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Conformational investigation of some macrobicyclic compounds and of their monoprotonated cations through a comparison between x-ray crystal structures and molecular dynamics simulations

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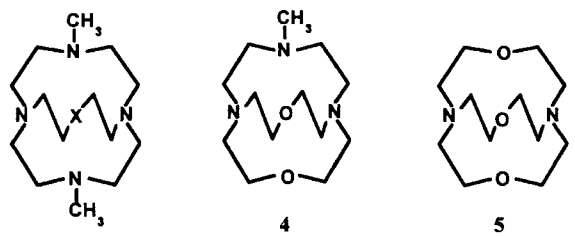
In preceding works, which have dealt with the synthesis and characterisation of a series of macrobicyclic compounds with five donor atoms, the unusually high basicity constants of these polyaminic cage-like molecules have been ascribed to the inclusion of the proton inside the macrobicyclic cavity which results in a very efficient hydrogen-bond network. The present paper, based on previously reported X-ray crystal structures regarding five-atoms bridging units and on molecular modelling studies shows that the disposition of the five donor atoms in the monoprotonated species is related to the protonation site. Precisely, if the protonation occurs on a bridge-head nitrogen the resulting geometry of the donors is a trigonal bipyramid, whereas it is square pyramidal when the proton is bound to a nitrogen belonging to a macrobicyclic chain. For what concerns the geometrical array of the donor atoms in the free amines, the favoured array seems to be the trigonal bipyramidal.

INTRODUCTION

In the following scheme are reported some macrobicyclic compounds that have been synthesised and characterised during these last years.[1–7]

Systematic studies by means of potentiometric, calorimetric and NMR techniques, of macrobicyclic compounds with different chain length and with different donor atoms and substituents on the nitrogen atoms of the chains, allowed to individuate a remarkable molecular rigidity due to the topological features of these cage-like ligands. This geometrical preorganisation influences the basicity behaviour of these molecules, since the nitrogen atoms show higher basicity constants[1–5,7] than those found for analogous acyclic or monocyclic compounds.[8] This higher basicity has been explained as the consequence of a dense H-bonding network formed by the acidic proton inside the macrobicyclic cavity. Our work has been performed with the aim to highlight the influence of the protonation on the cage-like topology. Notably, in order to correlate the first protonation site and the geometrical disposition of the five donor atoms we



4 5

X = -N(CH_3)-	1
-N(Bz)-	2
-NH-	3
-CH_2-NH-CH_2	6

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have undertaken molecular mechanics calculations on 4,10,15-trimethyl-1,4,7,10,15-pentaazabicyclo[5.5.5] heptadecane (**1**), 4-benzyl-10,15-dimethyl-1,4,7,10,15-pentaazabicyclo[5.5.5]heptadecane (**2**), 4,10-dimethyl-1,4,7,10,15-pentaazabicyclo[5.5.5]heptadecane (**3**), 10-methyl-4,15-dioxo-1,7,10-triaza[5.5.5]cycloheptadecane (**4**), 4,7,15-trioxo-1,10-diaza[5.5.5]cycloheptadecane (**5**) and on their monoprotonated species.

EXPERIMENTAL SECTION

Material

The X-ray crystal structures of $[H1]^+$,[1] $[Li1]^+$,[1] $[H2]^+$,[2] $[Li3]^+$,[3] $[Cu3]^{2+}$,[3] $[H4]^+$,[4] **5** and $[H5]^+$ (ref. 6) published in previous works were taken into account during the development of the present paper.

Computer Simulation

The conformational space of each molecule and of its monoprotonatd species obtained taking into account all the available protonation sites was investigated by means of molecular dynamics (MD) simulations in vacuo. All calculations were carried out with an IBM RISC;RISC/6000 computer, model 320H using CFF91[9] and AMBER[10] force fields both supplied by Discover[11] version 2.9.5. For the calculations performed with the AMBER force field atomic charges obtained by means of the semiempirical AM1 method of the MOPAC[12] package version 6.0 were used. A series of MD simulations was done by varying both separately and simultaneously, in order to evaluate the dependence of the results on their values, the following user-defined parameters: simulation length, sampling frequency and temperature. For each compound X-ray, when available, or model-built structures were used as starting conformation in the MD simulation. Once starting conformations have been fully minimised the best results have been obtained when the system was allowed to equilibrate at 1200 K for 5 ps and then running MD for 100 ps at ca. 1200 K with snapshot conformations from the trajectories saved every 0.1 ps. The equations of motion were integrated with the Verlet leapfrog algorithm with a time step of 1 fs. The 1000 conformers obtained from each MD run were then minimised using 300 steps of the steepest descent and conjugate gradient minimisers and finally the Newton—Raphson method until the first derivative of the energy was <0.001 Kcal mol^{-1} $Å^{-1}$. Minimised conformers were then ordered on the basis of their energy contents and for each compound the conformer having the lowest energy was selected and its conformation analysed.

RESULTS AND DISCUSSION

Three different geometrical dispositions of the five donors corresponding to three conformations of the macrobicyclic molecule have been identified from an analysis of the conformations adopted by the ligands in the X-ray crystal structures above cited. Notably, in the conformation labelled as tbp(I) the five donor atoms are at the vertices of a regular trigonal bipyramid and a ternary axis and a perpendicular symmetry plane have been located. The three twelve-membered macrocycles can be described by the sequence of their dihedral angles as [2424]* (Fig. 1). These structural features were found in **5**[6] and in its monoprotonated form,[6] in the lithium complexes of **1**[1] and **3**[3] and in $[Cu3]Br_2 \cdot 3H_2O$.[3] In $[H1]^+$ (ref. 1) and $[H2]^+$ (ref. 2) the five donors describe a distorted trigonal bipyramid indicated as tbp(II), the three equatorial nitrogen being significantly displaced

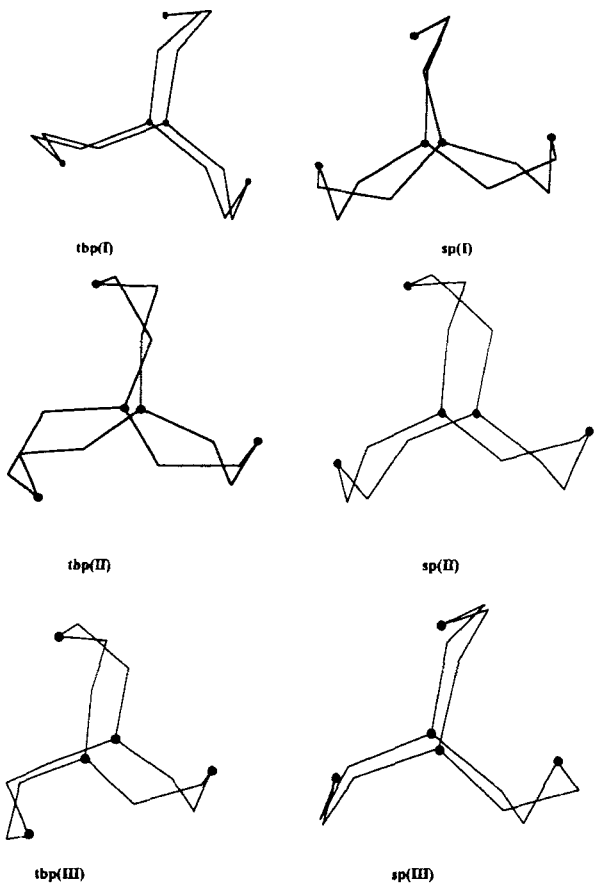

Figure 1 Schematical drawing of the six conformations found by X-ray diffraction and molecular dynamics search.

*This formalism, proposed by J. Dale in Acta Chem. Scand., **1973**, 27, 1115, consists of a series of numbers within brackets corresponding to the number of bonds between bends.

towards a bridge-head nitrogen, maintaining thus only the threefold axis in respect to the tbp(I) conformation above described. Distances separating the two bridge-head nitrogens from the plane containing the three equatorial ones are 1.31 and 1.71 Å in $[H1]^+$ and 1.30 and 1.69 Å in $[H2]^+$. Also in this case, as expected from symmetry considerations, the sequences of the dihedral angles of the three macrocycles are identical and result in a [13233] conformation indicated as tbp(II) (Fig. 1). From a geometrical point of view the tbp(II) conformer differs from the tbp(I) one for a significant "axial shrinking" along the $N_{bridgehead}$-$N_{bridgehead}$ direction. As a consequence, the shape of the molecular cavity of this latter is modified from the spherical one of the tbp(I) conformation to a compressed ellipsoid. In $[H4]^+$ (ref. 4) the arrangement of the donor atoms yields a square pyramid, where the basal macrocycle has a [3333] conformation and the other two a [12423] sequences of dihedral angles giving the sp(I) conformer (Fig. 1). All the above reported macrocyclic rings have the carbon atoms at the corners of the resulting geometrical figure.

Results deriving from the MD simulations performed on each molecule and on its monoprotonated forms obtained considering all the available protonation sites can be summarised as follows:

Conformers displaying *exo* conformations for the lone pair belonging to tertiary nitrogen atoms have a significantly higher energy contents. An analogous energy increase is observed for those conformers of **3**, **4** and **5** and of their corresponding monoprotonated forms when secondary nitrogen (**3**) and oxygen atoms (**4** and **5**) are pointing outward the molecular cavity.

Although in each MD run many conformers, both trigonal bipyramidal and square pyramidal were met, the examination of the conformer with the lowest energy contents for each studied species shows six different conformations only, with carbon atoms at the corners. Precisely three of them are those found in the solid state X-ray crystal structures previously reported, while the other ones can be described as follow. In the fourth conformer donor atoms are disposed at the vertices of a trigonal bipyramid in which the symmetry plane and the ternary axis are both absent (conformer tbp(III), Fig. 1). In this case the dihedral angles sequence results in a [13233] and in two [12333] conformations for the three macrocyclic rings. In the two square pyramidal conformers, labelled as sp(II) and sp(III) and reported in Fig. 1, conformations characterising the three twelve-membered rings are [2334], [12423] and [12333] in the sp(II) one, and [2334], [12423] and [2424] for sp(III). In Table 1 conformers displaying the lowest energy contents obtained by using both CFF91 and AMBER force fields are reported in detail for each compound together with the conformation type found in the solid state by X-ray diffraction, when available.

For all the free forms of the molecules under investigation both force field employed indicate a trigonal bipyramidal disposition of the donors as the most stable (see Table 1). Notably, as expected on the basis of the repulsion of five donors pointing inside the macrocyclic hole, and as experimentally found in the lithium and copper (II) complexes and in the free form of **5**, the tbp(I) seems to be the preferred conformer with the only exceptions of **1** and **2**. For these ones CFF91 force field

Table 1 Conformations of minimum energy found from MD simulations with CFF91 and AMBER force fields, together with conformations showed by diffraction analyses

1	Free Amine	H^+ on N-Bridged	H^+ on N-Me	
CFF91	tbp(III)	tbp(II)	sp(II)	
AMBER	tbp(I)	tbp(II)	sp(I)	
X-rays		tbp(II)		
2	Free Amine	H^+ on N-Bridged	H^+ on N-Me	H^+ on N-Benzyl
CFF91	tbp(III)	tbp(II)	sp(II)	sp(II)
AMBER	tbp(II)	tbp(II)	sp(I)	sp(II)
X-rays		tbp(II)		
3	Free Amine	H^+ on N-Bridged	H^+ on N-Me	H^+ on N-H
CFF91	tbp(I)	tbp(II)	tbp(I)	sp(III)
AMBER	tbp(I)	tbp(II)	tbp(I)	tbp(I)
X-rays				
4	Free Amine	H^+ on N-bridged	H^+ on N-Me	
CFF91	tbp(I)	tbp(II)	sp(III)	
AMBER	tbp(I)	tbp(I)	sp(III)	
X-rays			sp(I)	
5	Free Amine	H^+ on N-bridged		
CFF91	tbp(I)	tbp(I)		
AMBER	tbp(I)	tbp(I)		
X-rays	tbp(I)	tbp(I)		

prefers tbp(III) conformers, while for **2** AMBER prefers the tbp(II) conformer.

MD results concerning the monoprotonated species underline unequivocally that if the protonation occurs on a bridge-head nitrogen the favoured conformation is a tbp one, while a square pyramidal disposition of the donors is preferred if the protonation interests a donor on the chain, occupying this one the apical position. Only for the $[H3]^+$ species some anomalous finding have been found. In detail, the following results have been obtained.

1. In the solid state, the cation displays a tbp(II) conformation, but the X-ray analysis did not allow to localise the hydrogen ion involved in the protonation. However, as the bridge-head nitrogen closer to the three nitrogen atoms of the chains shows a conspicuous pyramidalization in regard to the other ones and on account of the MD results, which indicate the tbp(II) conformer as the preferred one if the acidic proton is on the bridge-head nitrogen, we can presume this one to be the place of the proton.
2. Also in this case the crystal structure arrangement of the five donors in the $[H2]^+$ cation gives rise to a tbp(II) conformation, where the bridging nitrogen closer to the three nitrogens of the chains displays a significant degree of pyramidalization in respect to the other ones. MD indicates this conformer as the preferred when the protonation interests the bridging nitrogen. These evidences allow to localise the proton on the same position assumed for the $[H1]^+$ species.
3. The lack of the X-ray crystal structure of the monoprotonated species did not allow to advance any hypothesis about the protonation site as previously done. However, due to the presence of a secondary nitrogen atom on a bridging chain this one can be thought to be the protonation site. In this case the CFF91 and AMBER force fields give the sp(III) and the tbp(I), respectively, as conformers of minimum energy.
4. Diffraction data showed the $[H4]^+$ cation in the sp(I) conformation but did not exactly permit to localise the hydrogen ion. However, as previously reported from the higher degree of pyramidalization of the methylated nitrogen atom in respect to that of the bridgehead ones, we can infer the first one to be involved in the protonation. On the other hand a square pyramidal disposition of the donors, sp(III), even if different from that showed in the X-ray structure, was obtained from the MD simulation when the protonation interests the methylated nitrogen atom.
5. The X-ray structures of **5** and $[H5]^+$ already reported show a similar arrangement of the donors resulting in tbp(I) conformers, in agreement with the MD simulations.

In Figure 2a and 2b diagrams reporting the energy differences between trigonal bipyramidal and square pyramidal conformations of every free amine studied and its corresponding cations, protonated on a bridge-head or on a N-methylated nitrogen atom, are reported. In addition, analogous results concerning the protonation on the N-benzyl and the secondary nitrogen atoms for **2** and **3** are also presented. Briefly we can note that points corresponding to the free amines and their monoprotonated species on a bridging nitrogen are always charac-

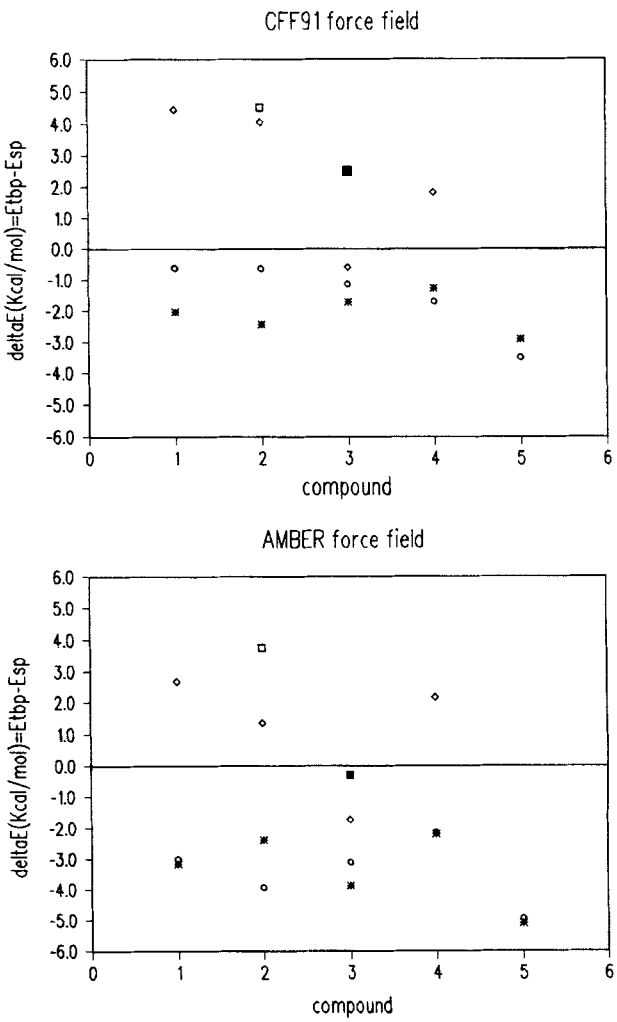

Figure 2 Energy differences (2a from CFF91, 2b from AMBER force fields) between trigonal bypiramidal and square pyramidal conformations of all the studied free amines (○) and their corresponding cations protonated on a bridge-head (*) or on a N-methylated (◇) nitrogen atom. For **2** and **3**, analogous results are reported concerning the N-benzyl (□) and the secondary (■) nitrogen atoms. The $[H3]^+$ cation with the proton linked to a methylated nitrogen atom (◇) prefers a tbp conformation instead of a sp one. In fact, this latter is destabilized, since the hydrogen atom bound to the secondary nitrogen and the hydrogen bound to a methylated one are both pointing inside the molecular cavity, thus exerting a mutual steric hindrance.

terised by a $\Delta E < 0$, indicating thus that the tbp conformation is favoured by the free form and when the proton is bound to a bridge-head nitrogen as above stated. On the contrary N-chain protonated forms prefer sp conformations ($\Delta E > 0$). It is noteworthy that CFF91 indicates the sp conformation as preferred for **3** only if the protonation occurs on the secondary nitrogen atom (see caption to Figure 2), as presumed.

Finally it is interesting to observe that the substitution of N-chain atoms with oxygen atoms, as it occurs going from **1** to **4** and **5**, progressively stabilises the tbp(I) conformation in respect to the tbp(II) one for the corresponding N-bridge-head monoprotonated species as exemplified in Fig. 3.

The stabilisation of the tbp(I) conformer can be explained presuming that the oxygen atoms are interacting with the proton attached to the bridge-head nitrogen, causing thus a longer linear N-H...N hydrogen bond. The small decrease observed for the N...O distances, obtained from X-ray diffraction, passing from **5** to $[\mathbf{H5}]^+$, both having a tbp(I) conformation nicely supports this hypothesis. Only the passage from a tbp(I) to a tbp(II) conformer as consequence of the proton inclusion causes an "axial shrinking" (Fig. 4) which can be evaluated from MD simulation results to be about 1 Å. An analogous reduction of the distance between nitrogen atoms involved in the hydrogen bond was found in diamminic compounds with exceptional basicity properties.[13,14]

CONCLUSION

The aim of this work was to correlate the protonation site with the conformation adopted by the ligand with X-ray and molecular dynamics data. Collected results indicate

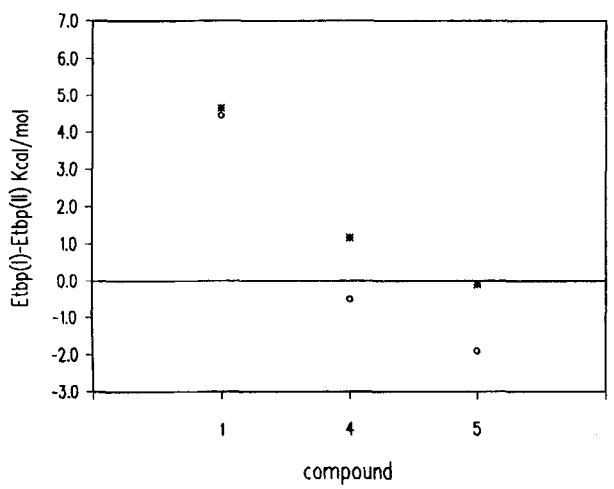

Figure 3 Energy differences between the tbp(I) and tbp(II) conformations for the monoprotonated species of **1**, **4** and **5**, calculated by means of CFF91 (*) and AMBER (O) force fields.

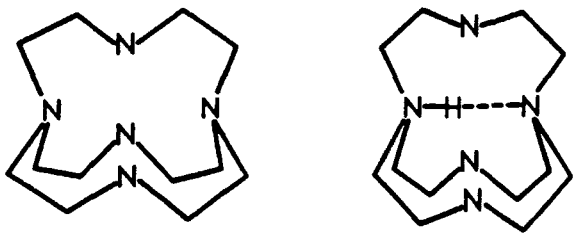

Figure 4 Schematical drawing representing the tbp(I) and tbp(II) conformations showing how the molecular cavity varies its shape as consequence of proton inclusion.

that protonation of a macrobicycle with donors of comparable basicity interests a bridge-head nitrogen and preserves a tbp disposition of the donors, even if we can observe an "axial shrinking". If a nitrogen of the chain has a higher basicity in respect to that of the bridge-head ones, the protonation of this one causes a larger conformational change which results in a sp arrangement of the donors as found in $[\mathbf{H3}]^+$ and in $[\mathbf{H4}]^+$. In fact in $[\mathbf{H3}]^+$ the square pyramidal geometry is due to the presence of a secondary nitrogen on the lateral chain, while in the protonated form of **4** the proximity of the oxygen atoms to the bridge-head nitrogens decreases their basicity in respect to that of the more distant nitrogen on the chain. A square pyramidal disposition of the donors, with the proton localised on the apical nitrogen, is also common to monoprotonated macrobicycles having 7-5-5 atoms bridging chain (see Scheme).[7,15] On the other hand, these latter macrobicycles assume a square pyramidal geometry also when they are involved in metals complexation, in contrast with that observed in the 5-5-5 ones, being this geometry favoured by the different length of the chains. In this case, therefore, the rigid conformation of the macrobicycle imposes the protonation on the chain.

In conclusion, we report a hint about the protonation constants of the products here studied (see Table 2). The analogous to **3** 7-5-5 macrobicycle **6** is a proton sponge, i.e., it does not release the proton even in strong alkaline solution (pH > 14).

The X-ray crystal structure[7] shows that the hydrogen ion of $[\mathbf{H6}]^+$ is bound to the secondary nitrogen, occupying this one the apical position of the resulting square pyramid. A comparison of this structure (Fig. 5i) with that of $[\mathbf{H3}]^+$ (Fig. 5ii) having an sp disposition of the donors obtained from the MD simulation reveals that even if the N-H...N distances in $[\mathbf{H3}]^+$ and $[\mathbf{H6}]^+$ are comparable, the higher basicity of **6** can be accounted for

Table 2 First basicity constants (logarithms) in aqueous solution[1-5,7]

	Cage					
Reaction	*1*	*2*	*3*	*4*	*5*	*6*
$H^+ + L = HL^+$	11.8[a]	11.8[a]	12.48[a]	11.46[a]	>18[b]	>14[a]

[a] measured by potentiometric titration at 25 °C, I = 0.5 mol dm^{-3}
[b] estimated from kinetic data

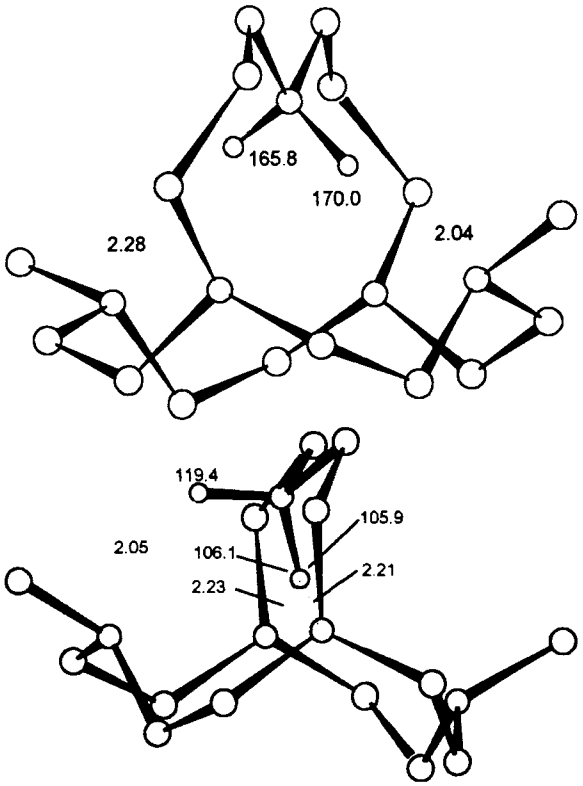

Figure 5 (i) ORTEP view of the $[H6]^+$ cation reporting distances (Å) and angles (°) of the H-bond interactions as found in the crystal structure (ref. 2); (ii) structure of the $[H3]^+$ cation derived from the MD simulation and showing distances (Å) and angles (°) for the hydrogen-bonds.

by the presence of a longer bridging chain which allows the formation of two quasi-linear N-H...N bonds in contrast with that observed in the $[H3]^+$ cation where bent H-bonds are present.

For **5** also it is necessary to destroy the ligand to extract the internal proton (see Table 2).[5] This high basicity can not be explained taking into account the linearity and the length of the N-H...N hydrogen bond only. In fact, although the lower basicity constant of **1** and **2**, the X-ray structures of $[H1]^+$ and $[H2]^+$ displays $N_{bridge\text{-}head}$-$N_{bridge\text{-}head}$ distances about 0.60 Å smaller than that found in $[H5]^+$. To support the surprising behaviour in solution of **5** the authors evoke a fast exchange of the proton between the two nitrogens through the intermediation of the oxygen atoms.[6]

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