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Mechanistic And Synthetic Investigations In Sulfonyl Chemistry And Acyl Transfer

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MECHANISTIC AND SYNTHETIC INVESTIGATIONS IN SULFONYL CHEMISTRY AND ACYL TRANSFER

by

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ABSTRACT

This thesis contains three chapters dealing with the organic chemistry of sulfonyl and carbonyl compounds. The first chapter describes the synthesis and rate studies of a series of β-methoxy sulfones and their unsubstituted parent compounds designed to test some basic ideas of the nature of the electronic effects of substituents in saturated systems. The substrates were designed to illustrate the effect of the change of the H_α-C_α-C_β-O dihedral angle on the rate of base-promoted H-D exchange reaction. The presence of a β-methoxy group affected the H-D exchange rates by factors varying from a few hundred to greater than ten thousands. This study leads to the conclusion that the effect of a β-alkoxy substituent cannot be accounted for by the conventional polar effect (i.e. inductive and field effects), but must involve a kinetic anomeric effect.

The second chapter describes synthesis, hydrolysis, and pK_a determination of sulfonamides and sulfonimides. Ethane-1,2-disulfonimide has been synthesized for the first time. More than twenty other sulfonamides and sulfonimides were synthesized to examine the effect of ring strain and a stereoelectronic effect in acidities and hydrolysis rates. It has been found that the acidities of five-membered cyclic sulfonimides are one to two orders of magnitude greater than six-membered cyclic sulfonimides or acyclic sulfonimides. It has also been found that ethane-1,2-disulfonimide

hydrolyses 430 times faster than its six-membered analogue, propane-1,3-disulfonimide, and 320 times faster than its open chain analogue, dimethanesulfonimide.

In the third chapter pH optimization in acyl transfer has been described. The reaction of amines with Ac_2O in water gave variable yields of the *N*-substituted acetamide. From the pK_a's of the amines and k_w and k_{OH} for Ac_2O, both k_{DN} and k_{GB} may be readily evaluated by fitting the pH-yield data to pH-yield or pH-product ratio profiles. The extent of general base catalysis is evidently dependent on the amount of steric hindrance and the pK_a of the amine. The reactions of PhCOCl with $PhCH_2NH_2$ and piperidine in aqueous solution show no sign of the general base assisted hydrolysis. A general equation for obtaining the maximum yield in competition with hydrolysis is presented and verified with the benzoylation and acetylation reactions.

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I would also like to thank Professor N.C. Payne for his doing the x-ray crystal structures.

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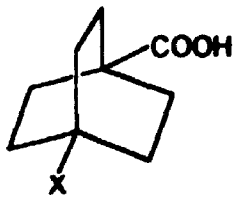
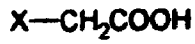
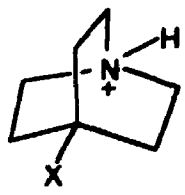
Variation of the Rate of Hydrogen-Deuterium Exchange in α-Sulfonyl Carbanions with the Orientation of a β-Alkoxyl Substituent. The Anomeric Effect as a Component of the Polar Substituent Effect

1.1 INTRODUCTION

Much effort[1] has been put into the endeavour to explain and predict the effect of substituents on the reactivities of organic molecules. Such effects can be broadly subdivided into electronic and steric components. When a substituent is attached to a σ-bonded system, its electronic effect is usually referred to as a polar effect[2]. It is generally put forward[3] that there are two basic effects by which a polar or charged substituent can affect some measurable property of a molecule or a reaction in a saturated system. One component is the field effect, which is assumed to be transmitted directly or through space, and the other is the inductive effect (or electronegativity effect) which involves successive polarization of the intervening σ bonds. Reynolds[4] has summarized the investigations of the relative importance of field and inductive effects upon the dissociation constants of aliphatic acids for the following systems,







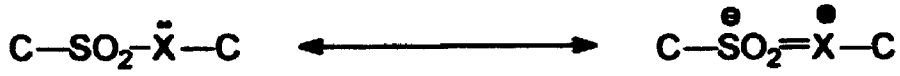
and concluded that the major polar effect on aliphatic acid acidities is the field effect, with no evidence for substantial inductive effect contributions.

Topsom *et al.*[5] found that the carbon-13 substituent c[illegible]al shift for a wide variety of unsaturated probe groups attached to position 1 of the bicyclo[2.2.2]octane molecule followed the field effect of 4-substituents with no evidence for any significant inductive effect.

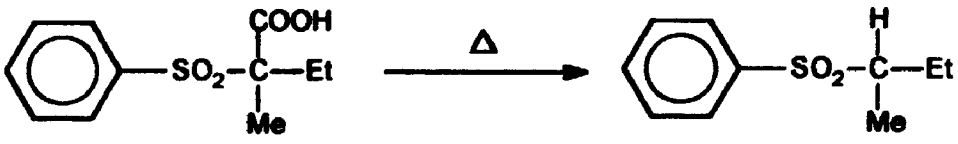
In 1977 Stirling and Thomas[6] reported that the detritiation of β-substituted acyclic phenyl sulfones, $PhSO_2CHTCH_2Z$, in ethanolic sodium ethoxide showed a very high dependence of rate on the nature of the substituent, Z ($\rho^* = 4.89$). The size of this effect raised the question of whether the conventional polar effect terms, i.e. field and inductive effects, were sufficient to account for these observations. This in turn raises the possibility that a third effect, namely the anomeric effect, might be contributing as well. Experimental evidence[7] has shown that this kind of electronic interaction takes place only when the electron pairs are properly oriented in space. To test such an idea it would therefore be necessary to determine if the effect of the substituent depended on the orientation of the substituent with respect to the hydrogen being removed in the hydrogen exchange process. Accordingly a study designed to determine the effect of the geometry of a β-alkoxyl group on the rate of α-sulfonyl carbanion formation was initiated by Dr. Rathore in this laboratory; this work was continued in the present study and the results described in this chapter. Before these results can be presented in detail, however, it is necessary to present

some background information on α-sulfonyl carbanions.

It has long been accepted that the delocalization of electron pairs shown below is important in sulfonyl compounds of the general structure $-SO_2-X-$, where X is an



atom with non-bonded or π-bonded electrons[8]. Since the chirality of α-chiral sulfones is preserved in hydrogen-deuterium exchange and other reactions believed to involve the α-sulfonyl carbanions, the geometry of the α-sulfonyl carbanion has received intensive experimental and theoretical attention[9]. The first observation of this phenomenon was made by Taylor and Verhoek[10] in 1959. They carried out a decarboxylation reaction using an optically

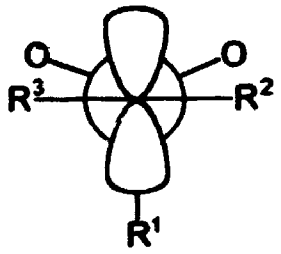


1 2

active compound (1) which gave an optically active product (2) (stereochemistry unknown). They assumed that the carbanion was an intermediate.

One commonly used procedure provided by Cram[11] and co-workers for studying the steric stability of the carbanion is comparison of the rate of base catalyzed H-D exchange reaction (k_{ex}) with the rate of racemization (k_{rac}). Racemization of pyramidal form is due to rotation around the C_α-S bond followed by pyramidal inversion, while that of the planar form is caused by rotation around the C_α-S bond. The values of k_{ex}/k_{rac} were employed as criteria of the stereochemical pathway for reaction. When $k_{ex}/k_{rac} > 1$, the reaction should proceed through an intrinsically asymmetric carbanion and lead to retention of configuration. When $k_{ex}/k_{rac} = 1$, the reaction proceeds through a symmetric carbanion and racemization is the net result.

Corey *et al.*[12] suggested that α-sulfonyl carbanions are asymmetric because of restricted rotation about the C_α-S bond and that the hybridization at C_α in the carbanion is either sp^2 or close to it (see 3).



3

Planar (sp^2)

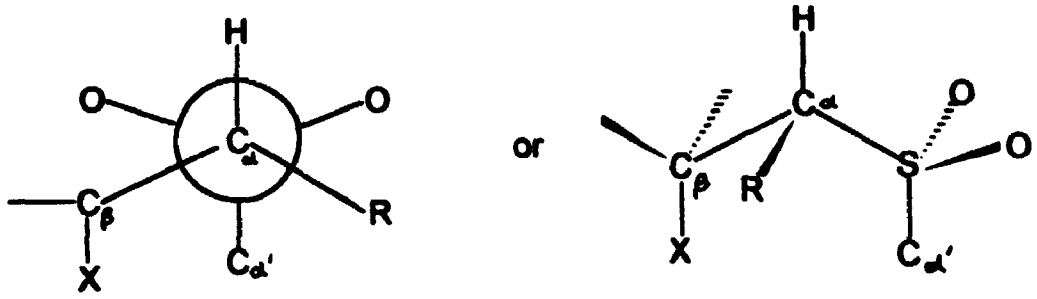
Wolfe *et al.*[13] made a simple *ab initio* MO calculation of an α-sulfonyl carbanion and proposed that the participation of 3*d* orbitals on the S atom would not

contribute to its stabilization. They suggested that the pyramidal structure is the most stable configuration. Later Wolfe *et al.*[14] carried out a calculation at the 3-21G* level and found that the participation of 3*d* orbitals on the S atom does contribute to the stability of the α-sulfonyl carbanion. They concluded that the α-sulfonyl carbanion is planar. Bors and Streitwieser[15] also made the calculation at the 3-21G* level and confirmed the results of Wolfe *et al.* Bors and Streitwieser found the conformation in which the electron lone pair in α-sulfonyl carbanion is located between the two oxygens is a thermodynamic minimum on the potential surface that has a rotational barrier of over 14 kcal mol^{-1}. This result indicates that α-sulfonyl carbanion (3) requires rather high energy for rotation and this leads to retention of configuration.

Boche *et al.*[16] and Gais *et al.*[17] have recently examined the solid state structure of lithium-coordinated α-sulfonyl carbanions using single crystal x-ray structure determination and found that the lone pair of electrons at the anionic α-C atom adopts a *gauche* conformation to the two oxygen atoms on sulfur and periplanar to the S-C bond because this conformation is the most thermodynamically stable. It seems that α-carbon atoms having phenyl substituents are largely planar because of the partial stabilization of the negative charge by p_π-p_π interactions with the phenyl ring[18]. Alkyl substituted sulfones, on the other hand, have a pyramidalized α-C atom. Boche[18]

concluded that the energy difference between planar and pyramidalized α-C atoms is small.

Bors and Streitwieser concluded that the α-sulfonyl carbanions show a strong stereoelectronic preference for the conformation depicted as 3. The ease of formation of an α-sulfonyl carbanion, >C-SO_2-, as discussed above, depends on the orientation of the bond being cleaved to yield the carbanion. The readiest deprotonations, for example,



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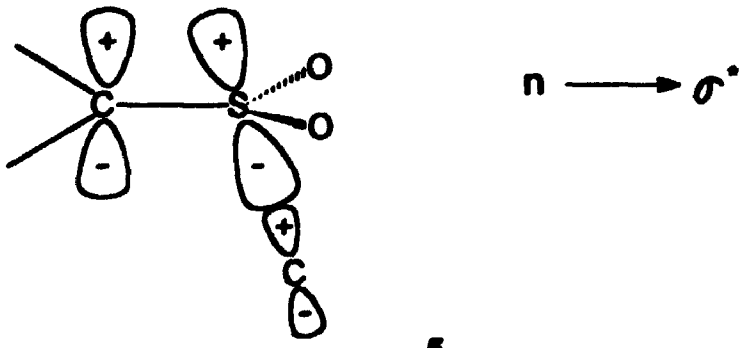
are observed when the C_α-H bond is shown in 4, i.e., aligned with the internal bisector of the O-S-O angle, or, in other words, antiperiplanar to the S-C_α bond.

Wolfe *et al.*[11] suggested that this conformational preference (4) in α-sulfonyl carbanion may be ascribed to the donation of the lone pair electrons from the anionic α-C

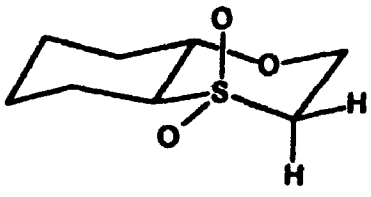


5

atom to the antibonding orbital (σ^*) of S-C_α bond (5), i.e. a version of the anomeric effect.

As mentioned earlier Stirling and Thomas found that the deuteration of β-substituted acyclic phenyl sulfones $PhSO_2CHTCH_2Z$, showed an rate increase of about 5 x 10^4 on changing Z from CH_3 to OPh. A Taft plot indicated a very strong dependence of the rates on the electronic properties of this substituent (Z). In the light of (a) the clear geometric requirements of α-sulfonyl carbanions (b) the large substituent dependence, it seemed that the dependence of the rate of α-sulfonyl carbanion formation on the geometry of a particular β-substituent would be an ideal system in which to examine the general question of the nature of electronic effects in chemistry.

In the first stage of this project King and Rathore[19] found that α-equatorial hydrogens exchange faster than α-axial, the rate differences in six-membered cyclic sulfones 7, 8, and 9 being, respectively, 200, >25, and 90. This result was precisely what was expected on the basis of (a) the antiperiplanar orientation of the α-equatorial hydrogens



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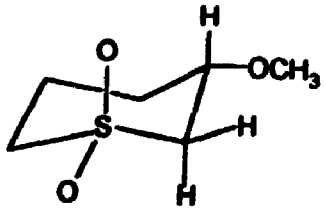

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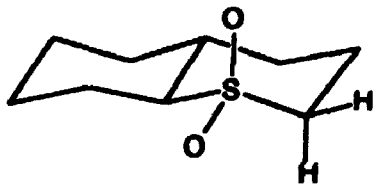


(9)

k_{ex} (M^{-1} s^{-1}) 3.2 x 10^{-2} 4.5 x 10^{-4} 1.2 x 10^{-6}

with respect to the S-C_α bond and (b) the comparative difficulty for the α-axial hydrogens to achieve this arrangement.

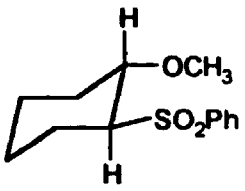
By comparing the rates of H-D exchange of **8** and **9** (4.5×10^{-4} M^{-1} s^{-1} and 1.2×10^{-6} M^{-1} s^{-1} respectively) it was shown that the presence of a β-synclinal oxygen accelerates the reaction by a factor of 370. An antiperiplanar oxygen, however, as in **7** increases the rate more than 10^4 times relative to **9**. Alternatively, comparing **7** with **8**, changing the oxygen from the synclinal to the antiperiplanar orientation increases the rate by 71-fold. They concluded that the important factor in the rapid exchange of the α-equatorial hydrogen in **7** relative to **8** is the orientation of the hydrogen with respect to the oxygen - specifically, the antiperiplanar geometry in **7**. They suggested that the incipient carbanion in the transition state is stabilized by donation of its electrons into the carbon-oxygen σ^* orbital, i.e., that it is a "kinetic anomeric effect".[20]

Extending this study to be carried out in this laboratory was carried out by Rathore who showed in the preliminary experiments on the H-D exchange for β-methoxy cyclohexyl system sulfones **10** and **11** which have the approximate dihedral angles O(3)-C(2)-C(1)-H(1) of 180° in **10** and 60° in **11**, that sulfone **10** exchanges faster than **11** under the same conditions. This preliminary experiment indicated that these H-D exchange reactions are indeed affected by the geometry of the phenylsulfonyl group and the

methoxy group.

In order to provide a more complete picture of the geometry-dependence of the substituent effect in α-sulfonyl carbanion formation it is necessary to synthesize the β-alkoxyl sulfones which have other O(3)-C(2)-C(1)-H(1) dihedral angles such as 0°, 120°, and to compare their rates of reaction to "parent compounds" which do not have the β-substituent groups.

In the present study we have synthesized six bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane system sulfones which have a methoxy group beta to the sulfonyl group to examine the effect of various orientation of the oxygen substituent on the rates of the base catalyzed H-D exchange reactions (see Scheme 1.1). To confirm the structures of these compounds and to obtain precise information on the dihedral angles in these starting materials the x-ray crystal structures of these compounds have been determined by Professor N. C. Payne in this department. A systematic study of rates of H-D exchange on various β-methoxy sulfones is described in the present chapter.



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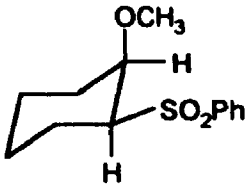

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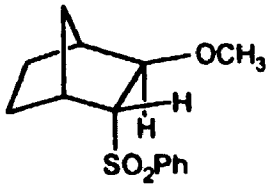

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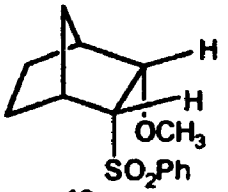

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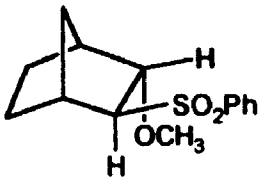

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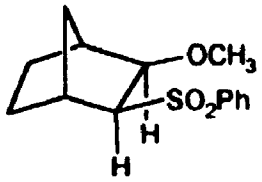

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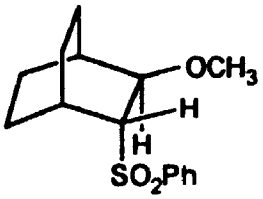

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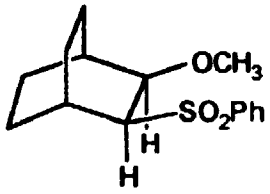

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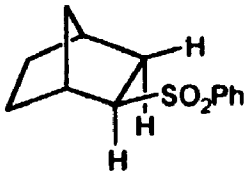

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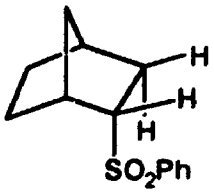

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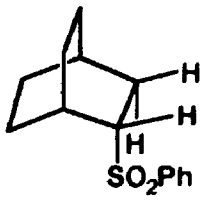

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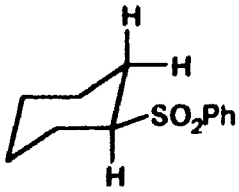

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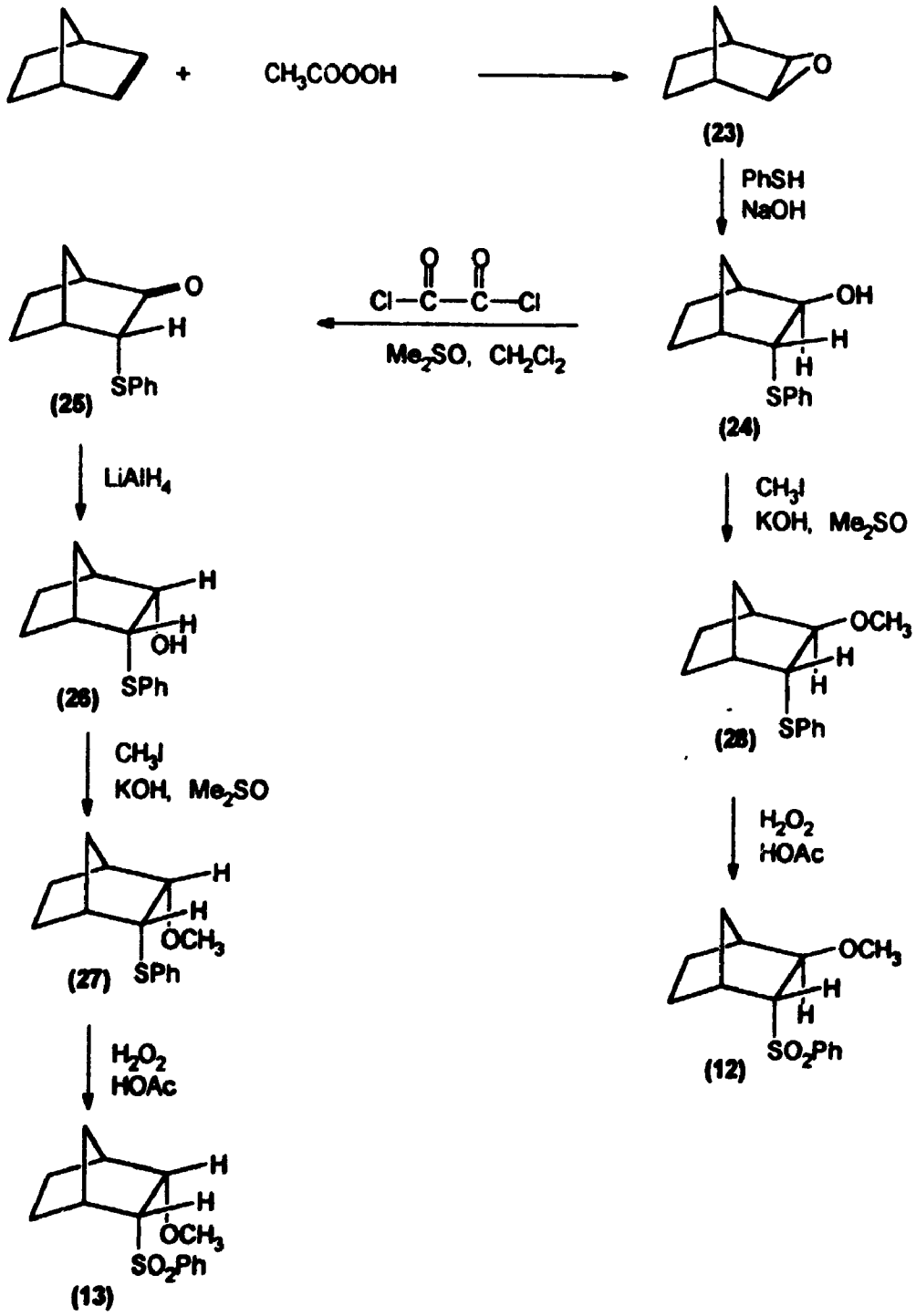
Scheme 1.1

1.2 Results and Discussion

1.2.1 Preparation of Sulfones and NMR Spectral Analysis

In this study 12 cyclic and bicyclic sulfones were synthesized. The preparations of the intermediates to four bicyclo[2.2.1] sulfones followed the similar routes of Kleinfelter *et al.*[21] The structures of compounds **12**, **13**, **14**, **15**, **16**, and **17** were elucidated by IR, ^{1}H NMR, ^{13}C NMR, exact mass, and confirmed by x-ray crystal structure determination. Compounds **18**, **19**, **20** were determined by IR, ^{1}H NMR, ^{13}C NMR, and exact mass.

The synthesis of *endo*-3-phenylsulfonyl-*exo*-2-methoxy-norbornane (**12**) and *endo*-3-phenylsulfonyl-*endo*-2-methoxy-norbornane (**13**) began with the treating norbornene with peracetic acid to form *exo*-norbornene oxide (**23**) in 71% yield. *exo*-Norbornene oxide (**23**) reacted with thiophenol in the presence of sodium hydroxide to give the trans product, *endo*-3-phenylthio-*exo*-2-norbornanol (**24**) in 90% yield using the procedure of Kleinfelter *et al.*[22] It is important to choose a suitable oxidation method in converting **24** to *endo*-3-phenylthio-2-norbornanone (**25**). Chromic acid, for example, was unsuccessful because the sulfide was oxidized to the sulfone more readily than the alcohol to the ketone. Kleinfelter *et al.* used DMSO and *N,N*-dicyclohexyl-carbodi-imide as the oxidation reagent and found that the dicyclo-hexylurea (by-product), was a contaminant which could not be completely removed. We found that the conversion of **24** to


+ CH3COOOH
(23)
PhSH
NaOH
(24)
Cl—C—C—Cl
Me2SO, CH2Cl2
(25)
LiAlH4
(26)
CH3I
KOH, Me2SO
(27)
H2O2
HOAc
(13)
CH3I
KOH, Me2SO
(28)
H2O2
HOAc
(12)

Scheme 1.2

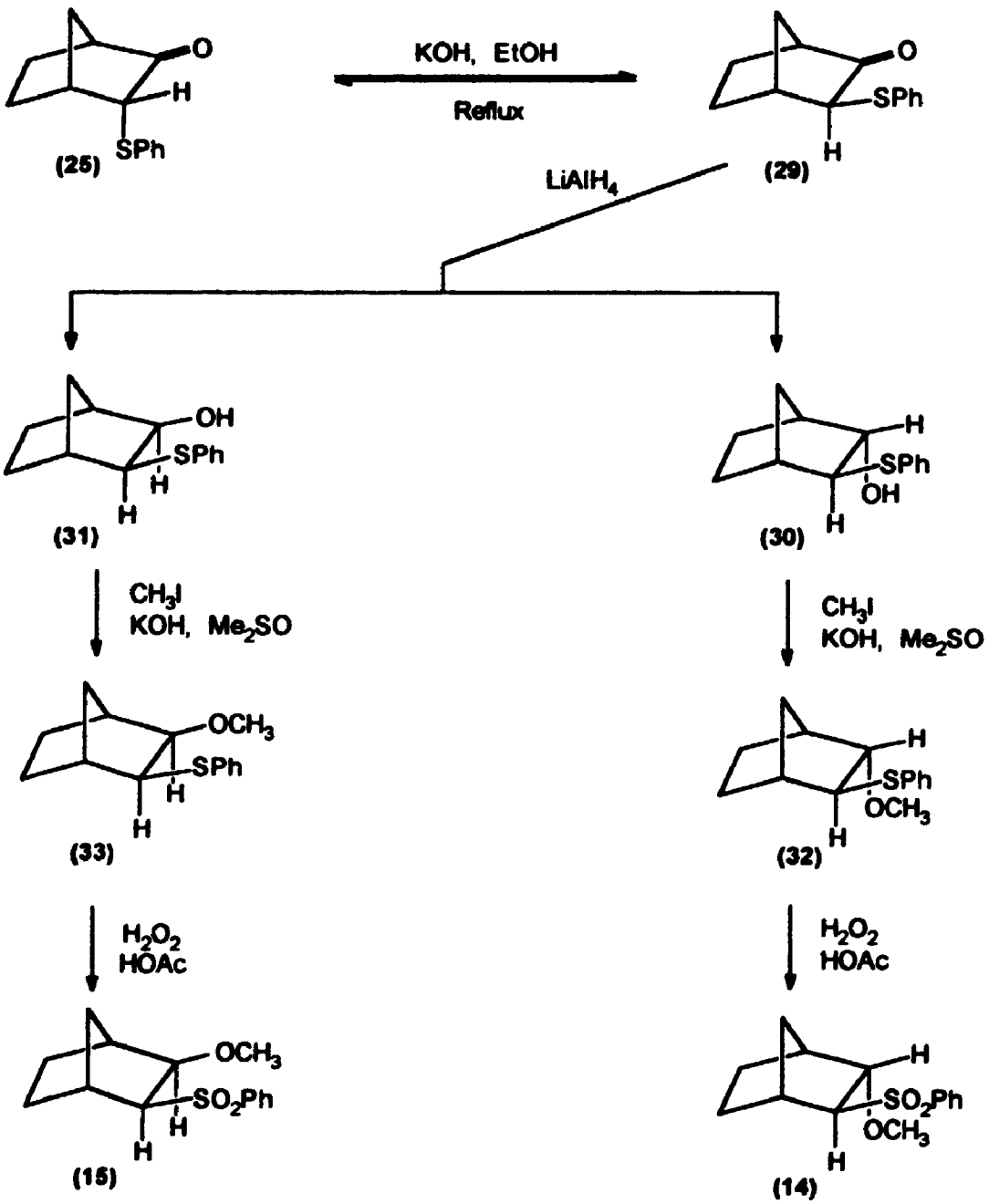
endo-3-phenylthio-2-norbornanone (25) could be conveniently carried out in 99% yield without any difficulty in purification, by treating 24 with oxalyl chloride and dimethyl sulfoxide using the procedure of Omura and Swern[22] for oxidation of alcohols. Compound 25 was reduced using lithium aluminum hydride to give *endo*-3-phenylthio-*endo*-2-norbornanol (26) in 94% yield; this was reacted with iodomethane and potassium hydroxide in DMSO to form *endo*-3-phenylthio-*endo*-2-methoxynorbornane (27) in 99% yield using the procedure of Johnstone and Rose[23] for alkylation of alcohols. Treatment of 27 with hydrogen peroxide in acetic acid gave *endo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane (13) in 95% yield (see Scheme 1.2).

To synthesize *endo*-3-phenylsulfonyl-*exo*-2-methoxy-norbornane (12) *endo*-3-phenylthio-*exo*-2-norbornanol (24) was treated with hydrogen peroxide in acetic acid to give (91% yield) *endo*-3-phenylsulfonyl-*exo*-2-norbornanol (28) which was methylated as above to give 12 (89% yield) (see Scheme 1.2). Rathore in this laboratory also made compound 12 by using the similar procedure of Cristol *et al.*[24] who synthesized *endo*-3-phenylsulfonyl-*exo*-2-ethoxynorbornane. Addition of benzenesulfenyl chloride to norbornene formed *endo*-3-phenylthio-*exo*-2-chloro-norbornane which was oxidized using hydrogen peroxide to give *endo*-3-phenyl-sulfonyl-*exo*-2-chloro-norbornane; this was treated with sodium methoxide in methanol to give 12.

Scheme 1.3 outlines the preparation of *exo*-3-phenyl-

sulfonyl-*endo*-2-methoxynorbornane (**14**) and *exo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane (**15**). The first step in synthesis of **14** was the treatment of *endo*-3-phenylthio-2-norbornanone (**25**) with potassium hydroxide in aqueous ethanol to form a mixture of **25** (40%) and *exo*-3-phenylthio-2-norbornanone (**29**) (60%). These two isomers can be identified by the different chemical shifts of the H next to the phenylthio group. The *exo*-H in **25** showed a signal at δ 3.71 (J = 4.5 Hz), and that of the *endo*-H in **29** at δ 3.30 (J = 3.3 Hz). Separation of **25** and **29** by column chromatography using diethyl ether and petroleum ether as the eluate gave pure **29**. Compound **29** was reduced using lithium aluminum hydride to give a mixture of *exo*-3-phenylthio-*endo*-2-norbornanol (**30**) (76%), *exo*-3-phenylthio-*exo*-2-norbornanol (**31**) (19%), and *endo*-3-phenylthio-*endo*-2-norbornanol (**26**) (5%). Pure **30** was obtained by recrystallization of the mixture of **30** and **31**. Compound **30** was methylated with iodomethane and potassium hydroxide to give *exo*-3-phenylthio-*endo*-2-methoxynorbornane (**32**) in 95% yield. Treatment of **32** with hydrogen peroxide in acetic acid gave *exo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane (**14**) in 95% yield.

The synthesis of *exo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane (**15**) encountered difficulties in separation and purification. Separation of the mixture of **30**, **31** and **26** using column chromatography was incomplete giving a mixture of **30** (20%) and **31** (80%). The mixture of **30** and **31** was

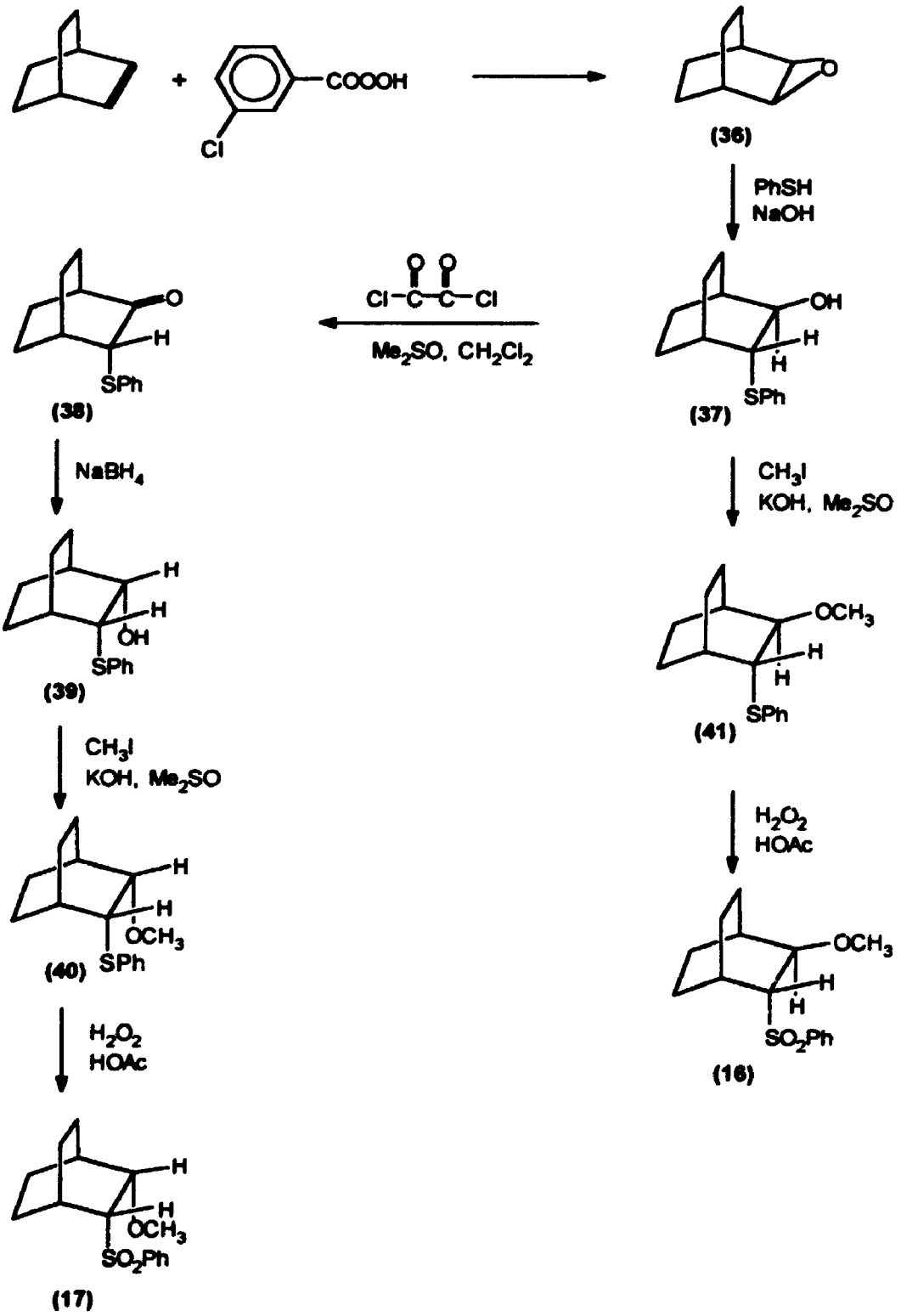

KOH, EtOH
Reflux
LiAlH4
(25)
(29)
(31)
(30)
CH3I
KOH, Me2SO
(33)
(32)
H2O2
HOAc
(15)
(14)

Scheme 1.3

methylated as above to give a mixture of **32** and **33**. This mixture was oxidized using hydrogen peroxide to give a mixture of **14** and **15** in 95% yield. Pure **15** was obtained from this by column chromatography using ethyl acetate (20%) and petroleum ether (80%) as the eluate.

The synthesis of *trans*-3-phenylsulfonyl-2-methoxy-bicyclo[2.2.2]octane (**16**) was carried out as outlined in Scheme 1.4. Bicyclo[2.2.2]oct-2-ene was reacted with 3-chloroperoxybenzoic acid to give 2,3-epoxybicyclo[2.2.2]-octane (**36**). Treatment of **36** with sodium thiophenoxide gave *trans*-3-phenylthio-2-bicyclo[2.2.2]octanol (**37**) in 90% yield. Compound **37** was reacted with iodomethane and potassium hydroxide to form *trans*-3-phenylthio-2-methoxy-bicyclo[2.2.2]octane (**41**) in 91% yield, which was oxidized using hydrogen peroxide in acetic acid to give *trans*-3-phenylsulfonyl-2-methoxybicyclo[2.2.2]octane (**16**) in 85% yield. Rathore in this laboratory also synthesized compound **16** by treating bicyclo[2.2.2]oct-2-ene with benzenesulfenyl chloride to give *trans*-3-phenylthio-2-chloro-bicyclo[2.2.2]-octane which was oxidized to *trans*-3-phenylsulfonyl-2-chloro-bicyclo-[2.2.2]octane; this was refluxed with sodium methoxide in methanol to form **16**.

The synthesis of *cis*-3-phenylsulfonyl-2-methoxybicyclo-[2.2.2]octane (**17**) also used *trans*-3-phenylthio-2-bicyclo-[2.2.2]octanol (**37**) converting it in 99% yield with dimethyl sulfoxide and oxalyl chloride into 3-phenylthio-2-bicyclo-[2.2.2]octanone (**38**). Compound **38** was reduced using sodium


COOOH
Cl
(36)
PhSH
NaOH
OH
H
SPh
(37)
Cl–C–C–Cl
Me2SO, CH2Cl2
O
H
SPh
(38)
NaBH4
CH3I
KOH, Me2SO
OCH3
H
SPh
(41)
H
H
OH
SPh
(39)
CH3I
KOH, Me2SO
H
H
OCH3
SPh
(40)
H2O2
HOAc
OCH3
H
SO2Ph
(16)
H2O2
HOAc
H
H
OCH3
SO2Ph
(17)

Scheme 1.4

borohydride in isopropanol to give a mixture of **37** (22%) and *cis*-3-phenylthio-2-bicyclo[2.2.2]octanol (**39**) (78%). Lithium aluminum hydride reduction of **38** was also investigated and afforded a mixture of **37** (37%) and **39** (63%). Compounds **37** and **39** were separated by column chromatography over silica gel eluting with a mixture of diethyl ether and petroleum ether. Compound **39** was methylated to give *cis*-3-phenylthio-2-methoxybicyclo-[2.2.2]octane (**40**) in 96% yield followed by oxidation using hydrogen peroxide to give *cis*-3-phenylsulfonyl-2-methoxy-bicyclo[2.2.2]octane (**17**) in 96% yield (see Scheme 1.4).

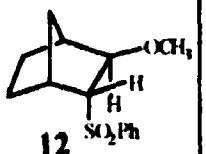
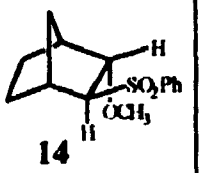
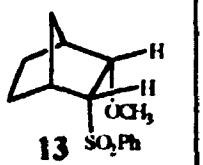
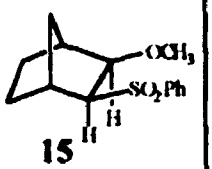
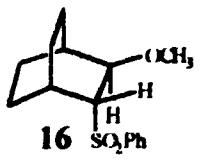
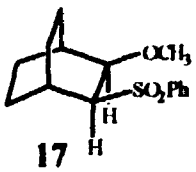
exo-2-Phenylsulfonylnorbornane (**18**) was prepared by following the procedure of Cristol and Brindell[25] who prepared *exo*-2-*p*-tolyl-sulfonyl-norbornane. Thiophenol was added *exo* to norbornylene *via* a free-radical intermediate to form exclusively *exo*-2-phenylthionorbornane (**34**) in 84% yield[26]. Treatment of compound **34** with hydrogen peroxide gave **18** in 99% yield. *endo*-2-Phenylsulfonylnorbornane (**19**) was prepared by [2+4] cycloaddition using phenyl vinyl sulfone and cyclopentadiene which followed the Alder[27] rule of predominant *endo* addition to form the *endo*-2-phenylsulfonyl-5-norbornene (**35**) as a major product which was reduced to *endo*-2-phenylsulfonylnorbornane (**19**) by Pd-C and formic acid. 2-Phenylsulfonylbicyclo[2.2.2]octane (**20**) was prepared by the same procedure as compound **18**.

trans-2-Phenylsulfonyl-1-methoxycyclohexane (**11**), *cis*-2-phenylsulfonyl-1-methoxycyclohexane (**10**), and cyclohexyl

phenyl sulfone (21) were prepared by Rathore in this laboratory; the mp, ^{1}H NMR, ^{13}C NMR, IR, and exact mass spectra were carried out in this study. Treatment of cyclohexene with sulfuryl chloride and phenyl thioacetate in carbon tetrachloride at 0 °C gave *trans*-2-phenylthio-1-chlorocyclohexane which was reacted with methanol in basic solution to form *trans*-2-phenylthio-1-methoxycyclohexane. This was oxidized by treating with hydrogen peroxide in acetic acid to give 11. *trans*-2-Methoxy-1-bromocyclohexane was reacted with thiophenol and potassium hydroxide in 2-butanol to give *cis*-2-phenylthio-1-methoxycyclohexane. This was oxidized by treating with hydrogen peroxide in acetic acid to give 10. Treatment of cyclohexene with thiophenol at 50 °C for 4 h gave cyclohexyl phenyl sulfide which was oxidized to form 21.

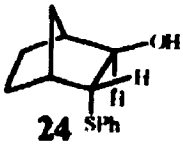
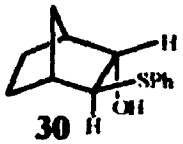
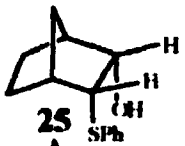
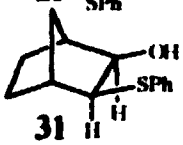
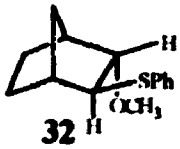
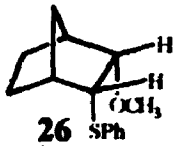
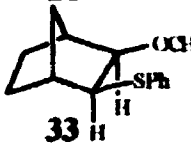
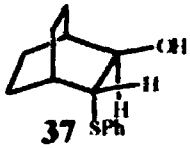
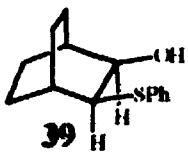
The chemical shifts (δ) and coupling constants (J) of the bicyclic sulfides and sulfones are listed in Tables 1.1 and 1.2. In analyzing the data from these tables several general trends may be noted. The *exo*-2 protons of the substituted norbornanols and methoxy sulfones appear at lower fields than the corresponding *endo*-2 protons. Analysis of the data from Table 1.2 reveals that sulfide groups, whether *exo* or *endo*, shield their corresponding eclipsed hydrogens, with the shielding effect being significantly greater for the *endo* orientation (e.g. *exo*-2 protons, 4.18 - 4.06 = 0.12; *endo*-2 protons, 3.90 - 3.56 = 0.34). In contrast to the effect of eclipsed sulfide,

Table 1.1 The NMR Spectral Data for the Bicyclic Sulfones[a]

Compound	Chemical shift, ppm (*J*, Hz)			
	2-*exo*	2-*endo*	3-*exo*	3-*endo*
 **12**		3.65 (t) (2.4)	3.14 (m) (~3.0)	
 **14**	4.05 (t) (3.6)			2.73 (dd) (4.1, 2.4)
 **13**	3.81 (dd) (9.7, 4.2)		3.41 (dd) (9.8, 3.7)	
 **15**		3.22 (dd) (9.6, 6.8)		3.02 (dd) (9.9, 6.9)
 **16**		3.77 (m) (~3.5)	3.05 (m) (~1.6)	
 **17**		3.53 (dd) (9.8, 4.9)		3.38 (dd) (8.3, 1.2)

a. The solvent used in the NMR is CD_3Cl; t = triplet; m = multiplet; dp = doublet of doublets.

Table 1.2 The NMR Spectral Data for the Bicyclic Sulfides[a]

Compound	Chemical shift, ppm (*J*, Hz)			
	2-*exo*	2-*endo*	3-*exo*	3-*endo*
 **24**		3.56 (t) (2.2)	3.29 (m) (~2.1)	
 **30**	4.06 (t) (3.6)			2.85 (t) (3.1)
 **25**	4.18 (m) (~9.4)		3.62 (dd) (9.4, 4.2)	
 **31**		3.90 (d) (6.4)		3.36 (dd) (6.3, 1.9)
 **32**	3.47 (dt)			2.90 (t)
 **26**	3.79 (dd) (9.6, 4.1)		3.69 (dd) (9.4,3.9)	
 **33**		3.47 (d)		3.41 (d)
 **37**		3.73 (m) (~3.1)	3.24 (t) (4.7)	
 **39**		4.01 (t) (8.4)		3.62 (t) (10.6)

a. The solvent used in the NMR is CD_3Cl; t = triplet; d = doublet; m = multiplet; dd = doublet of doublets.

sulfone groups deshield both eclipsed *exo* and *endo* hydrogens (e. g. *exo*-2 protons, 3.81 - 4.05 = -0.24; *endo*-2 protons, 3.22 - 3.65 = -0.43). In the Tables 1.1 and 1.2 it is apparent that all of the *cis*-isomers have relative larger coupling constants than the *trans*-isomers and the results are consistent with the results of Leyden and Cox[28] for norbornane.

1.2.2 The X-ray Crystal Structure Determination

The x-ray crystal structures of compound **12**, **13**, **14**, **15**, **16**, and **17** have been determined (see Figures 1.1 to 1.3). The dihedral angles of these five compounds are listed in Tables 1.11 to 1.13 and bond lengths and angles are listed in Tables 1.14 to 1.16 (see experimental part). It is interesting to note that the crystal unit cell of compound **15** contains two conformations; and that of **13** has four conformations. The bond angles of O(1)-S-O(2) in all of these sulfones are in the normal range[29]. The bond angle of O(1)-S-C(3) (105.2°) in **17** is five degrees smaller than that of its *trans*-isomer, **16** (110.3°). The bond angle of O(2)-S-C(3) (112.6°) in **17**, however, is five degrees larger than that of its *trans*-isomer, **16** (107.6°). The bond angle of O(3)-C(2)-C(7) (107.5°) in **12** is 6.6 degrees smaller that of its analogue **14** (114.1°). It is interesting to look at the torsion angles in these sulfones. The most important dihedral angle for the purposes of this study is the H(3)-C(3)-C(2)-O(3) angle. Those dihedral angles of the

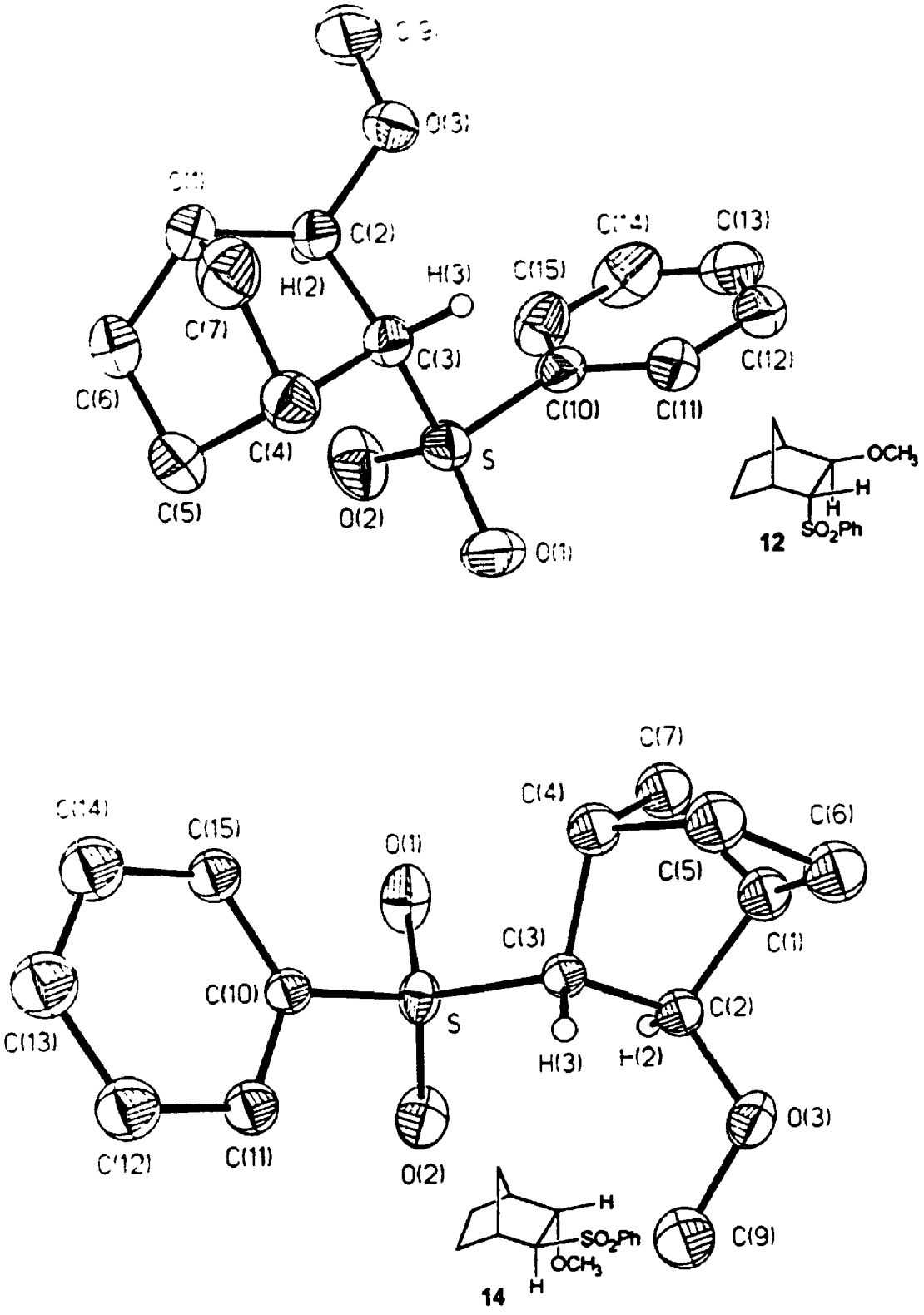


Figure 1.1 The x-ray crystal structures of *endo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane (**12**) and *exo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane (**14**)

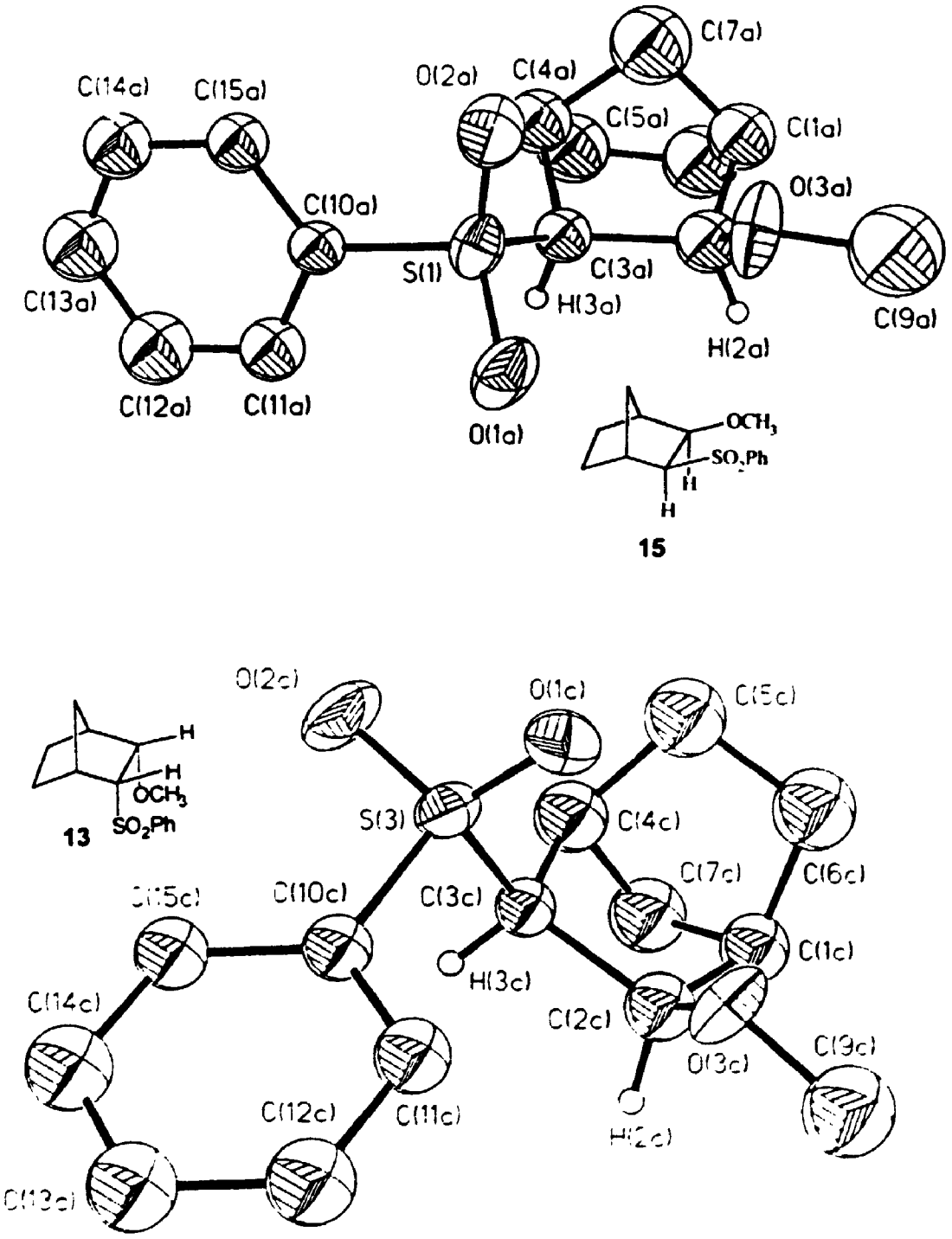


Figure 1.2 The x-ray crystal structures of *endo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane (**13**) and *exo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane (**15**)

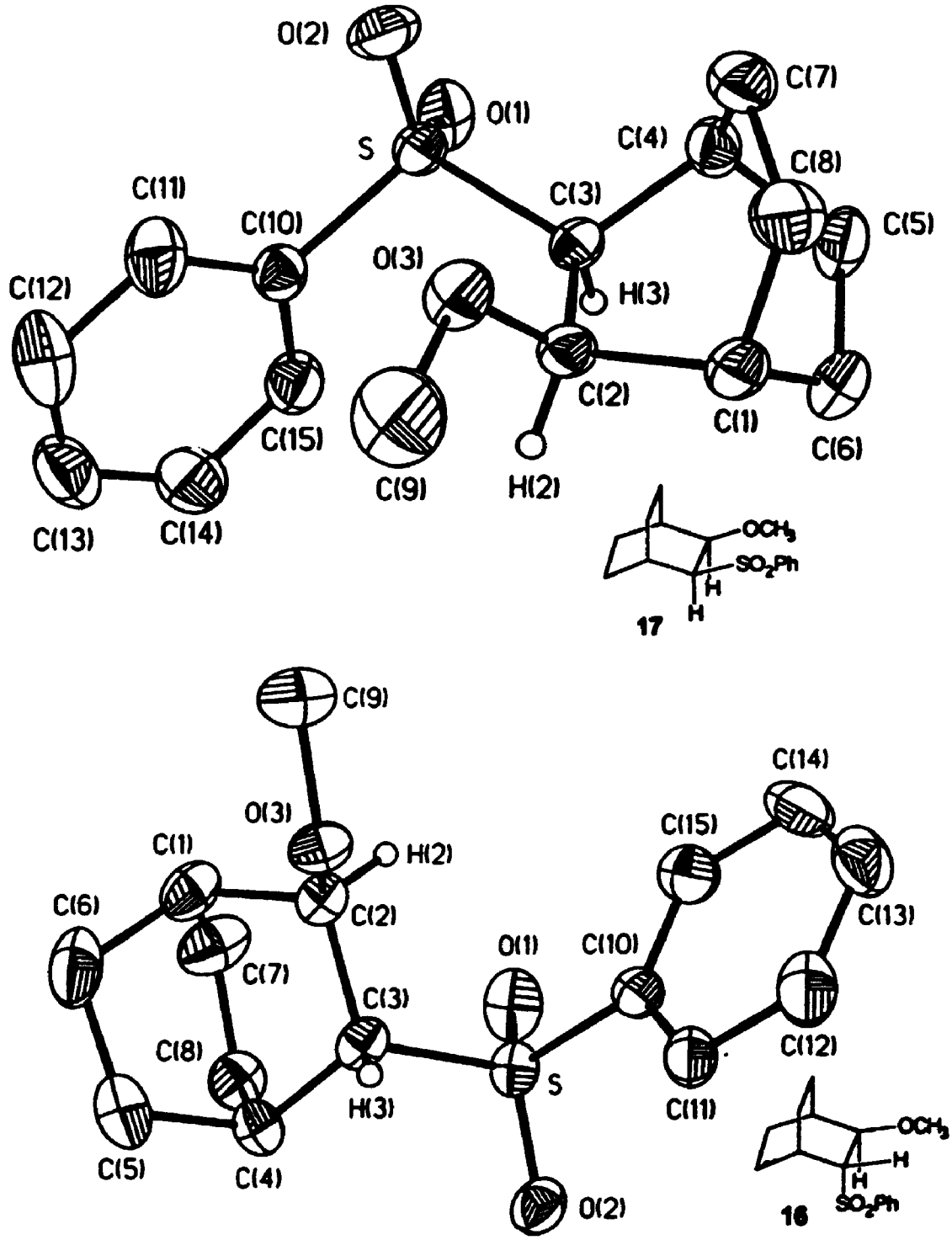


Figure 1.3 The x-ray crystal structures of *trans*-3-phenylsulfonyl-2-methoxybicyclo[2.2.2]octane (**16**) and *cis*-3-phenylsulfonyl-2-methoxybicyclo[2.2.2]octane (**17**)

H(3)-C(3)-C(2)-O(3) in the *trans*-isomers **12**, **14** and **16** would be expected to be 0° if these molecules were not twisted. These sulfones are indeed twisted to varying degrees, presumably because of the interaction of the two bulky methoxy and phenylsulfonyl groups in the neighbourhood. It was found that the dihedral angles of H(3)-C(3)-C(2)-O(3) in *endo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane (**12**) is 9.5° which is 3.1 degrees larger than that of its analogue **14** (6.4°). The same tendency was also found in the *trans*-bicyclo[2.2.2] sulfone, **16** which has the H(3)-C(3)-C(2)-O(3) dihedral angle 6.2°. The dihedral angle of H(3)-C(3)-C(2)-O(3) in the *cis*-isomers, **13**, **15** and **17** would be expected to be 120° if these molecules were not twisted. it was surprising to find that the *cis*-bicyclo[2.2.2] sulfone, **17** has a dihedral angle of H(3)-C(3)-C(2)-O(3) -147.6°, indicating that the *cis*-bicyclo[2.2.2] sulfone, **17** is twisted by 27.6° from the 120° angle. This may be understandable because the two bulky groups, the methoxy and phenylsulfonyl are eclipsed. In the conformation A of *cis*-bicyclo[2.2.1] sulfone, *exo*-3-phenylsulfonyl-*exo*-2-methoxy-norbornane (**15**), the dihedral angle of H(3)-C(3)-C(2)-O(3) is -132.8°. In the conformation B this angle, however, is -123.9°; i.e. there is a difference of 9 degrees between these two conformations. It is notable that conformation B is quite close to the untwisted conformation, in which the dihedral angle H(3)-C(3)-C(2)-O(3) would be 120°. For *endo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane (**13**), the difference

of the dihedral angles H(3)-C(3)-C(2)-O(3) among the four conformations is 8.8°. The largest H(3)-C(3)-C(2)-O(3) dihedral angle of 135.3° is found in conformation B which twisted 15.3 from 120°. Comparing the *endo cis*-isomer, **13** with the *exo cis*-isomer, **15**, one may see that the *endo cis*-isomer is 2.5 degrees more twisted than the *exo cis*-isomer. Comparing these dihedral angles H(3)-C(3)-C(2)-O(3) in the *cis*-bicyclic sulfones, it may be concluded that the *cis*-bicyclo[2.2.1] sulfones **13** and **15** are much less twisted than the *cis*-bicyclo[2.2.2] sulfone **17** (at least 12°), presumably because the ring of the bicyclo[2.2.1]heptane is more rigid than that of bicyclo[2.2.2]octane skeleton.

1.2.3 Kinetics of the H-D Exchange Reaction

The H-D exchange rates of the sulfones in this study were measured under pseudo-first-order conditions by ^{1}H NMR spectroscopy in sodium deuteroxide using a mixed solvent, either acetonitrile-d_3 and deuterium oxide (1:1 v/v) at 21 °C , or dioxane-d_8 and deuterium oxide (1:1 v/v) at 21 °C or 77 °C. Figure 1.4 shows the plot of concentration *vs.* time for the base catalyzed H-D exchange reaction of *trans*-3-phenylsulfonyl-2-methoxybicyclo-[2.2.2]octane (**16**). The lines are calculated from the first-order rate equation and the points are experimental. One may see that the experimental and theoretical calculation agree. This indicates that the H-D exchange reaction of **16** is first order under the pseudo-first-order conditions. The pseudo

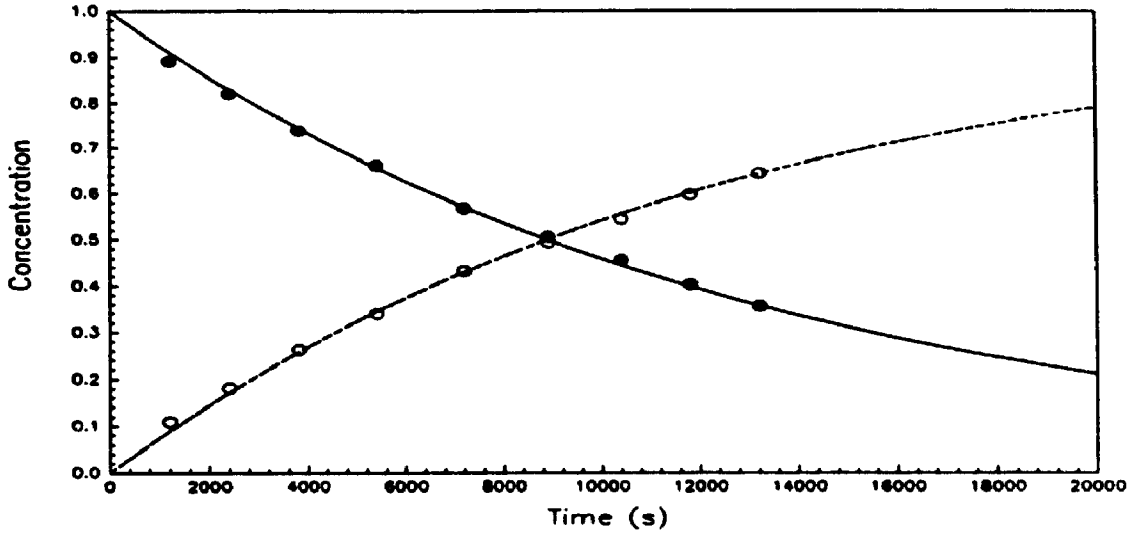


Figure 1.4 The plot of concentration *vs.* time for the H-D exchange reaction of *trans*-3-phenylsulfonyl-2-methoxy-bicyclo[2.2.2]octane (**16**) in 0.15 M sodium deuteroxide using $CD_3CN:D_2O$ (1:1) as solvent at 21 °C. The solid line is calculated from the first-order rate equation (k_{obs} = 7.5 x 10^{-5} s^{-1}) for the starting material and the dashed line is for the H-D exchange product; the points are experimental.

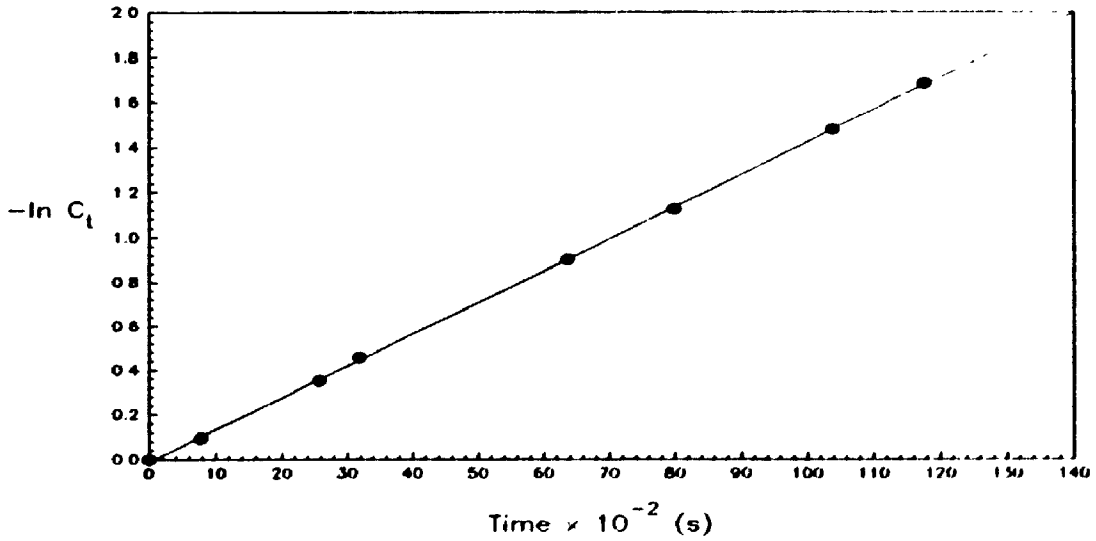


Figure 1.5 The plot of -ln C_t *vs.* time (s) for the H-D exchange reaction of *endo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane (**12**) in 0.125 M sodium deuteroxide using $CD_3CN:D_2O$ (1:1) as solvent at 21 °C.

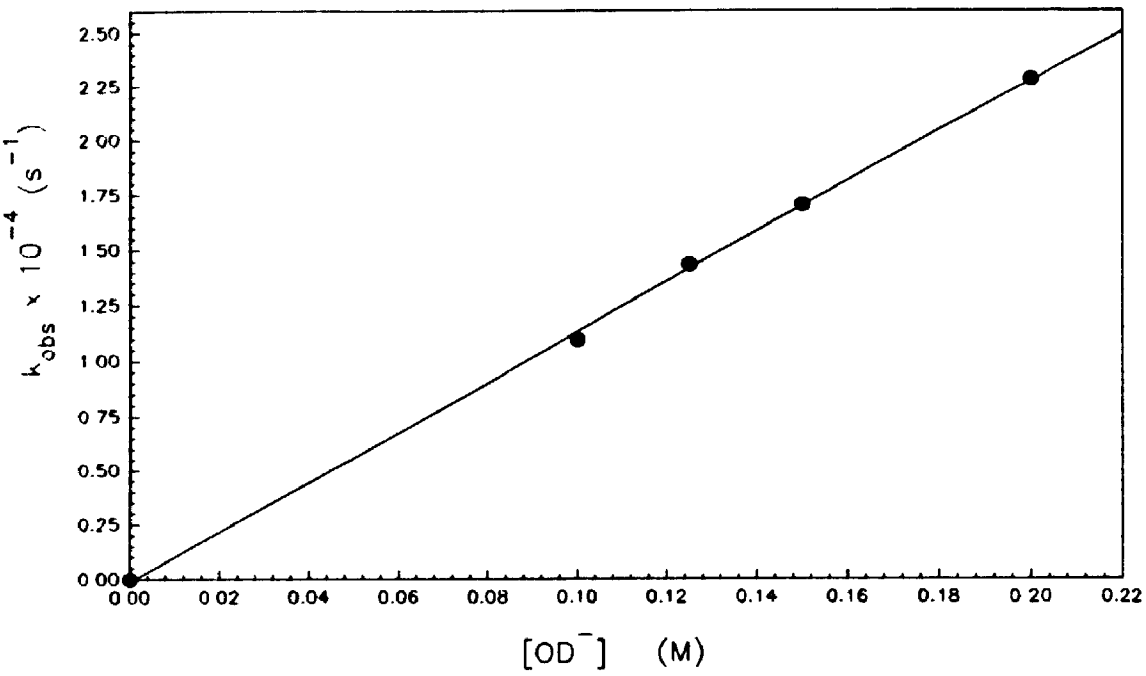
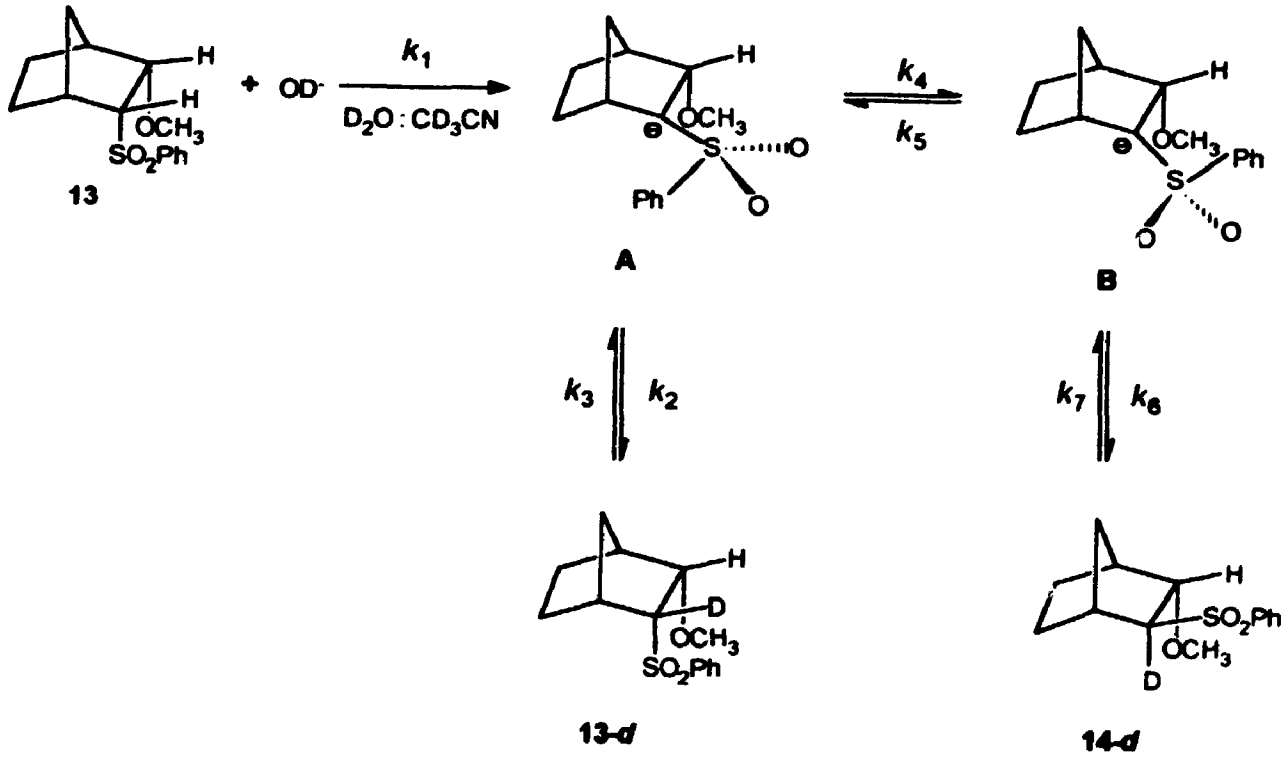


Figure 1.6 The plot of k_{obs} *vs.* [OD^-] for the H-D exchange reaction of *endo*-3-phenylsulfonyl-2-*exo*-methoxy-norbornane (**12**) in CD_3CN:D_2O (1:1) at 21 °C.

first-order rate constant was obtained by the plot of the logarithm of the concentration of unreacted starting material *vs.* time (for a typical plot, see Figure 1.5). The results are listed in Tables 1.8 to 1.10 (see experimental part). For each compound a plot of the observed rate constant, k_{obs} *vs.* [OD^-] gave a straight line (for a typical plot, see Figure 1.6). The second-order rate constant, k_{ex} (the H-D exchange rate constant obtained by observing the disappearance of the starting material), was obtained from the slope of the straight line and the results are listed in Table 1.4.

In this study it was found that the exchange reaction in all of the three *cis* compounds **13**, **15**, **17** and also *endo*-2-phenylsulfonylnorbornane (**19**) was accompanied by epimerization of the phenylsulfonyl group.

A likely mechanism for the reaction of *endo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane (**13**) is shown in Scheme 1.5; the other two *cis*-isomers, **15**, and **17** and *endo*-2-



Scheme 1.5

phenylsulfonylnorbornane (**19**) are expected to follow the same pattern. From this mechanism of H-D exchange and inversion one may see that the hydrogen on the α-C is

removed by the OD^- in the starting material **13** to generate a carbanion **A**. This carbanion may either (a) take up a deuterium from the solvent to form the H-D exchange product **13-*d*** with retention of configuration, or (b) form another carbanion **B** by rotation of S-C_α bond, followed by deuteration of the carbanion **B** to form the inversion product **14-*d***.

Computer simulation was used to calculate the rate constants in Scheme 1.5. As is detailed in the Appendix A the rate constants were obtained from two successive approximations. In the first approximation k_5/k_6 was set equal to zero and rough values of k_3 and k_2/k_4 obtained. In the second approximation a value of k_5/k_6 was inserted into the simulation. This value was obtained from a simple thermochemical calculation using knowledge of k_1 ($\equiv k_{ex}$), k_2/k_4, $\Delta G_{cis} - \Delta G_{trans}$ (from the equilibrium constant for the *trans* ⇌ *cis* equilibrium) and k_{ex} for **14**. (This calculation is perhaps more easily seen with the aid of the energy diagram in section 1.2.4, where the point is specifically taken up again; for further details of the program and calculations see Appendix A). The rate constants so obtained are listed in Tables 1.5 and 1.10 (see experimental section). The simulation directly provides values of k_2/k_4. It has been argued[30] that the protonation of simple α-sulfonyl carbanions in such protic media as water or ethanol is at or close to the diffusion (or solvent reorientation) controlled limit; a rate constant of 2.0 x

10^{10} M^{-1} s^{-1} was suggested by Williams[31]. For simplicity we have assigned a value of 2.0 x 10^{10} M^{-1} s^{-1} to the rate constants (k_2 and k_6) for the fastest of the deuteration reactions in Scheme 1.5, and calculated the others accordingly. It is of interest to point out that the values of k_{ex}/k_3 in Tables 1.4 and 1.5 give the kinetic isotope effects for reactions of these *cis*-isomers and **19**. The isotope effects for the *cis*-isomers, **13**, **15**, and **17** are in the range of 4.0-5.2 at 21 °C. Compound **19** has an isotope effect of 2.1 at 77 °C.

An example of the correspondence between simulation and experiment is shown in Figure 1.7 which shows that the calculated values (the lines) and the experimental data (the points) for the concentrations of unreacted starting material, the H-D exchange product, and the inversion product, are in good agreement for the reaction of **15** in sodium deuteroxide.

The values of k_{inv} which are listed in Table 1.5 were calculated from equation 1 (see Appendix A):

$$k_{inv} = \frac{k_1 k_4}{k_2 + k_4} \qquad (1)$$

No inversion was observed in the H-D exchange reactions of the three *trans*-isomers at 21 °C. A small amount of *trans* to *cis* inversions was observed by HPLC, however, when the H-D exchange reactions were carried out at 77 °C for 15

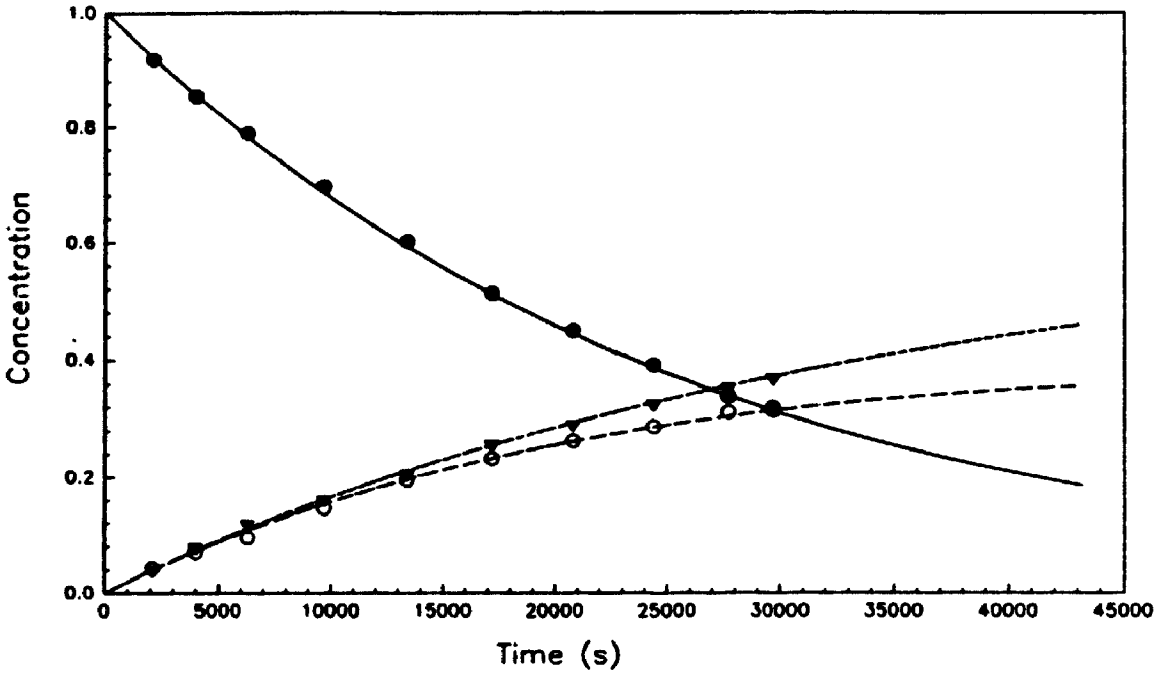


Figure 1.7 The plot of concentrations *vs.* time (s) for the kinetics of H-D exchange of *exo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane (**15**) in acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. The lines were calculated using computer simulation using the rate constants in Table 1.10; the points were experimental. The solid line is the concentration of starting material, **15**; long dashed line, the H-D exchange product, *endo*-3-*d*-*exo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane; the short dashed line, inversion product, *exo*-3-*d*-*endo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane.

days. The equilibrium concentrations and equilibrium constants of the *trans* to *cis* inversions are listed in Table 1.3.

Table 1.3 The equilibrium parameters for the *trans* to *cis* interconversion at 77 °C.

Reaction	Equilibrium Parameters			
	Cis isomer (%)	*trans* isomer (%)	*K*	ΔG^{o} (kcal/mol)
12 ⇌ **15**	2.4 ± 1	97.6	0.025	2.5±0.3
14 ⇌ **13**	0.3 ± 0.3	99.7	0.003	4 ± 1
16 ⇌ **17**	2.9 ± 1	97.1	0.030	2.4±0.3
18 ⇌ **19**	*endo* isomer ~15	*exo* isomer ~85	0.18	1.2±0.3

Where $K = C_{cis} / C_{trans}$

K is the equilibrium constant; C_{cis} and C_{trans} are the equilibrium concentrations of *cis* isomer and *trans* isomer, respectively. ΔG^{o} is the free energy difference between the *cis* isomer and *trans* isomer and obtained from the following equation:

$$\Delta G^{o} = -RT \ln K$$

where R is equal to 1.987 cal mol^{-1} K^{-1}; T (350 K) is the absolute temperature. The large error for the ΔG^{o} of **14** and **13** is due to the equilibrium concentration of **13** being too low to measure accurately.

Table 1.4 The second-order rate constants of H-D exchange reaction and dihedral angles[a]

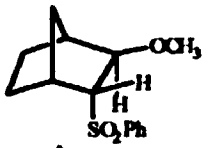
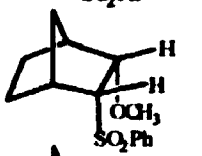
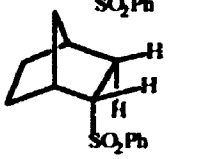
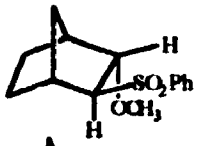
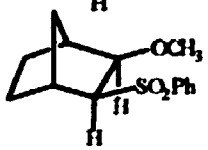
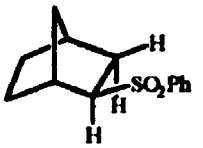
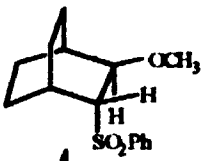
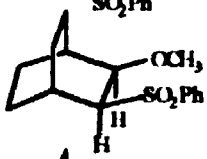
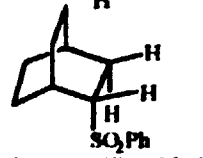
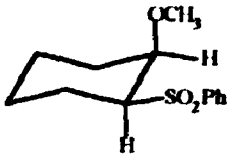
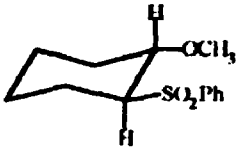
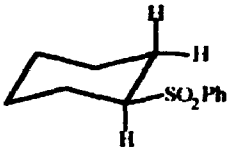
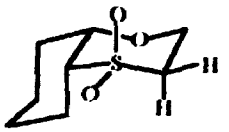
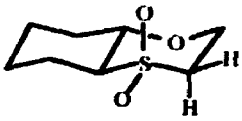
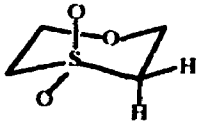
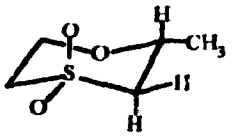
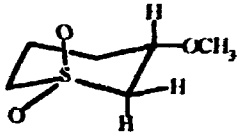
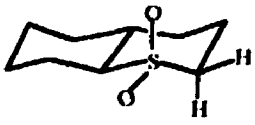
Compound	Structure	Dihedral angle H_{α}-C_{α}-C_{β}-O	k_{ex} (M^{-1} s^{-1})	k_N^e
12		9.5 [f]	11.43×10^{-4}	25344
13		130.3 [f]	4.13×10^{-4}	9157
19			9.20×10^{-4} [c] 4.5×10^{-8} [d]	1
14		6.4 [f]	1.04×10^{-4}	6887
15		128.4 [f]	2.00×10^{-4}	13245
18			1.5×10^{-8} 3.1×10^{-4} [c]	1
16		6.2 [f]	4.90×10^{-4} 8.88×10^{-4} [b]	11611
17		147.6 [f]	13.60×10^{-4}	32227
20			4.2×10^{-8}	1

Table 1.4 Continued

The second-order rate constants of H-D exchange reaction and dihedral angles

Compound	Structure	Dihedral angle H_α-C_α-C_β-O	k_{ex} (M^{-1} s^{-1})	k_N
10		178 [g]	4.4×10^{-4} [a]	8980
11		52 [g]	7.6×10^{-6} [a]	155
21			4.9×10^{-8} [a]	1
43		174 [g]	4.8×10^{-2} [h]	40000
7		177 [g]	3.2×10^{-2} [h]	26666
44		172 [g]	2.2×10^{-2} [h]	18333
45		176 [g]	2.3×10^{-2} [h]	19167
8		54 [g]	4.5×10^{-4} [h]	375
9			1.2×10^{-6} [h]	1

a. Solvent: $CD_3CN:D_2O$ (1:1), 21 °C, except where otherwise noted.

b. Solvent: Dioxane-d_8:D_2O (1:1), 21 °C.

c. Solvent: Dioxane-d_8:D_2O (1:1), 77 °C.

d. Roughly estimated values for 21 °C obtained by multiplying the rate constant, k_{ex}, for **18** at 21 °C by the rate constant ratio of **19** to **18** at 77 °C.

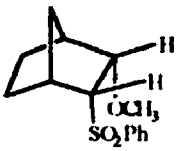
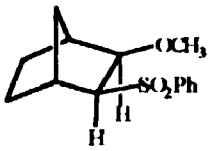
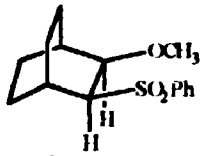
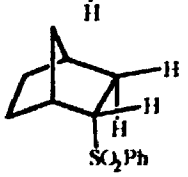
e. $k_N = k_{ex}/(k_{ex})_o$, where $(k_{ex})_o$ refers to k_{ex} for compound of analogous ring structure lacking the OCH_3 or O in ring; i.e. for the bicyclo[2.2.2] series $(k_{ex})_o$ is the k_{ex} for **20**.

f. The dihedral angles were obtained from the x-ray crystal determinations.

g. The dihedral angles were estimated by calculation using PCMODEL (PCM4).

h. These data are taken from reference 33 , solvent: D_2O.

Table 1.5 The second-order rate constants of H-D exchange and inversion reactions for *cis* isomers in mixed solvent[a]

Compound	Structure	k_{inv} (M^{-1} s^{-1}) (x 10^{-4})	k_3 (M^{-1} s^{-1}) (x 10^{-4})	k_4 (M^{-1} s^{-1}) (x 10^{10})	k_5 (M^{-1} s^{-1}) (x 10^{10})
13		1.88	0.80	1.67	0.007
15		1.01	0.50	2.00	0.005
17		5.53	2.85	1.37	0.063
19		0.038[b]	4.30[b]	0.0083[b]	0.0048[b]

a. Solvent: CD_3CN:D_2O (1:1); temperature: 21 °C; $k_2 = k_6 = 2.0 \times 10^{10}$ (M^{-1} s^{-1}) except where otherwise noted.

b. Solvent: dioxane-d_8:D_2O (1:1); temperature 77 °C.

1.2.4 Free Energy Relationships Among the Bicyclic Sulfones

The kinetic and equilibrium experiments described in the previous section may be used to construct free energy diagrams as shown in Figures 1.8 to 1.11. Each free energy of activation for formation of the carbanion from the sulfone is calculated from the Eyring equation[32] (2) and the k_{ex} values in Table 1.4; the free energy differences between the sulfones are taken from Table 1.3.

$$\Delta G^{\ddagger} = -RT \ln (k_{ex}/(kT/h)) \qquad (2)$$

In equation 2 k (1.38×10^{-23} J K^{-1}) is Boltzmann's constant; h (6.626×10^{-34} J K^{-1}, 1 cal = 4.184 J) is Planck's constant; and T (294 K) is the absolute temperature of the reaction. The "first" energy difference between the activated complexes ($\Delta\Delta G^{\ddagger}_{24}$) is calculated from the k_4/k_2 values obtained from Table 1.5 using equation 3.

$$\Delta\Delta G^{\ddagger}_{24} = -RT \ln (k_4/k_2) \qquad (3)$$

The energy difference ($\Delta\Delta G^{\ddagger}_{56}$) between the activated complexes of the k_5 and k_6 processes had been assigned earlier (see section 1.2.3); specifically, in Figure 1.8

$$\Delta\Delta G^{\ddagger}_{56} = (\Delta\Delta G^{\ddagger}_{24} + \Delta G^{\ddagger}_{19} + \Delta G) - \Delta G^{\ddagger}_{18} \qquad (4)$$

The free energy difference between the carbanions is taken

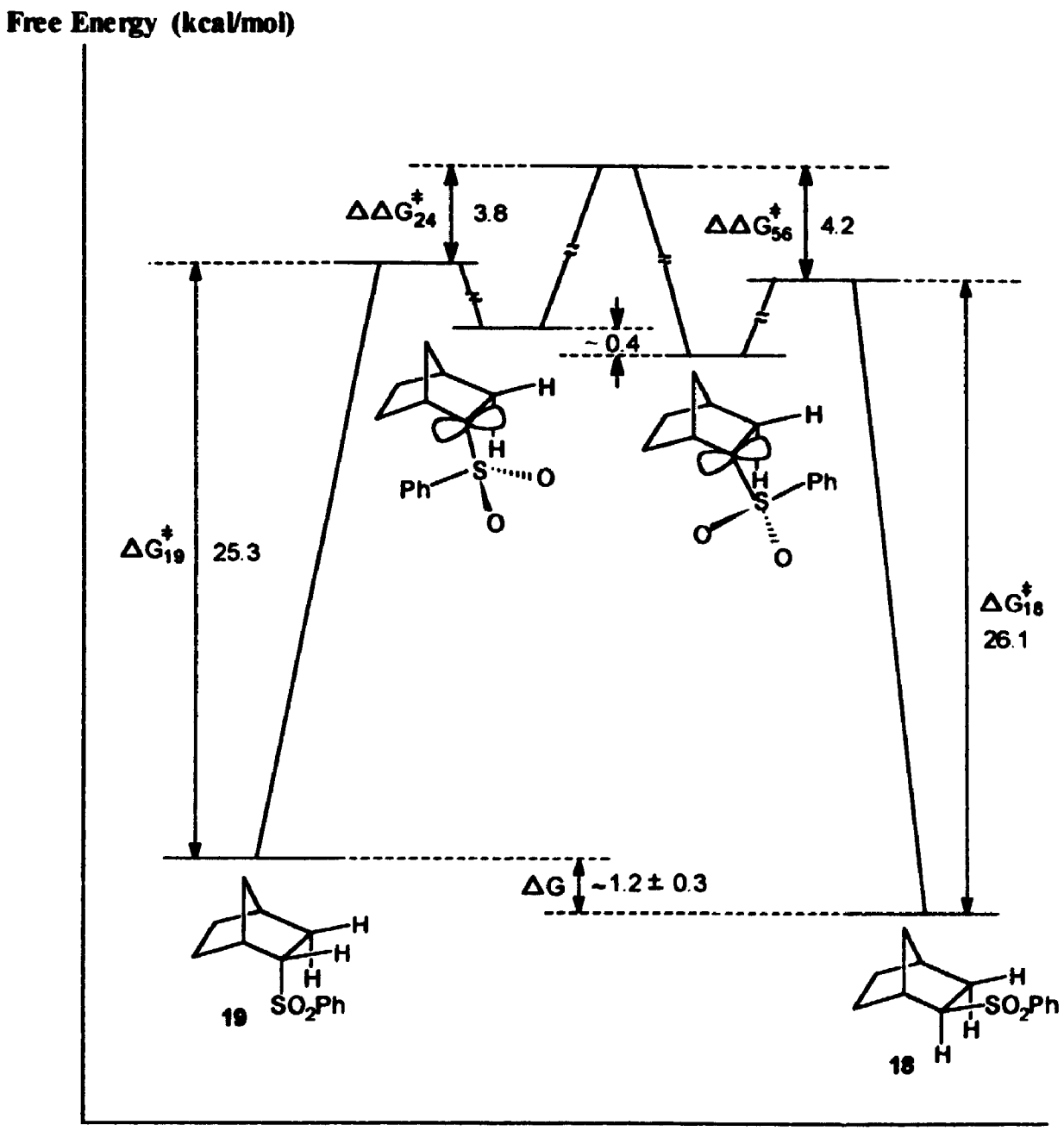


Figure 1.8 Free energy *vs.* reaction coordinate diagram for the H-D exchange and inversion reactions of 18 and 19 in sodium deuteroxide.

as the difference between the two $\Delta\Delta G^{\ddagger}$ values. This explicitly assumes that $k_2 = k_6$ (assigned the values of 2 x 10^{10} $M^{-1}s^{-1}$, as discussed earlier); this assumption is believed to be a reasonable rough approximation, but to make it clear which values are affected by this, the appropriate lines in Figures 1.8 to 1.11 are shown with breaks and the affected energy differences indicated as approximate. This assumption is made merely for convenience of presentation in Figures 1.8 to 1.11 and has no influence on any of the conclusions drawn in this thesis.

The energy diagrams raise the question of the origin of the energy differences between the epimeric sulfones. From Figure 1.8 we note that the *endo* sulfone (**19**) has 1.2 kcal mol^{-1} more free energy than the *exo* isomer (**18**), and in Figures 1.9 to 1.11 the *cis* methoxy sulfones (**13**, **15**, and **17**) all have higher energy than their *trans* isomers.

These energy differences are almost certainly due to steric effects. For the *endo vs. exo* sulfone (**19** and **18**), this probably arise primarily from the non-bonding interaction between the $PhSO_2$ group and the *endo* C-5 hydrogen.

With the *cis* methoxy sulfones the picture is slightly more complex. From the fact that all of the *cis* isomers are of higher energy than the *trans* there must be a strong non-bonding interaction between the syn-periplanar phenylsulfonyl and methoxy groups. If we compare **15** with **12**, it is evident that **15** has such a syn-periplanar

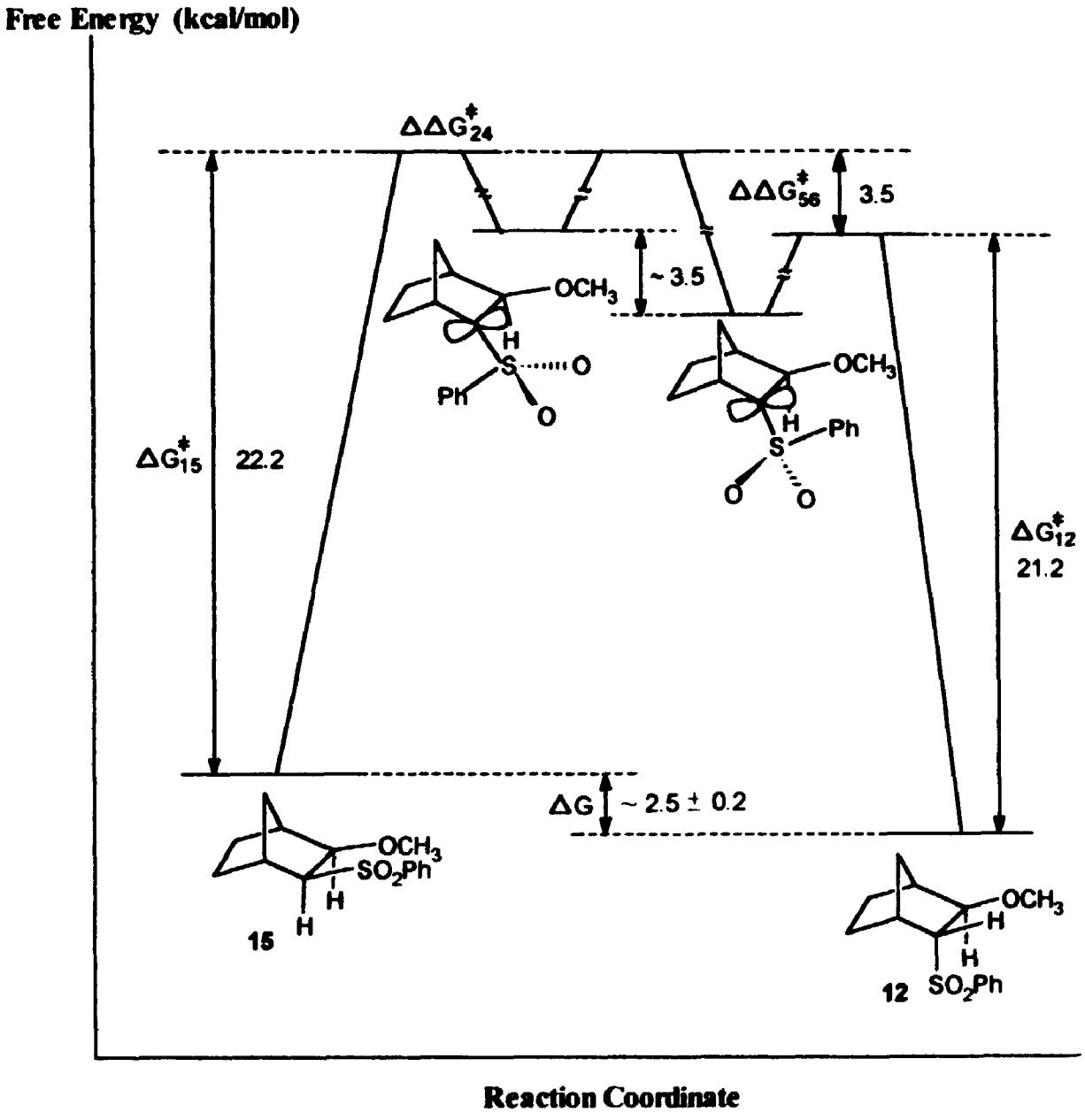


Figure 1.9 Free energy *vs.* reaction coordinate diagram for the H-D exchange and inversion reactions of **12** and **15** in sodium deuteroxide.

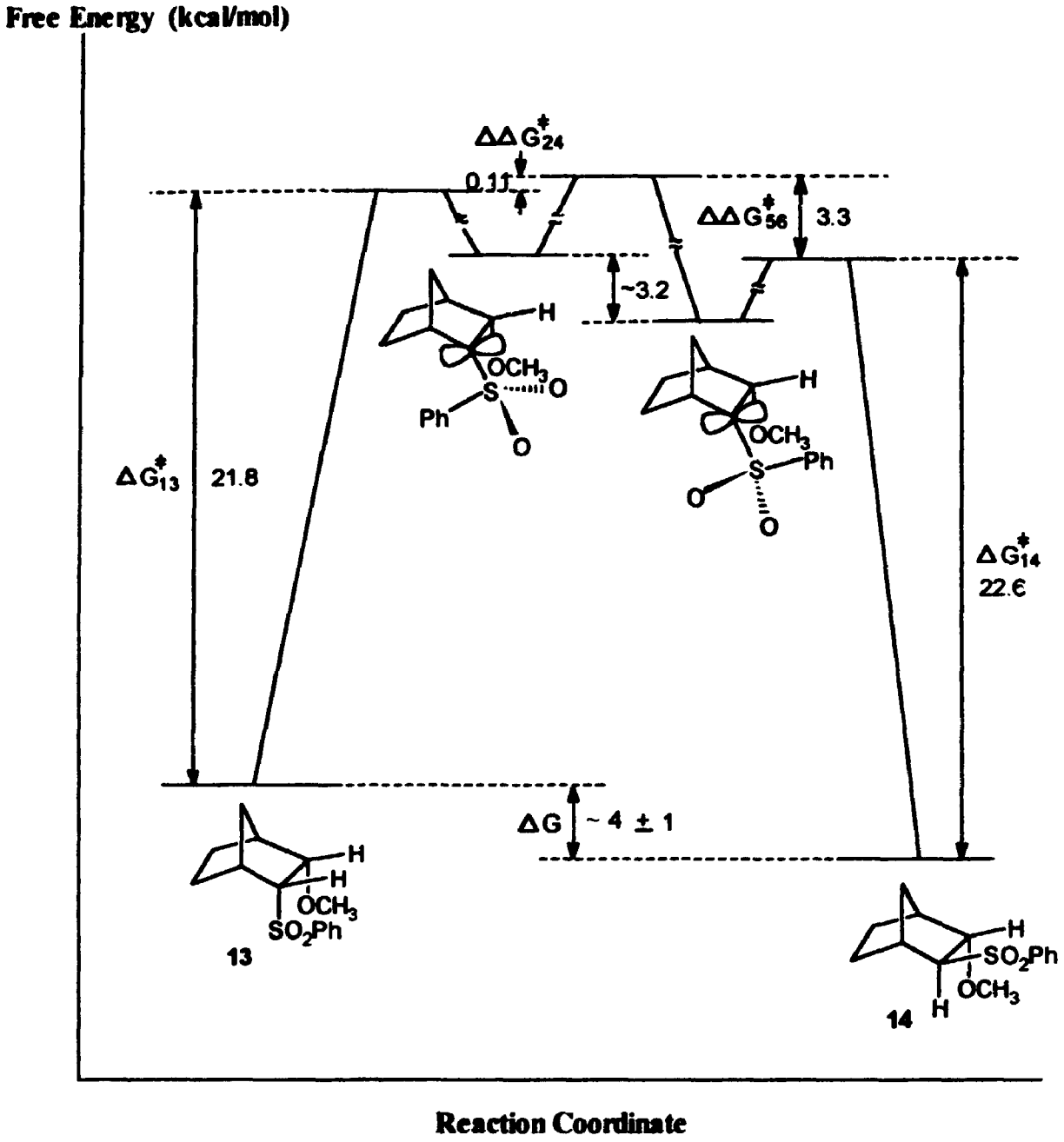


Figure 1.10 Free energy *vs.* reaction coordinate diagram for the H-D exchange and inversion reactions of **13** and **14** in sodium deuteroxide.

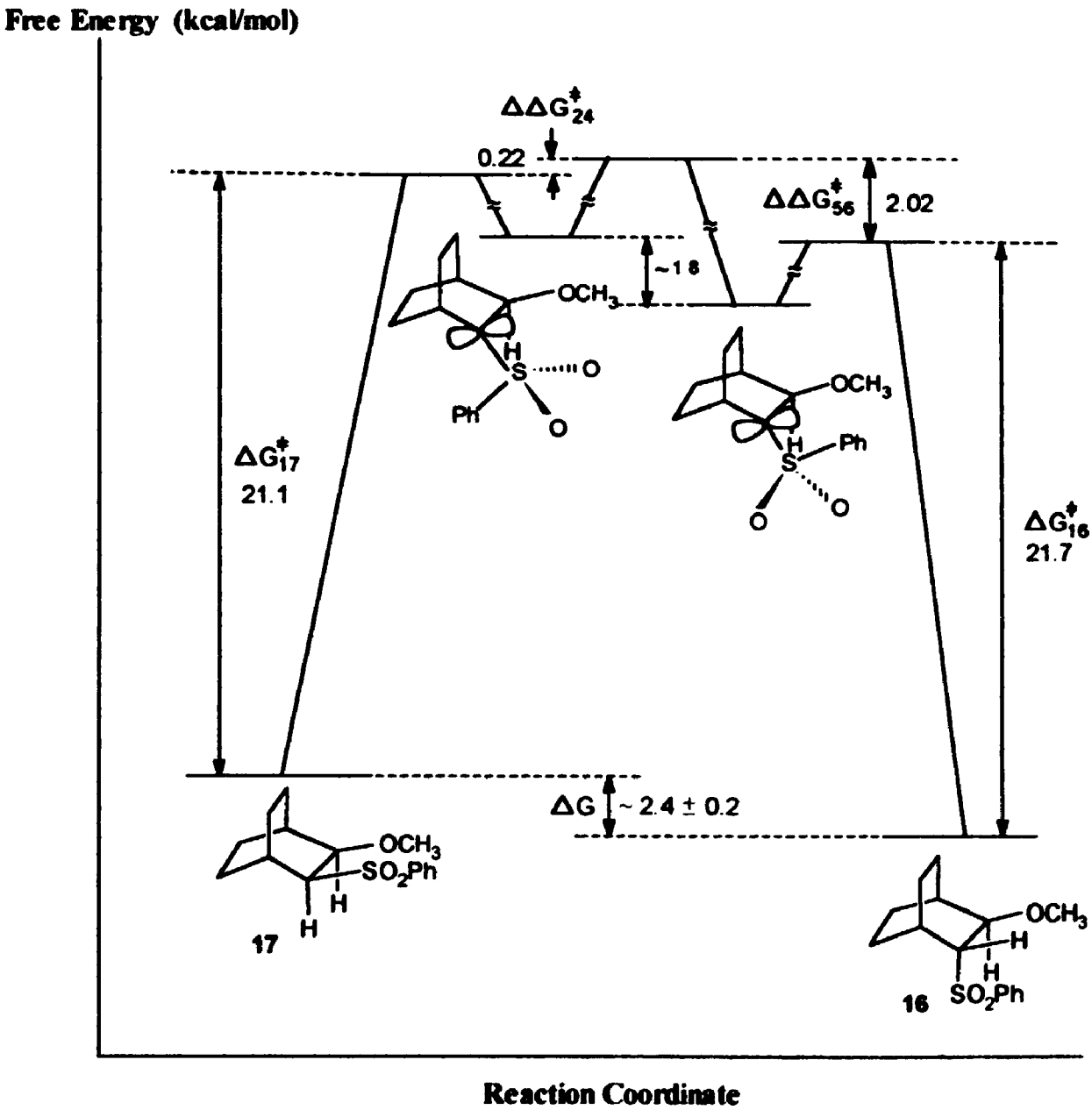


Figure 1.11 Free energy *vs.* reaction coordinate diagram for the H-D exchange and inversion reactions of 16 and 17 in sodium deuteroxide.

interaction, whereas **12** has a measure of steric strain from the *endo* conformation of the phenylsulfonyl group. More quantitatively ΔG for **15** *vs.* **12** may be given by

$$\Delta G = G_{sp} - G_N$$

where G_{sp} is the strain energy resulting from the syn-planar arrangement of the two substituents, and G_N is the strain energy of the *endo* (*vs. exo*) substituent. Since ΔG for **15** *vs.* **12** is 2.5 kcal mol^{-1} and G_N = 1.2 kcal mol^{-1} (from Figure 1.8), we find G_{sp} = 3.7 ± 0.5 kcal mol^{-1}. Similarly for **13** *vs.* **14**,

$$\Delta G = G_{sp} + G_N$$

and since $\Delta G \approx 4 \pm 1$ kcal mol^{-1}, we obtained $G_{sp} = 4 - 1.2 \approx 2.8$ (± 1) kcal mol^{-1}. In the bicyclo[2.2.2]octane isomers, **17** and **16**, G_{sp} is simply ΔG, i.e. 2.4 kcal mol^{-1}. It is of interest to note that, as expected, the G_{sp} values vary inversely with the S···O internuclear distances, *r*: **15**, $G_{sp} \approx 3.7$ kcal mol^{-1}, *r* = 2.830 Å; **13**, $G_{sp} \approx 2.8$ kcal mol^{-1}, *r* = 2.888 Å; **17**, $G_{sp} \approx 2.4$ kcal mol^{-1}, *r* = 2.930 Å.

1.2.5 The Effect of the β-Alkoxyl Group on the Rates of H-D Exchange of Sulfones

As stated above three different ring systems, i.e. cyclohexyl, bicyclo[2.2.1], and bicyclo[2.2.2] rings were

involved in this study. In order to compare the results of the H-D exchange reaction it is necessary to normalize the k_{ex} data. We define k_N, the normalized constant for the exchange, by $k_N = k_{ex}/(k_{ex})_o$ where $(k_{ex})_o$ refers to the k_{ex} for the compound of analogous ring structure lacking the β-OCH_3 (or β-O in the ring); values of k_N are listed in Table 1.4. Table 1.4 also includes data of Rathore[33] for the base catalyzed H-D exchange reaction of a number of other β-alkoxy sulfones. The H_α-C_α-C_β-O dihedral angles shown in Table 1.4 for bicyclo[2.2.1] and bicyclo[2.2.2] methoxy sulfones were obtained from the x-ray crystal structure determination; those for the cyclohexylic and heterocyclic sulfones were estimated from PCMODEL (PCM4) calculations.

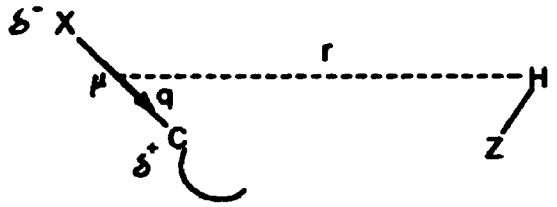
The values in Table 1.4 show that the presence of a β-alkoxy substituent may alter the H-D exchange rate by factors varying from 4.0×10^4 (for **43**), 2.5×10^4 (for **12**) and 3.2×10^4 (for **17**) on the one hand, and 3.8×10^2 (for **8**) and 1.5×10^2 (for **11**) on the other. One may immediately conclude that the alkoxy substituent is not acting exclusively *via* the inductive effect since (a) the observed effect appears much too large to be accommodated by any reasonable inductive effect (as discussed in section 1.1), and (b) this effect would be expected to depend only on the *number* of bonds between the substituent and the reaction site and hence should be the same for all of the β-alkoxy compounds. The field effect, on the other hand, is a function of the internuclear distance between the polar

centres and it is appropriate to see if the results in Table 1.4 may be accounted for on this basis.

The field effect on acidity of a dipolar substituent may be calculated using the Kirkwood-Westheimer[34] equation:

$$\log (K_X/K_H) = e\mu \cos q/(2.3\ RT\ r^2\ D_{eff}) \qquad (5)$$

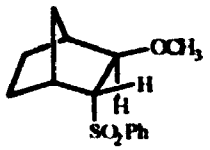
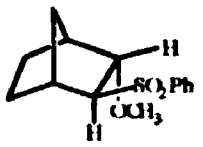
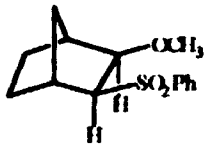
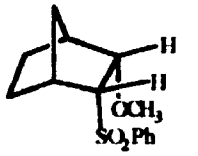
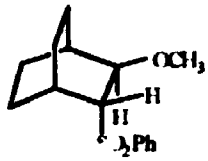
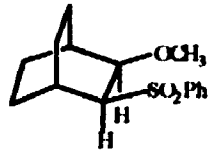
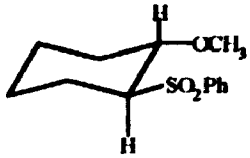
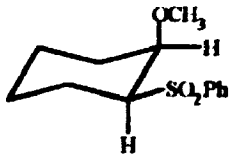
where K_X and K_H are the acid dissociation constants of substituted and unsubstituted derivatives and μ is the substituent dipole moment; D_{eff} is the "effective dielectric constant." The q and r variables are defined as follows:



Equation 5 indicates that the field effect for the same substituent and solvent should vary with $(\cos q)/r^2$. We have calculated the values of $(\cos q)/r^2$ based on the x-ray crystal structure determination data and PCMODEL calculations. The results are listed in Table 1.6 and $\log k_N$ *vs.* $(\cos q)/r^2$ shown in Figure 1.12.

It is clear from Figure 1.12 that there is no evident dependence of $\log k_N$ on $(\cos q)/r^2$. If we ignore the point at $(\cos q)/r^2 = 0.07$, the remaining points correspond to a horizontal straight line; i.e. it would appear that the

Table 1.6 The estimated parameters of q, r, and $(\cos q)/r^2$

Compound	Structure	log k_N [a]	q (degree)	r (Å)	$(\cos q)/r^2$
12		4.40	78	2.24	0.041
14		3.84	74	2.28	0.053
15		4.12	39.5	2.69	0.107
13		3.96	39.2	2.65	0.110
16		4.06	80.8	2.21	0.033
17		4.51	35	2.69	0.113
11		2.19	67.5	2.32	0.071
10		3.95	30.9	2.73	0.115

a. The k_N values were taken from Table 1.4.

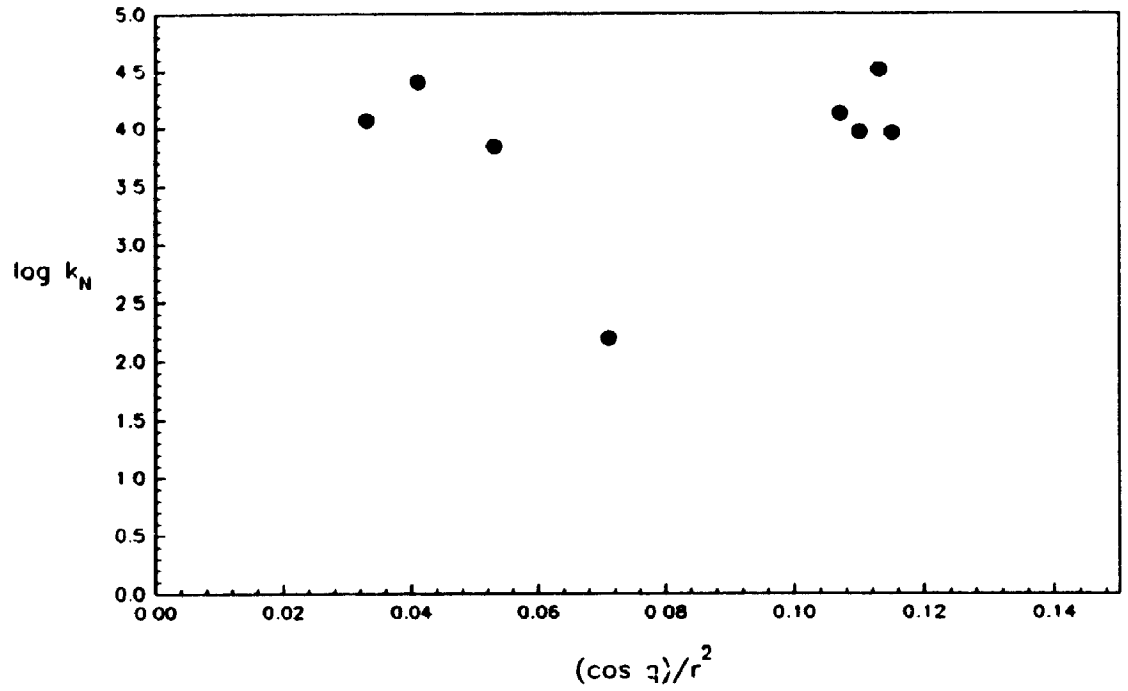


Figure 1.12 The plot of log k_N *vs.* (cos q)/r^2 for the β-methoxy phenylsulfone based on the data in Table 1.6. The points are experimental.

log k_N is independent of (cos q)/r^2. Alternatively if the stray point is included there then is no linear correlation between log k_N and (cos q)/r^2. In either case it would appear that these calculations indicate that the field effect is not the chief influence leading to the observed variation of k_N with structure reported in Table 1.4.

In the light of these conclusions we return to the topic that prompted these experiments, i.e. the anomeric effect. As currently defined, the anomeric effect is believed to arise from n → σ^* overlap, as shown in **5** (see

section 1.1). Such overlap is expected to be maximal when the overlapping orbitals are periplanar and miminal when they are clinal, in other words, this may be expected to correlate with cos 2θ; where θ is the dihedral angle. This point can be examined by comparing the experimental points with the line defined in equation 6, which has the cos 2θ dependency together with parameters adjusted to fit as many of the points as possible. The agreement with the clusters of points around ~0, ~50, and ~180° is encouraging but the deviation of the three points around 120-150° due to the three *cis* isomers (**13**, **15**, and **17**) clearly requires explanation.

$$\log k_N = 1.6\ (1.7 + \cos\ (2\theta)) \qquad (6)$$

where θ is the H_α-C_α-C_β-O dihedral angle of β-alkoxy sulfones.

The deviation of these points is positive, i.e. the rates of these H-D exchange reactions are faster than what would be predicted by equation 6. Insight into the possible origins of these deviations may be obtained by inspecting the energy diagrams for these compounds (Figures 1.9 to 1.11), where we see that the three *cis* compounds which deviate from the cos 2θ line are the isomers with the higher free energy in each pair. It will be recalled that this was ascribed in the earlier discussion (section 1.2.4) to non-

bonding repulsions between the two syn-periplanar bulky groups. In this light it is eminently reasonable to assign the apparent 'extra' speed of H-D exchange in the *cis* isomers to a release of non-bonding repulsions on going from the starting material to the transition state for the carbanion formation. For the two *cis* isomers of the bicyclo[2.2.1]heptane system (**13** and **15**) eclipsing effects of 2.8 kcal mol^{-1} and 3.7 kcal mol^{-1} have been estimated; for the *cis* bicyclo[2.2.2]octane compound (**17**) the eclipsing energy was simply $\Delta G_{cis} - \Delta G_{trans}$, i.e. 2.4 kcal mol^{-1}. The eclipsing energy is almost certainly not completely lost on proceeding to the transition state for the carbanion. As a rough estimate of this energy loss we note that the three-fold faster rate of H-D exchange observed with *endo*-phenylsulfonylnorbornane (**19**) corresponds to $\Delta G_{19}^{\ddagger} - \Delta G_{18}^{\ddagger} = 0.8$ kcal mol^{-1}, or in other words, if we assign the faster rate of **19** primarily to release of the non-bonding energy presumed to be responsible for (most of) the 1.2 kcal mol^{-1} energy difference between **19** and **18**, then 0.8 kcal mol^{-1} or 2/3 of this is lost in proceeding to the transition state for carbanion formation. If we then assume that much the same energy loss may be expected on going from a *cis* isomer to the transition state for the carbanion formation, we may then 'correct' the k_N values for the *cis* compounds by adding 2/3 x 3.7 = 2.4 kcal mol^{-1} to the $\Delta G^{\ddagger}$ value for **15**, 2/3 x 2.8 = 1.9 kcal mol^{-1} to the $\Delta G^{\ddagger}$ for **13**, and 2/3 x 2.4 = 1.6 kcal mol^{-1} to that for **17**. The estimated log k_N values for

the three *cis* isomers thus 'corrected' for the eclipsing energy acceleration are shown as the open circles in Figure 1.13. Gratifyingly the 'corrected' points are within experimental error of the line obtained from eq 6.

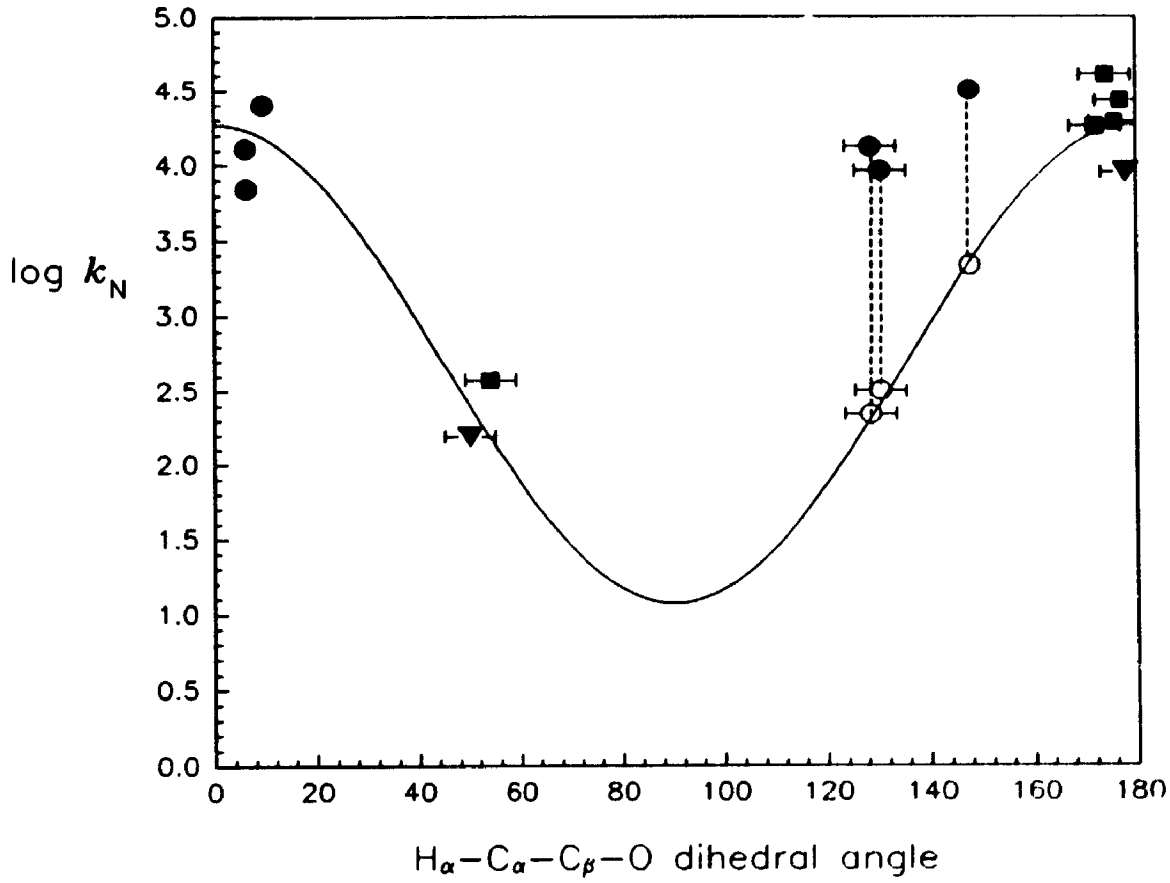


Figure 1.13 The plot of log k_N *vs.* the H_α-C_α-C_β-O dihedral angle for the base catalyzed H-D exchange reactions of β-alkoxy sulfones. The filled circles are from the bicyclo[2.2.1] and bicyclo[2.2.2] systems in CD_3CN:D_2O (1:1); the filled triangles are from cyclohexyl systems in CD_3CN:D_2O (1:1); the filled squares are from cyclohexylic or bicyclohexylic systems in D_2O; the open circles are corrected *cis* bicyclo[2.2.1] and bicyclo-[2.2.2] sulfones. The curve was calculated from eq 6.

We note that (a) neither the inductive effect nor the field effect account even qualitatively for the variation of k_N with β-alkoxy substituent, (b) when steric effects are taken account of (by an independently derived estimate) the thirteen values of k_N listed in Table 1.4 are accounted for (at a rough quantitative level, at least) by the anomeric effect.

1.2.6 The Effect of the β-Methoxy Substitution on the Rate of Stereomutation of the Sulfones

From Table 1.5 and Figures 1.8 to 1.11, it is clear that the β-methoxy group dramatically facilitates the conversion of one epimer into the other. This section considers the origin of this effect.

To convert one α-sulfonyl carbanion into the other it is necessary to rotate around the $-C^{-}-SO_2-$ bond. At the energy maximum (presumably when the bond is rotated from its stable conformation by 90°) the stabilization of the carbanion by the stereoelectronic effect of the sulfonyl group is minimized, i.e. the charge density on the carbon is distinctly greater than when the carbanion has the stable conformation. When the only substituents in the system are hydrogen and carbon atoms, the stabilization of this extra charge density is minimal and the $-C^{-}-SO_2-$ bond rotation requires considerable energy, as is indeed noted in the conversion of **19** into **18**.

In the presence of a β-alkoxy substituent the energy of

the carbanion is lowered considerably relative to the unsubstituted analogue. On rotating the $-C^{-}-SO_2-$ bond by 90° from the minimum energy conformation, the increased negative charge on the carbon atom can be stabilized by the β-alkoxy substituent, and because the charge density on the carbon is increased by rotation of the $-C^{-}-SO_2-$ bond, the anomeric and field effects of the alkoxy substituent are also increased. One way of describing the phenomenon is to state that the ρ^* for substituents with the half-rotated (90°) conformation of the carbanion is larger than ρ^* for β-substituents for the stable conformation of the sulfonyl carbanion.

A related variation in ρ^* with β-substituents has, in fact, been observed by Stirling and Thomas[6] for hydrogen exchange in a series of compounds of the general structure $EWG-CH_2-CH_2-Z$ (see Table 1.7).

Table 1.7 The ρ^* Values for Different Substituents

EWG	ρ^*
$PhSO_2$	4.9
CN	3.8
PhCO	3.2
NO_2	1.9

These results are consistent with a variation in ρ^* with variation in charge density in the carbon. As Stirling and Thomas put it the "effect of the polar substituent" is at a maximum "when the negative charge of the carbanion is located primarily on the single atom nearest the polar substituents". With the nitroalkanes ρ^* is small because much of the negative charge of the (incipient) nitronate anion is located on the oxygen atoms, rather than the carbon, whereas with the sulfones most of the charge (even with the favourable orientation of the sulfonyl group) resides on the α-carbon.

1.3 CONCLUSION

The initial premise upon which this study was based appears to have been demonstrated. The large dependence on β-substituents found by Stirling and Thomas to be shown by exchange of hydrogen alpha to a sulfonyl group has been demonstrated to be inconsistent with simple inductive or field effects and at least semiquantitatively consistent with a sizeable anomeric effect.

It has also been found that the presence of a β-alkoxy substituent accelerates the stereomutation of α-sulfonyl carbanions. The observation is consistent with a picture in which there is increased charge on the α-carbon, and hence increased influence by the β-substituent, in the transition state for the interconversion of the carbanions.

1.4 EXPERIMENTAL

Melting points were determined on a Kofler Hot Stage and uncorrected. Infrared spectra were obtained with a Bruker IFS 32 FTIR Spectrometer. ^{1}H NMR spectra were obtained by using Varian XL-200 , Gemini 200 and Gemini 300 spectrometers. ^{13}C NMR spectra were determined on the Varian XL-300 or Gemini 300 instruments. Me_4Si (TMS) was used as a reference for solvents $CDCl_3$ and acetone-d_6, and sodium trimethylsilylpropanesulfonate (DSS) for D_2O. Mass Spectra were run on a Finnigan MAT-311A Spectrometer.

High performance liquid chromatography (HPLC) (Waters, Model 510, and Waters 490 Programmable Multiwavelength Detector) was used to determine the trace products in H-D exchange (Column: C18, wavelength: λ = 260 nm, and solvent: $CH_3OH:H_2O$=1:1).

Reagent grade chemicals and solvents were used without additional purification unless otherwise noted. Triethylamine was distilled from calcium hydride. Solvents such as acetonitrile, absolute ethanol, tetrahydrofuran (THF), and dimethylsulfoxide were dried over calcium hydride and distilled; dichloromethane was dried over phosphorus pentoxide and diethyl ether dried by refluxing with $LiAlH_4$, prior to distillation.

Preparation of *endo*-3-Phenylsulfonyl-*endo*-2-methoxy-norbornane (13)

a) *exo*-Norbornene oxide (23)

Peracetic acid (32%, 30 mL) which was saturated with sodium acetate was added dropwise to a mixture of norbornene (11.2 g, 118.9 mmol) and sodium carbonate (12.6 g, 118.9 mmol) in dichloromethane (150 mL) at 0 °C. The mixture was stirred for 1 h and then neutralized with 25% sodium hydroxide solution. The mixture was filtered and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate. The solvent was removed and the residue was distilled to give *exo*-norbornene oxide (**23**) (9.50 g, 84.7 mmol, 71.2% yield) as a colourless liquid which solidified on standing, mp 124-126 °C [lit.[9] mp 125-127 °C]; IR (KBr) ν_{max}: 2963 (s), 2874 (m), 1740 (s), 1454 (s), 1329 (m), 1242 (s), 849 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.18-1.34 (m, 4H), 1.45-1.52 (m, 2H), 2.44 (s, 2H), 3.06 (s, 2H); ^{13}C NMR ($CDCl_3$) δ: 25.9, 27.1, 37.5, 52.3.

b) *endo*-3-Phenylthio-*exo*-2-norbornanol (24)

The mixture of thiophenol (13.00 g, 0.118 mol) and *exo*-norbornene oxide (**23**) (8.50 g, 0.077 mol) was added to a solution of sodium hydroxide (6.00 g, 0.15 mol) in 50% EtOH aqueous solution (v/v, 75 mL). The mixture was refluxed for 100 h, and then cooled to room temperature. The mixture was extracted with dichloromethane (4 x 50 mL). The organic phases were combined and washed with aqueous sodium

hydroxide (5%, 2 x 30 mL), aqueous hydrochloric acid (5%, 30 mL), saturated sodium bicarbonate (30 mL) and water (30 mL), and dried over anhydrous magnesium sulfate. The solvent was removed to give a brown oil (**24**) which solidified on standing. Compound **24** was recrystallized from toluene and petroleum ether to give white crystals (15.21 g, 0.069 mol, 89.7% yield), mp 64-65 °C; IR (KBr) ν_{max}: 3291 (s), 3055 (s), 2940 (s), 2961 (s), 1582 (m), 1482 (m), 1437 (s), 1318 (m), 1117 (m), 1053 (s), 1005 (s), 814 (m), 737 (s), 688 (s); ^{1}H NMR ($CDCl_3$) δ: 1.22 (m, 1H), 1.39 (m, 2H), 1.58 (m, 1H), 1.78 (m, 3H), 2.20 (d, 1H), 2.42 (d, 1H), 3.29 (m, 1H), 3.56 (t, 1H), 7.21-7.28 (m, 3H), 7.42-7.46 (m, 2h); ^{13}C NMR ($CDCl_3$) δ: 22.3, 24.7, 35.6, 40.6, 44.9, 59.1, 81.9, 126.1, 128.9, 130.0, 136.6; exact mass calculated for $C_{13}H_{16}OS$: 220.0922; found: 220.0924.

c) *endo*-3-Phenylthio-2-norbornanone (25)

Dimethyl sulfoxide (3.438 g, 44 mmol) was added dropwise during ca. 5 min to a solution of oxalyl chloride (2.539 g, 20 mmol) in dichloromethane (30 mL) at -78 °C. The reaction mixture was stirred for 15 min at -78 °C. *endo*-3-Phenylthio-*exo*-2-norborneol (**24**) (3.50 g, 15.9 mmol) in dichloromethane (10 mL) was added dropwise in about 5 min to this mixture. The reaction mixture was stirred for 30 min at -78 °C. Triethylamine (7.26 g, 71.7 mmol) was added dropwise in 5 min. Stirring was continued at -78 °C for 30 min. The cooling bath was removed and water (30 mL) was

added at room temperature. The mixture was stirred for ca. 10 min and the organic layer was separated. The aqueous phase was extracted with dichloromethane (20 mL). The combined organic phases were washed with water (30 mL), aqueous hydrochloric acid (3 M, 30 mL), saturated sodium bicarbonate (30 mL), and water (2 x 30 mL), and dried over anhydrous magnesium sulfate. The solvent was evaporated to give the *endo*-3-phenylthio-2-norbornanone (**25**) (3.47 g, 15.9 mmol, 99% yield) which was distilled at 245 °C (oil-bath, 8 Torr) to give a slightly yellowish oil. IR (neat) ν_{max}: 3478 (w), 3058 (m), 2967 (s), 2876 (m), 1746 (s), 1583 (m), 1480 (s), 1439 (m), 1316 (m), 1293 (m),1157 (s), 1073 (s), 1026 (m), 941 (m), 742 (s), 693 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.62-2.06 (m, 6H), 2.73 (m, 2H), 3.71 (dd, 1H), 7.24 (m, 3H), 7.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.8 25.2, 36.2, 40.7, 49.8, 59.7, 126.9, 128.9, 131.0, 134.9, 213.4; exact mass calculated for $C_{13}H_{14}OS$: 218.0765; found: 218.0769.

d) *endo*-3-Phenylthio-*endo*-2-norbornanol (26)

endo-3-Phenylthio-2-norbornanone (**25**) (1.50 g, 6.87 mmol) in anhydrous diethyl ether (10 mL) was added dropwise in 6 min to a slurry of lithium aluminum hydride (0.508 g, 6.87 mmol) in anhydrous diethyl ether (20 mL) at 0 °C. The mixture was stirred for 0.5 h at 0 °C. Ethylene glycol (1.706 g, 27.48 mmol) was then added slowly at 0 °C. Stirring was continued for 5 min at 0 °C, and the mixture filtered. The solid was washed with dichloromethane (3 x 30

mL). The combined filtrate was washed with water (3 x 30 mL), and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated to give the product (26) (1.426 g, 6.41 mmol, 94.2% yield) as a colourless liquid. IR (neat) ν_{max}: 3443 (s), 3058 (w), 2957 (s), 2876 (s), 1586 (s), 1480 (s), 1452 (m), 1383 (m), 1320 (m), 1296 (m), 1125 (m), 1090 (s), 1063 (s), 1026 (s), 738 (s), 691 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.47 (m, 4H), 1.65 (m, 1H), 1.87 (m, 1H), 2.55 (d, 2H), 2.96(d, 1H), 3.62 (dq, 1H), 4.18 (m, 1H), 7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 19.49, 23.53, 36.09, 42.63, 42.68, 55.64, 69.68, 126.36, 129.02, 129.46, 136.38; exact mass calculated for $C_{13}H_{16}OS$: 220.0922; found: 220.0920.

e) *endo*-3-Phenylthio-*endo*-2-methoxynorbornane (27)

endo-3-Phenylthio-*endo*-2-norbornanol (26) (1.200 g, 5.45 mmol) in dimethyl sulfoxide (3 mL) was added to a solution of potassium hydroxide (1.220 g, 21.8 mmol) in dimethyl sulfoxide (7 mL) at room temperature. The mixture was stirred at room temperature for 1-2 min. Iodomethane (3.094 g, 21.8 mmol) was added, and stirring was continued for 15 min. Water (30 mL) and dichloromethane (40 mL) were added. The two layers were separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with water (3 x 30 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated to give the product (27) (1.263, 5.39 mmol, 99%

yield) as a slightly yellowish liquid. IR (neat) ν_{max}: 3058 (w), 2955 (s), 2872 (s), 2824 (m), 1585 (m), 1480 (s), 1439 (s), 1360 (m), 1294 (w), 1190 (m), 1129 (s), 1109 (s), 957 (m), 909 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.34 (m, 4H), 1.78 (m, 1H), 2.05 (m, 1H), 2.30 (s, 1H), 2.53 (s, 1H), 3.33 (s, 3H), 3.69 (dd, 1H), 3.81 (dd, 1H), 7.24 (m, 3H), 7.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 19.9, 22.8, 35.8, 40.0, 41.1, 52.6, 57.9, 80.4, 125.8, 128.7, 130.2, 137.1; exact mass calculated for $C_{14}H_{18}OS$: 234.1078; found: 234.1077.

f) *endo*-3-Phenylsulfonyl-*endo*-2-methoxynorbornane (13)

Hydrogen peroxide (30%, 8.5 mL) was added dropwise to a solution of *endo*-3-phenylthio-*endo*-2-methoxynorbornane (27) (1.03 g, 4.4 mmol) in acetic acid (3 mL) at room temperature. The mixture was heated on a steam bath for 30 min. Water (30 mL) and dichloromethane (40 mL) were added. The two layers were separated and the aqueous layer was extracted with dichloromethane (40 mL). The combined organic layer was washed with saturated sodium bicarbonate (30 mL) and water (30 mL). After the organic phase was dried over anhydrous magnesium sulfate, the solvent was evaporated to give the product 13 (1.12 g, 4.2 mmol, 95% yield) as white crystals which recrystallized from 85% methanol, mp 96-98 °C; IR (KBr) ν_{max}: 3058 (w), 2946 (s), 2874 (s), 2830 (m), 1447 (s), 1327 (s), 1310 (s), 1279 (s), 1248 (m), 1144 (s), 1113 (s), 1084 (s), 1073 (s), 720 (s), 693 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.43 (m, 4H), 2.06 (m, 1H),

2.46 (m, 1H), 2.60 (m, 2H), 3.29 (s, 3H), 3.45 (ddd, 1H), 3.84 (ddd, 1H), 7.56 (m, 3H), 7.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 19.4, 22.6, 36.8, 40.1, 40.5, 58.1, 67.0, 80.0, 128.4, 128.8, 133.0, 141.4; exact mass (MH^+) calculated for $C_{14}H_{19}O_3S$: 267.1055; found: 267.1060.

Preparation of *endo*-3-Phenylsulfonyl-*exo*-2-methoxy-norbornane (12)

a) *endo*-3-Phenylsulfonyl-*exo*-2-norbornanol (28)

Hydrogen peroxide (30%, 34 mL) was added dropwise to a solution of *endo*-3-phenylthio-*exo*-2-norbornanol (24) (3.93 g, 17.8 mmol) in acetic acid (13 mL) at room temp. ature. The mixture was heated on a steam bath for 30 min and worked up as above. The solvent was removed to give the compound 28 (4.08 g, 16.2 mmol, 91.0% yield) as a white solid which was recrystallized from 60% ethanol, mp 114-115 °C; IR (KBr) ν_{max}: 3453 (s), 3067 (w), 2940 (s), 2872 (m), 1304 (m), 1284 (s), 1269 (s), 1134 (s), 1086 (s), 1067 (s), 720 (s), 604 (s); ^1H NMR ($CDCl_3$) δ: 1.39 (m, 2H), 1.70 (m, 2H), 2.13 (m, 2H), 2.33 (d, 1H), 2.51 (d, 1H), 3.19 (dt, 1H), 4.29 (m, 1H), 7.61 (m, 3H), 7.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 22.2, 24.3, 37.0, 39.3, 45.2, 74.7, 76.2, 127.9, 129.3, 133.6, 140.2; exact mass calculated for $C_{13}H_{16}O_3S$: 252.0820; found: 252.0822.

b) *endo*-3-Phenylsulfonyl-*exo*-2-methoxynorbornane (12)

endo-3-Phenylsulfonyl-*exo*-2-norborneol (28) (0.25 g,

1.0 mmol) was added to a solution of potassium hydroxide (0.224 g, 4.0 mmol) in dimethyl sulfoxide (2 mL) at room temperature. The mixture was stirred at room temperature for 2 min. Iodomethane (0.57 g, 4.0 mmol) was added, and stirring was continued for 15 min. This mixture was worked up as stated in the preparation of **27**. The solvent was removed to give the product (**12**) (0.238 g, 0.89 mmol, 89% yield) as a white solid which was recrystallized from 60% methanol, mp 125-126 °C; IR (KBr) ν_{max}: 3069 (w), 2976 (m), 2940 (m), 2880 (m), 1447 (s), 1363 (m), 1298 (s), 1269 (s), 1150 (s), 1130 (s), 1084 (s), 756 (s), 720 (s), 689 (s), 606 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.27-1.41 (m, 3H), 1.58-1.67 (m, 2H), 2.20 (m, 1H), 2.50 (m, 2H), 3.16 (s, 3H), 3.18 (m, 1H), 3.67 (m, 1H), 7.29 (m, 3H), 7.63 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 22.9, 23.7, 37.0, 38.8, 41.3, 56.9, 74.0, 83.5, 127.8, 129.0, 133.3, 140.2; exact mass (MH^+) calculated for $C_{14}H_{19}O_3S$: 267.1055; found: 267.1059.

Preparation of *exo*-3-Phenylsulfonyl-*endo*-2-methoxy-norbornane (14)

a) *exo*-3-Phenylthio-2-norbornanone (29)

endo-3-Phenylthio-2-norbonanone (**25**) (3.80 g, 17.4 mmol) was added to a solution of potassium hydroxide (1.95 g, 34.8 mmol) in methanol (70 mL) and water (10 mL). The mixture was refluxed for 2 h and water (20 mL) was added. After most of methanol was removed on a rotary evaporator, the residue was extracted with dichloromethane (3 x 50 mL).

The organic layer was washed with aqueous hydrochloric acid (1 M, 30 mL), saturated sodium bicarbonate (30 mL), water (30 mL), and dried over anhydrous magnesium sulfate. The solvent was evaporated to give the products (**29**) and (**25**) (3.59 g, 16.5 mmol, 94.5% yield) as a yellowish liquid.

The ^{1}H NMR spectrum showed that the products contained *endo*-3-phenylthio-2-norbornone (**25**) (40%) and *exo*-3-phenylthio-2-norbornone (**29**) (60%). These two isomers were separated by column chromatography on silica gel using diethyl ether:petroleum ether = 20:80 as solvents. The *exo*-isomer (**25**) eluted first. Compound **29** was distilled by a cold-finger apparatus at 235-237 °C (oil-bath, 8 Torr) to give a colourless oil; IR (neat) ν_{max}: 3476 (w), 3058 (w), 2963 (s), 2876 (s), 1748 (s), 1581 (m), 1480 (s), 1439 (s), 1304 (s), 1172 (s), 1073 (s), 1026 (m), 937 (m), 911 (m), 747 (s), 691 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.55 (m, 3H), 1.86 (m, 2H), 2.17 (d, 1H), 7.45 (m, 2H), 2.61 (s, 1H), 2.69 (s, 1H), 3.31 (d, 1H), 7.30 (m, 3H); ^{13}C NMR ($CDCl_3$) δ: 24.3, 27.2, 35.1, 42.0, 49.3, 56.5, 127.2, 129.0, 131.3, 134.4, 213.3; exact mass calculated for $C_{13}H_{14}OS$: 218.0765; found: 218.0765.

b) *exo*-3-Phenylthio-*endo*-2-norbornanol (30)

exo-3-Phenylthio-2-norbornanone (**29**) (1.330 g, 6.09 mmol) in tetrahydrofuran (10 mL) was added dropwise to a slurry of lithium aluminum hydride (0.300 g, 4.06 mmol) in tetrahydrofuran (15 mL) at 0 °C, and after the mixture was

stirred at 0 °C for 1.5 h, it was worked up as described for **26**. The solvent was removed to give a mixture of *exo*-3-phenylthio-*endo*-2-norbornanol (**30**) and *exo*-3-phenylthio-*exo*-2-norbornanol (**31**) (1.070 g, 4.86 mmol, 79.7% yield) as a colourless oil which gave white crystals on standing.

The ^{1}H NMR spectrum showed that the mixture contained cis isomer (**31**): 24% and trans isomer (**30**): 76%. The solid (**30**) was recrystallized from petroleum ether (60-80 °C) to give pure *exo*-3-phenylthio-*endo*-2-norbornanol (**30**) as white crystals, mp 69-70 °C; IR (KBr) ν_{max}: 3237 (s), 2957 (s), 2943 (s), 2869 (s), 1584 (m), 1480 (s), 1437 (m), 1337 (m), 1318 (w), 1157 (m), 1067 (s), 1053 (s), 740 (s), 700 (m), 689 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.31-1.46 (m, 3H), 1.61-1.80 (m, 4H), 2.23 (m, 1H), 2.36 (m, 1H), 2.85 (m, 1H), 4.05 (m, 1H), 7.18-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 19.5, 29.4, 35.3, 43.0, 43.7, 57.4, 80.2, 126.1, 129.0, 129.6, 136.6; exact mass calculated for $C_{13}H_{16}OS$: 220.0922, found: 220.0924.

c) *exo*-3-Phenylthio-*endo*-2-methoxynorbornane (32)

A mixture of dimethyl sulfoxide (6.5 mL) and powdered potassium hydroxide (0.759 g, 13.5 mmol) was stirred for 5 min at room temperature. *exo*-3-Phenylthio-*endo*-2-norbornanol (**30**) (0.745 g, 3.38 mmol) was added followed immediately by iodomethane (2.399 g, 16.9 mmol), and after stirring for 15 min worked up as described for **27**. The solvent was evaporated to give the product **32** (0.750 g, 3.2 mmol, 94.7% yield) as a slightly yellowish liquid. ^{1}H NMR

($CDCl_3$) δ: 1.37 (m, 3H), 1.79 (m, 3H), 2.22 (m, 1H), 2.51 (m, 1H), 2.89 (t, 1H), 3.30 (s, 3H), 3.55 (m, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 20.7, 30.1, 35.8, 40.9, 44.0, 55.6, 58.2, 89.3, 126.7, 129.7, 130.2, 138.0.

d) *exo*-3-Phenylsulfonyl-*endo*-2-methoxynorbornane (14)

Hydrogen peroxide (30%, 8.0 mL) was added dropwise to a solution of *exo*-3-phenylthio-*endo*-2-methoxynorbornane (0.75 g, 3.20 mmol) in acetic acid (3 mL) at room temperature. The mixture was heated on a steam-bath for 30 min and worked up as described for **13**. The solvent was removed to give *exo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane (**14**) (0.814 g, 3.06 mmol, 95.5% yield) as white crystals. Compound **14** was recrystallized from 50% MeOH, mp 87-88 °C; IR (KBr) ν_{max}: 2979 (m), 2959 (s), 2876 (s), 2836 (m), 1451 (m), 1304 (s), 1291 (s), 1215 (m), 1148 (s), 1111 (s), 1084 (s), 903 (m), 760 (m), 725 (s), 692 (s), 606 (s), 550 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.30 (m, 3H), 1.63 (m, 2H), 1.94 (d, 1H), 2.59 (d, 2H), 2.73 (dd, 1H), 3.17 (s, 3H), 4.05 (t, 1H), 7.57 (m, 3H), 7.91 (d, 2H); ^{13}C NMR ($CDCl_3$) δ: 19.5, 29.8, 34.9, 39.0, 39.1, 57.4, 72.9, 81.9, 128.4, 129.1, 133.5, 138.8; exact mass (MH^+) calculated for $C_{14}H_{19}O_3S$: 267.1055; found: 267.1057.

Preparation of *exo*-3-Phenylsulfonyl-*exo*-2-methoxy-norbornane (15)

a) *exo*-3-Phenylthio-*exo*-2-norbornanol (31)

Compound **31** was partially separated from the mixture of **30** and **31** by column chromatography on silca gel. ^{1}H NMR ($CDCl_3$) δ: 1.15-1.77 (m, 4H), 2.35 (m, 2H), 2.85 (m, 2H), 3.35 (dd, 1H), 3.92 (dd, 1H), 7.21-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 25.2, 30.0, 34.5, 44.4, 45.3, 59.8, 76.0, 127.2, 130.1, 130.4, 137.7.

b) *exo*-3-Phenylthio-*exo*-2-methoxynorbornane (33)

Powdered potassium hydroxide (0.20 g, 3.6 mmol) was added to a solution of a mixture of *exo*-3-phenylthio-*exo*-2-norbornanol (**31**) (80%) and *exo*-3-phenylthio-*endo*-2-norbornanol (**30**) (20%) (0.115 g, 0.52 mmol) in DMSO (2 mL). This mixture was stirred for 2 min and iodomethane (0.74 g, 5.2 mmol) was added. The mixture was continued stirring for 15 min and worked up as stated in **32**. The solvent was removed to give a mixture of **33** (80%) and **32** (20%) as a yellowish oil (0.114 g, 0.49 mmol, 94% yield). The NMR spectra of **33** are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.30-1.70 (m, 4H), 1.92 (m, 2H), 2.22 (m, 1H), 2.57 (m, 1H), 3.39 (s, 3H), 3.41 (m, 1H), 3.45 (m, 1H), 7.29 (m, 3H), 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 24.8, 34.0, 39.8, 41.5, 43.5, 56.6, 59.9, 86.7, 126.4, 129.8, 130.2, 138.9.

c) *exo*-3-Phenylsulfonyl-*exo*-2-methoxynorbornane (15)

Hydrogen peroxide (30%, 2 mL) was added dropwise to a solution of a mixture of *exo*-3-phenylthio-*exo*-2-methoxy-norbornane (**33**) (80%) and **32** (20%) (0.114 g, 0.49 mmol) in

acetic acid (1 mL) at room temperature. The mixture was heated on a steam-bath for 0.5 h and worked up as stated in **13**. The solvent was removed to give a mixture of *exo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane (**15**) and *exo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane (**14**) (0.125 g, 0.47 mmol, 95.9% yield) as a colourless oil which solidified slowly on standing. Compound **15** was separated from the mixture by column chromatography using ethyl acetate (20%) and petroleum ether (80%) as the eluate and recrystallized from ethyl acetate and petroleum ether, mp 98-99 °C; IR (KBr) ν_{max}: 2980 (s), 2877 (s), 1450 (m), 1303 (s), 1124 (s), 1103 (s), 719 (m), 691 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.97 (m, 1H), 1.14-1.1.20 (m, 2H), 1.58 (m, 2H), 1.95 (m, 1H), 2.38 (s, 1H), 2.78 (s, 1H), 3.23 (s, 3H), 3.29 (m, 1H), 3.47 (m, 1H), 7.52 (m, 3H), 7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 23.4, 29.6, 34.2, 38.5, 40.1, 58.4, 72.0, 85.2, 128.6, 128.7, 132.9, 141.4; exact mass (MH^+) calculated for $C_{14}H_{19}O_3S$: 267.1055; found: 267.1057.

Preparation of *exo*-2-Phenylsulfonylnorbornane (18)

a) *exo*-2-Phenylthionorbornane (34)

Thiophenol (3.51 g, 31.9 mmol) was added in small portions to norbornylene (3.0 g, 31.9 mmol) at room temperature. The temperature rose to 60 °C about 5 min after the first portion. The remainder of thiophenol was added at such a rate that the temperature remained between 60-70 °C. After all of thiophenol was added, the mixture

was heated at 75-80 °C for 30 min with stirring. The mixture was then subjected to vacuum distillation. The product was collected at 128-130 °C (5 Torr) to give a colourless oil (**34**) (5.50 g, 26.9 mmol, 84.4% yield). IR (neat) ν_{max}: 3059 (w), 2955 (s), 2869 (s), 1586(s), 1480 (s), 1451 (s), 1439 (s), 1313 (s), 1239 (m), 1269 (m), 1138 (m), 1068 (m), 1091 (s), 1026 (s), 953 (m), 736 (s), 690 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.18-1.84 (m, 8H), 2.27 (m, 2H), 3.17 (m, 1H), 7.11-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 31.3, 31.5, 38.2, 39.1, 41.2, 44.9, 50.7, 128.1, 131.4, 131.5, 140.4.

b) *exo*-2-Phenylsulfonylnorbornane (18)

Hydrogen peroxide (30%, 20 mL) was added dropwise to a solution of *exo*-2-norbornyl phenyl thioether (**34**) (3.0 g, 14.7 mmol) in acetic acid (10 mL). This mixture was heated for 0.5 h on a steam bath, and worked up as stated in **13**. The solvent was evaporated to give white crystals (**18**) (3.456 g, 14.6 mmol, 99.5% yield) which was recrystallized from methanol, mp 80-81 °C; IR (KBr) ν_{max}: 3063 (w), 2965 (s), 2872 (m), 1445 (m), 1325 (m), 1298 (s), 1271 (s), 1242 (m), 1146 (s), 1086 (s), 721 (s), 696 (s), 612 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.18 (m, 3H), 1.80 (m, 1H), 2.01 (m, 1H), 2.40 (dd, 1H), 2.68 (dd, 1H), 3.00 (ddd, 1H), 7.60 (m, 3H), 7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 28.1, 29.8, 32.6, 36.1, 38.8, 66.7, 128.4, 129.1, 133.4, 139.1.

Preparation of *endo*-2-Phenylsulfonylnorbornane (19)

a) *endo*-2-Phenylsulfonyl-5-norbornene (35)

A mixture of cyclopentadiene (freshly distilled from dicyclopentadiene) (3.20g, 48.4 mmol) and phenyl vinyl sulfone (2.0 g, 11.9 mmol) in benzene (5 mL) was stirred for 5 days at room temperature. The solvent and excess cyclopentadiene were removed to give a colourless liquid (2.65 g, 11.3 mmol, 95% yield) which was shown by ^{1}H NMR to contain *endo*-2-phenylsulfonyl-5-norbornene (**35**) (83%) and *exo*-2-phenylsulfonyl-5-norbornene (17%). The two isomers were separated by column chromatography using benzene as solvent. The pure **35** was recrystallized from benzene and petroleum ether, mp 63-65 ^{o}C [lit. mp[35] 64-65 ^{o}C]. ^{1}H NMR ($CDCl_3$) δ: 1.27 (m, 1H), 1.45 (m, 1H), 1.59 (m, 1H), 1.99 (m, 1H), 2.97 (m, 1H), 3.08 (m, 1H), 3.65 (m, 1H), 6.13 (dd, 1H), 6.26 (dd, 1H), 7.55 (m, 3H), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 28.8, 42.7, 45.0, 49.8, 64.7, 127.9, 129.2, 131.3, 133.4, 137.4, 140.3.

b) *endo*-2-Phenylsulfonylnorbornane (19)

A mixture of formic acid (3.05 g, 66.3 mmol), 10% palladium on charcoal catalyst (Pd-C) (0.35 g), and *endo*-2-phenylsulfonyl-5-norbornene (**35**) (0.49 g, 2.1 mmol) in absolute ethanol (80 mL) was refluxed for 2 h. The Pd-C was filtered off. The solvent was removed to give a colourless liquid (**19**) (0.40 g, 1.7 mmol, 81% yield) which solidified on standing. Compound **19** was recrystallized from 50%

aqueous methanol, mp 61-62 °C; IR (KBr) ν_{max}: 2975 (m), 2883 (w), 1445 (m), 1276 (s), 1152 (s), 1086 (s), 722 (s), 703 (s), 603 (s); ^{1}H NMR ($CDCl_3$) δ: 1.37 (m, 5H), 1.77 (m, 2H), 2.38 (m, 2H), 2.52 (m, 1H), 3.32 (m, 1H), 7.52 (m, 3H), 7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 23.6, 28.9, 31.2, 37.3, 39.8, 40.4, 65.8, 127.9, 129.2, 133.3, 140.6; exact mass calculated for $C_{13}H_{16}O_2S$: 236.0871; found: 236.0874.

Preparation of *cis*-3-Phenylsulfonyl-2-methoxybicyclo-[2.2.2]octane (17)

a) 2,3-Epoxybicyclo[2.2.2]octane (36)

A mixture of bicyclo[2.2.2]oct-2-ene (2.40 g, 22.2 mmol), 3-chloroperoxybenzoic acid (9.00 g, 52.2 mmol) and sodium bicarbonate (4.5 g, 53.6 mmol) in dichloromethane (200 ml) was stirred for 72 h at room temperature. The precipitate was filtered off and washed with dichloromethane (50 mL). The filtrate was washed with aqueous sodium thiosulfate (20%, 60 mL), saturated sodium bicarbonate (50 mL), and water (3 x 50 mL). The organic layer was dried over anhydrous magnesium sulfate. The solvent was removed to give the product (**36**) (2.70 g, 21.7 mmol, 97.9% yield) as white crystals which was recrystallized from 50% MeOH aqueous solution, mp 190-191 °C [lit. mp[36] 190-190.3 °C]; IR (KBr) ν_{max}: 1790 (s), 1765 (s), 1574 (w), 1470 (w), 1219 (s), 1034 (w), 1011 (s), 812 (w),725 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.22 (m, 2H), 1.55 (m, 4H), 1.67 (m, 2H), 2.06 (m, 2H), 3.22 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 22.8, 23.6, 27.6,

53.2.

b) *trans*-3-Phenylthio-2-bicyclo[2.2.2]octanol (37)

Thiophenol (3.42 g, 31.0 mmol) and 2,3-epoxybicyclo-[2.2.2]octane (36) (2.80 g, 25.5 mmol) was added to a solution of potassium hydroxide (2.5 g, 44.6 mmol) in 50% aqueous ethanol (25 mL). This solution was refluxed for 120 hours with stirring. The mixture was extracted repeatedly with dichloromethane (5 x 25 mL). The extracts were washed with aqueous sodium hydroxide (5%, 2 x 20 mL), hydrochloric acid (5%, 20 mL), saturated sodium bicarbonate (20 mL), and water (30 mL). The organic phase was dried over anhydrous magnesium sulfate. The solvent was removed to give the product (37) (4.736 g, 20.2 mmol, 89.6% yield) as a slightly yellowish oil. Compound 37 was distilled from a cold-finger apparatus at 235-240 °C (oil-bath, 8 Torr) to give a colourless oil. IR (neat) ν_{max}: 3393 (s), 3057 (w), 2940 (s), 2864 (s), 1583 (m), 1479 (s), 1454 (m), 1061 (m), 1026 (s), 738(s), 691(s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.38 (m, 2H), 1.69 (m, 6H), 1.84 (m, 2H), 2.28 (S, 1H), 3.24 (m, 1H), 3.73 (m, 1H), 7.27 (m, 3H), 7.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 18.1, 19.7, 23.4, 26.1, 29.9, 32.6, 56.3, 76.0, 126.5, 128.9, 130.9, 135.7; exact mass calculated for $C_{14}H_{18}OS$: 234.1078; found: 234.1077.

c) 3-Phenylthio-2-bicyclo[2.2.2]octanone (38)

Dimethyl sulfoxide (4.008 g, 51.3 mmol) in

dichloromethane (10 mL) was added dropwise to oxalyl chloride (4.341 g, 34.2 mmol) in dichloromethane (75 mL) with stirring at -78 °C. The stirring was continued at -78 °C for 15 min followed by addition of *trans*-3-phenylthio-2-bicyclo[2.2.2]octanol (4.00 g, 17.1 mmol) in dichloromethane (15 mL) in 10 min. Stirring was continued for 15 min and triethylamine (15.2 g, 150 mmol) was added dropwise during 10 min. The mixture was stirred for 10 min at -78 °C. Water (60 mL) was added at room temperature and stirring was continued for 10 min. The mixture was worked up as stated in the preparation of **25**. The solvent was evaporated to give the product (**38**) (3.950 g, 17.0 mmol, 99.5% yield) as a yellowish oil. Compound **38** was distilled using a cold-finger apparatus at 225-230 °C (oil-bath, 8 Torr) to give a slightly yellowish oil. IR (neat) ν_{max}: 3060 (w), 2946 (s), 2870 (s), 1724 (s), 1581 (m), 1480 (s), 1455 (s), 1325 (w), 1111 (m), 1062 (s), 1026 (m), 741 (s), 691 (s), 666 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.58 (m, 3H), 1.84 (m, 4H), 2.15 (m, 2H), 2.38 (m, 1H), 3.74 (t, 1H), 7.27 (m, 3H), 7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 20.0, 22.7, 23.5, 25.3, 33.1, 42.5, 57.6, 127.2, 129.0, 131.8, 134.4, 213.5; exact mass calculated for $C_{14}H_{18}OS$: 232.0922; found: 232.0923.

d) *cis*-3-Phenylthio-2-bicyclo[2.2.2]octanol (39)

Method A:

3-Phenylthio-bicyclo[2.2.2]octan-2-one (**38**) (3.0 g, 12.9 mmol) in anhydrous diethyl ether (15 mL) was added

dropwise in 10 min to a slurry of lithium aluminum hydride (0.855 g, 11.6 mmol) in anhydrous diethyl ether (30 mL) at -78 °C. The mixture was stirred for 2.5 h at -78 °C. Ethylene glycol (2.88 g, 46.4 mmol) was added to destroy the excess lithium aluminum hydride at room temperature. The precipitate was filtered off and washed repeatedly with dichloromethane (3 x 30 mL). The filtrate was washed with aqueous hydrochloric acid (1 M, 50 mL), saturated sodium bicarbonate (50 mL), and water (2 x 50 mL). The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated to give the product (**39**) (2.75 g, 11.7 mmol, 90.7% yield) as a slightly yellowish oil. The ^{1}H NMR spectrum showed the product to be a mixture of the *cis* isomer (**39**) (63%), and the *trans* isomer (**37**) (37%).

Method B:

3-Phenylthio-bicyclo[2.2.2]octan-2-one (**38**) (4.50 g, 19.4 mmol) in 2-propanol (15 mL) was added dropwise to a solution of sodium borohydride (0.733 g, 19.4 mmol) in 2-propanol (95 mL). The mixture was stirred overnight at room temperature. Concentrated hydrochloric acid (6 mL) was added to destroy the excess sodium borohydride and the esters. The 2-propanol was removed on a rotary evaporator. The residue was extracted with dichloromethane (3 x 50 mL). The organic phase was washed with saturated sodium bicarbonate (50 mL), and water (50 mL), and dried over anhydrous magnesium sulfate. The solvent was removed to

give the mixture of (37) and (39) (4.31 g 18.4 mmol, 94.8% yield) as an oil. The ^{1}H NMR spectrum showed the mixture to contain the *cis*-isomer (39) (78%) and the *trans*-isomer (37) (22%). The two isomers were separated by column chromatography on silica gel using a mixture of diethyl ether (20%) and petroleum ether (80%) as the solvent. The *cis*-isomer (39) came out first from the column. Compound 39 was distilled in a cold-finger apparatus, bp 225-228 °C (oil-bath, 8 Torr). IR (neat) ν_{max}: 3440 (s), 3058 (w), 2936 (s), 2865 (s), 1584 (m), 1480 (s), 1456 (m), 1439 (s), 1067 (s), 1044 (s), 1026 (m), 738 (s), 691 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.36 (m ,2H), 1.60 (m, 4H), 1.88 (m, 4H), 3.07 (s, 1H), 3.62 (dt, 1H), 4.01 (dt, 1H), 7.27 (m, 3H), 7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 18.1, 20.7, 23.0, 25.9, 31.3, 31.4, 55.0, 68.2, 126.4, 129.0, 129.9, 136.3; exact mass calculated for $C_{14}H_{18}OS$: 234.1078, found: 234.1074.

e) *cis*-3-Phenylthio-2-methoxybicyclo[2.2.2]octane (40)

A mixture of dimethyl sulfoxide (35 mL) and powdered potassium hydroxide (3.93 g, 70 mmol) was stirred for 5 min at room temperature. *cis*-3-Phenylthio-2-bicyclo[2.2.2]-octanol (39) (4.10 g, 17.5 mmol) was added to the mixture followed immediately by iodomethane (9.94 g, 70.0 mmol). Stirring was continued for 25 min and the mixture worked up as stated in the preparation of 32. The solvent was evaporated to give a yellow oil (4.169 g, 16.8 mmol, 95.9% yield). The ^{1}H NMR spectrum showed that the product

contained the *cis*-isomer (40) (86%) and the *trans*-isomer (37) (14%). The two isomers were separated by column chromatography on silica gel to give pure 40. IR (neat) ν_{max}: 3057 (w), 2938 (s), 2865 (s), 1584 (m), 1482 (m), 1439 (m), 1102 (s), 739 (s), 691 (s); ^{1}H NMR ($CDCl_3$) δ: 1.27-1.42 (m, 4H), 1.51-1.68 (m, 4H), 1.85-1.94 (m, 2H), 3.37 (s, 3H), 3.65 (s, 2H), 7.20-7.28 (m, 3H), 7.33-7.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 18.7, 20.3, 22.6, 25.6, 27.8, 29.0, 51.5, 58.1, 79.2, 125.9, 128.8, 130.6, 136.5.

f) *cis*-3-Phenylsulfonyl-2-methoxybicyclo[2.2.2]octane (17)

Hydrogen peroxide (30%, 20 mL) was added dropwise to a solution of *cis*-3-phenylthio-2-methoxybicyclo[2.2.2]octane (40) (2.0 g, 8.0 mmol) in acetic acid (8.5 mL). The mixture was heated on a steam bath for 30 min and worked up as stated in 13. The solvent was removed to give the product 17 (2.15 g, 7.7 mmol, 96.3% yield) as a colourless oil which solidified on standing. Compound 6 was recrystallized from ethyl acetate (10%) and petroleum ether (90%) to give white crystals, mp 127-128 ^{o}C; IR (KBr) ν_{max}: 3065 (w), 2984 (s), 2818 (s), 2924 (s), 2864 (s), 1448 (s), 1316 (s), 1302 (s), 1269 (s), 1284 (s), 1234 (m), 1144 (s), 1103 (s), 1086 (s), 995 (w), 762 (s), 721 (s), 692 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.19 (s, 3H), 3.39 (dt, 1H), 3.53 (dd, 1H), 7.57 (m, 3H), 7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 18.4, 20.9, 21.6, 25.4, 26.6, 27.0, 57.4, 66.4, 76.9, 128.6, 128.8, 133.0, 141.0; exact mass (MH^+) calculated for $C_{15}H_{20}O_3S$: 281.1211; found:

281.1207.

Preparation of *trans*-3-Phenylsulfonyl-2-methoxybicyclo-[2.2.2]octane (16)

a) *trans*-3-Phenylthio-2-methoxybicyclo[2.2.2]octane (41)

The mixture of dimethyl sulfoxide (15 mL) and powdered potassium hydroxide (1.50 g, 26.7 mmol) was stirred for 5 min at room temperature. *trans*-3-Phenylthio-2-bicyclo-[2.2.2]octanol (37) (1.50 g, 6.4 mmol) was added followed immediately by iodomethane (4.54 g, 32 mmol). The mixture was stirred for 25 min and worked up as stated in the preparation of 27. The solvent was removed to give the product 41 (1.45 g, 5.8 mmol, 90.6% yield) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 1.03-1.40 (m, 4H), 1.50-1.70 (m, 4H), 1.80-1.85 (m, 2H), 2.97 (m, 2H), 3.06 (s, 3H), 7.15-7.26 (m, 3H), 7.35-7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 19.3, 21.0, 24.1, 27.2, 29.4, 30.5, 54.6, 57.7, 85.9, 127.4, 129.9, 131.8, 137.0.

b) *trans*-3-Phenylsulfonyl-2-methoxybicyclo[2.2.2]octane (16)

Hydrogen peroxide (30%, 12 mL) was added dropwise to a solution of *trans*-3-phenylthio-2-methoxybicyclo[2.2.2]octane (41) (1.20 g, 4.8 mmol) in acetic acid (5.0 mL). The mixture was heated on a steam bath for 30 min and worked up as stated in the preparation of 13. The solvent was removed

to give the product **16** (1.15 g, 4.1 mmol, 85.4% yield) as a white solid. Compound **16** was recrystallized from 60% methanol to give white crystals, mp 84-86 °C; IR (KBr) ν_{max}: 3061 (w), 2948 (s), 2863 (s), 2824 (m), 1447 (s), 1337 (m), 1306 (s), 1289 (s), 1246 (w), 1148 (s), 1107 (m), 1086 (s), 758 (m), 723 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.37-1.69 (m, 7H), 1.97 (m, 1H), 2.23 (m, 2H), 3.03 (s, 3H), 3.05 (m, 1H), 3.77 (m, 1H), 7.60 (m, 3H), 7.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 17.9, 20.6, 22.6, 25.6, 26.9, 27.3, 56.3, 70.7, 77.8, 128.4, 129.0, 133.4, 139.2; exact mass (MH^+) calculated for $C_{15}H_{20}O_3S$: 281.1211; found: 218.1212.

Preparation of 2-Phenylsulfonyl-bicyclo[2.2.2]octane (20)

a) 2-Phenylthio-bicyclo[2.2.2]octane (42)

Thiophenol (1.22 g, 11.1 mmol) was added in small portions to bicyclo[2.2.2]oct-2-ene (1.20 g, 11.1 mmol). The temperature rose to about 50 °C. The remainder of thiophenol was added at such a rate that the temperature was not over 70 °C. After the addition of thiophenol was complete, the mixture was heated at 70 °C for 8 h with stirring. The mixture was then subjected to vacuum distillation at 185-190 °C (oil-bath, 8 Torr) to give the product (**42**) (2.07 g, 9.5 mmol, 85.6% yield) as a colourless oil. IR (neat) ν_{max}: 3073 (w), 2934 (s), 2863 (s), 1586 (m), 1479 (s), 1439 (s), 1267 (w), 1092 (m), 1026 (m), 739 (s), 691 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.62 (m, 10H), 2.10 (m, 2H), 3.50 (m, 1H), 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 20.5,

24.7, 24.9, 25.5, 26.4, 28.3, 34.4, 45.3, 126.0, 128.8, 130.3, 136.7; exact mass calculated for $C_{14}H_{18}S$: 218.1129, found: 218.1125.

b) 2-Phenylsulfonylbicyclo[2.2.2]octane (20)

Hydrogen peroxide (30%, 16 mL) was added dropwise with stirring to a solution of 2-phenylthiobicyclo[2.2.2]octane (**42**) (2.00 g, 9.17 mmol) in glacial acetic acid (6 mL) at room temperature. The mixture was heated for 30 min on a steam-bath and worked up as stated in the preparation of **13**. The solvent was evaporated to give the product (**20**) (2.15 g, 8.59 mmol, 93.7% yield) as a colourless oil which solidified on standing. Compound **20** was recrystallized from 60% methanol, mp 61-63 °C (lit.[37] mp 58-59 °C for 2-phenylsulfonyl-(5,6-d_2)bicyclo[2.2.2]octane); IR (KBr) ν_{max}: 3073 (w), 2942 (s), 2867 (s), 1451 (m), 1306 (s), 1275 (s), 1148 (s), 1086 (m), 767 (m), 723 (s), 702 (m) cm^{-1}; ^1H NMR ($CDCl^3$) δ: 1.39-1.78 (m, 9H), 2.10 (m, 2H), 2.27 (m, 1H), 3.16 (m, 1H), 7.59 (m, 3H), 7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 20.9, 24.1, 24.3, 24.6, 24.9, 26.8, 27.0, 62.5, 128.4, 129.1, 133.3, 139.1.

Preparation of *trans*-2-Phenylsulfonyl-1-methoxycyclohexane (11)

A sample prepared by Dr. R. Rathore in this laboratory was recrystallized from 85% methanol, mp 69-70 °C; IR (KBr) ν_{max}: 2927 (s), 1447 (s), 1303 (s), 1141 (s), 1100 (s), 745

(s), 690 (s), 605 (s) cm^{-1}; ^1H NMR ($CDCl^3$) δ: 1.16 (m, 4H), 1.78 (m, 4H), 2.20 (m, 1H), 3.05 (s, 3H), 3.42 (m, 1H), 7.48 (m, 3H), 7.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 23.1, 23.9, 24.4, 29.7, 55.4, 67.1, 78.2, 127.8, 128.4, 132.8, 141.2; exact mass calculated for $C_{13}H_{18}O_3S$: 254.0977; found: 254.0973.

Preparation of *cis*-2-Phenylsulfonyl-1-methoxycyclohexane (10)

A sample prepared by Dr. R. Rathore in this laboratory was recrystallized from 85% methanol, mp 97-98 °C ; IR (KBr) ν_{max}: 2935 (s), 1447 (m), 1288 (s), 1131 (s), 1087 (s), 758 (m), 691 (m) cm^{-1}; ^1H NMR ($CDCl^3$) δ: 1.15-1.23 (m, 2H), 1.36-1.42 (m, 2H), 1.66-1.71 (m, 1H), 1.75 (m, 1H), 1.90-1.94 (m, 1H), 2.06-2.11 (m, 1H), 2.96 (m, 1H), 3.22 (s, 3H), 4.00 (m, 1H), 7.50 (m, 3H), 7.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 18.7, 21.7, 25.0, 27.4, 55.8, 68.1, 73.2, 128.4, 129.3, 133.2, 139.0; exact mass calculated for $C_{13}H_{18}O_3S$: 254.0977; found: 254.0976.

Preparation of Cyclohexyl Phenyl sulfone (21)

A sample prepared by Dr. R. Rathore was recrystallized from 85% methanol, mp 72-73 °C ; IR (KBr) ν_{max}: 2953 (m), 2928 (s), 2853 (m), 1443 (m), 1300 (s), 1289 (s), 1146 (s), 1082 (s), 756 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.14-1.44 (m, 5H), 1.69 (m, 1H), 1.89 (m, 2H), 2.09 (m, 2H), 2.85-2.97 (m, 1H), 7.52 (m, 3H), 7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 24.8, 25.2, 63.1, 128.7, 128.8, 133.4, 136.9.

1.4.2 Kinetic Measurements of H-D Exchange

a) General procedure:

All kinetic measurements were carried out by ^1H NMR spectrometry using the Gemini 300 NMR spectrometer. The concentration of unreacted starting material, as determined from the integral of one of its peaks relative to that of an inert peak, was monitored with respect to time.

The solutions of sodium deuteroxide (0.10 M to 0.50 M) in deuterium oxide were prepared by dissolving sodium metal in deuterium oxide under nitrogen. These solutions were titrated using 0.01 M hydrochloride acid.

A typical kinetic measurement was carried out as follows: A sample (9 mg) was dissolved in acetonitrile-d_3 (0.35 mL) in a NMR tube. Sodium deuteroxide solution (0.35 mL) was added into the NMR tube by a 0.5 mL syringe and the NMR tube was sealed right away using a flame. The mixture was shaken vigorously. The rate of the reaction was then followed by ^1H NMR. For slow hydrogen-deuterium exchange reactions the sealed NMR tube was kept in a 21 ± 2 °C water bath or a 77 °C oil bath. For the fast reactions the NMR tube was placed into the Gemini 300 NMR instrument which the temperature had been set at 21 ± 2 °C. The amount of unexchanged starting material was determined by comparing the integral of the disappearing signal α to the sulfonyl group divided by the integral of the signal α to the methoxyl group. The time for each measurement was taken as an average of the start of data collection and the stop of

Table 1.8 The Pseudo-first-order Rate Constants for Hydrogen-Deuterium Exchange in Mixed Solvent[a] at 21.0 °C.

Compounds	NaOD (M)	k_{obs} (s^{-1}) (x 10^5)
12	0.100	10.93
	0.125	14.32
	0.150	17.05
	0.200	22.81
13	0.125	5.20
	0.150	6.25
	0.175	7.27
	0.200	8.29
14	0.125	1.39
	0.150	1.54
	0.175	1.82
	0.200	2.08
16	0.075	3.82
	0.100	5.10
	0.125	6.32
	0.150	7.50
16	0.125[b]	11.1
	0.150[b]	13.5
	0.175[b]	15.6
	0.200[b]	17.8

a. The solvents are $CD_3CN:D_2O$ (1:1).

b. The solvents are dioxane-d_8:D_2O (1:1).

Table 1.8 Continued

The Pseudo-first-order Rate Constant for Hydrogen-Deuterium Exchange in Mixed Solvent[1] at 21.0 °C.

Compounds	NaOD (M)	k_{obs} (s^{-1}) (x 10^5)
11	0.150	0.109
	0.175	0.126
	0.200	0.144
10	0.100	4.57
	0.150	6.67
	0.200	8.81
	0.238	10.60

1. The solvents are $CD_3CN:D_2O$ (1:1).

Table 1.9 The Pseudo-first-order Rate Constants for Hydrogen-Deuterium Exchange in Mixed Solvent[a]

Compound	NaOD (M)	k_{obs} (s^{-1})
18	0.125	1.92×10^{-9}
	0.150	2.28×10^{-9}
	0.175	2.65×10^{-9}
	0.200	3.06×10^{-9}
	0.300[b]	9.24×10^{-5}
19	0.300[b]	2.76×10^{-4}
20	0.125	5.41×10^{-9}
	0.150	6.50×10^{-9}
	0.175	7.33×10^{-9}
	0.200	8.48×10^{-9}
21	0.125	7.14×10^{-9}
	0.150	8.49×10^{-9}
	0.175	9.69×10^{-9}
	0.200	11.40×10^{-9}

a. The solvents are $CD_3CN:D_2O$ (1:1), temperature 21 °C.

b. The solvents are dioxane-d_8:D_2O (1:1), temperature 77 °C.

Table 1.10 The Pseudo-first-order Rate Constants for the H-D Exchange and Inversion of *cis* Compounds in Sodium Deuteroxide[a]

Compound	$[OD^-]$ (M)	k_{1obs} x 10^{-5}	k_{3obs} x 10^{-5}	k_{4obs} x 10^{7}	k_{5obs} x 10^{7}	k_{7obs} x 10^{-5}
13	0.125	5.20	1.00	1670	17.7	0.09
	0.150	6.25	1.20	1670	17.7	0.11
	0.175	7.27	1.40	1670	17.7	0.13
	0.200	8.29	1.60	1670	17.7	0.15
15	0.175	3.50	0.85	2050	5.0	0.35
	0.200	4.00	1.00	2050	5.0	0.40
	0.300	4.97	1.50	2050	5.0	0.60
17	0.075	9.0	2.20	1370	63.0	0.12
	0.125	16.1	3.60	1370	63.0	0.20
	0.150	20.4	4.30	1370	63.0	0.25
	0.200	24.0	5.70	1370	63.0	0.30
19[b]	0.300	27.7	22.0	8.3	3.1	5.0

a. The solvents are $CD_3CN:D_2O$ (1:1), temperature 21 °C. $k_2 = k_6 = 2.0 \times 10^{10}$ (s^{-1}).

b. The solvents are dioxane-d_8:D_2O (1:1), temperature 77 °C.

data collection. The value of k_{obs} was obtained from the slope of a plot of ln C_t (C_t is the concentration % of starting material in time t) *vs.* time (s). The second-order rate constant (k_{ex}) was obtained from the slope of a plot of k_{obs} *vs.* [OD^-]; ([OD^-] is the concentration of sodium deuteroxide in the mixed solvent (acetonitrile-d_3 and deuterium oxide).

b) Kinetics of H-D Exchange of *endo*-3-Phenylsulfonyl-*exo*-2-methoxynorbornane (12)

(i) The H-D exchange of **12** (9 mg) was carried out as described in the general procedure with four different concentrations of sodium deuteroxide (0.10, 0.125, 0.15, and 0.20 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. A plot of ln C_t *vs.* time (s) gave a straight line (see Figure 1.5). The pseudo-first-order rate constant was obtained from the slope of the line. The results are listed in Table 1.8. The plot of k_{obs} *vs.* [OD^-] gave a straight line. The second-order rate constant k_{ex} was obtained from the slope of the line and the result is included in Table 1.4.

(ii) A sample (9 mg) in sodium deuteroxide (0.30 M) in methanol-d_4:D_2O (1:1) was heated for 15 days at 77 °C in a sealed NMR tube. The solution was neutralized with concentrated hydrochloride acid. This mixture was used directly in HPLC analysis. It was found that the mixture contained *exo*-3-*d*-*endo*-3-phenylsulfonyl-*exo*-2-methoxy-

norbornane (**12**) (97.6%) and *endo*-3-*d*-*exo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane (**15**) (2.4% ± 1).

c) Kinetics of H-D Exchange of *endo*-3-Phenylsulfonyl-*endo*-2-methoxynorbornane (13)

The H-D exchange of **13** (9 mg) was carried out as described in the general procedure with four different concentrations of sodium deuteroxide (0.125, 0.15, 0.175, and 0.20 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. The ^{1}H NMR spectra showed that compound **13** in sodium deuteroxide underwent H-D exchange to form *exo*-3-*d*-*endo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane, and inversion to form *endo*-3-*d*-*exo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane. A plot of ln C_t (C_t is the percentage concentration of unreacted **13**) *vs.* time (s) gave a straight line. The pseudo-first-order rate constant for **13** to generate α-sulfonyl carbanion was obtained from the slope of the line. The pseudo-first-order rate constant for inversion was obtained by computer simulation (see Appendix A). The results are listed in Table 1.10. The plot of k_{obs} *vs.* [OD^-] gave a straight line. The second-order rate constant k_{ex} was obtained from the slope of the line and the result is included in Tables 1.4 and 1.5.

d) Kinetics of H-D Exchange of *exo*-3-Phenylsulfonyl-*endo*-2-methoxynorbornane (14)

(i) The H-D exchange of **14** (9 mg) was carried out as described in the general procedure with four different concentrations of sodium deuteroxide (0.125, 0.15, 0.175 and 0.20 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. A plot of ln C_t *vs.* time (s) gave a straight line. The pseudo-first-order rate constant was obtained from the slope of the line. The results are listed in Table 1.8. The second-order rate constant k_{ex} is obtained from the slope of the plot of k_{obs} *vs.* [OD^-] and the result is included in Table 1.4.

(ii) A sample (9 mg) of **14** in sodium deuteroxide (0.30 M) in methanol-d_4:D_2O (1:1) was heated for 15 days at 77 °C in a sealed NMR tube. The solution was neutralized with concentrated hydrochloride acid. This mixture was used directly in HPLC analysis. It was found that the mixture contained *endo*-3-*d*-*exo*-3-phenylsulfonyl-*endo*-2-methoxy-norbornane (**14**) (99.7%) and *exo*-3-*d*-*endo*-3-phenylsulfonyl-*endo*-2-methoxynorbornane (**13**) (0.3% ± 0.3).

e) Kinetics of H-D Exchange of *exo*-3-Phenylsulfonyl-*exo*-2-methoxynorbornane (15)

The H-D exchange of **15** (9 mg) was carried out as described in the general procedure with three different concentrations of sodium deuteroxide (0.175, 0.20 and 0.30 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. The ^1H NMR spectra showed that compound **15** in sodium deuteroxide underwent H-D exchange to form *endo*-3-

d-*exo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane, and inversion to form *exo*-3-*d*-*endo*-3-phenylsulfonyl-*exo*-2-methoxynorbornane. The plot of percentages of unreacted starting material, H-D exchange and inversion products *vs.* time (s) is shown in Figure 1.7. A plot of ln C_t (C_t is the percentage concentration of unreacted **15**) *vs.* time (s) gave a straight line. The pseudo-first-order rate constant for **15** to generate α-sulfonyl carbanion was obtained from the plot of ln C_t (C_t is the percentage concentration of unreacted **15**) *vs.* time (s). The pseudo-first-order rate constant for inversion was obtained by computer simulation. The results are listed in Table 1.10. The second-order rate constant k_{ex} was obtained from the plot of k_{obs} *vs.* [OD^-]; the result is included in Tables 1.4 and 1.5.

f) Kinetics of H-D Exchange of *trans*-3-Phenylsulfonyl-2-methoxybicyclo[2.2.2]octane (16)

(i) The H-D exchange of **16** (9 mg) was carried out as described in the general procedure at four different concentrations of sodium deuteroxide (0.075, 0.10, 0.125, and 0.15 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. The pseudo-first-order rate constant was obtained from the plot of ln C_t *vs.* time (s) and the results are listed in Table 1.8. The second-order rate constant k_{ex} was obtained from the plot of k_{obs} *vs.* [OD^-] and the result is included in Table 1.4.

(ii) The H-D exchange of **16** (9 mg) was carried out as described in the general procedure at four different concentrations of sodium deuteroxide (0.125, 0.15, 0.175 and 0.20 M) in a mixed solvent of 1,4-dioxane-d_8 and deuterium oxide (1:1) at 21 °C. The pseudo-first-order rate constant was obtained from the plot of ln C_t *vs.* time (s) (for a typical plot, see Figure 1.14). The results are listed in Table 1.8. The second-order rate constant k_{ex} was obtained from the plot of k_{obs} *vs.* [OD^-] and the result is included in Table 1.4.

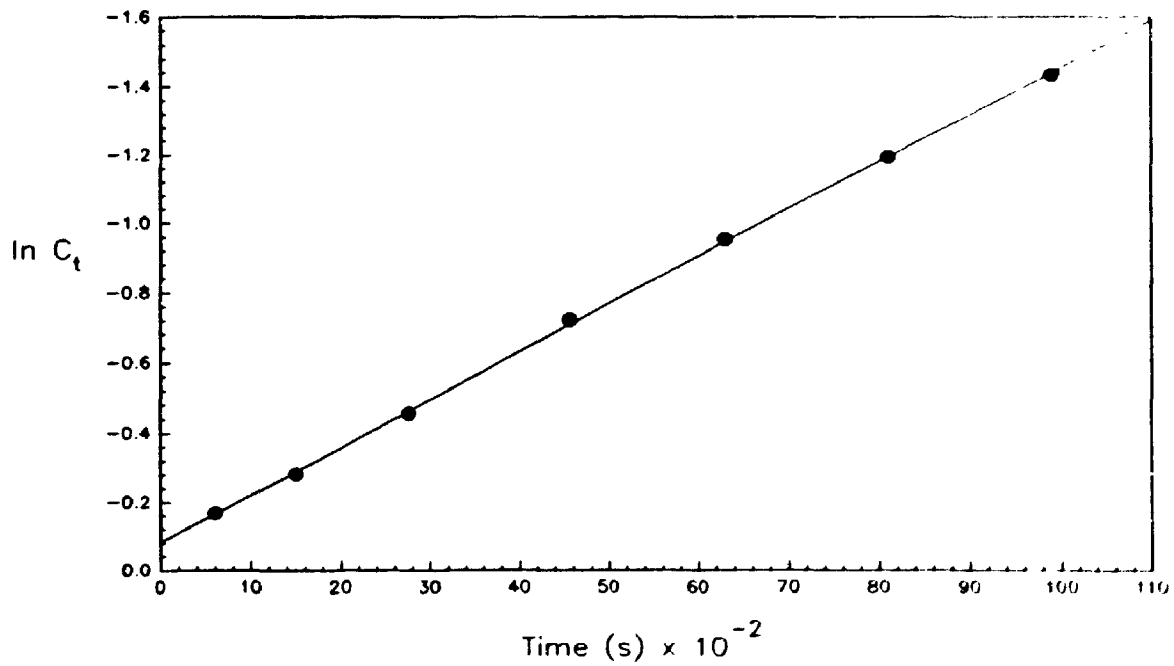


Figure 1.14 The plot of ln C_t *vs.* Time (s) for the H-D exchange of *trans*-3-phenylsulfonyl-2-methoxybicyclo-[2.2.2]octane (**16**) in sodium deuteroxide (0.15 M) in a mixture solvent of 1,4-dioxane-d_8 and deuterium oxide (1:1) at 21 °C.

(iii) A sample (9 mg) of **16** in sodium deuteroxide (0.30 M) in methanol-d_4:D_2O (1:1) was heated for 15 days at 77 °C in a sealed NMR tube. The solution was neutralized with concentrated hydrochloride acid. This mixture was used in the HPLC analysis. It was found that the mixture contained *trans*-3-*d*-3-phenylsulfonyl-2-methoxynorbornane (**16**) (97.1%) and *cis*-3-*d*-3-phenylsulfonyl-2-methoxynorbornane (**17**) (2.9% ± 1).

g) Kinetics of H-D Exchange of *cis*-3-Phenylsulfonyl-2-methoxybicyclo[2.2.2]octane (17)

The H-D exchange of **17** (9 mg) was carried out as described in the general procedure at four different concentrations of sodium deuteroxide (0.075, 0.10, 0.125, and 0.15 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. The ^1H NMR spectra showed that compound **17** in sodium deuteroxide underwent H-D exchange to form *endo*-3-*d*-*exo*-3-phenylsulfonyl-*exo*-2-methoxybicyclo[2.2.2]octane, and inversion to form *exo*-3-*d*-*endo*-3-phenylsulfonyl-*exo*-2-methoxybicyclo[2.2.2]octane. The pseudo-first-order rate constant for **17** to generate α-sulfonyl carbanion was obtained from the plot of ln C_t (C_t is the percentage concentration of **17**) *vs.* time (s). The pseudo-first-order rate constant for inversion was obtained by computer simulation. The results are listed in Table 1.10. The second-order rate constants k_{ex} were obtained from the plots of k_{obs} *vs.* [OD^-] and the result are included

in Tables 1.4 and 1.5.

h) Kinetics of H-D Exchange of *trans*-2-Phenylsulfonyl-1-methoxycyclohexane (11)

The H-D exchange of **11** (9 mg) was carried out as described in the general procedure at four different concentrations of sodium deuteroxide (0.10, 0.15, 0.20, and 0.238 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. The pseudo-first-order rate constant was obtained from the plot of ln C_t *vs.* time. The results are listed in Table 1.8. The second-order rate constant k_{ex} was obtained from the plot of k_{obs} *vs.* [OD^-] and the result is listed in Table 1.4.

i) Kinetics of H-D Exchange of *cis*-2-Phenylsulfonyl-1-methoxycyclohexane (10)

The H-D exchange of **10** (10 mg) was carried out as described in the general procedure at four different concentrations of sodium deuteroxide (0.15, 0.175, and 0.20 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. The pseudo-first-order rate constant was obtained from the plot of ln C_t *vs.* time. The results are listed in Table 1.8. The second-order rate constant k_{ex} was obtained from the plot of k_{obs} *vs.* [OD^-] and the result is included in Table 1.4.

j) Kinetics of H-D Exchange of *exo*-2-Phenylsulfonyl-

norbornane (18)

i) The H-D exchange of **18** (10 mg) was carried out as described in the general procedure at four different concentrations of sodium deuteroxide (0.125, 0.15, 0.175, and 0.20 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. Because the reaction of H-D exchange was very slow, the NMR tubes were kept in a 21 °C water bath. The pseudo-first-order rate constant was obtained from the plot of ln C_t *vs.* time. The results are listed in Table 1.9. The second-order rate constant k_{ex} was obtained from the plot of k_{obs} *vs.* [OD^-] and the result is included in Table 1.4.

ii) The kinetic reaction of H-D exchange of **18** (10 mg) was carried out as described in the general procedure at the concentration of sodium deuteroxide 0.30 M in a mixed solvent of dioxane-d_8 and deuterium oxide (1:1) at 77 °C by keeping the NMR tube in a 77 °C oil bath. The pseudo-first-order rate constant was obtained from the plot of ln C_t *vs.* time. The results are listed in Table 1.9. The second-order rate constant k_{ex} was obtained by dividing the k_{obs} with the concentration of [OD^-] and the result is included in Table 1.4. It was found that H-D exchange reaction finished in one day, but an inversion of 6.8% was found after 70 days at 77 °C.

k) Kinetics of H-D Exchange of *endo*-2-Phenylsulfonyl-norbornane (19)

The H-D exchange of **19** (10 mg) was carried out as described in the general procedure at the concentration of sodium deuteroxide 0.30 M in a mixed solvent of dioxane-d_8 and deuterium oxide (1:1) at 77 °C. Because the inversion was very slow, the NMR tube was kept in a 77 °C oil bath. The pseudo-first-order rate constant was obtained from the plot of ln C_t *vs.* time. The results are listed in Table 1.9. The second-order rate constant k_{ex} was obtained by dividing the k_{obs} with the concentration of [OD^-] and the result is listed in Tables 1.4 and 1.5. It was found that H-D exchange reaction finished in a few hours, but an inversion of 42.8% was found after 70 days at 77 °C. From the data of inversion of **18** and **19** we estimate the equilibrium concentrations of **18** and **19** are 15% ± 5 and 85% ± 5, respectively.

1) Kinetics of H-D Exchange of 2-Phenylsulfonyl-bicyclo-[2.2.2]octane (20)

The H-D exchange of **20** (10 mg) was carried out as described in the general procedure at four different concentrations of sodium deuteroxide (0.125, 0.15, 0.175, and 0.20 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. Because the reaction of H-D exchange was very slow, the NMR tubes were kept in a 21 °C water bath. The pseudo-first-order rate constant was obtained from the plot of ln C_t *vs.* time. The results are listed in Table 1.9. The second-order rate constant k_{ex} was

obtained from the plot of k_{obs} *vs.* $[OD^-]$ and the result is included in Table 1.4.

m) Kinetics of H-D Exchange of Cyclohexyl Phenyl Sulfone (21)

The H-D exchange of **21** (9.5 mg) was carried out as described in the general procedure at four different concentrations of sodium deuteroxide (0.125, 0.15, 0.175, and 0.20 M) in a mixed solvent of acetonitrile-d_3 and deuterium oxide (1:1) at 21 °C. Because the reaction of H-D exchange was very slow, the NMR tubes were kept in a 21 °C water bath. The pseudo-first-order rate constant was obtained from the plot of ln C_t *vs.* time. The results are listed in Table 1.9. The second-order rate constant k_{ex} was obtained from the plot of k_{obs} *vs.* $[OD^-]$ and the result is included in Table 1.4.

Table 1.11 The Torsion Angles of Compounds **14**, **16**, and **17**

Torsion Angle (°)	**14**	**16**	**17**
H(3)-C(3)-C(2)-O(3)	6.4	6.2	-147.6
H(3)-C(3)-C(2)-H(2)		131.6	-27.9
H(3)-C(3)-C(2)-C(1)	-112.3		90.1
H(3)-C(3)-C(4)-C(5)	42.2	76.3	-39.0
H(3)-C(3)-C(4)-C(7)	147.8	-165.9	-156.6
H(2)-C(2)-C(1)-C(6)		173.8	73.2
O(1)-S-C(3)-H(3)	159.9	174.5	-42.9
O(1)-S-C(3)-C(2)	-79.1	-49.3	-159.8
O(1)-S-C(3)-C(4)	37.5	78.6	71.5
O(2)-S-C(3)-H(3)	-70.6	44.9	-171.8
O(2)-S-C(3)-C(2)	50.3	-178.9	71.3
O(2)-S-C(3)-C(4)	166.9	-51.0	-57.4
C(10)-S-C(3)-H(3)	44.4	-70.8	71.0
C(10)-S-C(3)-C(2)	165.4	65.4	-45.8
C(10)-S-C(3)-C(4)	-78.0	-166.7	-174.6
S-C(3)-C(2)-O(3)	-114.8	-111.3	-30.8
S-C(3)-C(2)-H(2)		14.1	88.9
S-C(3)-C(2)-C(1)	126.5	125.8	-153.1
S-C(3)-C(4)-C(5)	164.7	172.5	-153.4
S-C(3)-C(4)-C(7)	-89.7	-69.7	89.0
O(3)-C(2)-C(1)-C(6)	-53.2	-58.2	-165.1
O(3)-C(2)-C(1)-C(7)	-160.2		
O(3)-C(2)-C(3)-C(4)		120.3	98.8
C(3)-C(2)-C(1)-C(7)	-38.7		
C(3)-C(2)-C(1)-C(6)	68.3	60.3	-44.9
C(2)-C(3)-C(4)-C(7)	31.6	58.5	-43.0
C(2)-C(3)-C(4)-C(5)	-74.1	-58.3	74.7

Table 1.12 The Torsion Angles of Compounds **12** and **15**

Torsion Angle (°)	**12**	**15** Conf. A	**15** Conf. B
H(3)-C(3)-C(2)-O(3)	9.5	-132.8	-123.9
S-C(3)-C(2)-O(3)	-110.1	-11.2	-0.7
H(3)-C(3)-C(2)-H(2)	130.0	-9.7	-1.9
H(3)-C(3)-C(2)-C(1)	-110.6	109.6	114.9
H(3)-C(3)-C(4)-C(5)	-178.9	-41.5	-44.2
H(3)-C(3)-C(4)-C(7)	75.5	-143.8	-149.9
H(2)-C(2)-C(1)-C(6)	44.6	52.7	46.2
H(2)-C(2)-C(1)-C(7)	151.3	159.2	152.1
O(1)-S-C(3)-H(3)	69.3	58.6	-178.2
O(1)-S-C(3)-C(2)	-171.2	-62.8	58.3
O(1)-S-C(3)-C(4)	-49.8	178.3	-60.7
O(2)-S-C(3)-H(3)	-161.0	-168.7	-49.7
O(2)-S-C(3)-C(2)	-41.5	69.9	-173.2
O(2)-S-C(3)-C(4)	79.9	-49.0	67.8
C(10)-S-C(3)-H(3)	-45.7	-54.5	62.9
C(10)-S-C(3)-C(2)	73.8	-175.8	-60.6
C(10)-S-C(3)-C(4)	-164.8	65.2	-179.6
S-C(3)-C(2)-H(2)	11.4	112.0	121.4
S-C(3)-C(2)-C(1)	129.8	-128.8	-121.9
S-C(3)-C(4)-C(5)	-59.8	-161.3	-161.4
S-C(3)-C(4)-C(7)	-165.4	96.4	92.9
O(3)-C(2)-C(1)-H(1)		47.7	41.9
O(3)-C(2)-C(1)-C(6)	171.0	176.2	170.5
O(3)-C(2)-C(1)-C(7)	-82.3	-77.3	-83.6
C(3)-C(2)-C(1)-C(7)	33.2	39.3	34.8
C(3)-C(2)-C(1)-C(6)	-73.5	-67.2	-71.0
C(2)-C(3)-C(4)-H(4)		-157.5	-160.6
C(2)-C(3)-C(4)-C(5)	67.4	72.9	70.8

Table 1.13 The Torsion Angles of Compounds **13**

Torsion Angle (°)	Conf.A	Conf.B	Conf.C	Conf.D
H(3)-C(3)-C(2)-O(3)	-131.3	135.3	-126.5	-128.2
S-C(3)-C(2)-O(3)	-13.9	17.3	-6.2	-10.9
H(3)-C(3)-C(2)-H(2)	-11.0	14.1	-4.4	-7.7
H(3)-C(3)-C(2)-C(1)	105.1	-102.0	111.9	109.6
H(3)-C(3)-C(4)-C(5)	-175.1	174.8	177.4	179.4
H(3)-C(3)-C(4)-C(7)	-71.4	68.4	-75.4	-73.5
H(2)-C(2)-C(1)-C(6)	-167.9	166.9	-172.5	-173.1
H(2)-C(2)-C(1)-C(7)	86.0	-87.8	79.4	81.4
O(1)-S-C(3)-H(3)	-175.8	-174.1	162.6	-176.8
O(1)-S-C(3)-C(2)	66.6	-55.7	41.9	65.9
O(1)-S-C(3)-C(4)	-57.6	69.6	-80.6	-60.9
O(2)-S-C(3)-H(3)	52.4	57.1	-67.4	51.8
O(2)-S-C(3)-C(2)	-65.2	175.5	171.9	-65.6
O(2)-S-C(3)-C(4)	170.6	-59.2	49.4	167.6
C(10)-S-C(3)-H(3)	-61.3	-56.3	45.6	-62.0
C(10)-S-C(3)-C(2)	-178.9	62.0	-75.0	-179.4
C(10)-S-C(3)-C(4)	56.9	-172.6	162.4	53.8
S-C(3)-C(2)-H(2)	106.4	-103.9	115.9	109.6
S-C(3)-C(2)-C(1)	-137.5	140.0	-127.7	-133.1
S-C(3)-C(4)-C(5)	67.0	-69.0	60.9	64.0
S-C(3)-C(4)-C(7)	170.7	-175.4	168.1	171.1
O(3)-C(2)-C(1)-H(1)	84.8	-85.6	81.1	82.9
O(3)-C(2)-C(1)-C(6)	-44.9	43.0	-49.3	-46.5
O(3)-C(2)-C(1)-C(7)	-151.1	148.3	-157.5	-152.0
C(3)-C(2)-C(1)-C(7)	-30.2	28.6	-37.2	-36.5
C(3)-C(2)-C(1)-C(6)	75.9	-76.7	71.0	69.0
C(2)-C(3)-C(4)-H(4)	162.9	-164.8	159.3	156.3
C(2)-C(3)-C(4)-C(5)	-63.1	64.0	-70.5	-71.0

Table 1.14 The Bond Lengths of Compounds 12, 14, 16, and 17

Bond Length (Å)	12	14	16	17
S-C(3)	1.777	1.793	1.793	1.789
S-C(10)	1.766	1.757	1.763	1.773
S-O(1)	1.431	1.443	1.442	1.443
S-O(2)	1.439	1.439	1.443	1.442
O(3)-C(2)	1.424	1.407	1.430	1.411
O(3)-C(9)	1.403	1.426	1.419	1.409
C(10)-C(11)	1.386	1.399	1.384	1.372
C(10)-C(15)	1.385	1.388	1.385	1.380
C(11)-C(12)	1.383	1.386	1.390	1.384
C(12)-C(13)	1.372	1.384	1.369	1.376
C(13)-C(14)	1.369	1.383	1.375	1.364
C(14)-C(15)	1.386	1.392	1.382	1.386
C(3)-C(2)	1.537	1.569	1.541	1.538
C(3)-C(4)	1.547	1.543	1.538	1.544
C(2)-C(1)	1.541	1.536	1.530	1.544
C(1)-C(6)	1.536	1.532	1.523	1.524
C(4)-C(8)			1.527	1.537
C(1)-C(7)	1.524	1.525		
C(6)-C(5)	1.544	1.548	1.541	1.544
C(5)-C(4)	1.531	1.541	1.526	1.534
C(7)-C(8)			1.536	1.547
C(4)-C(7)	1.528	1.539	1.528	1.531

Table 1.14 Continuted

The Bond Lengths of Compound 13

Bond Length (Å)	Config A	Config B	Config C	Config D
S-C(3)	1.785	1.779	1.801	1.770
S-C(10)	1.750	1.748	1.748	1.746
S-O(1)	1.441	1.433	1.434	1.432
S-O(2)	1.441	1.442	1.445	1.439
O(3)-C(2)	1.409	1.411	1.416	1.395
O(3)-C(9)	1.406	1.397	1.399	1.405
C(1)-C(2)	1.537	1.541	1.550	1.509
C(1)-C(6)	1.531	1.509	1.522	1.527
C(1)-C(7)	1.521	1.524	1.514	1.518
C(2)-C(3)	1.554	1.562	1.571	1.566
C(3)-C(4)	1.538	1.543	1.531	1.564
C(4)-C(5)	1.526	1.531	1.507	1.417
C(4)-C(7)	1.546	1.528	1.531	1.550
C(5)-C(6)	1.556	1.547	1.543	1.586
C(1)-H(1)	0.960	0.960	0.960	0.960
C(2)-H(2)	0.960	0.960	0.960	0.960
C(3)-H(3)	0.960	0.960	0.960	0.960
C(4)-H(4)	0.960	0.960	0.960	0.960

Table 1.15 The Bond Angles of Compounds 12, 14, 16, and 17

Bond Angle (°)	12	14	16	17
O(1)-S-O(2)	118.0	117.8	118.2	117.2
O(1)-S-C(10)	108.3	107.9	107.5	108.3
O(2)-S-C(10)	107.7	108.3	108.3	108.3
O(1)-S-C(3)	107.7	108.7	110.3	105.2
O(2)-S-C(3)	109.8	107.9	107.6	112.6
C(1)-S-C(3)	104.5	104.5	103.9	104.4
S-C(10)-C(11)	118.8	119.1	119.8	120.3
S-C(10)-C(15)	119.9	119.8	119.2	119.1
S-C(3)-C(2)	115.3	111.7	113.1	116.8
S-C(3)-C(4)	114.3	113.5	111.5	112.1
C(2)-O(3)-C(9)	113.6	114.4	112.6	112.7
C(5)-C(4)-C(7)	101.3	101.2		
O(3)-C(2)-C(3)	107.5	114.1	105.9	109.4
O(3)-C(2)-C(1)	114.0	110.1	113.8	112.8
C(3)-C(2)-C(1)	101.9	102.1	109.1	106.7
C(2)-C(1)-C(6)	107.3	110.1	109.7	109.4
C(2)-C(1)-C(7)	101.7	101.4	107.3	107.8
C(1)-C(7)-C(8)			109.9	109.0
C(6)-C(1)-C(7)	102.0	101.8		
C(6)-C(1)-C(8)			110.5	109.3
C(3)-C(4)-C(5)	111.1	106.7	105.8	105.2
C(3)-C(4)-C(7)	98.6	101.7		
C(1)-C(7)-C(4)	94.9	94.7		
C(1)-C(6)-C(5)	103.6	103.5	109.8	109.8
C(6)-C(5)-C(4)	102.9	103.1	109.6	108.7
C(5)-C(4)-C(8)			109.2	109.2
C(3)-C(4)-C(8)			111.7	110.1
C(4)-C(8)-C(7)			109.3	109.3

Table 1.16 The Bond Angles of Compound 13

Bond Angle (°)	Config A	Config B	Config C	Config D
O(1)-S-O(2)	118.0	117.1	118.2	118.4
O(1)-S-C(10)	107.1	108.8	107.5	108.0
O(2)-S-C(10)	108.2	107.5	107.7	108.7
O(1)-S-C(3)	112.8	112.0	113.4	111.9
O(2)-S-C(3)	107.5	105.9	104.3	107.3
C(3)-S-C(10)	102.0	104.7	104.9	101.2
S-C(3)-C(4)	117.0	116.5	113.8	116.4
S-C(3)-C(2)	116.4	119.3	119.8	120.8
S-C(3)-H(3)	105.8	105.1	106.1	104.6
O(3)-C(2)-C(1)	115.2	114.9	113.7	116.0
O(3)-C(2)-C(3)	111.0	110.6	111.9	106.4
O(3)-C(2)-H(2)	108.9	109.7	109.5	110.7
C(2)-O(3)-C(9)	113.2	112.1	111.6	109.5
C(1)-C(2)-C(3)	102.7		101.5	102.4
C(1)-C(6)-C(5)	102.7	104.8	102.6	103.1
C(1)-C(7)-C(4)	96.0	95.3	94.0	94.6
C(1)-C(2)-H(2)	109.4	109.4	109.9	110.0
C(2)-C(3)-C(4)	104.3	103.5	103.1	103.4
C(2)-C(1)-C(7)	101.3	102.5	100.4	101.7
C(3)-C(2)-H(2)	109.5	109.9	110.1	110.9
C(3)-C(4)-C(5)	112.0	110.8	111.6	114.0
C(3)-C(4)-C(7)	97.2	98.2	99.9	98.2
C(3)-C(4)-H(4)	114.9	114.7	113.4	113.2
C(4)-C(3)-H(3)	106.3	105.5	106.6	105.4
C(4)-C(5)-C(6)	104.7	102.1	103.4	102.8
C(5)-C(4)-C(7)	99.8	102.2	102.0	102.0
C(5)-C(4)-H(4)	115.3	114.2	113.9	114.1

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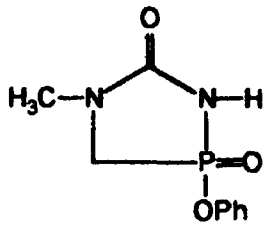
Chapter 2

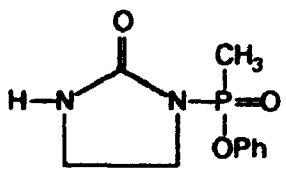
Synthesis, pK_a Determination and Hydrolysis of Sulfonamides and Sulfonimides

2.1 INTRODUCTION

Extraordinary differences have been reported between the rates of alkaline hydrolysis of five-membered cyclic esters of oxy-acids of phosphorus and sulfur on the one hand, and their six-membered ring and open-chain analogues on the other. Westheimer *et al.*[1] investigated the hydrolysis in acid or base of five-membered cyclic phosphates[2] and phosphonates[3] and found that five-membered cyclic phosphates and phosphonates hydrolyse 10^5-10^8 times faster than either their open-chain analogues or their six- and seven-membered ring counterparts. More recently, Kluger and Thatcher[4] reported that the rate constant for P-N bond cleavage by the alkaline hydrolysis of the five-membered cyclic compound **1** is about 5 x 10^5 times as large as that for its acyclic analogue **2**.



(1)

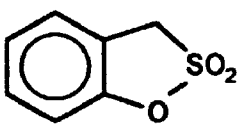


(2)

The cause of kinetic acceleration in those cyclic esters has been assigned to ring strain[5]. It was shown by thermochemical measurements[6] that ethylene phosphate was

indeed strained relative to an open-chain phosphate by 21-25 kJ mol^{-1} which correspond to a rate difference of 2.1 x 10^4 times if fully expressed in a rate acceleration at room temperature. Further evidence for strain was provided by x-ray crystallographic structure determinations on five-membered cyclic phosphates[7] which indicated considerable angle strain in the ring arising from small O-P-O bond angles. In *o*-phenylene cyclic phosphate, for example, the endocyclic O-P-O bond angle was 98.4° (the RO-P-OR angle for dibenzyl phosphate[8] was found to be 104°). The N-P-C bond angle in compound **1** is only 93.1°. Kluger and Thatcher[4] concluded that the tendency for strained cyclic phosphate ester derivatives to undergo rapid hydrolysis has been established as due to a reduction of strain in the transition state of the rate-determining step.

A similar effect[9] has been found with compounds containing a sulfonyl group. The five-membered aromatic sulfate, *o*-phenylene sulfate[10] (**6**) hydrolyses 2 x 10^7 times faster than diphenyl sulfate, and *o*-hydroxytoluene-α-sulfonic acid sultone (**3**) shows a rate enhancement of 7 x 10^6 over its open-chain analogue, phenyl phenylmethane-sulfonate[11] in alkaline solution. Laleh *et al.*[12] have studied the alkaline hydrolysis of cyclic and open-chain sulfonate esters and found that the five-membered cyclic sultone **3** reacts 2.1 x 10^4 times faster than its six-membered analogue **4**, 2.2 x 10^6 times faster than its seven-membered analogue **5**, and 1.1 x 10^5 times faster than its



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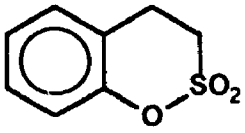

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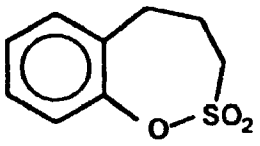

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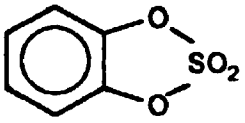

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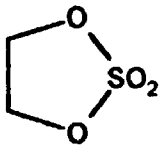

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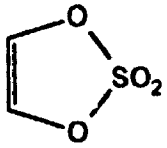

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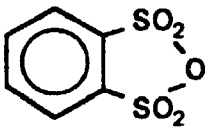

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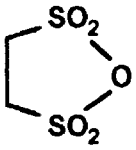

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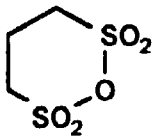


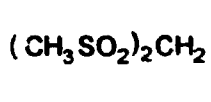
(11)

open-chain analogue, phenyl benzenesulfonate. These results are quite similar to those of Izbicka and Bolen[13] who also confirmed the large differences in hydrolysis enthalpy changes exhibited by the five- and six-membered ring sulfonate esters, 3 and 4, respectively.

The presence of considerable ring strain in five-membered cyclic sulfates and sulfonates has been confirmed by x-ray structure analysis. The six-membered sultone (4) is much less strained than the five-membered ring (3). X-

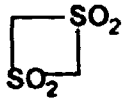
ray crystal analyses[14] have shown that the six-membered sultone has a larger internal C-S-O bond angle of 101.4° compared to its five-membered analogue **3** , 96.1°, and a larger C-O-S bond angle of 116.5° compared to its five-membered analogue, 108.9°. Similarly, in *o*-phenylene sulfate (**6**) it has been shown that all the angles are strained[15], and the five-membered ring is distorted into a non-planar envelope conformation. The O-S-O bond angle of 97.1° is also smaller than the C-S-O angle of 101.4° in **4**; the two O-C-C angles are distorted to values of 112.5 and 110.7°, respectively, which are much smaller than the normal 120° angle for sp^2-hybridised carbon. Boer and Flynn[15] suggested that a 1,3-nonbonding interaction in the five-membered ring between the lone-pair electrons of the ring oxygen and the sulfonyl oxygens could be another source of ring strain and that such interactions would be minimised in the five-membered ring by bending into the non-planar conformation. Ethylene sulfate (**7**)[16] was also found to show considerable ring strain, with an internal O-S-O bond angle of 98.4°, and the very reactive vinylene sulfate (**8**) has an O-S-O bond angle of 93.6°.

Geometric effects are also known to enhance the acidity of hydrogens in α positions to functional groups capable of stabilizing a negative charge. Block *et al.*[17] reported that the four-membered disulfone **13** is 2.5-3.0 pK_a units more acidic in DMSO than its open and six-membered analogues, **12** and **14**, respectively.



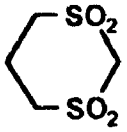
(pK_a 15.0)

(12)



(pK_a 12.5)

(13)

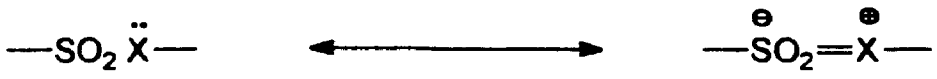


(pK_a 15.5)

(14)

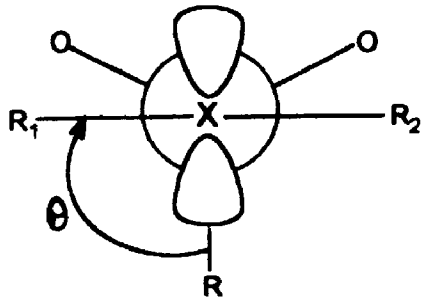
Laird and Spence[18] investigated the solvolyses of cyclic and acyclic sulfonic anhydrides in methanol at room temperature and found that the five-membered cyclic anhydride **10** reacted 3 times faster than the aromatic five-membered cyclic anhydride **9**, about 850 times faster than six-membered cyclic anhydride **11**, and 500 times faster than the acyclic analogue, methanesulfonic anhydride. They pointed out that the ring strain can not be the only factor facilitating the reactions of five-membered rings of benzene-1,2-disulfonic anhydride (**9**) and ethylene-1,2-disulfonic anhydride (**10**) over the six-membered ring of propane-1,3-disulfonic anhydride (**11**) and the acyclic analogues, as the less-strained **10** is more reactive than **9**.

Recently, King *et al.*[19] suggested that a stereo-electronic effect may contribute to the reactivity of cyclic sultones. One may recall that delocalization of an electron pair from an attached atom into a sulfonyl group has been postulated:[20]



X = N, O, F, C=C, etc

There is a considerable body of evidence indicating that this delocalization is greatest when the free electron pair (or π-bond) is arranged as shown in **15**. The most



(15)

extensive work in this topic has been done with α-sulfonyl carbanions, which are discussed in detail in Chapter 1. The same line of reasoning was extended by Jordan *et al.*[21] to sulfonamides, with further evidence in support of such a picture provided by Jennings and Spratt[22]. More recently King *et al.*[23] have searched the Cambridge Crystallographic Data Centre files about the geometry of sulfonic esters as well as sulfonamides and provided relevant information about the geometry of sulfonyl compounds. These C-S-X-C dihedral angles (where X = O, N, or Ar) in sulfonic esters, aryl sulfones and sulfonamides were distributed as shown in Figures 2.1, 2.2, and 2.3 respectively.

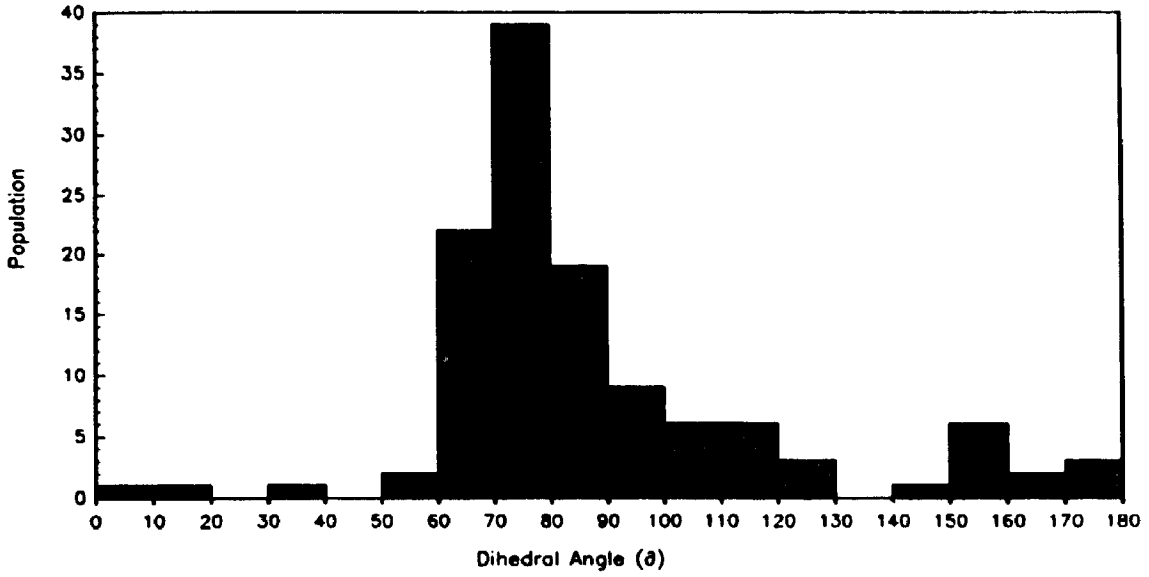


Figure 2.1 Population distribution of the C-S-O-C dihedral angle (θ) in sulfonic esters.

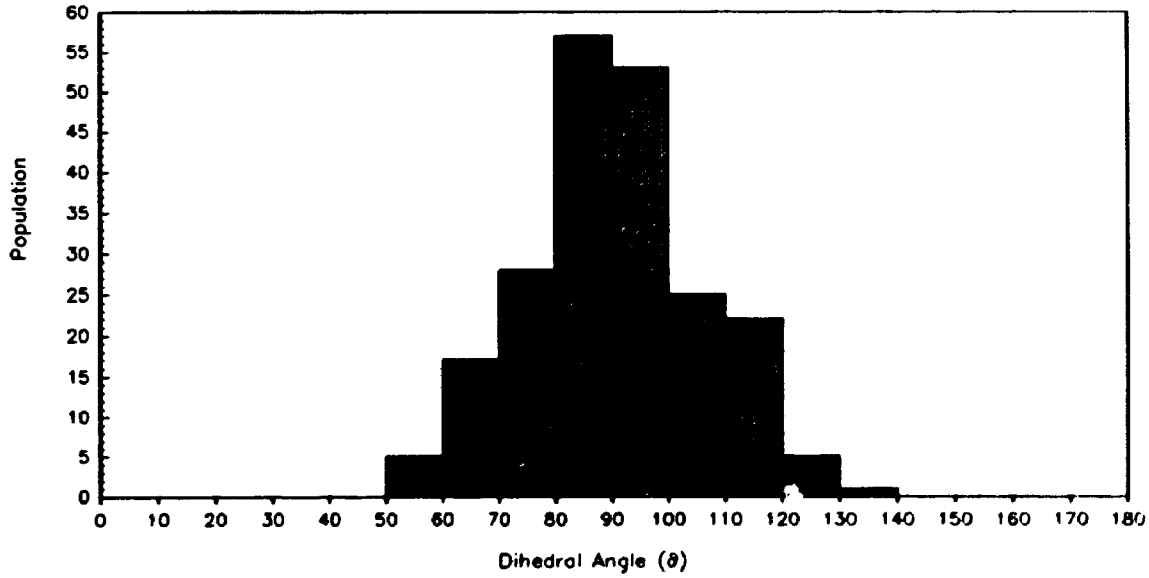


Figure 2.2 Population distribution of the C-S-C_{ipso}-C_{ortho} dihedral angle (θ) in aryl sulfones.

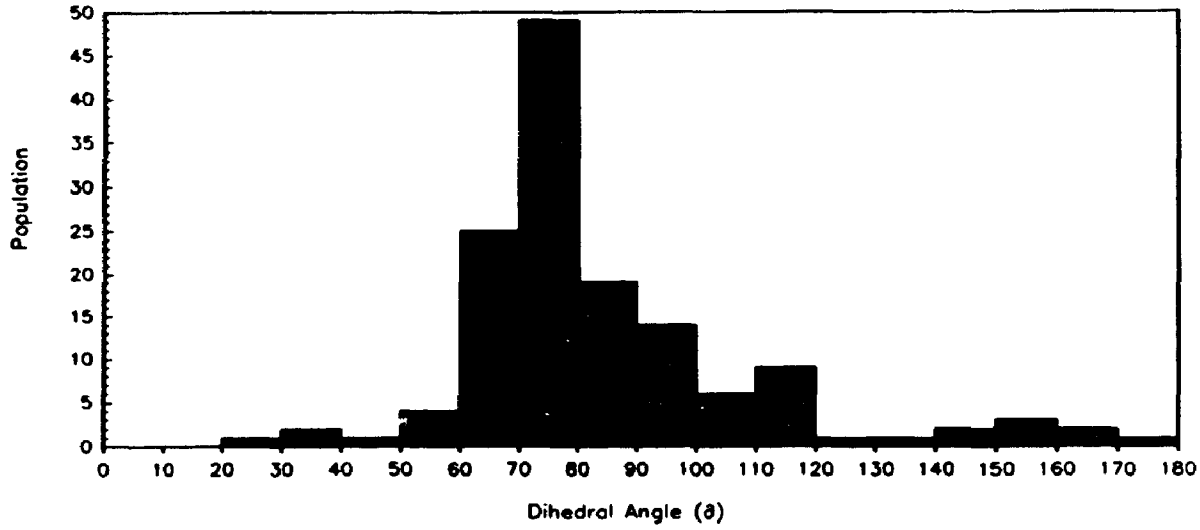
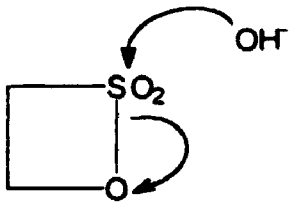


Figure 2.3 Population distribution of the C-S-N-C dihedral angle (θ) in *N,N*-dialkylsulfonamides.

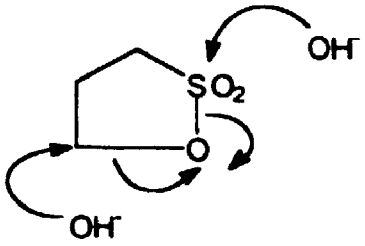
From Figure 2.1 one may find that most of the dihedral angles (80 out 121) in sulfonic esters are in the range 60-90° with no sulfonic esters having θ less than 50° except for three five-membered ring sultones.

The dihedral angles C-S-C_{ipso}-C_{ortho} in aryl sulfones also display the same geometric preference, e.g. 94% of the dihedral angles are in the 60-120° range and none are less than 50° (see Figure 2.2). In *N,N*-dialkylsulfonamides 88% of the C-S-N-C dihedral angles are in much the same range as in aryl sulfones (see Figure 2.3).

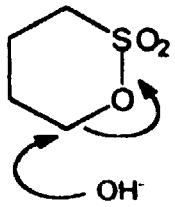
King *et al.*[19] found that for the hydrolysis of cyclic sultones with hydroxide the four-membered cyclic sultone **16**



(16)



(17)



(18)

reacted only by S-O bond cleavage, the five-membered cyclic sultone **17** 55% by S-O cleavage, 45% by C-O cleavage, but the six-membered cyclic sultone **18** only by C-O cleavage.

It was suggested that the OH^- attacked sulfur rather than carbon in four and five-membered cyclic sultones because the oxygen lone pair of electron does not bisect the sulfonyl oxygens effectively; this in turn causes lessened O→S electron donation which leads to a lower S-O bond order, a decreased δ^+ on the oxygen-bearing carbon, and an increased δ^+ on sulfur. King *et al.*[19] suggested that alteration of θ to values less than 50° would lead to (a) an increase in energy and hence perhaps to higher reactivity, and (b) to diminished electron delocalization onto the sulfur atom and hence to altered reactivity patterns.

This chapter is concerned with cyclic and acyclic sulfonamides $RSO_2NR'R''$ and sulfonimides RSO_2-NR'-SO_2R'', specifically, those with five-membered rings. Sulfonamides and sulfonimides with at least one hydrogen atom on the nitrogen are Brønsted acids in aqueous media. Methanesulfonamide and benzenesulfonamide have pK_a values[24] of

10.8 and 10.1, respectively, indicating sulfonamides to be weak acids. Sulfonimides are much stronger acids than sulfonamides, with a pK_a value of 1.45 having been reported for $PhSO_2$-NH-SO_2Ph[25].

The hydrolysis of sulfonamides has been carried out in acidic solution[26]. The cleavage of sulfonamides has been utilized frequently since the discovery of the Hinsberg reaction in 1890[27]. In the hydrolysis of sulfonamides cleavage of sulfur-nitrogen, carbon-nitrogen, and carbon-sulfur bonds has been observed[24]. Although sulfonamides are very stable and very difficult to hydrolyse, certain sultams, notably four-membered ring sultams (β-sultams) undergo ring opening in water, alkaline, or acidic solution[28]. Erman and Kretschmar[29] reported that *N*-alkyl five-membered sultams were cleaved by hydrochloric acid, hydrogen bromide, and acetic acid, with cleavage by methanoic hydrogen bromide or chloride taking place readily at 20 °C. Feichtinger and Puschoff[30] reported that 1,3-propane and *N*-methyl 1,3-propanesultam were cleaved by HCl in benzene at 25 °C. The sulfonimides, however, are more stable than the sulfonamides, and the hydrolysis of sulfonimides has been but little studied.

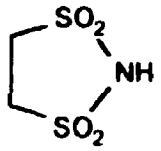
A mechanism of acid-catalysed hydrolysis of sulfonamides was proposed by Klamann and Hofbauer[31]. They suggested that protonation was required as an initial step in the rate-determining process followed by dissociation into an intermediate amino alkanesulfonylonium ion. Erman

and Kretschmar[29] presented evidence that the first step involves protonation of the nitrogen because the ease of cleavage was governed by the strength of the acid employed.

Li[32] in this laboratory found that the major products of hydrolysis of *N*-alkyl sultams in concentrated hydrochloric acid were the open chain sulfonyl chloride ammonium salts, and the k_{obs} for hydrolysis of *N*-methyl sultams depended linearly on [Cl^-]. Li[32] and Rathore[33] in this laboratory also found that hydrolysis of *N*-methyl propane-1,3-sulfonamide in concentrated hydrochloric acid at 21 °C was 3100 times faster than that of *N*-methyl butane-1,4-sulfonamide; 8650 times faster than *N,N*-dimethyl methane-sulfonamide. They suggested that the distinct difference of hydrolysis rate between the five-membered ring sultam and its six-membered ring, or open chain analogues may be ascribed to a combination of the ring strain effect and the stereoelectronic effect. Further confirmation of this proposal has been obtained by Klassen.[34]

In this study, we investigated the ring effects on the pK_a of sulfonimides and sulfonamides and on the hydrolysis of sulfonimides in concentrated hydrochloric acid, specifically, for the five-membered ring sulfonimides and sulfonamides to see if any unusual effects are presented in the five-membered ring compounds. In order to carry out our goal a procedure for synthesis of the simplest five-membered sulfonimide, ethane-1,2-disulfonimide (**19**), which has not been reported in literature, was developed. A number of

cyclic sulfonamides and sulfonimides, such as, cyclic sulfonimides **19**, **20**, and **21**, and sulfonamides **22**, **23**, **24**, and **25**, as well as acyclic analogues, were also prepared.



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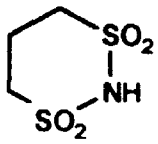

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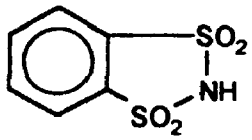

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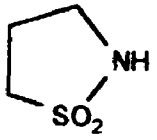

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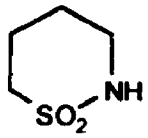

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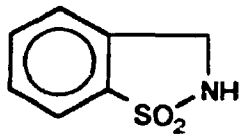

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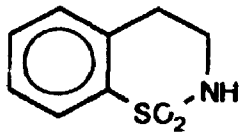

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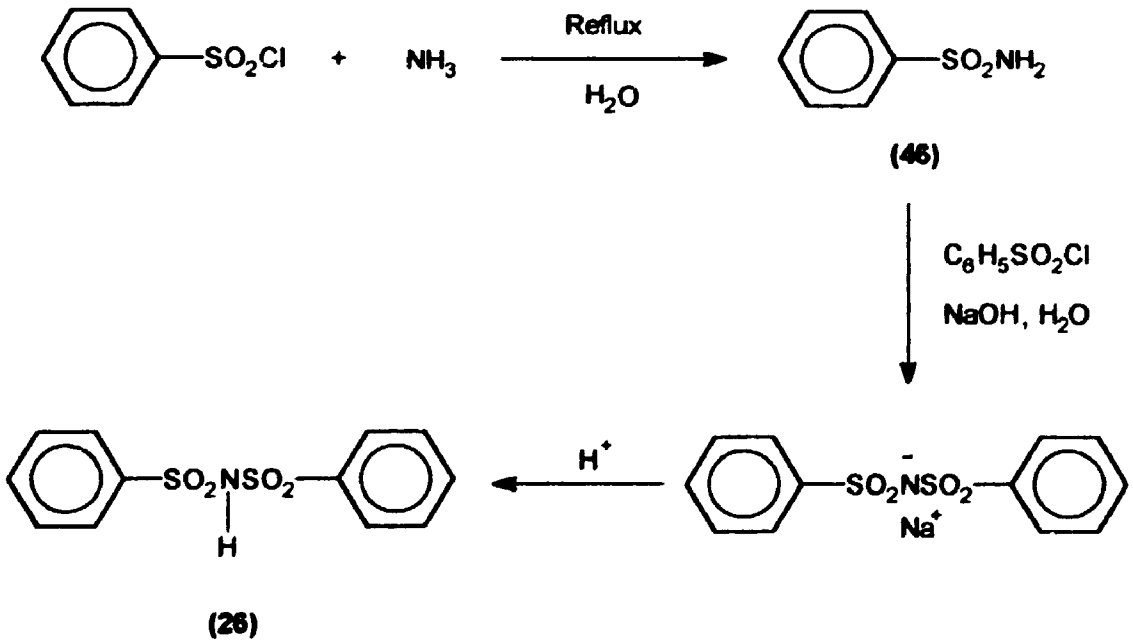
2.2 RESULTS AND DISCUSSION

2.2.1 Preparation of Cyclic and Acyclic Sulfonimides

The synthesis of a simple aromatic sulfonimide, dibenzenesulfonimide, was first achieved in 1854 by Gerhardt, by the reaction of benzenesulfonyl chloride on the silver salt of benzenesulfonamide[35]. Symmetrical aryl sulfonimides are also obtained by the reaction of 2 moles of arenesulfonyl chloride with 1 mole of ammonia in aqueous solution[36]. Dykhanov[37] synthesized a number of symmetrical unsubstituted and *para*-substituted dibenzene-sulfonimides by the reaction of a sulfonamide with a sulfonyl chloride in an aqueous sodium hydroxide solution. This procedure is outlined in Scheme 2.1.



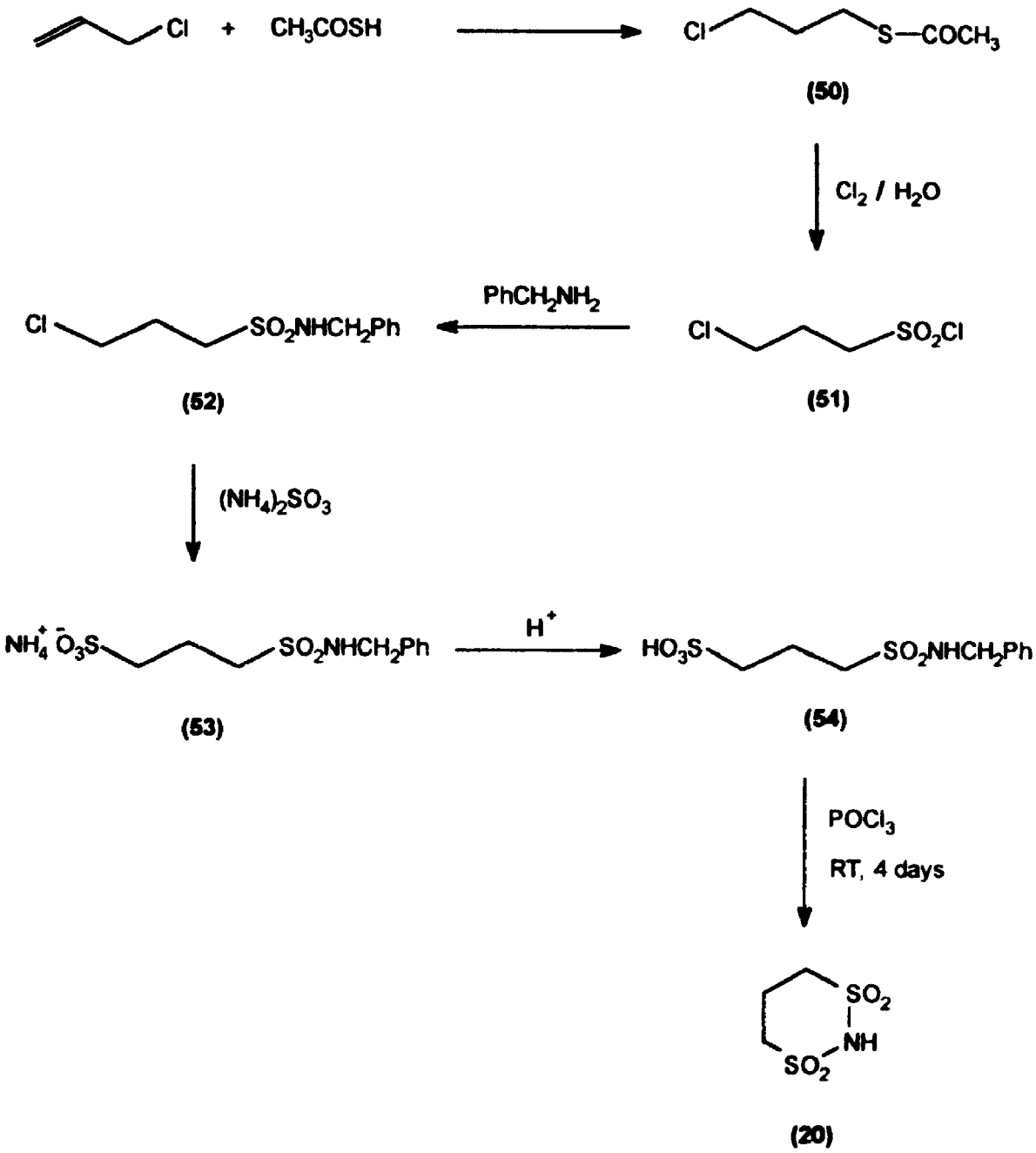
Scheme 2.1

The acyclic alkylsulfonimides were usually made from one mole of ammonium chloride and two moles of alkanesulfonyl chloride in basic aqueous solution[38].

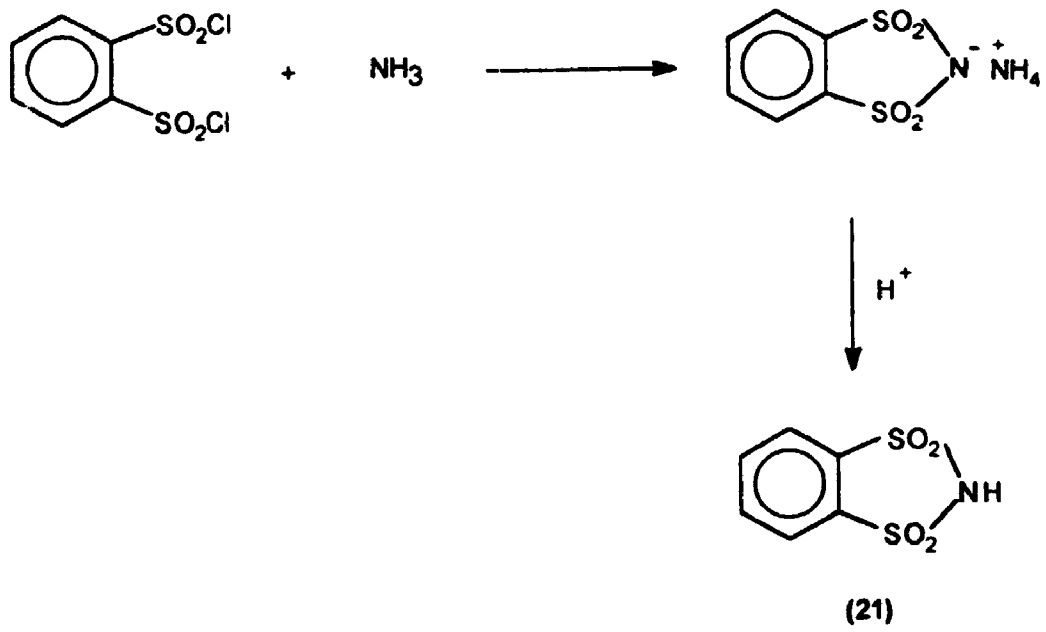
Only a few free cyclic sulfonimides have been synthesized. Propane-1,3-disulfonimide (**20**) was prepared by the procedure of Helferich and Hoffmann[39] as outlined in Scheme 2.2. Allyl chloride was treated with thiolacetic acid to form 3-chloropropyl thiolacetate (**50**) which on chlorination in water gave 3-chloropropanesulfonyl chloride (**51**). On reaction with benzylamine in benzene **51** gave *N*-benzyl 3-chloropropanesulfonamide (**52**) in 90% yield. This in turn when treated with ammonium sulfite hydrate in ethanol, formed ammonium 3-(benzylaminosulfonyl)-propanesulfonate (**53**) in 80% yield. Ion exchange of **53** with H^+ resin gave 3-(benzylaminosulfonyl)propanesulfonic acid (**54**) in 98% yield, which was stirred with phosphorus oxychloride at room temperature for four days to give propane-1,3-disulfonimide (**20**) in 65% yield.

Benzene-1,2-disulfonimide (**21**) was synthesized by the procedure of Hendrickson *et al.*[40] as outlined in Scheme 2.3. Benzene-1,2-disulfonyl chloride in benzene was reacted with ammonia in ethanol to form the ammonium benzene-1,2-disulfonimide which gave the free sulfonimide **21** by H^+ ion exchange.

Ethane-1,2-disulfonimide (**19**) has not been reported in the literature. A route of preparation of **19** was designed in this laboratory.


Cl + CH3COSH
Cl S—COCH3
(50)
Cl2 / H2O
PhCH2NH2
Cl SO2NHCH2Ph
Cl SO2Cl
(52)
(51)
(NH4)2SO3
NH4+ -O3S SO2NHCH2Ph
H+
HO3S SO2NHCH2Ph
(53)
(54)
POCl3
RT, 4 days
SO2
NH
SO2
(20)

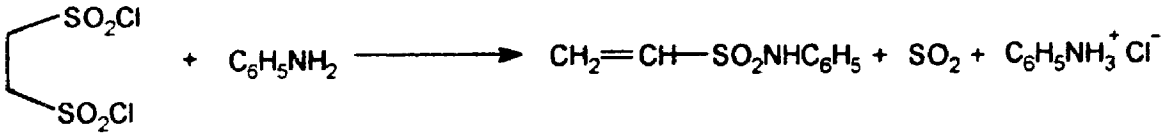
Scheme 2.2



(21)

Scheme 2.3

It was not possible to prepare ethane-1,2-disulfonimide (**19**) following the same route as that for **21**, since it is known that ethane-1,2-disulfonyl chloride gives a vinylsulfonamide[41] when it was treated with an amine; the reaction with aniline is outlined in Scheme 2.4. An

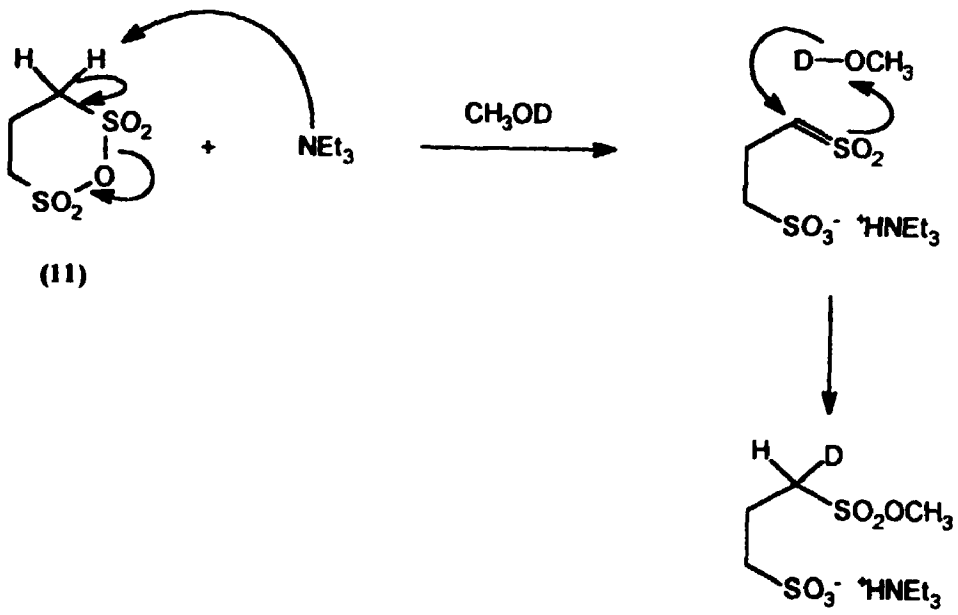


Scheme 2.4

explanation for this transformation was provided by King *et al.*[42] who found that ethane-1,2-disulfonyl chloride reacted with pyridine by a route involving initial formation of ethenesulfonyl chloride followed by vinylogous reaction

to form the sulfene.

It seemed possible, however, that the cyclic five-membered sulfonic anhydride (**10**) might be used as the starting material for the preparation of ethane-1,2-disulfonimide (**19**) if the amine acts as a general base rather than attacks the α-hydrogen to give a sulfene. To test for this possibility we carried out the reactions of triethylamine with the six-membered cyclic anhydride **11** and the five-membered cyclic anhydride **10** in methanol-*d* to find out how the amine promoted reaction takes place with these two cyclic sulfonic anhydrides. It was found that for the reaction of triethylamine with **11** in methanol-*d*, the triethylammonium 3-(methoxy-sulfonyl)propanesulfonate-d_1 was obtained. The reaction of triethylamine with **10** under the same conditions, however, gave only the undeuterated product, triethylammonium 2-(methoxysulfonyl)ethane-sulfonate. It is obvious from the products that the reactions of these two anhydrides with triethylamine and methanol take place by different mechanisms. With triethyl-amine and propane-1,3-disulfonic anhydride (**11**) the mechanism is very likely that shown in Scheme 2.5. From the mechanism in Scheme 2.5 one may see that the amine attacks a α-hydrogen to form the sulfene first, and the sulfene then reacts with the solvent (methanol-*d*) to give the deuterated product. For the reaction of triethylamine with ethane-1,2-disulfonic anhydride (**10**), the amine does not yield the sulfene but rather acts as a general base to help



(11)

Scheme 2.5

the methanol to attack the sulfur to give the undeuterated product. Lack of sulfene formation in the reaction of five-membered disulfonic anhydride **10** with triethylamine and methanol may be ascribed to the fact that the reaction would have to be a 5-endo-trig process which has been shown by Baldwin[43] to be disfavoured. This result is also consistent with the result of Farrar and Williams[44] who found that the reaction of the five-membered aromatic cyclic sultone **3** with an amine does not involve elimination-addition pathway because of the high energy of the sulfene-like transition state.

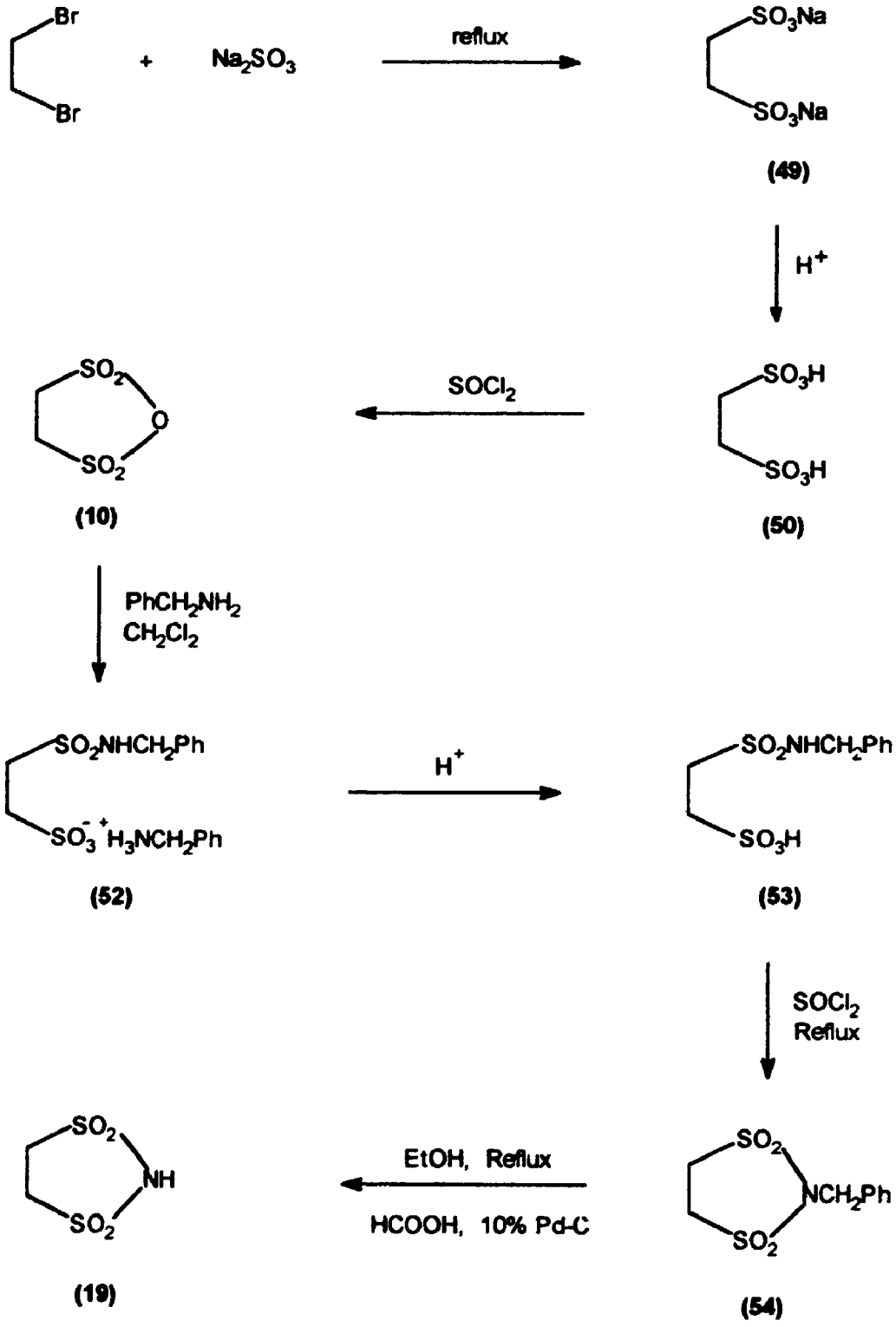
These considerations led to the route of preparation of

ethane-1,2-disulfonimide (**19**) outlined in Scheme 2.6. 1,2-Dibromoethane was treated with sodium sulfite in aqueous medium to give sodium ethane-1,2-disulfonate (**49**) which on ion exchange on a H^+ resin gave 1,2-ethanedisulfonic acid (**50**). On being refluxed with excess thionyl chloride, **50** formed ethane-1,2-disulfonyl anhydride (**10**). This was treated with benzylamine to give benzylammonium 2-(benzylaminosulfonyl)ethanesulfonate (**52**), which was followed by H^+ ion exchange to give 2-(benzylaminosulfonyl)-ethanesulfonic acid (**53**), which was in turn refluxed with thionyl chloride to form *N*-benzyl ethane-1,2-disulfonimide (**54**). Finally, the *N*-benzyl sulfonimide was hydrogenolysed with formic acid and 10% palladium on activated carbon in ethanol to give the ethane-1,2-disulfonimide (**19**). Ethane-1,2-disulfonimide was characterized with the help of ^1H NMR, ^{13}C NMR, ir and mass spectroscopy.

N-Benzoyl benzenesulfonamide[45] (**31**) was prepared in 72% yield by the pyridine-assisted acylation of benzenesulfonamide (**46**) with benzoyl chloride. *N*-Acetyl methanesulfonamide[46] (**32**) was synthesized from methanesulfonamide (**61**) and acetyl chloride in 94% yield.

2.2.2 Preparation of Sulfonamides

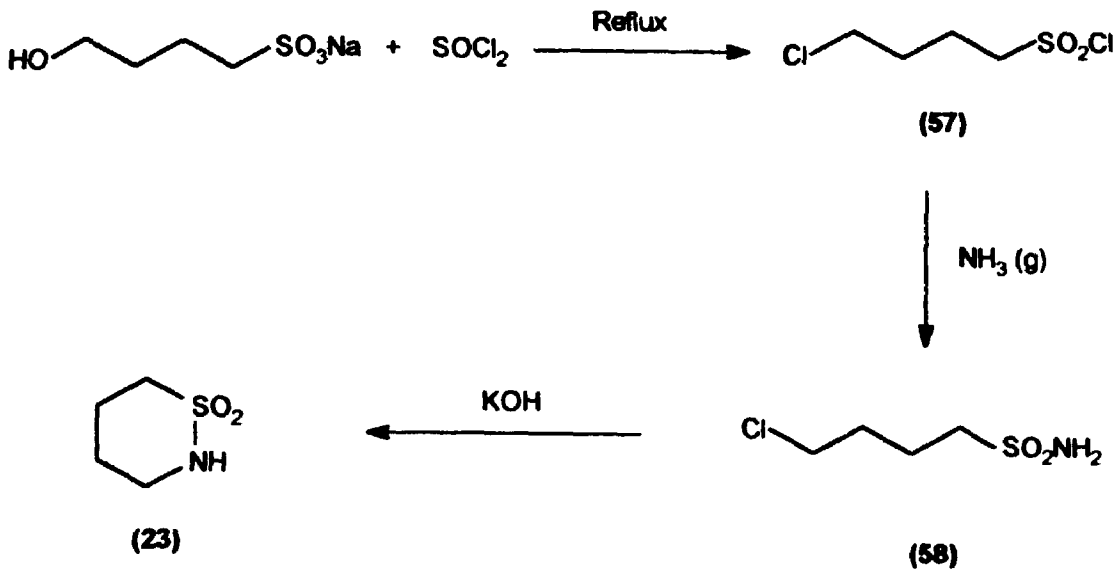
Cyclic sulfonamides (sultams) and acyclic sulfonamides were prepared in a number of ways. One of the most general synthetic route to acyclic sulfonamides is the reaction of ammonia[47], or primary amines[48] with a sulfonyl chloride


Br
Br
+
Na_2SO_3
reflux
SO_3Na
SO_3Na
(49)
H^+
SO_3H
SO_3H
(50)
$SOCl_2$
SO_2
O
SO_2
(10)
$PhCH_2NH_2$
CH_2Cl_2
SO_2NHCH_2Ph
$SO_3^- {}^+H_3NCH_2Ph$
(52)
H^+
SO_2NHCH_2Ph
SO_3H
(53)
$SOCl_2$
Reflux
SO_2
NCH_2Ph
SO_2
(54)
EtOH, Reflux
HCOOH, 10% Pd-C
SO_2
NH
SO_2
(19)

Scheme 2.6

in the presence of a base. All of the acyclic sulfonamides (34) to (42) were synthesized by this procedure.

1,4-Butanesultam (23) was prepared as outlined in Scheme 2.7. 4-Chloro-1-butanesulfonyl chloride (57) was



Scheme 2.7

obtained in 83.8% yield by treating commercial 4-hydroxy-1-butanesulfonate with thionyl chloride. Sulfonyl chloride 57 with dry ammonia in diethyl ether gave 4-chloro-1-butane-sulfonamide (58) (94% yield) which was refluxed with potassium hydroxide in ethanol to yield 1,4-butanesultam (23) in 87% yield.

1,3-Propanesultam (22) was synthesized by a procedure of Bliss *et al.*[49] 3,4-Dihydro-1-H-2,3-benzothiazine-2,2-dioxide (24) was prepared in 72.4% yield by the reaction of

phenylmethanesulfonamide (59) with 1,3,5-trioxane and methanesulfonic acid in dichloromethane according to the method of Orazi *et al.*[50] 2,3-Dihydro-1,2-benzisothiazole 1,1-dioxide (25) was synthesized by the procedure of Teeninga and Engbert[51].

2.2.3 The Results of pK_a Determination and Hydrolysis of Sulfonamides and Sulfonimides

The pK_a's of the sulfonamides were determined by titration, and those of the sulfonimides were determined by NMR, UV, or titration methods. The hydrolysis of sulfonimides was carried out in concentrated hydrochloric acid.

2.2.3.1 pK_a Determination of Sulfonamides

The most convenient method for the determination of ionization constants of acidic compounds in water is potentiometric titration. The lower limit is imposed by the uncertainty of applying activity coefficients in the pH range 1-2. Albert and Serjeant[52] pointed out that the lower limit for accuracy should be pK_a 2.5, but reasonable estimates of pK_a in the range 1.2-2.5 could be obtained provided activity corrections are applied. The upper limit is imposed by the unreliable performance of the glass electrode at high pH. Hall and Sprinkle[53], and Thamsen[54] have determined a pK_a value as high as 13.65. In addition to the limitation of the pH range over which the glass

electrode is thought to be accurate, there is also a limitation upon the concentration range over which it is applicable for the accurate determination of pK_a values. In the concentration range 0.005-0.050 M, the results obtainable by use of precision pH apparatus can closely approach the true thermodynamic value[52].

The potentiometric titration method for pK_a determination is very useful and quite simple. Kaiser *et al.*[55] found that pK_a of pentafluorobenzenesulfonamide was 3.1 in 0.042 M sodium sulfate aqueous solution using this method. In this study the pK_a's of all of sulfonamides are determined by the potentiometric titration, and results are listed in Table 2.1.

2.2.3.2 pK_a Determination of Sulfonimides

Sulfonimides are generally distinctly more acidic than the sulfonamides. Foropoulos and DesMarteau[56] reported that the pK_a value of $(CF_3SO_2)_2NH$ as determined by titration is 1.7 in water. Ruff[57] found that $(FSO_2)_2NH$ has a pK_a value of 1.3 using the same method. Potentiometric titration, however, is not satisfactory with all of the sulfonimides because some sulfonimides are very acidic and the titration method can not measure their pK_a's accurately. In this study the NMR and UV methods were used for the determination of the pK_a (or H_o value at 50% protonation) of some sulfonimides.

Laughlin[58] determined the equilibrium constants for

Table 2.1 The pK_a Values of Sulfonamides Determined by Titration

Sulfonamides	pK_a	Temp. (°C)
$CH_3SO_2NHCH_3$ (34)	11.79	25.0
CH_3SO_2NHPh (35)	8.98	20.0
	8.85	25.0
$CH_3SO_2NHC_6H_4$-*p*-CH_3 (36)	9.29	20.0
$CH_3SO_2NHC_6H_4$-*p*-NO_2 (37)	6.76	20.0
$CH_3SO_2NHC_6H_4$-*m*-NO_2 (38)	7.52	20.0
$CH_3SO_2NHC_6H_4$-*p*-Cl (39)	8.42	20.0
$CH_3SO_2NHC_6H_4$-*m*-Cl (40)	8.20	20.0
$CH_3SO_2NHC_6H_4$-*p*-OMe (41)	9.20	20.0
$CH_3SO_2NHC_6H_4$-*o*-OMe (42)	8.69	20.0
$C_3H_5SO_2NHPh$ (43)	9.26	20.0
$CH_3SO_2NHC_6H_{11}$ (44)	11.64	20.0
$CH_3CH_2SO_2NHCH_3$ (45)	11.84	25.0
$C_6H_5SO_2NH_2$ (46)	10.07	20.0
	10.10[a]	
$C_6H_{11}CH_2SO_2NHC_6H_4$-*p*-$CH_3$ (47)	11.54[b]	20.0
$CH_3CH_2SO_2NHC_6H_4$-*p*-CH_3 (48)	11.40[b]	20.0
1,3-Propanesultam (22)	11.39	25.0
	11.54	20.0
1,4-Butanesultam (23)	12.02	25.0
	12.34	20.0
2,3-Dihydro-1,2-benzisothiazole 1,1-Dioxide (24)	9.97	20.0
	11.43[b]	20.0
3,4-Dihydro-1-H-2,3-benzothiazine-2,2-dioxide (25)	12.30[b]	20.0

a. reference 24.

b. titrations were carried out in 50% EtOH/H_2O solution

the protonation (i.e. pK_a's of the conjugate acids) of *N*-methyl, *N*-ethyl, and *N,N*-dimethyl-methanesulfonamides by ^1H NMR in aqueous sulfuric acid and found a clear-cut inflection occurred at the H_o of half protonation. The NMR method involved the determination of ^1H NMR chemical shifts as a function of acidity in aqueous sulfuric acid using the H_o scale of Jorgenson and Hartter[59]. The success of this method requires that there be a significant difference in chemical shift between protonated and unprotonated forms, and that the influence of medium on chemical shifts be small.

In this study, the pK_a's of four sulfonimides were determined by the ^1H NMR method. Figures 2.4 to 2.7 show the plots of chemical shifts of CH_2SO_2 or CH_3SO_2 signals vs. H_o for ethane-1,2-disulfonimide (**19**), propane-1,3-disulfonimide (**20**), dimethanesulfonimide (**28**), and *N*-methylsulfonyl benzenedisulfonimide (**30**). The lines in Figures 2.4 to 2.7 are calculated using equation 6, and m and n are the respective slopes of the dependence of δ_B and δ_{BH+} on H_o. If no acid dependence on the chemical shifts of either the neutral (**B**) or the protonated sulfonimides ($\mathbf{BH^+}$) is found then m and n are both set equal to zero (see experimental section). When the data of dimethanesulfonimide (**28**) was treated by excess acidity method[60], a pK_a value of -1.67 was obtained (see Figure 2.8). The values of pK_a (or H_o values at half protonation) of these four sulfonimides are listed in Table 2.2.

Table 2.2 The pK_a Values of Sulfonimides

Sulfonimides	pK_a	Temp. (°C)	Method
$(CH_3SO_2)_2NH$ (28)	1.36	25.0	Titration
	2.10	20.0	
	-1.30	20.0	NMR
	-1.67	20.0	Excess acidity
$(C_2H_5SO_2)_2NH$ (29)	2.04	25.0	Titration
$CH_3SO_2NHSO_2Ph$ (30)	1.76	20.0	Titration
	-1.60	20.0	NMR
	-1.70	21.0	UV
$(C_6H_5SO_2)_2NH$ (26)	1.79	20.0	Titration
	-1.78	21.0	UV
$(p\text{-}CH_3C_6H_4SO_2)_2NH$ (27)	2.45	20.0	Titration
Benzene-1,2-disulfonimide (21)	-4.12	21.0	UV
$(CH_2SO_2)_2NH$ (19)	-3.10	20.0	NMR
$(CH_2)_3(SO_2)_2NH$ (20)	-1.68	20.0	NMR
$PhSO_2NHCOPh$ (31)	4.99[a]	20.0	Titration
$CH_3SO_2NHCOCH_3$ (32)	6.02[a]	20.0	Titration
	5.13	20.0	
Saccharin (33)	1.84	25.0	Titration
	1.20	21.0	UV

a. These titrations were carried out in 50% ethanol solution.

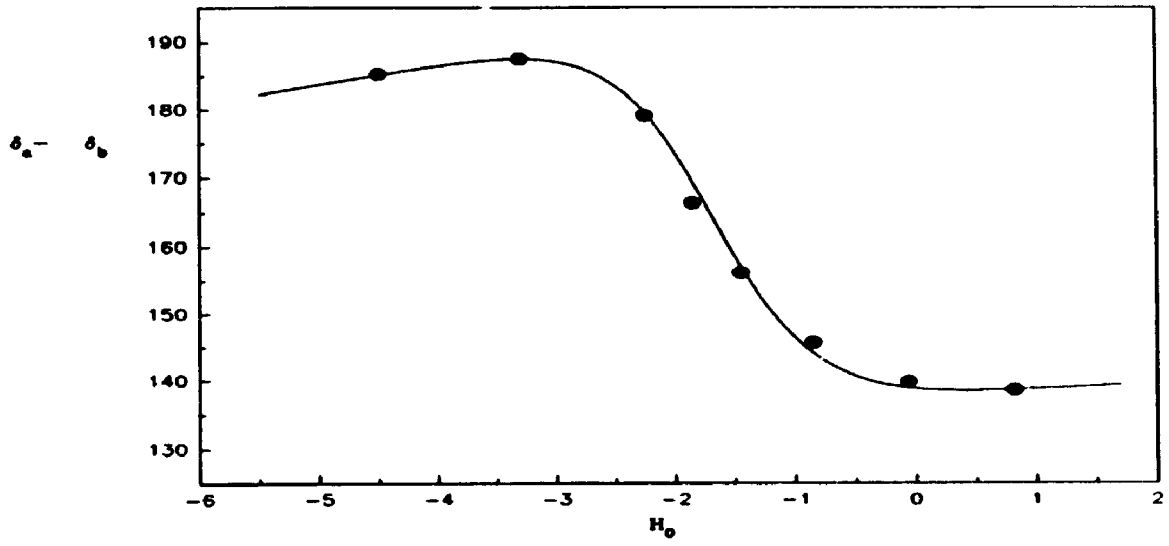


Figure 2.4 The plot of chemical shift *vs.* H_o for propane-1,3-disulfonimide (**20**) in sulfuric acid solution at 20 °C. The points are experimental; the curve was calculated from equation (6), with m = 1.0, n = 3.0, pK_a = -1.7.

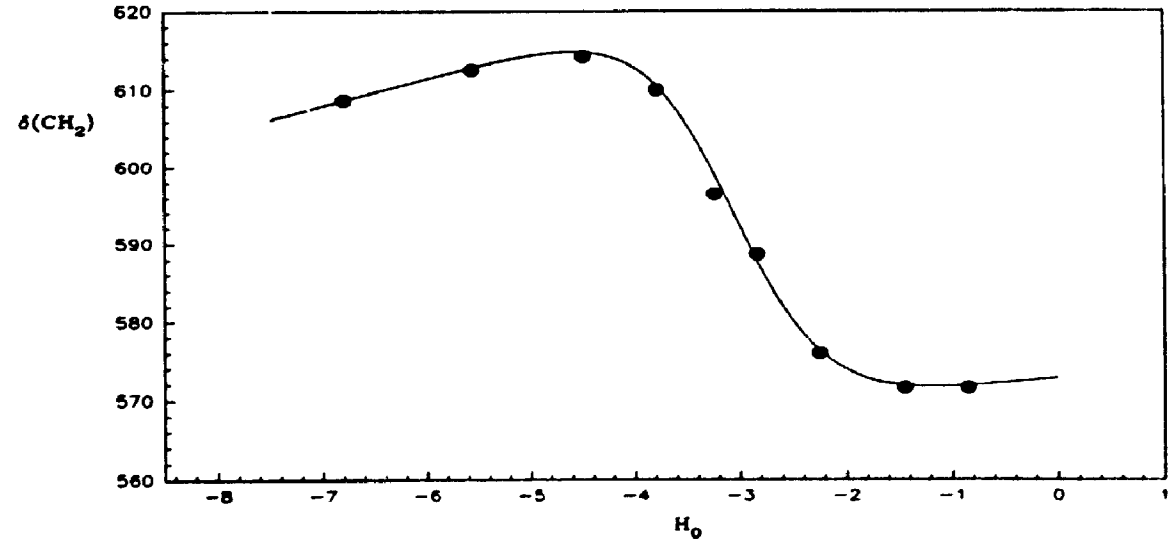


Figure 2.5 The plot of chemical shift *vs.* H_o for ethane-1,2-disulfonimide (**19**) in sulfuric acid solution at 20 °C. The points are experimental; the curve was calculated from equation (6), with m = 1.5, n = 3.5, pK_a = -3.1.

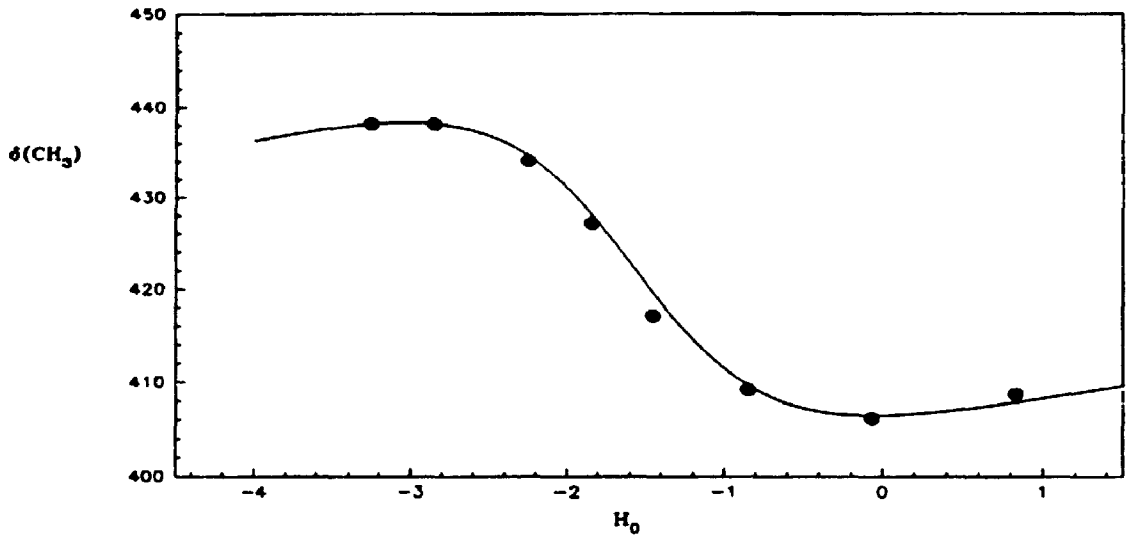


Figure 2.6 The plot of chemical shift *vs.* H_0 for *N*-methylsulfonyl benzenedisulfonimide (**30**) in sulfuric acid solution at 20 °C. The points are experimental; the curve was calculated from equation (6), with m = 2.8, n = 3.5, pK_a = -1.6.

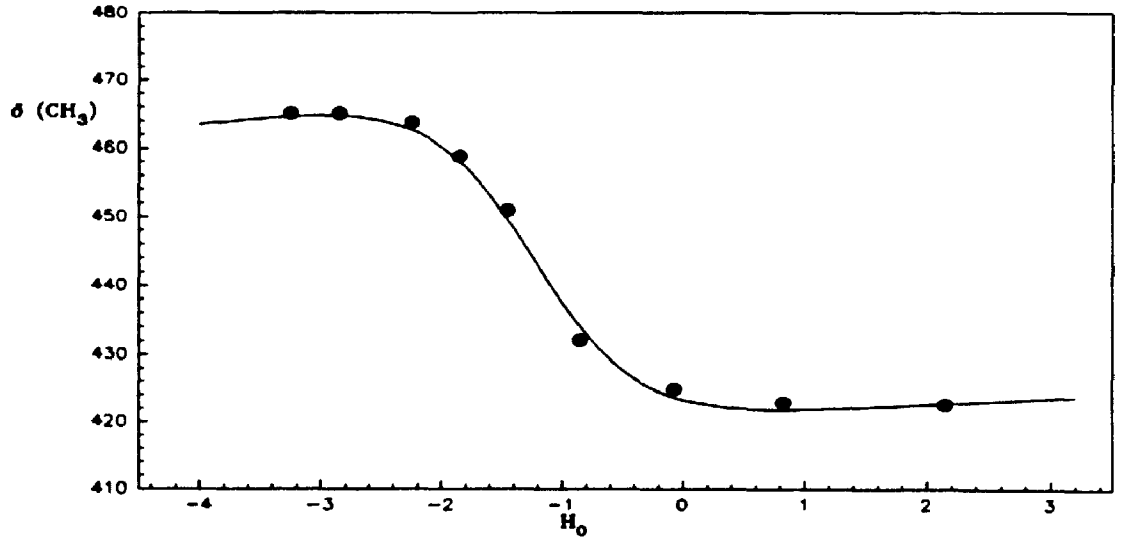


Figure 2.7 The plot of chemical shift *vs.* H_0 for dimethanesulfonimide (**28**) in sulfuric acid solution at 20 °C. The points are experimental; the curve was calculated from equation (6), with m = 1.0, n = 2.0, pK_a = -1.3.

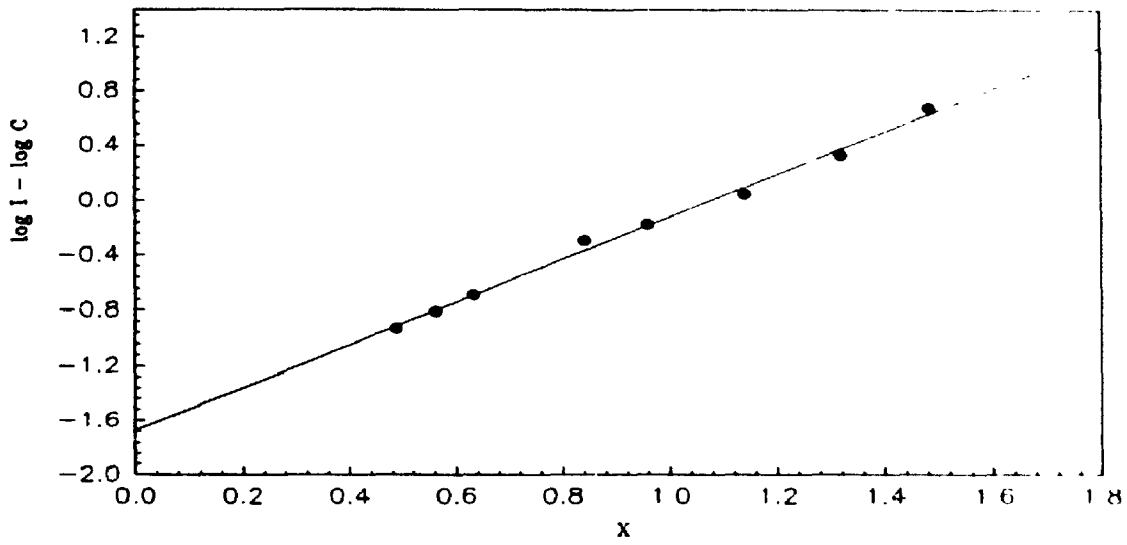


Figure 2.8 Determination of the pK_a of dimethanesulfonimide (**28**) by the excess acidity method in sulfuric acid solution.

Ultraviolet spectrophotometry is an ideal method when a substance is too insoluble for potentiometric titration or when its pK_a value is particularly low or high (e.g. less than 2). This method depends upon the direct determination of the ratio of molecular species (neutral molecule) to ionized species in a series of non-absorbing solutions (whose H_o values are either known or measured). A wavelength is chosen at which the greatest difference between the absorbances of the two species is observed. Telder and Cerfontain[61] determined pK_a values of a number of monosubstituted derivatives of benzenesulfonic acid in concentrated aqueous sulfuric acid by the UV method[62].

They found that the result of UV method was similar to the result of NMR, but this method was restricted to aromatic organic compounds and further required an isolated B band. Cerfontain and Schnitger[63] found that there was a medium effect on A_I and not on A_M (A_I is the absorbency of the ionized species and A_M is the absorbency of the unionized acid) for arenesulfonic acid. Lemaire and Lucas[64] had previously measured the pK_a of *p*-toluenesulfonamide in glacial acetic acid solution by the UV method and found the pK_a value to be -3.20.

In present study, the pK_a values of four sulfonimides were determined by the UV procedure. It was found that there is a small medium effect on both A_I and A_M. Figures 2.9 to 2.12 show the dependence of absorbance on H_o for *N*-methylsulfonyl benzenesulfonimide (**30**), benzene-1,2-disulfonimide (**21**), dibenzenesulfonimide (**26**), and saccharin (**33**). The pK_a values are listed in Table 2.2.

2.2.3.3 Kinetics of Hydrolysis of Sulfonimides in Concentrated Hydrochloric Acid

In this study, we have examined the hydrolysis of four sulfonimides, ethane-1,2-disulfonimide (**19**), propane-1,3-disulfonimide (**20**), dimethanesulfonimide (**28**), *N*-methylsulfonyl benzenesulfonimide (**30**), as well as methanesulfonamide (**61**) in concentrated hydrochloric acid at 80 °C. The rate constants of the hydrolysis of these compounds were measured by ^{1}H NMR spectra by following the

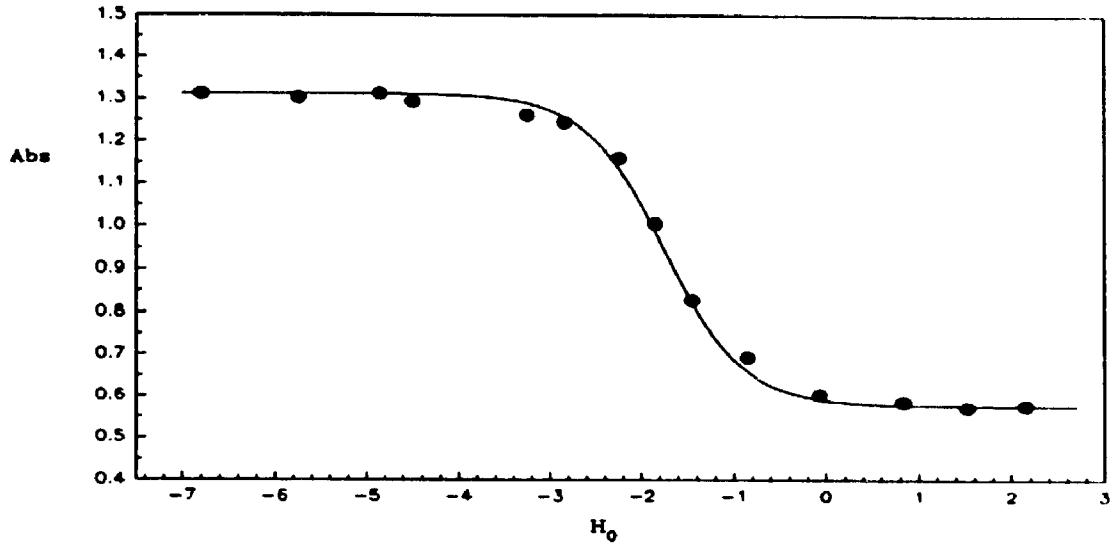


Figure 2.9 The plot of *A* at 267 nm *vs.* H_o for *N*-methylsulfonyl benzenesulfonimide (**30**) in sulfuric acid solution at 21 °C. The points are experimental; the curve was calculated from equation 7, where m = 0, n = 0, pK_a = -1.7.

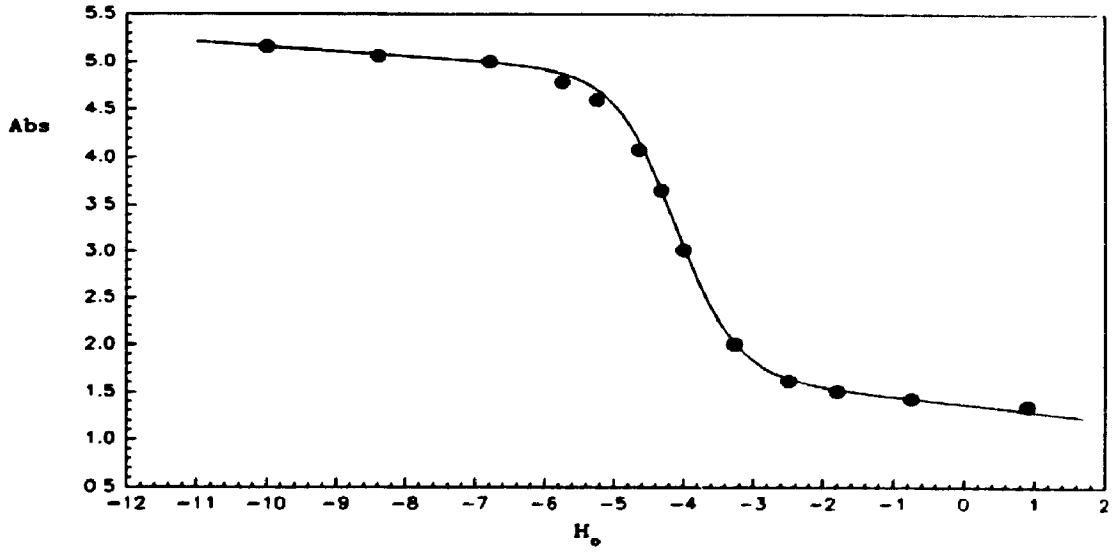


Figure 2.10 The plot of *A* at 275 nm *vs.* H_o for benzene-1,2-disulfonimide (**21**) in sulfuric acid solution at 21 °C. The points are experimental; the curve was calculated from equation 7, where m = -0.08, n = -0.05, pK_a = -4.12.

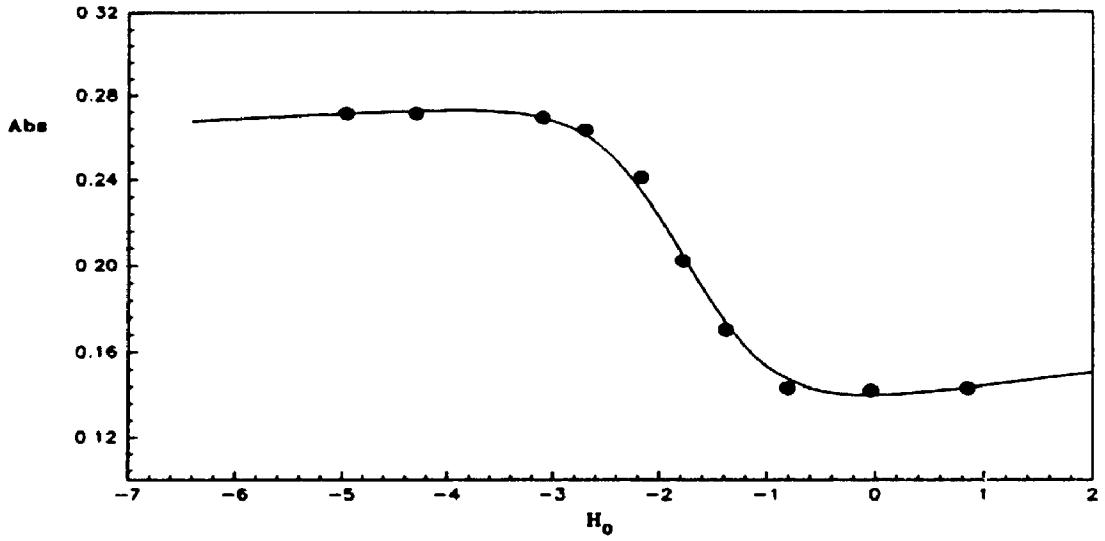


Figure 2.11 The plot of *A* at 267 nm *vs.* H_0 for dibenzenesulfonimide (**26**) in sulfuric acid solution at 21 °C. The points are experimental; the curve was calculated from equation 7, where m = 0.5, n = 1.5, pK_a = -1.78.

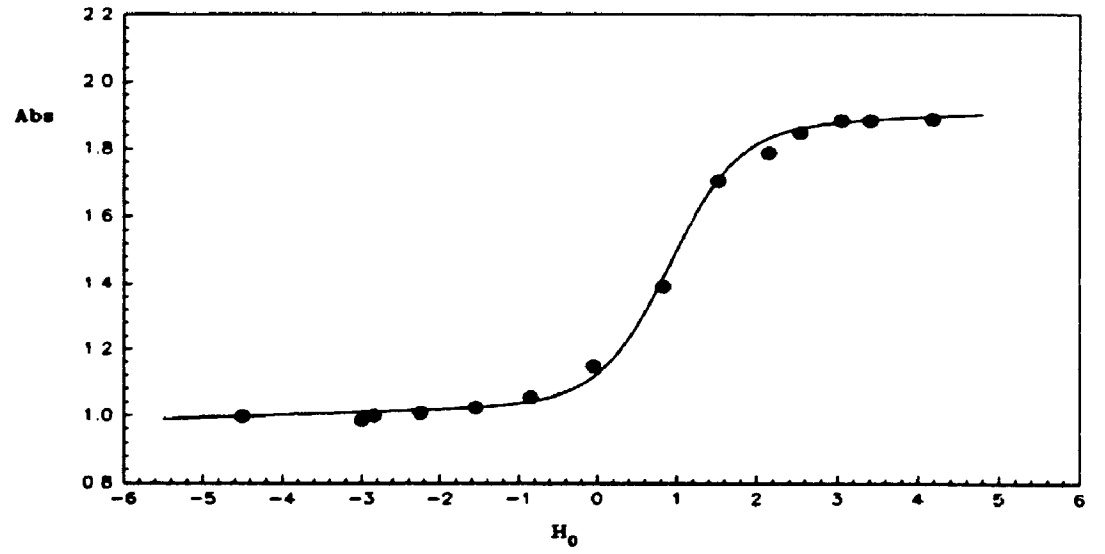


Figure 2.12 The plot of *A* at 221 nm *vs.* H_0 for saccharin (**33**) in sulfuric acid solution at 21 °C. The points are experimental; the curve was calculated from equation 7, where m = 0.008, n = 0.01, pK_a = 0.90.

disappearance of the starting material peaks. The plots of ln C_t (C_t is the concentration of unreacted starting material) vs. time give good straight lines (see Figures 2.13 to 2.15). This indicates that the hydrolysis of sulfonimides in concentrated hydrochloric acid are pseudo-first-order reactions under these conditions. The results are listed in Table 2.3.

In the ^1H NMR spectrum of hydrolysis of ethane-1,2-disulfonimide (**19**) in concentrated hydrochloric acid, five peaks were found (see Figure 2.16). Peak 2 is that of the unreacted starting material **19**, peaks 4 and 5 are those of 2-(aminosulfonyl)ethanesulfonic acid (**45**), and peaks 1 and 3 are those of 2-(aminosulfonyl)ethanesulfonyl chloride. It was found that **45** was further hydrolysed to give ethane-1,2-disulfonic acid (**50**) which was confirmed by comparing the NMR spectrum with that of an authentic sample. 2-(Aminosulfonyl)ethanesulfonyl chloride was proved by these facts: (a) it underwent further hydrolysis to give **45**; (b) the chemical shift of peak 1 ($-CH_2SO_2Cl$) is down field with respect to the starting material **19**. It should be noted that the reaction of *N*-methyl-1,3-propanesultam in concentrated hydrochloric acid was shown by Li[32] to yield the sulfonyl chloride, $MeNH_2^+$ $CH_2CH_2CH_2SO_2Cl$, as the major primary product; the $-CH_2SO_2Cl$ signals were down field from those of *N*-methyl-1,3-propanesultam. The same phenomenon of $-CH_2SO_2Cl$ signals in down field was observed by Klassen[34] who carried out hydrolysis of a set of cyclic and acyclic *N*-

Table 2.3 Rate Constants of Hydrolysis of Sulfonimides in Concentrated Hydrochloric Acid at 80 °C.

Sulfonimides	$k_{obs}(s^{-1})$	pK_a
$(CH_2SO_2)_2NH$ **(19)**	1.59×10^{-4}	-3.10
$(CH_2)_3(SO_2)_2NH$ **(20)**	3.69×10^{-7}	-1.68
$C_6H_5SO_2NHSO_2CH_3$ **(30)**	6.52×10^{-6}	-1.60
$(CH_3SO_2)_2NH$ **(28)**	4.98×10^{-7}	-1.30
$CH_3SO_2NH_2$ **(61)**	1.48×10^{-6}	10.80[a]

a. Reference[65]

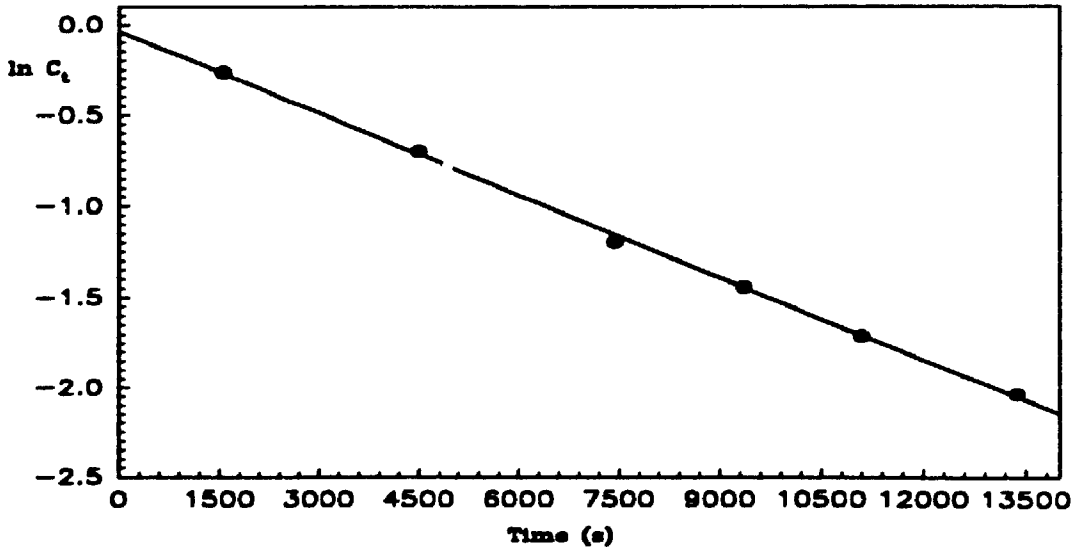


Figure 2.13 The plot of ln C_t *vs.* time for hydrolysis of ethane-1,2-disulfonimide **(19)** in concentrated hydrochloric acid at 80 °C.

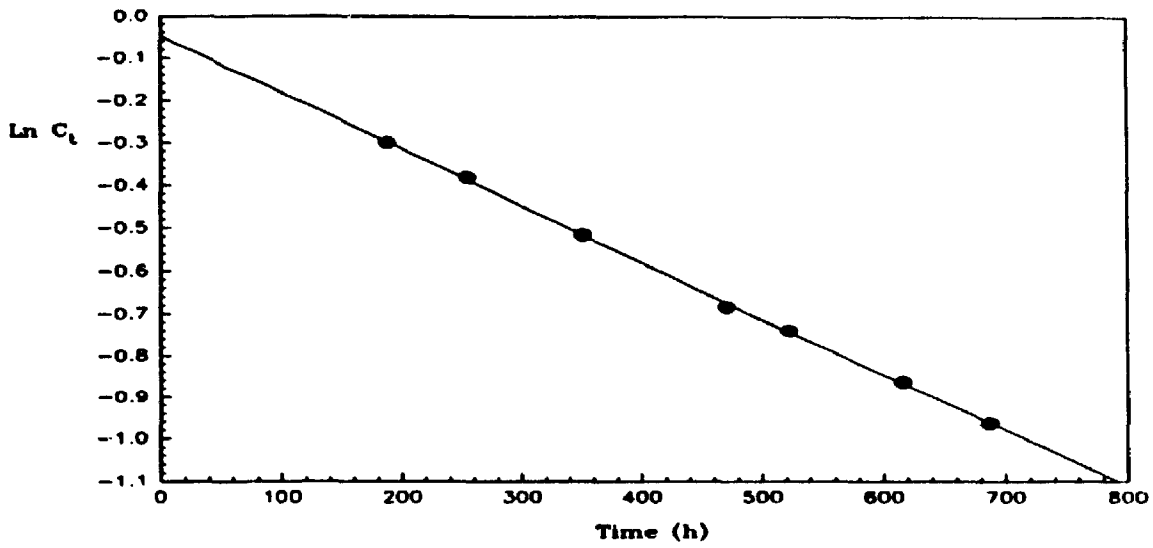


Figure 2.14 The plot of ln C_t *vs.* time for hydrolysis of propane-1,3-disulfonimide (**20**) in concentrated hydrochloric acid at 80 °C.

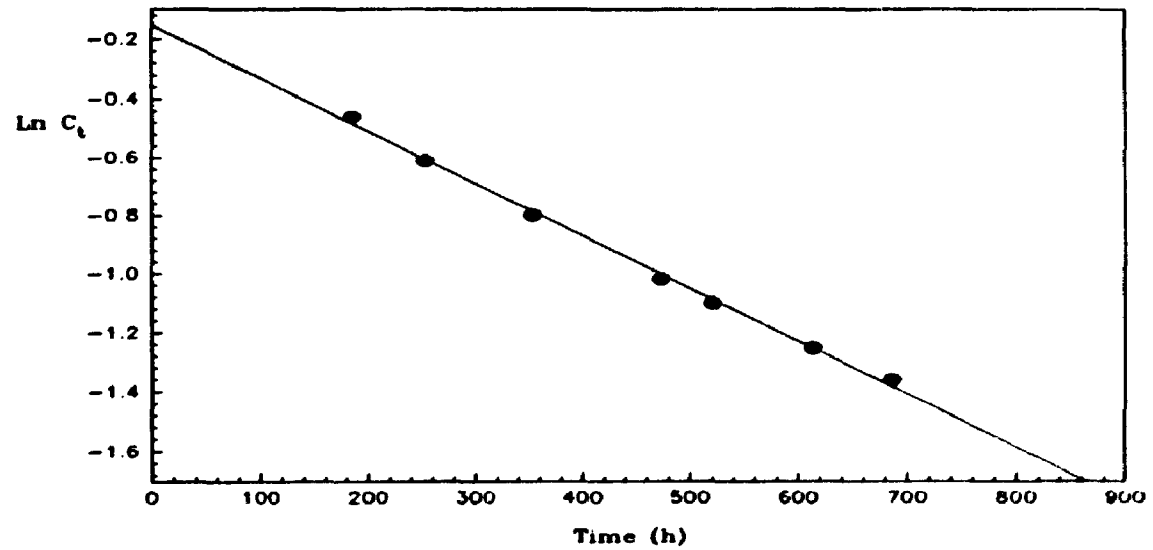
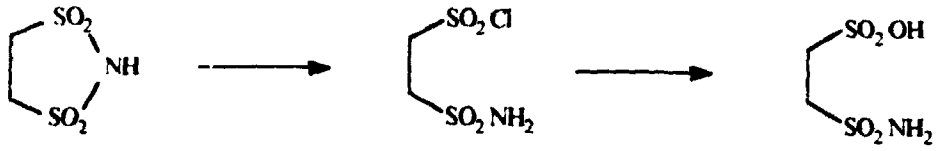


Figure 2.15 The plot of ln C_t *vs.* time for hydrolysis of dimethanesulfonimide (**28**) in concentrated hydrochloric acid at 80 °C.



(19) (45)

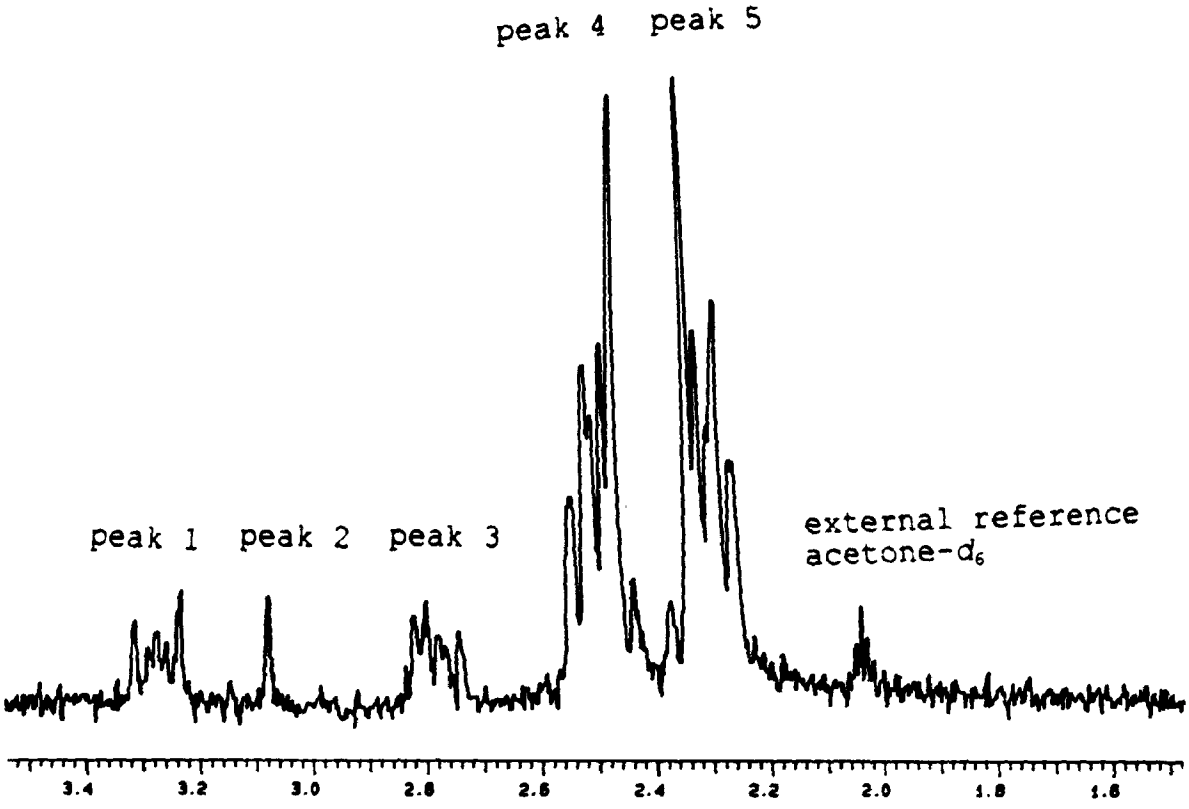


Figure 2.16 The ^{1}H NMR spectrum of hydrolysis of ethane-1,2-disulfonimide in concentrated hydrochloric acid.

methyl sulfonamides in concentrated hydrochloric acid.

For the hydrolysis of propane-1,3-disulfonimide (**20**), 3-(aminosulfonyl)propanesulfonic acid and propane-1,3-disulfonic acid were found and were confirmed by comparing the NMR spectra with authentic samples. We failed to see the 3-(aminosulfonyl)propanesulfonyl chloride in the NMR spectra because the hydrolysis of the 3-(aminosulfonyl)-propanesulfonyl chloride to give the 3-(aminosulfonyl)-propanesulfonic acid (**65**) was much faster than the hydrolysis of **20**. 3-(Aminosulfonyl)propanesulfonic acid (**65**) hydrolysed to give the propane-1,3-disulfonic acid (**63**). The hydrolysis of dimethanesulfonimide (**28**) was similar to that of propane-1,3-disulfonimide.

In this study we have found that the hydrolysis of ethane-1,2-disulfonimide (**19**) in concentrated hydrochloric acid at 80 °C is about 430 times faster than that of its six-membered ring analogue, propane-1,3-disulfonimide (**20**), and 320 times faster than its acyclic analogue, dimethanesulfonimide (**28**). The hydrolysis of *N*-methyl-sulfonyl benzenesulfonimide (**30**) is 13 times faster than that of dimethanesulfonimide (**28**). The methanesulfonamide is 3 times more reactive than dimethanesulfonimide in the hydrolysis.

2.2.4 Discussion

2.2.4.1 The pK_a values for the Sulfonamides

Dauphin and Kergomard[66,67] have made an extensive

tabulation of pK_a values for derivatives of benzenesulfonamide. They have given the following expression for the sulfonamides of general structure $ArSO_2NH_2$ in water at 20 °C:

$$pK_a = 10.05 - 0.93\Sigma\sigma$$

where σ is the substituent constant.

In addition, Dauphin, Kergomard, and Verschambre[51] have determined pK_a values for a large number of sulfonamides with aromatic rings. Because of the low solubility of many of these compounds in water most of the pK_a determinations were made on ethanol-water (50% by weight) solutions. The results can be expressed as follows:

$ArSO_2NH_2$: $pK_a = 11.34 - 1.45\Sigma\sigma$

$PhSO_2NHAr$: $pK_a = 9.94 - 2.61\sigma$

$PhCH_2SO_2NHAr$: $pK_a = 10.18 - 2.36\sigma$

$ArSO_2NHPh$: $pK_a = 9.98 - 1.66\Sigma\sigma$

Trepka and coworkers[68] found that the trifluoromethyl group attached to the sulfonyl group made the sulfonamide more acidic than its methyl-substituted counterpart by about 4 pK_a units. The pK_a values of a series of sulfonamides of general structure CF_3SO_2NHAr when plotted vs. σ showed a good correlation with the expression:

CF_3SO_2NHAr: $pK_a = 4.42 - 2.15\sigma$

In present study (see Table 2.1), we have found that the pK_a's of sulfonamides of general structure CH_3SO_2NHAr are correlated by the following expression (see Figure 2.17):

CH_3SO_2NHAr: $pK_a = 8.96 - 2.13\sigma$

In Figure 2.17 one may find the all of experimental points are correlated well except the point of $CH_3SO_2NHC_6H_4$-

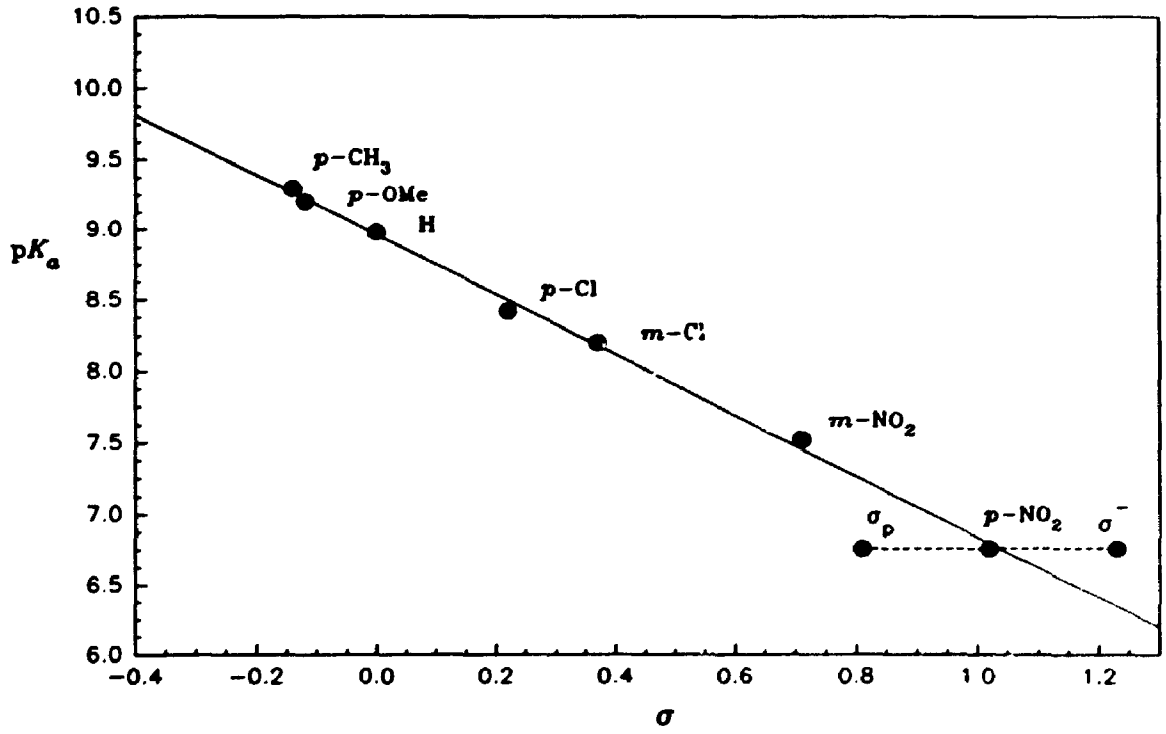


Figure 2.17 The plot of pK_a *vs* σ for CH_3SO_2NHAr in water at 20 °C. The middle point for *p*-NO_2 is the average of σ_p and σ^-.

p-NO_2 (**37**). A best fit is obtained when the average of σ_p and σ^- is used for **37**. This is probably due to the direct conjugation of the *para*-nitro group. This causes **37** to be a stronger acid than would be expected from the σ_p value of *para*-NO_2, but the delocalization into the *para*-NO_2 is not as great as in *p*-nitroaniline[69] or *p*-nitro-phenoxide, which define σ^-.

N-Alkylation, as in the conversion of $CH_3SO_2NH_2$ (pK_a 10.80) into $CH_3SO_2NHCH_3$ (**34**) (pK_a 11.79) raises the pK_a by 1 unit, perhaps as a result of poorer solvation of $CH_3SO_2N^-$-CH_3 as compared to $CH_3SO_2N^-$-H[70]. *N*-Phenylation, as in $CH_3SO_2NH_2 \rightarrow CH_3SO_2NHPh$ (**35**) (pK_a 8.98) leads to a ΔpK_a of -1.8 units, as would be expected from the increased delocalization in the aromatic ring available in $CH_3SO_2N^-$-Ph. The effect is not nearly as large as that which occurs on *N*-phenylation of ammonia, which may be estimated to be about 7 units (from the pK_a values of 27.7 and about 35 for aniline and ammonia as acids[71]). The smaller ΔpK_a found with sulfonamides is not unreasonable in light of the evidence of N → S electron delocalization in both sulfonamides and their conjugated bases (as discussed in section 2.1). Since to the extent that electrons are delocalized onto the sulfur the charge on the nitrogen is made more positive, and any tendency for the nitrogen to donate electrons into the phenyl ring accordingly lessened[72] (see Scheme 2.8).

Substitution of the benzene ring, particularly in the

para position, is expected to cause further changes in electron charge distribution within the aromatic ring. The effect of various structural variations may be gauged from the pK_a values listed in Table 2.1. The large difference of

Scheme 2.8

pK_a values (ΔpK_a 2.4) between $CH_3SO_2NHC_6H_4$-*p*-OCH_3 (**41**) (pK_a 9.2) and $CH_3SO_2NHC_6H_4$-*p*-NO_2 (**37**) (pK_a 6.76) can be ascribed that the electron-releasing group, *p*-OCH_3 in **41** donates electron density into the aromatic ring, thereby reducing the delocalization into the aromatic ring; the strong electron withdrawing *para*-nitro group in **37** can stabilize the negative charge in the nitrogen by delocalization through the aromatic ring.

The sultams show some distinct differences from acyclic sulfonamides. The five-membered sultam (**22**) (pK_a 11.39 at 25.0°C) is somewnat more acidic than both its acyclic isomer, $CH_3CH_2SO_2NHCH_3$ (**45**) (pK_a 11.84, at 25.0°C, ΔpK_a 0.45), and its six-membered ring analogue, 1,4-butanesultam (**23**) (pK_a 12.34, at 20.0 °C, ΔpK_a 0.80). Almost the same difference (ΔpK_a 0.87) of pK_a value was also observed

between the five-membered ring, 2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (**24**) (pK_a 11.43, measured in 50% ethanol aqueous solution) and the six-membered ring, 3,4-dihydro-1-H-2,3-benzothiazine-2,2-dioxide (**25**) (pK_a 12.30, also measured in 50% ethanol aqueous solution). Rathore[33] in this laboratory measured the pK_a of protonated *N*-methylsultams and a similar difference (ΔpK_a 0.62) of pK_a value is also observed between the conjugated acids of six-membered ring, (*N*-methyl 1,4-butanesultam, pK_a -4.62) and five-membered ring (*N*-methyl 1,3-propanesultam, pK_a -4.00) compounds. A difference (ΔpK_a 1.51) of pK_a's between five-membered, *N*-methyl 1,3-propanesultam and its open chain analogue, *N,N*-dimethyl methanesulfonamide was observed.

A conclusion may be made that the small five-membered ring effects, perhaps mainly a stereoelectronic effect are involved in those five-membered sultams. This conclusion is supported by Rathore[33] who concluded by examination of molecular models and a rough crystal structure of *N*-methyl 1,3-propanesultam, that the lone pair of electrons on nitrogen can not get to the bisector of the sulfonyl oxygens without introducing considerable ring strain in the molecule. More detailed discussion will be presented in next section.

2.2.4.2 The pK_a Values for the Sulfonimides

In this study the pK_a values of 11 *N*-acyl sulfonamides and sulfonimides have also been determined (see Table 2.2).

It appears from comparing H_o values at half-neutralization with pK_a values determined by titration in water that there is a difference of about 3 pK_a units between the spectrometric and titration methods, except for saccharin which has a smaller difference, 0.64 pK_a units. With $CH_3SO_2NHSO_2CH_3$ for example, titration gave 2.10, NMR gave -1.3 as the H_o at half-protonation, and -1.7 by excess acidity calculations; titration of $CH_3SO_2NHSO_2Ph$ gave 1.76, NMR gave -1.60, and UV gave -1.7. The discrepancy between titration and spectrometric results may be due to the difference between dissociation constants (measured by titration) and ionization constants (determined by spectrometers).[73]

N-benzoyl benzenesulfonamide (**31**) which has a pK_a 4.99 (measured in % ethanol aqueous solution) is a somewhat stronger acid than its alkyl analogue, *N*-acetyl methanesulfonamide (**32**) (pK_a 5.02 in 50% ethanol aqueous solution, 5.13 in water). Compound **32** has an identical pK_a with $CH_3SO_2NHCONH_2$ (pK_a 5.10)[24]. Saccharin (**33**) which is a five-membered cyclic aromatic *N*-acyl sulfonamide and perhaps the best known member of this class of compounds has the pK_a value 1.84 by the potentiometric titration method and a pK_a 1.2 by the UV method, by either measure **33** is much more acidic than its open-chain analogue, *N*-benzoyl benzenesulfonamide (**31**) (pK_a 4.99).

As one might expect from the greater acidity of sulfonamides vs carboxylic amides (pK_a about 15), the

introduction of the second sulfonyl group increases the acidity more than that of an acyl group. This may be seen by comparing benzene-1,2-disulfonimide (**21**) with saccharin (**33**), or the acyclic sulfonimides, $CH_3SO_2NHSO_2CH_3$ (**28**) (pK_a 1.36) and $CH_3CH_2SO_2NHSO_2CH_2CH_3$ (**29**) (pK_a 2.04), with $CH_3SO_2NHCOCH_3$ (**32**) (pK_a 5.13). The difference between $(RSO_2)_2NH$ and RSO_2NHCOR is about 3-4 pK_a units.

Benzene-1,2-disulfonimide (**21**) has been described as 'fully ionized in (and not extractable from) water and said to possess acidity comparable to that of hydrochloric acid'. It was indeed found that the H_o value at half-neutralization of **21** (see Table 2.2) is -4.1, indicating that **21** is one of the strongest neutral nitrogen acids.

An interesting result is the acid-strengthing effect accompanying incorporation of these functions in a five-membered ring. Both the benz-fused and saturated five-membered ring disulfonimides (**21**) and (**19**) with H_o values at half-protonation of -4.1 and -3.1, are more acidic than either of their acyclic counterparts $(PhSO_2)_2NH$ (**26**) (H_o values at half-protonation -1.7) and $CH_3SO_2NHSO_2CH_3$ (**28**) (-1.3), respectively, or the six-membered cyclic analogue, **20** (-1.7). As has been noted already, saccharin, which is an aromatic five-membered *N*-acyl sulfonamide, is also more acidic than its open chain analogue $PhSO_2NHCOPh$.

One possible explanation for the difference in acidity between five-membered ring sulfonimides and their six-membered analogue is the ring strain effect. Attig and

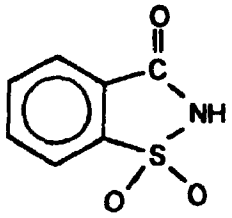
Mootz[74] determined the structure of dimethanesulfonimide and found that the S-N bond length is 1.645 Å and S-N-S bond angle is 125.0°. A very similar result[75] was found in $(CH_3CH_2SO_2)_2NH$, the S-N bond length, 1.646 Å, S-N-S bond angle, 125.3°, and C-S-N bond angle, 105.6°. They concluded that the configuration of the N atom is planar with sp^2-hybridization. This was supported by the result of Cotton and Stokely[76] who determined the crystal structures of dibenzenesulfonimide and its sodium salt. They found that the S-N-S bond angles in dibenzenesulfonimide and its sodium salt are almost identical, 127.7° and 127.5°, respectively; and the C-S-N bond angles are 108.3° and 106.6° respectively. It is notable that the S-N bond lengths in sodium dibenzenesulfonimide (1.598 Å and 1.571 Å respectively) are significant shorter than those in dibenzenesulfonimide (1.657 Å and 1.643 Å respectively); the O-S-O bond angles in sodium dibenzenesulfonimide (115.8° and 115.7° respectively) is much smaller than that in dibenzenesulfonimide (121.0° and 120.3° respectively). The results of Cotton and Stokely support the conclusion of a strong π bond character of the S-N bond and the sp^2-hybridization of the nitrogen atom in sulfonimides. Similar sp^2-hybridization was also observed in methanesulfonanilide[77] in which the S-N-C angle is 120°.

Bart[78] and Okaya[79] determined independently the crystal structure of saccharin (**33**) and found that C-N bond length is 1.375 Å which appears to possess considerable

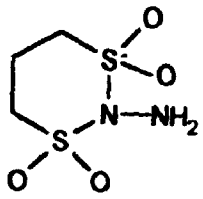
double-bond character, the C=O bond (1.220 Å) is slightly longer than a 'pure' double bond (1.205 Å for amides), the S-N bond (1.66 Å) is appreciably shorter than the 1.735 Å for a single bond (based on the conventional radii and the electronegativity correction)[80], and a substantial amount of conjugation of the *p*-orbital on the nitrogen atom with the *d*-orbital of S is expected. Bart[78] concluded that a considerable positive charge will be expected to reside on the nitrogen atom, making the attached hydrogen atom acidic. Bart and Okaya also found that the angle distortions in the C-C bond at five-membered ring indicates considerable strain. The angles around the S are very different from those of regular tetrahedron, especially the O-S-O angle (117.4°) which is larger than a normal tetrahedral angle, but smaller than 121° in dibenzenesulfonimide; and the small internal angle C-S-N (92.7°) which is much smaller than the same angle in open sulfonimides, for example, 105.6° in diethylsulfonimide or 106.6° in dibenzenesulfonimide (see above). The C-N-S angle was found to be 115.0°, which is also much smaller than the same angle in open sulfonimides, e.g. the bond angle S-N-S, 127.7° in dibenzenesulfonimide, 125.3° in diethylsulfonimide. These data again show that considerable ring strain exists in the five-membered ring of saccharin.

Camerman, *et al.*[81] determined the crystal structure of *N*-[4'-sulfamylphenyl]-1,4-butanesultam (73). Their results indicate that the ring strain in six-membered ring

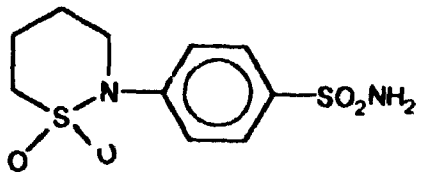
sultam is much smaller than in five-membered ring sultam. Linke, et *al.*[82] examined the crystal structure of *N*-amino propane-1,3-disulfonimide (**72**) and confirmed that no ring strain is expected in this six-membered ring compound. Using PCMODEL (PCM4) the S-N-S bond angle is estimated to be 115.6° in propane-1,3-disulfonimide (**20**), which is close to the same angle in **72**. The estimated bond angle of S-N-S



(33)



(72)

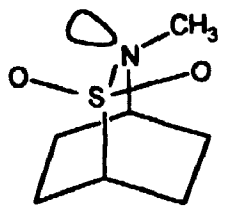


(73)

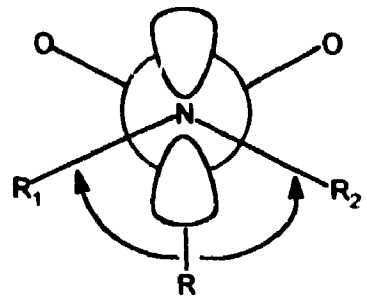
(108.3°) in ethane-1,2-disulfonimide (**19**), however, is 7 degrees less than that in **20**. The bond angles of N-S-C are 104.0°, 94.5° and 92.7° in **20**, **19** and benzene-1,2-disulfonimide (**21**) respectively. This indicates that the angle of N-S-C in **20** is 9.5 degrees larger than that in **19** and 11.3 degrees larger than that in **21**. The bond angle of S-C-C in **20** (111.9°) is 4.1 degrees larger than that in **19** (107.8°). These bond angles in five-membered ring disulfonimides are significantly smaller than those in their six-membered ring analogues. These data show that the ring strain in six-membered sulfonimides may be expected to be much smaller than that in five-membered sulfonimides. As

pointed out earlier that sodium dibenzenesulfonimide[76] has shorter S-N bonds and longer S-O bonds compared with dibenzene-sulfonimide, it is reasonable to assume that part of the ring strain in the five-membered ring sulfonimides or sulfonamides is released when they are in the ionic forms because the S-N-S bond angle is expected to be larger as the S-N bond is shorter and S-O bonds are longer. The ring strain release in the ionic form of five-membered ring sulfonimides would cause the five-membered sulfonimides to be more acidic than their six-membered ring and open analogues.

In addition to the ring strain effect as discussed above, another effect which may affect the acidities of five-membered sulfonamides and sulfonimides is the stereoelectronic effect. One may recall that Laughlin[58] suggested that the difference in acidity between RSO_2NHR' and R_3NH^+ (about 16 pK_a units) was too large to be accounted for on the basis of an inductive effect, and argued that N→S delocalization of electrons (i.e. **76** ↔ **77**) is important in sulfonamides. King, *et al*[23]. found that for most sulfonamides the C-S-N-C dihedral angle θ (and θ' defined in **75**) is in the range 60-120°. This suggested that if the most favourable arrangement for N→S delocalization occurs when θ ~80°, then a sulfonamide in which θ was required to be ~0° would have less N → S delocalization and that this might be expected to show itself in increased base strength in the sulfonamide. The protonated bicyclic sultam **74** (H_o -



74



75

76 77

3.6) in which θ = 0° (and θ'~170°) was indeed found to be distinctly more basic than its acyclic counterpart, *N,N*-dimethylmethanesulfonamide (H_o -5.5). The large pK_a difference (ΔpK_a 1.9) between these two *N*-methyl sulfonamides is not surprising because in **74** the lone pair of electrons on the nitrogen is not at the bisector of the sulfonyl oxygens (i.e. θ is not 80°) in contrast to *N,N*-dimethylmethanesulfonamide in which θ = 80°; it then is more readily available for protonation in **74** (less N → S delocalization) than in *N,N*-dimethylmethanesulfonamide.

It is evident as discussed above that change from the normal C-S-N-C dihedral angle (~80°), or in other words, when the lone pair of electrons on nitrogen can not bisect

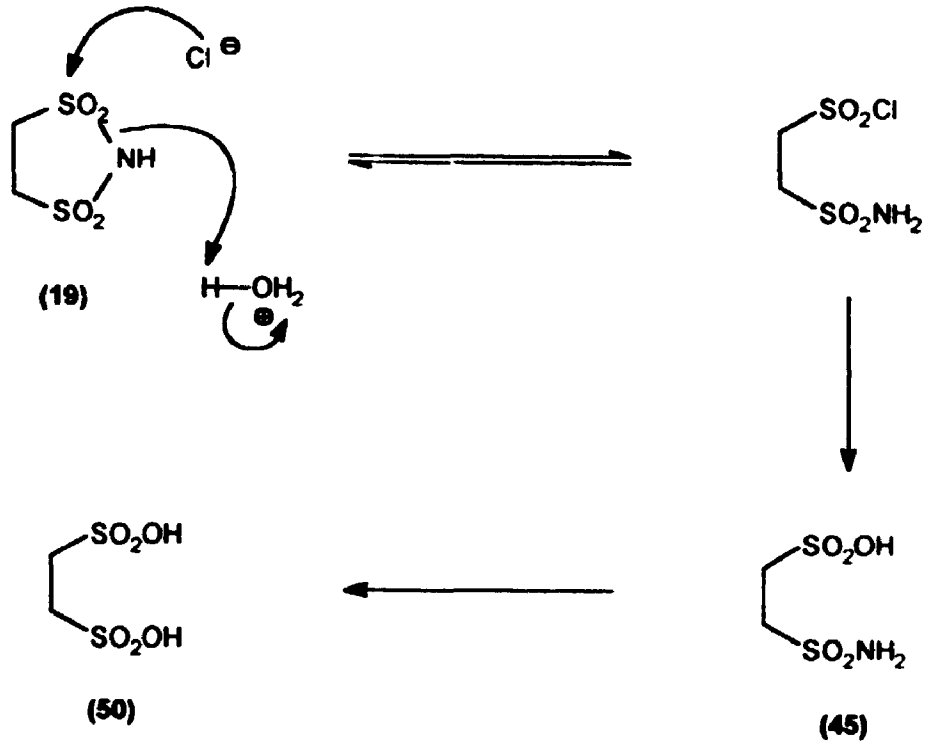
the sulfonyl oxygens, the N → S delocalization decreased, and the base strength of *N*-methyl sulfonamides increased.

This may explain why five-membered ring sultams **22** and **25**, five-membered sulfonimides **21**, **19** and saccharin are more acidic than their six-membered ring or acyclic analogues because of the ring effect and the stereoelectronic effect.

2.2.4.3 The Kinetics of the Hydrolysis of Sulfonimides in Concentrated Hydrochloric Acid

Because sulfonimides are much stronger acids than sulfonamides (there is 14.6 pK_a units difference between ethane-1,2-disulfonimide and 1,3-propanesultam, see Tables 2.1 and 2.2) it is much more difficult to protonate the nitrogen of the sulfonimides than that of the sulfonamides. It has been found that *N*-methylsulfonyl benzenesulfonimide hydrolyses 13 times faster than dimethanesulfonimide. This indicates that the aromatic sulfonimide is more reactive than alkylsulfonimide in the acidic hydrolysis. A proposed mechanism of hydrolysis of cyclic five-membered sulfonimide in concentrated hydrochloric acid solution is shown in Scheme 2.10.

In this mechanism the chloride ion attacks the sulfur, perhaps with assistance by general acid catalysis at the nitrogen, leading to ring opening to form 2-(aminosulfonyl)-ethanesulfonyl chloride; this subsequently hydrolyses to give 2-(aminosulfonyl)ethanesulfonic acid (**45**). This proposed mechanism is similar to the mechanism of hydrolysis



Scheme 2.10

of cyclic sulfonamides proposed by Rathore[33] and Li[32] in this laboratory, except that the sulfonamide was protonated in the first step. We can not exclude the possibility of specific acid catalysed hydrolysis of sulfonimides at this stage, though it is to be expected that they are extremely weak bases with only a very small portion of the sample protonated under these conditions.

Helferich and Kleh[83] reported that the six-membered sultam, *N*-4-acetamidophenylbutanesultam, was not cleaved in boiling 18% sulfuric acid solution, whereas the corresponding five-membered sultam was cleaved under these conditions. They suggested that the difference in behaviour of the five-membered sultam and other sulfonamides was due

to the strain which was relieved as the sulfur-nitrogen bond was partially broken in the five-membered sultam. Klassen[34] investigated the hydrolysis of *N*-methyl 1,3-propanesultam in concentrated hydrochloric acid and estimated that the ring strain effect (by a factor of 3000 out of 86000) is the major component and the stereoelectronic effect (by a factor of 29) is the minor component under the particular conditions used.

The difference (e.g. 430 times between five- and six-membered ring sulfonimides and 320 times between five-membered ring and open chain sulfonimides) of hydrolysis between the five-membered cyclic sulfonimide on the one hand and, six-membered cyclic and open chain analogues on the other are also ascribed to the ring strain and the stereo-electronic effects as discussed in the pK_a determination section. The stereoelectronic effect in five-membered ring sulfonimides may arise because the electron lone pair on the nitrogen is not at the bisector of the sulfonyl oxygens. The major contribution of these effects (ring strain and stereoelectronic) is expected, however, to be the ring strain effect as observed in the five-membered ring sultam by Klassen[34] although we can not separate quantitatively the effects in the five-membered ring sulfonimides at this stage.

2.3 CONCLUSION

In this chapter a set of pK_a values of sulfonamides and sulfonimides were determined by the potentiometric titration, ^1H NMR, and UV methods. Ethane-1,2-disulfonimide (**19**) which has not been reported in literature has been synthesized. It is found that the cyclic five-membered ring sulfonimides, benzene-1,2-disulfonimide, (**21**) and ethane-1,2-disulfonimide (**19**), are distinctly more acidic (by about 1.5-2.5 pK_a units) than the cyclic six-membered ring sulfonimide, propane-1,3-disulfonimide (**20**), and the open chain sulfonimides, dimethanesulfonimide (**28**) and dibenzenesulfonimide (**26**). These phenomena are ascribed to either or both the effect of ring strain and a stereoelectronic effect. The sulfonamides show qualitatively the same tendency as the sulfonimides, but the difference (about 0.4-0.9 pK_a units) between five-membered cyclic sulfonamides and six-membered cyclic or open chain sulfonamides is smaller than that in the sulfonimides.

The pK_a's of a series of sulfonamides of general structure CH_3SO_2NHAr were determined and found that these sulfonamides except for CH_3SO_2NH-*p*-NO_2-C_6H_4 are correlated well by the equation:

$$pK_a = 8.96 - 2.13\sigma$$

The hydrolysis of sulfonimides was carried out in

concentrated hydrochloric acid solution at 80 °C. The results indicated the five-membered ring sulfonimide, ethane-1,2-disulfonimide (**19**), is much more reactive than its six-membered analogue, propane-1,3-disulfonimide (**20**), and its open-chain analogue, dimethanesulfonimide (**28**). It is likely that the same effects as in the pK_a determinations, e.g. ring strain effect and stereoelectronic effect are involved, but the relative importance of each is not known.

2.4 EXPERIMENTAL

The general procedure and instrumentation are as described in the experimental part of chapter 1, except for the following points.

The UV spectra were obtained by using Shimadzu UV-160 spectrometer. The apparatus used for the pK_a determinations of sulfonamides by titration consisted of a Radiometer Model 25 pH meter equipped with a Radiometer Titrator 11 automatic titrator, a Radiometer GK2401C glass electrode and an Aminco automatic burette with a 3 mL syringe reservoir. The temperature was maintained constant (± 0.1 °C) by means of a Haake FJ constant temperature circulating apparatus.

Reagent grade chemical and solvents were used without additional purification except where otherwise noted. Methanesulfonyl chloride, ethanesulfonyl chloride, benzenesulfonyl chloride, benzoyl chloride, acetyl chloride, aniline, *m*-chloroaniline, *p*-toluidine, thiolacetic acid and formic acid were distilled before use. *p*-Nitroaniline, *m*-nitroaniline, *p*-chloroaniline, and *p*-toluenesulfonyl chloride were recrystallized before use. Benzylamine, methylamine, and solvents such as acetonitrile, absolute ethanol, tetrahydrofuran (THF), and benzene were dried over calcium hydride; dichloromethane was dried over phosphorus pentoxide.

Solvent evaporation was carried out using a Büchi Rotary Evaporator connected to a water aspirator.

2.4.1 Preparation of the Sulfonamides and Sulfonimides

Preparation of Cyclopropanesulfonanilide (43)

This sulfonanilide (**43**) was made by Dr. Joe Lam[84] in this laboratory. IR (KBr) ν_{max}: 3256, 3058, 1327, 1148 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.92 (m, 2H), 1.14 (m, 2H), 2.50 (m, 1H), 7.12 (s, NH), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 5.6, 29.8, 121.7, 125.5, 129.4, 136.9.

Preparation of Dimethanesulfonimide (28)

Methanesulfonyl chloride (4.60 g, 40.2 mmol) was added dropwise to a solution of ammonium chloride (1.07 g, 20.0 mmol) in water (2.5 mL) at 0 °C. The medium was maintained weakly alkaline with aqueous sodium hydroxide (5 M) and was stirred for 0.5 h after the addition of the methanesulfonyl chloride. The mixture was acidified to pH 2 with concentrated hydrochloric acid at room temperature. The water was removed by distillation on a steam-bath under reduced pressure leaving white crystals which were dried in a desiccator over potassium hydroxide overnight. The crystals were then extracted with acetone (3 x 300 mL). The extract was washed with saturated sodium bicarbonate (30 mL) and water (30 mL), and dried with anhydrous magnesium sulfate. The solvent was evaporated to give white crystals (**28**) which were recrystallized from acetic acid to give the pure product (2.469 g, 14.3 mmol, 71.3% yield); mp 153-155 °C [lit. mp[85] 155 °C]; IR (KBr) ν_{max}: 3598 (s), 3033 (s), 2944 (s), 1620 (m), 1352 (s), 1154 (s), 968 (s), 897 (s),

770 (s) cm^{-1}; ^1H NMR (acetone-d_6) δ: 3.32 (s, 6H); ^{13}C NMR (acetone-d_6) δ: 43.4.

Preparation of Diethanesulfonimide (29)

Ethanesulfonyl chloride (12.90 g, 100 mmol) was added dropwise to a solution of ammonium chloride (2.70 g, 50.5 mmol) in water (5 mL) at 0 °C. The solution was kept weakly basic (tested by pH paper) with aqueous sodium hydroxide (5 M). After all of the ethanesulfonyl chloride was added, the mixture was stirred for 2 h at room temperature. The mixture was acidified with concentrated hydrochloric acid until all of the diethanesulfonimide precipitated out. The precipitate was removed by filtration giving the diethanesulfonimide (8.111 g, 40.3 mmol) as white crystals in 79.9% yield, which on recrystallization from acetic acid, melted at 76-78 °C [lit. mp[38] 78.5-79 °C]; IR (KBr) ν_{max}: 3146 (s), 2988 (m), 1456 (m), 1345 (s), 1237 (m), 1150 (s), 1051 (m), 878 (s), 725 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.47 (t, 6H), 3.46 (q, 4H); ^{13}C NMR ($CDCl_3$) δ: 8.0, 50.1.

Preparation of Di-*p*-toluenesulfonimide (27)

p-Toluenesulfonyl chloride (3.513 g, 18.4 mmol) was added slowly over a period of about 1 h to a solution of *p*-toluenesulfonamide (2.869 g, 16.8 mmol) in aqueous sodium hydroxide (5%, 15 mL) at 75 °C where the pH of the solution was maintained a 7.5-8.5 (as determined by pH paper) with aqueous sodium hydroxide (5%). Stirring was continued for

20 min and aqueous sodium hydroxide (40%, 1.8 mL) was then added. The mixture was cooled to room temperature and a white precipitate appeared. The precipitate was filtered off to give white crystals which were dissolved in water (20 mL); concentrated hydrochloric acid was added until all of product precipitated. The precipitate was filtered off to give a white solid (**27**) (3.976 g, 12.2 mmol, 72.8% yield), which on recrystallization from acetic acid melted at 168-170 °C [lit. mp[86] 168-169 °C]; IR (KBr) ν_{max}: 3158 (s), 2926 (w), 1595 (s), 1448 (m), 1358 (s), 1294 (s), 1167 (s), 1084 (s), 1040 (m), 855 (s), 808 (s), 665 (s), 604 (s) cm^{-1}; ^1H NMR (acetone-d_6) δ: 2.45 (s, 6H), 7.36 (dd, 4H), 7.73 (dd, 4H); ^{13}C NMR (acetone-d_6) δ: 21.5, 128.3, 130.3, 138.4, 145.3.

Preparation of *N*-Methylsulfonyl Benzenesulfonamide (30)

Methanesulfonyl chloride (2.89 g, 25.2 mmol) was added dropwise to a solution of benzenesulfonamide (1.32 g, 8.4 mmol) in aqueous sodium hydroxide (1 M, 20 mL) at 70-75 °C in 1.5 h. The mixture was stirred for 3 h at 70-75 °C and was then cooled to room temperature. Concentrated hydrochloric acid was added carefully until the solution became acidic (about pH 2, as determined from pH paper) and a white precipitate appeared. The precipitate was filtered off to give the *N*-methylsulfonyl benzenesulfonimide (**30**) (1.915 g, 8.1 mmol, 96.8% yield) as white crystals which were recrystallized from benzene; mp 141-142 °C [lit. mp[87]

141-142 °C]; IR (KBr) ν_{max}: 3216 (s), 3049 (s), 3029 (m), 2946 (m), 1584 (m), 1480 (m), 1453 (s), 1348 (s), 1152 (s), 1088 (s), 992 (s), 849 (s), 759 (s), 658 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.38 (s, 3H), 7.46-8.02 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 44.0, 128.0, 129.2, 134.3, 139.1.

Preparation of Dibenzenesulfonimide (26)

Benzenesulfonyl chloride (3.79 g, 20.99 mmol) was added a little at a time over a period of 40 min to benzenesulfonamide (3.00 g, 19.1 mmol) in aqueous sodium hydroxide (5.0%, 20 mL) at 50-55 °C. The medium was maintained weakly basic (tested by pH paper) with aqueous sodium hydroxide (5.0%). After all of the benzenesulfonyl chloride was added, the mixture was stirred for 20 min at 50 -55 °C. Aqueous sodium hydroxide (40%, 2.0 mL) was then added. After the mixture was cooled to room temperature, water was added to dissolve all of the precipitate. The mixture was acidified until all of the dibenzenesulfonimide precipitated out with concentrated hydrochloric acid. The precipitate was filtered off to give white crystals (**26**) (4.99 g, 16.0 mmol, 83.9% yield) which were recrystallized from water, mp 156-157 °C [lit. mp[37] 157-158 °C]; IR (KBr) ν_{max}: 3218 (s), 3040 (s), 1476 (s), 1451 (s), 1354 (s), 1311 (s), 1086 (s), 1024 (s), 756 (s), 685 (s) cm^{-1}; ^1H NMR (acetone-d_6) δ: 7.59-7.93 (m, 10H); ^{13}C NMR (acetone-d_6) δ: 128.2, 130.0, 134.5, 141.2.

Preparation of Ethane-1,2-disulfonimide (19)

a) Sodium Ethane-1,2-disulfonate (49)

1,2-Dibromoethane (30.0 g, 160.0 mmol) was added dropwise over a period of 40 min to a refluxing solution of sodium sulfite (20.20 g, 317.4 mmol) in water (130 mL). The mixture was refluxed for 1 h after the organic layer had disappeared. On cooling the resulting aqueous solution to 5 °C, crystals of sodium ethane-1,2-disulfonate separated and were filtered off. The filtrate was evaporated to incipient crystallization. The mixture was cooled to 0 °C, and a second crop of crystals separated. The two crops of crystals were combined and recrystallized from water by dissolving in the minimum quantity of boiling water to give the sodium ethane-1,2-disulfonate (**49**) (22.96 g, 98.1 mmol, 62.0% yield); IR (KBr) ν_{max}: 3400 (m), 3020 (m), 2960 (w), 2940 (w), 1210 (s), 1040 (s), 770 (s) cm^{-1}; ^1H NMR (D_2O) δ: 3.27 (s, 4H); ^{13}C NMR (D_2O) δ: 49.1.

b) Ethane-1,2-disulfonic Acid (50)

A solution of sodium ethane-1,2-disulfonate (**49**) (10.0 g, 42.7 mmol) in water (60 mL) was passed through a column which contained Rexyn 101 (H^+) (110 g). The product was eluted with water and the water removed on a rotary evaporator to give the ethane-1,2-disulfonic acid dihydrate (**50**) (9.50 g, 42.0 mmol, 98.3% yield); mp 110-112 °C [lit. mp[88] 111-112 °C]; neutralization equivalent: 112 (calculated 113); IR (Nujol) ν_{max}: 3328 (s), 3004 (s), 2924

(s), 2855 (s), 1462 (s), 1377 (m), 1282 (s), 1265 (m), 1102 (s), 766 (s), 538 (s) cm^{-1}; ^1H NMR (D_2O) δ: 3.27 (s, 4H); ^{13}C NMR (D_2O) δ: 49.1.

c) Ethane-1,2-disulfonic Anhydride (10)

A mixture of ethane-1,2-disulfonic acid dihydrate (**50**) (0.748 g, 3.2 mmol) and thionyl chloride (15.0 mL) was heated at reflux for 16 h. The excess thionyl chloride was removed by distillation and further dried under vacuum to give ethane-1,2-disulfonic anhydride (**10**) (0.539 g, 3.1 mmol, 98.1% yield); mp 145-147 °C (in a sealed mp tube) [lit. mp[88] 145-146 °C]; IR (Nujol) ν_{max}: 3034 (m), 3017 (m), 2923 (s), 2855 (s), 1458 (s), 1246 (m), 1383 (s), 1275 (s), 1225 (s), 1196 (s), 1169 (s), 817 (m), 729 (m), 673 (s) cm^{-1}; ^1H NMR (CD_3NO_2) δ: 4.45 (s, 4H); ^{13}C NMR (CD_3NO_2) δ: 53.0.

d) Benzylammonium 2-(Benzylaminosulfonyl)ethanesulfonate (52)

Benzylamine (0.893 g, 8.3 mmol) in dry dichloromethane (20 mL) was added slowly to a flask containing ethane-1,2-disulfonic anhydride (**10**) (0.683 g, 4.0 mmol) at room temperature. After all of benzylamine was added, the mixture was stirred for 30 min and the precipitate filtered off to give benzylammonium 2-(benzylaminosulfonyl)-ethanesulfonate (**52**) (1.413 g, 3.66 mmol, 92.1% yield) as a white solid which was recrystallized from water, mp 181-

182 °C; IR (KBr) ν_{max}: 3298 (s), 3034 (s), 1626(m), 1541 (m), 1456 (s), 1387 (m), 1320 (s), 1281 (m), 1181 (s), 1055 (s), 1038 (s), 750 (s), 696 (s) cm^{-1}; ^1H NMR (D_2O) δ: 3.20 (m, 2H), 3.37 (m, 2H), 4.18 (s, 2H), 4.30 (s, 2H), 7.42 (m, 5H), 7.47 (m, 5H); ^{13}C NMR (D_2O) δ: 45.8, 47.6, 49.0, 50.4, 130.6, 130.8, 131.5, 131.7, 131.9, 135.3, 139.9.

e) 2-(Benzylaminosulfonyl)ethanesulfonic Acid (53)

Benzylammonium 2-(benzylaminosulfonyl)ethanesulfonate (**52**) (2.817 g, 7.29 mmol) in water (20 mL) was passed through a column of Rexyn 101 (H^+) resin (25 g). After all of products were washed out with water, the water was removed on a rotary evaporator and the solid so obtained dried to give 2-(benzylaminosulfonyl)ethanesulfonic acid (**53**) (1.95 g, 6.98 mmol, 95.8% yield) which was recrystallized from acetic acid:toluene (1:1) to give white crystals, mp 125-126 °C; IR (KBr) ν_{max}: 3264, 2988, 1649, 1445, 1424, 1296, 1231, 1134, 1034 cm^{-1}; ^1H NMR (D_2O) δ: 3.21 (m, 2H), 3.37 (m, 2H), 4.31 (s, 2H), 7.42 (m, 5H); ^{13}C NMR (D_2O) δ: 66.9, 68.3, 69.7, 149.9, 150.1, 151.3, 159.3.

f) *N*-Benzyl Ethane-1,2-disulfonimide (54)

The mixture of 2-(benzylaminosulfonyl)ethanesulfonic acid (0.984 g, 3.52 mmol) and thionyl chloride (25 mL) was refluxed for 17 h. After the excess thionyl chloride was removed by distillation, brown crystals were obtained. The residue was extracted with chloroform (3 x 100 mL). The

extract was washed with saturated sodium bicarbonate (30 mL) and water (30 mL), and dried over anhydrous magnesium sulfate. The solvent was evaporated to give *N*-benzylethane-1,2-disulfonimide (**54**) (0.826 g, 3.16 mmol, 89.7% yield) as white crystals which were recrystallized from 70% ethanol, mp 148-149 °C; IR (KBr) ν_{max}: 3026 (s), 1458 (m),1318 (m), 1215 (s), 1179 (s), 1028 (s), 752 (m), 696 (m), 534 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.92 (s, 4H), 4.69 (s, 2H), 7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 44.97, 48.92, 128.61, 128.65, 128.84, 134.4; exact mass calculated for $C_9H_{11}NO_4S_2$: 261.0130, found: 261.0131.

g) Ethane-1,2-disulfonimide (19)

Formic acid (2.070 g, 45.0 mmol) was added to a mixture of *N*-benzylethane-1,2-disulfonimide (**54**) (0.215 g, 0.82 mmol), 10% palladium on carbon (Pd/C) (0.2125 g) and, absolute ethanol (40 mL). The mixture was refluxed for 24 h. After the mixture was cooled to room temperature, the catalyst was filtered off. The excess formic acid and ethanol from the filtrate were evaporated to give ethane-1,2-disulfonimide (**19**) (0.141 g, 0.82 mmol, 99.6% yield) as grey crystals which were recrystallized from trifluoroacetic acid, and melted at 235-237 °C (with decomposition); IR (KBr) ν_{max}: 3171 (s), 3029 (m), 1969 (m), 1354 (s), 1281 (s), 1152 (s), 1138 (s), 994 (m), 855 (s), 743 (s), 695 (s) cm^{-1}; ^{1}H NMR (acetone-d_6) δ: 4.24 (s, 4H); ^{13}C NMR (acetone-d_6) δ: 53.9; exact mass calculated for $C_2H_5NO_4S_2$: 170.9660;

found 170.9661.

Preparation of Propane-1,3-disulfonimide (20)

a) 3-Chloropropyl Thiolacetate (50)

Freshly distilled thiolacetic acid (2.50 g, 32.8 mmol) was added slowly to allyl chloride (2.50 g, 32.7 mmol). The mixture was stirred for 6 h at 60 °C and then distilled under reduced pressure to give **50** as a colourless liquid (bp 85 °C, 10 Torr, [lit.[89] bp 74-76 °C], 2.92 g, 19.1 mmol, 58.4% yield); IR (neat) ν_{max}: 3369 (m), 2961 (s), 2869 (m), 1694 (s), 1433 (s), 1354 (s), 1312 (s), 1271 (s), 1136 (s), 949 (s), 858 (m), 777 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.05 (q, 2H), 2.35 (s, 3H), 3.02 (t, 2H), 3.59 (t, 2H); ^{13}C NMR ($CDCl_3$) δ: 26.3, 30.6, 43.3, 32.3, 195.4.

b) 3-Chloropropanesulfonyl Chloride (51)

i) Gaseous chlorine was passed through a solution of 3-chloropropyl thiolacetate (**50**) (2.90 g, 19.0 mmol) in water (5 mL) and crushed ice (3.0 g) at 0 °C. The temperature was maintained at 5-10 °C with addition of crushed ice. After a persistent colour of chlorine appeared in the solution, the flow of Cl_2 was stopped. The mixture was extracted with dichloromethane (3 x 25 mL). The organic layer was separated and washed with water (2 x 25 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated to give a slightly yellow liquid (3.20 g, 18.1 mmol, 94.6% yield) which was distilled at reduced

pressure to give **51** as a clear, colourless liquid, bp 109-110 °C (6 Torr) [lit. bp[90] 82-85 °C (1 Torr)]; IR (neat) ν_{max}: 3065 (m), 2974 (m), 2876 (w), 1443 (m), 1375 (s), 1314 (s), 1269 (s), 1225 (m), 1167 (s), 1026 (w), 963 (m), 864 (m), 844 (m), 746 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.51 (m, 2H), 3.74 (t, 2H), 3.88 (t, 2H); ^{13}C NMR ($CDCl_3$) δ: 27.4, 41.5, 62.4.

ii) A mixture of thionyl chloride (25 mL), 1,3-propanesultone (5.240 g, 42.90 mmol) and a few drops of *N,N*-dimethylformamide was refluxed for 30 h. The excess thionyl chloride was evaporated to give a slightly yellow oil which was distilled under reduced pressure to give the 3-chloropropanesulfonyl chloride (**51**) (6.550 g, 37.00 mmol, 86.2% yield) as a clear colourless liquid with the same IR, ^1H NMR, ^{13}C NMR spectra and bp as the material prepared above.

c) *N*-Benzyl 3-Chloropropanesulfonamide (52)

Benzylamine (2.40 g, 22.6 mmol) in benzene (4 mL) was added dropwise to a solution of 3-chloropropanesulfonyl chloride (**51**) (2.0 g, 11.3 mmol) in benzene (6 mL) at 0-5 °C with stirring. A white precipitate appeared immediately. Stirring was continued for 0.5 h after the benzylamine was added. Water was then added until all of precipitate was dissolved. The mixture was acidified to pH 3 with aqueous hydrochloric acid (4 M). The organic layer was separated and washed with saturated sodium bicarbonate (5 mL) and

water (2 x 5 mL), and dried over anhydrous magnesium sulfate. The solvent was evaporated to give the *N*-benzyl 3-chloropropanesulfonamide (**52**) (2.53 g, 10.2 mmol, 90.3% yield) as slightly yellowish crystals which were recrystallized from ethanol to give white crystals, mp 61-63 °C [lit. mp[91] 61-62 °C]; IR (KBr) ν_{max}: 3235 (s), 2967 (m), 1454 (s), 1437 (s), 1316 (s), 1300 (s), 1277 (m), 1161 (s), 1136 (s), 1055 (m), 883 (s), 767 (s), 735 (s), 696 (s) cm^{-1}; ^1H NMR 2.20 (m, 2H), 3.07 (t, 2H), 3.58 (t, 2H), 4.30 (s, 2H), 4.80 (s, 1H), 7.35 (m, 5H).

d) Ammonium 3-(Benzylaminosulfonyl)propanesulfonate (53)

A mixture of *N*-benzyl 3-chloropropanesulfonamide (**52**) (4.07 g, 16.4 mmol) and freshly prepared ammonium sulfite hydrate (4.07 g, 30.3 mmol) [obtained by introducing NH_3 and SO_2 (mole ratio 2:1)] in ethanol (14 mL) and water (14 mL) was refluxed for 18 h. This solution was concentrated by distillation until a precipitate appeared. Water (120 mL) was then added with stirring. The precipitate was filtered off. The filtrate was evaporated to dryness. The residue was extracted with boiling acetic acid (3 x 5 mL). The acetic acid solution was allowed to stand for 3 h at room temperature, and was then filtered to give the ammonium 3-(*N*-benzylaminosulfonyl)propanesulfonate (**53**) (4.084 g, 13.2 mmol, 80.1% yield) as white crystals. these were recrystallized from ethanol, mp 209-212 °C [lit. mp[91] 208-212 °C]; IR (KBr) ν_{max}: 3222 (s), 1667 (m), 1404 (s), 1333

(s), 1194 (s), 1146 (s), 1046 (s), 900 (m), 758 (s) cm^{-1}; ^1H NMR (D_2O) δ: 2.10 (m, 2H), 2.89 (t, 2H), 3.18 (t, 2H), 4.30 (s, 2H), 7.40 (m, 5H); ^{13}C NMR (D_2O) δ: 41.1, 68.4, 71.1, 72.6, 150.2, 151.2, 154.9, 159.6.

e) 3-(*N*-Benzylaminosulfonyl)propanesulfonic Acid (54)

Ammonium 3-(*N*-benzylaminosulfonyl)propanesulfonate (**53**) (0.565 g, 1.80 mmol) in water (10 mL) was passed through a column of Rexyn 101 (H^+) (6.0 g). The column was washed with water until the eluate was neutral. The water was evaporated to give 3-(*N*-benzylaminosulfonyl)propanesulfonic acid (**54**) (0.518 g, 1.70 mmol, 98.1% yield) as a white solid; mp 71-73 °C [lit. mp[91] 71.5-74 °C]; ^1H NMR (D_2O) δ: 2.10 (m, 2H), 2.89 (t, 2H), 3.18 (t, 2H), 4.30 (s, 2H), 7.43 (m, 5H); ^{13}C NMR (D_2O) δ: 41.1, 68.4, 71.1, 72.6, 150.2, 151.2, 154.9, 159.6.

f) Propane-1,3-disulfonimide (20)

3-(*N*-Benzylaminosulfonyl)propanesulfonic acid (**54**) (2.155 g, 7.55 mmol) was suspended in phosphorus oxychloride (12 mL). This mixture was kept for 4 days at room temperature with occasional shaking. It was cooled to 0 °C in an ice-bath until a precipitate appeared. The mixture was filtered to give propane-1,3-disulfonimide (**20**) (0.879 g, 4.75 mmol, 64.6% yield) as a white solid which was recrystallized from acetic acid, mp 275-276 °C (with decomposition); IR (KBr) ν_{max}: 3222 (s), 2988 (m), 2940 (m),

1366 (s), 1296 (s), 1231 (m), 1175 (s), 1148 (s), 1117 (m), 932 (s), 831 (s) cm^{-1}; ^1H NMR (acetone-d_6) δ: 2.62 (m, 2H), 3.53 (t, 4H); ^{13}C NMR (acetone-d_6) δ: 19.7, 50.0.

Preparation of *o*-Benzenedisulfonimide (21)

a) *o*-Benzenedisulfonyl Chloride (55)

The mixture of potassium *o*-benzenedisulfonate (0.623 g, 2.0 mmol) and phosphorus pentachloride (1.217 g, 5.8 mmol) was heated at 182 °C (oil-bath) under reflux for 3.5 h. Water (3 mL) was added after the mixture was cooled to room temperature. The mixture was filtered and the solid washed with water (2 mL) to give *o*-benzenedisulfonyl chloride (**55**) (0.394 g, 72.4% yield) as a grey solid. IR (KBr) ν_{max}: 3108 (m), 1570 (s), 1455 (s), 1429 (s), 1377 (s), 1186 (m), 1107 (s), 1040 (s), 749 (s), 666 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.05 (m, 2H), 8.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 132.3, 136.1, 141.3.

b) Benzene-1,2-disulfonimide (21)

Aqueous ammonia solution (4.5 M, 4 mL) was added dropwise to a solution of *o*-benzenedisulfonyl chloride (**55**) (0.980 g, 3.56 mmol) at room temperature. The mixture was stirred for 1 h and filtered to give ammonium *o*-benzenedisulfonimide. This was recrystallized from water to give white crystals (0.822 g, 97.6% yield). A solution of ammonium *o*-benzenedisulfonimide (0.730 g 3.09 mmol) in water (10 mL) was passed through a Rexyn 101 (H^+) (15.0 g) column.

The solvent was removed to give a white solid (**21**) (0.61 g, 90.1% yield) which was recrystallized from benzene to give white needles; mp 186-188 °C [lit. mp[92] 187-189 °C]; IR (KBr) ν_{max}: 3598 (s), 3512 (m), 3144 (s), 1634 (m), 1446 (s), 1402 (s), 1281 (s), 1184 (s), 1049 (s), 999 (s), 854 (s), 760 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.92 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 124.2, 137.1, 142.2.

Preparation of *N*-Benzoyl Benzenesulfonamide (31)

Benzenesulfonamide (**42**) (0.40 g, 2.54 mmol) was mixed with benzoyl chloride (0.79 g, 5.60 mmol) and pyridine (2.9 mL) at 0 °C. The mixture was stirred for 3 h at 0 °C. Aqueous hydrochloric acid (6 M) was added to acidify the mixture until precipitation was complete. The precipitate was filtered off and dried under reduced pressure to give the *N*-benzoyl benzenesulfonamide (**31**) (0.48 g, 1.82 mmol, 71.7% yield) as a white solid which was recrystallized from benzene, mp 147-149 °C [lit. mp[93] 146 °C]; IR (KBr) ν_{max}: 3281 (s), 3094 (m), 3063 (s), 1698 (s), 1452 (s), 1415 (s), 1335 (s), 1250 (s), 1179 (s), 1063 (s), 1028 (s), 897 (s), 721 (s), 686 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.43-8.19 (m, 10H), 8.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 127.7, 128.7, 129.0, 131.1, 133.6, 134.1, 138.4.

Preparation of *N*-Acetylmethanesulfonamide (32)

Methanesulfonamide (**61**) (0.80 g, 8.41 mmol) was mixed with acetyl chloride (0.88 g, 11.2 mmol) at room temperature

and the mixture was stirred for 1.5 h. Plate crystals were formed. The excess acetyl chloride was evaporated under reduced pressure to give a crystalline product (1.09 g, 7.96 mmol, 94.7% yield). This was recrystallized from benzene to give white needles, **32**, mp 98-100 °C [lit. mp[46] 99 °C]; IR (KBr) ν_{max}: 3133 (s), 2909 (s), 1690 (s), 1337 (s), 1242 (s), 1156 (s), 1044 (m), 1009 (s), 978 (s), 868 (m), 754 (s), 691 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.16 (s, 3H), 3.32 (s, 3H), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 23.7, 41.6.

Preparation of *N*-(*p*-Methylphenyl)methanesulfonamide (36)

Methanesulfonyl chloride (5.879 g, 51.3 mmol) was added to a solution of *p*-toluidine (5.0 g, 46.7 mmol) and triethylamine (5.19 g, 51.3 mmol) in toluene (50 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C. It was worked up as above to give a white solid (**36**) (7.36 g, 85.1% yield) which was recrystallized from 85% ethanol to give white crystals, mp 104-105 °C [lit. mp[94] 102.0-102.7 °C]; IR (KBr) ν_{max}: 3291 (s), 3022 (m), 2928 (m), 2867 (m), 1615 (m), 1511 (s), 1476 (s), 1395 (s), 1329 (s), 1300 (s), 1230 (s), 1151 (s), 978 (s), 926 (s), 812 (s), 772 (s), 741 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.34 (s, 3H), 2.99 (s, 3H), 6.88 (s, 1H), 7.16 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 20.9, 39.0, 121.6, 130.3, 131.1, 135.6.

Preparation of *N*-(*p*-Nitrophenyl)methanesulfonamide (37)

Methanesulfonyl chloride (5.00 g, 43.6 mmol) was added

to a solution of *p*-nitroaniline (5.00 g, 36.2 mmol) and triethylamine (5.00 g, 49.4 mmol) in toluene at 80 °C. The mixture was stirred for 25 min at 80 °C. The solvent was removed and the residue was extracted three times with sodium carbonate. The combined extracts were acidified with concentrated hydrochloric acid to precipitate the *N*-(*p*-nitrophenyl)methanesulfonamide. The mixture was filtered to give a yellowish solid (**37**) (6.50 g, 30.1 mmol, 83% yield). This was recrystallized from 85% ethanol to give slightly yellowish crystals, mp 184-186 °C [lit. mp[95] 186 °C]; IR (KBr) ν_{max}: 3283 (s), 3011 (w), 2930 (w), 1597 (s), 1522 (s), 1477 (s), 1329 (s), 1294 (s), 1142 (s), 970 (s), 918 (s), 851 (s), 749 (s) cm^{-1}; ^1H NMR (acetone-d_6) δ: 3.18 (s, 3H), 7.53 (m, 2H), 8.22 (m, 2H); ^{13}C NMR (acetone-d_6) δ: 40.4, 118.8, 126.1, 135.0, 139.5.

Preparation of *N*-(*m*-Nitrophenyl)methanesulfonamide (38)

Methanesulfonyl chloride (2.50 g, 21.8 mmol) was added to a solution of *m*-nitroaniline (2.50 g, 18.1 mmol) and triethylamine (2.50 g, 24.7 mmol) in toluene at 80 °C, and worked up as above to give a white solid (**38**) (3.10 g, 14.3 mmol, 79% yield) which was recrystallized from 85% ethanol to give a white crystal, mp 164-165 °C [lit. mp[95] 164 °C]; IR (KBr) ν_{max}: 3298 (s), 3036 (m), 1526 (s), 1485 (s), 1399 (s), 1345 (s), 1331 (s), 1267 (s), 1156 (s), 968 (s), 737 (s) cm^{-1}; ^1H NMR (acetone-d_6) δ: 3.12 (s, 3H), 7.60-7.76 (m, 2H), 7.95-8.01 (m, 1H), 8.20 (m, 1H); ^{13}C NMR (acetone-d_6)

δ: 40.0, 114.6, 119.3, 126.2, 131.5, 140.8.

Preparation of *N*-(*p*-Chlorophenyl)methanesulfonamide (39)

Methanesulfonyl chloride (4.94 g, 43.1 mmol) was added to a solution of *p*-chloroaniline (5.0 g, 39.2 mmol) and triethylamine (4.36 g, 43.1 mmol) in toluene (50 mL) at room temperature. The mixture was stirred for 30 min, and the precipitate was filtered off. The filtrate was evaporated to dryness to give a grey solid. The solid was dissolved in 15% aqueous sodium hydroxide (40 mL), and concentrated hydrochloric acid added to precipitate the *N*-(*p*-chlorophenyl)methanesulfonamide. The mixture was filtered to give a white solid (**39**) (6.45 g, 80.0% yield) which was recrystallized from 85% ethanol to give white crystals, mp 150-151 °C [lit. mp[96] 148 °C]; IR (KBr) ν_{max}: 3285 (s), 3007 (w), 2928 (w), 1491 (s), 1453 (s), 1387 (s), 1325 (s), 1294 (s), 1148 (s), 1090 (s), 1017 (m), 982 (s), 818 (s), 766 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.02 (s, 3H), 6.71 (s, 1H), 7.13-7.35 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 39.5, 122.2, 129.9, 135.2.

Preparation of *N*-(*m*-Chlorophenyl)methanesulfonamide (40)

Methanesulfonyl chloride (2.50 g, 21.8 mmol) was added to a solution of *m*-chloroaniline (2.50 g, 19.6 mmol) and triethylamine (2.21 g, 21.8 mmol) in toluene (30 mL) at room temperature, and worked up as above to give a grey solid (**40**) (4.05 g, 19.7 mmol, 90.4% yield) which was

recrystallized from 85% ethanol to give white crystals, mp 95-96 °C [lit. mp[96] 90.5 °C]; IR (KBr) ν_{max}: 3252 (s), 3019 (m), 1593 (s), 1480 (s), 1391 (s), 1318 (s), 1250 (s), 1152(s), 1090 (s), 970 (s), 928 (s), 785 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.06 (s, 3H), 7.18-7.40 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 39.7, 118.4, 120.3, 125.5, 130.8, 135.6, 138.0.

Preparation of *N*-(*p*-Methoxyphenyl)methanesulfonamide (41)

Methanesulfonyl chloride (2.558 g, 22.3 mmol) was added to a solution of *p*-methoxyaniline (2.50 g, 20.3 mmol) and triethylamine (2.48 g, 24.5 mmol) in diethyl ether (50 mL) at 0 °C. The mixture was stirred for 30 min, and worked up as above to give a slightly pink solid (**41**) (3.26 g, 79.8% yield) which was recrystallized from 85% ethanol to give white crystals, mp 118-119 °C [lit. mp[94] 116 °C]; IR (KBr) ν_{max}: 3260 (s), 3019 (m), 2936 (w), 2840 (w), 1512 (s), 1462 (m), 1395 (s), 1321 (s), 1246 (s), 1217 (s), 1154 (s), 1109 (s), 1026 (s), 972 (s), 826 (s), 768 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.96 (s, 3H), 3.81 (s, 3H), 6.71 (s, 1H), 6.90 (m, 2H), 7.19 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 38.9, 55.6, 114.9, 124.8, 129.1, 158.1.

Preparation of 1,3-Propanesultam (22)

a) 3-Chloropropanesulfonamide (56)

Anhydrous ammonia was bubbled through a stirred solution of 3-chloropropanesulfonyl chloride (**51**) (5.50 g, 31.1 mmol) in dichloromethane (200 mL) at 0 °C until no

further formation of precipitate was observed. The mixture was stirred for additional 0.5 h at 0 °C and then warmed to room temperature. The solvent was evaporated and the residue was extracted with acetone (3 x 50 mL). The extract was dried over anhydrous magnesium sulfate. The solvent was evaporated to give a white solid (**56**) (4.55 g, 28.8 mmol, 92.6% yield). This was recrystallized from 90% ethanol to give white needle crystals, mp 63-65 °C [lit. mp[97] 63 °C]; ^{1}H NMR ($CDCl_3$) δ: 2.34 (m, 2H), 3.33 (t, 2H), 3.71 (t, 2H), 4.77 (s, 2H); ^{13}C NMR ($CDCl_3$) δ: 27.4, 42.8, 52.6.

b) 1.3-Propanesultam (22)

3-Chloropropanesulfonamide (**56**) (4.00 g, 25.3 mmol) in absolute ethanol (freshly distilled from calcium hydride) (30 mL) was added dropwise to a solution of potassium hydroxide (1.571 g, 28.0 mmol) in absolute ethanol (20 mL). The mixture was refluxed for 2.5 h; a solution of potassium hydroxide (5%) in absolute ethanol was added to keep the solution basic. The mixture was cooled to room temperature, and the precipitate was removed by filtration. The solid was washed with absolute ethanol (20 mL) and filtered again. The combined filtrate was neutralized with aqueous hydrochloric acid (1 M) and the precipitated NaCl filtered off. The solvent was evaporated to give a slightly yellow liquid (**22**) (2.20 g, 18.1 mmol, 71.6% yield). This was distilled to give a colourless liquid, bp 156-158 °C (2 Torr) [lit. bp[49] 180 °C (5 Torr)]; IR (neat) ν_{max}: 3565 (w),

3267 (w), 2900 (w), 1388 (m), 1299 (s), 1137 (s), 1044 (m), 998 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.46 (m, 2H), 3.10 (t, 2H), 3.42 (t, 2H), 4.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 23.9, 42.2, 46.6.

Preparation of 1,4-Butanesultam (23)

a) 4-Chloro-1-butanesulfonyl Chloride (57)

The mixture of sodium 4-hydroxy-1-butanesulfonate (5.00 g, 28.4 mmol) and thionyl chloride (20 mL) with a catalytic amount of DMF (0.5 mL) was refluxed for overnight. After the excess thionyl chloride was removed by distillation, the residue was poured into ice water (100 mL), and extracted with dichloromethane (3 x 30 mL). The organic phases were combined and dried over magnesium sulfate. The solvent was evaporated to give a clear colourless oil (4.55 g, 83.8% yield). Fractional distillation gave the pure 4-chloro-1-butanesulfonyl chloride (57), bp 115-118 °C at 1.5 Torr [lit. bp[98] 96-100 °C, 0.3 Torr); IR (neat) ν_{max}: 2960 (w), 2873 (m), 1560 (m), 1374 (s), 1165 (s), 911 (m), 732 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.95-2.08 (m, 2H), 2.15-2.32 (m, 2H), 3.65 (t, 2H), 3.75 (t, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.9, 30.1, 43.8, 64.4.

b) 4-Chlorobutanesulfonamide (58)

Ammonia gas was pass through a solution of 4-chloro-butanesulfonyl chloride (57) (8.889 g, 46.5 mmol) in diethyl ether (30 mL) at 0 °C until no more precipitate was formed.

The solvent was evaporated and the residue was extracted with dichloromethane (3 x 100 mL). The extract was washed with aqueous hydrochloric acid (1 M, 30 mL), saturated sodium bicarbonate (30 mL) and water (30 mL). The solvent was removed to give a brown liquid (**58**) (7.503 g, 43.7 mmol, 94% yield). IR (neat) ν_{max}: 3355 (s), 1399 (s), 1281 (s), 1213 (s), 1183 (s), 1082 (m), 718 (s), 685 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.98 (m, 4H), 3.19 (t, 2H), 3.60 (t, 2H), 5.24 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.5, 30.7, 44.2, 54.3.

c) 1,4-Butanesultam (23)

4-Chlorobutanesulfonamide (**58**) (6.80 g, 39.6 mmol) in absolute ethanol (35 mL) was added dropwise to a solution of potassium hydroxide (2.556 g, 45.6 mmol) in absolute ethanol (35 mL). The mixture was refluxed for 1.5 h and neutralized with concentrated hydrochloric acid to pH 7. The precipitate was removed by filtration and the filtrate was evaporated under vacuum to dryness. The residue was extracted with dichloromethane (3 x 50 mL). The extract was washed with water (30 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated to give a brown solid (**23**) (4.658 g, 34.5 mmol, 87% yield) which was recrystallized from chloroform-petroleum ether (30-60 °C), mp 114-115 °C [lit. mp[99] 115 °C]; IR (KBr) ν_{max}: 3233 (s), 2965 (m), 1424 (s), 1315 (s), 1291 (m), 1255 (s), 1177 (m), 1130 (s), 1067 (s), 1032 (s), 955 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.63 (m, 2H), 2.23 (m, 2H), 3.10 (t, 2H), 3.42 (q, 2H),

4.24 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 23.7, 24.5, 45.4, 50.2.

Preparation of *N*-(*p*-Methylphenyl)cyclohexylmethanesulfonamide (47)

Cyclohexylmethanesulfonyl chloride (5.0 g, 25.4 mmol) was added to a solution of *p*-toluidine (2.71 g, 25.3 mmol) and triethylamine (2.57 g, 25.4 mmol) in diethyl ether (60 mL) at 0 °C. The mixture was stirred for 30 min, and worked up as above to give a slightly yellowish solid (47) (5.08 g, 19.0 mmol, 75.1% yield) which was recrystallized from 85% ethanol solution, mp 114-115 °C; IR (KBr) ν_{max}: 3227 (s), 3038 (w), 2932 (s), 2851 (s), 1506 (s), 1447 (s), 1395 (s), 1320 (s), 1296 (s), 1198 (s), 1165 (s), 1140 (s), 922 (s), 773 (s), 559 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.05-1.31 (m, 5H), 1.67-2.05 (m, 6H), 2.33 (s, 3H), 2.96 (d, 2H), 6.55 (s, 1H), 7.10-7.27 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 20.9, 22.2, 25.8, 32.9, 33.7, 58.0, 121.2, 130.2, 134.2, 135.4.

Preparation of *N*-(*p*-Methylphenyl)ethanesulfonamide (48)

Ethanesulfonyl chloride (3.50 g, 27.2 mmol) was added to a solution of *p*-toluidine (2.92 g, 27.2 mmol) and triethylamine (2.75 g, 27.2 mmol) in toluene (50 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and worked up as above to give a white solid (48) (4.38 g, 22.0 mmol, 81% yield) which was recrystallized from 85% ethanol to give white crystals, mp 80-81 °C [lit. mp[94] 80-80.5 °C]; IR (KBr) ν_{max}: 3252 (s), 2993 (w), 1512 (s), 1455 (m), 1389 (s), 1329

(s), 1302 (s), 1275 (s), 1148 (s), 912 (s), 814 (s), 729 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.37 (t, 3H), 2.33 (s, 3H), 3.12 (q, 2H), 6.86 (s, 1H), 7.15 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 20.9, 45.6, 121.2, 130.2, 134.2, 135.2.

Preparation of 3,4-Dihydro-1-H-2,3-benzothiazine-2,2-dioxide (24)

(a) Phenylmethanesulfonamide (59)

Gaseous ammonia was passed through a solution of phenylmethanesulfonyl chloride (3.70 g, 33.7 mmol) in diethyl ether (200 mL) at 0 °C until no more precipitate was formed. The solvent was removed and the residue was extracted with acetone (3 x 50 mL). The acetone was evaporated to give a white solid (**59**) (3.04 g, 91.7% yield) which was recrystallized from water to give white crystals, mp 104-105 °C; IR (KBr) ν_{max}: 3381 (s), 3316 (s), 3245 (s), 2995 (w), 1497 (m), 1323 (s), 1172 (s), 1147 (s), 1127 (s), 914 (m), 808 (m), 779 (s), 700 (s) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ: 61.0, 128.9, 129.5, 130.7, 131.5.

(b) 3,4-Dihydro-1-H-2,3-benzothiazine-2,2-dioxide (24)

Methanesulfonic acid (3.00 g, 31.2 mmol) was added slowly to a mixture of phenylmethanesulfonamide (**59**) (0.856 g, 5.0 mmol) and 1,3,5-trioxane (0.153 g, 1.7 mmol) in dichloromethane (18 mL) at 35 °C. Acetic anhydride (0.650 g, 6.4 mmol) was added after an interval of 20 min. The mixture was stirred for 6 h at 35 °C, and then cooled to 0

°C. Dichloromethane (30 mL) was added and the mixture was washed with water (25 mL), aqueous sodium bicarbonate (5%, 2 x 25 mL), and water (25 mL). The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated to give a white solid (**24**) (0.663 g, 3.6 mmol, 72.4% yield) which was recrystallized from ethyl acetate, mp 143-144 °C [lit. mp[100] 142-143 °C]; IR (KBr) ν_{max}: 3287 (s), 3021 (w), 2920 (w), 1439 (s), 1401 (s), 1325 (s), 1171 (s), 1132 (s), 1073 (s), 884 (m), 766 (s), 756 (s), 540 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.35 (s, 2H), 4.62 (s, 2H), 7.10 (m, 2H), 7.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 47.9, 51.3, 126.4, 127.6, 128.3, 130.3.

Preparation of 2,3-Dihydro-1,2-benzisothiazole 1,1-Dioxide (25)

a) Pseudosaccharin Chloride (60)

A mixture of saccharin (3.534 g, 19.3 mmol) and phosphorus pentachloride (4.418 g, 21.2 mmol) was heated at 175 °C for 1.5 h. A crystalline product formed which was filtered off to give a white solid. This was recrystallized from benzene to give white crystals (**60**) (3.014 g, 15.0 mmol, 77.5% yield), mp 139-142 °C [lit. mp[101] 141-144 °C]; IR (KBr) ν_{max}: 3098 (m), 3017 (m), 1723 (w), 1605 (m), 1551 (s), 1534 (s), 1347 (s), 1237 (s), 1181 (s), 1125 (m), 1017 (m), 776 (s), 623 (m), 580 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.81-7.94 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 122.5, 125.1, 129.9, 134.4, 135.0, 135.1, 136.1.

b) 2,3-Dihydro-1,2-benzisothiazole 1,1-Dioxide (25)

Sodium borohydride (0.772 g, 20.4 mmol) was added in small portions to a solution of pseudosaccharin chloride (**60**) (1.028 g, 5.1 mmol) in freshly distilled THF (30 mL) at 0 °C. After the mixture was stirred for 24 h at room temperature, water (5 mL) was added at 0 °C. The solvent was evaporated in vacuo at 20 °C, aqueous hydrochloric acid (4 M) was added to the mixture until pH 4. The aqueous layer was extracted with chloroform (3 x 20 mL). The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated to give a white solid (**25**) (0.695 g, 4.1 mmol, 80.5% yield) which was recrystallized from 90% ethanol, mp 110-112 °C [lit. mp[102] 111-113 °C]; IR (KBr) ν_{max}: 3224 (s), 2941 (w), 2874 (w), 1452 (m), 1395 (s), 1284 (s), 1204 (s), 1167 (s), 1125 (s), 1028 (m), 752 (s), 735 (s), 704 (s), 567 (s) cm^{-1}; ^1H NMR (acetone-d_6) δ: 4.55 (d, 2H), 4.88 (br s, 1H); 7.27- 7.82 (m, 4H); ^{13}C NMR (acetone-d_6) δ: 45.9, 121.4, 126.1, 129.7, 133.4.

Preparation of *N*-Cyclohexyl Methanesulfonamide (44)

Methanesulfonyl chloride (2.50 g, 21.8 mmol) was added dropwise to a solution of cyclohexylamine (2.60 g, 26.2 mmol) and triethylamine (2.21 g, 21.8 mmol) in toluene at room temperature. The mixture was stirred for 30 min, and worked up as above to give a white solid (**44**) (3.28 g, 18.5 mmol, 85% yield) which was recrystallized from benzene, mp

106-107 °C [lit. mp[103] 103 °C]; ^{1}H NMR ($CDCl_3$) δ: 1.28 (m, 4H), 1.60 (m, 2H), 1.71 (m, 2H), 2.01 (m, 2H), 2.98 (s, 3H), 3.33 (m, 1H), 4.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 24.8, 25.1, 34.4, 42.1, 52.8.

Preparation of Ammonium 2-(aminosulfonyl)ethanesulfonate (45)

Gaseous ammonia (dried by passing through a gas bottle filled with pellets of potassium hydroxide) was bubbled into a solution of ethane-1,2-disulfonyl anhydride (**10**) (0.646 g, 3.7 mmol) in nitromethane (20 mL) for 5 min at room temperature. The mixture was stirred for 10 min, and the precipitate was filtered off to give a white solid which was recrystallized from 75% ethanol to give white crystals (**45**) (0.334 g, 1.6 mmol, 43.2% yield). ^{1}H NMR (D_2O) δ: 3.38 (m, 2H), 3.57 (m, 2H), ^{13}C NMR (D_2O) δ: 45.9, 49.2.

Preparation of Benzenesulfonamide (46)

Benzenesulfonyl chloride (7.466 g, 42.3 mmol) was added slowly to a concentrated ammonia solution (75 mL) at room temperature. The mixture was refluxed for 40 min. After the mixture was cooled to room temperature, a white precipitate appeared. The excess ammonia solution was evaporated and the residue was dried under vacuum. The residue was then extracted with acetone (3 x 150 mL). The extract was dried over anhydrous magnesium sulfate, and the solvent was evaporated to give benzenesulfonamide (**46**) (5.71

g, 36.3 mmol, 85.9% yield) as white crystals which were recrystallized from 85% ethanol, mp 154-155 °C [lit. mp[104] 156-157 °C]; IR (KBr) ν_{max}: 3351 (s), 3260 (s), 1557 (m), 1449 (m), 1333 (s), 1163 (s), 1092 (m), 905 (m), 756 (s), 689 (s) cm^{-1}; ^1H NMR (acetone-d_6) δ: 7.60-8.00 (m, 5H); ^{13}C NMR (acetone-d_6) δ: 126.8, 129.7, 132.7, 145.1.

Preparation of Methanesulfonamide (61)

Ammonia gas (dried by passing through a gas bottle filled with pellets of potassium hydroxide) was bubbled into a solution of methanesulfonyl chloride (10.00 g, 87.3 mmol) in anhydrous diethyl ether (250 mL) at 0 °C for 0.5 h. The mixture was stirred for 0.5 h at room temperature. The solvent was evaporated to give a white solid. The solid was extracted with acetone (2 x 300 mL). The organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated to give methanesulfonamide **(61)** (7.545 g, 79.3 mmol, 90.9% yield) as white crystals which were recrystallized from benzene, mp 90-92 °C [lit. mp[105] 91-92 °C]; IR (KBr) ν_{max}: 3274 (s), 3021 (s), 2938 (m), 1580 (s), 1320 (s), 1160 (s), 992 (s), 884 (s) cm^{-1}; ^1H NMR (D_2O) δ: 3.16 (s, 3H); ^{13}C NMR (D_2O) δ: 45.0.

Preparation of Propane-1,3-disulfonic Acid (63)

a) Sodium Propane-1,3-disulfonate (62)

Trimethylene bromide (10.0 g, 49.5 mmol) was added dropwise to a boiling solution of sodium sulfite (12.6 g,

100.0 mmol) in water (50 mL). Refluxing was continued for a further hour after the organic layer had disappeared. After the mixture was cooled to 0 °C, the precipitate was removed by filtration to give the product (**62**) (5.2 g, 21.0 mmol, 42.3% yield) as white crystals which were recrystallized from water. ^{1}H NMR (D_2O) δ: 2.12-2.21 (m, 2H), 3.05 (t, 4H); ^{13}C NMR (D_2O) δ: 22.7, 52.2.

b) Propane-1,3-disulfonic Acid (63)

Sodium propane-1,3-disulfonate (**62**) (2.0 g 8.1 mmol) in water was passed through a Rexyn 101 (H^+) resin column. The water was removed to give a clear liquid which was heated at 80 °C at 2 Torr for 8 h to remove any traces of water giving **63** as a solid (1.60 g, 7.8 mmol, 96.3% yield) with a neutralization equivalent of 104.0 (calculated: 102.1). ^{1}H NMR (D_2O) δ: 2.17 (m, 2H), 3.05 (t, 4H); ^{13}C NMR (D_2O) δ: 22.4, 52.0.

Preparation of Ammonium 3-(aminosulfonyl)propanesulfonate (65)

a) Propane-1,3-disulfonic Anhydride (64)

A mixture of propane-1,3-disulfonic acid (**63**) (0.332 g, 1.6 mmol) and thionyl chloride (20 mL) was refluxed for 18 h. The excess thionyl chloride was removed by distillation and the residue dried at room temperature (1 mm) for 2 h to give a grey powder (**64**) (0.294 g, 97.0% yield), mp 196-197 °C [lit. mp[88] 194-196 °C]; IR (KBr) ν_{max}: 3006 (s), 2953 (s),

1379 (s), 1309 (s), 1294 (s), 1179 (s), 1038 (s), 1021 (s), 925 (m), 870 (s), 843 (s), 723 (s) cm^{-1}; ^1H NMR (CD_3NO_2) δ: 2.73 (m, 2H), 3.72 (t, 4H).

b) Ammonium 3-(Aminosulfonyl)propanesulfonate (65)

Gaseous ammonia was passed through a solution of propane-1,3-disulfonic anhydride (0.524 g, 2.8 mmol) in acetonitrile (25 mL) at 0 °C for 15 min. The mixture was stirred for 15 min, and the precipitate was removed by filtration to give a white solid (**65**) (0.564 g, 2.6 mmol, 91.0% yield). IR (KBr) ν_{max}: 3200 (s), 3081 (s), 2947 (w), 1429 (S), 1323 (s), 1296 (s), 1204 (s), 1146 (s), 1036 (s), 525 (s) cm^{-1}; ^1H NMR (D_2O) δ: 2.25 (m, 2H), 3.07 (t, 2H), 3.40 (t, 2H).

2.4.2 Determination of pK_a 's of the Sulfonamides and Sulfonimides

2.4.2.1 Determination of pK_a of Sulfonamides and Sulfonimides by Potentiometric Titration

In this study, the pK_a values of 27 sulfonamides and sulfonimides were measured by this method. The general procedure for potentiometric titration is as follows: 1.0-2.0 x 10^{-3} mole of sulfonamide was dissolved in water (50 mL) at 20.0 °C or 25.0 °C. This solution was titrated with 0.10 N standard sodium hydroxide solution. The pH values of the solution and the volumes (mL) of the consumed sodium hydroxide solution were recorded. The pK_a values are

calculated by Equation 1[67], and listed in Table 2.2 and Table 2.3.

$$pK_a = pH + \log \frac{\frac{a*V}{(V+W)} - \frac{b*W}{(V+W)} + [OH^-] - [H^+]}{\frac{(b*W)}{(V+W)} - [OH^-] + [H^+]} \quad \ldots\ldots\ldots (1)$$

Where

V = volume of solvent (mL)

W = volume of consumed sodium hydroxide solution (mL)

a = molar concentration of sulfonamide or sulfonimide

b = molar concentration of added sodium hydroxide solution (M)

2.4.2.2 Determination of pK_a of Sulfonimides by ^1H NMR

Aqueous sulfuric acid solutions were standardized by a titrating a measured volume with standard 1 N sodium hydroxide. H_o values were determined from a plot of Jorgenson and Hartter's data[59]. NMR spectra were determined on solutions prepared within 5-10 min of measurement, using an acetone-d_6 or a mixture of acetone-d_6 and TMS capillary reference. The NMR data were obtained on 1.0% solution (by weight) for the sulfonimides. All ^1H NMR spectra were measured with a Varian XL-200 NMR spectrometer at 20 °C and the results are listed in Table 2.4 and Table 2.5.

The shapes of the curves, for the determination of H_o's

at 50% protonation of sulfonimides, can be calculated[106] from the equation 2 shown below if there is not a significant difference in chemical shifts of unprotonated and protonated forms (B and BH^+ respectively) from a medium effect, and also assuming that is linearly related to $[BH^+]/[B]$[58].

$$pK_a = H_o + \log \frac{\delta - \delta_B}{\delta_{BH} - \delta} \qquad (2)$$

The above equation 2 can be rearranged to give:

$$\delta = \frac{\delta_B + \delta_{BH}\, e^{2.303(pK_a - H_o)}}{1 + e^{2.303(pK_a - H_o)}} \qquad (3)$$

In practice, in most cases there is a substantial medium effect on the chemical shifts of B and BH^+. For the calculation of $[BH^+]/[B]$ ratio the assumption was made that the medium effect on δ_B and δ_{BH} remains linear with H_o[107]; the equation 3 may be modified to equation 4.

$$\delta = \frac{m(H_o - (H_o)_a) + (\delta_B)_a + [n(H_o - (H_o)_b) + (\delta_{BH})_b]\, e^{2.303(pK_a - H_o)}}{1 + e^{2.303(pK_a - H_o)}} \qquad (4)$$

In eq 4 $(\delta_B)_a$ is the value of δ_B at a particular value of H_o (i.e. $(H_o)_a$) and $(\delta_{BH})_b$ is the value of δ_{BH} at another particular value of H_o (i.e. $(H_o)_b$), and where m and n are the respective slopes of the dependence of δ_B and δ_{BH} on H_o; when m and n = 0, this equation reduces to equation 3.

Table 2.4 The Chemical Shift Values of Sulfonimides in Sulfuric acid Solutions Determined by NMR at 20 °C.

Sulfonimde	H_2SO_4 (H_o)	Chemical Shift (Hz)	Chemical Shift (ppm)
$CH_3SO_2NHSO_2CH_3$ **(28)**	2.14	422.6	2.112
	+0.83	422.5	2.112
	-0.07	424.9	2.114
	-0.85	432.1	2.160
	-1.45	450.9	2.254
	-1.85	458.8	2.293
	-2.25	463.7	2.318
	-2.85	464.32	2.321
	-3.25	465.8	2.325

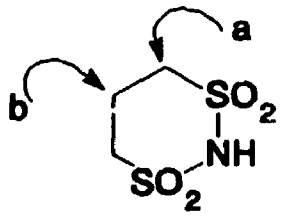
Table 2.4 continued.....

e Chemical Shift Values of Sulfonimides in Sulfuric Acid Solutions Determined by NMR at 20 °C.

Sulfonimde	H_2SO_4 (H_o)	Chemical Shift (Hz)	Chemical Shift (ppm)
$C_6H_5SO_2NHSO_2CH_3$ (30)	+0.82	408.7	2.024
	-0.07	406.1	2.030
	-0.85	409.2	2.046
	-1.45	417.1	2.085
	-1.84	427.1	2.130
	-2.25	434.2	2.170
	-2.84	438.1	2.190
	-3.25	438.1	2.190
Ethane-1,2-disulfonimide (19)	-0.85	571.55	2.857
	-1.45	571.55	2.857
	-2.25	575.97	2.879
	-2.84	588.64	2.942
	-3.25	596.46	2.981
	-3.80	607.11	3.035
	-4.50	614.24	3.070
	-5.57	612.51	3.062
	-6.80	608.67	3.042

Table 2.5 The Chemical Shift Values of Propane-1,3-disulfonimide in Sulfuric Acid Solutions Determined by NMR at 20 °C.

H_2SO_4 (H_o)	Chemical Shift (Hz) $(CH_2)_a$	Chemical Shift (Hz) $(CH_2)_b$	$\delta = \delta_a - \delta_b$ (Hz)
+0.82	428.98	290.34	138.64
-0.06	429.39	289.52	139.87
-0.85	430.56	284.81	145.75
-1.45	441.22	284.96	156.26
-1.85	454.46	288.03	166.43
-2.25	472.66	293.56	179.10
-3.30	479.07	291.57	187.50
-4.50	478.02	292.79	185.23



2.4.2.3 Determination of the pK_a's of Sulfonimides by Ultraviolet Spectrophotometry

The aqueous sulfuric acid solutions were standardized, and the H_o values were determined as above. The concentration of sulfonimide in the sulfuric acid solution was about 1.0×10^{-3} M. All of UV spectra were measured

with a Shimadzu UV-160 spectrometer and the results were listed in Tables 2.6 to 2.8.

The pK_a's of *N*-methanesulfonyl benzenesulfonamide (**30**), benzene-1,2-disulfonimide (**21**), dibenzenesulfonimide (**26**), and saccharin (**33**) were determined by the UV method. The shapes of the curves, for the determination of H_o's at 50% protonation of sulfonimides, can be calculated from the equation 5[46] shown below:

$$pK_a = pH + \log \frac{A_I - A}{A - A_M} \qquad (5a)$$

or

$$pK_a = pH + \log \frac{A - A_I}{A_M - A} \qquad (5a)$$

and

$$A = \frac{A_I + A_M\, e^{2.303\,(pK_a - H_o)}}{1 + e^{2.303\,(pK_a - H_o)}} \qquad (6)$$

Where A is the observed absorbency at the analytical wavelength; A_I is the absorbency of the ionized species, and

A_M is the absorbency of the unionized species.

If we also consider the substantial medium effect on the absorptions of B and BH^+, the equation of 6 can be modified to equation 7.

$$A=\frac{m(H_o-(H_o)_a)+(A_N)_a+[n(H_o-(H_o)_b)+(A_I)_b]\,e^{2.303(pK_a-H_o)}}{1+e^{2.303(pK_a-H_o)}} \quad (6)$$

Table 2.6 The pK_a Determination of Benzene-1,2-disulfonimide (21) by UV in Sulfuric Acid Solution at 21 °C

H_2SO_4 H_o	A (x 10^{-2}) (λ=275 nm)
+0.90	1.35
-0.75	1.43
-1.80	1.51
-2.49	1.62
-3.27	2.01
-4.00	3.02
-4.32	3.66
-4.65	4.08
-5.25	4.60
-5.75	4.79
-6.80	5.00
-8.40	5.06
-10.00	5.16

Table 2.7 The pK_a Determination of *N*-Methylsulfonyl Benzenesulfonamide (**30**) by UV in Sulfuric Acid Solution at 21 °C

H_2SO_4 (H_o)	A ($\times 10^{-2}$) (λ=267nm)
+2.15	0.577
+1.52	0.573
+0.83	0.585
-0.07	0.603
-0.85	0.694
-1.45	0.828
-1.85	1.006
-2.25	1.160
-2.84	1.245
-3.25	1.262
-4.50	1.293
-4.86	1.312
-5.75	1.302
-6.80	1.312

Table 2.8 The pK_a Determination of Saccharin (33) by UV in Sulfuric Acid Solutions at 21 °C

H_2SO_4 (H_o)	A ($\times 10^{-2}$) (λ=221nm)
4.18	1.887
3.41	1.883
3.05	1.883
2.54	1.846
2.15	1.787
1.52	1.704
0.83	1.391
-0.05	1.148
-0.85	1.054
-1.55	1.023
-2.25	1.008
-2.84	1.000
-3.00	0.987
-4.50	0.998

2.4.3 Kinetics of Hydrolysis of Sulfonimides in Concentrated Hydrochloric Acid Solution

General procedure:

A 10 mg sample of the sulfonimide was dissolved in concentrated hydrochloric acid in an nmr tube and the nmr tube was sealed. The progress of the reaction was followed using a Varian XL-200 NMR spectrometer at a probe temperature of 80 °C by measuring the integration of -CH_2SO_2- or CH_3SO_2- peaks of starting sulfonimides and the -

CH_2SO_2- or CH_3SO_2- peaks of the products produced by the hydrolysis reactions. Propane-1,3-disulfonimide (**20**) and dimethanesulfonimide (**28**) were kept in a oil-bath at 80 °C bath. The percentage of the remaining starting material at a time *t* during the reaction was then calculated by taking the ratio of the integration of -CH_2SO_2- (for ethane-1,2-disulfonimide (**19**) and propane-1,3-disulfonimide (**20**)) or CH_3SO_2- (for dimethanesulfonimide (**28**), *N*-methylsulfonyl benzenesulfonamide (**30**), and methanesulfonamide (**61**)) peaks of the starting sulfonimides to the sum of the -CH_2SO_2- or CH_3SO_2- of the starting material and the products. The natural logarithm of the percentage of starting sulfonimide *vs*. time was plotted to give a straight line as shown in Figure 2.13 for the hydrolysis of ethane-1,2-disulfonimide (**19**), Figure 2.14 for propane-1,3-disulfonimide (**20**) and Figure 2.15 for dimethanesulfonimide (**28**) in concentrated hydrochloric acid. The value of the pseudo-first-order rate constant was obtained from the slope of the straight line. The observed rate constants of hydrolysis of three sulfonimides are listed in Table 2.3.

The products of the hydrochlorinolysis of sulfonimides were characterized by comparing the ^1H NMR and ^{13}C NMR spectra with those of the authentic samples and found to be identical. The NMR spectra (acetone-d_6 + TMS as extra reference) of authentic samples in concentrated hydrochloric acid are recorded below:

Propane-1,3-disulfonic acid

^{1}H NMR (HCl): 0.98 (m, 2H), 2.03 (t, 4H).

Ammonium 3-(aminosulfonyl)propanesulfonate

^{1}H NMR (HCl): 1.09 (m, 2H), 2.05 (t, 2H), 2.30 (t, 2H).

2.4.4 The Reaction of Anhydrides with Triethylamine

a) Propane-1,3-disulfonic Anhydride

Propane-1,3-disulfonic anhydride (0.10 g, 0.54 mmol) in acetonitrile (2 mL) was added dropwise to a mixture of methanol-*d* (0.355 g, 10.7 mmol) and triethylamine (0.071 g, 0.7 mmol) in benzene (3 mL) at room temperature. The mixture was stirred for 10 min. Water (10 mL) and dichloromethane (25 mL) were added. The two layers were sepa~ated. The organic layer was dried over anhydrous magnesium sulfate. The solvent was removed to give no product. For the aqueous layer sodium hydroxide (1 M, 10 mL) was added, and was then extracted with dichloromethane (2 x 20 mL) to remove the excess triethylamine. For the aqueous phase water was removed to give the product, Et_3NH^+ $^-O_3SCH_2CH_2CHDSO_2OCH_3$, (0.167 g, 96.8% yield) as a white solid. This solid was ion-exchanged by passing a H^+ resin column and refluxed with 2 M NaOH to form the product, Na^+ $^-O_3SCH_2CH_2CHDSO_2O^-$ ^+Na. ^{1}H NMR (D_2O) δ: 2.07 (m, 2H), 2.90 (m, 3H); ^{13}C NMR (D_2O) δ: 22.5, 51.8 (t), 52.1.

b) Ethane-1,2-disulfonic Anhydride

Ethane-1,2-disulfonic anhydride (0.10 g, 0.58 mmol) in acetonitrile (3 mL) was added dropwise to a mixture of methanol-*d* (0.384 g, 11.6 mmol) and triethylamine (0.076 g, 0.75 mmol) in benzene (3 mL) at room temperature. The mixture was stirred for 10 min. Water (5 mL) and dichloromethane (20 mL) were added, and the mixture worked up as above to give the product, $Et_3NH^+ \ ^-O_3SCH_2CH_2SO_2OCH_3$, (0.166 g, 93.4% yield) as a white solid. This solid was ion-exchanged by passing a H^+ resin column and refluxed with 2 M NaOH to give a salt of $Na^+ \ ^-O_3SCH_2CH_2SO_2O^- \ ^+Na$. ^1H NMR (D_2O) δ: 3.27 (s, 4H), 2.90 (m, 3H); ^{13}C NMR (D_2O) δ: 49.1.

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Chapter 3

pH Optimization in Acyl Transfer

3.1 INTRODUCTION

In the light of the variety and efficiency of reactions in aqueous media in nature, it is remarkable that water is so little used as the reaction solvent in organic synthesis. This arises in part because of the relatively low solubility of many organic compounds in water, but also because the desired process often competes with hydrolysis. In this chapter it is shown how one may estimate the pH for obtaining the maximum yield in competition with hydrolysis and, in addition, how to use pH control of an aqueous solution to obtain selective reaction at either of two nucleophilic sites in the acylation and sulfonylation of amines and C-alkylation of acidic ketones. Three other members in this laboratory, Dr. R. Rathore, Dr. J. Lam, and Dr. D. Klassen, joined in this research[1]. This chapter is devoted chiefly to one specific aspect of this study, pH optimization in reactions of amines with benzoyl chloride and acetic anhydride.

3.1.1 Optimisation of Yields

Equation 1 gives the pseudo-first-order rate constant ($k_{\psi O}$) for the hydrolysis of an electrophile (E) taking place by both uncatalyzed and hydroxide-promoted pathways, while equations 2 and 3 give, respectively, $k_{\psi N}$, the pseudo-first-order rate constant for reaction of a nucleophile (Nu) with E to yield the product (P), and $k_{\psi T}$, that for the total

consumption of E.

$$k_{\psi o} = k_w + k_{OH}[OH^-] = k_w + k_{OH}K_w/[H^+] \quad (1)$$

$$k_{\psi N} = k_N[Nu] = k_N Nu_T K_a/([H^+] + K_a) \quad (2)$$

We may conveniently show the variation in pseudo-first order rate constant with change in $[H^+]$ by plots of log k_ψ vs pH as in Figure 3.1, from which one may see that P is the major product for the pH range in which $k_{\psi N} > k_{\psi o}$. In other words, the roughly parallelogram-shaped region enclosed by

$$k_{\psi T} = k_{\psi o} + k_{\psi N}$$

$$= k_w + k_{OH}K_w/[H^+] + k_N Nu_T K_a/([H^+] + K_a) \quad (3)$$

Symbols: (i) Rate constants: k_w, hydrolysis of E by water; k_{OH}, hydrolysis of E by hydroxide ion; k_N, reaction of E with Nu. (ii) K_a, the acid dissociation constant of NuH^+; $K_w = [H^+][OH^-]$; $Nu_T = [Nu] + [NuH^+]$; pH_i, the point of intersection of the sloped and flat limbs of the $k_{\psi o}$ curve; pH_{iN}, the analogous point of intersection with respect to the $k_{\psi N}$ curve; at pH_i, $K_w = k_{OH}[OH^-]_i$; at pH_{iN}, $k_N Nu_T = k_N Nu_T K_a/[H^+]_i$, i.e., $K_a = [H^+]_i$ or $pH_i = pK_a$; pH_{max}, the pH value for maximum yield of P. (iii) In eq 8-11: k_x, the rate constant for the reaction of E to form P_x; $Nu_{xT} = [Nu_x] + [Nu_xH^+]$; pH_{xmax}, the pH value for maximum yield of P_x; pH_{ix}, the point of intersection of the tangents to the sloped and flat limbs of the log $k_{\psi x}$ curve; pH_a and pH_b, the points of intersection of the log $k_{\psi o}$ curve with the sloped limb of the log $k_{\psi y}$ curve and the flat limb of the log $k_{\psi x}$ curve, respectively; the y-subscripted terms are defined analogously.

the log $k_{\psi o}$ and log $k_{\psi N}$ curves may be regarded as the "window" for the formation of P. Defining f_p, the theoretical yield of P under pseudo-first-order conditions (expressed as a fraction), we write equation 4.

$$f_p = k_{\psi N}/k_{\psi T} = \frac{k_N Nu_T K_a/([H^+] + K_a)}{k_w + k_{OH}K_w/[H^+] + k_N Nu_T K_a/([H^+] + K_a)} \qquad (4)$$

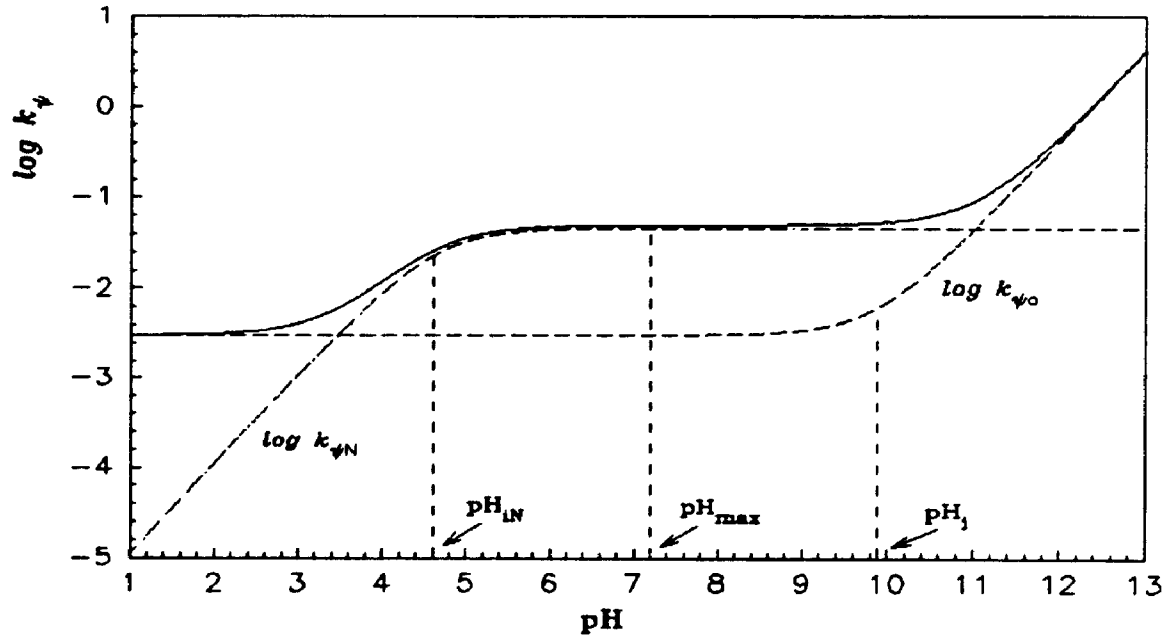


Figure 3.1 pH-rate profiles for reaction of a nucleophile with an electrophile in water competing with hydrolysis. The broken lines are calculated for the reactions of benzenesulfonyl chloride, $PhSO_2Cl$, (1) with water (log $k_{\psi o}$) and with aniline, $PhNH_2$, (2) (log $k_{\psi N}$) in 0.05 M NaCl at 25 °C, using eqs 1 and 2 and Roghe's parameters k_w 3.06 x 10^{-3} s^{-1}, k_{OH} 40.4 M^{-1} s^{-1}, k_N 6 M^{-1} s^{-1}. Solid line: log ($k_{\psi o}$ + $k_{\psi N}$).

Lam[2] in this laboratory has investigated the reaction of benzenesulfonyl chloride (**1**) with aniline (**2**). The variation of f_p with pH may be calculated from equation 4 and rate constants reported by Rogne[3] and is shown by the solid line in Figure 3.2. The experimental yields of benzenesulfonanilide (**3**) found by Lam[2] under pseudo-first-order conditions are given by the circles; theory and experiment clearly agree.

Figure 3.2 (broken line and triangles) also shows the corresponding pH-yield profile for the reaction of **1** with benzylamine (**4**) to give *N*-benzylbenzenesulfonamide (**5**). It is evident from the two curves in Figure 3.2 that both pH_{max} and the widths of the regions of relatively high yields, vary with the reaction. To obtain pH_{max} as a function of pH, one may set the first derivative of the right side of eq 4 with respect to $[H^+]$ equal to zero, and transform the resultant expression into its equivalent form with respect to pH, as in eq 5. The same relation may be derived more simply by inspection of Figure 3.1, from which it is apparent that pH_{max} is simply halfway between pH_i and pH_{iN}, i.e. $pH_{max} = \frac{1}{2}(pH_i + pH_{iN})$; since one may easily show[4] that $pH_{iN} = pK_a$ and $pH_i = \log(k_w/k_{OH}) + pK_w$, eq 5 immediately follows.*

$$pH_{max} = \tfrac{1}{2}[\log(k_w/k_{OH}) + pK_w + pK_a] \qquad (5)$$

---

* The equation for pH_i given here corresponds to the expression deduced by Kurz[5] for $pK_a(\ddagger)$, the pK_a of a protonated transition state.

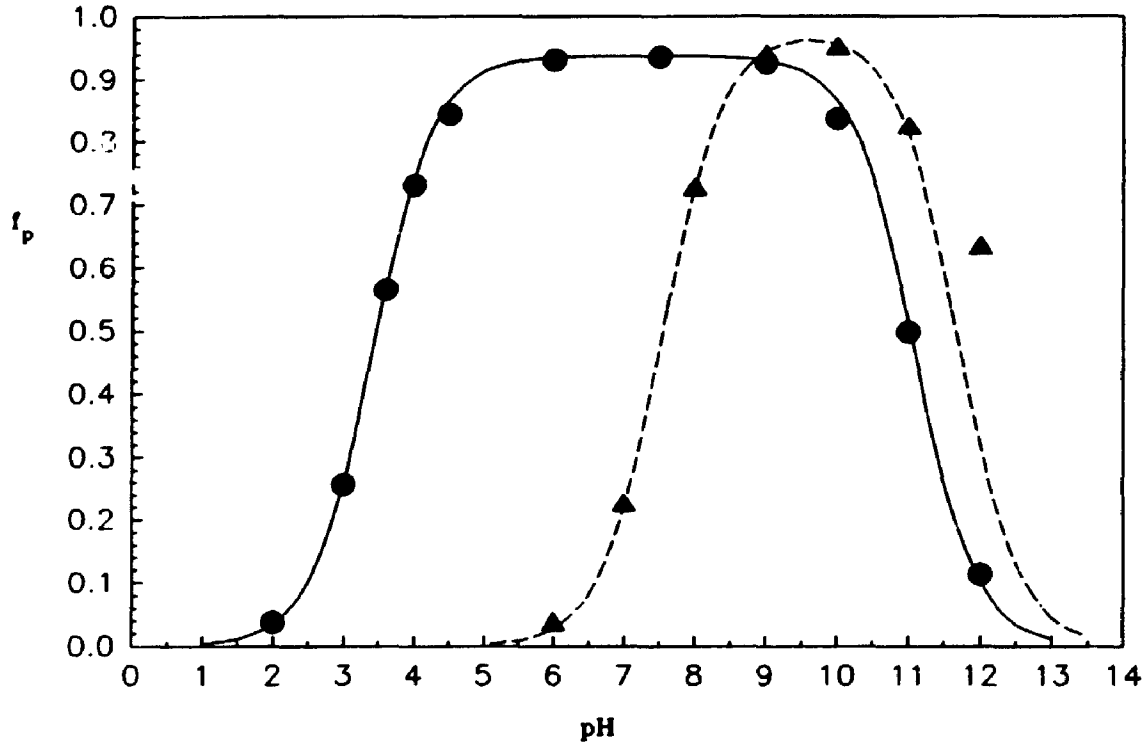


Figure 3.2 pH-yield profiles for the reactions, under pseudo-first-order conditions, of benzenesulfonyl chloride (**1**) (C_o 7.8 x 10^{-4} M) with (a) aniline (**2**) (C_o 0.01 M) to form $PhSO_2NHPh$ (**3**) (solid line and filled circles) and (b) benzylamine (**4**) (0.01 M) to form $PhSO_2CH_2Ph$ (**5**) (broken line and filled triangles). The solid line is calculated from eq 4 and the parameters in the caption to Figure 3.1, plus pK_a 60 for **2**; the dotted line is also from eq 4, but uses k_N 19 M^{-1} s^{-1} (best fit to curve) and pK_a 9.34 for **3**.

As a simple, concentration-independent measure of the width of the window we suggest

$$\text{width} = |pH_i - pH_{iN}|$$

and that both components defining the region of best yield for a reaction be given by the descriptor $pH_{max} \pm \frac{1}{2}$ width, as in eq 6.

$$pH_{max} \pm \tfrac{1}{2} \text{ width} = \tfrac{1}{2}(pH_i + pH_{iN}) \pm \tfrac{1}{2}(pH_i - pH_{iN})$$

$$= \tfrac{1}{2}[\log(k_w/k_{OH}) + pK_w + pK_a] \pm \tfrac{1}{2}[\log(k_w/k_{OH}) + pK_w - pK_a] \quad (6)$$

where pH_i is the point of intersection of the tangents to the sloped and flat limbs of the $k_{\psi o}$ curve; pH_{iN} is the analogous point of intersection with respect to the $k_{\psi N}$ curve.

Two important conclusions may be drawn from eq 6: (a) pH_{max} is independent of k_N and Nu_T, and can be obtained simply from k_w/k_{OH} (or pH_i) for E and the pK_a of NuH^+, and (b) the window is narrowest (width equals zero) when $pK_a = pH_i$, becoming wider with increasing separation of pK_a and pH_i. For the reaction of **1** (pH_i = 9.88) with **2** (pK_a 4.60[6]) $pH_{max} \pm \frac{1}{2}$ width is 7.2 ± 2.6, a relatively wide window, whereas that (9.6 ± 0.3) for the corresponding reaction of benzylamine (**4**) (pK_a 9.34) to give $PhSO_2NHCH_2Ph$ (**5**), is

narrow (cf. Figure 3.2).

Equation 6 has been applied to the sulfonylation of amines (pH-controlled Schotten-Baumann conditions). Benzenesulfonyl chloride (**1**) and benzylamine (**4**) (C_o 0.105 and 0.10 M, respectively) at pH 9.6 for 1 h gave, after simple workup, clean **5** in >99% yield. In a set of experiments starting with 0.10 M benzenesulfonyl chloride (**1**) and 0.105 M benzylamine (**4**) the following yields were found: pH 7.5, 69%; pH 9.6, 96%; pH 12.0, 87%.

Rathore[1] in this laboratory illustrated carbon-carbon bond formation in pH-controlled aqueous medium by choosing as his examples of the allylation of acidic ketones. The k_w/k_{OH} ratio for allyl bromide was unavailable from literature sources. In order to obtained the k_w/k_{OH}, we can simply transform eq 5 to eq 7:

$$\log(k_w/k_{OH}) = 2pH_{max} - pK_a - pK_w \qquad (7)$$

By using eq 7, values of k_w/k_{OH} = 2 x 10^{-2} M and pH_i = 12.6 were obtained from the pH_{max} (12.2) observed for the reaction of allyl bromide with *N*-methylmethanesulfonamide (pK_a 11.79) to form *N*-allyl-*N*-methylmethanesulfonamide.

In these examples the yields around the calculated pH_{max} are clearly satisfactory for many needs. The procedure is very simple and the cost of materials and

apparatus minimal; all that one has to know in order to find pH_{max} is the pK_a of the conjugate acid of the nucleophile and the k_w/k_{OH} ratio for hydrolysis of the electrophile. Tables of pK_a's are available[6] and, where these are lacking, sufficiently accurate pK_a values can be estimated by analogy or with the aid of linear free energy relationships, as described by Perrin, *et al*[7]. When pH_i's are not available the simple procedure of finding pH_{max} for a convenient reaction and applying eq 7, works well for synthetic purposes and mechanistic studies.

3.1.2 Selectivity Optimization.

By extension we can depict the reaction of E with two different nucleophiles, Nu_x and Nu_y, as in Figure 3.3. The respective windows for the formation of the products, P_x and P_y, appear as the lower left and upper right "rounded parallelogram" zones, with the fractions of the products given by eq 8 and 9.

$$f_x = k_x[Nu_x]/(k_w + k_{OH}[OH^-] + k_x[Nu_x] + k_y[Nu_y]) \qquad (8)$$

$$f_y = k_y[Nu_y]/(k_w + k_{OH}[OH^-] + k_x[Nu_x] + k_y[Nu_y]) \qquad (9)$$

Reasoning similar to that in the previous section leads to approximate equations 10 and 11. From these we estimate

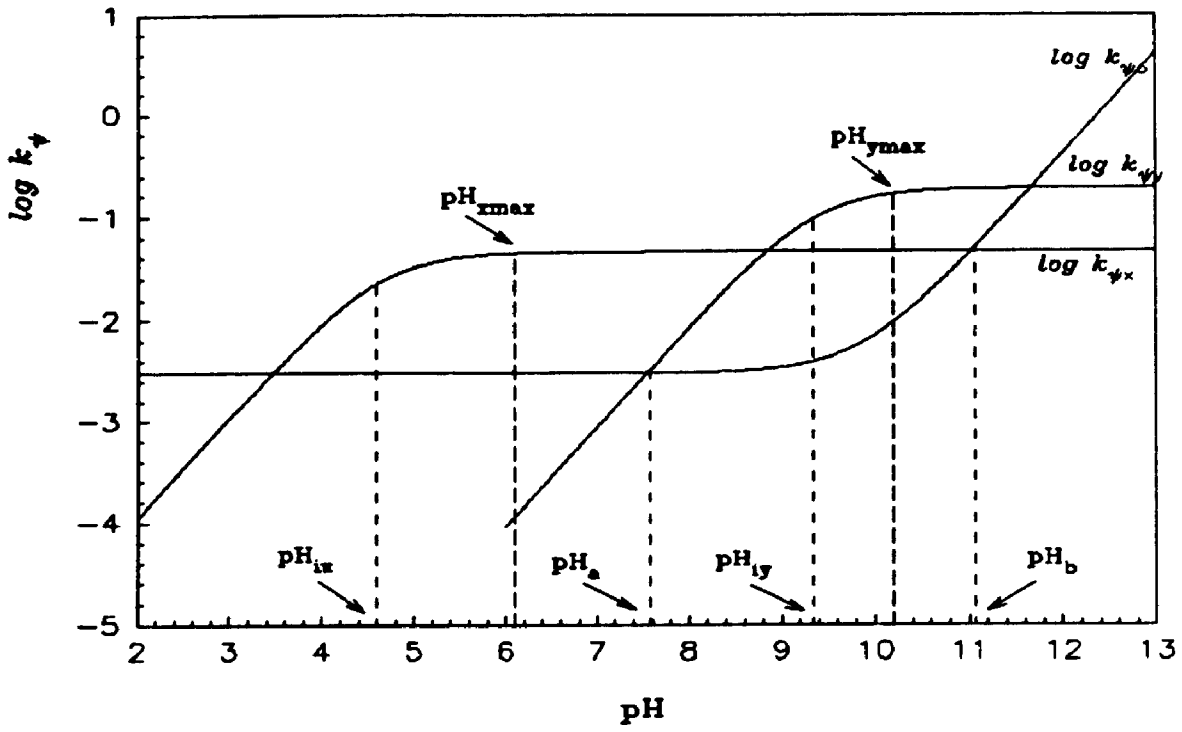


Figure 3.3 pH-rate profiles for the reactions of two nucleophiles with an electrophile in the face of competing hydrolysis. The lines are calculated from eqs 1 and 2 and the parameters given in the captions to Figure 3.1 and 3.2.

for the reaction of **1** with the mixture of **2** and **4**, respectively pH_{xmax} 6.1 ± 1.5 and pH_{ymax} 10.2 ± 0.9, in good agreement with the experimental points[1].

pH_{xmax} ± ½ width ≈

$$\tfrac{1}{2}[\log(k_w/k_yNu_{yT}) + pK_y + pK_x] \pm \tfrac{1}{2}[\log(k_w/k_yNu_{yT}) + pK_y - pK_x] \qquad (10)$$

$$pH_{ymax} \pm \tfrac{1}{2} \text{ width} \approx$$

$$\tfrac{1}{2}[\log(k_x Nu_{xT}/k_{OH}) + pK_w + pK_y] \pm \tfrac{1}{2}(\log(k_x Nu_{xT}/k_{OH}) + pK_w - pK_y] \quad (11)$$

Closely related to the system described by Figure 3.3 and eqs 8-11 is the general problem of obtaining selective reaction at either of two nucleophilic sites in the same molecule; Klassen[8] in this laboratory chose monoacetylation of 4-aminobenzylamine (14) as a specific example. Using the k_w and k_{OH} value[9] , plus rough k_x's and k_y's estimated from related rate constants in the literature[10], he obtained plots of f_x and f_y vs pH. From these, with minimal further exploration for reaction conditions, the selective acetylation of either amino group was obtained; e.g. at pH 4.15, a yield of 84% of 4-acetamidobenzylamine was obtained, at pH 11.25, the *N*-(4-aminobenzyl)acetamide was obtained in 85% yield; the yields refer to the isolated, crystalline hydrochloride salts.

In the study described in this chapter we have examined the reactions of benzoyl chloride with amines and acetic anhydride with amines to estimate the pH for obtaining the maximum yield in competition with hydrolysis in aqueous solution. The experiments with acetic anhydride led to the discovery of an additional mode of reaction of the amines in aqueous media, which prompted further examination of the reactions of acetic anhydride, and of the use of pH-yield data to discover new reaction pathways.

3.2 Results and Discussion

3.2.1 pH Optimization of Reactions of Benzoyl Chloride with Amines

The reaction of benzoyl chloride with an amine is one of the classic reactions of a nucleophile with an electrophile in water. In 1884, Schotten[11] carried out a reaction of benzoyl chloride with piperidine in aqueous medium using sodium hydroxide solution to neutralize the HCl formed. Baumann[12] reported in 1886 the reaction of benzoyl chloride with glucose to form an ester using 10% sodium hydroxide solution to neutralize the HCl formed. Schotten-Baumann reactions are still extensively used in organic chemistry[13]. It seemed appropriate to see if eq 6 accurately predicted pH_{max} for these transformations, and we have tested eq 6 in the acylation of amines, i.e. pH-controlled Schotten-Baumann conditions. In this study two amines, benzylamine and piperidine, were used in acyl transfer reactions with benzoyl chloride (**6**) in water under pseudo-first-order conditions at 25 °C.

3.2.1.1 The Reaction of Benzoyl Chloride with Benzylamine

To predict the optimized pH for the Schotten-Baumann reaction of benzoyl chloride (**6**) with amines, we required the ratio k_w/k_{OH} for **6**. A value for k_w (1.8 s^{-1}) had been reported[14], but a search of the literature turned up no reliable reports of k_{OH} for the reaction in water at 25 °C.

Table 3.1 Rate constants for the reactions of benzoyl chloride (**6**) with amines in water at 25 °C

Amines	k_N[b] (M^{-1} s^{-1})
$(CH_2)_5NH$[a]	1.8×10^4
$C_6H_5CH_2NH_2$	1.6×10^4

a. Piperidine

b. k_N was obtained from pH-yield profile, $K_a = 6.03 \times 10^{-12}$ (piperidine), $K_a = 5.7 \times 10^{-10}$ (benzylamine), $k_W = 1.8$ s^{-1}, and $k_{OH} = 510$ M^{-1} s^{-1}.

In order to obtain the k_{OH} for hydrolysis of benzoyl chloride, we determined pH_{max} by carrying out a series of reactions determining the yield as a function of pH. The reaction of benzoyl chloride (**6**) with benzylamine (**4**) was carried out using the pH-stat technique, with the total concentration of benzylamine C_o 0.01 M, and the initial concentration of benzoyl chloride (**6**) 0.001 M. These reactions were carried out with variation in pH, and the yields are listed in Table 3.2 and shown in Figure 3.4 (triangles). Table 3.2 lists two sets of data, one obtained

Table 3.2 The variation in yield of the amide with change in pH for the reaction of benzoyl chloride with benzylamine in water at 25 °C

pH	$C_6H_5CONCH_2Ph$ Weight (mg)	f_p
6.0[a]	6.3	0.060
6.5[a]	17.0	0.161
7.0[a]	33.2	0.314
7.5[a]	64	0.610
8.3[a]	99.7	0.944
9.3[a]	105.3	0.997
10.3[a]	105	0.990
11.6[a]	104	0.989
12.2[a]	100.7	0.954
13.0[a]	85.2	0.807
13.4[a]	61.5	0.582
7.0[b]	32.0	0.303
8.0[b]	86.8	0.822
8.7[b]	98.8	0.936
10.8[b]	102	0.987
12.6[b]	93	0.893
13.4[b]	70.1	0.664

a. Reactions were carried out by direct injecting benzoyl chloride (C_o = 0.001 M) to a solution of benzylamine ($[C_6H_5CH_2NH_2]_T$ = 0.01 M) in water (500 mL) at 25°C.

b. Reactions were carried out by injecting the benzoyl chloride (C_o = 0.001 M in 2.5 mL DME) to a solution of benzylamine ($[C_6H_5CH_2NH_2]_T$ = 0.01 M in H_2O (500 mL).

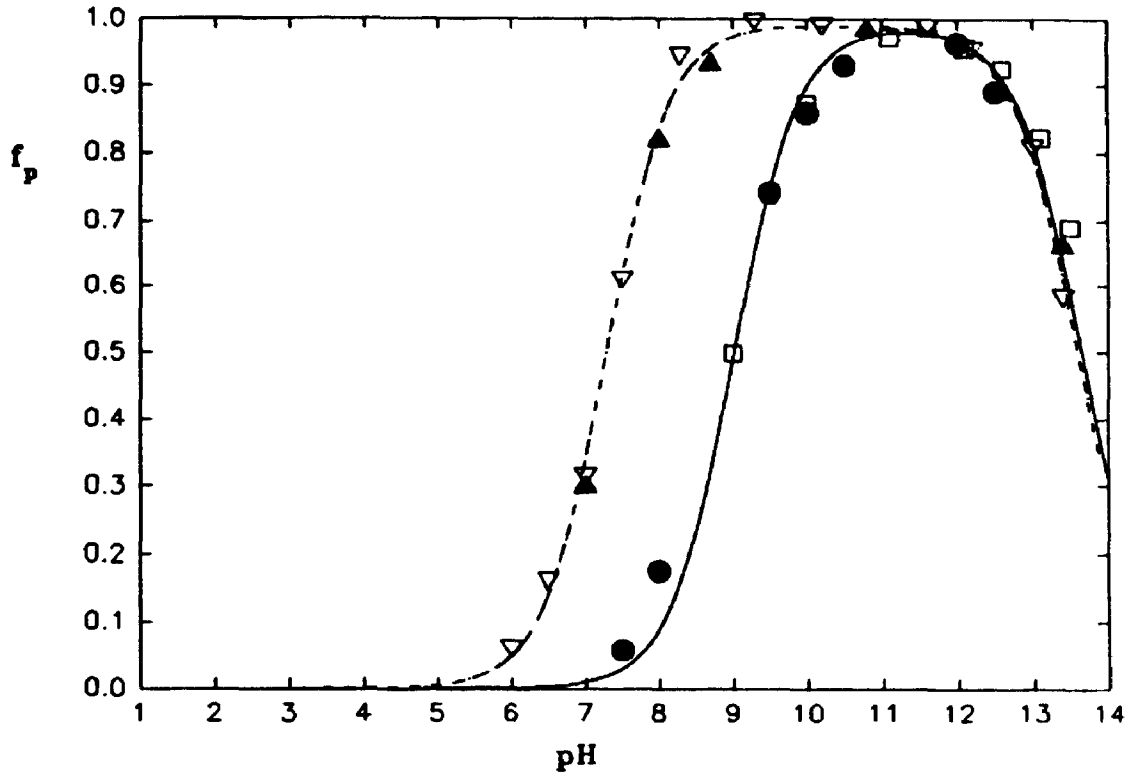


Figure 3.4 pH-yield profile for the pseudo-first-order reactions at 25 °C of benzoyl chloride (C_o 0.001 M) with amine (C_o 0.01 M) (a) piperidine, to form *N*-benzoyl piperidine (7) , open squares (in water) and filled circles (in 0.5% DME), and (b) benzylamine (4), to form *N*-benzylbenzamide, filled triangles (in water), open triangles (in 0.5% DME). The line were calculated from eq 6 using k_W 1.8 s^{-1}, k_{OH} 510 M^{-1} s^{-1} and for (a) the dashed line (piperidine), k_N 1.8 x 10^4 M^{-1} s^{-1}, (b) the solid line (benzylamine), k_N 1.6 x 10^4 M^{-1} s^{-1}.

by directly injecting the pure benzoyl chloride to the benzylamine solutions which were previously adjusted to the desired pH, and the other by injecting the solution of benzoyl chloride in 1,2-dimethoxyethane (DME, 2.5 mL). The two methods of addition gave similar results. A value of pH_{max} of 10.44 was obtained in the reaction of benzylamine (4) with benzoyl chloride (6). When inserted into eq 7 (a simple transformation of eq 5), this gave k_w/k_{OH} = 3.5 x 10^{-3} M (and hence k_{OH} = 5.1 x 10^2 M^{-1} s^{-1}).

$$f_p = \frac{k_N[PhCH_2NH_2]}{k_w + k_{OH}[OH^-] + k_N[PhCH_2NH_2]} \qquad (12)$$

To obtain the rate constant (k_N) for the nucleophilic substitution reaction of benzoyl chloride 6 with 4, we used eq 12 to correlate our experimental data; by plotting the variation of f_p with pH, we found k_N = 1.8 x 10^4 M^{-1} s^{-1} from the best fit to the experimental data (see Figure 3.4 and Table 3.1).

3.2.1.2 The Reaction of Benzoyl Chloride with Piperidine

The reaction of benzoyl chloride (6) with piperidine (7) was carried out under pseudo-first-order condition similar to those with benzylamine (4). The variation of yield with pH is given in Table 3.6 (see experimental part) and shown by the circles and squares in Figure 3.4. The

$$f_p = \frac{k_N[(CH_2)_5NH]}{k_w + k_{OH}[OH^-] + k_N[(CH_2)_5NH]} \qquad (13)$$

rate constant k_N = 1.6 x $10^4 M^{-1}$ s^{-1} for reaction of **6** and **7** is obtained from eq 13 and the pH-yield profile (best fit of the curve to the experimental data). The fit of calculated with experimental points is good and it is concluded that the results are fully consistent with the value of k_w/k_{OH} = 3.5 x 10^{-3} M obtained from the reaction of **6** with benzylamine.

The above results indicate that the reactions of benzoyl chloride (**6**) with piperidine (**7**) and benzylamine (**4**) are direct nucleophilic substitution reactions by amines competing only with hydrolysis by water and by hydroxide ion. This result is consistent with those of Bentley and Freeman[15] who investigated the aminolysis reactions of benzoyl chloride with substituted anilines in water-acetone, or in methanol by using HPLC. Their results demonstrated that the reactions of **6** with anilines involve these amines as nucleophiles, not as general base catalysts. This mechanism is different from that of the reaction of acetic anhydride with amines, in which general base catalysis was found to be involved (see section 3.2.2).

3.2.1.3 The Variation of Yield in Preparative Reactions

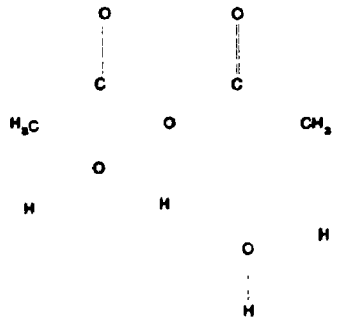
The reactions of benzoyl chloride with benzylamine and piperidine described above were carried out under pseudo-

first-order conditions, i.e. with a ten-fold excess of the amine. We have also carried out runs using comparable concentration of the reagents, to see if the results obtained under pseudo-first-order conditions were directly applicable to concentrations more appropriate to preparative conditions. It was found that at pH 10.4 (the pH_{max}), benzoyl chloride (**6**) and benzylamine (**4**) (C_o 0.011 and 0.010 M, 30 min reaction time) gave *N*-benzylbenzamide (**8**) showing no sign of impurity, in 97% isolated yield; with **6** and piperidine the same conditions, except for pH 11.4, gave *N*-benzoylpiperidine (**9**) in 98% yield. A series of experiments with variation of the pH with the initial concentration of benzylamine (**4**) set at 0.010 M and initial concentrations of benzoyl chloride (**6**) of 0.010 and 0.012 M gave the following yields of *N*-benzylbenzamide (**8**): pH 7.5, 53% and 55%; pH 10.45, 86% and 99%; pH 13.0, 39% and 48% (see Tables 3.8 and 3.9 in experimental part).

3.2.2 pH-Optimization of Reactions of Acetic Anhydride with Amines

The hydrolysis of acetic anhydride (**19**) has been extensively studied for over half a century, most notably by Kilpatrick[16] and Gold[17]. The effects of solvent[18], salt concentration[19], and isotope effects[20], acid[21] and pyridine catalysis[22] for hydrolysis of acetic anhydride have been investigated, but the reactions with nucleophiles in aqueous medium have not been extensively studied.

Batts and Gold[23] studied the hydrolysis of acetic anhydride and found that the solvent isotope effect is 2.9 and the catalytic coefficient of acetate ions is *ca.* 1.7. They concluded that two molecules of water were involved in the hydrolysis of acetic anhydride. The solvent isotope effect (k^H/k^D = 3) was further confirmed by Bunton et al.[24] for the hydrolysis of carboxylic anhydrides. Butler and Bruice[25] pointed out that the acetate ion resulting from the hydrolysis of acetic anhydride could act as a general base to catalyze the hydrolysis of acetic anhydride. Davis and Hogg[26] investigated the hydrolysis of cyclic and acyclic carboxylic acid anhydrides under a variety of conditions over a wide range of temperature. They concluded that two protons were involved in the transition state of hydrolysis of acyclic anhydrides, and they suggested a water catalyzed transition state such as the following.



For the above transition state, the carbonyl carbon in the acetic anhydride is attacked by the first molecule of

water, and the second molecule of water acts as a general base to remove the proton from the first molecule of water.

In this study we have investigated the acyl transfer reactions of acetic anhydride (**19**) with eight different primary or secondary amines to further test eq 6; the results are described in the following sections.

3.2.2.1 Yields of the Reaction of Acetic Anhydride with Amines under Pseudo-first-order Conditions

The yields of *N*-benzylacetamide (**10**), acetanilide (**11**), *N*-cyclohexylacetamide (**12**), *N*-*t*-butylacetamide (**13**), *N*-(3-methylbutyl)acetamide (**15**), *N*,*N*-diethylacetamide (**16**), *N*,*N*-diisopropylacetamide (**17**), *N*-acetylpiperidine (**18**) with variation of pH are listed in Table 3.4 and Table 3.5. In control experiments, it was found that some of the reaction products, *N*-*t*-butylacetamide (**13**), *N*,*N*-diethylacetamide (**16**), and *N*-acetylpiperidine (**18**) underwent significant loss during workup (see Table 3.7), and it was necessary to correct the yields of these acetamides as described in the Experimental part. The uncorrected and corrected results are listed in Table 3.5 (see experimental part).

For the reaction of acetic anhydride (**19**) with aniline ($[C_6H_5NH_2]_T$ = 0.01 M), we first tried to use eq 14 to calculate the theoretical yields and plot the variations of pH by using k_w = 2.8 x 10^{-3} (s^{-1}) and k_{OH} = 9.70 x 10^2 (M^{-1} s^{-1}) reported by Kirsch and Jencks[27]. It may be seen in Figure 3.5, the agreement between experimental points and

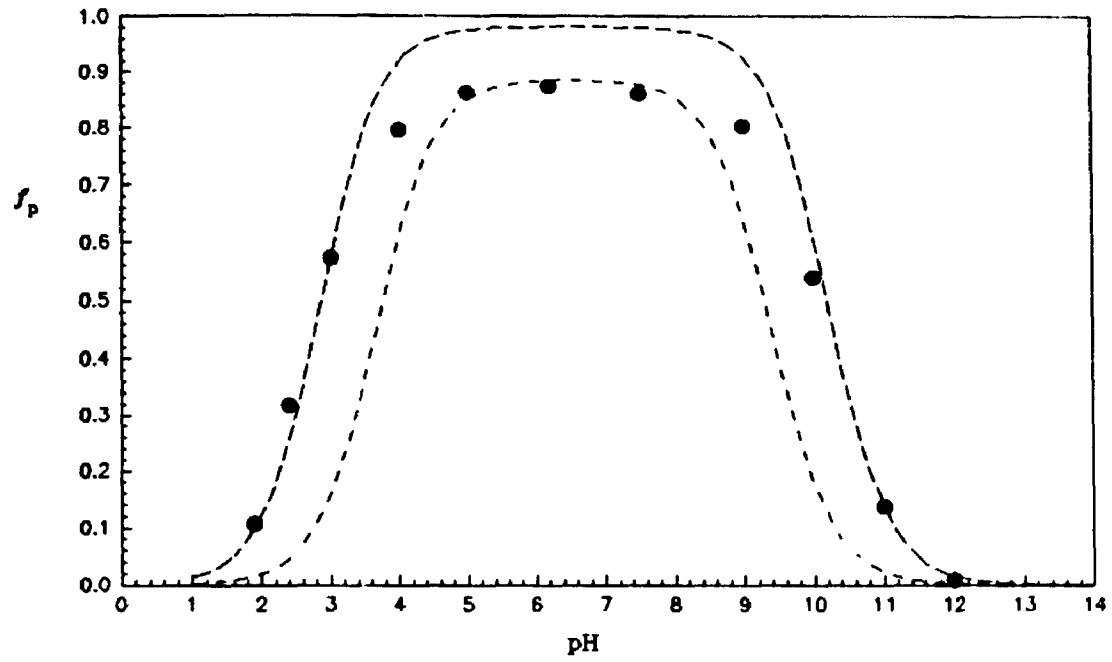


Figure 3.5 pH-yield profile for the reaction of acetic anhydride with aniline in water; where $[C_6H_5NH_2]_T$ = 0.01 M, K_a = 2.51 x 10^{-5}. The points are experimental; the long-dashed line is calculated from eq 14 with k_N = 15.5 $M^{-1}s^{-1}$; the short-dashed line is calculated from eq 14 with k_N = 2.2 $M^{-1}s^{-1}$; k_w = 2.8 x 10^{-3} s^{-1}; k_{OH} = 9.70 x 10^2 M^{-1} s^{-1}.

$$f_p = \frac{k_N[C_6H_5NH_2]}{k_w + k_{OH}[OH^-] + k_N[C_6H_5NH_2]} \qquad (14)$$

calculated curve was poor.

Any basic nucleophile in water may in principle lead to

either (a) direct nucleophilic substitution or (b) general base catalysis of the hydrolysis of the electrophile, i.e., in addition to nucleophilic substitution to form the acetamide, the amine may also act as a general base catalyst to assist water in the hydrolysis of acetic anhydride (19).

In this light it is natural to suggest that general base catalysis of the hydrolysis is also involved in the reactions of acetic anhydride (19) with aniline. Eq 14 is then rewritten as a general equation for the reactions of acetic anhydride with amines (see eq 15), where k_{DN} is the rate constant of direct nucleophilic substitution, k_{GB} is the rate constant of general base catalyzed hydrolysis, and [amine] is the concentration of the amine.

$$f_p = \frac{k_{DN}[\text{amine}]}{k_w + k_{OH}[OH^-] + k_{DN}[\text{amine}] + k_{GB}[\text{amine}]} \qquad (15)$$

Figure 3.6 shows that the solid line calculated from eq 15 and the parameters of k_{DN} = 15.5 M^{-1} s^{-1} and k_{GB} = 1.9 M^{-1} s^{-1} fits the experimental data within experimental uncertainty.

To test the generality of this picture pH-yield profiles for four other representative primary amines and three secondary amines have been obtained similarly and are shown in Figures 3.7 and 3.8. It has been found that the

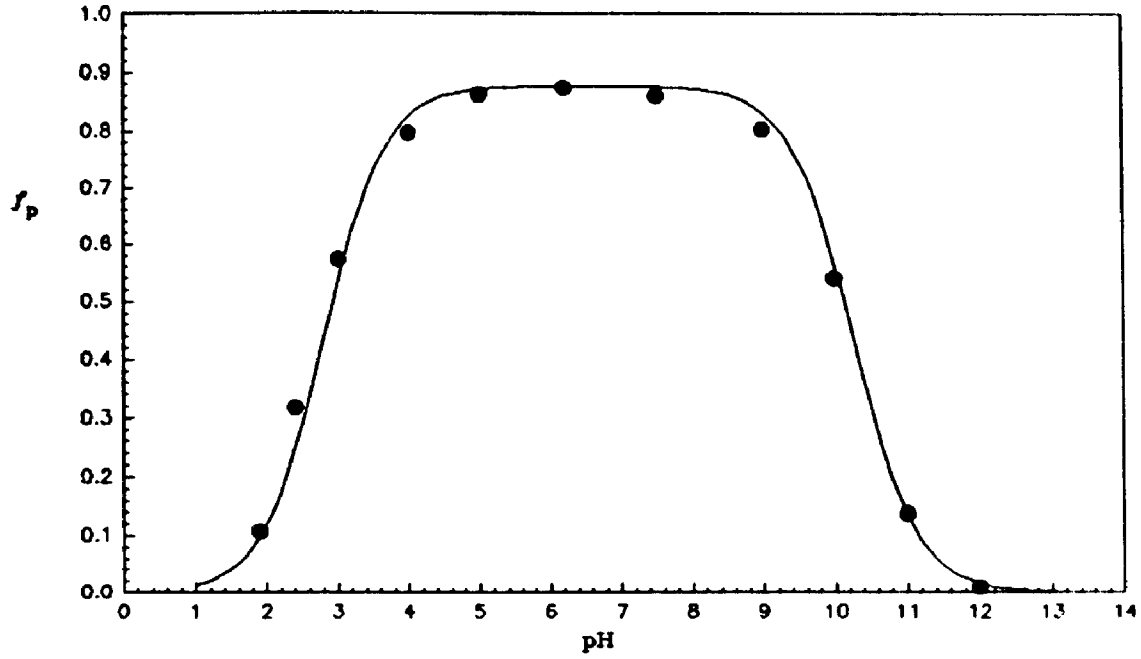


Figure 3.6 pH-yield profile for the reaction of acetic anhydride with aniline in water; where $[C_6H_5NH_2]_T$ = 0.01 M, K_a = 2.51 x 10^{-5}. The points are experimental; the solid line is calculated from eq 15 with k_{DN} = 15.5 $M^{-1}s^{-1}$, k_{GB} = 1.9 $M^{-1}s^{-1}$, k_w = 2.8 x 10^{-3} s^{-1}, and k_{OH} = 9.70 x 10^2 M^{-1} s^{-1}.

reactions of acetic anhydride with other amines also involve the general base catalysis of hydrolysis.

It may be concluded that the reaction of acetic anhydride with amines in water has four distinct pathways: (1) hydrolysis of acetic anhydride by water, (2) hydrolysis by hydroxide anion, (3) general base assisted hydrolysis of acetic anhydride by amines, and (4) nucleophilic substitution reaction of acetic anhydride with amine to form the acetamide. The yield of acetamide should follow eq 15.

When we plot the variations of the yields of acetamides with pH for the reactions of acetic anhydride with amines according to eq 15, the experimental data are consistent with the theoretical data within experimental uncertainty (see Figures 3.7 and 3.8). The values of k_{DN} and k_{GB} for the reactions of acetic anhydride (19) with amines were obtained from the lines of best fit for the plots of yields (f_p) *vs* pH. The results are listed in Table 3.3. With 3-methyl-butylamine and piperidine, however, the curves calculated without the general base term gave a passable fit, though this was improved if a relatively small k_{GB} term was included; it is clear that with these bases the intervention of general base promotion of hydrolysis is not certain and the values of k_{GB} given in Table 3.3 for those bases are highly approximate.

Diisopropylamine, on the other hand, gave no sign of formation of any *N,N*-diisopropylacetamide; an authentic sample was found to be stable to the conditions of reaction and workup. We conclude that the direct nucleophilic attack of diisopropylamine on acetic anhydride in water under these conditions is simply too slow to compete detectably with the hydrolytic reactions. We can not conclude at this stage, however, whether a general base assisted hydrolysis is involved or not.

To test the results obtained from the pH-yield profiles, the rates of reactions of acetic anhydride with amines in water were measured (see next part).

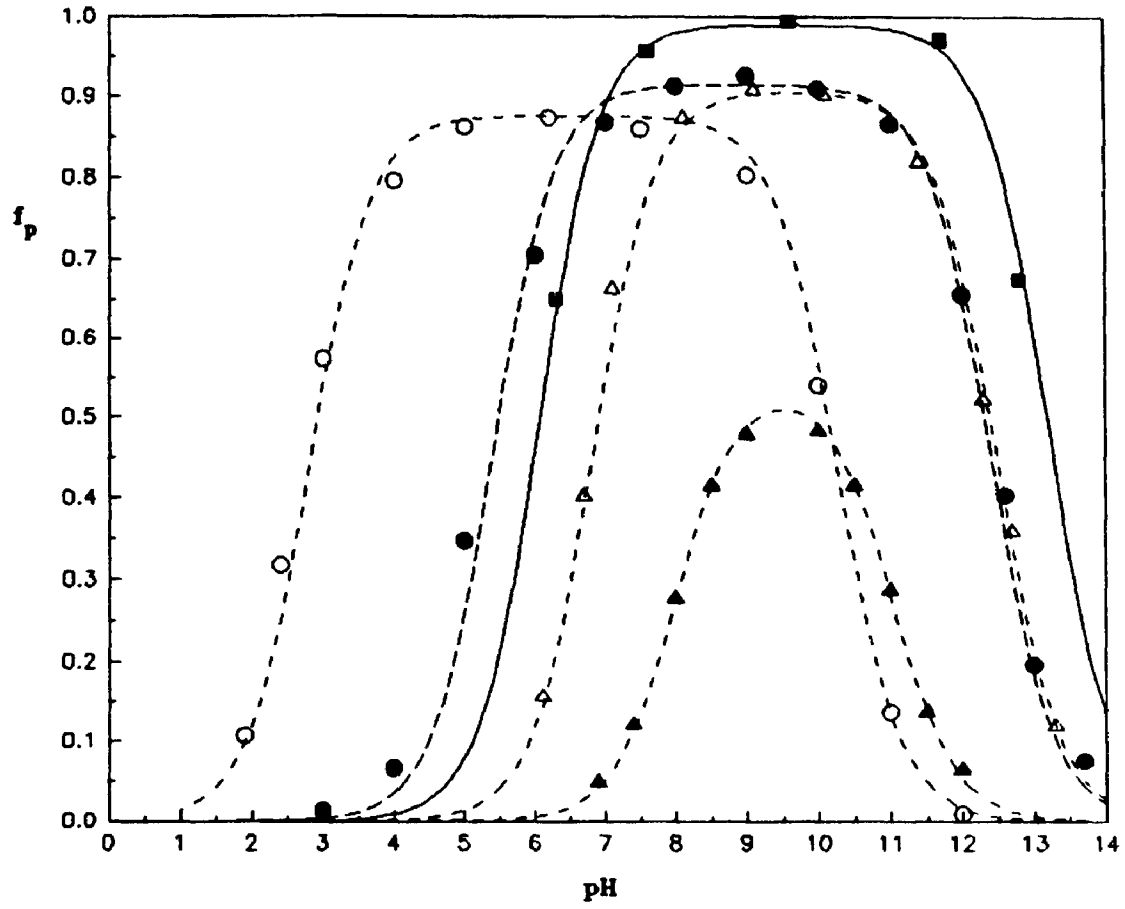


Figure 3.7 pH-yield profiles for the pseudo-first-order reactions at 25 °C of acetic anhydride (C_o 0.001 M) with primary amines (C_o 0.01 M) (a) 3-methylbutylamine, to form *N*-3-methylbutylacetamide, filled squares, (b) *t*-butylamine, to form *N*-*t*-butylacetamide, filled triangles, (c) benzylamine, to form *N*-benzylacetamide, filled circles, (d) cyclohexylamine, to form *N*-cyclohexyl-acetamide, open triangles, and (e) aniline, to form acetanilide, open circles. The lines were calculated from eq 15 using k_W 2.8 x 10^{-3} s^{-1}, k_{OH} 970 M^{-1} s^{-1} and the k_{DN} and k_{GB} parameters listed in Table 3.3 for the following amines: (a) top solid line, 3-methylbutylamine, (b) bottom solid line, *t*-butylamine, (c) long dashed line, benzylamine, (d) short dashed line cyclohexylamine, and (e) middle solid line, aniline.

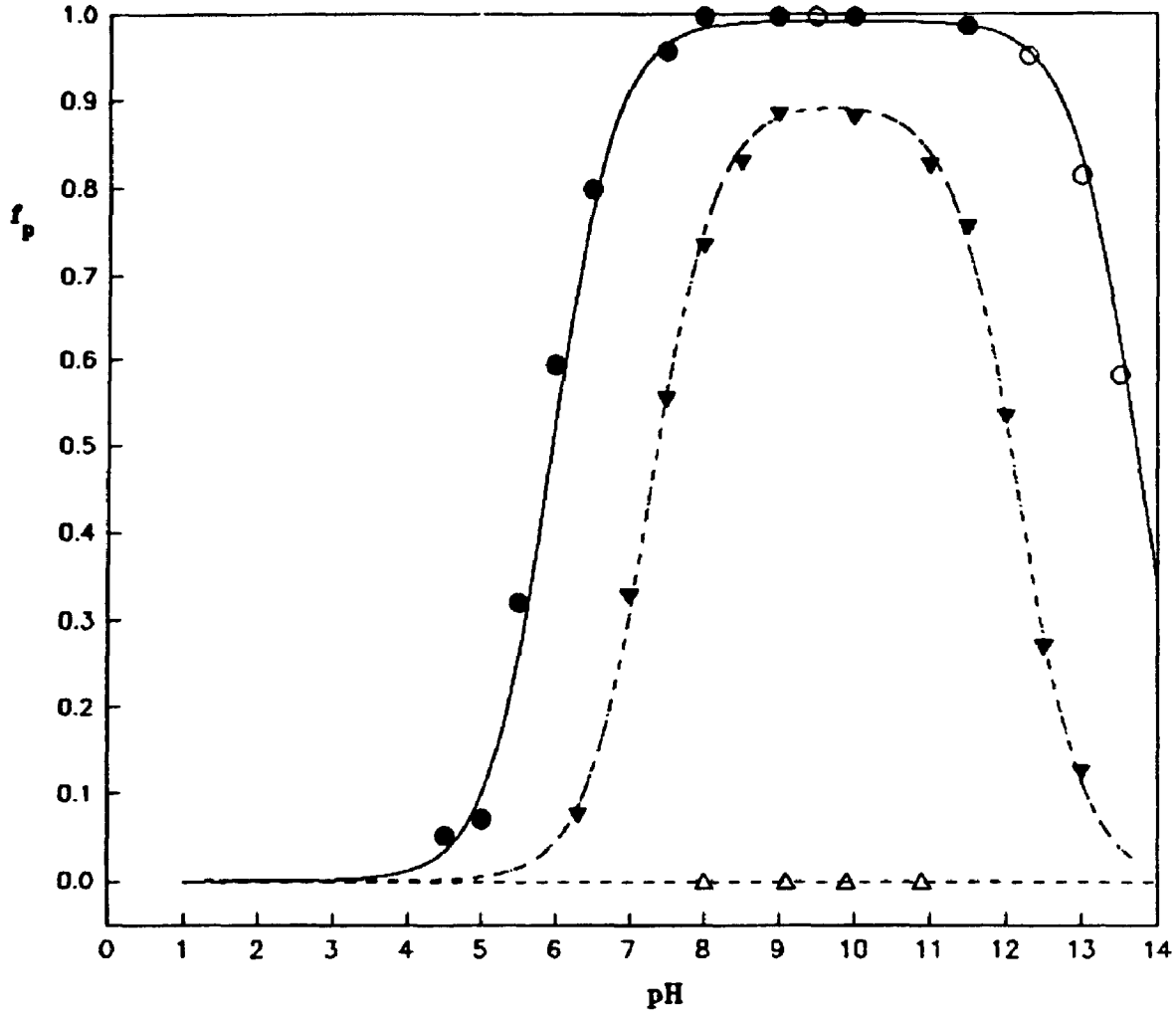


Figure 3.8 pH-yield profiles for the pseudo-first-order reaction at 25 °C of acetic anhydride (C_o 0.001 M) with secondary amines (C_o 0.01 M) (a) piperidine, to form *N*-acetylpiperidine, filled circles (in water) and open circles (in 0.5% DME), (b) diethylamine, to form *N,N*-diethylacetamide, filled triangles, and (c) diisopropylamine, to form *N,N*-diisopropylacetamide, open triangles. The lines were calculated from eq 15 using k_W 2.8 x 10^{-3} s^{-1}, k_{OH} 970 M^{-1} s^{-1} and the k_{DN} and k_{GB} parameters listed in Table 3.3 for the following amines: (a) the solid line, *N*-acetylpiperidine, (b) the middle dashed line, *N,N*-diethylacetamide, and (c) the short dashed line *N,N*-diisopropylacetamide.

Table 3.3 Rate Constants for the Reaction of Acetic Anhydride with Amines in Water

Amine (pK_a)	k_{DN} x 10^{-3}	k_{GB} x 10^{-3}	k_N[a] x 10^{-3}	k_N[b] x 10^{-3}
$(CH_3)_2CHCH_2CH_2NH_2$ (10.6)	10.00	~0.40	10.40	10.40
$C_6H_5CH_2NH_2$ (9.34)	2.20	0.20	2.40	2.48
$C_6H_{11}NH_2$[c] (10.64)	2.10	0.17	2.27	2.25
$(CH_3)_3CNH_2$ (10.55)	0.056	0.014	0.07	0.068
$C_6H_5NH_2$ (6)	0.0155	0.0019	0.0174	0.0179
$(CH_2)_5NH$[d] (11.22)	51.60	~0.25	51.85	51.73
$(C_2H_5)_2NH$ (10.98)	1.25	0.05	1.30	1.36
$[(CH_3)_2CH]_2NH$ (11.05)		(0.031)[b]		0.031

a. k_{DN} and k_{GB} were obtained from a best fit of the pH-yield profile; k_N (product) from $k_N = k_{DN} + k_{GB}$

b. From rate measurements.

c. Cyclohexylamine.

d. Piperidine.

3.2.2.2 The kinetics of the reactions of acetic anhydride with amines

To verify the results obtained from the pH-yield profiles, the rate constants (k_{obs}) for the reactions of acetic anhydride (19) with amines were measured with the pH-stat apparatus at 25.0 °C in water under pseudo-first-order conditions (see Table 3.11 in the experimental part).

$$k_N = \frac{k_{obs} - k_w - k_{OH}[OH^-]}{[amine]} \qquad (16)$$

The values of k_N were calculated from these k_{obs} values using eq 16; the results are listed in Table 3.3.

Figure 3.9 shows the pH-rate profiles for the reactions of acetic anhydride with primary amines, and also for the hydrolysis in pure water and in presence of sodium acetate at 25.0 °C, while Figure 3.10 shows the pH-rate profiles for the reactions of acetic anhydride with secondary amines. In those figures, the lines are calculated by using eq 16 and all of these lines are fully consistent with the experimental points (circles, triangles, and squares). Butler and Gold[28] investigated the hydrolysis of acetic anhydride (0.088 M) in presence of sodium acetate (0 to 0.18 M) in buffer solutions. They found that sodium acetate showed a weak acceleration of the hydrolysis of acetic anhydride (acting as a general base). In the present study

when 0.02 M sodium acetate was added, the rate constant of hydrolysis of acetic anhydride did not increase significantly (see Table 3.12 and Figure 3.9). The results we obtained are consistent with previous results, and the low concentration of acetate anion which is produced in the reaction evidently has no detectable influence on the rate.

The values of k_N obtained from the kinetic measurements, as indicated by eq 16, are simply the sums of k_{DN} and k_{GB}; these k_N values are listed in Table 3.3 along with the k_{DN} and k_{GB} values obtained from pH-yield profiles. From Table 3.3 one may find that the second-order rate constant, k_N, for the reaction of acetic anhydride (19) with aniline (20) in water at 25.0 ^{o}C, for example, is 17.9 M^{-1} s^{-1}, which is very close the value, 17.4 M^{-1} s^{-1}, obtained from the pH-yield profile. Similarly, the second-order rate constant, k_N = 2.48 x 10^3 M^{-1} s^{-1}, for the reaction of acetic anhydride (19) with benzylamine (4) also accords well with the value of k_N = 2.10 x 10^3 (M^{-1} s^{-1}) obtained from the pH-yield profile. The rate constants obtained by rate measurement and from the pH-yield profiles for the reaction of acetic anhydride with the other primary and the secondary amines are also fully consistent with this picture.

It is interesting to look the maximum yield of each acetamide in Table 3.4 and Table 3.5. It is obvious that the maximum yields of acetamides of primary amine vary with the basicity and structure of the amine. For example, with *N*-3-(methylbutyl)acetamide (15) the maximum yield is 99.5%,

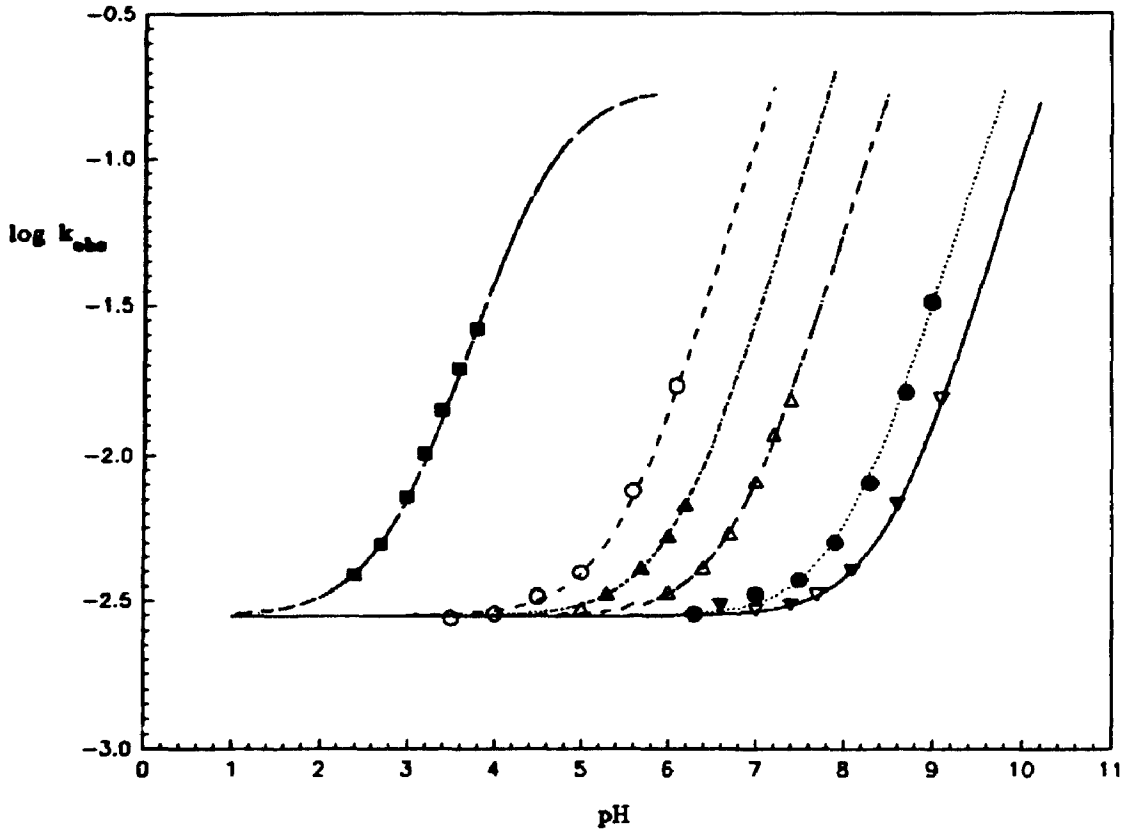


Figure 3.9 pH-rate profiles for the pseudo-first-order reactions of acetic anhydride (C_o 0.001 M) with primary amines (C_o 0.01 M): (a) aniline, filled squares, (b) benzylamine, open circles, (c) 3-methylbutylamine, filled triangles (up), (d) cyclohexylamine, open triangles (up), (e) *t*-butylamine, filled circles, and (f) water, filled triangles (down), (g) sodium acetate (C_o 0.02 M), open triangles (down). The lines are calculated from eq 16. (a) the long dashed line (left), aniline k_N = 17.9 M^{-1} s^{-1}, (b) the middle dashed line, benzylamine, k_N = 2.48 x 10^3 M^{-1} s^{-1}, (c) the short dashed line, 3-methylbutylamine, k_N = 10.4 x 10^3 M^{-1} s^{-1}, (d) the long dashed line (right), cyclohexylamine, k_N = 2.25 x 10^3 M^{-1} s^{-1}, (e) the dotted line, *t*-butylamine, k_N = 68 M^{-1} s^{-1}, and (f) the solid line, water, k_w = 2.8 x 10^{-3} s^{-1}; k_{OH} = 9.70 x 10^2 M^{-1} s^{-1}.

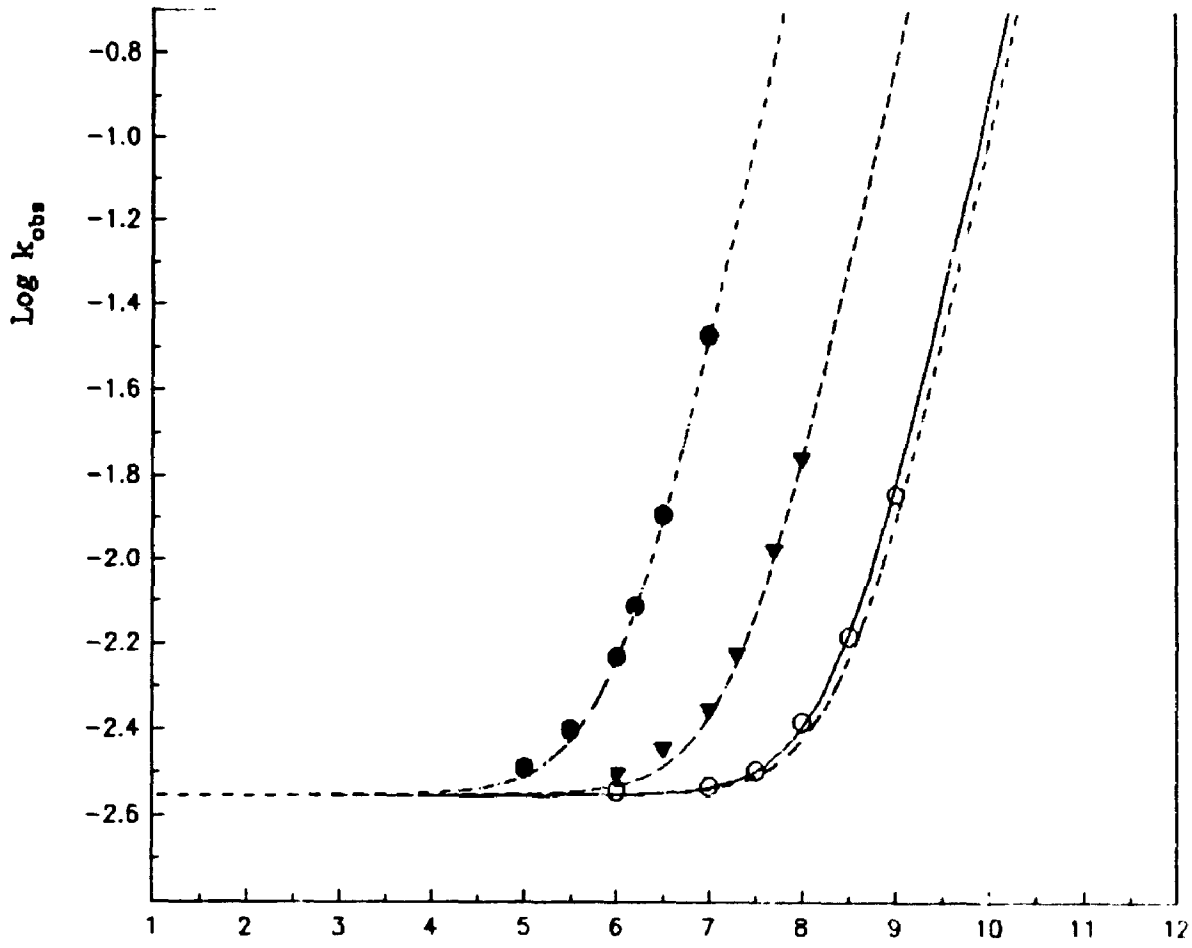


Figure 3.10 pH-rate profiles for the pseudo-first-order reactions at 25 °C of acetic anhydride (C_o 0.001 M) with secondary amines (C_o 0.01 M): (a) piperidine, filled circles, (b) diethylamine, filled triangles, and (c) diisopropylamine, open circles. The lines were calculated from eq 16, (a) the short dashed line, piperidine, k_N = 51.73 x 10^3 M^{-1} s^{-1}, (b) the middle dashed line, diethylamine, k_N = 1.36 x 10^3 M^{-1} s^{-1}, (c) the solid line, diisopropylamine, k_{GB} = 31 M^{-1} s^{-1}, and (d) the long dashed line, water, k_w = 2.8 x 10^{-3} s^{-1}; k_{OH} = 9.70 x 10^2 M^{-1} s^{-1}.

N-benzylacetamide (**10**), 92.6%, *N*-cyclohexylacetamide (**12**), 91.0% and acetanilide (**11**), 87.4%, with, *N*-t-butylacetamide (**13**), however, the yield in only 48.5%. The secondary amines also show the same tendency as the primary amines. The maximum yields are, with *N*-acetyl piperidine (**18**), 99.7% and *N,N*-diethylacetamide (**16**), 88.4%, but with *N,N*-diisopropylacetamide (**17**), the yield is 0%. The effect of structure of an amine for the yield of acetamide is so varied that we can change the maximum yields of acetamides for the reactions of acetic anhydride with amines from almost 100% to 0% by changing the structures of amines.

One may compare the results obtained from the pH-yield profile and kinetic measurements for the reaction of acetic anhydride with diisopropylamine (**25**). From the pH-yield profile, we could not obtain the k_N term because no *N,N*-diisopropylacetamide (**17**) was obtained in the reaction of acetic anhydride with diisopropylamine even with the amine 0.1 M in water. We therefore assume that the term of direct nucleophilic substitution for this reaction is zero within experimental uncertainty (i.e. $k_{DN} = 0$). In the kinetic measurement $k_N = 31\ M^{-1}\ s^{-1}$ was found. Taken with the result obtained from the pH-yield profile ($k_{DN} = 0$), we can conclude $k_{GB} = k_N = 31\ M^{-1}\ s^{-1}$ for the reaction of acetic anhydride with diisopropylamine. This result indicates that the reaction of acetic anhydride (**19**) with diisopropylamine in water proceeds only by hydrolysis, i.e. general base catalyzed hydrolysis as well as hydrolysis by water and

hydroxide ion. This result would suggest that for the reaction of acetic anhydride with very hindered amines the mechanism is different with that of unhindered amines, which mainly undergo direct nucleophilic substitution and general base catalyzed hydrolysis.

From Table 3.3, one may find that in the reactions of acetic anhydride with primary amines the rate constant of direct nucleophilic substitution of 3-methylbutylamine (**23**) (pK_a 10.6), k_{DN} = 1.0 x 10^4 (M^{-1} s^{-1}), is 178 times larger than that of *t*-butylamine (**22**) (pK_a 10.55), k_{DN} = 56 (M^{-1} s^{-1}) although both amines have almost identical pK_a values. The rate constant, k_{DN} = 2.1 x 10^3 (M^{-1} s^{-1}), for cyclohexylamine (**21**) which has a similar pK_a value (10.64), is about 5 times less than that of 3-methylbutylamine (**23**), but is 37.5 times larger than that of *t*-butylamine (**22**). Benzylamine (**4**) (pK_a 9.34) has a slightly larger rate constant, k_{DN} = 2.2 x 10^3 (M^{-1} s^{-1}), than that of cyclohexylamine (**21**) although the latter is more basic (ΔpK_a 1.3) than benzylamine (**4**). It is understandable that aniline (**2**) has the smallest k_{DN} (15.5 M^{-1} s^{-1}) because **2** is the least basic amine. These results indicate that k_{DN} of the reaction of acetic anhydride with an amine is increased with the increase of the pK_a of the amine and decreased with the increase of size of the alkyl group in the amine.

It is also interesting to look at the rate constants of reactions of acetic anhydride with secondary amines. Piperidine (**7**) which is the most basic amine (pK_a 11.22) in

this series has the largest rate constant, k_{DN} = 5.16 x 10^4 (M^{-1} s^{-1}). However, diisopropylamine, which is almost as basic (pK_a 11.05) and the most hindered amine in this study, apparently does not go by direct nucleophilic substitution at all under the same conditions, k_{DN} = 0. Diethylamine (**24**) (pK_a 10.98), which is close in basicity to diisopropylamine, is 41 times less reactive than piperidine (k_{DN} = 1.25 x 10^3 M^{-1} s^{-1}).

It was also found that the amount of k_{GB}/k_{DN} varies with the structure and basicity of the amine. For the reaction of acetic anhydride (**19**) with 3-methylbutylamine (**23**) which is one of the most basic, and the least hindered amine, we found the ratio of k_{GB}/k_{DN} 0.04, which means that only 4% of **23** acts as a general base to catalyze the hydrolysis of acetic anhydride. For cyclohexylamine (**21**) which is similar in basicity, but is more hindered than **23**, the amount of general base catalysed amine is increased to 7.5%, but for *t*-butylamine (**22**) which is the most hindered of these amines, this term reaches 20%.

The amount of general base catalyzed hydrolysis for the reaction of acetic anhydride with a secondary amine is changed dramatically with the structure of the amine. With piperidine (**7**), which is the least hindered amine, at most only 0.5% of the reaction is the general base promoted process. With diethylamine, which is more hindered than piperidine but less hindered than diisopropylamine, 3.8% of the reaction is the general base reaction. For diisopropyl-

amine (**25**) which is the most hindered amine, all of the reaction is the general base catalyzed hydrolysis.

In this part of the study we have also applied eq 6 to the acylation reaction of acetic anhydride (**19**) with cyclohexylamine (**21**) under preparative conditions. It is found that at pH_{max} 9.5, with cyclohexylamine, C_o 1.0 M, and acetic anhydride, C_o 1.2 M, the yield of *N*-cyclohexyl-acetamide (**12**) is as high as 99.9%; but in the same ccnditions except at pH 6.5, the yield of **12** dropped to 76.9%, while at pH 12.5, the yield is only 78.2% (see Table 3.10 in experimental part). This result confirms that it is important to control the pH to reach the maximum yield for the reaction of acetic anhydride with amines in water because of competition with hydrolysis. Because of the presenc of general base catalyzed hydrolysis in the reactions of acetic anhydride with amines, it is probably necessary, of course, to add an excess acetic anhydride (which is less expensive than most amines) to obtain full conversion of the amine to the amide.

3.3 Presentation of Yield Data by pH-Product Ratio Profiles

It is also useful to express the yields in terms of the product ratio, r, defined by eq 17.

$$r = \frac{\text{[nucleophilic attack product]}}{\text{[hydrolysis product]}} = \frac{f_p}{(1 - f_p)} \qquad (17)$$

Under pseudo-first-order conditions and in the absence of the general base assisted hydrolysis, r is given by eq 18.

$$r = \frac{k_{DN}Nu_T K_a/([H^+] + K_a)}{k_w + k_{OH}K_w/[H^+]} \qquad (18)$$

A plot of log r *vs.* pH takes the form shown in Figure 3.11 by the dashed line, which may be regarded as assembled from three lines of slopes 1, 0, and -1, respectively, with rounded intersections (see Figure 3.11). It may be readily shown that the pH value of the two points of intersection of these (tangential) straight lines are at the pK_a (of NuH^+) and the pH_i (of E). In the example shown in Figure 3.3, $pK_a < pH_i$ and hence it is the intersection at lower pH which corresponds to the pK_a and the intersection at higher pH which corresponds to pH_i. For those reactions in which $pK_a > pH_i$ this picture is reversed, and for the special case in which $pK_a = pH_i$ log r takes the shape of a (rounded) inverted V with the point of intersection at $pH = pK_a = pH_i$.

When general base catalysis of hydrolysis by Nu is also present r is given by eq 19.

$$r = \frac{k_{DN}Nu_T K_a/([H^+] + K_a)}{k_w + k_{OH}K_w/[H^+] + k_{GB}Nu_T K_a/([H^+] + K_a)} \qquad (19)$$

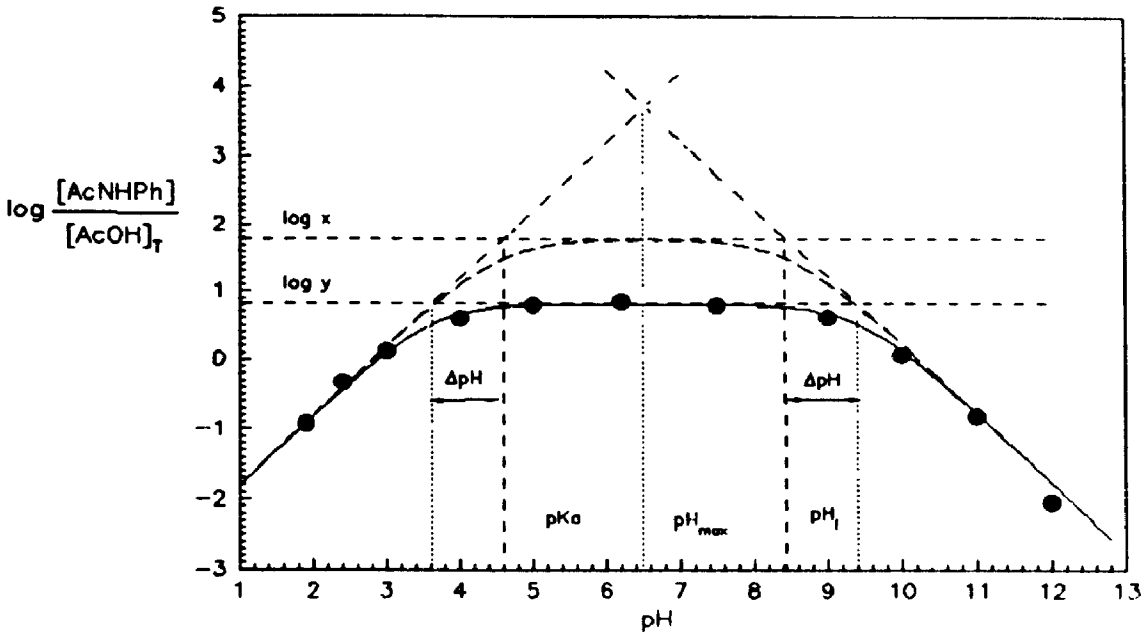


Figure 3.11 pH-product ratio profiles for the reaction of acetic anhydride with aniline with and without general base catalysis; heavy dashed line, (hypothetical) reaction without general base catalysis (from eq 19, k_{DN} 15.0 M^{-1} s^{-1}); dotted line, (actual) reaction with general base catalysis (from eq 20, k_{DN} 15.0 M^{-1} s^{-1}, k_{GB} 2.1 M^{-1} s^{-1}); light solid lines: slope = 1, from $r = k_{DN}Nu_T K_a/k_w[H^+]$; upper horizontal line from $r = k_{DN}Nu_T/k_w$; slope = -1 line from $r = k_{DN}Nu_T[H^+]/K_{OH}K_w$; lower horizontal line from $r = k_{DN}Nu_T/(k_w + k_{GB}Nu_T)$; points, experimental (from $r = f_p/(1-f_p)$; $AcOH_T$ = [AcOH]+[AcO^-].

The horizontal line is lowered while the two sloped lines are unchanged; the result is the dotted line in Figure 3.11. The basic shape is the same as the dashed line but the intersections are no longer at pK_a and pH_i. Instead the pH at the low pH intersection is lowered (by $|\Delta pH|$ and that at the high pH intersection raised (also by $|\Delta pH|$); in the plot of log *r vs* pH for the reaction of aniline with acetic anhydride shown in Figure 3.11, the intersections are pH 3.62 and 9.42 rather than at the pK_a and pH_i values of 4.60 and 8.44, respectively.

A practical result of this mode of presentation is that a simple plot of log *r vs* pH will disclose the presence or absence of general base catalysis of the hydrolysis by Nu provided one knows either the pK_a or the pH_i for E (and the reaction has the rate law given by eq 20).

$$k_{\psi T} = k_w + k_{OH}[OH^-] + k_{DN}[Nu] + k_{GB}[Nu] \qquad (20)$$

No rate measurements are required.

3.4 Conclusions

The work described in this chapter has its origins in the application of reaction mechanisms to organic synthesis. The results are relevant to both topics.

In the field of mechanisms we show how pH-yield information, either in the form of pH-yield profiles or pH-product ratio profiles may be used to ascertain the presence or absence of general base assistance of hydrolysis by the nucleophile (Nu), provided one knows (minimally) either the pK_a (of NuH^+) or pH_i (for E). Where k_w and k_{OH} for the hydrolysis of E and the pK_a are known, the pH-yield data readily give k_N and k_{GB} without any rate measurements involving the nucleophile being needed, though where these are readily obtained they would be useful in verifying the pH-yield results.

General base assisted hydrolysis in the reaction of acetic anhydride with amines has been found. The amount of general base assisted hydrolysis of acetic anhydride varies with the pK_a and structure of the amine, e.g. changing from about 0.5% with an unhindered amine (e.g. piperidine) to 100% with a very hindered amine (e.g. diisopropylamine). The rate constant for the reaction of acetic anhydride with an amine depends on the basicity and steric factors associated with the amine. The more basic and less hindered amine tends to have a large k_N and small ratio of k_{GB}/k_{DN}. Less basic or more hindered amines show opposite behaviour.

The reactions of benzoyl chloride with benzylamine or piperidine, on the other hand, show no sign of the general base promoted hydrolysis. Although a general base catalyzed hydrolysis was involved in the reactions of acetic anhydride with amines, it should be noted that pH_{max} values are accurately calculated from eq 5.

Looked at from the viewpoint of organic synthesis, the present results point to a factor that may seriously affect yields of nucleophile-electrophile reactions in water. When one seeks to maximize the yield of the product from the Nu-E process, any general base assisted hydrolysis simply wastes the electrophile. A method for predicting when the general base assisted hydrolysis will or will not manifest itself would be a valuable asset for predicting the outcome of synthetic reactions in aqueous media.

We have also deduced the equations which indicate the pH_{max} and f_p for the reactions of acyl transfer. By using these equations, one may easily carry out electrophile-nucleophile reactions in water with high yield. In this study we have used those equations to find the pH_{max} for the reactions of benzoyl chloride with piperidine and benzylamine in water. The maximum yields of 99.3% at pH 11.4 for piperidine, and 98.5% at pH 10.45 for benzylamine have been found. For the reactions of acetic anhydride with amines, in the preparative condition at pH 9.5, a yield of 99.9% has been obtained for the reaction of an appropriate excess of acetic anhydride with cyclohexylamine.

3.5 Experimental

The general procedure and the instrumentation are as described in chapter 1, except for the following points.

Diethylamine (**24**), diisopropylamine (**25**), benzylamine (**4**), aniline (**20**), cyclohexylamine (**21**), t-butylamine (**22**), 3-methylbutylamine (**23**), piperidine (**7**) (used for pH-yield experiments), and 1,2-dimethoxyethane (DME) were commercial materials dried by distillation from calcium hydride. Acetic anhydride (**19**) was refluxed over magnesium turnings for 24 h and fractionally distilled[29]; the fraction collected at 140-141 ^{o}C was used. Benzoyl chloride (**6**) was distilled before use. Water used for kinetics was purified by preliminary distillation and then, ion exchanged over Barnstead cartridges D8921 and D8922. Dichloromethane was reagent grade used without further purification.

Preparation of Acetamides

a) *N*-Benzylacetamide (10)

Acetic anhydride (**19**) (2.042 g, 20.0 mmol) was added slowly with stirring at room temperature to a solution of benzylamine (**4**) (2.572 g, 20 mmol) in water (200 mL) previously set at pH 9.0. The pH of the solution was kept between 8.0 and 10.0 with aqueous sodium hydroxide (2 M). After all of the acetic anhydride was added, stirring was continued for 0.5 h. The mixture was acidified to pH 2 with hydrochloric acid (2 M) and extracted with dichloromethane

(4 x 50 mL). The extract was washed with saturated sodium bicarbonate (30 mL) and water (30 mL) and dried over magnesium sulfate. The solvent was evaporated to give a white solid (**10**) (2.856 g, 19.1 mmol, 96% yield); mp 61-62 °C (lit.[30] mp 61 °C); IR (KBr) ν_{max}: 3295 (s), 3036 (m), 3033 (m), 1646 (s), 1549 (s), 1455 (m), 1375 (m), 1358 (m), 1283 (m), 1076 (s), 752 (m), 741 (s), 696 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.92 (s, 3H), 4.34 (d, 2H), 6.72 (s, 1H), 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 23.2, 43.7, 127.5, 127.8, 128.7, 138.2, 169.9.

b) Acetanilide (11)

Acetic anhydride (**19**) (2.042 g, 20.0 mmol) was added slowly with stirring at room temperature to a solution of aniline (**20**) (2.235 g, 20 mmol) in water (200 mL) previously set at pH 6.0. The pH of the solution was kept between 5.5 and 6.5 with aqueous sodium hydroxide (2 M), and worked up as above to give a white solid (**11**) (2.649 g, 19.6 mmol, 98% yield) which recrystallized from 85% ethanol; mp 112-113 °C (lit.[31] mp 113-114 °C); IR (KBr) ν_{max}: 3294 (s), 3194 (m), 3136 (m), 1665 (s), 1599 (s), 1558 (s), 1489 (s), 1435 (s), 1323 (s), 1264 (m), 754 (m), 695 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.16 (s, 3H), 7.09 (q, 1H), 7.26 (q, 2H), 7.48 (q, 2H), 7.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 24.5, 120.0, 124.2, 128.9, 137.9, 168.6.

c) *N*-Cyclohexylacetamide (12)

Acetic anhydride (19) (0.613 g, 6.0 mmol) was added slowly with stirring at room temperature to a solution of cyclohexylamine (21) (0.496 g, 5.0 mmol) in water (50 mL) previously set at pH 9.5. The pH of the solution was kept between 9.0 and 10.0 with aqueous sodium hydroxide (1 M), and worked up as above to give a white solid (12) (0.705 g, 99 mmol, 99.8% yield) which was recrystallized from ethyl acetate, mp 106-107 °C (lit.[5] mp 103-104 °C); IR (KBr) ν_{max}: 3291 (s), 3088 (m), 2934 (s), 2853 (s), 1640 (s), 1561 (s), 1443 (s), 1373 (m), 1314 (m), 1288 (m), 1117 (s), 981 (s), 737 (s), 608 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.06-1.91 (m, 10H), 1.93 (s, 3H), 3.74 (m, 1H), 5.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 24.4, 25.8, 26.4, 31, 49.1, 170.0.

d) *N,N*-Diethylacetamide (16)

Acetic anhydride (19) (7.657 g, 75.0 mmol) was added slowly with stirring at room temperature to a solution of diethylamine (24) (1.829 g, 25.0 mmol) in water (250 mL) previously set at pH 9.5. The pH of the solution was kept between 9.0 and 10.5 with aqueous sodium hydroxide (1 M), and worked up as above to give a colourless liquid (2.706 g, 23.5 mmol, 94% yield) which was distilled under reduced pressure, bp 88-90 °C (30 Torr) (lit.[30] bp 88.5-91 °C (31 Torr)); IR (neat) ν_{max}: 3532 (s), 2974 (s), 2878 (m), 1646 (s), 1485 (s), 1428 (s), 1379 (s), 1364 (s), 1311 (m), 1279 (s), 1223 (s), 1169 (m), 1097 (m), 1038 (s), 791 (s), 612

(s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.12 (t, 3H), 1.19 (t, 3H), 2.08 (s, 3H), 3.36 (dt, 4H); ^{13}C NMR ($CDCl_3$) δ: 12.8, 13.9, 21.0, 39.8, 42.7, 169.4.

e) *N*-*t*-butylacetamide (13)

Acetic anhydride (19) (3.063 g, 30.0 mmol) was added slowly with stirring at room temperature to a solution of *t*-butylamine (22) (1.829 g, 25.0 mmol) in water (250 mL) previously set at pH 9.5. The pH of the solution was kept between 9.0 and 10.0 with aqueous sodium hydroxide (1 M), and worked up as above to give the product (2.299 g, 20.0 mmol, 80.0% yield) as white crystals (13) which was recrystallized from ethyl acetate, mp 100-101 °C [lit.[32] mp 98 °C]; IR (KBr) ν_{max}: 3293 (s), 3086 (m), 2977 (s), 2930 (m), 1644 (s), 1561 (s), 1455 (m), 1393 (m), 1364 (s), 1304 (m), 1225 (s), 1036 (s), 965 (s), 725 (s), 610 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.29 (s, 9H), 1.86 (s, 3H), 5.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 25.3, 29.6, 51.9, 170.4.

f) *N*-Acetylpiperidine (18)

Acetic anhydride (19) (3.063 g, 30.0 mmol) was added slowly with stirring at room temperature to a solution of piperidine (7) (2.130 g, 25.0 mmol) in water (250 mL) previously set at pH 9.8 . The pH of the solution was kept between 9.0 and 10.5 with aqueous sodium hydroxide (1 M). After all of the acetic anhydride was added, stirring was continued for 15 min, and worked up as above to give a

colourless liquid (3.150 g, 28 mmol, 99% yield) which was distilled, bp 227-229 °C [lit.[33] bp 60 °C (0.4 Torr)]; n_D^{25} 1.4779 [lit.[34] n_D^{25} 1.4776]; IR (neat) ν_{max}: 3536 (w), 3004 (m), 2934 (s), 2857 (s), 1642 (s), 1441 (s), 1362 (s), 1267 (s), 1055 (m), 1028 (s), 987 (s), 853 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.46 (m, 6H), 1.93 (s, 3H), 3.25 (t, 2H), 3.39 (t, 2H); ^{13}C NMR ($CDCl_3$) δ: 22.3, 25.3, 26.3, 27.2, 43.2, 48.2, 169.5.

g) ***N,N*-Diisopropylacetamide (17)**

Acetyl chloride (2.79 g, 35.6 mmol) in ether (50 mL) was added dropwise to a solution of diisopropylamine (**25**) (3.0 g, 29.7 mmol) and triethylamine (3.6 g. 35.6 mmol) in ether (150 mL) at room temperature, and the mixture was stirred for 15 min. Water was added until all of the precipitate was dissolved. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed to give a slightly yellow liquid, which distilled to give a colourless liquid (**17**) (4.15 g, 29.0 mmol, 98% yield); bp 72-74 °C (6 Torr) [lit.[35] bp 87-88 °C (17 Torr)]; IR (neat) ν_{max} 3002 (s), 2968 (s), 2934 (s), 1642 (s), 1441 (s), 1371 (s), 1325 (s), 1219 (s), 1161 (m), 1136 (s), 939 (m), 884 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.75 (m, 1H), 3.38 (m, 1H), 1.91 (s, 3H), 1.23 (d, 6H), 1.07 (d, 6H); ^{13}C NMR ($CDCl_3$) δ: 169.4, 49.3, 45.4, 24.0, 21.0, 20.6.

h) *N*-3-Methylbutylacetamide[11] (15)

Acetyl chloride (1.033 g, 13.2 mmol) was added slowly to a solution of 3-methylbutylamine (**23**) (1.499 g, 17.2 mmol) and triethylamine (1.740 g, 17.2 mmol) in dichloromethane (50 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C, and worked up as above. The organic solvent was removed to give a slightly yellow liquid (**15**) (1.671 g, 12.9 mmol, 98%). It was distilled under reduced pressure to give a colourless liquid, bp 108-109 °C (0.7 Torr) [lit.[36] bp 234 °C]; n_D^{25} 1.4399 [lit.[9] n_D^{25} 1.4393]; IR (neat) ν_{max}: 3289 (s), 3088 (m), 2959 (s), 2874 (s), 1653 (s), 1561 (s), 1469 (s), 1437 (s), 1368 (s), 1296 (s), 1229 (s), 1157 (w), 1017 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.92 (d, 6H), 1.36 (m, 2H), 1.60 (m, 1H), 1.96 (s, 3H), 3.22 (m, 2H), 5.50 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.4, 23.0, 25.8, 37.8, 38.3, 170.5.

Preparation of *N*-Benzoyl Piperidine (9)

Benzoyl chloride (**6**) (5.60 g, 39.8 mmol) was added dropwise to a mixture of piperidine (**7**) (3.40 g, 39.9 mmol) and sodium hydroxide (2.10 g, 52.5 mmol) in water (20 mL). The mixture was stirred for 0.5 h at 35-40 °C, and acidified to pH 3 with dilute hydrochloric acid solution. After the mixture was cooled to room temperature, it was extracted with dichloromethane (3 x 100 mL). The organic layer was separated and washed with saturated sodium bicarbonate (30 mL) and water (30 mL), and dried over anhydrous magnesium

sulfate. The solvent was evaporated to give an oil (**9**) (7.43 g, 39.3 mmol, 98.6%) which was distilled under reduced pressure, bp 173-175 °C (12 Torr) [lit.[37] bp 180-184 °C (20 Torr)]; IR (neat) ν_{max}: 3584 (w), 3058 (w), 2938 (s), 2855 (s), 1632 (s), 1433 (s), 1277 (S), 1111 (m), 1003 (m), 708 (s), 632 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.42-1.58(d, 6H), 3.25 (s, 2H), 3.62 (s, 2H), 7.30 (s, 5H); ^{13}C NMR ($CDCl^3$) δ: 25.0, 26.1, 27.0, 43.5, 49.2, 127.2, 128.8, 129.8, 136.9, 170.7.

Preparation of *N*-benzoylbenzamide (8)

Benzoyl chloride (**6**) (0.703 g, 5.0 mmol) in DME (2.5 mL) was added to benzylamine (**4**) (0.536 g, 5.0 mmol) in water (500 mL) which had previously been adjusted to pH 10.5 at 25 °C. The mixture was stirred for 30 min, and acidified to pH 2 with aqueous hydrochloric acid (4.0 M), and extracted with dichloromethane (3 x 50 mL), and worked up as above to give a white solid (**8**) (0.9138 g, 4.33 mmol, 86.5%); mp 104-105 °C [lit.[38] mp 105 °C]; IR (KBr) ν_{max}: 3294 (s), 3060 (w), 3031 (w), 1640 (s), 1547 (s), 1418 (m), 1315 (s), 1259 (m), 1057 (m), 1028 (m), 989 (m), 727 (s), 695 (s) cm^{-1} ^1H NMR ($CDCl_3$) δ: 4.64 (d, 2H), 6.78 (s, 1H), 7.34-7.83 (m, 10H); ^{13}C NMR ($CDCl_3$) δ: 44.0, 127.0, 127.5, 127.8, 128.5, 128.7, 131.5, 133, 138.2, 167.5.

Table 3.4 The variation in yield of the amide with change in pH for the reactions of acetic anhydride with amines[a] under pseudo-first-order condition.

Amides	pH	Weight (mg)	f_p
$CH_3CONHCH_2C_6H_5$	3.0	4.0	0.012
	4.0	9.8	0.066
	5.0	51.7	0.347
	6.0	105.2	0.705
	7.0	129.5	0.868
	8.0	136.2	0.913
	9.0	138.2	0.926
	10.0	135.7	0.910
	11.0	129.2	0.866
	12.0	97.8	0.656
	12.6	54.5	0.403
	13.0	29.4	0.197
	13.6	12.7	0.085
$CH_3CONHC_6H_5$	1.9	14.5	0.107
	2.4	43.0	0.318
	3.0	77.5	0.573
	4.0	107.5	0.796
	5.0	116.5	0.862
	6.2	118.2	0.874
	7.5	116.3	0.860
	9.0	108.5	0.803
	10.0	73.0	0.540
	11.0	17.8	0.132
	12.0	1.2	0.009

Table 3.4 Continued

The variation in yield of the amide with change in pH for the reactions of acetic anhydride with amines[a] under pseudo-first-order condition.

Amides	pH	Weight (mg)	f_p
$CH_3CONHC_6H_{11}$	6.0	22.5	0.159
	6.6	57.2	0.405
	7.0	94.0	0.666
	8.0	123.7	0.876
	9.0	128.5	0.910
	10.0	127.6	0.904
	11.3	115.9	0.821
	12.2	74.0	0.524
	12.6	51.0	0.361
	13.2	17.2	0.122
$CH_3CONHCH_2CH_2CH(CH_3)_2$	6.2[b]	33.6	0.650
	7.0[b]	50.0	0.967
	9.5	128.5	0.995
	11.6[b]	50.3	0.973
	12.7[b]	34.8	0.674

a. Reactions were carried out by injecting acetic anhydride ($[Ac_2O]_T$ = 0.001 M) to an amine solution ($[amine]_T$ = 0.01 M) in water (1000 mL) at 25 °C.

b. Reactions were carried out by injecting acetic anhydride ($[Ac_2O]_T$ = 0.001 M) to an amine solution ($[amine]_T$ = 0.01 M) in water (400 mL) at 25 °C.

Table 3.5 The variation in yield of the amide with change in pH for the reactions of acetic anhydride with amines[a] under pseudo-first-order condition

Amides	pH	Weight (mg) Uncorrect	Weight (mg) Corrected	f_p
$CH_3CONHC(CH_3)_3$	6.9	5.2	5.9	0.050
	7.4	12.6	14.2	0.123
	8.0	28.5	32.2	0.280
	8.5	42.5	48.0	0.417
	9.0	49.1	55.4	0.481
	10.0	49.5	55.9	0.485
	10.5	42.5	48.0	0.417
	11.0	29.6	33.4	0.290
	11.5	14.2	16.0	0.139
	12.0	6.7	7.6	0.066
$CH_3CONH(C_2H_5)_2$	6.3	8.1	8.6	0.075
	7.0	35.4	37.7	0.328
	7.5	59.8	63.6	0.553
	8.0	79.5	84.6	0.735
	8.5	89.7	95.4	0.829
	9.0	95.7	101.8	0.884
	10.0	95.2	101.3	0.880
	11.0	89.2	94.9	0.825
	11.5	81.7	86.9	0.755
	12.0	57.7	61.4	0.533
	12.5	29.2	31.1	0.270
	13.0	13.5	14.4	0.125

Table 3.5 Continued

The variation in yield of the amide with change in pH for the reactions of acetic anhydride with amines[a] under pseudo-first-order condition

Amides	pH	Weight (mg) Uncorrect	Weight (mg) Corrected	f_p
$CH_3CONH(CH_2)_5$	4.5	6.2	6.6	0.052
	5.0	8.5	9.1	0.071
	5.5	38.1	40.9	0.321
	6.0	70.4	75.6	0.594
	6.5	94.5	101.6	0.799
	7.5	113.2	121.7	0.957
	8.0	118.0	126.9	0.997
	9.0	118.0	126.9	0.997
	9.5[b]	118.0	126.9	0.997
	10.0	118.0	126.9	0.997
	11.5	116.7	125.5	0.986
	12.3[b]	112.6	121.1	0.952
	13.0[b]	96.3	103.6	0.814
	13.5[b]	68.7	73.9	0.581

a. Reactions were carried out by injecting acetic anhydride ($[Ac_2O]_T$ = 0.001 M) to an amine solution ($[amine]_T$ = 0.01 M) in water (1000 mL) at 25 °C.

b. Reactions were carried out by injecting the acetic anhydride solution ($[Ac_2O]_T$ = 0.001 M) in DME (5 mL) to an amine solution ($[amine]_T$ = 0.01 M) in water (1000 mL) at 25 °C.

pH-Product Ratio Measurements: Acetic Anhydride with Amines

(a) General Procedure for pH-Product Ratio Measurement

Acetic anhydride (**19**) was injected from a 1-mL syringe into a solution of amine in water (1000 mL) at 25 °C which had previously been set at the specified pH value with aqueous hydrochloric acid or sodium hydroxide, 6 M unless otherwise specified. The reaction was allowed to run to completion with monitoring of the pH with a Sargent-Welch pH 6000 digital display meter equipped with a Fisher all-range (pH 1 to 14) combination electrode and manual addition of aqueous sodium hydroxide (1.0 M). The solution was stirred rapidly for further 0.5 h with the pH of the solution kept constant. The mixture was acidified to pH 2 with aqueous hydrochloric acid (6.0 M) and extracted with dichloromethane (5 x 70 mL). The organic layer was separated and washed with saturated sodium bicarbonate (50 mL) and water (50 mL), and dried over anhydrous magnesium sulfate. The solvent wa evaporated and the product dried to constant weight under vacuum.

b) Benzylamine (4)

Acetic anhydride (**19**) (0.102 g, 1.0 mmol) was injected into a solution of benzylamine (**4**) (1.072 g, 10.0 mmol). The reaction was performed as above. Evaporation of solvent gave white crystals (**10**) which was dried to constant weight under vacuum. The results are listed in Table 3.4. The product, *N*-benzylacetamide, was identical by ^{1}H NMR, ^{13}C

NMR, and mp with the authentic sample.

c) Cyclohexylamine (21)

Acetic anhydride (**19**) (0.102 g, 1.0 mmol) was injected into a solution of cyclohexylamine (0.992 g, 10.0 mmol), and after 20 min worked up as above. The solvent was evaporated to give white crystals (**12**) which was dried to constant weight under vacuum. The results are listed in Table 3.4. The product, *N*-cyclohexylacetamide (**12**), was identical by ^{1}H NMR, ^{13}C NMR, and mp with the authentic sample.

d) *t*-Butylamine (22)

Acetic anhydride (**19**) (0.102 g, 1.0 mmol) was injected to a solution of *t*-butylamine (**22**) (0.731 g, 10.0 mmol), and after 20 min worked up as above except that the mixture was extracted with dichloromethane (8 x 100 mL). The solvent was evaporated to give white crystals (**13**) which was dried to constant weight under vacuum. The results are listed in Table 3.5. The product, *N*-*t*-butylacetamide (**13**), was identical by ^{1}H NMR, ^{13}C NMR, and mp with the authentic sample.

e) Aniline (20)

Acetic anhydride (**19**) (0.102 g, 1.0 mmol) was injected into a solution of aniline (**20**) (0.931 g, 10.0 mmol), and after 20 min worked up as described in the general procedure. The solvent was evaporated to give white

crystals (**11**) which was dried to constant weight under vacuum. The results are listed in Table 3.4. The product, acetanilide (**11**), was identical by ^{1}H NMR, ^{13}C NMR, and mp with the authentic sample.

f) Piperidine (7)

1) Acetic anhydride (**19**) (0.102 g, 1.0 mmol) was injected into a solution of piperidine (**7**) (0.852 g, 10.0 mmol), and after 15 min worked up as described in the general procedure. The solvent was evaporated to give a colourless liquid which dried under vacuum. The results are listed in Table 3.5. The product, *N*-acetyl piperidine (**18**), was identical by ^{1}H NMR, ^{13}C NMR, and IR with the authentic sample.

2) Acetic anhydride (**19**) (0.102 g, 1.0 mmol) in DME (5 mL) was injected into a solution of piperidine (**7**) (0.852 g, 10.0 mmol), after 15 min worked up as above. The results are listed in Table 3.5. The product, *N*-acetylpiperidine (**18**), was identical by ^{1}H NMR, ^{13}C NMR, and IR with the authentic sample.

g) Diethylamine (24)

Acetic anhydride (**19**) (0.102 g, 1.0 mmol) was injected into a solution of diethylamine (**24**) (0.731 g, 10.0 mmol), and after 20 min worked up as described in the general procedure. The solvent was evaporated to give a colourless liquid (**16**) which was dried under vacuum. The results are

listed in Table 3.4. The product, *N*,*N*-diethylacetamide (**16**), was identical by ^{1}H NMR, ^{13}C NMR, and IR with the authentic sample.

h) 3-Methylbutylamine (23)

Acetic anhydride (**19**) (0.041 g, 0.4 mmol) was injected to a solution of 3-methylbutylamine (**23**) (0.349 g, 0 mmol) in water (400 ml), and after 20 min worked up as described in the general procedure. The solvent was evaporated to give a colourless liquid (**15**) which was dried under vacuum. The results are listed in Table 3.4. The product, *N*-3-methylbutylacetamide (**15**), was identical by ^{1}H NMR, ^{13}C NMR, and IR with the authentic sample.

i) Diisopropylamine (25)

1) Acetic anhydride (**19**) (0.102 g, 1.0 mmol) was injected into a solution of diisopropylamine (0.731 g, 10.0 mmol), and after 30 min worked up as described in the general procedure. The solvent was evaporated to give no product.

2) Acetic anhydride (**19**) (3.063 g, 30.0 mmol) was injected into a solution of diisopropylamine (2.530 g, 25.0 mmol) in water (250 mL) which had previously been adjusted to pH 9.8 at 25 ^{o}C. The solution was stirred rapidly for further 2.0 h with the pH of the solution kept constant with adding sodium hydroxide solution (2 M). The mixture was acidified to pH 2 with aqueous hydrochloric acid (6.0 M) and

extracted with dichloromethane (4 x 50 mL). The organic layer was separated and washed with saturated sodium bicarbonate (50 mL) and water (50 mL), and dried over anhydrous magnesium sulfate. No sign of any *N,N*-diisopropylacetamide (17) was seen after the solvent was removed.

pH-Production Ratio Measurement: Benzoyl Chloride with Amines

a) Piperidine (7)

(i) Benzoyl chloride (6) (0.562 g, 2.0 mmol) was injected into a solution of piperidine (7) (3.406 g, 20.0 mmol) in water (2000 mL) which had been previously adjusted to the desired pH value with aqueous sulfuric acid (6 M) or sodium hydroxide (6 M) at 25 °C. The solution was stirred rapidly for further 15 min with the pH of solution kept constant with dilute sodium hydroxide solution. The mixture was acidified to pH 2 with aqueous sulfuric acid (6 M) and extracted with dichloromethane (5 x 80 mL). The organic layer was separated and washed with saturated sodium bicarbonate (50 mL) and water (50 mL), and dried over anhydrous magnesium sulfate. The solvent was evaporated to give a colourless liquid which was dried to constant weight under vacuum. The results are listed in Table 3.6. The product, *N*-benzoylpiperidine (9) was identical by ^{1}H NMR, ^{13}C NMR, and bp with the authentic sample.

Table 3.6 The variation in yield of the amide with change in pH for the reaction of benzoyl chloride with piperidine

pH	$C_6H_5CON(CH_2)_5$ Weight (mg)	f_p
9.0[a]	188.5	0.498
10.0[a]	330.1	0.872
11.0[a]	368.2	0.973
11.5[a]	370	0.988
12.0[a]	362.2	0.957
12.5[a]	350.1	0.925
13.0[a]	311.2	0.822
13.4[a]	260.7	0.689
7.5[b]	22.1	0.058
8.0[b]	66.2	0.175
9.5[b]	280.5	0.741
10.0[b]	325.2	0.859
10.5[b]	352.0	0.930
12.0[b]	360	0.964
12.5[b]	337.0	0.890

a. Reactions were carried out by direct injecting benzoyl chloride (C_o = 0.001 M) to a solution of piperidine ($[C_5H_{10}NH]_T$ = 0.01 M) in water (2000 mL) at 25°C.

b. Reactions were carried out by injecting the benzoyl chloride (C_o = 0.001 M in 10 mL DME) to a solution of piperidine ($[C_5H_{10}NH]_T$ = 0.01 M) in H_2O (2000 mL).

(ii) Benzoyl chloride (6) (0.562 g, 2.0 mmol) in 10 mL DME was injected into a solution of piperidine (7) (3.406 g, 20.0 mmol) in water (2000 mL), and after 15 min worked up as above. The results are listed in Table 3.6. The product, *N*-benzoylpiperidine (9) was identical by ^{1}H NMR, ^{13}C NMR, and bp with the authentic sample.

b) Benzylamine (4)

(i) Benzoyl chloride (6) (0.141 g, 0.5 mmol) was injected into a solution of benzylamine (4) (0.536 g, 5.0 mmol) in water (500 mL), and after 15 min worked up as above. The results are listed in Table 3.2. The product, *N*-benzylbenzamide (8) was identical by ^{1}H NMR, ^{13}C NMR, and mp with the authentic sample.

(ii) Benzoyl chloride (6) (0.141 g, 0.5 mmol) in 10 mL DME was injected into a solution of benzylamine (4) (0.536 g, 5.0 mmol) in water (500 mL), and after 15 min worked up as above. The results are listed in Table 3.2. The product, *N*-benzylbenzamide (8) was identical by ^{1}H NMR, ^{13}C NMR, and mp with the authentic sample.

Recovery of Acetamides on Extraction from Water

a) General Procedure

A weighed amount of the acetamide was added to water (1000 mL) at pH 9 at room temperature. The mixture was stirred for 0.5 h and acidified to pH 2 with aqueous hydrochloric acid (6 M), and extracted with dichloromethane

(5 x 70 mL). The extract was washed with saturated sodium bicarbonate (50 mL) and water (50 mL), and dried over anhydrous magnesium sulfate. The solvent was evaporated to recover the acetamide which was dried to constant weight under vacuum. The product was identical by ^{1}H NMR, ^{13}C NMR, mp, or bp and IR with the authentic sample.

b) *N,N*-Diisopropylacetamide (17)

N,N-Diisopropylacetamide (**17**) (0.143 g, 1.0 mmol) was added to water (1000 mL), and worked up as described in the general procedure. The solvent was evaporated to give a colourless liquid (0.142 g, 0.99 mmol, 99% yield). The product, *N,N*-diisopropylacetamide (**17**), was identical by ^{1}H NMR, ^{13}C NMR, and IR with the authentic sample.

c) *N,N*-Diethylacetamide (16)

A weighed amount of *N,N*-diethylacetamide (**16**) in the range 49.2 mg to 117.4 mg was added to water (1000 mL), and worked up as described in the general procedure. The results are listed in Table 3.7. The product, *N,N*-diethylacetamide (**16**), was identical by ^{1}H NMR and ^{13}C NMR with the authentic sample. A plot of the weight of recovered *N,N*-diethylacetamide (**16**) (y) vs. initially added the amide (x) gave a straight line corresponding to:

$$y = 0.940x - 0.0027$$

d) *N*-*t*-Butylacetamide (13)

A weighed amount of *N*-*t*-butylacetamide (**13**) in the range 21.3 mg to 86 mg was added to water (1000 mL), and worked up as described in the general procedure. The results are listed in Table 3.7. The product, *N*-*t*-butylacetamide (**13**) was identical by ^{1}H NMR, ^{13}C NMR, and mp with the authentic sample. A plot of the weight of recovered *N*-*t*-butylacetamide (**13**) (*y*) vs. initially added the amide (*x*) gave a straight line (see Figure 3.12) corresponding to:

$$y = 0.886x + 0.0004$$

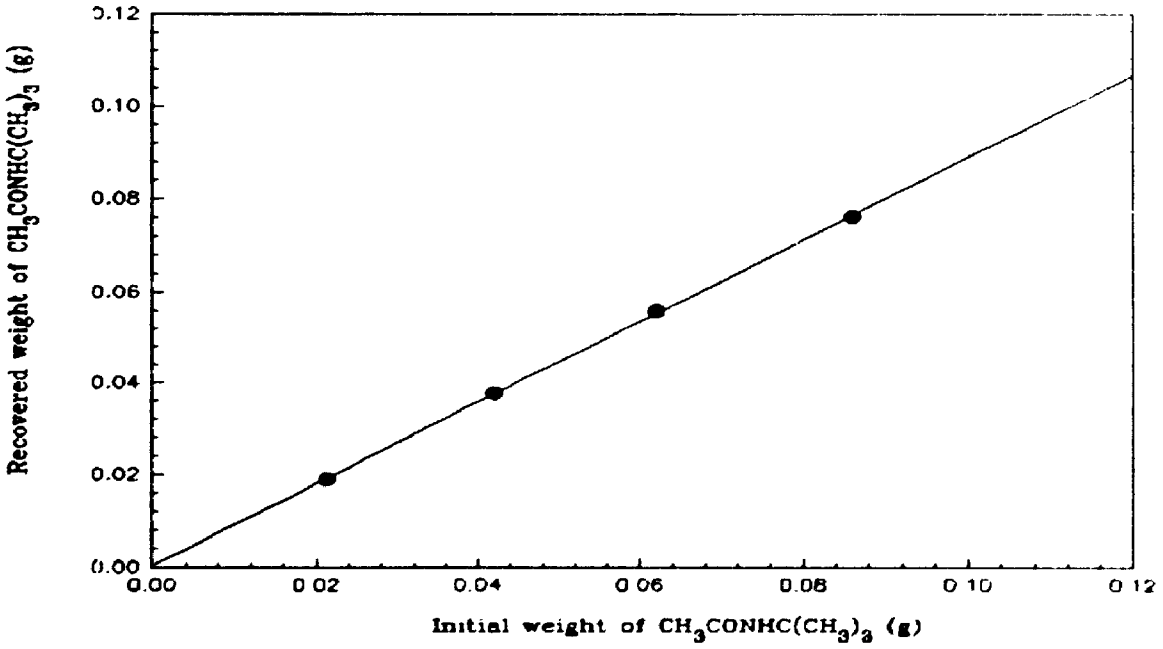


Figure 3.12 Recovery of *N*-*t*-butylacetamide by extraction with dichloromethane from aqueous solution of *N*-*t*-butylacetamide (**13**) at 25 °C.

Table 3.7 The control experiment of acetamides in water[a]

Acetamide	Initial added (mg)	Recovered (mg)
$CH_3CONHC(CH_3)_3$	86.0	76.2
	62.0	55.9
	42.0	37.7
	21.3	19.0
$CH_3CON(C_2H_5)_2$	117.4	107.4
	89.6	81.8
	73.8	67.2
	49.2	43.2
$CH_3CON(CH_2)_5$	124.0	113.5
	84.0	76.0
	47.5	43.0
	13.0	10.0

a. The acetamides were added to water (1000 mL) and extracted with dichloromethane (100 mL x 5) at 25 °C.

e) *N*-Acetylpiperidine (18)

A certain amount of *N*-acetylpiperidine (**18**) in the range 13 mg to 124 mg was added to water (1000 mL), and worked up as described in the general procedure. The results are listed in Table 3.7. The product, *N*-acetylpiperidine (**18**) was identical by ^1H NMR, ^{13}C NMR, and IR with the authentic sample.

A plot of the weight of recovered *N*-acetylpiperidine (*y*) vs. initially added the amide (*x*) gave a straight line ccrresponding to:

$$y = 0.93x - 0.0018$$

f) *N*-Cyclohexylacetamide (12)

The *N*-cyclohexylacetamide (**12**) (0.141 g, 1.0 mmol) was added into water (1000 mL), and worked up as described in the general procedure. The solvent was removed to give a white solid (0.140 g, 99% yield). The product, *N*-cyclohexylacetamide (**12**) was identical by ^{1}H NMR, ^{13}C NMR, and mp with the authentic sample.

g) Acetanilide (11)

The acetanilide (**11**) (0.135 g, 1.0 mmol) was added into water (1000 mL), and worked up as described in the general procedure. The solvent was removed to give a white solid (0.134 g, 99% yield). The product, acetanilide (**11**) was identical by ^{1}H NMR, ^{13}C NMR, and mp with the authentic sample.

h) *N*-Benzylacetamide (10)

The *N*-benzylacetamide (**11**) (0.149 g, 1.0 mmol) was added into water (1000 mL), and worked up as described in the general procedure. The solvent was removed to give a

white solid (0.148 g, 99.4% yield). The product, *N*-benzyl acetamide (**10**) was identical by ^{1}H NMR, ^{13}C NMR, and mp with the authentic sample.

Variation of Yield with pH under Preparative Conditions

1) *N*-Benzoylpiperidine (9)

Benzoyl chloride (**6**) (0.703 g, 5.0 mmol or 0.773 g, 5.5 mmol) was added to piperidine (**7**) (0.426 g, 5.00 mmol) in water (500 mL) which had been previously adjusted to pH 11.4 with sodium hydroxide at room temperature. The mixture was stirred for 15 or 30 min with the pH of the solution kept constant with aqueous sodium hydroxide (1 M). The mixture was acidified to pH 2 with aqueous hydrochloric acid (6 M) and extracted with dichloromethane (3 x 150 mL). The organic layer was separated and washed with saturated sodium bicarbonate (30 mL) and water (30 mL), and dried with anhydrous magnesium sulfate. The solvent was evaporated, and further dried under vacuum to give a colourless oily liquid (**9**). The results are listed in Table 3.9. The product, *N*-benzoylpiperidine (**9**), was identical by ^{1}H NMR, ^{13}C NMR, and IR with the authentic sample.

2) *N*-Benzylbenzamide (8)

Benzoyl chloride (**6**) (0.010 M to 0.012 M) in DME (2.5 mL) was added dropwise to a solution of benzylamine (**4**) (0.536 g, 0.01 M) in water (500 mL) which had been previously adjusted to pH 7.5, 10.45 or 13.0 with aqueous

hydrochloric acid or sodium hydroxide (6 M). The mixture was stirred for 30 min at room temperature with the pH of solution kept constant with aqueous sodium hydroxide, and worked up as above to give a white solid product (**8**). The results are listed in Table 3.8. The product, *N*-benzyl benzamide (**8**), was identical by with ^{1}H NMR, ^{13}C NMR, ir, and mp with the authentic sample.

Table 3.8 The variation of preparative yield of reaction of benzoyl chloride with benzylamine[a] at different pH

pH	C_6H_5COCl (M)	$C_6H_5CONHCH_2C_6H_5$ Weight (g)	$C_6H_5CONHCH_2C_6H_5$ Yield (%)
10.4	0.010	0.9138	86.5
10.4	0.011	1.0240	96.9
10.4	0.012	1.0403	98.5
13.0	0.010	0.4115	39.0
13.0	0.012	0.5090	48.2
7.5	0.010	0.5565	52.7
7.5	0.012	0.5790	54.8

a. These reactions are carried out in $[C_6H_5CH_2NH_2]$, C_o = 0.010 M, in water (500 mL) at 25 °C for 30 min.

Table 3.9 The variation of preparative yield of reaction of benzoyl chloride with piperidine[a] with different reaction times

Time (min)	C_6H_5COCl (M)	$C_6H_5CONC_5H_{10}$ Weight (g)	$C_6H_5CONC_5H_{10}$ Yield (%)
15	0.010	0.9235	97.6
30	0.010	0.9260	97.9
30	0.011	0.9395	99.3

a. These reactions are carried out in $[(CH_2)_5NH]$, C_o = 0.010 M, at pH 11.4 in water (500 mL) at 25 °C.

Table 3.10 Variation of yield with pH and concentrations under preparative conditions of the reaction of acetic anhydride with cyclohexylamine[a]

pH	$[Ac_2O]$ (M)	$CH_3CONHC_6H_{11}$ Weight (g)	$CH_3CONHC_6H_{11}$ yield (%)
9.5	1.0	0.663	93.9
9.5	1.1	0.678	96.0
9.5	1.2	0.707	99.9
6.5	1.2	0.543	76.9
12.5	1.2	0.552	78.2

a. Reactions were carried out in $[C_6H_{11}NH_2]$, C_o = 1.0 M, in water (50 mL) at 25 °C.

3) *N*-Cyclohexylacetamide (12)

Acetic anhydride (**19**) (0.613 g, 6.0 mmol or 0.510 g, 5.0 mmol) was added slowly to a solution of cyclohexylamine (**21**) (0.496 g, 5.0 mmol) in water (50 mL) which had been previously adjusted to pH 6.5, 9.5, or 12.5 with aqueous hydrochloric acid or sodium hydroxide at room temperature. The mixture was stirred for 30 min at room temperature with the pH of solution kept constant with aqueous sodium hydroxide, and worked up as above to give a white solid product (**12**). The results are listed in Table 3.10. The product, *N*-cyclohexylacetamide (**12**), was identical by with ^{1}H NMR, ^{13}C NMR, ir, and mp with the authentic sample.

Kinetic Determinations of Acetic Anhydride with Amines

a) General Procedure

The kinetics of nucleophilic substitution reactions of acetic anhydride (**19**) with amines were determined using the pH-stat technique. The general procedure was as follows.

Acetic anhydride (**19**) (0.001 M) was injected (using a 10 μL syringe) into a solution of amine (0.01 M) in 50 mL of 0.1 M aqueous potassium chloride which had been previously adjusted to the desired pH value with aqueous hydrochloric acid (1 M) or sodium hydroxide (1 M) at 25 ^{o}C. The solution was stirred rapidly and the pH of solution kept constant with aqueous sodium hydroxide (0.1 M). The rate of the nucleophilic reaction was then monitored by recording the volume (mL) of titrant (sodium hydroxide) delivered with

time (s).

Plots of $-\ln(V_\infty - V_t)$ versus time were constructed from the volume of sodium hydroxide titrant delivered. Examples are shown in Figure 3.13; the straight lines were drawn from parameters obtained by method of least squares. The pseudo-first-order rate constants were then attained from the slopes of these lines, and the results are listed in Table 3.11.

b) Benzylamine (4)

Acetic anhydride (**19**) (0.010 g, 9.5 μL) was injected into a solution of benzylamine (**4**) (0.054 g, 0.5 mmol) in 50 mL of aqueous potassium chloride (0.1 M), and performed as described in the general procedure. From the plot of $-\ln(V_\infty - V_t)$ *vs.* time (s) the pseudo-first-order rate constant was obtained (see Table 3.11).

c) *t*-Butylamine (22)

Acetic anhydride (**19**) (0.005 g, 8 μL) was injected into a solution of *t*-butylamine (**22**) (0.037 g, 0.5 mmol) in 50 mL of aqueous potassium chloride (0.1 M), and performed as described in the general procedure. From the plot of $-\ln(V_\infty - V_t)$ *vs.* time (s) (see Figure 3.13) the pseudo-first-order rate constant was obtained (see Table 3.11).

Table 3.11 Pseudo-first-order rate constants for the reactions of acetic anhydride with amines[a]

Amines	pH	k_{obs} (s^{-1}) (x 10^{-3})	k_N ($M^{-1}s^{-1}$)
$C_6H_5CH_2NH_2$	4.0	2.51[b]	2.48×10^3
	4.5	2.83[b]	
	5.0	3.35[b]	
	5.5	4.35[b]	
	6.2	10.14[b]	
	6.7	24.72[b]	
	3.5	2.75[c]	
	4.0	2.87[c]	
	4.5	3.25[c]	
	5.0	3.95[c]	
	5.6	7.55[c]	
	6.1	17.01[c]	
$C_6H_5NH_2$	2.4	3.86	17.9
	2.7	4.94	
	3.0	7.19	
	3.2	10.11	
	3.4	14.12	
	3.6	19.32	
	3.8	26.31	
$(CH_3)_2CHCH_2CH_2NH_2$	5.3	3.35	10.4×10^3
	5.7	4.09	
	6.0	5.27	
	6.2	6.78	

Table 3.11 Continued

Pseudo-first-order rate constants for the reaction of acetic anhydride with amines in water at 25 °C

Amines	pH	k_{obs} (s^{-1}) (x 10^{-3})	k_N (M^{-1} s^{-1})
$C_6H_{11}NH_2$[d]	5.0	2.95	2.25×10^3
	6.0	3.37	
	6.4	4.09	
	6.7	5.40	
	7.0	8.13	
	7.2	11.67	
	7.4	15.21	
$(CH_3)_3CNH_2$	6.3	2.85	68.1
	7.0	3.18	
	7.5	3.72	
	7.9	5.02	
	8.3	8.07	
	8.7	16.90	
	9.0	32.28	
$(C_2H_5)_2NH$	6.0	3.11	1.36×10^3
	6.5	3.57	
	7.0	4.42	
	7.3	5.94	
	7.7	10.52	
	8.0	17.30	

Table 3.11 Continued

Pseudo-first-order rate constants for tne reaction of acetic anhydride with amines in water at 25 °C

Amines	pH	k_{obs} (s^{-1}) ($\times 10^{-3}$)	k_N (M^{-1} s^{-1})
$(CH_2)_5NH$[e]	5.0	3.24	51.73×10^3
	5.5	3.98	
	6.0	5.89	
	6.2	7.76	
	6.5	12.88	
	7.0	33.88	
$[(CH_3)_2CH]_2NH$	6.0	2.87	31.0
	7.0	2.94	
	7.5	3.20	
	8.0	4.15	
	8.5	6.59	
	9.0	14.39	

a. Kinetic runs were carried out in $[Ac_2O]_T$ = 0.001 M, [KCl] = 0.1 M, and $[amine]_T$ = 0.01 M in water (50 mL) at 25 °C, where $[amine]_T$ = [amine] + [aminomium ion]

b. Kinetic runs reactions were carried out in $[Ac_2O]_T = 5.0 \times 10^{-4}$ M, $[C_6H_5CH_2NH_2]_T = 4.0 \times 10^{-3}$ M in water at 25 °C.

c. Kinetic runs were carried out in $[Ac_2O] = 2.0 \times 10^{-3}$ M, $[C_6H_5CH_2NH_2]_T = 1.0 \times 10^{-2}$ M in water at 25 °C.

d. Cyclohexylamine.

e. Piperidine.

Table 3.12 Pseudo-first-order rate constants for the hydrolysis of acetic anhydride in water and in sodium acetate at 25 °C

pH	k_{obs} (s^{-1}) ($\times 10^{-3}$)
6.6	3.05[a]
7.4	3.07[a]
8.1	4.03[a]
8.6	6.82[a]
7.0	2.94[b]
7.7	3.30[b]
9.1	15.35[b]

a. Kinetic runs were carried out in $[Ac_2O]_T$ = 0.002 M, water at 25.0 °C

b. Kinetic runs were carried out in $[Ac_2O]_T$ = 0.002 M and $[AcONa]_T$ = 0.002 M in water at 25 °C.

d) Piperidine (7)

Preliminary measurements of the rate of reaction of acetic anhydride with piperidine (7) which was purified by distillation from calcium hydride gave inconsistent results. The UV spectrum of the piperidine showed absorption at 257 nm suggesting contamination with small ammount of pyridine. The piperidine was purified through ethoxycarbonylpiperidine as follows.

The mixture of piperidine (17.22 g, 0.202 mol) and ethyl chloroformate (26.34 g, 0.243 mol) in dichloromethane (200 mL) was stirred for 30 min at room temperature. Water (50 mL) was added and the two layers were separated. The organic layer was washed with hydrochloric acid (0.5 M, 30 mL), saturated sodium bicarbonate (30 mL), and water (30 mL). The organic layer was dried and the solvent was removed to give a colourless liquid (27.75 g, 0.177 mol, 87.6% yield). The pure ethoxycarbonylpiperidine was obtained by distillation under reduced pressure, bp 57 °C (1 Torr), [lit.[39] bp 56 °C (1 Torr)]; IR (neat) ν_{max}: 2982 (m), 2936 (s), 2857 (s), 1701 (s), 1431 (s), 1264 (s), 1235 (s), 1171 (s), 1149 (s), 1096 (s), 1032 (s), 855 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.13 (t, 3H), 1.44 (m, 6H), 3.32 (t, 4H), 4.02 (q, 2H); ^{13}C NMR ($CDCl_3$) δ: 15.5, 25.2, 26.5, 45.5, 61.8, 156.3.

The ethoxycarbonylpiperidine was converted back to piperidine (7) by refluxing with aqueous potassium hydroxide. The mixture of ethoxycarbonylpiperidine (15.0 g, 95.4 mmol) and potassium hydroxide (15.0 g, 267 mmol) in a mixed solvent of water:DME (150 mL, 1:1, V/V) was refluxed for 2 h. The mixture was extracted with dichloromethane (4 x 50 mL). The organic layer was dried, and the solvent was removed by distillation to give a colourless liquid (7) (6.86 g, 80.6 mmol, 85% yield) which gave no sign of pyridine (checked by UV). This preparation of piperidine was used in the kinetic measurements described below.

Acetic anhydride (19) (0.005 g, 8 μL) was injected to a solution of piperidine (7) (0.043 g, 0.5 mmol) in 50 mL of aqueous potassium chloride (0.1 M) which had been previously adjusted to desired pH at 25.0°C, and performed as described in the general procedure. From the plot of $-\ln(V_\infty - V_t)$ *vs.* time (s) the pseudo-first-order rate constant was obtained (see Table 3.11).

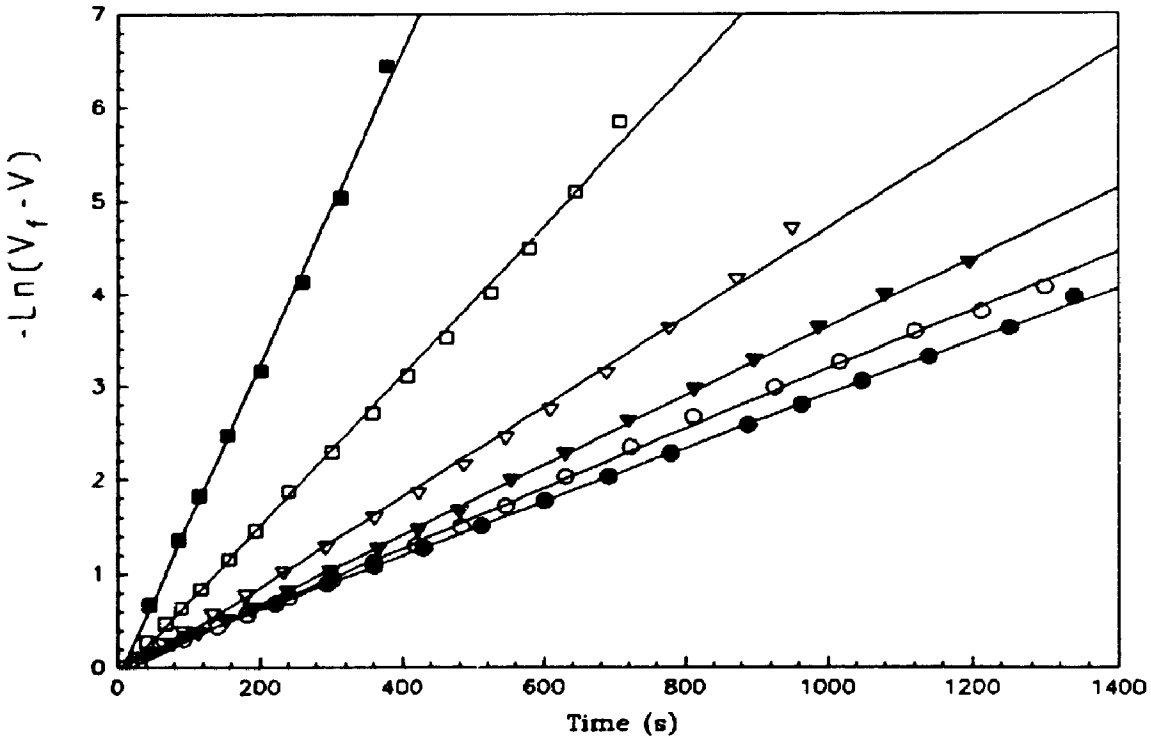


Figure 3.13 The $-\ln(V_\infty - V_t)$ *vs.* time profile for kinetics of acetic anhydride (C_o 0.001 M) with *t*-butylamine (C_o 0.01 M) in water (50 mL) in different pH values at 25 °C. (a) filled squares, pH 8.7, (b) open squares, pH 8.3, (c) open triangles, pH 7.9, (d) filled triangles, pH 7.5, (e) open circles, pH 7.0, and (f) filled circles, pH 6.3.

e) Aniline (20)

Acetic anhydride (**19**) (0.005 g, 8 μL) was injected into a solution of aniline (**20**) (0.047 g, 0.5 mmol) in 50 mL of aqueous potassium chloride (0.1 M), and performed as described in the general procedure. From the plot of $-\ln(V_\infty - V_t)$ *vs.* time (s) the pseudo-first-order rate constant was obtained (see Table 3.11).

f) Cyclohexylamine (21)

Acetic anhydride (**19**) (0.005 g, 8 μL) was injected into a solution of cyclohexylamine (**21**) (0.050 g, 0.5 mmol) in 50 mL of aqueous potassium chloride (0.1 M), and performed as described in the general procedure. From the plot of $-\ln(V_\infty - V_t)$ *vs.* time (s) the pseudo-first-order rate constant was obtained (see Table 3.11).

g) 3-Methylbutylamine (23)

Acetic anhydride (**19**) (0.005 g, 8 μL) was injected into a solution of 3-methylbutylamine (**23**) (0.044 g, 0.5 mmol) in 50 mL of aqueous potassium chloride (0.1 M), and performed as described in the general procedure. From the plot of $-\ln(V_\infty - V_t)$ *vs.* time (s) the pseudo-first-order rate constant was obtained (see Table 3.11).

h) Diethylamine (24)

Acetic anhydride (**19**) (0.005 g, 8 μL) was injected into a solution of diethylamine (**24**) (0.037 g, 0.5 mmol) in 50 mL

of aqueous potassium chloride (0.1 M), and performed as described in the general procedure. From the plot of $-\ln(V_\infty - V_t)$ *vs.* time (s) the pseudo-first-order rate constant was obtained (see Table 3.11).

i) Diisopropylamine (25)

Acetic anhydride (**19**) (0.005 g, 8 μL) was injected into a solution of diisopropylamine (**25**) (0.051 g, 0.5 mmol) in 50 mL of aqueous potassium chloride (0.1 M), and performed as described in the general procedure. From the plot of $-\ln(V_\infty - V_t)$ *vs.* time (s) the pseudo-first-order rate constant was obtained (see Table 3.11).

j) Sodium acetate

Acetic anhydride (**19**) (0.010 g, 9.3 μL) was injected into a solution of sodium acetate (0.008 g, 0.1 mmol) in 50 mL water, and performed as described in the general procedure. From the plot of $-\ln(V_\infty - V_t)$ *vs.* time (s) the pseudo-first-order rate constant was obtained (see Table 3.12).

k) water

Acetic anhydride (**19**) (0.010 g, 9.6 μL) was injected into water (50 mL), and performed as described in the general procedure. From the plot of $-\ln(V_\infty - V_t)$ *vs.* time (s) the pseudo-first-order rate constant was obtained (see Table 3.12).

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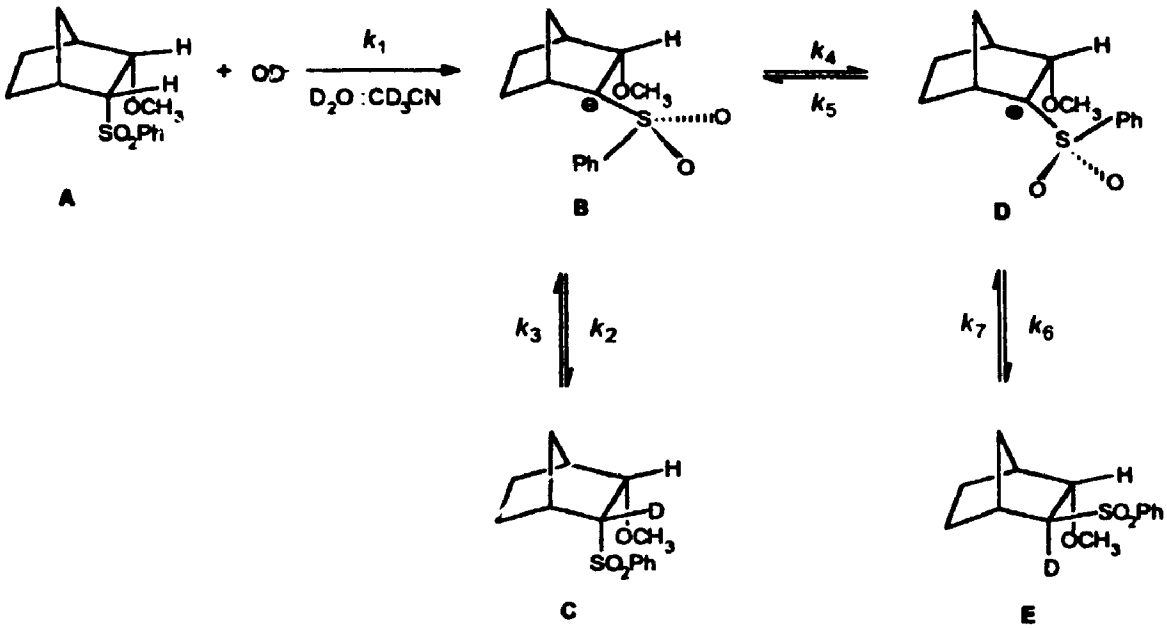
Appendix A



$$d[A]/dt = -k_1[A]$$

$$d[B]/dt = k_1[A] + k_3[C] + k_5[D] - (k_2 + k_4)[B]$$

$$d[C]/dt = k_2[B] - k_3[C]$$

$$d[D]/dt = k_4[B] + k_7[E] - (k_5 + k_6)[D]$$

$$d[E]/dt = k_6[D] - k_7[E]$$

$\because d[B]/dt = 0$

$$\therefore [B] = \frac{k_1[A] + k_3[C] + k_5[D]}{k_2 + k_4}$$

$\because d[D]/dt = 0$

$$\therefore [D] = \frac{k_4[B] + k_7[E]}{k_5 + k_6}$$

$$[D] = \frac{k_7[E] + k_4(k_1[A] + k_3[C])/(k_2 + k_4)}{k_5 + k_6 - k_5/(k_2 + k_4)}$$

$$[B] = \frac{k_1[A] + k_3[C] + \dfrac{k_5(k_7[E]+k_4(k_1[A]+k_3[C]))/(k_2+k_4))}{k_5 + k_6 - k_5/(k_2 + k_4)}}{k_2 + k_4}$$

For the inversion:

$$V_{inv} = k_4[B] - k_5[D]$$

$$\because \quad k_4[B] > k_5[D]$$

$$\therefore \quad V_{inv} \approx k_4[B]$$

$$= \frac{k_4(k_1[A] + k_3[C])}{k_2 + k_4}$$

$$\because \quad k_3[C] > k_1[A]$$

$$\therefore \quad V_{inv} = \frac{k_4 k_1[A]}{k_2 + k_4}$$

$$k_{inv} = \frac{k_1 k_4}{k_2 + k_4}$$

The program for the simulation

```
10   Print "Simulation of a reaction"
20   Input "Values of k1, k2 are"; k1, k2
30   Input "Values of k3, k4 are"; k3, k4
40   Input "Values of k5, k6 are"; k5, k6
50   Input "Value of k7 is"; k7
60   Input "Value of A0 is"; A0
70   Input "Step size for DT is"; T1
80   Input "Total simulation time is"; Tmax
```

```
90   L = INT(Tmax/T1)
100  Input "Results to be printed after how many time
     steps"; TSTEP
110  Print
120  Print
130  Print TAB(10); "Time"; TAB(35); "Relative
     Concentrations"
140  Print TAB(15); "[A]"; TAB(25); "[B]"; TAB(35); "[C]";
     TAB(45); "[D]"; TAB(55); "[E]"
150  A = A0
160  B = 0
170  C = 0
180  D = 0
190  E = 0
200  T = 0
210  Print
220  FOR K = 0 TO L
230  A1 = -k1 * A
240  B1 = (k1 * A + k3 * C + (k5 * k7 * E + k4 * k1 * k6 * A
          /(k2 + k4) + k4 * k3 * k5 * C / (k2 + k4)) / (k6 + k6))
          /(k2 + k4)
250  C1 = k2 * B1 - k3 * C
260  D1 = (k7 * E + k4 * k1 * A / (k2 + k4) + k4 * k3 * C /
          (k2 + k4)) / (k5 + k6))
270  E1 = k6 * D1 - k7 * E
280  A = A + A1 * T1
290  B = B + B1 * T1
300  C = C + C1 * T1
310  D = D + D1 * T1
320  E = E + E1 * T1
330  IF INT(K / TSTEP) = K / TSTEP THEN 280
340  GOTO 360
350  PRINT T; TAB(15); A; TAB(25); B; TAB(35); C; TAB(45);
     D; TAB(55); E
360  T = T + T1
370  NEXT K
380  END
```