167. *Optical Activity in Relation to Tautomeric Change. Part IV. Comparison of the Rates of Racemisation and of Bromination of a Ketone.*

By Christopher K. Ingold and Christopher L. Wilson.

It is frequently assumed, on account of the evidence of reaction dynamics, that, in the halogenation of ψ-acidic ketones, the elementary process which determines the measured rate is the enolisation of the ketone. All that the dynamical evidence really proves is, of course, that the measured speed is that of some change which precedes the attack of the halogen. The modern theory of prototropy does not permit the unequivocal identification of that preliminary change with enolisation in all circumstances, for ionisation is assumed to intervene, and the conditions of catalysis have to be taken into account.

The simplest case is that of basic catalysis :

$$B + H\cdot C\cdot C{:}O \rightleftharpoons BH + [C\cdot C{:}O]^- \rightleftharpoons B + C{:}C\cdot OH$$

In this scheme the reactive entity for electrophilic agents is the anion, and the rate of halogenation will therefore be equal to the rate of ionisation.

In acid catalysis the fundamental step is the conversion of the original prototropic system into a salt or salt-like complex in which the newly introduced positive electrical field creates sufficient additional reactivity to permit the subsequent removal of the tautomeric proton by some weak base which would not have sufficed for the ionisation of the original prototropic system, *e.g.*,

$$\begin{aligned} &HB + H\cdot C\cdot C{:}O \rightleftharpoons H\cdot C\cdot C{:}O,HB \\ &B' + H\cdot C\cdot C{:}O,HB \rightleftharpoons B'H + [C\cdot C{:}O]^-,HB \rightleftharpoons B'H + C{:}C\cdot OH + B \end{aligned}$$

In this case the reactive entity would be the salt or complex from which a proton has been removed; but this is the product of two consecutive reversible reactions, and therefore its rate of formation, on which the rate of halogenation depends, may be controlled either by the speed of formation of the complex, or by its speed of ionisation, or by both processes acting together. These cases will doubtless all arise in different circumstances which, for any given ketone, will depend on the relative efficiencies of the acid and base available under the prevailing conditions of acid catalysis.

In Part II it was shown (Ingold and Wilson, this vol., p. 93) that the rate of racemisation of a tautomeric substance, wherein the centres of dissymmetry and dissociation were identical, was equivalent to its rate of isomerisation ; and in Part III (Wilson, this vol., p. 98) evidence was cited in support of the conclusion that this relation applies generally to enolisable ketones.

Further consideration of the theory of racemisation in ψ-acidic ketones again necessitates recognition of the distinction between basic and acid catalysis. The prototropy of ψ-acidic systems by the former process is characterised by a great disparity in the rates of establishment of the successive equilibria involving the ions :

$$\psi\text{-Form} \underset{\text{(slow)}}{\rightleftharpoons} \text{Ions} \underset{\text{(fast)}}{\rightleftharpoons} \textit{aci}\text{-Form}$$

This is shown not only by the demonstrably slower rates of reaction of ψ-forms than of *aci*-forms with alkalis, but also by the circumstance that thermodynamically unstable *aci*-forms may often be isolated by the cautious addition of an acid to the alkali-metal salt of the tautomeric substance.* It follows that under conditions of basic catalysis the rates of enolisation of ψ-acidic ketones should be very nearly identical with their rates of ionisation, and, consequently, that experimentally observed rates of racemisation and halogenation should be the same.

Inspection of the scheme given for the acid catalysis of the prototropy of ketones shows that optical activity, dependent on dissymmetry centred at the seat of dissociation of the ketone, would be lost on the removal of the proton from the complex, for the derivative thus formed is evidently either the enol itself or a complex of the enol with a base. It therefore follows that the rate of racemisation under conditions of acid catalysis may be determined either by the formation of the complex, or by its ionisation, or by both processes acting together. However, for a given ketone and given conditions of catalysis, whatever may be the reaction stages which control the rate of racemisation, the same stages will determine the rate of halogenation, and therefore once again the measured rates of racemisation and halogenation should be identical. A connexion of this character has frequently been assumed, but not always on grounds which can be regarded as acceptable, and we know of no previous attempt at experimental control.

The ketone selected for the proposed experimental test was 2-*o*-carboxybenzylindan-1-one, $CO_2H{\cdot}C_6H_4{\cdot}CH_2{\cdot}\underline{CH{\cdot}CO{\cdot}C_6H_4{\cdot}CH}_2$, which was first prepared and optically resolved by Leuchs and his collaborators (*Ber.*, 1912, **45**, 194 ; 1913, **46**, 2425). The chosen experimental conditions were those of acid catalysis. Preliminary experiments showed that the speed of racemisation of the *d*-ketone was markedly influenced by solvents and catalysts, and that the rate of bromination of the *dl*-ketone exhibited a parallel variation with conditions. For instance, in chloroform and glacial acetic acid, racemisation of the *d*-ketone was extremely slow but became very rapid in the presence of traces of hydrogen bromide ; correspondingly, bromination of the *dl*-ketone in chloroform and in glacial acetic acid was so strongly autocatalytic that exact dynamical measurements were impossible. The addition of water to the acetic acid solvent greatly reduced the catalytic efficacy of hydrogen bromide, and in 90% or 80% acetic acid the amount of hydrogen bromide which it was necessary to add in order to produce a conveniently measurable speed of racemisation of the *d*-ketone was considerably greater than the amount that would be developed during the bromination of the *dl*-ketone ; and correspondingly, when bromination of the *dl*-ketone was carried out in 90% or 80% aqueous acetic acid in the presence of sufficient added hydrogen bromide to produce a conveniently measurable reaction velocity, the autocatalytic effect, although still observable, had become a subsidiary factor in the control of the velocity. For the quantitative correlation of racemisation with bromination, 90% acetic acid (actually 16·00*N*) was chosen as solvent, the temperature being 25° throughout.

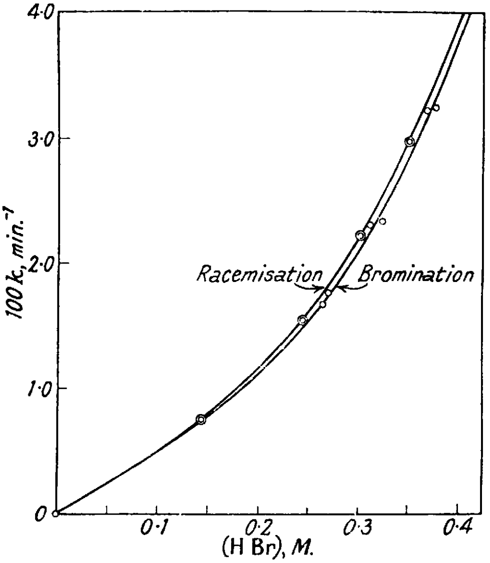
Explanation of the method of comparison is necessary on account of the allowance which has to be made for the autocatalytic effect present in the bromination experiments. First,

---

* Hugh and Kon have obtained analogous evidence (J., 1933, 775) showing that a similar disparity in the speeds of establishment of ionic equilibria may apply to Δ^{α}- and Δ^{β}-unsaturated esters, *i.e.*, to two different ψ-forms belonging to the same *aci*-form.

the velocity of racemisation in the presence of various concentrations of hydrogen bromide was observed. Owing to the low equilibrium concentration of the enolic form of the ketone, it is necessary that racemisation should follow the unimolecular law, $-(d\overset{*}{a}/dt) = k_r\overset{*}{a}$, where $\overset{*}{a}$ is the concentration of optically active ketone and t is the time; it was indeed found that the integrated equation $(\overset{*}{a}/\overset{*}{a}_0) = e^{-k_r t}$ was satisfied quite accurately. On the other hand, the racemisation velocity coefficients, k_r, increased definitely more rapidly than the first power of the concentration h of the hydrogen bromide; the form of the connexion is shown in the diagram. If the value of k_r is expressed by a series in ascending powers of h, a cubic equation is required to represent the variation over the experimental region. On the other hand, an inspection of the diagram shows that, for *ranges* of h not exceeding 0·05*M*, the relation between k_r and h may be treated as linear. For any such short range we may write $k_r = \alpha h + \beta$, where α and β are constant for the range, although they depend on the range selected. For any chosen range the constants α and β can be calculated from the cubic equation.

The speed of bromination of the optically inactive ketone was shown to be independent of the concentration of the bromine; we may therefore write $-(db/dt) = k_b a$, where a is the concentration of the ketone, b is that of the bromine, and k_b is a velocity coefficient which is expected to depend on the instantaneous concentration of the hydrogen bromide. The initial concentration of ketone was uniformly 0·05*M*; that of bromine was sometimes greater than this and sometimes less; the increase in the concentration of hydrogen bromide during any particular experiment is equal to whichever of these two initial concentrations is the smaller, and this increase therefore was never greater than 0·05*M*. In all these experiments, however, a considerable concentration of hydrogen bromide was added initially so that, during reaction, the concentration of this substance travelled over the kind of range for which we are entitled to assume a linear variation of the racemisation constant. For such a short range we may *try* the assumption that k_b is n times k_r, since this hypothesis gives an integrable velocity equation from which n may be calculated. If the assumption of proportionality holds sufficiently well for the range of h corresponding to the experiment, n will be found to be constant, and, naturally, if the two coefficients k_r and k_b are equal, then the constant n will be unity; and, furthermore, if k_r and k_b are equal *in principle*, then n should be unity for all ranges of h, *i.e.*, for all experiments.



The curves show the dependence of the unimolecular constants for the rates of racemisation and of bromination of 2-o-*carboxybenzylindan*-1-*one on the concentration of hydrogen bromide in* 16N-*acetic acid at* 25°. *The double circles refer to racemisation, and the single ones to bromination; each process has a point at the origin.*

According to this procedure, the trial equation is $-(db/dt) = k_b a = n(\alpha h + \beta)a$. The measured variables being b and t, we substitute $a_0 - b_0 + b$ for a, and $h_0 + b_0 - b$ for h, and then integrate:

$$n = \frac{1}{t}\,\frac{1}{\alpha a_0 + \alpha h_0 + \beta}\log_e \frac{a_0}{h_0 + \beta/\alpha}\left[\frac{h_0 + b_0 + \beta/\alpha - b}{a_0 - b_0 + b}\right]$$

The values of n thus obtained were constant for each experiment to within the error of measurement, and were in all experiments close to unity. The mean value of n, for any one experiment, when multiplied by the value of k_r, which corresponds to the mean value of h

for that experiment, gives the related value of k_b. The values of k_b thus obtained are shown on the diagram, and it will be seen that the points fall close to the curve drawn through the values of k_r. The mean value of n for all the experiments was 0·95. The difference between this and unity is somewhat greater than the probable error, but this most likely is due to some systematic imperfection of measurement, and the only conclusion which seems justified is that the velocities of racemisation and bromination are identical to within the limits of experimental precision. This result is quite analogous to that obtained by Weissberger and his collaborators (*Ber.*, 1931, **64**, 1200; 1932, **65**, 1815; *Annalen*, 1933, **502**, 74), who found the rates of auto-oxidation of certain benzoins to be substantially the same as their rates of racemisation under equivalent conditions of alkaline catalysis.

EXPERIMENTAL.

Preparation of 2-o-*Carboxybenzylindan*-1-*one*.—Ethyl dibenzylmalonate, b. p. 238°/18 mm., 250°/30 mm., was prepared in the usual way, and hydrolysed as directed by Leuchs and Radulescu (*Ber.*, 1912, **45**, 194). The yield of dibenzylmalonic acid was 40%, calculated on the ethyl malonate; a large amount of dibenzylacetic acid was also obtained. Great difficulties were experienced in the conversion of dibenzylmalonic acid into indane-2 : 2′-*spiro*-indane-1 : 1′-dione by the method described by Leuchs and his collaborators, although many samples of aluminium chloride were employed for the Friedel–Crafts condensation, and the experimental conditions were varied widely. The following modified process gave the most reproducible results. The malonic acid (65 g.) was converted into its chloride by means of a slight excess (100 g.) of phosphorus pentachloride in chloroform (60 c.c.). After removal of the solvent and the phosphoryl chloride at 100° under reduced pressure, the unchanged phosphorus pentachloride was removed by heating at 160° (bath temperature) for 15—20 minutes. The temperature having been adjusted to 140°, anhydrous ferric chloride (0·2 g.) was added, and the temperature was raised to 160° during 4 hours. Ferric chloride (0·1 g.) was again added, and the temperature was maintained at 160—170° for a further 14 hours. The temperature was then raised to 200—220°, whilst the flask was evacuated by means of a water pump during a period of 2 hours. The product, distilled in the vacuum of an oil pump, yielded first the by-products mentioned by Leuchs and Wutke (*Ber.*, 1913, **46**, 2425), then unchanged acid chloride (not more than 12 g.), and finally the spiran which, crystallised from benzene, had m. p. 171° (yield, 20—30%). It was found essential to use the crude acid chloride for the Friedel–Crafts condensation, as the distilled substance reacted only slightly on the addition of anhydrous ferric chloride or aluminium chloride, and no marked reaction was induced by the addition also of chloroform, phosphorus pentachloride, phosphorus trichloride, phosphorus oxychloride, phosphoric oxide or phosphoric acid. In addition to the various by-products described by the original workers, one experiment, which involved more prolonged heating than advised above, yielded a *substance* which crystallised from benzene in buff needles, m. p. 195—205° [Found : C, 87·8; H, 5·2; *M* (Rast), 211, 220. $C_{18}H_{12}O$ requires C, 87·9; H, 5·2%; *M*, 232]. The substance did not give a dinitrophenylhydrazone, but was precipitable by carbon dioxide from its solution in sodium hydroxide, yielded a deep green coloration with alcoholic ferric chloride, and dissolved in concentrated sulphuric acid to a deep yellow solution.

The conversion of the *spiro*-ketone into the required ketonic acid by hydrolysis with alcoholic sodium hydroxide presented no difficulties, but an attempt to dry the acid at 110° led to its conversion into a non-acidic material, from which crystalline products of different molecular complexity were isolated by crystallisation from nitromethane or from nitrobenzene. In the former case, the *product* formed prisms, m. p. 278° [Found : C, 72·2; H, 4·5; *M* (Rast), 240. $C_{17}H_{12}O_4$ requires C, 72·8; H, 4·3%; *M*, 280]. The latter *product* was obtained as laminæ, m. p. 285—287° [Found : C, 72·2; H, 4·3; *M* (Rast), 830, 804. $(C_{17}H_{12}O_4)_3$ requires *M*, 840].

Resolution and Optical Stability.—The acid was resolved with brucine (Leuchs and Wutke, *loc. cit.*), and the alkaloid was removed by shaking the chloroform solution with 2*N*-sulphuric acid until the acid extract gave no coloration with concentrated nitric acid. The chloroform solution was washed with water, dried with anhydrous sodium sulphate, and evaporated below 25°. The optically active acid (*M*, by titration, 265·6. Calc. : 266·1) had $[a]_{\mathrm{C}}^{20^\circ} + 59^\circ$, $[\alpha]_{\mathrm{D}}^{20^\circ} + 77^\circ$, $[\alpha]_{5461}^{20^\circ} + 93^\circ$ (chloroform, $c = 1{\cdot}6$) and $[\alpha]_{\mathrm{D}}^{25^\circ} + 50^\circ$ (90% aqueous acetic acid, $c = 1{\cdot}33$). The solid acid underwent no change in rotation on keeping for several months. The following table indicates its behaviour in various solvents at 20°.

Solvent.	HBr (*M*).	Approx. half-life.
$CHCl_3$ (dry)	0	α unchanged in 24 hours
$CHCl_3$ (50%), $CH_3{\cdot}CO_2H$ (50%)	0	,, ,, ,,
,, ,, ,,	0·25	<15 secs.
$CH_3{\cdot}CO_2H$ (glacial)	0	α unchanged in 24 hours
,, ,,	0·0020	4 mins.
$CH_3{\cdot}CO_2H$ (80%), H_2O (20%)	0·0013	*ca.* 100 hours
,, ,, ,,	0	,, ,,
$CH_3{\cdot}CO_2H$ (90%), H_2O (10%)	0·03	21 hours
,, ,, ,,	0·13	4 ,,
,, ,, ,,	0·25	50 mins.

Velocity of Racemisation of the d-*Ketone.*—Acetic acid was purified by Orton and Bradfield's method (J., 1924, **125**, 960), and diluted to 16·00*N*. Hydrogen bromide, generated from its aqueous solution by means of phosphoric oxide, was passed over moist red phosphorus and phosphoric oxide and absorbed in the acetic acid, its concentration being determined argentometrically. Rotations were taken in a 2-dm. tube, the mean temperature of which was 25·00° ± 0·02°. The solutions were always 0·05*M*, with respect to the ketone; the concentrations of hydrogen bromide and the corresponding unimolecular velocity coefficients are shown in the following table. Owing to the difficulty of fixing the time of the commencement of reaction, the velocity constants were deduced by plotting the logarithms of the rotation against the corresponding times, and measuring the slopes of the straight lines thus obtained.

Concn. HBr (*h*), *M*	0·142	0·245	0·303	0·352
Racemisation velocity const. (k_r), min.$^{-1}$	0·0075	0·0154	0·0221	0·0297

These data correspond to the equation $k_r = h\,(0{\cdot}492h^2 - 0{\cdot}0948h + 0{\cdot}0567)$.

Velocity of Bromination.—The solvents employed and the monobromo-ketone formed were found to be completely stable towards the bromine under the conditions of the experiment. The necessary amount of pure bromine was added to a known volume of a 0·05*M*-solution of the ketone at 25·00° ± 0·01°. Portions of 5 c.c. were mixed with 50 c.c. of water, and the bromine was determined iodometrically, the water present inhibiting reduction of the bromo-ketone. Chloroform was added during the titrations in order to prevent adsorption of iodine by the organic material which otherwise would have been precipitated. The initial titre was deduced by extrapolation with but little error. The following two tables exhibit respectively the details of a typical run, and a summary of the results of the series of experiments.

Expt. 2 : $a_0 = 0{\cdot}05$; $b_0 = 0{\cdot}0675$; $h_0 = 0{\cdot}245$; $\alpha = 0{\cdot}113$; $-\beta = 0{\cdot}0124$.

t, mins.	12	25	32	38	53·5	72	85
b, *M*	0·0578	0·0514	0·0467	0·0437	0·0366	0·0315	0·0282
n	1·06	0·92	0·98	0·98	0·98	0·97	0·98

t, mins.	101	104	111	126	163	183	
b, *M*	0·0253	0·0246	0·0239	0·0222	0·0198	0·0193	
n	0·97	0·99	0·96	0·96	0·92	0·87	(Mean 0·97)

Summary of Results for Velocity of Bromination, and Comparison with Racemisation Velocities.

No.	a_0.	b_0.	h_0.	h_∞.	α.	$-\beta$.	*n*.	h_{mean}.	k_r.	k_b.
1	0·05	0·0417	0·245	0·287	0·110	0·0117	0·94	0·266	0·0176	0·0166
2	,,	0·0675	,,	0·295	0·113	0·0124	0·97	0·270	0·0181	0·0176
3	,,	0·0255	0·303	0·329	0·144	0·0216	0·96	0·316	0·0240	0·0230
4	,,	0·0615	,,	0·353	0·154	0·0246	0·90	0·328	0·0258	0·0232
5	,,	0·0334	0·352	0·385	0·187	0·0364	0·98	0·369	0·0327	0·0321
6	,,	0·0550	,,	0·402	0·195	0·0392	0·94	0·377	0·0342	0·0322

UNIVERSITY COLLEGE, LONDON.

[*Received, April* 11*th*, 1934.]
