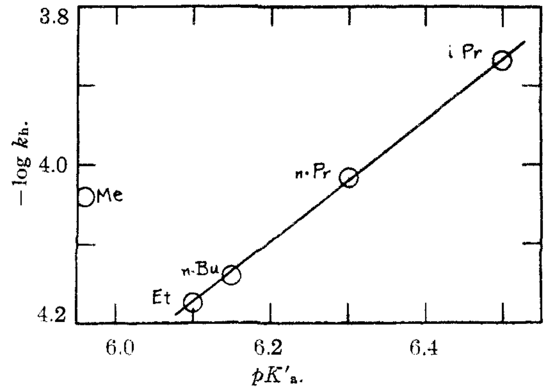

Fig. 1.—Relation of pK'_a of homologous parent amines to the hydrolysis rate of their cyclic ethylenimonium ions at 37°: $RR'^{+}NCH_2CH_2$, R = CH_2CH_2Cl; R' = Me = methyl; Et = ethyl; *n*-Bu = *n*-butyl; *n*-Pr = *n*-propyl; i-Pr = isopropyl.

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

$$RR'\overset{+}{N}CH_2CH_2 \qquad R' = CH_2CH_2Cl$$

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

$$\underset{\text{I}}{RR'NCH_2CH_2Cl} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \underset{\text{II (EI)}}{RR'\overset{+}{N}CH_2CH_2} + Cl^- \quad (1)$$

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).

$$\text{II} + H_2O \xrightarrow{k_h} \underset{\text{III}}{RR'NCH_2CH_2OH} + H^+ \qquad (2)$$

$$\text{II} + \text{III} \xrightarrow{k_a} RR'NCH_2CH_2\overset{+}{N}(RR')CH_2CH_2OH \qquad (3)$$

$$\text{II} + \text{I} \xrightarrow{k_d} \text{linear and cyclic dimers} \qquad (4)$$

$$\text{II} + Cl^- \xrightarrow[(k_x)]{k_{-1}} RR'NCH_2CH_2Cl \qquad (5)$$

Hydrolysis (2) with evolution of acid, represents an example of the reaction with compounds of the type HX, *e.g.*, H_2O, RSH, and was considered in the preceding paper[4]; equations (3) and (4) are representative of the general reaction with electron donors of the type RX, *e.g.*, R_3N, R_2S; and these processes can be avoided by operating at sufficiently low *p*H where the proton density interferes. At present, we are concerned with equation (5), representative of a general reaction with anions. As the reaction with Cl^- is the reverse of equation (1), this enables us to compute a theoretical equilibrium constant for this reversible process.

Results and Discussion

The Thiosulfate Reaction.—A typical series of observations is given for the EI of isopropyl-bis-(β-chloroethyl)-amine in Table I. Similar determinations were made on the first ethylenimonium ions of the *n*-propyl, ethyl, methyl homologs and of tris-(β-chloroethyl)-amine.

TABLE I

FIRST EI OF ISOPROPYL-BIS-(β-CHLOROETHYL)-AMINE + $S_2O_3^=$

(Rate of formation of the monothiosulfate) 0.252 mmole of amine·HCl + 0.277 mmole NaOH in 95 ml. of H_2O held at *p*H 9.0 for 25 min. Adjusted to *p*H 4.0 with 0.0082 ml. of 2.473 *N* HCl. At zero time added 5.0 ml., 0.0991 *M* $Na_2S_2O_3$; initial [EI] = 0.002537 *M*; initial $[S_2O_3^=]$ = 0.004955 *M*; *p*H 4.00, 15°; $\sqrt{\Gamma/2} = 0.139$; (at 0°, $k_t = 38.8$; E = 13,300 cal. at $\sqrt{\Gamma/2} = 0$).

Time, min.	2.473 *N* HCl ml. × 100	Reaction, %	k_t, l./mole min.
0.37	2.19	21.4	139
.67	3.47	33.8	131
.95	4.47	43.6	139
1.32	5.43	52.9	137
1.63	6.10	59.5	137
2.04	6.87	67.0	137
2.67	7.60	74.1	139
3.43	8.29	80.8	135
3.98	8.63	84.1	135
4.37	8.88	86.5	133
73.0	11.57	100	...
130.0	11.57	100	...
		Av.	136

Effect of Ionic Strength.—The rates of reaction between ions are strongly influenced by the ionic environment. This primary salt effect which involves activity coefficients can be described for dilute solutions by the well known equation (5a) derived from the Debye–Hückel theory of electrolytes.

$$\log k_{obs} = \log k_t^0 + 2\,Az_1z_2\sqrt{\Gamma/2} \qquad (5a)$$

where k_t^0 is the rate constant at zero ionic strength, A is the Debye–Hückel constant[5] (0.4977 at 25°), z_1 and z_2 are the charges on the reacting species, and $\Gamma/2$ is the ionic strength. For the reaction between $S_2O_3^=$ and EI, the slope of the plot relating log k_{obs} to $\sqrt{\Gamma/2}$ at 15° should be −1.991 if the EI is indeed a singly charged positive ion as postulated, and it is clear that this is the case as seen from Table III, last two columns.

To save space, we dispense with a diagram of log k_{obs} *vs.* $\sqrt{\Gamma/2}$ which shows that the data of Table III conform almost exactly to the relations involved in the reaction of thiosulfate ion with a singly charged cation (ethylenimonium ion) and none other.

Table II gives the data for the EI of ethyl-bis-(β-chloroethyl)-amine and shows the good concordance with theory. On the last line of Table II is included an example in which $\Gamma/2$ was built up with Na_2SO_4. It was not the best choice because of specific effects but its effect in bringing k_t^0 within fair approximation to the theoretical value serves as additional evidence for the predicted influence upon the reaction process.

TABLE II

EFFECT OF IONIC STRENGTH ON REACTION RATE OF $S_2O_3^=$ + EI OF ETHYL-BIS-(β-CHLOROETHYL)-AMINE; *p*H 4.00, 15°

Initial concn., mmole/liter $S_2O_3^=$	EI	Average $\sqrt{\Gamma/2}$ × 100	k_{obs}, l./mole min.	k_t^0
0.99	0.99	7.03	83.3	116
1.98	1.00	8.83	74.1	111
1.98	0.99	8.90	76.3	115
4.96	2.50	13.85	63.0	119
4.96	2.50	14.07	60.8	116
1.98	1.00	15.11	61.9	(124)
			Av.	116

Table III summarizes the data on the thiosulfate reaction with the EI of the 5 compounds examined on a uniform basis of temperature, *p*H and zero ionic strength. It should be noted that the rate values for the EI of tris-(β-chloroethyl)-amine are approximate; nevertheless, its reaction rate stands out as very much greater than those of the other compounds studied.

TABLE III

SUMMARY OF RATE DATA REFERRED TO $\sqrt{\Gamma/2} = 0$

Reaction: EI + $S_2O_3^=$ → monothiosulfate; *p*H 4.00, 15°

EI from β-chloroethyl-amine	Initial concn. mmole/liter EI	$S_2O_3^=$	Average $\sqrt{\Gamma/2}$	k_{obs}, liter/mole min.	k_t^0, liter/mole min.
Tris-	1.28	1.98	0.101	...	2500[a]
	1.33	1.98	.100	...	
Isopropyl-bis-	2.51	4.96	.139	138.9	260
	2.54	4.96	.139	136.4	
n-Propyl-bis-	2.50	4.96	.139	84.9	160
	2.49	4.96	.139	84.2	
Methyl-bis-	2.40	4.96	.139	71.0	140
	2.44	4.98	.139	76.6	
Ethyl-bis-	2.50	4.96	.139	63.0	118
	2.50	4.96	.141	60.8	

[a] Extrapolated from 0°, assuming 13,300 cal. for activation energy (see Table I).

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(4) B. Cohen, E. R. Van Artsdalen and J. Harris, THIS JOURNAL, **74**, 1875 (1952).

(5) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1944, p. 119.

The Bicarbonate Reaction.—The rates of disappearance of EI in the presence of bicarbonate were followed in five of the homologous compounds. The concentration of bicarbonate, 25 mmolar, was selected because it is comparable to the concentration in blood serum. An example of the results obtained is given in Table IV, where $k'_{\text{obs}} = k'_{\text{h}} + k'_{\text{b}}$.

TABLE IV

HCO_3^- + EI OF METHYL-BIS-(β-CHLOROETHYL)-AMINE

Initial [EI] = 0.0025 *M*; 0.0002% phenol red; initial $[HCO_3^-]$ = 0.025 *M*; NaOH to *p*H 7.6; *p*H 7.6; 37°; average $\Gamma/2 = 0.027$

Time, min.	EI, %	k'_{obs} $10^3 \times$ min.$^{-1}$
25	89.7	...
50	76.0	6.7
80	63.8	5.8
123	49.4	5.9
165	38.3	6.1
215	27.0	7.0
275	19.8	5.2
353	12.3	6.2
391	9.4	7.0
	Slope	6.2
	Replicates,	6.2; 6.4

A control experiment in which $NaNO_3$ was substituted for $NaHCO_3$ gave $k'_{\text{obs}} = 0.0052$, within the experimental error of 0.00503 for k'_{h} in water alone as previously[4] reported. Therefore, the observed difference is not due to a simple salt effect. In 10 m*M* bicarbonate, under the same conditions k'_{obs} was found to be 0.0054 min.$^{-1}$.

The results obtained with the five compounds are given in Table V. The data in Table V are concerned with one level of ionic strength (0.027) only; as the lack of materials prevented further study. The last column in the table gives the second order rate constants, k_{b}. A calculation of the ratio $k'_{\text{b}}/k'_{\text{h}}$ for each of the compounds gives values of the same order of magnitude. This would seem to be an indication that the mechanisms of the hydrolysis and bicarbonate reactions may probably be similar dynamically.

TABLE V

SUMMARY OF RATE DATA IN 25 m*M* BICARBONATE

*p*H 7.6; 37°; average $\Gamma/2 = 0.027$

EI from bis-(β-chloroethyl)-amine	$k'_{\text{obs.}}$, $10^3 \times$ min.$^{-1}$	k'_{b},[a] $10^3 \times$ min.$^{-1}$	k'_{b}, $10^3 \times$ min.$^{-1}$	k_{b}, $10^3 \times$ liter/mole min.
Isopropyl-	10.00	7.57	2.43	9.72
n-Propyl-	6.80	5.33	1.47	5.88
Methyl-	6.25	5.03	1.22	4.88
n-Butyl-	5.09	4.02	1.07	4.28
Ethyl-	4.87	3.73	1.14	4.56

[a] See Table I of ref. 4.

The apparent instability of the carbonic ester suggests that the presence of bicarbonate may provide a more rapid by-pass for the decomposition of EI than is offered by the much slower reaction with H_2O. That is, hydrolysis of the ester would accomplish the same end result much more rapidly. Our knowledge of these compounds suggests this possibility.

Reaction of EI with Cl^-.—In dilute solutions of the EI of the bis-(β-chloroethyl)-amines (0.001 to 0.005 *M*), the back reaction is negligibly small as judged by the great uniformity of the hydrolysis constants obtained in such solutions. To secure an observable effect, it was necessary to operate with added NaCl at high levels. An example of a determination is given in Table VI which shows the data obtained at $[Cl^-] = 0.340$ *M* with the EI of methyl-bis-(β-chloroethyl)-amine, the only compound studied in sufficient detail.

TABLE VI

REACTION OF EI OF METHYL-BIS-(β-CHLOROETHYL)-AMINE WITH Cl^- AT *p*H 3.6, 37°

0.3755 mmole amine·HCl + 123.9 ml. of H_2O containing 0.38 mmole of NaOH. Aged 15.2 min., during which 0.034 mmole of NaOH was required to hold *p*H at 9.0. During the next 3.2 min., the mixture was acidified to *p*H 3.6 with 0.069 mmole of HCl; and 50 mmoles of NaCl added (= zero time); total vol. = 149.6 ml.; $[Cl^-]$ = 0.340 *M*.

Time, min.	EI,[a] %	Amine, %	k_{-1} $10^2 \times$ min.$^{-1}$	Time, min.	EI,[a] %	Amine, %	k_{-1} $10^2 \times$ min.$^{-1}$
2.2	..	3.69	1.72	18.9	59.1	...	..
4.1	..	6.78	1.73	22.3	..	31.14	1.75
6.7	..	11.04	1.77	26.3	...	35.18	1.74
7.7	..	12.60	1.77	30.0	46.6	...	..
8.5	72.3	...	..	33.5	...	41.47	1.73
10.2	..	16.24	1.77	38.1	...	45.11	1.72
13.2	..	20.42	1.77	43.1	35.05	Average	1.75
15.1	..	22.83	1.77	48.5	32.13		

[a] Slope, log % *vs.* time (Eq. 6) = 0.0211; 0.0211 − 0.0175 = 0.0036 = k'_{h}.

In the concentrated NaCl solutions at *p*H 3.6, the hydrolysis rates of EI are lower than in the absence of NaCl and the values of k'_{h} appear to pass through a minimum, presumably the result of an effect of increasing ionic strength upon the activity of the water. These hydrolysis rate data, obtained as differences between large numbers are not sufficiently precise for further analysis.

The effect of ionic strength on this reaction is best described by the following approximation derived from the Debye–Hückel equation for the activities of ions in solution

$$\log k_{-1} = \log k^0_{-1} - 2S\sqrt{\Gamma/2} + B\Gamma/2$$

where B is an empirical constant and $S = 0.5188$[5] at 37°.

Values of B were calculated from the simultaneous equations by substituting the five experimental values in the above equation. The average value was $B = 0.553 \pm 0.048$. This value was substituted into each of five possible equations corresponding to experimental points to give $\log k^0_{-1} = -0.875 \pm 0.008$. This corresponds to $k^0_{-1} = 0.13_3 \pm 0.003$ for the bimolecular rate constant at $\Gamma/2 = 0$. A plot of $\log k_{-1}$ against $(2S\sqrt{\Gamma/2} + B\Gamma/2)$ shows a good linear fit of the experimental data to the theoretical line. In Table VII, attention is directed to the progressive rise in first order rate constants, k'_{-1}, with increasing $[Cl^-]$ and to the progressive fall in the second order constants, k_{-1} as accounted for by the effect of increasing ionic strength.

TABLE VII

REACTION OF EI OF METHYL-BIS-(β-CHLOROETHYL)-AMINE WITH Cl^-

Rate constants at different $[Cl^-]$, pH 3.6, 37°

$[Cl^-]$ $\Gamma/2$	k'_h $10^3 \times$ min.$^{-1}$	Reaction with Cl^- k'_{-1} $10^3 \times$ min.$^{-1}$	k_{-1} l./mole min.
0	..	..	0.133[a]
0.005	5.02	..	.114[a]
.072	(3.0?)	5.5	.076
.139	3.4	9.4	.068
.206	3.7	11.7	.057
.340	3.6	17.5	.052
.520	4.4	24.0	.046

[a] Computed, see text.

Practically the same value for k_{-1} in Table VII calculated for $\Gamma/2 = 0.005$, namely, 0.11, can be obtained by introducing the experimental values $k_1 = 0.42$, $t = 1.65$, $a = 0.005$, $x = 0.0025$ together with trial and error substitutions for k_{-1} in the following unwieldy theoretical equation for the course of the reversible process, Amine ⇄ EI + Cl^-

$$\frac{a}{x} - \frac{1}{2} = \frac{k_{-1}}{k_1} A \coth k_{-1} tA, \text{ where } A^2 = \frac{k_1}{k_{-1}} \left(a - \frac{k_1}{4k_{-1}} \right)$$

It has been shown[3b] in acetone–water solutions that k_{-1} of this EI and of its ethyl homolog are sensitive to changes in ionic strength of the medium. The value of $k_{-1} = 1.4$ in acetone solution at 25° is of a higher order of magnitude than that here recorded (0.13 to 0.05) for aqueous solutions at 37°.

Theoretical Equilibrium.—For the initial reversible process: Amine ⇄ EI + Cl^-, we may now calculate a theoretical equilibrium constant to show the extent of the process. This represents a largely theoretical calculation, because usually the conditions favor the further decomposition of EI to shift the process to completion.

Assuming an upper limit of 0.005 M for a "dilute" solution of methyl-bis-(β-chloroethyl)-amine at 37° with the appropriate experimental constants, (Table VII and ref. 2), we have

$$K_{eq} = \frac{k_1}{k_{-1}} = \frac{[EI][Cl^-]}{[Amine]} = \frac{0.42}{0.114} = 3.68 \text{ moles/liter}$$

from which one finds that at equilibrium, [Amine] = 6.8×10^{-6} M, corresponding to 99.86% conversion to EI and Cl^-. Estimates on the other homologous members of the series of aliphatic t-bis-(β-chloroethyl)-amines indicate that they all go essentially to completion in this reaction.

Reactions with Propionate and Benzoate.—Only one of the compounds was studied in these processes, namely, the EI from methyl-bis-(β-chloroethyl)-amine, the object being to establish a tentative base line. At pH 7.4 and the relatively low concentrations of sodium propionate and benzoate there was no detectable effect on the hydrolysis rate, $k'_h = 0.0050$. The observations are condensed and summarized in Tables VIII and IX.

TABLE VIII

REACTIONS OF PROPIONATE + H_2O + EI OF METHYL-BIS-(β-CHLOROETHYL)-AMINE, pH 7.4, 37°

Ratio [EI]/[Prop.], M	Average $\Gamma/2$	$k'_{obs.}$, $10^3 \times$ min.$^{-1}$	k^0_p, $10 \times$ liter per mole min.
0.00125/0.0251	0.166	7.55	1.51
.001235/0.0248	.171	6.87	1.13
.0025/0.0499	.234	9.43	1.55
.00235/0.0235	.167	6.72	1.09
.00251/0.0149	.140	6.28	1.20
		Av.	1.3

TABLE IX

REACTIONS OF BENZOATE + H_2O + EI OF METHYL-BIS-(β-CHLOROETHYL)-AMINE, pH 7.4, 37°

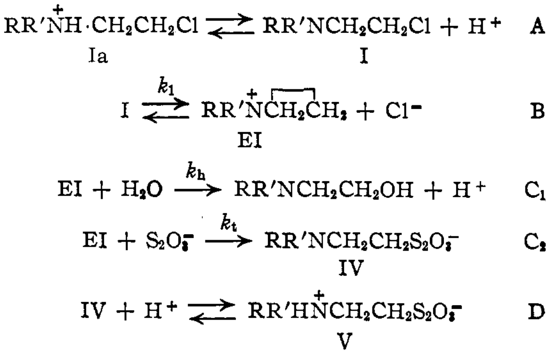
Ratio [EI]/[Benz.], M	Av. $\Gamma/2$	k'_{obs}, $10^3 \times$ min.$^{-1}$	k^0_{benz}, $10 \times$ liter per mole min.
0.00249/0.0250	0.173	6.96	1.2
.0025/0.0219	.170	6.94	1.2
.00257/0.0250	.175	7.11	1.2

It will be observed that the second order reaction rates, k°, of this EI with Cl^-, propionate or benzoate at zero ionic strength are substantially alike, namely, 0.133, 0.13 and 0.12 liter per mole min. This would indicate that steric factors among these various anions seem to play a negligible part in the mechanism of these reactions. The initial acid production in the reactions with propionate and benzoate ran according to prediction, but the later stages indicated rather definitely that, certainly in the case of propionate, the monoester was disappearing and, indeed, experiments with the dipropionic ester showed that this was the case.

Experimental

Materials.—The ethylenimonium compounds studied were produced under proper conditions from the pure tertiary β-chloroethylamines by methods already described. Unless otherwise specified other reagents were purified or A.R. grade materials.

Rate Measurements with $S_2O_3^=$.—Consider the following series of reactions of a dilute aqueous solution of a bis-(β-chloroethyl)-amine, [R′ = β-chloroethyl]



$$RR'\overset{+}{N}H \cdot CH_2CH_2Cl \rightleftharpoons \underset{I}{RR'NCH_2CH_2Cl} + H^+ \quad A$$
Ia

$$I \underset{}{\overset{k_1}{\rightleftharpoons}} \underset{EI}{RR'\overset{+}{N}CH_2CH_2} + Cl^- \quad B$$

$$EI + H_2O \xrightarrow{k_h} RR'NCH_2CH_2OH + H^+ \quad C_1$$

$$EI + S_2O_3^= \xrightarrow{k_t} \underset{IV}{RR'NCH_2CH_2S_2O_3^-} \quad C_2$$

$$IV + H^+ \rightleftharpoons \underset{V}{RR'H\overset{+}{N}CH_2CH_2S_2O_3^-} \quad D$$

Starting with the amine hydrochloride, I_a, suitable adjustment of the pH of its solution will produce the free amine, I. The latter, on sufficient ageing, can be converted quickly and practically completely to its first ethylenimonium ion, EI. Hydrolysis can be estimated from previously determined constants.[4] If now a known excess amount of thiosulfate is added to the solution, the monothiosulfate, IV, will be formed at a bimolecular rate and if, further, the solution is sufficiently acid, the free base, IV, will be converted almost instantly to the stable ammonium ion, V, thereby blocking subsequent cyclization of the second (R′) β-chloroethyl group. Hence, successive determinations of the acid uptake in processes C_2 and D at a suitable fixed pH can be used as a measure of the rate of formation of the thiosulfate ester in C_2. Process C_1 is negligibly small by comparison in the compounds under study.

The above principle presupposes a knowledge of the pK'_a of the monothiosulfate formed. It is obvious that the monothiosulfate must be more basic than the parent β-chloroethylamine, and knowing the latter, one can fix on a level of *p*H at which the monothiosulfates can be completely titrated acidimetrically. Hence *p*H 4.0 was selected because the pK'_a of all these bis-(β-chloroethyl)-amines is greater than 6.0. Tris-(β-chloroethyl)-amine involves several complications and will be considered separately.

The solution of bis-(β-chloroethyl)-amine was aged at constant temperature and sufficiently alkaline *p*H to permit 98–100% conversion to its first ethylenimonium ion. *p*H was measured by means of a glass electrode and controlled by the addition of 2 *N* NaOH from a microburet until conversion was completed (processes A and B, above). A microburet containing 2.5 *N* HCl replaced the one with NaOH, and the *p*H was accurately adjusted to 4.00 ± 0.03. Then with vigorous stirring, a predetermined amount of thiosulfate solution, at the same temp., was added from a calibrated syringe, the time of half-delivery (about 0.03 min.) of the thiosulfate being taken as zero time. Hydrochloric acid was then added at short successive intervals to maintain *p*H 4.00, and the times and acid volumes were recorded.

The validity of the method is shown in Table I. Here the reaction was allowed to go to completion and the *p*H was found to remain constant until the run was terminated an hour later.

The errors in these runs was estimated to be between 5 and 10%, though reproducibility of rate constants was about 2 or 3%.

The reaction of bis-(β-chloroethyl)-ethylenimonium ion [from tris-(β-chloroethyl)-amine] with $S_2O_3^=$ is very rapid. It cannot be isolated completely owing to a combination of unfavorable properties associated with the pK'_a and the reactions of the parent amine, the cyclical imonium ions and their thiosulfate esters. However, the initial part of the process can be followed to an extent sufficient to give a fair estimate of the magnitude of the reaction rate.

The experimental procedure follows: 0.211 mmole of the hydrochloride of tris-(β-chloroethyl)-amine + 0.219 mmole of NaOH in 98 ml. of H_2O were aged at 25°, *p*H 7.6 ($t_{1/2}$ = 2.4 min.) for 17 min. The solution was then iced to 0° (28 min.), after which it was adjusted to *p*H 4.0 with 0.0155 ml. of 2.473 *N* HCl. At zero time 2.00 ml. of 0.0991 *M* $Na_2S_2O_3$ was added, and the solution titrated to *p*H 4.0 with 2.473 *N* HCl. Table X gives the results. The initial concentration of the bis-(β-chloroethyl)-ethylenimonium ion, EI, was computed on the simple, but not accurate, assumption that its hydrolysis was the only interfering factor. It is emphasized that the data of Table X are an approximation (probably too low) of the magnitude of this reaction rate.

TABLE X

FIRST EI OF TRIS-(β-CHLOROETHYL)-AMINE

(Rate of formation of the monothiosulfate); initial [EI] = 0.001283 *M*; *p*H 4.0, 0°; initial $[S_2O_3^=]$ = 0.001982 *M*; $\Gamma/2$ = 0.101; (see text for comment).

Time, min.	2.473 *N* HCl, ml. × 100	Reaction, %	k_t, l./mole min.
0.36	1.28	24.7	435
.83	2.33	44.9	436
1.19	2.90	55.9	445
1.68	3.48	67.2	462
2.18	3.90	75.2	477
2.57	4.16	80.3	(495)
3.15	4.47	86.2	(528)
3.94	4.76	91.8	(581)
		Av.	451
		Dupl.	443 447

Reaction with HCO_3^-, Propionate or Benzoate.—The principle employed was substantially the same as for the reaction with $S_2O_3^=$, with several changes in detail. With HCO_3^-, the product would be the monocarbonic ester which is presumably insufficiently stable for isolation.[3] Other things being equal, when the simultaneous reactions with H_2O and with HCO_3^- are independent and of the same order, the proportion of EI consumed in the hydrolysis will be $k'_h/(k'_h + k'_b)$, and that reacting with HCO_3^- will be $k'_b/(k'_h + k'_b)$. (Primes on the *k*'s indicate first order rates, with water and bicarbonate in sufficient excess.) Then the ratio k'_b/k'_h represents the relative reactivities.

Observations were made at *p*H 7.6, 37°. The initial concentration of (β-chloroethyl)-amine was 0.0025 *M*; that of the anion varied from 0.015 to 0.05 *M*. The atmosphere over the reaction mixture with HCO_3^- was not equilibrated. Measurements of the chloride evolution at *p*H 7.4 or 7.6 from the second rapid cyclization were taken as indications of the progress of the sum of the very much slower reactions with H_2O and anion. NaOH was added from a microburet to hold the *p*H as indicated and to measure the apparent rate of acid formation. The samples were quenched in 0.014 *N* HNO_3 and the Cl^- then determined potentiometrically.[6]

The Back Reaction with Cl^-.—Consider the simultaneous reactions C_1 and C_2 above, and substitute Cl^- for $S_2O_3^=$ in C_2. In dilute water solution at *p*H 3.6, the EI from process B will produce the chlorohydrin and an equivalent amount of H^+ to block its further cyclization; and with NaCl in relatively large excess, titratable free base will be produced as the parent (β-chloroethyl)-amine is reformed.

Then a determination (by $S_2O_3^=$ titration) of the EI concentration at time *t* will give $a - x$, where

$$x = a(1 - e^{-(k'_{-1} + k'_h)t}) \qquad (6)$$

(a = initial concn. of EI, and x = amount decomposed) from which the sum $k'_{-1} + k'_b$ can be computed. Also the amount of parent amine at any time can be determined acidimetrically. Since the two simultaneous processes are of the same order, the proportions of the products remain constant, and the theoretical yield of parent amine will be

$$\frac{[\text{Amine}]_t}{x_t} = \frac{k'_{-1}}{k'_{-1} + k'_h}$$

Hence

$$[\text{Amine}]_t = (k'_{-1}/k'_{-1} + k'_h)\, a(1 - e^{-(k'_{-1} + k'_h)t}) \qquad (7)$$

Therefore, k'_{-1} and k'_h can be computed from equations (6) and (7).

The experiments were performed only with methyl-bis-(β-chloroethyl)-amine at 37°, *p*H 3.6. Stock solution of the amine hydrochloride was added to water containing 1 equivalent of NaOH. The *p*H was held near 9 (glass electrode control) until practically all of the amine had cyclized. The solution was then carefully acidified with HCl to *p*H 3.6, after which NaCl solution was added (= zero time) to fix the $[Cl^-]$ at a high, predetermined level. The hydrolysis rate of EI at *p*H 3.6 in the absence of added Cl^- was determined separately and found to be 0.00502 min.$^{-1}$, the same as at *p*H 7.4.

Thereafter, careful maintenance of the *p*H at 3.6 by successive small additions of HCl from a microburet gave the data for calculating the amounts of parent amine produced. At intervals, 25-ml. samples of the solution were removed and analyzed for residual EI. This was done by allowing the sample to react for 15 min. with excess thiosulfate at *p*H 3.6 and determining excess $S_2O_3^=$ iodometrically. The iodometric titration was reproducible to 1 part in 400. The reaction between EI and $S_2O_3^=$ reached the same endpoint when the mixture was held as long as 45 minutes. The amounts of EI thus determined yielded a uniform first order rate curve.

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[6] D. A. MacInnes and M. Dole, THIS JOURNAL, 51, 1119 (1929).