

Solvent Deuterium Isotope Effect on the Rate of the Uncatalyzed Hydrolysis of Phenyl Dimethyl Orthoformates

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Rates of hydrolysis of substituted phenyl dimethyl orthoformates (dimethoxyphenoxy-methanes) were measured in dilute aqueous base solutions. A spontaneous unimolecular mechanism is suggested for this hydrolysis on the basis of structural effects. A solvent deuterium isotope effect, $k(\text{H}_2\text{O})/k(\text{D}_2\text{O}) \approx 1.6$, is observed. The consistency of this value with the suggested mechanism for the uncatalyzed hydrolysis is discussed in terms of free energies of transfer of the species from H_2O to D_2O and fractionation factors for the hydrogen atoms of the water molecules solvating the activated complex. An isotopic rate-equilibrium relationship is suggested, in which the α -coefficient represents the extent of C–O bond cleavage.

Carboxylic acid ortho-esters, which are more reactive toward acid hydrolysis than almost any other class of compounds, are inert, or nearly so, to aqueous alkali.¹ The hydrolysis of acetals (1,1-dialkoxyalkanes), which are structurally related to ortho-esters (1,1,1-trialkoxyalkanes), has been reported to occur by a pH-independent pathway in a few cases.^{2,3} The rate of uncatalyzed hydrolysis of acetals depends on the ease of C–O bond cleavage, which is affected by the stability of the products of the rate-limiting step, i.e. the oxocarbenium ion and the leaving anion.

Phenols are much stronger acids than aliphatic alcohols because of the increased stabilization of phenoxide ions by resonance. The same stabilization makes phenoxide ions better leaving groups than anions of aliphatic alcohols in hydrolytic reactions. Accordingly, an uncatalyzed pathway for hydrolysis has been observed for acetals with a phenolic leaving group.^{4–7}

In the hydrolysis of ortho-esters, dioxocarbenium ion is formed in the rate-limiting step. The resonance stabilization of this ion is greater than that of the oxocarbenium ion formed in the hydrolysis of acetals.

The hydrolysis of ortho-esters with a phenolic leaving group has been studied in dioxane/water

solvents.⁸ Pronounced general acid catalysis was observed in the hydrolysis of these compounds, but no uncatalyzed hydrolysis was reported. Yet, the same factor as that required for observation of uncatalyzed hydrolysis, viz. ease of C–O bond cleavage, is regarded as important for detecting general acid catalysis.² The uncatalyzed pathway should be very favourable in the hydrolysis of such ortho-esters.

Kinetic data are therefore presented here for the hydrolysis of substituted phenyl dimethyl orthoformates in dilute aqueous base solutions. A mechanism for the reaction is suggested and the possible basis for the solvent deuterium isotope effect on the reaction is discussed.

Experimental

Materials. The methods used for the preparation of the mixed orthoformates from methyl dimethoxyacetate and the synthesis of the initial reagent were those described by Scheeren and Stevens.⁹ The following R-substituted phenyl dimethyl orthoformates were purified by distillation under reduced pressure: R = 4-OCH₃, $t(\text{vap.}) = 84\text{--}86^\circ\text{C}$ at $p = 3$ mmHg (400 Pa); R = 4-CH₃, $t(\text{vap.}) = 67^\circ\text{C}$ at $p = 6$ mmHg (800 Pa); R =

3-CH₃, $t(\text{vap.}) = 54^\circ\text{C}$ at $p = 2$ mmHg (270 Pa);
 R = H, $t(\text{vap.}) = 58^\circ\text{C}$ at $p = 2$ mmHg (270 Pa);
 R = 3-OCH₃, $t(\text{vap.}) = 104^\circ\text{C}$ at $p = 3$ mmHg
 (400 Pa); R = 4-Cl, $t(\text{vap.}) = 80^\circ\text{C}$ at $p = 1$
 mmHg (130 Pa).

The prepared compounds were identified by their ¹H NMR spectra. Since the signals for each compound exhibited the expected intensity ratios and since no other signals were detected, the products were regarded as being sufficiently pure for kinetic measurements.

Reaction solutions. Sodium hydroxide solutions were prepared by dilution of standard solutions (Titrisol, E. Merck AG) with carbon dioxide-free distilled water. Sodium chloride was added to maintain the ionic strength at 0.100 mol dm⁻³.

Sodium deuterioxide solution was prepared by dissolving metallic sodium in deuterium oxide under toluene in a separatory funnel. Deuterium oxide was supplied by NEN Chemicals GmbH. The deuterium mole fraction in the product was 0.997 according to the supplier.

Kinetic measurements. Rates of hydrolysis were measured spectrophotometrically by following the appearance of the products at the absorption maxima of the liberated phenoxide ions. The measurements were performed with a Perkin Elmer 46 BCD spectrophotometer. Details of the procedure and the method of calculation of rate constants have been described earlier.⁴

The precision of the rate constants was better than 3 per cent in the standard error of the mean of six determinations. Since there is no dependence on any catalyst concentration which may introduce error, even the accuracy of these values is of that magnitude.

Results and discussion

The rates of the water-induced or uncatalyzed hydrolysis of substituted phenyl dimethyl orthoformates were measured in dilute aqueous base solutions in order to eliminate the presence of any acidic species. Both ordinary and heavy water were used as the solvent. A summary of the relevant data is presented in Table 1.

The observed first-order rate constants were independent of the base concentration. No base or nucleophilic catalysis by the hydroxide ion could be detected. Thus, the hydrolysis is due to

Table 1. Rate constants for the water-induced hydrolysis of substituted phenyl dimethyl orthoformates in aqueous sodium hydroxide^a and deuterioxide^b solutions at 25°C.

| Subst. | $t/^\circ\text{C}$ | $k(\text{H}_2\text{O})/10^{-3} \text{ s}^{-1}$ | $k(\text{D}_2\text{O})/10^{-3} \text{ s}^{-1}$ | $k(\text{H}_2\text{O})/k(\text{D}_2\text{O})$ | |
|--------------------|--------------------|--|--|---|--|
| 4-OCH ₃ | 15 | 0.458 | 0.272 | 1.68 | |
| 4-CH ₃ | | 0.567 | 0.320 | 1.77 | |
| 3-CH ₃ | | 1.24 | 0.777 | 1.60 | |
| H | | 1.79 | 1.09 | 1.64 | |
| 3-OCH ₃ | | 5.76 | 3.44 | 1.67 | |
| 4-Cl | 25 | 7.15 | 4.44 | 1.61 | |
| 4-OCH ₃ | | 1.58 | 0.987 | 1.60 | |
| 4-CH ₃ | | 1.82 | 1.06 | 1.72 | |
| 3-CH ₃ | | 3.69 | 1.93 | 1.91 | |
| H | | 5.45 | 3.19 | 1.71 | |
| 3-OCH ₃ | | 15.9 | 10.4 | 1.53 | |
| 4-Cl | | 20.0 | 12.0 | 1.67 | |
| H | | 35 | 13.1 | | |
| H | | | 45 | 33.2 | |
| H | | | | | |

^a $c(\text{NaOH}) = 0.100\text{--}0.001$ mol dm⁻³; sodium chloride added to maintain ionic strength 0.100 mol dm⁻³.

^b $c(\text{NaOD}) = 0.001$ mol dm⁻³.

the solvent water only. The water-induced reaction may be regarded as a general acid-catalyzed reaction, where the proton is transferred from the water molecule to the oxygen atom of the substrate; this process may or may not be concerted with the C–O bond rupture. An alternative mechanism for the reaction involves an uncatalyzed unimolecular decomposition of the substrate without a water molecule acting as a proton-transfer agent in the transition state. These mechanistic possibilities differ with respect to the charge development on the oxygen atom of the phenolic leaving group.

Structural effects of the substituents on the benzene ring can be used to distinguish between mechanisms involving different charges adjacent to the aromatic ring in the transition state. The correlation between the Hammett substituent constants σ and σ^+ and $\log k$ is illustrated in Fig. 1. The curvature of the plot for σ^+ -constants shows that no reaction centre (a positive charge) which acts as an electron acceptor is formed in the reaction. A straight-line relationship with satisfactory correlation is obtained when σ -constants are used. The slope of this line, the Hammett reaction constant ρ , has a high positive value of

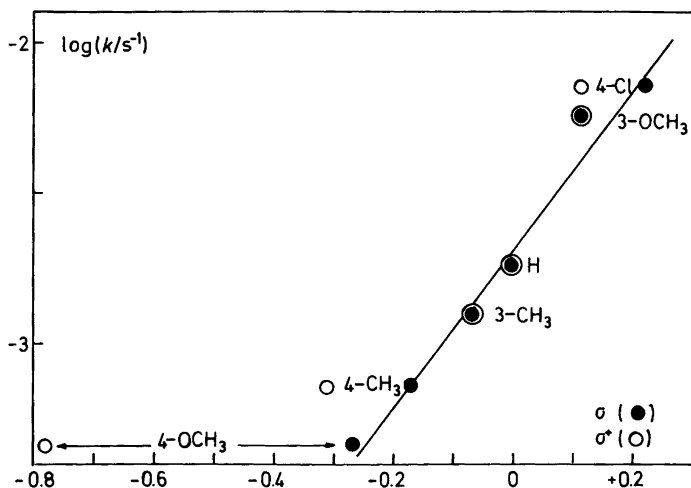


Fig. 1. Structural effects on the rate of water-induced hydrolysis of substituted phenyl dimethyl orthoformates at 15°C, presented as the Hammett relationship with different substituent constants.

2.69(26). This indicates that electron-withdrawing substituents accelerate the water-induced reaction. These substituents increase the ease of C–O bond cleavage, which thus must be the most important of the bond-making and bond-breaking processes. In general, the value of ρ is an indication of the extent of the charge development at the atom adjacent to the aromatic ring on passing from initial to transition state. A high positive value refers to a negative charge at the oxygen atom of the activated complex. Protonation of the oxygen atom by a water molecule acting as an acid catalyst would diminish the negative charge at that atom and therefore cannot have taken place in the transition state. This observation supports a spontaneous unimolecular mechanism for the reaction investigated here.

In discussions of studies on a related class of compounds, acetals, the distinction between the two alternative mechanisms has been made mainly on the basis of solvent deuterium isotope effects. Values near unity have been taken as indicative of spontaneous unimolecular cleavage^{7,10,11} and values larger than unity have been ascribed to a mechanism in which a water molecule acts as a general acid catalyst.¹² The value of the solvent deuterium isotope effect for the water-induced hydrolysis of phenyl dimethyl orthoformates, $k(\text{H}_2\text{O})/k(\text{D}_2\text{O}) \approx 1.6$, seems to be inconsistent with the spontaneous unimolecular mechanism deduced from the structural effects, since a reaction involving no solvent par-

ticipation would not be expected to show any solvent isotope effect.

The observed solvent deuterium isotope effect on the rate of uncatalyzed hydrolysis may be explained in terms of a change in the ease of C–O bond cleavage. The latter is affected by the stability of the products, viz. oxo-carbenium ion and leaving anion. An increase in the stability of the anion corresponds to an increase in the acidity of the leaving phenol; the more acidic a phenol is, the better its anion is as a leaving group in a reaction. Protolytic dissociation constants for weak oxyacids, including phenols, are almost always larger in water than in deuterium oxide.¹³ On this basis it is easy to understand the retardation in the rate of uncatalyzed hydrolysis when the solvent is changed from ordinary water to heavy water.

It has been suggested that uncatalyzed hydrolysis may be incorporated in the Brønsted relation, in the form of the acidity constant for the phenol corresponding to the leaving group in the reaction.⁴ The same is possible when both the rate of uncatalyzed hydrolysis and the acidity of the phenol are affected by a change of the solvent to deuterium oxide. The rate-equilibrium relationship in this case is then given by eqn. (1).

$$\log \frac{k(\text{H}_2\text{O})}{k(\text{D}_2\text{O})} = \alpha \log \frac{K_a(\text{PhOH}; \text{H}_2\text{O})}{K_a(\text{PhOD}; \text{D}_2\text{O})} \quad (1)$$

Values for the solvent deuterium isotope effect upon the acid strength of some phenols have been reported.¹³ The difference in acidity, $\Delta pK = pK_a(\text{PhOD}; \text{D}_2\text{O}) - pK_a(\text{PhOH}; \text{H}_2\text{O})$, for phenol, 4-methoxy- and 3-methoxyphenol is 0.62, 0.61 and 0.58, respectively.¹³ These, and the observed solvent deuterium isotope effects on the rate (Table 1), yield values for the α -coefficient of eqn. (1) of 0.38, 0.39 and 0.32, respectively. The values obtained are nicely in accordance with the Brønsted α value (0.41) for carboxylic acid-catalyzed hydrolysis of phenyl dimethyl orthoformate.¹⁴ The physical significance of the α -coefficient obtained is suggested to be the extent of C–O bond cleavage in the transition state.

The solvent deuterium isotope effect may be separated into isotopic exchange and transfer effects.¹⁵ When no exchangeable hydrogen atoms are present in reactants or activated complex, the observed effect is due solely to the transfer effect, which is usually represented by transfer activity coefficients or free energies of transfer [eqn. (2)].

$$\frac{k(\text{H}_2\text{O})}{k(\text{D}_2\text{O})} = \frac{y(\neq)}{y(\text{S})} = \exp \left\{ \frac{1}{RT} [\Delta G_{\text{tr}}^{\ominus}(\neq) - \Delta G_{\text{tr}}^{\ominus}(\text{S})] \right\} \quad (2)$$

Owing to the separation of charges in the activation process for uncatalyzed hydrolysis, a larger free energy of transfer for the activated complex than for the reactants is to be expected. Assignments of individual ionic contributions to free energies of transfer of electrolytes indicate that the major part of the total free energy is due to the anion.^{16–18} Thus, a rough estimate of the ratio of transfer activity coefficients is obtained by taking into account only the anionic contribution to the free energy of transfer of the activated complex, since the smaller contributions from substrate in the initial state and the cationic part of the transition state may be considered to cancel out each other.

The free energy of transfer of the anionic part of the activated complex is estimated as being that of phenoxide ion. Combining the available data for picrate ion, 1,3,5-trinitrobenzene¹⁹ and benzene²⁰ a value of $\Delta G_{\text{tr}}^{\ominus}(\text{PhO}^-) = 600 \text{ J mol}^{-1}$ can be obtained. Eqn. (2) then gives a value of 1.25 for the solvent deuterium isotope effect on the hydrolysis of phenyl dimethyl orthoformate.

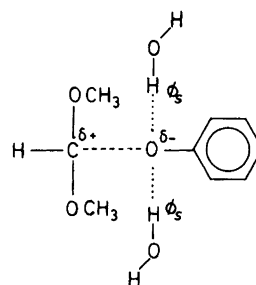
This value is smaller than the observed value, but demonstrates that values larger than unity are possible for the spontaneous hydrolysis.

The entropy of activation, ΔS^\ddagger , for the water-induced hydrolysis of phenyl dimethyl orthoformate can be calculated from the results in Table 1. The value of $-50(5) \text{ J K}^{-1} \text{ mol}^{-1}$ is highly negative and may be regarded as inconsistent with a unimolecular mechanism; it rather suggests water involvement in the transition state. This water involvement may take the form of differences in solvation of the transition state and the reactant, as shown by the solvent deuterium transfer effect.

The separation of the solvent deuterium isotope effect into transfer and exchange factors is arbitrary.²¹ The primary solvation shell may be regarded as being part of the activated complex, and the isotope effect can be discussed in terms of fractionation factors for its hydrogen atoms. Hydrogen-bonding of two water molecules to lone electron pairs of the oxygen atom with partial negative charge in the transition state is proposed (Scheme 1) by analogy with three-fold hydration of the hydroxide ion.²² Two distinct models for the hydroxide isotope effects have been proposed.^{15,22} In one model, these are dominated by the hydroxy hydrogen; in the other, the dominating influence is due to the hydrogens of the solvation shell. The latter model is preferred, and a value of about 0.7 is proposed for the fractionation factor for the solvating hydrogens.^{22–24}

The solvent deuterium isotope effect on the rate of the water-induced hydrolysis is expressed by the fractionation factors for the hydrogens in the activated complex [eqn. (3)].

$$\frac{k(\text{H}_2\text{O})}{k(\text{D}_2\text{O})} = \phi_s^{-2} \quad (3)$$



Scheme 1.

The observed solvent deuterium isotope effects can be explained in terms of this model if the fractionation factor for the hydrogens solvating the activated complex has a value of 0.77. This value for a hydrogen bonding to an oxygen with a partial negative charge is in accordance with that suggested for hydrogens bonding to hydroxide ion.²²⁻²⁴

On the basis of the above discussion, the spontaneous unimolecular mechanism for the hydrolysis of the phenyl dimethyl orthoformates studied can be regarded as reasonable in spite of a solvent deuterium isotope effect of about 1.6 and a highly negative entropy of activation.

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