Kinetics and Mechanism for the Hydrolysis of Phenyl Orthoformate[1]

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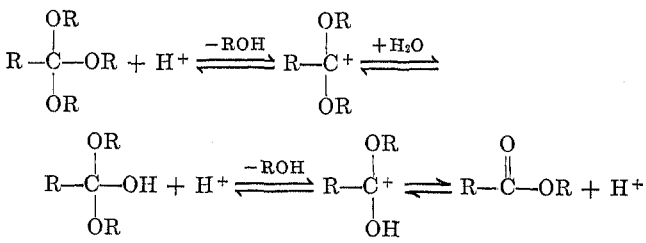
The kinetics of hydrolysis of phenyl orthoformate in moderately concentrated solutions of mineral acids have been investigated in both 40% aqueous dioxane and in water containing approximately 0.01 *M* tetradecyltrimethylammonium chloride as solubilizing agent. The observed rate constants for this reaction in both solvents increase with increasing acid concentration but do so less rapidly than the increase in h_0 values. The entropy of activation for this reaction in the presence of 1 *M* hydrochloric acid is near −6.6 eu in water containing surfactant and −11.5 eu in 40% aqueous dioxane. The kinetic solvent deuterium isotope effect for phenyl orthoformate hydrolysis, k_{D_2O}/k_{H_2O}, is near 2 in 0.01 *M* surfactant solution and unity in 40% aqueous dioxane. These findings are consistent with and provide modest support for the involvement of proton transfer in the rate-determining step for this reaction.

The acid-catalyzed hydrolysis of orthoesters proceeds along a reaction pathway involving substrate protonation and unimolecular decomposition of the protonated, or partially protonated, substrate.[3-6] Such a decomposition yields a carbonium ion which is irreversibly converted into carboxylic ester.[4] In view of these considerations, it is surprising that rates of orthoester hydrolysis do not follow the expected stabilities of the corresponding carbonium ions. Among the several explanations that have been offered to account for this behavior[3,7,8] is that of Bunton and DeWolfe, which suggests that protonation of the substrate is partially or completely rate-determining for ortho ester hydrolysis.[6] This suggestion derives from a comparison of rate constants for the hydrolytic reactions and those calculated for protonation from estimated basicities and the assumption that the reverse reaction is diffusion controlled.[6] Recent measurements indicate that the estimated basicities are substantially correct and provide support for this conclusion.[9] We now wish to report kinetic evidence consistent with rate-determining proton transfer for the hydrolysis of phenyl orthoformate.



Experimental Section

Materials.—Phenyl orthoformate was synthesized as previously described.[10] The product was recrystallized three times from ethanol to a melting point of 74.6–75.2° (lit.[10] mp 75°). A proton magnetic resonance spectrum of phenyl orthoformate in deuteriochloroform recorded on a Varian Associates A-60 spectrometer revealed a singlet at 6.6 ppm and a complex multiplet centered at 7.2 ppm downfield from tetramethylsilane. These signals exhibited an intensity ratio near 1:15 as expected. A satisfactory elemental analysis was obtained for this compound (Midwest Microlab, Inc., Indianapolis, Ind.). Dioxane was carefully purified according to the procedure of Fieser.[11] Dioxane was stored under nitrogen in the cold until use. Deuteriohydrochloric acid was prepared through decomposition of phosphorus oxychloride in D_2O followed by distillation of the constant-boiling acid (6.2 *M*). Standard hydrochloric acid was a British Distributing House product and was diluted with glass distilled water to the desired concentrations. Acid concentrations of hydrochloric and sulfuric acid solutions were determined by titration against a previously standardized sodium hydroxide solution. All other chemicals employed were reagent grade. Deuterium oxide was redistilled prior to use. Glass distilled water was employed throughout.

Kinetic Measurements.—Kinetics were followed spectrophotometrically with the aid of a Zeiss PMQ II spectrophotometer equipped with a heatable cell holder through which water from a thermostated bath was constantly circulated. All reactions were followed by observing the appearance of phenol at 270 mμ; reaction solutions initially contained 1.5–1.8 × 10^{-4} *M* phenyl orthoformate. All kinetic measurements were performed at 25° unless noted otherwise. First-order rate constants were obtained from plots of log ($OD_\infty - OD_t$) against time in the usual manner. Activation parameters were obtained from the variation in second-order rate constants as a function of temperature and the appropriate ancillary equations.[12]

Results

In Table I, first-order rate constants for the hydrolysis of phenyl orthoformate at 25° in 40% aqueous dioxane are collected as a function of the concentration of hydrochloric and sulfuric acids. The dioxane solutions contained 40 ml of dioxane in a total of 100 ml. In hydrochloric and sulfuric acids the first-order rate con-

TABLE I
FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF PHENYL ORTHOFORMATE AT 25° AND IN 40% AQUEOUS DIOXANE AS A FUNCTION OF THE CONCENTRATION OF HYDROCHLORIC AND SULFURIC ACIDS[a]

(HCl), *M*	$k_{obsd} \times 10^3$, sec^{-1}	(H_2SO_4), *M*	$k_{obsd} \times 10^3$, sec^{-1}
1.0	0.78, 0.77, 0.78	1.025	0.77
2.0	3.1, 3.1, 3.1	1.115	0.76
3.0	8.7, 9.5, 7.4	2.12	3.3
4.0	10.6, 11.5, 10.5	2.08	3.0
5.0	10.3, 10.5, 10.8	3.07	8.1
6.0	15.1, 15.7	3.01	7.7
		4.13	5.7
		4.06	5.8

[a] Reactions followed spectrophotometrically at 270 mμ; phenyl orthoformate 1.5 × 10^{-4} *M*.

(1) Supported by Grant AM 08232 from the National Institutes of Health.
(2) Career Development Awardee of the National Institutes of Health.
(3) For a discussion of these points, see E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).
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(6) C. A. Bunton and R. H. DeWolfe, *J. Org. Chem.*, **30**, 1371 (1965).
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(10) H. Baines and J. E. Driver, *J. Chem. Soc.*, **125**, 907 (1924).
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(12) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961.

stants increase slowly with increasing acid concentration. A set of similar measurements was made in aqueous solutions containing approximately 0.01 *M* tetradecyltrimethylammonium chloride. The results are collected in Table II. The inclusion of the surfactant is necessitated by the insolubility of the ortho-ester in water. Although the rate constants are about an order of magnitude smaller than those obtained under similar conditions in 40% aqueous dioxane solutions, they show the same type of dependence on acid concentration as observed in the latter solvent. The inhibition of the hydrolysis of phenyl orthoformate by the cationic surfactant is not surprising: previous results have revealed that the hydrolysis of methyl orthobenzoate is inhibited by this surfactant.[13]

TABLE II

FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF PHENYL ORTHOFORMATE AT 25° IN AQUEOUS SOLUTIONS OF TETRADECYLTRIMETHYLAMMONIUM CHLORIDE AS A FUNCTION OF THE CONCENTRATION OF HYDROCHLORIC AND SULFURIC ACIDS[a]

(HCl), *M*	$k_{obsd} \times 10^4$, sec^{-1}	(H_2SO_4), *M*	$k_{obsd} \times 10^4$, sec^{-1}
1.0	0.6	1.0	0.9
2.0	1.8	2.0	1.6
3.0	6.3	3.0	9.7
4.0	16.0	4.0	13.0

[a] Tetradecyltrimethylammonium chloride concentration is 0.0085 *M* in hydrochloric acid solutions and 0.01 *M* in sulfuric acid solutions.

Two lines of evidence establish that the reaction studied was, in fact, the hydrolysis of phenyl orthoformate and not the hydrolysis of phenyl formate. A prior conversion of the ortho ester into the carboxylic ester might have been very rapid under the reaction conditions and, thus, the possibility existed that we were observing only the decomposition of the latter product. However, the optical density at 270 mμ typically increased by more than a factor of 2 during the course of kinetic runs. This result is impossible on the basis of rapid orthoester hydrolysis followed by slow ester hydrolysis since 2 mol of phenol would be liberated in the first process and only 1 additional mol in the second. An increase in optical density of not more than 50% can be accounted for on this basis. Furthermore, direct investigation of the rate of hydrolysis of phenyl formate in 0.5–5 *M* hydrochloric acid in 40% aqueous dioxane solutions revealed that hydrolysis of this ester is more rapid by three- to fivefold than that for the corresponding ortho ester. Hence, the kinetics observed were certainly those for ortho ester hydrolysis and the products of this reaction were formic acid and 3 mol of phenol. In some of the kinetic runs, particularly those in surfactant solutions at high acid concentrations, some deviation from strict first-order behavior was observed. This is almost certainly a consequence of approximately equal rates of hydrolysis for ortho ester and ester under these reaction conditions. For these reactions, first-order rate constants were evaluated from the data obtained during the first stages of the reaction.

Activation parameters for the hydrolysis of phenyl orthoformate in 40% aqueous dioxane and in water containing 0.01 *M* tetradecyltrimethylammonium chloride have been evaluated from the variation in second-order rate constants as a function of temperature; data are collected in Table III. All kinetic measurements were carried out in the presence of 1.1 *M* hydrochloric acid. Both sets of data yielded excellent Arrhenius plots. Of particular note are the small negative values of the entropy of activation observed under both sets of conditions.

TABLE III

ACTIVATION PARAMETERS FOR ACID-CATALYZED HYDROLYSIS OF PHENYL ORTHOFORMATE IN 40% AQUEOUS DIOXANE AND IN WATER[a]

Temp, °K	k_2, M^{-1} sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
	Aqueous Surfactant		
298.1	1.12×10^{-4}	20.86	−6.6
302.5	1.84×10^{-4}		
308.0	3.50×10^{-4}		
312.5	5.99×10^{-4}		
	40% Aqueous Dioxane		
298.9	9.23×10^{-4}	18.21	−11.5
303.5	1.48×10^{-3}		
308.4	2.46×10^{-3}		
313.1	3.80×10^{-3}		

[a] All reaction mixtures contained 1.1 *M* hydrochloric acid. Those reactions carried out in water contained 0.01 *M* tetradecyltrimethylammonium chloride as solubilizing agent.

Solvent deuterium isotope effects on the rate of hydrolysis of phenyl orthoformate have been investigated in both 40% aqueous dioxane and in water containing 0.0085 *M* tetradecyltrimethylammonium chloride at several concentrations of H(D)Cl at 25°. The data are collected in Table IV. Values of k_{D_2O}/k_{H_2O} near unity were obtained in the former solvent and values near 2 in the latter.

TABLE IV

SOLVENT DEUTERIUM ISOTOPE EFFECTS FOR THE HYDROLYSIS OF PHENYL ORTHOFORMATE AT 25° IN 40% AQUEOUS DIOXANE AND IN WATER[a]

H(D)Cl, *M*	$k_{obsd}^{H_2O}$, sec^{-1}	$k_{obsd}^{D_2O}$, sec^{-1}	k^{D_2O}/k^{H_2O}
	40% Aqueous Dioxane		
1.0	8.4×10^{-4}	9.0×10^{-4}	1.07
2.0	2.7×10^{-3}	2.4×10^{-3}	0.89
3.0	8.0×10^{-3}	7.7×10^{-3}	0.96
	Aqueous Surfactant		
1.0	6.0×10^{-5}	1.3×10^{-4}	2.20
2.0	1.83×10^{-4}	4.9×10^{-4}	2.65
3.0	6.25×10^{-4}	9.8×10^{-4}	1.57

[a] Reactions in water contained 0.0085 *M* tetradecyltrimethylammonium chloride as solubilizing agent.

Discussion

Despite the basic similarity in the mechanisms for acid-catalyzed hydrolysis of acetals and ketals on one hand and ortho esters on the other, a central distinction between the two seems to exist. For the former class of substrates, the protonation reaction appears to be rapid and reversible so that the decomposition of the protonated substrates is the rate-determining step.

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For the latter class, the protonation seems to be involved in the rate-determining step, either as a process which precedes carbonium ion formation or as one which is concerted with it. Evidence which favors these conclusions is derived from two principal sources. First, calculations of the rate constants for substrate protonation, based on estimated or measured substrate basicities and on the assumption that the reverse reaction is diffusion controlled, reveal that protonation of acetals and ketals is much more rapid than the over-all rate constant for hydrolysis while those for protonation of ortho esters are nearly equal to the over-all rate constants.[6,9] Second, the hydrolysis of ortho esters is subject to general acid catalysis while the hydrolysis of ketals and acetals is not.[3,5,14-18] Evidence obtained in this investigation is consistent with these conclusions.

Studies of the kinetics of hydrolysis of ortho esters in moderately concentrated solutions of mineral acids are generally quite difficult since the rates of decomposition are exceptionally rapid. However, phenyl orthoformate has proved to be the least reactive ortho ester studied, by several orders of magnitude, and its use permits such measurements to be made by ordinary spectrophotometric techniques. Consequently, direct comparisons between the behavior of ortho esters and that of acetals in such solutions may be made employing this substrate.

Perhaps the most striking feature of the kinetics of hydrolysis of phenyl orthoformate is the inertness of this species to acid-catalyzed hydrolysis. This is certainly the only known case in which an ortho ester is less reactive to hydrolysis than the corresponding carboxylic ester. This inertness, which must reflect the very weakly basic character of this ortho ester (see below), is itself evidence favoring proton transfer in the rate-determining step. Were protonation rapid and reversible and decomposition of the protonated species rate determining, the over-all rate constant for hydrolysis ought not to be greatly sensitive to the basicity of the leaving alcohol. This is true since changes in basicity will affect the extent of protonation and the rate of departure of the leaving group in opposite ways. In contrast, if the protonation of the substrate is rate determining or partially so, such changes in basicity will be fully reflected in the over-all rate constants for the hydrolytic reactions. Thus, values of the Hammett ρ for acid-catalyzed hydrolysis of substituted phenyl β-D-glucosides[19,20] and 2-(*para*-substituted phenoxy)tetrahydropyrans[18] are small and negative. One disquieting note is introduced by the observation that rates of hydrolysis of certain formals do seem to depend strongly on the nature of the leaving alcohol.[21]

One additional important observation concerning the hydrolysis of phenyl orthoformate in moderately concentrated solutions of mineral acids is the modest effect of increasing acid strength on the first-order rate constants (Tables I and II). In general, the rate constants increase with increasing acid concentration but increase less rapidly than the increase in the protonating power of the medium as measured by the Hammett acidity function.[22,23] These observations are in contrast to the behavior exhibited by certain acetals whose rate constants for hydrolysis are linearly related to the h_0 acidity function with slopes between 1 and 1.5.[24-26] The behavior of phenyl orthoformate cannot be accounted for on the basis of complete or substantial protonation of this substrate since the pK_a for the conjugate acid of this species ought to be near -9 or -10 and no media were employed in the kinetic measurements with a value of H_0 more negative than -3. The estimate of the basicity of phenyl orthoformate is based on the measured basicities of ortho esters and on the relative basicities of dimethyl ether and anisole.[9,27] The distinct acidity-rate behaviors exhibited by acetals and phenyl orthoformate are most easily accounted for on the basis of preequilibrium proton transfer in the former case and proton transfer in the transition state in the latter. Owing to uncertainties concerning validity of acidity-rate correlations in the media employed here, more detailed considerations are not warranted.

The entropies of activation for hydrolysis of phenyl orthoformate in aqueous surfactant and 40% aqueous dioxane are consistent with this interpretation. These moderate negative values are in contrast to those observed both for the hydrolysis of acetals and ketals, and for other ortho esters for which values near zero or slightly positive have been observed, although it is possible that the difference is due in part to the media employed in this study.[28] The negative entropy of activation observed for phenyl orthoformate hydrolysis may be accounted for in terms of the involvement of one or more solvent molecules as proton transfer agents in the transition state. Solvent organization for proton transfer may be rather more extensive for this substrate than for other ortho esters since this one is the least basic thus far investigated. It is worth noting that the observed entropies of activation are not nearly as negative as those for reactions believed to occur with the involvement of solvent as nucleophilic reagent (*ca.* -20 to -25 eu).[24,29]

The solvent deuterium isotope effects on phenyl orthoformate hydrolysis are similar to those observed for the hydrolysis of acetals, ketals, and other ortho esters.[30] The rather smaller value observed in 40% aqueous dioxane, near unity, compared with that in aqueous surfactant, near two, may be the consequence of the lesser ion-solvating power of the former medium.

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(15) R. H. DeWolfe and R. M. Roberts, *J. Amer. Chem. Soc.*, **76**, 4379 (1954).
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(17) Fife and Jao[18] have recently reported general acid catalysis for hydrolysis of certain 2-aryloxytetrahydropyrans, acetals with very weakly basic leaving groups. Since the distinction between acetal and ketal hydrolysis on one hand and ortho ester hydrolysis on the other depends on the lesser basicity of the latter species, this observation is consistent with the arguments developed here.
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(30) For a collection of pertinent data, see ref 3, p 16.

This change in medium will tend to cause proton transfer in the transition state to be rather less complete than in the case of an entirely aqueous solution. The surprising point about kinetic solvent deuterium isotope effects for ortho ester hydrolysis is that they are larger than unity. This must indicate that, even if proton transfer is involved in the transition state, the transfer must be nearly complete. This is consistent with the observation of large Brønsted α values for general acid catalysis of ortho ester hydrolysis.[15,16]

While the above results suggest that proton transfer is involved in the transition state for ortho ester hydrolysis, it is unlikely that this process is solely rate determining. This would require that the decomposition of the protonated intermediate and the diffusion apart of the reaction products be much faster than the diffusion-controlled loss of a proton. In addition, it would require that the Brønsted α value for general acid-catalyzed ortho ester hydrolysis be unity; observed values are near 0.7.[15,16] All the data are best rationalized by depicting the first step in ortho ester hydrolysis as involving unimolecular carbon–oxygen bond cleavage concerted with proton transfer to the leaving group from the hydrated proton or other acid.

It ought to be specifically recognized that, for the case of phenyl orthoformate hydrolysis, protonation need not necessarily occur on oxygen. It is possible that the most basic site of this molecule is at aromatic carbon and the proton transfer to the aromatic rings may, then, be involved in the transition state.

Registry No.—Phenyl orthoformate, 16737-44-3.

Carbenoid Decomposition of Aryldiazomethanes with Lithium and Zinc Halides. A Convenient Method for the Synthesis of Arylcyclopropanes[1]

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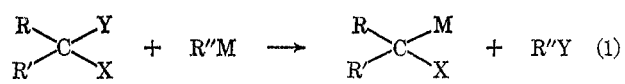
The carbenoid decompositions of phenyl-, *p*-tolyl-, and *p*-anisyldiazomethane catalyzed by lithium salts and zinc halides were investigated. The yields, stereochemistry, and relative rates of cyclopropane formation with olefins were studied and compared with other carbenoid systems. In all cases the thermodynamically less stable *syn* isomer was formed predominantly. The isomer ratios were found to be influenced by both cation and anion of the catalyst and also to be a function of the aryl substituents. Rates of the zinc halide catalyzed decompositions of the diazo compounds were measured by stopped-flow methods. The lifetimes of the organozinc intermediates were estimated by flow techniques. The preparative aspects of the zinc salt catalyzed reactions were explored and found to be superior to other methods of synthesizing arylcyclopropanes.

Considerable evidence has been accumulated in this and other laboratories that many reactions initially thought to be characteristic of divalent carbon compounds are also given by certain organometallics.[3-8] The common structural feature of the latter reagents is the binding of an electropositive element, usually a metal of group I or II, and an electronegative element or group to the same carbon atom. Because reactivities are qualitatively similar to those expected for carbenes, the name carbenoids has been suggested for such compounds.[4]

Several methods for the preparation of carbenoids have been reported, but the majority may be classified as acid–base reactions on alkyl halides as shown in reaction 1. Another method involves the reaction



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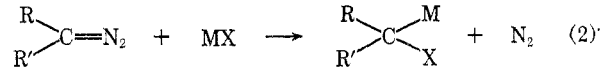
of diazoalkanes with metal salts. Many examples of this reaction type were examined by Wittig and collaborators, who postulated the formation of metal organic compounds according to reaction 2.[9]



(2)

It is worthwhile pointing out, however, that the proposed structures of carbenoids are based on rather circumstantial evidence and that a formulation such as I should be regarded as the simplest possible description which is in reasonable agreement with most of the observed chemistry. On the other hand, there exists a considerable body of evidence suggesting that I is an oversimplification and that specific solvent complexes and perhaps dimeric or even polymeric forms of I would be better descriptions of the actual structures.[4,6,10]

Since carbenoids are usually short-lived reaction intermediates, only a few of which have been isolated at very low temperatures,[6] little direct structural evidence has been reported so far. Also, very few quantitative studies exist which may serve as a basis of simple structure–reactivity relationships. For example, little is known about the effect on reactivity of changing either the cationic (M) or the anionic (X) leaving groups. Or even more fundamental, it is not even known whether methods 1 and 2 really do give the same carbenoid when all of the substituents and leaving groups are identical.

In a previous study carried out in this laboratory,

(1) Supported by National Science Foundation Grants GP-4214 and GP-7043.

(2) Uniroyal Predoctoral Research Fellow, 1967–1968.

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