Structural Aspects of the Protonation of Small Cages. Preparation of the New Aza-cage 12,17-Dimethyl-1,9,12,17-tetra-azabicyclo[7.5.5]nonadecane (L). Thermodynamic Studies on Solution Equilibria. Crystal Structures of $[H_2L][CoCl_4]$ and $[H_2L1][CoCl_4]$ Salts†

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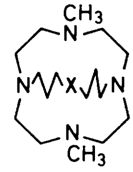
The synthesis and characterization of the new aza-cage 12,17-dimethyl-1,9,12,17-tetra-azabicyclo-[7.5.5]nonadecane (L) are described. The basicity behaviour in both aqueous and water–DMSO (50:50, mol:mol) solutions has been investigated by potentiometric and microcalorimetric (25 °C, 0.15 mol dm^{-3} NaCl) techniques. L behaves, in aqueous solution, as a fairly strong base ($\log K_1 = 12.00$; $\Delta H_1^\circ = -54.0$ kJ mol^{-1}; $T\Delta S_1^\circ = 14.5$ kJ mol^{-1}) in the first protonation step and as a moderate base in the second step ($\log K_2 = 7.86$; $\Delta H_2^\circ = -44.8$ kJ mol^{-1}; $T\Delta S_2^\circ$ *ca.* 0). The enthalpic and entropic contributions are discussed in terms of molecular topology and translational entropy. The Cu^{II} ion is encapsulated by L, the electronic spectra being diagnostic of a square-planar structure. The molecular structures of the diprotonated salts $[H_2L][CoCl_4]$ and $[H_2L1][CoCl_4]$ (L1 = 5,12,17-trimethyl-1,5,9,12,17-penta-azabicyclo[7.5.5]nonadecane) have been determined by single-crystal X-ray analysis.

Crystals of $[H_2L][CoCl_4]$ are orthorhombic, space group $Pbn2_1$, with $a = 9.311(3)$ Å, $b = 15.480(2)$ Å, $c = 16.636(6)$ Å, and $Z = 4$. Final R values of 0.043 ($R_w = 0.037$) for 1 358 observed reflections. X-Ray analysis shows that the protonation occurs on the $N\text{–}CH_3$ groups. Each hydrogen atom of the $NH^+\text{–}CH_3$ interacts with the two bridgehead nitrogen atoms.

The compound $[H_2L1][CoCl_4]$ crystallizes in a monoclinic unit cell (space group $P2_1$) with lattice constants $a = 8.877(3)$ Å, $b = 14.088(8)$ Å, $c = 10.122(5)$ Å, $\beta = 105.51(4)°$, and $Z = 2$. Final R values of 0.064 ($R_w = 0.049$) for 2 374 observed reflections. In this case the conformation of the diprotonated cage is different and the protonation probably occurs at one of the two methylated nitrogens and at the apical nitrogen atom.

Recent studies, carried out in our laboratory,[1–6] on a series of small macrobicyclic cages containing cavities with convergently arranged binding sites (see the Scheme), have demonstrated that the molecular topology and molecular size confer special proton-transfer and ligational properties to these cages. However, a quite remarkable variation of ligational properties can be achieved by changing the nature of the donor atom ('apical group') present in the bridging unit (X, in the Scheme). The inclusion in the cage of other types of donor atoms may induce a range of different effects by changing the affinity towards protons and some metal ions while maintaining unchanged the overall molecular topology. With the aim of better understanding the role played by the apical group, we report here the synthesis and characterization, as well as some ligational properties of the title compound, hereafter abbreviated as L.



X	
CH_2	L
$N\text{–}CH_3$,	L1
N–H,	L2
S,	L3
O,	L4

Scheme.

Experimental

Synthesis of the Macrobicycle 12,17-*Dimethyl*-1,9,12,17-*tetra-azabicyclo*[7.5.5]*nonadecane* (*L*) (*Scheme*).—The macrocycle 1,7-dimethyl-1,4,7,10-tetra-azacyclododecane (**1**) has been prepared as described.[7]

Heptane-1,7-*dioic Acid Chloride* (**2**).—A sample of heptanedioic acid (1.6 g, 0.01 mol) was treated with thionyl chloride (24 g, 0.2 mol) at 50 °C for 20 h. The unchanged $SOCl_2$ was removed under reduced pressure, and the resulting yellowish oil was used without further purification.

Bicyclic Amide (**3**).—A sample of (**2**) (2 g, 0.01 mol) in 500 cm^3

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† L1 = 5,12,17-Trimethyl-1,5,9,12,17-penta-azabicyclo[7.5.5]nonadecane.

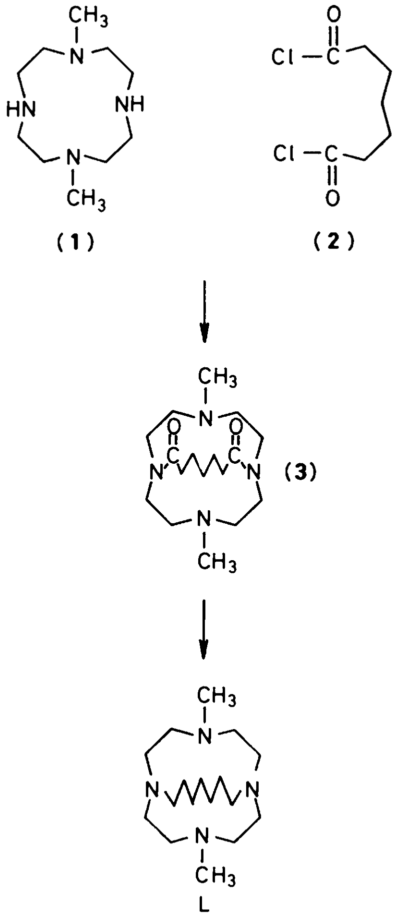

Figure 1. Reaction sequence for the synthesis of the macrobicyclic cage 12,17-dimethyl-1,9,12,17-tetra-azabicyclo[7.5.5]nonadecane (L).

of dry benzene and (**1**) (2 g, 0.01 mol) in 500 cm^3 of dry benzene containing triethylamine (3 g, 0.03 mol) were added simultaneously to 500 cm^3 of dry benzene, with mechanical stirring, over a period of 7 h at room temperature. The reaction mixture was filtered and evaporated to dryness using a rotary evaporator. The pale yellow product obtained was dissolved in hot cyclohexane: on cooling a white crystalline product separated. Yield 1.5 g (46%), m.p. 220 °C (decomp.) (Found: C, 62.8; H, 10.0; N, 17.1. Calc. for $C_{17}H_{32}N_4O_2$: 62.9; H, 9.8; N, 17.2%).

12,17-*Dimethyl*-1,9,12,17-*tetra-azabicyclo*[7.5.5]*nonadecane Diperchlorate* ($L{\cdot}2HClO_4$).—A sample of diborane [a solution of 0.05 mol in 50 cm^3 of tetrahydrofuran (THF)] was added dropwise, in a nitrogen atmosphere, to a solution of (**3**) (1.4 g, 4 mmol) in dry THF (15 cm^3) cooled to ice temperature. The addition was performed over a period of 30 min. After removal of the cooling bath the reaction mixture was allowed to warm to room temperature and was then refluxed for 6 h. The resulting solution was cooled and the excess of diborane was destroyed with methanol (30 cm^3) and water (10 cm^3). The solution was then evaporated to dryness. The white solid obtained was dissolved in an $HCl-H_2O-MeOH$ mixture (3:9:30) and refluxed for 6 h; the resulting solution was evaporated to dryness and then the residue was dissolved in 15 cm^3 of water. The solution was made alkaline by addition of a concentrated NaOH solution. The white solid which separated was filtered off and washed with water. The diperchlorate salt $L{\cdot}2HClO_4$ was obtained by the addition of a slight excess of $HClO_4$ to an ethanolic solution containing the crude, free ligand cooled to 0 °C. The white crystalline product was filtered off, washed and recrystallized from an ethanol–H_2O–$HClO_4$ mixture. Yield 1.8 g (90%) (Found: C, 40.9; H, 7.8; N, 11.2. Calc. for $C_{17}H_{38}Cl_2N_4O_8$: C, 41.0; H, 7.7; N, 11.2%); δ_c (D_2O, pH > 12) 27.0, 28.3, 29.0, 42.0, 54.8, 57.2, and 59.2.

Preparation of $[H_2L][CoCl_4]$.—A solution containing L (0.2 g, 0.67 mmol) in acetonitrile (50 cm^3), concentrated HCl (0.5 cm^3) and $CoCl_2{\cdot}6H_2O$ (0.16 g, 0.67 mmol) was refluxed for 30 min. The resulting solution, cooled to room temperature, was filtered and on addition of diethyl ether a blue compound precipitated. This compound was dissolved in a methanol–butan-1-ol mixture and by slow evaporation of the solvent, well-formed crystals, suitable for X-ray analysis, were obtained. (Found: C, 40.6; H, 7.7; N, 11.1. Calc. for $C_{17}H_{38}Cl_4CoN_4$: C, 40.9; H, 7.7; N, 11.2%).

Preparation of $[H_2L1][CoCl_4]$.—A solution containing L1 (0.2 g, 0.64 mmol) in MeOH (50 cm^3), concentrated HCl (0.5 cm^3) and $CoCl_2{\cdot}6H_2O$ (0.15 g, 0.67 mmol) was refluxed for 30 min. To the cooled solution was added butan-1-ol, and by slow evaporation of the resulting solution, well-formed crystals of the compound were obtained. (Found: C, 39.8; H, 7.7; N, 13.5. Calc. for $C_{17}H_{39}Cl_4CoN_5$: C, 39.7; H, 7.6; N, 13.6%).

Copper Complex.—A solution of $Cu(ClO_4)_2$ (0.2 mmol) in methanol (5 cm^3) was added to an hot solution of L (0.2 mmol) in methanol (5 cm^3). The violet crystals which formed on cooling were filtered off, washed with ethanol–methanol and dried under reduced pressure (**CAUTION**! Perchlorate salts of metal complexes can be explosive and must be handled with care. Compounds should **not** be heated as solids) (Found: C, 36.4; H, 6.5; N, 10.0. Calc. for $C_{17}H_{36}Cl_2CuN_4O_8$: 36.5; H, 6.5; N, 10.0%).

Lithium Complex.—A solution of LiOH (0.1 g, 4.2 mmol) in methanol (40 cm^3) was slowly added to a boiling solution of $[H_2L][ClO_4]_2$ (0.1 g, 0.21 mmol) in methanol (20 cm^3). The reaction mixture was refluxed for 30 min and evaporated to dryness on a rotary evaporator. The white product was extracted with $CHCl_3$ (20 cm^3) and the suspension obtained was filtered. The white crystalline product, obtained on addition of 50 cm^3 of cyclohexane was washed with cyclohexane and dried *in vacuo*. (Found: C, 50.5; H, 9.1; N, 13.8. Calc. for $C_{17}H_{36}N_4ClLiO_4$: C, 50.7; H, 9.0; N, 13.9%).

Potentiometric Measurements.—NaCl (Merck Suprapur) was used as an ionic medium, and standardized CO_2-free solutions of NaOH were prepared according to the procedure reported in ref. 8. The potentiometric apparatus (potentiometer, burette, stirrer, cell, microcomputer) and operation have already been reported.[9] The standard potential of the cell, E°, was calculated for both solvent systems (water, water–DMSO) by application of the Gran method.[10] For the mixed solvent water–DMSO (50:50, mol:mol) the value found for the ionic product of water was $pK_w = 17.63$, in agreement with that reported previously.[11] The program SUPERQUAD[12] was used to treat the data and calculate the protonation constants.

Enthapy of Protonation.—The enthaplies of protonation of L were determined with a Thermometric AB thermal activity monitor (Model 2277) equipped with Perfusion/Titration system and a Hamilton pump (model Microlab M). The calorimetric system as well as the Hamilton pump were controlled by an IBM Personal Computer (Personal System 2 Model 30) and the program AUTOTAM.[13] The enthalpy of ionization of water was determined by adding aqueous NaOH

Table 1. Crystallographic data for $[C_{17}H_{38}N_4][CoCl_4]$.

Formula	$C_{17}H_{38}N_4CoCl_4$
M	499.26
a/Å	9.311(3)
b/Å	15.480(2)
c/Å	16.636(6)
V/Å^3	2 398(2)
Z	4
Space group	$Pbn2_1$
D_{calc}/g cm^{-1}	1.38
Radiation	Mo-K_α, graphite monochromated
λ/cm^{-1}	0.7107
T/°C	25
μ/cm^{-1}	10.69
R^a	0.043
$R_w{}^b$	0.037

[a] $R = \Sigma\|F_O| - \|F_c\|/\Sigma|F_O|$. [b] $R_w = [\Sigma w(|F_O| - |F_c|)^2/\Sigma w(F_O)^2]^{1/2}$.

Table 2. Crystallographic data for $[C_{17}H_{39}N_5][CoCl_4]$.

Formula	$C_{17}H_{39}CoCl_4N_5$
M	514.27
a/Å	8.877(3)
b/Å	14.088(8)
c/Å	10.122(5)
β/°	105.51(4)
V/Å^3	1 220(1)
Z	2
Space group	$P2_1$
D_{calc}/g cm^{-1}	1.40
Radiation	Mo-K_α, graphite monochromated
λ/cm^{-1}	0.7107
T/°C	25
μ/cm^{-1}	10.53
R^a	0.064
$R_w{}^b$	0.049

[a] $R = \Sigma\|F_O\| - \|F_c\|/\Sigma|F_O|$. [b] $R_w = [\Sigma w(|F_O| - |F_c|)^2/\Sigma w(F_O)^2]^{1/2}$.

to a solution of HCl contained in the calorimetric vessel. The measured value, −13.55(5) kcal mol^{-1}, was in agreement with the accepted literature value.[14] The calorimetric ampoule was charged with 2 cm^3 of ligand (0.003 mol dm^{-3}). After equilibration time (1 h), injections involving 20 mm^3 of NaOH (0.02 mol dm^{-3}) as the titrant were made by use of a 0.250 cm^3 gas-tight Hamilton syringe (model 1750 LT) attached to a Microlab M system. The timing and sequence of injections were regulated by a microcomputer which was used for integration of the titration curves.[13] Under the reaction conditions and employing the determined stability constants, the amount of each species present at equilibrium before and after each addition were calculated together with the corresponding enthalpies of reaction, by means of the KK88 program.[15]

Spectroscopy.—^{1}H and ^{13}C NMR spectra were recorded with a Varian VXR-300 spectrometer. The ^{13}C NMR spectra were recorded at an operating frequency of 75.43 MHz.

X-Ray Structure Analysis.—Investigations on single crystals of $[H_2L][CoCl_4]$ and $[H_2L1][CoCl_4]$ were carried out with an Enraf-Nonius CAD4 X-ray diffractometer. A summary of the crystallographic data is reported in Tables 1 and 2.* Cell parameters were determined from the setting angle of 25 reflections, measured on a Enraf-Nonius CAD4 automatic diffractometer.

Table 3. Atomic co-ordinates (× 10^4) for $[C_{17}H_{38}N_4][CoCl_4]$ with their esds in parentheses.

Atom	x/a	y/b	z/c
Co	276(2)	756(1)	5 000
Cl(1)	2 681(3)	944(2)	4 827(2)
Cl(2)	−439(3)	1 855(2)	5 839(2)
Cl(3)	−823(3)	936(2)	3 810(2)
Cl(4)	−178(4)	−582(2)	5494(2)
N(1)	6 754(10)	1 605(5)	−1 858(5)
C(1)	6 621(12)	1 979(7)	−1 050(6)
C(2)	5 857(13)	1 387(8)	−483(6)
N(2)	4 479(9)	1 049(6)	−840(5)
C(3)	4 037(12)	220(7)	−415(7)
C(4)	3 269(12)	1 676(7)	−863(7)
C(5)	2 232(12)	1 409(8)	−1 495(6)
N(3)	2 790(8)	1 429(5)	−2 301(5)
C(6)	2 557(13)	2 291(7)	−2 642(7)
C(7)	3 392(13)	2 439(8)	−3 395(7)
N(4)	4 976(13)	2 188(7)	−3 281(7)
C(8)	5 635(11)	2 022(7)	−4 069(7)
C(9)	5 836(13)	2 773(7)	−2 270(7)
C(10)	7 133(12)	2 310(7)	−2 438(8)
C(11)	7 847(11)	910(7)	−1 877(7)
C(12)	7 537(14)	272(7)	−2 550(8)
C(13)	6 339(15)	−363(8)	−2 287(9)
C(14)	5 509(14)	−766(7)	−2 973(7)
C(15)	4 306(14)	−145(8)	−3 277(7)
C(16)	2 986(12)	−79(7)	−2 749(8)
C(17)	2 189(11)	738(6)	−2 829(6)

Table 4. Atomic co-ordinates (× 10^4) for $[C_{17}H_{39}N_5][CoCl_4]$ with esds in parentheses.

Atom	x/a	y/b	z/c
Co	1 950(4)	0	2 067(3)
Cl(1)	3 961(7)	−1 019(5)	2 112(7)
Cl(2)	−440(8)	−723(6)	1 323(7)
Cl(3)	2 069(8)	583(5)	4 180(7)
Cl(4)	2 003(7)	1 182(5)	568(6)
N(1)	7 182(19)	1 785(13)	1 704(17)
N(2)	6 514(21)	1 872(14)	4 458(20)
N(3)	5 763(23)	3 497(16)	2 374(22)
N(4)	9 067(21)	3 483(14)	2 513(20)
N(5)	10 749(24)	2 680(16)	6 752(23)
C(1)	7 108(26)	1 025(16)	2 627(23)
C(2)	5 915(25)	1 217(18)	3 376(23)
C(3)	5 462(27)	2 744(19)	4 426(26)
C(4)	5 854(28)	3 588(17)	3 730(25)
C(5)	6 522(27)	4 315(18)	1 771(27)
C(6)	8 166(24)	4 406(16)	2 395(23)
C(7)	8 943(25)	2 996(15)	1 212(22)
C(8)	8 756(24)	1 931(15)	1 445(22)
C(9)	6 037(23)	1 631(16)	363(22)
C(10)	4 155(24)	3 470(18)	1 470(25)
C(11)	10 707(26)	3 663(18)	3 266(23)
C(12)	10 967(25)	3 695(17)	4 842(22)
C(13)	10 316(34)	2 712(21)	5203(32)
C(14)	12 384(26)	2 395(17)	7 403(27)
C(15)	9 723(31)	1 818(19)	7010(30)
C(16)	8 123(30)	2 013(18)	6 908(26)
C(17)	6 931(27)	1 505(18)	5 831(23)

By using a crystal of the compound $[H_2L][CoCl_4]$, with dimensions 0.6 × 0.4 × 0.4 mm, 2 446 reflections were collected on the same diffractometer, in the range 5 ≤ 2θ ≤ 50.

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* Tables of thermal parameters, complete bond lengths and angles, and hydrogen atom co-ordinates have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Instructions for Authors (1990),' *J. Chem. Soc., Perkin Trans. 2*, in the January issue.

Table 5. Basicity constants (logarithms) of cages in aqueous solution, at 25 °C, I = 0.15 mol dm^{-3} (NaCl).

	Cages (apical group)				
Step	L[a]($>CH_2$)	L1[b]($>N-CH_3$)	L2[c]($>NH$)	L3[d]($>S$)	L4[e]($>O$)
1	12.00(6)[f]	11.83	>14[g]	11.91	>14[g]
2	7.86	9.53	8.41	8.78	11.21
3	—	3.43	—	—	—

[a] This work. [b] From ref. 5. [c] From ref. 1. [d] From ref. 3. [e] From ref. 4. [f] Values in parentheses are standard deviations on the last significant figure. [g] Kinetically active or fast 'proton sponges.'

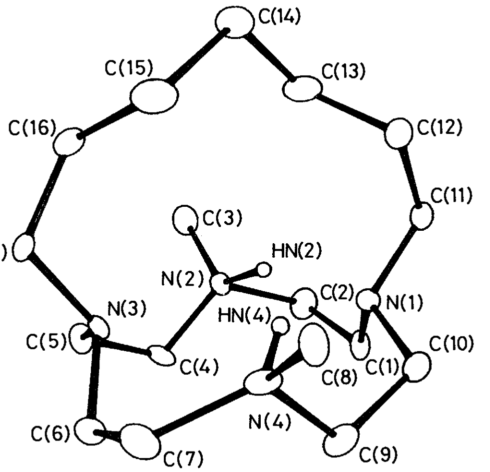

Figure 2. ORTEP drawing of the $[H_2L]^{2+}$ cation. Thermal ellipsoids for non-hydrogen atoms at 20% probability.

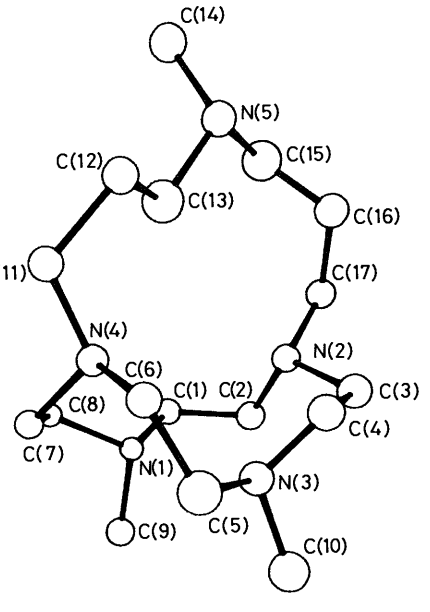

Figure 3. ORTEP drawing of the $[H_2L1]^{2+}$ cation. Thermal ellipsoids for non-hydrogen atoms at 20% probability.

The 1 358 reflections with $I \geqslant 3\sigma(I)$ were used in the structure analysis and corrected for absorption effects empirically once the structure had been solved.[16] The structure was solved by the heavy-atom method. Successive Fourier synthesis showed all non-hydrogen atoms. Hydrogen atoms of the macrobicycle were included in calculated positions (U = 0.06), except for the hydrogen atoms bonded to nitrogen atoms N(2) and N(4); these were found in the last Fourier difference map and refined isotropically. Anisotropic temperature factors were used for non-hydrogen atoms.

For L1 a crystal of $[H_2L1][CoCl_4]$, with dimensions 0.80 × 0.6 × 0.4 mm was used. 2 374 reflections were collected in the range $5 \leq 2\theta \leq 50$. The 772 reflections with $I \geq 3\sigma(F)$ were used in structure analysis. The data set was corrected for absorption effects empirically once the structure had been solved.[16] The structure was solved by the heavy-atom technique and then refined by means of the full-matrix least-squares method. Hydrogen atoms were included in calculated positions with a temperature factor U of 0.06. Isotropic temperature factors were used for all the other atoms except for the cobalt and chloride atoms which were refined anisotropically.

All calculations were performed on an IBM personal computer model Personal System 2/80 with the SHELX-76 set of programs[17] which uses the analytical approximation for the atomic scattering factors and anomalous dispersion corrections for all the atoms from ref. 18. Tables 3 and 4 report the list of the final atomic coordinates for non-hydrogen atoms with estimated standard deviations. The molecular plots were produced by the program ORTEP.[19]

Results and Discussion

Solutions Studies.—The macrobicycle L behaves at most as a diprotic base in aqueous solution. In the solid state, only diprotonated salts have been isolated (see the Experimental section). In aqueous solution, the proton-transfer properties of L have been investigated by potentiometry. The basicity constants of L are reported in Table 5 together with those of the other cages of the series so far investigated. In aqueous solution L behaves as a relatively strong base in the first protonation step, and logK_1 12.0 (see Table 5) is certainly very high for a compound with only tertiary nitrogen atoms. For example, the cage L is significantly more basic in the first protonation step than the monocyclic 1,4,8,11-tetramethyl-1,4,8,11-tetra-azacyclotetradecane (logK_1 = 9.7, see ref. 20), where only tertiary nitrogen atoms are present. L is even more basic than the tetra-azamacrocycle 1,7-dimethyl-1,4,7,10-tetra-azacyclodecane (**1**), (logK_1 = 10.76, taken from ref. 9) where both secondary and tertiary nitrogen atoms are present. This is a clear indication of the key role played by molecular topology in determining the proton-binding characteristics of L. The high basicity of L in the first protonation step is due to a very favourable enthalpic term ($\Delta H_1^\circ = -54.0 \pm 0.4$ kJ mol^{-1}) indicating a strong interaction between proton and nitrogen atoms. In the second protonation step L behaves as a moderate base, and logK_2 = 7.86. Also in this step the basicity of L is essentially due to a very favourable enthalpic term ($\Delta H_2^\circ = 44.8 \pm 0.4$ kJ mol^{-1}). Considering now the entropic contribution to the stepwise protonation of L, the first step is characterized by a favourable entropic term (ΔS_1° = 48.5 ± 0.9 J mol^{-1} K^{-1}), very likely translational in nature. In the second protonation step the entropic contribution is much reduced, being *ca.* 0 (ΔS_2° *ca.* 0). Compensation between two opposite effects: (i) the increase in the translational entropy due

Table 6. Basicity constants (logarithms) of cages in water–DMSO mixtures (50:50, mol:mol), at 25 °C, I = 0.15 mol dm^{-3} (NaCl); pK_w = 17.6.

	Cages (apical group)				
Step	L[a](>CH$_2$)	L1[a](>N–CH$_3$)	L2[a](>NH)	L3[a](>S)	L4[b](>O)
1	<13[c]	*c*	14.8	12.7	14.0
2	4.1	*c*	5.6	5.5	8.2
3	—	*c*	—	—	—

[a] This work. [b] From ref. 4. [c] The low solubility do not allow accurate determination of basicity constants.

Table 7. Selected bond distances/Å and angles/° for [$C_{17}H_{38}N_4$]-($CoCl_4$), with esds in parentheses.

Bond distances			
N(1)–C(1)	1.468(13)	C(6)–C(7)	1.492(16)
N(1)–C(10)	1.499(15)	C(7)–N(4)	1.537(17)
N(1)–C(11)	1.481(14)	N(4)–C(8)	1.469(15)
C(1)–C(2)	1.496(16)	N(4)–C(9)	1.479(16)
C(2)–N(2)	1.508(15)	N(4)–HN(4)	0.76 (13)
N(2)–C(3)	1.521(14)	C(9)–C(10)	1.509(17)
N(2)–C(4)	1.488(14)	C(11)–C(12)	1.520(17)
N(2)–HN(2)	1.24 (13)	C(12)–C(13)	1.550(18)
C(4)–C(5)	1.486(15)	C(13)–C(14)	1.514(18)
C(5)–N(3)	1.438(13)	C(14)–C(15)	1.560(17)
N(3)–C(6)	1.467(13)	C(15)–C(16)	1.515(17)
N(13)–C(17)	1.494(13)	C(16)–C(17)	1.472(15)
Bond angles			
C(10)–N(1)–C(11)	110.6(8)	N(3)–C(6)–C(7)	112.8(9)
C(1)–N(1)–C(11)	111.4(8)	C(6)–C(7)–N(4)	111.0(9)
C(1)–N(1)–C(10)	108.7(8)	C(7)–N(4)–C(9)	115.80(10)
N(1)–C(1)–C(2)	112.1(9)	C(7)–N(4)–C(8)	109.6(9)
C(1)–C(2)–N(2)	111.6(8)	C(8)–N(4)–C(9)	113.2(9)
HN(2)–N(2)–C(2)	79(6)	HN(4)–N(4)–C(7)	131(12)
HN(2)–N(2)–C(3)	124(6)	HN(4)–N(4)–C(8)	91(11)
HN(2)–N(2)–C(4)	114(6)	HN(4)–N(4)–C(9)	94(12)
C(2)–N(2)–C(4)	115.4(8)	N(4)–C(9)–C(10)	110.7(9)
C(2)–N(2)–C(3)	109.9(8)	N(1)–C(10)–C(9)	113.1(9)
C(3)–N(2)–C(4)	110.9(8)	N(1)–C(11)–C(12)	110.9(9)
N(2)–C(4)–C(5)	109.2(9)	C(11)–C(12)–C(13)	109(1)
C(4)–C(5)–N(3)	114.8(9)	C(12)–C(13)–C(14)	115(1)
C(5)–N(3)–C(17)	113.5(8)	C(13)–C(14)–C(15)	110.9(9)
C(5)–N(3)–C(6)	109.1(8)	C(14)–C(15)–C(16)	116(1)
C(6)–N(3)–C(17)	111.6(8)	C(15)–C(16)–C(17)	114(1)
N(3)–C(17)–C(16)	111.9(9)		

Table 8. Selected bond distances/Å and angles/° for [$C_{17}H_{39}N_5$]-($CoCl_4$), with esds in parentheses.

Bond distances			
N(1)–C(1)	1.43(3)	N(4)–C(11)	1.47(3)
N(1)–C(8)	1.50(3)	N(5)–C(13)	1.51(4)
N(1)–C(9)	1.48(2)	N(5)–C(14)	1.48(3)
N(2)–C(2)	1.42(3)	N(5)–C(15)	1.58(4)
N(2)–C(3)	1.54(3)	C(1)–C(2)	1.48(4)
N(2)–C(17)	1.44(3)	C(3)–C(4)	1.47(4)
N(3)–C(4)	1.36(3)	C(5)–C(6)	1.43(3)
N(3)–C(5)	1.54(4)	C(7)–C(8)	1.53(3)
N(3)–C(10)	1.48(3)	C(11)–C(12)	1.55(3)
N(4)–C(6)	1.51(3)	C(12)–C(13)	1.58(4)
N(4)–C(7)	1.46(3)	C(15)–C(16)	1.42(4)
C(16)–C(17)	1.48(3)		
Bond angles			
C(8)–N(1)–C(9)	108(2)	C(13)–N(5)–C(15)	115(2)
C(1)–N(1)–C(9)	110(2)	N(1)–C(1)–C(2)	111(2)
C(1)–N(1)–C(8)	115(2)	N(2)–C(2)–C(1)	110(2)
C(3)–N(2)–C(17)	108(2)	N(2)–C(3)–C(4)	116(2)
C(2)–N(2)–C(17)	117(2)	N(3)–C(4)–C(3)	117(2)
C(2)–N(2)–C(3)	114(2)	N(3)–C(5)–C(6)	113(2)
C(5)–N(3)–C(10)	103(2)	N(4)–C(6)–C(5)	114(2)
C(4)–N(3)–C(10)	114(2)	N(4)–C(7)–C(8)	108(2)
C(4)–N(3)–C(5)	115(2)	N(1)–C(8)–C(7)	108(2)
C(7)–N(4)–C(11)	112(2)	N(4)–C(11)–C(12)	113(2)
C(6)–N(4)–C(11)	109(2)	C(11)–C(12)–C(13)	104(2)
C(6)–N(4)–C(7)	115(2)	N(5)–C(13)–C(12)	105(2)
C(14)–N(5)–C(15)	105(2)	N(5)–C(15)–C(16)	117(2)
C(13)–N(5)–C(15)	101(2)	C(15)–C(16)–C(17)	118(2)
N(2)–C(17)–C(16)	119(2)		

to release of water molecules, and (ii) the molecular stiffening due to charge repulsion, may occur and this would explain such an entropic trend. These thermodynamic features are in agreement with the X-ray analysis of the H_2L^{2+} cation, discussed in the next section.

In comparing the basicity behaviour of L with that of the other cages in the series it is worth remembering that in the case of L the apical group is a carbon atom, while for all other cages a different donor atom is present. For two cages of the series with > NH and > O, respectively, as apical groups (L2 and L4 in Table 5) the basicity for the first protonation step is so high that it cannot be measured in aqueous solution.[1,4] In the case of L, where the apical group does not contribute directly to the proton binding, the increase in basicity for the first protonation step with respect to monocycles containing only tertiary nitrogens, can be ascribed to the special molecular topology with the cavity having convergently arranged proton-binding sites. Whenever possible the basicity constants have been measured in mixed water–DMSO (50%, mol:mol) solvent. The values of these basicity constants are reported in Table 6, together with those for the other cages in the series. The low solubility of the free amine L in this solvent system prevents an accurate determination of the first basicity constant which can be only estimated to be $< 10^{13}$. The value of the second basicity constant, $\log K_2 = 4.1$ (see Table 6), is the lowest of the series, confirming the influence of the apical group on the basicity behaviour. As already found in aqueous solution—and also in the mixed solvent—all equilibria are fast on the potentiometric time scale.

In order to better elucidate the basicity behaviour of L, we have carried out an X-ray analysis on its diprotonated salt [H_2L][$CoCl_4$]. To compare some structural features of diprotonated species the crystal structure analysis of the related species [H_2L1][$CoCl_4$] has also been carried out.

Crystal Structures of [H_2L][$CoCl_4$] *and* [H_2L1][$CoCl_4$].—The structures of both compounds consist of discrete [H_2L]$^{2+}$ and [H_2L1]$^{2+}$ cations, respectively, and [$CoCl_4$]$^{2+}$ anions. Figures 2 and 3 show ORTEP drawings of the cations with the atom labelling. Tables 7 and 8 list selected bond lengths and angles, Table 9 contains some interatomic contacts for the cations. The structure of [H_2L]$^{2+}$ shows that the four nitrogen atoms are in the *endo*-conformation, all the methylenic carbon atoms being below the average plane passing through N(1), N(2), N(3), and N(4). The two hydrogen atoms HN(2) and

Table 9. Interatomic contacts/Å for some protonated cages.

	$[H_2L]^{2+a}$	$[H_2L1]^{2+b}$	$[H_2L1]^{2+a}$	$[H_2L4]^{2+c}$
H_3C–N–N–CH_3	4.45(2)	4.72(3)	2.88	4.24
N(bh)–N(bh)[d]	3.77(2)	3.84(3)	4.07	3.96
X–N–CH_3	4.62(2)–4.63(2)	3.44(3)–3.56(3)	5.39–5.48	3.03–3.25
X–N(bh)	4.27(2)–4.38(2)	3.07(3)–3.09(3)	4.01–4.30	3.01–3.05

[a] This work. [b] From ref. 5. [c] From ref. 4. [d] Bridgehead nitrogen atoms. X is the apical group, see the Scheme.

HN(4) are bound to the methylated nitrogen atoms N(2) and N(4), respectively, and are encapsulated within the cavity. The electrostatic repulsion between them (they are 2.98 Å apart), is apparently overwhelmed by the electrostatic attractions between each proton and N(1) and N(3). A somewhat similar situation exists with the diprotonated species $[H_2L4]^{2+}$ in which the two protons, also bound to the methylated nitrogens, form strong hydrogen bonds with the apical oxygen atom.[4] Probably because of such additional interactions, L4 behaves as a stronger biprotic base than L. Such an overall conformation of the diprotonated cage, however, is not the only situation possible, as shown by the structure of the $[H_2L1]^{2+}$ species (Figure 3). In this case the two acidic hydrogens have not been located but it is evident that the conformation of the macrobicyclic frame of $[H_2L1]^{2+}$ is different from that of $[H_2L]^{2+}$ and $[H_2L4]^{2+}$ as well as from that of its monoprotonated species $[HL1]^+$.[5] The methylated nitrogens of the base are at a very short distance of 2.88 Å whereas they are >4.2 Å apart in $[H_2L]^{2+}$ and $[H_2L4]^{2+}$ (Table 9). This fact strongly suggests the protonation of one of these nitrogens and the occurrence of a strong linear hydrogen bond between them. On the other hand, the apical nitrogen keeps far apart from the basal nitrogens (4.01–5.48 Å *vs.* 3.01–3.25 Å for $[H_2L4]^{2+}$ and 3.07–3.56 Å for $[HL1]^+$) and its lone pair points away from the cage cavity. At the same time the lone pairs of the bridgehead nitrogens do not seem to be directly involved in the protonation. It seems likely that the other protonation occurs at the apical nitrogen, possibly in order to minimize the electrostatic repulsions between the protons. This is not possible with $[H_2L]^{2+}$ and $[H_2L4]^{2+}$, for both of which the apical atom X is less basic than the amine nitrogen. In conclusion, it appears that the conformation of the diprotonated cages is not imposed solely by the molecular geometry of the macrobicyclic frame but depends also on a delicate balance between electrostatic attractions and repulsions.

Metal Complex.—The electronic spectra of the $[CuL]^{2+}$ complex in aqueous solution (18 900 cm^{-1}, $\varepsilon = 40$) and in the solid state (18 150 cm^{-1}) are essentially the same and are diagnostic of a square-planar structure.[21] As found in all copper(II) complexes of this series of cages,[1,3] $[CuL]^{2+}$ is very inert toward strong acid solutions: it can exist in 0.1 mol dm^{-3} HCl for 30 days without any detectable decomposition. This experimental evidence suggests the encapsulation of the copper(II) ion into the cage cavity.

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