Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article Dapporto, Paolo , Fusi, Vieri , Giorgi, Claudia , Micheloni, Mauro , Palma, Pierangela , Paoli, Paola and Pontellini, Roberto(1999) 'Conformational Change of an Azamacrocycle Containing Nitrophenol Side Arms by Proton Coordination. Crystal Structures, Heat of reaction and Molecular Mechanics Calculations', Supramolecular Chemistry, 10: 4, 243 — 252

To link to this Article: DOI: 10.1080/10610279908054508

URL: http://dx.doi.org/10.1080/10610279908054508

SUPRAMOLECULAR CHEMISTRY, Vol. 10, pp. 243–252
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Printed in Malaysia.

Conformational Change of an Azamacrocycle Containing Nitrophenol Side Arms by Proton Coordination. Crystal Structures, Heat of reaction and Molecular Mechanics Calculations

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(Received 9 March 1998; In final form 2 February 1999)

The crystal structures of the azamacrocycle 1,7-bis(2-hydroxy-5-nitrobenzyl)-4,10-dimethyl-1,4,7,10-tetraazadodecane (L) (zwitterionic form) ($L \cdot 0.5CH_3OH \cdot 3.5H_2O$) and the monocharged derivative (HL^+) ($HL \cdot Br \cdot 2C_2H_5OH$) are reported. The crystals of $L \cdot 0.5CH_3OH \cdot 3.5H_2O$ are rhombohedral (hexagonal axes), space group R3, $a = b = 42.472(7)$, $c = 9.415(9)$ Å, $Z = 18$, $R = 0,084$, whereas the crystals of $HL \cdot Br \cdot 2C_2H_5OH$ are monoclinic, space group C2/c, $a = 20.418(5)$, $b = 13.814(4)$, $c = 11.785(3)$ Å, $\beta = 99.00(2)^\circ$, $Z = 4$, $R = 0.067$. The differences in their conformation are discussed. Molecular mechanics calculations were carried out and indicate that the energy difference between the two species is very small. The stepwise enthalpies of protonation in solution were determined by direct microcalorimetry: $\Delta H^\circ = -23.8(4)$ kJ mol^{-1} for $H_{-1}L^- + H^+ = L$; $\Delta H^\circ \cong 0$ for reactions $L + H^+ = HL^+$ and $HL^+ + H^+ = H_2L^{2+}$. The addition of the third proton is also athermic and fully entropy-controlled.

Keywords: Crystal structures, molecular mechanics, azamacrocycles, protonations

INTRODUCTION

Synthetic macrocycles are a wide class of compounds [1], among which the small but important group of ligands carrying chromophoric functional groups within the molecule can be used as probes or as photometic reagents selective for alkaline, alkaline-earth metal ions. [2] The present paper reports a further investigation of one of these compounds. The values of stepwise basicity constants of the macrocycle 1,7-bis(2-hydroxy-5-nitrobenzyl)-4,10-dimethyl-1,4,7,10-tetraazacyclododecane (L) are $\log K_1 > 13$, $\log K_2 = 10.59$, $\log K_3 = 7.18$ and

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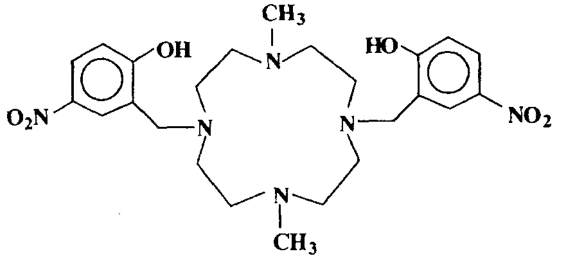
*Corresponding author.



L

SCHEME 1

$\log K_4 = 4.86$ [3]. Since the value of $\log K_1$ is unusually high, while the value of $\log K_4$ is very low, we decided to further investigate the proton transfer properties of (L), both in solution and in the solid state. For this purpose, crystals of the neutral zwitterionic (L) and triprotonated $(HL)^+$ species were grown from aqueous solutions of different pH.

RESULTS AND DISCUSSION

(L, $C_{24}H_{34}N_6O_6 \cdot 0.5 \cdot CH_3OH \cdot 3.5H_2O$). The crystal structure is made up of **L** species, which are present in the zwitterionic form, dispersed methanol molecules and water crystallisation molecules. The molecular structure of **L** is shown in Figure 1, together with the atom numbering scheme. The two acidic protons are localised on the *trans* nitrogen atoms N1 and N3, both pointing inside the macrocyclic cavity (see Fig. 1) where a thick network of intramolecular hydrogen bonds is present. As summarised in Table I, both H1N and H3N interact *via* hydrogen bonds with the methylated nitrogens N2 and N4 and the phenolic oxygen atom O4 provided by a side arm. This "face to face" (*i.e.*, 1–7) disposition of the acidic hydrogens, which are 2.70(6) Å apart, in fact allows the electrostatic repulsion between the charged quaternary nitrogen atoms to be minimized. The macrocyclic conformation, which can be described as [2424] C-corners from the sequence of its dihedral angles [4] with the carbon atoms at the corners (see Scheme 2) had a rectangular profile, with the two protonated nitrogens in the middle of the shortest sides.

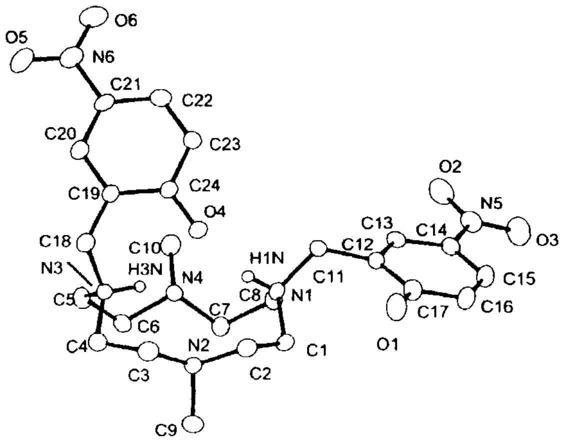
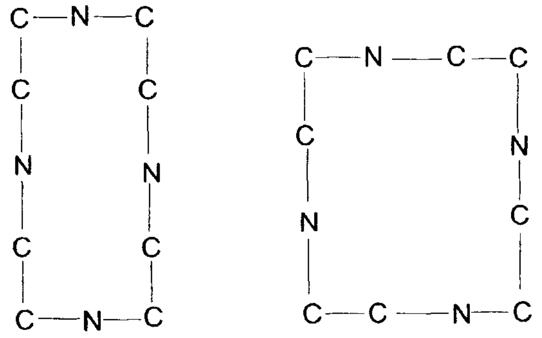


FIGURE 1 ORTEP-generated structure of (L).



[2424] C corners [3333] C corners

SCHEME 2

This conformation allows the *trans* protonated nitrogens to be ca. 0.7 Å farther apart than the corresponding unprotonated ones. Furthermore it is remarkable that the two methyl groups point in a direction opposite to that of the mean plane described by the macrocycle. For comparative purposes, a search was performed on the Cambridge Crystallographic Data Centre (CCDC) [5] (version 5.12) to retrieve diprotonated 1,4,7,10-tetraazacyclododecane rings. As

TABLE I Intramolecular hydrogen bond distances (Å) and angles (°) involving the localised acidic protons in L and HL^+

Bond distance Donor-H...Acceptor	Bond angle Donor-H...Acceptor
L	
N1—H1N...N2 2.87(6)	N1—H1N...N2 102(4)
N1—H1N...N4 2.60(5)	N1—H1N...N4 109(4)
N1—H1N...O4 2.02(4)	N1—H1N...O4 160(5)
N3—H3N...N2 2.53(5)	N3—H3N...N2 108(4)
N3—H3N...N4 2.28(5)	N3—H3N...N4 122(3)
N3—H3N...O4 2.14(5)	N3—H3N...O4 130(4)
HL^+	
N1—H1N...N2 2.39(7)	N1—H1N...N2 110(5)
N1—H1N...N2′ 2.53(7)	N1—H1N...N2′ 112(5)
N1—H1N...O1 2.15(7)	N1—H1N...O1 132(5)

expected in all the cations found the two acidic hydrogens are located on the facial nitrogens; however, it is worth noting that the conformation of the diprotonated tetraazacyclododecane ring in all the deposited crystal structures is of [3333] C-corners types, [4] with the carbon atoms at the corners (see Scheme 2), and the four nitrogen atoms all pointing above the macrocyclic hole. In these "square"-shaped macrocyles, the largest difference in the distance between the *trans*-positioned nitrogens is ca. 0.39 Å. In the present case, the uncommon conformation of the ring could be related to the fifth donor atom, O4, provided by the *p*-nitro-phenate side arm, which is involved in the H-bond network. This oxygen atom, as a consequence of the *gauche* conformation of the H3N—N3—C18—C19 dihedral angle (38(3)°), is in fact localised 2.361(3) Å above the macrocyclic cavity outlined by the four nitrogen atoms N1—N4 and significantly closer to the two protonated nitrogens (O4...N1 and O4...N3, 2.796(4) and 2.825(5) Å, respectively) than to the two methylated ones (O4...N2 and O4...N4, 3.367(5) 3.318(5) Å, respectively) justifying its involvement in the H-bond. However, the deposited crystal structures containing the diprotonated 1,4,7,10-tetraazacyclododecane fragments with a fifth donor involved in a bridging H-bond (HAVFEP [6], PIWBEC [7] and SECPEL [8] refcodes) always show a preference for a [3333] ring conformation. This result prompted us to study the conformational behaviour of the L species by using the molecular mechanics tool (see below). It was found that the benzene ring forms an angle of about 40° with respect to the mean plane described by the four nitrogen atoms and is almost parallel (ca. 10°) to the N1—N3 direction, *i.e.*, the main axis of the rectangle. The other *p*-nitrophenate group is pointing away from the macrocyclic hole because of the *trans* conformation of the H1N—N1—C11—C12 torsion angle −176(4)°. Besides some intramolecular contact with the hydrogens of the neighbouring methylenic carbons, O1 also interacts, *via* H-bonding, with a methanol molecule (O1...O7, 2.81(1)Å) and a water molecule (O1...O9, 2.75(6)Å). Lastly, all the crystallisation water molecules are, as expected, involved in a network of hydrogen bond interactions (O...O distances < 3 Å).

(HL^+, $C_{24}H_{34}N_6O_6{\cdot}HBr{\cdot}2C_2H_5OH$). HL^+ cations with a twofold symmetry axis, bromine counterions and ethanol molecules were present in the crystals. The molecular structure of the cation HL^+ is shown in Figure 2, together with the atom numbering scheme. Also in this case, two protons are bound to the *trans* benzyl-substituted nitrogen atoms (see Fig. 2), while the third proton did not appear in the ΔF map. Interestingly, the addition of a third proton on the zwitterionic form of L produces a remarkable

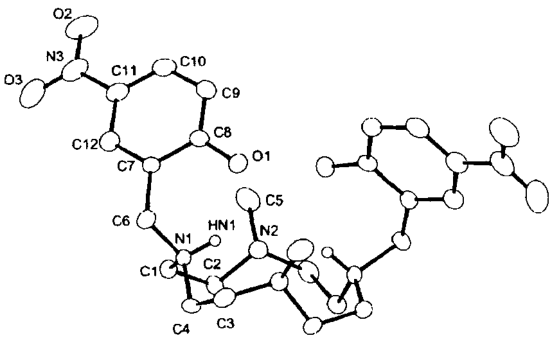


FIGURE 2 ORTEP-generated structure of (HL^+). Only symmetry-independent atoms are labelled.

change in the molecular shape, involving both the conformation of the macrocyclic ring and the relative orientation of the *p*-nitro-phenate side arms (see Fig. 3). The latter, in fact, are both bent HN1—N1—C6—C7, 49.5(4)°) towards the macrocyclic cavity, with the two symmetry-related oxygen atoms, O1 and O1′, standing above it. In this case, however, the phenate atoms are significantly farther from the mean plane passing through the nitrogens of the tetra-aza ring than is the corresponding O4 atom in **L**, 2.612(6) Å *vs.* 2.361(3) Å, respectively. The [12]aneN_4 ring shows the usual [3333] C-corners conformation (see Scheme 2), with a distance between the *trans* diprotonated nitrogens of 4.37(1) Å, while the methylated ones are 3.88(1) Å apart ($\Delta d = 0.49$ Å). In this case as well, the localised acidic protons are pointing towards the centre of the macrocyclic hole (HN1 ... HN1′, 2.9(1) Å) and each one interacts, *via* the H-bond, with the symmetry-related nitrogens, N2 and N2′, which are 2.39(7) Å and 2.53(7) Å apart, respectively (see Tab. I). In the case of **L**, O4 acts as a bidentate donor with respect to the two protons, but here each of the phenolic oxygen atoms interacts with only one of the two acidic protons (N1—HN1 ... O1 2.15(7) Å), with the other proton 3.33(7) Å away (see Tab. I). Moreover, the location of the third protonation site still remains to be demonstrated. However, taking into account the distances between the donor nitrogens in the [12]aneN_4 ring and their relative symmetrical disposition, we can reasonably exclude the possibility that the macrocyclic ring is also involved in the third protonation step. In fact, this hypothesis would bring the third hydrogen atom very close to the other two ($d < 1.7$ Å). On the other hand, the rather short distance (2.400(9) Å) which separates the two oxygens of the phenate groups, together with their lesser involvement in the H-bond network as compared to that observed for O4 in **L**, may suggest that the third proton is bound to one of these groups, thus acting as a bridge between the two *p*-nitro-phenate groups. This proton is probably bound in a statistically disordered way, and therefore it is practically impossible to establish its localisation in the ΔF map. The crystal packing does not show any particularly remarkable intermolecular contact.

Molecular Mechanics Calculations

The structures of $L_{[2424]}$ and $L_{[3333]}$ (see experimental part) optimised by molecular mechanics are not significantly different from their respective input geometries, with the $L_{[3333]}$ species more stable by about 6 kcal mol^{-1}. Roughly the difference in the conformers' energy arises from

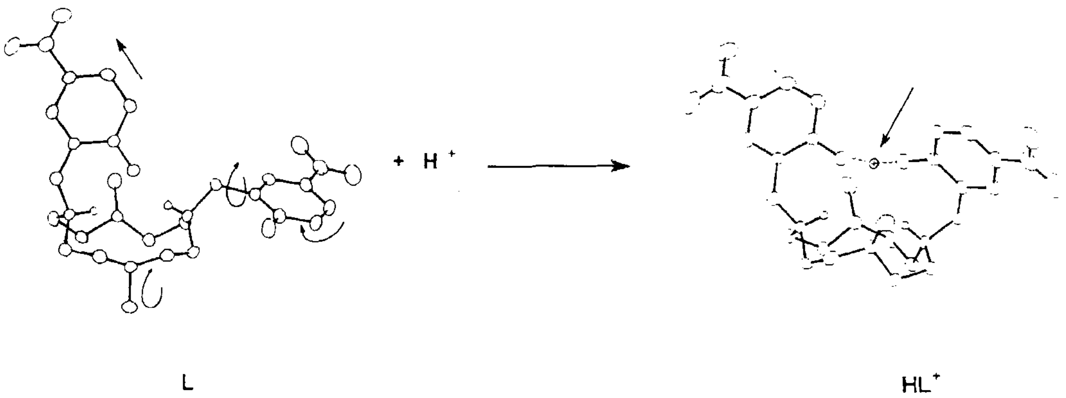


FIGURE 3 Pictorial scheme of the molecular rearrangement $L \rightarrow HL^+$.

the torsional (ca. 4 kcal mol^{-1}) and the non-bonding terms, *i.e.*, van der Waals, electrostatic and hydrogen bond contributions (ca. 2 kcal mol^{-1}). This result, which is in contrast with our experimental evidence of a [2424] conformation for the diprotonated [12]aneN$_4$ ring, in reality well agrees with all the structural data retrieved from the CSD for the dicationic tetraazacyclododecane moiety. On the other hand, the molecular dynamics simulations performed with the purpose of gaining new insight into the conformational freedom of the **L** species show that, at the MD parameters used, both conformers are quite flexible. Indeed, in both trajectories the conformers show differences in the ring conformation and inversion of the methylated nitrogens. On the contrary, the lateral chains appear to be rather free to move around the macrocycle in the simulation performed on the $\mathbf{L}_{[2424]}$ starting conformer, while for $\mathbf{L}_{[3333]}$ both chains are bent toward the ring hole, with only one exception: the [12]aneN$_4$ ring is of [3333] type with branches arranged as in $\mathbf{L}_{[2424]}$, and is only 1 kcal mol^{-1} higher in energy than the corresponding $\mathbf{L}_{[3333]}$ conformer residing in the absolute minimum. The energy contents of the 100 conformers revealed by the MD study carried out on $\mathbf{L}_{[2424]}$ range from 27 to 40 kcal mol^{-1} ($E_{\text{mean}} = 33$ kcal mol^{-1}) while for $\mathbf{L}_{[3333]}$ we obtained: $21 < E < 29$ kcal mol^{-1}, $E_{\text{mean}} = 24$ cal mol^{-1}.

In conclusion, the conformation exhibited by the [12]aneN$_4$ ring of the zwitterionic form of **L** in our sample, which constitutes an exception to the "[3333] rule", appears to be less favorable from an energetic stand point. However, our simulations did not take into consideration the crystal environment, which could play an important role in inducing the conformation. As previously reported, the *p*-nitrophenate group pointing away from the macrocyclic framework is involved in moderately short H-bond contacts with methanol and water crystallisation molecules. On the other hand, because of the intrinsic pliancy of this conformer, as inferred from the MD simulations, we can presume that the significant conformational change (see Fig. 3), which occurs upon the protonation, is not very expensive in terms of energy. In this respect, the simple optimisation of the HL$^+$ species starting from the X-ray crystal structure confirmed our hypothesis about the location of the third proton. In fact, the minimised structure with the third proton shared between the two oxygens of the *p*-nitrophenate groups is almost identical to the experimental one, with the two H-bound oxygens only 0.4 Å farther apart.

Microcalorimetric Studies

The stepwise enthalpies of protonation were determined by direct microcalorimetry in aqueous solution and, combining these values with those of the stability constants previously reported [3], the thermodynamic quantities $\Delta G°$, $\Delta H°$, and $T\Delta S°$ relative to the protonation equilibria were calculated and are reported in Table II. Because the basicity constant in the first step of protonation was too high to be accurately determined under the experimental conditions used, the enthalpy of reaction was not determined. In the second protonation step, an enthalpy of -23.8 kJ mol^{-1} was measured (see Tab. II). This value is quite low and not easily comparable with those found for protonation steps involving tertiary nitrogen atoms in a macrocyclic framework, in that only a few values have been reported in the literature, and those reported were in any case for azamacrocycles with different molecular dispositions [9]. Previous solution studies on (L), based on ^{1}H and ^{13}C NMR, as well as UV-VIS spectroscopic measurements, demonstrated that nitrogen atoms are involved in the first two steps of protonation, while phenolic oxygen atoms are involved in the third and fourth protonation steps [3]. The enthalpies of reaction of the two last steps of protonation confirm the change in donor atom type: both reactions are athermic and fully entropically-controlled, the marked

TABLE II Thermodynamic quantities $\Delta G°$, $\Delta H°$, and $T\Delta S°$ ($kJ\,mol^{-1}$, 298.15 K, $I = 0.15\,mol\,dm^{-3}$) for the protonation equilibria of **L** in aqueous solution

Reaction	LogK	$\Delta G°$	$\Delta H°$	$T\Delta S°$
$\mathbf{H_{-2}L^{2-} + H^+ = H_{-1}L^-}$	> 13[a]	–	–	–
$\mathbf{H_{-1}L^- + H^+ = L}$	10.59[a]	−60.4(1)[b]	− 23.8(1)[c]	36.6(1)
$\mathbf{L + H^+ = HL^+}$	7.18[a]	− 41.0(1)	$\cong 0$[c]	41.0(1)
$HL^+ + H^+ = H_2L^{2+}$	4.86[a]	− 27.7(1)	$\cong 0$[c]	27.7(1)

[a] Values from Ref. [3].

[b] Values in parentheses are the standard deviations in the last significant figure.

[c] This study.

decrease in the heat of reaction is between the second and the third step of protonation.

It is always difficult to compare results obtained in the solid state or calculated by MM with those obtained in solution: it is impossible to say whether the structures of the diprotonated (**L**) and triprotonated ($\mathbf{HL^+}$) species in solution are like those found in the solid state. However, also in solution the energetics of the addition of the third proton indicate that very little heat is involved, as was found by MM calculation.

EXPERIMENTAL

Microcalorimetry

The stepwise enthalpies of **L** were determined in aqueous solution with a Thermometric AB thermal activity monitor (Model 2277) equipped with a perfusion/titration system and a Hamilton pump (Model Microlab M). The calorimeter system as well as the Hamilton pump were computer-controlled [10a]. In a typical calorimetric experiment, the calorimetric ampoule was charged with $1.5\,cm^3$ of HL·Br ($0.005\,mol\,dm^{-3}$) and $0.3\,cm^3$ of HCl ($0.1\,mol\,dm^{-3}$). After thermal equilibration, $0.014\,cm^3$ of NH_4OH ($0.1\,mol\,dm^{-3}$) as titrant were injected. The microcalorimeter was checked by determining the enthalpy of reaction of strong acid (HCl) with strong base (NaOH). The value obtained, − 13.55(5) kcal mol^{-1}, was in agreement with literature values [10b]. Under the reaction conditions used and employing the determined basicity constants, the amounts of each species present at equilibrium before and after each addition were calculated, together with the corresponding enthalpies of reaction, by means of the KK95 computer program [11].

Synthesis of Crystals Suitable for X-ray Analysis

$L \cdot 0.5CH_3OH \cdot 3.5H_2O$. $L \cdot HBr \cdot H_2O$ (60 mg, 0.1 mmol) was dissolved in $40\,cm^3$ of water and the pH adjusted to 9 with $N(CH_3)_4OH$ ($0.1\,mol\,dm^{-3}$). At this pH, yellow precipitate formed and was subsequently dissolved with methanol ($30\,cm^3$). Crystals of ($L \cdot 0.5CH_3OH \cdot 3.5H_2O$) suitable for X-ray analysis were obtained by slow evaporation of the above solution at room temperature. Yield 28 mg (48%) (Found: C : 50.6; H : 7.5; N : 14.5. Calcd. for $C_{24.5}H_{43}N_6O_{10}$ C : 50.59; H : 7.45; N : 14.45).

$L \cdot HBr\,2C_2H_5OH$. Crystals of this compound, suitable for X-ray analysis, were obtained in almost quantitative yield by slow evaporation at room temperature of $HL \cdot Br \cdot H_2O$ (67 mg, 0.1 mmol) in ethanol ($50\,cm^3$). (Found : C : 49.8; H : 7.0; N : 12.5. Calcd. for $C_{28}H_{47}BrN_6O_8$ C : 49.78; H : 7.01; N : 12.44).

Crystal Data

(**L**), $C_{24}H_{34}N_6O_6 \cdot 0.5 \cdot CH_3OH \cdot 3.5H_2O$, $M = 582.04$, colourless crystals of $0.3 \times 0.4 \times 0.7$ mm size, $T = 298$ K, rhombohedral (hexagonal axes), space group R3, $a = b = 42.472(7)$ Å, $c = 9.415(9)$ Å, $V = 14708(14)$ Å [3], $Z = 18$, $Dc = 1.18\,g\,cm^{-3}$, graphite-monochromated Cu-Kα radiation, $\lambda = 1.5418$ Å, $\mu = 7.67\,\mathrm{cm}^{-1}$; data was collected on an Enraf Nonius CAD4 automatic diffractometer, θ-2θ scan, $2\theta < 100°$, 3527 reflections, 2952 observed [$I > 2\sigma(I)$] data. The structure, solved by direct methods of SIR92 [12] and refined [13] by full-matrix least squares against F^2 (the non-H atoms anisotropic, the acidic hydrogens bound to the N1 and N3 nitrogen atoms were located in a difference Fourier map and individually refined, the other H-atoms belonging to L were placed in calculated positions and treated with an overall temperature factor refined to 0.073 Å [2], 397 variables/2952 data) to $wR2 = 0.245$, goodness-of-fit 1.02, R(F, obs. data) = 0.084, $\Delta\rho_{\max} = 0.41$ e Å3. Table III reports selected bond distances and angles.

(HL^+), $C_{24}H_{34}N_6O_6{\cdot}HBr{\cdot}2C_2H_5OH$, $M = 675.62$, yellow pale crystals of $0.2 \times 0.3 \times 0.4$ mm size, $T = 293$ K, monoclinic, space group $C2/c$, $a = 20.418(5)$ Å, $b = 13.814(4)$ Å, $c = 11.785(3)$ Å, $\beta = 99.00(2)°$, $V = 3283(1)$ Å [3], $Z = 4$, $Dc = 1.37\,\mathrm{g\,cm}^{-3}$, graphite-monochromated Mo-Kα radiation, $\lambda = 0.71073$ Å, $\mu = 13.07\,\mathrm{cm}^{-1}$; data was collected on an Enraf Nonius CAD4 automatic diffractometer, θ-2θ scan, $2\theta < 40°$, 2102 reflections, 1094 observed [$I > 2\sigma(I)$] data. The structure, solved by direct methods of SIR92 [12]. The HL^+ species

TABLE III Selected bond distances (Å) and angles (°) for **L**

O(1)—C(17)	1.283(5)	N(6)—C(21)	1.440(6)
O(2)—N(5)	1.229(5)	C(1)—C(2)	1.503(6)
O(3)—N(5)	1.230(5)	C(3)—C(4)	1.508(7)
O(4)—C(24)	1.303(5)	C(5)—C(6)	1.513(6)
O(5)—N(6)	1.225(5)	C(7)—C(8)	1.514(6)
O(6)—N(6)	1.236(5)	C(11)—C(12)	1.513(5)
N(1)—C(8)	1.496(5)	C(12)—C(13)	1.367(5)
N(1)—C(1)	1.509(5)	C(12)—C(17)	1.443(6)
N(1)—C(11)	1.518(5)	C(13)—C(14)	1.391(6)
N(1)—H(1N)	0.81(5)	C(14)—C(15)	1.385(6)
N(2)—C(3)	1.460(5)	C(15)—C(16)	1.371(6)
N(2)—C(2)	1.459(6)	C(16)—C(17)	1.407(6)
N(2)—C(9)	1.465(6)	C(18)—C(19)	1.486(6)
N(3)—C(5)	1.490(6)	C(19)—C(20)	1.382(5)
N(3)—C(4)	1.501(5)	C(19)—C(24)	1.427(6)
N(3)—C(18)	1.504(5)	C(20)—C(21)	1.380(6)
N(3)—H(3N)	0.90(5)	C(21)—C(22)	1.389(6)
N(4)—C(7)	1.463(5)	C(22)—C(23)	1.366(6)
N(4)—C(6)	1.466(5)	C(23)—C(24)	1.414(6)
N(4)—C(10)	1.465(5)	C(25)—O(7)	1.04(4)
N(5)—C(14)	1.425(6)		
C(8)—N(1)—C(1)	112.8(3)	N(1)—C(8)—C(7)	112.4(3)
C(8)—N(1)—C(11)	112.5(3)	C(12)—C(11)—N(1)	114.7(3)
C(1)—N(1)—C(11)	111.7(3)	C(13)—C(12)—C(17)	119.8(4)
C(8)—N(1)—H(1N)	109(3)	C(13)—C(12)—C(11)	119.7(3)
C(1)—N(1)—H(1N)	109(3)	C(17)—C(12)—C(11)	120.2(3)
C(11)—N(1)—H(1N)	101(3)	C(12)—C(13)—C(14)	121.0(4)
C(3)—N(2)—C(2)	115.6(4)	C(13)—C(14)—C(15)	120.7(4)
C(3)—N(2)—C(9)	109.4(4)	C(13)—C(14)—N(5)	120.3(4)
C(2)—N(2)—C(9)	110.5(3)	C(15)—C(14)—N(5)	119.0(4)
C(5)—N(3)—C(4)	114.4(3)	C(16)—C(15)—C(14)	119.0(4)
C(5)—N(3)—C(18)	112.9(3)	C(15)—C(16)—C(17)	122.6(4)
C(4)—N(3)—C(18)	111.6(3)	O(1)—C(17)—C(16)	121.3(4)
C(5)—N(3)—H(3N)	101(3)	O(1)—C(17)—C(12)	121.9(4)
C(4)—N(3)—H(3N)	110(3)	C(16)—C(17)—C(12)	116.8(4)
C(18)—N(3)—H(3N)	106(3)	C(19)—C(18)—N(3)	111.8(3)
C(7)—N(4)—C(6)	112.8(3)	C(20)—C(19)—C(24)	119.7(3)
C(7)—N(4)—C(10)	112.0(3)	C(20)—C(19)—C(18)	121.9(4)
C(6)—N(4)—C(10)	111.4(3)	C(24)—C(19)—C(18)	118.4(3)

TABLE III (Continued)

O(2)—N(5)—O(3)	121.5(4)	C(19)—C(20)—C(21)	120.3(4)
O(2)—N(5)—C(14)	119.0(4)	C(20)—C(21)—C(22)	120.9(4)
O(3)—N(5)—C(14)	119.4(4)	C(20)—C(21)—N(6)	119.9(4)
O(5)—N(6)—O(6)	122.9(4)	C(22)—C(21)—N(6)	119.2(4)
O(5)—N(6)—C(21)	117.9(4)	C(23)—C(22)—C(21)	120.1(4)
O(6)—N(6)—C(21)	119.2(4)	C(22)—C(23)—C(24)	120.7(4)
C(2)—C(1)—N(1)	112.7(3)	O(4)—C(24)—C(23)	122.1(3)
N(2)—C(2)—C(1)	110.8(4)	O(4)—C(24)—C(19)	119.5(3)
N(2)—C(3)—C(4)	109.0(4)	C(23)—C(24)—C(19)	118.4(4)
N(3)—C(4)—C(3)	109.8(4)		
N(3)—C(5)—C(6)	109.7(3)		
N(4)—C(6)—C(5)	110.4(3)		
N(4)—C(7)—C(8)	111.5(3)		

admits a twofold symmetry axis. Refinement [13] was achieved by full-matrix least squares against F [2] (non-H atoms anisotropic, the acidic hydrogen atom bound to the N1 nitrogen atom was found in a difference Fourier map and individually refined). The quality of the data did not allow us to individuate the third acidic proton. Hydrogen atoms linked to the carbon atoms were placed in calculated positions and treated with an overall temperature factor refined to 0.092 Å [2], 201 variables/1094 data) to $wR2 = 0.200$, goodness-of-fit 1.13, R(F, obs. data) = 0.067, $\Delta\rho_{max} = 0.53\,e\,Å^{-3}$. Table IV lists selected bond distances and angles.

Molecular Mechanics Calculations

The Biosym Technologies [14] software programs InsightII and Discover version 95.0/3.00, were used for all the molecular modelling studies. The force field used was AMBER [15] (all the 1–4 non-bond interactions were scaled by a factor of 0.5 by default and a distance-dependent dielectric constant $\epsilon = 4r$ was used). The atomic charges of the species studied were derived by fitting them to the electrostatic potential at points selected according to the Merz-Singh Kollman [16] scheme using Gaussian 94 (revision D3) [17], at the RHF 6–31G** single point level of theory. Two charge distributions for the neutral ligand (zwitterionic form) were computed starting from the X-ray structures of **L** and HL^+ (the latter obviously without the third proton), hereafter indicated as $L_{[2424]}$ and $L_{[3333]}$ respectively. The same procedure was used to calculate atomic charges for the HL^+ species, placing the third proton between the two oxygen atoms of the *p*-nitrophenate groups. These input structures were then optimised by using the following algorithms: first, the steepest descent, then the conjugate gradient and finally Newton-Raphson. The convergence criterion utilised to stop the minimisation procedure was rms derivative $< 0.001\,\text{Kcal mol}^{-1}\,Å^{-1}$. In addition, two molecular dynamics (MD) simulations were run starting from $L_{[2424]}$ and $L_{[3333]}$ at 600 K. The system was allowed to equilibrate for 1 ps and then MD simulations were run for 100 ps, with snapshot conformations from the trajectories saved every ps. The motion equations were integrated with the Verlet leapfrog algorithm with a time step of 1 fs. The 100 conformations obtained from each MD run were then minimised using the steepest descent, the conjugate gradient and finally the Newton-Raphson methods until the first derivative of the energy was $< 0.001\,\text{Kcal mol}^{-1}\,Å^{-1}$. All calculations were performed on a 3AT Risc System 6000 IBM computer.

TABLE IV Selected bond distances (Å) and angles (°) for HL^+

N(1)—C(1)	1.497(11)	C(7)—C(8)	1.406(12)
N(1)—C(4) #1	1.495(10)	C(8)—O(1)	1.327(10)
N(1)—C(6)	1.501(10)	C(8)—C(9)	1.382(12)
N(1)—HN1	0.92(7)	C(9)—C(10)	1.397(14)
C(1)—C(2)	1.506(11)	C(10)—C(11)	1.357(14)
C(2)—N(2)	1.449(10)	C(11)—C(12)	1.380(13)
N(2)—C(5)	1.450(11)	C(11)—N(3)	1.443(13)
N(2)—C(3)	1.490(11)	N(3)—O(2)	1.233(11)
C(3)—C(4)	1.492(12)	N(3)—O(3)	1.231(13)
C(4)—N(1) #1	1.495(10)	C(13)—C(14)	1.29(2)
C(6)—C(7)	1.491(12)	C(14)—O(4)	1.39(2)
C(7)—C(12)	1.389(12)		
C(1)—N(1)—C(4) #1	111.6(7)	C(8)—C(7)—C(6)	118.8(8)
C(1)—N(1)—C(6)	111.9(6)	O(1)—C(8)—C(9)	123.2(9)
C(4) #1—N(1)—C(6)	112.9(6)	O(1)—C(8)—C(7)	116.8(8)
C(1)—N(1)—HN1	110(4)	C(9)—C(8)—C(7)	120.0(9)
C(4) #1—N(1)—HN1	106(4)	C(8)—C(9)—C(10)	119.4(9)
C(6)—N(1)—HN1	104(4)	C(11)—C(10)—C(9)	120.1(9)
N(1)—C(1)—C(2)	112.1(7)	C(10)—C(11)—C(12)	121.8(10)
N(2)—C(2)—C(1)	111.1(7)	C(10)—C(11)—N(3)	119.5(11)
C(2)—N(2)—C(5)	111.5(7)	C(12)—C(11)—N(3)	118.6(11)
C(2)—N(2)—C(3)	111.1(7)	O(2)—N(3)—O(3)	121.9(11)
C(5)—N(2)—C(3)	108.3(7)	O(2)—N(3)—C(11)	118.8(12)
N(2)—C(3)—C(4)	112.2(7)	O(3)—N(3)—C(11)	119.3(11)
C(3)—C(4)—N(1) #1	112.9(7)	C(11)—C(12)—C(7)	119.0(9)
C(7)—C(6)—N(1)	111.4(7)	C(13)—C(14)—O(4)	119(2)
C(12)—C(7)—C(8)	119.7(8)		
C(12)—C(7)—C(6)	121.4(8)		

(# $1-x, y, 0.5-z$).

Acknowledgements

Support for this research by MURST (Ministero per l'Università e la Ricerca Scientifica e Tecnologica) and CNR (Consiglio Nazionale delle Ricerche) is gratefully acknowledged.

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