ORGANIC AND BIOLOGICAL CHEMISTRY

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

The Mechanism of the Alkaline Hydrolysis of Methyl 2,4,6-Trimethylbenzoate[1]

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RECEIVED SEPTEMBER 6, 1955

Methyl 2,4,6-trimethylbenzoate (mesitoate) was hydrolyzed under basic conditions at 126.0 ± 0.1° in a solvent containing 60% dioxane and 40% water containing excess H_2O^{18}. The mesitoic acid recovered from the hydrolysis was found to have an O^{18}-content equivalent to that resulting from the introduction of one oxygen atom of the labeled water into the carboxylic acid group. Acyl–oxygen fission is postulated to explain the increase in O^{18}-content in the carboxylic acid group. Isotopic oxygen exchange was observed between the ester and solvent during alkaline hydrolysis. The ratio of the rate constant of hydrolysis to the rate constant of exchange is 6.8 ± 0.5. The alkaline hydrolysis of methyl mesitoate is apparently similar to that of ethyl benzoate in that a symmetrical addition compound, capable of exchange, is formed. The former process is much slower than the latter largely because of a much higher energy of activation in the former process but the mechanism of the reaction does not change even with this extremely hindered ester.

A classical example of "steric hindrance" as it was termed by Meyer[2,3] or of the "*ortho* effect" or "proximity effect" as it was termed by Dippy and co-workers[4] has been the pronounced retardation of the reactions of di-*ortho*-substituted benzoic acids and their derivatives. Recently the rates of saponification of a series of methyl 4-substituted-2,6-dimethylbenzoates were measured in 60% dioxane–40% water solution.[5] From the magnitude of the log PZ terms for the alkaline hydrolysis of the di-*ortho*-substituted esters and from the value of rho[6] which was found for this reaction, it was proposed that the reactions proceed with a mechanism differing from that of benzoic acid esters. It was suggested that the alkaline hydrolysis of methyl 2,4,6-trimethylbenzoate (mesitoate) occurred with alkyl–oxygen fission whereas the hydrolysis of methyl benzoate was known to occur with acyl–oxygen fission.[7] It is the purpose of the present research to provide isotopic tracer and exchange evidence concerning the mechanism of the alkaline hydrolysis of methyl mesitoate, a typical di-*ortho*-substituted benzoic acid ester. The present work involves the determination of the type of fission of the ester by the isotopic tracer method of Polanyi and Szabo[8] involving the hydrolysis of the ester in water enriched in H_2O^{18} and determination of the isotopic oxygen exchange between the carbonyl oxygen of the ester and the solvent water during the hydrolytic process.[9] Such an exchange was shown to occur during the alkaline hydrolysis of a number of esters which are known to cleave *via* acyl–oxygen fission. However, such exchange would not be expected to occur during an alkyl–oxygen fission.

Experimental

Methyl Mesitoate.—Mesitoic acid, m.p. 152–153°, was converted to the acid chloride with thionyl chloride and treated with excess methanol. The ester distilled at 77–79° (1 mm.); $n^{20}D$ 1.5083.

Dioxane.—Commercial dioxane was purified by the method of Fieser[10]; b.p. 99.6–100.0°, $n^{20}D$ 1.4221.

Kinetic Studies.—The rate constant of hydrolysis of methyl mesitoate in 60% dioxane and 40% water (by volume) at 126.0 ± 0.1° was determined. The conditions of Goering, Rubin and Newman[5] were employed except that glass ampules (Corning alkali resistant glass No. 728) were used instead of stainless steel tubes. The ampules were sealed under nitrogen. The extent of hydrolysis was determined by titration of aliquots from the ampules using standardized hydrochloric acid solution and phenolphthalein indicator. The second-order rate constant was corrected for solvent expansion using the densities determined previously.[5] The mean value of the second-order rate constant for the reaction was $2.2 \pm 0.2 \times 10^{-3}$ l./mole-sec. This value is significantly different from that reported by Goering, Rubin and Newman of $1.40 \pm 0.054 \times 10^{-3}$. It was thought that the discrepancy might lie in the reaction of sodium hydroxide with the "alkali resistant" glass or with the dioxane. A blank experiment with aqueous sodium hydroxide in the alkali resistant glass indicated no reaction, but a blank experiment containing sodium hydroxide in dioxane–water in the alkali resistant glass indicated that a reaction did indeed take place. However at one half-life of the hydrolysis reaction, the percentage decrease in the sodium hydroxide concentration in the blank was only 1.1%.

Isotopic Oxygen Experiments.—The determination of the position of cleavage in the alkaline hydrolysis of methyl mesitoate was carried out by hydrolyzing an ester of normal isotopic oxygen content in a solvent enriched in H_2O^{18}. A solution of water approximately 0.5% in H_2O^{18} was prepared by the dilution of water 1.5% in H_2O^{18} obtained from the Stuart Oxygen Co. through the Atomic Energy Commission. This water was then used to prepare the 60–40 dioxane–water mixture. Runs identical in all respects with those of the kinetic determinations except for the isotopic composition of the water were made. These runs were carried out to 82 and 99% completion at 126.0 ± 0.1°. The mesitoate ion so produced was recovered as mesitoic acid by distilling part of the solvent, adding water and distilling again to about one-fifth of the original volume, acidifying this solution to *p*H 1 with hydrochloric acid and cooling the mixture. The acid crystals were filtered and sublimed at 25 mm.; m.p. 152.0–152.8°.[11] The isotopic oxygen compositions of the mesitoic acid samples were determined as described later. The results are shown in Table I.

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(1) V in the series, Intermediates in the Reactions of Carboxylic Acid Derivatives.

(2) V. Meyer, H. Gumbel and J. J. Sudborough, *Ber.*, **27**, 510 (1894).

(3) *Cf.* F. Kehrmann, *ibid.*, **21**, 3315 (1888); G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 378–386; and S. Goldschmidt in K. Freudenberg, "Stereochemie," F. Deuticke, Leipzig, 1933, pp. 451 ff. for a comprehensive review.

(4) J. F. J. Dippy, D. P. Evans, J. J. Gordon, R. H. Lewis and H. B. Watson, *J. Chem. Soc.*, 1421 (1937). *Cf.* other papers of this series.

(5) H. L. Goering, T. Rubin and M. S. Newman, THIS JOURNAL, **76**, 787 (1954).

(6) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII.

(7) J. N. E. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).

(8) M. Polanyi and A. L. Szabo, *ibid.*, **30**, 508 (1934).

(9) M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).

(10) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 368.

(11) Results of M. L. Bender, R. R. Stone and R. S. Dewey, THIS JOURNAL, **78**, 319 (1956), indicate that the oxygen exchange between mesitoic acid and aqueous acid is extremely slow at room temperature and could not affect the isotopic oxygen composition of these samples. It has also been shown by means of a blank experiment that mesitoate ion does not exchange oxygen with water at 126.0 ± 0.1° over a period of 6 hours.

Oxygen exchange between the carbonyl oxygen of methyl mesitoate and water during alkaline hydrolysis was measured using an ester of normal isotopic oxygen composition and a solvent enriched in H_2O^{18} as above. Runs identical with those used in the kinetic determinations were again performed. After appropriate amounts of time, the ampules were removed from the thermostat, cooled and the contents were extracted five times with methylene chloride. The combined organic layers were dried with magnesium sulfate, the solvent removed and the methyl mesitoate samples were distilled in a microdistillation apparatus at 1 mm. The isotopic oxygen composition of the methyl mesitoate samples were then determined as described later. The results are given in Table II.

Oxygen-18 Analysis.—The method employed for the oxygen-18 analysis of the solvent water, the mesitoic acid and the ester consisted of conversion of the oxygen in these compounds to carbon dioxide, followed by analysis of the carbon dioxide samples by means of a Consolidated-Nier model 21-201 isotope ratio mass spectrometer. The method utilized for the conversion of the samples to carbon dioxide is that of Doering and Dorfman.[12] The equations of these workers were used to calculate the atom % O^{18} in the various compounds. In the cases of the mesitoic acid and methyl mesitoate analyses, it was assumed that an isotopic oxygen atom could be introduced into only one of the two possible positions in the molecule, the other atom maintaining its normal isotopic composition. A discussion of the details of the method, together with an evaluation of the errors involved, can be found in another paper in this series.[13] A blank which arose during the conversion of the samples to carbon dioxide was considered to be the main source of error. The size of this blank was systematically measured (the average blank was 5% of the sample) and corrected as a dilution containing normal isotopic composition.

Results and Discussion

Acyl–oxygen fission is postulated for the alkaline hydrolysis of methyl mesitoate on the basis of the increase in the oxygen-18 content of the mesitoic acid recovered from the hydrolysis as indicated in Table I. The oxygen-18 content of the acid was calculated on the basis that only one oxygen-18 atom was introduced into the carboxylic acid group. When this result is compared with the analysis of the solvent water used in the hydrolysis experiment, it is apparent that the mesitoic acid contains one oxygen-18 atom which originated in the solvent.

TABLE I

O^{18} ANALYSIS OF MESITOIC ACID PRODUCED FROM THE ALKALINE HYDROLYSIS OF METHYL MESITOATE IN H_2O^{18}

Run	Reaction, %	Atom % O^{18}[c] H_2O^{18} used	Atom % O^{18}[c] Recovered mesitoic acid[e]
1[a]	99	0.50[d]	0.505[f]
2[b]	82	.517	.539

[a] (NaOH) = 0.0556 *N*, (ester) = 0.0176 *N*; temperature 126.0 ± 0.1°. [b] (NaOH) = 0.0494 *N*, (ester) = 0.0230 *N*; temperature 126.0 ± 0.1°. [c] Based on an arbitrary carbon dioxide sample taken as 0.204 atom % O^{18}. [d] Based on volumetric dilution of a sample of water that had been analyzed as 1.50 atom % O^{18}. [e] The O^{18} composition of the initial methyl mesitoate was 0.195. [f] Average of four determinations.

Further support for the acyl–oxygen fission process is indicated by the fact that oxygen exchange between the ester and solvent water occurred during the hydrolysis. In previous work, such exchange reactions have been observed during the hydrolysis of a number of esters which are known to cleave *via* acyl–oxygen fission.[9] In this work, the ester was originally of normal isotopic oxygen composition while the solvent was enriched in oxygen-18, which is the reverse of the experimental procedure used in previous work. However, a similar equation can be developed in this case for the calculation of the ratio of the rate constant of hydrolysis to the rate constant of exchange. By a set of chemical equations and differential equations, it can be shown that $k_h/k_e = \beta(\ln E_0/E)/(E'/E)$ where the symbols employed are the same as those used previously,[9] except for β which equals (hydroxide ion containing excess O^{18})/(total hydroxide ion). Using this equation, an average value of k_h/k_e was found to be 6.8 ± 0.5 as shown in Table II. This value is strikingly similar to those found with ethyl benzoate even though the solvent and temperature are somewhat different.[14] The recovered mesitoic acid showed a small but definite excess of oxygen-18 over that expected from the introduction of one atom of oxygen-18 into the carboxylic acid (see Table I, run 2). This can readily be explained as arising from an ester which has undergone a partial oxygen exchange and thus corroborates the oxygen exchange during the hydrolysis.

TABLE II

OXYGEN EXCHANGE DURING THE ALKALINE HYDROLYSIS OF METHYL MESITOATE IN H_2O^{18}[a]

Hydrolysis, %	Carbonyl oxygen of ester, atom % O^{18}[c]	k_h/k_e
49	0.226	6.8[b]
62	.254	6.1
82	.275	7.6
	Av.	6.8 ± 0.5

[a] (NaOH) = 0.0494 *N*; (methyl mesitoate) = 0.0230; temperature = 126.0 ± 0.1°. [b] This value is the average of two analyses. [c] The O^{18} composition of the original ester was 0.206.

On the basis of the isotopic tracer and exchange work described above, it is suggested that the mechanism of the alkaline hydrolysis of methyl mesitoate is similar in all respects to that of ethyl benzoate except that the former process is much slower. It is postulated that in the alkaline hydrolysis of methyl mesitoate a symmetrical addition compound capable of exchange is formed, and further that this intermediate breaks down with consequent acyl–oxygen fission. Since Goering, Rubin and Newman[5] found a constant rho for five methyl di-*ortho*-substituted benzoates, it is probable that the above mechanism is applicable to that whole series of compounds. It should be noted that it has been reported that the alkaline hydrolysis of methyl 2,4,6-triphenylbenzoate in aqueous 95% methanol also proceeds by acyl–oxygen fission.[15]

It has been pointed out that the large slowdown in the rate of hydrolysis of methyl mesitoate when compared to ethyl benzoate is due to the energy of activation and not to the log *PZ* term which remains essentially constant.[5] It is not apparent to us at this time why this extreme example of steric

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[12] W. E. Doering and E. Dorfman, THIS JOURNAL, **75**, 5595 (1953); *cf.* M. L. Bender and R. D. Ginger, *ibid.*, **77**, 348 (1955).

[13] M. L. Bender and K. C. Kemp, unpublished results.

[14] Unpublished results of M. L. Bender and R. D. Ginger indicate that the ratio k_h/k_e is temperature dependent to a slight extent in the hydrolysis of benzamide.

[15] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 764.

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).

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

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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

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[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.