[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Mechanism of Substitution Reactions

BY A. R. OLSON AND F. A. LONG

A short time ago Olson[1] published a theory of the mechanism of substitution reactions. According to this theory, if a compound AB reacted with another substance C to form AC, and if the bond AB were strong enough so as to eliminate the probability of a primary dissociation, then the configuration of A would be inverted in this reaction. It was further pointed out in this article that the study of the reactions of optically active substances was peculiarly favorable for testing this theory. About the same time Bergmann, Polanyi and Szabo[2] published a similar theory. These theories require that if an optically active substance can be produced from another substance by two different paths which differ from each other by an odd number of steps, then one path should result in the optical enantiomorph of the product of the other path. Thus starting with *l*-aspartic acid we can produce *l*-chlorosuccinic acid by treating the aspartic acid with sodium nitrite and hydrochloric acid. We can produce *l*-bromosuccinic acid by the same process if we substitute hydrobromic acid for hydrochloric acid. Then if the *l*-bromosuccinic acid is dissolved in water and treated with hydrochloric acid, *d*-chlorosuccinic acid is produced. Without discussing either the number of steps involved in producing the halogen succinic acids from aspartic acid, or the configuration of the aspartic acid itself, it is obvious that the two paths which differ by one step produce chlorosuccinic acids of opposite configurations.

The above-mentioned theory can be examined not only from a loose qualitative standpoint as above, but also from a rigorous quantitative point of view. This quantitative test will be the burden of the work discussed below. The reaction chosen for this test was that between *l*-bromosuccinic acid and chloride ion to give *d*-chlorosuccinic acid and bromide ion. However, in order to study this reaction it was found necessary to study also the reactions of those substances which might be formed under our experimental conditions either from the reactants themselves or the products of this reaction. In other words, we must study the loss of hydrobromic or hydrochloric acid by bromo or chlorosuccinic acids, the racemizing actions of the halide ions and any interchange reactions of the substituted succinic acids with halide ions. A great deal of work already has been done on these substances, notably by Walden,[3] Holmberg,[4] Rørdam,[5] Ölander,[6] Clough,[7] and Bancroft and Davis,[8] and while their results are of qualitative interest in this connection, the experimental conditions differ so much from author to author that we found it necessary to carry out a complete study under definite and comparable experimental conditions in order to get a quantitative test of the theory.

Preparation of Materials

l-Chloro and *l*-bromosuccinic acids were prepared from *l*-aspartic acid by Holmberg's[4] method by treating it with sodium nitrite and the corresponding halogen acid. After the usual recrystallizations, products were obtained whose specific rotations agreed with the published values within the limits of experimental error. Furthermore, fresh solutions of these acids gave no precipitate with silver nitrate, showing the absence of contamination by halide ions, and titrations with sodium hydroxide corresponded to the calculated values. The fact that *l*-chloro and *l*-bromosuccinic acids can be prepared from the same substance by analogous processes is very strong evidence for the assumption that chloro and bromosuccinic acids, which have rotations of the same sign, have similar configurations. This assumption, which is vital for the conclusions which are to be reached in this paper, is in agreement with the opinions of those who have worked on these compounds.

Apparatus

The polarimeter was designed by Bellingham and Stanley in such a way that the 30-cm. polarimeter tubes did not have to be removed from the thermostat for observation. The thermostat was kept constant at 50 ± 0.1°. The Hg 5461 line, which was used for all readings, was obtained by filtering the light from a mercury arc through a Wratten filter Number 77. All rotations were read to a hundredth of a degree.

Experimental Procedure

In all the runs which we discuss below, the solid substances were dissolved in water and a sufficient amount of

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[1] Olson, *J. Chem. Phys.*, **1**, 418 (1933).

[2] Bergmann, Polanyi and Szabo, *Z. physik. Chem.*, **B20**, 161 (1933).

[3] Walden, *Ber.*, **29**, 133 (1896).

[4] Holmberg, *J. prakt. Chem.*, **87**, 456 (1913); *ibid.*, **88**, 553 (1913); *Ber.*, **60**, 2194 (1927).

[5] Rørdam, *J. Chem. Soc.*, 2931 (1932).

[6] Ölander, *Z. physik. Chem.*, **A144**, 49 (1929).

[7] Clough, *J. Chem. Soc.*, **129**, 1674 (1926).

[8] Bancroft and Davis, *J. Phys. Chem.*, **35**, 1253 (1931).

stock solution of acid was added so that when the solution was heated to 50° the hydrogen-ion concentration was 1.978 *N* and the concentration of the active acid was 0.178 *M* unless otherwise specified. Four or five minutes usually elapsed after the tube was put into the thermostat before it became clear enough to make polarimetric readings. The zero time was taken as the time of the first reading. The greatest error produced by this lapse of time between mixing and reading occurs in the reaction between bromosuccinic acid and chloride ion, but even here the error is only about one one-hundredth of a degree. We have therefore neglected any corrections due to this factor.

The reaction between chloride ion and bromosuccinic acid by which it is proposed to test the theory, involves six rate constants. It therefore was necessary to devise a series of experiments each of which involved only one undetermined constant.

(1) The rate of formation of fumaric acid from bromosuccinic acid: Ölander[6] has done a great deal of work on the formation of fumaric acid from bromosuccinic acid in neutral and dilute acid solutions. According to him, fumaric acid does not form directly from the bromosuccinic acid but goes through a lactone structure. It should be pointed out here that we are not concerned at present with the mechanism by which bromide ion is produced from bromosuccinic acid. We are concerned merely with the rate of this production and with the fact that the residue, *i. e.*, fumaric acid, has no optical rotation. Accordingly we dissolved two samples of bromosuccinic acid in perchloric acid and kept the solutions at 50°. At this temperature the concentration of perchloric acid was 1.978 *M* and that of the bromosuccinic acid was 0.1780 *M*. After a lapse of about ten thousand minutes the solutions were taken out and titrated with silver nitrate in the usual manner. Assuming a unimolecular reaction we have $\text{Br}^- = a(1 - e^{-k_1t})$. Table I gives the results of these runs.

TABLE I

Run	a in M/liter	t, min.	Br^-	k_1
1	0.1780	10,000	0.0467	0.000030
2	.1780	9,730	.0465	.000031
			Average	0.0000305

(2) The reaction between bromosuccinic acid and bromide ion: This reaction has been studied extensively by Holmberg[4] at 25°, not considering, however, the fumaric acid reaction. When this is not neglected, we get the rate equations

$$dx/dt = -k_2bx + k_2bz - k_1x \qquad (1)$$

$$dz/dt = -k_2bz + k_2bx - k_1z \qquad (2)$$

where b is the concentration of bromide ion, x is the concentration of *l*-bromosuccinic acid, z that of the *d*-bromosuccinic acid and k_1 is the rate constant determined in the previous section. Integrating we obtain

$$\frac{1}{t}\ln\frac{x - z}{a} = -(2k_2b + k_1) = \frac{1}{t}\ln\frac{\alpha}{\alpha_0}$$

where a is the initial concentration of bromosuccinic acid, α is the rotation at the time t, and α_0 is the initial rotation.

Four independent runs were made in which hydrobromic acid was added to solutions of *l*-bromosuccinic acid so that $(\text{H}^+) = 1.978$ *M*, initial $(\text{Br}^-) = 1.978$ *M*, and a was approximately 0.178 *M*.

In Table II are given the details of only one run.

TABLE II

Run	Time in min.	α	$2k_2b + k_1$	k_2
1	0	−5.38		
	30	−4.41	0.00660	0.00166
	60	−3.64	.00648	.00163
	90	−2.98	.00656	.00165
	150	−2.02	.00652	.00164
	210	−1.37	.00652	.00164
	425	−0.32	.00648	.00163
2	Av.	of 6 readings	.00650	.00163
3	Av.	of 5 readings	.00653	.00164
4	Av.	of 6 readings	.00659	.00166
			Average	0.00164

In an additional run in which one mol of perchloric acid was substituted for one mol of hydrobromic acid, we obtained a somewhat lower rate constant, probably due to the fact that the activity of bromide ion in these concentrated solutions is not equal to its concentration. However, since we wished eventually to use this rate in experiments in which the concentration of halide ion was approximately two molar, it was the rate constant as determined above which had to be used.

(3) Formation of fumaric acid from chlorosuccinic acid: Chlorosuccinic acid was dissolved in two molar perchloric acid and kept at 50° for forty thousand minutes. Titration with silver nitrate showed that the reaction was so slow that no appreciable error was introduced into our calculations by setting $k_3 = 0$.

(4) Racemization of chlorosuccinic acid by chloride ion: Following the same procedure as in section two but substituting chlorosuccinic acid and hydrochloric acid for the corresponding bromo compounds, we get the rate equations

$$dy/dt = -k_4by + k_4bw$$
$$dw/dt = k_4by - k_4bw$$

where y and w indicate *d*- and *l*-chlorosuccinic acids, respectively. From these equations we obtain

$$-2k_4b = \frac{1}{t}\ln\frac{w-y}{a} = \frac{1}{t}\ln\frac{\alpha}{\alpha_0}$$

The average of six runs which agree very well with each other gives $k_4 = 0.0000106$.

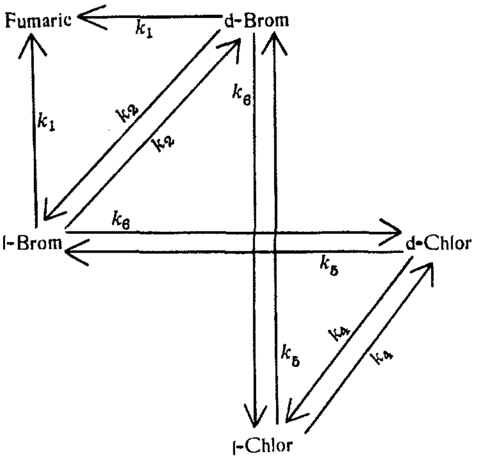

Fig. 1.—System of reactions which occur when a solution of chloro or bromosuccinic acid is treated with bromide or chloride ion assuming no direct substitution can take place.

(5) Reaction between *l*-chlorosuccinic acid and bromide ion: When *l*-chlorosuccinic acid is dissolved in a solution containing hydrobromic acid the reactions shown in Fig. 1 occur. If, as before, we identify y and w with the concentrations of *d*- and *l*-chlorosuccinic acids, respectively, and z and x with the corresponding bromo compounds and n with the concentration of fumaric acid, then we have the following expressions for the rates of these reactions

$$dw/dt = -k_5(\mathrm{Br}^-)w - k_4(\mathrm{Cl}^-)w + k_6(\mathrm{Cl}^-)z + k_4(\mathrm{Cl}^-)y \quad (1)$$
$$dy/dt = -k_5(\mathrm{Br}^-)y - k_4(\mathrm{Cl}^-)y + k_6(\mathrm{Cl}^-)x + k_4(\mathrm{Cl}^-)w \quad (2)$$
$$dx/dt = +k_5(\mathrm{Br}^-)y - k_6(\mathrm{Cl}^-)x - k_2(\mathrm{Br}^-)x + k_2(\mathrm{Br}^-)z - k_1x \quad (3)$$
$$dz/dt = +k_5(\mathrm{Br}^-)w - k_6(\mathrm{Cl}^-)z - k_2(\mathrm{Br}^-)z + k_2(\mathrm{Br}^-)x - k_1z \quad (4)$$
$$dn/dt = +k_1(x + z) \quad (5)$$
$$(\mathrm{Br}^-) = c - (x + z) \quad (6)$$
$$(\mathrm{Cl}^-) = x + z + n \quad (7)$$

It will be noticed that two new constants, k_5 and k_6, occur in these equations. Fortunately we can obtain very good approximate solutions by neglecting those terms in which chloride-ion concentration occurs, and by setting the bromide-ion concentration equal to its initial value, c. The justification for these approximations lies in the following considerations: (1) the concentration of chloride ion is small at all times, especially at the beginning of a run; (2) the concentration of bromide ion is large compared to the change in it; (3) the racemization of bromosuccinic acid by bromide ion is very fast compared to any other reaction in this set and so rotations contributed by the bromosuccinic acid and particularly by the chlorosuccinic acid which is reformed from it, are very small. Since our observational data deal with rotations and not with titrations, we are interested only in the excess of one optical form of a compound over the other. Anticipating somewhat, it can be seen from Fig. 2 that these approximations are valid up to the time which we need to consider in order to determine k_5.

The solutions of the simplified set of equations are

$$w' = ae^{-k_5ct}$$
$$(z - x) = \frac{k_5ca}{2k_2c + k_1 - k_5c}\,\frac{e^{(2k_2c + k_1 - k_5c)t} - 1}{e^{(2k_2c + k_1)t}}$$

In the equations above, w' represents the concentration of *l*-chlorosuccinic acid which has undergone no reaction, since by our approximations the return reaction has been neglected. The exact solution of equations (1) to (7) would replace this w' by $(w - y)$, the excess of *l*-chlorosuccinic acid over *d*-chlorosuccinic acid. However, the values of these two quantities, w' and $(w - y)$, are very nearly equal, due to the reasons mentioned above.

The quantities w' and $(z - x)$ thus suffice to determine k_5 from the rotational data for this system, *i. e.*, $\Theta_{\text{obs.}} = w'\Theta_{l\text{-Cls}} + (z - x)\Theta_{d\text{-Brs}}$ where the term $\Theta_{l\text{-Cls}}$ is defined as the rotation which one mole of *l*-chlorosuccinic acid in 1000 cc. of solution which contains 1.978 moles of hydrobromic acid exhibits at 50°, in a 30-cm. tube when Hg 5461 light is used.

The value of $\Theta_{l\text{-Cls}}$ was actually determined by dissolving *l*-chlorosuccinic acid in a 1.978 *M* solution of hydrobromic acid and was found to be −11.46°. The value of $\Theta_{d\text{-Brs}}$, +30.85°, is for bromosuccinic acid in hydrochloric acid. Strictly speaking, it should have been measured in hydrobromic acid but, due to the rapid racemizing effect of bromide ion, it was impossible to obtain a good value under these conditions. For the *l*-chlorosuccinic acid the difference under these two conditions is about one per cent. Since

$\Theta_{d\cdot\mathrm{Br}_3}$ is multiplied by $(z - x)$, which throughout this experiment is small, the error due to the approximate value of $\Theta_{d\cdot\mathrm{Br}_3}$ is at the most of the order of one-tenth of one per cent. of the total rotation.

Using the values of k_1 and k_2 as determined in previous experiments and $k_5 = 0.000047$, we get the curve shown in Fig. 2. The large majority of experimentally observed points of five separate runs, only three of which are plotted, coincide with the calculated curve within the limits of experimental error. A change in k_5 to 0.000048 lowers the calculated curve about two one-hundredths of a degree at $t = 10{,}000$ whereas corresponding changes in k_1 and k_2 produce changes of about a thousandth of a degree.

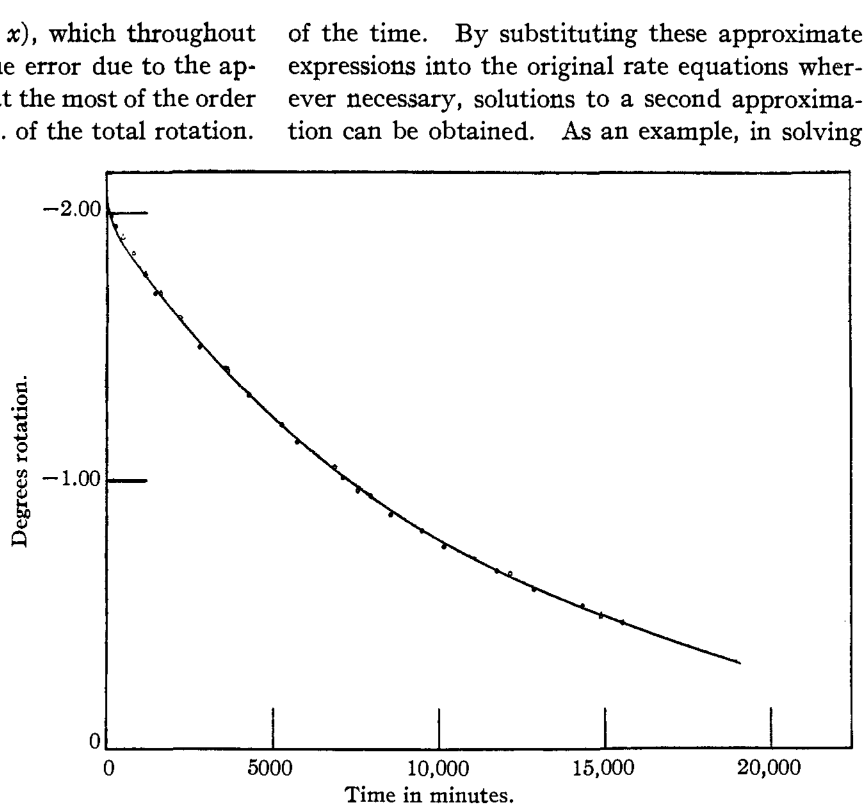

Fig. 2.—Reaction of *l*-chlorosuccinic acid with bromide ion. The solid line is calculated for $k_5 = 0.000047$.

(6) The reaction between *l*-bromosuccinic acid and chloride ion: When *l*-bromosuccinic acid is dissolved in hydrochloric acid we again have the reactions shown in Fig. 1 to consider. However, since the chloride-ion concentration is large, we no longer can neglect those terms involving it, and therefore we must solve the complete set of equations shown in the preceding section. Equations (6) and (7) will be changed due to different initial conditions.

Approximate solutions of this set of equations can be obtained by assuming that $k_5 = 0$ and the chloride-ion concentration is constant. We thus obtain expressions for x, y, z, w and n as functions of the time. By substituting these approximate expressions into the original rate equations wherever necessary, solutions to a second approximation can be obtained. As an example, in solving the equation for $(x - z)$, we replace all variables except $(x - z)$ and t by their functions of time as obtained in the first approximate solution; and so we arrive at the expressions

$$y - w = -e^{K_3 - K_{10}t + K_{11}e^{-K_4t}}\left[K_{12}\sum_{n=0}^{\infty}(-1)^n\frac{(K_3 + K_{11})^n}{n!(K_{10} - K_{13} - nK_4)}\left(1 - e^{(K_{10} - K_{13} - nK_4)t}\right) + K_{14}\sum_{n=0}^{\infty}(-1)^n\frac{(K_3 + K_{11})^n}{n!\{K_{10} - K_{13} - (n+1)K_4\}}\left(1 - e^{\{K_{10} - K_{13} - (n+1)K_4\}t}\right)\right]$$

$$x - z = -K_5e^{K_6t - K_7e^{-K_4t}}\sum_{l=0}^{\infty}\sum_{n=0}^{\infty}(-1)^n\frac{K_7^l}{l!}\frac{K_3^n}{n!(K_2 + nK_4)}\left[e^{-(2k_3b + K_6 + lK_4)t}\left(\frac{1}{2k_3b + K_6 + lK_4} - \frac{e^{-(K_2 + nK_4)t}}{2k_3b + K_6 + K_2 + (n + l)K_4}\right) - e^{-\{2k_3b + K_6 + (l+1)K_4\}t}\left(\frac{1}{2k_3b + K_6 + (l + 1)K_4} - \frac{e^{-(K_2 + nK_4)t}}{2k_3b + K_6 + K_2 + (n + l + 1)K_4}\right)\right] + C$$

where

$$C = ae^{K_7} + K_5\sum_{l=0}^{\infty}\sum_{n=0}^{\infty}(-1)^n\frac{K_7^l}{l!}\frac{K_3^n}{n!(K_2 + nK_4)}\left(\frac{1}{2k_3b + K_6 + lK_4} - \frac{1}{2k_3b + K_6 + (l + 1)K_4} - \frac{1}{2k_3b + K_6 + K_2 + (n + l)K_4} + \frac{1}{2k_3b + K_6 + K_2 + (n + l + 1)K_4}\right)$$

where b, the initial concentration of chloride ion, is equal to 1.978 M, a, the initial concentration of *l*-bromosuccinic acid, is equal to 0.178 M, and the K's have the following values in terms of these and the rate constants

$$K_1 = k_6ba$$
$$K_2 = k_6b + 2k_2a + k_1 - 2k_4b$$
$$K_3 = \frac{2k_2a}{k_6b + k_1}$$

$$K_4 = k_6b + k_1$$
$$K_5 = k_5aK_1e^{K_3}$$
$$K_6 = -k_6b + \frac{k_6^2ba}{K_4} - 2k_2a - k_1$$
$$K_7 = -\left(\frac{k_6^2ba}{K_4} - 2k_2a\right)\frac{1}{K_4}$$
$$K_{10} = 2k_4b - \frac{2k_4k_6ba}{K_4} + k_5a$$
$$K_{11} = \left(\frac{2k_4k_6ba}{K_4} - k_5a\right)\frac{1}{K_4}$$
$$K_{12} = k_6ba - \frac{k_6^2ba^2}{K_4}$$
$$K_{13} = k_6b + k_1 + 2k_2a$$
$$K_{14} = \frac{k_6^2ba^2}{K_4}$$

These expressions could again be substituted into the original rate equations and thus solutions to a third approximation could be secured. We have not done this, however, partly because of the long tedious labor which this would involve, and partly because of a firm conviction that the second approximation represents the exact solution within the limits of experimental accuracy.

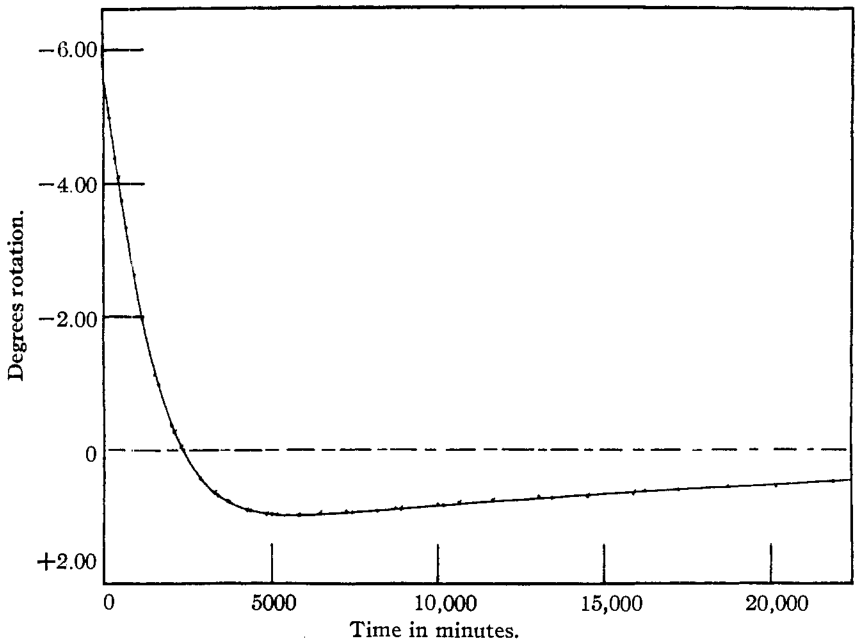

Fig. 3.—Reaction of *l*-bromosuccinic acid with chloride ion. The solid line is calculated for $k_6 = 0.000233$.

In the above expressions k_6 is the only undetermined constant. In Fig. 3 the observed rotation has been plotted against the time. If we take $k_6 = 0.000233$ and set $\Theta_{\text{calcd.}} = (x - z)\Theta_{l\text{-Br}_s} + (y - w)\Theta_{d\text{-Cl}_s}$, we get the solid line of Fig. 3. Θ_{Br_s} and Θ_{Cl_s} are defined as in the preceding section except that the solution will be in 1.978 *M* hydrochloric acid instead of hydrobromic acid. The value for $\Theta_{l\text{-Br}_s}$ is the negative of the value used in the preceding section, but $\Theta_{d\text{-Cl}_s}$ is now 11.56. The experimental points in Fig. 3 represented by open circles and circles with an arrow are individual points from two different runs. The solid circles up to $t = 2300$ are averages of three separate runs which were read at the same time, and from $t = 2300$ on, are the averages of two separate runs. At 2300 minutes one tube was taken out for analysis. In only one case is the deviation from the calculated curve as much as 0.04° and for only three additional points is it as much as 0.03°. It will thus be seen that the large majority of experimental points fall on the calculated curve within the limits of experimental error. It should be borne in mind that all our calculations are done on the explicit assumption that inversion occurs at every substitution and therefore the theory which we set out to test is in complete agreement with the experimental data.

While we have shown that the theory of complete inversion is in agreement with experimental facts, we have not yet shown that a theory of reaction by direct replacement is completely contrary to these facts. To show this let us assume that when chloride ion reacts with bromosuccinic acid and when bromide ion reacts with chlorosuccinic acid, a fraction, α, occurs by direct replacement, *i. e.*, no inversion, and that for the fraction, $1 - \alpha$, inversion occurs. Or, stated in other words, when a mole of *l*-bromosuccinic acid reacts with chloride ion, we would get α moles of *l*-chlorosuccinic acid and $1 - \alpha$ moles of *d*-chlorosuccinic acid if the reaction could be stopped after the first substitution. Since we obviously cannot stop these reactions at this point, we will now have to deal with the set of reactions shown in Fig. 4 in place of those of Fig. 1. We must therefore have recourse to our rate equations in which we make proper allowance for the assumption that α is different from zero.

Our rate equations then become

$$\mathrm{d}x/\mathrm{d}t = -k_6(\mathrm{Cl}^-)x + k_5(1 - \alpha)(\mathrm{Br}^-)y - k_2(\mathrm{Br}^-)x + k_2(\mathrm{Br}^-)z + k_5\alpha(\mathrm{Br}^-)w - k_1x$$

$$\mathrm{d}y/\mathrm{d}t = +k_6(1 - \alpha)(\mathrm{Cl}^-)x - k_4(\mathrm{Cl}^-)y + k_4(\mathrm{Cl}^-)w - k_5(\mathrm{Br}^-)y + k_6\alpha(\mathrm{Cl}^-)z$$

$$\mathrm{d}z/\mathrm{d}t = -k_6(\mathrm{Cl}^-)z + k_5(1 - \alpha)(\mathrm{Br}^-)w + k_5\alpha(\mathrm{Br}^-)y - k_2(\mathrm{Br}^-)z + k_2(\mathrm{Br}^-)x - k_1z$$

$$\mathrm{d}w/\mathrm{d}t = +k_6(1 - \alpha)(\mathrm{Cl}^-)z + k_6\alpha(\mathrm{Cl}^-)x - k_5(\mathrm{Br}^-)w - k_4(\mathrm{Cl}^-)w + k_4(\mathrm{Cl}^-)y$$

$$\mathrm{d}n/\mathrm{d}t = k_1(x + z)$$

These equations can be solved in exactly the same way as the former set. When this is done then in order to make the calculated curve agree with the experimental data for some one point, say at $t = 2340$, in addition to the initial point, $t = 0$, it is found that a new value of k_6 must be chosen. Of the other constants k_5 alone might be affected but fortunately the change is negligible.

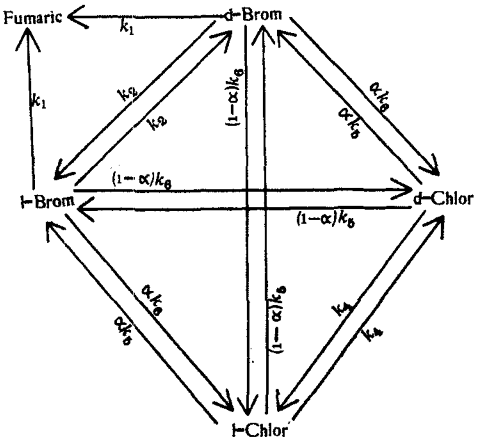

Fig. 4.—Same system as in Fig. 1, but assuming a fraction, α, goes by direct replacement.

The value of k_6 which must be chosen will depend on the value assumed for α. Thus for α equal to 0.096, k_6 is increased to 0.000260. While the calculated curve will agree with the experimental for those times chosen for calculating the constant, it will be completely below the experimental points for times less than 2340 minutes and above for times greater than 2340 minutes. This is shown in Fig. 5 where we have plotted the deviations of the curve so calculated from the experimental points. From the magnitude of these deviations we can conclude that within the limits of experimental error, which themselves are quite small, α must be equal to zero.

If it were possible accurately to determine the concentration of bromide ion in the presence of these halogen acids and a large amount of chloride ion, then a direct determination of k_6 could be made. This, in conjunction with our other data, would give an independent means of determining α. While preliminary analytical attempts so far have yielded results which are qualitatively in agreement with the conclusions reached in the earlier paragraphs of this paper, they are not sufficiently accurate to warrant discussion at this time.

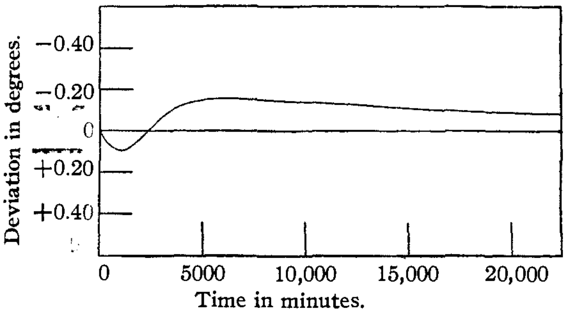

Fig. 5.—Deviation of the curve calculated for α = 0.096 from the experimental curve.

In conclusion the authors wish to acknowledge their indebtedness to Dr. E. C. Goldsworthy and Dr. Lee H. Swinford for valuable discussions of some of the mathematical problems encountered in this work.

Summary

1. The rate constants at 50° for the following reactions in aqueous solutions containing 2 *N* hydrogen ion have been determined

(1) *l*-bromosuccinic acid = fumaric acid + H^+ + Br^-

(2) *l*-bromosuccinic acid + Br^- = *d*-bromosuccinic acid + Br^-

(3) *l*-chlorosuccinic acid + Cl^- = *d*-chlorosuccinic acid + Cl^-

(4) *l*-chlorosuccinic acid + Br^- = *d*-bromosuccinic acid + Cl^-

(5) *l*-bromosuccinic acid + Cl^- = *d*-chlorosuccinic acid + Br^-

2. It has been proved, within the limits of experimental error (approximately one per cent.), that, for these reactions, Olson's theory of inversion accompanying every substitution is correct, and that replacement without inversion does not occur.

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