

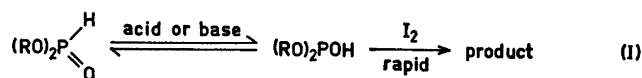
Deuterium Isotope Effect in the Acid Catalysed Hydrolysis and Iodine Oxidation of Dialkyl Phosphites

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The rates of the acid catalysed hydrolysis of P-deuterated dialkyl phosphites, $(RO)_2P(O)D$, are 20–30 % higher than the corresponding rates of the undeuterated compounds. This indicates that the P–D bond is not broken in the rate determining step of the hydrolysis. The rate of the acid catalysed iodine oxidation of the same deuterated phosphites is approximately one third of the rate of the corresponding undeuterated compounds, in agreement with a rate determining formation of a trivalent phosphite state prior to oxidation.

The hydrolysis as well as the iodine oxidation of dialkyl phosphites have been thoroughly studied by Nylén.^{1,2} Both reactions show general acid-base catalysis. Since the rate of the iodine oxidation is proportional to the concentration of the acid or base species involved, but independent of the concentration of iodine, the rate determining step has been assumed to be a protolytic transformation of the dialkyl phosphite to its trivalent state:



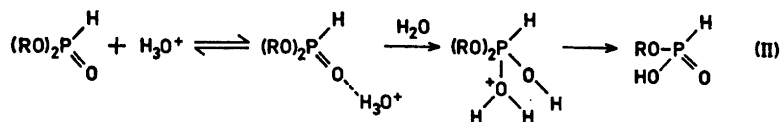
Luz and Silver³ studied the acid catalysed proton exchange of dialkyl phosphites in deuterium oxide, and found that the rate of exchange was only slightly lower than the rate of the acid catalysed iodine oxidation. The minor difference in the rate was ascribed to different medium effects for the two reactions: The exchange was studied in deuterium oxide, whereas the hydrolysis was performed in water.

Experiments have shown that trialkyl phosphites are very unstable towards hydrolysis by water, especially in the presence of acids.⁴ It might therefore seem possible that the acid catalysed hydrolysis of dialkyl phosphites could proceed through a trivalent phosphite intermediate. Under like conditions, the rate of the proton catalysed iodine oxidation is, however, approximately six times as rapid as the hydrolysis. Thus, if there should be a common

intermediate, the formation of the trivalent phosphite state cannot be rate determining for the acid catalysed hydrolysis.

Kilpatrick and Kilpatrick⁵ have pointed out the similarity of the acid hydrolysis of diisopropyl fluorophosphate, $[(\text{CH}_3)_2\text{CHO}]_2\text{P}(\text{O})\text{F}$, and dialkyl phosphites. They suppose that the compounds are hydrolysed by similar mechanisms. Since diisopropyl fluorophosphate has no hydrogen atom attached to phosphorus, its hydrolysis cannot proceed over a trivalent state.

In order to explain the decrease of the specific rate constant of hydronium ions, k_{H^+} , with increasing acid concentration in the hydrolysis of dialkyl phosphites and diisopropyl fluorophosphate, one of us⁶ previously proposed a hydrogen bond complex between the phosphoryl compound and the hydronium ion. A nucleophilic attack of water on phosphorus in this complex was assumed to be the rate determining step of the hydrolysis:



In the present work the acid catalysed hydrolysis and iodine oxidation of P-deuterated dialkyl phosphites have been studied in water. Any reaction which requires the rupture of the P—D bond in the rate determining step must exhibit a primary isotope effect, and will cause a strong decrease of reaction rate of the deuterated dialkyl phosphites as compared with the corresponding undeuterated compounds.

EXPERIMENTAL

Materials. The undeuterated and deuterated dialkyl phosphites were made from trialkyl phosphite by treatment with water respectively deuterium oxide in acetonitrile. This method has been shown previously to give pure dialkyl phosphites.⁴ Procedure: 0.2 mole of trialkyl phosphite was mixed with 0.3 mole of water respectively deuterium oxide. The mixture was diluted with 30 ml of acetonitrile and the solution boiled for 2 h. The acetonitrile was then distilled off and the dialkyl phosphite fractionated *in vacuo*. The trialkyl phosphites used were made according to earlier description.⁴ Gas chromatographic analysis showed that the dialkyl phosphites contained less than 1 % impurities.

The deuterium oxide employed was 99.7 % by weight, and infrared analysis showed that the resulting P-deuterated dialkyl phosphites contained less than 2 % undeuterated compound.

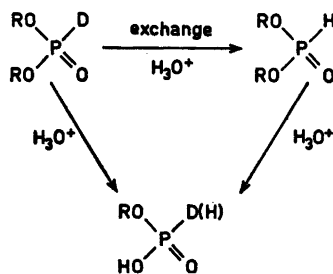
Kinetic measurements. The acid hydrolysis of dialkyl phosphites as well as the acid catalysed iodine oxidation of dialkyl phosphites were performed as described by Nylén.^{1,2}

ISOTOPE EFFECT IN ACID HYDROLYSIS

In Table 1 are shown data from a typical kinetic run for the acid catalysed hydrolysis of diethyl phosphite. The calculated first order rate constant of the deuterated diethyl phosphite is seen to decrease markedly with time. This effect is due to a competing proton exchange proceeding with a rate comparable to that of the hydrolysis:

Table 1. Acid hydrolysis of undeuterated and deuterated diethyl phosphite. Temp. 25°C. Concentration of hydrochloric acid: 0.2 M.

	Time, min	Conc. of ester M $\times 10^3$	Rate constant, min ⁻¹ $\times 10^3$
$\begin{array}{c} \text{H} \\ \\ -\text{P}=\text{O} \\ \end{array}$	0	4.997	—
	50	4.637	1.49
	110	4.234	1.49
	140	4.091	1.43
	200	3.768	1.41
	230	3.591	1.44
	260	3.443	1.43
	320	3.150	1.44
$\begin{array}{c} \text{D} \\ \\ -\text{P}=\text{O} \\ \end{array}$	0	4.964	—
	180	3.680	1.66
	240	3.373	1.61
	300	3.126	1.54
	360	2.876	1.52
	420	2.642	1.50
	555	2.189	1.48



The true values of the rate constants of acid catalysed hydrolysis of P-deuterated dialkyl phosphites are found on extrapolation of the apparent rate constants to zero time. The extrapolated values for the different phosphites are recorded in Table 2. The rate constants are seen to be 20–30 % higher than the rate constants of the undeuterated compounds. The data thus definitely show that the rupture of the P–H or the P–D bond is not the rate determining step in the hydrolysis. This conclusion is based on the following arguments:⁷ The difference between the vibrational zero-point energy of the P–H and P–D bond, approximately estimated from $\Delta E_0 = \frac{1}{2}h(\nu_H - \nu_D)$, where h = Planck's constant and ν_H and ν_D are the stretching frequencies of the P–H and P–D bond, respectively, amounts to 1 kcal. Apart from other effects, a difference of ΔE_0 in zero-point energy will contribute a factor, $\exp(\Delta E_0/RT)$, to the isotope effect in reactions where breaking of the P–D, respectively P–H bond is involved. With $\Delta E_0 = 1$ kcal, the ratio between the rate of hydrolysis of the undeuterated and deuterated dialkyl phosphites is estimated as 4.9. The observed ratio is approximately 0.9 (Table

Table 2. Comparison of rate constants for acid hydrolysis of undeuterated and deuterated dialkyl phosphites. Temp. 25°C. Concentration of hydrochloric acid: 0.2 M.

Substituent R	Rate constant, $\text{min}^{-1} \times 10^3$		$k_{\text{H}}/k_{\text{D}}$
	$(\text{RO})_2\text{P}(\text{O})\text{H}$	$(\text{RO})_2\text{P}(\text{O})\text{D}$	
Methyl	2.90	3.40	0.8
Ethyl	1.45	1.60	0.9
Propyl	1.31	1.55	0.9
Isopropyl	0.29	—	—
Butyl	1.20	1.35	0.9

2). This excludes the possibility of rupture of the P—H or P—D bond in the rate determining step of the hydrolysis.

The small rate increase of the acid hydrolysis of P-deuterated dialkyl phosphites as compared with the undeuterated compounds (Table 2) must be due to a secondary isotope effect. From theoretical considerations,⁸ the secondary isotope effect is expected to result in a small rate decrease. This is usually also observed. Lately, however, several reactions have been observed which exhibit an "inverse" secondary isotope effect.^{9,10} The hydrolysis of dialkyl phosphites seems therefore to be another example of a reaction in this category.

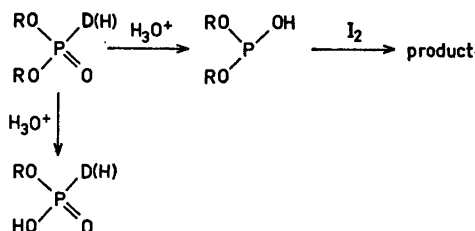
The present result for the deuterium isotope effect is in accordance with earlier suggestions that the rate determining step in the acid hydrolysis of dialkyl phosphites is a nucleophilic attack of water on phosphorus (reaction scheme II).^{5,6}

Table 3. The time dependence of the first order rate constants for the acid catalysed iodine oxidation of diethyl phosphite in water. Temp. 25°C. Concentration of hydrochloric acid: 0.2 M.

$(\text{EtO})_2\text{P}(\text{O})\text{H}$		$(\text{EtO})_2\text{P}(\text{O})\text{D}$	
Time, min	$k, \text{min}^{-1} \times 10^3$	Time, min	$k, \text{min}^{-1} \times 10^3$
15	8.17	20	2.98
30	8.25	40	2.84
45	8.19	75	2.79
60	8.13	105	2.73
75	8.10	135	2.69
90	8.03	180	2.58
105	7.83	225	2.48
120	7.91	270	2.39

ISOTOPE EFFECT IN ACID CATALYSED IODINE OXIDATION

In Table 3 are recorded the calculated first order rate constants for kinetic runs of the acid catalysed iodine oxidation of undeuterated respectively deuterated diethyl phosphite. The rate constants of both phosphites decrease with time, but the decrease is much more pronounced in the case of the deuterated phosphite. This is due to the competing acid hydrolysis of the dialkyl phosphites. On comparison of the data in Tables 1 and 3 it is seen that whereas the ratio between the rate constants for hydrolysis and iodine oxidation is only 0.18 for the undeuterated compound, it is approximately 0.6 for the deuterated diethyl phosphite. The competing acid hydrolysis during iodine oxidation of dialkyl phosphites is therefore of much greater importance for the deuterated compounds:



When the apparent rate constants (Table 3) are extrapolated to zero time, the true rate constants for the acid catalysed iodide oxidation of undeuterated as well as deuterated dialkyl phosphites are obtained. These values for various dialkyl phosphites are recorded in Table 4. The nearly three times higher rate of the undeuterated as compared with the deuterated dialkyl phosphites is of the right order of magnitude for a primary isotope effect, leaving no doubt that rupture of the P—H respectively P—D bond is rate determining for the oxidation process (reaction scheme I).

The minor influence of isopropyl groups on the acid catalysed iodine oxidation of dialkyl phosphites (Table 4), differs from the strong effect of isopropyl groups on the acid catalysed hydrolysis of dialkyl phosphites (Table 2). This fact is also a strong indicium for different mechanisms of oxidation

Table 4. Comparison of rate constants for acid catalysed iodine oxidation of undeuterated and deuterated dialkyl phosphites. Temp. 25°C. Concentration of hydrochloric acid: 0.2 M.

Substituent R	Rate constant, min ⁻¹ × 10 ³		<i>k_H</i> / <i>k_D</i>
	(RO) ₂ P(O)H	(RO) ₂ P(O)D	
Methyl	13.95	5.16	2.7
Ethyl	8.68	2.97	2.9
Propyl	9.70	3.30	2.9
Isopropyl	6.54	2.13	3.1

and hydrolysis: the rate determining rupture of the P—H or P—D bond during oxidation will not be sterically hindered by the isopropyl groups in the same way as the rate determining nucleophilic substitution of water on phosphorus during acid hydrolysis (reaction scheme II). In the acid hydrolysis of dialkyl fluorophosphate where nucleophilic attack of water on phosphorus is the only plausible reaction mechanism, a similar strong rate retarding effect is observed when secondary alkyl groups are substituted for primary alkyl groups in the fluorophosphate.^{5,11}

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