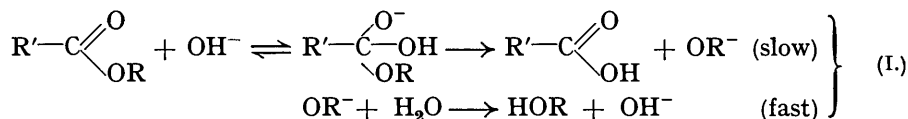**178.** *Mechanism of Hydrolysis of Carboxylic Esters and of Esterification of Carboxylic Acids. Acid Hydrolysis of an Ester with Heavy Oxygen as Isotopic Indicator.*

By S. C. Datta, J. N. E. Day, and C. K. Ingold.

The standard mechanisms for the alkaline and the acid hydrolysis of carboxylic esters are set forth (I, II, and III, see text). All have now been established by methods dependent on optical activity, on the principle of mesomerism, and on the principle of the chemical identity of isotopes. The final items of this evidence are furnished by observations in this and the following paper. It is shown in this paper that in the acid hydrolysis of methyl hydrogen succinate in heavy-oxygen water, the oxygen atom passes into the acidic, and not into the alcoholic, hydrolysis product.

THE experiments here reported are complementary to those of several other workers in a field which must be reviewed as a whole for the sake of perspective. The subject falls into three parts.
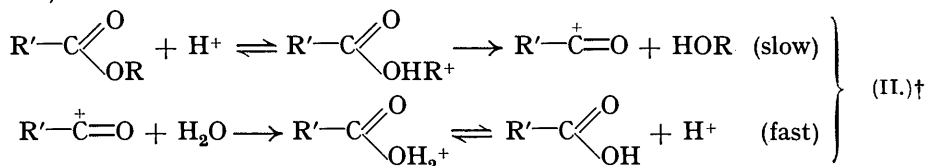
(i) *Alkaline Hydrolysis.*—This case is treated first because, from our present point of view, it is simple theoretically and complete experimentally. Modern views on reaction mechanism provide only one mechanism for the hydrolysis of carboxylic esters by hydroxide ions in water :

$$R'-C{\overset{O}{\underset{OR}{\lll}}} + OH^- \rightleftharpoons R'-\overset{O^-}{\underset{OR}{\overset{|}{C}}}-OH \longrightarrow R'-C{\overset{O}{\underset{OH}{\lll}}} + OR^- \quad \text{(slow)}$$
$$OR^- + H_2O \longrightarrow HOR + OH^- \qquad \text{(fast)}$$

$$\left. \right\} \quad \text{(I.)}$$

This mechanism implies fission of the original ester molecule in the position $R'\cdot CO\!\mid\!-OR$ with separation of OR, rather than according to the alternative $R'\cdot CO\cdot O\!-\!\mid R$ with separation of R.

Three proofs have been given that the molecule does really divide in this way. (1) The first uses a form of R which is asymmetric at the point of attachment, and assumes that, if liberated, R would not preserve its configuration; which it does in fact preserve during hydrolysis (Holmberg, *Ber.*, 1912, **45**, 2997). (2) The second selects a form of R, which, if liberated, would exhibit mesomerism and ultimately yield an isomeric alcohol; which is not in fact produced in hydrolysis (Prévost, *Ann. Chim.*, 1928, **10**, 147; Ingold and Ingold, J., 1932, 758). (3) The third uses water whose oxygen is distinguishable by the presence of an enhanced proportion of the heavier isotopes; and shows that oxygen from this source does not enter into the alcohol, and hence must enter into the acid, formed by hydrolysis (Polanyi and Szabo, *Trans. Faraday Soc.*, 1934, **30**, 508). Probably nobody would deny the assumptions underlying methods (1) and (2) (especially 2); but method (3) involves no assumptions, and therefore affords the most self-contained proof.

(ii) *Acid Hydrolysis.*—Unlike the case of alkaline hydrolysis, our modern views of reaction mechanism do not uniquely point out the course pursued by acid hydrolysis : they suggest three possible alternatives. As these have been set down in a previous paper (Ingold and Ingold, J., 1932, 756),* it is necessary to mention here only the alternative which we now know, on experimental grounds, to be the correct one (called " C " in the paper cited) :

$$R'-C{\overset{O}{\underset{OR}{\lll}}} + H^+ \rightleftharpoons R'-C{\overset{O}{\underset{OHR^+}{\lll}}} \longrightarrow R'-\overset{+}{C}{=}O + HOR \quad \text{(slow)}$$
$$R'-\overset{+}{C}{=}O + H_2O \longrightarrow R'-C{\overset{O}{\underset{OH_2^+}{\lll}}} \rightleftharpoons R'-C{\overset{O}{\underset{OH}{\lll}}} + H^+ \quad \text{(fast)}$$

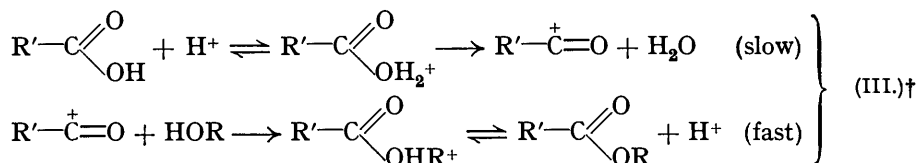$$\left. \right\} \quad \text{(II.)}\dagger$$

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* This paper also contains a brief history of the older theories of ester hydrolysis.

† We do not know to what extent the two written stages are separated in time, and envisage all possibilities from complete separation to simultaneity. For simplicity one extreme only is formulated.

This is the only one of the three theoretically indicated mechanisms which involves fission in the sense of the formula R'·CO⫽—OR, rather than according to the alternative R'·CO·O—⫽R.

The reason why mechanism (II) is known to be correct is that an application of methods (1) and (2) has shown that fission of the ester molecule proceeds in the required manner (Holmberg, *loc. cit.*; Ingold and Ingold, *loc. cit.*). However, it seemed desirable, in view of the importance of the subject and because abstract theory helps here so little, to provide also a self-contained proof of the Polanyi–Szabo type, and therefore we have applied method (3). We show that isotopically-distinguished oxygen from the solvent does not appear in the alcohol, and therefore must enter into the acid, produced by the acid hydrolysis of an ester. Therefore mechanism (II) may now be said to have an experimental basis as substantial as that of mechanism (I).

(iii) *Acid-catalysed Esterification.*—Part of the importance of establishing the correct mechanism for acid hydrolysis is that by reversing it one obtains a mechanism of acid-catalysed esterification. Thus, if we accept (II), the mechanism of esterification should be (III) :

$$
\begin{array}{l}
\text{R'}-\text{C}\!\!\!\begin{array}{c}{}^{\diagup\text{O}}\\{}_{\diagdown\text{OH}}\end{array} + \text{H}^+ \rightleftharpoons \text{R'}-\text{C}\!\!\!\begin{array}{c}{}^{\diagup\text{O}}\\{}_{\diagdown\text{OH}_2{}^+}\end{array} \longrightarrow \text{R'}-\overset{+}{\text{C}}\!\!=\!\!\text{O} + \text{H}_2\text{O} \quad \text{(slow)}\\[2ex]
\text{R'}-\overset{+}{\text{C}}\!\!=\!\!\text{O} + \text{HOR} \longrightarrow \text{R'}-\text{C}\!\!\!\begin{array}{c}{}^{\diagup\text{O}}\\{}_{\diagdown\text{OHR}^+}\end{array} \rightleftharpoons \text{R'}-\text{C}\!\!\!\begin{array}{c}{}^{\diagup\text{O}}\\{}_{\diagdown\text{OR}}\end{array} + \text{H}^+ \quad \text{(fast)}
\end{array} \Bigg\} \quad \text{(III.)}\dagger
$$

This is distinguished from the other possible mechanisms in that oxygen from the acid, and not from the alcohol, appears in the formed water; *i.e.*, we have

$$\text{R'·CO}\,|\,\text{OH} + \text{H}\,|\,\text{OR} \quad \text{and not} \quad \text{R'·CO·O}\,|\,\text{H} + \text{HO}\,|\,\text{R}$$
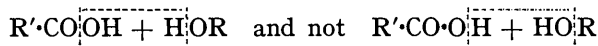
An experiment establishing this by method (1) is described in the following paper. Method (2) was applied incidentally in the experiments of Ingold and Ingold, since one cannot carry an acid hydrolysis almost to equilibrium without much accompanying esterification, and esterification by a mechanism liberating R would have confused what was actually a simple result. A self-contained proof by method (3) has recently been furnished by Roberts and Urey (*J. Amer. Chem. Soc.*, 1938, **60**, 2391). Using an ordinary acid and an alcohol with an enhanced proportion of the heavier oxygen isotopes, they showed that it is the acid, and not the alcohol, which provides the oxygen of the eliminated water. Thus all three divisions of the subject now have an equally satisfactory experimental basis.

EXPERIMENTAL.

Acid Hydrolysis of Methyl Hydrogen Succinate in Heavy-oxygen Water.—Heavy water obtained from Professor H. E. Watson's still was electrolysed in a divided cell, the heavy hydrogen being discarded and the heavy oxygen combined with ordinary hydrogen (cf. Datta, Day, and Ingold, J., 1937, 1968). From the heavy-oxygen water thus produced and dry hydrogen chloride, dilute solutions of hydrochloric acid were prepared, with which to carry out the hydrolyses.

Methyl hydrogen succinate was chosen as the ester because it is easily soluble in water : a concentrated hydrolysis solution is desirable to facilitate the isolation of satisfactory quantities of methyl alcohol. Hydrolysis was effected by heating the solutions to 100° for 24 hours. The isolated and fully rectified methyl alcohol, dried finally with sodium, was reduced to water by Russell and Fulton's method (*Ind. Eng. Chem., Anal.*, 1933, **5**, 384), and the density of this water was determined.

Oxygen isotopic compositions are expressed in parts per million (p.p.m.) of excess density of water prepared from the oxygen and normal hydrogen, corrections being applied for the small departures from normality of the cylinder hydrogen actually employed. Densities were determined pyknometrically. For the water derived from the methyl alcohol a rather small pyknometer (0·39 c.c.) was employed, and hence the error of measurement (3 p.p.m.) is greater than usual.

Of course the experiments might have failed in their object if water and methyl alcohol had

exchanged their oxygen under the conditions employed; but the results themselves (see Table) show that this does not occur (cf. also Roberts, *J. Chem. Physics*, 1938, **6**, 294).

Expt. No.	Weights (g.) of reagents.		Concn. of HCl (N).	Excess density (p.p.m.) of water.	
	HCl soln.	Ester.		Original.	From MeOH.
1	25·61	15·30	0·5610	+242	+17 *
2	21·64	15·89	0·1843	+242	+ 2
3	22·18	13·05	0·3044	+307	+ 1

* This result is due to incomplete drying of the methyl alcohol, a defect corrected in the two later experiments; but unsatisfactory as Expt. 1 is technically, it proves the point and is therefore included.

Koizumi and Titani (*Bull. Chem. Soc. Japan*, 1938, **13**, 463, 607) have shown that succinic acid and water exchange their oxygen at 130°. If this reaction were to take place completely under the conditions of our experiments (100° with added hydrion) it would make the difference that we should take the average density of the solvent water, and not its original density, for comparison with the density of the water derived by reduction of the methyl alcohol. Thus, in place of the figures in the second column from the right, we should tabulate the *average* excess densities +212, +208, +270 p.p.m. for the three experiments taken in order. This, of course, makes no difference to the conclusions.

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        University College, London. W.C. 1.