

METAL ION COMPLEXATION BY THE PHOSPHORYL AND THE CARBONYL GROUPS PROBED BY ^{17}O NMR SPECTROSCOPY

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Interactions between compounds containing phosphoryl, carbonyl, or hydroxyl groups (or combinations of these groups) with metal ions (Na^+ , Mg^{2+}) were probed in CD_3CN solutions by ^{17}O NMR spectroscopy. For all phosphoryl and carbonyl substrates a strong high-field shift of the $\text{P}=\text{O}$ and $\text{C}=\text{O}$ signals was observed on the addition of a salt; no shift was observed, however, for the OH group signal, indicating that no chelation takes place in the hydroxyphosphoryl (or hydroxycarbonyl) derivatives. For 2-hydroxy-3-benzoylpropylphosphonic diester the ^{17}O NMR studies, together with conformational analysis based on the ^1H spectroscopy, demonstrated the chelation of a metal ion by the $\text{P}=\text{O}$ and $\text{C}=\text{O}$ functions (formation of an eight-membered cyclic structure) with the OH group involved in the intramolecular hydrogen bonding, but not in the complexation to the metal ion.

1. INTRODUCTION

In previous papers we reported solvent and metal ion effects on the conformational preferences for esters of β,γ -disubstituted propylphosphonic acids, $\text{YCH}_2\text{CHXCH}_2\text{PO}_3\text{R}_2$ (**1**), as probed by ^1H (Ref. 1) and ^{13}C (Ref. 2) NMR spectroscopy. The main conclusion was that the conformational preferences for the rotation about the $\text{C}_1\text{—C}_2$ bond are determined by attractive interactions (hydrogen bonding and/or $n(p)\rightarrow d$ electron donation) between the oxygen-containing substituents ($\text{X}=\text{OH}, \text{OMe}$) and the phosphoryl group (Figure 1), and that the effect is enhanced by metal ions, presumably *via* chelation. One of the substrates of particular interest was dimethyl 2-hydroxy-3-benzoylpropylphosphonate (**1a**; $\text{R}=\text{Me}$, $\text{X}=\text{OH}$, $\text{Y}=\text{PhCO}$), a system in which three oxygen centres (phosphoryl, hydroxyl and carbonyl) are present in a 1,3,5-arrangement at a five-atom backbone ($\text{P—C}_1\text{—C}_2\text{—C}_3\text{—C}_{\text{carbonyl}}$) of the molecule. ^1H NMR spectroscopy indicated that for **1a** the addition of metal

ions ($\text{Na}^+, \text{Mg}^{2+}$) increased the population of the conformer X_1 , hence suggested the chelation effect of the $\text{O}=\text{P}_1\text{—C}_2\text{—C—OH}$ system.^{2b} At the same time, the results pointed to the participation of another type of complex, an eight-membered chelate involving the carbonyl and the phosphoryl oxygens as the binding sites. However, those two conclusions are somehow contradictory, as the conformation X_1 cannot accommodate an eight-membered cyclic structure involving the PO_3R_2 and CH_2Y groups as the elements of the ring.

In view of those ambiguities and problems of the relative contributions of phosphoryl, carbonyl and hydroxyl oxygens in the complexation of metal ions,

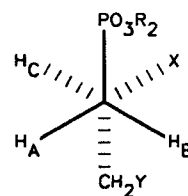


Figure 1. Preferred conformation of **1** in solution

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we decided to study the effect of metal ions on the ^{17}O NMR spectra of some hydroxyalkylphosphonates (including **1a**) and related carbonyl derivatives. Lanthanide-induced shifts in the ^{17}O NMR spectra have proved very successful in identifying the binding centres in hydroxypyranoses³ and 2-sulphonylcyclohexanols.⁴ Both the line broadening effect and the upfield chemical shift effect of metal ions on the ^{17}O NMR signals of phosphate groups in nucleotides are specific to binding sites.⁵

RESULTS AND DISCUSSION

Two carbonyl (**2a** and **b**) compounds, three phosphoryl (**3a**, **3b** and **1b**) compounds and the trifunctional

compound **1a** were selected as substrates (Figure 2), and the effect of sodium and magnesium ions on their ^{17}O NMR spectra was determined in acetonitrile. The observed chemical shifts are given in Table 1. Since hydrogen bonding makes a strong contribution to ^{17}O NMR chemical shifts,⁶ IR spectra of some of the substrates were recorded (Table 2) in order to evaluate the importance of the intramolecular hydrogen bonding in substrates containing the hydroxyl group. Table 1 shows that in each case both low-field signals (carbonyl and phosphoryl) undergo significant upfield shifts on addition of a metal ion, whereas the high-field signals of the sp^3 oxygens (OH, OR) are little affected by the addition. Since upfield shifts of *ca* -9 ppm of the ^{17}O NMR chemical shifts have been reported for crown

Table 1. Effects of metal ions on the ^{17}O NMR spectra of phosphoryl and carbonyl substrates in CD_3CN ; $[\text{S}] = 0.37 \text{ M}$

Substrate	Metal ion (mol equiv.)	$\delta_{\text{P=O}}$	$\Delta\delta_{\text{P=O}}$	$\delta_{\text{C=O}}$	$\Delta\delta_{\text{C=O}}$	$\delta_{\text{OH/OR}}$	$\Delta\delta_{\text{OH/OR}}^a$
2a	None			552.9			
	Na^+ , 0.5			550.0	-2.9		
	Na^+ , 1.0			547.2	-5.7		
	Mg^{2+} , 0.5			544.3	-8.6		
2b	None			566.9		57.2	
	Na^+ , 0.1			566.5	-0.4	56.2	-1.0
	Na^+ , 0.3			564.9	-2.0	56.6	-0.6
	Na^+ , 0.6			562.8	-4.1	56.1	-1.1
	Na^+ , 1.0			560.7	-6.2	55.4	-1.8
3a	None	104.4					
	Na^+ , 0.3	99.6	-4.8				
	Na^+ , 0.6	96.8	-7.6				
	Na^+ , 1.2	93.9	-10.5				
	Mg^{2+} , 0.5	86.8	-17.6				
3b	None	91.1				64.9	
	Na^+ , 0.1	89.9	-1.2			64.3	-0.6
	Na^+ , 0.2	89.0	-2.1			64.8	-0.1
	Na^+ , 0.3	88.2	-2.9			64.4	-0.5
	Na^+ , 0.5	86.4	-4.7			64.5	-0.4
	Na^+ , 1.0	83.9	-7.2			64.1	-0.8
1b	None	102.8				39.4	
	Na^+ , 0.1	100.6	-2.2			39.3	-0.1
	Na^+ , 0.6	95.4	-7.4			39.8	+0.4
	Na^+ , 1.2	93.3	-9.5			38.4	-1.0
	Mg^{2+} , 1.0	84.7	-18.1			39.0	-0.4
1a	None ^b	99.6		543.3		35.4	
	Na^+ , 0.1	97.3	-2.3	537.6	-5.7	35.7	+0.3
	Na^+ , 0.2 ^c	95.7	-3.9	519.3	-24.0	34.8	-0.6
	Na^+ , 0.3	94.9	-4.7	518.3	-25.0	33.9	-1.5
	Na^+ , 0.5	92.1	-7.5	— ^d		35.0	-0.4
	Na^+ , 1.0	88.7	-10.9	— ^d		33.9	-1.5
	Na^+ , 1.2	87.2	-12.4	— ^d		34.0	-1.6
	Mg^{2+} , 0.1	92.3	-7.3	536.1	-7.2	33.9	-1.5
	Mg^{2+} , 0.3	83.9	-15.7	— ^d		34.3	-1.1

^a In most cases signals of the OR and OH groups overlapped.

^b Line width at half-height ($\Delta\delta$): $\Delta\delta_{\text{P=O}} = 108 \text{ Hz}$; $\Delta\delta_{\text{C=O}} = 434 \text{ Hz}$;

^c $\Delta\delta_{\text{P=O}} = 108 \text{ Hz}$; $\Delta\delta_{\text{C=O}} = 551 \text{ Hz}$.

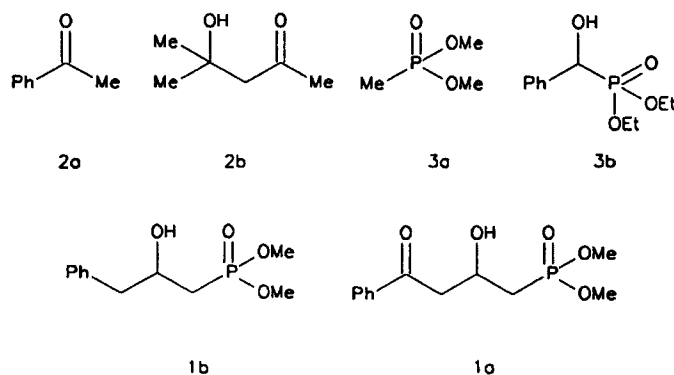
^d Further broadening of the signal prevented determination of the $\delta_{\text{C=O}}$ value.

Table 2. IR stretching frequencies (cm^{-1}) for the X=O groups (X = C, P) in selected substrates; [S] = 0.037 M^a

Substrate	$\nu_{\text{C=O}}$	$\nu_{\text{P=O}}$
Acetone	(CCl_4)	1718.2
	(MeCN)	1712.8
	(MeCN/ Na^+) ^b	1712.7
2b	(CCl_4)	1709.3
	(MeCN)	1703.7
	(MeCN/ Na^+) ^b	1703.7
2a	(CCl_4)	1683.0
	(MeCN)	1682.9
3a	(CCl_4)	1252.3
	(MeCN)	1248.3
	(MeCN/ Na^+) ^b	1247.7
1b	(CCl_4)	1237.9
	(MeCN)	1242.8
	(MeCN/ Na^+) ^b	1245.1
1a	(CCl_4)	1682.5
	(MeCN)	1683.6
	(MeCN/ Na^+) ^b	1682.7
	(MeCN/ Na^+) ^b	1245.6

^aNo change in $\nu_{\text{X=O}}$ was observed on further dilution.

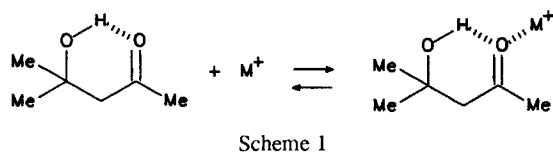
^bIn the presence of 1 mol equiv. of NaBPh_4 .

Figure 2. Substrates used for ^{17}O NMR studies

ethers complexed with alkali metal ions,⁷ we conclude that the negligible shifts observed for the OH groups in our substrates are evidence against any chelating effects by the 2-hydroxy group in the alkylphosphonic or keto systems. The effect of the Mg^{2+} ion is always much greater than that of the Na^+ ion; the same order was observed for the upfield shift in the ^{17}O NMR spectrum of DMF, where the shifts for Na^+ and Mg^{2+} had values of $\Delta\delta_{\text{C=O}} = -4.3$ and -12.6 ppm, respectively.⁸

Comparison of the IR spectra of acetone and **2b** (Table 2) shows the presence of intramolecular hydrogen bonding, both in CCl_4 and in MeCN ($\Delta\nu_{\text{C=O}} = -8.9$ and 9.1 cm^{-1} , respectively). The addition of Na^+ ions had no effect on the stretching frequency of the carbonyl group. On the other hand, comparison of the ^{17}O

NMR spectra of **2a** and **2b** (Table 1) demonstrates approximately the same upfield shift for the C=O group in both substrates, and a negligible shift for the OH group in **2b**. It can be concluded, therefore, that the complexation of a metal ion involves the carbonyl, but not the hydroxyl, group and that the complex of **2b** can be represented by a structure given in Scheme 1. Similar conclusions can be reached by examining the IR spectra of **1b** and **3a**, and the ^{17}O NMR spectra of **3a**, **3b** and **1b**. Although the low-frequency IR shift of the phosphoryl band for **1b** relative to **3a** is more pronounced in CCl_4 ($\Delta\nu_{\text{P=O}} = -14.4$ cm^{-1}) than in MeCN ($\Delta\nu_{\text{P=O}} = -5.5$ cm^{-1}), it can be concluded that **1b** exists in the latter medium, at least partially, also as an intramolecularly hydrogen-bonded species. As was



observed for the ketones, addition of the Na^+ ions had very weak effect on the $\nu_{\text{P=O}}$ values. As far as the ^{17}O NMR spectra of **3a**, **3b**, and **1b** are concerned, the respective values of $\Delta\delta_{\text{P=O}}$ resulting from the addition of 1 mol equiv. of Na^+ are -10.5 , 7.2 and -9.5 ppm, respectively (Table 1). Similarity of the $\Delta\delta_{\text{P=O}}$ shift, irrespective of the presence or the location of the hydroxyl group, does not support the hypothesis of a chelation effect. The proposed interactions of those two simple hydroxyalkylphosphonates with metal ions are presented in Scheme 2.

The results obtained for **1a** were most interesting and informative. IR spectroscopy clearly showed that it is the phosphoryl group (relative to **3a**, $\Delta\nu_{\text{P=O}} = -36.6 \text{ cm}^{-1}$ in CCl_4 and -4.6 cm^{-1} in MeCN) that is involved in the intramolecular hydrogen bonding (possibly broken to a certain extent in MeCN), leaving the carbonyl group free (relative to **2a**, $\Delta\nu_{\text{C=O}} < 1 \text{ cm}^{-1}$). This result in itself provides useful information about the relative hydrogen bonding acceptor abilities of these two important functional groups. The effect of metal ions on the ^{17}O NMR spectrum of **1a** is very distinctive: a strong high-field shift for the P=O signal (very similar to that observed for **3a**, **3b** and **1b**), negligible shift observed for the OH/OME signals and a large high-field shift for the carbonyl signal (at molar equivalents of Na^+ or Mg^{2+} ions greater than *ca* 0.3, the broadening of the C=O signal prevented determination of the $\delta_{\text{C=O}}$ value). The conclusions from these results are clear. Whereas the intramolecular hydrogen bonding involves oxygens of the 1,5-arrangement of the phosphoryl and the 2-hydroxyl group, the metal ion is chelated by the phosphoryl and the carbonyl group, giving rise to the previously suggested^{2b} eight-membered cyclic structure. The most stable conformation of a saturated eight-membered ring is that of the boat-chair (BC).⁹ A Dreiding model of an eight-membered cyclic structure consisting of **1a** and a tetracoordinated Na^+ ion (or a *cis*-bonded hexa-coordinated Mg^{2+} ion) incorporated between the P=O and the C=O oxygens was therefore constructed and made to adopt the BC conformation. The model thus prepared (Figure 3) revealed some

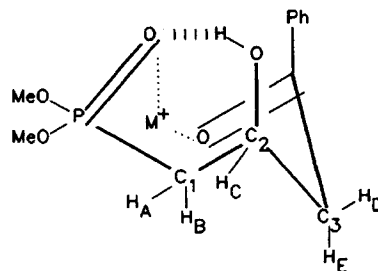
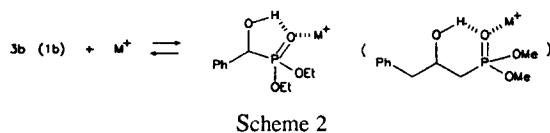


Figure 3. Proposed structure of the metal ion complex of **1a**

interesting features that remain in full agreement with the experimental results. First, the distance between the oxygen atoms of the P=O and the OH groups is of the order of 2.5 \AA , within the usual range (2.4 – 2.8 \AA) observed for the $\text{O}\cdots\text{O}$ distance in the hydrogen bonded $\text{P=O}\cdots\text{H}-\text{O}-\text{C}$ system.¹⁰ In other words, the intramolecular hydrogen bonding indicated by IR spectroscopy can be preserved in an eight-membered chelate structure. It was even more satisfying, however, to find in the model that the trigonal geometry of one atom in the ring (carbonyl carbon) resulted in some distortion of the BC conformation, in which the bonds at carbon C_2 (CHOH) are forced into an almost eclipsed relationship with respect to the bonds at C_1 . In consequence, the torsion angles $\text{H}_A-\text{C}_1-\text{C}_2-\text{H}_C$ and $\text{H}_B-\text{C}_1-\text{C}_2-\text{H}_C$ approach the values of 0° and 120° rather than the values of 60° and 180° postulated in the previous discussion.^{2b} According to the Karplus equation, the calculated values of the proton–proton vicinal coupling constants for the torsion angles of 0° and 120° are 8.2 and 2.1 Hz , respectively, whereas for the *anti/gauche* ($180^\circ/60^\circ$) relationship the respective values are 9.2 and 1.8 Hz . Since the experimental values of J_{AC} and J_{BC} observed for **1a** on addition of Na^+ or Mg^{2+} ions are 8.4 and 4.4 Hz ,^{2b} it is not possible to distinguish between the X_1 (Figure 1) and the eclipsed (X_1 after the counter-clockwise rotation of group X by 60°) conformations of **1a** on the basis of the vicinal coupling constants involving hydrogens H_A , H_B , H_C . In addition, an equilibrium between the complex and the metal ion-free substrate, or some flexibility of the cyclic complex itself, can be responsible for the observed deviation of the ^1H NMR vicinal coupling constants from the ideal values expected for a particular conformation. ^{17}O NMR spectroscopy, on the other hand, offers a much more specific and selective approach for monitoring any electronic changes that occur at the potential binding sites when metal ions are added to a system. The metal ion–organic substrate interactions discussed above are too weak to be detected by IR spectroscopy (negligible changes of $\nu_{\text{C=O}}$ on addition of Na^+). They are, however, strong enough to be conveniently monitored by ^{17}O NMR spectroscopy.

EXPERIMENTAL

General. ^1H NMR spectra were recorded in CD_3CN on a Bruker AC300 NMR spectrometer at a probe temperature 30°C . Acetonitrile- d_3 (Aldrich, 99.5 atom% D) was dried over molecular sieves. Sodium tetraphenylborate (Aldrich, min 99.5%) and magnesium perchlorate (Aldrich) were dried in an oven at 150°C and stored in a desiccator over P_4O_{10} immediately before use. Preparations of the solutions containing the salts were carried out in dry atmosphere in a glove-box. IR spectra were recorded on a Bomem Michelson 100FT spectrometer as solutions in tetrachloromethane or in acetonitrile (both from Merck, spectroscopic grade). Acetophenone (**2a**) (Merck) was distilled immediately before use.

Compounds. 4-Methyl-4-hydroxypentan-2-one (**2b**) was prepared from acetone;¹¹ b.p. $78\text{--}80^\circ\text{C}/13$ Torr.

Dimethyl methylphosphonate (**3a**) was prepared from trimethyl phosphite as described in the literature;¹² b.p. $66\text{--}68^\circ\text{C}/14$ Torr.

Diethyl hydroxyphenylmethylphosphonate (**3b**) was prepared by the Abramov reaction from diethyl phosphite and benzaldehyde;¹³ yield 94%; m.p. $64\text{--}65^\circ\text{C}$ (from benzene-light petroleum). ^1H NMR (CDCl_3), δ 1.23 (t, 2H, $J = 5.2$ Hz), 4.04 (quint, 4H, $J = 5.2$ Hz), 5.00 (d, 1H, $J = 10.4$ Hz), 7.44 (m, 5H); m/z 244 (M^+); Anal., calculated for $\text{C}_{11}\text{H}_{17}\text{O}_4\text{P}$, C 54.1 H 7.0; found, C 53.7 H 7.0%.

Dimethyl 2-hydroxy-3-phenylpropylphosphonate (**1b**)¹⁴ and Dimethyl 2-hydroxy-3-benzoylpropylphosphonate (**1a**)¹⁴ were prepared as described previously.

^{17}O NMR spectroscopy. The 67.8 MHz ^{17}O NMR spectra were recorded on a Bruker AMX-R500 NMR spectrometer equipped with a 10 mm broadband probe. Spectra were acquired at natural abundance at probe temperature of 60°C . A 9:1 mixture of CH_3CN and CD_3CN was used as solvent with the deuterated solvent used as lock signal. The signals were referenced to external deionized water. The instrumental settings were spectral width 819.4 ppm, 90° pulse width of 29 μs , acquisition delay 190 μs , acquisition time 0.018 s, and 4000–60000 scans. The spectra were recorded with no sample spinning, with lock and no

broadband proton decoupling. The signal-to-noise ratio was improved by applying a 40 Hz exponential line broadening factor to the FID prior to Fourier transformation. The reproducibility of the chemical shifts data is estimated to be ± 1.00 ppm.

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