KINETICS AND MECHANISMS OF NUCLEOPHILIC DISPLACEMENTS AT sp^3 HYBRIDIZED CARBON ATOMS WITH HETEROCYCLIC LEAVING GROUPS

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Abstract - Following a description of experimental methods, kinetic results are summarized, dealing successively with 2nd order and 1st order rates. In each of these sections, studies of product formation are described, followed by the effects of leaving group (steric and electronic), alkyl group structure, solvent, nucleophile and temperature. Finally, overall conclusions are presented together with the outlook for further work.

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I. INTRODUCTION

A. POSSIBLE MECHANISMS

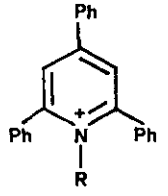
The discovery that pyrylium mediated conversions of primary amino groups in aliphatic amines to other functionality constituted a preparative method of considerable synthetic value[1] initiated a search for better leaving groups (see Chart 1). The first kinetic measurements were originally carried out to assess the leaving ability of different heterocyclic rings, and much preparatively useful information was thus obtained. For example, it was ascertained that nucleofugacity increased markedly for (1) < (2) < (3) and later preparative work has utilised compounds of type (2) and (3) extensively. However, it rapidly became clear that mechanistically the reactions also had considerable interest.[2]

The vast majority of mechanistic studies on nucleophilic substitution reactions at sp^3 hybridized carbon atoms have been carried out with negatively charged leaving groups such as tosylates or halides. The substrate is thus neutral at the beginning of the reactions, and during an S_N1 type reaction charge is created. This means that such reactions do not usually take place in non-polar solvents, and in the polar solvents where they can be studied there have been perennial difficulties in distinguishing between the nucleophilicity and the polarity of the solvent.

By contrast, reactions we shall be considering here involve neutral leaving groups. Thus, the substrates to begin with are positively charged and in an S_N1 type reaction no charge is created. In consequence, S_N1 type reactions can occur in non-polar solvents where nucleophilic participation by solvent can be excluded. This simplifies considerably the interpretation of the detailed reaction mechanism and allows identification of reactions which proceed via ion - molecular pair intermediates (which correspond to ion-pair intermediates for neutral substrates). Moreover, the positively charged substrates used here offer the possibility of electron transfer for a negatively charged nucleophile, and such S.E.T. reactions have been identified.[3]

The possible types of reaction paths are shown in Scheme 1 and have already been discussed.[2] As will become apparent during this review, the present work offers powerful evidence for the operation of separate unimolecular and bimolecular nucleophilic substitution reaction mechanisms, and does not support the view of a continuous spectrum of reactions spanning S_N2 to S_N1.

Chart 1.



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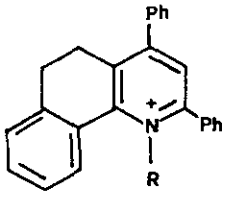

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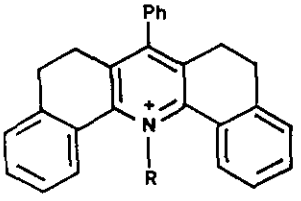

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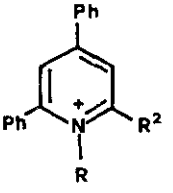
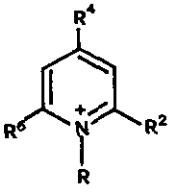


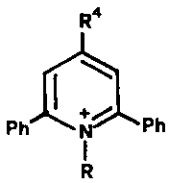
R^2	
(4)	H
(5)	Me
(6)	i-Pr
(7)	t-Bu
(8)	o-$O_2NC_6H_4$
(9)	2-Pyridyl
(10)	3-Pyridyl
(11)	N-Oxido-2-pyridyl
(12)	Benzothiazol-2-yl
(13)	Benzimidazol-2-yl
(14)	2-Thienyl
(15)	$CONHBu^n$
(16)	CO_2Et



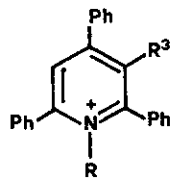
	R^2=R^6	R^4
(17)	2-Thienyl	Ph
(18)	i-Pr	Ph
(19)	CO_2Et	p-MeC_6H_4

Designation of N-substituents (R) in compounds (1)-(58)

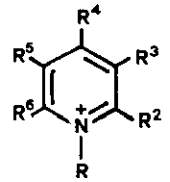
(a)	Benzyl	(o)	i-Propyl	(bb)	p-$MeC_6H_4CH_2$
(b)	Methyl	(p)	s-Butyl	(cc)	m-$MeC_6H_4CH_2$
(c)	Ethyl	(q)	2-Pentyl	(dd)	p-$FC_6H_4CH_2$
(d)	n-Propyl	(r)	2-Heptyl	(ee)	p-$ClC_6H_4CH_2$
(e)	n-Butyl	(s)	3-Methyl-2-butyl	(ff)	m-$ClC_6H_4CH_2$
(f)	n-Pentyl			(gg)	p-$O_2NC_6H_4CH_2$
(g)	n-Hexyl	(t)	3-Pentyl	(hh)	p-$MeOC_6H_4CH_2$
(h)	n-Heptyl	(u)	$CH_2CH=CH_2$	(ii)	2-Furyl-CH_2
(i)	n-Octyl	(v)	$CH_2CH=CHCH_3$	(jj)	2-Pyridyl-CH_2
(j)	CH_2CHMe_2	(w)	cyclo-Propyl	(kk)	3-Pyridyl-CH_2
(k)	$CH_2CHMeEt$	(x)	cyclo-Butyl	(ll)	4-Pyridyl-CH_2
(l)	neo-Pentyl	(y)	cyclo-Pentyl	(mm)	CH_2CO_2Et
(m)	CH_2-cyclo-Propyl	(z)	cyclo-Hexyl	(nn)	1-Phenylethyl
(n)	CH_2-cyclo-Hexyl	(aa)	cyclo-Heptyl		



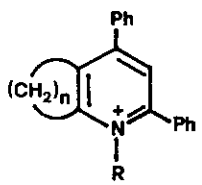
	R^4
(20)	p-$MeOC_6H_4$
(21)	p-MeC_6H_4
(22)	p-FC_6H_4
(23)	p-ClC_6H_4
(24)	p-BrC_6H_4
(25)	m-ClC_6H_4
(26)	m-BrC_6H_4
(27)	m-$O_2NC_6H_4$
(28)	4-Pyridyl
(29)	CO_2Et



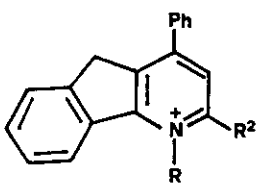
	R^3
(30)	Me
(31)	Et
(32)	Ph



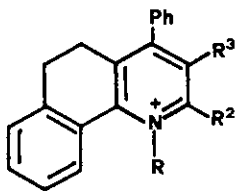
	R^2	R^3	R^4	R^5	R^6
(33)	Ph	Ph	H	Ph	Ph
(34)	Ph	Ph	Ph	H	Ph
(35)	H	H	Ph	H	H



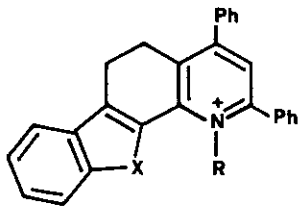
	n
(36)	3
(37)	4



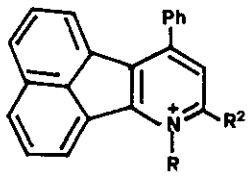
	R^2
(38)	Ph
(39)	t-Bu



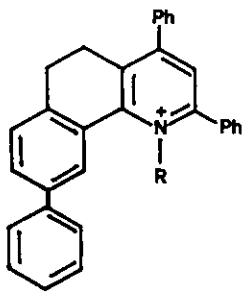
	R^2	R^3
(40)	Ph	Et
(41)	Ph	Ph
(42)	t-Bu	H
(43)	Et	Me
(44)	Me	H
(45)	Benzothiazol-2-yl	H



	X
(46)	S
(47)	NH



	R^2
(48)	Ph
(49)	t-Bu



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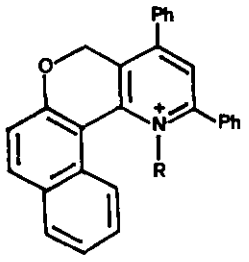

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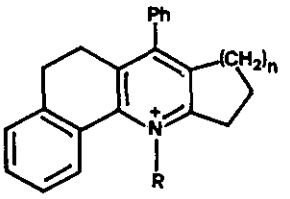
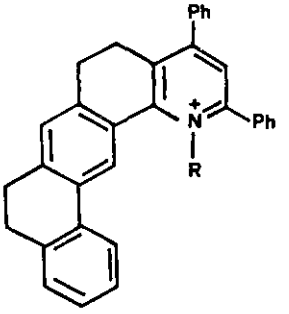


	n
(55)	1
(56)	2



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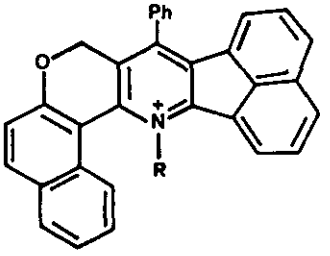

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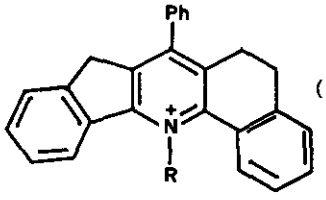

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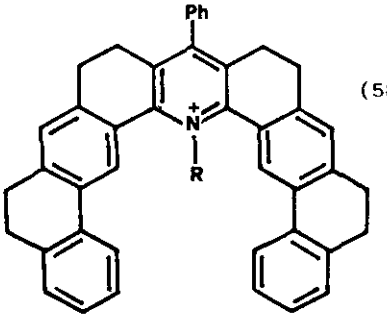

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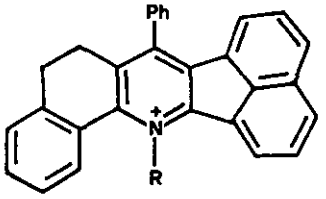

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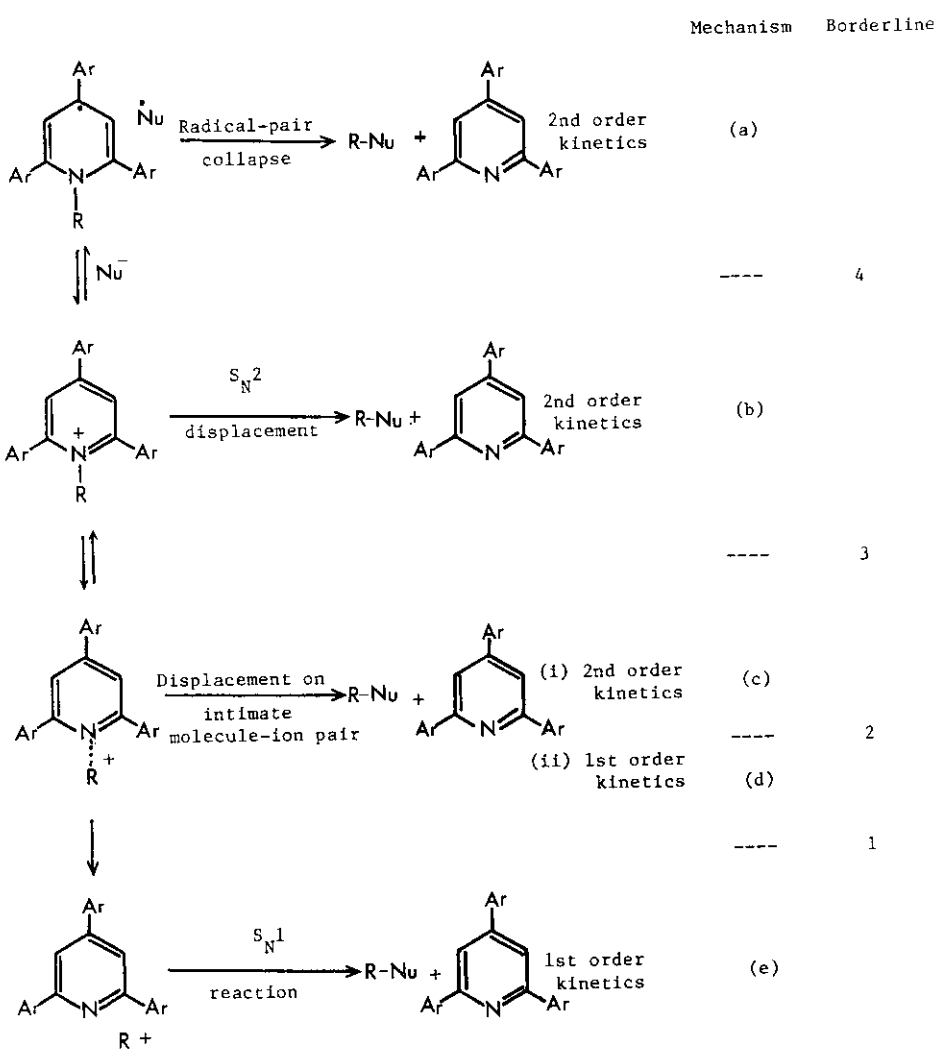
Scheme 1


Mechanism
Borderline
Radical-pair collapse
R-Nu
2nd order kinetics
(a)
Nu⁻

4
S_N2 displacement
R-Nu
2nd order kinetics
(b)

3
Displacement on intimate molecule-ion pair
R-Nu
(i) 2nd order kinetics
(c)

2
(ii) 1st order kinetics
(d)

1
S_N1 reaction
R-Nu
1st order kinetics
(e)

B. SCOPE AND ARRANGEMENT OF REVIEW

This review covers work carried out up until 1984, but it omits work on radicaloid and electron transfer reactions,[3] and also kinetic work carried out in aqueous solution.[4] After consideration of experimental methods, we discuss bimolecular (S_N2 type) reactions in which the nucleophile is implicated in the transition state, and then unimolecular S_N1 types.

C. EXPERIMENTAL METHODS

1. Preparation of Compounds

The preparative aspects of these reactions and particularly the preparation of the starting pyridinium salts have been reviewed up to 1980 in reference 2, and up to 1984 in reference 5.

2. The Spectrophotometric Method

Kinetics were followed by monitoring the decrease of absorbance of the pyridinium cation at a fixed wavelength.[6] In typical runs under pseudo-first-order conditions the concentration of pyridinium was either 1.6×10^{-3} or 3.2×10^{-5} mol l^{-1}, while that of nucleophile varied from approximately 10^{-4} to 1.0 mol l^{-1}. Pseudo-first-order rate constants were calculated from the slope of conventional plots of $\ln[a/(a-x)] = \ln[(\epsilon_1-\epsilon_2)/(\epsilon-\epsilon_2)]$ with ϵ_1 and ϵ_2 depicting the extinction coefficients of the pyridinium and of the pyridine at the kinetic wavelength) *vs.* time. Such plots are usually linear to at least 80% completion. Under pseudo-first-order conditions ([nucleophile] > 10[substrate]) k_{obs} values are equal within experimental error for substrate concentrations varied 50 times for a variety of different substrates at different temperatures.[7] Second-order rate constants were calculated as the slopes of the plots of k_{obs} *vs.* nucleophile concentrations. In many cases these plots passed through the origin within the experimental uncertainty indicating that the reactions were accurately first order in nucleophile. However,in other cases, a significant intercept on the y-axis (interpreted as a first order rate) was observed, indicating a reaction component zeroth-order in nucleophile. Examples of both possibilities are provided in Figures 1 and 2.

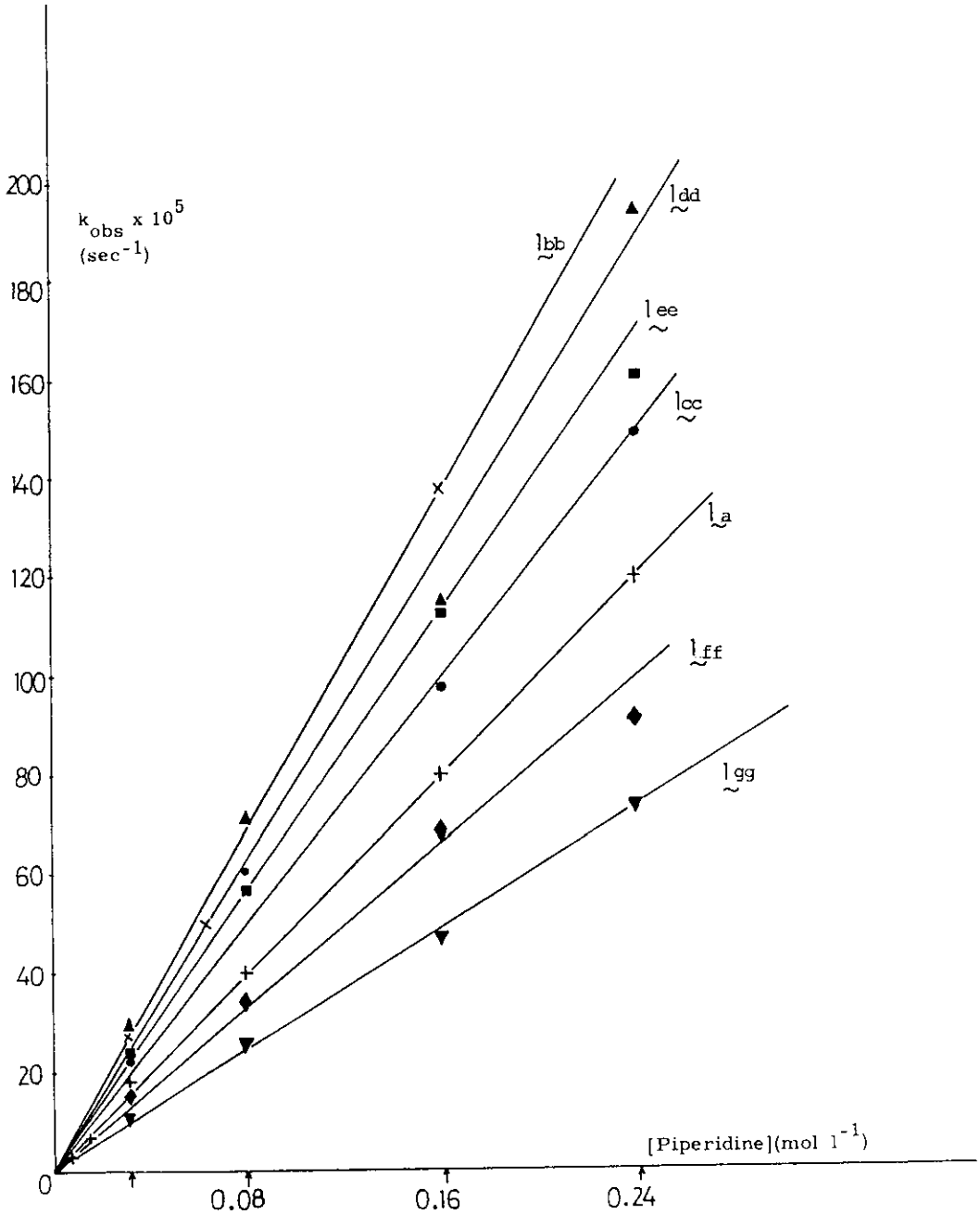


Fig. 1. Plot of observed rate constants ($k_{obs.}$) vs piperidine concentration for the reaction of 2,4,6-triphenyl-1-(substituted benzyl)pyridinium cations (1a, 1bb-1gg) with piperidine in chlorobenzene at 100 °C.

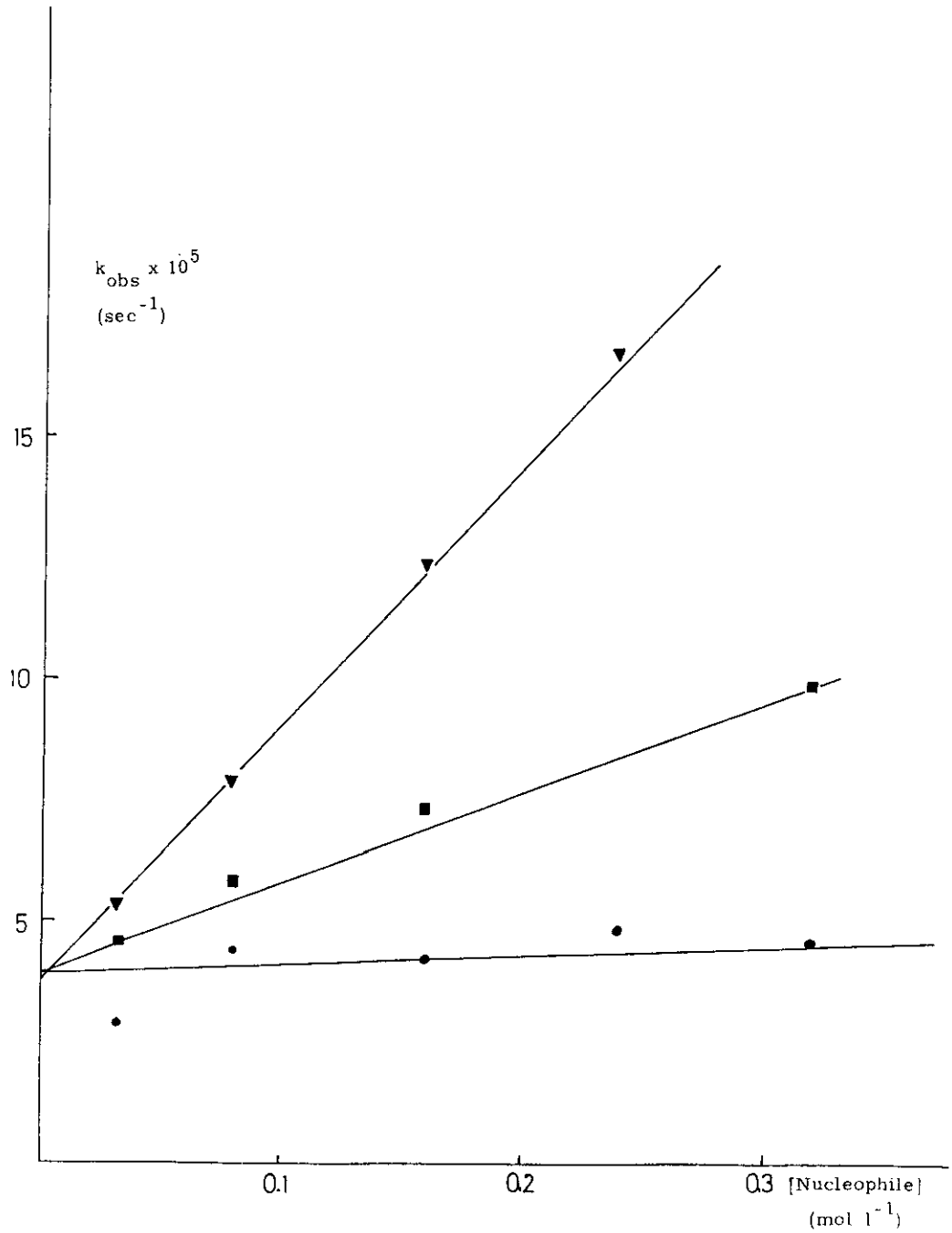


Fig. 2. Plot of pseudo first order rate constants ($k_{obs.}$) vs nucleophile concentration for reactions of 1-p-methoxy benzyl 2,4,6-triphenylpyridinium tetrafluoroborate in chlorobenzene solution with piperidine (▼), morpholine (■), and pyridine (●) at 40 °C.

3. The Conductimetric Method

The reaction was followed by monitoring the decrease in conductivity with time. The conductivity at infinite time (G infinite) was nearly equal to that of chlorobenzene (G_{PhCl}) and close to zero. Observed rate constants under pseudo-first-order conditions (k_{obs}) were calculated from equation 1:

$$k_{obs} = 1/t[\ln (G_o/G)] \quad (1)$$

Eight compounds have been studied by both the UV and conductivity methods. In all cases the k_2 second-order rate constants from both methods agreed within the experimental error.[8]

4. Association and Dissociation of Substrates

Vapor pressure measurements on the N-benzyl derivatives (1a)-(3a) and on the N-(n-octyl) (3i) provided information on the aggregation of these compounds.[9] In all cases, at the concentrations used for the kinetic measurements the compounds existed as ion pairs in chlorobenzene solution, with negligible association to more highly aggregated species.

II. SECOND-ORDER RATES

A. STUDIES OF PRODUCT FORMATION

Table 1 gives details of some of the preparative reactions that have been carried out with amine nucleophiles to give substitution products: they cover a wide range of N-alkyl groups, nucleofuges, and nucleophiles.

B. EFFECT OF THE LEAVING GROUP

1. Monocyclic Pyridines

Rate constants for the reactions of N-benzyl monocyclic pyridiniums with piperidine in chlorobenzene at 100°C are given in Table 2. Entries 1-11 show the effect of variation in the 2-substituent while holding the 4,6-diphenyl substitiuents constant. Compared with hydrogen as the 2-substituent (4a, Entry 2) a 2-methyl group reduces the rate significantly in (5a, Entry 3) but a 2-t-butyl group has very little effect on the rate, of (7a, Entry 4). This finding is in contrast both with experimental rates for the demethylation of 2-substituted pyridinium cations and with molecular mechanics calculations, which indicate large steric effects for t-butyl substituents in the 2 position.[23-25]

Table 1. Reactions of Pyridinium Cations with Neutral Nucleophiles

Entry No.	Substr.	N-Subst.	Nucleophile	[Nu]/[Sub.]	Solvent	Reaction Time (h)[a]	t °C	Substitution Product (%)
1	(1a)	$C_6H_5CH_2$	pyridine	21	pyridine	4	115	88[b,c]
2			2-picoline	28	2-picoline	48	128	91[b,c]
3			3-picoline	28	3-picoline	48	144	72[c]
4			4-picoline	28	4-picoline	6	145	81[b,c]
5			piperidine	20	piperidine	6	106	85[b,c]
6			morpholine	14	morpholine	6	129	92[b,c]
7			DABCO[d]	1.1	chlorobenzene	2	132	92[e]
8			aniline	13	aniline	5 min	184	76[c]
9	(1b)	Me	pyridine	-	pyridine	-	115	84[f]
10	(1e)	n-Bu	pyridine	-	pyridine	-	115	90[f]
11	(1o)	i-Pr	pyridine	6	pyridine	3	115	63[g]
12	(1p)	s-Bu	pyridine	6	pyridine	3	115	56[g]
13	(1bb)	p-$MeC_6H_4CH_2$	pyridine	26	pyridine	16	115	94[c]
14			piperidine	35	piperidine	6	106	79[c]
15			morpholine	29	morpholine	6	129	96[c]
16			DABCO[d]	1.1	chlorobenzene	2	132	99[e]
17	(1ee)	p-$ClC_6H_4CH_2$	pyridine	27	pyridine	4	115	92[c]
18			morpholine	14	morpholine	6	129	88[c]
19			DABCO[d]	1.1	chlorobenzene	2	132	95[e]
20	(1hh)	p-$MeOC_6H_4CH_2$	pyridine	7	pyridine	30 min	100	84[h]
21	(1ii)	furfuryl	pyridine	-	pyridine	-	115	61[b]
22	(1jj)	2-pyridylmethyl	pyridine	29	pyridine	24	115	49[c]
23			4-picoline	25	4-picoline	22	145	55[c]
24			isoquinoline	16	isoquinoline	12	140	92[c]
25			piperidine	31	piperidine	14	106	90[c]
26			morpholine	26	morpholine	14	129	23[c]
27	(1kk)	3-pyridylmethyl	pyridine	29	pyridine	20	115	97[c]
28			4-picoline	25	4-picoline	12	145	32[c]
29			isoquinoline	16	isoquinoline	18	110	86[c]
30			piperidine	14	piperidine	14	106	20[c]
31			morpholine	12	morpholine	14	129	28[c]

Table 1 (continued)

Entry No.	Substr.	N-Subst.	Nucleophile	[Nu]/[Sub.]	Solvent	Reaction Time (h)[a]	t °C	Substitution Product (%)
32	(111)	4-pyridylmethyl	pyridine	29	pyridine	14	115	75[b,c]
33			4-picoline	113	4-picoline	14	145	70[c]
34			isoquinoline	12	AcOH	12	242	83[c]
35			piperidine	14	piperidine	14	106	82[c]
36			morpholine	23	morpholine	1	129	70[b,c]
37	(2a)	$C_6H_5CH_2$	pyridine	-	pyridine	-	115	84[f]
38			piperidine	-	piperidine	-	106	80[f]
39			morpholine	-	morpholine	-	129	88[f]
40			hexamine	2	chloroform	12	61	95[f]
41	(2b)	Me	pyridine	-	pyridine	-	115	92[f]
42			piperidine	-	piperidine	-	106	96[f]
43			DABCO[d]	1.1	chlorobenzene	2	132	98[e]
44			hexamine[i]	2	chloroform	12	61	75[e]
45	(2e)	n-Bu	pyridine	-	pyridine	-	115	96[f]
46			morpholine	-	morpholine	-	129	66[f]
47	(2bb)	p-$MeC_6H_4CH_2$	hexamine[i]	2	chloroform	12	61	92[e]
48	(2ee)	p-$ClC_6H_4CH_2$	hexamine[i]	2	chloroform	12	61	94[e]
49	(2kk)	3-pyridylmethyl	hexamine[i]	2	chloroform	12	61	77[e]
50	(3a)	$C_6H_5CH_2$	pyridine	-	pyridine	-	115	96[f]
51			morpholine	-	morpholine	-	129	91[f]
52	(3b)	Me	pyridine	-	pyridine	-	115	84[f]
53	(3c)	Et	DABCO[d]	1.1	chlorobenzene	2	132	70[e]
54	(3e)	n-Bu	pyridine	-	pyridine	-	115	98[f]
55			morpholine	-	morpholine	-	129	71[f]
56	(7a)	$C_6H_5CH_2$	pyridine	-	pyridine	-	115	74[e]
57			piperidine	-	piperidine	-	106	62[e]
58	(7b)	Me	pyridine	-	pyridine	-	115	75[e]

[a] Except where otherwise stated; [b] From ref. 10; [c] From ref. 11; [d] DABCO = 1,4-diazabicyclo[2,2,2]octane; [e] From ref. 12; [f] From ref. 13; [g] From ref. 14; [h] From ref. 15; [i] hexamine = hexamethylenetetramine.

Table 2. Second-order Rate Constants (k_2, l mol^{-1} sec^{-1}) for the Reactions of N-Benzyl- and N-Alkyl-pyridiniums with Piperidine in Chlorobenzene at 100 °C.

Entry	Compound	R^2	R^3	R^4	R^5	R^6	$k_2 \times 10^3$	Ref.
1	(1a)	Ph	-	Ph	-	Ph	4.94	6,16
2	(4a)	-	-	Ph	-	Ph	0.93	8
3	(5a)	Me	-	Ph	-	Ph	0.119	17,18
4	(7a)	t-Bu	-	Ph	-	Ph	1.07	17,18
5	(8a)	o-$O_2NC_6H_4$	-	Ph	-	Ph	8.82	19
6	(9a)	2-pyridyl	-	Ph	-	Ph	18.0	19
7	(10a)	3-pyridyl	-	Ph	-	Ph	11.2	19
8	(11a)	N-oxido-2-pyridyl	-	Ph	-	Ph	6.70	19
9	(12a)	benzothiazol-2-yl	-	Ph	-	Ph	316[a]	19
10	(13a)	benzimidazol-2-yl	-	Ph	-	Ph	43.5	19
11	(14a)	2-thienyl	-	Ph	-	Ph	8.19	19
12	(1c)	Ph	-	Ph	—	Ph	0.0306	20
13	(12c)	benzothiazol-2-yl	-	Ph	-	Ph	0.45	21
14	(1o)	Ph	-	Ph	-	Ph	0.14	16,22
15	(12o)	benzothiazol-2-yl	-	Ph	-	Ph	1.40	21
16	(17a)	2-thienyl	-	Ph	-	2-thienyl	19.9	19
17	(20a)	Ph	-	p-$MeOC_6H_4$	-	Ph	3.16	6,16
18	(21a)	Ph	-	p-MeC_6H_4	-	Ph	4.40	19
19	(22a)	Ph	-	p-FC_6H_4	-	Ph	5.70	19
20	(23a)	Ph	-	p-ClC_6H_4	-	Ph	6.89	19
21	(24a)	Ph	-	p-BrC_6H_4	-	Ph	7.24	19
22	(25a)	Ph	-	m-ClC_6H_4	-	Ph	6.74	19
23	(26a)	Ph	-	m-BrC_6H_4	-	Ph	9.15	19
24	(27a)	Ph	-	m-$O_2NC_6H_4$	-	Ph	9.06	19
25	(28a)	Ph	-	4-pyridyl	-	Ph	11.3	19
26	(30a)	Ph	Me	Ph	-	Ph	0.82	17,18
27	(31a)	Ph	Et	Ph	-	Ph	8.0	17
28	(32a)	Ph	Ph	Ph	-	Ph	1.62	17
29	(33a)	Ph	Ph	-	Ph	Ph	1.64	17
30	(34a)	Ph	Ph	Ph	-	Ph	1.62	8
31	(35a)	-	-	Ph	-	-	0.27	8

[a] Extrapolated value.

A 2-phenyl group (1a, Entry 1) gives a significant rate acceleration, which is somewhat greater for 2-o-nitrophenyl (8a), 2-(2'-thienyl) (14a), and 2-(3'-pyridyl) (10a) (Entries 5, 11, 7). 2-(2'-Pyridyl) (9a) is significantly faster than 2-phenyl (1a), but the 2-(N-oxido-2-pyridyl) (11a) hardly at all, (cf Entries 6 and 8). Fastest of all are 2-(benzimidazol-2-yl) (13a) and 2-(benzothiazol-2'-yl) (12a) (Entries 9 and 10).

These results indicate that steric acceleration can occur, and we believe that this is the reason why the 2-phenyl group produces acceleration relative to hydrogen. However, a methyl group evidently causes steric hindrance to the reaction, and with tertiary butyl the steric effect is apparently almost same on the ground and the transition state. The phenyl group tends to become coplanar with the pyridine ring to enhance overlap: the steric acceleration would thus be maximized; however, steric hindrance in the ground state twists the phenyl group out of the plane. Such twisting will be less for a 2'-thienyl group, a 2'-pyridyl group, and especially 2'-benzothiazolyl and 2'-benzimidazolyl groups. In addition, the inductive electron-withdrawing effects of these groups increase the reaction rate. This can also be seen for the 3'-pyridyl group, and evidently is important for the o-nitrophenyl. In the N-oxide-2'-pyridyl group, however, the electronic effect is evidently offset by hindrance to planarity.

Table 2, Entries 17-25 shows rate variations induced by a substituent in a 4-phenyl group. Electron-withdrawing groups increase and electron-donor groups decrease the rate relative to the unsubstituted 4-phenyl derivative: the effects, however, are small. A quantitative treatment gives a reasonable correlation with Hammett sigma values (r 0.950, rho 0.46). The low rho value demonstrates the insensitivity of the displacement reaction towards substitution in the 4-phenyl group: the reaction centre is far from the structural modification. The rate for the 4-(4'-pyridyl) compound (28a) fits well into the Hammett plot (Entry 25).[19]

If a further substituent is placed at the 3-position of 1-benzyl-2,4,6-triphenylpyridinium cation, the rate of reaction is significantly decreased when the 3-substituent is a methyl or a phenyl group (Table 2, Entries 26, 28). The steric effect of an ortho-substituent is usually enhanced by an additional substituent in the adjacent meta-position. This is known as buttressing. In previous examples, buttressing has invariably influenced rates in a direction corresponding to an enhanced steric size of the group. In clear contrast, simple buttressing has a rate reducing effect in the present series. Almost certainly

this is because the 3-methyl or 3-phenyl substituent causes the 2-phenyl group to twist out of the plane of the ring, and therefore to be less effective in steric acceleration. This can be considered a manifestation of the "gear effect"[25,27] defined as conformational transmission caused by the interaction between polyhedral substituents.

It is clear that no single substituent parameter can describe the steric effects of substituents in influencing the rates of the present reactions.The steric shape of substituents can be conveniently described by the five Verloop parameters,[28] which provide the substituent length (L) and the distances (B_1-B_4) in four directions along two axes orthogonal to each other and to the L axis, and the treatments of this type are more successful (see section II. C. 3).

As is shown in section II. E, alpha-ethoxycarbonyl groups cause considerable rate accelerations, but in this case piperidine cannot be used as a nucleophile.

2. Pyridiniums fused to One Other Ring

Rates are shown in Table 3. Keeping the 2,4-diphenyl substituents constant, a fused 5,6-trimethylene system (36a) has a rate very similar to that for a 6-methyl group, whereas the corresponding tetramethylene derivative (37a) reacts at double the rate (cf Entries 1 and 2). This once again demonstrates the sensitivity of the steric acceleration to the precise shape of the adjacent group.

Preventing the 6-phenyl group from moving out of the plane has a large rate enhancing effect in the indeno derivative (38a), and still larger in the dihydronaphtho derivative (2a), but in the 5,6-acenaphtheno derivative (48a) the rate is actually smaller than for the 2,4,6-triphenylpyridine analogue (see Table 3, Entries 3, 4, 12).

The pendant phenyl group in compound (50a) decreases the rate by a factor of 3 (Entry 14). Considerable rate decreases are also found (Entries 5,6) for the insertion of 3-ethyl or 3-phenyl groups into the 2,4-diphenyl-5,6-dihydronaphtho derivatives as in (40a) and (41a): further examples of the negative buttressing effect that was already discussed for the monocyclic series.

Entries 15-17 of Table 3 provide some comparisons for N-butyl compounds for cases where it was not possible to prepare the N-benzyl analogues. The substitution of the 2-(2'-benzothiazolyl) group for 2-phenyl in this series has relatively little effect on the rate (Entry 16). The rather rigid tetracyclic fusion found in compound (52e) causes a considerable rate reduction relative to

Table 3. Second-order Rate Constants (k_2, 1 mol^{-1} sec^{-1}) for the Reactions of N-Substituted Pyridinium and Related Cations with Piperidine in Chlorobenzene at 100 °C (Compounds with Pyridinium Ring Fused to One Other Ring).

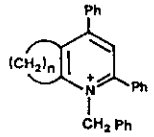
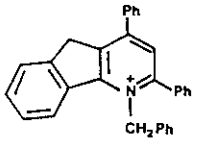
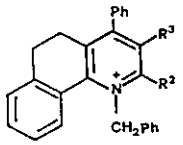
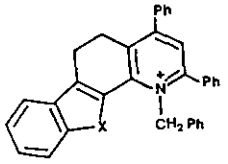
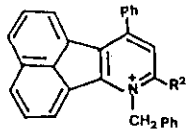
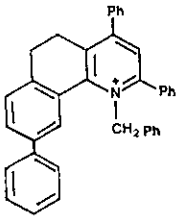
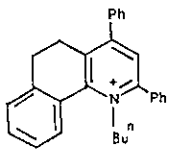
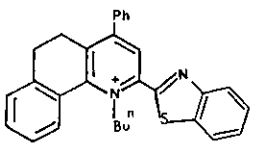
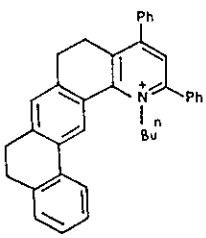
	Entry	Comp.	n		$k_2 \times 10^3$	Ref.
	1	(36a)	3		0.220	17,18
	2	(37a)	4		0.431	17,18
	3	(38a)			106	17
			R^2	R^3		
	4	(2a)	Ph	H	343	17
	5	(40a)	Ph	Et	25.5	17
	6	(41a)	Ph	Ph	15.8[a]	17
	7	(42a)	t-Bu	H	608[a]	17
	8	(43a)	Et	Me	8.1	17
	9	(44a)	Me	H	3.31	17
			X			
	10	(46a)	S		92	21
	11	(47a)	NH		69	21
			R^2			
	12	(48a)	Ph		0.98	29
	13	(49a)	t-Bu		0.39	29

Table 3 (continued)

Entry	Comp.	$k_2 \times 10^3$	Ref.
	14 (50a)	93.8	30
	15 (2e)	0.69	20
	16 (45e)	1.5	21
	17 (52e)	0.037	30

[a] Extrapolated value.

(2e), presumably because of additional steric hindrance in the transition state (cf Entry 17).

3. Pyridiniums with Additional Rings Fused in Both the 2,3 and the 5,6 Positions

Available results are summarized in Table 4. The bis-dihydronaphtho derivative (3a) has a very fast rate, which is considerably reduced in the analogue containing one less CH_2 group (53a) and much further where one of the ring fusions has been replaced by an acenaphtheno group (54a) (cf Entries 1-3). However, in the nonacyclic derivative (58e, Entry 8), the comparison with the reactivity of the n-butyl pentacyclic analogue (3e) (see Table 5) indicates approximately the same activation. The marked difference to the behavior of (2e) and (52e) discussed above again emphasizes the non additivity of steric effects.

Where the rings are fused on one side to dihydronaphtho and on the other side to cycloalkane ring, much slower rates are found, but again the compound with 6-membered ring fusion (56a) is faster than the analogue with the 5-membered ring fusion (55a) (Entries 4 and 5).

The one example of ring fusion with an oxygen-containing ring (57a, Entry 6) indicates that this could be a favourable feature in increasing rates of reaction.

C. *DEPENDENCE OF S_N2 RATES ON ALKYL GROUP STRUCTURE*

1. Comparisons of Rates for Heterocycle Displacement with those for Anionic Leaving Groups

Second-order rate constants are given in Table 5. The tricyclic series (2) is the most complete and the discussion will concentrate on this. The generally accepted[34,35] order for S_N2 rates with anionic leaving groups such as halide, sulfonate, etc., is:

benzyl > allyl > methyl > primary alkyl > secondary alkyl >> neopentyl.

However, in the series now under discussion, e.g. (2), we find the sequence:

benzyl > allyl > methyl = secondary alkyl > primary alkyl = neopentyl

That this modified rate sequence applies to many of the present leaving groups is supported by the less complete data for series (1), (3), (12), and (46).

Within the series of primary alkyl groups, the rate sequence for n-butyl, i-butyl and cyclohexylmethylene (compounds e, j, n) in both series (2) and (3) are in good agreement with those for the reactions of alkyl bromides with chloride ion

Table 4. Second-order Rate Constants (k_2, 1 mol^{-1} sec^{-1}) for the Reactions of N-Substituted Pyridinium and Related Cations with Piperidine in Chlorobenzene at 100 °C (Compounds with Pyridinium Ring Fused to Two Other Rings).

Entry	Compound	n	$k_2 \times 10^3$	Ref.
1	(53a)	1	223	17,18
2	(3a)	2	4446[a]	17
3	(54a)		13.4	27
4	(55a)	1	0.532	17
5	(56a)	2	1.34	17
6	(57a)		85.4	29
7	(3e)		2.41	20
8	(58e)		2.2	30

[a] Extrapolated value.

Table 5. *Second-order* Rate Constants (k_2, 1 mol^{-1} sec^{-1}) for the Reactions of N-Substituted Pyridinium Cations in Series (1)-(3), (12), and (46) with Piperidine in Chlorobenzene.

		Series (1)		Series (2)		Series (3)		Series (12)		Series (46)	
	N-Subst.	(100 °C)		(100 °C)		(100 °C)		(100 °C)		(60 °C)	
	(R)	$k_2 \times 10^3$	Ref.	$k_2 \times 10^3$	Ref.	$k_2 \times 10^3$	Ref.	$k_2 \times 10^3$	Ref.	$k_2 \times 10^3$	Ref.
(a)	Benzyl	4.94	6,16	343	17	4446[a]	17	316	19	-	-
(b)	Me	0.60	20	5.02	20	24.90	20	-	-	3.7	21
(c)	Et	0.0306	20	1.32	20	6.70	20	0.45	21	4.4	21
(d)	n-Pr	-	-	0.49	20	2.75	20	-	-	-	-
(e)	n-Bu	-	-	0.69	20	2.41	20	0	0	5.3	21
(f)	n-pentyl	-	-	0.14[b]	20	1.99	20	-	-	-	-
(g)	n-hexyl	0.008	20	0.098[b]	20	3.05	20	-	-	-	-
(h)	n-heptyl	-	-	0.106[b]	20	2.51	20	-	-	-	-
(j)	CH_2CHMe_2	-	-	0.0564	31	0.72	31	-	-	-	-
(k)	$CH_2CHMeEt$	-	-	0.0458	31	0.40	31	-	-	-	-
(l)	neo-pentyl	0.008	20	0.13[b]	20	-	-	-	-	-	-
(m)	CH_2-c-propyl	-	-	3.01	31	3.62	31	-	-	-	-
(n)	CH_2-c-hexyl	-	-	0.0453	31	0.307	31	-	-	-	-
(o)	i-Pr	0.140	6,22	2.77	20	-	-	1.4	21	8.5	21
(p)	s-Bu	0.11	6,22	17	20	-	-	-	-	-	-
(q)	2-pentyl	-	-	13	32	-	-	-	-	-	-
(r)	2-heptyl	-	-	27	32	-	-	-	-	-	-
(s)	3-Me-2-butyl	-	-	3	32	-	-	-	-	-	-
(t)	3-pentyl	-	-	11	32	-	-	-	-	-	-
(u)	CH_2-CH=CH_2	0.97[c]	20	47	20	56.2	20	-	-	-	-
(v)	CH_2-CH=CH-CH_3	2.98	33	140[a]	33	-	-	-	-	-	-
(x)	c-butyl	-	-	0.0593	14	-	-	-	-	-	-
(y)	c-pentyl	0.15	20	1	14	-	-	-	-	-	-
(z)	c-hexyl	0.020	20	0.1	14	-	-	-	-	-	-
(aa)	c-heptyl	-	-	5	14	-	-	-	-	-	-

[a] Extrapolated value. [b] Kinetics were followed up to 30% conversion only. [c] Kinetics were followed up to 45% conversion only.

in acetone-water[36] and with methoxide in methanol.[37] Second order rate constants for cyclopropylmethyl compounds (2m and 3m), however, are higher than those of the analogous cyclohexylmethyl derivatives (2n and 3n), in contrast with the usual rate enhancement on increasing the ring size from 3 to 6 observed for the S_N2 reactions of bromomethyl-cycloalkanes with methoxide[37] and thiophenoxide[38] ions.

Within the series of secondary alkyl groups, the S_N2 reaction is swamped by fast S_N1 reaction for the N-cyclopentyl (1y), N-cyclohexyl (1z) and N-cycloheptyl (1aa) derivatives. For the cyclobutyl analogue (1x) the much slower S_N1 rate enables the S_N2 rate for this compound, although itself very slow, to be measured.[14]

2. Comparison of Relative Rates Within the Heterocyclic Series

The S_N2 reaction of the pentacyclic derivatives (3) is invariably faster than that of the tricyclic analogues (2),[17,20] however, the rate enhancement varies widely for different N-substituents.

We have compared relative rates, based on Et = 1, for these series with literature data for halide leaving groups (Table 6). Compared to the ethyl analogues:

(a) Methyl in series (2) and (3), and allyl in series (3), react more slowly than typical.

(b) Straight chain primary alkyl derivatives react at approximately the same rate as expected.

(c) Benzyl in series (2) and (3), sec-alkyl, and neo-pentyl react faster than expected.

For benzyl, the tricyclic or pentacyclic leaving groups are respectively faster by ca. 70 and 900 times, compared to the 2,4,6-triphenylpyridinium analogue, but these rate enhancements vary widely for other groups. Thus allyl shows enhancements of 48 and 58, methyl 8 and 42, ethyl 43 and 220. These factors are related to the overall steric requirements of the N-substituents.[20] Thus allyl and ethyl both respond much more than methyl to the change from (1) to (2), but methyl and ethyl respond much more than allyl to the second annulation involved in going from (2) to (3). A much higher rate increase (up to 30 times) due to the second annulation is found for n-pentyl, n-hexyl and n-heptyl groups. The biggest enhancements are found for benzyl. Thus, the enhancement in rate for primary alkyl groups tends to increase with the bulk of the alkyl groups. For the

Table 6. Second-order Rates Relative to the Corresponding Ethyl Derivative for the Reactions of N-Alkyl- and N-Benzyl-pyridiniums 1-3 with Piperidine in Chlorobenzene at 100 °C and for the Reactions of Benzyl and Alkyl Halides with Nucleophiles.

	1	2	3	4	5	6	7	8	9	10	11
Alkyl	Ser.1[a]	Ser.2[a]	Ser.3[a]	RI	RBr	RI	RBr	RBr	RCl	RBr	RLG
Nucleophile	pip.	pip.	pip.	PhO^-[b]	EtO^-[c]	NEt_3[d]	Cl^-[e]	Br^-*[h]	KI[g]	MeO^-[h]	Nu[i]
(a) Benzyl	161	245	664	-	-	-	-	-	80	-	120
(b) Me	20	3.8	3.7	4.5	18	11	3.7	76	80	9.0	30
(c) Et	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
(d) n-Pr	-	0.37	0.41	0.39	0.31	0.19	0.69	0.65	0.43	0.37	0.4
(e) n-Bu	-	0.50	0.36	0.36	0.23	0.14	-	-	0.40	0.37	0.4
(f) n-Pentyl	-	0.11	0.30	0.16	0.20	-	-	-	0.53	-	-
(g) n-Hexyl	<0.3	0.07	0.50	0.34	-	-	-	-	0.52	-	-
(h) n-Heptyl	-	0.08	0.37	0.33	-	0.10	-	-	0.50	-	-
(j) i-Bu	-	0.043[j]	0.11[j]	0.14	-	-	0.03	-	-	0.074	0.03
(k) 2-Me-1-Bu	-	0.035[j]	0.061[j]	-	-	-	-	-	-	-	-
(l) neo-Pentyl	<0.3	0.10	-	-	0.0042	-	6×10^{-6}	10^{-5}	-	-	10^{-5}
(m) CH_2-c-Prop.	-	2.3[j]	0.54[j]	-	-	-	-	-	-	-	-
(n) CH_2-c-Hexyl	-	0.034[j]	0.46[j]	-	-	-	-	-	-	-	-
(o) i-Pr	4.6	2.1	-	0.34	-	0.02	0.02	0.01	0.008	-	0.025
(p) s-Bu	3.6	13	-	0.38	-	-	-	-	0.008	-	-
(u) Allyl	32[h]	35	8.4	-	-	-	-	-	32	-	40
(v) γ-Me-allyl	-	106[k]	-	-	-	-	-	-	-	-	-

[a] From ref. 20, except where otherwise stated. [b] In dry EtOH at 42.5 °C; from: D. Segaller, J. Chem. Soc., 1919, 103, 1154; 1914, 105, 106. [c] In dry EtOH at 55 °C; from: C.K. Ingold, 'Structure and Mechanism in Organic Chemistry', Bell; London, 1969, 2nd edn. pp. 432-436; I. Dostrovsky, E.D. Hughes, J. Chem. Soc., 1946, 157; M.L. Dhar, E.D. Hughes, C.K. Ingold, S. Masterman, Ibid. 1948, 2055. [d] In acetone at 100 °C, from: ref. 34, p. 435 and N. Menschutkin, Z. Phys. Chem., 1980, 5, 589. [e] In DMF at 25 °C, from: S. Hartshorn, "Aliphatic Nucleophilic Substitution"; Cambridge University Press; Cambridge, 1973, p. 32. [f] In acetone at 25 °C, from: ref. 34, p. 436 and P.B.D. De la Mare, J. Chem. Soc., 1955, 3180. [g] In acetone at 50 °C, from: J. Hine, "Physical Organic Chemistry", 2nd Ed.; McGraw Hill; New York, 1962, p. 176; J.B. Conant, R.E. Hussey, J. Am. Chem. Soc., 1925, 47, 476; J.B. Conant, W.R. Kirner, R.E. Hussey, Ibid., 1925, 47, 488. [h] In MeOH at 80 °C, from: K. Okamoto, I. Nitta, T. Imoto, H. Shingh, Bull. Soc. Chem. Japan, 1967, 40, 1905. [i] Average relative rates of alkyl systems from ref. 35a. [j] From ref. 31. [k] Extrapolated value, from ref. 33.

secondary alkyl groups, the effect of annulation is greater on s-butyl than i-propyl. Stable pentacyclic compounds of series (3) cannot be prepared with secondary alkyl N-substituents, because of spontaneous fast S_N1 reaction.

3. Statistical Treatment of Rate Variations

Kinetic data on the S_N2 reactivity, with variation of both the alkyl and the nucleofuge in these and other conventional bimolecular substitutions (i.e. the logarithms of second-order rates relative to ethyl for reactions 1-10 in Table 6) were used for multivariate statistical analysis. Principal component analysis (PCA) allowed the study of the simultaneous dependence of S_N2 rates on both alkyl group structure and leaving group nucleofugacity.[31] The PCA analysis of a data matrix reporting log k_2 for the S_N2 reactions 1-10 in Table 6 provided a one PC model describing 70% of the total variance, confirming previous findings on the leaving group ability of quinoliniums (2) and acridiniums (3) as compared to halides and differentiating N-alkyl groups capable of resonance delocalization and secondary alkyls from primary alkyls. As Table 6 shows, groups larger than ethyl (where it is size near to the point of attachment that is significant) tend to react faster than expected, those smaller than ethyl more slowly.

By contrast, no correlation exists between log k_2 for series (1)-(3) and the Taft E_s parameters.[39] Whereas a single parameter could measure the bulk of substituents, it cannot measure the shape of the substituents, and changing shape with constant bulk may well affect different reactions in a different way, as shown by numerous literature examples.[26] Thus, the 3-fold symmetry of the methyl group in pyridines was needed to rationalize both the quaternization kinetics and the conformational preference in isopropyl derivatives.[27] In the present case, the shape of N-alkyl substituents was accounted for using the recently developed method of partial least squares (PLS) analysis.[31] PLS has several advantages over the usual multiple regression analysis (MRA), the usual approach of physical organic chemistry. PLS needs none of the assumptions of MRA, i.e., that all the variables are independent, error free, relevant to the specific problem, and the absence of non-random grouping of the data points, (for a detailed comparison of the above statistical methods, see ref. 31).

The relative reactivity in the quinolinium series was described as a function of eight structural parameters ("descriptors") for the alkyls, which indicate electronic (sigma*),[40] steric effects in terms of size (E_s)[39,40] and shape (the

five Verloop parameters),[28] and polarizability (MR)[40] of each alkyl linked to the carbon atom undergoing substitution. The results of the PLS analysis provided further support for the importance of the steric shape of branched primary alkyls (as measured by the Verloop parameters) in such nucleophilic displacements.

4. Effect of Substituents in the N-Benzyl Group

We have also investigated the effect of para-substituents in the benzyl group on the rates of various N-benzyl substituted systems (Table 7). 1-(p-Methoxybenzyl)- (1hh) and 1-(2-furfuryl)-pyridinium (1ii) react by S_N1 and S_N2 mechanisms, the proportion of S_N1 increasing with temperature, while other 1-(substituted benzyl) derivatives show only S_N2 reaction.[15,41] No quantitative relationship was found between log k_2 and sigma, $sigma_R^o$ and $sigma^+$ substituent parameters in series (1)[15], the Hammett plot showing a pronounced curvature for the p-methoxybenzyl (hh) and furfuryl (ii) derivatives which, in both series (1) and (5) react much faster than the unsubstituted derivatives (a) (see Table 7). p-Methyl substitution causes a low rate increase in all the examined series, while the reactivities of the p-chloro compounds (ee) do not differ significantly from those of the unsubstituted derivatives (a), being slightly higher in series (1), (5) and (7), and lower in series (3) and (44) (Table 7).

5. Effect of N-(alpha-Alkoxycarbonylalkyl) Groups

N-Alkoxycarbonylpyridinium salts such as (1mm) proved extraordinarily unreactive towards nucleophiles,[42] in contrast with the activation towards nucleophilic substitution shown for halogen atoms by alpha ethoxycarbonyl groups.[43] Thiourea gave mixtures, approximate rate measurements with piperidine in chlorobenzene indicated rates much less than, for example, the N-benzyl analogue (1a). We believe that this low reactivity towards nucleophilic displacement is due to stereolectronic reasons. Activation by the ethoxycarbonyl group is believed to involve overlap of an approaching nucleophile with the C=O pi^* orbital.[35] Examination of models shows that the ethoxycarbonyl group is constrained by the 2,6-diphenyl groups so that the C=O pi-orbital is orthogonal to the N-CH_3 sigma orbital. Hence, an approaching nucleophile cannot interact simultaneously with both the sigma N-C and the pi^* C=O orbitals.

D. COMPARISON OF LEAVING GROUP NUCLEOFUGACITY WITH THAT OF HALOGENS

Second-order rate constants for the reaction of N-benzylpyridiniums (2a) and (3a) with thiourea in MeOH at 35 °C [20] are respectively 600 and 15 times lower than that of benzyl bromide,[44] showing the pentacyclic pyridinium to be a leaving group somewhat poorer than bromide.

The second-order rate constant for the reaction of benzyl chloride with piperidine at 80 °C in dimethylformamide is 0.0555 (l mol^{-1} sec^{-1}),[45] while those for the analogous reactions of the tricyclic and pentacyclic derivatives (2a) and (3a) at 80 °C, in chlorobenzene are respectively 0.0966 and 1.96 (l mol^{-1} sec^{-1}).[17] The second-order rate constant for the reaction of the monocyclic derivative (1) with piperidine at 100 °C in chlorobenzene was found to be twice that in dimethylformamide.[6] Hence, we concluded that in the reaction with piperidine at 80 °C, the tricyclic compound (2) is a leaving group as good as chloride, while the pentacyclic (3) is considerably better than chloride when attached to benzyl.[20] Support for this hypothesis was provided by the PCA parameters for the different reactions (variables).[31] In the b_1 values (the "loadings"), which can be related to the leaving group ability of the nucleofuge, showed that the tricyclic (2) and pentacyclic (3) nitrogen heterocycles are as good as chloride ion and somewhat poorer than bromide in leaving group activity.

E. RATE DATA FOR PYRIDINIUMS CONTAINING RING ETHOXYCARBONYL GROUPS

Results obtained at 100 °C with N,N'-dimethylthiourea as nucleophile[8] (Table 8) show that replacement of an alpha-phenyl in (1a) by an ethoxycarbonyl group to give (16a) causes an increase in k_2 by a factor of 38; no significant part of the reaction proceeds by the S_N1 route. With pyridine, (16a) again shows an increase in k_2 by a factor of ca. 40 compared to (1a).[6]

When both the alpha-phenyl groups of (1a) are replaced by ethoxycarbonyl to give (19a), the reaction rate at 100 °C is too fast for convenient measurement, but comparison with piperidine as nucleophile at 30 °C, with those for the triphenylpyridinium (1a) at 40 °C,[17] indicates an increase in k_2 for (1a) by a factor of ca. 2300.[8] Replacement of the gamma-phenyl in (1a) by an ethoxycarbonyl group to give (29a) leads to smaller rate increase (ca. 12 at 60 °C).

Quantitative assessment of the effect of the replacement of alpha-phenyl in (1a) by a carbamido group (compound 15a) is difficult because of curvature in the rate plots; however, initial rates indicate a rate reduction by a factor of ca. 4,

Table 7. Second-order Rate Constants for the Reactions of N-Substituted Benzylpyridinium and Related Cations with Piperidine in Chlorobenzene.

		Series (1) (100 °C)		Series (3) (30 °C)		Series (4) (60 °C)		Series (5) (100 °C)		Series (7) (100 °C)	
	Ar	$k_2 \times 10^3$	Ref.	$k_2 \times 10^3$	Ref.	$k_2 \times 10^3$	Ref.	$k_2 \times 10^3$	Ref.	$k_2 \times 10^3$	Ref.
(a)	C_6H_5	4.94	6,16	105	17	36.3	17	0.119	17	1.07	17
(bb)	p-MeC_6H_4	8.52	15	133	41	75.8	41	0.191	41	6.01	41
(cc)	m-MeC_6H_4	6.04	15	-	-	-	-	-	-	-	-
(dd)	p-FC_6H_4	7.81	15	-	-	-	-	-	-	-	-
(ee)	p-ClC_6H_4	6.11	15	70.6	41	29.4	41	0.191	41	1.68	41
(ff)	m-ClC_6H_4	3.70	15	-	-	-	-	-	-	-	-
(gg)	p-$O_2NC_6H_4$	2.96	15	-	-	-	-	-	-	-	-
(hh)	p-$MeOC_6H_4$	18[a]	15	-	-	-	-	0.510	41	-	-
(ii)	2-furyl	98[a]	15	-	-	-	-	1.16	41	-	-

[a] Extrapolated value.

Table 8. Second-order Rate Constants ($k_2 \times 10^3$, l mol^{-1} sec^{-1}) for the Reactions of Pyridinium and Related Cations with Neutral Nucleophiles in Chlorobenzene at 100°C [a].

			Nucleophile						
Comp.	R	R^2	Piperidine	Morpholine	Pyridine	2-Picoline	Thiourea	$(MeNH)_2CS$	2,6-Lutidine
(1a)	$PhCH_2$	Ph	1.87[b,c]	-	-	-	0.183[d,e]	0.147[b,c]	-
			4.94[e]	2.37[f]	0.0323[e]	0.00556[e]	-	6.53[c]	-
(1hh)[g]	p-$MeOC_6H_4CH_2$	Ph	0.549[h]	0.177[h]	0.0250[h]	-	-	-	-
(1o)	i-Pr	Ph	0.14[i]	0.064[f,i]	0.006[i]	-	-	-	-
(1p)	s-Bu	Ph	0.11[i]	0.052[f,i]	0.006[i]	-	-	-	-
(2a)	$PhCH_2$	Ph	343[j,k]	-	2.18[l]	0.48[l]	-	-	0.23[l]
(3a)	$PhCH_2$	Ph	4450[j,k]	-	31.7[l]	9.2[l]	-	-	3.3[l]
(3a)[m]	$PhCH_2$	Ph	105[k]	35.2[l]	-	-	-	-	-
(3h)	n-C_7H_{15}	Ph	2.51[i]	0.74[i]	0.013[i]	-	-	-	-
(15a)	$PhCH_2$	CONH-n-Bu	-	-	-	-	-	1.67[c]	-
(16a)	$PhCH_2$	CO_2Et	-	-	1.63[c]	-	-	250[c]	-

[a] Except where otherwise stated. [b] In sulpholane. [c] From ref. 8. [d] In $HCONHMe_2$. [e] From ref. 6. [f] From ref. 16. [g] At 40°C. [h] From ref. 15. [i] From ref. 20. [j] Extrapolated value. [k] From ref. 17. [l] From ref. 7. [m] At 30°C.

an effect opposite to that of the alpha-ethoxycarbonyl.

The large rate enhancement shown for alpha-ethoxycarbonyl (16a) is similar to that for alpha-2'-benzothiazolyl[19] (12a), and confirms that electronic as well as steric effects of substituents can influence greatly the leaving group ability of the pyridine.

F. EFFECT OF SOLVENT

Second-order rate constants for three primary and two secondary N-alkyl substrates in a range of different solvents are reported in Table 9. For the S_N2 rates of the N-benzyl (1a), N-(p-methoxbenzyl) (1hh), and N-methyl compounds (1b), factors of ca. 20 span the rates. Rates are slowest in the hydroxylic solvents, intermediate in the dipolar aprotic solvents, and fastest in the non-polar solvents. The pattern is similar for the S_N2 rates of the N-i-propyl (1o) and N-s-butyl (1p) derivatives except that rates are now as fast in the dipolar aprotic solvents as those for non-polar solvents.

In all solvents, the observed S_N2 rate sequence is analogous to that observed in chlorobenzene[6,16]: p-methoxybenzyl (1hh) > benzyl (1a) > methyl (1b) > i-propyl (1o) > s-butyl (1p), except that in protic solvents the sec-butyl derivative (1p) appears to be faster than the isopropyl compound (1o).

According to the Hughes and Ingold theory of solvent effects on the rates of nucleophilic substitutions, for the reaction of a positively charged substrate with a neutral nucleophile, a small rate decrease on increasing solvent polarity is predicted for both bimolecular and unimolecular mechanisms.[46,47] This is indeed as observed for the substrates examined (cf Table 9).

The logarithms of second-order rates for the N-benzyl and N-methyl derivatives correlate linearly with the E_T parameter.[48] The correlation is poor for the N-isopropyl, the N-s-butyl, and the N-p-methoxybenzyl compounds (r 0.65-0.75).

No significant correlations with other solvents parameters were apparent for the substrates examined. Principal component analysis of the logarithms of second-order rate constants provided three principal components (PC).[22] The first PC parameters for the solvents (the "scores" i.e. theta values) differentiate aprotic solvents from protic ones, while the second PC parameters are linearly related to the basicity parameter B. The PC parameters for the pyridinium cations (the "loadings", i.e. beta values) point out the peculiarity of rate data for the

Table 9. Second-order Rate Constants ($k_2 \times 10^3$, 1 mol^{-1} sec^{-1}) For the Reactions of N-Substituted 2,4,6-Triphenylpyridinium Cations with Piperidine in Various Solvents

	Compound, N-substituent and t (°C)				
Solvent	(1a) Me[a] (100)	(1b) CH_2Ph[b] (100)	(1o) i-Pr[a] (100)	(1p) s-Bu[a] (100)	(1hh) p-$MeOC_6H_4CH_2$[a] (40)
PhCl	0.600	4.94	0.140	0.110	0.549
o-$Cl_2C_6H_4$	-	6.56	0.0851	0.109	0.513
PhOMe	0.436	4.14	0.148	0.131	0.281
Me_2SO	0.435	3.62	0.134	0.130	0.0520
$HCONMe_2$	0.378	2.47	0.270	0.156	0.111
MeOH	-	-	-	-	0.0831
n-BuOH	0.100	0.837	0.0128	0.0190	-
1-Pentanol	-	0.777	-	-	-
$Me_2CHCH_2CH_2OH$	0.0666	0.943	0.0348	0.0655	-
$(CH_2OH)_2$	0.0254	0.359	0.0333	0.0538	-

[a] From ref. 22. [b] From ref. 6.

Table 10. Relative Second-order Rates for the Reactions of N-Alkyl- and N-Benzyl-pyridinium Salts with Neutral Nucleophiles in Chlorobenzene[a]

Comp.	N-Subst.	t (°C)	1st-order component	Piperidine	Morpholine	Pyridine	2-Picoline	2,6-Lutidine
(1a)	$PhCH_2$	100	no	153[b]	73[c]	1[b]	0.2[b]	-
(1o)	i-Pr	100	yes	23[d]	11[d]	1[d]	-	-
(1p)	s-Bu	100	yes	37[d]	17[d]	1	-	-
(1hh)	p-$MeOC_6H_4CH_2$	40	yes	22[e]	7[e]	1[e]	-	-
(2a)	$PhCH_2$	100	no	162[d]	-	1	0.22	0.11
		60		207	81	1	-	-
(3a)	$PhCH_2$	100	no/yes[f]	140[d]	-	1	0.29	0.10
		60		20[g]	-	1	-	-
		30		3[g,h]	1[h]	-	-	-

[a] k_2 Values from ref. 7, except where otherwise noted. [b] From ref. 6. [c] From ref. 16. [d] From ref. 20. [e] From ref. 15. [f] First-order component observed in the reaction with 2-picoline and 2,6-lutidine. [g] From ref. 17. [h] Relative rate with respect to morpholine.

p-methoxy derivative (1hh) (measured at 40°C) and discriminate the compounds reacting only by the S_N2 mechanism (such as 1a and b) from those exhibiting both S_N1 and S_N2 components (1o and p).

G. EFFECT OF NUCLEOPHILE

Decreasing the nucleophilicity of the nucleophile decreases the k_2 values. As shown in Table 8, rates decrease in the order piperidine, morpholine, pyridine, 2-picoline, 2,6-lutidine, as expected. The second-order rates relative to those for pyridine for these N-benzyl compounds (1a, 2a, 3a) (Table 10) are consistent with previous work.[62] For pyridine, 2-picoline and 2,6-lutidine they are similar to those found in the Menschutkin reaction with methyl iodide in nitrobenzene at 25°C (1:0.47:0.042),[49] with methyl iodide and trans-$[Pt(Py)_2Cl_2]$ in MeOH at 25°C (1:0.29:0.002)[50] and with methyl iodide in MeCN at 25°C (1:0.43:0.04)[51,52] and in DMSO at 23°C (1:0.38:0.02)[53].

Dimethylthiourea reacts with N-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate in chlorobenzene at 100°C at a rate 1.3 times that for piperidine.[8]

Dimethylthiourea has been used as nucleophile for cases where piperidine is either too volatile or reacts in a different way with the substrate.

H. EFFECT OF TEMPERATURE

Activation parameters for S_N2 reactions are shown in Table 11. The activation entropies to within experinemtal error all lie within the range -15 to -30 cal mol^{-1} K^{-1}, in agreement with the large negative values previously found for the S_N2 reaction of benzyl halides with anilines,[54-56] and with pyridine.[57] The clear differentiation between these large negative values and the much smaller negative or positive values found for the unimolecular components of these reactions (see section III G) supports the separation into S_N1 type and S_N2 type components. The origin of the S_N2 rate decrease with nucleophiles poorer than piperidine, such as pyridine for (2a) and (3a), is seen from Table 11 to be due mainly to a higher activation enthalpy.

I. EFFECT OF PRESSURE

As shown in Table 7 and discussed in section II. C. 4, at atmospheric pressure and 100°C, 1-p-methoxybenzyl-2,4,6-triphenylpyridinium perchlorate (1hh)

Table 11. Activation Parameters for the S_N2 Reactions of Pyridinium and Related Cations with Piperidine[a] in Chlorobenzene

Entry	Comp.	R	R^2	R^3	R^4	R^5	R^6	Ref.	$\Delta H^{\ddagger}_{373}$ (kcal-mol^{-1})	$\Delta S^{\ddagger}_{373}$ (cal mol^{-1} K^{-1})	$k_2 \times 10^3$ (100 °C)[a]
1	(1a)	$PhCH_2$						15,17	16.3	-26.2	4.94
2	(1bb)	p-$MeC_6H_4CH_2$						15	16.4	-24.6	8.52
3	(1hh)	p-$MeOC_6H_4CH_2$						15	13.6	-30.4	18
4	(1ii)	2-furylCH_2						15	20.0	-10[b]	98
5	(12a)	benzothiazol-2-yl		H	Ph	H	Ph	19	20.3	-7[c]	316
6	(16a)	CO_2Et		H	Ph	H	Ph	8	16.3[d]	-17.9[d]	-
7	(31a)	Ph		Ph	H	Ph	Ph	17	15.7	-29.8	1.64
8	(2a)	$PhCH_2$	Ph		H			17	15.8	-19.0	343
								7	19[e]	-20[e]	2.18
9	(2b)	Me	Ph		H			20	19.4	-17.0	5.02
10	(2o)	i-Pr	Ph		H			20	14.0	-31.0	2.77
11	(40a)	$PhCH_2$	Ph		Et			17	17.6	-19.3	25.5
12	(41a)	$PhCH_2$	Ph		Ph			17	12.4	-34.0	15.8
13	(42a)	$PhCH_2$	t-Bu		H			17	17.2	-13.8	608
14	(3a)	$PhCH_2$						17	11.4	-25.4	4446
								7	14[e]	-27[e]	31.7
15	(3ee)	p-$ClC_6H_4CH_2$						41	12.0	-26.7	70[f]
16	(3h)	n-C_7H_{15}						20	16.0	-28.2	2.51

[a] Except where otherwise stated. [b] ± 5 [c] ± 9, High error. [d] Nu = $(MeNH)_2CS$. [e] Nu = pyridine. [f] At 30 °C, k_2 for (3a) at 30 °C equal to 105×10^{-3}.

reacts with piperidine in chlorobenzene predominantly by the first-order route; however, at lower temperatures, a second order path offers increasing competition (activation enthalpy equal to = 13.6 ± 3.1 kcal/mole, vs 26.6 ± 3.6 kcal/mole for the first order path), and at 30°C it is the only one detectable.[15] A study of the effect of pressure on the second-order reactions of (1hh) with piperidine[58] showed that the reaction rate decreases with increasing pressure. A positive activation volume (18.9 ± 1 cm^3/mole) was found; the reaction remains cleanly second-order as the pressure is raised. This reaction is clearly dominated by bond cleavage, and it was postulated that the substrate undergoes heterolysis to give a pyridine-benzyl cation pair (probably in the form of a charge transfer complex) followed by rate-controlling capture with piperidine.

For the N-benzyl pentacyclic derivative(3a) the reaction rate first decreases with increasing pressure, but then passes through a minimum and then starts to increase again. This minimum is, of course, indicative of competing pathways, with opposite pressure dependence. The low pressure reaction has an activation volume of ca +22 cm^3/mole; the high pressure branch upon extrapolation back to zero pressure is found (with less precision) to have an activation volume of about -20 cm^3/mole.

This behavior has been interpreted as a way to distinguish between the classical S_N2 mechanism and an S_N2 mechanism proceeding on an intimate ion-molecule pair as proposed by Sneen,[59] who emphasized that bimolecular nucleophilic displacements of sec-alkyl tosylates and similar neutral substrates could occur at an intimate ion pair stage of the Winstein solvolysis Scheme.[60] The classical S_N2 reaction should be rate-enhanced by pressure, whereas an S_N2 reaction on an intimate ion-molecule pair which involves a pre-equilibrium of the type:
$RX^+ \rightleftharpoons R^+ + X$ is expected to be decreased by pressure.

This criterion hence indicates that both the substrates mentioned react at normal pressure by the ion-molecule pair mechanism, although as the pressure increases, the N-benzyl pentacyclic substrate (3a) changes its predominant mechanism to that of a classical S_N2 path.

III. FIRST-ORDER REACTIONS

A. PRODUCT FORMATION

Most first-order reactions have involved secondary alkyl groups and, for convenience, preparative reactions of such groups are considered here all

together. Preparatively we find that secondary alkyl groups can give unrearranged or rearranged products of nucleophilic displacement together with olefins. We also find that primary alkyl groups can give rearranged products under some conditions.

1. Formation of unrearranged products.

Although 1-(n-alkyl)-2,4,6-triphenylpyridinium salts on moderate heating failed to give olefins,[61] the corresponding 1-(s-alkyl)derivatives do give olefins in rather good yields.[14] Nevertheless,substitution reactions succeed even with relatively poor nucleophiles. Thus, on heating in pyridine the N-isopropyl (1o) and N-s-butyl compounds (1p) gave mainly substitution products in 63 and 56% isolated yield, respectively. However, for the N-cyclopentyl (1y) and N-cyclohexyl derivatives (1z), similar treatment led to greater proportions of elimination.[14] The poor yields of olefin from E1 reactions of unbranched secondary halides[62] and the relatively high proportions of olefin formed in the reactions of pyridinium cations[14] (22% or greater) suggest considerable bimolecular character.

The formation of substantial amounts of substitution products using pyridine, which is a relatively poor nucleophile, indicates that with better nucleophiles substitution should be easier. This was confirmed in experiments with sulphur nucleophiles. Pyrolysis of 1-(s-butyl)- (1p) and 1-cyclohexyl-2,4,6-triphenylpyridinium thiocyanate (1z) each gave mixtures of the corresponding s-alkyl thiocyanate and the s-alkyl isothiocyanate in ca. 70:30 ratio, in overall yields of 90 and 40%, respectively. However, mainly elimination occurred on pyrolysis of the 1-s-alkyl-pyridinium chlorides: from the 1-cyclohexyl derivative 90% of cyclohexene was isolated.[14]

The reaction of 1-phenylethylamine with various 2,4,6-triphenylpyrylium salts were studied by ^{13}C nmr.[14] In the absence of added nucleophile the main product was the alcohol PhCH(Me)OH, presumably formed by reaction of the carbonium ion with the water released in the reaction. A trace of styrene was also detected in the reaction mixture. In the presence of pyridine, the main product was the 1-phenylethylpyridinium salt. These experiments provide strong evidence for the spontaneous formation of carbonium ions in the reaction of 1-phenylethylamine and triphenylpyrylium cations. This carbonium ion and that from 1-phenylbenzylamine were trapped preparatively. Thus the use of primary or secondary alcohols as reaction solvent at 25°C led to the isolation of ethers in moderate yield. p-Cresol gave the O-alkylated product (25%) and probably also C-alkylated

products. N,N-Dimethylaniline gave a 38% yield of 1-(4-dimethylaminophenyl)-1-phenylethane. Use of a 1:5:1 mol ratio of amine : acetic acid : triethylamine without solvent resulted in the formation of 1-phenylethyl acetate or 1-phenylbenzyl acetate.

N-(2-Pentyl)- (2q) and N-(3-pentyl)-quinolinium cations (2t) were solvolysed in different solvents, and the product mixtures were analysed by ^{13}C nmr and g.l.c.-mass spectrometry.[63] In solvolysis reactions in acetic acid or 2,2,2-trifluoroethanol without an added nucleophile, no rearrangement products were observed. Thus, the 1-(2-pentyl)-5,6-dihydro-2,4-diphenylbenzo[h]quinolinium cation (2q) gave only 2-pentyl acetate and 2-pentyl 2,2,2-trifluoroethyl ether, respectively. Similarly, the 1-(3-pentyl) derivative (2t) gave only the corresponding 3-pentyl acetate and 3-pentyl ether, respectively. Some olefin (elimination reaction) was also detected by g.l.c.-mass spectrometry.

Reactions of the 2-pentyl compound (2q) and the 3-pentyl derivative (2t) in chlorobenzene in the presence of piperidine, were kinetically of first-order, and no rearrangement products were detected. Similarly, in the solvolysis in hexafluoropropan-2-ol in the presence of morpholine as nucleophile, the 2-pentyl derivative (2q) gave only the non-rearranged product N-(2-pentyl)morpholine.

Reactions of sec-alkyl-primary amines with 5,6,8,9-tetrahydro-7-phenyldibenzo[c,h]xanthylium trifluoromethanesulfonate in the nucleophilic solvents acetic acid, various alcohols, phenols, and N,N-dimethylaniline gave O- and C-(secondary alkyl) products.[64] In acetic acid, the corresponding sec-alkyl acetates were formed without rearrangement. Thus, 2- heptyl-, cycloheptyl-, 2-pentyl-, and 3-pentyl-amines gave only 2-heptyl, cyclopentyl, 2-pentyl and 3-pentyl acetates, respectively. In the corresponding primary alcohols as solvent at 25°C, 2-pentyl methyl and 2-pentyl ethyl ethers were produced from 2-pentylamine and similarly, 3-pentyl methyl and 3-pentyl ethyl ethers from 3-pentylamine. Use of phenol and p-cresol gave mixtures of O- and C-alkylated compounds.

2. Formation of Rearranged Products.

Reactions of N-sec-alkyl quinoliniums (2) without external nucleophiles in solvents of low nucleophilicity, such as trifluoroacetic acid and 1,1,1,3,3,3-hexafluoropropan-2-ol gave mixtures (ca. 50%) of rearranged and non-rearranged products.[63] The reactions were followed with time: the ratio of the two products was constant. Thus, solvolyses of 1-(2-pentyl)-5,6-dihydro-2,4-

diphenylbenzo[h]quinolinium (2q) in trifluoroacetic acid and in 1,1,1,3,3,3-hexafluoropropan-2-ol gave mixtures of 2-pentyl and 3-pentyl trifluoroacetates, and of 2-pentyl and 3-pentyl 1,1,1,3,3,3-hexafluoroisopropyl ethers respectively. Similarly reactions carried out starting from the 1-(3-pentyl) derivative (2t) afforded mixtures identical with those formed from the 1-(2-pentyl) analogue (2q) as shown by g.l.c.-mass spectrometry and ^{13}C studies.

The n-propyl-, n-pentyl-, and n-octyl-acridiniums (3d), (3f), and (3i) solvolyzed in CH_3OD and CH_3CO_2D to give mixtures of normal and rearranged products, none of which contained deuterium and therefore were not formed via olefin intermediates.[65] Methanolysis of the iso-butyl compound (3j) occurred via olefin, but the acetolysis also involved an important non-olefinic pathway yielding iso-butyl and sec-butyl acetates. Methanolysis products from the neo-pentyl derivative (3l) were heavily deuterated, but acetolysis yielded undeuterated neo-pentyl acetate as well as deuterated tert-pentyl acetate. The proportions of the products formed in these reactions were calculated using GC/MS.

B. EFFECT OF LEAVING GROUP AND N-SUBSTITUENT FOR TERTIARY ALKYL GROUPS

S_N1 rates for pyridiniums with tertiary alkyls as N-substituents have been determined.[66] The solvolysis of N-triphenylmethylpyridinium tetrafluoroborate in methanol and ethanol at 20°C was too fast for the UV technique. The solvolysis rates for N-(1-adamantyl)-, N-(t-butyl)- and N-(1-methyl-1-phenylethyl)-pyridinium perchlorates were measured at various temperatures in different solvents. The first-order rate constant for the solvolysis in water at 190°C of the 1-adamantyl derivative was found to be 0.77×10^{-4} (sec^{-1}), while first-order rates for the t-butyl and for the 1-methyl-1-phenylethyl analogues extrapolated under the same conditions, showed the latter substrates to be faster by factors of 24 and 25,000 respectively.[66] Changing the solvent from water to acetic acid produced small variations on the solvolysis rates of all three substrates.

C. EFFECT OF LEAVING GROUP AND N-SUBSTITUENT FOR SECONDARY ALKYL GROUPS

Table 12 compares the S_N1 rates for the compounds investigated. The benzoquinoline (2) is a better S_N1 leaving group than triphenylpyridine (1) for these secondary alkyl substituents by factors of ca. 100. N-sec-Alkyl derivatives (3) react spontaneously at 20°C (see section III.A.1): rough calculations indicate that the S_N1 rate ratio (3):(2) must be greater than 1000.[20] Table 12 shows also

Table 12. First-order Rate Constants (k_1,sec^{-1}) for the Reactions of N-sec-Alkylpyridinium Cations in Series (1) and (2) with Piperidine in Chlorobenzene at 100°C[a].

		Series (1)			Series (2)		
	N-Substituent	$k_1 x 10^5$	k_1/k_1(i-Pr)	Ref.	$k_1 x 10^5$	k_1/k_1(i-Pr)	Ref.
(o)	i-Pr	0.72	1	22	112	1	20
(p)	s-Bu	3.20	4.4	16,22	330	2.9	20
(q)	2-Pentyl	-	-	-	311	2.8	32
(r)	2-Heptyl	-	-	-	398	3.6	32
(s)	3-Methyl-2-Butyl	-	-	-	553	4.9	32
(t)	3-Pentyl	-	-	-	539	4.8	32
(x)	cyclo-Butyl	-	-	-	3.29	0.03	14
(y)	cyclo-Pentyl	25.4	35	20	1110	9.9	14
(z)	cyclo-Hexyl	3.10	4.3	20	505	4.5	14
(aa)	cyclo-Heptyl	-	-	-	1090	9.7	14

[a] k_1 for (46o) at 60 °C equal to $8.5 x 10^{-5}$, ref. 21.

Table 13. Comparison of S_N1 Rate Constants for Reactions of N-cycloalkylpyridiniums with those for Cycloalkyl Tosylates

	Absolute rates ($k_1 \times 10^5$, s^{-1})			Relative rates (Me_2CHX = 1)		
Leaving group	OTs	Triphenyl-pyridine	Benzo-quinoline	OTs	Triphenyl-pyridine	Benzo-quinoline
Solvent	AcOH	PhCl	PhCl	AcOH	PhCl	PhCl
t (°C)	60	100	100	60	100	100
Reference	67,68	20	14	67,68	20	14
Me_2CHX	0.98	0.72	112	1	1	1
$(CH_2)_3CHX$	13.8	-	3.29	14	-	0.03
$(CH_2)_4CHX$	15.8	25.4	1110	16	35	10
$(CH_2)_5CHX$	0.98	3.1	505	1	4	5
$(CH_2)_6CHX$	30.5	-	1090	31	-	10

a small rate increase in series (2) in the order i-Pr, s-Bu, 2 pentyl, 2-heptyl and a further rate increase from 2- to 3-pentyl.[32]

Comparisons with the solvolysis rates (at 60°C) in acetic acid of secondary tosylates (Table 13), shows for the isopropyl, cyclopentyl and cyclohexyl substrates a rough correspondence with those for the corresponding triphenylpyridinium cations (at 100°C). However, the small difference in rate between the cyclopentyl and cyclobutyl tosylates[67,68] contrasts with the much slower relative rate for cyclobutyl among the benzoquinoliniums (2); this could indicate an S_N2 character for the tosylate solvolysis.[69] The rates are similar for the cyclopentyl and cycloheptyl derivatives, both for series (2), and for the tosylates. The rates for the cyclohexyl analogues (Table 13) are lower, by small factors for the heterocyclic leaving groups, and by somewhat larger ones for the tosylates.

The reaction of the di-isopropyl derivative (18nn) with piperidine occurs predominantly by the bimolecular route at 60°C, but mainly by S_N1 at 100°C. The temperature coefficients for the S_N1 reactions are larger than those for S_N2.[15]

All the N-(alpha-methylbenzyl) derivatives show faster S_N1 rates than 1-sec-butyl-2,4,6-triphenylpyridinium (1p), but the factors vary considerably: 540, 50, 1.2 for (6nn), (18nn) and (36nn) respectively.[33] As expected (6nn) is faster than (18nn); the rather slow rate for (36nn) underlines the small steric influence of the five membered fused ring. The S_N2 rate of (36nn) is at 100°C ca. 20 times as fast as that[20] for the N-benzyl analogue (36a).

D. EFFECT OF LEAVING GROUP AND N-SUBSTITUENT FOR PRIMARY ALKYL AND BENZYL

First order rate constants for primary alkyl groups are shown in Table 14. In most cases only an upper limit can be given as the rates are very low indeed. The highest k_1 values are found for the CH_2-cyclopropyl derivative m in both series (2) and (3). The n-butyl compounds (45e),[21] (46e),[21] (51e),[29] (52e),[30] and (58e)[30] show hardly significant S_N1 rates, as already observed for the corresponding derivatives (2e) and (3e) (Table 14).

Available data for first-order reactions of N-benzyl derivatives are collected in Table 15. Again, in many cases only an upper limit can be given because the reaction goes mainly by the second order mechanism. However, it is clear that there are two structural features which favour the first-order rates: an alpha-tertiary butyl group in (7a), (42a), (49a) and a cyclo-penteno in (38a)

Table 14. First-order Rate Constants ($k_1 \times 10^5$, sec^{-1}) for the Reactions of N-(Primary Alkyl) Pyridinium and Related Cations in Series (2) and (3) with Piperidine in Chlorobenzene at 100°C.

	N-Substituent	Series (2)	Series (3)	Ref.
(b)	Me	<23	<26	20
(c)	Et	<1.1	<11	20
(d)	n-Pr	<0.2	<0.5	20
(e)	n-Bu	<2.5	<12	20
(f)	n-Pentyl	2.58	<0.5	20
(g)	n-Hexyl	0.62	<0.7	20
(h)	n-Heptyl	4.58	<1.5	20
(j)	CH_2CHMe_2	<0.1	<1	31
(k)	$CH_2CHMeEt$	<0.1	0	31
(l)	neo-Pentyl	<0.92	-	-
(m)	CH_2-cyclo-Propyl	29.1	27.2	31
(n)	CH_2-cyclo-Hexyl	<0.1	<0.3	31
(u)	$CH_2CH=CH_2$	<3.5	<16	20

and (53a) (or indeno, but not azanaphthalino) fused ring. Examination of the individual rates and limits indicates that both these features probably increase the first order rate by a factor of around 10. A significant S_N1 component ($k_1 = 10^{-9}$, s^{-1}) was observed for the reaction of the alpha-ethoxycarbonyl compound (16a) with pyridine;[8] alpha-ethoxycarbonyl substituents, however, increase still more the S_N2 rates (cf. Section II.E).

First-order rate constants for reactions of N-(substituted benzyl)- and N-furfuryl-pyridiniums are shown in Table 16. The S_N1 rate is enormously increased for the p-methoxybenzyl and 2-furfuryl derivatives. Again, a tert-butyl group in the alpha position produces significant rate increases in series (7), (39), and (42).

Table 15. First-order Rate Constants (k_1, sec^{-1}) for the Reactions of N-Benzyl-pyridinium and Related Cations with Piperidine in Chlorobenzene at 100 °C.

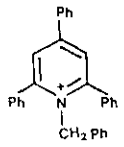
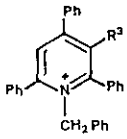
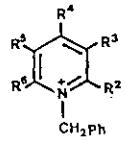
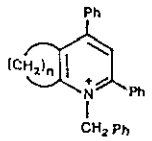
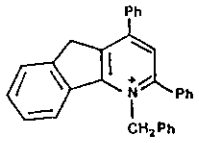
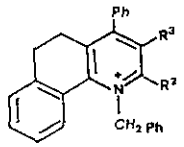
	Entry	Comp.						$k_1 \times 10^5$	Ref.
			R^2						
	1	(1a)	Ph					<2	17
	2	(4a)	H					<2	8
	3	(5a)	Me					<1	17
	4	(7a)	t-Bu					8.0	17,18
			R^3						
	5	(30a)	Me					<5	17
	6	(31a)	Et					<30	17
	7	(32a)	Ph					<3	17
			R^2	R^3	R^4	R^5	R^6		
	8	(33a)	Ph	Ph	H	Ph	Ph	<5	17
	9	(34a)	Ph	Ph	Ph	H	Ph	<3	8
	10	(35a)	H	H	Ph	H	H	<1	8
			n						
	11	(36a)	3					<2	17
	12	(37a)	4					5.10	17,18
	13	(38a)						11.2	17
			R^2	R^3					
	14	(2a)	Ph	H				<2[a]	17
	15	(40a)	Ph	Et				<3	17
	16	(41a)	Ph	Ph				<4[a]	17
	17	(42a)	t-Bu	H				6.2[a]	17
	18	(43a)	Et	Me				<3	17
	19	(44a)	Me	H				<25	17

Table 15 (continued)

Entry	Comp.		$k_1 \times 10^5$	Ref.
		X		
20	(46a)	S	<18	21
21	(47a)	NH	<13[a]	21
		R^2		
22	(48a)	Ph	0.035	29
23	(49a)	t-Bu	0.40	29
24	(50a)		<5	30
		n		
25	(53a)	1	52	17
26	(3a)	2	<1[b]	17
27	(54a)		<8	29
		n		
28	(55a)	1	<3	17
29	(56a)	2	<9	17
30	(57a)		10.2	29

[a] At 60 °C. [b] At 30 °C.

Table 16. First-order Rate Constants (k_1,sec^{-1}) for the Reactions of N-Substituted Benzyl- and N-Furfuryl-pyridinium and Related Cations with Piperidine in Chlorobenzene.

	Series (1)			Series (5)[a]		Series (7)[a]		Series (39)[b]		Series (42)[b]	
N-Subst.	$k_1 \times 10^5$		Ref.	$k_1 \times 10^5$	Ref.	$k_1 \times 10^5$	Ref.	$k_1 \times 10^5$	Ref.	$k_1 \times 10^5$	Ref.
(a) $C_6H_5CH_2$	<2[a]	-	17	<1	17	8.0	17	-	-	6.2	17
(bb) p-$MeC_6H_4CH_2$	<2.5[a]	-	15	<0.4	41	123	41	-	-	297	41
(ee) p-$ClC_6H_4CH_2$	<15[a]	-	15	0	41	<5	41	-	-	4.8	41
(hh) p-$MeOC_6H_4CH_2$	5300[a]	54[b]	15	23.1	41	-	-	33	41	-	-
(ii) 2-FurylCH_2	2400[a]	39[b]	15	17.7	41	-	-	146	41	-	-

a At 100°C. b At 60°C

Table 17. First-order Rate Constants ($k_1 \times 10^5$, sec^{-1}) for the Reactions of N-Substituted 2,4,6-Triphenylpyridinium Cations with Piperidine in Various Solvents.[a]

	Compound, R		
	(1o), i-Pr	(1p), s-Bu	(1hh), p-Me-$C_6H_4CH_2$
	at 100°C	at 100°C	at 40°C
Solvent			
PhCl	0.717	3.20	3.56
o-$C_6H_4Cl_2$	0.620	1.58	3.75
PhOMe	0.800	3.60	5.75
Me_2SO	13.0	22.3	8.22
$HCONMe_2$	4.91	10.2	8.41
MeOH	-	-	9.26
n-BuOH	3.11	5.06	-
$Me_2CHCH_2CH_2OH$	2.93	3.40	-
$(CH_2OH)_2$	1.88	3.44	-

a From ref. 22.

E. EFFECT OF SOLVENT

Available data is gathered in Table 17. The first-order rates for the isopropyl and s-butyl derivatives (1o and 1p) are higher in dipolar aprotic solvents such DMSO and DMF, and lower for protic solvents and for aprotic solvents of low polarity. The p-methoxybenzyl compound (1hh) again exhibits the highest S_N1 rates for dipolar aprotic solvents, but here the rate variation with solvent is very low: in all solvents measured, rates are of the same order of magnitude.

The presence of a first-order component in the rates for the reactions of (1o), (1p), and (1hh) with piperidine in various solvents does not depend on the solvent, and is thus characteristic of the substrate. The logarithms of the first-order rate constants show no satisfactory correlation with any solvent parameter.

Data for the first-order rates of N-substituted tricyclic derivatives (2) with neutral nucleophiles in various solvents at 100^0C are shown in Table 18.

Reactions in the presence of piperidine (in chlorobenzene, acetonitrile, or chloroform) or pyridine (in 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoropropan-2-ol) under pseudo-first-order conditions showed good straight lines to at least 80% completion.[63] The observed rate constants ($k_{obs.}$) were independent of nucleophile concentration, demonstrating the absence of a second-order component. In the monocyclic series 1-(s-alkyl) pyridinium cations also usually react mainly by S_N1 mechanism.[16,20,32]

Table 18. First-order Rate Constants ($k_1 x10^{-5}$, sec^{-1}) for the Reactions of N-Substituted 5,6-Dihydro-2,4-diphenylbenzo[h]quinolinium Cations in Various Solvents at 100 °C.

			Compound, N-Substituent					
Solvent	Nu	Ref	(2o)	(2p)	(2q)	(2r)	(2s)	(2t)
			i-Pr	s-Bu	2-Pentyl	2-Heptyl	3-Methyl-2-Butyl	3-Pentyl
PhCl	Piperidine	20	112	330	311	398	553	539
MeCN[a]	Piperidine	63	37	104	105	117	370	222
$CHCl_3$[a]	Piperidine	63	257	436	680	805	1040	1020
2,2,2-Trifluoroethanol[a]	Pyridine	63	2.07	8.24	8.77	10.5	-	26
1,1,1,3,3,3-Hexafluoroisopropanol[a]	Pyridine	63	0.44	-	2.98	-	-	6.96

[a] Reaction carried out in sealed tubes.

F. EFFECT OF NUCLEOPHILES

First-order rate constants should not be affected by nucleophile, and the data gathered in Table 19 support this.

G. EFFECT OF TEMPERATURE

Activation parameters for the S_N1 reactions of pyridinium and related cations with neutral nucleophiles are reported in Table 20. The activation enthalpies found for the unimolecular reactions, which are higher than those of the S_N2 reaction of the same substrates (cf. Table 11), can be compared with the activation energies reported for the solvolysis of benzyl chloride in Me_2SO/water[72] (18-21 Kcal mol^{-1}) and for the solvolysis of alpha-methyl-p-methoxybenzyl chloride (17.6 Kcal mol^{-1})[73].

The activation entropies for the S_N1 reactions are close to zero and correspond to log A values in the range 12.5-14.5. These log A values are in good agreement with those found for the solvolysis of alpha-methyl-p-methoxybenzyl chloride[73] (11.7) and those for the solvolysis of substituted benzyl chlorides in Me_2SO/water mixtures[72] which are in the range 7-11. Positive activation entropies are also found for the solvolysis in water of tert-butyl and neo-pentyl halides.[74] Long[75,76] predicted positive or small negative entropies for S_N1 reactions.

IV. CONCLUSIONS AND OUTLOOK

This review has summarized the strong evidence for the existence of discrete mechanisms as outlined in Scheme 1 at the beginning. Future studies will concentrate particularly on the borderlines between the various mechanisms in this Scheme 1. There are four borderlines of particular interest:

1. The borderline where we believe competition occurs between two alternative first order reactions: d, capture by solvent or nucleophile at the ion/molecule pair stage (i.e. rate determining formation of the ion/molecule pair) and e, dissociation of the ion/molecule to give a free cation followed by further reaction with solvent or nucleophile (i.e. rate determining formation of a carbocation).

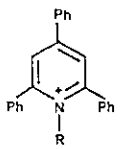
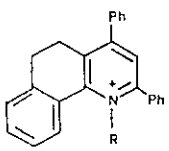
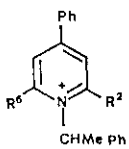
2. The borderline in reactions proceeding by the solvent or nucleophile capture of an ion/molecule pair between: c, rate-determining formation of the ion/molecule pair (i.e. unimolecular reaction mode) and d, rate-determining attack

Table 19 First-order Rates (k_1 x 10^5, sec^{-1}) for the Reactions of N-alkyl and N-(p-methoxybenzyl) Pyridinium Compounds with Neutral Nucleophiles in Chlorobenzene.

Compound	N-substituent	t(°C)	piperidine	morpholine	pyridine
(1o)	i-Pr	100	0.72[a]	0.88[a]	0.94[a]
(1p)	s-Bu	100	3.2[a]	2.9[a]	3.0[c]
(1hh)	p-$MeOC_6H_4CH_2$	40	3.56[b]	4.3[b]	3.9[b]

[a] From ref. 20. [b] From ref. 15. [c] From ref. 7.

Table 20. Activation Parameters for the S_N1 Reactions of Pyridinium and Related Cations with Piperidine in Chlorobenzene.

	Entry	Comp.		Ref.	$\Delta H^{\ddagger}_{373}$	$\Delta S^{\ddagger}_{373}$	$k_1 x 10^5$
			R				
	1	(1hh)	p-$MeOC_6H_4CH_2$	15	26.6	6.7	5290[a]
	2	(1ii)	2-FurylCH_2	15	25.4	-0.7	2400[a]
			R				
	3	(2o)	i-Pr	20	25.6	-4	112[a]
			R^2 R^6				
	4	(6nn)	Ph i-Pr	33	28	-	196[b]
	5	(18nn)	i-Pr i-Pr	33	24	-	25[b]

[a] At 100 °C. [b] At 80 °C.

on the ion/molecule pair (i.e. bimolecular reaction mode).

3. The borderline where we believe competition exists between two alternative second-order, bimolecular reactions: b, proceeding by direct displacement of nucleophile on the substrate (classical S_N2) and c, proceeding by displacement of nucleophile on the ion/molecule pair (ion/mole pair S_N2).

4. The borderline between those second-order, bimolecular reactions which proceed by b or c, the classical displacement (either on substrate or on ion/mole pair) and those which proceed by a, electron transfer. We have identified and described the electron transfer nature (non-chain radicaloid mechanism) of the reaction using nitronate anions as nucleophiles.[3]

Preliminary results[4,77] (in aqueous solution) point to small effects of charge type of the leaving group which are an indication that the conclusions from this work will be of general relevance to nucleophilic substitution reaction mechanisms at sp^3-hybridized carbon centres. Further work is proceeding.

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