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Reaction Kinetics of Aliphatic Tertiary β-Chloroethylamines in Dilute Aqueous Solution. II. Hydrolysis of the Ethylenimonium Ion[1]

BY BARNETT COHEN, ERVIN R. VAN ARTSDALEN AND JOSEPH HARRIS

Study was made at fixed *p*H of the kinetics of hydrolysis of the ethylenimonium ions resulting from the first order cyclization of a series of seven aliphatic tertiary β-chloroethylamines in 0.001 to 0.0025 *M* aqueous solutions at 37° and 47°. This hydrolysis appeared to be uncomplicated in the case of the (β-chloroethyl)-ethylenimonium ions; but definite complications were observed in the case of (β-hydroxyethyl)-ethylenimonium ion, caused in large part by reaction with the end-product. It is shown that the rate of hydrolysis of these ethylenimonium ions increases with increasing *p*Ka of the parent amine and hence is closely related to the electron density at the atom under attack by the water molecule. A mechanism of hydrolysis is proposed.

The chemical transformations of the aliphatic tertiary β-chloroethylamines subsequent to the initial, reversible, monomolecular cyclization[2]

$$\mathrm{RR'NCH_2CH_2Cl} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathrm{EI}}{\mathrm{RR'\overset{+}{N}CH_2CH_2}} + \mathrm{Cl^-} \quad (1)$$

center mainly around the reactivity of the cyclic ethylenimonium ion, EI, toward electron-donating compounds.[3] Experimental proof that EI is a singly charged cation will be presented in Paper III of this series. The reaction of EI and water resulting in ring rupture and evolution of a proton is characteristic of the general reaction with uncharged electron donors of the type HX and may be represented schematically as

$$\mathrm{EI} + \mathrm{HOH} \xrightarrow{k_h} \underset{\mathrm{I}}{\mathrm{RR'NCH_2CH_2OH}} + \mathrm{H^+} \quad (2)$$

The resulting amino alcohol, I, if it contains one or two N-β-chloroethyl groups, can cyclize at proper *p*H, and each successive ethylenimonium ion can be similarly hydrolyzed as it is generated. Unless otherwise specified, this report deals with the hydrolysis of the first EI resulting from reaction (1), in which R and R′ in the cyclic ion represent an alkyl and a β-chloroethyl group.

Process (2) is subject to the following three possible complications: (a) Reversal of reaction (1) to regenerate the parent β-chloroethylamine; this is negligible in dilute aqueous solution,[2] (b) interaction of EI with hydroxyl ion to produce I, a reaction which was not observed within the range *p*H 3.6 to 8.5 in the case of the type compound, N-methyl-(β-chloroethyl)-ethylenimonium ion or any of its homologs; (c) combination of EI with its ethanolamine. The last can be eliminated in solutions sufficiently acid to block the nitrogen of the amino alcohol by forming the corresponding substituted ammonium ion. Also, the amino alcohols resulting from each of the cyclic imonium ions that contain one or more β-chloroethyl groups (see Table I) are quickly withdrawn by rapid conversion to the corresponding second cyclic ions, the hydrolysis products of which appear in appreciable concentration only after reaction (2) has run 40% or more of its course. Thus, by suitable choice of conditions, hydrolytic process (2) can be isolated sufficiently for direct kinetic study. The results constitute the second link in the description of the series of reactions which the aliphatic tertiary β-chloroethylamines can undergo at controlled *p*H in dilute aqueous solution. Analysis of the kinetic and qualitative data provides an insight into the possible mechanism of the hydrolysis with accompanying opening of the ethylenimonium ring.

The hydrolysis of the N-alkyl-(β-chloroethyl)-ethylenimonium compounds under consideration is the rate-determining step for the subsequent rapid cyclization, therefore the course of process (2) can be followed conveniently and accurately

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[1] The work described in this report was performed in part under a contract recommended by the National Defense Research Committee, between the Office of Scientific Research and Development and the Johns Hopkins University.

[2] B. Cohen, E. R. Van Artsdalen and J. Harris, THIS JOURNAL, **70**, 281 (1948).

[3] (a) C. Golumbic, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946), and subsequent papers; (b) P. D. Bartlett, S. D. Rose and C. G. Swain, THIS JOURNAL, **69**, 2971 (1947).

TABLE I

KINETIC CONSTANTS OF HYDROLYSIS OF FIRST CYCLIC ETHYLENIMONIUM IONS, $RR'\overset{+}{N}CH_2CH_2$, IN WATER AT 37° AND 47°

R	R′	pK'_a[a] 37°	$k_h \times 10^4$[e] liter/mole min. 37°	47°	E kcal.[f] per mole	$\Delta F^{\ddagger}$, kcal.[g] per mole	$-\Delta S^{\ddagger}$ e.u.[h]
$(CH_3)_2CH$	$ClCH_2CH_2$	6.5	1.36	2.67	13.4	26.2	43
$CH_3(CH_2)_2$	$ClCH_2CH_2$	6.3	0.960	2.49	18.8	26.4	27
$CH_3(CH_2)_3$	$ClCH_2CH_2$	6.15[b]	.724	2.14	21.4	26.6	19
C_2H_5	$ClCH_2CH_2$	6.10	.672	1.59	17.0	26.6	33
CH_3	$ClCH_2CH_2$	5.97	.906	2.38	19.8[i]	26.4	23
CH_3	$HOCH_2CH_2$	7.02	.168[c]	0.44[c]	19.1	27.5	29
$ClCH_2CH_2$	$ClCH_2CH_2$	4.0[b]	17.6[d]	...	...	..	..

[a] Values refer to the parent *t*-amines. Extrapolated from 0° and 15° data, $\Gamma/2 = 0.0025$. [b] $\Gamma/2 = 0.0010$–0.0015. [c] At *p*H 4.0 and 5.0, see text. [d] Extrapolated, assuming $E = 15$ kcal., from 25° where $k_h = 6.60 \times 10^{-4}$. [e] At *p*H 7.4. [f] ±1 kcal. [g] At 37°; ±2 kcal. [h] ±4 e.u.· Calcd. for 37° assuming transmission coef. = 1 (ref. 8). [i] Includes data at 25°.

by measuring the rate of evolution of chloride ion by this subsequent cyclization. Likewise, the uptake of thiosulfate can usually be used to follow the change in concentration of EI. The rate of acid production during the early stages of the hydrolysis can be employed also, but less accurately.

Experimental

Materials.—The ethylenimonium compounds (see Table I) were produced in solution by cyclization of the corresponding pure tertiary β-chloroethylamines as described in Paper I of this series.[2] Most of the chlorohydrin of methyl-bis-(β-chloroethyl)-amine was prepared from the picryl sulfonate[3] and found to behave kinetically as did that from the chloride.

Rate Measurements.—The general experimental procedures were substantially the same as those described in ref. 2, except as follows. In order to obtain maximum speed of production of EI, the 2-ml. sample of stock 0.25 *M* amine hydrochloride was added to 198 ml. of alkalinized test solution and held at *p*H 9.0 for 2 to 20 min., depending on the temperature and specific rate of cyclization. The acidity was then allowed to rise (or 0.05 *M* HNO_3 was added) to the predetermined *p*H. In sufficiently acid solution, *e.g.*, *p*H 3.6, for the methyl compound, the hydrolysis products neutralized each other and the *p*H remained constant throughout the hydrolysis. At a *p*H within significant range of the pK'_a of the aminoethanol formed, the acid produced was neutralized under colorimetric control by frequent successive small additions of 0.05 *N* NaOH. A check determination under glass electrode control showed that 0.0002–0.0004% sulfonphthalein indicator, *e.g.*, phenol red, did not affect the hydrolysis of EI. The periodic additions of NaOH served also to measure the H^+ production, the rate of which was substantially the same as that of the Cl^- evolution through at least the first 30% of the hydrolysis.

Errors.—For most of the compounds studied, the probable over-all error was within 10%; for the last two compounds of Table I, it was within 15%. Duplicate experiments generally agreed to about 3% or better.

Results and Discussion

The hydrolysis of each of the seven compounds specified in Table I followed a first order course. In the case of the last two compounds listed, the reaction involves some complications which will be discussed presently. The results of a representative determination are shown in Table II for the simplest compound, N-methyl-(β-chloroethyl)-ethylenimonium ion.

TABLE II

HYDROLYSIS OF $CH_3\overset{+}{N}(CH_2CH_2Cl)CH_2CH_2$ AT 37.0°

Initially, [amine·HCl] = [NaOH] = 0.002457 mole/liter; neutralized phenol red, 0.0002%; adjusted to *p*H 7.4 14 min. before first sample.

Reaction time, min.	Cl^- produced %[a]	$k \times 10^3$ min.$^{-1}$
20	6.3	
50	19.5	5.07
80	31.0	5.14
120	42.8	4.66
160	53.6	5.22
251	70.2	4.91
	Slope	5.00
	Duplicate	4.93

[a] 100% = 1 equivalent of Cl^- per mole of EI.

The rate observed at 37° was the same, within experimental error, at *p*H 3.6, 7.4 and 8.5 when determined by measurements of residual EI, of chloride evolution, or of acid production. This is shown in Table III, which gives the apparent first order rate constants as evaluated from the best slopes through the experimental data. A computation based on two successive first order processes at *p*H 7.4 shows that the maximum concentration of EI (94.3% of stoichiometric) was reached in 10.5 min. At this time, less than 2% of N-methyl-bis-(β-chloroethyl)-amine remained in the mixture, and there was practically none at the time of removal of the first sample.

TABLE III

APPARENT FIRST ORDER RATES AT 37° (DETERMINED FROM SLOPES)

$0.00503/55.5 = k_h = 9.06 \times 10^{-5}$ liter/mole min.

*p*H	Anal. method	Reaction, %	$k \times 10^3$ min.$^{-1}$
3.6	$S_2O_3^{=}$ uptake	63	5.02
7.4	Cl^- production	72	4.96
8.5	Cl^- production	86	5.18
8.5	H^+ production	30	(5.0)
		Av.	5.03

Hydrolysis of bis-(β-chloroethyl)-ethylenimonium ion (Table I, last compound) occurred too rapidly for confident measurement at 37°. At 25°, the production of chloride proceeded in two readily distinguished first order steps, the first representing the above compound and the second that of the succeeding hydroxyethyl-(β-chloroethyl)-ethylenimonium ion (see Table IV). The uncorrected acid production ran generally parallel with that of chloride ion in the first case but diverged in the second, evidently as the result of fixation of H^+ by accumulating triethanolamine (pK'_a 7.75), the final product.

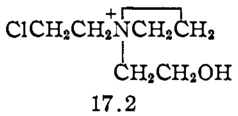
TABLE IV

A. HYDROLYSIS OF $(Cl_2CH_2CH_2)_2\overset{+}{N}CH_2CH_2$ AT 25°

Initially, [tris-(β-chloroethyl)amine·HCl] = [NaOH] = 0.001 mole/liter; neutralized phenol red, 0.0002%; pH 7.4

Reaction time, min.	Cl^- produced, %[a]	$k \times 10^2$ min.$^{-1}$
10.0	7.7	
13.0	18.0	3.95
16.0	26.1	3.45
20.0	37.0	3.99
24.0	45.7	3.73
29.0	59.0	(5.6)
From av. slopes, 3 replicates		3.66

B. SECOND CHLORIDE; HYDROLYSIS OF


$ClCH_2CH_2\overset{+}{N}(CH_2CH_2OH)CH_2CH_2$

81	17.2	
100	27.2	0.68
121	39.1	.85
150	49.2	.63
180	59.4	.74
222	69.9	.72
330	83.5	(0.6)
From av. slope, 3 replicates		0.68

[a] 100% = 1 equivalent of Cl^- per mole of EI.

Compared with the other compounds studied, these cyclic transformation products of tris-β-chloroethylamine have notably high hydrolysis rates which are obviously associated with the effects of the substituents on the central nitrogen atom. A similar trend has been observed in acetone–water solution.[4]

Under the conditions specified, *i.e.*, low concentration of EI and moderate pH, the hydrolysis of all the initial (chloroethyl)-ethyleneimonium ions produced by cyclization of the alkyl tris- and bis-(β-chloroethyl)-amines was apparently uncomplicated by cyclic dimerizations. This is attributable to the rapid cyclization in the first and third steps of decomposition, thus leaving the middle, hydrolytic, step unencumbered. The kinetics and accompanying analyses did not disclose the presence of any by-products, *e.g.*, piperazinium derivatives, in the reaction mixtures. The observation[5] that tris-β-chloroethylamine is transformed almost completely to triethanolamine in buffered, dilute solution indicates that the kinetics of this complex system in water may yield to complete analysis after the establishment of the specific rates of the final steps not touched upon in this study.

A comparison was made between our analytical data for the total series of changes from methyl-bis-(β-chloroethyl)-amine to methyldiethanolamine and the computed values based on the simple assumption that we were dealing with four consecutive irreversible first-order reactions. For this purpose we employed the experimentally determined four rate constants at 37°, pH 7.4, and the pK'_a values for the parent amine, the intermediate β-hydroxyethylamine and the final methyldiethanolamine.

The computed data were in rather good agreement with the observed values for Cl^- and H^+ produced and for $S_2O_3^=$ consumed at different times from the start of the reaction to the end of the third step. However there were serious deviations from the assumed uncomplicated terminal step to methyldiethanolamine.[6] This brings us to a consideration of this terminal hydrolysis.

Hydrolysis of the Imonium Ion of N-Methyl-β-chloroethyl-β-hydroxyethylamine.—The amine cyclizes rather quickly (half-life = 2.2 min. at 37°, pH 9.2) to the imonium ion. If the pH is changed after 10 min. to 4.0 or 5.0, the subsequent hydrolysis rate of the imonium ion runs a simple first order course, $k_4 = 0.0093$ min.$^{-1}$ (*i.e.*, $k_h = 0.168 \times 10^{-4}$ min.$^{-1}$). As the pH is increased, the rate constant increases to 0.00112 min.$^{-1}$ at pH 7.4, but remains first order for at least 80% of the reaction. However, at pH 9.2 the constant not only increases but does so at an accelerating speed with time. Obviously, the last effect is due in large part to interaction of the imonium ion with the end product methyldiethanolamine, pK'_a 8.32, because this effect can be reproduced at pH 9.2 by the addition of extraneous methyldiethanolamine.

However, prolonged experiments and calculations have not permitted us to account for the pH effect as due simply to the end-product. In fact, it seems that hydroxyl ion concentration introduces an additional complication which we have not yet been able to unravel kinetically.

In short the slow terminal process and the production of free methyldiethanolamine in alkaline solution seem to complicate the simple hydrolysis through the formation of a dimer (tentatively confirmed by the isolation of a small amount of a picryl sulfonate, m.p. 203°, corresponding to that of the linear dimer.[3a] This and the apparent action of hydroxyl ion tend to accelerate the disappearance of this imonium ion as the pH increases.

Examination of Fig. 1 shows again the general proportionality of the hydrolysis constants found among the homologous ethylenimonium ions and the free energy changes involved in the acid–base dissociations of the corresponding parent amines. The interpretation we offered in ref. 2 seems to apply here equally well. The linear relation found between $-\log k_h$ of four of the homologous cyclic ions and the pK'_a of the antecedent β-chloroethylamines is clear. The methyl compound occupies an aberrant position. A direct comparison should involve the dissociation exponents of the compounds hydrolyzed, namely, the ethylenimonium ions; but the latter are extremely weak acids (in the Brönsted sense). It seems logical to carry the reasoning a step further. Since $-\log k_h$ of the ethylenimonium ion is linearly related to the pK'_a of the parent amine, then this correlation should extend to the pK'_a value of each of the ethylenimonium ions. Although these pK'_a values are undeterminable the *differences*, $\Delta pK'_a$, of those that conform to the linear relationship can be estimated.

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(4) P. D. Bartlett, S. D. Ross and C. G. Swain, THIS JOURNAL, **71**, 1415 (1949).

(5) C. Golumbic, M. A. Stahmann and M. Bergmann, *J. Org. Chem.*, **11**, 550 (1946).

(6) We are indebted to Dr. Lawson L. Rosenberg for much of the laboratory work and computations involved in this phase of the study.

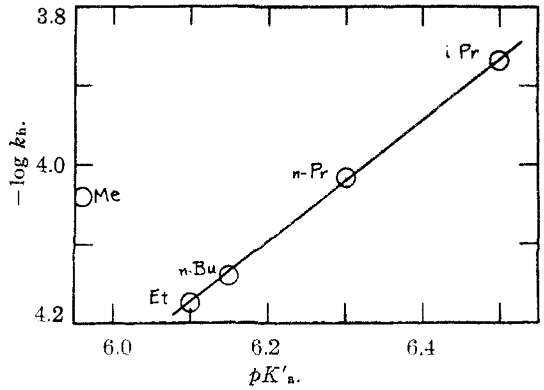

Fig. 1.—Relation of pK'_a of homologous parent amines to the hydrolysis rate of their cyclic ethylenimonium ions at 37°: $\mathrm{RR'^{+}\overline{NCH_2C}H_2}$, R = CH_2CH_2Cl; R' = Me = methyl; Et = ethyl; *n*-Bu = *n*-butyl; *n*-Pr = *n*-propyl; i-Pr = isopropyl.

From the slope shown in Fig. 1, they should be

$$\mathrm{RR'\overset{+}{\overline{NCH_2C}}H_2} \qquad R' = CH_2CH_2Cl$$

R =	Et	*n*-Bu	*n*-Pr	*i*-Pr
$\Delta pK'_a$ =		0.05	0.15	0.20

Mechanism of Hydrolysis of the Ethylenimonium Ion.—The EI ion may be regarded as an intramolecularly stabilized carbonium ion and, as such, it can undergo the reactions characteristic of the C^+ ion. Among these are reactions with anions, *e.g.*, Cl^-, OH^-, $S_2O_3^=$, as well as with uncharged electron-donors such as R_3N, etc. The polar nature of the EI ion indicates that it is undoubtedly highly solvated in water.

At *p*H levels between 3.0 and 8.5, the rate values remained constant for the hydrolysis of the first ethylenimonium ions of the compounds studied. Therefore we have no evidence for the participation of hydroxyl ions in these cases; although we did find this to be apparently the case for the *second* EI ion of methyl-bis-(β-chloroethyl)-amine. Hence, we must assume generally a direct interaction of H_2O through the polarized C–N linkage to produce a substituted ethanolamine and a proton. Where the reaction is exceedingly slow, or the concentration of hydroxyl ions is appreciable, or both, then the effect of the latter ion is superposed. It has been pointed out that the high reactivity of the EI ion is the combined result of the strain of the 3-membered ring and the polarizing effect of the positive charge on the C–N linkage.[3b] The ion is thus very reactive toward any nucleophilic agent capable of attacking the carbon of the 3-membered ring.

The energy of activation of the hydrolytic process lies from 13.4 to 21.4 kcal. (Table I), values rather less than that for cyclization, which is about 25 kcal.[2] As expected for the formation of a polar, solvated intermediate, the entropies of activation were all large negative values.[7] This accounts for the relative slowness of the reaction, despite the more favorable energy of reaction.

From the data presented here, one can readily select a series of 4 compounds with increasing β-chloroethyl substitution and observe that there is a considerable increase in the hydrolysis rate associated with a decrease in the electron density of the ring carbon under attack.

(7) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, SCHOOL OF MEDICINE, THE JOHNS HOPKINS UNIVERSITY]

Reaction Kinetics of Aliphatic Tertiary β-Chloroethylamines in Dilute Aqueous Solution. III. Reactions of the Ethylenimonium Ion with Certain Anions[1]

BY BARNETT COHEN, ERVIN R. VAN ARTSDALEN AND JOSEPH HARRIS

The kinetics of the reactions between thiosulfate, bicarbonate, chloride, propionate and benzoate ions with the first ethylenimonium ions of several aliphatic tertiary β-chloroethylamines was studied and the rate constants of these reactions established. Variation of ionic strength causes pronounced changes in rates which can be explained quantitatively by the Brönsted–Debye relationship only if the ethylenimonium ion is a singly charged cation. Rate of the reversal of the initial cyclization of the parent amine by reactions of the ethylenimonium ion with chloride ion was investigated, and from this it was shown that this initial cyclization in dilute aqueous solution is over 99.5% complete.

The ethylenimonium ion produced in the cyclization of an aliphatic tertiary β-chloroethylamine acts like an internally stabilized carbonium ion, consequently a great variety of reactions is possible. In this, the final paper of the series, we report studies on the kinetics of the interaction with $S_2O_3^=$, HCO_3^-, Cl^-, propionate and benzoate to form the corresponding esters. By suitable manipulations, we were able to isolate the reactions and examine many of them in considerable detail.

After the initial reversible cyclization,[2] the

$$\underset{\mathrm{I}}{\mathrm{RR'NCH_2CH_2Cl}} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \underset{\mathrm{II\ \ (EI)}}{\mathrm{RR'\overset{+}{\overline{NCH_2C}}H_2}} + \mathrm{Cl^-} \quad (1)$$

reactions of II in water may be represented schematically as[3]

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(1) The work described in this report was performed in part under a contract recommended by the National Defense Research Committee, between the Office of Scientific Research and Development and the Johns Hopkins University.

(2) B. Cohen, E. R. Van Artsdalen and J. Harris, THIS JOURNAL, **70**, 281 (1948).

(3) C. Golumbic, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 518, 543, 550 (1946); (b) P. D. Bartlett, S. D. Rose and C. G. Swain, THIS JOURNAL, **69**, 2971 (1947).