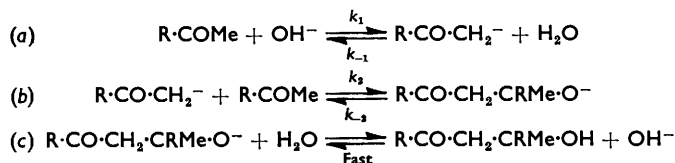


334. Deuterium Exchange in the Aldol Condensation of Acetaldehyde.

By R. P. BELL and MOYRA J. SMITH.

The aldol condensation of acetaldehyde has been carried out in borate buffers in deuterium oxide solution, and the amount of deuterium in the unchanged aldehyde has been studied as a function of aldehyde concentration and extent of reaction. The results are interpreted in terms of successive ionisation and condensation reactions, and values are obtained for the ratio of velocity constants and for the magnitude of the kinetic isotope effect.

It is generally agreed¹ that the aldol condensation of an aldehyde or ketone $R\cdot\text{COMe}$, catalysed by hydroxyl ions, takes place according to the following scheme:



where k_1 and k_2 are second-order velocity constants, and k_{-1} and k_{-2} are first-order velocity constants. The condensation of acetone ($R = \text{Me}$) is reversible, and there is good evidence that the slow step in both directions is reaction (b), reaction (a) being effectively at equilibrium. The evidence for this is two-fold: first, the condensation reaction is kinetically of the second order with respect to acetone, and secondly it was shown by Bonhoeffer and Walters² that the rate of deuterium exchange of acetone in alkaline deuterium oxide is very much greater than its rate of condensation to give diacetone alcohol, being in fact equal to its rate of ionisation as measured by its reaction with iodine. These facts are consistent with $k_2[R\cdot\text{COMe}] \ll k_{-1}$ in the above scheme, and lead to the prediction that the reaction should not exhibit general base-catalysis, but only specific catalysis by hydroxyl ions, since the slow step (b) does not involve a proton-transfer.³ This is consistent with the experimental facts, since the catalytic effect of ammonia and of primary and secondary amines (Miller and Kilpatrick⁴) is not a basic catalysis: tertiary amines and phenoxide ions do not catalyse this reaction⁵ and the effect of the other amines has been traced to the formation of addition products.⁶

The aldol condensation of acetaldehyde ($R = \text{H}$) is irreversible, and shows different kinetic behaviour. The later stages of the reaction are complicated by crotonisation and further polymerisation, but it was found by Bell⁷ that the reaction is essentially of the first-order with respect to acetaldehyde. Bell suggested originally that the slow step involved might be the reaction $\text{Me}\cdot\text{CH}(\text{OH})_2 \longrightarrow \text{Me}\cdot\text{CHO} + \text{H}_2\text{O}$, catalysed by hydroxyl ions, but later work⁸ showed that this reaction is much too fast to be rate-determining: moreover, aqueous solutions of acetaldehyde contain about 40% of unhydrated aldehyde,⁹ which on this hypothesis should react very rapidly. It seems certain that the slow step is in fact reaction (a) above, corresponding to $k_2[\text{Me}\cdot\text{CHO}] \gg k_{-1}$. This implies that if the reaction takes place in deuterium oxide, no deuterium should become attached to carbon,

¹ See, e.g., Frost and Pearson, "Kinetics and Mechanism," Wiley & Sons, New York, 1953, p. 291.

² Bonhoeffer and Walters, *Z. phys. Chem.*, 1938, **181**, A, 441.

³ Bell, "Acid-Base Catalysis," Oxford Univ. Press, 1941, p. 124.

⁴ Miller and Kilpatrick, *J. Amer. Chem. Soc.*, 1931, **53**, 3217.

⁵ French, *ibid.*, 1929, **51**, 3215.

⁶ Westheimer and Cohen, *ibid.*, 1938, **60**, 90; Westheimer and Jones, *ibid.*, 1941, **63**, 3283; Westheimer, *Ann. New York Acad. Sci.*, 1940, **39**, 401.

⁷ Bell, *J.*, 1937, 1637.

⁸ Bell and Higginson, *Proc. Roy. Soc.*, 1949, A, **197**, 141; Bell and Darwent, *Trans. Faraday Soc.*, 1950, **46**, 1; Bell and Clunie, *Proc. Roy. Soc.*, 1952, A, **212**, 33; Bell, Rand, and Wynne-Jones, *Trans. Faraday Soc.*, 1956, **52**, 1093.

⁹ Bell and Clunie, *ibid.*, 1952, **48**, 439.

agreeing with the observations by Bonhoeffer and Walters² on the aldolisation of 10M-acetaldehyde solution. General base-catalysis would also be predicted on this interpretation: this has not been detected, but few experiments have been carried out to test this point.

Recent work by Broche¹⁰ and by Broche and Gibert¹¹ has shown that the assumption $k_2[\text{Me}\cdot\text{CHO}] \gg k_{-1}$ is justified only for high aldehyde concentrations. They studied the initial reaction velocity over a wide range of aldehyde and hydroxyl-ion concentrations, and found that in the range $[\text{Me}\cdot\text{CHO}] = 0.1\text{--}0.5$ the order with respect to acetaldehyde was intermediate between 2 and 1, as would be predicted if $k_2[\text{Me}\cdot\text{CHO}]$ is of the same order of magnitude as k_{-1} . On this basis the reaction should be accompanied by isotopic hydrogen exchange at fairly low aldehyde concentrations, though not at the very high concentration used by Bonhoeffer and Walters.² The object of the present work was therefore to investigate deuterium exchange over a range of aldehyde concentrations.

EXPERIMENTAL

Kinetic and isotopic-exchange measurements were carried out at 25°.

Materials.—Acetaldehyde was distilled (b. p. 20.7—21°) in a current of oxygen-free nitrogen and condensed in a trap surrounded with solid carbon dioxide. It was immediately transferred and sealed in a number of small weighed bulbs previously swept out with nitrogen. These samples contained <0.2% of acid by titration, and gave a mass-spectrometer trace identical with that reported for pure acetaldehyde. Water used was twice distilled and freed from carbon dioxide by boiling it or by bubbling nitrogen through it. Deuterium oxide was supplied by the Norsk Hydro-Elektrisk Kvaestof A/S and contained 99.7% of D₂O. Many experiments were carried out with deuterium oxide recovered from previous experiments, purified, and distilled to a constant density corresponding to 93% of D₂O. Inorganic reagents were of "AnalaR" grade.

Isotopic-exchange Measurements.—In these measurements the acetaldehyde was allowed to react for a known time in deuterium oxide containing either sodium hydroxide or a buffer solution, and the reaction then stopped by adding a slight excess of hydrochloric acid. In principle the extent of isotopic exchange could be determined by isotopic analysis of the aldol formed, of the water, or of the unchanged acetaldehyde. For dilute solutions the last of these is the most suitable, since the acetaldehyde can be removed either by volatilisation in a current of nitrogen or by extraction with an organic solvent. In some preliminary experiments the reaction mixture was saturated with sodium chloride and extracted with bromobenzene. After drying of the extract the acetaldehyde was removed by a current of nitrogen and condensed by solid carbon dioxide for examination in the mass spectrometer. Although these experiments gave qualitative evidence of the presence of deuterated acetaldehyde, the mass spectrometer traces were difficult to interpret quantitatively, since the samples obtained invariably contained bromobenzene and impurities probably derived from the oxidation or polymerisation of the aldehyde.

In the method finally adopted, the acetaldehyde was removed in a current of nitrogen and absorbed in a solution of 2:4-dinitrophenylhydrazine. The hydrazone was filtered off and heated with pyruvic acid to regenerate the acetaldehyde, which was then oxidised; the resulting water was analysed for deuterium by density determinations. The detailed procedure was as follows.

Three small bubblers were connected in series by glass joints. The first contained the reaction solution after acidification (about 2 c.c.) and the second a two-fold excess of 0.015M-2:4-dinitrophenylhydrazine in 1.6N-hydrochloric acid. The exact concentration of this solution was determined by titration with 0.0125M-potassium iodate, according to the equation $5(\text{NO}_2)_2\text{C}_6\text{H}_3\cdot\text{NH}\cdot\text{NH}_2 + 4\text{KIO}_3 + 9\text{HCl} = 3(\text{NO}_2)_2\text{C}_6\text{H}_3\text{N}_2\text{Cl} + 2(\text{NO}_2)_2\text{C}_6\text{H}_3\text{I} + 4\text{KCl} + 2\text{ICl} + 2\text{N}_2 + 12\text{H}_2\text{O}$ (cf. Iddles,^{12, 13} Barker and Cole¹⁴), the end-point being detected by the disappearance of the iodine colour in a carbon tetrachloride layer. The third bubbler was a guard-tube containing sodium hydrogen sulphite solution, and any acetaldehyde escaping

¹⁰ Broche, "Colloque National de Cinétique," Strasbourg, 1953.

¹¹ Broche and Gibert, *Bull. Soc. chim. France*, 1955, 131.

¹² Iddles and Jackson, *Ind. Eng. Chem., Anal.*, 1934, **6**, 454.

¹³ Iddles, Rosen, and Hart, *ibid.*, 1939, **11**, 102.

¹⁴ Barker and Cole, *J. Appl. Chem.*, 1955, **5**, 477.

absorption in the second bubbler was titrated after the experiment by the procedure described by Friedemann, Cotonio, and Shaffer:¹⁵ the amount of acetaldehyde thus estimated was always negligible.

Oxygen-free nitrogen was passed through the three bubblers at about 40 c.c. per minute for $1\frac{1}{2}$ hr. Control experiments showed that this was sufficient to remove 98% of the acetaldehyde. The 2 : 4-dinitrophenylhydrazone was then filtered off through a sintered-glass crucible, washed with 2*N*-hydrochloric acid and water, and weighed after at least 12 hr. *in vacuo* over sulphuric acid. The weight of the hydrazone served as a measure of the extent of reaction in the original mixture, and a second estimate was made by titrating the 2 : 4-dinitrophenylhydrazine remaining in the filtrate with potassium iodate solution, as described above. The two estimates agreed within better than 2%, but control experiments showed that the amounts of acetaldehyde thus calculated corresponded to only $93 \pm 2\%$ of that present in the original solution, and this was allowed for in the calculations. The formation of the hydrazone does not involve the hydrogen atoms of the acetaldehyde, and it is therefore safe to assume that no isotope effect is involved in this reaction, and that the degree of deuteration is not affected by the incompleteness of the conversion.

In a few experiments the infrared absorption of the solid 2 : 4-dinitrophenylhydrazone was examined.* An ordinary specimen showed a peak at 1365 cm.^{-1} , corresponding to the symmetrical deformation vibration of the CH_3 group, also peaks at 1126 and 1144 cm.^{-1} . A specimen obtained from an aldol condensation carried to 75% completion in 97% deuterium oxide with 0.1*M*-acetaldehyde showed no peak at 1365 cm.^{-1} , but a new one at about 1138 cm.^{-1} : this can be ascribed to C-D deformations, and the spectrum indicates that a considerable amount of deuteration had taken place. A third specimen was obtained from a reaction carried to 75% completion with 2.5*M*-acetaldehyde, and showed weak bands at both 1365 and 1138 cm.^{-1} . These observations indicate (in agreement with later results) that some deuteration does take place, and that its extent is greater in more dilute solutions of aldehyde, but the method is not suitable for a quantitative study, especially as the important band at 1138 cm.^{-1} is obscured by those at 1126 and 1144 cm.^{-1} .

The normal oxidation procedure was carried out in a train of three small glass bubblers, of which the first two were fitted with cold fingers. In a typical experiment the first contained about 20 mg. of the dried hydrazone, together with about 0.1 g. of pyruvic acid and 3 c.c. of water. (Since no isotopic exchange takes place in acid solution between water and acetaldehyde or its hydrazone, the presence of water is not objectionable at this stage.) The second bubbler contained an oxidation mixture¹⁶ consisting of about 0.5 g. of potassium persulphate and 0.05 g. of silver nitrate in about 0.6 c.c. of water mixed with glass beads. The amount of water was accurately known, since it enters into the calculation of the extent of deuteration. The third bubbler contained sodium hydrogen sulphite solution to absorb unoxidised acetaldehyde, which was estimated by titration.¹⁴ In carrying out an oxidation the first bubbler was heated gently in a Bunsen flame and oxygen-free nitrogen passed for an hour at 20 c.c. per minute. The second bubbler was then heated to $70\text{--}78^\circ$ and kept at this temperature until the black oxidation mixture had become colourless, usually about 20 min. Control experiments showed that under these conditions $95 \pm 1\%$ of the acetaldehyde was removed from the sample of hydrazone and transferred to the second bubbler, and that all the acetaldehyde remaining in the second bubbler was oxidised to carbon dioxide and water. On the other hand a considerable amount of acetaldehyde (about 30%) passed unchanged through the oxidation mixture: however, this was absorbed and titrated in the third bubbler and could be allowed for in making the final calculation. In these reactions the isotopically substituted hydrogen atoms of the acetaldehyde are not involved until the last stage in which acetic acid is oxidised to carbon dioxide and water. Control experiments showed that no acetic acid escaped oxidation, and there is therefore no danger of an appreciable isotopic discrimination in the conversion of the acetaldehyde into water.

The water in the oxidation mixture was distilled off into a trap surrounded by solid carbon dioxide, and distilled a second time after being made alkaline with sodium hydroxide. A final

* These measurements were carried out by Mr. O. G. Malan of this laboratory, to whom our thanks are offered.

¹⁵ Friedemann, Cotonio, and Shaffer, *J. Biol. Chem.*, 1927, **73**, 342.

¹⁶ Calvin, Heidelberg, Reid, Tolbert, and Yankwich, "Isotopic Carbon," Wiley & Sons, New York, 1949, p. 94.

distillation was carried out at 1 mm., and it was found that further distillations produced no change in the density. Densities were determined by measuring the rate of fall of a drop of water in a column of *o*-fluorotoluene at 26.8°. A drop of constant size (about 8 mm.³) was formed below the surface of the *o*-fluorotoluene at the tip of a graduated capillary, and was detached by raising the capillary slowly out of the liquid. The *o*-fluorotoluene was contained in a vertical tube 50 cm. high and 1 cm. in diameter, and the falling drop was timed between two marks on the lower part of the tube 15 cm. apart. The time of fall for pure water was about 165 sec., the reproducibility being about ± 0.5 sec. The apparatus was calibrated with sucrose solutions of known density, and also with deuterium oxide solutions of known composition. The density changes measured were usually in the range 30—100 p.p.m., and in this range 1 p.p.m. produces a change of about 0.5 sec. in the time of fall. The same change would be produced by a temperature variation of 0.001°: the thermostat fluctuations did not exceed this over a period of a few hours, but there were larger variations over long periods. For this reason each estimation was coupled with a calibration in which two standard solutions were used closely bracketing the unknown density, which was then determined by linear interpolation.

Density changes were referred to boiled-out distilled water which had been subjected to the same distillation as the test samples. Control experiments showed that water of the same density (within 1 p.p.m.) was obtained when the whole procedure of an exchange experiment was carried out with ordinary distilled water in place of deuterium oxide.

All the exchange experiments were carried out in a buffer solution made by adding solid borax and concentrated sodium hydroxide solution to deuterium oxide in amounts sufficient to give a solution with $[D_3BO_3] = 0.02$, $[D_2BO_3^-] = 0.18$. This solution gives convenient amounts of reaction for times of a few hours, and is insensitive to traces of carbon dioxide. The results obtained are tabulated. Since the extent of deuteration is small in all the experiments it has been expressed in terms of the monodeuterated species $CH_2D \cdot CHO$.

Deuterium exchange in borate buffer solution at 25°.

a = Initial acetaldehyde concentration in moles/l.

x = Fraction of acetaldehyde converted into aldol.

y = Fraction of initial acetaldehyde appearing as monodeuteroacetaldehyde.

100 <i>a</i>	4.94	4.78	5.43	8.42	8.24	7.76	7.52	7.65	15.3	15.8	14.5	30.8	140
100 <i>x</i>	15	23	30	10	19	27	29	43	25	37	38	35	64
100 <i>y</i>	2.5	5.9	6.3	1.0	3.0	3.7	4.8	6.2	2.4	3.8	3.9	2.2	0.15

DISCUSSION

It is apparent from the Table that for a given initial concentration of acetaldehyde the percentage deuteration increases as the reaction progresses (at least for the first half of the reaction), while for a given extent of reaction it decreases with increasing acetaldehyde concentration, becoming almost zero with an initial aldehyde concentration of 1.4*M*. These findings are in qualitative agreement with the reaction scheme given in the introduction, and will now be treated quantitatively.

The buffer solution used contains three acid-base systems, D_2O-OD^- , $D_3O^+-D_2O$ and $D_3BO_3-D_2BO_3^-$, each of which can take part in the interconversion of the aldehyde molecule and its anion. However, since all the experiments were carried out in the same buffer solution, the forward and the reverse reactions can be characterised by first-order velocity constants k_1 and k_{-1} . The rate of production of the anion A^- from the aldehyde AH is thus $k_1[AH]$. As soon as some deuteration has taken place anions can also be produced from AD ; since a proton is always lost considerably more rapidly than a deuteron, the appropriate velocity constant will be taken as $\frac{2}{3}k_1$, the factor $\frac{2}{3}$ being a statistical factor for comparing the groups CH_2D and CH_3 . This gives $k_1([AH] + \frac{2}{3}[AD])$ for the rate of production of A^- , where A^- represents both $CH_2 \cdot CHO^-$ and $CHD \cdot CHO^-$. A^- can now react in two ways, either with the acids in the solution, which increases the deuterium content of the acetaldehyde, or with a second molecule AH or AD to give aldol. The rates of these two processes are respectively $k_{-1}[A^-]$ and $k_2[A^-]([AH] + [AD])$, where

¹⁷ Keston, Rittenberg, and Schoenheimer, *J. Biol. Chem.*, 1936, **122**, 227.

it is assumed that isotopic substitution does not affect the velocity constant k_2 for the condensation reaction. This gives the following expressions:

$$(1) \text{ Rate of deuteration} = \frac{k_1 k_{-1} ([\text{AH}] + \frac{2}{3} [\text{AD}])}{k_{-1} + k_2 ([\text{AH}] + [\text{AD}])}$$

$$(2) \text{ Rate of aldolisation} = \frac{2k_1 k_2 ([\text{AH}] + \frac{2}{3} [\text{AD}]) ([\text{AH}] + [\text{AD}])}{k_{-1} + k_2 ([\text{AH}] + [\text{AD}])}$$

where the factor of 2 in the second equation arises because each condensation reaction removes two molecules of acetaldehyde. However, equation (1) cannot be applied directly to our results, since we have measured only the deuterium in the remaining acetaldehyde, and not in the aldol, and must therefore allow for the removal of deuterium by the reactions $\text{CH}_2\text{D}\cdot\text{CHO} + \text{CH}_2\cdot\text{CHO}^-$, $\text{Me}\cdot\text{CHO} + \text{CHD}\cdot\text{CHO}^-$, and $\text{CH}_2\text{D}\cdot\text{CHO} + \text{CHD}\cdot\text{CHO}^-$.

Arguments similar to the above give:

$$(3) \text{ Rate of loss of deuterium} = \frac{\frac{2}{3}k_1 k_2 [\text{AD}] ([\text{AH}] + 2[\text{AD}])}{k_{-1} + k_2 ([\text{AH}] + [\text{AD}])} + \frac{k_1 k_2 [\text{AH}] [\text{AD}]}{k_{-1} + k_2 ([\text{AH}] + [\text{AD}])}$$

$$= \frac{\frac{5}{3}k_1 k_2 [\text{AD}] ([\text{AH}] + \frac{7}{6} [\text{AD}])}{k_{-1} + k_2 ([\text{AH}] + [\text{AD}])} \sim \frac{\frac{5}{3}k_1 k_2 ([\text{AH}] + \frac{2}{3} [\text{AD}])}{k_{-1} + k_2 ([\text{AH}] + [\text{AD}])}$$

The last approximation simplifies the subsequent calculation, and is legitimate since $[\text{AD}]$ never exceeds 6% of $[\text{AH}]$. From (1) and (3) we have the following expression for the net rate of formation of $\text{CH}_2\text{D}\cdot\text{CHO}$, introducing the symbols used in Table I:

$$(4) \quad \frac{dy}{dt} = \frac{k_1(1-x-\frac{1}{3}y)(k_{-1}-\frac{5}{3}k_2ay)}{k_{-1}+k_2a(1-x)}$$

Combining (2) and (4) gives

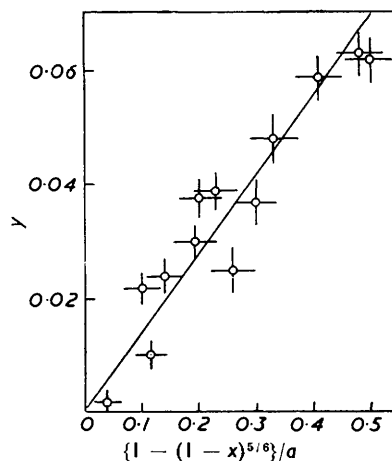
$$(5) \quad dy/dx = (k_{-1} - \frac{5}{3}k_2ay)/2k_2a(1-x)$$

and hence on integration

$$(6) \quad y = \frac{2}{5}\{1 - (1-x)^{5/6}\}k_{-1}/k_2a$$

which for small values of x reduces to $y = k_{-1}x/2k_2a$.

The Figure shows a plot of y against $\{1 - (1-x)^{5/6}\}/a$. Within the rather large experimental error the points corresponding to aldehyde concentrations 0.05—1.4M and 10—64% reaction fall on a single straight line, thus confirming the reaction scheme proposed. The slope of the line gives $k_{-1}/k_2 = 0.023$ mole l.⁻¹. The corresponding value in Broche's measurements¹⁰ in light water at 25° is 0.100, and if k_2 is the same in both solvents this gives $k_{-1}(\text{H}_2\text{O})/k_{-1}(\text{D}_2\text{O}) = 4.3$. If in our experiments all the deuteration is brought about by D_2O molecules (*i.e.*, if the aldolisation is catalysed specifically by OD^-), then 4.3 represents the ratio of the rates of proton and deuteron transfer from H_2O and D_2O molecules respectively. Actually there is some evidence from unpublished measurements in this laboratory that the aldol condensation exhibits appreciable general basic catalysis by borate ions: if this is so, some of the deuteration is brought about by D_3BO_3 molecules, and 4.3 is then a lower limit for the ratio $k_{-1}(\text{H}_2\text{O})/k_{-1}(\text{D}_2\text{O})$. There are no measurements of isotope effects for other reactions of H_2O and D_2O with anions, but the figure 4.3 is well below the maximum ratio 10.6 predicted for 25° from the zero-point energies of O-H and O-D bonds (*cf.*



Wiberg¹⁸). A full interpretation demands a further kinetic study in buffer solutions, and would also take into account the fact that the exchange experiments were carried out in 93% rather than 100% D₂O.

It is therefore concluded that the deuterium exchange observed during the aldol condensation of acetaldehyde is quantitatively consistent with a mechanism in which the consecutive steps become of comparable speed at low acetaldehyde concentrations, and with a kinetic isotope effect of reasonable magnitude.

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¹⁸ Wiberg, *Chem. Rev.*, 1955, **55**, 713.
