Aziridines related to Some β-Adrenergic Blocking Agents. Kinetics of Formation and Reaction, and Some Unusual Salt Effects

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The cyclisation rates of some β-chloroethylamines to the aziridine have been measured. Rates and activation parameters are used to demonstrate mechanistic differences between those cyclisations that can, and those that cannot, obtain further assistance from benzylic or neighbouring aryl participation. The reactions of the aziridines with water and thiosulphate ion are studied. While primary products are obtained from one aziridine and secondary products from another, this does not allow a reliable distinction to be made between S_N2 and S_N1 pathways, to which the activation parameters provide a better guide. Unexpectedly large and specific salt effects are found for certain of the aziridine formation and solvolysis reactions. These enable conclusions to be drawn concerning all four transition states, for which tentative activity coefficients are derived. This analysis is incorporated in a scheme that consistently explains rates, salt effects, and activation parameters.

SINCE aziridines are known to possess carcinogenic properties,[1,2a] the observation [3,4] that the ethanolamine (9) (pronethalol,[5] ' Alderlin ' †) and its chloro-derivative (7) both give rise to thymic tumours in mice led to the suggestion [4] that the formally related aziridine (8) might be responsible. By contrast, neither the analogue (6) (propranolol,[6] ' Inderal ' †) nor its chloro-derivative (4) possess such properties.[7] Two chemical explanations are possible: [4] either the corresponding aziridine (5) is much less reactive, or it is formed much less readily. We now show that, at 37 °C, (8) is formed from the β-chloroethylamine 2000 times faster than (5), and its hydrolysis is 40 times more rapid. However, it has since been discovered [8] that the aziridine (5) possesses neither carcinogenic nor, apparently, other ill effects; it follows that chemical differences can only account in part for this contrast in toxicity.

In the course of our kinetic studies we encountered a number of unexpected phenomena in connection with rates, activation parameters, and especially salt effects, and we report them here.

EXPERIMENTAL

Materials.—Compounds (1)—(12) [9,10] were supplied by Dr. R. Howe, the four β-chloroethylamines as their hydrochlorides,‡ and compounds (16) and (17) by Dr. A. J. Floyd. Water was distilled deionised; other materials were of analytical reagent grade. Titration of aqueous Cellosolve mixtures gave blank titres for acid, base, and chloride ion (composition is quoted as volume % non-aqueous component).

pK Determinations.—The full titration curve was obtained on a Metrohm Potentiograph and pK_a values were estimated at intervals along it from the Henderson equation.[11] Values quoted (Table 1) have a standard error of ±0·03 except for the aziridines (5) and (8), s.e. ±0·1. Those for (7) and (10) are inaccessible since cyclisation is too rapid (see below). At temperatures above ambient or in mixed aqueous solvents, pK_a and solution pH values were obtained after allowing a time shown to be sufficient for equilibration of the electrodes; their speed of response was unaffected in solvents containing up to 80% cellosolve.

TABLE 1

pK_a Values at 20 °C in (a) water, (b) 50% Cellosolve

Compound	(a)	(b)
(1)		8·00
(2)		6·85
(3)		9·45
(4)		7·62
(5)	6·3	5·65
(6)	9·45	8·98
(7)	*a*	*a*
(8)	6·4	5·65
(9)	9·42	8·95
(10)	*a*	*a*
(11)		7·80

[a] Unmeasurable; see Experimental section.

Liquid junction corrections are known [12] to be small for aqueous alcohols and have not been estimated. While therefore uncertainty attaches to the absolute values of pH and pK_a measured in aqueous Cellosolve, the relative values on which calculations were based are unaffected (see below).

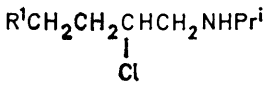
Kinetics of Aziridine Formation.—The β-chloroethylamines (1) and (4) were dissolved as their hydrochlorides in Cellosolve, and the solution was made up to volume with aqueous sodium tetraborate in excess (final composition; 50% Cellosolve, 0·01M-β-chloroethylamine, 0·045M-sodium ion, I = 0·045, pH *ca.* 10). For the much more reactive

† The terms ' Alderlin ' and ' Inderal ' are registered trade marks of Imperial Chemical Industries Limited.

‡ *CAUTION:* Compound (7) is a potent carcinogen in mice.

[1] W. C. J. Ross, ' Biological Alkylating Agents,' Butterworths, London, 1962.
[2] O. C. Dermer and G. E. Ham, ' Ethylenimine and Other Aziridines,' Academic Press, New York and London, 1969 (*a*) p. 400; (*b*) p. 4; (*c*) p. 26; (*d*) p. 24; (*e*) p. 213; (*f*) p. 11.
[3] S. J. Alcock and P. A. Bond, *Proc. European Soc. of Drug Toxicity*, 1964, **4**, 30.
[4] R. Howe, *Nature*, 1965, **207**, 594.
[5] J. S. Stephenson, B.P. 909,357.
[6] A. F. Crowther and L. H. Smith, B.P. 944,918.
[7] J. W. Black, A. F. Crowther, R. G. Shanks, L. H. Smith, and A. C. Dornhurst, *Lancet*, 1964, 1080; M. J. Tucker, S. J. Alcock, and S. B. de C. Baker, *Brit. Medical J.*, 1965, 363.
[8] S. B. de C. Baker, unpublished results.
[9] R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Medicin. Chem.*, 1968, **11**, 1000; A. F. Crowther and L. H. Smith, *ibid.*, p. 1009.
[10] R. Howe, *J. Medicin. Chem.*, 1970, **13**, 398.
[11] A. Albert and E. P. Serjeant, ' Ionisation Constants of Acids and Bases,' Methuen, London, 1962.
[12] C. L. de Ligny and M. Rehbach, *Rec. Trav. chim.*, 1960, **79**, 727.

β-chloroethylamines (7) and (10), an acid buffer was substituted (final composition; 50% Cellosolve, 0·01M-β-chloroethylamine, 0·045M-NaOAc, *ca.* 0·4M-HOAc, I = 0·055, pH 4·54). All stock solutions were pre-equilibrated



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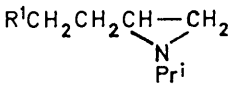

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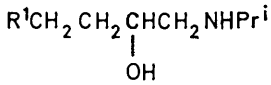

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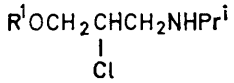

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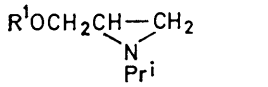

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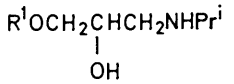

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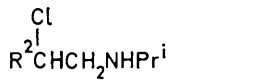

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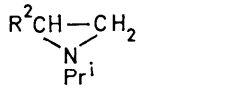

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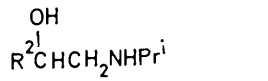

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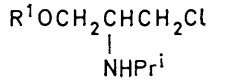

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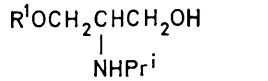

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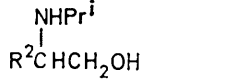

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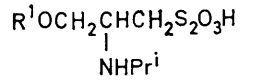

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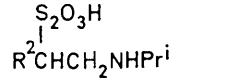

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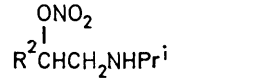

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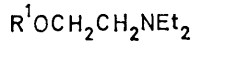

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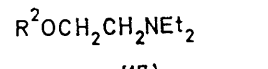
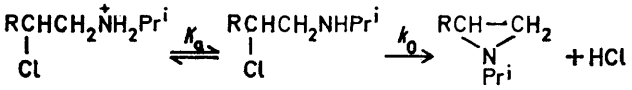


(17)

R^1 = 1-Naphthyl; R^2 = 2-naphthyl

at the reaction temperature, which was measured with N.P.L.-calibrated thermometers. Aliquot portions of the reaction mixture were quenched by addition to an equal volume of 2M aqueous acetic acid; for (7) and (10) this quenching is not efficient, and estimations were carried out at once.

The reaction [equation (1)] was followed by argentometric estimation [2b] of the chloride ion liberated. This employed



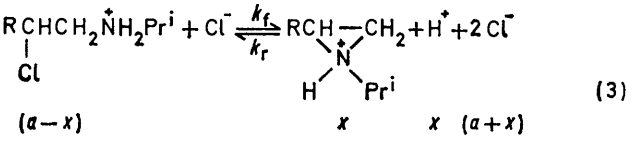
(1)

a silver–silver chloride/calomel electrode system in which saturated aqueous potassium sulphate provided the salt bridge; the potential difference as a function of titre (against 0·01M-silver nitrate) was measured with an E.I.L. model 23A pH meter, and the end point was taken as the inflection on the titration curve. It was shown that, under all circumstances, only chloride ions were estimated this way.

Reactions were followed for 2—3 half-lives. Zero titres were estimated by graphical extrapolation of the results to zero time, and infinity titres (but see exception below) by taking duplicate final readings after 24 h or more when necessary (measured half-lives ranged from 6 h to 6 min). Cyclisation of (1), (4), and (10) liberated the expected amount of chloride ion, and t.l.c. examination of the products when reaction was complete [in the case of (10) after making the solution alkaline] showed only the aziridine to be present. Observed rate constants k_{obs} were estimated by equation (2); error estimations [13] give a mean s.e. of ±4·3%.

$$\ln a/(a - x) = k_{obs}\, t \qquad (2)$$

Cyclisation of (7) does not go to completion; at 37 °C, reaction is 75, 80, and 100% complete after 2·5, 5, and 24 h in terms of chloride ion production. In this case, an equilibrium between (7) and (8) results which is slowly displaced by the hydrolysis of (8) to (9). Pseudo-equilibria are known in some parallel cases; [2c,14] as previously,[15] the secondary (benzylic) product (7) exclusively results from re-combination. T.l.c. examination detects none of the position isomer.[10] The first 75—80% of the reaction can be analysed by reversible first-order kinetics based on equation (3). The appropriate equation for k_f (≡ k_{obs})



(3)

is (4) (see Supplementary Publication No. SUP 20520 (18 pp.) for the derivation of the rate equations and for detailed experimental data; * results mentioned in this paper without attribution refer to the Supplementary Publication). The result of applying equation (4) to duplicate runs is

* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20.

[13] S. W. Benson, ' Foundations of Chemical Kinetics,' McGraw-Hill, London, 1960.
[14] H. Freundlich and G. Salomon, *Z. physik. Chem.*, 1933, *A***166**, 161.
[15] F. Wolfheim, *Chem. Ber.*, 1914, **47**, 1450.

illustrated in Figure 1; the same value of x_e (= 83% reaction) was used for both.

$$\ln\left\{\frac{x_e[a(a+x_e)+x(a-x_e)]}{a(x_e-x)(a+x_e)}\right\} = k_f\left\{\frac{a(a+x_e)+x_e(a-x_e)}{x_e(a+x_e)}\right\}t \quad (4)$$

Aziridine formation is expected [2d] to follow equation (1), from which equation (5) can be derived.[16] For the β-

$$k_0 = k_{obs}(K_a + [H^+])/K_a \quad (5)$$

chloroethylamines (1) and (4), the true rate constant $k_0 = k_{obs}$ since solution pH ≫ pK_a. However, k_0 for (7) and (10) proved too rapid for direct measurement, so equation (5) had to be employed. Its use demands accurate values of pH and pK_a, and the knowledge that k_{obs} contains no important term for buffer catalysis or salt effects. The pK_a values of (7) and (10) are inaccessible to experiment for the same reason as is k_0. Since the pairs (5) and (8), and (6) and (9), possess virtually identical pK_a values, we presume that (7) ≡ (4) = pK_a 7·62. Comparison of (4), (6) and (11) suggests pK_a 6·44 for (10). The pH dependence of k_{obs} for (7) at pH ≪ pK_a is shown in Table 2 (pH was adjusted by varying the excess of acetic acid). In the absence of buffer or salt effects, k_0 should be constant. It is not, but no systematic trend appears, so we presume these variations to result from experimental scatter. Since buffer effects are minimised when the reaction is fast, a standard buffer pH near the top of the usable range was adopted. No systematic tests were carried out elsewhere, so the k_0 values for the cyclisation of (7) and (10) must be regarded as approximate. That of (7) at 37 °C possesses an e.s.d. of ±10%; errors elsewhere are believed to be of the same order.

TABLE 2

Cyclisation of (7) at 37·0 °C in 50% aqueous Cellosolve

pH	I	[OAc⁻]/M	10^3k_{obs}/min⁻¹	k_0/min⁻¹
4·54	0·055	0·045	12·4	6·8
4·12	0·055	0·045	6·38	9·2
3·90	0·0325	0·0225	3·68	8·8
3·56	0·055	0·045	1·08	5·7

TABLE 3

Temperature variation of pH and pK_a values

t/°C	20·0	25·0	37·0	50·0
Buffer pH	4·72	4·67	4·54	4·41
pK_a of (4)	7·62	7·51	7·28	7·05

TABLE 4

Variation of pH and pK_a values with added salt at 37·0 °C

[NaClO₄]/M [a]	Nil	0·1	0·5	1·0
Buffer pH	4·54	4·46	4·25	4·09
pK_a of (4)	7·28	7·25	7·15	7·03

[a] True I = [NaClO₄] + 0·055.

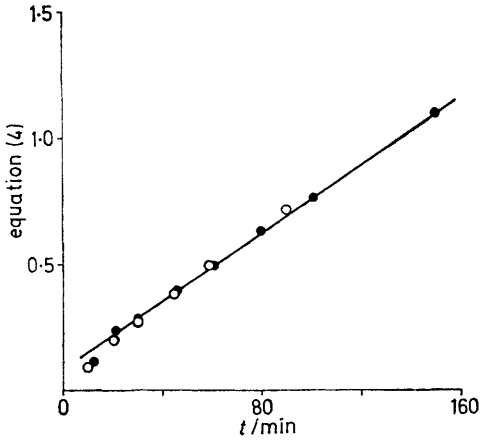


FIGURE 1 Rate plot for the cyclisation of (7) to (8) using equation (4) where x_e = 83%; ○ and ● represent duplicate runs at 37 °C in 50% Cellosolve

Calculation of the activation parameters,[17] straightforward elsewhere, is complicated for the cyclisation of (7) and (10) by the need to know pH and pK_a as a function of temperature [*cf.* equation (5)]. Similar complications arise in the evaluation of salt effects. Temperature coefficients for the standard buffer and for (4), used as a model for (7) and (10), appear in Table 3, and salt effects in Table 4; the latter are known only for sodium perchlorate, and departures from linearity on Figure 4 may result from the unwarranted assumption that other salts will follow this relation. Standard errors for the activation parameters appear in Table 5.

TABLE 5

Rates (at 37 °C), $\Delta H^\ddagger$, and $\Delta S^\ddagger$, for aziridine formation and reactions in water and in 50% Cellosolve at low ionic strength

Reaction	Solvent	10^3k_1/min⁻¹	$\Delta H^\ddagger$/ kcal mol⁻¹	$\Delta S^\ddagger$/ cal mol⁻¹ K⁻¹	10^3k_2/ l mol⁻¹ min⁻¹	$\Delta H^\ddagger$/ kcal mol⁻¹	$\Delta S^\ddagger$/ cal mol⁻¹ K⁻¹
(1) ⟶ (2)	50% Cellosolve	36·0	21·1 ± 0·9	−5 ± 3			
(4) ⟶ (5)	50% Cellosolve	3·06	22·9 ± 1·0	−5 ± 3			
(10) ⟶ (5)	50% Cellosolve	505	26·3 ± 2·8	16 ± 10			
(7) ⟶ (8)	50% Cellosolve	6800	20·3 ± 2·3	3 ± 7			
(5) + H_2O	50% Cellosolve	0·256	19·2 ± 1·4	−21 ± 5			
(5) + H_2O	Water	0·053	22·5 ± 1·7	−14 ± 6	0·00095	22·5 ± 1·7	−22 ± 6
(8) + H_2O	50% Cellosolve	2·64	23·2 ± 1·4	−4 ± 5			
(8) + H_2O	Water	2·24	23·4 ± 1·5	−3 ± 5	0·0402	23·4 ± 1·5	−11 ± 5
(5) + $S_2O_3^{=}$	Water				4660	16·1 ± 1·2	−12 ± 4
(8) + $S_2O_3^{=}$	Water				21,400	14·0 ± 1·4	−15 ± 5

[16] B. Cohen, E. R. Van Artsdalen, and J. Harris, *J. Amer. Chem. Soc.*, 1948, **70**, 281; correction p. 4275.

[17] K. J. Laidler and H. Eyring, *Ann. New York Acad. Sci.*, 1940, **39**, 303.

Kinetics of Aziridine Hydrolysis.—The aziridine (*ca.* 1 mmol) was dissolved in water or aqueous Cellosolve at the reaction temperature, and the reaction was started by adding two equiv. of perchloric acid. Aliquot portions were

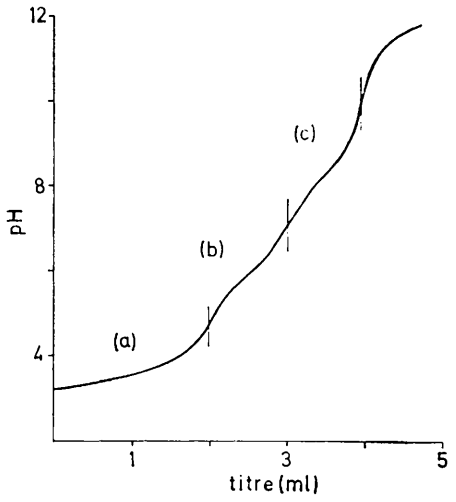


FIGURE 2 Specimen titration curve for the hydrolysis of (5) (0·01M) in aqueous perchloric acid (0·02M); titres (a) for excess of acid, (b) for (5), (c) for (11)

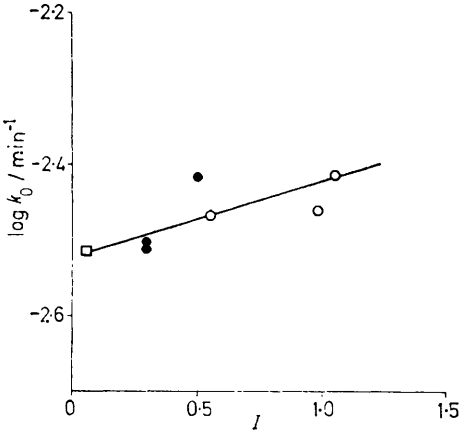


FIGURE 3 Salt effects on the cyclisation of (4) at 37 °C in 50% Cellosolve; ●, Na_2SO_4; ○, $NaClO_4$; □, no added salt

titrated potentiometrically by means of a Metrohm potentiograph. A specimen titration curve is shown as Figure 2; reactant and product occupy separate and easily identifiable regions. On a total titre of *ca.* 2 ml, an end-point precision of $\pm 0{\cdot}02$ ml is readily attainable with titres of 0·2 ml or greater. In these strongly acid solutions no special precautions to exclude carbon dioxide are necessary provided that the titration is carried out quickly (addition of titrant < 1 ml min^{-1}) and that the titrant (0·05M-potassium hydroxide solution) is free of carbonate. Rates were measured for 2—3 half-lives by using each titre in its most accurate region, *i.e.* product except near the beginning and reactant except near its end; a in equation (2) was taken as the infinity titre (10 half-lives) of ethanolamine product. A mean s.e.[13] of $\pm 6\%$ was obtained.

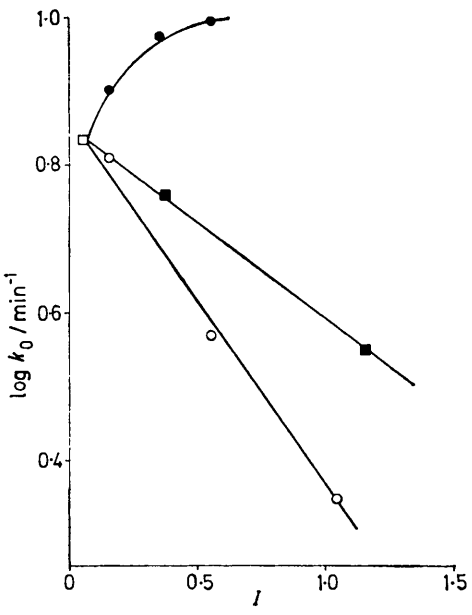


FIGURE 4 Salt effects on the cyclisation of (7) at 37 °C in 50% Cellosolve; ●, Na_2SO_4; ○, $NaClO_4$; ■, $Ca(ClO_4)_2$; □, no added salt

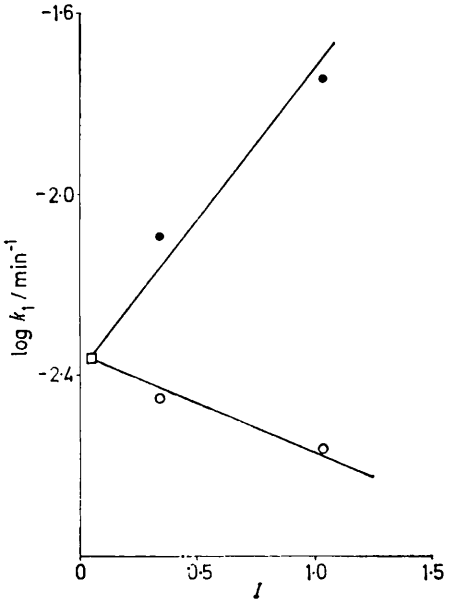


FIGURE 5 Salt effects on the hydrolysis of (5) at 75 °C in water; ●, Na_2SO_4; ○, $NaClO_4$; □, no added salt

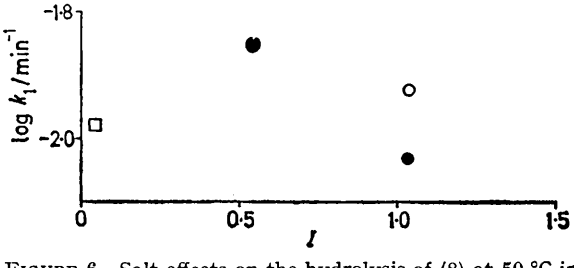


FIGURE 6 Salt effects on the hydrolysis of (8) at 50 °C in water: ●, Na_2SO_4; ○, $NaClO_4$; □, no added salt

Howe [10] reports the aziridine (8) to go cleanly to the ethanolamine (9) with no trace of the position isomer (12) and we confirm this by t.l.c. examination. This is expected.[2e] Under our reaction conditions we do not find that, as previously reported,[10] the aziridine (5) gives the ethanolamines (11) and (6) in 3 : 1 ratio; the only isolable product was the hydrochloride of (11) unmixed, on spectroscopic evidence, with (6). Also, g.l.c. examination of our total product suggests >90% formation of (11), so the reaction may be more selective at lower temperatures. On t.l.c. evidence neither aziridine (5) or (8) appears to give other products in aqueous Cellosolve. We believe therefore that the reactions (5) ⟶ (11) and (8) ⟶ (9) in water and aqueous Cellosolve are 'clean' enough to allow mechanistic discussion of the results.

Addition of perchloric acid to aqueous solutions of the aziridines (5) and (8) gives a precipitate of the perchlorate which had to be removed before the above rate estimations could be carried out. Neutral perchlorate salts behave similarly. Nitric acid precipitates the nitrate of the nitrocompound (15); hydrochloric and sulphuric acid do not give precipitates.

Under alkaline conditions at 50 °C in 50% aqueous Cellosolve, neither (5) nor (8) showed any detectable hydrolysis in 6 months.

Kinetics of Thiosulphate Addition.—The reaction in water was followed by adding the aziridine (5) or (8) to a twofold excess of sodium thiosulphate in the presence of 5 equiv. of 1 : 1 acetate buffer; the actual concentrations were chosen to lead to a convenient reaction rate. Aliquot portions were added to a precise amount of ice-cold aquous iodine solution to destroy most of the excess of thiosulphate, the rest of which was titrated against further reagent. The infinity titre was taken after a sufficient length of time to allow the reaction to go substantially to completion, *e.g.* after 3 days for a reaction 70% complete in 6 h. Reactions were followed to 70—90% completion and good second-order plots were observed till 60—80% reaction; curvature sometimes appeared in the later stages. Rates were calculated for the linear portion and possess a mean s.e. of ±5%; results are summarised in Table 5.

The Bunte salts obtained by precipitation from concentrated solution were substantially a single product. Compound (5) gives (13) and (8) gives (14). Spot checks were carried out on the whole mixture at the end of some kinetic runs, with similar results; it is thought that >10% of the position isomer could have been detected.

TABLE 6

Solubility (mol l^{-1}) of (4) in 50% Cellosolve and of (5) in water (pH 11) at 23 °C

Added salt	Nil	0·1M-Na_2SO_4	0·33M-Na_2SO_4	1·0M$NaClO_4$
Solubility (4)	0·051	0·058		0·146
log γ (4)	0·000	−0·055		−0·455
Solubility (5)	1·43 ×10^{-4}		2·85 × 10^{-5}	1·12 × 10^{-4}
log γ (5)	0·000		+0·70	+0·105

Solubility and Partition Measurements.—The solubility of (4) at 23° was measured by dissolving the base in Cellosolve, adding water or salt solution, and measuring its concentration by u.v. spectrophotometry after shaking for 1 h and filtering (Table 6). The solubilities of (5), and of (16) and (17) as their hydrochlorides, were measured similarly, except that 24 h was allowed for equilibration (Table 7).

TABLE 7

Solubilities (g l^{-1}) of (16) and (17) hydrochlorides in aqueous solutions at 23 °C

Compound	Water	0·33M-Na_2SO_4	1·0M-$NaClO_4$
(16)	690	830	0·11
(17)	1620	980	0·15

TABLE 8

Partition ratio (P = solubility in cyclohexane/solubility in 0·01M aqueous HCl) for (5) at 23 °C

Added salt	P	log γ
Nil	4·37	0·000
0·33M-Na_2SO_4	1·88	−0·365
1·0M-$NaClO_4$	10·6	+0·385

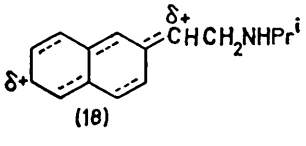
The partition ratio of (5) was measured by dissolving the free base in cyclohexane, shaking with an equal volume of acid, and, after equilibration for 10 min, measuring the concentration of (5) in both layers by u.v. spectrophotometry (Table 8).

RESULTS AND DISCUSSION

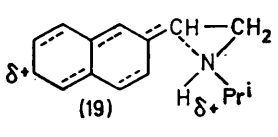
Aziridine Formation.—The β-chloroethylamine (1) cyclises to the aziridine (2) at much the rate that might be expected. The cyclisation of $EtN(CH_2CH_2Cl)_2$ at 25 °C is *ca.* six times faster in water [16] than in 67% acetone; [18] if 50% Cellosolve is comparable to the latter, the cyclisation rate of (1) in water at 25 °C can roughly be estimated as $k = 0{\cdot}05$ min^{-1}. A value of $k = 0{\cdot}1$ min^{-1} at 25 °C in water has been reported [19] for that of $MeCHClCH_2NMe_2$. Solvent effects on the cyclisation rate of (1) are unknown, but its analogues (4) and (7) show the expected [2f] solvent sensitivity.

The 12-fold reduction in rate (Table 5) on passing to (4) is consistent [2f] with its lower basic strength. Almost the whole rate difference lies in $\Delta H^{\ddagger}$, as fits a purely electronic origin.

The 2000-fold enhancement in rate between (4) and (7) is particularly striking in view of their (presumed) equal basicity. Similarly, $PhCHClCH_2NH_2$ cyclises 600 times faster than β-chloroethylamine itself.[14,20] This difference is reminiscent of that between S_N2 and S_Ni processes.[21]



(18)



(19)

However, the comparison is in some respects misleading. In a 'pure' S_Ni process [22] it is normal to find that,

[18] P. D. Bartlett, S. D. Ross, and C. G. Swain, *J. Amer. Chem. Soc.*, 1947, **69**, 2971; 1949, **71**, 1451; P. D. Bartlett, J. W. Davis, S. D. Ross, and C. G. Swain, *ibid.*, 1947, **69**, 2977.

[19] B. Hansen, *Acta Chem. Scand.*, 1963, **17**, 1483.

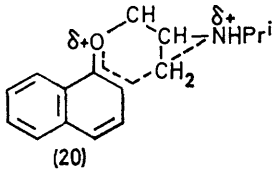
[20] G. Salomon, *Helv. Chim. Acta*, 1933, **16**, 1361.

[21] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Bell, London, 2nd edn., 1969.

[22] G. R. Cowie, H. J. M. Fitches, and G. Kohnstam, *J. Chem. Soc.*, 1963, 1585; A. Queen, *Canad. J. Chem.*, 1967, **45**, 1619.

while $\Delta S^{\ddagger}$ rises, so does $\Delta H^{\ddagger}$, since charge separation is no longer assisted by the attacking reagent. The essential characteristic of such a process is that bond breaking wholly precedes bond making;[23] however, this can scarcely happen even in the formation of (8), or the cation of (7) would still be appreciably reactive, and (except slowly to thiosulphate ion) it is not. One may rather envisage a situation in which the carbon–chlorine bond is so reactive that the nitrogen lone pair electrons can assist in its fission at internuclear distances much greater than is usual, *i.e.* (19) rather than (18) represents the transition state. This lesser steric requirement will lead to a more favourable value of $\Delta S^{\ddagger}$, the lower value of $\Delta H^{\ddagger}$ resulting from the smaller degree of orbital overlap required. This close comparison of the activation parameters is only possible because the steric and electronic factors operative in (4) and (7) are otherwise very similar. No such trend emerges from a comparison of β-chloroethylamine[20] with $PhCHClCH_2NH_2$,[14] probably because neither condition is satisfied.

The cyclisation rate of (10) refuses to fit this analysis: it is far faster than that of (4) than would be expected[2c] merely on account of the transition from a secondary to a primary halide. The enormously raised values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ suggest an essentially S_N1 process, but one to which there exists an unusually large potential energy barrier. We are constrained to suggest neighbouring aryl participation[24] possibly as in the transition state (20), where the oxygen atom with its charge-sharing ability is also involved. Neighbouring oxygen participation cannot alone be the cause; there is no sign of it in (4) or elsewhere,[16] and it is generally little more effective in four- than in three-membered rings.[24] Unfavourable steric interactions may preclude neighbouring aryl participation in (4) itself.



(20)

Aziridine Reactivity.—From published data,[25] the second-order rate constants k_2 for the hydrolysis of aziridine, 2-ethylaziridine, and 2,2-dimethylaziridine in water at 37 °C may be calculated to be 3·55, 2·24, and $17·8 \times 10^{-6}$ l mol^{-1} min^{-1} respectively. That for (5) is $0·95 \times 10^{-6}$ l mol^{-1} min^{-1}, a particularly low figure when its low basicity by normal aziridine standards (commonly[26] pK_a 8·0—8·6) is remembered; electrostriction of the solvent[27] by the hydrophobic naphthyl substituent may be the cause.

The hydrolysis of (8) in water is 40 times faster, and its reaction with thiosulphate ion 5 times faster, than that of (5); once again rates can fairly be compared, since steric factors and aziridine basicity are much the same. The enhanced hydrolysis rate of 2,2-dimethylaziridine (see above) has been attributed[25,26,28] to the incursion of S_N1 solvolysis, since attack at the tertiary position accounts for 80% of the reaction. On purely steric grounds, primary attack would be expected; 2-ethylaziridine gives *ca.* 75% of the primary product.[25] This difference has been generalised into the postulate[25,28] that product ratio reflects the extent to which each mechanism operates. Consistently,[25] 2,2-dimethylaziridine shows a $\Delta H^{\ddagger}$ value 1·2 kcal mol^{-1} more positive than for 2-ethylaziridine, and a $\Delta S^{\ddagger}$ value 8·1 cal mol^{-1} K^{-1} less negative, as expected[22,29] for a shift towards a 'pure' S_N1 process (contrast the effect on anchimeric assistance discussed in the preceding section). Both criteria work when applied to the hydrolysis of the aziridines (5) and (8). These give primary and secondary (benzylic) products respectively, and the expected differences between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are also present (Table 5). They do not work when applied to the reaction with thiosulphate ion. Since primary attack on (5) and secondary attack on (8) again largely occurs, the product criterion would classify this as S_N2 and S_N1 behaviour respectively. In fact, the rates are fast because $\Delta H^{\ddagger}$ is unusually low; the almost identical $\Delta S^{\ddagger}$ values are indeed surprisingly[30] negative for a reaction between oppositely-charged ions. The difference in rate is contained in $\Delta H^{\ddagger}$. This is evidence for a particularly ready S_N2 process, not for S_N1 reactivity.[21]

Salt Effects.—No appreciable salt effect has been found for the cyclisation[16,31] or hydrolysis[32b] reactions of aziridines, and on simple theory[30] none would be expected. We searched for salt effects in the hope of throwing more light on the S_N2 *vs.* S_N1 dichotomy described above; the non-nucleophilic anions sulphate and perchlorate were chosen as probes.

Salt effects on the cyclisation of (4), and the hydrolysis of (8), are small and non-specific (Figures 3 and 6). The cyclisation of (7), and the hydrolysis of (5), show large and specific salt effects. In the light of the activation parameters discussed above, this situation may in part be rationalised as shown in Scheme 1. Predictably, the reactions in which (4‡) and (8‡) are formed show no salt effect; the other reactions do.

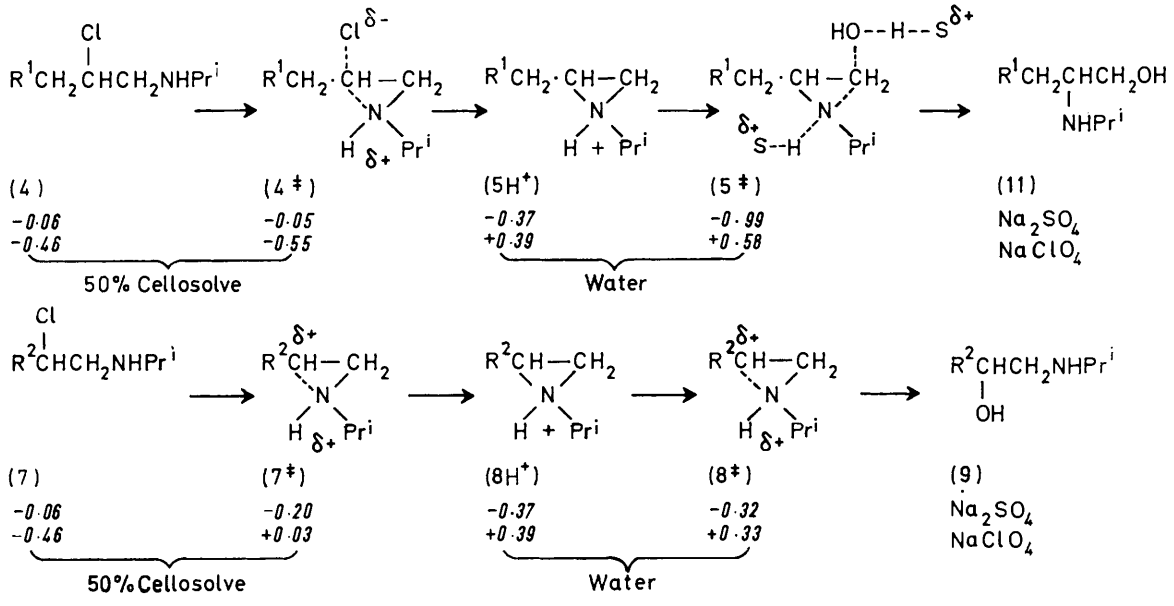
[23] R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59**, 737.
[24] B. Capon, *Quart. Rev.*, 1964, **18**, 45.
[25] J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Amer. Chem. Soc.*, 1958, **80**, 3458.
[26] G. J. Buist and H. J. Lucas, *J. Amer. Chem. Soc.*, 1957, **79**, 6157.
[27] R. W. Taft, in 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956; A. G. Evans and S. D. Hamann, *Trans. Faraday Soc.*, 1951, **47**, 34; D. J. G. Ives and P. D. Marsden, *J. Chem. Soc.*, 1965, 649.
[28] V. B. Schatz and L. B. Clapp, *J. Amer. Chem. Soc.*, 1955, **77**, 5113.
[29] F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 2362.
[30] A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism,' Wiley, New York, 1953, ch. 7.
[31] M. Simonetta and N. V. di Modrone, *Gazzetta*, 1949, **79**, 800, 814; M. Simonetta, N. V. di Modrone, and G. Favini, *ibid.*, 1950, **80**, 129.
[32] (*a*) B. Cohen, E. R. Van Artsdalen, and J. Harris, *J. Amer. Chem. Soc.*, 1952, **74**, 1875; (*b*) p. 1878.

Salt effects on the cyclisation rate of (7) in 50% Cellosolve (Figure 4) have the same sign as the Setschenow parameters found by Long and McDevit [33] for γ-butyrolactone in water with these salts, but their magnitudes

	Charge on Reactant	Charge on Transition state
(4) ⟶ (4‡)	0	*ca.* 0
(7) ⟶ (7‡)	0	*ca.* +
(5) ⟶ (5‡)	+	*ca.* 0
(8) ⟶ (8‡)	+	*ca.* +

SCHEME 1

are greater. Effects very similar in both sign and magnitude have been found by Bunton and his co-workers [34] for the uncatalysed hydrolysis of acetic anhydride in water, and there traced to an initial state activity effect. To test this point, we have measured the solubility of (4) [used also as a model for (7)] in 50% Cellosolve containing added salts (Table 6); the log less so. It follows that the direction of the salt effect (*cf.* Scheme 1) should be reversed, yet it remains in the same direction (Figure 5). We have observed that perchlorate ion precipitates (8) as its perchlorate from quite dilute solution (see Experimental section), and the same is probably true for (5). Sulphate appears to salt-in both compounds. This strongly suggests that the usual [33] salting-out order is reversed for large organic cations. Quantitative solubility data cannot be obtained for the cations of (5) or (8) since both are too reactive, but we have measured the solubilities of (16) and (17), chosen for their structural resemblance to (5), as their hydrochlorides in water and various salt solutions (Table 7). While the effect of sulphate is slight, salting-out due to perchlorate is enormous. Qualitatively similar conclusions result from an attempt (Table 8) to derive activity coefficients from partition ratios (*cf.* ref. 34), which are obtainable much more rapidly than solubilities, so enabling one to work with (5) directly.



SCHEME 2 R^1 = 1-Naphthyloxy, R^2 = 2-naphthyl; italicised figures are activity coefficients, see text

$\gamma_\ddagger$ for each log γ_i (Scheme 2) follows from the Brönsted–Bjerrum equation (6). The salt effect does, indeed,

$$k/k_o = \gamma_i/\gamma_\ddagger \qquad (6)$$

appear to be largely an initial-state phenomenon, the similar behaviour of (4) and (4‡) implying that the cationic charge of the latter is barely developed. However, sulphate ion appreciably salts in the cationic transition state (7‡), a point of some importance in what follows.

Cyclisation of (7) leads to a transition state more polar than the reactants, hydrolysis of (5) to one that is

The difficulty is to interpret these results. They cannot merely be some artefact due to the small fraction of free base present at pH 2, since salts have the opposite effect on free base solubility (Table 6). Very tentatively, therefore, these results have been used to derive the activity coefficients of Scheme 2. We have additionally supposed that (8) behaves like (5), and (see above) that (7) behaves like (4).

It is illuminating to discuss Scheme 2 in the light of Bunton's recent postulate [35] that ions of low charge density, *e.g.* perchlorate, stabilise carbonium-ion transition states, whereas those of high charge density, here sulphate, stabilise those that form extensive hydrogen bonds. On present evidence, we will add a rider: ***this***

[33] F. A. Long and W. F. McDevit, *Chem. Rev.*, 1952, **51**, 119.
[34] C. A. Bunton, N. A. Fuller, S. G. Perry, and I. H. Pitman, *J. Chem. Soc.*, 1962, 4478.
[35] C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 1258.

phenomenon is not confined to transition states.† The aziridinium cations are hydrogen bonded; sulphate salts-in and perchlorate salts-out. The transition states (7‡) and (8‡) are still hydrogen bonded enough to behave similarly, and these effects are magnified in (5‡), even though its charge is dispersed, since the opportunities for hydrogen bonding are so much enhanced: S here could be sulphate ion. The behaviour of (4), (4‡), and (7) is, by contrast, characteristic of neutral species, for which the more normal pattern of salt effects is found.

Conclusions.—Finally we attempt a consistent picture based on Scheme 2. Our essential postulate is that the transition states (7‡) and (8‡) closely resemble the central aziridinium cation, whereas (4‡) and (5‡) do not. The latter is product-like; bond making more probably precedes than follows bond breaking, and appreciable carbonium ion character is never developed. The transition from water to thiosulphate ion attack is from difficult to ready orbital overlap, from close to more distant approach in the transition state, so that $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ both become more favourable. (This distant approach is presumably the reason why $\Delta S^{\ddagger}$ is not more favourable than it is; the solvent shells of the two ions have barely started to coalesce.) The case of the aziridine (8) is more complicated. The main driving force behind its solvolysis is ring strain, hence the relative insensitivity of rate to solvent composition (Table 5). The intermediate carbonium ion (8‡) is quite stable, so is largely formed before solvent capture can occur. However, more reactive nucleophiles intervene in this process at an earlier stage. The attack of thiosulphate (and probably of chloride) is S_N2 in character despite the fact that the secondary position remains the more reactive. The product criterion [25,28] fails. Similar considerations explain the seeming paradox that (aryl substitution apart) it is precisely the most reactive aziridines that are *least* likely to hydrolyse by the S_N1 route, as the published activation parameters [25,32a] make clear: decreased stability in the cation has the same effect as increased nucleophilic power in the attacking reagent, in that $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ both fall.

We conclude that the activation parameters, aided here by salt effects, provide a better guide than product ratio to the nature of aziridine reactivity.

We thank Dr. R. Howe for suggesting the problem, for the supply of chemicals, and for discussions.

[2/073 *Received*, 13*th January*, 1972]

† We are indebted to Professor E. M. Arnett for the suggestion that this reversal may be largely electrostatic in origin, the amines and their cations being stabilised by anions of low and high charge density respectively.