276. *Isotopic Exchange Reactions of Organic Compounds. Part IV. The Mechanism of Racemisation of Phenyl-*p*-tolylacetic Acid.*

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The racemisation and isotope exchange of phenyl-*p*-tolylacetic acid are studied kinetically in two ways. (1) Optically active phenyl-*p*-tolyldeuteroacetic acid is racemised by treatment with excess alkali in aqueous solution; loss of optical activity occurs at the same rate as loss of deuterium, the velocity constants being 0·0050 hr.$^{-1}$ in each case. (2) Phenyl-*p*-tolylacetic acid is racemised under the same conditions, but in a solvent containing 3% of deuterium oxide; loss of activity occurs faster than in the previous case (k = 0·023 hr.$^{-1}$) and also faster than the accompanying exchange reaction (k = 0·0077 hr.$^{-1}$). It is possible to identify the rates of racemisation with the rates of ionisation of the α-deuterium and α-hydrogen atoms respectively, and it is therefore concluded that the racemisation proceeds by an ionisation mechanism.

It has been shown that the racemisation by alkali of a pseudo-acidic ketone is accompanied by an exchange reaction of the α-hydrogen atom of identical velocity (Hsü, Ingold, and Wilson, this vol., p. 78). This is in accordance with a mechanism of racemisation involving an intermediate ion in which asymmetry is not retained, but enolisation is not a necessary corollary either of the racemisation or of the exchange. It has also been shown, however, that the rate of racemisation of a methyleneazomethine is slower than would be anticipated from isotopic exchange data : this is attributed, not to the retention of asymmetry by the intermediate ion, but to a special kind of termolecular exchange reaction which proceeds without a Walden inversion (de Salas and Wilson, this vol., p. 319). Since carboxylic acids fall in a position between ketones and methyleneazomethines in the series of decreasing prototropic mobility, and since a change of mechanism of prototropic isomerisation occurs in this series (Hsü, Ingold, and Wilson, J., 1935, 1778), it is of interest, in relation to these facts, to study the racemisation of an optically active carboxylic acid with a view to identify the mechanism of the process. Phenyl-*p*-tolylacetic acid has been selected for this purpose because it is known to racemise on treatment with alkali (McKenzie and Widdows, J., 1915, **107**, 702), and information available on exchange reactions indicated that it was likely to undergo an exchange of conveniently measurable velocity under the same conditions (Part II, this vol., p. 81).

The interpretation of the results of exchange experiments is complicated by the strongly unbalanced rates of transference of protons and deuterons, unless both solute and solvent are initially homogeneous (as far as the exchangeable hydrogen is concerned) and the solvent is in large excess. The use of pure deuterium oxide to comply with these conditions is inconvenient, and the alternative procedure has been adopted of studying the rate of loss of deuterium from a " heavy " solute in a large excess of " light " solvent. Under these conditions, every deuteron removed from the solute molecule by the basic catalyst must necessarily be replaced by a proton from a normal solvent molecule: the measured rate of loss of deuterium is then identical with its rate of ionisation.

Phenyl-*p*-tolyldeuteroacetic acid was accordingly prepared from the ordinary acid by two successive treatments at 100° with excess of sodium deuteroxide in deuterium oxide, and partially resolved by crystallisation of the cinchonidine salt from alcohol. Samples of both diastereoisomerides were racemised in 0·2N-aqueous solution at 100° in presence of 10% excess of sodium hydroxide, in pure silver vessels. At suitable intervals, the alkaline solutions were examined polarimetrically, the catalyst neutralised, the solvent removed, and the residue analysed for deuterium. The results are shown in Table I.

TABLE I.

Time, hrs.	α_D.		% of original activity.	% of D in α-position.	$\frac{\%\ \text{acty.}}{\%\ \text{D}}$.	$10^5 k_{\text{rac.}}$ (hr.$^{-1}$).	$10^5 k_{\text{exch.}}$ (hr.$^{-1}$).
0	0·365°	−0·431°	—	—	—	—	—
19·5	0·348	—	95·3	90·1	1·058	—	531
42·5	—	−0·338	78·4	80·4	0·975	572	513
68	0·254	—	69·6	70·2	0·991	533	520
94	—	−0·264	61·3	62·3	0·984	521	504
120	0·200	—	54·8	54·4	1·007	501	508
142	—	−0·214	49·7	49·3	1·008	493	498
172	0·157	—	43·0	43·0	1·000	490	490
214	—	−0·160	37·1	36·7	1·011	463	468
				Means	1·004	508	504

There is no doubt that the rates of racemisation and of loss of deuterium are identical, and since the latter must be equal to the rate of ionisation of the α-deuterium, it can be inferred that the racemisation proceeds by an ionisation mechanism, and there can be no reasonable doubt that the same process operates in the racemisation of the ordinary acid. It can also be concluded that, if the intermediate ion postulated in the theory of prototropy is kinetically free (*i.e.*, if the reaction proceeds by the bimolecular mechanism), then it must also be symmetrical. This conclusion, however, requires examination in the light of the known fact that the *aci*-form of a ψ-acidic system usually ionises, and is regenerated from the ions, more rapidly than the ψ-form. Ionisation and enolisation occur in these systems at substantially the same rate, and the racemisation might therefore occur at either stage. There is, however, no evidence for the formation of an enolic form of a carboxylic acid, and in any event it is clear that the exchange reaction of the α-hydrogen atom is a function of the formation of the ψ-form from the ion: the generation of an enol and its subsequent reconversion into an ion is only a reversible side reaction which cannot affect exchange. It is apparent that proton (or deuteron) addition to any given ion, which constitutes completion of the exchange, will occur independently of the past history of the ion, whether it has been produced the instant previously from a ψ-acidic molecule, or whether it has been interconverted one or more times with the *aci*-form. If, therefore, loss of asymmetry occurred only in the enolisation stage, it would be reasonable to suppose that a certain proportion of the molecules would undergo exchange without an intermediate enolisation at all, and the exchange reaction would be at least fractionally faster than the racemisation. The observed fact that this is not so indicates that racemisation occurs during ionisation and that the ion does not retain asymmetry. The alternative interpretation that the reaction occurs by a termolecular enolisation, in which the intermediate ions do not attain kinetic independence, presents certain difficulties in view of the fact that the reaction is alkali-catalysed in aqueous solution, and that the carboxylate group must be more or less uniformly solvated. Indeed, it is questionable whether such a mechanism can be distinguished from a bimolecular one, except as the extreme case in which the velocity of conversion of the ion into the enol approaches infinity. This is equivalent to the supposition that the ion is directly produced as one of the unperturbed forms of a system which is more likely to be mesomeric : mesomerism in the free, but solvated, ion would equally well explain the lack of retention of asymmetry (cf. Hsü, Ingold, and Wilson, *loc. cit.*).

The difficulty of maintaining a uniform velocity in a slow, alkali-catalysed reaction has not been entirely eliminated by the substitution of silver for glass reaction vessels : the observed velocity constants show a slight fall with increasing time of heating. The earlier values of the racemisation constant are in any case irregular owing to the very small changes in the observed angle of rotation : the first two and the last experimental values have therefore been neglected in calculating the mean constants.

The racemisation of ordinary phenyl-*p*-tolylacetic acid in a solvent of dilute deuterium water was also carried out under the same conditions of concentration, catalyst, and temperature, with the view of estimating the relative rates of transference of protons and deuterons and the equilibrium constant of the exchange reaction. The results are shown in Table II.

TABLE II.

Time, hrs.	α_D.	% of original activity.	$10^4 k_{rac.}$ (hr.$^{-1}$).	Atoms % of D in α-position.	$10^5 k_{exch.}$ (hr.$^{-1}$).
0	1·025°	—	—	—	—
5	0·904	88·2	251	0·151	—
21·1	0·634	58·9	228	0·354	792
46	0·355	34·6	230	0·675	755
70	0·207	20·2	229	0·981	795
94	0·137	13·4	214	1·161	774
360	—	—	—	2·158	774
∞ (by extrapolation)				2·300	
		Means	230×10^{-4}		773×10^{-5}

Atoms % of D in solvent, 2·952. $K_{eq.} = 0·797$.

The rate constant for the ionisation of the α-hydrogen atom, k_{iH}, can be estimated from the relationship

$$k_{iH} = k_1 k_{iD}/(k_{iD} - k_2)$$

where k_{iD} is the rate constant for the ionisation of deuterium, k_1 the velocity constant for the complete change $\vdots CH \longrightarrow \vdots CD$, and k_2 that for the change $\vdots CD \longrightarrow \vdots CH$. On substitution of the determined values, this gives $k_{iH} = 0·0229$ hr.$^{-1}$, in agreement with the measured rate of racemisation and in accordance with the ionisation theory. This close agreement, however, is fortuitous, since the expression for k_{iH} involves a small difference between two velocity constants which are both subject to large experimental error. Moreover, the value of $K_{eq.}$ is uncertain : the exchange reaction is slow and is accompanied by a side reaction which produces a pronounced turbidity in the solutions subjected to long heating. Indeed, the value quoted is justified only by the fact that it satisfies the requirements of the velocity data, and also, of course, by the identity of k_{iH} and $k_{rac.}$.

The burden of proof of the suggested mechanism of the racemisation therefore rests solely on the experiments with the deutero-acid : the experiments with the ordinary acid are not incompatible with the theory, but can be given no weight as direct evidence. The comparison of k_{iH} (assumed identical with $k_{rac.}$) and k_{iD}, however, is probably free from this uncertainty, and it can be stated that under the experimental conditions employed, hydrogen ionises 4·5 times as fast as deuterium.

EXPERIMENTAL.

Preparation of Materials.—Phenyl-*p*-tolylacetic acid was prepared by the method of McKenzie and Widdows (*loc. cit.*) and purified by crystallisation from dilute acetic acid; m. p. 115°. The cinchonidine salt (1 : 1) was prepared and crystallised from alcohol, but an extensive series of crystallisations failed to produce the *d*-acid in an optically pure condition. Eight successive crystallisations gave an acid of $[\alpha]_D = 13·0°$ which was used in the second series of racemisation experiments (Found : equiv., by titration, 226·4. Calc. : 226·1).

Phenyl-*p*-tolyldeuteroacetic acid was prepared by dissolving the anhydrous normal sodium salt (12 g.) in 20 g. of deuterium oxide (97%) containing an equivalent amount of sodium deuteroxide produced by the previous action of sodium amalgam on the solvent. The solution was heated at 100° for 2 days, the alkali neutralised by treatment with carbon dioxide, the solvent recovered, and the resulting sodium salt dried in a vacuum. The process was repeated with 99·6% deuterium oxide, and the deutero-acid extracted and purified. The cinchonidine salt was prepared and crystallised twice from alcohol; samples of partially active acid were recovered from the crop and mother-liquor and had the following properties : *d*-Acid, 2·3 g., $[\alpha]_D = 4·5°$ (Equiv., by titration, 227·7. Calc. : 227·1); % deuterium in α-position, 98·5. *l*-Acid, 2·2 g., $[\alpha]_D = -5·1°$ (Equiv., by titration, 226·6); % deuterium in α-position, 99·9.

The other materials were prepared by the usual methods.

Racemisation and Exchange Experiments.—In order to eliminate the difficulty of the removal of the alkaline catalyst by attack on glass reaction vessels, the solutions were heated in pure silver capsules of such a size as to slip easily into ordinary Pyrex boiling-tubes. After introduction of a portion of the solution under examination (about 10 c.c.), each tube was sealed and transferred to a boiling water-bath. There was little tendency for the solvent to distil out of the capsule into the annular space between the latter and the boiling-tube, and the possibility of appreciable error due to this effect may be neglected.

After the determined period of heating for a given sample, the tube was opened, the solution transferred (after filtration, if necessary) to a 2-dm. polarimeter tube, and the activity measured. This was immediately followed by transfer to a solvent-recovery apparatus similar to that described in Part II (*loc. cit.*), in which the solution was first treated with dry carbon dioxide until a sample withdrawn was found to be neutral to phenolphthalein. The solvent was then removed, the residue being heated to 130° during the later stages of the process. The dry residue was scraped out and transferred to a boat, which was heated to 150° in a high vacuum until the last traces of sodium bicarbonate had been destroyed. Combustion of the sodium salt was carried out in oxygen, and the combustion water finally collected in vacuum, in a thin-ended sampling tube similar to that described in Part II (*loc. cit.*).

Isotopic Analysis.—This was carried out by a density method similar to that already described, but much simplified. The elaborate cleaning of the apparatus and the preliminary heating of the sample with silver oxide previously used have been entirely discarded without any appreciable loss in accuracy. The dilution of the combustion waters, which was necessary in the case of the " heavier " samples, was carried out in a closed vessel containing a suitable amount of diluent tap-water, a trace of silver oxide and the sampling tube containing the heavy sample. After distillation of the tap-water into the purification apparatus, the loss in weight of the dilution vessel was determined. The sampling tube was then broken, the heavy sample distilled into the same receiver, and the dilution vessel weighed again. Admission of air to the sample was avoided, and the removal of the dilution vessel from the apparatus for the purpose of weighing was facilitated by suitable taps and ground connexions.

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