Kinetics and Mechanisms of Nucleophilic Displacements with Heterocycles as Leaving Groups. Part 5.[1] Solvent Effects

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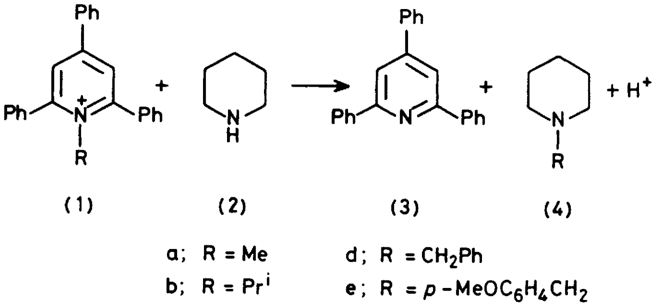
First- and second-order rates for the reactions of 1-methyl-, 1-isopropyl-, 1-s-butyl-, 1-benzyl-, and 1-*p*-methoxybenzyl-2,4,6-triphenylpyridiniums with piperidine in chlorobenzene in protic and dipolar aprotic solvents are reported. For the 1-isopropyl, 1-s-butyl and 1-*p*-methoxybenzyl derivatives the bimolecular reaction is accompanied by a unimolecular process in all solvents. Second-order rate constants for the 1-methyl and for the 1-benzyl compounds are correlated with the E_T solvent parameter. Principal component analysis of second-order rates provided a three-component model. The first component differentiates aprotic solvents from protic ones, while the second component is linearly related to the basicity parameter B for aprotic solvents.

IN Part I[2] we studied the solvent rate dependence of the transfer of the *N*-benzyl group of 1-benzyl-2,4,6-triphenylpyridinium (1d) to piperidine (2). We now report similar rates for the corresponding 1-methyl (1a), 1-isopropyl (1b), 1-s-butyl (1c), and 1-(*p*-methoxybenzyl) (1e) derivatives.



Kinetics and Mechanism.—Observed rate constants for the reactions with piperidine in various solvents of (1a—c) at 100 °C and of (1e) at 40 °C are given in Tables 1—4, respectively. In all cases plots of $k_{obs.}$ *versus* [piperidine] gave straight lines. For the 1-methyl compound (1a) these lines passed through the origin; *i.e.* $k_{obs.}$ is directly proportional to [piperidine] and the total reaction is second order (S_N2).

For the 1-isopropyl, 1-s-butyl, and 1-*p*-methoxybenzyl compounds significant intercepts were found, *i.e.*, a unimolecular component (independent of piperidine concentration) as well as the bimolecular component.

The presence of simultaneous bimolecular and unimolecular processes in such reactions was found to depend on the nature of the N-substituents[3] and on the structure of the leaving group[4] in chlorobenzene solution. The mechanistic significance of such findings has been discussed.[3,4] In our opinion they confirm the traditional S_N1–S_N2 duality in contrast to the Sneen hypothesis of unification of nucleophilic substitution mechanisms.[5] The present data, confirming the presence of a unimolecular component for the *N*-isopropyl, the *N*-s-butyl, and the *N*-*p*-methoxybenzyl derivatives in all the examined solvents, support our previous[3,4] mechanistic

TABLE 1

Observed rate constants ($10^5k_{obs.}$/s^{-1}) for the reactions of 1-methyl-2,4,6-triphenylpyridinium fluoroborate with piperidine at 100 °C [a]

	[Pip]/M			
Solvent	0.08	0.16	0.24	0.32
PhCl [b]	4.36		13.5	
PhOMe		6.52	10.2	13.5
Me_2SO	3.58	7.41		14.1
$HCONMe_2$	2.57	5.89		11.7
Bu^{n}OH	0.825	1.75	2.54	3.23
$Me_2CHCH_2CH_2OH$	0.695	1.29	1.86	2.28
$(CH_2OH)_2$	0.162	0.367	0.620	0.755

[a] Concentration of pyridinium equal to 1.6×10^{-3}M.
[b] Additional values ([Pip]/M, $10^5k_{obs.}$/s^{-1}): 0.04, 2.21; 0.477, 28.4.

TABLE 2

Observed rate constants (10^5 $k_{obs.}$/s^{-1}) for the reaction of 1-isopropyl-2,4,6-triphenylpyridinium fluoroborate with piperidine at 100 °C [a]

	[Pip]/M							
Solvent	0.04	0.08	0.12	0.16	0.24	0.32	0.36	0.48
PhCl	1.25	1.77		3.12		5.09		7.45
o-$C_6H_4Cl_2$		1.29		1.98	2.70	3.32		
PhOMe		1.90		3.29	4.36	5.49		
Me_2SO	13.2	14.0	15.4	14.9	16.2	17.2		
$HCONMe_2$		7.14	8.03		11.5		13.5	
Bu^{n}OH		3.21		3.31	3.40	3.52		
$Me_2CHCH_2CH_2OH$		3.18		3.52	3.78	4.02		
$(CH_2OH)_2$		2.15			2.68	2.95		

[a] Concentration of pyridinium 1.6×10^{-3}M.

TABLE 3

Observed rate constants ($10^5\ k_{obs.}/s^{-1}$) for the reaction of 1-s-butyl-2,4,6-triphenylpyridinium fluoroborate with piperidine at 100 °C [a]

	[Pip]/M				
Solvent	0.08	0.16	0.24	0.32	0.40
PhCl [b]	3.98	5.30		6.42	
o-$C_6H_4Cl_2$		3.30	4.23	5.07	5.93
PhOMe		5.70	6.68	7.90	8.79
Me_2SO	23.2	24.6	25.3	26.5	
$HCONMe_2$	11.4	12.6	14.0	15.1	
Bu^nOH		5.36	5.35	5.67	5.82
$Me_2CHCH_2CH_2OH$		4.44	4.96	5.52	6.00
$(CH_2OH)_2$		4.30	4.71	5.17	5.58

[a] Concentration of pyridinium 1.6×10^{-3}M. [b] Additional values ([Pip]/M, $10^5 k_{obs.}/s^{-1}$): 0.04, 3.63; 0.48, 8.64.

interpretation and demonstrate that the simultaneous occurrence of S_N1 and S_N2 mechanisms is a characteristic of the substrate structure, independent of solvent.

General Trends in Solvent Effects on Rates.—First- and second-order rate constants are reported in Tables 5 and 6. For the S_N2 rates of the N-methyl compound, a factor of *ca.* 20 spans the rates with those in the hydroxylic solvents slowest, the dipolar aprotic solvents intermediate and rates in the non-polar solvents fastest: this trend is similar to the solvent effects found for the N-benzyl derivative.[2] The pattern again is fairly similar for the S_N2 rates of the N-isopropyl and N-s-butyl derivatives except that the dipolar aprotic solvent rates are relatively faster. For the N-p-methoxybenzyl compound, the dipolar aprotic solvents appear to give rise to slower S_N2 rates. The observed S_N2 rate sequence for N-substituted pyridiniums (1a—e) in all solvents is analogous to that observed in chlorobenzene: [2,3] p-methoxybenzyl > benzyl > methyl > isopropyl ≈ s-butyl. In protic solvents the s-butyl derivative S_N2 rate appears to be faster than the isopropyl compound.

TABLE 4

Observed rate constants ($10^5\ k_{obs.}/s^{-1}$) for the reactions of 1-p-methoxybenzyl-2,4,6-triphenylpyridinium perchlorate with piperidine at 40 °C

	[Pip]/M						
Solvent	0.0032	0.032	0.04	0.08	0.16	0.24	0.32
o-$C_6H_4Cl_2$ [a]			5.62 [b]	7.67	12.6	15.9	20.0
PhOMe	5.85 [c]	6.84 [c]		7.87 [c]	10.2 [a]	12.2 [a]	15.0 [a]
Me_2SO [a]				8.60	9.08	9.49	9.85
$HCONMe_2$	8.44 [c]	8.79 [c]			10.2 [a]	11.0 [a]	12.0 [a]
MeOH [a]				9.84	10.6	11.4	11.8

[a] Concentration of pyridinium 1.6×10^{-3}M. [b] Anion tetrafluoroborate. [c] Concentration of pyridinium 3.2×10^{-5}M.

TABLE 5

Second-order rate constants (k_2) for the reactions of 1-methyl-2,4,6-triphenylpyridinium fluoroborate with piperidine at 100 °C [a]

Solvent	N [b]	r [c]	$10^4 k_2$/l mol^{-1} s^{-1}
PhCl	4	0.9996	6.00 ± 0.34
PhOMe	3	0.9995	4.36 ± 0.86
Me_2SO	3	0.999	4.35 ± 0.95
$HCONMe_2$	3	0.999	3.78 ± 0.81
Bu^nOH	4	0.998	1.00 ± 0.14
$Me_2CHCH_2CH_2OH$	4	0.997	0.666 ± 0.110
$(CH_2OH)_2$	4	0.994	0.254 ± 0.058

[a] 90% confidence limit; first-order rate constants (intercept) equal to zero within experimental error. [b] Number of runs. [c] Correlation coefficient.

The first-order rates for the isopropyl and s-butyl derivatives (1b and c) are higher in dipolar aprotic solvents such as DMSO and DMF, and lower for protic solvents and for aprotic solvents of low polarity. The p-methoxybenzyl compound (1e) 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.

Attempted Correlation with Known Solvent Parameters.—According to the Hughes and Ingold theory [6] of solvent effects on 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,[6,7] as qualitatively observed for the examined substrates (1a—e) (*cf.* Tables 5 and 6). Subsequent studies of solvent effects on the rates and the mechanism of nucleophilic substitutions have included the evaluation of free energies and activation enthalpies of transfer from one solvent to another.[8] In these studies major attention has been devoted to the Menschutkin reaction of benzyl and alkyl halides with triethylamine,[9,10] of tripropylamine with methyl iodide,[11] and of benzyl halides with pyridine.[12] In all these reactions rates in dipolar aprotic solvents are faster than in protic solvents. Studies of solvent effects on the rates of benzylation of aniline,[13] as well as on the reactions of methyl iodide with tertiary amines [14] and ethyl halides with pyridines [15] have been reported.

We attempted single-parameter correlations of the logarithms of first- and second-order rate constants with known solvent parameters such as the Dimroth E_T,[16] the electrophilicity parameter E,[17] the basicity parameter B,[17] the Kamlet and Taft π^* [18] and β [19] scales, and the θ_1 and θ_2 parameters recently derived by Sjöström and

TABLE 6

First- (k_1) and second- (k_2) order rate constants for the reactions of 1-Pr^i (1b) and 1 -Bu^s (1c)-2,4,6-triphenylpyridinium fluoroborate with piperidine at 100 °C and of 1-*p*-methoxybenzyl-2,4,6-triphenylpyridinium perchlorate (1e) with piperidine at 40 °C

				Slope		Intercept		
Compd.	Solvent	N [a]	r [b]	$10^5 k_2$ [c]/ l mol^{-1} s^{-1}	% error	$10^5 k_1$ [c]/ s^{-1}	% error	$\frac{10^3 k_1}{k_2 + 10 k_1}$ [d]
(1b)	PhCl	5	0.999	14.0 ± 0.50	4	0.717 ± 0.209	29	34
	o-$C_6H_4Cl_2$	4	0.999	8.51 ± 0.52	6	0.620 ± 0.113	18	42
	PhOMe	4	0.997	14.8 ± 1.8	12	0.800 ± 0.391	49	35
	Me_2SO	6	0.923	13.4 ± 4.1	31	13.0 ± 0.77	6	91
	$HCONMe_2$	4	0.999	27.0 ± 2.0	7	4.91 ± 0.42	9	65
	Bu^{n}OH	4	0.998	1.28 ± 0.15	12	3.11 ± 0.03	1	96
	$Me_2CHCH_2CH_2OH$	4	0.997	3.48 ± 0.60	17	2.93 ± 0.13	4	89
	$(CH_2OH)_2$	3	0.9999	3.33 ± 0.09	3	1.88 ± 0.03	1	85
(1c)	PhCl	5	0.993	11 ± 2	16	3.2 ± 0.5	15	74
	o-$C_6H_4Cl_2$	4	0.9997	10.9 ± 0.5	5	1.58 ± 0.14	9	59
	PhOMe	4	0.998	13.1 ± 1.6	12	3.60 ± 0.46	13	73
	Me_2SO	4	0.993	13 ± 3	23	22.3 ± 0.7	3	94
	$HCONMe_2$	4	0.999	15.6 ± 1.0	6	10.2 ± 0.3	3	87
	Bu^{n}OH	4	0.9992	1.9 ± 0.2	11	5.06 ± 0.05	1	96
	$Me_2CHCH_2CH_2OH$	4	0.9996	6.55 ± 0.39	6	3.40 ± 0.11	3	84
	$(CH_2OH)_2$	4	0.9997	5.38 ± 0.26	5	3.44 ± 0.08	2	86
(1e)	PhCl [e]	4	0.9995	54.9 ± 1.1	2	3.56 ± 0.17	5	39
	o-$C_6H_4Cl_2$	5	0.998	51.3 ± 4.3	8	3.75 ± 0.85	23	42
	PhOMe	6	0.998	28.1 ± 1.7	6	5.75 ± 0.31	5	67
	Me_2SO	4	0.998	5.20 ± 0.69	13	8.22 ± 0.15	2	94
	$HCONMe_2$	5	0.9996	11.1 ± 0.4	4	8.41 ± 0.09	1	88
	MeOH	4	0.991	8.31 ± 2.42	29	9.26 ± 0.53	6	92

[a] Number of runs. [b] Correlation coefficient. [c] 90% Confidence limit. [d] *i.e.* % Reaction by S_N1 route at [piperidine] 10^{-1}M. [e] From ref. 4.

Wold[20] by statistical analysis of solvatochromic shift data. The results of such correlations for second- and first-order rates are published in Supplementary Publication No. SUP 23308 (5 pp.).*

The logarithms of second-order rates for the *N*-benzyl and *N*-methyl derivatives, which exhibit only a second-order component, are linearly correlated with the E_T parameter (Figure 1) and the correlation is poor for the *N*-isopropyl, the *N*-s-butyl, and the *N*-*p*-methoxybenzyl compounds (r 0.65—0.75).

The logarithms of the first-order rate constants show no satisfactory correlation with any solvent parameter, although some correlation with the B and β parameters in dipolar aprotic solvents can be discerned for (1e) (r 0.99 and 0.93, respectively, *cf.* Table B in SUP 23308).

Dual-parameter correlations were not attempted since the present data set was estimated to be insufficient for such treatment.

Internal Consistency.—The lack of satisfactory correlations of first- and second-order rates with known solvent parameters could be due to the complexity of peculiar solvent effects for the present reactions. We checked the internal consistency of our data by plotting values for (1a, b, c, and e) *versus* those of the ' parent ' compound (1d). A reasonable correlation (r 0.984; slope 1.20; s.d. of slope 0.10) was found for (1a) (Figure 2) while (1b, c, and e) (derivatives which show also a first-order component) showed a poor correlation (r 0.70—0.90).

We tried to correlate the logarithms of second-order rates for the derivatives which show a first-order component; in the plot of the rate logarithms for the 1-s-butyl derivative (1c) *versus* those for the isopropyl (1b) (Figure 3) a correlation was found (r 0.955; slope 0.65; s.d. of slope 0.08), while no correlation was observed for the *p*-methoxybenzyl derivative (1e), measured at another temperature (40 °C).

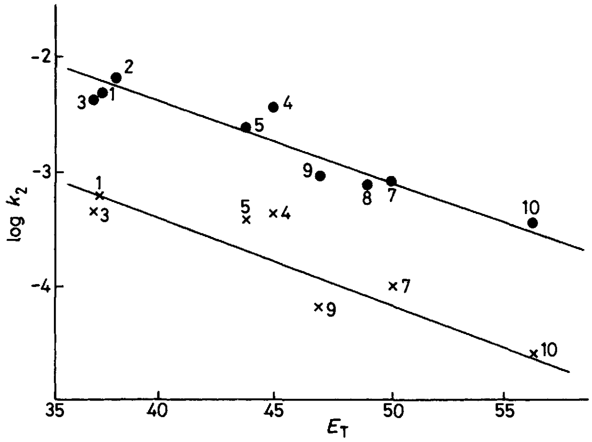


FIGURE 1 Plot of the logarithms of second-order rate constants for the reactions of 1-benzyl- (●, from ref. 2) and 1-methyl-2,4,6-triphenylpyridiniums (×) with piperidine *versus* E_T solvent parameter (from ref. 16). Numbering of solvents as follows: 1, PhCl, 2, o-$C_6H_4Cl_2$; 3, PhOMe; 4, Me_2SO; 5, $HCONMe_2$; 6, MeOH; 7, Bu^{n}OH; 8, n-C_5H_9OH; 9, $Me_2CHCH_2CH_2OH$; 10, $(CH_2OH)_2$

Principal Component Analysis of the Rate Data.—The present nucleophilic substitution rates for the reactions of compounds (1a—e) in various solvents represent a suitable data set for multivariate analysis.[21-23] Such

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* For details of Supplementary Publications see Notice to Authors No. 7, in *J. Chem. Soc., Perkin Trans. 2*, 1981, Index issue.

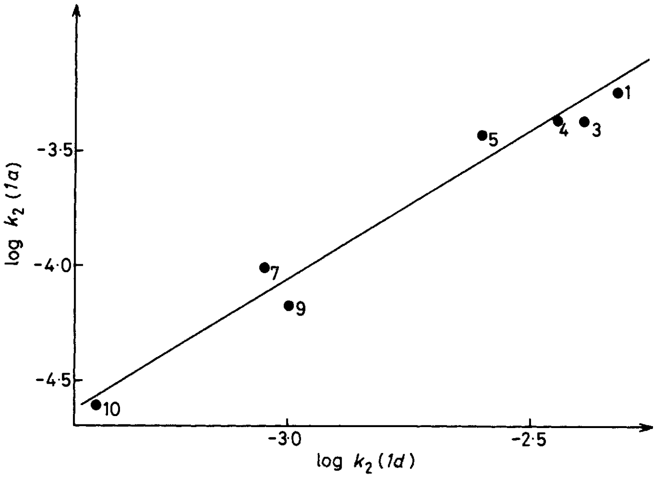

FIGURE 2 Plot of the logarithms of second-order rate constants for the reaction of 1-methyl-2,4,6-triphenylpyridinium (1a) with piperidine *versus* those for the analogous reaction of the 1-benzyl compound (1d); solvents numbered as in Figure 1

analysis, based solely on the empirical data available, defines a mathematical model for one (or more) class(es) in which each solvent (object) is described by the nucleophilic substitution rates of the various compounds (variables). This approach provides: (i) classification of the solvents (objects) and identification of those not fitting the model (outliers); (ii) parameters θ from the class model which are a type of ' solvent parameter ', and which may correspond to known ' solvent parameters '.

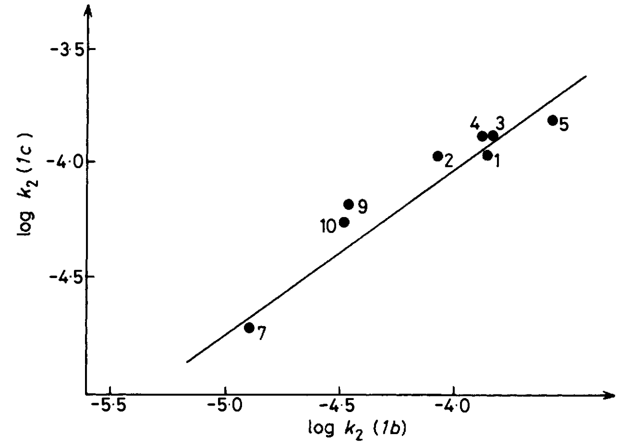

FIGURE 3 Plot of the logarithms of second-order rate constants for the reaction of 1-s-butyl-2,4,6-triphenylpyridinium (1c) with piperidine *versus* those for the analogous reaction of the 1-isopropyl derivative (1b); solvents numbered as in Figure 1

In contrast with attempts to rationalize rates in different solvents by multiparameter correlation with known ' solvent parameters ', parameters from the present analysis provide the best fit for the analysed rate data. The present type of analysis thus offers a good check of the applicability of known solvent parameters to a given data set. If the θ parameters derived are unrelated to known solvent parameters, new types of regularities are present in the investigated data.

(a) *The principal component (PC) analysis.* The PC analysis of the log k_2 matrix (Figure 4) gave β_1—β_3 parameters characteristic of the rates of each compound and θ_1—θ_3 parameters characteristic of each solvent. The plot of θ_1 *versus* θ_2 (Figure 5) reflects the relationships among the solvents (objects). For dipolar aprotic solvents (1—5, group A) we find θ_1 values clearly different from those of aprotic ones (7, 9, and 10, group B).

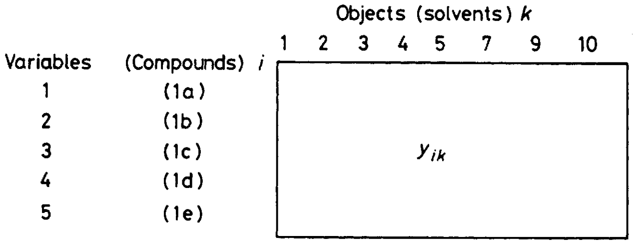

FIGURE 4 The data matrix y with elements y_{ik} denoting the logarithms of the second-order rate constants for compound i in solvent k. Numbering of solvents as in Figure 1

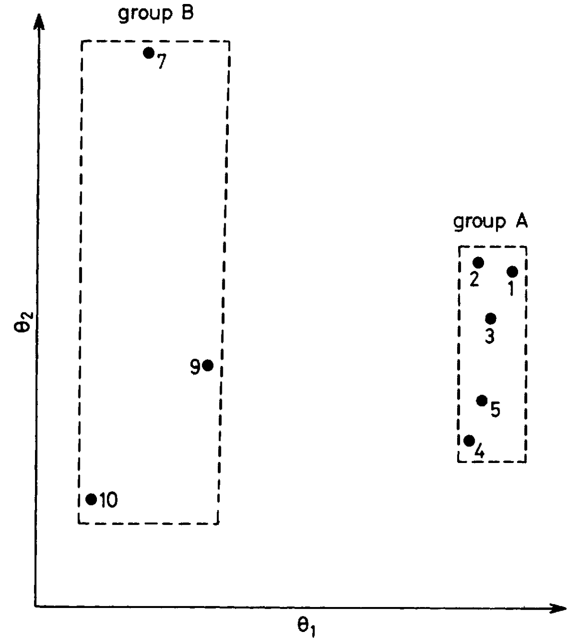

FIGURE 5 Plot of parameters θ_{2k} against θ_{1k}

Figure 6, a plot of β_1 *versus* β_2 indicates relationships among the pyridinium second-order rates (variables) and shows the peculiarity of rate data for (1e) (measured at 40 °C, not at 100 °C, *cf.* Table 6); moreover β_2 values discriminate the compounds reacting only by the S_N2 mechanism (1a and d) from those exhibiting both S_N1 and S_N2 components (1b and c).

Although one principal component was produced for the k_1 matrix, the θ_1 parameter showed no obvious correlation with any solvent property and the limited number of data pieces in the matrix render the significance of this θ in doubt.

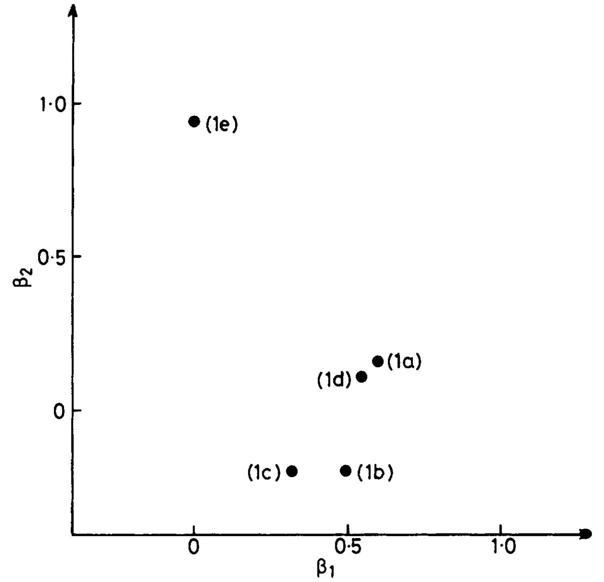

FIGURE 6 Plot of parameter values β_{2i} against β_{1i}

(b) *Interpretation of* θ *and* β *parameters.* θ_1 Differentiates aprotic solvents (1—5) from protic ones (7, 9, and 10). The second component gives θ_2 values linearly related to the basicity parameter for aprotic solvents (this parameter has not been reported for protic ones) with r 0.995; slope -0.0068; and intercept 0.69 (see Figure 7). No such significant correlation was previously found between log k_2 and B for single substrates (see Table A in the deposited data). Our correlation with B applies to all substrates and all aprotic solvents, on the residuals after we have taken out the first component (θ_1).

Conclusions.—The presence of a first-order component in the rates for the reactions of (1a—e) with piperidine in various solvents does not depend on the solvent, and is thus characteristic of the substrate. Qualitative prediction of the rate variations with solvent is possible on the basis of the Hughes–Ingold theory; [6,7] a quantitative correlation with the E_T parameter [16] is found only for compounds (1a and d). No other appreciable correlations with known solvent parameters were apparent for the substrates examined (1a—e). Principal component analysis of the logarithms of second-order rate constants provides three principal components. The first one differentiates aprotic solvents from protic ones, the second one is linearly related to the basicity parameter B, the third one is chemically insignificant.

EXPERIMENTAL

Compounds.—The synthesis and the physical properties of N-methyl- (1a),[24] N-isopropyl- (1b),[24] N-s-butyl- (1c),[25] and N-benzyl- (1d) [26] 2,4,6-triphenylpyridinium fluoroborates and N-p-methoxybenzyl-2,4,6-triphenylpyridinium perchlorate [3] and tetrafluoroborate [27] (1e) were or will be reported.

Kinetic Measurements.—The kinetics were followed by u.v. spectrophotometry using the procedure described.[2] In typical runs under pseudo-first-order conditions the concentration of pyridinium was either 1.6×10^{-3} or 3.2×10^{-5}M, while those of piperidine ranged from 0.0032 to 0.48M. Pseudo-first-order rate constants were calculated from the plot of $\ln[a/(a - x)] = \ln[(\varepsilon_1 - \varepsilon_3)/(\varepsilon - \varepsilon_3)]$ against time. The extinction coefficients for 2,4,6-triphenylpyridine (3) in various solvents at the kinetic wavelength are recorded in Table 7. As the extinction coefficient of the pyridiniums (ε_1) does not affect the slope of the above plots, average values at 307 nm for (1a—c) and at 310 nm for (1e) were used (see Table 7). Second-order rate constants were

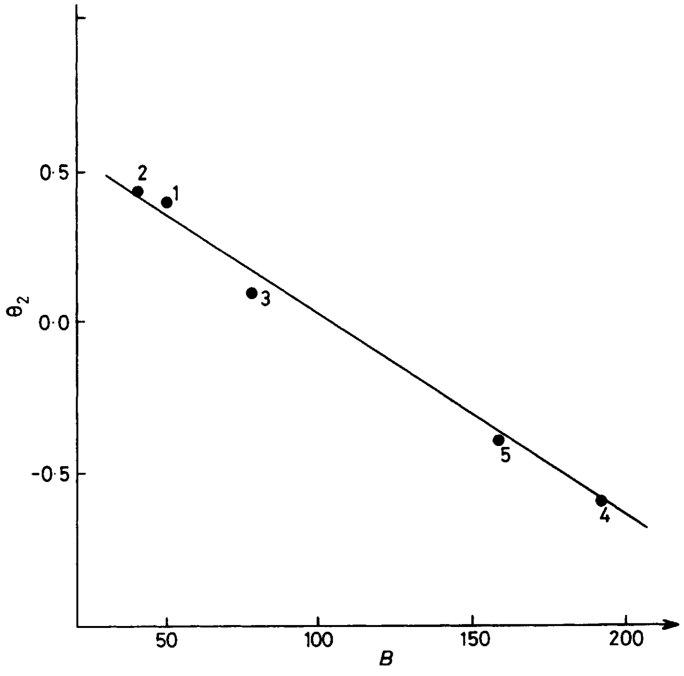

FIGURE 7 Plot of θ_2 *versus* the basicity parameter B (from ref. 17), numbering of solvents as in Figure 1

TABLE 7

Extinction coefficients for 2,4,6-triphenylpyridine (3) at the kinetic wavelength in various solvents [a]

Pyridinium	(1a) [b]		(1b) [c]		(1c) [c]		(1e) [d]	
Solvent	λ/nm	ϵ_3	λ/nm	ϵ_3	λ/nm	ϵ_3	λ/nm	ϵ_3
o-$C_6H_4Cl_2$			307	7.250	312	8.000	311	7.600
PhOMe	307	7.40	307	7.400	308	7.400	308	6.900
							308 [e]	6.900 [e]
Me_2SO	309	6.70	309	6.700	309	6.700	310	6.700
$HCONMe_2$	306	7.20	306	7.200	306	7.200	310	6.100
							310 [f]	6.100 [f]
MeOH							310	6.000
Bu^nOH	307	6.800	305	6.500	307	6.80		
$Me_2CHCH_2CH_2OH$	307	4.900	307	4.900	307	4.900		
$(CH_2OH)_2$	306	6.300	306	6.300	306	6.300		

[a] Solvent 2% (v/v) in ethanol, except where differently stated. [b] Average value of extinction coefficient at 307 nm equal to 30.000 (see Experimental section). [c] Average value of extinction coefficient at 307 nm equal to 27.500 (see Experimental section). [d] Average value of extinction coefficient at 310 nm equal to 27.000 (see Experimental section). [e] Solvent anisole. [f] Solvent $HCONMe_2$.

calculated from the slope of the plot of $k_{\text{obs.}}$ *versus* piperidine concentration.

Principal Component Analysis.—(a) *The Method*. Each data set (see Figure 4) is fitted to an expression of type (1).[21,22] Here Y_{ik} denotes the (possibly scaled) observed value

$$Y_{ik} = \alpha_i + \sum_{a=1}^{A} \beta_{ia}\theta_{ak} + \varepsilon_{ik} \qquad (1)$$

of logarithm of second-order rate for compound i (variable i) on solvent k (object k). The parameters α_i are averages of the corresponding variables i. The PC parameters β_{ia} and θ_{ak} ($a = 1,2, \ldots ,A$) are computed to minimize the residuals, ε_{ik}. The smaller these residuals, the better is the fit of the model. The appropriate number of components (product terms $\beta\theta$) A, for a given data set was found by cross-validation [23] to give the model the best predictive properties, with respect to data elements y_{ik} kept out of the analysis. For details of the analysis, see refs. 21—23.

(b) *The matrix*. The logarithms of second-order rates were arranged into a matrix (Figure 4) containing eight objects (solvents) described by the rate data for five compounds (variables). The analysis of the logarithms of first-order rates was also attempted analysing an analogous matrix containing eight objects (solvents) described by three variables [compounds (1b, c, and e)].

(c) *Scaling of the variables*. No scaling was made since the variation in log k for each substrate was of the same order.

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