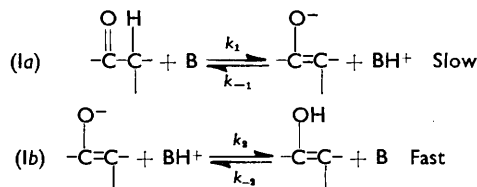


410. Deuterium Isotope and Solvent Effects in the Base-catalyzed Keto-Enol Transformation of Methylacetylacetone (3-Methylpentane-2:4-dione).

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The rates of bromination of methylacetylacetone (3-methylpentane-2:4-dione) and of its 3-deutero-analogue have been measured at 25° in water and D₂O with the basic catalysts water and acetate ion. When the solvent and catalyst are the same, the monodeutero-ketone reacts about four-fold more slowly than the proton compound. With either of the catalysts the ratio of the rates of bromination of a given compound in the two solvents, k^H/k^D , is about 1.3. For acetate ion as catalyst this value must be due to a pure solvent effect. If the same solvent effect enters for the water-catalyzed reaction one can conclude that the base strengths of H₂O and D₂O are the same. Data on the keto-enol equilibrium for the two solvents permit calculations of the rates of the reverse, ketonization reactions. Since the mechanism of this reverse reaction is known, one can also calculate rate ratios for the slow acid-catalyzed formation of ketone from the enolate ion. The interesting result is that the k^H/k^D ratio for catalysis by acetic acid is about 6. Combination of these and related data permits a detailed analysis of the acid-base properties of H₂O and D₂O and their ions.

MEASUREMENT of relative rates in the solvents D₂O and H₂O is frequently utilized in studies of the mechanisms of acid and base catalysis and data are available for a variety of reactions.^{1,2} Even so, there is still a lack of data for reactions of known mechanism and this is perhaps the more serious for catalysis by bases. In this paper we present results for the reversible, base-catalyzed transformation of ketones into enols. The mechanism for this reaction is quite firmly established as:^{3,4}



It is usual to follow reaction (1a) by measuring the rate of halogen uptake, since the enolate ion which is formed is halogenated almost instantaneously. The reaction is subject to general base-catalysis and rate data are available for a variety of ketones and catalysts.^{5,6,7} A few studies of hydrogen-isotope effects have also been reported. Reitz and Kopp⁸ showed that the reaction of [6-²H]acetone in aqueous solution, catalyzed by acetate ion, was about 7-fold slower than that of ordinary acetone. (A similar ratio also holds for catalysis in ordinary water by the acids acetic and hydrogen ion.) The bromination of acetone, catalyzed by acetate ion, is 1.15 times faster in H₂O than in D₂O.⁸ This must be a pure "solvent effect" since both the reactant and the catalyst are identical for the two solvents.

Nachod⁹ has studied both the rate of bromination of the ketone and the keto-enol

¹ Bell, "Acid-Base Catalysis," Oxford Univ. Press, 1941, Chap. VII.

² Wiberg, *Chem. Rev.*, 1955, **55**, 713.

³ Hammett, "Physical Organic Chemistry," McGraw Hill Book Co., New York, 1940, Chap. IV.

⁴ Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Chap. X, 1953.

⁵ Dawson and his co-workers, *J.*, 1929, 1884, and earlier.

⁶ Pederson, *J. Phys. Chem.*, 1934, **38**, 999, and earlier.

⁷ Bell and his co-workers, *Proc. Roy. Soc.*, 1949, *A*, **197**, 308, and earlier.

⁸ Reitz and Kopp, *Z. phys. Chem.*, 1939, *A*, **184**, 429.

⁹ Nachod, *Z. phys. Chem.*, 1938, *A*, **182**, 193.

equilibrium for the β -diketone, 3-methylacetylacetone, in solutions of hydrochloric acid in H_2O and D_2O . The kinetic data were reported to be for catalysis by hydrogen ion, but it is now known that they are really for base catalysis by the solvent water since this and similar β -diketones show only base-catalyzed enolization.^{10,11} Nachod's results are not directly comparable with those for acetone since his kinetic data are actually for the hydrogen compound in water and for the monodeutero-compound, $\text{CH}_3\cdot\text{CO}\cdot\text{CDMe}\cdot\text{CO}\cdot\text{CH}_3$, in D_2O , *i.e.*, for the "equilibrated" mixtures.

3-Methylacetylacetone is a favourable compound for study because only one hydrogen atom is normally replaced by bromine (or by deuterium), and because it is possible to obtain data for both the forward and the reverse reactions. We have consequently repeated Nachod's measurements and have extended them to include other catalysts and other reactions. Table 1 summarizes the kinetic results for the bromination of the ketone. In this and in subsequent discussions the symbol KH is used for the protonated ketone and KD for the ketone which has the single active hydrogen atom replaced by deuterium (similarly ED will refer to the enol with the hydroxyl hydrogen replaced by D). Finally, the solvents H_2O and D_2O are indicated by the superscripts H and D respectively. The k_1 values of Table 1 are for the second-order reaction of ketone and catalyst; those for acetate ion are calculated after subtraction of the contribution of the water reaction to the observed rate.

TABLE 1. *Rate of bromination of methylacetylacetone in H_2O and D_2O at 25°.*

No.	Reactant	Solvent	Catalyst	k , obs. ($\text{sec.}^{-1} \times 10^5$)	k_1 , calc.* (1. mole $^{-1}$ sec. $^{-1} \times 10^5$)
1	KH	H_2O	H_2O	9.6	0.173
2	KH	D_2O	D_2O	7.0	0.126
3	KD	H_2O	H_2O	2.75	0.049
4	KD	D_2O	D_2O	2.1	0.038
5	KH	H_2O	0.2M-NaOAc	155	725
6	KH	D_2O	0.2M-NaOAc	123	580
7	KD	H_2O	0.2M-NaOAc	28	125
8	KD	D_2O	0.2M-NaOAc	23	104

* Calc. for water catalysis from $k_1 = k/55.5$.

Information is available from earlier studies for reactions 1 and 4 of Table 1. Our results for reaction 1 agree fairly well with those of Nachod⁹ and of Pearson and Mills.¹¹ However, for reaction 4, Nachod's data lead to $k = 0.00004$, which is twice as large as our value. We do not know the reason for this discrepancy.

The data of Table 1 lead to the following ratios for the reaction of KH in the two solvents:

$$(k^{\text{H}}/k^{\text{D}})_{\text{H}_2\text{O}} = 1.37 \text{ and } (k^{\text{H}}/k^{\text{D}})_{\text{OAc}^-} = 1.25$$

The ratio for the acetate ion as catalyst is similar to that reported for the bromination of acetone⁸ and again indicates that the pure "solvent effect" leads to slightly faster reaction in H_2O than in D_2O . It is then of considerable interest that virtually the same ratio is observed for catalysis by water as by acetate ion. Since ratios of close to 1.3 are also found for reaction of the monodeutero-compound with the two catalysts, it seems safe to conclude that this value represents a general solvent effect for the reactions of ketones in H_2O as compared with those in D_2O .

The other ratios of interest are those for reaction of the ordinary and deuterated ketones. For reaction in the same solvent, ordinary water, these are:

$$(k^{\text{H}}_{\text{KH}}/k^{\text{H}}_{\text{KD}})_{\text{H}_2\text{O}} = 3.5 \text{ and } (k^{\text{H}}_{\text{KH}}/k^{\text{H}}_{\text{KD}})_{\text{OAc}^-} = 5.8$$

Ratios for reaction in the solvent D_2O are essentially the same as these. Since the reaction involves rupture of a carbon-hydrogen bond, these large ratios are the expected

¹⁰ Bell and Lidwell, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88.

¹¹ Pearson and Mills, *J. Amer. Chem. Soc.*, 1950, **72**, 1692.

result. They are in fact quite similar to those found for related systems.^{2,8} The substantial difference in the ratios for the catalysts water and acetate ion is unexpected but appears to be real.

For some purposes it is useful to have the related ratios for the "equilibrated" systems, *i.e.*, for reaction of KH in H₂O relative to that of KD in D₂O. The values are

$$(k^H_{KH}/k^D_{KD})_{H_2O} = 4.6 \text{ and } (k^H_{KH}/k^D_{KD})_{OAc^-} = 6.9$$

They are slightly larger than the previous values because they include both the above isotope effect and the previously discussed solvent effect.

Two chemical equilibria are involved in this keto-enol reaction. One is that for ionization of the enol as an acid. For the enol in water the value of K^H_{EH} is given as 5×10^{-10} by Pearson and Mills.¹¹ The ionization constant for the deuterio-enol (ED) in D₂O has not been measured but on the basis of the data from studies with both carboxylic acids¹² and phenols¹³ it is reasonable to assume that the ratio K^H_{EH}/K^D_{ED} is approximately 3. The other equilibrium of interest is the overall equilibrium between the keto- and the enol form. Table 2 gives available data for the two solvents.

TABLE 2. Values of $K_{eq} = C_{enol}/C_{ketone}$ for methylacetylacetone at 25°.

Source	$\frac{C_{EH}}{C_{KH}}$ (in H ₂ O)	$\frac{C_{ED}}{C_{KD}}$ (in D ₂ O)	K^H_{eq}/K^D_{eq}
Nachod ⁹	0.0373	0.0254	1.5
Schwarzenbach <i>et al.</i> ¹⁴	0.028	—	—
Pearson ¹¹	0.032	—	—
This research	0.037	0.025	1.5
This research	—	—	1.25 ^a
Best values	0.034	0.025	1.35 ^b

^a From spectroscopic comparison of the equilibrium solutions; see experimental. ^b From the quoted best values for K^H and K^D .

The overall equilibrium constant can be written

$$K_{eq} = C_{enol}/C_{acetone} = k_i/k_{-i}$$

where k_i and k_{-i} are the second-order rate coefficients for reaction of ketone with catalyst and of enol with catalyst respectively. In terms of mechanism (I), k_i is identical with k_1 whereas k_{-i} involves both k_{-1} and the equilibrium constant for step (Ib). Value of the overall coefficient k_{-i} can, however, be calculated directly from the k_1 and K_{eq} values of the previous tables, and data for the four reactions for which calculations can be made are listed below:

Reaction	$10^5 k_{-i}$ (l. mole ⁻¹ sec. ⁻¹)	k^H_{EH}/k^D_{ED}
EH + H ₂ O (in H ₂ O)	5.1	3.4
ED + D ₂ O (in D ₂ O)	1.5	—
EH + OAc ⁻ (in H ₂ O)	21,000	5
ED + OAc ⁻ (in D ₂ O)	4200	—

For the ketonization, just as for reaction of the "equilibrated" ketones, the k^H_i/k^D_i ratios are considerably greater than unity and not very dependent on strength of catalyst.

It seems reasonable to conclude that for general base-catalysis, independently of whether there is a one-step slow proton removal or whether a pre-equilibrium proton-transfer is involved, there will be no significant dependence of k^H/k^D ratio on base strength for bases of the weakness of acetate ion and water. It remains to be seen whether there will be a change in ratio for catalysis by the strong base OH⁻. However, the fact that $(k^H/k^D)_{OH^-}$ for the base-catalyzed ionization of nitroethane and nitropropane at 5° is not far from unity¹⁵ at least suggests that there will be no great change.

¹² Rule and LaMer, *J. Amer. Chem. Soc.*, 1938, **60**, 1981.

¹³ Martin and Butler, *J.*, 1939, 1366.

¹⁴ Schwarzenbach and Felder, *Helv. Chim. Acta*, 1944, **27**, 1701.

¹⁵ Maron and LaMer, *J. Amer. Chem. Soc.*, 1938, **60**, 2588.

In sharp contrast to the situation for base-catalysis, there is good reason to believe that for general acid-catalysis the relative rates in H_2O and D_2O will depend markedly on the strength of the catalyst.¹⁶ For a pre-equilibrium proton-transfer this expectation is particularly easy to justify and is, in addition, borne out by experiment. However, for a one-step slow proton-transfer, which is the obvious alternative mechanism for general acid-catalysis, the situation is considerably less certain. It is therefore of some importance that acceptance of the validity of mechanism (I) guarantees that an acid-catalyzed slow proton-transfer enters for the slow step of the reverse reaction. Furthermore, the available data permit calculation of the individual k_{-1} values for this step, *i.e.*, for the reverse of reaction (Ia), and also of the k^H/k^D ratios. From the mechanism it follows that the ratios for the two catalysts are given by

$$\begin{aligned} (k^H_{E^-}/k^D_{E^-})_{H_3O^+} &= (k^H_{KH}/k^D_{KD})_{H_2O} (K^D_{eq}/K^H_{eq}) (K^D_{ED}/K^H_{EH}) \\ (k^H_{E^-}/k^D_{E^-})_{HOAc} &= (k^H_{KH}/k^D_{KD})_{OAc^-} (K^D_{eq}/K^H_{eq}) (K^D_{ED}/K^H_{EH}) (K^H_{HOAc}/K^D_{DOAc}) \end{aligned}$$

All but one of the ratios on the right side of these equations are known and for this one the assumption that $K^H_{EH}/K^D_{ED} = 3$ is highly plausible. However, it is worth emphasizing that if one wishes the "ratio of the ratios" (to determine the dependence of ratio on strength of catalyst) the only terms which enter are the ratio of rate coefficients for KH relative to KD and the relative ionization of acetic acid in H_2O and D_2O . Both of these are quite firmly established.

TABLE 3. Results for acid catalysis by one-step slow proton-transfer.

Values of k_{-1} (l. mole ⁻¹ sec. ⁻¹)	Ratios
$k^H_{E^-+H_3O^+} = 5.6 \times 10^6$	} $(k^H_{E^-}/k^D_{E^-})_{H_3O^+} = 1.1$
$k^D_{E^-+D_3O^+} = 5.0 \times 10^6$	
$k^H_{E^-+HOAc} = 7.3 \times 10^8$	} $(k^H_{E^-}/k^D_{E^-})_{HOAc} = 5.6$
$k^D_{E^-+DOAc} = 1.3 \times 10^8$	

The important conclusion is that for this slow proton-transfer, just as for a mechanism with a pre-equilibrium proton-transfer, the k^H/k^D ratio is considerably larger for catalysis by a weak acid than for catalysis by the solvated proton. The further conclusion is that the binding of a proton to a weak base species such as acetate ion is of a considerably different character from that which binds the proton from a strong acid to the solvent. In this sense it may be somewhat misleading to utilize the specific formula H_3O^+ for the latter species.

The k^H/k^D ratio in Table 3 for catalysis by hydronium ion lends support to the expectation that studies with this catalyst can aid in determining mechanisms of general acid-catalysis. For a mechanism with a pre-equilibrium proton-transfer, and where the hydrogen atom which is ultimately removed does not exchange rapidly with the solvent, one can expect the $(k^H/k^D)_{H_3O^+}$ ratio to be considerably less than unity. (An example is the acid-catalyzed bromination of acetone for which this ratio is 0.45.⁸) For a mechanism with a one-step slow proton-transfer the usual assumption is that $(k^H/k^D)_{H_3O^+}$ will be unity or slightly greater, but no data have been available for reactions of established mechanism. The ratio in Table 3 provides an example and is in agreement with the usual assumption.

One of the most interesting aspects of the data of Tables 2 and 3 is their bearing on the properties of the solvents H_2O and D_2O . The self-dissociation of water can be conventionally written as $H_2O + H_2O = H_3O^+ + OH^-$. It is well known that the ion product for H_2O is about 6-fold larger than that for D_2O and there have been frequent speculations on the origin of this difference. The present kinetic data show that it is *not* due to a difference in base strength between H_2O and D_2O . Similar kinetic data for catalysis by hydroxide ion make it unlikely that there is any large difference in the base strengths of OH^- and OD^- ions. Finally, the analysis of the rates of formation of ketone from enolate ion indicates that the acids H_3O^+ and D_3O^+ are of virtually the same acid strength. The implication then is that the large difference in the ion products must be

¹⁶ Long and Bigeleisen, unpublished work.

almost entirely due to a difference in acid strength of H_2O compared to D_2O . This is not an unreasonable conclusion and is consistent both with expectations from a general analysis along lines developed by Bigeleisen¹⁷ and with the herein reported difference in catalytic effectiveness of another pair of weak acids, HOAc and DOAc.

EXPERIMENTAL

The 3-methylpentane-2 : 4-dione was prepared by Renfrow and Renfrow's procedure.^{11, 18} Fractionation of the yellow original product led to a pure colourless liquid (b. p. 172—174°; n_D^{20} 1.4440). A slow deterioration occurs on storage, since the yellow colour returns and, simultaneously, the material when dissolved in water gives a considerably more acidic solution than does the freshly prepared material. This decomposition is greatly retarded if the material is stored in the cold. There is no evidence that the decomposition products interfere with the kinetics, since identical rates were obtained from studies with fresh and old material.

The monodeutero-compound, 3-deutero-3-methylpentane-2 : 4-dione, was prepared by shaking the normal compound with a large excess of D_2O for several days, followed by extraction with light petroleum and then a second equilibration with D_2O . Examination in a mass spectrometer showed that only one of the ten possible hydrogen atoms had been replaced by deuterium, and this can safely be assumed to be the active 3-hydrogen atom. For the particular case of reaction in D_2O as solvent, the kinetic behaviour of this prepared compound was identical with that of the normal compound after equilibration.

Rates of reaction of the ketones were measured by following the rate of uptake of bromine with a "Unicam" spectrophotometer. This was done by measuring the change in optical density of the reaction mixture at 3900 Å. The reactions were carried out in the spectrometer, optical cells of 1 cm. path length being used. These were mounted in a cell holder in a thermostat which was kept at $25^\circ \pm 0.05^\circ$.

For most studies of the acetate-ion catalysis and for a few experiments on the water reaction, the starting concentrations of ketone and bromine were comparable (normally a slight excess of bromine) and of the order of 0.004 mole per l. When the reactants were mixed there was an initial very rapid reaction of the enol form of the material. This was followed by a typical first-order reaction of the ketone, *i.e.*, with a rate which was independent of bromine concentration. For most of the measurements on the water reaction a large excess of ketone was used, roughly 0.04M-compound to 0.001M-bromine. This gave zero-order kinetics; the desired first-order rate coefficient was calculated from the known initial concentration of ketone.

For the reaction of ketone with acetate ion it was found that there was a slow zero-order uptake of bromine after the calculated end of reaction was reached. Similar behaviour has been found by other investigators of the reactions of β -diketones and is presumably due to the entrance of a slow side reaction.¹⁹ It was assumed that this side reaction also occurred during the period of the normal bromination and appropriate corrections were made before calculating the rate coefficients.

All of the rate studies used for comparisons were made at ionic strength 0.2. The acetate-ion catalyst was added as sodium acetate, and the water reaction was normally studied in the presence of 0.05M-sulphuric acid and 0.15M-sodium chloride. In a few studies reactions were carried out with much higher concentrations of acid ranging up to 5M. There was virtually no change in the first-order rate coefficient, showing both that there is no acid catalysis and that the rate of the water reaction is not perceptibly influenced by the concentration of electrolyte.

Studies by Bell and his co-workers²⁰ on the base-catalyzed hydrolysis of several very similar β -diketones have shown that catalysis by hydroxide ion is not normally detectable at pH values smaller than 7. In the present case, all studies of acetate catalysis have been made in buffered solutions with acetate-ion concentrations of 0.2M or higher and with pH values of less than 5. Hence any contribution to the rate from a reaction with hydroxide ion can be safely ruled out. The results of a few approximate rate measurements with varying buffer ratios were in accord with this conclusion.

The accuracy of the kinetic results is best assessed by noting their reproducibility.

¹⁷ Bigeleisen, *J. Chem. Phys.*, 1949, **17**, 675.

¹⁸ Renfrow and Renfrow, *J. Amer. Chem. Soc.*, 1946, **68**, 1801.

¹⁹ Bell and Gelles, *Proc. Roy. Soc.*, 1951, *A*, **210**, 310.

²⁰ See especially: (a) Ref. 8; (b) Bell, *Trans. Faraday Soc.*, 1943, **39**, 253; (c) Bell, Gelles, and Möller, *Proc. Roy. Soc.*, 1946, *A*, **186**, 443.

Reference to Table 1 shows that all the rate coefficients (except for reactions 1 and 4) are easily reproducible to within 4%. In the case of reactions 3 and 8 both first-order and zero-order techniques were used and gave similar results. Wider deviations were found in the case of reactions 1 and 4. Ten determinations of the first-order rate constant for reaction 1 gave a mean value of $9.6 \times 10^{-5} \text{ sec.}^{-1}$, and there was a mean deviation of $0.6 \times 10^{-5} \text{ sec.}^{-1}$. The deviation among the results for reaction 4 was similar and the mean of eight determinations is given.

The data relating to the equilibrium between keto- and enol forms have been supplemented in two ways. First, Nachod's measurements⁹ on this equilibrium have been repeated. An excess of bromine was added to an equilibrated aqueous solution of the compound, kept at 0° to inhibit reaction of the keto-form. After 1 min. (to permit complete bromination of the enol), the bromine remaining was estimated by addition of potassium iodide and titration of the liberated iodine with sodium thiosulphate solution. The experiment was repeated with a solution of the deuterio-compound in D₂O. Secondly, the ratio of the keto-enol equilibrium constants in H₂O and D₂O was estimated directly by comparing extinction coefficients of the hydrogen- and deuterio-compound in H₂O and D₂O respectively at 2900 Å. The absorption which occurs at this wavelength is due to the enol content.²¹ It may be shown that the ratio of the extinction coefficients is related to the equilibrium constants in H₂O and D₂O as follows:

$$\frac{\epsilon_{\text{E}}^{\text{H}}}{\epsilon_{\text{E}}^{\text{D}}} = \frac{C_{\text{E}}^{\text{H}}}{C_{\text{E}}^{\text{D}}} = \left(\frac{K_{\text{eq}}^{\text{H}}}{K_{\text{eq}}^{\text{D}}} \right) \times \left(\frac{1 + K_{\text{eq}}^{\text{D}}}{1 + K_{\text{eq}}^{\text{H}}} \right)$$

In this case both equilibrium constants are very small and so the second ratio on the right-hand side approximates to unity. The ratio of the equilibrium constants is therefore simply the ratio of the extinction coefficients.

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²¹ Grossman, *Z. phys. Chem.*, 1924, **109**, 305.