

The Kinetics of Ring-opening of 1,1-Dimethylaziridinium Ion with Sodium Methoxide in Methanol. The Anomalous S_N2 Reactivity of Small Rings

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The current belief that ring strain relief is the major driving force in the reactivity of small rings is disproved by quantitative data obtained for the S_N2 ring-opening reaction of cyclic ammonium ions.

The notion that strain relief is responsible for the high reactivity of small rings towards ring-opening is firmly established, but only very recently studies have been carried out to quantify the contribution of the strain to the reactivity.¹ Small rings undergo reactions that hardly can be observed in the case of strainless rings or open-chain systems and this fact has so far prevented extensive comparison.

Our approach to the problem has been to study the reactivity of cyclic ammonium ions, whose reaction with sodium methoxide in methanol turned out to be very useful in efforts to assess the role of strain on reactivity.²⁻⁴ We now report results concerning a 3-membered cyclic ammonium ion, the 1,1-dimethylaziridinium ion (1), whose S_N2 ring-opening reactivity was found to be much greater than that previously reported for the 4-membered ring,⁴ and also provide a picture which is not predicted by the ring strains of the parent rings aziridine and azetidione.⁵

The present results were made possible by a solution to the problem of the difficulty in synthesising† (1), due especially to the lack of stabilizing substituents on the aziridinium ring. The reaction of (1) with sodium methoxide in methanol is solely a ring-opening substitution and yields the amino-ether (2), which was identified by n.m.r. and gas chromatographic comparison with an authentic sample.

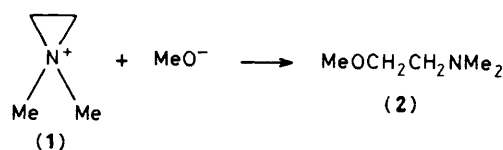
Second-order rate constants ($k_2/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$)‡ were as follows (temp. °C in parentheses): 1.22×10^{-3} (-20.0), 6.21×10^{-3} (-10.0), 2.80×10^{-2} (0.0), and 1.11×10^{-1} (9.9). From these figures we have calculated the value at 130 °C§ as $1 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. The reactivity ratios at 130 °C between the 3-membered ring and the 4-, 5-, and 6-membered rings are 1.2×10^3 ,¶ 3.2×10^7 , and 3.9×10^9 , respectively.^{3,4}

† Details of the synthesis will be given elsewhere.

‡ Rate constants were measured as previously described;² their precision was better than $\pm 4\%$, apart from that at -20.0 °C for which the precision was better than $\pm 8\%$.

§ $\Delta H^\ddagger = 20.9 \pm 0.1 \text{ kcal mol}^{-1}$; $\Delta S^\ddagger = 11.3 \pm 0.1 \text{ cal K}^{-1} \text{ mol}^{-1}$ (1 cal = 4.184 J); $r = 0.9995$.

¶ The ratio at 20 °C is 6.8×10^3 .



The results with the 1,1-dimethylaziridinium ion combined with our previous data^{3,4} form the first set of quantitative data for the S_N2 ring-opening substitution in which it is possible to compare the reactivity of a 3-membered ring with that of a wide series of compounds including small, common, medium, and large rings, as well as an open-chain reference compound. The importance of quantitative data on the aziridinium ion stems also from the possibility to use it as a model for other 3-membered rings which are important in organic synthesis, such as ethylene oxide, for which a comparable set of quantitative data is not available.

Reactivity data can be discussed in terms of ΔG^\ddagger values, calculated from the rate constants at 130 °C and related to the 6-membered ring, which is the least reactive in the series. The changes in ΔG^\ddagger values ($\delta\Delta G^\ddagger$) for the 3- and 4-membered rings are -17.7 and $-12.0 \text{ kcal mol}^{-1}$ respectively.

Figure 1 is a plot of $\delta\Delta G^\ddagger$ values** against the strain energy values of the corresponding cycloalkanes,⁶ relative to the 6-membered ring. In the 6-16 range there is a definite tendency for the reactivity to increase with increase in ring strain, showing that the initial-state strain relief is the driving force of the reaction. The 3-, 4-, and 5-membered rings all strongly deviate from the above trend in the direction of higher reactivity than would be expected from the strain energies of the corresponding cycloalkanes, the deviations amounting to 13, 7, and 3 kcal mol^{-1} , respectively. As stated above, the reaction of the 3-membered ring is more than 10^3 times as high as that of the 4-membered ring. In contrast, the strain energies of the latter rings are presumably similar as suggested by the fact that the strain energies of aziridine and azetidione are closely similar to those of the corresponding cycloalkanes and are quite close to each other.^{5,6}

** $\delta\Delta G^\ddagger$ values for the other rings are from ref. 3.

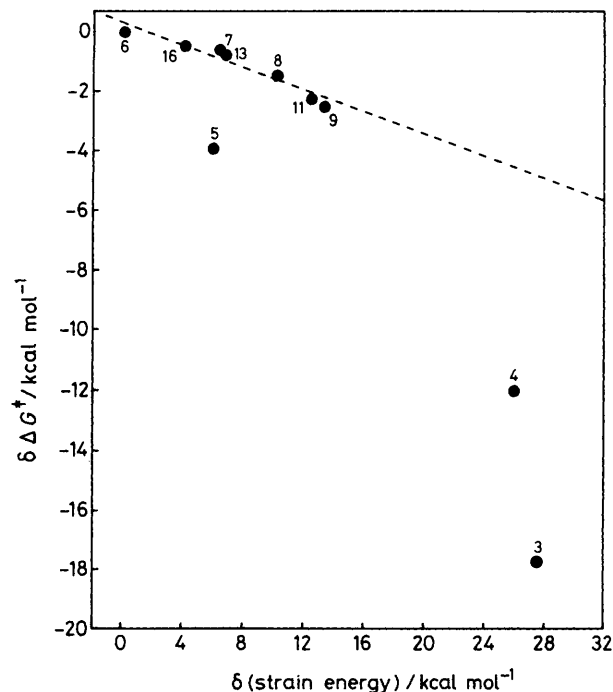


Figure 1. Plot of ΔG^\ddagger changes for the ring-opening substitution vs. strain energy changes of the cycloalkanes⁶ (changes are relative to the six-membered ring).

The strong deviations noted above indicate that ring strain relief is not the only factor affecting the reactivity of small rings even though the cycloalkanes and the cyclic amines are admittedly imperfect models for the cycloalkylammonium systems. In this connection it is of interest that the pK_a values of azetidinium, pyrrolidinium, and piperidinium are close to each other and similar to the pK_a of a secondary open-chain amine,⁷ showing that the introduction of a positive charge does not change the relative stabilities of these amines. In contrast, the pK_a of aziridinium is 3 units lower than those of the other amines, indicating that the introduction of a positive charge makes the related ammonium ion less stable. However, in energy terms the influence of this effect on the observed discrepancy of the 3-membered ring in Figure 1 (amounting to 13 kcal mol⁻¹) is relatively minor and does not change the validity of our conclusions. Furthermore, the

3-to-4 reactivity ratio herein observed for the cyclic ammonium ions is similar to that reported for the 3-to-4 reactivity ratio for the reaction of OH⁻ with cyclic ethers,⁸ whose strain energies are known⁵ and are similar to those of aziridine and azetidinium.

We believe that the observed anomalies are related to some stereochemical effect at the reaction centre for the S_N2 reaction, such as a reduced steric hindrance on the approach of the nucleophile, as the rings become smaller than 6-membered.

A more detailed consideration of this factor together with some peculiarities of S_N2 ring-closure reactions of small rings⁹ will deserve further attention. It is clear, however, that there is a definite inconsistency of the experimental picture in quantitative terms with the commonly accepted belief that small rings are very reactive simply because of their strain; in an S_N2 ring-opening reaction, strain relief is far from being the only factor controlling the reaction in small rings.

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