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Kinetics of the Hydrolysis of Arsenate(V) Triesters
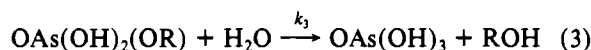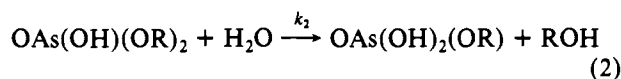
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The rates of hydrolysis of $OAs(OR)_3$, R = methyl, ethyl, *n*-pentyl, or isopropyl, were measured by stopped-flow spectrophotometry. The color change of phenolphthalein indicator was used to monitor the hydrolysis reaction. Data obtained referred to the first hydrolysis step, the second step being fast and the third step unobservable under the experimental conditions employed. The hydrolysis of trimethyl arsenate in methanol solution was first order in ester and in water with $k_1(25 °C)$ = 73 M^{-1} s^{-1}, $\Delta H^* = 13 \pm 1$ kJ mol^{-1}, and $\Delta S^* = -167 \pm 13$ J mol^{-1} K^{-1}. Hydrolysis rates of the esters decreased in the order methyl > ethyl > *n*-pentyl > isopropyl. An associative mechanism is proposed.

Introduction

Although many of their chemical and physical properties are similar, arsenates and phosphates demonstrate considerably different physiological actions.[1] To more fully understand these differences, some of which we ascribe to rate phenomena, we have been investigating some reactions of simple arsenates such as the hydrolysis of pyroarsenate[2] and the degenerate alcohol exchange in trialkyl arsenates.[3,4] These studies and others[5] have shown that the arsenates generally react some 10^4–10^6 times more rapidly than analogous phosphates and react with mechanisms that are more associative in nature. This trend is at least partially explainable by the somewhat larger arsenic radius, thereby facilitating attack by entering nucleophile, as indicated by the longer As–O vs. P–O bond length expected in compounds and observed in the X–ray crystal structures of tribenzyl arsenate[6] and phosphate.[7]

Here we report on the hydrolysis of several trialkyl arsenates $OAs(OR)_3$, where R = methyl, ethyl, *n*-pentyl, and isopropyl. For the three stages of hydrolysis (reactions 1–3), we have been

$$OAs(OR)_3 + H_2O \xrightarrow{k_1} OAs(OH)(OR)_2 + ROH \quad (1)$$

$$OAs(OH)(OR)_2 + H_2O \xrightarrow{k_2} OAs(OH)_2(OR) + ROH \quad (2)$$

$$OAs(OH)_2(OR) + H_2O \xrightarrow{k_3} OAs(OH)_3 + ROH \quad (3)$$

able to obtain data on k_1, an indication of k_2, but nothing on k_3. We present rate constants and activation parameters for reaction 1 in several solvent systems.

Although no quantitative rate studies have been found in the literature, it is known that hydrolysis proceeds exclusively with As–O bond fission.[8]

Experimental Section

Materials. Arsenate triesters were prepared, following the method of Crafts,[9] from silver arsenate and the appropriate alkyl halide refluxed in ether under nitrogen for 24–48 h. Phenolphthalein was recrystallized from ethanol by slow addition of distilled water and vacuum dried at 100 °C. Tetraethylammonium bromide was recrystallized from isopropyl alcohol. Anhydrous sodium hydroxide was prepared by the method of Kelly and Snyder.[10] Reagent grade

acetonitrile was refluxed over calcium hydride followed by two distillations over phosphorus pentoxide under nitrogen. Alcohols were dried by refluxing over calcium hydride followed by distillation. Methanol and ethanol were dried further by refluxing over and distilling from the corresponding magnesium alkoxide. Sodium ethoxide (Alfa) and deuterium oxide were used without further purification.

Procedure. The hydrolysis reactions were followed on a Durrum-Gibson D-110 stopped-flow spectrophotometer by monitoring the absorbance of phenolphthalein in the 475–520-nm region. The absorbance of the colored phenolphthalein dianion decreases as the acidic products of reactions 1 and 2 are formed. Reaction 3 is not observable by this method since $HAsO_4^{2-}$ is too weak an acid (pK_3 is too weak an acid (pK_3 = 11.5) to affect the phenolphthalein indicator equilibrium, $HIn^- \rightleftharpoons H^+ + In^{2-}$, pK_2 = 9.2. The indicator equilibrium is much faster than the hydrolysis reactions; indeed Whittaker et al.[11] have used a similar method in temperature-jump kinetic studies to measure reaction rates more rapid than those reported here.

Analysis of the indicator absorbance vs. time curves assumed a linear relation between the concentration of acid generated by the hydrolysis reactions and the observed decrease in absorbance. As shown in Figure 1, the linearity is not perfect. In practice, however, good linear plots of ln $[(A_0 - A_\infty)/(A_t - A_\infty)]$ vs. time were obtained for data obtained in the regions labeled A and B of Figure 1; good agreement was found between data obtained in the two regions. While the data of Figure 1 were obtained in ethanol solvent, similar results were found with acetonitrile/water solvents, though with somewhat different molar absorptivities.

The solubility characteristics of the indicator necessitated use of a variety of solvents. Thus the trimethyl and triethyl arsenate hydrolysis reactions were studied in methanol and ethanol, respectively, at low water concentrations while other experiments (hydrolysis of triethyl, tri-*n*-pentyl, and triisopropyl arsenates) were performed in acetonitrile with water concentrations ranging from 10 to 24 M. Tetraethylammonium bromide, 0.100 M, was added in all cases to control ionic strength, although total ionic strength did vary somewhat due to the different indicator concentrations employed.

The stopped-flow apparatus was fitted with various ratio drive syringes. The larger syringe contained a solution of indicator, added base (NaOH or NaOEt), and tetraethylammonium bromide, the smaller syringe contained the arsenate triester in pure solvent. This procedure allowed relatively high concentrations of arsenate triester in the stock solutions, thereby avoiding any significant initial hydrolysis. Kinetic studies were done at four temperatures over a 30 °C range with temperature control to ±0.1 °C.

Photographs of the oscilloscope traces were digitized on a Hewlett-Packard 9864A digitizing board and the pseudo-first-order rate constants, k_{obsd}, calculated with a Hewlett-Packard 9830 calculator by a linear least-squares fit of ln $[(A_0 - A_\infty)/(A_t - A_\infty)]$ vs. time. Experiments were repeated at least seven times and the results averaged. In some experiments, where pseudo-first-order conditions were not practical, the method of initial rates was used for order determination. This was true at low water concentrations where use of high ester concentrations was not feasible due to a side reaction between the indicator and the arsenate esters that became competitive only under these conditions.[12]

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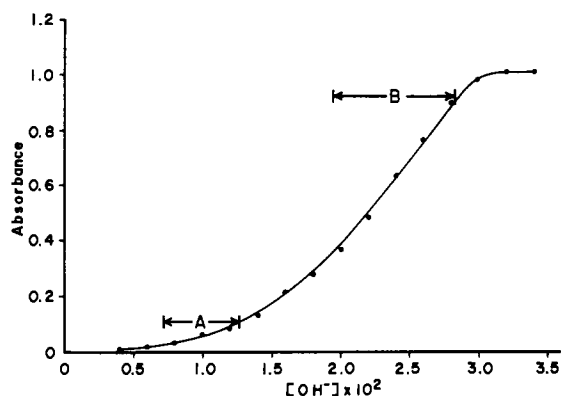
Figure 1. Absorbance at 500 nm (1-cm cell) of 0.015 M phenolphthalein in ethanol as a function of total base concentration. The regions marked A and B correspond to base concentration ranges employed in the hydrolysis experiments.

Table I. Experimental Conditions and Values of k_{obsd}

| ester	solvent	$t/°C$	k_{obsd}/s^{-1}	no. of runs
methyl,	MeOH,[a] 0.123 M	25.5	9.5 ± 0.3	10
4.8 mM	H_2O	35.2	11.5 ± 0.6	10
		43.0	13.0 ± 0.6	10
		50.0	15.3 ± 0.8	12
ethyl,	EtOH,[b] 0.25 M	25.0	3.9 ± 0.1	10
10 mM	H_2O	34.5	5.4 ± 0.3	11
		44.7	6.9 ± 0.4	11
		53.5	10.2 ± 0.8	11
ethyl,	CH_3CN,[b] 13.1 M	16.4	126 ± 8	13
7.4 mM	H_2O	25.9	162 ± 9	11
		36.0	214 ± 7	9
		45.8	272 ± 14	8
		25.5[c]	87 ± 4	15
ethyl,	EtOH,[a] 0.40 M	25.3	7.5 ± 0.6	14
3.0 mM	H_2O	35.3	12.3 ± 0.8	12
		44.0	15.9 ± 0.8	10
		53.5	18.9 ± 0.8	12
n-pentyl,	CH_3CN,[b] 19.1 M	25.6	94 ± 3	10
9.6 mM	H_2O	36.1	131 ± 9	11
		45.9	162 ± 6	8
		55.0	179 ± 8	11
isopropyl,	CH_3CN,[b] 13.1 M	16.4	1.8 ± 0.1	13
6.3 mM	H_2O	25.8	2.8 ± 0.1	7
		35.1	4.0 ± 0.1	10
		45.1	5.8 ± 0.3	9
isopropyl,	CH_3CN,[a] 24.0 M	18.6	2.9 ± 0.1	12
3.3 mM	H_2O	25.7	4.4 ± 0.2	11
		35.2	6.0 ± 0.1	10
		45.1	8.7 ± 0.4	12
		53.0	12.0 ± 0.6	10

[a] With 0.015 M phenolphthalein and 0.028 M base. [b] With 0.030 M phenolphthalein and 0.025 M base. [c] With 13.1 M D_2O.

Results and Discussion

Under conditions where $[H_2O] \gg [OAs(OR)_3]$, the hydrolysis reaction proceeds with pseudo-first-order kinetics; plots of $\ln [(A_0 - A_\infty)/(A_t - A_\infty)]$ vs. time gave good straight lines with zero intercepts, in accordance with the rate law

$$-d[OAs(OR)_3]/dt = k_{obsd}[OAs(OR)_3]$$

The experimental conditions and values of k_{obsd} are given in Table I. Values of A_0 were as expected from dilution of the indicator on mixing in the stopped-flow apparatus. Values of A_∞ corresponded to the transfer of two protons to the indicator from each molecule of ester. Preliminary attempts to monitor the hydrolysis of triisopropyl arsenate by proton NMR or by pH-stat titration of the hydrolysis products showed that the reaction is complete within seconds of mixing. Thus all three
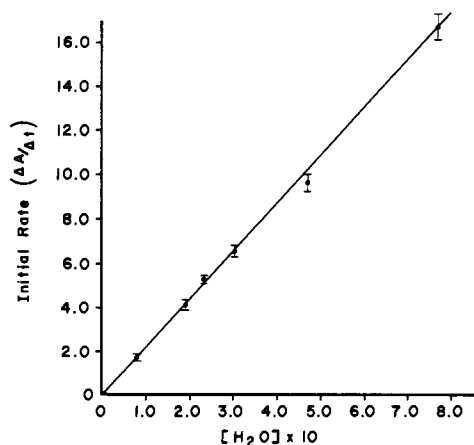
Figure 2. Plot of initial rate vs. $[H_2O]$ for triethyl arsenate in ethanol.
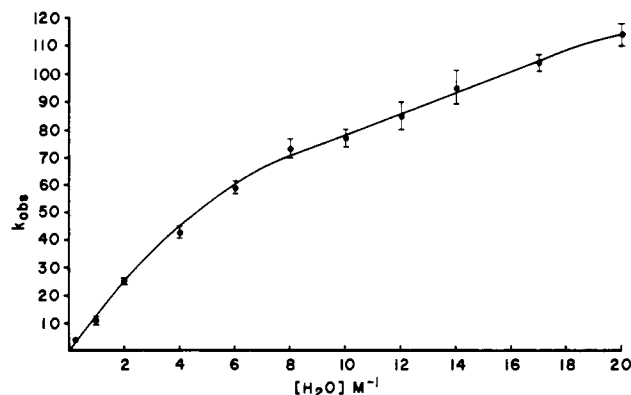
Figure 3. Plot of k_{obsd} vs. $[H_2O]$ for triethyl arsenate in ethanol.

hydrolysis steps are fast. furthermore, since good first-order plots were obtained from the stopped-flow experiments, we conclude that reaction 1 is rate determining with the second hydrolysis step following rapidly; thus the measured values of k_{obsd} corresponds to the first hydrolysis step of the arsenate triesters. Although there is some buffer action from the indicator, the hydroxide concentration changes significantly during the course of the reaction; the good first-order kinetic plots thus suggest that water, rather than hydroxide ion, is acting as the nucleophile in these reactions. Initial experiments to determine the kinetic order in water for the hydrolysis of triisopropyl and tri-*n*-pentyl arsenates in acetonitrile solutions indicated only a small rate dependence. Rather stringent requirements on the range of water concentrations usable are imposed by the solubility of the indicator in acetonitrile/water mixtures. Thus, further experiments studied the hydrolysis of triethyl arsenate in ethanol over a wide range of water concentrations, 0.10–20 M. Since alcohol exchange with arsenate esters occurs rapidly,[3,4] only the triethyl ester could be studied in ethanol. We assume that the other esters demonstrate a qualitatively similar dependence of rate on water concentration.

At relatively low water concentrations, the rate dependence on water is first order as evidenced by a plot of initial rate, $\Delta A/\Delta T$, vs. $[H_2O]$ (Figure 2). The rate law in this region is therefore

$$-d[OAs(OR)_3]/dt = k_1[OAs(OR)_3][H_2O]$$

Increasing the concentration of water beyond about 2 M leads to an apparent decrease in the kinetic order as shown in Figure 3.

Over the water concentration range from 0 to 20 M, the solvent nature must change considerably. Nevertheless the general features of Figure 3 can be rationalized. Given the
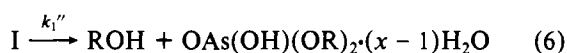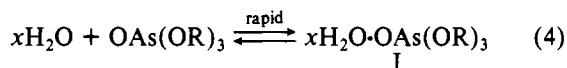
Table II. Rate Constants and Activation Parameters

a. Low Water Concentrations

ester	solvent	k_1-(25 °C)/ M^{-1} s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
ethyl[a]	ethanol	15.0	24 ± 2	−143 ± 19
ethyl[b]	ethanol	19.0	24 ± 4	−140 ± 29
methyl[b]	methanol	73.0	13 ± 1	−167 ± 13

b. High Water Concentrations in CH_3CN

ester	[H_2O]	k_{obsd}-(25 °C)/ s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
ethyl[a]	13.1	167.0	18 ± 1	−143 ± 3
n-pentyl[a]	19.1	96.0	15 ± 2	−156 ± 23
isopropyl[a]	13.1	2.9	29 ± 1	−140 ± 10
isopropyl[b]	24.0	4.2	29 ± 2	−136 ± 11

[a] Data obtained in region A; see Figure 1.   [b] Data obtained in region B; see Figure 1.

evidence for hydrogen bonding between arsenate triesters and alcohols,[4] it seems reasonable to assume that some specific solvation of the esters by water can occur in a rapid pre-hydrolysis step; water molecules will also participate in solvent cage formation about the ester. Thus we can formulate Scheme I, where x represents the variable number of water molecules involved in specific solvation and cage formation, k_1' represents the step that obtains at low water concentration, and k_1'' represents the reaction at higher levels of water. A distinct first-order behavior for water obtains at low concentrations (step 5), but the order decreases as expected when water becomes a significant fraction of solvent (step 6).

Scheme I

$$x H_2O + OAs(OR)_3 \underset{}{\overset{\text{rapid}}{\rightleftharpoons}} \underset{I}{x H_2O \cdot OAs(OR)_3} \quad (4)$$

$$I + H_2O \xrightarrow{k_1'} ROH + OAs(OH)(OR)_2 \cdot x H_2O \quad (5)$$

$$I \xrightarrow{k_1''} ROH + OAs(OH)(OR)_2 \cdot (x-1) H_2O \quad (6)$$

The activation parameters are reported in Table II. It should be noted that for reactions at higher water concentrations, k_{obsd} values were used in the ln (k/T) vs. $1/T$ plots without attempting to factor out the water dependence. The resultant error in the entropies of activation can be shown to be at most 25 J mol^{-1} K^{-1} in the positive direction. Given the large negative values found (from −136 to −167 J mol^{-1} K^{-1}), a correction of this magnitude does not influence interpretation at all. It may be noted that the values of $\Delta H^{\ddagger}$ are small (13 to 29 kJ mol^{-1}), which was also the case for pyroarsenate hydrolysis (49 kJ mol^{-1})[2] and arsenate ester–alcohol exchange (from −3 to 18 kJ mol^{-1}).[4] The entropies of activation are very negative, similar to that found for pyroarsenate hydrolysis (−107 J mol^{-1} K^{-1}) and the range obtained for ester–alcohol exchange (−153 to −226 J mol^{-1} K^{-1}). Further, the values of $\Delta H^{\ddagger}$ monotonically increase with increasing substitution on the carbon atom β to arsenic, undoubtedly due to increasing steric effects; comparable changes were found in the ester–alcohol exchange reactions.[4]

The experimental data are consistent with a highly associative mechanism and probable formation of a five-coordinate arsenic intermediate, $OAs(OR)_3(OH_2)$, where only the first coordination sphere is depicted. A similar mechanism was proposed for the arsenate ester–alcohol exchange reaction.[4]

There is a distinct deuterium isotope effect; when H_2O was replaced by D_2O in the ethyl arsenate hydrolysis in acetonitrile, the ratio $k_H/k_D = 1.86$ was found (see Table I). The exact role of the indicated proton transfer is open to conjecture.

The neutral hydrolysis of phosphate triesters is slow at 100 °C and complicated by C–O bond cleavage in some cases. Although it is not therefore possible to compare quantitatively the hydrolytic behavior of phosphate and arsenate triesters, it is clear that the latter hydrolyze many powers of 10 more rapidly.

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Origin of the Hydrogen–Deuterium Kinetic Isotope Effect for Porphyrin Metalation

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It has been previously observed that the metalation of a porphyrin is slower in D_2O than H_2O. Discussion of this effect has focused on the role of dissociation of the hydrogen or deuterium atoms bound at the coordination site of the porphyrin. The importance of proton dissociation in determining the overall rate of porphyrin metalation is an essential feature of the intimate reaction mechanism. We have monitored the reaction of tetraphenylporphyrin with Zn(II) using protonated and deuterated forms of the porphyrin free base in dimethylformamide. The rates were found to be identical. The addition of either H_2O or D_2O increases the reaction rate, but the effect of H_2O is greater, leading to a k_H/k_D ratio of 2.3 at high [H_2O] and [D_2O]. These results and the previously reported hydrogen–deuterium kinetic isotope effects found in aqueous solution can be explained by a mechanism involving a hydroxo complex of the metal ion. The isotope effect arises from a difference in the concentrations of reactive metal complexes, not from a difference in the reactivities of protonated and deuterated free-base porphyrins.

Introduction

Herein we report results of hydrogen–deuterium kinetic isotope effect experiments for metalloporphyrin formation. The data demonstrate that kinetic isotope effects observed for such reactions are due to changes in the reactive metal ion species rather than reactivity differences of protonated and deuterated free-base porphyrins.

The roles of metalloporphyrins and related complexes in respiration, photosynthesis, and electron-transfer processes have led to an interest in the mechanism of metalloporphyrin formation.[1–3] A prominent feature of proposed metalation

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