

tion to light results in a magnetic change which could be interpreted as being due to appreciable dissociation.

A considerable degree of free radical formation

is observed with 2,2'-dibenzothiazyl disulfide. The concentration of the thiol radicals in toluene has been measured up to 150°.

EVANSTON, ILLINOIS

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## Reaction Kinetics of Aliphatic Tertiary $\beta$ -Chloroethylamines in Dilute Aqueous Solution. I. The Cyclization Process<sup>1</sup>

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In contrast to ordinary alkyl halides, alkylamines possessing a halogen atom in the beta to omega position undergo a distinctive intramolecular transformation as the initial detectable reaction in polar solvents. The transformation yields halide ion and a more or less stable heterocyclic compound. In the case of the primary and secondary amines, the heterocycle may be either an imine or an imonium ion, depending on the pH of the solution. The tertiary amines can yield only the corresponding imonium ions.

The kinetics of the initial cyclization of a number of primary halogenated alkylamines has been reported.<sup>3</sup> The forward process of ring-formation was established as a unimolecular reaction, the rate of which was shown to be influenced by the length of the side-chain, by the substituents thereon, by the nature of the halogen and, especially, by the nature of the solvent.<sup>4</sup> The process is known to be reversible, but the kinetics of the reverse reaction seems not to have been studied, except for unsuccessful attempts<sup>5</sup> to determine an equilibrium constant in the  $\beta$ -bromoethylamine system. The failure was due to interference by side-reactions. It is known that in certain cases, at least, cyclic dimerization and linear polymerizations of the haloalkylamines can take place and become quantitatively important,<sup>6</sup> especially in concentrated solutions and at elevated temperatures.<sup>7</sup>

This report on a series of nine tertiary  $\beta$ -chloroethylamines supplements the older observations on the analogous primary amines. The compounds were of the general type RR'NCH<sub>2</sub>CH<sub>2</sub>Cl,

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

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(3) Freundlich, *et al.*, *Z. physik. Chem.*, **76**, 99 (1911); **79**, 681 (1912); **191**, 177 (1922); **122**, 39 (1926); **166A**, 161 (1933).

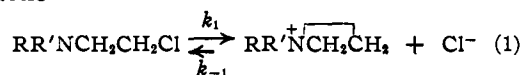
(4) Salomon, *Helv. Chim. Acta*, **16**, 1361 (1933); *Trans. Faraday Soc.*, **32**, 153 (1936).

(5) Freundlich and Neumann, *Z. physik. Chem.*, **87**, 69 (1914).

(6) Golumbic, Fruton and Bergmann, *J. Org. Chem.*, **11**, 518 (1946). This and the seven succeeding papers describe the chemical properties of the tertiary  $\beta$ -chloroethylamines.

(7) Cf. Lehmann, Thompson and Marvel, *THIS JOURNAL*, **55**, 1977 (1933).

where R and R' represent an alkyl group or a  $\beta$ -substituted ethyl group. Analytic evidence adduced here and elsewhere<sup>6,8</sup> shows that these compounds undergo the following initial reversible reaction



The first-order kinetics of the forward reaction can be established with relative ease because the reverse reaction is very much slower. The cyclic imonium ion is a reactive compound, but it possesses in many cases a fair degree of stability in water and can accumulate as reaction (1) proceeds.<sup>6</sup> The properties in solution and the reaction kinetics of the ethylenimonium ion will be considered in a subsequent report. In connection with the present discussion, it may be stated that the reaction kinetics indicates unequivocally that this ion is a singly charged cation.

Cyclization cannot occur when a proton is coordinated with the nitrogen atom of the amine. Consequently, in the case of these compounds, which are more or less weak bases, the rate of cyclization becomes a function of pH in solutions of moderate and low pH. In such cases, the observed rate constant,  $k'_1$ , is defined by the relation

$$k'_1 = \alpha k_1 = \frac{K'_a k_1}{K'_a + [\text{H}^+]}$$

where  $k_1$  is the rate constant at pH conditions under which the ammonium ion is fully dissociated ( $\alpha = 1$ ), and  $K'_a$  is the apparent dissociation constant of the ammonium ion as an acid.

It is obvious that the subsequent cyclization of a second and a third  $\beta$ -chloroethyl group, if present in these tertiary amines, is possible only after the antecedent heterocycle has been broken down,<sup>9</sup> *e. g.*, by hydrolysis. The rates of such subsequent cyclizations can best be determined by kinetic study of the corresponding chlorohydrins, as has been done in the case of N-methyl-bis-( $\beta$ -chloroethyl)-amine and its chlorohydrin (see

(8) Hartley, Powell and Rydon, 1942, 1943. Unpublished data obtained in Great Britain; also *J. Chem. Soc.*, 513, 519, 527 (1947).

(9) This restriction need not apply to analogous secondary bis- $\beta$ -halogenated amines which should permit double cyclization at a pH favorable to the ionization of the coordinated proton created by the initial cyclization.

TABLE I

TERTIARY ALKYL  $\beta$ -CHLOROETHYLAMINES:  $\begin{matrix} R \\ \diagdown \\ N \\ \diagup \\ R' \end{matrix} \text{CH}_2\text{CH}_2\text{Cl}$ . ANALYSES OF THE HYDROCHLORIDES, APPARENT ACID DISSOCIATION EXPONENTS, AND KINETIC CONSTANTS FOR THE INITIAL CYCLIZATION OF THE AMINES IN WATER

| R   | R'                                  | M. p.,<br>°C.<br>cor. | Analyses, % |                       |     |                      | $pK'_a$ ( $\Gamma/2 = 0.0025$ ) |                |                   | $10^4 k_1$<br>(min. <sup>-1</sup> )<br>15° | E<br>kcal. <sup>a</sup><br>per<br>mole | $\Delta F^\ddagger$<br>kcal. <sup>b</sup><br>per<br>mole | $\Delta S^\ddagger$<br>E.<br>U. <sup>c</sup> |      |      |
|---|-------------------------------------|-----------------------|-------------|-----------------------|-----|----------------------|---------------------------------|----------------|-------------------|--|--|--|--|------|------|
|   |                                     |                       | N           | Calcd.<br>Total<br>Cl | N   | Found<br>Total<br>Cl | 0°                              | 25°            | 0°                |  |  |  |  |      |      |
| -CH(CH <sub>3</sub> ) <sub>2</sub>                | -CH <sub>2</sub> CH <sub>2</sub> Cl | 211-212               | 6.35        | 48.22                 | 6.3 | 48.3                 | 7.3                             | $\approx 0.05$ | 7.0               | $\approx 0.05$                             | 5.51                                   | 49.0   | 23.0   | 19.7 | 10.0 |
| -(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub>  | -CH <sub>2</sub> CH <sub>2</sub> Cl | 118-119 <sup>a</sup>  | 6.35        | 48.22                 | 6.4 | 48.2                 | 7.02                            | $\approx .02$  | 6.7               | $\approx .05$                              | 2.02                                   | 21.7   | 24.8   | 20.3 | 14.6 |
| -(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub>  | -CH <sub>2</sub> CH <sub>2</sub> Cl | 95-96                 | 5.97        | 45.34                 | 6.1 | 45.3                 | 6.97 <sup>f</sup>               | $\approx .02$  | 6.63 <sup>f</sup> | $\approx .02$                              | 1.54                                   | 15.4   | 24.0   | 20.4 | 11.1 |
| -CH <sub>2</sub> CH <sub>2</sub>                  | -CH <sub>2</sub> CH <sub>2</sub> Cl | 210-211 <sup>b</sup>  | 8.14        | 41.21                 | 8.0 | 41.3                 | 9.18                            | $\approx .02$  | 8.82              | $\approx .02$                              | 1.58                                   | 14.5   | 23.1   | 20.4 | 7.8  |
| -CH <sub>2</sub> CH <sub>2</sub>                  | -CH <sub>2</sub> CH <sub>2</sub> Cl | 141-142               | 6.78        | 51.50                 | 6.8 | 51.6                 | 6.8                             | $\approx .05$  | 6.57              | $\approx .05$                              | 1.17                                   | 12.8   | 25.0   | 20.6 | 14.2 |
| -CH <sub>2</sub> CH <sub>2</sub> Cl               | -CH <sub>2</sub> CH <sub>2</sub> Cl | 130-131 <sup>c</sup>  | 5.81        | 58.85                 | 5.7 | 59.2                 | 4.66 <sup>g</sup>               | $\approx .02$  | 4.39 <sup>g</sup> | $\approx .02$                              | 0.69                                   | 7.3  | 24.7   | 20.9 | 12.1 |
| -CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> | -CH <sub>2</sub> CH <sub>2</sub> Cl | 132-133               | 5.92        | 44.96                 | 5.9 | 45.0                 | 5.73 <sup>f</sup>               | $\approx .02$  | 5.47 <sup>f</sup> | $\approx .02$                              | .49                                    | 5.2  | 24.6   | 21.1 | 11.0 |
| -CH <sub>3</sub>                                  | -CH <sub>2</sub> CH <sub>2</sub> Cl | 109-110 <sup>d</sup>  | 7.28        | 55.25                 | 7.2 | 55.1                 | 6.78                            | $\approx .02$  | 6.45              | $\approx .02$                              | .23                                    | 2.4  | 24.1   | 21.5 | 7.7  |
| -CH <sub>3</sub>                                  | -CH <sub>2</sub> CH <sub>2</sub> OH | e                     | 8.05        | 40.74                 | 7.9 | 40.6                 | 7.83                            | $\approx .02$  | 7.5               | $\approx .05$                              | .27                                    | 2.3  | 21.9 <sup>i</sup>                            | 21.5 | 0.0  |

<sup>a</sup> Reported 118-119.5° by G. H. Coleman, personal communication. <sup>b</sup> Reported 211° by R. L. Shriner, personal communication; 210-211° by Gough and King, *J. Chem. Soc.*, 2426 (1928). <sup>c</sup> Reported 130-131° by Ward, *THIS JOURNAL* 57, 916 (1935). <sup>d</sup> Reported 110° by Jensen and Lundquist, *Dansk. Tid. Farm.*, 15, 201 (1941). <sup>e</sup> Hygroscopic; chief impurity water, m. p. 50°, R. L. Shriner, personal communication; 54° (ref. 8). <sup>f</sup>  $\Gamma/2 = 0.0015$ . <sup>g</sup>  $\Gamma/2 = 0.001$ . <sup>h</sup>  $\approx 1$  kcal. Reported for primary  $\beta$ -bromoethylamine and  $\beta$ -chloroethylamine, 24.9 and 27.5 kcal., respectively (ref. 4). <sup>i</sup>  $\approx 2$  kcal. <sup>j</sup>  $\approx 4$  E. U. Calcd. for 0° assuming transmission coef. = 1 (ref. 18).

Table I, last two compounds). Unless otherwise specified, this report deals with the first cyclization process.

### Experimental

Temperatures (except at 0°) were maintained to  $\pm 0.05^\circ$  in an electrically controlled, light-oil bath. Crushed melting ice surrounded the vessel of well-stirred solution in the measurements at 0°.

**Materials.**—The stable crystalline hydrochlorides of nine tertiary  $\beta$ -chloroethylamines<sup>10</sup> were employed. The free amines were sufficiently soluble in water for the purposes of these studies; however, the low solubilities of *N*-benzyl- and *N*-cyclohexyl-bis-( $\beta$ -chloroethyl)-amines did not permit comparable evaluation of their properties. The purity and identity of the hydrochlorides is indicated by our analytical data shown in Table I. Total chlorine was determined after digestion of the samples in strong NaOH. Ionic chlorine (not recorded in Table I) was also determined and found to check the analyses reported. The melting points were accompanied by more or less sintering and decomposition.

**Determination of  $pK'_a$ .**—The apparent acid dissociation constant of each amine was determined by electrometric titration. The measuring system consisted of a glass electrode and a Type 7660 Leeds and Northrup potentiometer-electrometer. The electrode was standardized with 0.05 *M* potassium acid phthalate (primary standard, reagent grade) on the basis of the following values: *pH* 4.005<sup>11</sup> at 0° and *pH* 4.00<sup>11,12</sup> at 10° and 25°. Linearity in response of the electrode to *pH*-change was checked in standardized (Clark and Lubs) phosphate buffers at *pH* 6 and 8. In more alkaline regions, the electrode was standardized in borate buffers of known *pH*.

The titrations were made with standardized 2 *N* sodium hydroxide delivered from a calibrated microburet graduated in 0.001 ml. into 100 ml. of an aqueous 0.0025 *M* solution of each amine hydrochloride. The volume change was negligible, and the added Na<sup>+</sup> ion was too low in concentration to influence the glass electrode significantly in the alkaline region. Instability of some of the compounds made it necessary to complete their titrations within 5 to 8 min. The degree of contamination from

carbon dioxide of the air during a titration was found to be  $1 \times 10^{-4}$  milliequiv./minute per 100 ml. of water at *pH* 9.0, and 15°. Titrations of the amines were so conducted as to hold the maximum carbon dioxide-contamination to less than 0.001 milliequiv. for the total of 0.250 milliequiv. of compound titrated. The apparent dissociation constant, in terms of  $pK'_a$ , was calculated from the titration data in the usual manner,<sup>13</sup> using for  $pK'_a$  the values: 14.940 at 0°, and 14.340 at 15° (ionic strength 0.0025).<sup>14</sup> The  $pK'_a$  values thus determined are shown in Table I. The temperature coefficient,  $-\Delta pK'_a/\Delta 10^\circ$ , was found to be 0.2 (range, 0.17 to 0.23  $\pm$  0.02). Increase in ionic strength from 0.0025 to 0.15, with sodium chloride, produced the same increase (0.05) in  $pK'_a$  as that reported for the NH<sub>4</sub><sup>+</sup> ion.<sup>14</sup>

**Rate Measurements.**—In order to hold side reactions, such as polymerizations, within negligible limits, the compounds were studied at sufficiently low concentrations. The criterion for this was established by the uniformity of the first order rate constants found for the cyclization in 0.0005 to 0.1 *M* solutions of the type compound, *N*-methyl-bis-( $\beta$ -chloroethyl)-amine. In general, the concentration used was 0.0025 *M*. The kinetics of the cyclization was determined most conveniently and accurately by the rate of production of Cl<sup>-</sup>, and confirmed on occasion by measurement of the rate of decrease of the parent amine or of production of the cyclic imonium ion.

The stock solution of each amine hydrochloride, 0.1 to 0.5 *M*, was prepared by dissolving the appropriate, accurately weighed amount of carefully dried hydrochloride in iced 0.001 to 0.05 *N* HCl. In sufficiently acid stock solutions, cyclization with Cl<sup>-</sup> evolution did not occur at a measurable rate. The solutions of compounds with  $pK'_a > 6$  could be preserved for one to three days at 0 to 5° without detectable decomposition. The usual procedure in making a rate measurement was as follows. The aqueous medium, 99 ml., containing the calculated amount of sodium hydroxide for the predetermined *pH*, plus 0.0002 to 0.0004% sulfophthalcin indicator and other reagents as required, was brought to constant temperature; and then, under vigorous stirring, there was added rapidly from a chilled, calibrated, all-glass syringe, 1.00  $\pm$  0.005 ml. of the stock solution. Zero time was taken at the half-time of delivery of the solution. The momentary, initial change in temperature was negligible. The reaction was quenched in successive samples by withdrawing usually 10 ml. and adding it with stirring to 0.01 to 0.02 *N* nitric or sulfuric acid. Time of quenching was taken

(10) We are indebted to Dr. George H. Coleman, Dr. Ralph L. Shriner and Dr. Calvin Golumbic for furnishing one or more samples of these compounds.

(11) M. Dole, "The Glass Electrode," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 156.

(12) MacInnes, Belcher and Shedlovsky, *THIS JOURNAL*, 60, 1094 (1938).

(13) Van Slyke, *J. Biol. Chem.*, 52, 525 (1922).

(14) Everett and Wynne-Jones, *Proc. Roy. Soc. (London)*, 169A, 190 (1938).

at the half-time of delivery of the sample.  $\text{Cl}^-$  evolved in the cyclization process was determined in the quenched samples by differential potentiometric titration with standardized silver nitrate.<sup>16</sup> Ethylenimmonium ion was measured by its uptake of thiosulfate<sup>6</sup> and the residual  $\text{S}_2\text{O}_3^{2-}$  was determined iodometrically. Residual amine was only roughly determined, after acidification of the mixture to quench the reaction, by rapid potentiometric acid-base titration at 0 to 5°.

The pH was held constant without buffers by adding micro-quantities of alkali or acid to the reaction mixture as required and using a glass electrode or the appropriate sulfonphthalein as pH indicator. The acid production was evaluated according to the experimental conditions and was assignable (a) to more or less slight hydrolysis of the initial cyclic product of the amine, (b) to  $\text{H}^+$  from the ammonium ion of the amine when the cyclization was conducted at a pH at which  $\alpha < 1$ , or (c) to zero-order contamination by atmospheric carbon dioxide during prolonged runs. Under proper conditions, there was little or no pH-change during the major part of the cyclization process when the product was one of the more stable ethylenimmonium ions.

A stopwatch, reading to 0.01 minute and standardized against an electric clock, was used to time the reactions.

**Errors.**—In the case of the more strongly basic amines, the reaction was necessarily conducted at a pH at which  $\alpha$  was less than 1. This involved an error of  $\pm 0.02$  to 0.05 in the  $pK'_a$  determination and the pH maintenance. In the case of those compounds having a  $pK'_a$  between 6.5 and 7.0, the corresponding maximum probable error in the rate constant was 2 to 3%. For the two compounds with a  $pK'_a$  higher than 7 (see Table I), the corresponding maximum probable errors were three to five times as great. The fact that duplicate determinations agreed to  $\pm 5\%$  was probably due to a compensation of errors. Errors due to temperature variations and the preparation and analysis of the solutions were small. In most cases the over-all error was within 10%; it was somewhat greater, within 15%, for the last compound of Table I.

### Results and Discussion

Rapid, successive acid-base titrations of one of these tertiary amines as the reaction progressed gave symmetrical titration curves, centered at  $\text{pH} = pK'_a$ , which finally merged with the titration curve of water of the same ionic strength. The disappearance of the amine during the reaction, and the absence of other titratable base in

TABLE IIa

INITIAL CYCLIZATION RATE OF  $\text{C}_2\text{H}_5\text{N}(\text{CH}_2\text{CH}_2\text{Cl})_2$

Temp. 0.0°. Initially, [amine·HCl] = [NaOH] = 0.0026 mole/liter; neutralized thymol blue, 0.0004%; pH 9.1;  $\alpha \cong 1.00$ .

| Reaction time, min. | $\text{Cl}^-$ produced, % <sup>a</sup> | $k_1 \times 10^3$ min. <sup>-1</sup> |
|---------------------|--|--------------------------------------|
| 2.15                | 3.0                                    | (1.4)                                |
| 8.1                 | 11.9                                   | 1.27                                 |
| 15.0                | 17.8                                   | 1.02                                 |
| 25.2                | 26.7                                   | 1.12                                 |
| 40.0                | 39.2                                   | 1.26                                 |
| 60.0                | 51.3                                   | 1.11                                 |
| 90.0                | 66.3                                   | 1.23                                 |
| 123.0               | 77.2                                   | 1.18                                 |

Av. 1.17  $\pm$  0.09

Duplicate 1.17

<sup>a</sup> 100% = 1 equivalent of  $\text{Cl}^-$  per mole of amine.

(15) MacInnes and Dole, THIS JOURNAL, 51, 1119 (1929).

TABLE IIb  
CYCLIZATION RATE OF  $\text{CH}_3\text{N}(\text{CH}_2\text{CH}_2\text{OH})$   
 $\text{CH}_2\text{CH}_2\text{Cl}$

Temp. 15.0°. Initially, [amine·HCl] = 0.0025 mole/liter; NaOH to pH 7.9,  $\alpha = 0.715$ ; neutralized phenol red, 0.0002%.

| Reaction time, min. | $\text{Cl}^-$ produced, % | $\alpha k_1 \times 10^3$ min. <sup>-1</sup> |
|---------------------|---------------------------|---|
| 5.0                 | 9.7                       | (2.03)                                      |
| 10.0                | 15.8                      | 1.41  |
| 20.0                | 28.1                      | 1.58  |
| 30.0                | 40.5                      | 1.88  |
| 40.0                | 48.5                      | 1.48  |
| 60.0                | 63.0                      | 1.65  |
| 90.0                | 77.4                      | 1.64  |

Av. 1.61  $\pm$  0.16

$k_1 = 0.0161/0.715 = 0.023$  min.<sup>-1</sup>

the pH range 3 to 11 are consistent with the interpretation that the transformation product is a quaternary ammonium ion.

The initial cyclization of each of the compounds followed a uniform unimolecular course throughout the major portion of the process. By way of illustration, Tables IIa and IIb show the results of two typical determinations based on measurements of the production of chlorine ion.

Within the experimental error, the rate of  $\text{Cl}^-$  evolution from the type compound, N-methyl-bis-( $\beta$ -chloroethyl)-amine, was independent of the ionic strength of the solution (Table III).

TABLE III

EFFECT OF IONIC STRENGTH ON RATE OF CYCLIZATION

0.005 M  $\text{CH}_3\text{N}(\text{CH}_2\text{CH}_2\text{Cl})_2$ , pH 8.0, 30.0°

| [Na <sub>2</sub> SO <sub>4</sub> ] mole/liter | Total ionic strength | $k_1$ min. <sup>-1</sup> |
|---|----------------------|--------------------------|
| 0   | 0.005                | 0.197                    |
| 0.005   | .020                 | .190                     |
| .050  | .155                 | .187                     |
| .50   | 1.51                 | .199                     |
| .93   | 2.80                 | .202                     |

Subsequent hydrolysis of the cyclic imonium ion was generally much slower, so that the second cyclization, if any, did not make a detectable appearance until the initial cyclization was well advanced. This is in accord with repeated observations that the early phase of the cyclization, when conducted under appropriate pH conditions, occurred without detectable acid production at 0° and 15°. A closer examination was made of the acid production during the initial cyclization of N-methyl-bis-( $\beta$ -chloroethyl)-amine at 25°, with the aid of the glass electrode. The titration, compared with the per cent. cyclization (computed), during the first eight minutes gave the results shown in Table IV. The very small amount of acid produced and its progressive increase agree, within experimental error, with the values computed from the separately determined constants for a system of two consecutive first-order proc-

esses. There was no evidence during any of these cyclizations for the appearance of extra acid assignable to a concurrent reaction of water with the postulated intermediate carbonium ion.

TABLE IV

ACID PRODUCTION DURING CYCLIZATION OF  $\text{CH}_3\text{N}(\text{CH}_2\text{CH}_2\text{Cl})_2$ 

Temp. 25.0°. Initially,  $[\text{amine}\cdot\text{HCl}] = [\text{NaOH}] = 3.513 \times 10^{-3}$  mole/liter;  $\text{pH} 8.8$ ;  $\alpha = 1.00$ .

| Reaction time, min. | Cyclization, % | Acid produced, % |                     |
|---------------------|----------------|------------------|---------------------|
|                     |                | Obs.             | Calcd. <sup>a</sup> |
| 2.0                 | 17.8           | 0.02             | 0.02                |
| 3.0                 | 25.3           | .03              | .05                 |
| 4.0                 | 32.4           | .07              | .08                 |
| 5.0                 | 38.7           | .10              | .12                 |
| 6.0                 | 44.5           | .15              | .17                 |
| 7.0                 | 49.6           | .20              | .23                 |
| 8.0                 | 54.3           | .28              | .28                 |

<sup>a</sup> % Acid =  $100 [1 - (k_2/(k_2 - k_1))e^{-k_1 t} + (k_1/(k_2 - k_1))e^{-k_2 t}]$ ;  $k_1 = 0.098 \text{ min.}^{-1}$ ;  $k_2 = 1.16 \times 10^{-3} \text{ min.}^{-1}$  (unpublished data).

In the presence of  $\text{S}_2\text{O}_3^{2-}$ , the rates of initial cyclization of the bis-( $\beta$ -chloroethyl)-amines determine the rates of thiosulfate uptake by the corresponding cyclic transformation products. In such cases, the cyclization rates measured by the thiosulfate uptakes agreed well with those measured by the production of  $\text{Cl}^-$ . An example is shown in Table V which includes also the result obtained by direct titrimetric estimation of the decomposing amine.

The results of the kinetic measurements at 0 and 15° are summarized in Table I in which the compounds are listed in the order of decreasing  $k_1$  at 15°. Inspection of this table shows that the rate constants for members of the homologous series of

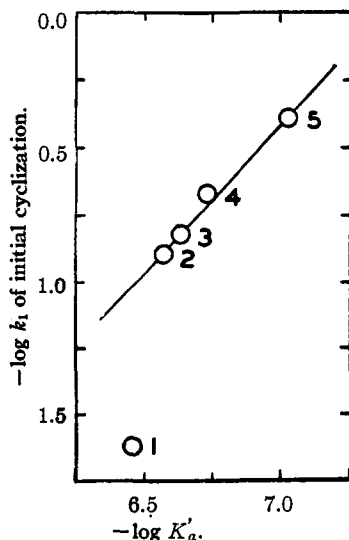


Fig. 1.—Relation of rate and dissociation constants at 15° of homologous tertiary bis-( $\beta$ -chloroethyl)-amines,  $\text{RN}(\text{CH}_2\text{CH}_2\text{Cl})_2$ : 1, R = methyl; 2, ethyl; 3, *n*-butyl; 4, *n*-propyl; 5, isopropyl.

TABLE V

INITIAL CYCLIZATION RATE OF  $(\text{CH}_3)_2\text{CHN}(\text{CH}_2\text{CH}_2\text{Cl})_2$   
Temp. 0.0°. Initially,  $[\text{amine}\cdot\text{HCl}] = 0.0025$ , and  $[\text{Na}_2\text{S}_2\text{O}_3] = 0.025$  mole/liter; 0.0002% phenol red; NaOH to  $\text{pH} 7.4$ ;  $\alpha = 0.557$ .

| Reaction time, min. | $\text{S}_2\text{O}_3^{2-}$ uptake, % | $\alpha k_1 \times 10^3$ min. <sup>-1</sup> |
|---------------------|---------------------------------------|---|
| 2.0                 | 5.0                                   | (2.5)                                       |
| 5.0                 | 15.6                                  | 3.41  |
| 9.0                 | 22.8                                  | 2.87  |
| 20.1                | 49.8                                  | 3.44  |
| 28.1                | 62.0                                  | 3.45  |

Av.  $3.29 \pm 0.28$

$k_1 = 0.0329/0.557 = 0.059 \pm 0.005 \text{ min.}^{-1}$

By  $\text{Cl}^-$  production =  $.055 \pm 0.004 \text{ min.}^{-1}$

By amine decomp. =  $.057 \pm 0.007 \text{ min.}^{-1}$

<sup>a</sup> 100% = 1 mole  $\text{S}_2\text{O}_3^{2-}$  per mole of amine.

compounds, N-methyl- through N-*n*-butyl-bis-( $\beta$ -chloroethyl)-amine, including the isopropyl homolog, fall in the order of the electron-donating abilities of these amines as measured by the respective  $\text{p}K'_a$  values.

Figure 1 shows that the relation between  $\log k_1$  and  $\log K'_a$  is linear for these homologous bis-( $\beta$ -chloroethyl)-amines, with appreciable deviation only in the case of the N-methyl homolog. Deviation is often observed in the case of the first member of a series of alkyl homologs in numerous properties. The similar, but not strictly homologous compound N- $\beta$ -methoxyethyl-bis-( $\beta$ -chloroethyl)-amine does not fit into this linear relation, its cyclization rate being about ten times greater than would be predicted from its  $\text{p}K'_a$  value. The significance of this behavior has not been established. The effect might be due to the basicity of the methoxyl group or to direct interaction of this group with the  $\beta$ -chlorine atom. The unlikely possibility of competitive cyclization involving displacement of the methoxyl group is excluded because such competition would be expected to retard the apparent rate of normal cyclization as measured by production of  $\text{Cl}^-$ .

Illustrative of the importance of the properties determining the  $\text{p}K'_a$  in controlling the rate of cyclization is the following comparison in which the amines *a* to *c* are arranged in decreasing order of  $\text{p}K'_a$  and  $k_1$ . On ordinary statistical grounds,

|   | $\text{p}K'_a$ | $k_1$ |
|---|----------------|-------|
| (a) $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{Cl}$        | 8.82           | 0.145 |
| (b) $\text{C}_2\text{H}_5\text{N}(\text{CH}_2\text{CH}_2\text{Cl})_2$ | 6.57           | .128  |
| (c) $\text{N}(\text{CH}_2\text{CH}_2\text{Cl})_2$                     | 4.39           | .073  |

compound *a* might be regarded as having one, *b* two, and *c* three chances for the initial cyclization to occur; yet compound *a*, despite this least favorable chance, undergoes the most rapid cyclization. In the above series of three compounds, the progressive decrease in  $\text{p}K'_a$  is due to the cumulative decrease in basicity of the central nitrogen atom induced by successive  $\beta$ -substitutions of chlorine.

In terms of the transition state theory of chemical reaction, the linear relationship between  $\log k_1$  and  $\log K'_a$  suggests that the free energy changes ( $-RT \ln k_1$ ) associated with the equilibrium between the initial and transition states in the cyclization of the homologous bis-( $\beta$ -chloroethyl)-amines is directly proportional to the free energy changes ( $-RT \ln K'_a$ ) involved in the acid-base dissociations of the corresponding amines. Such a relation in a group of closely related reactions has been observed<sup>16</sup> frequently, for example in general acid-base catalysis,<sup>17</sup> and in the second order reactions of certain types of substituted benzene derivatives.<sup>16</sup> The present limited series of homologous aliphatic tertiary amines involving a unimolecular process provides a further instructive example of this correlation.

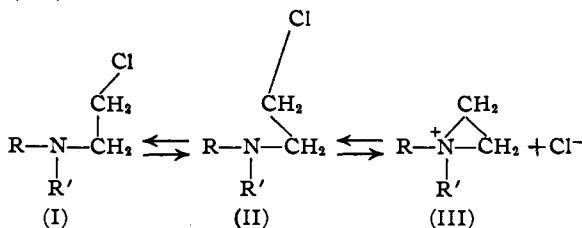
The parameters  $E$  and  $A$  of the empirical Arrhenius equation

$$k_1 = Ae^{-E/RT}$$

have been computed. The values for the activation energy,  $E$ , are given in Table I. The frequency factor,  $A$ , in the kinetics of this series of compounds is found to have values between  $10^{14.9}$  to  $10^{16.4}$  sec.<sup>-1</sup>, and compares with the value of  $10^{16}$  sec.<sup>-1</sup> recomputed from the data<sup>4</sup> for the cyclization of primary  $\beta$ -bromoethylamine. This level of  $A$ , associated with the displacement of the halogen for closure of the three-membered ring, is about  $10^1$  to  $10^3$  times greater than the values,  $10^{13}$  to  $10^{13.7}$  sec.<sup>-1</sup>, reported for the closure of analogous primary amines to 4-, 5- and 6-membered rings,<sup>4</sup> or the values  $10^{13}$  to  $10^{14}$  sec.<sup>-1</sup> predictable from the theory of absolute reaction rates for unimolecular reactions with low entropy of activation and high transmission coefficient.<sup>18</sup> The higher frequency factor, which can be regarded as a measure of the greater occurrence of cyclization, is consistent with the concept of a coiled configuration of the side chain incident to formation of the incipient ring in the activated complex of the  $\beta$ -chloroethylamines in water.

The process of cyclization evidently consists of an intramolecular displacement of the alkyl halogen by the basic nitrogen atom of the tertiary  $\beta$ -chloroethylamine. In this process, the strongly polar molecule tends to coil up toward the ring position under the influence of the polar solvent,

so that the general configuration of the activated complex (II) would be expected to resemble both the normal molecule (I) and the cyclic end-product (III).



The thermally activated complex, upon rupture of its stretched C-Cl bond, would yield a carbonium ion. The latter, however, should have but a momentary existence, because its need for sharing an electron pair is most easily satisfied by the unshared pair on the nitrogen, the positive charge moving from C to N in the newly formed ring compound. The ring closure must be much more rapid than either the possible reaction of the carbonium ion with water or the activation of the parent amine with ejection of  $\text{Cl}^-$ , because electron donor-acceptor reactions are much faster than those associated with thermally activated covalent bond dissociations, which in the present case involve the not inconsiderable strengths of the oxygen-hydrogen and carbon-chlorine bonds. Thus the carbonium ion concentration during the cyclization of these amines should be practically nil, and the experimental observations previously discussed, and illustrated in Table IV, are in harmony with this interpretation.

### Summary

1. The apparent acid dissociation exponents ( $pK'_a$ ) of nine tertiary  $\beta$ -chloroethylamines have been measured in dilute aqueous solution at 0 and 15°.

2. Studies of the initial, detectable reaction of these compounds, in dilute aqueous solution under controlled conditions of  $pH$  at temperatures between 0 and 30°, show that a chloride ion and a relatively stable cyclic imonium ion are formed by a strictly first order process. A mechanism for this reaction has been proposed. A linear correlation has been shown to exist between  $pK'_a$  and  $-\log k_1$  for this process in the case of a series of homologous alkyl bis-( $\beta$ -chloroethyl)-amines.

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