PhD Thesis

Kinetic and Product Analytical Study of the Effect of Substituents upon the Solvolysis of Benzyl Azoxytosylate in Aqueous Trifluoroethanol.

Isobel M. Gordon

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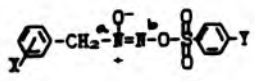
Acknowledgements

I should like to thank Dr. Howard Maskill for his guidance and unfailing patience. My thanks also go to Dr. Phil Methercote for his invaluable assistance with the hplc.

CONTENTS

ABSTRACT

Six variously substituted benzyl azoxytosylates, ((1)a: X = 4-OCH_3, 4-CH_3, 3-CH_3, H, 4-Cl, 3-Cl; Y = 4-CH_3), three 4-methylbenzyl 4-substituted-azoxyarenesulphonates, ((1)b: X = 4-CH_3; Y = CN, Br, OCH_3), three 3-chlorobenzyl 4-substituted-azoxyarenesulphonates, ((1)c: X = 3-Cl; Y = CN, Br, OCH_3) and three 3-chlorobenzyl 4-substituted-arenesulphonates, ((2): X = 3-Cl; Z = CN, Br, OCH_3) have been prepared, and the rates and activation parameters of their solvolyses in 1:1 v/v aqueous 2,2,2-trifluoroethanol studied. For each series of compounds $k^{25.0}$ has been correlated with σ or σ^+ in a Hammett-type study and the following ρ-values were obtained:- (1)a: $\rho(\sigma^+) = -3.27$, $r > 0.999$; (1)b: $\rho(\sigma) = +1.07$, $r = 0.996$; (1)c: $\rho(\sigma) = +0.730$, $r = 0.988$ (three fastest compounds correlated), $\rho(\sigma^+) = +0.685$, $r = 0.989$ (all compounds correlated); (2): $\rho(\sigma) = +1.37$, $r > 0.999$. Using these ρ-values, it has been established, that, in the transition state of the solvolysis of (1), the cleavage of bonds (a) and (b) is concerted. In addition, from the relative magnitudes of the ρ-values, the position of the transition state on the reaction map has been deduced. The unusual correlation of compounds (1)c with σ^+ (ρ is positive) is discussed in terms of resonance stabalisation of the ground state by electron withdrawing substituents. Product analyses (some of a preliminary nature) have been carried out for the solvolyses of (1)a: X = 4-CH_3, 4-OCH_3, 3-Cl and the arenesulphonates, (2).



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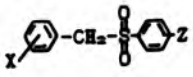

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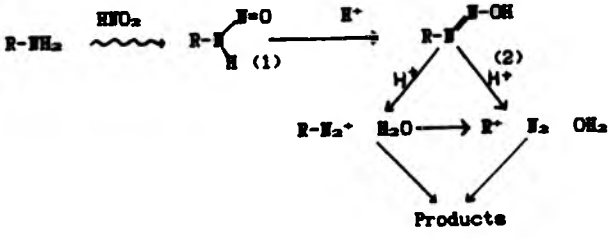
SECTION 1

INTRODUCTION

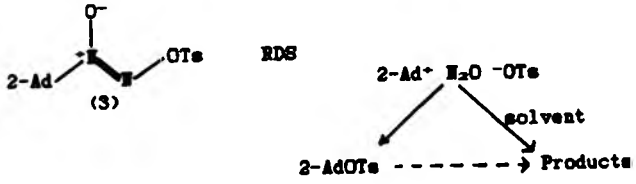
1 **Introduction**

Solvolytic deamination of primary alkylamines by nitrous acid is a complex reaction proceeding through several steps and involving unstable diazo-intermediates, Scheme (1)[1]. The complicated rate laws of the process relate to the initial nitrosation steps and therefore the early kinetic studies yielded no information about the product-forming steps. That is, no direct evidence could be gained from kinetics about the step involving the cleavage of the carbon-nitrogen bond, or about subsequent reactions of the carbonium ion intermediates which were believed to be involved.



Scheme (1)

When 2-adamantyl azoxytosylate (3) was prepared and was found to undergo solvolytic reactions[2], Scheme (2), it became clear that a much sought-after stable analogue of intermediate (2) in Scheme (1) had been



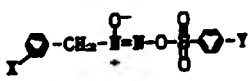
Scheme (2)

discovered. Further, the solvolysis of 2-adamantyl azoxytosylate was obviously related to the solvolysis of 2-adamantyl arenesulphonates and halides - substrates of central importance in modern solvolytic studies[3]. Indeed, in various solvents, (3) was found to react by an initial rate-limiting fragmentation[2], Scheme (2), and although the rate-determining step in the solvolysis of (3) mechanistically resembles the fragmentation of diazo intermediates in the deamination of 2-adamantylamine, it is much slower and the subsequent formation of products from the cationic intermediate from (3) resembles more closely that from the solvolysis of 2-adamantyl tosylate than that in the deamination of 2-adamantylamine[4].

Of great interest, then, is the nature of the transition state in the solvolysis of azoxytosylates and its position on the reaction co-ordinate. As a recent product analytical study has established that benzyl azoxytosylate also reacts by an initial rate-determining fragmentation[5] (although the products are subsequently formed through two intermediates of different activity) the obvious route to this information is a Hammett-type investigation of the benzyl system. This work has been carried out and forms the basis of this thesis.

Six substituted benzyl azoxytosylates ((4), X = 4-OCH_3, 4-CH_3, 3-CH_3, H, 4-Cl, 3-Cl; Y = CH_3), four substituted 4-methylbenzyl azoxyarenesulphonates ((4), X = 4-CH_3; Y = 4-CN, 4-Br, 4-OCH_3, 4-CH_3) and four substituted 3-chlorobenzyl azoxyarenesulphonates ((4) X = 3-Cl; Y = 4-CN, 4-Br, 4-OCH_3, 4-CH_3) have been prepared and the kinetics of their solvolyses in 1:1 v/v aqueous 2,2,2-trifluoroethanol have been investigated. The activation parameters have been determined and the rate constants at 25°C have been correlated by Hammett plots, (Figures

(3) and (4), Appendix (1)). In addition, the solvolysis of three substituted 3-chlorobenzyl arenesulphonates ((5) X = 3-Cl; Z = 4-Br, 4-CH_3, 4-OCH_3) have been studied in the same solvent and another Hammett plot constructed, (Figure (3), Appendix (1)). Product analyses, (some of a preliminary nature) have also been carried out.



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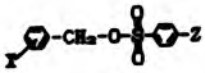

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SECTION 2

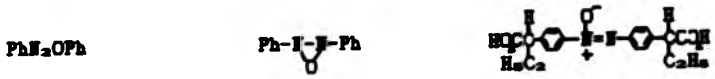
BACKGROUND

2 **BACKGROUND**

2.1 Azoxy Compounds

2.1.1 History

The existence of the azoxy grouping, (-N(O)=N-), was first reported almost 150 years ago when azoxybenzene (6) was obtained on the reduction of nitrobenzene with alcoholic potassium hydroxide[6]. Initially it was proposed that the structural formula involved a 3 membered ring[7] (7), but when four stable optical isomers of α-p-azoxyphenylbutyric acid (8) were resolved and characterised it became clear that the azoxy group was unsymmetrical, and the oxygen was attached not to both nitrogens but only to one[8]. As a result, asymmetrically substituted azoxybenzenes can exist as two structural isomers, (9) and (10), and indeed, most methods of preparation of azoxybenzenes (see Section 2.2) yield mixtures of isomers. In the early days the assignment of



(6) (7) (8)

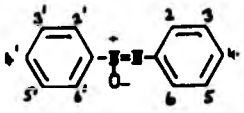
(9) (10)

structure to an isomer was imprecise and was usually made by comparison of their substitution reactions. For this reason surprisingly little is known of how the isomers' properties and reactivities compare, (see Section 2.3).

Cis/trans isomerism (11) also occurs and rearrangement between isomers is catalysed by heat, light and halogens[9]. These isomers have different UV spectra and dipole moments[10]. It has been found that in general the known cis (Z) aliphatic azoxy compounds are all high melting, in contrast to the trans (E) isomers[11]. This is thought to be due either to their higher dipole moment or to partial dimeric association.

(11)

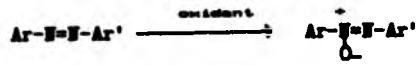
The structural formulae are now written and numbered as:



and in the IUPAC naming system the prefix NNO- or ONN- identifies the nitrogen to which the oxygen is attached.

2.1.2 Preparation[11,12]

There are several methods of preparation, including a) the reduction of nitro and nitroso compounds; b) condensation of a nitrosobenzene with an arylhydroxylamine; c) oxidation of arylamines and N-arylhydroxylamines, and d) by selective substitution on an aromatic azoxy compound, which are fully catalogued in reference 11a, pages 118-121. Until recently, however, the most common and reliable method of preparing unsymmetrical azoxy compounds was by oxidation of the suitably substituted azo compound, (Scheme (3)). Various



Scheme (3).

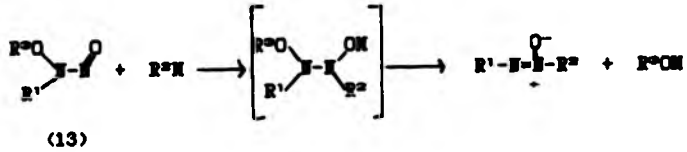
oxidants have been used, including hydrogen peroxide[13], peroxyacetic acid[14] and peroxybenzoic acid[15].

A more versatile method was developed by Stevens[16] in 1964, when he prepared a series of azoxytosylates, (12). The tosylate anion was found to be easily displaced using Grignard reagents, (Scheme (4)) which enabled large variety of substituents to be introduced to the azoxy group.

(12)

Scheme (4)

Organometallic reagents were also used by Bean and his co-workers[17] in their attempt to use N-nitroso-O,N-dialkylhydroxylamines, ((13), (Scheme (5))



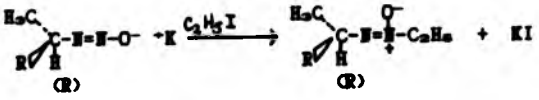
(13)

Scheme (5)

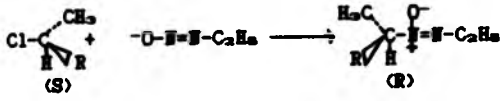
to prepare unsymmetrical azoxyalkanes. However the synthesis is effectvely restricted to primary alkyllithium reagents and the low yields obtained make the reaction of little preparative value. It should be mentioned here that some cyclic azoxy compounds have been prepared using UV radiation[18], (see also Section 2.1.4.3), but again the preparative value of this method is small.

More recently an unambiguous synthesis of azoxyalkanes containing two different primary or secondary alkyl groups has been developed by Moss[19]. Amines are converted to diazoates[20] and are then alkylated using Meerwein's reagent or alkyl iodides. Alkylation is on nitrogen, giving trans-azoxyalkanes with the oxygen on the nitrogen that bears the group from the alkylating agent, (Scheme (6)). This method can be used to prepare optically pure azoxy compounds with a chiral centre α to the N on either side[21], (Schemes (7) and (8)).

Scheme (6)



Scheme (7)



Scheme (8)

2.1.3 Structure and Properties[22].

X-ray studies show that the azoxy N(O)=N double bond is shorter than the azo linkage, probably due to the change in electronegativity of the nitrogen to which the oxygen is attached[23]. Both C-N bonds are longer than in the

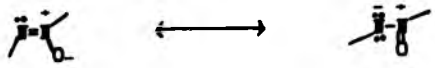
corresponding azo compound. As one nitrogen atom is tetravalent, some increase in its C-N bond length is expected, but why the other C-N is also increased is not known.

The dissociation enthalpies of the N-O bonds (D(N-O)), in azoxybenzene, n-propyldiazene N-oxide, di-t-butyldiazine N-oxide and a series of nitrones have

Table (1)

SUBSTRATE	D(N-O)/kJmol^{-1}
Ph-N(O)=N-Ph	321.5
C_6H_7-N(O)=N-C_6H_7	331.5
$(CH_3)_3C$-N(O)=N-$C(CH_3)_3$	321.5
Ph-CH=N(O)-Ph	264.9

been determined[24], (Table (1)). It can be seen that D(N-O) is about 10kJmol^{-1} less in the di-t-butyl azoxy compound than in the n-propyl analogue, consistant with the greater steric strain in the former. D(N-O) of azoxybenzene is similar to that of the alkylazoxy compounds but around 60kJmol^{-1} greater than in the diphenyl nitrone. It was concluded that the double bond character of the N-O bond is greater in the azoxy grouping than in nitrones (as the electronegativity of nitrogen is higher than that of carbon, resonance forms of the type in Scheme (9) are possible with the azoxy group) a suggestion supported by some qualitative valence bond studies[25].



Scheme (9)

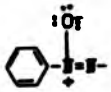
2.1.3.1 Spectra[26]

Little is known about the molecular orbitals present on the azoxy structure. In increasing energy are thought to be a non-bonding orbital located mainly on O (n_-), a non-bonding orbital mainly on the N that is not attached to

the O (n_N) and π and π^* orbitals. It is assumed that the electronic transitions of lowest energy are π-π^*, n_N-π^* and n_O-π^*. In the infrared spectrum three characteristic absorptions are observed at 1500, 1460 and 1295cm^{-1}.

2.1.3.2 Electronic Effects of the Azoxy Group

The σ_p and σ_m values of the phenyl-ONN-azoxy, (14) and phenyl-NNO-azoxy, (15) groups have been determined by measuring the pKa values of the four phenylazoxybenzoic acids in 50% aqueous ethanol[27], (Table, (2)).



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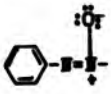


(15)

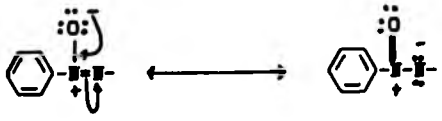
Table (2)

ACID	pKa	σ
3-Phenyl-ONN-azoxybenzoic acid	5.17	+0.24
3-Phenyl-NNO-azoxybenzoic acid	4.79	+0.50
4-Phenyl-ONN-azoxybenzoic acid	5.12	+0.27
4-Phenyl-NNO-azoxybenzoic acid	4.70	+0.56

While it was predicted from its assumed electronic structure that the phenyl-NNO-azoxy group is electron attracting by induction (-I), and by resonance (-R), the results of the rates and products of chlorination[28] and other electrophilic substitutions[29] of azoxybenzene show that the phenyl-ONN-azoxy group is also ortho/para directing and activating. This isomer therefore, as with the phenylazo group, can be +R or -R depending on the electronic demands placed on it.

The results in Table (2) indicate that phenyl-NNO-azoxy and phenyl-ONN-azoxy can be regarded as modified nitro (with one of the oxygens replaced by

phenylimino group) and phenylazo groups respectively. In the former case introduction of the less electronegative group leads to a reduction of σ_m by one third. (σ_m for NO_2 = 0.74). The σ values for the phenyl-CNN-azoxy and the phenylazo groups are very close, (σ_m for phenylazo = +0.28) surprisingly so as it was expected that there would be a large increase in -I character of the group with the addition of oxygen to the -N=N- moiety, in view of the increase in -I on the conversion of pyridine to its N-oxide[20]. This expected effect is thought to be offset by a resonance interaction that effectively increases the electron density on the adjacent nitrogen, (Scheme (10)).



Scheme (10)

2.1.4 Reactions of Azoxy Compounds.

2.1.4.1 Oxidation and Reduction.

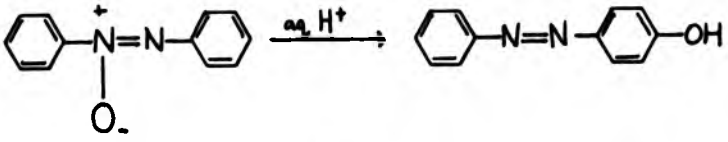
Little work has been done on the oxidation of azoxy compounds other than to observe the difference in ease of oxidation of the CNN and NNO isomers of some compounds; the azoxy-oxygen has been shown to protect the substitutents in the adjacent ring from oxidation. For example, NNO-p-aminoazoxybenzene is readily oxidised whereas the CNN isomer is not[21].

The action of various reducing agents (eg. zinc, $LiAlH_4$, sulphide $SnCl_2/HCl$[22] and nickel/aluminium alloy[23]) on azoxy compounds results in the formation of azo and hydrazo compounds,and finally the corresponding

arylamines. Photochemical, electrochemical and polarographic methods have also been employed[21,24] to bring about reduction.

2.1.4.2 The Wallach Reaction.

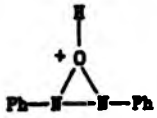
The Wallach rearrangement, (Scheme, (11)) is the most investigated of the reactions of azoxy compounds. It was first observed in 1880 that the action of



Scheme (11)

warm dilute sulphuric acid causes azoxybenzenes to rearrange to the corresponding para-hydroxy azo compound[25]. Studies showed that in the products of rearrangement of unsymmetrical azoxybenzenes the hydroxyl group is always found on the unsubstituted ring, depending neither on the substituent present in the other ring, nor on the distance between the oxygen atom and the available position[26].

The reaction has been studied in depth with different combinations of substituents and reaction conditions, but it was not until the advent of isotopic labelling techniques that it became obvious that the rearrangement is intermolecular; the hydroxy oxygen in the rearranged product comes from the reaction medium[27]. In explanation, various intermediates, of the type of (16)[28] and even (17)[29] (a symmetrical dication), have been invoked. These species can be attacked by a molecule of water with equal readiness in either ring.



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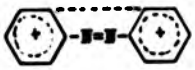
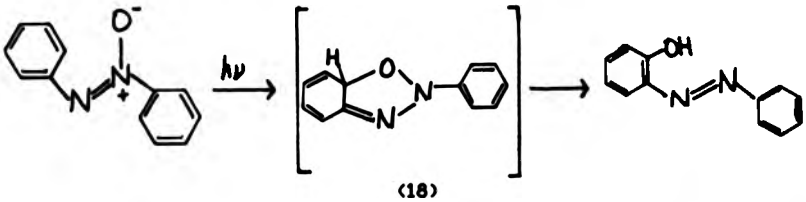


(17)

Under the influence of UV light (cf. also Section 2.1.4.3) an ortho rearrangement occurs[40]. Tracer studies indicated an intramolecular mechanism[41] involving a 5 membered oxygen bridged ring[42], (Scheme (12)).The involvement of radicals has been suggested[43], but during ^{18}O labelling studies no magnetic



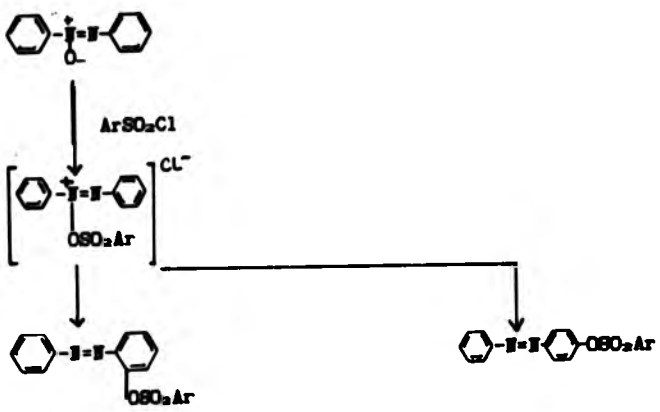
(18)

Scheme (12)

isotope effects associated with radical pairs were observed[44]. It has been concluded from the lack of a nitrogen kinetic isotope effect that if the oxadiazole intermediate (18) is involved in the rearrangement, then its formation rather than its decomposition is rate limiting. In addition, it is suggested that the formation of (18) is a ground state, rather than an electronically excited state reaction[45]. There is also evidence that some diphenyloxadiaziridine is formed in a side reaction at the beginning of irradiation[46].

Similar to the Wallach rearrangement is the reaction that occurs between azoxybenzene and arenesulphonyl chlorides[47]. The ortho- and para-

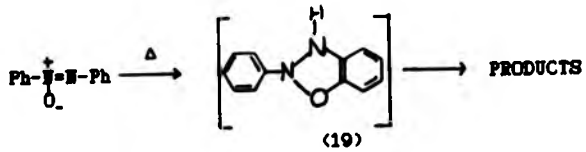
arenesulphonyloxyazobenzenes are the products of the proposed five step mechanism, (Scheme (13)). Isotopic labelling studies show the ortho and para rearrangements are intra and intermolecular respectively.



Scheme (13)

2.1 4.3 Reactions Involving Radicals

Heating azoalkanes generally causes loss of N_2, but the analogous loss of N_2O from azoxyalkanes does not occur[48]. It is suggested from molecular orbital arguments that this reaction is at least partially forbidden[48]. Instead, pyrolysis of azoxybenzene at 600°C yields a variety of products[50,51]

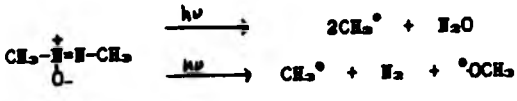


(19)

Scheme (14)

biphenyl (34%), aniline (30%), phenol (15%) and diphenylamine (10%). A radical mechanism initially involving the cyclic intermediate (19) was suggested to account for this product distribution, (Scheme 14).

The photolysis of aromatic azoxy compounds has already been discussed in Section 2.1.4.2 in terms of the much studied Wallach Reaction, so only the photolysis of azoxyalkanes are considered here. Gowenlock[82] studied the gas phase photolysis of azoxymethane, (20) and found it similar to that of the azoalkanes. Relatively short wavelengths of radiation were required (λ=220nm) and the reaction was found to go via two primary dissociation pathways, (Scheme (15)). In the case of the photolysis of some higher azoxy compounds, the intermediacy of oxaziridines has been established[83,84], and the first documented example of a cis azoxyalkane was prepared, (Scheme (16))[84].



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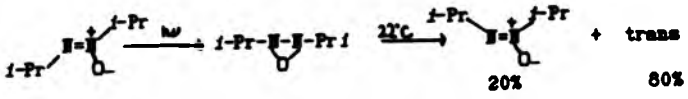
Scheme (15)

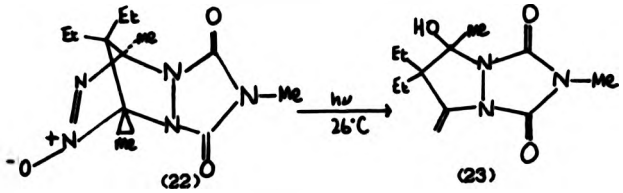


Scheme (16)

A radical mechanism is also implicated in the photolysis of simple bicyclic azoxy compounds[83], (eg. 2,3-diazabicyclo[2.2.1]hept-2-ene N-oxide, (21)) when polymeric products were obtained. However, photolysis of (22) gave (23), a product that was stable to heat. This relatively clean conversion could not be

explained. It was assumed that the presence of the cross-ring non bonded nitrogens influence the photochemical behaviour of the azoxy group.

(21)

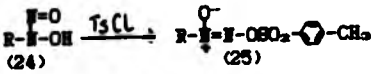


(22) (23)

2.1.5 **Azoxytosylates**

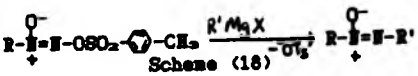
2.1 5.1 **Background**

As mentioned in Section 2.1.2, these compounds were first synthesised from the reaction of N-substituted,N-nitrosohydroxylamines (24) with tosyl chloride in the presence of a base, (Scheme (17)) by Stevens in 1964[16], but only with the view to using a Grignard reagent to displace the tosylate by an R'- group (aryl or alkyl) of choice, (Scheme, (18)). Several azoxytosylates



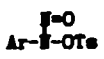
(24) (25)

Scheme (17)



Scheme (18)

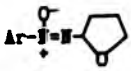
((25), R = alkyl and aryl) were synthesised as crystalline solids in high yield. An alternative structure (26) was ruled out as an attack by Grignard reagents on the available N=O function of (26) was predicted to lead to azoxy compounds isomeric with those actually obtained. In addition, an attempt to prepare (26)



(26)

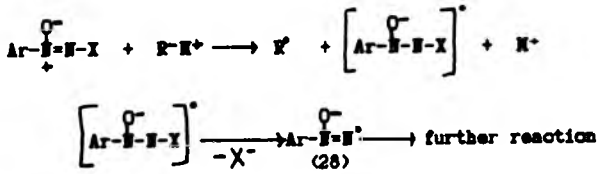
by the nitrosation of O-tosyl-N-methylhydroxylamine yielded only methyl tosylate and N_2O[22a]. Nmr[18,22,27], UV[22a] and X-ray[22a] studies confirmed the postulated structure, and it was also apparent by X-ray that for (25), (R=C_6H_5[22a] and 2-adamantyl[22a]) the oxygens attached to the nitrogens are cis orientated.

Evidence that the Grignard reaction (Scheme, (18)), involved radical intermediates was found when the major by-products of the reactions in tetrahydrofuran (THF) were isolated and found to be N-aryl-N'-(2-tetrahydrofuryl)diimide N-oxides[24] (27). To take this into account a radical



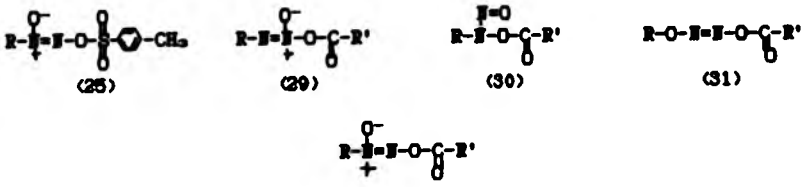
(27)

mechanism, (Scheme (19)) was proposed; radical abstraction of H from THF would lead to the 2-tetrahydrofuryl radical. However attempts to identify (28) by esr were not successful.



Scheme (19)

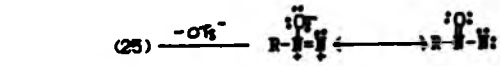
In 1970[89] during work aimed at the determination of the mechanisms and intermediates involved in deamination reactions (Section 2.3), it became obvious that the N'-tosyloxydiimide-N-oxide structure (25) was surprisingly stable, especially in comparison with analogous acyl species of the type (29), (30) and (31). However, the attempt to prepare (32) by acylation of salts of nitrosohydroxylamines failed.



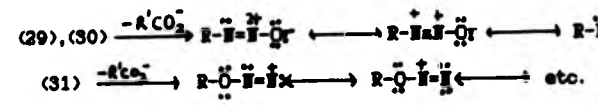
(25) (29) (30) (31)

(32)

The factor that was invoked to explain the stability of (25) was the resonance stabilisation of the reaction intermediates; ionisation of (25) leads to a cation for which no resonance contributor can be drawn with a full octet about each atom, (Scheme (20)), but no such difficulty occurs with the ions derived from (29), (30), (Schemes (21)), and (31).



Scheme (20)

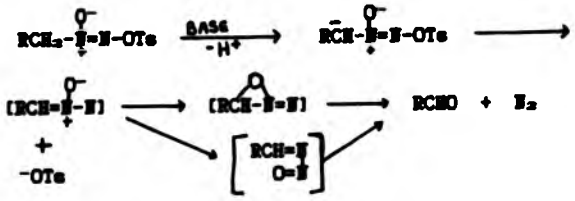


Scheme (21)

2.1 5.2 Reactions of Azoxytosylates

The treatment of a series of primary alkyl azoxytosylates with potassium t-butoxide in t-butyl alcohol produced the corresponding aldehyde, nitrogen and tosylate ion. Secondary alkyl derivatives reacted similarily but more slowly,

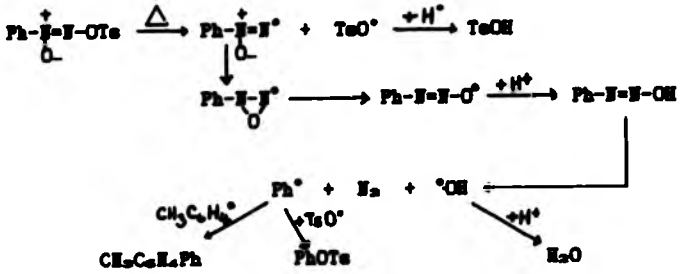
yielding the corresponding ketone[80]. The mechanism in Scheme (22) was proposed, and when the reactions were carried out in the deuterated alcohol, (R=C_6H_5 and $(CH_2)_2$), no deuterium were detected in unreacted starting material; decomposition was faster than exchange.



Scheme (22)

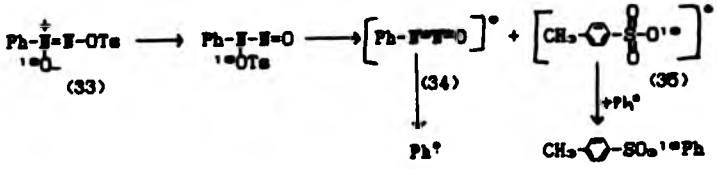
No information was obtained about the oxygen transfer step, but the authors speculated that it is intramolecular, either through oxaziridine formation followed by nitrogen elimination, or by isomerisation to a nitrosimine, (Scheme (22)). There was no evidence that any solvolysis reaction was taking place, unlike in the case of the acyl analogues (32) which are found to solvolyse in chloroform[80]. In the absence of base, decomposition did not occur until the temperature was raised to over 180°C, whereupon thermal elimination of nitrous oxide and toluenesulphonic acid yielded the corresponding olefin. The azoxytosylates also decomposed photochemically eliminating nitrous oxide and forming alkyl tosylate[80].

In general aromatic azoxytosylates have been found to be stable to heat up to 110°C, whereupon they decompose, largely to the corresponding tosylates. Dorko and Stevens[80b] suggested that the reaction of phenyl azoxytosylate in boiling toluene proceeded through an oxadiaziridinyl radical, with migration of the azoxy oxygen from one nitrogen to the other, (Scheme, (23)). Then when Shemyakin and his co-workers[81] refluxed isotopically labelled phenyl azoxytosylate (^{18}O in the azoxy-oxygen, (33)) in toluene they found the mass



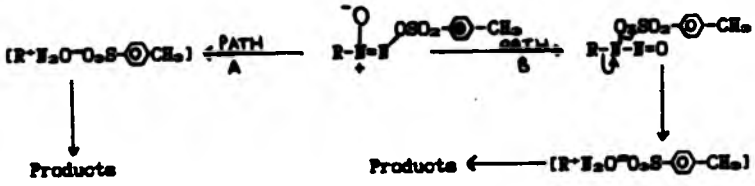
Scheme (23)

spectrum of the product tosylate contained the label equally distributed amongst all the three oxygens. They concluded that an initial migration of the tosyl group from oxygen to oxygen was required to accomodate this and the Scheme (24) was proposed. The formation of the tosyloxy radical (35) allows the oxygens to become equivalent. The subsequent decomposition of radical (34) to Ph· was thought to proceed as in Scheme (23).



Scheme (24)

In contrast, when the thermal decompositions of benzyl and isobutyl azoxytosylates in chloroform were studied[23], the kinetics were first order, the products were the corresponding esters, alkenes and H_2O, and the fact that no hexachloroethane was formed suggested that the reaction was ionic. Rather than a direct ionisation (Path A, Scheme (25), a more complex mechanism was thought to be involved (Path B) as there is only a relatively small rate difference between R=isobutyl and R=benzyl.



Scheme (25).

2.1.5.3 Solvolysis of Azoxytosylates

It is surprising that the solvolysis reactions of these substrates have not been investigated before as they represent an important mechanistic link between solvolytic deamination and the solvolysis of alkyl arenesulphonates (cf. Sections 2.3 and 2.2 respectively). However it was not until the beginning of the 1980s and the advent of the use of highly-ionising weakly-nucleophilic solvents like hexafluoroisopropan-2-ol (HFIP) and trifluoroethanol (TFE) that the solvolysis of alkyl and benzyl azoxytosylates began to be studied in depth[2,5,63], and this has resulted in a fuller understanding of the processes involved in both of the above reaction-types.

The direction that the work in this area has taken is recounted briefly here and the consequences of the results are discussed more fully in the relevant Sections, (2.2 and 2.3).

2-Adamantyl Azoxytosylate[2,63].

The products of solvolysis of 2-adamantyl azoxytosylate (36) were found to change with solvent. In highly ionising solvents such as HFIP, TFE and 50% aqueous ethanol the reaction was fastest and the adamantyl products were

(36)

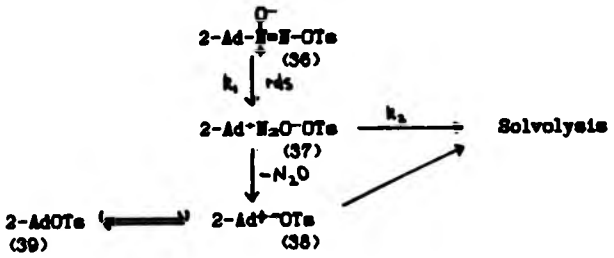
exclusively solvent derived. In ethanol, low yields of the arenesulphonate (2-AdOTs) were obtained, and in non-nucleophilic solvents with poor ion-pair stabilising properties such as chloroform and toluene the arenesulphonate was the only product, and the reaction was slowest. It was concluded that neither a radical mechanism nor a base induced mechanism of the type established by Freeman and Lillwitz[80] (Section 2.1.5.2) were involved, as neither adamantane nor adamantanone were detected as products.

An appreciable secondary α-deuterium kinetic isotope effect was found showing that the cleavage of the C-H bond is involved in the rate determining step, and a sequential two step mechanism via 2-AdOTs as a relatively long lived intermediate was ruled out by the observed identical first order rate constants for the decrease in concentration of (36) by UV spectroscopy and the increase in acid concentration by conductivity.

These results agree with a mechanism involving an initial unimolecular rate-determining synchronous fragmentation of the substrate to give nitrous oxide-separated ion-pair, ((37), Scheme (26)). This ion-pair is then captured by solvent to give solvolysis products or in less polar media undergoes ion-pair combination to yield 2-adamantyl tosylate (39). In ethanol and aqueous ethanol (39) is formed in parallel with the solvolysis product.

This formation of 2-AdOTs (39) from the ion-pair (37) separated by several bond lengths by the N_2O molecule in such a nucleophilic medium as ethanol indicates that ion-pair recombination should also occur by internal return of the intimate ion-pair (38) implicated in the solvolysis of 2-

adamantyl tosylate (39) itself, and therefore this evidence requires the initial ionisation in the solvolysis of such simple secondary substrates to be reversible.(see Section 2.2).

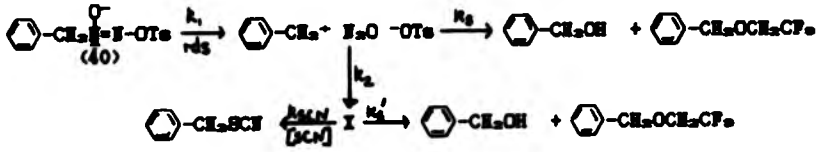


Scheme (26)

Benzyl azoxytosylates[64].

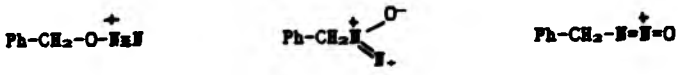
The prospect of the unambiguous generation of a range of variously substituted benzyl carbonium ions in solution led to an initial study of the solvolysis of benzyl azoxytosylate (40). Its solvolysis in 1:1 v/v H_2O/TFE yielded the expected benzyl alcohol and benzyl trifluoroethyl ether as products[64a] and, by inference from the solvolysis of 2-adamantyl azoxytosylate, the results were interpretated in terms of an initial rate-determining ionisation, and this was confirmed when added nucleophilic solutes (SCN^-, Br^-, I^-) formed substitution products but did not significantly effect the rate. This indicated that an intermediate was formed, in or after the rate-determining step, which was long enough lived to diffuse through the bulk solvent and be trapped by the nucleophile. While increasing the concentration of the NaSCN in the reaction medium increased the yield of the substitution product, extrapolation to infinite concentration of NaSCN (by a double reciprocal plot of $1/[PhCH_2SCN]$ versus $1/[NaSCN]$) led to a limiting yield of 47% $PhCH_2SCN$, and it

was concluded that another shorter lived intermediate, too short-lived to escape the solvent cage and intercept the solute, was required to account for the other 53% of the product, (Scheme (27)).



Scheme (27)

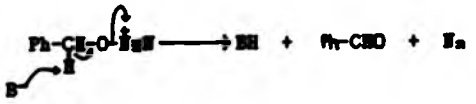
It was assumed that the benzyl carbonium ion itself was the short-lived intermediate, and initially it was thought that benzyl tosylate was the other, longer lived intermediate. However, comparison of the kinetic analysis of Scheme (27) with data of SCN^- trapping experiments with benzyl tosylate itself showed that the unknown intermediate was a more reactive, shorter-lived species than $PhCH_2OTs$. Other likely candidates were sought, and although H_2O is only a weak nucleophile it is well positioned to intercept the benzyl carbonium ion, and



(41) (42) (43)

therefore structures (41), (42) and (43) were then considered as possible intermediates. Direct evidence that combination occurs at the oxygen to give (41) was provided when the benzaldehyde was detected as a minor product in the solvolysis of (40) in the presence of bases, (see below). A theoretical study using *ab initio* molecular-orbital theory confirms that linkage with the H_2O is likely to be through the oxygen[ee], and proton abstraction and loss of H_2, from

(41) (Scheme (28)) was considered a reasonable mechanism for the generation of benzaldehyde in the presence of bases.



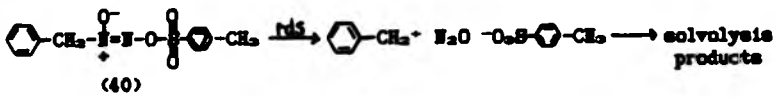
(41)

Scheme (28)

When the effects of adding non-nucleophilic basic solutes like sodium acetate to the reaction medium were investigated[54], an appreciable rate effect and two new products (trifluoroethyl tosylate and benzaldehyde (mentioned above)) were detected by HPLC. In addition acidification of the reaction medium allowed analysis of N-nitrosobenzylhydroxylamine by isolation and comparison with an authentic sample. When the sodium acetate was buffered with acetic acid, the rate enhancements were small but dependant on the buffer ratio, indicating that catalysis was by the small equilibrium concentration of the conjugate base of the solvent, $CF_3CH_2O^-$. The kinetic results of the reaction with unbuffered sodium acetate are not so clearcut but it is thought that the larger rate enhancement is induced mainly by $CF_3CH_2O^-$ too.

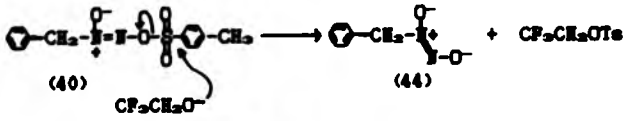
The formation of trifluoroethyl tosylate required nucleophilic attack at the sulphur of the substrate with displacement of the N-benzylazoxy anion (44) (isolated as N-nitrosobenzylhydroxylamine after acidification) in a non-solvolytic reaction, (Scheme (30)). Benzyl azoxytosylate was thus found to be an unusual substrate in that it undergoes concurrent solvolytic and non-solvolytic reactions involving electron flow in opposite directions. In the unimolecular heterolysis of benzyl azoxytosylate ((40), Scheme (29)), the electron flow is in one direction and the bimolecular nucleophilic attack at sulphur it is in the

other, (Scheme (30)). In addition, it was found that imidazole (buffered with imidazolium perchlorate) was a better catalyst for the reaction of CF_3CH_2OH



(40)

Scheme (29)



Scheme (30)

with (40) than acetate, and here the identification of another product - N-tosylimidazole - implies the involvement of another non-solvolytic reaction: direct nucleophilic attack by the base at the sulphur of benzyl azoxytosylate.

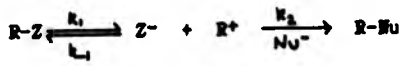
The logical step to follow this work on benzyl azoxytosylate is a Hammett-type investigation (see Section 2.4) of the behaviour during solvolysis of a series of substituted benzyl azoxytosylates, as this approach would be expected to yield useful information about the nature and position of the transition state of the solvolysis of azoxytosylates. An additional benefit was expected to be the unambiguous generation in solution of benzyl carbonium ions of a wide range of reactivity. This has not previously been possible as benzyl arenesulphonates and halides cease to react via the S_N1 mechanism when electron-withdrawing groups are introduced to the ring, and therefore it has been impossible to separate confidently the effect of a substituent upon the S_N1 reaction from its effect upon a potential concurrent S_N2 reaction, (see Section 2.2). The Hammett approach to azoxytosylate solvolysis has been made and forms the basis of this thesis.

2.2 Nucleophilic Substitution Mechanisms[cont.]

2.2.1 S_N1 and S_N2

During the 1930s, in a brilliant series of studies, Hughes and Ingold established the existence of the now well known mechanistic duality in nucleophilic substitution reactions: the one step, concerted S_N2 mechanism, (Scheme (31)), and the dissociation mechanism, termed S_N1, (Scheme (32))[67].

Scheme (31)

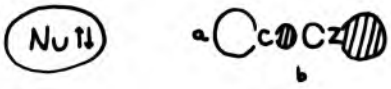


Scheme (32)

The S_N2 mechanism is characterised by second order kinetics, and by inversion of configuration at the site of nucleophilic attack. When it was determined that the rate of inversion was, within experimental error, the same as the rate of reaction, it was established that inversion accompanied each and every nucleophilic attack, and was not just an occasional event. The stereochemistry of the reaction meant that the nucleophile must approach the site of substitution from the side opposite to the leaving group, and the stereochemical correlation

between the two showed that both the groups were associated in the transition state[29].

This behaviour was originally rationalised in terms of the electrostatic repulsion between the nucleophile and the leaving group, however even a reaction like that between N_3^- + R-SMe_2^+ occurs with inversion, where it might have been expected that Coulombic forces would encourage front side attack. Frontier molecular orbital theory provides a more satisfactory theory, (Scheme (33)). The HOMO of the nucleophile and the LUMO of the substrate are the molecular orbitals that are chiefly involved. The overlap is bonding when the nucleophile approaches from the opposite side to the leaving group, (at *a*) but the approach



Scheme (33)

from the front, (at *b*) is both bonding and anti-bonding. The former is preferred[29].

S_N1 reactions are more difficult to characterise, however the common ion effect and the effect of added salts are indicative of its presence. If the steady state approximation is applied to the equation in Scheme (32), the following expression can be derived. In the early stages

$$\text{Rate} = k_1k_2[RZ][Nu^-] \;/\; (k_{-1}[Z^-] + k_2[Nu^-])$$

Equation (1)

of the reaction, $[Z^-]$ is small and the kinetics simplify to first order with the rate equal to $k_1[RZ]$, independant of the concentration or nature of the nucleophile. As the reaction proceeds $[Z^-]$ builds up and the reaction should slow down according to Equation (1). The addition of extra Z^- should also slow the reaction, (the common ion effect)[70]. When the reactions of benzhydryl chloride with different nucleophiles in liquid sulphur dioxide were studied, both of these experimental predictions were observed[71].

However solvolytic reactions are usually carried out in solvents that facilitate the ionisation step and also act as the nucleophile in the second step. The nucleophile concentration is then effectively constant and to achieve significant changes in concentration of a nucleophilic solvent, fundamental changes to the whole system must be made. This makes the origin of rate changes ambiguous.

The addition of a non-common ion that is itself strongly nucleophilic (azide is often used) is often useful in distinguishing between S_N1 and S_N2 behaviour[72]. If the added nucleophile reacts directly with the substrate in a S_N2 mechanism, then it will accelerate the reaction in direct proportion to the amount of alkyl azide produced. In an S_N1 reaction the rate-limiting and product-forming steps are independent of each other, and the formation of the alkyl azide is not associated with any increase in rate.

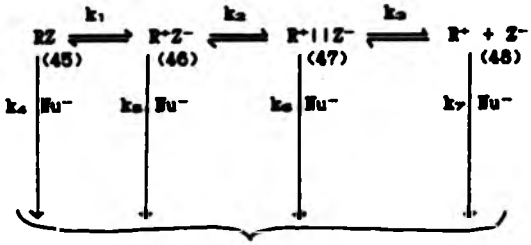
It can be seen that in the extreme case the S_N1 mechanism generates a free, dissociated, planar carbonium ion. This species is equally susceptible to attack by nucleophile from either side and therefore an S_N1 substitution on a chiral substrate should lead to total racemisation. Although some first-order substitutions do give complete

racemisation, many others do not. Typically there is 5 to 20% inversion[68a]. Several suggestions have been made in explanation including the theories that the carbonium ion may not become completely free, and is shielded from attack on one side by the leaving group, (see also Section 2.2.2) or it may have a lifetime so short that it does not have time to attain planarity before the nucleophile attacks.

In summary, the difference between Hughes' and Ingold's S_N1 and S_N2 mechanisms is the timing of the steps. In the former, first the leaving group leaves, then the carbonium ion is captured by the nucleophile. In the latter, approach of the nucleophile and departure of the leaving group are concerted. These mechanisms are still relevant today and are useful models for the description of many substitution reactions. However they are not adequate models for the description of all S_N1 reactions (see Section 2.2.2) or the processes that occur in "borderline" solvolyses (see Section 2.2.3).

2.2.2 Ion Pairs

In 1956 it was suggested by Winstein[73] that a mechanism that involved ion pairs (Scheme (34)) gave the best explanation of the observation that many first order substitutions proceeded without complete racemisation. The complete ionisation of a chiral substrate to a planar carbonium ion destroys all chirality. The two alternative product-forming transition states (front-side and rear-side attack) are enantiomeric and of equal energy. Partial racemisation implies that



Scheme (34)

there are two transition states of different energies, as in Figure (1). Where R*-Z represents the substrate and R*-Nu and Nu-R* represent the substitution products with retained and inverted configurations respectively. In 1940 Hammett[74] had proposed that the nature of the

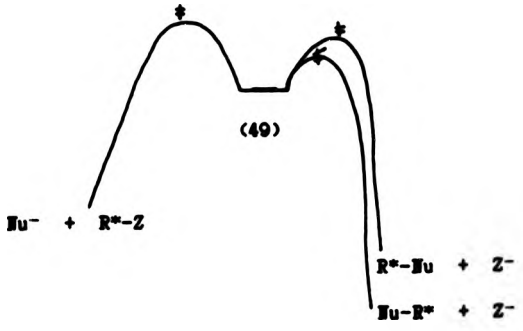
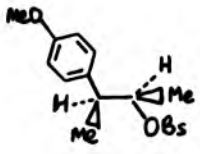


Figure (1)

intermediate (49) was a partially dissociated system in which the covalent bonding was largely replaced by electrostatic attraction but with the two ions still held intimately together with a solvent cage, called an ion pair. Winstein confirmed this idea and extended it to show that in some cases there must be two different types of ion pair on the

path between the covalent compound and the fully dissociated ions. His mechanism includes the following ion pair types; intimate, where the ions are still in the same solvent cage, solvent separated, where perhaps only a single solvent molecule separates them, and finally the fully dissociated ions where the two separated ions are each surrounded by ordered solvation shells, (Structures (46), (47) and (48) respectively in Scheme 34).

Winstein formed his theory from the interpretation of the results of the following experiment[78]. He noticed during the acetolysis of (+)-threo-3-anisylbut-2-yl brosylate (ROBs, (50)), that the rate of racemisation was faster than the rate of solvolysis. The free anisylbutyl cation has a bridged structure, (51) and is achiral, but the racemisation could not be an S_N1-type process with fast reversible dissociation followed by a slower nucleophilic attack as there was no common ion retardation. An ion pair mechanism was a better explanation;



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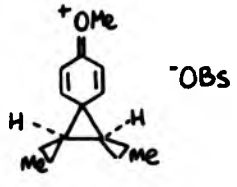
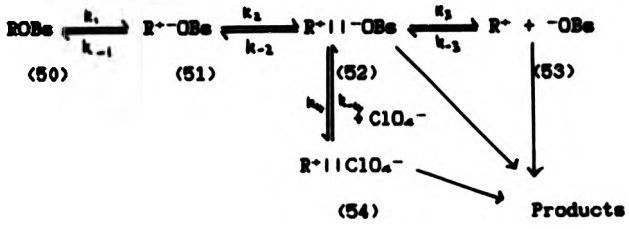


(51)

the racemisation occurred in a rapid equilibrium with the intimate ion pair and in the reverse step the brosylate could easily move to the adjacent carbon to the one it had just left. This was considered to be an intramolecular process with the anion never becoming free, so the addition of more anion did not effect the kinetics. Addition of very low concentrations of perchlorate, a negligibly nucleophilic solute, to the

reaction resulted in a large and unexpected solvolytic rate acceleration. Winstein suggested that the perchlorate intervened in the reaction in an ion pair, thus cutting out a rate-retarding return process. But this could not be the same ion pair, (51) as that above; if there was efficient competition for k_{-1}, (Scheme (35)), the racemisation would be slowed and this was not observed. Winstein proposed that the addition of the perchlorate provided an extra product forming route, (k_4 in Scheme (35)), which accelerates the reaction and, at higher concentrations of perchlorate, k_4 is the main product-forming route. Fast racemisation continues unaffected by later changes in the reaction path.



Scheme (35)

Addition of brosylate was now found to exert a common ion effect on the perchlorate catalysed reaction, in agreement with the proposed mechanism in Scheme (35).

The exact structures of the ion pairs are not known, and it is not even certain that there are only two discrete energy minima on the path between (45) and (48) in Scheme (34) but even using only the two types of ion pair that Winstein proposed there is the possibility of a wide range of reaction types. Reactions with steps 1, 2 or 3 rate-limiting are unimolecular; reactions with steps 4 to 7 rate limiting are bimolecular. In these terms S_N2 mechanism of Hughes and Ingold is

represented by path k_4 and the S_N1 mechanism, originally envisaged with complete dissociation, could have k_1, k_2 or k_3 rate-limiting as long as the product was formed through step 7. The partial racemisation that occurs in many substitution reactions can now be rationalised in terms of the difference in product-forming steps. Usually a reaction that does not go further than the intimate ion-pair proceeds with inversion of configuration (exceptions include the anisylbutyl system where the anion does not have to move round to the other face to induce racemisation), and cases where the cation that is formed is very stable and long-lived enough to allow racemisation to occur within the intimate ion pair, (eg $p\text{-MeOC}_6H_4\overset{+}{C}HMe$)[76]. Partial racemisation comes via step 6 or from a mixture of product-forming steps.

2.2.3 Borderline Behaviour[77]

It is generally agreed that simple primary alkyl substrates (where the saturated system precludes any mesomeric stabilisation of a carbonium ion) react via the classical S_N2 mechanism. The attack of nucleophiles on tertiary substrates is sterically hindered and they are believed to react via one of the S_N1 mechanisms even in the most unfavourable circumstances[78]. However, in most aspects of their reactivity, simple secondary derivatives exhibit behaviour which is intermediate between that of the tertiary and primary substrates. Table (3)[79] presents a broad summary of the data obtained for solvolysis of the three types of alkyl derivative.

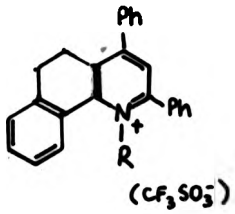
Table (3).

	Primary alkyl	Secondary alkyl	Tertiary alkyl	Expected for S_N1	Expected for S_N2
Stereochemistry	100%inv.	100%inv.	equal inv. and ret	50%inv. 50%ret.	100%inv
Kinetic Effects					
Effect of added nucleophile	large	large	small	small	large
Effect of solvent polarity	small	medium	large	large	small
Effect of solvent nucleophilicity	large	medium	small	small	large

There have been several theories put forward to account for the intermediate behaviour in this borderline region and the controversy is far from settled yet. The ion pair theory can account for a wide variety of mechanistic behaviour but it is so flexible it leaves vague the exact mechanism of reactions that fall between the clearly defined extremes. In terms of S_N1-S_N2 mechanism there had been considerable debate as to whether borderline behaviour arises from a gradual merging of one mechanism into another or whether it could be due to the two mechanisms running in parallel.

The earliest explanation postulated that in the borderline region the S_N1 and S_N2 mechanisms were operating simultaneously on the same substrate[80]. Typical of the evidence for this was the behaviour of the S_N1-hydrolysis of 4-methoxybenzyl chloride in 70% aqueous acetone in the presence of an added azide ions[80a,b], discussed in Section 2.2.4.1.

More recent evidence for the coexistance of concurrent mechanisms in the borderline region is provided by Katritzky and his coworkers[81] in their studies of the nucleophilic displacements of the N-substituents in pyridinium cations, (eg. (55), R = a)2-pentyl, b)3-pentyl; (56), R = $CH_2C_6H_5$), and of the O-substituents in pyrylium cations. Their use of these positively charged substrates which give rise to neutral leaving



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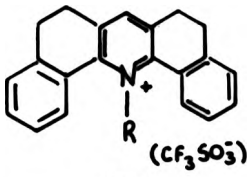
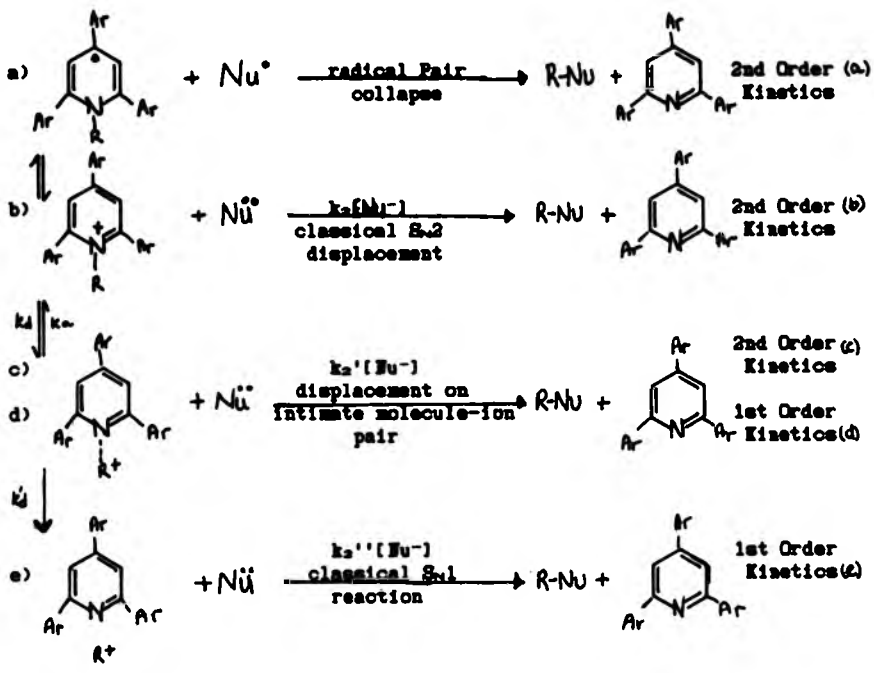


(56)

groups is a new approach to the study of solvolysis mechanisms and has several advantages. Unimolecular reactions of a neutral substrate require to be carried out in media of high dielectric constant as they involve charge creation, and it is not always easy to distinguish the extent to which the solvent is acting as a nucleophile. Substrates with neutral leaving groups can undergo unimolecular reactions in media of low dielectric constant. It is also claimed that the reaction scheme is less complex in that the distinction between a solvent-separated ion pair and a free carbocation disappears: for positively charged substrates simply have intimate ion-molecule pairs and free carbocations, (Scheme (36)). For example, nucleophilic displacement of the N-substituents of pyridinium cations have been shown to proceed by one of five mechanisms[a,c,d] (Scheme (36)) ranging from classical S_N2 displacement to the classical S_N1 reaction depending on the conditions present, and the nature of the alkyl group[a,b,c,d].

The reactions of (55a,b) in chlorobenzene with added nucleophiles (eg. morpholine, anisole, acetic acid etc.) were used to explore the borderline region between classical S_N1, and S_N1 by nucleophilic capture of an ion-molecule pair, (where the formation of the ion-molecule pair is rate-determining), (reactions (c) and (d) in Scheme (36))[a,c,d]. By



Scheme (36)

comparison of the rates and products of each substrate when solvolysed in the presence of nucleophiles of varying strengths and concentrations, the authors conclude that at the borderline both mechanisms (c) and (d) proceed independently without merging. Further, studies of the rates and products of the solvolysis of (56) in chlorobenzene with added nucleophiles provided evidence that there is no merging of the unimolecular (S_N1-type) and bimolecular (S_N2-type) reactions of intimate ion-molecule pairs[9,14]. That is, mechanisms (c) and (d) in scheme (36) were also found to proceed independently.

However the results of more conventional studies have shown that this concurrent mechanism explanation does not fit all borderline

solvolysis data. In some cases common ion rate depression is not observed[78], and in others the products are found to depend on the leaving group[92]. Complete inversion of configuration has also been found[93], whereas with S_N1 and S_N2 mechanisms running concurrently, partial inversion would be expected.

Of the other possibilities that can explain the borderline behaviour of nucleophilic displacement reactions, there are two main schools of thought. The first, proposed by Shiner[94], employs the ion-pair model (Section 2.2.2, Scheme (34)) with any of k_1, k_2, k_3 or k_4 rate-limiting depending on the nature of the secondary alkyl group, leaving group and solvent. It has been suggested, by Sneen that even methyl compounds react via ion pairs[95], but this has been discounted[96] and it has been shown that the ionisation of primary alkyl halides would require more energy than the observed energy of activation of their solvolyses[97].

Shiner's proposal is based on the stereochemistry of the solvolyses and on observation of the wide variation of the size of the secondary kinetic isotope effects in α- and β-deuterated substrates[98]. The magnitude of the α-kinetic isotope effect (α-kie) is used as a measure of the amount of bonding there is between the carbon and the leaving group. The effect is maximal when k_2 is rate limiting. When k_1 is the rate determining step, the C-leaving group bond is less fully broken in the transition state and the α-kie is less. The β-kie is assumed to arise mainly from hyperconjugative interaction in an incipient $H\text{-}C_\beta\text{-}C_\alpha^+$ carbonium ion and is also a measure of bond cleavage.

Some doubt was cast on Shiner's theories when it was claimed that calculations show that the maximum α-kie values expected for reactions with k_2 rate limiting are greater than those actually obtained[99]. This

suggests that there is some S$_N$2 character in all of the solvolysis reactions studied with some nucleophilic bonding by the solvent in the transition state lessening the α-kie effect.

The other school of thought maintains that there is only one type of mechanism, of which the S$_N$1 and S$_N$2 processes represent extremes. It was first postulated by Swain[30] that all nucleophilic substitutions occur with some extent of push on the leaving group from the nucleophile (nucleophilic assistance) and pull on the leaving group by the solvent, (by solvation of the resultant ions). In the "pure" S$_N$1 case there is no nucleophilic assistance and the reaction is favoured in those solvents which promote ionisation of the substrate. The "pure" S$_N$2 case involves full nucleophilic assistance, and the reaction takes place largely independently of the ionising ability of the solvent. In borderline cases different extents of 'push' and 'pull' are involved, and the transition state is like that of the S$_N$2 reaction in which substantial positive charge on carbon has developed and the nucleophilic attachment of the entering group has facilitated the weakening of the carbon to leaving group bond.

Bentley, Schleyer and co-workers[31] have modified this theory slightly by suggesting that varying degrees of nucleophilic solvent assistance to ion pair formation provides the key to the solution of the problem. They measured trends in a variety of mechanistic criteria of the solvolyses of substrates known to react by "borderline" mechanisms. The magnitude of the α-deuterium isotope effect, reflecting the changes in the bonding at the site of substitution; the Winstein-Grunwald "m" parameter[32], measuring the susceptibility of the substrate to the ionising power of the solvent and the effect of the nucleophilicity of

the solvent on the rates of solvolysis all showed progressive change from methyl substrates, through ethyl, isopropyl and then bulkier secondary systems to 2-adamantyl. This final substrate had been shown to solvolyse with a complete lack of nucleophilic assistance[9,10], due to steric hindrance.

Equation (2), where k_0 is the solvolytic rate coefficient in a reference solvent and Q_R is a scaling parameter, found to be independent of solvent, was used to correlate all the secondary tosylates between 2-adamantyl and isopropyl[9,10]. Some values of Q_R are in Table (4), and

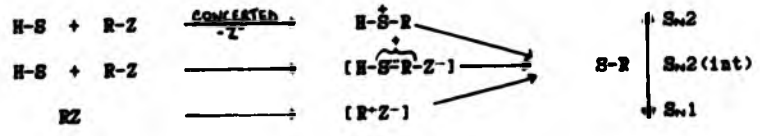
$$\log(k/k_0)_R = Q_R \log(k/k_0)_{2\text{-Ad}} + (1-Q_R)\log(k/k_0)_{i\text{-Pr}}$$

Equation (2)

indicate a progressive lessening of involvement of the nucleophile in the transition state. Bentley and Schleyer interpret their results as showing a gradual merging of mechanisms from a classical S_N2, through a nucleophilically solvated ion pair to the adamantyl ion pair where there is no nucleophilic solvation at all, (Scheme (37)).

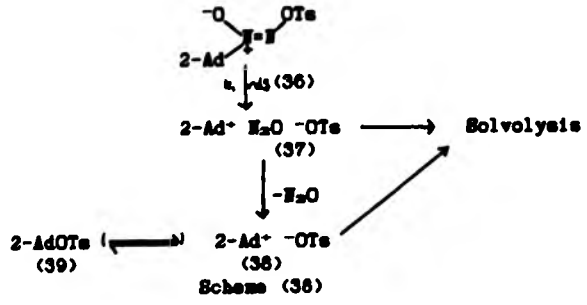
Table (4)

	Me-CH-MR	Et-CH-Me	Et-CH-Et	iPr-CH-Me	tBu-CH-Me	2-Ad
Q_R	0.00	0.20	0.30	0.42	0.76	1.00



Scheme (37)

The above two models both accept the validity of Winstein's ion pair theory, and the contention is over the nature of the first step. Shiner argues that it is unimolecular, with no nucleophilic participation. It constitutes a pre-equilibrium and internal return (k_{-1}, Scheme (34)) is important. It is the change in the relative rates of k_1, k_{-1} and k_2 that explains the intermediate behaviour. Bentley and Schleyer disagree, they argue that it is caused by differing extents of nucleophilic assistance. They claim that internal return is insignificant, and indeed does not occur[9,10]. However the existance of internal return has recently been established by two sets of workers. Bunnett[29] was able to measure internal return directly in his ^{18}O scrambling experiments, and Haskill implicated its existance by observing that 2-adamantyl tosylate (39) is a product of the solvolysis of 2-adamantyl azoxytosylate, ((36), Scheme (38)) in ethanol[3,29]. 2-Adamantyl azoxytosylate solvolyses by an initial rate determining unimolecular ionisation to produce the adamantyl cation and tosylate anion separated by a molecule of H_2O (37). The formation of (39) from ion-pair (37) in a solvent as nucleophilic as ethanol requires that (39) should also be formed by internal return from the intimate ion-pair (38) in the solvolysis of 2-adamantyl tosylate (39) itself[3,29] (see also Section 2.1.5.3).



Scheme (36)

2.2.4 Reactions of Primary Benzyl Substrates

Over the years considerable time has been spent in the study of the solvolytic mechanisms of benzyl substrates. Much of the interest has stemmed from the borderline nature of these reactions so that assignment to either of the classical S$_N$1 or S$_N$2 mechanisms has not been possible in many cases. For example, on the basis of kinetic studies, solvolyses of benzyl halides and arenesulphonates with electron-releasing substituents are believed to react via S$_N$1 mechanisms in aqueous-type media[94], but with electron-withdrawing substitutents in the benzyl residue an S$_N$2 mechanism is implicated[95]. The parent compounds appear to be at the mechanistic borderline and here the early evidence is not clearcut.

Almost all Hammett correlations (*cf.* Chapter 2.4) of the reactions of benzyl halides are curved[96a-c,96], and U-shaped Hammett plots, with the unsubstituted compound at the minimum are obtained[96b,c,97] in the reactions of benzyl halides with anionic nucleophiles. All the borderline mechanisms of nucleophilic substitution discussed previously in this chapter have been invoked in one situation or another to explain this behaviour.

2.2.4.1 Concurrent S$_N$1 and S$_N$2 Mechanisms

It has been postulated by Queen and co-workers[98a] that the reaction of 4-methoxybenzyl chloride in 70% aqueous acetone takes place with the participation of concurrent uni- and bimolecular processes. In this solvent the hydrolysis of the substrate to 4-methoxybenzyl alcohol was found to take place by the S$_N$1 mechanism. When azide ions were added,

4-methoxybenzyl azide was also formed as a product. The addition of the solute was found to increase the rate of ionisation of the chloride (by the salt effect) but decreased the rate of hydrolysis to form the alcohol. As it appeared that more carbonium ions were being produced but fewer were going to form alcohol then some azide must have been formed by reaction with carbonium ions; an S_N1 process. However, the rate of ionisation was always less than the total rate of reaction, so that some azide must also have been formed by an S_N2 mechanism acting simultaneously. Subsequent studies of the reaction with different added nucleophiles, (pyridine and thiourea)[cccc] have also been discussed in terms of the concurrent operation of the S_N1 mechanism and a bimolecular process.

Recent work by Katritsky[61] on the processes occurring at mechanistic borderlines has touched on the mechanism of solvolysis of a benzyl substrate, with a pyridinium leaving group ((56), p35) in chlorobenzene[61d]. Evidence was found that at the borderline between the first-order (rate-determining formation) and second-order, (rate-determining nucleophilic attack) reactions of intimate ion-molecule pairs, both reactions proceed independently, (cf. Section 2.2.3).

2.2.4.2 Change in reaction mechanism

Hammond and co-workers[64d,cc] studied the solvolyses of substituted benzyl tosylates in aqueous acetone and found that, in a Hammett plot, their data could not be fitted by a single linear correlation over the whole range. Instead their data were best described by a smooth curve for substituents ranging from 4-methoxy to 4-nitro. This was taken as a good indication that there was a gradual change in solvolysis mechanism

from one reactivity extreme to the other[99]. The results of the solvolysis of substituted benzyl tosylates at 40°C in acetic acid, (a less ionising and less nucleophilic solvent) also yielded a curved Hammett plot, (Figure (2))[99]. However, this time Streitwieser and his co-workers determined that the data were best interpreted by dividing

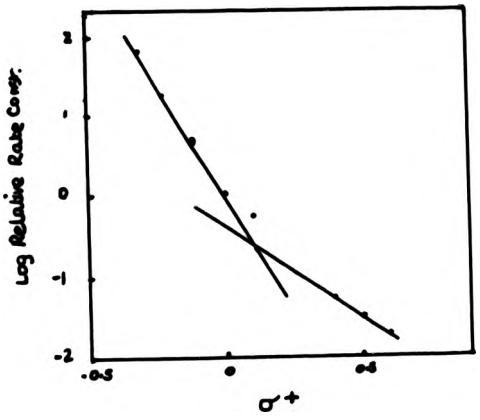


Figure (2)

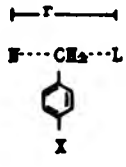
the curve into two straight lines. The correlation for electron donating substituents, ($\rho(\sigma^+)$ = -5.71, r = 0.9997) is typical of those observed for S_N1 reactions, the large ρ indicating a high degree of carbonium character in the transition state. The correlation for electron withdrawing substitutents, however, ($\rho(\sigma^+)$ = -2.33, r = 0.9998) indicates that with these substiutents a mechanism with greater displacement by solvent and less carbonium ion character is involved, ie. an S_N2-type mechanism.

Although there are other occasions documented where a change from S_N2 to S_N1 or ion-pair mechanism with change from electron-withdrawing to electron-donating substituent is the most likely explanation of the

behaviour of the reactions of benzyl halides and arenesulphonates[redacted], more often the observed results have been accounted for by postulating that there is a change in structure of the transition state of a single mechanism.

2.2.4.3 Variable S_N2 Transition State

When the rates and α-D isotope effects were determined for the reaction of a range of nucleophiles, (Et_3N:, SCN^-, N_3^-, $S_2O_3^{2-}$) with three benzyl bromides, (the parent and the 4-methoxy and 4-nitro derivatives) the variable transition state theory was found to be the most appropriate[244]. It was found that in nearly all cases the second order rate constant for each nucleophile with each benzyl bromide went through a minimum for the unsubstituted compound, while the α-D isotope effect increased monotonically in the sequence p-NO_2 < p-H < p-OCH_3. That is, both the electron acceptor and the donor increased the rate, but the α-D isotope effect increased regularly with increasing electron donation suggesting that there is a progressive weakening of the C-Br bond in the transition state. This behaviour was interpreted in terms



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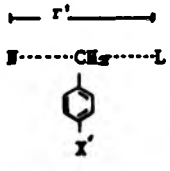


(58)

of a gradual change from a tight S_N2 transition state, (57) in which an electron-withdrawing aryl group causes the nucleophile to bond more closely to the reaction centre, to a looser, more S_N1-like transition state, (58) with substantial carbonium ion character.

Several groups of workers studying the kinetic isotope effects (primary and secondary) of many reactions of the benzyl moiety have also come to the conclusion that their results are best interpreted in terms of a variable S$_N$2-type transition state[91b,96a,97-4,97b,101]. However the results of the studies by Young and Jencks[102] suggest that most of the curvature in Hammett plots for the S$_N$2 reactions of nucleophiles with benzyl halides can be explained by envisioning a more or less invariable transition state structure which is stabilised both by polar electron withdrawal (facilitating attack by an anionic nucleophile) and by mesomeric electron donation (because of conjugation in the transition state with an electron deficient benzylic carbon atom).

Using the results of their studies of the reactions of substituted acetophenones with bisulphite, they established the validity and usefulness of their slightly modified version of the Yukawa-Tsuno equation, (Eq.(3); cf.Eqs.(8) and (9), Section 2.4). Their approach was

$$\log (k/k_0) = \rho\sigma + \rho^r(\sigma^+ - \sigma) \qquad \text{Equation (3)}$$

based on the separation of ρ and ρ^r parameters for polar and resonance effects, respectively. The r^+-value, of the original Yukawa-Tsuno equation, which is a measure of the relative contribution of polar and resonance effects[103], (but which can vary in magnitude and sign for a series of reactions with a constant resonance contribution if ρ varies independently of ρ^r) was replaced by ρ^r (= ρr^+).

The approach was applied to the reactions of substituted benzyl bromides with substituted benzenethiolate anions[102], which were found to

have "normal" U-shaped Hammett plots, (Figure (3)). The $\rho(\sigma)$ values for the correlation of the electron-attracting substituents on the benzyl bromides were 1.35, 1.06 and 0.86 for 4-$MeOC_6H_4S^-$, PhS^- and 4-$MeCOC_6H_4S^-$ respectively, but of course, the points for the electron-releasing

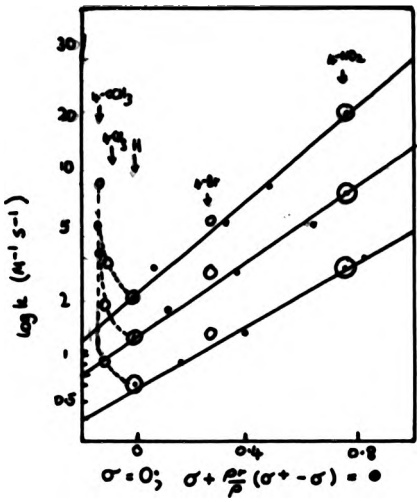


Figure (3)

substituents deviated strongly from these lines. The value of ρ' (= -1.3) was determined from a plot against $(\sigma^+ - \sigma)$ of the deviations from correlations with $\rho\sigma$. Using these values when σ was replaced by $\sigma + \rho'/\rho(\sigma^+ - \sigma)$ in the Hammett-type plot, all the data were correlated linearily.

Jencks and Young conclude that the reaction is facilitated both by polar electron withdrawal, (because the ρ values were positive) and by electron donation by resonance, (as ρ' is negative), and that by using this approach it is not required that the transition-state structure should alter with a change in substituent. This, they claim, is

consistent with the fact that qualitively similar behaviour is observed for a large number of different reactions of benzyl halides with nucleophiles of a given charge type in different solvents. This similarity of behaviour would be difficult to explain using the 'change in mechanism' or 'change in transition state structure' theories where it would be expected that the required changes in mechanism or transition state would occur at a different point or not at all with different reactions and conditions.

2.2.4.4 Ion Pair Model

In some cases an ion pair model provides the best explanation of the behaviour of the reactions of benzyl substrates. When activation parameters for the reaction of bromide ion with secondary benzyl substrates ($ArCHBrCH_3$) were obtained from the kinetics of racemisation, the results show the customary U-shaped Hammett plot[104]. However the enthalpy of activation did not show this behaviour and increased when the substituents were changed from 4-Me to H to 4-NO_2. In terms of the 'change in transition state structure' theory the tighter transition state (with 4-NO_2) would be expected to have more bonding than the looser one, resulting in a smaller enthalpy of activation. The authors suggest that their results are best accommodated by a dissociative, ion-pair mechanism in which it would be expected that the substrate with the most stable carbonium ion (4-Me) would have the lowest enthalpy of activation.

Pross[94a,94d,108] and co-workers have looked into the question in more detail in their study of the selectivity, (ie. the ability of the substrate to differentiate between competing nucleophiles), of the

solvolytic species formed during the aqueous ethanolysis of para-substituted benzyl chlorides. Their results ruled out the possibility of significant product formation by an S_N2-type mechanism. In 95% aqueous ethanol (a medium of low polarity) they found that the selectivity order (expressed as the ratio, k_z/k_t obtained from product analysis) decreased for more electron-attracting substituents, i.e. 4-MeO > 4-Me > H > 4-Cl[108a]. This finding indicated that an ionising step, to form a carbonium ion pair, was occurring before the product-forming step, as by application of the reactivity-selectivity principle (r.s.p.)[108], more stable ion pairs are more selective. If an S_N2-type of process had been occurring the selectivity order was expected to be the reverse of that actually obtained, as a substrate with an electron-releasing substituent such as 4-MeO would be expected to have a looser transition state than that substituted with 4-Cl. In a loose transition state, low selectivity is expected as the interaction between substrate and nucleophile is as yet weak. In a tight transition state where the substrate and the nucleophile are more strongly associated, greater selectivity is expected. This is the opposite to the experimentally-obtained trends.

A study of the change of selectivity of each substrate with change in solvent ionising power, Y[108a], (Figure (4)), was made. In the cases of the parent and the 4-Cl compounds (Figure (4)a) the selectivity was found to increase regularly as the water content (and hence the polarity) of the solvent increased, this was explained by reference to previous work by Prose which had shown that the linear increase in selectivity as a function of solvent ionising power was attributable to changes in the relative nucleophilicity of ethanol and water; as the aqueous component of the solution increases, ethanol exhibits greater

nucleophilicity relative to water, resulting in enhanced selectivity values.

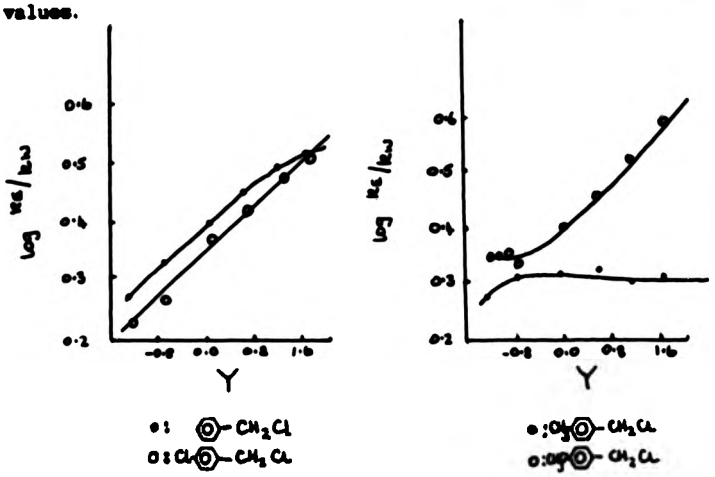


Figure (4)a

Figure (4)b

The selectivities of the 4-Me and 4-MeO compounds are found to behave differently, (Figure (4)b). The selectivity of the former decreases slightly and that of the latter is initially constant then increases regularly over the range of solvent compositions. It was concluded that the parent benzyl and the 4-chlorobenzyl compounds undergo product formation via intimate ion-pairs, 4-methylbenzyl derivatives via intimate ion pairs at low solvent polarity but through an increasing proportion of solvent separated ion pairs as the polarity of the medium is increased, and 4-methoxybenzyl chloride forms product predominantly through solvent separated ion pairs.

It is the change in the equilibrium between the two solvolytic intermediates that causes the difference in the pattern of selectivity for the latter two substrates. In the 4-Me case, as the solvent polarity

increases the dissociation of intimate ion pairs to solvent separated ion pairs is promoted. However, these latter species are known to exhibit low selectivity values (due to the fact that during front side attack in the solvent separated ion pair, water is more nucleophilic than ethanol[108a,c]) and the "normal" increase in selectivity, expected as a result of the above solvent effect is compensated for by the reduction in selectivity due to increasing formation of solvent separated ion pairs.

In the case of the 4-MeO-substituted derivative, where greater dissociation to solvent separated ion pairs occurs due to the more powerful electron-releasing substituent, the constant selectivity is seen in solutions of low polarity, where both types of intermediate are formed, but in solvents of higher polarity, product formation occurs almost entirely from solvent separated ion pair so that only the "normal" increase in selectivity due to solvent effect is observed.

This work was extended by the examination of the same series of benzyl derivatives towards a different pair of competing nucleophiles, 3-chloroaniline and ethanol. This resulted in a confirmation of the above conclusions, although the possiblity that 3-chloroaniline, a relatively strong nucleophile, may attack at the undissociated, neutral species could not be ruled out, and Ross concedes that the weight of evidence does suggest that with powerful anionic nucleophiles, (eg azide or thiolate ions) that attack on neutral substrate does occur[94a].

2.2.4.5 Benzyl Tosylate

The effects of several electrolytes, including sodium perchlorate, thiocyanate, acetate, and halides, upon the rate and products of

solvolysis of benzyl tosylate in 1:1 (v/v) aqueous trifluoroethanol at 25°C have been investigated[107]. Despite all the controversy about the nature of the solvolysis mechanisms of benzyl substrates (mentioned above), no evidence was found to show that benzyl tosylate reacts by anything other than a S$_N$2 mechanism in these conditions. This work was carried out as a preliminary to the study of the solvolysis mechanisms of benzyl azoxytosylate[8] the findings of which are discussed in Section 2.1.5.3.

2.3 Deamination

The reaction of arylamines with nitrous acid yields the relatively stable arenediazonium ion, ((59),Scheme (39)). N_2 is an excellent leaving group, and nucleophilic replacement reactions of the diazonium ion (with, for example, hydroxide and iodide) have been of great use in aromatic synthetic chemistry[108].

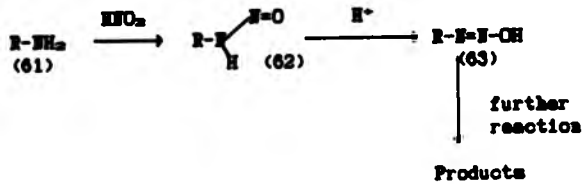
$$ArNH_2 \xrightarrow[H_3O^+]{HNO_2} \underset{(59)}{ArN_2^+} \xrightarrow{rds} \underset{(60)}{Ar^+} + N_2 \xrightarrow[HX]{Y^-} ArY \quad ArI + H^+$$

Scheme (39).

In general, the loss of N_2 from (59) in solution is an S$_N$1 type process, independent of the concentration of nucleophilic species present. Solvent effects, isotope effects and substituent effects are all in agreement with the rate-determining, unimolecular decomposition of (59)[108]. In contrast, the reaction processes of the more reactive alkanediazonium ions are in general much more complicated.

2.3.1 Deamination of Alkyl Substrates

Deamination of primary aliphatic amines with nitrous acid has also been known for many years[1], but in this case as it is the nitrosation step which is rate limiting, the early kinetic studies yielded no information about the subsequent product-forming steps. These days there is general agreement[110,111] that the initial nitrosation yields the N-nitrosamine (62), which swiftly rearranges in the acid conditions to the unstable diazohydroxide (63), which is the precursor of the diazonium and carbonium ions. (Scheme (40)).



Scheme (40).

By analogy with the deamination of aromatic systems (Scheme (39))[108], it was first thought that the aliphatic diazonium ion intervened as an intermediate, but the products were derived from carbonium ions. With the advent of gas liquid chromatography, (glc), which yielded reliable product analytical evidence, this model was proved inadequate. It was found that generally the product fallout from deamination was different from the S_N1 solvolysis of the corresponding halide or arenesulphonate, which ostensibly generated the same carbonium ion[112]. In the case of the 2-adamantyl system, for example, over 99% of the product of acetolysis of the tosylate[113,114] was unrearranged solvolytic substitution, while in the triazene[115] method of

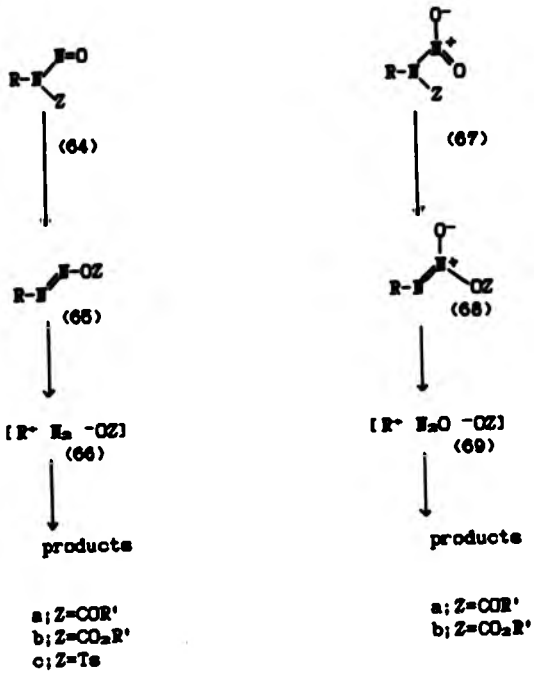
deamination[114], higher yields of rearranged substitution product and hydrocarbon were observed, leaving less than 80% of the product unrearranged. Different reactions proceeding through the same intermediate should generate the same products in the same proportions.

An early theory[116] proposed that the elimination of nitrogen from aliphatic diazonium ions led to high energy "hot" carbocations not in thermal equilibrium with their surroundings. These ions were thought to possess excess energy arising from their exothermic mode of formation and therefore were more reactive than the carbocations generated by the loss of less good leaving groups, (e.g. halide or tosylate). This difference in reactivity, and thus selectivity was thought to be responsible for the different product distributions. The theory, although popular for a while has little experimental backing[110].

Streitwieser[117] pointed out that the diazonium ions are relatively unstable and the activation barrier for the fragmentation step to yield the carbo-cation is small compared to that for the ionisation step of alkyl halides. Correspondingly, the scale of energy differences for competing reactions of the diazonium ion is compressed when compared with that of the solvolysis reaction. Because of this, the diazonium ion has a greater variety of different reaction pathways open to it, including rearrangement.

It is not surprising that a great deal of effort has been put into finding stable isolable analogues of the diazohydroxide (63), with the objective of making a direct kinetic investigation of the carbonium-ion-formation steps of alkyl deamination. The initial attempt was to solvolyse nitrososulphonamides (64 c) but these were of little use as they tended to denitrosate under the acid conditions rather than

isomerise to the diazo-tosylate(65)[62]. However, as a result of the development of newer, more reliable methods of deamination[63,64], it was found that nitroso and nitroamides ((64)a and (67)a) and carbamates ((64)b, and (67)b), are relatively stable analogues of the of the nitroamines((62),Scheme (40)), and give diazo and anoxy intermediates (65) and (68) on rearrangement prior to heterolytic fragmentation, (Scheme (41)). However, as the rearrangement is rate limiting, no direct

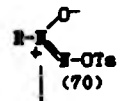


Scheme (41)

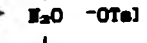
kinetic information about the fragmentation can be obtained. This work did establish, however, the important result that N_2O and N_2 behave almost identically as leaving groups.

2.3.2 Azoxytosylates

Alkyl azoxytosylates ((70), Scheme (42)) are clearly analogues of reactive intermediates (65) and (68) (Scheme (41)), but unlike (63), (65) and (68) they are surprisingly stable[1c,2a] (cf. Section 2.1.6). In ionising solvents these species undergo a deaminative type of solvolytic reaction, involving an initial rate-limiting concerted fragmentation (cf. Section 2.1.5.3, Scheme (26)) and as the leaving group is arenesulphonate, this reaction relates not only to deamination but also to alkyl tosylate solvolysis.

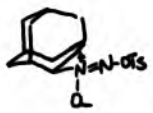


(70)

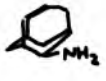


Products

(39)



(36)



(71)

Scheme (42)

When the product analyses of the acetolysis of (39) and (36) were compared with the corresponding deamination of 2-adamantylamine, (71), by the triazene method (Table (5)), it was seen that although

Table 5

Product	Reactant (39)	(36)	(71)
Protoadamantene	0	0.5	3.7
2,4-Dehydroadamantane	0	0.5	11.4
2-Adamantyl acetate	99.5	98.4	79.0
exo-Protoadamantyl acetate	0.5	0.6	5.9

appreciable yields of protoadamantane and dehydroadamantane were formed in the deamination of (71), only very small yields of these products

were obtained for the acetolysis of (36), and none for (39)[4]. Also exo-protoadamantyl acetate is a very small product indeed in the reactions of (39) and (36) but is formed to an appreciable extent from (71). It is obvious that the product distribution from (36) bears a greater resemblance to that from (39) than to that from (71).

This result was explained in terms of Streitwieser's argument in conjunction with an appreciation of microenvironmental considerations. The slow solvolytic reaction of the tosylate is relatively unfavourable and requires several events to occur in conjunction: the substrate must be in the correct conformation, the nucleofuge electrophilically solvated through hydrogen bonding, and perhaps also the potential carbonium ion may require specific nucleophilic solvation. Therefore the range of configurations of the resultant ion pair is very limited, and their lifetimes are too short to allow diffusion into bulk solvent or rearrangement. In contrast, the far more favourable deaminative fragmentation is much faster. The exact nature of the solvation of the substrate and intermediates is much less stringent allowing the carbocation greater access to possible reaction routes and a more diverse range of products.

The alkyl azoxytosylates solvolyse by a concerted fragmentation to give the carbocation, nucleofuge and N_2O[2,43], (Section 2.1.5.3) and this resembles deaminative fragmentation. However, the azoxytosylate reaction is much slower, and in this respect it compares with solvolysis of the alkyl tosylate as it requires similar facilitation by solvation. The product forming steps are constrained in the same way as in the tosylate case leading to a product distribution which more closely resembles that of tosylate solvolysis than that of deamination. Thus the solvolysis of

azoxytosylate does constitute a mechanistic link between solvolytic deamination and tosylate solvolysis.

2.4 The Hammett Equation

For the last fifty years, the Hammett Equation[74,119,120,121] (represented by Equations (4) and (5)) and its subsequent modifications have been used to evaluate empirically the electronic effects that para- and meta- substituents on a benzene nucleus have on the reactivity of a process that is occurring on a side chain. The exact origins and

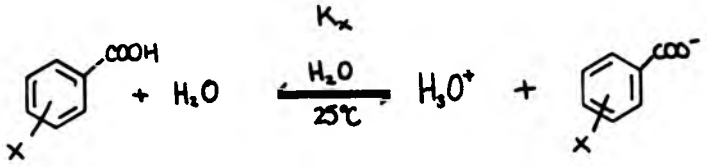
$$\log K/K_o = \sigma\rho \qquad \text{Equation (4)}$$

$$\log k/k_o = \sigma\rho \qquad \text{Equation (5)}$$

modes of transmission of these electronic effects, namely induction and resonance, are not completely understood, (see Section 2.4.1). However, the effect that a given meta- or para-substituent causes through its induction and resonance interactions is consistent at least qualitatively over a large range of reaction types. This is not so for substituents in the ortho position as the steric hindrance they cause affects different reaction processes and equilibria in different ways and to different extents[122].

The quantitative measure of the effect of a meta- or para-substituent was originally obtained by observing the difference between the extent of the equilibrium (or pKa) of the substituted benzoic acid and that of benzoic acid itself, (Scheme (43)). Thus a parameter, σ, the

substituent constant for substituent X, is defined in aqueous solution and at 25°C by Equation (6), where K_o and K_x are dissociation constants for benzoic acid and the substituted benzoic acid respectively. When X



Scheme (43)

$$\sigma_x = \log K_x - \log K_o \qquad \text{Equation (6)}$$

is electron withdrawing or attracting, the acidity of the substituted benzoic acid is increased, the dissociation constant increases hence σ is positive. Electron-repelling or donating groups decrease the dissociation constant, and so their σ values are negative. For tables of σ values see the first chapter of reference 119.

It was discovered later that these σ-values, could also be applied to the rates of reactions. If a family of compounds, which differ only in the benzene-ring substituent, react by the same mechanism at a side chain, then the rates of reaction of the individual reactants are related linearily according to Equation (7), where σ is the substituent constant, ρ is the reaction constant and k_x and k_o are the rate

$$\log k_x - \log k_o = \sigma\rho \qquad \text{Equation (7)}$$

constants of reaction of the substituted and the unsubstituted compound, respectively. If the reaction proceeds from reactant to transition state with a reduction of electron density on the atom adjacent to the benzene ring then electron releasing/donating substituents (those with negative σ-values) facilitate the process and ρ (the gradient in a $\log k_x$ or $\log K_x$ vs. σ plot) is negative. The accelerating effect of the substituent is in proportion to the magnitude of its (negative) σ. Electron accepting/attracting substituents (where σ is positive) retard the reaction by an amount proportional to the size of the σ-value in this example but of course increase the rate of reactions that proceed from reactant to transition state with an increase of electron density on the side-chain atom adjacent to the ring. In this case ρ is positive. It can be seen that the sign of ρ depends on the nature of the reaction or equilibrium that is under consideration, (by definition ρ is +1.00 for the dissociation of benzoic acids in water at 25°C). In terms of substituent effects on reaction rates, the magnitude of ρ can be interpreted as an indication of the extent of charge development at the atom of the reacting side chain in passing from ground to transition state[123].

2.4.1 Resonance Effects[119,120]

It is well established[124] that the quantitative effects of substituents on rates and equilibria cannot be expressed accurately in terms of a single scale of substituent constants, σ, (cf. Section 2.4.2). This is generally explained in terms of there being at least two independent kinds of substituent effect[125], summarised below, although

this is considered by some to be an oversimplification of the situation[1,2a].

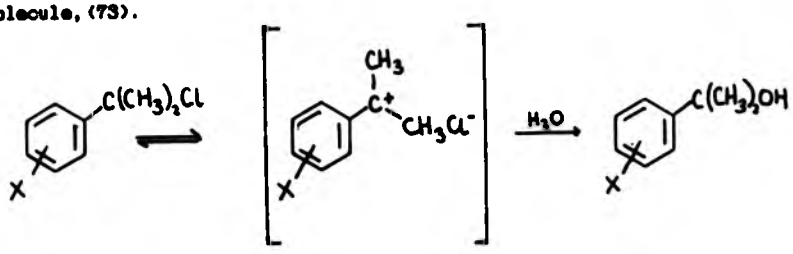
The inductive effect (I) of a substituent originates in the polarisation of the electrons in the σ bond connecting it to the ring. As the orbital overlap in σ bonds is along the axis of the orbital, the resulting bond is strong and its electrons are of low polarisability. Therefore perturbation of the benzene ring by attachment of other groups or by approach of a reagent molecule is small.

The resonance effect (R) of the substituent involves interaction between orbitals in the substituent which are in the same plane as the π electron orbitals of the benzene ring. This π resonance interaction affects the positions ortho and para to it. The overlap of these orbitals is not efficient and resonance effects are of high polarisability, sensitive to the influence of other groups in the benzene ring or to approaching reagents. The inductive effect is transmitted about equally to the meta- and para- positions, therefore it can be considered that σ_m is an approximate measure of the inductive effect of a substituent, and $(\sigma_p-\sigma_m)$ is an approximate measure of the resonance effect.

The σ values can often be interpreted in simple electronic terms. For Cl, $\sigma_m>\sigma_p$ because the electron-attracting effect, (I), is opposed by the electron-donating resonance effect, (R), of p-Cl. In the case of OMe the I effect results in a small positive value for σ_m, but the R effect is so large for p-OMe that σ_p is large and negative.

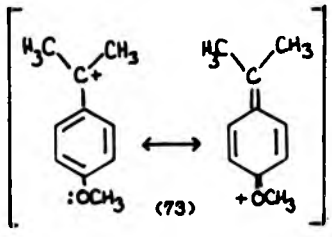
2.4.2 Modifications to the Hammett Equation

If during a reaction an electron-deficient site is created in direct conjugation with the benzene ring, such as in the hydrolysis of t-cumyl chlorides, (Scheme (44)), the presence of substituents that are electron releasing by resonance in the para position can greatly facilitate the reaction by conjugation. The transition state for the rate-determining step resembles the carbonium ion intermediate (72), and substituents such as OMe supply π electron density not present in the reactant molecule, (73).



(72)

Scheme (44)



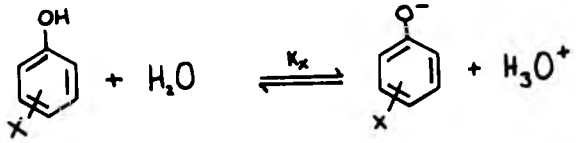
(73)

When a plot of log k versus σ_m is set up, (substituents meta to the electron deficient site cannot conjugate with it) the points for the electron-releasing para substituents deviate from the line. The deviations are all in the same sense and the altered σ-values necessary to correlate these points with the σ_m Hammett plot are called σ^+ values. The S_N1 hydrolysis of substituted t-cumyl chlorides in 90% aqueous

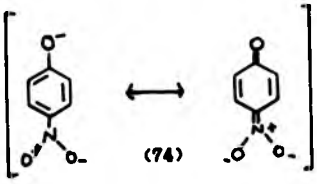
acetone at 25°C, is the standard reaction used to determine σ^+ constants[127].

The rates of side chain reactions that involve the formation of an electron-rich centre in direct conjugation with the benzene ring are enhanced by the conjugation that exists when there are substituents that are electron accepting by resonance at the para position.

When pKa is plotted against σ for meta-substituted phenols, (Scheme (45)), a straight-line correlation is obtained. The enhanced σ^- values required (due to conjugation of the type in (74)) to correlate those phenols with electron-accepting para-substituents are called the σ^- constants.



Scheme (45)



(74)

However, the rigid assignment of discrete σ, σ^+ and σ^- constants to a substituent can be considered to be artificial as the resonance effect of a substituent is expected to vary continuously as the electron-demanding quality of the reactions sites under study vary. And as the σ^+ and σ^- constants are derived from the above standard equations, they cannot always be expected to correlate the reactions occurring at more or less electron-demanding reaction sites.

Various modifications to the Hammett equation have been made to allow for these factors. One approach was to set up a sliding scale of σ values[120] for a substituent depending on the reaction type under study, but this can tend to the situation that the substituent constant becomes reaction dependant and the correlation analysis is devalued.

The Yukawa-Tsuno equations[120,180], (Equations (8) and (9)) retain σ, σ^+ and σ^-, but introduce another reaction parameter, r. It measures the extent of the conjugative interaction between the substituent and the reaction centre. When r = 0, the equations simplify to the original Hammett equation. When r = 1, there is a direct correlation with either σ^+ or σ^-. Values of r greater than 1 indicate that the resonance

$$\log k/k_o = \rho(\sigma+r(\sigma^+-\sigma)) \qquad \text{Equation (8)}$$

$$\log k/k_o = \rho(\sigma+r(\sigma^--\sigma)) \qquad \text{Equation (9)}$$

involvement in the reaction is greater than that in the hydrolysis of t-cumyl chlorides, on one hand and on the equilibrium constant of ionisation of anilines and phenols on the other.

Other modified forms of the basic equation have allowed correlations to include ortho-substituted benzene rings[122], non-aromatic unsaturated systems[121], polycyclic arenes and heteroaromatic compounds[122] and aliphatic systems[123].

2.4.3 Elucidation of Reaction Mechanisms

It is very useful to find out whether the change in reaction rate λ with change in substitutent in a family series correlates with σ, σ^+ or

σ^-. If the correlation is with σ, the sign of ρ indicates whether the reaction is facilitated by introducing electron-withdrawing (ρ is positive) or electron-donating groups, (ρ is negative). Correlation with σ^+ or σ^-, is expected when the probe site is conjugated to the benzene ring.

The sign of ρ indicates only the net change of charge that occurs on the reaction centre on going from reactant to transition state. During a reaction the charge on the probe site can increase, as in the solvolysis of t-cumyl chlorides (Scheme (44)) or decrease, as in the S$_N$2 reaction between the substituted phenolate anion and alkyl iodide, (Scheme (46)).

Scheme (46)

In both these reactions there is a net gain of positive charge on the probe site on going to the transition state, ρ is negative and as both sites are capable of conjugation with the ring, the correlation is with σ^+.

Knowledge of the size of ρ is also important, as this is a measure of the sensitivity of the reaction to changes in substituent, and can give useful information about the extent of charge development on the transition state. If $\rho = 0$, then either there is no electronic charge redistribution as reactant becomes transition state, or the reaction site is remote or well insulated from the benzene ring to the extent that the reaction site does not "detect" different substitution in the benzene ring. Larger values for ρ are obtained when there is

significant change in the charge distribution at the probe site, and maximal values result when one whole unit of charge is either formed or dissipated during formation of the transition state. It follows that ρ-values can be taken as an indication of the extent of bond making or bond breaking that exists in the transition state.

For the reaction in Scheme (47) the ρ-value was found to be small (+0.79)[124], indicating a small build up of electron density on the CH_2 of the reaction site as the nucleophile approaches to form the activated

$$ArCH_2Cl + I^- \xrightarrow[\text{acetone}]{k,\ 20^\circ C} ArCH_2I + Cl^-$$

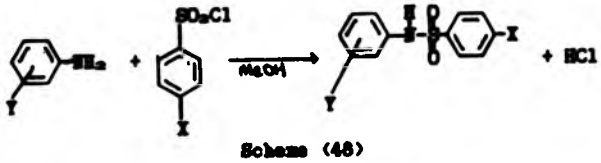
Scheme (47)

complex. An S_N2 mechanism is assumed for the reaction, and the positive ρ indicated that the bonding with I^- slightly precedes the unbonding of the Cl^-.

However ρ-values are very dependent on the reactants, the reaction and the reaction conditions, and absolute values of ρ are of little use in mechanistic interpretations. It is of more significance to compare ρ-values obtained for similar reactions.

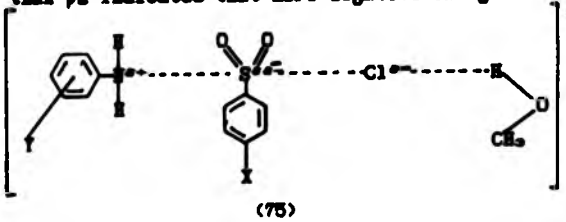
More information about the transition state of a reaction can be obtained when the Hammett approach is applied to more than one probe site. In a study of the mechanism of nucleophilic substitution at sulphonyl sulphur[125], a reaction was chosen where substituents could be changed in the aromatic rings of both the nucleophile and the electrophile, thus allowing the reaction to be followed at two probe sites, (Scheme (48)). The reactions of benzenesulphonyl chlorides with a series of anilines, yielded Hammett plots with large negative slopes, (ρ_N = -2.0 → -2.9), indicating a build up of positive charge on the

nitrogen of the nucleophilic aniline in the transition state. The reactions of the anilines with a series of benzenesulphonyl chlorides



Scheme (48)

yielded smaller positive ρ values, (ρ_o = 0.5 → 1.0). That ρ_N is greater in magnitude than ρ_o indicates that more negative charge was transferred



(75)

from the nucleophile than was developed on the sulphur during the formation of the transition state. The authors claimed that this is due to the partial transfer of electron density towards the leaving group which is starting to leave in the transition state (75). That is, the bond formation and bond cleavage are concerted. These results were used to rule out the other suggested mechanism of nucleophilic substitution at sulphur, where addition of the nucleophile to form a 5 coordinated intermediate takes place before elimination of the leaving group.

When a Hammett plot is made, explanation of the result in mechanistic terms generally depends on obtaining a straight line relationship. However, a break in the linearity of a Hammett plot can be straightforward to explain as it often indicates a mechanistic change as the reactants in a series become more or less reactive with changing

substituent. For example, the ρ vs σ^+ plot for the acetolysis of substituted benzyl tosylates (Fig (2), Section 2.2.4.2, p43), is not linear but the points have been interpreted as falling on two straight lines with different gradients[89,90]. For the more reactive substrates $\rho(\sigma^+)$ is large and negative (-5.58) corresponding to a S_N1 mechanism. The less reactive compounds correlate with a smaller negative $\rho(\sigma^+)$-value of -2.81. The smaller ρ-value corresponds to a solvent-induced S_N2 mechanism.

Generally a curved Hammett plot is more difficult to interpret mechanistically. The value of ρ is not constant but changes with change in substituent. If for example there is a decrease in slope, ρ, as σ is increased, (Fig. (5)), a sense of order can be retained if the change in slope is described in terms of the interaction coefficient, $\rho_{\sigma\sigma}$, in Equation (10), which is a second derivative of log k.

$$\rho_{\sigma\sigma} = \delta\rho/\delta\sigma = \delta^2 \log k/\delta\sigma^2 \qquad \text{Equation (10)}$$

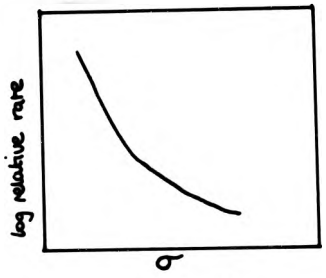


Figure (5)

A change in ρ can also occur when a substituent is changed in the other reactant, and such a change can be described by a cross-interaction coefficient $\rho_{\sigma\nu}$. (Equations (11) and (12)), where $\rho_{\sigma\sigma}$ and

ρ_{lg} are the ρ-values obtained when the substituents are varied on the nucleophile, and leaving group respectively.

$$\rho_{nlg} = \delta\rho_{nuc}/\delta\sigma_{lg} = \delta\rho_{lg}/\delta\sigma_{nuc} \qquad \text{Equation (11)}$$

$$\rho_{nlg} = \delta^2 \log k/\delta\sigma_{lg}\delta\sigma_{nuc} \qquad \text{Equation (12)}$$

The measurement of cross coefficients is an empirical approach to the characterisation of changing transition state structures. They are often expressed in terms of another linear free energy relationship, the Bronsted Equation[106]. Work in this field is being carried out by Lee[107] and by Jencks[108,109] and is reviewed in Reference 139.

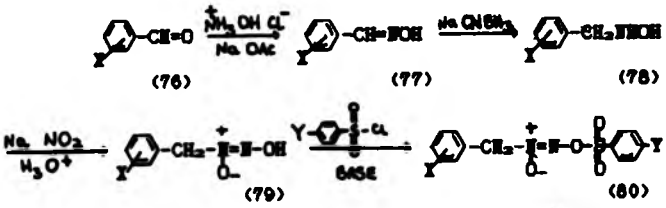
SECTION 3

RESULTS

3 Results

3.1 Preparation of the Azoxy Compounds

All the substituted benzyl azoxyarenesulphonates (80) were generated by following the same synthetic route starting from the aldehyde, shown in Scheme (49).



Scheme (49)

The substituents on the starting aldehydes were chosen with their Hammett σ value in mind, in order that the solvolyses of the benzyl azoxyarenesulphonates could be studied over a wide reactivity range. When it became clear that a future avenue of work may be a similar Hammett type exploration of the 1-phenylethyl azoxytosylate system, the preparation of the parent α-CH_3 substituted compound was also attempted.

3.1.1 Oximes (77)

The oximes (which are all literature compounds) were prepared in high yields by refluxing a solution of the aldehyde (76), hydroxylamine hydrochloride and sodium acetate in aqueous methanol, for about 3 hours. The material obtained was then recrystallised from aqueous methanol.

3.1.2 Hydroxylamines. (78).

The reduction of the oxime was achieved using buffered sodium cyanoborohydride in methanol[140]. The oxime and one small crystal of the indicator methyl orange were dissolved in methanol. As the successful reduction of aldoximes to the monoalkylated hydroxylamines requires the reacting solution to be kept at the correct acidity, and as the reaction consumes acid, sodium cyanoborohydride and methanolic HCl were added alternately in batches in order to hold the acidity of the solution at the orange/red colour change of the indicator. After the solution's colour stopped changing on addition of further reductant, the reaction mixture was stirred for about 20 minutes at room temperature and then worked up, (see Section 5).

It was necessary to purify the resulting crude product to ensure the success of the following nitrosation. The parent unsubstituted benzylhydroxylamine was sublimed (0.1mmHg, 55°C)[141]. However trituration with mixtures of diethyl ether and pentane also furnished sufficient purity and this method was used for all the other hydroxylamines.

Generally the yields were good (>75%), but for the 4-CH_3, 4-$N(CH_3)_2$ and αCH_3 substituted benzylhydroxylamines yields of only 51%, 32% and 56% were obtained respectively. Identification was by ^1H nmr.

3.1.3 N-Nitroso-N-benzylhydroxylamines. (79).

At all times care was taken when handling these substances as they closely resemble the carcinogenic N-nitrosamines. The hydroxylamines were nitrosated with acidified sodium nitrite in aqueous methylated spirits at 0°C, under argon. Generally the product precipitated after the addition of all the nitrite whereupon ice cold water was added, and

the precipitate was filtered immediately and dried under vacuum. The aqueous filtrate was then extracted with diethyl ether, and the organic phase was dried (sodium sulphate), filtered and evaporated to yield another crop, which generally looked less pure but was indistinguishable by nmr with the first crop. In two cases no precipitation occurred (3-CH_3, αCH_3) so the reaction mixture was saturated with sodium chloride and worked up by extraction with diethyl ether, as described above.

For most of the N-nitrosohydroxylamines the yields (two crops combined) were good (>75%), but the 3-Cl, αCH_3 and 4-OCH_3 substituted compounds yielded only 36%, 38% and 41% respectively. Identification was by ^1H nmr and IR. The incorporation of the electron-withdrawing nitroso group in the N-nitrosohydroxylamines deshields the methylene protons, and shifts their resonance downfield towards higher δ values, making the spectra easily distinguishable from those of the parent hydroxylamines.

3.1.4 Substituted Benzyl Azoxybenzenesulphonates (80).

The Tipson method[142] was used to synthesise all the azoxytosylates ((80), Y = CH_3)) and the 4-methylbenzyl-ONN-azoxy-4-bromobenzenesulphonate, ((80), X = CH_3; Y = Br). The N-nitroso-N-benzylhydroxylamines were treated with the required para-substituted benzenesulphonyl chloride in ice cold dry pyridine, under a stream of argon. The reaction mixture was left to stand for ≈14hours at <0°C, before the product was extracted during work up, (see Section 5). The yields varied considerably; from 30% to over 90% for the 3-Cl and 4-OCH_3 substituted benzyl azoxytosylates respectively. Attempts to synthesise the p-dimethylaminobenzyl azoxytosylate met with failure due to the high reactivity of this compound. During the addition of the tosyl chloride

effervescence was observed, indicating that the azoxytosylate was decomposing, with loss of N_2O as it formed.

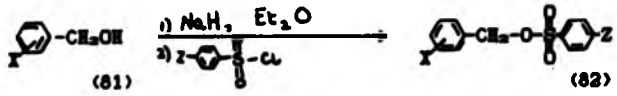
The Tipson method proved to be less successful in the preparation of the other azoxyarenesulphonates, and an aqueous method[18] was then used, where the N-nitroso-N-benzylhydroxylamine is treated with the benzenesulphonyl chloride and aqueous sodium hydroxide in acetone at 0°C and under argon. On the addition of iced water the product precipitated out of solution. Yields from this process were also varied; from over 90% in the case of 4-methylbenzyl-ONN-azoxy-4-methoxybenzenesulphonate to less than 40% for the 4-methylbenzyl-ONN-azoxy-4-cyanobenzenesulphonate.

In most cases the azoxy compounds were purified by trituration with combinations of pentane and diethyl ether prior to kinetic rate determinations, (p-cyanobenzyl-ONN-azoxytosylate was sufficiently stable to be recrystallised from hot diethyl ether), but this did not yield sufficient purity for product analysis and the m-Cl, 4-CH_3 and 4-OCH_3 benzyl azoxytosylates were also recrystallised at low temperature from diethyl ether and pentane.

Identification was by ^{1}Hnmr, IR, and elemental analysis. The presence of the azoxy grouping was indicated in ^{1}Hnmr spectra by the downfield shift of the methylene protons adjacent to the deshielding electron deficient nitrogen. When decomposition of the compound by loss of N_2O occurred, it could be readily seen. Some such decompositon is thought to have occurred in several of the most reactive of the azoxy compounds when subjected to the conditions required for elemental analysis. Thermal decomposition by loss of N_2O has previously been observed[4a,b].

3.2 Preparation of the Substituted Benzyl Arenesulphonates (82).

After an initial attempt to prepare 3-chlorobenzyl tosylate ((82), Scheme 50, X = Cl; Z = CH_3) by the Tipson method[143], which failed as the product hydrolysed in contact with water during the work-up, all the benzyl arenesulphonates were prepared by the treatment of the required benzyl alcohol with sodium hydride in dry diethyl ether for 14 hours at <0°C. The substituted benzenesulphonyl chloride was then added at -25°C, under argon[143], (Scheme (50)).



Scheme (50)

The precipitate which resulted was filtered off with minimum exposure to the air, and the product was recovered by reduction of the filtrate. Difficulties in handling these substrates have previously been reported[143] and great care was taken to minimise their contact with moisture and air. The 4-methyl and 4-methoxy compounds were especially reactive and decomposed to a red amorphous polymeric material at temperatures above -15°C.

Purification was by recrystallisation from diethyl ether/pentane or diethyl ether/40-60 petrol mixtures. The yields were all very low, usually less than 25%, and the products were identified by ^{1}Hnmr, elemental analysis (the 3-chlorobenzyl compounds) and melting point in the cases of the 3-chloro and 4-methyl benzyl tosylates.

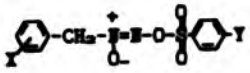
3.3 Kinetic Results[144].

Rates of solvolysis were followed as described in the Experimental Section, and rate constants at 25°C ($k^{25.0°C}/s^{-1}$), enthalpies ($\Delta H^{\neq}$) and entropies ($\Delta S^{\neq}$) of activation were obtained. The results for all the solvolyses are presented in Tables (1) to (4) in Appendix (1).

In all cases the solvolyses were carried out in 1:1 v/v aqueous TFE; a highly ionising weakly-nucleophilic medium used in the previous comprehensive studies of the solvolyses of benzyl azoxytosylate[8] and benzyl tosylate[107].

3.3.1 [illegible]

3.3.1.1 Substituted Benzyl Azoxytosylates.



(80)

The rate constants at 25°C and the activation parameters of the reactions of substituted benzyl azoxytosylates ((80), Y = CH_3) are listed in the table below and in Table (1), Appendix (1).

Y	10^5 k/s^{-1} (25°C)	$\Delta H^{\neq}$/kJmol^{-1}	$\Delta S^{\neq}$/JK^{-1}mol^{-1}
mCl	0.031	107	-11
pCl	0.23	103	- 6
H	0.47	100	-12
mCH_3	0.76	101	- 6
pCH_3	6.0	92	-17
$pOCH_3$	170	86	- 9

The plot of $\log k^{25.0°C}$ versus σ^+ [148]for the 6 points obtained has a good linear Hammett correlation (Fig.(3), Appendix (1)); $r > 0.999$), with a ρ-value of -3.27.

The enthalpies of activation decrease regularly with the increase in electron releasing ability of the substituent, but no trend can be seen in the entropies of activation, which are very similar to each other. The error in $k_{25 \cdot c}$ is calculated to be < 1% and the uncertainties in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are estimated to be 3kJmol^{-1} and 7JK^{-1}mol^{-1}, respectively.

4-Cyanobenzyl azoxytosylate ((80), X = 4-CN; Y = CH_3) was prepared and fully characterised, but its s solvolysis reaction did not behave as expected. During the reaction the UV absorbance did not decrease uniformly; an increase was observed midway through the reaction. It was assumed that the solvolysis reaction of this compound was so slow that other, non-solvolytic processes were competing successfully to form products. Competing non-solvolytic reactions with benzyl azoxytosylate have previously been reported, (see Section 2.1.5.3, p24).

3.3.1.2 4-Methylbenzyl-CNN-Azoxyarenesulphonates

The rate constants at 25°C and the enthalpies and entropies of activation obtained for the 4-methylbenzyl-CNN-azoxyarenesulphonates ((80), X = 4-CH_3, Y = OCH_3, CH_3, Br, CN) are listed in the table below and in Table (2), Appendix (1)), and a 4 point Hammett plot was constructed, which correlated well with σ^{-}, ρ=1.07; (Fig.(3), Appendix (1); r=0.996).

Again a trend shows in the values for the enthalpies of activation; they decrease as the electron-withdrawing ability of the substituent on the leaving group increases. The entropies of activation show no trends but are again very similar to each other. Errors in $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $k_{25 \cdot c}$ are as above.

Y	10^6 k/s^{-1} (25°C)	$\Delta H^{\neq}$/kJmol^{-1}	$\Delta S^{\neq}$/JK^{-1}mol^{-1}
OCH_3	4.24	96	-11
CH_3	6.0	92	-17
Br	19.1	87	-25
CN	46.5	89	-9

3.3.1.3 3-Chlorobenzyl-CNN-Arenesulphonamides.

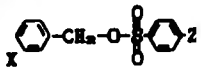
The rate constants at 25°C and activation parameters obtained for the 3-chlorobenzyl-CNN-arenesulphonates ((80), X = 3-Cl, Y = OCH_3, CH_3, Br, CN) are listed below, and in Table (3), Appendix (1). The plot of logk_{2H}·c versus σ is curved; the reactions of the three most reactive compounds (Y = CN, Br, CH_3)are correlated by σ, ($\rho(\sigma)$ = +0.730, r = 0.986), and, unexpectedly, a better correlation (that is, for all the compounds) is obtained with σ^+, ($\rho(\sigma+)$ = 0.685, with r = 0.999), (Fig.(4), Appendix (1)).

The estimated uncertainties in k_{2H}·c, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ remain the same as before, but in this case no trend can be seen either in the enthalpies or the entropies of activation.

Y	10^6 k/s^{-1} (25°C)	$\Delta H^{\neq}$/kJmol^{-1}	$\Delta S^{\neq}$/JK^{-1}mol^{-1}
OCH_3	0.013	114	+4
CH_3	0.031	107	-11
Br	0.074	109	+4
CN	0.14	114	26

3.3.2 Arenesulphonates.

3.3.2.1 3-Chlorobenzyl Arenesulphonates.



(82)

The rate constants and activation parameters for the three

3-chlorobenzyl arenesulphonates ((82), X = 3-Cl; Z = OCH_3, CH_3, Br) are tabulated below, and in Table (4), Appendix (1). The 3-point Hammett plot correlated well with σ; ρ=1.37, (Fig (3), Appendix (1); r>0.999).

Here, no trends can be seen in either the enthalpies or the entropies of activation with change in rate of the reaction. The estimated uncertainties are as before.

Z	10^5 k/s^{-1} (25°C)	$\Delta H^{\ddagger}$/kJmol^{-1}	$\Delta S^{\ddagger}$/JK^{-1}mol^{-1}
OCH_3	3.08	82	-67
CH_3	4.48	78	-67
Br	15.6	79	-51

3.4 Product Analysis.

The product analyses (by hplc) were carried out for three of the substituted benzyl azoxytosylates ((80), X = 3-Cl, 4-CH_3, 4-OCH_3; Y = CH_3) in 50/50 v/v aqueous TFE. The reaction mixtures were injected directly and quantification of the product alcohol was achieved by using external standards, as the injection loop was found reliably to introduce the same volume of sample with each injection, (see Section 5.4.1). The analysis for the other main products, the trifluoroethyl ethers, was required to be more indirect, as we were unable to purify these compounds sufficiently. To get round this, the relative molar response factor of 3-chlorobenzyl trifluoroethyl ether with respect to 3-chlorobenzyl alcohol was obtained from the analysis of the products of solvolysis of three 3-chlorobenzyl-4-substituted-arenesulphonates ((84), X = 3-Cl; Z = OCH_3, CH_3, Br) in 1:1 v/v aqueous TFE. The procedure is described below and more fully in Section (5.4.2).

3.4.1 Development of Procedure

Initial injections of the reaction products from 3-chlorobenzyl tosylate showed that the retention times of 3-chlorobenzyl alcohol and 3-chlorobenzyl trifluoroethyl ether were very different. It proved impossible to find a single eluant composition that was suitable for the analysis of both. The alcohol was much less well retained on the column and came off at the solvent front with compositions of eluant that were suitable for the analysis of the trifluoroethyl ether, (≈67% methanol). In turn when a suitable eluant composition for the alcohol was used (≈55% methanol), the trifluoroethyl ether was retained so long on the column that its signal became too misshapen for accurate integration.

Attempts to use a concentration gradient failed. The products that were analysed were of relatively low concentration, and did not have powerful chromaphores so it was necessary to set the detector at quite a high sensitivity, which meant that the gradual change in methanol content of the eluant during the gradient programme was accompanied by a drifting baseline which was found to affect the ability of the integrator to find the start of the trifluoroethyl ether peak; therefore accuracy of the integration was lessened. For these reasons, the analyses for the product alcohol and trifluoroethyl ether of all the tosylates and azoxytosylates were carried out separately at different eluant compositions.

3.4.2 Preparation of Authentic Samples and Determination of RRF

By comparison with the product analysis already carried out on the parent unsubstituted benzyl azoxytosylate in 50/50 v/v aqueous TFE[a], it

was expected that the main products of the reactions of the substituted benzyl arenesulphonates should be the correspondingly substituted benzyl alcohol and benzyl trifluoroethyl ether. Therefore an authentic sample of each of the substituted benzyl alcohols was purified by distillation for use as an external standard. In the case of each alcohol, several solutions of different but accurately known concentrations were analysed and the U.V.detector's response to each solution was used to set up a calibration curve, (see for example Fig.(1), Appendix (2)). The absolute response of the detector to each alcohol was thus determined. Calibration data are presented in Tables (1)-(3), Appendix (2); (see also Section 5.4.1).

It was not possible to apply the same method to the analyses of the trifluoroethyl ethers as attempts to prepare pure, authentic samples of these were not successful. After refluxing 3-chlorobenzyl bromide with a little base in TFE for 5 hours the presence of the desired product was confirmed by ^{1}Hnmr, but attempts to purify the trifluoroethyl ether enough for use in quantitative analysis failed. Instead, its molar response factor (mrf) relative to the alcohol was determined by analysing the solvolysis products from three 3-chlorobenzyl arenesulphonates. The results are in Section 5.4.3 and Table (4), Appendix (2). In each case only two products were found: 3-chlorobenzyl alcohol and the 3-chlorobenzyl trifluoroethyl ether. The absolute concentration of the alcohol was found from the above mentioned calibration graph. The concentration of trifluoroethyl ether was taken to be the difference between the initial concentration of arenesulphonate and the measured concentration of alcohol product. Using

these data, the mrf of the trifluoroethyl ether relative to the alcohol was calculated as detailed in Section 5.4.2.

The percentages of 3-chlorobenzyl alcohol and 3-chlorobenzyl trifluoroethyl ether in the product mixture were identical (averaging 87.9% and 12.1% respectively) from the tosylate and the 4-methoxybenzenesulphonate, giving rise to relative mrf values of 1.12 ± 0.01 for the tosylate and 1.08 ± 0.01 for the 4-methoxy substituted compound, (see Table (4), Appendix (2)). These values are in good agreement with the value of 1.12 obtained earlier (using a different procedure) for benzyl trifluoroethyl ether versus benzyl alcohol[a]. [The mrf value obtained from the product analysis of the brosylate (average percentage of product alcohol and trifluoroethyl ether: 89.2% and 10.8% respectively) is higher, at 1.4 ± 0.2. However, the results for the tosylate and the p-methoxybenzenesulphonate are more reliable than that for the brosylate due to an improvement in experimental technique and experience.]

As their arenesulphonates were too reactive to prepare in a pure form, it was not possible to obtain the relative molar response factors for the 4-methylbenzyl and 4-methoxybenzyl trifluoroethyl ethers by this method. In practice it is thought that it is unlikely that their relative mrfs would differ significantly from that for the benzyl and the metachlorobenzyl trifluoroethyl ethers so the relative mrf was assumed to be 1.10 ± 0.02 for all the trifluoroethyl ethers which were studied.

3.4.3 Azoxytosylates.

3-Chlorobenzyl, and 4-methoxybenzyl azoxytosylates were chosen for product analysis as they were, respectively, the least and most reactive of the azoxytosylates studied kinetically. In addition, the products of 4-methylbenzyl azoxytosylate, a compound of intermediate reactivity, were analysed. The results are summarised here and given more fully in Section (3.4.4) and Tables (5) and (6), Appendix (2).

3-Chlorobenzyl Azoxytosylate

Two solutions of 3-chlorobenzyl azoxytosylate were reacted in 1:1 v/v aqueous TFE for at least 10 half-lives, and both sets of products were analysed no fewer than 5 times. Using the values of 1.10 and 96[a] for the relative molar response factors towards the alcohol of the trifluoroethyl ether and the aldehyde respectively, and assuming that the relative molar response factor of the N-nitrosohydroxylamine to the alcohol is 1, (probably an underestimate), then the corresponding alcohol, trifluoroethyl ether, aldehyde and N-nitrosohydroxylamine were found to represent 74.9%, 22.6%, 0.12% and 0.84% of the product respectively, (see Table (6), Appendix (2). When combined these product yields represent 98.4% of the theoretical yield, indicating that there is virtually total product recovery as was found in the product analysis of the parent unsubstituted benzyl azoxytosylate[a].

4-Methylbenzyl Azoxytosylate

In the solvolysis, in the same solvent of, 4-methylbenzyl azoxytosylate, ((80) X = 4-CH_3; Y = CH_3) no N-4-methylbenzyl N-nitrosohydroxylamine was detected, and 4-methylbenzyl alcohol,

4-methylbenzyl trifluoroethyl ether and 4-methylbenzaldehyde were the only products, (see Tables (5) and (6), Appendix (2)). When the previously mentioned relative mrf values were used for quantification, (it was not possible to obtain the relative mrf of 4-methylbenzyl trifluoroethyl ether to 4-methylbenzyl alcohol, (see Section 3.4.2)) the absolute yields of alcohol, trifluoroethyl ether and aldehyde (using the values in Table (5), Appendix (2)) were found to represent 74.1%, 18.7% and 0.01% of the theoretical product yield, respectively. It can be seen that the total actual yield represents only 92.8% of the total theoretical yield. However, by analogy with the results obtained from the parent and 3-chlorobenzyl azoxytosylates, it was considered improbable that the product recovery should be less than total.

As there was no trace of any other minor products on the chromatograms, it is difficult to explain the loss of over 7% of the theoretical product without assuming that the relative mrf that was used may be unrepresentative. However, subsequent experiments have shown that 4-methylbenzyl trifluoroethyl ether is very insoluble in aqueous methanol, the eluant used for the hplc, and the error may lie here. The analysis of the products of the solvolysis of 4-methylbenzyl azoxytosylate now may only be made by using the assumption that a percentage of the product trifluoroethyl ether may have come out of solution and been permanently adsorbed onto the hplc column. If this is the case then it is obvious that the yield of trifluoroethyl ether detected as product is anomolously low. The 'clean' nature of the chromatograms allows the assumption that apart from the low yield of aldehyde, the alcohol and trifluoroethyl ether are the only products, and as the absolute yield of the alcohol was found to be 74.1%, it is

now assumed that the trifluoroethyl ether is present at a yield of 25.9%, (see Table (6), Appendix (2)).

4-Methoxybenzyl Azoxytosylate.

This compound is highly reactive and was found to be too unstable to purify easily. In this case the absolute product yields could not be evaluated, but only the relative yields. Four solutions of the azoxytosylate were reacted and each analysed at least five times. In each case the absolute concentration of alcohol in the product was found from the calibration graph, and the concentration of the trifluoroethyl ether was estimated using the relative molar response factor of 1.10. Trace amounts of aldehyde were identified, but no N-nitrosohydroxylamine. The average value for the ratio of alcohol/trifluoroethyl ether was found to be 7.74. When this is expressed in terms of percentages the ratio is: 88.5% : 11.5%.

SECTION 4

DISSCUSSION

4.1 Preparations.

Substituted Benzyl Arenesulphonates

All the N-substituted-benzyl-N-nitrosohydroxylamines (79) were prepared by the same synthetic route, starting from the benzaldehyde[a], (see Scheme (49), Section (3), p69). The initial steps were found to be straightforward and in general furnished good yields, however the nitrosation step proved to be less well behaved and good results depended very much on the purity of the hydroxylamine. In general, the less reactive para-substituted compounds were prepared in the best yields.

Two methods were used to prepare the arenesulphonates, ((80), Scheme (49), p69) from the N-nitrosohydroxylamines. The first, the Tipson[142] method, used for all the arenesulphonates and 4-methylbenzyl benzene-4-bromobenzenesulphonate, employs dry pyridine as both a solvent and a base and was for the most part quite successful although relatively poorer yields were again obtained for the meta-substituted compounds. The Tipson method, however, was not suitable for the tosylation of all the N-nitrosohydroxylamines; some of the arenesulphonates were too reactive to survive, without hydrolysis, the long aqueous work-up required to remove all traces of pyridine. In the other method used to perform the last step of the reaction sequence, the N-nitrosohydroxylamine was treated with the required benzenesulphonyl chloride and aqueous sodium hydroxide in acetone at 0°C. This method also met with varying degrees of success but had the advantage of a simpler, quicker work-up.

The following arenesulphonates were successfully prepared: (80), X = 4-CH_3O, 4-CH_3, 3-CH_3, H, 4-Cl, 4-CN; Y = CH_3. Also prepared were the following

azoxyarenesulphonates: (80), X = 4-CH_3; Y = OCH_3, Br, CN and (80), X = 3-Cl; Y = OCH_3, Br, CN.

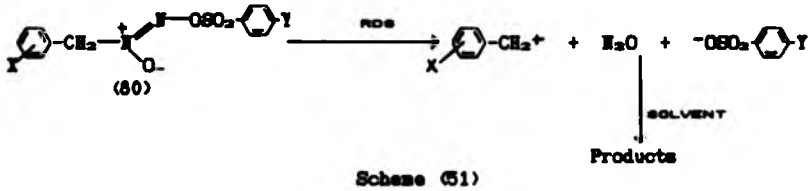
3-Chlorobenzyl Arenesulphonates

An initial attempt to prepare 3-chlorobenzyl arenesulphonates ((82), p73) from the alcohol by the Tipson method failed as hydrolysis occurred during the work-up, and so instead the alcohol was treated with sodium hydride and the benzenesulphonyl chloride in dry diethyl ether at low temperature under argon[143], (Scheme (50), p73). The following 3-chlorobenzyl arenesulphonates were successfully prepared: (82), X = 3-Cl; Z = OCH_3, CH_3, Br. The 4-methylbenzyl tosylate and 4-methoxybenzenesulphonate were also prepared by this method, but were too reactive to purify sufficiently for their solvolysis kinetics to be measured accurately.

4.2 Kinetics Results for Substituted Benzyl Azoxyarenesulphonates.

4.2.1 Nature of the Transition State

It has been proposed that the solvolyses of 2-adamantyl and the parent unsubstituted benzyl azoxytosylates in 1:1 TFE:H_2O (v/v) take place by an initial unimolecular, rate-determining ionisation to give the corresponding cation, H_2O and tosylate anion which then go on to form products in subsequent steps[2,5,42], (Scheme (51). In principle, the rate-limiting, solvolytic



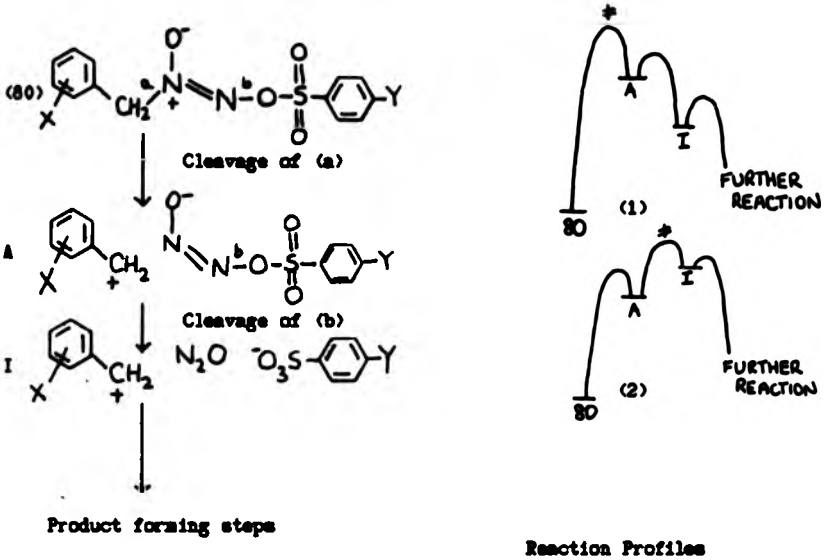
(80)

Scheme (51)

fragmentation could be stepwise or concerted. If stepwise, then four extreme possibilities are identifiable as shown in the 4 reaction profiles below, (Schemes (52) and (53)). The reaction profile for the concerted reaction is shown in Scheme (54).

Heterolysis of bond (a) precedes that of bond (b).

If the heterolysis of bond (a) precedes that of bond (b), (Scheme (52)) there are two possible reaction profiles, (1) and (2) where either the cleavage



Reaction Profiles

Scheme (52)

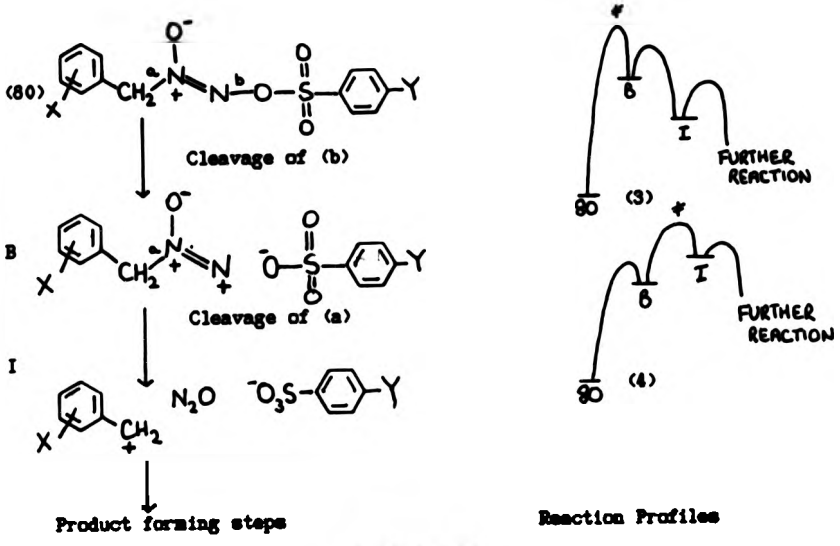
of bond (a) or the cleavage of bond (b) is rate determining. If the former is the case, then in the activated complex, bond (b) is still intact, and therefore $\rho(\sigma)$ for Y = 0. Bond (a) is undergoing heterolysis and developing electron

deficiency on the benzylic carbon which would result in a large and negative ρ for X correlating with σ^+ (rather than with σ).

If the cleavage of bond (b) is rate limiting (Profile (2)) then, in the activated complex, bond (a) is completely broken, and there is a full positive charge on the benzylic carbon. This would result in a very large negative ρ for X with σ^+ (rather than σ). At this time, bond (b) is undergoing cleavage, and negative charge is developing on the sulphonate group and a substantial positive $\rho(\sigma)$ should result for Y.

Heterolysis of bond (b) precedes that of bond (a).

Here again there are two possible reaction profiles, (3) and (4). If the cleavage of bond (b) is rate determining, (3), then in the activated complex,



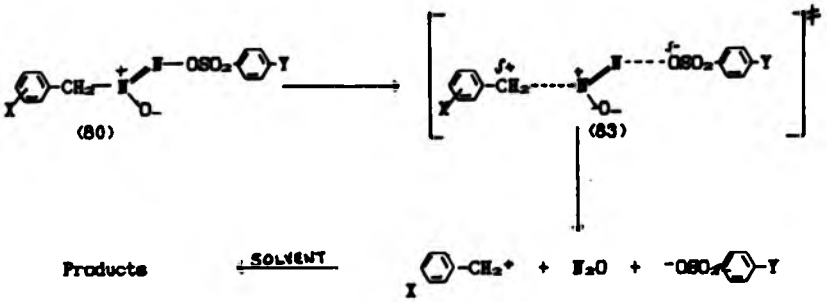
Scheme (53)

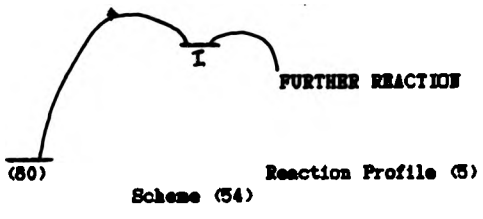
bond (a) is intact and $\rho(\sigma)$ for X should be zero, or small and negative. Meanwhile, bond (b) is undergoing heterolysis resulting in a substantially positive $\rho(\sigma)$ for Y.

Alternatively the cleavage of bond (a) is rate determining, in which case, in the activated complex, there is a development of positive charge on the benzylic carbon. The value of ρ for X should be large, and negative correlating with σ^+ (rather than σ). In the activated complex, (b) is already completely broken, so there is a full negative charge on the sulphonate resulting in a large positive $\rho(\sigma)$ for Y.

Concerted cleavage of bonds (a) and (b).

If the rate-determining formation of the N_2O-separated ion pair is the concerted fragmentation of bonds (a) and (b), then in the activated complex there is partial heterolysis of both (a) and (b) which should result in a large

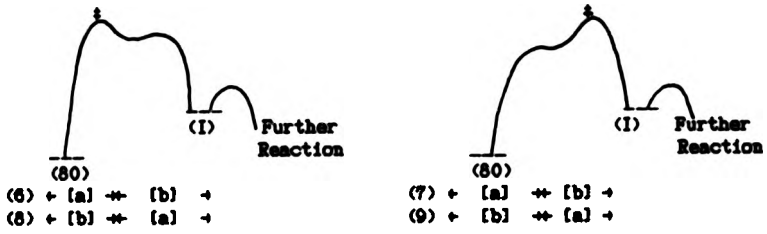




Reaction Profile (5)

Scheme (54)

negative $\rho(\sigma^+)$ for X and substantial positive $\rho(\sigma)$ for Y. Reaction profile (5) illustrates a synchronous concerted reaction where bonds (a) and (b) are cleaving to the same extent at the same time. However, a concerted reaction may also be uncoupled, where although in the rate-determining step both bonds are breaking, the cleavage of one bond is in advance of the other in the activated complex. The possible reaction profiles for this are represented by (6), (7), (8) and (9) in Scheme (55), where the horizontal axis of each of the profiles is labelled twice; the sections on the axes labelled [a] and [b] are where the cleavage of bonds (a) and (b) respectively represent the most important component of the reaction co-ordinate. In this case it should be noted that there are no minima (and thus no intermediates) between reactant and H_2O-separated ion pair.



Scheme (55)

By consideration of the actual results for ρ obtained in this work and their comparison with literature values of ρ for similar reactions, eight of the above reaction profiles are ruled out, (see the following Sections) and the nature of the transition state for the solvolytic ionisation of azoxyarenesulphonates is determined.

4.2.2 Substituted Benzyl Azoxytosylates

For the solvolysis of a series of substituted benzyl azoxytosylates ((80), X = 3-Cl, 4-Cl, H, 3-CH_3, 4-CH_3, 4-OCH_3; Y = CH_3[144], ((80), X = 4-CN; Y = CH_3 did not give a clean solvolysis reaction, see Section 3.3.1, p74)) in 1:1 TFE:H_2O the Hammett correlation with σ^+ is better than with σ, and $\rho(\sigma^+)$ = -3.27 (Figure (3), R > 0.999, Appendix (1)). This indicates that there is a depletion of electron density on the benzylic carbon in the transition state, which implies that the carbon nitrogen bond, (*a*) in Scheme (51) is undergoing cleavage in the activated complex, and reaction profile (3) is immediately ruled out.

However, the ρ-value, although strongly negative (-3.27), is towards the lower end of the range found in the (non-linear) correlation for acetolysis of substituted benzyl tosylates ($\rho(\sigma^+)$ = -5.71 → -2.33; see Fig.(2), Section 2.2.4.2, p43)[99]. Here, the more negative ρ-value, obtained when there are electron-donating substituents present, indicates a high degree of carbonium character in the transition state; that is, the carbon-tosylate bond is very nearly if not completely broken in the transition state, and the reaction resembles closely the classical S_N1 mechanism. The less negative ρ, obtained in the presence of electron-withdrawing substituents indicates that here in the transition state, less positive charge is developed on the benzylic carbon which is, therefore, still appreciably bonded to the leaving group. In this case, an S_N2-type mechanism, though probably strongly uncoupled, is taking place. The intermediate value of -3.27 obtained for the solvolysis of the azoxytosylates therefore suggests that at the transition state of the initial rate-determining fragmentation, the nucleofuge is still partially bonded to the benzylic carbon, and this rules out reaction profile (2) of Scheme (52), (p66). In addition, the

linearity of the correlation of the anonytosylates shows that there is no change in mechanism over a substantial range in reactivity (5.6 × 10^{9} at 25°C).

Activation Parameters

The enthalpies of activation found for the solvolyses of the substituted benzyl anonytosylates are high, ranging from 86 to 107 $kJmol^{-1}$, (Table (1), Appendix (1)). These correspond to activated complexes where bonds are looser than in the ground state, and agrees with the proposed activated complex where heterolysis is taking place. Further, a trend is seen; $\Delta H^{\ddagger}$ decreases with increase in the electron-donating ability of the substituent in the benzene ring. This is to be expected from consideration of the reaction co-ordinate in Figure (6). A more electron releasing substituent will better stabilise a positively charged benzylic carbon by the donation of electron density, and the enthalpy of formation of the reactive intermediate is lowered from ΔH_a to ΔH_b, (Fig. (6)). This in turn has an effect on the enthalpy of activation, and the

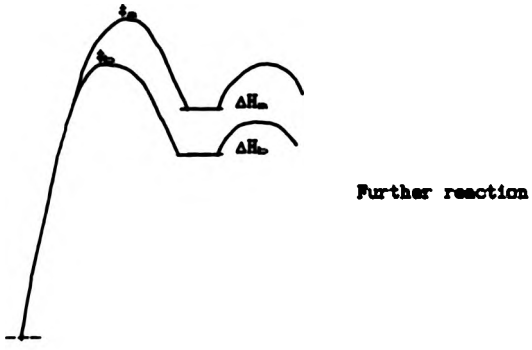


Figure (6)

position in the reaction co-ordinate of the activated complex, which moves down and left on the figure as drawn, from 4_a to 4_b. The activated complex containing the electron-releasing substituent thus now bears more resemblance to the reactant; the bond heterolysis is less advanced, and $\Delta H^{\ddagger}$ is smaller.

The values obtained for the entropies of activation show no such trend; they are small and negative ranging from -17 to -6 $JK^{-1}mol^{-1}$, (Table (1), Appendix (1)). That they are so small when there is appreciable bond loosening in the molecule on going from ground to transition state with the attendant increase in rotational and translational entropy, indicates that there must also be an accompanying decrease in entropy in the system, presumably due to solvent ordering. The formation of partial charges, positive on the benzylic carbon and negative of the tosylate group, have a polarising and thus ordering effect on the solvent molecules, whose rotational and translational entropy is reduced. These effects are large and opposing, and the difference in magnitude between them shows itself in the modestly negative entropies of activation. It can be seen that it is $\Delta H^{\ddagger}$ that has greater influence on the free energy of activation and hence the rate of the reaction.

4.2.3 Substituted 4-Methylbenzyl Arenesulphonates[144]

For the series of substituted 4-methylbenzyl arenesulphonates ((80), X = CH_3; Y = OCH_3, CH_3, Br, CN) a linear Hammett correlation is found with σ, (ρ = +1.07, R = 0.996; Figure (3), Appendix (1)). The enthalpies of activation again exhibit a trend; they decrease as the electron-withdrawing ability of the substituent increases. The entropies of activation are all small and negative. The interpretation of these activation parameters is straightforward and similar to that given above; again the kinetic change is due principally to changes in $\Delta H^{\ddagger}$ rather than $\Delta S^{\ddagger}$.

The positive ρ-value indicates that there is a build-up of electron density on the incipient arenesulphonate leaving group in the activated complex; that is, the N-O bond ((b), in Scheme (51)) is in the process of cleaving, ruling out reaction profile (1) of Scheme (52), (p. 86). The correlation was better with σ than with σ^-, as expected since the accumulation of negative charge is on the oxygen of the sulphonate leaving group and not conjugated to the ring.

However, the ρ-value is low when compared to that obtained for the solvolysis of 2-adamantyl arenesulphonates ($\rho(\sigma) = +1.86$)[146] which is considered to solvolyse by an ion-pair mechanism with a rate-limiting step that occurs after the formation of the intimate ion-pair[147]. That is, in the activated complex, the Ad-OTs bond is completely broken and there is a full negative charge on the arenesulphonate group. In a situation like this, the ρ-value that is obtained is maximal. It is obvious, from the smaller ρ obtained for the azoxyarenesulphonates, that, in this case, less electron density accumulates on the tosyl group in the transition state, and therefore there is still appreciable bonding between the azoxy nitrogen and the tosyl oxygen in the activated complex and reaction profile (4) of Scheme (53), (p87), is ruled out.

The results of the Hammett studies on the 4-methylbenzyl azoxyarenesulphonates and the substituted-benzyl azoxytosylates show that the cleavage of bonds (a) and (b), are concerted, that is, in the activated complex heterolytic cleavage is occurring to some extent in both bonds flanking the central azoxy residue and reaction profile (5), Scheme (54) best illustrates the process which is occurring. Further implications of the magnitudes of the ρ-values are discussed below.

4.2.4 Position of the Transition State

Figure (7) is a reaction map[140] of the solvolytic ionisation of substituted-benzyl anoxyarenesulphonates to form the H_2O-separated ion pair. It is a contour diagram in which the lines join points representing molecular configurations of equal potential energy and the reaction proceeds from the bottom left to the top right corners, (from (A) to (D)). It has already been established that the ionisation is a single-step process involving concerted

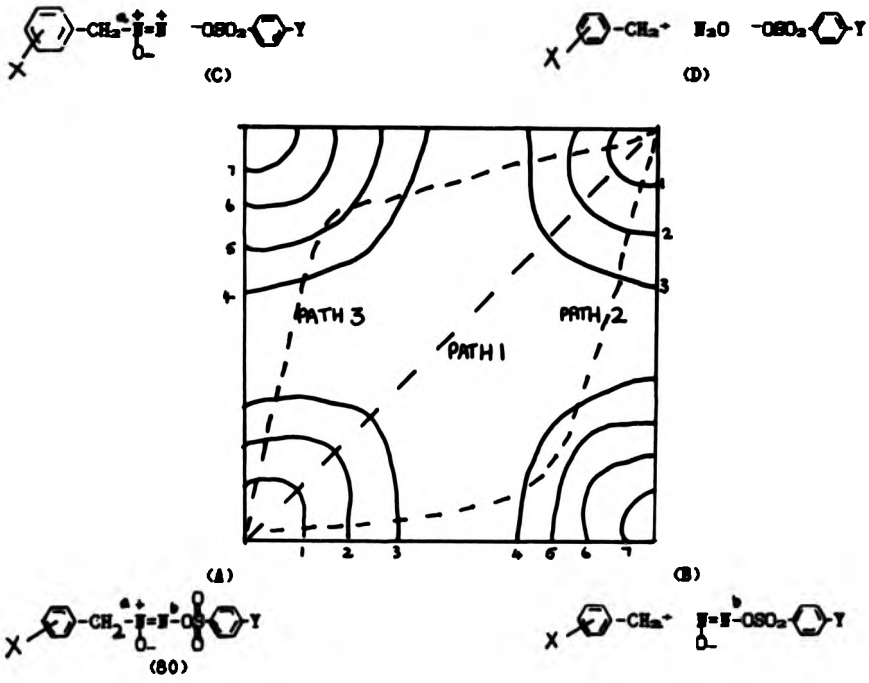


Figure (7)

bond cleavage, and does not involve intermediates of the type at corners (B) and (C), and therefore the reaction map is drawn without potential energy wells

that would correspond to these intermediates. The three possible concerted pathways are indicated by dotted lines. Pathway (1) represents a synchronous, concerted mechanism where the cleavages of bonds (a) and (b), ((80), Figure (7)) takes place to the same extent throughout the ionisation, (see.Reaction Profile (5), Scheme (54), p88). The activation barrier may in principle be situated anywhere on this reaction route. Pathways (2) and (3) correspond to the uncoupled, concerted reactions, where although both bonds (a) and (b) are broken in the concerted rate-determining step, the cleavage of one bond is far in advance of the other in the activated complex. In Pathway (2), the cleavage of bond (a) is initially ahead of that of bond (b), and in Pathway (2) the opposite is true. The activation barrier may be situated early or late on each of these leading to the Reaction Profiles (6) to (9) of Scheme (55), (p89).

It is by the determination of the the position of the activation barrier on the reaction map, that it can be established by which route the ionisation takes place. This is achieved by resolving step (A) to (D) into its perpendicular components and considering the hypothetical steps (A) to (B) and (A) to (C) separately. The extent to which the reaction proceeds from (A) to (B) (the extent of cleavage of the carbon-nitrogen bond, (a), Structure (80)) can be estimated by comparing the ρ-value obtained for the change in benzyl

(80)

substituents in the azoxytosylates with the ρ-value for the reaction that occurs during the S_N1-type acetolysis of substituted benzyl tosylates. In the latter, there is a high degree of carbonium character in the transition state and the benzyl-tosylate bond is very nearly cleaved in the rate-determining step and a

large amount, if not a full unit, of positive charge is developed on the benzylic carbon in the activated complex, resulting in a large, negative ρ, ($\rho(\sigma^+)$ = -5.71). Although the reactions (in one case it is a C-O bond which is breaking and in the other a C-N bond) and experimental conditions are different, a similarly highly negative ρ would be expected for the hypothetical step (A)→(B), (Figure (7)). The actual value for $\rho(\sigma^+)$ obtained for the solvolysis of substituted benzyl azoxytosylates is -3.27 and which is a little more than half of the likely maximal value. The less negative ρ indicates that less positive charge has been developed on the incipient benzyl cation in the activated complex, and therefore the cleavage of the bond in question is less far advanced. On the reaction map, the activated complex on the reaction pathway is thus positioned between ⅓ and ½ of the distance between (A) and (B), (see the vertical shaded area in Figure (8), where the reaction co-ordinates are expressed in terms of ρ; $\rho_1 = \rho_{(a)}/\rho_{max1}$, and $\rho_2 = \rho_{(b)}/\rho_{max2}$, where $\rho_{(a)}$ and $\rho_{(b)}$ are the ρ-values obtained by changing the X- and Y-substituents of the azoxyarenesulphonates respectively and ρ_{max1} and ρ_{max2} are the maximum theoretical values of ρ for steps (A) to (B) and (A) to (C)).

The hypothetical step from (A) to (C) can be treated similarly. At (C), bond (b) in Structure (80) is completely broken while the bond (a) remains intact. Information about the likely maximal value of ρ for the cleavage of bond (b) is obtained from consideration of the solvolysis of 2-adamantyl arenesulphonates. In this case the rate-determining step occurs after the formation of the intimate ion pair; in the activated complex the cleavage of the leaving-group bond is complete, with a full negative charge on the tosylate group, ($\rho(\sigma)$ = +1.86[148]). Again, although the reaction and conditions are different, the hypothetical step (A) to (C) would be expected to have a similarly sized ρ. The actual value obtained is +1.07 which is, again,

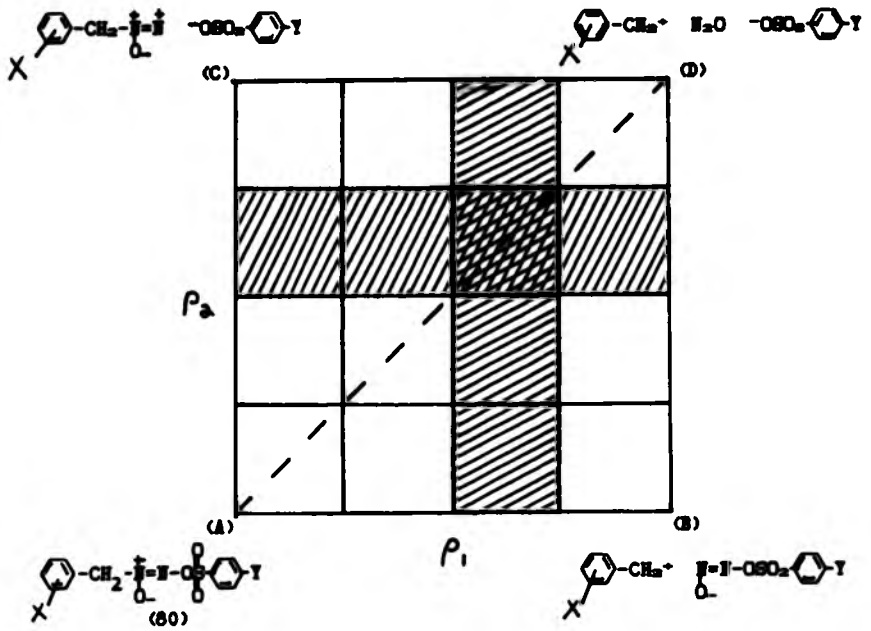


Figure (8)

a little more than half of the likely maximal value. This places the activated complex of the ionisation of substituted benzyl azoxyarenesulphonates at a situation between ⅝ and ¾ of the distance between (A) and (C) as in the horizontal shaded area in Figure (8).

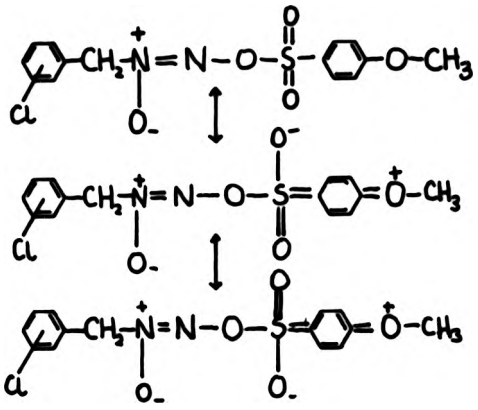
These results limit the position that the transition state of the solvolytic ionisation of benzyl azoxyarenesulphonates can be to within a small section of the area of the reaction map, (see Figure (8)). This section is positioned on the diagonal, and while ruling out the uncoupled mechanisms of Pathways (2) and (3) of Figure (7), (p94), confirms the synchronous, concerted route of Pathway (1).

4.2.5 [redacted]

The kinetic results of the solvolysis of the 3-chlorobenzyl arenesulphonates ((80), X = 3-Cl; Y = OCH_3, CH_3, Br, CN) in 1:1 v/v TFE:H_2O are presented in Table (3) and Figure (4), Appendix (1). In the Hammett plot, the three most reactive (Y = CN, Br, CH_3) fit reasonably well on a straight line, ($\rho(\sigma)$ = +0.730, correlation coefficient = 0.988). As the ρ-value is positive, there is an accumulation of electron density on the tosylate group as the reaction proceeds from ground to transition states. However, the ρ-value is smaller than that obtained from the solvolysis of the 4-methylbenzyl arenesulphonates, ($\rho(\sigma)$ = +1.07) indicating, that in comparison, the tosylate develops less negative charge, and therefore the cleavage of bond (b), ((80), Fig.7, p94) is less far advanced, in the activated complex when the benzene ring contains the 3-chloro substituent.

The least reactive of the 3-chloro-substituted compounds, (Y = OCH_3) is found to be much less reactive than expected and its point falls well off the straight line that correlates the other family members. However, when σ is replaced by σ^+, the Hammett plot can correlate all four points, ($\rho(\sigma^+)$ = +0.685, correlation coefficient = 0.989); (Figure (4), Appendix (1)). As substituent effects are usually thought of as affecting principally the stability of the transition state of a reaction, the correlation with σ^+ is unexpected; the charge that develops on the tosylate group in the transition state is negative which would be stabilised by electron withdrawing substituents. It is concluded that in this case electron-donating substituents are having more effect in the ground state than in the activated complex. It is proposed that these substituents, here principally the 4-methoxy and

perhaps also the 4-methyl groups, donate electron density to the electrophilic sulphur in the sulphonate in the reactant by conjugation as in Scheme (56). The delocalisation of charge in this way stabilises



Scheme (56)

the ground state relative to the transition state and increases the free energy of activation. Thus the reaction has a positive ρ but correlates with σ^+.

This type of conjugation seems to be far less important in the ground state of the 4-methylbenzyl azoxyarenesulphonates as their solvolysis reactions correlate linearily with σ. It follows that, by some means, the change of substituent, X at one end of the molecule affects the electron distribution at the other. It is assumed that this is due to the different inductive effects (it cannot be due to resonance effects as suitable canonical forms cannot be drawn) of the 3-chloro and 4-methyl substituents at the benzyl end.

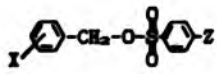
Activation Parameters.

It can be seen, by inspection of the values of the rate constants ($k^{25.0°C}$) in Tables (2) and (3), Appendix (1), that the replacement in the benzene ring of 4-methyl with 3-chloro slows the reaction of the benzyl azoxyarenesulphonates by about 200 times. This is reflected in the enthalpies of activation which are generally about 20kJmol^{-1} higher for the 3-Cl-substituted than for the 4-CH_3-substituted azoxyarenesulphonates. For the three most reactive 3-chlorobenzyl azoxyarenesulphonates there appears to be a slight increase in the enthalpy of activation with increase in electron-withdrawing ability of the substituent on the leaving group. This trend is unexpected as it is opposite to that of the 4-methylbenzyl azoxyarenesulphonates and the azoxytosylates. However, in the 3-chlorobenzyl azoxyarenesulphonate case, the entropies of activation of the 3 most reactive compounds also increase with the incorporation of increasingly electron-withdrawing substituents in the leaving group, while in the 4-CH_3-substituted case, common with the azoxytosylates studied, $\Delta S^{\ddagger}$ shows no trend. It appears to be the contribution of $\Delta S^{\ddagger}$ to the free energy of activation of the 3-chlorobenzyl azoxyarenesulphonates that allows the compounds with better electron-withdrawing substituents in the leaving group to react faster.

These trends in the enthalpies and entropies of activation of the 3-chlorobenzyl azoxyarenesulphonates are slight, especially when the estimated uncertainties are considered and therefore not too much importance can be attached to them when considering the mechanism. It can only be said that substitution in the benzyl end of the molecule seems, again, to be affecting processes that are occurring at the other end of the molecule.

4.3 Kinetics Results for 3-Chlorobenzyl Arenesulphonates

The 3-point Hammett plot for the solvolysis of the series of 3-chlorobenzyl arenesulphonates ((82), X = 3-Cl; Z = OCH_3, CH_3, Br) in 1:1 v/v TFE/H_2O, correlates well with σ, ($\rho(\sigma)$ = +1.37, correlation coefficient > 0.999; Table (4) and Fig.(3), Appendix (1)). It has been



(82)

established that in aqueous acetone[94d,99] and acetic acid[99] (see Section 2.2.4.2, p42) substituted benzyl tosylates react via an uncoupled S_N2 mechanism involving varying degrees of carbonium ion character depending on the substituent in the benzene ring, and a subsequent rate and product-analytical study of the solvolysis of benzyl tosylate in 1:1 v/v TFE/H_2O in the presence of added electrolytes[107] concluded that there was no evidence that benzyl tosylate in this solvent reacts by anything other than an S_N2 mechanism.

The ρ-value for the solvolysis of the 3-chlorobenzyl arenesulphonates was found to be positive, as expected, and, its magnitude proved to be less than that of the ρ-value obtained for the ethanolysis of 2-adamantyl arenesulphonates ($\rho(\sigma)$ = 1.86 at 25°C[148]), a reaction which is considered to take place with a fully developed negative charge on the nucleofuge in the transition state[147], and therefore, the maximal $\rho(\sigma)$. This indicates that in comparison, the development of negative charge on, and the cleavage of, the leaving group in the solvolysis of 3-chlorobenzyl arenesulphonates are less far advanced in the transition state. However, the ρ-value obtained here

($\rho(\nu)$ = +1.37) is almost equal to ¾ of the maximal value, suggesting that the mechanism for the S_N2 solvolysis of the arenesulphonates is, to a large extent, uncoupled. The cleavage of the leaving-group bond is far in advance of the formation of the bond to the nucleophile in the activated complex, even though the two processes are concerted. This is in agreement with the established view which is mentioned above.

Activation Parameters.

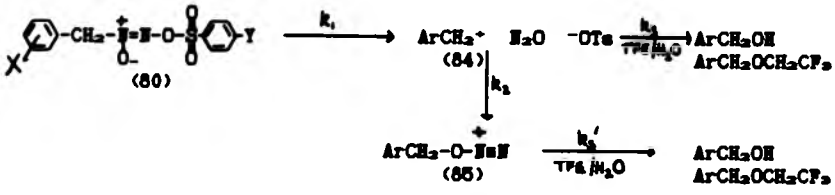
The activation parameters for the solvolysis of the 3-chlorobenzyl arenesulphonates (Table (4), Appendix (1)) are in agreement with an uncoupled S_N2 mechanism. The enthalpies of activation are relatively large, being only slightly smaller than those for the solvolysis of the azoxyarenesulphonates. This rules out a synchronous S_N2 reaction, in the transition state of which both bond formation, with a release of energy, and bond cleavage, which requires energy would be taking place. Broadly speaking these two effects would be expected to cancel each other out resulting in low enthalpies of activation. The relatively high $+\Delta H^{\ddagger}$ -values here indicate that in this case the S_N2 mechanism is uncoupled, with bond cleavage in advance of bond formation in the transition state.

The entropies of activation for the solvolysis of the 3-chlorobenzyl arenesulphonates, (Table (4), Appendix (1)) are negative and relatively large, indicating a loss of entropy on going from ground to transition states. In general, this is expected for S_N2-type mechanisms where two molecules, the nucleophile and reactant are required to react together in the activated complex with the attendant loss of translational entropy. But in the case of the uncoupled S_N2 mechanism, which is considered to be taking place here, the nucleophile is less strongly

associated with the arenesulphonate in the activated complex which results in a smaller loss of translational entropy on going from reactant to the transition state and thus a less negative entropy of activation. However, the departure of the leaving group is further advanced in the uncoupled reaction, leading to the development of a substantial amount of positive charge on the benzylic residue, and negative charge on the leaving group in the transition state, and this would be expected to have the effect of ordering the solvent by non-specific solvation, and thus increasing the loss of entropy experienced in the system as the reaction goes from ground to transition states. It can be seen that both the relatively high enthalpies and entropies (negative) of activation found for the solvolysis of the 3-chlorobenzyl arenesulphonates are compatible with their reacting by an uncoupled S_N2 mechanism.

4.4 Product Analysis

Due to the complexity of the mechanism of solvolysis of the parent unsubstituted benzyl azoxytosylate ((80), Scheme (49) p69, see also Section 2.1.5.3, p22), the results of any product analytical study of the effects of substitution in the benzene ring of azoxytosylates will not be easily interpreted mechanistically. Substitution not only

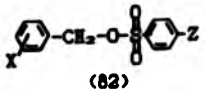


Scheme (57)

affects the reactivity of the benzylic cation (84), but also that of the intermediate (85), altering the selectivity of both towards competing solvent molecules. This in turn would be expected to affect the partitioning of the reaction between the two reaction routes open to it. Extensive and detailed procedures, involving the study of the effects of added solutes, would be required for a conclusive analysis of the effect on the reaction mechanism of substitution (at both ends of the azoxyarenesulphonate molecule), therefore the present investigation of the products of three of the substituted benzyl azoxytosylates, ((80), X = 3-Cl, 4-CH_3, 4-OCH_3; Y = CH_3); chosen as they are azoxytosylates of low, intermediate and high reactivity respectively) reacted in 1:1 v/v aqueous TFE (see Sections 3.4, 5.4) must be considered as being of a preliminary nature.

In order to obtain the relative mrf of 3-chlorobenzyl alcohol to 3-chlorobenzyl trifluoroethyl ether, the product analyses of three 3-chlorobenzyl arenesulphonates were also carried out. The interpretation of the results of the product analysis of these species is more straightforward and is presented below.

4.4.1 3-Chlorobenzyl Arenesulphonates



(82)

The products of the solvolysis of three 3-chlorobenzyl arenesulphonates ((82), X = 3-Cl; Z = OCH_3, CH_3, Br) in 1:1 v/v TFE/H_2O were analysed, and in each case the alcohol and the trifluoroethyl ether

were the only products. The absolute yield of the alcohol was very similar in each case, and averaged 87.9% of the total theoretical yield for the the OCH_3- and CH_3- substituted arenesulphonates and 89.2% for the Br-substituted compound, (Table (4), Appendix (2)). The remaining 12.1% (Z = OCH_3, CH_3) and 10.8% (Z = Br) of the product was attributed to the trifluoroethyl ether. These results lead to a water/TFE selectivity ratio for the 3-chloro-substituted benzylic intermediate of 7·3 (Z = OCH_3, CH_3) and 8·3 (Z = Br); the analogous value found for the unsubstituted benzyl tosylate was 4.9[107].

It is assumed that these compounds solvolyse by an uncoupled S_N2-type reaction wherein the departure of the leaving group is in advance of the concerted but not synchronous attack of the nucleophile. As, in the transition state the benzylic electrophile is very loosely bound to the incipient leaving group, it is to be expected that change in the substitution on the leaving arenesulphonate should not have much (if any) effect on the selectivity of the benzylic carbonium ion towards the competing nucleophiles, and the closely similar results for (82), X = 3-Cl, Z = CH_3, OCH_3 bear this theory out. It should be remembered that the product analysis of the brosylate ((82), X = 3-Cl; Z = Br) contains greater errors than those for the other two 3-chlorobenzyl arenesulphonates, (see Section 3.4.2, p80) and so the 12% difference in alcohol/trifluoroethyl ether product ratio between them is not considered mechanistically significant.

Alteration of the substituent, X on the incipient benzyl cation should have an effect on the selectivity. In comparison of unsubstituted and 3-chlorobenzyl tosylates, the introduction of the chlorine in the meta position has a destabilising effect on the transition state and

slows the reaction down, ($10^4 k_{obs}^{25\cdot0}$ = 19·07 and 0.448 s^{-1} for benzyl and 3-chlorobenzyl tosylates in 1:1 aqueous TFE, respectively). The S_N2 transition state becomes tighter and the nucleophile becomes more closely involved in the activated complex. It is clear that the better nucleophile (here the water) is now the more effective agent, and indeed it can be seen from the figures calculated for the selectivities above that the 3-chloro-benzylic compound does select more for water (compared with TFE) than does the more reactive unsubstituted benzylic compound.

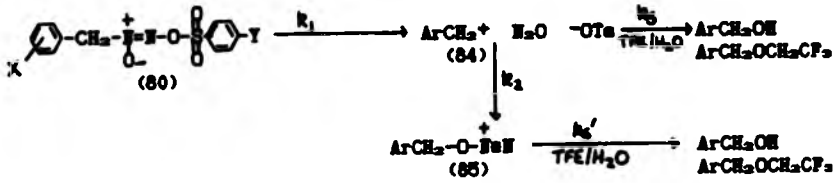
4.4.2 Azoxytosylates

The analysis, by hplc, for the products of solvolysis in 1:1 v/v aqueous TFE of three of the substituted benzyl azoxytosylates, ((80), X = 3-Cl, 4-CH_3, 4-OCH_3) was carried out. The major products were found, as expected, to be the corresponding alcohol and trifluoroethyl ether. The corresponding aldehyde was detected as a minor product in all three cases and N-3-chlorobenzyl, N-nitrosohydroxylamine was detected in low yields as a product of the solvolysis of the 3-chlorobenzyl azoxytosylate. Other possible products, the corresponding oximes and N-hydroxylamines, were not present. When the ratios of product alcohol to trifluoroethyl ether are calculated, values of 3·3 : 1, 2·9 : 1 and 7·7 : 1 are obtained for the 3-chlorobenzyl, 4-methylbenzyl (using the adjusted value for the product trifluoroethyl ether (see Section 3.4.3, p80)) and 4-methoxybenzyl azoxytosylates respectively.

4.4.3 Reactivity and Selectivity

It was mentioned in the introduction to this section that complexity of the solvolytic reaction of the azoxytosylates cannot allow extensive

mechanistic interpretation to be made from these preliminary results. Here the selectivities are discussed in terms of the overall reaction, where the reactant azoxytosylates solvolyse to form product alcohol and trifluoroethyl ether, via the electrophilic intermediates (84) and (85) which cannot be treated separately.



Scheme (57)

If the reaction took place solely through one electrophilic intermediate, it would be expected that its selectivity, as monitored by the size of the alcohol/trifluoroethyl ether product ratio, would decrease with increasing reactivity of the cationic intermediate. That is, the more stable the intermediate the more time it has to diffuse through the solvent media to find and react with the best nucleophile present, resulting in a high selectivity ratio. On the other hand the more reactive and short-lived the intermediate, the less time it has to diffuse out of its solvent cage and the more likely it is to react with the first available nucleophile. That is, the more reactive the intermediate, the more likely it is to form products from the available nucleophilic species in the ratio that these species are present.

However, in the case of the parent unsubstituted benzyl azoxytosylate, another process was found to be at work as the overall selectivity ratio of the electrophilic intermediates in 1:1 v/v aqueous TFE was found to be 2·1 : 1, smaller than the proportion of water to TFE

in the solvent (the molar proportion of H_2O-CF_3CH_2OH in this solvent is 4 : 1); there was an approximately 2-fold selectivity in favour of TFE over the much more nucleophilic water. This feature has also been found in the product ratios of the less reactive 3-chloro- and more reactive 4-methylbenzyl azoxytosylates whose ratios are 3·3 : 1 and 2·9 : 1 respectively.

In contrast, when the 4-methoxy substituent is introduced, the electrophilic intermediates are much better stabilised and are expected to be much longer-lived. These species would be expected to be more selective, in favour of the more nucleophilic water molecules, resulting in its having a higher alcohol/trifluoroethyl ether product ratio. The figure determined above for this ratio (7·7 : 1) bears this theory out.

SECTION 5

EXPERIMENTAL

5 Experimental Section

5.1 General Details

Infrared (IR) spectra were determined with a Shimadzu 435 infrared spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained on a Perkin-Elmer R24 or R32 spectrometer using tetramethylsilane (TMS) as an internal standard. Ultraviolet (UV) spectra were determined on a Perkin-Elmer Lambda 5 UV/Visible spectrophotometer and kinetic experiments following changes in UV spectra were carried out on a Pye Unicam SP8-300 UV/Visible spectrophotometer interfaced with an Apple II Europlus microcomputer[149]

Analyses by high performance liquid chromatography (hplc) were carried out on Gilson Instruments (pumps, model 303; manometric module, model 802c; gradient manager, model 702) using a Gilson UV detector and a 20µl injection loop, and connected to a Pye Unicam PU 4810 computing integrator and an Apple II Europlus microcomputer. Melting points were determined using a Kofler hot stage and are uncorrected.

Pentane that was used for purification purposes was washed three times with concentrated sulphuric acid, then with aqueous sodium carbonate solution and water and then was dried over calcium chloride and fractionally distilled from phosphorus pentoxide. Diethyl ether was purified by passing it down a column of alumina (grade 1) immediately prior to use. 2,2,2-Trifluoroethanol (TFE) (Fluorochem) was refluxed over polyphosphoric acid for 1½ hours, then distilled on to molecular sieve (type 3A) from which it was fractionally distilled (74-75°C) before being used as solvolytic medium. The 4-toluenesulphonyl chlorides were all freshly recrystallised from 40-60 petrol before use. Hplc grade methanol (May and Baker) and distilled water were filtered before being used for hplc analysis.

5.2 Preparations

5.2.1 Oximes

All the variously substituted benzaldehyde oximes were prepared from their aldehydes by the same general method, illustrated by the preparation of the parent, unsubstituted benzaldehyde oxime. Sodium acetate trihydrate (97.93g, 0.72mol), hydroxylamine hydrochloride (25.0g, 0.36mol) and benzaldehyde (38.21g, 0.36mol) were dissolved in a water: methanol mixture (200ml:100ml) and the solution was refluxed for three hours. The methanol was distilled off and the residue was extracted three times with dichloromethane. The combined organic phase was washed with saturated sodium bicarbonate solution, dried (sodium sulphate), filtered and evaporated to give the liquid oxime which was purified by distillation at atmospheric pressure, (b.p. 128-130°C; 31.76g, 0.26mol, 87%); δ_H(CDCl$_3$,60MHz) 9.1(1H,br,exch D_2O), 8.0(1H,s), 7.3 (5H,s). The other oximes prepared were all crystalline solids and were recrystallised from methanol/water mixtures.

2-Chlorobenzaldehyde oxime: 12.47g, 80mmol, 80%; mp 71-75°C, lit'[80]75°C; (E isomer) 75°C; δ_H(CDCl$_3$, 60MHz) 9.3(1H br, exch D_2O), 8.0(1H,s), 7.1-7.6 (4H,s).

4-Chlorobenzaldehyde oxime: 19.9g, 0.13mol, 68%; mp 103-107°C, lit'[80](E isomer 110°C); δ_H(CDCl$_3$ 60MHz) 8.7(1H br, exch D_2O), 8.15(1H,s), 7.4(4H,s).

4-Cyanobenzaldehyde oxime: 9.5g, 65mmol, 87%; mp 174-176°C, lit'[81] 143-145°C; δ_H(CDCl$_3$, 60 MHz) 8.1(1H,s), 7.5(4H,s), exchangeable proton was not seen.

2-Methylbenzaldehyde oxime: 7.9g, 58mmol, 58%; mp 58-60°C; δ_H(CDCl$_3$, 60MHz) 9.2(1H br, exch D_2O), 8.1(1H,s), 7.1-7.4(4H,s), 2.3(3H,s).

4-Methylbenzaldehyde oxime: 12.02g, 89mmol,89%; mp 74-76°C, lit'[80](E isomer) 80°C; δ_H(CDCl$_3$,60MHz) 8.1(1H,s), 7.0-7.5(4H,q), 2.3(3H,s), exchangeable proton was not seen.

[redacted]: 38.91g, 0.28mol, 80%; mp 55-58°C, lit'[80]60°C; δ_H ($CDCl_3$, 60MHz) 8.8(1H, br, exch. D_2O), 7.6-7.2(5H,s), 2.3(3H,s).

[redacted]'[82]: mp 60-64°C, lit'[80](E isomer) 65°C; δ_H($CDCl_3$ 60MHz) 8.1(1H,s), 7.6-6.8(4H,q), 3.8(3H,s), exchangeable proton was not observed.

4-Dimethylaminobenzaldehyde oxime'[83]: mp 135-150°C, lit'[80] (E isomer) 144°C; δ_H($CDCl_3$ 60MHz) 8.1(1H,s), 6.5-7.5(4H,q), 2.9(6H,s), exchangeable proton was not observed.

5.2.2 N-Substituted Hydroxylamines

All the oximes were reduced by the same method, illustrated by the preparation of the parent, unsubstituted benzylhydroxylamine. Portions of sodium cyanoborohydride (1.06g, 16.9mmol) and a solution made up from ice cold methanol (30ml) and acetyl chloride (10ml) were added alternately over about 20 minutes to a stirred solution of benzaldehyde oxime (3.0g, 24.5mmol) and a single crystal of methyl orange in methanol. Sufficient methanolic HCl was added to maintain the colour on the pink side of the red-yellow colour change. The methanol was then evaporated under reduced pressure at room temperature, and enough dilute aqueous NaOH was added to the residue to bring the pH up to 9.5. The solution was then saturated with sodium chloride and extracted three times with dichloromethane. The combined extracts were washed with brine, dried (sodium sulphate), filtered and evaporated to give an oil which crystallised under a stream of argon, and was dried in a vacuum desiccator, (2.8g). The hydroxylamine was purified by sublimation (0.1mmHg, 55°C); 2.03g, 16.48mmol, 67.3%; mp 53-55°C, lit'[40] 58-58°C; δ_H($CDCl_3$ 60MHz), 7.2(5H,s), 6.65(2H, br, exch. D_2O), 3.89(2H,s).

3-Chlorobenzylhydroxylamine: 2.26g, 14.3mmol, 82%; mp 45-49°C; δ_H ($CDCl_3$ 60MHz) 7.4-7.2(4H,s), 6.6(2H, br, exch. D_2O), 3.89(2H,s).

4-Chlorobenzylhydroxylamine: 2.68g, 17.0mmol, 97%; mp 79-83°C, lit[18] 87-88.5; δ_H ($CDCl_3$ 60MHz) 7.2(4H,s), 6.1-5.7(2H, br, exch. D_2O), 3.9(2H,s).

4-Cyanobenzylhydroxylamine. The same procedure was followed but with different relative amounts of materials (p-CN-C_6H_4CHNOH (0.91g, 6.23mmol), $NaCNBH_3$ (0.52g, 8.30mmol)) and the reaction was stirred overnight. Yield: 0.69g, 4.66mmol, 75%; mp 120-122°C, lit[18] 127-128.5°C; δ_H ($CDCl_3$ 60MHz) 7.75-7.45(4H,s), 5.25(2H,br, exch. D_2O), 4.05(2H,s).

3-Methylbenzylhydroxylamine: 1.5g, 10.93mmol, 73%; mp 39-40°C; δ_H ($CDCl_3$ 60MHz) 7.0(4H,s), 5.85-5.50(2H,br, exch. D_2O), 3.85(2H,s), 2.30(3H,s).

4-Methylbenzylhydroxylamine: 1.29g, 9.4mmol, 51%; mp 59-61; δ_H ($CDCl_3$ 60MHz) 7.05(4H,s), 5.9(2H,br, exch. D_2O), 3.85(2H,s), 2.75(3H,s).

1-Phenylethylhydroxylamine: mp(recryst. ether:pentane, 3:1) 66-70°C, lit[20]69-70°C; 1.05g, 7.65mmol, 32%; δ_H ($CDCl_3$ 60MHz) 7.2(5H,s), 6.4(2H,br. exch. D_2O), 4.15-3.80(1H,q), 1.35(3H,d).

4-Methoxybenzylhydroxylamine: 3.36g, 21.9mmol, 94%; δ_H ($CDCl_3$ 60MHz) 7.20-6.65(4H,q), 6.35(2H,br. exch. D_2O), 3.80(2H,s), 3.67(3H,s).

4-Dimethylaminobenzylhydroxylamine: Here the indicator used was thymol blue and a greater proportion of reductant was required: ($(CH_3)_2NC_6H_4CH$=OH (2.8g, 17mmol), $NaCNBH_3$ (1.1g, 17mmol)); 1.59g, 9.6mmol, 56%; mp 78-83°C; δ_H ($CDCl_3$ 60MHz) 7.20-6.55(4H,q), 6.47(2H,br. exch.D_2O), 3.82(2H,s), 2.85(6H,s).

5.2.3 N-Nitroso,N-arylmethylhydroxylamines

All the N-nitroso,N-arylmethylhydroxylamines were prepared by the same method as illustrated by the preparation of the parent, N-nitroso,N-benzylhydroxylamine[84b,184]. An ice cold solution of sodium nitrite (2.17g,

31.1mmol) in water (5ml) was added over about five minutes to a stirred solution of benzylhydroxylamine (1.90g, 15.43mmol), aqueous hydrochloric acid (2.1N, 11cm³, 23.1mmol),and methylated spirits (5cm³). After about 5 minutes a thick white precipitate formed, ice cold water was added, and the diluted solution was filtered through a precooled glass sinter using the suction from a water pump. The crystals were dried in a vacuum desiccator at room temperture; 1.70g, 11.2mmol, 72%; mp 68-74°C, lit[188]74-76°C; δ_H ($CDCl_3$ 60MHz) 7.25(5H,s), 6.5(1H,br. exch.D_2O), 5.15(2H,s). The aqueous filtrate was extracted with ice cold ether three times. The combined ether phase was dried at 0°C (sodium sulphate), filtered and evaporated under reduced pressure to leave pale yellow crystals identical by nmr with the first batch (0.18g, 1.2mmol,7.8%).

N-Nitroso N-(3-chlorobenzyl)hydroxylamine. First batch: 0.31g, 1.66mmol, 26%; mp 42-46°C; δ_H ($CDCl_3$ 60MHz) 9.4(1H,br. exch. D_2O), 7.15(4H,s), 5.26(2H,s); $\bar{\nu}$(KBr) 2700(m), 1600(w), 1555(s), 1490(m), 1470(m), 1440(m), 1330(m), 1270(s), 1190(m), 1070(s), 1000(w), 970(w), 940(m), 910(w), 870(m), 810(m), 740(s), 680(m), 630(w), 510(w), 470(w) cm^{-1}. Second batch (from aqueous filtrate): 0.12g, 0.64mmol, 10%; ^{1}Hnmr spectrum is identical to that of the first batch.

N-Nitroso N-(4-chlorobenzyl)hydroxylamine[188]. First batch: 0.7g, 3.75mmol, 59.5%; mp 125-127°C; δ_H ($CDCl_3$ 60MHz) 7.3(4H,s), 5.15(2H,s), exchangeable proton was not observed; $\bar{\nu}$(KBr) 3450(w), 2500(s), 1630(m), 1490(m), 1420(m), 1250(m), 1210(m), 1160(m), 1140(m), 1090(m), 1015(m), 850(m), 815(m), 755(s), 695(m) cm^{-1}

Second batch (aqueous filtrate): 0.14g, 0.75mmol, 17.0%; ^{1}Hnmr spectra is identical to that of the first batch.

N-Nitroso N-(4-cyanobenzyl)hydroxylamine. First batch: 0.19g, 1.1mmol, 50.0%; mp 105-111°C; δ_H ($CDCl_3$ 60MHz) 7.20(4H,s), 5.15(2H,s), exchangeable proton was not observed; $\bar{\nu}$(KBr) 3050(m), 2225(m), 1460(m), 1070(s), 960(m),

770(m), 690(m), 555(s) cm^{-1}. Second batch: 0.11g, 0.62mmol, 28.7%; ^{1}Hnmr spectrum is identical to that of the first batch.

N-Nitroso N-(4-methoxybenzyl)hydroxylamine. First batch (0.49g, 2.69mmol, 41.2%) mp 45-56°C; δ_H ($CDCl_3$ 60MHz) 7.3-6.6(4H,q), 5.05(2H,s), 4.75(1H,br. exch. D_2O), 3.7(3H,s). Second batch: (0.33g, 1.81mmol, 27.7%); ^{1}Hnmr spectrum is identical to that of the first batch.

N-Nitroso N-(dimethylaminobenzyl)hydroxylamine. First batch: 0.32g, 1.64mmol, 54%; δ_H ($CDCl_3$ 60 MHz) 7.4-6.6(4H,q), 5.10(2H,s), 2.95(6H,s), exchangeable protons were not observed. Second batch: 0.23g, 1.18mmol, 39%; ^{1}Hnmr identical to that of first batch.

N-Nitroso N-(4-methylbenzyl)hydroxylamine. Single batch: 0.69g, 4.2mmol, 93.9%; mp 125-131°C; δ_H ($CDCl_3$ 60MHz) 7.2(4H,s), 6.6(1H,br. exch D_2O), 5.15(2H,s), 2.35(3H,s); $\bar{\nu}$(KBr) 3400(m), 2350(m), 1750(m), 1440(m), 1420(m), 1400(m), 1250(m), 1190(m), 1120(m), 915(m), 740(m), 690(m), 585(m), 465(m) cm^{-1}.

N-Nitroso N-(3-methylbenzyl)hydroxylamine. Single batch obtained as an oil isolated from the ether extraction of the reaction mixture. Yield: 0.56g, 3.37mmol, 75%; δ_H ($CDCl_3$ 60MHz) 7.20(4H,s), 5.15(2H,s), 2.30(3H,s), exchangeable proton was not observed; $\bar{\nu}$(thin film) 3250(m), 2900(m), 1480(m), 1440(m), 780(m), 690(m) cm^{-1}.

N-Nitroso N-(1-phenylethyl)hydroxylamine. Single batch was isolated as an oil by ether extraction of the reaction mixture. Yield: 0.48g, 2.89mmol, 38%; mp(trit. diethyl ether) 39-42°C; δ_H ($CDCl_3$ 60MHz) 7.25(5H,s), 5.65-5.25(1H,q), 1.95-1.76(3H,d), exchangeable proton was not observed; $\bar{\nu}$(KBr) 2330(m), 1580(m), 1360(s), 1230(s), 980(m), 910(m), 770(m), 660(m), 590(w), 510(w) cm^{-1}. It proved to be difficult to obtain this compound in sufficient quantity and in a pure enough state to proceed to the tosylation step, so this preparation was not carried any further.

5.2.4 Substituted Benzyl-ONN-Azoxybenzenesulphonates.

Two methods were employed to prepare these compounds.

Tipson method[142].

p-Toluenesulphonyl chloride (recryst.,0.33g, 1.68mmol) was added in portions to a stirred solution of N-nitroso,N-benzylhydroxylamine (0.17g, 1.12mmol) in dry pyridine (1.5cm³) at 0°C under argon. The reaction mixture was kept at 0°C overnight, then 3 drops of ice cold water were added and the solution was stirred for another 10 minutes. The mixture was then diluted with water and extracted three times with diethyl ether. The combined ether phase was washed twice with an ice cold saturated aqueous solution of copper sulphate and twice with ice cold aqueous sodium bicarbonate before being dried (magnesium sulphate),filtered and evaporated under reduced pressure to give colourless crystals which were dried at room temperture in a vacuum desiccator. [0.25g, 0.82mmol, 72.9%; 87-90°C,lit[146] 90°C; δ_H ($CDCl_3$ 60MHz) 7.90-7.65(4H,ABq), 7.25(5H,s), 5.10(2H,s), 2.42(3H,s)]. The following compounds were also prepared by this method.

3-Chlorobenzyl Azoxytosylate: 0.11g, 0.32mmol, 30.2%; mp(trit.(i)ether, (ii)pentane) 82-85°C; δ_H ($CDCl_3$ 60MHz) 7.95-7.20(4H,ABq), 7.25(4H,s), 5.12(2H,s), 2.46(3H,s); $\tilde{\nu}$(KBr) 3100(m), 2900(m), 1590(m), 1575(m), 1510(m), 1375(m), 1290(m), 1180(m), 1085(m), 975(m), 915(m), 870(m), 815(m), 755(m), 730(m), 775(m), 655(m), 615(m), 540(m), 500(m), 470(w) cm^{-1}; found C 49.94, H 3.93, N 8.26; calculated for $C_{14}H_{13}ClN_2O_4S$: C 49.34, H 3.84, N 8.22.

4-Chlorobenzyl Azoxytosylate: 0.26g, 0.76mmol, 48%; mp(recryst. at low temp., diethyl ether) 111-112°C; δ_H ($CDCl_3$ 60MHz) 7.90-7.10(4H,ABq), 7.17(4H,s), 5.07(2H,s), 2.45(3H,s); $\tilde{\nu}$(KBr) 3400(w), 2950(w), 1590(m), 1500(m), 1380(m), 1285(m), 1185(m), 1085(m), 1015(m), 972(m), 915(m), 810(m), 760(m), 725(m),

670(m), 635(m), 610(m), 555(m), 535(m), 510(m) cm^{-1}; found C 49.37, H 3.64, N 8.19; calculated for $C_{14}H_{12}ClN_3O_4S$: C 49.34, H 3.84, N 8.22.

4-Cyanobenzyl Azoxytosylate: 0.24g, 0.72mmol, 67.7%; mp(recryst. diethyl ether) 143-145°C; δ_H ($CDCl_3$ 60MHz) 7.90-7.15(8H,multiplet), 5.15(2H,s), 2.46(3H,s), $\bar{\nu}$(KBr) 3080(w), 3030(w), 2220(m), 1517(m), 1391(s), 1195(s), 1182(s), 922(m), 815(m), 781(s), 682(m), 561(m), 542(m) cm^{-1}; found C 54.48, H 3.90, N 12.66; calculated for $C_{15}H_{13}N_3O_4S$: C 54.37, H 3.95, N 12.68.

3-Methylbenzyl Azoxytosylate: after the usual procedure, the product was isolated as a paste; several triturations with diethyl ether were required before white crystalline material was obtained; mp 87-88°C; δ_H ($CDCl_3$ 60MHz) 7.85-6.95(8H,multiplet), 5.05(2H,s), 2.4(3H,s), 2.25(3H,s); $\bar{\nu}$(KBr) 2920(m), 1590(m), 1500(m), 1475(m), 1170(s), 1085(m), 900(m), 810(m), 750(m), 710(m), 680(m), 660(m), 610(m), 545(m), 490(m) cm^{-1}; decomposed under the conditions required for CHN analysis.

4-Methylbenzyl Azoxytosylate: 0.16g, 0.49mmol, 41%; mp(trit. ether) 91-93°C (dec); δ_H ($CDCl_3$ 60MHz) 7.90-6.95(4H,ABq), 7.02(4H,s), 5.00(2H,s), 2.41(3H,s), 2.28(3H,s); $\bar{\nu}$(KBr) 2920(w), 2850(w), 1590(w), 1500(m), 1380(m), 1190(s), 1115(m), 1085(m), 1034(m), 1015(m), 900(m), 815(m), 748(m), 715(m), 660(m), 548(m), 528(m) cm^{-1}; decomposed under the conditions required for CHN analysis.

4-Methoxybenzyl Azoxytosylate: 0.23g, 0.68mmol, 97%; the yellow crystals obtained were triturated several times with diethyl ether, and still remained intensely yellow; mp 63-65°C; δ_H ($CDCl_3$ 60MHz) 7.90-7.25(4H,ABq), 7.25-6.70(4H,ABq), 5.05(2H,s), 3.77(3H,s), 2.43(3H,s); $\bar{\nu}$(KBr) 1600(m), 1500(s), 1375(s), 1240(s), 1170(s), 1115(m), 1085(m), 1020(s), 900(s), 815(s), 775(m), 745(s), 715(m), 675(m), 655(m), 605(m), 535(s) cm^{-1}; decomposed under the conditions of CHN analysis.

4-Dimethylaminobenzyl Azoxytosylate: attempts to prepare this compound failed. Effervescence was observed on the addition of the tosyl chloride and it was assumed that the compound was reacting as it was formed.

4-Methylbenzyl Azoxy-4-bromobenzenesulphonate: 0.13g, 0.34mmol, 57%; mp(trit. diethyl ether) 88-90°C (dec.); δ_H ($CDCl_3$ 60MHz) 7.90-7.45(4H,ABq), 7.07(4H,s), 5.05(2H,s), 2.33(3H,s); $\tilde{\nu}$(KBr) 3090(w), 2885(w), 1610(w), 1510(m), 1390(m), 1195(s), 1175(s), 1070(m), 905(m), 825(m), 770(m), 740(m), 620(m), 590(m), 555(m) cm^{-1}; found C 43.94, H 3.51, N 5.96; calculated for $C_{14}H_{13}BrN_2O_4S$: C 43.65, H 3.40, N 7.27.

Aqueous Method[16]

The aqueous method is illustrated by the preparation of 4-methylbenzyl azoxy-4-methoxybenzenesulphonate. To an ice cold stirred solution of N-nitroso,N-(4-methylbenzyl)hydroxylamine (0.19g, 1.14mmol) and p-methoxybenzenesulphonyl chloride (freshly recrystallised, 0.59g, 2.85mmol) dissolved in acetone (5cm^3), was added dropwise an aqueous solution of sodium hydroxide (1.2cm^3, 2Molar, 2.4mmol) over a period of about 15 minutes. When a precipitate appeared, water (0.5cm^3) was added and the mixture was stirred at ice temperture for a further 30 minutes. More water was then added (2cm^3), the precipitate was filtered cold and dried in a vacuum desiccator,(0.39g). The material was purified by low temperature recrystallisation from a diethyl ether/pentane mixture followed by trituration with diethyl ether; mp 86-87°C (dec.); δ_H ($CDCl_3$ 90MHz) 7.95-6.85(4H,ABq), 7.15(4H,s), 5.10(2H,s), 3.87(3H,s), 2.34(3H,s); $\tilde{\nu}$(KBr) 3100(w), 2950(w), 1590(s), 1515(s), 1490(s), 1385(m), 1265(s), 1200(m), 1170(s), 1085(m), 1020(s), 800(m), 770(s), 685(m), 665(m), 560(s) cm^{-1}; The following compounds were also prepared by this method.

4-Methylbenzyl Acetoxy-4-cyanobenzenesulphonate: 0.11g, 0.33mmol, 36%; mp(trit. diethyl ether)70-75°C; δ_H ($CDCl_3$ 60MHz) 8.15-7.60(4H,ABq), 7.15(4H,s), 5.12(2H,s), 2.41(3H,s); $\bar{\nu}$(KBr) 3100(w), 2900(w), 2250(m), 1515(m), 1387(m), 1220(s), 1190(s), 1120(m), 1015(m), 890(m), 845(m), 762(m), 635(m), 565(s), 515(m) cm^{-1}; decomposed under the conditions for CHN analysis.

3-Chlorobenzyl Acetoxy-4-methoxybenzenesulphonate: 0.17g, 0.48mmol, 59%; mp(trit. diethyl ether) 85-90°C; δ_H ($CDCl_3$ 90MHz) 7.95-6.80(4H,ABq), 7.25(4H,m), 5.11(2H,s), 3.88(3H,s); $\bar{\nu}$(KBr) 3065(w), 3025(w), 2930(w), 1565(s), 1465(m), 1365(s), 1290(s), 1250(s), 1160(s), 1080(m), 1010(m), 965(m), 910(m), 860(m), 790(m), 710(s), 770(s) cm^{-1}; found C 47.28, H 3.75, N 7.72; calculated for $C_{14}H_{13}ClN_2O_6S$: C 47.13, H 3.67, N 7.85.

3-Chlorobenzyl Acetoxy-4-bromobenzenesulphonate After the usual procedure, not enough material came out of solution to be filtered so the reaction medium was extracted three times with diethyl ether. The combined extractions were washed with brine, dried (sodium sulphate), filtered and evaporated down. Yield: 0.14g, 0.35mmol, 44%; mp(recryst. diethyl ether/pentane at low temp.) 101-104°C; δ_H ($CDCl_3$ 60MHz) 7.95-7.25(8H,multiplet), 5.1(2H,s); $\bar{\nu}$(KBr) 3080(w), 2910(w), 1595(w), 1570(s), 1525(s), 1470(m), 1437(m), 1395(s), 1375(m), 1347(m), 1190(s), 1177(s), 1090(m), 1067(m), 1010(m), 942(m), 802(s), 771(s), 742(s), 585(s), 550(s) cm^{-1}.

3-Chlorobenzyl Acetoxy-4-cyanobenzenesulphonate: 0.36g, 1.25mmol, 58%; mp(recryst. diethyl ether) 102-106°C; δ_H ($CDCl_3$ 60MHz) 8.80-7.20(8H, multiplet), 5.35(2H,s); $\bar{\nu}$(KBr) 3050(w), 2910(w), 2220(w), 1590(w), 1570(m), 1470(m), 1430(m), 1350(m), 1315(m), 1270(m), 1205(m), 1170(s), 1055(m), 872(m), 792(s), 710(s), 680(m), 635(w), 540(s), 500(m) cm^{-1}; decomposed under the conditions required for elemental analysis.

5.2.5 Substituted Benzyl Arenesulphonates.

The benzyl arenesulphonates were all prepared by the same method; illustrated by the preparation of 3-chlorobenzyl tosylate[149a]. Sodium hydride (0.178g, 7.43mmol) was added to 3-chlorobenzyl alcohol (1.06g, 7.43mmol) in dry diethyl ether and the mixture was stirred at room temperature for ca. 14 hours, then cooled to -25°C. An ethereal solution of tosyl chloride (1.42g, 7.43mmol) was added, and the reaction mixture was left at <0°C for about 14 hours. The suspension became white and the precipitate was filtered off with minimum exposure to the air. The filtrate was evaporated leaving the colourless product: 0.38g, 1.18mmol, 15.9%; mp(recryst. twice from pentane) 79-81°C, lit[149a]81.5-82°C; δ_H ($CDCl_3$ 60MHz) 7.80-7.15(4H, ABq), 7.15(4H, m), 4.98(2H,s), 2.42(3H,s); found C 56.38, H 4.45; calculated for $C_{14}H_{13}ClO_3S$: C 56.66, H 4.42.

3-Chlorobenzyl 4-bromobenzenesulphonate: 0.43g, 1.19mmol, 22.3%; mp (recryst. 1:1 diethyl ether:pentane at R.T.) 51-53°C; δ_H ($CDCl_3$ 60MHz) 7.76-7.45(4H, ABq), 7.25-6.98(4H,m), 4.99(2H,s); found C 43.22, H 2.80; calculated for $C_{13}H_{10}BrClO_3S$: C 43.18, H 2.80.

3-Chlorobenzyl 4-methoxybenzenesulphonate: mp(recryst. twice diethyl ether) 49-51°C; 0.38g, 1.21mmol, 18.0%; δ_H ($CDCl_3$ 60MHz) 7.90-6.75(4H,ABq), 7.12(4H,m), 4.89(2H,s), 3.54(3H,s); found C 53.56, H 4.20; calculated for $C_{14}H_{13}ClO_4S$: C 53.76, H 4.19.

4-Methylbenzyl tosylate: 1.29g, 4.67mmol, 47.6%; mp(recryst. from 3:1 petrol(40-60): diethyl ether) 50-57°C, lit[149a]57.9-58.5°C; δ_H ($CDCl_3$ 60MHz) 8.00-7.25(4H,ABq), 7.15(4H,s), 5.01(2H,s), 2.45(3H,s), 2.30(3H,s), $\bar{\nu}$(KBr) 3400(w), 2900(w), 1590(m), 1470(m), 1210(m), 1175(m), 1095(m), 1085(m), 925(m), 815(m), 658(m), 570(m), 530(m) cm^{-1}; decomposed when subjected to the conditions required for elemental analysis.

4-Methylbenzyl methoxybenzenesulphonate. This compound was found to be too reactive at room temperture to provide a melting point, IR, or nmr spectra. It needed to be kept below -15°C, above which temperature the white crystals would decompose into a red amorphous material. Difficulties in handling these very reactive substrates have been reported previously[143b].

5.3 Kinetic Measurements

The rates of solvolysis were measured by monitoring the decrease in UV absorbance at a suitable wavelength, (usually between 260 and 230nm), in the thermostatted cell compartment of a Pye Unicam Spectrophotometer interfaced with a controlling computer[149]. The solvolysis of each compound was followed in triplicate at each of 4 different temperatures spanning a 30 centigrade degree range. Each time, the reaction was followed for between 4 and 5 half lives and between 80 and 100 data points were collected. First order rate constants were calculated using a non linear least squares programme; for illustration the first-order plots of the solvolysis of 3-chlorobenzyl azoxytosylate at four temperatures are presented in Figure (1), Appendix (1). The activation parameters were calculated by a computer programme using an Eyring type plot, of the type in Figure (2), Appendix (1) again for 3-chlorobenzyl azoxytosylate.

In all cases the solvolysis medium was 1:1 v/v aqueous trifluroethanol (TFE). For the less reactive compounds, a stock solution of the substrate in the solvolysis medium, (ca.10^{-3}mol l^{-1}) was made up, kept at low temperature, and used as required. The more reactive materials were added, with much shaking, to cuvettes of the solvolytic medium at the temperature required immediately prior to the kinetic run. In general, each run was done in triplicate, and the average rate constant was obtained. The standard deviations within each run,

and between runs at the same temperature were normally less than 1% and 3%, respectively. The activation parameters and the calculated rate constant at 25°C ($k_{obs}^{25°C}$) for the variously substituted benzyl arenesulphonates and ascuyarenesulphonates and are tabulated in Tables (1)-(4) in Appendix (1). The Hammett plots derived from these data are shown in Figures (3) and (4) in Appendix (1).

5.4 Product Analysis

The product analyses were carried out by high performance liquid chromatography (hplc) at various temperatures on a reverse phase C-18 Spherisorb (5μ) column using aqueous methanol as eluant. Samples were introduced to the column via a Rheodyne valve (7125) fitted with a 20μl injection loop, and the pump maintained the eluant flow at $1.5cm^3min^{-1}$. The UV detector was set at 257nm, and at sensitivity = 0.05. The integrator was used with the attenuation set at 8. Quantitative analyses were made using external standards as the injection loop reliably injected the same volume of liquid each time. Compounds whose products were to be analysed were accurately weighed and dissolved in the reaction medium (4ml, ca. $10^{-2}mol\ l^{-1}$) in a sealed flask and maintained at an appropriate temperature for over 10 half lives. The solutions of reaction products were then analysed by direct injection.

5.4.1 Absolute Molar Response Factors of the Alcohols

The alcohols were commercially available and were purified until no trace of aldehyde could be detected by hplc. 3-Chlorobenzyl and 4-methoxybenzyl alcohols were distilled under low pressure (oil pump, bpt.= 83-84°C; water pump, bpt.= 134-136°C, respectively) and 4-methylbenzyl alcohol was recrystallised

from heptane (mpt.= 60-61°C). All the calibration data are in Tables (1)-(3) Appendix (2), and the method used for setting up the calibration graph is illustrated below for the case of the 3-chlorobenzyl alcohol.

0.0853g of the alcohol was accurately weighed into a 50ml volumetric flask which was filled to the mark with 50% aqueous methanol, (0.0186M). This solution was diluted 3 times, to give concentrations of 0.0149M, 0.0119M and 0.0101M. Each solution was injected five times and the average area integration was used to set up the calibration graph, (Figure 1, and Table 1, Appendix 2); peak heights were found to be less reliable. The standard deviation found for the areas was always less than 1% of the area and usually under 0.5%. The correlation coefficient, obtained from a linear regression programme run on an Apple Europlus 2 computer, for the calibration graph was always greater than 0.999. The same process was carried out with dilutions from another weighing of alcohol (12.0×10^{-3}, 9.60×10^{-3}, 4.80×10^{-3} and 2.40×10^{-3}M) and the resultant points plotted on the same graph without significantly affecting the correlation coefficient. After the product analyses, two of the solutions used for the calibration graph were injected again to ensure that the calibration was still valid. The linear regression programme was used to obtain the concentration of alcohol product in each reaction mixture from its integrated analysis and the calibration data.

5.4.2 Relative MRF of 3-Chlorobenzyl Trifluoroethyl Ether

It was not possible to obtain easily the substituted benzyl trifluoroethyl ethers in a pure enough state to obtain their absolute molar response factors directly, (see Section 3.4.2), so the following method was employed to obtain the relative molar response factor of 3-chlorobenzyl trifluoroethyl ether with respect to 3-chlorobenzyl alcohol. The products of the reactions of three 3-

chlorobenzyl arenesulphonates in 1:1 aqueous TFE were analysed, (see next Section) as in all of these three cases, the only expected (and the only observed) products were the alcohol and the trifluoroethyl ether. The absolute and thus the percentage yields of the alcohol were obtained from the relevant calibration curve, (see previous Section). By difference, the percentage and hence absolute yields of the trifluoroethyl ether were calculated. Comparison of the areas under the signals for the now known molarities of the two products allowed the relative mrf to be calculated, using the equation below.

$$\text{rel. mrf} = \frac{\text{trifluoroethyl ether integration} \times [\text{alcohol}]}{\text{mCl-benzyl alcohol integration} \times [\text{trifluoroethyl ether}]}$$

The results from the three 3-chlorobenzyl arenesulphonates are presented in the next Section and in Table (4) Appendix (2) show that the average value of 1.10±0.02 was obtained.

5.4.3 Analysis of the Arenesulphonates

The analyses of the following experimental results are presented in Table (4), Appendix (2), and in Section 3.4, and are discussed in Section 4.4.1

3-Chlorobenzyl 4-methylbenzenesulphonate

The compound was reacted in duplicate overnight at 50°C (more than 10 half-lives) and each reaction was analysed at least 5 times. The eluant composition was 65% methanol for the analysis of the alcohol (retension time = 4 min) and 78% methanol for the trifluoroethyl ether (retension time = 4.5 min). The column temperature was between 21°C and 23°C.

In Solution (1), 0.0136g and in Solution (2), 0.0131g were dissolved in 4ml of the reaction medium, yielding concentrations of 0.0137 mol l^{-1} and 0.0110 mol l^{-1} respectively. The mean integration results are presented below; the standard deviation is presented as a percentage.

Products	Average Integration Solution (1)	Solution (2)
Alcohol	673929 ± 1.4%	543324 ± 0.4%
Trifluoroethyl ether	105765 ± 1.1%	81296 ± 1.8%

The concentration of alcohol in the reaction products was found from consultation of the calibration data in Table (1), Appendix (2) and the relative-mrf of the trifluoroethyl ether to alcohol was calculated using the equation in the above Section. The results obtained are presented in Table (4), Appendix (2).

3-Chlorobenzyl 4-methoxybenzenesulphonate.

The conditions for the analysis of this compound are as above. The compound was reacted in duplicate overnight at 40°C (that is, for at least ten half-lives), and each reaction was analysed a minimum of 5 times. In both Solution (1) and Solution (2), 0.0161g were dissolved in 4ml of the reaction medium yielding a concentration of 0.01447 mol l^{-1} in both cases. The mean integration results are presented below and the standard deviation is presented as a percentage.

Products	Average Integration Solution (1)	Solution (2)
Alcohol	710712 ± 0.7%	710642 ± 0.7%
Trifluoroethyl ether	106401 ± 1.7%	104686 ± 4%

As in the previous case, these results are presented in Table (4), Appendix (2).

3-Chlorobenzyl 4-bromobenzenesulphonate.

A different hplc column was used for the analysis of this compound, with a different 3-chlorobenzyl alcohol calibration curve, (X-axis: mol l^{-1}; Y-axis: integration counts; gradient, 54522471; intercept, -6619; correlation coefficient, 0.9996). A concentration gradient was used in the analysis, whereby the percentage of methanol in the eluant increased from 65% to 80% during the chromatographic run. The compound was reacted in duplicate in 1:1 aqueous TFE and each reaction was analysed 5 times. In Solution (1), 0.0187g and in Solution (2), 0.0130g were dissolved in 4ml of reaction medium giving concentrations of 0.0129 mol l^{-1} and 0.0089 mol l^{-1} respectively. The mean integration results are presented below and the standard deviation is presented as a percentage.

Products	Average Integration Solution (1)	Solution (2)
Alcohol	617599 ± 2.9%	434990 ± 1.8%
Trifluoroethyl ether	100081 ± 2.2%	77299 ± 6.4%

As above, the analysis of this data are presented in Table (4), Appendix (2).

5.4.4 Analyses of the Acetoxylates

The analyses of the following experimental results are presented in Tables (5) and (6), Appendix (2), in Section 3.4.3, and are discussed in Section 4.4.2.

3-Chlorobenzyl Acetoxylate.

The compound was reacted in duplicate for at least ten half-lives (3 days at 60°C) and each reaction was analysed a minimum of 5 times. Eluant composition was 55% methanol for the analyses of the alcohol and aldehyde, (retention times ca. 4.9 and 7.0 minutes respectively) and 67% methanol for the

trifluoroethyl ether, (retention time between 8.5 and 9 minutes). The column temperature was held at 40°C in all cases.

In Solution (1), 0.0121g and in Solution (2), 0.0157g were dissolved in 4ml 1:1 v/v aqueous TFE, yielding concentrations of 8.8767×10^{-3} and 11.52×10^{-3} mol l^{-1} respectively. The mean integration results are in the table below, where the standard deviation is presented as a percentage.

Products	Average Integration Solution (1)	Solution (2)
Alcohol	375511 ± 0.4%	490972 ± 0.4%
Trifluoroethyl ether	131602 ± 1.5%	168230 ± 1.5%
Aldehyde	56593 ± 6.2%	75173 ± 10%
N-Nitrosohydroxylamine	4482 ± 8%	4942 ± 30%

4-Methylbenzyl Azoxytosylate.

As above, this compound was reacted in duplicate for at least ten half-lives (10 hours at 35°C) and the products of the reaction were analysed a minimum of 5 times. Eluant composition was 65% methanol for the analysis of the alcohol (retention time around 3.6 minutes) and 78% for the trifluoroethyl ether, (retention time ≈ 4.6min). The analyses were carried out at 21-24°C. The integration data, with their percentage standard deviations, are presented in the table below. It has subsequently been shown that 4-methylbenzyl trifluoroethyl ether is very insoluble in aqueous methanol and because of this the validity of the integration results for this compound are now suspect, (see Section 3.4.3).

In Solution (1), 0.0146g of azoxytosylate was dissolved in 4ml, resulting in a concentration of 11.39×10^{-3}mol l^{-1} and in Solution (2), 0.0111g were dissolved in the same volume, equivalent to 8.662×10^{-3} mol l^{-1}.

Products	Average Integration Solution (1)	Solution (2)
Alcohol	657056 ± 0.6%	500780 ± 0.9%
Trifluoroethyl ether	180519 ± 0.8%	143634 ± 1.6%
Aldehyde	10050 ± 7%	5452 ± 9%
N-Nitrosohydroxylamine	----	----

4-Methoxybenzyl Acetoxylate.

Due to the reactivity of this compound its purity could not be established with accuracy, therefore analysis could only establish the ratio of alcohol to trifluoroethyl ether and not their absolute yields, (see Section 3.4.3). The compound was reacted four times (2 hours at 25°C) and the products of reaction from each were analysed a minimum of 5 times at 40°C. The eluant composition was 45% methanol for the analysis of the alcohol (retention time = 4.5 minutes), and 65% methanol for the trifluoroethyl ether, (retention time = 6.0 minutes). The average integrations for the products of each reaction are tabulated below.

Solution	Average Integration Alcohol	Trifluoroethyl Ether
(1)	172191 ± 0.9%	19481 ± 3.8%
(2)	551237 ± 1.6%	73546 ± 2.8%
(3)	348732 ± 1.7%	42874 ± 3.5%
(4)	626003 ± 3.1%	100410 ± 3.0%

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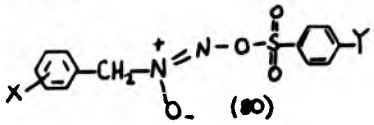
APPENDICES

APPENDIX 1, TABLE1.

Rates and Activation Parameters of
SUBSTITUTED BENZYL AZOXYTOSYLATES, (80) Y=CH_3



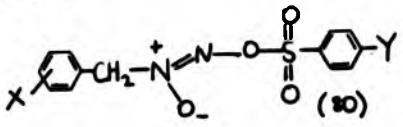
(80)

X	T/°C [b]	10^5 k/s^{-1} [c]	10^5 k^{298}/s^{-1} [d]	$\Delta H^{\ddagger}_{298}$ / kJmol^{-1} [e]	$\Delta S^{\ddagger}_{298}$ /JK^{-1}mol^{-1} [f]	Correlation Coefficient
mCl	80.3	30.0 ± 1.0%				
	71.4	11.7 ± 2.6%				
	61.9	4.24 ± 1.1%				
	50.1	0.924± 1.6%	0.0310	107	-11	>0.999
pCl	71.1	69.9 ± 1.0%				
	63.5	31.3 ± 0.5%				
	54.1	10.5 ± 0.5%				
	45.2	3.42 ± 1.6%	0.232	103	-6	>0.9999
H	61.5	43.8 ± 0.1%				
	52.7	15.4 ± 0.8%				
	44.9	5.97 ± 1.6%				
	39.2	3.18 ± 0.3%	0.467	100	-12	>0.999
mCH_3	70.2	182 ± 1.4%				
	60.0	61.2 ± 0.7%				
	51.9	24.0 ± 1.4%				
	42.0	7.14 ± 0.5%	0.764	101	-6	>0.9999
pCH_3	60.0	316 ± 2.0%				
	51.4	141 ± 1.0%				
	42.7	51.3 ± 0.8%				
	34.9	19.7 ± 0.1%	5.95	92	-17	>0.999
$pOCH_3$	44.0	1380 ± 9.0%				
	39.5	906 ± 1.4%				
	30.6	406 ± 1.6%				
	21.1	94.3 ± 15 %				
	16.9	65.8 ± 7 %	174	86	-9	>0.99

a Solvolysis carried out in 1:1 v/v T.F.E.: H_2O
b Standard deviation of temperature <0.2 °C
c In general, three runs were made at each temperature (see Section 5.3)
-standard deviation within a run was always <1%
d Estimated uncertainty : 1%
e Estimated uncertainty : 3 kJ mol^{-1}
f Estimated uncertainty : 7 JK^{-1}mol^{-1}

APPENDIX 1, TABLE 2.

Rates and Activation Parameters of 4-Methylbenzyl Anoxyarenesulphonates[a] ((80), X=4-CH_3; Y= OCH_3, CH_3, Br, Cl)



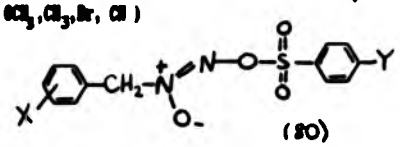
(80)

Y	T/°C [b]	10^5 k/s^{-1} [c]	10^5 k^{298}/s^{-1} [d]	$\Delta H^{\ddagger}$ / kJmol^{-1} [e]	$\Delta S^{\ddagger}$/JK^{-1}mol^{-1} [f]	Correlation Coefficient
OCH_3	60.4	269 ± 1.3%				
	51.1	99.7 ± 0.3%				
	42.4	37.6 ± 0.7%				
	32.8	11.4 ± 0.9%	4.24	95	-11	>0.9999
CH_3	60.0	316 ± 2.0%				
	51.4	141 ± 1.0%				
	42.7	51.3 ± 0.8%				
	34.9	19.7 ± 0.1%	5.95	92	-17	>0.999
Br	59.6	812 ± 1.0%				
	51.1	336 ± 4.0%				
	41.3	130 ± 0.4%				
	31.8	41.8 ± 0.1%	19.1	87	-25	>0.999
Cl	50.8	828 ± 3.0%				
	37.2	217 ± 0.2%				
	27.0	59.2 ± 0.9%				
	18.1	18.8 ± 1.0%	46.5	89	-9	>0.999

a Solvolysis carried out in 1:1 v/v aqueous T.F.E.
b Standard deviation of the temperature carried out during each run ≤ 0.5°C
c In general three runs were made at each temperature (Section 5.3)
-standard deviation within a run was always <1%
-standard deviation between runs at the same temperature is expressed as a percentage in the table.
d Estimated uncertainty :1%
e Estimated uncertainty :5kJ mol^{-1}
f Estimated uncertainty :7JK^{-1}mol^{-1}

APPENDIX 1, TABLES.

Rates and Activation Parameters of 3-Chlorobenzyl Anacyarenesulphonates[a] ((80), I=3-Cl; Y= OCH_3, CH_3, Br, Cl)



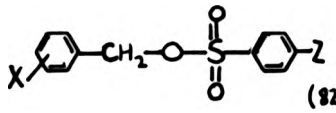
(80)

Y	T/°C [b]	10^5 k/s^{-1} [c]	10^5 k^{25}/s^{-1} [d]	$\Delta H^{\ddagger}$ / kJmol^{-1} [e]	$\Delta S^{\ddagger}$/JK^{-1}mol^{-1} [f]	Correlation Coefficient
OCH_3	82.3	24.4 ± 0.4%				
	72.3	7.97 ± 0.5%				
	60.4	1.83 ± 0.5%				
	56.7	1.15 ± 0.8%	0.0128	114	4	>0.9999
CH_3	80.3	30.0 ± 1.0%				
	71.4	11.7 ± 2.6%				
	61.9	4.24 ± 1.1%				
	50.1	0.924± 1.6%	0.0310	107	-11	>0.999
Br	82.4	165 ± 0.5%				
	76.2	55.8 ± 0.7%				
	57.8	6.43 ± 0.5%				
	48.0	1.84 ± 0.5%	0.074	109	4	>0.9999
Cl	83.2	299 ± 0.4%				
	74.6	117 ± 0.4%				
	60.6	20.4 ± 0.7%				
	51.0	6.02 ± 2.0%	0.136	114	26	>0.9999

a Solvolysis carried out in 1:1 v/v aqueous T.F.E.
b Standard deviation of the temperature carried out during each run <± 0.5°C
c In general three runs were made at each temperature (Section 5.3)
-standard deviation within a run was always <1%
-standard deviation between runs at the same temperature is expressed as a percentage in the table.
d Estimated uncertainty :1%
e Estimated uncertainty :3kJ mol^{-1}
f Estimated uncertainty :7JK^{-1}mol^{-1}

TABLE 4, APPENDIX 1.

Rates and Activation Parameters of 3-Chlorobenzyl Arenesulphonates[a] (82), X=3-Cl ; Z = OCH_3, CH_3, Br, Cl)



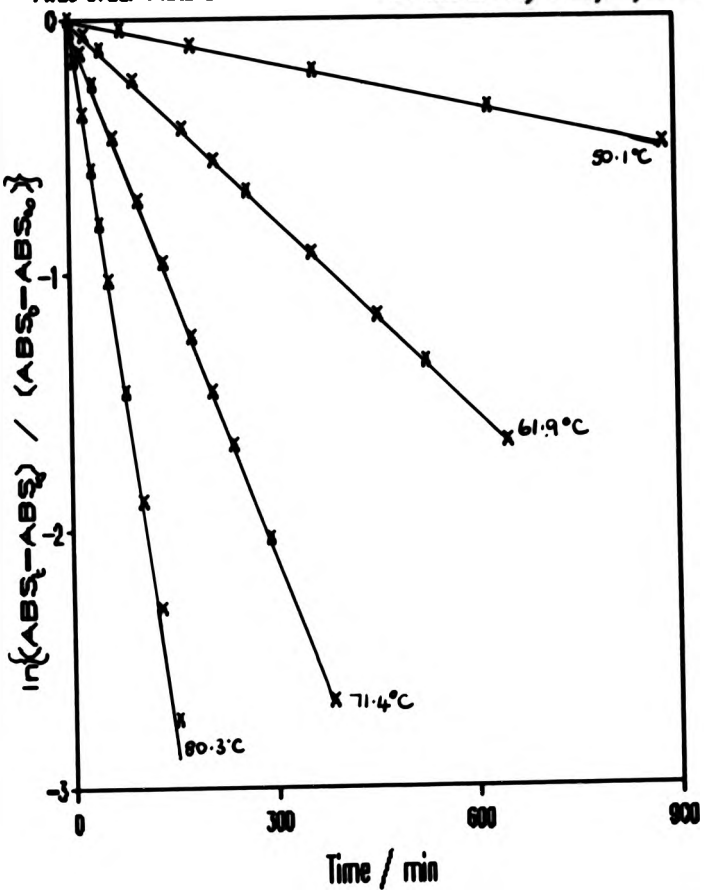
(82)

Z	T/°C [b]	$10^5 k/s^{-1}$ [c]	$10^5 F/s^{-1}$ [d]	$\Delta H^{\ddagger}$ / kJmol^{-1} [e]	$\Delta S^{\ddagger}$/JK^{-1}mol^{-1} [f]	Correlation Coefficient
OCH_3	64.5	169 ± 2.5%				
	51.7	48.1 ± 4.4%				
	41.8	20.3 ± 2.5%				
	34.5	8.52 ± 1.0%	3.08	82	-57	>0.9999
CH_3	68.7	276 ± 1.6%				
	59.7	135 ± 0.3%				
	50.4	58.6 ± 0.4%				
	29.9	7.41 ± 1.1%	4.48	78	-67	>0.999
Br	56.0	347 ± 1.1%				
	42.7	180 ± 0.8%				
	32.2	34.8 ± 0.4%				
	21.4	10.2 ± 4.4%	15.6	80	-51	>0.9999

a Solvolysis carried out in 1:1 v/v aqueous T.F.E.
b Standard deviation of the temperature during each run <±0.5 °C
c In general three runs were made at each temperature(cf. Section 5.3)
-standard deviation of the rate constant within a run was always <1%
-standard deviations from the rate constant between runs at the same temperature are expressed as a percentage in the table.
d Estimated uncertainty :1%
e Estimated uncertainty :3kJ mol^{-1}
f Estimated uncertainty :7JK^{-1}mol^{-1}

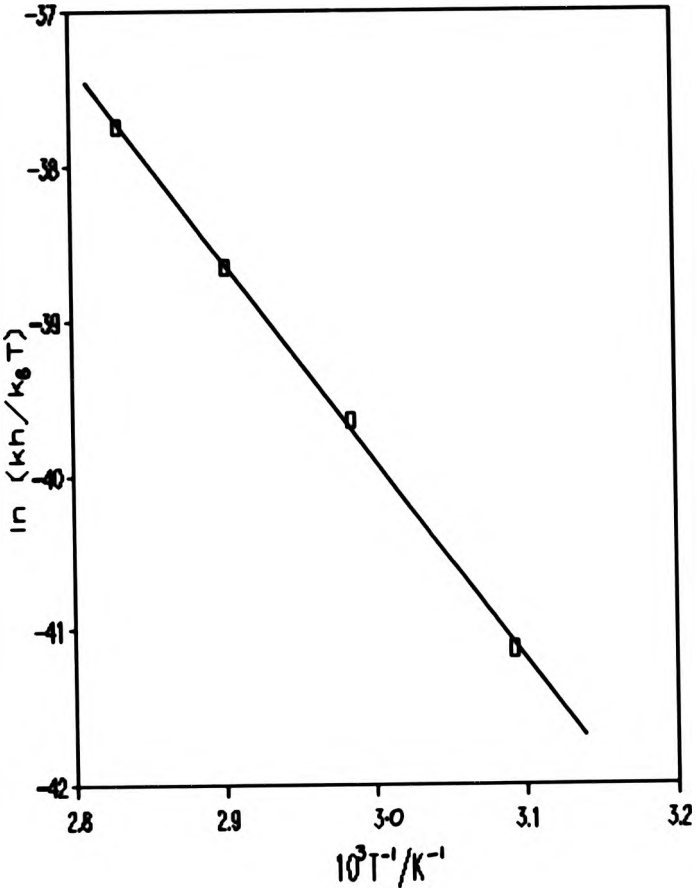
APPENDIX 1, FIGURE 1

First Order Plots of the Reaction of 3-Chlorobenzyl Azoxylosylates.



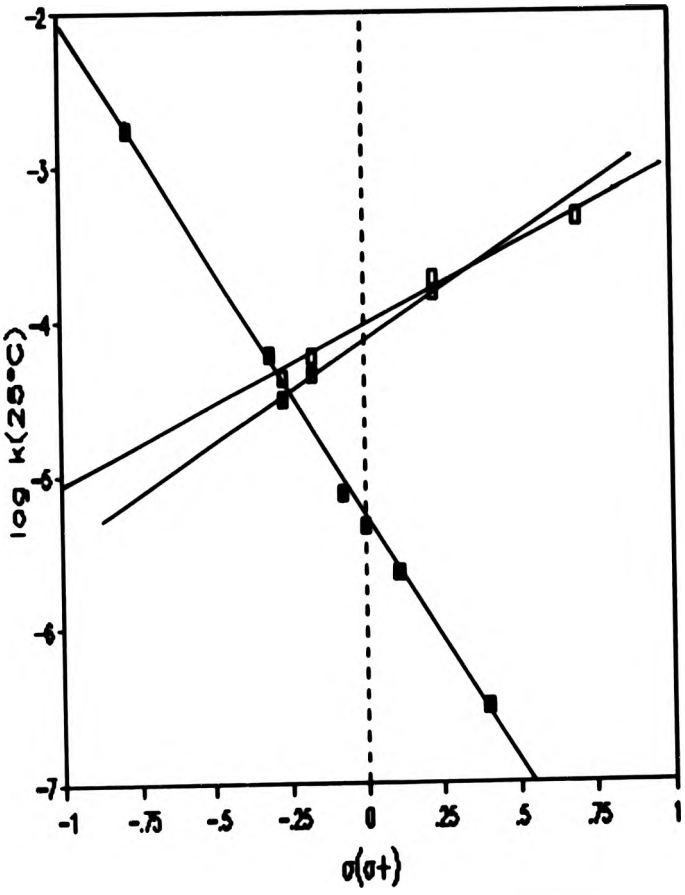
APPENDIX 1, FIGURE 2

ERYING PLOT of SOLVOLYSIS of 3- CHLOROBENZYL AZOXYTOSYLATE



APPENDIX 1, FIGURE 3:

HAMMETT PLOT



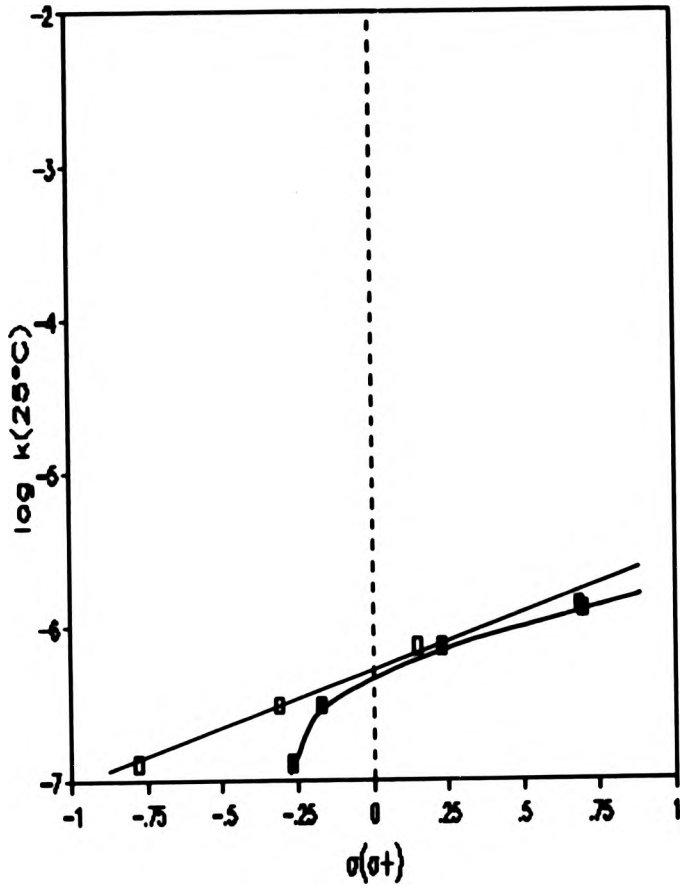
■ SUBSTITUTED BENZYL AZOXYTOSYLATES; (σ+).

□ 4-METHYLBENZYL 4-SUBSTITUTED-AZOXYARENESULPHONATES; (σ).

▨ 3-CHLOROBENZYL 4-SUBSTITUTED-ARENESULPHONATES; (σ).

APPENDIX 1, FIGURE 4

HAMMETT PLOT



3-CHLOROBENZYL
4-SUBSTITUTED-AZOXYARENESULPHONATES

■ CORRELATION WITH σ

□ CORRELATION WITH σ+

APPENDIX 2.TABLES 1,2,3.

DATA USED FOR QUANTIFICATION OF ANALYSIS.

In all cases:- Detector 257nm ,40°C,1.5 $cm^3 min^{-1}$ flow, 20µL loop; minimum of 5 analyses made for each solution.

TABLE 1 3-Chlorobenzyl Alcohol.[b]

10^3 conc /mol L^{-1}	INTEGRATION /0·5 Vs	STANDARD DEVIATION EXPRESSED AS PERCENTAGE	
18.6	1033445	0.2	
14.9	829990	0.4	SLOPE: 55614618
12	694514	0.1	INTERCEPT: 7940
11.9	668257	0.4	R >0.9993
10.1	572324	0.4	
9.6	549560	0.4	
4.8	277756	1.30	
2.4	138817	0.4	

a See fig 1, APPENDIX 2.

TABLE 2 4-Methylbenzyl Alcohol.

10^3 conc /mol L^{-1}	INTEGRATION /0·5 Vs	STANDARD DEVIATION EXPRESSED AS PERCENTAGE	
14.9	1160299	0.6	SLOPE: 77574049
9.95	696169	0.6	INTERCEPT: 2811
5.97	465042	1.20	R >0.9999
2.98	235044	0.7	

TABLE 3 4-Methoxybenzyl Alcohol.

10^3 conc /mol L^{-1}	INTEGRATION /0·5 Vs	STANDARD DEVIATION EXPRESSED AS PERCENTAGE	
12.3	1949754	0.3	SLOPE: 1 59129975
9.84	1576430	0.4	INTERCEPT: 629
6.27	986315	0.3	R >0.999
5.01	789686	0.8	
4.92	786492	0.3	
2.51	393363	0.4	
1.25	199749	0.8	

APPENDIX 2. TABLE 4

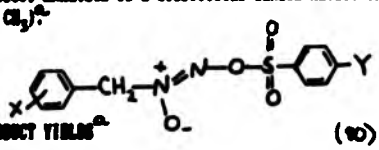
PRODUCT ANALYSIS OF SOLVOLYSIS OF 3-CHLOROBENZYL p-Y-SUBSTITUTED ARENESULPHONATES;a,b
The nrf of 3-Chlorobenzyl Trifluoroethyl Ether relative to 3-Chlorobenzyl Alcohol.

Y	Alcohol area count[c]	% Alcohol in product	Average	T.F.Ethyl ether area count[c]	% T.F.Ethyl ether in product[d]	Average	nrf	Average f
$-CH_3$ 1	673929 ± 1.4%	87.76	87.94	105765 ± 1.1 %	12.24	12.06	1.13	1.12
$-CH_3$ 2	543324 ± 0.4%	88.12		81296 ± 1.8 %	11.88		1.11	
$-OCH_3$ 1	710712 ± 0.7%	87.91	87.91	106401 ± 1.7 %	12.09	12.09	1.09	1.08
$-OCH_3$ 2	710642 ± 0.7%	87.91		104686 ± 4.0 %	12.09		1.07	
-Br 1[e]	617599 ± 2.9%	88.37	89.22	100081 ± 2.2 %	11.63	10.79	1.23	1.42
-Br 2[e]	434990 ± 1.8%	90.06		77299 ± 6.4 %	9.94		1.61	

a 2 reactions were analysed not fewer than 5 times for each compound
b Reactions analysed using data in tables 1,2,3 Appendix 1.
c 1 area count = 0.5 Vs
d % of trifluoroethyl ether in product = 100 - % alcohol in product.
e Analysis made on a different column. Calibration for 3-Chlorobenzyl alcohol: gradient=54522471, intercept = -6619, correlation coefficient = 0.9996
This result contains larger errors in determination,(cf. Section 3.4.2.)
f The relative nrfs from the analysis are averaged yielding an overall nrf of 1.10 ± 0.02

APPENDIX 2, TABLE 5

PRODUCT ANALYSIS of 2-SUBSTITUTED BENZYL ACETOXYLATES ((XC), X= 3-Cl, 4-CH_3; Y= CH_3)[a]



PRODUCT YIELDS[a] (%)

X conc / 10^3 mol l^{-1}	3-Cl SOLUTION - 1	3-Cl SOLUTION - 2	4-CH_3 SOLUTION - 1	4-CH_3 SOLUTION - 2
REACTANTS / PRODUCTS	8.877	11.52	11.39	8.662
ALCOHOL	6.61 ± 0.05[f]	8.69 ± 0.05[f]	8.43 ± 0.05[h]	6.42 ± 0.05[h]
TRIFLUOROETHYL ETHER[b]	2.01 ± 0.01[g]	2.61 ± 0.05[g]	2.08 ± 0.05[e]	1.65 ± 0.05[e]
ALDEHYDE[c]	0.011 ± 0.001[h]	0.014 ± 0.001[h]	0.0014 ± 0.0001[j]	<0.001
N-NITROSO N-HYDROXYLAMINE[d]	0.001 ± 0.007[i]	0.009 ± 0.007[i]	-	-

a The products of the analysis of 4-methoxybenzyl acetoxylate are not included here as the absolute yields could not be obtained. (Sections 3.4.3 and 5.4.4).

b Relative mrf of tri fluoroethyl ether / alcohol = 1.10

c Assumed relative mrf of aldehyde / alcohol = 96[f]

d Maximal values calculated assuming the relative mrf of N-nitrosohydroxylamine / alcohol = 1.10

e This analysis has subsequently proved to be invalid, (Section 3.4.3)

Errors calculated assuming 0.4% error in calibration curves

f 0.4%

g 1.5%

h 8.0%

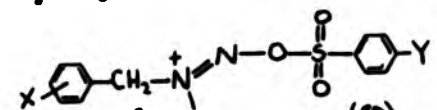
i 9.0%

j 8.0%

k 0.8%

APPENDIX 2, TABLE 6

PRODUCT ANALYSIS of X-SUBSTITUTED BENZYL ACETYTOLATES, ((60,) X=3-Cl, 4-CH_3, 4-OCH_3; Y= CH_3).[a]



(60)

PERCENTAGE YIELDS[a]

X	ALCOHOL	TRIFLUORO ETHYL ETHER	ALDEHYDE	N-NITROSO BENZYL AMINE	TOTAL
3-Cl Solution 1	74.4 ± 0.6	22.6 ± 0.6	0.12 ± 0.01	0.91 ± 0.08	98.0
3-Cl Solution 2	75.3 ± 0.5	22.6 ± 0.5	0.12 ± 0.01	0.77 ± 0.06	98.8
AVERAGE	74.9 ± 0.5	22.6 ± 0.5	0.12 ± 0.01	0.84 ± 0.07	98.4

4-CH_3 Solution 1	74.0 ± 0.5	25.9 ± 0.6[b]	0.011 ± 0.001	-	100
4-CH_3 Solution 2	74.1 ± 0.7	25.9 ± 0.7[b]	< 0.01	-	100
AVERAGE	74.1 ± 0.6	25.9 ± 0.6	0.01 ± 0.001	-	100

continued overleaf

APPENDIX 2, TABLE 6 continued.

4-OCH_3[c] Solution 1	89.1 ± 0.9[d]	10.9 ± 0.3[e]	N/A	N/A	100
4-OCH_3[c] Solution 2	88.7 ± 0.9[d]	11.3 ± 0.3[e]	N/A	N/A	100
4-OCH_3[c] Solution 3	89.1 ± 0.9[d]	10.9 ± 0.3[e]	N/A	N/A	100
4-OCH_3[c] Solution 4	86.9 ± 0.9[d]	13.1 ± 0.3[e]	N/A	N/A	100
AVERAGE	88.5 ± 0.9	11.5 ± 0.3	-	-	100

a Information from Table 5 expressed as percentages.

b It is assumed that the yield for 4-methylbenzyl trifluoroethyl ether, (see previous table) is anomously low. Here the percentage yield is calculated on the assumption that there was total product recovery, (see Section 3.4.3).

c Absolute yields were not measured (Section 3.4.3.); only the ratio of alcohol to trifluoroethyl ether could be obtained. It was assumed that there was total recovery and the relative mrf of trifluoroethyl ether to alcohol was 1.10

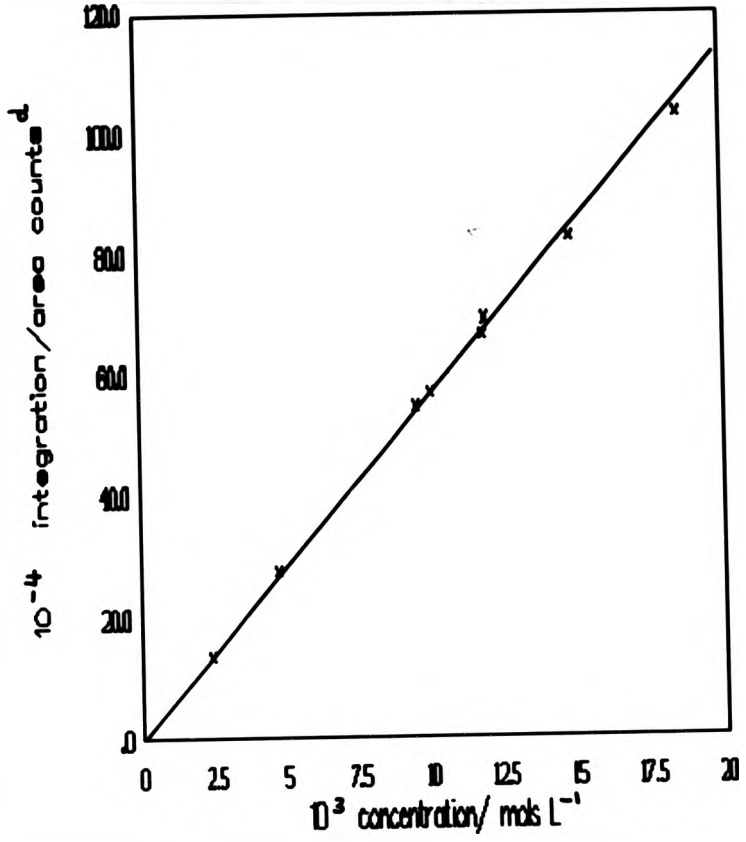
d 1.8% error in integration, 0.5% error in calibration.

e 3.5% error in integration, 0.5% error in calibration.

APPENDIX 2, FIGURE 1.

Calibration curve for 3-Chlorobenzyl Alcohol [a,b,c]

Detector's Response to Standard solutions (20 μL injection loop)



a. DATA FROM TABLE 1, APPENDIX 2.

b. TWO SOLUTIONS OF ACCURATELY KNOWN CONCENTRATION WERE DILUTED THREE TIMES. EACH SOLUTION WAS ANALYSED A MINIMUM OF FIVE TIMES, AND THE AVERAGE VALUE WAS USED FOR THE CALIBRATION CURVE.

c. CONDITIONS: DETECTOR, 257 nm; SENSITIVITY, 0.05; ELUANT, 55% MEOH; 40°C; ca. 2.7 kpsi; RETENTION time 4.97min.

d. 1 AREA COUNT = 0.5 VOLT SECOND (Vs).