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REVIEW COMMENTARY

NUCLEOPHILIC SUBSTITUTION AT SATURATED CARBON ATOMS. MECHANISMS AND MECHANISTIC BORDERLINES: EVIDENCE FROM STUDIES WITH NEUTRAL LEAVING GROUPS

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ABSTRACT

Substrates with neutral leaving groups undergo unimolecular solvolysis in nonpolar solvents. Whereas *t*-alkyl substrates invariably solvolyze by a unimolecular mechanism, *s*-alkyl and primary alkyl substrates can undergo both uni and bimolecular reactions, and the bimolecular step can take place on either the substrate itself or on an intimate ion–molecule pair formed in either a pre-equilibrium or in a rate determining step. Study of reactions at borderlines indicates that the individual reaction types remain distinct and do not merge.

INTRODUCTION

The recognition by Ingold[1] of distinct S_N1 and S_N2 reaction mechanisms for nucleophilic substitution at saturated carbon atoms was a milestone in the development of organic chemistry. Although the reality of these distinct reaction types is now universally recognized, the fundamental question of whether S_N1 and S_N2 reactions remain distinct at the borderline or gradually merge is still very controversial. As emphasized by March in the most recent edition of his text book[2a] this uncertainty complicates the teaching of this important subject and serves to confuse beginners and advanced students alike.

We believe that we have provided clear and unambiguous evidence to resolve this controversy and uncertainty; i.e. that we have proved that S_N1 and S_N2 type reactions can indeed remain distinct and that at a mechanistic borderline reaction can occur by both reaction types proceeding independently and simultaneously. Because of the importance of these conclusions we believe that it is appropriate to bring our results to the notice of the wider audience of organic chemists; no literature rebuttal of our views has appeared although we have sometimes been subjected to vigorous attacks by referees.

In 1978, one of use commenced a study of the mechanistic aspects of nucleophilic substitiution at saturated carbon atoms where a neutral heterocyclic species was the leaving group.[3] This study was originally motivated by the need for understanding a reaction of

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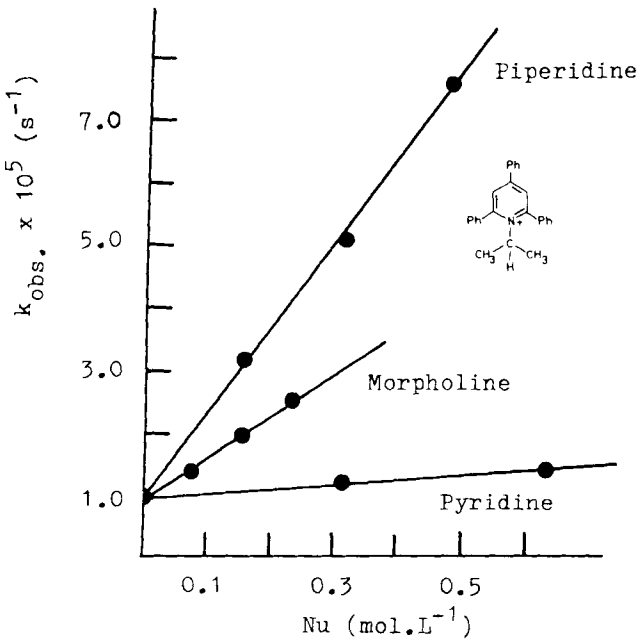


Figure 1. Nucleophilic substitution by simultaneous S_N1 and S_N2 reactions: k_{obs} for 1-isopropyl-2,4,6-triphenylpyridinium cation (**14a**) (1·6 mM) plotted vs. nucleophilic concentration (chlorobenzene solution, 100 °C). (Reproduced from Reference 5 with permission)

considerable synthetic potential,[4] but it soon became evident that it could lead to a deeper understanding of the mechanisms of nucleophilic substitution in general.

The first key observation[5] was that plots of substrate rates vs. nucleophile concentration under pseudo first order conditions, while nearly always straight lines, often showed a positive intercept on the *y*-axis. This behaviour was found for secondary alkyl groups, and the intercept (but not the slope) for each compound was invariant with nucleophile as seen, for example in Figure 1, for the 1-isopropyl-2,4,6-triphenylpyridinium cation. By contrast, primary alkyl groups generally did not show such intercepts: in Figure 2 this is illustrated for a series of benzo[h]quinolinium cations.

The simplest inference from the above results was that unimolecular and bimolecular reactions were proceeding simultaneously and independently for the secondary alkyl substrates; to settle this, we commenced a series of detailed investigations. These confirmed the above inference, and disclosed a rich variety of mechanistic behavior.

We summarized the results of our mechanistic observations up to 1983 in a review[6] entitled 'New insights into aliphatic nucleophilic substitution reactions from the use of pyridines as leaving groups'. By 1983, it was already clear that nucleophilic displacements via direct displacements, via free carbonium, via intimate ion–molecule pairs and via electron transfer had all been demonstrated (Scheme 1). During the past four years we have extended our work to cover nucleophilic displacements at tertiary[7] as well as at primary[8] and at secondary[9–12] saturated carbon atoms, and have consolidated our position particularly by a detailed examination of the behavior at mechanistic borderlines. These further investigations have left unchanged, and indeed have greatly strengthened, the conclusions of the earlier work.

The present review attempts to provide a contemporary summary of the overall position, emphasizing the results obtained in the more recent work, and drawing specific conclusions

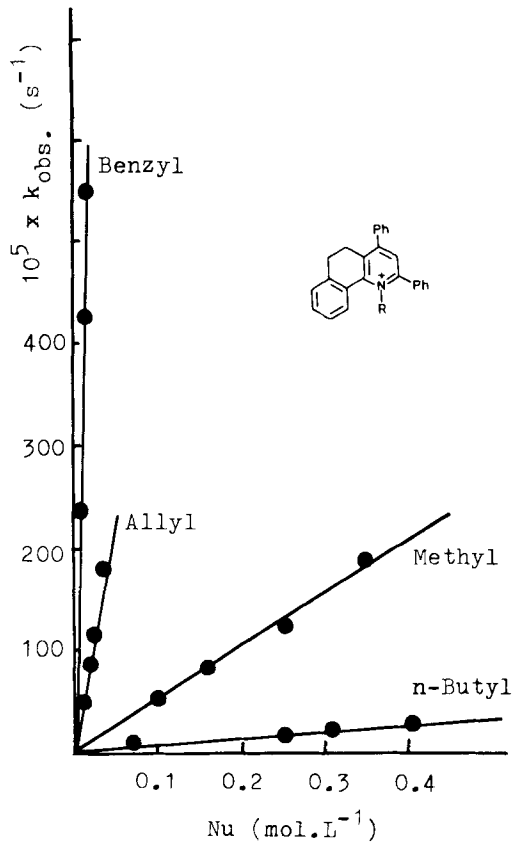


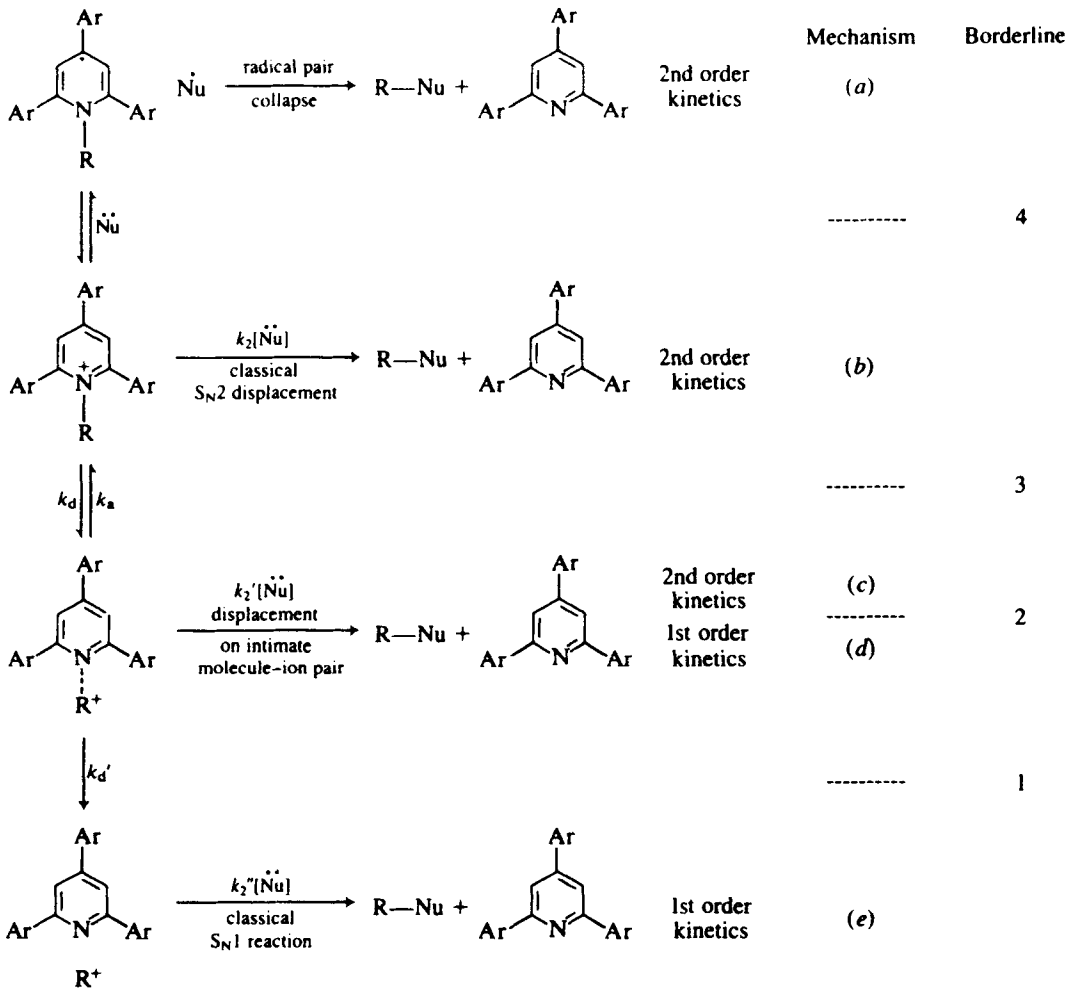
Figure 2. Rate variation with N-substituent: k_{obs} for reactions of N-substituted-2,4-diphenyl-5,6-dihydrobenzo[h]quinolinium cations (64 μmol.l $^{-1}$) with piperidine in chlorobenzene at 100°C. (Reproduced from Reference 6 with permission)

regarding the independence vs. gradual merging of mechanisms and, in particular, the behavior at borderlines. It must be emphasized that the present results are for positively charged substrates and neutral leaving groups, and any extension of the conclusions to the more common class of neutral substrates with negatively charged leaving groups is by inference only. However, we believe that such inferences are often rather compelling.

SOLVOLYSIS* REACTIONS IN NON-POLAR SOLVENTS

As has been pointed out previously, the use of positively charged substrates and neutral leaving groups has several advantages for the study of nucleophilic substitution mechanisms.[6] Unimolecular reactions of a neutral substrate involve charge creation in the transition state, such reactions therefore require media of high dielectric constant to proceed at measurable rates. Unfortunately, the roles of such a medium as solvent and as nucleophile are not easily

*We define the term 'solvolysis' as 'a reaction which is induced by the dissolution of a substrate in a solvent'. Note that in solvolysis a solvent molecule need not be involved in the rate determining step (cf 'thermolysis' a reaction induced by heat, and 'photolysis' induced by light).



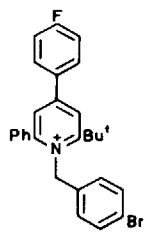
Scheme 1. Nucleophilic substitutions with pyridine-leaving group. (Reproduced from Reference 6 with permission)

disentangled. Advantageously, substrates with neutral leaving groups can undergo unimolecular reactions in media of low dielectric constant. Furthermore, the reaction scheme is less complex in that the distinction in the Winstein scheme between a solvent-separated ion pair and a free carbocation (caused by strong electrostatic attraction) disappears: for positively charged substrates we simply have intimate ion–molecule pairs as the only distinct intermediate between the original substrate and a free carbocation.

It has sometimes been suggested[13] that solvolysis reactions in non-polar solvents such as chlorobenzene are induced by small quantities of water dissolved in the solvent: this possibility has now been rigorously excluded by demonstrating that the addition of measured amounts of water well in excess of those originally in the solvent causes no significant change in the reaction rates.[12] We have also reconfirmed the linearity of the bimolecular component of the reaction rate with nucleophile concentration, and the independence of the intercept with the nature as well as the concentration of the nucleophile (as illustrated in Figure 1). [At the

concentrations of nucleophiles (always below 4% v/v) used in this work, the polarity of the solvent is affected by the bulk effect of nucleophile only very slightly (e.g., the dieletric constant of chlorobenzene will be increased from 5·61 to 5·62 by 4% of piperidine if the effect is additive). Thus, the influence on rate constants, especially for positively charged systems is negligible.] Further, it has been shown that the rate constants are not significantly affected by the use of different gegenions, such as perchlorate, tetrafluoroborate or triflate.[12]

The question of the products of solvolysis reactions which proceed in a non-nucleophilic solvent in the absence of nucleophile has also been elucidated.[14] Mono-, tri-, and pentacyclic N-benzylpyridinium tetrafluoroborates undergo solvolysis in the absence of nucleophiles in chlorobenzene as solvent to give products of benzylation both of the solvent and of the pyridine leaving group. Thermolysis alone, and thermally induced solvolysis in nitrobenzene, yielded mainly products of benzylation of the solvent or of the leaving group. Thus, monocyclic N-benzyl cation (**1**) in chlorobenzene as solvent in the absence of other nucleophiles gives two products [(**2a**) and (**2b**)] of benzylation of the solvent and three *p*-bromobenzylated pyridines [(**3**), (**4**), and another isomer in which the position of the *p*-bromobenzyl group was not established]. The pyridinium salt (**1**) on solvolysis in nitrobenzene behaves similarly; *C*-(*p*-bromobenzylation) of nitrobenzene was observed (any products of O-benzylation would be unstable under the g.l.c. conditions) and the *p*-bromobenzylpyridines (**3**) and (**4**) were found, together with three more *p*-bromobenzylated isomers and some bis-(*p*-bromobenzyl)pyridine (**5**). Thermolysis of the pyridinium salt (**1**) neat gave compounds (**3**) and (**4**), two *p*-bromobenzylated isomers, and a trace of bis-(*p*-bromobenzyl)pyridine (**5**).



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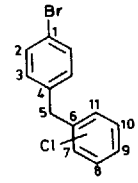
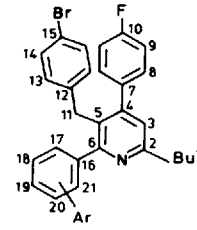


2 a: meta
b: para



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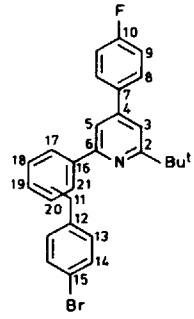

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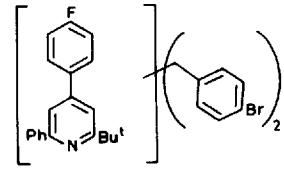

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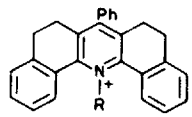
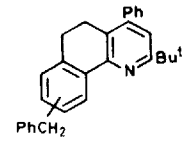
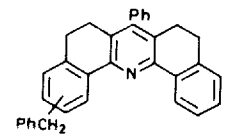
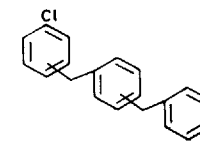




6 **a**: R = methyl
b: R = ethyl
c: R = n-propyl
d: R = n-pentyl
e: R = n-octyl
f: R = n-dodecyl
g: R = isobutyl
h: R = neopentyl
i: R = 2-phenylethyl
j: R = 2-methoxyethyl
k: R = benzyl

7 **8**





9 **10**

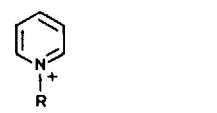
The pentacyclic N-benzyl cation (**6k**) behaves similarly to the cation (**7**) in chlorobenzene as solvent in that it gives (**8**) and a benzylated base (**9**). However, five isomeric products (**10a–e**) of the reaction of two benzyl cations with one solvent molecule was also found. Those probably arise from the reaction of ion conglomerates: it has been shown that at concentrations > 5 mmol.kg^{-1}, N-benzyl pyridinium cation (**6k**) forms associated species even at elevated temperatures.[15] Such conglomerates can be both nonionic (quadrupoles or higher dipole–dipole aggregates) and ionic (e.g. triple ions). Thus, formation of isomeric products (**10a–e**) is not surprising. However, the aggregation is negligible at concentrations < 2 mmol.kg^{-1}, in the range used for kinetic measurements.[15]

These results support the experimental basis of the previous interpretation[6] of the kinetic behavior of N-subsitituent displacement, in particular the occurrence of distinct unimolecular and bimolecular reaction modes. We now provide a summary of some of our more recent results which have dealt with the solvolyses and nucleophilic substitutions of the three fundamental substrate types (primary, secondary, and tertiary alkyl), and the behavior at borderlines (note: a detailed review of our experimental data up to 1984 is available[16]).

NUCLEOPHILIC SUBSTITUTIONS CLASSIFIED BY SUBSTRATE TYPE

Nucleophilic Substitution of *t*-Alkyl Substrates

Nucleophilic displacements at *t*-alkyl centers have generally been assumed to occur exclusively by a unimolecular S_N1 type mechanism with[1] or without[17] the intermediacy of ion-pairs: for a recent review see March.[2b] The work of Taft and Kamlet[18] also indicates that the participation of electrophilic assistance in the solvolysis of *t*-butyl halides is important and that nucleophilic participation plays a negligible role in such solvolyses. In contrast, Bentley and his co-workers have recently advocated nucleophilic solvent assistance in the solvolysis reactions of *t*-alkyl substrates.[19] However, our work on *t*-alkyl substrates[7] does not support this last claim.



$t\text{-BuSMe}_2^+$

12

11 a: R = 1-adamantyl
b: R = t-butyl
c: R = 1-(1-methyl-1-phenylethyl)

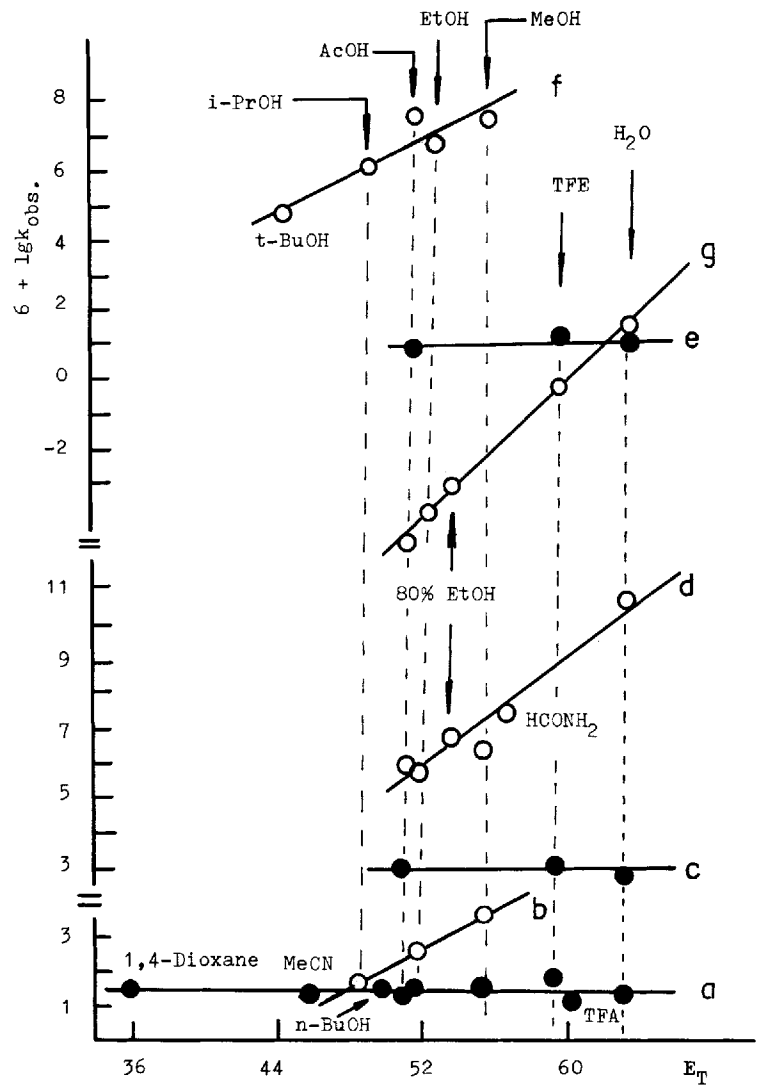


Figure 3. Plots against E_T of logarithms of observed rate constants for the solvolysis in various solvents of *a* 1-(1-methyl-1-phenylethyl)pyridinium perchlorate (**11c**) at 80 °C, *b* cumyl chloride at 25 °C, *c* 1-*t*-butylpyridinium perchlorate (**11b**) at 180 °C, *d* *t*-butyl chloride at 180 °C, *e* 1-(1-adamantyl)pyridinium perchlorate (**11a**) at 190 °C, *f* 1-adamantyl tosylate at 190 °C and *g* 1-adamantyl chloride at 50 °C. (Reproduced from Reference 4 with permission)

Solvolysis rates for 1-(1-adamantyl)- (**11a**), 1-*t*-butyl- (**11b**), and 1-(1-methyl-1-phenylethyl)pyridinium cations (**11c**) depend neither on solvent polarity, nor electrophilicity, nor solvent nucleophilicity. In Figure 3, the solvent polarity parameter of Dimroth, E_T,[20] is used as a comprehensive measure of the overall solvation ability of the solvent. It has been shown, that the E_T scale corresponds to a linear combination of solvent dipolarity, Π^*, and hydrogen bond donor acidity, α (α in turn corresponds to solvent electrophilicity).[18] Thus, E_T is a combined measure of general solvent power and specific electrophilic solvation of the leaving group. The solvolysis rates of **11a–c** show less variation with the substrate structure than do those of the corresponding compounds with anionic leaving groups. Furthermore, these rates are not affected by pH change, nor by the presence of NEt_3, piperidine, nor NaN_3. In addition, no evidence is shown for nucleophilic assistance by the solvent for the solvolysis of the *t*-butyldimethylsulfonium cation (**12**), when a plot of rate vs. E_T is compared with similar plots for pyridinium cations (Figure 4): such assistance has been postulated by Kevill, Kamil and Anderson.[21]

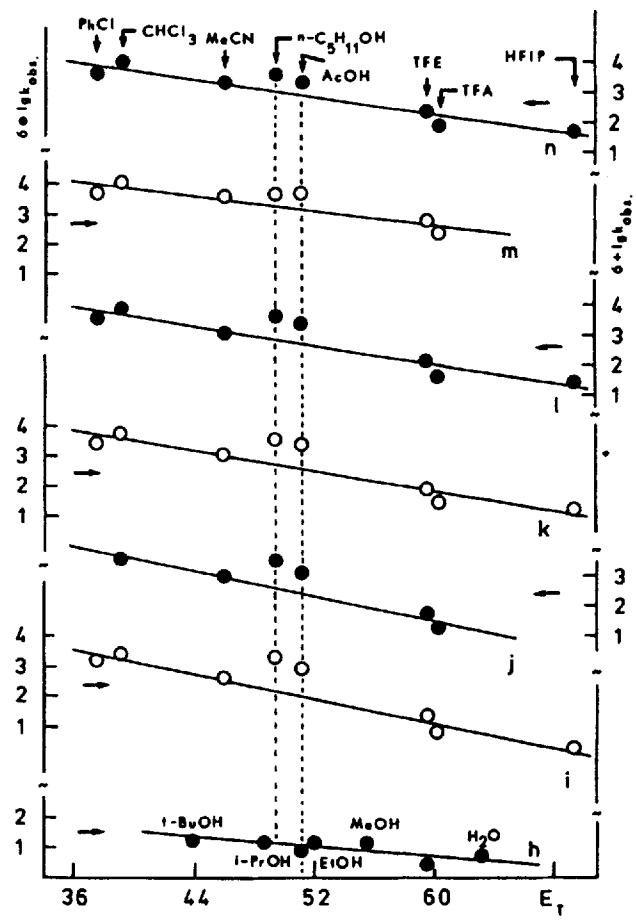
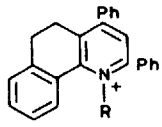


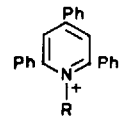
Figure 4. Plots of logarithms of observed rate constants for the solvolysis in various solvents of *h* *t*-BuS^+Me_2 (**12**) ($CF_3SO_3^-$ as gegenion in *t*-butanol, isopropanol, acetic acid, 2,2,2-trifluoroethanol and water at 50 °C and Cl^- as gegenion in methanol and ethanol at 50·4 °C) and *i–n* of, respectively: *i* 1-isopropyl-(**13c**), *j* 1-*s*-butyl-(**13d**), *k* 1-(2-pentyl)-(**13a**), *l* 1-(2-heptyl)-(**13e**), *m* 1-(3-methyl-2-butyl-(**13f**), *n* 1-(3-pentyl)-5,6-dihydro-2,4-diphenylbenzo[h] quinolinum tetrafluoroborates (**13b**) at 100 °C. (Reproduced from Reference 4 with permission)

Conclusion. *t*-Alkylpyridinium cations solvolyze by an S_N1 type mechanism. It is tempting to extend this conclusion to other *t*-alkyl substrates.

Nucleophilic Substitution of Secondary Alkyl Substrates

The mechanism of the solvolysis of secondary alkyl substrates has long been controversial, particularly as regards the role of the solvent in the process. Our detailed study[9,10] of the solvolyses of a series of 1-(s-alkyl)pyridinium cations (**13a–e**) in different solvents demonstrates clearly the operation of the Winstein–Ingold mechanism (Scheme 2) and the satisfactory interpretation of our results requires no 'intermediate' type mechanisms.





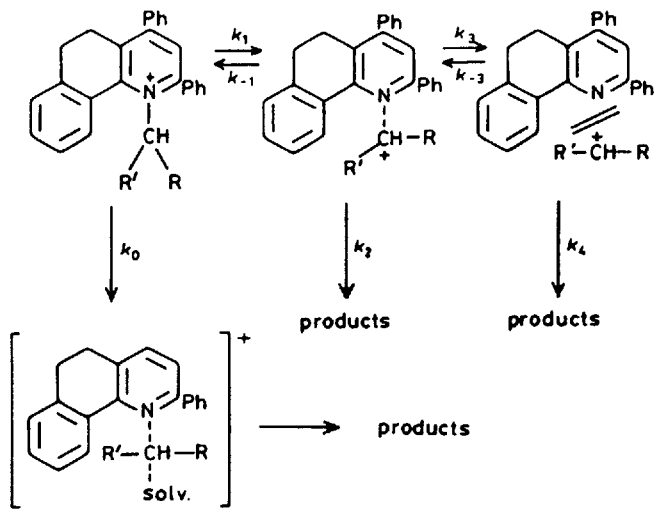
13 a: R = 2-pentyl
b: R = 3-pentyl
c: R = isopropyl
d: R = s-butyl
e: R = 2-heptyl
f: R = 3-methyl-2-butyl

14 a: R = isopropyl
b: R = p-methoxybenzyl

In particular, our studies[9,10] of the solvolysis of N-(*sec*-alkyl)pyridinium cations in non-nucleophilic solvents (chlorobenzene, acetonitrile, chloroform) with added nucleophile (piperidine) showed no rate dependence on nucleophile concentration and gave products with no rearrangement of the carbon skeleton. Solvolysis in weakly nucleophilic solvents (1,1,1,3,3,3-hexafluoropropan-2-ol, trifluoroacetic acid, 2,2,2-trifluoroethanol) gave partially rearranged products in the absence of added nucleophile; however in the presence of added nucleophile (morpholine) the products of solvolysis in 1,1,1,3,3,3-hexafluoropropan-2-ol are not rearranged although the rates are unaffected by the nucleophile concentration. Solvolysis in nucleophilic solvents (pentanol, acetic acid) gave unrearranged products.

Although originally thought to describe steric effects,[22] it is now generally accepted that σ^* values are a measure of the electron-donor ability of alkyl groups.[23] Hence, the sum of ($\sigma^*_{R'} + \sigma^*_{R''}$) for secondary alkyl groups R′R″CH is a measure of the sum of the stabilization afforded by R′ and R″, and hence of that of R′R″CH itself, to the reaction center. Rate plots vs. σ^* or $\Sigma\sigma^*$ for series of similar substrates are frequently linear, and the slopes (ρ^* values) provide mechanistic criteria. As σ^* becomes more negative, the ability of the alkyl group to stabilize a positive charge increases. Hence a large negative ρ^* value indicates that reaction proceeds via a transition state in which positive charge stabilization of an incipient carbonium ion is important.

The rates for the solvolysis of cations (**13a–f**) in the three non-nucleophilic, the three weakly nucleophilic and the two strongly nucleophilic solvents mentioned above in every case plotted as straight lines against $\Sigma\sigma^*$. The ρ^* values thus derived correlate well with the parameter of Dimroth, E_T,[20] for (a) the non-nucleophilic solvents and (b) the weakly nucleophilic solvents



Scheme 2. Nucleophilic displacements and solvolytic pathways for secondary systems. (Reproduced from Reference 10 with permission)

whether in the absence or presence of external nucleophile (Figure 5), displaying a steady decrease in ρ^* as E_T increases.

This is in accord with the Hughes and Ingold theory[1b] of solvent effects on rates of nucleophilic substitutions: the reaction rate for a positively charged substrate with a neutral nucleophile should decrease with increasing solvent polarity for both the unimolecular and bimolecular mechanisms. In the solvolyses of pyridinium cations, charge is more localized in

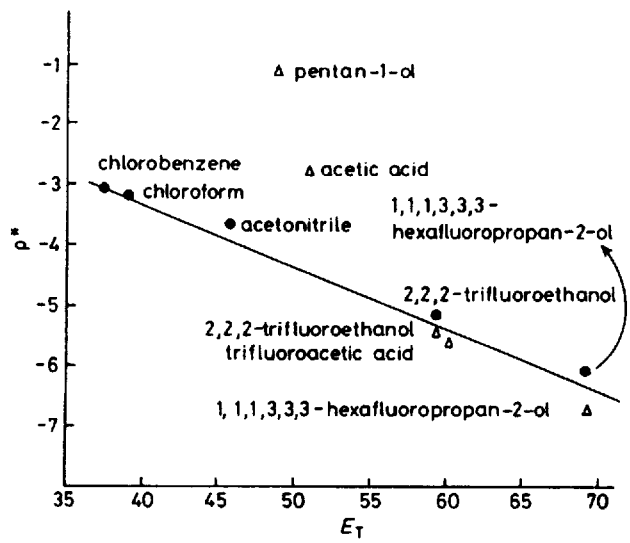


Figure 5. Plot of ρ^* vs. E_T for solvolyses of 1-(secondary alkyl)-5,6-dihydro-2,4-diphenylbenzo[h]quinolinum cations (**13a–f**) in the presence (○) and in the absence of external nucleophile (△). (Reproduced from Reference 7 with permission)

the starting material than in the transition state, and the more localized charge is stabilized by more polar solvents. In the polar, but weakly nucleophilic solvents, the absolute rates are therefore slower, but the dependence of rate on stabilization of R^+ is greater and ρ^* is more negative.

As the reactions in the non-nucleophilic solvents are clearly of unimolecular S_N1 type, we deduce that the rate-determining stage for the solvolyses in the weakly nucleophilic solvents is also S_N1, whether or not there is added nucleophile (the significance of rearrangement in the absence, and non-rearrangement in the presence, of nucleophile, is discussed later). However, in the nucleophilic solvents (pentanol, or acetic acid) the ρ^* values are far less negative than expected on the basis of solvent polarity (Figure 5). This indicates that in addition to the S_N1 mechanism, a competitive S_N2 mechanism occurs in the nucleophilic solvents, where the acetic acid or pentanol moleculaes are acting not simply as solvent but also as nucleophiles.

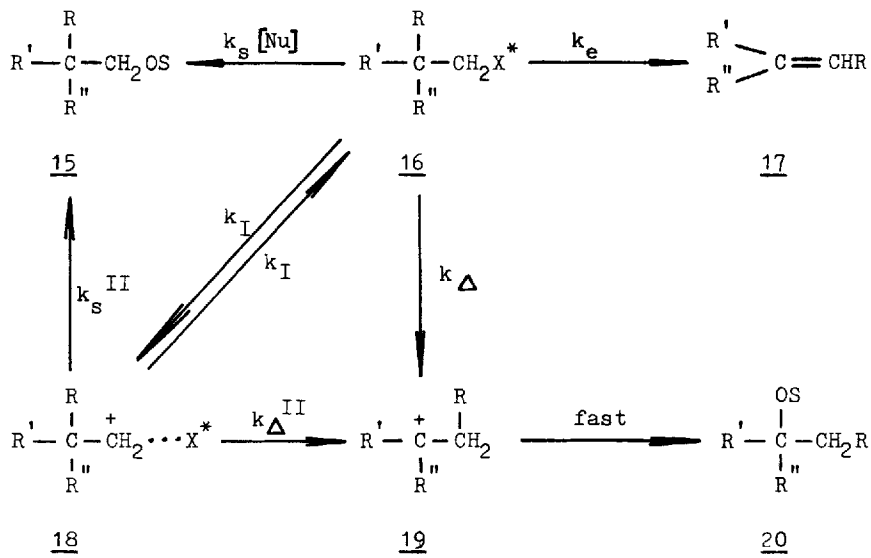
In nucleophilic solvents such as pentanol or acetic acid, $k_0 > k_1$, (Scheme 2). For all solvolyses in the presence of an external nucleophile the S_N1 mechanism applies: $k_2[Nu] > k_3 > k_1 \gg k_0$ in Scheme 2. The separation of the initially formed ion-molecule pair, while it is not the rate determining step, becomes important for product determination in weakly non-nucleophilic solvents such as trifluoroacetic acid and 1,1,1,3,3,3-hexafluoropropan-2-ol ($k_3 > k_2 > k_1 > k_0$ in the Scheme 2).

Conclusion. The solvolyses of N-(secondary)alkyl pyridinium cations occur by unimolecular S_N1 mechanisms in non-nucleophilic and in weakly nucleophilic solvents and the S_N1 mechanism can continue to dominate even in the presence of sufficiently small concentrations of good nucleophiles. However, in nucleophilic solvents the solvent acts not only as a solvent but also as a nucleophile and a bimolecular S_N2 mechanism competes effectively with the S_N1 reaction. For other secondary substrates, in the absence of good evidence to the contrary, a similar pattern must be seriously considered.

Nucleophilic Substitution of Primary Alkyl Substrates

Available Mechanisms

Potential mechanistic pathways for the solvolytic nucleophilic substitution of primary alkyl substrates are shown in Scheme 3. The interpretation of the considerable body of available experimental evidence has been controversial. Winstein and Marshal[24] postulates a normally dominant direct S_N2 displacement (**16** → **15**, Scheme 3) with solvent as nucleophile to yield unrearranged product, together with an occasionally observed competitive rate-determining first-order anchimerically assisted heterolysis (**16** → **19**, Scheme 3) which was followed by fast formation of rearranged product (**19** → **20**, Scheme 3). However, other workers have denied the existence of anchimeric assistance by H or Me transfer and have interpreted the results in terms of path **16** → **15**, path **16** → **18** → **19** → **20**, and path **16** → **18** → **15** → of Scheme 3.[25–27] In 1966, Nordlander, Schleyer *et al.*[26] summarized previous evidence for and against participation in the rate determining stage; they concluded that none was definitive, but provided new evidence from the 1-adamantylcarbinyl system which they (and we) consider strongly favours nonparticipation. However, the subject remains controversial; thus, in his review,[17] Harris tentatively decides in favor of the $k_s + k_\Delta$ theory, and Ando *et al.*[28] and Shiner[29,30] have presented secondary kinetic isotope effect evidence in favor of participation in neopentyl solvolyses.



Scheme 3. Nucleophilic displacements and solvolytic pathways for primary systems. (X is positively charged or neutral group in **16** and negatively chared or neutral group in **18**. (Reproduced from Reference 8 with permission)

We have studied this area by considering both the behavior of β-branched primary alkyl derivatives, and of longer chain primary alkyl pyridiniums.

Products and Rates of Solvolysis of β-Branched N-(Primary-alkyl)pyridiniums

Our work[8] on the solvolysis rates of N-(primary-alkyl)-5,6,8,9-tetrahydro-7-phenyldibenzo[c,h]acridiniums (**6a–e**, **6g–j**) in methanol, ethanol, *n*-pentanol, acetic acid, and trifluoroacetic acid allows resolution of the controversy, at least for the positively charged substrates studied.

The *n*-propyl-, *n*-pentyl-, and *n*-octyl-acridiniums (**6c–e**) solvolyze in deuterated methanol (CH_3OD) and deuterated acetic acid (CH_3CO_2D) to give mixtures of normal (**16** → **15**) and rearranged (**16** → **20**) methyl ethers and acetate esters,, respectively. None of these solvolysis products contain deuterium and hence none of them are formed via olefin intermediates (**17** in Scheme 3). The rearranged product (**20**, Scheme 3) therefore arises by an S_N1 type mechanism, which could be either path **16** → **18** → **19** → **20**, or path **16** → **19** → **20** (Scheme 3). However, the absolute rate discloses no evidence for rate-enhancing anchimeric assistance even when β-phenyl or β-methoxy groups are present and this evidence favors route **16** → **18** → **19** → **20** (Scheme 3).

Methanolysis of the isobutylacridinium (**6g**) occurs via olefin (**17**), but the acetolysis also involves an important nonolefinic pathway yielding both isobutyl and sec-butyl acetate. Methanolysis products from the neopentyl derivative (**6h**) are heavily deuterated, but acetolysis of **6h** yields undeuterated neopentyl acetate (cf. **16**) as well as deuterated *tert*-pentyl acetate (cf. **20**).

Individual product yields were calculated using GC/MS, and these were used to derive individual rates; literature data were used to obtain individual rates for the corresponding tosylate solvolyses (Table 1 and 2). The unrearranged products (Table 1) could arise by either

(or both) of path **16** → **15** and path **16** → **18** → **15** of Scheme 3. For the tosylates, the rate falls dramatically for the isobutyl and neopentyl compounds (as compared to methyl and ethyl) in both EtOH and AcOH (rate range ca. 10^5), and the same trend is found for the N-alkylacridiniums in MeOH. All this is consistent with the S_N2 path **16** → **15** of Scheme 3. However, for the N-alkylacridiniums in AcOH, the rates for all the alkyl groups are constant within a factor of ~ 4; this cannot be reconciled with path **16** → **15**, but is just what is expected for the ionization path **16** → **18** → **15**.

For the rearranged products, the rates in Table 2 represent products formed by path **16** → **19** → **20** and/or path **16** → **18** → **19** → **20** of Scheme 3 (products deduced to have been formed by way of elimination reaction in the initial step have been omitted from consideration). For the solvolyses of the 1-alkylacridiniums in AcOH, we have already implicated the ion–molecule pair (**18**) as an intermediate in the formation of the unrearranged products by path **16** → **18** → **15**. If path **16** → **18** → **19** → **20**, with the common intermediate (**18**), operates for the formation of the rearranged products, the ratio of migration to direct substitution is expected to remain near constant (with perhaps a statistical factor) over the series for H migration and over the series for Me migration. Table 3 shows that this is approximately so for the 1-alkylacridinium salts in acetic acid. This evidence strongly supports the intimate ion pair (or ion–molecule pair) intermediate **18**.

By contrast, where the direct substitution occurs by path **16** → **15**, i.e. as deduced for the 1-alkylacridiniums in MeOH and for the tosylates in EtOH and AcOH, such constancy of ratios are neither expected nor observed (Table 3).

The above reasoning is a firm basis to assign path **16** → **18** → **19** → **20** to the formation of the rearranged products for the 1-alkylacridiniums in AcOH. We believe that path **16** → **15** probably also applies for these compounds in MeOH in view of the absence of anchimeric assistance found for the β-methoxyethyl (**6j**) and especially the β-phenylethyl (**6i**) compounds. Presumably, the reason for this is the crowded transition state that would be involved in the formation of bridged intermediates when the leaving group is the acridine.

It is more difficult to draw conclusions regarding the mechanisms of formation of rearranged products in the tosylate solvolyses; however, the similarity between the rate of H or Me migration in a tosylate in CF_3CO_2H (at 75 °C) with that for the corresponding alkylpyridinium in AcOH (at 150 °C) (Table 2) is striking, and certainly suggests that a similar mechanism by path **16** → **18** → **19** → **20** operates.

Table 1. Individual rates ($10^5 k_{obs}/s^{-1}$) for formation of unrearranged substituted products from solvolyses of primary alkyl acridinium cations (**6**) and primary alkyl tosylates.[a]

Reaction	temperature (°C)	Me	Et	*n*-Pr	*n*-Pent	*n*-Oct	i-Bu	neo-Pent
Rpy^+ + MeCH	150	1·9	11·0	8·6	8·6	4·3	<0·1	<0·03
Rpy^+ + AcOH	150	1·3	2·9	1·8	2·3	1·6	0·76	0·86
ROTs + EtOH	75	6·9	2·9	1·94			0·12	0·0001
ROTs + AcOH	75	0·085	0·077	0·061			0·0049	<0·0002
ROTs + CF_3CO_2H	75	0·0018	0·023	0·022			<11	<0·2

[a]Data for tosylates taken from references 17 and 37; other data from reference 8.

Table 2. Individual rates ($10^5 k_{obs}/s^{-1}$) for solvolyses of primary alkyl acridinium cations (**6**) and primary alkyl tosylates[a] for products formed by proton- or methyl-migration step.

Reaction	temperature (°C)	H migration			Me migration		
		n-Pr	*n*-Pent	*n*-Oct	i-Bu	i-Bu	neo-Pent
Rpy^+ + MeOH	150	0·02	0·09	0·52	≪5	<0·1	1·6
Rpy^+ + AcOH	150	0·24	0·28	0·44	<2	0·73	4·8
ROTs + EtOH	75	<0·04			0·006	<0·003	0·0016
ROTs + AcOH	75	0·0001			0·018	<0·0005	0·0083
ROTs + CF_3CO_2H	75	0·15			4·4	1·1	11

[a]Data for tosylates taken from references 17 and 37; other data from reference 8.

Table 3. Ratio of migration to direct substitution for solvolyses of primary alkyl acridinium cations (**6**) and primary alkyl tosylates.[a]

Reaction	H migration			Me migration		
	n-Pr	*n*-Pent	*n*-Oct	i-Bu	i-Bu	neo-Pent
Rpy^+ + MeOH	0·002	0·01	0·1			>50
Rpy^+ + AcOH	0·1	0·1	0·3	<3	1	5
ROTs + EtOH	<0·02			0·05	<0·02	16
ROTs + AcOH	0·001			4	<0·1	42
ROTs + CF_3CO_2H	7			>0·4	>0·1	>55

[a]Data for tosylates taken from references 17 and 37; other data from reference 8.

We have demonstrated a change-over in mechanism for the alkylpyridiniums between MeOH and AcOH as solvents. The solvent MeOH species appears to be a better nucleophile for conventional S_N2 path reaction than AcOH, but the inverse may be the case for reactions via the ion–molecule pairs (**18**). In addition, the greater polarizability of AcOH should help in the formation of the ion–molecule pairs, in which part of the charge has been concentrated from the delocalized pyridinium system onto the saturated carbocation.

The relative rates of formation of products by direct substitution and of products derived by hydrogen or methyl migration from 1-alkylacridiniums (Table 3) offer no evidence for path **16** → **19** → **20** of Scheme 3, i.e. of rate-enhancing participation in the rate determining step.

Thermolysis and Solvolysis of Straight Chain N-(Primary-alkyl)pyridiniums

Thermolyses (**6e**) of N-*n*-octyl- and N-*n*-dodecyl-acridinium trifluoromethanesulfonates (**6f**)[31] give terminal olefins accompanied by appropriate amounts of *cis*-2-, *trans*-2-, *cis*-3-, and *trans*-3-olefinic isomers, all with non-branched carbon chains. Thus, the N-*n*-dodecyl derivative (**6f**) gave these dodecenes in the ratio of 44·0:15·4:25·9:6·0:8·7. This product

distribution indicates an E1 elimination mechanism involving the formation of primary carbonium ions which partially rearrange before proton loss.

Solvolysis of N-*n*-dodecyl- (**6f**) and N-*n*-octyl-acridinium (**6e**) ions in phenol gave the *n*-alkyl phenyl ethers, unaccompanied by any rearranged ethers, but accompanied by all of the corresponding isomeric secondary straight-chain *o*-alkyl- and *p*-alkyl-phenols.[32] The 1-octyl and 1-dodecyl phenyl ethers could have arisen by either S_N1 and S_N2 pathways. However, the C-alkylated products implicate rearrangement of the corresponding secondary-octyl and *sec*-dodecyl phenyl ethers (the corresponding primary ethers do not rearrange under the condition of the reaction).[33] These secondary-alkyl phenyl ether precursors in turn arose from intermediate secondary carbonium ions which had been formed by rearrangement before reaction. The high ortho : para ratio of the substituted phenols indicates that the conversion of *s*-alkyl phenyl ethers into C-alkylated phenols was mainly intramolecular.

Solvolyses of (**6e**) in carboxylic acids yielded a mixture of isomeric octyl carboxylic esters.[32] Significantly, the solvolyses of (**6e**) in acetic acid and benzoic acid gave an almost identical ratio of the 1-, 2-, 3-, and 4-octyl esters. This result again indicates the formation of primary carbonium ions before being trapped by solvent molecules in such reactions.

Conclusion. N-(Primary alkyl)pyridinium cations can react by either an S_N1 or an S_N2 type mechanism depending on the circumstances. We suggest that a similar behavior is likely by implication for other primary alkyl substrates.

STUDIES OF MECHANISTIC BORDERLINES

To better understand the detailed mechanism of nucleophilic substitution of sp^3-hybridized carbon atoms, we recently investigated,[11,34] utilizing pyridines as leaving groups, three of the four mechanistic borderlines depicted in Scheme 1. These borderlines were: (1) that between first-order reactions involving ion–molecule pairs and first-order reactions proceeding via dissociation into free carbocations; (2) that between first-order and second-order reactions of nucleophiles with ion–molecule pairs; (3) that between classical S_N2 displacement and S_N2 displacement on an intimate ion–molecule pair.

Borderline [1] Between Classical S_N1 and S_N1 by Nucleophilic Capture of an Ion–Molecule Pair

At this borderline, there is competition between two alternative first-order reactions: (i) mechanism *d* (see Scheme 1) in which the ion–molecule pair stage is captured by solvent or nucleophile (i.e. rate determining formation of the ion–molecule pair) and (ii) mechanism *e* in which dissociation occurs of the ion–molecule pair into a free carbocation which subsequently react further with solvent or nucleophile (in this case the rate determining step could be either the formation of a ion–molecule pair or its dissociation).

Reaction is expected to occur via ion–molecule pair (without any skeletal rearrangement of the secondary alkyl groups) for those secondary substrates which display first-order kinetics (no dependence of nucleophile concentration) in non- or very weakly nucleophilic solvents in the presence of small amounts of strong nucleophiles (piperidine or morpholine). By contrast the solvolysis reaction for these same substrates should occur by a classical S_N1 unimolecular

reaction via free carbocations, if only weak nucleophiles such as 1,1,1,3,3,3-hexafluoropropan-2-ol or trifluoroacetic acid are present, and in this case equilibriation of the secondary alkyl group by carbocation rearrangements should occur.

Such behavior has indeed been found. 1-(2-Pentyl)-5,6-dihydro-2,4-diphenylbenzo-[h]quinolinum trifluoromethanesulfonate (**13a**) and 1-(3-pentyl)-5,6-dihydro-2,4-diphenylbenzo[h]quinolinum tetrafluoroborate (**13b**) underwent solvolysis in chlorobenzene at 65 °C in the presence of a range of nucleophiles (piperidine, morpholine, pyridine, lutidine, anisole, *p*-chlorophenol, acetic acid, or trifluoroacetic acid) under pseudo first-order conditions:[11] when the observed rate constants ($k_{obs.}$) were plotted against nucleophile concentration good straight lines were obtained to at least 70% completion (Figure 6). Effects on the rate were negligible for weak nucleophiles (*p*-chlorophenol, anisole or acetic acid) and small for strong nucleophiles (piperidine, morpholine) demonstrating that first-order reactions predominated over second-order in all these cases.

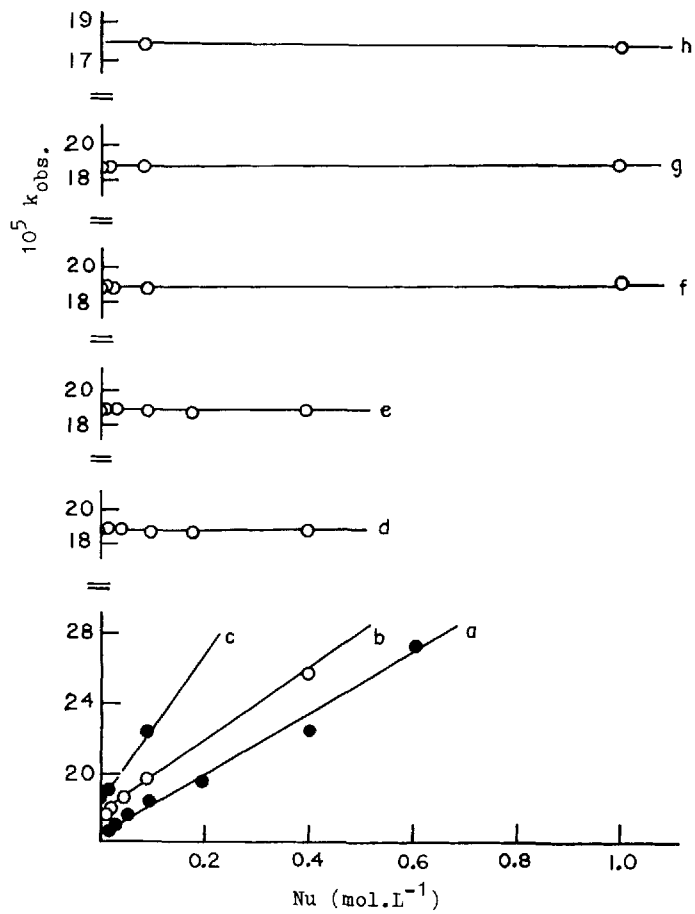


Figure 6. Plots of observed rate constants for the solvolyses of 1-(2-pentyl)-5,6-dihydro-2,4-diphenylbenzo[h]quinolinum trifluoromethanesulfonate (**13a**) in chlorobenzene at 65 °C vs. nucleophilic concentration; *a* – morpholine; *b* – isopropylamine; *c* – piperidine; *d* – pyridine; *e* – 2,6-lutidine; *f* – *p*-chlorophenol; *g* – anisole; *h* – acetic acid; (Reproduced from Reference 8 with permission)

Where such first-order reaction dominated, with a rate determining stage not involving the nucleophile, the solvolysis of (**13a**) in chlorobenzene containing morpholine gave pent-2-ene (14·4 ± 2·0%; elimination product) together with N-2-pentylmorpholine (85·6 ± 2·0%; non-rearrangement product). Significantly, N-3-pentylmorpholine was sought but not detected. Similarly, the solvolysis of (**13a**) in chlorobenzene containing acetic acid (1 M) gave only 2-pentyl and no 3-pentyl acetate.

The behavior of the 2-pentyl derivative (**13a**) was studied in chlorobenzene containing in each of the additive morpholine, *p*-chlorophenol and anisole respectively. In these experiments, the proportion of elimination varied 14–100%, but the reaction rate was invariant with nucleophile concentration, and the intercepts were identical. The rate determining step is thus shown to occur before the elimination or the substitution step.

Likewise 3-pentyl derivative (**13b**) solvolysed in chlorobenzene containing morpholine (0·1 M) to form only 2-pentene (88%) and N-3-pentylmorpholine (12%). Again no N-2-pentylmorpholine was detected. Solvolysis of (**13b**) in chlorobenzene in the presence of acetic acid produced only the 3-pentyl acetate. As shown by kinetic measurements, 0·1 M morpholine or 0·1 M acetic acid in the chlorobenzene solvent do not significantly accelerate reactions of (**13a**) and (**13b**). Nevertheless, morpholine or acetic acid effectively intercepted the incipient 2- or 3-pentyl carbocations prior to rearrangement so that only the 2-pentyl, or only the 3-pentyl products, respectively, were formed. Once again, this confirms that the solvolyses of (**13a**) and (**13b**) take place via intimate ion–molecule pairs.

The above results support conclusions made from earlier work with 1,1,1,3,3,3-hexafluoropropan-2-ol as solvent:[10] separate solvolyses of (**13a**) and (**13b**) in this fluorinated solvent each gave identical mixtures of the same ratio of the 2-pentyl and 3-pentyl products, by a mechanism involving a free carbocation. Again solvolysis in 1,1,1,3,3,3-hexafluoropropan-2-ol of (**13a**) and (**13b**) in the presence of morpholine as nucleophile, gave solely non-rearranged products N-(2-pentyl)- and N-(3-pentyl)-morpholine, respectively. The 2-pentyl (**13a**) and the 3-pentyl (**13b**) substrates both solvolysed in trifluoroacetic acid to afford 2-pentyl and 3-pentyl trifluoroacetates in the same proportions. Again, (**13a**) and (**13b**) both solvolysed in chlorobenzene containing trifluoroacetic acid (1 M) to yield mixtures of 2-pentyl and 3-pentyl trifluoroacetates.

These and other kinetic and product analyses are evidence for the involvement of free carbocations in solvolyses in the highly non-nucleophilic protic solvents trifluoroacetic acid and 1,1,1,3,3,3-hexafluoropropan-2-ol, as well as in chlorobenzene with added trifluoroacetic acid. In the foregoing instances fast attack on a free carbocation (formed in the rate determining step) by the solvent explains the preparative and kinetic results. On the other hand, with acetic acid as solvent, or in chlorobenzene containing morpholine or acetic acid as added nucleophiles, the results are rationalized by fast attack of solvent, or of the added nucleophile, on intimate ion–molecule pairs which were irreversibly formed in the rate-determining step.

The fast reactions of secondary alkyl primary amines of type $RR'CHNH_2$ with the pentacyclic pyrylium cation in which the secondary alkyl groups were captured from the intermediate highly reactive pyridinium cations by various nucleophiles without rearrangement, provide further evidence for intimate ion–molecule pair intermediates.[35]

Conclusion. S_N1 type reactions can occur by two distinct mechanisms involving intimate ion–molecule pairs or involving free carbonium ions. There is no indication of any merging of mechanism.

Borderline [2]: Between Rate Determining Formation of an Ion–Molecule Pair and Rate Determining Attack on an Ion–Molecule Pair by a Nucleophile

At this borderline, reactions proceed by capture of an ion–molecule pair by the solvent or added nucleophile, and there is competition between two alternative mechanisms: (i) mechanism *d* of Scheme 1 in which formation of the ion–molecule pair (or of the free carbocation) is rate determining, i.e. unimolecular reaction mode; (ii) mechanism *c* of Scheme 1 in which nucleophilic attack is rate determining, i.e. bimolecular mode.

We solvolysed[11] 1-benzyl-5,6,8,9-tetrahydro-7-phenyldibenzo[c,h]acridinium trifluoromethanesulfonate (**6k**) and 1-(*p*-methoxybenzyl)-2,4,6-triphenylpyridinium tetrafluoroborate (**14b**) in pure chlorobenzene and in chlorobenzene, containing nucleophiles in small concentrations. Under these conditions, both mechanisms could be of comparable importance. The behavior of the N-benzylpentacyclic derivative (**6k**) depends on the nucleophile: it reacts almost exclusively via a bimolecular route with morpholine but almost entirely via a unimolecular mechanism with the much less powerful nucleophile, lutidine. Solvolysis in the presence of pyridine displayed both unimolecular and bimolecular components.

Studies of the variation of the reaction ratio with pressure (see below) indicate that the N-benzylpentacyclic derivative (**6k**) undergoes reactions with piperidine by a dominant second-order reaction of the intimate ion–molecule pair with nucleophile at low pressures, whereas at high pressures a competing reaction by the classical S_N2 process predominates.[34] At atmospheric pressure the second-order reaction of (**6k**) with morpholine should thus also be that of the intimate ion–molecule pair. However, the first-order rates of the N-benzylpentacyclic derivative (**6k**) do no vary with change of the nucleophile and indeed the same solvolysis rate is found for (**6k**) in the absence of added nucleophile. This constant rate demonstrates the absence of merging of the unimolecular (S_N1 type) and (S_N2 type) ion–molecule mechanisms; thus both of these mechanisms proceed independently. As the bimolecular mode is that of the reaction of the ion–molecular pair with nucleophile (mechanism *c*), then it follows that the unimolecular mode is dissociation of the ion–molecular pair to form the free carbocation (mechanism *e*).

It follows from Scheme 1, that the total reaction rate for mechanisms (*c*) and (*d*) is proportional to $k'_2[\mathrm{Nu}]k_d/(k'_2[\mathrm{Nu}] + k_a$. If $k_a \gg k'_2[\mathrm{Nu}]$ then mechanism (*c*) dominates and the rate is proportional to $k'_2[\mathrm{Nu}]k_a/k_d$. If $k'_2[\mathrm{Nu}] \gg k_a$, mechanism (*d*) dominates and the rate is proportional to k_d. If k''_2 is fast, mechanism (*e*) dominates and the rate is proportional to $k_d k'_d/(k_a + k'_d)$. The kinetic results are entirely consistent with Scheme 1 and with competition between two distinct mechanisms at borderlines.

Conclusion. Reactions via intimate ion–molecule pairs can be either second-order (when rate determining attack by nucleophile occurs), or first-order (rate determining formation of an ion–molecular pair). There is no evidence for any merging of these mechanisms.

Borderline [3]: Between Classical S_N2 Displacement and S_N2 Displacement on Intimate Ion–Molecule Pair

In this region, competition exists between two alternative second-order bimolecular reactions: (i) mechanism *b*; proceeding by direct displacement of nucleophile on the substrate (classical S_N2 reaction) and (ii) mechanism *c*; proceeding by displacement of nucleophile on the ion–molecule pair (ion–molecule pair S_N2 reaction).

The reaction of 1-benzyl-5,6,8,9-tetrahydro-7-phenyldibenzo[c,h]acridinium tetrafluoroborate (**6k**) with piperidine in chlorobenzene is a function of pressure which clearly indicates a change-over in mechanism.[34] The classical S_N2 reaction should be rate enhanced by pressure; i.e., the $\Delta V^{\#}$ is expected to be negative, because the two reactants will be pushed closer together. By contrast an S_N2 reaction on an intimate ion–molecule pair involves a pre-equilibrium of the type $RX^+ \Longrightarrow R^+ \ldots X$, for which we should expect a large positive $\Delta V^{\#}$: thus, the equilibrium will be pushed considerably to the left by increasing pressure.

The reaction rates of the N-benzylpentacyclic derivative (**6k**) first decreases with increasing pressure, but then passes through a minimum and starts to increase. This indicates that the reaction at normal and fairly low pressures is via the intimate ion–molecule pair, but that at higher pressures reaction by the classical S_N2 process takes over. The extraordinarily large difference in the volumes of activation (ca. 40 $cm^3\ mol^{-1}$) of the two transition states is strong evidence for such a structural difference.[34]

Conclusion. Bimolecular S_N2 reactions can proceed by rate-determining attack of a nucleophile either on the substrate or on an ion–molecule pair formed in a fast pre-equilibrium. There is no evidence for any merging of these mechanisms.

Borderline [4]. Between Classical S_N2 Displacement and Second-Order Reactions by Radical Pair Collapse

In the region of this borderline, competition between two alternative second-order reactions occurs: (i) bimolecular reactions which proceed by mechanism *b*, the classical S_N2 reaction, and (ii) reactions which proceed by mechanism *a* involving electron transfer. Kinetic data exist for both mechanisms, and these have recently been summarized[36] for the electron-transfer mechanism *a*. The borderline between these two mechanisms is at present under study in our laboratory, and no final conclusion is yet possible regarding the possibility of merging at this borderline.

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