

Experimental

Infrared Spectral Measurements. A Perkin-Elmer Model 21 spectrophotometer equipped with a LiF prism and a Perkin-Elmer Model 421 grating spectrophotometer were used for determination of the infrared spectra. The solvent, A.R. grade CCl_4 , was decanted from P_2O_5 before use. Matched silica cells, 1 or 2 cm. in length, permitted the observation of dilute solutions (0.005 M or less) and the use of different concentrations. The calibration of the instruments was checked daily against indigenous water vapor in the standard manner; the data reported are corrected. Samples were run at room temperature. The position of the peaks was evaluated by determining the center of the band envelope at various positions and averaging. Sharp peaks were determined with an accuracy of $\pm 1 \text{ cm.}^{-1}$; broad peaks and shoulders to ± 2 or 3 cm.^{-1} . The separation of the peaks, $\Delta\nu$, could be measured with an accuracy of $\pm 2 \text{ cm.}^{-1}$ since the difference was dependent on the relative and not the absolute position of the peaks. Reproducibility was shown to be good.

Sources of Compounds. Compounds **1**, **2**, and **4** were commercial samples, recrystallized before use. The preparation of **7a-d**, **8**, **9a,b**, **13b**, **13d**, and **14** has been reported earlier.⁵

2-Hydroxy-2'-methylbiphenyl (14). Reduction of the lactone of 2'-hydroxybiphenyl-2-carboxylic acid (m.p. $92-93^\circ$),¹⁸ prepared by the method of Emmons and Lucas,¹⁹ with LiAlH_4 in ether gave 2-hydroxy-2'-methylbiphenyl, m.p. $131.4-132.6^\circ$. *Anal.* Calcd. for $\text{C}_{13}\text{H}_{12}\text{O}_2$: C, 77.98; H, 6.04. Found: C, 77.58; H, 6.05.

1,2,3,4-Dibenz-1,3-cycloheptadien-6-ol (13c).²⁰ Reduction of 1,2,3,4-dibenz-1,3-cycloheptadien-6-one²¹ by LiAlH_4 in the usual manner gave a product which was distilled at 150° (0.1-0.5 mm.). Crystals formed on standing. Recrystallization from cyclohexane gave material, m.p. $81.5-82.5^\circ$. *Anal.* Calcd. for $\text{C}_{18}\text{H}_{14}\text{O}$: C, 85.68; H, 6.71. Found: C, 85.34; H, 6.70.

Acknowledgment. One of us (P. R. S.) wishes to express appreciation for the hospitality extended to him at the Institute for Organic Chemistry of the University of Munich, where the final draft of this manuscript was written.

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Concerning the Mechanism of Acid-Catalyzed Hydrolysis of Ketals, Ortho Esters, and Orthocarbonates¹

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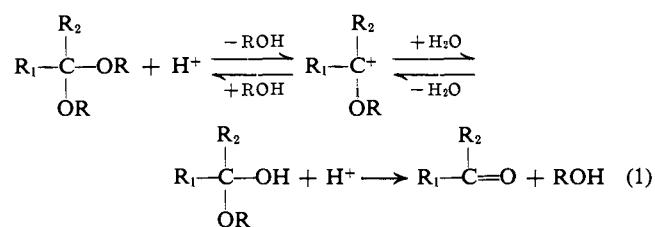
Contribution No. 1285 from the Department of Chemistry, Indiana University, Bloomington, Indiana. Received March 31, 1965

Proton magnetic resonance spectroscopy has been employed to follow simultaneously the kinetics of disappearance of methoxy protons of substrate, appearance of methyl protons of methanol, and appearance of methoxy protons of product for the hydrolysis of 2,2-dimethoxypropane, methyl orthobenzoate, 6,6,6-trimethoxyhexanonitrile, and methyl orthocarbonate in weakly acidic mixtures of deuterium oxide and methanol- d_4 at 25° . In all cases, the first-order rate constants for each of these reactions were approximately the same. This result is interpreted in terms of rate-determining carbonium ion formation. This conclusion is corroborated by the finding, from product analysis studies, that little exchange of the methoxy functions of substrate with deuteriomethoxy functions of solvent occurred in the course of hydrolysis. On the basis of kinetic and product analysis studies, deuteriomethanol and deuterium oxide appear to exhibit approximately equal reactivities toward the carbonium ions derived from the above substrates.

Introduction

Several independent lines of evidence strongly suggest that the acid-catalyzed hydrolysis of acetals,

ketals, ortho esters, and, by analogy, orthocarbonates proceeds by a reaction pathway not involving solvent as nucleophilic reagent (eq. 1). (i) These substrates are



extremely resistant to nucleophilic attack by hydroxide ion and other nucleophilic reagents; (ii) volumes of activation for the acid-catalyzed hydrolysis of dimethoxymethane, dimethoxy- and diethoxyethane, and ethyl orthoformate are close to zero or slightly positive²; (iii) entropies of activation for the hydrolysis of several acetals, ketals, orthoformates, and orthobenzoates are near zero or slightly positive²⁻⁷; (iv) the

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(7) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

(1) Supported by grants from the National Science Foundation (GB-431) and from the National Institutes of Health (AM-08232-01).

hydrolysis of certain acetals and ketals in moderately concentrated solutions of mineral acids yields rate constants which are correlated with the Hammett H_0 acidity function^{4,8,9}; (v) correlation of rate constants for acetal hydrolysis with activity of water yields values of Bunnett's w -parameter which are characteristic of reactions which occur by unimolecular reaction paths¹⁰; (vi) rate constants for the hydrolysis of a series of aliphatic acetals and ketals are well correlated by Taft's σ^* parameters (plus a hyperconjugation term) indicating the absence of steric effects expected for reactions involving participation of a nucleophilic reagent¹¹; (vii) the observed value of ρ^* for hydrolysis of aliphatic acetals and ketals is -3.60 ¹¹; (viii) the first-order rate constants for the decomposition of methyl orthobenzoate in aqueous solutions are independent of the concentration of several amines under conditions in which a substantial fraction of the ortho ester yields aminolysis products.⁶

Furthermore, reaction pathways of the type indicated in eq. 1 are consistent with the observation of general acid catalysis for certain of these reactions,^{12,13} with the observed solvent deuterium isotope effects,^{3,5,6,14-17} and with the observation of catalysis of ortho ester hydrolysis by certain anionic detergents.^{18,19}

Contrary to the above conclusions, Kwart and Price, on the basis of correlation of rate constants with an empirical solvent composition-acidity function, have suggested that the hydrolysis of methyl *p*-nitroortho-benzoate occurs with solvent participation as nucleophilic reagent.¹² The basis for this conclusion has been pointedly criticized by DeWolfe and Jensen.⁵ Kaeding and Andrews, in a study of the hydrolysis of the dimethyl ketal of *p*-nitrobenzophenone, have obtained results consistent with either a unimolecular or bimolecular reaction path, the latter alternative being favored by these authors.²⁰ This study was carried out in largely alcoholic media in which reaction of the carbonium ion with solvent would be expected to be rate determining and, hence, provides no evidence for the nature of the reaction pathway in aqueous solution.

On the basis of these results, the conclusion that, for most reactions at least, acetal, ketal, and ortho ester hydrolysis occurs without the nucleophilic participation of solvent is warranted.

Despite numerous assumptions in the literature that carbonium ion formation is the rate-determining step for these reactions, nearly all of the above data is equally consistent with rate-determining decomposition of the tetrahedral intermediate (eq. 1). Only the results of the aminolysis experiments of Fullington and Cordes (point viii above) are difficult to reconcile with the latter possibility. Consequently, experiments, re-

ported herein, have been undertaken in an effort to establish unequivocally the nature of the rate-determining step for these interesting reactions.

As revealed by a preliminary study of the hydrolysis of methyl orthobenzoate, kinetic and product composition studies, employing n.m.r. as analytical tool, provide a simple and straightforward experimental distinction between the possible rate-determining steps for reactions of this type when carried out in deuterium oxide-methanol- d_4 mixtures.²¹ The experimental quantities determined by this method include the first-order rate constants for the disappearance of the methoxy protons of the ortho ester, $k_{\text{ortho ester}}$, for the appearance of the methyl protons of methanol, k_{MeOH} , and for the appearance of the methoxy protons of the carboxylic ester, k_{ester} . Since the proton resonance singlets for each of these groups are well separated, these rate constants can be determined simultaneously as described in the Experimental section. In addition, the ratio of integrated proton intensities at infinite time of the products to some internal, time-independent standard provides a quantitative measure of product composition.

Both the product composition and the relative magnitudes of the various rate constants are functions of the nature of the rate-determining step. If carbonium ion formation were rapid and reversible (*i.e.*, carbonium ion formation not rate determining), the methoxy groups of the starting material would be rapidly exchanged for deuteriomethoxy groups through reaction of the carbonium ion with solvent deuteriomethanol. The ortho ester would be converted more slowly to carboxylic ester product. Thus, $k_{\text{ortho ester}}$ and k_{MeOH} would be considerably larger than k_{ester} . Furthermore, little or no carboxylic ester product containing methoxy protons would be formed since virtually all of the ortho ester would have been converted into the corresponding deuterated material in the pre-equilibrium exchange reactions. In contrast, if carbonium ion formation were rate determining, methanol would not be exchanged for deuteriomethanol in a pre-equilibrium reaction; hence, $k_{\text{ortho ester}}$, k_{MeOH} , and k_{ester} would be nearly identical. In addition, only protonated carboxylic ester would be produced as reaction product.

These considerations clearly apply with equal force to the hydrolysis of methyl orthocarbonates and, in part, to the hydrolysis of methyl ketals. This manuscript fully describes results obtained with methyl orthobenzoate and extends the previous work to a ketal, an aliphatic ortho ester, and an orthocarbonate.

Experimental

Materials. Methyl orthobenzoate was prepared according to the procedure of McElvain and Venerable.²² 6,6,6-Trimethoxyhexanonitrile and methyl orthocarbonate were the generous gifts of Mr. M. Matta of this department and Professor Robert Taft, Pennsylvania State University, respectively.

The 6,6,6-trimethoxyhexanonitrile was purified of a slight carboxylic ester contaminant by treatment with 4 ml. of a 4 *N* sodium hydroxide solution per gram of

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(17) M. Kilpatrick, *ibid.*, **85**, 1036 (1963).

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(21) A. M. Wenthe and E. H. Cordes, *Tetrahedron Letters*, 3163 (1964).

(22) S. M. McElvain and J. T. Venerable, *J. Am. Chem. Soc.*, **72**, 1661 (1950).

sample. Methanol was added in an amount sufficient to solubilize the mixture. The resulting solution was then stirred well for about 10 min. and extracted three times with ether. The collected ether washings were dried over sodium carbonate and the ether was removed. The n.m.r. spectrum of the remaining fraction showed only a sharp singlet at 3.25 p.p.m., indicative of the methoxy protons of the ortho ester, and the characteristic splitting of the methylene proton signals between 1.4 and 2.5 p.p.m. No signal was observed in the region (3.6–3.7 p.p.m.) where the methyl protons of normal carboxylic ester would be expected to appear.

The methyl orthocarbonate sample was separated from methanol and dimethyl carbonate impurities by distillation through a micro spinning-band column. The pure methyl orthocarbonate (b.p. 114°) gave a single, sharp peak at 3.3 p.p.m., again indicating the presence of only one kind of methyl proton, that of the methoxy functions of orthocarbonate.

Deuterium oxide and 2,2-dimethoxypropane were commercial products purified by distillation. Methanol-*d*₄, obtained from Nuclear Research Chemical Corp., was employed without further purification. N.m.r. spectra revealed no detectable protomethanol.

Kinetic Measurements. All kinetics studied were carried out at 25 ± 0.5° with the aid of a Varian Associates A-60 n.m.r. spectrometer. Relative concentrations of all reacting species of interest were determined as a function of time by comparison of their integrated proton intensities with that of an appropriate, time-independent internal standard. For the hydrolysis of methyl orthobenzoate, the aromatic protons were employed as internal standard; for the hydrolysis of 6,6,6-trimethoxyhexanonitrile, the methylene protons; for the hydrolysis of 2,2-dimethoxypropane, the total methyl protons of ketal and acetone; for the hydrolysis of methyl orthocarbonate, the methyl protons of added acetonitrile. First-order rate constants were obtained from semilogarithmic plots of the ratio of the integrated intensities of the protons of interest to those of the internal standard against time. In all cases, satisfactory first-order plots were obtained. First-order rate constants indicated in this paper are considered to be accurate to within ±20%. All reactions were monitored for varying periods following their completion to ensure that the reaction products were stable to the reaction conditions. Only in the case of acetone, the product of 2,2-dimethoxypropane hydrolysis, was exchange of protons with the solvent noted. In this case, the exchange was sufficiently slow so that appreciable errors were not introduced into the experimental results.

Product Composition. Product compositions were estimated from the ratio of integrated intensities at infinite time of the protons of interest to those of the internal standard.

Results

A. 2,2-Dimethoxypropane. Figure 1 shows the course of hydrolysis of 0.8 *M* 2,2-dimethoxypropane in an equimolar mixture of deuteriomethanol and deuterium oxide at 25° in the presence of a 0.006 *M* acetate buffer, 50% base (eq. 2). The peak seen at 2.1 p.p.m. in the spectrum taken at zero time is not due to an initial rapid reaction but rather to acetone present as

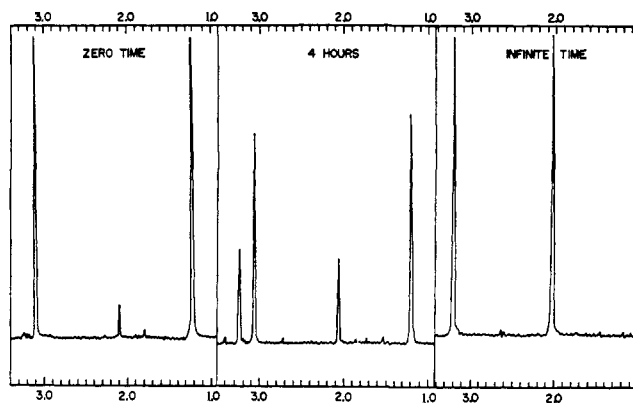
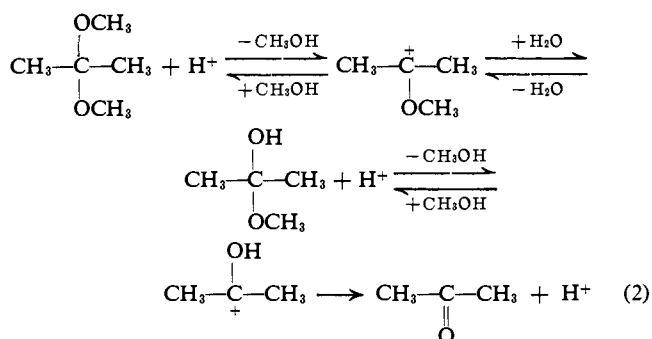


Figure 1. Proton magnetic resonance spectra indicating the course of hydrolysis of 2,2-dimethoxypropane in a deuterium oxide–deuteriomethanol mixture at 25° in the presence of a 0.006 *M* acetate buffer, 50% base. The peak near 3.1 p.p.m. is due to the methoxy protons of the ketal, that near 1.2 p.p.m. to the methyl protons of the ketal, that near 2.1 p.p.m. to methanol, and that near 2.1 p.p.m. to acetone.



a slight contaminant of the 2,2-dimethoxypropane. This necessitated a small correction for the integrated intensity of this signal in all spectra taken thereafter. The ratio of the integrated proton intensity at zero time to that of the internal standard was subtracted from the corresponding value at all later times to arrive at the true value for acetone produced in hydrolysis.

First-order rate constants were calculated for the disappearance of the methoxy protons of ketal, k_{ketal}^1 , for the appearance of the methyl protons of methanol, k_{MeOH} , for the disappearance of the methyl protons of ketal, k_{ketal}^2 , and for the appearance of the methyl protons of acetone, k_{acetone} . These rate constants are collected in Table I. The identity, within experimental error, of k_{ketal}^1 and k_{MeOH} and of k_{ketal}^2 and k_{acetone} is required by the stoichiometry of the reaction. First-order rate constants for disappearance of ketal, k_{ketal}^1 , and appearance of acetone, k_{acetone} , differ by only a

Table I. First-Order Rate Constants for the Hydrolysis of 2,2-Dimethoxypropane in an Equimolar Mixture of Deuteriomethanol and Deuterium Oxide at 25°^a

$k_{\text{ketal}}^1,^b$ min. ⁻¹	$k_{\text{ketal}}^2,^c$ min. ⁻¹	k_{MeOH} min. ⁻¹	k_{acetone} min. ⁻¹	R_M^d
1.4×10^{-3}	8.1×10^{-4}	1.3×10^{-3}	8.1×10^{-4}	1.05

^a Carried out in the presence of 0.006 *M* acetate, 50% base; 2,2-dimethoxypropane concentration, 0.8 *M*. ^b First-order rate constant for the disappearance of the methoxy protons of the ketal. ^c First-order rate constant for the disappearance of the methyl protons of the ketal. ^d Ratio of the integrated intensities at infinite time of the methyl protons of methanol to the methyl protons of acetone.

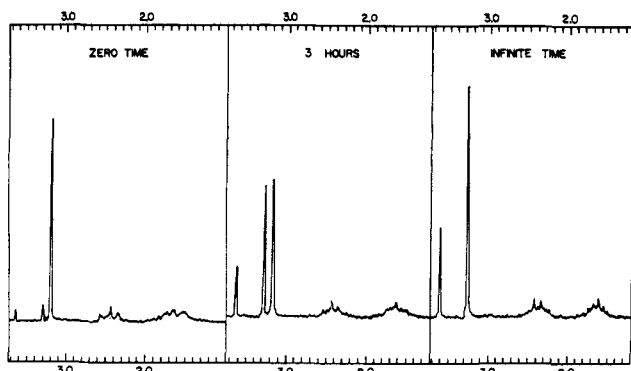
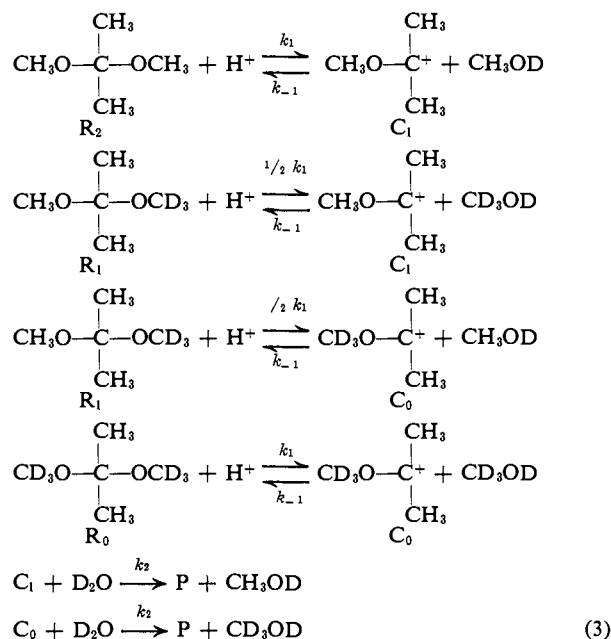


Figure 2. Proton magnetic resonance spectra indicating the course of hydrolysis of 6,6,6-trimethoxyhexanonitrile in a deuterium oxide-deuteriomethanol mixture at 25° in the presence of 0.006 *M* acetate buffer, 80% base. The peak near 3.2 p.p.m. is due to the methoxy protons of ortho ester, that near 3.25 p.p.m. to methanol, that near 3.65 p.p.m. to the methoxy protons of carboxylic ester, and the complex multiplets to the methylene protons of the ortho ester and carboxylic ester.

factor of two. This result is inconsistent with decomposition of dimethylmethoxycarbinol as the principal rate-determining step for which the disappearance of ketal would occur more rapidly than the appearance of acetone, *i.e.*, $k_{\text{ketal}^1} > k_{\text{acetone}}$. Qualitatively, these first-order rate constants strongly suggest slow carbonium ion formation followed by rapid partitioning of the carbonium ion between deuterium oxide and deuteriomethanol.

The disparity in first-order rate constants can be quantitatively accounted for on the above basis by the following kinetic analysis. Secondary deuterium isotope effects, which are neglected throughout the kinetic treatment, are reasonably expected to introduce only small errors in the calculation. In this and all subsequent schemes, R identifies substrate, C, carbonium ion, and P, product. Subscripts indicate the number of proto-methoxy groups in a species.

Reactions involved in the hydrolysis of 2,2-dimethoxypropane in deuteriomethanol-deuterium oxide solution are written below (eq. 3). Derivation of the rate ex-



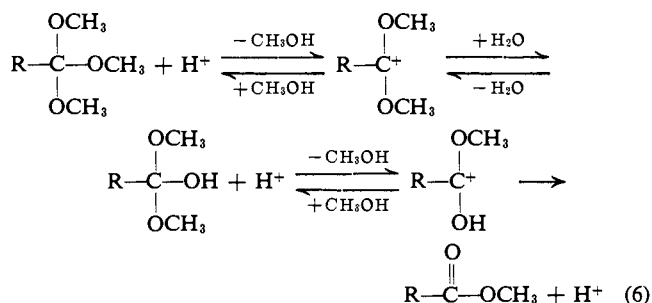
pressions for the reactions in eq. 3 is markedly simplified by recognizing that, since the concentration of methanol is small throughout the course of the reaction compared to the concentration of deuteriomethanol and deuterium oxide, reaction of the carbonium ions with methanol may be neglected. Employing this assumption and the steady-state assumption for the carbonium ions, the following expressions for the first-order rate constants are obtained in which *a* is defined as $k_{-1}(\text{CD}_3\text{OD})/(k_{-1}(\text{CD}_3\text{OD}) + k_2(\text{D}_2\text{O}))$.

$$k_{\text{ketal}^1} = k_{\text{MeOH}} = k_1(\text{H}^+)(1 - 1/2a) \quad (4)$$

$$k_{\text{ketal}^2} = k_{\text{acetone}} = k_1(\text{H}^+)(1 - a) \quad (5)$$

Clearly, $k_{\text{acetone}}/k_{\text{MeOH}} = 2k_2/(k_{-1} + 2k_2)$ when, as is the case here, the molar concentrations of deuteriomethanol and deuterium oxide are equal. Since the experimental value for this ratio of first-order rate constants is 0.5 (Table I), it follows directly that deuteriomethanol is approximately twice as reactive as deuterium oxide toward the dimethylmethoxymethane carbonium ion.

B. 6,6,6-Trimethoxyhexanonitrile. Spectra found in Figure 2 exhibit the progress of hydrolysis of 0.5 *M* 6,6,6-trimethoxyhexanonitrile in an equimolar mixture of deuteriomethanol and deuterium oxide at 25° in the presence of 0.006 *M* acetate buffer, 80% base.



The first-order rate constants for the disappearance of the methoxy protons of ortho ester, $k_{\text{ortho ester}}$, for the appearance of the methyl protons of methanol, k_{MeOH} , and for the appearance of the methoxy protons of the carboxylic ester product, k_{ester} , were obtained and are presented, along with integrated intensities at infinite time, in Table II. These results are qualitatively similar to those for the orthobenzoate discussed below and the same conclusions apply.

Table II. First-Order Rate Constants and Product Composition for the Hydrolysis of 6,6,6-Trimethoxyhexanonitrile in an Equimolar Mixture of Deuteriomethanol and Deuterium Oxide at 25°^a

$k_{\text{ortho ester}}$, min. ⁻¹	k_{MeOH} , min. ⁻¹	k_{ester} , min. ⁻¹	R_M^b	R_E^c
4.2×10^{-3}	4.1×10^{-3}	4.2×10^{-3}	0.74	0.30

^a Carried out in the presence of 0.006 *M* acetate buffer, 80% base; ortho ester concentration, 0.5 *M*. ^b Ratio of integrated intensities at infinite time of the methyl protons of methanol to the methylene protons. ^c Ratio of the integrated intensities at infinite time of the methoxy protons of the carboxylic ester product to the methylene protons.

C. Methyl Orthobenzoate. Spectra in Figure 3 were taken during the hydrolysis of 0.5 *M* methyl orthobenzoate in an equimolar mixture of deuteriomethanol and deuterium oxide at 25° in the presence of 0.006

Table III. First-Order Rate Constants and Product Composition for the Hydrolysis of Methyl Orthobenzoate in Deuteriomethanol-Deuterium Oxide Solutions at 25°^a

Run	(CD ₃ OD)/(D ₂ O)	Buffer	$k_{\text{ortho ester}}$, min. ⁻¹	k_{MeOH} , min. ⁻¹	k_{ester} , min. ⁻¹	R_M^b	R_{MB}^c
1	1.0	0.006 M acetate, 50% base	2.2×10^{-4}	2.9×10^{-4}	2.6×10^{-4}	1.46	0.45
2	2.0	0.014 M formate, 50% base	1.1×10^{-3}	1.4×10^{-3}	1.3×10^{-3}	1.38	0.38
3	1.0	0.027 M DCl	1.53	0.40

^a Methyl orthobenzoate concentration 0.5 M. ^b Ratio of the integrated intensities at infinite time of the methyl protons of methanol to the aromatic protons. ^c Ratio of the integrated intensities at infinite time of the methoxy protons of methyl benzoate to the aromatic protons.

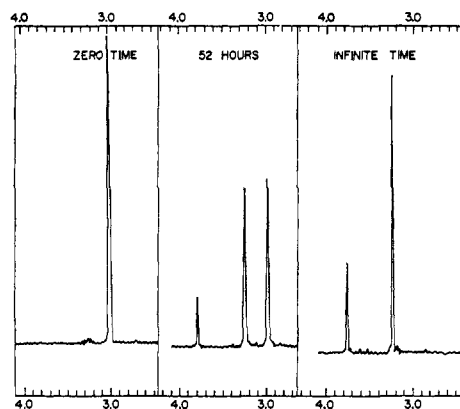
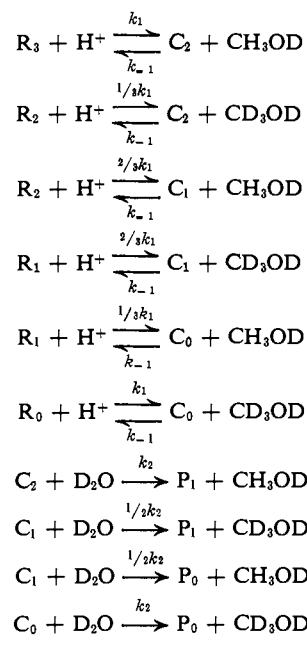


Figure 3. Proton magnetic resonance spectra indicating the course of hydrolysis of methyl orthobenzoate in a deuterium oxide-deuteriomethanol mixture at 25° in the presence of a 0.006 M acetate buffer, 50% base. The peak near 3.0 p.p.m. is due to the methoxy protons of ortho ester, that near 3.25 p.p.m. to methanol, and that near 3.80 p.p.m. to the methoxy protons of methyl benzoate.

M acetate buffer, 50% base. A second run, for which spectra are similar but not included here, involved the same concentration of methyl orthobenzoate but in a solution whose molar concentration ratio of deuteriomethanol to deuterium oxide was 2 and in the presence of 0.014 M formate buffer, 50% base. A third run in an equimolar mixture of deuteriomethanol-deuterium oxide in the presence of 0.027 M DCl was made to confirm product composition at infinite time. The data are summarized in Table III. The first-order rate constants for the disappearance of the methoxy protons of the orthobenzoate, $k_{\text{ortho ester}}$, for the appearance of the methyl protons of methanol, k_{MeOH} , and for the appearance of the methoxy protons of methyl benzoate, k_{ester} , are essentially equal in the two kinetic runs. Furthermore, a rather large fraction of the original ortho ester yields methyl benzoate without exchanging with solvent deuteriomethanol. If no exchange had occurred, values of R_M and R_{MB} of 1.2 and 0.6, respectively, would be obtained. If complete exchange had occurred the corresponding values would be 1.8 and 0.0. These results are certainly inconsistent with pre-equilibrium carbonium ion formation but are accounted for by a slow formation of carbonium ion followed by rapid partitioning between water, yielding product, and deuteriomethanol, yielding partially deuterated ortho ester, which finally yields, in part, deuterated methyl benzoate. These results may be quantitatively accounted for by the following kinetic analysis in which secondary deuterium isotope effects are neglected.

Employing the notation indicated above, the pertinent reactions may be formulated as indicated in eq. 7.



Proceeding as above, the following expression for the first-order rate constants may be derived.²⁴ If, for

$$k_{\text{ortho ester}} = k_1(H^+)[1 - 2/3a] \tag{8}$$

$$k_{\text{MeOH}} = k_1(H^+)[1 - 1/2a] \tag{9}$$

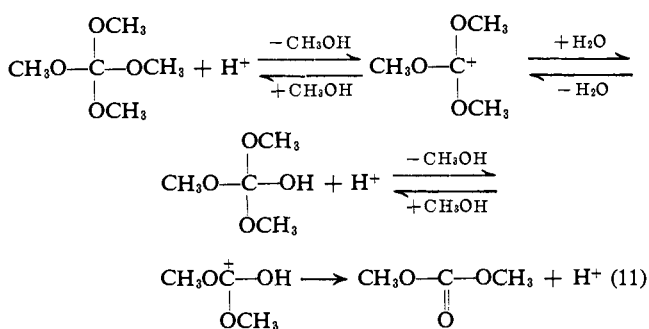
$$k_{\text{ester}} = k_1(H^+)[1 - a] \tag{10}$$

example, the concentrations of deuteriomethanol and deuterium oxide are equal, and deuteriomethanol and deuterium oxide are considered to be equally reactive toward the intermediate carbonium ions (an assumption consistent with and supported by the degree of pre-equilibrium methoxy group exchange), then the value of a is 0.5 and the above treatment predicts that the observed rate constants should be approximately equal,^{23,24} in accord with experimental fact.

(23) In performing the derivations for the rate expressions herein, it is important to bear in mind that the n.m.r. spectrometer records signals which are proportional to the total number of protons only. Hence, the expression of the total amount of 2,2-dimethoxypropane is $R_T = R_2 + 1/2R_1$. For the case of methyl orthocarbonate, the appropriate expression is $R_T = R_3 + 3/4R_2 + 1/2R_1 + 1/4R_0$, and so forth.

(24) The rate expressions derived hereafter, in contrast to those for 2,2-dimethoxypropane hydrolysis, are not rigorously correct. This arises from the fact that the occurrence of some methoxy function exchange has not been explicitly introduced into the calculations. Since, in all cases, the amount of exchange was small, this approximation introduces only a modest error into the derived values and does not affect, in any fashion, the conclusions derived herein. Were the exchange to be included into the rate equations, the agreement between the observed and calculated ratios of rate constants would be substantially improved.

D. *Methyl Orthocarbonate*. Spectra in Figure 4 follow the course of hydrolysis of 0.375 *M* methyl orthocarbonate in an equimolar deuteriomethanol-deuterium oxide solution at 25° in the presence of 0.006 *M* acetate buffer, 50% base. Acetonitrile, the



added internal standard present in a concentration of 0.4 *M*, produces the singlet at 2.0 p.p.m.

First-order rate constants for the disappearance of the methoxy protons of orthocarbonate, $k_{\text{orthocarbonate}}$, for the appearance of the methyl protons of methanol, k_{MeOH} , and for the appearance of the methoxy protons of dimethyl carbonate, k_{ester} , are presented in Table IV. These data suggest that methyl orthocarbonate, like the previously discussed ortho esters, reacts with slow carbonium ion formation. Extensive exchange is not observed even under conditions in which the molar ratio of deuteriomethanol to deuterium oxide is four. These results are quantitatively accounted for by the following kinetic analysis. Formulating the hydrolysis of methyl orthocarbonate in deuterium oxide-deuteriomethanol mixtures as before yields the reactions indicated in eq. 12. Proceeding as before, these reactions

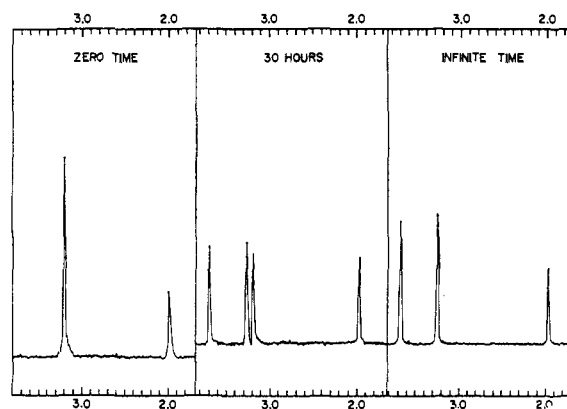
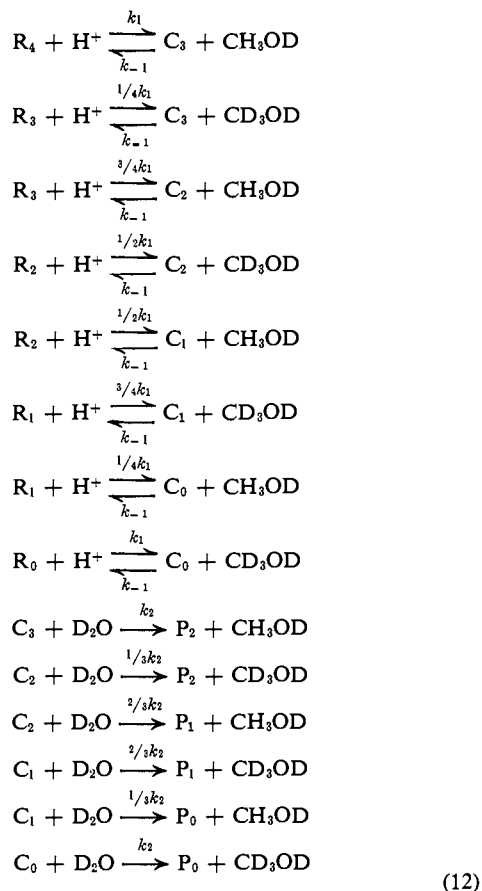


Figure 4. Proton magnetic resonance spectra indicating the course of hydrolysis of methyl orthocarbonate in a deuterium oxide-deuteriomethanol mixture at 25° in the presence of a 0.006 *M* acetate buffer, 50% base. The peak near 3.2 p.p.m. is due to the methyl orthocarbonate, that near 3.25 p.p.m. to methanol, and that near 3.8 p.p.m. to dimethyl carbonate.

yield the following rate expressions²⁴ (eq. 13-15) in

$$k_{\text{orthocarbonate}} = k_1(\text{H}^+)[1 - 3/4a] \quad (13)$$

$$k_{\text{MeOH}} = k_1(\text{H}^+)[1 - 1/2a] \quad (14)$$

$$k_{\text{ester}} = k_1(\text{H}^+)[1 - a] \quad (15)$$

which a is defined as above. If, in accord with the degree of observed exchange, we assume that deuterium oxide and deuteriomethanol are equally reactive toward the intermediate carbonium ions, values of a for the experiments indicated in Table IV indicate that the observed rate constants should be approximately equal, a prediction concordant with the observed facts.

Discussion

The observation that first-order rate constants for disappearance of methoxy protons of substrate, appearance of methyl protons of methanol, and appearance of the methoxy protons of product for the hydrolysis of 2,2-dimethoxypropane, methyl ortho esters, and methyl orthocarbonate in deuteriomethanol-deuterium oxide solutions requires that carbonium ion formation be the principal rate-determining step for each of these reactions in dilute aqueous solutions. In the cases of the ortho esters and orthocarbonate, this conclusion is corroborated by the observation that rather little exchange of methoxy functions of substrate with deuteriomethoxy functions of solvent occurred in the course of the hydrolysis, as evidenced by the product compositions. The small disparities in rate constants and modest degree of exchange that were observed are quantitatively accounted for, within the limits of experimental error of the determinations, by the assumption that deuteriomethanol and deuterium oxide are equally reactive, within a factor of two, toward the carbonium ion intermediates. This assumption finds positive support from the studies of 2,2-dimethoxypropane hydrolysis (see Results) and is in accord with the relative reactivities of methanol and water toward, for example, the *t*-butyl and benzhydryl carbonium

Table IV. First-Order Rate Constants and Product Composition for the Hydrolysis of Methyl Orthocarbonate in Deuteriomethanol-Deuterium Oxide Solutions at 25°^a

Run	(CD ₃ OD)/ (D ₂ O)	Buffer	$k_{\text{orthocarbonate}},$ min. ⁻¹	$k_{\text{MeOH}},$ min. ⁻¹	$k_{\text{ester}},$ min. ⁻¹	R_M^b	R_{DMC}^c
1	1.0	0.006 M acetate, 50% base	8.3×10^{-4}	7.4×10^{-4}	8.0×10^{-4}	2.1	1.7
2	4.0	0.014 M formate, 50% base	1.3×10^{-3}	1.1×10^{-3}	1.1×10^{-3}	2.6	2.0

^a Methyl orthocarbonate concentration, 0.375 M. ^b Ratio of integrated intensities at infinite time of the methyl protons of methanol to the methyl protons of 0.4 M acetonitrile. ^c Ratio of integrated intensities at infinite time of the methoxy protons of dimethyl carbonate to the methyl protons of 0.4 M acetonitrile.

ions.²⁵⁻²⁷ Thus, in solutions containing high concentrations of methanol, as those employed in these studies, reaction of the carbonium ion with water is partially rate determining. It follows directly that, for the case of dilute aqueous solutions in which the concentration of methanol is small compared to that for water throughout the course of the reaction, carbonium ion formation will be largely rate determining. Our results do not rigorously exclude a small contribution of the rate of tetrahedral intermediate decomposition to the over-all rate.

These conclusions are in accord with expectations based on chemical arguments. In solutions containing little methanol, rate-determining reaction of the carbonium ion with water is extremely unlikely since this requires that methanol react with the carbonium ion, regenerating starting material, more rapidly than water reacts with the carbonium ion, yielding products. Since the *rate constants* for reaction of methanol and water are almost certainly about the same, the *rate* for the latter reaction must be greater. A similar argument suggests that decomposition of the tetrahedral intermediates is not rate determining. Since the over-all equilibrium constant for interconversion of, for example, methyl orthobenzoate and dimethyl orthobenzoate should be about unity, the latter would be present in much greater concentration than the former, were equilibrium established, due to the high concentration of water relative to methanol. Since the *rate constants* for the decomposition of these species should be about equal (the dimethyl orthobenzoate might actually be expected to decompose somewhat more rapidly since a specific acid-general base catalyzed reaction pathway is uniquely available to it), the *rate* for dimethyl orthobenzoate decomposition should be greater than the corresponding quantity for methyl orthobenzoate.

The carbonium ions derived from ketals, ortho esters, and orthocarbonates have been directly observed as stable chemical species in anhydrous strongly acidic media by Ramsey and Taft.²⁸ In addition, Bender has prepared (in solution) compounds closely related to those proposed as intermediates in the hydrolysis of ortho esters.²⁹ Thus, the suggested intermediates for the hydrolysis of the compounds under consideration are largely known.

Rate-determining carbonium ion formation for the hydrolysis of ketals, ortho esters, and orthocarbonates

is consistent with and supported by all of the known facts concerning these reactions as outlined in the Introduction. One aspect of these reactions deserves further comment. Naively, one might expect that the reactivities of ketals, ortho esters, and orthocarbonates should parallel carbonium ion stabilities. Second-order rate constants collected for several of these reactions suggest that this expectation is not fulfilled.^{5,30} Indeed, within a limited series of compounds just the opposite appears to be true, alkyl ortho esters being more reactive than aryl ortho esters which, in turn, are more reactive than orthocarbonates. Several explanations for this order of reactivity have been advanced, each assuming that carbonium ion formation is rate determining. DeWolfe and Jensen, noting that the reactivities parallel the electron-donating power by inductive effects alone of the substituent attached to the ortho ester carbon, have suggested that the transition state for these reactions is reached so early that only inductive, and not resonance, effects are important in affecting the stability of the transition state.⁵ Although this explanation cannot be rigorously ruled out, the importance of hyperconjugation on the rate of hydrolysis of aliphatic acetals and ketals¹¹ and the large Bronsted α -value for general acid catalysis of methyl orthobenzoate hydrolysis¹² suggest that the transition states for these reactions partake of considerable carbonium ion character.

An alternative explanation has been advanced by Hine on the basis of variation in starting material stabilities.³⁰ Arguing that double bond-no bond resonance in the substrates, which is certainly lost in the transition state to some extent, will be most important for the orthocarbonate and least important for the alkyl ortho ester, one has a factor which may offset the reverse order of carbonium ion stabilities. This argument is weakened somewhat by the lack of definitive data as to the importance of double bond-no bond resonance for compounds of this type.

A most interesting finding, which provides a more direct explanation of the observed reactivities, is the observation of Taft and his associates that, in the gas phase at least, the stabilization energy of the cations do not vary in the series $\text{CH}_3\text{OC}(\text{CH}_3)_2^+$, $(\text{CH}_3\text{O})_2\text{CH}^+$, $(\text{CH}_3\text{O})_2\text{CCH}_3^+$, and $(\text{CH}_3\text{O})_3\text{C}^+$.³¹ These results were based on appearance potential measurements for the formation of these cations employing monoenergetic electron beams. These results may not be directly extrapolated to aqueous solution since differences in solvation energies for the different carbonium ions may be of some importance. Nevertheless, the suggestion

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is strong indeed that the stabilities of these cations will not be greatly different in aqueous solution and, consequently, one needs rather small effects to account for the observed order of reactivities.

Acknowledgment. We are indebted to Professor Robert Taft, Jr., for critical comments concerning this work and for communication of pertinent data prior to publication.

Mass Spectrometry in Structural and Stereochemical Problems. LXXIII.¹ The Negative Ion Mass Spectra of Some Simple Organic Compounds²

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The negative ion mass spectra of alkylbenzenes, substituted benzenes, aliphatic acids, esters, nitriles, and ketones have been measured. The spectra are compared with their positive ion counterparts and with other work on negative ion mass spectrometry. The utility of this type of mass spectrometry under the experimental conditions used (20–70-e.v. electron energy) with respect to molecular weight and structure determination is considered to be only of limited value, at least as far as the compounds under discussion are concerned.

Introduction

In the last few years studies involving positive ion mass spectra have been applied to a great variety of organic compounds.^{4–6} However, very little has been published with respect to negative ion mass spectrometry. There also appear to be discrepancies in the published experimental results, which demonstrate the need for further work. The most recent discussion of this subject is by Melton,⁷ who classifies the formation of negative ions by electron bombardment under the following headings: (a) dissociative resonance capture, $AB + e \rightarrow A\cdot + B^-$; (b) resonance capture, $AB + e \rightarrow AB^-$; and (c) ion pair formation, $AB + e \rightarrow A^+ + B^- + e$.

In mechanisms a and b negative ions are formed exclusively by electron impact, whereas negative ion production by mechanism c may be induced by any ionizing radiation, e.g., photons, α particles, etc., as

well as by electrons. Process a occurs when AB captures an electron and undergoes an electronic transition to give the negative ion B^- and the radical $A\cdot$. Process b is also initiated by electron capture. When AB captures a low-energy electron (<1 e.v.), an excited negative species AB^{*-} is formed. This excited species may be stabilized by collision with a neutral molecule or by radiation; otherwise the captured electron is expelled. Dissociation into $A\cdot$ and B^- will occur if the captured electron has sufficient energy to produce an electronic transition to a higher energy than that of the dissociation energy. In the generation of negative ions by process c the molecule after electron impact receives sufficient energy to dissociate into A^+ and B^- , both of which may be in the excited state.

Under the normal operating conditions (50–70 e.v.) of a mass spectrometer, all three processes may occur. As they are pressure dependent in different ways, the relative intensities of negative ion mass spectra change with sample pressure. A further complication is the low yield of negative ions as compared with positive ions, generally by a factor of 10^3 lower. In an attempt to overcome these difficulties, Ardenne and his collaborators⁸ have employed a gas discharge source (argon, 10^{-2} mm.) with a sample partial pressure of approximately 10^{-6} mm. The low-energy electrons created (2–4 e.v.) form negative ions by resonance capture (process b), which gives very little fragmentation. However, the high over-all source pressure (10^{-3} – 10^{-2} mm.) can cause ion–molecule reactions. For alcohols, species have been observed⁹ corresponding to the combination of an alcoholate anion and a neutral molecule. This type of negative ion mass spectrometry has been employed in the determination of the molecular weights of steroids,¹⁰ and natural products in general,¹¹ where the general absence of extensive fragment ions has been considered to be an advantage. However, recent

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(2) This study has been made possible by financial assistance from the National Institutes of Health (Grant No. AM-04257). The National Aeronautics and Space Administration (Grant No. NsG 81-60) provided funds for the purchase of the Atlas CH-4 mass spectrometer.

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