Macrocyclic Ligands with Pendant Phosphonic Acid Groups*

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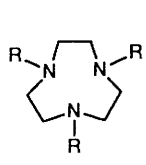
Small aza- and oxaaza-macrocycles bearing two aliphatic nitrogens have been derivatised with pendant methylenephosphonates. Multinuclear NMR studies (^{31}P and ^{1}H) have elicited the protonation behaviour of one of these macrocycles. Improved methods of separation and purification of the ligands are discussed. The crystal structure of the parent 1,4,7-triazacyclononane-1,4,7-triyltris(methylenephosphonic acid) has been determined, indicating that two of the nitrogens are protonated under the conditions of crystallisation. Extensive hydrogen-bonding networks are evident in the structure. The Cambridge Structural Database has been used to survey structures based on 1,4,7-triazacyclononane and other amino(alkylphosphonates), amino(alkylphosphinates), and amino(alkanecarboxylates) and their metal complexes, for comparison.

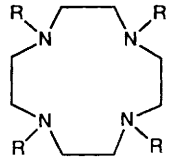
Amines and ammonia may be converted into aminomethylphosphonic acids using the reaction with formaldehyde and phosphorous acid [see equation (1), the Moedritzer–Irani

$$RNH_2 + 2H_3PO_3 + 2CH_2O \rightleftharpoons RN(CH_2PO_3H_2)_2 + 2H_2O \quad (1)$$

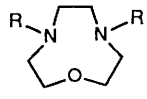
reaction [1]. The ligands thus obtained provide a plentiful series of new co-ordination compounds, interesting stereochemistry and a wide range of commercial applications.[2] The importance of the ligands as phosphorus analogues of the amino acids can scarcely be exaggerated. They have also been extensively used as pseudo-substrates in biological studies, a recent example being the use of a set with planned variation, to probe the ditopic anion-binding site implicated in the iron uptake of transferrin.[3] The ligands are moderately acidic and have been widely used in descaling, and to prevent the build-up of scale. Characterisation has usually been in solution, by titrimetric and by NMR methods, while few crystal structures of free acids or of salts have been obtained.[4] A natural extension of this range of aminophosphonate ligands is to the smaller macrocyclic amines such as 1,4,7-triazacyclononane **1a**, the special co-ordinating properties of which have been widely exploited [5] in complexation of d-block metals which prefer nitrogen donors. The triphosphonic acid ligand **1b** derived from **1a** was first made by Polikarpov *et al.*[6] who obtained crystal structures of the iron(III) and copper(II) complexes.[7,8] A number of workers interested in co-ordinating the larger lanthanide ions with a view to the production of NMR imaging reagents, have similarly synthesised the larger tetraazacyclododecane derivative **2a** and related tetraaza macrocycles.[9] Parker and co-workers [10] have also made a range of phosphinic acid derivatives of small polyaza macrocycles, many with potential applications in bioimaging and nuclear medicine. We report the derivatisation of two small macrocycles **3b** and **4b** containing two aliphatic nitrogens, together with some ether links. The ligands have been investigated mostly by NMR methods, to elucidate the protonation behaviour, and by the production of a lead complex of **4c**. The crystal structure obtained in the present work for **1b** has been compared with information on the general ligand type, extracted from the Cambridge Structural Database.



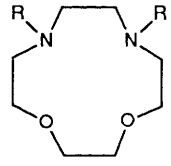
R
1a H
1b $CH_2PO_3H_2$



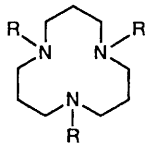
R
2a H
2b $CH_2PO_3H_2$



R
3a p-$MeC_6H_4SO_2$
3b H
3c $CH_2PO_3H_2$



R
4a p-$MeC_6H_4SO_2$
4b H
4c $CH_2PO_3H_2$



5 R = $CH_2PO_3H_2$

Experimental

Preparation of Macrocyclic Amino(methylphosphonic acids).—General method. The ditosylated glycols were synthesised using a modification [11] of an established method.[12] Ditosylated ethylenediamine was synthesised using a published procedure.[13] The purity of all tosylates was checked by TLC analysis (on Kieselgel 60 F_{254} plates, run in MeOH–CH_2Cl_2 mixtures) and by comparison of the melting points with literature values. The cyclisation reactions were carried out according to the original method of Richman and Atkins.[14] The ^{1}H NMR data for the

* *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1992, Issue 1, pp. xx–xxv.

Table 1 Proton NMR of macrocyclic tosylates, amines and methylphosphonates[a]

Ligand	OCH_2CH_2O	OCH_2CH_2N[b]	OCH_2CH_2N[b]	NCH_2CH_2N	CH_2P
3a		3.89 (4 H, *N* 10.0)	3.25 (4 H)	3.45 (4 H, s)	
4a	3.50 (4 H, s)	3.63 (4 H, *N* 8.5)	3.26 (4 H)	3.50 (4 H, s)	
3b		3.89 (4 H, *N* 10.2)	3.03 (4 H)	3.07 (4 H, s)	
4b	3.95 (4 H, s)	4.07 (4 H, *N* 10.0)	3.64 (4 H)	3.84 (4 H, s)	
3c		3.97 (4 H, *N* 12.0)	3.57 (4 H)	3.73 (4 H, s)	3.41 [4 H, d, *J*(PH) 12.0]
4c		3.87 (8 H, m)		3.6 (8 H, br)	3.39 [4 H, d, *J*(PH) 12.63]

[a] 200 MHz spectra run in $CDCl_3$ (**3a**, **4a**), CD_3OD (**3b**, **4b**) or D_2O (pD ≈ 1.6) (**3c**, **4c**). [b] These signals for an AA'BB' system are apparent triplets from which only $N = J + J'$ (the sum of the averaged *vicinal* couplings) can be extracted, *J*, *N* in Hz.

tosylated macrocycles, derived amines and corresponding methylphosphonates are shown in Table 1.

Preparations.—4,7-*Ditosyl*-1-*oxa*-4,7-*diazacyclononane* **3a**. The ditosylate was obtained in 42% yield after recrystallisation from hot ethanol, m.p. 196–198 °C (from EtOH) (lit.,[15,16] 199–201, 194–195 °C {Found: C, 54.9; H, 5.9; N, 6.3%; (M + H^+) 439 [fast atom bombardment (FAB)]. Calc. for $C_{20}H_{26}N_2O_5S_2$: C, 54.8; H, 6.0; N, 6.4%; *M* 438}. $\delta_C(CDCl_3)$ 21.2 ($CH_3C_6H_4$) 48.0, 48.7 (OCH_2CH_2N, NCH_2CH_2N), 73.8 (OCH_2CH_2N) and 124.3, 129.0 ($CH_3C_6H_4$) (TLC: single spot, 1.5% MeOH–CH_2Cl_2). Mass spectrum (FAB): *m/z* 283 (M − $CH_3C_6H_4SO_2$)$^+$.

7,10-*Ditosyl*-1,4-*dioxa*-7,10-*diazacyclododecane* **4a**. The product was isolated in a similar manner to the N_2O derivative **3a**. Yield = 23%, m.p. 216.5–217.5 °C [from dimethylformamide (dmf)–water] (lit.,[15] 223–224 °C).

Tosyl groups were removed using a modification of a published method,[17] detailed for the preparation of **3b** below.

1-*Oxa*-4,7-*diazacyclononane* **3b**. A sodium amalgam was prepared by carefully adding Na (1.8 g, in small pieces) to Hg (110 g) under nitrogen. A slurry containing the ditosylate **3a** (3.97 g, 9.06 mmol) in absolute ethanol (500 cm^3) was then added to the amalgam. The stirred reaction mixture was heated to reflux and left for 24 h. After this time, a TLC in 1.5% MeOH–CH_2Cl_2 indicated that there was only a small amount of ditosylate starting material left. The product was isolated by adding water (100 cm^3) and then extracting with $CHCl_3$ (3 × 500 cm^3). The yellow oil obtained after removal of the $CHCl_3$ was then dissolved in propan-2-ol. Most of the remaining tosylated starting material precipitated immediately from the alcoholic solution. A small amount of concentrated HCl was added to the solution but the dihydrochloride could not be precipitated as a solid. The propan-2-ol was stripped off and the brown oil was then used without further purification for the preparation of **3c**. The NMR data for the free amine **3b** in Table 1 refer to a pure sample of the amine which was isolated as an oil using a Kugelrohr (Büchi GKR-51) at 150 °C (10^{-1} mmHg, ≈13.3 Pa).

1,4-*Dioxa*-7,10-*diazacyclononane* **4b**. The reaction conditions were similar to those used for **3b**. No further purification was necessary after extraction with $CHCl_3$ (yield = 66%).

1-*Oxa*-4,7-*diazacyclononane*-4,7-*diylbis*(*methylenephosphonic acid*) **3c**. Phosphorous acid (0.49 g, 6 mmol) and the dihydrochloride of **3b** (0.73 g, 3.596 mmol) were initially dissolved in distilled water (5 cm^3). After slow addition of 37% w/v HCl (5 cm^3) the temperature was raised to reflux (≈110 °C) and 37% w/v aqueous formaldehyde (1 cm^3, 0.012 mol) was added dropwise to the stirred solution over 30 min. The reaction was then continued for a further 3 h. The HCl–H_2O solvent mixture was concentrated almost to dryness and then a small amount of ethanol was layered over the oil. The *product* crystallised overnight and was eventually purified in very low yield after a further crystallisation from ethanol–water (≈9:1) and two recrystallisations from water–propan-2-ol (≈1:1), m.p. 258–260 °C (from water–propan-2-ol) (Found: C, 27.2; H, 6.5; N, 8.0. $C_8H_{20}N_2O_7P_2 \cdot 2H_2O$ requires C, 27.1; H, 6.8; N, 7.9%). δ_C (50 MHz, solvent D_2O, pD ≈ 1.6) 53.66 (OCH_2CH_2N), 55.0 (d, $^1J_{CP}$ 138.6 Hz, CH_2P), 55.82 (NCH_2CH_2N) and 66.66 (OCH_2CH_2N). δ_P (121.495 MHz, solvent D_2O, pD ≈ 1.6) 16.25 (t, $^2J_{PH}$ 11.3 Hz*).

1,4-*Dioxa*-7,10-*diazacyclododecane*-7,10-*diylbis*(*methylenephosphonic acid*) **4c**. The product made by the general method described was found to be soluble in water, methanol and ethanol and insoluble in propan-2-ol, but could not be crystallised from mixtures of these solvents. A lead salt was prepared from the crude product in the following manner: 0.81 g of oil from the crude reaction mixture was dissolved in water (25 cm^3). It was estimated that ≈0.5 g of the oil was in the form of the disubstituted product (60% by weight). The pH of the solution was raised to 6.5 with NaOH (5 mol dm^{-3}). A solution of $Pb(NO_3)_2$ (0.91 g, 2.76 mmol) in distilled water (25 cm^3) was then added dropwise to the stirred ligand solution. The lead salt of **4c** precipitated at *ca.* 5 °C after the volume of the solution had been reduced to 10 cm^3. The precipitate was filtered off and washed with ethanol, affording a white solid (0.65 g, 29%). The best fit for the elemental analysis was obtained for the presence of half a nitrate ion and three Pb atoms per disubstituted ligand (Found: C, 11.6; H, 1.9; N, 3.2. $C_{10}H_{22}N_2O_8P_2Pb_3 \cdot 0.5NO_3$ requires C, 11.9; H, 2.2; N, 3.5%). The lead was removed using the hydrogen sulfide technique of Rajan *et al.*,[18] and the product **4c** was isolated in low yield after three recrystallisations from water–propan-2-ol (≈1:2), m.p. 210–214 °C (from water propan-2-ol) (Found: C, 29.5; H, 6.4; N, 6.6. $C_{10}H_{24}N_2O_8P_2 \cdot 2.5H_2O$ requires C, 29.5; H, 7.2; N, 6.9%). δ_P(121.495 MHz, D_2O, pD ≈ 1.6) 8.52 (t). See Table 1 for ^1H NMR data.

NMR Studies.—NMR spectra were run on Brüker WB300 and AC200 instruments with ^1H, ^{13}C and ^{31}P nuclei. Table 1 contains the ^1H NMR data. For studies of the protonation behaviour of ligands, standard solutions at different pD values were prepared containing the ligand (≈0.034 mol dm^{-3}), KCl (1 mol dm^{-3}) and varying amounts of KOH (0.1 mol dm^{-3}) in D_2O. The sample at pD 0.1 was obtained using dilute DCl instead of KOH in D_2O. The final pD values were corrected for a deuterium isotope effect by using the equation pD = pH + 0.4.[19]

Structure of 1,4,7-*Triazacyclononane*-1,4,7-*triyltris*(*methylenephosphonic acid*) *Monohydrate* **1b**.—A crystal suitable for the structure determination was obtained on slow cooling of a saturated aqueous solution of the ligand at 70 °C and pH ≈ 1.2.

Crystal data. $C_9H_{24}N_3O_9P_3 \cdot H_2O$, M_r = 429.2, orthorhombic, space group *Pccn*, *a* = 10.537(1), *b* = 27.464(3), *c* = 11.989(1) Å, *U* = 3469.5 Å^3, *Z* = 8, D_c = 1.643 g cm^{-3}, λ(Mo-Kα) = 0.710 73 Å, μ = 0.39 mm^{-1}, *F*(000) = 1808, *T* = 240 K.

Data collection and treatment. Colourless crystal, size 0.40 × 0.40 × 0.25 mm, on glass fibre, Stoe–Siemens diffractometer, unit-cell parameters from 2θ values of 32 reflections (20–25°) measured at ±ω. Data collection in ω–θ scan mode with on-line profile fitting,[20] $2\theta_{max}$ 50°, index ranges, *h* 0–12,

* *J* could not be determined at pD 1.6; this value refers to pD 3.0.

Table 2 Atomic coordinates for ligand **1b**

Atom	*x*	*y*	*z*
N(1)	0.007 29(14)	0.442 10(5)	0.677 31(11)
N(2)	0.165 02(15)	0.365 55(5)	0.619 86(11)
N(3)	−0.086 92(15)	0.346 16(6)	0.556 15(13)
C(11)	−0.041 00(17)	0.493 52(6)	0.677 97(14)
C(12)	0.126 86(17)	0.435 34(7)	0.744 38(15)
C(13)	0.176 00(18)	0.383 22(6)	0.734 22(14)
C(21)	0.263 57(18)	0.382 70(7)	0.542 78(15)
C(22)	0.127 09(19)	0.314 70(7)	0.608 10(15)
C(23)	−0.015 12(20)	0.309 02(6)	0.625 89(15)
C(31)	−0.170 90(18)	0.324 23(7)	0.467 86(17)
C(32)	−0.166 21(17)	0.380 92(7)	0.624 63(15)
C(33)	−0.095 99(18)	0.407 51(6)	0.716 29(15)
P(1)	0.069 34(4)	0.539 81(2)	0.622 87(4)
P(2)	0.424 42(4)	0.359 97(2)	0.561 64(4)
P(3)	−0.090 22(5)	0.285 63(2)	0.365 17(4)
O(11)	−0.009 92(14)	0.574 00(5)	0.554 77(11)
O(12)	0.123 37(13)	0.565 96(5)	0.730 03(12)
O(13)	0.177 47(14)	0.514 83(5)	0.565 56(11)
O(21)[a]	0.469 36(15)	0.371 96(6)	0.677 81(12)
O(22)[a]	0.507 20(15)	0.382 61(5)	0.469 78(12)
O(23)[a]	0.415 16(16)	0.304 61(6)	0.543 98(16)
O(24)[b]	0.482 9(14)	0.345 7(7)	0.457 3(10)
O(25)[b]	0.410 6(13)	0.311 3(4)	0.643 5(9)
O(26)[b]	0.482 9(16)	0.401 4(5)	0.620 5(13)
O(31)	0.034 88(13)	0.312 54(6)	0.338 18(13)
O(32)	−0.178 01(14)	0.285 40(4)	0.263 73(10)
O(33)	−0.067 49(15)	0.236 70(5)	0.414 41(12)
O(4)	0.420 69(25)	0.530 89(10)	0.532 25(29)

[a] Major disorder component, occupancy 0.908(2). [b] Minor disorder component, occupancy 0.082(2), ignored in the discussion of the structure.

k 0–32, *l* 0–14, together with some equivalent reflections, correction for approximately 6% decay in intensities of three standard reflections, no absorption or extinction corrections, 3831 reflections measured, 3065 unique, 2596 with $F > 4\sigma_c(F)$ (σ_c from counting statistics only), $R_{int} = 0.026$.

Structure determination. Solution by direct methods and difference syntheses, blocked-cascade least-squares refinement on *F*, weighting $w^{-1} = \sigma^2(F) = \sigma_c^2(F) + 59 - 71G + 227G^2 - 155H + 100H^2 + 70GH$ [$G = F_o/F_{max}$, $H = \sin\theta/\sin\theta_{max}$],[21] anisotropic thermal parameters for all non-H atoms, H atoms constrained [C–H 0.96 Å, H–C–H 109.5°, N–H and O–H soft-restrained to 0.9 Å, $U(H) = 1.2U_{eq}(C)$, H atoms bonded to O and N with freely refined thermal parameters]. Two-fold disorder was resolved and refined for one of the phosphonic acid groups. $R = 0.0397$, $R' = (\Sigma w\Delta^2/\Sigma wF_o^2)^{\frac{1}{2}} = 0.0393$, $S = 1.34$ for 284 parameters, mean $\Delta/\sigma = 0.14$, max. $\Delta/\sigma = 0.93$, $(\Delta\rho)_{max} = 0.75$, $(\Delta\rho)_{min} = -0.87$ e Å^{-3}. Scattering factors were taken from ref. 22. SHELXTL[23] and local computer programs were used. The final fractional atomic coordinates are given in Table 2. The structure of ligand **1b** is shown in Fig. 1, with its numbering system.

Modelling Calculations.—The CHARMm/QUANTA programs, version 3.2.3, were used for geometric calculations as implemented on Silicon Graphics Personal Iris 4D/20G. Crystal structure coordinates were obtained from the SERC CDS System.

Results and Discussion

Ligands **3c** and **4c** are the first amino(alkylphosphonic acids) to be described for small-ring oxaza macrocycles; after extensive research they have been obtained analytically pure, and the known ligand **1b**, prepared as part of the work, was obtained in suitable crystalline form for X-ray structure analysis.

The protonation sequence of ligand **3c** was followed by

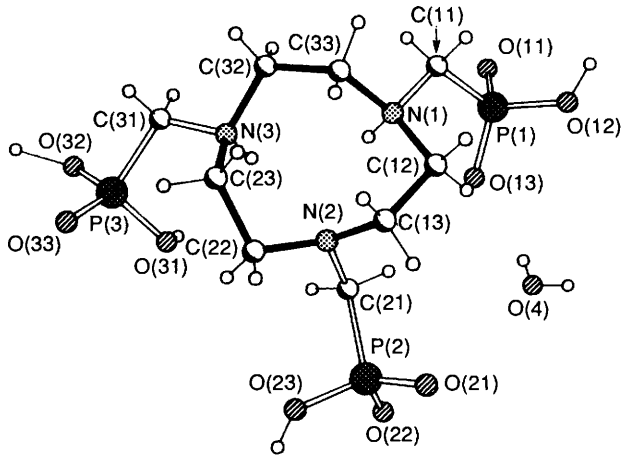


Fig. 1 Structure of ligand **1b**, with the labelling of the non-hydrogen atoms. Bonds in the macrocycle ring are shown filled, others hollow. The minor component of disorder is not shown

studying the variation of ^{31}P and ^{1}H NMR chemical shifts with pD. At pD 0.1 a broad signal appeared in the ^{31}P spectrum. As the pD was raised, the resolution increased and a sharp triplet was observed at pD 2.50.* The sharp signal was observed for the remainder of the titration (up to pD 13.1). It is not clear why the ligand signals are broader at low pD: possibly this indicates a pD-dependent relaxation of the NCH_2 protons, consequent on N deuteron exchange. A similar phenomenon has been observed in a series of triaza macrocyclic tricarboxylates.[24] In this case the broadening, which was only present in the asymmetric ligands studied, was attributed to a slow rate of nitrogen inversion which reduced the rate of interconversion between the various conformers. Geraldes *et al.*[24] suggested that the slow rate of nitrogen inversion may have been due to intramolecular hydrogen bonding between protonated nitrogens and non-protonated carboxylates or *vice versa*. The line broadening observed by Geraldes *et al.* was observed in the ^{1}H and the ^{13}C spectra while in this study, the line broadening was only observed in the ^{31}P spectra.

Fig. 2 shows a plot of chemical shift (δ_P) *vs.* pD, for this ligand. There are two large upfield shifts in the ^{31}P NMR titration. The first of these, from pD 13–10, is probably due to the deuteriation of the first nitrogen atom in the completely deprotonated ligand. This large shift ($\approx$5 ppm) may in part be due to complexation of K^+ (the counter ion present) within the macrocyclic cavity. A similarly large shift ($\approx$3 ppm) was observed for the first protonation of 1,4,7-triazacyclononane-1,4,7-triyltris(methylenephosphonic acid) **1b** using sodium hydroxide as titrant, but when the titration was repeated using tetramethylammonium hydroxide instead the change in chemical shift (δ_P) was reduced to 0.7 ppm.[25] The upfield shift (which has been found to decrease as the number of CH_2 groups between the phosphorus and nitrogen atoms was increased[26]) has recently been interpreted in terms of the formation of an intramolecular hydrogen bond between the protonated nitrogen atom and an unprotonated phosphonate group.[25] A strong hydrogen bond is hypothesised when there is one methylene group between the phosphorus and nitrogen atoms and a five-membered ring is formed. The strength of the intramolecular hydrogen bond is proposed to decrease as the number of CH_2 groups increases and the size of the ring is also increased.

The ^{31}P NMR titration curve shown in Fig. 2 is very similar to that obtained for ligand **1b** and its symmetrical

* The presence of only *one* sharp triplet, from the CH_2P coupling, indicates that there is a rapid exchange between the various protonated species in solution.

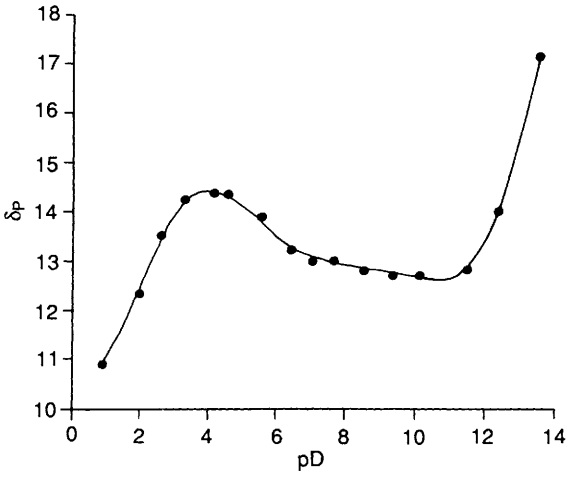


Fig. 2 NMR titration curve. Plot of ^{31}P chemical shift of a solution of compound **3c** in D_2O as pD is varied

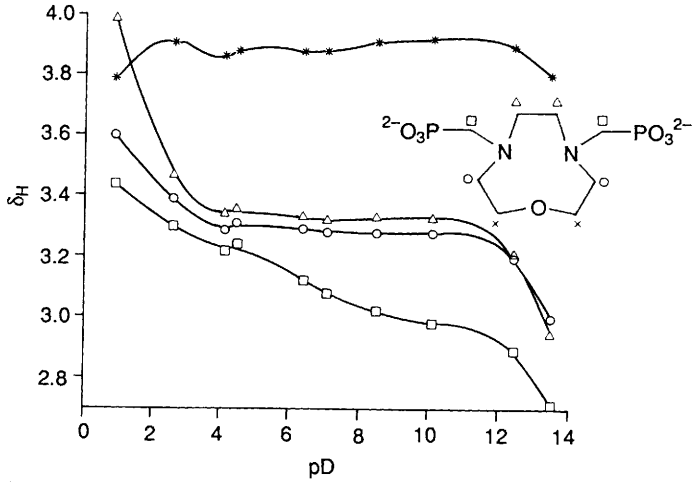


Fig. 3 Plot of identifiable ^1H NMR chemical shifts of a solution of compound **3c** in D_2O as pD is varied: labels on graph correspond to labelling scheme shown

triazacyclododecane analogue **5**, for which it was concluded that two nitrogen atoms were deuteriated at high pD.[25] There is some discrepancy in the numerical values of the pK_a obtained by Geraldes *et al.*[25] and those reported by Delgado *et al.*[27] The general interpretation is not in doubt, and is applicable here. As the pD is lowered, the NMR titration curve of ligand **3c** indicates that the phosphorus atoms are deshielded in two distinct stages. These shifts are much smaller (0.7 and 1 ppm) and in the opposite direction to that which was observed for the deuteriation of the first nitrogen atom. It is likely that these shifts are associated with the deuteriation of one oxygen atom in each of the phosphonate groups. The final large upfield shift (3.6 ppm) is consistent with the deuteriation of the second nitrogen atom. Substantiation of these assignments is given by the ^1H NMR titration curves of the macrocyclic and methylphosphonate CH_2 protons which are shown in Fig. 3.

Deuteriation of the nitrogen atoms results in large downfield shifts of the methylene protons in the macrocyclic ring which are adjacent to the ring nitrogen atoms (see labelling of **3c** in Fig. 3). During the remainder of the titration (pD 10–3), these proton shifts are relatively unaffected while the shifts of the CH_2P groups continue to increase as the protons are deshielded by the deuteriation of the phosphonate oxygen atoms. The methylene protons adjacent to the ether oxygen atom in the macrocyclic ring exhibit much smaller shifts on deuteriation of the nitrogens, and appear to be unaffected by deuteriation of the phosphonate oxygen atoms.

Although the deuteriation sequence seems relatively straightforward in this case, it must be stressed that the above assignments should remain tentative in the absence of a more thorough study involving the determination of accurate protonation/deuteriation constants and the degree of deuteriation of the nitrogen and oxygen sites. The tentative nature of the assignments can be illustrated by studying the last three deuteriations in the ^{31}P titration curve of ligand **3c**. The phosphonate and nitrogen deuteriations would be expected to deshield and shield respectively the phosphorus nucleus. Although part of the assignment was based on this 'rule', it does not necessarily always hold true. Several possible electronic effects, potentially of opposite signs, might contribute to the ^{31}P shifts. Although the protonation of a phosphonate group is likely to deshield the phosphorus atom in the same phosphonate group, it may have the opposite effect on the phosphorus atom in the other phosphonate group. When the protonation equilibria are fast, the observed chemical shift is a weighted average for the two phosphorus atoms and as a result the phosphorus signal may appear to be shielded or deshielded in the corresponding ^{31}P spectrum.

The method of Sudmeier and Reilley[28] was originally used to calculate the degree of protonation of oxygen and nitrogen sites in open-chain polyamine and aminocarboxylate ligands and in modifications has since been applied to macrocyclic amines,[24] aminocarboxylates,[29] and aminoalkylphosphonates.[25] In this method, the changes in chemical shift of the methylene protons consequent on the basic centres becoming fully protonated are referred to as shielding constants. The Sudmeier and Reilley method requires protonation constants, chemical shift values for the non-labile methylene protons and accurate shielding constants for the calculation of the degree of protonation of phosphonate oxygen and nitrogen sites. In linear aminocarboxylates the shift effects of protonation at the basic sites are assumed to be additive and a pH-independent set of shielding constants may be obtained.[28] The chemical shift effects are not additive in macrocyclic ligands. This is the result of pH-dependent conformational changes in the macrocycles which vary the average relative orientations throughout the pH range. The shielding 'constants' derived have been found to be very dependent on the protonation stage, macrocyclic ring size and type of proton considered within each molecule. In this study, the ^1H and ^{31}P NMR chemical shift data obtained during the protonation of ligand **3c** indicated that the first protonation was also associated exclusively with the nitrogen sites. The symmetrical nature of the ligand suggests that both nitrogen sites are protonated equally (on average) during the first protonation.

X-Ray Structure of Ligand **1b**.—The crystal structure analysis of ligand **1b** is shown in Fig. 1. Bond lengths and angles are given in Table 3. A sufficient number of related structures is available for a detailed analysis to be made of certain general features of the amino(alkylphosphonic acid) ligands in the crystalline state, which are also compared with the details of the current structure **1b**. An outstanding feature of the structure presented in Fig. 1, and one which correlates well with the NMR titration data just discussed, is that two of the three nitrogens [N(1) and N(3)] are protonated (*cf.* the solution NMR data[25]) partly balanced by the loss of a proton from the phosphonic acid group connected to the unprotonated N(2) atom.

Database Studies.—In view of the importance of the amino(alkylphosphonic acid) ligands as substitutes for amino acids, as enzyme substrates, and as a coherent set of anions with plannable variability in biochemical investigations,[3] a study of significant similarities and differences in the structures of each was undertaken. A search indicated that 38 aminoalkylphosphonic/phosphinic acid structures (with an N–C–P link)

[amino(alkylphosphonic acid)] (**A**), 4 with an N–C–C–P link (**B**), and 2 with an N–C–C–C–P link (**C**) could be accessed in the literature. Of type **A**, 22 are free phosphonate ligands, 13 are salts or metal complexes of phosphonates, there is one phosphinate ligand and two phosphinate complexes. All of types **B** and **C** are free phosphonate ligands. Many structures have been solved of aminoalkyl carboxylates and their metal complexes, but only the relevant few will be discussed in this paper. The search was conducted using the SERC Chemical Databank System (CDS) (January 1992 update), which accesses the Cambridge Structural Database of organic and organometallic crystal structures.[30,31] The CSSR program within CDS[30] was used for retrieval of the structures, with the FPROBE command. Structures with the e.s.d. flag set to 3 (indicating relatively poor precision) or with $R > 0.08$ were rejected in numerical averaging to be described in this paper. Of the selected structures, 23% have R values between 0.05 and 0.08, and 34% have the e.s.d. flag set to 2. Mean bond lengths for C–N, C–P, P–O, P–O(H), P=O and angles C–P–O, C–P–O(H), O–P–O and O–P–OH have been obtained for type **A**; these are shown in Table 4.

Table 3 Bond lengths (Å) and angles (°) in ligand **1b**

N(1)–C(11)	1.501(2)	N(1)–C(12)	1.506(2)
N(2)–C(33)	1.518(2)	N(2)–C(13)	1.459(2)
N(2)–C(21)	1.468(2)	N(2)–C(22)	1.460(2)
N(3)–C(23)	1.520(2)	N(3)–C(31)	1.505(3)
N(3)–C(32)	1.511(2)	C(11)–P(1)	1.845(2)
C(12)–C(13)	1.527(3)	C(21)–P(2)	1.820(2)
C(22)–C(23)	1.522(3)	C(31)–P(3)	1.834(2)
C(32)–C(33)	1.513(3)	P(1)–O(11)	1.499(1)
P(1)–O(12)	1.578(2)	P(1)–O(13)	1.497(2)
P(2)–O(21)	1.507(2)	P(2)–O(22)	1.536(2)
P(2)–O(23)	1.538(2)	P(2)–O(24)	1.448(13)
P(2)–O(25)	1.664(11)	P(2)–O(26)	1.474(14)
P(3)–O(31)	1.546(2)	P(3)–O(32)	1.528(1)
P(3)–O(33)	1.487(2)		
C(11)–N(1)–C(12)	113.4(1)	C(11)–N(1)–C(33)	110.1(1)
C(12)–N(1)–C(33)	111.0(1)	C(13)–N(2)–C(21)	115.4(1)
C(13)–N(2)–C(22)	115.5(1)	C(21)–N(2)–C(22)	116.1(1)
C(23)–N(3)–C(31)	114.3(1)	C(23)–N(3)–C(32)	113.6(1)
C(31)–N(3)–C(32)	108.0(1)	N(1)–C(11)–P(1)	115.6(1)
N(1)–C(12)–C(13)	110.9(1)	N(2)–C(13)–C(12)	111.1(1)
N(2)–C(21)–P(2)	118.1(1)	N(2)–C(22)–C(23)	110.7(1)
N(3)–C(23)–C(22)	110.1(1)	N(3)–C(31)–P(3)	115.5(1)
N(3)–C(32)–C(33)	115.4(2)	N(1)–C(33)–C(32)	115.4(1)
C(11)–P(1)–O(11)	106.0(1)	C(11)–P(1)–O(12)	104.4(1)
O(11)–P(1)–O(12)	111.1(1)	C(11)–P(1)–O(13)	109.2(1)
O(11)–P(1)–O(13)	117.5(1)	O(12)–P(1)–O(13)	107.9(1)
C(21)–P(2)–O(21)	109.4(1)	C(21)–P(2)–O(22)	107.5(1)
O(21)–P(2)–O(22)	113.3(1)	C(21)–P(2)–O(23)	105.2(1)
O(21)–P(2)–O(23)	111.3(1)	O(22)–P(2)–O(23)	109.7(1)
C(21)–P(2)–O(24)	112.4(6)	C(21)–P(2)–O(25)	105.5(5)
O(24)–P(2)–O(25)	109.2(8)	C(21)–P(2)–O(26)	100.6(6)
O(24)–P(2)–O(26)	116.4(9)	O(25)–P(2)–O(26)	112.0(7)
C(31)–P(3)–O(31)	105.0(1)	C(31)–P(3)–O(32)	104.8(1)
O(31)–P(3)–O(32)	110.6(1)	C(31)–P(3)–O(33)	109.3(1)
O(31)–P(3)–O(33)	112.2(1)	O(32)–P(3)–O(33)	114.2(1)

Amino(alkanecarboxylic acid) and Amino(alkylphosphonic acid) Crystal Structures.—Both types of ligand exist as zwitterions in the solid state. This involves deprotonation of a phosphonic (or carboxylic) acid oxygen and protonation of a nitrogen atom. Studies have shown that the more acidic phosphonic acid groups are deprotonated in preference to carboxylic acid groups.[4] The overall molecular conformations are determined by extensive intra- and inter-molecular hydrogen bonding.* This usually involves N–H · · · O or O–H · · · O bonds although weak C–H · · · O bonds have been observed in the crystal structure of ethylenediamine-*N*,*N*,*N*′,*N*′-tetramethylenephosphonic acid **6**.[32] Weak C–H · · · O bonding has also been observed in amino acids.[33] Intramolecular hydrogen bonding is much stronger in amino(alkanecarboxylic acids) than in amino(alkylphosphonic acids), many examples of which contain no IAHB. It has been argued that non-bonded interactions between the tetrahedral methylene and phosphonic acid groups make such bonding less favourable because the most eclipsed conformation is necessary for approach of the phosphonate oxygen (O) atom to the protonated N atom.[4] The weakness of the IAHB means that the conformation of the molecules can change under the influence of the stronger IEHB.

Structure of Ligand **1b** *and Comparisons.—The macrocycle ring.* It is interesting to compare the ring geometries of the free ligand and its corresponding copper(II) and iron(III) complexes.[7,8] Mean values for the macrocyclic bond lengths, angles and dihedral angles have been calculated from a group of 1,4,7-triazacyclononane complex structures. The Fe^{3+} and Cu^{2+} atoms are both connected to all three ring-nitrogen atoms and three and two oxygen atoms from different phosphonate groups respectively. The C–N bond lengths in ligand **1b** involving N(1) and N(3) are longer than those involving N(2), the longest C–N length occurring in the bond between the two protonated N atoms. Thus, the protonation of N(3) must also have the effect of increasing the length of the adjacent C(33)–N(1) bond. Both sets of lengthened C–N bonds in ligand **1b** are longer than the calculated mean value (1.490 Å), while the bonds around N(2) are much shorter than this mean value. The ring C–N bond lengths in the iron(III) and copper(II) complexes in which the N atoms are co-ordinated to the metal ion are close to the calculated mean value. The C–N bond lengths in these complexes are relatively short although not as short as those associated with the unprotonated N(2) in ligand **1b**. The only other example of an X-ray structure of a 1,4,7-triazacyclononane type ligand and a corresponding transition metal complex is that described by Moore *et al.*[34] The gallium(III) complex of 1,4,7-tris(2-hydroxy-3,5-dimethylbenzyl)-1,4,7-triazacyclononane has C–N bonds of similar length, which are close to the calculated mean for other 1,4,7-triazacyclononane type complexes ($\bar{x}$ = 1.493 Å). The C–N bonds in the free ligand

* Abbreviations: IAHB = intramolecular hydrogen bonding, IEHB = intermolecular hydrogen bonding as employed by Shkol'nikova and Porai-Koshits[4] are used in the following text.

Table 4 Mean bond lengths and angles in amino(alkylphosphonic acid) ligands[a]

Length	Mean $\bar{x}$/Å	σ_n	n	Angle	Mean $\bar{x}$/°	σ_n	n
C–N[b]	1.495	0.017	58	N–C–P	112.5	3.6	58
C–P	1.826	0.012	58	O–P–O	114.9	2.3	65
P–O(H)[c]	1.561	0.013	40	O–P–OH	109.9	2.3	77
P–O(H)[d]	1.544	0.012	14	O=P–OH	114.8	2.1	11
P=O	1.474	0.007	8	HO–P–OH	107.9	1.7	6
P–O	1.507	0.014	107	C–P–O	107.0	2.5	106
				C–P–OH	105.0	2.6	52

[a] Data from the CDS system. [b] Of the N–C–P link. [c] Phosphonate. [d] Phosphonic acid.

Table 5 Mean 1,4,7-triazacyclononane ring angles (°) (n = 33)

Angle	Mean $\bar{x}$/°	σ_n
C–N–C	112.1	1.36
C–C–N*	111.1	0.95
C–C–N*	110.1	1.07

* Two types of C–C–N angle were distinguished in each N–C–C–N dihedral angle.

Table 6 Ring dihedral angles (°) for ligand **1b** and its copper(II) and iron(III) complexes

Angle	**1b**	Cu^{2+}	Fe^{3+}
N(1)–C(12)–C(13)–N(2)	41.25	−51.0	−44.8
N(2)–C(22)–C(23)–N(3)	49.1	−47.5	−44.8
N(1)–C(33)–C(32)–N(3)	64.4	−43.4	−44.8

Ring dihedral angle $\bar{x}$ = ±45.6°, σ_n = 2.74, no. of angles = 33.

Table 7 $NH^+ \cdots N$ lengths (Å) and angles (°) in IAHB

	N–H	H···N	N···N	N–H···N
1b N(1)–H(1)···N(2)	0.833	2.391	2.767	108
1b N(3)–H(3)···N(2)	0.856	2.386	2.813	111
7 N–H···N	0.99	2.25	2.825	116
8 N–H···N	0.95	2.23	2.830	120

are much shorter ($\bar{x}$ = 1.476 Å). Thus protonation or co-ordination of the N atoms appears to increase the length of the ring C–N bonds. Other factors may also have an effect. Both the C–N–C and the C–C–N angles in the 1,4,7-triazacyclononane complexes tend to be very similar, illustrated by the small standard deviations in Table 5. The two C–C–N angles around the N atom attached to the unco-ordinated phosphonate group in the copper(II) derivative are smaller than those around the co-ordinated N atoms attached to the co-ordinated phosphonate groups.

The C–C–N angles in ligand **1b** are very similar to those of Table 5, except for those connecting the two protonated N atoms. Both of these angles are larger (by ≈4°) than the other C–C–N angles in the ring, and the largest N–C–C–N dihedral angle (Table 6) is that between the two protonated N atoms [N(1) and N(3)]. The increased size of these angles relative to the others in the ring may be the result of one or more of the following factors, IAHB between the NH^+ and N atoms in the ring, and/or Coulombic NH^+ repulsions. The lengths and angles between these atoms shown in Table 7 seem to indicate relatively strong IAHB in both cases. Intramolecular N–H···N bonds in other amino(alkanecarboxylate) and amino(alkylphosphonic acid) ligands are rare and there only appear to be two other examples (see Table 7) in the literature.[4] This is probably because there are only a very few ligands which contain both protonated and unprotonated N atoms.

It is conceivable that the relatively large C–C–N and N–C–C–N dihedral angles around the protonated N atoms are a result of the ring adjusting its conformation to form these stabilising, IAHB N–H···N bonds. Another possible reason for the size of these angles is that the conformation of the macrocyclic ring is set to keep the repulsion between the NH^+ groups to a minimum. Thus, although the H atoms on N(1) and N(3) are further apart (2.290 Å) than those in CH_2 groups, the charge on the NH^+ groups and hence the Coulombic repulsion between these NH^+ protons is likely to be greater than that between the protons in the ring and pendant-arm CH_2 groups.

The pendant groups: bond distances. Protonation of N atoms results in a lengthening of C–N bonds in the N–C–P link of methylphosphonate groups. For the 58 methylphosphonate/phosphinate C–N bond lengths compared, no significant trends or differences were observed between aminomethylphosphonic/phosphinic ligands and complexes when the N atoms were protonated. The shortest distance found was for the guanidinomethylphosphonic acid (C–N 1.455 Å);[35] the apparent shortening of C–N bonds attached to a guanidine nitrogen (*e.g.* arginine residues) is common.

The methylphosphonate C–N bonds in ligand **1b** involving the protonated N atoms, N(1) and N(3), are slightly longer than the mean bond length (1.495) shown in Table 4. They are also slightly shorter than those in the 1,4,7-triazacyclononane macrocyclic ring. The C–N bond length involving the *unprotonated* N atom in ligand **1b** is much shorter and it compares well with the value quoted for other 'normal' C–N bonds (1.47 Å)[36] in which the N atom is not quaternised. The C–N, C–P bond lengths and N–C–P angles in the unco-ordinated phosphonate group in the corresponding copper(II) complex are similar to those in the methylphosphonate group attached to the unprotonated N atom in **1b**. The two C–P bonds in the methylphosphonate groups attached to the protonated N atoms are the longest of the three in ligand **1b**. A comparison can be made with two aminomethyl carboxylate ligand structures which contain both quaternised and unquaternised N atoms. In *trans*-cyclohexane-1,2-diamine-*N*,*N*,*N*′,*N*′-tetraacetic acid **7** both methylenecarboxylate C–N bonds involving the quaternised N atom are longer than those involving the unquaternised N atom. The methylenecarboxylate C–C bonds are of similar length except in the deprotonated methyl carboxylate group.[37] A similar situation exists in diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid **8**,[38] where the methylene carboxylate C–C bond associated with the deprotonated $CH_2CO_2^-$ group is longer than all the other C–C bonds in the CH_2CO_2H groups, irrespective of whether the adjacent N atom is quaternised or unquaternised. On this evidence it appears that the effect is associated with the deprotonated carboxylate oxygen atom rather than the protonated N atom. A similar trend is observed in amino(alkylphosphonic acid) ligands such as iminobis(methylenephosphonic acid) **9** and cyclohexyliminobis(methylenephosphonic acid) **10**.[39]

In ligand **1b** the longest C–P bond length is associated with that methylenephosphonate group containing both the protonated N atom and deprotonated group. Interestingly, this bond [C(11)–P(1) 1.845 Å] is the longest out of 58 studied C–P bonds. The next longest [C(31)–P(3) 1.834 Å] is associated with a protonated N atom and a *protonated* phosphonic acid group. Both of these bonds are longer than the calculated mean for such bonds ($\bar{x}$ = 1.826). The shortest C–P bond in ligand **1b** is in the methylphosphonate group containing the unprotonated N atom and the *deprotonated* phosphonate group [C(21)–P(2) 1.820 Å]. Thus, in contrast to the previously mentioned amino carboxylate structures **7** and **8** and the two amino bis(alkylphosphonic acid) ligands, **9** and **10**, the C–P bond lengths in ligand **1b** seem to be lengthened more when associated with the protonated N atom rather than the deprotonated phosphonate groups.

Attempted Correlation of P–O *Bond Length with Hydrogen-bonding Characteristics.*—The P–O bonds can be divided into four different groups. These are double bonds, partial double bonds, single bonds to protonated O atoms in phosphonate groups and single bonds to protonated O atoms in phosphonic acid groups. All of the O atoms in ligand **1b** are involved in IEHB, with significant effect on the lengths of P–O bonds. The IEHB for **1b** listed in Table 8 were visualised with the QUANTA[40] molecular modelling program. Previous workers have discovered that the lengths of C–O(H), C=O and C–O bonds in aminoalkyl carboxylates are definitely related to the nature of the hydrogen bonds formed by these groups.[38] Twenty-three amino(alkylphosphonic acid) ligand structures (found in the database) have been studied in this project to establish whether such a relationship exists between P–O distances and the nature of the hydrogen bonds in amino

Table 8 Intermolecular hydrogen bonds for ligand **1b**: distances in Å, angles in °

Donor	Acceptor	Angle	O–H	O···O	H···O	Transformation*
O(12)–H(12)	O(21)	171	0.88	2.60	1.73	$-\frac{1}{2}+x, 1-y, \frac{3}{2}-z$
O(23)–H(23)	O(33)	178	0.90	2.51	1.61	$\frac{1}{2}-x, \frac{1}{2}-y, -z$
O(31)–H(31)	O(21)	177	0.84	2.52	1.68	$\frac{1}{2}-x, y, -\frac{1}{2}+z$
O(4)–H(41)	O(13)	158	0.66	2.63	2.01	x, y, z
O(4)–H(42)	O(22)	159	0.80	2.49	1.74	$1-x, 1-y, 1-z$
			N–H	N···O	H···O	
N(1)–H(1)	O(11)	160	0.83	2.82	2.02	$-x, 1-y, 1-z$
N(3)–H(3)	O(11)	149	0.86	2.76	1.99	$-x, 1-y, 1-z$

* Symmetry operation for acceptor atom.

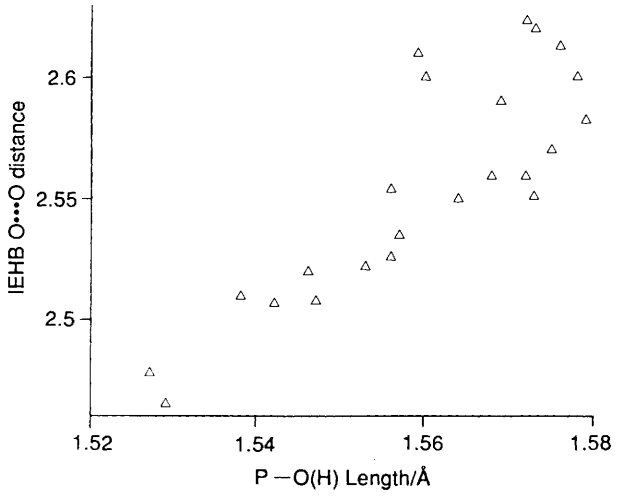


Fig. 4 Plot of the O···O distance for intermolecular hydrogen bonds found in amino(alkylphosphonic acid) crystal structures (taken from the CSD) *vs.* P–O(H) bond length

alkylphosphonates/phosphinates. It has already been observed that P–O(H) lengths in phosphonate groups are generally longer than those in phosphonic acid groups.[32] It appears that the single IEHB formed by the O(H) atoms in these P–O(H) bonds is generally stronger in the phosphonic groups than in the phosphonate groups, permitting the hypothesis that strong O–H···O IEHB bonding reduces the length of the corresponding P–O(H) bonds. A plot of P–O(H) distances *vs.* O···O distances in the corresponding IEHB bonds, shown in Fig. 4, indicates that generally a correlation exists between the P–O(H) bond length and the IEHB O···O distance. Shorter P–O(H) bonds are associated with shorter O–H···O IEHB distances for these molecules. In ligand **1b**, the P–O distances involving atoms O(12), O(23) and O(31) are 1.578, 1.538 and 1.546 Å while the corresponding O···O distances are 2.60, 2.51 and 2.52 Å.* Intermolecular hydrogen bonding involving the P–O(H) single bonds have O···O distances varying between 2.465 and 2.613 Å. It is often accepted that the different IEHB bond lengths and hence P–O(H) distances are due to constraints of molecular packing.[41] The mean IEHB distance is 2.545 Å, $\sigma_n = 0.046$, less than the contact (van der Waals) distance of two O atoms (3.00 Å).[33] The P=O bond length of 1.487 Å in ligand **1b** is 0.013 Å longer than the calculated mean for such bonds. It is intermediate between the mean value for a double bond and that for a partial double bond. With the limited amount of data available, there does not seem to be any correlation between the P=O lengths and the nature of the corresponding IEHB interactions, as noted previously.[32] The formation of the characteristic zwitterionic structure involves the deprotonation of a phosphonic acid group and the protonation of an N atom. The methylphosphonate groups around P(1) and P(2) are deprotonated in the structure of ligand **1b**. The P(1)–O(11) and P(1)–O(13) lengths of 1.499 and 1.497 Å indicate that the negative charge is spread over the O–P–O group and that the bonds are intermediate between single and double. In the other deprotonated methylphosphonate group, the P–O distances in P(2)–O(21) and P(2)–O(22) are 1.507 and 1.536 Å. This indicates that the P(2)–O(21) bond has more double-bond character than P(2)–O(22). Although the difference in the lengths of these bonds is almost certainly related to the nature of the IEHB interactions involving the O atoms, there does not seem to be any correlation between the P–O distances and the strength, nature or number of the IEHB bonds formed.

Hydrogen Bonding Interactions in Ligand **1b**.—The major hydrogen-bonding interactions in ligand **1b** are intermolecular in nature; of the seven IEHB bonds two are N–H···O interactions involving protonated N atoms in the macrocyclic ring and three are O–H···O interactions involving phosphonate and/or phosphonic O and OH atoms. The remaining two are O–H···O interactions, found between the water molecule [H(41)–O(4)–H(42)] and phosphonate O atoms, and show large deviations from linearity (158 and 159°), whilst those involving the phosphonate O and OH atoms are almost linear (171–178°). The O···O distances in ligand **1b** vary between 2.49 and 2.63 Å. The lengths in the two N–H···O IEHB bonds are similar but the angles around the H atoms are very different and show significant deviations away from linearity (160 and 149°). Although the QUANTA program did not find it in its search, there is also a possible weak intramolecular hydrogen bonding interaction between N(1) and O(13): N–H···O 97°, N–H 0.83, N···O 3.00, O···H 2.80 Å. This would result in the formation of a five-membered ring. The corresponding dihedral angle of N(1)–C(11)–P(1)–O(3) 11.8° is close to the eclipsed conformation which is necessary for the formation of such bonds. Although the formation of similar IAHB bonds in aqueous solution has also been suggested by Geraldes *et al.*[25] in studies on the protonation of ligand **1b**, the general inference from the crystal structure of **1b** is that IAHB would be diminished. In aqueous solution, the effect of hydrogen bonding to solvent may swamp any IAHB.

Angles of the Pendant Group.—The N–C–P angles in ligand **1b**, involving the protonated N atoms [N(1) and N(3)], are very similar, while those around N(2) in ligand **1b** and the 'same' atom in the corresponding copper(II) complex are the highest out of 58 studied N–C–P angles. The C–P–O and O–P–O angles fall into different groups depending on the nature of the P–O bonds. Mean angles and their standard deviations calculated using the data from 38 amino alkylphosphonic/phosphinic ligand X-ray structures are shown in Table 4. Only a small number of HO–P–OH and C–P=O angles could be

* The H atom connected to O(32) is disordered and as a result the nature of the O(32)–H(32)···O IEHB could not be determined.

included in the survey because they are only found in amino(alkylphosphonic acid) ligands containing unquaternised N atoms (ligand **1b**) or in ligands containing more than one methylphosphonate group attached to an N atom. As a result the mean values for these angles must remain tentative in the absence of more examples of their type. Two of the largest O–P–O angles in ligand **1b** occur between the two P–O partial double bonds [O(11)–P(1)–O(13) and O(21)–P(2)–O(22)]. Modified neglect differential overlap (MNDO) calculation shows that the O atoms involved in these angles are the most negatively charged. It therefore seems reasonable to suggest that these angles are the largest because of the increased Coulombic repulsion between the two O atoms, and the calculated mean value for this type of angle is larger than that for any of the other O–P–O or C–P–O angles (114.9°) in Table 4. It would appear, however, that IEHB and the subsequent packing involved during the crystallisation must have an effect on these angles as there is a difference of 4° between the two examples of this type of angle in ligand **1b**. Since the amino(alkylphosphonic acids) are analogues of the biologically important α amino acids, the analysis of the differences in IEHB and IAHB tendencies can be very important in the design of experiments using amino(alkylphosphonic acids) as biological substrates.[3] Recent work has demonstrated that hydrogen bonding of itself may be a major means by which anions are recognised in biological systems.[42]

Packing of Ligand **1b**.—Symmetry codes for IEHB are shown in Table 8. A single ligand molecule is involved in IEHB bonding interactions with *five* other ligand molecules. Atoms N(1), N(3) and O(11) have direct interactions with a second ligand molecule (ligand 2), while atoms O(13) and O(22) are indirectly 'attached' to ligand 2 *via* hydrogen-bonding interactions with the water molecule of crystallisation. Thus H(41)–O(4)–H(42) can be considered as a linking molecule which forms chains in the overall structure. Finally, atoms O(12) and O(21) are hydrogen-bonded to ligand 3, O(23) and O(33) to ligand 4, O(21) to ligand 5 and O(31) to ligand 6. This complicated set of strong intermolecular hydrogen bonds must have a significant stabilising effect on the overall structure of ligand **1b**.

Acknowledgements

We wish to thank SERC and Courtaulds Coatings for financial support, and acknowledge the use of the SERC funded Chemical Databank Service at Daresbury for part of the work described in this paper.

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Received 29*th May* 1992; *Paper* 2/02830A