New Insights into Aliphatic Nucleophilic Substitution Reactions from the use of Pyridines as Leaving Groups*

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1 Introduction

Since 1976,[1] our group has developed a pyrylium-mediated transformation of amines into other functionalities by a two-step process (Scheme 1). The first step involves the reaction of the primary amine with a pyrylium salt to give a corresponding pyridinium derivative, and the second step is a nucleophilic substitution reaction in which the *N*-substituent is transferred from the pyridine nitrogen atom to the nucleophile. The first step can be carried out at 20 °C in CH_2Cl_2 in high yields,[2] and using superior leaving groups, the second step can be carried out in solution at 50—100 °C.[3] The preparative utility of these reactions is considerable,[4] but will not be considered here. The present account is concerned with the light that information from the kinetics of *N*-substituent transfer can shed on the mechanism of aliphatic nucleophilic substitution in general.

2 The Background

The fundamental difference between the S_N2 and S_N1 reaction mechanisms in aliphatic compounds was first described by Ingold.[5] Winstein expanded this distinction by pointing out that there was evidence that the S_N1 mechanism took place in distinct variations involving intimate ion-pairs, solvent-separated ion-pairs, and free carbocation (Scheme 2).[6] Sneen put forward the hypothesis that all S_N2 mechanisms took place over intimate ion-pairs formed reversibly in a pre-

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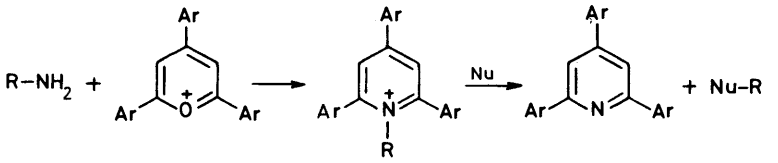
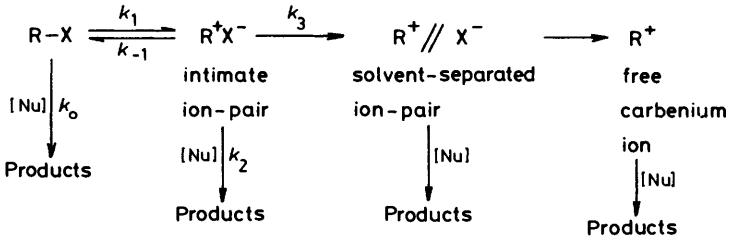
[1] J. B. Bapat, R. J. Blade, A. J. Boulton, J. Epsztajn, A. R. Katritzky, J. Lewis, P. Molina-Buendia, P. L. Nie, and C. A. Ramsden, *Tetrahedron Lett.*, 1976, 2691.
[2] A. R. Katritzky, R. H. Manzo, J. M. Lloyd, and R. C. Patel, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 306.
[3] (*a*) A. R. Katritzky and S. S. Thind, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1895; (*b*) *Ibid.*, 1981, 661.
[4] For a review see A. R. Katritzky, *Tetrahedron*, 1980, **36**, 679.
[5] See C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', 2nd Edn., Bell, London, 1969.
[6] S. Winstein, B. Appel, R. Baker, and A. Diaz, in 'Symposium on Organic Reaction Mechanisms', Chemical Society (London), Special Publication No. 19, 1965, p. 109.



Scheme 1



Scheme 2

equilibrium followed by rate-determining nucleophilic attack on the intimate ion-pair.[7] Schleyer and Bentley have emphasized the concept of variable nucleophilic assistance by solvent.[8]

Recently it has been suggested, and amply demonstrated, that electron transfer may cause nucleophilic substitution.[9]

A perennial difficulty in the interpretation of nucleophilic substitution reactions with a halide, tosylate, or similar leaving group, is that such substrates are neutral and during the reaction charge is created in an S_N1 type reaction. This means that such reactions may not take place in non-polar solvents, and in those solvents where they do occur the possibility arises that the solvent is acting as nucleophile, rather than just as a polar medium, and this complicates considerably the interpretation.

The advent of substituted pyridines as *neutral* leaving groups changes this. Here the substrates start off by being positively charged, and no charge is created in the bond heterolysis which produces R^+ and a neutral leaving group. Hence, such S_N1 reactions are expected to be much less affected by solvent polarity and can be studied in non-polar media where there is no doubt that the solvent is acting truely as a solvent and not as a nucleophile. Because of this, interpretation is simpler and findings from the non-polar solvents can be extrapolated to polar solvents, thus shedding light on the whole question of the reaction mechanisms.

[7] (*a*) R. A. Sneen, *Acc. Chem. Res.*, 1973, **6**, 46; (*b*) R. A. Sneen and J. W. Larsen, *J. Am. Chem. Soc.*, 1969, **91**, 362; (*c*) R. A. Sneen and J. W. Larsen, *J. Am. Chem. Soc.*, 1969, **91**, 6031.

[8] (*a*) T. W. Bentley and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1976, **98**, 7658; (*b*) F. L. Schadt, T. W. Bentley, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1976, **98**, 7667; T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, 1977, **14**, 1.

[9] (*a*) I. P. Beletskaya and V. N. Drozd, *Russ. Chem. Rev.* (*Engl. Transl.*) 1979, **48**, 431; (*b*) M. Chanon and M. L. Tobe, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 1.

3 The Kinetic Investigation of Nucleophilic Displacements with Pyridines as Leaving Groups

Kinetic investigation of reactions of the type depicted has shown the following characteristics:

(a) Whereas salt effects are found in non-polar solvents for charged nucleophiles, the neutral nucleophiles show clean kinetics under second order or, very conveniently, under pseudo first-order conditions.

(b) A wide range of solvents can be used, *e.g.* PhCl, MeCN, pentanol, DMSO.

(c) Changing the gegen ion from BF_4^- to ClO_4^- has no influence on the reaction rate.

(d) A wide range of *N*-substituents, leaving groups, and nucleophiles can be studied.

(e) Temperature and pressure can be conveniently varied to give $\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta V^{\neq}$.

(f) Rates can be followed either spectrophotometrically ot conductometrically, although the former is normally the more convenient method.

A typical spectrophotometric determination of rate is shown in Figure 1a from which the data in Figure 1b were plotted to give the k_{obs} value. As can be seen, very good straight line plots are obtained for k_{obs} under pseudo first-order conditions.

Figure 2 shows the result of plotting k_{obs} against nucleophile concentration for the three different nucleophiles piperidine, morpholine, and pyridine with 1-benzyl-2,4,6-triphenylpyridinium at 100 °C in chlorobenzene solution. For each nucleophile, a straight line is found which passes through the origin, showing that the reaction is first order in the nucleophile. Separate experiments show that it is also first order in substrate. In other words, overall it is a second-order reaction characteristic of the S_N2 mechanism. The second-order rate-constant is proportional to the slope of the line in the plot, and is as expected greatest for piperidine, less for morpholine, and by comparison very much smaller for pyridine, which is a much less powerful nucleophile.[10]

However, a dramatically different result is found for the *N*-isopropyl analogue in Figure 3. Here, although three straight lines are found, they do not pass through the origin, but give a significant intercept at zero nucleophile concentration. This shows clearly that alongside the second-order component there is also a first-order component, which is independent of the amount and nature of the nucleophile. In other words, we have alongside our S_N2 reaction, an S_N1 component.[10]

Such behaviour is typical for substrates with secondary alkyl groups. Figures 4 and 5 show results in which now the nucleophile is kept constant as piperidine, but the *N*-substituent is varied for the monocyclic series (Figure 4), and for the tricyclic series (Figure 5). It can be seen that in Figure 4 methyl, allyl, benzyl, and *p*-methylbenzyl all give results, in the monocyclic series, that are (within experimental precision) completely second order and no first-order component can be detected.

[10] A. R. Katritzky, G. Musumarra, K. Sakizadeh, S. M. M. El-Shafie, and B. Jovanovic, *Tetrahedron Lett.*, 1980, **21**, 2697.

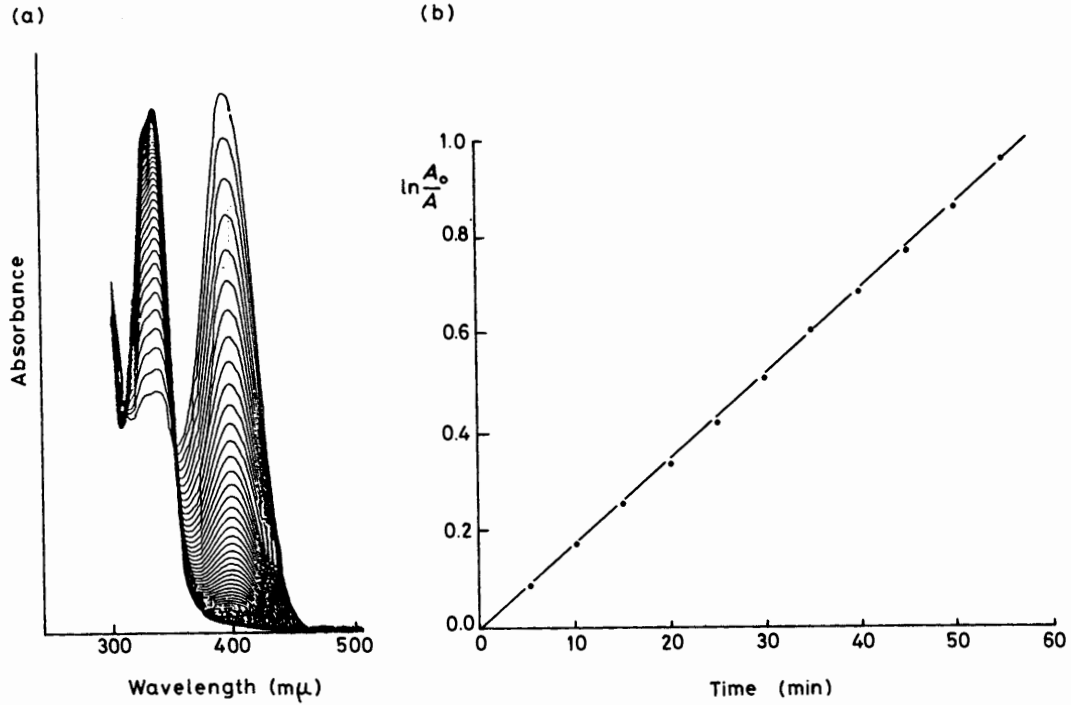


Figure 1 *Displacement kinetics in chlorobenzene solution at* 25 °C: N-p-*methylbenzyl*-5,6,8,9-*tetrahydro*-7-*phenyl*-*bis*-*benzo*[*a,h*]*acridinium tetrafluoroborate with piperidine. (a) Ultraviolet spectrum* (5 min *intervals*) (*substrate* 5.0×10^{-5}M; *piperidine* 5.0×10^{-3}M). *(b) Pseudo first-order plot*

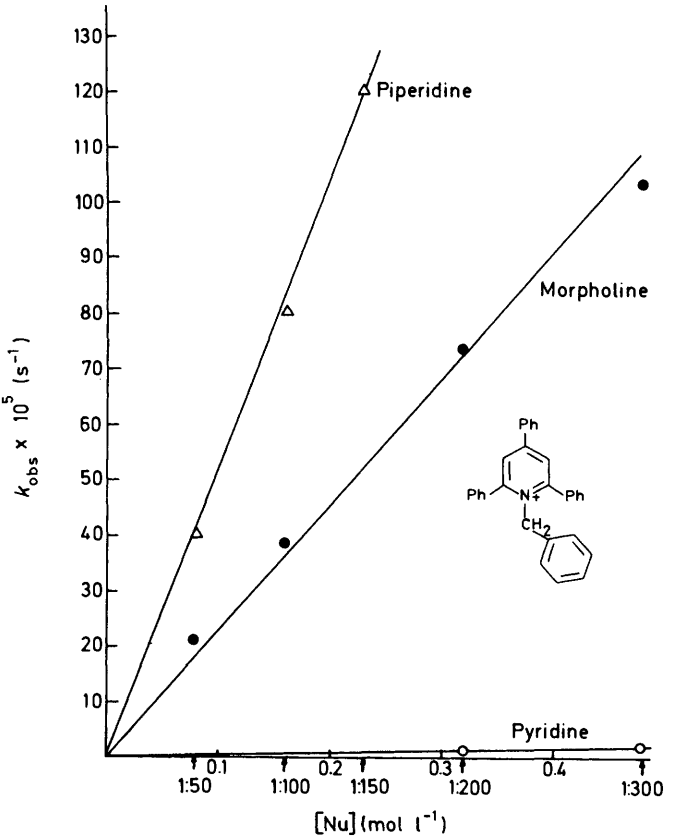


Figure 2 *Nucleophilic substitution by* S_N2 *reaction only:* k_{obs} *for* 1-*benzyl*-2,4,6-*triphenylpyridinium cation* (1.6×10^{-3}M) *plotted* vs. *nucleophilic concentration* (*chlorobenzene solution*, 100 °C)

By contrast all the secondary alkyl derivatives (isopropyl, secondary butyl, cyclopentyl, and cyclohexyl) show a clear first-order component.[11]

The same pattern is repeated for the tricyclic series. Here, the benzoquinoline is a much more active leaving group, and rates at the same temperature of 100 °C are much greater. We can now follow the rates for the primary alkyl groups other than methyl, and see that they react essentially only by the S_N2 mechanism, but at relatively slow rates.[11]

[11] A. R. Katritzky, K. Sakizadeh, Y. X. Ou, B. Jovanovic, G. Musumarra, F. P. Ballistreri, and R. Crupi, *J. Chem. Soc., Perkin Trans. 2*, in press.

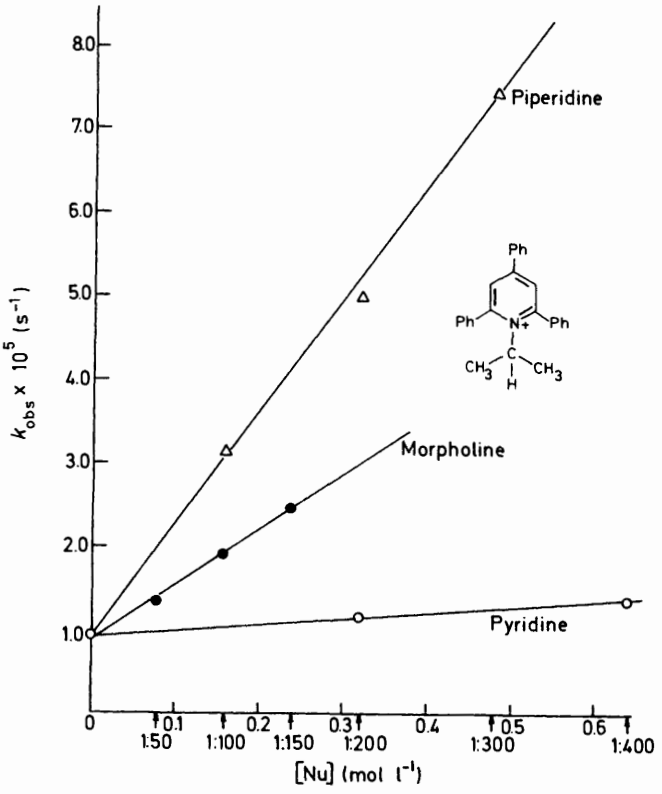


Figure 3 *Nucleophilic substitution by simultaneous S_N1 and S_N2 reactions: k_{obs} for 1-isopropyl-2,4,6-triphenylpyridinium cation* (1.6×10^{-3}M) *plotted* vs. *nucleophilic concentration (chlorobenzene solution,* 100 °C)

4 Activation Parameters

It has long been known that the magnitude of the activation entropy is characteristically less negative for S_N1 than for S_N2 reactions. We have measured the activation parameters for a number of the reactions depicted in Figures 4 and 5, and the results are given in Table 1. It will be seen that the expected pattern is reproduced.[11,12]

5 RHO Star Plots

ρ^*-Plots have been used particularly by Schleyer and Bentley to gain evidence regarding the degree of solvent participation in solvolysis reactions.[8] A series of secondary alkyl substrates (*e.g.* tosylates) are used and ρ^* is defined as the slope of a plot of the logarithms of the solvolysis rates (keeping the same solvent) against

[12] A. R. Katritzky, G. Musumarra, and K. Sakizadeh, *J. Org. Chem.*, 1981, **46**, 3831.

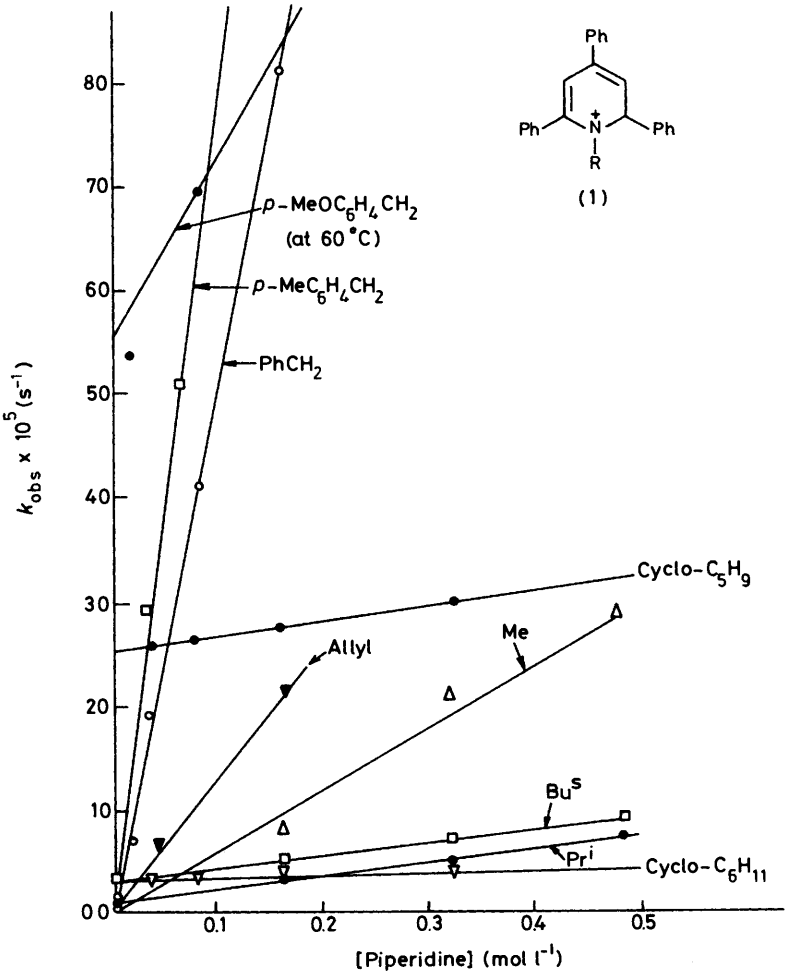


Figure 4 *Rate variation with* N-*substituent:* k_{obs} *for reactions of* N-*substituted*-2,4,6-*triphenylpyridinium cations* (1) (1.6×10^{-3}M) *with piperidine in chlorobenzene at* 100 °C

the sum of the σ^* of each of R^1 and R^2 in the groups R^1R^2CHX used. The value of σ^* for an alkyl group is a measure of its electron donor ability. Hence the sum $(\sigma^*_{R^1} + \sigma^*_{R^2})$ is a measure of the stabilization afforded by R^1 and R^2 to $R^1R^2CH^+$. The argument is that the greater the solvent assistance the less will be the necessity of the developing carbonium ion centre to rely on electron donation from R^1 and R^2. Hence the ρ^* should be high for solvents affording little solvent assistance and low for solvents offering much assistance.

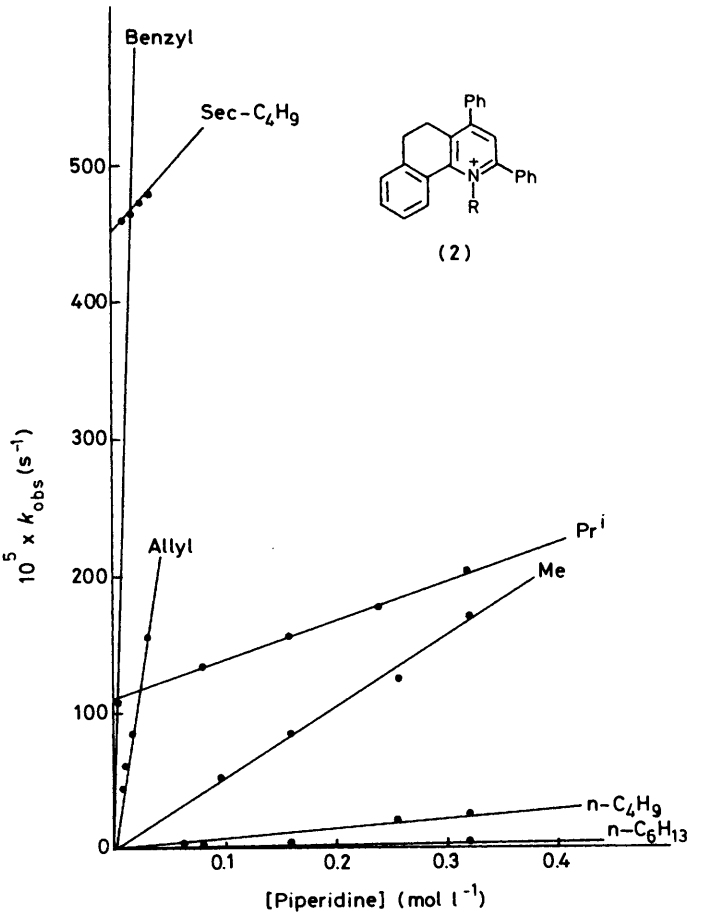


Figure 5 *Rate variation with* N-*substituent:* k_{obs} *for reactions of* N-*substituted*-2,4-*diphenyl*-5,6-*dihydrobenzo*[*h*]*quinolinium cations* (2) (6.4×10^{-5}M) *with piperidine in chlorobenzene at* 100 °C

Table 1 *Activation parameters*

Ring	N-*Substituent*	*Reaction*	$\Delta H^{\neq}_{373}$ (kcal mol^{-1})	$\Delta S^{\neq}_{373}$ (cal mol^{-1} K^{-1})
(1)	Benzyl	S_N2	16.3 ± 0.6	−26.2
(1)	*p*-$MeC_6H_4CH_2$	S_N2	16.4 ± 0.2	−24.6
(1)	*p*-$MeOC_6H_4CH_2$	S_N2	13.6 ± 3.1	−30.4
		S_N1	22.3 ± 0.5	− 7.0
(2)	Methyl	S_N2	19.4 ± 2.1	−17 ± 6
(2)	Isopropyl	S_N2	14.0 ± 4.0	−31 ± 13
		S_N1	25.6 ± 0.8	− 4 ± 2
(2)	Benzyl	S_N2	15.8 ± 1.5	−19 ± 5

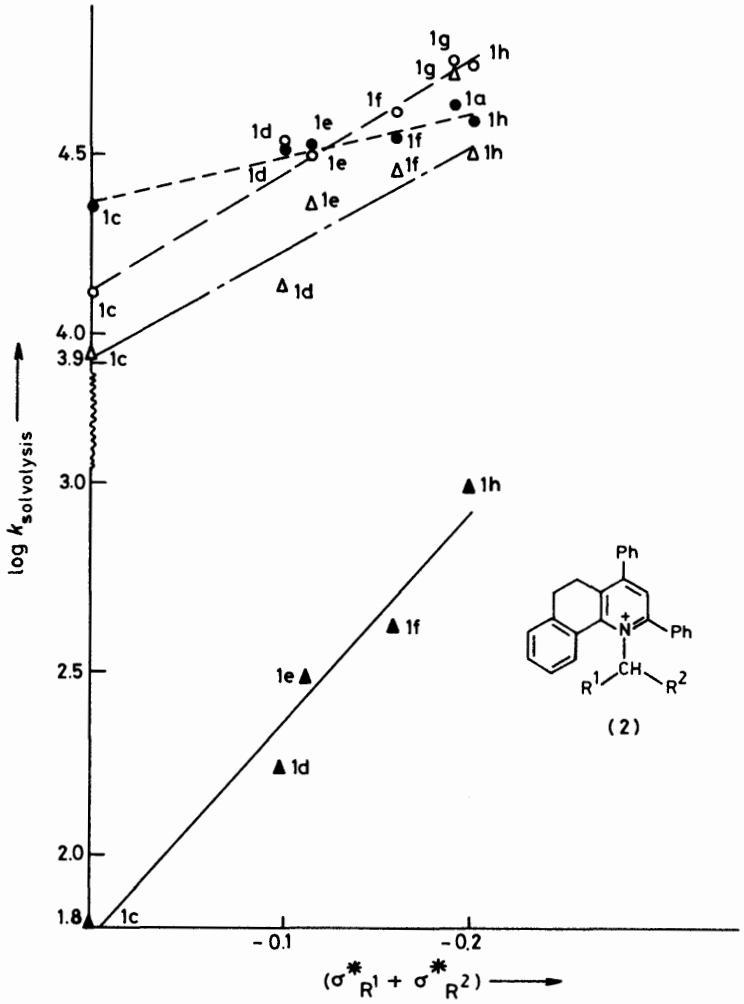
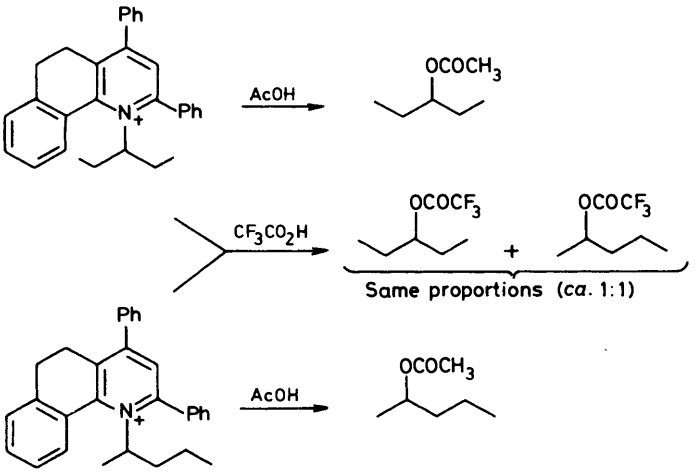


Figure 6 *Rho star plots of solvolysis rates at* 100 °C *of* 1-(*sec-allyl*)-2,4-*diphenyl*-5,6-*dihydrobenzo[h]quinolinium cations* (2): ▲ ——— *trifluoroacetic acid,* △ — - — *acetic acid,* ● - - - - *pentanol,* ○ —— —— *chlorobenzene*

However, Figure 6 shows that this simple picture is incomplete, because the ρ^* plot in chlorobenzene solution (which can be obtained for the substrates shown, but not of course for tosylates) is considerably less than that for trifluoroacetic acid.[13]

[13] A. R. Katritzky, J. Marquet, and M. L. Lopez-Rodriguez, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1443.



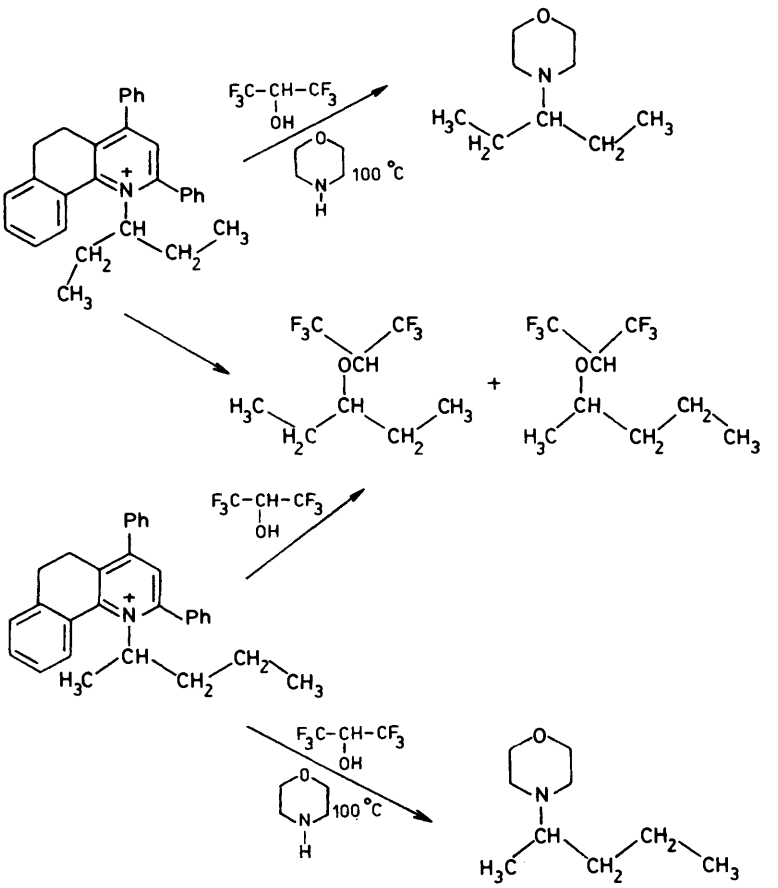
Scheme 3 *Product analysis* (^{13}C *n.m.r.*)

This finding led us to study the product analysis (Scheme 3) of some of these reactions.[14] We found that both 2-pentyl and 3-pentyl substrates underwent solvolysis in trifluoroacetic acid to give the same mixture of 3-pentyl and 2-pentyl trifluoroacetates. This indicates a carbocation mechanism where the carbocation has time to equilibrate. By contrast the same two substrates undergo acetolysis in acetic acid to give only the 2-pentyl acetate from the 2-pentyl substrate, and only the 3-pentyl acetate from the 3-pentyl substrate showing that here no *free* carbocation is involved.

The solvolyses in hexafluoroisopropanol (Scheme 4) are still more revealing.[14] Again, both the substrates undergo solvolysis to yield the same mixture of the 3-pentyl and the 2-pentyl hexafluoroisopropyl ethers, showing reaction through a free carbocation. When some morpholine is added to this solvent, it is found that there is no large rate acceleration. However, morpholine is able to intercept the pentyl carbocation and the major product is now a *N*-pentylmorpholine. Significantly, the 3-pentyl derivative gives only 3-pentyl morpholine, and the 2-pentyl gives only 2-pentylmorpholine. This indicates that no free carbocation is formed, and the evidence together strongly suggests that the solvolysis occurs through an intimate ion–molecule pair. Morpholine is a sufficiently strong nucleophile to intercept the pentyl carbocation at the ion–molecule pair stage, whereas in the absence of morpholine, the pair drifts apart to generate a free carbocation, which then equilibrates before reaction with a solvent molecule.

A plot of ρ^*against E_T as a measure of solvent polarity (Figure 7) indicates that as the solvent polarity increases the ρ^* value becomes less negative. There are two main exceptions to this correlation: acetic acid and pentan-1-ol. We believe that this indicates that substantial solvent assistance is being given by pentan-1-ol and

[14] A. R. Katritzky, M. L. Lopez-Rodriguez, and J. Marquet, *J. Chem. Soc., Perkin Trans. 2*, 1984, 349.



Scheme 4 *Solvolyses in hexafluoroisopropanol (at* 100 °C)

acetic acid in these reactions, which are thus essentially of S_N2 type, but that in the other solvents we have essentially S_N1 solvolysis.[14]

6 Other Evidence For Intimate Ion–Molecule Pairs

Both α-methylallylamine and γ-methylallylamine react with 2,4,6-triphenylpyrylium to give the expected pyridinium cations. However, the *N*-α-methylallylpyridinium cation, on gentle heating in an inert solvent, rearranges to the γ-methylallyl analogue (Scheme 5a). This reaction must take place *via* an intimate ion–molecule pair rearrangement.[15]

Furthermore, when optically active α-phenylethylamine reacts with 2,4,6-

[15] A. R. Katritzky, Y. X. Ou, and G. Musumarra, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1449.

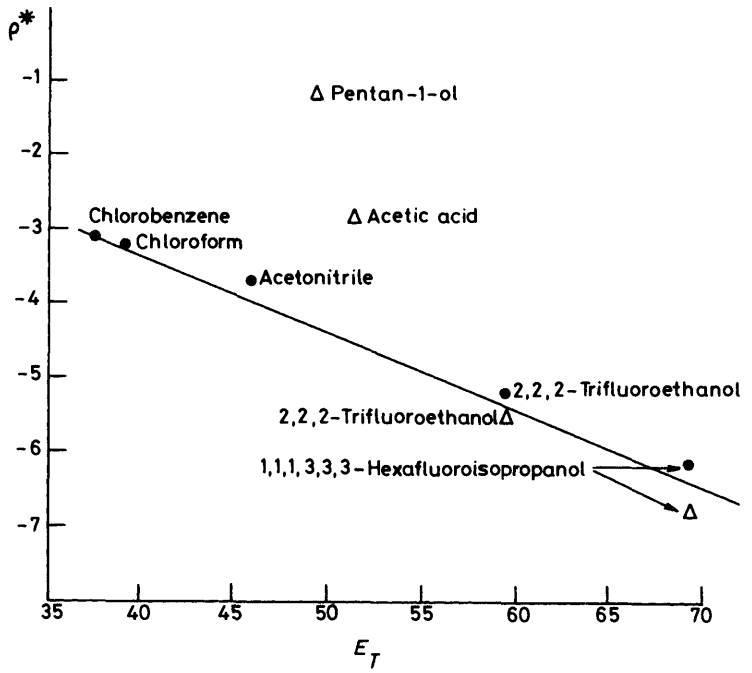


Figure 7 *Plot of* ρ^* vs. E_T

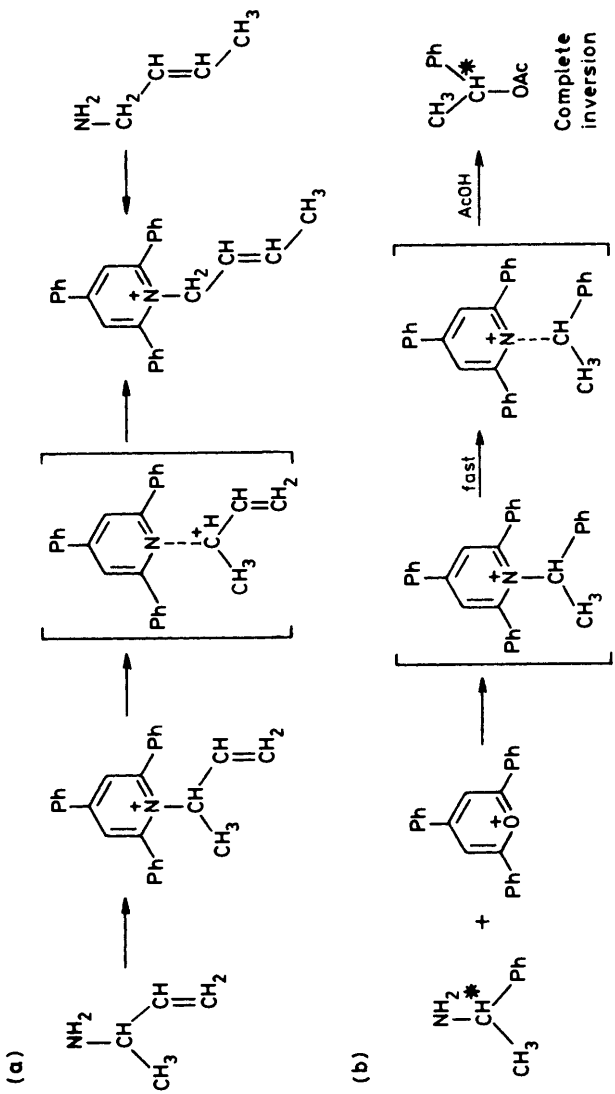
triphenylpyrylium cation in acetic acid solvent the initially formed pyridinium is so reactive that it immediately gives the corresponding acetate. However, the α-phenylethyl acetate is formed with complete inversion. This reaction is likely also to occur *via* an intimate ion–molecule pair (Scheme 5b).[15]

To summarize, the evidence so far indicates we have distinguished between two types of S_N1 reaction; that *via* the free carbonium ion and that involving an intimate ion–molecule pair as intermediate. We now go on to distinguish between the two types of bimolecular mechanism: the classical S_N2 reaction and the S_N2 reaction on the intimate ion–molecule pair.

7 The Pressure Criterion for Mechanistic Distinction between S_N2 Classical and S_N2 Intimate Ion–Molecule Pair Reaction Pathways

The classical S_N2 reaction should be rate enhanced by pressure; *i.e.*, the $\Delta V^{\neq}$ is expected to be negative, because the two reactants will be pushed close together. This naive interpretation receives support from several pieces of evidence in the literature.[16]

[16] (*a*) T. Asano and W. J. Le Noble, *Chem. Rev.*, 1978, **78**, 407; (*b*) M. Okamoto, M. Sasaki, and J. Osugi, *Rev. Phys. Chem. Jpn.*, 1977, **47**, 33.



Scheme 5 *Evidence for intimate ion-molecule pairs*

By contrast an S_N2 reaction on an intimate ion–molecule pair involves a pre-equilibrium of the type $RX^+ \leftrightharpoons R^+ \cdots X$, for which we should expect a large positive ΔV^o. In other words, the equilibrium will be pushed considerably to the left by increasing pressure. Although the second stage of the reaction $R^+ \cdots X + Nu \rightarrow NuR^+ + X$ should have a negative $\Delta V^{\neq}$ the magnitude should be smaller; thus overall the reaction rate should be decreased by pressure.

1-*p*-Methoxybenzyl-2,4,6-triphenylpyridinium perchlorate shows (Figure 8) a reaction rate which clearly decreases with pressure indicating that this reaction involves an intimate ion–molecule pair (this reaction was carried out at temperatures at which the only measurable reaction is second order.)[17]

Still more interesting is the result for the *N*-benzylpentacyclic derivative, seen in Figure 9. Here the reaction rate first decreases with increasing pressure, but then passes through a minimum and starts to increase. This clearly indicates a change in mechanism and furthermore that the reaction at normal and fairly low pressure is *via* the intimate ion–molecule pair, but that at higher pressures reaction by the classical S_N2 process takes over.[17]

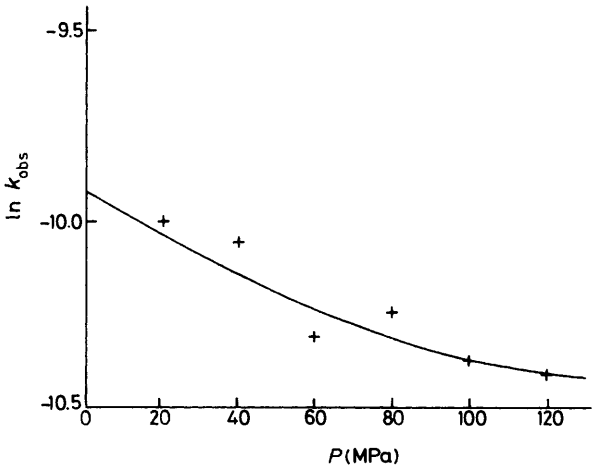
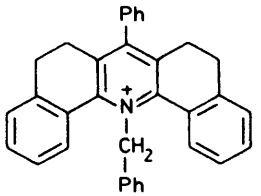


Figure 8 *Reaction* via *intimate ion–molecule pairs: reaction of* 1-p-*methoxybenzyl*-2,4,6-*triphenylpyridinium perchlorate* (1) (2.0×10^{-5}M) *with piperidine* (0.1M) *at* 30 °C *in chlorobenzene solution at varying pressures* (*activation volume* $\Delta V^{\neq}$ $+18.9 \pm 1$ cm^3/mole)

8 Reaction by an Electron Transfer Mechanism

We have shown that *N*-substituents are transferred from pyridinium cations to the carbon atom of nitro-alkane anions.[18] For reasons detailed below we believe that this reaction involves an electron transfer mechanism, but not of the normal radical chain variety.

[17] A. R. Katritzky, K. Sakizadeh, W. J. Le Noble, and B. Gabrielsen, *J. Am. Chem. Soc.*, in press.
[18] A. R. Katritzky, G. Z. de Ville and R. C. Patel, *Tetrahedron Lett.*, 1980, **21**, 1723.



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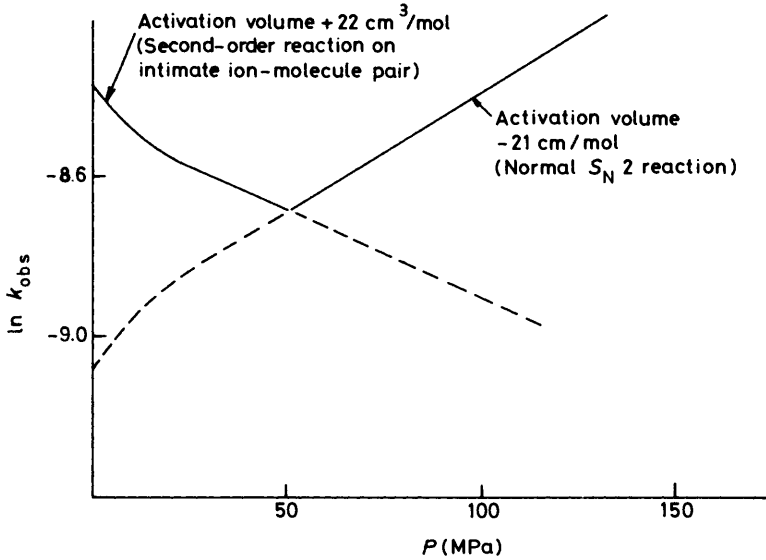


Figure 9 *Competing reactions at high pressure: the pseudo first-order rate-constant for the reaction of* N-*benzyl*-5,6,8,9-*tetrahydro*-7-*phenyl*-*bis*-*benzo*[*a*,*h*]*acridinium tetrafluoroborate* (3) (2.0×10^{-5}M) *with piperidine* (2.0×10^{-3}M) *at* 30 °C *in chlorobenzene as a function of pressure*

The reaction is very fast for the *N*-benzyl substituent. Figure 10a shows the overall spectral changes for a reaction taking place at 25 °C in DMSO.[19] These data give a good second order plot when k_{obs} is plotted under pseudo first-order conditions against nucleophile concentration (Figure 10b). Here there is no evidence for the formation of any intermediate.

However, when the *N*-substituent is *N*-n-butyl, at 25 °C in DMSO, although a change occurs in the ultra-violet spectrum (Figure 11), no product is formed (as shown by preparative experiments). Evidently an intermediate is formed in equilibrium in the starting materials. However, when the mixture is heated up above 60 °C, product formation begins at an appreciable rate and at 100 °C the rate is quite fast as shown in Figure 12.[19]

[19] (*a*) A. R. Katritzky, M. A. Kashmiri, G. Z. de Ville, and R. C. Patel, *J. Am. Chem. Soc.*, 1983, **105**, 90; (*b*) M. A. Kashmiri, unpublished.

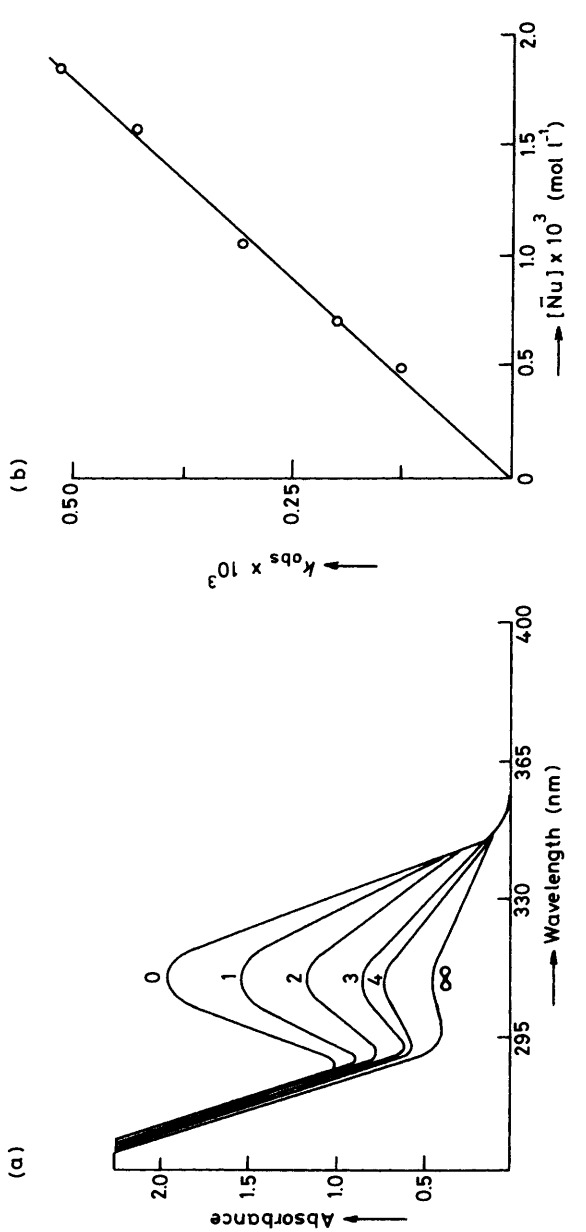


Figure 10 *Reaction of* 1-*benzyl*-2,4,6-*triphenylpyridinium with sodium propane-2-nitronate in DMSO at* 25 °C: *(a) Spectral changes (pyridinium* 6.597×10^{-5} m/l, $CMe_2NO_2^-$ (1.320×10^{-3} m/l; *time intervals* 3 min). *(b) Plot of* k_{obs} *vs. concentrations of* $CMe_2NO_2^-$

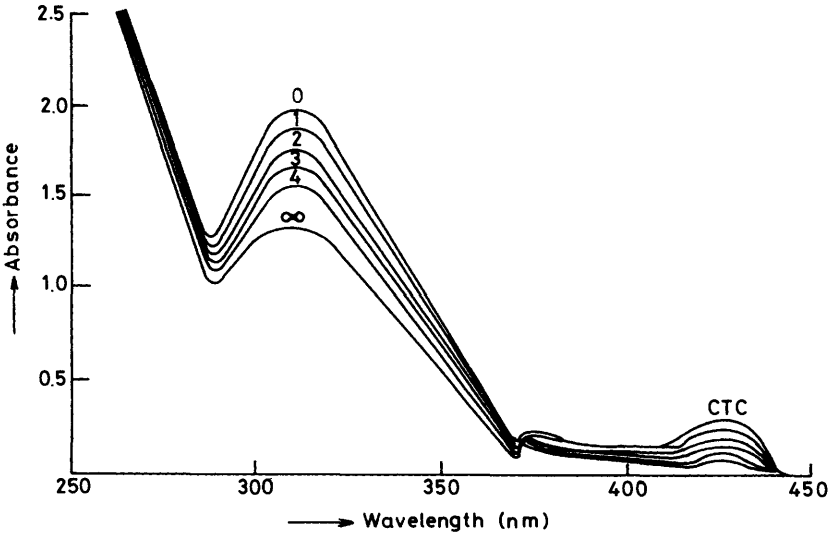
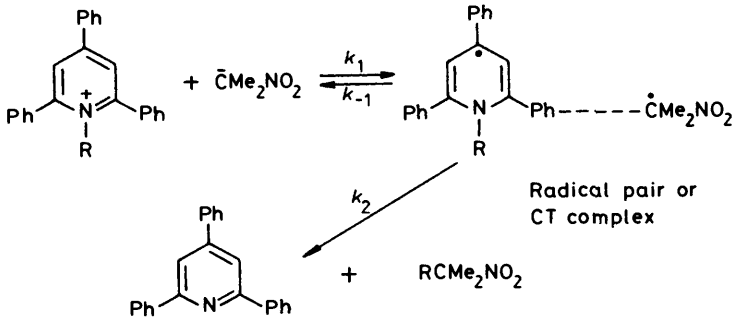


Figure 11 *Formation of charge-transfer intermediate radical pair: reaction of* 1-*n-butylpyridinium* (6.597 × 10^{-5}m/l) *with* $CMe_2NO_2^-$ (1.320 × 10^{-3}m/l) *in DMSO at* 25 °C

We believe that these observations can be explained by the reaction mechanism presented in Scheme 6. The pre-equilibrium involves formation of an intermediate which can be considered either as a radical pair or a charge-transfer complex. This



Scheme 6 *Proposed radicaloid non-chain mechanism*

then breaks down to products. In the case of the *N*-benzyl substituent the breakdown process is fast even at 25 °C and no build up of intermediate is seen. In the case of the *N*-n-butyl substituent, at low temperatures we get the equilibrium formation of a charge-transfer complex, which then breaks down only at higher temperatures. Although the rate of formation of a charge transfer is usually fast, examples are known of CTC formation at measurable rates.[20]

[20] (*a*) C. Walling and C. Zhao, *Tetrahedron*, 1982, **38**, 1105; (*b*) D. P. N. Satchell, personal communication.

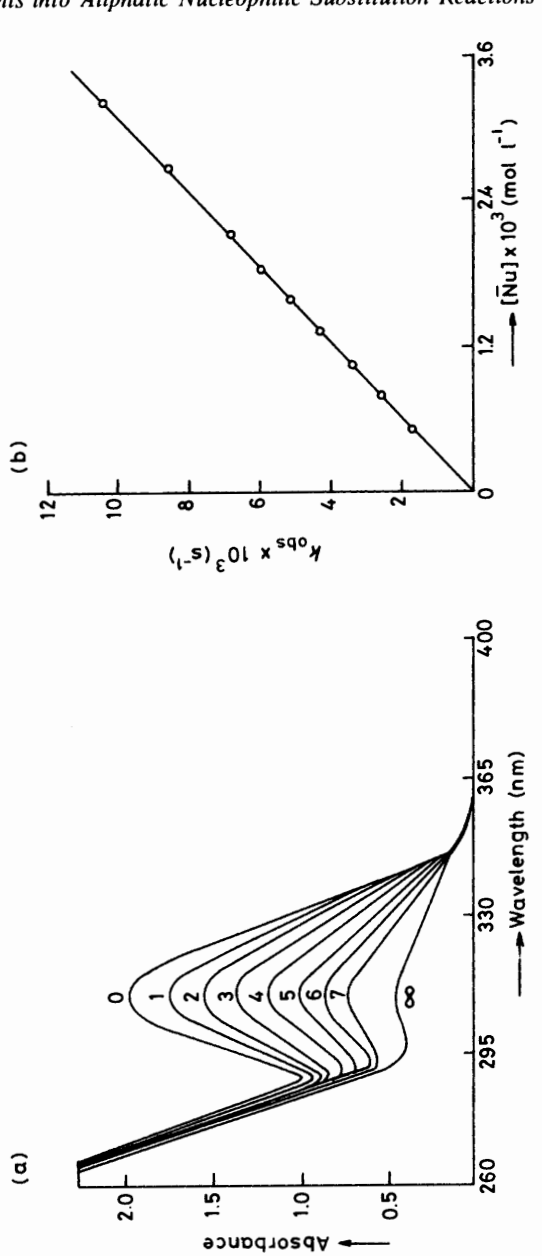


Figure 12 *Reaction of* 1-n-*butyl*-2,4,6-*triphenylpyridinium* (6.597×10^{-5} m/l) *with sodium propane-2-nitronate in DMSO at* 100 °C: *(a) Spectral changes at time intervals of* 30 min ($CMe_2NO_2^-$ = 1.320×10^{-3} m/l). *(b) Plot of* k_{obs} *vs. nucleophilic concentration*

As this reaction mechanism proposed is an unusual one, it is important to summarize the evidence that has caused us to eliminate the mechanisms with more precedents.

9 Evidence Against a Chain Mechanism for the Reaction with Nitronate Anions

We believe that a chain reaction can be eliminated for the following four reasons:

(a) The kinetic dependence expected for a radical-chain mechanism is generally complex (see for example *ref.* 21): although a radical mechanism in which chain initiation and termination rates were identical could give simple kinetics, these could not persist over a variety of conditions.

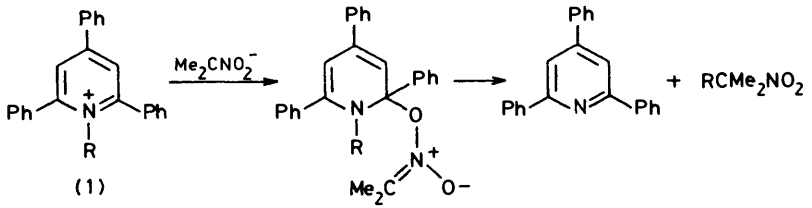
(b) Radical non-chain mechanism should indeed give simple kinetic dependence. Examples are known, including the decomposition of phenyldiimide (PhN_2H) into benzene and nitrogen.[22]

(c) Light, which acts as an initiator for many radical-chain reactions, has no effect on the rate of these reactions.[19]

(d) Inhibitors such as di-t-butyl nitroxide and *m*-dinitrobenzene have little effect on rates of these reactions.[19]

10 Evidence Against a Cyclic Mechanism for the Reaction with Nitronate Anions

We believe the mechanism depicted in Scheme 7 can be rejected for the following reasons:



Scheme 7 *Possible cyclic mechanism*

(a) Pyridinium cations normally add nitronate at the 4-position to form a C—C bond, rather than at the 2-position.[23]

(b) The transposition depicted in the scheme is unfavourable on orbital grounds.

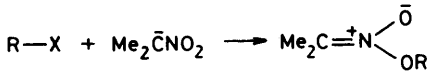
(c) Complexes formed do not show the n.m.r. expected for such an adduct, unlike the complexes formed with methoxide or cyanide ion.[23,24]

(d) Bulky groups at α-position do not inhibit reaction, and in fact compounds of type (1) react particularly well and quickly.

[21] J. Hine, 'Physical Organic Chemistry', 2nd Edn., McGraw Hill, New York, 1962, pp. 424—438.
[22] P. C. Huang and E. M. Kosower, *J. Am. Chem. Soc.*, 1967, **89**, 3910.
[23] S. W. H. Damji, C. A. Fyfe, D. Smith, and F. J. Sharom, *J. Org. Chem.*, 1979, **44**, 1761.
[24] Unpublished work with J.-L. Chen.

11 Evidence in Favour of a Radicaloid rather than a Heterolytic Mechanism for the Reaction with Nitronate Anions

A. Structure of Products.—It is well known that the alkylation of nitronate anions by halides or tosylates, which are ionic reactions, give exclusively *O*-alkylation as shown in Scheme 8.[25]



Scheme 8

The few previous examples of free-radical alkylation of nitronate anions, which have utilized either very specially substituted alkyl groups (*p*-nitrobenzyl or similar)[26] or mercury compounds,[27] do indeed give *C*-alkylation. The fact that our reaction gives exclusively *C*-alkylation even with the neopentyl derivatives strongly indicates a free-radical mechanism.

B. Rate Dependence on *N*-Substituents.—As shown in Figures 4 and 5, the S_N2 reaction with piperidine is far faster for benzyl than for *N*-methyl and far faster for *N*-methyl than for *N*-isopropyl substituents. By contrast we find that, for reactions with the nitronate ion from 2-nitropropane, although the rate for *N*-benzyl is still the most rapid, that for *N*-isopropyl is nearly as fast and is far higher than the rate for *N*-methyl. This change in rate dependence on the *N*-substituent is not compatible with the ionic mechanism, but is very readily compatible with a free-radical mechanism.

Moreover, for a series of *para*-substituted benzyl groups at nitrogen the second-order rate-constants for displacements vary quite differently for the reaction with piperidine than for the reaction with the anion from 2-nitropropane, as shown in Table 2. In the ionic reaction the rate is greatest for the electron-donor methoxy-group, intermediate for hydrogen, and least for the electron-acceptor nitro-group. By contrast, for the radical reaction the rate is least for hydrogen, and higher for all substituents, particularly for the electron-acceptor nitro-group. Again this behaviour is consistent with that expected for a free-radical reaction mechanism.

Table 2 *Second-order rate-constants for displacement reactions of* 1-(p-*substituted benzyl*)-2,4,6-*triphenylpyridinium cations with piperidine and with nitroalkane anions*

R	OMe	Me	H	Cl	NO_2
$k_2 \times 10^3$ [a]	18.0 [b]	8.52	4.95	5.88	2.96
k_2 [c]	4.2	4.1	3.30	5.9	12.4

[a] For reaction with piperidine in chlorobenzene solution at 100 °C, 1 $mol^{-1}s^{-1}$. [b] Extrapolated for values at 70 °C. [c] For reaction with CMe_2NO_2 in DMSO solution at 25 °C, 1 $mol^{-1}s^{-1}$

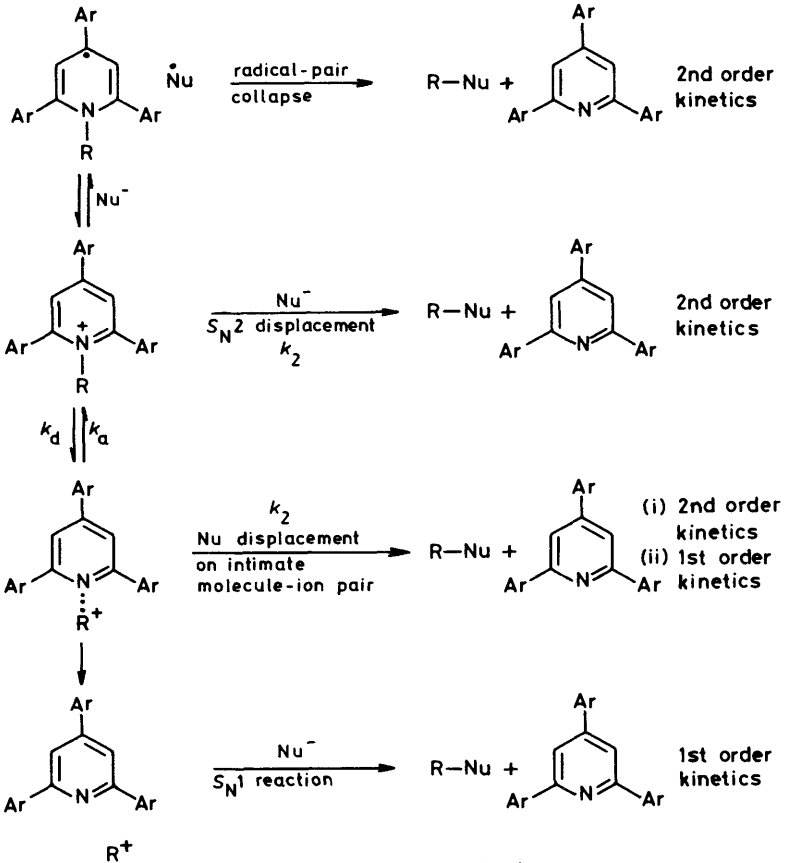
[25] L. Weisler and R. W. Helmkamp, *J. Am. Chem. Soc.*, 1945, **67** , 1167.
[26] (*a*) N. Kornblum, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 734; (*b*) *cf.* N. Kornblum, S. C. Carlson, and R. G. Smith, *J. Am. Chem. Soc.*, 1979, **101**, 647.
[27] G. A. Russel, J. Bershberger, and K. Owens, *J. Am. Chem. Soc.*, 1979, **101**, 1312.

C. Absolute Comparisons of Kinetic Rates and Activation Parameters— A straight comparison of the second-order rate-constants in dimethyl sulphoxide at 25 °C for the reaction of 1-benzyl-2,4,6-triphenylpyridinium cations with piperidine and with the anion from 2-nitropropane shows that the former is 1.16×10^{-4} $l\,mol^{-1}\,s^{-1}$ whereas the latter is $3.30\ l\,mol^{-1}\,s^{-1}$. Such a large difference in rates would not be expected, particularly in the direction shown, if both reactions are going by the same mechanism.[19]

Moreover, the activation parameters are quite different. We find for the S_N2 reaction with piperidine a $\Delta S^{\neq}$ of -26 ± 2, whereas for the radicaloid reaction with a nitronate anion a $\Delta S^{\neq}$ of -58 ± 2.

12 Conclusions

Evidence has been presented in this review that nucleophilic displacement of *N*-substituents in pyridinium cations can proceed by the five mechanisms shown in Scheme 9. Only time will tell how far these conclusions apply to nucleophilic



Scheme 9 *Nucleophilic substitutions with pyridine leaving groups*

displacements at sp^3-hybridized carbon atoms in general. However, the results discussed here certainly suggest that we must take very seriously the concept of competitive distinct individual pathways for nucleophilic substitution reactions.

Acknowledgements. We thank all our co-workers mentioned in the References, and particularly Drs. M. Lopez-Rodriguez and K. Sakizadeh. A.R.K. is grateful to many colleagues who have vigorously discussed these results with him where he has presented them and to Professor W. le Noble for his collaboration with the pressure measurements.