Ring-opening Reactions. Part 4.† The Role of Strain and Stereochemical Effects on the Elimination and Substitution Reactions of Small Rings; the Reactivity of 1,1-Dimethylaziridinium Systems

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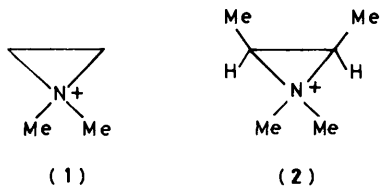
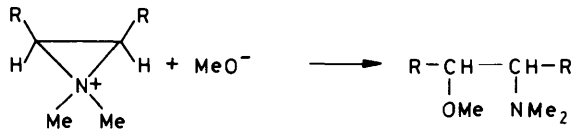
The kinetic behaviour of 1,1-dimethyl- and 1,1,2,3-tetramethyl-aziridinium ions has been compared in the light of the strong tendency of 1,1,2,ω-tetramethyl cyclic ammonium ions to undergo ring opening *via* the exocyclic elimination reaction. Surprisingly, with the aziridinium member of the latter series, ring-opening substitution takes place more readily than exocyclic elimination by a large factor. The operation of combined strain and stereochemical rate-enhancing effects in substitution, as suggested by previous work on the 1,1-dimethyl cyclic ammonium ions, is now confirmed.

The effect of strain on reactivity has received much attention, and extensive studies on some reactions are available.[1] Our previous work[2-4] on the ring-opening substitution and elimination reactions of cyclic ammonium ions showed that this type of compound is suitable for assessing the role of ring strain in reactivity. Extension of these studies to the three-membered rings is of great interest; comparison of the reactivity of the strained three-membered ring with those of less strained or strainless rings might help to elucidate the factors affecting competition between substitution and elimination reactions in small ring systems.

For this purpose we have prepared the aziridinium ions (**1**) and (**2**), and studied kinetically their reactions with sodium methoxide in methanol.‡ These ions belong to the series of 1,1-dimethyl cyclic ammonium ions and of 1,1,2,ω-tetramethyl cyclic ammonium ions, respectively, that have been the object of our previous studies in the field.[2-4]



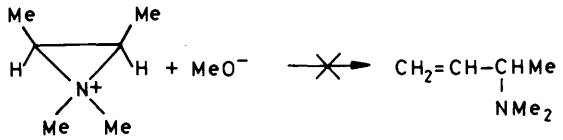
(**1**) (**2**)



(**1**) R = H (**3**)

(**2**) R = Me (**4**)

Scheme 1.



(**2**) (**5**)

Scheme 2.

Results

Synthesis.—The synthesis of the ion (**1**) has not been easy. Indeed, the well known difficulties[6] in the synthesis of aziridinium ions, such as the great sensitivity to the presence of nucleophilic reagents and the possibility of side reactions (especially polymerization and cyclodimerization),[7] were enhanced by the lack of substituents on the carbon atoms of the ring. We made many attempts to obtain this material by following different synthetic routes: from an open-chain precursor [$ClCH_2CH_2NMe_2$], from aziridine, and from 1-methylaziridine. The only successful preparation was that based on the reaction of 1-methylaziridine with methyl trifluoromethanesulphonate (see Experimental section), which, to our knowledge, represents the first example of isolation of a 1,1-dimethylaziridinium salt.§

Product Analysis.—The results refer to the reaction of the aziridinium ions (**1**) and (**2**) with sodium methoxide in methanol (Scheme 1), as carried out under the same conditions used in the kinetic runs. In all cases the only product of the reaction was that resulting from the ring-opening substitution reaction.

1,1-Dimethylaziridinium (**1**) trifluoromethanesulphonate yielded 2-dimethylaminoethyl methyl ether (**3**) in the temperature range −20 to +10 °C. *cis*-1,1,2,3-Tetramethylaziridinium (**2**) trifluoromethanesulphonate yielded 2-dimethylamino-3-methoxybutane (**4**) in the temperature range 0 to +30 °C (Scheme 1). In the case of the ion (**2**), particular care was taken in the search for the product of the elimination reaction, *i.e.* 3-dimethylaminobut-1-ene (**5**) (Scheme 2): g.l.c. comparison with an authentic sample of the latter showed that its amount in the reaction mixture was below the limit of detection (≤0.5%).

Runs were carried out on the aziridinium salts in the absence of sodium methoxide, in order to check whether solvolysis reactions were occurring. N.m.r. spectra of the reaction mixtures

† Part 3, is ref. 4.

‡ An account of the kinetic behaviour of compound (**1**) has been reported in a recent communication.[5]

§ Some studies on 1,1-dimethylaziridinium ions are available in the literature,[8,9] but they do not report the isolation of a salt. Some authors[10] claim to have isolated an *N,N*-dimethylaziridinium hexachloroantimonate, but the reported ^1H n.m.r. spectrum is not in agreement with literature data[9] and with our own results.

Table 1. Second-order rate constants[a] and activation parameters for the ring-opening substitution reaction of the aziridinium ions (**1**) and (**2**) with sodium methoxide in methanol at various temperatures

Ion[b]	T/°C	k_2 / dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$ / kcal mol^{-1}	$\Delta S^{\ddagger}$ / cal K^{-1} mol^{-1}
(**1**)[c]	−20.0	1.22×10^{-3}		
(**1**)[c]	−10.0	6.21×10^{-3}		
(**1**)[c]	0.0	2.80×10^{-2}		
(**1**)[c]	9.9	1.11×10^{-1}		
(**1**)[c]	130	1×10^{4}[d]	20.9 ± 0.1	11.3 ± 0.1
(**2**)	0.0	2.09×10^{-3}		
(**2**)	9.9	7.15×10^{-3}		
(**2**)	20.0	2.34×10^{-2}		
(**2**)	30.0	7.38×10^{-2}		
(**2**)	130	2.4×10^{2}[d]	18.9 ± 0.2	−1.3 ± 0.6

[a] Precision better than ±4%, apart from the rate constant of (**1**) at −20.0 °C, for which the precision was ±8%. [b] As the trifluoromethanesulphonate salt. [c] Data from ref. 5. [d] Value obtained by extrapolation.

recorded at various reaction times showed that products of solvolysis are formed, but that all such reactions are negligibly slow as compared with the reaction with methoxide.

Rate Measurements.—In Table 1 we show the experimental rate constants of the S_N2 ring-opening reactions of ions (**1**) and (**2**) at various temperatures. We also give the rate constants at 130 °C for ions (**1**) and (**2**) as calculated from the rate constants at lower temperatures from the Eyring plots (r = 0.9999 for both compounds) and the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

In an early stage of the work, when the synthesis of the ion (**1**) seemed unattainable, we examined, as an alternative to ion (**1**), 1,1-diethylaziridinium perchlorate. In the reaction with sodium methoxide in methanol at 0 °C this compound gave quantitatively the product of the ring-opening substitution reaction, *i.e.* the 2-diethylaminoethyl methyl ether; the rate constant at 0 °C for this reaction was 5.0×10^{-2} dm^3 mol^{-1} s^{-1}. Since the reactivity of 1,1-diethylaziridinium perchlorate turned out to be very close to that of the ion (**1**) (Table 1), we did not consider it further.

Table 2. Second-order rate constants for the exocyclic ring-opening elimination reaction of 1,1,2,ω-tetramethyl cyclic ammonium ions with sodium methoxide in methanol at 130 °C, and, for comparison, strain energy data[a] for cycloalkanes.

Ring size	k_2/dm^3 mol^{-1} s^{-1}	k_{rel}[b]	Strain energies[c]
3	≤1.2[d]	$\leq 5.7 \times 10^{2}$	26.9
4[e]	1.1	5.2×10^{2}	26.0
5[e]	3.6×10^{-3}	1.7	5.9
6[e]	2.1×10^{-3}	1	0

[a] Values expressed in kcal mol^{-1}. [b] Rates relative to the six-membered ring. [c] Changes relative to cyclohexane; data from ref. 11. [d] Evaluated as an upper limit of reactivity. [e] Data from ref. 4.

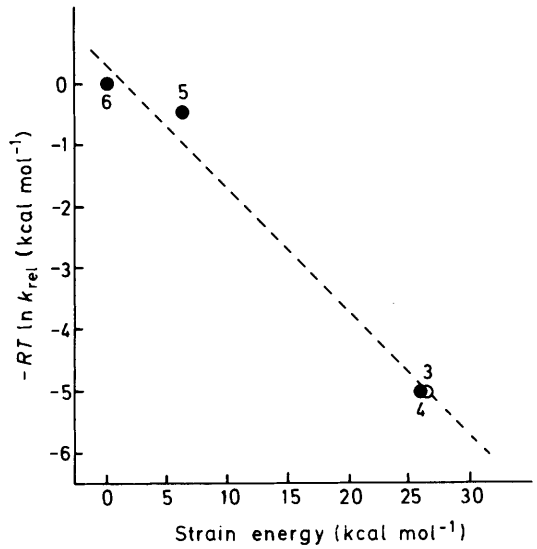


Figure. Plot of activation free energy changes for the exocyclic ring-opening elimination *versus* strain energy changes of the cycloalkanes[11] (changes are relative to the six-membered ring): ●, values calculated from experimental reactivity data; ○, value calculated from the estimated upper limit of reactivity

Discussion

Our previous work concerning the 1,1-dimethyl cyclic ammonium ions showed two ring-opening reactions in competition with each other, *viz.* substitution and elimination. Comparison of reactivity data with ring-strain energies of cycloalkanes[11]* allowed us to evaluate the influence of strain on the two reactions.

The behaviour of the ring-opening substitution[2-5] differs widely according to ring size. In the 6—16 ring-member range we observed a definite linear trend of reactivities, increasing with increase in ring strain, showing that ring-strain relief is the driving force of the reaction. The effect of strain relief is not large, only 23% of the strain in the initial state being released in the transition state. In contrast, the five-, four-, and three-membered rings showed strong deviations from the observed trend, amounting to 3, 7, and 13 kcal mol^{-1}, respectively. As a consequence of these discrepancies, we suggested that ring-strain relief cannot be the only factor responsible for the high reactivities of small rings in the S_N2 ring-opening process, and attributed such a high reactivity to an 'extra' driving force arising from a particular stereochemical situation in the transition state of the S_N2 reaction in the small rings which should make the approach of the nucleophile to the reaction centre easier when the ring size is ≤5.[5]

With respect to the endocyclic elimination reaction,† 1,1-dimethyl cyclic ammonium ions showed in the 6—16 range a behaviour substantially similar to that found in the substitution reaction, 25% of the strain being released in the transition state.[3] The five-membered ring[3] turned out to be less reactive than expected from its strain because of the unfavourable geometry of the molecule with regard to the stereochemical requirements of the elimination reaction. This effect is still more critical in the four- and three-membered rings, which do not show the elimination reaction at all.[4,5]

The series of 1,1,2,ω-tetramethyl cyclic ammonium ions was

* A detailed discussion on the suitability of cycloalkanes as models for ring strain of cyclic ammonium ions is available in ref. 5.

† In order to avoid confusion between the two ring-opening elimination reactions, we term 'endocyclic' the elimination reaction found in the 1,1-dimethyl series, and 'exocyclic' that found in the 1,1,2,ω-tetramethyl series. In the former reaction the double bond is formed between two carbon atoms belonging to the ring; in the latter reaction the double bond is formed between a carbon atom of the ring and the exocyclic methyl group.

examined with the aim of elucidating the factors affecting the ring-opening elimination reaction, since the presence of the exocyclic methyl groups should ensure that the stereochemical requirements of the elimination reaction are satisfied. Indeed, the members of this series, *i.e.*, six-, five-, and four-membered rings, yielded the elimination products as the sole or major product in the reaction with sodium methoxide in methanol.[4] The rate constants of these compounds[4] at 130 °C are shown in Table 2 and plotted in the Figure *versus* ring-strain energies. The kinetic data show that in the exocyclic elimination reaction the strain relief is the driving force of the reaction, but that its effect is felt in a moderate manner in the transition state (*ca.* 20%), as calculated from the line drawn in the Figure. We now find the interesting result that the ion (**2**) reacts only by the ring-opening substitution route. In this series also, the four-membered ring[4] showed this as a concomitant reaction. The ratio between the rate constants of the three- and four-membered rings amounts to 2.7×10^3, a value very close to that (1.2×10^3) found in the 1,1-dimethyl series for the same ring-opening substitution reaction. Examples of a three-membered ring being much more reactive than a four-membered ring in an S_N2 reaction are reported in the literature: thus, the reactivity ratios between oxirane and oxetane is reported to be 10^3:1 in the reaction with OH^- at 25 °C,[12] and 2×10^3:1 in the reaction with thiosulphate at 50 °C.[1] This reactivity difference is not explicable on the grounds of strain relief, since the strain energies of this and of other such pairs of compounds[13] differ by less than 2 kcal mol^{-1}. We consider that this reactivity difference too is due to the effect previously discussed[5] for the S_N2 ring-opening reaction.

It is of interest that the rate of the substitution reaction for ring size 3 in the 1,1-dimethyl series is higher than that in the 1,1,2,ω-tetramethyl series, the reactivity ratio amounting to 40:1 at 130 °C. This is consistent with the effect of the replacement of a hydrogen atom by a methyl group on the reaction centre in an S_N2 reaction.

As we have discussed in the product analysis section, we failed to detect the product of the elimination reaction in the reaction mixture from the ion (**2**) with sodium methoxide in methanol. This observation is not to be related to the size of the ring: it is known, for instance, that epoxides can be transformed into allylic alcohols by an elimination reaction.[14] In principle the elimination cannot be excluded, but the enhancement of reactivity of the substitution reaction is presumably such as to prevent the elimination from showing up. An upper limit of the rate constant of the elimination reaction can be evaluated as a partial rate coefficient of the overall reaction, taking into account that the sensitivity of our gas chromatographic analyses is $\leqslant 0.5\%$. The rate constant thus calculated at 130 °C for the exocyclic elimination reaction of the ion (**2**) is $\leqslant 1.2$ dm^3 mol^{-1} s^{-1}. Comparison of this rate constant with those of the other members of this series in Table 2 and in the Figure implies that the true position of the three-membered ring point in the Figure would be expected to be anywhere from the indicated position in the line upwards, but not below the point for the four-membered ring as in the S_N2 reaction. In other words, the three-membered ring does not seem to enjoy in the elimination reaction an 'extra' driving force as found in the substitution reaction.

Experimental

^1H N.m.r. spectra were obtained with a Bruker WP 80 SY instrument for all the compounds described in this work; only spectra of the new compounds, that is, of the trifluoromethanesulphonate salts of the ions (**1**) and (**2**), and of compound (**4**), are described: unreported spectra were consistent with the proposed structures. Mass spectra were obtained with an A.E.I. MS 12 or a Kratos MS 80 spectrometer. Elemental analyses were performed by the Servizio Microanalisi of the C.N.R. 'Area della Ricerca' (Montelibretti, Roma). 'Ether' refers to diethyl ether.

Gas Chromatography (*G.l.c.*).—G.l.c. analyses were carried out with a Hewlett-Packard 5830 instrument [6 ft × 2 mm i.d. glass column packed with 10% Carbowax 20M–2% KOH on 80—100 mesh Chromosorb W (Supelco) for amine analysis and a 10 ft × 1/8 in. o.d. column packed with 10% SP-1000 on 80—100 mesh Supelcoport (Supelco) for epoxide analysis]. G.l.c.–mass spectrometry experiments were carried out on a 6 ft × 2 mm i.d. glass column packed with 3% SP-2250 on 80—100 mesh Supelcoport (Supelco).

Materials.—1-Methylaziridine was obtained in 41% yield from 2-methylaminoethanol (EGA Chemie) according to a known procedure.[15]

1,1-*Dimethylaziridinium* (**1**) *Trifluoromethanesulphonate.*—This salt was prepared in 34% yield by adding 1-methylaziridine to an excess (4:1) of methyl trifluoromethanesulphonate (Fluka) in dry ether at −60 °C. The crude product was recrystallised from acetone–benzene and dried under vacuum; m.p. 210 °C (decomp.) (Found: C, 26.9; H, 4.4; N, 6.2. $C_5H_{10}F_3NO_3$ requires C, 27.15; H, 4.6; N, 6.3%); δ (CD_3CN) 3.0 (two partially overlapped singlets, ratio 3:2).[9]

1,1-Diethylaziridinium perchlorate was obtained in 59% yield by cyclization of 1-chloro-2-diethylaminoethane with dry $AgClO_4$ in dry acetone at 0 °C.[16] 1-Chloro-2-diethylaminoethane was obtained from its hydrochloride (Fluka) as described in the literature.[17] The crude product was recrystallised from propan-2-ol and dried under vacuum; m.p. 185 °C (lit.,[16] 189 °C).

cis-1,2,3-Trimethylaziridine was obtained in 14% overall yield according to the following procedure: *cis*-but-2-ene (Matheson) was transformed into *cis*-2,3-epoxybutane by treatment with 3-chloroperbenzoic acid;[18] *cis*-2,3-epoxybutane yielded 3-methylaminobutan-2-ol with aqueous methylamine;[19] this amino alcohol was transformed into its sulphate with sulphuric acid;[19] the sulphate gave *cis*-1,2,3-trimethylaziridine on treatment with NaOH.[19] The amine distilled off from the reaction mixture was 99.5% pure by g.l.c., b.p. 63—64 °C (lit.,[19] 61.5—62.0 °C).

cis-1,1,2,3-*Tetramethylaziridinium* (**2**) *Trifluoromethanesulphonate.*—The salt was prepared in 99% yield by the procedure used to obtain (**1**). The crude product was recrystallised from acetone–benzene and dried under vacuum; m.p. 170—172 °C (Found: C, 33.6; H, 5.6; N, 5.5. $C_7H_{14}F_3NO_3$ requires C, 33.7; H, 5.7; N, 5.6%); δ (CD_3CN) 3.3—3.1 (2 H, m, 2 CHN^+), 3.0 (3 H, s, CH_3N^+), 2.7 (3 H, s, CH_3N^+), and 1.5—1.4 (6 H, m, 2 × CCH_3).

Authentic Specimens.—The following preparations were intended to be independent syntheses of authentic specimens for use in product analyses.

2-Dimethylaminoethyl methyl ether (**3**) and 2-diethylaminoethyl methyl ether were obtained in 63 and 49% yield from 1-chloro-2-dimethylaminoethane and 1-chloro-2-diethylaminoethane (supplied by Fluka as their hydrochlorides), respectively, and sodium methoxide in refluxing methanol; b.p. 100—102 °C (lit.,[20] 101 °C) and 140 °C (lit.,[21] 138 °C), respectively.

2-*Dimethylamino*-3-*methoxybutane* (**4**). This compound was obtained at room temperature from the reaction of the ion (**2**) with sodium methoxide in methanol carried out on a preparative scale; b.p. 118—119 °C (Found: C, 64.0; H, 13.0; N,

10.7. $C_7H_{17}NO$ requires C, 64.1; H, 13.1; N, 10.7%); δ ($CDCl_3$) 3.5—3.2 (4 H, m, $CHOCH_3$), 2.6—2.2 [7 H, m, $CHN(CH_3)_2$], 1.1 (3 H, d, $OCHCH_3$), and 0.9 (3 H, d, $NCHCH_3$); *m/z* 131 (M^+) and 72 [$^+CH(CH_3)N(CH_3)_2$] (100%).

3-Dimethylaminobut-1-ene (**5**) was prepared in very low yield from 1-chlorobut-2-ene by the following sequence of reactions: 1-chlorobut-2-ene (Fluka) was transformed into 3-isothiocyanatobut-1-ene;[22] the latter gave 3-methylaminobut-1-ene on reduction with $LiAlH_4$;[23] 3-methylaminobut-1-ene yielded (**5**) on treatment with formic acid and formaldehyde.[23]

Product Analysis.—The product composition was determined under the same conditions used in the kinetic runs. A portion of the reaction mixture was allowed to react to completion at the appropriate temperature. A 2 ml sample was transferred into a 10 ml flask, acidified with 6N-HCl, and evaporated to dryness at 30 °C. The solid residue was treated with 9N-NaOH (3 ml), and the organic bases were extracted with ether. The identification was performed by g.l.c. comparison between the actual reaction mixtures and authentic samples of the expected products.

Rate Measurements.—Preliminary experiments were carried out in CD_3ONa–CD_3OD solution by ^1H n.m.r. at low temperature, keeping the probe at the reaction temperature and recording the spectra at fixed time intervals. In addition, these experiments confirmed the product analyses.

The kinetics were measured by a batchwise procedure using a vessel provided with a thermostatic jacket.[24] The rates were measured by acid–base potentiometric microtitration of the amine product according to a previously described procedure.[2]

Acknowledgements

We are grateful to Professor L. Mandolini for discussions and to Mr. G. Frachey for technical assistance with the n.m.r. measurements. We thank the Ministero della Pubblica Istruzione for partially financing this research.

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Received 25th February 1985; *Paper* 5/304