DALTON

A reinforced polyaza[*n.n*]paracyclophane containing piperazine rings

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The new [*n.n*]paraazacyclophane 3,7,10,14,21,25,28,32-octaazapentacyclo[32.2.2^{7,10}.2^{16,19}.2^{25,28}]tetratetraconta-1(37),16(41),17,19(40),34(38),35-hexaene (L) has been prepared. Its protonation has been studied by means of potentiometry and direct microcalorimetry in 0.15 mol dm^{-3} $NaClO_4$ at 298.1 K. A NMR analysis shows that protons bind alternately at both sides of L, the benzylic nitrogens being the first sites to be protonated. From dynamic variable-temperature NMR analysis an activation enthalpy of 61(2) kJ mol^{-1} has been derived for the chair–chair interconversion of the piperazine ring. The entropy is almost negligible. Compound L forms with Cu^{2+} in aqueous solution complexes $[Cu(H_3L)]^{3+}$ and $[Cu_2L]^{4+}$ with stability constants log β_{CuH_3L} = 33.20(6) and log β_{Cu_2L} = 16.6(1) in 0.15 mol dm^{-3} $NaClO_4$ at 298.1 K, respectively. The low stability of the binuclear complex is attributed to the energy loss due to interconversion between the chair and boat conformers of the piperazine moieties. The interaction of Pd^{2+} with L has been monitored by NMR analysis. The spectral features show formation of strong binuclear complexes with the involvement of all eight nitrogens of the macrocycle.

In order to achieve selectivity in the binding of metal ions rigid preorganized ligands are needed. One strategy to obtain them has been to introduce double chelate bridges within the framework of either open-chain or cyclic saturated polyamines.[1–5]

Very recently some of us have reported the synthesis, protonation and co-ordination abilities towards Cu^{2+} of a series of new paraazacyclophanes characterized by the presence of a single aromatic spacer in between saturated polyamine chains with different numbers of nitrogen atoms as well as sequences and sizes of chelate rings (see for instance L^1).[6–9] These compounds were obtained by treating the corresponding tosylated polyamine with 1,4-bis(bromomethyl)benzene in acetonitrile.[6] The toluene-*p*-sulfonyl (tosyl) groups seemed to be of importance in order to achieve a conformation enabling 1:1 cyclization. The aromatic spacer introduced enough strain into these molecules to avoid simultaneous co-ordination of both benzylic nitrogens to a single metal centre. Thus, somehow, this feature helped in the preorganization to give low symmetry metal co-ordination sites and leading to particular properties.[10]

A further step in the development of this family of compounds was the introduction of double rings within the polyamine chain. However, reaction of *N*,*N*′-bis[3-(*p*-tolylsulfonylamino)propyl]piperazine with 1,4-bis(bromomethyl)benzene under the same experimental conditions leads to the formation of the [*n.n*]paraazacyclophane 3,7,10,14,21,25,28,32-octaazapentacyclo[32.2.2^{7,10}.2^{16,19}.2^{25,28}]tetratetraconta-1(37),16(41),17,19(40),34(38),35-hexaene (L) instead of the single 1:1 paraazacyclophane (Scheme 1). The piperazine ring seems to favour 2:2 condensations over 1:1 ones, and could be a good building block to form large receptors as advanced by several groups in recent reports.[3–5]

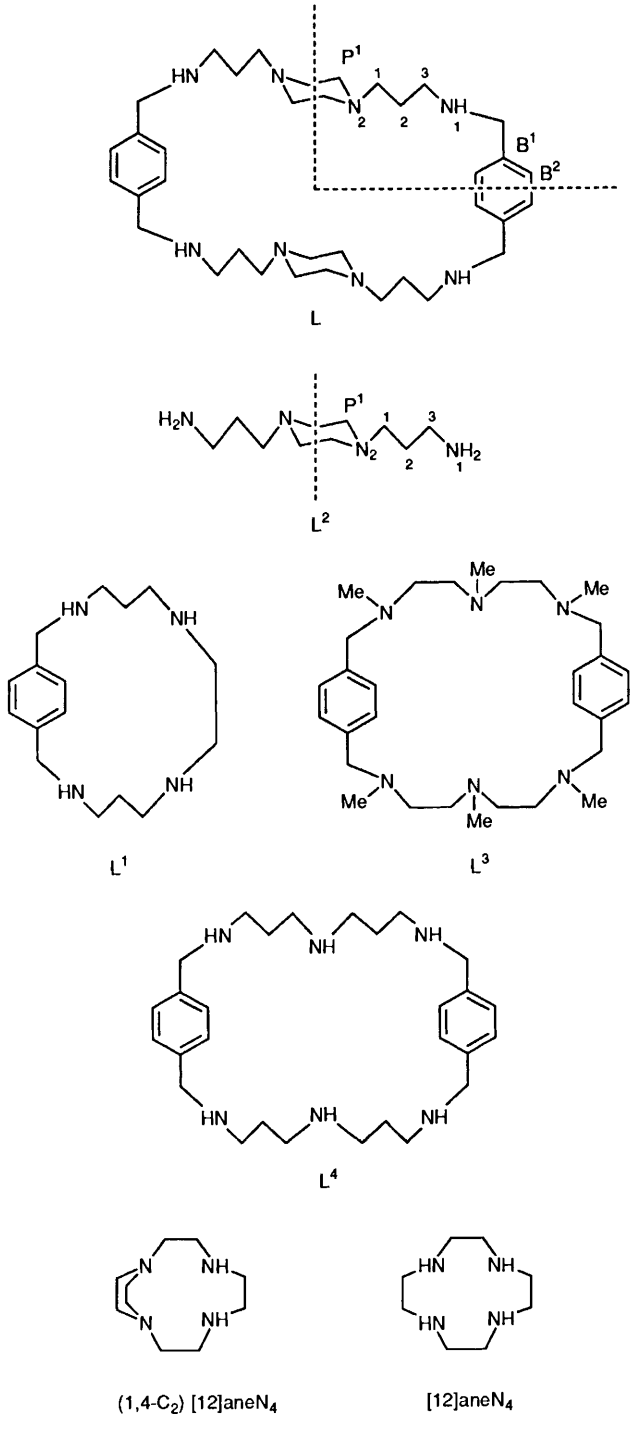
Here we report on the synthesis, protonation and copper(II) and palladium(II) co-ordination chemistry of L. The aim of the present work is to provide information on how the rigidity of a ligand may affect its co-ordination abilities toward metal ions. For this purpose we have chosen Cu^{2+} and Pd^{2+} as examples of metal ions which can adapt to the characteristics of the ligand (Cu^{2+}) or impose their own stereochemical requirements (Pd^{2+}). For comparison we include some data concerning the open-chain compound 1,4-bis(3-aminopropyl)-1,4-diazacyclohexane (L^2).

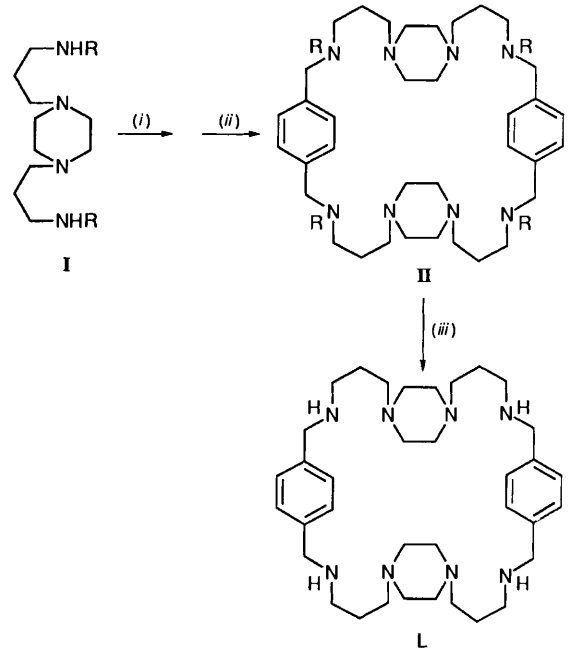
Experimental

Synthesis of 3,7,10,14,21,25,28,32-octaazapentacyclo[32.2.2^{7,10}.2^{16,19}.2^{25,28}]tetratetraconta-1(37),16(41),17,19(40),34(38),35-hexaene (L)

***N*,*N*′-Bis[3-(*p*-tolylsulfonyl)aminopropyl]piperazine I.** Compound **I** was prepared by the general procedure described in ref. 6 (yield 85%), m.p. 178–180 °C. NMR ($CDCl_3$): ^{1}H, δ 1.57–1.65 (m, 4 H), 2.39–3.43 (m, 18 H), 3.01 (t, 4 H, *J* = 5), 7.26 (d, 4 H, *J* = 8), and 7.70 (d, 4 H, *J* = 8 Hz); ^{13}C, δ 21.6, 23.9, 44.3, 53.1, 57.9, 127.0, 129.6, 137.1, and 143.1 (Found: C, 56.8; H, 7.2; N, 11.0. Calc. for $C_{24}H_{36}N_4O_4S_2$: C, 56.6; H, 7.15; N, 11.0%).

3,14,21,32-Tetrakis(*p*-tolylsulfonyl)-3,7,10,14,21,25,28,32-octaazapentacyclo[32.2.2^{7,10}.2^{16,19}.2^{25,28}]tetratetraconta-1(37),16(41),17,19(40),34(38),35-hexaene II. A suspension of Na (0.48 g, 0.021 mol) in ethanol (100 cm^3) was added to a solution of compound **I** (5.09 g, 0.01 mol) in ethanol (100 cm^3). The mixture was refluxed for 30 min and the solvent vacuum evaporated. The solid residue was suspended in anhydrous dimethylformamide (dmf) (50 cm^3) and then a solution of 1,4-bis(bromomethyl)benzene (2.64 g, 0.01 mol) in anhydrous dmf (100 cm^3) was added dropwise (*ca.* 4 h). The mixture was kept at 110 °C for 2 h, then cooled at room temperature and the solvent vacuum evaporated. The resulting solid was taken up in CH_2Cl_2 (100 cm^3) and the suspension filtered. Ethanol was then added to precipitate a white solid, which was dissolved in the minimum volume of CH_2Cl_2–MeOH and purified by chromatography on neutral alumina (70–230 mesh) using CH_2Cl_2–MeOH (100:1) to obtain compound **II** (yield 74%), m.p. 226–228 °C; NMR ($CDCl_3$): H, δ 1.41–1.44 (m, 4 H),





Scheme 1 R = *p*-tolylsulfonyl. (*i*) NaOEt; (*ii*) $C_6H_4Br_2$[1,4]; (*iii*) Li, NH_3

2.05–2.16 (m, 12 H), 2.43 (s, 4 H), 4.25 (s, 4 H), 7.22 (s, 4 H), 7.31 (d, 4 H, J = 8) and 7.71 (d, 4 H, J = 8 Hz); ^{13}C, δ 21.4, 25.6, 46.5, 52.1, 52.8, 56.2, 127.1, 128.5, 129.7, 136.2, 136.6 and 143.3. FAB mass spectrum: m/z 1220 ($[M + H]^+$) (Found: C, 62.8; H, 7.0; N, 9.1. Calc. for $C_{64}H_{84}N_8O_8S_4$: C, 62.9; H, 6.95; N, 9.15%).

L·8HCl. Liquid NH_3 (250 cm^3) was condensed into a suspension of compound **II** (3.05 g, 0.003 mol) in diethyl ether (30 cm^3) and methanol (1 cm^3) cooled at −70 °C. Lithium was added in small portions (*ca.* 10 mg each); the stirred reaction mixture turned blue and then more lithium was added until the blue colour remained for at least 5 min. The salt NH_4Cl (12 g, 0.02 mol) was then added in small amounts and the suspension taken to room temperature. After evaporating all the NH_3 a white solid appeared which was treated with 3 mol dm^{-3} HCl and the suspension obtained washed three times with $CHCl_3$ (100 cm^3). The aqueous solution was filtered and the solvent vacuum evaporated to obtain a white solid which was dissolved in the minimum volume of water and the resulting solution then made alkaline with concentrated NaOH. The solution was extracted with $CHCl_3$ (6 × 100 cm^3), the organic layer dried over Na_2SO_4 and vacuum evaporated to give 0.95 g of compound L as a colourless oil (yield 63%). NMR ($CDCl_3$): ^{1}H, δ 1.80–2.01 (m, 4 H), 2.98–3.00 (m, 4 H), 3.14–3.16 (m, 4 H), 3.45 (s, 8 H) and 4.15 (s, 4 H); ^{13}C, δ 21.9, 44.3, 49.7, 51.6, 54.3, 132.1, 132.7. The octahydrochloride salt was obtained quantitatively by adding an excess of HCl to an ethanolic solution of the free amine. The white solid obtained was recrystallized from a water–ethanol solution (Found: C, 71.3; H, 10.1; N, 18.4. Calc. for $C_{36}H_{72}Cl_8N_8$: C, 71.5; H, 10.0; N, 18.5%).

Materials

Sodium perchlorate used as background electrolyte in the potentiometric measurements was purified according to a literature procedure.[11] Carbon dioxide-free NaOH solutions and HCl or $HClO_4$ solutions were prepared following the procedure in ref. 12. Ethane-1,2-diamine used for checking the microcalorimetric equipment was prepared and purified as its hydrochloride salt. Compound L^2 was obtained as its tetrahydrochloride salt by adding an excess of HCl to an ethanolic solution of the free amine (Fluka product) (Found: C, 34.8; H, 8.1; N, 16.1. Calc. for $C_{10}H_{28}Cl_4N_4$: C, 34.7; H, 8.15; N, 16.2%).

Electromotive force measurements

The potentiometric titrations were carried out, in 0.15 mol dm^{-3} $NaClO_4$ at 298.1 ± 0.1 K, by using an experimental procedure (burette, potentiometer, cell, stirrer, microcomputer, *etc.*) fully described elsewhere.[13] The electromotive force (emf) data were obtained with the computer program PASAT.[14] The reference electrode was an Ag–AgCl electrode in saturated KCl solution. The glass electrode was calibrated as a hydrogen-ion concentration probe by titration of well known amounts of HCl with CO_2-free NaOH solutions and determining the equivalence point by the Gran method,[15] which gives the standard potential, $E°'$, and the ionic product of water [pK_w = 13.73(1)]. The concentrations of the different metal ions

employed were determined gravimetrically by standard methods.

The computer program SUPERQUAD[16] was used to calculate the protonation and stability constants. The titration curves for each system (*ca.* 200 experimental points corresponding to at least three measurements, pH range investigated 2–10, ligand concentration ranging from 1×10^{-3} to 5×10^{-3} mol dm^{-3} and that of the metals in the co-ordination studies 1×10^{-3} to 2×10^{-3} mol dm^{-3}) were treated either as a single set or as separate curves without significant variations in the values of the stability constants. Finally, the sets of data were merged and treated simultaneously to give the final stability constants.

Microcalorimetry

The enthalpies of protonation of the ligand were determined in 0.15 mol dm^{-3} $NaClO_4$ by means of an automated system comprised of a Thermometric AB thermal activity monitor (model 2277) equipped with a perfusion/titration device and a Hamilton pump (model Microlab M) coupled with a 0.250 cm^3 gas-tight Hamilton syringe (model 1750 LT). The measuring vessel was housed in a 25 dm^3 water thermostat maintained at the chosen temperature within $\pm 2 \times 10^{-4}$ K. The microcalorimeter was checked by determining the enthalpy of reaction of a strong base (NaOH) with a strong acid (HCl). The value obtained, $-56.7(2)$ kJ mol^{-1}, was in agreement with literature values.[17] Further checks were performed by determining the enthalpies of protonation of ethane-1,2-diamine. In a typical ligand-protonation experiment, a NaOH solution (0.15 mol dm^{-3}, volumes added 15 μl) was added to 1.5 cm^3 solutions of the ligand ($0.01–5 \times 10^{-3}$ mol dm^{-3}). In the complexation experiment, an (5×10^{-3} mol dm^{-3}) acidic solution of L^2 (1.5 cm^3) in $NaClO_4$ (0.15 mol dm^{-3}) containing Cu^{2+} (1×10^{-3} mol dm^{-3}) was charged into the calorimetric ampoule and titrated with standardized NaOH solutions. Corrections for the heat of dilution were applied. The corresponding enthalpies of reaction were determined from the calorimetric data by means of the KK95 program.[18]

At least three titrations were performed for each system studied. The titration curves for each system were treated either as a single set or as separate entities without significant variations in the values of the enthalpy changes.

Spectroscopy

The ^1H and ^{13}C NMR spectra were recorded on Varian UNITY 300 and UNITY 400 spectrometers, operating at 299.95 and 399.95 MHz for ^1H and at 75.43 and 100.58 MHz for ^{13}C. The spectra were obtained at room temperature in D_2O or Me_2SO solutions. For the ^{13}C NMR spectra dioxane was used as a reference standard (δ 67.4) and for the ^1H spectra the solvent signal. The pH was calculated from the measured pD values using the correlation pH = pD − 0.4.[19] Computer simulations of the NMR spectra were carried out with a locally developed package containing the programs LAOCOON[20] and DAVINS[21] running on a personal computer. Line-shape analysis of the variable-temperature NMR spectra was accomplished by means of the DNMR 3 program[22] also included in the package.

Results and Discussion

Protonation

Compound L behaves in the range pH 2.5–11 as heptaprotic base, its stepwise basicity constants being given in Table 1. The eighth constant is too low to be detected under the experimental conditions employed. The values of these constants are organized, up to the sixth, in groups of two having similar values, namely K_{HL} and K_{H_2L}, K_{H_3L} and K_{H_4L} and, K_{H_5L} and K_{H_6L}.

Table 1 Stepwise protonation constants for compounds L and L^2 determined in 0.15 mol dm^{-3} $NaClO_4$ at 298.1 K. Values for L^1 from ref. 4 are also included

Reaction	L	L^1	L^2
$H + L \rightleftharpoons HL$[a]	9.97(2)[b]	9.93[c]	10.27(1)
$H + HL \rightleftharpoons H_2L$	9.67(1)	9.09	9.23(2)
$H + H_2L \rightleftharpoons H_3L$	8.58(2)	7.44	6.88(2)
$H + H_3L \rightleftharpoons H_4L$	8.08(2)	3.61	2.81(3)
$H + H_4L \rightleftharpoons H_5L$	6.71(3)		
$H + H_5L \rightleftharpoons H_6L$	6.24(2)		
$H + H_6L \rightleftharpoons H_7L$	3.13(3)		

[a] Charges omitted for clarity. [b] Values in parentheses are standard deviations in the last significant figure. [c] Taken from ref. 7; 0.15 mol dm^{-3} $NaClO_4$ at 298.1 K.

For instance, while the difference between the first and second constants is 0.30 logarithmic units, that between the second and third one is 1.09. The difference between the third and fourth constants is again much reduced [$\Delta(\log k) = 0.50$] and that between K_{H_4L} and K_{H_5L} larger [$\Delta(\log K) = 1.37$]. The larger basicity differences observed for the constants of the different groups clearly reveal the existence of shorter range electrostatic interactions at these protonation stages. In particular, of note is the very large difference in the values of K_{H_6L} and K_{H_7L} [$\Delta(\log k) = 3.1$]. These trends suggest that protons alternately bind nitrogens on alternate sides of L and therefore the values of consecutive odd and even constants are similar, since they take place at different sites of L and the electrostatic repulsion should be similar for each step. The great drop in basicity observed on going from K_{H_6L} to K_{H_7L} may be explained by taking into account that the seventh proton would be attached to a nitrogen of an already monoprotonated piperazine subunit.

Compound L^2 which may be considered as the linear counterpart of a single subunit of L, presents large constants for the first two protonations, an intermediate value for the third and a much lower one for the last. Comparison of these constants[23] with those of the different groups of L shows that while L^2 has a slightly higher basicity than L in the first two protonation steps [$\log K_{HL^2} = 10.27(1)$ and $\log K_{H_2L^2} = 9.23(2)$] the basicity of the last two steps is practically the same as that of L [$\log K_{H_3L^2} = 6.88(2)$ and $\log K_{H_4L^2} = 2.81(3)$] (Table 1).

The variations of the ^1H and ^{13}C NMR signals with pH have been analysed in order to deduce the successive protonation sites. All the assignments have been made on the basis of two-dimensional ^1H–^1H and ^1H–^{13}C correlation experiments at the different pH values studied. The ^1H NMR spectrum of L at pH 12.0, where the free amine is the only species existing in solution, consists of an $A_2B_2C_2$ spin system with a quintuplet signal at δ 1.38 corresponding to the central methylene protons of the propylenic chain (H^2), two triplets at δ 2.09 and 2.41 corresponding to the methylene protons H^1 and H^3 and two singlets at δ 3.59 and 7.19 which can be assigned to the benzylic (H^4) and aromatic protons (HB^2). At this pH and at room temperature the signal of the piperazine protons is very near to coalescence and appears as a very broad signal around δ 2.0. The ^{13}C NMR spectrum, at the same pH, exhibits seven different signals at δ 26.42, 46.69, 52.58, 52.98, 56.49, 130.42 and 139.11 which can be assigned to carbon atoms C^2, C^3, CP^1, C^4, C^1, CB^2 and CB^1 respectively. This number of peaks indicates a four-fold symmetry on the NMR time-scale.

The ^1H NMR spectrum at pH 12 of the related open-chain polyamine L^2 also consists of an $A_2B_2C_2$ spin system with a quintuplet signal at δ 1.37 ppm (H^2) and two triplets at δ 2.13 (H^1) and 2.36 (H^3). The signal for the piperazine hydrogens is extremely broad and lies within the baseline of the spectrum. The ^{13}C NMR spectrum at the same pH displays a four-line pattern at δ 29.56 (C^2), 39.97 (C^3), 52.68 (CP^1) and 56.27 (C^1).

The proton spectral features and the number of ^{13}C signals, which in this case is half the total number of carbon atoms in the molecule, is indicative of binary symmetry. For both compounds, when the pH is decreased the proton signals shift downfield and the carbon ones upfield but the number of proton and carbon resonances remains unaffected indicating that the binary symmetry is preserved throughout the whole of the pH range. However, the protons of the propylenic chains of L^2 appear at acidic pH as an AA'BB'CC' spin system (δ_A 3.23, δ_B 2.01, δ_C 2.92) with geminal coupling constants $J_{AA'}$, $J_{BB'}$ and $J_{CC'}$ *ca.* −16.0 Hz and vicinal ones J_{AB} = 6.01, $J_{AB'}$ = 11.01, J_{BC} = 10.01, $J_{B'C}$ = 4.51 and J_{BC} = 10.01 Hz indicating an *anti* conformation of the methylene groups. The ^1H piperazine signals show, with pH and temperature, changes in their shape as a consequence of the different rates of dynamic exchange between the two different chair conformations. This point will be discussed further below.

It has been possible to differentiate between the resonances of protons H^1 and H^3 of the propylenic chain of L by virtue of ^1H–^1H correlations in Me_2SO.[7] For instance, when L·4HCl is dissolved in Me_2SO a signal at δ 9.65 corresponding to the amine protons (NH^1) is observed. This signal correlates with the benzylic protons (H^4 at δ 4.16) and with a signal of the propylenic chain which must be that of protons H^3 (δ 2.96). Therefore, from these experiments and from two-dimensional ^1H–^{13}C correlations all the methylene carbons can be unambiguously assigned.

The variation with the pH of the NMR resonances of the β-carbon atoms and of the α-hydrogens with respect to the nitrogens bearing protonation are of great help in establishing the protonation schemes in polyamine molecules.[24] In Fig. 1(*a*) we present such plots for L. In the range pH 11.0–8.0 where the first four protons bind to L a noticeable upfield shift of the signal of the aromatic carbon atom CB^1 β to N^1 occurs. This together with the non-significant variation, in this pH range, of the CP^1 signal and with the downfield shifts of those of H^3 and H^4, both α to the benzylic nitrogens, strongly suggests that the first four protonations take place on the benzylic nitrogens (N^1). For L^2 the almost negligible variations in the chemical shift of the signal of the piperazine carbons in the range pH 11–5, together with its upfield shift below pH 5 where the third and fourth protonations occur, support a double protonation of the primary nitrogens in both the first two steps. The variations with pH of the ^1H signals agree with the proposed protonation trend [see Fig. 1(*b*)]. Indeed, the larger downfield shifts of the H^1 and HP^1 signals, which are in parallel, occur at pH < 5 while those of H^3, α to the terminal nitrogens, are observed in the range pH 11–8.

The enthalpy and entropy terms for L and L^2 (Table 2) give further insight into the protonation mechanisms. Also included are the corresponding terms for L^1 for comparison. The first two protonations of L, which mainly involve the benzylic nitrogens as inferred from the NMR study, are accompanied by similarly favourable enthalpic contributions. Of note are the remarkable entropy terms associated with the first protonation of L which significantly contributes to the spontaneity of these reactions. A similar situation was found for the first protonation of L^1 (see Table 2) and was ascribed to a large release of water molecules due to the hydrophobicity afforded by the benzene moiety to these sites.[7] The first two protonations of L^2, which occur on the primary terminal nitrogens, display larger enthalpy terms and lower entropy ones than those of L on account of the different nature and hydrophobicity of the protonation sites.

The influence on the thermodynamic parameters of the type of sites bearing protonation is further reflected in the enthalpy and entropy contributions associated with the fifth protonation of L and the third one of L^2, in which the piperazine nitrogens start to protonate. Indeed, for both compounds, a marked diminution in exothermicity and increases in the entropic

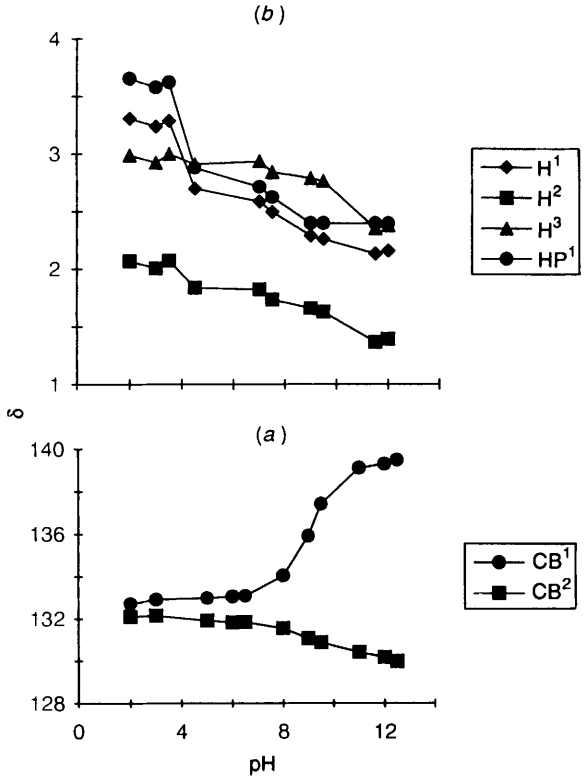


Fig. 1 Variation of chemical shifts with the pH for (*a*) aromatic carbons of L, and (*b*) proton resonances of L^2. Spectra were recorded at room temperature

contributions are observed at these stages probably denoting stiffening of the piperazine ring as well as the tertiary nature of the protonation sites.

It is interesting that the enthalpy change for the fourth protonation step of L is significantly more negative than those for the preceding steps. A similar behaviour has recently been observed for the hexamethylhexaaza[9.9]paracyclophane L^3.[25] In that case the more favourable enthalpic contribution was explained assuming that, as observed in the crystal structure of $[H_4L^3][ClO_4]_4$, also in solution the unprotonated amino groups contribute to the stabilization of the $[H_4L^3]^{4+}$ species. It seems reasonable that an analogous arrangement of the protonated centres could be present also in our compound.

The lower seventh enthalpy term of L provides evidence for the shorter-range electrostatic interactions caused by protonation of a nitrogen separated from the adjacent polyammonium sites by the ethylenic chains of piperazine and by a propylenic chain.[26] The similarity between the thermodynamic parameters associated with the fifth and sixth protonations of L gives further support to the proposed protonation mechanism.

Dynamic variable-temperature NMR analysis

Variable-temperature ^1H NMR spectra of free L and L^2 recorded in $CDCl_3$ and CD_3OD in the temperature range 40–50 °C show, for both compounds, exchange processes characteristic of chair–chair interconversion of the piperazine ring. At room temperature a broad signal is observed denoting rapid exchange processes resulting in magnetic equivalence of all the piperazine protons. At higher temperatures the signal is much narrower while at lower ones these protons appear as AA'BB' spin systems. The coalescence temperature for the equilibrium AA'BB' $\rightleftharpoons$ BB'AA' is *ca.* 10 °C for both compounds. The rate constants at different temperatures were calculated by means of a modified version of the DNMR 3 program[22] by varying their values until satisfactory fits between simulated and experimental spectra were obtained. From the values of the rate constants at different temperatures

Table 2 Stepwise enthalpy and entropy terms (kJ mol^{-1}) for the protonation of compounds L and L^2. Values for L^1 from ref. 8 are also included

	$-\Delta H°$			$T\Delta S°$		
Reaction	L	L^1	L^2	L	L^1	L^2
$H + L \rightleftharpoons HL$[a]	40.6(8)[b]	40.0[c]	50.8(2)	16.3(8)	17[c]	7.9(2)
$H + HL \rightleftharpoons H_2L$	45.6(8)	45.6	51.9(2)	9.6(8)	6.3	2.7(2)
$H + H_2L \rightleftharpoons H_3L$	42.3(8)	44.8	25.1(2)	6.7(8)	−2.5	14.2(2)
$H + H_3L \rightleftharpoons H_4L$	49.4(8)	29.3	19.7(3)	−2.9(8)	−8.8	−3.8(3)
$H + H_4L \rightleftharpoons H_5L$	33.0(8)			5.0(8)		
$H + H_5L \rightleftharpoons H_6L$	31.8(8)			3.3(8)		
$H + H_6L \rightleftharpoons H_7L$	25(1)			−7(1)		

[a] Charges omitted for clarity. [b] Values in parentheses are standard deviations in the last significant figure. [c] Taken from ref. 9.

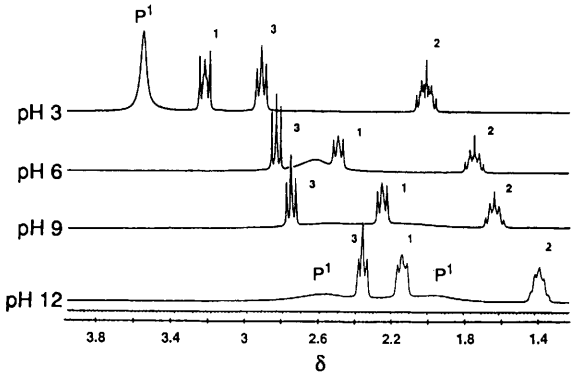


Fig. 2 Proton NMR spectra at room temperature at different pH values in D_2O solution for L^2

and applying the Eyring-plot method, straight lines were obtained from which the activation parameters were derived. The activation enthalpies for both compounds are almost equal within the experimental errors [$\Delta H^‡ = 61(2)$ for L, 63(4) kJ mol^{-1} for L^2] the entropy terms are almost negligible [$\Delta S^‡ = 0.3(1)$ kJ K^{-1} mol^{-1}]. Therefore the cyclic topology and the presence of the *p*-phenylene moieties in L does not seem to affect the chair–chair interconversion.

The dynamic processes are strongly dependent on the protonation of the piperazine ring, and a decrease of the coalescence temperature is observed upon increasing the acidity of the medium (see Fig. 2). For instance, the activation enthalpy term of L^2 under these conditions is $\Delta H^‡ = 20(4)$ kJ mol^{-1}. Similar values are obtained for the macrocycle L. This suggests that protonation of the piperazine ring facilitates nitrogen inversion and consequently the chair–chair interconversion process.

Copper(II) co-ordination

Compound L forms with Cu^{2+} the complexes $[Cu(H_3L)]^{5+}$ and $[Cu_2L]^{4+}$ in the range pH 3–7 with stability constants log $\beta_{CuH_3L} = 33.20(6)$ and log $\beta_{Cu_2L} = 16.6(1)$.* Solubility problems prevented us from investigating higher pH ranges. The UV/VIS electronic spectrum of $[Cu_2L]^{4+}$ consists of a broad band centred around 16 000 cm^{-1}.

The first aspect of note is the low stability of the binuclear species in comparison with those of related ligands containing bridges with only secondary nitrogen atoms. For instance, Pietraszkiewics and co-workers[27] have reported a value of log $K_{Cu_2L} = 26.3$ for the formation in dmf of the binuclear complex of L^4 containing two dipropylenetriamine bridges separated by *p*-phenylene spacers. Furthermore the $[Cu_2L]^{4+}$ complex is

* The constants β_{CuH_3L} and β_{Cu_2L} refer to the equilibria $Cu + 3H + L \rightleftharpoons Cu(H_3L)$ and $2Cu + L \rightleftharpoons Cu_2L$, respectively, charges omitted.

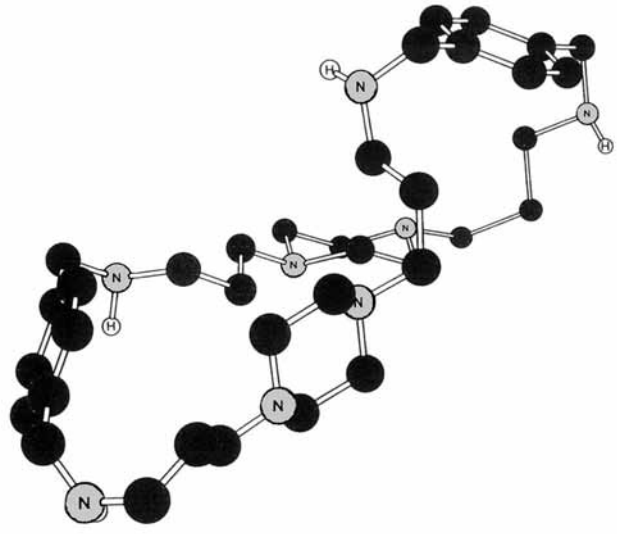


Fig. 3 The MACROMODEL minimum-energy drawing for L

even less stable than that formed by L^3 (log K 18.35) containing three tertiary amino groups in each co-ordination site.[25] Reductions in stability have also been observed for tetraaza macrocycles containing piperazine subunits. Indeed, reinforced (1,4-C_2)[12]aneN$_4$ forms a $[CuL]^{2+}$ complex three logarithmic units less stable than that with the well known [12]aneN$_4$ (1,4,7,10-tetraazacyclododecane).[2] Larger reductions are observed in the case of open-chain ligands, for instance 7.8 logarithmic units between the formation constants of the $[CuL]^{2+}$ complexes of 4,7-diazadecane-1,10-diamine and L^2 [log $K_{CuL^2} = 13.810(5)$ in 0.15 mol dm^{-3} $NaClO_4$ at 298.1 K, broad UV/VIS band centred at 17 500 cm^{-1}].[2,23] This large destabilization has been ascribed to the fact that L^2 has to reorganize the piperazine ring from the low-energy chair form to the boat form to co-ordinate the metal ion in a tetradentate mode. The two conformers are about 29 kJ mol^{-1} apart in energy[2] which means about five logarithmic units in the value of the stability constant, and thus reorganization of the piperazine ring strongly reduces the thermodynamic ability of L^2 to incorporate the metal ion. In fact the enthalpy term we have determined for the formation of $[CuL^2]^{2+}$ is very low in comparison with related tetraazaalkanes [$\Delta H°_{CuL^2} = -35.0(2)$, $T\Delta S°_{CuL^2} = 43.9(4)$ kJ mol^{-1}]. The compound (1,2-C_2)[12]aneN$_4$ is in the boat conformation before complexation and consequently the reduction in stability is not so drastic as for open-chain ligands.

Model studies show for L a minimum-energy situation in which both piperazine rings are in the low-energy chair conformation (Fig. 3).[28] Therefore, to achieve co-ordination of both metal centres the piperazine rings have to change their conformation, with the corresponding energy loss.

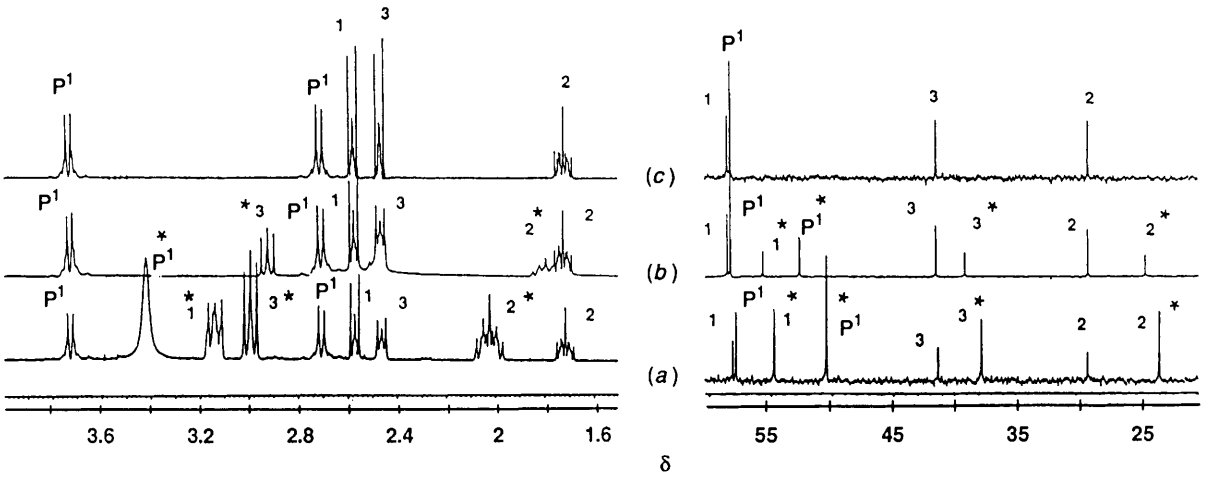


Fig. 4 Proton (left) and carbon (right) NMR spectra in D_2O at different pH values and with different molar ratios $R = [Pd^{2+}]:[L^2]$: (*a*) pH 3 and $R = 0.3$; (*b*) pH 6 and $R = 0.6$; (*c*) pH 10 and $R = 1$

Palladium(II) co-ordination

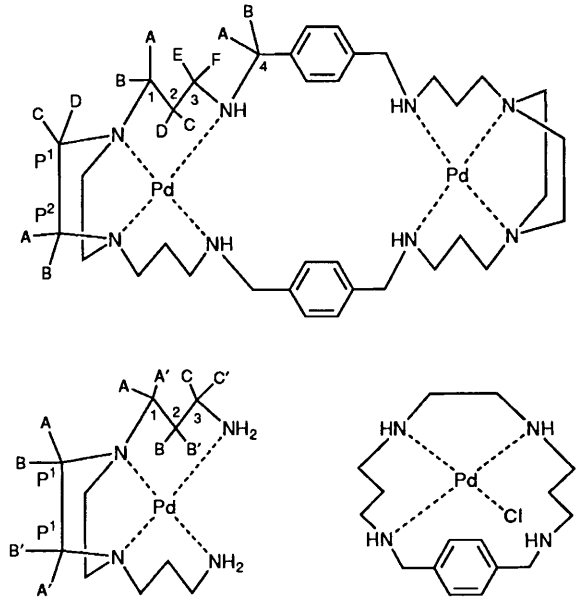
The formation of palladium(II) complexes in D_2O solutions by L and L^2 has been monitored by ^1H and ^{13}C NMR spectroscopy. In contrast with the observed fluxionality for both free compounds, palladium(II) imposes high rigidity on the ligand fixing the piperazine moieties.

In Fig. 4 are shown ^1H and ^{13}C NMR spectra of L^2 and palladium(II) solutions containing increasing molar ratios $R = [Pd^{2+}]:[L^2]$ at different pH values. As R increases the peaks of free L^2 (marked with an *) progressively disappear, while those of the complex species appear. For molar ratios $R \geqslant 1$ no further changes are observed.

The ^{13}C NMR spectrum of solutions containing Pd^{2+} and L^2 with a molar ratio $R = 1$, at pH 10 [Fig. 4(*c*)], consist of four signals at δ 29.02, 41.35, 57.86 and 58.12 which can be assigned to carbon atoms C^2, C^3, CP^1 and C^1 respectively. The ^1H NMR spectrum of the same solutions displays an AA'BB'CC' spin system for the propylenic chain with chemical shifts δ_B 1.72 (H^2), δ_C 2.47 (H^3) and δ_A 2.58 (H^1) with geminal coupling constants $J_{AA'} = -15.76$, $J_{BB'} = -16.87$ and $J_{CC'} = -16.21$ Hz and vicinal ones $J_{AB} = 2.90$, $J_{AB'} = 8.22$, $J_{BC} = 6.83$ and $J_{BC'} = 3.34$ Hz. These patterns show, for the ethylenic chains of the propylenic bridge, *trans-gauche* disposition. The piperazine protons (P^1) appear at this pH as an AA'BB' spin system with δ_A 2.71, δ_B 3.73, $J_{AB} = -12.47$ Hz and vicinal coupling constants $J_{AA'} = 5.65$, $J_{AB'} = 5.54$ and $J_{BB'} = 4.36$ Hz, as a consequence of the boat conformation adopted by the piperazine ring in the complex. The number of peaks in the spectra of the complex species and their chemical shifts remain unaffected when decreasing the pH, and even at pH 3 [Fig. 4(*a*)] they remain constant.

The ^1H NMR spectra behave similarly and the peaks attributable to free amine fully disappear for molar ratios $R \geqslant 1$. These facts demonstrate the strong interaction between Pd^{2+} and L^2, which blocks piperazine in the boat conformation, as well as the non-labile characteristics of the complexation process. Additionally, the displacements of the ^1H and ^{13}C NMR signals upon complexation reveal the involvement of all the nitrogen atoms of L^2 in the co-ordination to Pd^{2+} (Scheme 2).

On the other hand, the ^{13}C NMR spectrum of solutions of Pd^{2+} and L with molar ratio $R = [Pd^{2+}]:[L] = 2:1$ at pH 7 (for lower ratios the peaks of the complex species coexist with those of free L) consists of four signals at δ 57.00 (C^4), 58.90 (C^1), 24.30 (C^2) and 50.16(C^3) for the benzylic and for the carbon atoms of the propylenic chains, and of two different signals at δ 56.31 and 60.74 for the carbon atoms P^1 and P^2 of the piperazine moieties (see Fig. 5). The proton NMR spectrum is rather complex and does not allow one to determine the



Scheme 2

coupling constants, however by using ^1H–^1H and ^1H–^{13}C correlations it is possible to assign the chemical shifts of all the different peaks. As seen in Fig. 5, each carbon signal correlates with two proton signals indicating that co-ordination to Pd^{2+} imposes, in this case, an even greater rigidity than for L^2 and, apart from blocking the piperazine ring in the boat conformation, removes the equivalence of the protons of each of the methylene groups. Indeed, the benzylic protons (H^4) display an AB spin system (δ_A 4.30, δ_B 3.75, $J_{AB} = -13.2$ Hz) and the propylenic carbons appear as an ABCDEF spin system (H^1, δ_A 2.75, δ_B 2.56; H^2, δ_C 1.97, δ_D 1.87; H^3, δ_E 2.45, δ_F 2.46). A similar situation was found in the binuclear palladium(II) complex of the polyazamacrocycle 1,4,7,10,13,16,19,22-octaazacyclotetracosane.[29] While in $[PdL^2]^{2+}$ the piperazine carbons are equivalent and the protons show an AA'BB' spin system, in the binuclear complex of L these carbons are non-equivalent and the protons consist of an ABCD spin system (P^2, δ_A 3.91, δ_B 2.81; P^1, δ_C 3.75, δ_D 2.59).

The analysis of these spectral features also suggests for L a symmetric mode in which all the nitrogens are involved in co-ordination to both metal centres. Recently we have shown[8,9] that the presence of the *p*-phenylene moieties precludes simultaneous co-ordination of the benzylic nitrogens at each side of a benzene moiety to the same metal centre. The ^{13}C NMR spectrum of the complex $[PdL^1]^{2+}$, in which co-

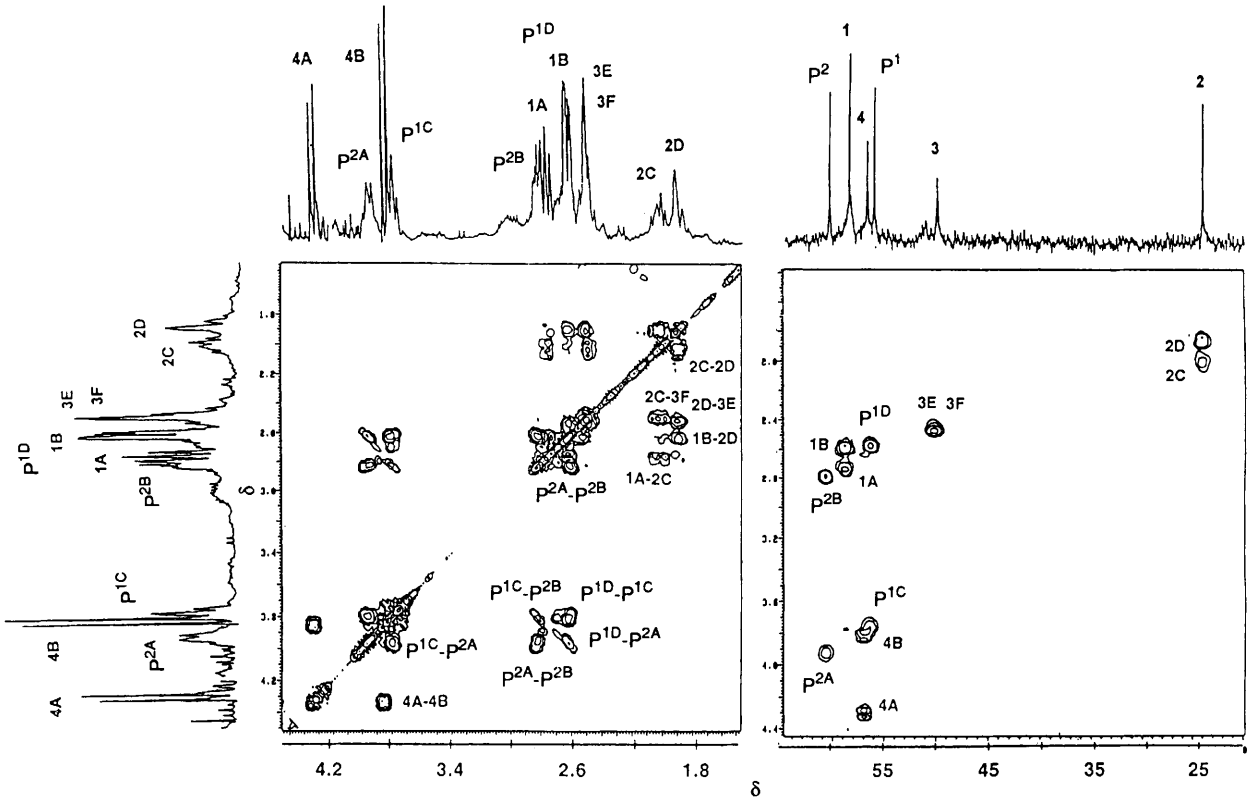


Fig. 5 Correlated ^1H–^1H (left) and ^1H–^{13}C (right) NMR spectra for $[Pd_2L]$ in D_2O solution at pH 7. All the different cross-peaks have been labelled according to Scheme 2

ordination occurs in a non-symmetric way through three out of the four nitrogens in the macrocycle (Scheme 2), shows as many signals as there are carbon atoms in the molecule.[30]

Hence all these data, together with the non-labile characteristics of the complexes formed, indicate that the only possible symmetric co-ordination mode of Pd^{2+} by L is the one depicted in Scheme 2, in which both of the piperazine nitrogens and two benzylic nitrogens of different *p*-phenylene subunits participate in the co-ordination of each metal centre.

Conclusion

The synthesis of the novel compound L demonstrates the preference of the piperazine rings for 2:2 over 1:1 condensations. A similar synthetic procedure yields 1:1 cyclizations when no double rings are present in the polyamine fragment. Protonation of L occurs alternately on each side of L, the first entropically favoured protonations occurring at the benzylic nitrogens. Variable-temperature NMR analysis of L and L^2 shows similar activation parameters for the chair–chair interconversion. However, this dynamic process depends on the pH and protonation of the piperazine nitrogen favours the interconversion, decreasing its activation enthalpy.

Copper(II) complexes of L and L^2 are characterized by low stabilities in comparison with those of related ligands, which can be attributed to the reorganization upon co-ordination of the piperazine ring from the low-energy chair conformation to the boat form. The NMR data for the palladium(II) complexes of L and L^2 indicate high rigidity of the ligand conformation, particularly for L, allowing for a full structural characterization in solution of these species.

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