KINETIC and PRODUCT ANALYTICAL STUDIES of the SOLVOLYSIS of 2-ADAMANTYL AZOXYTOSYLATE and RELATED COMPOUNDS in a RANGE of SOLVENTS

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Thesis submitted to the University of Stirling
for the degree of Doctor of Philosophy

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November 1989

ABSTRACT

Rate constants for the solvolysis of 2-adamantyl azoxytosylate were measured in, (a) acetic acid, (b) 50%v/v trifluoroethanol: water, (50TFE) and (c) 80%v/v trifluoroethanol: water, (80TFE); and for 2-adamantyl tosylate in (a) 50TFE, (b) 80TFE and (c) 90%v/v trifluoroethanol: water, (90TFE). The products from the solvolysis of 2-adamantyl azoxytosylate in acetic acid, ethanol, aqueous ethanol, trifluoroethanol and aqueous trifluoroethanol were analyzed by a combination of capillary glc and hplc. Significant yields of 2-adamantyl tosylate are obtained from internal ion pair combination (32% in acetic acid) which decrease with the increasing ionising power of the solvent. Products from the solvolysis of bicyclo[2.2.2]octan-2-yl azoxytosylate in 97%w/w hexafluoroisopropan-2-ol: water have also been analyzed. Product distributions from the azoxytosylate systems are much closer to those obtained from the corresponding tosylates than those from the corresponding solvolytic deamination even though the rate-determining step in the solvolysis of the azoxytosylates resembles much more closely the deaminative fragmentation. These results allow new insights into the nature of deamination generally, and an explanation is offered as to the reason behind the formation of rearranged products in these reactions.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. H. Maskill, for his patience and guidance, and the Science and Engineering Research Council for a Research Studentship. I should also like to thank Glaxochem, Montrose, for the use of the computer facilities to compile this thesis and to the computing staff for their assistance.

Most of all, I would like to thank my son, Ian Jr., whose love was a constant source of inspiration.

DECLARATION

This thesis has been entirely composed by myself. The work therein is part of a research programme under the supervision of Dr. H. Maskill. Acknowledgements to results used in this work which came from elsewhere have been included in the text of this thesis. In all other aspects the work is my own.

CONTENTS

CHAPTER 1

INTRODUCTION

Why should the product distribution from a carbocation depend on how that carbocation is generated? Some solvolytic reactions, deamination in particular, generally give rise to larger yields of rearranged products than do others, such as arenesulphonate solvolysis[1]. Solvolytic deamination of alkyl primary amines by nitrous acid is a complex reaction proceeding through several steps and involving unstable diazo-intermediates[2] (Scheme 1, p4).

Although deaminations have been known and studied for many years there are still major uncertainties regarding mechanism. The principal difficulty is that the rate laws are complicated and relate to the early nitrosation steps of the reaction. Solvolysis of alkyl halides and arenesulphonates are other reactions which may involve carbonium ion intermediates, but which are usually amenable to interpretable kinetic analysis. The volume and quality of results from mechanistic studies of alkyl halide and arenesulphonate solvolysis, therefore, far outweigh those from deamination. Clearly, a very desirable objective is to prepare model compounds that would allow direct kinetic investigations of the crucial carbonium ion forming steps in deamination reactions, i.e. isolable analogues of the diazohydroxide (2) in Scheme 1, which would undergo fragmentation under solvolytic conditions. Various nitro and nitroso amides

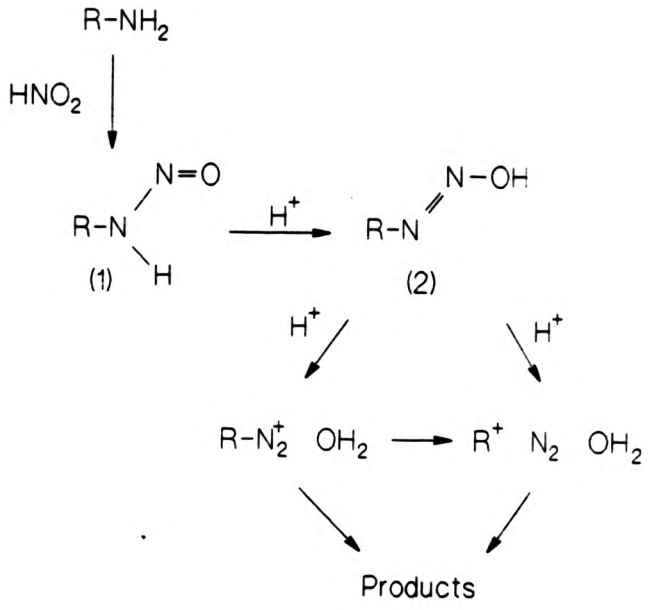
and carbamates were prepared[3,4,5] which are analogous to the N-nitroso-amine (1) in Scheme 1. These react, however, *via* a rate-limiting rearrangement to the diazo and azoxy analogues, *e.g.* (3) and (4) in Scheme 2, p5 and hence provide no direct information on the subsequent fragmentation. Nevertheless, this work did establish that the same outcome was observed for N_2O as for N_2 as leaving group in fragmentations. Likewise the 1-alkyl-3-aryltriazenes[6] (5) in Scheme 3, p6, isomerize under acid catalysis before undergoing fragmentation. Alkyl azoxytosylates (6) in Scheme 4, p7, are clearly analogous to the azoxy intermediate (4) in Scheme 2 and hence of the diazo intermediates (2) in Scheme 1 and (3) in Scheme 2. However, unlike (2),(3) and (4), compounds (6) are surprisingly stable[7].

It was thought at first that alkyl azoxytosylates did not undergo fragmentation when R=primary and secondary alkyl groups[8]. However, using a more ionizing range of solvents and with a more favourable choice of alkyl group, it was shown that these compounds did undergo a deaminative type of solvolytic reaction[9,10]. Moreover, since the nucleofuge in this fragmentation, in contrast to those of Schemes 1, 2 and 3, is arenesulphonate, this solvolysis relates not only to deamination, but also to the solvolysis of alkyl tosylates (Scheme 5, p7). This new reaction, therefore, appeared to be a mechanistic link between the two types of carbonium-ion-forming reactions and capable, in principle, of elucidating some

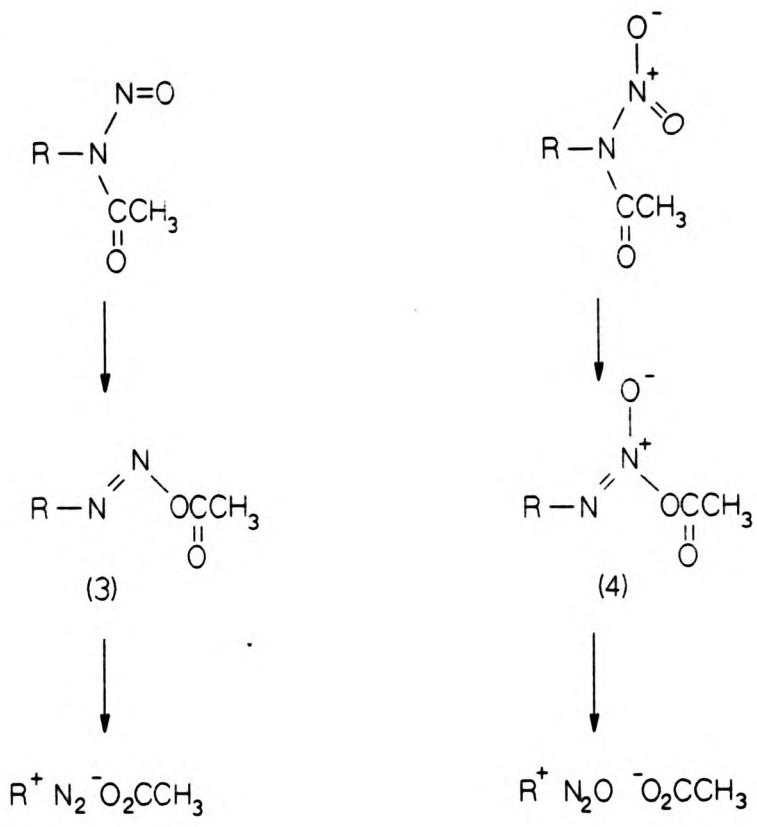
of the problems mentioned above.

Some kinetic results for the 2-adamantyl, bicyclo[2.2.2]octan-2-yl, cyclohexyl, and benzyl azoxytosylates have already been reported[10,11]. These results, together with more recent ones including a double Hammett investigation[12] of the effect of substituents upon the solvolysis of benzyl azoxybenzenesulphonates, indicate that, indeed, the initial rate-determining fragmentations are concerted and yield in a single step the corresponding carbonium ions, nitrous oxide, and arenesulphonate anions. This initial step in the solvolysis of these azoxytosylates does, therefore, relate directly to the carbocation-forming fragmentation in deamination[3,10].

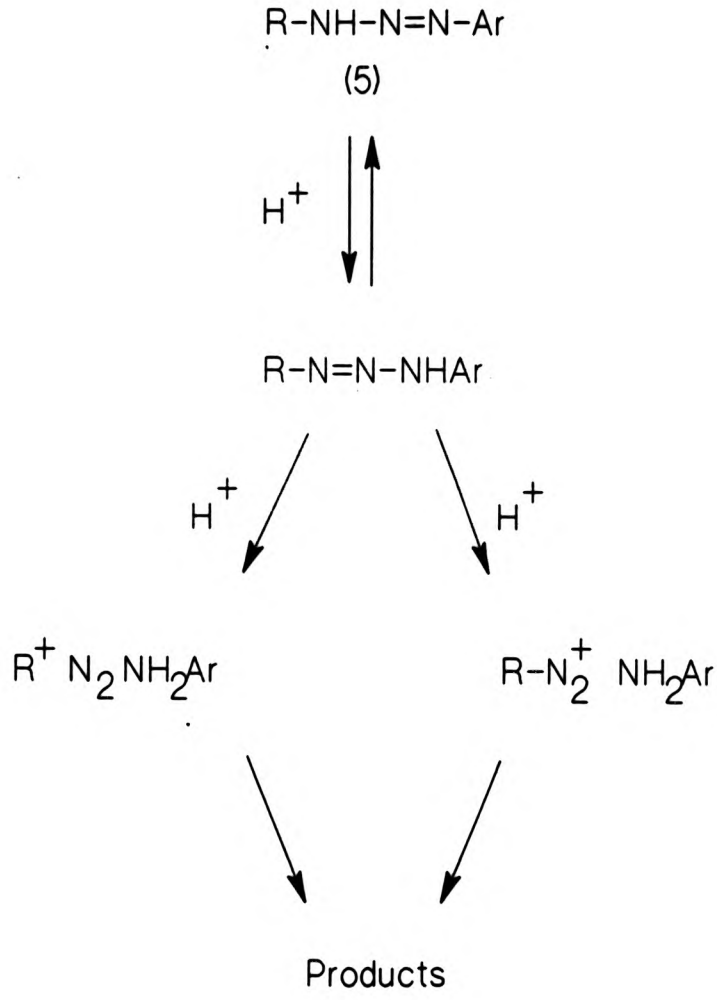
The work described in this thesis is an extension, mainly by high performance gas and liquid chromatography, of earlier kinetic work on the solvolysis of adamantyl and bicyclo[2.2.2]octan-2-yl azoxytosylates in a range of solvents. The principal aim was to characterise more fully the nature of the rate-determining carbocation-forming step, and to investigate more comprehensively the relationship between solvolytic deamination and solvolysis of the corresponding alkyl tosylate.



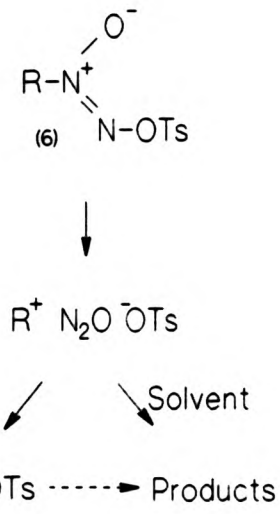
Scheme 1. Nitrous Deamination of Primary Amines via Diazonium and Carbonium Ion Intermediates.



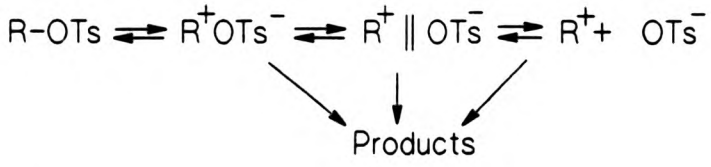
Scheme 2. Deamination by Nitroso- and Nitro-amide Routes.



Scheme 3. Deamination by the Triazene Route



Scheme 4. Solvolysis of Alkyl Azoxytosylates via N_2O-Separated Ion-pair.



Scheme 5. Solvolysis of Alkyl Tosylates via Ion Pair Formation.

CHAPTER 2

SOME PREVIOUS WORK.

2.1 Deamination.

It was thought that aliphatic amines react with nitrous acid to form diazonium salts analogous to aromatic systems. But unlike their aromatic counterparts, these diazonium ions rapidly lose nitrogen to yield products that strongly suggest intermediate carbonium ion formation[13]. For example, a series of experiments were carried out by Collins on the deamination of optically active 2-amino-1,1-diphenyl-1-propanol[14] (Figure 2.1). His starting material was labelled stereospecifically with carbon-14 in one of the phenyl groups. After resolving the products and determining the position of the radioactive label in each, he found that the inverted product (88%) had been formed exclusively by migration of the labeled group, Ph^*. The product of retained configuration (12%) was obtained by migration of the unlabeled phenyl, Ph. If migration of phenyl were concerted with loss of N_2, attack would necessarily have been back-side, resulting in complete inversion. Therefore, a carbonium ion had to have been formed.

This work also showed that the lifetimes of such carbonium ions are very short lived. If they were long-lived equilibration between the equally stable conformers X and Y (Figure 2.1) would have occurred, leading to

complete racemization and equal migration of Ph and Ph*.

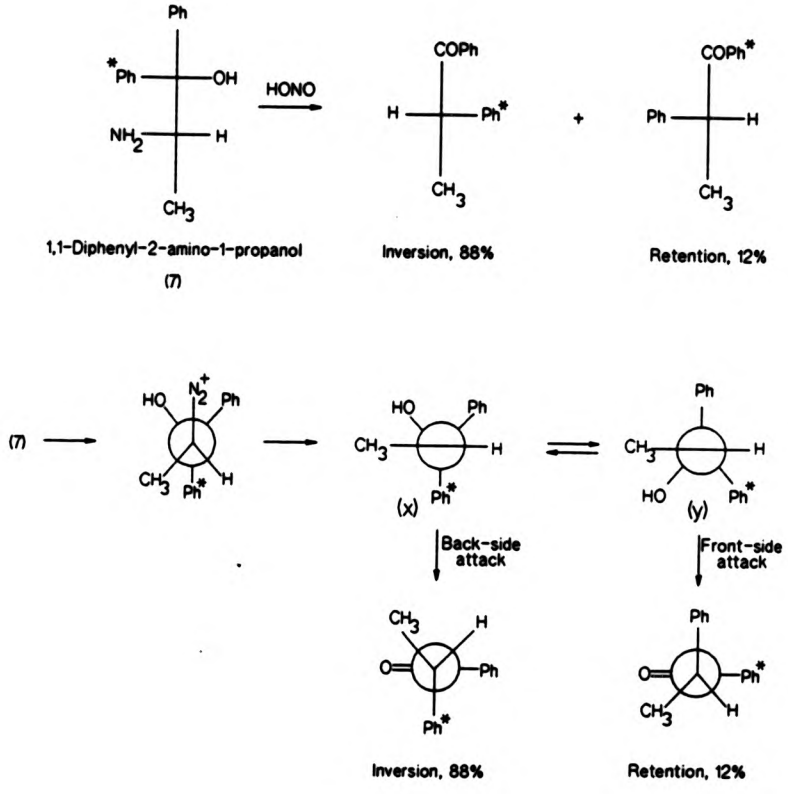


Figure 2.1

On the other hand, it has become increasingly clear that numerous primary aliphatic diazonium ions decompose with the assistance of an external or intramolecular co-reactant[15]. The mechanism of these decompositions has been described by Kirmse as being analogous to secondary alkyl tosylates *i.e* S_N1-S_N2 borderline. Whiting and coworkers have stressed the importance of the timing of the breaking of the C-N and N-X bonds[16]. They described the deamination reaction in terms of two competing pathways.

$$R\text{-}N{=}N\text{-}X \rightarrow R\text{-}\overset{+}{N}{\equiv}N\ {}^{-}X \rightarrow \text{Products} \qquad \text{ROUTE A}$$

$$R\text{-}N{=}N\text{-}X \rightarrow R^{+}\ N_2\ {}^{-}X \rightarrow \text{Products} \qquad \text{ROUTE B}$$

Results obtained by Huisgen and Ruchardt[17] for the deamination of n-propylamine by various methods (*i.e.* X^- is variable) and by Southam[18] for octylamine in acetic acid indicate that when R is primary then route A is followed with little or no carbocation formation.

2.2 Carbocation Rearrangements.

Identical intermediates should give identical products. According to this criterion product distributions from a carbocation in a given environment should be the same, irrespective of how it is generated. Indeed, cases are known where the S_N1 reactions of halides or sulphonic esters and decomposition of diazonium type ions lead to very similar results which

seems to indicate the presence of a common intermediate[15]. Generally speaking, however, results from the two types of reactions are not identical and the intermediates in diazonium type decompositions are more prone to rearrangemant and seem to be less selective than those of alkyl halide or alkyl arenesulphonate S_N1 solvolyses.

For example, the deamination of 2-arylalkylamines (8) is accompanied by competing 1,2-shifts of all groups (aryl, alkyl, hydrogen) attached to the β-C atom[19-21]. Only the aryl group migrates in the solvolysis of the corresponding sulphonic ester[21, 22] (9).

$PhC(R^1R^2)CH_2X$ $(CH_3)_2CHCH(Y)CH_3$

R^1, R^2 = H, Alkyl.

(8) X = NH_2 (10) Y = NH_2

(9) X = OSO_2R (11) Y = Tosylate

Similarly, deamination of 3-methyl-2-butylamine (10) involves not only a hydrogen shift but also a methyl shift (although the latter, as a degenerate rearrangement, does not lead to any drop in energy and can only be detected by isotopic labelling)[23]. Solvolysis of the *p*-toluenesulphonate (11) proceeds almost exclusively with H shift[24].

In an attempt to explain such differences in product distribution, Young proposed that elimination of nitrogen from aliphatic diazonium ions should lead to high-energy,

"hot" carbocations[25]. This hypothesis constantly reccurs in various forms right up to the very latest publications, although its original foundation - product ratios in the substitution of allyldiazonium ions - has since collapsed. The term "hot" carbocation means an intermediate still possessing excess energy arising from its exothermic mode of formation and not in thermal equilibrium with its environment. Transformation of heat of reaction into excitation energy of a product ("chemical activation") is well known for gas phase reactions[26], but there are no unequivocal examples of such reactions occurring in solution[27].

Of more significance than energy differences is the structure of transition states and intermediates of the various cation-forming reactions. The facile process of diazonium decomposition requires far less assistance from neighbouring groups or external nucleophiles than the dissociation of halides or sulphonic esters. The above differences in behavior of (8)/(9) and (10)/(11) can be rationalized in this way. Skell[28] therefore describes the intermediates of diazonium decomposition as "free" cations, while poorer leaving groups afford "encumbered" cations. This mode of expression places greater emphasis on the influence of external factors (gegenion, co-reactant, *etc.*). However, according to Kirmse, it is often precisely intramolecular effects (neighbouring group participation) which account for the differences between deamination and solvolysis.

In the classical theory of carbocation rearrangements[30], a precursor gives a cation which rearranges to an isomeric cation, products being formed from each by substitution and elimination. Generally, the products isolated should contain a predominance of products derived from the more stable of the two intermediate cations. Accordingly, it is customary to represent carbocation rearrangments as taking place in a direction which leads to a more stable cation, that is, primary alkyl (if these ever form at all) -> secondary alkyl -> tertiary alkyl. However, more recently, with more sophisticated analytical techniques, evidence of primary products from a secondary substrate has been reported[31, 32].

For example, when cyclohexylamine was treated with nitrous acid[31], the formation of cyclopentylmethanol, along with cyclohexanol, was observed. Here a precursor has given a secondary cation which would appear to have rearranged to a much less stable primary cation and this has collapsed to a primary alcohol in significant quantity. A similar reaction, the solvolysis of *trans*-N-nitroso-N-acetylamino cyclohexane in acetic acid[32] (Figure 2.2), gave two solvolysis substitution products; one had the same retention time as *trans*-cyclohexyl acetate, the other (0.95% of substitution product) was inseparable, on columns of 27,000 theoretical plates, from cyclopentylmethyl

separable from 1-methylcyclopentyl and *cis*- and *trans*-2-methylcyclopentyl acetates.

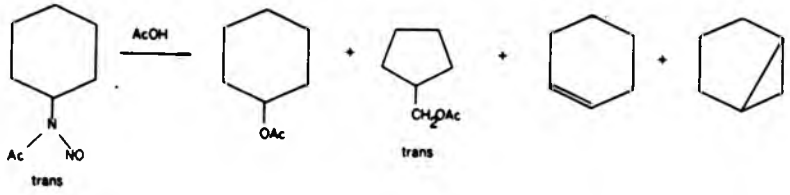


Figure 2.2

Adamantyl Systems

Deamination and arenesulphonate solvolysis have been carried out on other alicyclic systems, of which the 2-adamantyl has provided some of the most interesting results. The 2-adamantyl system appeared to show resistance to rearrangement by hydride shift during arenesulphonate acetolysis[33]. The 1-2 shift was measured as the yield of 1-adamantyl acetate formed using gas liquid chromatography (g.l.c.). The same tests were then applied to deamination reactions. It was assumed that the notoriously stable adamantane nucleus would resist skeletal rearrangement[34]. Deamination was carried out using the aryltriazene method[35] and no 1-adamantyl acetate was detected; the upper limit was estimated at 0.02%.

This result, however, was surpassed in interest by ones that had not been predicted. As well as 2-adamantyl acetate (12), and a basic compound (ca. 30% presumed to

be mainly the N-2-adamantylarylamine), g.l.c. of the triazene decomposition products revealed six additional products. Three were relatively minor ; they were 2-adamantanol (2%), adamantane (0.4%) and adamantanone (1.5%), the latter two evidently formed by some reaction from the already formed 2-acetate. When the concentration of the 2-acetate was greatly increased by adding authentic material to the reaction mixture, the yields of these products increased to 25 and 40% ; it seems from the lower yield of adamantane that recovery of such volatile products was incomplete. A fourth by-product was 2,4-didehydroadamantane (13) (7.8%), which under the mild deamination conditions survives. The two remaining products were shown to be protoadamantene (14), then unreported, and exo-4-protoadamantyl acetate (15).

12 13 14 15

This work prompted a reinvestigation of the acetolysis of 2-adamantyl toluene-p-sulphonate[35] in the presence of a buffer salt, which had been stated by Schleyer and Nicholas[33a] to give only 2-adamantyl acetate. When g.l.c. methods known to be capable of separating the two acetates, exo-4-protoadamantyl acetate

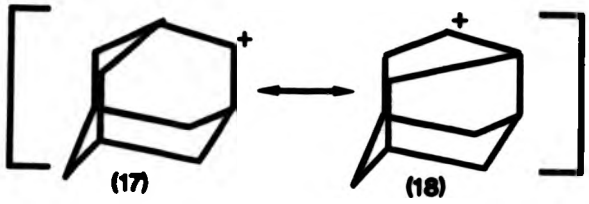
was readily observed in a yield of 0.4-0.5% in addition to 2-adamantyl acetate itself. Its identity with the deamination product followed not only from g.l.c. inseparability at 10,000 plates, but also from the measurement of its rate of disappearance (isomerisation to 2-adamantyl acetate) in similar solutions of toluenesulphonic acid in acetic acid. Under these conditions *endo*-4-protoadamantyl was unreactive. This latter compound was absent (yield<0.001%) from the toluenesulphonate acetolysis products also. Thus, whereas in the deamination (at 25°C) the relative yields of protoadamantyl acetate, protoadamantene, and didehydroadamantane are about 1:0.6:2, in the arenesulphonate solvolysis (at 100°C) they are about 1:0.01:<0.7. It was interpreted from these findings that if the rearranged products came from one intermediate in the deamination and one in the tosylate solvolysis, the two intermediates, although related, cannot be identical, since the variation of such ratios with temperature would be expected to be, and in related cases is[36], much less drastic than this.

Further investigations were carried out to determine whether the protoadamantyl compounds were derived from a classical carbocation. The direct equilibration of *exo*-4-protoadamantyl and 2-adamantyl acetates was attempted in acetic acid containing toluenesulphonic acid at 20°C[35]. The measured ratio of 2-adamantyl acetate to *exo*-4-protoadamantyl acetate was estimated to be at least

400,000:1. If this ratio is then applied to the hypothetical equilibrating 2-adamantyl and 4-protoadamantyl cations, as to a good approximation it should, then the observed yield ratio of 13:1 in the deamination requires that the 4-protoadamantyl cation reacts with acetic acid about 30,000 times more quickly than the 2-adamantyl cation. But even the 2-adamantyl cation cannot react at more than the diffusion-controlled rate, while on the other hand it is known to react with aniline, liberated in the immediate vicinity of the cation, faster than the 2-adamantyl cation can diffuse away (since the products from the triazene decomposition include 30% of N-2-adamantylamine). It was therefore concluded that the protoadamantyl compounds could not have come from a classical protoadamantyl cation in equilibrium with a 2-adamantyl cation. Other attempts at direct equilibration have also shown that the protoadamantyl structure is too highly strained to exist in amounts measurable by ordinary techniques. For example, no protoadamantane is detectable by glc (<0.01%) in $AlBr_3$ equilibration with adamantane[37].

To explain the observed amounts of rearranged products in both the deamination and tosylate solvolysis of the adamantane system, Whiting and Staresund postulated the intervention of a sigma delocalised intermediate (16)[35].

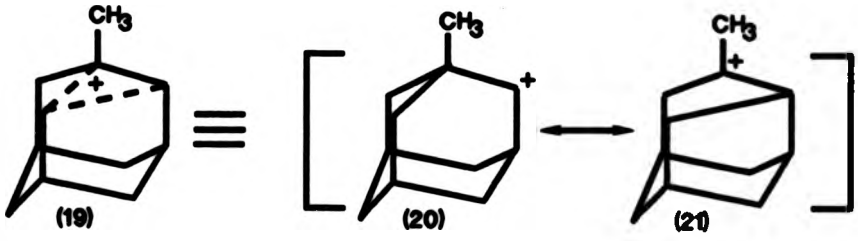
(16)



(17) (18)

Other investigations of the protoadamantyl system have led to proposals that in the bridged 2-adamantyl cation, structures (17) and (18) cannot contribute equally. The actual structure should therefore, resemble more closely the classical 2-adamantyl cation rather than the more highly strained 4-protoadamantyl cation.

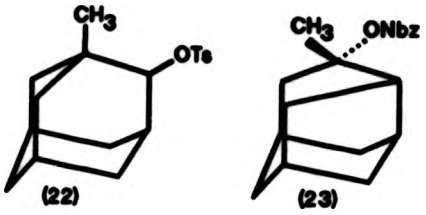
Addition of a 1-methyl group should increase bridging in both the intermediate (19) and in the 1-methyl 2-adamantyl tosylate solvolysis transition state. Because of the presence of the cation stabilising-methyl group, (19) should contribute significantly, and the result of the hybrid should be intermediate between the more strained but tertiary 4-methyl-4-protoadamantyl cation (21) and the less strained but secondary 1-methyl-2-adamantyl cation (20).



(19) (20) (21)

In classical carbocation systems, the observed inductive-hyperconjugative effect of β-methyl substitution on solvolysis rates is relatively minor[38]. For example, the 2-butyl tosylate/isopropyl tosylate ratio is 5.9 for solvolysis in trifluoroacetic acid[39]; smaller values are observed in other solvents[38]. In tertiary substrates - β-methyl groups typically produce much larger rate enhancements in nonclassical systems due to the possibility of more efficient electron donation[38]. Thus 1-methyl-exo-2-norbornyl derivatives solvolyse 52-68 times faster than the corresponding exo-2-norbornyl analogues[40]. The 1-methyl rate enhancement in the endo-2-norbornyl series is only 1.1, indicating the classical nature of the solvolytic transition states of these compounds[40].

A methyl group at the 1 position would be expected to influence the solvolysis of a secondary 2-adamantyl derivative significantly and to enhance the bridged nature of the ensuing intermediate. This seems to be confirmed by the work of Lenoir, Raber and Schleyer[41] on the 1-methyl-2-adamantyl cation. The predicted enhanced yield of protoadamantyl species was observed in the solvolysis of 1-methyl-2-adamantyl tosylate (22) in 60% acetone (Table 2.1). Further evidence of the same single intermediate ion was obtained from the solvolysis of 4-methyl-exo-4-protoadamantyl dinitrobenzoate (23), when almost the same product distribution was obtained[41].



(22) (23)

Where ONbz = dinitrobenzoate

Table 2.1 Solvolysis Products in 60% Acetone, 75°C[a]

Starting Material	Yields (%) 1-methyl-2-adamantanol	4-methyl-exo-4-protoadamantanol	Olefins
(22)	70	28	2
(23)	69	24	7

(a) Buffered with 0.01M lutidine.

Also, no 4-methyl-*endo*-4-protoadamantanol (<1%) was detected in the solvolysis products, consistant with steric hindrance due to partial bonding from a sigma delocalised structure.

The presence of the 1-methyl substituent in (22) produces a 24-38-fold solvolysis rate enhancement. That this appreciable effect is due to bridging and not to steric or inductive effects is shown by the very low β-CH_3/H ratio of 1.2 in the tertiary series, *ie.* 1,2-dimethyl-2-adamantyl bromide versus 2-methyl-2-adamantyl bromide[41].

Thus it was interpreted by Lenoir, Raber and Schleyer that the appreciable β-CH_3 rate enhancement was indicative of a bridged intermediate. They argue that if

the intermediate was the classical 1-methyl-2-adamantyl cation (20), no appreciable rate enhancement would be expected. If the intermediate were the classical 4-methyl-4-protoadamantyl cation (21), it would have to be much more stable than the classical 1-methyl-2-adamantyl cation in order to explain the observed 1-methyl rate enhancement. In that case, the product not only would be expected to be completely tertiary, but probably a mixture of the *exo* and *endo* epimers, contrary to observation.

If the classical 1-methyl-2-adamantyl cation (20) and 4-methyl-4-protoadamantyl cation (21) were comparably stable, and rapidly equilibrating, then one could not account for the large 1-methyl rate enhancement observed in the solvolysis of 1-methyl-2-adamantyl tosylate.

The most reasonable explanation, then, is that the bridged ion (19) is the intermediate involved. The bridged ion benefits from some methyl stabilisation without incurring very much destabilization due to strain energy.

Free energy diagrams have been utilised to estimate the relative ground state energies of the protoadamantyl and adamantyl systems[41]. Free energy diagrams, first specifically applied to solvolytic systems by Goering and Schewene[42], are very useful analytically. This approach can be used to derive the relative ground state energies of systems interconnected by a common intermediate[41, 43].

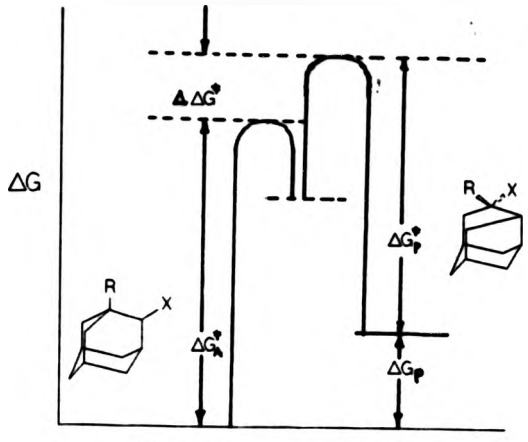


Figure 2.3 Free energy diagram relating protoadamantane and adamantane systems.

Figure 2.3 illustrates the free energy diagram to be applied. $\Delta G^{\ddagger}_{P}$ and $\Delta G^{\ddagger}_{A}$ are the activation free energies for the 4-protoadamantyl and 2-adamantyl systems respectively, obtained from the solvolysis rate constants; $\Delta\Delta G^{\ddagger} = -RT\ln(A/P)$, where A/P is the kinetically controlled product ratio in the solvent where the solvolysis rates were carrried out. With these data available, the ground state of the protoadamantane system, relative to the adamantane, ΔG_P, can be evaluated from

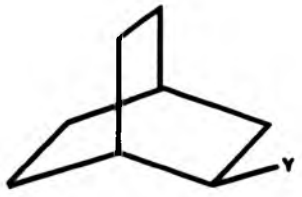
$$\Delta G^{\ddagger}_{P} = \Delta G^{\ddagger}_{A} + \Delta\Delta G^{\ddagger} - \Delta G_P$$

The ΔG_P value derived from the secondary systems, 11.0 kcal/mol, is probably the best estimate for the protoadamantyl system itself, since the oxygen-based substituents should introduce little perturbation in the

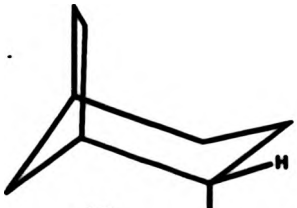
systems. This value is in good agreement with that (11.3 kcal/mol) derived from molecular mechanics calculations for the parent hydrocarbons[44]. At 25°C this free energy difference is equivalent to an equilibrium constant of 10^8. Little wonder, then, that protoadamantane and its derivatives cannot be detected in equilibrium with adamantane isomers.

The Bicyclooctyl System.

The bicyclooctyl cation produced through ionization of the carbon-oxygen bond in various derivatives of (24) has been shown to give extensive rearrangment products leading to products of the bicyclo[2.2.2]octyl and bicyclo[3.2.1]octyl systems.



24a, Y = $OSO_2C_6H_4$-p-CH_3 (tosylate)
b, Y = $OSO_2C_6H_4$-p-Br (brosylate)
c, Y = OSAr (sulfonate)
d, Y = $OCOCH_3$ (acetate)
e, Y = NH_2 (amine)
f, Y = OH



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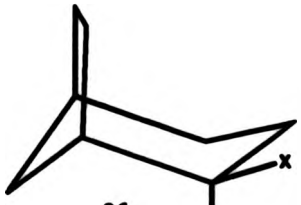
a, X = $OCOCH_3$
b, X = Cl
c, X = OH



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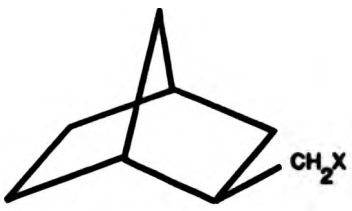
Walborsky and coworkers[45] found that acetolysis of (24b) resulted in about one-third exo-bicyclo[3.2.1]octan-2-yl acetate, (25a), and two-thirds bicyclo[2.2.2]octan-2-yl acetate, (24d). Goering and Sloan[46] found that nearly the same ratio of (24f) to (25c) results from the deamination of (24e) in aqueous acetone, while acetolysis of the corresponding tosylate (24a) yields almost a 1:1 ratio of the isomeric acetates (25a:24d). None of the *endo* isomer (26) was detected in either of these reactions.



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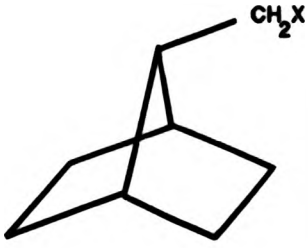


28

X = NH_2, OH

Berson and Wilner[47] have reported that exo-2-aminomethylnorbornane, (27), produces nearly equal amounts of (24) and (25) alcohols in deamination. Later these authors[48] found that the same substrate gave a small amount of the *endo*-alcohol,(26c), as well.

A study[49] of the ring expansions of the brosylate and amino derivatives of the 7-norbornylmethyl system, 28,

indicated product compositions entirely similar to those found for the substrate(27).

2.3 Ion Pairs

The elaboration of the S_N1-S_N2 framework to explain many phenomena uncovered since the original Hughes-Ingold hypotheses relies primarily on ideas about ion pairs[50]. The main theory currently in use was introduced by Winstein, who also provided much of the experimental evidence on which it is based[51]. Winstein identified two types of ion pairs important in nucleophilic substitutions.The contact ion pair (or intimate ion pair), R^+X^-, has the positive and negative ions close together surrounded by a single solvent shell. In the solvent separated ion pair, $R^+//X^-$, the positive and negative ions are still specifically associated but are separated by one or more solvent molecules. The final stage of dissociation leads to the independent ions, $R^+ + X^-$, each within its own solvation shell. Each stage may in principle return to the previous stage, advance to the next stage, or may react with solvent or with some other nucleophile to yield products. It is also possible for a nucleophile to be involved in the initial step either to give direct substitution (Hughes-Ingold S_N2) or to assist departure of the leaving group by providing nucleophilic solvation of the incipient ion. Figure 2.4 is an outline of these possibilities.

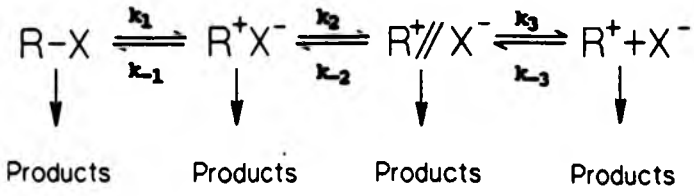


Figure 2.4. Winstein's general ion-pair mechanism for sequential ionization.

The original evidence that there is more than one kind of ion pair in the solvolysis pathway, in some systems at least, comes from the effect of added salts on solvolysis rates. Nearby ions affect the free energy of ions in solution so a change in concentration of dissolved salt may alter the rate of any elementary step in which ions are produced or destroyed. For S_N1 solvolysis, the rate increases with addition of a non-common ion salt. In the usual solvolysis solvents, for example, acetic acid, aqueous acetone, and ethanol, the increase follows the linear Equation (2.1), where k_{salt} is the rate constant with added salt and k_o is the rate constant in the absence of salt[52].

$$k_{salt}=k_o(1+b[salt]) \qquad (2.1)$$

Winstein and his associates studied salt effects on the solvolysis in acetic acid of alkyl halides and alkyl arenesulphonates, for which there was believed to be stereochemical evidence of a unimolecular type of mechanism[53]. They have described two kinds of salt effect. In most cases the rate rises linearly with salt

concentration, often to quite high concentrations, *e.g.* 0.1M of salt. Many substrates, *e.g.* neophyl and pinacolyl halides or arenesulphonates, showed no other salt effect. A few substrates[54], *e.g.* 1-p-anisyl-2-propyl toluene-p-sulphonate, showed additionally a "special" salt effect, *i.e.*, a sharp acceleration by the first 10^{-3}M of salt, curving off at about $3x10^{-3}$M into the "normal" much milder, and essentially linear effect (Figure 2.5).

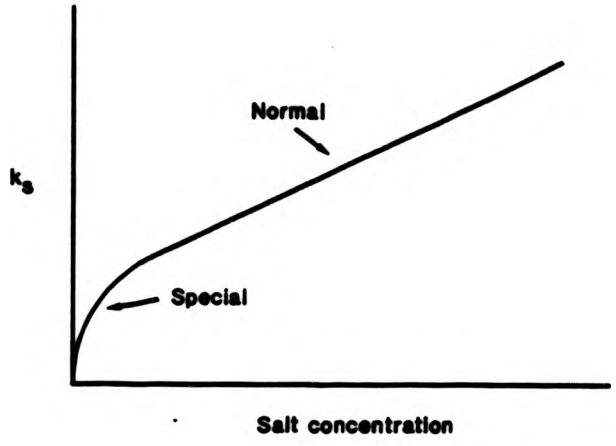


Figure 2.5

Winstein found that the "special" effect of lithium perchlorate on the solvolysis of an alkyl arenesulphonate was suppressed by the addition of the common-ion salt, lithium arenesulphonate, and that the latter salt, when used alone, could produce a rate lower than the salt-free rate.

The normal salt effect was regarded as an effect on k_1. The special salt effect was described as displacing the anion from the solvent-separated ion pair, and thus suppressed the return step, k_{-2}. A common-ion salt would promote k_{-3} and so inhibit solvolysis through dissociated ions.

Other more recent results have confirmed the importance of intimate and solvent-separated ion pairs. For example, solvolysis of chiral 2-adamantyl derivatives yields a slight excess of retention of configuration[55], a result consistant with reaction from a solvent-separated ion pair rather than from an intimate ion pair. A selectivity dependence on leaving group identity has also been observed[56] as expected for product formation by attack on an ion pair intermediate.

In the aqueous ethanolysis of 2-adamantyl arenesulphonates[56] it appeared, according to the observed ether-alcohol product ratios, that water was surprisingly more nucleophilic than ethanol. The interpretation of this was that the solvent-separated ion pair with water between the ions is slightly favoured over that with ethanol because water provides more hydrogen-bonding sites for stabilization of the oxygens of the arenesulphonate and leads to an increased abundance of water in the vicinity of the carbocation.

2.4 Internal Return

A central question in mechanistic organic chemistry

is whether the ionization of simple secondary alkyl arenesulphonates and halides is reversible (Figure 2.6).

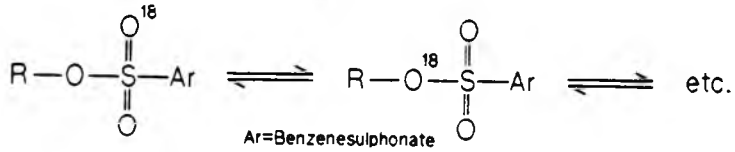
Figure 2.6

Recombination of the first formed ion pair (internal return) has been established when the secondary alkyl cation is stabilised in some way as in norbornyl[57] or bicyclo-octyl[58] derivatives, but evidence of internal return in simpler secondary systems has been less widely accepted and some of it has been disputed[40, 59].

Thermolysis of 2-adamantyl azoxytosylate was shown by nmr spectroscopy to give the corresponding tosylate cleanly, a result which was corroborated by actual isolation of 2-adamantyl tosylate and its characterization by m.p. and i.r[10]. 2-Adamantyl tosylate was also detected by tlc in low yield from the faster reaction in anhydrous ethanol[10].

However, up until now, perhaps the strongest evidence of internal return comes from the ^{18}O scrambling experiments carried out by Paradisi and Bunnett[60]. The heavy-oxygen-labeled substrates (28)-(31) (Figure 2.7), having 18-28% ^{18}O in the sulphonyl moiety, were submitted to solvolysis in a chosen solvent for about two half-lives. Experiments with (30) had also to be conducted

for shorter times because scrambling is relatively fast with this ester and is nearly complete at two solvolysis half-lives.



Ar=Benzenesulphonate

29. R=Isopropyl

30. R=Cyclopentyl

31. R=2-Adamantyl

32. R=3,3-Dimethyl-2-butyl

Figure 2.7

The amounts of ^{18}O in the alkoxy and sulphonyl moieties were established by cleaving the alkyl arenesulphonate with two equivalents of sodium in liquid ammonia, derivatising the sulphinate to methyl phenyl sulphone and analysing both the alcohol and sulphone by g.c.-m.s. This was carried out on the ester prior to solvolysis and at a chosen time during the solvolysis on the recovered unsolvolysed ester. By comparing the two sets of results the minimum amount of scrambling that had occurred could be estimated.

If the scrambling was due to internal return, the results showed that the incidence of internal return during solvolysis of secondary alkyl arenesulphonates is strongly dependent on the identity of the substrate. Scrambling was shown to be extensive during the

solvolysis of (31) in three solvents, moderate during solvolysis of (29) and (30) in CF_3COOH, significantly less during solvolysis of (30) in 90% HFIP:water, and undetectable during solvolysis of (32) in four solvents.

The possibility that scrambling occurred by external return or attack by external ions on the substrate was also investigated. Solvolysis of (30) and (31) was carried out under conditions of the scrambling experiments except that a substantial amount of sodium p-toluenesulphonate was also present. Solvolyses of (30) and (31) in CF_3COOH buffered with excess CF_3COONa, and of (31) in 80% ethanol:water were interrupted and the recovered unsolvolysed ester examined by NMR spectroscopy. No alkyl p-toluenesulphonate was found, although control experiments showed that as little as 1% was easily detectable. The possibility of external return was therefore excluded.

A major assumption made in this work is that the ion pairs that undergo ^{18}O scrambling are the same as those that undergo solvolysis. This assumption has been disputed[61], and it has also been suggested that ^{18}O scrambling occurs by a concerted process[62]. This work, therefore, in itself may not provide unambiguous evidence of internal return.

2.5 Influence of Solvent and Nucleophile.

The Hughes-Ingold S_N1-S_N2 scheme has provided an appropriate overall framework for classification of

aliphatic nucleophilic substitution. It focuses attention on what is perhaps the most fundamental aspect of the process, the presence or absence of bonding between a nucleophile and the substitution centre during the breaking of the bond between the substitution center and the leaving group. However, the S_N1 and S_N2 mechanisms in the original Hughes-Ingold hypotheses are better regarded as limiting cases at either end of a continuum of nucleophilic participation between the methyl and 2-adamantyl extremes[40].

2.5.1 The Solvent

(a) As nucleophile

The term "solvolysis" was introduced by Steigman and Hammett[63] for kinetically first-order nucleophilic displacements by solvent present in large excess, and considerable attention has been devoted to studying such processes, over the past few decades[64].

The solvent plays two roles in nucleophilic substitutions. It is the medium for the reaction, and affects it by solvating the starting compounds and the transition state, and also frequently itself acts as nucleophile.

The rates of nucleophilic substitution and elimination reactions are markedly solvent dependent[50(c), 65], and much research has been directed towards interpreting the detailed role of solvents in such processes[66]. The mechanisms of these reactions,

based on the S_N1-S_N2 framework of Ingold and coworkers, were among the first to be studied in detail and form one of the cornerstones of physical organic chemistry. The firm foundations provided by investigations, carried out over many years by independent research groups, have led to solvolytic reactions being used as testing grounds for new interpretations and new mechanistic criteria.

Solvolytic reactions were frequently used to derive structure/reactivity relationships (*e.g.* acetolysis of series of tosylates) and the results were implicitly assumed to be independent of the solvent. However, from more recent studies in weakly nucleophilic, highly ionising media such as hexafluoroisopropanol and trifluoroacetic acid, it is now known that the solvent dependence of relative rates was underestimated[67]. For solvolytic reactions thought to proceed *via* carbocations or ion pairs, it is of interest to compare the solvent effects with those obtained in strongly acidic media such as "magic" acid and in the gas phase. The activation energy for formation of a tert-butyl cation and a chloride anion from tert-butyl chloride, can be calculated and is 159 kcal mol^{-1} [68]. This is much greater than the activation energy of 23 kcal mol^{-1} for the hydrolysis of t-BuCl, which probably proceeds *via* an ion pair intermediate. However, despite minor mechanistic differences, it is clear that solvation of charged intermediates must greatly reduce the energies of solvolytic reactions compared with the corresponding gas

phase reaction. Considering these large solvation energies, which would correspond to over 80 powers of ten in relative rates at 25°C, it is perhaps surprising that even larger solvent effects are not observed, *e.g.* the rate constant for hydrolysis of *tert*-butyl chloride is only five powers of ten greater than the corresponding ethanolysis rate constant. Also, the relative stabilities of carbocations ions appear to be surprisingly similar in strongly acidic media and in the gas phase[69].

Since solvolytic reactions are thought to involve nucleophilic "push" and electrophilic "pull"[70], it is possible to derive quantitative empirical measures of the role of solvent molecules as ionizing medium, electrophile and nucleophile. By comparing the sensitivity of various reactions to solvent polarity or "ionizing power" and nucleophilicity, it is possible to deduce mechanistic information which can supplement other evidence for reaction mechanisms. The basic ideas behind this approach are the qualitative proposals of Hughes and Ingold[71]; *e.g.* for a reaction during which charge separation increases in the transition state, an increase in solvent polarity should increase the rate of reaction. This approach was put on a quantitative basis by Grunwald and Winstein with their development of the Y-scale of solvent ionizing power[72].

The Grunwald-Winstein *m*-Y correlation has been the relationship most widely used for analysis of solvent

effects in reactions of the S_N1 type[73]. The standard reaction is solvolysis of tert-butyl chloride and the standard solvent is 80% aqueous ethanol; for that combination m=1 and Y=1.According to Equation 2.4.1, the Y parameters characteristic of various solvents are established as the logarithm of the ratio of tert-butyl chloride solvolysis rate in the solvent S to the rate in 80% ethanol; then a plot of this rate ratio for some other substrate *versus* Y will give the slope m for the substrate.

$$\log (k_s/k_{EtOH}) = mY \qquad \text{Equation 2.4.1}$$

The parameter, m, can be used as a criterion of mechanism, because a substrate solvolyzing with nucleophilic assistance will have reduced separation of positive and negative charge in the transition state and will therefore require less assistance from the ionizing power of the solvent, and hence will have m less than unity. However, the same effect would be observed for an unassisted S_N1 reaction if there was an unusually early transition state, as might happen with a particularly good leaving group or relief of steric strain[74].

The tert-butyl substrate was thought of as a good choice for the reference, since, in solvolysis reactions, it appeared that there was no nucleophilic assistance, *i.e.* it was limiting S_N1. When compared with 2-adamantyl tosylate, however, it appears that even in the solvolysis of tert-butyl chloride there may be some nucleophilic assistance[75]. Although a lot of useful

information can be obtained from using the Grunwald-Winstein Y scale it must be remembered that it is purely empirical and gives relatively little insight into the reasons for the observed solvent effects.

(b) The solvent as electrophile.

The idea that electophilic attachment to the leaving group assists heterolytic cleavage is well established[78]. In the case of metal salts such as those of silver and mercury, the importance of the metal ion in the transition state is apparent from the rate law[79]. For solvolytic reactions carried out in the absence of metal salts, evidence for electrophilic solvation is less direct but extensive. Farinacci and Hammett[80] showed that addition of small amounts of water increased the rate of alcoholysis of diphenylmethyl chloride, whilst the product remained almost entirely the corresponding diphenylmethyl ether. Thus it appeared that the water may hydrogen bond to the developing chloride ion in the transition state, and presumably in the absence of water, ethanol performs the same function but does it less effectively[81].

Quantitative indications of the relative magnitudes of solvation of the anions during solvolytic reactions can be obtained using the Grunwald-Winstein mY equation. By comparing the rate constants for solvolysis in acetic or formic acids with the rate constant for the ethanol/water mixture having the same Y value, a parameter $[k_{EW}/k_{RCOOH}]_Y$ can be calculated. As Y is

conventionally the abscissa of a correlation, this parameter corresponds to the "vertical gap" or "dispersion" between a correlation line for mixtures of ethanol and water and a correlation line for acetic and formic acids[66(a), 82]. Although most of the $[k_{EW}/k_{AcOH}]_Y$ ratios obtained are complicated by the effect of ion pair return on titrimetric rate constants, the values of these ratios vary with leaving group in the order Br>Cl>OTs>>F. This can be explained by hydrogen bonding to the leaving groups, which is greater in acetic acid than in ethanol/water mixtures and much greater for fluorides than tosylates; similarly, hydrogen bonding is greater for tosylates than for chlorides[78, 83].

2.5.2 The Nucleophile in S_N1 reactions

The rate of an S_N1 reaction proceeding exclusively by the k_C (unassisted ionization) or k_Δ (assisted by an internal nucleophile) should be unaffected by the presence of a nucleophile, except for salt effects and possibly the common ion effect. The carbocation formed, however, will react with a nucleophile, but what would its selectivity be if given the choice of more than one nucleophile? On the basis of the Hammond postulate, a highly reactive intermediate, facing low activation barriers, will find small differences in reaction paths and will be relatively nondiscriminating in its choice of reaction partner; whereas a more stable intermediate, facing larger activation barriers, will find larger differences and will be more selective. When coupled

with the expectation that a less reactive ion is formed more rapidly, this principle predicts a correlation between solvolysis rate and selectivity[84].

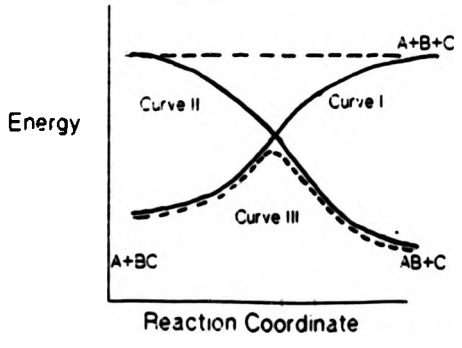
Leffler[85] has proposed a more general relationship (hence known as the Leffler-Hammond postulate) which represents an extension of the Hammond postulate as it treats the whole spectrum of reaction types. Thus the transition state is viewed as changing from reactant-like in exothermic reactions, to product-like for endothermic reactions. The rationale for the Leffler-Hammond postulate may be found in a model first proposed by Evans and Polanyi[86] and Bell[87] and later discussed by Dewar[88].

For a general substitution reaction, represented by,

$$A + B\text{-}C \rightarrow A\text{-}B + C$$

the effect of perturbations on transition state structure and energy may be qualitatively estimated by considering the intersection of potential energy curves, as shown in Figure 2.8.

Figure 2.8 The Bell-Evans-Polanyi treatment for the reaction A+BC→AB+C indicating the reaction profile.



Curves I and II represent the energy profiles for the dissociation of B-C and A-B respectively. The reaction pathway (represented by curve III) may be considered as being approximated by the portions of these two curves below their point of intersection.

For a series of reactions where BC combines with A_1, A_2, ..., A_n to give A_1B, A_2B, ..., A_nB whose dissociation is variable, a series of dissociation profiles is obtained as illustrated in Figure 2.9.

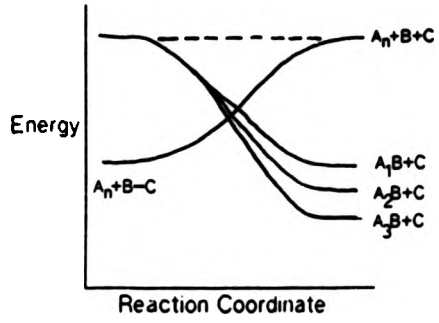


Figure 2.9 The effect of product stability on the transition state for the reaction A_n+BC $\rightarrow$ A_nB+C

The intersection of each dissociation profile with the dissociation curve for the species BC, indicates the approximate position of the transition state for each reaction of the series. As Dewar[88] has noted, this treatment leads to a number of conclusions.

1. Product stabilisation brings about a corresponding reduction in the activation energy.
2. As each reaction in the series becomes more

exothermic, so the transition state increasingly resembles the reactants in accordance with the Leffler-Hammond postulate.

3. Due to the variation in the slopes of the dissociation curves, a continual increase in stability of the product brings about a progressively smaller stabilization of the transition state.

CHAPTER 3

PREPARATIVE METHODS

3.1 Preparation of the Compounds for Solvolysis.

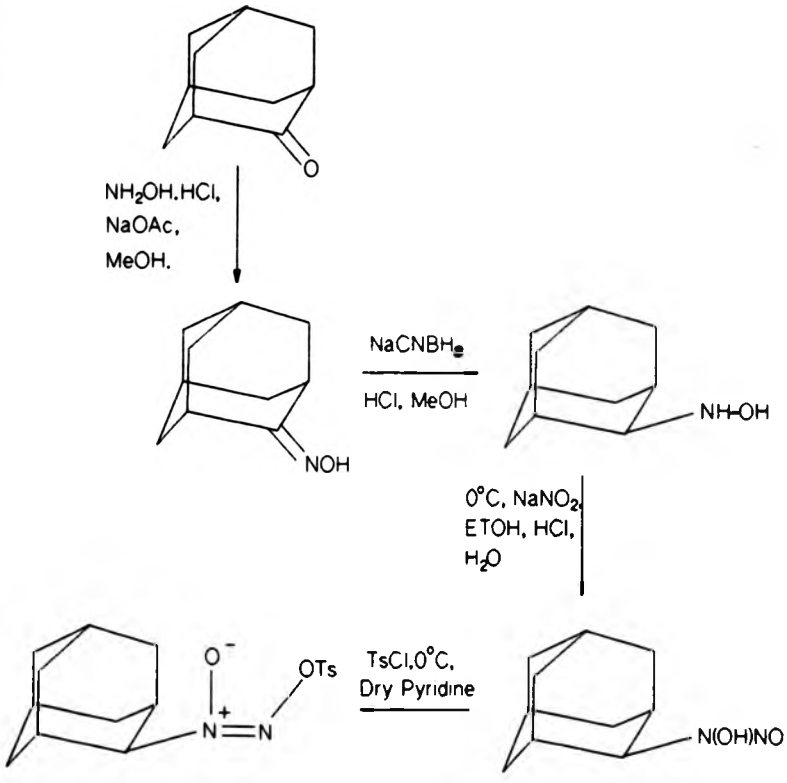
3.1.1 Adamantyl Azoxytosylate.[89]

Adamantanone oxime was prepared in quantitative yield from adamantanone in the usual manner[89] (Scheme 3.1). Reduction to the hydroxylamine was effected by sodium cyanoborohydride in methanol, using methanolic HCl to keep the solution acidic. After removing the methanol, the hydroxylamine was extracted between H_2O (kept at pH9) and CH_2Cl_2. The CH_2Cl_2 fraction was removed and evaporated under vacuum to yield a solid, which was purified by sublimation. The product was identified by its nmr spectral properties. Nitrosation was effected by adding $NaNO_2$ to a solution of the hydroxylamine in acidic aqueous ethanolic solution. Addition of H_2O resulted in precipitation of the nitrosohydroxylamine in high yield which was filtered and dried. The product was identified by its melting point and nmr and ir spectral properties. Treatment of the nitrosohydroxylamine following the Tipson procedure gave the azoxytosylate in good yield which was recrystallised at -78°C from ether. The azoxytosylate was identified by its melting point and nmr and ir spectral properties.

3.1.2 Bicyclo[2.2.2]octan-2-yl Azoxytosylate.[89]

The bicyclo[2.2.2]octyl skeleton with functionality at the two position was generated from the reaction of vinyl acetate with 1,3-cyclohexadiene. The reaction

mixture was distilled to give a residue which was hydrogenated then treated with aqueous KOH. Steam



Scheme 3.1 Preparation of 2-Adamantyl Azoxytosylate.

distillation of the resultant mixture yielded bicyclo[2.2.2]octan-2-ol. Oxidation to bicyclo[2.2.2]octan-2-one was effected by the slow addition of chromic acid to a stirred solution of the alcohol in ether. The reaction mixture was extracted with ether when the alcohol could no longer be detected by glc. The ether fraction was dried and the ether removed under vacuum to give white crystals of bicyclo[2.2.2]octan-2-one. Procedures were then followed through to the nitrosohydroxylamine as described for the adamantyl analogue. The bicyclo[2.2.2]octan-2-yl azoxytosylate was then prepared at 0°C following the Tipson procedure. Recrystallisation was carried out as described for the adamantyl analogue. The azoxytosylate was identified by its melting point and its nmr and ir spectral properties.

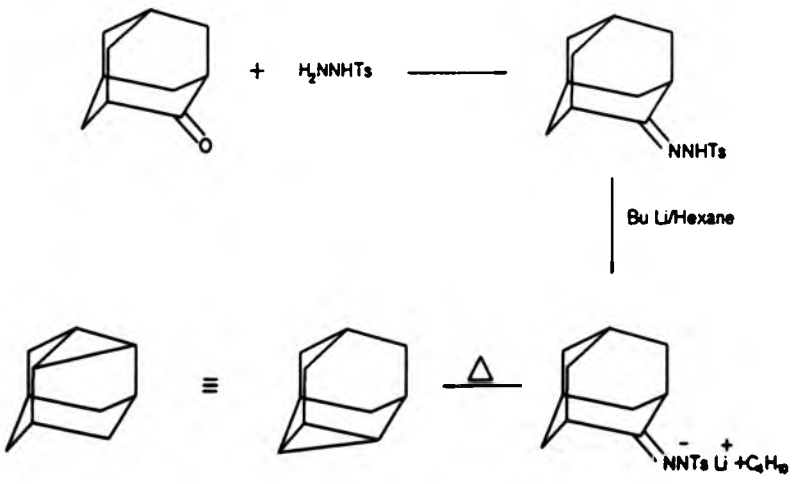
3.1.3 2-Adamantyl Tosylate.

This was prepared from 2-adamantanol and tosyl chloride following the Tipson procedure (Scheme 3.2). The reaction mixture was stirred for one week at room temperature then poured into ice-water. The resulting precipitate was filtered under vacuum to give the tosylate in quantitative yield. Recrystallisation was effected from pentane at low temperature. The product was identified by its melting point.

3.2 Authentic Samples for GLC and HPLC Analyses.

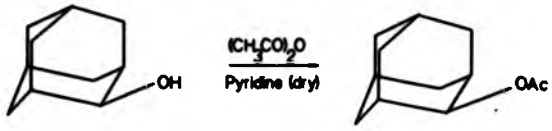
3.2.1 Adamantyl Derivatives.

Didehydroadamantane.[90] Adamantanone *p*-tosylhydrazone was prepared in good yield from the reaction of adamantanone and *p*-tosylhydrazine by the usual method (Scheme 3.3). Butyl lithium in hexane was added slowly under a stream of argon to the hydrazone in tetrahydrofuran to give the lithium salt. Pyrolysis of the lithium salt in a sublimation apparatus gave a white crystalline product which was shown by capillary glc to consist of two minor compounds and one major compound. Gc-ms showed the major peak to be didehydroadamantane.



Scheme 3.3 Preparation of Didehydroadamantane.

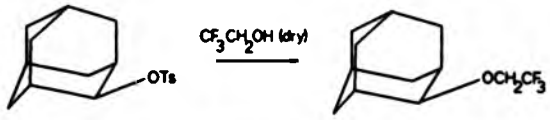
2-Adamantyl Acetate. This was prepared by adding adamantanol to a solution of acetic anhydride in pyridine (Scheme 3.4).



Scheme 3.4 Preparation of 2-Adamantyl Acetate

exo-4-Protoadamantyl Acetate was prepared in the same manner from exo-protoadamantanol.

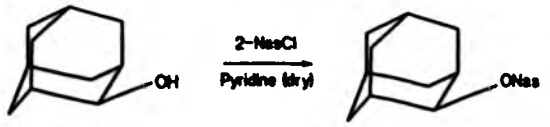
2-Adamantyl Trifluoroethyl Ether. Solvolysis of 2-adamantyl tosylate in trifluoroethanol gave 2-adamantyl trifluoroethyl in quantitative yield (Scheme 3.5).



Scheme 3.5 Preparation of 2-Adamantyl Trifluoroethyl Ether.

exo-4-Protoadamantyl Trifluoroethyl Ether was prepared in the same manner from exo-4-protoadamantyl tosylate. No additional peak was detected by capillary glc (<1%) due to the *endo*- isomer.

2-Adamantyl 2-Naphthalenesulphonate. A viscous oil was obtained from the reaction of adamantanol and 2-naphthalenesulphonyl chloride employing the Tipson procedure (Scheme 3.6). Crystallisation was effected from methanol in high yield. The product was identified by its melting point and elemental analysis.



Scheme 3.6 Preparation of 2-Adamantyl 2-Naphthalenesulphonate.

2-Adamantyl Thiocyanate.

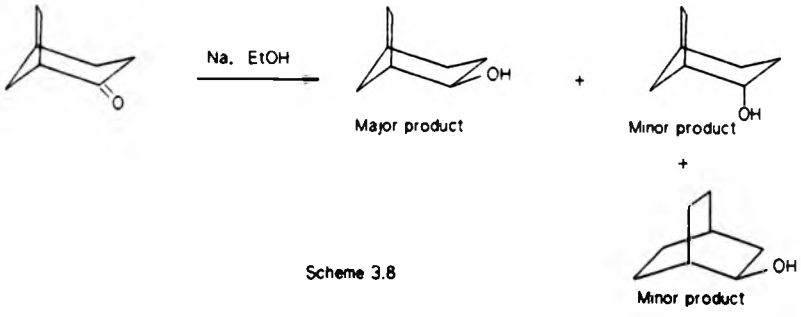
2-Adamantyl tosylate was refluxed in dimethylformamide (DMF) containing tetrabutylammonium-thiocyanate (15 mmol) and diazabicyclo[2.2.2]octane. The reaction mixture was then extracted with ether and investigated by capillary g.l.c.. It was hoped that enough 2-adamantyl thiocyanate (or isothiocyanate) would be generated that it could be detected by g.l.c. and confirmed by g.l.c.-m.s. However, analysis by capillary g.l.c. showed more than one unknown compound to be present.

Analysis by capillary g.l.c.-m.s. was carried out on the reaction mixture (Scheme 3.7) by the SERC mass spectrum service at the University of Swansea. A small peak in the gas chromatogram gave a mass spectrum which included an ion which corresponded to adamantyl thiocyanate. However, analysis conditions at Stirling were very different from those at Swansea and no single peak could be unambiguously attributed to 2-adamantyl thiocyanate.

Scheme 3.7 The attempted preparation of 2-Adamantyl Thiocyanate.

3.2.2 Bicyclooctyl Derivatives.

***endo*-Bicyclo[3.2.1]octan-2-ol.** Sodium metal was added to a stirred solution of bicyclo[3.2.1]octan-2-one in ethanol (Scheme 3.8). The ethanolic solution was extracted between brine and ether. A yellow oil was obtained from the combined ether extracts. The oil was chromatographed through a column of aluminium oxide using ethyl acetate as eluent. The ethyl acetate was removed from the appropriately combined fractions to give a waxy residue which was sublimed to yield colourless crystals. The product was identified by high resolution mass spectrometry and capillary glc.

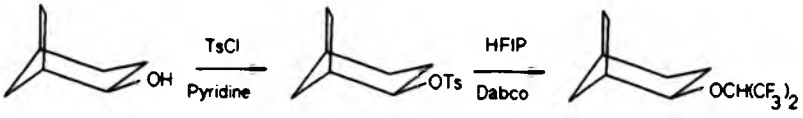


Scheme 3.8

Bicyclooctyl Hexafluoroisopropyl Ethers.

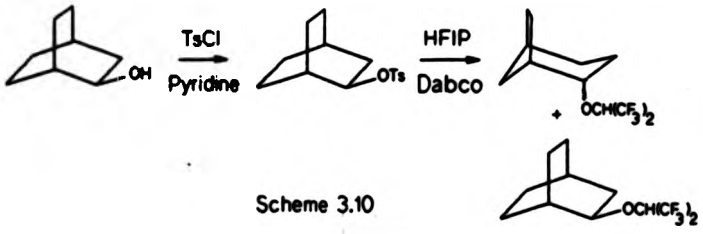
(I) *endo*-Bicyclo[3.2.1]octan-2-yl Hexafluoroisopropyl Ether. The *endo*-bicyclo[3.2.1]octan-2-yl tosylate was made from the corresponding alcohol by the Tipson procedure. Solvolysis of the tosylate in anhydrous HFIP (Scheme 3.9) yielded one major product, *endo*-[3.2.1]HFIP ether, and two minor products, the [2.2.2] and *exo*-[3.2.1] isomers. The yields of the HFIP ethers were in good agreement with the relative amounts of the

corresponding alcohols used in the preparation of the tosylate.



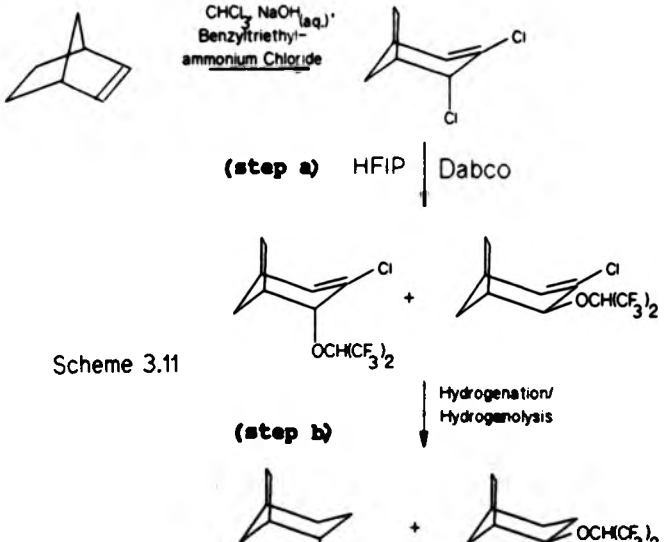
Scheme 3.9

(II) Solvolysis of bicyclo[2.2.2]octan-2-yl tosylate was also carried out in anhydrous HFIP and yielded equal amounts of the bicyclo[2.2.2]octan-2-yl and exo-bicyclo[3.2.1]octan- 2-yl hexafluoroisopropyl ethers (Scheme 3.10). A little *endo*-[3.2.1]octan-2-yl hexafluoroisopropyl (*endo*-[3.2.1]HFIP) ether was formed since the bicyclo[2.2.2]octan-2-ol used to make the tosylate contained a small amount of *endo*-bicyclo[3.2.1]octan-2-ol (*endo*-[3.2.1]OH). However, the amount of the *endo*-[3.2.1]HFIP ether seemed to be greater than anticipated. There was still uncertainty, at this stage, as to which one of the two major peaks was due to the [2.2.2] isomer and which one was due to the exo-[3.2.1] isomer.



Scheme 3.10

(III) Addition of dichlorocarbene to norbornene was carried out using the method described by Kraus and developed by Banks[89]. Fractional distillation of the crude product gave exo-3,4-dichlorobicyclo[3.2.1]oct-2-ene in good yield which was identified by high resolution mass spectroscopy and its nmr spectrum. The product from solvolysis of the dichloro compound in HFIP (step a, Scheme 3.11) was shown by nmr spectroscopy to be a mixture of *exo*- and *endo*-3-chloro-4-hexafluoroisopropoxybicyclo[3.2.1]-oct-2-ene. Hydrogenation-hydrogenolysis (step b) yielded the *exo*- and *endo*-bicyclo[3.2.1]octan-2-yl HFIP ethers which were shown by capillary glc to be present in a ratio of approximately 1:1. Since the retention time of the *endo*-isomer was identified from the solvolysis of the *endo*-tosylate, the retention time of the *exo*-isomer, and hence the [2.2.2]-isomer, could now be identified.



Scheme 3.11

CHAPTER 4

KINETICS METHODS and RESULTS

Reaction rates were measured by monitoring the decrease in uv absorbance in a thermostatted cell within a spectrophotometer. The temperature of the cell block was controlled by a water bath fitted with a circulating pump. The temperature of the block was monitored by means of a platinum resistance thermometer which had been previously calibrated. Temperature variation during a run was normally less than 0.1°C. Pure solvents used had been freshly distilled and dried by the appropriate methods. Reactions were typically monitored in duplicate at a wavelength between 240nm and 250nm for not less than three half-lives. The first order rate constants were calculated from about forty points by a computer program using a non-linear minimisation routine written by Dr. J.T. Thompson, of this department. The relative standard deviation of the rate constant for an individual run was always less than 0.5%, showing that good first order kinetics were followed. Rates were determined over at least three temperatures, normally between 30°C and 70°C, and these were used to calculate the activation parameters. A correlation coefficient of not less than 0.999 was always obtained.

Rate constants for 2-adamantyl azoxytosylate were determined in (a) acetic acid, (b) 50%v/v trifluoroethanol: water, (50TFE) and (c) 80%v/v trifluoroethanol: water, (80TFE); and for 2-adamantyl tosylate in (a) 50TFE, (b) 80TFE and (c) 90%v/v

trifluoroethanol: water, (90TFE). The results are given in Tables 4.3 - 4.8 along with the derived activation parameters. Graphs of mole fraction TFE *versus* entropy of activation and enthalpy of activation were plotted for both the azoxytosylate and tosylate (Graphs 4.3 and 4.4 respectively, pages 63 - 66). The activation parameters for both compouds in pure TFE were obtained from the literature. Solvolysis of 2-AdOTs in 90TFE was carried out since this appeared to be close to a minimum predicted by the other points in the graph. This indeed seems to be the case as shown by graphs 4.4 (I) and (II), pages 65 and 66. A similar trend was found in the azoxytosylate solvolyses, although at least one additional solvolysis has to be carried out to increase the confidence in the suggested correlation.

Included in the following pages are:

(1) An example of an Arrhenius plot, p52 and 53.

(2) An example of an Eyring plot, p54 and 55.

(3) Summary of results from solvolysis of 2-adamantyl azoxytosylate in:

(a) Acetic acid, p56; (b) 50TFE, p57; (c) 80TFE, p58.

(4) Summary of results from solvolysis of 2-adamantyl tosylate in:

(a) 50TFE, p59; (b) 80TFE, p60; (c) 90TFE, p61.

(5) Tables of activation parameters versus mole fraction for 2-adamantyl azoxytosylate and 2-adamantyl tosylate, p62, followed by the corresponding graphs, p63-66.

The following is an example of an Arrhenius plot used to calculate the activation energy.

Table 4.1 Plot of lnk versus 1/T in the solvolysis of 2-adamantyl azoxytosylate in 50:50, TFE:H_2O.

lnk	$10^3T^{-1}/K^{-1}$
-9.11	3.22
-7.77	3.11
-7.69	3.11
-6.68	3.03
-6.78	3.03
-5.62	2.94

$$k = Ae^{-Ea/RT}$$

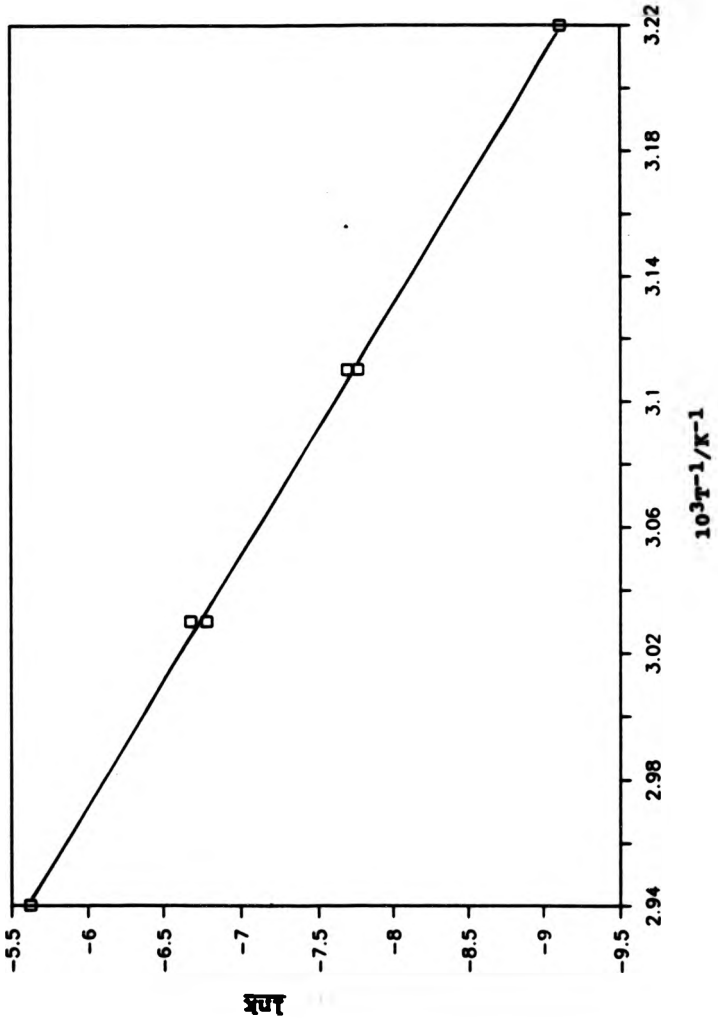
Therefore, $lnk = lnA - Ea/RT$

From graph 4.1,

$$-Ea/R = -12.5 \text{ kJ mol}^{-1}$$

Therefore, $Ea = 104 \text{ kJ mol}^{-1}$.

Graph 4.1 Plot of lnk vs 1/T for the Solvolysis of 2-Adamantyl Azoxytosylate in 50:50v/v. TFE:H_2O.



The following is an example of an Eyring plot used to calculate the activation parameters $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$.

Table 4.2 Plot of $\ln(k_o h/k_b T)$ versus $1/T$.

$\ln(k_o/k_b T)$	$1/T$ ($\times 10^{-3}$)
38.61	3.22
-37.30	3.11
-37.22	3.11
-36.24	3.03
-36.34	3.03
-35.21	2.94

$$k_o = (k_b T/h) e^{\Delta S^{\ddagger}/R} \cdot e^{-\Delta H^{\ddagger}/RT}$$

Where k_b = Boltzmann's constant; h = Planck's constant; and k_o = Oberved rate constant.

Therefore, $\ln(k_o h/k_b T) = \Delta S^{\ddagger}/R - \Delta H^{\ddagger}/RT$ -Equation 4.2

From graph 4.2,

$$-\Delta H^{\ddagger}/R = -12.1 \text{ kJ mol}^{-1}$$

therefore, $\Delta H^{\ddagger} = 101 \text{ kJ mol}^{-1}$

and by substituting into equation 4.2 and rearranging,

$$\Delta S^{\ddagger} = (\ln(k_o h/k_b T) + \Delta H^{\ddagger}/RT)R$$

Therefore, $\Delta S^{\ddagger} = 4 \text{ J K}^{-1}\text{mol}^{-1}$

The values obtained by the activation parameter program were, $\Delta H^{\ddagger} = 99 \text{ kJ mol}^{-1}$ and $\Delta S^{\ddagger} = -3 \text{ J K}^{-1}\text{mol}^{-1}$.

Graph 4.2 Plot of $\ln(k_0h/k_bT)$ versus 1/T in the Solvolysis of 2-Adamantyl Azoxytosylate in 50:50. TFE:H_2O.

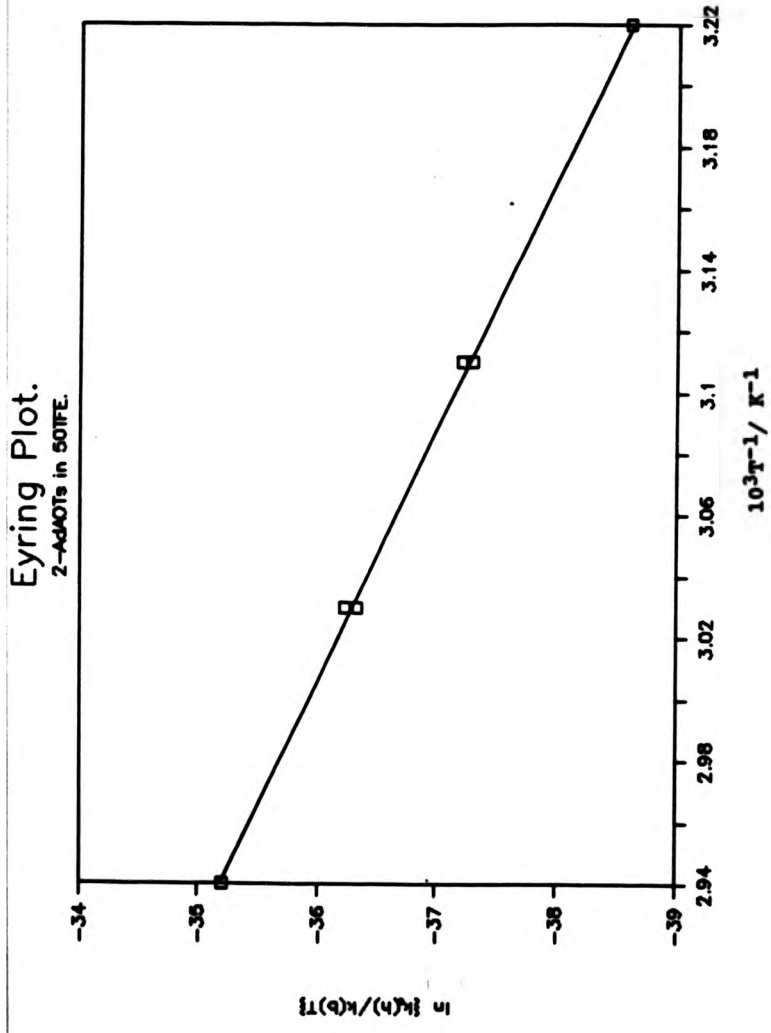


Table 4.3 Acetolysis of 2-Adamantyl Azoxytosylate.

Temperature/°C	Rate Constant (k) $10^6 k/s^{-1}$	Mean $10^6 k/s^{-1}$*	Number of half-lives of reaction
41.88	6.80		2.9
41.88	6.72	6.76 (0.06)	3.0
53.74	30.9		3.4
53.74	29.5	30.2 (0.1)	3.2
62.56	95.5		3.6
62.56	94.6	95.1 (0.45)	3.6
71.03	254		3.0
71.03	249	251.5 (2.5)	2.9

Activation parameters.

Enthalpy of activation = 109.4kJ mol^{-1}

Entropy of activation = 3J $K^{-1}mol^{-1}$

Correlation Coefficient = -0.9998

* Standard deviation in parenthesis.

Table 4.4 Solvolysis of Adamantyl Azoxytosylate in 50:50 (v/v), TFE:H_2O

Temperature/°C	Rate constant (k) $10^4 k/s^{-1}$	Mean $10^4 k/s^{-1}$	Number of half-lives of reaction.
37.56	1.0	1.1 (0.5)	2.2
37.56	1.2		2.5
37.56	1.1		2.3
48.10	4.2		5.8
48.42	4.6		6.2
57.57	12		9.7
57.18	11		4.8
67.66	37	36 (0.4)	7.2
67.66	36		5.7

Activation parameters

Enthalpy of activation = 98.7 kJ mol^{-1}

Entropy of activation = -3J $K^{-1}mol^{-1}$

Correlation coefficient = -0.9995

Table 4.5 Solvolysis of Adamantyl Azoxytosylate in 80:20 (v/v), TFE:H_2O

Temperature/^oC	Rate constant $10^4k/s^{-1}$	Mean $10^4k/s^{-1}$	Number of half-lives of reaction.
43.39	2.0		6.5
43.39	2.1	2.0 (0.1)	6.8
52.35	5.6		3.1
52.35	5.2	5.4 (0.2)	2.9
62.24	17		5.0
62.24	17	17 (0.0)	5.0
70.05	40		3.4
70.05	39	39 (0.9)	3.3

Activation parameters

Enthalpy of activation = 97.0 kJ mol^{-1}

Entropy of activation = -10 J $K^{-1}mol^{-1}$

Correlation coefficient = -0.9998

Table 4.6 Solvolysis of 2-Adamantyl Tosylate in 50:50 (v/v), TFE:H_2O

Temperature/^oC	Rate constant $10^5k/s^{-1}$	Mean $10^5k/s^{-1}$	Number of half-lives of reaction.
47.20	5.4		5.1
47.20	5.3	5.3 (0.05)	5.1
59.10	24		4.0
59.10	23	23 (0.5)	4.0
69.01	63		4.6
69.01	62	62 (0.5)	4.6
77.18	158		4.7
77.18	150	154 (4)	4.5

Activation parameters

Enthalpy of activation = 100.5 kJ mol^{-1}

Entropy of activation = -13 J $K^{-1}mol^{-1}$

Correlation Coefficient = -0.9994

Table 4.7 Solvolysis of 2-Adamantyl Tosylate in 80:20 (v/v), TFE:H_2O

Temperature/°C	Rate constant $10^5 k/s^{-1}$	Mean $10^5 k/s^{-1}$		Number of half-lives of reaction.
49.52	3.8			3.8
49.52	3.9	3.8	(0.05)	3.9
58.47	11			8.6
58.47	10	10	(0.5)	8.5
67.54	27			4.0
67.54	28	27	(0.5)	4.2
77.61	72			5.4
77.61	72	72	(0)	5.3

Activation parameters

Enthalpy of activation = 95.5 kJ mol^{-1}

Entropy of activation = -34 J $K^{-1}mol^{-1}$

Correlation coefficient = -0.9998

Table 4.8 Solvolysis of 2-Adamantyl Tosylate in 90:10 (v/v), TFE:H_2O

Temperature/^oC	Rate constant $10^5k/s^{-1}$	Mean $10^5k/s^{-1}$	Number of half-lives of reaction.
49.96	3.2		2.8
49.96	3.3	3.2 (0.05)	2.8
58.70	8.7		5.0
67.90	22		3.4
67.90	22	22 (0)	3.6
76.36	48		2.5
76.36	51	50 (1.5)	2.6

Activation parameters

Enthalpy of activation = 94 kJ mol^{-1}

Entropy of activation = -40 J $K^{-1}mol^{-1}$

Correlation coefficient = -0.9999

Table 4.9 Activation Parameters versus Mole Fraction TFE in the Solvolysis of 2-Adamantyl Azoxytosylate.

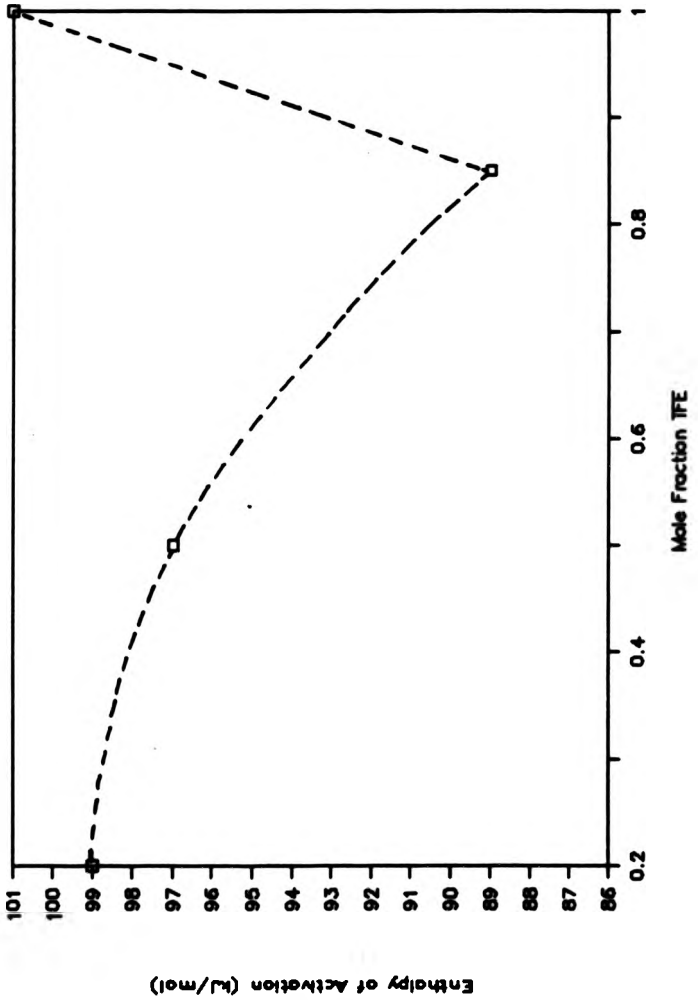
Mole Fraction TFE	Enthalpy of Activation ($kJ\ mol^{-1}$)	Entropy of Activation ($J\ K^{-1}mol^{-1}$)
0.20	99	-3
0.50	97	-10
0.85	89	-35
1.00	101	3

Table 4.10 Activation Parameters versus Mole Fraction TFE in the Solvolysis of 2-Adamantyl Tosylate.

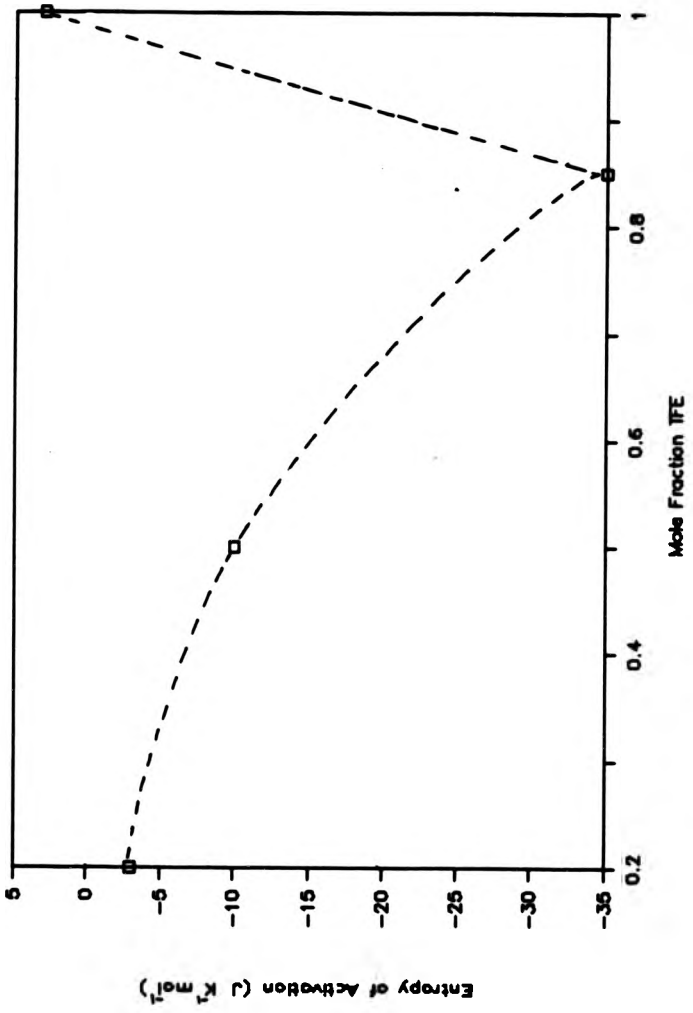
Mole Fraction TFE	Enthalpy of Activation ($kJ\ mol^{-1}$)	Entropy of Activation ($J\ K^{-1}mol^{-1}$)
0.20	100	-13
0.50	96	-34
0.69	94	-40
0.85	97	-30
1.00	102	-15

Graph 4.3 Activation Parameters versus Mole Fraction TFE in the Solvolysis of 2-Adamantyl Azoxytosylate.

(I) Graph of Enthalpy of Activation versus Mole Fraction TFE.

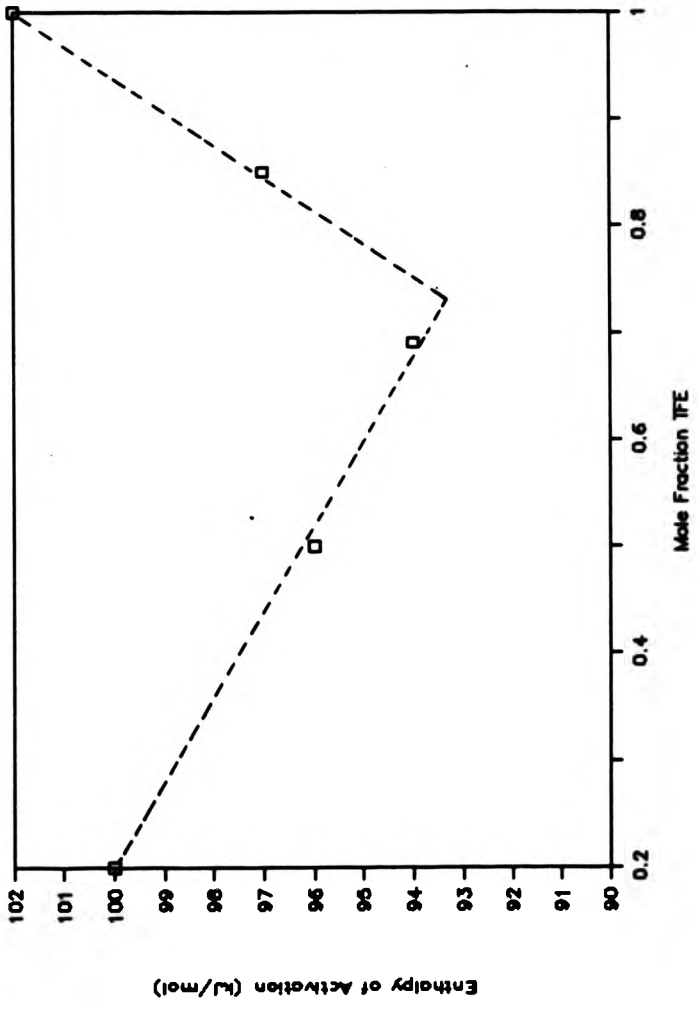


(II) Graph of Entropy of Activation versus Mole Fraction TFE.

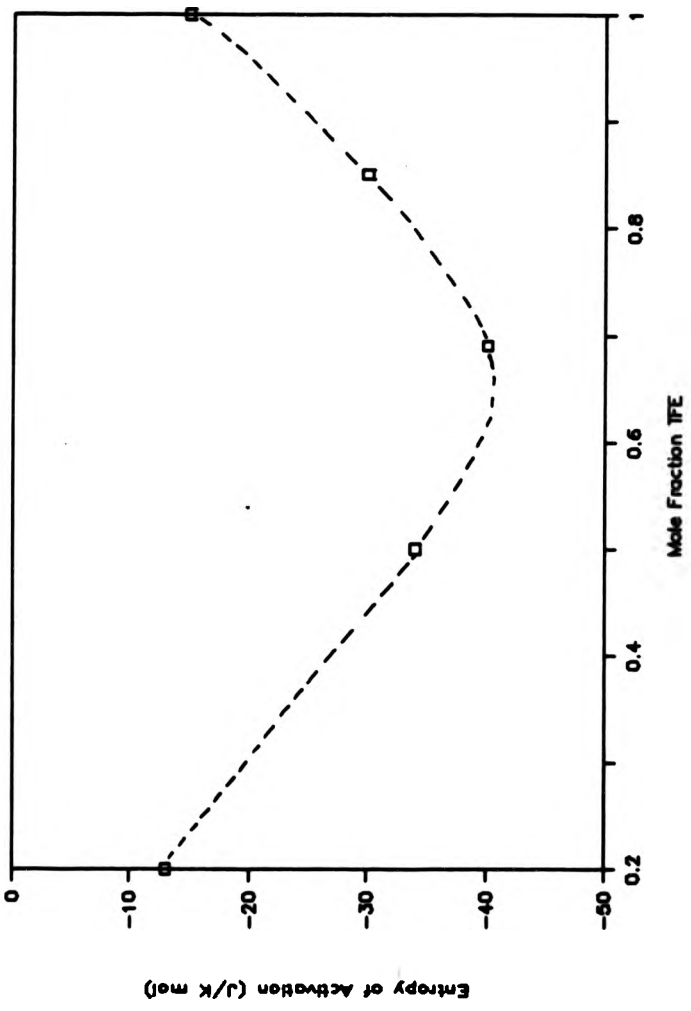


Graph 4.4 Activation Parameters versus Mole Fraction TFE in the solvolysis of 2-Adamantyl Tosylate.

(I) Graph of Enthalpy of Activation versus Mole Fraction TFE.



(II) Graph of Entropy of Activation versus Mole Fraction TFE.



CHAPTER 5

ANALYSIS METHODS and RESULTS

5.1 Solvolysis of 2-Adamantyl Azoxytosylate in Acetic Acid.

The reaction times of the solvolyses were at least seven half-lives of the azoxytosylate, but much less than one half-life of 2-adamantyl tosylate which was one of the products. The solvent contained either sodium acetate or potassium acetate as buffer. Determination of the volatile compounds was carried out by capillary glc, and hplc was used to determine the adamantyl tosylate.

Sample preparation was necessary prior to both glc and hplc analyses. For glc analysis, brine was added to the reaction solution and the solvolysis products were extracted with ether. The ether solution was dried with anhydrous sodium sulphate before it was injected into the gas chromatograph. Sample preparation for hplc analysis involved taking an aliquot from the reaction solution and diluting it to volume with mobile phase.

Absolute yields were determined in both analyses. In the case of the glc analysis an internal standard (*trans*-decalin) was employed and the molar response factors were calculated based on carbon number. A graph of 2-adamantyl tosylate concentration versus peak area was used in the hplc analysis. The average value for each compound was calculated from at least five injections of the samples in both analyses. Total

recovery was approximately 100%, i.e no major products not identified.

Table 5.1 Product Yields from the Acetolysis of 2-Adamantyl Azoxytosylate by GLC.

Product	% Yield (Sample)	Mean of the two runs*
2-AdOAc	(i) 68	
	(ii) 64	66(2)
exo-P-AdOAc	(i) 0.42	
	(ii) 0.38	0.40(0.02)
Adamantanone	(i) 0.28	
	(ii) 0.25	0.26(0.02)
Protoadamantene	(i) 0.44	
	(ii) 0.33	0.38(0.06)
DHadamantane	(i) 0.26	
	(ii) 0.26	0.26(0.00)
Total glc recovery	(i) 69	
	(ii) 65	67(2)

*Standard deviation in parentheses.

Where, 2-AdOAc = 2-adamantyl acetate

exo-P-AdOAc = exo-protoadamantyl acetate

DHadamantane = 2,4-didehydroadamantane

Table 5.2 Yields of 2-Adamantyl Tosylate from the Solvolysis of 2-Adamantyl Azoxytosylate in Acetic Acid by HPLC.

Sample	% Yield of 2-Adamantyl Tosylate
(i)	32
(ii)	32

5.2 Solvolysis of 2-Adamantyl Azoxytosylate and 2-Adamantyl Tosylate in Various TFE:H_2O Mixtures.

The solvolyses and sample preparations were carried out in the same manner as described above for the solvolyses in acetic acid. In the glc analyses, the molar response factor for 2-adamantanol to 2-adamantyl ether was determined, so the relative yields of these two compounds were obtained. The signal to noise ratio was not as good as that for the acetolyses above, therefore, the yields of rearrangment products were not determined. Analysis by glc was carried out on the products from solvolyses of both the azoxytosylate and tosylate in 50TFE, 80TFE and 97TFE.

Yields of 2-adamantyl tosylate were determined from solvolyses of the azoxytosylate in TFE, 97TFE and 50TFE. Since the rates of solvolysis of 2-adamantyl tosylate are much more significant in these three solvents than in acetic acid, its concentration was monitored throughout the course of the reactions, and the maximum value recorded.

Table 5.3 Yields of 2-Adamantyl Trifluoroethyl Ether and 2-Adamantanol from 2-Adamantyl Azoxytosylate in TFE:H_2O mixtures.

TFE:H_2O Mixture	TFE:H_2O Molar Ratio	2-AdOCH$_2$CF$_3$:2-AdOH* (Sample)	
50:50 (v/v)	20:80	(i)	35:64
		(ii)	36:64
80:20 (v/v)	50:50	(i)	51:49
		(ii)	52:48
97:3 (w/w)	85:15	(i)	84:16
		(ii)	85:15

Table 5.4. Yields of 2-Adamantyl Trifluoroethyl Ether and 2-Adamantanol from 2-Adamantyl Tosylate in TFE:H_2O Mixtures.

TFE:H_2O Mixture	TFE:H_2O Molar Ratio	2-AdOCH$_2$CF$_3$:2-AdOH* (Sample)	
50:50 (v/v)	20:80	(i)	25:75
		(ii)	24:76
80:20 (v/v)	50:50	(i)	47:53
		(ii)	47:53
97:3 (w/w)	85:15	(i)	84:16
		(ii)	83:17

* Yield normalised to 100%

Table 5.5 Peak Area of 2-Adamantyl Tosylate versus Time in the Solvolysis of 2-Adamantyl Azoxytosylate in Trifluoroethanol (1st Run).

Time (seconds)	Peak Area ($x10^3$)*
270	58.7
528	105
751	103
1325	72.0
1784	73.0
2533	70.5

* Average of three results.

Table 5.6 Peak Area of 2-Adamantyl Tosylate versus Time in the Solvolysis of 2-Adamantyl Azoxytosylate in Trifluoroethanol (2nd Run).

Time (minutes)	Peak Area ($x10^3$)**
21.5	8.9
40.0	15.2
87.7	36.5
127	46.6
157	54.1
197	61.2
237	66.0
275	66.0

* Average of two results.

Table 5.7 Peak Areas of 2-Adamantyl Tosylate and 2-Adamantyl Azoxytosylate versusTime in the Solvolysis of 2-Adamantyl Azoxytosylate in 97TFE.

Time (minutes)	Peak Areas ($x10^3$)*	
	Azoxytosylate	Tosylate
1.0	2560	2.5
20.0	2000	9.7
40.5	1560	17
80.0	1330	33
116	1036	43
165	794	59
199	568	60
237	417	62
328	207	64

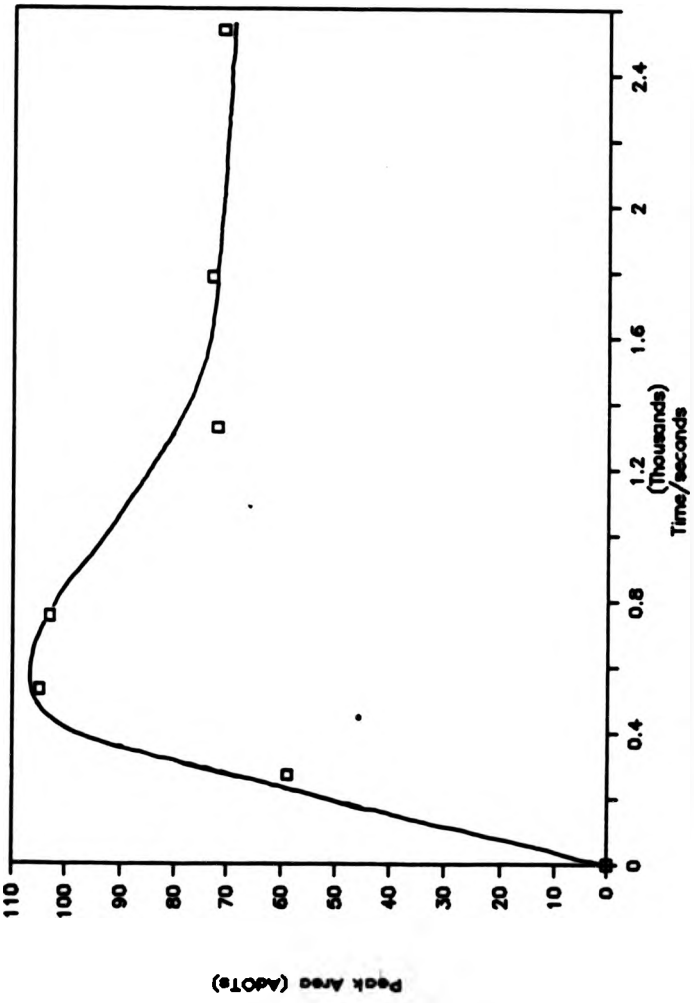
* Average of three results.

Table 5.8 Peak Areas of 2-Adamantyl Tosylate and 2-Adamantyl Azoxytosylate versus time in the Solvolysis of 2-Adamantyl Azoxytosylate in 50TFE.

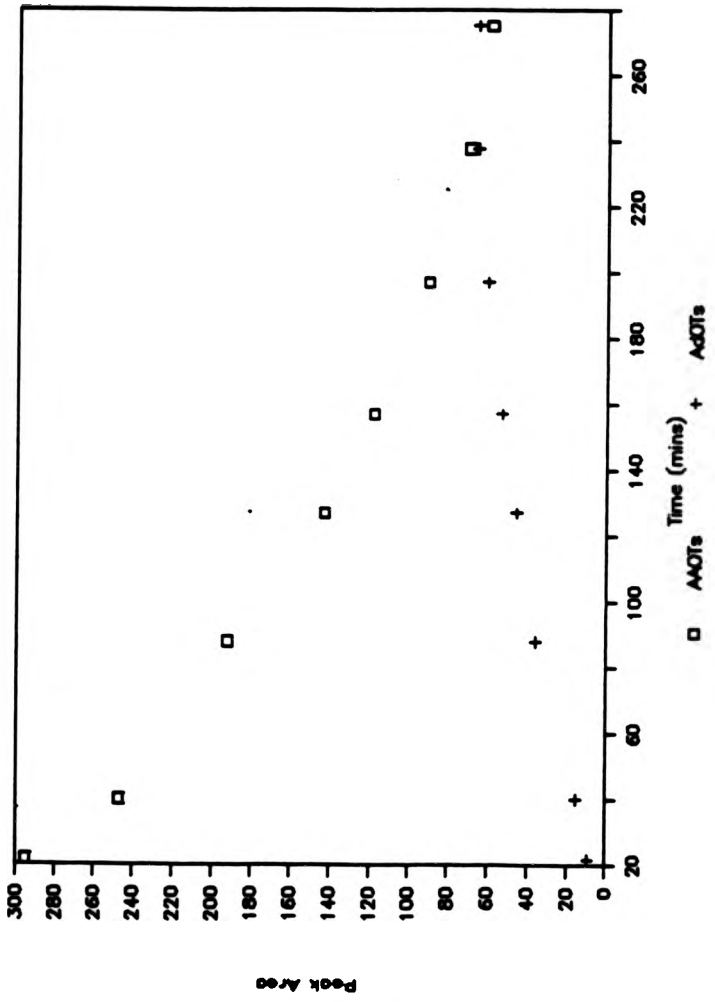
Time (minutes)	Peak Areas ($x10^3$)**	
	Azoxytosylate	Tosylate
0	915	0
22	520	0.4
40	550	6.9
69	200	10
91	120	11
117	75	12
138	50	12

** Average of two results.

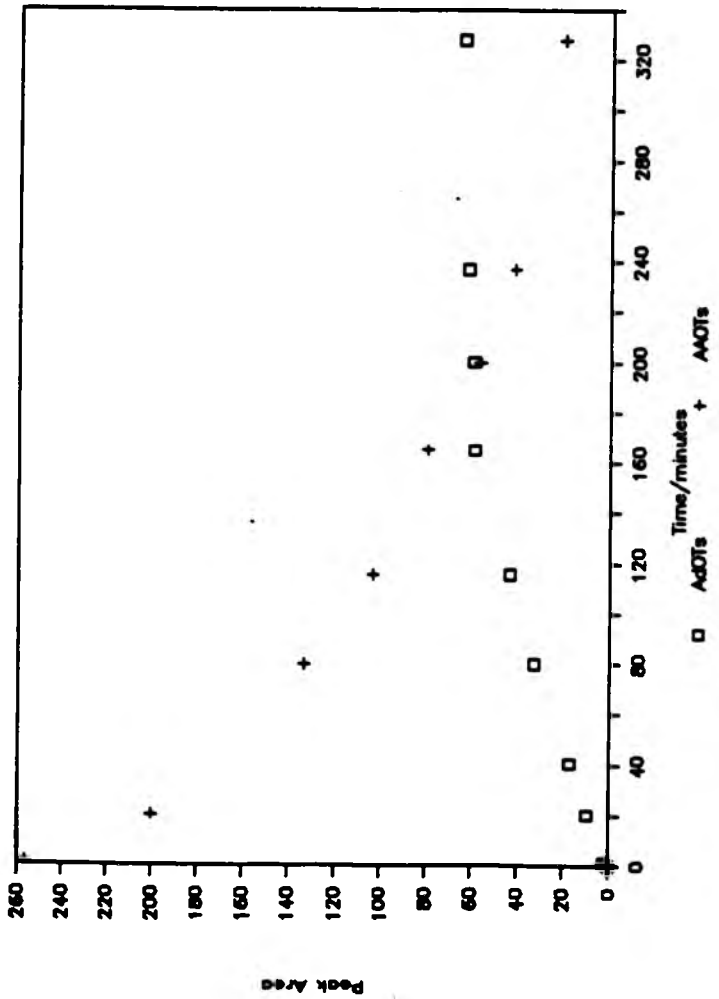
Graph 5.1 **Peak Area of 2-Adamantyl Tosylate versus Time in the Solvolysis of 2-Adamantyl Azoxytosylate in Trifluoroethanol (1st Run).**



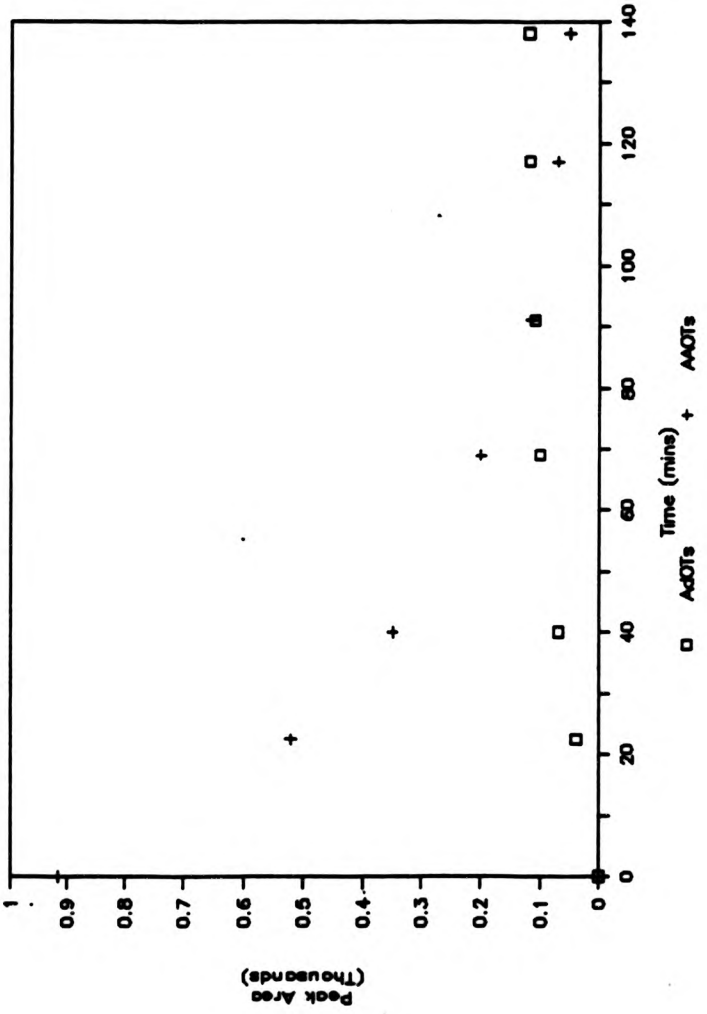
Graph 5.2 **Peak Areas of 2-Adamantyl Tosylate and 2-Adamantyl Azoxytosylate versus Time in the Solvolysis of 2-Adamantyl Azoxytosylate in Trifluoroethanol (2nd Run)**



Graph 5.3 Peak Areas of 2-Adamantyl Tosylate and 2-Adamantyl Azoxytosylate versus Time in the Solvolysis of 2-Adamantyl Azoxytosylate in 97TFE.



Graph 5.4 **Peak Areas of 2-Adamantyl Tosylate and 2-Adamantyl Azoxytosylate versus Time in the Solvolysis of 2-Adamantyl Azoxytosylate in 50TFE.**



5.3 Yields of 2-Adamantyl Tosylate from the Solvolysis of 2-Adamantyl Azoxytosylate in Some Other Common Solvolytic Media.

Yields of 2-adamantyl tosylate were determined in ethanol; 80%v/v ethanol, water (80ETOH); 60%v/v ethanol, water (60ETOH) and 97%w/w hexafluoroisopropanol, water, (97HFIP) using the solvolysis procedure and sample preparation described above. For the solvolyses in ethanol, 80ETOH and 60ETOH, reaction times of at least six half-lives of the azoxytosylate, but much less than one of the tosylate, were calculated from the respective activation parameters. This allowed a single determination of the tosylate concentration at the end of the reaction. The rate of solvolysis of 2-adamantyl tosylate in 97HFIP is much more significant, therefore its concentration was monitored throughout the course of the reaction in this solvent. Concentrations of 2-adamantyl tosylate were calculated from a graph of known concentration of tosylate versus peak area. The mean value for the tosylate concentration was taken from at least four injections of each sample in the ethanol and ethanol:water reactions , and from at least two injections in the reactions in 97HFIP. Two reaction reactions were carried out in all the above solvents except for 97HFIP, where only one reaction was carried out.

Table 5.9 Yields of 2-Adamantyl Tosylate from the Solvolyses of 2-Adamantyl Azoxytosylate.

Solvent	% Yield of 2-Adamantyl Tosylate (Sample)
Ethanol	(i) 25
	(ii) 27
80EtOH[a]	(i) 12
	(ii) 12
60EtOH[b]	(i) 7
	(ii) 7
	(ii) 18
97HFIP[c]	(i) 27

(a) 80:20 v/v, ethanol:water; (b) 60:40 v/v, ethanol:water; (c) 97:3 w/w, hexafluoroisopropanol:water.

5.4 Solvolysis of 2-Adamantyl Azoxytosylate in Solvents Containing Tetrabutylammonium Naphthalene-2-sulphonate (TNas).

Solvolysis of 2-adamantyl azoxytosylate was repeated in acetic acid, ethanol, 80ETOH and TFE containing tetrabutylammonium naphthalenesulphonate using the same procedures. Apart from increasing the methanol concentration in the mobile phase, the hplc conditions were the same as before. Reaction times were at least six half-lives of the azoxytosylate. Absolute concentrations of 2-adamantyl naphthalenesulphonate (AdONas) were calculated by comparing the peak area obtained with a graph of known concentration versus peak area. The mean value for each sample was calculated from at least four injections.

Table 5.10 Yields of 2-AdONas in the Solvolysis of 2-Adamantyl Azoxytosylate in Solvents containing TNas.

Solvent	[TNas]	% Yield AdONas
Acetic acid	0.27	1.3
	0.135	1.3
Ethanol	0.19	3.2
	0.09	2.0
80EtOH	0.15	1.4
Trifluoroethanol	0.18	0.7

5.5 Solvolysis of Bicyclo[2.2.2]octan-2-yl Azoxytosylate in 97HFIP.

The solvolysis procedure and sample preparation for glc analysis were the same as those described for the acetolysis of 2-adamantyl azoxytosylate above. The molar response factor of the purified exo-bicyclo-[3.2.1]octan-2-ol to the internal standard (pentadecane) was determined and it agreed excellently with the molar response factor calculated from carbon number (0.532 and 0.533 respectively). It was assumed that the isomeric alcohols would have the same response factor. This allowed absolute yields for the alcohols to be determined; the total hydrocarbon and ether yield was obtained by difference from 100%, and relative hydrocarbon and ether yields were calculated from an estimated molar response factor based on carbon number. In both samples, the mean value for each compound was calculated from at least four injections. It was necessary to analyse the hydrocarbon and ethers on a different column from the one used for the alcohols.

Table 5.9 Determination of Molar Response Factor of exo-Bicyclo[3.2.1]octan-2-ol versus Pentadecane.

Injection	Peak Areas		
	exo-[3.2.1]OH	$C_{15}H_{32}$	MRF (Mean)
(i)	14803	53991	
(ii)	16841	64422	0.532
(iii)	16433	65306	
(iv)	16118	64346	

Where MRF = $\frac{\text{no. moles pentadecane x area exo-[3.2.1]OH}}{\text{no. moles exo-[3.2.1]OH x area pentadecane}}$

Table 5.11 Product yields from Bicyclo[2.2.2]octan-2-yl Arenoxytosylate in 97%HFIP.

Compound	(Sample)	% Yield	Mean of the two runs
Tricyc.	(i)	14	
	(ii)	13	13.5
[2.2.2.]HFIP	(i)	9	
	(ii)	9	9
exo-[3.2.1]HFIP	(i)	10	
	(ii)	10	10
endo-[3.2.1]HFIP	(i)	3	
	(ii)	3	3
[2.2.2]OH	(i)	37	
	(ii)	37	37
exo-[3.2.1]OH	(i)	27	
	(ii)	27	27
endo-[3.2.1]OH	(i)	<0.1	
	(ii)	<0.1	<0.1

Where, Tricyc. = triyclo[3.2.1.$0^{2,7}$]octane.

[3.2.1]HFIP = bicyclo[3.2.1]octan-2-yl hexafluoro-isopropyl ether.

[2.2.2]HFIP = bicyclo[2.2.2]octan-2-yl hexafluoro-isopropyl ether.

[3.2.1]OH = bicyclo[3.2.1]octan-2-ol.

[2.2.2]OH = bicyclo[2.2.2]octan-2-ol.

CHAPTER 6

DISCUSSION

6.1 The Adamantyl System.

6.1.1 Internal Ion Pair Combination in the Solvolysis of 2-Adamantyl Azoxytosylate.

A great deal of effort went into establishing absolute yields for products of the solvolyses where possible, and ensuring maximum recovery. It was something of an initial surprise then, in the acetyolysis of 2-adamantyl azoxytosylate, to find the total yield by g.l.c. to be *ca.* 70%, since all the expected products had been shown to be readily detectable by g.l.c. After reconsidering the probable reaction mechanism of the solvolysis, it could be seen that there was a possibility of the adamantyl cation and the tosylate anion combining to form adamantyl tosylate. Although general opinion regards such an ion pair combination to be unlikely[40,59], there is qualitative evidence from previous work that 2-adamantyl tosylate is formed from thermolysis of the corresponding azoxytosylate in $CDCl_3$[10], and from solvolysis in ethanol[10].

Further investigations of the acetolyses reaction mixture by hplc did indeed show 2-adamantyl tosylate to be one of the products formed. When the yield was determined it was found to be precisely the amount required to account for the difference in observed yield by glc and the theoretical yield based on the amount of starting material.

The most probable route for the formation of 2-adamantyl tosylate from the azoxytosylate involves fragmentation followed by combination of the 2-adamantyl cation and tosylate anion. Another mechanism which was considered involves *Z*-*E* isomerization of the azoxytosylate followed by a concerted cyclic reaction with the extrusion of nitrous oxide. However, there is sufficient evidence from earlier work in this laboratory to show that azoxytosylates do not fragment in this manner[12].

If an ion-pair is involved, the extent of combination might be expected to be affected by both the nucleophilicity and ionising ability of the solvent. In the series of solvolyses in ethanol and ethanol:water mixtures, a significant drop in the yield of 2-adamantyl tosylate was observed as the medium became more aqueous. This drop in ion-pair combination occurs at approximately constant solvent nucleophilicity. Also, the yield of 2-adamantyl tosylate from the solvolysis in 100% trifluoroethanol is significantly less than that in 100% ethanol despite the fact that ethanol is a more powerful nucleophile. The nucleophilicity of the solvent, therefore, has been shown to have little or no effect on the extent of ion-pair combination.

On the otherhand, the ionising ability of the solvent appears to play a major role in combination of the internal ion pair. One interpretation is that as the solvent's dielectric constant increases, as is the case when ethanol becomes more aqueous, the initially-formed

ion pair becomes longer lived. Consequently, diffusional separation becomes more favourable leading to decreased yields of 2-adamantyl tosylate. This view is consistant with the observed decrease in 2-adamantyl tosylate yield in going from ethanol to the more weakly nucleophilic, but better ionising solvent, trifluoroethanol.

If up to one third of the total reaction 2-adamantyl azoxytosylate in solvents such as acetic acid and ethanol is internal nucleophilic capture of the carbocation by tosylate in an ion pair separated at its genesis by N_2O, the extent of ion pair recombination from the intimate ion pair produced by ionization of 2-adamantyl tosylate must be very much higher. In other words, internal return in the solvolysis of 2-adamantyl tosylate itself is not kinetically insignificant but takes place to a very major extent. Consequently, ionization of 2-adamantyl tosylate cannot any longer be regarded as the rate determining step in its solvolysis in these media, a conclusion arrived at recently on the basis of independent evidence[60].

(II) The Product Forming Step in the Solvolysis of Adamantyl Azoxytosylate.

From the rate data, it can be seen that the nucleophile has little or no effect on the rate determining step. But, in the product determining step, would a stronger nucleophile trap the 2-adamantyl cation better than a weaker one? When given the choice of a weak nucleophile (trifluoroethanol), and a relatively

much stronger one (H_2O) this does not seem to be the case. In the solvolyses of 2-adamantyl azoxytosylate and the corresponding tosylate in 97TFE, the ratio of 2-adamantanol: 2-adamantyl trifluoroethyl ether is virtually identical with the molar ratio of TFE: H_2O of the solvent. Indeed, in 50TFE and to a lesser extent in 80TFE, there is a slight but significant selectivity in favour of the less nucleophilic trifluoroethanol. It is interpreted from these findings that the 2-adamantyl cation will react with the first molecule it encounters regardless of how strong or weak a nucleophile it is. The slight selectivity actually in favour of trifluoroethanol observed in the most aqueous solvents is probably due to an enhanced concentration of trifluoroethanol in the vicinity of the incipient 2-adamantyl cation; which would be the case if the TFE H-bonded better at the pendant oxygen of the azoxytosylate. These findings show the 2-adamantyl cation to be highly reactive and it is unlikely that it has any significant existance other than as half of an ion pair.

Of the four possible product forming routes in Winsteins ion pair mechanism (Figure 2.4, page 26), it can be seen from the evidence presented here that the most likely routes are those involving the intimate and solvent-separated ion pairs. Nucleophilic attack on the covalent substrate (*i.e.* the first route) can be discounted on the basis of the rate data, where good first order kinetics in the presence of added

nucleophiles, are obeyed and independence of the rate of reaction on nucleophilicity of the solvent was observed. It is also highly unlikely that the 2-adamantyl cation diffuses through the solvent to any significant extent, and so no product would be expected to be formed from the independently solvated cation. It is proposed, therefore, that the carbocation involved in the product determining step is, to some degree, probably from both the intimate and solvent separated ion pairs.

How then do we account for disproportionately large amounts of carbocation capture by an added nucleophile present in only small concentrations? For example, it has been reported that up to 1% of 2-adamantyl azide is formed from the solvolysis of 2-adamantyl tosylate in ethanol containing only 0.06 mol dm^{-3} sodium azide[84]. There is also provisional evidence from the work carried out here that a 0.25 mol dm^{-3} solution of tetrabutylammonium thiocyanate leads to a similarly small but significant extent of carbocation capture in the solvolysis of 2-adamantyl azoxytosylate and 2-adamantyl tosylate in TFE. Naphthalene-2-sulphonate compares with tosylate as a nucleophile, and is very much weaker than thiocyanate or azide. However, when tetrabutylammonium naphthalene-2-sulphonate was employed as a dilute weakly nucleophilic solute in the solvolysis of 2-adamantyl azoxytosylate it also led to comparable yields of carbocation capture, this time to give 2-adamantyl naphthalene-2-sulphonate (Table 5.10, page79). How then can the picture of a 2-adamantyl cation too short lived to

diffuse through the solvent be reconciled with the observations of low but mechanistically significant yields of products evidently formed from the 2-adamantyl cation and a very dilute nucleophilic solute? And why should the yields in such trapping experiments be so apparently insensitive to the nucleophilicity of the solute?

It is suggested here that ionization of 2-adamantyl tosylate, or fragmentation of 2-adamantyl azoxytosylate occurs after preassociation of substrate and nucleophile. The 2-adamantyl cation is then formed in close proximity not only to the tosylate nucleofuge, but also to the other anion, *i.e.* azide, thiocyanate, or naphthalene-2-sulphonate, and exchange of the nucleofuge and anion occurs inside the solvent cage. The trapping products, therefore, arise from the 2-adamantyl cation in a process more akin to internal ion pair combination but not with the original nucleofuge. This would conceivably occur with little or no dependance upon the intrinsic nucleophilicity of the alternative nucleophile.

(III) Carbocation Rearrangements.

Rearrangement products from the solvolysis of 2-adamantyl azoxytosylate in acetic acid are compared with those from the corresponding tosylate solvolysis, and solvolytic deamination by the triazene method in Table 6.1. Interestingly, the yield of rearrangement products from the azoxytosylate was very much closer, although slightly greater, to the tosylate than to the

triazene. One of the reasons suggested in the past for the enhanced yield of rearrangement products from deamination compared to tosylate solvolysis has been the formation of a "hot" or vibrationally excited carbocation resulting from the formation of a nitrogen molecule[21,35]. Another has been

Table 6.1. Product Yields from Acetolysis[a] of 2-Adamantyl Azoxytosylate (I) compared with Results for 2-Adamantyl Tosylate (II) and 1-(2-Adamantyl)-3-phenyltriazene (III).

	Reactant		
Product	(I)[b]	(II)[c]	(III)[c,d]
Protoadamantene	0.5	0[e]	3.7
2,4-Dehydroadamantane	0.5	0[f]	11.4
2-Adamantyl Acetate	98.4	99.5	79.0
exo-4-Protoadamantyl Acetate	0.6	0.5	5.9

(a), Acetic acid contains 0.15M CH_3CO_2Na or CH_3CO_2K. (b), Solvolytic yields normalized to total = 100%; actual absolute recovery = 68 (±2)% (mean of two reactions), the remainder being 2-adamantyl tosylate by ion pair combination, page 67. (c), Reference 35. (d), Acetolysis yield normalized to 100%; actual recovery = 68.3%, the remainder being mainly N-phenyladamantylamine. (e), Less than 0.005%. (f), Less than 0.3%.

Streitwieser's "pull" effect of the departing nitrogen in the deamination type reactions[35]. Following this

reasoning, extrusion of a nitrous oxide molecule should lead to a similarly excited carbocation, or cause such a "pull" effect, and hence the yield of rearrangement product from the azoxytosylate should resemble more closely that of the triazene than that of the tosylate. However, the product analytical data presented here show the yield of rearrangement product from the azoxytosylate to resemble much more closely that from the tosylate than that from the triazene. Therefore, extrusion of nitrous oxide or nitrogen in the ionisation cannot be the major significant cause of the "deamination type" of product distributions, as for the first time these results demonstrate.

Why then, are the protoadamantyl products formed in greater yield from the triazene? To tackle this question, the problem of *how* they are formed must be addressed first. Equilibrium studies have shown that it is highly unlikely that there is any rearrangement to give a classical 4-protoadamantyl cation[35,41]. Absence of the *endo*- isomer in the product analytical data from all three systems supports this view, since the classical 4-protoadamantyl cation should give rise to equivalent amounts of *endo*- and exo- isomers. However, a bridged non-classical ion would explain the absence of the *endo*-isomer, for the presence of the partial bond would hinder nucleophilic attack from the *endo*- side.

The idea of a non-classical ion in adamantyl systems is not a new one and a few reasons have been suggested as to why such a carbocation may be formed[35, 41]. These

include those discussed above, *i.e.* Streitwiesers "pull" effect and "hot carbonium ions", and anchimeric assistance. One or more of these suggested reasons have then been used to argue that it is a totally different carbocation which is generated from tosylate solvolysis than from deamination. From the discussion above the first two reasons must now be thought of as being highly unlikely, and if anchimeric assistance was the cause then surely more bridging would be expected in the tosylate reaction than in the triazene, since the former requires a great deal more assistance for ionisation.

What is proposed here is that in all three adamantyl systems, *i.e.* the tosylate, azoxytosylate and the triazene, a classical 2-adamantyl cation is formed first which then rearranges to give a non-classical carbonium ion. The extent to which the 2-adamantyl cation is allowed to rearrange is governed by how tightly the ion pair is solvated. In the case of the tosylate, the ion pair is only formed when a number of facilitating events occur together. These include attainment of the appropriate conformation of the substrate, electrophilic solvation of the nucleofuge through hydrogen bonding, and (perhaps) specific nucleophilic solvation of the incipient carbocation. Consequently, the microenvironment of the ion pair from the tosylate is very limited, and the life-times of these states are too short for major conformational change to take place. The triazene reaction, on the other hand, requires much less assistance from the solvent and is therefore much

more loosely solvated which allows more time for rearrangement.

(IV) The Position of the Transition State in the Solvolysis of the Adamantyl Systems.

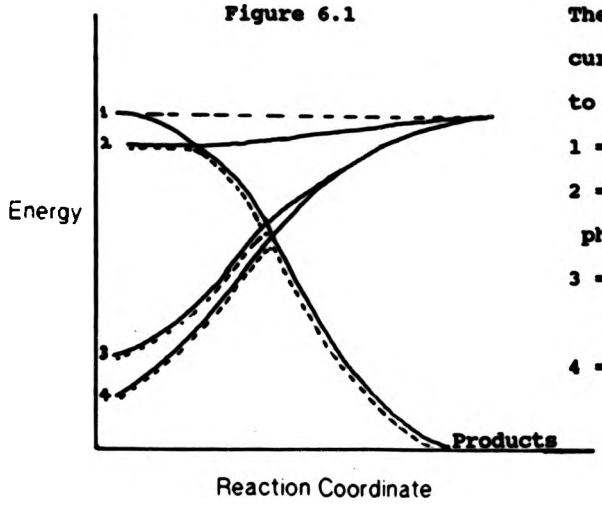
The proposal that the 2-adamantyl cation generated from the triazene has more time to rearrange to a non classical ion, compared to the other two carbocation forming reactions, implies that the transition state occurs at an earlier stage along the reaction coordinate. Furthermore, if the extent of rearrangement is mainly due to the relative position of the transition state then the transition states of the tosylate and azoxytosylate must be at a similar position and very much later than that from the triazene. However it is not immediately obvious that this is the case.

It is stated by Dewar[88] in his treatment of the Leffler-Hammond postulate, that the position of the transition state along the reaction coordinate and its free energy can be affected by the stability of the products. He then goes on to predict that an increase in stabilization of the product will bring about a corresponding decrease in the activation energy, which will in turn, make the transition state more reactant like.

If this is then applied to the three types of carbocation generation under consideration, the predicted relative positions of the transition states of the azoxytosylate and triazene should be similar and earlier relative to the tosylate since, in each of the

former reactions, a stable gas molecule is among the products. In other words, formation of the gas molecules, N_2 and N_2O, in deamination and azoxytosylate solvolysis respectively, will significantly lower the sum of the free energies of the products from these reactions relative to that of tosylate solvolysis. This would mean that the transition states, and hence the product distributions, from the two former reactions would be similar, but very different from those from the latter. Therefore, it would seem by considering the free energy of the products only, there is no correlation between the relative position of the transition state and amount of observed rearrangement.

Figure 6.1



The dissociation curves correspond to the following:

1 = Products

2 = 2-Adamantyl phenyl triazene

3 = 2-Adamantyl azoxytosylate

4 = 2.Adamantyl tosylate.

However, what would the estimated relative position of the transition states along the reaction coordinate be if the ground state energies of the precursors were also taken into account? If the activation energies of each of the three types of carbocation generation are taken as a guide to the relative ground state energies of the precursors, and the dissociation curves for all three reactions are superimposed on one another, the reaction profiles now clearly show the transition states to be at the positions along the reaction coordinate expected from the observed product distributions (Figure 6.1, p92). Moreover, although it is only a qualitative picture, it is clear that the distance between the transition states is proportional to the difference in free energy between the precursors, and not due to artistic licence.

6.2 The Bicyclo[2.2.2]octyl System.

Similar conclusions to those above may be drawn from the results for the bicyclo[2.2.2]octane system. The complete analysis of products from bicyclo[2.2.2]octan-2-yl azoxytosylate ([2.2.2]AOTs) in 97% aqueous hexafluoroisopropanol is shown in Table 5.7, page 79.

We have already seen that conventional deamination in this system initially produces a "classical" carbocation[92] which suffers external nucleophilic capture (by solvent), capture by the internal nucleophile (the nucleofuge other than N_2 in the fragmentation), and, principally, relaxation to an unsymmetrical non-classical carbocation (which then goes on itself to suffer nucleophilic capture

or proton loss). The products from bicyclo[2.2.2]octan-2-yl tosylate ([2.2.2]OTs) are essentially by solvent reaction with the same non-classical carbocation and comprise 87% of bicyclo[2.2.2]octan-2-yl plus exo-bicyclo[3.2.1]octan-2-yl substitution products in the ratio 54:46, and 13% of tricyclo[3.2.1.$0^{2,7}$]octane.

The relative proportions of the total substitution products from [2.2.2]AOTs are very much closer indeed to those found in the acetolysis of the tosylate than to those found from the deamination of 1-(bicyclo[2.2.2]octan-2-yl)-3-phenyltriazene in acetic acid (Table 6.2, p95).

Trapping of a first-formed classical carbocation in 97% aqueous hexafluoroisopropanol before it has time to relax to the non-classical ion, therefore, is not indicated by the total substitution yields, but may just be evident from the alcohol products (Table 6.3, p96). There is, at the moment no ready explanation for the relative yields of the bicyclo-octyl hexafluoropropan-2-yl ethers formed from [2.2.2]AOTs.

Table 6.2. Products from the Solvolysis of Bicyclo[2.2.2]octan-2-yl Azoxytosylate (IV) in 97HFIP compared with Products from the Acetolysis of Bicyclo[2.2.2]octan-2-yl Tosylate (V) and 1-(Bicyclo[2.2.2]octan-2-yl)-3-Phenyltriazene (VI).

	Reactant		
Product	(IV)	(V)[a]	(VI)[b]
Tricyclo[3.2.1.$0^{2,7}$]octane	14	13	21.9
Bicyclo-octenes	0	0	17.5
Bicyclo[2.2.2]octan-2-ol	37 (9)[c]	46.5[d]	30.2[d]
exo-Bicyclo[3.2.1]octan-2-ol	27 (10)[c]	40.2[d]	17.7[d]
endo-Bicyclo[3.2.1]octan-2-ol	0 (3)[c]	0.3[d]	0[d]

(a), From results reported in reference 91. (b), From results reported in reference 92; 12.7% N-bicyclo-octylanilines formed by internal return not included. (c), Yields of the corresponding hexafluoroisopropan-2-yl ethers shown in parentheses. (d), Bicyclo-octyl acetates.

Table 6.3. Proportions of Solvent-derived Substitution Products (2.2.2): (exo-3.2.1): (endo-3.2.1) from (IV), (V) and (VI).

Reaction	Product Ratio[a] 2.2.2	exo-3.2.1	endo-3.2.1
(IV) in 97HFIP (alcohols, 64%)	58	42	0
(V) in CH_3CO_2H (acetates, 87%)[b]	53.4	46.2	0.3
(VI) in CH_3CO_2H (acetates, 48%)[c]	63	37	0

a, (2.2.2) = bicyclo[2.2.2]octan-2-yl
(exo-3.2.1) = exo-bicyclo[3.2.1]octan-2-yl
(endo-3.2.1) = endo-bicyclo[3.2.1]octan-2-yl.

b, Results from reference 91.

c, Results from reference 92.

6.3 Summary

The product analytical data presented here have shown that the solvolysis of 2-adamantyl azoxytosylate is a mechanistic link between the corresponding tosylate and triazene solvolyses. The initial rate-determining fragmentation of the azoxytosylate is analogous to the carbocation-forming step in the corresponding deamination, although it is much slower, but the product-forming step(s) resemble(s) more closely those in the solvolysis of the tosylate. It has also been shown that the 2-adamantyl cation has no significant existence other than as half of an ion pair. It follows from the collapse of this ion pair in the solvolysis of 2-adamantyl azoxytosylate to give 2-adamantyl tosylate, that internal return in the solvolysis of 2-adamantyl

tosylate must take place to an even greater extent. Ionization of 2-adamantyl tosylate cannot, therefore, any longer be regarded as the rate-determining step in these media. The "early" transition state of the deamination reaction allows the 2-adamantyl cation time for conformational relaxation to a non-classical ion, hence the large amount of rearrangement products. In the case of the corresponding tosylate and azoxytosylate solvolyses, the 2-adamantyl cation is formed much later, after a much more product-like transition state. The work presented here has shown that the reason for this is due mainly to the activation energy of the carbocation forming step and not, as was previously thought, due to formation of a relatively short-lived and vibrationally excited cation. In otherwords, emphasis for the reason for rearrangement has moved from the products towards reactants.

CHAPTER 7

EXPERIMENTAL

7.1 General Details

All n.m.r. spectra were recorded using either a 60MHz Hitachi Perkin-Elmer R-24, or a 90MHz Perkin-Elmer R-32, n.m.r. spectrometer. Mass spectrometry and gas-liquid chromatography-mass spectrometry (g.l.c.-m.s.) were carried out on a Jeol D-100 double focussing gas chromatograph-mass spectrometer.

Capillary g.l.c. was carried out on a Perkin-Elmer F30 equipped with a flame ionisation detector and a split injection system with nitrogen as the carrier gas. The g.l.c. conditions for the g.l.c.-m.s. were first determined on a Perkin-Elmer F17 gas chromatograph with nitrogen again as the carrier gas. High performance liquid chromatography (h.p.l.c.) was carried out on a Gilson 303 instrument equipped with a u.v. detector. Peak areas in the g.l.c. analyses were integrated on a Supergrator-1, and in the h.p.l.c. analyses, on a Pye Unicam 4810.

Pentane and petroleum ether were purified by washing with concentrated sulphuric acid, then aqueous sodium carbonate solution and finally fractional distillation. The methanol (BDH h.p.l.c. grade) and water (distilled) used for the h.p.l.c. were degassed by filtering under reduced pressure, and had helium bubbled through them during the analyses. The methanol used for making

methanolic HCl and recrystallisation of 2-adamantyl naphthalene-2-sulphonate was BDH h.p.l.c. grade. The ether used for recrystallizations was redistilled from sodium hydride, and the ether used in the g.l.c. analysis work-ups was percolated through alumina.

Melting points were determined on a Kofler hot stage and are uncorrected.

7.2 Purification of the Solvents for Kinetics and Product Analysis

7.2.1 Acetic acid

The acetic acid was heated under reflux with acetic anhydride overnight then fractionally distilled, b.p. 117.5-118°C.

7.2.2 2,2,2-Trifluoroethanol (TFE)

The TFE (500g) was heated under reflux over ground calcium hydride (10g) for 2 hours then fractionally distilled, b.p. 74-75°C.

7.2.3 1,1,1,3,3,3-Hexafluoropropan-2-ol (HFIP)

The HFIP was heated under reflux over molecular sieve overnight then fractionally distilled, b.p. 57-59°C.

7.2.4 Ethanol

The absolute ethanol used for the product analyses was spectroscopic grade and was not purified further.

7.3 Preparative Details

7.3.1 Adamantanone Oxime

A solution of adamantanone (4.65g, 31.0mmol), hydroxylamine hydrochloride (3.36g, 48.3mmol) and sodium acetate (5.28g, 64.4mmol) in aqueous methanol (1:1 v/v, 80ml) was heated under reflux for 4 hours. The mixture was cooled and most of the methanol was removed under vacuum. The resulting solution was diluted with water and the precipitate which formed was filtered under vacuum . The filtrate product was washed several times with water then placed in a vacuum desiccator to dry [4.84g, 94%; m.p. 168 -170°C, lit. 165 - 166°C[93], δH^1 ($CDCl_3$): 1.9(12 H, s), 2.6(2 H, s), 3.6(1 H, s) and 8.5 (1 H, br s, exch. D_2O); $\nu_{max.}$ (KBr) 3210, 3120, 1657, 1480, 1455, 965, and 955cm^{-1}.]

7.3.2 N-(2-Adamantyl)hydroxylamine

A single small crystal of Bromocresol Green was added to a stirred solution of adamantanone oxime (3.60g,21.8mmol) in methanol (*ca.*3ml). Portions of sodium cyanoborohydride (2.10g,33.4mmol) and a methanolic solution of HCl (prepared from 30ml methanol and 5ml acetyl chloride) were then added alternately in order to keep the colour of the solution on the yellow side of the yellow-green borderline. The mixture was left stirring under argon overnight. The methanol was removed on the rotary evaporator and the residue extracted between CH_2Cl_2 and water (pH9 with Na_2CO_3). The water layer was

extracted a further twice with CH_2Cl_2 and the organic extracts were combined, washed with water and dried over anhydrous Na_2SO_4. After the organic phase had been filtered, the CH_2Cl_2 was removed on a rotary evaporator to give 2.60g of colourless crystalline crude product. The product was purified by sublimation [120°C, ca.15torr, 1.83g (50%); δ^1H ($CDCl_3$) 1.4-2.0 (14 H, m), 3.1(1 H), 5.8-6.3 (2 H, br. s exch. D_2O);].

7.3.3 N-Nitroso,N-(2-Adamantyl)hydroxylamine.

A solution of sodium nitrite (0.60g, 8.7mmol) in water (2ml) was added dropwise over 10 minutes to a stirred solution of N-(2-adamantyl)hydroxylamine (0.90g, 5.4mmol) in ethanol (6ml) and aqueous HCl (2M, 3ml, 6.0mmol) at 0°C. The solution became cloudy towards the end of the addition of the $NaNO_2$. The mixture was stirred at 0°C for a further 1.5 hours, then poured into ice-water (200ml). The colourless precipitate was filtered at the pump and dried in a vacuum desiccator [0.98g(93%), m.p136-139°C, lit.[3]137-139°C[10]; δH($CDCl_3$) 1.4-2.2(12H,m), 2.6(2H,m),4.2(1H,m), 9.6-10.2(1H, br. s exch. D_2O); $\bar{\nu}_{max.}$ (KBr) 3600-3200, 3050, 2920, 2860, 1450, 1080, 1060, 1040, 980, 790, 710, 410, and 370cm^{-1}].

7.3.4 2-Adamantyl Azoxytosylate

Following the Tipson procedure, recrystallised p-toluenesulphonyl chloride (1.20g, 6.28mmol) was added to a stirred mixture of N-nitroso-N-(2-adamantyl)-hydroxylamine(0.68g,3.5mmol) in dry pyridine (3ml) and the mixture was left stirring for 24 hours. A few drops

of water were then added and the mixture was left stirring at 0°C for a further 2 hours to hydrolyse the excess tosyl chloride. The product was extracted between water and ether at 0°C. The combined ether extracts were washed with $CuSO_4$(aq), water, Na_2CO_3(aq) and dried over anhydrous Na_2SO_4. The drying agent was filtered off and the ether removed on the rotary evaporator to leave a slightly yellow residue (0.90g). No 2-adamantyl tosylate or tosyl chloride were detected by hplc (<0.1%).

The crude azoxytosylate was recrystallised at -78°C as follows. A sample (0.23g) was dissolved in ether (*ca.* 15ml, redistilled). The solution, which had a distinct yellow tinge, was treated with charcoal (*ca.* 0.1g) , percolated through a small Na_2SO_4 column, and washed through with a little ether, to give a colourless solution. The ether was evaporated by a gentle stream of argon until the first sign of crystals appeared. The flow of argon was reduced and the solution cooled to -78°C over a period of half an hour. It was kept at this temperature for 1 hour then the mother liquor was removed by pipette and the crystals were triturated with a little ether (twice). The flask was allowed to come slowly up to room temperature whilst under vacuum (*ca.* 0.1 Torr) to leave colourless crystals [(0.142g), m.p. 114-114.5°C, lit. 111-113°C[10]; δ_H($CDCl_3$) 1.0-2.4 (12 H, m), 2.5 (5 H, m), 4.3 (1 H,m), and 7.6 (4 H, q); $\nu_{max.}$ (KBr) 2920, 2860, 1600, 1505, 1455, 1390, 1195, 1180, 1090, 920, 900, 820, 805, 795, 770, 725, 665, 565, and 550cm^{-1}]

7.3.5 2-Adamantyl 2,2,2-trifluoroethyl ethers.

2-Adamantyl iodide and $CaCO_3$ were heated under reflux in 2,2,2-trifluoroethanol for 48 hours. The mixture was extracted between water and pentane (acid washed and redistilled). Analysis by g.l.c on a 50ft capillary MEMA column showed one major peak and one minor peak (<3%) due to the 2-adamantyl ether and 2-adamantanol respectively.

exo-4-Protoadamantyl and 1-adamantyl 2,2,2-trifluoroethyl ethers were prepared by solvolysis of the corresponding tosylates in trifluoroethanol.

7.3.6 Adamantanone p-tosylhydrazone.

Adamantanone (4.70g, 31.28mmol), p-tosylhydrazine (9.02g, 48.46mmol) and sodium acetate trihydrate (8.83g, 64.91mmol) were heated under reflux in 50% aqueous methanol (80ml) for 6 hours. The solution was then allowed to cool overnight. The white precipitate which had formed was filtered under vacuum, washed with 50% methanol and dried in a vacuum desiccator [5.26g (63%)].

7.3.7 Lithium salt of adamantanone p-tosylhydrazone.

Standardisation of the butyl lithium-hexane solution was carried out as follows.The hexane solution of n-butyl lithium (1ml) was measured out into a volumetric flask, quenched with water, and the aqueous solution was made up to the mark with distilled water. Aliquots of the aqueous solution were titrated with standardised HCl and the concentration of butyl lithium calculated.

The standardised butyl lithium-hexane solution (5ml, 8mmol) was slowly added, under argon, to the hydrazone (2g, 6mmol) in distilled tetrahydrofuran (15ml). The mixture was stirred for 30 minutes then the solvent was allowed to evaporate under a stream of argon overnight.

7.3.8 2,4-Didehydroadamantane.

Heating the lithium salt of the hydrazone (*ca* 0.5g) in a sublimation apparatus gave a small amount of white crystalline product; m.p. 209-213°C, lit. 202.5-203.5°C[89]. Analysis by capillary g.l.c on a MBMA column gave 3 peaks; adamantane (*ca*.10%), dehydroadamantane (*ca*. 70%) and adamantanone (*ca*.20%). Adamantanone and adamantane were identified by their mass spectra and comparison of g.l.c. retention times with authentic samples. High resolution mass spectrometry (hr/ms) on didehydroadamantane: found $M^{+\cdot}$, 134.1100; calculated for $C_{10}H_{14}$ 134.1096.

7.3.9 2-Adamantyl Acetate.

2-Adamantanol (0.013g, 0.08mmol) was added to a solution of acetic anhydride (0.03ml, 0.17mmol) in pyridine (1.5ml) The mixture was heated under reflux for 2 hours. It was allowed to cool to room temperature and a few drops of water were added (but not enough to generate a separate phase). After leaving the solution for a further hour at room temperature, it was poured into water (40ml) then extracted with ether (5 x 2ml). The combined ether fractions were washed with $CuSO_4$(aq),

water and Na_2CO_3(aq.). The ether was dried over $MgSO_4$ (anhydrous) and analysed by g.l.c.

7.3.10 2-Adamantyl Tosylate.

A solution of 2-adamantanol (1.5g, 9.86mmol) and tosyl chloride (3.0g, 15.74mmol) in dry pyridine (40ml)was stirred for one week at room temperature. The solution was then poured into ice water and stirred for 10 minutes. The precipitate was filtered under vacuum and recrystallised at low temperature from pentane to give colourless crystals [2.78g (92%); m.p 82-83°C, lit. 82.7-83.7°C[10]].

7.3.11 Bicyclo[2.2.2]octan-2-ol

1,3-Cyclohexadiene (50g) was divided equally between 3 glass tubes. To each of these tubes was added vinyl acetate (50ml) and a small amount of quinol. The tubes were cooled in liquid nitrogen, degassed and sealed. They were placed in an oven at 172°C for two weeks, then allowed to come to room temperature. The excess of vinyl acetate was distilled from the combined contents of two of the tubes. The residue was dissolved in ethanol and hydrogenated over 5% rhodium on charcoal (0.6g) at 50°C for three days under approximately 40atm of hydrogen. The mixture was filtered and the volume reduced to 200ml by distillation. An aqueous solution (45ml) of potassium hydroxide (24.7g, 0.44mol) was added and the mixture was heated under reflux for 3 hours. Ethanol was then distilled from the reaction mixture and discarded until

the product was detected in the distillate. Thereafter the product was distilled in steam and isolated from the distillate by ether extraction in the normal way 10.23g (13%).

7.3.12 Bicyclo[2,2,2]octan-2-one.

A solution of $Na_2Cr_2O_7.2H_2O$ (1.65g) and concentrated H_2SO_4 (1.2ml) in water (40ml) was added dropwise over 30 minutes to a stirred solution of bicyclo[2,2,2]octan-2-ol (1.00g) in ether (2ml). When the amount of alcohol remaining was <0.25% (SCOT DEGS column, 80°C), the phases were separated and the aqueous phase mixture was extracted with more ether (2 x 30ml). The combined ether extracts were washed with $NaHCO_3$(aq.) and water, dried over anhydrous Na_2SO_4, filtered and evaporated down. [0.82g (83%) of white crystals].

7.3.13 Bicyclo[2,2,2]octan-2-one Oxime

A mixture of bicyclo[2,2,2]octan-2-one (1.20g, 9.68mmol), hydroxylamine hydrochloride (1.50g, 21.4mmol) and anhydrous sodium acetate (2.02g) in aqueous methanol (3.5ml MeOH, 16ml H_2O) was heated under reflux for 12 hours. White needle-like crystals formed on cooling and were filtered at the pump. 1.27g (94%); m.p. 120-121°C (lit., 116-119°C)[94].

7.3.14 N-(Bicyclo[2.2.2]octan-2-yl)hydroxylamine

The substituted hydroxylamine was prepared from the oxime [83%, m.p. 94-96°C, lit. 94-95°C[10]; δ^1_H ($CDCl_3$) 0.8-2.5 (12 H, m), 3.0-3.4 (1 H, m), 6.5 (2 H, br s);

$\bar{\nu}_{max.}$ (KBr) 3600-3200, 2940, 2860, 1450, 1360, 925, and 850 cm^{-1}] in the same manner as the adamantane adalogue.

7.3.15

N-Nitroso-N-(Bicyclo[2,2,2]octan-2-yl)hydroxylamine

This compound was prepared from the hydroxylamine (100%) in the manner described above for the adamantane analogue . Due to its apparent instability, the product was tosylated directly without purification.

7.3.16 Bicyclo[2,2,2]octan-2-yl Asoxytosylate

This compound was prepared by the above-described Tipson procedure from tosyl chloride (0.67g, 3.51mmol, recrystallised) and the N-nitroso-hydroxylamine (0.30g, 1.76mmol), at 0°C to give crude product (0.52g), which was recrystallised in the normal way [0.45g(79%); m.p. 84-85°C, lit. 82-83°C[10]; δ^1_H ($CDCl_3$) 1.2-2.1 (12 H, m), 2.5 (3 H, s), 4.6 (1 H, m), and 7.6 (4 H, ABq); $\bar{\nu}_{max.}$(KBr) 2940, 2870, 1530, 1385, 1195, 1175, 750, 560, and 550 cm^{-1}].

7.3.17 exo-3,4-Dichlorobicyclo[3,2,1]oct-2-ene.

A sodium hydroxide solution (48.40g in 85ml water) was added dropwise to a mechanically stirred mixture of norbornene (14.33g, 0.15mol), $CHCl_3$ (71.00g, 0.60mol) and benzyltriethylammonium chloride (0.56g) at room temperature. This was stirred for a further 55 hours then water (150ml) was added and the mixture extracted with $CHCl_3$ (3x75ml). The combined extracts were washed with water (2 x 50ml), dilute HCl (1M, 40ml) and brine

(40ml) then dried over $CaCl_2$ and filtered. The $CHCl_3$ was removed on the rotary evaporator leaving a dark reddish liquid which, after vacuum distillation (78-82°C, 0.1 Torr, lit. 72-73°C, 0.9mm), yielded a colourless liquid (19.2g, 0.108mol; 72%). H.r-m.s: $M^{+\cdot}$ calculated for $C_8H_{10}Cl_2$, 176.0159; found 176.0154; δ^1H ($CDCl_3$): 1.1-2.9(8H,m), 4.2(1H,d) and 6.1 (1H,d).

7.3.18 exo-3-Chloro-4-hydroxybicyclo[3,2,1]oct-2-ene[1]

A solution of exo-3,4-dichlorobicyclo[3,2,1]oct-2-ene (0.27g, 1.5mmol), $CaCO_3$(0.30g, 3mmol), acetone (0.75ml) and water (2.5ml) was heated under reflux for three days. The solution was extracted with ether (3 x 4ml) and the combined ether extract washed with water, dried over $NaSO_4$ and filtered. The ether was then removed on the rotary evaporator to leave a waxy solid. δ^1H ($CDCl_3$): 1.0-2.7 (8H,m), 3.5 (1H,d), 3.7 (1H,m) and 6.0 (1H,d).

7.3.19 Reaction of exo-3,4-Dichlorobicyclo-[3,2,1]oct-2-ene in HFIP, and Subsequent Hydrogenation/ Hydrogenolysis.

(i) A solution of exo-3,4-dichloro[3,2,1]oct-2-ene (0.76g, 4.32mmol) and 1,4-diazabicyclo[2,2,2]octane [DABCO(0.52g, 4.64mmol)] in hexafluoroisopropanol [HFIP(3ml)] was heated under reflux for 24 hours. The solution was extracted between water (50ml) and ether (20ml), the solvent removed using a Kugelrohr distillation apparatus and the residue chromatographed on alumina (60 x 12cm column) with pentane as eluent. The fractions were monitored by capillary g.c, appropriately

combined, and the pentane removed on the rotary evaporator to leave an oily liquid. A solution of this in pentane (2ml) was then washed with 1M HCl (2 x 1ml, 2mmol) and water (1ml) then percolated through a small anhydrous Na_2SO_4 column. Evaporation of the solvent under a stream of argon left white crystals. Low resolution mass spectrometry (l.r./m.s.), m/z: 207(100%), 77(64.8), 273(58.2), 105(47), 51(29.7), 141(27.5), 113(33.4), 112(25.7), 308(26.4). H.r/m.s., $C_{11}H_{11}ClF_6O$ requires $M^{+\cdot}$, 308.0402. Found: $M^{+\cdot}$, 308.0396. n.m.r. ($CDCl_3$); δ^1H 1.0-2.2(m), 2.4-2.9(m), 3.4-3.9 (two doublets), 4.1-4.7 (septet), 6.0-6.3 (two doublets)

(ii) Sodium hydroxide (2M, 1.5ml) and 5% rhodium on charcoal (50mg) were added to a solution of 3-chloro-4-hexafluoroisopropoxybicyclo[3,2,1]oct-2ene (50mg) in tetrahydrofuran (30ml, redistilled) and the mixture was hydrogenated at 45psi for 48 hours. The solution was carefully withdrawn by pipette and the solvent removed under reduced pressure on the rotary evaporator. A solution of the residue in ether (5ml) was washed with dilute HCl and $NaCO_3$aq., then percolated through a small column of anhydrous Na_2SO_4. Analysis by g.l.c showed the presence of two compounds believed to be the *endo*- and exo-bicyclo[3,2,1]octan-2-yl hexafluoroisopropyl ethers.

7.3.20 *endo*-Bicyclo[3,2,1]octan-2-ol.

Sodium metal (5g) was added in small pieces to a stirred solution of bicyclo[3,2,1]octan-2-one in ethanol

(100ml) at room temperature under a stream or argon. The mixture was left stirring for a further half hour then the excess sodium was separated. The ethanolic solution was extracted between ether and brine, the aqueous phase being exctracted a further twice with more ether (150ml in total). The ether extracts were combined, washed with water (50ml), dried over anhydrous Na_2SO_4, filtered and the ether was then removed on the rotary evaporator to leave a yellow oil.

The was oil chromatographed (75g of type H aluminium oxide) using ethyl acetate (redistilled):petroleum ether (b.p. 60-80°C) (70:30) as eluent. Fractions were monitored by g.c., appropriately combined, and evaporated under reduced pressure. The residue was sublimed to yield colourless crystals (1.80g) [$C_8H_{14}O$ requires $M^{+\cdot}$, 126.1044. Found: $M^{+\cdot}$, 126.1042]. Analysis by capillary g.l.c. showed that there was <3% contamination by the *exo*-isomer.

7.3.21 *endo*-Bicyclo[3.2.1]octan-2-yl Hexafluoroisopropyl Ether

Hexafluoroisopropanol (2ml, redistilled) was added to *endo*-bicyclo[3,2,1]octan-2-yl tosylate (180mg, 0.64mmol) and DABCO (0.090g, 0.8mmol) in a stoppered test-tube which was then immersed in a water bath at 50°C for three days. Most of the HFIP was removed on the rotary evaporator and the residue extracted between dilute hydrochloric acid (5ml) and ether (3 x 2ml). The

combined ether extracts were washed with aqueous $NaHCO_3$ solution and water, then dried over anhydrous Na_2SO_4 and filtered. The ether was removed on the rotary evaporator to yield the crude product [0.14g (80%)]. Analysis by capillary g.l.c (MBMA) showed a single major product contaminated with ca. 5% exo-bicyclo[3,2,1]octan-2-yl and bicyclo[2,2,2]octan-2-yl hexafluoroisopropyl ethers.

7.3.22 exo-Bicyclo[3,2,1]octan-2-yl Tosylate

This was prepared from exo-bicyclo[3,2,1]- octan-2-ol in the same manner as the adamantyl derivative, giving the crude product in 86% yield.
($CDCl_3$):δ^1H 0.8-2.5(15H,m)4.3-4.6(1H,m) and 7.1-7.9(4H,q).

7.3.23 exo-Bicyclo[3,2,1]octan-2-yl and Bicyclo-[2,2,2]octan-2-yl Hexafluoroisopropyl Ethers.

A mixture of these compounds was made from the exo-bicyclo[3,2,1]octan-2-yl tosylate in HFIP as described above for the *endo* isomer. The reaction mixture was worked up in the usual way to give an ether solution which was shown by capillary g.l.c analysis to contain three compounds. Two major peaks were due to the two desired bicyclo-octyl ethers and a minor peak was due to the *endo* isomer.

7.3.24 2-Adamantyl 2-Naphthalenesulphonate

This compound was prepared from 2-adamantanol (0.34g,2.23mmol) and 2-naphthalenesulphonyl chloride (1.00g, 4.4mmol) by the Tipson procedure. The crude

product was a viscous oil which crystallised from methanol at room temperature (0.60g; 79%).

Analysis by h.p.l.c. of the methanol from the recrystallisation showed two peaks. Analysis of the crystals showed one peak with any other peak <0.4% of the peak due to the product. 0.60g (79%);m.p. 94-95°C. $C_{20}H_{22}SO_3$ requires C,70.15. H,6.48. Found: C,70.13; H,6.46.

7.3.25 Tetrabutylammonium Thiocyanate

A solution of NaSCN. H_20(23.57g, 0.20mol) in water (30ml) was added to a stirred aqueous solution of tetrabutylammonium hydroxide (40%, 42ml, 0.065mol Bu_4NOH). A white precipitate formed immediately. The mixture was extracted with CH_2Cl_2(2 x 50ml) and the solvent was removed on the rotary evaporator without being dried. The residue was dried in a vacuum desiccator at *ca.* 0.1Torr [19.4g(100%); m.p. 109 - 114°C, lit. 125°C[6]].

A sample (5.6g) was recrystallised from ethyl acetate (redistilled) to yield colourless, needle-like crystals [3.6g(64%); m.p. 125-126°C].

7.3.28 Attempted Preparation of 2-Adamantyl Thiocyanate.

Tetrabutylammonium thiocyanate (0.398g, 1.32mmol), 2-adamantyl tosylate (45.6mg, 14.9mmol) and DABCO (20mg, 17.8mmol) were weighed into a boiling tube with a ground glass neck. Dimethylformamide (2ml), which had been redistilled and left sitting over potassium hydroxide,

was added; the boiling tube was tightly sealed and immersed in a water bath at 64°C for 5 days. The solution was checked by t.l.c. which showed that a substantial amount of 2-adamantyl tosylate remained, therefore the contents were transferred to a pear-shaped flask which was heated under reflux for 3 days. The dark brown solution was cooled then extracted between ether (2ml) and water (10ml). The water fraction was extracted again with ether (2ml), the ether layers were bulked and percolated through a small anhydrous Na_2SO_4 column. The solution was analysed by capillary g.l.c. and capillary g.l.c - m.s., and some evidence of the adamantyl thiocyanate was found.

7.4 Solvolysis Procedures

7.4.1 Solvolysis of 2-Adamantyl Azoxytosylate.

(A) In buffered Acetic Acid (0.15M sodium acetate).

(i) G.l.c analysis. Buffered acetic acid (0.15M, 2ml) was added to 2-adamantyl azoxytosylate (*ca.* 20mg accurately weighed) and the internal standard, trans-decalin (*ca.* 20mg accurately weighed) in a test-tube with a ground glass neck. The tightly stoppered test-tube was immersed in a water bath for approximately ten half-lives. The reaction mixture was then extracted between brine (4ml) and ether (2ml). The ether was percolated through a small anhydrous Na_2SO_4 column which was washed through with a little more dry

ether. Products from the solvolysis were then analysed by capillary g.l.c

(ii) H.p.l.c. analysis. The procedure for the solvolysis was the same as that for the g.l.c analysis without the addition of trans-decalin. After approximately ten half-lives the solvolysis mixture was accurately made up to 10ml with 80:20 MeOH,H_2O ready for direct h.p.l.c analysis. The 2-adamantyl tosylate concentration was calculated from a calibration graph of known concentrations versus peak area.

(B) In TFE:H_2O Mixtures (0.05M DABCO)

(i) G.l.c analysis. The solvolysis in the TFE:H_2O mixtures and the work-up procedures were carried out in the same manner as those for the solvolyses in acetic acid.

(ii) H.p.l.c. analysis. The solvent mixture (2.0ml) was added to the accurately weighed azoxytosylate and DABCO. The reaction vessel was immersed in a water bath as for the g.l.c. analysis. Aliquots (0.10 and 0.20ml made up to 1.0ml in 82:18, methanol:H_2O) were taken at appropriate intervals and the concentrations of 2-adamantyl tosylate calculated form a calibration graph as described above.

Due to the poor solubility of the substrate in 50TFE, 9.5ml of solvent were used with *ca.* 25mg of accurately weighed substrate. The aliquots for analysis, therefore, had to be larger (0.5ml made up to 1.5ml with MeOH).

(C) In Ethanol:H_2O Solvent Mixtures

The solvolysis and h.p.l.c analysis procedures were the same as those used in the acetolyses.

(D) In Solvents Containing Tetrabutylammonium Naphthalene-2-Sulphonate (TNas)

(i) Acetic acid. Tetrabutylammonium naphthalenesulphonate (12.21g, 0.027mol) and anhydrous sodium acetate (0.6150g, 0.075mol) were weighed out into a volumetric flask (100ml) and made up to the mark with dry acetic acid. The mixture was stirred overnight. A portion of this solution was also diluted with dry acetic acid to give final concentrations of TNas (0.135M) and NaOAc (0.033M). Solvolysis and work-up procedures were followed as described for the determination of 2-adamantyl tosylate.

(ii) Ethanol. Tetrabutylammonium naphthalenesulphonate (0.8440g, 1.88mmol) was dissolved in ethanol (10ml). A portion of this was also diluted in an equivalent volume of ethanol to give half the concentration of TNas (0.094M TNas). Solvolysis and work-up procedures were followed as described for the determination of 2-adamantyl tosylate.

(iii) 80% Ethanol. Ethanol (0.188M TNas, 1.6ml), and water (0.4ml) were added to the test-tube containing the azoxytosylate and DABCO. The solvolysis and work-up procedures were the same as described above.

(iv) TFE. The azoxytosylate (*ca.* 20mg accurately

weighed) was added to a solution of TWas (0.8281g) in TFE (10ml). A solution with no adamantyl azoxytosylate was analysed in tandem with the actual sample to ensure no spurious peaks resulted from the TWas. Apart from that, the solvolysis and work-up procedures were the same as those for the 2-adamantyl tosylate determination.

(E) Solvolysis in trifluorethanol containing tetrabutylammonium thiocyanate.

DABCO (12mg, 1.07mmol) and 2-adamantyl azoxytosylate (16.8mg, 0.048mmol) were weighed into a boiling tube with a ground glass neck and TFE (0.267M tetrabutylammonium thiocyanate, 1ml) was added. The tightly sealed tube was immersed in a water bath at 56°C for 2 hours 40 minutes (19 half-lives of the azoxytosylate) then extracted between ether (2ml) and brine (2g NaCl in 10ml water). The ether extract was then percolated through a small anhydrous Na_2SO_4 column and analysed by both capillary g.l.c. and capillary g.l.c. - m.s.

7.4.2 Solvolysis of 2-Adamantyl Tosylate.

(A) In TFE:H_2O Mixtures

The g.l.c. analysis was carried out in the same manner as that for the solvolysis of 2-adamantyl azoxytosylate.

(B) In Trifluoroethanol Containing Tetrabutylammonium Thiocyanate.

The solvolysis and work-up procedures for 2-adamantyl

tosylate were the same as those for 2-adamantyl azoxytosylate.

7.4.3 Solvolysis of Bicyclo[2.2.2.]octan-2-yl Azoxytosylate in 97HFIP.

The materials were kept close to 0°C in the work-up procedure, but otherwise the solvolysis procedure was the same as that for 2-adamantyl azoxytosylate.

7.5 Gas Liquid Chromatography

7.5.1 2-Adamantyl Azoxytosylate in Acetic Acid (0.15M Sodium Acetate)

Two columns were used for the analysis of the products; one for alcohols and acetates (SCOT DEGS), and one for hydrocarbons (SCOT MEMA). A hydrocarbon (*trans*-decalin) was used as an internal standard. The molar response factors (m.r.f.) were calculated based on carbon number:-

m.r.f = number of carbons in product/number of carbons in standard.

The retention times of the products and internal standard are recorded in Table 7.1.

Table 7.1 Retention times of the products and internal standard from the solvolysis of 2-adamantyl azoxytosylate in acetic acid (0.15M sodium acetate).

Compound	Column	Temperature (°C)	Retention Time (mins)
t-decalin	50 SCOT DEGS	100	2.25
2-AdOAc	"	"	3.58
Adamantanone	"	"	4.07
exo-P-AdOAc	"	"	4.31
2-AdOH	"	"	4.87
Protoadamantene	50 SCOT MBMA	"	4.98
t-decalin	"	"	3.60
DHadamantane	"	"	5.87

exo-P-AdOAc = exo-protoadamantyl;

DHadamantane = didehydroadamantane;

2-AdOAc = 2-adamantyl acetate;

2-AdOH = 2-adamantanol.

7.5.2 Solvolysis of 2-Adamantyl Azoxytosylate and 2-Adamantyl Tosylate in TFE:H_2O Mixtures.

Conditions were established which allowed yields of the adamantyl trifluorethyl ethers and adamantanols to be determined directly in a single analysis and are given in Table 7.2. The m.r.f. of 2-adamantyl trifluoroethyl ether versus 2-adamantanol was determined directly from authentic samples and this allowed relative yields to be calculated for these products.

Determination of the M.R.F. of 2-Adamantyl Trifluoroethyl Ether *versus* 2-Adamantanol.

Recrystallised 2-adamantyl tosylate (54.48mg, 0.178mmol), 2-adamantanol (51.16mg, 0.337mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) (35.0mg, 0.21mmol) were weighed into a test-tube, to which redistilled TFE (3ml) was added. The tightly sealed test-tube was immersed in a water bath at 50°C for 3 days. The work-up procedure was as described above for the solvolyses in TFE:H_2O solvent mixtures. This reaction was repeated on the same scale. Both samples were run six times to give a mean m.r.f. of 1.216 $\pm$ 0.023, which is in good agreement with the m.r.f calculated from carbon number (1.200).

The product ratio of 2-adamantanol:2-adamantyl trifluoroethyl ether was then determined from both 2-adamantyl tosylate and 2-adamantyl azoxytosylate in 50:50 (v/v), 80:20 (v/v) and 97:3 (w/w) trifluoroethanol:H_2O. Injections in the g.l.c. analyses were increased from 1ul to 5ul in an attempt to detect any rearrangement products. The signal to noise ratio was not as good as that achieved in the acetolyses, and were therefore not determined.

Table 7.2 Retention times of the products from the solvolysis of 2-adamantyl azoxytosylate and 2-adamantyl tosylate in TFE:H_2O mixtures.

Compound	Column	Temperature	Retention Time (mins)
2-AdOCH$_2$CF$_3$	50 SCOT DEGS	100°C	1.15
1-AdOCH$_2$CF$_3$			1.98
exo-P-AdOCH$_2$CF$_3$			2.25
1-AdOH			4.16
2-AdOH			5.55
Adamantanone			4.66
exo-P-AdOH			6.98

AdOCH2CF3 = adamantyl trifluoroethyl ether;

exo-P-AdOH = exo-protoadamantanol;

exo-P-AdOCH$_2$CH$_3$.

The analytical conditions for the determination of the hydrocarbons were the same as in the acetolyses.

7.5.3 Solvolysis of Bicyclo[2.2.2]octan-2-yl Azoxytosylate in 97HFIP.

The products were analysed on two columns; one for alcohols (SCOT DEGS), and one for hydrocarbons and hexafluoroisopropyl ethers. The m.r.f. of *endo*-bicyclo[3.2.1]octan-2-ol versus pentadecane was determined (0.532) using the following equation.
m.r.f. = ((no. moles internal standard x peak area of alcohol) / (no. moles of alcohol x peak area of internal standard)).

It was assumed that the isomeric alcohols would have the same m.r.f. The absolute yields for the alcohols were determined and it was assumed that the total yield of hydrocarbons and ethers would make up the remainder, i.e. assuming a 100% g.l.c. recovery. The yields for the individual ethers and hydrocarbons were determined using relative m.r.f.'s calculated from carbon number.

Table 7.3 Bicyclo[2.2.2]octan-2-yl Azoxytosylate in 97HFIP.

Compound	Column	Temperature	Retention Time (mins)
Pentadecane			3.33
[2.2.2]OH	50'SCOT DEGS	80°C	6.59
exo-[3.2.1]OH			5.86
endo-[3.2.1]OH			7.10
Hydrocarbon			4.36
[2.2.2.]HFIP	50'SCOT MBMA	80°C	8.77
exo-[3.2.1]HFIP			9.08
endo-[3.2.1]HFIP			10.41

[2.2.2]OH = bicyclo[2.2.2]octan-2-ol;
[3.2.1]OH = bicyclo[3.2.1]octan-2-ol;
Hydrocarbon = tricyclo[3.2.1.$0^{2,7}$]octane;
[2.2.2.]HFIP = bicyclo[2.2.2]octan-2-yl hexafluoroisopropyl ether
[3.2.1]HFIP = bicyclo[3.2.1]octan-2-yl hexafluoroisopropyl ether.

7.6 H.P.L.C. Analyses

7.6.1 Determination of 2-Adamantyl Tosylate

The analytical conditions for the determination of 2-adamantyl tosylate were as follows:-

Mobile phase;82:18, methanol:water

Flowrate; 1.5ml/min

Wavelength of U.V. detector; 254nm

Stationary phase; ODS HYP-2974

Injection volume: 20µl (loop)

The retention times of 2-adamantyl azoxytosylate and 2-adamantyl tosylate were 5.16 and 6.60 minutes respectively.

7.6.2 Determination of 2-Adamantyl Naphthalene-2-sulphonate

To optimise the conditions for the determination of 2-adamantyl naphthalene-2-sulphonate the mobile phase was set at 80:20, methanol:water. The conditions were such that the values for 2-adamantyl tosylate, although in good agreement with those obtained above, were not as reproducible and therefore disregarded. Apart from these points the analytical conditions were the same as those listed above for 2-adamantyl tosylate. The retention times are listed in Table 7.4.

Table 7.4 Hplc retention times with the mobile phase at 80:20, MeOH:H_2O.

Compound	Retention Time (mins)
2-Adamantyl Azoxytosylate	8.42
2-Adamantyl Tosylate	10.17
2-Adamantyl Naphthalene-2-sulphonate	12.12

7.7 Kinetics

The reactions were monitored spectrophotometrically using a Pye Unicam SP8-300 double beam uv spectrophotometer with a cell-changer and an Apple II microcomputer fitted with a Mountain Hardware clock. The first order rate constants were evaluated by a computer program using a non-linear minimisation routine written by Dr J T Thompson, of this department. Rate constants were determined over a range of temperatures and used to calculate the activation parameters from an Eyring type lot, incorporated in a computer Program, also written by Dr J T Thompson.

After the substrates (*ca.* 2mg) had been added to the solvent in the silica cells, vigorous shaking of the cells was required to ensure that the substrates were completely dissolved. Two 1cm silica cells fitted with PTFE stoppers were used in each run. The reactions were monitored for a minimum of three half-lives and approximately 40 points recorded for each reaction.

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