DALTON
FULL PAPER

Preparation of the copper(II) complex of the binucleating hexaaza macrocycle 2,5,8,17,20,23-hexaaza[9.9]paracyclophane and its solution chemistry, hydrolytic activity and acid dissociation kinetics ‡

Thomas Clifford,[a]* Andrew M. Danby,[a] Philip Lightfoot,[b] David T. Richens[b] and (the late) Robert W. Hay[b]†

[a] *Department of Chemistry, University of Kansas, Malott Hall, Lawrence, Kansas 66045, USA*
[b] *School of Chemistry, University of St. Andrews, St. Andrews, Fife, UK KY16 9ST*

Received 1st August 2000, Accepted 21st November 2000
First published as an Advance Article on the web 11th January 2001

The binucleating hexaaza macrocycle 2,5,8,17,20,23-hexaaza[9.9]paracyclophane (PEA) and its *N*-permethylated derivative 2,5,8,17,20,23-hexamethyl-2,5,8,17,20,23-hexaaza[9.9]paracyclophane (Me_6PEA) have been prepared. The copper(II) complex of PEA has been prepared and the stability constants of the copper complexes determined in aqueous solution by potentiometric and spectrophotometric methods. The protonation sites of PEA have been identified by NMR titration. The crystal structure of the complex $[Cu_2(PEA)Cl_3]^+Cl^-\cdot 2.6MeCN\cdot 2.9H_2O$ has been determined. The copper centres have an N_3Cl_2 donor set with a square pyramidal geometry. The Cu · · · Cu distance is 7.02 Å. The copper complex catalyses hydrolysis of the phosphotriester 2,4-dinitrophenyl diethyl phosphate (DNPDEP) and the $[Cu_2(PEA)(OH)_2]^{2+}$ and $[Cu_2(PEA)(OH)]^{3+}$ complexes have been identified as the active species. The acid catalysed dissociation of the copper complex has been studied by stopped-flow methods. The reaction is monophasic and displays saturation kinetics at high acidities.

Introduction

There has been considerable interest in the chemistry of binucleating macrocycles capable of incorporating two metal centres and the topic has been the subject of several recent reviews.[1] In part, this interest has arisen due to the occurrence of binuclear metal centres in enzymes such as red kidney bean purple acid phosphatase (see Fig. 1)[2] and urease.[3] Metal complexes of some binucleating hexaaza macrocycles form host–guest complexes with a range of anions such as maleate, pyrophosphate and triphosphate.[4] In addition they can display catalytic activity in the hydrolysis of phosphate derivatives[5] and peptides.[6] For these reasons we have been interested in the coordination chemistry of large ring macrocycles capable of incorporating two metal centres. There have been many studies of the acid catalysed dissociation of mononuclear complexes[7] but very few with binucleating macrocycles. Fernández-Trujillo *et al.*[8] have recently studied the acid catalysed dissociation of the binuclear copper(II) complex of the related *m*-xylyl bridged ligand, MEA (see Fig. 1).

In the present paper we describe the synthesis of the ligand PEA (Fig. 1) and its *N*-permethylated derivative and the characterisation of the copper complex of PEA. We have also determined formation constants for the copper(II) complexes by potentiometric and spectrophotometric methods and identified the major active species in the hydrolysis of 2,4-dinitrophenylphosphate (DNPDEP, Fig. 1) as the dihydroxy binuclear copper complex of PEA ($[Cu_2(PEA)(OH)_2]^{2+}$). The crystal structure of the binuclear complex $[Cu_2(PEA)Cl_3]^+Cl^-\cdot 2.6MeCN\cdot 2.9H_2O$ has been determined. The kinetics of the acid catalysed dissociation has been studied by stopped flow techniques.

† Deceased 8th January 1999 and submitted in his memory.
‡ Electronic supplementary information (ESI) available: 2-D NOESY NMR spectra, experimental details of the potentiometric, spectrophotometric and crystallographic studies. See http://www.rsc.org/suppdata/dt/b0/b006199i/

Experimental

Characterisation

Infrared spectra were recorded on a Perkin-Elmer 1710 Infrared Fourier Transform Spectrometer as KBr pellets. Melting points were obtained using a Gallenkamp melting point apparatus. Conductivities were measured in a Vernier conductivity probe and meter the method of calibration is discussed elsewhere.[9] UV/Visible spectra were recorded on a Lambda 14P Spectrometer, NMR spectra using a 200 MHz Varian Gemini, in D_2O (reference sodium 4,4-dimethyl-4-silapentane-1-sulfonate) or $CDCl_3$ (reference TMS).

Materials

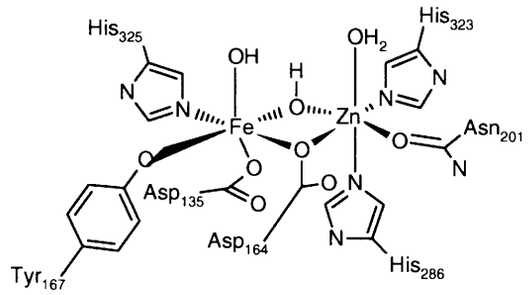
High purity potassium chloride, 3-azapentane-1,5-diamine (dien), copper salts, and sodium tetrahydroborate were obtained from Aldrich and used without further purification. Terephthalaldehyde was obtained from Avocado.

Synthesis

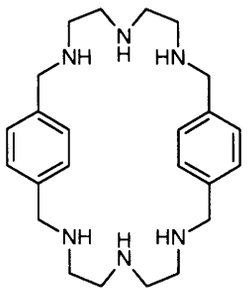
The ligand was prepared by a non-template [2+2] condensation of dien with terephthalaldehyde to form a tetramine followed by a $NaBH_4$ reduction.

2,5,8,17,20,23-Hexaaza[9.9]paracyclophane (PEA) I. Under a nitrogen atmosphere, a filtered acetonitrile solution (50 cm^3) of terephthalaldehyde (3 g, 22.4 mmol) was added dropwise (3 h) to a rapidly stirred acetonitrile solution (100 cm^3) of dien (2.93 g, 22.4 mmol). After approximately half of the dialdehyde had been added a fine white precipitate formed. The mixture was left stirring overnight before the solid was collected by filtration and dried at reduced pressure at 50 °C (4.15 g, 80%). The tetramine Schiff base could be recrystallised from toluene or ethyl acetate (if the temperature did not exceed 70 °C) but the crude product could be used directly in the reduction step.

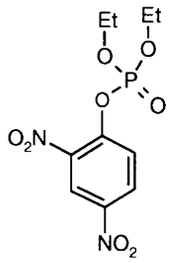
 DOI: 10.1039/b006199i



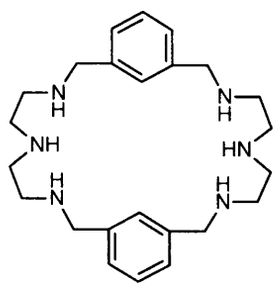
Purple Acid Phosphatase



PEA



DNPDEP



MEA

Fig. 1 2,5,8,17,20,23-hexaaza[9.9]paracyclophane (PEA) **I**, 2,4-dinitrophenyl diethyl phosphate (DNPDEP), red kidney bean purple acid phosphatase.

The Schiff base (4.15 g, 8.96 mmol) was dissolved in ethanol (100 cm^3) and cooled in an ice bath. With rapid stirring, $NaBH_4$ (6 g) was added in 0.5 g quantities. The mixture was left stirring overnight, then acidified with concentrated hydrochloric acid (until pH was less than 2) and ethanol added (30 cm^3). The white precipitate of crude PEA was filtered off and dried at 50 °C at reduced pressure. The solid was redissolved in water (100 cm^3) and basified with sodium hydroxide (a white precipitate formed immediately). The mixture was extracted with dichloromethane (4 × 20 cm^3), the extracts were combined and dried over anhydrous sodium sulfate. The solid residue, after removal of solvent, was recrystallised from hot (70 °C) toluene giving fine white needles of compound **I** (3.42 g, 82%) (Found: C, 70.21; H, 9.35; N, 20.44%. Calc. for $C_{12}H_{19}N_3$: C, 70.20; H, 9.33; N, 20.47%). $\tilde{\nu}_{max}/cm^{-1}$: 3340s, broad(O–H str.); 3293, 3227, 2942, 2901s(N–H str.); 2873, 2800, 2731s (C–H str); 1503, 1471(N–H bend); 1447, 1434, 1139, 1122, 1113, 1018(C–N bend); 998, 969, 945, 926, 817, 800, 485(KBr).

2,5,8,17,20,23-Hexamethyl-2,5,8,17,20,23-hexaaza[9.9]paracyclophane hydrochloride hydrate (1/6/1.5) (Me_6PEA·6HCl·1.5H_2O) II. Formic acid (8 cm^3, 98%), formaldehyde (7 cm^3, 35% aqueous solution) and compound **I** (1.52 g, 3.21 mmol) were refluxed under argon for 18 hours. The solution was cooled and basified with sodium hydroxide (9 g) in water (10 cm^3) then extracted with dichloromethane (3 × 20 cm^3). The combined extracts were dried over $MgSO_4$. Removal of the solvent at reduced pressure gave the crude product as a pale yellow oil. This was dissolved in ethanol (*ca.* 20 cm^3) and concentrated HCl (37%) added until the solution became turbid. The white precipitate formed was filtered off, washed first with Pr^iOH and then diethyl ether. The product was recrystallised from aqueous methanol and dried at reduced pressure (2.42 g, 91%) (Found: C, 48.80; H, 7.96; N, 11.26%. Calc. for $C_{30}H_{59}Cl_6N_6O_{1.5}$: C, 48.66; H, 8.03; N, 11.35%). $\tilde{\nu}_{max}/cm^{-1}$(KBr):3453s broad (O–H str.); 2975s (C–H str.); 2663, 2380s broad (N^+–H str.); 1664s (N^+–H bend); 1537, 1474, 1439, 1230 (C–N str.); 1113, 947, 791, 567 (KBr).

[Cu_2(PEA)Cl_4]·3H_2O·MeOH 1. Copper(II) chloride dihydrate (0.832 g, 4.88 mmol) was dissolved in ethanol (20 cm^3) and added dropwise to a boiling solution ethanol solution (20 cm^3) of compound **I** (1.0 g, 2.44 mmol). After half the copper dichloride had been added to the rapidly stirred amine solution, a fine pale blue-green precipitate formed. This was filtered off, washed with ethanol (3 × 10 cm^3) and diethyl ether (1 × 10 cm^3) and dried at reduced pressure at 50 °C. The complex was further purified by dissolving it in aqueous methanol (*ca.* 50%) then adding an equal volume of acetonitrile to give blue plate like crystals which were washed with ethanol and air dried (1.65 g, 88%) (Found: C, 39.10; H, 5.52; N, 11.06%. Calc. for $C_{25}H_{48}Cl_4Cu_2N_6O_4$: C, 39.22; H, 6.32; N, 10.98%). $\tilde{\nu}_{max}/cm^{-1}$: 3404s (O–H str.), 3182s (N–H str.); 2879s (C–H str.); 1617m (N–H bend); 1520, 1451, 1065, 1019 (C–N str.); 871, 837, 803 (CH_2 rock); 656, 478 (KBr). λ_{max}/nm ($\varepsilon_{max}/dm^3\ mol^{-1}\ cm^{-1}$) 617(238), water Λ_M /S $cm^2\ mol^{-1}$ 391 (water).

Potentiometric titrations

Potentiometric titrations were carried out using a Radiometer ABU9 Autoburette dispensing sodium hydroxide solution (0.1 mol dm^{-3}) into a ligand solution (*ca.* 1 × 10^{-3} mol dm^{-3}) also containing appropriate amounts of copper(II) (approximately 1:1 or 1:2 ligand to copper ratios or in absence of copper(II)) maintained at 25.0 °C. The ionic strength was adjusted to 0.1 mol dm^{-3} with potassium chloride as the protonated forms of the ligand gave insoluble nitrate salts. The titrations were carried out under nitrogen throughout. The pH was measured with an Orion Ross combination electrode calibrated with borate and phthalate buffers. A value of $10^{-13.86}$ $mol^2\ dm^{-6}$ for K_w was assumed. NaOH (prepared from dilution of a Rhone Poulenc Volucon ampule) was standardised with potassium hydrogenphthalate. Carbonate contamination of the NaOH was checked by Gran's method (> 0.5%). Hydrochloric acid solutions were standardised against standard sodium hydroxide and the copper(II) nitrate stock solution by EDTA complexometric titration. All sample solutions were prepared with freshly boiled out water cooled in a nitrogen stream. Plots of pH *versus* the volume of standard sodium hydroxide added were collected on a Radiometer VIT90 and passed to an Elonex 386 PC. The methods used to pick the species model have been described elsewhere.[10] Equilibrium constants were calculated using HYPERQUAD.[11] Eight curves with a total of 327 points were used in calculation of the protonation constants and six curves with a total of 205 points in calculation of the copper complexation constants.

NMR titrations

Deuteriated compounds were obtained from Aldrich. NMR spectra were obtained in D_2O, the required pH being adjusted with NaOD (30% w/w in D_2O) or DCl (37% in D_2O). Quoted ^{13}C chemical shifts are relative to sodium 4,4-dimethyl-4-silapentane-1-sulfonate (Aldrich) dissolved in D_2O and sealed into a capillary. The ligand concentration was approximately 0.01 mol dm^{-3}. Spectra were recorded on a Varian Gemini

200 MHz Spectrometer. 2-D spectra (HMQC, heteronuclear multiple quantum correlation, and NOESY) were obtained on a Bruker 500 MHz spectrometer.

Spectrophotometric titrations

Under approximately the same conditions as for the potentiometric titrations, a visible spectrum (wavelength range 850–400 nm) was taken after each aliquot of standard sodium hydroxide (0.1 mol dm^{-3}) was added. Spectra taken at 28 H^+ concentrations (26 wavelengths) in duplicate, giving a total of 1456 data points, were used in the calculation. The data were processed using the HYPERQUAD suite of programs. Details of the computation of the copper(II) binding constants with PEA were carried out by procedures described in detail elsewhere.[11]

Kinetic measurements

Phosphate ester hydrolysis. The hydrolysis of the triester DNPDEP was measured spectrophotometrically by following the production of 2,4-dinitrophenolate at 360 nm with a Lambda 14P Spectrometer. The temperature was maintained at 25 ± 0.1 °C by a Perkin-Elmer Peltier System. Solutions at various pH were prepared by making up solutions 4.65×10^{-3} mol dm^{-3} with respect to Cu^{II} and 2.52×10^{-3} mol dm^{-3} with respect to PEA with the buffers MES (2-morpholinoethanesulfonic acid) (pH 5.0–6.0), HEPES (6.5–7.5), TAPS {3-[tris(hydroxymethyl)methylamino]propanesulfonic acid} (8.0–9.0), CHES [2-(*N*-cyclohexylamino)ethanesulfonic acid] (9.5) and CAPS [3-(cyclohexylamino-1-propanesulfonic acid] (10.5) at 0.05 mol dm^{-3} and the pH noted immediately before initiation of the reaction using a glass electrode. Ionic strength was adjusted to 0.1 mol dm^{-3} with KCl. The reaction was initiated by the addition of a 2 μl acetonitrile stock solution of DNPDEP to a 2 cm^3 sample of the solution in a 1 cm path length plastic cuvette. The final DNPDEP concentration was 2×10^{-4} mol dm^{-3}. For slow reactions (below pH 7) data were collected over one half-life only, then the infinity value was obtained after two weeks at room temperature. Above pH 7 data could be collected up to three half-lives. The absorbance *vs.* time curves were fitted by a first order rate equation using a linear least squares method (quoted rates are the averages of two runs). Duplicate runs showed that the rate constants could be replicated to within 5%.

Acid hydrolysis of the $[Cu_2(PEA)Cl_4]\cdot 3H_2O\cdot MeOH$ complex. The acid catalysed dissociation of the copper(II) complex of PEA occurred rapidly and was measured spectophotometrically at 640 nm using a Hi-Tech SF-51 stopped-flow spectophotometer. Hydrochloric acid solutions (Volucon standard concentrate) adjusted to $I = 0.1$ mol dm^{-3} were used. Pseudo first order conditions were maintained by using at least a tenfold excess of acid. Values of k_{obs} were obtained by fitting the experimental data by a single exponential and quoted k_{obs} are the averages of at least 3 runs. Rapid scan spectrophotometry was carried out using a Spectrascan rotating monochromator accessory with the Hi-Tech SF-51 stopped flow instrument. Temperature was maintained to ± 0.1 °C using a Heto thermostatted bath of circulating water.

X-Ray determination of the crystal structure of $[Cu_2(PEA)Cl_3]^+\text{-}Cl^-\ 2.6MeCN\cdot 2.9H_2O$

A single crystal of $[Cu_2(PEA)Cl_3]^+Cl^-\cdot 2.6MeCN\cdot 2.9H_2O$ was grown by diffusion of acetonitrile into an aqueous methanolic solution of the complex to give well formed dark blue blocks. The crystals were efflorescent so the experiment was run at low temperature (120 K).

Crystal data. $C_{29.19}H_{51.60}Cl_4Cu_2N_{8.60}O_{2.90}$, $M = 838.37$, orthorhombic, space group *Ibca* (no. 73), $a = 14.971(8)$, $b = 42.24(4)$, $c = 25.32(3)$ Å, $U = 16012(26)$ Å^3, $Z = 16$, μ(Mo-Kα) = 13.68 cm^{-1}, 5676 reflections measured, 3195 independent (R_{int} = 0.0164), 2306 observed ($I > 2\sigma[I]$), $wR2 = 0.3101$, $R1 = 0.1011$.

Structure analysis and refinement. Structure solution and refinement were carried out using SHELXTL.[12] Cu, Cl and N atoms were refined anisotropically, C and O isotropically. Hydrogens were included but not refined. The rather large *R* factor reflects the samples weak scattering of X-rays. Intensity data were collected only to 38° in 2θ. Considerable difficulty was also encountered in modeling the disordered solvent present in the structure. Unfortunately the ease with which solvent was lost from the crystals prevented determination of the degree of solvent of crystallisation by microanalysis of fresh samples of the complex. A freshly recrystallised sample was found to give a stable weight after 15 min. Microanalysis of this sample indicated the presence of at least three water molecules. IR spectra of fresh samples showed no CN stretch attributable to acetonitrile however acetonitrile had to be included in the structure to give a reasonable fit. Three acetonitrile and one water site were disordered and modeled in two orientations with refined occupancies of 0.40(2) for N(4S)–C(6S) and O(4) and 0.60(2) for N(4S′)–C(6S′) and N(7S)–C(9S). Restraints on the displacement parameters of the light atoms in the cation were required for the refinement to achieve convergence.

CCDC reference number 186/2281.

See http://www.rsc.org/suppdata/dt/b0/b006199i/ for crystallographic files in .cif format.

Results and discussion

Synthesis

Reaction of dien with *tert*-phthalaldehyde in acetonitrile gives the tetraimine in reasonable yield and purity to allow $NaBH_4$ reduction to the amine without further purification. Although this [2+2] addition reaction has found great utility in recent years to prepare large macrocycles, Pietraszkiewicz and Gasiorowski[13] have reported that the reaction in THF results in formation of polymeric material, indicating that these reactions are very solvent dependant. The amine is simply purified by recrystallisation from toluene to give analytically pure crystalline material. The amine can also fully be methylated by the standard Eschweiler–Clarke[14] procedure which is a distinct improvement, in terms of yield and ease of synthesis, on the halogenoalkane [1 + 1] cyclisation route of Paoletti and co-workers.[15]

With copper(II), PEA forms a binuclear complex, but even after prolonged drying at reduced pressure the microanalytical data showed the presence of solvent of crystallisation. The presence of solvent has been noted in similar complexes.[16] The copper(II) complex has a molar conductivity greater than 300 S cm^2 mol^{-1} which, although rather low for a 1:4 electrolyte,[17] may be due to the bulky nature of the complex, as conductivity will depend upon the ionic mobility. Low ionic mobility has been used to explain the unusually low conductivities of tetraphenylborate salts.[18] The visible spectrum of the complex (absorption coefficient 119 dm^3 mol^{-1} cm^{-1} per copper centre) is consistent with a d^9 five-co-ordinate metal ion.

Description of the crystal structure of $[Cu_2(PEA)Cl_3]^+Cl^-\cdot 2.6MeCN\cdot 2.9H_2O$

Assorted bond lengths and angles are collected in Table 1. The copper centres have an N_3Cl donor set, with square pyramidal geometry. Three nitrogens from the macrocycle and one of the chlorides make up the base of the pyramid with the copper somewhat displaced above the plane towards the apical chloride (as is commonly found with square pyramidal complexes). The apical chloride is directed away from the macrocyclic cavity

Table 1 Assorted bond lengths (Å), angles (°) and Cu···Cu (Å) separation for $[Cu_2(PEA)Cl_3]^+Cl^-\cdot 2.6MeCN\cdot 2.9H_2O$

Cu(1)–Cl(2)	2.731(5)	Cl(1)–Cu(1)–Cl(2)	96.6(2)
Cu(1)–Cl(1)	2.241(5)	N(1)–Cu(1)–Cl(2)	88.8(5)
Cu(1)–N(1)	2.03(2)	N(2)–Cu(1)–Cl(2)	90.7(5)
Cu(1)–N(2)	1.99(2)	N(3)–Cu(1)–Cl(2)	87.9(5)
Cu(1)–N(3)	2.02(2)	N(1)–Cu(1)–N(2)	85.5(7)
Cu(2)–Cl(4)	2.56(2)	N(1)–Cu(1)–N(3)	83.8(6)
Cu(2)–Cl(3)	2.270(8)	Cl(3)–Cu(2)–Cl(4)	104.2(3)
Cu(2)–N(4)	2.01(2)	N(6)–Cu(2)–Cl(3)	97.7(7)
Cu(2)–N(5)	2.00(2)	N(5)–Cu(2)–Cl(3)	171.7(6)
Cu(2)–N(6)	2.06(2)	N(4)–Cu(2)–Cl(3)	95.2(6)
Cu(1)···Cu(2)	7.02	N(6)–Cu(2)–N(5)	83.9(9)
		N(6)–Cu(2)–N(4)	168.0(9)

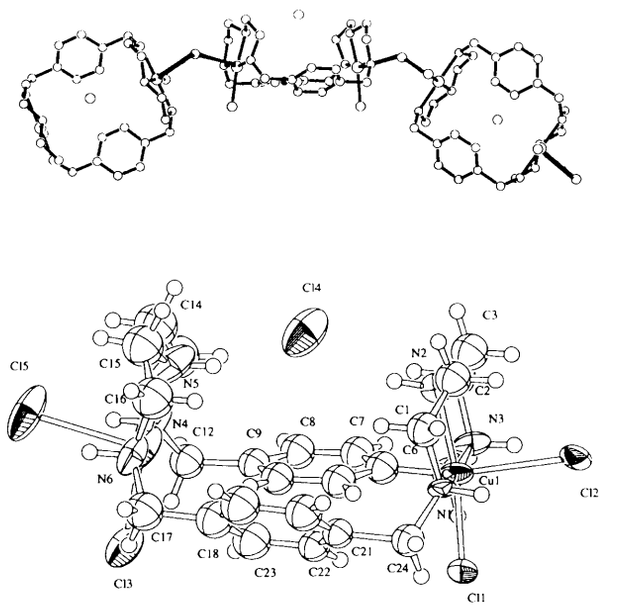


Fig. 2 An ORTEP[19] diagram of $[Cu_2(PEA)Cl_3]^+Cl^-\cdot 2.6MeCN\cdot 2.9H_2O$ showing the atom labeling scheme and ball-and-stick diagram showing chloro-bridging. Solvent molecules not shown. Thermal ellipsoids are at 50% probability.

to form a bridge to a copper center in an adjacent macrocycle. One of the bridging chlorides is located on a crystallographic 2-fold axis and the other just off this axis. The bridging occurs throughout the structure to form chains of chloro-bridged complexes running parallel to the *b* axis (Fig. 2). The copper to nitrogen distances are not unusual (the mean distance found for five-co-ordinate secondary amine complexes in the Daresbury database is 2.029 Å compared to 2.01(2) Å for this complex). The copper to chloride distance is normal for the basal chloride but that to the apical chloride is a little longer than expected and may be due to a small degree of electron withdrawal in bridge formation. The Cu···Cu distance is 7.02 Å.

The complex has C_2 symmetry with the reflection plane bisecting the Cu···Cu axis. The nitrogen donor ends of the ligand are folded back-to-back giving a basket like structure with the benzene rings forming the base of the basket and one unbound chloride within the cavity.

Potentiometric titration

A speciation plot is shown in Fig. 3 and the β constants are collected in Table 2. As for the related ligand studied by Martell and co-workers,[20] the weakly basic nitrogens may be assigned to the amino groups at ring positions 5 and 20, Coulombic repulsion from the two adjacent protonated benzylic nitrogens (positions 2 and 8, 17 and 23) favours deprotonation of the nitrogens 5 and 20.

The protonation sites were confirmed by measurement of the chemical shift of the ^{13}C resonances over the pH range

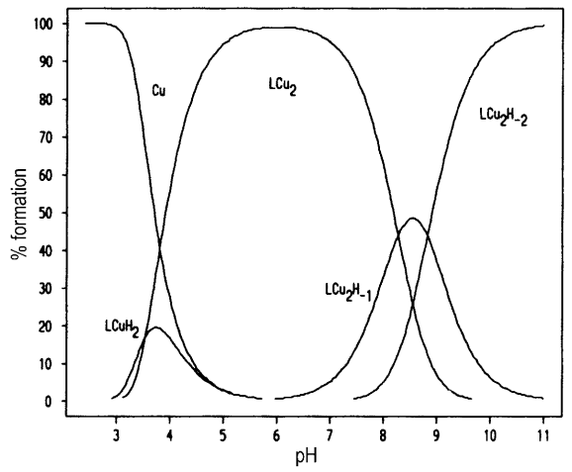


Fig. 3 % speciation curves of metal complexes in the presence of two equivalents of copper(II).

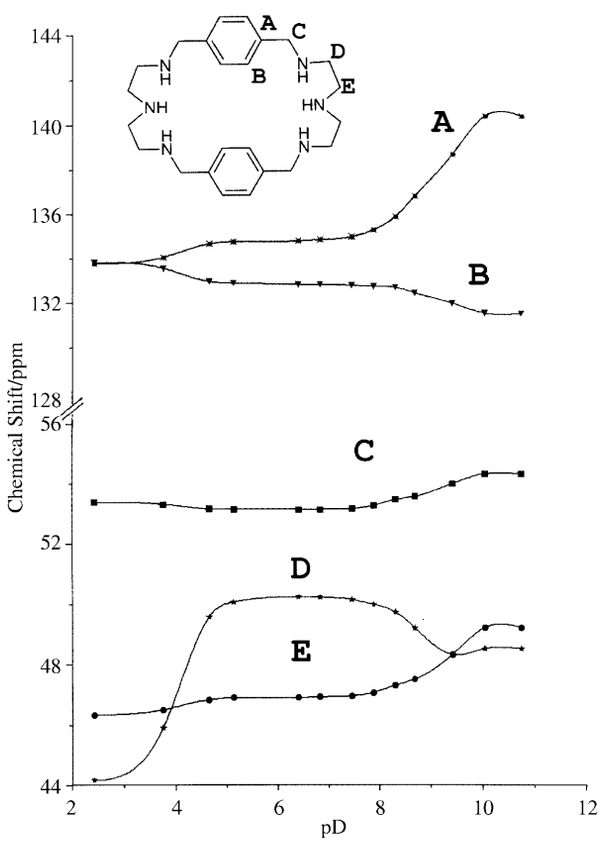


Fig. 4 Variation of ^{13}C NMR chemical shifts of PEA resonances with pH, and assignments.

2.5 to 11. Unambiguous assignment of the ^{13}C resonances as made possible by correlating ^{13}C resonances to ^{1}H signals using the 2-D NMR technique HMQC. Proton spectra assignments were made by identifying NOEs found in NOESY spectra (see ESI).

In the acidic region (pH 2 to 5) the resonance of carbon D (labeling scheme in Fig. 4) shows a large upfield shift (shielding) on protonation, indicative of a carbon β to an amine protonation site. This is consistent with protonation of H_4L at ring positions 5 and 20 to form H_6L. Inspection of the basic region (pH 8 to 11) confirms that amine nitrogens located at ring positions 2, 8, 17 and 23 are involved in formation of the species HL, H_2L, H_3L and H_4L. Protonation of the ligand at these sites results in an upfield movement (shielding) of the ^{13}C resonance of carbon E, consistent with its position β to the amine protonation sites. The ^{13}C resonance of carbon D

Table 2 Protonation constants and copper(II) stability constants of PEA

Ion	Reaction	log β	Symbol
H^+	$L + H^+ \rightleftharpoons [HL]^+$	9.48 ± 0.01	β_1
	$L + 2H^+ \rightleftharpoons [H_2L]^{2+}$	18.355 ± 0.009	β_2
	$L + 3H^+ \rightleftharpoons [H_3L]^{3+}$	26.58 ± 0.01	β_3
	$L + 4H^+ \rightleftharpoons [H_4L]^{4+}$	33.95 ± 0.01	β_4
	$L + 5H^+ \rightleftharpoons [H_5L]^{5+}$	36.87 ± 0.02	β_5
	$L + 6H^+ \rightleftharpoons [H_6L]^{6+}$	40.44 ± 0.01	β_6
Cu^{2+}	$L + 2Cu^{2+} \rightleftharpoons [M_2L]^{4+}$	25.24 ± 0.03	β_{LM2}
	$L + 2Cu^{2+} + OH^- \rightleftharpoons [M_2L(OH)]^{3+}$	16.96 ± 0.02	β_{LM2OH}
	$L + 2Cu^{2+} + 2OH^- \rightleftharpoons [M_2L(OH)_2]^{2+}$	8.13 ± 0.06	$\beta_{LM2(OH)2}$
	$L + Cu^{2+} + 2H \rightleftharpoons [MLH_2]^{4+}$	29.75 ± 0.05	β_{LMH2}

Table 3 Copper(II) stability constants of PEA determined spectrophotometrically

Ion	Reaction	log β	Symbol
Cu^{2+}	$L + 2Cu^{2+} \rightleftharpoons [M_2L]^{4+}$	25.27 ± 0.04	β_{LM2}
	$L + 2Cu^{2+} + OH^- \rightleftharpoons [M_2L(OH)]^{3+}$	16.11 ± 0.10	β_{LM2OH}
	$L + 2Cu^{2+} + 2OH^- \rightleftharpoons [M_2L(OH)_2]^{2+}$	8.77 ± 0.12	$\beta_{LM2(OH)2}$
	$L + Cu^{2+} + 2H \rightleftharpoons [MLH_2]^{4+}$	29.37 ± 0.13	β_{LMH2}

shows a downfield (deshielding) movement indicative of a ^{13}C resonance α to the amine protonation site. Such behaviour has also been observed in protonation of amino acids,[21] peptides[22] and amines.[23]

Titration in the presence of copper indicated the formation of binuclear complexes and of hydroxo species at higher pH. Although previous potentiometric studies of similar binucleating ligands have demonstrated significant amounts of mononuclear species, this ligand appears to be almost exclusively binucleating. The initial model picked for the input for SUPERQUAD included a number of hydroxo and protonated mononuclear complexes. The first minimisation with curves from titrations of PEA in the presence of one equivalent of copper(II) gave reasonably low error values, but on introducing stability constants for the binuclear species resulted in rejection of hydroxo and neutral species in subsequent runs; those mononuclear species left (the protonated copper complexes) had poor standard deviations and their presence did not significantly decrease sigma. All, apart from the minor complex $CuLH_2$, were removed from the model and the final calculated equilibrium constants derived from these calculations are presented in Table 2. Although the related polyazacyclophane, MEA, investigated by Martell and co-workers,[20] gives a number of other mononuclear complexes, the MH_2L species have formation constants of comparable magnitude (log β_{LMH2} is 29.75 and 29.86 for ligands PEA and MEA respectively), however the formation constant for the binuclear complex is rather larger for PEA (log β_{LM2} is 25.24 for PEA compared to 23.47 for MEA).

After obtaining this interesting result we investigated the system spectrophotometrically to check the validity of this equilibrium model.

Spectrophotometric titration of PEA

Stability constants determined spectrophotometrically are shown in Table 3. The species model for the copper PEA system determined spectrophotometrically compares exceedingly well with that of the potentiometric method and confirms the hypothesis that the introduction of a rigid spacer has increased the tendency of this molecule to form binuclear complexes. This may be due to two factors: stabilisation of the binuclear complexes and destabilisation of the mononuclear complexes. The presence of the unco-ordinated end of the molecule possibly makes the co-ordinated end more strained, resulting in destabilisation of the mononuclear complexes. When both sets of donors become co-ordinated to form a binuclear complex a lower energy conformation is formed, resulting in extra stabilisation of the binuclear complex. Large macrocycles with much greater flexibility are able to form more stable mononuclear complexes by simultaneous co-ordination of both donor sets to a single metal centre [OBISDIEN (1,4,7,13,16,19-hexaaza-10,22-dioxacyclotetracosane) for example], a binding mode prevented by the presence of the *p*-xylyl linkages.

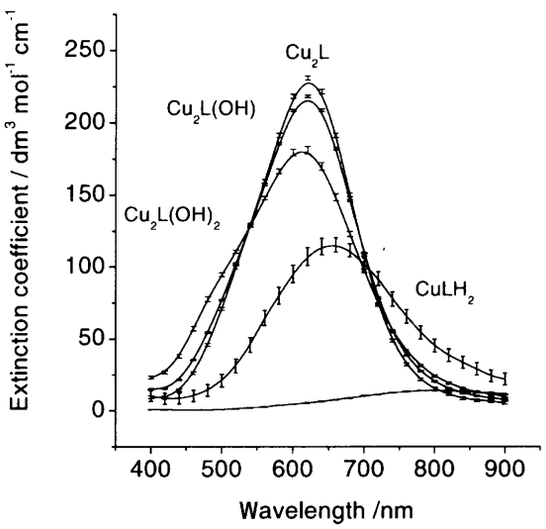


Fig. 5 Visible spectra of the species $CuLH_2$, Cu_2L, $Cu_2L(OH)$, and $Cu_2L(OH)_2$ calculated from the spectrophotometric titration data.

Comparison with MEA suggests that the *p*-xylyl linkages have increased the stability of the binuclear complex relative to that with *m*-xylyl linkages and substantially destabilised the mononuclear complexes resulting in only a single protonated mononuclear copper PEA complex $[Cu(PEA)H_2]^{4+}$.

The extraction of absorption coefficients (Fig. 5) for the species found in solution by HYPERQUAD shows that the ε_0 of the mononuclear species, *per copper centre*, is nearly the same as that of the binuclear species, inferring that the co-ordination geometries of the metal centres are approximately the same, the magnitude suggesting a five-co-ordinate geometry. The hydroxo complexes are blue shifted as one might expect for co-ordination of higher field ligands.

DNPDEP hydrolysis kinetics

The solvolytic and hydroxide contributions to the hydrolysis of DNPDEP have been investigated in an earlier publication[24]

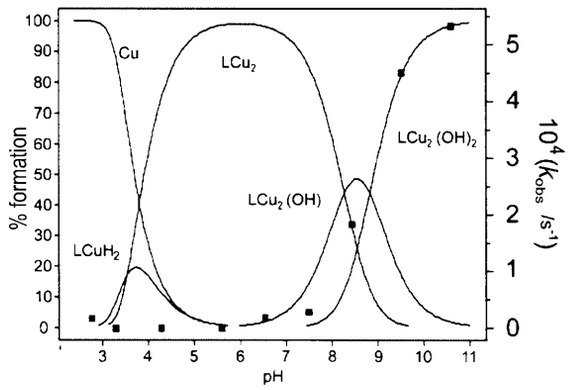


Fig. 6 pH Dependence of the Cu_2(PEA) promoted hydrolysis of DNPDEP (filled squares) superimposed over % species in aqueous solution (solid lines).

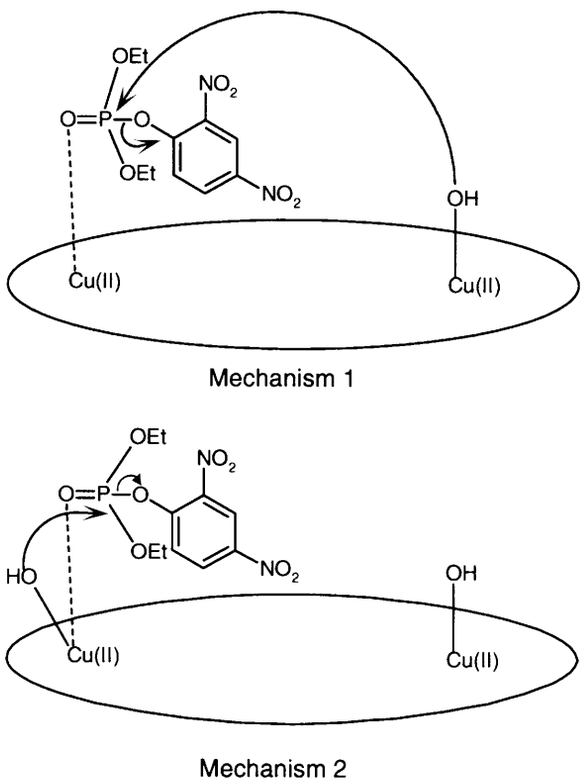


Fig. 7 Diagram showing the mechanism of Cu_2PEA promoted hydrolysis of DNPDEP.

and were shown to occur *ca.* 2 orders of magnitude slower than the complex catalysed hydrolysis. The pseudo first order rate constants for hydrolysis of DNPDEP are plotted over a scaled diagram of the species distribution curves of PEA in the presence of two equivalents of copper(II) in Fig. 6. The low activity below pH 7 but substantial rate increases above pH 7 are consistent with the hypothesis that the active species is a hydroxo species. The midpoint of the sigmoidal curve is at approximately 8.8 pH units, indicating that the active species has a pK_a at approximately this pH. The pK_a of the dihydroxo binuclear PEA species (8.83) matches the kinetic pK_a the closest, therefore this is likely to be the active species. The monohydroxo dicopper complex may also be active but cannot be the only active species as the observed rate is still seen to increase above pH 8.5 even though the concentration of the monohydroxo species is decreasing above pH 8.5. This suggests that the attacking and co-ordination sites reside on the same copper centre (Fig. 7) rather than on separate copper atoms. Of course this does not preclude the possibility that the two mechanisms are operating at similar rates simultaneously.

Table 4 k_{obs} for acid catalysed dissociation of $[Cu_2(PEA)]^{4+}$

$10^3[H^+]$/ mol dm^{-3}	*T*/°C					
	19.7	24.4	29.3	34.1	38.9	43.9
49.1	0.74	1.14	1.72	2.71	3.95	6.28
36.8	0.73	1.11	1.68	2.56	3.75	5.62
24.5	0.65	1.01	1.56	2.37	3.37	5.09
12.3	0.55	0.89	1.35	1.95	2.94	4.16
4.91	0.44	0.65	0.98	1.40	2.04	2.83
3.68	0.39	0.58	0.83	1.21	1.68	2.33
2.45	0.29	0.45	0.61	0.92	1.23	1.75
1.23	0.16	0.26	0.34	0.46	0.62	0.77
0.49	0.05	0.10	0.12	0.17	0.22	0.32

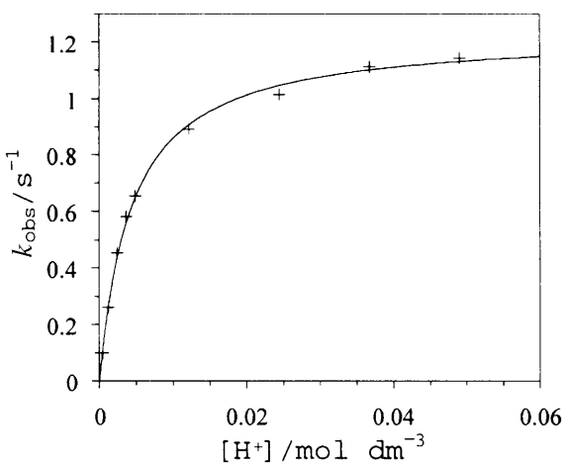


Fig. 8 $[H^+]$ Dependence of the acid dissociation rate (k_{obs}) of $[Cu_2$-(PEA)$]^{4+}$.

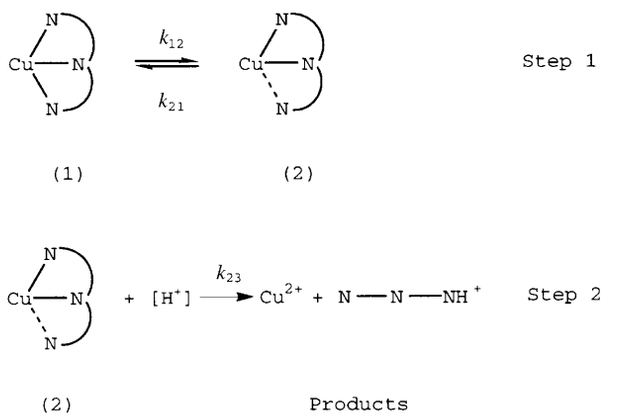
However the Cu···Cu separation suggests that mechanism 2 might be unlikely.

Acid dissociation kinetics

The acid dissociation of $[Cu_2(PEA)Cl_4]\cdot 3H_2O\cdot MeOH$ displayed simple pseudo first order kinetics and there was no evidence of a biphasic reaction. Time lapse rapid scanning spectrophotometric measurements show simple first order decay of the d–d transition at *ca.* 640 nm and the changes in the molar absorption coefficient indicate that the reaction being observed is metal dissociation of the 2:1 copper:ligand complex. This result suggests that both metal centres in the complex act independently of each other and have identical dissociation rates. Values of k_{obs} over a range of temperatures and acidities are summarised in Table 4 and Fig. 8 shows a plot of k_{obs} *vs.* $[H^+]$ at 24.4 °C. At each temperature the reaction demonstrates saturation kinetics with an initial linear dependence of k_{obs} on $[H^+]$, but at higher concentrations of $[H^+]$ k_{obs} becomes independent of hydrogen ion concentration. The linear parts of the plots at low acidities all intercept the origin indicating the absence of a solvolytic pathway resulting in metal ion dissociation which is sometimes observed in reactions of this type. The dissociation can be represented as shown in Scheme 1. One nitrogen donor is dissociated from the metal ion without its replacement by a solvent molecule and remains within the inner co-ordination sphere (Step 1). This activated species is susceptible to protonation after which the complex rapidly dissociates (Step 2). Application of the steady state assumption to species 2 leads to the rate equation $k_{obs} = k_{12}k_{23}[H^+]/(k_{21} + k_{23}[H^+])$. Since $K = k_{12}/k_{21}$, $k_{obs} = k_{23}K[H^+]/(1 + k_{23}k_{21}^{-1}[H^+])$. Values of k_{12}, $k_{23}K$ and k_{23}/k_{21} were determined for each temperature and are summarised in Table 5. The temperature dependence of k_{12} gives the activation parameters $E_a = 68 \pm 1$ kJ mol^{-1}, $\Delta H^{\ddagger} = 66 \pm 1$ kJ mol^{-1} and $\Delta S^{\ddagger} = -22 \pm 3$ J K^{-1} mol^{-1}.

Table 5 Rate and equilibrium constants for the acid catalysed dissociation of $[Cu_2(PEA)]^{4+}$

T/°C	k_{12}/s^{-1}	$k_{23}K$/dm^3 mol^{-1} s^{-1}	$k_{23}k_{21}^{-1}$/dm^3 mol^{-1}
19.7	0.79	182.6	231.2
24.4	1.23	281.2	229.1
29.3	1.90	381.0	200.6
34.1	2.97	513.4	173.0
38.9	4.38	711.0	162.7
43.9	6.97	892.0	128.2



Scheme 1

Recently Fernández-Trujillo and co-workers[8] have studied the acid dissociation kinetics of the binuclear copper(II) complex of MEA. This dissociation is also monophasic and clearly exhibits a solvolytic reaction with $k_0 = 14 \pm 3$ s^{-1} at 25 °C. In this case the rate equation is $k_{obs} = k_0 + k_{23}K[H^+]/(1 + k_{23}k_{21}^{-1}[H^+])$ which gives a value of $k_{12} = 118$ s^{-1}. Interestingly this value is some 100-fold greater than for PEA. Macrocyclic complexes usually have k_{12} values in the range[25] 0.005 to 0.5 s^{-1} while open chain ligands have much faster rates.[26] $[Cu_2(MEA)]^{4+}$ behaves more like an open-chain polyamine ligand with respect to the lability of the Cu–N bond, whereas the Cu–N bond of $[Cu_2(PEA)]^{4+}$ is much less labile having a k_{12} value closer to that determined for smaller polyamine macrocycles. The absence of a solvolytic dissociation pathway for PEA is to be expected due to the bulk of the macrocyclic ligand preventing a solvent water molecule from entering the coordination sphere of the metal.

Acknowledgements

MOD is acknowledged for the funding of this project. Dr N. Govan is thanked for guidance at CBDE, Porton Down, and Dr Douglas R. Powell, University of Kansas, for a second look at the crystallography data.

References

1 D. E. Fenton, *Adv. Inorg. Bioinorg. Mech.*, 1983, **2**, 187; T. Sorrel, *Tetrahedron*, 1989, **45**, 3; D. E. Fenton and H. Okawa, in *Perspectives in Bioinorganic Chemistry*, eds. R. W. Hay, J. R. Dilworth and K. B. Nolan, JAI Press, Connecticut, 1993, vol. 2.
2 T. Klabunde and B. Krebs, *Struct. Bonding* (*Berlin*), 1997, **89**, 177; D. Gani and J. Wilkie, *Struct. Bonding* (*Berlin*), 1997, **89**, 133; N. Sträter, W. N. Lipscomb, T. Klabunde and B. Krebs, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2025.
3 N. E. Dixon, C. Gazzola, R. L. Blakeley and B. Zerner, *J. Am. Chem. Soc.*, 1975, **97**, 4131; J. B. Sumner, *J. Biol. Chem.*, 1926, **69**, 435; E. Jabri, M. H. Lee, R. P. Hausinger and P. A. Karplus, *J. Mol. Biol.*, 1992, **227**, 934.
4 T. F. Pauwels, W. Lippens, G. G. Herman and A. M. Goeminne, *Polyhedron*, 1998, **17**, 1715.
5 P. Jurek and A. E. Martell, *Inorg. Chim. Acta*, 1999, **287**, 47; D. A. Nation, Q. Lu and A. E. Martell, *Inorg. Chim. Acta*, 1997, **263**, 209.
6 L. Bordignon, T. Marilde, B. Szpoganicz, M. Rizzoto, A. E. Martell and M. G. Basallote, *Inorg. Chim. Acta*, 1997, **254,** 345.
7 See, for example, W.-J. Lau and C.-S. Chung, *J. Chem. Soc., Dalton Trans.*, 1994, 191 and references therein.
8 M. J. Fernández-Trujillo, B. Szpoganicz, M. A. Máñez, L. T. Kist and M. G. Basallotte, *Polyhedron*, 1996, **15**, 3511; M. G. Basallote, J. Durán, M. J. Fernández-Trujillo and A. Máñez, *J. Chem. Soc., Dalton Trans.*, 1999, 3817.
9 R. J. Angelici, in *Synthesis and Technique in Inorganic Chemistry*, W. B. Saunders Company, London, 1977.
10 A. E. Martell and R. J. Motekaitis, in *Determination and Use of Stability Constants*, VCH, New York, 1988.
11 P. Gans, A. Sabatini and A. Vacca, *Talanta*, 1996, **43**, 1739.
12 G. M. Sheldrick, SHELXTL Version 5, Reference Manual, Bruker-AXS, Madison, WI, 1994.
13 M. Pietraszkiewicz and R. Gasiorowski, *Chem. Ber.*, 1990, **123**, 405.
14 W. Eschweiler, *Chem. Ber.*, 1905, **38**, 880.
15 C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, C. Giorgi, P. Paoletti, A. Stefani and B. Valtancoli, *Inorg. Chem.*, 1995, **34**, 552.
16 C. J. McKenzie, H. Toftlund, M. Pietraszkiewicz, Zb. Stojec and K. Slowinski, *Inorg. Chim. Acta*, 1993, **210**, 143.
17 M. Sneed and J. Maynard, *General Inorganic Chemistry*, Van Nostrand, New York, 1942, p. 813.
18 J. F. Coetzee and G. P. Cunningham, *J. Am. Chem. Soc.*, 1969, **91**, 568.
19 C. K. Johnson, ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.
20 R. Menif, A. E. Martell, P. J. Squattrito and A. Clearfield, *Inorg. Chem.*, 1990, **29**, 4723.
21 A. R. Quirt, J. R. Lyerla, I. R. Peat, J. S. Cohen, W. F. Reynolds and M. H. Freeman, *J. Am. Chem. Soc.*, 1974, **96**, 570.
22 M. Christl and J. D. Roberts, *J. Am. Chem. Soc.*, 1972, **94**, 4565.
23 J. G. Batchelor, *J. Am. Chem. Soc.*, 1975, **97**, 3410; M. Periasamy, *Heterocycles*, 1982, **18**, 127; J. G. Batchelor, J. Feeney and G. C. K. Roberts, *J. Magn. Reson.*, 1975, **20**, 19; J. E. Sarneski, H. L. Surprenant, F. K. Molen and C. N. K. Reilley, *Anal. Chem.*, 1975, **47**, 211.
24 R. W. Hay and N. Govan, *Polyhedron*, 1996, **15**, 2381.
25 R. W. Hay, M. P. Pujari and R. Bembi, *Transition Met. Chem.*, 1986, **11**, 261.
26 L. H. Chen and C. S. Chung, *Inorg. Chem.*, 1989, **28**, 1402.