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Kinetics and Mechanism of the Reactions of Tertiary β-Chloroethylamines in Solution. I. Methyl-bis-β-chloroethylamine[1]

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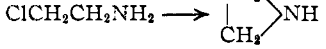
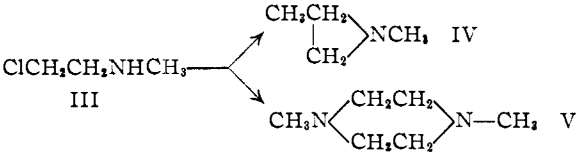
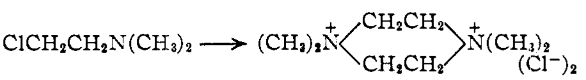
It is characteristic of ω-halogenated amines that they readily undergo intramolecular alkylation with the formation of cyclic ammonium salts.[2,3] The rate of this reaction depends upon the size of the ring so formed, being greatest for five- or six-membered rings.[4] The β-chloroethylamines occupy an interesting position in this series; the primary amine I yields ethyleneimine (II), the secondary amine (III) yields N-methylethyleneimine (IV) and N,N-dimethylpiperazine (V) and



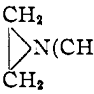
I II



III IV V



VI VII



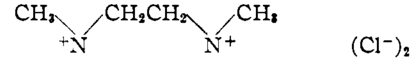
VIII

the tertiary amine (VI) yields only N,N-tetramethylpiperazinium chloride (VII). Since intramolecular displacement of chlorine by nitrogen to form a three-membered ring is a very easy process with the primary and secondary amines it is a clear possibility that the analogous formation of a cyclic ethyleneimmonium ion (VIII) plays an important part in the dimerization observed in the tertiary amine. The kinetic study described in this and the following two papers of the series has revealed that ethyleneimmonium ions of the type of VIII are involved not only in the dimerization, but in hydrolysis and in all displacement reactions of the tertiary β-chloroethylamines studied. This conclusion is established, first, by the observation that there appears to be a common first step in all these reactions, whose rate can never be exceeded by the process as a whole, and which becomes unimolecularly rate-determining for displacement reactions with very active reagents; second, by the possibility of quantitative calculation of the rate of the over-all dimerization. Although the dimerization consists of a succession of reactions of which neither is ordinarily rate-determining, it has been possible in the case described in this paper to determine the separate rate constants by comparison of the experimentally observed progress of the dimerization with the figures predicted by means of a mechanical differential analyzer. In a related case, described in the second paper, a similar resolution into individual reactions, and determination of their rate constants, has been effected by graphical means.

Experimental

Methyl-bis-β-chloroethylammonium chloride is prepared by the action of thionyl chloride on methyldiethanolamine. Most of the material used in our work was prepared in quantity by Dr. George Coleman and his research group at the University of Iowa, to whom we are indebted for coöperation which greatly expedited our work. When an aqueous solution of this salt is made alkaline, the free base immediately begins to dimerize and, in part, to hydrolyze. *The free base* can be isolated by extraction from the alkaline solution into ether, drying and evaporation of the ether. Dimerization of the pure anhydrous amine is very slow and can be made still slower by solution in dry benzene or pentane. A solution of the amine in acetone is sufficiently stable to serve as a solution for starting a kinetic run.

Conditions of Dimerization.—In aqueous solution the dimerization of methyl-bis-β-chloroethylamine leads to partially hydrolyzed products.[5] Since acetone is inert toward the amine, mixtures of acetone and water were adopted as reaction media in which to study the rates of dimerization and hydrolysis. For the work described in this paper, the solvent was 2:1 acetone–water by volume.



IX

Upon concentration of these solutions *the dimer* was isolated as a white crystalline solid readily soluble in water and insoluble in organic solvents. Its aqueous solution was neutral and did not decolorize permanganate solution. The same product was obtained in 85% yield by letting the amine stand in absolute ethanol solution. The molecular weight, determined cryoscopically in water by Dr. Hyp J. Dauben, Jr., was 117. The calculated value is 104 for **1,4-dimethyl-1,4-bis-β-chloroethylpiperazinium dichloride** (IX). This is about the same ratio between observed and calculated as was found by Turner and Pollard[6] for a series of quaternary ammonium salts. These strong electrolytes are very non-ideal solutes except at high dilution.

Anal. Calcd. for $C_{10}H_{22}N_2Cl_4$: C, 38.48; H, 7.11; Cl, 45.44; Cl^-, 22.72. Found: C, 38.16; H, 7.41; Cl, 40.12; Cl^-, 21.44.

This analysis, performed on the product from absolute ethanol, suggests that as much as one-fifth of the chlorine

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[1] The work presented in this paper was performed under Contract NDCrc 136 between Harvard University and the National Defense Research Committee of the Office of Scientific Research and Development in 1942 and 1943.

[2] Knorr, *Ber.*, **37**, 3507 (1904).

[3] Marvel, THIS JOURNAL, **57**, 1137 (1935), and previous papers of the series.

[4] Salomon, *Trans. Faraday Soc.*, **32**, 153 (1936).

[5] Golumbic, Fruton and Bergmann, *J. Org. Chem.*, **11**, 518, 536 (1946).

[6] Turner and Pollard, *J. Chem. Soc.*, **105**, 1760 (1914).

in the dimer may have been replaced by ethoxyl groups. Quantitative experiments in which the appearance of hydrogen ion as well as of chloride ion was followed show that in the 2:1 acetone–water medium there is much less replacement of the chlorine than this. Suitable conditions have not been found for recrystallizing the dimer.

The dimer forms a **picrate**, m. p. 199–201° dec., recrystallized from water.

Anal. Calcd. for $C_{22}H_{26}O_{14}N_8Cl_2$: C, 37.89; H, 3.76. Found: C, 37.74; H, 3.93.

Inertness toward Hydrolysis of the Dimer IX.—A sample of the dimer IX was dissolved in 2:1 acetone–water and allowed to stand for three days. No new chloride ion was liberated.

Kinetic Method.—The rates of reaction were determined by titration of the free chloride ion by the Volhard method. A weighed amount of the amine, prepared immediately before use, was made up to 100 cc. with reagent grade acetone and brought to 25.00 ± 0.05° in a thermostat. The reaction was started by adding 50 cc. of similarly thermostatted water or an aqueous solution of the reagent (thiosulfate, sodium hydroxide, etc.). At appropriate time intervals, a 5- or 10-cc. aliquot was removed by a syringe pipet and shaken rapidly with a mixture of 25 cc. of water and 25 cc. of benzene to separate reaction products from unconverted amine. The water layer was separated and subjected to the Volhard titration. In the runs described in this paper the water and acetone solutions were both at 25° at the time of starting the run. The heat of mixing of the two liquids caused a disturbance in the first few points of the run, which was eliminated in the later work in this series by controlled precooling of the water. The use of a syringe pipet was an important precaution because of the very toxic properties of methyl-bis-β-chloroethylamine.[7]

With the amines containing at least two β-chloroethyl groups it was possible to titrate hydrochloric acid in the presence of the amine by using sodium hydroxide and thymolphthalein as an indicator.

Dimerization of Methyl-bis-β-chloroethylamine in the Absence of Competing Reagents.—The formation of the cyclic dimer IX is attended by the liberation of one chloride ion per molecule of original amine, and this is the basis of the ion-titration method described for following the reaction. The degree of hydrolysis attending dimerization of the amine was determined in one run (Table I, section 1, plotted in part in Fig. 1) by alkali titration of the aqueous extracts, with thymolphthalein as an indicator, prior to the Volhard titrations. In this run, hydrolysis in 2:1 acetone–water at 25° appears as a minor side-reaction attending dimerization (less than 5% hydrolysis at 75% dimerization). Sections 2 and 3 of Table I record the rate of total reaction at two initial amine concentrations without added electrolyte, and section 4 records a similar run at the lower concentration with the ionic strength raised by 0.1 *M* sodium fluoborate.

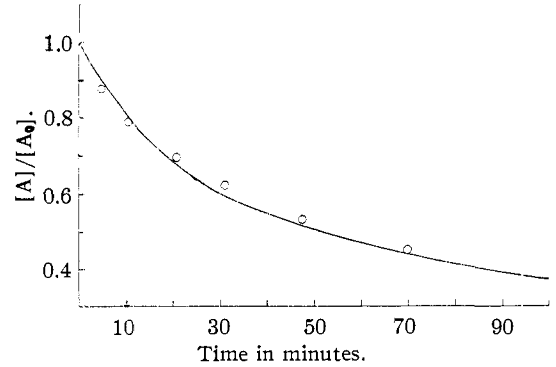

Fig. 1.—Liberation of chloride ion by 0.1180 *M* methyl-bis-β-chloroethylamine in 2:1 acetone–water at 25° in the absence of added reagents. The solid line is the curve calculated by the differential analyzer.

TABLE I

1			2		3		4	
0.1180 *M* Amine			0.08090 *M* Amine		0.04407 *M* Amine		0.0461 Amine 0.10 *M* $NaBF_4$	
Time, min.	Re-act.,[a,c] %	Hy-drol.[d] %	Time, min.	Re-act.,[c] %	Time, min.	Re-act.,[b,c] %	Time min.	Re-act.,[c] %
0	0	0	0		0		0	0
5	12.7	1.1	13	24.6	19	29.7	5.80	14.5
10.5	21.8	1.5	30	36.7	33	36.5	12.82	26.0
21	30.8	2.0	52	46.0	51	43.6	22.25	37.7
31	39.2	2.2	85	57.5	84	51.8	41.32	49.4
47.6	47.4	2.5	156	70.1	174	65.3	72.83	59.0
70	55.4	3.1	247	79.5	210	69.7	112.67	66.4
125	67.0	3.9					186.30	76.5
178.7	76.4	4.9						

[a] 5-cc. aliquots. [b] 20-cc. aliquots. [c] Determined by titration with 0.1000 *N* silver nitrate. [d] Determined by titration with 0.03346 *N* sodium hydroxide.

Figure 2 represents the data of sections 3 and 4 of Table I.

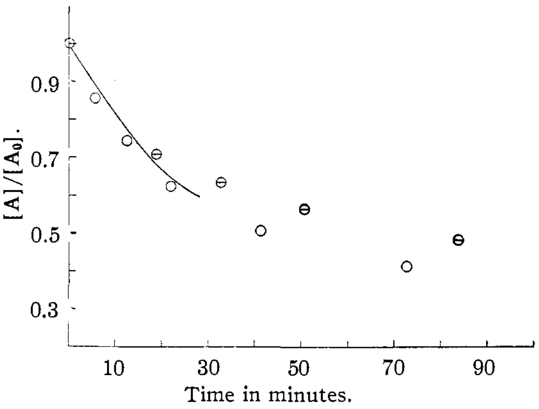

Fig. 2.—Liberation of chloride ion by: ○, 0.0461 *M* methyl-bis-β-chloroethylamine in 2:1 acetone–water solution in the presence of 0.10 *M* sodium fluoborate at 25°; ϴ, by 0.04407 *M* amine *without added salt.* Solid line shows curve calculated by the differential analyzer.

Dimerization in the Presence of Added Sodium Chloride.—Table II and Fig. 3 show the data for a run on the dimerization of the amine in the presence of 0.987 *M* sodium chloride.

TABLE II

0.0460 *M* Amine		0.0987 *M* Sodium chloride			
Time, min.	Re-act.,[a] %	Time min.	Re-act.,[a] %	Time min.	Re-act.[a] %
0					
1.80	6.68	10.30	14.2	112.15	36.2
2.97	8.99	20.97	17.2	152.18	44.1
4.12	10.97	21.05	15.6	185.35	50.3
5.15	11.2	48.35	23.6	268.77	56.8
6.43	11.2	57.60	29.3	319.00	66.3

[a] By titration with 0.1000 *N* silver nitrate.

Reactions of Methyl-bis-β-chloroethylamine with Hydroxyl and Thiosulfate Ions.—In the presence of sodium thiolsulfate or sodium hydroxide in as much as double the molar concentration of the amine, no observable dimerization takes place; instead, both chlorine atoms of the amine are displaced by thiosulfate or hydroxyl. The initial rate

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[7] A. Gilman and F. S. Philips, *Science*, **103**, 406 (1946).

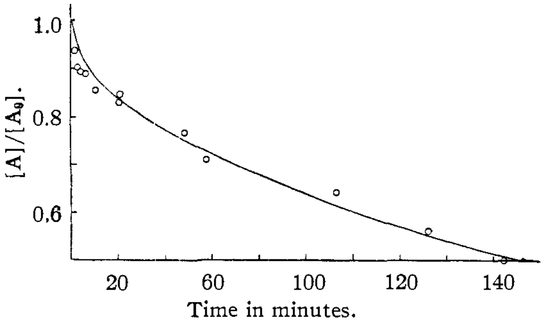


Fig. 3.—Liberation of chloride ion by 0.0460 *M* methyl-bis-β-chloroethylamine in 2:1 acetone–water at 25° in the presence of 0.0987 *M* sodium chloride. The solid line is the curve calculated from the differential analyzer.

of reaction, however, is not greater than in the absence of these displacing reagents, and the reaction becomes of first order with respect to the amine and independent of the concentration and nature of the displacing reagent.

The addition of thiosulfate diminishes the solubility of the amine and it was found necessary to use higher dilutions than in the absence of this reagent. The reaction in this case was followed by titrating the unused thiosulfate with iodine. Since iodine reacts with the acetone of the solvent medium at an appreciable rate under the acid conditions of the titration, a substantial blank correction was necessary amounting to 2.96 cc. for a 5-cc. aliquot. The iodine end-points obtained in a standardized procedure were reproducible and sharp. Table III and Fig. 4 show the data for one run with thiosulfate and two with hydroxyl ions added.

TABLE III

0.005337 *M* Amine 0.0151 *M* $Na_2S_2O_3$		0.0465 *M* Amine 0.0135 *M* NaOH		0.0136 *M* Amine 0.0482 *M* NaOH	
Time, min.	React.,[a,b] %	Time, min.	React.,[c] %	Time, min.	React.,[d] %
0		0		0	
10.72	17.5	1.58	2.7	9.53	13.8
19.63	26.6	2.85	5.6	19.12	28.6
33.73	43.8	4.12	8.1	31.10	43.4
49.78	54.4	5.95	11.7	44.37	57.7
70.47	71.5	19.05	30.7	62.85	72.3
91.28	82.0	31.65	35.3	82.33	81.2
112.55	97.8	61.73	70.0	106.07	89.0
		134.38	91.8		
		1155	100.5		

[a] 5-cc. aliquots. [b] By titration with 0.003099 *N* iodine. [c] By titration with 0.1000 *N* silver nitrate. [d] By titration with 0.0500 *N* silver nitrate.

Reaction of Methyl-bis-β-chloroethylamine with Triethylamine.—Table IV and Fig. 5 show the data for this reaction. Like the hydroxyl and thiosulfate ions, triethylamine intercepts an intermediate which is formed unimolecularly from the chlorinated amine and forestalls the formation of the cyclic dimer. Unlike the hydroxyl and thiosulfate ions, it displaces the first chlorine much more readily than the second, as is shown by the two plots of Fig. 5. The fact that the plot of log (a – (Cl$^-$)), and not that of log (a – (Cl$^-$)/2), against time is linear shows that the reaction is approaching a much slower stage with the replacement of only one chlorine atom. Since the reaction does not actually stop at this point, the rate constant determined in this way will be somewhat too high.

TABLE IV

0.0450 *M* Chloroamine		0.1073 *M* Triethylamine	
Time, min.	React.[a] %	Time, min.	React.[a] %
0			
10.08	11.6	70.05	41.5
20.16	19.6	109.17	46.1
36.23	29.1	182.67	56.8
49.82	35.1	255.55	59.6
		303.47	62.4

[a] By titration with 0.0500 *N* silver nitrate.

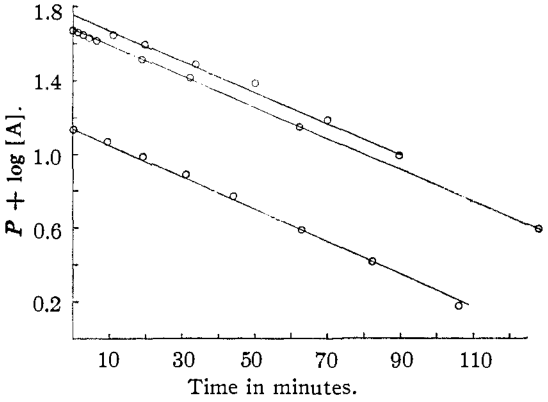


Fig. 4.—Upper curve at $P = 4$: rate of consumption of thiosulfate in presence of 0.005337 *M* methyl-bis-β-chloroethylamine in 2:1 acetone–water at 25°. Middle curve at $P = 3$: rate of liberation of chloride ion by 0.0405 *M* methyl-bis-β-chloroethylamine in presence of 0.0135 *M* sodium hydroxide. Lower curve at $P = 3$: rate of liberation of chloride ion by 0.0136 *M* methyl-bis-β-chloroethylamine in presence of 0.0482 *M* sodium hydroxide.

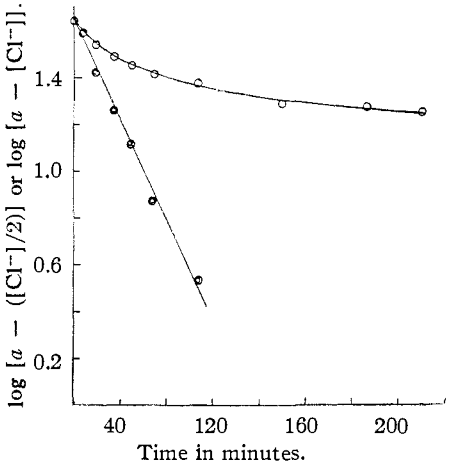


Fig. 5.—Reaction of methyl-bis-α-chloroethylamine with triethylamine: O, 3 + log [a – (Cl$^-$)/2]; Ⓗ, 3 + log [a + log (Cl$^-$)].

Discussion

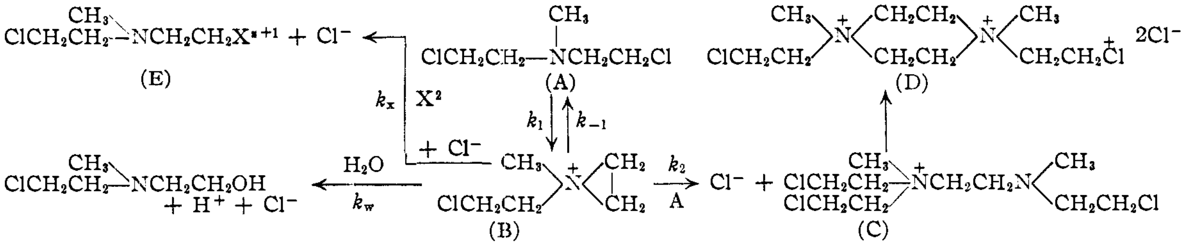
The key to the mechanism of these reactions is provided by three observations. (1) The dimerization in the absence of added reagents is not first-order with respect to amine, but the first-order plots of runs under different conditions approach the same slope at zero time. (2) In the presence of hydroxyl or thiosulfate ion or triethylamine the reaction is displacement to the exclusion of dimerization and the reaction becomes truly first-order in amine. (3) The first-order rate constant is nearly the same for the displacement reaction with hydroxyl ion (0.018 min.$^{-1}$), with thiosulfate ion (0.017 min.$^{-1}$), with triethylamine (0.025 min.$^{-1}$), and for the early stage of dimerization. These facts clearly indicate that some internal transformation of methyl-bis-β-chloroethylamine necessarily precedes any of these four reactions, the amine being converted unimolecularly into a reactive form. In the three displacement reactions this conversion is completely rate-determining, the reactive intermediate being attacked as fast as it is formed. In the dimerization the second step is comparable in speed to the first, and hence the kinetic course of the dimerization does not approximate any simple order of reaction. The reactive intermediate possessing these properties must be the ethylene-immonium ion of the type of VIII. Its high reactivity, like that of the conjugate acid of an ethylene oxide,[8] is the combined result of the strain of the three-membered ring and the polarizing effect of the positive charge upon the carbon–nitrogen linkage. The ion is thus very reactive toward any nucleophilic reagent capable of attacking the carbon of the three-membered ring. Among such reagents hydroxyl and thiosulfate ions are relatively powerful in the present case. The original chlorinated amine itself is the nucleophilic reagent in the case of dimerization, but does not react rapidly enough with the cyclic intermediate to prevent it from accumulating and its formation from being reversed to some extent. Triethylamine is a considerably stronger base than ethyl-bis-β-chloroethylamine, and accordingly competes successfully with the chlorinated amine for the intermediate. Water is the weakest competitor of those reacting here, since even though it comprises one-third of the medium it combines with much less of the intermediate than does the unconverted amine itself. Chloride ion is a competitor of far from negligible activity: the fact that the steady rate of dimerization in the presence of tenth-molar chloride ion is only one-seventh of that with no chloride added indicates that the formation of the cyclic intermediate is reversed to an important extent. The reactions are summarized in the scheme.

Because this scheme of reactions will prove to be common to all the β-chloroethylamines studied in this series, it will be convenient to denote the original amine in general by A and the ethylene-immonium ion by B in each case. B is shown as consumed by four reactions: reconversion into A by reaction with chloride ion, dimerization through reaction between B and A, hydrolysis, and reaction with other nucleophilic competitors, designated in general as X^z, the superscript z referring to the algebraic value of the charge (O for triethylamine, -2 for thiosulfate, etc.).

The inertness toward displacement of the chlorine in the cyclic dimer must be due to the lack of a nucleophilic center within the molecule such as is possessed by the original amine and by the linear dimer C which is visualized as an intermediate. In C there are alternative possibilities of cyclization, to a three-membered or to a six-membered ring. That the six-membered ring is produced, and so rapidly that no accumulation of C occurs, is consistent with the general experience that intramolecular reactions are most favored when leading to rings of five or six members. The possibility that D might be produced directly by reaction of two B ions must be considered, but is improbable *a priori* and is rendered more so by kinetic evidence to be presented later. Although the structure of D is unfavorable to displacement of the chlorines, it is favorable to elimination reactions initiated by strong base, and this has been shown to occur easily in the case of the ethyl homolog.

The hydrolysis is the only one of the reactions shown which results in the liberation of hydrogen ion, and this is the basis of the titration method distinguishing between hydrolysis and dimerization in the absence of competitors. The hydrolysis product is of course capable of further reaction in the same sense as A, and all the reactions of A and B have their counterparts starting with the chlorohydrin instead of A. This fact renders the chemistry of methylbis-β-chloroethylamine in pure water, where there is much hydrolysis,[5] even more complicated than in 2:1 acetone–water, where hydrolysis occurs to a minor extent.

When the reagent X^z is one which competes strongly for the cyclic intermediate B, the reaction series will lead to successive replacements of the two chlorine atoms in A, and the relative rates of these two displacements should be determined by the nature of X^z. In the case of hydroxyl ion the



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[8] Brønsted, Kilpatrick and Kilpatrick, THIS JOURNAL, 51, 428 (1929).

replacement of Cl by OH results in a first displacement product more basic and no more hindered than A, and hence somewhat more reactive in the initial cyclization step. The result would be expected to be, and is, the displacement of both chlorine atoms without any break in the rate. The same is true of the reaction with thiosulfate because the negative charge of the —$CH_2S_2O_3$— group tends to enhance the nucleophilic character of the nitrogen atom. On the other hand, when X^z is the electrically neutral triethylamine, E has a positive charge. The effect of this being unfavorable to the nucleophilic character of the remaining tertiary nitrogen atom, E is cyclized much more slowly than A, and the kinetics is that of displacement of a *single* chlorine atom instead of both.

That a sulfur-containing anion should be a vigorous competitor for the ethylene-immonium ion is consistent with the findings of Brønsted, Kilpatrick and Kilpatrick[8] with respect to the ethylene oxides, as well as with Ogston's[9] series of competitors in the case of β,β-dichlorodiethyl sulfide, which reacts by a similar mechanism. It is noteworthy, however, that the hydroxyl ion, which was found by Brønsted, Kilpatrick and Kilpatrick to be entirely inert to ethylene oxide, ranks as a vigorous reagent toward the ethylene-immonium and ethylene-sulfonium ions alike. The position of the hydroxyl ion in the present series seems more in accord with its strongly nucleophilic character than does its mysterious inertness toward the epoxide ring.

In any reaction in which B is attacked and directly converted into reaction product by a strong competitor, the chloride ion would have little chance to react with it and the concentration of chloride ion would be without effect upon the over-all rate. To the extent to which the initial cyclization is reversed through reaction between Cl^- and B, the presence of chloride ion should lower the over-all rate of reaction by recapturing intermediate which might otherwise go directly to product. This explains both the inhibitory effect of sodium chloride upon the dimerization in the absence of competitors and the initial rapid jump before this inhibition becomes apparent.

The formation of the cyclic intermediate B from a β-chloroethylamine has the typical features of an intramolecular S_N2 reaction, since a primary chlorine atom is displaced by a nucleophilic group. The unfavorable effect of high dielectric constant upon rate, which is a characteristic of S_N2 reactions between a neutral molecule and a negative ion,[10] is reversed in S_N2 reactions, such as quaternary ammonium salt formation,[11] occurring between two neutral molecules where the transition state has a higher electrostatic potential than the reactants. The fact that dimerization of the β-chloroethylamines is arrested in non-polar solvents and rapid in water is therefore consistent with the conception of the reaction as an intramolecular nucleophilic displacement.

Determination of the Separate Rate Constants

The most complete confirmation of the theory would be attained if the values of the rate constants k_1, k_{-1}, k_2 and k_w could be determined and used to calculate the changes in concentration of A with time during simple dimerization under different sets of conditions. Because he rate constants of the successive reactions e comparable in magnitude, none of the simplifying approximations can be used which might make the differential equations describing the system capable of integration. A few direct calculations were therefore undertaken with the differential equations themselves, namely

$$\mathrm{d(A)/d}t = -k_1(\mathrm{A}) + K_{-1}(\mathrm{B})(\mathrm{Cl^-}) - k_2(\mathrm{A})(\mathrm{B}) \qquad (1)$$

$$\mathrm{d(B)}\quad \mathrm{d}t = k_1(\mathrm{A}) - k_{-1}(\mathrm{B})(\mathrm{Cl^-}) - (\mathrm{B})\,[k_w + k_2(\mathrm{A}) + k_3(\mathrm{X^z})] \qquad (2)$$

Without added salts other than chlorides, $(X^z) = 0$, and this term drops out. Introducing the substitutions

a = initial concentration of A
b = initial concentration of Cl^-
$(Cl^-) = a + b - (A)$

the differential equations can be thrown into the form

$$\mathrm{d(A)/d}t = -k_1(\mathrm{A}) + k_{-1}(a + b)(\mathrm{B}) - (k_{-1} + k_2)\,(\mathrm{A})(\mathrm{B}) \qquad (3)$$

$$\mathrm{d(B)}\quad \mathrm{d}t = k_1(\mathrm{A}) - [k_{-1}(a + b) + k_w](\mathrm{B}) + (k_{-1} - k_2)(\mathrm{A})(\mathrm{B}) \qquad (4)$$

Of the six constants in these equations, a and b are of course controlled in carrying out any experiment; k_1 has been determined from the displacement experiments to have the average value 0.020. (Actually this is a composite of k_1 and k_1' for the dichloro compound and its first displacement product, but judging by an analysis in Part II, p. 2977, this is unlikely to result in an error greater than about 25%.) The constant k_w has not been measured directly, but the ratio k_w/k_2 can be evaluated from the degree of hydrolysis measured in one of the experiments (a = 0.1180) by noting that when (B) reaches its maximum value $d(H^+)/d(Cl^-) = k_w/k_2(A)$. The selection of the point where (B) was assumed to be a maximum was later verified by the results of the calculations. It gave $k_w/k_2 = 0.003$.

From differential equations like (3) and (4), by means of assumed values for the unknown constants k_{-1} and k_2, one may calculate (A) and (B) as functions of time in laborious fashion by taking successive small increments of time and calculating the changes in (A) and (B) for those increments in turn from the slope and average curvature of the curve as given by the equations. This problem can be solved more rapidly and accurately

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(9) Ogston, British Report II-5-1046, May 18, 1942, and previous reports from Prof. Peters's laboratory. These reports are now available from the Ministry of Supply of Great Britain.

(10) Hughes, *Trans. Faraday Soc.*, **37**, 608 (1941).

(11) von Halban, *Z. physik. Chem.*, **84**, 129 (1913).

by the use of a mechanical differential analyzer.[12] We had the opportunity of using Differential Analyzer No. 2 at the Massachusetts Institute of Technology for two days in August, 1942, and this made it feasible to determine the separate rate constants for the present system and to confirm the mechanism by calculating the course of dimerization without added competitors.

A trial value of k_{-1} was selected by assuming that the point where the first-order plot of the dimerization run with chloride added first becomes linear corresponds to an equilibrium between A, B and Cl^-.

Curves of (A) against time were calculated on the differential analyzer for the following pairs of values of k_{-1} and k_2

k_{-1}	k_2
2.0	0.5
1.5	.2
1.0	.2
1.35	.4
1.5	1.0

The calculated curves resulting are shown in Fig. 6. It is evident that the position and shape of the curve is sensitive to changes in the assumed values of both constants. Continual comparison of the curves with the experimental guided the choice of trial values until the pair of constants, $k_{-1} = 1.35$ and $k_2 = 0.4$, was arrived at, which yielded a curve (solid line of Fig. 3) agreeing within 2% with the experimental points from $t = 20$ to beyond one hundred and eighty minutes. The deviations below $t = 20$ are probably due to the temperature rise which occurred in these uncorrected runs on mixing the acetone and water solutions to start the run.

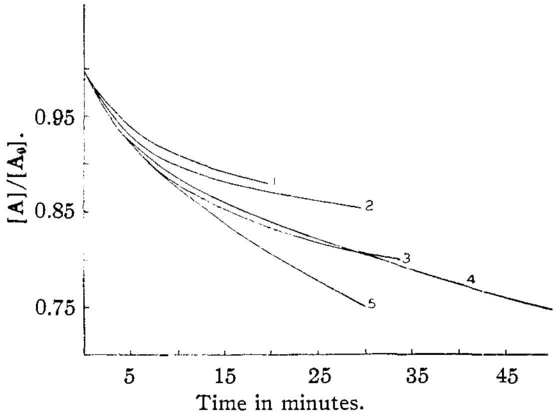

Fig. 6.—Curves from the differential analyzer with different assumed values of the rate constants: curve 1, $k_{-1} = 2.0$, $k_2 = 0.5$; curve 2, $k_{-1} = 1.5$, $k_2 = 0.2$; curve 3, $k_{-1} = 1.0$, $k_2 = 0.2$; curve 4, $k_{-1} = 1.35$, $k_2 = 0.4$; curve 5, $k_{-1} = 1.5$, $k_2 = 1.0$.

Variation of Experimental Conditions.—The experiment upon which this first fit was based was a dimerization of methyl-bis-β-chloroethylamine (0.0460 M) in the presence of 0.0987 M sodium chloride (Table I). The rate constants therefore refer to a medium of mean ionic strength about 0.11. The correctness of the formulation can be tested by using the same values of k_{-1} and k_2 to calculate the course of the reaction with different initial concentrations of amine and chloride ion. Simple omission of the sodium chloride in an experimental run yielded a set of experimental points (Fig. 2) which could not be fitted by the use of the previously determined constants in the differential analyzer. This was traced to the neglect of the ionic strength; when a run was made similar to this one, but with the introduction of the inert salt, sodium fluoborate, in 0.10 molar concentration, the results were in good agreement with those from the differential analyzer (Fig. 2).

On the basis of the Brønsted theory of the kinetic salt effect k_{-1} would be expected to be diminished by increasing ionic strength, since it is the only constant of the group being considered which has to do with the reaction between ions of opposite charge. A diminution in k_{-1} means an increase in the over-all rate of appearance of chloride ion, which accounts for the direction of the observed salt effect.

As a third test of the assignment of k's, a calculated curve was made and compared with the experimental points in a run without added salt, but with the amine at an initial concentration of 0.1180 M, more than twice that in the run with chloride added. At 50% reaction this yields a dimer concentration affording an ionic strength of 0.177, so that the mean ionic strength over the period in which we are interested is of comparable magnitude with that in the other two runs. The differential analyzer was no longer available when this calculation was undertaken. The curve was therefore calculated by the method of small increments, with the use of a calculating machine. The comparison of the calculated curve and the experimental points is shown in Fig. 1. The agreement, nowhere showing deviations of more than 3.5%, is all that can be expected and constitutes strong support for the mechanism on which this formulation is based.

Because there is some uncertainty in the magnitude of k_w, this curve was also calculated with a k_w 2.5 times as great. The true hydrolysis constant is certainly not greater than this. The curve of (A) against time was only 1% lower at 110 minutes (65.2% reaction), because hydrolysis is an almost negligible part of the total reaction in the case of this amine under these experimental conditions.

Concentration of the Cyclic Intermediate B.—An interesting by-product of these calculations is that the differential analyzer, in tabulating (A) in any calculated run, also tabulates (B), a quantity which at the time of doing this work there was no direct experimental way of estimat-

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(12) Bush and Caldwell, *J. Franklin Inst.*, **240**, 255–326 (1945).

ing.[13] Figure 7 shows the fraction of starting material in the form of the cyclic ethylene-immonium intermediate B as a function of time for the three sets of experimental conditions for which the calculations were made. The effect of added chloride ion is (1) to lower the steady-state concentration of the intermediate B; (2) to make (B) reach a stable concentration earlier in the run; (3) to retard the decline of its concentration. All these effects would be intuitively predicted from the chemical equations. Figure 7 also shows how a lower initial concentration of amine results in a larger fraction being converted into the cyclic intermediate, this fraction reaching about 30% in the run with $a = 0.044$.

Acknowledgment.—We received indispensable aid in the application of the differential analyzer to our problem from Mr. John Löf of the Massachusetts Institute of Technology.

Summary

Methyl-bis-β-chloroethylamine, stable in non-polar solvents, is converted rapidly into a cyclic dimer in aqueous and part-aqueous solution. In 2:1 acetone–water solution the reaction proceeds at a convenient rate for measurement and is attended by a small amount (less than 10%) of hydrolysis. The dimerization involves successive reactions at comparable rates and corresponds to no simple kinetic order. It is markedly retarded by sodium chloride.

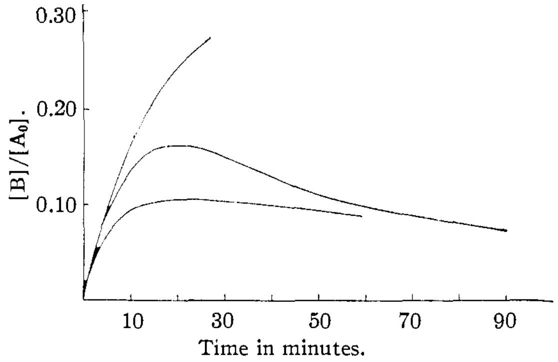

Fig. 7.—Concentration of cyclic intermediate B during reaction of methyl-bis-β-chloroethylamine in 2:1 acetone-water at 25° according to the differential analyzer: upper curve, $[A]_0 = 0.04407$; middle curve, $[A]_0 = 0.1180$; lower curve, $[A]_0 = 0.0460$, $[Cl^-]_0 = 0.0987$.

In the presence of sodium hydroxide, sodium thiosulfate or triethylamine displacement of the chlorine supersedes dimerization and the reactions all proceed at the same rate, first order with respect to the amine. These and other facts are interpreted as indicating that a cyclic ethylene-immonium ion is intermediate in both dimerization and displacement. Final proof of the mechanism is obtained by evaluating the separate rate constants involved in the dimerization by trial from the differential equations, and calculating the course of the reaction under different conditions.

CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 27, 1947

[13] Later Golumbic, Fruton and Bergmann[5] showed that the concentration of B could be determined by titration with thiosulfate.

[CONTRIBUTION FROM THE WOLCOTT GIBBS LABORATORY OF HARVARD UNIVERSITY]

Kinetics and Mechanism of Reactions of Tertiary β-Chloroethylamines in Solution. II. Ethyl-bis-β-chloroethylamine[1]

BY PAUL D. BARTLETT, JAMES W. DAVIS, SIDNEY D. ROSS AND C. GARDNER SWAIN

In Part I of this series[2] it was shown that methyl-bis-β-chloroethylamine, dissolved in 2:1 acetone–water, undergoes dimerization to a quaternary piperazinium dichloride with only a small amount of hydrolysis as a side reaction. It was also shown that dimerization, as well as hydrolysis and other displacements of the chlorine atoms, proceeds through a cyclic ethylene-immonium ion which is formed unimolecularly and reversibly from the β-chloroethylamine. The same types of product are found when the next homolog, ethyl-bis-β-chloroethylamine, is dissolved in 2:1 or 1:3 acetone–water. In this case, however, hydrolysis is the principal reaction and dimerization constitutes less than 50%, and under some conditions practically none, of the reaction. The present study was undertaken to account for this quantitative difference between the homologs. It has been found that because of the special relations existing in this case between the magnitudes of the rate constants of the several reactions occurring, it is again possible, this time by a graphical method, to evaluate these rate constants separately and to confirm the correctness of the general mechanism already put forward.

Experimental

Material.—Ethyl-bis-β-chloroethylamine hydrochloride was most advantageously prepared by the reaction of ethyldiethanolamine (Carbide and Carbon) with thionyl chloride. The free base was prepared, like its lower homolog, by making an aqueous solution of the hydrochloride alkaline in the presence of benzene or ether, extracting rapidly, drying and evaporating the solvent. Solutions of the free base so prepared in dry acetone or ether could be kept for days without developing appreciable amounts of ionic chlorine.

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[1] The work presented in this paper was performed under Contract NDCrc-136 between Harvard University and the National Defense Research Committee of the Office of Scientific Research and Development in 1943.

[2] Bartlett, Ross and Swain, THIS JOURNAL, **69**, 2971 (1947).