

Reversible Closure and Cleavage of the Aziridinium Ring by Nucleophilic Substitution: Solvent Effects

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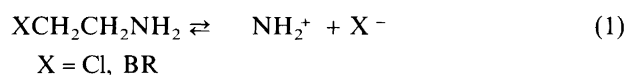
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The kinetics of ring opening of aziridinium ion by chloride and bromide ions in DMSO–water mixtures have been studied and compared with previously reported data on the reverse reaction. Activation parameters indicate that the C–Hal bond in the transition state of the reaction develops to a minor extent. This assumption is corroborated by the bromide:chloride ratio. Correlations with Kamlet–Taft solvent parameters showed that both opening and closure of the aziridinium ring are characterized by a similar nucleophilic solvation term. Taking this fact into account we assume a considerable degree of ring formation in the transition state of the reaction under study.

The relative rates of opening of small rings vs. intermolecular reaction have been a long-standing topic of study. First explanations suggesting that favourable entropy change would compensate the strain of small rings¹ failed to rationalize experimental data. In recent years the role of strain on the formation of activated cyclopropanes has been thoroughly investigated by Stirling and co-workers.^{2–6} Studies on the effect of leaving groups in reactions of 1,2-elimination and eliminative ring opening² as well as examination of activation parameters^{3,4} and Hammett parameters of leaving groups⁵ in cyclizations to rings of various size suggest that the bond with the leaving group is ruptured to a considerable degree in the transition state of these reactions.⁶ Earlier data on heterocycle formation, however, contradict this assumption.⁷ In the present study we reinvestigate this problem in order to obtain information on the structure of the transition state in the cyclization to small rings.

One of the most fruitful approaches to mechanistic investigations is the study of reversible reactions in order to compare the rates of the forward and reverse processes.^{8,9} This method makes it possible to estimate directly the position of transition state along the reaction coordinate in terms of the Hammond postulate.¹⁰ At the same time, there are only few reports of nucleophilic equilibria, because high activation barriers to most of S_N2 reactions hamper the study of such equilibria.⁸ Formation and opening of small rings proceed under similar conditions and with comparable rates,^{11,12} therefore it is pos-

sible to investigate both forward and reverse reactions. However, no communications about such studies have been published. Therefore we chose for the investigation the reversible opening of the aziridinium ring which is known to occur by a straightforward mechanism.



Since the right-hand side of the equilibrium (1) involves charged species, solvent effects are expected to be strong. Thanks to Kamlet–Taft theory the total action of media may now be separated into several types of solvation effect, in order to obtain important information on the specific solvation of functional groups.¹³ Nevertheless, solvent effects on formation and opening of small cycles has not been studied except for a few qualitative examples.^{7,14} Recently we investigated the cyclization of 2-chloro- and 2-bromoethylamines in DMSO–water mixtures.¹⁵ These two solvents differ significantly in their capability of specific solvation, their mixtures covering a wide range of solvent properties. In this paper we present the results of a study of reverse reaction, *viz.* opening of aziridinium ion by chloride and bromide ions in the same solvent mixtures.

Results

Equilibria of nucleophilic substitution. The system under study is a sequence of equilibria, their positions depending on pH value of the medium. In alkaline media

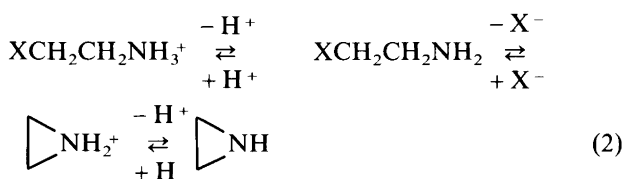
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Table 1. Pseudo-first-order rate constants of the opening of protonated aziridine by Cl⁻ and Br⁻ ions.^a

Composition of mixed solvent, [DMSO]/H ₂ O (w/w) %									
0		40		60		80		99	
T/°C	k/10 ⁻⁴ s ⁻¹	T/°C	k/10 ⁻⁴ s ⁻¹	T/°C	k/10 ⁻⁴ s ⁻¹	T/°C	k/10 ⁻⁴ s ⁻¹	T/°C	k/10 ⁻⁴ s ⁻¹
Reaction with Cl ⁻									
60.3	5.11±0.08	50.7	7.55±0.32	30.7	2.26±0.02	21.5	4.29±0.09	16.4	11.7±0.1
69.2	12.6±0.2	60.8	22.0±0.5	40.2	7.58±0.25	32.1	14.2±0.3	20.3	20.1±0.3
78.4	34.2±0.5	69.5	59.8±1.5	49.4	22.1±0.3	40.3	36.1±0.7	24.4	31.5±0.4
Reaction with Br ⁻									
60.5	7.29±0.08	50.5	9.75±0.30	30.7	3.41±0.05	17.0	4.80±0.08	15.7	11.0±0.1
67.8	15.2±0.3	68.9	69.5±2.4	40.0	10.8±0.2	24.6	11.7±0.3	20.4	19.6±0.3
78.3	46.3±0.6	69.5	81.4±4.1	49.1	29.8±0.4	34.2	36.0±0.5	34.2	91.4±1.0

^a In solvent mixtures, containing 0, 40, 60, 80% DMSO [Cl⁻]=1 M, [Br⁻]=0.25 M, in 99% DMSO [Cl⁻]=0.1 M, [Br⁻]=0.25 M. Rate constants are the means of at least two observations.

aziridinium ions are deprotonated. This prevents the opening of aziridine and equilibrium (2) is shifted to ring formation.



Protonation of 2-haloethylamines in acidic media hampers cyclization resulting in a shift of the equilibrium (2) to the left. Variation of pH therefore permits the separate study of either closure or opening of aziridinium ions. Neutral media allow the observation of mobile equilibria provided both amines are partially protonated.

An NMR study proved that under appropriate conditions these equilibria actually exist. ¹H NMR spectra of reaction mixtures containing neutralized 2-chloroethylamine and a certain amount of chloride ion (see the Experimental) revealed the rapid formation of aziridine at the initial stage of the reaction according to eqn. (1). However the acid formed during the course of the reaction effected partial protonation of the amino groups resulting in the start the reverse reaction of aziridinium ion opening. The equilibrium attained was indicated when the intensity of signals remained constant. Addition of acid

or base resulted in new changes of the signal intensities until the corresponding equilibrium state was established.

Kinetics of aziridine cleavage. Since the nucleophilic opening of aziridinium ion results in the formation of basic species [amine XCH₂CH₂NH₂, eqn. (2)], whereas to suppress cyclization acidic media are necessary, the pH-stat technique was regarded as the most suitable to monitor the reaction. Rate constants of aziridine opening were measured in DMSO–water mixtures containing 0, 40, 80 and 99% (w/w) of DMSO. The latter was chosen instead of pure DMSO in order to avoid changes of solvent composition due to the release of water.¹⁶

Kinetic runs were conducted under pseudo-first-order conditions and on complete protonation of both final and initial amines. Under these conditions the reaction rates are not affected by changes in pH. NMR spectra of reaction mixtures of higher initial concentration showed the absence of by-products, i.e., the high selectivity of the process. Current concentrations of reactants were estimated by the titrant volume needed to maintain the desired constant pH (see the Experimental). Pseudo-first-order rate constants thus obtained are given in Table 1.

Activity of halogen ions. Since the range of reaction rates was fairly wide, we had to perform kinetics measurements at various halide concentrations (Table 1) and to

Table 2. Rate constants of aziridine cleavage at various nucleophile concentrations in 80% (w/w) DMSO.^a

[Cl ⁻]/mol l ⁻¹	k _r (Cl)/10 ⁻³ s ⁻¹	[Br ⁻]/mol l ⁻¹	k _r (Br)/10 ⁻⁴ s ⁻¹
0.5	1.25±0.02	0.0833	5.57±0.12
0.67	1.36±0.02	0.125	8.36±0.17
1.0	1.41±0.03	0.25	11.6±0.2
1.5	1.70±0.03	0.375	14.9±0.2
2.0	1.78±0.04		

^a Slope of relationship log γ vs. I^{1/2} is 1.44±0.12 for Cl⁻ and 1.70±0.25 for Br⁻. Calculated by means of the Debye–Hückel limiting law 1.77. rate constants are given at 30 °C.

Table 3. Thermodynamic and activation parameters of aziridine cleavage.^a

	Composition of mixed solvent, [DMSO]/H ₂ O (w/w) %				
	0	40	60	80	99
Reaction (1), X=Cl					
$\Delta H_f^\ddagger/\text{kJ mol}^{-1}$	104.5±1.0	91.4±0.4	85.7±1.6	79.9±0.4	73.6±0.4
$\Delta S_f^\ddagger/\text{J mol}^{-1} \text{K}^{-1}$	12.6±2.0	-24.5±0.9	-41.8±2.8	-59.3±1.5	-82.4±1.5
$\Delta G_f^\ddagger/\text{kJ mol}^{-1}$	100.71±0.10	98.70±0.07	98.20±0.14	97.57±0.07	98.11±0.07
$\Delta H_r^\ddagger/\text{kJ mol}^{-1}$	99.7±2.0	97.8±2.0	95.4±2.1	84.6±0.9	81.5±1.5
$\Delta S_r^\ddagger/\text{J mol}^{-1} \text{K}^{-1}$	0.3±4.1	7.3±4.1	14.7±4.2	-9.2±1.6	6.6±1.2
$\Delta G_r^\ddagger/\text{kJ mol}^{-1}$	99.58±0.23	95.65±0.23	91.05±0.20	87.32±0.09	79.50±0.13
$\Delta G^\ddagger/\text{kJ mol}^{-1}$	1.13±0.33	3.05±0.40	7.15±0.34	10.25±0.16	18.62±0.20
Reaction (1), X=Br					
$\Delta H_f^\ddagger/\text{kJ mol}^{-1}$	96.3±1.2	88.5±0.8	80.9±0.9	75.6±1.8	72.6±2.0
$\Delta S_f^\ddagger/\text{J mol}^{-1} \text{K}^{-1}$	16.3±2.5	-3.2±2.0	-22.6±2.1	-33.1±3.0	-37.1±3.5
$\Delta G_f^\ddagger/\text{kJ mol}^{-1}$	91.42±0.12	89.50±0.09	87.66±0.09	85.48±0.18	83.60±0.20
$\Delta H_r^\ddagger/\text{kJ mol}^{-1}$	98.4±2.4	97.5±2.8	93.1±1.0	84.8±1.1	81.7±0.9
$\Delta S_r^\ddagger/\text{J mol}^{-1} \text{K}^{-1}$	6.2±3.8	15.4±4.0	12.6±2.0	2.3±2.4	15.9±2.2
$\Delta G_r^\ddagger/\text{kJ mol}^{-1}$	96.61±0.25	92.93±0.23	89.37±0.12	84.10±0.13	76.99±0.09
$\Delta G^\ddagger/\text{kJ mol}^{-1}$	-5.23±0.37	-3.43±0.32	-1.72±0.21	1.38±0.31	6.61±0.29

^a All the parameters are given at 25 °C. Symbols *f* and *r* refer to the forward (i.e., 2-halogenoethylamines cyclization) and reverse (i.e., aziridinium ion opening) reaction (1), respectively. Activation parameters were calculated from second-order rate constants $k_2/\text{M}^{-1} \text{s}^{-1}$ using the Eyring equation.

take into account activity coefficients. For this purpose we applied the Debye–Huckel limiting law. Table 2 presents the rate constants of ring-opening of the aziridinium ion at various nucleophile concentrations. One can see that the Debye–Huckel law describes experimental data only to a rough approximation. As the concentrations of halide ions are high, we used non-linear equations.¹⁷ However, this did not result in a better correlation. Since activity coefficients are necessary only to consider data obtained at various DMSO concentrations, we considered the Debye–Huckel limiting law as suitable for our purposes.

Second-order rate constants of aziridine opening k_2 were thus calculated by the equation $k_2 = k_{\text{obs}}/(C_{\text{Hal}} \times 10^{A/2})$ where k_{obs} is the first-order rate constant, *A* is the Debye–Huckel coefficient and *I* is ionic strength of the reaction mixture. Activation parameters of ring opening obtained from second-order rate constants k_2 using the Eyring equation are listed in Table 3. Symbols *f* and *r* hereafter refer to forward (i.e., cyclization) and reverse (i.e., ring-opening) reaction (1), respectively. Activation parameters for the cyclization of 2-haloethylamines have already been obtained.¹⁵ Thermodynamic parameters ΔG^\ddagger , ΔH^\ddagger and ΔS^\ddagger of reaction (1) (Table 3) were calculated by combining the activation parameters of the forward reaction with those for reverse reaction. First-order rate constants for aziridine opening in water have been published.¹⁸ Recalculation of literature data according to the Debye–Huckel equation leads to fairly good agreement with our results.

Discussion

Comparison of parameters of the forward and reverse reaction (1). In accordance with the principle of microscopic reversibility the transition state in any equilibrium is the same for both forward and reverse reactions. Comparison of parameters for forward and reverse reaction parameters thus allows one to relate transition state characteristics to those of initial or final states of the reaction.

Comparison of $k_{\text{Br}}:k_{\text{Cl}}$ ratios, in spite of the reasonable criticism, has been successfully applied in mechanistic studies, assuming that the higher the value of the ratio, the greater the degree of leaving-group departure in the reaction.⁷ Typical values for S_N2 reactions are in the range 30–100.⁷ $k_{\text{Br}}:k_{\text{Cl}}$ ratios for closure and opening of the aziridinium ring are shown in Table 4. It is seen that this ratio for ring opening is abnormally low, whereas that for ring closure is relatively large. These data suggest that the opening of the aziridinium ring proceeds with a very small degree of C–Hal bond generation in the transition state. Thus the bond with the leaving group undergoes notable change in the course of cyclization, being on the verge of cleavage in the transition state.

Comparison of activation parameters of opening of the aziridinium ion with those for the reverse reaction (Table 3) corroborates this conclusion. In fact, activation parameters of ring-opening by chloride and bromide ions are surprisingly close to each other in the solvent mixtures studied here. At the same time, parameters of cyclization for 2-bromo- and 2-chloroethylamines differ

Table 4. Leaving-group effect.^a

	Composition of mixed solvent, [DMSO]/H ₂ O (w/w) %				
	0	40	60	80	99
$k_f(\text{Br}):k_f(\text{Cl})$	42.9	41.5	70.4	142.9	352.0 ^b
$k_r(\text{Br}):k_r(\text{Cl})$	3.4	3.0	3.3	3.7	2.8

^a Rate constants are given at 25 °C. ^b The corresponding value for *N*-tosylaziridine formation in 99% DMSO is 241.²⁸

markedly. Consequently the extent to which the C–Hal bond is already formed in the transition state of reaction (1) is presumably much closer to that in the final state than in the initial one.

Correlations with solvent parameters. To analyse the solvent effect on the reaction under investigation, we chose Kamlet–Taft solvent parameters π^* , α and β , that describe dipolarity–polarizability of the solvent and its H-bond donor and acceptor capabilities, respectively.¹³ Recently we calculated these parameters for DMSO–H₂O mixtures (Table 5).¹⁹ The correlation analysis yielded eqns. (3)–(5) (leaving group indicated in parentheses).

$$\Delta G_r^\ddagger(\text{Br}) = 135.7 (\pm 39) - 25.5 (\pm 2.5)\pi^* - 35.2 (\pm 0.7)\beta \quad (3)$$

$$n = 5 \quad r_2 = 0.99 \quad s = 0.089$$

$$\Delta G_r^\ddagger(\text{Br}) = 54.4 (\pm 2.8)\pi^* + 21.8 (\pm 0.5)\alpha + 26.4 (\pm 2.8)\beta \quad (4)$$

$$n = 5 \quad r_2 = 0.999 \quad s = 0.048$$

$$\Delta G^\circ(\text{Br}) = 146.8 (\pm 11.0) - 85.6 (\pm 6.3)\pi^* - 22.9 (\pm 1.2)\alpha - 68.0 (\pm 6.2)\beta \quad (5)$$

$$n = 5 \quad r_2 = 0.999 \quad s = 0.11$$

Previously we have shown that activation parameters for cyclization of 2-bromo- and 2-chloroethylamines follow an isokinetic relationship.¹⁵ Isokinetic temperatures

were 160 and 55 °C, respectively. Since activation parameters for the cyclization of 2-chloroethylamine were measured near the isokinetic temperature, they failed to correlate with solvent parameters.

It should be noted that 2-bromoethylamine cyclization is controlled only by nucleophilic solvation [eqn. (3)]. This fact is unexpected because halide ions are known to be strongly electrophilically solvated. In order to determine the role of electrophilic solvation, we measured rates of cyclization of 2-bromoethylamine at 25 °C in solvent mixtures, containing 10, 20, 30, 50, 70 and 90% (w/w) DMSO. The corresponding Gibbs energies were 91.34 ± 0.17 , 90.88 ± 0.15 , 90.25 ± 0.15 , 89.08 ± 0.14 , 86.78 ± 0.10 and 84.56 ± 0.12 kJ mol⁻¹, respectively. The general equation describing the total set of data is given below [eqn. (6)].

$$\Delta G_r^\ddagger(\text{Br}) = 128.1 (\pm 5.1) - 18.6 (\pm 4.4)\pi^* - 34.6 (\pm 1.2)\beta \quad (6)$$

$$n = 11 \quad r_2 = 0.993 \quad s = 0.24$$

Therefore, the absence of an electrophilic term in eqn. (3) was proved to be valid. In addition to the halide, the uncharged amino group in the initial 2-haloethylamine is also strongly electrophilically solvated due to H-bond formation with the unshared electron pair of nitrogen atom. The amino group in the transition state cannot be solvated electrophilically, as the electron pair interacts with the reaction centre. Apparently, electrophilic solvation of the incipient bromide ion in the course of cyclization is compensated by desolvation of the amino group. This fact seems to account for the lack of an electrophilic term in eqns. (3) and (6).

Table 5. Properties of DMSO–water mixtures, pK_a values of reactants and pH maintained in the reaction mixtures during kinetic runs.

	Composition of mixed solvent, [DMSO]/H ₂ O (w/w) %				
	0	40	60	80	99
π^*	1.09	1.05	1.04	1.07	1.01
α	1.17	1.00	0.79	0.42	0.12
β	0.47	0.55	0.61	0.65	0.70
$pK_a(\text{ClCH}_2\text{CH}_2\text{NH}_2)^a$	8.45	8.22	8.18	8.03	8.74
$pK_a(\text{BrCH}_2\text{CH}_2\text{NH}_2)^a$	8.37	8.07	7.87	7.75	8.36
$pK_a(\text{aziridine})^a$	7.91	7.43	7.21	6.42	7.26
pH of reaction mixtures	3.6	3.3	3.7	2.8	5.0

^a From Ref. 22.

The amino group is the only group undergoing nucleophilic solvation, due to H-bond formation of N-H...B type, where B is a solvent molecule. One may expect the strength of such bonds to be closely associated with the charge on the nitrogen atom. Consequently the nucleophilic term (β) in eqns. (3) and (4) reflects variations in the nitrogen atom charge in the course of cyclization and ring-opening, respectively.

A comparison of correlations (3) and (4) shows that the solvent effect in both forward and reverse reactions (1) is characterized by similar absolute values of the β coefficients. Consequently, the change in the charge on the nitrogen atom (or in the extent of C-N bond formation) during the course of these reactions is similar. In other words, C-N bond formation is fairly advanced in the transition state. Our analysis of the solvent effect on the reversible closure and opening of aziridine thus suggests a considerable extent of ring formation in the transition state.

Conclusions

Our investigation of the reversible closure and opening of aziridine by halide ions indicated a considerable degree of C-Hal bond cleavage in the transition state of the reaction. Thus conclusions based on studies of the closure of activated cyclopropane rings is extended to three-membered heterocycles. Presumably, formation of the three-membered ring is characterized by a significant extent of leaving-group departure.

A quantitative analysis of the solvent effect revealed that both forward and reverse reactions are characterized by nearly the same change in the charge on the nitrogen atom. Consequently, the extent of C-N bond formation in the transition state is significant. The transition state of reaction (1) may thus be regarded as a late one, with a considerable degree of both leaving-group departure and ring formation.

Experimental

NMR spectra were recorded on a Bruker AC-200 spectrometer.

pH values of reaction mixtures were determined using a glass electrode with low internal resistance. The Ag/AgCl electrode was used as the reference. The electrolytic bridge was filled with saturated aqueous NaNO₃. An autotitrator in conjunction with a pH meter was used to maintain the pH value. The pH meter was calibrated with known buffers for all solvent mixtures studied.²⁰

Chemicals. Pure DMSO was distilled *in vacuo* over NaOH and mixed with the desired amount of distilled water. The water content in mixed solvents was controlled by Fisher titration. Pure ammonium chloride and ammonium bromide were recrystallized from water.

Aziridine was synthesized by a known method²¹ and purified by distillation.

Despite fast hydrolysis of aziridine in aqueous solutions, it was found that its solutions in 99% aqueous DMSO can be stored for months without significant decomposition. Therefore for rate measurements we used a 3% solution of aziridine in 99% DMSO as a stock solution instead of the highly toxic, volatile pure aziridine. The amount of added DMSO did not significantly change the solvent composition in kinetic runs. The titrant was prepared by mixing 1 ml of conc. aqueous HCl solution (pure grade) with 20 ml of the corresponding solvent mixture.

¹H NMR spectra data of reaction mixtures containing neutralized 2-chloroethylamine and an appropriate amount of chloride ion, [200 MHz; 80% (w/w) DMSO; DSS]: δ 3.1 (t, ClCH₂CH₂NH₂), 3.8 (t, ClCH₂CH₂NH₂), 1.7 (s, aziridine).

Kinetic measurements. Rate constants of aziridine opening were measured at pH values shown in Table 5. The pK_a of 2-haloethylamines²² exceed these values in the same solvent mixtures at least by two orders of magnitude. Cyclization was thus completely suppressed. The observed rate was consequently the rate of ring opening and involved no contribution from the rate of ring formation. pH-stat runs were conducted for low concentrations of aziridine (5×10^{-3} mol l⁻¹) under *pseudo*-first-order conditions. The desirable concentration of halogen ions was achieved by addition of corresponding ammonium salts. The electrode response being rapid (ca. 1–2 min),²³ we managed to monitor relatively fast reactions. Rate constants were calculated according to the *pseudo*-first-order rate, eqn. (7), where C is the current

$$C = C_0 e^{-kt} \quad (7)$$

concentration of aziridine, C_0 is its initial concentration, k is the rate constant. Since addition of the titrant (total volume of ca. 0.5 ml) did not significantly dilute the reaction mixture (20 ml), $C = C_0 - (v - v_0)/\tau$, where v is total volume of titrant added, v_0 is the initial volume of titrant needed to achieve the desired pH, τ is the titre thereof, and eqn. (7) may be rewritten in the form of eqn. (8).

$$v = (v_0 + C_0\tau) - C_0\tau \times e^{-kt} \quad (8)$$

It was difficult to determine accurately the initial aziridine concentration C_0 and even a small mistake led to considerable error for calculated rates. That is why these concentrations were considered here to be unknown parameters. Rate constants were found using the method of non-linear regression, *viz.* minimizing the expression $\Sigma\{v_i - [a - b \cdot \exp(-kt_i)]\}^2$, where $a = v_0 + C_0\tau$ and $b = C_0\tau$ were considered as unknown constants along with rate constants k .²⁴ Second-order rate constants were calculated in terms of the Debye-Huckel limiting law, using

relative permittivities and mixed solvent densities listed in Refs. 25 and 26, respectively.

Rate constants for the 2-bromoethylamine cyclization were determined using a procedure similar to that described earlier.¹⁵

The errors quoted for rate constants are the standard deviations calculated from the above non-linear regression. Second-order rate constants were then taken as experimental data and errors of ΔH^\ddagger and ΔS^\ddagger (standard deviations) were calculated by means of the Eyring equation by a non-weighted least-squares analysis. Errors quoted for ΔG^\ddagger were obtained as follows. Standard deviations of $\log k$ were estimated at 25°C from the regression $\log k - 1/T$ by the error corridor equation.²⁷ These values were then recalculated to give the standard errors of ΔG^\ddagger in the usual way. Errors of ΔH° , ΔS° and ΔG° were obtained as the sum of the standard deviations of the corresponding activation parameters.

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