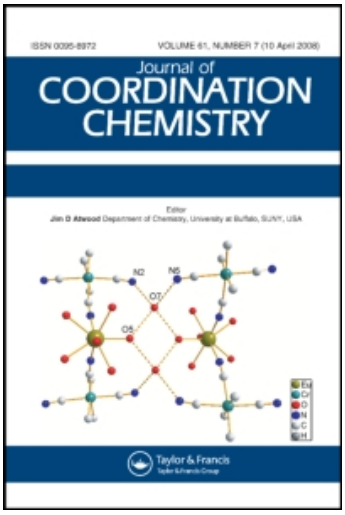

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SMALL SYNTHETIC MACROCYCLIC CAGES. PROTON TRANSFER PROPERTIES AND METAL COMPLEXES

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Abstract The synthesis, characterization and ligational properties of a series of small macrocyclic cages are discussed.

Keywords: Macrocyclic cages, H. L. synthesis, characterization, ligational properties

INTRODUCTION

The challenge of designing and synthesizing new macrocyclic compounds in order to achieve new chemical properties is one of the most fascinating aspects of the macrocyclic chemistry. The present report will review the chemistry of a series of small synthetic cages with the general formula reported in Figure 1.

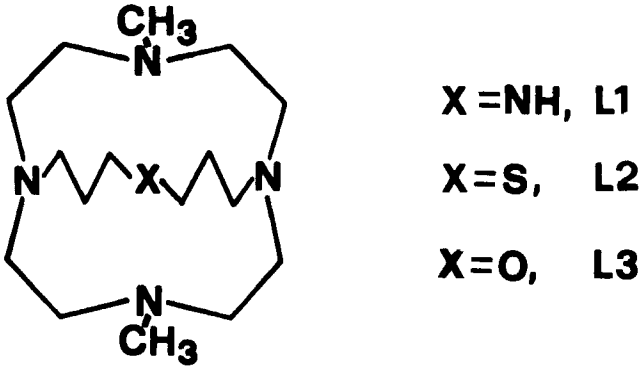

FIGURE 1. General formula indicating the macrocyclic cages belonging to the series.

The presence of a 'tridimensional' cavity allows to explore the influence of this molecular topology on the chemical properties of these compounds. The chemistry of these compounds is very much influenced by three main characteristics: i) size of the cavity; ii) rigidity; iii) nature of the donor atoms. The size of the cavity is very small and only small ions can be encapsulated. Rigidity is the second important characteristics: the presence of short ethylenic chains on the twelve-membered macrocycle makes this part of the molecule rather rigid. The two methyl groups further contributes to the overall rigidity. The only part of the molecule which is relatively more flexible is the unit which bridges the two unmethylated nitrogen atoms, which contains two propylenic chains. Finally the donor atoms, which are all or mainly nitrogens.

Synthesis of cages

The synthetic strategy followed for the preparation of these macrocycles is schematically reported in Figure 2. The first important step, which is common for all cages, is the preparation of a trans-dimethylated twelve membered tetra-azamacrocycle (1). The synthesis of this key-compound is fully described in ref.1. The creation of the tridimensional cavity, by bridging with the appropriate unit the two secondary nitrogen atoms, is the second step of the synthesis. In the synthesis of the nitrogen derivative[2] 12,17-dimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane (L1) the key step is represented by the formation of the macrobicyclic compound 12,17-dimethyl-5-tosyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane (3) (see Figure 2). The stirred suspension constituted by powdered sodium carbonate,

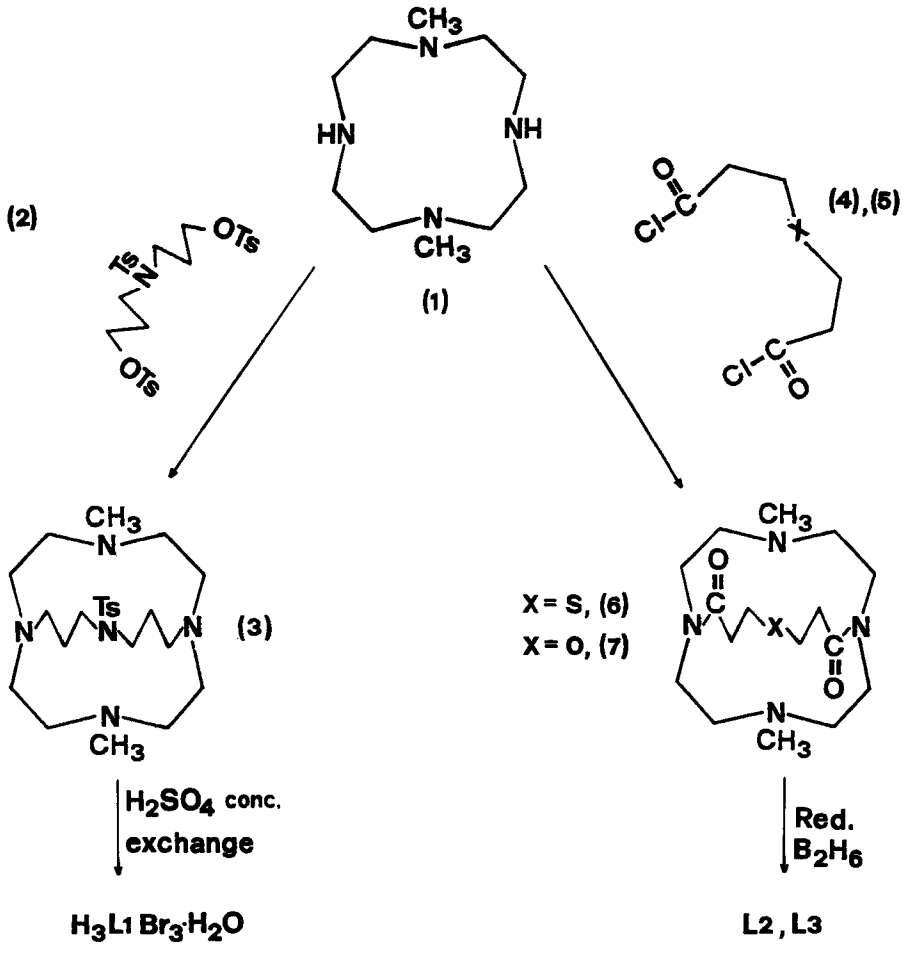

FIGURE 2. Synthetic route followed to obtain the cages.

compounds (1) and (2) was refluxed for 32 h. The yield of this reaction was found to be 31%. Longer reaction times resulted in markedly lower yields. The tosyl group was removed by using concentrated 96% sulfuric acid[3], the final product was purified as trihydro-

bromide monohydrate salt $(H_3L1)Br_3 \cdot H_2O$. White crystals of the slightly soluble monoperchlorate salt $HL1 \cdot ClO_4$ were isolated by addition of concentrated sodium perchlorate solution to the aqueous solution of the trihydrobromide salt. The synthesis of the sulphur derivative[4] (L2) 12,17-dimethyl-5-thia-1,9,12,17-tetraazabicyclo[7.5.5]nonadecane was carried out by using, as bridging unit, the chloride derivative (4) of the 3,3'-thiodipropionic acid. By using high dilution technique the bicyclic thiodiamide (6) was obtained. The reduction of the last product with diborane in dry THF yielded impure (L2). The final purification was achieved by sublimation in vacuo at 80 °C of the impure mixture. The monoperchlorate salt $(L2) \cdot ClO_4$ was obtained by adding a slight excess of perchloric acid in ethanol to an ethanolic solution of the free cage. The synthesis of the oxygen derivative[5] 12,17-dimethyl-5-oxo-1,9,12,17-tetraazabicyclo[7.5.5]nonadecane (L3) has been carried out by using as bridging unit the β,β'-Oxydipropionic acid chloride (5), obtained by chlorination of the corresponding acid. The last product was obtained by acidic hydrolysis of the commercial dinitrile. The final product was purified as monoperchlorate salt $(HL3) \cdot ClO_4$. It is worthwhile to note that all the synthesis so far used for obtaining the macrocyclic cages of the series are non-templated synthesis. This means that at the end of the synthetic route what we obtain is the free, or at most the monoprotonated cage, which can be used for studying both protonation and metal complex formation reactions.

Protonation behavior

The precursor compound of the series (L1) can take up at maximum three protons, even if potentially five protonation sites are available. In the solid state mono- and tri-protonated salts of L1 have been obtained. In aqueous solution this macrocycle behaves as a very weak base in the third protonation step ($\log K_3 < 2$ for the stepwise equilibria (1) and as

$$H_{(i-1)}L1^{(i-1)+} + H^+ = H_iL1^{i+} \qquad (1)$$

moderate base in the second protonation step ($\log K_2 = 8.41$)[2,6]. In the first protonation step L1 behaves as an extremely strong base: the proton can not be removed even in strong alkaline solution. The ^{13}C n.m.r. spectra of $HL1^+$ in water and in 3 mol dm^{-3} KOH solution are the same. The spectrum of $HL1^+$ species (see Figure 3) shows six sharp signals accounting for

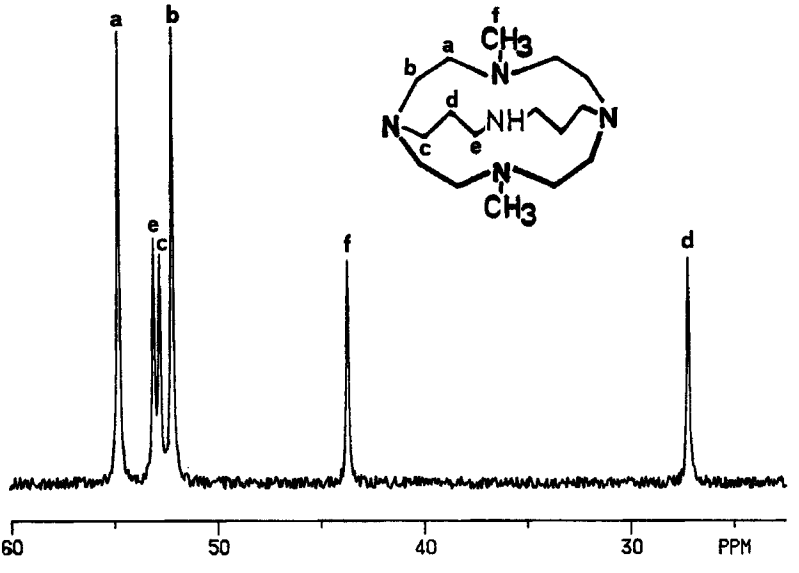

FIGURE 3. ^{13}C n.m.r. spectrum of the $HL1^+$ species with the relative assignments.

an overall C_{2v} symmetry, possibly time averaged among lower-symmetry conformers and/or tautomers. No changes in both the pure water and 3 mol dm^{-3} KOH spectra were detected after one week. The assignments were made by using APT technique[8,9] and two-dimensional ^{1}H-^{13}C n.m.r. The ^{1}H n.m.r. spectrum of [HL1](ClO_4) in dry CD_3CN or $CDCl_3$ shows a complicate multiplet pattern (see Figure 4) between 1.5 and 3.0 p.p.m., where the

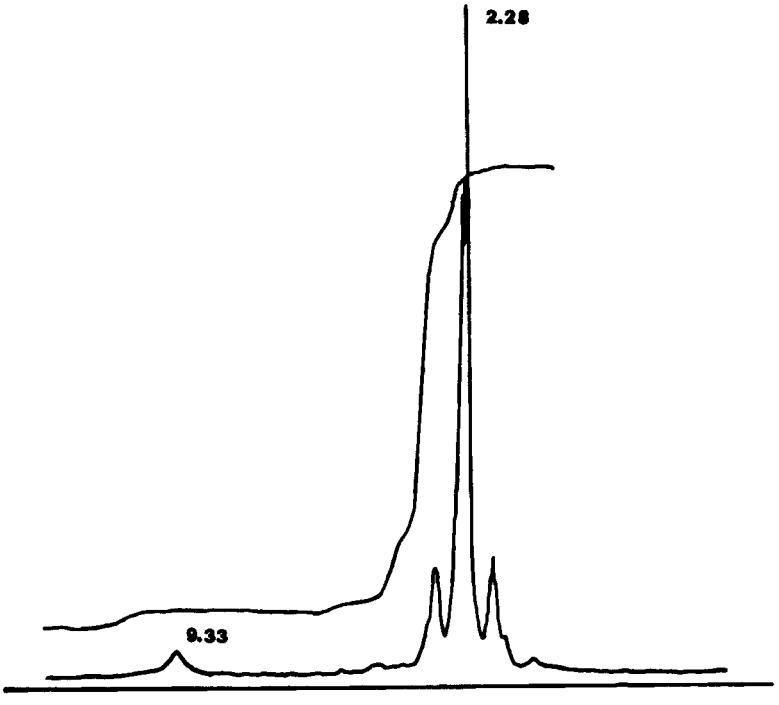

FIGURE 4. ^{1}H n.m.r. spectrum of [HL1](ClO_4) in dry CD_3CN

signal of the methyl group is recognizable at 2.28 p.p.m. and a broad signal at 9.3 p.p.m. The last signal, which integrates for two protons, is attributable to the 'trapped' deshielded $-NH^{+}_{2}$ protons. This signal disappears by adding two equivalents of

CH_3OH or water, due to excessive linewidth, indicating intermediate or fast proton exchange on the n.m.r. experiment time-scale with 'external' active hydrogens. The experimental findings, i.e. the extremely high basicity (unmeasurable in aqueous solution) and the fast proton exchange, allow us to classify L1 as 'FAST PROTON SPONGE'. In order to better investigate the origin of both the high thermodynamic stability and the high kinetic lability of the monoprotonated species $HL1^+$, the X-ray crystal structure of the [HL1]Br salt was carried out.[10] Good crystals for X-ray analysis were obtained by slow diffusion of diethyl ether into a concentrated solution of the [HL1]Br salt in tetrahydrofuran. In Figure 5 a view of the $HL1^+$ cation is

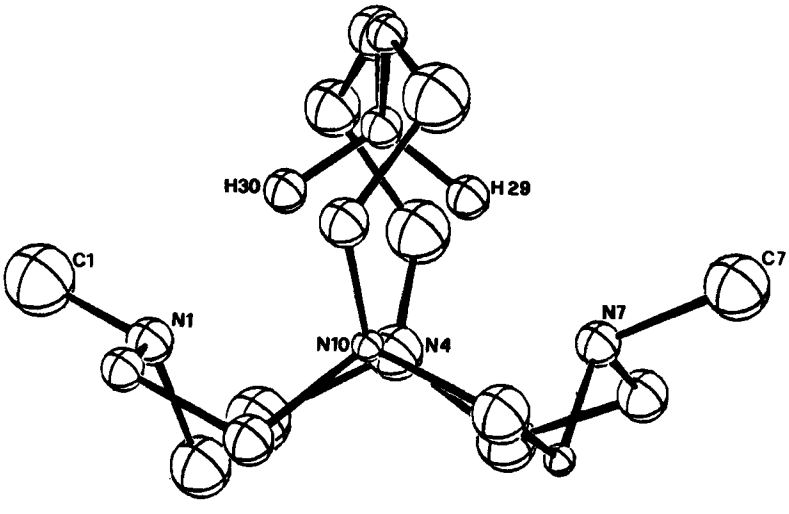

FIGURE 5. View of the HL1+ cation showing only part of the labelling scheme.

reported. The structure shows that the five nitrogen atoms are located at the apices of a slightly distorted square pyramid, with the four tertiary nitrogens forming the basal plane and the secondary nitrogen atom the vertex. The nitrogen atoms are in the endo conformation, the ethylenic chains are all below the basal plane. The structural data confirm that protonation occurs on the secondary amino group. The two hydrogen atoms H29 and H30, bonded to the secondary nitrogen N16, form hydrogen bonds with N7 and N1 respectively. The H···N distances, 2.28 and 2.04 Å, show that these hydrogen bonds are rather weak[11], perhaps due to the steric repulsions between the secondary nitrogen and the methyl groups and/or to internal constraints of the macrocyclic backbone. However, each hydrogen of the NH_2^+ group further interacts with both bridgehead nitrogen atoms. The distances of these hydrogen bonds are 2.44 and 2.76 Å respectively. In conclusion the array of six hydrogen bonds between the hydrogen atoms of the NH_2^+ group with the four tertiary nitrogen atoms makes the structure particularly stable from the thermodynamic point of view, albeit no single hydrogen bond is peculiarly strong. These structural features of the $HL1^+$ species allow also to explain the fast protonation/deprotonation kinetic. Indeed, the hydrogen atoms of the NH_2^+ group, since they lie on the 'surface' of the molecule, can easily interact with the solvent and be in fast exchange with the active hydrogen atoms of the solvent molecules. These results are in sharp contrast with the behavior observed for the monoprotonated forms of the [1.1.1] cryptand[12,13] and diazabicycloalkanes[14], where the proton, located inside the intramolecular cavity, shows slow transfer

reaction. The addition of the second proton to form the H_2L1^{2+} species produces marked changes in the ^{13}C n.m.r. spectra indicating consistent conformational changes in the second protonation step. When the average number of bound protons to L1 is 2, two sets of six signals in the ^{13}C n.m.r. spectrum are present. One set, accounting for ca. 80% of the total carbon, belongs to one or more isomers in fast exchange with $HL1^+$ and H_3L1^{3+}. The second set instead, accounting for ca. 20% of carbon, belongs to one or more isomers which exchange slowly, on the n.m.r. time-scale, with all the above species. The value of the second protonation constant ($\log K_2$ = 8.41) is slightly smaller than those usually found for the second protonation step of secondary amino groups of monocyclic polyazacycloalkanes[15,16]. The addition of the third proton to the cage L1 to form H_3L1^{3+} is difficult and the relative equilibrium constant cannot be accurately measured in the usual pH-range. $\log K_3$ is estimated to be less than 2. The electrostatic repulsions among close positive charges can explain such low value for $\log K_3$. For the species H_3L1^{3+} only one set of six peaks is found for the ^{13}C n.m.r. spectrum. The interesting protonation behavior of L1 (PROTON SPONGE) is due to the presence of the secondary nitrogen atom and to a suitable molecular shape which allows hydrogen-bond framework formation. To better understand the role played by the group present in the di-propylenic bridging unit we have synthesized the sulphur cage (L2), by replacing the NH group with sulphur. In this way the overall molecular topology should not change. Both in the solid state and in aqueous solution the cage L2 can take up at most two protons. L2 behaves as a rather strong base

in both protonation steps[4] ($\log K_1$=11.91; $\log K_2$=8.78). As expected L2 does not show protonic sponge behavior even if the stepwise protonation constants are unexpectedly high for tertiary nitrogen atoms.[17] The stepwise protonation enthalpies have been determined by direct calorimetry. The results show that both protonation steps are very exothermic reactions (ΔH°_1=-13.3 and ΔH°_2=-11.5 Kcal mol^{-1}). The high basicity of L2 in the first protonation step is entirely due to a very favorable enthalpic term (ΔH°_1=-13.3 Kcal mol^{-1}). This means that the added proton should interact very strongly with the tertiary nitrogen atoms to form the monoprotonated species $HL2^+$. In other words the hydrogen atom of the NH^+ group should be well embedded within the electron density of all the nitrogen atoms. As we have already seen in the case of the precursor cage L1 the first proton is so strongly bound that it cannot be removed in 3 mol dm^{-3} KOH solution (PROTON SPONGE). The sulphur cage L2, in which one sulphur atom has replaced the secondary nitrogen -NH in L1 without substantial modification of the overall molecular topology, is less basic than L1 and its basicity is measurable. Nevertheless the basicity of L2 is very high for a compound having only tertiary nitrogens, thus indicating the very important role played by the molecular topology in the proton transfer reactions.

The oxygen derivative (L3) has been the third cage of the series so far synthesized. The presence of the electronegative oxygen atom in the bridging unit allows a better understanding of the role played by this group on the protonation behavior of the cage. The cage L3 behaves as a diprotic base, both in solid state and solution. The first proton cannot be removed even in

strong alkaline solution[5,18], showing a protonic sponge behavior. In conclusion all the macrocyclic cages belonging to the series are powerful proton receptors. Two of them, the precursor compound L1 and the oxygen derivative L3 are FAST PROTON SPONGES. They compete successfully with OH^- in binding proton in aqueous solution. Interesting to note that if we replace the solvent from pure water to water/DMSO mixture (50% by mole), in which the pK_w=17.8, all protonation constants are measurable, also those which are not in pure water[18].

METAL COMPLEXES

Many metal ions: Li^+, Na^+, K^+, Be^{2+}, Mg^{2+}, Al^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} were tested for complex formation with the precursor cage L1. By using the ^{13}C n.m.r. spectroscopy no evidences for metal coordination were found for Na^+, K^+, Be^{2+}, and Al^{3+}, whereas only weak interaction occurs for Mg^{2+} ion. With all the other metal ions, except lithium, solid complexes were isolated by mixing the appropriate metal salt and [HL1]Br in boiling methanol. Reaction times varied from 10 min for copper to 24 h for cobalt and nickel complexes. For the diamagnetic ions the formation of the complex was followed by ^{13}C n.m.r., considerable variations in the spectra were found when the metal ion was encapsulated. In the case of the copper complex the ability of L1 to encapsulate metal ions was confirmed by the X-ray crystal structure analysis of $[CuL1](ClO_4)_2 \cdot H_2O$. The structure consists of $[CuL1]^{2+}$ cations, $(ClO_4)^-$ anions and water molecules[2]. The copper ion is wholly enclosed by the cage (see Figure 6) adopting a five-co-ordinate geometry, which can be described as a distorted square

pyramid with the secondary nitrogen in the apical position. The M-N distances are whithin the range expected for five-coordinated amine-copper complexes.

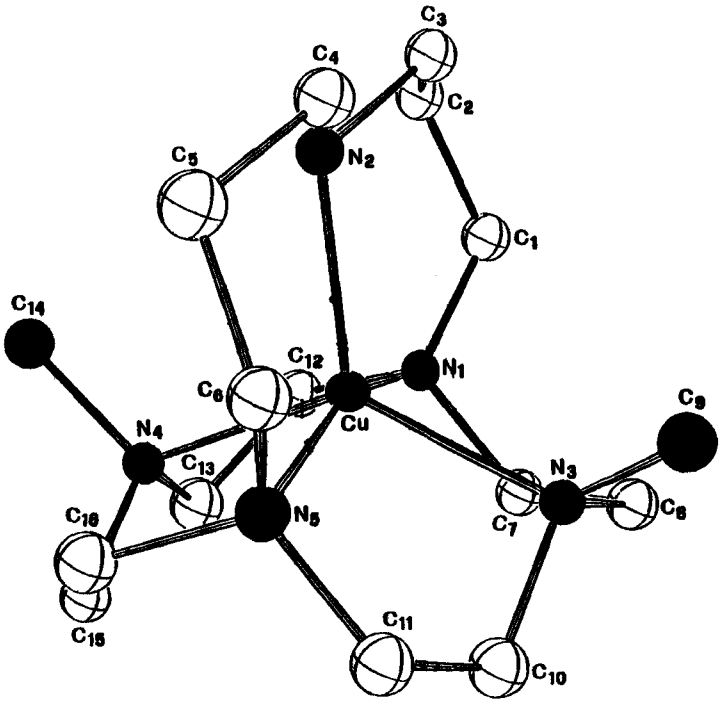

FIGURE 6. Drawing of the $[CuL1]^{2+}$ cation.

The two angles N(2)-Cu-N(3) and N(2)-Cu-N(4), not subtended by chelate rings are 106.7 and 118.9 degrees. These high values indicate an intramolecular repulsion between the propylenic chains and the methyl groups. In principle four diastereoisomers are possible for a square-pyramidal complex of this cage. The methyl groups and the hydrogen atom of the secondary amino group can each assume two different configurations. The copper complex however occurs as only one diastereoisomer. In solution the copper complex shows the same

stereochemistry as in the solid state as demonstrated by its electronic spectrum which is diagnostic of a distorted square-pyramidal structure. Another important experimental evidence supporting the encapsulation is the great inertness of the complex towards strong acid solutions: samples of $[CuL1](ClO_4)_2$ dissolved in perchloric acid of different concentration (0.1 up to 10 mol dm^{-3}) at 60 °C for many days did not show any detectable decomposition. Cobalt and nickel ions are also encapsulated into the cage cavity. The electronic spectra of the cobalt and nickel complexes show essentially the same features both in the solid state and in solution of CH_3CN or 1 mol dm^{-3} HCl. These spectra are diagnostic of high-spin distorted square-pyramidal geometries[19] for both complexes. Both complexes shows great inertness towards acidic decomposition: no detectable changes were found in their electronic spectra on standing for several days in strong acidic solutions.

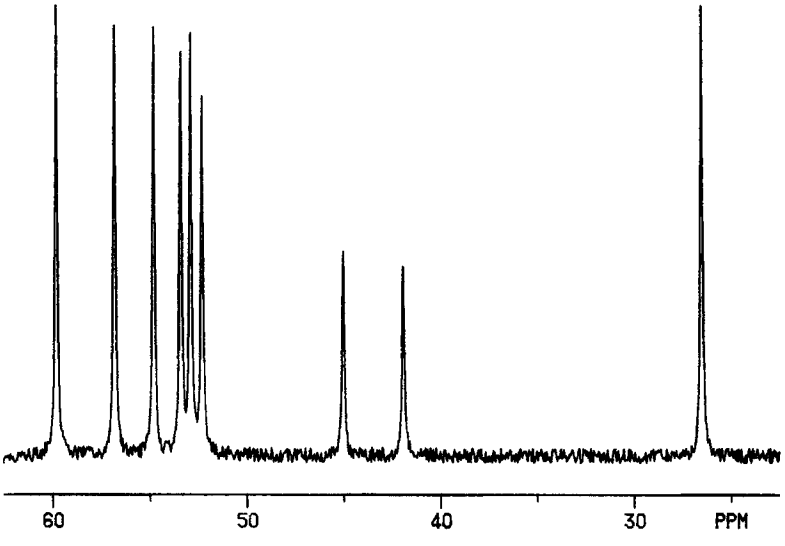

FIGURE 7. ^{13}C n.m.r. of the zinc complex of L1.

The ^{13}C n.m.r. spectrum of the zinc complex with L1 indicates the encapsulation of the zinc ion. The spectrum consists of nine sharp signals (see Figure 7) at room temperature in water or DMSO solution. The methyl groups give rise to two signals. The spectrum is indicative of C_s symmetry with the zinc atom and the nitrogen atoms of the $N\text{-}CH_3$ and NH groups lying in the symmetry plane. The zinc complex is also very inert towards strong acid media; its ^{13}C n.m.r. spectrum does not change in 3 mol dm^{-3} HCl for a few days. After 3 months at room temperature only ca. 20% of H_3L1^{3+} is formed, the chemical shifts of the remaining complex were unchanged. These results confirm the encapsulation of the zinc ion by the cage which involves all five nitrogen donor atoms. The lithium ion reacts with $HL1^+$ only at high pH. In 1 mol dm^{-3} KOH the formation of the lithium complex is complete as demonstrated by the occurrence of a nine-line ^{13}C n.m.r. spectrum, similar to that of the zinc complex and indicating C_s symmetry. With a 1:2 lithium to $HL1^+$ ratio the nine-line pattern occurs along with the six-line pattern due to $HL1^+$. The two patterns integrate for the same amounts of carbon, indicating a 1:1 metal-to-ligand ratio for the lithium species. All signals are sharp, indicating slow exchange rates between the two species on the n.m.r. time-scale. Upon addition of 1 mol dm^{-3} HCl the ^{13}C n.m.r. spectrum showed only signals due to H_3L1^{3+}, indicating the destruction of the lithium complex within the recording time. The selective encapsulation of the lithium ion by the cage L1 is a remarkable ligational property of this cage. Even more interesting is the fact that lithium can be encapsulated but sodium ion is not, showing 100% discrimination between these two

alkaline ions.

The sulphur cage L2 shows a much less tendency to bind metal ions than the other cages. A solid compound of composition $CuL2(ClO_4)_2$ was isolated and characterized[4]. The electronic spectra of the complex are the same in the solid state and in solution and are diagnostic of a distorted square-pyramidal structure[19] (aqueous solution 10900 (ϵ=164), 15100(ϵ=221), 35900 cm-1 (ϵ=1372)). The $(CuL2)^{2+}$ is also very inert toward acid solution: no appreciable decomposition was detected after a week in 5 mol dm^{-3} perchloric acid solution. As discussed previously for the cage L1, these experimental evidences are consistent with the hypothesis of the encapsulation of the copper(II) ion into the cage cavity. The formation of $(CuL2)^{2+}$, at room temperature, is rather slow. Due to the long time required to reach the chemical equilibrium in the reaction between Cu(II) and L2, a batchwise potentiometric procedure was used to determine the stability constant of $(CuL2)^{2+}$.[4,20] The enthalpy of complex formation reaction was determined by direct batch-microcalorimetry. The thermodynamic paramethers for the reaction Cu^{2+} + L2 = $(CuL2)^{2+}$ are: logK=18.2, ΔH° =-14.0 Kcal mol^{-1} and T ΔS°=10.8 Kcal mol^{-1}. The stability of the $(CuL2)^{2+}$ complex is not very high, but what is more relevant is the extremely favorable entropic contribution to the overall stability. The enthalpic contribution is also favorable but is not large compared with those for the formation of many Cu(II)-polyaza macrocyclic complexes.[1,21,22] The relatively low enthalpy of formation indicates that unfavorable contributions to the enthalpy of reaction, such as conformational changes and desolvation, should play an important role

in determining the overall enthalpy of formation of the $[CuL2]^{2+}$ complex. Furthermore the very favorable entropic term can be interpreted in terms of ligand pre-orientation and large release of solvent molecules as consequence of the encapsulation of the Cu(II) ion in the cage cavity. We conclude therefore that the thermodynamic parameters of formation of $[CuL2]^{2+}$ confirm the hypothesis that the Cu(II) ion is located inside the cavity.[4] Although the ligational properties of the oxygen cage L3 towards metal ions are still under study, some preliminary results[6,18] indicate that the coordination behavior of L3 is somehow similar to that of the precursor cage L1.

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