Mechanism of Metal Ion Promoted Hydrogen Exchange Reactions. Magnesium(II) and Acetonyl Phosphonate[1a]

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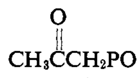
Abstract: Acetonyl phosphonate (**1**), an analog of acetyl phosphate and of acetoacetate, has been prepared and the rate of deuteration of the 2 position determined for a 0.2 *M* solution of substrate from pD 5.0 to 12.1 in the absence of magnesium ion and from pD 5.0 to 10.0 in the presence of 0.2 *M* magnesium ion. All rates were measured at 35 ± 1° by nmr methods. Effects of substrate and metal ion concentration on rates of exchange have been determined, and these data together with the pD–rate profiles have been used to determine apparent rate constants for specific processes. A table summarizing these rate constants is presented. The reaction whose rate is proportional to deuteroxide concentration has an apparent second-order rate constant that is over 2000 times larger in the presence of magnesium ion. Data from spectral studies are presented which indicate that acetonyl phosphonate has a high affinity for magnesium ion, that rate enhancements are not due to specific chelation of magnesium by the enolate ion of the substrate, and that acetonyl phosphonate coordinates as a bidentate (carbonyl–phosphoryl) ligand. Possible mechanisms for the metal-promoted proton exchange reaction are discussed.

Although it has been observed that certain carbonyl compounds in the presence of metal ions have a tendency to exchange α protons with deuterium oxide at a rate somewhat greater than in the absence of metal,[2,3] no attempts to define catalytic species or specific paths for this reaction have been made. The proton exchange reactions in the absence of metals have received thorough study and the catalytic patterns are known.[4] With appropriate additional information, the incorporation of the effects of metal ions into these mechanisms can add considerably to what is known about the role of metals in the catalysis of aqueous reactions.

We have prepared acetonyl phosphonate (**1**), an analog of acetyl phosphate and of acetoacetate, and have examined the effect of magnesium ion on the rate of exchange with deuterium oxide of the hydrogen atoms in the 2 position. Under certain circumstances magnesium ion greatly enhances the rate of that exchange. The situations under which this enhanced exchange occurs fit patterns which can be compared with patterns of metal ion catalysis of other reactions.



$$CH_3\overset{O}{\overset{\|}{C}}CH_2PO_3^{2-}$$

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Experimental Section

All inorganic salts were reagent grade. Magnesium chloride hydrate was converted to the anhydrous form by heating at 100° (25 Torr). Deuterated solvents were purchased from Merck and Co. or Thompson–Packard, Inc. Alkaline titrants were standardized against primary reagent oxalic acid. Water was twice distilled in a Corning all glass still. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Synthesis of Sodium Acetonylphosphonic Acid (1). Dimethylacetonyl phosphonate[5,6] was refluxed with excess sodium iodide in acetone[7] for 24 hr. The monomethyl ester sodium salt of acetonyl phosphonic acid was isolated by filtration, dissolved in a minimum volume of water and converted to a solution of the monomethyl ester of acetonyl phosphonic acid by passage through a column of Dowex 50 (H^+ form) ion-exchange resin. The resulting solution was concentrated *in vacuo*. The residue was dissolved in acetone containing a twofold molar excess of sodium iodide. The solution was refluxed for 72 hr and the precipitated sodium acetonyl phosphonic acid was collected by filtration in 65% yield (based on dimethylacetonyl phosphonate). The material was recrystallized quantitatively from moist acetone; the melting point of the crystals was 164° (dec): ir (KBr) 3450, 1690, 1355, 1180, 1030, and 900 cm^{-1}; nmr (D_2O, internal DSS), δ 2.3 (s, 3, $CH_3C{=}O$), 3.1 (d, 2, J_{P-H} = 22 Hz, $O{=}CC\mathit{H}_2PO_3D$). The assignment of heteronuclear coupling was confirmed by decoupling the doublet with a Micro-Now crystal oscillator at an approximate phosphorus frequency of 40.3 MHz. *Anal.* Calcd for $C_3H_6O_4PNa$: C, 22.52; H, 3.78; P, 19.35; mol wt, 160. Found: C, 22.38; H, 3.58; P, 19.57; mol wt (titration), 159 ± 2.

Kinetic Methods. Samples of acetonyl phosphonate were dissolved in solutions containing salts in deuterium oxide. The solutions were brought to the desired pD.[8] A Radiometer meter, Type PHM 28 with a G2302B low sodium error electrode, was used for these readings. Samples were transferred to Wilmad 506 pp nmr tubes. These were maintained at 35.0 ± 1° when spectra were not being recorded. A Varian A-60 nmr spectrometer (probe temperature 35.0 ± 1.0°) was used to record successive integrations of the doublet at δ 3.1, corresponding to the remaining concentration of hydrogen atoms at the 2 position of acetonyl phosphonate. The δ 2.3 singlet ($C\mathit{H}_3C{=}O$) decreased much more slowly. The pD of each solution was checked after each run. Plots were made of the logarithms of the periodically recorded integrals as a function of time. Pseudo-first-order rate constants were derived from the slopes of these linear plots. Values obtained by this method have an approximate uncertainty of 10%. Second-order rate constants were derived from variation of pD, magnesium ion concentration, and substrate concentration, as discussed in the Results Section.

pK_a' Determinations. Titrations were performed in an apparatus that has previously been described[9] using deuterium oxide as solvent. Potassium chloride (0.2 *M*) was used as an added salt.

Product Analysis. Sodium acetonylphosphonic acid was dissolved in deuterium oxide at pD 5.5 and 8 in the presence and ab-

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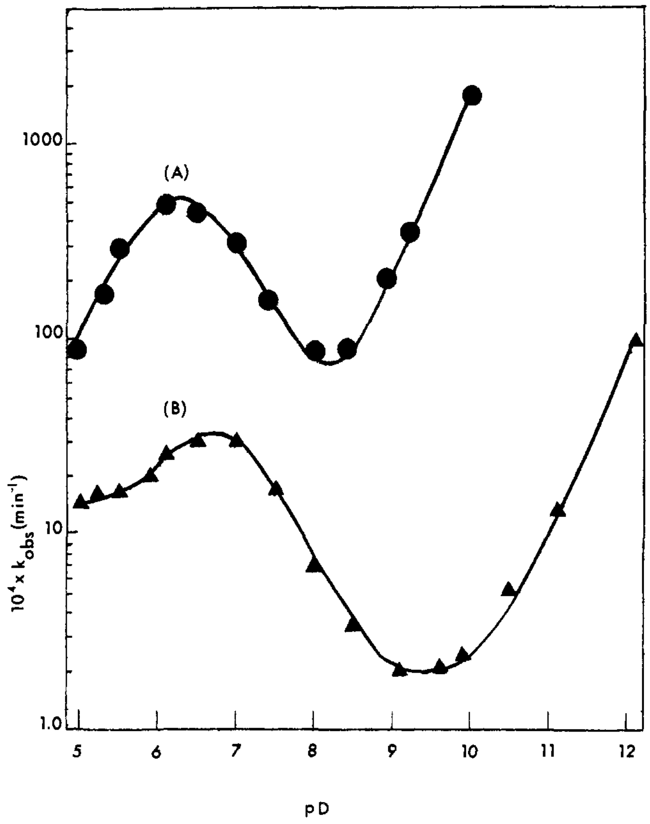

Figure 1. Variation in the observed pseudo-first-order rate constant for deuteration of acetonyl phosphonate (0.2 M) in the 2 position as a function of pD in the presence (A) and absence (B) of equimolar Mg^{2+} at 35 ± 1° in deuterium oxide. The points are experimentally determined. The curves are calculated from the rate constants in Table II.

sence of equimolar magnesium chloride. Solutions stood at 35° for 24 hr and were then evaporated to dryness. The residues were dissolved in water to attain the original volumes, left for 72 hr, and evaporated. Recovery of acetonyl phosphonate was quantitative. Infrared spectra of the twice dissolved and twice evaporated materials were identical with freshly prepared samples, indicating that no structural reorganization or decomposition accompanies the exchange reaction.

Ultraviolet Studies. Sodium acetonyl phosphonic acid was dissolved in water (pH 7, 0.05 M potassium phosphate buffer) and the uv spectrum recorded with a Unicam SP1800A spectrophotometer. Solutions showed the expected n to π^* absorption of carbonyl compounds[10] (in this case $\lambda_{max > 220}$ = 272 nm, ϵ = 90). Addition of magnesium chloride (0.2 M) had no effect on this absorption nor did any new peaks appear. Equilibria of acetonyl phosphonate with magnesium ion were estimated using Burton's method.[11]

Infrared Studies. Infrared spectra of acetonyl phosphonate in deuterium oxide in the presence and absence of magnesium ion were determined in silver chloride cells of 0.05-mm path length (Wilks Mini Cell) with a Beckman IR10 ir spectrophotometer.

Results

Kinetic Data. In order to determine apparent rate constants for the various catalytic processes occurring in this system, data were obtained which relate pseudo-first-order rate constants for the disappearance of integrated nmr absorptions of the hydrogen atoms in the 2 position of acetonyl phosphonate to several experimental variables. Figure 1 contains the experimentally determined pseudo-first-order rate constants observed for α-proton exchange of an 0.2 M solution of substrate as a function of pD in the presence and absence of equimolar magnesium ion. Local rate maxima occur at pD 6.8 in the absence of equimolar magnesium ion and at pD 6.3 in its presence. The dissociation of the deuteron from acetonyl phosphonate monoanion in deuterium oxide has pK's of 6.8 in the absence of magnesium ion and 6.3 in the presence of magnesium ion when titrated under conditions comparable to those under which the rate constants were obtained. This, along with the patterns of catalysis known for other systems,[4,12] suggests that the local rate maxima are probably due to the dianionic form of acetonyl phosphonate acting as a general base toward the monoanionic form. Further data complete the information necessary to begin to understand the variation in k_{obsd} with pD. Figure 2 shows the variation in k_{obsd} for a 0.2 M solution of acetonyl phosphonate at pD 7 as a function of magnesium ion concentration. To obtain the plotted curve in Figure 2, the pD–rate profile (Figure 1) was utilized as well as the data in Figure 2. Finally, determinations of k_{obsd} *vs.* substrate concentration at various pD's were made (Table I) to enable us to extrapolate the data to zero substrate concentration to estimate the contributions of any reaction between substrate and solvent ("water rate"). A summary of apparent second-order rate constants, obtained by empirical fitting to the experimental results and constrained by the complicated set of limits imposed by the various data plots, is given in Table II. The theoretical curves in Figures 1 and 2 were obtained from these rate constants and from the pK of deuterium oxide at 35°.[13]

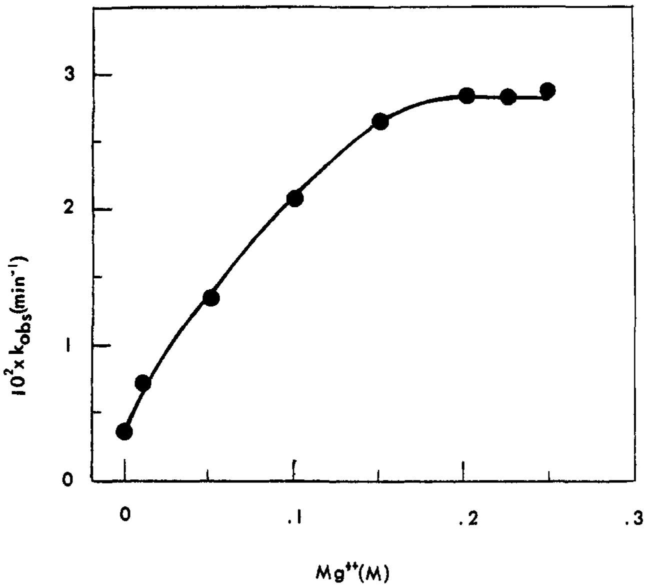

Figure 2. Variation in the observed pseudo-first-order rate constant for deuteration of the 2 position of acetonyl phosphonate (0.2 M) at pD 7, 35 ± 1°, as a function of the concentration of Mg^{2+}. The points are experimentally determined. The curve is calculated from the rate constants in Table II.

Rate measurements at pD 8.8 and 9.1 for the exchange reaction in the presence of excess magnesium ion indicate that the observed rate does not increase (but rather

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Table I. Observed Pseudo-First-Order Rate Constants for Deuteration of the 2 Position of Acetonyl Phosphonate at 35 ± 1° (in Addition to Data Presented in Figures 1 and 2)[a]

pD	[Acetonyl phosphonate], *M*	[$MgCl_2$], *M*	[KCl], *M*	$10^4 k_{obsd}$, min^{-1}
5.2	0.05	0.2		60
5.2	0.1	0.2		91
5.2	0.4	0.4		310
5.2	1.0	1.0		890
8.0	0.1	0.1		38
8.0	0.4	0.4		115
8.0	0.6	0.6		160
5.7	0.1			11
5.7	0.4			32
5.7	1.0			57
9.0	0.1			1.6
9.0	0.4			2.9
9.0	1.0			4.5
5.0	0.2		0.4	15
5.5	0.2		0.4	16
6.1	0.2		0.4	26
8.1	0.2		0.4	5.3

[a] These were used to extrapolate the rate constants for various "water" reactions. In the high pD region, the rates of deuterioxide-catalyzed reactions were subtracted from the extrapolated values. The last four values in the table indicate that enhanced rates on addition of magnesium chloride are not due to chloride ion or ionic strength effects.

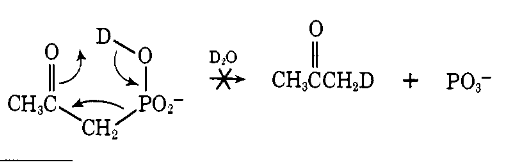
Table II. Apparent Rate Constants for Exchange Reactions of Acetonyl Phosphonate[a]

Species	$k \times 10^4$, min^{-1} M^{-1} [b]	Species	$k \times 10^4$, min^{-1} M^{-1} [b]
$A^- + A^-$	31	$MA^- + MA^-$	42
$A^{2-} + A^{2-}$	1.0	$MA^{2-} + MA^{2-}$	100
$A^- + D_2O$	6.1 min^{-1}	$MA^- + D_2O$	26 min^{-1}
$A^{2-} + D_2O$	1.3 min^{-1}	$MA^{2-} + D_2O$	<5 min^{-1}
$A^- + A^{2-}$	540	$MA^- + MA^{2-}$	10,000
$A^{2-} + OD^-$	30,000	$MA^- + A^{2-}$	21,000
		$MA^{2-} + OD^-$	64×10^6

[a] A^- = monoanion, monoacid of acetonyl phosphonate. A^{2-} = dianion of acetonyl phosphonate. Prefix "M" denotes magnesium complex of these species. [b] Except where noted.

decreases, perhaps due to medium effects resulting from uncoordinated but aquated magnesium ion), confirming that magnesium deuteriohydrate ion is not the catalytic species responsible for the rate component that is proportional to deuteroxide concentration.

Structural Stability of Acetonyl Phosphonate. The structural integrity of acetonyl phosphonate is maintained under the conditions of the exchange reactions (see Experimental Section). No rearrangements occur although the tendency of β-ketophosphonic acid derivatives to undergo Perkov rearrangements[14] is well documented.[15] Further, no decomposition of substrate in solution was observed despite the possibility of its dephosphorylation to yield metaphosphate and acetone (eq 1) in analogy to the decarboxylation of acetoacetic acid[16] and the uncatalyzed hydrolysis of acetyl phosphate.[17]



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Infrared Spectral Changes on Chelation. Bellamy[18] and Nakamoto[19] have summarized observations of infrared absorption frequencies of carbonyl groups and the changes of those frequencies when coordination of substrates to metal ions occurs. In particular, it can be expected that coordination of a keto group to a metal ion will result in a lowering of the stretching absorption energy of the carbonyl group of about 20 cm^{-1}. Similarly, phosphoryl absorption frequencies will be perturbed but since this particular structural feature has more complex absorption characteristics,[18] straightforward conclusions on the perturbation of phosphoryl frequencies are more difficult to draw. The ir absorption of the carbonyl group of acetonyl phosphonate in deuterium oxide occurs at 1690 cm^{-1} and the phosphoryl absorptions are most likely[18] the peaks at 1150 and 1240 cm^{-1}. In the presence of excess magnesium ion, the carbonyl frequency maintains its intensity but is shifted to 1670 cm^{-1} and there is a single intense absorption in the phosphoryl region at 1200 cm^{-1}. The carbonyl shift is similar to what is observed when the *ketonic* form of acetylacetone coordinates to cobalt.[20] There are no characteristic enol absorptions[21] in the 1400–1500-cm^{-1} region in the presence or absence of magnesium ion. We take these results to indicate that bidentate coordination *via* carbonyl and phosphoryl to magnesium does occur.

Effect of Magnesium Ion on Ultraviolet Spectra. Keto–enol equilibria may also be estimated from ultraviolet absorption spectra,[6] since the coordinated enol of acetonyl phosphonate is expected to have a rather intense absorption with a maximum at about 240 nm.[6] Studies on the esters of acetonyl phosphonate reveal no enol content in neutral solution by this test[6] and none is seen in our case (see Experimental Section). Addition of magnesium ion in no way affects the uv spectrum of acetonyl phosphonate at pH 7, although the kinetic and infrared data indicate coordination occurs. Nmr and ir spectra show no evidence for enol being present. Thus, it may be assumed that magnesium does not specifically chelate the enolate of acetonyl phosphonate and exchange is not enhanced by perturbation of the keto–enol equilibrium.

The visible spectrum of magnesium-bound 8-hydroxyquinoline is perturbed by addition of acetonyl phosphonate at pH 8 to an extent that indicates that acetonyl phosphonate's affinity for magnesium ion is such that at equimolar concentrations over 95% of both species are in a complex with one another, according to calculations based on Burton's method.[11]

Discussion

The enhancement of the rate of deuteration of the 2 position of acetonyl phosphonate caused by the addition of equimolar magnesium ion appears to result from complexation of the metal ion by the substrate. From

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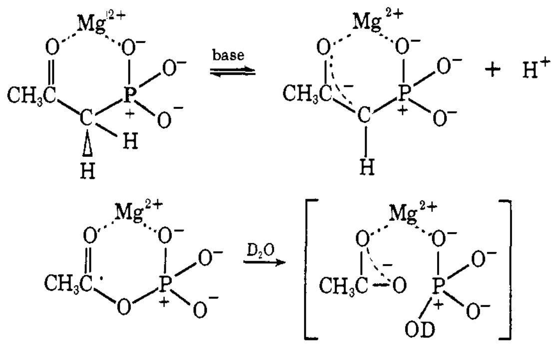
the kinetic data presented in the Results section, it would appear that metal complexation makes acetonyl phosphonate's α protons more readily transferrable to proton acceptors. Complexation also decreases the ability of acetonyl phosphonate to act as a base toward another molecule, consistent with the decrease in the apparent pK_a' of acetonyl phosphonate monoanion in the presence of magnesium ion. The deuteroxide-catalyzed exchange reaction increases over 2000-fold in rate in the complex while the rate constant for the reaction between uncomplexed acetonyl phosphonate dianion and the complexed monoanion is apparently about forty times as great as that for the same species in the absence of magnesium. The various rates correlate well with expected Brønsted β values for exchange reactions.[4] It should be noted, however, that rate constants obtained directly from the pD–rate profile (Figure 1; that is, those for the deuteroxide-catalyzed reactions) are necessarily of greater accuracy than those that result from extrapolations of concentration dependence data and calculations based on apparent dissociation constants.

The effect of magnesium ion on exchange rates can be considered in terms of models proposed for other metal-catalyzed reactions. Bjerrum's structural conditions for effective chelate formation[22] are met by the acetonyl phosphonate–magnesium system and our results support the prediction of chelation. Considering one role of the metal ion to be analogous to that of a proton in specific acid catalysis,[23,24] our system has features in common with the metal ion-catalyzed decarboxylation of oxaloacetic acid,[25] the metal ion-promoted hydrolysis of acetyl phosphate,[26] the metal ion-promoted hydrolysis of ATP,[27] and the copper-catalyzed bromination of ethyl acetoacetate,[28] among others. Formally, hydrogen exchange can provide a role for a metal ion similar to the ones suggested in these cases; that is, the substrate, coordinated to the metal ion as a bidentate ligand, donates electron density in the transition state to the metal ion as negative charge is transferred or shifted. The parallel between the exchange reaction of acetonyl phosphonate and that proposed for the hydrolysis of acetyl phosphate[26] in terms of this particular model is illustrated (reaction 2). Alternative modes of coordination of magnesium ion to the phosphonate may exist in addition and may be of significance for catalysis of the exchange reaction. Several of the more recent proposals discussed for the case of acetyl phosphate's hydrolysis[29] could possibly extend to our case.



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Some other factors that may specifically affect the rate of the exchange reaction in the presence of bound magnesium ion include electrostatic attractions and repulsions between the substrate and anionic base catalysts, and the steric bulk of the coordinated compared to the uncoordinated substrate species. Certainly, neutralization of negative charges on the substrate by the positively charged metal ion will permit acetonyl phosphonate dianion to remove protons from acetonyl phosphonate dianion *via* reaction paths that are lower in free energy than those in the absence of the metal ion, if only electrostatic factors are of import. Solvation of the metal ion[30] should increase the effective steric bulk and apparent hydrophilicity of the substrate, making the ease of approach by catalysts more dependent on the size and hydrophilicity of the catalysts than on the metal's absence. These factors should be able to be sorted out as more examples of substrates, base catalysts, and metal ions are found. The beginnings of such extensions are currently in progress.

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