Ring-opening Reactions. Stability and Reactivity of Aziridinium and Azetidinium Ions in Solution

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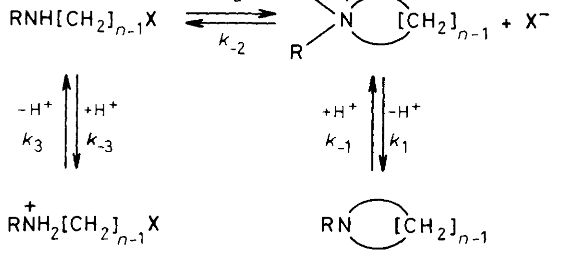
Measurement of the equilibrium constant for the formation of 1-phenylazetidinium ion in solution together with an estimate of the upper limit of the corresponding quantity for 1-phenylaziridinium, reveals an unexpected difference of at least 10^9 in favour of the 4-membered ring.

Many papers dealing with ring-closure[1] or ring-opening[2] reactions have been published in recent years. Unfortunately, different systems have generally been investigated, so that it is generally impossible either to obtain the equilibrium constants for the formation of small rings or even to make consistent comparison of the transition states involved.†

We have studied the reactions reported in Scheme 1 in the direction of ring opening, with bromide as a nucleophile for comparison with the cyclisation reaction of this system that has already been studied by Stirling *et al.*[4] In this way it is now possible to calculate the equilibrium constant for azetidinium ion ($n = 4$) formation and to estimate its magnitude for aziridinium ion ($n = 3$) formation.



Scheme 1

The ring opening of 1-phenylazetidinium ion was followed by ^{1}H n.m.r. spectroscopy at various temperatures with different nucleophiles (Table 1), monitoring the disappearance of the substrate (triplet of α-CH_2 at δ 4.65 and quintuplet of β-CH_2 at δ 2.8) and/or the appearance of *N*-(3-X-substituted propyl)anilinium (C-1 and C-3 propyl protons at δ 3.6). When deuteriated acids were used (DCl or D_2SO_4) it was possible to monitor the starting reagent until 99.8% completion of the reaction. From the ring-opening rate constants (k_{-2}) in ethanol–water (60:40) (Table 1) and the ring-closure rate constants (k_2) measured in the same solvent by Stirling *et al.*,[4] it is possible to calculate the equilibrium constant ($K = k_2/k_{-2}$) for the formation of 1-phenylazetidinium bromide at various temperatures (Table 2). From a plot of ln K *vs.* $1/T$ we calculate $\Delta H^\circ = 1.6$ kcal mol^{-1}‡ and $\Delta S^\circ = -9.5$ cal K^{-1} mol $^{-1}$ for formation of 1-phenylazetidinium bromide starting from *N*-(3-bromopropyl)aniline. The

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† Data are available for the cyclisation of ω-hydroxyaldehydes.[3]

‡ 1 cal = 4.184 J.

Table 1. Second-order rate constants and activation parameters for the ring-opening reaction of 1-phenylazetidinium cation.

Acid	Solvent (Nucleophile)	$10^5 k_{-2}$/dm^3 mol^{-1} s^{-1} at 50 °C	$\Delta H^‡$/kcal mol^{-1}	$\Delta S^‡$/cal K^{-1} mol^{-1}
HBr	CD_3CD_2OD–D_2O, 60:40 (Br^-)	48.1	23.1	−2.3
HBr	CD_3OD–D_2O, 60:40 (Br^-)	17.1	24.5	0.0
D_2SO_4	CD_3OD–D_2O, 89:11 (CD_3OD)	0.069	23.0	−15.6
DCl	CD_3OD–D_2O, 60:40 (Cl^-)	5.13	—	—

Table 2. Equilibrium constants for the formation of 1-phenylazetidinium bromide.

T/°C	K/mol dm^{-3}	T/°C	K/mol dm^{-3}
−60	0.348	+45	0.101
−30	0.220	+50	0.0984
+25	0.119	+74	0.0810
+37	0.109		

negative entropy is probably due to the increase in order of the solvent molecules surrounding the two ions that are formed.

The reaction of 1-phenylaziridinium ion ($n = 3$) was too fast to be followed by ^1H n.m.r. spectroscopy, even at −60 °C in D_2SO_4 in CD_3OD–D_2O (89:11 v/v) solution.

^1H Fourier transform n.m.r. measurements carried out 50—60 s after mixing the reagents did not show any signal due to the substrate. This implies that under these conditions 1-phenylaziridinium ion disappears with a half-life $\leqslant$ 6 s. Considering that bromide ion is at least 100 times better as a nucleophile than methanol, this finding indicates that the ring-opening rate constant for aziridinium ion is $> 6 \times 10^{-1}$ dm^3 mol^{-1} s^{-1} at −60 °C.§

The corresponding equilibrium constant for the formation of 1-phenylaziridinium ion is therefore $\leqslant 10^{-10}$ mol dm^{-3}. The difference in equilibrium constants for formation of the four- and three-membered rings ($K_{n=4}/K_{n=3}$ 10^9) corresponds to a free energy difference of at least 9 kcal mol^{-1} at −60 °C.

While this difference is larger than the difference in conventional ring strain energies (1.5 kcal mol^{-1})[6] between aziridine and azetidine in the gas phase, it is unfortunate that strain differences between the parent cyclic ammonium ions are not available. It is therefore difficult to decide whether the strain difference between these two compounds is the major factor in determining their relative stability. On the other hand aziridine is 10^3 times less basic than azetidine[7] reflecting the different character of the lone pair as a result of the cyclic structure. We therefore suggest that the positive charge introduced on protonation of nitrogen could be responsible for a decrease in stability of the three-membered ring, a topic that has been discussed by Dewar[8] in terms of σ-aromaticity.

The activation parameters (Table 1) suggest that desolvation plays an important role in the ring opening-reaction, solvation being consistently important in the ring-closing reaction.[4]

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§ The ring-opening reaction of protonated 1-tosylaziridine with water as a nucleophile can be estimated to have a rate constant of at least 10^3 dm^3 mol^{-1} s^{-1} at 25 °C.[5]