26. *Optical Activity in Relation to Tautomeric Change. Part II. Comparison between the Rate of Racemisation of a Tautomeric Substance and the Rate of its Tautomeric Interconversion.*

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In Part I (J., **1933**, 1493) we studied the question of the retention of optical activity during the interconversion of a pair of triad tautomerides so constituted that in the course of isomeric change the single centre of asymmetry migrates from the atom left by the mobile group to that to which it becomes attached. It was shown that, in a system devoid of any " locking mechanism " such as ring formation which can, either permanently or during reaction, fix the direction of the double bond relatively to that of the link attaching the mobile group, the asymmetric centre loses its enantiomeric identity on being carried over to the new position. For instance, in the methyleneazomethine prototropic system, the optically active modifications of compound A on conversion yielded isomeride B in a substantially racemic condition :

(A.)  (B.)

$$\begin{matrix}CH_3\\C_6H_5\end{matrix}\!>\!C[H]\cdot N{:}C\!<\!\begin{matrix}C_6H_5\\C_6H_4Cl\ (p)\end{matrix} \rightleftharpoons \begin{matrix}CH_3\\C_6H_5\end{matrix}\!>\!C{:}N\cdot C[H]\!<\!\begin{matrix}C_6H_5\\C_6H_4Cl\ (p)\end{matrix}$$

Since the conversion of A into B is reversible, it follows that, under the conditions conducive to the formation of an equilibrium mixture, isomeride A must progressively lose optical activity as the original substance becomes replaced by the material formed by reconversion from B. Accordingly, we have measured the velocity of racemisation of compound A, together with its speed of isomerisation and the corresponding equilibrium constant; for it appeared that theoretical consequences of some interest would emerge should the rate of racemisation prove to be equal to, and not greater than, that accounted for by the effect of reversible tautomeric conversion.

The method of the comparison is as follows. First, the system (I) is studied experimentally using optically inactive materials, and the constant of the equilibrium, $K = k_1/k_2$, and that representing the speed of approach to equilibrium, $k = k_1 + k_2$, are determined by ordinary analytical methods, thus enabling the individual velocity coefficients, k_1 and k_2, to be calculated. Next, the system (II) is considered, in which the bars denote externally

$$\text{(I.)}\quad A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \qquad\qquad \overset{*}{A} \xrightarrow{k_1} \bar{B} \underset{k_1}{\overset{k_2}{\rightleftharpoons}} \bar{A}\quad \text{(II.)}$$

compensated forms whilst the asterisk indicates an uncompensated enantiomeride. It is assumed that $\overset{*}{A}$ cannot be converted into $\bar{A}$ otherwise than through the route shown, all the velocity coefficients relating to which have been independently ascertained. The extent of the racemisation of A at any time, *t*, is conveniently expressed by calculating the rotatory power of A at that time as a fraction of its value at zero time. In terms of concentrations, this fraction, Γ, of original rotatory power is defined by

$$\Gamma = \frac{\overset{*}{a}}{\overset{*}{a} + \bar{a}} \bigg/ \frac{\overset{*}{a}_0}{\overset{*}{a}_0 + \bar{a}_0} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \qquad (1)$$

where small letters denote concentrations, and the zero subscript refers to zero time. It is necessary to express Γ in terms of the velocity coefficients, k_1 and k_2, and the time, *t*, and the dynamical equations (2) and (3) are available for this purpose :

$$-(d\overset{*}{a}/dt) = k_1\overset{*}{a} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \qquad (2)$$

$$-(d\bar{a}/dt) = k_1\bar{a} - k_2\bar{b} = k_1\bar{a} - k_2(\overset{*}{a}_0 + \bar{a}_0 - \overset{*}{a} - \bar{a}) \quad . \quad . \quad . \quad . \qquad (3)$$

These equations have to be solved and the constants of integration in the solutions evaluated by reference to the initial conditions; a sufficient number of relations is then available to permit substitution for the concentrations in equation (1). The result of this elimination may be expressed in the form

$$\Gamma = (k_1 + k_2)/(k_2e^{-k_1t} + k_1e^{-k_2t}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \qquad (4)$$

and since the right-hand side of this equation is entirely independent of the polarimetric observations it remains only to compare the latter with the curve of the equation.

Equation (4) is, of course, a general one for racemisation by reversible conversion into a single inactive tautomeride. In the example studied, *K* happened to have the value 1·00, so that k_1 and k_2 were each equal to $\frac{1}{2}k$, and equation (4) assumed the simple form $\Gamma = \text{sech}\ (\frac{1}{2}kt)$, where *k* had the experimentally determined value 0·0145 hour^{-1}. The graph of equation (4) with these values of the constants is shown in the diagram,* from which it will be seen that the observed and calculated rates of racemisation are identical to within the limits of experimental accuracy.

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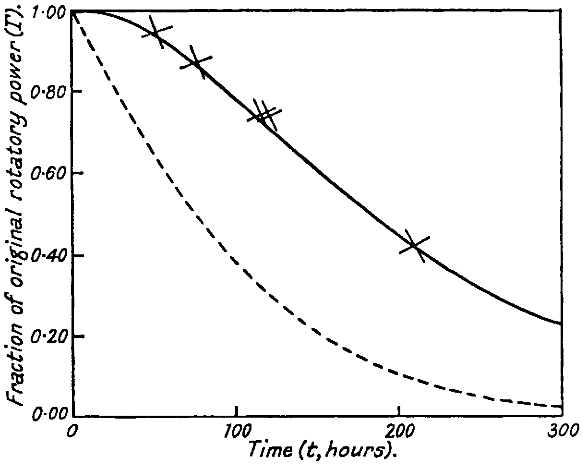
* In racemisation by tautomeric change the most rapid decline of optical activity does not occur at the commencement of reaction; it does, however, lie nearer to the commencement the smaller the equilibrium proportion of the inactive isomeride.

The ionic theory of tautomerism is now so widely accepted that we may introduce the theoretical scheme (III) in place of the simple observational scheme (I) without further ado :

$$A \underset{\kappa_3}{\overset{\kappa_1}{\rightleftharpoons}} \text{Ions} \underset{\kappa_4}{\overset{\kappa_2}{\leftrightharpoons}} B \quad \text{(III.)}$$

The ions indicated are regarded as a single pair of which the organic member is a mesomeric form involving complex duplet-sharing (Ingold and Ingold, J., 1926, 1312 ; Ingold, Shoppee, and Thorpe, *ibid.*, 1480; Burton and Ingold, *Proc. Leeds Phil. Soc.*, 1929, 1424; Ingold, J., 1933, 1120). Since the ions can be present only in very low concentrations, it follows that the four coefficients, $\kappa_1 \ldots \kappa_4$, introduced to represent the velocities of formation and dissociation of the ions, must be related to the observable equilibrium and velocity constants as shown in the following equations :



The full-line curve represents the theoretical equation (which does not contain any arbitrary constants) for racemisation by tautomerisation. The crosses indicate the polarimetric observations. The broken-line curve typifies the theoretical curve for racemisation by ionisation.

$$K = \frac{\kappa_1\kappa_4}{\kappa_2\kappa_3}, \qquad k = \frac{\kappa_1\kappa_4 + \kappa_2\kappa_3}{\kappa_3 + \kappa_4}, \qquad k_1 = \kappa_1 \cdot \frac{\kappa_4}{\kappa_3 + \kappa_4}, \qquad k_2 = \kappa_2 \cdot \frac{\kappa_3}{\kappa_3 + \kappa_4}.$$

The equations for k_1 and k_2 are of the form $k_1 = \alpha_1\kappa_1$, etc., where α_1 is a proper fraction, and this, of course, merely means that the speed of isomerisation of a tautomeric substance must always be smaller than its speed of ionisation.

From the present point of view the main circumstance in which scheme (III) goes beyond scheme (I) is in the provision of a second conceivable mechanism of racemisation. We now have to consider as possible, not only racemisation by tautomerisation (hypothesis α), but also racemisation by ionisation (hypothesis β), the difference between the two hypotheses being merely that, according to the first, optical activity is retained in the ions and is lost only on the formation of the isomeride, whereas, according to the second, optical activity is lost in the ions independently of their conversion into the isomeride :

Active ----- *Active* ----- *Inactive* ----------- Hypothesis α
$A \rightleftharpoons \text{Ions} \rightleftharpoons B$
Active ---- *Inactive* ---- *Inactive* ----------- Hypothesis β

Corresponding respectively to these two hypotheses we now set up schemes (IV) and (V) in place of scheme (II), and investigate the related values of Γ :

$$\text{(IV.)} \quad \overset{*}{A} \underset{\kappa_3}{\overset{\kappa_1}{\rightleftharpoons}} \overset{*}{\text{Ions}} \xrightarrow[\kappa_4]{} \bar{B} \underset{\kappa_4}{\overset{\kappa_2}{\rightleftharpoons}} \overline{\text{Ions}} \underset{\kappa_3}{\overset{\kappa_1}{\leftrightharpoons}} \bar{A}$$

$$\begin{tikzcd} & & \bar{A} \arrow[dl, shift right, "\kappa_1"'] \\ \overset{*}{A} \arrow[r, "\kappa_1"] & \overline{\text{Ions}} \arrow[ur, shift right, "\kappa_3"'] \arrow[dr, shift right, "\kappa_4"'] & & \text{(V.)} \\ & & \bar{B} \arrow[ul, shift right, "\kappa_2"'] \end{tikzcd}$$

When this calculation is carried out on the basis of scheme (IV), an expression is obtained which reduces to equation (4) if the κ's are replaced by k's in accordance with the relations contained in the preceding paragraph. This result is, of course, merely the mathematical equivalent of the evident fact that the mechanism of racemisation underlying scheme (IV) (hypothesis α) is essentially identical with that already considered on the basis of scheme (II). When, however, Γ is calculated in accordance with scheme (V) (hypothesis β) an equation (5) is obtained which in general represents a definitely more rapid loss of optical activity than that required by equation (4), although, if the proper fraction α_1 happens to have a value very close to its upper limit, the disparity between the two rates may not be considerable :

$$\Gamma = e^{-k_1 t/\alpha_1} \Big/ \frac{k_1 e^{-(k_1 + k_2)t} + k_2}{k_1 + k_2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

In order to illustrate the general relationship between these two time-functions, a graph of equation (5) corresponding to $\alpha_1 = 0{\cdot}5$ and to the determined values of k_1 and k_2 is included in the diagram.

Two further remarks may now be made concerning our experimental results. First, since they represent the *smallest* rate of decay of optical activity that is consistent with either of the hypotheses discussed above, we need not fear that any part of the observed speed of racemisation is due to the incursion of mechanisms completely foreign to considerations of the type of those advanced in this paper, a possibility which, had the rate been above the minimum, could not have been disregarded. Secondly, the observations, whilst they agree very closely with the unique requirements of the hypothesis α of racemisation by tautomeric change, can be accommodated by the alternative hypothesis β of racemisation by ionisation only through the assumption of a coincidental relationship between the velocities of formation and dissociation of the ions. It will be possible more justly to assess the degree of probability that a coincidence of this character is responsible for the observed results after the experimental method has been extended to other examples; in the meantime the former of the two hypotheses seems the more natural, and, if that view be adopted, it is difficult to resist the inference that mesomeric ions generally may be able in greater or less degree to retain the optical activity of a related tautomeride in which the point of attachment of the mobile group is the centre of asymmetry. That this is true for the anions of nitro-paraffins of the form $R^1R^2CH{\cdot}NO_2$ is definitely established (Kuhn and Albrecht, *Ber.*, 1927, **60**, 1297; Shriner and Young, *J. Amer. Chem. Soc.*, 1927, **49**, 1765; Mills and Cole, *Brit. Assoc. Reports*, 1932, 41). It is not to be expected that the remarkably high optical stability shown by these particular anions will necessarily reappear in other cases, but there is at least one indication in the previous literature that the occurrence of optical activity, and its retention for an appreciable period of time, in tautomeric ions of the kind considered, is not a peculiarity of nitro-paraffin anions. Leuchs and Wutke (*Ber.*, 1913, **46**, 2425) brominated an optically active ketone of the form $R^1R^2CH{\cdot}CO{\cdot}R^3$ and obtained an active α-bromo-derivative. The whole of the evidence concerning the bromination of ketones can be interpreted just as well by the hypothesis that halogenation takes place through the anion as by the customary theory that it occurs by way of the enol, and there are many analogies which favour the former alternative. Its application to the experiment of Leuchs and Wutke is, of course, that the mesomeric keto-enol anion is capable of optical activity and can retain it for the period pending the attack of the halogen.

EXPERIMENTAL.

Dynamical Investigation of the Isomerisation of Optically Inactive p-*Chlorobenzhydrylidene-α-phenylethylamine.*—Interconversion was effected in sodium ethoxide solution, and the mixtures of isomerides obtained were analysed by hydrolysis to the corresponding amines, and estimation of the content of chloride ion in the mixed hydrochlorides derived from the latter.

Method. The ethyl alcohol employed was dried with magnesium ethoxide (Lund and Bjerrum, *Ber.*, 1931, **64**, 210). The azomethine was heated for various periods of time at 85° in solution in 30 parts of $1{\cdot}33N$-ethyl-alcoholic sodium ethoxide. The product was poured into much water, extracted with pure ether, washed with water, and, after removal of the ether, hydrolysed by warming for 15 minutes on the water-bath with distilled 20% hydrochloric acid free from ammonia. Water was added to avert the precipitation of *p*-chlorobenzhydrylamine hydrochloride, and the ketones were then removed by extraction with chloroform. After subsequent extraction with ether, the aqueous solution was evaporated to dryness under reduced pressure over sulphuric acid and potassium hydroxide, and the residue was repeatedly ground, well mixed together, and redried at pressures below 1 mm. over phosphoric oxide and potassium hydroxide (α-phenylethylamine hydrochloride is hygroscopic). The chloride ion was estimated gravimetrically after precipitation by means of 0·05*N*-silver nitrate from 0·1*N*-nitric acid solution.

Results. These are shown in the following table, wherein col. 1 shows the lengths of time for which treatment with the sodium ethoxide catalyst was continued, and col. 3 records the mean values of consistent analytical results where, as indicated in col. 2, the determinations were carried out in triplicate. The coefficient of the velocity of approach to equilibrium, $k = k_1 + k_2$, calculated from the individual observations by means of the formula $(a - a_\infty) = (a_0 - a_\infty)e^{-kt}$, is shown in col. 4. The value of a_∞ which is required for the calculation was obtained by plotting $\log \{(a_0 - a_\infty)/(a - a_\infty)\}$ against t for various assumed values of a_∞, the value which gave the closest approach to a straight line passing through the origin being taken as the true value. This procedure was more accurate than a single analytical determination after a long period of isomerisation would have been. Thus it was found that the equilibrium proportion of the original isomeride was almost exactly 50%, since this value gave a linear plot, whilst the corresponding graphs for the assumed proportions 49·0 and 51·0% were curved to about equal extents in opposite directions.

Time (t) (hours).	No. of expts.	Conversion (%) $\{100(a_0 - a)/a_0\}$.	k (hour^{-1}).	Time (t) (hours).	No. of expts.	Conversion (%) $\{100(a_0 - a)/a_0\}$.	k (hour^{-1}).
48·0	1	25·9	0·01522	121·5	3	42·2	0·01530
63·0	1	30·8	0·01519	144·0	1	43·0	0·01366
77·0	3	32·4	0·01359	173·5	3	45·8	0·01429

From these data we deduce the values $K = 1{\cdot}00$, $k = 0{\cdot}0145$ hour^{-1}, and $k_1 = k_2 = 0{\cdot}00725$ hour^{-1}.

Measurement of the Speed of Racemisation during the Isomerisation of Optically Active p-*Chlorobenzhydrylidene-α-phenylethylamine.*—It was shown in Part I (*loc. cit.*) that optically active α-phenylethylamine could be converted into the above azomethine and subsequently recovered by hydrolysis therefrom without loss of optical activity. The following method was based on these facts.

Method. The azomethine was isomerised for varying lengths of time under conditions identical with those employed in the study of the optically inactive compound, and the mixture of tautomerides was separated and hydrolysed as already described. The acid solution of the hydrolysis products, after dilution with water and complete removal of the ketones by extraction with chloroform, was basified with potassium hydroxide, the amines were extracted thoroughly with ether, the extract dried (potassium carbonate), the ether removed, and the amines distilled under a pressure of a few mm. from a bath the temperature of which was not allowed to rise above 100°. Under these conditions the α-phenylethylamine could be sharply separated from the accompanying *p*-chlorobenzhydrylamine, and a further distillation, in which small head and tail fractions were neglected, rendered the material suitable for the measurement of rotatory power.

Results. The specimens of azomethine employed were prepared from various lævorotatory samples of α-phenylethylamine. The rotations of the recovered amine were measured in a 50-mm. tube using the mercury green line, λ 5461. The results are shown in the following table; line 1 indicates the identity of the sample of azomethine employed, line 2 records the time allowed for isomerisation, line 3 the observed rotations, and line 4 the temperatures at which the polarimetric observations were made. The last line contains the fractions of original rotatory power calculated from the rotations of line 3. These values, Γ, are plotted against the corresponding times of isomerisation, *t*, in the diagram on p. 95.

Sample	i	ii	i	ii	i	ii	i
t (hours)	0·0	0·0	52·3	77·0	117·8	121·5	210·0
α	8·64°	5·89°	8·13°	5·13°	6·41°	4·37°	3·62°
Temp.	20°	17°	20°	20°	19°	—	20°
Γ	1·000	1·000	0·941	0·870	0·742	0·742	0·419

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[*Received, November* 11*th*, 1933.]