Pyrylium-mediated Transformations of Natural Products. Part 9.[1] The Effect of Temperature and Ionic Strength on the Mechanism and Rate of Reactions of Pyridinium Ions in Aqueous Solution

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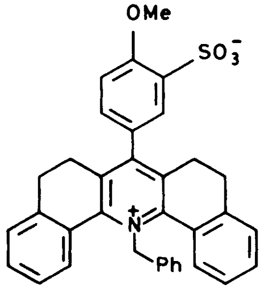
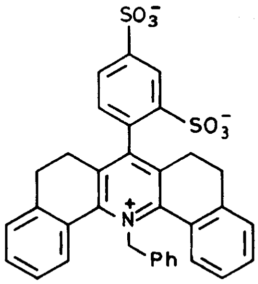
Increasing ionic strength decreases nucleophilic substitution rates both of the formally neutral (**1**) and of the formally negatively charged pyridinium substrate (**2**) with azide, indicating the dominating effect of interactions with the positively charged nitrogen monopole. For (**1**) and (**2**), both solvolysis and bimolecular reaction components show small entropies of activation, whereas solvolysis of (**3**) displays a large negative entropy of activation.

The preceding paper[1] describes a kinetic investigation of the nucleophilic displacements of nitrogen substituents from several pyridinium cations in aqueous solution, encompassing a range of different leaving groups and nitrogen substituents. To gain more insight into the details of these reactions, we have now studied three of these substrates (**1**)—(**3**) in more detail. In particular, we have examined their solvolysis rates in the absence of nucleophile (other than solvent) and the effect of temperature and ionic strength on rates.

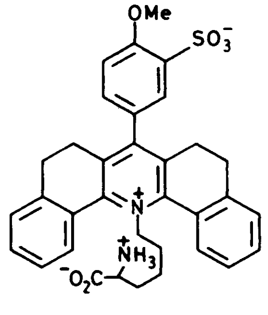
Solvolysis in the Absence of Nucleophile.—The pyridiniums (**1**)—(**3**) solvolyse in aqueous buffer at pH 10.4 in the absence of nucleophiles. Over a range of temperatures, they display clean first-order kinetics up to *ca.* 80% reaction (Table 1). The values of k_1 at 80.0 °C are compared in Table 2 with those previously obtained[1] from a plot of pseudo-first-order rate constants against nucleophile concentrations. Good agreement is shown with the previous values[1] for piperidine. For thioglycolate dianion, the values[1] from the intercepts are lower than those in Table 1, possibly because of the air-oxidation of thioglycolate in aqueous solution.[2]



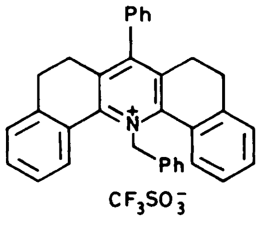
(**1**)



(**2**)



(**3**)



(**4**)

Table 1. Variation of pseudo-first-order rate constant k_1 with temperature for the solvolyses of the pyridiniums[a] (**1**)—(**3**) in aqueous buffer at pH 10.4

Pyridinium	t/°C	$10^5 k_1$/s^{-1} [b]	r [c]
(**1**)	39.9	0.19 ± 0.03	0.985
	49.3	0.59 ± 0.03	0.999
	58.0	1.81 ± 0.03	0.9998
	67.2	5.8 ± 0.1	0.9995
	80.0	22.0 ± 0.3	0.9998
(**2**)	39.9	0.09 ± 0.01	0.989
	49.3	0.38 ± 0.03	0.9922
	58.0	0.97 ± 0.04	0.9984
	67.2	3.02 ± 0.07	0.9994
	80.0	11.6 ± 0.2	0.9996
(**3**)	39.9	0.24 ± 0.02	0.9968
	49.3	0.48 ± 0.02	0.9988
	58.0	1.22 ± 0.01	0.9999
	67.2	2.62 ± 0.04	0.9996
	80.0	7.82 ± 0.03	0.999 96

[a] At an initial concentration of *ca.* 10^{-4} mol l^{-1}. [b] 90% confidence limit. [c] Correlation coefficient.

Table 2. Comparison of first-order rate constants, k_1, for the solvolyses of the pyridinium ions (**1**)—(**3**) with intercepts obtained from plots of pseudo-first-order rate constants against nucleophile concentration

	$10^4 k_1$/s^{-1}		
Nucleophile	(**1**)	(**2**)	(**3**)
$^-SCH_2CO_2^-$ [a]	0.4 ± 0.6	0.21 ± 0.02	0.1 ± 0.2
Piperidine[a]	2.9 ± 0.3	1 ± 1	0.7 ± 0.7
(None)[b]	2.20 ± 0.03	1.16 ± 0.02	0.782 ± 0.003

[a] From ref. 1. [b] Solvent only, at pH 10.4 (*cf.* Table 1).

Effect of Temperature.—Reactions of the pyridiniums (**1**) and (**2**) with piperidine and with azide in aqueous buffer at pH 10.4 each afford excellent pseudo-first-order kinetics up to *ca.* 90% conversion over a range of temperatures (Table 3). Arrhenius plots for these reactions and for the solvolyses of (**1**)—(**3**) in the absence of nucleophile provide the activation parameters reported in Table 4.

The small, negative entropies of activation found for the solvolyses of (**1**) and (**2**) are consistent with a unimolecular dissociative rate-determining step:[3] similar values have been obtained for the solvolyses of *N*-isobutyl- and *N*-neopentyl-acridinium cations in acetic acid.[4]

Table 3. Variation of pseudo-first-order rate constant k_{obs} with temperature for the reaction of the pyridiniums[a] (1) and (2) with piperidine[b] and azide anion[c] in aqueous buffer at pH 10.4

Pyridinium	Nucleophile	t/°C	$10^5 k_{obs}/s^{-1}$ [d]	r[e]	$10^3 k_2/$ l $mol^{-1} s^{-1}$ [f]
(1)	Piperidine	39.9	1.63 ± 0.02	0.9997	0.36 ± 0.01
		49.3	5.18 ± 0.03	1.0000	1.15 ± 0.02
		58.0	14.1 ± 0.3	0.9998	3.07 ± 0.08
		67.2	36.5 ± 0.8	0.9994	7.7 ± 0.2
		80.0	176 ± 4	0.9996	39 ± 1
	Azide	39.9	0.343 ± 0.003	0.9996	0.15 ± 0.13
		49.3	0.98 ± 0.01	0.9996	0.40 ± 0.04
		58.0	3.6 ± 0.1	0.9986	1.8 ± 0.1
		67.2	11.5 ± 0.2	0.9997	5.7 ± 0.3
		80.0	33.0 ± 0.2	0.9994	11.0 ± 0.5
(2)	Piperidine	39.9	0.579	0.9999	0.122 ± 0.004
		49.3	1.18 ± 0.01	1.0000	0.38 ± 0.01
		58.0	5.51 ± 0.03	1.0000	1.14 ± 0.02
		67.2	18.9 ± 0.8	0.9981	4.0 ± 0.2
		80.0	75 ± 2	0.9994	16.0 ± 0.5
	Azide	39.9	0.162 ± 0.001	0.9999	0.07 ± 0.01
		49.3	0.545 ± 0.004	0.9999	0.17 ± 0.03
		58.0	1.44 ± 0.04	0.9982	0.47 ± 0.08
		67.2	4.89 ± 0.05	0.9998	1.9 ± 0.1
		80.0	16.4 ± 0.3	0.9998	4.8 ± 0.5

[a] At an initial concentration of *ca.* 10^{-4} mol l^{-1}. [b] [Piperidine] 0.04 mol l^{-1}. [c] $[NaN_3]$ 0.01 mol l^{-1}. [d] 90% confidence limit. [e] Correlation coefficient. [f] Calculated using the expression $k_{obs} = k_2[Nu] + k_1$; values of k_1 are given in Table 1.

Table 4. Arrhenius parameters for the reaction of the pyridiniums (1) and (2) with piperidine and azide anion in aqueous buffer at pH 10.4 and for the solvolyses of the pyridiniums (1)—(3) in the absence of nucleophile

Nucleophile	Pyridinium	E_a/kcal mol^{-1} [a]	Activation entropy at 373 K (cal $mol^{-1} K^{-1}$)[a]
Piperidine	(1)	25.4 ± 1.5	4.4 ± 4.5
	(2)	27.0 ± 1.0	7.1 ± 2.9
Azide	(1)	26.0 ± 1.0	4.2 ± 3.2
	(2)	23.7 ± 0.6	−4.6 ± 1.6
None[b]	(1)	26.2 ± 0.7	−3.4 ± 1.9
	(2)	25.8 ± 6.0	−5.8 ± 2.3
	(3)	19.9 ± 0.4	−23.7 ± 1.2

[a] Errors quoted at the 90% confidence interval. [b] In aqueous buffer at pH 10.4.

Table 5. Variation of pseudo-first-order rate constant with ionic strength μ for the reaction of the pyridiniums (1)[a] and (2)[a] with sodium azide[a] in aqueous buffer at pH 10.4 at 80.0 °C

Pyridinium	$[NaClO_4]$/ mol l^{-1}	μ/mol kg^{-1}	$10^{-4} k_{obs}/s^{-1}$ [b]	r[c]
(1)		0.009 98	3.30 ± 0.02	0.9999
	0.1	0.109 78	2.88 ± 0.02	1.0000
	1.0	1.007 98	1.79 ± 0.02	0.9999
(2)		0.009 98	1.64 ± 0.03	0.9998
	0.1	0.109 78	1.47 ± 0.01	0.9999
	1.0	1.007 98	1.31 ± 0.01	0.9999

[a] At an initial concentration of 2.0 × 10^{-4} mol l^{-1}; $[N_3^-]$ 0.01 mol l^{-1}. [b] 90% confidence limit. [c] Correlation coefficient.

By contrast, the large negative activation entropy, and comparatively small activation energy, for the solvolysis of (3) are indicative of a bimolecular, associative rate-determining step.[3] These parameters are similar to those for the second-order reaction in chlorobenzene solvent of piperidine with the pyridinium (4).[5] The solvolysis of (3) is indeed expected to proceed by intramolecular displacement of the pyridine by the amino group as piperidine-2-carboxylate has been isolated from this reaction under preparative conditions.[6] In agreement, solvolysis of the *N*-butyl analogue of (3) is very slow judging by the zero intercepts found from plots of pseudo-first-order rate constants against nucleophile concentrations.[1]

Interestingly, the activation parameters for the kinetically second-order[1] reactions of (1) and (2) with nucleophiles are similar to those for their solvolyses in the absence of nucleophile (Table 4). This may possibly indicate reversible dissociation (formation of an ion–molecule pair)[7] before the rate-determining nucleophilic attack.

Variation with Ionic Strength.—The Hughes–Ingold theory of salt effects predicts that increasing ionic strength decreases rates for the reactions between oppositely charged ions, has little effect when one of the reactants is uncharged, and increases rates between ions of the same charge.[8] We now find that a rate decrease occurs (Table 5) for reactions of azide anion with the pyridiniums (1) and (2) with increasing ionic strength. At the reaction pH of 10.4, the sulphonic acid substituents are fully ionised and thus (1) is overall neutral and (2) is overall negatively charged. However, the rate decreases in both cases, and this indicates that interactions between the incoming azide anion and the nitrogen monopole exert the dominant effect on the rates of both (1) and (2).

Experimental

Kinetics.—The u.v. spectra were measured on a Pye–Unicam 8800 spectrophotometer in matched, stoppered u.v. cells. The temperature was controlled to ±0.1 °C (checked by external thermocouple) by a Pye–Unicam 798026 cell-temperature controller. Reactions were followed at 393, 384, and 388 nm [absorption maxima of the pyridinium ions (**1**)—(**3**) respectively],[1] to *ca.* 80—90% conversion. Pseudo-first-order rate constants were obtained from the slope of a plot of $\ln[a/(a - x)] = \ln[(\varepsilon_1 - \varepsilon_2)/(\varepsilon - \varepsilon_2)]$ *versus* time. The unweighted 'linear least-squares' method was used throughout,[9] except in the calculation of the Arrhenius parameters, where the rate constants were weighted inversely according to their absolute error.[10]

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