Nuclear Magnetic Resonance Studies of 4-Hydroxypiperidinomethylphosphonic Acid and its Polyoxomolybdate Conjugates†

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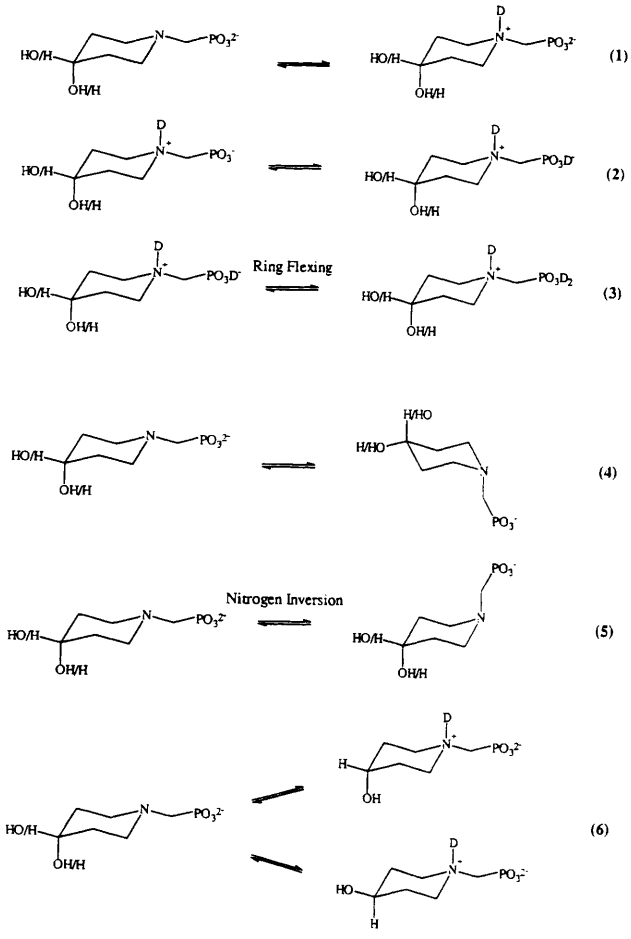
The pD behaviour of 4-hydroxypiperidinomethylphosphonic acid has been investigated using multinuclear NMR (^{1}H, ^{13}C and ^{31}P) techniques in D_2O solvent. On deuteriation, ^{1}H, ^{13}C and ^{31}P signals for two deuteriated isomers were observed, with the 4-hydroxy group occupying either an axial or equatorial position. The interaction of this compound with molybdate anion as the pH and temperature of the solution were varied was investigated using ^{31}P NMR spectroscopy. The spectra revealed the formation of several phosphonomolybdate conjugates, one of which can be assigned as the pentamolybdodiphosphonate. Isomerism of the conjugate was also evident. Conversions between several phosphorus-containing entities occurred at rates detectable on the ^{31}P NMR time-scale, providing evidence as to the exchange routes.

Many recent investigations[1–5] have focused on the NMR spectra of aminomethylphosphonic acids in aqueous solution, especially the study of macrocycles where the phosphonic acid is pendant. For the simplest compounds there are three conventional Brønsted equilibria in aqueous solutions exemplified in Scheme 1 as equations (1)–(3); those for compound **1** have already been discussed in the literature.[5] The pK_a values of the three equilibria range from typical amine[6] values (*ca.* 10–8) to typical phosphonate ones[7] (6–0). These equilibria may overlap slightly in the pD ranges in which they occur. Each atom type N, C, H, P, O presents at least one magnetic isotope for investigation, ^{1}H, ^{13}C and ^{31}P being the usual choice for NMR work. Sudmeier and Reilley[8] attempted a quantitative description of NMR shifts assuming additivity of effects.

The acid considered in this paper is that, **2**, derived from 4-hydroxypiperidine. For acid **2** the six-membered ring is fluxional [equation (4)] with interconversion of equatorial and axial positions in the chair form, the steric preference of the aminomethylphosphonate group being equatorial. Additionally there is inversion at the nitrogen atom at the junction of the ring with this group, equation (5). These equilibria further complicate the spectral changes, especially when they overlap with those in equation (1)–(3), with consequences for the NMR shielding from the additional conformations possible. There is also a hydroxyl ring substituent in **2**, which may be axial or equatorial [equation (6)]. From a detailed study of the ^{1}H, ^{13}C and ^{31}P NMR spectra over the range pD 1–14, the equilibria (1)–(6), and the additional features just described, may be understood in systems containing **2**.

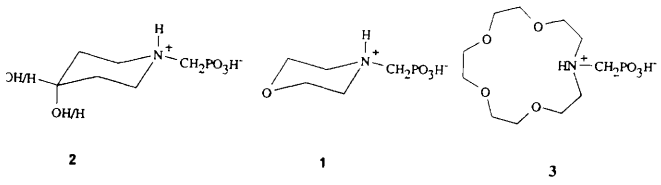
The interaction of phosphonic acids with molybdate anions in aqueous solutions is well established.[9–12] However the interaction with aminomethylphosphonic acids (which can be readily synthesised[13] from simple amine-bearing molecules) has only recently been reported[14] for small heterocyclic and macrocyclic compounds (*e.g.* **3**) bearing such groups. The pentamolybdodiphosphonato cage can be readily self-assembled from simple molybdate and phosphonate precursors. The interaction between the two initial reactants can be investigated



Scheme 1 Solution equilibria for aminomethylphosphonic acids

in solution by ^{31}P NMR spectroscopy. The use of 4-hydroxypiperidinomethylphosphonic acid **2** has enabled the course of formation of the pentamolybdo conjugates to be examined in more detail. Two features of this molecule are relevant here. First it exists in isomeric forms present in a defined ratio, and secondly the solubility of its conjugates

† *Supplementary data available* (No. SUP 57 100, 7 pp.): variation of ^{13}C NMR spectrum and δ_C with pD for compound **2**. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1995, Issue 1, pp. xxv–xxx.
Non-SI unit employed: cal = 4.184 J.



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exceeds that of analogues previously studied,[14] such that, even at pH as low as 2, and temperatures of 0 °C the molybdo conjugates do not precipitate. Thus it has proved possible to probe the nature of the conjugates formed, as to their dynamic nature and other features.

Results and Discussion

^{1}H NMR Spectra of Compound **2**.—The isomerisation of acid **2** is highlighted extremely well by the ^{1}H NMR spectra pertaining to its titration. The complex set of spectra can be readily interpreted with the knowledge that two isomeric species exist in solution and with the aid of the NUMARIT NMR simulation package.[15] Fig. 1 shows the proton labelling used for each isomer along with a Newman projection looking down the C–C bond from the carbon bearing the hydroxyl group. The ^{1}H NMR spectra are shown in Fig. 2. At high pD values (14–9) the spectra of the species in solution are relatively similar in terms of coupling patterns, the only difference being one of chemical shift. However on passing from this region to lower pD a dramatic change in the nature of the signals takes place, which can be explained in terms of successive deuteriation of the species.

At high pD values the nitrogen is undeuteriated which results in a fluxional, conformationally mobile state (Scheme 2). Rapid conformational changes occur *via* nitrogen inversion and ring flipping as shown in Scheme 1 [equations (4) and (5)]. The four possible chair conformers shown interchange so fast that an average signal is seen for the protons. The NMR spectrum (Fig. 2) consists of six sets of signals, corresponding to the methylphosphonic protons (H_A), axial and equatorial protons ($H_{B/B'}$ and $H_{C/C'}$) and the proton next to the hydroxyl group (H_D).

As the pD is lowered there is a broadening of the signals, prior to their splitting into two sets, and finally a sharply resolved spectrum consisting of double the number of signals found at high pD. If deuteriation occurs when the compound exists in conformer **A** or **B** then two deuteriated species **A′** and **B′** are formed (Scheme 3). However these are interchangeable *via* ring flipping, with the equilibrium lying to the left where the hydroxyl group lies axial and the methylphosphonic acid group equatorial. The equatorial position for the methylphosphonic acid group is expected for steric reasons, and is observed in the solid-state structures of small-ring aminomethyl-phosphonic[16] and phosphinic[17] acids. If deuteriation occurs when the equilibrium position lies at **C** or **D** again two interchangeable deuteriated species C′ and D′ are formed. Here D′ is expected to be the favoured conformation, by the same argument, *i.e.* the methylphosphonic acid group lies equatorial but this time the hydroxyl group also lies equatorially.

Once the nitrogen is fully deuteriated (2–3 pD units below the p*K*) the two sets of isomers are not interconvertible. Before deuteriation the two isomers **A** and **B** could be converted into **C** and **D** respectively by the process of nitrogen inversion. However, this is no longer possible due to the deuteron attached to the nitrogen. Since nitrogen inversion is prevented, the route to interconversion of the two isomers is blocked and only ring flipping is possible, leading predominantly to the conformer with the methylphosphonic acid group equatorial. In the slow exchange at low pD values, signals for the **A′** and **D′** isomers (Scheme 3) are clearly visible in the NMR spectra (Fig. 2).

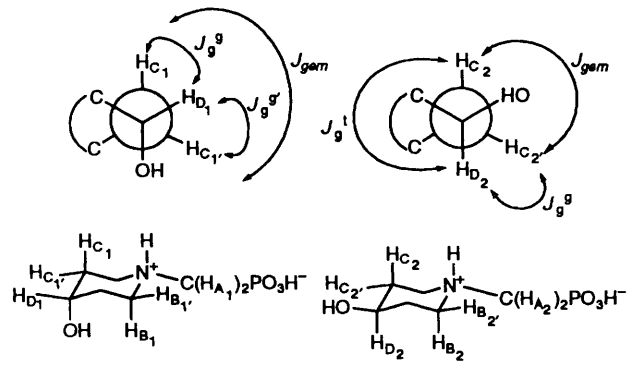


Fig. 1 Labelling and Newman projection of the two isomers of compound **2**

The signal for methylphosphonic protons labelled H_A is a characteristic sharp doublet due to coupling to the phosphorus at high pD. As the nitrogen becomes deuteriated it causes a deshielding effect on the protons and hence a large downfield shift of 0.55 ppm. On deuteriation of one of the phosphonate oxygens the doublet undergoes another smaller downfield shift of 0.25 ppm due to the removal of the shielding effect caused by the PO^- group. At this point the signal broadens as the compound begins to form two isomers, for which two sharp doublets are resolved at pD 2.46. A plot of pD *vs.* δ_H is shown in Fig. 3.

At high pD the ring protons closest to the nitrogen ($H_{B/B'}$) show an AB part of an $(ABCD)_2$ type coupling pattern in the ^{1}H NMR spectrum which consists of two sets of peaks for the axial and equatorial protons. The broad quasi-doublet signal has been assigned to the equatorial protons, and the quasi-triplet signal to the axial protons. A large downfield shift again occurs on deuteriation of the nitrogen ($\Delta\delta_B = 0.9$, $\Delta\delta_{B'} = 0.6$ ppm) followed by a smaller downfield shift as the phosphonate oxygen is deuteriated. Accurate shifts are not obtained for the second change, since the relatively well defined spectra observed at high pD collapse to extremely broad peaks at these intermediate pD values (Fig. 2), and then two groups of signals corresponding to the two isomeric species in solution emerge as sharp and well defined signals at low pD.

The signals for ring protons $H_{C/C'}$ behave similarly. The coupling pattern is however different due to coupling to the proton H_D as well as $H_{B/B'}$. The $H_{C/C'}$ protons exhibit the CD part of an $(ABCD)_2E$ type spectrum. Again they occur in two groups, one corresponding to the equatorial protons (a quasi-doublet signal) and the other to the axial ones (a quasi-quartet signal). At low pD the coupling pattern is not as well defined as for $H_{B/B'}$ where four sets of signals were seen (two for each isomer). The pattern observed at high pD is preserved but the expected identical, shifted version of this (as for $H_{B/B'}$) is not observed. Instead a complex signal was found in the centre of the equatorial and axial signals observed at high pD. This can be explained by considering a Newman projection (Fig. 1). For protons $H_{B_1/B_1'}$ and $H_{B_2/B_2'}$ different chemical shifts are expected from the different isomers, but the Newman projection shows that the same coupling pattern will be preserved as these protons couple only to the protons $H_{C_1/C_1'}$ and $H_{C_2/C_2'}$ respectively. However in the case of the protons $H_{C_1/C_1'}$ and $H_{C_2/C_2'}$ coupling to H_{D_1} and H_{D_2} respectively has to be considered. In the case where the hydroxyl group occupies an axial position the proton H_{D_1} lies between the H_{C_1} and $H_{C_1'}$ protons, giving $J_g{}^g$ and $J_g{}^{g'}$ couplings respectively. Both of these *gauche–gauche* type couplings are expected to be relatively small as predicted by the Abraham–Gatti method,[18] about 2–4 Hz. In the case where the hydroxyl group lies equatorially the couplings to H_{C_2} and $H_{C_2'}$ will be $J_g{}^t$ and $J_g{}^g$ respectively. In this case the calculated value of $J_g{}^t$ will be quite

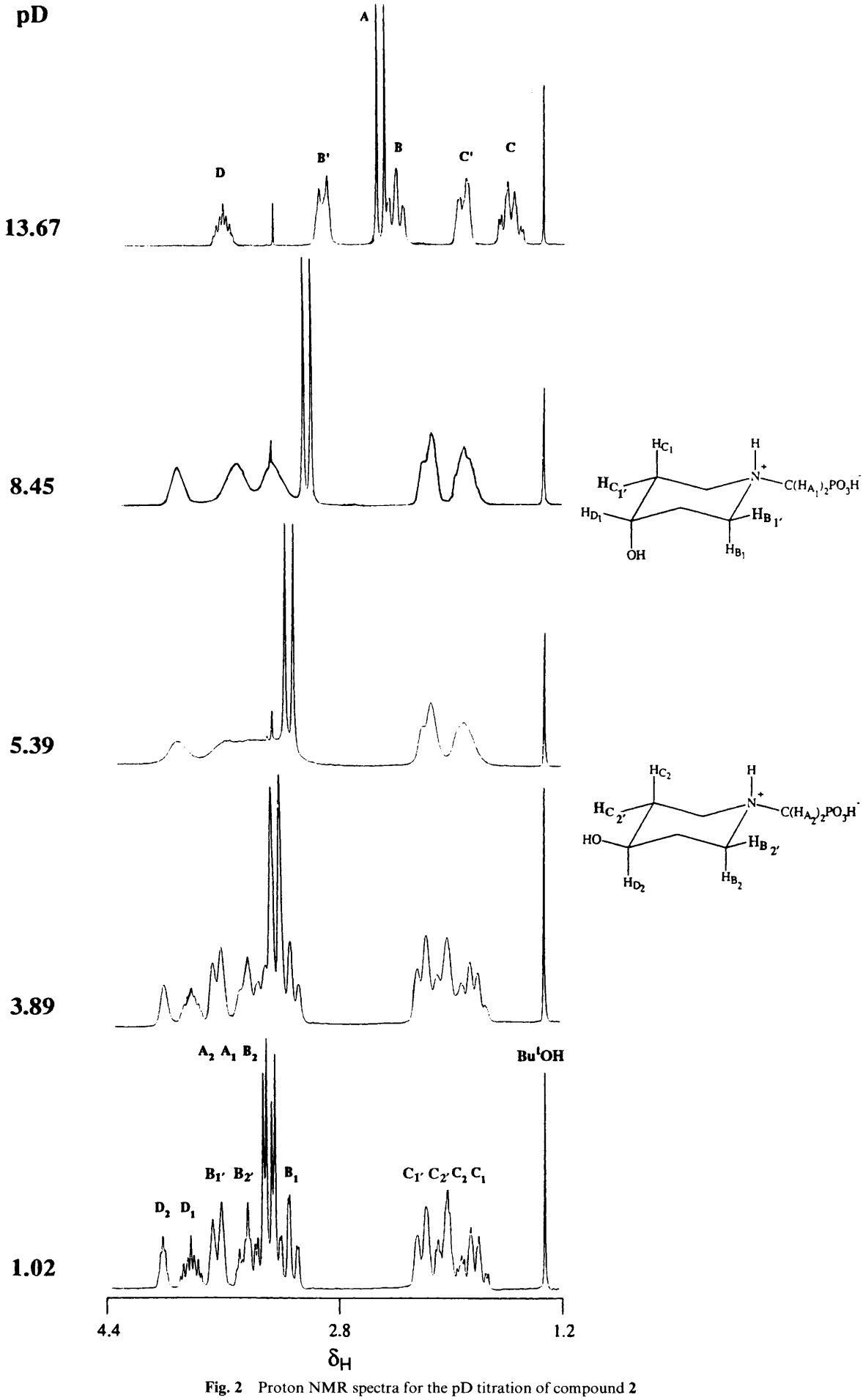
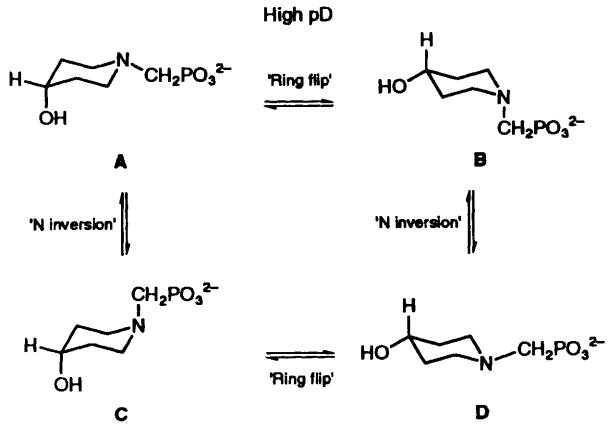
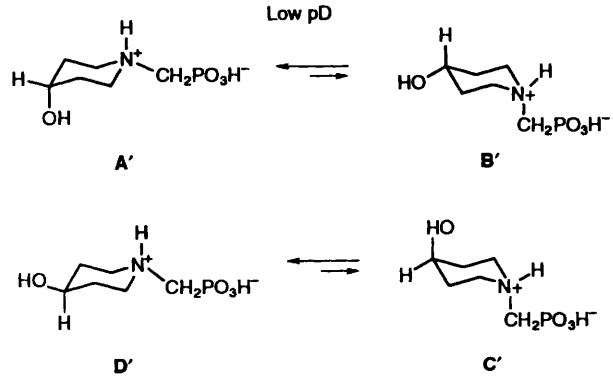


Fig. 2 Proton NMR spectra for the pD titration of compound **2**



Scheme 2 Conformational changes of compound **2** at high pD



Scheme 3 Conformational changes of compound **2** at low pD

large, ≈12–16 Hz, with J_g[8] again 2–4 Hz. Clearly these are two vastly different coupling patterns which will result in a very different spectrum for the $H_{C_2/C_{2'}}$ protons. Therefore the isomer with the hydroxyl group axial will still show axial and equatorial signals for the $H_{C_1/C_{1'}}$ protons, but where the hydroxyl group lies equatorially ($H_{C_2/C_{2'}}$) a different coupling pattern will be observed. In this case a complex pattern is seen but in a single area, *i.e.* not separated into two distinct signals.

This last argument is highlighted much more clearly for the remaining proton H_D which is on the same carbon as the hydroxyl group. This exhibits the E part of the $(ABCD)_2E$ type coupling pattern. In this case at low pD two signals are observed, one for each isomer. One consists of a wide seven-line symmetrical multiplet which is well resolved. The other is a narrower more blurred multiplet, the shoulders of which suggest five lines. Although the spectra were not sufficiently resolved for NUMARIT to be used to obtain accurate coupling constants, NUMARIT simulations for both axial and equatorial isomers suggest the better resolved multiplet belongs to the isomer where the hydroxyl group lies axially, *i.e.* H_{D_1}. It is this coupling pattern which is also observed at high pD values.

The ratio of isomers in solution can be easily gauged by integration of the proton signals: the H_{D_1} and H_{D_2} proton signals were used. Based on assignments from NUMARIT simulations, the ratio of the isomers with axial hydroxyl : equatorial hydroxyl was found to be *ca.* 3:2, *i.e.* the axial hydroxyl is the preferred conformation.

^{13}C NMR Spectra of Compound **2**.—The ^{13}C NMR spectra as for the ^{1}H clearly show isomerisation of the species in solution, highlighted by a dramatic broadening of the signals. The spectra and details of the assignment are deposited as SUP 57 100.

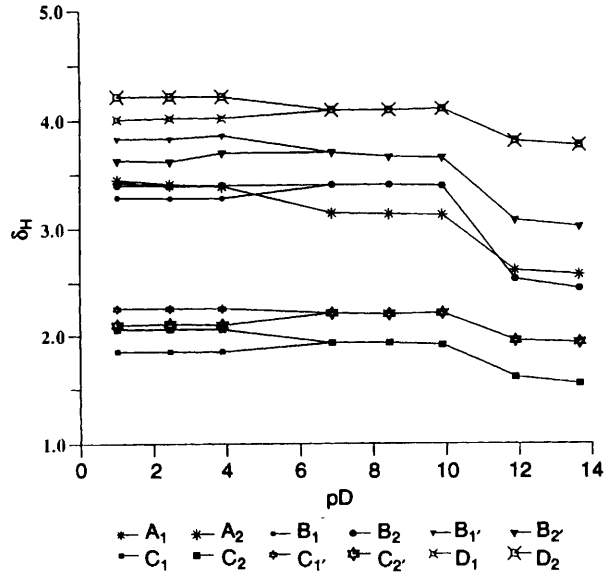


Fig. 3 Plot of pD *vs.* δ_H for compound **2**

^{31}P NMR Spectra of Compound **2**.—The spectra are shown in Fig. 4 and a plot of pD *vs.* δ_P in Fig. 5. At pD 1.02 the species in solution give rise to two overlapping triplets (due to coupling to CH_2), with the most upfield signal being the slightly more intense. As the pD was raised the signals began to merge, forming one broad triplet at pD 5.39 which then sharpens as the pD is raised even higher, consistent with the existence in solution of two isomeric species at low pD as described previously.

The plot of pD *vs.* δ_P (Fig. 5) shows two distinct movements of signal, one large upfield shift (+7.8 ppm) along with two smaller downfield shifts. The large upfield shift occurs in the range pD 14–10, due to deuteriation of the nitrogen which causes a shielding effect on the phosphorus nucleus. Such an exceptionally large shift has been observed in the deuteriation of macrocyclic amines bearing methylphosphonic acid groups and has been attributed to complexation of Na^+ within the macrocyclic cavity,[1] since titrations repeated with tetramethylammonium hydroxide instead of sodium hydroxide showed a reduced effect. However a similarly large shift is present in the system being discussed and no macrocyclic cavity is present. These exaggerated shifts are clearly due to the complexation of Na^+, possibly due to the formation of a five-membered chelate ring involving Na^+ and the N–C–P–O moiety. A smaller downfield ^{31}P shift (−1.3 ppm) is observed in the range pD 6–4, attributed to deuteriation of one of the phosphonate oxygens causing a smaller deshielding effect. The deuteriation of the second phosphonate oxygen is revealed by the second downfield shift (−0.8 ppm) at pD 2–1. The shape of the titration curve is similar to that obtained in the titration of $NH_2CH_2PO_3H_2$ by Appleton *et al.*[7]

Ternary Molybdate Conjugates.—Knowledge of the NMR behaviour of the phosphonic acid species was then used to assist interpretation of the NMR spectra of the phosphonic acid–molybdate system recently investigated.[4] It has been known for some time that the W_5P_2 cage is fluxional.[9–11] The dynamic NMR observed here permits an investigation of this point for the Mo_5P_2 cage with the hydroxypiperidine substituents. Since the hydroxypiperidine methylphosphonic acid is present in two forms (axial and equatorial hydroxy, the bulky phosphomolybdate cage being equatorial on the piperidine), a conjugate with one phosphorus only should have two ^{31}P signals in a defined ratio, while a conjugate with two phosphorus units should have three ^{31}P signals (aa, ae and ee forms; a = axial, e = equatorial)

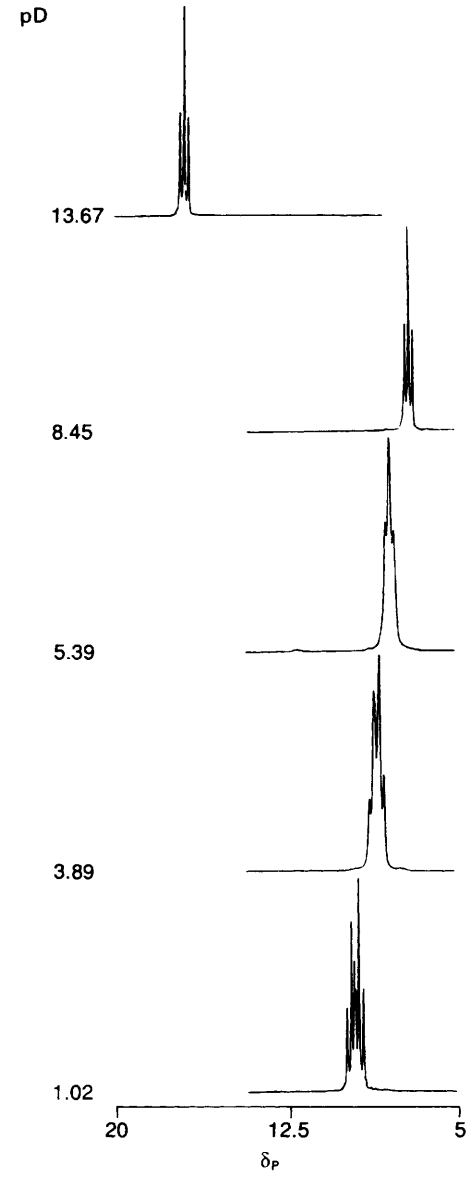


Fig. 4 The ^{31}P NMR spectra for the pD titration of compound **2**

in its slow-exchange limit. Similarly additional ^{31}P signals were expected for each additional phosphorus added to the cage (for a static cage).

Titration of a mixture of compound **2** *and* Na_2MoO_4 (5Mo : 2P) *with* HCl. An attempt to synthesise the pentamolybdodiphosphonate derivative of this acid was monitored by ^{31}P NMR titration. No solid conjugate was crystallised, possibly owing to the enhanced solubility of the phosphonate caused by the hydroxyl group and existence of the two isomeric forms at low pH. In view of this an NMR titration was carried out (ratio 5Mo : 2P) to determine whether the (*p*, 5, 2)* species was indeed present in solution. The initial low-resolution (JEOL) ^{31}P NMR spectrum taken at pH 7.00 indicated no ternary species. On lowering the pH $\leqslant$6.00 ternary species were evident in a pattern typical of the previous titrations.[14] A third signal at $\delta \approx 17$ is thought by analogy to the titration of acid **1** to correspond to the ternary (*p*, 5, 2) conjugate (see below).

Identification of multicomponent polyanions in the pH-dependent assembly of PO_4^{3-}, VO_4^{3-}, AsO_4^{3-} *etc.*, with

* The *p,q,r* notation is commonly used to describe such conjugates, where *p* refers to the number of protons, *q* to the number of molybdenums and *r* to the number of heteroatoms.

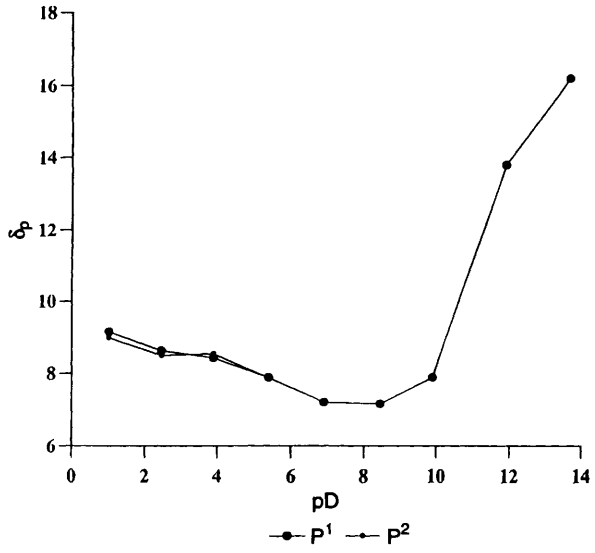


Fig. 5 Plot of pD *vs.* δ_P for compound **2**

MoO_4^{2-} has been subject to NMR analyses[9] using appropriate nuclei, including ^{17}O. However, the parameters varied have been composition (*e.g.* ratio Mo : X, where X is the heteroatom) and pH, seldom temperature. The system investigated here remained in solution at low temperatures, enabling investigation in aqueous solution from 0 to 60 °C. The system RPO_3^{2-}–MoO_4^{2-} also appeared to have the simplifying advantage that the cage size of phosphorus-containing aggregates would be limited to (*p*, 5, 2), (*p*, 7, 1) and (*p*, 6, 1) species, with variable protonation. In Pettersson's analysis of the $PhPO_3^{2-}$ system[11,12] only three ^{31}P signals were observed, corresponding to the free phosphonate, the (*p*, 5, 2) species and a third (thought to be composite) signal: electromotive force data suggested this was a composite of (*p*, 7, 1) and (*p*, 6, 1) species with different numbers of protons. Unfortunately, more species were discovered in our reaction mixture. We looked at the ^{95}Mo, ^{13}C and ^{1}H spectra for our system, but found high-resolution ^{31}P NMR spectroscopy was more informative. The presence of pairs of ^{31}P signals indicated isomerism. Since the large cage substituent attached to the P would be equatorial on the piperidine ring, the isomerism arises from a,e hydroxy groups (Scheme 3). No additional multiplicity of signal which could indicate the numbers of phosphonic groups on the cage was observed in this series, *e.g.* aa, ee and ae isomers.

Temperature and pH *variation of* ^{31}P *NMR spectra*. The pH of the Mo : P 5 : 2 composite was varied from 6 down to 2 at ambient temperature. The phosphonic acid signal (L) was observed at δ 7.5–8.5 depending on pH. At pH < 4.08 it was distinctly split revealing the a,e isomers. Two new broad signals B and B′ (also split into a,e sets) emerged at pH 5 but these appeared to coalesce at pH *ca.* 3.50. Signal A was present at pH $\leqslant$ 5, and was split into the pattern for a,e isomers at pH < 4.08. An additional signal C increased at lower pH and appeared as sharp a,e lines. In the 202.5 MHz spectrum it appeared as four very sharp lines, two pairs of a,e signals in the region δ 11.2–11.5 at ambient temperature. Temperature variation of the pH 4.08 mixture gave the most informative set of spectra. At 273 K five sets of signals were well resolved, labelled (Fig. 6) A,B, B′, C and L, even the L signal being partly resolved into a,e components. The greatest a,e shift separation (0.27 ppm) was for signal C.

As the temperature was raised, coalescence of the a,e signals was noted first at 278 K for L, at 288 K for B and between 288 and 293 K for B′. The B and B′ signals then approached coalescence, complete between 308 and 318 K; above this temperature the composite signal B became narrower, while the L signal got wider as the temperature was raised further. In the

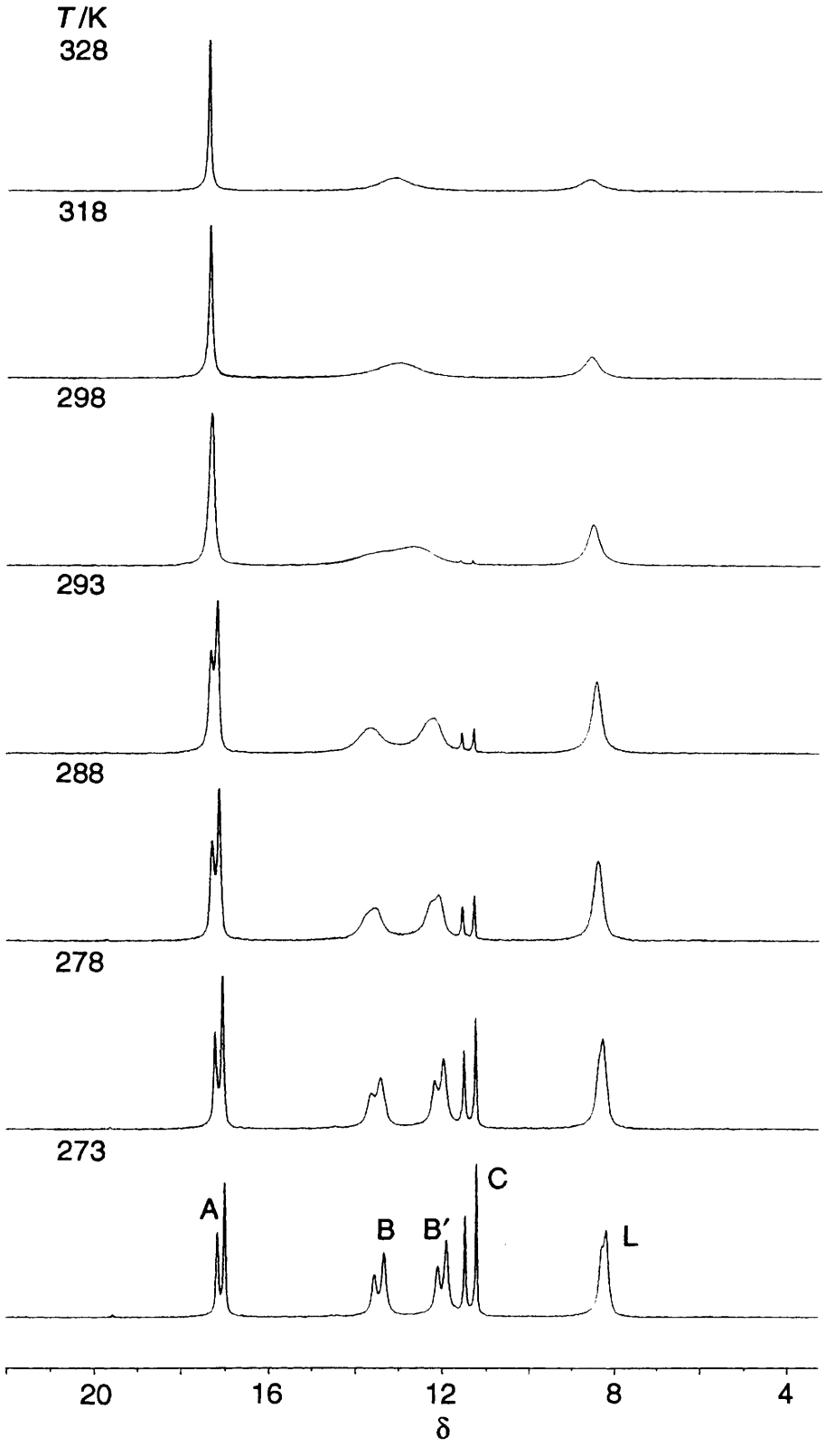


Fig. 6 Temperature variation of the ^{31}P-{H}NMR signals for the Mo:P 5:2 composite at pH 4.08

meantime signal A has a,e averaging between 293 and 298 K and the averaged signal constantly sharpened up to 338 K, when it contained 40% of the phosphorus, at the expense mostly of signal C. Signal C dwindled at high temperature and had almost gone at 308 K, despite having been 19% of the ^{31}P present at 273 K. The B, B′ signals remained similar in intensity to each other as the pH or temperature was varied, up to coalescence, so they are not connected by a protonation step: the overall percentage of ^{31}P present as B(B′) dwindled to 33% at 338 K. Table 1 shows the variation of signal area with increasing temperature.

Coalescence of the a,e pairs for signals A, B, B′ and of the

Table 1 Percentage of total phosphorus corresponding to ^{31}P NMR signals of the 5Mo:2P mixture at pH 4.08

T/K	L	B'		B	C	A
273	25	19		18	19	18
278	25	20		16	15	23
288	24	21		19	6	29
293	26	20		20	3	31
298	26		37.5*		< 1	32
308	24		39		—	35
318	26		38		—	36
328	25		37		—	38
338	22		33		—	40

* Signals B' and B had coalesced at this temperature and the values given represent the sum for these signals.

bulk signals of species B and B' was also observed. The $\Delta G^{\ddagger}$ value corresponding to coalescence for each of these is approximately 14.5–15.2 kcal mol^{-1}. Since the values are so similar, it suggests each is a consequence of a similar process. The B–B' exchange is probably of two isomeric forms perhaps of a (*p*, 7, 1) cage. The earlier discussion indicates that protonation of a phosphonate oxygen in the range pD 4–6 slows the a,e exchange in the piperidine ring (see Fig. 4) on the ^{31}P NMR time-scale; lowering the temperature raises the pH at which this occurs. It seems reasonable to suppose that ternary conjugates which do not show an a,e split are fluxional, with a free PO unit intermediate in a jump mechanism between two 'caged' PO units one of an a and one of an e conformation. The a,e split would then be observed when the time-scale of the process was increased, as observed here at lower pD and temperature.

Exchange involving species C is too slow to be seen on the NMR time-scale, the a,e signals remaining sharp throughout, but it is converted into A in mole fraction terms. Since an Mo_6P species was prominent in the $PhPO_3^{2-}$ system, it is proposed by analogy as the origin of signal C. Conversion into the Mo_5P_2 cage by addition of ligand L and loss of an MoO_4 fragment is readily envisaged.

It should be remembered that binary molybdate species (*p*, *q*, 0) with Mo_7 and Mo_8 cages are present, but transparent to ^{31}P NMR spectroscopy. The broadening of certain ^{31}P signals may indicate exchange with such species. For example addition–elimination of MoO_4^{2-} is rapid between Mo_7 and Mo_8 cages; a similar exchange between Mo_7P and Mo_6P is proposed by Pettersson.[12] However, the spectra shown here can only indicate the exchange of ternary species. It is also possible that intramolecular exchange of ^{31}P within a cage may cause signal broadening. It is quite clear that the L signal is broadening at the highest temperature reached, while the remaining A and B signals are narrowing. Thus each is part of an additional exchange but it is not mutual. There could be another ^{31}P signal (either small, or very wide) with which the fast exchange occurs.

The temperature variation of the ^{31}P NMR spectrum of the solution with a Mo:P ratio of 5:1 was examined (see Fig. 7) along with the pH variation (see Fig. 8). There are three sets of signals, with no residual compound **2** under these conditions. Signals A and B,B' are present, but not C, and there is a new signal, D. In Table 2 are compared the shifts of the signals for the 5:2 and 5:1 mixtures at closely comparable temperatures and pH. Signal A is of low intensity and is thus confirmed as due to the (*p*, 5, 2) species. The signals B,B' coalesce similarly to those in the 5:2 mixture. However, the third signal, D, has no counterpart in the 5:2 mixture and has no analogue in the Pettersson study.[12] Firm assignment of these solution species must await a complete computer-aided analysis of the equilibria.

The signals labelled A have however been assigned from the Mo:P variation experiments and by analogy with the earlier

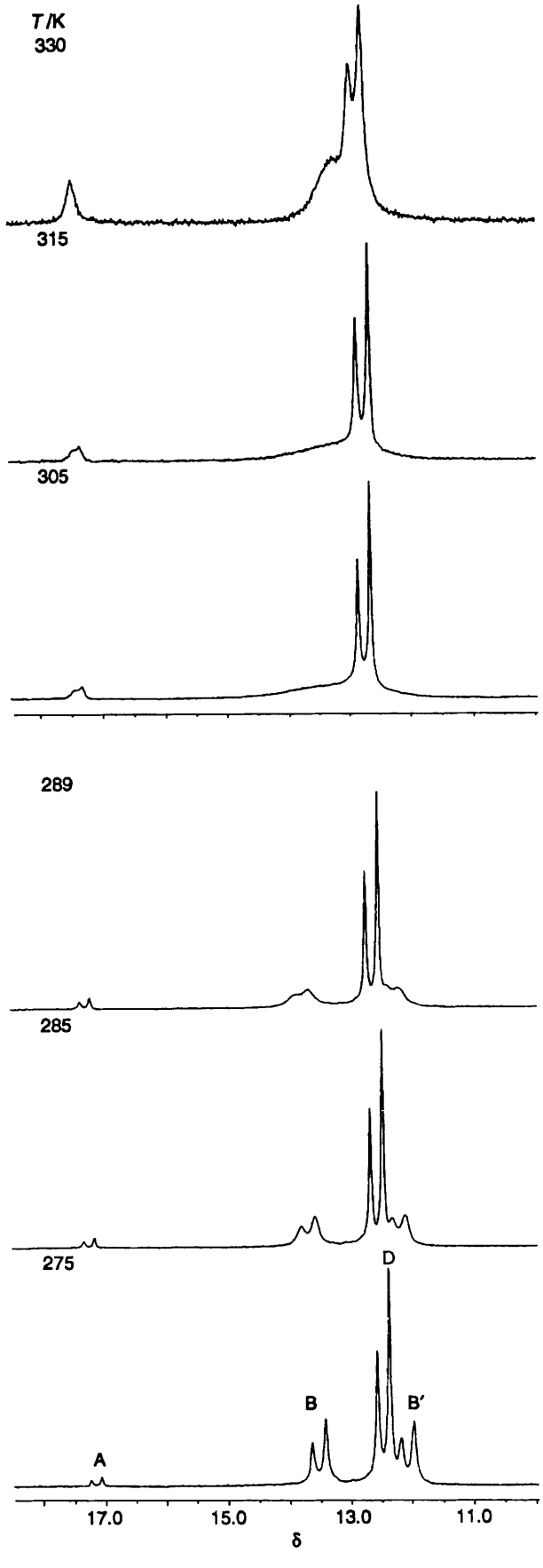


Fig. 7 Temperature variation of the ^{31}P-{H}NMR signals for the Mo:P 5:1 composite at pH 4.18

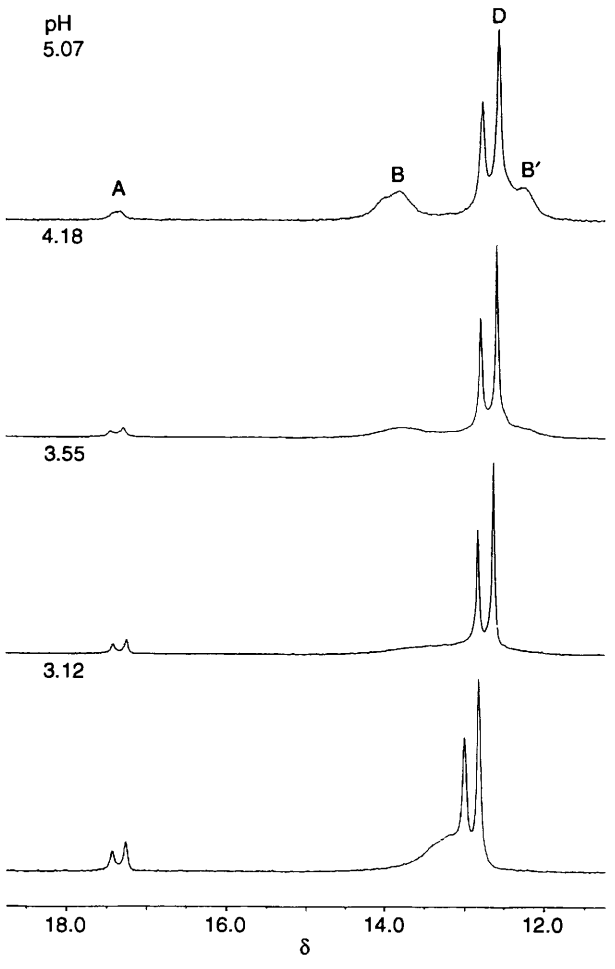


Fig. 8 The pH variation of the ^{31}P-{H}NMR signals for the Mo:P 5:1 composite at 291 K

Table 2 Comparison of ^{31}P NMR shifts in the Mo–P mixtures

Signal	5:2 Mixture[a]	5:1 Mixture[b]	Signal area[b,c]	5:1 Mixture[d]
A	17.16 17.00	17.23 17.07	2	17.07
B	13.55 13.32	13.64 13.41	22.5	13.33
B'	12.09 11.89	12.167 11.96	21.8	11.80
C	11.47 11.20	— —		
D	— —	12.56 12.37	54	12.08
L	8.27 8.18	— —		

[a] At 273 K and pH 4.08, with compound **2**. [b] At 275 K and pH 4.18, with compound **2**. [c] Signal area for comparison with Table 1 as % of total phosphorus signals. [d] At 291 K and pH 5.07, with compound **1**.

work [11,14] as those for the Mo_5P_2 cage. The spectrum of a 5:1 mixture of molybdate with compound **1** was examined in this work in the same pH range as that for the 5:1 mixture with **2**. This showed single signals, with A (*ca.* 3% of signal area) at δ 16.82, B and B' nearly at coalescence and D the major component. Signal A was previously identified as that of the cage (*p*, 5, 2) with **1**, for which crystallographic structural evidence was obtained. Although three signals were expected (a,a a,e and e,e isomers) for the analogue with **2** at the shift for A, only two were seen, with the same a,e ratio as those of the rest of the signals. This could result from chemical shift equivalence of the 'a' and the 'e' signals between species or between isomers; rapid intramolecular exchange is unlikely since the a,e distinction is preserved.

In summary, the hydroxypiperidine **2** has proved an important new tool in the NMR investigation of complete phosphomolybdate cages, since the existence of its isomers and its unusual solubility permit variable-temperature investigation of a range of exchange processes occurring in aqueous solution at low pH and hypotheses relating to these have been made.

Experimental

Instruments.—Proton and ^{13}C NMR spectra were run on a Bruker WP200 spectrometer (^{1}H, 200.13; ^{13}C, 50.32 MHz). The ^{31}P NMR spectra were run on a Bruker WB300 (121.50 MHz) spectrometer for the titration of compound **2**, and additionally with JEOL FX90Q (36.2 MHz) and Bruker 500 WB (202.5 MHz) spectrometers with proton decoupling for the titration of a mixture of **2** and Na_2MoO_4 with HCl. Both were referenced to external 85% H_3PO_4. All ^{13}C NMR spectra were broad-band decoupled. Elemental analysis was obtained on a Carlo Erba 1106 Elemental Analyser.

Preparation of 4-Hydroxypiperidinomethylphosphonic Acid.—This was prepared by a modification of the Moedritzer–Irani [13] synthesis of aminomethylphosphonic acids. Phosphorous acid (4.05 g, 49.40 mmol) and 4-hydroxypiperidine (5.00 g, 49.43 mmol) were dissolved in distilled water (25 cm^3). After slow addition of 37% w/v HCl (25 cm^3) the temperature was raised to reflux (≈110 °C) and 37% w/v aqueous formaldehyde (8.02 g, 98.91 mmol) was added dropwise to the stirred solution over a period of 30 min. The reaction was then continued for 5 h after which time the HCl–water solvent mixture was concentrated almost to dryness and then taken up in hot methanol (100 cm^3). Diethyl ether (150 cm^3) was added and the solution left slowly to evaporate to half of the original volume. A white precipitate formed which was a mixture of the two possible isomeric products. Yield 8.42 g (80%), m.p. 191–193 °C (Found: C, 33.6; H, 7.0; N, 6.4. $C_6H_{14}NO_4P{\cdot}H_2O$ requires C, 33.8; H, 7.6; N, 6.6%); δ_H(200.13 MHz, solvent D_2O, pD 9.90) 3.12 (d, $^2J_{PH}$ 11.68, NCH_2P), 4.10 (m, $HOCHCH_2CH_2N$), 3.65 (m, $HOCHCH_2CH_2N$ equatorial), 3.39 (m, $HOCHCH_2CH_2N$ axial), 2.21 (m, $HOCHCH_2CH_2N$ equatorial) and 1.91 (m, $HOCHCH_2CH_2N$ axial); δ_C(50.32 MHz, solvent D_2O, pD 9.90) 56.99 (d, $^1J_{CP}$ 126.10, NCH_2P), 53.74 (d, $^3J_{CNCP}$ 6.85, $HOCHCH_2CH_2N$), 65.32 (s, $HOCHCH_2CH_2N$) and 32.41 (s, $HOCHCH_2CH_2N$); δ_P(36.2 MHz, solvent D_2O, pD 9.90) 7.89 (t, $^2J_{PH}$ 11.68 Hz).

NMR Titrations.—*Acid* **2**. Solutions were prepared containing 4-hydroxypiperidinomethylphosphonic acid (0.26 mol dm^{-3}), sodium chloride (1.00 mol dm^{-3}) and Bu^{t}OH (0.03 mol dm^{-3}) in D_2O then titrated with sodium deuteroxide (37% w/v). Samples were removed at regular intervals of pD and their ^{1}H, ^{13}C and ^{31}P NMR spectra obtained (the amount of NaOD added being negligible compared to the total volume of solution). The Bu^{t}OH signal was used as an internal reference, since it is known [19] to be largely independent of pD (δ_H 1.3, δ_C 31.6). The chemical shifts obtained in the titration were adjusted accordingly. The phosphorus chemical shifts were referenced to an external 85% H_3PO_4 solution.

Mixtures of acid **2** *and* Na_2MoO_4 *with* HCl. A solution containing $Na_2MoO_4{\cdot}2H_2O$ (0.93 g, 3.84 mmol) and compound **2** (0.30 g, 1.54 mmol) in water (15 cm^3) was titrated with HCl (11.34 mol dm^{-3}). Samples were removed at regular intervals of pH and their ^{31}P NMR spectra obtained. A second solution was similarly prepared, except that **2** (0.15 g, 0.77 mmol) was supplied in lower ratio.

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