39. *Aliphatic Substitution and the Walden Inversion. Part III. Comparison, using Radioactive Bromine, of the Rates of Inversion and Substitution in the Reaction of Bromide Ions with α-Bromopropionic Acid.*

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The rates of racemisation and of exchange in the reaction of α-bromopropionic acid with lithium bromide, containing a proportion of radioactive bromine, have been measured in acetone solution at 22°. The results show that in the system studied substitution is accompanied by inversion.

Substitution theories which have been developed in recent years (cf. Parts I and II, J., 1935, 1525; 1936, 1173; Cowdrey, Hughes, Ingold, Masterman, and Scott, J., 1937, 1252) predict that reactions of type (A), involving the attack of a negative ion on a saturated carbon atom, are accompanied by an inversion of configuration :

$$Y^- + R{-}X \longrightarrow Y{-}R + X^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

In Parts I and II (*locc. cit.*) a direct demonstration of the correctness of this view was obtained in the case of two simple organic halides containing, besides the halogen, only hydrogen and alkyl or aryl groups at the seat of substitution. The method consisted of a comparison of the rate of substitution in the presence of the corresponding halide ions containing a proportion of a radioactive isotope with the rate of racemisation of the optically active halide under comparable conditions, and the replacement of halogen by halogen was shown essentially to involve inversion.

In recent publications from these laboratories (cf. especially Ingold *et al.*, *loc. cit.*) an attempt has been made to relate the steric orientation of substitution with the structure of the reactants and the conditions of reaction. Homogeneous nucleophilic substitutions being treated as either unimolecular (S_N1) or bimolecular (S_N2), it was shown that, although unimolecular substitution may involve inversion, racemisation or retention of form, depending, *inter alia*, on the nature of the groups attached to the seat of reaction, yet bimolecular substitution invariably leads to inversion. Of the structures examined in this connection, various modifications of the carboxyl group proved to be of the greatest interest. We have therefore examined the reaction between α-bromopropionic acid and lithium bromide in anhydrous acetone solution by the method indicated above.

Our object was to compare the bimolecular rate constants for inversion and exchange, obtained under the same experimental conditions. For inversion this constant (k_I) is given by the equation $k_I = 1/2\,Bt\,.\,\log_e \alpha_0/\alpha_t$, where B is the concentration of the lithium bromide, and α_0 and α_t are the optical rotations of the organic acid at zero time and time t respectively. To analyse the substitution data in a comparable manner it is necessary to assume that the bromine isotopes are chemically equivalent. Exchange is then the sum total of the simultaneous reactions (1)—(4), each governed by an identical bimolecular constant k_E (radioactivity is designated by an asterisk).

$$(1)\ \mathrm{RBr} + \mathrm{Br}^- \longrightarrow \mathrm{RBr} + \mathrm{Br}^- \qquad (2)\ \mathrm{RBr} + \overset{*}{\mathrm{Br}}{}^- \longrightarrow \mathrm{R}\overset{*}{\mathrm{Br}} + \mathrm{Br}^-$$

$$(3)\ \mathrm{R}\overset{*}{\mathrm{Br}} + \mathrm{Br}^- \longrightarrow \mathrm{RBr} + \overset{*}{\mathrm{Br}}{}^- \qquad (4)\ \mathrm{R}\overset{*}{\mathrm{Br}} + \overset{*}{\mathrm{Br}}{}^- \longrightarrow \mathrm{R}\overset{*}{\mathrm{Br}} + \overset{*}{\mathrm{Br}}{}^-$$

If we represent the concentration of $\overset{*}{\mathrm{Br}}{}^-$ after time t by x, we may write (since throughout the reaction, $[\mathrm{RBr}] + [\mathrm{R}\overset{*}{\mathrm{Br}}] = [\mathrm{Br}^-] + [\overset{*}{\mathrm{Br}}{}^-] = B$)

$$-\,dx/dt = k_E\{[\mathrm{RBr}][\overset{*}{\mathrm{Br}}{}^-] - [\mathrm{R}\overset{*}{\mathrm{Br}}][\mathrm{Br}^-]\} = k_E B(2x - x_0)$$

where the suffix zero refers to the start of the reaction. Integration gives

$$k_E = -\,1/2\,Bt\,.\,\log_e\,(2x/x_0 - 1)$$

The technique which we adopted directly measured x/x_0, and in Table I we give the exchange data and the corresponding constants (k_E).

TABLE I.

Bimolecular velocity coefficient (k_E) *for the exchange of radioactive halogen ions with α-bromopropionic acid at* 22° (B = 0·333M).

Time (mins.)	20	20	30	30	40	50	60	60
x/x_0	0·846	0·854	0·761	0·737	0·726	0·660	0·642	0·662
10^4k_E(sec.$^{-1}$ g.-mol.$^{-1}$ l.)	4·62	4·32	5·43	6·22	4·97	5·72	5·25	4·69

The average value of k_E is 5·15 × 10^{-4} (sec.$^{-1}$ g.-mol.$^{-1}$ l.) with a mean deviation of ± 0·50 × 10^{-4} and a probable error of ± 0·15 × 10^{-4}. We consider the accuracy is good in view of the difficulties inherent in the radioactive measurements. Agreement with the more accurate constant for inversion (k_I = 5·24 × 10^{-4} ± 0·05 × 10^{-4} sec.$^{-1}$ g.-mol.$^{-1}$ l.) is within the experimental error, and the data amply justify the conclusion that in the system studied substitution leads to inversion.

EXPERIMENTAL.

Purification of Materials.—Acetone was purified by careful fractionation from phosphoric oxide (cf. Spence and Wild, J., 1937, 352). Lithium bromide was recrystallised from acetone and dried.

Preparation of d-*α-Bromopropionic Acid.*—A commercial sample of lactic acid was converted into the methyl ester [$\alpha_D^{20°}$ (l = 2) − 11·9°], hence into the bromo-ester [$\alpha_D^{20°}$ (l = 1) + 31·8°], and finally into the bromo-acid [$\alpha_D^{20°}$ (l = 1) + 20·7°] (cf. Cowdrey, Hughes, and Ingold, J., 1937, 1227). The rotation of the bromo-acid in acetone solution remained constant during the period of time required for complete racemisation by bromide ions under the conditions employed in the comparative experiments. Racemic bromo-acid for the exchange was a B.D.H. sample which was carefully fractionated.

Racemisation.—An acetone solution, N/3 with respect to each reactant, was prepared and introduced into a jacketed 2-dm. polarimeter tube maintained at 22·0°, and the fall in rotation followed in the usual way. The bimolecular velocity coefficients (k_I) were calculated from the expression given above. The results of a typical experiment are recorded in Table II.

TABLE II.

[*d*-α-Bromopropionic acid] = 0·334M.; [LiBr] = 0·314M.; Temp. = 22·0°; t is the time in secs., α the rotation, and k_I the bimolecular velocity coefficient in sec.$^{-1}$ g.-mol.$^{-1}$ l.

t	0	342	678	942	1254	1548	1974	2316	2742	3222	3828	4458	5310	6900
α	1·60	1·40	1·26	1·15	1·02	0·91	0·79	0·70	0·60	0·51	0·42	0·33	0·23	0·13
10^4k_I	—	5·19	5·16	5·14	5·26	5·35	5·24	5·23	5·25	5·20	5·12	5·19	5·36	5·33

Average k_I = 5·23 × 10^{-4}.

Exchange.—A simple form of Geiger-Müller counter and recording circuit was used for measuring radioactivity. The ionisation chambers were made from aluminium tubing, as described in Part I (*loc. cit.*). The activity of lithium bromide was measured in solution (cf. Olson, Libby, Long, and Halford, *J. Amer. Chem. Soc.*, **1936**, **58**, **1313**), and for this purpose the window of the ionisation chambers was surrounded by a glass jacket fitted to the aluminium by rubber. The procedure adopted necessitated the comparison of activities of two samples; the chambers were therefore constructed in pairs as nearly identical as possible and placed so that they could alternately be switched to the counting circuit. The latter was a one-stage amplifier battery coupled to a thyratron and telephone counter (Fay and Paneth, J., **1936**, 384). Each discharge chamber had its appropriate high-tension supply, and, although the response of each chamber to the same stimulus might differ by as much as 10%, their sensitivity ratio was determined by preliminary measurement and remained constant over long periods of use and greatly varying rates of counting.

Exchange was carried out under the conditions already given for racemisation. Lithium bromide was activated in acetone solution by a radium sulphate–beryllium neutron source.

The irradiated solution was divided into two parts : one portion was used for the exchange, the other was evaporated to dryness, the residue dissolved in 4N-sodium hydroxide, made slightly acid with 3N-nitric acid and the resulting solution placed around one of the ionisation chambers.

In the exchange, reaction was arrested after a given time by neutralising with 4N-sodium hydroxide. The acetone was evaporated in a vacuum, and 3N-nitric acid (1·5 equivs.) added. The solution was then extracted seven times with an equal volume of ether, under which conditions supplementary experiment had shown that at least 99% of the organic acid was extracted. The aqueous layer, containing the bromide, was placed around the second ionisation chamber. It is to be noted that both samples of lithium bromide were treated as far as possible in the same way.

Comparison of the activities of the two solutions of bromide ions was made by alternately switching each ionisation chamber to the counting circuit for a period of one minute. The minute counts were first corrected for coincidence by the usual quadratic formula and the background count was then subtracted. The figures obtained were summed for each sample over periods of an hour or more, and the sums further adjusted for the different sensitivities of the two chambers and the unequal concentrations of the two solutions of bromide ions. The latter were measured by Volhard titration after the radioactive measurements had been completed.

The final corrected ratio is given as x/x_0 in Table I.

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