acid and water has been measured at 80° in dilute aqueous solution using hydrochloric acid as a catalyst. The reaction was followed by decomposing into benzene and carbon dioxide samples of benzoic acid crystallized from the reaction mixture and analyzing the carbon dioxide

in the mass spectrometer. The rate is first order in the difference of O^{18} content of the reactants, first order in hydrogen ion, independent of the concentration of benzoic acid, and free of salt effects.

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The Mechanisms of Acid Catalyzed Ester Hydrolysis, Esterification and Oxygen Exchange of Carboxylic Acids

BY IRVING ROBERTS AND HAROLD C. UREY

In addition to the known kinetic data on the acid hydrolysis of esters and on the esterification of carboxylic acids, we now have available the results of heavy oxygen studies of both the esterification[1] and the exchange[2] of carboxylic acids. The purpose of this paper is to show that by combining these data it is possible to eliminate all but a few of the large number of mechanisms which may be proposed for all three reactions.

The three reactions show a number of striking similarities. Besides the structural similarity of reactants and products, the reactions are all catalyzed by acids. In addition, there seems to be little doubt that both the hydrolysis and esterification are general acid catalyzed. Dawson[3] has shown that the hydrolysis of ethyl acetate is catalyzed by acetic acid molecules, chloroacetic acid molecules and bisulfate ions. Hinshelwood[4] has demonstrated catalysis of the esterification by a number of fatty acid molecules and Goldschmidt[5] has done the same for such acids as trichlorobutyric acid. On the basis of this general acid catalysis the retardation of esterification in alcoholic media by the addition of water discovered by Goldschmidt[6] is explained by the fact that $ROH_2{}^+$ is a stronger acid than H_3O^+ in the Brönsted sense. The exchange of oxygen between benzoic acid and water is first order in hydrogen ion[2]; as yet there are no data to determine whether the reaction is general acid catalyzed.

A further correlation lies in the fact that the

rates of the three reactions are of the same order of magnitude. The nearness of the rates of hydrolysis and esterification is well known; one of the problems in studying the kinetics of either reaction has been the elimination of the reverse one. Furthermore, in a methyl alcoholic medium containing about 5% water, the rate of esterification is about twice the rate of exchange of benzoic acid[1]; when these rates are corrected to the same concentrations of methanol and water, the latter is about four times as fast as the former. Finally, in water as a medium, the rate of exchange of benzoic acid is about ten times the rate of hydrolysis of methyl benzoate at the same temperature.[2]

A similarity in the linkages broken on esterification and exchange is also known. In the esterification of benzoic acid a carbon–oxygen bond of the benzoic acid is broken rather than that of the methyl alcohol.[1] The same must of course be true for the exchange of oxygen between benzoic acid and water. A recent heavy oxygen study of acid catalyzed ester hydrolysis has shown that the same linkage is broken in this reaction.[7]

Because of the above evidence, we are assuming that the mechanisms of all three reactions are entirely similar. This would presuppose a symmetrical mechanism for esterification and hydrolysis, since it is reasonable to assume that the reverse of one would be the mechanism of the other. The term "symmetrical mechanism" is used here in the sense that the reverse of such a mechanism for esterification will be a mechanism for hydrolysis which is structurally similar to it. A symmetrical mechanism must obviously be the case for the oxygen exchange reaction, where for example the mechanism of the reaction of $RCO^{16}O^{18}H$

(1) Roberts and Urey, THIS JOURNAL, 60, 2391 (1938).

(2) Roberts and Urey, ibid., 61, 2580 (1939).

(3) Dawson and Lowson, J. Chem. Soc., 2444 (1927); 393 (1929); Dawson, Pycock and Spivey, ibid., 291 (1933).

(4) Rolfe and Hinshelwood, Trans. Faraday Soc., 30, 935 (1934); Newling and Hinshelwood, J. Chem. Soc., 1357 (1936); Fairclough and Hinshelwood, ibid., 593 (1939).

(5) Goldschmidt, Trans. Faraday Soc., 24, 662 (1928).

(6) Goldschmidt, Ber., 28, 3224 (1895); Goldschmidt and Udby, Z. physik. Chem., 60, 728 (1907).

(7) Dalla, Day and Ingold, J. Chem. Soc., 838 (1938).

with H_2O^{16}, would be similar to its reverse, the reaction of RCO^{16}_2H with H_2O^{18}. Finally, as a further simplification, we are making the usual assumption that each mechanism will contain only one rate controlling step, i. e., that there is only one activated complex whose disappearance controls the rate of the reaction.

An important consideration which does not seem to have been emphasized previously is that the esterification and hydrolysis reactions are very probably first order in alcohol and water, respectively. The existence of the relationship

$$\frac{\text{moles ester} \times \text{moles water}}{\text{moles alcohol} \times \text{moles acid}} = K$$

which is so universal as to be largely independent of medium as well as temperature,[8] would argue at least at equilibrium for a first order dependence of esterification rate on the alcohol concentration and of hydrolysis rate on the water concentration. While some reactions are known to change in mechanism while approaching equilibrium, this would not be expected to take place for these comparatively simple reactions. This is especially true for the exchange reaction, where the equilibrium constant is undoubtedly very close to unity. It is therefore difficult to see how the first order dependence on the alcohol and water concentration would apply to the condition of equilibrium and not to other conditions.

In addition, a first order dependence of the rate of esterification on the alcohol concentration is known in formic and acetic acid as media from the cryoscopic measurements of Kailan and co-workers,[9] who have also demonstrated different esterification rates for different alcohols.

The Reactive Complex

It is possible to eliminate immediately a large number of mechanisms by a consideration of the reactive complex for each of the three reactions under discussion. As Wynne-Jones and Eyring[10] have emphasized, kinetics of a reaction alone can only determine the compounds entering into the rate controlling step, i. e., the composition of the reactive complex. Granting that the exchange, esterification, and hydrolysis reactions are general acid catalyzed and first order in alcohol or water,

(8) Berthelot and Pean de St. Gilles, *Ann. chim. phys.*, [3] **65**, 385 (1862); **66**, 5 (1862); **68**, 225 (1863); Schultz, This Journal, **61**, 1443 (1939).
(9) Kailan and co-workers, *Monatsh.*, **51**, 334 (1929); **60**, 386 (1932); **61**, 116 (1932); **62**, 284 (1933); **63**, 52 (1933); **63**, 155 (1933).
(10) Wynne-Jones and Eyring, *J. Chem. Phys.*, **3**, 492 (1935).

their reactive complexes must be, respectively, $R'COOH \cdot H_2O \cdot HA$, $R'COOH \cdot ROH \cdot HA$, and $R'COOR \cdot H_2O \cdot HA$. Of course, the last two are identical since the reactive complex must be the same for forward and reverse reactions.

Having determined the composition of the critical complex, we can state that all mechanisms which do not form this complex are incorrect. Under this classification falls a group of bimolecular mechanisms (i. e., mechanisms consisting of a series of bimolecular steps) several of which have been widely supported. For example, the esterification mechanism of Watson,[11] although not given as a symmetrical one, may be written
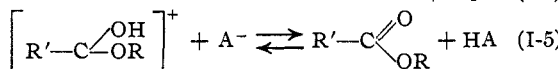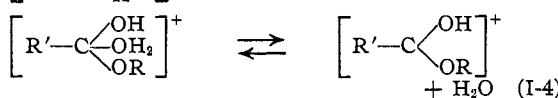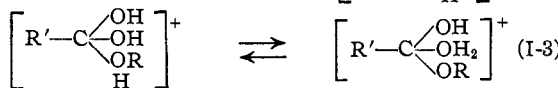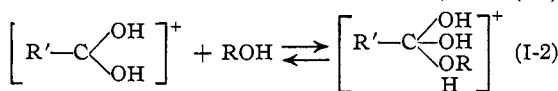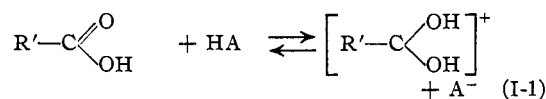
The reverse of this mechanism will be seen to be a similar mechanism for ester hydrolysis.

None of these steps produces the critical complex required by the kinetic data for step (I-1) lacks a molecule of alcohol, steps (I-2), (I-3), and (I-4) lack an A^- ion, and step (I-5) lacks a water molecule. Or, from another point of view, one may state that step (I-1) cannot be rate controlling, since the reaction would then be independent of the alcohol concentration, and that step (I-2) cannot be rate controlling, for then the reaction would be specific hydrogen ion catalyzed. This last may be seen from the rate expressions

$$V = k_2[ROH]\left[R'-C{\overset{\displaystyle OH}{\underset{\displaystyle OH}{\Big<}}}\right]^+ =$$

$$k_2K_1\frac{[ROH][RCOOH][HA]}{[A^-]}$$

$$= \frac{k_2K_1}{K_a}[ROH][RCOOH][H^+]$$

where k_2 is the rate constant for step (I-2), K_1 is the equilibrium constant for step (I-1), and K_a is the dissociation constant of the acid HA.

(11) Evans, Morgan, and Watson, *J. Chem. Soc.*, 1168 (1935); Watson, "Modern Theories of Organic Chemistry," Oxford University Press, 1937, pp. 130, 211.

Similar reasoning would apply to the other steps, but this is sufficient to demonstrate that the much simpler consideration of the critical complex involved would eliminate these steps as possibilities.

The mechanism proposed by Ingold[7,12] for ester hydrolysis involving the intermediate ion RCO^+ is eliminated similarly since none of its steps contains the correct reactive complex. In fact, on this basis we have eliminated eight other such bimolecular mechanisms, any of which are as reasonable as the two mentioned above.
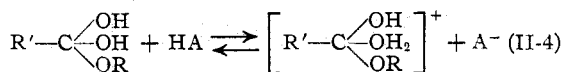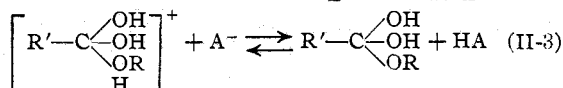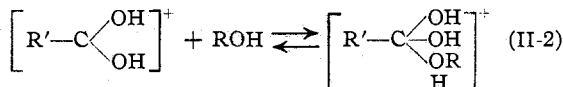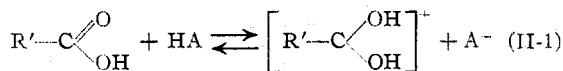
There are three possible mechanisms, however, which do lead to the reactive complex required by the kinetics. One of these is a bimolecular mechanism

$$R'-C\overset{O}{\underset{OH}{\big\langle}} + HA \rightleftharpoons \left[R'-C\overset{OH}{\underset{OH}{\big\langle}} \right]^+ + A^- \quad (II\text{-}1)$$

$$\left[R'-C\overset{OH}{\underset{OH}{\big\langle}} \right]^+ + ROH \rightleftharpoons \left[R'-C\overset{OH}{\underset{\underset{H}{OR}}{\big\langle}}\raisebox{1ex}{OH} \right]^+ \quad (II\text{-}2)$$

$$\left[R'-C\overset{OH}{\underset{\underset{H}{OR}}{\big\langle}}\raisebox{1ex}{OH} \right]^+ + A^- \rightleftharpoons R'-C\overset{OH}{\underset{OR}{\big\langle}}\raisebox{1ex}{OH} + HA \quad (II\text{-}3)$$

$$R'-C\overset{OH}{\underset{OR}{\big\langle}}\raisebox{1ex}{OH} + HA \rightleftharpoons \left[R'-C\overset{OH}{\underset{OR}{\big\langle}}\raisebox{1ex}{OH_2} \right]^+ + A^- \quad (II\text{-}4)$$

$$\left[R'-C\overset{OH_2}{\underset{OR}{\big\langle}}\raisebox{1ex}{OH} \right]^+ \rightleftharpoons \left[R'-C\overset{OH}{\underset{OR}{\big\langle}} \right]^+ + H_2O \quad (II\text{-}5)$$

$$R'-C\overset{OH}{\underset{OR}{\big\langle}} + A^- \rightleftharpoons R'-C\overset{O}{\underset{OR}{\big\langle}} + HA \quad (II\text{-}6)$$
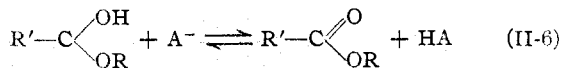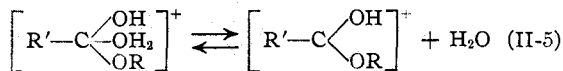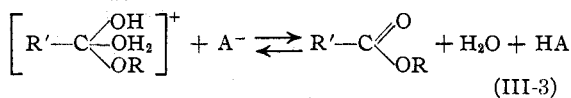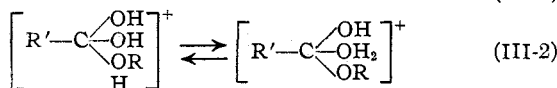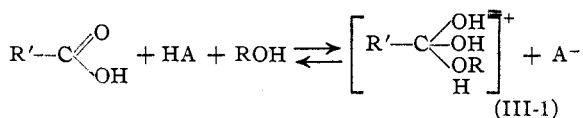
Reaction (II-1) cannot be rate controlling since it does not contain the alcohol. If (II-2) or (II-5) were rate controlling the reaction would be specific hydrogen ion catalyzed. (II-6) cannot be rate controlling since it does not contain the water. Only (II-3) or (II-4) contain the required reactive complex and hence can be rate controlling. Modifications of this reaction mechanism may be made. Thus instead of (II-1) a reaction donating the proton to the OH group giving $\left[R-C\overset{O}{\underset{OH_2}{\big\langle}} \right]^r$ is possible. This might be followed by the addition of the ROH to the double bond giving $\left[R'-C\overset{OH}{\underset{OR}{\big\langle}}\raisebox{1ex}{OH_2} \right]^+$. The remainder of the mechanism could then be written in a symmetrical way.

This mechanism II, or its modification discussed above, is in line with current mechanisms of similar reactions. From this point of view, the formation of an acid or ester ion by the addition of a proton seems probable. Only after the forma-
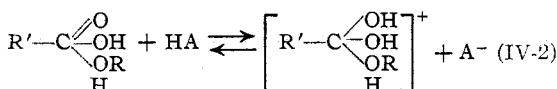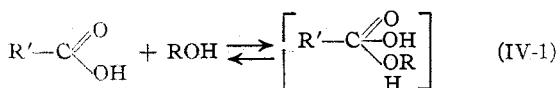
tion of such an ion or when HA is in the neighborhood of the acid or ester could water or alcohol take part in the reaction since otherwise the reaction would not be catalyzed. The addition and subtraction of protons represented by steps (II-3) and (II-4) are commonly assumed mechanisms.

Lowry[13] has proposed a termolecular mechanism for esterification of the following nature

$$R'-C\overset{O}{\underset{OH}{\big\langle}} + HA + ROH \rightleftharpoons \left[R'-C\overset{OH}{\underset{\underset{H}{OR}}{\big\langle}}\raisebox{1ex}{OH} \right]^+ + A^- \quad (III\text{-}1)$$

$$\left[R'-C\overset{OH}{\underset{\underset{H}{OR}}{\big\langle}}\raisebox{1ex}{OH} \right]^+ \rightleftharpoons \left[R'-C\overset{OH}{\underset{OR}{\big\langle}}\raisebox{1ex}{OH_2} \right]^+ \quad (III\text{-}2)$$

$$\left[R'-C\overset{OH}{\underset{OR}{\big\langle}}\raisebox{1ex}{OH_2} \right]^+ + A^- \rightleftharpoons R'-C\overset{O}{\underset{OR}{\big\langle}} + H_2O + HA \quad (III\text{-}3)$$

where either step (III-1) or (III-3) may be rate controlling. This mechanism is entirely possible, since it would yield both general acid catalysis and a first order dependence on the alcohol concentration or on the water concentration in the case of the hydrolysis reaction.

An alternative mechanism would be obtained by separating step (III-1) into the equivalent reactions

$$R'-C\overset{O}{\underset{OH}{\big\langle}} + ROH \rightleftharpoons \left[R'-C\overset{O}{\underset{\underset{H}{OR}}{\big\langle}}\raisebox{1ex}{OH} \right] \quad (IV\text{-}1)$$

$$R'-C\overset{O}{\underset{\underset{H}{OR}}{\big\langle}}\raisebox{1ex}{OH} + HA \rightleftharpoons \left[R'-C\overset{OH}{\underset{\underset{H}{OR}}{\big\langle}}\raisebox{1ex}{OH} \right]^+ + A^- \quad (IV\text{-}2)$$

in which step (IV-2) would be rate controlling. This differs from mechanism (III) merely in that it supposes a time interval between addition of alcohol and catalyst molecules, rather than a simultaneous addition of the two to the carboxylic acid. In the case of ester hydrolysis this mechanism is lent some support by cryoscopic studies which demonstrate the existence of ester–water compounds in aqueous solution.[14]

The complex formed in step (IV-1) cannot be of the type $\left[R'-C\overset{OH}{\underset{OR}{\big\langle}}\raisebox{1ex}{OH} \right]$ since this reaction and its reverse would result in uncatalyzed esterification (if a water molecule were removed) as well as rapid uncatalyzed exchange of carboxylic

(12) Ingold and Ingold, J. Chem. Soc., 756 (1932).

(13) Lowry, ibid., 1381 (1925); ibid., Trans. Faraday Soc., 24, 545 (1928); Waters and Lowry, "Physical Aspects of Organic Chemistry," Van Nostrand, New York, 1936, pp. 270-272.

(14) Kendall and Harrison, Trans. Faraday Soc., 24, 588 (1928).

acids. Step (IV-3) could be divided into two steps in an entirely similar manner.

The reactive complex method also proves to be more than a method of simplification; it may, in addition, bring out mechanisms which might otherwise have been missed. For example, in the exchange of oxygen between acetone and water, not only is the bimolecular mechanism of Cohn and Urey[15] a possibility, but several other mechanisms, including a termolecular one, will yield the same reactive complex. At the present time there seems to be no method of distinguishing among these mechanisms for acetone exchange, and also of distinguishing among the mechanisms proposed for the three reactions discussed in this paper. However, the elimination process which we have presented above does lead to a criticism of current theory of the relative rates of acid catalyzed reactions in light and heavy water.

The criterion of pre-equilibrium proposed by Bonhoeffer and Reitz[16] is based on a two step mechanism similar to the first two steps of mechanism I. The criterion may be stated as follows. If the rate of an acid catalyzed reaction is increased on going from H_2O to D_2O, then a pre-equilibrium exists and the reaction is specific hydrogen ion catalyzed. If, however, the rate is decreased on going from H_2O to D_2O, the first step is not an equilibrium but is rate controlling, and the reaction is general acid catalyzed.

It has been demonstrated that the rate of ester hydrolysis is greater in D_2O than in H_2O for both methyl acetate[17] and ethyl acetate.[18] Thus, by the above criterion, we would expect the reaction to be specific hydrogen ion catalyzed. Actually, the data of Dawson quoted above show that

ester hydrolysis is general acid catalyzed. A similar contradiction exists for the esterification reaction. Since the equilibrium constant for the equilibrium ester + water $\rightleftarrows$ alcohol + acid does not change on going from H_2O to D_2O,[19,20] and since the rate of hydrolysis is known to be greater in D_2O than in H_2O, the rate of esterification must also increase on going from H_2O to D_2O. Here again the data quoted above show general acid catalysis, whereas the Bonhoeffer criterion would predict a pre-equilibrium.

The source of these difficulties lies in the assumption of a simple two step mechanism, a mechanism which, as we have shown in the discussion given previously, is very improbable for ester hydrolysis and esterification since neither of these steps contains the correct reactive complex.

Summary

1. By combining recent heavy oxygen studies with the available kinetic data for acid catalyzed ester hydrolysis, esterification and oxygen exchange of carboxylic acids, it has been shown to be very probable that all three reactions are similar in mechanism.

2. On the basis that these reactions are general acid catalyzed and first order in alcohol or water, it is possible to write the composition of the reactive complexes whose disappearance will control the reaction rates.

3. Of the large number of mechanisms which have been proposed for these reactions, only three yield the critical complex required by the kinetics.

4. The Bonhoeffer criterion of pre-equilibrium in light and heavy water has been criticized on the ground that the mechanism assumed is incorrect for the reactions discussed here.

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(15) Cohn and Urey, THIS JOURNAL, **60**, 679 (1938).

(16) Bonhoeffer and Reitz, Z. physik. Chem., **A179**, 135 (1937); Bonhoeffer, Trans. Faraday Soc., **34**, 252 (1938); Reitz, Z. Elektrochem., **44**, 72 (1938).

(17) Hornel and Butler, J. Chem. Soc., 1361 (1936).

(18) Schwarz, Z. Elektrochem., **40**, 474 (1934).

(19) Nachod, ibid., **44**, 72 (1938).

(20) Kailan and Ebeneder, Z. physik. Chem., **A180**, 157 (1937).