Ring-Opening Reactions. 1. Decomposition of Some Quaternary Ammonium Ions with Sodium Methoxide in Methanol

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Product analysis and partial rate coefficients have been obtained for the reaction of five- and six-membered cyclic ammonium ions with sodium methoxide in methanol. The overall process consists of three competing reactions, two of which involve ring opening and are controlled by steric and stereochemical factors as functions of ring structure and reaction type; related data for the dibutyldimethylammonium ion have also been obtained for comparison.

The olefin-forming decomposition of quaternary ammonium salts and of the related amine *N*-oxides has drawn the attention of several groups[1-4] and owes much of its importance to the structure elucidation of alkaloids by the well-known Hofmann exhaustive methylation procedure.[5]

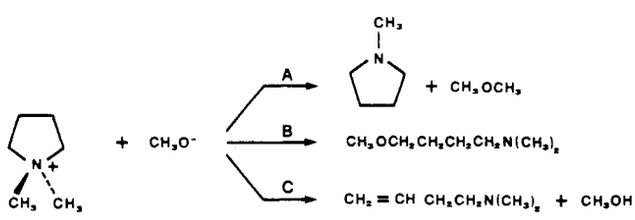
The reaction is generally accompanied by nucleophilic substitution at the nitrogen-bonded saturated carbon.[5,6] Starting from cyclic ammonium ions both olefin-forming β-elimination and endocyclic substitution lead to ring opening. The relative importance of the competitive changes is expected to depend on the conformational and other structural features of the ring as well as on the anionic reagent, reactant concentrations, and other experimental conditions. Although several studies have dealt with the product composition of these reactions under varying conditions, no rate study is available for use in reactivity–structure correlations.

Knowledge of the diverse response of ring opening to competitive reactions having different mechanistic requirements should throw light on the nature of the major factors involved in reactivity parameters. In connection with our current interest in ring-forming and ring-opening reactivity,[7,8] we have undertaken quantitative investigations on the degradation of cyclic quaternary ammonium salts. In this paper we wish to report on the product analyses and partial rate factors for the reaction of *N,N*-dimethylpyrrolidinium (I) and *N,N*-dimethylpiperidinium (II) iodides and, for comparison, the open-chain dibutyldimethylammonium iodide (III) with sodium methoxide in methanol.

Results and Discussion

The reactions were carried out in 0.05–0.10 M solution and followed to complete conversion at 130 °C in sealed ampules. Product analyses were performed by a VPC method and reaction rates measured by acid–base potentiometric titration of the total amine product formed. The results are reported in Table I. The overall process for the cyclic substrates consists of three competing reactions, A, B, and C, that are shown typically for compound I in Scheme I. The reactions observed

Scheme I



for the open-chain compound are the demethylation (A), the debutylation (B), and the olefin-forming elimination (C) (see Experimental Section). The observed product composition data are in agreement with known trends caused by the influence of reactant concentrations[5,9] and of the base/solvent system.[5,10,11] At concentrations as low as those used in this work β-elimination from compounds I and II and sodium methoxide occurs to a much lesser extent than from the corresponding hydroxides under typical Hofmann exhaustive methylation concentrations.[1] In contrast, when the PhS^-/HMPT system is used[12] no β-elimination product is formed at all.

The degradation followed second-order kinetics and was assumed to consist of three bimolecular components (A, B, and C) whose rate constants were calculated by combining the overall rate constant value (k_T) with the composition data (Table I). The k_A, k_B, k_C are partial rate coefficients that are related to free energies of activation for changes having substantially similar ground states and differing by their transition states. The diverse factors[13] related to the ring structure of substrates I and II, such as ring strains and ease of approach of the reagent, are expected to influence such transition states in different ways and, therefore, to yield useful information on their relative importance.

The reactivities of compounds I and II toward the exocyclic displacement (A) are essentially the same and similar to that of the open-chain compound III. It is of interest that the quaternization of cyclic amines by methyl iodide,[13] which involves a reversal of the change experienced at the nitrogen atom and an increase in coordination number from 3 to 4, shows some selectivity when the five- and six-membered rings are compared, the five-ring/six-ring reactivity ratio being about 4. In both reactions a transition state of the type $[N^{\delta+}\cdots CH_3\cdots X^{\delta-}]$ is involved. Apparently C–N bond breaking for the demethylation reaction (X = CH_3O) is less important than C–N bond making for the quaternization reaction (X = I), largely as a consequence of the nature of X.

The strain energy is known to be higher for a five-membered than for a six-membered ring.[14] Consequently, the ease of ring opening should be greater in the former case. This is consistent with the fact that the endocyclic displacement (B) is faster than reaction A for compound I, whereas it is markedly slower for compounds II and III, by factors of 24 and 32, respectively. In the former case the rate-depressing steric effect expected for the "more branched" alkyl group (k_B) is presumably more than offset by ring strain relief. However, the relatively high k_B value for I may also be partly caused by a reduced steric requirement of the transition state for reaction B due to the different geometry of the five-membered ring as compared to the six-membered ring.[12]

The results on reaction C show a major point of stereochemical interest; the reaction rate for compound I is 75-fold lower than that of reaction B, whereas it is 3- and 15-fold higher for compounds II and III, respectively. As models indicate, compound II is expected to attain a more closely anti-periplanar conformation than the five-membered ring in the transition state of the E2 mechanism, whereas syn elimination can be excluded. As a result of the competition

Table I. Product Analysis and Second-Order Rate Constants (M^{-1} s^{-1}) for the Reaction of Some Quaternary Ammonium Iodides with Sodium Methoxide in Methanol at 130 °C[a]

	I	II	III
10^4k_T	3.80	0.702	1.40
Reaction A, %	16.4	86.0	67.0
10^4k_A	0.623	0.604	0.938
Reaction B, %	82.5	3.6[b]	2.1
10^4k_B	3.14	0.0251	0.0294
Reaction C, %	1.1[c]	10.4	30.9
10^4k_C	0.0418	0.0729	0.433

[a] The precision in the product analysis was better than ±3% unless stated otherwise; that in the overall rate constants was better than ±2%. [b] ±6%. [c] ±7%.

between the ring-opening reactions B and C elimination is more important than substitution for the more flexible structures II and III, whereas the opposite is true for compound I. Also, the more flexible structure III (open chain) is more prone to elimination than II (six-ring) by a rate factor of about 6. A still more marked drop in rate of elimination would be expected in going from II to I (five-ring). A rate depression of only 1.7 is found, however, and can be consistently explained by the intervention of some steric strain relief which would accompany the opening of the five-membered ring in both reactions C and B.

It should be noted that, although conclusions similar to the above discussion can be drawn from the composition data of Table I, on comparing different substrates they are fortuitous unless reaction rates are obtained. Such information has been provided here for the first time. Another example of composition data which can be correctly interpreted in terms of reactivity comes from the decomposition of the spiro-*N,N*-tetramethylenepiperidinium ion[15,16] where five- and six-membered rings compete for the same reaction in the same molecule. The results, though qualitative, are in essential agreement with the present data since only the five-membered ring of the spiro ion is reported to undergo cleavage for the endocyclic displacement whereas for the β-elimination reaction both rings are cleaved in approximately equal amounts.

We plan to extend this investigation to other cyclic ammonium ions in the small- and medium-ring region and to other base–solvent media.

Experimental Section

Proton magnetic resonance spectra were obtained in $CDCl_3$ solution on a JEOL JNM-C60HL spectrometer, using Me_4Si as the internal standard. Mass spectra were performed either on a AEI MS12 at 70 eV or Varian MAT 111 spectrometer at 80 eV. The preparative VPC experiments were carried out on a Carlo Erba Fractovap Model B instrument. For the VPC analyses and the potentiometric microtitrations see the appropriate section.

Materials. *N*-Methylpyrrolidine (Schuchardt), *N*-methylpiperidine (Schuchardt), butyl methyl ether (Fluka), *n*-butylamine (Erba), and dibutylamine (Fluka) were commercial samples.

N,N-Dimethylpyrrolidinium iodide (I) and *N,N*-dimethylpiperidinium iodide (II) were prepared as described in the literature,[17] in 96 and 92% yields, respectively. Iodide ion content was checked by potentiometric titration and indicated a purity of 100% for both salts.

Dibutyldimethylammonium iodide (III) was prepared according to the procedure used for the preceding salts. It was purified by recrystallization from ethanol–ethyl acetate to give white crystals in 76% yield, mp 148–149 °C (lit.[18] 149–150 °C). Iodide ion analysis indicated a purity of 99%.

4-Dimethylamino-1-butene and 5-dimethylamino-1-pentene were prepared as described in the literature,[19] in 26 and 57% yields, respectively.

Butyldimethylamine was obtained in 86% yield by methylation of butylamine by the Clarke–Eschweiler method,[20] bp 93–95 °C (lit.[21] 94 °C). Dibutylmethylamine was similarly obtained in 80% yield, bp 56–57 °C (18 mm) [lit.[18] 49–51 °C (10 mm)].

The purity and structure of the synthesized amines were thoroughly checked by gas chromatography and ^1H NMR spectrometry.

Kinetics. The overall rates were measured by acid–base potentiometric titration of the total amine product formed. A solution of dried (Adberhalden) ammonium iodide in anhydrous methanol was mixed with the required volume of a stock solution of sodium methoxide in the same solvent. The resulting mixture, 0.1 M in methoxide and 0.05 M in the ammonium salt, was transferred in 1.3-mL aliquots, by an automatic pipet, to dried ampules which were flushed with dry nitrogen and sealed. Two ampules were kept for blank determination. A set of 15–20 ampules was placed in a thermostat at 130 °C, and zero time started 5 min after immersion. A 1-mL aliquot of solution was transferred with a pipet from the ampule to a titration vessel containing 20 mL of acetone and an excess of *p*-toluenesulfonic acid (1 mL, added from a stock methanolic solution), and titrated with 0.05 M tetrabutylammonium hydroxide in MeOH/*i*-PrOH using Radiometer glass G202C and calomel K401 electrodes. Microtitrations were performed with a Radiometer SBR2c-TTT1c-ABU1b apparatus, fitted with a 2.50-mL microburet. End points were determined graphically from the recorded titration curves. Blank determinations were carried out by the same procedure and the value of the actual determination was corrected accordingly. The extent of reaction at infinity time was determined either by potentiometric titration or by VPC measurement (with an internal standard) and found to be no less than 92% for a reaction range wider than 2 half-lives.

Runs were made on the ammonium salts in the absence of sodium methoxide, in order to check the occurrence of solvolyses and of any attack by iodide ion. All such reactions were negligibly slow in comparison with the reaction with methoxide (VPC analysis).

The rate constant of the overall process, k_T, has been evaluated from the integrated second-order rate equation. A least-squares treatment, as carried out with the aid of a Hewlett-Packard 9820A calculator, gave the slope (k_T).

Product Analysis and Partial Rate Coefficients. A. Preparative scale experiments were carried out for the identification of the reaction products. A methanolic solution, 0.5 M in methoxide and 0.25 M in the ammonium iodide, was prepared in a 200-mL Carius tube by adding the required volume of stock methanolic sodium methoxide to a solution of dried ammonium iodide. The tube was sealed and heated in an oven at 130 °C for 48–72 h, than cooled and opened. The content was transferred into a flask, acidified with concentrated HCl, and evaporated to dryness on a rotary evaporator. The solid residue was dissolved in water and the organic bases set free with 18 M NaOH. The aqueous layer was extracted with pentane, and the extract was separated, dried over anhydrous Na_2CO_3, and concentrated. The latter was shown to consist of three compounds by TLC, which were purified by column chromatography on grade II–III alumina (Merck) using petroleum ether (bp 40–60 °C) with an increasing concentration of ether. The three bases thus separated were recovered by removal of the solvents, purified by preparative gas chromatography, and identified by ^1H NMR, mass spectrum, and C, H, N analysis, unless direct VPC comparison was made possible with the aid of an authentic sample.

In the reaction of I two of the components were identified as 4-dimethylamino-1-butene and *N*-methylpyrrolidine by VPC comparison with authentic samples. The third component was identified as 4-dimethylamino-1-butyl methyl ether from the following data: ^1H NMR δ 3.2–3.5 (m, 5 H, CH_2OCH_3 protons), 2.1–2.4 [m, 8 H, $CH_2N(CH_3)_2$ protons], 1.3–1.8 (m, 4 H, "central" methylene protons). In the mass spectrum the product showed a molecular peak at *m/e* 131 (calcd 131) together with a base peak at *m/e* 58, probably due to the fragment $(CH_3)_2{}^+N{=}CH_2$.

Anal. Calcd for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.67. Found: C, 63.91; H, 13.00; N, 10.64.

In the reaction of II two of the components were identified as 5-dimethylamino-1-pentene and *N*-methylpiperidine by comparison with authentic samples. The third component was identified as 5-dimethylamino-1-pentyl methyl ether from the following data: ^1H NMR δ 3.2–3.5 (m, 5 H, CH_2OCH_3 protons), 2.0–2.4 [m, 8 H, $CH_2N(CH_3)_2$ protons], 1.2–1.8 (m, 6 H, "central" methylene protons). In the mass spectrum the product showed a molecular peak at *m/e* 145 (calcd 145), together with a base peak at *m/e* 58, probably due to the fragment $(CH_3)_2{}^+N{=}CH_2$.

In the reaction of III all the components were identified by VPC comparison with authentic samples as butyl methyl ether, butyldimethylamine, and dibutylmethylamine.

B. The rate constants for the individual reactions A, B, and C (Table I) were calculated from the overall rate constant and the composition data. To this end the product composition was determined under kinetics conditions. Four ampules from each set of rate measurements were kept at 130 °C for a time interval corresponding to 80–100% reaction. The content of the ampules (5 mL) was transferred into a 10-mL flask, acidified with 0.2 M HCl, and evaporated to dryness on a rotary evaporator at 40 °C. The solid residue was treated with 5 M NaOH (2 mL) and the organic bases extracted with pentane (3 mL). The pentane extract was analyzed by gas chromatography which was carried out with a Carlo Erba Fractovap Model GI instrument, fitted with a 20% Carbowax 20M on a firebrick (pretreated with sodium hydroxide) column operating in the range 70–180 °C. In the case of compound III a portion of the content (2–3 μL) of the ampules was directly injected into the gas chromatograph. The peaks were identified by comparison with authentic specimens of the compounds. The areas were measured and the molar ratios among the various components were determined by internal calibration based on the analysis of "synthetic" mixtures. Correction factors used for the quantitative evaluation of peak areas were obtained by subjecting standard mixtures of the three reaction products (prepared by accurately mixing weighed amounts of the three products) to the operations involved in the actual isolation procedure. For the cyclic ammonium salts I and II, the percentage found for each tertiary amine in the reaction mixture was the actual percentage of the corresponding reaction; for the open-chain ammonium salt III, the tertiary amine $CH_3CH_2CH_2CH_2N(CH_3)_2$ was produced by both reactions B and C. The contribution of reaction B was evaluated by the VPC determination of the content of $CH_3CH_2CH_2CH_2OCH_3$.

Registry No.—I, 872-44-6; II, 3333-08-2; III, 61134-94-9; sodium methoxide, 124-41-4; methanol, 67-56-1; 4-dimethylamino-1-butene, 55831-89-5; *N*-methylpyrrolidine, 120-94-5; 4-dimethylamino-1-butylmethyl ether, 33962-95-7; 5-dimethylamino-1-pentene, 1001-91-8; *N*-methylpiperidine, 626-67-5; 5-dimethylamino-1-pentylmethyl ether, 58390-18-4; butyl methyl ether, 628-28-4; butyldimethylamine, 927-62-8; dibutylmethylamine, 3405-45-6.

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Synthesis and Structure of Alloxazine 5,10-Dioxides

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Various alloxazine 5,10-dioxides (**7–9**) have been synthesized by direct H_2O_2/trifluoroacetic acid oxidation and their structures proven to consist preferentially in the 1H tautomeric lactam configuration. The three methyl blocked tautomeric forms **12–14** of 3-methylalloxazine 5,10-dioxide (**8**) could be obtained by diazomethane methylation of **8**. Comparisons of the UV spectra are used for the structural assignments.

The first alloxazine *N*-oxide was prepared by Petering,[1,2] who oxidized 8-chloroalloxazine with 30% H_2O_2 in 88% formic acid at 65–95 °C and believed that the 5,10-dioxide was synthesized. In trying to repeat this procedure Berezovskii et al.[3–5] claimed to have obtained only the 10-oxides when oxidizing alloxazine and its methyl derivatives with H_2O_2 in formic acid, with peracetic acid, and with monopersulfuric acid. However, Gladys and Knappe[6] were unable to confirm this.

There is some agreement that the conditions used by Petering will lead to mono-*N*-oxides, specifically the *N*-10-oxide if the N-1 is unsubstituted and the *N*-5-oxide if there is an alkyl substituent in the 1-position. This sensitivity toward steric (peri) hindrance parallels the findings with lumazine *N*-oxides by Pfeiderer and Hutzenlaub.[7] In related studies, alloxazine 5-oxides were prepared by the "indirect" cyclization methods[8–14] which permitted unambiguous placement of the *N*-oxide grouping in the 5-position. Alloxazine 5,10-dioxides have not yet been synthesized via this route.

Since close relationships can be expected between the published structures of lumazine 5,8-dioxides and its alloxazine analogues, we decided to study the structure of alloxazine 5,10-dioxides. These compounds can exist mainly in two energetically favored tautomeric forms, where A would be con-