Influence of Substituents on the Rate of Formation of Ethylenimonium Compounds

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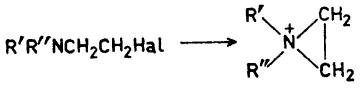
In a previous paper [1] the rates of formation of ethylenimonium compounds from R′R″NCH$_2$CH$_2$Hal have been reported.



The rate constants were found to be strongly dependent on R′ and R″ and increased in the following order: methyl <ethyl< isopropyl. It was suggested that while the differences in rate constants depend to some extent on the differences in electronic density on the nitrogen atoms, it is mostly of steric origin. When R′ and R″ are more bulky, particularly when branched at the carbon atom adjacent to the nitrogen atom, the bond angle R′NR″ is increased because of increased repulsive forces between R′ and R″. The difference between this angle and the angle R′NR″ of the reaction product, which has a three-membered ring, is then smaller. This may result in a lower activation energy and a higher reaction rate. To find further evidence for this, the rates of formation of ethylenimonium ions from compounds in which R′ and R″ are linked in a ring have now been measured. The rates of cyclization of 1,2- and 2,1-dimethylaminochloropropane have also been determined. The latter compounds were investigated to see how alkyl substituents in the 2-haloethyl group affect the reaction rates.

Materials. The preparation of the 2-bromoethylamine hydrobromides has been previously described [1].

N-(2-Bromoethyl)-pyrrolidine (I) hydrobromide. M.p. 174° after recrystallization from acetone/ethanol (3:1). (Found: C 27.8; H 5.0. Calc. for $C_6H_{13}Br_2N$ (259.0): C 27.8; H 5.0).

N-(2-Bromoethyl)-piperidine (II) hydrobromide. M.p. about 240° after recrystallization from acetone/ethanol (1:1). (Found: C 30.8; H 5.6. Calc. for $C_7H_{15}Br_2N$ (273.0): C 30.8; H 5.6). Bany [2] found m.p. 219—220° when the compound was prepared from the hydrochloride of the chloro derivative and $CaBr_2$.

Schultz's and Sprague's method [3] was used for preparation of 1-dimethylamino-2-chloropropane (III) hydrochloride (m.p. about 180°; in Ref.[3] m.p. 185—186° is given) and 2-dimethylamino-1-chloropropane (IV) hydrochloride (m.p. 100°; in Ref.[3] m.p. 103—104° is given) from the corresponding aminoalcohols.

Kinetics. The method described in Ref. [1] was used. The results are presented in Table 1. The pK_a'-values were calculated as described in Ref. [1], using the equation given by Hall [4] together with his constants and those in Ref. [1].

Discussion. The previous investigation [1] showed that the rate of cyclization of tertiary 2-aminoethyl bromides increased with increasing pK_a'. Applying this rule to I, II, and V the order of increasing rate constants should be II < V < I. The observed order is I < II < V. For closely related amines the one having the highest pK_a'-value is normally regarded to be the best nucleophile. Consequently the cyclizations cannot be reactions for which the rate constants can be correlated with the basicity of the nitrogen atoms.

I and V have almost identical structures except that in I R′ and R″ are bound together in a ring. The repulsion forces between R′ and R″ may therefore result in a greater bond angle, R′NR″, in V than in I, where the bond angles must be normal because of ring strain. Also, in a six-membered ring such as II, it is likely that the angle R′NR″ is smaller than in V. The theoretical difference between R′NR″ in the folded six-membered ring and the flat five-membered ring is about 1.5°. Accordingly, applying the theory mentioned in the introduction, I and II are expected to react more slowly than V. This is as found (Table 1) and the relative rates are 1, 4, and 20.

The products of the cyclization of I and II, 3-azoniaspiro[2.4]heptane bromide and 3-azoniaspiro[2.5]octane bromide, respectively, are spiro compounds having a common quaternary nitrogen atom for the two rings. The rates of reaction between the spiro compounds and thiosulphate ions were measured as previously described [1]. For both compounds the rates were found to be approximately proportional to $[S_2O_3^{2-}]^{1.1}$ when $[S_2O_3^{2-}]$ had values in the

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Table 1. pK_a' and rate constants for the cyclization of some 2-haloethylamines. Temperature 25°. μ = 0.07. k_{obs} = observed rate constant for an equilibrium mixture of the amine and the ammonium forms of the compounds. k_1 = rate constants of the amine forms. Units of k_{obs} and k_1 are sec^{-1}. The values of pK_a' and log k_1, where error limits are not given, are values for which the accuracy is estimated as better than ± 0.2 units.

	Compound	pK_a'	pH at which log $k_{obs} = -3.5$	log k_1	Measurements in pH-range
I	$(CH_3)_4NCH_2CH_2Br$	8.9	7.14±0.02	−1.7	6.70−7.60
II	$(CH_2)_5NCH_2CH_2Br$	8.6	6.07±0.01	−1.1	5.90−7.40
III	$(CH_3)_2NCH_2CHClCH_3$	8.31±0.03	7.68±0.02	−2.79±0.02	7.00−9.20
IV	$(CH_3)_2NCH(CH_3)CH_2Cl$	8.6	6.96±0.03	−1.8	7.10−8.00
V[1]	$(CH_3CH_2)_2NCH_2CH_2Br$	8.7		−0.4	
VI[6]	$(CH_3)_2NCH_2CH_2Cl$	8.2		−3.54	
VII[1]	$(CH_3CH_2)_2NCH_2CH_2Cl$	8.80		−2.03	
VIII[1]	$(CH_3)_2NCH_2CHBrCH_3$	8.0		−1.1	
IX[1]	$(CH_3)_2NCH_2CH_2Br$	8.0		−2.0	

interval (0.25−1.0) × 10^{-2} M. Based on the mean values of measurements in solutions with $[S_2O_3^{2-}]$ = 0.005 M the second order rate constants, k_2, for reactions with the spiro-compounds from I and II were found to be 7 × 10^{-2} and 3.2 × 10^{-2} M^{-1} sec^{-1}, respectively. These values are within the limits reported [1] for ethylenimonium compounds where R′ and R″ are acyclic alkyls. The reactions with thiosulphate ions therefore seem to be only slightly affected by the second, larger ring.

The rate of cyclization increases when in 2-dimethylaminoethyl chloride, VI, one of the hydrogen atoms on the carbon atoms between the nitrogen atom and chlorine atom is substituted by a methyl group, III and IV. This result may be compared with intermolecular substitutions of alkyl halides. The hydrolyses of ethyl bromide and isopropyl bromide have approximately the same rate constants when the reaction is of the S_N1 type but when the reaction is of the S_N2 type isopropyl bromide is hydrolyzed about 40 times more slowly than ethyl bromide [5]. The higher reaction rate for III, which is a derivative of isopropyl chloride, than for VI, a derivative of ethylchloride, shows that the formation of ethylenimonium ring may not be compared with intermolecular S_N2 reactions. IV reacts about 50 times faster than VI and also faster than 2-diethylaminoethyl chloride VII. To explain this it is suggested that the methyl group that differentiates IV from VI may increase the reaction rate in the same way as an *a*-methyl group in R′ and R″ by reducing the bond angle N−C−CCl.

In Ref. [1] the reaction rate was reported for a compound said to have the structure $(CH_3)_2NCH_2CHBrCH_3$ (VIII). The log k_1-value for VIII is about 1.7 units higher than for III and 0.7 units higher than for IV which are both chlorine-containing analogues of VIII and its isomer. The difference in log k_1 between V and its chlorine analogue VII is 1.6 units and between IX and VI 1.5 units. These values are much closer to 1.7 than to 0.7 implying that the suggested structure of VIII is correct.

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