2,4-dinitrophenyl thiocyanate (8%), when poured into water. *After* 20% reaction KF began to precipitate.[42] In methanol the reaction gave 2,4-dinitroanisole and became acidic. No thiocyanate ion was consumed.

Potassium or lithium iodide with 1-bromo-2,4-dinitrobenzene in acetone at 100° gave 1-iodo-2,4-dinitrobenzene (95% with KI,[43] 45% with LiI). With LiI, 45% 1-bromodinitrobenzene was recovered unchanged. In methanol at 120°, 1-bromo-2,4-dinitrobenzene and 1-iodo-2,4-dinitrobenzene were recovered in proportions corresponding closely to the equilibrium value (67 and 33%, respectively). It made no difference whether LiI or KI was used.

Potassium or lithium iodide with 1-fluoro-2,4-dinitrobenzene gave a black tar, some hydrogen fluoride and unchanged 1-fluoro-2,4-dinitrobenzene[44] (80%) when poured into water after heating in acetone at 121° for 24 hours.

(42) This reaction is not a simple SnAr displacement. It would not proceed beyond 40% consumption of thiocyanate ion. We assume

ii
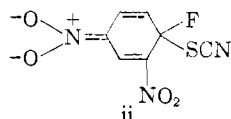
that the complex ii is formed, but not in high concentration. Decomposition of the complex *via* other paths involving displacements from sulfur[21] accounts for the products and the consumption of SCN⁻.

(43) Precipitation of KBr in acetone drives the equilibrium to the right.

(44) The complex iii is formed in low concentration, apparently

iii
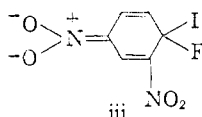
cannot dispose of fluoride in the usual (SnAr) way, and decomposes slowly by some other (radical?) path at high temperature.

The Existence of an SnAr Intermediate Complex.—A 0.05 M red solution of sodium azide and 4-fluoronitrobenzene in DMF was warmed at 60° for 1 hour. A yellow homogeneous solution resulted and no sodium fluoride could be seen. The solution absorbed strongly at 397 mμ[45] although neither 4-nitrophenyl azide (361 mμ) nor 4-nitrofluorobenzene (367 mμ) absorb at this wave length in DMF. In all other dipolar aprotic solvents intense red colors developed, with a transient blue color in acetone.

The following experiments were performed on 50-ml. portions of the reaction mixture: (a) Poured into excess water at 25°[46]; no azide ion was present and pure 4-nitrophenyl azide (100%) was obtained. The solution fluoresced and for a few moments became quite viscous. (b) A little water (1 ml.) was added. Crystals of sodium fluoride appeared on warming. These were insoluble in anhydrous DMF or the original reaction mixture. The experiment was repeated using acetone in place of water, but the solution remained homogeneous. The 397 mμ absorption slowly disappeared when 1 ml. of water was added.[47] (c) A weighed portion of NaF was added and warmed. It was recovered by filtration without change in weight.[48] Attempts are now being made to isolate the sodium salt of this complex.

(45) Measurements made by Mr. R. Bolton.

(46) Azide ion was not consumed by 4-fluoronitrobenzene in 50% aqueous DMF at 25° after 2 hours.

(47) It should be possible to measure the rate of formation and of decomposition of the complex spectrophotometrically.

(48) Sodium fluoride was not present as a colloidal suspension or a supersaturated solution in the reaction mixture.

Acylium Ion Formation in the Reactions of Carboxylic Acid Derivatives. II. The Hydrolysis and Oxygen Exchange of Methyl Mesitoate in Sulfuric Acid[1a]

BY MYRON L. BENDER[1b,c] HARRY LADENHEIM AND MARK C. CHEN

The hydrolysis and oxygen exchange of methyl mesitoate-*carbonyl-O¹⁸* have been studied at 25, 35, 45 and 90°, and at 3.09, 5.78, 9.8 and 11.5 M sulfuric acid. A spectrophotometric method has been developed for the determination of the kinetics of this hydrolytic process. The half-life of the hydrolysis of methyl mesitoate in 11.5 M sulfuric acid at 25° is 9 minutes, utilizing conditions considerably milder than those reported previously for obtaining high yields of mesitoic acid. The kinetic results at the higher acidities agree well with the Hammett-Zucker correlation between logarithm of the rate constant and H_0. The enthalpy and entropy of activation of the hydrolytic reaction in 9.8 and 11.5 M sulfuric acid are 28.4 kcal./ mole and 17.0 e.u. and 22.5 kcal./mole and 4.1 e.u., respectively. Carbonyl oxygen exchange is absent at 3.09, 5.78 and 11.7 M sulfuric acid. Most significant is the absence of exchange at the lowest acidity where another path, such as a bimolecular mechanism, would offer most competition. The H_0 correlation, the entropies of activation and the lack of oxygen exchange indicate that the reaction proceeds by a unimolecular heterolysis, presumably because of particularly favorable conditions of structure and solvent.
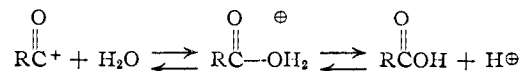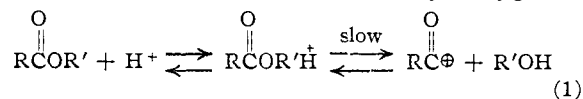
Introduction

The purpose of this continuing study is to provide an insight into the conditions and mechanism of acylium ion formation, using kinetic and oxygen-18 tracer techniques. The plan of the program is given in detail in a previous publication[2]; briefly, it is to generalize the use of oxygen exchange results as corroborative evidence for various types of hydrolytic reaction mechanisms. In reactions involving acylium ion formation, it is

(1) (a) This research was supported by a grant from the National Science Foundation. (b) Alfred P. Sloan Foundation Research Fellow. (c) Dept. of Chemistry, Northwestern University, Evanston, Ill.

(2) H. Ladenheim and M. L. Bender, THIS JOURNAL, 82, 1895 (1960).

predicted that concurrent carbonyl ex-

$$\underset{\text{RCOR'}}{\overset{O}{\underset{\|}{}}} + H^+ \rightleftharpoons \underset{\text{RCOR'H}}{\overset{O}{\underset{\|}{}}}{}^+ \overset{\text{slow}}{\rightleftharpoons} \underset{\text{RC}^\oplus}{\overset{O}{\underset{\|}{}}} + R'OH \quad (1)$$

$$\underset{\text{RC}^+}{\overset{O}{\underset{\|}{}}} + H_2O \rightleftharpoons \underset{\text{RC—OH}_2}{\overset{O \oplus}{\underset{\|}{}}} \rightleftharpoons \underset{\text{RCOH}}{\overset{O}{\underset{\|}{}}} + H^\oplus$$

change and hydrolysis will *not* occur, in contrast to the results occurring in reactions involving the formation of a tetrahedral addition intermediate.[3] Therefore, in a reaction where an acylium ion path occurs, absence of carbonyl oxygen exchange should serve as a non-kinetic criterion of mechanism.

(3) M. L. Bender, *Chem. Revs.*, 60, 53 (1960).

In a recent study concerning the acid-catalyzed solvolysis of alkoxymethyl esters, Salomaa presented evidence of a correlation between rate and h_0 for reactions involving competing unimolecular and bimolecular paths.[4-6] This finding raises a serious objection to the presently accepted experimental basis of such relationships,[7] and implies that the h_0 function is not sufficiently sensitive to detect a concurrent bimolecular reaction. Even more significantly, k is still proportional to h_0 for methoxymethyl formate, where the bimolecular reaction is appreciably faster than the unimolecular one. Salomaa concludes that only when proportionality between k and $c_{H_3O^+}$ is observed can unambiguous conclusions be drawn, and that when a linear relation of k and h_0 is observed other criteria must be employed to detect or eliminate other possible competitive mechanisms.[5,6]

The study of oxygen exchange during the hydrolysis of methyl mesitoate in sulfuric acid offers an opportunity for testing the prediction concerning the absence of carbonyl oxygen exchange in a reaction involving acylium-ion formation. Furthermore, the exchange study provides an additional criterion which may clarify the situation described by Salomaa.

The cryoscopic behavior of methyl mesitoate in 100% sulfuric acid, which shows an immediate van't Hoff "i" factor of 5[8] has been explained by the formation of the mesitylium ion, 2,4,6-$(CH_3)_3$-$C_6H_2C^+$ in the reaction

$$RCOR' + 3H_2SO_4 \rightleftharpoons RC^{\oplus} + R'OSO_3H + H_3O^+ + 2HSO_4^- \quad (2)$$
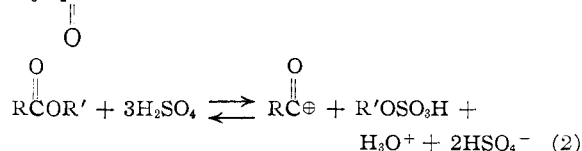
Isolation of mesitoic acid in high yield by pouring such a solution into ice-water indicates complete hydrolysis. Kinetic evidence that the hydrolysis of this ester involves acylium-ion formation has been given by Chmiel and Long.[9] The results of hydrolysis in 1.0–5.8 M perchloric acid and 3.1–6.1 M sulfuric acid yield a proportionality between the rate constant and h_0. These data indicate that this reaction can be ideally used for the purposes stated above. It is true, of course, that methyl mesitoate no longer enjoys the distinction of being the only ester shown to undergo hydrolysis in 100% sulfuric acid; some ordinary ones such as methyl benzoate also undergo hydrolysis, except that they do so only upon heating or prolonged standing.[10] Methyl mesitoate remains the only ester which quantitatively forms a stable acylium ion in 100% sulfuric acid, exhibits the rate–h_0 correlation and reacts by acyl–oxygen fission in solutions more aqueous than anhydrous sulfuric acid,[9] making the proposed study convenient over a wide range of acidity.

Experimental

Materials.—Sulfuric acid solutions of desired molarity were diluted from commercial concentrated sulfuric acid (B and A quality, C.P. reagent grade). Diluted aliquots of the stock solutions were titrated with standard sodium hydroxide.

Labeled methyl mesitoate and mesitoic acid were prepared in the following manner. Unlabeled mesitoic acid (3.05 g.) was allowed to stand overnight with purified[11] thionyl chloride, the latter in 20% molar excess. Then, after a short reflux period of 20 minutes, thionyl chloride and gaseous products were removed under vacuum. A 10–20% molar excess of H_2O^{18} (1.85 atom % O^{18}, The Weizmann Institute of Science, Rehovoth, Israel) was added dropwise, and with stirring, to an ice-cooled solution of the acid chloride dissolved in 5 ml. of anhydrous ether (Mallinckrodt, analytical reagent), and the mixture then was refluxed for 15 minutes. The ether was removed under vacuum. The labeled acid was recrystallized from ethanol–water and dried *in vacuo;* m.p. 153.3–153.8° cor., yield 64%. The mesitoic acid-O^{18} was treated with thionyl chloride as above. After refluxing and removal of excess thionyl chloride and gaseous by-products, the acid chloride-O^{18} was added dropwise, with stirring, to an ice-cooled solution containing a 30% molar excess of anhydrous methanol (Baker, reagent grade) and a few drops of pyridine (Baker, reagent grade, stored over potassium hydroxide pellets). The mixture was refluxed for 0.5 hour. The ester solution was dissolved in methylene chloride (Matheson, Coleman and Bell), washed with 5% sodium carbonate solution and dried overnight over anhydrous sodium sulfate. The labeled ester was distilled, exhibiting the same properties as reported in the literature.[8]

Kinetic Procedure.—A direct spectrophotometric method has been developed in this work. It involves reading of the absorption of the reacting solution with time, and can be used in this case since the rate constant of the consecutive (decarboxylation) reaction is much smaller than that of the primary (hydrolytic) one. The spectrophotometric method avoids the operational complication found in the work of Chmiel and Long.[9] The latter method involves separation of mesitoic acid from the reaction mixture and determination of its concentration spectrophotometrically. This laborious method was used to prevent kinetic complications arising from the decarboxylation of mesitoic acid. Chmiel and Long have shown, however, that the decarboxylation is smaller than hydrolysis, by thirty-fold at 5.78 M sulfuric acid, and by seventy-fold at 11.7 M.[12] Thus, the secondary reaction can be considered negligible and direct spectrophotometric reading will lead directly to the kinetics of hydrolysis. The values for k_1 given in Table I, determined by this procedure, are in good agreement with the values interpolated from Chmiel and Long's work, whose data are somewhat modified by application of more recent values of H_0 (first reference in Table I).

Measurements at 25, 35 and 45° were followed at 235 or 247 mμ in a thermostated Beckman DK-2 recording spectrophotometer or a thermostated Beckman DU spectrophotometer. Owing to the small solubility of the ester in sulfuric acid, the speed of the reaction, and the small difference in initial and final absorption, it sometimes was found convenient to use cells of 5-cm. path length, containing approximately 15 ml. of solution. After the cells containing the sulfuric acid solutions were thermostated, 50 lambda of a solution of the methyl ester in acetonitrile (0.043 M) was added, rapidly shaken and the recorder started. Acetonitrile (spectral grade, Eastman Kodak Co.) was found to be stable in the acid solution for the duration of the hydrolysis runs, as shown by the constancy of the (very low) acetonitrile absorption contribution.

For the 90° runs, sealed ampoules (10 × 190 mm., Pyrex) were used. Each ampoule contained 4 ml. of a 1.9 × 10^{-4} M solution of the ester in sulfuric acid. In this instance, the solution was prepared by shaking the two components at room temperature for a half to one hour, as the hydrolysis

(4) P. Salomaa, *Acta Chem. Scand.*, 11, 132, 141, 235, 239 (1957).

(5) P. Salomaa and R. Linnantie, *ibid.*, 12, 2051 (1958).

(6) P. Salomaa, private communication.

(7) F. A. Long and M. A. Paul, *Chem. Revs.*, 57, 935 (1957).

(8) M. S. Newman, H. G. Kuivila and A. B. Garrett, THIS JOURNAL, 67, 704 (1945), and references therein.

(9) C. T. Chmiel and F. A. Long, *ibid.*, 78, 3326 (1956).

(10) (a) M. S. Newman, R. A. Craig and A. B. Garrett, *ibid.*, 71, 869 (1949); (b) L. P. Kuhn and A. H. Corwin, *ibid.*, 70, 3370 (1948); (c) A. Bradley and M. E. Hill, *ibid.*, 77, 1575 (1955); (d) J. A. Leisten, *J. Chem. Soc.*, 1572 (1956).

(11) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1957, p. 345.

(12) Interpolation of data in ref. 7, p. 949, ref. 9, p. 3328, and the present work.

is quite slow under the conditions used in these experiments. The ampoules were withdrawn at various times, chilled instantly, allowed to warm up to room temperature, and the absorption of the solution then determined at 240 mμ on a Beckman DU spectrophotometer.

Exchange Runs.—At 25°, the labeled ester, weighed in a small glass boat (59–62 mg.), was added to the previously thermostated sulfuric acid solution (200–240 ml.). The mixture was shaken rapidly and immersed in a 25° bath. At predetermined times, the solutions were chilled to −10°, and concurrently diluted with an equal amount of water, thereby quenching the reaction. The solution was extracted with methylene chloride, and washed with 5% sodium carbonate solution and water. To avoid sample contamination by stopcock grease, a separatory funnel with a Teflon plug was used throughout. The dried solution was concentrated to a small volume by atmospheric distillation and the residue distilled in a micro-distillation apparatus[13] (modified in that bulb A has been eliminated).

At 90°, ampoules of large volume (46 × 240 mm.), holding 380 ml., were used for the oxygen exchange experiments. They were constructed with a small side-arm and a neck of 15-mm. diameter at the edge, rather than the center of the cylinder. The ester (21–35 mg.), in a boat, was dropped into the side-arm, the acid (180–300 ml.) into the body of the ampoule and the neck was sealed under atmospheric pressure. The ester and acid were shaken thoroughly at room temperature. The ampoule was immersed in a 90° bath for 1 minute, shaken for a half minute, and heated for a minute. This procedure was repeated three more times. Though the ester was partially insoluble at room temperature, indicated by a hazy solution and floating globules, at the elevated temperature after four shakings, the solutions were perfectly clear and homogeneous. The ampoules were chilled at appropriate times, quenching the reaction. The remainder of the procedure is identical with that described above.

In a majority of the runs, the carbonate washings were acidified, extracted with methylene chloride, and the latter evaporated to obtain the mesitoic acid. This served to indicate that reaction had occurred, and gave a fair approximation of the kinetics of hydrolysis.

It was necessary to determine the solubility of methyl mesitoate in various concentrations of sulfuric acid, so that the minimal volumes of sulfuric acid could be used. This was done by constructing Beer's law plots for methyl mesitoate in the various sulfuric acid solutions at 25°. As expected, Beer's law was obeyed to a higher ester concentration in the more concentrated acid solution. The region of deviation was considered to correspond to a saturated solution. It was assumed that the solubility at 90° would be appreciably higher than at 25°.

Isotopic Oxygen Analysis.—The ester was pyrolyzed to carbon dioxide with mercuric chloride at 510° and the carbon dioxide analyzed mass spectrometrically as described previously.[2] The following derivation gives X, the atom fraction of O^{18} in the carbonyl position of the ester, calculated from the mass spectrometric data. The pyrolysis reaction is given by

$$y \, R\overset{O^{18}}{\overset{\|}{C}}OR' + C \longrightarrow y \, CO_2^{18}$$
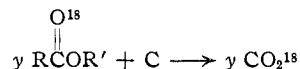
fract. of CO_2 as $CO^{18}O^{16} = X(0.99796) + (1 - X)0.00204$

fract. of CO_2 as $CO^{16}O^{16} = (1 - X)0.99796$

The assumption is made that the oxygen atoms of the ester molecule appear in the same carbon dioxide molecule. The number of molecules of CO_2 species is the fraction of that species multiplied by yA, where A is Avogadro's number. The remainder of the mathematical manipulation is identical with that used before.[2] Finally

$$X = \frac{(R_u/R_s)0.00408 - 0.00204}{(R_u/R_s)0.00408 + 0.99592}$$

where

R_u = mass spectrometric reading for CO_2 from pyrolysis

R_s = mass spectrometric reading for CO_2 standard (normal) CO_2

(13) M. J. Babcock, *Anal. Chem.*, **21**, 632 (1949).

Results and Discussion

The kinetics of hydrolysis of methyl mesitoate in various sulfuric acid solutions are shown in Table I. It is interesting to note that at 11.5 M sulfuric acid the half-life for the hydrolysis of methyl mesitoate at 25° is 9 minutes. This result confirms the qualitative finding of Schubert that it is unnecessary to use 100% sulfuric acid to hydrolyze methyl mesitoate in high yield.[14] He has reported that the ester is hydrolyzed in 83% sulfuric acid (14.8 M) on standing for 20 minutes, or in 75% sulfuric acid (12.7 M) with slight warming on the steam-bath. The present results indicate that even milder conditions suffice for hydrolysis of methyl mesitoate, with concentrations of sulfuric acid much below 100%.

TABLE I

THE KINETICS OF HYDROLYSIS OF METHYL MESITOATE IN SULFURIC ACIDS SOLUTIONS

H_2SO_4, M	$-H_0{}^a$	25.4°	35.3°	44.6°	90.4°
		$k \times 10^2$, sec.${}^{-1}$			
3.09	1.44				0.0096^b
5.78	2.67				0.32
9.8	4.78	0.037^c	0.27	0.85	
11.5	5.62	1.31	5.1	9.9	

^{a} Values at 25°, interpolated from M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957). ^{b} Interpolated from ref. 9. ^{c} 24.2°.

At the highest acid concentrations reported in Table I, the hydrolysis certainly proceeds by way of the A-1 (acylium ion) mechanism. This hypothesis is based on the known acylium ion formation of methyl mesitoate in 100% sulfuric acid, on the relative rates of hydrolysis of methyl mesitoate and methyl benzoate in sulfuric acid solutions,[15] and on the correlation between the logarithm of the hydrolytic rate constant and H_0. This proportionality has been demonstrated by Chmiel and Long in the region below 6.1 M sulfuric acid and also appears to hold in the high acidity region investigated here although the differentiation between dependence on H_0 and the log of the concentration of the hydronium ion is not unambiguous in the high acidity region.

From the data in Table I it is possible to calculate the enthalpy and entropy of activation of the hydrolysis of methyl mesitoate in 9.8 and 11.5 M sulfuric acid. These results are shown in Table II.

TABLE II

ACTIVATION PARAMETERS OF THE HYDROLYSIS OF METHYL MESITOATE IN SULFURIC ACID SOLUTIONS

Sulfuric acid, M	ΔH^*, kcal./mole	ΔS^*, e.u.
9.8	28.4 ± 1	17.0 ± 5
11.5	21.5 ± 1	6.0 ± 5

The most significant results are the entropies of activation which are in both instances positive values and considerably different from the ordinary acidic hydrolysis of methyl acetate, for example, which exhibits an entropy of activation of −21.3 entropy units.[16] Taft has suggested that hydro-

(14) W. M. Schubert, THIS JOURNAL, **71**, 2639 (1949).

(15) The relative rate argument will be elaborated on in a subsequent paper.

(16) R. W. Taft, Jr., THIS JOURNAL, **74**, 5372 (1952); R. W. Taft, Jr., E. L. Purlee, P. Riesz and C. A. De Fazio, *ibid.*, **77**, 1584 (1955).

lytic reactions proceeding by A-1 mechanisms (with either a carbonium ion or an acylium ion intermediate) should have more positive entropies of activation than those involving A-2 mechanisms since the latter mechanisms involve more constraint on the reaction system in the transition state due to the orientation and participation of a specific water molecule from the solvent.[16] Long, et al.,[17] have calculated entropies of activation from available data for a large number of acid-catalyzed reactions for which the mechanisms are quite well known and showed empirically that the entropies of activation fall into two distinct groups separated by some 25 to 30 entropy units, corresponding to the two types of mechanism. The entropies of activation of the hydrolysis of methyl mesitoate in sulfuric acid solution fall into the region characterized by other A-1 reactions, confirming the other criteria presented earlier which point to a mechanism involving an acylium ion intermediate.

Leisten has shown that in nearly 100% sulfuric acid, methyl and ethyl benzoate undergo hydrolysis through acylium ion formation.[10d] From his data, ΔH^* is calculated as 26.5 kcal./mole for methyl benzoate and 29.2 kcal./mole for the ethyl ester. The higher value is expected for the ethyl compound, as electron donation in the alkyl portion of the ester hinders reaction by this mechanism (see ref. 10d, p. 1573). A comparison of the values for these two esters in 100% sulfuric acid and those of methyl mesitoate in much more dilute sulfuric acid sheds light on the nature of acylium ion formation, and the conditions facilitating such reaction.

The acid-catalyzed hydrolysis of methyl mesitoate can be discussed in terms of steric assistance to reaction. This is interpreted to be due to congestion of atoms at the reactive site in the reactant, a situation which is relieved considerably in passing to the transition state for acylium ion formation. The protonated reactant, the conjugate acid of the ester, will be of higher energy than a normal protonated ester due to steric inhibition of resonance and hindrance to rotation of the single bond connecting the carboxyl carbon atom and the carbon atom of the ring in the former substance. Rather than attempt to localize the proton, one may visualize the protonated ester as with the 2- and 6-methyl groups sterically minimizing the
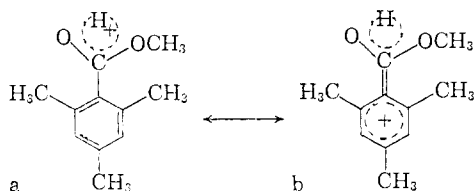
contribution of the various forms of b. The acylium ion, on the other hand, possesses an almost linear carbonyl group. In the acylium ion the strain of the reactant has been relieved, and the ion now can be stabilized by both the inductive and hyperconjugative contributions of the methyl groups. These two factors will contribute to a lowering of the transition state energy.

(17) F. A. Long, J. G. Pritchard and F. E. Stafford, THIS JOURNAL, 79, 2362 (1957).
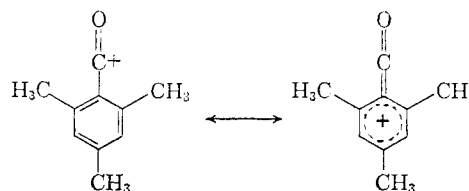
With sterically unhindered esters such as the benzoates, these factors do not come into play. The energy level of the reactant will be lower and that of the acylium ion higher, than in the mesitoate case, with a resulting increase in activation energy. Leisten has shown that the benzoyl acylium ion is unstable even in 100% sulfuric acid, and that it combines with water immediately to give C_6H_5-$CO_2H_2^+$. Even the p-anisoyl acylium ion, CH_3-$OC_6H_4CO^+$, which would be considerably more stable than the unsubstituted one, is found to exist to an extent of only 15% in 100% sulfuric acid.[10b]

The results of oxygen exchange provide further information on the hydrolysis of methyl mesitoate and are given in Table III.

TABLE III

CARBONYL OXYGEN EXCHANGE OF METHYL MESITOATE-carbonyl-O^{18} DURING HYDROLYSIS IN SULFURIC ACID SOLUTION

H_2SO_4, M	Reaction, %	Atom fraction O^{18} in C=O (X)	H_2SO_4, M	Reaction, %	Atom fraction O^{18} in C=O (X)
	0	0.811[b]	5.93	40	0.795
	0	.750[c]	5.93	55	.833
3.09[a]	75	.812	11.7	76	.748
5.93	20	.776	11.7	94	.765

[a] Temperatures are identical with those given in Table I. The slightly higher acidity of 5.93 was taken into account in determining the withdrawal times of the samples. [b] Pyrolysis performed on neat ester. [c] Error involved in extraction procedure, in which ester was dissolved in water, extracted with methylene chloride, and isolated.

The results of Table III show that oxygen exchange is absent at three acidities. These results are in agreement with prediction made earlier, and are explained by the inability of exchange to occur with a mechanism involving an acylium ion intermediate. Although exchange is not found, it is a priori not possible to state whether this is due to the formation of an acylium ion intermediate as assumed, to preferential heterolysis of the carbon-alkyl oxygen bond over the carbon-hydroxyl oxygen bond of a tetrahedral intermediate, or to an SN2 type of reaction, since the latter two account as well for the absence of oxygen exchange.

That a tetrahedral intermediate can exist in reactions of methyl mesitoate is unquestioned, as shown in the alkaline hydrolysis of methyl mesitoate at 125°, for which carbonyl oxygen exchange was found to occur (k_h/k_e = 6.8).[18] The tetrahedral intermediate in this reaction would differ from that of an acid-catalyzed reaction only by a proton, which hardly would be affected sterically, so that such an intermediate is certainly possible in the latter case. If one assumes constant steric factors

(18) M. L. Bender and R. S. Dewey, ibid., 78, 317 (1956).

for a (hypothetical) acid-catalyzed tetrahedral intermediate and the corresponding base-catalyzed tetrahedral intermediate, the difference in rates for the two types of catalysis can be expressed in terms of their activation energies. It is well known that the rates of acid-catalyzed ester hydrolysis are much slower than saponification (for ethyl benzoate, under conditions suitable for the bimolecular mechanism, $k_{base}/k_{acid} = 2,640^{19}$). This reflects the nucleophilicity of the hydroxyl ion with respect to the carboalkoxyl group as compared to that of water toward a protonated group. As a result, considerably more energy is required to affect a bimolecular reaction in the acid-catalyzed case, with the result that the probability of a tetrahedral intermediate will be very small. Because the species involved in the rate-determining step of either the uni- or bimolecular mechanism is the same, i.e., the conjugate acid of the ester, that path will be chosen that offers least resistance to reaction, both energetically and sterically, namely, the unimolecular heterolysis to give an acylium ion. Indeed, it is quite probable that in the base-catalyzed hydrolysis of methyl mesitoate a unimolecular path would also be most preferable, but in the latter case, the solvent does not possess sufficient solvating power for such an ionization, nor is there enough driving force for the heterolysis, which is provided by protonation of the carboalkoxyl group in acid catalysis.

The argument of preferential cleavage at the methoxonium site of the (hypothetical) tetrahedral intermediate is not valid if based on steric effects. The methoxyl group, being larger than the hydroxyl, might be ejected more easily by the crowding of the two methyl groups, a manifestation of "B" strain. As such, exchange would not be observed. But a similar criterion then would have to be applied in the base-catalyzed case of the ester (disregarding the effect of the proton), and has been shown to be invalid. Secondly, on the basis of polar effects, the hydroxyl group would be preferentially protonated, leading to exchange as

(19) Ph.D. Thesis of R. D. Ginger, Illinois Institute of Technology, 1958, p. 105.

observed in the case of acid-catalyzed hydrolysis of ethyl benzoate.[20]

The concept of the SN2 reaction must be considered but, again, a similar reaction would be predicted for basic catalysis; this is not found. Nucleophilic attack by methoxide ion at the methyl group of the carbomethoxyl linkage, displacing carboxylate ion, has been observed, but the analogous acid-catalyzed reaction ($A_{Al}2$ in Ingold's terminology) has not yet been found.[21]

The absence of oxygen exchange at the highest acidity is not unexpected. The same observation in the lower acid region, down to 3.09 M, is more significant, and serves to corroborate the argument and conclusions presented for the case of acylium-ion formation. The bimolecular path should become of increasing importance as more water is made available for reaction. In the present case, the concentration of water is considerably increased as the acidity is lowered. Further, the higher temperature used at lower acidities should also favor a bimolecular reaction. Yet a combination of these two factors still does not suffice to promote the incursion of another reaction path. The formation of the acylium ion is apparently so much more favored, that it dominates the reaction completely, even at the acid concentration where the bimolecular path would be most competitive.

The results of this study support the previous kinetic evidence for the acylium-ion mechanism of the hydrolysis of methyl mesitoate in strong acid. More important, the absence of oxygen exchange confirms the prediction made for the application of exchange criteria to acylium ion formation and shows that the mesitoate hydrolysis is to be considered to follow a single mechanistic pathway, due to the particular structural and solvent effects found in this reaction.

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

(21) C. K. Ingold. "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 754.

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Metal Chelates of Imines Derived from Pyridoxal and Amino Acids[1]

BY LEODIS DAVIS, FRANCES RODDY AND DAVID E. METZLER

The formation of metal chelates of imines derived from pyridoxal plus alpha amino acids in aqueous solutions has been studied. It is shown that with Zn(II), Cu(II) and Ni(II) the principal chelates formed contain the metal, pyridoxal and amino acid in a 1:1:1 ratio and accept one proton at lower pH values. Formation constants for several of the chelates have been evaluated, as have the dissociation constants of the conjugate acids of the chelates. The relative stabilities of these and various other chelates are compared. The zinc pyridoxylidene valine chelate is extremely sensitive to light, being converted rapidly in laboratory light into an unidentified compound or compounds with a characteristic ultraviolet absorption spectrum.

The aldehyde form of vitamin B₆, pyridoxal, I, is believed to function in biological catalysis by forming imines (Schiff bases, pyridoxylidene amino

acids), II, with substrate amino acids at the active centers of appropriate enzymes. Subsequent re-