

The Small Cage 12,17-Dimethyl-5-oxa-1,9,12,17-tetra-azabicyclo[7.5.5]nonadecane (L): its Synthesis, Characterization, and 'Proton Sponge' Behaviour. The Crystal Structure of the Dipicrate Salt $[H_2(L)](Picrate)_2$

Antonio Bianchi, Mario Ciampolini,* Mauro Micheloni,* Nicoletta Nardi, and Barbara Valtancoli
 Department of Chemistry, University of Florence, Via Maragliano 75/77, I-50144-Florence, Italy

Stefano Mangani

Department of Chemistry University of Siena, Italy

Enrique Garcia-España

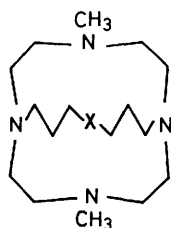
Department of Inorganic Chemistry, University of Valencia, Spain

Jose Antonio Ramirez

I.S.S.E.C.C. (CNR), Florence, Italy

The synthesis and characterization of the new oxa-azamacrocyclic compound 12,17-dimethyl-5-oxa-1,9,12,17-tetra-azabicyclo[7.5.5]nonadecane (L) are described. Its basicity behaviour in both aqueous and water–Me₂SO (50:50 mol/mol) solutions has been investigated by potentiometric and spectroscopic (¹H and ¹³C n.m.r.) techniques. In aqueous solution it behaves as a very strong base (proton sponge) in the first protonation step, and as a relatively strong base in the second step (log $k_2 = 11.21$). In the mixed water–Me₂SO solvent both protonation constants have been measured: log $k_1 = 14.0$ and log $k_2 = 8.2$. ¹H N.m.r. experiments indicate that in the monoprotonated species H(L)⁺ the proton is rapidly exchanged with acidic hydrogens on the n.m.r. timescale. ¹H–¹H and ¹H–¹³C two-dimensional n.m.r. experiments allowed the unequivocal assignment for all the ¹H proton and ¹³C resonances of both species H(L)⁺ and H₂(L)²⁺. Crystals of [H₂(L)](picrate)₂ are monoclinic, space group $P2_1/n$, with $a = 12.868(8)$, $b = 17.201(2)$, $c = 16.614(2)$ Å, $\beta = 110.18(1)^\circ$, and $Z = 4$; final R values of 0.090 ($R_w = 0.090$) for 3 801 observed reflections. The four basal nitrogen atoms and the apical oxygen atom are located at the apices of a slightly distorted square pyramid. X-Ray analysis shows that protonation occurs on the NCH₃ groups. Each hydrogen atom of the NH⁺CH₃ interacts with the oxygen atom, the O...H distances 2.328(16) and 2.112(18) Å, and with both bridgehead nitrogen atoms, the H...N distances ranging from 2.32 to 2.34 Å. This arrangement makes the overall structure very stable from the thermodynamic point of view and explains the unusually high basicity of (L) in both first- and second-protonation step.

The synthesis of new macrobicyclic compounds is recognized as a very active field.¹ The current interest stems from different points of view, including selective ion recognition, transport processes, reaction catalysis, proton-transfer reaction and others.^{2,3} We are interested in small macrobicyclic cages because the molecular size, topology and nature of the donor atoms confer special proton-transfer and ligational properties to these molecules. We report in this paper on the title compound [hereafter abbreviated as (L)] which belongs to a series of small macrobicyclic cages of general formula as shown.



(L) X = O
 (L1) X = NH
 (L2) X = S

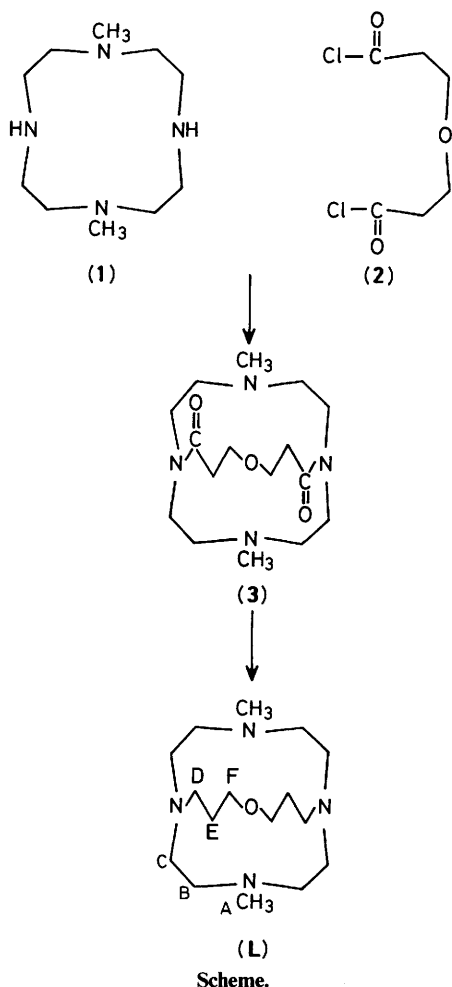
These compounds are made up of a basal twelve-membered tetra-azamacrocyclic (1) in which two diametrically opposed nitrogen atoms are connected by a bridging unit formed by two propylenic chains bound to the donor atom X.

Experimental

Synthesis of the Macrobicyclic (L).—The synthetic path followed to obtain the macrobicyclic (L), reported in the Scheme, was modelled on similar procedures described in refs. 4 and 5 for related compounds. The macrocycle 1,7-dimethyl-14,7,10-tetra-azacyclododecane (1) was prepared as already described.⁶

3,3'-Oxydi(propionyl) Chloride (2).—3,3'-Oxydipropionic acid was obtained by acid hydrolysis of the corresponding 3,3'-oxydipropionitrile as described in ref. 7. A sample of 3,3'-oxydi(propionic acid) (4.2 g, 0.026 mol) was treated with thionyl chloride (62.9 g, 0.52 mol) at 50 °C for 20 h. The unchanged SOCl₂ was removed under reduced pressure, the residue was dissolved in dry benzene (35 dm³) and the solvent was then evaporated. The last operation was repeated three times, and the resulting yellowish oil was used without further purification.

The Bicyclic Diamide (3).—A sample of the *trans*-dimethylated tetra-azamacrocyclic (1) (5.1 g, 0.026 mol) in dry benzene (500 cm³) and a sample of 3,3'-oxydipropionic acid chloride (2) (5.2 g, 0.026 mol) in dry benzene (500 cm³) containing triethylamine (5.2 g, 0.049 mol) was added simultaneously to dry benzene (500 cm³), with vigorous stirring, over a period of 7 h at room temperature. The reaction mixture was then evaporated to dryness under reduced pressure. The crude product obtained was dissolved in concentrated NaOH (3 mol dm⁻³; 30 cm³) and



the resulting solution was extracted with chloroform ($4 \times 20 \text{ cm}^3$). The combined extracts were dried (Na_2SO_4) and then evaporated under reduced pressure. The sticky yellowish oil obtained was extracted for two days with cyclohexane by using a Soxhlet apparatus. After the solvent had been evaporated the bicyclic diamide (3) was obtained (2 g, 24%), m.p. 198–200 °C, ν_{max} (Nujol): 1 635w (C=O) cm^{-1} (Found: C, 59.0; H, 9.4; N, 17.1. Calc. for $\text{C}_{16}\text{H}_{30}\text{N}_4\text{O}_3$: C, 58.87; H, 9.26; N, 17.16%).

12,17-Dimethyl-5-oxa-1,9,12,17-tetra-azabicyclo[7.5.5]nona decane (L).—The reduction of (3) to (L) was carried out with diborane in dry THF. Diborane (0.05 mol) in dry THF (50 cm^3) was added dropwise under an inert atmosphere to a cooled solution (20 cm^3) of dry THF containing (3) (2 g, 0.006 mol), over a period of 30 min. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature before being refluxed for 6 h. The solution was then cooled to 0 °C, and the excess of diborane was destroyed with methanol (20 cm^3) and water (7 cm^3). The white solid obtained was dissolved in $\text{HCl-H}_2\text{O-MeOH}$ (2:6:20 cm^3) and refluxed for 4 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was treated with water (15 cm^3) and the resulting solution filtered and made strongly alkaline with sodium hydroxide. This solution was extracted with dichloromethane ($4 \times 20 \text{ cm}^3$), and the combined extracts were dried over sodium sulphate. The dichloromethane was removed under reduced pressure, the residue was dissolved in ethanol (40 cm^3) and 47% hydrobromic acid (4.3 cm^3). Addition of a small amount of ether gave a white solid which was filtered off,

washed with ethanol and ether to yield (L)·2HBr·H₂O (2.6 g, 94%) (Found: C, 41.5; H, 8.0; N, 12.1. Calc. for $\text{C}_{16}\text{H}_{36}\text{Br}_2\text{N}_4\text{O}$: C, 41.75; H, 7.88; N, 12.17%). δ_{c} (water) $\text{H}_2(\text{L})^{2+}$: $\delta_{\text{c}} = 77.2$ (C-f), 56.5 (C-d), 56.2(C-b), 51.5 (C-c), 44.1 (C-a), 30.9 (C-e). HL^+ : $\delta_{\text{c}} = 76.6$ (C-f), 59.4 (C-d), 57.7 (C-b), 55.0 (C-c), 43.2 (C-a), 30.0 (C-e).

The diperchlorate salt (L)·2HClO₄ was obtained by the same procedure employed to obtain the dihydrobromic salt by treating the residue dissolved in ethanol with perchloric acid.

Reagents.—NaCl (Merck Suprapur) was used as ionic medium for both solvent systems. Me₂SO (Carlo Erba ACS grade) was purified by double distillation under reduced pressure. Standardized CO₂-free solutions of NaOH were prepared according to the procedure reported in ref. 8.

Potentiometric Measurements.—The potentiometric apparatus (potentiometer, burette, stirrer, cell, and microcomputer) and its mode of operation have already been reported.⁹ The standard potential of the cell E° , was calculated for both solvent systems (water, water–Me₂SO) by applying the Gran method.¹⁰ For the mixed solvent water–Me₂SO (50:50, mol:mol) the value found for the ionic product of water was $\text{p}K_{\text{w}} = 17.63$, in agreement with that reported previously under slightly different experimental conditions.¹¹ The computer program SUPERQUAD¹² was used to treat the data and calculate the protonation constants.

Spectroscopy.—200 MHz ¹H n.m.r. spectra were recorded with Bruker AC-200 and Varian VXR-300 spectrometers for D₂O solutions. The same instruments were used to record the ¹³C n.m.r. spectra at operating frequencies of 50.32 and 75.43 MHz, respectively. Computer simulation of the ¹H spectra was carried out on a Gould 27 computer using a locally constructed package¹³ based on the LAOCN¹⁴ and DAVINS¹⁵ refinement programs. The input for DAVINS was made up using the digitized spectrum captured on a Macintosh from the VXR-4000 computer via the serial communication RS-232 port. U.v.–vis spectra were recorded on a Perkin-Elmer Lambda 9 spectrophotometer.

Preparation of [H₂(L)](picrate)₂.—Crystals of [H₂(L)](picrate)₂ suitable for X-ray analysis were obtained by slow evaporation of an aqueous solution containing the perchlorate salt [H₂(L)](ClO₄)₂ and picric acid (Erba RPE grade). After some time, yellow crystals separated which were washed with ethanol–diethyl ether (Found: C, 44.5; H, 5.1; N, 18.4. Calc. for $\text{C}_{28}\text{H}_{40}\text{N}_{10}\text{O}_{15}$: C, 44.44; H, 5.33; N, 18.51%).

X-Ray Structure Analysis.—Crystal data and other experimental details are summarized in Table 1. A yellow crystal of approximate dimensions 0.2 × 0.2 × 0.12 mm was mounted on an Enraf-Nonius CAD4 automatic diffractometer and used for data collection at room temperature with graphite-monochromatized Mo-K_α radiation. Cell constants were determined by least-squares fitting of 25 accurately centred reflections. Intensity data were corrected for Lorentz and polarization effects. Absorption corrections were not applied. The intensities of three standard reflections were monitored periodically during data collection. The structure was solved by direct methods and subsequently refined by full-matrix least-squares techniques. The function minimized was $\sum w(|F_o| - |F_c|)^2$ and unit weights were maintained throughout the refinement. Isotropic temperature factors were used for all of the atoms except for the heteroatoms of the picrate anions which were refined with anisotropic temperature factors to compensate a marked rotational disorder. One of the nitro groups [N(45), O(46), O(47)] appeared to be heavily affected by disorder, so the model used for the refinement of this group consisted of three slightly

Table 1. Crystal data and intensity collection parameters for $[\text{H}_2(\text{L})]$ -picrate) $_2$.

Formula	$\text{C}_{28}\text{H}_{40}\text{N}_{10}\text{O}_{15}$
<i>M</i>	756.65
Space group	$P2_1/n$
<i>a</i> /Å	12.868(2)
<i>b</i> /Å	17.201(2)
<i>c</i> /Å	16.614(2)
β /°	110.18(1)
<i>U</i> /Å ³	3 451.6
<i>Z</i>	4
<i>D_c</i> /g cm ⁻³	1.46
<i>F</i> (000)	1 592
μ (Mo- <i>Kα</i>)/cm ⁻¹	0.77
<i>T</i>	Ambient
Scan rate/° min ⁻¹	2–12
Scan mode	θ–2θ
Scan width/°	0.90 + 0.35 tanθ
θ range/°	3–25
No. of reflections collected	6 485
Unique obs. reflections	
[<i>I</i> > 3.0 σ(<i>I</i>)]	3 801
Refined parameters	375
<i>R^a</i>	0.093
<i>R_w^b</i>	0.093

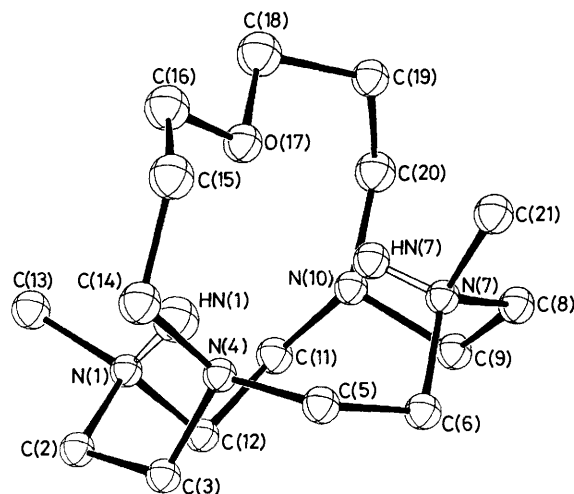
$$^a R = \Sigma \|F_o\| - |F_c| / \Sigma \|F_o\|. \quad ^b R_w = [\Sigma_w (|F_o| - |F_c|)^2 / \Sigma_w F_o^2]^{1/2}.$$

rotated, isotropic, NO₂ groups with occupancy factors of 0.5, 0.25, and 0.25, respectively. Disorder is also present for one of the atoms of the propylenic chain [C(19)] which is located on two different positions with an occupancy factor of 0.5. The positions of all the hydrogen atoms, except those located on the disordered propylenic chain, and on the two OH groups of the picrate anions were revealed by a difference Fourier map, but only those of the quaternary nitrogens of the ligand and those of the picrate anions were refined as individual isotropic atoms, the others being included in calculated positions and constrained to ride the corresponding carbon atoms with free thermal parameters. All of the calculations were performed with the SHELX-76 set of programs¹⁶ which use the analytical approximation for the atomic scattering factors and anomalous dispersion corrections for all the atoms from the International Tables.¹⁷ The molecular plot was produced by ORTEP.¹⁸ Table 2 shows the final atomic co-ordinates with estimated standard deviations from the least squares inverse matrix.

Tables of thermal parameters, complete bond lengths and angles, hydrogen atom co-ordinates (5 pages) have been deposited at the Cambridge Crystallographic Data Centre.*

Results and Discussion

Crystal Structure of $\text{H}_2(\text{L})(\text{picrate})_2$.—The structure of the compound consists of discrete $[\text{H}_2(\text{L})]^{2+}$ cations and picrate anions. Figure 1 shows an ORTEP¹⁸ drawing of the cation with atomic labelling. Selected bond lengths and angles are reported in Table 3, in which are also reported some significant non-bonding distances for the cation. The macrocycle is protonated on the methylated tertiary nitrogens N(1) and N(7) and displays a conformation similar to that of the related cage 12,17-dimethyl-1,5,9,12,17-penta-aza[7.5.5]nonadecane.¹⁹ The four nitrogen atoms are coplanar, within experimental error, and form the basal plane of a slightly distorted square pyramid with the oxygen atom at the apex. The four nitrogens are in the *endo*

**Figure 1.** ORTEP drawing of the $[\text{H}_2(\text{L})]^{2+}$ cation. Thermal ellipsoids for non-hydrogen atoms at 20% probability.

conformation, all of the ethylenic carbon atoms being below the basal plane.

The hydrogen atoms bonded to N(1) and N(7) form hydrogen bonds with the apical oxygen. The mean value of the N–H...O distances (3.13 Å) are comparable to that of the N–H...N distances (3.04 Å) for the monoprotonated penta-azabicyclic.¹⁹ Although the difference is small, it contrasts with the usual trend for N–H...O and N–H...N distances (mean values 2.9 and 3.1 Å, respectively).²⁰ This suggests weaker H-bond interactions in the present $\text{H}_2(\text{L})^{2+}$ cation with respect to $\text{H}(\text{L})^+$, probably on account of the larger electrostatic repulsions within the doubly charged cation.

The two hydrogen bonds are nearly linear. Each hydrogen atom of the CH_3NH^+ group can further interact electrostatically with both bridgehead nitrogen atoms N(4) and N(10), these distances ranging from 2.32 to 2.54 Å (see Table 3).

Solution Studies.—In the solid state, the small cage-like macrobicyclic (**L**) behaves, at most, as a diprotic base; only diprotonated salts have been isolated (see the Experimental section). In aqueous solution, proton-transfer properties of (**L**) were first investigated by potentiometry. The macrocyclic cage (**L**) behaves as a very strong base in the first protonation step since the proton from the $\text{H}(\text{L})^+$ species cannot be removed even in strong alkaline solution (see Table 4). Indeed deprotonation of $\text{H}(\text{L})^+$ in 0.5 mol dm⁻³ aqueous NaOH is undetectable (¹³C n.m.r. spectra), so that the logarithm of the first basicity constant can be estimated to be higher than 13.5. Even in the second protonation step (**L**) behaves as a relatively strong base with log *k*₂ = 11.21 (see Table 4), a value which is much higher than those reported for tertiary nitrogens of saturated, monocyclic, azamacrocycles. For comparison, the value of log *k*₂ = 9.31 for the *N*-methylated 14-membered tetra-azamacrocyclic 1,4,8,11-tetra-azacyclotetradecane can be recalled.²¹

The protonation equilibria are all fast. The ¹H n.m.r. spectrum of $\text{H}_2(\text{L})\cdot\text{Br}_2$ in deuterated Me₂SO exhibits a broad signal at 7.3 ppm, integrating for two protons, attributable to deshielded hydrogen-bonded $\geq\text{NH}^+$ protons.⁴ This signal disappears, due to excessive linewidth, upon addition of 2 equivalents of exchangeable protons (methanol or water), indicating fast proton exchange on the n.m.r. timescale. Indeed, potentiometric and n.m.r. experiments indicate that (**L**) behaves as a 'fast proton sponge,' *i.e.*, a very high basicity for the first protonation step, not measurable in water solution, coupled with fast proton transfer. These are remarkable properties, in

* For details of the crystallographic data deposition scheme see: 'Instructions for Authors' (1989), *J. Chem. Soc., Perkin Trans. 2*, 1989, issue 1.

Table 2. Atomic co-ordinates ($\times 10^4$) of $[\text{H}_2(\text{L})](\text{picrate})_2$.

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
N(1)	2 598(4)	8 401(3)	4 568(3)
HN(1)	2 389(55)	8 618(41)	4 003(45)
C(2)	2 992(5)	7 582(4)	4 499(4)
C(3)	2 331(5)	7 219(4)	3 654(4)
N(4)	2 235(4)	7 723(3)	2 926(3)
C(5)	1 371(5)	7 445(4)	2 151(4)
C(6)	261(5)	7 792(4)	2 092(4)
N(7)	311(4)	8 661(3)	2 038(3)
HN(7)	1 028(47)	8 843(32)	2 395(36)
C(8)	-613(5)	9 055(4)	2 252(4)
C(9)	-410(5)	9 056(4)	3 195(4)
N(10)	662(4)	9 388(3)	3 693(3)
C(11)	981(5)	9 162(4)	4 606(4)
C(12)	1 540(5)	8 383(4)	4 768(4)
C(13)	3 504(5)	8 848(4)	5 219(4)
C(14)	3 318(6)	7 816(5)	2 798(5)
C(15)	3 429(8)	8 565(5)	2 347(5)
C(16)	3 456(7)	9 307(5)	2 770(6)
O(17)	2 476(4)	9 486(3)	2 942(3)
C(18)	2 413(7)	10 303(5)	3 118(5)
C(19) ^a	1 175(11)	10 549(8)	3 033(9)
C(191) ^a	1 905(14)	10 517(10)	3 636(10)
C(20)	685(6)	10 253(4)	3 589(5)
C(21)	284(6)	8 917(4)	1 169(4)
C(22)	3 110(5)	1 993(4)	6 791(4)
H(22)	2 893(50)	1 569(39)	7 027(39)
C(23)	3 461(5)	1 872(4)	6 112(4)
C(24)	3 907(5)	2 471(4)	5 708(4)
C(25)	3 953(5)	3 206(3)	6 145(4)
C(26)	3 593(5)	3 335(4)	6 814(4)
H(26)	3 547(42)	3 876(32)	7 016(32)
C(27)	3 183(5)	2 722(4)	7 142(4)
O(28)	4 166(4)	2 395(3)	5 063(3)
N(29)	3 339(5)	1 092(4)	5 757(4)
O(30)	2 553(5)	698(3)	5 788(4)
O(31)	4 017(5)	855(3)	5 452(4)
N(32)	4 440(5)	3 866(3)	5 855(3)
O(33)	5 329(4)	3 783(3)	5 762(4)
O(34)	3 969(5)	4 466(4)	5 728(6)
N(35)	2 816(5)	2 870(4)	7 862(3)
O(36)	2 853(5)	3 533(4)	8 125(3)
O(37)	2 486(5)	2 320(4)	8 173(3)
C(38)	655(5)	3 519(4)	5 990(4)
C(39)	858(5)	3 496(4)	5 186(4)
C(40)	1 239(5)	4 109(4)	4 835(4)
H(40)	1 373(53)	4 011(39)	4 373(43)
C(41)	1 458(5)	4 799(4)	5 269(4)
C(42)	1 282(5)	4 900(4)	6 022(4)
C(43)	871(5)	4 292(3)	6 368(4)
O(44)	329(4)	2 958(3)	6 293(3)
N(45)	666(6)	2 750(4)	4 716(4)
O(46) ^a	821(8)	2 147(5)	5 114(6)
O(47) ^a	144(17)	2 839(7)	3 912(8)
O(461) ^b	1 575(20)	2 567(13)	4 396(15)
O(462) ^b	219(18)	2 237(13)	4 759(13)
O(471) ^b	798(34)	2 642(19)	4 054(28)
O(472) ^b	-326(35)	2 903(25)	4 017(28)
N(48)	1 901(5)	5 440(4)	4 910(4)
O(49)	1 996(5)	4 348(3)	4 210(4)
O(50)	2 160(5)	6 034(3)	5 332(4)
N(51)	653(5)	4 467(4)	7 159(4)
O(52)	846(7)	5 109(4)	7 452(5)
O(53)	259(5)	3 974(4)	7 482(4)

^a Occupancy factor 0.5. ^b Occupancy factor 0.25.**Table 3.** Selected bond distances/Å and angles/°, with estimated standard deviations in parentheses, and some significant intramolecular non-bonding distances/Å.

N(1)-HN(1)	0.960(72)	N(1)-C(2)	1.515(9)
N(1)-C(12)	1.508(9)	N(1)-C(13)	1.499(7)
C(2)-C(3)	1.504(8)	C(3)-N(4)	1.459(9)
N(4)-C(5)	1.462(7)	N(4)-C(14)	1.489(10)
C(5)-C(6)	1.520(10)	C(6)-N(7)	1.501(9)
N(7)-HN(7)	0.962(53)	N(7)-C(8)	1.512(9)
N(7)-C(21)	1.499(9)	C(8)-C(9)	1.498(9)
C(9)-N(10)	1.459(7)	N(10)-C(11)	1.481(8)
N(10)-C(20)	1.500(9)	C(11)-C(12)	1.499(10)
C(14)-C(15)	1.522(12)	C(15)-C(16)	1.452(12)
C(16)-O(17)	1.419(12)	O(17)-C(18)	1.443(10)
C(18)-C(19)	1.607(17)	C(19)-C(20)	1.382(19)
C(18)-C(191)	1.300(16)	C(191)-C(20)	1.611(17)
C(12)-N(1)-C(13)	112.9(5)	C(2)-N(1)-C(13)	109.5(5)
C(2)-N(1)-C(12)	110.5(5)	HN(1)-N(1)-C(13)	113.1(42)
HN(1)-N(1)-C(12)	104.7(44)	HN(1)-N(1)-C(2)	105.9(42)
N(1)-C(2)-C(3)	111.2(5)	C(2)-C(3)-N(4)	112.7(5)
C(3)-N(4)-C(14)	111.5(5)	C(3)-N(4)-C(5)	110.9(5)
C(5)-N(4)-C(14)	112.0(5)	N(4)-C(5)-C(6)	109.9(5)
C(5)-C(6)-N(7)	109.7(5)	C(6)-N(7)-C(21)	111.3(5)
C(6)-N(7)-C(8)	112.2(5)	C(6)-N(7)-HN(7)	109.8(35)
C(8)-N(7)-C(21)	109.7(5)	HN(7)-N(7)-C(21)	101.4(35)
HN(7)-N(7)-C(8)	112.0(36)	N(7)-C(8)-C(9)	112.3(5)
C(8)-C(9)-N(10)	112.6(5)	C(9)-N(10)-C(20)	112.1(5)
C(9)-N(10)-C(11)	110.6(5)	C(11)-N(10)-C(20)	111.7(5)
N(10)-C(11)-C(12)	111.4(5)	N(1)-C(12)-C(11)	110.9(5)
N(4)-C(14)-C(15)	114.4(7)	C(14)-C(15)-C(16)	119.8(7)
C(15)-C(16)-O(17)	114.4(7)	C(16)-O(17)-C(18)	111.6(6)
O(17)-C(18)-C(19)	111.2(8)	C(18)-C(19)-C(20)	120.8(11)
N(10)-C(20)-C(19)	118.3(8)	N(10)-C(20)-C(191)	109.3(8)
C(18)-C(191)-C(20)	126.3(13)	O(17)-C(18)-C(191)	119.1(10)
N(1)-O(17)	3.224(7)	N(4)-O(17)	3.049(7)
N(7)-O(17)	3.027(7)	N(10)-O(17)	3.006(7)
HN(1)-O(17)	2.328(17)	HN(7)-O(17)	2.112(18)
N(1)-N(4)	2.853(7)	N(1)-N(10)	2.950(7)
N(4)-N(7)	2.896(7)	N(7)-N(10)	2.909(7)
HN(1)-N(4)	2.315(73)	HN(1)-N(10)	2.484(69)
HN(7)-N(4)	2.440(56)	HN(7)-N(10)	2.540(66)

Table 4. Logarithms of the basicity constants of (L) in aqueous solution and in water-Me₂SO mixture (50:50 mol:mol). The last digit(s) in parentheses are the standard deviations on the last significant figure. Measurements were taken at 25 °C and ionic strength (*I*) = 0.15 (NaCl).

Reaction	log <i>k</i>	
	Water	Me ₂ SO-water
H ⁺ + (L) = H(L) ⁺	> 13.5	14.0(1)
H ⁺ + H(L) ⁺ = H ₂ (L) ²⁺	11.21(4)	8.2(1)
H ⁺ + OH ⁻ = H ₂ O	13.76(1)	17.73(3)

dynamics of protonation of (L) and to measure both basicity constants, we changed the solvent by replacing the aqueous solution with a water-Me₂SO (50:50 mol:mol) mixture. In this mixed solvent all protonation equilibria are fast and the titrant basic species OH⁻ competes ($pK_w = 17.63$, see Table 4) with the base (L) and the first protonation constant can be measured (see Table 4). The observed value of log $k_1 = 14.0$ is high and is expected to be even higher in aqueous solution as shown by comparison of log k_2 in both media (Table 4).

Undoubtedly the oxygen atom of the bridging unit does play a key role in the proton-sponge behaviour of (L). There is a remarkable increase in proton affinity if we compare the first

sharp contrast with those found for small cryptands,²² where the proton, contained inside the molecular cavity, shows a slow transfer reaction.

In order to obtain a deeper understanding of the thermo-

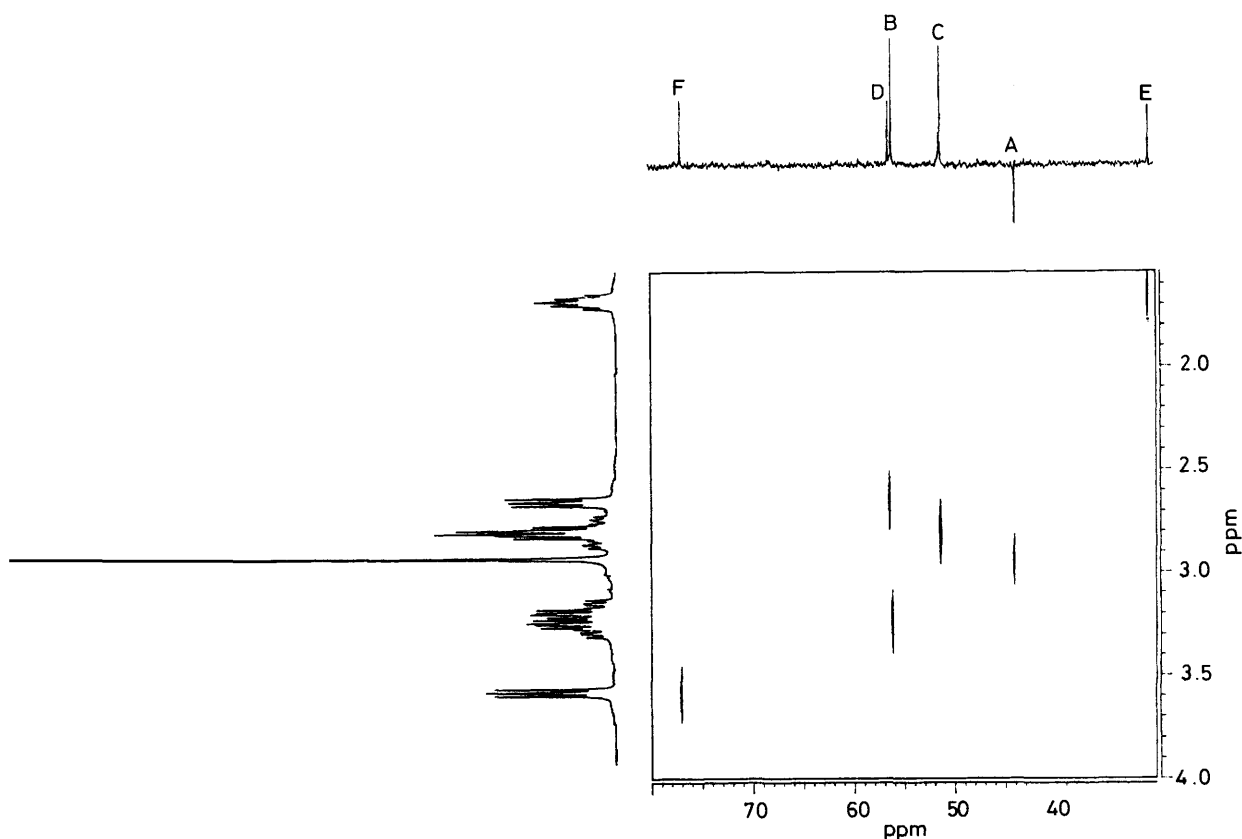


Figure 2. 75.43 MHz ^{13}C - ^1H shift-correlated 2D n.m.r. spectrum of $[\text{H}_2(\text{L})]^{2+}$.

Table 5. Proton chemical shifts and coupling constants for basal protons (BB'CC') and bridging protons (DD'EE'FF')

Species $\text{H}_2(\text{L})^{2+}$			
Proton	δ	Coupling	J/Hz
A	3.00	BB'	13.99
B'	3.34	CC'	15.21
B	3.25	BC	3.81
C'	2.89	B'C'	3.80
C	2.84	B'C	7.78
D'	2.72	BC'	7.07
D	2.72	DE	3.24
E'	1.73	EF	6.78
E	1.73	D'E	7.25
F'	3.66	E'F	3.41
F	3.66	DD'	15.0
		EE'	15.0
		FF'	15.0
Species $\text{H}(\text{L})^+$			
A	2.39	BC	5.88
B	2.76	DE	6.42
B'	2.76	EF	5.39
C	2.67		
C'	2.67		
D	2.66		
D'	2.66		
E	1.70		
E'	1.70		
F	3.58		
F'	3.58		

basicity constant of the *trans*-dimethylated tetra-azamacrocyclic (1) ($\log k_1 = 10.8$, see ref. 6) and that of the cage (L) (\log

$k_1 > 13.5$, see Table 4). This increase in basicity is even more significant if one considers that, with the tetra-azamacrocyclic (1), the nitrogen atom involved in the first protonation is a secondary one, which is expected to be more basic than a tertiary nitrogen such as that involved in the cage (L).

It is useful to compare the first basicity constant of (L) and that of the related sulphur-cage (L2), in which the oxygen atom in the bridging unit has been replaced by the bulky sulphur atom. (L2) is significantly less basic than is (L) ($\log k_1 = 11.7$, see ref. 5) and does not show proton-sponge behaviour. These considerations allow us to conclude that the high thermodynamic stability of the monoprotonated species $\text{H}(\text{L})^+$ is achieved by the formation of a hydrogen-bond network, involving the proton, tertiary nitrogens, and the oxygen atom of the bridge.

Similar considerations should also account for the still high basicity of (L) in the second protonation step ($\log k_2 = 11.21$, see Table 4). Indeed, in spite of the increase in charge, the diprotonated species $\text{H}_2(\text{L})^{2+}$ is unusually thermodynamically stable. An H-bond network which stabilizes this species is in agreement with the crystal structure of the diprotonated salt $[\text{H}_2(\text{L})](\text{picrate})_2$ (see the crystal-structure description).

In order to obtain more structural information on the cage in solution we recorded its ^1H and ^{13}C n.m.r. spectra over a wide pH range. Each of the ^{13}C spectra shows six different signals for both protonated species $\text{H}(\text{L})^+$ and $\text{H}_2(\text{L})^{2+}$, indicative of their apparent C_{2v} symmetries. Obviously, the lowest-field signal is that of carbon F (see the Scheme for carbon labelling), and from the ^{13}C DEPT spectrum the resonance at 43–44 ppm can be assigned to the methyl carbon A. The highest-field signal can be assigned to carbon E of the propylenic chain.

The combination of two different two-dimensional n.m.r. techniques: 2D ^1H - ^1H COSY 45° and 2D ^1H - ^{13}C correlation, has allowed a univocal assignment for all the ^1H and ^{13}C

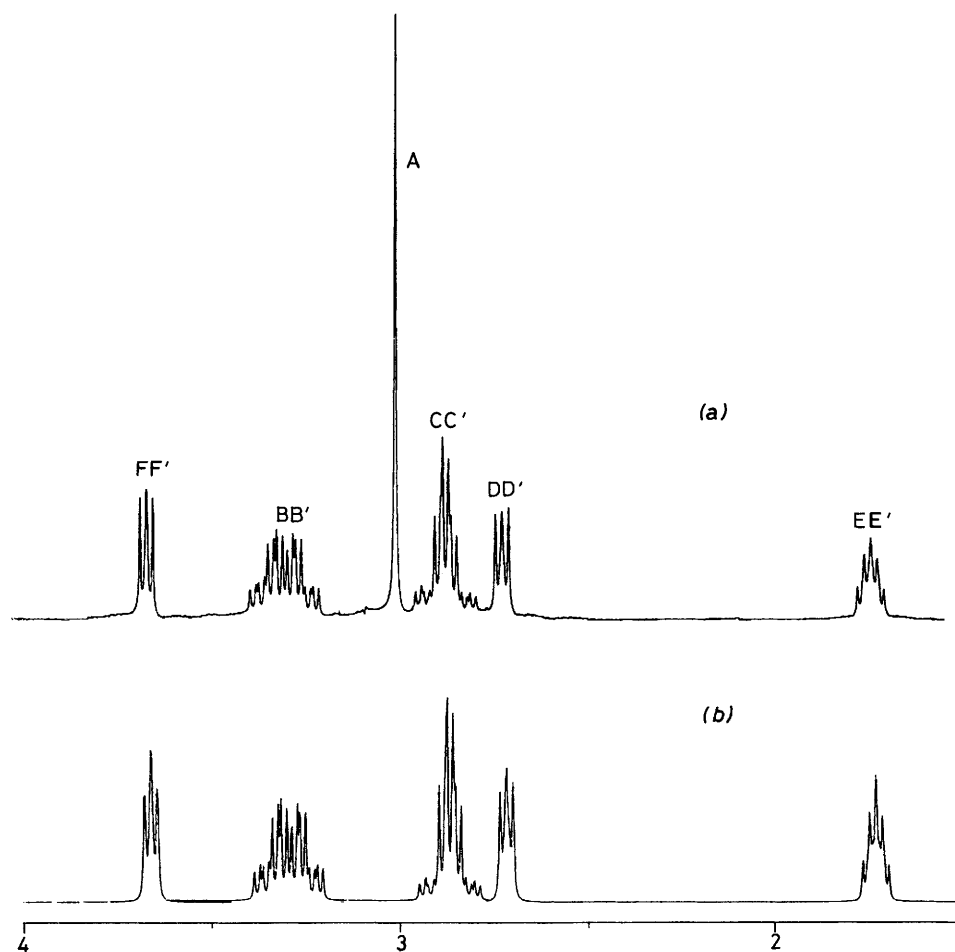


Figure 3. Experimental (a) and computer-simulated (b) proton n.m.r. spectra of $[H_2(L)]^{2+}$: (a) basal protons (BB'CC'); (b) bridging protons (DD'EE'FF').

resonances of both species $H(L)^+$ and $H_2(L)^{2+}$ (see Figure 2). The 1H n.m.r. shifts and 1H - 1H coupling constants, deduced by iterative analysis, allow a complete simulation of the experimental data (see Table 5 and Figure 3). According to this full assignment, the proton spectrum of $H_2(L)^{2+}$ is consistent with two different spin systems, CC'BB' for the methylenic protons of the basal network and DD'EE'FF' for the methylenic protons of the bridge. The most significant difference in the 1H n.m.r. spectra for $H(L)^+$ is the higher equivalence of protons within each CH_2 group (C_2B_2 and $D_2E_2F_2$ protons). This suggests less rigidity in the basal ring for the species $H(L)^+$ than for $H_2(L)^{2+}$.

The values obtained for the vicinal coupling constants of the basal protons in $H_2(L)^{2+}$ are in agreement with a configuration in which both nitrogens joined by an ethylenic chain are *gauche*. This structural configuration is also found in the solid state as established by the X-ray analysis of the $H_2(L)^{2+}$ dipicrate salt in which the torsion angles between the nitrogen atoms at the end of the ethylenic chains are in the range 49–62°. A similar configuration has been also found in the case of the related cage 12,17-dimethyl-1,5,9,12,17-penta-aza[7.5.5]-nonadecane in its monoprotonated form.²⁰ The protons of all the other methylenic groups [bridge protons for the protonated species $H_2(L)^{2+}$ and $H(L)^+$ and basal protons just for $H(L)^+$] are equivalent and their vicinal coupling constants show an average value between *trans* and *gauche* positions which suggests again less rigidity of the carbon chains and the existence of equilibria between some conformers.

Finally note that on going from $H(L)^+$ to $H_2(L)^{2+}$, fairly large n.m.r. shifts with proton A (+0.61 ppm, see Table 5) and B

(+0.54 ppm) are observed. Other chemical shift changes are less than 0.2 ppm. Since A and B are the positions closest to the methylated nitrogen atoms, it can be confidently concluded that protonation in aqueous solution takes place preferentially at these sites.

Acknowledgements

We thank Prof. Alberto Vacca for computer programs used in the n.m.r. spectra simulation and Dr. S. Seniori Constantini for microanalyses. One of us (J. A. R.) thanks the Generalitat Valenciana (Spain) for a maintenance grant.

References

- 1 J. M. Lehn and P. G. Potvin, in 'Synthesis of Macrocycles, the Design of Selective Complexing Agents,' eds. J. J. Christensen and R. M. Izatt, Wiley, New York, 1987, p. 167.
- 2 G. A. Melson, 'Synthetic Multidentate Macrocyclic Compounds,' Plenum Press, New York, 1979; M. Hiraoka, 'Crown Compound,' Elsevier, Amsterdam, 1982; F. Vögtle and E. Weber, 'Host-Guest Complex Chemistry, Macrocycles,' Springer-Verlag, Berlin, Heidelberg, New York, 1985.
- 3 H. C. Hayward, *Chem. Soc. Rev.*, 1983, **12**, 285; P. A. Kollman, J. M. Lehn, and G. Wipff, *J. Mol. Struct.*, 1983, **93**, 153; J. M. Lehn, *Science*, 1985, **227**, 849; H. M. Colquhoun, J. F. Stoddart, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 487; F. P. Schmidtchen, *J. Am. Chem. Soc.*, 1986, **108**, 8249.
- 4 M. Ciampolini, M. Micheloni, F. Vizza, F. Zanobini, S. Chimichi, and P. Dapporto, *J. Chem. Soc., Dalton Trans.*, 1986, 505.

- 5 A. Bianchi, E. Garcia-España, M. Micheloni, N. Nardi, and F. Vizza, *Inorg. Chem.*, 1986, **25**, 4379.
- 6 M. Ciampolini, M. Micheloni, N. Nardi, P. Paoletti, P. Dapporto, and F. Zanobini, *J. Chem. Soc., Dalton Trans.*, 1984, 1357.
- 7 USP 2 837 568.
- 8 M. Micheloni, A. Sabatini, and A. Vacca, *Inorg. Chim. Acta*, 1977, **25**, 41.
- 9 A. Bianchi, L. Bogni, P. Dapporto, M. Micheloni, and P. Paoletti, *Inorg. Chem.*, 1984, **23**, 1201.
- 10 G. Gran, *Analyst*, 1952, **77**, 661; F. J. C. Rossotti and H. Rossotti, *J. Chem. Educ.*, 1965, **42**, 375.
- 11 H. R. Jimenez, M. Julve, J. M. Moratal, and J. Faus, *J. Chem. Soc., Chem. Commun.*, 1987, 910.
- 12 P. Gans, A. Sabatini, and A. Vacca, *J. Chem. Soc., Dalton Trans.*, 1985, 1195.
- 13 A. Vacca, to be published.
- 14 S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, 1964, **41**, 3863.
- 15 D. S. Stephenson and G. Binsch, *J. Magn. Reson.*, 1980, **37**, 395.
- 16 G. M. Sheldrick, SHELX-76, Program for Crystal Structure Determination, University of Cambridge, 1976.
- 17 'International Tables for X-Ray Crystallography,' Kynoch Press, Birmingham, 1974, vol. 4.
- 18 C. K. Johnson, ORTEP, Report ORNL 3794, Oak Ridge National Laboratory, Tennessee, 1971.
- 19 M. Ciampolini, S. Mangani, M. Micheloni, P. Orioli, F. Vizza, and F. Zanobini, *Gazz. Chim. Ital.*, 1986, **116**, 189.
- 20 W. C. Hamilton and J. C. Ibers, in 'Hydrogen Bonding in Solids,' Benjamin, New York, 1968, p. 16.
- 21 M. Micheloni, A. Sabatini, and P. Paoletti, *J. Chem. Soc., Perkin Trans. 2*, 1978, 828.
- 22 J. Cheney and J. M. Lehn, *J. Chem. Soc., Chem. Commun.*, 1972, 487; P. B. Smith, J. L. Dye, J. Cheney, and J. M. Lehn, *J. Am. Chem. Soc.*, 1981, **103**, 6044; H. J. Brugge, D. Carboo, K. von Deuten, A. Knöchel, J. Kopf, and W. Dreissig, *ibid.*, 1986, **108**, 107.

Received 28th June 1988; Paper 8/02581F