348. *Acid Catalysis in Non-aqueous Solvents.   Part VI.   The Racemisation of Phenylmethylacetophenone and Phenylisobutylacetophenone in Various Solvents.*

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The kinetics of the acid-catalysed racemisation of phenylmethylacetophenone and phenyl*iso*butylacetophenone have been investigated in various non-dissociating solvents at 100°.   The results resemble, in general, those already obtained for the inversion of menthone in chlorobenzene solution.   A mechanism is suggested to explain the observed dependence of the velocity upon the acid concentration.   Attempts were made to study catalysis by amines in inert solvents, but owing to complications it was only possible to establish qualitatively that the racemisation is catalysed by triethylamine in chlorobenzene, no acid species being present.

IN Part V (Bell and Caldin, this vol., p. 382) prototropic change in the group $>CH-\overset{|}{C}=O$ was studied by measuring the rate of inversion of menthone in chlorobenzene.   Owing to the low rotation of *d*-menthone, it was necessary to use rather concentrated solutions, thus introducing some complications.   The ketones used in the present investigation have

high molecular rotations, so that dilute solutions could be used. Further, since only one asymmetric centre is present, the final value of the rotation is zero, and velocity constants can be conveniently and accurately obtained from the measured rotations. Previous kinetic measurements on the racemisation of ketones (Conant, *J. Amer. Chem. Soc.*, 1932, **54**, 4048; Bartlett and Stauffer, *ibid.*, 1935, **57**, 2580; Ingold and Wilson, J., 1934, 773; Hsü and Wilson, J., 1936, 623) have dealt chiefly with the relation between rates of enolisation, racemisation, and halogenation, or with the effects of substitution on the velocity. The results obtained in the present work give information about the effect of the concentration and nature of acid catalysts, the effect of the solvent, and the kinetic mechanism of the reaction.

<div align="center">EXPERIMENTAL.</div>

Preparation of Materials.—Phenylmethylacetophenone was prepared by two methods. (i) Hydratropic acid was prepared from phenylacetonitrile (Meyer, *Annalen*, 1889, **250**, 123), resolved through the quinine salt (Levene, Mikeska, and Passoth, *J. Biol. Chem.*, 1930, **88**, 27), and converted into the ketone by a Grignard reaction (Conant, *loc. cit.*). The specimens obtained had m. p. 37—38°, but were about half racemised. (ii) *d*-Alanine ester hydrochloride (from silk) was treated with phenylmagnesium bromide (McKenzie, Roger, and Wills, J., 1926, 785), and the resulting amino-alcohol converted into the ketone by the action of nitrous acid (McKenzie, J., 1925, **127**, 287). This product had m. p. 29—30°, $[\alpha]_D^{20°} + 188°$ (in chlorobenzene). McKenzie gives m. p. 34°, $[\alpha]_D^{20°} + 207°$ (in alcohol).

Phenyl*iso*butylacetophenone was prepared from *l*-leucine (from ox blood) through the amino-alcohol as described by Kaneo and Yaguchi (*Chem. Zentr.*, 1928, ii, 51). After recrystallising twice from aqueous alcohol and once from absolute alcohol, the product had m. p. 51—53°, $[\alpha]_D^{20°} + 150°$ (in alcohol), and was thus of higher optical purity than the ketone obtained by Kaneo and Yaguchi, who give m. p. 33—36°, $[\alpha]_D^{20°} + 109°$. The rotation of this ketone was determined at 20° in a number of solvents, the values of $[\alpha]_D^{20°}$ being : alcohol, 150°; chlorobenzene, 167°; anisole, 179°; nitrobenzene, 138°; amyl acetate, 212°; decalin, 180°. Increase of temperature to 100° caused a decrease in rotation of 20—30%.

The acids were pure commercial specimens distilled or recrystallised as described in previous papers of this series. The solvents were dried over sodium or phosphoric oxide and fractionally distilled, slightly reduced pressure being used for decalin and nitrobenzene.

Measurement of Reaction Velocity.—The kinetic measurements were carried out at *ca.* 100°, the thermostat used being a modified form of that described by Bell and Caldin (*loc. cit.*). The polarimeter tubes were 200 mm. long, with sintered end-plates. They were placed in narrow metal troughs which extended well above the level of the thermostat oil. The base of the trough consisted of a length of brass tubing which was a close fit on the polarimeter tubes and was half cut away in the middle where it joined the vertical sides of the trough. The brass tubes extended beyond the ends of the troughs and were soldered through the sides of the thermostat. In order to improve thermal contact, the lower part of the troughs was filled with brass filings. After insertion of the polarimeter tubes, tops were soldered on to the troughs, an aperture being left for the vertical extension to the filling cup of the polarimeter tube. This construction eliminates any danger of the thermostat oil leaking into the tube or on to the end-plates, and it obviates the use of cement. Tests showed that, when the polarimeter tubes were filled with solutions originally at 90°, they reached thermostat temperature (within 0·1°) in 10 minutes.

The polarimeter was a Hilger instrument giving readings reproducible to 0·01°, and the initial rotation obtained was 1—2°. The source of light was a mercury-vapour lamp, with filters transmitting only the 5770 and 5790 A. lines. For the measurements in nitrobenzene (where a green colour was developed), a filter transmitting only the 5461 A. line was used. With phenylmethylacetophenone, readings were continued over about two-thirds of the reaction. With the other ketone, this was not always possible owing to darkening in the solutions. The first-order velocity constants were determined graphically by plotting the logarithm of the rotation against the time. The course of the reaction was always unimolecular within the experimental error.

Results in Chlorobenzene.—Measurements were made with phenylmethylacetophenone and four catalysing acids in this solvent. In the absence of acid, no change in rotation was detectable when the solution was kept at 100° for a fortnight. The concentration of the ketone was kept constant at 0·025 mol./1000 g. (0·75% by weight). A three-fold increase in ketone concentration

affected the velocity by not more than 15%. In the following tables k = first-order constant ($\log_{10}$, min.$^{-1}$), c = catalyst concentration (mols./1000 g.). The calculated values of k are given by one of the two equations $k = k_A c + a\sqrt{c}$ or $k = k_A c + bc^2$. The best values of the constants in these equations were calculated by a modification of the usual least-square treatment, and are given with their probable errors in Table II. It will be seen from Table I that there is agreement between the observed and the calculated velocity constants to within the experimental error of about 3%.

TABLE I.

Racemisation of Phenylmethylacetophenone in Chlorobenzene at 99·4°.

Trichloroacetic acid.

c	0·0251	0·0989	0·123	0·246
$10^4 k$ { obs.	2·19	12·2	16·0	45·8
$10^4 k$ { calc.	2·20	11·9	16·1	45·8

Dichloroacetic acid.

c	0·0538	0·0634	0·0925	0·186	0·313
$10^4 k$ { obs.	1·34	1·53	2·15	4·24	6·90
$10^4 k$ { calc.	1·30	1·53	2·17	4·18	6·87

o-Nitrobenzoic acid.

c	0·0842	0·170	0·272	0·423
$10^4 k$ { obs.	0·472	0·781	1·05	1·56
$10^4 k$ { calc.	0·474	0·774	1·09	1·53

Monochloroacetic acid.

c	0·0781	0·155	0·310	0·425	0·533
$10^4 k$ { obs.	0·31	0·52	0·79	0·97	1·14
$10^4 k$ { calc.	0·32	0·50	0·79	0·98	1·15

TABLE II.

Acid.	$10^4 k_A$.	$10^4 a$.	$10^4 b$.	K_A (25°).
Trichloroacetic	76 $\pm$ 1	—	445 $\pm$ 10	8 $\times 10^{-1}$
Dichloroacetic	20·1 $\pm$ 0·4	1·0 $\pm$ 0·1	—	5·5 $\times 10^{-2}$
o-Nitrobenzoic	2·0 $\pm$ 0·2	1·05 $\pm$ 0·08	—	6·3 $\times 10^{-3}$
Monochloroacetic	0·96 $\pm$ 0·07	0·88 $\pm$ 0·04	—	1·6 $\times 10^{-3}$

A few similar experiments were carried out with phenyl*iso*butylacetophenone catalysed by mono-, di-, and tri-chloroacetic acids; the velocity was throughout 3·5 $\pm$ 0·1 times smaller than with phenylmethylacetophenone.

In the work with menthone (Bell and Caldin, *loc. cit.*) it was shown that there was instantaneous complex formation between the acid and the ketone, followed by a subsequent slow change leading to inversion, and this complex formation was studied quantitatively by observing the instantaneous depression of the optical rotation at 20°. In the present work the reactions were sufficiently slow for similar observations to be made at 100°. The results are given below,

Rotation of ketones in trichloroacetic acid solutions at 100°.

	Phenylmethylacetophenone.					Phenyl*iso*butylacetophenone.			
c (acid)	0·025	0·051	0·103	0·157	0·264	0·048	0·100	0·149	0·245
Decrease in rotation, %	2·0	3·0	10·5	14·4	27	3·2	6·0	10·4	16

The ketone concentration was in each case 0·025M, and it will be seen that the rotation is still decreasing in a roughly linear manner even when the acid concentration is more than 10 times as great. This shows directly that the degree of complex formation must be small at 100°, as must be assumed in any simple treatment of the kinetics. Trichloroacetic acid is the strongest acid used, and the same will be true *a fortiori* of the weaker acids.

Results in Various Solvents.—The object of these measurements was to investigate the effect of solvent variations upon the catalytic behaviour of this type of reaction. Only non-dissociating solvents were used, so that the acid molecules were the only catalytic species present. The ketone used was the more readily accessible phenyl*iso*butylacetophenone. Some difficulty was experienced owing to the gradual darkening of the solutions at 100°, which is presumably due to some impurity, since it was much greater in samples which had not been recrystallised from

absolute alcohol. It only develops in the presence of acids, and the colour varies between yellow, red, purple, and green, suggesting a colloid in different states of dispersion. With the solutions of dichloroacetic acid used, it was normally possible to follow about 40% of the reaction, but in nitrobenzene the solutions became opaque after only about 15% racemisation. For this reason the results are not so accurate as those for phenylmethylacetophenone, but they are sufficiently consistent to illustrate the differences between the various solvents. The concentration of the ketone was 0·028M throughout. The results are given in Table III.

TABLE III.

Racemisation of phenylisobutylacetophenone in different solvents.

Temperature, 100°. Catalyst, dichloroacetic acid.

$k/c \times 10^4$.

Solvent.	$c = 0.6$.	0·5.	0·4.	0·3.	0·2.	0·1.
Anisole	1·11	—	1·04	0·59	0·46	—
Nitrobenzene	2·17	2·38	2·65	2·00	2·31	2·33
Chlorobenzene	5·16	5·11	4·98	—	4·66	4·27
Decalin	15·4	14·7	13·1	—	12·5	8·6

Attempts to study Basic Catalysis.—Attempts were made to study catalysis by amines in chlorobenzene solution, since current views assume (cf. Pedersen, *J. Physical Chem.*, 1934, **38**, 581; *Trans. Faraday Soc.*, 1938, **34**, 237; Bonhoeffer and Reitz, *Z. physikal. Chem.*, 1937, *A*, **179**, 135) that in the base-catalysed prototropy of ketones there is no preliminary equilibrium with the catalyst, the initial proton transfer determining the rate. The addition of piperidine to a chlorobenzene solution of phenylisobutylacetophenone at 100° caused a slight decrease in rotation, but the solution rapidly darkened and a white crystalline solid was deposited. This may be analogous to the compound reported by Goetschmann (*Annalen*, 1879, **197**, 27) between acetone and diethylamine. With solutions of triethylamine, 0·01—0·10N, at 100° no solid was formed, though there was considerable darkening. The rotation in all cases decreased initially, passed through a minimum, and then increased slowly to a steady value *higher* than the initial rotation. There seems to be no possibility of compound formation between a ketone and a tertiary amine, and it seems probable that the increase in rotation is due to the formation of an optically active hydroxy-ketone by an aldol condensation between two ketone molecules. This condensation would be catalysed by bases, and the resulting ketone cannot racemise by enolisation, since there is no hydrogen atom on the α-carbon atom. It can be shown that under suitable conditions simultaneous racemisation and condensation will lead to a rotation—time curve of the type found experimentally, though there are too many unknown factors to attempt a quantitative treatment. It is however of interest to observe that racemisation can be effected by a base alone without the presence of any other acidic species; no doubt the ion Et_3NH^+ provides the proton necessary for the second stage of the prototropic change.
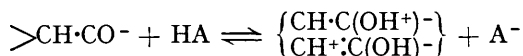
DISCUSSION.

The results for racemisation in chlorobenzene bear a general resemblance to the corresponding data for the inversion of menthone (Bell and Caldin, *loc. cit.*). In particular, there is a correlation between the catalytic power of an acid (as measured by the coefficients k_A in Table II) and its dissociation constant in water (K_A), though the data are not so extensive as in the case of menthone. It may be noted that recent indicator measurements in chlorobenzene (Griffiths, this vol., p. 818) show that the relative strengths of acids in that solvent are (as previously assumed) represented fairly closely by their dissociation constants in water.

The velocity is not, in general, a linear function of the acid concentration c, it being necessary to add either a term in $c^{\frac{1}{2}}$ or a term in c^2 to represent the experimental results. (This applies to all the results obtained, both with menthone and with the synthetic ketones.) The term in $c^{\frac{1}{2}}$ can be reasonably accounted for by the equilibrium known to exist between double and single molecules of carboxylic acids. The term in c^2 was tentatively attributed by Bell and Caldin to a medium effect of the acid; however, in view of the relatively small effect caused by change of solvent (cf. Table III) this explanation no longer seems likely. The occurrence of the acid concentration to a power higher

than the first (which appears to be a fairly common phenomenon in aprotic solvents) may be more plausibly accounted for along the following lines.

The first step in the prototropic change is the setting up of the equilibrium

$$\text{>CH·CO}^- + \text{HA} \rightleftharpoons \left\{ \begin{matrix} \text{CH·C(OH}^+)\text{-} \\ \text{CH}^+\text{:C(OH)-} \end{matrix} \right\} + \text{A}^-$$

where the cation in brackets is a hybrid of the two forms shown. The subsequent rate-determining step is the removal of a proton from the carbon atom, leading·to racemisation. In a solvent of high dissociating power, the cation and the anion A^- will exist separately, and the removal of the proton can take place by a collision between them, HA being re-formed. It has previously been assumed that the same mechanism is the only one operating in a solvent of low dielectric constant like chlorobenzene, where the cation and the anion will be held firmly together by electrostatic forces. However, in the hybrid cation the charge is predominantly on the $\text{C(OH}^+)$ group, and the anion A^- will be attracted strongly to this part of the molecule : hence it may be relatively difficult for the proton on the neighbouring carbon atom to become attached to the anion. We therefore suggest an alternative mechanism in which the proton is lost to *a second acid molecule acting as a base*. Carboxylic acids are known to have weak basic properties, as shown by the fact that they have a measurable conductivity in the pure state, due to the reaction $2 \text{ R·CO}_2\text{H} \rightleftharpoons \text{R·CO·O}^- + \text{R·CO·OH}_2{}^+$, and by their behaviour in strongly acid solvents (cf. Hammett, *J. Amer. Chem. Soc.*, 1935, **57**, 2103). The molecule $\text{R·CO}_2\text{H}$ is, of course, a very much weaker base than the ion R·CO·O^-, but it is present at a high concentration, and since it is uncharged it will not be diverted to the part of the ketone molecule bearing the bulk of the positive charge. It therefore seems feasible to assume that both species may play a comparable part in removing the relevant proton from the cation. This assumption leads to an equation of the form $k = k_A c + bc^2$, as found experimentally. On the other hand, the square-root term which is predominant for the weaker acids will no doubt be present to some extent throughout, so the experimental values of the coefficient b have no simple quantitative significance.

The results for different solvents (Table III) show relatively small variations in rate, in contrast to the results obtained for the depolymerisation of paraldehyde by trichloro-acetic acid at 20° (Bell, Lidwell, and Vaughan-Jackson, *J.*, 1936, 1792). In the present work the rate is smallest in anisole, which is probably due to chemical interaction between the acid and the basic oxygen atom. In the three remaining solvents the velocity varies less than ten-fold, and appears to bear no relation to the dielectric constant of the solvent. The same is true for the solvents investigated in the rearrangement of *N*-bromoacetanilide (Bell, *Proc. Roy. Soc.*, 1934, **143**, *A*, 377).

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