First Structural Characterisation of an Amino Phosphonate Monoester Metal Complex

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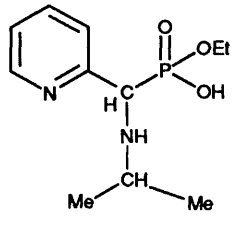
A new type of tetradentate amino phosphonate monoester has been synthesized by alkaline hydrolysis of the parent phosphonate diester; the crystal structure of its copper complex reveals a monoester ligand-bridged centrosymmetric dimeric five-co-ordinate copper(II) complex.

The increased interest in the synthesis of specific phosphorus ligands able to complex a range of biologically important metals for use in physiological media has prompted the use of a variety of structural motifs in order to enhance their potential suitability for use *in vivo*.[1–3] Amino phosphonic acids and their diesters have been widely used for a variety of applications,[4] but suffer from the disadvantage of rapid polymerisation in the presence of metal ions;[5] in addition the utility of the diesters is limited because of their low solubility in aqueous medium and weak complexation properties. With the intention of overcoming the limitations inherent in these species we are synthesizing new phosphonate monoesters which are designed to have properties intermediate between the acids and the diesters, and so form discrete complexes with enhanced solubility relative to the diester. Previous work has shown that phosphonate monoesters have interesting biological properties such as anti-cancer activity,[6] but so far very little is known about their metal complexing ability. We report here the first structural characterisation of an amino phosphonate monoester metal complex.

The new tetradentate monoester L was prepared by alkaline hydrolysis with NaOH of the corresponding diethyl phosphonate[7] in methanol in good yield (65%) and gave good elemental analysis.† The compound is a white crystalline, high melting material, stable in air and very soluble in water and all common polar solvents. Analysis by liquid secondary ion mass spectrometry (LSIMS)† shows a base peak corresponding to the monoester with the loss of the phosphonate arm. The ^{1}H NMR spectrum shows an ABX splitting pattern for the ester methylene protons, and the isopropyl methyl groups are diastereotopic due to the chiral carbon giving two doublets with a $\Delta\delta_H$ of 0.1 ppm which is confirmed by two separate methyl resonances observed in the ^{13}C NMR spectrum.



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From reaction of the monoester L (0.1 g, 0.30 mmol) with copper(II) chloride dihydrate (0.03 g, 0.18 mmol) in methanol (2 cm^3) a crystalline product has been isolated. The elemental analysis of the royal blue crystals obtained corresponded to an empirical formula CuLCl, and the LSIMS of the complex indicated a dimeric nature for the copper complex.‡ The magnetic moment obtained at 21 °C is 1.81 μ_B (9.27×10^{-24} J T^{-1}) per copper atom which is in the expected range for copper(II) complexes.[8] That there is no exchange interaction between the copper atoms is confirmed by powder EPR measurements which give an axial symmetrical spectrum with $g_{\|} = 2.272$ and $g_{\perp} = 2.050$.

The IR spectrum of the Cu^{II} complex shows significant differences from the ligand. A strong broad feature in the ligand (3385 and 3467 cm^{-1}) disappears leaving a band at 3167 cm^{-1} assigned to a co-ordinated secondary amine stretch. Broad bands associated with phosphonate OH stretches at 2543 cm^{-1}

† L·HCl·2H$_2$O (Found: C, 39.80; H, 7.40; N, 8.50. $C_{11}H_{19}N_2O_3P$·HCl·2H$_2$O requires C, 39.95; H, 7.30; N, 8.45%); m.p. 174–176 °C; mass spectrum (LSIMS): *m/z* 332 $[M + H]^+$ (not found), 259 (69%) $[M + H - HCl - 2H_2O]^+$, 149 (base peak) $[M + H - HCl - 2H_2O - HP(O)(OH)(OEt)]^+$. NMR (250 MHz): δ_H(Me$_2$SO, SiMe$_4$) 1.10 (3 H, t, ^3J 7.0, CH$_2$C*H*$_3$), 1.23 and 1.33 (6 H, 2d, ^3J 6.5, 2CHC*H*$_3$), 3.35 (1 H, septet, ^3J 6.5, C*H*CH$_3$), 3.86 (2 H, m, C*H*$_2$CH$_3$), 5.03 (1 H, d, J_{PH} 17.7, CHP), 7.55 (1 H, t, ^3J 6.9, β-NC$_5$H$_4$), 7.90 (1 H, d, ^3J 7.9, β′-NC$_5$H$_4$), 8.05 (1 H, t, ^3J 7.8, γ-NC$_5$H$_4$) and 8.69 (1 H, d, ^3J 4.5 Hz, α-NC$_5$H$_4$); δ_P(Me$_2$SO, H$_3$PO$_4$) 10.91; δ_C(Me$_2$SO, SiMe$_4$) 16.22 (d, $^3J_{PC}$ 5.9, CH$_2$*C*H$_3$), 17.8 and 18.5 (s, 2CH*C*H$_3$), 49.9 (d, $^3J_{PC}$ 4.9, *C*HCH$_3$), 55.8 (d, J_{PC} 134.9, CHP), 62.0 (d, $^2J_{PC}$ 6.2, *C*H$_2$CH$_3$), 124.1 (s, β-NC$_5$H$_4$), 125.1 (d, ^3J 3.5, β′-NC$_5$H$_4$), 138.6 (s, γ-NC$_5$H$_4$), 147.3 (s, α-NC$_5$H$_4$) and 150.7 (d, ^2J 5.5 Hz, α′-NC$_5$H$_4$).

‡ [Cu$_2$L$_2$Cl$_2$] (Found: C, 37.40; H, 5.00; N, 7.70. $C_{22}H_{36}Cl_2Cu_2N_4O_6P_2$ requires C, 37.10; H, 5.10; N, 7.85%); m.p. 225 °C (decomp.); mass spectrum (LSIMS): *m/z* 714 $[M + H]^+$ (not found), 642 (6) $[M + H - 2HCl]^+$, 578 (21) $[M + H - 2HCl - Cu]^+$, 321 (15), 277 (58), 211 (80), 149 (89%), 167 (base peak).

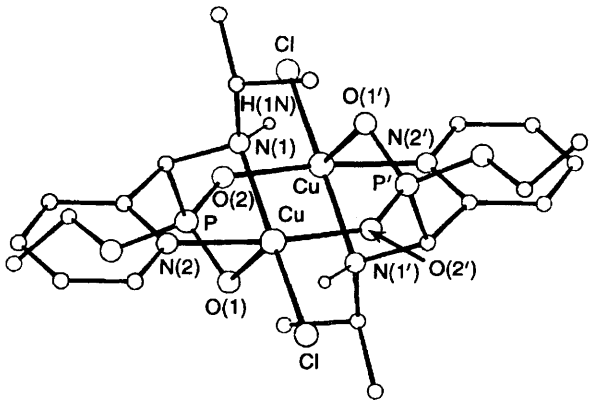

Fig. 1 A perspective view of the centrosymmetric ligand-bridged dimeric copper(II) complex $[Cu_2L_2Cl_2]$. Selected bond lengths (Å) and angles (°): Cu–Cl 2.236(3), Cu–O(1) 2.405(6), Cu–O(2') 1.957(7), Cu–N(1) 2.081(8), Cu–N(2) 2.028(8), H(1N) · · · O(1') 1.91; N(1)–Cu–Cl 166.2(2), N(2)–Cu–O(2) 172.5(3), O(1)–Cu–N(1) 82.92

completely disappear suggesting that the phosphonate oxygen is co-ordinating to the copper(II) ion. The pair of absorptions at 1629 and 1550 cm^{-1} in the ligand which are characteristic of the pyridyl group become much sharper (1609 cm^{-1}) indicating donation by the heterocyclic nitrogen. The phosphoryl (P=O) bands at 1230 cm^{-1} in the ligand shift to 1210 cm^{-1} indicating reduction of the double bond character of the P=O due to probable co-ordination to the metal.

X-Ray crystallography* shows a novel ligand-bridged centrosymmetric dimeric complex (Fig. 1) linked by bridging phosphoryl oxygen atoms reinforced by the two strong hydrogen bonds from the amino proton of one ligand to the phosphoryl oxygen of the second [H(1N) · · · O(1') 1.91, N(1) · · · O(1) 2.98 Å]. The co-ordination of each copper atom may be envisaged as distorted square pyramidal, the basal sites being occupied by two *cis* nitrogen atoms from the amine and pyridine groups [Cu–N(1) 2.081(8) and Cu–N(2) 2.028(8) Å respectively], a chlorine ligand [Cu–Cl 2.236(3) Å] and a bridging phosphoryl oxygen donor O(2') from the second monomer unit [Cu–O(2') 1.957(7) Å]; the apical site is occupied by a second phosphoryl oxygen atom giving a much longer bond, Cu–O(1) 2.405(6) Å. This is the first time that a metal complex of an amino phosphonate monoester has been structurally characterized, and it confirms the potential of this type of water soluble ligand to form metal complexes with limited oligomerization. This demonstrates a potential advantage of monoesters over the free acids and diesters in biological applications.

* Crystal data. $C_{22}H_{36}Cl_2Cu_2N_4O_6P_2$, M = 712.54, monoclinic, space group $P2_1/n$ (no. 14), a = 10.736(2), b = 8.439(2), c = 17.576(3) Å, β = 98.38(2)°, U = 1575.4 Å^3, Z = 4, $F(000)$ = 732, D_c = 1.502 g cm^{-3}, μ(Mo-Kα) = 1.63 mm^{-1}, λ = 0.710 69 Å. Crystal dimensions 0.41 × 0.48 × 0.50 mm. Full-matrix least-squares refinement with $w = 1/\sigma^2(F)$ applied to all reflections converged at R = 0.0543 (R' = 0.0542) for 1132 absorption corrected data[9] with $I/\sigma(I) \geqslant 3.0$.[10] Atomic coordinates, thermal parameters and bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1994, Issue 1, pp. xxiii–xxviii.

Acknowledgements

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