088\RMSD=9.504e-09\PG=C01 [X(C8H8N1O4)]\\@

Appendix N. Relative rates of reaction of the glycine derivatives **6** and **111**

Compound	6	12	111	116
^{1}H NMR signal	4.27 (2H)	6.68 (1H)	3.63 (3H)	5.26 (1H)
t_0	1.8280		2.7258	
t_1	0.9355	0.3871	1.8710	0.2112
$\log(t_0/t_1)$	0.291		0.163	
% reaction	49%		31%	
% final	51%	42%	69%	23%
% accounted for	93%		92%	
k_{rel} (NBS)	1		0.56	

Compound	6	12	111	116
^{1}H NMR signal	4.27 (2H)	6.68 (1H)	3.63 (3H)	5.26 (1H)
t_0	2.2131		3.0451	
t_1	0.9615	0.5770	2.1538	0.3462
$\log(t_0/t_1)$	0.362		0.150	
% reaction	57%		29%	
% final	43%	52%	71%	34%
% accounted for	95%		105%	
k_{rel} (NBS)	1		0.42	

Compound	6	12	111	116
^{1}H NMR signal	4.27 (2H)	6.68 (1H)	3.63 (3H)	5.26 (1H)
t_0	2.0803		2.9927	
t_1	0.9444	0.500	1.8636	0.2273
$\log(t_0/t_1)$	0.343		0.206	
% reaction	55%		38%	
% final	45%	48%	62%	23%
% accounted for	93%		85%	
k_{rel} (NBS)	1		0.60	

Appendix O. Relative rates of reaction of **171** and **169**

Compound	**169**	**173**	**171**	**174**
^{1}H NMR signal	1.83 d 6H (/6)	3.47 d 2H (/2)	1.81 d 6H (/6)	4.09 s 2H (/2)
t_0	0.3094		0.3405	
t_1	0.2047	0.0673	0.2181	0.1060
$\log(t_0/t_1)$	0.1795		0.1935	
% reaction	34%		36%	
% final	66%	22%	64%	31%
% accounted for	88%		95%	
k_{rel} (NBS)	1		1.08	

Compound	**169**	**173**	**171**	**174**
^{1}H NMR signal	1.83 d 6H (/6)	3.47 d 2H (/2)	1.81 d 6H (/6)	4.09 s 2H (/2)
t_0	0.9045		0.9329	
t_1	0.5597	0.1744	0.5627	0.2381
$\log(t_0/t_1)$	0.2084		0.2196	
% reaction	38%		40%	
% final	62%	20%	60%	26%
% accounted for	82%		86%	
k_{rel} (NBS)	1		1.05	

Compound	**169**	**173**	**171**	**174**
^{1}H NMR signal	1.83 d 6H (/6)	3.47 d 2H (/2)	1.81 d 6H (/6)	4.09 s 2H (/2)
t_0	0.4666		0.5356	
t_1	0.3175	0.1130	0.3563	0.1712
$\log(t_0/t_1)$	0.1671		0.1770	
% reaction	32%		33%	
% final	68%	24%	67%	32%
% accounted for	92%		99%	
k_{rel} (NBS)	1		1.06	

Appendix O. Relative rates of reaction of **172** and **170**.

Compound	**172**	**170**
^{1}H NMR signal	αH, 4.51, 1H	βHs, 1.30, 6H
t_0	1.8304	11.0268
t_1	1.5857	7.9571
$\log(t_0/t_1)$	0.0623	0.1417
% reaction	13%	28%
% final	87%	72%
% accounted for	-	-
k_{rel} (NBS)	1	2.3

Compound	**172**	**170**
^{1}H NMR signal	αH, 4.51, 1H	βHs, 1.30, 6H
t_0	0.8505	5.8879
t_1	0.6324	3.2432
$\log(t_0/t_1)$	0.1287	0.2590
% reaction	26%	45%
% final	74%	55%
% accounted for		
k_{rel} (NBS)	1	2.0

Compound	**172**	**170**
^{1}H NMR signal	αH, 4.51, 1H	βHs, 1.30, 6H
t_0	0.6198	4.9752
t_1	0.4014	2.1107
$\log(t_0/t_1)$	0.1887	0.3724
% reaction	35%	58%
% final	65%	42%
% accounted for		
k_{rel} (NBS)	1	2.0

Appendix P. GAUSSIAN 94 Archive entries for RMP2/6-31G(d)//B3LYP/6-31G(d) calculations from Chapter Five.

$C_6H_5CH_3$ (177)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C7H8\AKC501\21-Apr-1998\0\\#P RMP2/6-3
1G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\C6H5-CH
3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.0046769365,0.,-2.425420004\C,-
0.013014267,0.,-0.9138495404\H,1.0328374868,0.,-2.8119747885\H,-0.4940
823287,-0.8860211215,-2.832835363\H,-0.4940823287,0.8860211215,-2.8328
35363\C,-0.0092819941,1.202368082,-0.1942527369\C,0.0044568031,1.20540
85393,1.2011789483\C,0.0120793853,0.,1.9050319014\C,-0.0092819941,-1.2
02368082,-0.1942527369\C,0.0044568031,-1.2054085393,1.2011789483\H,-0.
019117063,2.1468307961,-0.7344541543\H,0.0047435337,2.1504320394,1.738
5491636\H,0.0195241932,0.,2.991766816\H,-0.019117063,-2.1468307961,-0.
7344541543\H,0.0047435337,-2.1504320394,1.7385491636\\Version=SGI-G94R
evE.2\State=1-A'\HF=-269.7387423\MP2=-270.6283853\RMSD=7.532e-09\PG=CS
[SG(C3H2),X(C4H6)]\\@

$C_6H_5CH_2^{\bullet}$ (178)

1\1\GINC-RSCQC9\SP\ROMP2-FC\6-31G(d)\C7H7(2)\ANNA\21-Apr-1998\0\\#P RO
MP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=39321600\\C6
H5-CH2 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.0000031355,0.,-2.4019591
445\C,-0.0000012845,0.,-0.9953537381\H,0.9279760438,0.,-2.9645186387\H
,-0.9279837628,0.,-2.9645162006\C,-1.2180718767,0.,-0.2519916723\C,-1.
2119193972,0.,1.1338480921\C,0.0000023897,0.,1.839860937\C,1.218071232
9,0.,-0.2519948336\C,1.2119223392,0.,1.1338449711\H,-2.1607278383,0.,-
0.7939211944\H,-2.1537905392,0.,1.6766168755\H,0.0000037947,0.,2.92612
69624\H,2.1607258005,0.,-0.7939267861\H,2.1537948932,0.,1.6766113116\\
Version=IBM-RS6000-G94RevE.1\State=2-A"\HF=-269.1108791\MP2=-269.98388
96\RMSD=5.710e-09\PG=CS [SG(C7H7)]\\@

$CH_3OC_6H_4CH_3$ (181)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C8H10O1\AKC501\22-Apr-1998\0\\#P RMP2/
6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\CH3O
-C6H4-CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.0162708316,0.28981391
99,-3.3332366841\C,-0.0058907753,0.2192937135,-1.8236775823\H,0.887335
4521,0.7769418609,-3.7216006369\H,-0.0699774893,-0.7090775757,-3.77830
77657\C,0.059300061,1.3890221517,-1.0470120834\C,0.0696137005,1.339772
0187,0.3400227783\C,0.0143476549,0.1034830488,1.001541144\C,-0.0601750
497,-0.9999351107,-1.1472528189\C,-0.0509426858,-1.0729872416,0.250665
71\H,0.1028132321,2.357490703,-1.5412629075\H,0.1200444515,2.245411781
1,0.9368466338\O,0.0297402917,0.1603769481,2.3682425122\H,-0.111328718
8,-1.9249980805,-1.7175435165\H,-0.0946843923,-2.0435546785,0.73176968
45\C,-0.0241898058,-1.0595562865,3.0870441874\H,-0.0009498328,-0.78712
35845,4.1440339433\H,-0.9491007092,-1.6136625895,2.8766932625\H,0.8373
057712,-1.7023145128,2.8602651801\H,-0.8741337066,0.8644338091,-3.7054
018801\\Version=SGI-G94RevE.2\HF=-383.6173772\MP2=-384.8158354\RMSD=7.
928e-09\PG=C01 [X(C8H10O1)]\\@

$CH_3OC_6H_4CH_2^{\bullet}$ (182)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C8H9O1(2)\AKC501\22-Apr-1998\0\\#P RO
MP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\
CH3O-C6H4-CH2 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.2924286549,0.,-3.
3067671881\C,-0.2309904701,0.,-1.9033030606\H,0.6098334443,0.,-3.90955
18667\H,-1.2442515179,0.,-3.8276159021\C,-1.4135845066,0.,-1.099162985
9\C,-1.3524417407,0.,0.2781317657\C,-0.1069895683,0.,0.9382168323\C,1.
0103233691,0.,-1.2048442128\C,1.0763491209,0.,0.1818736871\H,-2.381931
6875,0.,-1.5934115988\H,-2.2543045204,0.,0.88288308\O,-0.1618119082,0.
,2.3012649188\H,1.9331997962,0.,-1.7795922165\H,2.0458912597,0.,0.6675

194985\C,1.0584107315,0.,3.0248619533\H,0.7805498319,0.,4.0804276555\H
,1.6568094867,-0.8947077104,2.8075906267\H,1.6568094867,0.8947077104,2
.8075906267\\Version=SGI-G94RevE.2\State=2-A"\HF=-382.989582\MP2=-384.
1721398\RMSD=5.020e-09\PG=CS [SG(C8H7O1),X(H2)]\\@

$NO_2C_6H_4CH_3$ (179)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C7H7N1O2\AKC501\22-Apr-1998\0\\#P RMP2
/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\NO2
-C6H4-CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,-0.0000061742,-0.0033128
865,-3.5740401886\C,-0.0000036034,0.016928989,-2.0649210344\C,1.205633
9071,0.0147107266,-1.3466404722\C,1.2171354988,0.0038921427,0.04461334
63\C,0.0000012913,-0.0020946282,0.723230216\C,-1.2056385969,0.01471124
01,-1.3466362981\C,-1.2171353044,0.0038926548,0.0446176066\H,2.1494260
615,0.0231972777,-1.8856442786\H,2.1425280583,0.0037618743,0.607299852
7\N,0.0000038734,-0.0103180655,2.1921640665\H,-2.1494326455,0.02319819
06,-1.8856368025\H,-2.1425259533,0.0037627734,0.6073073465\H,-0.000004
8278,-1.0347944414,-3.9507463106\H,-0.8869885856,0.4919154055,-3.98187
95991\H,0.8869729832,0.4919187516,-3.9818826448\O,1.0899526494,-0.0139
441457,2.7652916464\O,-1.0899431887,-0.0139437048,2.7652952182\\Versio
n=SGI-G94RevE.2\HF=-473.207378\MP2=-474.6392966\RMSD=5.719e-09\PG=C01
[X(C7H7N1O2)]\\@

NO2C6H4CH2• (180)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C7H6N1O2(2)\AKC501\22-Apr-1998\0\\#P
ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000
\\CH3O-C6H4-NO2 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.0000046445,0.,-
3.5405010792\C,-0.0000028073,0.,-2.1399979989\C,1.2228481001,0.,-1.397
9582881\C,1.2248966646,0.,-0.0177913621\C,0.0000008726,0.,0.6651487974
\C,-1.2228517672,0.,-1.3979550666\C,-1.2248967007,0.,-0.0177881373\H,2
.1647875522,0.,-1.9391789963\H,2.1463321068,0.,0.5512151266\N,0.000002
7869,0.,2.1244701418\H,-2.1647926432,0.,-1.9391732982\H,-2.1463306421,
0.,0.5512207816\H,-0.9278170807,0.,-4.1030272306\H,0.9278062896,0.,-4.
1030296696\O,1.0918599367,0.,2.6994823986\O,-1.0918528595,0.,2.6994852
394\\Version=SGI-G94RevE.2\State=2-A"\HF=-472.5786949\MP2=-473.9945742
\RMSD=4.903e-09\PG=CS [SG(C7H6N1O2)]\\@

$C_6H_5CH_2CH_3$ (183)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C8H10\AKC501\26-Apr-1998\0\\#P RMP2/6-
31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\C6H5-C
H2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.0305008696,0.1902816957,-2
.0059425352\C,0.0079984232,0.2331163853,-0.492217748\C,1.1996988654,0.
2339447555,0.2452845099\C,1.1820262906,0.2359777145,1.6408072532\C,-0.
0341616796,0.237881766,2.3260549934\C,-1.2053063934,0.2366825154,0.209
3283705\C,-1.229369523,0.2387439801,1.604652503\H,2.1522621061,0.23762
39883,-0.2809581785\H,2.1187354239,0.2409969466,2.1925502018\H,-0.0505
000633,0.2431772414,3.4126863759\H,-2.141649202,0.2425229219,-0.345249
9451\H,-2.1820881338,0.2459529557,2.1282487141\H,0.9166176629,0.722237
6658,-2.3751126986\C,0.0351319743,-1.2446087639,-2.5642321651\H,0.0509
924375,-1.2384642476,-3.6602817201\H,0.9131256391,-1.7985922902,-2.213
6128645\H,-0.8552542365,-1.7944241728,-2.2392087502\H,-0.8413545972,0.
7268486998,-2.4014722252\\Version=SGI-G94RevE.2\HF=-308.7731927\MP2=-3
09.7950192\RMSD=8.929e-09\PG=C01 [X(C8H10)]\\@

$C_6H_5CH_2CH_2^{\bullet}$ (184)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C8H9(2)\AKC501\26-Apr-1998\0\\#P ROMP
2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\CH
3CH-C6H5 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.1725909159,0.,-1.93621
28569\C,-0.1728080891,0.,-0.5205832433\C,1.0282926317,0.,0.2466653674\
C,0.9919019709,0.,1.6339878879\C,-0.2313835905,0.,2.3168778417\C,-1.40
31525119,0.,0.1999471253\C,-1.4279453636,0.,1.5854386741\H,1.986327015
4,0.,-0.2647673732\H,1.9234671701,0.,2.1947291819\H,-0.2527900568,0.,3
.4029632161\H,-2.3350989058,0.,-0.3609358039\H,-2.3818127906,0.,2.1070

751978\H,-1.1389479433,0.,-2.4350815327\C,1.0573713949,0.,-2.790038066
1\H,0.7994563021,0.,-3.8529238903\H,1.6906430249,0.8806754071,-2.60377
76881\H,1.6906430249,-0.8806754071,-2.6037776881\\Version=SGI-G94RevE.
2\State=2-A"\HF=-308.1482743\MP2=-309.1539469\RMSD=4.620e-09\PG=CS [SG
(C8H7),X(H2)]\\@

$CH_3OC_6H_4CH_2CH_3$ (187)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C9H12O1\AKC501\28-Apr-1998\0\\#P RMP2/
6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\CH3O
-C6H4-CH2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.2338512066,0.067650
2068,-2.9101293832\C,0.2404464769,0.0096667643,-1.3968434586\H,1.22369
40214,0.3769557654,-3.2706722584\H,0.0587895901,-0.9374905046,-3.31461
1772\C,0.9625516938,0.9455543076,-0.6381075226\C,0.9441537541,0.924461
2712,0.7506023944\C,0.1935549419,-0.0464043786,1.4293216958\C,-0.49799
9248,-0.9510672292,-0.7020006094\C,-0.5312972231,-0.9909384662,0.69568
59978\H,1.5542969158,1.7035846571,-1.1474672205\H,1.5072047632,1.64631
71247,1.3343732635\O,0.2409305654,0.013316187,2.7950473326\H,-1.063641
0131,-1.695297075,-1.25925457\H,-1.1149735603,-1.7579769151,1.19215853
39\C,-0.5035329422,-0.9416354435,3.5312177889\H,-0.3308994496,-0.71044
87138,4.5841694425\H,-1.5785096388,-0.8703905719,3.3168507983\H,-0.164
7104907,-1.966261876,3.3260989791\C,-0.828210119,1.0292344438,-3.47301
>0479\H,-0.8015411117,1.047890272,-4.5689947825\H,-1.8344410182,0.7265
961862,-3.1615654724\H,-0.663824778,2.0508632976,-3.1118307334\\Versio
n=SGI-G94RevE.2\HF=-422.6517814\MP2=-423.9825303\RMSD=7.691e-09\PG=C01
[X(C9H12O1)]\\@

$CH_3OC_6H_4CH_2CH_2^{\bullet}$ (188)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C9H11O1(2)\AKC501\28-Apr-1998\0\\#P R
OMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\
\CH3O-C6H4-CHCH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.0002627063,0.,
-2.8521055191\C,-0.0082691658,0.,-1.4382211618\H,0.9682518188,0.,-3.34
66304841\C,-1.2274762248,0.,-3.7108514362\C,-1.2126518694,0.,-0.670669
8646\C,-1.1905385031,0.,0.7103111879\C,0.0319217101,0.,1.4075401641\C,
1.2092267965,0.,-0.7019175084\C,1.2368420428,0.,0.6859566138\H,-2.1702
368559,0.,-1.1827012511\H,-2.1107101857,0.,1.2870632819\O,-0.062778114
3,0.,2.7698020273\H,2.1491477002,0.,-1.2490508497\H,2.1924440487,0.,1.
1985749321\C,1.1364568954,0.,3.5266545291\H,0.8298672284,0.,4.57434265
9\H,1.7413512301,-0.8945263637,3.3265463659\H,1.7413512301,0.894526363
7,3.3265463659\H,-0.9648653018,0.,-4.7728622402\H,-1.8629349254,-0.880
8165538,-3.5302135135\H,-1.8629349254,0.8808165538,-3.5302135135\\Vers
ion=SGI-G94RevE.2\State=2-A"\HF=-422.0267337\MP2=-423.3419485\RMSD=7.7
69e-09\PG=CS [SG(C9H7O1),X(H4)]\\@

$NO_2C_6H_4CH_2CH_3$ (185)

1\1\GINC-PC\SP\RMP2-FC\6-31G(d)\C8H9N1O2\AKC501\26-Apr-1998\0\\#P RMP2
/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000\\NO2
-C6H4-CH2CH3 sp RMP2/6-31G*//B3LYP/6-31G*\\0,1\C,0.029544136,0.1321689
186,-3.1565797651\C,0.0153861062,0.1703447687,-1.6444263108\C,1.214343
7123,0.1686605449,-0.914714589\C,1.2131289024,0.1668955307,0.476708490
8\C,-0.0106747128,0.1674623937,1.1435312868\C,-1.1969743864,0.17192547
42,-0.9372654893\C,-1.2217839825,0.170191999,0.453966971\H,2.163191995
9,0.1732751344,-1.445265172\H,2.1329186705,0.1695021872,1.0485239495\N
,-0.0243949585,0.169876302,2.6126083453\H,-2.1357457147,0.1790812743,-
1.4854213315\H,-2.1521282814,0.1752896931,1.0084295655\H,0.9128867745,
0.6664110325,-3.5272557165\C,0.0345082875,-1.3040528245,-3.7131373079\
O,1.0601078205,0.1689442164,3.1959773416\O,-1.1196123472,0.1717641201,
3.1755949419\H,0.0447948681,-1.2934163212,-4.808561616\H,0.9159128478,
-1.8567943661,-3.3697195908\H,-0.8533968544,-1.856449941,-3.386317944\
H,-0.8465017584,0.6667196691,-3.5437485479\\Version=SGI-G94RevE.2\HF=-
512.2418233\MP2=-513.8059091\RMSD=6.791e-09\PG=C01 [X(C8H9N1O2)]\\@

$NO_2C_6H_4CH_2CH_2^{\bullet}$ (186)

1\1\GINC-PC\SP\ROMP2-FC\6-31G(d)\C8H8N1O2(2)\AKC501\22-Apr-1998\0\\#P
ROMP2/6-31G* SCF=DIRECT GUESS=CHECK GEOM=CHECK TEST MAXDISK=5242880000
\\CH3CH-C6H4-NO2 sp RMP2/6-31G*//B3LYP/6-31G*\\0,2\C,-0.1034451371,0.,
-3.091203866\C,-0.0993457946,0.,-1.6819429302\C,1.1076791687,0.,-0.917
0876268\C,1.0819278587,0.,0.4640851885\C,-0.1533337463,0.,1.1263379902
\C,-1.3331525434,0.,-0.9605649992\C,-1.3642883407,0.,0.4190367447\H,2.
0644324629,0.,-1.429178911\H,1.993392585,0.,1.0491272288\N,-0.17976121
04,0.,2.5836068468\H,-2.2654140639,0.,-1.5189686357\H,-2.2973705128,0.
,0.9687177938\H,-1.0731304612,0.,-3.5835395735\C,1.118637609,0.,-3.954
3034316\O,0.9014309133,0.,3.1799129593\O,-1.2820861194,0.,3.1396789574
\H,0.8522798217,0.,-5.014332725\H,1.7506529225,0.881001105,-3.76997542
83\H,1.7506529225,-0.881001105,-3.7699754283\\Version=SGI-G94RevE.2\St
ate=2-A"\HF=-511.6168273\MP2=-513.1655764\RMSD=9.020e-09\PG=CS [SG(C8H
6N1O2),X(H2)]\\@

Appendix Q. Relative rates of reaction of the phenylalanine derivatives **47** and **52–55**.

1. The dimethoxyphenylalanine ester **54** and the dimethoxyphenylalaninamide **55**.

Compound	**55**	**198**	**54**	**44**
^{1}H NMR signal	α-H, δ4.96	α-H, δ5.20, 5.31	α-H, δ5.14	α-H, δ5.48, 5.58
t_0	0.1496		0.2080	
t_1	0.0240	0.0802	0.1081	0.0370
$\log(t_0/t_1)$	0.7947		0.2842	
% reaction	84%		48%	
% final	16%	54%	52%	18%
% accounted for	70%		70%	
k_{rel} (NBS)	2.8		1	

Compound	**55**	**198**	**54**	**44**
^{1}H NMR signal	α-H, δ4.96	α-H, δ5.20, 5.31	α-H, δ5.14	α-H, δ5.48, 5.58
t_0	0.1702		0.2165	
t_1	0.0552	0.1160	0.1486	0.0773
$\log(t_0/t_1)$	0.4888		0.1636	
% reaction	68%		31%	
% final	32%	68%	69%	36%
% accounted for	100%		105%	
k_{rel} (NBS)	3.0		1	

Compound	**55**	**198**	**54**	**44**
^{1}H NMR signal	α-H, δ4.96	α-H, δ5.20, 5.31	α-H, δ5.14	α-H, δ5.48, 5.58
t_0	0.1558		0.2130	
t_1	0.0751	0.0802	0.1524	0.0476
$\log(t_0/t_1)$	0.3165		0.1454	
% reaction	52%		28%	
% final	48%	51%	72%	22%
% accounted for	99%		94%	
k_{rel} (NBS)	2.2		1	

2. The methyltyrosine ester **52** and the methyltyrosinamide **53**.

Compound	**53**	**197**	**52**	**43**
^{1}H NMR signal	α-H, δ4.95	α-H, δ5.21, 5.30	α-H, δ5.11	α-H, δ5.47, 5.56
t_0	0.1443		0.1526	
t_1	0.0377	0.1020	0.1019	0.0541
$\log(t_0/t_1)$	0.5825		0.1754	
% reaction	74%		33%	
% final	26%	71%	67%	35%
% accounted for	97%		102%	
k_{rel} (NBS)	3.3		1	

Compound	**53**	**197**	**52**	**43**
^{1}H NMR signal	α-H, δ4.95	α-H, δ5.21, 5.30	α-H, δ5.11	α-H, δ5.47, 5.56
t_0	0.1481		0.1567	
t_1	0.0216	0.1019	0.0875	0.0619
$\log(t_0/t_1)$	0.8362		0.2529	
% reaction	85%		44%	
% final	15%	69%	56%	40%
% accounted for	84%		96%	
k_{rel} (NBS)	3.3		1	

Compound	**53**	**197**	**52**	**43**
^{1}H NMR signal	α-H, δ4.95	α-H, δ5.21, 5.30	α-H, δ5.11	α-H, δ5.47, 5.56
t_0	0.2892		0.3563	
t_1	0.0528	0.2140	0.2111	0.1296
$\log(t_0/t_1)$	0.7387		0.2273	
% reaction	82%		41%	
% final	18%	74%	59%	36%
% accounted for	92%		95%	
k_{rel} (NBS)	3.3		1	

3. The dimethoxyphenylalanine ester **54** and the phenylalaninamide **47**.

Compound	**47**	**39**	**54**	**44**
^{1}H NMR signal	α-H, δ4.99	α-H, δ5.22, 5.32	α-H, δ5.14	α-H, δ5.48, 5.58
t_0	0.1813		0.1878	
t_1	0.1282	0.0346	0.0532	0.1222
$\log(t_0/t_1)$	0.1506		0.5477	
% reaction	29%		72%	
% final	71%	19%	28%	65%
% accounted for	90%		93%	
k_{rel} (NBS)	1		3.6	

Compound	**47**	**39**	**54**	**44**
^{1}H NMR signal	α-H, δ4.99	α-H, δ5.22, 5.32	α-H, δ5.14	α-H, δ5.48, 5.58
t_0	0.1478		0.1532	
t_1	0.0907	0.0363	0.0231	0.0653
$\log(t_0/t_1)$	0.2121		0.8220	
% reaction	39%		85%	
% final	61%	25%	15%	43%
% accounted for	86%		58%	
k_{rel} (NBS)	1		3.9	

Compound	**47**	**39**	**54**	**44**
^{1}H NMR signal	α-H, δ4.99	α-H, δ5.20, 5.31	α-H, δ5.14	α-H, δ5.48, 5.58
t_0	0.2914		0.3176	
t_1	0.1357	0.1650	0.0251	0.2244
$\log(t_0/t_1)$	0.3320		1.1017	
% reaction	53%		92%	
% final	47%	57%	8%	71%
% accounted for	104%		79%	
k_{rel} (NBS)	1		3.3	

4. The methyltyrosine ester **52** and the phenylalaninamide **47**.

Compound	47	39	52	43
^{1}H NMR signal	α-H, δ4.99	α-H, δ5.20, 5.31	α-H, δ5.11	α-H, δ5.47, 5.56
t_0	0.2520		0.2992	
t_1	0.1186	0.1172	0.0813	0.1482
$\log(t_0/t_1)$	0.3273		0.5659	
% reaction	53%		73%	
% final	47%	47%	27%	50%
% accounted for	94%		77%	
k_{rel} (NBS)	1		1.7	

Compound	47	39	52	43
^{1}H NMR signal	α-H, δ4.99	α-H, δ5.20, 5.31	α-H, δ5.11	α-H, δ5.47, 5.56
t_0	0.3126		0.3437	
t_1	0.2002	0.1052	0.1427	0.1643
$\log(t_0/t_1)$	0.1934		0.3818	
% reaction	36%		58%	
% final	64%	34%	42%	48%
% accounted for	98%		90%	
k_{rel} (NBS)	1		2.0	

Compound	47	39	52	43
^{1}H NMR signal	α-H, δ4.99	α-H, δ5.20, 5.31	α-H, δ5.11	α-H, δ5.47, 5.56
t_0	0.1972		0.2446	
t_1	0.1338	0.0805	0.1002	0.1346
$\log(t_0/t_1)$	0.1684		0.3878	
% reaction	32%		59%	
% final	68%	41%	41%	55%
% accounted for	109%		96%	
k_{rel} (NBS)	1		2.3	

Appendix R. Relative rates of reaction for the compounds in Chapter Six.

1. The trifluoroacetamide **206** and pentafluorobenzoyl ester **208**.

Compound	**206**	**212**	**208**	**214**
^{1}H NMR signal	δ3.63 2H	δ5.08 1H	δ4.58 2H	δ4.83 2H
t_o	1.141		0.873	
t_1	0.139	0.313	0.249	0.603
$\log(t_o/t_1)$	0.915		0.544	
% reaction	88%		71%	
% final	12%	55%	29%	69%
% accounted for	67%		98%	
k_{rel}(NBS)	1		0.6	

Compound	**206**	**212**	**208**	**214**
^{1}H NMR signal	δ3.63 2H	δ5.08 1H	δ4.58 2H	δ4.83 2H
t_o	0.699		0.575	
t_1	0.158	0.209	0.228	0.347
$\log(t_o/t_1)$	0.647		0.402	
% reaction	77%		60%	
% final	23%	60%	40%	60%
% accounted for	83%		100%	
k_{rel}(NBS)	1		0.6	

Compound	**206**	**212**	**208**	**214**
^{1}H NMR signal	δ3.63 2H	δ5.08 1H	δ4.58 2H	δ4.83 2H
t_o	1.438		1.077	
t_1	0.369	0.355	0.455	0.574
$\log(t_o/t_1)$	0.591		0.374	
% reaction	74%		58%	
% final	26%	49%	42%	53%
% accounted for	75%		95%	
k_{rel}(NBS)	1		0.6	

2. The benzoyl ester **207** and the trifluoroacetamide **206**.

Compound	**207**	**213**	**206**	**212**
^{1}H NMR signal	δ4.58 2H	δ4.83 2H	δ3.63 2H	δ5.08 1H
t_o	1.403		1.168	
t_1	0.716	0.666	0.615	0.201
$\log(t_o/t_1)$	0.292		0.279	
% reaction	49%		47%	
% final	51%	47%	53%	34%
% accounted for	98%		87%	
k_{rel}(NBS)	1		0.95	

Compound	**207**	**213**	**206**	**212**
^{1}H NMR signal	δ4.58 2H	δ4.83 2H	δ3.63 2H	δ5.08 1H
t_o	0.713		0.562	
t_1	0.193	0.480	0.181	0.162
$\log(t_o/t_1)$	0.568		0.492	
% reaction	73%		68%	
% final	27%	67%	32%	58%
% accounted for	94%		90%	
k_{rel}(NBS)	1		0.87	

Compound	**207**	**213**	**206**	**212**
^{1}H NMR signal	δ4.58 2H	δ4.83 2H	δ3.63 2H	δ5.08 1H
t_o	1.322		1.116	
t_1	0.612	0.729	0.536	0.242
$\log(t_o/t_1)$	0.334		0.318	
% reaction	54%		52%	
% final	46%	55%	48%	43%
% accounted for	101%		91%	
k_{rel}(NBS)	1		0.95	

3. The trifluoroacetamide **206** and the pentafluorobenzamide **202**.

Compound	**206**	**212**	**202**	**210**
^{1}H NMR signal	δ3.63 2H	δ5.08 1H	δ3.73 2H	δ5.23 1H
t_o	1.236		1.235	
t_1	0.696	0.269	0.429	0.345
$\log(t_o/t_1)$	0.249		0.459	
% reaction	44%		65%	
% final	56%	43%	35%	56%
% accounted for	99%		91%	
k_{rel}(NBS)	1		1.84	

Compound	**206**	**212**	**202**	**210**
^{1}H NMR signal	δ3.63 2H	δ5.08 1H	δ3.73 2H	δ5.23 1H
t_o	1.209		1.164	
t_1	0.635	0.244	0.404	0.317
$\log(t_o/t_1)$	0.280		0.460	
% reaction	47%		65%	
% final	53%	40%	35%	54%
% accounted for	93%		89%	
k_{rel}(NBS)	1		1.64	

Compound	**206**	**212**	**202**	**210**
^{1}H NMR signal	δ3.63 2H	δ5.08 1H	δ3.73 2H	δ5.23 1H
t_o	1.632		1.684	
t_1	1.070	0.276	0.765	0.365
$\log(t_o/t_1)$	0.183		0.343	
% reaction	34%		55%	
% final	66%	34%	45%	43%
% accounted for	100%		88%	
k_{rel}(NBS)	1		1.87	

4. The pentafluorobenzamide **202** and the acetamide **205**.

Compound	**202**	**210**	**205**	**211**
^{1}H NMR signal	δ3.73 2H	δ5.23 1H	δ3.52 2H	δ5.08 1H
t_o	0.958		1.671	
t_1	0.671	0.110	0.904	0.254
$\log(t_o/t_1)$	0.155		0.267	
% reaction	30%		46%	
% final	70%	23%	54%	30%
% accounted for	93%		84%	
k_{rel}(NBS)	1		1.7	

Compound	**202**	**210**	**205**	**211**
^{1}H NMR signal	δ3.73 2H	δ5.23 1H	δ3.52 2H	δ5.08 1H
t_o	0.337		0.502	
t_1	0.213	0.078	0.182	0.130
$\log(t_o/t_1)$	0.199		0.441	
% reaction	37%		64%	
% final	63%	46%	36%	52%
% accounted for	109%		88%	
k_{rel}(NBS)	1		2.2	

Compound	**202**	**210**	**205**	**211**
^{1}H NMR signal	δ3.73 2H	δ5.23 1H	δ3.52 2H	δ5.08 1H
t_o	0.548		0.691	
t_1	0.323	0.090	0.242	0.140
$\log(t_o/t_1)$	0.229		0.455	
% reaction	41%		65%	
% final	59%	33%	35%	41%
% accounted for	92%		76%	
k_{rel}(NBS)	1		2.0	

5. The acetamide **205** and the benzamide **199**.

Compound	205	211	199	209
^{1}H NMR signal	δ3.52 2H	δ5.08 1H	δ2.95 2H	δ5.23 1H
t_o	2.421		2.673	
t_1	1.252	0.398	1.146	0.390
$\log(t_o/t_1)$	0.286		0.368	
% reaction	49%		57%	
% final	51%	32%	43%	29%
% accounted for	83%		72%	
k_{rel}(NBS)	0.78		1	

Compound	205	211	199	209
^{1}H NMR signal	δ3.52 2H	δ5.08 1H	δ2.95 2H	δ5.23 1H
t_o	1.224		1.224	
t_1	0.739	0.143	0.662	0.131
$\log(t_o/t_1)$	0.219		0.267	
% reaction	40%		46%	
% final	60%	23%	54%	21%
% accounted for	83%		75%	
k_{rel}(NBS)	0.82		1	

Compound	205	211	199	209
^{1}H NMR signal	δ3.52 2H	δ5.08 1H	δ2.95 2H	δ5.23 1H
t_o	1.058		1.488	
t_1	0.764	0.221	0.986	0.260
$\log(t_o/t_1)$	0.141		0.179	
% reaction	28%		34%	
% final	72%	42%	66%	35%
% accounted for	114%		101%	
k_{rel}(NBS)	0.79		1	

6. The trifluoroacetamide **206** and the benzamide **199**.

Compound	**206**	**212**	**199**	**209**
^{1}H NMR signal	δ3.63 2H	δ5.08 1H	δ3.73 2H	δ5.23 1H
t_o	1.368		1.361	
t_1	1.037	0.153	0.580	0.265
$\log(t_o/t_1)$	0.120		0.370	
% reaction	24%		57%	
% final	76%	22%	43%	39%
% accounted for	98%		82%	
k_{rel}(NBS)	0.32		1	

Compound	**206**	**212**	**199**	**209**
^{1}H NMR signal	δ3.63 2H	δ5.08 1H	δ3.73 2H	δ5.23 1H
t_o	0.907		0.973	
t_1	0.580	0.126	0.253	0.134
$\log(t_o/t_1)$	0.194		0.585	
% reaction	36%		74%	
% final	64%	27%	26%	28%
% accounted for	91%		54%	
k_{rel}(NBS)	0.33		1	

Compound	**206**	**212**	**199**	**209**
^{1}H NMR signal	δ3.63 2H	δ5.08 1H	δ3.73 2H	δ5.23 1H
t_o	0.432		0.418	
t_1	0.340	0.039	0.209	0.104
$\log(t_o/t_1)$	0.104		0.301	
% reaction	21%		50%	
% final	79%	18%	50%	50%
% accounted for	97%		100%	
k_{rel}(NBS)	0.35		1	

Compound	206	212	199	209
^{1}H NMR signal	δ3.63 2H	δ5.08 1H	δ3.73 2H	δ5.23 1H
t_o	0.980		1.013	
t_1	0.766	0.103	0.487	0.197
$\log(t_o/t_1)$	0.107		0.318	
% reaction	22%		52%	
% final	78%	21%	48%	39%
% accounted for	99%		87%	
k_{rel}(NBS)	0.34		1	

7. The ethylbenzamide **199** and the propylpentafluorobenzamide **203**

Compound	199	209	203	216
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.456		0.417	
t_1	0.304	0.047	0.155	0.120
$\log(t_o/t_1)$	0.180		0.430	
% reaction	33%		63%	
% final	67%	21%	37%	58%
% accounted for	88%		95%	
k_{rel}(NBS)	1		2.39	

Compound	199	209	203	216
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.721		0.605	
t_1	0.502	0.095	0.177	0.180
$\log(t_o/t_1)$	0.157		0.534	
% reaction	30%		71%	
% final	70%	26%	29%	60%
% accounted for	96%		89%	
k_{rel}(NBS)	1		3.40	

Compound	199	209	203	216
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	1.047		1.000	
t_1	0.731	0.126	0.282	0.285
$\log(t_o/t_1)$	0.156		0.550	
% reaction	30%		72%	
% final	70%	24%	28%	57%
% accounted for	94%		85%	
k_{rel}(NBS)	1		3.52	

Compound	199	209	203	216
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	1.134		0.764	
t_1	0.644		0.186	0.260
$\log(t_o/t_1)$	0.246	0.138	0.614	
% reaction	43%		76%	
% final	57%	24%	24%	68%
% accounted for	81%		92%	
k_{rel}(NBS)	1		2.5	

Compound	199	209	203	216
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.713		0.566	
t_1	0.415	0.105	0.179	0.186
$\log(t_o/t_1)$	0.235		0.500	
% reaction	42%		68%	
% final	58%	29%	32%	66%
% accounted for	87%		98%	
k_{rel}(NBS)	1		2.1	

Compound	199	209	203	216
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	1.055		0.752	
t_1	0.666	0.162	0.164	0.248
$\log(t_o/t_1)$	0.200		0.661	
% reaction	37%		78%	
% final	63%	31%	22%	66%
% accounted for	94%		88%	
k_{rel}(NBS)	1		3.3	

8. The ethylbenzamide **199** and the propylbenzamide **200**.

Compound	**199**	**209**	**200**	**215**
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.600		0.651	
t_1	0.495	0.026	0.290	0.144
$\log(t_o/t_1)$	0.084		0.351	
% reaction	17%		55%	
% final	83%	9%	45%	44%
% accounted for	92%		99%	
k_{rel}(NBS)	1		4.2	

Compound	**199**	**209**	**200**	**215**
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.660		0.679	
t_1	0.542	0.036	0.256	0.157
$\log(t_o/t_1)$	0.086		0.424	
% reaction	18%		62%	
% final	82%	11%	38%	46%
% accounted for	93%		84%	
k_{rel}(NBS)	1		4.9	

Compound	**199**	**209**	**200**	**215**
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.397		0.407	
t_1	0.337	0.016	0.152	0.082
$\log(t_o/t_1)$	0.071		0.428	
% reaction	15%		63%	
% final	85%	8%	37%	40%
% accounted for	93%		77%	
k_{rel}(NBS)	1		6.0	

Compound	199	209	200	215
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.640		0.707	
t_1	0.464	0.044	0.233	0.150
$\log(t_o/t_1)$	0.140		0.482	
% reaction	27%		67%	
% final	73%	14%	33%	42%
% accounted for	87%		75%	
k_{rel}(NBS)	1		3.45	

Compound	199	209	200	215
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.533		0.509	
t_1	0.385	0.023	0.153	0.109
$\log(t_o/t_1)$	0.141		0.522	
% reaction	28%		70%	
% final	72%	8%	30%	43%
% accounted for	80%		73%	
k_{rel}(NBS)	1		3.7	

Compound	199	209	200	215
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.753		0.758	
t_1	0.639	0.020	0.289	0.168
$\log(t_o/t_1)$	0.071		0.419	
% reaction	15%		62%	
% final	85%	5%	38%	44%
% accounted for	90%		82%	
k_{rel}(NBS)	1		5.9	

Compound	199	209	200	215
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	1.116		1.264	
t_1	0.915	0.009	0.369	0.221
$\log(t_o/t_1)$	0.086		0.535	
% reaction	18%		71%	
% final	82%	2%	29%	35%
% accounted for	84%		64%	
k_{rel}(NBS)	1		6.2	

Compound	199	209	200	215
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.893		1.014	
t_1	0.736	0.013	0.452	0.279
$\log(t_o/t_1)$	0.084		0.351	
% reaction	18%		55%	
% final	82%	3%	45%	55%
% accounted for	85%		100%	
k_{rel}(NBS)	1		4.2	

Compound	199	209	200	215
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	1.081		1.091	
t_1	0.845	0.056	0.369	0.353
$\log(t_o/t_1)$	0.107		0.471	
% reaction	22%		66%	
% final	78%	10%	34%	64%
% accounted for	88%		98%	
k_{rel}(NBS)	1		4.4	

Compound	199	209	200	215
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.778		0.747	
t_1	0.599	0.052	0.221	0.209
$\log(t_o/t_1)$	0.114		0.529	
% reaction	23%		70%	
% final	77%	13%	30%	56%
% accounted for	90%		86%	
k_{rel}(NBS)	1		4.6	

Compound	199	209	200	215
^{1}H NMR signal	δ2.94 2H	δ5.23 1H	δ1.97 2H	δ5.15 1H
t_o	0.900		0.889	
t_1	0.744	0.026	0.378	0.216
$\log(t_o/t_1)$	0.083		0.371	
% reaction	17%		57%	
% final	83%	6%	43%	49%
% accounted for	89%		82%	
k_{rel}(NBS)	1		4.5	

9. The propylbenzamide **200** and the butylpentafluorobenzamide **204**.

Compound	**200**	**215**	**204**	**218**
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.952		1.738	
t_1	0.399	0.202	0.825	0.240
$\log(t_o/t_1)$	0.378		0.323	
% reaction	58%		53%	
% final	42%	42%	47%	55%
% accounted for	84%		102%	
k_{rel}(NBS)	1		0.86	

Compound	**200**	**215**	**204**	**218**
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	1.066		1.763	
t_1	0.389	0.064	0.824	0.135
$\log(t_o/t_1)$	0.438		0.330	
% reaction	64%		53%	
% final	36%	12%	47%	31%
% accounted for	48%		78%	
k_{rel}(NBS)	1		0.75	

Compound	**200**	**215**	**204**	**218**
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.880		1.631	
t_1	0.442	0.246	0.934	0.175
$\log(t_o/t_1)$	0.299		0.242	
% reaction	50%		43%	
% final	50%	56%	57%	43%
% accounted for	106%		100%	
k_{rel}(NBS)	1		0.81	

Compound	200	215	204	218
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.617		1.008	
t_1	0.284	0.138	0.537	0.127
$\log(t_o/t_1)$	0.337		0.273	
% reaction	54%		47%	
% final	46%	45%	53%	50%
% accounted for	91%		103%	
k_{rel}(NBS)	1		0.81	

Compound	200	215	204	218
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.685		1.299	
t_1	0.350	0.102	0.746	0.143
$\log(t_o/t_1)$	0.292		0.241	
% reaction	49%		43%*	
% final	51%	30%	57%	44%
% accounted for	81%		101%	
k_{rel}(NBS)	1		0.83	

10. The propylbenzamide **200** and the butylbenzamide **201**.

Compound	200	215	201	217
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	1.104		2.068	
t_1	0.612	0.179	1.017	0.198
$\log(t_o/t_1)$	0.256		0.308	
% reaction	45%		51%	
% final	55%	32%	49%	38%
% accounted for	87%		87%	
k_{rel}(NBS)	1		1.2	

Compound	200	215	201	217
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.734		1.455	
t_1	0.389	0.115	0.731	0.145
$\log(t_o/t_1)$	0.276		0.299	
% reaction	47%		50%	
% final	53%	31%	50%	40%
% accounted for	84%		90%	
k_{rel}(NBS)	1		1.1	

Compound	200	215	201	217
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.475		1.065	
t_1	0.316	0.081	0.588	0.092
$\log(t_o/t_1)$	0.177		0.258	
% reaction	33%		45%	
% final	67%	34%	55%	35%
% accounted for	101%		90%	
k_{rel}(NBS)	1		1.46	

Compound	200	215	201	217
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.973		1.871	
t_1	0.631	0.077	0.997	0.119
$\log(t_o/t_1)$	0.188		0.273	
% reaction	35%		47%	
% final	65%	16%	53%	25%
% accounted for	81%		78%	
k_{rel}(NBS)	1		1.45	

Compound	200	215	201	217
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.772		1.632	
t_1	0.534	0.062	0.886	0.124
$\log(t_o/t_1)$	0.160		0.265	
% reaction	31%		46%	
% final	69%	16%	54%	30%
% accounted for	85%		84%	
k_{rel}(NBS)	1		1.66	

11. The propylpentafluorobenzamide [F3, 7] and the butylpentafluorobenzamide **204**.

Compound	**203**	**216**	**204**	**218**
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.393		0.889	
t_1	0.211	0.078	0.403	0.147
$\log(t_o/t_1)$	0.270		0.344	
% reaction	46%		55%	
% final	54%	40%	45%	66%
% accounted for	94%		111%	
k_{rel}(NBS)	1		1.27	

Compound	**203**	**216**	**204**	**218**
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.666		1.437	
t_1	0.360	0.118	0.626	0.219
$\log(t_o/t_1)$	0.267		0.361	
% reaction	46%		56%	
% final	54%	35%	44%	61%
% accounted for	89%		105%	
k_{rel}(NBS)	1		1.35	

Compound	**203**	**216**	**204**	**218**
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	0.618		1.199	
t_1	0.312	0.096	0.497	0.166
$\log(t_o/t_1)$	0.297		0.382	
% reaction	50%		59%	
% final	50%	31%	41%	55%
% accounted for	81%		96%	
k_{rel}(NBS)	1		1.29	

12. The pentafluoropropyl derivative **203** and the pentafluorobutyl derivative **201**

Compound	**203**	**216**	**201**	**217**
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	1.662		3.658	
t_1	0.990	0.277	1.926	0.381
$\log(t_o/t_1)$	0.214		0.279	
% reaction	40%		47%	
% final	60%	33%	53%	42%
% accounted for	93%		95%	
k_{rel}(NBS)	1		1.30	

Compound	**203**	**216**	**201**	**217**
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	1.871		4.169	
t_1	1.282	0.282	2.180	0.398
$\log(t_o/t_1)$	0.164		0.282	
% reaction	31%		48%	
% final	69%	30%	52%	38%
% accounted for	99%		90%	
k_{rel}(NBS)	1		1.72	

Compound	**203**	**216**	**201**	**217**
^{1}H NMR signal	δ1.97 2H	δ5.15 1H	δ1.65 4H	δ5.08 1H
t_o	1.435		3.142	
t_1	0.844	0.200	1.343	0.287
$\log(t_o/t_1)$	0.231		0.369	
% reaction	41%		57%	
% final	59%	28%	43%	37%
% accounted for	87%		80%	
k_{rel}(NBS)	1		1.60	