Protonation Tendencies of Azaparacyclophanes. A Thermodynamic and NMR Study

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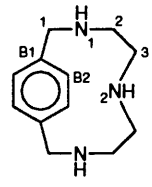
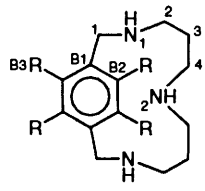
The interaction of hydrogen ions with the series of macrocyclic receptors 2,5,8-triaza[9]paracyclophane, 2,6,10-triaza[11]paracyclophane, 13,14,16,17-tetramethyl-2,6,10-triaza[11]paracyclophane, 14,15,17,18-tetramethyl-2,5,8,11-tetraaza[12]paracyclophane and 16,17,19,20-tetramethyl-2,6,9,13-tetraaza[14]paracyclophane has been studied by potentiometry at 298.1 ± 0.1 K as well as by direct microcalorimetry and ^1H and ^{13}C NMR spectroscopy. Correlations of the basicity with the atomicity of the macrocycle, the type of chains within the bridge and the nature of the aromatic spacer are envisaged.

Recently we have reported on the preparation[1,2] of a new series of azaparacyclophanes containing a single benzene or durene spacer in between a saturated polyamine bridge. Studies on the protonation of the receptors containing benzene spacers[1,3] 2,6,9,13-tetraaza[14]paracyclophane (**L1**), 2,5,8,11-tetraaza[12]paracyclophane (**L2**) and 2,5,8,11,14-pentaaza[15]paracyclophane (**L3**) showed that the electronic, hydrophobic and conformational characteristics induced by the aromatic moiety had important consequences for the stabilization of the determined polyammonium sites along the hydrocarbon chains which led to interesting protonation behaviour.

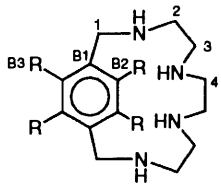
In this work and with the goal of quantifying the interactions and obtaining a general view of the factors controlling the protonation patterns of these molecules we have extended our study to the remaining members of the series containing either benzene or durene as aromatic spacers: 2,5,8-triaza[9]paracyclophane (**L4**), 2,6,10-triaza[11]paracyclophane (**L5**), 13,14,16,17-tetramethyl-2,6,10-triaza[11]paracyclophane (**L6**), 14,15,17,18-tetramethyl-2,5,8,11-tetraaza[12]paracyclophane(**L7**) and 16,17,19,20-tetraaza[14]paracyclophane (**L8**). To develop this analysis we have applied potentiometric, direct microcalorimetric and NMR techniques. The thermodynamic data presented here constitutes one of the most complete sets of thermodynamic parameters to date for the protonation of macrocyclic compounds.



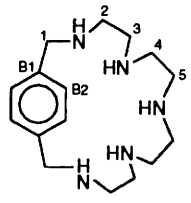
L4



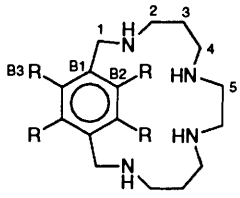
R = H **L5**
R = CH_3 **L6**



R = H **L2**
R = CH_3 **L7**



L3



R = H **L1**
R = CH_3 **L8**

Experimental

Materials.—Ligands **L1**–**L8** were synthesized as described in refs. 1 and 2 and handled as their hydrochloride or hydroperchlorate salts. Satisfactory elemental analyses were obtained for all the compounds. $NaClO_4$ used as the background electrolyte in the potentiometric measurements was purified according to a procedure described in the bibliography.[4] CO_2-free NaOH solutions and HCl, or $HClO_4$ solutions were prepared following the procedure reported in ref. 5. Ethylenediamine used for checking the microcalorimetric equipment was prepared and purified as its hydrochloride salt.

emf Measurements.—The potentiometric titrations were carried out, in 0.15 mol dm^{-3} $NaClO_4$ at 298.1 ± 0.1 K, by using the experimental procedure (burette, potentiometer, cell, stirrer, microcomputer, *etc.*) that has been fully described elsewhere.[6] The acquisition of the emf data was performed with the computer program PASAT.[7] 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 equivalent point by the Gran method,[8] which gives the standard potential, $E°'$, and the ionic product of water [pK_w = 13.73(1)]. The concentrations

Table 1 Stepwise protonation constants of the azaparacyclophanes **L4–L8** determined at 298.1 ± 0.1 K in 0.15 mol dm^{-3} $NaClO_4$; protonation constants of **L1–L3** have also been included

Reaction	L1	L2	L3	L4	L5	L6	L7	L8
$H + L = HL$[a]	9.93[b]	9.39[c]	10.68[c]	9.42(1)[d]	10.13(1)	9.96(1)	9.44(3)	10.54(1)
$H + HL = H_2L$	9.09	8.45	9.29	7.31(1)	8.34(1)	8.59(1)	8.67(3)	9.23(2)
$H + H_2L = H_3L$	7.44	5.38	8.66	3.26(3)	6.82(2)	7.04(1)	5.64(6)	7.44(2)
$H + H_3L = H_4L$	3.61	2.51	7.23				2.5(1)	3.59(3)
$H + H_4L = H_5L$			3.93					

[a] Charges have been omitted by means of clarity. [b] Taken from ref. 1, 0.15 mol dm^{-3} $NaClO_4$, 298.1 K. [c] Taken from ref. 3, 0.15 mol dm^{-3} $NaClO_4$, 298.1 K. [d] Numbers in parentheses are standard deviations in the last significant number.

of the different metal ions employed were determined gravimetrically by standard methods.

The computer program SUPERQUAD,[9] was used to calculate the protonation and stability constants. The DISPO[10] program was used to obtain the distribution diagrams. The titration curves for each system (*ca.* 200 experimental points corresponding to at least three measurements, pH range investigated 2–10, concentration of ligands ranging from 1×10^{-3} to 5×10^{-3} mol dm^{-3}) were treated either as a single set or as separated curves without significant variations in the values of the stability constants. Finally, the sets of data were merged together and treated simultaneously to give the final stability constants.

Microcalorimetry.—The enthalpies of protonation of the ligand have been determined in 0.15 mol dm^{-3} $NaClO_4$ by means of an automated system composed of a Thermometric AB thermal activity monitor (model 2277) equipped with 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 which was maintained at the chosen temperature within $\pm 2 \times 10^{-4}$ K. The microcalorimeter was checked by determining the enthalpy of reaction of strong base (NaOH) with strong acid (HCl). The value obtained, −13.55(5) kcal mol^{-1},† was in agreement with the literature values.[11] Further checks were performed by determining the enthalpies of protonation of ethylenediamine. In a typical ligand protonation experiment, an NaOH solution (0.15 mol dm^{-3}, addition volumes of 15 μl) was added to solutions of the free ligand ($0.01 - 5 \times 10^{-3}$ mol dm^{-3}; 1.5 cm^3). Corrections for the heat of dilution were applied. The corresponding enthalpies of reaction were determined from the calorimetric data by means of the KK88 program.[12] Considering a general system in which the protonated species HL, H_2L, H_3L, $\cdots$ H_nL are formed, the total heat after each addition is given by eqn. (1)

$$Q = \Sigma x_i \Delta H_i \quad (1)$$

where x_i are the quantities (mol) of the ith species formed (x_i is negative if the ith species is consumed) and ΔH_i is the enthalpy of formation, eqn. (1).

Using the known values of the protonation constants, the concentration of the species present in solution before and after each addition are calculated for each titration point and the corresponding x_i values are obtained. Thus m ($m > n$) titration steps are required to obtain, by using the standard least-squares method, the best set of ΔH values which satisfy eqn. (1).

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

† 1 cal = 4.184 J.

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.[13]

Results and Discussion

Potentiometry.—In Table 1 are presented the successive stepwise protonation constants determined for ligands **L4–L8** at 298.1 ± 0.1 K in 0.15 mol dm^{-3} $NaClO_4$. In Table 1, the results previously obtained for the ligands **L1–L3** under the same experimental conditions are also included. The distribution diagrams for ligands **L4**, **L5**, **L7** and **L8** are shown in Fig. 1.

A first analysis of the data allows for deriving several general trends. First of all, as it can be seen in Fig. 2 the overall basicity of these ligands steadily increases with the atomicity of the ligands and a straight line is obtained when representing the overall basicity constants *vs.* the number of atoms within the polyamine chain bridging the aromatic spacer. When comparing the pairs of ligands with the same polyamine chains and benzene or durene spacers, namely **L1–L8**, **L2–L7** and **L5–L6**, it was noted that the stepwise protonation constants for the ligands of each couple are similar; therefore the inductive effects, as could be expected, and the possible solvation effects originated by the methylation of the aromatic spacer do not seem significantly to affect the basicity of the azaparacyclophanes.

L1 and **L8** which present a symmetrical array of two propylenic chains and one central ethylenic chain display relatively large constants for the three first protonation steps and a much lower constant for the last step. **L2** and **L7**, with only ethylenic chains in the bridge, present, however, a group of two high constants, an intermediate one and another one much lower (see Table 1, Fig. 1). The triazaparacyclophane **L4**, which also contains only ethylenic chains, presents relatively large constant for the two first protonations and a much lower constant for the last protonation step. Finally the triazaparacyclophanes with only propylenic chains, **L5** and **L6** in the bridge, display high basicity in all their three protonation steps. On the other hand, the ligands with propylenic chains display higher basicity in all the protonation steps than those containing ethylenic chains, for instance, the stepwise basicity constants for the triazaparacyclophane **L4** are $\log K_1 = 9.42$, $\log K_2 = 7.31$ and $\log K_3 = 3.26$ while those for **L5** are $\log K_1 = 10.13$, $\log K_2 = 8.34$ and $\log K_3 = 6.82$ (see Table 1, Fig. 1).

At first sight, these protonation sequences may be explained by considering that the situations of minimum energy are represented by the structures in which the electrostatic repulsions between protonated sites are also minimum. In this sense, the two first protons of the tetraazaparacyclophanes **L7**

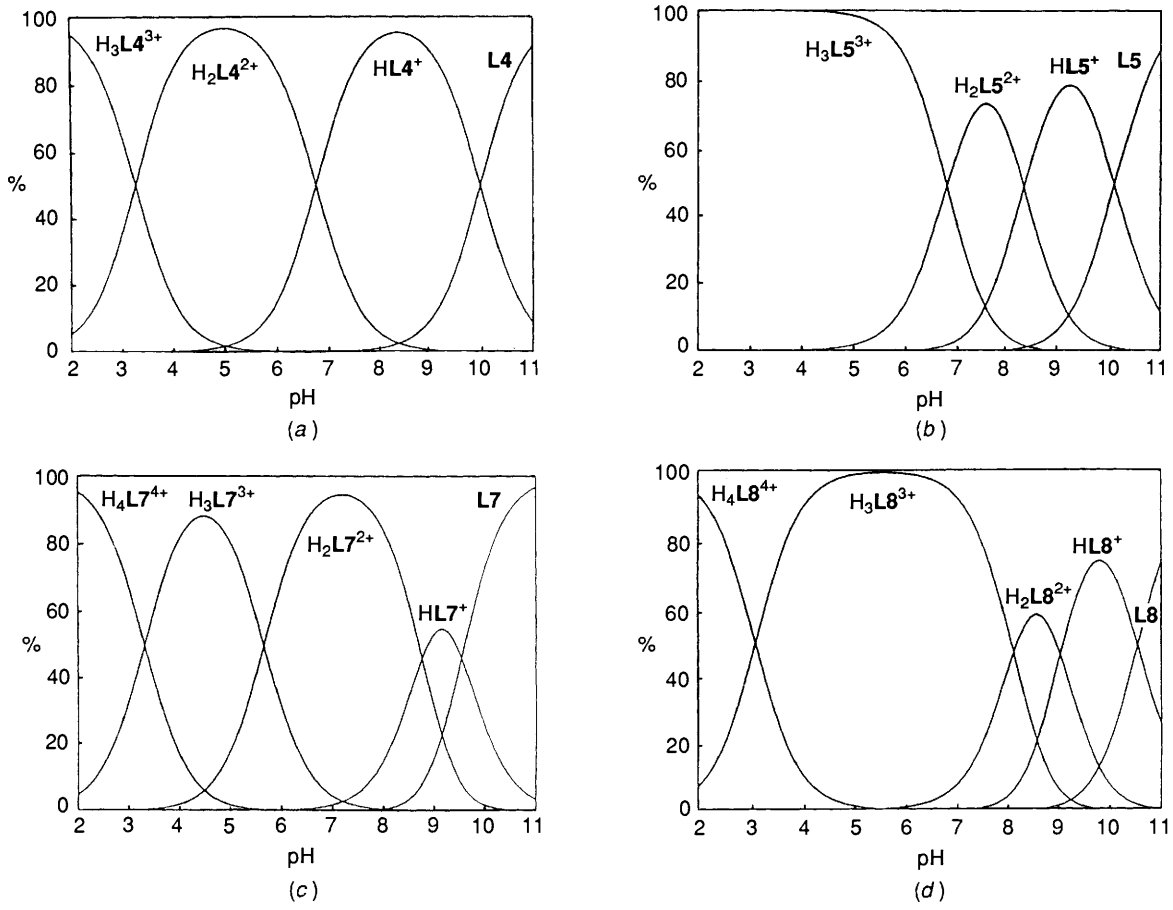


Fig. 1 Distribution diagrams for species present in solution in the systems: (*a*) H^+-**L4**, (*b*) H^+-**L5**, (*c*) H^+-**L7** and (*d*) H^+-**L8**. The distribution diagram for the system H^+-**L6** is analogous to that of H^+-**L5**. The distribution diagram for the system H^+-**L6** is analogous to that of the system H^+-**L5**.

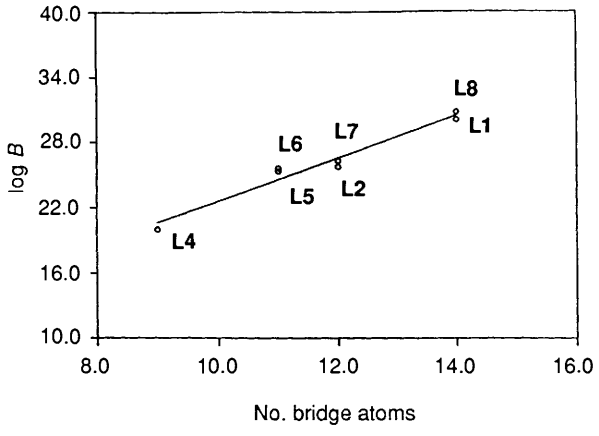


Fig. 2 Plot of the logarithms of the overall basicity constants β as a function of the number of atoms in the bridge for the different azaparacyclophanes

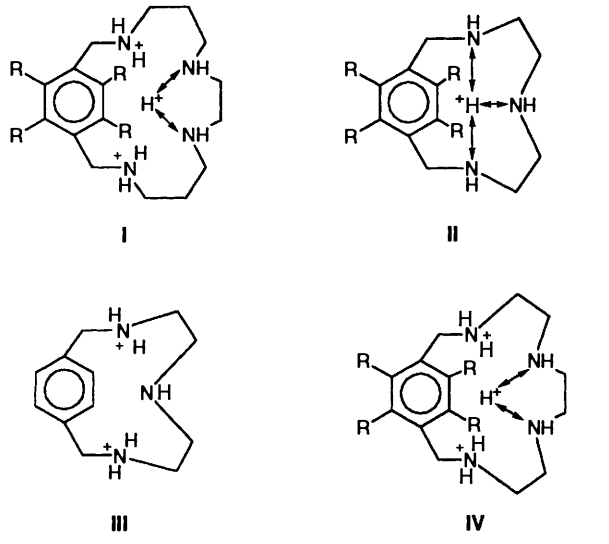
and **L8** can take place on any one of the nitrogen atoms as long as they are not adjacent. The third protonation has to occur necessarily adjacent to one protonated nitrogen. However, while for **L7** this protonation would affect a nitrogen separated from the adjacent polyammonium site by an ethylenic chain, for **L8** it would affect a nitrogen separated from the next polyammonium site by a propylenic chain which would yield different electrostatic situations for both molecules. In fact, while for **L7** the difference between the second and third stepwise protonation constants is 3.03 logarithm units, for **L8** it is 1.79. Moreover, while the difference between the stepwise constants for the first and third protonation steps of **L8** is 3.10 that between the third and the fourth one, in which protonation would occur in polyammonium sites separated by just an ethylenic chain, is 3.85 logarithm units. Therefore, the propylenic chains seem to keep the protonated sites far away enough not to severely influence each other from an electrostatic point of view and other factors, apart from statistical ones,[14] should play also an important role in the protonation pattern. This point is highlighted even more clearly in the data for the triazacyclophanes **L5** and **L6** which have slightly decreasing regular differences of about 1.5 logarithm units between the basicity constants of the different protonation steps. Statistical factors would account for decreases of 0.5 logarithm units between the successive stepwise protonation constants.

Microcalorimetry.—The enthalpy terms, determined by direct microcalorimetry, and the calculated entropy terms for the protonation of macrocycles **L5**, **L6**, **L7** and **L8** are shown in Table 2. The enthalpy terms for the triazaparacyclophanes **L5** and **L6** are very similar for both ligands [**L5**: $\Delta H°_1 = -9.81(7)$, $\Delta H°_2 = -10.4(1)$ and $\Delta H°_3 = -10.3(1)$ kcal mol^{-1}; **L6**: $\Delta H°_1 = -9.6(1)$, $\Delta H°_2 = -10.2(1)$ and $\Delta H°_3 = -10.5(1)$ kcal mol^{-1}] and highly exothermic for all three protonation steps; the enthalpic contributions to the second and third protonations almost identical within the experimental error, and slightly more exothermic than those associated with the first ones.[15] The similarities between the enthalpy terms of both ligands and between those of the different protonation steps strongly support both that methylation of the aromatic ring does not have any significant effect on the basicity of the polyammonium sites, and that the location of a propylenic spacer in between two protonated sites strongly reduces the

Table 2 Stepwise enthalpy and entropy terms (kcal mol^{-1}) for the successive protonations of the ligands **L5–L8**, results for **L1–L2** taken from ref. 3 have also been included

Reaction	L1	L2	L5	L6	L7	L8
	$-\Delta H°$					
H + L = HL[a]	9.55[b]	8.22[b]	9.81(7)[c]	9.6(1)	9.2(2)	10.35(3)
H + HL = H_2L	10.91	9.7	10.4(1)	10.2(1)	9.4(3)	11.01(7)
H + H_2L = H_3L	10.70	8.7	10.3(1)	10.5(1)	9.1(3)	11.01(7)
H + H_3L = H_4L	7.01	4.1	—	—	3.9(4)	6.7(1)
	$T\Delta S°$					
H + L = HL[a]	4.0[b]	4.7	4.0(1)	4.0(1)	3.5(2)	4.0(1)
H + HL = H_2L	1.5	1.7	1.0(1)	1.5(1)	2.4(2)	1.6(1)
H + H_2L = H_3L	−0.6	−1.4	−1.1(1)	−0.7(1)	−1.3(3)	−1.0(1)
H + H_3L = H_4L	−2.1	−0.5	—	—	−0.5(2)	−1.8(2)

[a] Charges have been omitted for clarity. [b] Taken from ref. 3. [c] Numbers in parentheses are standard deviations in the last significant number.



coulombic repulsions between both centres. A similar situation is found in the three first protonations of the tetraazamacrocycle **L8**. The most stable structure for H_3**L8**$^{3+}$ from an electrostatic point of view would be structure **I** in which the positive charges are separated by at least a propylenic chain, and again, a similar sequence of the enthalpy terms can be observed. Fourth protonation of **L8** is accompanied by an important reduction in exothermicity [$\Delta H°_4$ = −6.7(1) kcal mol^{-1}] according to the higher electrostatic repulsions due to the location of the entering proton between protonated nitrogens separated by an ethylenic and a propylenic chain. This result agrees well with the few values found in the literature for related saturated macrocycles, for instance, separation by one ethylenic and one propylenic chain would occur in the fourth protonation step of 1,5,8,12-tetraazacycloheptadecane and 1,4,8,11-tetraazacyclopentadecane and values of −7.29 and −8.01 kcal mol^{-1} have been reported, respectively.[16] The analogous ligand **L1** displays a similar sequence of enthalpy terms.

L7, containing all ethylenic chains, displays a reduced exothermicity in all its protonation steps and $\Delta H°_4$ = −3.9 kcal mol^{-1} reflects the shorter range electrostatic repulsions originated by the location of the incoming proton between protonated nitrogens separated by ethylenic chains.

NMR Spectroscopy.—To perform a more thorough analysis of the protonation schemes of these ligands we have recorded their ^{1}H and ^{13}C NMR spectra at different pH values. All the assignments have been made on the basis of 2D ^{1}H–^{1}H and ^{1}H–^{13}C correlation experiments at the different pH values studied.

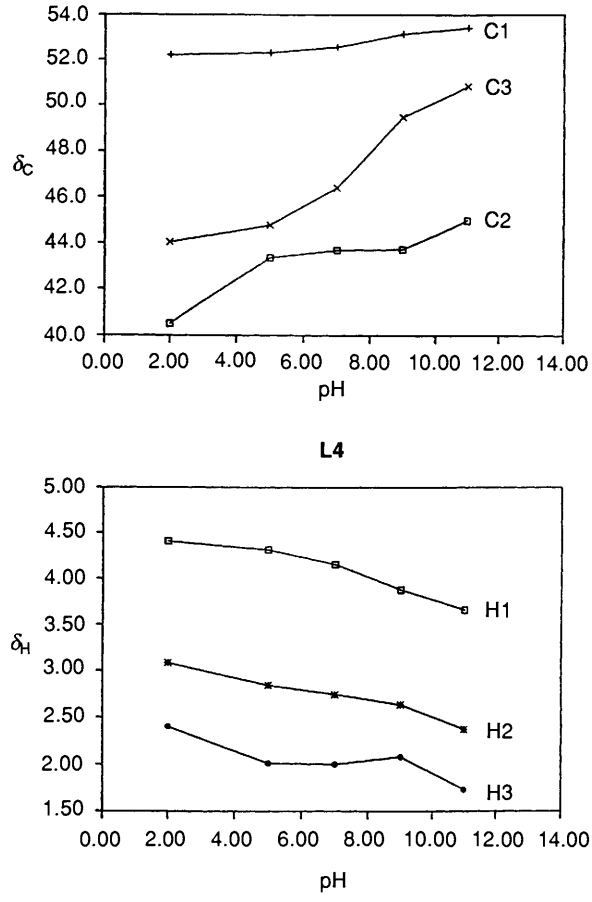


Fig. 3 Plots of the variations of the ^{1}H NMR and ^{13}C NMR chemical shifts (ppm) as a function of pH for the system H$^+$-**L4**

The ^{1}H spectrum of **L4** at pH 11, where the non-protonated species predominates, consists of two singlet signals at δ 7.33 and at 3.66, corresponding to the aromatic protons (HB2) and to the benzylic protons (H1), respectively, and of two triplet signals at δ 2.37 and 1.73 corresponding to the protons of the ethylenic chain (H2 and H3). The ^{13}C NMR spectrum presents five signals at δ 141.17 (CB1), 131.81 (CB2), 53.43 (C1), 50.83 (C3) and 45.00 (C2). These spectral features stand for the presence of a binary element of symmetry in the molecule. When the pH is diminished the proton chemical shifts move downfield and the carbon ones upfield but the proton NMR pattern as well as the number of ^{13}C NMR signals are the same whatever the pH and the binary symmetry is preserved throughout the pH range. From pH 11 to 9, where the first

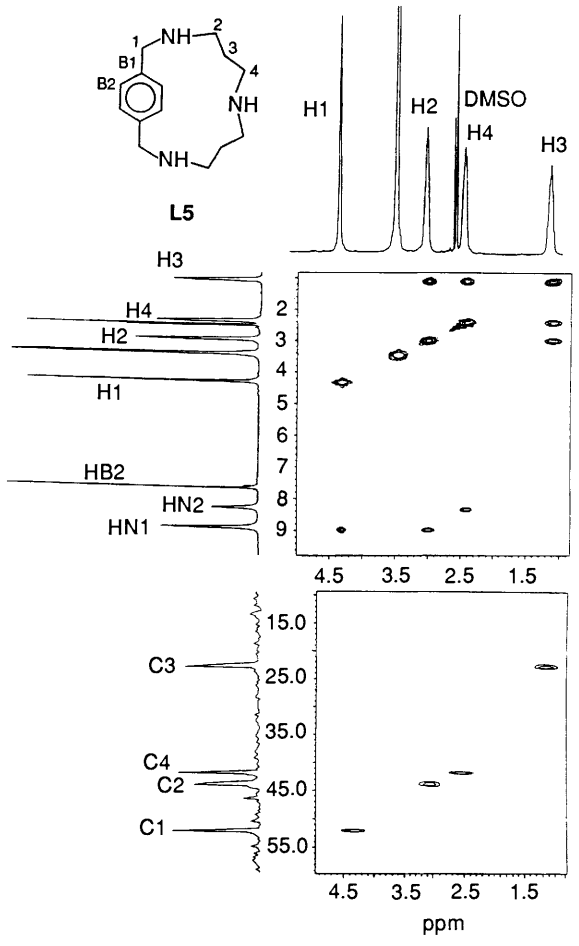


Fig. 4 ^1H–^1H and ^1H–^{13}C 2D correlated NMR spectra for **L5**·3$HClO_4$ in Me_2SO

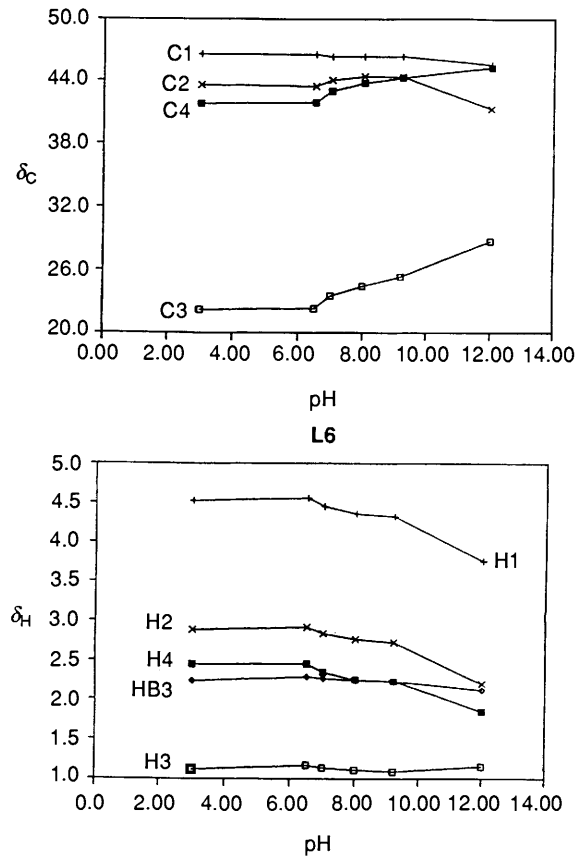


Fig. 5 Plots of the variations of the ^1H NMR and ^{13}C NMR chemical shifts (ppm) as a function of pH for the system H^+-**L6**

protonation occurs (see Figs. 1 and 3) all the ^1H signals move downfield and the ^{13}C ones upfield suggesting that this first proton is shared by all three nitrogen atoms of the molecule (see structure **II**).

The binding of the second proton (pH range 9–5) induces downfield shifts in the resonances of H1 and H2 but that of H3 remains almost unaffected. In the ^{13}C spectrum while marked upfield shifts are observed for the signals corresponding to the quaternary carbon atoms CB1 and C3, both in a β-position to N1,[17] the signal for C2, which is in a β-position to N2, does not shift at all. These data indicate that both protons are located on the benzylic nitrogens (N1) (see structure **III**). Finally, in the pH range where the third protonation occurs a noticeable downfield shift of the signal of H3 in the ^1H NMR spectra and an upfield shift of that of C2 in the ^{13}C NMR spectra are observed in accordance with the protonation of the central nitrogen atom N2.

L5 and **L6** display similar spectroscopic features, the only differences resting in the presence of the methyl groups in the aromatic spacer of **L6**. The ^1H spectrum of **L5** at pH 11 consists of two singlets at δ 7.34 and 3.62 corresponding to the aromatic (HB2) and benzylic protons (H1), two triplet signals at δ 2.37 and 2.00 (H2 and H4, respectively) and a quintet centred at δ 1.20 corresponding to the central methylene protons of the propylenic chain (H3). **L6** presents, at the same pH two singlets at δ 2.12 (HB3) and 3.76 (H1), two triplets at δ 2.20 (H2) and 1.84 (H4) and a quintet at δ 1.15 (H3). Distinction between the resonances of protons H2 and H4 of the propylenic chain was made possible by ^1H–^1H correlations performed in Me_2SO. For instance, when dissolved in this solvent **L5**·$HClO_4$ gives two signals at δ 8.91 and 8.28 corresponding to the amine protons (see Fig. 4). The first signal, which integrates doubly, correlates with the benzylic protons (H1) (δ 4.26) and with another signal of the propylenic chain which must necessarily be that of protons H2 (δ 2.94), the signal at δ 8.28 correlates only with one signal of the propylenic chain which must be that of protons H4 (δ 2.36). Therefore all the methylene protons can be uniquivocally assigned in this way.

The ^{13}C NMR spectra of **L5** at pH 11 consists of six resonances at δ 140.38 (CB1), 130.91 (CB2), 52.64 (C1), 45.41 (C4), 42.50 (C2) and 28.76 (C3) and that of **L6** of seven signals at δ 134.52 (CB1), 134.00 (CB2), 45.41 (C1), 45.24 (C4), 41.23 (C2), 28.70 (C3) and 17.10 (CB3) indicating again a twofold symmetry for both ligands.

In accordance with the higher basicity of these ligands no significant variations in the chemical shifts are observed below pH 6. The changes in the chemical shifts of these two ligands upon protonation (pH range 11–6) are analogous. In the pH range where the two first protons are attached to these ligands, the ^1H NMR spectrum shows downfield shifts for the signals of protons H1, H2 and H4 and the ^{13}C NMR spectra show upfield shifts for CB1 and C3 which are positioned β to the protonation sites (see Fig. 5). In the pH range corresponding to the attachment of the third proton, pH 8–6, the accommodation of the protons on the three nitrogens yields a further downfield shift of the signals of CB1 and C3. Therefore, it becomes difficult to establish definite protonation sites for the two first steps, and it seems that the protons are randomly distributed on nitrogens N1 and N2 (structure **II**).

L7 displays at pH 12 in the ^1H NMR spectrum three singlet signals at δ 3.89 (H1), 2.19 (HB3) and 1.94 (H4) and two triplet signals at δ 2.39 and 2.17 that can be assigned to protons H2 and H3. The ^{13}C NMR spectrum recorded at the same pH shows seven signals at δ 136.76 (CB1), 134.75 (CB2),

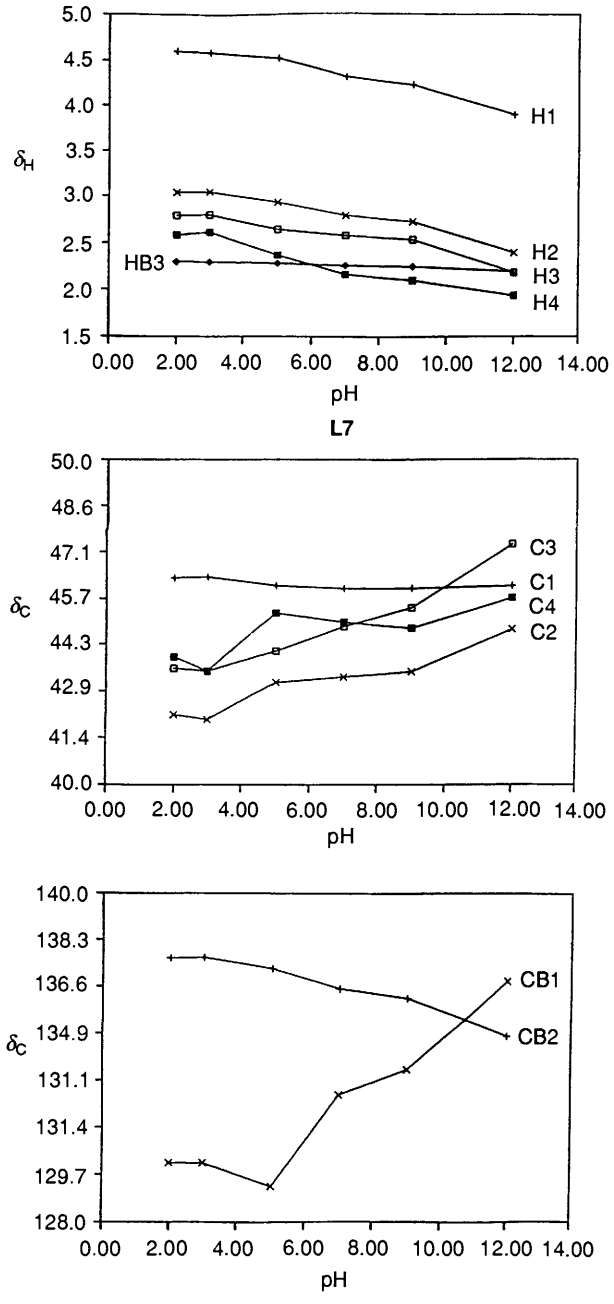


Fig. 6 Plots of the variations of the ^1H NMR and ^{13}C NMR chemical shifts (ppm) as a function of pH for the system H^+-**L7**

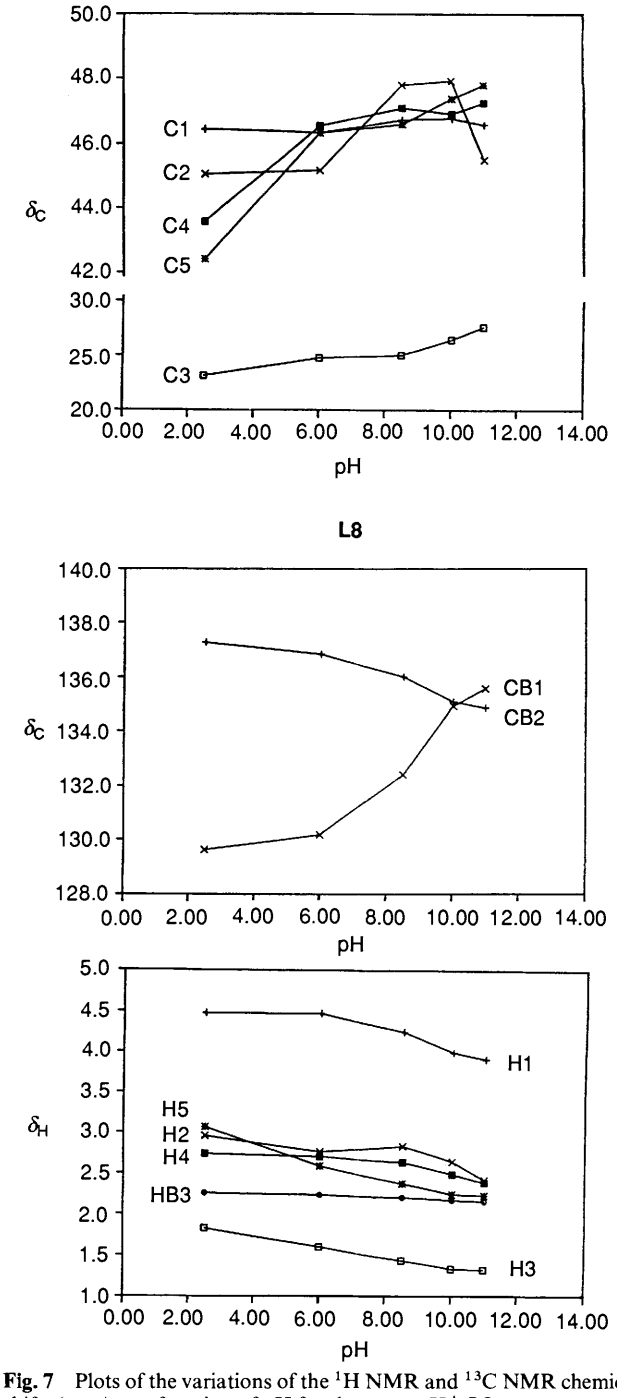


Fig. 7 Plots of the variations of the ^1H NMR and ^{13}C NMR chemical shifts (ppm) as a function of pH for the system H^+-**L8**

47.40 (C3), 46.12 (C1), 45.74 (C4), 44.76 (C2) and 17.29 (CB3). For this ligand the first protonation is accompanied by noticeable downfield shifts of all the ^1H signals and upfield shifts of the resonances of carbon atoms CB1, C2, C3 and C4 which support that this proton is shared by the benzylic (N1) and middle nitrogens (N2) of the polyamine bridge. With the binding of the third proton no significant variations are observed for C2 and C4, while C3 placed in the β-position to the benzylic nitrogens shifts appreciably upfield. Hence, it can be concluded that two out of these three protonations affect the benzylic positions (N1) (Fig. 6, structure **IV**). The fourth protonation takes place on the central nitrogens N3 as can be deduced from the upfield shifts of C4 and C2 between pH 5.0 and 3.0; the signal of CB1 undergoes a slight downfield shift in this pH range.

L8 *presents* at pH 11 a ^1H NMR spectrum characterized by three singlet signals at δ 3.92 (H1), 2.24 (H5) and 2.17 (HB3) and two triplet signals corresponding to protons H2 and H4 of the propylenic chains that, at this pH, lie very close to each other (*ca.* δ 2.42). The ^{13}C NMR spectrum shows eight signals at δ 135.37 (CB1), 134.84 (CB2), 47.70 (C5), 47.15 (C4), 46.48 (C1), 45.37 (C2), 27.57 (C3) and 17.21 (CB3). The downfield variations in the chemical shift of the signals of all protons in α-position to the nitrogen sites and the upfield shifts of C3 and C5 in the pH range 12–8.5 would suggest that both N1 and N2 are involved in the first two protonation steps (Fig. 7). In this ligand, similarly to **L7**, the continuous upfield shift experienced by carbon CB1 between pH values 11 and 6, where the three first protonations occur, indicates that two out of the three protons bind the benzylic nitrogens. The significant variation in the chemical shift of C5 and the lack of variation of CB1 below pH 6 support that the fourth protonation occurs in the central nitrogens of the bridge.

Some additional points deserve to be noted. First of all,

Table 3 Carbon chemical shifts (ppm) for the free amine and fully protonated forms of the different azaparacyclophanes in D_2O

	pH	C-1	C-2	C-3	C-4	C-5	CB-1	CB-2	CB-3
L4	11.0	53.43	50.83	45.01			141.17	131.81	
H_3**L4**	2.0	52.21	44.04	40.50			132.44	134.16	
L5	11.0	52.64	42.50	28.76	45.41		140.38	130.91	
H_3**L5**	3.0	52.16	43.89	22.79	41.96		133.55	133.23	
L6	12.0	45.51	41.23	28.70	45.24		134.52	134.02	17.10
H_3**L6**	3.0	46.54	43.58	22.22	41.79		130.13	137.51	17.73
L2	12.0	52.88	45.34	48.47	47.24		140.55	130.91	
H_4**L2**	2.0	51.42	41.74	43.45	43.09		133.20	133.13	
L7	12.0	46.12	44.76	47.40	45.75		136.76	134.75	17.29
H_4**L7**	2.0	46.36	42.13	43.56	43.91		130.15	137.60	17.75
L1	12.0	53.80	46.10	29.60	48.10	49.80	140.10	132.10	
H_4**L1**	2.0	52.90	45.20	24.70	47.10	45.00	134.20	134.50	
L8	11.0	46.48	45.37	27.57	47.15	47.70	135.57	134.84	17.21
H_4**L8**	2.5	46.42	45.02	23.13	43.56	42.40	129.63	137.27	17.75
L3	12.0	52.66	46.39	47.93	47.59	47.93	139.69	130.18	
H_5**L3**	2.0	51.55	42.08	43.93	47.04	44.99	132.34	132.94	

the remarkable downfield shift observed for C2 with the first protonation for all the azaparacyclophanes containing propylenic chains (**L5**, **L6** and **L8**); an explanation of this fact may be the conformational changes produced by the protonation that expands the molecule and reduces the shielding effect of the aromatic π-cloud on these atoms. For the ligands with only ethylenic chains similar features are not observed on account of their higher rigidity.

Also of interest are the inductive effects experienced by the benzylic carbon atoms upon methylation of the aromatic spacer. In Table 3 are presented the ^{13}C NMR chemical shifts for the non-protonated and fully protonated forms of the azaparacyclophanes and variations of about 7 ppm in the benzylic carbon between the different couples of analogous ligands containing benzene or durene spacers are observed.

Conclusions

Azaparacyclophanes **L1**–**L8** can be classified, according to their protonation behaviour, into three different groups. The first group includes those ligands containing only ethylenic chains in the bridge with the exception of **L3** which displays particular behaviour.[3] The second group is represented by those with only propylenic chains, **L5** and **L6**. The third group contains **L1** and **L8** which have both propylenic and ethylenic chains in the bridge.

The first group of ligands display lower basicities in their protonation steps. In their diprotonated forms, H_2L^{2+}, both protons seem to bind to benzylic nitrogens as confirmed by the NMR spectra and thermodynamic data. Within this group **L2** presents a higher stabilization of the first proton in the benzylic positions as derived from the NMR data as well as from the reduced exothermicity and large entropic contribution associated with the first step. This could indicate that a large desolvation accompanies a process taking place in a highly hydrophobic part of the molecule.

The second group of ligands presents a large enthalpic term for all the protonation steps. The NMR analysis does not show preferred coordination sites and the protons should be randomly shared over all three protonation sites. As already observed for other compounds, the presence of propylenic chains between the protonation sites strongly reduces the electrostatic repulsions.

The third group of compounds displays, in their three first protonation steps, analogous basicities to that of the second group. Very large exothermic contributions for these three steps are also obtained. NMR data analysis shows that the entry of the third proton blocks two of the protons in the benzylic positions. As a general conclusion, it should be noted that methylation does not influence the basicity of the molecules.

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