# Synthesis and Protonation Behaviour of the Macrocyclic Ligand 1,4,7,13-Tetramethyl-1,4,7,10,13,16-hexaazacyclooctadecane and of its Bicyclic Derivative 4,7,10,17,23-Pentamethyl-1,4,7,10,13,17,23-heptaazabicyclo[11.7.5]-pentacosane. A Potentiometric and $^1H$ and $^{13}C$ NMR Study

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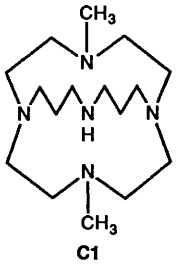
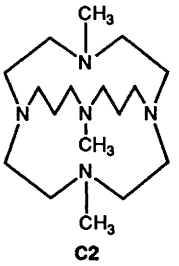
The synthesis and characterization of the new macrocyclic ligand 1,4,7,13-tetramethyl-1,4,7,10,13,16-hexaazacyclooctadecane (**L**) and of its bicyclic derivative 4,7,10,17,23-pentamethyl-1,4,7,10,13,17,23-heptaazabicyclo[11.7.5]pentacosane (**L1**) is reported. The basicity behaviour of both polyamines has been studied by potentiometry in 0.15 mol $dm^{-3}$ $NaClO_4$ solution at 298.15 K and the relevant protonation constants have been determined. $^1H$ and $^{13}C$ NMR spectroscopy of **L** and **L1**, at various pH values, allows the main features of the protonation patterns to be determined.

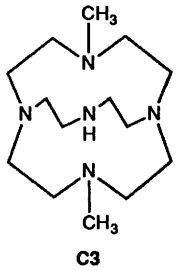
In the last few years great interest has been shown in the synthesis of aza-ligands with a macrobicyclic arrangement of donor atoms.[1–5] The first work on this topic dealt with metal–ion template reactions yielding 'cryptate' complexes.[1] The impossibility of obtaining metal-free ligands from these complexes prevented the complexation equilibria from being studied. More recently a series of small macrobicyclic cage-like ligands containing five nitrogen atoms in their framework (**C1**–**C4**) have been obtained in our laboratories by means of



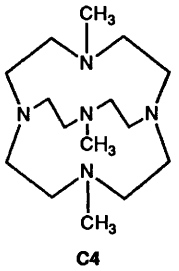
**C1**



**C2**

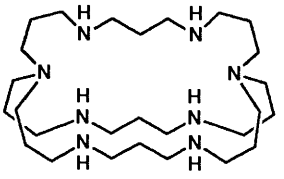


**C3**

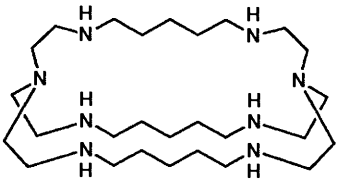


**C4**

non-template reactions.[2–4] These ligands have shown particular properties such as extremely high basicity ('proton sponge' behaviour),[2] ability to form very stable $Li^+$ complexes in aqueous solution and selectivity towards $Li^+$ among alkali metal ions.[3,4] In addition, larger macrobicyclic ligands com-



**I**



**II**

posed of two tripodal subunits and containing eight nitrogen atoms (**I** and **II**) have been synthesized by a non-template reaction and used for both cation and anion complexation.[5] These results have prompted us to further investigate how the dimensions of the macrobicyclic cavity and the number of nitrogen donor atoms determine the coordination properties of ligands with such a topology. With this aim, we have adopted the synthetic pathway used for the synthesis of small macrobicyclic aza-ligands to obtain the larger cage 4,7,10,17,23-pentamethyl-1,4,7,10,13,17,23-heptaazabicyclo[11.7.5]pentacosane (**L1**) (Scheme 1) containing seven nitrogen atoms. Along this new synthetic pathway (Scheme 1) we have prepared the tetramethylated hexaazamacrocycle 1,4,7,13-tetramethyl-1,4,7,10,13,16-hexaazacyclooctadecane (**L**) in which the presence of two unprotected nitrogen groups allows for the insertion of bridging arms. In this paper we report the synthesis of **L** and **L1** as well as the results of a thermodynamic and $^{13}C$ NMR spectroscopic study on the interaction of both polyamines with $H^+$ in aqueous solution.

## Experimental

*Synthesis of* 1,4,7,13-*Tetramethyl*-1,4,7,10,13,16-*hexaazacyclooctadecane* (**L**) *and* 4,7,10,17,23-*Pentamethyl*-1,4,7,10,13,17,23-

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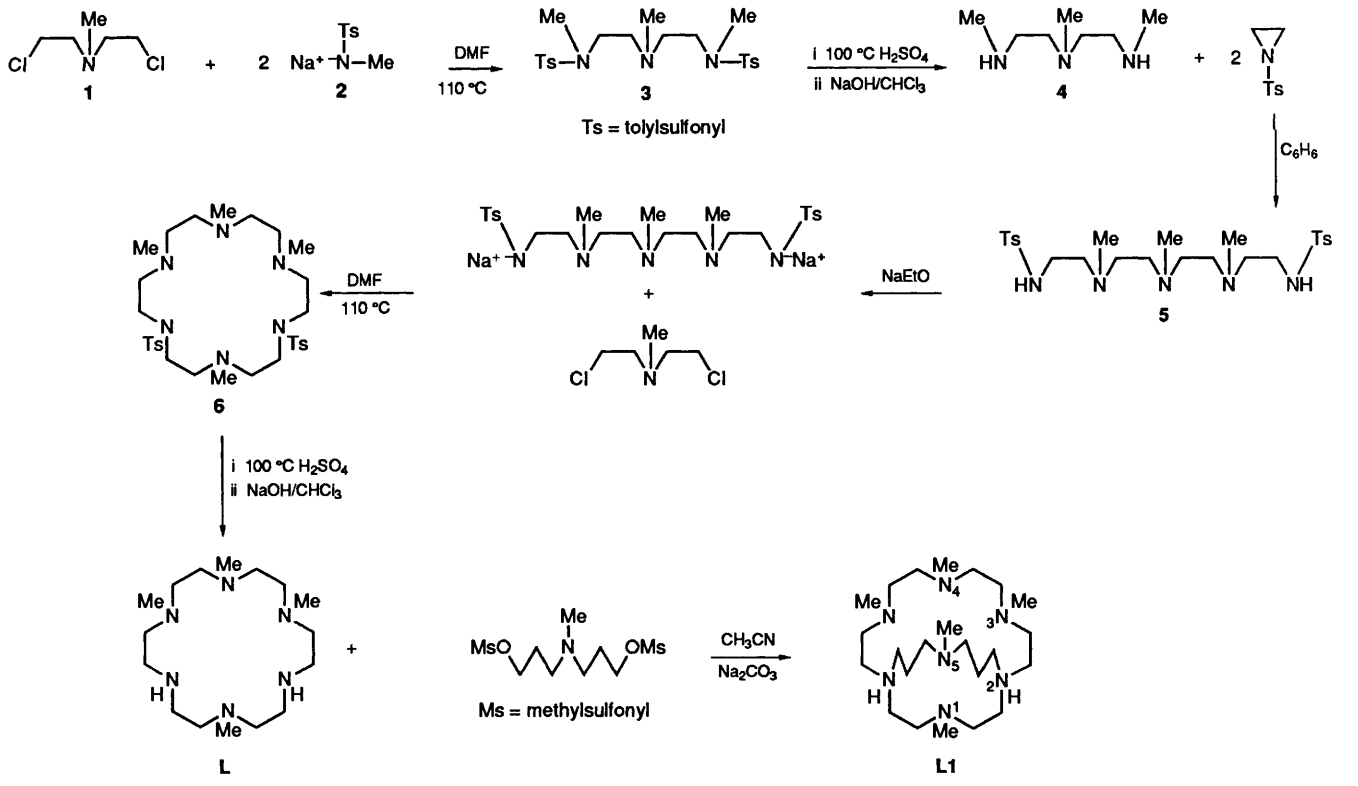



Scheme 1

*heptaazabicyclo*[11.7.5]*pentacosane* (**L1**).—The synthetic procedure followed to prepare compounds **L** and **L1** is shown in Scheme 1.

1,4,7-*Trimethyl*-1,7-*bis*(p-*tolylsulfonyl*)-1,4,7-*triazaheptane* (**3**).—All reactions were carried out in a nitrogen atmosphere. A solution of sodium (5.1 g, 0.22 mol) in dry ethanol (150 $cm^3$) was added to a hot solution of *N*-(*p*-tolylsulfonyl)-*N*-methylamine (36.6 g, 0.2 mol) in dry ethanol (150 $cm^3$). The resulting suspension was refluxed for *ca.* 30 min and then solvent was evaporated under reduced pressure to give the solid compound **2**. This was dissolved in dry DMF (200 $cm^3$) and to the resulting solution, heated at 110 °C, was added bis(2-chloroethyl)methylamine[6] (**1**) (15.6 g, 0.1 mol) in 100 $cm^3$ of dry DMF with stirring over a period of *ca.* 2 h. The solution was maintained at 110 °C for a further hour and the crude compound **3** was precipitated by addition of 1.5 $dm^3$ of water. The product was filtered off, washed with water, dissolved in the minimum quantity of hot ethanol and boiled for *ca.* 20 min in the presence of activated carbon. Water was added to the filtered hot solution till it became turbid. On cooling the crystalline white compound **3** separated. This was filtered off, washed with diethyl ether and dried *in vacuo* at 40 °C (37 g, 81.5%). M.p. 88–89 °C (Found: C, 55.5; H, 6.9; N, 9.2. Calc. for $C_{21}H_{31}N_3O_4S_2$: C, 55.60; H, 6.89; N, 9.26%).

1,4,7-*Trimethyl*-1,4,7-*triazaheptane* (**4**).—Compound **3** (63 g, 0.14 mol) was dissolved in 130 $cm^3$ of 96% $H_2SO_4$ and the resulting solution was kept at 100 °C for 72 h. The solution was cooled and added dropwise to *ca.* 700 $cm^3$ of diethyl ether with stirring to give a thick oil which was separated and washed with diethyl ether. The residue was dissolved in the minimum amount of water and made alkaline by addition of concentrated aqueous NaOH. A crystalline white compound (sodium sulfate) formed. The solid was separated by filtration and the alkaline solution containing compound **4** was extracted a few times with chloroform. The solid residue was washed with chloroform and the resulting organic solution was combined with those derived from the extractions, dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure to obtain a yellowish oil. This was purified by distillation at 30 mbar, recovering the fraction at 85 °C (13,5 g, 66%).

1,13-*Bis*(p-*tolylsulfonyl*)-4,7,10-*trimethyl*-1,4,7,10,13-*pentaazatridecane* (**5**).—A solution of *N*-(*p*-tolylsulfonyl)aziridine[7] (8.5 g, 0.043 mol) in anhydrous benzene (200 $cm^3$) was added dropwise, at room temperature in a nitrogen atmosphere, to a stirred solution of **4** (6.13 g, 0.043 mol) in anhydrous benzene (400 $cm^3$) during a period of 7 h. The resulting solution was kept at room temperature for *ca.* 12 h and then a further 8.5 g (0.043 mol) of *N*-(*p*-tolylsulfonyl)aziridine in 200 $cm^3$ of anhydrous benzene was added under the same conditions. After 12 h the turbid solution was filtered and evaporated under reduced pressure to give the solid, crude compound **5**. The product was dissolved in 200 $cm^3$ of ethanol, and boiled for *ca.* 20 min in the presence of activated carbon. After filtration, excess of 37% HCl was added to the solution to obtain **5**·3HCl as a white solid. The hydrochloride salt was filtered off, washed with ethanol and dried *in vacuo* at 100 °C (20.9 g, 76%). M.p. 177–179 °C (Found: C, 46.2; H, 6.9; N, 10.7. Calc. for $C_{25}H_{44}N_5Cl_3O_4S_2$: C, 46.26; H, 6.83; N, 10.79%).

10,16-*Bis*(p-*tolylsulfonyl*)-1,4,7,13-*tetramethyl*-1,4,7,10,13,16-*hexaazacyclooctadecane* (**6**).—All reactions were carried out in a nitrogen atmosphere. A solution of sodium (1.25 g, 0.052 mol) in dry ethanol (50 $cm^3$) was added to a hot solution of **5**·3HCl (6.71 g, 0.01 mol) in dry ethanol (100 $cm^3$). The resulting suspension was refluxed for *ca.* 30 min then the solvent was evaporated under reduced pressure. The solid residue was dissolved in dry DMF (50 $cm^3$) and to the resulting solution, heated at 110 °C, was added a solution of **1** (1.76 g, 0.11 mol) in 100 $cm^3$ of dry DMF with stirring over a period of *ca.* 4 h. The reaction mixture was kept at 110 °C for a further 2 h. The solution was then cooled, filtered and evaporated under reduced

**Table 1** Logarithms of the protonation constants of **L**, **L1** and **L2** in 0.15 mol $dm^{-3}$ aqueous $NaClO_4$ at 298.15 K

| Reaction | log *K* | | |
|---|---|---|---|
| | **L**[a] | **L1**[a] | **L2**[b] |
| $L + H^+ = LH^+$ | 9.75(1)[c] | 10.85(1) | 10.15(1) |
| $L + 2H^+ = LH_2^{2+}$ | 18.87(1) | 19.95(2) | 19.63(1) |
| $L + 3H^+ = LH_3^{3+}$ | 26.40(1) | 27.90(2) | 28.52(1) |
| $L + 4H^+ = LH_4^{4+}$ | 28.99(2) | 34.14(2) | 32.76(1) |
| $L + 5H^+ = LH_5^{5+}$ | | 36.19(5) | 35.00(1) |
| $L + 6H^+ = LH_6^{6+}$ | | | 36.0(1) |
| $LH^+ + H^+ = LH_2^{2+}$ | 9.11 | 9.10 | 9.48 |
| $LH_2^{2+} + H^+ = LH_3^{3+}$ | 7.53 | 7.95 | 8.89 |
| $LH_3^{3+} + H^+ = LH_4^{4+}$ | 2.59 | 6.24 | 4.27 |
| $LH_4^{4+} + H^+ = LH_5^{5+}$ | | 2.05 | 2.21 |
| $LH_5^{5+} + H^+ = LH_6^{6+}$ | | | 1.0 |

[a] This work. [b] Taken from ref. 11. [c] Values in parentheses are standard deviation in the last significant figure.

pressure to give a yellowish oil which was dissolved in the minimum quantity of chloroform and chromatographed on neutral alumina (70–230 mesh, activity I). The fractions were analysed by TLC over neutral alumina using chloroform as eluent; those showing one product with $R_f$ 0.74 were collected and evaporated under reduced pressure to obtain a colourless oil (2.9 g, 47%).

1,4,7,13-*Tetramethyl*-1,4,7,10,13,16-*hexaazacyclooctadecane* (**L**).—A solution of **6** (2.9 g, 0.0047 mol) was dissolved in 8 $cm^3$ of 96% $H_2SO_4$ and the resulting solution kept at 100 °C for 72 h. The solution was cooled and added dropwise to 200 $cm^3$ of diethyl ether, with stirring, to give a thick oil which was separated and washed with diethyl ether. The residue was dissolved in the minimum amount of water and made alkaline with concentrated aqueous NaOH. A crystalline white precipitate (sodium sulfate) formed. The solid was separated by filtration and the alkaline solution containing compound **L** was extracted several times with chloroform. The solid residue was washed with chloroform and the resulting organic solution was combined with those derived from the extractions, dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure to obtain **L** as a colourless oil (1.3 g, 88%) (Found: C, 61.1; H, 12.2; N, 26.7. Calc. for $C_{16}H_{38}N_6$: C, 61.10; H, 12.18; N, 26.72%).

The hexamine **L** has been purified as its hexahydrochloride salt by treating a solution of **L** in ethanol with 37% HCl (Found: C, 36.0; H, 8.3; N, 15.8. Calc. for $C_{16}H_{44}N_6Cl_6$: C, 36.04; H, 8.32; N, 15.76%).

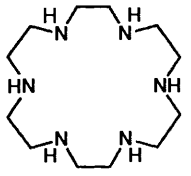
4,7,10,17,23-*Pentamethyl*-1,4,7,10,13,17,23-*heptaazabicyclo*-[11.7.5]*pentacosane* (**L1**).—In a nitrogen atmosphere a solution of the hydrochloride salt of *N*,*N*-bis(methylsulfonyloxy-*n*-propyl)methylamine[7] (**7**) (1.25 g, 0.0037 mol) in dry acetonitrile (100 $cm^3$) was added, over a period of 6 h, to a boiling, stirred solution of **L** (1.2 g, 0.0037 mol) in dry acetonitrile (100 $cm^3$) containing $Na_2CO_3$ (1.17 g, 0.011 mol). The suspension was heated to reflux for a further hour, then cooled and filtered. The resulting solution was evaporated under reduced pressure to give a yellowish oil, which was dissolved in chloroform and chromatographed on neutral alumina (70–230 mesh, activity II-III) with a 80:1 chloroform–ethanol mixture. The eluted solution was evaporated to dryness to give the crude compound **L1** as a colourless oil. The compound **L1** was purified as **L1**·4$HClO_4$ by treating the solution of **L1** in ethanol with 70% $HClO_4$ (0.6 g, 22%) (Found: C, 33.4; H, 6.7; N, 11.9. Calc. for $C_{23}H_{55}N_7Cl_4O_{16}$: C, 33.38; H, 6.70; N, 11.85%).

*EMF Measurements*.—The potentiometric titrations were carried out in 0.15 mol $dm^{-3}$ $NaClO_4$ at 298.15 K, using the equipment already described.[8] The reference electrode was an Ag/AgCl electrode in saturated aqueous KCl. The glass electrode was calibrated as a hydrogen concentration probe by titrating well-known amounts of HCl with $CO_2$-free NaOH solutions and determining the equivalent point by Gran's method[9] which allows the determination of the standard potential, $E^\circ$, and the ionic product of water. The computer program SUPERQUAD[10] was used to calculate the protonation constants.

*NMR Spectroscopy*.—200.0 MHz $^1H$ NMR and 50.32 MHz $^{13}C$ spectra were recorded on Varian Gemini and Bruker AC-200 spectrometers in $D_2O$ solutions with dioxane as reference standard ($\delta$ = 67.4 ppm).

## Results and Discussion

*Protonation Equilibria*.[11]—The behaviour of **L** and **L1** towards protonation has been studied in 0.15 mol $dm^{-3}$ $NaClO_4$ solution at 298.15 K in the pH range 2–11. The values of the basicity constant for each protonation step of these polyamines are presented in Table 1 together with those previously reported[12] for the related unmethylated analogue 1,4,7,10,13,16-hexaazacyclooctadecane (**L2**). By using these equilibrium data,



**L2**

the distributions of the protonated species of **L**–**L2** formed as a function of pH have been calculated and the results are plotted in Fig. 1. Under the experimental conditions employed **L** and **L1** behave at most as tetraprotic and pentaprotic bases, respectively [Fig. 1(*a*,*b*)], while, in the same pH range, **L2** gives rise to the formation of an appreciable amount of the fully protonated species $H_6L2^{6+}$ [Fig. 1(*c*)].

As far as the protonation behaviour of **L** and **L2** is concerned, we can note that methylation of some nitrogen atoms (four out of six) of **L2** causes a lowering of basicity at each step of protonation (Table 1). On the other hand, similarly to **L2**, a sharp decrease in basicity is observed between the third and fourth stepwise constants of **L**. In fact, the difference between the first and third protonation constants is only 2.22 logarithm units while that between the third and fourth is 4.94. As previously reported,[13] this behaviour can be easily rationalized taking into account the fact that the first three protons can bind the macrocycle in alternate positions while the fourth has to be necessarily placed between two already protonated nitrogen atoms. A general increase of basicity with respect to **L** is observed for the macrobicyclic polyamine **L1** (Table 1). The first basicity constant of **L1** is rather high; at least in the first protonation step **L1** is a stronger base than the larger macrobicyclic ligands (**I** and **II**). The value of the first basicity constant is, however, much lower than the corresponding values found for the smaller macrobicyclic cage-like ligands **C1**–**C4**. In the following protonation steps **L1** does not present the grouping of protonation constants observed for **L** and **L2**, resembling instead large polyazacycloalkanes with odd numbers of nitrogen atoms.[13]

$^{13}C$ *and* $^1H$ *NMR Study of the Protonation Pattern of* **L**.—It was reported[14] that the $^{13}C$ NMR spectra of [3*k*]ane$N_k$ ligands

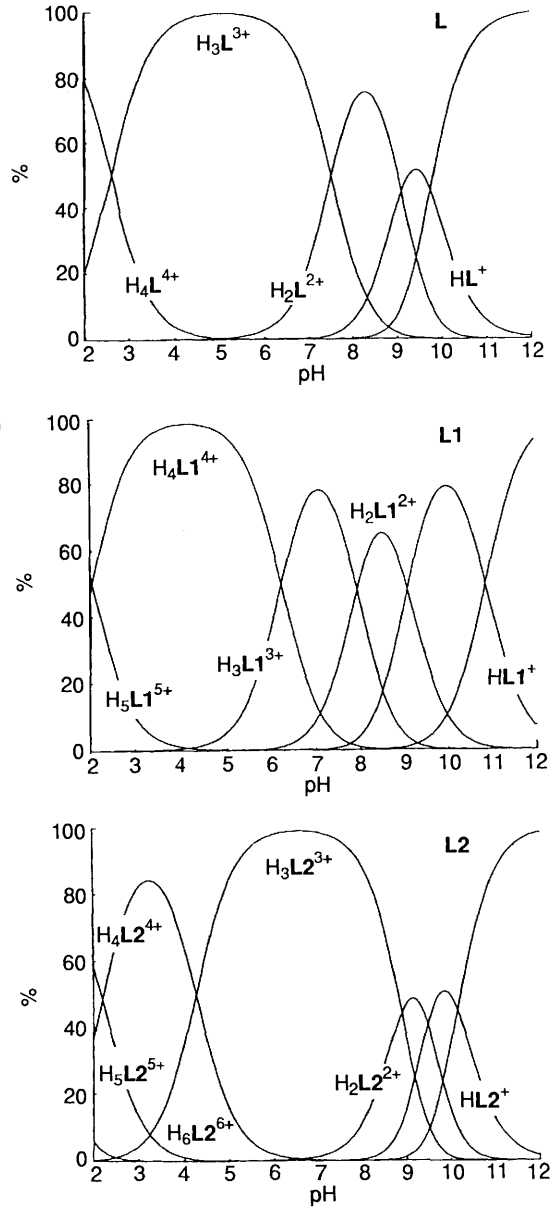
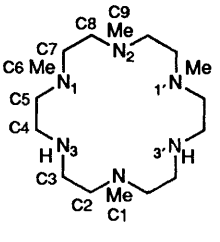



**Fig. 1** Distribution diagrams of the protonated species formed by **L**, **L1** and **L2**, as a function of pH, at 25 °C in 0.15 mol $dm^{-3}$ $NaClO_4$

consist of one resonance which undergoes, upon protonation, an upfield shift of *ca.* 4–5 ppm without splitting. All the carbon atoms remain magnetically equivalent independent of pH. The insertion of methyl groups in **L**, to give **L1**, removes the magnetic equivalence of the carbon atoms. The analysis of this spectra as well as $^1$H-$^1$H COSY and $^1$H-$^{13}$C HETCOR experiments performed at different pH values and the data available for similar amines allows one to deduce the main features of the protonation pattern.

Fig. 2 shows the $^{13}$C NMR chemical shifts of **L** as a function




**L**

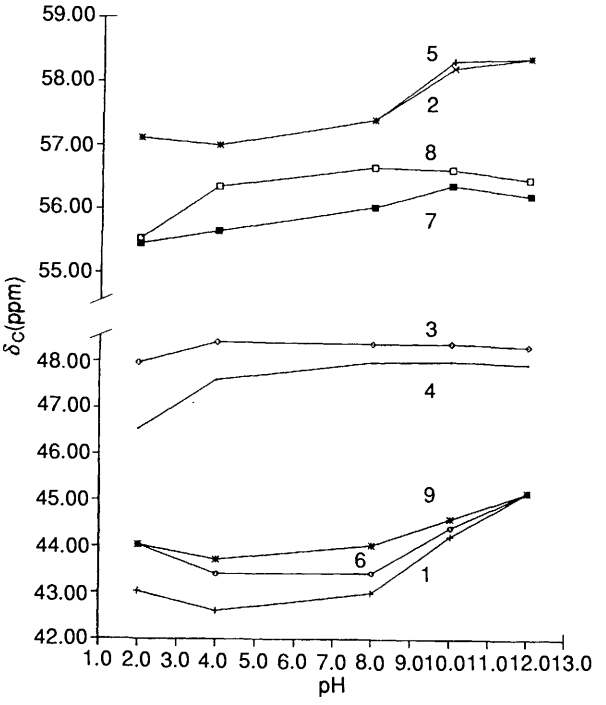



**Fig. 2** Experimental $^{13}$C NMR chemical shifts of **L** as a function of pH. Labels are reported as for **L**.

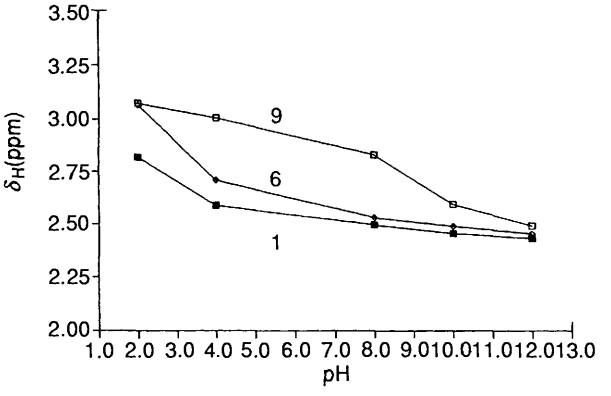



**Fig. 3** Experimental $^1$H NMR chemical shifts of the hydrogen atoms of the methyl groups of **L** as a function of pH. Labels refer to the carbon atoms as reported for **L**.

of pH. The spectrum of the free amine (pH 12) consists of six signals at 45.2, 47.9, 48.3, 56.2, 56.5 and 58.4 ppm, roughly integrating 4:2:2:2:2:4, respectively. The 45.2 ppm resonance corresponds to the methyl groups and the signals at 47.9 and 48.3 ppm to the carbon atoms labelled as C4 and C3, respectively.* At pH *ca.* 10 the methyl signal splits into three different signals integrating 1:2:1, while the signal at 58.4 ppm bears a small splitting. At this stage, all the other resonances do not bear significant changes. This suggests that the first proton binding the macrocycle is shared by the three contiguous methylated nitrogens (N1, N2 and N1′). At pH 8.0, both signals at lower fields (C2, C5) experience a clear upfield shift (Fig. 2). 2D $^1$H-$^1$H COSY and $^1$H-$^{13}$C HETCORR experiments performed at this pH indicated that such signals can be assigned to C2 and C5. It is well known that in these kinds of compound the carbon atoms shifting most upon protonation are those placed in the β-position with respect to the amino group that

* The numbering of the carbon atoms in the structures given does not correspond to systematic numbering.

protonates.[15] Therefore, the second proton attached to **L** should be shared by both secondary nitrogen atoms (N3 and N3′). On the other hand, the significant downfield shift (Fig. 3) experienced by the protons of one of the methyl carbon atoms (C9), integrating as one, suggests a localization of the first proton on the middle tertiary nitrogen (N2). The third protonation would take place also on the secondary nitrogens (Fig. 2). Below pH 4, the only resonances shifting upfield in the $^{13}C$ spectra are those of C4 and C8 (Fig. 2) according with protonation of the tertiary nitrogens N1 and N1′. It also agrees with the downfield shift experienced by the resonance of the protons of C6 (Fig. 3).

*$^{13}C$ and $^{1}H$ NMR Study of the Protonation Pattern of* **L1**.—The $^{13}C$ NMR spectra of **L1** (Fig. 4) display, over all the investigated pH range, one peak at *ca.* 25 ppm, corresponding to the carbon atom placed in the middle of the propylenic chain (C11), and two groups of signals. The first group (41–45 ppm) contains the resonances of the five methyl carbons and the other one (50–60 ppm) all the remaining carbon atoms of the

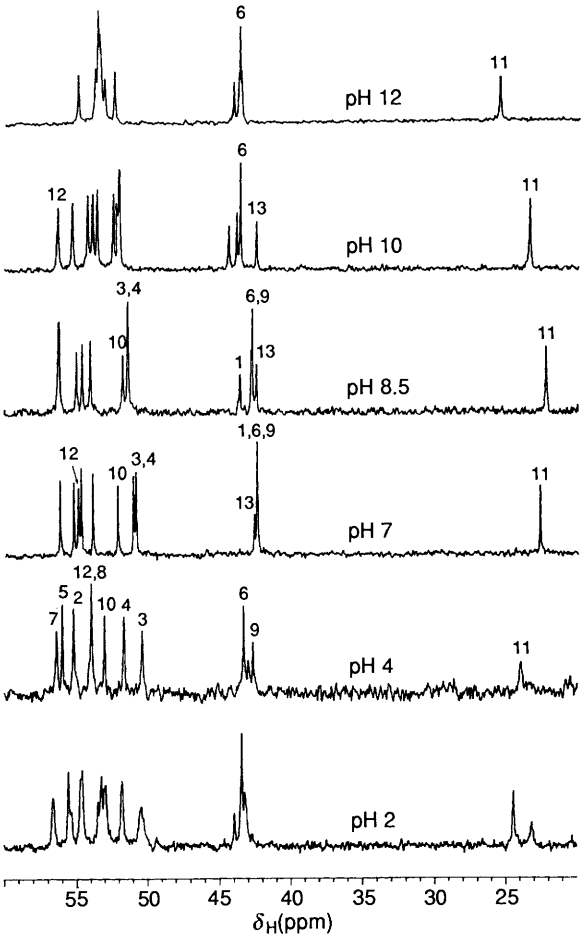
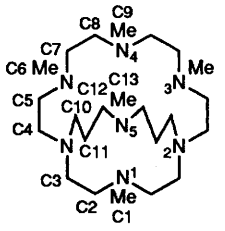



**Fig. 4** $^{13}C$ NMR spectra of **L1** at different pH values




**L1**

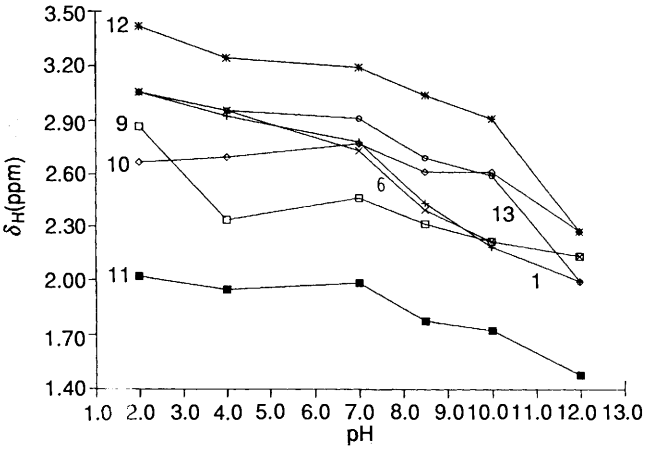



**Fig. 5** Experimental $^{1}H$ NMR chemical shifts of the hydrogen atoms of the methyl groups and of the propylenic bridge of **L1**. Labels are reported as for **L1**.

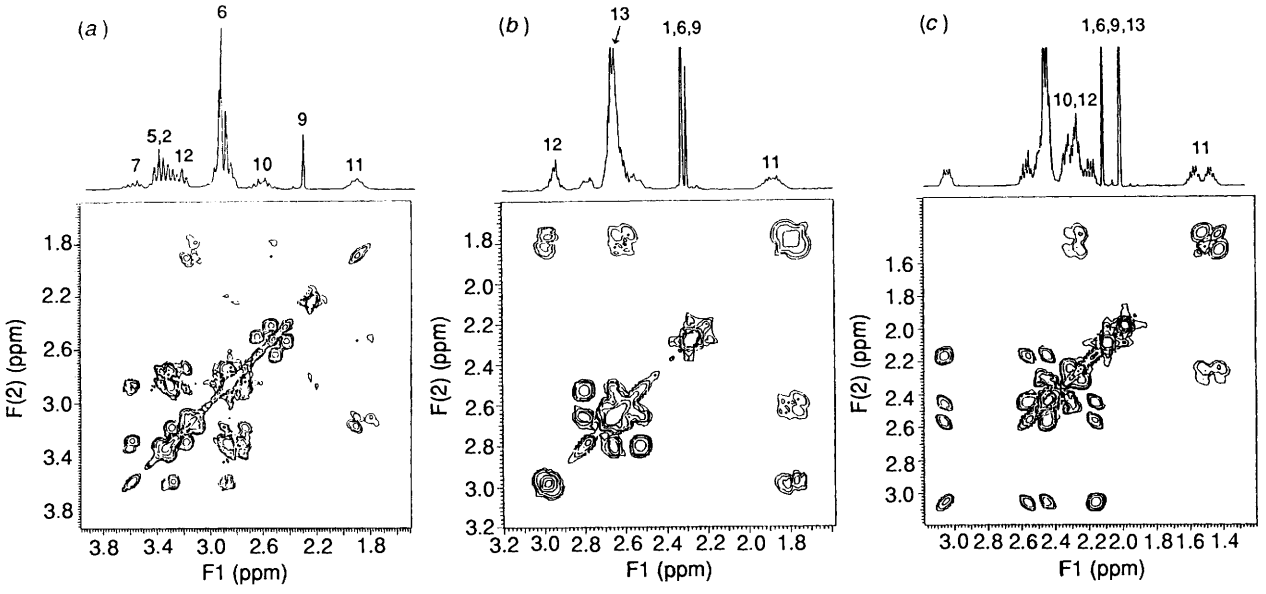



**Fig. 6** Correlated $^{1}H$-$^{1}H$ spectra of **L1**. (*a*) pH = 4; (*b*) pH = 10; (*c*) pH = 12.

propylenic chain (C10 and C12) and those of the different ethylenic chains. As can be seen in Fig. 4, protonation of **L1** yields both changes in the $^{13}C$ chemical shifts as well as in the number of signals. However, in the pH range 4–12 the number of signals does not exceed half of the overall carbon atoms of this molecule indicating $C_s$ time-averaged symmetry.

The variation in the $^1H$ chemical shifts of the hydrogens of the methyl groups with pH (Fig. 5) is of great interest in order to establish a possible protonation pattern.

At pH 12, where the free amine predominates, the $^1H$ NMR spectrum shows for the methyl hydrogens three different resonances at 2.00, 2.01 and 2.10 ppm with relative intensities 3:3:9. Their corresponding carbons appear in the $^{13}C$ spectrum as four different peaks at 43.35, 43.46, 43.52 and 43.91 ppm with relative intensities 1:2:1:1. From the 2D $^1H$-$^1H$ homonuclear [Fig. 6(*c*)] and $^1H$-$^{13}C$ heteronuclear correlations a tentative assignment of the methyl signals can be made. The $^1H$ signal at 2.10 ppm corresponds in the $^{13}C$ spectrum to the methyl carbons at 43.46 (C6) and 43.35 ppm. The hydrogens of the propylenic chain present at this pH a $C_2ABD_2$ spin system; it is to be noted that both protons of C11 are not magnetically equivalent (1.45–1.55 ppm). The hydrogens of the six ethylenic chains display two different spin systems [Fig. 6(*c*)], for four of them it would be $A_2B_2$ ($\delta_A$ and $\delta_B$ *ca.* 2.45 ppm) and for the other two ABCD (chemical shifts: $\delta_A = 3.05$, $\delta_B = 2.56$, $\delta_C = 2.47$ and $\delta_D = 2.16$ ppm; coupling constants: $J_{AB} = 6.56$, $J_{AC} = 6.02$, $J_{AD} = -12.94$, $J_{BC} = -13.51$, $J_{BD} = 6.41$ and $J_{CD} = 7.22$ Hz). The vicinal coupling constants are between those of the *gauche* and *trans* conformations. However, the great difference in chemical shift of one of the hydrogen atoms belonging to this spin system ($\Delta\delta_A = 0.5$ ppm) is surprising.

In the $^{13}C$ spectrum, apart from the signal at 25.32 ppm (C11), seven different signals are observed for the carbon atoms of the ethylenic and propylenic chains at 52.24, 52.89, 53.26, 53.39, 53.54 and 54.81 with relative intensities 1:1:2:2:1:1. From the $^1H$-$^{13}C$ correlation results it is evident that C10 and C12 have chemical shifts around 53 ppm and that the signal at highest field in the $^1H$ spectrum does not correspond with the $^{13}C$ signal lying at highest field in this spectral region.

From the $^1H$ and $^{13}C$ spectra recorded at pH 10, where $HL1^+$ prevails in solution, it can be concluded that the first protonation of **L1** takes place in the central amino group (N5) of the propylenic bridge. At this stage, the signals of the hydrogens of the methyl group (C13) at the middle of the propylenic chain as well as those of C12 [Fig. 5, 6(*b*)], situated at the α-position, shift downfield remarkably. The remaining protons appear at this pH as a complex multiplet that does not allow us to make further assignments. In the $^{13}C$ NMR spectrum the signal of C11 bears an upfield shift (Fig. 4) in agreement with the β-shift reported for the protonation of polyamines.[15] An upfield shift is also observed in the $^{13}C$ signal of C13. On the other hand, from the $^1H$-$^1H$ [Fig. 6(*b*)] and $^{13}C$-$^1H$ [Fig. 7(*c*)] correlations the signals at lowest field (56.4 ppm) can be assigned to C12, while that of C10 appears at higher field.

As seen in the distribution diagrams (Fig. 1) **L1** is mainly in its diprotonated form at pH 8.5. At this pH value the resonances of the hydrogens of the methyl groups, mostly those of C1 and C6, bear a downfield shift (*ca.* 0.3 ppm for those of C1 and C6). The hydrogens of the ethylenic chains appear at this pH as different AA′BB′ spin systems and those of the propylenic chain as an $ABC_2D_2$ spin system. Unlike the situation for the free amine, the protons of C11 are almost equivalent and those of C10 lose their magnetic equivalence. These spectral features suggest that both protons are at least shared by four out of the five methylated nitrogens (N1, N3, N3′, N5). This protonation scheme agrees well with the spectral characteristics of the $^{13}C$ spectrum. In this spectrum all the methyl carbons present similar chemical shifts and the signals of the methylenic carbons

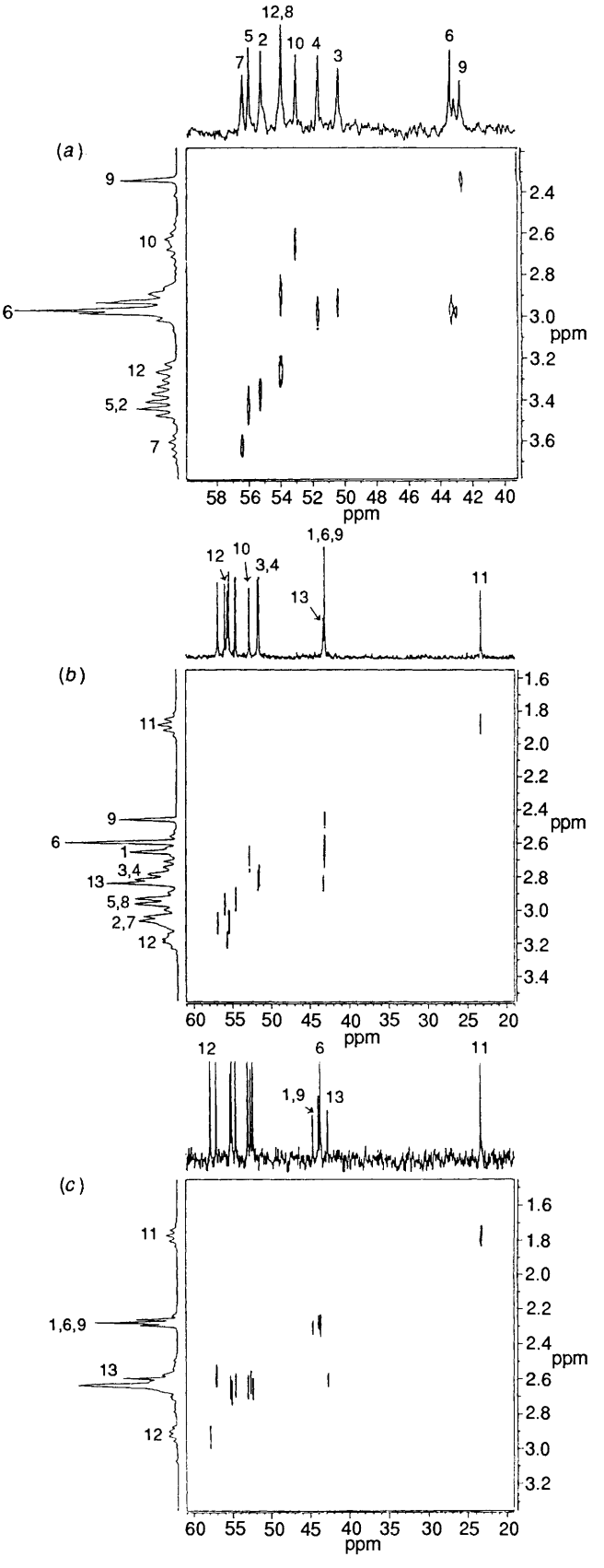



**Fig. 7** Correlated $^1H$-$^{13}C$ spectra of **L1**. (*a*) pH = 4; (*b*) pH = 7; (*c*) pH = 10.

are split into two groups (Fig. 4), the signals at higher field corresponding to C3, C4 and C10, situated at the α-position with respect to the nitrogen atom which would remain un-

protonated (N2), and the signals at lower field corresponding to C2, C5, C7, C8 and C12.

At pH 7, where $H_3L1^{3+}$ predominates, all the methyl signals but one (C9) shift remarkably downfield in the $^1H$ spectrum (Fig. 5). This fact, together with the unchanged chemical shift of the protons of the propylenic chain and the important chemical shift splitting experienced by the hydrogen of all the ethylenic chains, allows us to conclude that the three protons are located at N1, N3, N3′ and N5. The $^1H$ NMR spectrum displays three groups of signals, integrating 4:4:4 (3.15–3.05, 3.05–2.90 and 2.90–2.75 ppm) assigned to the hydrogen atoms of the ethylenic chains. By means of 2D $^1H$-$^1H$ and $^{13}C$-$^1H$ [Fig. 7(*b*)] correlations, the signals at lowest field can be assigned to the hydrogens of C2 and C7, those at the α-position to the protonated nitrogen atoms N1, N3 and N3′, and those at highest field to the hydrogen atoms of C3 and C4, at the α-position to the unprotonated bridgehead nitrogen atoms. This protonation pattern agrees with the unchanged chemical shift of C10 in the $^{13}C$ spectrum (Fig. 4).

At pH 4, where the $H_4L1^{4+}$ species predominates (Fig. 1), there are few significant changes in the $^1H$ NMR spectrum, those being the singlet corresponding to C9 at 2.20 ppm and the hydrogens of C10 at 2.50 ppm (Fig. 5). The most important feature in the $^1H$ NMR spectrum is the downfield shift of the signal assigned to the protons of C6 (Fig. 5). We can recognize for the hydrogens of the ethylenic chains three groups of protons at 3.55–3.70, 3.45–3.30 and 3.00–2.80 ppm for the two protons of C7, the four protons of C2 and C5, and the six protons of C3, C4 and C8, respectively. On the basis of $^1H$-$^1H$ and $^{13}C$-$^1H$ correlations [Fig. 6(*a*), 7(*a*)] we can fully assign the signals at the carbon atoms as reported in Fig. 4. The most noticeable changes are the upfield shifts showed by C4 and C8, which suggest that the four protonation sites are N1, N3, N3′ and N5. Since the protons occupy alternate positions, such a disposition would mean a minimum in electrostatic repulsions.

At pH 2, where the species $H_5L1^{5+}$ predominates, the $^{13}C$ signals (Fig. 4), even on heating, are much broader, most likely due to the formation of slowly-interchanging (on the NMR timescale) conformers, and do not allow a detailed characterization. However, in the $^1H$ spectrum the downfield shift of the hydrogens of C9 (*ca.* 0.5 ppm) (Fig. 5) is in agreement with the fifth protonation taking place on N4.

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