hindrance should not be reflected in the log PZ term. It should be noted that the apparent constancy of the log PZ term referred to in reference 5 compares values for benzoates determined in the range, 0–50°, with values for mesitoates determined in the range 120–170°.

It appears that the major hydrolytic path of methyl mesitoate with hydroxide ion is through acyl–oxygen fission although it has been shown that methyl mesitoate undergoes a very slow alkyl–oxygen cleavage with methoxide ion to yield dimethyl ether.[16] Although this alkyl–oxygen fission does occur, it has been pointed out that such a reaction is probably thermodynamically and not kinetically controlled and thus products of such reaction are not suitable general criteria of bond fission.[17]

Acknowledgment.—The authors wish to express their appreciation to Mr. Roger D. Ginger for assistance with the mass spectrometric analyses, to Dr. H. Taube of the University of Chicago through whose courtesy the mass spectrometer under AEC Contract At(11-1)-92 was made available and to Dr. Melvin S. Newman whose encouragement and suggestions facilitated this work. A Frederick Gardner Cottrell grant of the Research Corporation supported part of this work.

---

[16] J. F. Bunnett, M. M. Robison and F. C. Pennington, THIS JOURNAL, **72**, 2378 (1950).

[17] C. A. Bunton and A. Konasiewicz, *J. Chem. Soc.*, 1354 (1955).

CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Kinetics of Isotopic Oxygen Exchange between Substituted Benzoic Acids and Water[1]

BY MYRON L. BENDER, RICARDO R. STONE AND RAY S. DEWEY

RECEIVED SEPTEMBER 6, 1955

The kinetics of oxygen exchange between some substituted benzoic acids and water enriched in H_2O^{18} have been determined. The measurements were performed at 80° using a catalyst of about 0.07 *N* HCl in a solvent which consisted of 33% dioxane and 67% water containing approximately 0.6% H_2O^{18}. The rates of oxygen exchange of benzoic acid and of four *meta*- and *para*-substituted benzoic acids indicate that substituent effects in this reaction are quite small. Such small substituent effects have been noted previously in the acid-catalyzed hydrolysis of the corresponding esters. This similarity in substituent effects lends credence to the similar mechanisms involving addition intermediates that have been proposed for oxygen exchange of carboxylic acids and the hydrolysis of their carboxylic esters. The oxygen exchange of mesitoic acid was extremely slow, but detectable.

A study of the oxygen exchange between benzoic acid and water in aqueous acidic solution brought forth a number of similarities between the oxygen exchange of carboxylic acids and the acid-catalyzed hydrolysis of esters.[2,3] It was pointed out that both reactions were catalyzed by hydronium ion, that both involve acyl–oxygen fission and that the rates of the two reactions are of the same order of magnitude. On the basis of these observations, Roberts and Urey proposed that the mechanisms of these reactions are similar. Oxygen exchange between the carbonyl oxygen of an ester and the solvent water during the acidic hydrolysis of ethyl benzoate[4] indicated that ester hydrolysis must involve a symmetrical addition intermediate. The similarity of the mechanisms of the two reactions requires that the oxygen exchange of carboxylic acids must also involve a symmetrical addition intermediate.

One of the characteristics of the acidic hydrolysis of esters is that substituent effects on rate constants are small and do not necessarily follow a simple electronic effect of the substituent. This is in contrast to the substantial electronic effects encountered during the basic hydrolysis of esters.[5] For example the acidic hydrolysis of a series of *meta*- and *para*-substituted ethyl benzoates showed a variation in rate constant of less than 50% with both *p*-chloro and *p*-methoxy substituted esters possessing rate constants less than that of the unsubstituted ester.[6] The present work was designed to study the effect of substituents on the rate of oxygen exchange of benzoic acid in order to determine whether an effect similar to that observed in ester hydrolysis would be operative. Benzoic, *m*-chlorobenzoic, *p*-chlorobenzoic, *p*-anisic, *p*-toluic and mesitoic acids of normal isotopic composition reacted at 80° with a solvent of 33% dioxane and 67% water containing approximately 0.6% H_2O^{18} and with an over-all hydrochloric acid concentration of approximately 0.07 *N*.

Experimental

Materials.—Benzoic acid (Mallinckrodt analytical reagent) was recrystallized from a water–methanol solution; m.p. 122°. *p*-Chlorobenzoic acid (Mathieson and Co.) was recrystallized from ethanol; m.p. 234.5–235°. *m*-Chlorobenzoic acid, m.p. 154°, and *p*-toluic acid, m.p. 178°, were obtained through the courtesy of Dr. Martin Kilpatrick.[7] *p*-Anisic acid (Matheson and Co.) was recrystallized once from ethanol and once from water; m.p. 183.9–184.3°. Mesitoic acid was prepared by the carbonation of the appropriate Grignard reagent and was recrystallized twice from ethanol; m.p. 151.5–152.5°.

The solvent for the kinetic determinations consisted of one volume of dioxane and two volumes of an aqueous acidic solution enriched in H_2O^{18}. Commercial dioxane was purified by the method of Fieser.[8] The aqueous acidic solution was originally about 0.10 *N* in hydrochloric acid and 0.6% in H_2O^{18}. The enriched water was prepared by dilution of water containing *ca.* 1.5% H_2O^{18} (obtained from the Stuart

---

[1] VI in the Series, Intermediates in the Reactions of Carboxylic Acid Derivatives.

[2] I. Roberts and H. C. Urey, THIS JOURNAL, **61**, 2580 (1939).

[3] I. Roberts and H. C. Urey, *ibid.*, **61**, 2584 (1939).

[4] M. L. Bender, *ibid.*, **73**, 1626 (1951).

[5] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 211–214.

[6] E. W. Timm and C. N. Hinshelwood, *J. Chem. Soc.*, 862 (1938).

[7] See L. J. Minnick and M. Kilpatrick, *J. Phys. Chem.*, **43**, 259 (1939), for details of their purification.

[8] L. F. Fieser. "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1955, p. 285.

Oxygen Co. through the Atomic Energy Commission) with distilled water containing C.P. hydrochloric acid. The normalities of the hydrochloric acid in the final solution, as determined by titration with standard sodium hydroxide, are given in Table I.

Kinetics.—The oxygen exchange experiments were carried out using two methods. In one method, 10 ml. of dioxane–water solution was equilibrated in the thermostat in a 20-ml. long-necked glass-stoppered flask, and then a weighed quantity of carboxylic acid was lowered into the solvent in a small glass bucket. The carboxylic acid dissolved almost immediately. After appropriate periods of time, 1-ml. samples of the solution were removed and allowed to cool. Alternatively, Pyrex ampoules containing aliquots of the carboxylic acid in the dioxane–water solution were used. The ampoules contained about 1.2 ml. of solution; the contents were kept frozen until the ampoules were placed in the thermostat. After equilibration in the thermostat for appropriate lengths of time, the ampoules were cooled. Cooling of the samples usually effected crystallization of the carboxylic acid. In the case of benzoic acid, crystallization did not occur until a part of the solvent was removed under vacuum. After crystallization, the solvent was drawn off from the crystals by means of a capillary pipet. The carboxylic acid samples were then dried in a vacuum desiccator over phosphorus pentoxide. Drying was effected by pumping for at least 4 hr.,[2,8] or the desiccator was evacuated to about 0.2 mm. and left overnight.

The oxygen-18 analysis of the carboxylic acid samples was effected by conversion of the oxygen in the organic compounds to carbon dioxide according to the method of Doering and Dorfman[9] followed by mass spectrometric analysis of the carbon dioxide samples with a Consolidated-Nier isotope ratio mass spectrometer, model 21-201. A description of the details of this analytical procedure together with an analysis of the errors involved can be found in another paper of this series.[10] The blanks in the conversions to carbon dioxide which constituted one source of error in these analyses were never over 10% and usually under 5%.

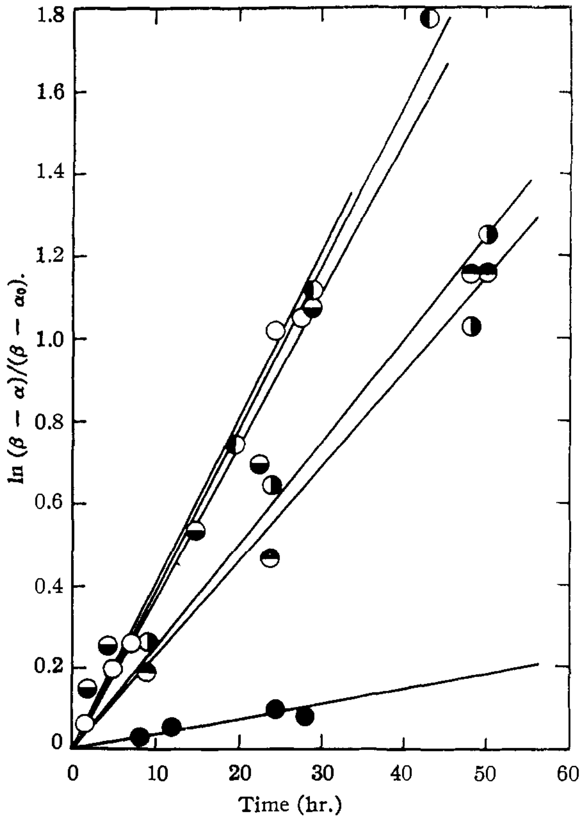


Fig. 1.—Oxygen exchange between substituted benzoic acids and water; temperature = 80.0°, solvent 33% dioxane–water.

	Acid	HCl (N)		Acid	HCl (N)
○	Benzoic	0.0708	◓	*p*-Anisic	0.0639
◐	*m*-Chlorobenzoic	.0639	◒	*p*-Toluic	.069
◑	*p*-Chlorobenzoic	.0639	●	Mesitoic	.069

Time scale for mesitoic acid, 10 hr. = 1000 hr.; α is the atom fraction of O^{18} in the carboxyl group of the acid; β is the atom fraction of O^{18} in the solvent water.

Results and Discussions

In Fig. 1 the results of the kinetics of oxygen exchange between six carboxylic acids and water are given. The mathematical derivation of Roberts and Urey[2] has been followed using that case in which the isotope enrichment is initially in the water. Rate constants were calculated from the slopes of the straight lines; these are listed in Table I.

TABLE I

THE KINETICS OF THE OXYGEN EXCHANGE OF SUBSTITUTED BENZOIC ACIDS[a]

Acid	(HCl)[b] N	10^5k, sec.$^{-1}$	10^4k_H[c], l./mole sec.
Benzoic	0.0708	1.14 ± 0.10	1.61
m-Chlorobenzoic	.0639	1.13 ± .04	1.77
p-Chlorobenzoic	.0639	0.70 ± .1	1.1
p-Anisic	.0639	0.64 ± .02	1.00
p-Toluic	.069	1.03 ± .3	1.5
Mesitoic	.069	0.00102 ± .00015	0.00148

[a] Temperature 80.0 ± 0.1° except for the mesitoic acid experiment which took four months and which temperature was 80.0 ± 0.5°. The rate constants have been corrected for solvent expansion. [b] The error in the normality of the hydrochloric acid was 0.0003 to 0.0013 N. [c] For HCl = 1 N.

In the calculation it was assumed that the rate of oxygen exchange is first order with respect to the difference in the isotope concentration between carboxylic acid and solvent water and that the reaction rate is proportional to the concentration of hydronium ion.[2] In converting the mass spectrometric readings into atom % O^{18} we have used an equation of Doering and Dorfman in which all oxygens of a compound exchange.[9] For *p*-anisic acid, in which two out of three oxygens can exchange, we have used equation 1, in which

$$\text{atom fraction } O^{18} = \frac{0.00612\text{Ru/Rs} - 0.00408}{0.99592 + 0.60408\text{Ru/Rs}} \quad (1)$$

Ru = 46/44 (sample) and Rs = 46/44 (standard).

The formation of double labeled carboxylic acid has been neglected in these equations. It is interesting to observe the difference in the rate constants for oxygen exchange in a purely aqueous solvent (k_H = 2.37 × 10^{-4} sec.$^{-1}$)[2] and in 33% dioxane–water (k_H = 1.61 × 10^{-4} sec.$^{-1}$). This diminution in the rate of oxygen exchange of benzoic acid in going from water to 33% dioxane parallels the diminution of rate in the acidic hydrolysis of ethyl benzoate when making such a change.

A comparison of the rates of oxygen exchange of benzoic acid and of the four *meta*- and *para*-substituted benzoic acids indicates that the effect of such substituents on the rates of the reaction is indeed small and that there is no direct correlation of the electronic effect of the substituent with the rela-

---

[9] W. E. Doering and E. Dorfman, THIS JOURNAL, **75**, 5595 (1953).

[10] M. L. Bender and K. C. unpublished results.

tive rates. The rate of oxygen exchange of benzoic acid is higher than that of the *p*-chloro- and *p*-methoxybenzoic acids. These results are similar to those previously mentioned for the acidic hydrolysis of the corresponding esters.[6] A comparison between the rate constants of oxygen exchange of the benzoic acids and the acidic hydrolysis of the corresponding ethyl benzoates is shown in Table II.

Table II

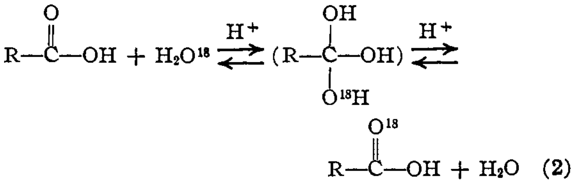
Rate Constants of Oxygen Exchange of Benzoic Acids and Acidic Hydrolysis of Ethyl Benzoates[a]

	$k_h \times 10^5$ of ethyl ester,[5] sec.$^{-1}$		$k_e \times 10^5$ of acid, sec.$^{-1}$	
Acid	60% ethanol–water	60% acetone–water	33% dioxane–water	k_h/k_e [b]
Benzoic	2.05	2.09	0.80	2.5
m-Chlorobenzoic			.88	..
p-Chlorobenzoic	1.87	1.85	.55	3.4
p-Anisic	1.41	1.34	.50	2.7
p-Toluic	1.65	1.68	.75	2.2

[a] HCl = 0.05 *N* and temperature = 80.0. [b] The k_e values contained in these k_h/k_e are for exchange between carboxylic acid and water as distinct from the k_e of oxygen exchange between esters and water during hydrolysis.[4] The values of k_h/k_e were obtained with the use of the average value of the two k_h values listed above.

The *meta*- and *para*-substituents appear to affect the oxygen exchange reaction and the acidic hydrolysis reaction in the same manner. The ratio of the rate constants for these two reactions remains fairly constant, varying from 2.2 for *p*-toluic acid to 3.4 for *p*-chlorobenzoic acid. A plot of log k_e *versus* σ following that of Hammett[11] produces a line with approximately the same slope as that of a plot of log k_h *versus* σ. Because of the small number of points and the large scatter in these plots it was not thought desirable to pursue this calculation. The fact that substituent effects in the oxygen exchange reaction parallel those in the acidic hydrolysis contributes an additional piece of evidence that indicates the similarity in the mechanisms of these reactions. It should be noted that, throughout the series of compounds, the absolute values of the velocity constants of these two reactions are very similar as has been pointed out before.[2,3] The rate constant for hydrolysis of the ethyl ester is somewhat larger than the rate constant for oxygen exchange of the acid perhaps because the addition to the ethyl ester is favored over addition to the carboxylic acid due to a higher degree of resonance stabilization in the latter molecule.

The oxygen exchange reaction can, with some degree of confidence, be postulated to proceed by means of addition of a molecule of water to the carboxylic acid to form an unstable intermediate, the *ortho* acid, which then can break down to give the exchanged products.



$$\mathrm{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}OH} + \mathrm{H_2O^{18}} \underset{}{\overset{H^+}{\rightleftarrows}} \left(\mathrm{R{-}\underset{\displaystyle O^{18}H}{\underset{|}{\overset{\displaystyle OH}{\overset{|}{C}}}}{-}OH}\right) \overset{H^+}{\rightleftarrows} \mathrm{R{-}\overset{\displaystyle O^{18}}{\overset{\|}{C}}{-}OH} + \mathrm{H_2O} \quad (2)$$

It is further postulated, because of the similarity of this process to that of ester hydrolysis, that the addition of water to the carboxylic acid is the slow step in the reaction and that the breakdown of the *ortho* acid is extremely rapid. In the scheme shown above the role of the hydronium ion is not specified. By analogy to other reactions involving addition to the carbonyl group, it must serve to polarize the carbonyl group, by the formation of the conjugate acid of the carboxylic acid, and thus promote the addition of the molecule of water. In an acidic medium all of the species shown in (2) would be in equilibrium with their respective conjugate acids.

Mesitoic acid appears to undergo oxygen exchange at a rate about 10^{-3} slower than benzoic acid. Although there are no data on acidic hydrolysis of methyl mesitoate, data on its alkaline hydrolysis indicate a similar diminution in rate with respect to the hydrolysis of methyl benzoate.[12] Tracer and exchange experiments conducted during the alkaline hydrolysis of methyl mesitoate provide evidence for an acyl–oxygen cleavage in this reaction together with the formation of a symmetrical addition compound capable of exchange.[13] In the oxygen exchange of mesitoic acid, a similar process involving the formation of an unstable *ortho* acid intermediate is postulated. The alkaline hydrolysis of methyl mesitoate and the oxygen exchange of mesitoic acid apparently proceed through mechanisms similar to those for the corresponding benzoic acid cases but at a much slower rate due to the steric hindrance or *ortho* effect associated with the di-*ortho* substitution.[13]

Acknowledgment.—The authors gratefully acknowledge the assistance of a Frederick Gardner Cottrell grant from the Research Corporation, and wish to thank Mr. R. D. Ginger for assistance with the mass spectrometric analyses and Dr. H. Taube through whose courtesy the mass spectrometer under AEC contract At(11-1)-92 was made available.

Chicago, Illinois

---

[11] Reference 5, p. 187.

[12] H. L. Goering, T. Rubin and M. S. Newman, This Journal **76**, 787 (1954).

[13] M. L. Bender and R. S. Dewey, *ibid.*, **78**, 317 (1956).