

case of the oxalate ester, all of the structures conform to the same lateral packing as is shown by the lower molecular chain compounds.

3. A discussion of the origin of the various fiber patterns is given. It is shown that in the

case of certain esters the presence of different crystal forms is indicated. A general interpretation of these forms on the basis of the theory of Schoon is presented.

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Kinetics of the Exchange of Oxygen between Benzoic Acid and Water¹

BY IRVING ROBERTS AND HAROLD C. UREY

The organic compounds which thus far have been found to exchange their oxygen with that of water are aldehydes, ketones, carboxylic acids, and a few very reactive alcohols.² A kinetic study of the exchange of oxygen between acetone and water in the medium 90% acetone-10% water was made by Cohn and Urey,³ who demonstrated a general acid catalysis which is significant for the mechanisms of both the hydration and the enolization of acetone. The obvious structural similarity of the acid catalyzed esterification and ester hydrolysis reactions to the oxygen exchange reactions of carboxylic acids indicates that a kinetic study of the latter should yield results at least as interesting as those obtained in the acetone exchange.

Benzoic acid exchanged both its oxygen atoms with that of water, the reaction being catalyzed by acids, as is the case for the exchange of carboxylic acids in general.⁴⁻⁶ The usual method for following exchange, that of mixing comparable amounts of the reacting substances, cannot be used at ordinary temperatures in the case of benzoic acid since the compound is not sufficiently soluble in water to cause an appreciable change in the heavy oxygen content of the water. Rather than introduce the complication of a mutual solvent, we have devised a method of determining the heavy oxygen content of benzoic acid and have carried out the kinetic experiments in dilute aqueous solution.

(1) Presented at the Baltimore meeting of the American Chemical Society, April, 1939.

(2) For a summary of the literature on this subject, see Reitz, *Z. Elektrochem.*, **45**, 100 (1939).

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

(4) Roberts, *J. Chem. Phys.*, **6**, 294 (1938).

(5) Senkins and Brown, *J. Org. Chem.*, **2**, 569 (1938).

(6) The present work shows that the statement of Koizumi and Titani [*Bull. Chem. Soc. Japan*, **13**, 607 (1938)] that only one oxygen atom of benzoic acid is readily exchangeable cannot be correct. Such a statement is quite unreasonable in the light of our present knowledge of the rapid dissociation of the hydrogen ion from a carboxylic acid and of the symmetrical structure of a carboxylate ion.

Experimental

Decarboxylation Apparatus.—The determination of the O¹⁸ content of benzoic acid depends upon the observation of Sabatier and Mailhe⁷ that benzoic acid will be converted almost quantitatively into benzene and carbon dioxide when passed over reduced copper at 500°. For the present work, it was necessary to construct an apparatus which would perform the decarboxylation of a few milligrams of benzoic acid in a stream of nitrogen gas, and which would be free of traces of oxygen, carbon dioxide, water, or copper oxide. In addition, after each conversion, the apparatus should be easily made ready for the succeeding one, since many samples must be converted for each kinetic experiment.

The apparatus finally used is shown in Fig. 1. Tank nitrogen was admitted at the left through a flowmeter (A) and successively through a tube of copper at 350° (B), a bubbler containing sulfuric acid (C), and tubes D and E, filled with potassium hydroxide and anhydrous calcium sulfate, respectively. At this point the nitrogen can be made to take one of two paths; if stopcock K is closed, it can pass through J into the decarboxylation tube (I) containing copper at 500° and into the air through stopcock F. On the other hand, with stopcock J closed, the nitrogen could enter tube I through stopcock F and pass successively through K, a trap (L), and into the air through stopcock O. Tube I was made of temperature-resistant glass (Corning 172), and sealed directly to the Pyrex tubing at either side. Tube H was 1.5 cm. in diameter and contained a ring seal with an opening of about 2 mm. diameter. The apparatus also contained a safety seal (G), a manometer (M), a sample tube fitted with a break seal (N), and a trap (P) surrounded with solid carbon dioxide to protect a Hyvac pump connected at the right.

After sweeping out with hydrogen gas to reduce the oxides of copper, the entire apparatus was evacuated and filled with nitrogen. Trap L was surrounded with liquid nitrogen. The nitrogen stream was then adjusted to 30 cc./min., and directed through J, through tubes I and H and into the air through F (stopcocks K and O being closed). The plug in tube H was removed, the tube containing the benzoic acid inserted around the ring seal and the plug replaced. The benzoic acid sample tubes, which were 10 mm. in diameter and of the shape shown in the upper left of Fig. 1, were first wiped with chamois to

(7) Sabatier and Mailhe, *Compt. rend.*, **159**, 219 (1914).

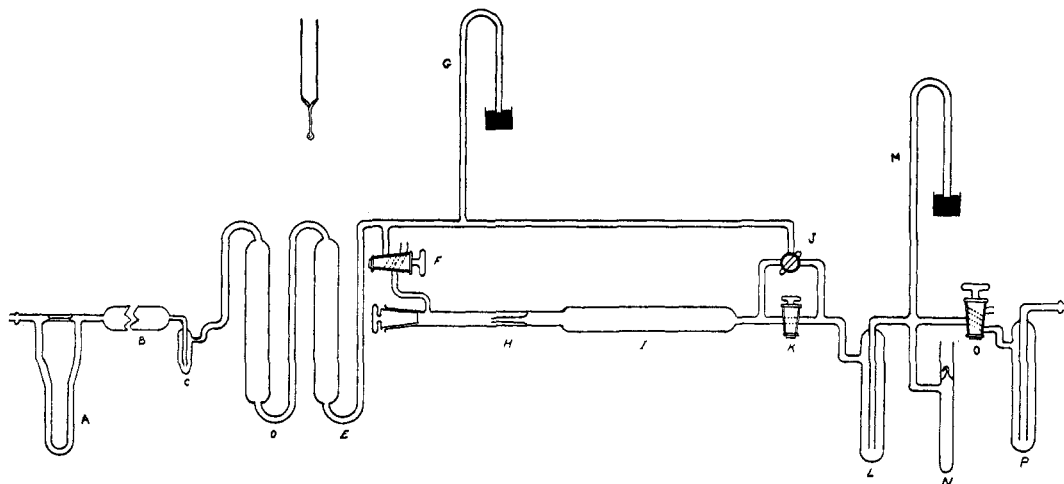


Fig. 1.

remove any organic material which would produce carbon dioxide on being heated. The purpose of the inner seal of tube H was to direct the stream of nitrogen into the benzoic acid sample tube when it was put into place.

After sweeping out the air introduced with the tube for four minutes, the nitrogen stream was reversed by turning stopcock F, closing stopcock J, opening stopcock K, and opening stopcock O to the air. The benzoic acid was then sublimed into I with an ordinary Bunsen flame, both the benzene and the carbon dioxide produced being caught in trap L. After allowing the nitrogen stream to continue for fifteen minutes, stopcocks O and K were closed, and the gas was again directed through J, I, H, and F, into the air. The nitrogen gas remaining in the portion of the apparatus to the right of stopcocks J and K was then pumped out through O and P. Stopcock O was turned off and the liquid nitrogen around trap L was removed and replaced with solid carbon dioxide-acetone mixture, thus keeping the benzene frozen while allowing the carbon dioxide to vaporize. After observing the pressure on the manometer (M), the carbon dioxide was distilled into the sample tube (N) by cooling it to liquid nitrogen temperature, the sample tube being then sealed off at the side-arm and set aside for mass spectrometer analysis.

To prepare the apparatus for the next conversion, the first benzoic acid sample, stopcock O was opened to the air and a new carbon dioxide sample tube sealed on. The air was then pumped out, liquid nitrogen placed around trap L, and the evacuated space filled with nitrogen through stopcock J (stopcock F having been closed). In this way no air was admitted to tube I at any time. The nitrogen stream was again directed from left to right through tube I and the process carried out as before. The time elapsed between the beginning of one conversion to the beginning of the next was about fifty-five minutes.

Materials and Solutions.—Benzoic acid, recrystallized twice from alcohol and water and once from water, was dried over phosphorus pentoxide. Hydrochloric acid solutions were prepared from the c. p. concentrated reagent and standardized against standard 0.1 *N* sodium hydroxide, the primary standard being Bureau of Standards potassium acid phthalate. C. p. potassium chloride was used directly.

Heavy oxygen water, prepared by fractional distillation,⁸ was refluxed with alkaline permanganate for one hour, fractionated, and distilled from chromic acid. Analysis by the method of Cohn and Urey⁸ showed that this water was 0.515% H_2O^{18} . Heavy oxygen benzoic acid was prepared as follows. A solution of 1.7 g. of benzoic acid in 65 cc. of heavy oxygen water which was also 0.1 *N* in hydrochloric acid was allowed to stand in the thermostat at 80° for forty-eight hours. The heavy oxygen water and the hydrochloric acid were completely distilled away *in vacuo*, and the remaining solid was powdered and dried over phosphorus pentoxide. Conversion of a sample to carbon dioxide by the above procedure and analysis in the mass spectrometer showed that this benzoic acid contained 0.465% O^{18} . Ordinary benzoic acid was found to contain 0.204% O^{18} .

Kinetics.—Kinetic measurements were made in an oil thermostat set at $80.00 \pm 0.03^\circ$ with a Bureau of Standards platinum resistance thermometer. In general, 10 cc. of hydrochloric acid solution (ordinary H_2O or H_2O^{18}) was pipetted into a 20-cc. long-necked flask fitted with a ground-glass joint and stopper. After allowing the flask to stand in the thermostat for at least thirty minutes, a glass bucket containing about 120 mg. of benzoic acid (heavy) was lowered into it by means of a platinum wire. The flask was shaken vigorously and the time recorded; the benzoic acid was completely dissolved within one minute. In calculating velocity constants, concentrations were corrected for expansion of the solution from room temperature to 80°; evaporation error was found to be negligible.

At known intervals, approximately 1-cc. portions were withdrawn by means of a long medicine dropper and delivered into the benzoic acid sample tubes of the type mentioned above and shown in the upper left of Fig. 1. The tubes were chilled immediately to room temperature, causing most of the benzoic acid to crystallize and effectively stopping the reaction. Most of the solution was then drawn off by means of a fine capillary pipet, the benzoic acid crystals being large enough to remain behind. Before decarboxylation, the last traces of water were

(8) Huffman and Urey, *Ind. Eng. Chem.*, **29**, 531 (1937).

pumped away from each sample by inserting the tube into a larger tube fitted with a ground cap and connected to a Hyvac pump.

The efficiency of this drying process was tested by crystallizing ordinary benzoic acid from heavy oxygen water in the absence of hydrochloric acid catalyst, drawing off the water, and pumping for various lengths of time. The benzoic acid was then decarboxylated and the carbon dioxide analyzed in the mass spectrometer. It was found that four hours of pumping were necessary to remove the water completely within the precision of analysis. About one-fourth of the benzoic acid was also lost during the pumping process.

Mass Spectrometer Analysis.—The carbon dioxide samples from the benzoic acid decarboxylations were analyzed for the ratio of mass 44 to mass 46, corresponding to the species CO_2^{16} and $\text{CO}^{16}\text{O}^{18}$, respectively. The relation of the heavy oxygen content of the carbon dioxide to this ratio can be seen from the following. If α is the atom fraction of O^{18} in the carbon dioxide, the amounts of the three species CO_2^{18} , $\text{CO}^{16}\text{O}^{18}$ and CO_2^{16} will be in the ratio $\alpha^2 : 2\alpha(1 - \alpha) : (1 - \alpha)^2$, assuming the gas to be in statistical equilibrium. The ratio of mass 44 to mass 46 will then be

$$R = (1 - \alpha)^2 / 2\alpha(1 - \alpha)$$

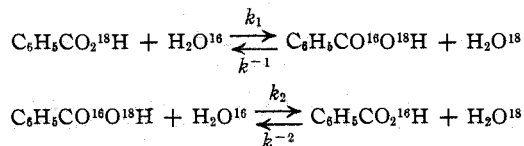
Solving for α , we have

$$\alpha = 1 / (2R + 1)$$

as the formula for calculating the mole fraction of O^{18} from the experimentally determined ratio. Only small amounts of gas are necessary for a mass spectrometer determination; the precision of these analyses was in general better than 1%.

Kinetics of the Reaction

In the exchange of O^{18} between benzoic acid and water, the three species of benzoic acid and two species of water react as follows



Assuming that there are no specific differences in reactivity between O^{16} and O^{18} species of the same compound, and that both oxygens of benzoic acid exchange with equal ease, the relations of the various rate constants to each other may be determined by inspection. For example, at equal concentrations, reaction 1 will be twice as successful as reaction 2, since only half the reactions of $\text{C}_6\text{H}_5\text{CO}^{16}\text{O}^{18}\text{H}$ with H_2O^{16} will result in exchange; that is, $k_2 = k_1/2$. In like manner, it will be seen that $k_{-1} = k_1/2$ and that $k_{-2} = k_1$.

If the three forms of benzoic acid are statistically distributed, their concentrations may be represented

$$\begin{aligned} [\text{C}_6\text{H}_5\text{CO}_2^{18}\text{H}] &= \alpha^2 [\text{C}_6\text{H}_5\text{CO}_2\text{H}] \\ [\text{C}_6\text{H}_5\text{CO}^{16}\text{O}^{18}\text{H}] &= 2\alpha(1 - \alpha) [\text{C}_6\text{H}_5\text{CO}_2\text{H}] \\ [\text{C}_6\text{H}_5\text{CO}_2^{16}\text{H}] &= (1 - \alpha)^2 [\text{C}_6\text{H}_5\text{CO}_2\text{H}] \end{aligned}$$

where α is the atom fraction of O^{18} in the benzoic acid and $[\text{C}_6\text{H}_5\text{CO}_2\text{H}]$ is the (constant) total concentration of the benzoic acid in moles/liter. Similarly, we may write

$$\begin{aligned} [\text{H}_2\text{O}^{18}] &= \beta [\text{H}_2\text{O}] \\ [\text{H}_2\text{O}^{16}] &= (1 - \beta) [\text{H}_2\text{O}] \end{aligned}$$

where $[\text{H}_2\text{O}]$ is the total concentration of water and β is the atom fraction of O^{18} or the mole fraction of H_2O^{18} in the water.

Considering the initial condition in which the benzoic acid contains the excess of O^{18} , the rate of the reaction will be

$$\begin{aligned} -\frac{d}{dt} \{ [\text{O}^{18}] \text{ in benzoic acid} \} &= \\ &= \frac{-d}{dt} \{ [\text{C}_6\text{H}_5\text{CO}^{16}\text{O}^{18}\text{H}] + 2[\text{C}_6\text{H}_5\text{CO}_2^{18}\text{H}] \} \\ &= k_1 [\text{C}_6\text{H}_5\text{CO}_2^{18}\text{H}] [\text{H}_2\text{O}^{16}] + k_2 [\text{C}_6\text{H}_5\text{CO}^{16}\text{O}^{18}\text{H}] [\text{H}_2\text{O}^{16}] \\ &\quad - k_{-1} [\text{C}_6\text{H}_5\text{CO}^{18}\text{O}^{16}\text{H}] [\text{H}_2\text{O}^{18}] - k_{-2} [\text{C}_6\text{H}_5\text{CO}_2^{16}\text{H}] [\text{H}_2\text{O}^{18}] \end{aligned}$$

Substituting for the various rate constants their equivalents in terms of k_1 and for the concentrations of reactants the values given above, we obtain, after cancelling terms

$$\begin{aligned} -2[\text{C}_6\text{H}_5\text{CO}_2\text{H}] \frac{d\alpha}{dt} &= k_1 [\text{C}_6\text{H}_5\text{CO}_2\text{H}] [\text{H}_2\text{O}] (\alpha - \beta) \\ \frac{d\alpha}{dt} &= k(\beta - \alpha), \text{ where } k = k_1 [\text{H}_2\text{O}] / 2. \end{aligned}$$

Therefore the change of the O^{18} content of the benzoic acid with time should be independent of the concentration of benzoic acid and first order in the difference of O^{18} content of the reactants. Integrating, holding β constant⁹

$$k = \frac{2.303}{t} \log \frac{\alpha - \beta}{\alpha_0 - \beta}$$

By an entirely similar derivation, it can be shown that when the water contains the excess of O^{18} initially

$$k = \frac{2.303}{t} \log \frac{\beta - \alpha_0}{\beta - \alpha}$$

(9) Under the conditions of these experiments, the water is in large excess over the benzoic acid so that the heavy oxygen content of the water does not change measurably. If the water were not in large excess, one would proceed by noting that the total O^{18} concentration is a constant, *i. e.*

$$[\text{O}^{18}] = 2\alpha [\text{C}_6\text{H}_5\text{CO}_2\text{H}] + \beta [\text{H}_2\text{O}] = \text{constant}$$

Substituting for β in the above rate expression

$$\frac{d\alpha}{dt} = \frac{k_1}{2} \{ [\text{O}^{18}] - \alpha([\text{H}_2\text{O}] + 2[\text{C}_6\text{H}_5\text{CO}_2\text{H}]) \}$$

an equation which is symmetrical in the water and the benzoic acid and which is easily integrated.

Results and Discussion

A typical set of data is shown in Table I and plotted in Fig. 2. The second column of Table I gives the amount of carbon dioxide at atmospheric pressure obtained from each benzoic acid sample; this was calculated from the volume of the apparatus and the pressure observed. The best straight line which is drawn through the points of Fig. 2, was calculated by the method of least squares. The length of the lines represents the probable error. Velocity constants were calculated from the slope of the least squares straight line, the time being in minutes.

TABLE I
KINETIC EXPERIMENT 4

[HCl] = 0.478 *N*; [C₆H₅CO₂H] = 0.0564 *M*; β = 0.00200;
α₀ = 0.00465

<i>t</i> , min.	Cc. CO ₂ at atm. P	<i>R</i>	α	-Log (α - β)
0	4.4	107.1	0.00465	2.5767
30	0.6	121.0	.00412	2.6737
45	.8	120.3	.00414	2.6696
60	.8	129.2	.00386	2.7305
75	.8	137.0	.00364	2.7852
90	1.0	150.8	.00330	2.8861
120	1.0	159.4	.00313	2.9469
150	0.8	172.9	.00288	3.0555
180	1.6	180.1	.00277	3.1135
210	0.5	189.4	.00263	3.2007

The results of the five experiments performed are shown in Table II. A comparison of Experiments 1 and 2 will show that the rate of the reaction is independent of which reactant contains the excess of O¹⁸ initially. In Experiment 3, the hydrochloric acid concentration was increased five-fold, causing a five-fold increase in the rate. Decreasing the concentration of benzoic acid by a factor of two in Expt. 4 had no effect on the reaction velocity, as predicted by our derivation above. Finally, addition of potassium chloride in Expt. 5 had no effect on the rate, demonstrating the absence of any salt effect. The variation of *k_H* is within the precision of about 4% for the determination of a rate constant.

TABLE II
RATES OF EXCHANGE AT 80°

Expt.	α ₀	β	[HCl]	[C ₆ H ₅ CO ₂ H]	<i>k</i>	<i>k_H</i> ^b
1	0.00204	0.00515	0.0932 <i>M</i>	0.1088 <i>M</i>	0.00129	0.0138
2	.00465	.00200	.0936	.1058	.00129	.0138
3	.00465	.00200	.478	.1082	.00693	.0145
4	.00465	.00200	.478	.0564	.00711	.0149
5 ^a	.00465	.00200	.0936	.1009	.00131	.0141

^a This reaction mixture was also 0.0937 *N* in potassium chloride. ^b *k_H* is the rate constant for 1 *N* hydrochloric acid. Mean *k_H* = 0.0142 ± 0.0004.

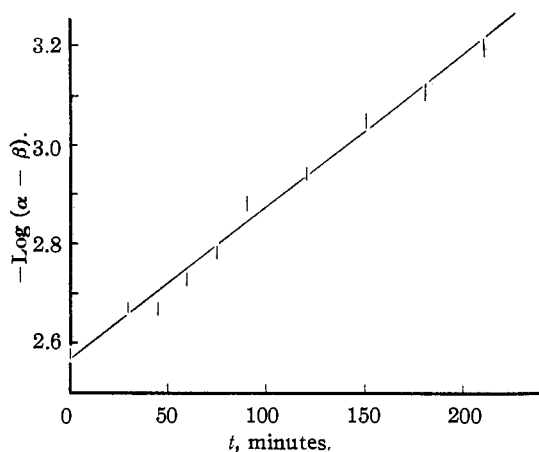


Fig. 2.—Expt. 4.

The fact that the exchange reaction is first order in hydrogen ion serves to further demonstrate the similarity of the nature of this reaction to the acid catalyzed esterification and ester hydrolysis reactions. The agreement of the rates of these three reactions with each other offers further evidence toward this conclusion. We already have demonstrated that in methyl alcohol as a medium the rates of esterification and exchange of benzoic acid are comparable.^{10,11} In addition, the rate of hydrolysis of methyl benzoate at 80° is of the same order of magnitude as the rate of exchange determined in the present work,¹² the exchange being about ten times faster.¹³ Discussion of the mechanisms of the three reactions on the basis of oxygen exchange work and the existing kinetic data is left for a succeeding paper.

From the point of view of reaction kinetics in general, further work on the exchange of oxygen between benzoic acid and water should include the temperature coefficient, the rate in H₂O-D₂O mixtures, and the effect of substituents in the benzene ring on the rate. It should be emphasized that oxygen exchange reactions proceed at convenient rates with no change in the medium and are of a simple first order dependence.

Summary

The rate of exchange of oxygen between benzoic

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

(11) Herbert and Lander, *Trans. Faraday Soc.*, **34**, 1219 (1938); *Nature*, **142**, 954 (1938), have predicted this result on the basis of our previous experiments.³

(12) Bolin, *Z. anorg. Chem.*, **177**, 227 (1938).

(13) The observed *k_H* for the exchange was multiplied by 2 to obtain *k₁*[H₂O] = 0.0284 as compared to *k*[H₂O] = 0.0028 calculated from the data of Bolin for the hydrolysis. *k₁* as defined in the derivation above is the constant which should be used for this comparison since it represents the rate constant for the exchange which is effective at every reaction.

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 O¹⁸ 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 esterification¹ and the exchange² 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. Dawson³ has shown that the hydrolysis of ethyl acetate is catalyzed by acetic acid molecules, chloroacetic acid molecules and bisulfate ions. Hinshelwood⁴ has demonstrated catalysis of the esterification by a number of fatty acid molecules and Goldschmidt⁵ 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 Goldschmidt⁶ is explained by the fact that ROH₂⁺ is a stronger acid than H₃O⁺ in the Brönsted sense. The exchange of oxygen between benzoic acid and water is first order in hydrogen ion²; as yet there are no data to determine whether the reaction is general acid catalyzed.

A further correlation lies in the fact that the

(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).

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 acid¹; 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 RCO¹⁸O¹⁸H

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