# CCLXXIX.—*Resolution of Racemic Chlorobromoacetic Acid.*

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THE remarkable behaviour of chlorobromomethanesulphonic acid, which according to Read and McMath (J., 1925, **127**, 1572) does not show optical activity in aqueous solution, led us to examine the related carboxylic acid, chlorobromoacetic acid, $CHClBr{\cdot}CO_2H$.

A preliminary study * had already shown the possibility of resolution. In the meantime Read and McMath stated (J., 1926, 2183) that only in some organic solvents might salts of optically active chlorobromoacetic acid be obtained, and in water, in consequence of immediate racemisation, no activity could be observed. A renewed investigation by the same authors (J., 1927, 537) failed to confirm our results.

We have now completed the resolution of this acid, have measured the molecular rotations of acid and salts, and have calculated the

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rotation of the undissociated acid by means of its dissociation constant. Finally we have examined the rate of racemisation in acid and in alkaline media and in presence of salts.

## EXPERIMENTAL.

Chlorobromoacetic acid is readily prepared from commercial trichloroethylene by the method of Crompton and his collaborators (J., 1920, **117**, 691; 1921, **119**, 1874; 1923, **123**, 1226).

The addition product of dichlorovinyl ether and bromine splits for the greater part into chlorobromoacetyl chloride and ethyl bromide (J., 1921, **119**, 1874) and also to a smaller extent into chlorobromoacetyl bromide and ethyl chloride :

$$\text{CHClBr·CClBr·O·C}_2\text{H}_5 = \text{CHClBr·COBr} + \text{C}_2\text{H}_5\text{Cl}.$$

Chlorobromoacetyl bromide distilled at 158—160°/normal pressure and at 47—49°/15 mm. (Found : Cl + Br, 82·5. Calc. for $C_2HOClBr_2$: Cl + Br, 82·65%). It was identified with the product obtained by heating chlorobromoacetic acid with phosphorus tribromide in chloroform solution on a water-bath (Found : Cl + Br, 82·45%).

The chlorobromoacetic acid obtained from the mixture of chloride and bromide, either by direct hydrolysis or by hydrolysis of the ester, distilled at 103—104°/11 mm. (Found : Cl + Br, 66·6; *M*, 173·4, 173·3. Calc. for $C_2H_2O_2ClBr$ : Cl + Br, 66·5%; *M*, 173·4). Under normal pressure it boiled at 214·5—215° with slight decomposition, the distillate containing a little hydrogen halide. It melted at 31·5°. Vanderstichele (J., 1923, **123**, 1227) found 25°, Read and McMath (*loc. cit.*) 38°.

When the acid is neutralised with a concentrated potassium hydroxide solution (*e.g.*, 4*N*), and the same quantity of acid added, the *acid potassium chlorobromoacetate* crystallises (Found : K, 10·2; equiv., 386·8. $C_2HO_2ClBrK,C_2H_2O_2ClBr$ requires K, 10·2%; equiv., 384·9).

The *normal potassium* salt is more soluble. It separates in anhydrous crystals from an aqueous solution on evaporation in a vacuum (Found : K, 18·65. $C_2HO_2ClBrK$ requires K, 18·5%).

*Electrical Conductivity of Chlorobromoacetic Acid.*—This was measured at 25° (± 0·02°).

| Conc., *c* (g.-mol./l.). | Mol. cond., $\mu$. | $\mu^2c$. | Conc., *c* (g.-mol./l.). | Mol. cond., $\mu$. | $\mu^2c$. |
|---|---|---|---|---|---|
| 1 × 0·2724 | $139·7 \times 10^{-3}$ | $5·32 \times 10^{-3}$ | $\frac{1}{32}$ × 0·2724 | $337·2 \times 10^{-3}$ | $0·97 \times 10^{-3}$ |
| $\frac{1}{2}$ × ,, | 180·5 | 4·44 | $\frac{1}{64}$ × ,, | 359·8 | 0·55 |
| $\frac{1}{4}$ × ,, | 225·3 | 3·46 | $\frac{1}{128}$ × ,, | 371·6 | 0·29 |
| $\frac{1}{8}$ × ,, | 267·7 | 2·44 | $\frac{1}{256}$ × ,, | 379·0 | 0·15 |
| $\frac{1}{16}$ × ,, | 305·3 | 1·59 | | | |

$$\mu^2 c = - K\mu_\infty \mu + K\mu_\infty^2 .$$

$\mu^2c$ plotted as a function of $\mu$ gives a straight line intersecting the ordinate axis at the value $K\mu_\infty^2$ and making with the axis of abscissæ an angle whose tangent is $K\mu_\infty$.

By this graphical method we found $K\mu_\infty^2 = 8{\cdot}38 \times 10^{-3}$ and $K\mu_\infty = 8{\cdot}38 \times 10^{-3}/382 \times 10^{-3} = 2{\cdot}19 \times 10^{-2}$. Therefore $K = (2{\cdot}19 \times 10^{-2})^2/(8{\cdot}38 \times 10^{-3}) = 0{\cdot}057$, that is, $K_{25^\circ} = 5{\cdot}7 \times 10^{-2}$.

*Resolution of Chlorobromoacetic Acid.*—In our preliminary study (*loc. cit.*) the dextrorotatory acid was isolated in the form of its quinine salt. The lævorotatory acid has now been obtained by means of the *brucine* salt, which separates when a solution of sodium chlorobromoacetate (0·1 mol.) and brucine acetate (0·1 mol.) in a total volume of 1 litre are mixed.

The alkaloidal salts may be purified by "cold crystallisation" (*Proc. K. Akad. Wetensch. Amsterdam*, 1925, **28**, 64). This precaution, however, is not necessary, since the tendency to racemisation is not very strong; a careful crystallisation from warm water is sufficient. The solution must not be heated long because of the instability of chlorobromoacetic acid in hot water.

The brucine salt, therefore, is shaken with 2 parts of water at room temperature and mixed with 20 parts of boiling water. The clear solution, obtained within a minute, is quickly cooled until crystallisation sets in. After about five such crystallisations, the brucine salt is optically pure. It crystallises with 2 or 3 molecules of water, which are given off at 110° and in a vacuum over phosphoric oxide (*a*. Found: $H_2O$, 6·3; calc. for $2H_2O$, 6·0%. *b*. Found: $H_2O$, 8·5; calc. for $3H_2O$, 8·7%. *c*. Found in salt dried in a vacuum: Cl + Br, 20·4. $C_2H_2O_2ClBr,C_{23}H_{26}O_4N_2$ requires Cl + Br, 20·4%).

In our first experiments the alkaloidal salts were converted into the ammonium salt, whose concentration was estimated by evaporation of its solution. More trustworthy results were obtained by decomposing 2 or 3 g. of the brucine salt with 15 c.c. of water and sodium hydroxide in excess, extracting the brucine with pure chloroform, and titrating the excess of alkali with sulphuric acid (0·2*N*) and phenolphthalein. The solution of the sodium salt (about 20 c.c.), the molecular concentration of which was thus known, was examined in a polarimeter.

In one experiment 200 g. of the brucine salt were recrystallised from 25 times its weight of water. The crystallisation was repeated four times, a sample being used after each crystallisation for polarimetric examination. The brucine salt then weighed only 14 g. and showed no rise of rotatory power.

About 2 g. were decomposed with 15 c.c. of water and 3·47 c.c. of sodium hydroxide (1·035*N*). The solution, after being extracted with chloroform and neutralised with 1·20 c.c. of sulphuric acid

(0·198*N*), showed $\alpha_D = +0{\cdot}21^\circ$ ($l = 2$). The rotation of the sodium salt was thus $[M]_D = +6{\cdot}3^\circ$.

The rotatory power of the free acid in aqueous solution is greater than that of the sodium salt and of opposite sign; it depends on the concentration and is raised by addition of strong acids. The reason is that chlorobromoacetic acid is a fairly strong acid which dissociates to a considerable extent in solution, giving an anion of opposite rotation.

The rotation of the undissociated acid cannot be measured by addition of sulphuric acid in excess, because the dissociation is not sufficiently reduced. Therefore the rotation of the pure acid was measured in different concentrations at 17°, and also the degree of dissociation was calculated from the dissociation constant by means of the equation $K = \alpha^2 c/(1 - \alpha)$. The value of $K_{17^\circ}$ was found to be $8{\cdot}1 \times 10^{-2}$.

The active acid was prepared by decomposing the brucine salt with sulphuric acid, extracting the chlorobromoacetic acid with ether, drying the solution with fused sodium sulphate, and evaporating the ether in a current of dry air at the ordinary temperature. The pure active acid was dissolved in water, and its concentration determined by titration.

If the molecular rotation observed for the mixture acid–ion is represented by $M_m$, the unknown rotation of the acid by $M_a$, and the rotation of the ion by $M_i$ ($= 6{\cdot}3^\circ$), we have $M_m = \alpha M_i + (1 - \alpha)M_a$ or $M_a = (M_m - 6{\cdot}3\alpha)/(1 - \alpha)$.

| c (g.-mol./l.). | $a_D$obs. ($l$=2). | $M_m$. | α. | $M_a$. |
|---|---|---|---|---|
| 0·150 | −0·335° | −11·2° | 0·50 | −28·6° |
| 0·208 | −0·525 | −12·6 | 0·44 | −27·5 |
| 0·250 | −0·695 | −13·9 | 0·42 | −29·0 |
| 0·347 | −1·14 | −16·4 | 0·37 | −26·0 |

The average value of $[M]_D$ for the undissociated acid is − 28°.

The rotations of the salt and of the acid were measured for different wave-lengths in order to determine the rotatory dispersion :

| λ (μμ)................................. | 656 | 589 | 546 | 516 | 486 |
|---|---|---|---|---|---|
| Anion (sodium salt) : [*M*] ... | +4·8° | +6·3° | +7·4° | +8·3° | +9·1° |
| Undissociated acid : [*M*] ... | −22° | −28° | −36° | −42° | −50° |

*Racemisation of Active Chlorobromoacetic Acid.*—An aqueous solution of the free acid does not show any tendency to racemise at the ordinary temperature. The salts racemise, but very slowly.

Only in presence of an excess of a strong base is the velocity of racemisation appreciable. Under these conditions, accurate measurements of the velocity coefficient are difficult, because the acid hydrolyses when it is kept for a long time in alkaline solution;

hydrogen halide is formed and the quantity of free alkali diminishes. The experiments were therefore stopped when the solutions gave a turbidity with nitric acid and silver nitrate. The velocity coefficient was calculated by aid of the formula $k = (\log \alpha_1 - \log \alpha_2)/t$. For a larger number of observations (*e.g.*, 4), Schmid's method (*Z. physikal. Chem.*, 1926, **119**, 8) was used,

$$k = (\log \alpha_1 + \log \alpha_2 - \log \alpha_3 - \log \alpha_4)/(t_3 + t_4 - t_1 - t_2).$$

Time was expressed in hours and Briggsian logarithms were used. The rotations were measured for the D and E lines in a tube of 2 dm. and their sum, $\alpha_D + \alpha_E$, was substituted for $\alpha$ in the formula.

1. *Acid solution.* Chlorobromoacetic acid (0·08 g.-mol./l.) in presence of sulphuric acid (1·38 equivs.) at 25°. The rotation, 0·65°, did not change in 77 hours and therefore there was no racemisation.

2. *Acid solution.* The same acid solution as in experiment 1 was examined at 100°. Titration of the acid, 1·46 equivs. per litre. The rotation was 0·665° and fell in 3¾ hours to 0·445°. The concentration of the acid titrated had not changed. Racemisation constant $k_{100^\circ} = 4{\cdot}5 \times 10^{-2}$. After 16¾ hours the solution was red and the quantity of acid had increased to 1·54.

3. *Neutral solution.* A solution of the ammonium salt with the rotation — 0·14° was kept at the ordinary temperature. After 90 days the rotation was —0·11° and after 570 days —0·07°. The racemisation of the salts in neutral solution is therefore negligible.

4. *Chloroform solution of a salt.* The racemisation of the brucine salt was studied in chloroform solution, because according to Read and McMath (J., 1926, 2184) salts of active chlorobromoacetic acid are stable in this solvent. A solution of 2 g. of the brucine salt in 25 c.c. of chloroform and 5 c.c. of methyl alcohol was examined at 25°; the lævorotation increased gradually owing to racemisation of the dextrorotating component.

| $t$ (hours)............... | 0 | 96 | 321 | 417 | 489 | 652 |
|---|---|---|---|---|---|---|
| $\alpha_D + \alpha_E$................. | −1·04° | −1·09° | −1·29° | −1·42° | −1·55° | −1·68° |

This racemisation, therefore, is not slower, but much faster than the racemisation of the neutral salts in water.

5. *Alkaline solution.* 0·15 G.-mol. of sodium chlorobromoacetate and 0·049 g.-mol. of sodium hydroxide per litre. Temperature 25°. The rotation observed was 0·325° * and after 4 hours 0·145°. The final titration indicated the presence of 0·047 g.-mol. of base, so that the hydrolysis was negligible. Racemisation constant $k_{25^\circ} = 9 \times 10^{-2}$.

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* For the pure active salt this value ($\alpha_D + \alpha_E$) should be 0·43°. The salt was thus one quarter racemic, which does not affect the calculation of the velocity coefficient.

6. *Alkaline solution.* 0·18 G.-mol. of sodium chlorobromoacetate and 0·031 g.-mol. of sodium hydroxide per litre. Temperature 25°. The rotation was 0·38° and after 5½ hours 0·225°. Final titration, 0·029 g.-mol. of base. Racemisation constant $k_{25°} = 4{\cdot}2 \times 10^{-2}$. The racemisation, therefore, is slower than in experiment 5, where the concentration of hydroxyl ions was greater.

7. *Alkaline solution with potassium nitrate.* (*a*) 0·0168 G.-mol. of sodium chlorobromoacetate and 0·0075 g.-mol. of sodium hydroxide per litre at 25°.

| | | | | |
|---|---|---|---|---|
| *t* .................. | 0 | 5¾ | 12¼ | |
| *a* .................. | 0·42° | 0·335° | 0·255°. | $k_{25°} = 17 \times 10^{-3}$. |

(*b*) 0·0168 G.-mol. of sodium chlorobromoacetate, 0·0072 g.-mol. of sodium hydroxide, and 0·2 g.-mol. of potassium nitrate per litre at 25°.

| | | | | |
|---|---|---|---|---|
| *t* .................. | 0 | 3¼ | 12¼ | |
| *a* .................. | 0·42° | 0·335° | 0·23° . | $k_{25°} = 26 \times 10^{-3}$. |

The presence of potassium nitrate, therefore, accelerates the racemisation in alkaline solution.

8. *Alkaline solution with calcium nitrate.* (*a*) 0·0168 G.-mol. of sodium chlorobromoacetate and 0·0039 g.-mol. of sodium hydroxide per litre at 25°.

| | | | | | |
|---|---|---|---|---|---|
| *t* ........... | 0 | 18½ | 29¼ | 42½ | |
| *a* ........... | 0·42° | 0·34° | 0·31° | 0·26°. | $k_{25°} = 4{\cdot}7 \times 10^{-3}$. |

(*b*) 0·0168 G.-mol. of sodium chlorobromoacetate, 0·0030 g.-mol. of sodium hydroxide, and 0·2 equiv. (0·1 mol.) of calcium nitrate.

| | | | | |
|---|---|---|---|---|
| *t* ........... | 0 | 18 | 29¼ | |
| *a* ........... | 0·42° | 0·18° | 0·11° . | $k_{23°} = 20 \times 10^{-3}$. |

The calcium nitrate causes a greater acceleration of the velocity than potassium nitrate in equivalent concentration.

## *Conclusions.*

1. Active chlorobromoacetic acid is stable at the ordinary temperature; the rotation of its aqueous solution does not change in several days.
2. The activity of the salts is not permanent in presence of strong bases. Hydroxyl ions catalyse the racemisation.
3. The racemising action of hydroxyl ions on the chlorobromoacetic anion is accelerated by salts, especially those with kations of higher valency.

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