19. *Prototropy in Relation to the Exchange of Hydrogen Isotopes. Part III. Comparison of the Rates of Racemisation and of Hydrogen Exchange in a ψ-Acidic Ketone.*

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According to the ionisation theory of prototropy the rates of enolisation of ψ-acidic ketones should equal their rates of ionisation. Two methods of measuring the rates of enolisation of ketones have been used in the past, *viz.*, by observations on bromination and on racemisation, and it has been shown that both methods give the same result. The rate of ionisation can be measured by observing the rate of hydrogen exchange with a readily ionising solvent. In order to make the observation quantitatively unambiguous it is convenient that the whole of the ionising hydrogen of the solvent should be deuterium. For satisfactory comparison with the former types of measurement it is therefore necessary to repeat either the bromination or the racemisation experiments in the deuterium solvent, inasmuch as the rates of reactions are appreciably affected by the isotopic nature of the solvent independently of whether or not the solvent is a reactant. The rates of racemisation and of deuterium uptake of *l*-phenyl β-*n*-butyl ketone in deuterium oxide–dioxan, with catalysis by deuteroxide ions, have been measured and found equivalent. It is concluded that bromination, racemisation and hydrogen exchange are all controlled by the same fundamental process, which is the ionisation of the ketone.

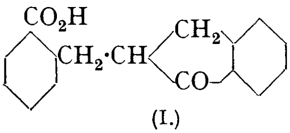
According to the ionisation theory of prototropy, ψ-acids, such as enolisable ketones and primary and secondary nitro-compounds, constitute a particularly simple set of cases for the quantitative study of mechanism. The special simplicity arises from the circumstance that equilibrium between a ψ-acid and its ions is established relatively slowly, whereas the same ions come into equilibrium with the true acid, *e.g.*, the enol or *aci*nitro-compound, practically instantaneously.

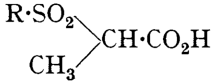
$$\psi\text{-Acid} \underset{\text{slow}}{\rightleftharpoons} \text{Ions} \underset{\text{fast}}{\rightleftharpoons} \text{True acid}$$

This means that, if a pair of ions, formed from the ψ-acid, reunite, they nearly always form the true acid and very seldom regenerate the ψ-acid. Thus, whereas in prototropy generally the rate of ionisation of one individual is greater by some unknown factor than the rate of its conversion into its isomeride, in the particular case of ψ-acidic systems the rate of ionisation of the ψ-form may be set equal to the rate of its isomerisation.

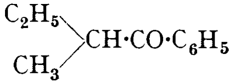
It is universally accepted that a large class of hydrogen exchanges, typified, for instance, by the exchange between acetone and water, are dependent on hydrogen ionisation, and hence the opportunity is furnished for a further test of the ionisation theory of prototropy : the test consists in comparing the rate of hydrogen exchange with the rate of isomerisation, where, as in a ψ-acid, the rate of isomerisation should equal the rate of ionisation. For instance, we can measure the rate of enolisation of acetone through the rate of its uptake of halogen in aqueous solvents, and, if the ionisation theory is right, this rate should be the rate of ionisation. The rate of hydrogen exchange between acetone and water will certainly measure the rate of ionisation of the acetone, not that of the water which is almost instantaneously ionised. Hence these two rates should be identical for given conditions of temperatures, solvent and catalysis. No test of this character appears as yet to have been made.

We already know of two methods of measuring the rate of enolisation of a ψ-acidic ketone, and it is established that they agree. The first is the bromination method, due essentially to Lapworth. The second is applicable when the ketone is optically active and the enol necessarily inactive, for we can then study the change by measurement of the rate of racemisation. The agreement between these two methods was first shown (Ingold and Wilson, J., 1934, 773; Hsü and Wilson, J., 1936, 623) in the example of the ketone (I), and has been confirmed for the carboxylic acids (II) (Ramberg, Mellander, and Hedlund, *Arkiv Kemi, Min. Geol.*, 1934, **11**, B, Nos. 31, 41; 1936, **12**, A, No. 1), and for the ketone (III) (Bartlett and Stauffer, *J. Amer. Chem. Soc.*, 1935, **57**, 2580).


(I.)


$\begin{matrix} R\cdot SO_2 \\ CH_3 \end{matrix}\!\!>\!CH\cdot CO_2H$

(II.)


$\begin{matrix} C_2H_5 \\ CH_3 \end{matrix}\!\!>\!CH\cdot CO\cdot C_6H_5$

(III.)

In contemplating the comparison of the enolisation rate, measured in either of these ways, with the rate at which the mobile hydrogen undergoes ionic interchange with isotopically labelled, ionisable hydrogen of the medium, we are confronted by an initial difficulty owing to the circumstance that for effective comparison the solvent must be the same : it is not enough that the solvents are isotopic modifications of the same compound, for it is known that the rates of reactions generally, even those which are not dependent on hydrogen exchange, are considerably altered by the substitution of deuterium for protium in the solvent. The above-mentioned bromination and racemisation experiments have, of course, been carried out in ordinary "light" solvents. If we attempt to maintain a substantial identity of solvent by employing for the proposed hydrogen exchange experiments a medium containing only a few units % of its hydrogen in the form of deuterium, we introduce another difficulty, since it has been established that, in one and the same reaction, protons and deuterons are transferred at different specific rates and we do not at the outset know the ratio of these rates. We want to deduce from the experiment the rate at which *original* protons are removed from the ketone; but if, in a mixed protium–deuterium solvent, the places vacated by these protons are going to be filled by protons and deuterons in a ratio bearing no known relation to the isotopic composition of the solvent, we are no further forward. The simplest way round this difficulty is to employ, in conjunction with the ordinary "light" ketone, a large excess of a protium-free deuterium solvent, so that *every* proton removed from the ketone has its place taken by a deuteron; then a determination of the deuterium uptake will accurately measure the extent of the separation of original protons. But, when comparison is made with the former experiments, the scheme outlined involves a change of solvent, the effect of which on the speed of reaction cannot be disregarded. Therefore the only way of making the comparison satisfactory is to commence by repeating one of the former experiments, a bromination or a racemisation, in a protium-free deuterium solvent, and then to use the same solvent for the measurement of hydrogen exchange.

This has been done with the ketone (III), which was chosen in preference to any acidic substance in order to avoid the complication of an exchangeable carboxylic hydrogen atom. Basic catalysis was employed in preference to acid catalysis, because of the greater theoretical simplicity of the former. We had intended to establish our reference rate in duplicate by measuring both the bromination and the racemisation rates in the pure deuterium solvent, but it turned out that rates convenient for measurement were attained only with more strongly basic catalysts than can be used in association with halogens; our reference rate is therefore based on measurements of racemisation. The solvent, both for these measurements and for those on hydrogen exchange, was a mixture of dioxan and deuterium oxide (about 2 : 1). The catalyst was sodium deuteroxide (about 0·13N), and the temperature 35·0°. The reaction was allowed to run for various known times in the thermostat, and was then stopped by large dilution with water, a process shown to cause no error; the isolated ketone was first polarimetrically examined and then burnt. The density of the combustion water gave, of course, the deuterium content of the whole of the hydrogen of the compound, and this value had to be multiplied by 14 in order to obtain the proportion of deuterium in the single position in which the hydrogen is exchangeable. Both sets of results, which conform to the first-order rate law, are included in the following table.

Comparison of the Rates of Racemisation and Hydrogen Exchange of l-*Phenyl* β-n-*Butyl Ketone in Deuterium Oxide–Dioxan containing Sodium Deuteroxide.*

Time (hours)		0·00	1·00	2·00	3·25	4·00	6·50
Racemisation	α_D (l = 10 cm.)	−4·43°	−3·92°	−3·12°	−2·62°	−2·38°	−1·54°
	Activity loss (%) [*R*]	0·0	11·6	27·3	40·9	46·2	65·2
Hydrogen exchange	Combn. H_2O : Δ*d* (p.p.m.)	—	774	1887	2952	3152	4380
	Combn. H_2O : D (atoms %) *	—	0·72	1·76	2·75	2·94	4·08
	Labile atom : D (atoms %) [*E*]	—	10·1	24·6	38·5	41·2	57·1
Activity loss/D uptake [*i.e.*, *R*/*E*]		—	1·15	1·11	1·06	1·12	1·14

* The figures in the corresponding line in the table of a former paper (Ingold, de Salas, and Wilson, J., 1936, 1334) are wrong by a constant factor (to correct, divide by $1{\cdot}08^2$). This makes no material difference, as it was not these derived figures but the observed densities (also tabulated) that were used in the calculations given.

As the last line of the table shows, racemisation proceeds rather uniformly about 12% faster than corresponds to the apparent rate of hydrogen exchange. This small difference can be explained as follows. The material which has hitherto been called pure deuterium oxide was not, in fact, quite pure. We at first believed the specimen used to contain 99·95 atoms % of deuterium, but, when it was too late to retract, an actual measurement of density showed the deuterium content to be only 99·16 atoms %. Furthermore, owing to the liberation of protons from the ketone during the experiments, the deuterium content, averaged through a run, of the aqueous part of the solvent was still lower, ranging in the different runs between 98·9% and 99·1%; thus for the whole series it is true to say that approximately 1% of the available hydrogen of the medium consisted of protium. Now all who have observed the relative rates at which protons and deuterons are transferred in various reactions agree that protons are transferred considerably more rapidly than deuterons: estimates of the ratio of the rates in different cases vary from 3 to "more than 10" (Wynne-Jones, *J. Chem. Physics*, 1934, **2**, 381).

If we make the reasonable assumption that in our case the ratio is 12, this would exactly account for the residual discrepancy; for, while the 99% of deuterium in the available solvent hydrogen were occupying 99, the 1% of protium would occupy not 1 but 12, out of every 99 + 12 vacant places in the ketone; so that the rate of loss of protons from initial combination with carbon would be 111/99 times the rate of deuteron uptake, *i.e.*, it would be 12% greater. In the circumstances we think that the correct conclusion to draw from the experiments is that the rates compared are equal to within the error of experiment.

We may summarise the conclusions reached as a result of this and the previous work on the rates of the reactions of enolisable ketones by means of the following scheme:

$$\begin{array}{rl} \text{Bromination in} & \left.\text{``light'' solvent}\right\} \text{ proved equal} \\ \text{Racemisation in} & \left\{\begin{array}{l}\text{``light'' solvent}\\ \text{``heavy'' solvent}\end{array}\right. \\ \text{Hydrogen exchange in} & \left.\text{``heavy'' solvent}\right\} \text{ proved equal} \end{array}$$

It seems clear from these results that all these reactions are controlled by the same fundamental process, and there is no cause to doubt that this is the ionisation of the ketone.

EXPERIMENTAL.

l-*Phenyl* β-n-*Butyl Ketone*.—*dl*-β-*n*-Butyl alcohol was successively converted by known methods into the chloride and carboxylic acid, the second step being modified by the employment of solid carbon dioxide instead of the gas in the Grignard reaction. Resolution of the acid through the brucine salt by Schütz and Marckwald's method (*Ber.*, 1896, **29**, 52) gave, after one crystallisation of the salt, 55·9% of the acid with $\alpha_D(l = 10\text{ cm.}) - 2{\cdot}40°$, whilst the salt from the mother-liquor yielded 38·4% of acid with $\alpha_D(l = 10\text{ cm.}) + 3{\cdot}50°$. The *l*-acid was converted (Bartlett and Stauffer, *loc. cit.*) successively into its chloride and the phenyl ketone, which had b. p. 64°/0·02 mm., $\alpha_D(l = 10\text{ cm.}) - 4{\cdot}43°$ (Found: C, 82·3; H, 8·58. Calc.: C, 81·5; H, 8·64%).

Racemisation and Hydrogen Exchange.—Equal portions of the *l*-ketone (1·463 g.), delivered from a pipette, were heated severally in sealed bulbs for known times at 35·00° ± 0·01° with mixtures of well-dried dioxan (20·0 c.c.) and 99·16% deuterium oxide (9·0 g.), in which sodium (0·0861 g.) had previously been dissolved, the weight of sodium being standardised by passing wire through a length of capillary tubing and cutting off the projecting ends. The rest of the technique has been outlined in the introduction or in previous papers, the method of combustion being that described by Wilson (J., **1936**, 1552; cf. also J., **1934**, 493, 1593; **1935**, 492; **1936**, 1328, 1550). The pyknometer employed was a little smaller than usual, *viz.*, 0·6 c.c. The accuracy of the density measurements was ± 2 p.p.m., and of the polarimetric readings ± 0·01°.

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