AMBIDENT PROPERTIES OF PHOSPHORAMIDATES AND SULPHONAMIDES

A Thesis submitted by

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ABSTRACT

The nucleophilic chemistry of amides, phosphoramidates and sulphonamides is reviewed. Particular reference is paid to the site of substitution and its variation with reaction conditions.

The phosphorimidate-phosphoramidate rearrangement is examined. The nature of electrophilic catalysis, particularly by alkyl halides is studied and the mechanism of the reaction is discussed. The relevance of this mechanism to the nucleophilic chemistry of phosphoramidates is outlined.

The behaviour of phosphoramidates in aqueous H_2SO_4, oleum and trifluoroacetic acid is briefly examined and the site of protonation in these media discussed.

The acylation of phosphoramidates by acyl halides and anhydrides is reported and the effect of base and electrophilic catalysis on the reactions is examined. The usual product of these reactions is the N-acylphosphoramidate although tertiary phosphoramidates undergo P-N bond cleavage. Factors affecting the reaction rates are studied and possible mechanisms for the reactions are discussed.

The sulphonimidate-sulphonamide rearrangement is described. Electrophilic catalysis is examined and the reaction mechanism is discussed in relation to its relevance to the nucleophilic properties of sulphonamides. The alkylation and arylation of sulphonamides is also described and the nature of the products discussed in terms of the reaction profile for the sulphonimidate-sulphonamide rearrangement.

The alkylation of [1,3]-amidic systems is discussed. Perturbational and transition-state structure approaches are used to describe the alkylation of carboxamides. Modified neglect of diatomic overlap (MNDO) SCF MO calculations are reported to test both theories. The relevance of these results to phosphoramidates and sulphonamides is discussed.

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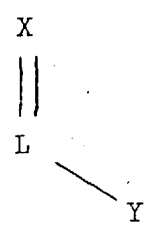
CHAPTER 1

INTRODUCTION: NUCLEOPHILIC REACTIVITY OF AMIDIC COMPOUNDS

1.1. AMBIDENT NUCLEOPHILICITY

A molecule which possesses two different sites which display nucleophilic reactivity may be described as ambident[1]. Of most interest are those in which the two nucleophilic sites interact with (or perturb) each other. The most common type of interaction involves tautomerism or resonance *via* one or more double-bonds. This class of nucleophile includes [1,3]- (1) and [1,5]- (2) ambident systems. Any interaction between the



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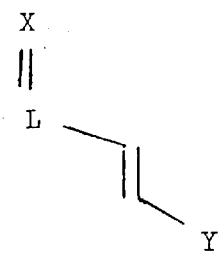


(2)

nucleophilic sites, X and Y, of these systems will change their relative reactivity and, obviously, the site of reaction. Compounds of structure (1) and (2) are numerous[2] and include the following anions: enolate and phenolate (1,X = O, L = Y = C), triazenido (1,X = L = Y = N), amide (1,X = O, L = C, Y = N), thioamide (1,X = S, L = C, Y = N), sulphonamide (1,X = O, L = S, Y = N) and phosphoramidate (1,X = O, L = P, Y = N); as well as the neutral phenol, triazene, enamine (1,X = L = C, Y = N), amide, thioamide, 4-pyridone (2,Y = N, L = C, X = O), sulphonamide and phosphoramidate moeties *etc*. Clearly, the widespread nature of such compounds necessitates an understanding of such interaction and its effect on product formation is of prime synthetic importance[3].

Kornblum[1] was the first to advance a theory explaining ambident reactivity. Results obtained from the alkylation of metal nitrites led

him to conclude that substitution in an S_N1 type reaction occurs at the most electronegative atom (to give alkyl nitrites), whereas reactions with strong S_N2 character proceed at the site of lower reactivity (to give nitroalkanes). He was able to generalise his findings to the alkylation of cyanide, thiocyanide, cyanate, amide, thioamide, diazotate and phenolate anions. However, it does only apply to anionic species, and cannot, without difficulty, be applied to neutral molecules. Even so, it only partly explains the results obtained for enolate and phenolate[4] anions and fails for those of oximes and nitroalkanes[2].

Pearson[5], in applying the Hard-Soft Acid-Base (HSAB) principle[6] to enolate anions, effectively reworded Kornblum's argument. Thus a 'hard' electrophile (e.g. alkyl sulphates) will react with the 'hardest' nucleophilic site, in this case the oxygen atom (thus restating Kornblum's S_N1-electronegativity rule). Conversely, 'soft' electrophiles (e.g. alkyl iodides) react at the 'soft' nucleophilic carbon atom.

A common failing of both Kornblum's and Pearson's rationalisations is that they assume that the most electronegative element will possess the greatest negative charge in the molecule. Any redistribution of charge, particularly via the σ-bond framework, is ignored. Thus the 'hardest' atom is usually the most electronegative. The rationalisation is successful for enols but is much less so for amides where the difference between the reactivity of oxygen and nitrogen is small.

A more comprehensive approach to ambident nucleophilicity is found in the perturbation treatment of chemical reactivity,[7,8] which considers the energy change during a chemical reaction to comprise mainly two terms: an electrostatic attraction and an orbital component.

In reactions where the highest occupied molecular orbital (HOMO) of the nucleophile and the lowest unoccupied molecular orbital (LUMO) of the electrophile are almost degenerate, then the orbital term is dominant and the reaction is said to be orbital controlled. The reactive site, X or Y, is then that atom which has the greatest electron density associated with

it in the HOMO. However, when a large difference exists between the HOMO of the nucleophile and the LUMO of the electrophile, the orbital term becomes insignificant and the charge term, which favours interaction between the atoms carrying the highest opposite charge densities, dominates the reaction. In this way the ambident reactivity of thiocyanate anion can be explained in terms of orbital control favouring S-substitution and charge control favouring N-substitution[9]. Reaction of enolate anions with methyl iodide (i.e. orbital control) gives C-substitution whereas with methoxonium ion substitution occurs on oxygen[7].

Although perturbation theory has found wide application in organic chemistry,[10,11] and, since it considers orbital energies, orbital populations and electron densities is a more exact treatment than either Kornblum's arguments or the HSAB principle (though it does give them a theoretical grounding), it suffers one major drawback. It assumes[7], as a general hypothesis, that the initial perturbation determines the course of a reaction i.e. the transition state is reactant-like. Thus, reactions for which this assumption does not apply are less successfully described by the perturbation theory and its generality is consequently limited.

General theories, therefore, seem prone to failure where factors controlling the stability of the transition state are ignored. Gompper[2] has mentioned that [1,3]-ambident systems (e.g. 1) will always react in such a way as to maintain maximum resonance in the transition state.

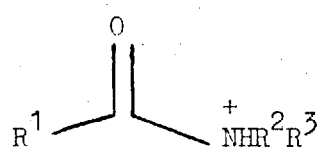
Amides, phosphoramidates and sulphonamides and their anions all possess the ability to react as [1,3]-ambident amidic compounds. It is the purpose of this report to review and explore those properties.

1.2. NUCLEOPHILIC PROPERTIES OF AMIDES

Amides and their anions have long been considered to be ambident nucleophiles,[1,2] reacting at both the oxygen and nitrogen atoms. Examples of reactions producing mixed O- and N- substituted products are well known. However, recent evidence, presented below, indicates conclusively that neutral amides react preferentially via the oxygen atom.

1.2.1. PROTONATION

The site of protonation of amides has been the subject of much debate[12]. Whereas some authors favour formation of the N-conjugate acid (3)[12,13] the issue is now largely settled in favour of O- conjugate



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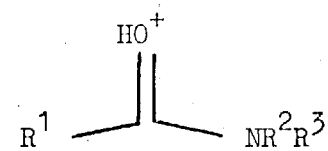
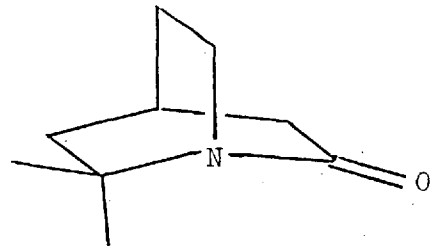


(4)

acid (4) formation[14]. The best evidence comes from ^{1}H [15] and ^{13}C [16] n.m.r. studies of either unlabelled or ^{15}N labelled compounds where it has been shown unambiguously that O- protonation occurs at all acidities. Significantly, amide salts can be prepared with anhydrous HF/BF_3 [17] and, on the basis of n.m.r. and i.r. data, are assigned the structure (4). Since oxygen protonation is considered to arise from resonance stabilisation of (4),[14] it is of interest to note that the quinuclidone (5), where delocalisation is severely restricted, has an abnormally high pKa value and is hydrolysed much more readily than normal amides.



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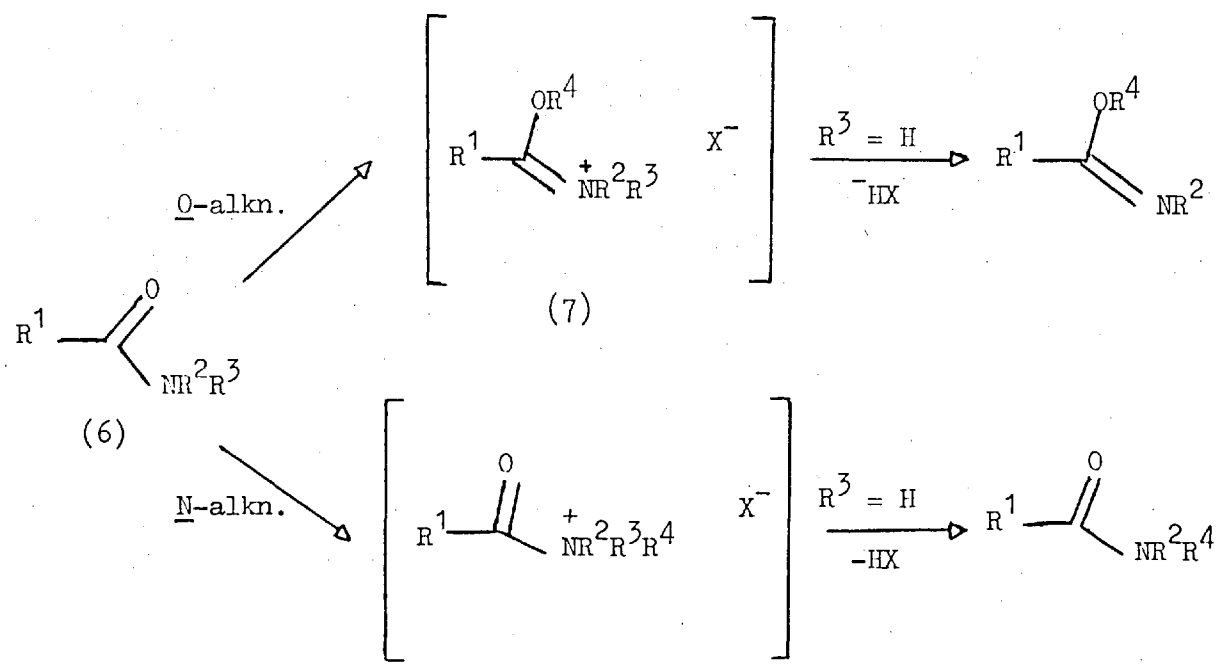
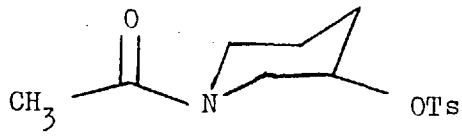
1.2.2. ALKYLATION

The alkylation of neutral amides by reactive alkylating agents *e.g.* trialkyloxonium fluoroborate[18], dialkyl sulphates[19], alkylfluorosulphonates[20] or trityl chloride[21] proceeds at low temperature to give products which only arise from O- alkylation (Scheme 1). The intermediate (7) can be isolated in most cases, especially if a tertiary amide is used. Carbamates (6, R^1 = alkoxy) have been shown to react preferentially with methyl fluorosulphonate at the O- atom[22] but due to steric interactions in the compounds



SCHEME 1. ALKYLATION OF AMIDES

studied N-alkylation is thermodynamically favoured. Only one example indicating preferential reactivity of the nitrogen atom is available[23]. Acetolysis of N-acetyl-3-tosylpiperidinol (8) proceeds exclusively via the N-substituted species (9).



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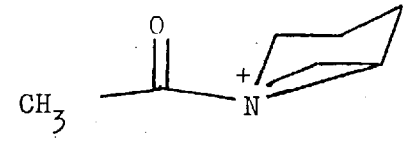


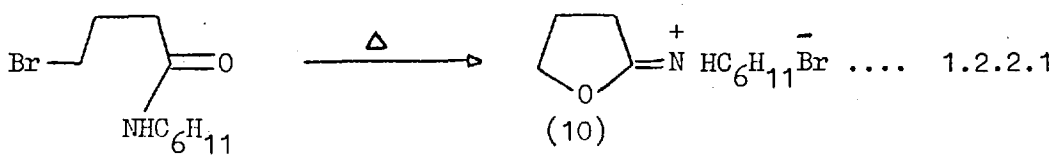
(9)

Alkylation with less reactive reagents, e.g. alkyl iodides, requires high reaction temperatures and often a metal catalyst. Under these conditions a mixture of both O- and N- alkylated isomers (Scheme 1.) is usually obtained[24]. Further, the ratio of O- to N- substituted products varied with the structure of the alkyl halide: N-substitution is favoured by alkyl halides forming relatively stable carbonium ions. Attempts to discuss these findings in terms of Kornblum's hypothesis[1] have been criticised,[15,24,25] since it requires the most S_N1-like transition state to be associated with the most electronegative atom i.e. oxygen, whereas these results associate it with the nitrogen atom.

Other evidence points to the high temperatures involved in these reactions as determining the O- to N- product ratio. Thus trityl chloride reacted with formamide at 20°C to give O- substitution, whereas at 110°C N-triphenylmethylformamide was produced[21]. Similarly, reaction of N-phenylformamide with ethyl iodide in the presence of silver oxide (a catalyst which promotes alkylation by alkyl halides) at 40°C gave only the O-ethyl imidate as the sole product whereas at 100°C a mixture of O- and N- alkylated products were obtained[26].

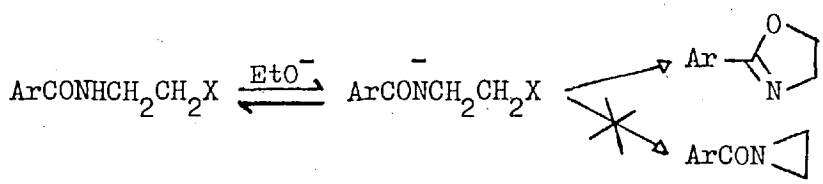
Finally, intramolecular cyclisation of 4-bromo-N-cyclohexylbutyramide under neutral conditions produced ONLY the tetrahydrofuran deriv-

ative (10)[27] (Equation 1.2.2.1.).



.... 1.2.2.1.

Amide anions might be expected to exhibit ambident properties. In practice, alkylation of an amide anion produces only the N-alkyl product except in intramolecular reactions where ring size becomes important (Equation 1.2.2.2.).



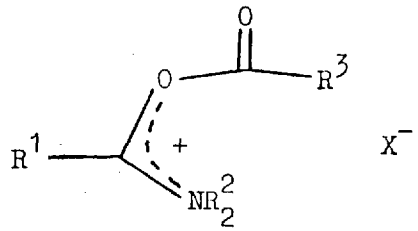
.... 1.2.2.2.

Reaction via the amide anion is the most synthetically useful method for N-alkylation of an amide.

Preference for N-alkylation can be reversed by addition of silver salts to the reaction medium. This effect also depends on solvent and O-alkylation predominates in heterogeneous reactions only[28]. Under these conditions Ag^+ is more likely to form a covalent bond with the amide anion, thus reducing its anionic nature, and the reactions therefore resemble those of the neutral molecule. Silver ion may also employ a specific orienting effect[24].

1.2.3. ACYLATION

Tertiary amides react with acyl halides to form 1:1 addition complexes which can be isolated at low temperatures[29,30]. On the basis of their chemical reactivity towards aniline, which is acetylated rather than formylated, they are formulated as the O-acylated structure (11). Primary and secondary amides on the other hand undergo N-substitution with acylating agents such as acid chlorides and anhydrides. Dehydration is



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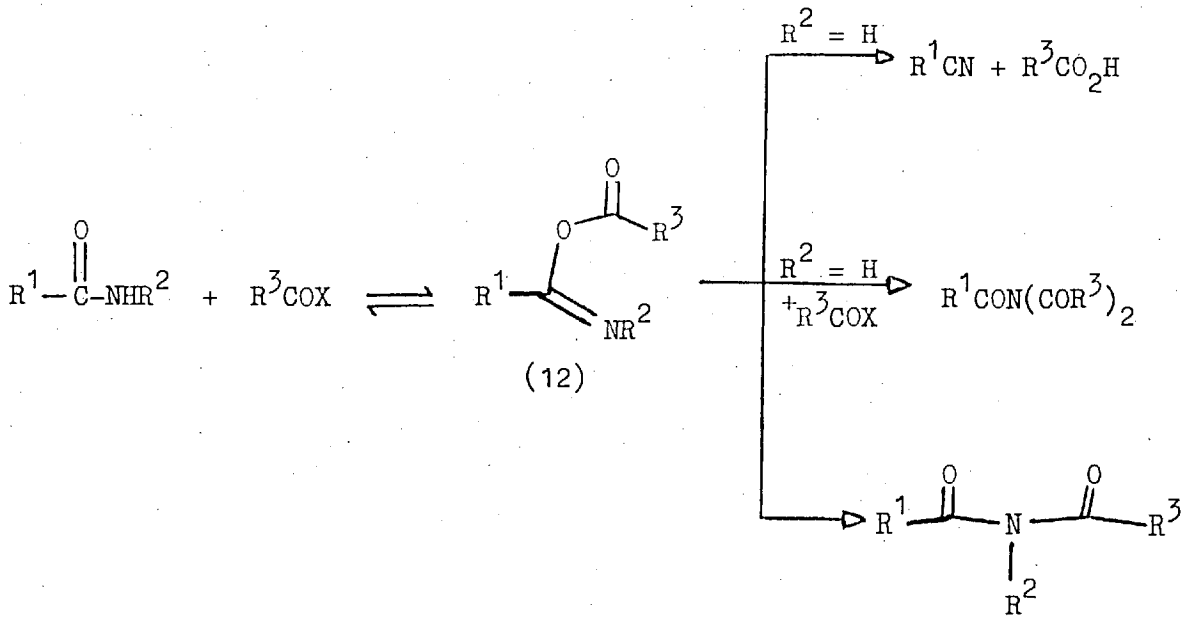
a competing process for primary amides and the implication is that both dehydration and N-acylation arise from a common intermediate, which, from analogy to tertiary amides, is formulated as the O-acylimidate (12) (Scheme 2).

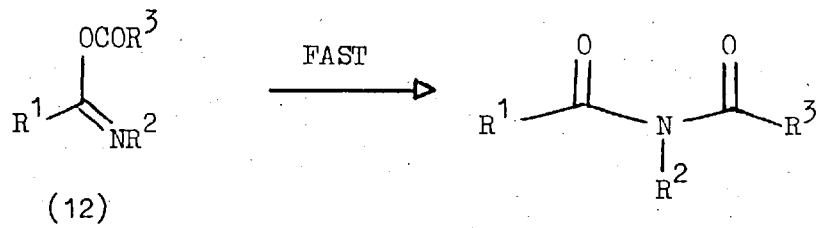


SCHEME 2. ACYLATION OF AMIDES

Further support for the intermediacy of (12) comes from the work of Thompson[31] who studied the benzoylation of benzamide. He noticed that tribenzoylamine was formed more rapidly from benzamide than from dibenzamide, thus ruling out the intermediacy of the latter. Formation of an O-acylimidate (12, $R^1 = R^3 = Ph$, $R^2 = H$) is favoured followed by acylation

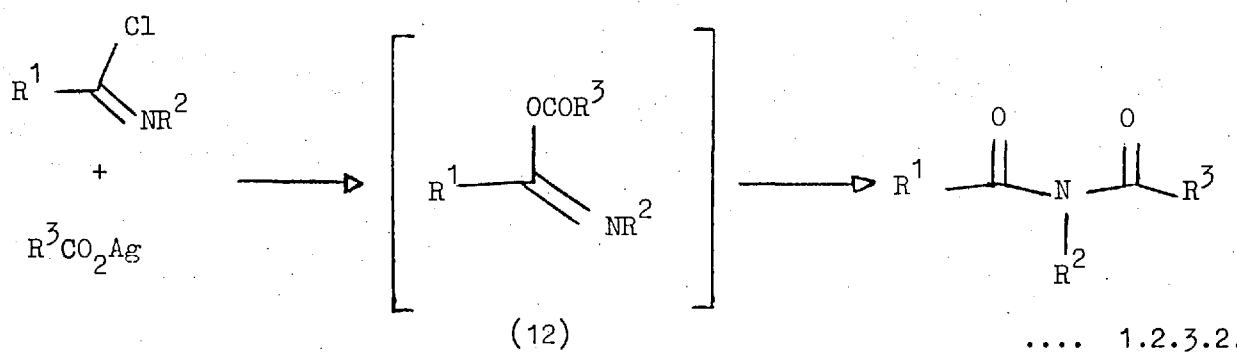
to give (12,R^1 = R^2 = Ph, R^3 = COPh) which on rearrangement yields tribenzoylamine.

These results imply that rearrangement of the O-acylimidate (12) to the N-acylamide is fast at ambient temperatures (Equation 1.2.3.1.). Support for this assumption comes from the reaction of imidoyl chlorides



(12) .... 1.2.3.1.

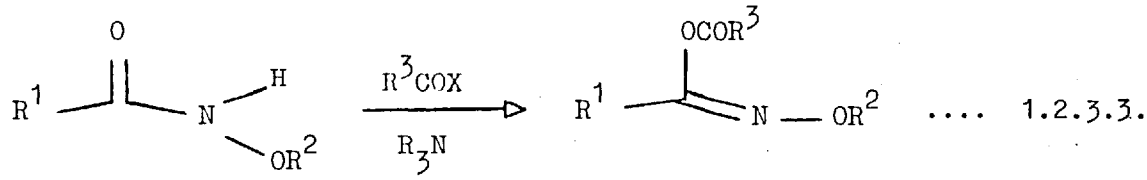
with silver acetate or benzoate[4,32] (Equation 1.2.3.2.) from which the only isolable product was the N-acylamide. Only with bulky electron-



.... 1.2.3.2.

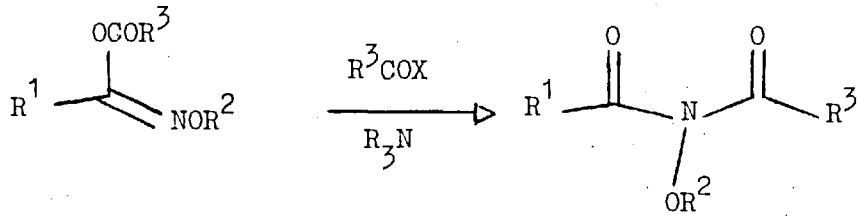
withdrawing substituents has the O-acylintermediate (12) been isolated *e.g.* (12; R^1 = R^3 = Ph, R^2 = 2,4-$(NO_2)_2C_6H_3$)[33]. Rearrangement to the N-acylamide was studied[4,33] and found to be intramolecular and was not catalysed by the addition of electrophilic reagents.

Significantly, the O-acylimidates of N-alkoxyamides, *e.g.* (12;R^2 = alkoxy) are stable[34] and can be synthesised directly from the parent amide by reaction with acyl halides or anhydrides[36] (Equation 1.2.3.3.).



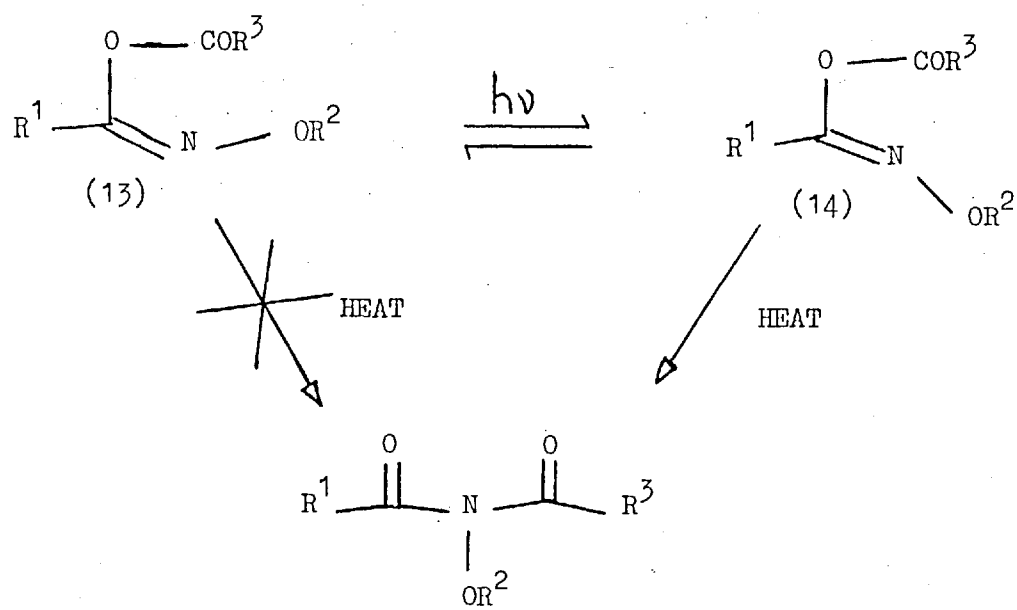
.... 1.2.3.3.

The reaction is complete within a few minutes. However, if reaction times are extented or an excess of acylating agent or base is used a mixture of both O- and N- acylated products are obtained. A kinetic study[35] has shown that the O-acylimidate rearranges under the reaction conditions (Equation 1.2.3.4.) to the N-acylamide, but demonstrates quite clearly



.... 1.2.3.4.

that acylation of the amide is some 10^3 times faster than rearrangement.



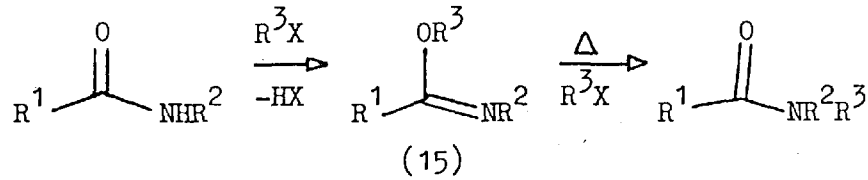
SCHEME 3. REARRANGEMENT OF O-ACYL-N-ALKOXYIMIDATES.

The O-acylalkoxyimidates exist as Z-isomers (13) and are stable to heat. Photolysis converts them to the E-isomers (14), which quantitatively rearrange to the N-acylamide on heating[34] (Scheme 3).

Amide anions exhibit similar reactivity towards acylating agents as towards alkylating agents. Thus N-acylation always occurs with sodium or potassium salts[24] whereas O-acylation is favoured with silver salts[35]. As mentioned previously, this may reflect a reduction in ionic character of the reaction or a specific directing effect of the silver ion.

1.2.4. SUMMARY

The pattern of reactivity outlined above led Challis and Challis[24] to postulate that neutral amides did not react as ambident moieties, but reacted *via* the oxygen atom solely. Attempts to explain product ratios in terms perturbation theory or Kornblum's hypothesis were criticised. An alternative, more satisfactory, explanation, that the O-substituted imidate (15) is the initial (kinetic) product and that this partially or wholly rearranges to the thermodynamically more stable amide under the reaction conditions (Equation 1.2.4.1.) was forwarded. Subsequently, positive proof for rearrangement under the reaction conditions has been found for alkylation[25,36] and acylation[4,35] and the rearrangement is significantly inhibited by silver salts, since Ag^+ precipitates the nucleophilic anions, *e.g.* I^-, which are required for this process. This offers one further explanation as to why silver ions favour O-substitution.

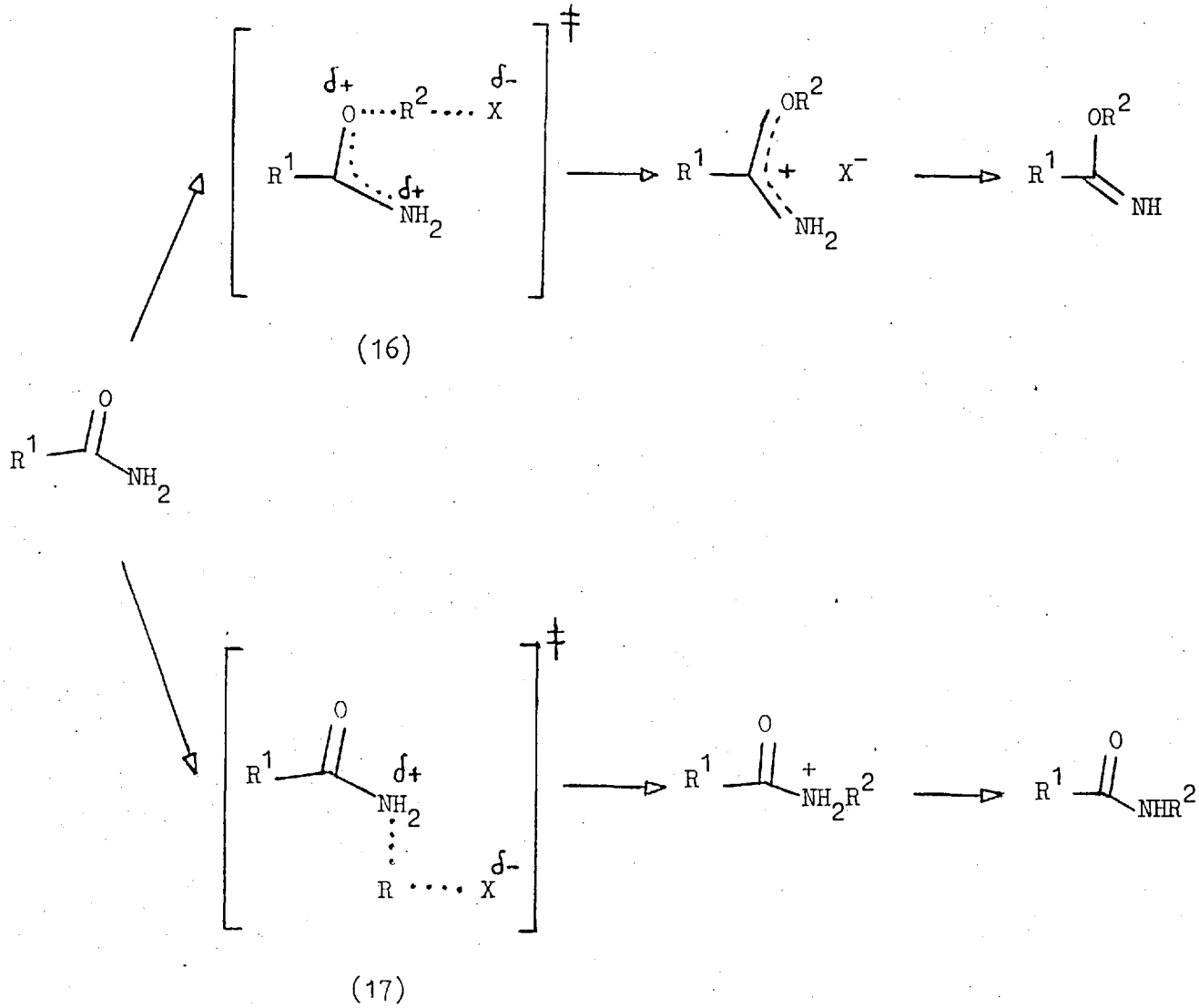


(15)

.... 1.2.4.1.

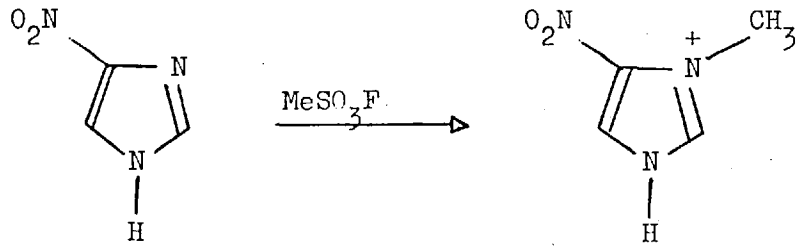
This argument is consistent with the site of protonation and derives

its origin from consideration of the initial transitions states derived from O- and N- attack (16) and (17) respectively (Scheme 4). Comparison



SCHEME 4.

of (16) and (17) suggests that (16) is of lower energy because delocalisation of the nitrogen lone pair electrons will dissipate the positive charge. Beak[20,37] has recently reformulated this theory by describing alkylation as occurring at the site remote from the proton and applied it to imidazoles, (Equation 1.2.4.2.), amidines and 4-hydroxypyrones (Equation 1.2.4.3.) as well as to amides.



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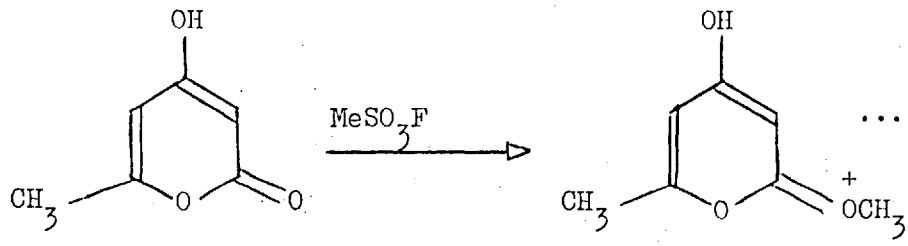
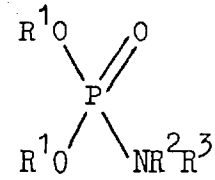


.... 1.2.4.3.

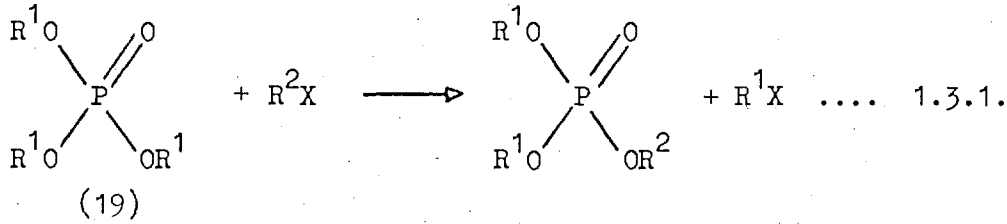
1.3. NUCLEOPHILIC PROPERTIES OF PHOSPHORAMIDATES

Although the phosphoryl group (P = O) is generally regarded as a weak nucleophile, phosphoramidates (18) and their anions have been considered to behave as ambident ions[2]. Proof of phosphoryl nucleophilicity has gradually accrued[38] and is best exemplified by alkyl exchange of



(18)

phosphate esters (19)[21] (Equation 1.3.1.).



(19)

Further, thiophosphoramidates have enhanced sulphur reactivity over thiophosphates[40] and these observations led Cadogan[41] to postulate that the phosphoryl group in (18) might be more reactive than in (19). The nucleophilic reactivity of phosphoramidates is reviewed below and critically discussed in terms of mono- or ambident reactivity.

1.3.1. PROTONATION

As for amides, the site of protonation of phosphoramidates is a contentious issue. Difficulty in determining the protonation site is exacerbated by rapid cleavage of the P-N bond under acidic conditions[42] (Equation 1.3.1.1.). Indeed phosphoramidates are hydrolysed 10^5 times faster than amides at comparable acidities. Much evidence therefore rests

$$(R^1O)_2PONR^2R^3 \xrightarrow{H_3O^+} (R^1O)_2PO(OH) + R^2R^3\overset{+}{N}H_2 \quad \ldots\ 1.3.3.1.$$

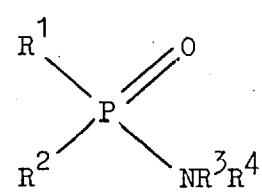
on the kinetic measurements of hydrolysis. Garrison and Boozer[43] favour the phosphoryl oxygen atom as the initial site of protonation but the large negative entropy of activation, $\Delta S^{\ddagger} \sim -35$E.U., observed for hydrolysis can accommodate either O- or N- protonation. The large value of ρ^* (3.6), however, is consistent with O-protonation[42]. In contrast, nitration of diethyl N-phenylphosphoramidate (Equation 1.3.1.2.) produced significant

$$(EtO)_2PONHPh + HNO_3 \xrightarrow[HNO_3]{80\%\ H_2SO_4} \underset{\%\ 47}{\text{o-}} + \underset{35}{\text{m-}} + \underset{18}{\text{p-}} \quad \ldots\ 1.3.1.2$$

(o-: NH_3^+, NO_2; m-: NH_3^+, NO_2; p-: NH_3^+, NO_2)

yields of m-nitroaniline which suggested a mechanism involving the m-directing effect of the N-protonated species[43a].

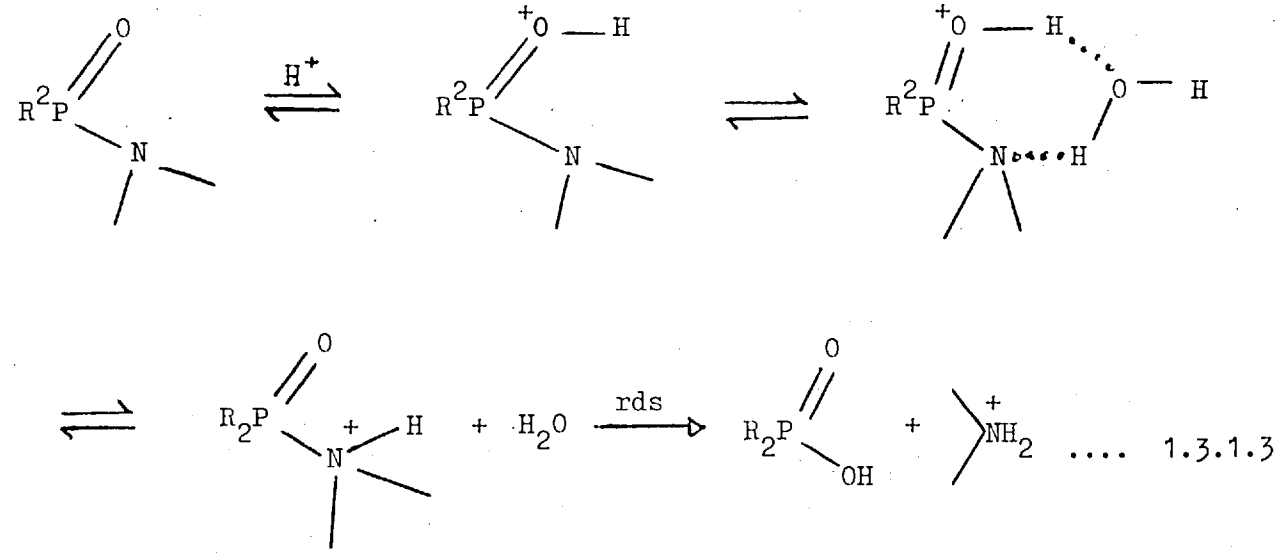
The acidic hydrolysis of phosphinamidates (20) has been well studied [42,44,45]. Assuming that amides O-protonate, the 10^4-10^5 rate increase in



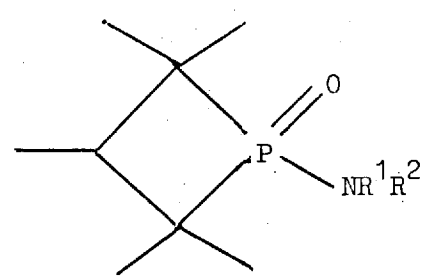
(20)

the hydrolysis of phosphinamidates over amides has been offered as evidence that reaction proceeds via an N-protonated species[42]. Hydrolysis of this intermediate is slow, and an excellent correlation of the rate constants for hydrolysis with pKa values of the corresponding anilinium ions is observed, which together with a negative Hammett ρ value for N-substitution, appear to support this view[44]. However, these results do not exclude O-protonation followed by proton transfer occurring before hydrolysis

(Equation 1.3.1.3.) and, significantly, these authors appear to favour an initial O-protonation.



Haake[46] found that the phosphinamidate (21) was stable enough in H_2SO_4 solutions to record its n.m.r. spectrum. Although signals for the



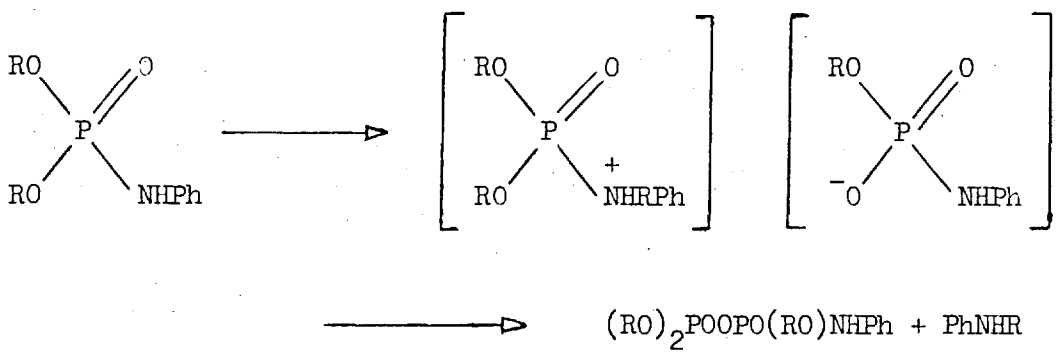
(21)

proton, on either oxygen or nitrogen, could not be observed, N-protonation on the basis of J(P-N-C-H) coupling constants was argued. However, the argument is weak, relying on transmission of charge via O, N and C atoms remaining constant. Significantly, hydrochloride salts of similar phosphinamidates have been synthesised in anhydrous media[47] and the position of the proton, even in these crystalline salts, could not be determined unambiguously. Conjugate acids of phosphoramidates are unknown,

presumably because alkyl-oxygen or phosphorus-nitrogen bond fission is so facile.

1.3.2. ALKYLATION

O-Alkyl phosphoramidates (but not O-aryl phosphoramidates) and phosphindiamidates undergo self-alkylation at high temperatures (250°C) to give amines derived from N-alkylation[48] (Scheme 5).



SCHEME 5. SELF ALKYLATION OF PHOSPHORAMIDATES

Reactions with external alkylating agents, e.g. alkyl halides, however require lower temperatures (100°C)[41]. Under these conditions products arise (Equation 1.3.2.1.) from both N- and O- alkylation, which has been

$$(EtO)_2\overset{\overset{O}{\|}}{P}\text{-}NH_2 + PrI \longrightarrow \begin{cases} (EtO)_2PONHPr + (EtO)(PrO)PONH_2 \\ + (PrO)_2PONH_2 + (PrO)_2PONHPr \\ + (EtO)(PrO)PONHPr \end{cases} \quad \ldots\ 1.3.2.1.$$

taken to show that nucleophilic attack by the O- and N- atoms is competitive for neutral phosphoramidates. A similar reaction was established for ethyl n-propyl N,N-di-n-propyl phosphoramidate with n-propyl iodide (Equation 1.3.2 2.) which gave di-n-propyl N,N-di-n-propylphosphoramidate, ethyl iodide and tetra-n-propylammonium iodide.

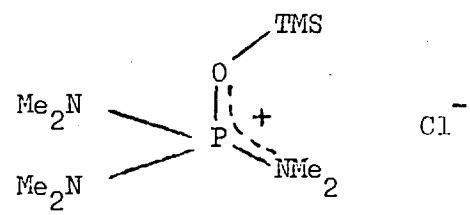
$$(EtO)_2(PrO)PONPr_2 \xrightarrow{PrI} (EtO)(PrO)_2\overset{+}{P}NR_2\overset{-}{I}$$
$$\downarrow$$
$$(PrO)PO_2 + Pr_3N \xleftarrow{PrI} (PrO)_2PONPr_2 + EtI \quad \ldots\ 1.3.2.2.$$

However, it was not established whether or not the amine was produced before or after alkyl exchange, a fact crucial to the argument for competitive O- and N- alkylation.

A similar reaction to alkylation is trialkylsilylation (Equation 1.3.2.3.). Although silyl halides generally favour enol formation,

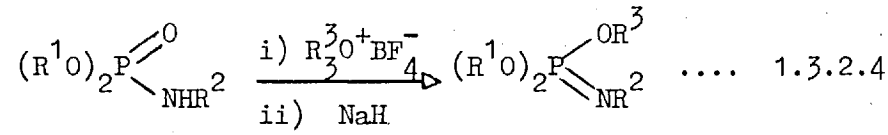
$$(R^1O)_2PONHR^2 + R^3_3SiCl \longrightarrow \underset{(22)}{(R^1O)_2PONR^2SiR^3_3} + \underset{(23)}{(R^1O)_2\overset{OSiR^3_3}{\overset{|}{P}}=NR^2} \quad \ldots\ 1.3.2.3.$$

Glidewell[49] reported that trimethylsilyl-, germanyl- and stannyl- chlorides reacted with phosphoramidates yielding the N-bonded isomers (22) only. Zon[50], however, reported that trimethylsilylation of diphenyl N-phenylphosphoramidate gave an equilibrium mixture of the O- and N- trimethylsilylated derivatives, (22) and (23), but it was noted that diisopropyl N-phenylphosphoramidate gave only the N- substituted product (22). The effect of P-substitution was not explored further. More recently, hexamethylphosphoric triamide on reaction with trimethylsilyl chloride formed a salt formulated as (24)[51].



(24)

Alkylation of phosphoramidates by more reactive alkylating agents *e.g.* diazoalkanes[52], and trialkyloxonium salts[53] takes place under mild conditions *i.e.* low temperature (Equation 1.3.2.4.).

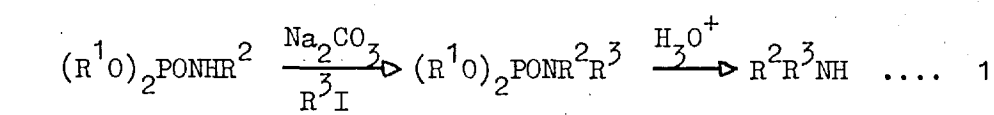


.... 1.3.2.4.

Whereas diazomethane gives a mixture of *O*- and *N*- methylated products, diazoethane and triethyloxonium hexafluorophosphate give the *O*-ethylated isomer only.

This pattern of reactivity parallels that of neutral amides toward alkylation.

Although the possibility of phosphoramidate anions exhibiting ambident behaviour has been noted, in practice alkylation, both intra- and intermoleculiarly, produces only the *N*-alkylated phosphoramidate[54,55]. Synthetic use has been made of this reaction to generate *N*,*N*-dialkyl substituted phosphoramidates and hence dialkylamines[56] (Equation 1.3.2.5.).



.... 1.3.2.5.

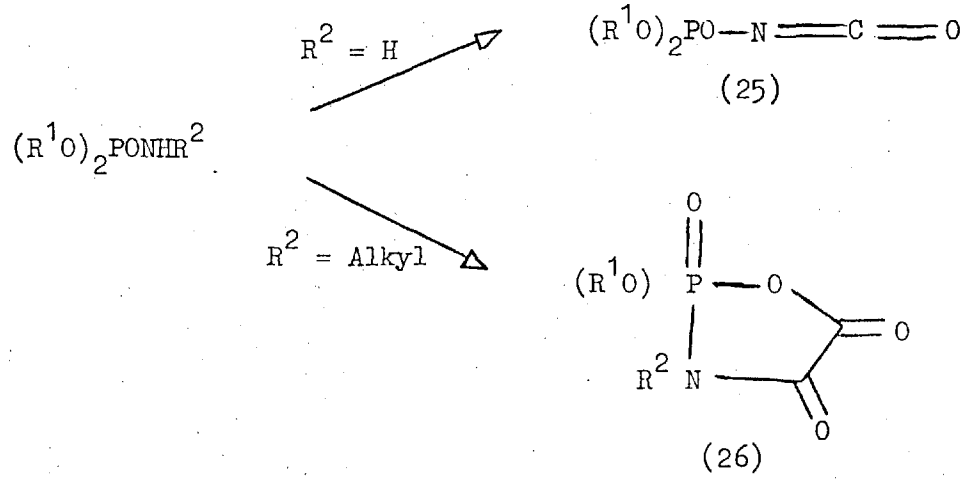
Silver salts of phosphoramidates, in contrast to those of amides, also give only the *N*-alkylated isomer[57].

1.3.3. ACYLATION

Unlike alkylation, acylation studies of neutral phosphoramidates are few. Acylation of diethyl phosphoramidate by acetyl chloride at 30°C in the presence of a tertiary amine gave diethyl *N*-acetylphosphoramidate as the sole product (Equation 1.3.3.1.)[58].

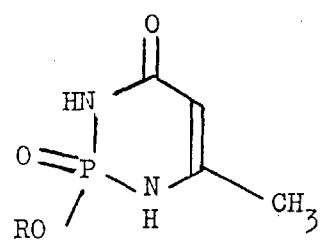
$$(EtO)_2PONH_2 + AcCl \xrightarrow[30^\circ C]{PhNEt_2} (EtO)_2PONHAC \quad .... \quad 1.3.3.1.$$

Similarly, dialkyl phosphoramidates react with oxalyl chloride to give (25)[59], whereas N-alkylated isomers give (26)[60], a product of both O- and N- attack (Scheme 6). Phosphordiamidates react with diketen, however, to



SCHEME 6. REACTION OF DIALKYL PHOSPHORAMIDATES WITH OXALYL CHLORIDE

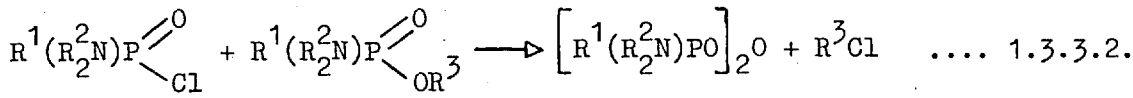
produce the uracil derivative (27), the product of N-acylation[61].



(27)

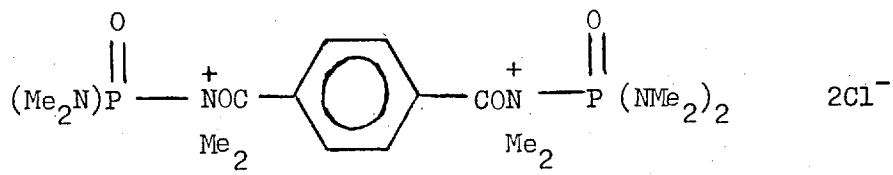
Phosphorylation, using $(EtO)_2POCl$, produced the N-phosphorylated phosphoramidate[62], a report claiming O-phosphorylation[63] being unsubstantiated.

However, dealkylation is observed in some reactions[64] and can only be explained by phosphorylation of phosphoryl oxygen (Equation 1.3.3.2.).



.... 1.3.3.2.

Hexamethylphosphoric triamide is reported to react with p-dibenzoyl chloride to give (28)[65], but sulphonation[66,67], via sulphonic anhydrides yields products from O-attack (Scheme 7).



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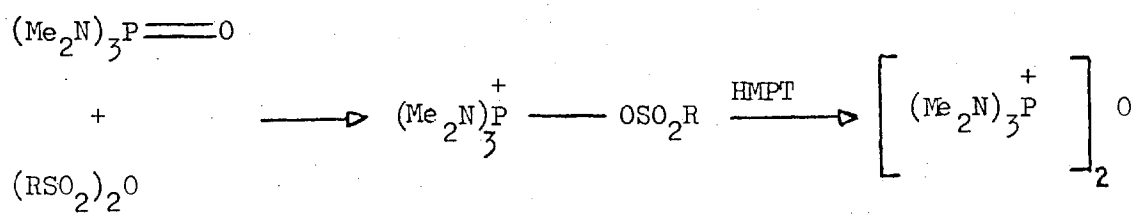
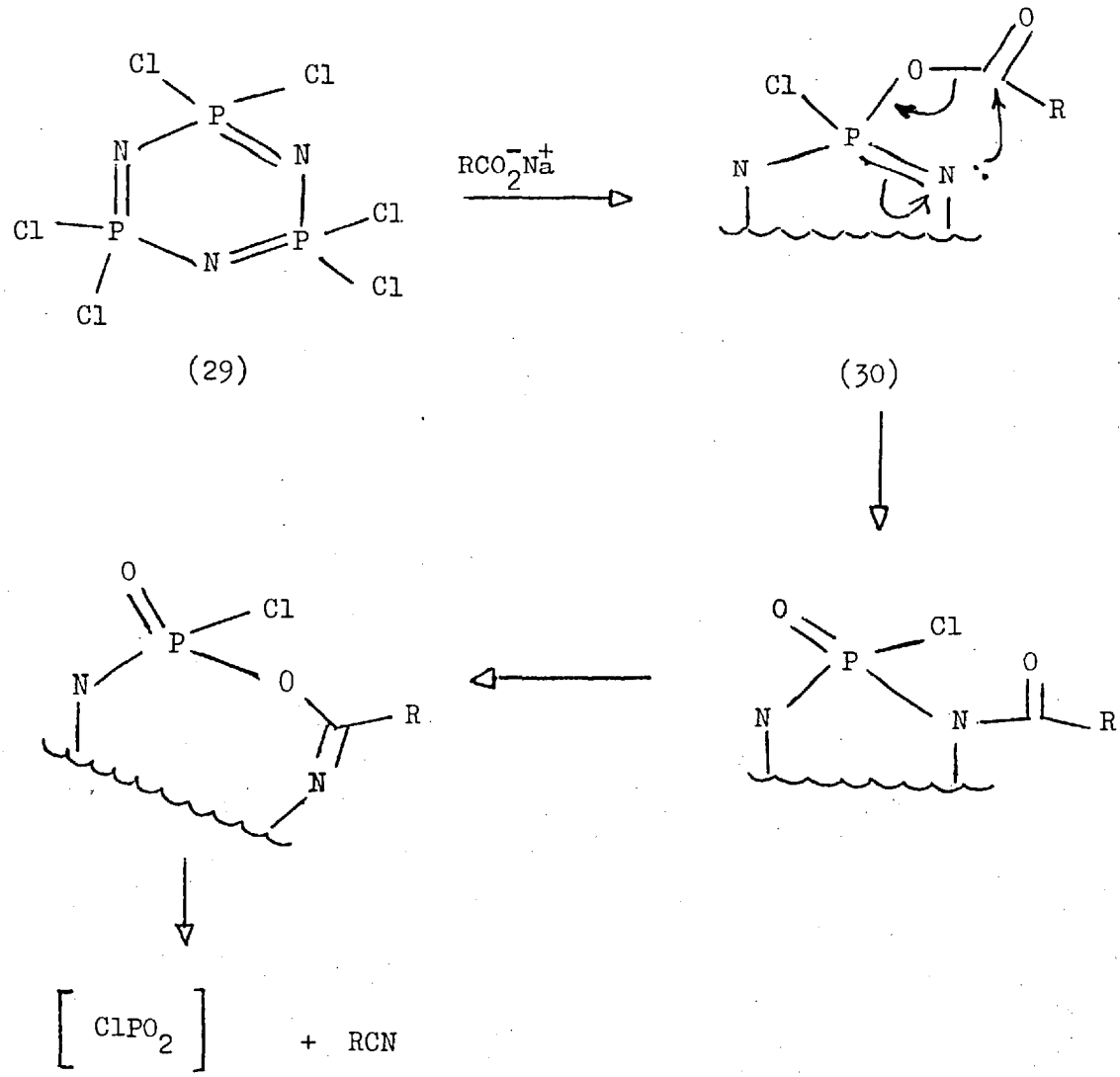


SCHEME 7. SULPHONATION OF HMPT

These results suggest that rearrangement of an O-acylphosphorimidate, if formed in these reactions, is fast. Significantly, reaction of the cyclophosphorimidic chlorides (29) with acetate[68] or benzoate[69] produced acetonitrile and benzonitrile (Scheme 8). Obviously, rapid rearrangement of the O-acylphosphorimidate (30) followed by elimination is involved in these reactions.

In contrast, acylation of the phosphoramidate anion results in only



SCHEME 8.

N-acyl products[70,71,72]. The reaction of sodium salts of phosphoramidates with aroyl halides and anhydrides results in P-N bond fission but the mechanism of this somewhat unusual reaction is not yet understood (Equation 1.3.3.3.)[72].

$$(EtO)_2P(=O)NPh + PhCOCl \longrightarrow (EtO)_2POCl + PhCONHPh \quad \ldots\ldots \quad 1.3.3.3.$$

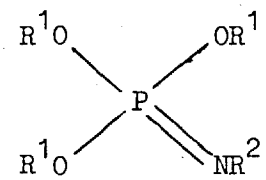
1.3.4. OTHER REACTIONS

Reaction of phosphoramidates under neutral, basic, or acidic conditions with electrophiles such as ^{+}NO[73] or Cl_2[74] produce only N-substituted prod-

ucts or their decomposition products.

1.3.5. SUMMARY

The pattern of reactivity of neutral phosphoramidates appears to parallel that of amides. Thus O-substituted products are favoured at low temperature with reactive reagents, whilst less reactive reagents requiring high temperatures favour N-substitution. This would imply that the O-substituted phosphorimidate is the kinetic product, whilst under the reaction conditions, *e.g.* high temperature, excess alkylating agent, rearrangement to the thermodynamically more stable N-alkylphosphoramidate occurs. Significantly, there is evidence that phosphorimidates (31) re-



(31)

arrange on both heating[75] and in the presence of electrophilic reagents[76]. Indeed, unsubstituted phosphorimidates (31; R^2 = H) are known to rearrange spontaneously[77].

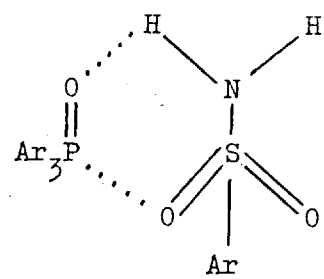
The purpose of the present work was to establish the mechanism of rearrangement in order to determine whether or not rearrangement is possible under the conditions of alkylation.

1.4. NUCLEOPHILIC CHEMISTRY OF SULPHONAMIDES

Although sulphonamides are well known and extensively used as drugs their chemistry has been little studied. The main body of work involves nucleophilic attack at the sulphur atom. However, their ability to act as a nucleophile is known, and is reviewed below.

1.4.1. PROTONATION, HYDROGEN-BONDING AND COMPLEXING PROPERTIES

Sulphonamides are very weak bases, pK_a values ~ -6 compared to ~ -2 for amides[78]. Hydrolysis in acidic media is extremely slow and this results in the ability to detect protonated species. Several reports indicate that N-protonation predominates[78,79,80], the evidence includes coupling of N-alkyl groups with the proton on nitrogen. However, the ability to assign such coupling has been criticised[80], and, it is noteworthy that protonation of $CH_3SO_2N(CH_3)_2$ and $CH_3SO_2NHCH_3$ causes less deshielding of the N-CH_3 group than the S-CH_3 group[78]. Consequently, the S-CH_3 signal suffers a greater downfield shift than that for the N-CH_3 group. Thus it may be argued that O-protonation occurs. No salts have been prepared in anhydrous media and doubts about the site of protonation remain.

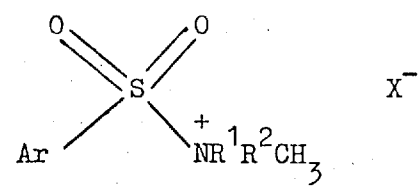


(32)

Studies of hydrogen bonding between sulphonamides and protic donors, e.g. phenol, are equally unconclusive. Both S=O[81] and S-N[82] association is reported. Reports of complex formation are rare, but primary sulphonamides complex triarylphosphine oxides to give adducts formulated as (32)[83].

1.4.2. ALKYLATION

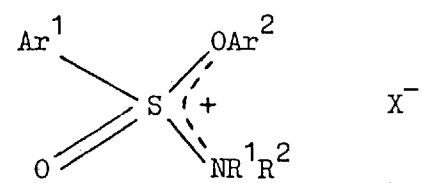
Tertiary sulphonamides react with alkyl iodides at high temperature e.g. 150°C to give S-N cleavage products[84] arising from N-alkylation. The same compounds react at low temperatures with reactive alkylating agents, e.g. CH_3SO_3F[85] and $(CH_3O)_2\overset{+}{C}H\ SbCl_6^{-}$[86], to give salts, which, on the basis of their n.m.r. spectra[86], independent synthesis[86] and hydrolysis[85] were assigned structure (33).



(33)

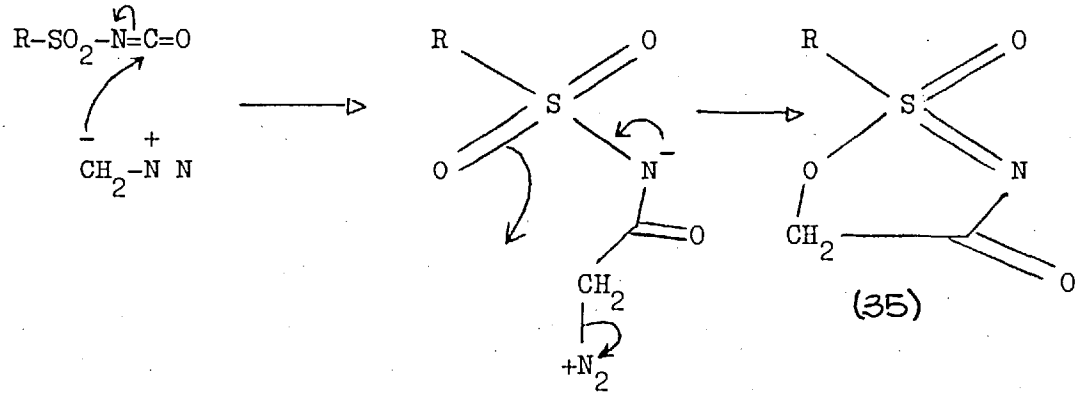
Alkylation of neutral primary and secondary sulphonamides has not been studied.

In contrast, arylation, using aryldiazonium hexafluorophosphates, of tertiary sulphonamides gives the O-arylated salts (34)[87,88]. Again, neutral primary and secondary sulphonamides were not studied.



(34)

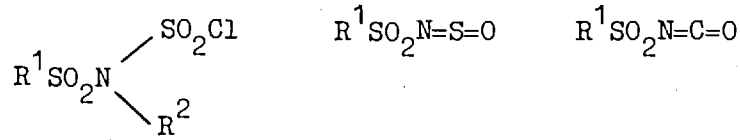
Alkylation of the sulphonamide anion or of sulphonamides under basic conditions, where presumably the anion, pKa ~ 9 is formed, results in N-substitution, a reaction used for the synthesis of secondary amines[89,90]. However, one report[91] appears, by implication, to suggest that, in special circumstances e.g. ring size, sulphonamide anions do exhibit reactivity at the oxygen atom. Thus, the sulphonylisocyanate reacts with diazomethane to give (35) presumably by the mechanism shown (Scheme 9).



SCHEME 9.

1.4.3. ACYLATION

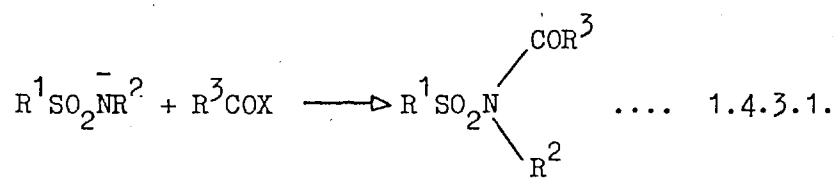
The acylation of neutral sulphonamides is rare. Reaction with sulphuryl chloride, thionyl chloride and phosgene however yields N-(chlorosulphonyl)-sulphonamides (36), N-sulphinylamines (37) and N-sulphonylisocyanates (38) respectively[91].



(36) (37) (38)

In the presence of a tertiary base, neutral sulphonamides and acyl halides yield N-acylsulphonamides[92].

Acylation of sulphonamide anions is more extensively explored[89,91] and results exclusively in N-acylation. Acylating agents include acid halides, anhydrides and esters, ketens and cyanates (Equation 1.4.3.1.).



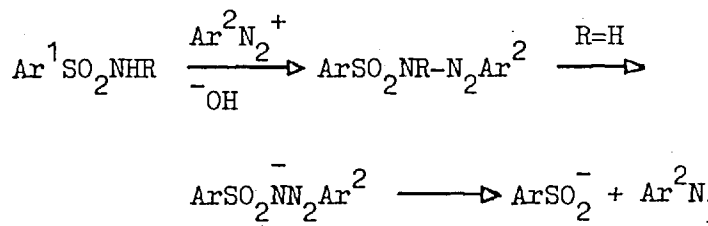
.... 1.4.3.1.

1.4.4. OTHER REACTIONS

Chlorination occurs under basic conditions to give either N- chloro or N,N-dichlorosulphonamides, well known for their antiseptic properties[92]. Reagents commonly used are molecular chlorine or hypochlorite.

Nitrosation occurs under acidic conditions to yield sulphonic acids from primary sulphonamides, or N-nitrososulphonamides from the secondary sulphonamides[89]. The latter compounds are well known for their use as diazoalkane precursors. Nitration, on the other hand, gives N-nitrosulphonamides with both primary and secondary sulphonamides.

Reaction with aryldiazonium ions under basic conditions produced the N-coupled triazene[89,93]. Primary sulphonyltriazenes react further to give sulphinate anions[89] (Scheme 10).

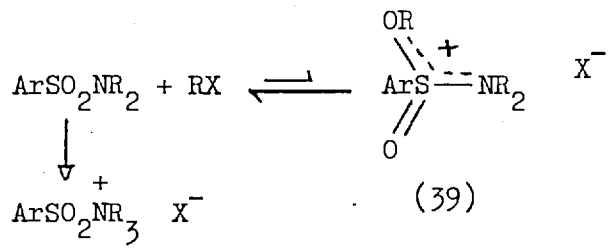


SCHEME 10.

1.4.5. SUMMARY

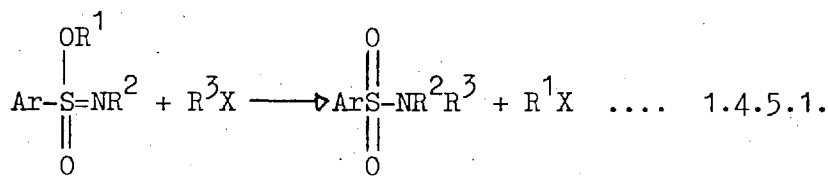
Although the sulphonamide moiety could behave as an ambident nucleo-

phile, reports of it reacting as such are rare. Only arylation of neutral, tertiary sulphonamides attacks the sulphonyl oxygen atom. However, almost all studies involve tertiary sulphonamides where the unfavourable equilibrium (Scheme 11) may be set up. Significantly, sulphonimidates

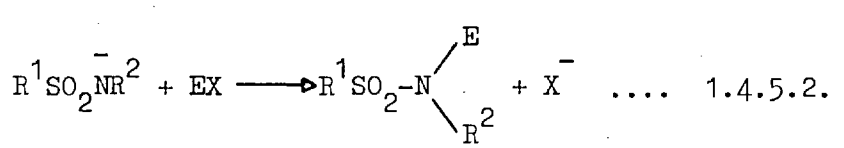


SCHEME 11.

(isomers of sulphonamides) are known to react with alkyl halides[94] yielding tertiary sulphonamides (Equation 1.4.5.1.), presumably <u>via</u> the cation (39). Thus, neutral sulphonamides may well exhibit reactivity at the oxygen atom and it was the purpose of this report to investigate this possibility.



Sulphonamide anions however, do not exhibit ambident reactivity, but invariably yield <u>N</u>-substituted products (Equation 1.4.5.2.).



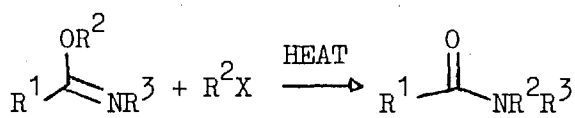
CHAPTER 2

THE PHOSPHORIMIDATE-PHOSPHORAMIDATE REARRANGEMENT

2.1. INTRODUCTION

The nucleophilic chemistry of phosphoramidates is similar to that of the analogous amides (see Chapter 1). Thus electrophilic attack should therefore occur at the oxygen atom, rather than the nitrogen atom, to form the imidate structure (31). Whether or not compounds of this structure can be isolated depends both on the reactivity of the electrophile and also the intermediate (31).

Recently, evidence for preferential O-substitution of amides was obtained for alkylation by studying the chemistry of the imidate intermediates (e.g. 15)[25,95]. Indeed, it was found that under conditions where N-substituted amides were produced, the rearrangement of the O-substituted imidate to the N-substituted amide occurred readily (Equation 2.1.1.). Significantly, the reagent required for alkylation (e.g. RX) promoted the rearrangement reaction. The potential energy profile for O-substitution of amide was deduced from these reactions and it well described the effect



.... 2.1.1.

of the counter ion, i.e. X^-, on the alkylation of amides: the poorer the nucleophile X^- the smaller the amount of rearrangement and thus the greater the amount of imidate formed.

The acylation of amides has been studied in a similar manner[4,35].

By applying a similar approach to the chemistry of phosphorimidates it was anticipated that the corresponding energy profile for phosphoramidates could be obtained. Significantly, phosphorimidates are known to react with alkyl halides to give N-disubstituted phosphoramidates (Equation 2.1.2.),[76b] and the rate of reaction depends on the substituents at

$$(EtO)_2EtP = NPh + EtI \xrightarrow[31h]{50^\circ C} (EtO)EtPONEtPh \quad .... \quad 2.1.2.$$

the phosphorus atom. Further, reaction with acyl halides has been demonstrated (Equation 2.1.3.)[76a] and synthetic use of this reaction has been taken[55].

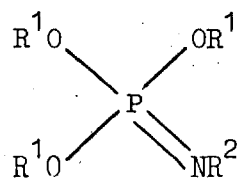
$$(R^1O)_3P = NPh + R^2COX \longrightarrow (R^1O)_2PON(COR^2)Ph \quad .... \quad 2.1.3.$$

Thermal rearrangement of phosphorimidates to phosphoramidates is known (Equation 2.1.4.): unsubstituted phosphorimidates (R^2=H) rearrange

$$(R^1O)_3P = NR^2 \xrightarrow{HEAT} (R^1O)_2PONR^2R^1 \quad .... \quad 2.1.4.$$

spontaneously[77] and O-allyl (R^1 = allyl) analogues undergo a [3,3]-sigmatropic shift[75c].

Thus, the rearrangement of (40; R^1 = Et, R^2 = Ph or PhCO) to (41; R^1 = Et, R^2 = Ph or PhCO) promoted by various electrophilic reagents was investigated to establish the mechanism and to determine whether the rearrangement is feasible under the conditions of alkylation in which N-alkylated products are formed.



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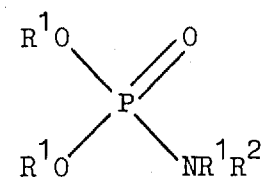


(41)

2.2. THERMAL REARRANGEMENT

In the absence of added electrophiles triethyl N-phenylphosphorimidate (42) rearranged slowly ($t_{\frac{1}{2}}$ ca. 30 days) to diethyl N-ethyl-N-phenylphosphoramidate (43) when heated at 100°C in acetonitrile (Equation 2.2.1.). The rearrangement was monitored (see Experimental) by

$$(EtO)_3P = NPh \xrightarrow{Heat} (EtO)_2PONEtPh \quad .... \quad 2.2.1.$$

following the increase in the N-Ph absorbtion of the product phosphoramidate (see Figure 2.2.1.) in the n.m.r. spectra of the reaction solution. The appearance of an ethylene signal in the n.m.r. spectrum (and also the presence of diethyl N-phenylphosphoramidate by t.l.c. on completion of the reaction) indicated that concurrent dealkylation was taking place (Equation 2.2.2.). The extent of dealkylation, calculated from the relative

$$(EtO)_3P = NPh \xrightarrow{Heat} (EtO)_2PONHPh + CH_2CH_2 \quad .... \quad 2.2.2.$$

intensities of the ethylene to N-Ph signals, was ca. 9% of the total reaction. The error involved in this calculation was $\pm$ 10%. The overall thermal reaction followed second-order kinetics (Table 2.2.1.), in accord with Equation 2.2.3., which implies that both rearrangement and dealkylation exhibit a second-order dependence on $\left[(42)\right]$, thus involving a bi-

$$\text{Rate} = k_\Delta \left[(42)\right]^2 = k_{rearr}\left[(42)\right]^2 + k_{dealk}\left[(42)\right]^2 \quad .... \quad 2.2.3.$$

molecular mechanism for both pathways. Rate coefficients for rearrangement, k_{rearr}, and dealkylation, k_{dealk}, were calculated from the overall rate coefficient, k_Δ, and the product ratios.

As indicated above, dealkylation accounts for 9% of the total reaction products.

Thus

$$k_{rearr} = \frac{91}{100} \times k_\Delta = 1.54 \times 10^{-6} M^{-1} s^{-1}$$

and

$$k_{dealk} = \frac{9}{100} \times k_\Delta = 1.52 \times 10^{-7} M^{-1} s^{-1}$$

FIGURE 2.2.1. TIME DEPENDENCE OF THE N.M.R. SPECTRUM OF THE REARRANGEMENT OF (42) ON HEATING IN ACETONITRILE AT 100°C.

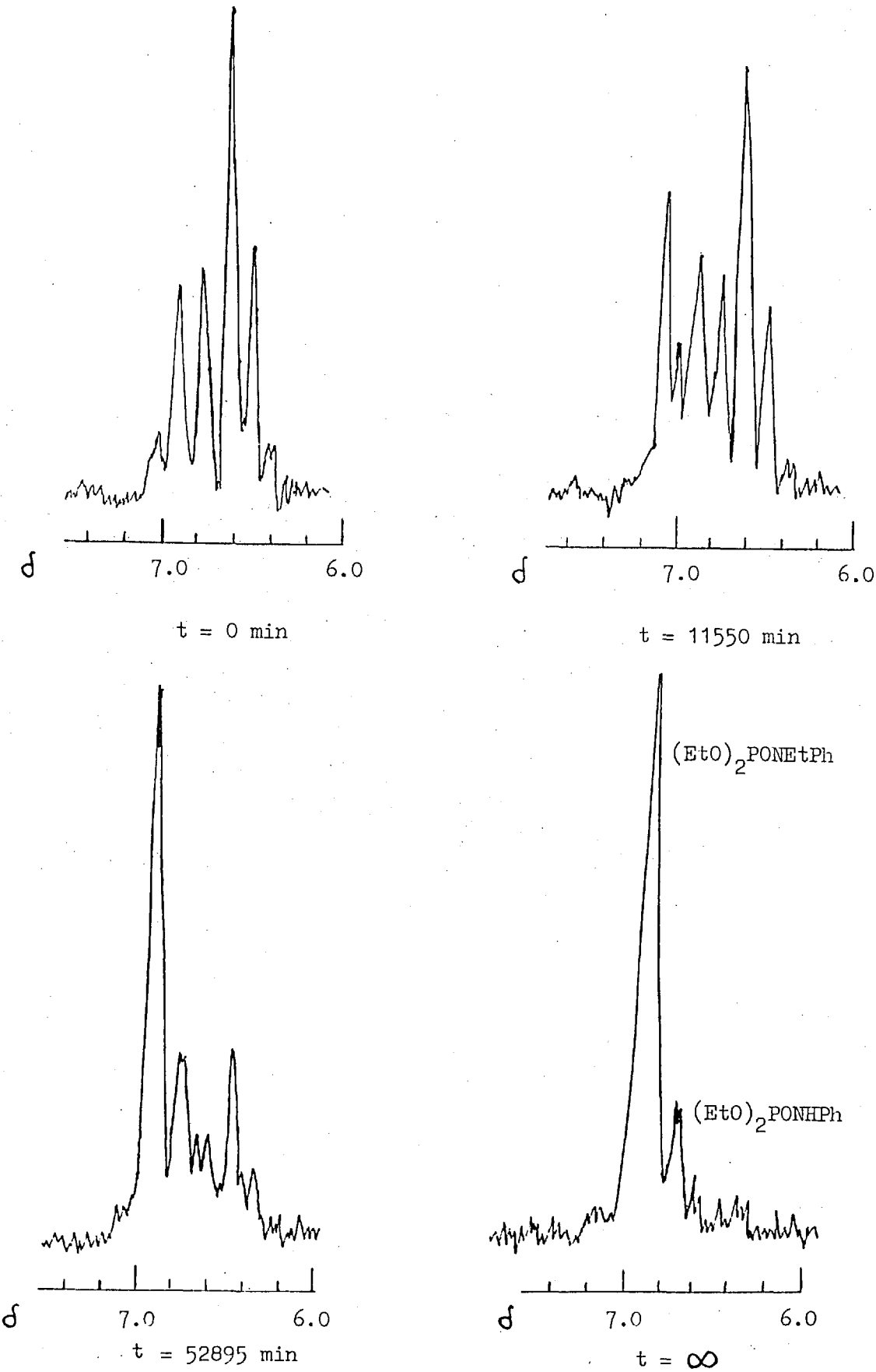


TABLE 2.2.1. REARRANGEMENT OF TRIETHYL N-PHENYLPHOSPHORIMIDATE TO DIETHYL N-ETHYL-N-PHENYLPHOSPHORAMIDATE IN ACETONITRILE AT 100°C. $[(42)]_o$ = ca. 0.2M.

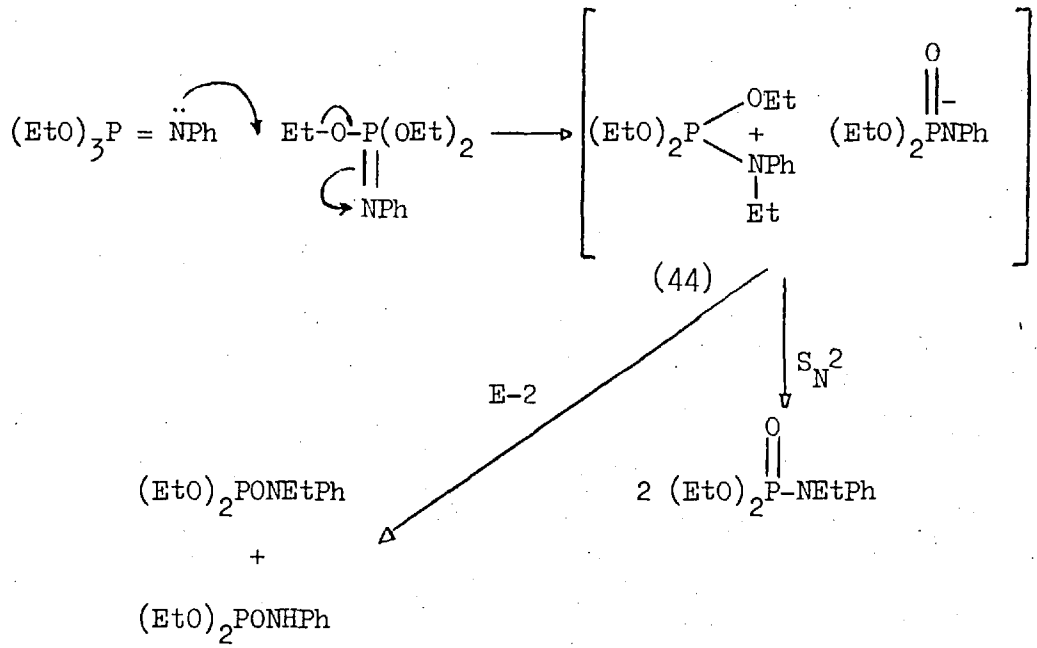
t (h)	$[(42)]$ (M)	$1/[(42)]$ (M^{-1})	$\ln[(42)]/[(42)]_0$	$10^7 k_\Delta^{1a}$ (s^{-1})	$10^6 k_\Delta^{b}$ ($M^{-1}s^{-1}$)
0	.200	5.000	.000	-	-
65	.187	5.341	-.067	2.87	1.46
89.3	.182	5.482	-.094	2.93	1.50
161	.172	5.827	-.153	2.64	1.43
208.5	.161	6.212	-.217	2.89	1.61
520.5	.122	8.170	-.491	2.62	1.69
668.5	.107	9.340	-.621	2.58	1.58
763	.099	10.119	-.705	2.57	1.61
881.5	.091	11.028	-.791	2.49	1.90
1025	.084	11.862	-.864	2.34	1.86
1224.5	.075	13.296	-.978	2.22	1.88
1417	.069	14.450	-1.064	2.09	1.85
1681	.065	15.420	-1.124	1.86	1.72
1917	.058	17.360	-1.238	1.79	1.79
2255	.052	19.350	-1.347	1.66	1.77
2490	.049	20.500	-1.406	1.57	1.73

a. Calculated assuming Rate = $k_\Delta^1 [\text{Substrate}]$.

b. Second-order rate coefficient from Equation 2.2.3.

$k = 1.69 \times 10^{-6} M^{-1} s^{-1}$

The second-order kinetics are consistent with rearrangement via an intermolecular S_N2 process such as alkylation of the phosphorimidate N-atom by a second substrate molecule followed by transalkylation of the phosphoramidate anion (Scheme 12).



Scheme 12. MECHANISM FOR THE THERMAL REARRANGEMENT OF TRIETHYL N-PHENYL-PHOSPHORIMIDATE TO DIETHYL N-ETHYL-N-PHENYLPHOSPHORIMIDATE.

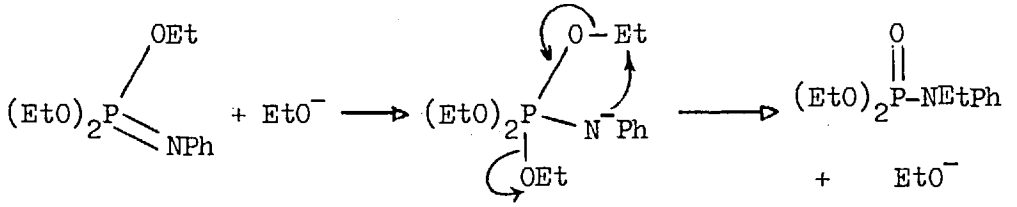
Dealkylation represents the usual competitive E-2 component, involving proton abstraction by either substrate molecule (42) or intermediate anion from a second substrate molecule or the intermediate cation. The most likely process, based on the known ability of phosphoramidate anions to effect elimination during alkylation[61], is proton abstraction from (44) by the intermediate phosphoramidate anion.

The results do not exclude a bimolecular concerted pathway or identify the rate-limiting step. The high nucleophilicity of the phosphoramidate anion, however, suggests that formation of the ion-pair in Scheme 12 would be slow.

The thermal rearrangement of phosphorimidates has previously been postulated to be intramolecular[96].

2.3. BASE CATALYSED REARRANGEMENT

The rearrangement of triethyl N-phenylphosphorimidate and O-methylbenzimidate in $C_6H_5NO_2$ in the presence of sodium ethoxide was also briefly examined. The second-order rate constant, $k_2 = 7.77 \times 10^{-5} M^{-1} s^{-1}$, for the



SCHEME 13.

phosphorimidate rearrangement at 100°C, and the lack of any rearrangement for the benz-imidate at 138°C, indicated that a base-catalysed process, such as Scheme 13, thought to be involved in the base-catalysed rearrangement of O-acyl benzohydroximates[4], was not present for these compounds.

2.4. ALKYL HALIDE PROMOTED REARRANGEMENT

In the presence of alkyl halides, however, the phosphorimidate (42) rearranged to the phosphoramidate (43) much more readily. For practical reasons CH_3CN was the most suitable solvent in which to study the rearrangement.

2.4.1. ORDER OF REACTION

Rearrangement of (42) to (43) in the presence of RX showed only first-order dependence on substrate concentration (Table 2.4.1.1.), unlike the thermal reaction (Equation 2.4.1.1.).

$$\text{Rate} = k_0[(42)] \quad \ldots\ldots \quad 2.4.1.1.$$

TABLE 2.4.1.1. FIRST-ORDER DEPENDENCE ON $[(42)]$ FOR THE REARRANGEMENT OF (42) TO (43) IN CH_3CN AT 100°C PROMOTED BY EtBr.

$[EtBr] = .032$ M

$[(42)]_0 = .200$ M

t/h	$[(42)]$/M	$\ln[(42)]/[(42)]_0$	$10^6 k_0/s^{-1}$	$10^5 k_2/M^{-1}s^{-1}$ a
0	.200	.000	-	-
29	.135	-.393	3.76	2.31
50.5	.108	-.614	3.38	2.34
75.5	.082	-.892	3.29	2.65
96	.068	-1.076	3.11	2.81
146.1	.038	-1.648	3.13	4.05

a. Calculated assuming Rate = $[(42)]^2$

By using appropriate alkyl halide concentrations it was possible to obtain rearrangement without any accompanying dealkylation and rates were significantly faster than rearrangement alone.

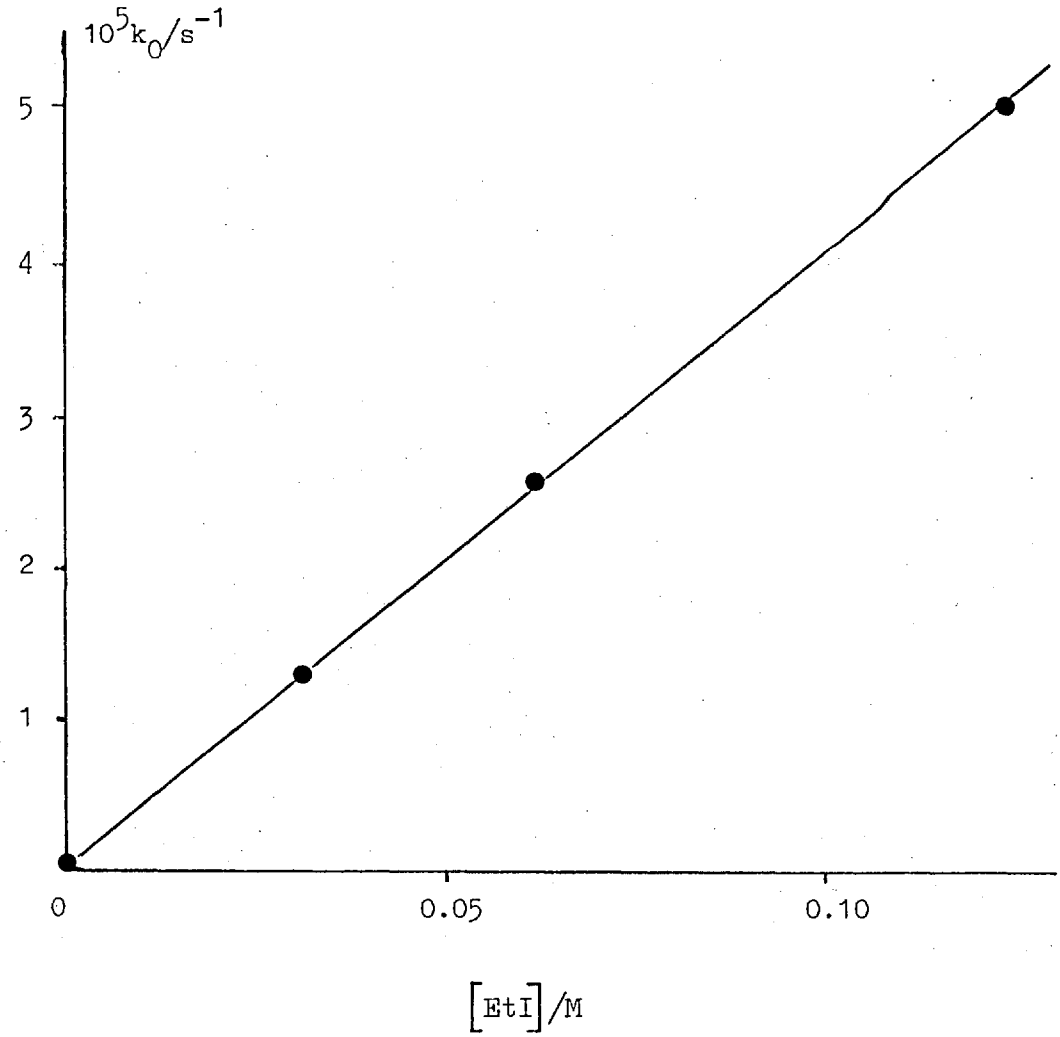
Pseudo-first-order rate coefficients, k_0, were found to vary linearly with alkyl halide concentration (Table 2.4.1.2., Figure 2.4.1.1.). It

TABLE 2.4.1.2. DEPENDENCE OF k_0 ON [ETHYL IODIDE] FOR THE REARRANGEMENT OF (42) TO (43) IN CH_3CN AT 100°C.

$[(42)] = 0.2$ M

$[EtI]$/M	$10^5 k_0/s^{-1}$
.031	1.33
.062	2.58
.124	5.03

FIGURE 2.4.1.1. DEPENDENCE OF k_0 ON ETHYL IODIDE FOR THE REARRANGEMENT OF (42) TO (43) IN CH_3CN AT 100°C.



SLOPE = k_2 = 400 x 10^{-6} $M^{-1}s^{-1}$

follows that the reaction is bimolecular and that the rates of the catalysed reaction are governed by Equation 2.4.1.2. The second-order rate

$$\text{Rate} = k_2\left[(42)\right]\left[\text{ALKYL HALIDE}\right] \quad \ldots. \quad 2.4.1.2.$$

coefficients, k_2, can be obtained by either the graphical method or by correcting Equation 2.4.1.2. for the presence of the thermal process (Equation 2.4.1.3.). In practise however, Equation 2.4.1.3. could be

$$\text{Rate} = k_2\left[(42)\right]\left[\text{ALKYL HALIDE}\right] + k_\Delta\left[(42)\right]^2 \quad \ldots. \quad 2.4.1.3.$$

further approximated to Equation 2.4.1.4., since the thermal reaction

$$\text{Rate} = k_2\left[(42)\right]\ \text{ALKYL HALIDE} + k'_\Delta\left[(42)\right] \quad \ldots. \quad 2.4.1.4.$$

($t_{\frac{1}{2}}$ *ca.* 30d) followed first-order kinetics over the period of the catalysed reactions (*ca.* 10d) (see Table 2.2.1.). Thus Equation 2.4.1.5. holds.

$$k_0 = k_2\left[\text{ALKYL HALIDE}\right] + k'_\Delta \quad \ldots. \quad 2.4.1.5.$$

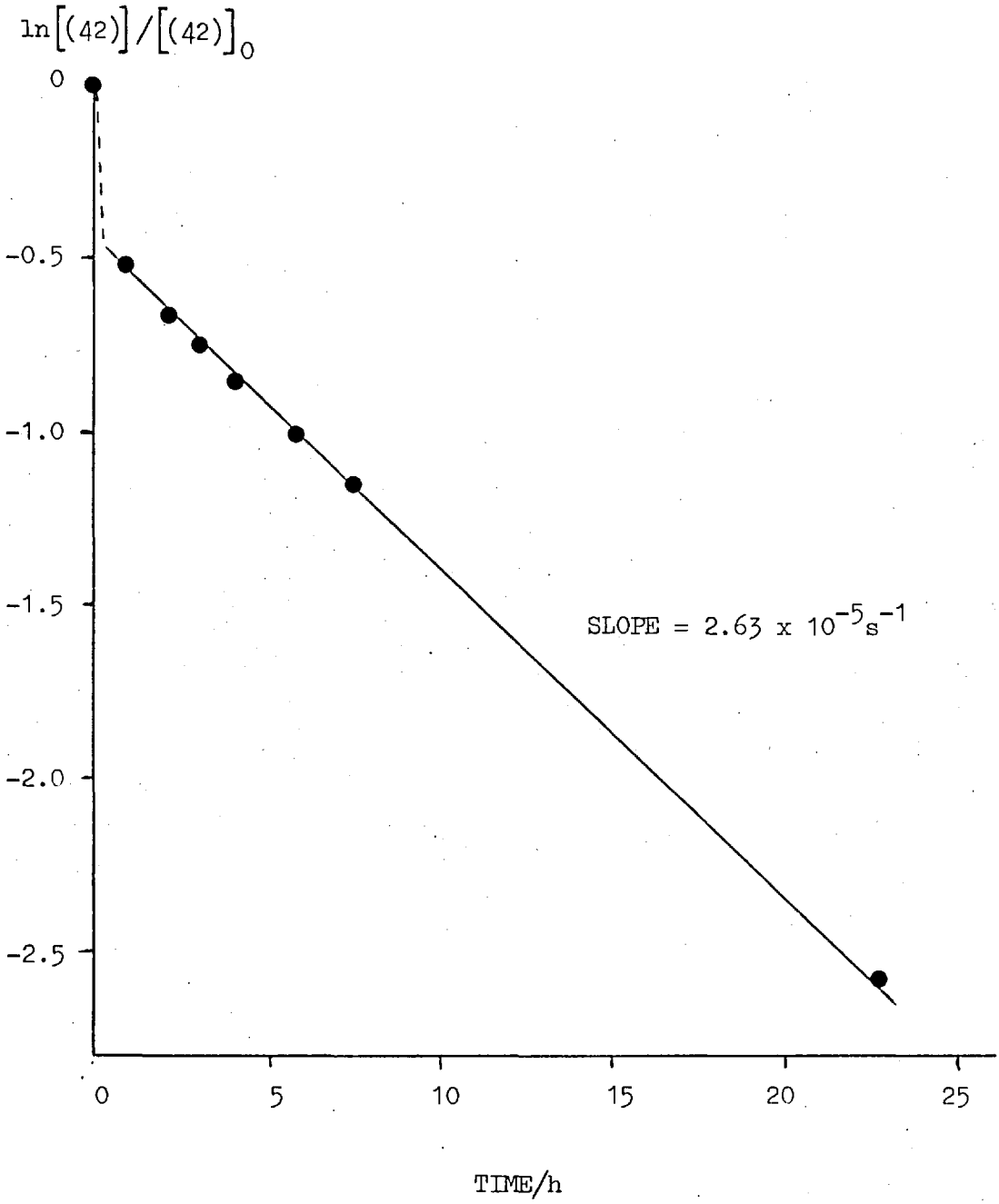
2.4.2. DEPENDENCE ON ALKYL HALIDE

Values of the second-order rate constant, k_2, were determined for various alkylating agents (Table 2.4.2.1.). Those reactions involving ethylating agents were determined by Equation 2.4.1.5., these being pseudo-first-order in $\left[\text{catalyst}\right]$, of which there is no change throughout the reaction. For MeI at 100°C however, plots of $\ln\left[(42)\right]/\left[(42)\right]_0$ *versus* time indicated that a rapid initial reaction occurred, followed by a subsequently slower rearrangement (Figure 2.4.2.1.). Further the loss of substrate corresponded to the amount of MeI added, and, significantly, the rate constant of the slow rearrangement was identical to that for EtI, assuming

FIGURE 2.4.2.1. FIRST-ORDER PLOT FOR THE REACTION OF (42) WITH MeI IN CH_3CN AT 100°C.

$[MeI] = 0.06M.$

$[(42)] = 0.2M.$



that EtI arose from reaction of (42) with MeI (Equation 2.4.2.1.). At

$$(EtO)_3P = NPh + MeI \longrightarrow (EtO)_2PONMePh + EtI \quad .... \quad 2.4.2.1.$$
(42)

34°C, the reaction of $(EtO)_3P = NPh$ with MeI was slow enough to be followed. The much faster catalysis by MeI over EtI at this temperature allowed the reaction to proceed cleanly and no evidence of competitive ethylation was detected. For isopropyl halides, rate constants were determined by the initial rate method, interference from ethyl halides released during the reaction being observed (Equation 2.4.2.2.).

$$(EtO)_3P = NPh + {}^{i}PrX \longrightarrow (EtO)_2PONPhPr^{i} + EtX \quad .... \quad 2.4.2.2.$$

Values of k_2 are listed in Table 2.4.2.1. Significantly, the rate of reaction decreases rapidly with increased steric hindrance in the alkyl group (MeI > EtI > Pr^{i}I). Dependence on the reagent reactivity is also observed (Pr^{i}I > Pr^{i}Br > Pr^{i}Cl) and may be related to either the nucleophilicity or leaving group ability of X^-. The finding that EtI > EtBr > $EtNO_3$ might imply that nuclephilicity is the dominant factor. However, for reasons discussed below the leaving group ability of X^- is favoured.

The effect of added $AgNO_3$ to the EtI catalysed rearrangement is worthy of note. Inspection of Table 2.4.2.1. shows that EtI is ca. 100 times as effective a catalyst as $EtNO_3$. It appeared likely that addition of $AgNO_3$ would inhibit the RX catalysed rearrangement as previously observed for benzimidates[36]. Significantly, when equimolar amounts of $AgNO_3$ and EtI were added to a 10-fold excess of (42) in CH_3CN precipitation of AgI occurred, but at 100°C the rate reduction was much smaller than the factor of 100 anticipated (Figure 2.4.2.2.). Centrifugation of the reaction mixture before heating at 100°C increases the amount of inhibition (Figure 2.4.2.2.)

TABLE 2.4.2.1. SECOND-ORDER RATE COEFFICIENTS, k_2, FOR THE REACTION OF (42) WITH ELECTROPHILIC REAGENTS IN CH_3CN.

$$\left[(42)\right]_0 = 0.2M, \left[\text{CATALYST}\right] = 10^{-2}\text{–}0.2M.$$

RX	T/°C	$10^6 k_2/M^{-1}s^{-1}$
MeI	34.2	39.5
EtI	34.2	4.12
EtI	100	400
EtBr	100	88
Pr^iI	100	60.8
Pr^iBr	100	8.52
Pr^iCl	100	0
$EtNO_3$	100	4.10
$EtI\text{–}AgNO_3$	100	27.5
$EtNO_3\text{–}AgI$	100	3.55

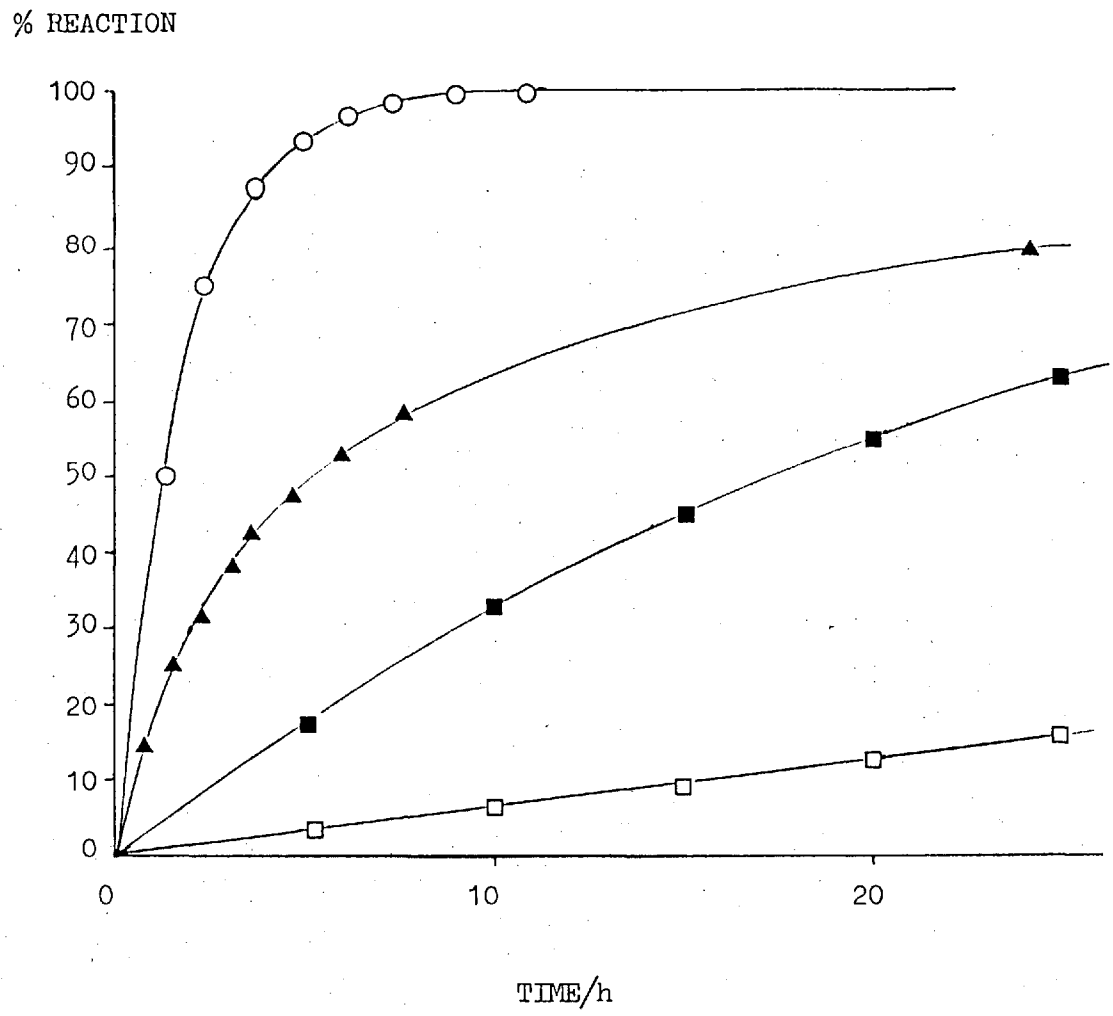
a. No catalysis observed, $k_2 = k_\Delta = 1.83 \times 10^{-6} M^{-1}s^{-1}$.

indicating that heterogeneous catalysis by AgI was possibly occurring, although addition of AgI itself had no effect (Table 2.4.2.1.). This may well be due to a difference in AgI particle size.

The reaction was not characterised by rational kinetics (Figure 2.4.2.2.) but the lowest value obtained for k_2 after centrifugation was $27.5 \times 10^{-6} M^{-1}s^{-1}$, a reduction of ca. 15 times on k_2 for EtI in the absence of ~~EtI~~ $AgNO_3$. It follows that silver salts will be less useful in the synthesis of phosphorimidates as they are in the analogous amide chemistry [15].

The effect of a slight excess of $AgNO_3$ was examined by addition of

FIGURE 2.4.2.2. EFFECT OF ADDED $AgNO_3$ ON THE RATE OF THE EtI - PROMOTED REARRANGEMENT OF (42) TO (43) IN CH_3CN AT 100°C.



○ 0.4M-EtI only.

▲ 0.43M-EtI plus 0.43M-$AgNO_3$ without centrifugation.

■ 0.39M-EtI plus 0.39M-$AgNO_3$ after centrifugation.

□ 0.4M-$EtNO_3$.

.008M $AgNO_3$ to a reaction catalysed by 0.2M $EtNO_3$. Assuming $AgNO_3$ produces an equivalent amount of $EtNO_3$ (*vide infra*) a rate acceleration of *ca.* 5 over that anticipated was observed (Figure 2.4.2.3.). The exact nature of this catalysis was not explored further. It was noted, however, that a silver mirror was formed. A free-radical process may be involved.

2.4.3. EFFECT OF OTHER ELECTROPHILIC REAGENTS

Electrophilic reagents other than alkyl halides also bring about rearrangement of $(EtO)_3P$ = NPh to $(EtO)_2POEtPh$. The second order rate coefficients, k_2, for various Y-X are listed in Table 2.4.3.1. The obser-

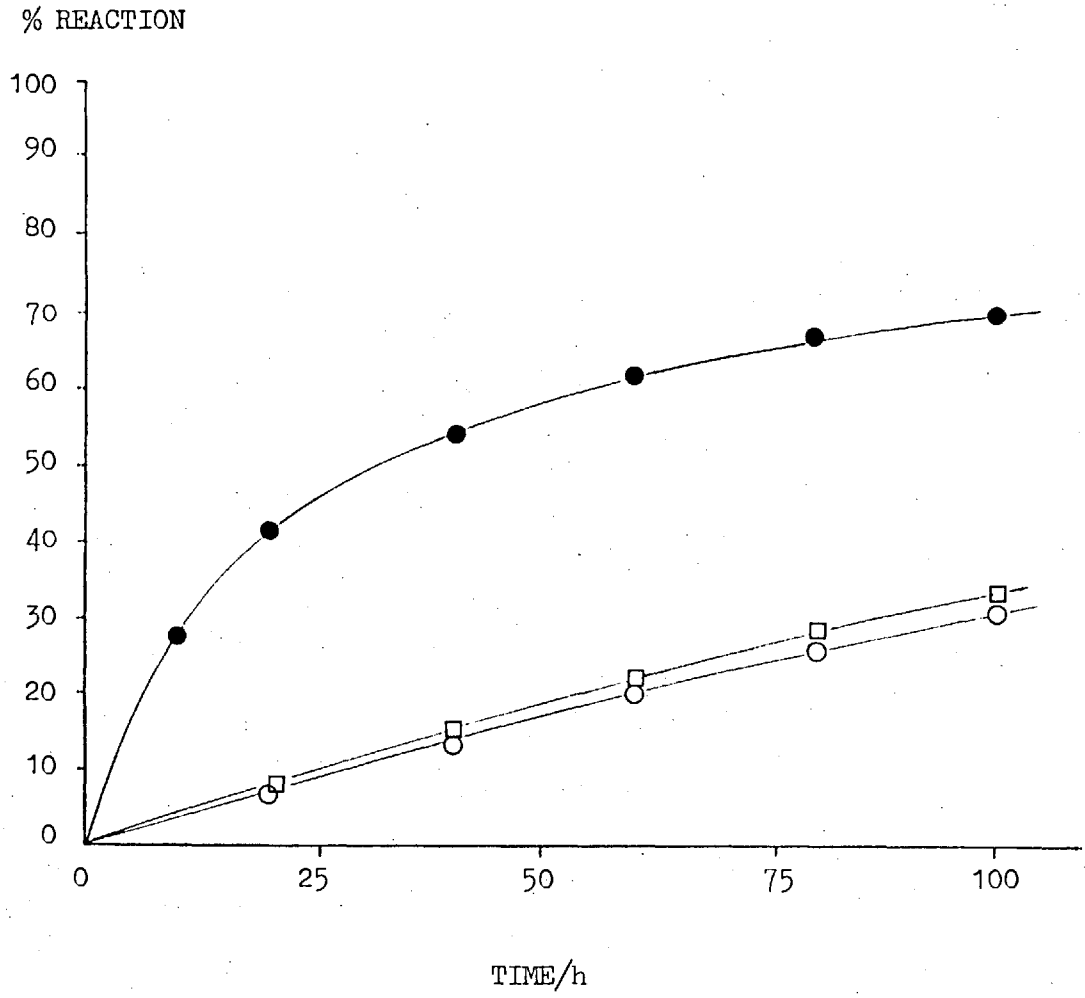
TABLE 2.4.3.1. SECOND-ORDER RATE COEFFICIENTS FOR THE REARRANGEMENT OF (42) TO (43) IN CH_3CN AT 100°C CATALYSED BY VARIOUS Y-X. $[(42)] = 0.2M$, $[Y\text{-}X] =$ *ca.* .02M.

CATALYST	$10^6 k_2/M^{-1}s^{-1}$
ZnI_2	380
$ZnBr_2$	91.6
$ZnCl_2$	0 [a]
I_2	378
MeCOBr	77.1
HBr (0.1 equiv.)	89.9
HI, HBr (1 equiv.)	b

a. No catalysis, $k_2 = k_\Delta = 1.34 \times 10^{-6} M^{-1}s^{-1}$.

b. No rearrangement but quantitative formation of $(EtO)_2PONHPh$ and EtX (X=I, Br) immediately which remained unchanged even after heating for 24h. at 100°C.

FIGURE 2.4.2.3. EFFECT OF $AgNO_3$ ON THE ETHYL NITRATE PROMOTED REARRANGEMENT OF (42) TO (43) IN CH_3CN AT 100°C.



● Observed curve for 0.2M-(42) plus 0.2M-$EtNO_3$ and 0.008M $AgNO_3$.

□ Calculated curve for 0.2M-(42) plus 0.2M-$EtNO_3$ and 0.008M $AgNO_3$.

○ Calculated for 0.2M-(42) plus 0.2M-$EtNO_3$ only.

vation that the k_2 values for ZnI_2 and I_2 are similar to that for EtI is of interest. Moreover, those for $ZnBr_2$, MeCOBr and HBr (0.1 equiv.) are similar to that for EtBr. These results can be explained by the formation of a phosphoramidate derivative and ethyl halide following nucleophilic attack by the phosphorimidate on the electrophile (Y-X) (Equation 2.4.3.1.). Rearrangement of (42) is subsequently promoted by the ethyl

$$(EtO)_3P = NPh + Y\text{-}X \longrightarrow (EtO)_2PONYPh + EtX \quad .... \quad 2.4.3.1.$$

halide, the observed k_2 values therefore corresponding to those for the ethyl halide itself. Indeed, n.m.r. absorbtion signals for the ethyl halides were observed relatively rapidly after addition of the electrophile and the intensity of these signals was proportional to the amount of added electrophile. Thus, on addition of 1 equivalent of HBr, quantitative dealkylation rather than rearrangement took place (Equation 2.4.3.2.), the

$$(EtO)_3P = NPh + HBr \longrightarrow (EtO)_2PONHPh + EtBr \quad .... \quad 2.4.3.2.$$

products being characterised by the n.m.r. spectrum and m.p. for $(EtO)_2$ PONHPh) . Addition of 0.1 equivalents of HBr, however, resulted in only 10% dealkylation (by n.m.r.) followed by rearrangement catalysed by EtBr (90%).

Rearrangement in the presence of $ZnCl_2$ (and, inter alia, EtCl), as with Pr Cl, is no faster than the purely thermal process alone, and in these cases ca. 10% dealkylation was also observed.

2.4.4. TEMPERATURE DEPENDENCE

The second-order rate coefficients, k_2, for the rearrangement of (42) to (43) in CH_3CN catalysed by EtI were determined at a variety of temperatures. The results (Table 2.4.4.1.) yield a linear Arrhenius plot of

FIGURE 2.4.4.1. ARRHENIUS PLOT FOR THE REARRANGEMENT OF (42) TO (43) BY EtI IN CH_3CN.

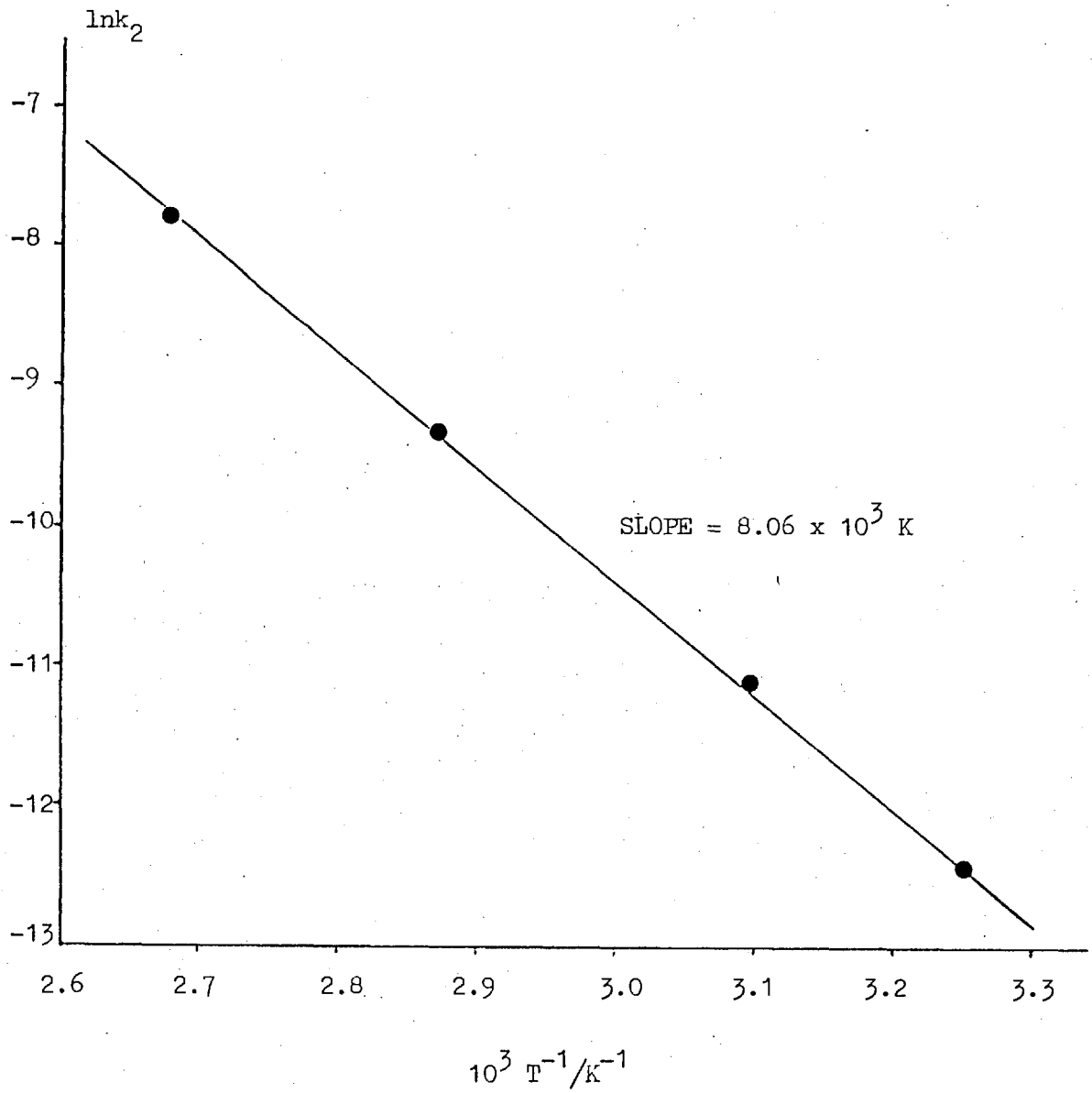


TABLE 2.4.4.1. TEMPERATURE DEPENDENCE OF k_2 FOR THE REARRANGEMENT OF (42) TO (43) CATALYSED BY EtI IN CH_3CN.

$[(42)] = 0.2M.$

$[EtI] =$ ca. 0.15M.

T/°C	$10^6 k_2/M^{-1}s^{-1}$	$10^3 T^{-1}/K^{-1}$	$\ln k_2$
34.2	4.11	3.253	-12.40
50	15.7	3.094	-11.06
74.2	94.3	2.876	- 9.27
100	401	2.680	- 7.82

$\ln k_2$ versus I/T (Figure 2.4.4.1.).This data yields the following thermodynamic quantities:

$$E_a \ 67 \pm 2 \text{ kJ mol}^{-1}$$
$$\Delta H^{\ddagger} \ 64 \pm 2 \text{ kJ mol}^{-1}$$
$$\Delta G^{\ddagger} \ 116 \pm 3 \text{ kJ mol}^{-1}$$
$$\Delta S^{\ddagger} \ -140 \pm 4 \text{ J.K}^{-1}\text{mol}^{-1} \ (-33.5 \text{ e.u.})$$

2.4.5. SOLVENT EFFECT

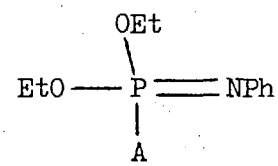
The rate of rearrangement catalysed by ethyl iodide shows a marked dependence on solvent polarity. Thus, at 100°C, the rate constants, k_2, decrease rapidly in order of decreasing solvent polarity (Table 2.4.5.1.) the implication being that charge development in the transition state is considerable.

TABLE 2.4.5.1. DEPENDENCE OF k_2 ON SOLVENT POLARITY FOR THE REARRANGEMENT OF (42) TO (43) AT 100°C CATALYSED BY EtI.

SOLVENT	ϵ	$10^6 k_2/M^{-1}s^{-1}$
CH_3CN	37.5	400
$C_6H_5NO_2$	34.8	307
CCl_4	2.2	7.2

2.4.6. SUBSTITUENT EFFECTS

A previous investigation[76b] of the reaction of phosphorimidates (45, a-d) with EtI at 50°C has shown that P-substituents influence the rate-



(45) a A = OEt
b A = Ph
c A = Me
d A = Et

constants, k_2, in the order of their +I effects. Thus Et > Me > Ph > EtO. The behaviour of triethyl N-benzoylphosphorimidate (46) was briefly examined, in order to determine the effect of N-substitution on reaction rate. Glidewell[49] had reported that this compound was unreactive towards RX.

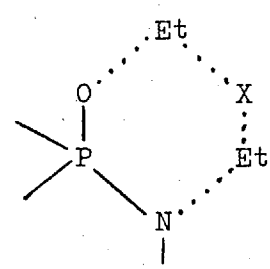
$$(EtO)_3P = N\text{-}COPh$$

(46)

It was found that (46) reacts, as did (42), with HBr to give quantitative yields of diethyl N-benzoylphosphoramidate and ethyl bromide. Moreover, unlike Glidewell[49], it was found that (46) did react with MeI in $[^3H_2]$-acetonitrile at 100°C in a sealed tube. The reaction is slow however, the rate of formation of the diethyl N-benzoyl-N-methyl phosphoramidate giving $k_2 = 13 \times 10^{-6} M^{-1} s^{-1}$. Allowing for the temperature difference, this is ca. 300 times less than the comparable coefficient for (42) (Table 2.4.2.1.), reflecting the reduced nucleophilicity of the benzoylated N-atom.

2.5. MECHANISM OF THE REARRANGEMENT REACTION

It has previously been suggested[76b], on the basis of P-substituent effects, that the alkyl halide catalysed conversion of phosphorimidates into phosphoramidates involves a cyclic, six-membered transition state [such as (47)] of low polarity. However, the finding that solvent polarity

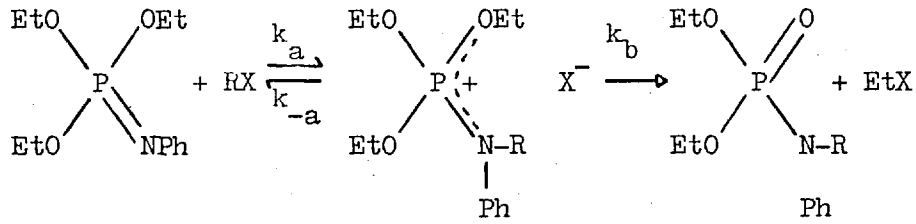


(47)

is important ($CH_3CN > C_6H_5NO_2 > CCl_4$) implies the formation of charged intermediates and charge development in the transition state.

The observation of bimolecular kinetics (Equation 2.4.1.2.), the rate reduction with increasing steric hindrance (Me > Et > Pr) in the reagent and the decrease in reagent reactivity along the series $Pr^iI > Pr^iBr > Pr^iCl$ have also been found in the analogous imidate-amide[25] rearrangement. The best explanation, as in the imidate-amide rearrangement, is one involving S_N2 attack by the phosphorimidate on the alkyl halide in a stepwise ,

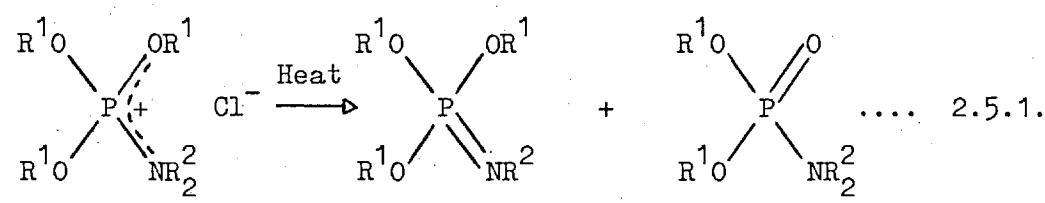
rather than a synchronous, manner (Scheme 14). Formation of the ionic intermediate (48) (step k_a) must be rate-determining to account for the dependence on the alkyl group, R. Rapid removal of the O-ethyl group



(48)

SCHEME 14. S_N2 MECHANISM FOR THE CONVERSION OF TRIETHYL N-PHENYLPHOSPHORIMIDATE INTO DIETHYL N-ETHYL-N-PHENYLPHOSPHORAMIDATE BY ALKYL HALIDES.

(step k_b) by attack of halide ion on (48) then follows. Supportive evidence for this mechanism arises from the report that triphenylphosphite reacts with chlorodialkylamine to give (49a), which yields the phosphor-



(49) a. R^1 = Ph
b. R^1 = Et

(50) (51)

imidate (50) and alkyl chloride (Equation 2.5.1.) on heating[97]. The strong aryl-oxygen bond allows N-dealkylation (step k-a) to effectively compete with O-dearylation (step k_b). In contrast (49b) yields the phosphoramidate (51) by O-dealkylation.

Further, the entropy of activation $\Delta S^{\ddagger} = -140\ JK^{-1}mol^{-1}$ (-33 e.u.) is indicative of a stepwise rather than a synchronous process (cf. the Diels-Alder reaction where $\Delta S^{\ddagger}$ = ca. $+6.7\ JK^{-1}mol^{-1}$ [98]).

This mechanism is consistent with an earlier investigation[76b] where

the rate decreasing in the order, Et > Me > Ph > EtO for $R_2P(OEt)$ = NPh, reflects the decreasing nucleophilicity of the N-atom arising from the decreasing +I P-substituent effects. These effects are therefore small (ca. 10) compared with those for N-substitution but are comparable to those for the imidate-amide rearrangement[25]. As noted above, there is a factor of ca. 300 between the N-Ph and N-COPh compounds which further indicates that nucleophilicity of the N-atom is important.

Rearrangement, initiated by the addition of ZnX_2 and other electrophiles proceeds similarly to RX and occurs via ethyl halide formed by a rapid initial reaction between the phosphorimidate and the added electrophile. Apart from $AgNO_3$ (vide supra), there is no evidence that the phosphoramidate derivative produced in this reaction plays a significant role in the ensuing rearrangement.

The low reactivity of $EtNO_3$ is inconsistent with its expected alkylating ability, and is best explained, as in the imidate rearrangement, by the decomposition of the ionic intermediate (48, $X=NO_3^-$) (step k_b) becoming rate limiting, which arises from the low nucleophilicity of NO_3^-.

2.6. AMBIDENT NUCLEOPHILIC PROPERTIES OF PHOSPHORAMIDATES

The ready conversion of (42) to (43) indicates that the recent explanation[24,35] for the apparent ambident nucleophilic properties of neutral amides may be extended to the related phosphoramidates. This requires that electrophilic substitution (e.g. by alkyl halides) of neutral phosphoramidates proceeds most readily at the O-atom, with N-substitution arising from subsequent rearrangement. Thus O-alkylphosphorimidates are the kinetic products and N-alkylphosphylamides are the thermodynamically stable ones. Significantly, there is independent evidence which suggests that reaction temperature influences product orientation. Thus O-alkylation is favoured under mild, neutral conditions (i.e. low temperature) by reactive reagents (e.g. triethyloxonium hexafluorophosphate)[58]. However, the use of higher

temperatures and less reactive reagents (e.g. alkyl halides, trialkylmetal chlorides) produces either a mixture of O- and N-substituted products[41,50] or N-substituted products only[49].

These conclusions are reinforced by consideration of the potential energy profile for the rearrangement reaction (Figure 2.6.1.) which can be deduced from the above results. Significantly, this is also the potential energy diagram for the O-alkylation of phosphoramidates by alkyl halides.

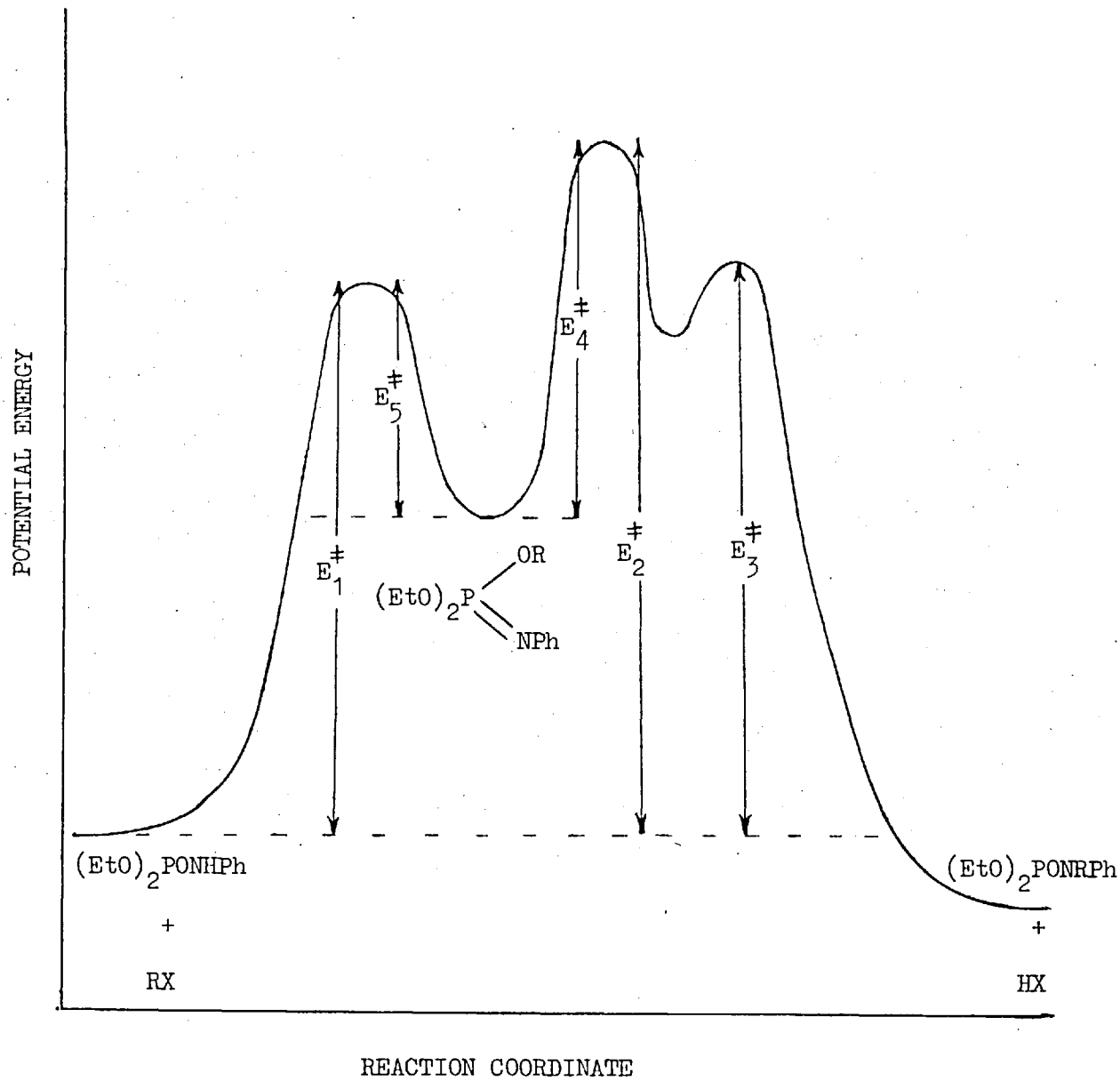
The diagram leads to some interesting conclusions. The inequality $E_1^{\ddagger} < E_2^{\ddagger}$ stems directly from the assumption of kinetic versus thermodynamic product control (but can also be deduced, see below) and $E_3^{\ddagger} < E_2^{\ddagger}$ from the above deduction that step k_a is rate-limiting for the rearrangement of (42) to (43) for alkyl halides (Scheme 14). The requirement that $E_5^{\ddagger} < E_4^{\ddagger} < E_1^{\ddagger}$ is less obvious but arises from the rapid and quantitative dealkylation of (42) in the presence of an equimolar amount of HBr or HI (Equation 2.6.1.) without significant concurrent or ensuing rearrangement to (43). This shows that dealkylation is faster than rearrangement of

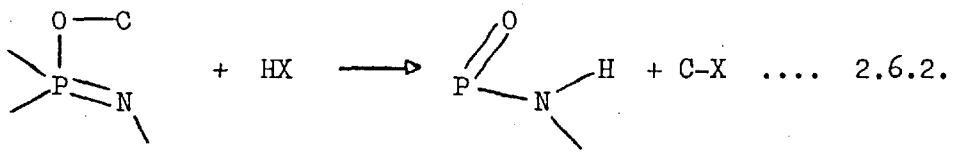
$$(EtO)_3P = NPh + HX \longrightarrow (EtO)_2PONHPh + EtX \quad .... \quad 2.6.1.$$
$$X = Br, I$$

(42) i.e. $E_5^{\ddagger} < E_4^{\ddagger}$ and that neither EtBr nor EtI alkylates diethyl N-phenylphosphoramidate under conditions where the catalysed rearrangement of (42) proceeds readily i.e. $E_4^{\ddagger} < E_1^{\ddagger}$. Moreover, the inequality $E_1^{\ddagger} < E_2^{\ddagger}$ now derives from the inequality $E_5^{\ddagger} < E_4^{\ddagger}$, since $E_1^{\ddagger} = E_5^{\ddagger} + E_1^{\ominus}$ and $E_2^{\ddagger} = E_4^{\ddagger} + E_1^{\ominus}$, and verifies the assumption of kinetic versus thermodynamic control.

Unfortunately, $E_1^{\ddagger}$ cannot be ascertained experimentally (the alkylation of phosphoramidates by alkyl halides proceeds with decomposition), but its lowest limit is given by the enthalpy difference, $E_1^{\ominus}$, for Equation 2.6.2. The relevant calculation for this process, using molar bond enthalpies[49,99]

FIGURE 2.6.1. POTENTIAL ENERGY DIAGRAM FOR THE ALKYLATION OF PHOSPHORAMIDATES WITH ALKYL HALIDES.





.... 2.6.2.

is given by Equation 2.6.3. which yields a value for $E_1^{\ominus}$ of 110 kJ mol^{-1}.

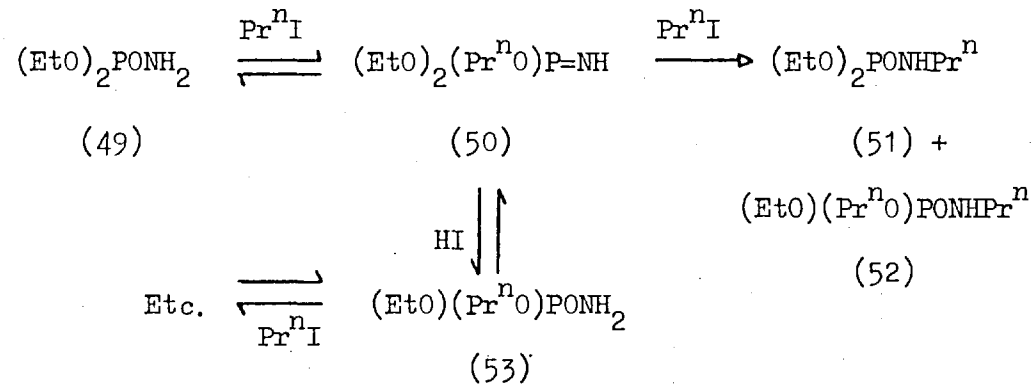
$$E_1^{\ominus} = \underline{D}(C\text{-}O) + \underline{D}(P\text{-}O) + \underline{D}(P{=}N) + \underline{D}(H\text{-}I) - \underline{D}(P{=}O) - \underline{D}(P\text{-}N) - \underline{D}(N\text{-}H) - \underline{D}(C\text{-}I) \quad .... \quad 2.6.3.$$

This is substantially higher than the experimental enthalpy of activation ($\Delta H^{\ddagger}$ = 64 kJ mol^{-1}) for the EtI-catalysed rearrangement of (42), and it follows that $E_4^{\ddagger} < E_1^{\ddagger}$ since $E_1^{\ddagger} > E_1^{\ominus}$ and $\Delta H^{\ddagger} \sim E_4^{\ddagger}$. This reaction profile appears to have wider applicability. A reduction of both $E_1^{\ddagger}$ and $E_2^{\ddagger}$ is anticipated for reaction with reactive alkylating agents and the salient feature in the successful synthesis of phosphinamidates with $Et_3O^+PF_6^-$ may be the low nucleophilicity of the PF_6^- counter ion.

Further, the finding that Ag^+ salts are likely to be less useful in the direct synthesis of phosphorimidates from phosphoramidates was borne out by the attempted alkylation of diethyl N-phenylphosphoramidate by EtI, $EtNO_3$ and MeI in the presence of either $AgNO_3$, AgI or Ag_2O. The reaction of MeI/Ag_2O apart, no reaction was observed at 35°C in CD_3CN or ether for any reagent combination. At 100°C no reaction was observed with $MeNO_3$ but MeI produced extensive P-N bond cleavage yielding metaphosphate gum. Dimethyl sulphate behaved similarly. In the presence of Ag_2O however, MeI yielded diethyl N-methyl-N-phenylphosphoramidate quantitatively in accordance with Rate = 1.7 x $10^{-5} M^{-1} s^{-1}$ [Substrate][MeI]. The direct N-alkylation apparent here may reflect either reaction via the phosphoramidate anion or rapid Ag^+-catalysed O- to N- rearrangement as noted earlier. Moreover Ag^+ salts of phosphoramidates are known to yield N-alkylated products[57].

Significantly, the earlier finding[41] that reaction of $(EtO)_2PONH_2$ (49)

with Pr^nI at 100°C gave five of eight possible phosphoramidates (Scheme 15) is also accounted for by the above mechanism. Initial reaction of (49) yields the phosphorimidate (50) which, under the reaction conditions, can undergo rearrangement to (51) and (52) with Pr^nI or dealkylation to (53). Although Pr^nI was in vast excess over HI, these processes would be competitive since $k^{HI} \gg k^{PrI}$ (<u>vide supra</u>). Reaction of (53) should pro-



SCHEME 15. REACTION OF $(EtO)_2PONH_2$ WITH Pr^nI.

ceed similarly leading eventually to $(Pr^nO)_2PONH_2$ and $(Pr^nO)_2PONHPr^n$. Both primary and secondary phosphoramidates are accounted for by this mechanism but the lack of any tertiary compounds is more difficult to explain. However, the finding that $(EtO)_2PONHPh$ did not give either $(EtO)_3P{=}NPh$ or $(EtO)_2PONEtPh$ on reaction with EtI indicates that either $E_1^{\ddagger}$ for primary phosphoramidates is less than $E_1^{\ddagger}$ for the corresponding secondary compounds or the ratio $E_4^{\ddagger}/E_5^{\ddagger}$ for the primary compounds is less than that for the secondary ones Significantly, $(MeO)_3P{=}NH$ is known to rearrange rapidly at ambient temperatures[77]. Propylammonium salts can be accounted for by cleavage of the phosphoramidates by HI (Equation 2.6.4.) yielding an amine

$$(RO)_2PONHR + HI \longrightarrow (RO)PO_2 + RNH_2 + RI \text{ } \underline{etc.} \quad .... \quad 2.6.4.$$

which can react further with PrI.

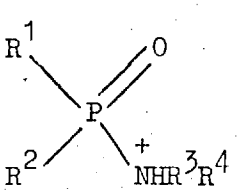
CHAPTER 3

THE PROTONATION OF PHOSPHORAMIDATES

3.1. INTRODUCTION

Having shown that, at least for alkylation, the nucleophilic chemistry of phosphoramidates can be interpreted in terms of reactivity residing at the O-atom, it was of interest to determine whether this scheme could be extended to reaction with other electrophilic reagents. The behaviour to one of the simplest electrophiles, the proton, was therefore briefly undertaken.

As with amides[12], there has been much speculation and controversy as to the exact site of protonation of phosphylamidates. The latter case is more complicated, however, by rapid cleavage of the P-N bond under acidic conditions[42]. Thus any protonated species is short lived making the relevant spectra unobservable. Much use, therefore, has been made of the kinetic data for hydrolysis. The evidence for phosphinamidates[42,44] points to hydrolysis occurring *via* an N-protonated species (*e.g.* 54) but it has been noted that phosphoramidates may well O-protonate to give (55, R^1,R^2 = alkoxy or aryloxy) [43]. It has also been suggested that protonated phos-



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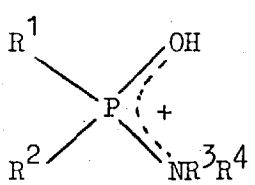
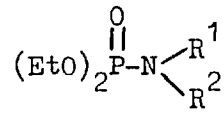


(55)

phinamidates may well exist as the O-protonated tautomer (55, R^1,R^2 = alkyl or aryl) with reaction occurring through the N-protonated species[44].

3.2 BEHAVIOUR IN AQUEOUS SULPHURIC ACID

In accord with previous observations[43], phosphoramidates (56, a - e) hydrolyse rapidly in aqueous H_2SO_4. Indeed, in 1.0 M to 17.5 M the reactions are too fast to be followed by n.m.r. spectroscopy ($t_{\frac{1}{2}} < 15s$).



(56) a $R^1=R^2=H$

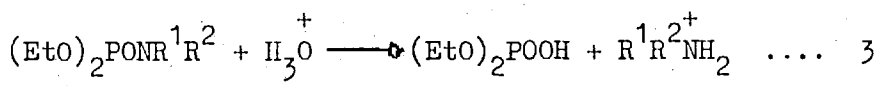
b $R^1=H$, $R^2=CH_3$

c $R^1=R^2=CH_3$

d $R^1=H$, $R^2=Ph$

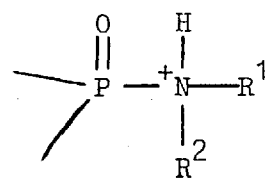
e $R=Et$, $R^2=Ph$

Only in 0.1 M and 18 M solutions was the hydrolysis (Equation 3.2.1.) slow enough to be observed.



$$(EtO)_2PONR^1R^2 + H_3O^+ \longrightarrow (EtO)_2POOH + R^1R^2NH_2^+ \quad .... \quad 3.2.1.$$

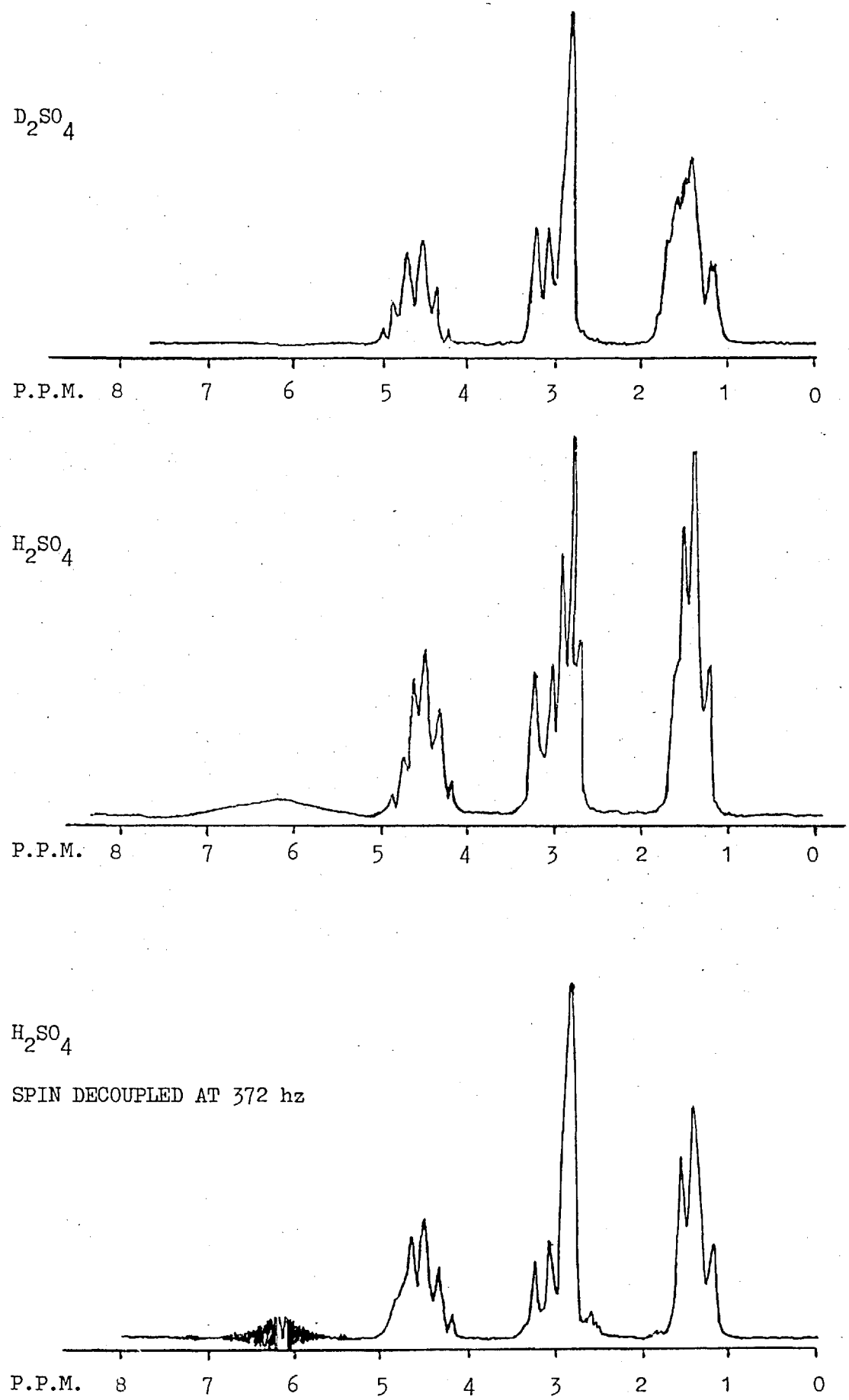
The ammonium ions were characterised by comparing the n.m.r. spectra of the reaction solutions with those obtained by dissolving the corresponding ammonium chloride or sulphate in identical $[H_2SO_4]$ solutions. Confirmation that the signals were due to ammonium ions and not a coincidence of P- and NH- coupling constants (e.g. in 57) was obtained both by



(57)

spin-decoupling and observing the behaviour of the phosphoramidates in D_2SO_4 solutions. Spin decoupling at the $-\underline{N}\underline{H}^+$-signal produced a singlet (Figure 3.2.1.) for the $-\underline{N}\underline{C}\underline{H}_3$ groups (in 56b,c) indicating that the latter was no longer coupled to P- as a result of P-N cleavage. In D_2SO_4, no ammonium protons were observed, as expected, and, as for the decoupling experiment, singlets for the $-\underline{N}\underline{C}\underline{H}_3$- signals (in 56b,c) were produced (Figure 3.2.1.).

FIGURE 3.2.1. ^{1}H N.M.R. SPECTRA OF $(EtO)_2PONMe_2$ IN 60% H_2SO_4 AND 60% D_2SO_4.



No loss of the EtO- groups for (56,a-e) was observed at any acidity and no competitive cleavage[100] of the N-C and P-N bonds was apparent.

The behaviour of (56d) in 97% H_2SO_4 and D_2SO_4 solutions was interesting. The n.m.r. spectra indicated that substitution of the aromatic nucleus had occurred. Significantly, anilinium sulphate did not react in 98% H_2SO_4 over the same period of time indicating that sulphonation of the phosphoranilidate must occur. Moreover, (56b) is only hydrolysed slowly in this medium ($t_{\frac{1}{2}} \sim 5$ min.) implying (56d) has a sufficient lifetime to sulphonate.

These results show that nitration of (56d), which yields substantial amounts of m-nitro-aniline[43a], does not proceed via the N-protonated species (54) but more probably occurs via the anilinium ion released by hydrolysis (Equation 3.2.2.).

$$(EtO)_2PONHPh \xrightarrow{H_2SO_4} PhNH_3 \xrightarrow{+\ HNO_3} \text{o-, m- and p-nitroanilines} \quad \ldots\ 3.2.2.$$

3.3. BEHAVIOUR IN OLEUM AND FLUOROSULPHONIC ACID

As the hydrolysis of (56 a-e) was found to be slow in 97% H_2SO_4, the stability of (56 a-c) in oleum and FSO_3H was examined. Oleum solutions were made by mixing oleum (1 ml, containing ca. 20% free SO_3) and 97% H_2SO_4 (4 ml).

As expected, (56 a-c) were stable enough in these solutions to record their n.m.r. spectra. No rapid cleavage of the P-N bond was observed for (56b,c): $\underline{P}NC\underline{H}_3$ coupling is preserved (Figure 3.3.1.). In FSO_3H, however, some cleavage to the ammonium salt was observed, although (56c) was stable enough to record its spectrum, which did not alter significantly at -50°C. Chemical shifts are presented in Table 3.3.1., where comparison to those in CCl_4 is valuable. Both (56b,c) show significant downfield shifts of the $-OC\underline{H}_2-$ and $-NC\underline{H}_3$ absorbtion signals on changing the solvent from CCl_4 to either oleum or FSO_3H, and, moreover, the extent of this shift for

FIGURE 3.3.1. ^{1}H N.M.R. SPECTRUM OF $(EtO)_2PONMe_2$ IN OLEUM/H_2SO_4 (2:3) SOLUTION.

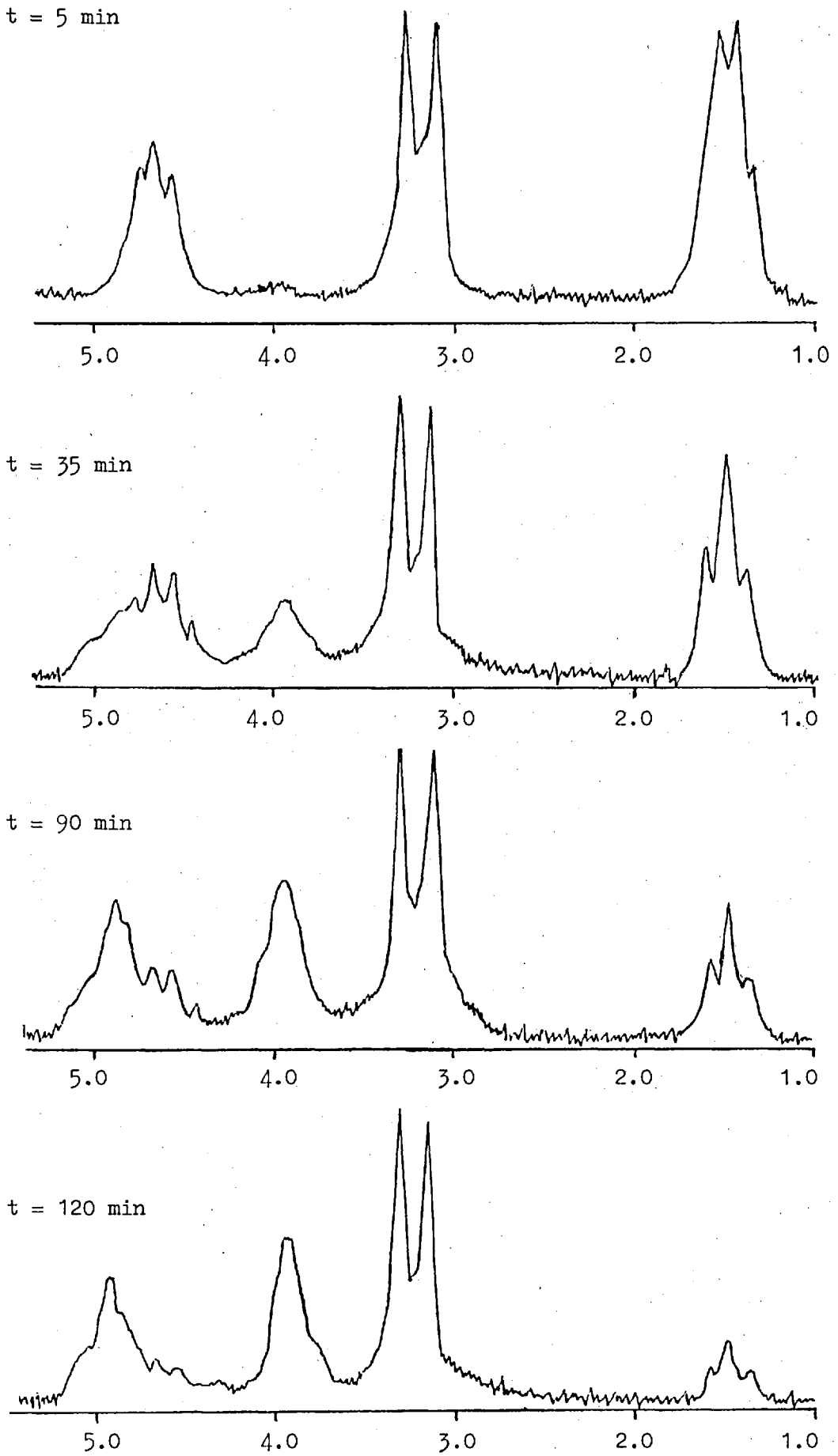


TABLE 3.3.1. H N.M.R. CHEMICAL SHIFTS (S) FOR PHOSPHORAMIDATES (56b,c) IN OLEUM, FSO_3H AND CCl_4 SOLUTIONS.

	$(EtO)_2PONHCH_3$		$(EtO)_2PON(CH_3)_2$	
	$POCH_2$	$PNCH_3$	$POCH_2$	$PNCH_3$
OLEUM	4.70	3.26	4.72	3.26
FSO_3H			4.61	3.11
CCl_4	4.00	2.52	4.06	2.67

$-OCH_2-$ is almost identical to that for $-NCH_3$ *viz.* 0.68 p.p.m. Considering the two protonated species, it may be anticipated that the $-NCH_3$ signal for the N-protonated form (54) would exhibit a greater downfield shift than the $-OCH_2-$ signal. For the O-protonated form (55), one might expect a comparable shift for both signals, assuming that the O- and N-atoms will not have a vastly different shielding effect.

No coupling of the $-NCH_3$ group to a proton (*e.g.* *via* N-protonation) was found, although broadening of this signal was observed. Phosphorus

TABLE 3.3.2. $J(PXCH_3)$ COUPLING CONSTANTS FOR $R_3P=O$.

COMPOUND	$J(CHCl_3)$/hz	$J(H_2SO_4)$/hz
$(CH_3CH_2)_3P=O$[a]	16.6	19.5
$Ph_2(CH_3O)P=O$[a]	11.1	12.1
$(EtO)_2(CH_3NH)P=O$	12.2	12.1
$(EtO)_2\ (CH_3)_2N\ P=O$	10.0	10.5 (10.25)[b]

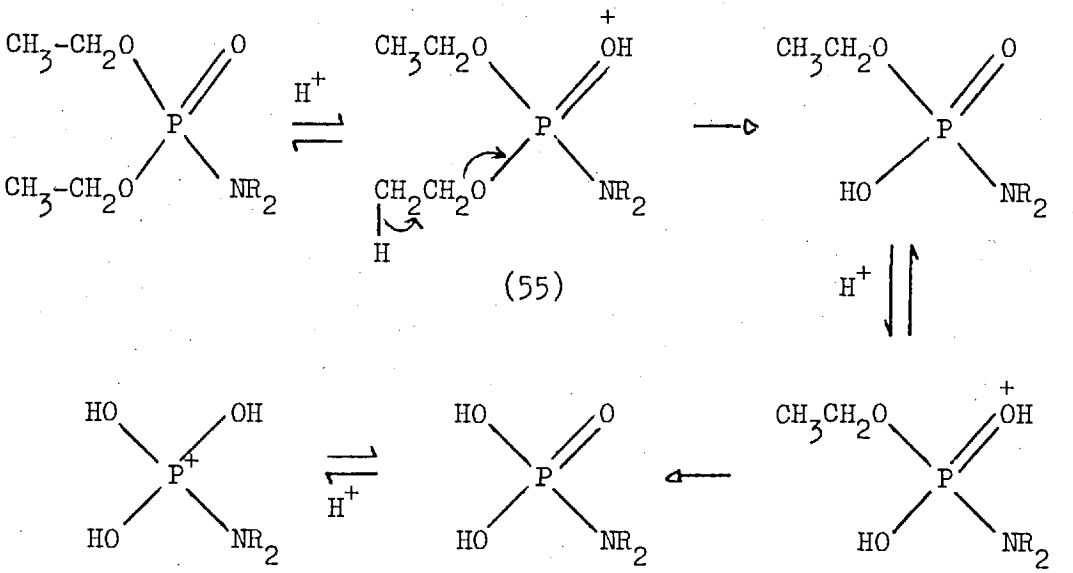
a. From ref. 46.

b. In FSO_3H.

coupling constants, J(PNCH), are not significantly changed from those in $CHCl_3$ (Table 3.3.2.). It has been argued[46] that PXCH coupling constants are increased on O-protonation (Entries 1 and 2, Table 3.3.2.). Since coupling occurs via different X-atoms it is unwise to attribute much meaning to such analysis. The above results show that there is very little change in P-coupling constants on protonation of phosphoramidates (56b,c) and do not indicate which protonated form [(54) or (55)] is dominant.

On standing, solutions of (56,a-c) show loss of both EtO- groups. This process was followed by monitoring the loss of the $-CH_3-$ triplet in the n.m.r. spectrum (Figure 3.3.1.). New signals at δ 3.93 (broad) and 4.85 (broad) p.p.m. were observed. Significantly, no cleavage of the P-N bond occurred: PNCH coupling was preserved (Figure 3.3.1.).

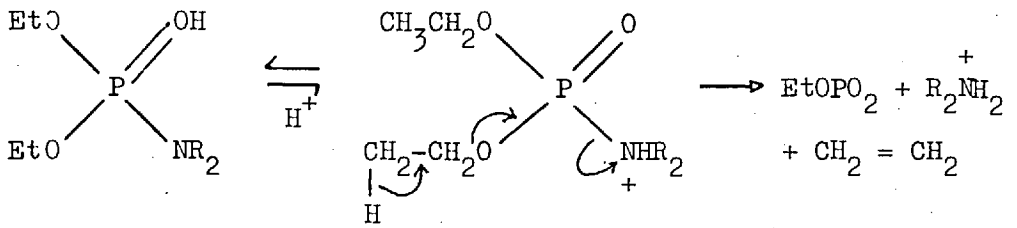
These results point to formation of the O-protonated species (55) in oleum solutions (Scheme 16). Dealkylation to the phosphoramidic acid then



SCHEME 16. PROTONATION AND DECOMPOSITION OF PHOSPHORAMIDATES IN OLEUM SOLUTION.

follows. If N-protonation had occurred, one would anticipate significant P-N bond cleavage (via the alternative process in Scheme 17): the P-N

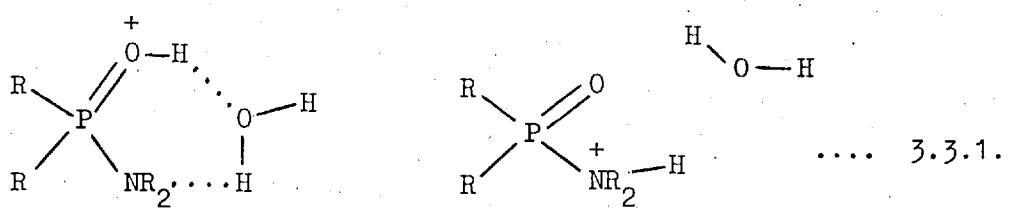
bond is resistant to alkali but is rapidly broken in aqueous acid[43].



SCHEME 17. ALTERNATIVE PROTONATION AND DECOMPOSITION OF PHOSPHORAMIDATES IN OLEUM SOLUTION.

Significantly, the change in chemical shifts is more adequately explained by O- rather than N-protonation.

The rapid cleavage of the P-N bond in aqueous acidic media probably involves a rapid proton transfer from the O- to the N-atom via a water molecule (Equation 3.3.1.) despite a qualitative argument to the contrary[42].



.... 3.3.1.

3.4. BEHAVIOUR IN CF_3CO_2H

In order to detect a protonated species, the stability of (56,a-c) was examined in CF_3CO_2H or CF_3CO_2H/CCl_4 solutions. Slow cleavage of the P-N bond was detected by the appearance of signals due to the corresponding ammonium ions. For (56b,c) no coupling of the NCH_3- signals to any proton was observed but downfield shifts of 0.11 p.p.m. for both the $-NCH_3$ and $-OCH_2$- signals from those in CCl_4 occurred. Further, for (56b) coupling to the -NH- proton is lost. Unfortunately no protonated species could be detected. Only one absorbtion signal, accounting for both the CF_3CO_2H and -NH- protons, was detected at all $\left[CF_3CO_2H\right]\left\{\left[CF_3CO_2H\right]\right. = 0.27$

(1 equiv.) - 12M} even on lowering the temperature to -20°C.

At all temperatures the -NE$\underline{H}_3$ signal remained a doublet, J(PNCH) = 12.4 hz [for (56b)] and J(PNCH)= 10 hz [for (56c)].

These results reinforce those obtained in oleum, where the similar shift of the -$\underline{O}CH_2$- and -$\underline{N}CH_3$ signals and the unchanged coupling constants favoured protonation on the phosphoryl oxygen atom.

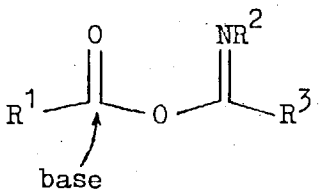
CHAPTER 4

THE ACYLATION OF NEUTRAL PHOSPHORAMIDATES

4.1. INTRODUCTION

Mixed anhydrides are widely used in peptide chemistry to form an amide bond. Often, however, they suffer the tendency to disproportionate to symmetrical anhydrides and lack of regiospecificity of nucleophilic attack[101]. Carbodiimide mediated condensations further undergo a wasteful O- to N- intramolecular acyl migration. The use of N-alkoxy or N-amino amides, however, was found to eliminate this thermal rearrangement, although the process was shown to be catalysed by base. Attack did proceed at the C=O, and not the C=N, function however[4] (cf. 58).

Mixed carboxylic-phosphoric anhydrides (59) are known to be useful acylating agents but they, too, suffer lack of regiospecificity. Thus alcohols generally attack the phosphoryl group whereas amines attack the carbonyl moiety[101].



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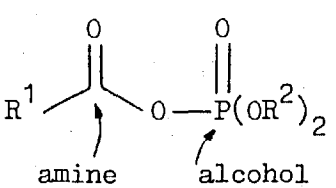

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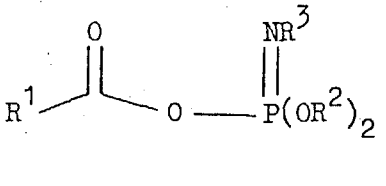


(60)

It was hoped that mixed anhydrides derived from phosphorimidic acid (60) may overcome these problems and provide useful peptide-linkage forming reagents.

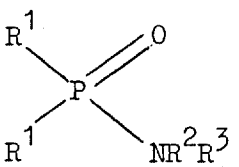
Since both alkylation and protonation of neutral phosphoramidates produces the O-substituted isomer, the acylation of these compounds by various acylating agents was explored towards a simple and convenient route to (60).

4.2. ACYLATION BY ACYL HALIDES

4.2.1. IN THE ABSENCE OF BASES

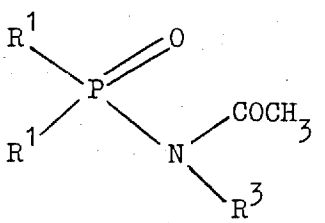
These reactions were examined in several solvents but most of the following results refer to benzene or carbon tetrachloride. These were chosen because rearrangement of O-alkyl phosphorimidates is slower in solvents of low polarity (cf. Chapter 2). The reactions were carried out at ca. 30°C to minimise any thermal rearrangement of products.

In the absence of added base, diethyl N-methylphosphoramidate (61a) reacted with acetyl chloride in carbon tetrachloride or benzene to give only diethyl N-acetyl-N-methyl-phosphoramidate (62a) by comparison of



(61)

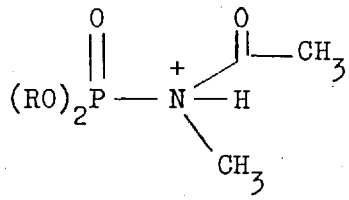
a. R^1=EtO, R^2=H, R^3=Me
b. R^1=EtO, R^2=H, R^3=Ph
c. R^1=EtO, R^2=H, R^3=$PhCH_2O$
d. R^1=EtO, R^2=R^3=Me
e. R^1=Me_2N, R^2=R^3=Me



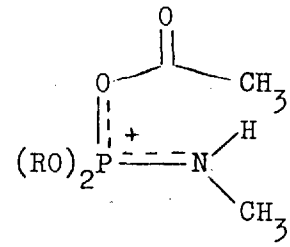
(62)

spectral data with an authentic sample. The reactions were followed by monitoring either the decrease of the N-Me n.m.r. signal of (61a) or the increase in the n.m.r. N-Me doublet J(PNCH) of the N-acetyl product (62a). Immediately after the addition of CH_3COCl the reaction solution showed that the N-Me quartet of (61a), due to coupling with both the P (J= 12.5 hz) and NH (J = 5.5 hz) atoms, had collapsed to a doublet (J = 12.5 hz). No N-acetyl product was observable at this stage which suggests that either: (a) an intermediate (possibly the O-acylphosphorimidate) is formed, or (b) a small amount of either (63) or (64) is produced which allows an exchange process to occur, destroying coupling to the -NH-proton.

Of the two interpretations, (b) is preferred because:



(63)



(64)

i) no change in the chemical shift of the N-CH_3 group is apparent : $\delta(CCl_4)$ 2.50, $\delta(CCl_4/AcCl)$ 2.50; $\delta(C_6H_6)$ 2.47, $\delta(C_6H_6/AcCl)$ 2.47.

ii) the P-N-C-H coupling constant is unaltered { $J(CCl_4)$ 12.5 hz, $J(CCl_4/AcCl)$ 12.5 hz } yet it is known that J(P-N-C-H_3) for O-alkyl N-methyl-phosphorimidates, ca. 24 hz, is larger than those for the corresponding phosphoramidates[96]. We have shown however, (Chapter 3), that O-protonation does not significantly alter the size of the J(P-N-C-H) coupling constant.

iii) with acetic anhydride { which does not react with $(EtO)_2PONHMe$, vide infra } containing 0.1% acetyl chloride, the conversion of the -NCH_3 quartet to a doublet was complete in ca. 15 min. No new acetyl signal is observable (Figure 4.2.1.1.) which suggests that the loss of coupling is not associated with complete conversion of the starting material to an O-acyl intermediate.

iv) The ^{31}P n.m.r. spectrum of a benzene/[$^2H_6$]-benzene solution of $(EtO)_2$PONHMe in the presence of an equimolar amount of Ac_2O and 0.1 equivalents of AcCl shows no evidence of a new species even after 1 h, i.e. after such time as the J(HNCH_3) coupling was destroyed in the ^1H n.m.r. spectrum (Table 4.2.1.1.). After 24 h a new ^{31}P absorbtion was observed (Table 4.2.1.1.) corresponding to the formation of $(EtO)_2PONMe(COCH_3)$.

v) The infra-red spectra of the reaction in either CCl_4 (at 0°C or 25°C) or benzene (at 7°C or 25°C) showed the sustained presence of the N-H stretching frequency at 3200 cm^{-1} (starting material) even when coupling in the n.m.r. spectrum was lost (Figure 4.2.1.2.). Even though it may be argued

FIGURE 4.2.1.1. N.M.R. SPECTRUM OF $(EtO)_2PONHMe$ IN CCl_4 IN THE PRESENCE OF $AcCl/Ac_2O$ AT 34°C.

$[(EtO)_2PONHMe] = .99M \quad [Ac_2O] = .73M \quad [AcCl] = 1.06 \times 10^{-2}M$

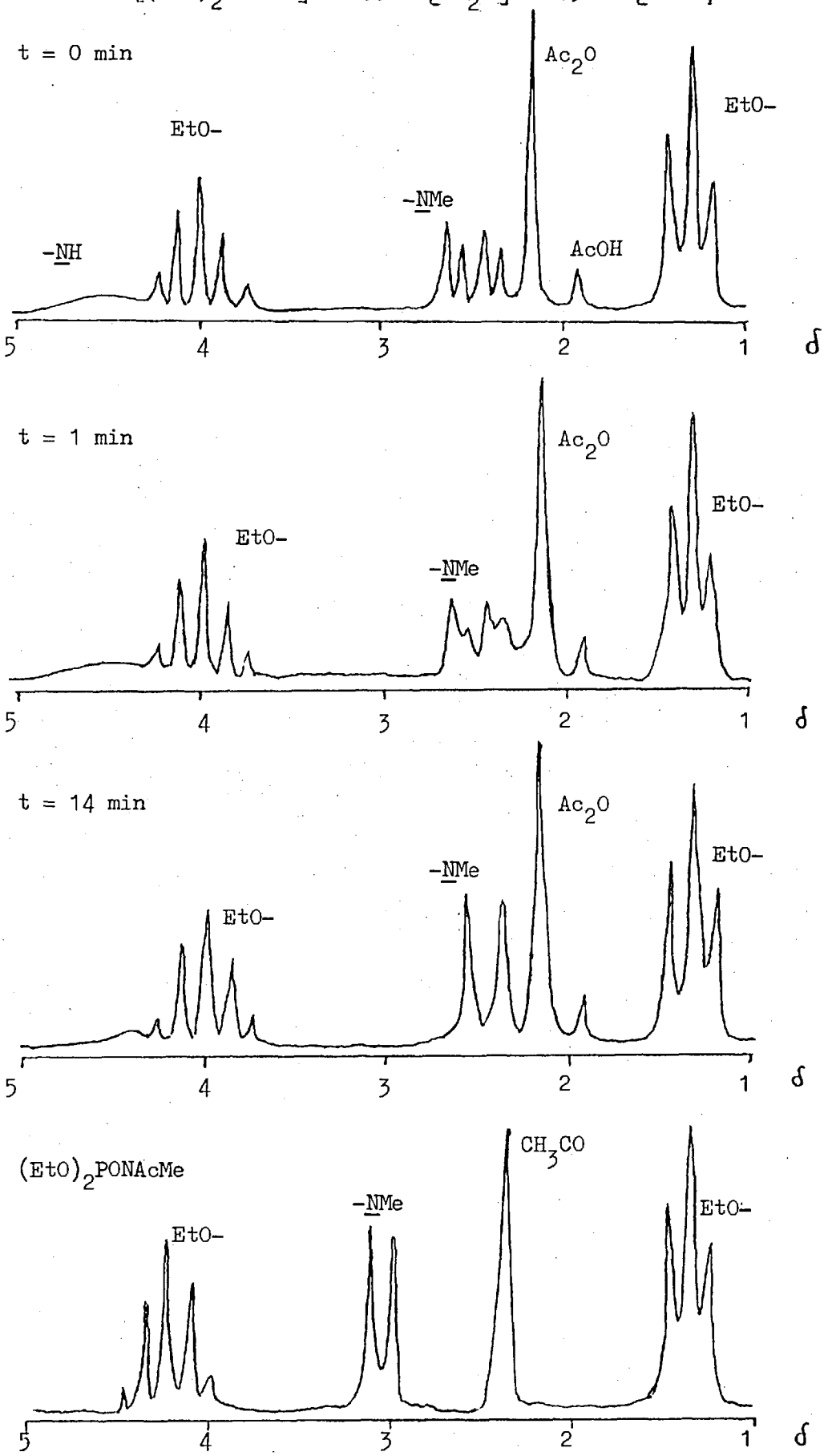


TABLE 4.2.1.1. PROTON-NOISE DECOUPLED ^{31}P CHEMICAL SHIFT STUDY OF THE ACYLATION OF $(EtO)_2PONHMe$ BY $Ac_2O/AcCl$ IN BENZENE AT 30^oC.

COMPOUND	δ^a
$(EtO)_2PONHMe$	+7.69
$(EtO)_2PONMe(COCH_3)$	-9.18
$(EtO)_3P = NCOPh$	+11.95
$(EtO)_2PONHMe + Ac_2O/AcCl$ [b]	+7.62
$(EtO)_2PONHMe + Ac_2O/AcCl$ [c]	+7.55, -0.23

a. Relative to external $(MeO)_3P$

b. After 1 h.

c. After 24 h.

that both (63) and (64) will exhibit similar N-H stretching frequencies the absence of new C=O absorbtions again suggests that no substantial concentration of an O-acyl intermediate is formed (Figure 4.2.1.2.). However, after 90 h, a decrease in the intensity of the N-H and acetyl chloride C=O absorbtions was found together with a concomitant appearance of new C=O and P=O absorbtion bands at 1700 and 1290 cm^{-1} corresponding to those of $(EtO)_2PON(COCH_3)CH_3$.

vi) the u.v. spectrum of (61a) and acetyl chloride in cyclohexane solution at 25^oC (Figure 4.2.1.3.) was identical to that expected from superimposing their individual spectra. Again, as the reaction was allowed to proceed, the spectrum indicated formation of $(EtO)_2PON(COCH_3)CH_3$.

Similar spectroscopic effects were observed using other acyl halides e.g. acetyl bromide, chloroacetyl chlorides and benzoyl chlorides. Thus, in the presence of 4-chlorobenzoyl chloride the $J(\underline{H}NC\underline{H}_3)$ coupling was destroyed immediately, although the N-H i.r. stretching frequency of

FIGURE 4.2.1.2. INFRA-RED SPECTRA OF THE REACTION OF $(EtO)_2PONHMe$ WITH AcCl IN CCl_4 AT 0°C.
$[(EtO)_2PONHMe]$ = 0.137M, [AcCl] = 0.137 M

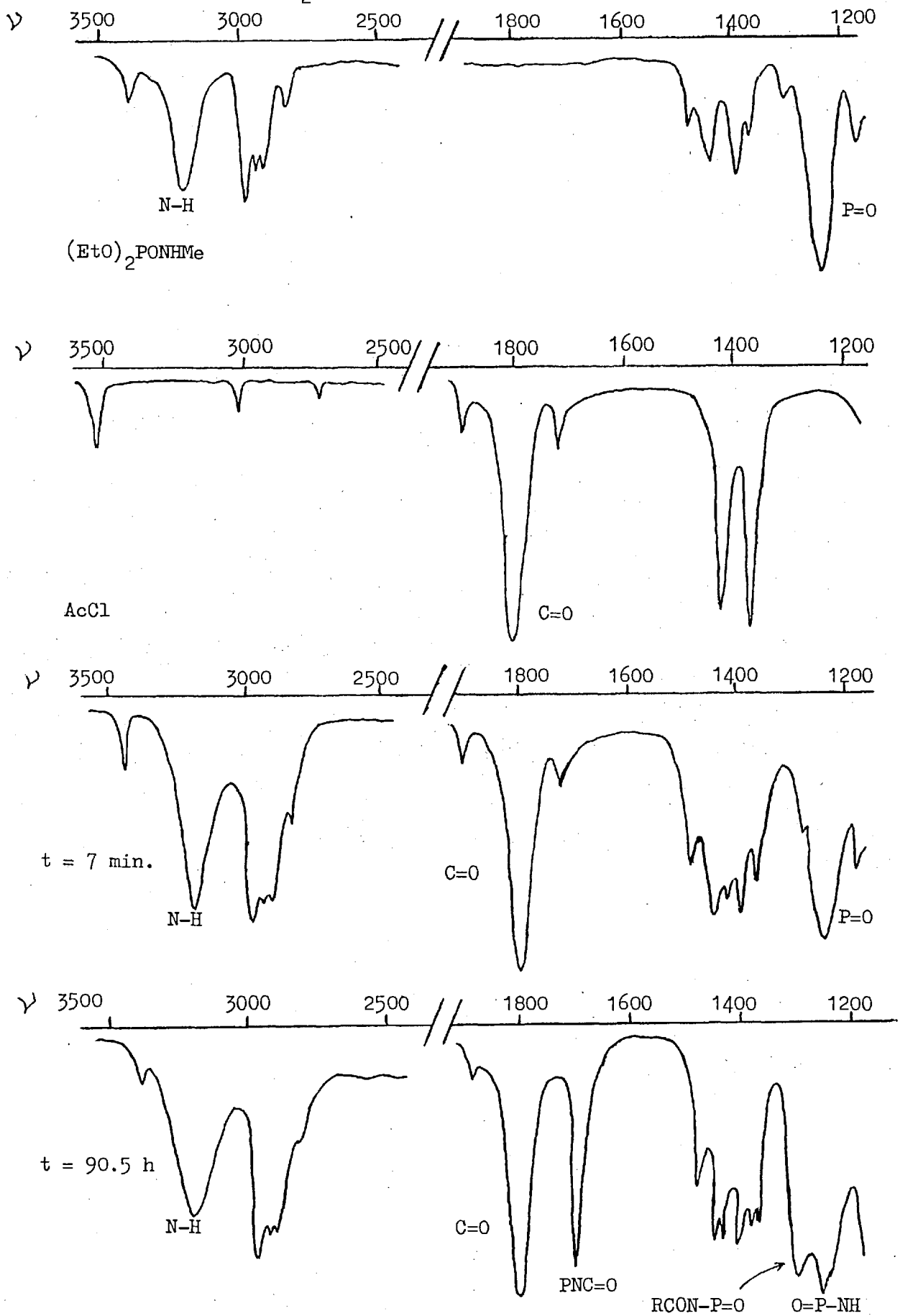
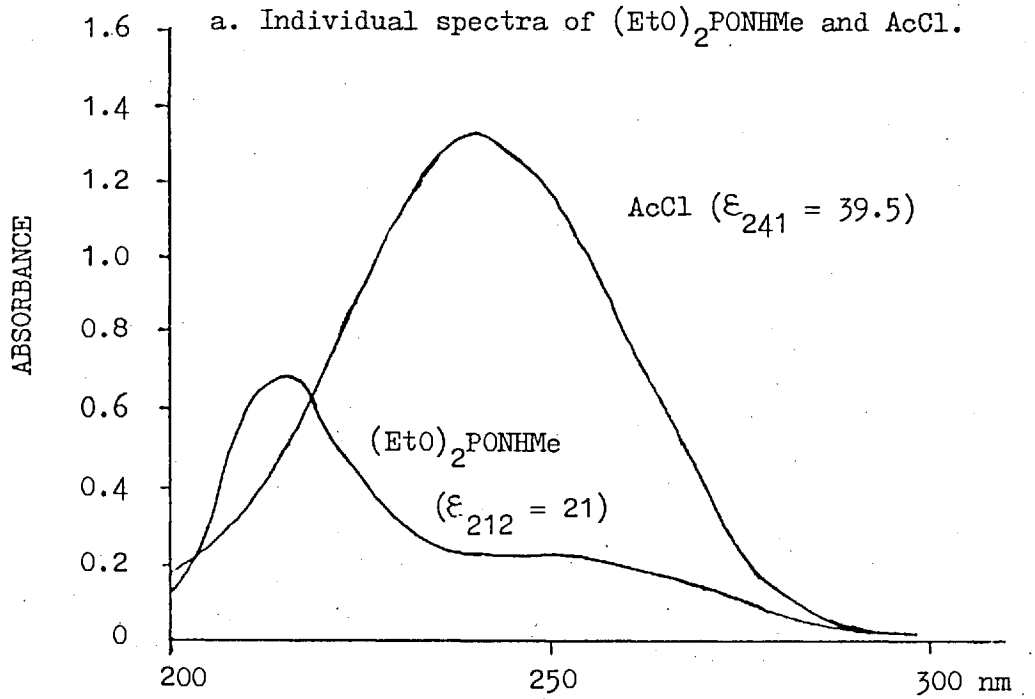


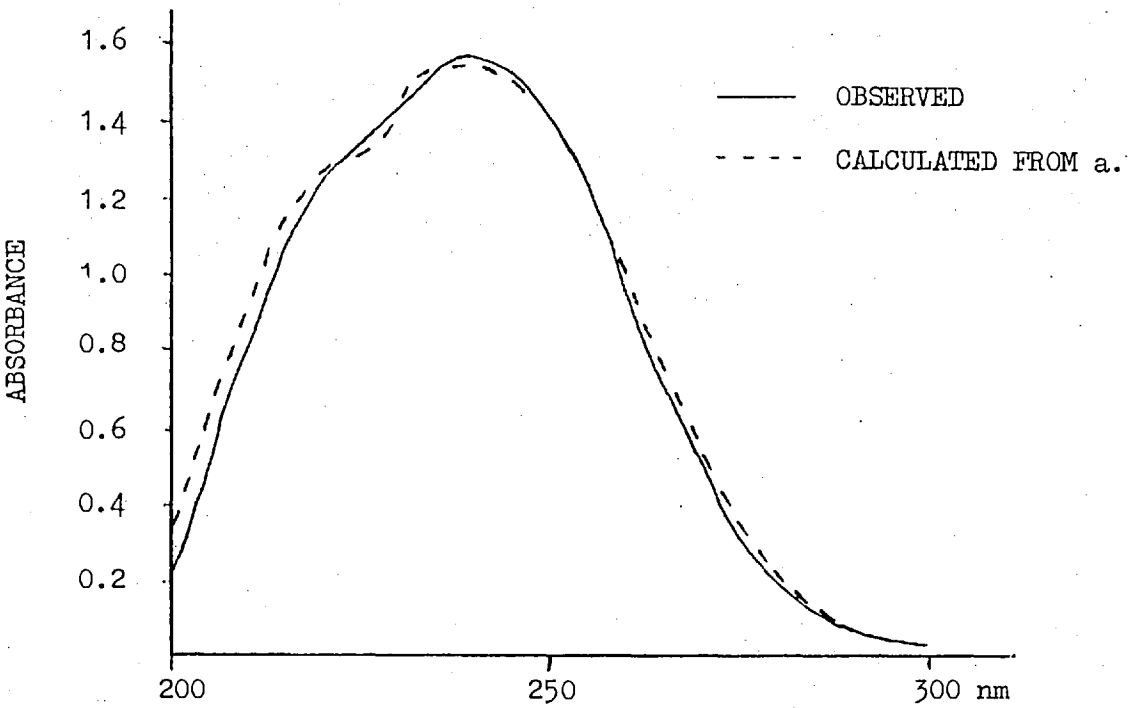
FIGURE 4.2.1.3. ULTRA-VIOLET SPECTRUM OF $(EtO)_2PONHMe$ IN CYCLOHEXANE IN THE PRESENCE OF AcCl AT 25°C.

$[(EtO)_2PONHMe] = [AcCl] = 3.325 \times 10^{-2}$ M

a. Individual spectra of $(EtO)_2PONHMe$ and AcCl.



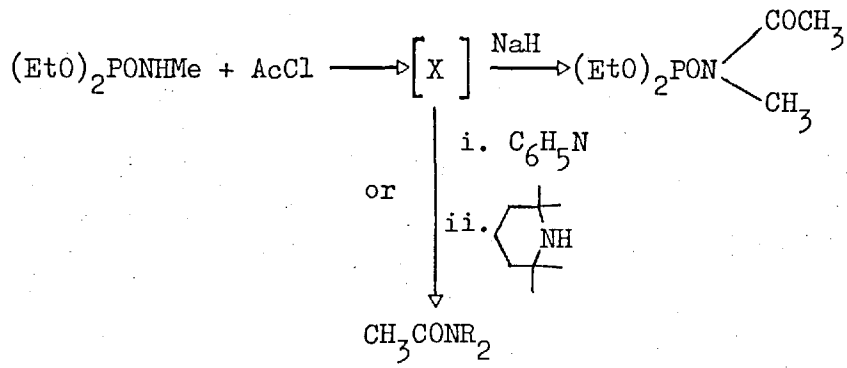
b. Spectrum of a solution of $(EtO)_2PONHMe$ and AcCl.



$(EtO)_2PONHMe$ at 3205 cm^{-1} was preserved.

These spectroscopic observations show that substantial formation of an O-acyl intermediate is unlikely and if formed it must rapidly rearrange to the N-acyl product. Attempts to trap any intermediate by chemical means were therefore undertaken (Scheme 18).

Thus acetyl chloride was added to (61a) in CCl_4 followed, 15 min. later, by pyridine. N-Acetylpyridinium chloride, rather than pyridine hydrochloride precipitated immediately. Similarly, 2,2,6,6-tetramethyl-



SCHEME 18.

piperidine formed N-acetyl-2,2,6,6-tetramethylpiperidine. Addition of sodium hydride in a similar fashion liberated hydrogen and formed (62a) quantitatively. As before, no new CH_3CO absorbtion signal was observed in the n.m.r. spectrum which could be attributed to an intermediate.

In the absence of added base the product obtained by acylation of the phosphoramidate undergoes P-N bond cleavage to form an amide (Equation 4.2.1.1.). The extent of cleavage appears to depend on both the N-acyl-

$$(EtO)_2PONHMe + RCOX \longrightarrow (EtO)_2PONMe(COR) + HX \longrightarrow RCONHMe \quad .... \quad 4.2.1.1.$$

phosphoramidate itself and HX. Thus acetyl chloride reacted with $(EtO)_2$ PONHMe to give $(EtO)_2PONACMe$ without significant cleavage whereas with acetyl bromide high yields of N-methyl-acetamide were obtained. This

probably relates to the enhanced nucleophilicity of Br^- over Cl^-. Similarly, 4-chlorobenzoyl chloride yielded N-methyl-4-chlorobenzamide [m.p. 156-159°C, ν_{max} 3280 (N-H), 1630 (C=O), 1430 cm^{-1}, $\delta(CCl_4)$ 3.00 (3H,d), 6.39 (1H,br) 7.60 (4H,Abq)] but monitoring the reaction solution by n.m.r. showed that cleavage of the N-acylphosphoramidate occurred almost as rapidly as its formation and CCl_3COCl gave $CCl_3CONHMe$ but no $(EtO)_2PON(COCl_3)Me$. The implication here is that P-N bond cleavage is more facile for strongly electron withdrawing acyl groups.

4.2.1.1. KINETICS

The rate of acylation of phosphoramidates (61, a-d) was also measured by ^1H n.m.r. spectroscopy. Reactions involving $(EtO)_2PONHMe$ or $(EtO)_2PONMe_2$ were followed by monitoring either the loss or the increase of the NMe absorbtion due to starting material or product respectively. Those for $(EtO)_2PONHPh$ were measured from the N-Ph singlet of the products and those involving $(EtO)_2PONHOCH_2Ph$ by the change in the OCH_2 signals of either starting material or product (Table 4.2.1.2.).

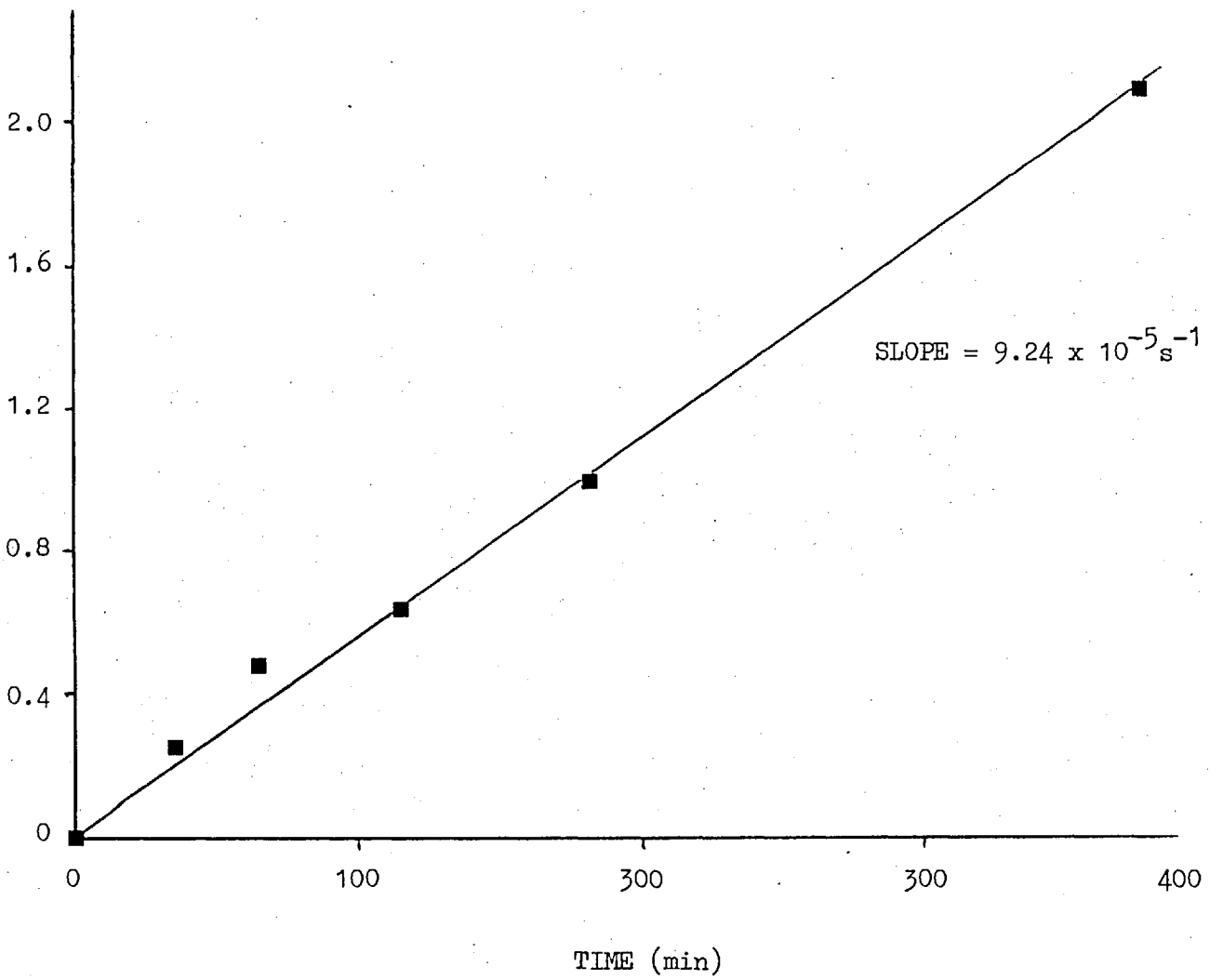
All the rates of reaction were found to exhibit a first-order dependence on [PHOSPHORAMIDATE]. Thus, the reaction of 0.665M (61 a) with 0.135M AcBr in the presence of 1.06M Ac_2O at 34°C which corresponds to pseudo-first-order conditions because Ac_2O does not react with the phosphoramidate (see Section 4.3) and [AcBr] is constant (vide infra) gave linear first-order plots of $\ln[(61a)]/[(61a)]_o$ (Figure 4.2.1.4.). Also an initial rate study of the reaction of 1-2M(61a) with 0.65M AcCl showed that increasing [(61a)] by a factor of 2 produced a 2.08 fold increase in the initial reaction rate (Figure 4.2.1.5.). These reactions also show a first-order dependence on [ACYL HALIDE]. This is apparent from observations that reaction of phosphoramidate (61a) with AcCl at two different [(61a)] follows overall second-order kinetics. Thus a plot of $\ln[(61a)]/[AcCl]$ versus

FIGURE 4.2.1.4. PSEUDO-FIRST ORDER PLOT OF THE ACYLATION OF (61a) BY $AcBr/Ac_2O$ IN CCl_4 AT 35°C.

$[AcBr] = 0.135$ M

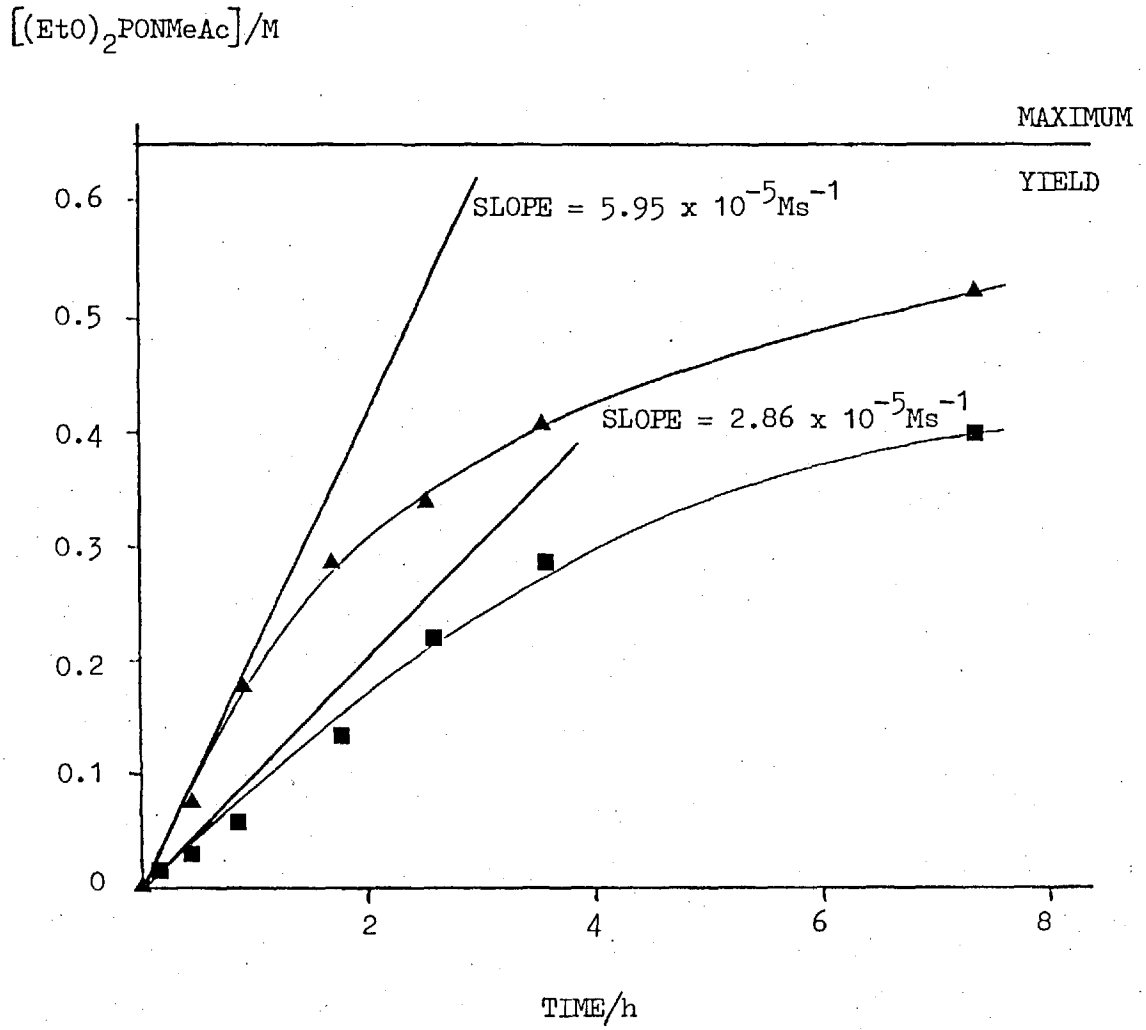
$[Ac_2O] = 1.06$ M

$[(EtO)_2PONHMe] = .665$ M



Second-order rate constant, $k_2 = 6.83 \times 10^{-4} M^{-1} s^{-1}$

FIGURE 4.2.1.5. INITIAL RATE STUDY OF THE ACYLATION OF (61a) BY AcCl AT 35°C.



▲ [(61a)] = 2 M [AcCl] = 0.65 M

■ [(61a)] = 1 M [AcCl] = 0.64 M

TABLE 4.2.1.2. ^{1}H N.M.R. SPECTRA OF (61;a-c) AND THE N-ACETYL DERIVATIVES (62;a-c) IN CCl_4.

	CH_3CH_2	N-R	CH_3CO	$-OCH_2$	NH
[61a]	1.33 t	2.60 dd		4.08 quin	3.20 br
[62a]	1.43 t	3.00 d	2.35 s	4.19 quin	
[61b]	1.35 t	7.05 m		4.10 quin	8.10 d
[62b]	1.21 t	7.33 s	2.07 s	4.10 quin	
[61c]	1.35 t	4.80 s[a] and 7.35 s[b]		4.17 quin	6.50 br
[62c]	1.43 t	5.01 s[a] and 7.43 s[b]	2.29 s	4.29 quin	

a. OCH_2-

b. $PhCH_2$-

time is linear (Figure 4.2.1.6.). Further acylation of (61c) under pseudo-first-order conditions *i.e.* in the presence of Ac_2O (see section 4.3) shows reasonable first-order dependence ($\pm$ 10%) on AcCl (Table 4.2.1.3.).

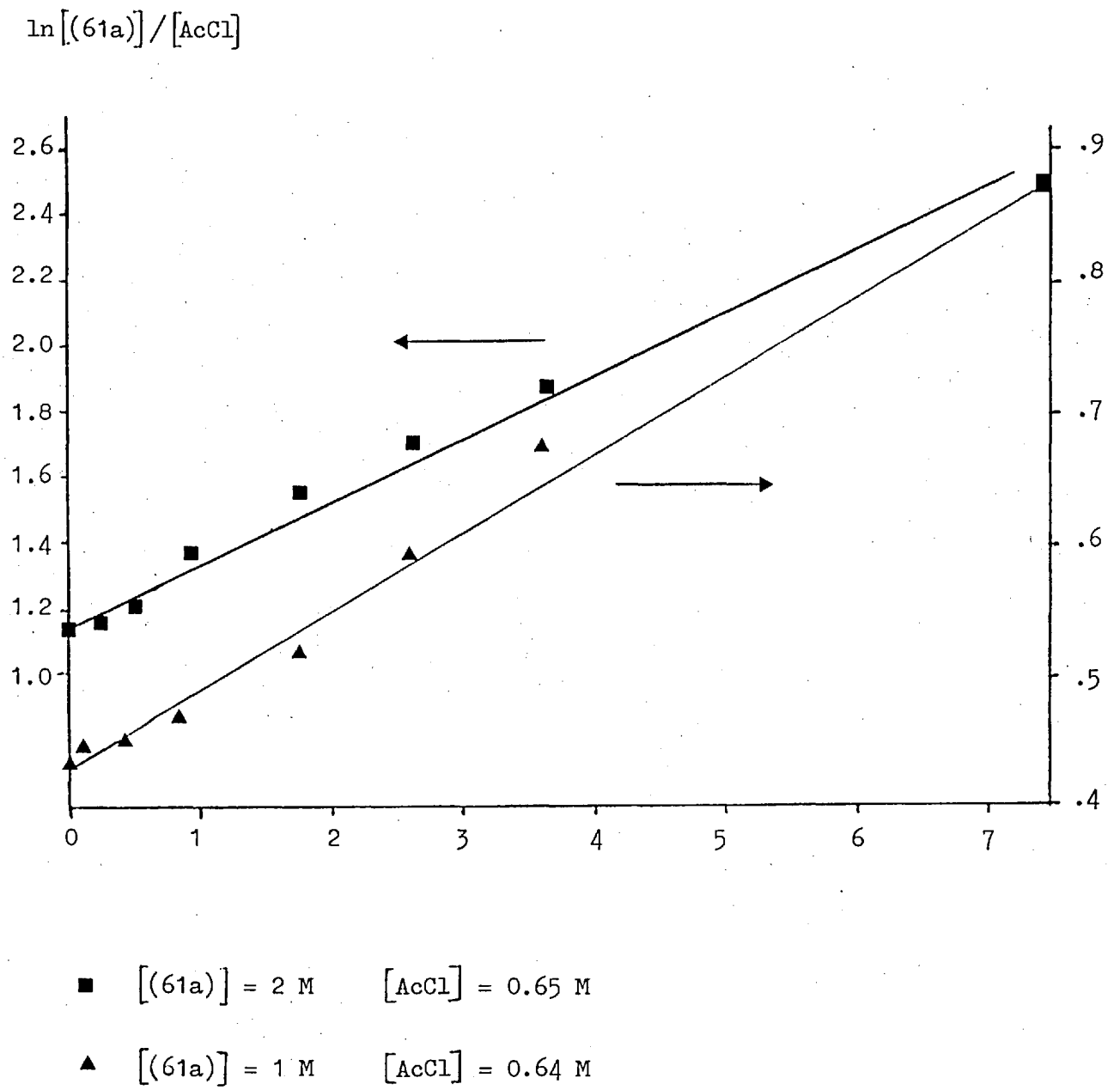
TABLE 4.2.1.3. FIRST-ORDER RATE CONSTANTS FOR THE ACYLATION OF (61c) BY AcCl IN CCl_4 AT 35°C.

$[(61c)]_0$ = *ca.* .53M

$[AcCl]$	$10^7 k_o/s^{-1}$	$10^6 k_2/M^{-1}s^{-1}$
.108	6.67	6.18
.710	52.1	7.34

Thus the rate equation governing these reactions is Rate = k_2

FIGURE 4.2.1.6. SECOND-ORDER PLOT FOR THE ACYLATION OF (61a) BY AcCl IN CCl_4 AT 35°C.



■ [(61a)] = 2 M [AcCl] = 0.65 M

▲ [(61a)] = 1 M [AcCl] = 0.64 M

$[\text{PHOSPHORAMIDATE}][\text{ACYL HALIDE}]$ and k_2 values calculated for various acyl halides and phosphoramidates are summarised in Table 4.2.1.4.

TABLE 4.2.1.4. SECOND-ORDER RATE CONSTANTS FOR THE ACYLATION OF PHOSPHORAMIDATES (61;a-d) BY VARIOUS ACYL HALIDES.

$[(61;a\text{-}d)]_o = 0.5 - 2M$ $\quad [RCOX] = 0.15 - 1.5M$

PHOSPHORAMIDATE	RCOX	SOLVENT	T°C	$10^6 k_2/M^{-1}s^{-1}$
(61a)	CH_3COCl	CCl_4	35	43.1
			25	24.1
	$CH_3COCl/AlCl_3$	CCl_4	25	a
	CH_3COCl	C_6H_6	25	13.2
	CH_3COCl	$CDCl_3$	35	102
	CH_3COBr	CCl_4	35	683
	$CH_2ClCOCl$	CCl_4	35	106.6
	$CHCl_2COCl$	CCl_4	35	72.5
	CCl_3COCl	CCl_4	35	2.9 [b]
	$4\text{-}ClC_6H_4COCl$	CCl_4	35	1.52
		C_5H_5N	35	20.4
	$4\text{-}CH_3C_6H_4SO_2Cl$	CCl_4	35	0
	$(CH_3)_3CCOCl$	CCl_4	35	0
(61b)	CH_3COCl	CCl_4	35	0
			100	0
(61c)	CH_3COCl	CCl_4	35	6.75
(61d)	CH_3COCl	CCl_4	35	5.69 [d]

a. See text.

b. Refers to formation of $CCl_3CONHMe$.

c. Cleavage yielding $CH_3CONHPh$, EtCl and polyphosphate gum.

d. Refers to formation of CH_3CONMe_2.

Examination of the results in Table 4.2.1.4. shows that acylation by acetyl bromide is ca. 16 times faster than by acetyl chloride at 35°C. This follows the anticipated reactivity of the two reagents. Of further interest is the reactivity of other acyl chlorides with (61a). The rate constants for CH_3COCl, $CH_2ClCOCl$, $CHCl_2COCl$ and ClC_6H_4COCl follow the Taft relationship (Equation 4.2.1.2.) with values of 0.58 and 0.64 for ρ^* and δ, respectively (Figure 4.2.1.7.). This indicates that both steric and

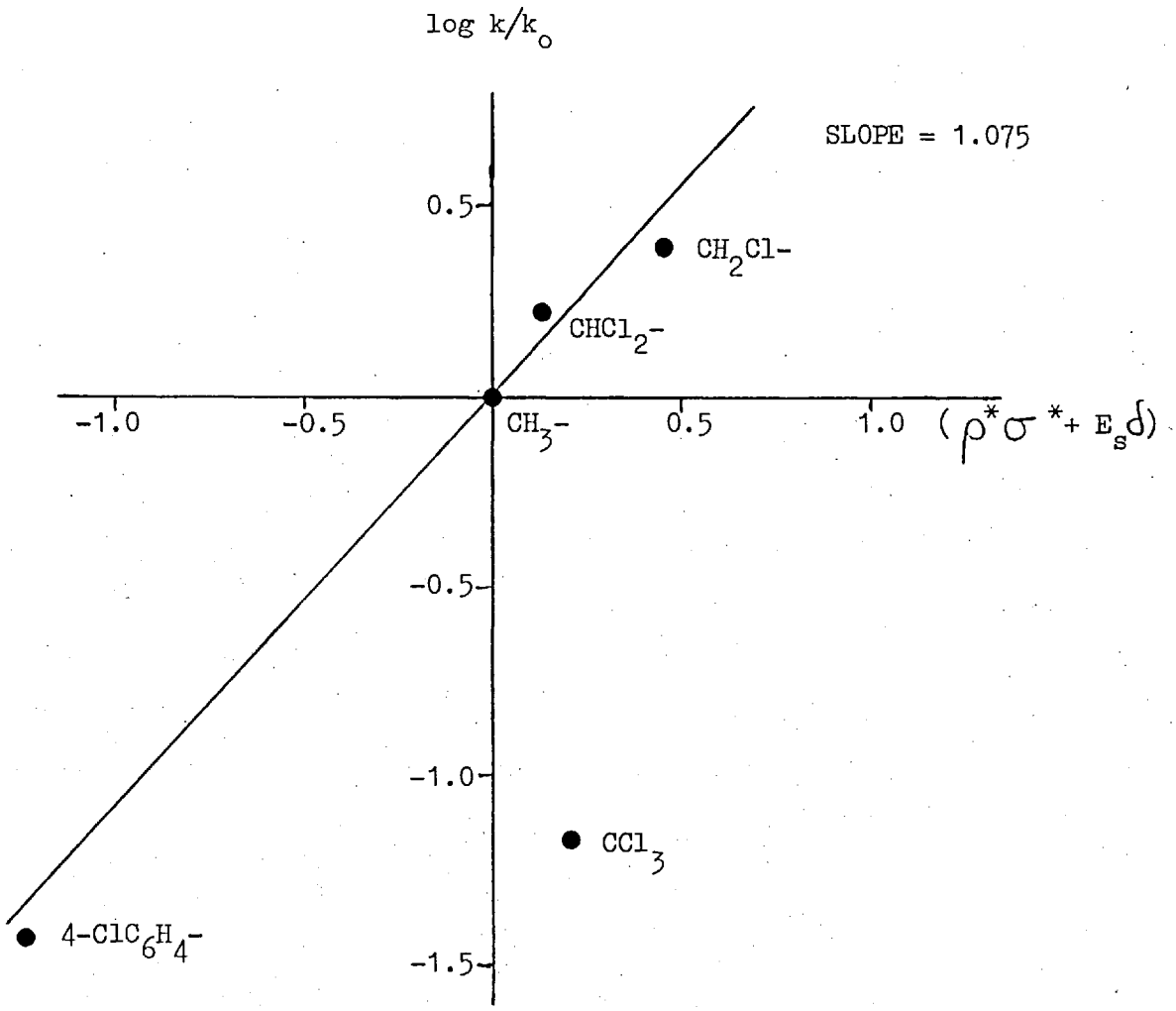
$$\log k/k_o = \rho^*\sigma^* + \delta E_s \quad .... \quad 4.2.1.2.$$

electronic effects have an almost equal influence on the reaction. Hence dichloroacetyl chloride is less reactive than chloroacetyl chloride as a result of the greater steric bulk of the alkyl group. Two exceptions to Equation 4.2.1.2. warrant further comment. Thus CCl_3COCl appears to give $CCl_3CONHMe$ without formation of the $(EtO)_2PON(COCl_3)Me$ intermediate and the rate constant for this reaction is lower than expected. Also pivaloyl chloride is totally unreactive towards (61a) probably because both steric and electronic factors are unfavourable.

The approximate activation energy for the acetylation of (61a) by acetyl chloride, derived from the rate constants at 25°C and 35°C, is 45 $kJ.mol^{-1}$ and the entropy of activation, $\Delta S^{\ddagger}$, at 25°C is -208 $Jk^{-1}mol^{-1}$ (-25 e.u.). The latter is consistent with S_N2 attack by the phosphoramidate on the acyl halide which has already been demonstrated by the kinetic dependence.

The dependence of the second-order rate constants on phosphoramidate structure shows that the reactivity decreases in the order NHMe $>$ $NHOCH_2Ph$ $\gg$ NHPh. Presumably this reflects both steric and nucleophilic differences. Diethyl N-phenylphosphoramidate (61b) was completely unreactive at 35°C, however at 100°C, at which temperature (61b) itself is stable, decomposition occurred yielding acetanilide and ethyl chloride and a gummy residue,

FIGURE 4.2.1.7. TAFT PLOT FOR THE ACYLATION OF (61a) BY ACYL CHLORIDES IN CCl_4 AT 35°C.



ρ^* = .58 δ = .64 r = 0.945

R	σ^*	E_s
CH_3	0	0
CH_2Cl	1.05	-0.24
$CHCl_2$	1.94	-1.54
CCl_3	2.65	-2.06
4-ClC_6H_4	(0.7)	(-2.55)

presumably polyphosphates (Equation 4.2.1.3.). No N-acetylphosphoramidate

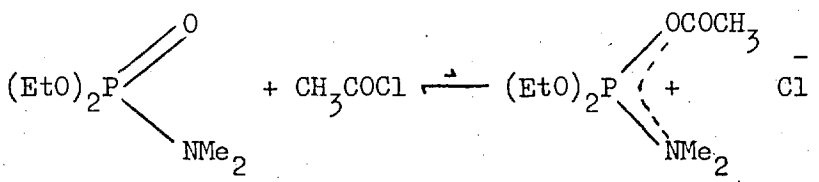
$$(EtO)_2PONHPh + AcCl \longrightarrow AcNHPh + EtCl + \left[(EtO)PO_2\right] \quad .... \quad 4.2.1.3.$$

could be detected in this reaction.

The reaction of diethyl N,N-dimethylphosphoramidate with acetyl chloride was of interest. Unlike the corresponding tertiary amides, which are known to form O-acylimidonium halides (see Section 1.2.3.) this reaction produced N,N-dimethylacetamide and diethyl chlorophosphate (Equation 4.2.1.4.) which shows that N-acylation must be much more facile than with amides.

$$(EtO)_2PONMe_2 + CH_3COCl \longrightarrow (EtO)POCl + CH_3CONMe_2 \quad .... \quad 4.2.1.4.$$

O-Acetylation (Equation 4.2.1.5.) is almost certainly reversible: triethyl



$$\quad .... \quad 4.2.1.5.$$

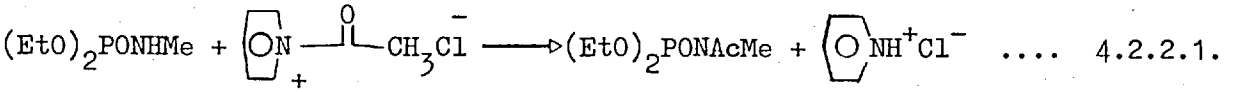
phosphate did not undergo alkyl exchange with acetyl chloride.

No reaction between (61a) and AcCl was observed in the presence of $AlCl_3$. Instead of forming the $AlCl_4^-$ ion, $AlCl_3$ brought about complete dealkylation of the phosphoramidate as well as P-N bond cleavage. Ethyl chloride was a product of this reaction.

4.2.2. IN THE PRESENCE OF BASES

In the presence of pyridine, acetyl chloride reacts with diethyl N-methylphosphoramidate in CCl_4 at 35°C to give diethyl N-acetyl-N-methylphosphoramidate. The reaction is heterogeneous, N-acetylpyridinium chloride,

which is the acylating agent, precipitating from solution. N-Acetylpyridinium chloride prepared independently brings about the same transformation (Equation 4.2.2.1.). Monitoring the reaction by both n.m.r. and i.r. spec-



troscopy shows that no intermediates are observable.

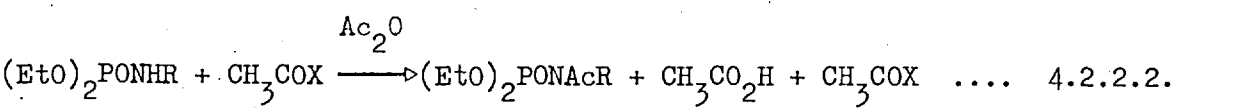
Diethyl N-phenylphosphoramidate does not react under these conditions but at 100°C again undergoes cleavage to give acetanilide and ethyl chloride.

Similar results were obtained in the presence of silver oxide. Thus (61a) gives the N-acetylphosphoramidate (62a) with acetyl chloride, whereas (61b) is unreactive.

The addition of sodium hydride to a solution of (61;a-c) and acetyl chloride in CCl_4 liberated hydrogen and yielded the N-acetylated phosphoramidate.

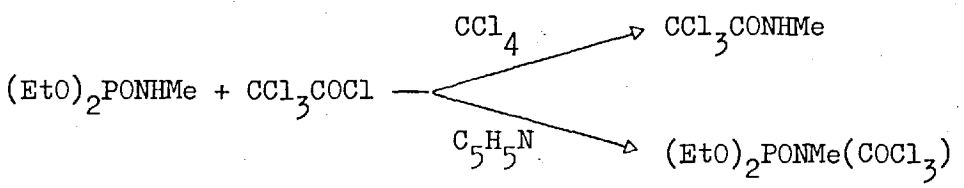
In the presence of 2,2,6,6-tetramethylpiperidine, no reaction between (61a) and acetyl chloride was observed. However, a solid was isolated and identified as N-acetyl-2,2,6,6-tetramethylpiperidine.

The acylation of (61;a,c) by acetyl chloride or bromide was also performed in the presence of acetic anhydride. Under these conditions, the cleavage reaction observed subsequently to acetylation (see Section 4.2.1.) did not occur. N-Acetylation still took place and the observation that acetic acid was also formed suggests that removal of the acidic proton inhibits the cleavage reaction (Equation 4.2.2.2.).



This explanation is substantiated by the reaction of CCl_3COCl with (61a) in pyridine. The product of this reaction is $(EtO)_2PONMe(COCl_3)$, whereas in CCl_4 in the absence of pyridine $CCl_3CONHMe$ forms without any

observation of the N-acylphosphoramidate (Scheme 19). Similarly, forma-



SCHEME 19. REACTION OF (61a) WITH CCl_3COCl.

tion of N-methyl-4-chlorobenzamide from reaction of (61a) with ClC_6H_4COCl in CCl_4, is inhibited carrying out the reaction in pyridine.

The acylation of (61a) by acyl chlorides in pyridine solvent follows second-order kinetics (e.g. Table 4.2.2.1.) and second-order rate constants, k_2, for various RCOX are summarised in Table 4.2.2.2.

TABLE 4.2.2.1. REACTION OF (61a) WITH CCl_3COCl IN PYRIDINE AT 35°C.

t/min	$[(61a)]$/M	$[CCl_3COCl]$/M	$\ln[CCl_3COCl]/[(61a)]$	$10^4k_2/M^{-1}s^{-1}$
0	.665	.535	0.218	5.26
10	.570	.440	0.259	5.26
28	.422	.292	0.368	6.87
48	.354	.224	0.458	6.41
122	.230	.100	0.833	6.46
310	.157	.027	1.760	6.38

These show that the faster rate expected for $R=CCl_3$ over $R=ClC_6H_4$ (not observed in CCl_4 solvent) is observed when the cleavage reaction is inhibited in pyridine. The 30-fold rate increase is about that anticipated from the Taft plot (Figure 4.2.1.7.) i.e. 44.

The effect of temperature on the reaction of (61a) with $4\text{-}ClC_6H_4COCl$ yields an approximate activation energy, E_a, for this process of 37 $kJmol^{-1}$.

TABLE 4.2.2.2. SECOND-ORDER RATE CONSTANTS FOR THE ACYLATION OF (61a) BY RCOCl IN PYRIDINE.

$[(61a)]_o$ = 0.665M $[RCOCl]_o$ = 0.5 - 0.7M

R	T/°C	$10^6 k_2/M^{-1}s^{-1}$
CCl_3	35	628
Bu^t	35	a
	60	b
Ph	35	10.8
$4\text{-}ClC_6H_4$	35	20.7
	61.2	64.3 [c]
$4\text{-}MeC_6H_4$	35	4.6

a. Very slow formation of $Bu^tCONHMe$; equimolar concentrations of reagents gave 25% reaction in 35d.

b. As for (a) with 50% reaction having occurred in 7d.

c. P-N Cleavage occurs after ca. 50% acylation.

The corresponding entropy of activation, $\Delta S^{\ddagger}$, was calculated to be -222 $JK^{-1}Mol^{-1}$ (~~-27~~ -53 e.u.) at 35°C. The latter value is consistent with a bimolecular process.

The reaction of (61a) with pivaloyl chloride (R = Bu^t) gave $Bu^tCONHMe$ (Equation 4.2.2.3.) and was extremely slow at 35°C, approximately 25% re-

$$(EtO)_2PONHMe + Bu^tCOCl \xrightarrow{N} Bu^tCONHMe \quad .... \quad 4.2.2.3.$$

action having occurred after 35 days. At 60°C formation of $Bu^tCONHMe$ occurred much more readily. No evidence for the intermediacy of the N-acylphosphoramidate was observed by n.m.r. spectroscopy.

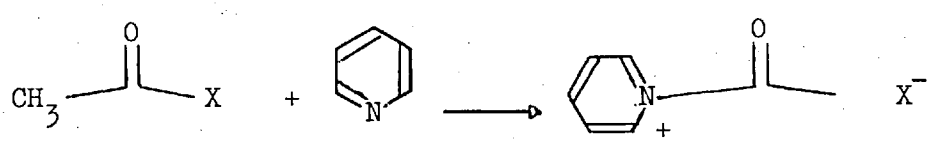
4.3. ACYLATION BY ACID ANHYDRIDES

4.3.1. ACETIC ANHYDRIDE

In the absence of base, none of the phosphoramidates studied (61,a-e) reacted with acetic anhydride either at room temperature or when heated under reflux in benzene, CCl_4 or acetonitrile. As a consequence, base catalysed acylation, extremely effective for the acylation of N-alkoxyamides was attempted.

4.3.1.1. BASE CATALYSED ACETYLATION

In the presence of pyridine, acetic anhydride did not react with (61,a-c) either at room temperature or at 100°C after 7 days. N.m.r. and i.r. spectra of the reaction solutions showed no products and work-up gave starting materials only. Even in the presence of excess pyridine, O-dealkylation was the only reaction observed. Their low reactivity must arise from the pyridine/acetic anhydride equilibrium (X = CH_3CO_2) (Scheme 20) favouring starting materials. Acetylpyridinium chloride (65;X=Cl) gave the N-acetyl



(65)

$$\xrightarrow{(EtO)_2PONHR} (EtO)_2PONAcR$$

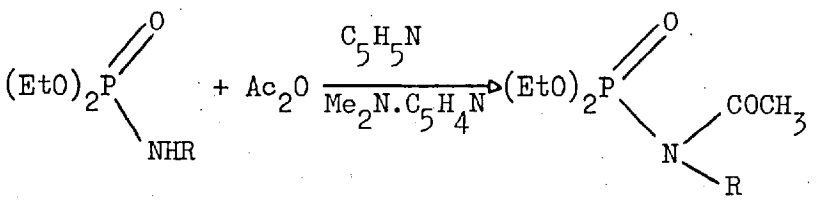
SCHEME 20. ACYLATION OF (61a) IN THE PRESENCE OF PYRIDINE.

product (62,a) even under heterogeneous conditions in CCl_4 or pyridine.

Remarkably, the N-alkoxyphosphoramidate (61c), unlike the analogous alkoxyamides, does not show enhanced reactivity over the N-alkylphosphor-

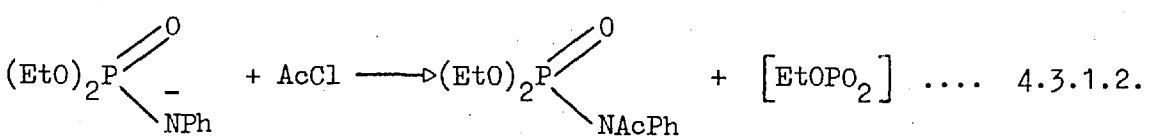
amidate. The reasons for this are unclear.

Other tertiary nitrogen bases were used but both triethylamine, pKa 10.7, and N-methylimidazole, pKa 7.3, were both unsuccessful at catalysing the acylation of either (61 a,c). However, in the presence of 4-dimethylaminopyridine, a well known catalyst for acylation of tertiary alcohols[102], the phosporamidates (61 b,c) were acetylated quantitatively to give the N-acetylphosphoramidates (62 b,c) (Equation 4.3.1.1.). Only catalytic amounts



.... 4.3.1.1.

(e.g. 10 - 15%) of the aminopyridine were required, but the rate of reaction increased with increasing $\left[(CH_3)_2NC_5H_4N\right]$. Thus the half-life for 0.36M $(EtO)_2PONHMe$ with ca. 0.36M Ac_2O in CCl_4 containing 0.5M pyridine was 8 h for $\left[(CH_3)_2NC_5H_4N\right]$ = 0.148M and 13 h for $\left[(CH_3)_2NC_5H_4N\right]$ = 0.07M as determined by n.m.r. Surprisingly, $(EtO)_2PONHMe$ was not acetylated under these conditions. However, the method proved particularly useful for $(EtO)_2PONAcPh$ which could only be synthesised with difficulty from the phosphoramidate ion (Equation 4.3.1.2.), a reaction which is known to give some cleavage of



.... 4.3.1.2.

the P-N bond[72].

As for the reactions with acyl halides direct N-acylation was observed and no O-acyl intermediates could be detected.

4.3.1.2. ELECTROPHILIC CATALYSED ACYLATION

Electrophilic catalysis of acetylation by acetic anhydride is well known[24]. Catalysts commonly employed are acyl halides, mineral acids and ammonium salts. Although an explanation for the mode of action by sulphuric acid has been advanced[24], much less is known about the catalytic behaviour of acyl halides and ammonium salts[24].

It was found that ca. 10% acetyl chloride catalyses the formation of diethyl N-acetyl-N-methylphosphoramidate and diethyl N-acetyl-N-benzyloxy-phosphoramidate from diethyl N-methyl- and diethyl N-benzyloxy- phosphoramidates respectively and acetic anhydride (Figure 4.3.1.1.). Further, the reaction proceeds at the rate ($\pm$ 15%) expected for acetyl chloride alone (Table 4.3.1.1.). Similar agreement is apparent for acetyl bromide and

TABLE 4.3.1.1. RATE CONSTANTS FOR THE CATALYSED ACYLATION OF (61a) WITH Ac_2O IN CCl_4 AT 35°C.

$[(61a)] = 1.0 - 2.0M$

$[Ac_2O] = 1.0 - 1.2M$

$[CATALYST] = .075 - .135M$

CATALYST	$10^5 k_2/M^{-1}s^{-1}$	$10^5 k_2^{Ac_2O}/M^{-1}s^{-1}$
AcCl	4.31	3.70
AcBr	77.2	68.3
HBr	-	60.0
$CH_3(CH_2)_{15}\overset{+}{N}Et_3\overset{-}{Br}$	-	0

an n.m.r. absorbtion signal for CH_3COX can be observed throughout the reaction.

Since acylation is brought about by AcX only (vide supra) these results are best explained (Scheme 21) by formation of the N-acetylphosphor-

FIGURE 4.3.1.1. ACETYL CHLORIDE CATALYSED ACYLATION OF (61a) BY ACETIC ANHYDRIDE IN CCl_4 AT 34°C.

$[AcCl] = .10$ M $\quad [Ac_2O] = 1.14$M $\quad [(61a)] = 2$ M

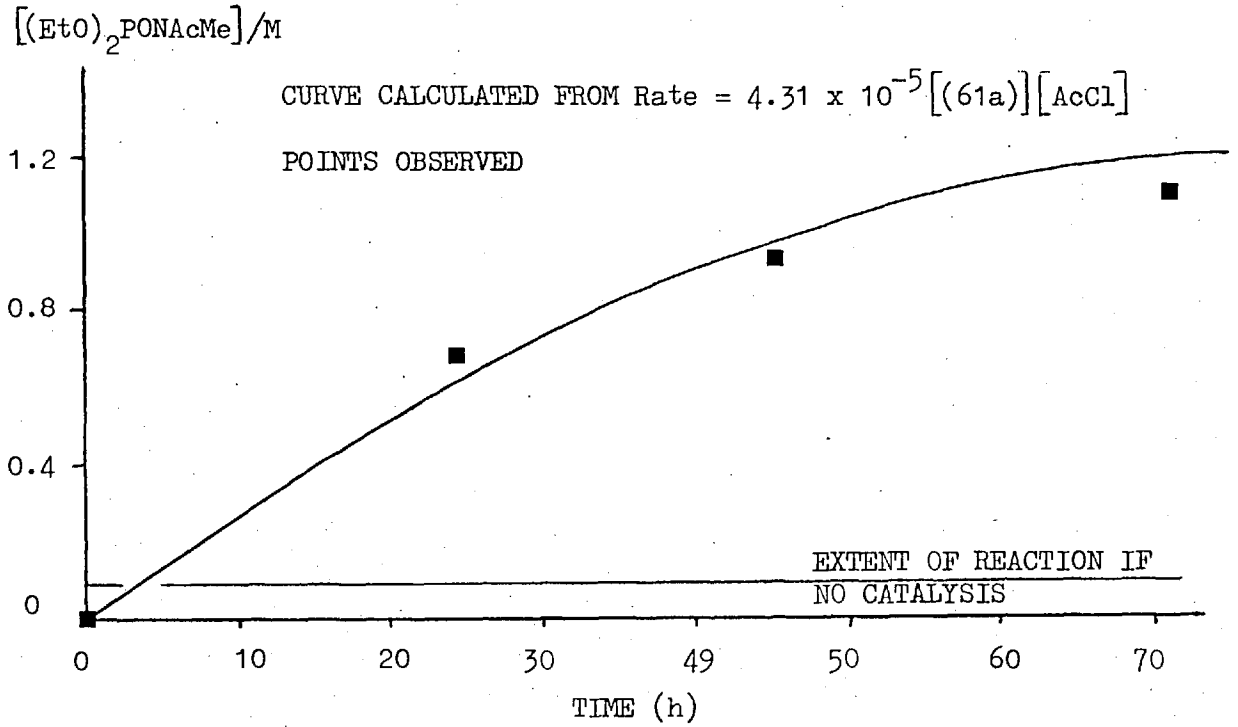
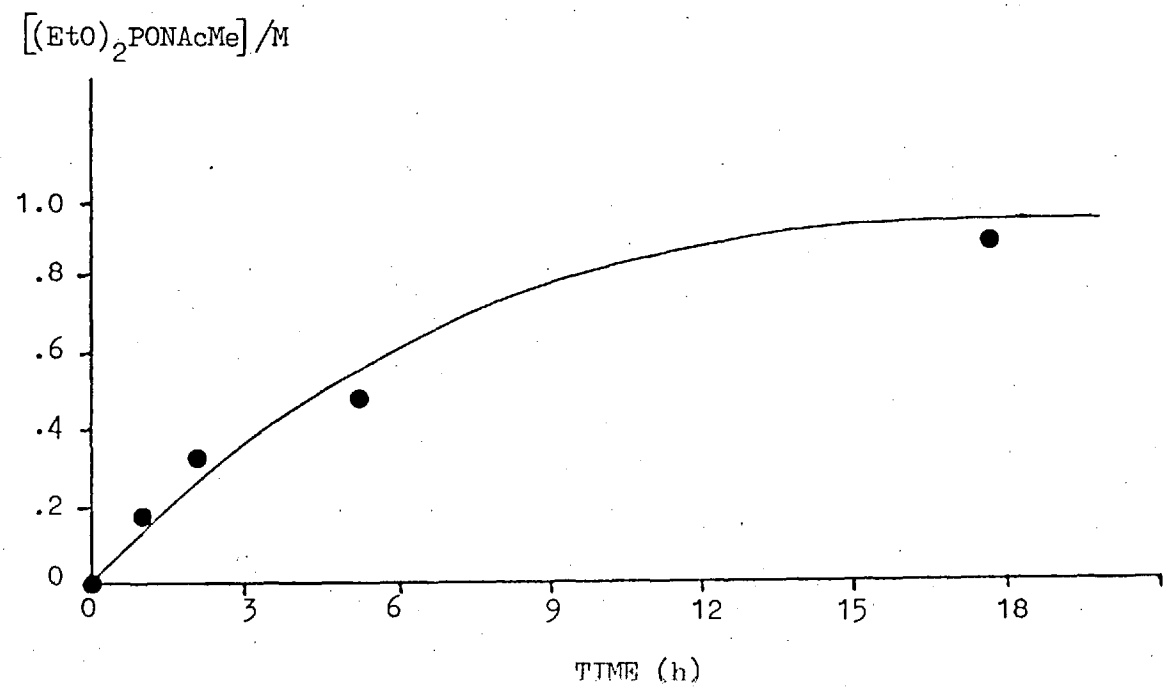


FIGURE 4.3.1.2. HBr CATALYSED ACETYLATION OF (61a) WITH ACETIC ANHYDRIDE IN CCl_4 AT 34°C.

$[HBr] = .075$ M $\quad [Ac_2O] = .97$ M $\quad [(61a)] = 1.03$ M

CURVE CALCULATED FROM Rate = 683 x 10^{-6} [(61a)] [HBr]
POINTS OBSERVED



amidate liberating HX coproduct. Reaction of HX with acetic anhydride generates more AcX acylating agent which implies k_b is fast compared to k_a, the acylation step. Support for this mechanism was obtained by observing

$$(EtO)_2PONHR + AcX \xrightarrow{k_a} (EtO)_2PONAcR + HX$$

$$\xrightleftharpoons{k_b Ac_2O} AcOH + AcX$$

SCHEME 21. MECHANISM OF THE CATALYSIS BY AcX OF THE ACYLATION OF PHOSPHORAMIDATES BY Ac_2O.

that anhydrous HBr also catalyses the acetylation of (61a) by acetic anhydride (Figure 4.3.1.2.) and, assuming all HBr is converted to AcBr, the second-order rate constant, k_2, calculated to be $60.0 \times 10^{-5} M^{-1} s^{-1}$, is similar to that for AcBr. Cetyltriethylammonium bromide, however, did not catalyse acetylation by acetic anhydride, presumably because the equilibrium 4.3.1.3. lies to the left-hand-side.

$$R_4\overset{+}{N}\ \overset{-}{Br} + Ac_2O \rightleftharpoons R_4\overset{+}{N}\ \overset{-}{AcO} + AcBr \quad .... \quad 4.3.1.3.$$

It has been suggested[24] that HX catalyses acetic anhydride acylation of amides by protonating the amide. More probable from the above results is protonation of the anhydride to generate a more reactive acylating agent which is regenerated throughout the reaction. Catalysis by acyl halides proceeds similarly.

4.3.2. OTHER ACID ANHYDRIDES

Whereas (61 a-e) did not react with acetic anhydride, reaction was observed with more reactive anhydrides such as $(CF_3CO)_2O$, and $(CCl_3CO)_2O$.

However, no reaction took place with benzoic, p-chlorobenzoic or p-nitrobenzoic anhydrides due to the insolubility of these compounds in CCl_4, C_5H_5N and CH_3CN.

Reaction of (61 a-c) with trifluoroacetic anhydride in CCl_4 proceeded rapidly and could be monitored by n.m.r. spectroscopy, following the appearance of the new N-Me doublet for (61a), the new N-Ph singlet for (61b) and the new N-OCH_2 singlet for (61c) (Table 4.3.2.1.).

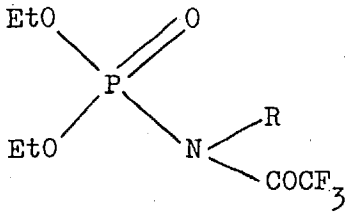
TABLE 4.3.2.1. ^1H N.M.R. ABSORBTION SIGNALS FOR (61,a-c) AND (66,a-c) IN CCl_4 RELATIVE TO T.M.S.

COMPOUND	CH_3CH_2	CH_3CH_2O	$PhCH_2$	$PhCH_2$	NCH_3	NPh	NH
(61a)	1.33t	4.08quin			2.60[a]		4.75br
(66a)	1.33t	4.23quin			3.30d[b]		
(61b)	1.35t	4.15quin				7.10M	8.13br.d
(66b)	1.13t	4.13quin				7.31s	
(61c)	1.28t	4.13quin	7.35s	4.79s			7.08br.d
(66c)	1.42t	4.40quin	7.39s	5.13s			

a. J_{PNCH} = 12.5 hz, J_{HNCH} = 4.5 hz.

b. J_{PNCH} = 9.0 hz.

The i.r. spectra of the products exhibit strong absorbtion bands at 1725-1735 cm^{-1} due to the $CF_3C=O$ group, and 1160-1170 cm^{-1}. The latter is characteristic of the P=O moiety rather than the P=N functionality (rarely below 1250 cm^{-1} and more commonly at or above 1200 cm^{-1} especially with electron-withdrawing substituents at phosphorus[103]). This strongly suggests that the products are N-acylated (i.e. 66).



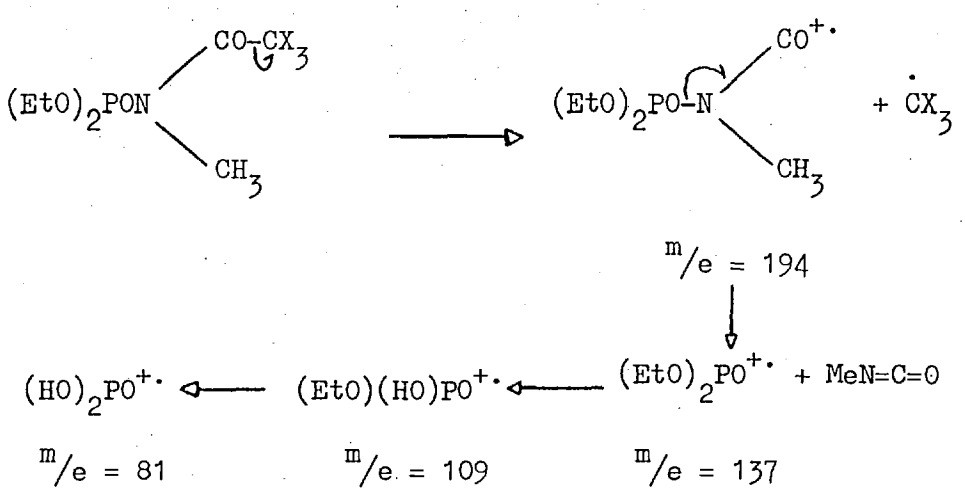
(66) a. R = Me

b. R = Ph

c. R = OCH_2Ph

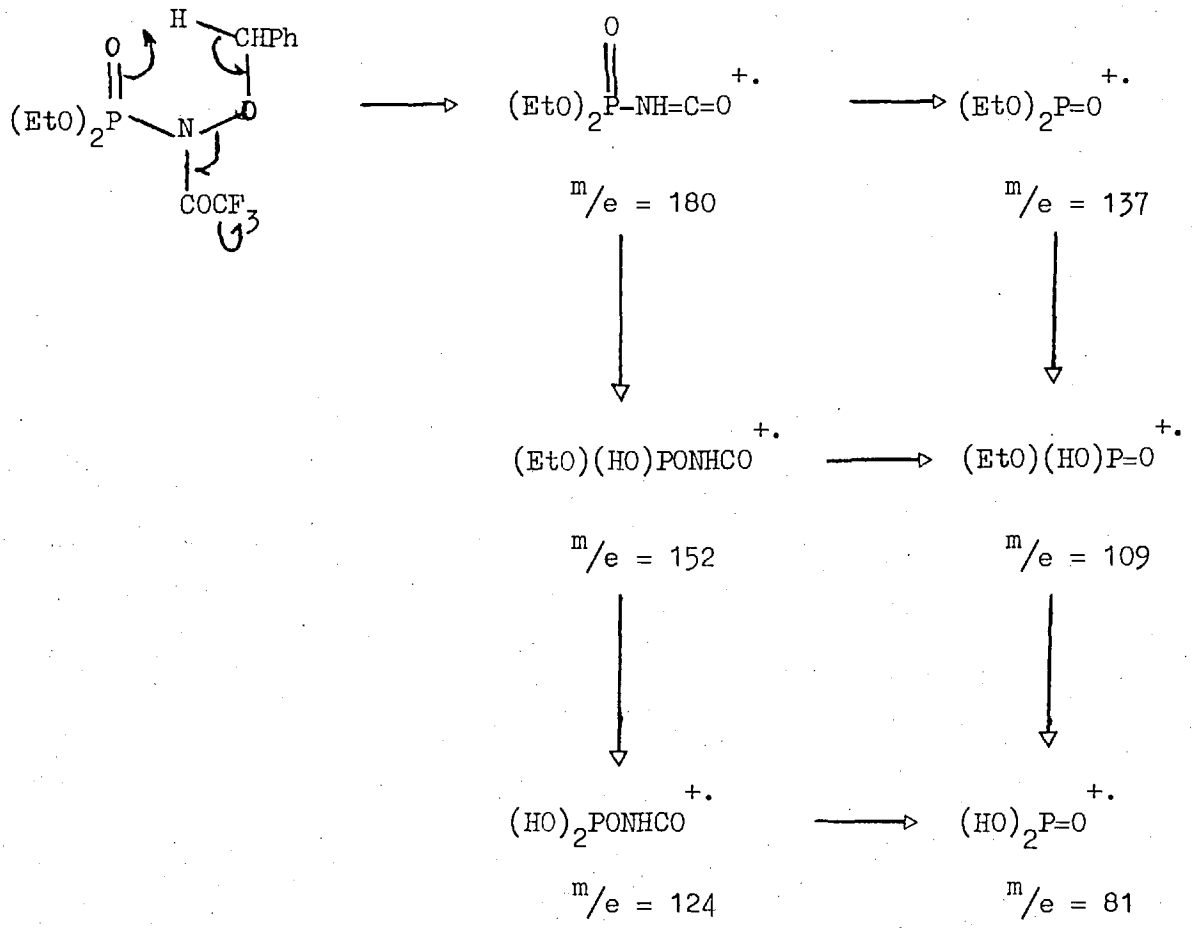
Further, the n.m.r. spectra of (66,a-c) are similar to those of the corresponding N-acetyl compounds (62,a-c). In particular, the J(PNCH) coupling constant of (66a), 9.0 hz, is similar to that for (62a) and both are smaller than that of the parent phosphoramidate, 12.5 hz. Goldwhite has shown[96] that the J(PNCH) coupling constants for O-alkylphosphorimidates are typically 25 hz, compared to 9.5 hz for the corresponding phosphoramidates.

Tentative confirmation of the N-substituted structure (66) was obtained by the mass spectra. Fragmentation of the trifluoroacetylated product (66a) followed Scheme 22, whereas the trifluoracetylated derivative



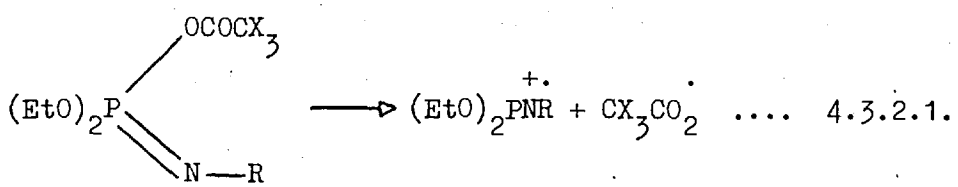
SCHEME 22. MASS SPECTRAL FRAGMENTATION OF TRIFLUOROACETYLATED DERIVATIVES OF (66a).

of (61c) fragments according to Scheme 23. No peaks were observed for



SCHEME 23. FRAGMENTATION OF (66c).

possible fragment ions arising from O-substituted products e.g. Equation 4.3.2.1.



.... 4.3.2.1.

Kinetically, the trifluoroacetylation of (66,a-c) was studied using initial rate measurements (Table 4.3.2.2.) and found to obey

$$\text{Rate} = k_2 \left[(61)\right]\left[\text{ANHYDRIDE}\right]$$

implying a bimolecular mechanism involving nucleophilic attack by the phosphoramidate on the anhydride. The rate constants observed here are some 10^2–10^3 larger than those for acyl halides (cf. Table 4.2.1.4.) which

TABLE 4.3.2.2. INITIAL RATE MEASUREMENTS FOR THE REACTION OF (61,a-c) WITH $(CF_3CO_2)_2O$ IN CCl_4 AT 25°C.

SUBSTRATE	$\left[(CF_3CO)_2O\right]$ M	$\left[(61)\right]$ M	10^4 Rate Ms^{-1}	$10^3 k_2$ $M^{-1}s^{-1}$
(61a)	0.557	1.109	37.5	7.07
	1.170	0.583	35.4	5.19
	0.665	0.665	22.9	5.18
	0.665	0.665	23.6	5.34
(61b)	1.277	0.795	17.4	1.71
	1.221	0.407	8.2	1.65
(61c)	0.442	0.442	3.1	1.60

follows from the anticipated reactivity of these reagents. The small differences in k_2 with N-substitution of the phosphoramidates probably reflects the lack of selectivity of the reactive $(CF_3CO)_2O$ reagent.

In contrast to (61;a-c), (61;d,e) react with $(CF_3CO)_2O$ to give CF_3CONMe_2. Obviously, P-N cleavage has occurred (Equation 4.3.2.2.) and

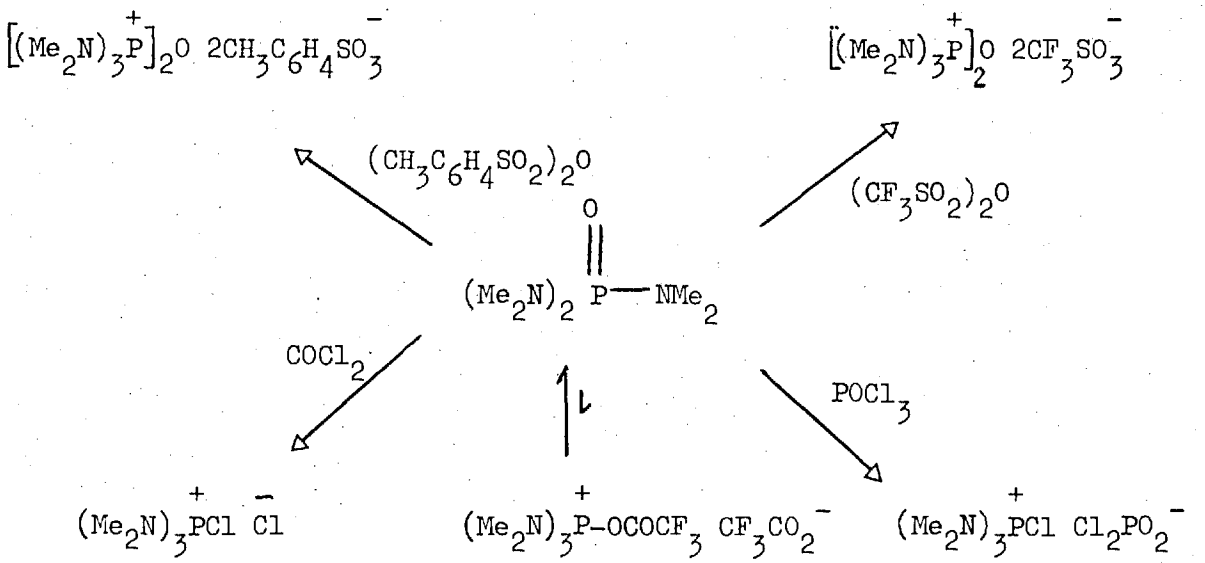
$$X_2PONMe_2 + (CF_3CO)_2O \longrightarrow CF_3CONMe_2 + X_2POOCOCF_3 \quad \ldots\ 4.3.2.2.$$

X = Me_2N,EtO

and the phosphorus containing coproduct for X = Me_2N was identified by its

mass spectrum [$^{m}/e$ = 248($M^{+\cdot}$), 179 ($M-CF_3$) and 135 ($M-CF_3CO_2$)] as $(Me_2N)POOCOCF_3$. No intermediates were observed by ^1H n.m.r. in these reactions and it would appear that the products arise from N-acylation followed by cleavage. The rate constants for cleavage of (61 d,e) are some 2000 times smaller than trifluoroacylation of (61 a-c).

These results confirm those for reaction of (61;d,e) with acetyl chloride (vide supra) and contrast those reported for reaction of (61e) with sulphonic anhydrides[66,67], phosgene[104] and phosphoryl chloride[105] which give products of O-attack (Scheme 24). One possible explanation here may lie with the enhanced nucleophilicity of $CF_3CO_2^-$ over RSO_3^- and $Cl_2PO_2^-$ favouring starting materials (Scheme 24).

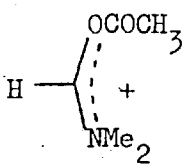


SCHEME 24.

As with $(CF_3CO)_2O$, (61a) reacts with other acid anhydrides. Bimolecular kinetics were observed and second-order rate constants are summarised in Table 4.3.2.3.

TABLE 4.3.2.3. SECOND-ORDER RATE CONSTANTS FOR THE ACYLATION OF (61a) IN CCl_4.

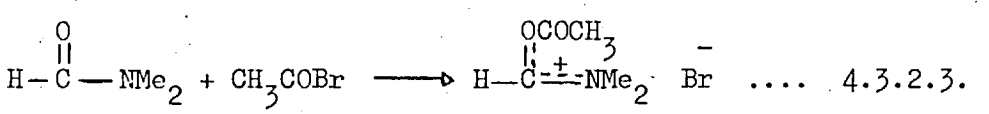
$[(61a)] = 0.665 - 1.33$ M $[ANHYDRIDE] = 0.6 - 2$ M

ANHYDRIDE	T°C	$10^4 k_2/M^{-1}s^{-1}$
$(CF_3CO)_2O$	25	54.4
$(CHCl_2CO)_2O$	35	a
$(CCl_3CO)_2O$	35	0.04 [b]
	35	15.6
$(CH_3CO)_2O$	35	0

a. Formation of $(EtO)_2PON(COCHCl_2)Me$ is followed by formation of $CHCl_2CONHMe$.

b. Formation of $CCl_3CONHMe$, k_2 refers to the rate constant for cleavage.

Significantly, O-acetyl N,N-dimethylformamidinium bromide acetylates (61a) yielding (62a). The anhydride, derived from reaction of acetyl bromide and dimethylformamide (Equation 4.3.2.3.), is ca. 2.5 times as fast as acetyl bromide ($k_2 = 6.8 \times 10^{-4} M^{-1}s^{-1}$) itself, indicating that formation



.... 4.3.2.3.

of such O-acylated amide derivatives increases the acylating potential of the original acyl halide.

Trichloroacetic anhydride, however, gave only $CCl_3CONHMe$ on reaction with (61a) in CCl_4 (Equation 4.3.2.4.), implying that cleavage of the P-N

bond is at least as fast as formation of the N-acylated product. Monitoring the reaction of (61a) with 1 equivalent of $(CCl_3CO)_2O$ by n.m.r.

$$(EtO)_2PONHMe + (CCl_3CO_2)O \longrightarrow (EtO)_2PON(COCCl_3)Me + CCl_3CO_2H$$
$$(67)$$
$$\longrightarrow CCl_3CONHMe + (EtO)_2POOCOCCl_3 \quad .... \quad 4.3.2.4.$$

showed a new product formed in ca 15% yield before cleavage occurred. By comparison of the chemical shift of the N-Me doublet (δ 3.53) with that for trifluoroacetylation (δ 3.30) and by synthesis of the same product in the presence of pyridine (see below) this new signal was assigned the N-trichloracetyl structure (67). No such intermediate was observed using a 3 fold excess of $(CCl_3CO)_2O$. Dichloroacetic anhydride behaved similarly. Rational kinetics could not be obtained but formation of the N-acylated phosphoramidate proceeded to ca. 40% completion before cleavage occurred at all anhydride concentrations.

In the presence of pyridine, (61 a-c) react with $(CF_3CO)_2O$ and $(CCl_3CO)_2O$ to give the N-trihaloacetylated phosphoramidates. Reactions were too fast to be monitored, the n.m.r. spectra indicating that reaction was complete within 2 minutes. ^{31}P N.m.r. of the reaction solution of (61a) with $(CF_3CO)_2O$ shows the presence of only one compound whose chemical shift, by comparison to those for (61a) and (62a) (Table 4.3.2.4.) indicate

TABLE 4.3.2.4. ^{31}P CHEMICAL SHIFTS OF (61a), (62a) AND (66a) IN PYRIDINE AT 30°C.

	δ^a (ppm)
$(EtO)_2PONHMe$	+8.26
$(EtO)_2PON(Me)COCH_3$	+0.05
$(EtO)_2PON(Me)COCF_3$	-4.22

a. Relative to $P(OMe)_3$.

that the compound is the N-trifluoroacetyl phosphoramidate. No other species could be detected in the n.m.r. spectrum.

On standing, further reaction occurred over 1 day which from the ^1H n.m.r. spectrum indicated that dealkylation of the $POCH_2CH_3$ groups was involved as well as cleavage (Equation 4.3.2.5.) of the P-N bond. No such reaction occurred in the absence of pyridine.

$$(EtO)_2PON(COCF_3)R \xrightarrow[TFAA]{PYRIDINE} C_6H_5\overset{+}{N}Et + RN(COCF_3)_2 + \overset{-}{PO_3} \text{ etc. .... } 4.3.2.5.$$

Similarly, (61a) and $(CCl_3CO)_2O$ gave $(EtO)_2PONMe(COCl_3)$ using pyridine as solvent. The product was identified by its mass spectral fragmentation $\{m/e = 194\ [M^{+\cdot} - CCl_3],\ 137\ [M^{+\cdot} - CCl_3CONMe],\ 109\ [(EtO)(HO)PO^{+\cdot}]\}$ (cf. Scheme 22) and i.r. spectrum $\{\nu_{max}$ 2990,1705 (C=O),1485,1440,1300-1260 (P=O),1030 (POEt),680 (CCl) $cm^{-1}\}$. The n.m.r. spectrum: $\delta(C_6H_5N)$ 1.25 (6H,t),3.60(3H,d,J = 10hz),4.30(4H,quin,J = 7,7 hz) is similar to that for $(EtO)_2PONMe(COCF_3)$: $\delta(C_6H_5N)$ 1.17(6H,t),3.30(3H,d,J = 9 hz) 4.15(4H,quin, J = 7,7 hz). Further, the product does not react with a five-fold excess of imidazole or piperidine implying that it was not the O-acylphosphorimidate which would be expected to be a powerful acylating agent.

When the reaction was carried out in the presence of $[^2H_5]$-pyridine formation of a quantitative amount of chloroform was observed by n.m.r. Moreover, liberation of a gas occurred. These results are best described by Scheme 25, and account for the inhibition of the formation of $CCl_3CONHMe$ from the reaction mixture.

$$(EtO)_2PONHMe + (CCl_3CO)_2O \xrightarrow{C_5H_5N} (EtO)_2PONMe(COCl_3)$$

$$\overset{+}{C_5H_5}\overset{+}{N}H\ \overset{-}{CCl_3CO_2}$$

$$\longrightarrow C_6H_5N + CHCl_3 + CO_2$$

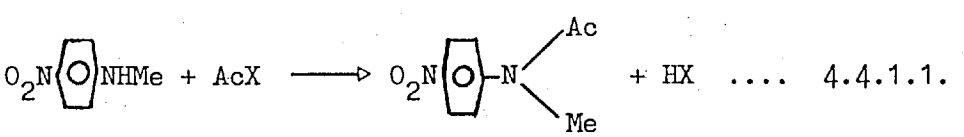
SCHEME 25.

4.4. ACYLATION OF AMINES IN THE PRESENCE OF $(EtO)_2PONHMe$ AND $CH_3CON(CH_3)_2$.

The inability to detect an O-acylphosphorimidate in the acylation of phosphoramidates does not preclude its involvement in the reaction. If formed, however, it should be a good acylating agent and accordingly acylation by reagents such as acid halides and anhydrides might be catalysed by phosphoramidates. This hypothesis was examined by the effect of added phosphoramidate on the acylation of amines.

4.4.1. ACYLATION OF N-METHYL-4-NITROANILINE

N-Methyl-4-nitroaniline was acylated (Equation 4.4.1.1.) by acetyl chloride, acetyl bromide and acetic anhydride in $CHCl_3$ at 25°C. The re-



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action was conveniently followed by U.V. spectroscopy at 374 nm. Reactions were found to be first-order in amine and first-order dependence on the acylating agent was observed (Table 4.4.1.1.). The order of reactivity, AcBr $\gg$ AcCl $>$ Ac_2O is that expected for these reagents.

The acylation of $O_2NC_6H_4NHMe$ by Ac_2O containing ca. 0.5% AcCl was studied in the presence and absence of $(EtO)_2PONHMe$. In the absence of the phosphoramidate, the amine was acylated at the rate expected for the sum of the independent rates for Ac_2O and AcCl. In the presence of an equivalent amount of phosphoramidate an increase in the observed rate occurs (Table 4.4.1.2., Figure 4.4.1.1.).

The increase, ca. 25%, may be attributed to either a solvent effect (addition of ca. 2% EtOH, i.e. $[EtOH]$ = 0.38M, increases the observed rate constant for AcCl from $5.68 \times 10^{-3} M^{-1}s^{-1}$ to $9.77 \times 10^{-2} M^{-1}s^{-1}$) or to add-

TABLE 4.4.1.1. FIRST-ORDER DEPENDENCE ON [AcX] OF THE ACYLATION OF N-METHYL-4-NITROANILINE IN $CHCl_3$ AT 25°C.

$[O_2NC_6H_4NHMe]$ = ca. 6.71×10^{-5} M

AcX	10^2 [AcX]/M	$10^5 k_o/s^{-1}$	$10^4 k_2/M^{-1}s^{-1}$
CH_3COCl	4.23	23.04	54.5
	2.82	15.99	56.7
	1.41	8.55	60.6
$(CH_3CO)_2O$	12.72	0.28	0.22
	8.48	0.20	0.23
	4.24	0.09	0.21
CH_3COBr	.161	76	4710
	.243	134	5510
	.586	279	4910

itional reaction via a phosphoramidate intermediate which also acylates the amine. The latter is represented by Scheme 26 from which the rate of

$$O_2NC_6H_4NHCH_3 + AcCl \xrightarrow{k^{AcCl}} O_2NC_6H_4NCH_3(COCH_3)$$

$$O_2NC_6H_4NHCH_3 + Ac_2O \xrightarrow{k^{Ac_2O}} O_2NC_6H_4NCH_3(COCH_3)$$

$$(EtO)_2PONHCH_3 + AcCl \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [X] \xrightarrow{k_2} (EtO)_2PONCH_3(COCH_3)$$

$$O_2NC_6H_4NHCH_3 + [X] \xrightarrow{k^X} O_2NC_6H_4NCH_3(COCH_3)$$

SCHEME 26. ACYLATION OF N-METHYL-4-NITROANILINE

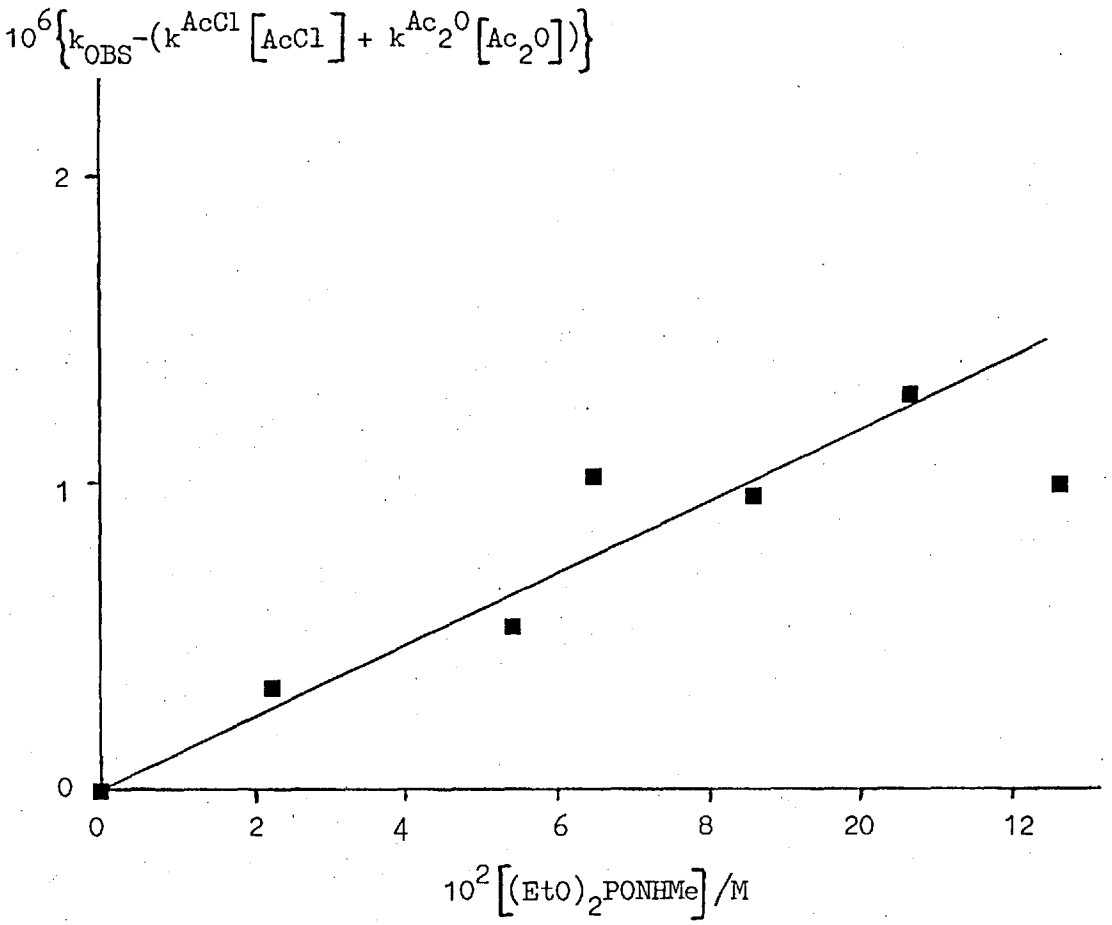
TABLE 4.4.1.2. OBSERVED RATE-CONSTANTS FOR THE ACYLATION OF $O_2NC_6H_4NHCH_3$ IN $CHCl_3$ IN THE PRESENCE OF $(EtO)_2PONHMe$ AT 25°C.

$[O_2NC_6H_4NHMe]$ = ca. 6.7×10^{-5}M

$10^2[Ac_2O]$/M	$10^4[AcCl]$/M	$10^2[(EtO)_2PONHMe]$/M	$10^6 k_o/s^{-1}$
2.12	1.67	0	1.42
2.12	1.67	2.13	1.75
5.25	1.47	0	2.02
5.25	1.47	5.33	2.53
6.36	2.25	0	2.70
6.36	2.25	6.38	3.75
8.48	2.30	8.51	4.16
10.60	2.65	0	3.87
10.60	2.65	10.66	5.19
12.72	2.35	12.76	5.12
14.84	2.87	0	4.93

FIGURE 4.4.1.1. CATALYSIS OF THE ACYLATION OF $O_2NC_6H_4NHCH_3$ BY $AcCl/Ac_2O$ BY $(EtO)_2PONHMe$ in $CHCl_3$ AT 25°C.

Initial $\left[O_2NC_6H_4NHCH_3\right]$ = ca. 6×10^{-5}M.



At $\left[(EtO)_2PONHMe\right] = 10 \times 10^{-2}$M.

$\left\{k_{OBS} -(k^{AcCl}\left[AcCl\right] + k^{Ac_2O}\left[Ac_2O\right])\right\} = 1.18 \times 10^{-6}\ s^{-1}$.

$\therefore [X] \leqslant 1.18 \times 10^{-6}/2 \times 57.3 \times 10^{-4}$ M.

$\leqslant 1.03 \times 10^{-4}$ M.

$\therefore [X] / (EtO)_2PONHMe \leqslant 1.03 \times 10^{-3} \sim .103\%$.

reaction is given by Equation 4.4.1.2.

$$-\frac{d[\text{Amine}]}{dt} = k^{AcCl}[\text{Amine}][\text{AcCl}] + k^{Ac_2O}[\text{Amine}][Ac_2O] + k^{X}[\text{Amine}][X] \quad \ldots \quad 4.4.1.2.$$

Both $[\text{AcCl}]$ and $[Ac_2O]$ are constant with respect to $[\text{Amine}]$. Assuming that $[X]$ is also constant with respect to $[\text{Amine}]$, either by being in excess or in a steady-state concentration, the observed rate constant, k_{OBS}, is given by Equation 4.4.1.3.

$$k_{OBS} = k^{AcCl}[\text{AcCl}] + k^{Ac_2O}[Ac_2O] + k^{X}[X] \quad \ldots \quad 4.4.1.3.$$

Thus

$$[X] = \frac{k_{OBS} - (k^{AcCl}[\text{AcCl}] + k^{Ac_2O}[Ac_2O])}{k^{X}}$$

Figure 4.4.1.1. is a plot of the right-hand numerator versus $[(EtO)_2PONHMe]$. Assuming k^X to be at least a factor of 2 greater than k^{AcCl}, [cf. the rate of acylation of $(EtO)_2PONHMe$ by $HC(OCOCH_3)\overset{+}{N}Me_2\overset{-}{Br}$ is ca. 2 times that for AcBr, Section 4.3.2.], the highest concentration of X is 0.115% of the phosphoramidate concentration, a value compatable with acylation of the phosphoramidate giving an O-acylphosphorimidate followed by rapid rearrangement.

The possibility that the rate increase arises from a change in solvent polarity is less likely since similar experiments in the presence of $CH_3CON(CH_3)_2$, a molecule of similar polarity, produces smaller rate increases (Table 4.4.1.3.).

The lack of catalysis by added $CH_3CON(CH_3)_2$ is surprising since amides are known to form O-acylimidates[24,29]. However, it was observed by ^1H n.m.r. that acetyl bromide and dimethylformamide in $CDCl_3$ at 30°C did not form the

TABLE 4.4.1.3. FIRST-ORDER RATE CONSTANTS FOR THE ACYLATION OF $O_2NC_6H_4NHCH_3$ BY $AcCl/Ac_2O$ IN THE PRESENCE OF $CH_3CON(CH_3)_2$ IN $CHCl_3$ AT 25°C.

$[O_2NC_6H_4NHCH_3]$ = ca. 6×10^{-5}M

$10^2[Ac_2O]$/M	$10^4[AcCl]$/M	$[CH_3CON(CH_3)_2]$/M	$10^6 k_{OBS}/s^{-1}$
5.25	2.29	0	2.49
5.25	2.29	0.053	2.88
10.6	2.21	0	3.59
10.6	2.21	0.106	3.74

O-acylimidonium bromide complex. Comparison of the n.m.r. spectrum of the AcBr - $HCONMe_2$ solution with that of the complex showed that only on heating at 100°C for 3 hr. was the complex formed. Reaction of the amine with the authentic complex, synthesised independently, was instantaneous.

4.4.2. ACYLATION OF 2,4-DINITROANILINE

The reaction of 2,4-dinitroaniline with acetyl chloride in $CHCl_3$ at 25°C was followed by u.v. spectroscopy at 327 nm. With excess AcCl it followed pseudo-first-order kinetics (Rate = $k_o[Amine]$) and k_o was proportional to [AcCl] (Table 4.4.2.1.).

The acetylation of the amine by AcCl was also studied in the presence of $(EtO)_2PONHMe$ and the results are also summarised in Table 4.4.2.1. It is clear that (61a) does not catalyse the acetylation of 2,4-dinitroaniline but inhibits the reaction by preferentially reacting with the AcCl. Thus O-acylphosphorimidate intermediate, if formed, must rearrange more rapidly to the N-acyl product than react with 2,4-dinitroaniline.

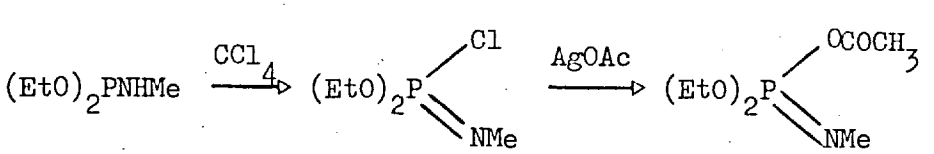
TABLE 4.4.2.1. PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE ACYLATION OF $2,4\text{-}(NO_2)_2C_6H_4NH_2$ IN $CHCl_3$ AT 25°C BY CH_3COCl.

Initial $\left[2,4\text{-}(NO_2)_2C_6H_4NH_2\right] = 1.836 \times 10^{-4}$ M.

$10^2[CH_3COCl]/M$	$10^2[(61a)]/M$	$10^7k_o/s^{-1}$	$10^5k_2/M^{-1}s^{-1}$
1.41	0	6.94	4.92
2.81	0	9.74	3.47
4.22	0	13.89	3.29
2.82	2.82	0	0
5.63	5.63	0	0
8.45	8.45	0	0

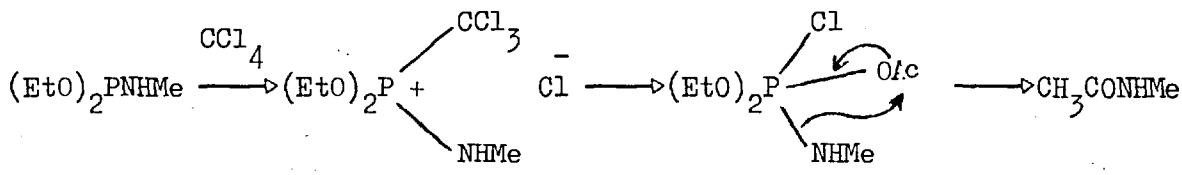
4.5. REACTION OF DIETHYL N-METHYLPHOSPHORAMIDITE WITH SILVER ACETATE IN CCl_4

In an attempt to synthesise diethyl O-acetyl-N-methylphosphorimidate by an independent route, the reaction of $(EtO)_2PNHMe$ with silver acetate in CCl_4 was carried out. It was anticipated that the so-formed phosphorimidoyl chloride[106] would react with AgOAc to yield the desired product (Equation 4.5.1.).



.... 4.5.1.

In the event, reaction of the phosphinamidite with CCl_4 in the presence of AgOAc yielded N-methylacetamide The reaction was not extensively studied but a possible route to this product is shown in Equation 4.5.2.

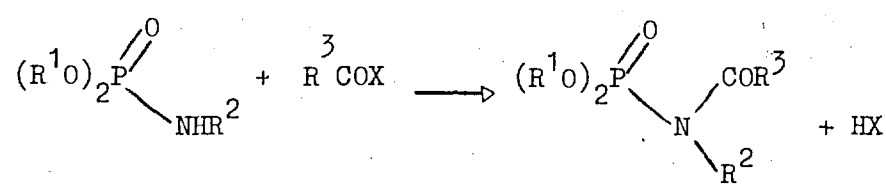


.... 4.5.2.

4.6. DISCUSSION

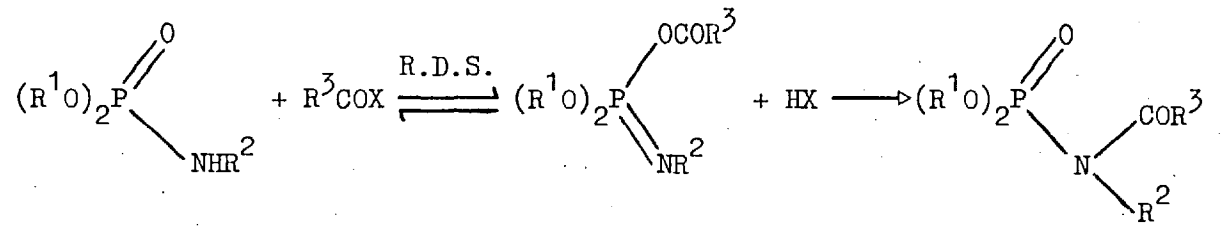
The results show that acylation of phosphoramidates under neutral conditions by acid chlorides and anhydrides yields the corresponding N-acyl-phosphoramidates, followed in certain cases by cleavage of the P-N bond. The observation of bimolecular kinetics for the acylation reaction with decrease in the rate constant following reagent reactivity (AcBr > AcCl) suggests that the reaction involves nucleophilic attack by the phosphoramidate on the acylating agent. The finding that the Taft relationship is dependent on both steric and electronic effects is consistent with this conclusion.

The results do not identify the initial reaction site and two mechanisms may describe the reaction. The first involves direct N-attack on the acyl halide followed by deprotonation (Scheme 27). The other involves an initial,



SCHEME 27. MECHANISM FOR DIRECT N-ACYLATION OF PHOSPHORAMIDATES.

rate-determining, attack by the phosphoryl oxygen atom to yield an O-acylphosphorimidate followed by rapid rearrangement to the thermodynamically stable N-acylphosphoramidate (Scheme 28).



SCHEME 28. MECHANISM OF THE O-ACYLATION OF PHOSPHORAMIDATES.

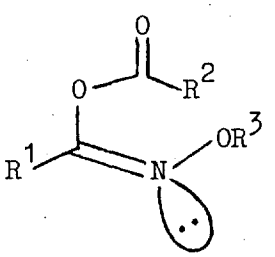
The solvent effect ($C_5H_5N > CDCl_3 > CCl_4 > C_6H_6$) is consistent with either mechanism. Pyridine undoubtedly acts as a base catalyst [addition of 1 equivalent to the 4-ClC_6H_4COCl acylation of (61a) increases the rate by ca. 2] although the 20 fold increase in the acylation of (61a) by 4-ClC_6H_4COCl in changing the solvent from CCl_4 to pyridine (Table 4.2.1.4.) suggests that such catalysis is not large.

The dependence of the second-order rate constants, k_2, on phosphoramidate reactivity towards acetyl chloride ($NHMe > NHOCH_2Ph \gg NHPh$) also suggests that nucleophilicity of the N-atom is important and might imply reaction via direct N-attack. However, with $(CF_3CO)_2O$ the reactivity varies, $NHMe > NHPh \sim NHOCH_2Ph$, and with $(CH_3CO)_2O$ in the presence of 4-dimethylaminopyridine $NHPh \sim NHOCH_2Ph \gg NHMe$ indicating that other, indeterminate factors influence the reactions.

The inability to detect any intermediate either spectroscopically or chemically in these acylation reactions does not preclude the formation of such O-acylphosphorimidates. A similar problem is found in the analogous amide chemistry where acylation gives rise to imides without the observed intermediacy of O-acylimidates. Independent syntheses of O-acylimidates from imidoyl halides are successful only in a few cases, and these compounds undergo a fast O- to N- intramolecular rearrangement which is not catalysed by external electrophilic agents. Significantly, Dreiding models of both the O-acylimidate and O- acylphosphorimidate moieties show that the N-lone pair electrons are equidistant from the carbonyl carbon

atom in both cases (Figure 4.6.1.), implying that a fast rearrangement is possible for O-acylphosphorimidates. Further, the phosphoramidates are more reactive than the analogous amides. N-Methylbenzamide and N-methylacetamide are not acetylated under conditions [$AcCl/Ac_2O$ (1:10), CCl_4, 35°C, 7d] where diethyl N-methyl phosphoramidate yields the N-acetylphosphoramidate quantitatively. The anticipated enhanced reactivity of P=O over C=O (cf. alkyl exchange of phosphate esters and carboxylic acid esters) would thus be preserved.

The problem over the fast rearrangement of the O-acylimidate was overcome in amide chemistry by inclusion of an N-alkoxy substituent[4]. In this case the N-lone pair electrons are fixed trans- to the carbonyl group (e.g. 68) which effectively inhibited the rearrangement reaction. Photochemical



(68)

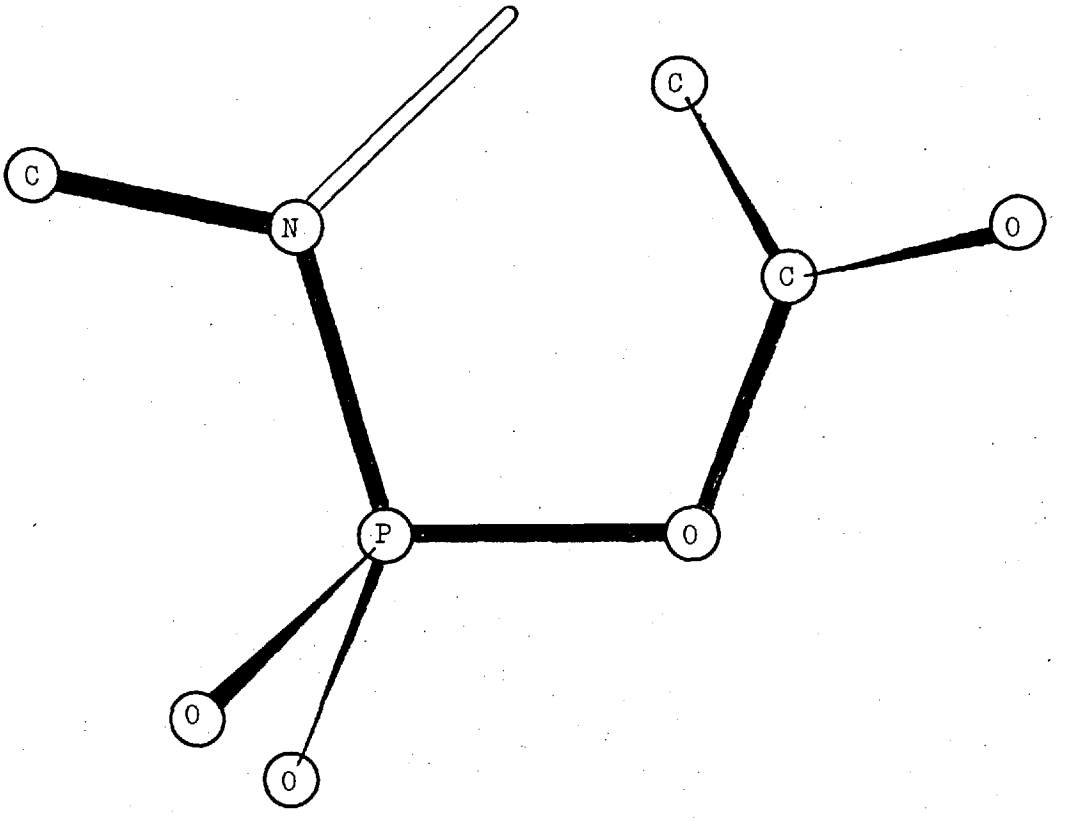
isomerisation about the C=N double-bond, however was accompanied by a rapid O- to N- rearrangement[34].

In the present study diethyl N-benzyloxyphosphoramidate gave only the N-acylphosphoramidate on acylation. An interesting feature here is the upper limit to rotation about the P=N bond is set at 29 kJ mol^{-1} [96,107], whereas that for the C=N bond is 95 kJ mol^{-1} [108]. The activation energy measured for acylation was 45 kJ mol^{-1}, from which it follows that rearrangement of an O-acyl phosphorimidate, if it is involved in these reactions, will be fast compared to acylation. The finding that diethyl N-methylphosphoramidate does not significantly catalyse the acylation of N-methyl-4-nitroaniline appears to bear this out.

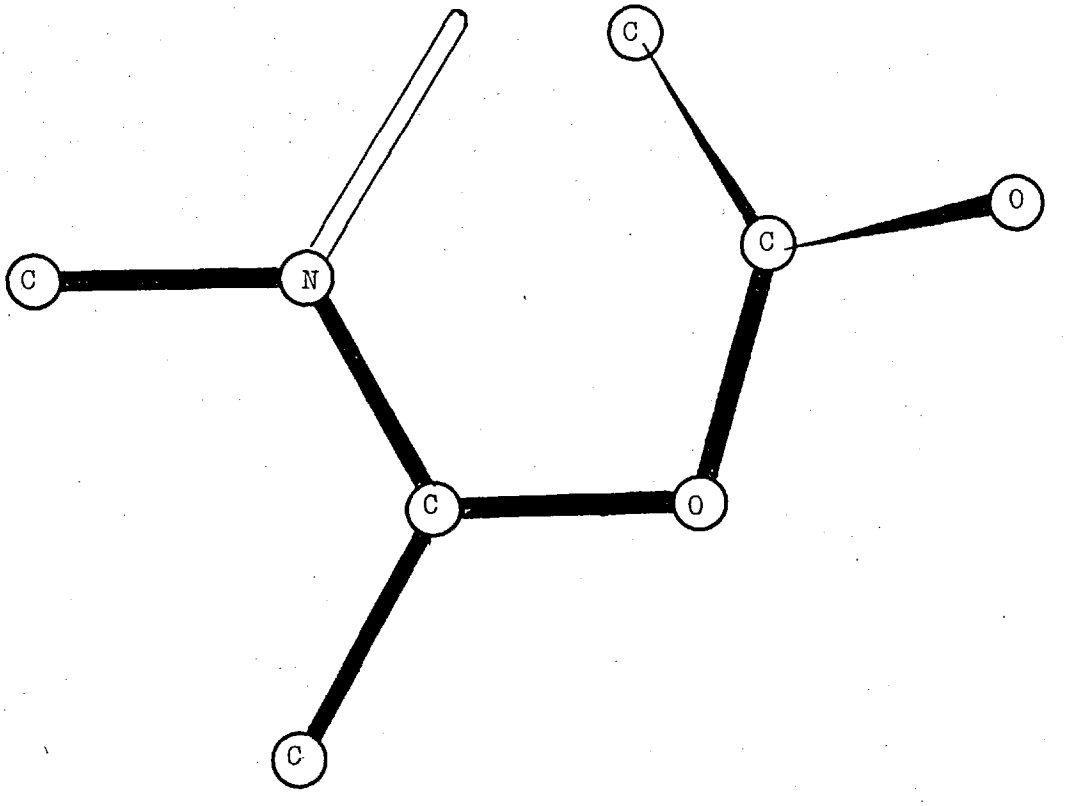
Unfortunately, the tertiary phosphoramidates $(EtO)_2PONMe_2$ and $(Me_2N)_3PO$

FIGURE 4.6.1. DREIDING MODEL STRUCTURES OF $(EtO)_2P(OAc)=NMe$ (a) AND $PhC(OAc)=NMe$ (b).

a



b



did not yield the O-acylimidonium salts with CH_3COCl and $(CF_3CO)_2O$ as anticipated but gave N,N-dimethylacetamide and N,N-dimethyltrifluoroacetamide respectively. Both products arise from N-acylation followed by P-N bond cleavage. As noted earlier these results do not exclude O-acylation since a reversible equilibrium may occur (Equation 4.2.1.5.).

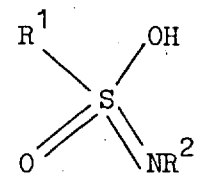
The outcome of these results is that neutral phosphoramidates are acylated yielding their N-acylated analogues, but the initial site of reaction remains uncertain. If O-acylphosphorimidates are involved in these reactions, their apparent instability would suggest that they are unsuitable as peptide-linking reagents.

CHAPTER 5

THE SULPHONIMIDATE-SULPHONAMIDE REARRANGEMENT AND THE ALKYLATION OF SULPHONAMIDES

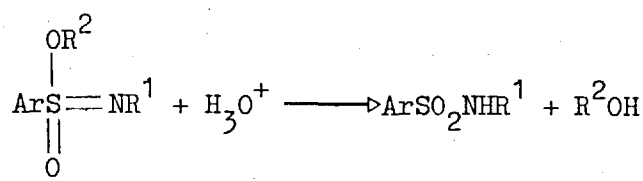
5.1. THE SULPHONIMIDATE-SULPHONAMIDE REARRANGEMENT

Since the report 13 years ago that esters of sulphonimidic acid (69) were unknown[109], several successful syntheses of these compounds have been reported[94,110].

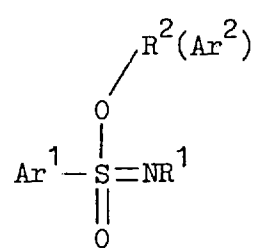


(69)

Relatively little is known, however, about their chemical properties. Hydrolysis of the alkyl esters (70) under acidic or neutral conditions gives the corresponding secondary sulphonamide, and, presumably R^2OH, (Equation 5.1.1.) whereas basic hydrolysis causes extensive decomposition.



Aryl esters (70) are similarly hydrolysed in acidic and neutral media but are also converted to the sulphonamides and phenols in base[94,110] although the nature of Ar^2 influences the rate of this reaction.



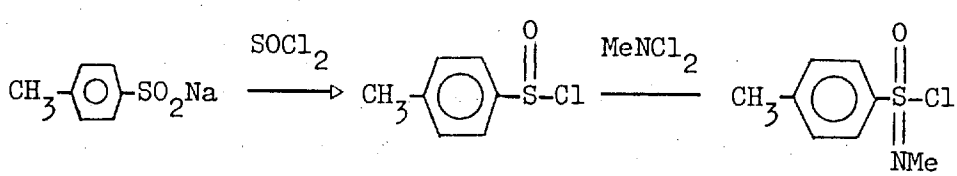
(70)

More significant to the present study are brief reports of their

alkylating ability, akin to that of the corresponding sulphonate esters [94,111]. Thus carboxylic acids are converted into the corresponding esters. Further, the alkyl esters (70) were found to thermally isomerise to the tertiary sulphonamide by a first-order process[94], but in the absence of cross-over experiments it is not possible to deduce whether this is an intramolecular or an intermolecular reaction. Finally, reaction of a sulphonimidate with methyl iodide gives rise to an N-methylated tertiary sulphonamide. Since the imidate-amide rearrangement was helpful in defining the nucleophilic reactivity of neutral carboxamides[25] and phosphylamides, a more detailed investigation of the mechanism of the sulphonimidate-sulphonamide rearrangement was undertaken.

5.1.1. SYNTHESIS OF SUBSTRATES

The procedure of Levchenko et al[94,112] was used to prepare both the O-ethyl- and O-phenyl-N-methyl-4-toluenesulphonimidates (72) (Scheme 29).



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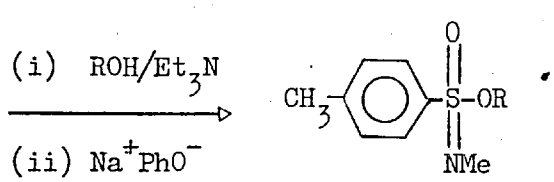


(72) a R=Et
b R=Ph
c R=Me

SCHEME 29 . SYNTHESIS OF SULPHONIMIDATES

The significant reaction in this synthesis is the oxidation of S^{IV} to S^{VI} using dichloromethylamine, to generate the sulphonimidoyl chloride (71).

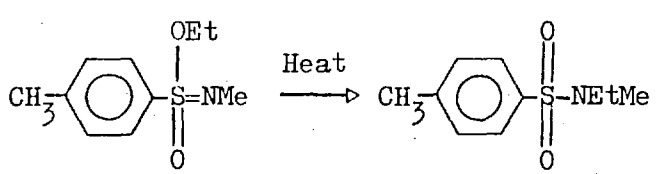
This can be isolated and characterised (*e.g.* hydrolysis gives $CH_3C_6H_4SO_2NHMe$) but it is usually generated *in situ* and used without isolation. Thus a CCl_4 solution of (71) treated with ethanol (methanol) and triethylamine at -20°C yields an oil. The n.m.r. spectrum of this oil shows a $-CH_2-$ quartet absorbtion at 3.97 p.p.m. Distillation at 100°C and 2×10^{-2} torr gave *N*-ethyl-*N*-methyl-4-toluenesulphonamide with $-CH_2-$ absorbtion signals at 3.0 p.p.m. but no signal at δ 3.97 expected for (72a) was observed which suggests that thermal rearrangement occurred. The sulphonimidate could be obtained however, by distillation at 45-55°C and 10^{-5} torr.

The *O*-phenyl ester (72b) was obtained from the sulphonimidoyl chloride and sodium phenoxide. Recrystallisation at low temperature gave the product.

5.1.2. THERMAL REACTION

5.1.2.1. *O*-Ethyl-*N*-methyl-4-toluenesulphonimidate (72a)

In the absence of solvent (72a) rearranges to *N*-ethyl-*N*-methyl-4-toluenesulphon~~imidate~~amide quantitatively at 100°C. In $[^2H_3]$-acetonitrile and $[^2H_6]$-acetone the rearrangement (Equation 5.1.2.1.) was followed by the decrease in the $-OCH_2-$ absorbtions in the n.m.r. spectrum. Signal intensities were normalised by using the aromatic signals as an internal reference.



(72a) (74) .... 5.1.2.1.

In both solvents rearrangement was slow and the reaction rate followed Rate = $k_\Delta [(72a)]^2$ up to at least two half-lives (Tables 5.1.2.1., 5.1.2.2. and 5.1.2.3.).

TABLE 5.1.2.1. REARRANGEMENT OF (72a) AT 100°C IN [$^2H_3$]-ACETONITRILE.

t/min	[(72a)]/M	1/[(72a)]/M^{-1}	ln[(72a)]/[(72a)]$_o$	$10^6k_1/s^{-1a}$	$10^6k_\Delta/M^{-1}s^{-1b}$
0	.388	2.579	0.000	-	-
2548	.308	3.250	-0.231	1.51	4.39
6832	.229	4.367	-0.527	1.29	4.36
9762	.208	4.799	-0.623	1.06	3.79
12645	.168	5.952	-0.837	1.10	4.45
16971	.147	6.822	-0.971	0.95	4.17
22719	.119	8.386	-1.182	0.87	4.26
33211	.087	11.494	-1.495	0.75	4.47
42941	.073	13.699	-1.671	0.65	4.32

a. First-order rate coefficient.

b. Second-order rate coefficient

TABLE 5.1.2.2. DECOMPOSITION OF (72a) AT 100°C IN [$^2H_3$]-ACETONITRILE.

t/min	[(72a)]/M	1/[(72a)]/M^{-1}	ln[(72a)]/[(72a)]$_o$	$10^7k_1/s^{-1a}$	$10^6k_\Delta/M^{-1}s^{-1b}$
0	.172	5.819	0.000	-	-
1107	.162	6.154	-0.057	8.58	6.55
2259	.155	6.457	-0.105	6.84	4.16
5848	.134	7.476	-0.251	7.15	4.72
10208	.112	8.955	-0.432	7.05	5.12
14043	.101	9.844	-0.531	6.30	4.82
20018	.083	12.019	-0.726	6.04	5.16
33242	.062	15.330	-0.973	4.88	4.77

a. First order rate constant.

b. Second-order rate constant.

TABLE 5.1.2.3. DECOMPOSITION OF (72a) AT 100°C IN $[^2H_6]$- ACETONE.

t/min	$[(72a)]/M$	$1/[(72a)]/M^{-1}$	$\ln[(72a)]/[(72a)]_o$	$10^7 k_1/s^{-1}$ [a]	$10^6 k_\Delta/M^{-1}s^{-1}$ [b]
0	.213	4.695	0.000	-	-
7200	.172	5.814	-0.214	4.95	2.59
15680	.135	7.407	-0.456	4.85	2.88
24324	.121	8.291	-0.566	3.87	2.46
34800	.097	10.287	-0.787	3.77	2.68
44955	.085	11.728	-0.919	3.41	2.61
55010	.076	13.082	-1.031	3.12	2.54
66990	.062	16.011	-1.234	3.07	2.82

a. First-order rate coefficient.

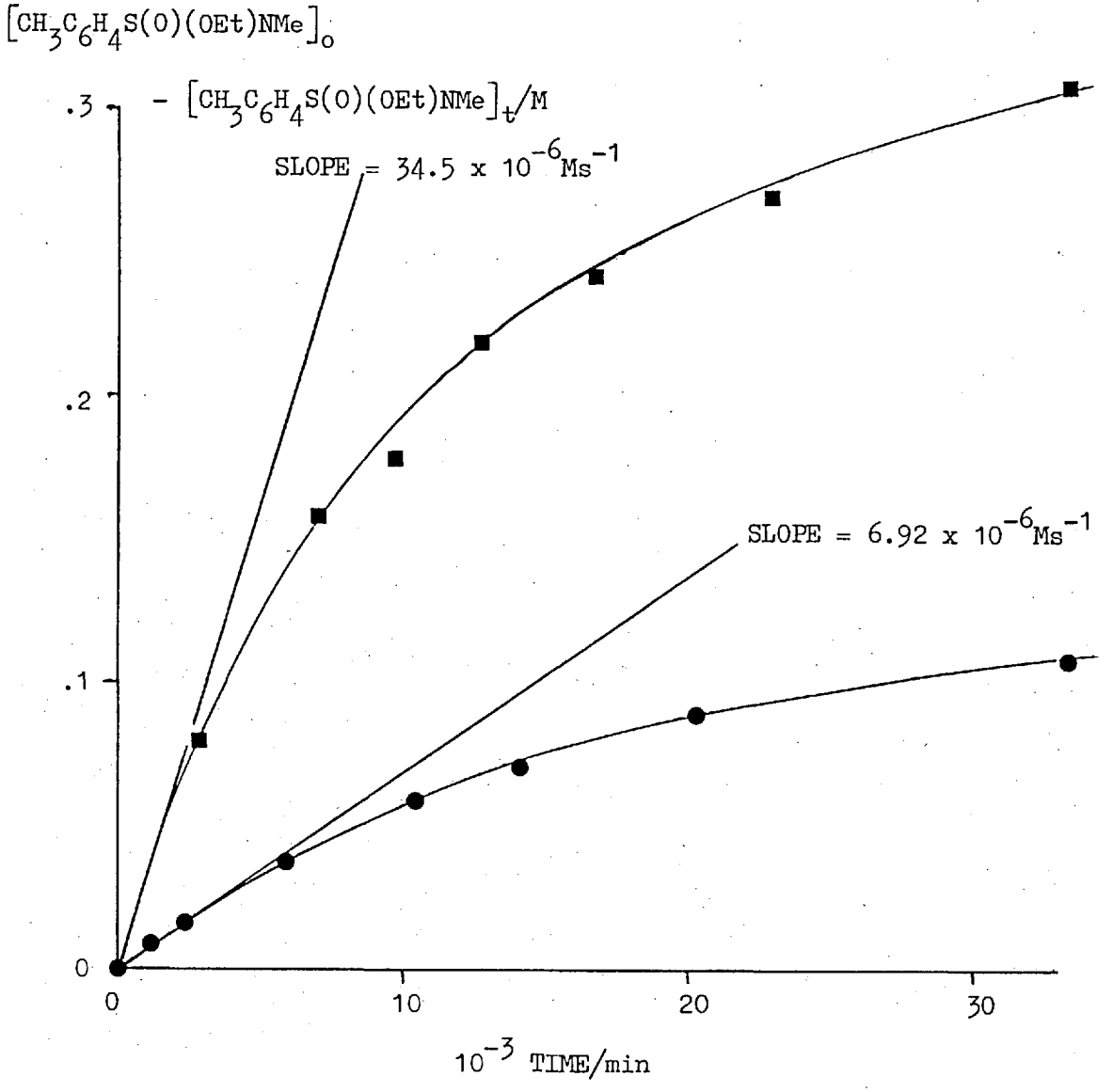
b. Second-order rate coefficient.

Furthermore, the initial-rate study (Figure 5.1.2.1.) from Tables 5.1.2.1. and 5.1.2.2. show that the initial rate at $[(72a)]_o$ = 0.388M is 4.99 times that for $[(72a)]_o$ = 0.172M indicating the reaction has a second-order dependence on $[(72a)]$.

The reaction solution spectra also show the presence of a signal at δ 5.48 (s) corresponding to the formation of ethylene. For the reaction where $[(72a)]_o$ = 0.388M this corresponds to 12(±3)% of the overall reaction. The presence of $CH_3C_6H_4SO_2NHMe$ was shown by t.l.c. and indicates that dealkylation is a competitive process to rearrangement. However, the observation of second-order kinetics for the loss of substrate indicates that both rearrangement and dealkylation occur <u>via</u> intermolecular pathways obeying Equation 5.1.2.2. Rate coefficients for both rearrangement,

$$\text{Rate} = k_\Delta[(72a)]^2 = k_{rearr}[(72a)]^2 + k_{dealk}[(72a)]^2 \quad \ldots. \quad 5.1.2.2.$$

FIGURE 5.1.2.1. SECOND-ORDER DEPENDENCE ON $[CH_3C_6H_4S(O)(OEt)NMe]$ OF THE THERMAL DECOMPOSITION OF $CH_3C_6H_4S(O)(OEt)NMe$ IN $[^2H_3]$-ACETONITRILE AT 100°C.



● $[CH_3C_6H_4S(O)(OEt)NMe]_o$ = .172
Initial Rate = $6.92 \times 10^{-6} Ms^{-1}$

■ $[CH_3C_6H_4S(O)(OEt)NMe]_o$ = .388
Initial Rate = $34.5 \times 10^{-6} Ms^{-1}$

k_{rearr}, and dealkylation, k_{dealk}, were calculated from k and the product ratios.

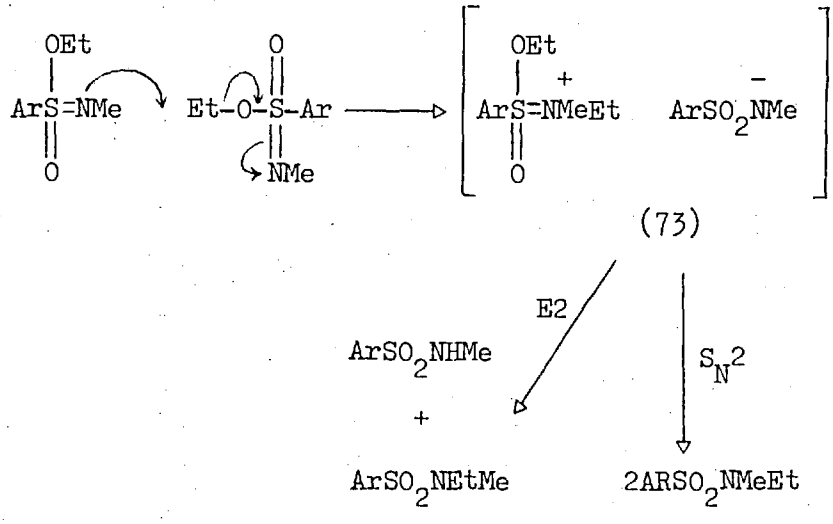
Thus

$$k_{rearr} = \frac{88}{100} \times 4.28 \times 10^{-6} = 3.77 \times 10^{-6} M^{-1} s^{-1}$$

and

$$k_{dealk} = \frac{12}{100} \times 4.28 \times 10^{-6} = 5.14 \times 10^{-7} M^{-1} s^{-1}$$

The most likely process for these reactions involves alkylation of the sulphonimidate N-atom by a second substrate molecule (Scheme 30). This is consistent with the anticipated alkylating ability of sulphonimidates[94] by comparison with sulphonates and sulphates.



SCHEME 30. THERMAL REARRANGEMENT OF (72a) TO N-ETHYL-N-MEHTYL-4-TOLUENESULPHONAMIDE.

The ionic intermediate (73) may then transalkylate to give the desired product. Dealkylation is the usual competitive elimination process involving proton abstraction from either a second substrate molecule or the intermediate cation.

The solvent effect, $k_{\Delta}[CD_3CN] \overset{2}{>} k_{\Delta}[(CD_3)_2CO]$ is consistent with the intermediacy of (73), the formation of which might be expected to be rate-determining since the nucleophilicity of the sulphonamide anion is high.

This mechanism is at variance with a previous literature report that the reaction was intramolecular[94].

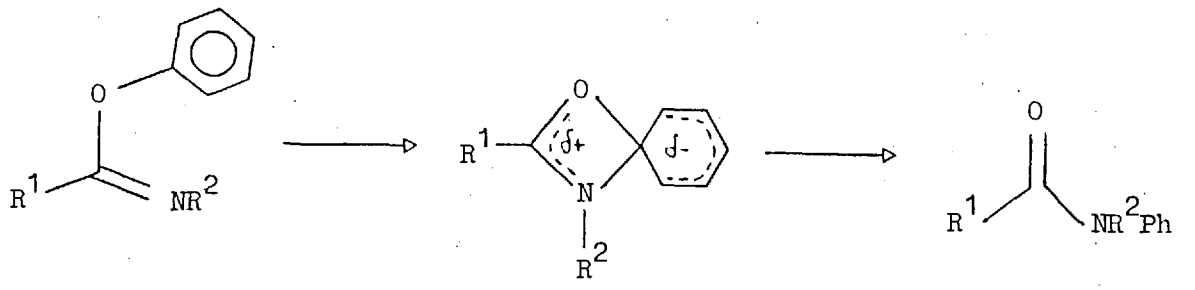
Of interest was the observation that the rate of rearrangement, sulphonimidate > phosphorimidate > imidate (Table 5.1.2.4.), parallels the order of alkylating ability of the corresponding esters.

TABLE 5.1.2.4. RATE CONSTANTS, k_{Δ}, FOR THE THERMAL DECOMPOSITION OF VARIOUS IMIDATES

	SOLVENT	T/°C	$10^6 k_{\Delta}/M^{-1}s^{-1}$
PhC(OEt)NMe	$PhNO_2$	138	0
$(EtO)_3P{=}NMe$	CH_3CN	100	1.69
$CH_3C_6H_4S(OEt)(O)NMe$	CD_3CN	100	4.54

5.1.2.2. O-Phenyl-N-methyl-4-toluenesulphonamidate (72b)

In contrast to the O-alkylsulphonimidate, (72b) did not undergo significant thermal rearrangement to N-methyl-N-phenyl-4-toluenesulphonamide even at temperatures of 150°C. Above this temperature decomposition occurred without formation of identifiable products. The Chapman rearrangement[113], i.e. the intramolecular O- to N- phenyl migration, is therefore unique to the imidate-amide conversion. The exact reason for this is unclear. Molecular models do not indicate substantial conformational differences for reaction of the planar imidate versus the tetrahedral sulphonimidate (Scheme 31) but the sulphonimidate N-atom is less nucleophilic than the imidate N-atom (vide infra).



SCHEME 31.

5.1.3. ALKYL HALIDE PROMOTED REARRANGEMENT

5.1.3.1. O-Ethyl-N-methyl-4-toluenesulphonimidate

In the presence of alkyl halides rearrangement of (72a) to the sulphonamide (74) occurred much more readily. The reaction was solvent dependent (*cf.* Section 5.1.3.) and for practical reasons $[^2H_3]$-acetonitrile was used for most experiments.

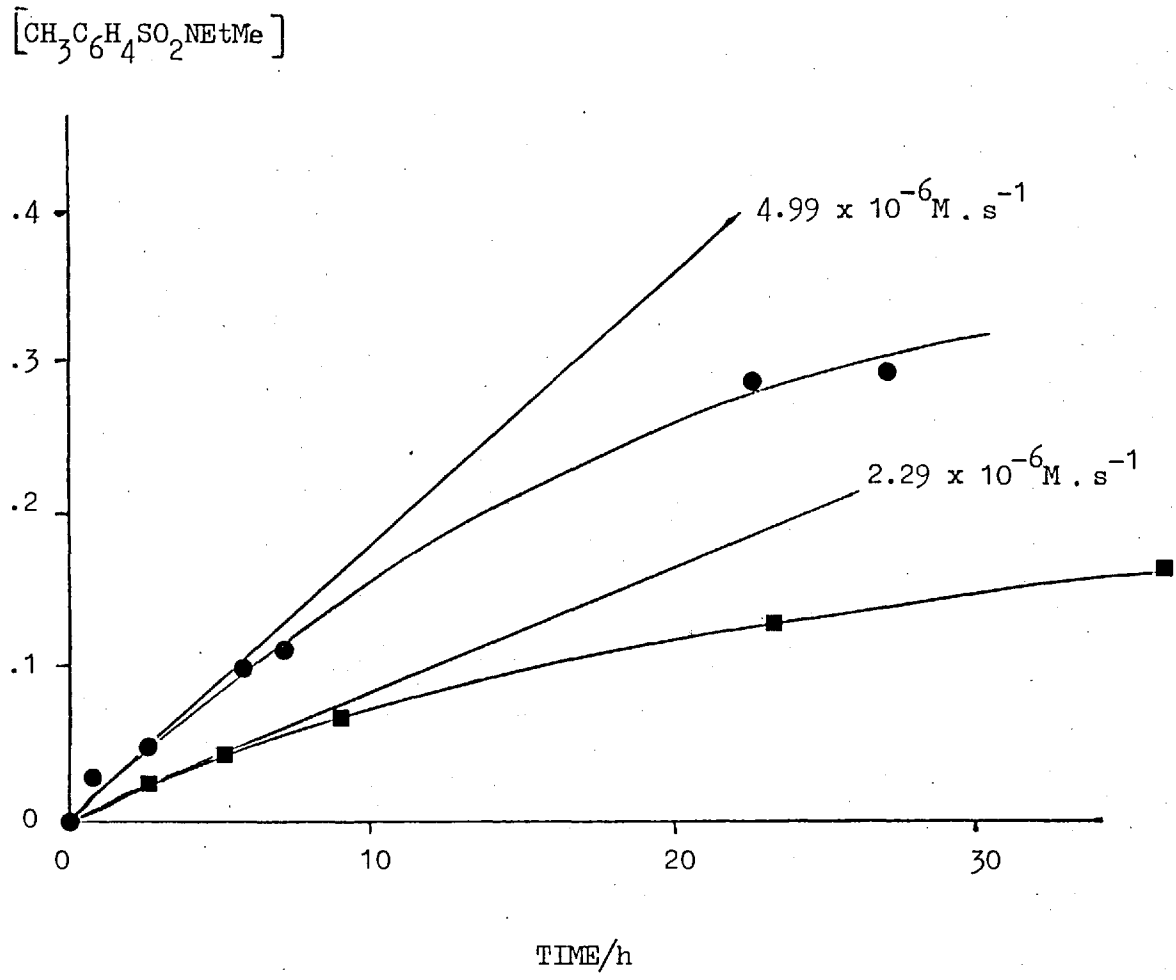
5.1.3.1.1. Order of the Reaction

Unlike the thermal rearrangement, conversion of (72a) to (74) in the presence of alkyl halides follows Rate = $k_o[(72a)]$ which has only first-order dependence on [substrate] (Table 5.1.3.1.). Further evidence for first-order dependence on [substrate] was obtained by varying the $[(72a)]_o$ (Figure 5.1.3.1.). Thus a 2.14-fold increase in $[(72a)]$ brings about a 2.18-fold increase in the initial rate.

The pseudo-first-order rate coefficients, k_o, obtained were found to vary linearly with the concentration of added alkyl halide (Table 5.1.3.2., Figure 5.1.3.2.) and, significantly, for ethyl halides inspection of the n.m.r. spectra on completion of the reaction indicated that no change in the initial alkyl halide concentration had occurred.

FIGURE 5.1.3.1. $[CH_3C_6H_4S(O)(OEt)NMe]$ DEPENDENCE OF THE REARRANGEMENT OF (72a) to (74) IN $[^2H_3]$-ACETONITRILE PROMOTED BY EtI.

$[EtI]$ = 0.26 M



● $[CH_3C_6H_4S(OEt)(O)NMe]_o$ = .407 M
Initial Rate = $4.99 \times 10^{-6} Ms^{-1}$

■ $[CH_3C_6H_4S(OEt)(O)NMe]_o$ = .190 M
Initial Rate = $2.29 \times 10^{-6} Ms^{-1}$

TABLE 5.1.3.1. TYPICAL FIRST-ORDER DEPENDENCE ON $[(72a)]$ FOR THE REARRANGEMENT OF (72a) TO (74) IN $[^2H_3]$-ACETONITRILE AT 100°C PROMOTED BY ETHYL IODIDE.

$[EtI] = 0.123$ M

$[(72a)] = 0.188$ M

t/min	$[(72a)]$/M	$1/[(72a)]/M^{-1}$	$\ln[(72a)]/[(72a)]_o$	$10^6 k_o/s^{-1}$	$10^5 k_2/M^{-1}s^{-1}$
0	.188	5.319	0.000	-	-
381	.158	6.329	-0.173	7.57	4.42
1308	.109	9.174	-0.549	7.00	4.91
1827	.087	11.494	-0.770	7.02	5.63
2802	.061	16.393	-1.126	6.70	6.58
3231	.048	20.833	-1.363	7.03	8.00
4301	.031	32.258	-1.818	7.04	10.44

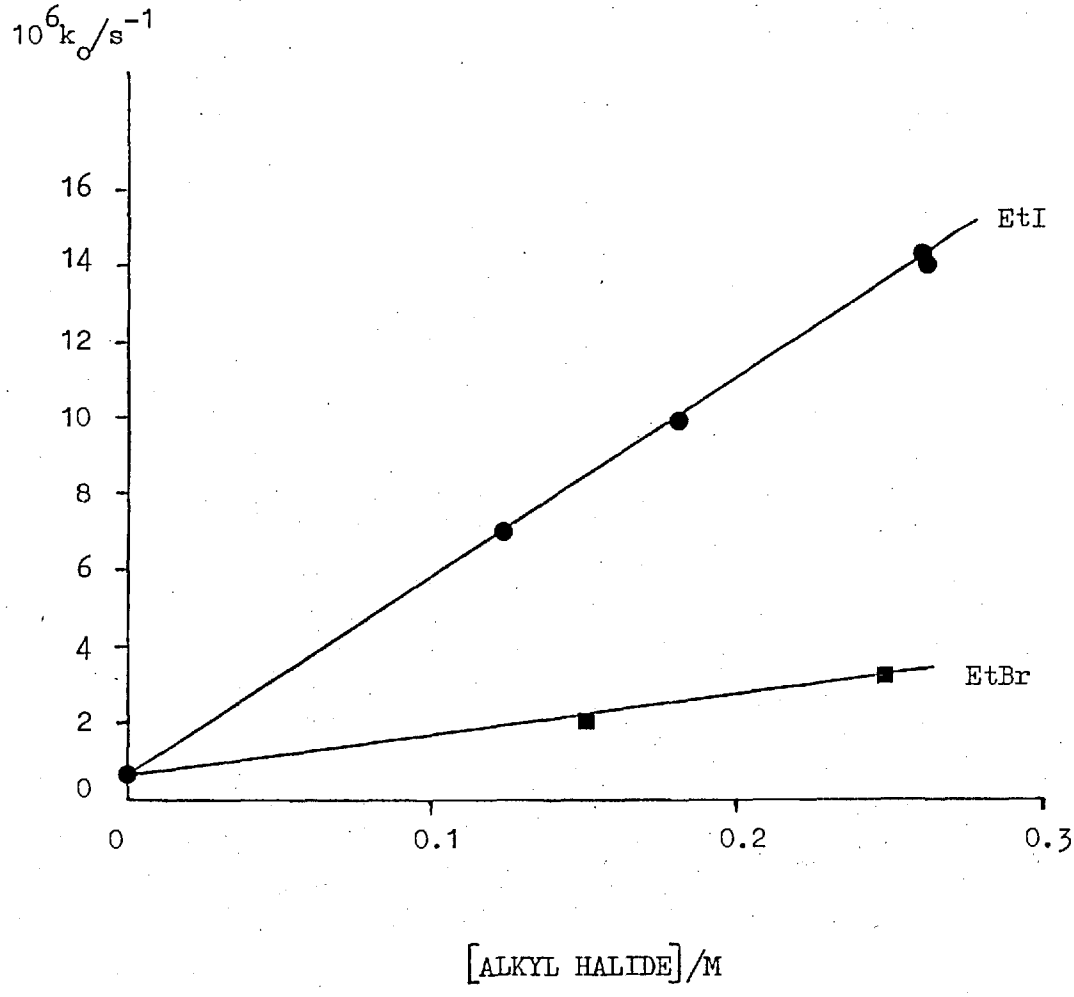
TABLE 5.1.3.2. PSEUDO-FIRST-ORDER RATE COEFFICIENTS FOR THE REARRANGEMENT OF (72a) TO (74) IN $[^2H_3]$-ACETONITRILE AT 100°C IN THE PRESENCE OF ALKYL HALIDES.

$[(72a)]_o = 0.15 - 9.40$ M

Alkyl Halide	[Alkyl Halide]/M	$10^6 k_o/s^{-1}$
EtI	0.260	14.3
	0.180	10.0
	0.123	7.1
EtBr	0.247	3.3
	0.151	2.1

FIGURE 5.1.3.2. DEPENDENCE OF k_o ON [ALKYL HALIDE] FOR THE REARRANGEMENT OF (72a) TO (74) IN [$^2H_3$]-ACETONITRILE AT 100°C.

$[(72a)]_o$ = 0.15 - 0.4 M



The intercept on Figure 5.1.3.2. indicates the presence of a small uncatalysed (i.e. thermal) process of similar magnitude to that obtained in the absence of alkyl halide (Tables 5.1.2.1. and 5.1.2.2.).

From the unimolecular dependence of the reaction on both substrate and alkyl halide concentration it follows that the catalysed reaction rates are governed by Equation 5.1.3.1. and that the overall process is bimolecular,

$$\text{Rate} = k_2\left[(72a)\right]\left[\text{Alkyl halide}\right] \quad \ldots\ldots \quad 5.1.3.1.$$

where

$$k_2 = k_o/\left[\text{Alkyl halide}\right] \quad \ldots\ldots \quad 5.1.3.2.$$

5.1.3.1.2. Effect of Catalyst

From the above treatment of results, the bimolecular rate constants, k_2, for a variety of alkylating agents can be computed. For ethylating agents the reactions are pseudo-first-order (i.e. catalyst concentration is constant) and values of k_2 are calculated using Equation 5.1.3.2. For isopropyl iodide, the plot of $\ln\left[(72a)\right]/\left[(72a)\right]_o$ versus t is curved, because as reaction proceeds ethyl iodide (a more effective catalyst than isopropyl iodide) is generated. Significatnly, both ethyl iodide and N-ethyl-N-methyl-4-toluenesulphonamide were identified by n.m.r. as products of the reaction.

A sensible rate coefficient for promotion by isopropyl iodide can be obtained from the initial reaction rate. Methyl iodide, however, reacts with (72a) much more rapidly than ethyl iodide to give a mixture of N,N-dimethyl-4-toluenesulphonamide and ethyl iodide as products. Thus ethyl iodide is unable to compete with methyl iodide and rate coefficients for the methyl iodide catalysed reaction can be calculated directly from Equation 5.1.3.3.

$$\ln[MeI]/[(72a)]_t = \ln[MeI]_o/[(72a)]_o - kt\{[MeI]_o - [(72a)]_o\} \quad \ldots\ldots \quad 5.1.3.3.$$

Values of the second-order rate coefficients obtained by these procedures and corrected for the thermal process are summarised in Table 5.1.3.3.

TABLE 5.1.3.3. SECOND-ORDER RATE COEFFICIENTS FOR THE REACTION OF O-ETHYL-N-METHYL-4-TOLUENESULPHONIMIDATE (72a) WITH ALKYL HALIDES IN [$^2H_3$]-ACETONITRILE AT 100°C.

Initial [(72a)] = ca. 0.15 M

[Alkyl halide] = 0.1 - 0.5 M

Alkyl halide	$10^6 k_2/M^{-1}s^{-1}$
MeI	853
EtI	52.1
EtBr	10.0
EtCl	0
Pr^iI	11.5
$EtNO_3$	1.1
$EtI-AgNO_3$	4.5

Examination of these data shows that the rate of reaction is sensitive to the amount of branching, i.e. steric hindrance in the alkyl halide. Thus the rate decreases down the series MeI >EtI >Pr^iI. Further, the nature of the leaving group influences the reaction rate, with EtI >EtBr >EtCl. Ethyl nitrate has a negligible effect which suggests that anion nucleophilicity is more important than alkylating ability. However, other evidence suggests that ethyl nitrate is best considered as a special case. This follows from observations (Table 5.1.3.3.) that addition of 1 equiv-

alent of silver nitrate reduces the rate of reaction in the presence of ethyl iodide by a factor of ca. 12 but does not reduce it to the rate for ethyl nitrate itself. The reason for this is unclear but catalysis from silver iodide and a slight excess of silver nitrate could well account for this effect as it did for phosphorimidates (see Section 2.4.2.).

Of further interest was the finding that, on reaction with EtI, the order of reactivity PhC(OEt) = NMe $>$ $(EtO)_3P$ = NPh $>$ $CH_3C_6H_4S(O)(OEt)$= NMe (Table 5.1.3.4.) is the reverse of that for the thermal reaction (Section 5.1.2.). The explanation here is that the nucleophilicity of the N-atom follows the above order but that the alkylating ability of the imidate esters follows the order for the thermal process.

TABLE 5.1.3.4. RATES OF REACTION BETWEEN SOME IMIDATE ESTERS AND EtI.

ESTER	SOLVENT	T/°C	$10^6 k_2/M^{-1}s^{-1}$
PhC(OEt)=NMe	$PhNO_2$	138	1540
$(EtO)_3P$=NPh	CH_3CN	100	400
$CH_3C_6H_4S(O)(OEt)$=NMe	CD_3CN	100	52.1

5.1.3.1.3. Effect of Other Electrophilic Reagents

The observation that alkyl halides reacted with (72a) suggested that more general electrophilic entities would effect the conversion of (72a) to (74). Results for several reagents are summarised in Table 5.1.3.5.

Significantly, the k_2 value for ZnI_2 is similar to that for EtI (k_2 = 52.1 x $10^{-6}M^{-1}s^{-1}$) and that for 0.3 equivalents of HBr is similar to EtBr (k_2 = 10.0 x $10^{-6}M^{-1}s^{-1}$) whereas on addition of 1 equivalent of HBr quantitative dealkylation rather than rearrangement took place. These results are best explained as generation of ethyl halide by nucleophilic

TABLE 5.1.3.5. SECOND-ORDER RATE COEFFICIENTS FOR REACTION OF (72a) WITH ELECTROPHILIC REAGENTS.

$[(72a)]_o$ = 0.2 - 0.5 M

ELECTROPHILE	T/°C	$10^6 k_2/M^{-1}s^{-1}$
ZnI_2 (0.1 equiv.)	100	55.3
HBr (0.33 equiv.)	100	12.2
HBr (1 equiv.)	25	a.
HSO_3F (1 equiv.)	25	b.
$MeSO_3F$ (0.25 equiv.)	34	1870 c.

a. No rearrangement but quantitative formation of $CH_3C_6H_4SO_2NHMe$ and EtX (X=Br) immediately which remained unchanged on heating at 100°C for 8 days.

b. Quantitative formation of $CH_3C_6H_4SO_2NHMe$ and EtX ($X=FSO_3$) immediately.

c. Formation of $CH_3C_6H_4SO_2NMe_2$ and EtX ($X=FSO_3$) over <u>ca</u>. 10 min. followed by formation of $CH_3C_6H_4SO_2NEtMe$. CCl_4 solvent.

attack of the sulphonimidate on the electrophile (Equation 5.1.3.4.).

$$ArS(O)(OEt)NMe + Y\text{-}X \longrightarrow ArSO_2NYMe + EtX \quad .... \quad 5.1.3.4.$$

The EtX reagent then effects rearrangement as before and the observed rates are those corresponding to those for added ethyl halide itself. Other evidence for this explanation was the rapid appearance of n.m.r. signals corresponding to the ethyl halides in the reaction solutions. These signals were proportional to the amount of electrophile added. There was no evidence to show that the sulphonamide derivative (Equation 5.1.3.4.) affected the subsequent rearrangement.

5.1.3.1.4. Effect of Temperature

The effect of temperature on the rate of rearrangement of (72a) to (74) in the presence of ethyl iodide was also examined. The results are summarised in Table 5.1.3.6.

TABLE 5.1.3.6. EFFECT OF TEMPERATURE ON THE REARRANGEMENT OF (72a) TO (74) IN $[^2H_3]$-ACETONITRILE BY ETHYL IODIDE.

$[(72a)]$ = ca. 0.15 M

$[EtI]$ = ca. 0.2 M

T/°C	$10^6 k_2/M^{-1}s^{-1}$	$10^3 T^{-1}/K^{-1}$	$\ln k_2$
100	52.1	1.680	-9.86
86	21.3	2.784	-10.76
73.5	10.8	2.884	-11.44

The corresponding Arrhenius plot of $\ln k_2$ versus $1/T$ is linear with E_a = 64.5($\pm$3) kJ.mol^{-1} and $\Delta S^{\ddagger}$ = -164($\pm$5) kJ^{-1}mol^{-1} (-39 e.u.) at 100°C.

5.1.3.1.5. Solvent Effects

As noted above, the reaction of (72a) with ethyl iodide at 100°C shows a solvent dependence. Rate constants for the reaction decrease in the order of decreasing solvent polarity (Table 5.1.3.7.).

TABLE 5.1.3.7. SECOND-ORDER RATE COEFFICIENTS FOR THE REARRANGEMENT OF (72a) TO (74) AT 100°C.

[(72a)] = ca. 0.15 M

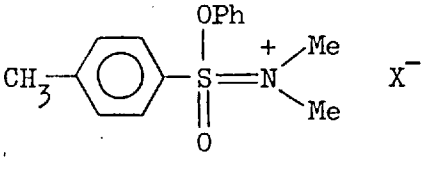
[EtI] = ca. 0.2 M

SOLVENT	ε	$10^6 k_2/M^{-1}s^{-1}$
$[^2H_3]$-ACETONITRILE	37	52.1
$[^2H_6]$-ACETONE	20	29
CCl_4	2.2	4.7 [a]

a. Uncorrected for the thermal reaction.

5.1.3.2. O-Phenyl-N-methyl-4-toluenesulphonimidate

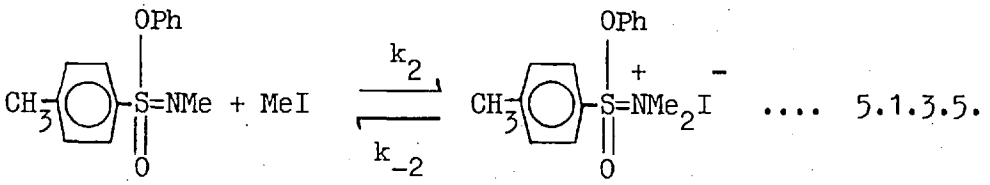
In contrast to (72a), O-phenyl-N-methyl-4-toluenesulphonimidate does not rearrange in the presence of electrophilic reagents. Reaction with methyl iodide at 100°C gives rise, however, to two new $-CH_3-$ signals at 2.60 and 3.27 in the ratio 1:2. These signals could be attributed to the sulphonimidonium ion (75); both are shifted downfield from the imidate



(75) a X=I^-

b X=FSO_3^-

(72b) (δ 2.43 and 3.10). Reaction proceeds only to 20% implying that an equilibrium (Equation 5.1.3.5.) is established. The second-order rate constant for the initial reaction is $k_2 = 66 \times 10^{-6} M^{-1}s^{-1}$ [cf. k_2 for the

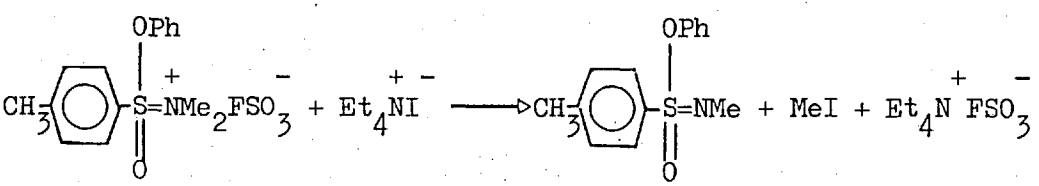


.... 5.1.3.5.

reaction of MeI with $CH_3C_6H_4S(OEt)(O)NMe$, 853 x $10^{-6}M^{-1}s^{-1}$].

Further, (72b) reacts with methyl fluorosulphonate in $MeNO_2$, at 34°C, to give (75b) in 100% yield with k_2 = 5930 x $10^{-6}M^{-1}s^{-1}$. (In a similar reaction in CCl_4 (75b) separates out as an oil). Similar salts to (75a,b) have been reported before[88]. The appearance of only a singlet for the $\underline{N}Me_2^+$ protons indicates a low barrier to rotation about the S=N bond.

Significantly, heating (75b) in the presence of $Et_4N^+I^-$ in $MeNO_2$ at 100°C gave (72b) and MeI (Equation 5.1.3.6.) proving the existence of the



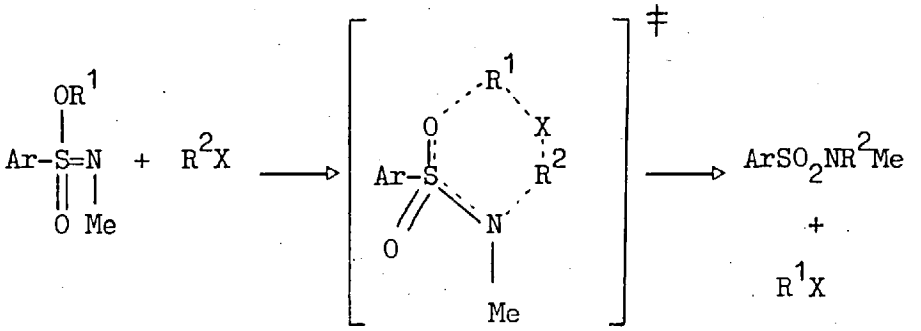
(75b) (72b) .... 5.1.3.6.

equilibrium 5.1.3.5. The extent to which (72b) is formed is 75% after 48 h which, allowing for change in solvent and the insolubility of $Et_4N^+I^-$ in $MeNO_2$, is in excellent agreement with Equation 5.1.3.5.

In FSO_3H the sulphonimidate (72b) displayed signals at δ 2.40 (3H,s), 2.90 (3H,s), and 6.73 - 8.07 (9H,m) { cf. δ ($CDCl_3$) 2.40 (3H,s), 3.10 (3H,s) and 6.77 - 8.03 (9H,m)} and could be recovered quantitatively on neutralisation. The absence of splitting of the $\underline{N}$-$\underline{CH_3}$ signal, indicative of coupling to $\underline{NH}$, suggests that rapid exchange with the solvent occurs. In 42% aqueous HBF_4, (72b) was stable enough to record its n.m.r. spectrum {δ 2.53 (3H,s), 3.02 (3H,s) and 7.07 - 8.30 (9H,m)} but hydrolysed to phenol and $\underline{N}$-methyl-4-toluenesulphonamide on standing.

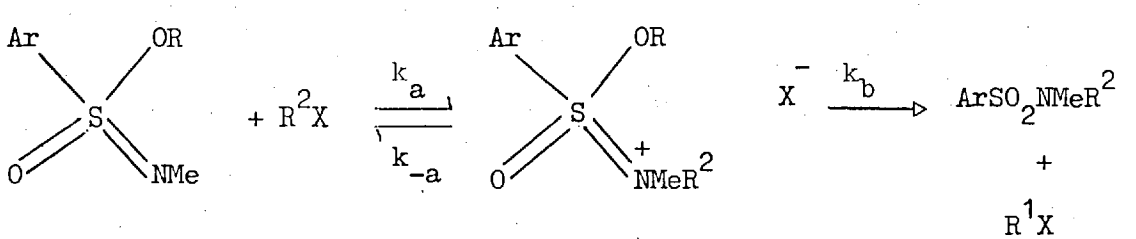
5.1.4. MECHANISM OF THE REARRANGEMENT REACTION

The occurrence of second-order kinetics for the reaction of (72a,b) with electrophilic reagents is best explained by an S_N2 process involving nucleophilic attack of the sulphonimidate on the alkyl halide. Either a synchronous (Scheme 32) or a stepwise (Scheme 33) mechanism may be invoked.



SCHEME 32. SYNCHRONOUS S_N2 MECHANISM FOR THE CONVERSION OF (72a) to (74) BY ALKYL HALIDES.

Both pathways would explain the ddpendence on reagent reactivity (EtI > EtBr ≫ EtCl) and the rate reduction with increased steric hindrance (MeI >EtI > Pr I). However, the finding that the rearrangement rate is



SCHEME 33. STEPWISE S_N2 MECHANISM FOR THE CONVERSION OF (72a) TO (74) BY ALKYL HALIDES.

dependent on solvent polarity $\left\{[^2H_3]\text{-}CH_3CN > [^2H_6]\text{-}(CH_3)_2CO > CCl_4\right\}$ implies development of charge in the transition state and therefore the

involvement of ionic intermediates as required by the stepwise mechanism (Scheme 33). Moreover, the entropy of activation, $\Delta S^{\ddagger} = -39$ e.u. at 100°C, is consistent with an ionic pathway. However cyclic processes such as the Claisen rearrangement, where charge development in the transition is low typically have values of ca. -10 e.u. for $\Delta S^{\ddagger}$ [114].

The observation that MeI > EtI > Pr^{i}I requires that attack by the sulphonimidate on the alkyl halide be rate limiting for the stepwise mechanism with subsequent rapid removal of the $-OR^{2}$ alkyl group by halide ion (step k_b). Reaction initiated by other electrophilic reagents proceeds similarly once ethyl halide is formed by rapid reaction of the sulphonimidate with the electrophile (vide supra).

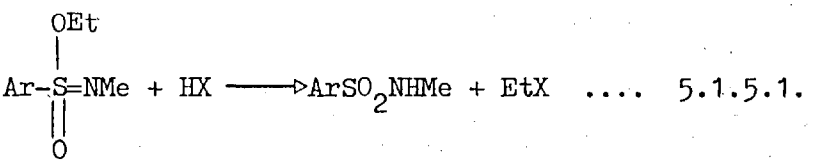
As noted above ethyl nitrate is a poorer catalyst than ethyl iodide which suggests that decomposition of the ionic intermediate may become slow for the weakest nucleophiles. However $MeSO_3F$ and, inter alia, $EtSO_3F$ are good rearrangement catalysts and since the pK_a value fo FSO_3^- is ca. -10 and that for NO_3^- is ca. -1.5 it is more probable that the low reactivity of $EtNO_3$ is related to its alkylating ability.

Furthermore, sulphonimidonium cations such as (76: R^1=Ph, R^2=Me, X=FSO_3) can be generated from O-phenyl-N-methyl-4-toluenesulphonimidate. The strong aryl-oxygen bond effectively increases the energy requirement of step k_b to such an extent that dearylation does not occur. Significantly, the equilibrium k_a/k_{-a} can be observed for (R^2X = MeI), the equilibrium constant, K = .08, indicating that it lies well to the left. O-Aryl phosphorimidate analogues of (76) behave similarly. Thus heating $(PhO)_3P{=}^{+}NEt_2Cl^{-}$ yields N-ethyltriphenylphosphorimidate and methyl chloride[97].

The difference in reactivity towards MeI (Section 5.1.3.) between the O-ethyl- and O-phenyl- sulphonimidates shows that the O-ethylsulphonimidate is ca. 10x more reactive than the O-phenylsulphonimidate which is consistent with the expected substituent inductive effects, EtO > PhO, on the nucleophilicity of the N-atom.

5.1.5. NUCLEOPHILIC PROPERTIES OF SULPHONAMIDES

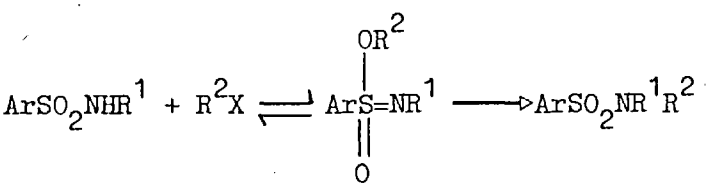
The mechanism (Scheme 33) for the conversion of (72) to (74) is illustrated in terms of the potential energy diagram (Figure 5.1.5.1.). Several features are apparent. The energy barrier $E_4^{\ddagger}$ is that obtained for the catalysed rearrangement of (72a) to (74), E_{act} = 64.5 kJ mol^{-1}. Since formation of the ionic intermediate in this reaction is believed to be rate-limiting, $E_2^{\ddagger} > E_3^{\ddagger}$. The reaction corresponding to $E_5^{\ddagger}$ is that between sulphonimidate and HX (Equation 5.1.5.1.). The relationship $E_5^{\ddagger} < E_4^{\ddagger}$



$$Ar\text{-}S(=O)(OEt)=NMe + HX \longrightarrow ArSO_2NHMe + EtX \quad .... \quad 5.1.5.1.$$

stems directly from the observation that dealkylation of the sulphonimidate (Equation 5.1.5.1.) is both quantitative and rapid at room temperature on addition of an equimolar amount of HX. Further, no concurrent or ensuing rearrangement to (74), due to EtX released during the reaction, takes place under the conditions of the experiment indicating that rearrangement does not compete with dealkylation and also shows that $E_4^{\ddagger} < E_1^{\ddagger}$ since neither EtI nor EtBr alkylates N-methyl-4-toluenesulphonamide under conditions where the catalysed reaction proceeds readily. A value for $E_1^{\ddagger}$ was therefore not obtained experimentally and insufficient data is available to calculate its lowest limit, $E_1^{\ominus}$ the bond enthalpy difference[115].

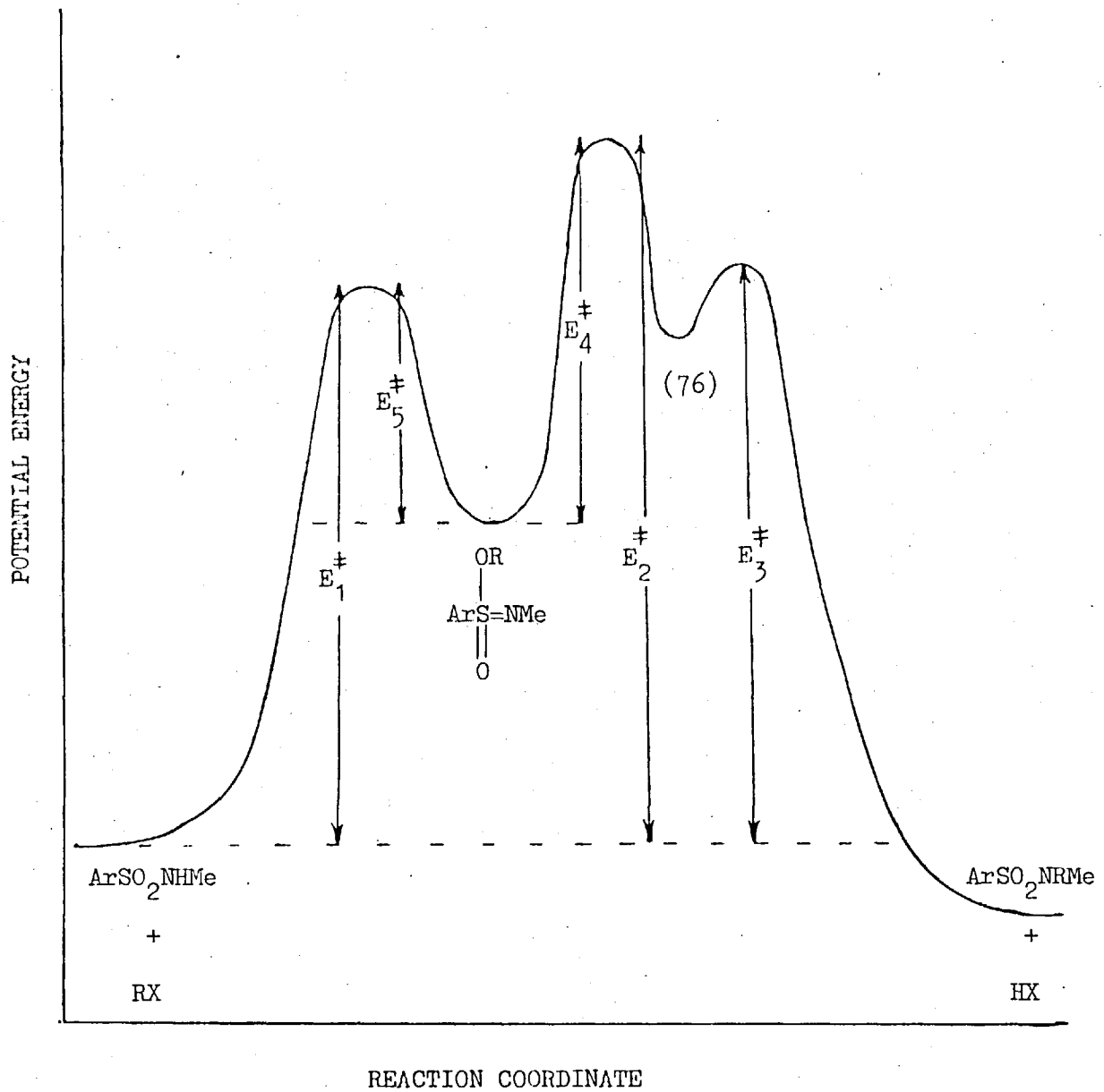
The complete potential energy diagram in Figure 5.1.5.1. is that for the O-alkylation of sulphonamides by alkyl halides (Scheme 34) and it



$$ArSO_2NHR^1 + R^2X \rightleftharpoons ArS(=O)(OR^2)=NR^1 \longrightarrow ArSO_2NR^1R^2$$

SCHEME 34. MECHANISM FOR THE O-ALKYLATION OF SULPHONAMIDES.

FIGURE 5.1.5.1. POTENTIAL ENERGY DIAGRAM FOR THE ALKYLATION OF SULPHONAMIDES WITH ALKYL HALIDES.



bears a strong similarity to that for the alkylation of carboxamides[25]. It predicts that alkylation of neutral sulphonamides should initially give rise to an O-alkylsulphonimidate as the kinetically stable product with formation of the thermodynamically more stable tertiary sulphonamides (i.e. N-substituted products) arising from a subsequent rearrangement of the sulphomimidate.

The corresponding potential energy diagram for direct N-substitution of neutral sulphonamides remains to be determined, but two possibilities for the relative positions of the two diagrams exist. Either a) O-alkylation has the lower energy pathway, or b) O-alkylation has the higher energy pathway.

The behaviour of some sulphonamides to alkylation was undertaken to determine whether reactivity resides with the O- or N- atoms.

5.2. THE ALKYLATION AND ARYLATION OF SULPHONAMIDES

5.2.1. ALKYLATION

Attempts to alkylate 4-toluene-, N-methyl-4-toluene- and N,N-dimethyl-4-toluene- sulphonamides with methyl iodide under neutral conditions were unsuccessful. No reaction occurred in nitrobenzene at 100°C in a sealed tube after 7 days. Unidentifiable decomposition products were produced on heating for a further 9 d at 155°C. However, in the presence of silver oxide N-methyl-4-toluenesulphonamide was cleanly alkylated by methyl iodide to give N,N-dimethyl-4-toluenesulphonamide, giving a second-order rate constant at 100°C, $k_2 = 4.54 \times 10^{-2} M^{-1} s^{-1}$. Ethylation to give N-ethyl-N-methyl-4-toluenesulphonamide occurred similarly with ethyl iodide. In the presence of Ag_2O reaction may well occur via the sulphonamide anion. Significantly, alkylation of the sodium salt of N-methyl-4-toluenesulphonamide gave N-substituted products.

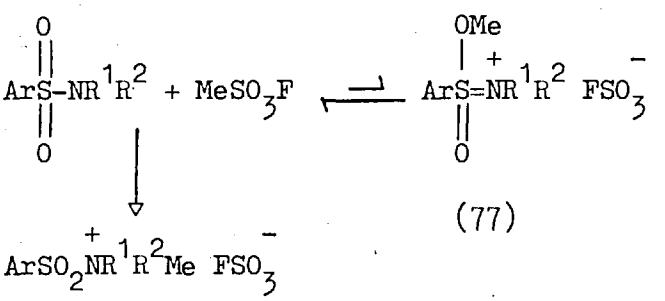
Alkylation did occur, however, under mild conditions with more reactive

alkylating agents. Thus, methyl trifluoromethanesulphonate reacted with an equimolar amount of N-methyl-4-toluenesulphonamide in $PhNO_2$ at 100°C for 1 h to give a mixture of both the N,N-dimethylsulphonamide and the N,N,N-trimethylsulphonylammonium salt (Equation 5.2.1.1.).

$$ArSO_2NHMe + CF_3SO_3CH_3 \longrightarrow ArSO_2NMe_2 + ArSO_2\overset{+}{N}Me_3\,CF_3SO_3^- \quad \ldots\ldots \quad 5.2.1.1.$$

The same salt was generated from N,N-dimethyl-4-toluenesulphonamide at 34°C within 15 min. using an excess of methyl fluorosulphonate. The crystalline solid could be isolated, and its n.m.r. spectrum (in CD_3NO_2) exhibited two methyl resonances at δ 2.40 and 3.17 in the ratio 1 (C-CH_3) :3 (N-CH_3). The $-SO_2-$ stretching frequencies of the starting material, 1335 and 1164 cm^{-1}, are shifted to 1380 and 1175 cm^{-1} in the product. This effect has been noted before[86]. The solid is rapidly attacked by moist air to yield the corresponding sulphonic acid.

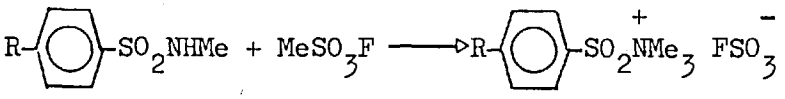
The formation of the cation may be interpreted in terms of Scheme 35. O-Alkylation produces the O-methyl-N,N-dialkylsulphonimidonium cation (77), which is known to dealkylate to yield the sulphonamide (cf. Section 5.1.3.). An unproductive equilibrium is set up allowing N-substitution, to give the sulphonylammonium cation, to compete.



SCHEME 35. ALKYLATION OF A TERTIARY SULPHONAMIDE.

Both N-methyl-4-toluene- and benzene- sulphonamides also react with excess methyl fluorosulphonate as solvent to yield the trimethylsulphonyl-

ammonium fluorosulphonates (Equation 5.2.1.2.). Following the reaction



R=H, CH_3 .... 5.2.1.2.

by n.m.r. showed that within 30 min. the starting sulphonamide had been converted in ca. 35% yield to the tertiary N,N-dimethyl compound. After 2 h the reaction mixture contained ca. 30% starting material, 55% tertiary sulphonamide and 15% sulphonammonium cation. Thus the tertiary sulphonamide is an intermediate in these reactions.

Alkylation, using equimolar amounts of methylfluorosulphonate and N-methylarenesulphonamide, in CCl_4, $CHCl_3$, CH_2Cl_2 and CH_3NO_2 solvents at room temperature or -20°C in the presence or absence of sodium carbonate yielded the N,N-dimethylsulphonamide only. Reactions were faster in CH_3NO_2 than $CHCl_3$ or CCl_4 and were also faster in the presence of Na_2CO_3. Typically, however, reactions were slow taking 2-3 weeks to reach 30% completion. The faster rate in the presence of Na_2CO_3 reflects the ability of the sulphonamide to react via its anion in this system.

No evidence for an O-methyl-sulphonimidate could be obtained but its intermediacy cannot be ruled out by the above experiments. Under the same conditions, i.e. CCl_4 at 34°C, the second-order rate constants, k_2, for rearrangement of O-ethyl-N-methyl-4-toluenesulphonimidate by methyl fluorosulphonate and methylation of N-methyl-4-toluenesulphonamide by methyl fluorosulphonate are 187 x $10^{-5}M^{-1}s^{-1}$ and 3 x $10^{-5}M^{-1}s^{-1}$ respectively. In CH_3NO_2 at 34°C the corresponding rate constants for rearrangement (O-phenyl-N-methylsulphonimidate) and alkylation are 593 x $10^{-5}M^{-1}s^{-1}$ and 10.6 x $10^{-5}M^{-1}s^{-1}$ (Table 5.2.1.1.). Thus catalysed rearrangement is some 60 times faster than direct alkylation so the inability to detect an O-alkylated product is not surprising. Further, O-alkylsulphonimidonium salts (77;R^1=H,R^2=alkyl) should be superb alkylating agents, as good as

TABLE 5.2.1.1. SECOND-ORDER RATE CONSTANTS FOR ALKYLATION OF SULPHONAMIDES AND SULPHONIMIDATES BY $MeSO_3F$.

SOLVENT	T/°C	$10^5k_2/M^{-1}s^{-1}$		
		$ArSO(OEt)NMe$	$ArSO(OPh)NMe$	$ArSO_2NHMe$
CCl_4	34	187 [a]	b	3.02
CH_3NO_2	34		593	10.6

a. ± 30%

b. Separates out as an oil.

$MeSO_3F$ itself. This may well explain why such salts are not isolable whereas those of carboxamides are[37].

5.2.2. ARYLATION

Since O-arylsulphonimidates are stable to thermal and catalysed rearrangement these compounds should be better probes for O- or N- reactivity. With this in mind reaction of both N-methylbenzene- and N-methyl-4-toluenesulphonamide with benzenediazonium tetrafluoroborate at ca. 80°C gave, after workup, O-phenyl-N-methylbenzene- and O-phenyl-N-methyl-4-toluenesulphonimidates in 25% yield as the only products (Equation 5.2.2.1.).

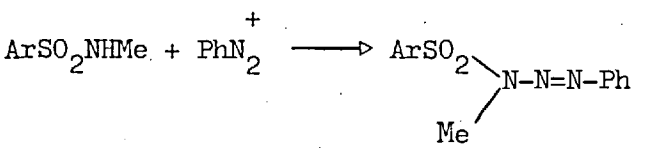
$$RC_6H_4SO_2NHMe \xrightarrow[\text{Heat}]{PhN_2^+BF_4^-} RC_6H_4S(=O)(=NMe)OPh \quad \ldots\ldots \quad 5.2.2.1.$$

R=H,4-CH_3

No N-phenylsulphonamides were detected.

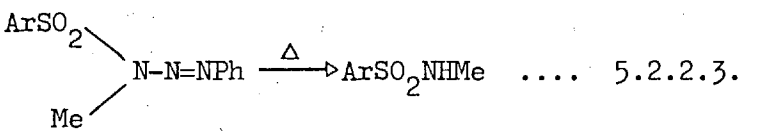
Four possible mechanisms could account for this observation: (a)

direct O-attack on the phenyl cation, (b) direct O-attack on the benzenediazonium cation followed by rearrangement, (c) direct N-attack on the benzenediazonium cation followed by rearrangement and (d) a radical pathway. The other possibility of direct N-attack on the phenyl cation is discounted since no N-phenyl substituted product was detected. Of these 4 possibilities (a) and (b) represent O-substitution *via* initial N-attack. Pathway (c) leads to formation of a triazene (Equation 5.2.2.2.) and it



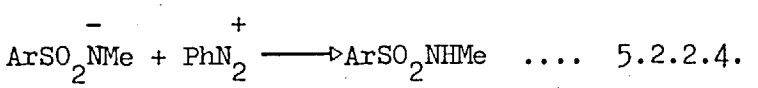
.... 5.2.2.2.

is possible that its decomposition may lead to the sulphonimidate. The triazene was synthesised independently and at 90°C was found to decompose to give N-methyl-4-toluenesulphonamide (Equation 5.2.2.3.) only. An iden-



.... 5.2.2.3.

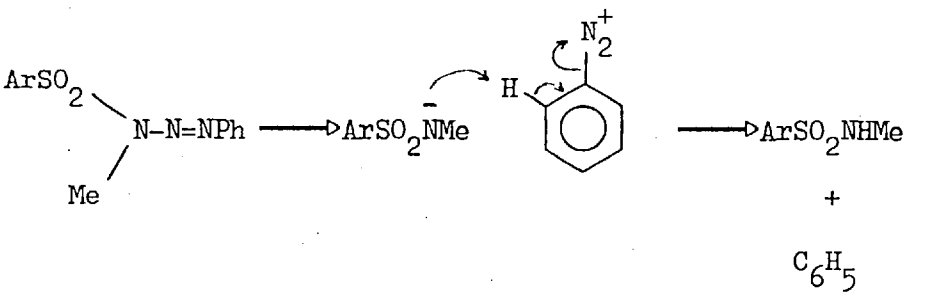
tical decomposition has been observed in the presence of $AlCl_3$.[116] Under the conditions of the experiment the sulphonimidate was stable. Further, N-methyl-4-toluenesulphonamide anion reacts with benzenediazonium tetrafluoroborate at room temperature in ether to give N-methyl-4-toluenesulphonamide. No phenylation or triazene formation was observed (Equation 5.2.2.4.).



.... 5.2.2.4.

It follows that the triazene heterolyses on thermolysis to yield sulphonamide anion and diazonium cation. Deprotonation with nitrogen elimation would give sulphonamide and benzyne (Scheme 36).

This process is analogous to the thermal decomposition of N-nitroso-



SCHEME 36. THERMOLYSIS OF 1-METHYL-1-(4-TOLUENESULPHONYL)-3-PHENYLTRIAZENE.

acetanilide[117]. Attempts to trap benzyne by addition of furan were unsuccessful. These results eliminate the triazene as a possible precursor to sulphonimidate formation.

These results also eliminate the possibility of a radical decomposition of the triazene to give the sulphonimidate. Other radical pathways were studied. N-Methyl-4-toluenesulphonamide was reacted with benzoyl peroxide, a source of phenyl radicals, both neat at 85°C and in refluxing cyclohexane. The reaction of neat reagents yields starting sulphonamide and phenyl benzoate. In cyclohexane, benzoic acid is a further product. No N-phenyl or O-phenyl substitution was observed in either reaction. N-Chloro-N-methyl-4-toluenesulphonamide, a source of sulphonamide radicals, was also reacted with benzoyl peroxide. At 80°C, addition of ca. .05 equivalents of the peroxide resulted in explosive decomposition of the sulphonamide from which no N-phenylsulphonamide or O-phenylsulphonimidate was isolated. The reaction is moderated by use of petroleum ether (60-80) solvent. At reflux for 72 h N-chloro-N-methyl-4-toluenesulphonamide gave N-methyl-4-toluenesulphonamide and benzoic acid on reaction with benzoyl peroxide. No N-phenylsulphonamide or O-phenylsulphonimidate was observed.

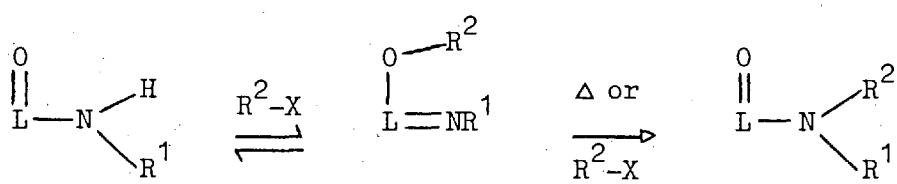
These results show that arylation of secondary sulphonamides by benzenediazonium ion occurs with exclusive sulphonyl oxygen attack and indicates that sulphonamides, as anticipated from the sulphonimidate-sulphonamide rearrangement, exhibit oxygen reactivity and as such amplify the recent findings for amides[25].

CHAPTER 6

MOLECULAR ORBITAL CALCULATIONS FOR AMIDE ALKYLATION

6.1. A GENERAL MECHANISM FOR ALKYLATION

The results presented in the previous chapters indicate that the reactivity of neutral phosphoramidates and sulphonamides towards alkylating agents and, for phosphoramidates, protonation, parallels that for the analogous amides. Thus all three groups of compounds, containing the potentially ambident [1,3]-O,N system, react at the O-atom and give rise to N-substitution products *via* an O- to N- rearrangement process. These amidic compounds are therefore monodent and not ambident and their chemistry can be collectively summarised by a general mechanism (Scheme 37). This requires that the initial, kinetic product is the O-substituted imidate (78) with the thermodynamically stable N-substituted amide (79)



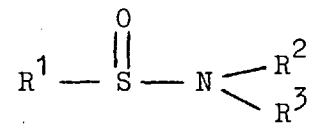
(78) (79)

L = P^{V}, S^{VI}, C, S^{IV}

SCHEME 37. GENERAL MECHANISM FOR THE ALKYLATION OF NEUTRAL [1,3]-AMIDIC COMPOUNDS.

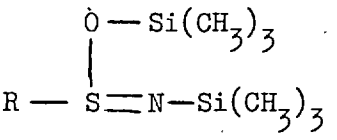
arising from a thermal or electrophilically catalysed rearrangement. Initial formation of the O-substituted product is consistent with the evidence for the site of protonation of these compounds.

Significantly, the alkylation of S^{IV} amides (sulphinamides e.g. 80) may also be described in terms of this mechanism. Thus, benzenesulphinamides



(80)

(80) react with alkyloxonium tetrafluoroborates[118] or alkyltrifluoromethyl-sulphonates in the presence of sodium tetraphenylborate[119] to give either the sulphinimidate or its salt. The bis-(trimethylsilyl)-sulphinamide exists as the imidate (81) exclusively[120], which is consistent with this

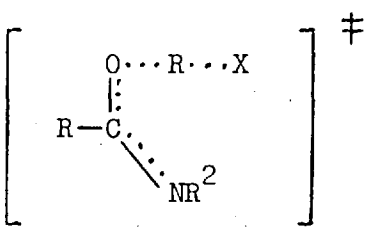


(81)

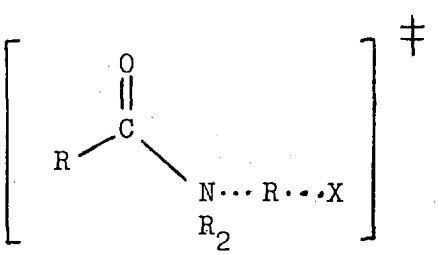
idea.

The question as to why oxygen attack is prefered over nitrogen attack arises and it was of interest to attempt to understand this preference of reactivity in terms of molecular orbital theory. Two possibilities present themselves. Either the transition state is reactant like, in which case the reaction can be described in terms of perturbation theory[8], or it is product like, in which case factors affecting the stability of the products will be transmitted to the transition state.

The alkylation of amides, for example, has been described in terms of product control of the transition state[24,25] where consideration of the transition states for O- and N- attack, (82) and (83) respectively, suggests that (82) is of lower energy due to delocalisation of the N-lone pair of electrons. However, a perturbational approach has been discounted



(82)



(83)

by intuitive arguments only[24,25]. For example, it is assumed that since oxygen is a more electronegative element than nitrogen nucleophilic attack

by a neutral amide in a charge controlled reaction (*e.g.* with Et_3OBF_4 or Ph_3CCl in an S_N1 sense) will give O-substitution. In practise Et_3OBF_4 gives O-, and Ph_3CCl N-substitution[121].

This argument, however, discounts completely the actual atomic charges in amides and in order to differentiate between reactant-control and product-control of the transition state it is necessary to calculate the charge distribution and orbital energies of the reactant. Here, the use of molecular orbital (MO) calculations is invaluable, and a description of the chemistry of amides using the semi-empirical modified neglect of diatomic overlap (MNDO)[122] method is described below. Since d orbitals have not been parametrised for the MNDO method this study involved amides and thioamides rather than phosphoramidates or sulphonamides.

6.2. THE PERTURBATIONAL APPROACH TO THE CHEMISTRY OF AMIDES

The total energy change, ΔE_{tot}, due to partial bond formation between an atom, s, of an electron donor molecule, S, and an atom, t, of an electron acceptor molecule, T, is given by Equation 6.2.1., as a result of applying the generalised polyelectronic peturbation theory[9,123] to the donor-acceptor interaction.

$$\Delta E_{tot} = - \frac{q_s q_t}{R_{st}\varepsilon} + 2 \sum_{\substack{\text{occ} \\ \text{orbitals} \\ \text{of S}}} \sum_{\substack{\text{unocc} \\ \text{orbitals} \\ \text{of T}}} \frac{(C_s^m C_t^n \Delta\beta_{st})^2}{E_m^* - E_n^*} \quad \ldots\ 6.2.1.$$

q_s, q_t = total charges of atoms, s,t in isolated S,T.

R_{st} = distance between s and t for which ΔE_{tot} is calculated.

ε = dielectric constant of solvent.

C_s^m = coefficients of atomic orbitals of atom s in various molecular orbitans m of molecule S.

C_t^n = coefficients of atomic orbitals of atom t in various molecular orbitals n of molecule T.

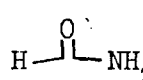
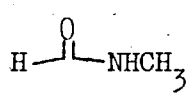
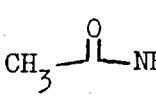
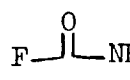
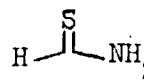
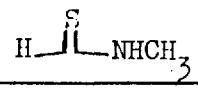
$\Delta\beta_{st}$ = change in resonance integral between interacting orbitals of atoms s and t at R_{st}.

E_m^*, E_n^* = orbital electronegativities.

This equation consists of two terms, an electrostatic term and a covalent term. It is best to consider two general cases.

a) $E_m^* - E_n^*$ is large, i.e. the energy gap between the two interacting molecular orbitals is large. In this case the electrostatic term is dominant and favours interaction between atoms carrying the highest opposite charges. For amides, the acceptor, t, is the same for both O-and N-interactions. Similarly R_{st} and ϵ are constant. Thus, the site of substitution in the amide molecule, S, is controlled by that atom, s, with the greatest atomic charge. The atomic charges for the oxygen(sulphur) and nitrogen atoms for a variety of amides and thioamides as calculated by the MNDO method are summarised in Table 6.2.1. These results show that,

TABLE 6.2.1. OXYGEN AND NITROGEN ATOMIC CHARGES FOR AMIDES AND THIOAMIDES

MOLECULE	$q_o(S)$	q_N
	-.37	-.43
	-.36	-.46
	-.34	-.34
	-.36	-.44
	-.36	-.41
	-.30	-.39
	-.33	-.34
	-.33	-.37

contrary to expectation, the nitrogen atom is the most negative indicating that under conditions where charge control is important the nitrogen atom and not the oxygen atom is the most reactive centre. Although this fits Kornblum's hypothesis[1] for reaction with $^{t}BuCl$ and $PhCH_2Cl$[21], the forcing reaction conditions allow these results open to alternative explanations. Under conditions which do not offer alternative explanations, e.g. $Et_3O^+BF_4^-$, 0°C, the oxygen (or sulphur) atom is attacked[124]. Clearly, the perturbation theory description of amide chemistry under charge control conditions is not convincing.

b) $E_m^* - E_n^* \sim 0$, i.e. the highest occupied orbital of the donor, s, and lowest unoccupied orbital of the acceptor, t, are nearly degenerate. Under this restriction the dominant term of Equation 6.2.1. is the covalent term which favours reaction between the two centres possessing the highest density of charge in the frontier orbitals. For amides, the dominant factor is $1/E_m^* - E_n^*$. Since E_n^*, the LUMO energy of the electrophile, is constant for either O- or N- substitution the orbital interaction is dependent on E_m^*. The orbital electronegativity for a nucleophile, E_m^*, is defined by Equation 6.2.2.[9] The second term of Equation 6.2.2. will have

$$E_m^* = -\left[\frac{\text{I.P.} + 3\text{E.A.}}{4}\right] + \frac{14.4\ (q + 0.5)}{R_{ION}}\left[1 - \frac{1}{\epsilon}\right] \quad \ldots. \quad 6.2.2.$$

I.P. = ionisation potential.

E.A. = electron affinity.

q = initial charge of ion.

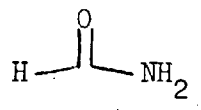
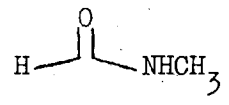
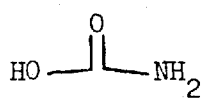
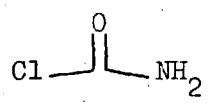
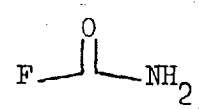
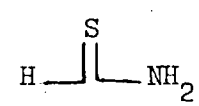
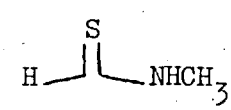
R_{ION} = effective ionic radius.

ϵ = dielectric constant of solvent.

an almost identical effect on all donor orbitals. Further, for a particular amide the electron affinity is constant. Thus E_m^* is mainly determined by the ionisation potential of the orbital in question and the site of substitution in the amide molecule, S, is controlled by the site, s, which has

the greatest coefficient of electron density in the HOMO. Values of the energies of the highest lying occupied orbitals and the coefficients of electron densities at the O- and N- atoms in these orbitals calculated by the MNDO method are given in Table 6.2.2.

TABLE 6.2.2. ORBITAL ENERGIES AND ELECTRON DENSITY COEFFICIENTS ($\sum c_i^2$) FOR SOME AMIDES AND THIOAMIDES

MOLECULE	ORBITAL ENERGY (eV)	$\sum c_{O(S)}^2$	$\sum c_N^2$
	-10.70 -11.09	.29 .78	.70 .09
	-10.40 -11.11	.22 .77	.66 .10
	-10.76 -11.42	.43 .57	.50 .29
	-11.03 -11.48	.36 .84	.62 .06
	-11.43 -12.22	.29 .72	.72 .06
	-11.52 -11.94	.29 .88	.71 .05
	- 9.49 - 0.84	.94 .66	.02 .28
	- 9.48 - 9.74	.93 .61	.02 .30

For formamide, the two highest lying molecular orbitals are calculated to be almost degenerate, within the accuracy of the method (ca. 0.3 eV). Significantly, the photelectron spectrum of formamide[125] shows the first two

ionisation processes, originating from the n_o- and antisymmetric π_2-orbitals, are almost degenerate. Unlike the calculations, however, the photoelectron spectrum indicates that the HOMO for formamide corresponds to the n_o-orbital which is attributable to an oxygen lone pair of electrons. The calculations on the other hand attribute the HOMO to the π_2-orbital which has most electron density at the nitrogen atom. It can be seen from Table 6.2.2. that N-alkylation increases the energy difference between the n_o- and π_2-orbitals and the π_2-orbital is now definitely favoured as the HOMO. Positive evidence for this effect has been reported [125,126] from the photelectron spectra of N-methyl- and N,N-dimethyl- formamides and acetamides. Similarly, other representative amides show that the HOMO is associated with the antisymmetric π_2-orbital and inspection of the electron density coefficients shows that most of the orbital charge resides with the N-atom.

Thus, both the charge and orbital terms of perturbation theory predict that the nitrogen atom of amides to be the most reactive nucleophilic site. This is not borne out by experimental evidence, as discussed above, and clearly an alternative mechanism must hold.

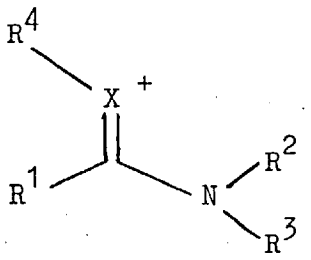
The two highest lying orbitals of thioamides correspond to the two pairs of sulphur lone-pair electrons which indicates that under orbital control these molecules react at sulphur. Thus the charge and orbital terms oppose each other and the chemistry of thioamides may be described in terms of S-alkylation occurring under reaction conditions where orbital control is preferred and N-alkylation under those of charge control. It is clear from the evidence [127] however, that thioamide chemistry is not easily described in this way, and, by analogy to the amides, is best explained as outlined below.

6.3. PRODUCT CONTROL OF THE TRANSITION STATE

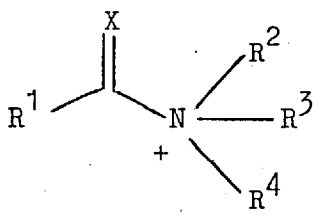
Perturbation theory assumes as its basis the formation of a reactant

like transition state[7]. Since it fails to describe amide and thioamide chemistry with any degree of accuracy it is appropriate to consider formation of a transition state which is product-like.

Alkylation of amides (X = O) and thioamides (X = S) at the oxygen (sulphur) or nitrogen atoms gives rise to the cations (84) and (85) respectively, and product-like transition states will bear resemblance to



(84)



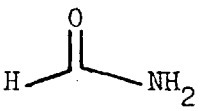
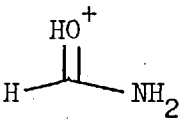
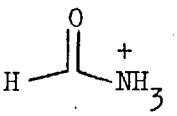
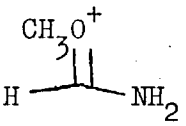
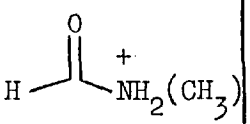
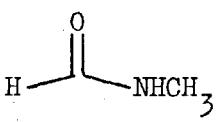
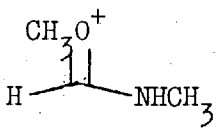
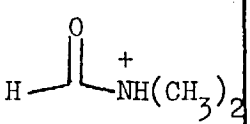
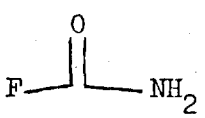
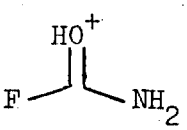
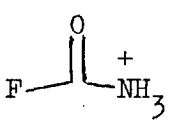
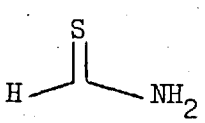
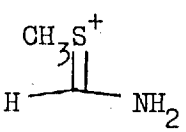
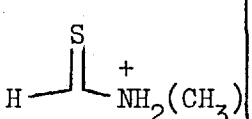
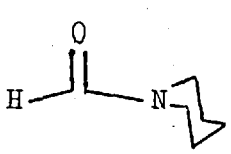
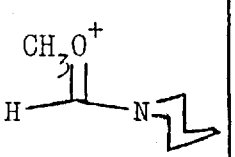
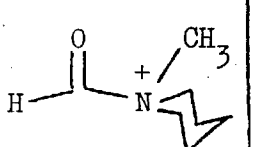
(85)

them. It is pertinent to compare the energies of formation of such species and the factors affecting their stability. Table 6.3.1. sets out relevant information calculated by the MNDO method for both (84) and (85) where R^4 = H or CH_3.

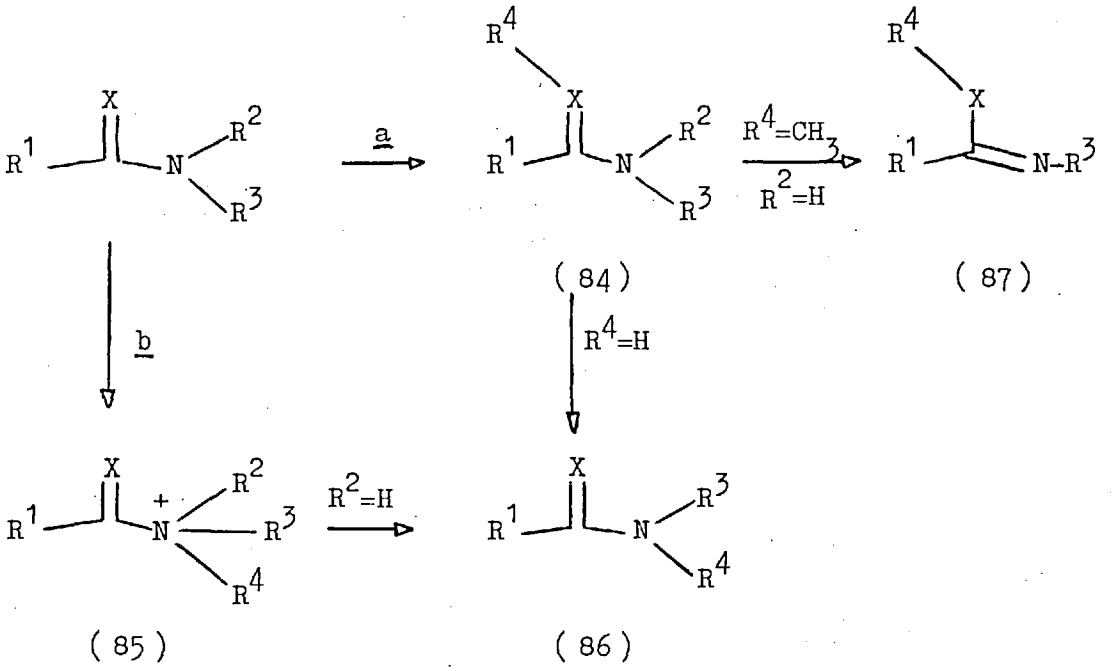
The most important observation to note is that cations of type (84), derived from reactivity at the X-atom, are about 20-25 kcal.mol^{-1} (ca. 100 kJ.mol^{-1}) more stable, for either protonation or methylation, than those cations (85) derived from N-substitution. The results for protonation are similar to those for ab initio calculations[128] which show O-protonated formamide to be ca. 6 kcal.mol^{-1} more stable than the N-protonated tautomer.

These results may be represented diagramatically (Figure 6.3.1.). Alkylation or protonation of an amide (or thioamide) (Scheme 38) occurs at either the O-(path a) or N-(path b) atoms. Attack will proceed preferentially by path a giving rise to the more stable intermediate (84). Significantly, the transition state for path a has at least ca. 90 kJ.mol^{-1} in hand before any competition from path b appears, which further points to O-substitution as the preferred pathway.

TABLE 6.3.1. HEATS OF FORMATION, ΔH_f, OF ALKYLATED AND PROTONATED AMIDE CATIONS.

NEUTRAL AMIDE	ΔH_f [a]	(84)	ΔH_f [a]	(85)	ΔH_f [a]
	-39.5		125.2		142.4
			128.5		144.3
	-40.8		124.7		146.1
	-91.7		86.2		107.6
	11.9		174.2		205.4
			120.9		149.0

a. $kcal.mol^{-1}$



SCHEME 38.

Deprotonation of (85) can only give the amide (86) whereas deprotonation of (84), even if $R^2 = R^3 = H$, will give the amide (86) when $R^4 = H$ (since this H atom bears most positive charge and is therefore most acidic*) or the thermodynamically less stable imidate (87) when $R^4 = CH_3$. That the imidate is indeed the thermodynamically less stable product can be seen by comparison of the heats of formation (Table 6.3.2.).

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* *e.g.* the charges on the O-protonated formamide cation are

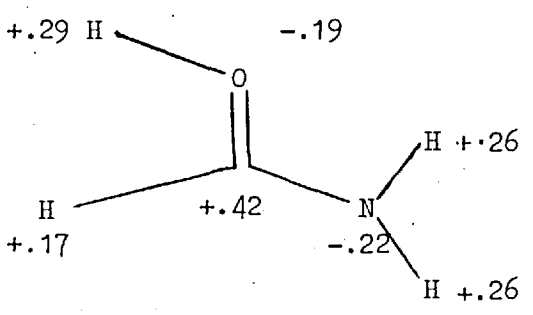


FIGURE 6.3.1. ENERGY DIAGRAM FOR THE ALKYLATION AND PROTONATION OF AMIDES AS CALCULATED BY THE MNDO METHOD.

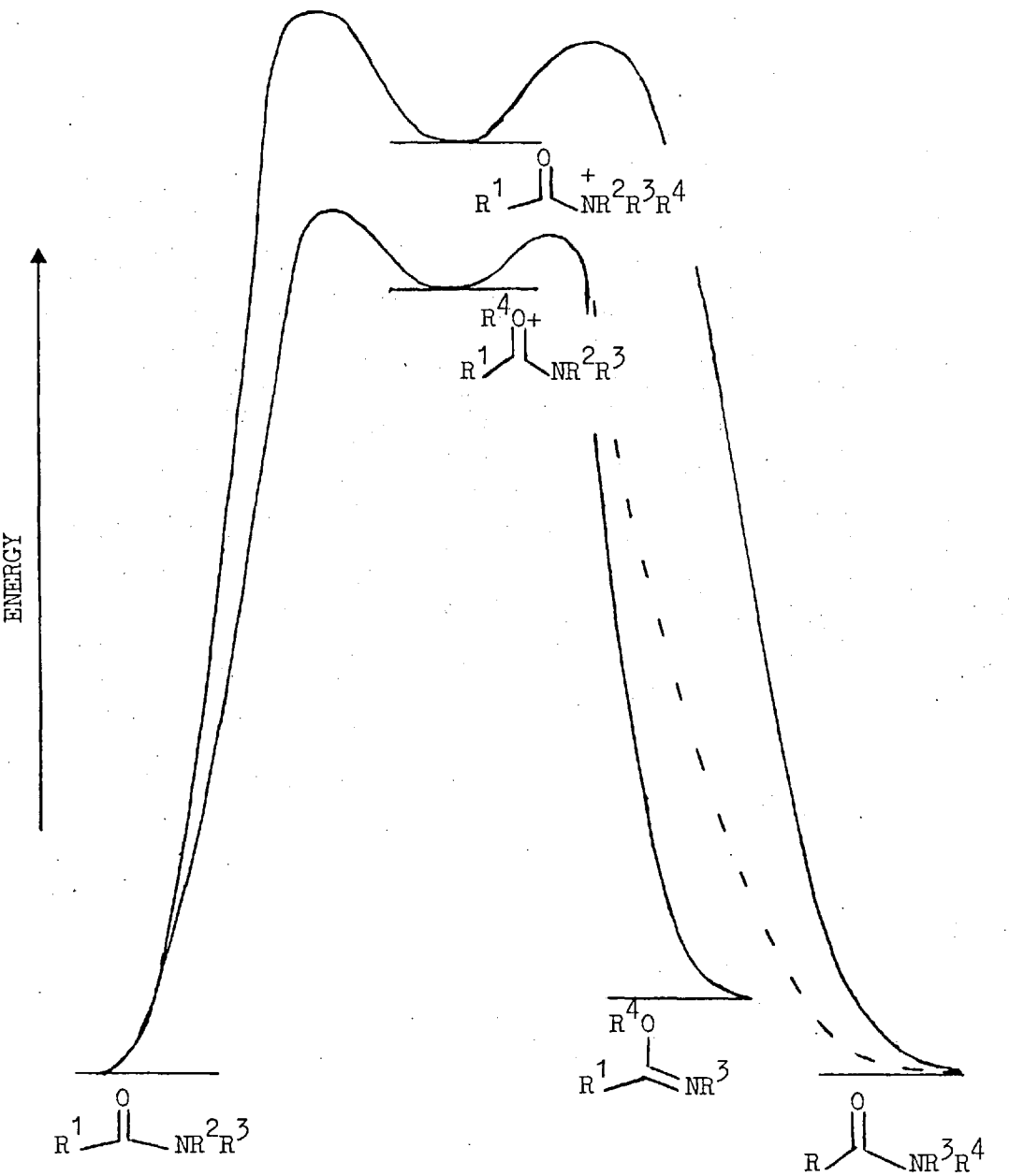
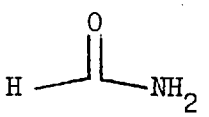
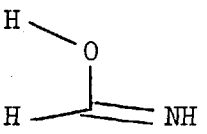
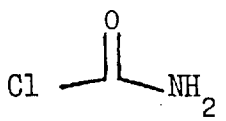
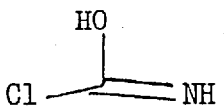
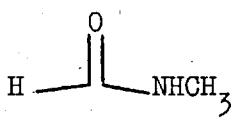
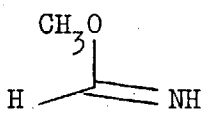


TABLE 6.3.2. HEATS OF FORMATION OF SOME AMIDES AND THEIR ISOMERIC IMIDATES.

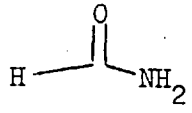
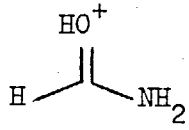
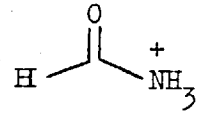
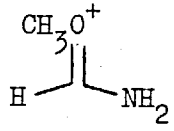
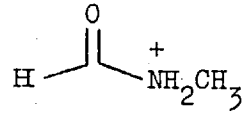
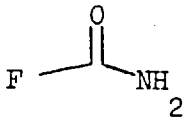
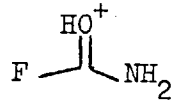
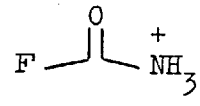
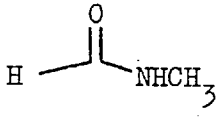
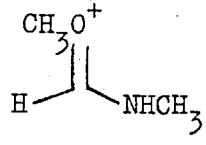
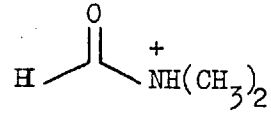
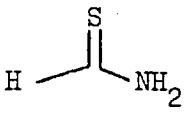
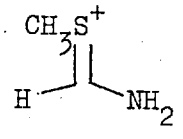
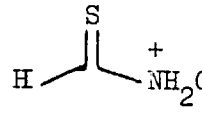
AMIDE	ΔH_f	IMIDATE	ΔH_f
	-39.5		-36.1
	-50.3		-41.9
	-40.8		128.2

The above results and discussion bear out and give a semi-empirical grounding to the previous intuitive arguments[24,25] that alkylation of amides gives rise to the thermodynamically less stable imidate *via* a thermodynamically more stable transition state, and *N*-alkylation arises from the known rearrangement of the imidate to the thermodynamically stable amide. These arguments offer a much more satisfactory explanation to the nucleophilic chemistry of neutral amides than does perturbation theory.

6.4. STABILISATION OF THE TRANSITION STATE

Why is the *O*-substituted amide (84) more stable than the *N*-substituted species (85)? The answer lies, as anticipated, with π-bond formation. Inspection of Table 6.4.1. shows that both amides and thioamides exhibit substantial π_{C-N} bond development in the neutral molecule, indicating a delocallisation of the *N*-lone pair electrons into the π_{C-O} system. *N*-Alkylation or *N*-protonation, which precludes this type of interaction,

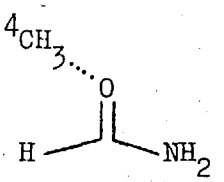
TABLE 6.4.1. PI-BOND ORDERS OF AMIDES AND THEIR PROTONATED AND ALKYLATED DERIVATIVES.

AMIDE	π_{C-O}	π_{C-N}	O-SUBSTITUTED	π_{C-O}	π_{C-N}	N-SUBSTITUTED	π_{C-O}	π_{C-N}
	.85	.47		.55	.76		.96	.11
				.57	.74		.96	.11
	.81	.44		.52	.71		.92	.12
	.85	.45		.55	.75		.96	.12
	77	.57		.50	.80		.98	.13

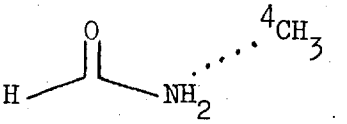
reduces the π_{C-N} value drastically and localises the π system almost entirely between the carbon and oxygen atoms, making this process an energy demanding one.

On the other hand, O-alkylation or protonation increases the π_{C-N} bond and enhances the original delocalisation. There is a concomitant reduction in the π_{C-O} bond, but significant π_{C-O} bond character is retained. Thus, the increased delocalisation of the N-lone pair electrons into the π_{C-O} system gives rise to the greater stability of the O-alkylated (protonated) species (84).

As anticipated, this effect is reflected in approach to the respective transition states. An estimate of the energy of the transition states for O- and N-attack was obtained by lengthening the O-C(4) and N-C(4) bonds in (88) and (89) respectively. Assuming the CH_3 group to attain a planar



(88)



(89)

configuration in the transition state for an S_N2 attack, the value for the O-C(4) and N-C(4) bond lengths in the respective transition states was found to lie between 2.0 - 2.5 Å. Between these two values, the O-substituted formamide was always of lower energy and, significantly, greater delocalisation was observed in this species (Table 6.4.2.).

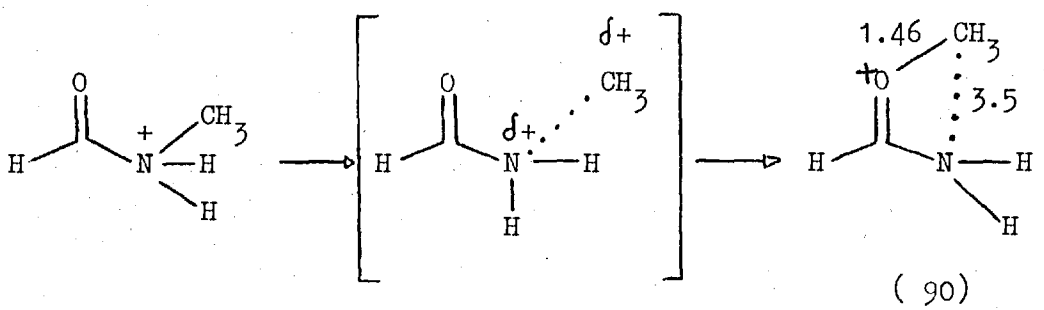
Of interest was the observation that extending the N-C(4) bond of (89) to 3.5Å results in the species (90), where the CH_3 group has migrated to the oxygen atom (Scheme 39)! The O-C(4) interatomic distance is 1.46Å, slightly shorter than that of (84). Concomitant delocalisation (π_{C-O} 0.60; π_{C-N} 0.70) occurs. The obvious inference from this result is that long-range interactions between the reactants will always favour O-atom attack.

TABLE 6.4.2. HEATS OF FORMATION AND PI-BOND VALUES FOR THE METHYLATION OF FORMAMIDE.

	O-SUBSTITUTED			N-SUBSTITUTED		
BOND LENGTH	ΔH_f	π_{C-O}	π_{C-N}	ΔH_f	π_{C-O}	π_{C-N}
∞	-39.5	.85	.47	-39.5	.85	.47
3.5[a]						
2.5	183.9	.76	.57	193.4	.93	.25
2.0	171.9	.68	.65	176.4	.96	.13
1.5[b]	128.5	.57	.74	144.3	.96	.11

a. See text.

b. C-O bond length for (84) is 1.52 A.
C-N bond length for (85) is 1.43 A.

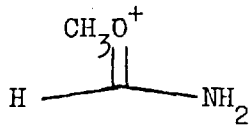
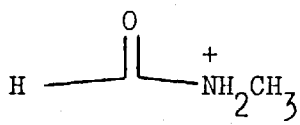
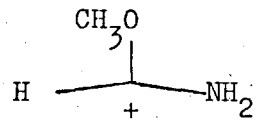
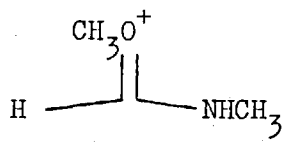
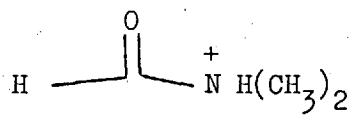
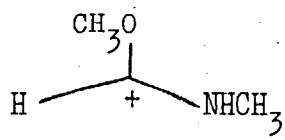
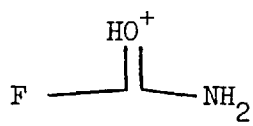
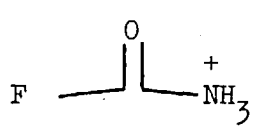
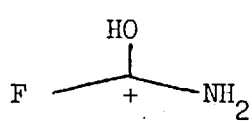


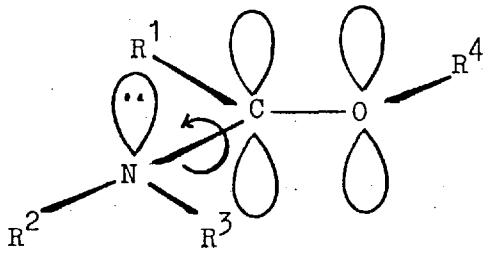
(90)

SCHEME 39.

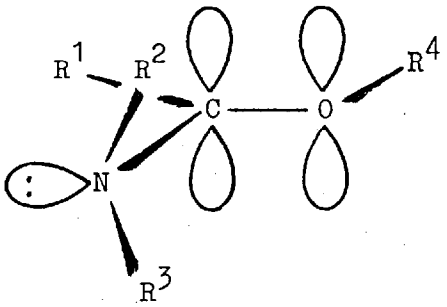
That delocalisation of the N-lone pair electrons alone is responsible for the increased stability of the O-substituted compounds was tested as follows. The O-alkylated or protonated compound (84) was rotated about the C-N bond by 90° to give the orthogonal form (91). The N-lone pair is now incapable of delocalisation into the π_{C-O} bond. The energy of (91) and the effect of rotation about the C-N bond was compared with (84) and the N-alkylated (or protonated) form. Plainly, (91) is the transition state for rotation about the C-N bond. The results are summarised in Table

TABLE 6.4.3. COMPARISON OF ΔH_f VALUES AND PI-BOND VALUES FOR ALKYLATED AND PROTONATED AMIDES.

MOLECULE	ΔH_f	π_{C-O}	π_{C-N}
	128.5	.57	.74
	144.3	.96	.11
	152.7	.78	.24
	124.7	.55	.75
	146.1	.96	.12
	152.3	.78	.25
	86.2	.52	.71
	107.6	.92	.12
	107.2	.68	.23



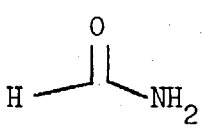
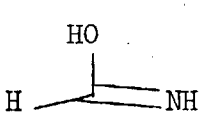
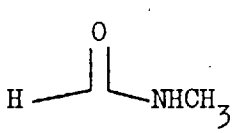
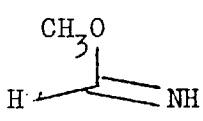
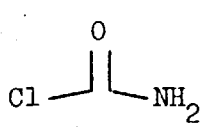
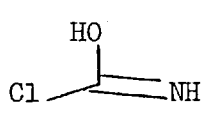
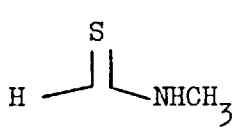
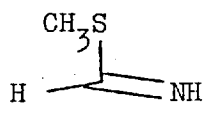
(84)



(91)

6.4.3., and show that the orthogonal O-substituted forms are either as stable or less stable than the N-substituted species, validating the proposal that the stabilisation of the product from O-attack arises from delocalisation of the N-lone pair electrons. It must be noted, however, that some π_{C-N} bond character is retained in these orthogonal species, and certainly the C-O bond does not attain full π-bond character. This may be due to a hyperconjugative effect. Nonetheless, significant loss of delocalisation of the N-lone pair is observed, enough to destabilise the molecule.

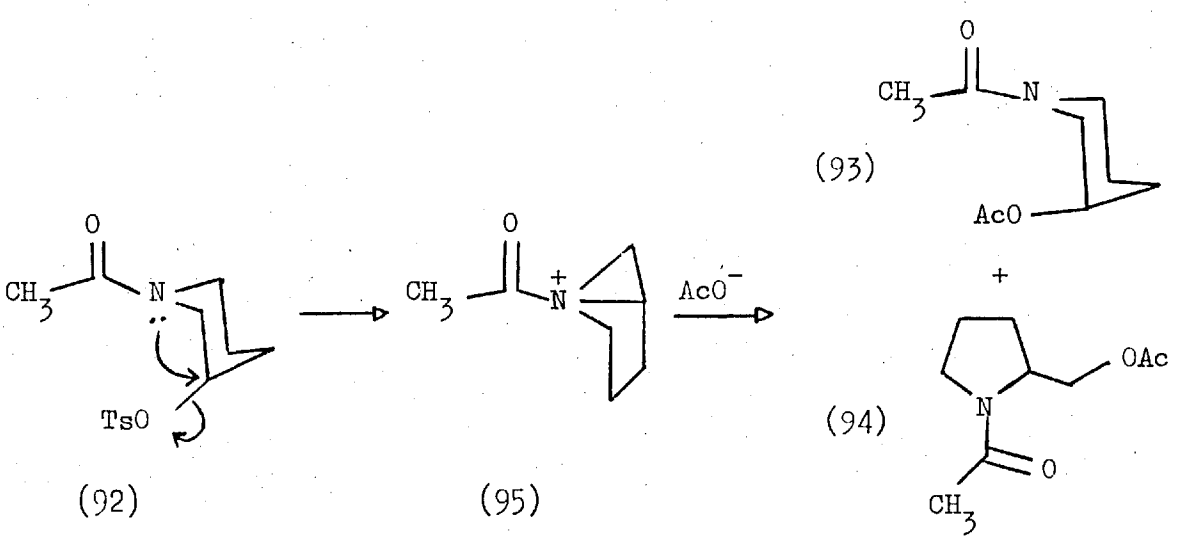
TABLE 6.4.4. PI BOND VALUES OF AMIDES AND THEIR IMIDATE ISOMERS.

AMIDE	π_{C-O}	π_{C-N}	IMIDATE	π_{C-O}	π_{C-N}
	.85	.47		.36	.92
	.85	.45		.32	.94
	.82	.48		.32	.93
	.78	.56		.26	.96

It is noteworthy, here, to observe that the imidate is almost certainly less stable than the amide due to bond delocalisation effects. As noted above, amides have significant π_{C-O} and π_{C-N} bond formation in the neutral molecule whereas imidates have significant π_{C-N} but little π_{C-O} development (Table 6.4.4.).

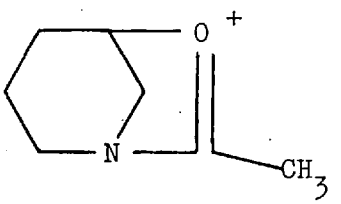
It has been elegantly shown however that, in rigid[129] and non-rigid[23] systems, some amides do in fact react *via* the nitrogen atom alone. Significantly, molecular models of these systems show that stabilisation of the oxygen substituted intermediate is sterically inhibited.

For example, acetolysis of *N*-acetyl-3-tosylpiperidinol (92) gave (93) and (94), and the intermediate was shown to be (95) *i.e.* the product of intramolecular *N*-attack (Scheme 40). Significantly, models



SCHEME 40. ACETOLYSIS OF *N*-ACETYL-3-TOSYL-PIPERIDINOL.

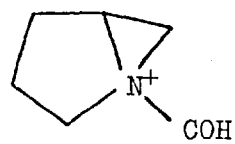
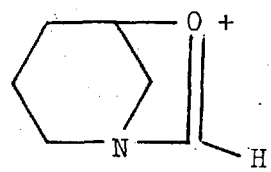
show that the corresponding *O*-intermediate (96) will not be stabilised by lone-pair π-bond interaction. This is reflected in the relative heats



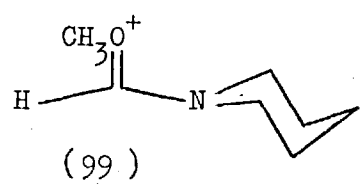
(96)

of formation of the formyl analogues of (97) and (98) as calculated by the MNDO method (Table 6.4.5.) which show that the O-alkylated intermediate

TABLE 6.4.5. HEATS OF FORMATION FOR THE POSSIBLE INTERMEDIATES IN THE ACETOLYSIS OF N-FORMYL-3-TOSYLPIPERIDINOL.

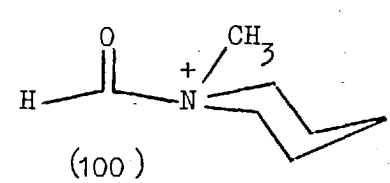
MOLECULE	ΔH_f (kcal.mol^{-1})
	159.1
	162.9

(98) is ca. 4 kcal.mol^{-1} LESS stable than the N-substituted analogue. Inspection of the ORTEP plot (Figure 6.4.1.) shows that indeed the N-lone pair electrons are unable to interact strongly with the π_{C-O} system. That this is a real effect is proved by considering intermolecular alkylation of N-formylpiperidine. Thus, the O-methylated cation (99) is 28 kcal. mol^{-1} (cf. Table 6.3.1.) more stable than the N-methylated form (100).



(99)

H_f = 120.9 kcal.mol^{-1}

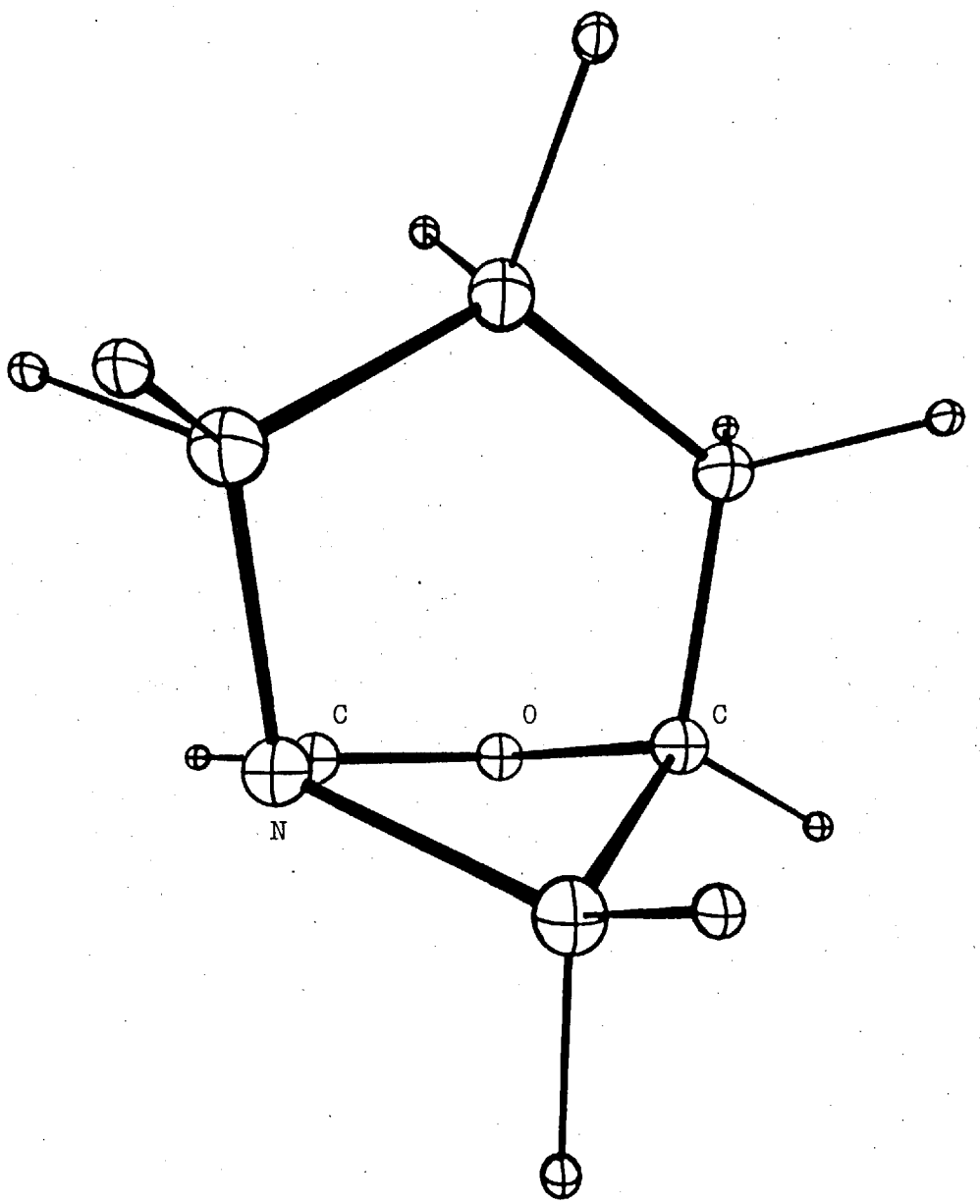


(100)

H_f = 149.0 kcal.mol^{-1}

The foregoing arguments conclusively show that the nucleophilic chemistry of neutral amides is best interpreted in terms of formation of a product-like transition state, and that the site of substitution is determined by the stabilisation of the transition state which reflects the

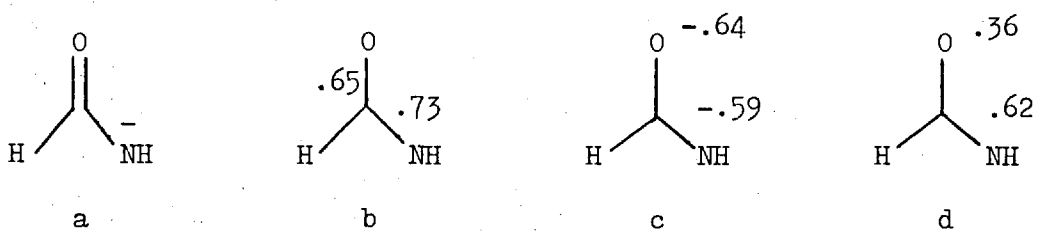
FIGURE 6.4.1. ORTEP DIAGRAM OF THE 1-AZA-3-OXA-BICYCLO- 3,2,1 -OCTYL CATION.



ability of the nitrogen lone-pair of electrons to conjugate with the π_{C-O} system.

6.5. AMIDE ANION

Significantly, alkylation of amide anions may be explained in similar terms. As expected, formamide anion (101a) exhibits greater delocalisation (101b) than the neutral molecule (cf. Table 6.4.1.) which results in greater charge residing on the oxygen atom(101c;Figure 6.5.1.). Thus alkylation



a b c d

(101)

FIGURE 6.5.1. (a) FORMAMIDE ANION
(b) π-BOND ORDERS
(c) CHARGE DISTRIBUTION.
(d) HOMO ELECTRON DENSITIES

under charge controlled conditions should give O-substitution, which is not the experimental finding[15]. Although electron density in the HOMO (101d) resides predominantly on nitrogen, it is probable that reactions are charge controlled.

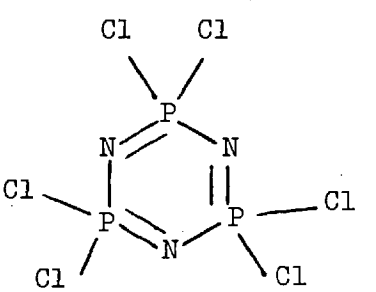
However, if one considers the stabilisation of the product, viz imidate or amide (Table 6.3.2.), it is obvious that a product-like transition state leading to the amide is the more stable. This results from greater delocalisation in the amide system compared to the corresponding imidates (cf. Table 6.4.3.). Hence N-alkylation of amide anions is favoured.

6.6. APPLICATION TO PHOSPHORAMIDATES AND SULPHONAMIDES

Although these results do not directly apply to sulphonamides or phosphoramidates, they may indicate that significant $d_\pi - p_\pi$ S-N or P-N bond development and delocalisation of the N-lone pair electrons into the S=O and P=O bonds are apparent in the neutral molecules and important in stabilisation of the transition state of nucleophilic substitution.

Certainly an x-ray study[130] of $(Me_2N)_2SO_2$ has shown that the nitrogen atom is at the $sp^{2.23}$ hybridisation level, which may be interpreted in terms of S-N $d_\pi - p_\pi$ overlap. There is shortening of the S-N bond. Another crystallographic study[131] offers evidence for $d_\pi - p_\pi$ bond delocalisation in sulphonamides: typical π-bond orders for S-O and S-N bonds are .75 and .25 respectively. Other evidence for $d_\pi - p_\pi$ overlap is offered by dynamic n.m.r.[132], which shows this type of bonding to be greatest when an electronegative substituent, *e.g.* Cl, is attached to the sulphur atom.

Much less is known about phosphoramidates. However, crystallographic data[133] for Ph_2PONMe_2 shows that the N-atom exhibits intermediate hybridisation between sp^2 and sp^3 and that both the P-N bond is substantially shorter than the value for a single bond[134] and the P-O bond is very slightly lengthened. The nitrogen lone pair is almost in the N-P-O plane and it has been argued[135] that delocalisation does not occur. However, orbital symmetry for correct overlap must be considered when arguing this point. Evidence for $d_\pi - p_\pi$ P-N overlap has also been shown by n.m.r.[136]. Cyclic phosphonitrilic chlorides (102) also show evidence of delocalisation: the P-N bonds are all the same length[137].



(102)

Unfortunately, M.O. calculations have not been carried out for either phosphoramidates or sulphonamides. Only one photoelectron spectroscopic study has been carried out on either type of compound. However, this study, of a phosphoramidate, measured only inner-orbital energies[138]. Consequently, the relative energies of the highest occupied molecular orbitals is not known. Whether perturbation theory or delocalisation of the transition state controls the chemistry of these compounds remains a problem which must wait for a semi-empirical MO approach.

CHAPTER 7

EXPERIMENTAL AND REFERENCES

^{1}H N.m.r. spectra were recorded using a Varian T60 spectrometer; ^{31}P n.m.r. spectra were recorded using a Perkin Elmer HA100 spectrometer operating in the Fourier Transform mode. Ultra-violet spectra were recorded on Unicam SP800 (for routine spectra) or Unicam SP1800 (for kinetic measurements) spectrophotometers. Infra-red spectra were recorded using either a Perkin-Elmer 157G or 597 instrument. Mass spectra were recorded on a VG Micromass 7070 spectrometer.

G.l.c. was performed using either a Perkin-Elmer F11 or F33 instrument.

Melting points were determined using a Kofler Hot Stage Apparatus.

Molecular orbital calculations were carried out on CDC 6600 (at ICCC) and CDC M7600 (at ULCC) computers.

7.1. THE PHOSPHORIMIDATE-PHOSPHORAMIDATE REARRANGEMENT

7.1.1. PREPARATION OF SUBSTRATES AND PRODUCTS

Diethyl N-phenylphosphoramidate

Diethyl phosphite (27.6g) in dry ether (100 ml) was added to a stirred solution of aniline (18.6g) and triethylamine (20.2g) in dry ether (50 ml) and carbon tetrachloride (20 ml). After addition was complete, stirring was continued for a further 3h. After filtration, the filtrate was evaporated leaving a solid which was recrystallised from EtOH - H_2O (27.5g, 60%)

m.p. 93-95°C (lit.[139] 92-94°C)

ν_{max} 3300-3100, 1600, 1500, 1225, 1160, 800 and 755 cm^{-1}.

δ See Table 7.1.1.

Diethyl N-ethyl-N-phenylphosphoramidate

This was prepared by the above procedure substituting N-ethylaniline for aniline. Distillation b.p. 135°C/1.5 mm.Hg (lit.[76b] 91°C/0.5 mm.Hg) gave the desired product (25g, 50%).

n_D^{21} 1.4875 (lit.[76b] n_D^{20} 1.4972)

ν_{max} 3060, 2980, 2935, 2910, 1600, 1495, 1255, 1165, 800, 765 and 700 cm^{-1}.

δ See Table 7.1.1.

Triethyl N-phenylphosphorimidate

Phenyl azide[140] (3.75 ml) in dry ether (10 ml) was added to an ice-cold solution of triethyl phosphite (5.35 ml, freshly distilled from sodium) in dry ether (20 ml) and stirred overnight. Removal of the ether followed by high vacuum distillation, using an oil-bath temperature of 150°C, afforded the imidate b.p. 84°C/2 x 10^{-4} mm.Hg (lit.[76b] 53-56°C/10^{-3} mm.Hg) (6.42g, 75%).

n_D^{21} 1.5014 (lit.[76b] n_D^{20} = 1.5015)

ν_{max} 3050, 2980, 2930, 2900, 1600, 1500, 1370, 1355, 1165, 800, 760 and 700 cm^{-1}.

λ_{max} (Ether) 246, 285 n.m.

δ See Table 7.1.1.

$C_{12}H_{20}NO_3P$ requires: C,56.02;H,7.84;N,5.44%

Found: C,56.12;H,7.68;N,5.40%

Benzoyl azide

Benzoyl chloride (28 g) in acetone (25 ml) was added to a solution of sodium azide (29 g) in water (40 ml). The mixture was shaken, cooled and extracted with ether (3 x 30 ml). The extracts were combined, the ether removed, and the resultant liquid solidified by cooling. Recrystallisation from acetone gave the desired product (25 g, 85%) m.p. 29°C.

ν_{max} 3080, 2170, 1700, 1608, 1460, 1260, 1190, 1000 and 705 cm^{-1}.

δ ($CDCl_3$) 7.27 - 8.50 m

Triethyl N-benzoylphosphorimidate

Benzoyl azide (18 g) in dry ether (30 ml) was added to a solution

TABLE 7.1.1. ^{1}H N.M.R. CHEMICAL SHIFTS (δ) RELATIVE TO Me_4Si AND COUPLING CONSTANTS FOR PHOSPHORIMIDATES AND PHOSPHORAMIDATES.[a]

	NPh	NH[b]	NCH_2[c]	NCH_2CH_3	OCH_2[d]	OCH_2CH_2[e]
$(EtO)_2PONHPh$	7.05m	8.10d			4.10[f] quint	1.35 tr
$(EtO)_2PONEtPh$	7.30s		3.55m[g]	1.25 tr	4.10 quint	1.25 tr
$(EtO)_3P{=}NPh$	6.85m				4.10[f]	1.35 tr
$(EtO)_3P{=}NCOPh$	7.05-8.10				4.10 quint	1.10 tr

a. ca. 0.2 - 0.8 M solutions in CCl_4.

b. J_{PNH} = 10 hz.

c. J_{PNCH} = 10 hz, J_{CHCH} = 7.5 hz.

d. J_{POCH} = 8 hz, J_{CHCH} = 7.5 hz.

e. J_{CHCH} = 7.5 hz.

f. Doublet J = 8 hz on decoupling at 81 hz.

g. Doublet J = 10 hz on decoupling at 74 hz.

triethyl phosphite (20.3 g) in ether at -30°C. After addition was complete, the solution was allowed to reach room temperature and left overnight. Removal of the ether followed by distillation gave the phosphorimidate (b.p. 60-65°C/0.2 mm Hg) (29.8 g, 85%).

ν_{max} 2980, 1615, 1570, 1350, 1182, 1162, 1040, 805, 712 and 665 cm^{-1}.

δ ($CDCl_3$) 1.10 (9H, t J= 7.5hz), 4105 (6H, quin. J = 7.5, 8 hz), 7.07 - 8.40 (5H, m)

O-Methyl-N-methylbenzimidate was synthesised according to a known procedure[95].

7.1.2. PURIFICATION OF SOLVENTS AND REAGENTS

AnalaR carbon tetrachloride was dried over $CaCl_2$ and distilled. Acetonitrile was dried over molecular sieves (4A), distilled from CaH_2 and stored over molecular sieves (4A). $[^2H_3]$-Acetonitrile (Merck, Sharp and Dohme) was stored over molecular sieves. AnalaR nitrobenzene was distilled under reduced pressure and stored over CaH_2.

Alkyl iodides were redistilled at atmospheric pressure and stored over mercury. All other alkyl halides were redistilled and stored over molecular sieves (4A).

Acetyl bromide was distilled from N,N-dimethylaniline.

Ethyl nitrate was kindly supplied by Dr. M.E.N. Rosa.

Iodine was recrystallised from benzene and sublimed at atmospheric pressure. All zinc halides were heated at 200°C for 2h. at reduced pressure and then sublimed in vacuo.

Anhydrous HBr gas was passed into acetonitrile until crystals of the conjugate acid crystallised out. The concentration of this solution was determined at various intervals by titration.

Sodium ethoxide was synthesised from sodium and ethanol in ether. The solid was dried in vacuo and stored under N_2.

7.1.3. MEASUREMENT OF REARRANGEMENT RATES

The most convenient method to monitor the rearrangement of triethyl N-phenylphosphorimidate to diethyl N-ethyl-N-phenylphosphoramidate was ^1H n.m.r. spectroscopy (see Table 7.1.1.). In particular, the change in the N-Ph signal was easiest to follow. In nitrobenzene, however, the increase in the N-CH_2 absorbtion was monitored.

Typically, the substrate (1×10^{-4} mol) was placed in an n.m.r. tube and dissolved in the appropriate solvent by means of a calibrated holder. The catalyst was added in a dry, inert (N_2) atmosphere and the tube was then sealed and placed in a thermostatted bath. Spectra were recorded and integrated at timed intervals. The product absorbtion signals were normalised by relating them to the total N-Ph or total -CH_2- signals for both starting imidate and product amidate.

The pseudo-first-order plots Rate=$k_0[(EtO)_3P{=}NPh]$ were calculated from Equation 7.1.3.1. where x = integral of either the N-Ph or NCH_2 signal for

$$k_0 t = \ln (1 - x/a) \quad .... \quad 7.1.3.1.$$

the product amidate at time t and a = total Ph or CH_2 signal. The pseudo-first-order rate constants, k_0, were obtained graphically and results for typical runs are shown in Figures 7.1.3.1. and 7.1.3.2. Linear plots were obtained up to ca. 80% reaction when the insensitivity of the n.m.r. procedure introduced errors in the measurement of small integrals. Rate coefficients obtained by this procedure were reproducible to $\pm$ 10%.

Product Analysis

Products were identified from comparison of the n.m.r. spectra of the reaction solutions with authentic materials. Several reaction solutions were injected directly on to an F11 gas chromatograph (employing a 2 m, 15% Carbowax on Chromosorb P, column) and signals were compared to authentic

samples. In other cases both the solvent and reagent were removed and the products isolated by m.p., refractive index and i.r. and n.m.r. spectroscopy (in CCl_4). For the reaction in the absence of any added catalysts the formation of ethene was apparent from the signal in the n.m.r. spectrum (δ 5.2).

FIGURE 7.1.3.1. TYPICAL FIRST-ORDER PLOT FOR THE REARRANGEMENT OF $(EtO)_3P{=}NPh$ TO $(EtO)_2PONEtPh$ CATALYSED BY EtI IN CH_3CN AT 100°C.

$\left[(EtO)_3P{=}NPh\right]_0 = 0.2M.$

$\left[EtI\right] = 0.062M.$

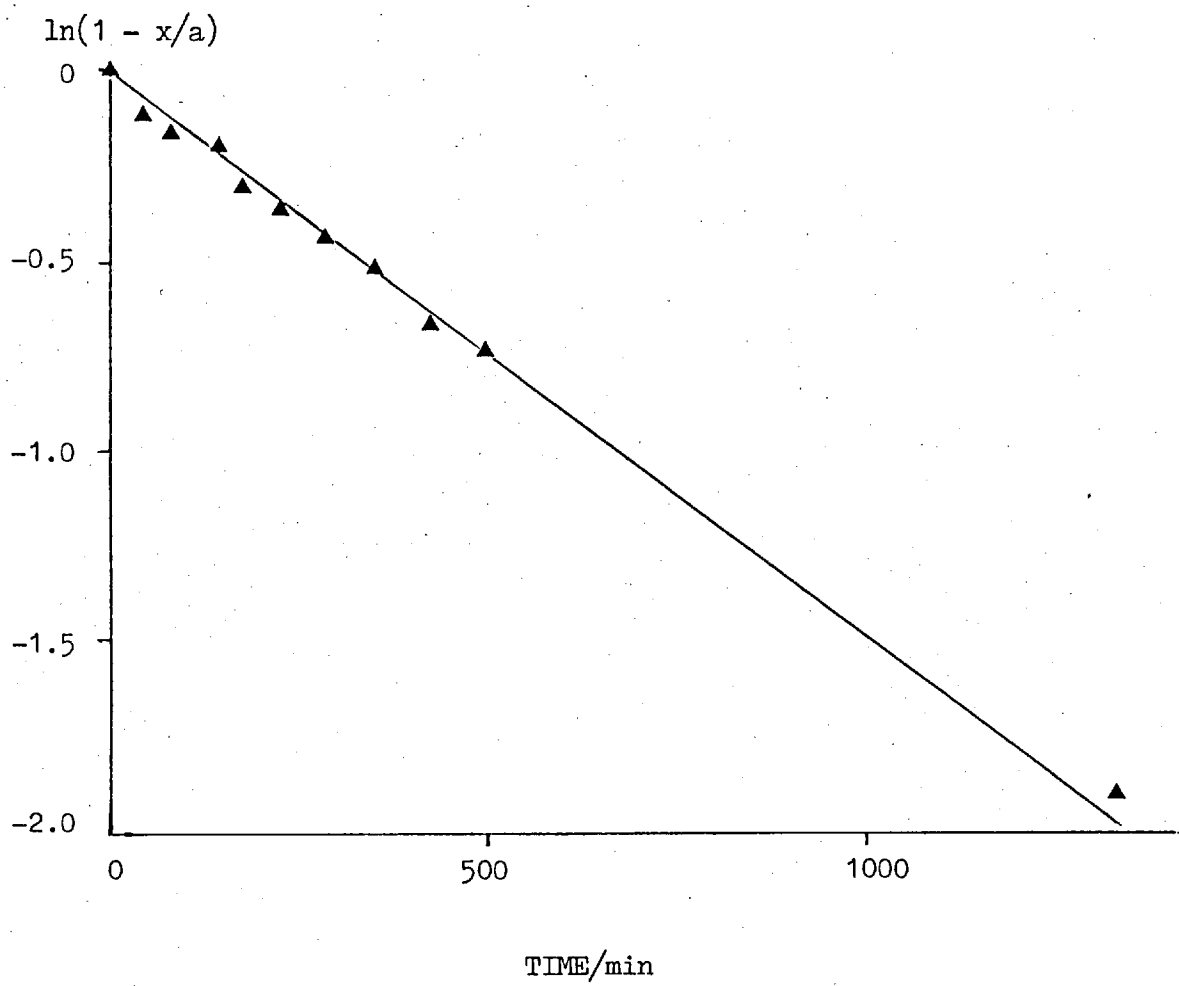
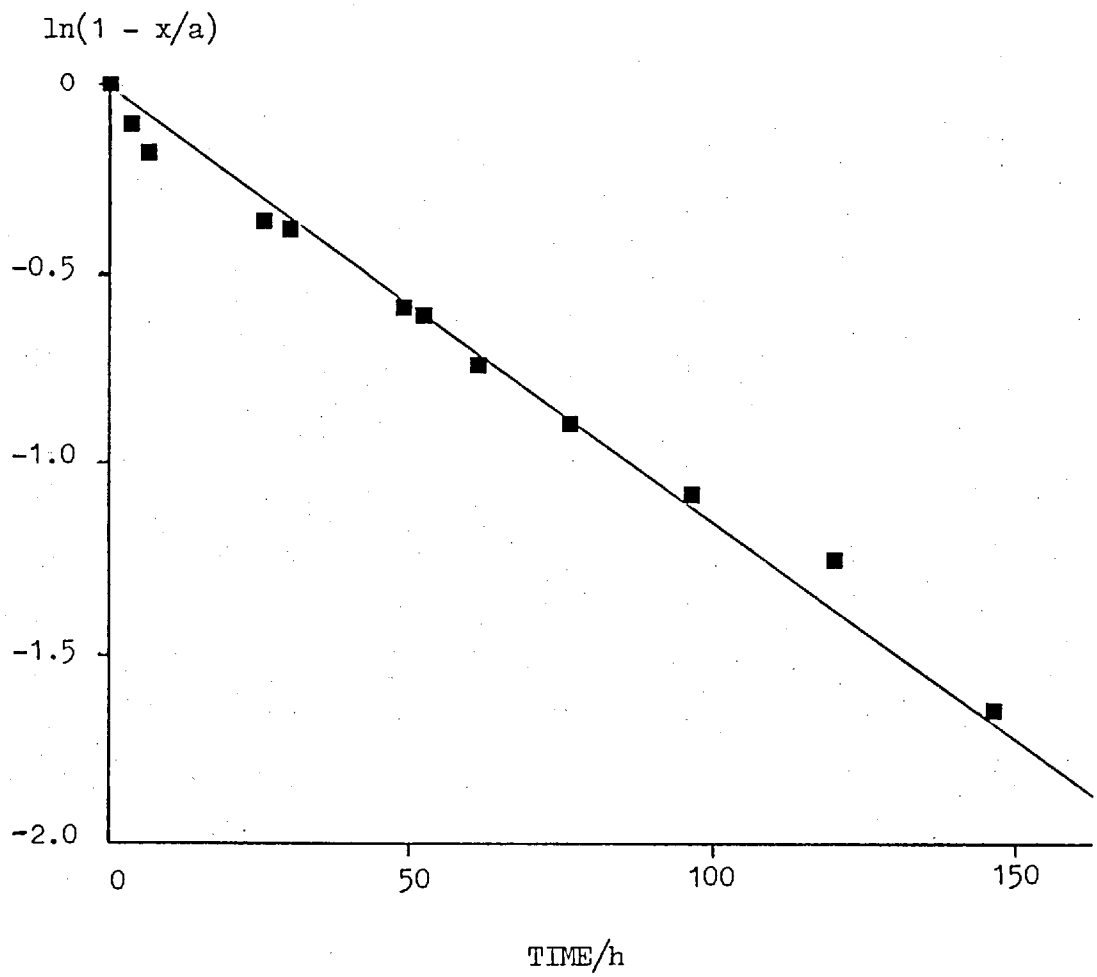


FIGURE 7.1.3.2. TYPICAL FIRST-ORDER PLOT FOR THE REARRANGEMENT OF $(EtO)_3P{=}NPh$ TO $(EtO)_2PONEtPh$ CATALYSED BY EtBr AT 100°C IN CH_3CN.

$\left[(EtO)_3P{=}NPh\right]_0 = 0.2M.$

$\left[EtBr\right] = 0.032M$



7.2. THE PROTONATION OF PHOSPHORAMIDATES

7.2.1. PREPARATION OF SUBSTRATES

Diethyl N-Methylphosphoramidate

Diethylphosphite (30 ml) in dry ether (20 ml) was added to methylamine (24 g) in CCl_4 (40 ml) and dry ether (20 ml) at -30°C with stirring. When addition was complete stirring was continued for a further 2h whilst the mixture attained room temperation. The solution was filtered and the filtrate evaporated to give an oil which yielded the phosphoramidate (33.5 g, 95%) on distillation (b.p. 80°C/0.9 mm Hg).

$\delta(CDCl_3)$ 1.33 (6H,t,J=7hz), 2.60(3H,dd,J=5,12hz), 3.20(1H,br), 4.08(4H, dq,J=7.5,7.5hz).

ν_{max} 3220(NH), 2980, 2930, 2900, 1438, 1380, 1232(P=O) 1030, and 955 cm^{-1}.

λ_{max}(cyclohexane) 214, 150 sh (0.83).

The following compounds were prepared in the same manner:

Diethyl phosphoramidate

m.p. 50-51°C.

ν_{max} 3250(NH), 2982, 2935, 2908, 1480, 1444, 1390, 1225(P=O) 1032, 968 and 800 cm^{-1}.

$\delta(CDCl_3)$ 1.33(6H,t,J=7hz), 3.47(2H,br), 4.11(4H,dq,J=7,7hz).

Diethyl N-N-dimethylphosphoramidate

b.p. 46-48°C/0.7 mm Hg.

ν_{max} 2980, 2935, 2905, 1480, 1468, 1390, 1308, 1245(P=O) 1060-1000, 965 and 785 cm^{-1}.

$\delta(CDCl_3)$ 1.32(6H,t,J=7hz), 2.68(6H,d,J=10hz), 4.03(4H,dq,J=7,7.5hz).

7.2.2. PREPARATION OF SOLVENTS

Aqueous sulphuric acid solutions were prepared by diluting AnalaR 98% H_2SO_4 with the appropriate amount of water. The solutions were standardised by titration with NaOH using methyl orange as indicator. Deuterosulphuric acid solutions were prepared similarly.

Oleum solutions were prepared by adding 97% H_2SO_4 to oleum containing 20% free SO_3.

Fluorosulphonic acid was redistilled from calcium fluoride.

Trifluoroacetic acid was redistilled.

7.2.3. PROCEDURE

A known amount of phosphoramidate (ca. 40 mg) was weighed into an n.m.r. tube and dissolved in the required solvent (0.5 ml). ^1H N.m.r. spectra were recorded immediately. Chemical shifts were the average of two or three scans. Products were determined by comparison of the spectra to those of authentic materials in similar solutions.

7.3. THE ACYLATION OF PHOSPHORAMIDATES

7.3.1. PREPARATION AND PURIFICATION OF REAGENTS AND SOLVENTS

Solvents

Carbon tetrachloride (AnalaR) was dried over $CaCl_2$ and redistilled. Benzene (Na dry, AnalaR) and cyclohexane (AnalaR) were used without further purification. Pyridine (AnalaR) was refluxed over barium oxide distilled and stored over molecular sieve (4A). $[^2H_1]$-Chloroform, $[^2H_3]$-acetonitrile and $[^2H_5]$-pyridine were stored over molecular sieve (4A). Hexane was dried by standing over $CaCl_2$.

Reagents

Acetyl chloride and acetyl bromide were redistilled from N,N-dimethylaniline.

Trichloroacetyl chloride was prepared from trichloracetic acid (10 g) by treatment, at reflux for 2h, with thionyl chloride (20 g) using DMF as a catalyst. The trichloroacetyl chloride was purified by distillation (b.p. 117°C/760 mm Hg, n_D^{21} = 1.4703).

Dichloroacetyl chloride was prepared in a similar manner (b.p. 105-107°C/760 mm Hg, n_D^{21} = 1.4598) as was pivaloyl chloride (b.p. 105°C/760 mm Hg, n_D^{22} = 1.4135).

Chloroacetyl chloride, benzoyl chloride, 4-chlorobenzoyl chloride and 4-methylbenzoyl chloride were redistilled before use.

O-acetyl-N,N-dimethylformamidinium bromide was prepared by treating acetyl bromide (15 ml) with dimethylformamide (ca. 3 ml) at -10°C with shaking. The solid was filtered and washed with ether (dry box) {δ($CDCl_3$) 2.83(3H,S), 2.95(3H,S), 3.10(3H,S), 8.43(1H,br.s)}[29].

N-Acetylpyridinium chloride was prepared by addition of acetyl chloride to 1 equivalent of pyridine in ether. The solid was filtered and dried in vacuo.

Anhydrous hydrogen bromide was prepared as noted previously (Section 7.1.2.).

Acetic anhydride was refluxed with P_2O_5 for 3h then distilled and stored over molecular sieve (4A).

Trifluoroacetic (Aldrich), trichloroacetic (Fluka) and dichloroacetic (Aldrich) anhydrides were used without further purification.

4-Chloro- and 4-nitro-benzoic anhydrides were synthesised by a literature procedure[141].

Cetyltrimethylammonium bromide was kindly supplied by Dr. D.A. Widdowson.

Imidazole was recrystallised from benzene.

Triethylamine was distilled from CaH_2 and stored over KOH.

2,6-Lutidine was distilled from BF_3.

2,2,6,6,-tetramethylpiperidine was redistilled before use.

4-(N,N-Dimethylamino) pyridine (Aldrich) was used as supplied.

7.3.2. PREPARATION OF SUBSTRATES

Diethyl N-phenyl-, N-methyl- and N,N-dimethyl- phosphoramidates were synthesised as described earlier. Hexamethylphosphoric triamide (Aldrich) was used as supplied

Diethyl N-benzyloxyphosphoramidate

O-Benzylhydroxylamine hydrochloride (8 g) was suspended in H_2O (100 ml) and NaOH pellets were added until the solution turned slightly alkaline. The aqueous solution was extracted with ether (5 x 50 ml) and the extracts were combined and dried (KOH). Removal of the ether gave an oil (6.2 g) which was dissolved in CCl_4 (50 ml). A solution of diethyl phosphite (8 g) and triethylamine (8 g) in ether (20 ml) was added to the O-benzylhydroxylamine solution over 1h with stirring. The mixture was left stirring overnight, filtered and the solvent removed. The product was distilled (b.p.

81-85°C/0.2 mm Hg) to give an oil (11.5 g, 77%).

$\delta(CCl_4)$ 1.35(6H,t,J=7.5hz), 4.17(4H,quin,J=7.5,7.5hz), 4.80(2H,S), 6.50(1H,br d,J=15hz), 7.35(5H,S).

ν_{max} 3180(NH), 2990, 1250(P=O) 1040, 980, 755 and 705 cm^{-1}.

Diethyl N-methylphosphoramidite

Diethyl phosphorchloridite (15.5 g) in ether (25 ml) was added dropwise to anhydrous methylamine (14.5 g) in ether (20 ml) at -30°C. On complete addition the mixture was allowed to attain room temperature and was stirred for a further 2h. The organic layer was decanted and the solvent removed. The residue was twice distilled (b.p. 56-58°C/0.8 mm Hg) to give a liquid (7.5 g).

$n_D^{20.5}$ 1.4337.

$\delta(CDCl_3)$ 1.27(6H,t,J=7hz), 2.58(3H,d,J=11hz), 3.82(4H,quin,J=7.5,7hz).

ν_{max} 3370(NH), 2980, 2930, 2880, 1478, 1446, 1390, 1065-1035(P-O-C), 915 and 730 cm^{-1}.

m/e 151($M^{+\cdot}$), 94, 78, 65.

7.3.3. PREPARATION OF PRODUCTS

Diethyl N-acetyl-N-methylphosphoramidate

Diethyl N-methylphosphoramidate (5 g) in benzene (10 ml) was added to a stirred suspension of sodium hydride (0.86 g) in benzene (20 ml) under nitrogen. Stirring was continued until hydrogen evolution ceased (ca. 5h). Acetyl chloride (2.25 g) in benzene (20 ml) was added and stirring continued for 6h. The solvent was removed and the residue triturated with ether/petroleum ether. Filtration followed by removal of the ether gave an oil which on distillation (b.p. 56-58/3.5 x 10^{-3} mm Hg) yielded diethyl N-acetyl-N-methylphosphoramidate (3.7g, 63%).

n_D^{23} 1.4315.

$\delta(CCl_4)$ 1.43(6H,J=7.5hz), 2.35(3H,S), 3.00(3H,d,J=8hz), 4.19(4H,quin,

J=7.5,7hz).

ν_{max} 2980, 2940, 2900, 1690(C=O), 1428, 1375, 1300-1260(P=O), 1060-1025, 994-948 and 805 cm^{-1}.

m/e 210 $(M+1)^{+}$, 167, 139, 111, 110, 95, 94, 81.

In the same way the following compounds were synthesised. However, purification by distillation or chromatography resulted in extensive decomposition of the products. Data therefore relate to the crude materials.

Diethyl N-acetyl-N-phenylphosphoramidate

$\delta(CCl_4)$ 1.21(6H,J=7hz), 2.07(3H,s) 4.10(4H,quin,J=7.5,7hz), 7.33(5H,s).

ν_{max} 2980, 1700(C=O), 1595, 1495, 1275(P=O), 1030, 970 and 700 cm^{-1}.

Diethyl N-acetyl-N-benzyloxyphosphoramidate

$\delta(CCl_4)$ 1.43(6H,t,J=7.5hz), 2.29(3H,s), 4.29(4H,quin,J=7.5,7.5hz), 5.01 (2H,s), 7.43(5H,s).

ν_{max} 2990, 1705(P=O), 1375, 1275(P=O) and 1030 cm^{-1}.

Diethyl N-methyl-N-trichloracetylphosphoramidate

$\delta(C_5H_5N)$ 1.23(6H,t,J=7.5hz), 3.57(3H,d,J=10hz), 4.29(4H,quin,J=7.5,7.5hz).

ν_{max} 2990, 1705(C=O), 1295(P=O), 1035, 840 and 680 cm^{-1}.

m/e 194($M-CCl_3$), 137($M-CCl_3$-MeNCO), 109, 81.

Diethyl N-(4-chlorobenzoyl)-N-methylphosphoramidate

$\delta(CCl_4)$ 1.30(6H,t,J=7hz), 3.12(3H,d,J=7hz), 4.05(4H,quin,J=8,7hz), 7.33-8.13(4H,ABq).

ν_{max} 2980, 1670(C=O), 1590, 1290(P=O), 1025,960, 872, 800 and 763 cm^{-1}.

Diethyl N-benzoyl-N-methylphosphoramidate

$\delta(CDCl_3)$ 1.25(6H,t,J=7hz), 3.13(3H,d,J=8hz), 4.02(4H,quin,J=7.5,7hz), 7.30-8.30(5H,m).

Diethyl N-methyl-N-trifluoroacetylphosphoramidate

Diethyl N-methylphosphoramidate (1 g) was added to a solution of trifluoroacetic anhydride (1.5 ml) in pyridine (5 ml). Pyridine and excess trifluoroacetic anhydride were removed *in vacuo*. Ether was added to the residue and the organic layer decanted. Removal of the ether yielded the N-trifluoroacetylphosphoramidate (1.5 g, 95%).

$\delta(CCl_4)$ 1.25(6H,t,J=7.5hz), 3.15(3H,d,J=9hz), 4.11(4H,quin,J=7.5,7.5 hz).

ν_{max} 2990, 1720(C=O), 1375, 1280, 1200-1150(P=O) and 1030 cm^{-1}.

m/e 194($M-CF_3$), 137($M-CF_3$-MeNCO), 109, 81.

The following compounds were synthesised in a similar manner:

Diethyl N-phenyl-N-trifluoroacetylphosphoramidate

$\delta(CCl_4)$ 1.13(6H,t,J=7.5hz), 4.13(4H,quin,J=7.5,7.5hz), 7.31(5H,s).

ν_{max} 2990, 1730(C=O), 1595, 1490, 1360, 1180-1150(P=O), 1135 and 700 cm^{-1}.

Diethyl N-benzyloxy-N-trifluoroacetylphosphoramidate

$\delta(CCl_4)$ 1.40(6H,t,J=7.5hz), 4.40(4H,quin,J=7.5,7.5hz), 5.13(2H,s), 7.39 (5H,s).

ν_{max} 2990, 1737(C=O), 1380, 1300, 1210-1160(P=O) and 1035 cm^{-1}.

N,N-dimethyl-trifluoroacetamide

Dimethylamine (1 equiv.) was added to trifluoroacetic anhydride (2 equiv.) in CCl_4. The n.m.r. spectrum showed the presence of the amide plus methylammonium trifluoroacetate.

$\delta(CCl_4)$ 3.15(6H,d).

N-Methyl-1,1,1-trimethylacetamide

1,1,1-Trimethylacetyl chloride (12 g) was added dropwise to anhydrous methylamine (3.1 g) in ether (25 ml) with stirring at -20°C. Filtration

and evaporation yielded a solid which was recrystallised from ether/ petroleum ether (10.2 g).

m.p. 82-84°C.

$\delta(CDCl_3)$ 1.20(9H,s), 2.80(3H,d,J=4hz), 5.2-6.1(1H,br).

ν_{max} 3350(NH), 2980, 1635(C=O) cm^{-1}.

N-Methyl-4-chlorobenzamide was prepared by the Schotten-Baumann reaction[142].

m.p. 156-159°C.

$\delta(CCl_4)$ 3.00(3H,d,J=4hz), 6.39(1H,br), 7.07-7.93(4H,Abq).

ν_{max} 3280(NH), 1630(C=O), 1540 cm^{-1}.

7.3.4. GENERAL PROCEDURE

Acylation of the phosphoramidates was initiated by addition of the required reagent to a solution of the phosphoramidate in the desired solvent. The reactions could be conveniently monitored by either i.r. or n.m.r. spectroscopy. For kinetic measurements n.m.r. spectroscopy proved more accurate. The n.m.r. method has already been described (Section 7.1.3.). Reactions were best followed by monitoring the $-\underline{NCH_3}$ signal for diethyl N-methylphosphoramidate, the $-\underline{OCH_2}-$ signal for diethyl N-benzyloxyphosphoramidate and the -NPh signal for diethyl N-phenylphosphoramidate (e.g. Table 7.3.4.1.). The extent of reaction was determined by integration of these signals and relating them to the overall signal. The substrate concentration, $[S]_t$, at time t was then determined using Equation 7.3.4.1.,

$$[S]_t = [S]_o \times \frac{\text{SUBSTRATE INTEGRAL}}{\text{SUBSTRATE INTEGRAL + PRODUCT INTEGRAL}} \quad \ldots\ldots \quad 7.3.4.1.$$

where $[S]_o$ is the initial substrate concentration. Typical results are summarised in Tables 7.3.4.2.-7.3.4.5. Rate constants obtained by this

TABLE 7.3.4.1. RELEVANT ^{1}H N.M.R. CHEMICAL SHIFTS FOR SOME PHOSPHORAMIDATES AND THEIR N-ACYLATED DERIVATIVES IN CCl_4.

COMPOUND	NMe	CH_3CO-	$-CH_2O$-	NPh
(EtO)PONHMe	2.60			
$(EtO)_2PON(COCH_3)Me$	3.00	2.35		
$(EtO)_2PON(COCF_3)Me$	3.15			
$(EtO)_2PON(COCl_3)Me$	3.57			
$(EtO)_2PON(COC_6H_4Cl)Me$	3.12			
$(EtO)_2PONHPh$				7.05
$(EtO)_2PON(COCH_3)Ph$		2.07		7.33
$(EtO)_2PON(COCF_3)Ph$				7.31
$(EtO)_2PONHOCH_2Ph$			4.80	
$(EtO)_2PON(COCH_3)OCH_2Ph$		2.29	5.01	
$(EtO)_2PON(COCF_3)OCH_2Ph$			5.13	

TABLE 7.3.4.2. ACYLATION OF $(EtO)_2PONHMe$ BY AcCl in CCl_4 AT 35°C.

TIME/MIN	$[(EtO)_2PONHMe]$	[AcCl]	$\ln\frac{[(EtO)_2PONHMe]}{[AcCl]}$	$10^5 k_2$/ $M^{-1}s^{-1}$
0	2.00	0.64	1.139	—
11	1.98	0.62	1.161	2.45
28	1.94	0.58	1.207	2.98
55	1.82	0.46	1.375	5.26
103	1.72	0.36	1.564	5.06
155	1.66	0.30	1.711	4.52
214	1.60	0.24	1.897	4.34
446	1.48	0.12	2.512	3.77

% REACTION = 81

$\langle k_2 \rangle = 4.05 \times 10^{-5} M^{-1}s^{-1}$

$k_2(\text{graph}) = 3.92 \times 10^{-5} M^{-1}s^{-1}$

TABLE 7.3.4.3. ACYLATION OF $(EtO)_2PONHMe$ BY AcBr IN THE PRESENCE OF Ac_2O IN CCl_4 AT 35°C.

$[Ac_2O] = 1.061$ M, $[AcBr] = .135$ M

TIME/MIN	$[(EtO)_2PONHMe]/M$	$\ln \frac{[(EtO)_2PONHMe]}{[(EtO)_2PONHMe]_o}$	$10^5 k_o/s^{-1}$
0	.665	0.000	---
31	.523	-0.240	12.9
61	.441	-0.411	11.2
116	.351	-0.640	9.2
179	.265	-0.921	8.6
369	.098	-1.911	8.6

% REACTION = 85

$\langle k_o \rangle = 10.1 \times 10^{-5} s^{-1}$

$k_2 = 7.48 \times 10^{-4} M^{-1} s^{-1}$

TABLE 7.3.4.4. ACYLATION OF $(EtO)_2PONHMe$ BY CCl_3COCl IN PYRIDINE AT $35^{\circ}C$.

TIME/MIN	$NCH_{3(SUB)}$	$\sum NCH_3$	[SUB]	$[CCl_3COCl]$	$\ln[SUB]/[CCl_3COCl]$	$10^4 k_2/M^{-1}s^{-1}$
0	-	-	.665	.535	.218	-
10	30	35	.570	.440	.259	5.26
28	22.5	35.5	.422	.292	.368	6.87
48	21	39.5	.354	.224	.458	6.41
122	14	40.5	.230	.100	.833	6.46
310	8	34	.157	.027	1.760	6.38

% REACTION = 95

$\langle k_2 \rangle = 6.28 \times 10^{-4} M^{-1}s^{-1}$

$k_2(\text{graph}) = 6.28 \times 10^{-4} M^{-1}s^{-1}$

TABLE 7.3.4.5. ACYLATION OF $(EtO)_2PONHOCH_2Ph$ BY AcCl IN THE PRESENCE OF Ac_2O IN CCl_4 AT 35°C.

$[Ac_2O] = 1.02$ M, $[AcCl] = .708$ M

TIME/MIN	$OCH_{2(SUB)}$	$\sum OCH_2$	[SUB]/M	$\ln[SUB]/[SUB]_0$	$10^6 k_o/s^{-1}$
0			.529	0.000	-
210	1	20.5	.503	-0.051	4.05
294	1.5	18.5	.488	-0.081	4.59
591	3.8	20	.432	-0.202	5.70
1588	6.5	17.5	.331	-0.469	4.92
2759	9	16	.219	-0.881	5.32
4100	11.5	15.5	.143	-1.308	5.32
5753	2	11.5	.090	-1.771	5.13

% REACTION = 83

$\langle k_o \rangle = 5.00 \times 10^{-5} s^{-1}$

$k_o(\text{graph}) = 5.21 \times 10^{-5} s^{-1}$

$k_2 = 7.36 \times 10^{-6} M^{-1} s^{-1}$

procedure were reproducible to ± 20%.

PRODUCT ANALYSIS

Products were identified by comparison of the n.m.r. spectra of the reaction solutions to those of authentic materials. Usually the acylated derivative was isolated and identified by i.r. and n.m.r. spectroscopy and in some cases by its mass spectral fragmentation. In others 'spiking' the reaction solutions with authentic materials was used.

Cleavage products were identified by isolation and comparison to authentic materials. The absence of any P-N-C-H coupling in the n.m.r. spectra of the reaction solutions was also indicative that cleavage had occurred.

7.3.5. REACTION OF DIETHYL N-METHYLPHOSPHORAMIDITE WITH SILVER ACETATE IN CCl_4

Silver acetate (1.2 g) and freshly distilled diethyl N-methylphosphoramidite (1 g) were stirred together in CCl_4 (25 ml) at 10°C. After 4h precipitation of silver chloride was complete. The solution was then filtered and the solvent evaporated. N.m.r. and i.r. of the resultant oil indicated the presence of N-methylacetamide. Chromatography on silica using chloroform as eluent furnished this amide. Diethyl N-methylphosphoramidate and acetic anhydride were not products of this reaction as evidenced by n.m.r. and i.r. spectroscopy.

A similar reaction using triethyl phosphite did not furnish ethyl acetate.

7.3.6. ACYLATION OF AMINES IN THE PRESENCE OF AMIDES AND PHOSPHORAMIDATES

7.3.6.1. SOLVENTS AND PRODUCTS

Chloroform (AnalaR) was washed with an equal amount of water (to remove EtOH), dried over $CaCl_2$, distilled from P_2O_5 and stored over $CaCl_2$.

N-Methyl-4-nitroaniline was kindly supplied by Mr. D.E.G. Shuker, λ_{max} 373 (4.32) nm.

N-Methyl-N-(4-nitrophenyl) acetamide was synthesised from N-methyl-4-nitroaniline and acetyl chloride in the presence of triethylamine. M.p. 154-156°C; λ_{max} 295(3.67) nm.

N-(2,4-Dinitrophenyl) acetamide was synthesised from 2,4-dinitroaniline and acetic anhydride in pyridine in the presence of 4-(N,N-dimethylamino) pyridine.

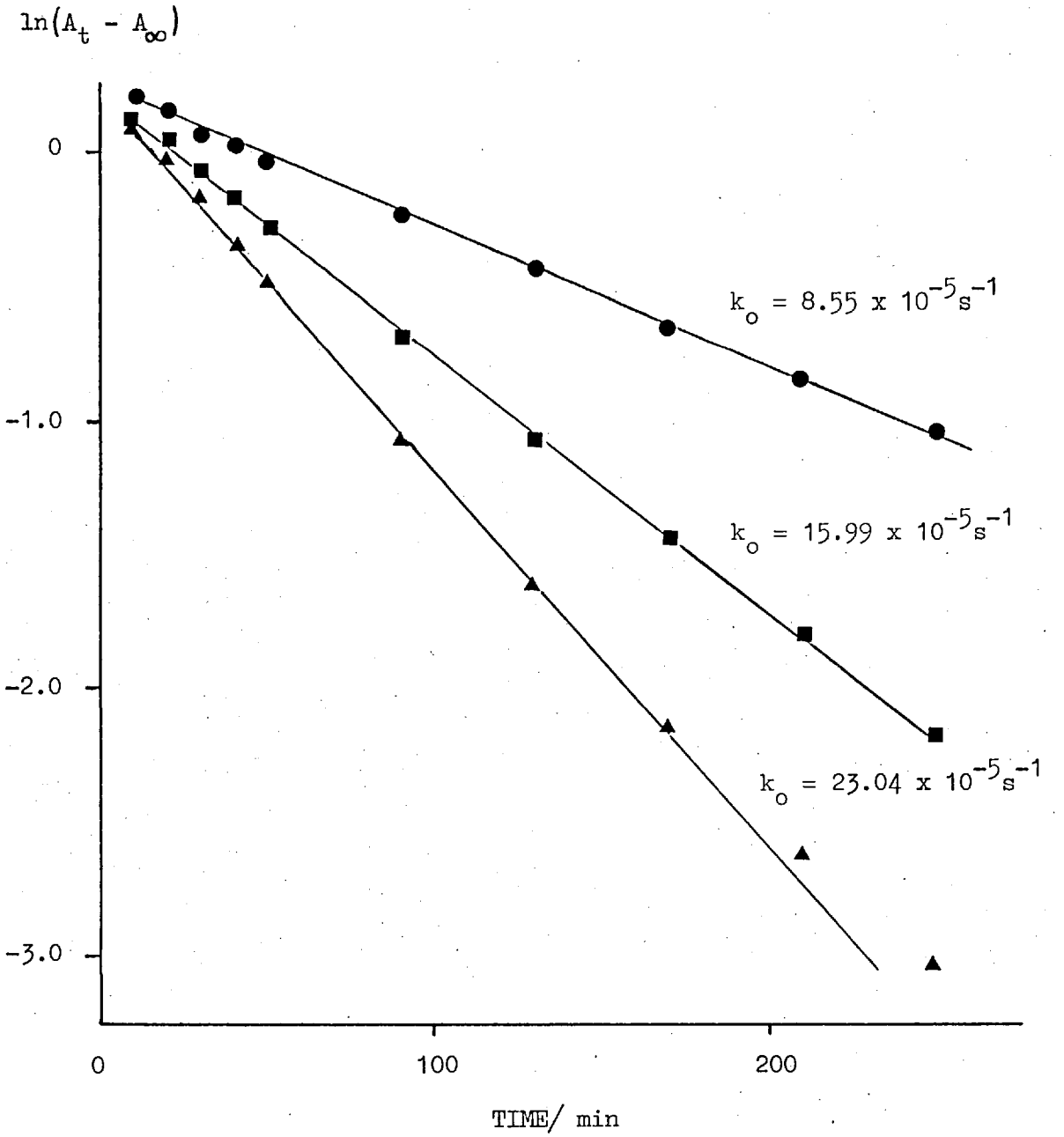
M.p. 121.5-123°C; δ ($CDCl_3$) 2.37(3H,s), 8.30-9.30(3H,m), 10.67(1H,br); λ_{max} 268(3.87), 301(3.86) and 351 sh (3.48) nm.

7.3.6.2. PROCEDURE

Acetylation of N-methy-4-nitroaniline and 2,4-dinitroaniline were carried out in $CHCl_3$ at 25°C. Reactions were monitored by U.V. spectroscopy at 374 nm for N-methyl-4-nitroaniline and 327 nm for 2,4-dinitroaniline. Pseudo-first-order rate coefficients $\{$ Rate = k_o [Amine] $\}$ were calculated by plotting $\ln(A_t - A_\infty)$ versus time. Rate constants measured this way were reproducible to $\pm$ 5%. Representative results are presented in Figures 7.3.6.1. and 7.3.6.2.

FIGURE 7.3.6.1. ACYLATION OF $O_2NC_6H_4NHCH_3$ BY ACETYL CHLORIDE IN $CHCl_3$ AT 25°C.

$[O_2NC_6H_4NHCH_3] = 6.7 \times 10^{-5}$ M



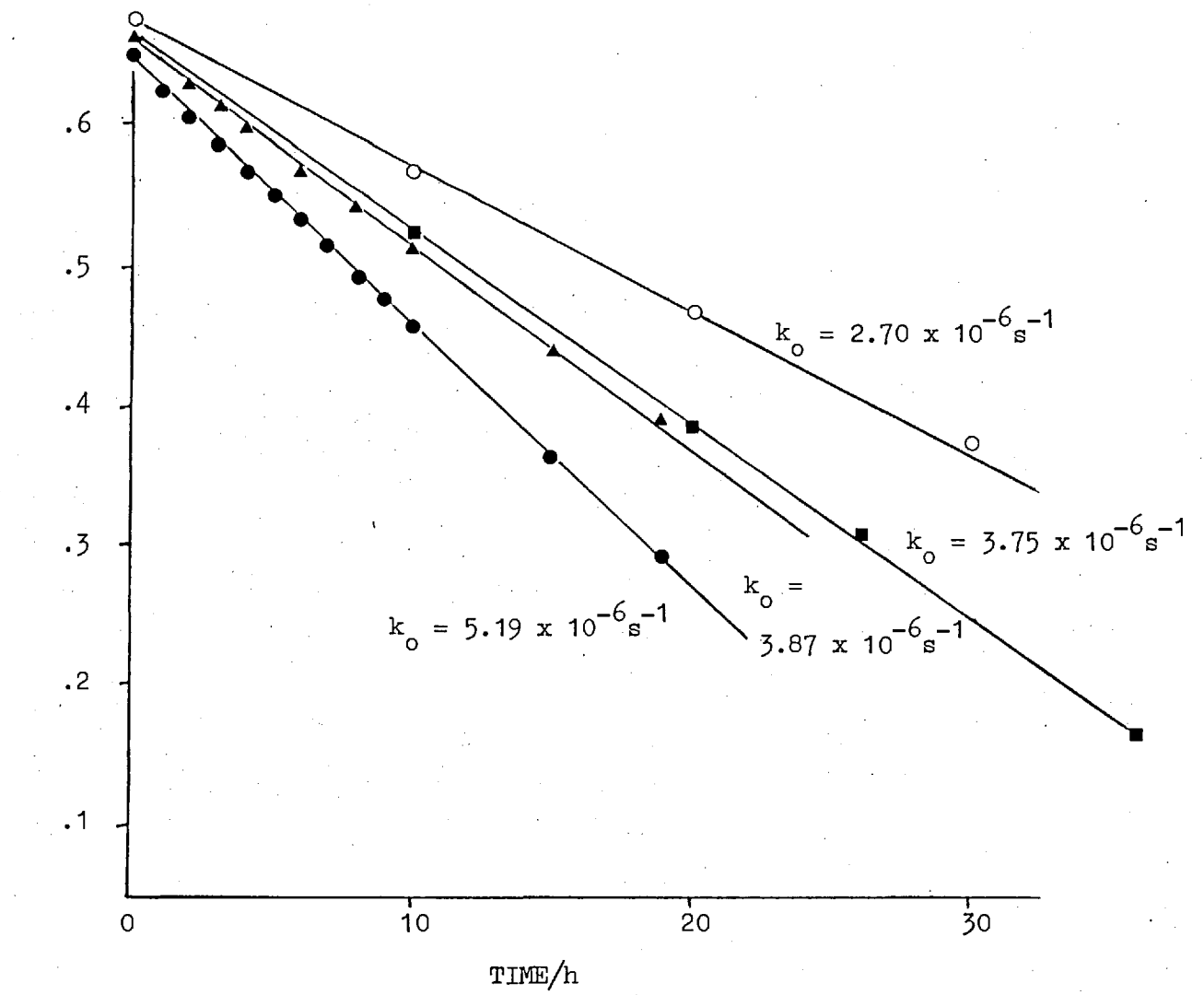
● 1.41 x 10^{-2}M AcCl

■ 2.82 x 10^{-2}M AcCl

▲ 4.23 x 10^{-2}M AcCl

FIGURE 7.3.6.2. ACYLATION OF $O_2NC_6H_4NHCH_3$ BY $AcCl/Ac_2O$ IN $CHCl_3$ AT 25°C IN THE PRESENCE OF $(EtO)_2PONHMe$.

$$[O_2NC_6H_4NHCH_3] = 6.7 \times 10^{-5} \text{ M}$$



○ $[Ac_2O]$ = .064M, $[AcCl]$ = 2.25 x 10^{-4}M, $[(EtO)_2PONHMe]$ = 0 M

■ $[Ac_2O]$ = .064M, $[AcCl]$ = 2.25 x 10^{-4}M, $[(EtO)_2PONHMe]$ = .064M

▲ $[Ac_2O]$ = .106M, $[AcCl]$ = 2.65 x 10^{-4}M, $[(EtO)_2PONHMe]$ = 0 M

● $[Ac_2O]$ = .106M, $[AcCl]$ = 2.65 x 10^{-4}M, $[(EtO)_2PONHMe]$ = .107M

7.4. THE CHEMISTRY OF SULPHONAMIDES

7.4.1. THE SULPHONIMIDATE-SULPHONAMIDE REARRANGEMENT

7.4.1.1. PREPARATION OF SUBSTRATES

4-Toluenesulphinyl chloride

4-Toluenesulphinic acid sodium salt (43.6 g) was added to thionyl chloride (87 ml) in small amounts over 0.5h. The mixture was then left for 24h. Trituration with ether, filtration and removal of both solvent and thionyl chloride gave 4-toluenesulphinyl chloride as a yellow/green mobile liquid.

Dichloromethylamine

Chlorine gas was passed into an aqueous solution of methylamine (25%, 50 ml) and sodium acetate (66 g) at 0°C with rapid stirring until a yellow/orange oil ceased to be produced. This oil was separated, washed with water (3 x 50 ml) and dried over molecular sieves (4A). Dichloromethylamine (38 g, 96%) could be stored at -20°C indefinitely.

ν_{max} 2985, 2962, 1428, 1125, and 980 cm^{-1}.

$\delta(CCl_4)$ 3.65 (s).

N-Methyl-4-toluenesulphonimidoyl chloride

Dichloromethylamine (3.2 g) was added to 4-toluenesulphinyl chloride (5 g) in CCl_4 (20 ml). Evolution of Cl_2 was accelerated by the addition of a few anti-bumping granules. Towards completion of the reaction (as indicated by the n.m.r. spectrum of the solution) the reaction mixture was warmed to 50°C. On completion N-methyl-4-toluenesulphonimidoyl chloride could be isolated by removal of the solvent, m.p. 38-40°C (lit.[112] 37-39°C).

$\delta(CDCl_3)$ 2.40(s,3H), 3.20(s,3H), 7.70(ABq,4H).

In general however, the reaction solution was used, without isolation of the sulphonimidoyl chloride, in the synthesis of the sulphonimidates.

O-Ethyl-N-methyl-4-toluenesulphonimidate

Ethanol (1.32 g, freshly distilled from Mg) and triethylamine (2.89 g) in CCl_4 (15 ml) were added, with stirring under dry N_2, at -20°C to a solution of N-methyl-4-toluenesulphonimidoyl chloride (5.85 g) in CCl_4 (35 ml). After addition was complete the solution was allowed to attain room temperature, stirred for a further 2h, then washed with water. The organic extract was dried (Na_2SO_4), evaporated and the residual oil distilled three times (b.p. 45-50°C/3 x 10^{-5}mm Hg) to yield O-ethyl-N-methyl-4-toluenesulphonimidate (1.9 g, 32%).

ν_{max} 2983, 2930, 2890, 2820, 1598, 1292, 1190, 1178, 1120, 1020, 900, 817 and 725 cm^{-1}.

δ see Table 7.4.1.

m/e(%) 214(4),213(3),185(31)(M-CH_2=CH_2),168(14)(M-OEt),155(30)(185-NHMe),139(33)(168-NMe),121(29)(185-SO_2),120(31)(168-SO),107(5)(155-SO),91(100)(139-SO).

Calc. for $C_{10}H_{15}NO_2S$: C,56.31;H,7.09;N,6.57%

Found: C,56.13;H,7.20;N,5.99%

O-Phenyl-N-methyl-4-toluenesulphonimidate

Sodium phenoxide (2.05 g) was added to a solution of N-methyl-4-toluenesulphonimidoyl chloride (3.05 g) in benzene (25 ml) and refluxed for 2h. After washing with water the organic phase was dried (Na_2SO_4), evaporated and the resulting oil recrystallised from methanol at -78°C. Several low temperature recrystallisations from methanol yielded O-phenyl-N-Methyl-4-toluenesulphonimidate (2.1 g, 45%) m.p. 63-65°C (lit.[112] 63-65°C).

ν_{max} 1588, 1485, 1315, 1300(N+S+O), 1205, 1185, 1158, 922, 880, 845 818, 785, 690 and 652 cm^{-1}.

δ see Table 7.4.1.

$^{m}/e$ (%) 261(2)($M^{+\cdot}$),168(100)(M-PhO),139(11)(168-NMe),120(53)(168-SO), 107(4)(139-S),91(35)(139-SO),77(4)($Ph^{+\cdot}$).

Calc. for $C_{14}H_{15}NO_2S$: C,64.34;H,5.79;N,5.36%

Found: C,64.46;H,5.77;N,5.30%

7.4.1.2. PREPARATION OF PRODUCTS

N-Methyl-4-toluenesulphonamide

The Schotten-Baumann procedure[142] was followed. 4-Toluenesulphonyl chloride (120 g) was added, with swirling, to an aqueous solution of methylamine (25% w/v, 175 ml). The reaction mixture was cooled under running water and the solid produced was collected and recrystallised from ethanol/water (105 g,90%) m.p. 77-79°C.

ν_{max} 3270(NH), 1598, 1323, 1295, 1160, 1095, 1065, 842, 828 and 668 cm^{-1}.

δ see Table 7.4.1.

The following compounds were prepared in the same manner:

N,N-Dimethyl-4-toluenesulphonamide

Yield 96%

m.p. 80-81°C.

ν_{max} 1595, 1335, 1260, 1190, 1164, 1092, 955, 818, 725, 706 and 647 cm^{-1}.

δ see Table 7.4.1.

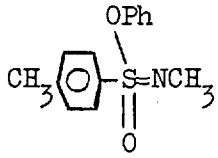
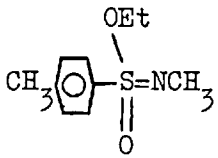
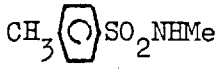
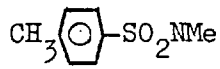
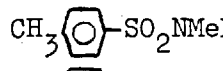
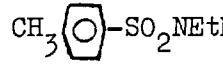
N-Methyl-N-phenyl-4-toluenesulphonamide

Yield 92%

m.p. 93-95°C.

ν_{max} 1596, 1492, 1342, 1293, 1260, 1170, 1152, 1067, 870, 815, 777, 720, 700 and 656 cm^{-1}.

TABLE 7.4.1. ^{1}H N.M.R. CHEMICAL SHIFTS (δ) RELATIVE TO $SiMe_4$ FOR SULPHONIMIDATES AND PRODUCT SULPHONAMIDES IN $[^{2}H_3]$-ACETONITRILE SOLUTIONS.[a]

COMPOUND	Ar[b]	$ArCH_3$	$OCH_2(Ph)$	$NCH_2(Ph)$	OCH_2CH_3	NCH_2CH_3	NCH_3	NH
	7.27-8.10	2.43(S)	7.17(m)				3.10(S)	
	7.20-7.97	2.39(S)	3.90(q)[c]		1.13(t)[c]		2.81(S)	
	7.20-7.90	2.40(S)					2.49(d)[d]	5.33(br)
	7.31-7.89	2.44(S)					2.64(S)	
	7.13-7.70	2.43(S)		7.33(S)			3.19(S)	
	7.27-7.87	2.41(S)		3.06(q)[e]		1.07(t)[e]	2.67(S)	

a. 0.2M solutions

b. AB quartet

c. J_{CHCH} = 7.5 hz

d. J_{NHCH} = 5.8 hz

e. J_{CHCH} = 7.0 hz

δ see Table 7.4.1.

N-Ethyl-N-methyl-4-toluenesulphonamide

(a) N-Methyl-4-toluenesulphonamide (5 g), ethyl iodide (30 ml) and silver oxide (10 g) were refluxed together in ether (30 ml) for 24h. Silver iodide was filtered off and the solvent removed to give an oil (5.5 g, 95%) which could be recrystallised at low temperature.

(b) N-Methyl-4-toluenesulphonamide (5 g) in benzene (50 ml) was added to sodium hydride (0.9 g) in ether under N_2 with stirring. After cessation of H_2 evolution, ethyl iodide (20 ml) was added and the whole refluxed for 72h. The solid was filtered off and the ether removed to give an oil (5.2 g,90%) which was recrystallised at low temperature, m.p. 25-26°C.

ν_{max} 2982, 2935, 2880, 1600, 1462, 1340, 1224, 1160, 1090, 998, 012, 818, 720, 702 and 646 cm^{-1}.

δ see Table 7.4.1.

7.4.1.3. PURIFICATION OF SOLVENTS AND REAGENTS

AnalaR carbon tetrachloride was dried over $CaCl_2$ and distilled. $[^2H_3]$-Acetonitrile and $[^2H_6]$-acetone (Merck, Sharp and Dohme) were used without further purification other than drying over molecular sieves.

Methyl iodide, ethyl iodide and isopropyl iodide were redistilled at atmospheric pressure and stored over mercury. All the other alkyl halides were redistilled and stored over molecular sieves (4A).

Ethyl nitrate was kindly supplied by Dr. M.E.N. Rosa.

Methyl fluorosulphonate (Aldrich) was used as supplied without further purification.

Fluorosulphonic acid was redistilled from calcium fluoride.

Zinc iodide was heated at 200°C for 2h at reduced pressure then sublimed in vacuo.

Anhydrous HBr gas was passed into acetonitrile until crystals of the conjugate acid, $CH_3CN^+H\ \bar{B}r$, crystallised out. The concentration of the solution was determined at various intervals by titration.

7.4.1.4. MEASUREMENT OF REARRANGEMENT RATES

The rearrangement of the sulphonimidate was monitored by following the disappearance of the $-OC\underline{H}_2-$ absorbtion signals of the substrate in the ^1H n.m.r. spectrum (see Table 7.4.1.). Reactions could also be followed by monitoring the $NC\underline{H}_3$ absorbtion signals (Table 7.4.1.). Samples were prepared by weighing the substrate into an n.m.r. tube, dissolved in the appropriate solvent (0.5 ml), the required catalyst added under an inert, dry atmosphere and the tube sealed. Reactions were started by immersing the tube in a thermostatted bath.

N.m.r. spectra were recorded at timed intervals. Errors in the n.m.r. absorbtion signals were minimised by integrating the signals three times. The substrate signals were normallised by relating them to the total aromatic signals for both substrate and product. The pseudo-first-order rate constants $\left\{ \text{Rate} = k_o\left[\text{ArS(O)(OEt)NMe}\right]\right\}$ for these reactions were calculated using Equation 7.4.1.1., where x = area of the $\underline{O}\text{-}C\underline{H}_2$ signal of the substrate

$$k_o t = \ln\left[\frac{2x}{a}\right] \quad \ldots. \quad 7.4.1.1.$$

and a = total aromatic signal. Pseudo-first-order rate coefficients, k_o, were obtained both graphically and arithmetically and results for typical kinetic reactions are shown in Figures 7.4.1.1. and 7.4.1.2. Linear plots were obtained up to 80% reaction. For reactions carried out under non-pseudo-first-order conditions (*e.g.* with MeI) standard second-order methods yielded the required rate-constant $\text{Rate} = k_2\left[\text{ArS(O)(OPh)NMe}\right]\left[\text{MeI}\right]$ *e.g.*

FIGURE 7.4.1.1. TYPICAL FIRST-ORDER PLOT FOR THE REARRANGEMENT OF $CH_3C_6H_4S(O)(OEt)NMe$ TO $CH_3C_6H_4SO_2NEtMe$ PROMOTED BY EtI IN $[^2H_3]$-ACETONITRILE AT 100°C.

$[CH_3C_6H_4S(O)(OEt)NMe] = 0.188M$
$[EtI] = 0.123\ M$

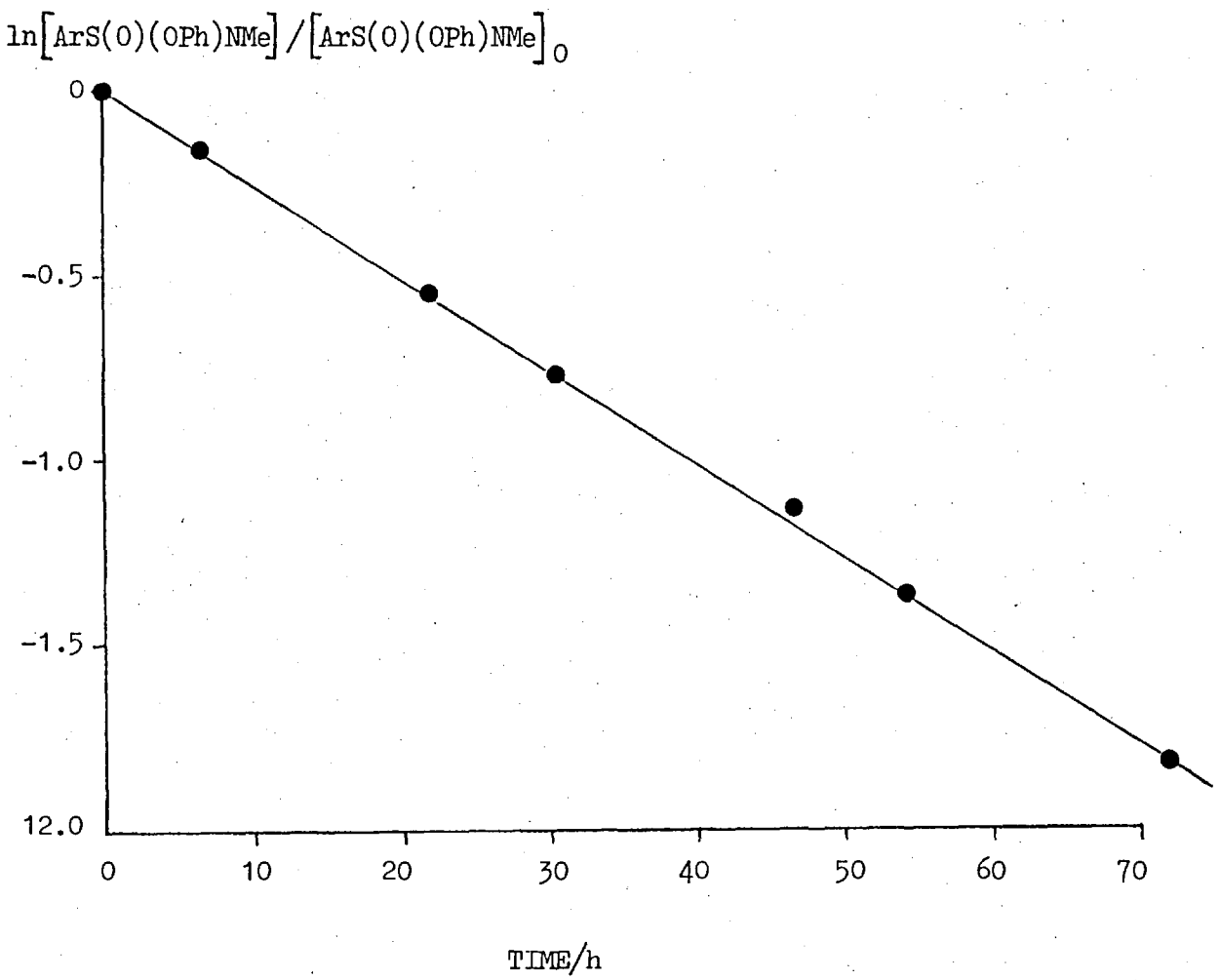


FIGURE 7.4.1.2. FIRST-ORDER PLOT FOR THE REARRANGEMENT OF $CH_3C_6H_4S(O)(OEt)NMe$ TO $CH_3C_6H_4SO_2NEtMe$ PROMOTED BY EtBr IN $[^2H_3]$-ACETONITRILE AT 100°C.

$[CH_3C_6H_4S(O)(OEt)NMe] = 0.161$ M
$[EtBr] = 0.247$ M

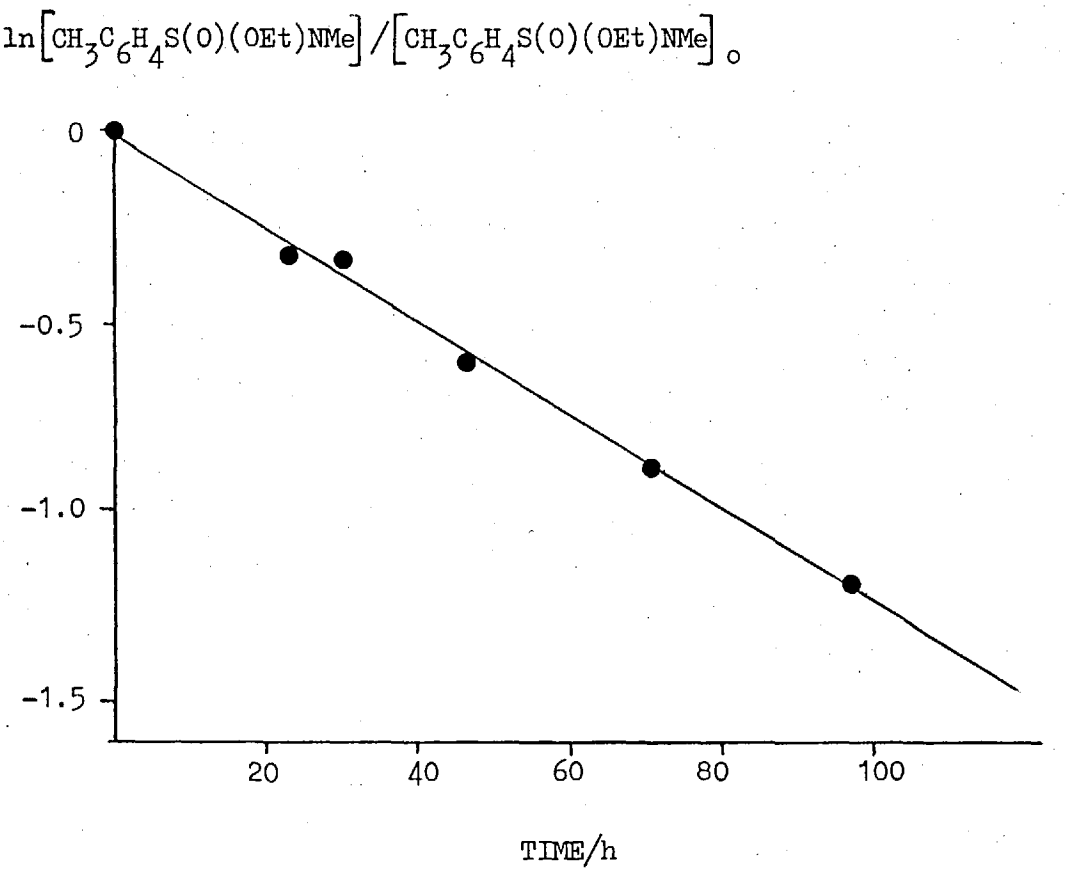


FIGURE 7.4.1.3. SECOND-ORDER PLOT FOR THE REACTION OF $CH_3C_6H_4S(O)(OEt)NMe$ WITH MeI IN $[^2H_3]$-ACETONITRILE AT 100°C.

$[CH_3C_6H_4S(O)(OEt)NMe] = 0.15M$

$[MeI] = 0.199M$

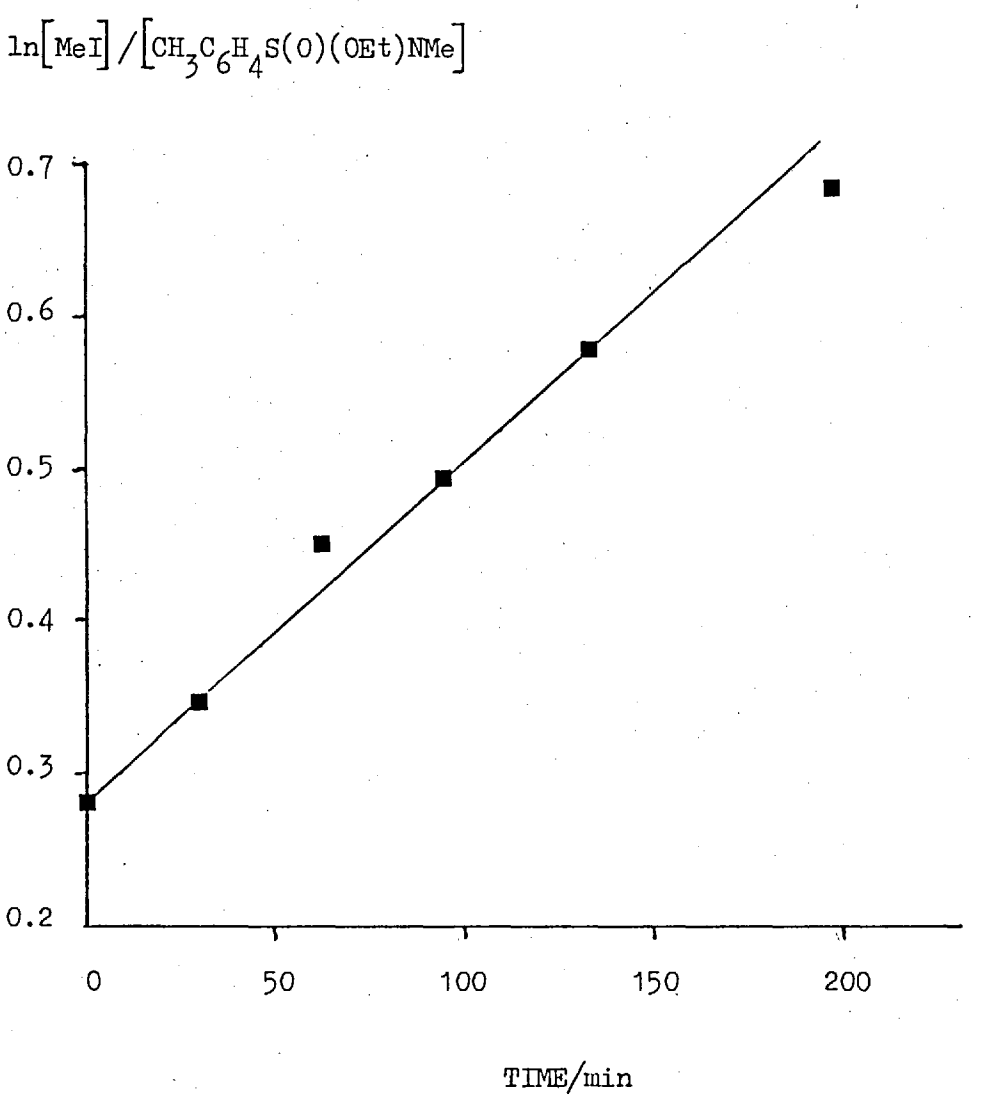


Figure 7.4.1.3. Rate coefficients obtained by both methods were reproducible to $\pm$ 15%.

7.4.1.5. PRODUCT ANALYSIS

Products were identified by comparison of the n.m.r. spectra of the reaction solutions with authentic samples and also by adding authentic materials to the reaction solutions. Products from several reaction solutions were determined by t.l.c. In certain cases reaction products were isolated and characterised by m.p., refractive index and i.r. and n.m.r. spectroscopy.

7.4.2. THE ALKYLATION OF SULPHONAMIDES

7.4.2.1. PREPARATION OF SUBSTRATES AND PRODUCTS

The synthesis of most substrates and products has already been described (see Sections 7.4.1.1. and 7.4.1.2.). Other compounds synthesised by the Schotten-Baumann procedure were:

N-Methylbenzenesulphonamide

Yield 98%

ν_{max} 3295(NH), 1475, 1446, 1412, 1315, 1161, 1092, 1070, 841, 758, 723 and 691 cm^{-1}.

$\delta(CDCl_3)$ 2.61(3H,d,J=4.5hz), 5.27(1H,br), 7.27-8.13(5H,m).

N-Methyl-N-phenylbenzenesulphonamide

Yield 87%

m.p. 78-79°C.

ν_{max} 1348, 1174, 1156, 1065, 868, 773, 729 and 690 cm^{-1}.

$\delta(CDCl_3)$ 3.17(3H,s), 6.97-7.50(5H,m), 7.53(5H,s).

$^m/_e$(%) 247(45),183(10),182(10),142(5),106(100),77(39).

N-Chloro-N-methyl-4-toluenesulphonamide

N-Methyl-4-toluenesulphonamide (10 g) was dissolved in CH_2Cl_2 (70 ml). Sodium hypochlorite solution (12% w/v, 73 ml) was added and the mixture cooled to 0°C. With vigorous stirring acetic acid (10 ml) was added. The solution was stirred for a further 0.5h. The organic layer was separated, washed with water, dried (Na_2SO_4) and evaporated to give a white solid which was recrystallised from ether/petroleum ether (10.7 g, 90%) m.p. 76-78°C.

ν_{max} 1593, 1355(SO_2), 1175(SO) and 670 cm^{-1}.

$\delta(CDCl_3)$ 2.50'3H,s), 3.11(3H,S), 7.37-8.07(4H,AA'BB')

1-Methyl-1-(4-toluenesulphonyl)-3-phenyltriazene

N-Methyl-4-toluenesulphonamide (2 g) in sodium hydroxide solution (1 g in 15 ml) was added to benzene diazonium chloride solution (1 equiv., synthesised by diazotising aniline[142]), and stirred for 1h. The precipitate was filtered and washed with ether. (The residual material was starting material.) Petroleum ether was added to the ethereal washings to precipitate more sulphonamide. The residual, dark-brown, solution was evaporated and the residue purified by p.l.c. on silica gel (ether/petroleum ether: 7/3) to give a mixture (3% yield) of triazene (80%) contaminated by O-phenyl-N-methyl-4-toluene sulphonimate (20%). The sulphonimidate could not be removed without substantial decomposition of the triazene.

ν_{max} 1598, 1372(SO_2), 1172(SO), 940, 770, 755 and 670 cm^{-1}.

$\delta(CDCl_3)$ 2.37(/H,s), 3.33(3H,s), 7.20-8.10(9H,m).

7.4.2.2. REAGENTS AND SOLVENTS

All chlorinated solvents ($CHCl_3$, CH_2Cl_2 and CCl_4) were washed with

aqueous $NaHCO_3$ then H_2O followed by drying over $CaCl_2$, distilled and stored over molecular sieves (4A). Nitromethane and nitrobenzene were redistilled.

Alkyl iodides were redistilled and stored over mercury. Methyl fluorosulphonate (Aldrich) was used without further purification.

Benzene diazonium tetrafluoroborate was synthesised by the procedure of Vogel[142] and stored at -20°C.

Diphenyliodonium tetrafluoroborate was synthesised by a known procedure[143].

7.4.2 3. Reaction of 4-toluenesulphonamides with methyl iodide

The sulphonamide (ca. 20 mg) was dissolved in nitrobenzene (0.5 ml) and an equimolar amount of methyl iodide added Solutions were transferred to an n.m.r. tube which was sealed and reactions started by immersing in a thermostatted bath. Reactions were followed by n.m.r. and products analysed by t.l.c.

7.4.2.4. Reaction of arenesulphonamides with methyl fluorosulphonate and methyl trifluoromethanesulphonate

The sulphonamide (500 mg) was dissolved in the appropriate solvent (5 ml). Reactions were started by adding a known amount of alkylating agent. Samples were removed at various times for n.m.r. analysis. On completion of reaction, solids were filtered off and washed with ether whilst oils were washed with CCl_4 and triturated with ether. N.m.r. spectra of the solids were recorded in CD_3NO_2 or CD_3CN solutions and i.r. spectra of nujol mulls taken. Identified in this way were:

Benzenesulphonyltrimethylammonium fluorosulphonate

m.p. 74-77°C.

$\delta(CD_3CN)$ 3.30(9H,s), 7.60-8.50(5H,M).

ν_{max} 3040, 1580, 1380, 1180 cm^{-1}.

4-toluenesulphonyltrimethylammonium fluorosulphonate

m.p. 90-92°C.

$\delta(CD_3NO_2)$ 2.57(3H,s), 3.33(9H,s), 7.63-8.33(4H,Abq).

ν_{max} 3040, 1588, 1378, 1175 cm^{-1}.

N,N-dimethyl-4-toluenesulphonamide

7.4.2.5. Reaction of arenesulphonamides with benzenediazonium tetrafluoroborate.

Benzenediazonium tetrafluoroborate (2 g) was added to N-methylbenzenesulphonamide or N-methyl-4-toluenesulphonamide at 80°C in small amounts till the reaction ceased. N.m.r. of the residue shows the presence of a new N-Me signal corresponding to ca. 25% reaction. Aqueous NaOH (20 ml, 1 N) was added and the solution extracted with ether (2 x 30 ml). The ether extracts were dried ($NaHCO_3$), concentrated and submitted to p.l.c. (silica gel, ether/petrol: 2/3) which yielded starting material and one other product identified as the O-phenyl-sulphonimidate. Identified in this way were:

O-phenyl-N-methyl-4-toluenesulphonimidate

m.p. 61-63°C.

$\delta(CDCl_3)$ 2.43(3H,s), 3.10(3H,s), 6.8-8.07(9H,m).

m/e 261,168,139,120,107,91,77,65.

O-phenyl-N-methylbenzenesulphonimidate

m.p. 88-90°C. (lit.[112] 88-89°C)

$\delta(CDCl_3)$ 3.11(3H,s), 6.67-8.10(10H,m).

$^m/e(\%)$ 247(4), 183(1),154(100),106(67),77(6)).

7.4.2.6. Thermolysis of 1-methyl-1-(4-toluene sulphonyl)-3-phenyltriazene.

The triazene (100 mg) was thermolysed at 90°C in a sealed n.m.r. tube for 45 min. ^{1}H N.m.r. and i.r. spectroscopy and m.p. showed the product to be N-methyl-4-toluenesulphonamide.

7.4.2.7. Reaction of sodium N-methyl-4-toluenesulphonamide with benzenediazonium tetrafluoroborate

N-Methyl-4-toluenesulphonamide (1 g) in ether (50 ml) was added to sodium hydride (150 mg) in ether (20 ml) with stirring under N_2. When H_2 evolution ceased benzenediazonium tetrafluoroborate (1.05 g) was added and the reaction stirred, under N_2, at room temperature for 7 days. Filtration followed by removal of solvent gave N-methyl-4-toluenesulphonamide in quantitative yield. A similar experiment in the presence of furan failed to furnish any benzyne-trapped product.

7.4.2.8. Reaction of N-methyl-4-toluenesulphonamide with benzoyl peroxide

a) The sulphonamide (200 mg) was heated to 90°C and benzoyl peroxide (270 mg) was added to the melt in small amounts. Phenyl benzoate (m.p. 77°C) was sublimed from the residue and the remaining material shown to be starting sulphonamide by i.r. and n.m.r.

b) Benzoyl peroxide (650 mg) and sulphonamide (500 mg) in cyclo-

hexane (30 ml) were heated to reflux for 12h. Removal of the solvent gave a residue whose i.r. and n.m.r. showed the presence of benzoic acid, phenyl benzoate and starting sulphonamide.

7.4.2.9. Reaction of N-chloro-N-methyl-4-toluenesulphonamide with benzoyl peroxide

a) The N-chlorosulphonamide (200 mg) was heated to melting and benzoyl peroxide (20 mg) added. An explosive reaction occurred in which all the N-chloro substrate was consumed. The reaction product has similar n.m.r.{$\delta(CDCl_3)$ 2.43, 2.61, 2.83, 4.63 and aromatic signals} as that from thermolysis.

b) Benzoyl peroxide (500 mg) and the N-chlorosulphonamide (45) mg) were heated in refluxing petrol (60-80) for 72h. On cooling, the petrol solution was decanted from a viscous oil which proved to be N-methyl-4-toluenesulphonamide. Removal of the petrol yielded a solid which proved to be a mixture of benzoic acid and phenyl benzoate.

7.5. AMIDE ALKYLATION: MOLECULAR ORBITAL CALCULATIONS

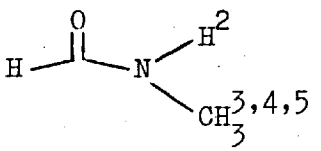
Molecular orbital calculations on amides and their derivatives were calculated by the MNDO method[122]. Calculations were performed on the CDC M7600 computer at the ULCC using programmes supplied by Dr. H.S. Rzepa.

Typically, trial geometry parameters, including bond length, bond angle and twist (or dihedral) angle, defining the positions of the atoms are used as starting co-ordinates, and the programme optimised the geometry by minimising the energy with respect to the co-ordinates using an iterative procedure. For structures resembling transition states the geometry was optimised by minimising the energy with respect to the slope of the configuration-energy profile. Either method yields a molecular configuration for which orbital energies, orbital electron densities, atomic charge, bond lengths, bond angles, twist angles, interatomic distances, ionisation potential and an electron density matrix are calculated.

These values allow comparison of stabilities, electron population in highest occupied molecular orbitals, charge distribution and π-bond formation. Typical computer calculations are summarised in Tables 7.5.1. and 7.5.2.

TABLE 7.5.1. SUMMARY OF MNDO CALCULATION.

N-METHYLFORMAMIDE



Heat of formation, ΔH_f = -40.776 kcal.mol^{-1}

Ionisation Potential = 10.370 eV

Molecular charge = 0

Net atomic charges:

Atom	Charge	Atom Electron Density
H(1)	.0604	0.9396
C	.3804	3.6196
O	-.3643	6.3643
N	-.4553	5.4553
H(2)	.1881	0.8119
C	.2160	3.7840
H(3)	-.0116	1.0116
H(4)	-.0131	1.0131
H(5)	-.0007	1.0007

π (C-O) .85

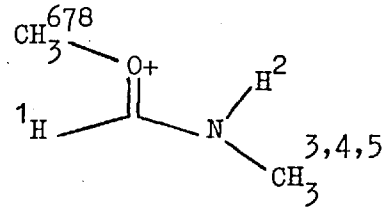
π (C-N) .45

TABLE 7.5.1. (CONT.) MOLECULAR GEOMETRY FOR N-METHYLFORMAMIDE.

ATOM NO. (I)	ATOM	BOND LENGTH (ANGSTROMS) NA:I	BOND ANGLE (DEGREES) NB:NA:I	TWIST ANGLE (DEGREES) NC:NB:NA:I	NA	NB	NC
1	H(1)						
2	C	1.1068			1		
3	O	1.2259	124.28		2	1	
4	N	1.3998	115.55	180.69	2	1	3
5	H(2)	1.0015	118.64	180.44	4	2	1
6	C	1.4500	126.00	-4.21	4	2	1
7	H(3)	1.1160	110.48	120.45	6	4	2
8	H(4)	1.1159	110.65	-120.22	6	4	2
9	H(5)	1.1125	111.74	.17	6	4	2

TABLE 7.5.2. SUMMARY OF MNDO CALCULATION

2-METHYL-N-METHYLFORMIMIDONIUM CATION - ORTHOGONAL FORM



Heat of formation, ΔH_f = 152.333 kcal.mol^{-1}

Ionisation potential = 15.451 eV

Molecular charge = +1

Net atomic charges:

Atom	Charge	Atom Electron Density
H(1)	.1412	0.8588
C	.6038	3.3962
O	-.1861	6.1861
N	-.5184	5.5184
H(2)	.2550	0.7450
C	.2303	3.7697
H(3)	.0173	0.9827
H(4)	.0508	0.9492
H(5)	.0146	0.9854
C	.1939	3.8061
H(6)	.0901	0.9099
H(7)	.0536	0.9464
H(8)	.0539	0.9461

π (C-O) .78

π (C-N) .25

TABLE 7.5.2. (CONTD.) MOLECULAR GEOMETRY FOR O-METHYL-N-METHYLFORMIMIDONIUM CATION.

ATOM NO. (I)	ATOM	BOND LENGTH (ANGSTROMS) NA:I	BOND ANGLE (DEGREES) NB:NA:I	TWIST ANGLE (DEGREES) NC:NB:NA:I	NC	NB	NA
1	H(1)						
2	C	1.1104			1		
3	O	1.2864	122.80		2	1	
4	N	1.3864	120.91	177.64	2	1	3
5	H(2)	1.0062	117.22	-89.30	4	2	1
6	C	1.4724	124.75	90.08	4	2	1
7	H(3)	1.1129	110.71	60.83	6	4	2
8	H(4)	1.1112	108.21	180.47	6	4	2
9	H(5)	1.1130	110.03	-60.10	6	4	2
10	C	1.4403	128.54	-1.07	3	2	1
11	H(6)	1.1138	105.65	179.79	10	3	2
12	H(7)	1.1133	109.90	60.73	10	3	2
13	H(8)	1.1133	109.87	-61.17	10	3	2

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Mechanism of the Pseudo-molecular Rearrangement of Triethyl *N*-Phenylphosphorimidate to Diethyl *N*-Ethyl-*N*-phenylphosphoramidate

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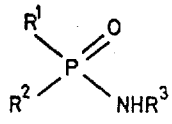
Mechanism of the Pseudo-molecular Rearrangement of Triethyl *N*-Phenylphosphorimidate to Diethyl *N*-Ethyl-*N*-phenylphosphoramidate

By **Brian C. Challis,* Judith A. Challis, and James N. Iley,** Department of Organic Chemistry, Imperial College, London SW7 2AZ

Kinetic studies are reported for the pseudo-molecular rearrangement of triethyl *N*-phenylphosphorimidate to diethyl *N*-ethyl-*N*-phenylphosphoramidate in MeCN. This transformation is shown to be readily catalysed by electrophilic reagents such as alkyl halides, zinc halides, I_2, MeCOBr, and halogen acids where Rate = k_2[Substrate]-[Catalyst]. For alkyl halides, the reaction proceeds *via* a two-step mechanism involving an ionic intermediate: formation of the intermediate by an S_N2 reaction between the substrate and alkyl halide is rate limiting. Other catalysts effect rearrangement by the intermediate formation of alkyl halides in an initial rapid reaction with the substrate. In the absence of electrophilic reagents, rearrangement proceeds in MeCN at 100 °C by a much slower thermal process which has a second order dependence on [Substrate].

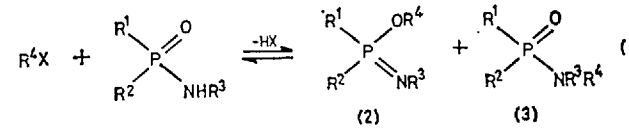
The results are compared with the related rearrangement of *N*-methylbenzimidates to tertiary amides and discussed in relation to the ambident nucleophilic properties of phosphylamidates. It is suggested that, like carboxylic acid amides, alkylation occurs most readily at the *O*-atom of neutral phosphylamidates to give a phosphylimidate (kinetic product) which then rearranges in the presence of electrophilic catalysts to an *N*-substituted phosphylamidate (thermodynamic product).

We have recently shown [1,2] that the 'ambident' nucleophilic properties of neutral amides can be well understood in terms of the formation of a kinetic product (an *O*-substituted imidate) which, under suitable conditions, rearranges to the thermodynamic product (an *N*-substituted amide). Phosphoramidates (1a), phosphonamidates (1b), and phosphinamidates (1c) (all closely related to amides) may be expected to behave similarly in their nucleophilic reactions, giving a kinetic product (2) (*O*-substituted phosphylimidate *) and, provided conditions are appropriate for rearrangement, the thermodynamic product (3) (*N*-substituted phosphylamidate) [equation (1)]. Of the few alkylation



(1) a; R^1, R^2 = alkoxy or aryloxy
b; R^1 = alkyl, aryl, R^2 = alkoxy, aryloxy
c; R^1, R^2 = alkyl or aryl
(1a),(1b),(1c); R^3 = H, alkyl or aryl

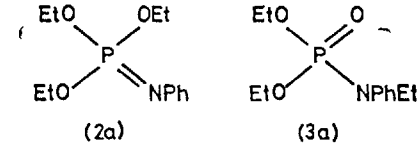
reactions of phosphylamidates so far studied, those taking place under mild conditions (such as reaction of *N*-t-butylmethylphenylphosphinamidate with triethyloxonium hexafluorophosphate [3]) produce only *O*-alkylated product (2), whilst those with less reactive reagents, which require higher temperatures, produce either a mixture of *O*- and *N*-alkylated products (2), (3) (as in the reaction of diphenyl *N*-phenylphosphoramidate with trimethylsilyl chloride at *ca.* 80 °C [4]) or the *N*-alkylated product (3) only (*e.g.* in the reaction of diethyl



(1)

(2) (3)

phosphoramidate with n-propyl iodide at *ca.* 100 °C [5] or of di-isopropyl *N*-benzylphosphoramidate with trimethyl-silyl, tin or germanium chlorides at *ca.* 101 °C [6]). This pattern of alkylation suggests product orientation is indeed dependent on the incidence of kinetic *versus* thermodynamic control. It is known that the transformation of (2) to (3) (R^1, R^2 = alkyl or alkoxyl, R^3 = Ph, R^4 = Et) does proceed in the presence of methyl or ethyl iodide in acetonitrile at 50 °C,[7] and that (2) and (3) ($R^1 = R^2 = R^3$ = Ph, $R^4 = Me_3Si$) are in equilibrium.[4] We have now investigated the kinetics of the conversion of triethyl *N*-phenylphosphorimidate (2a) into diethyl *N*-ethyl-*N*-phenylphosphoramidate (3a) by various electrophilic agents both to establish the



(2a) (3a)

reaction mechanism and to determine whether the rearrangement is feasible under the conditions of alkylation in which *N*-alkylated products are formed.

* In accord with recent practice 'phosphyl' is used as a collective term to include phosphoryl, phosphonyl, and phosphinyl groups.

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EXPERIMENTAL

Substrates and Products.—Triethyl *N*-phenylphosphorimidate (2a) was prepared from phenyl azide [8] and triethyl phosphite according to the procedure of Gilyarov and Kabachnik [9] [b.p. 84 °C/2 × 10^{-4} mmHg; n_D^{21} 1.501 4 (lit.,[7] b.p. 53—56 °C/10^{-3} mmHg; n_D^{20} 1.501 5); $\nu_{max.}$ 2 980, 1 595, 1 500, 1 370, 1 355 (P=N), 1 115, 1 030, 760, and 700 cm^{-1}; n.m.r. data are given in Table 1 (Found: C, 56.1; H, 7.7; N, 5.4. Calc. for $C_{12}H_{20}NO_3P$: C, 56.0; H, 7.8; N, 5.4%)]. Diethyl *N*-phenylphosphoramidate (4) and diethyl *N*-ethyl-*N*-phenylphosphoramidate (3a) were synthesized by the method of Atherton *et al.*[10] from diethyl phosphite and aniline or *N*-ethylaniline, respectively. [(4) gave m.p. 93—95 °C (lit.,[10] 92—94 °C), $\nu_{max.}$ 3 300—3 100 (N–H) and 1 225 (P=O) cm^{-1} and (3a) gave b.p. 135 °C/1.5 mmHg, n_D^{21} 1.487 5 (lit.,[7] b.p. 91 °C at 0.5 mmHg; n_D^{20} 1.497 2), and $\nu_{max.}$ 1 255 cm^{-1}. N.m.r. chemical shifts of both compounds are given in Table 1].

Reagents and Solvents.—AnalaR CCl_4 was dried over $CaCl_2$ and redistilled. Reagent Grade acetonitrile was distilled from CaH_2 and stored over molecular sieves (4A). [$^2H_3$]Acetonitrile (Merck, Sharp, and Dohme) was used without further purification other than drying by molecular sieves. AnalaR nitrobenzene was distilled under reduced pressure and dried over CaH_2. All the alkyl halides were redistilled. Acetyl bromide was distilled from *NN*-dimethylaniline. Iodine was recrystallised from benzene and sublimed. The zinc halides were heated at 200 °C for 2 h at reduced pressure and then sublimed *in vacuo*. Anhydrous hydrogen bromide was passed through acetonitrile until crystals of the conjugate acid ($MeCNH^+Br^-$) were formed. Anhydrous sodium ethoxide was prepared from ethanol and sodium.

Kinetics.—The rearrangement of (2a) to (3a) in acetonitrile, [$^2H_3$]acetonitrile, CCl_4, or nitrobenzene was followed by the n.m.r. method previously described.[2] Typically, kinetic measurements were carried out on a solution of the phosphorimidate (0.2M) and electrophile (10^{-2}—0.2M) in solvent (0.5 ml) contained in a sealed n.m.r. tube. Reactions in acetonitrile, [$^2H_3$]acetonitrile, and CCl_4 were monitored by following the increase in the *N*–Ph absorption (δ 7.3) of (3a) whilst those in nitrobenzene were followed by the increase in the *N*–CH_2 multiplet (δ 3.6), each spectrum being integrated at least three times to minimise errors arising from fluctuations in the n.m.r. signals.

Pseudo-first-order rate coefficients {Rate = k_0 [(2a)]} were calculated from equation (2), where x = area of either the *N*–Ph or the *N*–CH_2 signal for the product amidate at time t and a = total area of either the *N*–Ph or the *N*–CH_2 signals for both starting imidate and product amidate. Results for a typical run are shown in Figure 1. Linear plots

$$k_0 = 2.303 \log (1 - x/a)/t \qquad (2)$$

were obtained up to *ca.* 80% reaction when the insensitivity of the n.m.r. procedure introduced significant errors in the measurement of small integrals. Rate coefficients obtained by this method were reproducible to ±10%.

TABLE 1

^1H N.m.r. chemical shifts (δ) relative to $SiMe_4$ and coupling constants for phosphorimidate (2a) and product phosphoramidates (3a) and (4) [a]

	N–C_6H_5	N–H [b]	N–CH_2 [c]	NCH_2CH_3	OCH_2 [d]	OCH_2CH_3 [e]
(2a)	6.85m				4.1 quint 4.15d [f]	1.35tr
(3a)	7.3s		3.6m 3.55d [g]	1.25d tr	4.1m 4.1d	1.25d tr
(4)	7.05m	8.1d			4.1 quint 4.1d [f]	1.35tr

[a] *ca.* 0.2—0.8M solutions in CCl_4. [b] J_{PNH} 10 Hz. [c] J_{PNCH} 10 Hz, J_{CHCH} 7.5 Hz. [d] J_{POCH} 8 Hz, J_{CHCH} 7—7.5 Hz. [e] J_{CHCH} 7—7.5 Hz. [f] Spin decoupled at 81 Hz. [g] Spin decoupled at 74 Hz.

Product Analysis.—Products were identified from comparison of n.m.r. spectra of the reaction solutions with authentic materials. In several reactions the solvent and reagent were removed, and the products were isolated to be identified by g.l.c., m.p., and i.r. and n.m.r. spectroscopy (in CCl_4). For the thermal reaction in the absence of added electrophiles the formation of ethylene was evident from the n.m.r. spectrum (δ 5.2, d).

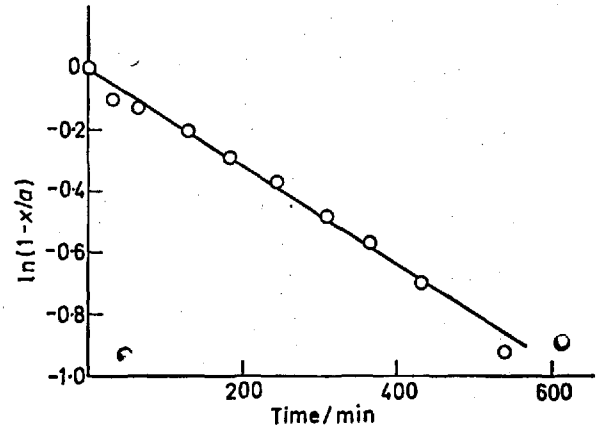


FIGURE 1 Typical first-order plot for the rearrangement of phosphorimidate (2a) catalysed by 0.062M-EtI in MeCN at 100 °C

RESULTS AND DISCUSSION

In the absence of any added electrophiles, triethyl *N*-phenylphosphorimidate (2a) rearranged very slowly ($t_{\frac{1}{2}}$ *ca.* 30 days) to diethyl *N*-ethyl-*N*-phenylphosphoramidate (3a) when heated in organic solvents at 100 °C [equation (3)]. Further, the appearance of an ethylene

$$(EtO)_3P{=}NPh \xrightarrow{Heat} (EtO)_2P(=O)NEtPh \qquad (3)$$

[8] R. O. Lindsay and C. F. H. Allen, *Org. Synth.* Coll. Vol. 3, 1955, 710.

[9] V. A. Gilyarov and M. I. Kabachnik, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, 1957, 790.

[10] F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 1945, 660.

doublet in the n.m.r. spectrum showed that dealkylation was taking place concurrently [equation (4)]. The

$$(EtO)_3P{=}NPh \xrightarrow{Heat} (EtO)_2P(=O)NHPh + CH_2{=}CH_2 \quad (4)$$
(4)

extent of dealkylation, calculated from the relative intensities of the ethylene to N–Ph signals was *ca.* 9% of the total reaction. The overall thermal reaction (k_Δ) followed second-order kinetics in accordance with equation (5) implying intermolecular pathways for both

$$\text{Rate} = k_\Delta[(2a)]^2 = k_{rearr}[(2a)]^2 + k_{dealk}[(2a)]^2 \quad (5)$$

rearrangement and dealkylation. Rate coefficients for rearrangement and dealkylation (k_{rearr} and k_{dealk}) were computed in the usual way from k_Δ and the product ratios, and their values are given in Table 2.

Conversion of (2a) into (3a) occurred much more readily in the presence of alkyl halides. These reaction rates were solvent dependent decreasing in the order $MeCN > PhNO_2 > CCl_4$ by factors of 1.21 and 46, respectively (see Table 2). This dependence suggests

TABLE 2

Second-order rate coefficients (k_2) for the reaction of triethyl *N*-phenylphosphorimidate (2a) with alkyl halides in MeCN; initial [(2a)] = 0.2M; [alkyl halide] = 10^{-2} — 0.2M

Alkyl halide	t/°C	10^6k_2/l mol^{-1} s^{-1}
MeI	34.2	39.5
EtI	34.2	4.12
EtI	50	15.7
EtI	74.5	94.3
EtI	100	400
EtI [a]	100	307
EtI [b]	100	7.15
EtBr	100	88.0
$EtNO_3$	100	4.10
EtI–$AgNO_3$	100	27.5
Pr^{i}I	100	60.8
Pr^{i}Br	100	8.52
Pr^{i}Cl	100	1.68 [c]
None	100	1.65 [d]

[a] In $PhNO_2$ solvent. [b] In CCl_4 solvent. [c] $k_2 = k_{rearr}$; $k_{dealk} = 1.50 \times 10^{-7}$ l mol^{-1} s^{-1}. [d] $k_2 = k_{rearr}$; $k_{dealk} = 1.66 \times 10^{-7}$ l mol^{-1} s^{-1}.

that solvent polarity is important and implies the formation of an ionic intermediate. For practical reasons MeCN was most suitable and all the following results refer to this solvent. Unlike the thermal rearrangement, the rate of conversion of (2a) to (3a) in the presence of alkyl halides (with the exception of isopropyl chloride where catalysis was negligible) follows equation (6)

$$\text{Rate} = k_0[(2a)] \quad (6)$$

which has only a first-order dependence on substrate. By using an appropriate alkyl halide concentration it was possible in most cases to obtain a much faster rearrangement rate than by heating alone. The reactions then followed equation (6) closely (see Experimental section) without any evidence of significant concurrent dealkylation. The pseudo-first-order rate coefficients (k_0) varied linearly with the concentration of added alkyl halide (Figure 2). It follows that the reaction is bimolecular and the catalysed reaction rates are governed by equation (7). Values of k_2 obtained for various alkyl

$$\text{Rate} = k_2[(2a)][\text{Alkyl halide}] \quad (7)$$

halides and $EtNO_3$ in MeCN are also summarised in Table 2.

In the presence of added isopropyl halides, the plot of log $(1 - x/a)$ *versus* t was curved, becoming of steeper

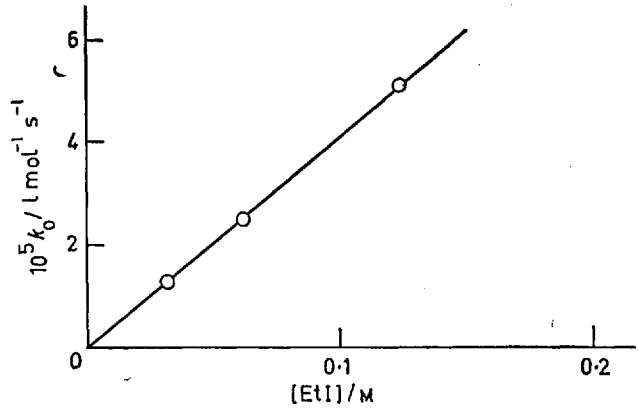


FIGURE 2 Linear dependence of k_0 on [EtI] for the rearrangement of (2a) in MeCN at 100 °C; initial [(2a)] = 0.2M

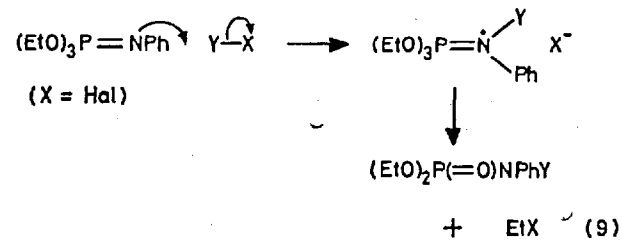
slope as the reaction proceeded. This arose from the formation of ethyl halides during reaction [equation (8)] which then acted as more effective reagents than the

$$(EtO)_3P{=}NPh + Pr^iX \rightleftharpoons (EtO)_2P(=O)NPhPr^i + EtX \quad (8)$$

corresponding isopropyl halides. Sensible rate coefficients for the isopropyl halides could be obtained, however, from the initial reaction and these values are cited in Table 2. The rate enhancement induced by isopropyl chloride was negligible, and rearrangement in this instance occurs predominantly by the thermal process.

The effect of electrophilic reagents other than alkyl halides was also examined and the second-order rate coefficients (k_2) obtained are listed in Table 3. It is significant that k_2 values for ZnI_2 and I_2 are similar to that for EtI, whilst those for $ZnBr_2$, MeCOBr, and HBr (0.1 equivalents) are similar to that for EtBr. These observations can be explained by the generation of a phosphoramidate derivative and ethyl halide following nucleophilic attack by the phosphorimidate (2a) on the electrophile (Y–X) [equation (9)]. The ensuing rearrangement of (2a) then arises from the usual reaction with ethyl halide, so the observed rates correspond to those for added ethyl halide itself. Independent evidence for this sequence of reactions was the relatively rapid appearance of absorption bands characteristic of ethyl halides in the n.m.r. spectrum of the reaction solutions after addition of the electrophilic reagent. Further, the intensity of these bands was proportional

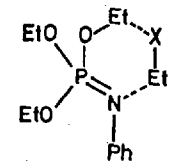
to the amount of electrophilic reagent added. Significantly, rearrangement in the presence of $ZnCl_2$ and, *inter alia*, by EtCl, is no faster than the purely thermal rate as found above for isopropyl chloride. When 1 equivalent of the electrophilic reagent X–Y (*e.g.* HBr) was added, no rearrangement occurred but dealkylation took place. The product [diethyl *N*-phenylphosphoramidate (4)] was characterised by comparison of spectral properties and m.p. with an authentic sample and the n.m.r. spectrum of the reaction solution indicated that the ethyl bromide co-product was formed in quantitative yield. When 0.1 equivalents of HBr was added, rearrangement took place at the rate expected for EtBr as noted above.



The effect of temperature on the rearrangement rate of (2a) in the presence of ethyl iodide was also examined. The data (Table 2) gave a linear Arrhenius plot of log k_2 *versus* $1/T$ leading to values of E_A 67 kJ mol^{-1}, $\Delta H^{\ddagger}$ 64 ± 2 kJ mol^{-1}, $\Delta S^{\ddagger}$ −140 ± 4 J K^{-1} mol^{-1}, and $\Delta G^{\ddagger}$ 116 ± 3 kJ mol^{-1}.

Examination of the results in Table 2 shows that $EtNO_3$ is *ca.* 100 times less effective than EtI in promoting the rearrangement of (2a) to (3a) at 100 °C. It follows that addition of $AgNO_3$ might inhibit the alkyl halide catalysed rearrangement as observed previously for benzimidate esters [2] and thereby lead to a new synthetic procedure for the direct *O*-alkylation of phosphoramidates with alkyl halides. When equimolar quantities of $AgNO_3$ and EtI were added to a 10-fold excess of (2a) in MeCN, precipitation of AgI was apparent, but at 100 °C the reduction in the rate of rearrangement was much smaller than the factor of 100 anticipated from the relative rate coefficients for $EtNO_3$ and EtI (Figure 3) indicating that heterogeneous catalysis by AgI was occurring. The lowest value obtained for k_2 after centrifugation was 2.75×10^{-5} l mol^{-1} s^{-1}, a reduction of *ca.* 15 times on k_2 for EtI in the absence of $AgNO_3$. These reactions were not examined exhaustively, but it was also found that 8×10^{-3}M-$AgNO_3$ accelerated the $EtNO_3$-catalysed rearrangement of (2a) to (3a) in MeCN at 100 °C by a factor of *ca.* 6.

Mechanism of the Rearrangement Reaction.—It has previously been suggested [7] that the alkyl halide-catalysed conversion of phosphorimidates into phosphoramidates proceeds by a cyclic six-membered transition state [such as (5)] of low polarity. However, our finding that the rearrangement rate is markedly dependent on solvent polarity ($MeCN > PhNO_2 > CCl_4$) implies considerable charge development in the transition state and the involvement of ionic intermediates. The observation of second-order kinetics [equation (7)], the decrease in reagent reactivity along the series



(5)

$Pr^iI > Pr^iBr \gg Pr^iCl$, and the rate reduction with increased branching (steric hindrance) of the reagent ($MeI > EtI > Pr^iI$) are also found in the analogous imidate–amide rearrangement.[2] They are best explained, as in the imidate–amide rearrangement, by an S_N2 process (Scheme 1) where rate-limiting attack by the phosphorimidate on the alkyl halide (step k_a) produces an ionic intermediate (6) followed by rapid removal of the *O*-ethyl group by halide ion to give the phosphoramidate (step k_b). Rearrangement, initiated by the addition of either metal halides, I_2, MeCOBr, or HBr proceeds similarly and is brought about, as noted above, by ethyl halide formed in a rapid initial reaction between the phosphorimidate and the added electrophile [equation (9)]. There is no evidence to show that the phosphoramidate derivative produced in this initial reaction plays a significant part in the ensuing rearrangement processes. The relatively slow rate of rearrangement obtained with $EtNO_3$, however, is inconsistent with its expected alkylating ability. The most likely explanation here is that decomposition of the ionic intermediate (6) to products (step k_b) becomes rate

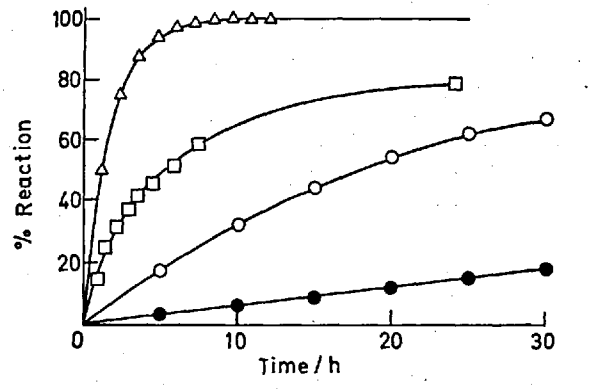
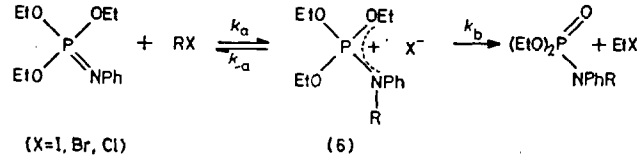


FIGURE 3 Effect of added $AgNO_3$ on the rate of the EtI-catalysed rearrangement of phosphorimidate (2a) in MeCN at 100 °C; △ 0.4M-EtI only, □ 0.43M-EtI plus 0.43M-$AgNO_3$ without centrifugation, ○ 0.39M-EtI plus 0.39M-$AgNO_3$ after centrifugation, ● 0.4M-$EtNO_3$

limiting for the reagent because of the low nucleophilic reactivity of NO_3^-. An analogous S_N2 mechanism to that described by Scheme 1 probably applies to thermal rearrangement. The second-order dependence on substrate concentration implies an intermolecular process such as alkylation of the phosphorimidate *N*-atom by a second substrate molecule to give the ionic intermediate (7), followed by transalkylation of the phosphorimidate

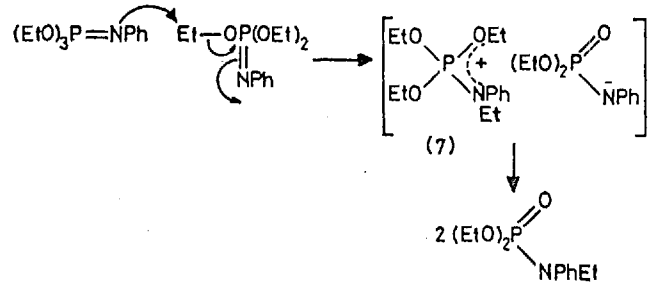
anion (Scheme 2). The results neither identify the rate-limiting step nor exclude a concerted bimolecular mechanism, but the high nucleophilicity of the phosphoramidate anion suggests that formation of (7) would



SCHEME 1 S_N2 Mechanism for the conversion of triethyl *N*-phenylphosphorimidate into diethyl *N*-ethyl-*N*-phenylphosphoramidate by alkyl halides

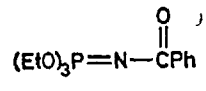
be slow for the stepwise pathway. The concurrent dealkylation under thermal conditions represents the usual competitive *E*-2 component of S_N2 processes involving proton abstraction by the substrate from either a second substrate molecule or the intermediate ion (7).

Our mechanism for the catalysed rearrangement



SCHEME 2 S_N2 Mechanism for the thermal rearrangement of triethyl *N*-phenylphosphorimidate to diethyl *N*-ethyl-*N*-phenylphosphoramidate

appears to have wider applicability. Thus previous qualitative work [7] suggests that the rearrangement rate for various phosphylimidates decreases in the order R = Et > Me > Ph > EtO for $R_2P(OEt)=NPh$, which is consistent with the expected substituent inductive effects on the nucleophilicity of the *N*-atom. Also we have briefly re-examined the behaviour of triethyl *N*-benzoylphosphorimidate (8) reported recently by Glidewell [6] not to form *N*-alkyl-*N*-benzoylphosphoramidate on treatment with either HBr or MeI. We have confirmed that (8) reacts rapidly with an excess of HBr to give quantitative yields of diethyl *N*-benzoylphosphoramidate and EtBr. This reaction is the same as that observed for triethyl *N*-phenylphosphorimi date(2a). Unlike Glidewell,[6] however, we have found that (8) does react, albeit slowly, with equimolar MeI in CD_3CN when heated in a sealed n.m.r. tube at 100 °C. The rate of



(8)

formation of the diethyl *N*-benzoyl-*N*-methylphosphoramidate product gives $k_2 = 1.3 \times 10^{-5}$ l mol^{-1} s^{-1}. Allowing for the temperature difference, this is *ca.* 300 times less than the comparable coefficient for (2a), reflecting the reduced nucleophilicity of the benzoylated *N*-atom.

Ambident Nucleophilic Properties of Phosphoramidates.—The ready conversion of (2a) into (3a) suggests that

TABLE 3

Second-order rate coefficients (k_2) for the rearrangement of phosphorimidate (2a) to phosphoramidate (3a) with electrophilic catalysis in MeCN at 100 °C.

Catalyst	$10^6 k_2$/l mol^{-1} s^{-1}
ZnI_2	380
$ZnBr_2$	91.6
$ZnCl_2$	1.34
I_2	378
MeCOBr	77.1
HBr	89.9
(0.1 equiv.) [a]	
HI (1 equiv.)	*b*

[a] When HBr (1 equiv.) was used, quantitative formation of $(EtO)_2PONHPh$ occurred after 10 min at 23 °C. [b] No rearrangement but quantitative formation of $(EtO)_2PONHPh$ and EtI immediately which remained unchanged even after heating for 24 h at 100 °C.

our recent explanation [1,2] for the apparent ambident nucleophilic properties of neutral amides can be extended to related phosphyl compounds. This requires that electrophilic substitution (*e.g.* by alkyl halides) of neutral phosphylamidates proceeds most readily at the *O*-atom, with *N*-substitution arising from subsequent rearrangement. Thus *O*-alkylphosphylimidates are kinetic products and *N*-alkylphosphylamidates are thermodynamically stable ones. Significantly, direct formation of phosphylimidates by *O*-alkylation has been reported only for $Et_3O^+PF_6^-$ at low temperature.[3] With alkyl halides, *N*-substituted compounds but not *O*-alkylphosphylimidates are obtained [5] presumably be-

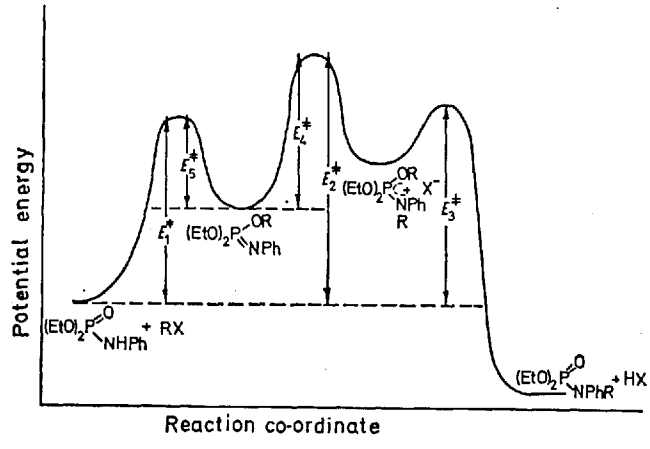


FIGURE 4 Potential-energy diagram for the alkylation of phosphoramidates with alkyl halides

cause of the higher reaction temperatures employed. The observation [5] of *O*-alkyl exchange concurrent with *N*-propylation in the reaction of diethyl phosphoramidate with an excess of Pr^nI at 100 °C implies, however, the formation of a phosphorimidate intermediate. Our results show that under the reaction conditions this

intermediate would quickly rearrange to an *N*-substituted product, so failure to isolate it is not unexpected.

These conclusions are reinforced by consideration of the potential energy profile (Figure 4) for the *O*- and *N*-alkylation of phosphoramidates by alkyl halides. The inequality $E_1^{\ddagger} < E_2^{\ddagger}$ stems directly from the assumption of kinetic and thermodynamic product control and $E_3^{\ddagger} < E_2^{\ddagger}$ from deductions that step k_a is rate limiting for alkyl halides in Scheme 1. The requirement that $E_5^{\ddagger} < E_4^{\ddagger} < E_1^{\ddagger}$ is less obvious, but it stems directly from the rapid and quantitative dealkylation of (2a) on addition of equimolar HBr or HI [equation (10)] without

$$(EtO)_3P{=}NPh + HX \rightleftharpoons (EtO)_2PONHPh + EtX \quad (10)$$

X = Br, I

significant concurrent or ensuing rearrangement to (3a). This shows that dealkylation is faster than rearrangement of (2a), *i.e.* $E_5^{\ddagger} < E_4^{\ddagger}$ and that neither EtBr nor EtI alkylates diethyl *N*-phenylphosphoramidate under conditions where their catalysed rearrangement of (2a) proceeds readily (*i.e.*, $E_4^{\ddagger} < E_1^{\ddagger}$). Unfortunately, $E_1^{\ddagger}$ cannot be ascertained experimentally, but its lowest limit is given by the enthalpy difference (E_1^0) for equation (10), which can be estimated from the relevant molar bond enthalpies.* The value calculated for HI ($E_1^0 = 110$ kJ mol^{-1}) is substantially higher than the experimental enthalpy of activation ($\Delta H^{\ddagger} = 64$ kJ mol^{-1}) for the EtI-catalysed rearrangement of (2a). It follows that $E_4^{\ddagger} < E_1^{\ddagger}$ since $E_1^{\ddagger} > E_1^0$ and $\Delta H^{\ddagger} \simeq E_4^{\ddagger}$.

The mechanism cited in Scheme 1 for the rearrangement of (2a) to (3a) requires formation of product by nucleophilic decomposition (step k_b) of the ionic intermediate (6). Apart from the low reaction temperatures, a salient feature in the successful synthesis of phosphinimidates with $Et_3O^+PF_6^{-3}$ may be the low nucleophilicity of the PF_6^- counter ion. Nonetheless, our attempts to prepare phosphorimidates by direct alkylation of diethyl *N*-phenylphosphoramidate with other reagents in the absence of strongly nucleophilic anions were singularly unsuccessful. For example, in CD_3CN at 100 °C, $EtNO_3$, Me_2SO_4, and MeI in the presence of either $AgNO_3$ or AgI, all gave products whose n.m.r. spectra indicated P–N bond cleavage. With equimolar MeI and Ag_2O in CD_3CN at 34 °C, however, diethyl *N*-methyl-*N*-phenylphosphoramidate was formed in accordance with Rate = 1.7×10^{-5} l mol^{-1} s^{-1} [Substrate][MeI]. The direct *N*-alkylation apparent here may reflect either reaction *via* the phosphoramidate anion or rapid Ag^+-catalysed *O*- to *N*-rearrangement as noted earlier for (2a). Our immediate conclusion is that Ag salts are not useful catalysts for promoting the *O*-alkylation of phosphoramidates.

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* For X = I, $E_1^0 = D$(C–O) + D(P–O) + D(P=N) + D(H–I) − D(P=O) − D(P–N) − D(N–H) − D(C–I) where D refers to the relevant molar bond enthalpy. Calculation of E_1^0 was made from D values in ref. 6.