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FULL PAPER

Methyl pyridine derivatives of 14-membered tetraaza macrocycles. A new host with high selectivity for cadmium †

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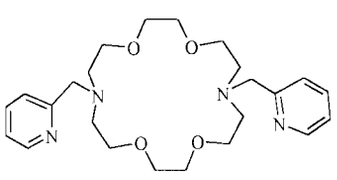
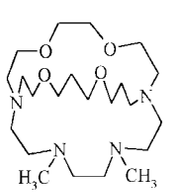
Two *N*-(2-pyridylmethyl) derivatives of a 14-membered tetraaza macrocycle containing pyridine have been synthesized, L^1 and L^2. The protonation constants of these compounds and the stability constants of complexes of both ligands with Co^{2+} to Zn^{2+}, Cd^{2+}, Pb^{2+}, Fe^{3+} and In^{3+} were determined by potentiometric methods at 25 °C and ionic strength 0.10 mol dm^{-3} in KNO_3. The values of the protonation constants for L^1 and L^2 are quite different. The metal complexes of both ligands present lower values of stability constants than expected. The only exception is the case of the Cd^{2+} complex with L^2 which exhibits a particularly high stability constant, indicating that this ligand has a remarkable selectivity for this metal ion relative to zinc. The Cd^{2+} complex seems to be the only one to bond to all the donor atoms of the ligand or at least to more than the other metal ions studied. The pM values determined at physiological pH, which take into account the competition of the protons for the ligand, have shown that L^2 is the most selective compound for cadmium relative to zinc. The single crystal structure of $[CuL^2][ClO_4]_2$ determined by X-ray diffraction has shown that the co-ordination geometry around the copper atom can be described approximately as a distorted square pyramid. To achieve this geometric arrangement the macrocycle adopts a folded conformation. Furthermore the nitrogen atom of one free pyridylmethyl pendant arm is directed towards the copper centre leading to a distance between these two atoms of 3.304(11) Å, which suggests a weak bonding interaction consistent with a [5+1] co-ordination.

Introduction

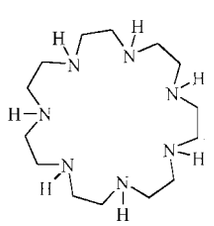
Although many complexes of macrocyclic ligands having 2-pyridylmethyl pendant arms have been studied in the last two decades, specially triaza-[1–5] and tetraaza-macrocycles,[6–11] values of stability constants have only been determined for the tetraoxadiaza macrocycle, $py_2[18]aneN_2O_4$, see below.[12] As the



$py_2[18]aneN_2O_4$



[N,N-2.2.2]



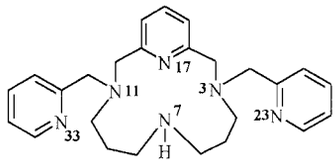
$[21]aneN_7$

N-pyridyl derivatives of macrocyclic compounds and their complexes are soluble in organic media, they mediate effective membrane transport of alkali, alkaline-earth, and some first-row transition and inorganic ammonium cations.[13]

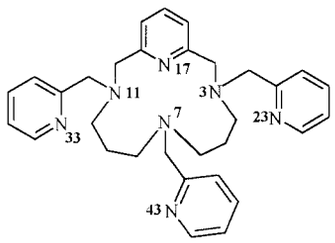
† *Supplementary data available*: rotatable 3-D crystal structure diagram in CHIME format. See http://www.rsc.org/suppdata/dt/1999/4331/

It was found that the thermodynamic stability constants of *N*-(2-pyridylmethyl) derivatives of linear amines with the divalent first-row-transition metal ions were higher than expected taking into account the low σ-donating ability of the pyridyl groups and consequently the low overall basicity of these compounds.[14] Additionally, it was found that in general, linear amines with pyridyl substituents show high affinities for heavy metals, such as cadmium, lead or mercury, and very low affinities for Mg^{2+} and Ca^{2+}. This property assists the removal from the environment or from living bodies (chelation therapy) of these toxic metal ions. Lehn *et al.*[15] have found that the cryptand [N,N-2.2.2] is very selective for cadmium, leaving Zn^{2+} and Ca^{2+} untouched. This cryptand displays a very high selectivity (10^6) for Cd^{2+} with respect to Zn^{2+}, with even higher ratios for lead (10^9) and mercury (10^{18}).[15b] However two major drawbacks for the general use of this ligand are its high cost and its relatively slow kinetics of complex formation.[12] Among the polyaza macrocycles $[21]aneN_7$ exhibits a relatively high selectivity for Cd^{2+} ($10^{4.77}$) in relation to Zn^{2+} [16] and Hancock *et al.*[12] have found that $py_2[18]aneN_2O_4$ is very selective for Pb^{2+} ($10^{4.7}$ and $10^{8.1}$ with respect to Zn^{2+} and Ca^{2+}, respectively). In spite of the lower selectivity of this macrocycle in comparison to those of the cryptand [N,N-2.2.2] the authors have considered $py_2[18]aneN_2O_4$ as a potential lead-detoxifying agent.[12]

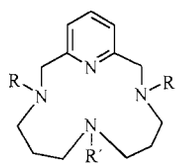
The promising results of Hancock *et al.*[12] obtained for *N*-pyridyl derivatives of macrocyclic ligands with heavy metal ions, and their ability of being lipid-soluble compounds and being able to cross artificial or natural membranes make them useful for the study of heavy metals inside cells,[13,17] prompted us to undertake a detailed study of two 2-pyridylmethyl derivatives of L^3, with two, L^1, and three pendant arms, L^2. Since the relative selectivity for different metals strongly depends on the overall basicity of the ligands, the acid–base behaviour of both compounds was studied and their stability constants with a



L^1



L^2



L^3 - R = R' = H

L^4 - R = CH_2CO_2H; R' = H

L^5 - R = R' = CH_2CO_2H

large range of metal ions, such as Ca^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Ga^{3+}, Fe^{3+}, and In^{3+}, were determined.

Experimental

Reagents

The parent macrocycle L^3 was synthesized by previously reported procedures.[7c,18] All the chemicals were of reagent grade and used as supplied without further purification. The reference used for the ^1H NMR measurements in D_2O was 3-(trimethylsilyl)propanoic acid-d_4 sodium salt and in $CDCl_3$ the solvent itself. For ^{13}C NMR spectra 1,4-dioxane was used as internal reference.

Synthesis

3,11-Bis(2-pyridylmethyl)-3,7,11,17-tetraazabicyclo[11.3.1]-heptadeca-1(17),13,15-triene (L^1). This compound was prepared and purified as described by Moore *et al.*[7c] To the yellow oil obtained was added 3 equiv. of HCl and the white salt, which precipitated, was characterised. Yield: 75%, mp 235 °C (decomp.). NMR (D_2O, pD = 3.55): δ 2.31 (4 H, q), 3.29 (4 H, t), 3.33 (4 H, t), 4.22 (4 H, s), 4.24 (4 H, s), 7.32 (2 H, d), 7.59 (4 H, m), 7.77 (1 H, t), 8.04 (2 H, t) and 8.70 (2 H, d). ^{13}C NMR (D_2O, dioxane): δ 22.52, 48.74, 51.42, 58.03, 59.71, 121.38, 122.01, 122.95, 136.38, 136.51, 148.66, 157.72 and 157.72. Found: C, 49.9; H, 7.1; N, 14.0. Calc. for $C_{25}H_{35}N_6Cl_3\cdot 4H_2O$: C, 50.2; H, 7.3; N, 14.1%.

3,7,11-Tris(2-pyridylmethyl)-3,7,11,17-tetraazabicyclo-[11.3.1]heptadeca-1(17),13,15-triene (L^2). To a solution of L^3 (4.5 mmol; 1.06 g) in dichloromethane (45 cm^3) was added a solution of NaOH (27 mmol; 1.08 g) in water (40 cm^3) and then a solution of 2-chloromethylpyridine hydrochloride (13.6 mmol; 2.4 g) in water (15 cm^3) was added dropwise over a period of 4 h. The mixture was stirred for 48 h at room temperature, and the organic layer separated. The aqueous layer was extracted with dichloromethane (6×80 cm^{-3}), the organic layers dried with $MgSO_4$ and concentrated under vacuum. The dark yellow oil obtained was purified through a neutral alumina (100–125 mesh) column (30 × 2.5 cm) and eluted with a mixture of dichloromethane/methanol (95 : 5 v/v). To the bright yellow oil obtained was added 3 equiv. of HCl and the pure compound precipitated as a white salt. Yield: 55%, mp 210 °C (decomp.). NMR (D_2O, pD = 4.8): δ 1.75 (4 H, q), 2.71 (8 H, m), 3.88 (2 H, s), 3.93 (4 H, s), 3.99 (4 H, s), 7.16 (4 H, m), 7.25 (2 H, d), 7.30 (2 H, d), 7.62 (1 H, t), 7.72 (3 H, m), 8.22 (1 H, d) and 8.33 (2 H, d). ^{13}C NMR (D_2O, dioxane): δ 21.26, 51.47, 51.62, 57.81, 58.90, 59.75, 123.90, 124.24, 125.00 (d), 125.46, 138.35 (d), 138.86, 148.62, 148.96, 151.90, 153.82 and 154.40. Found: C, 57.2; H, 7.0; N, 14.9. Calc. for $C_{31}H_{40}N_7Cl_3\cdot 2H_2O$: C, 57.0; H, 6.8; N, 15.0%.

CAUTION: although no problems were found in this work, perchlorates in the presence of organic matter are potentially explosive and should be prepared in small quantities.

$[CuL^2][ClO_4]_2$. $Cu(ClO_4)_2\cdot 6H_2O$ (1.27×10^{-4} mol, 0.047 g) was added to a stirred solution of L^2 (1.28×10^{-4} mol, 0.065 g) dissolved in a minimum volume of water (≈2 cm^3) and the pH increased to 5 by addition of KOH. The mixture was stirred for 2 h and then concentrated to dryness. The residue was taken up in methanol, the precipitate formed was filtered off and the filtrate was again concentrated to dryness and dissolved in acetonitrile. Blue crystals were formed in six weeks by slow evaporation of the solvent. Yield: ≈90%. Found: C, 48.1; H, 5.0; N, 12.9. Calc. for $C_{31}H_{37}N_7O_8CuCl_2$: C, 48.4; H, 4.8; N, 12.7%.

Potentiometric measurements

Reagents and solutions. Metal ion solutions were prepared at about 0.025 mol dm^{-3} from the nitrate salts of the metals, of analytical grade with demineralized water (obtained by a Millipore/Milli-Q system) and were standardised as described.[19] The solutions of the trivalent metal ions were kept in excess nitric acid to prevent hydrolysis. Carbonate-free solutions of the titrant, KOH, were obtained, maintained and discarded as described.[18,19]

Equipment and work conditions. The equipment used was as described previously.[18,19] The temperature was kept at 25.0 ± 0.1 °C; atmospheric CO_2 was excluded from the cell during the titration by passing purified argon across the top of the experimental solution in the reaction cell. The ionic strength of the solutions was kept at 0.10 mol dm^{-3} with KNO_3.

Measurements. The $[H^+]$ of the solutions was determined by the measurement of the electromotive force of the cell, $E = E'^\circ + Q\log[H^+] + E_j$. E'°, Q, E_j and $K_w = ([H^+][OH])$ were obtained as described previously.[19] The term pH is defined as $-\log [H^+]$. The value of K_w was found to be $10^{-13.80}$ mol^2 dm^{-6}.

The potentiometric equilibrium measurements were made on 20.00 cm^3 of $\cong 2.50 \times 10^{-3}$ mol dm^{-3} ligand solutions diluted to a final volume of 30.00 cm^3, in the absence of metal ions and in the presence of each metal ion for which the $c_M : c_L$ ratios were 1 : 1 and 2 : 1. A minimum of two replicates were made.

For Cu^{2+} solutions with both ligands and the Cd^{2+} solution of L^2, the degree of formation of the metal complexes at the beginning of the titration was too high for the use of the direct potentiometric method, and the values of stability constants were determined by ligand–ligand competitive titrations. For the Cu^{2+} cases, trien (triethylenetetramine) was used as the second ligand, for which values of protonation and stability constants have been determined before under these experimental conditions.[20] For $[CdL^2]^{2+}$, cdta (*trans*-1,2-cyclohexylenedinitrilo-*N*,*N*,*N*′,*N*′-tetracetic acid) was used and the value for $[CuL^2]^{2+}$ was also confirmed by competitive titration with cdta. However, for $[CuL^1]^{2+}$ other second ligands were tried without success, such as edta (ethylenedinitrilo-*N*,*N*,*N*′,*N*′-tetracetic acid), and dtpa (diethylenetrinitrilo-*N*,*N*,*N*′,*N*″,*N*″-pentacetic acid). For the determination of the stability constants of the Fe^{3+} complexes of L^2 a direct redox method was used[21] and the same method was also used for the In^{3+} complexes taking advantage of the competition between Fe^{3+} and In^{3+} for the ligand, at pH = 2.[21] The constants for the

Ga^{3+} complexes were too low to be determined and therefore precipitation of hydrolysed gallium species occurred at low pH values.

The competition reactions reached equilibrium only after 15 to 60 min at each point of the titration in the pH range where the competition reaction was carried out. The same values for the stability constants were obtained either using direct or back titration curves.

Calculation of equilibrium constants. Protonation constants $K_i^H = [H_iL]/[H_{i-1}L][H]$ were calculated by fitting the potentiometric data obtained for the free ligand to the SUPERQUAD program.[22] Stability constants of the various species formed in solution were obtained from the experimental data corresponding to the titration of solutions of different metal ion to ligand ratios, also using the SUPERQUAD program. The initial computations were obtained in the form of overall stability constants, $\beta_{M_mH_hL_l}$ values, $\beta_{M_mH_hL_l} = [M_mH_hL_l]/[M]^m[L]^l[H]^h$.

Only mononuclear species, ML, MHL and M-HL ($\beta_{M\text{-}HL} = \beta_{MLOH} \times K_W$) were found. Differences, in log units, between the values β_{MHL} (or $\beta_{M\text{-}HL}$) and β_{ML} provide the stepwise protonation reaction constants, shown in Table 2. The errors quoted are the standard deviations of the overall stability constants given directly by the program for the input data which include all the experimental points of all titration curves. The standard deviations of the stepwise constants were determined by the normal propagation rules.

The protonation constants were obtained from 150 to 170 experimental points (3 titration curves) for both ligands. The stability constants for each metal ion were determined from 100 to 150 experimental points (2 to 4 titration curves). All the points of a titration were used in the calculations except for those obtained with a simultaneous formation of a precipitate, which generally do not stabilise.

Hydrolysis species of the trivalent metal ions. The constants for the hydrolytic species formed by the trivalent metal ions studied in this work were taken from the literature, reported and previously discussed.[20,21]

Spectroscopic studies

^{1}H NMR spectra were recorded with a Bruker CXP-300 spectrometer at probe temperature. Solutions of the ligands for the measurements (≈0.01 mol dm^{-3}) were made up in D_2O and the pD was adjusted by addition of DCl or CO_2-free KOD with an Orion 420A instrument fitted with a combined Mettler Toledo U-402M3 microelectrode. The $-\log [D^+]$ was measured directly in the NMR tube, after the calibration of the microelectrode with buffered aqueous solutions. The final pD was calculated from pD = pH* + 0.40.[23] The value of pH* corresponds to the reading of the pH meter previously calibrated with two standard aqueous buffers at pH 4 and 7.[23] Phase-sensitive nuclear Overhauser effect spectroscopy (NOESY) was performed by collecting 4096 (t_2) × 512 (t_1) data points, using standard Bruker pulse programs. A 10.4 μs pulse width corresponding to 90° flip angle and a delay of 150 ms for the mixing time were used.

Crystallography

Single-crystals of $[CuL^2][ClO_4]_2$ **1** suitable for X-Ray determination were grown from a CH_3CN solution at room temperature. X-Ray data were measured using a MAR research image plate system using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) at room temperature. The selected single crystal, sealed in a glass capillary, was positioned 70 mm from the plate. 95 frames were collected with an exposure time of 5 min and a scan of 2° per frame. Data analysis was performed with the XDS program.[24] Intensities were not corrected for absorption effects.

Crystal data. $C_{31}H_{37}Cl_2CuN_7O_8$, $M = 770.12$, orthorhombic, space group $P2_12_12_1$, $a = 9.891(11)$ $b = 12.416(14)$, $c = 26.812(29)$ Å, $V = 3293(6)$ Å^3, $Z = 4$, $D_c = 1.554$ Mg m^{-3}, $F(000) = 1596$, $\mu = 0.888$ mm^{-1}.

The intensities of 8400 observations were collected of which 5688 were independent reflections giving a R_{int} of 0.1071. The structure was solved by direct methods and subsequent difference Fourier syntheses and refined by full-matrix least-squares refinement on F^2 using the SHELX97 software package.[25] Anisotropic displacements were refined for all non-hydrogen atoms. Hydrogen atoms were introduced in the refinement at idealized geometric positions with a $U_{iso} = 1.2 \times U_{eq}$ of the parent carbon atom. The final refinements of 444 parameters converged to $R = 0.1294$ and $R' = 0.2986$ for all unique *hkl* data and to $R = 0.0933$ and $R' = 0.2644$ for 4136 observed reflections with $I > 2\sigma(I)$.

Since the space group $P2_12_12_1$ is polar the absolute configuration was investigated inverting all co-ordinates ($x,y,z \rightarrow -x, -y, -z$), but unfortunately the values of the Flack parameter obtained in both cases indicate that the crystal chirality could not be determined with reliability from the X-ray data set. Molecular diagrams were drawn with graphical package PLATON.[26]

CCDC reference number 186/1726.

See http://www.rsc.org/suppdata/dt/1999/4331/ for crystallographic files in .cif format.

Results and discussion

Synthesis of macrocyclic ligands

Compound L^1 was prepared as described by Moore *et al.*[7c] However the trisubstituted derivative, L^2, was only observed to form in the synthesis of the first compound[7c] but was not characterized or studied before. Compound L^2 was prepared in this work by a similar procedure using a larger amount of 2-chloromethylpyridine. However a small percentage of L^1 was nevertheless formed due to the difficulty of introduction of the third arm on the nitrogen facing the pyridine of the macrocycle backbone. This is presumably due to the steric hindrance in this nitrogen by the carbon atoms of the adjacent propane chains. A similar but worse problem was found in the synthesis of the *N*-tris(carboxymethyl) derivative of the same parent macrocycle.[19,27]

Acid–base behaviour

The acid–base reactions of L^1 and L^2 have been studied by potentiometric and ^{1}H NMR spectroscopic techniques. The corresponding protonation constants are summarised in Table 1, together with values of other compounds for comparison. The compound L^1 has six basic centres, the constants of three of them could be determined by the potentiometric method and one more was obtained by the ^{1}H NMR spectroscopic titration. From the seven basic centres of L^2 only three were determined by potentiometry and two by the ^{1}H NMR titration.

The values of the protonation constants of L^1 and L^2 are quite different, in spite of an almost equal overall basicity (log β_4 of about 21). Indeed, the first protonation constant is higher for the first compound but all the other values are higher for the second one. The overall basicities of both compounds are low when compared with that of the parent macrocycle L^3 (log $\beta_4 \approx 24$)[18] or with that of compounds having the same ring framework but with *N*-carboxymethyl arms, L^4 and L^5 (≈ 24 and ≈26 for the bis- and tris-derivatives, respectively).[19] A similar decrease in the overall basicity of the derivatives having pyridylmethyl arms has been already verified for linear amines.[14,28]

^{1}H NMR titrations of L^1 and L^2 were carried out to clarify the protonation sequence of these compounds. Fig. 1 and 2 show the titration curves and the ^{1}H NMR spectra of L^1 at

Table 1 Protonation (log K_i^H) constants of L^1, L^2, other macrocycles and the cryptand [N,N-2.2.2] for comparison. $T = 25.0$ °C; $I = 0.10$ mol dm^{-3} in KNO_3

Equilibrium constant	L^1	L^2	L^3 [a]	$py_2[18]N_2O_4$ [b]	[N,N-2.2.2] [c]	[21]aneN_7 [d]
[HL]/[L] × [H]	10.65(1)	8.16(2)	9.92	7.44	10.01	9.83
$[H_2L]/[HL] \times [H]$	5.75(1)	6.20(2)	8.56	6.26	8.92	8.84
$[H_3L]/[H_2L] \times [H]$	3.29(2)	4.30(3)	4.66	1.38	2.75	6.72
$[H_4L]/[H_3L] \times [H]$	1.7(1) [e]	1.9(1) [e]	<1	—	—	4.04
$[H_5L]/[H_4L] \times [H]$	<0.5 [e]	1.3(1) [e]	—	—	—	2.43
$[H_6L]/[H_5L] \times [H]$	—	—	—	—	—	2.30
$[H_4L]/[L] \times [H]^4$	21.39	20.56	<24.1	—	—	29.43

[a] Ref. 18. [b] $I = 0.10$ mol dm^{-3} in $NaNO_3$, ref. 12. [c] $I = 0.10$ mol dm^{-3} in $N(Me)_4NO_3$ or $N(Me)_4Cl$, ref. 15(*b*). [d] $I = 0.15$ mol dm^{-3} in $NaClO_4$, ref. 16. [e] Determined by ^{1}H NMR titration, calculated as in ref. 23.

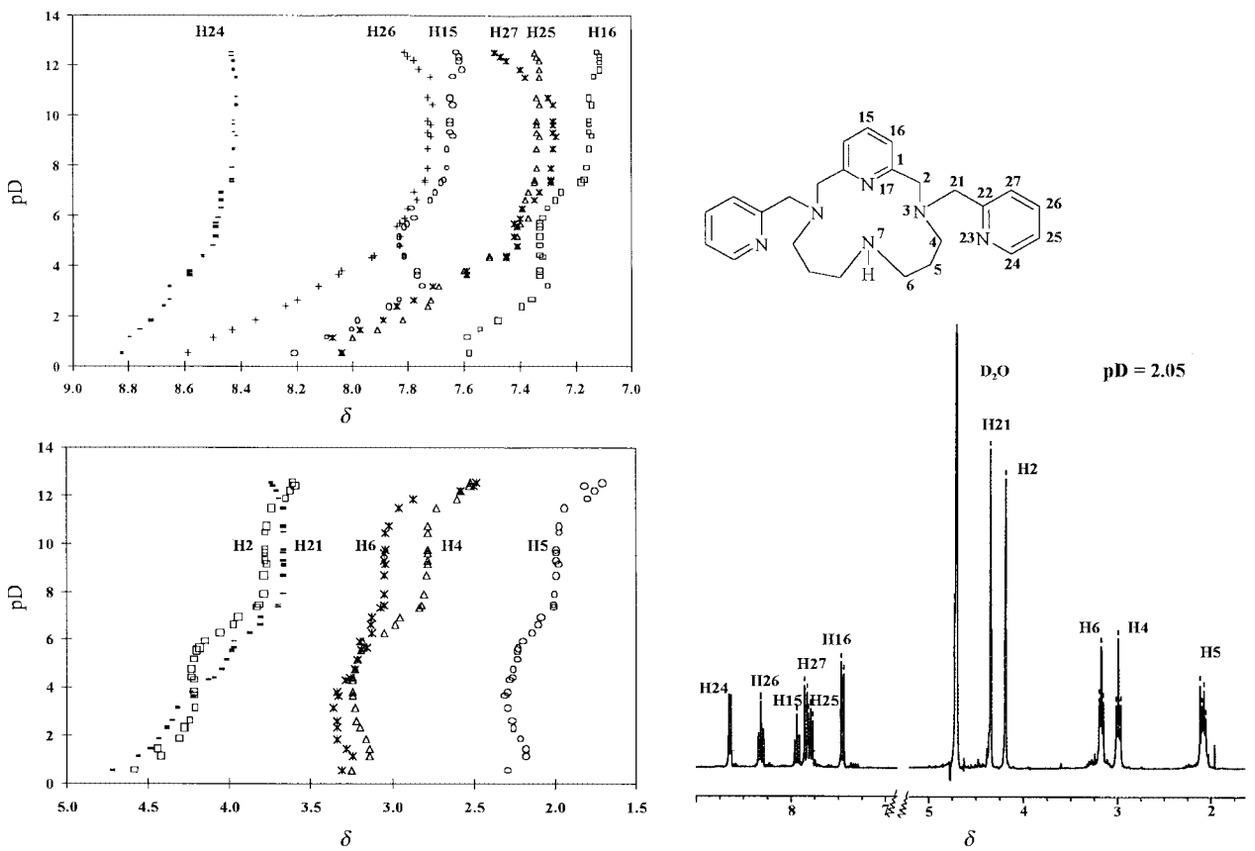


Fig. 1 ^{1}H NMR titration curves, pD as a function of the chemical shift (δ), for L^1 and the spectrum of this ligand at pD 2.05. Note that due to the large range of chemical shifts exhibited by this compound all the spectra are divided into two regions and presented here in two diagrams, for a better observation of the shift of each resonance with pD.

pD = 2.05 and of L^2 at pD = 6.59, respectively. These figures also include the labelling scheme used for the assignment of resonances.

Each ^{1}H NMR spectrum of L^1 recorded at different pD values shows eleven resonances for almost the entire pD range. The assignment of the resonances was managed by phase-sensitive NOESY experiments performed at pD = 10.85 and 2.05 and taking into account the pattern of each absorption and the area ratio, see Fig. 1.

The ^{1}H NMR titration curves show that the first equivalent of acid added to the basic form of L^1 ($n = 1$, where n is the number of equivalents of acid added per mole of macrocycle), above pD values of 10.5, protonates mainly the nitrogen N7 since resonances H6 and H5 shift to low-field, the latter to a smaller extent due to its larger distance from the centre being protonated. A slight shift of resonances H4 and H2 indicates a small percentage of protonation of the N3 centres. In the same pD region, a shift of the resonances H21, H25, H26 and H27 in the opposite direction is observed, which is probably due to a somewhat higher polarisation in the pyridine rings of the arms due to the protonation of the nearby nitrogen atoms. Further acidification to $n = 2$, between pD 7.7 and 5.7, protonates only N3 centres, because only H2, H4, H5 and H21 shift to low-field, the latter to a lesser extent than the others due to its relative position. The resonances corresponding to the protons of the pyridine rings, principally H15 and H16, also shift slightly in the same direction, which seems to indicate a certain percentage of protonation in the pyridine incorporated in the macrocycle and the simultaneous formation of hydrogen bonding between the pyridine of the arms and the protonated centres N3. For lower pD values, to $n = 3$, for 5.7 > pD > 3.2, resonances H21, H24, H25, H26 and H27 shift to low-field accounting for the protonation of 50% of the pyridine atoms in the arms. In the same pD region resonances H5 and H6 slightly shift to low field while resonances H15 and H16 shift in the opposite direction, probably indicating a charge rearrangement in the macrocycle cavity, with the complete deprotonation of the pyridine incorporated in the macrocyclic backbone and the simultaneous transfer to N7. For pD values between 3.2 and 0.8 all the pyridine resonances move to low field as do resonances H2

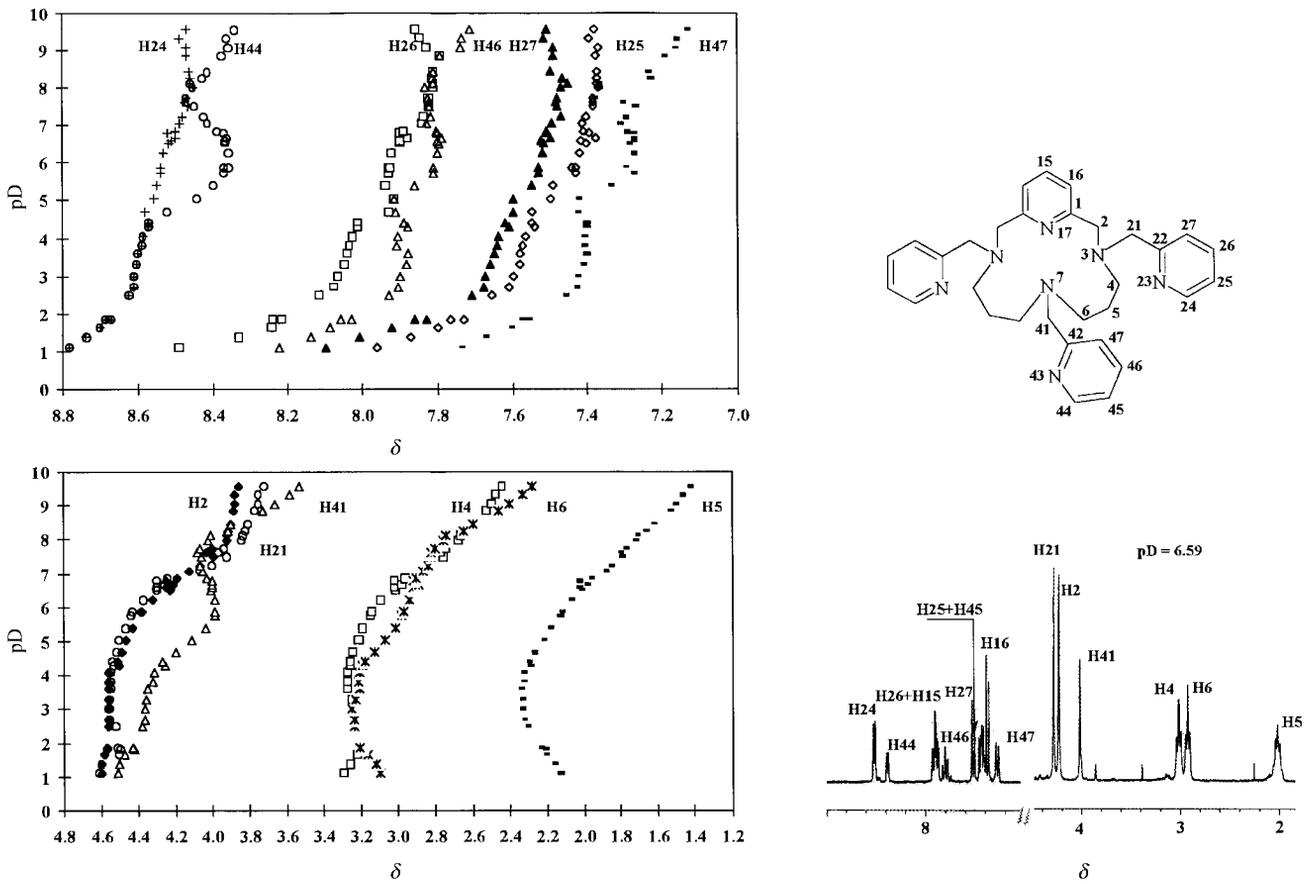


Fig. 2 ^{1}H NMR titration curves, chemical shift (δ) as a function of pD, for L^2 and the spectrum of this ligand at pD 6.59. See note in Fig. 1.

and H21 indicating the simultaneous protonation of the pyridine of the pendant arms and the pyridine of the macrocycle. For pD values lower than 1, all the resonances shift simultaneously indicating that the last equivalent of acid started to be distributed in the remaining centres of the macrocycle.

It is possible now to interpret the macroscopic protonation constants of L^1 shown in Table 1. The first protonation occurs mainly at N7 with the expected value for a secondary amine. The second one occurs at N3, its value being lower than the first one due to the repulsion effect from the centre already protonated at a relatively short distance away, and also because of the electron-withdrawing effect of the bound pyridine groups. At pD values of about 5.7 only two of the six basic centres of the molecule are protonated. The third protonation occurs on the pyridine of the pendant arms, N23, which will be 50% protonated in this stage. The fourth and fifth protonations occur simultaneously in the pyridine arm and in the pyridine of the macrocycle, and at lower pD values the last centre of the macrocycle also starts to be protonated, while the protonation of the last two centres is completed. The values of the last protonations which occur in the macrocycle are very low due to the strong repulsion effect into the cavity.

^{1}H NMR titration of L^2 was also performed, each spectrum exhibits thirteen independent resonances for almost the entire pD range. It was not possible to follow resonances H15 and H45 (superimposed with H26 and H25, respectively) and H16 (superimposed with H47 for high pD values and H25 for lower values). The assignment of the resonances was achieved taking into account the pattern of each absorption and the area ratio, but NOESY experiments were necessary at pD values 6.59 and 9.02, for the assignment of protons H2, H4, H6, H21 and the pyridine protons, see Fig. 2.

The ^{1}H NMR titration curves show that the first equivalent of acid added to the basic form of L^2, for pD values higher than 7.7, protonates mainly at the N7 centre, as resonances H5, H6, H41, H44, H46 and H47 shift to low-field, H5 to a lesser extent. A slight shift of resonances H2, H4, and H21 accounts for a small percentage of protonation of the N3 centres. Further acidification, to $n = 2$, between pD 7.7 and 5.9, protonates mainly N3 centres because the main shifts are of resonances H2, H4, H5 and H21, but simultaneously resonances H41, H44, H46 and H47 move in the opposite direction indicating the partial deprotonation of the N7 centre in favour of N3 centres. With this rearrangement the positive charges will be at a longer distance with the corresponding repulsion decrease in the macrocycle. The third equivalent of acid (5.9 > pD > 4.4) mainly protonates once again at the N7 centre, because H5, H6, H41, H44, H46 and H47 shift to low-field, but also a certain percentage of protonation occurs at the N3 centres as resonances H2, H4 and H21 also move slightly. Between pD values 4.4 and 2.95 no shift is observed. For lower pD values the resonances H24 to H27 but also H44 to H47 shift to low-field indicating the simultaneous protonation of the three pyridine arms.

Therefore, L^1 and L^2 present completely different sequences of protonation. In the last compound the first three protonations occur in the amines of the macrocyclic backbone and then, the remaining four take place in either of the pyridine nitrogens of the pendant arms starting at pD values lower than 2.95. The differences in log K_1 of both compounds are easily understandable because in L^1 it corresponds to the protonation of a secondary amine of the macrocycle while in L^2 it is a tertiary amine which is protonated. The higher log K_3 value of L^2 is due to the protonation of amines of the macrocyclic framework while the value of this constant determined for L^1 corresponds to the protonation of the pyridine arms. From these results the following question arises: why do two compounds having the same macrocyclic framework only differing in the number of N-pendant arms present different protonation sequences? If the K_1 values have a straightforward explanation,

Table 2 Stability constants (log $K_{M_mH_hL_l}$) of the complexes of L^1, L^2, other macrocycles and the cryptand [N,N-2.2.2] with some di- and tri-valent metal ions. $T = 25.0$ °C; $I = 0.10$ mol dm^{-3} in KNO_3

Ion	Equilibrium quotient	L^1	L^2	L^3 [a]	$py_2[18]N_2O_4$ [b]	[N,N-2.2.2] [c]	[21]aneN_7 [d]
Ca^{2+}	[ML]/[M] × [L]	3.43(4)	—	—	3.63	4.3	—
Co^{2+}	[ML]/[M] × [L]	13.5(1)	—	—	—	4.9	14.69
	[MHL]/[ML] × [H]	—	—	—	—	—	5.27
Ni^{2+}	[ML]/[M] × [L]	16.94(4)	15.61(1)	16.27	8.80	5.1	16.56
	[MHL]/[ML] × [H]	2.1(1)	2.01(3)	—	—	—	6.61
Cu^{2+}	[ML]/[M][L]	20.13(4)	19.42(4)	19.76	13.55	12.7	24.4
	[MHL]/[ML] × [H]	—	—	—	—	—	[e]
Zn^{2+}	[ML]/[M] × [L]	14.65(1)	11.92(1)	12.82	6.96	6.0	13.33
	[MHL]/[ML] × [H]	1.84(8)	3.07(2)	—	—	—	6.87
	[ML]/[MLOH] × [H]	8.35(1)	—	8.48	—	—	[f]
Cd^{2+}	[ML]/[M] × [L]	14.85(1)	16.55(2)	9.76	10.96	12.0	18.10
	[MHL]/[ML] × [H]	1.91(7)	1.96(4)	—	—	—	4.49
	[ML]/[MLOH] × [H]	—	11.40(4)	10.30	—	—	—
Pb^{2+}	[ML]/[M] × [L]	10.69(1)	9.62(1)	9.72	11.67	15.3	—
	[MHL]/[ML] × [H]	3.95(6)	3.55(4)	—	—	—	—
	[ML]/[MLOH] × [H]	10.59(4)	—	10.95	—	—	—
Fe^{3+}	[ML]/[M] × [L]	15.87(2)	15.70(3)	—	—	—	—
	[MHL]/[ML] × [H]	3.31(3)	2.75(5)	—	—	—	—
	[ML]/[MLOH] × [H]	—	4.11(4)	—	—	—	—
In^{3+}	[ML]/[M] × [L]	14.01(2)	14.10(1)	—	—	—	—
	[MHL]/[ML] × [H]	—	2.08(5)	—	—	—	—

[a] Ref. 18. [b] $I = 0.10$ mol dm^{-3} in $NaNO_3$, ref. 12. [c] $I = 0.10$ mol dm^{-3} in $N(Me)_4NO_3$ or $N(Me)_4Cl$, ref. 15(*b*). [d] $I = 0.15$ mol dm^{-3} in $NaClO_4$, ref. 16. [e] Other constants for this system: log $\beta(M_2L) = 30.7$, log $\beta(MH_2L) = 34.4$ and log $K(M_2LOH) = 4.8$.[16] [f] Other constant for this system: log $K(MH_2L) = 4.95$.[16]

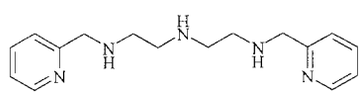
the same cannot be said about K_3. Similar results were obtained for the *N*-carboxymethyl derivatives L^4 and L^5, but for these compounds ^{1}H NMR titrations were not carried out to support the conclusions[19] which contradict those of Aime *et al.*[27] for L^5. Electronic more than structural reasons were proposed by us to explain this behaviour for the *N*-carboxymethyl derivatives,[19] because the negative charge of one more carboxylate group significantly contributes to the neutralisation of charges into the macrocyclic cavity. In the case of the *N*-(2-pyridylmethyl) derivatives it is probably the formation of hydrogen bonds between the protonated amines of the macrocycle and the nitrogen of the pyridine which is the main contribution to the decrease of the concentration of charge into the cavity of the macrocycle allowing the third protonation to occur in the ring in L^2.

Metal complex studies

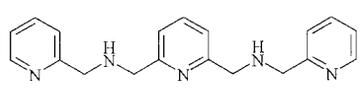
The stability constants of L^1 and L^2 with the metal ions studied in this work are collected in Table 2 together with the constants of the complexes of some other ligands for comparison taken from the literature. Only mononuclear species were found for the complexes of both ligands. In most cases only ML and MHL species are formed, but hydroxocomplexes (MLOH) were also found in some systems. We have checked the possibility of formation of other species, but they are not formed under our conditions. In the case of the Co^{2+} complexes the stability constants could not be determined with accuracy due to a strong tendency towards oxidation of these complexes, as was also found for the corresponding complexes of the parent amine[18] and the *N*-carboxymethyl derivatives.[19]

The values in Table 2 show that the complexes of the divalent first row-transition metal ions with both ligands follow the Irving–Williams order of stability. The plot of log K_{ML} *versus* atomic number exhibits the form of an inverted V with the maximum for Cu^{2+} as usual, but a very abrupt fall of constants for the Zn^{2+} and the Co^{2+} complexes is observed. This fall is even more accentuated than that observed for the *N*-carboxymethyl derivatives of the same macrocycle.[19]

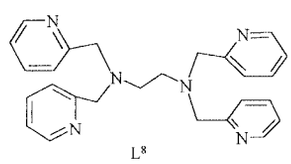
The values of the stability constants for the complexes of both ligands are of the order of the corresponding complexes of the parent amine, L^3, and, in general, are lower than expected taking into account the published numbers for the corresponding complexes of the linear ligands, L^6–L^8 (see below), specially in the Ni^{2+} case for which the complexes with the linear ligands present very high thermodynamic stability.[14,28] However, the values obtained in the present work are as expected when compared with those reported for [NiL^4] and [NiL^5]$^-$ and taking into account the differences in basicity of the ligands, as will be shown later.[19]



L^6



L^7



L^8

The values of the stability constants for the trivalent metal ions studied with both ligands are very low as expected for complexes with ligands having only nitrogen as donor atoms. The values for Ga^{3+} could not be determined because precipitation of gallium(III) hydroxides occurs at very low pH values.

The value of the stability constant of the Cd^{2+} complex with L^2 is particularly high, showing that this ligand has a remarkable selectivity for this metal ion. Indeed, L^2 forms complexes with lower thermodynamic stability than expected for a potentially hepta-co-ordinate ligand. For most of the complexes the values are lower than those of L^1, but still they are slightly lower than those of the parent amine, L^3, except for the Cd^{2+} one. It is possible to predict that the third pyridylmethyl arm of L^2 not only does not participate in the co-ordination to the metal ions but also that it increases considerably the steric hindrance of the ligand on complexation leading to lower values of the stability constants for most of them. In fact the only single crystal X-ray structure determination of a complex involving this ligand, $[CuL^2][ClO_4]_2$, presented below, shows that two of the

Table 3 Selected bond lengths (Å) and angles (°) for $[CuL^2]^{2+}$

Cu–N(17)	1.962(7)	Cu–N(33)	2.043(7)
Cu–N(3)	2.053(9)	Cu–N(11)	2.075(8)
Cu–N(7)	2.198(8)		
N(17)–Cu–N(33)	143.8(3)	N(17)–Cu–N(3)	81.5(3)
N(33)–Cu–N(3)	103.6(3)	N(17)–Cu–N(11)	82.5(3)
N(33)–Cu–N(11)	82.1(3)	N(3)–Cu–N(11)	159.3(3)
N(17)–Cu–N(7)	106.7(3)	N(33)–Cu–N(7)	107.8(3)
N(3)–Cu–N(7)	99.0(3)	N(11)–Cu–N(7)	98.1(3)

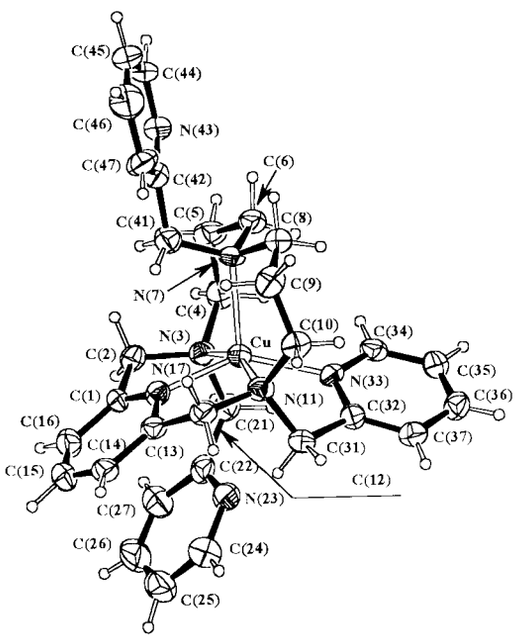


Fig. 3 Molecular structure of $[CuL^2]^{2+}$ in the crystal of **1** (thermal ellipsoids represent 30% of probability level) with labelling scheme adopted.

pyridyl arms are not involved in the co-ordination to the metal ion. The $[CdL^2]^-$ complex seems to be the only one to bond to all the donor atoms of the ligand or at least to more than the other metal ions studied.

Single crystal X-ray structure of $[CuL^2][ClO_4]_2$ 1

The crystal structure of **1** is built up from an asymmetric unit containing one discrete $[CuL^2]^{2+}$ cation and two ClO_4^- anions. Fig. 3 presents the molecular structure of the cationic entity with the atom labelling scheme used. Selected bond lengths and angles are listed in Table 3, indicating that the co-ordination geometry around the copper atom can be described approximately as a distorted square pyramid. The basal plane is defined by the three nitrogen atoms [N(3), N(11) and N(17)] of the macrocycle and one nitrogen atom [N(33)] from a pyridylmethyl pendant arm adjacent to the pyridine ring of the macrocyclic backbone. The apical co-ordination is accomplished *via* the nitrogen atom N(7) *trans* to the pyridine ring of the macrocyclic backbone. To achieve this geometric arrangement the macrocycle shows necessarily a remarkable fold through the line defined by the nitrogen atoms N(3) and N(11) leading to a dihedral angle between planes N(11), N(3), N(7) and N(11), N(3), N(17) of 76.5(3)°. The free pyridylmethyl pendant arm bound to the nitrogen N(7) is further away from the copper centre leading to a distance between the copper and nitrogen N(43) of 5.205(9) Å. By contrast the nitrogen atom N(23) of the remaining pyridylmethyl pendant arm is directed towards the copper centre leading to a distance between these two atoms of 3.304(11) Å, which suggests a weak bonding interaction consistent with a [5 + 1] co-ordination. The bond angle Cu···N(23)–C(24) of 138.9(10)° is deviated by *ca.* 19° from

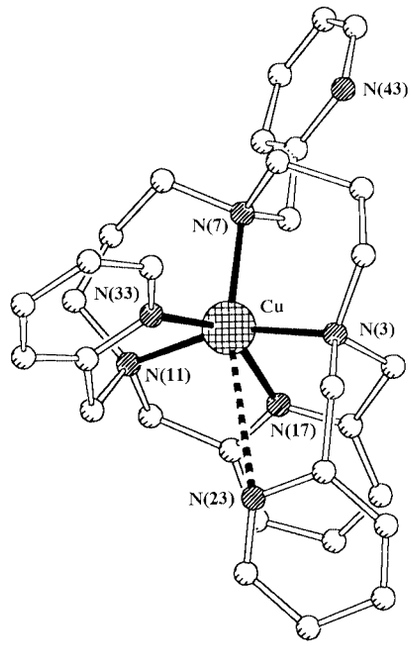


Fig. 4 A view of $[CuL^2]^{2+}$ approximately perpendicular to the pyridine ring containing the nitrogen atom N(23) showing the suitable orientation of this donor atom to establish with the copper centre a weak bonding interaction. Hydrogen atoms are omitted for clarity.

the ideal bond angle of 120° for an sp^2 nitrogen indicating that the lone pair of nitrogen atom N(23) displays a suitable orientation to interact with the metal centre. This structural particularity is clearly seen in Fig. 4, which shows the projection of the molecular structure on the plane of the pyridine ring containing the nitrogen atom N(23). These structural features suggest a comparison with the nickel(II) complex of L^1, $[NiL^1]^{2+}$ [ref. 7(*c*)], which exhibits an elongated *cis*-octahedral geometry, with Ni–N bond distances of 1.944(12) to 2.375(10) Å. In this complex the macrocyclic ligand is also folded about the axis defined by the two nitrogen atoms contiguous to the pyridine ring of the macrocyclic backbone. The two pyridylmethyl pendant arms occupy an axial and an equatorial position in the nickel co-ordination sphere.

In the $[CuL^2]^{2+}$ cation the least-squares plane through the nitrogen atoms N(3), N(17), N(11) and N(33), which define the equatorial co-ordination plane (see Fig. 3), shows significant tetrahedral distortion [±0.141(4) Å] indicating that these atoms are not coplanar. The copper lies 0.452(4) Å above this N_4 co-ordination plane towards the apical nitrogen giving a Cu–N(7) distance of 2.198(8) Å. This apical Cu–N distance is much longer than the Cu–N equatorial distances, which range from 1.962(7) to 2.075(8) Å. By contrast in the nickel complex the N_4 equatorial co-ordination plane shows only a slight tetrahedral distortion [±0.068 Å] and the metal centre is 0.096 Å from that plane. This structural comparison suggests that in the complex of L^2 the presence of the three bulky pyridylmethyl groups on the macrocyclic framework severely constrains the geometric arrangement of their nitrogen donor atoms around the metal centre and also restricts the co-ordination number. In other words in the copper complex the octahedral geometry cannot be completely achieved because of the steric hindrance caused by the three pyridylmethyl groups, while in the nickel complex the two pyridylmethyl groups of L^1 are used to complete the six-co-ordination number. However the axial N–Ni–N angle [165.4(4)°] is similar to the angle N(7)–Cu···N(23) involving the nitrogen atoms in the "pseudo axial" positions and copper centre [166.6(5)°].

A comparable situation was reported for the complex $[CuL^9]^{2+}$, L^9 being 1,4,7,10-tetrakis(pyridylmethyl)-1,4,7,10-tetraazacyclododecane, the *N*-pyridylmethyl derivative of the

twelve membered macrocycle cyclen.[10] Six nitrogen atoms of the ligand (four from the macrocycle and two from two arms) surround the copper centre in a strongly distorted octahedral geometric arrangement. The two remaining pyridylmethyl groups are unco-ordinated and the macrocycle also adopts a folded configuration. One of the Cu–N distances [2.82(1) Å] is considerably longer than the others [Cu–N range 2.10(1)–2.33(1) Å] indicating that a secondary bond between the copper and one pyridylmethyl pendant arm occurs in this complex. This long bond distance is shorter than that observed for the present complex, because in the cation $[CuL^9]^{2+}$ this interaction involves an sp^3 nitrogen of the macrocyclic ring and consequently the distance of the secondary Cu–N bond is restricted by the small cavity size of the 12-membered ring. In $[CuL^2]^{2+}$ this type of steric strain is absent since the secondary Cu–N bond occurs *via* a nitrogen atom of a free pyridylmethyl pendant arm. In order to shed some light on the influence of steric effects on the structural preferences of L^1 and L^2 in the metal transition complexes molecular mechanics calculations are in progress.

Conclusions

The values of the stability constants of the complexes of both ligands studied are lower than expected when comparing them with the published values for complexes of linear ligands with the same type of pendant arms.[14,28] Mainly structural features seem to be on the basis of this behaviour. In fact, the complexes of both macrocyclic ligands seem to adopt distorted structures due to the steric hindrance induced by the bulky pyridylmethyl pendant arms, which will be obviously more pronounced for the complexes of L^2, due to the presence of three methylpyridine pendant arms of this compound. This situation was observed for $[CuL^2]^{2+}$, for which the crystal structure shows that the copper is encapsulated by the macrocycle in a very distorted square pyramidal geometric arrangement, involving only one of the three pyridyl arms. Therefore, the presence of the three bulky methylpyridine pendant arms on L^2 severely constrains the geometric arrangement of their nitrogen donor atoms around the copper centre and also restricts the co-ordination number.

The particular selectivity of L^2 for cadmium makes it specially useful for the elimination of this poisonous heavy metal from the environment or from living bodies with little or no disturbance of the biologically essential metal ions, such as Mg^{2+}, Ca^{2+}, or Zn^{2+}. The selectivity relative to Zn^{2+} is 4.63 (in log units), which is smaller than the value of 6.0 found by Lehn *et al.*[15] for the cryptand [N,N-2.2.2], and of the order of those determined for $py_2[18]N_2O_4$ and $[21]aneN_7$, which also have a particular selectivity for cadmium,[12,16] and were detected in our search of the literature as having this property.[28] However the differences between the behaviour of these four ligands towards cadmium are only apparent as the competition with the proton was not taken into account. Considering this competition at the physiological pH by the determination of pM values,[20] see Table 4, it is found that our ligand is the best, followed by the other macrocycle with pyridylmethyl pendant arms, $py_2[18]N_2O_4$.[12] The (pCd–pZn) differences are 4.63 for L^2, 3.98 for $py_2[18]N_2O_4$, 3.3 for $[21]aneN_7$ and 2.8 for the cryptand [N,N-2.2.2], see Table 4. The lower overall basicity of the ligands containing pyridylmethyl arms accounts for the smaller differences between the values of the stability constants and the pM values, but does not explain the high selectivity of cadmium relative to zinc, because the known linear amines having the same pendant arms do not show this property.[14]

A better knowledge of the co-ordination behaviour of L^2 relative to Cd^{2+} would be of crucial relevance to understanding the special arrangement adopted by the macrocycle in the complex (the size of L^2 and the type of donor atoms more suitable to accommodate this metal ion). Unfortunately our best efforts to obtain single crystals of $[CdL^2]^-$ suitable for X-ray determination were not successful. However the crystal structure found for the copper(II) complex suggests that the macrocycle L^2 has enough flexibility to allow higher co-ordination numbers consistent with the stereo-electronic requirements of Cd^{2+} and its size, even in strongly distorted environments, probably managing to involve all the donor atoms of the ligand in the encapsulation of the metal centre.

Table 4 pM[a] values for the metal complexes of L^1–L^3, $py_2[18]N_2O_4$, [N,N-2.2.2] and $[21]aneN_7$ at pH = 7.4

pM	L^1	L^2	L^3[b]	$py_2[18]N_2O_4$[b]	[N,N-2.2.2][b]	$[21]aneN_7$[b]
pCa	5.0	—	—	5.01	5.0	—
pCo	10.2	—	—	—	5.0	10.74
pNi	13.68	14.76	12.56	8.46	5.0	12.67
pCu	16.87	18.57	16.05	13.21	8.6	20.45
pZn	11.44	11.07	9.14	6.64	5.1	10.85
pCd	11.59	15.70	6.12	10.62	7.9	14.15
pPb	7.43	8.77	6.08	11.33	11.2	
pFe	13.98	14.94	—	—	—	—
pIn	13.26	13.63	—	—	—	—

[a] Values calculated for 100% excess of free ligand at physiological conditions, pH = 7.4; $c_M = 1.0 \times 10^{-5}$ mol dm^{-3}, $c_L = 2.0 \times 10^{-5}$ mol dm^{-3}, using the Hyss program.[29] [b] Calculated from the published stability constants, see notes in Table 2.

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