Ab initio SCF MO calculations on triaza and tetraaza cyclic amines

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Molecular orbital *ab initio* calculations have been performed on some triaza and tetraaza cyclic amines aiming at the determination of their minimum energy geometries and of the relative conformational energies in different protonation states.

The results clearly show two factors governing the conformational preferences in these systems: the formation of intramolecular hydrogen bonds and the repulsions between two nitrogen protons or two nitrogen lone pairs.

For each protonation state there are distinct conformers depending on the number of NH bonds pointing 'inwards' relative to the macrocyclic cavity and on their ability to form intramolecular hydrogen bonds. All the systems display a marked preference for a helical geometry, with the ethylenediamine bridges in a *gauche* conformation. The triaza systems having propylenediamine bridges display an additional conformational freedom due to the large number of configurations available for these bridges. The calculated structures and energies are in good agreement with the experimental X-ray and NMR spectroscopy data available.

Introduction

1,4,7-Triazacyclononane ([9]aneN$_3$), 1,4,7-triazacyclodecane ([10]aneN$_3$), 1,4,8-triazacycloundecane ([11]aneN$_3$), 1,5,9-triazacyclododecane ([12]aneN$_3$) and 1,4,7,10-tetraazacyclododecane ([12]aneN$_4$) (Fig. 1) are precursors of polyfunctional cyclic ligands [containing distinct pendant arms bound to their nitrogen atoms, *e.g.* NOTA (1,4,7-triazacyclononane-*N*,*N'*,*N''*-triacetate) and DOTA (1,4,7,10-tetraazacyclododecane-*N*,*N'*,*N''*,*N'''*-tetraacetate)]. These ligands exhibit specific coordination properties in solution (high selectivity and a strong pH dependence),[1,2] mainly due to the nature of their functional groups and to the conformational characteristics of the macrocycle.

During the last two decades, there has been a growing interest in the study of these kinds of compounds on account of their usefulness either as chelating agents both in inorganic and bioinorganic chemistry or (in the case of their Gd^{3+} complexes) as contrast agents in Magnetic Resonance Imaging (MRI), a radiological technique used in medical diagnosis and therapy.

The cyclic nature of these compounds is responsible for their characteristic acid–base properties in aqueous solution due to the presence of pH dependent favoured geometries.[3–7] The present study aims to gain an understanding of this behaviour through the determination of the lowest energy conformers for each protonation state of the macrocycle.

For the smaller triaza and for the tetraaza amines, calculations have been performed using both the all-electron 3-21G(N*) basis set[8] and an effective core potential (ECP) approach.[9,10] The chosen ECP proved to be a good compromise between the computational effort and the quality of the results. Thus, for the larger triaza systems only ECP calculations have been carried out.

Owing to the high degree of freedom of these kinds of macrocyclic systems, their conformational study is not a trivial task. This problem has already been addressed in several published works, either for large cycloalkanes[11] or their derivatives having carbon atoms replaced by different types of heteroatoms (*e.g.* cyclic polyethers,[12] cyclic polyamines[13] or polythiocycloalkanes[14]). While the experimental techniques used to study these systems range from X-ray crystallography and electron diffraction to NMR and EPR spectroscopies, the theoretical approach remains mainly at the molecular mechanics (MM) level. While computational inexpensive MM calculations are known to have severe limitations at coping with the subtle effects of the electronic distribution, these effects, which are expected to be rather important in macrocyclic

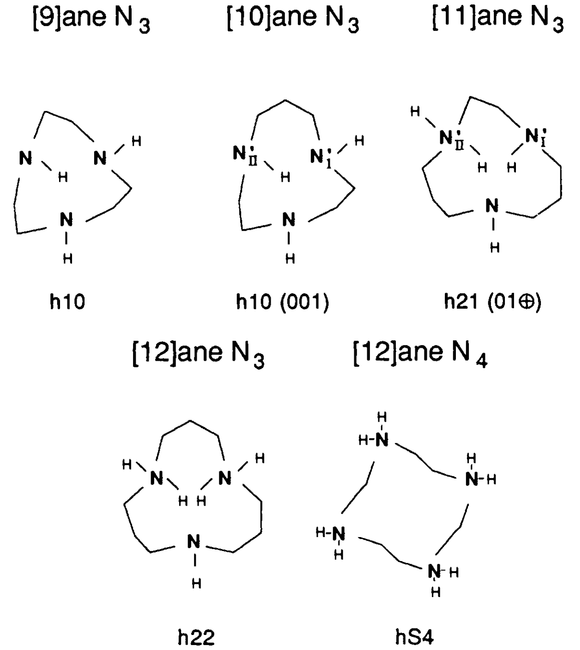

Fig. 1 Schematic representation and nomenclature of the macrocyclic amines studied in this work

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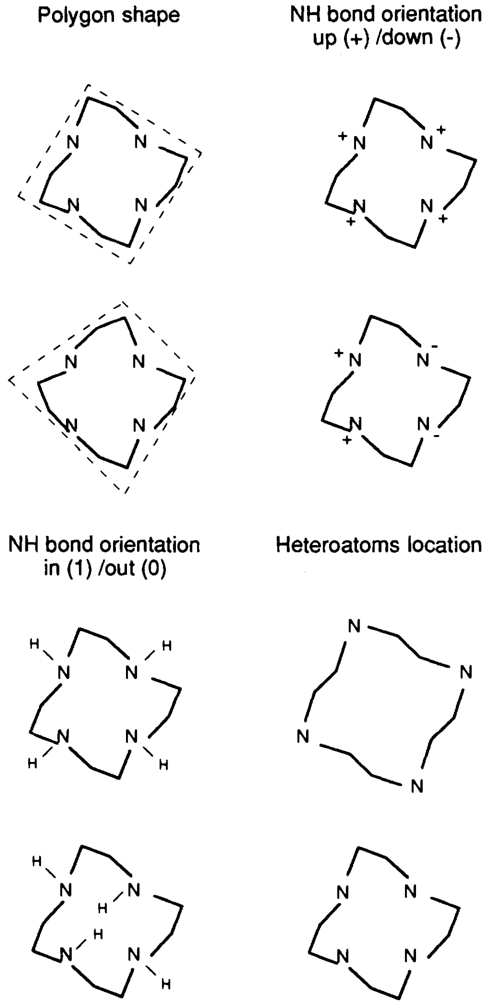


Fig. 2 Schematic representation of the conformational degrees of freedom available for macrocyclic amines (only the hydrogens bound to nitrogen atoms are shown)

systems containing heteroatoms are easily accessed by a quantum chemical approach. Neverthless, to the best of our knowledge the amount of work dealing with the problem at the *ab initio* level is scarce and limited to partial geometry optimizations.[15,16]

Fig. 2 illustrates the conformational degrees of freedom available in this kind of system using the [12]aneN$_4$ molecule as an example. Large attention has been paid to the 'shape of the polygon' resulting from the projection of the bonds on the main molecular plane.[11] However, the 'location of the heteroatoms', either at the 'side' or at the 'corner' of the polygon has only been considered marginally before this work. The orientation of the NH bonds (either in/out of the ring cavity, or above/below the plane that contains three nitrogens) is also determinant of the conformation of the polyazamacrocycles; in fact, the stability of the geometries displaying NH bonds pointing above and below the plane defined by the heteroatoms has been the subject of several studies related to the selectivity of coordination of these macrocycles;[13] on the other hand, the conformational energy of the free macrocycle is strongly dependent on the in/out orientation of the NH bonds, as will be discussed below.

Experimental

The *ab initio* calculations were performed using the GAUSSIAN92 package[17] adapted to a DEC Alpha 7000 computer.

For the [9]aneN$_3$ and [12]aneN$_4$ systems, molecular geometries were fully optimized using the 3-21G split valence basis set[18] with one set of nitrogen *d* functions ($\zeta = 0.8$) to account for the lone pair and electronegativity of the nitrogen atom.[8] Previous results[8,19,20] have shown that the 3-21G(N*) basis set allows a good compromise between the computer time requirements and the quality of the results. In particular, it took good account of geometrical parameters and energy differences between conformers for several amines.[19,20]

Additional calculations were performed using the pseudopotentials of Pacios and Christiansen[9] combined with the valence basis set of Stevens *et al.*[10] for the heavy atoms and the all-electron 3-21G basis set[18] for the hydrogen atoms. The accuracy of this combination was evaluated by comparison with the all-electron results for the [9]aneN$_3$ and [12]aneN$_4$ systems.

The final rms gradient length was, in all geometry optimizations, less than 1.0×10^{-4} hartree bohr^{-1} or hartree rad^{-1}, yielding geometries accurate to 0.05 pm or 0.1°, respectively, and energies stable below the microhartree level ($1\ \mu E_h = 2.6\ J\ mol^{-1}$).

The large number of possible geometries adopted by these kind of macrocyclic systems requests a careful search on the potential energy hypersurface, in order to locate all their meaningful minima. Since a systematic search of all the points at the hypersurface is not feasible, the following procedure was adopted: (*i*) starting with the smaller systems, all the different conformations possible (Fig. 2) were checked; (*ii*) for each one of these, several possible starting geometries were selected, based on the experimental data available and on results of previous calculations. For the larger macrocycles the information obtained for the previous smaller systems was used, whenever possible. Once the results clearly stress the strong stabilizing effect of the NH···N interactions, all the geometries favouring this interaction were carefully checked. Thus, we can conclude, with a reasonable degree of confidence, that there is no important low energy conformer missing from the results now presented.

The nomenclature used throughout the text for the triaza and tetraaza cyclic amines is schematically illustrated in Fig. 1. With few exceptions, all the systems studied were found to adopt preferentially a helical geometry with all the NH bonds lying above the plane defined by three nitrogen atoms (Fig. 1). These conformations are referred to as **helices** ***jn*** (h*jn*), where *n* represents the degree of protonation of the macrocycle (*i.e.* the number of additional protons on the nitrogen atoms) and *j* stands for the number of acute X–N–H angles, X being the centre of the macrocycle ('inwards' bonds). As to the asymmetric amines [10]aneN$_3$ and [11]aneN$_3$ (Fig. 1), the three nitrogen atoms are non-equivalent and the conformations are described by the notation h*jn*(*abc*) (*abc* = 0, 1, $\oplus$), where 0 and 1 represent the number of N–H bonds pointing 'inwards' relative to the macrocyclic cavity, for the N, N$_{I}'$ and N$_{II}'$ nitrogen atoms, respectively, and the $\oplus$ sign indicates a protonated nitrogen atom [*e.g.* geometry h21(01$\oplus$), Fig. 1].

While the propylenediamine bridges display a large conformational freedom having torsion angles either nearly *syn*, *gauche* or *skew*, the ethylenediamine bridges were found to adopt a *gauche* N–C–C–N conformation in all cases but one. The exception is shown in Fig. 1, in which the nitrogen atoms occupy the 'corners' of the polygon and the CN bonds are *skew* relative to each other. This structure is referred to and discussed below as hs*n*.

Results and discussion

All-electron calculations

1,4,7-Triazacyclononane ([9]aneN$_3$). Table 1 presents the torsion angles of the most stable conformations found for the different protonation states of [9]aneN$_3$ using the 3-21G(N*) basis set. As will be discussed below, the results clearly show two factors governing the conformational preferences in these

Table 1 Torsion angles for the optimized geometries of the conformers of [9]aneN_3 with a population higher than 10% at 25 °C [3-21G(N*) level of calculation]

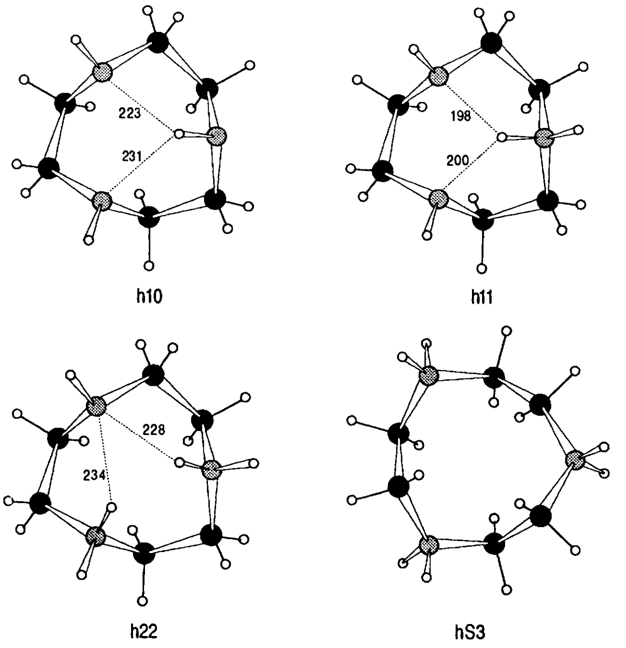
Conformer	Torsion angles[a]/° CNCC	NCCN	CCNC	CNCC	NCCN	CCNC	CNCC	NCCN	CCNC
h10	132.1	−48.8	−67.3	132.0	−48.7	−67.5	131.6	−48.5	−67.5
h20[b]	128.6	−51.6	−62.8	129.1	−51.8	−62.7	129.0	−51.7	−62.8
h11	136.7	−42.9	−75.2	136.2	−42.7	−75.4	136.3	−42.8	−75.2
h22	132.8	−47.9	−68.1	132.5	−48.0	−67.7	134.1	−48.7	−67.3
hS3	55.5	−122.2	55.5	55.5	−122.2	55.5	55.5	−122.2	55.5

[a] For the unsymmetrical geometries, the torsion angles are defined according to the following priority of nitrogen atoms: NH_2, NH_{in}, NH_{out}. [b] Higher energy minimum by 3.6 kJ mol^{-1} relative to the lowest minimum in the same protonation state.

Table 2 Protonation constants of the polyazamacrocycles [9]aneN_3, [10]aneN_3, [11]aneN_3, [12]aneN_3 and [12]aneN_4

	pK_1	pK_2	pK_3	pK_4
[9]aneN_3[a]	10.4 ± 0.06	6.9 ± 0.01	0.7 ± 0.10	—
[10]aneN_3[a]	12.9 ± 0.06	6.9 ± 0.05	*c*	—
[11]aneN_3[a]	13.4 ± 0.06	8.7 ± 0.04	*c*	—
[12]aneN_3[a]	12.3 ± 0.10	7.3 ± 0.06	2.4 ± 0.07	—
[12]aneN_4[b]	10.7	9.7	1.73	0.94

[a] Values determined by NMR pH titration.[7] [b] Values determined by potentiometry.[4] [c] Not determined due to limitation of the technique.



h10 h11 h22 hS3

Fig. 3 Perspective views of the 3-21G(N*) structures of the lowest energy conformers for the [9]aneN_3 amine in its different protonation states

systems: first, the formation of intramolecular hydrogen bonds, already known to be important in this kind of macrocyclic structure and secondly, the repulsions between either two nitrogen protons or two nitrogen lone pairs.

The totally deprotonated form of the [9]aneN_3 macrocycle presents several minima with the h*jn* conformation, but only two with significant population at 25 °C. Other geometries tested (*e.g.* having two NH bonds above and one NH bond below the plane containing the heteroatoms) were found to have a much higher energy. Conformer h10 is largely predominant, but structure h20 has an energy only 3.6 kJ mol^{-1} above. Both forms seem to be stabilized by the attractive interaction of positive and negative centres (NH bonds and nitrogen lone pairs, respectively) pointing to the centre of the ring. In fact, structures whose geometry inhibits this kind of stabilization, h00, h30 and hS0, are clearly unfavoured.

As to the protonated species of this amine, only one stable structure was found for each protonation state: h11, h22 and hS3, respectively, for the mono-, di- and tri-protonated forms (Table 1, Fig. 3).

The monoprotonated species h11 displays a particularly stable symmetric structure due to the position of the hydrogen atom pointing to the centre of the ring almost equidistant between the two opposing nitrogen atoms (Fig. 3), allowing the simultaneous interaction between that proton and the electron lone-pairs of the two other nitrogen atoms, thus forming a tricentred, energetically favoured, hydrogen bond. The NH • • • N distance is *ca.* 200 pm, much shorter than the one observed for the h20 form (*ca.* 250 pm). In addition, the conformation adopted by the ring is slightly distorted, deviating from the almost equilateral triangle found for the geometries where no strong intramolecular hydrogen bond interactions occur.

Also in this system, a tendency for a decrease in the energy difference between the h*jn* and hs*n* structures was detected as the degree of protonation increases. In fact, for the totally protonated amine there is an inversion of the relative stabilities of these geometries (conformer hS3 is the only populated species at 25 °C, Table 1). This is easily understandable in terms of the steric and electrostatic repulsions between the positively charged NH_2 groups of this relatively small macrocycle that will be minimized in the hS3 conformer. In fact, this geometry allows a large separation between the nitrogen atoms and corresponds to an orientation of all NH bonds 'outwards' relative to the ring. The repulsion effect of the positively charged NH_2 groups can account for the extremely low values of the third protonation constant of these kinds of cyclic amines ([9–12]aneN_3), as determined (in aqueous solution) both by ^1H NMR spectroscopy and potentiometric techniques (Table 2).[3,5,7]

The present results predict the existence of only one conformer significantly populated at room temperature for the protonated species of [9]aneN_3. This is in accordance with previous NMR studies performed in aqueous solution at 25 °C,[6,7] as a single, narrow proton resonance signal was observed in the whole pH range investigated (pH 0.5–13). A different situation arises with the unprotonated species, for which the energy of conformer h20 lies only 3.6 kJ mol^{-1} above h10. The fact that only one signal is detected in solution probably reflects a fast chemical exchange process between those protonated species (due to a corresponding low energy barrier) that renders them indistinguishable by NMR spectroscopy at room temperature.

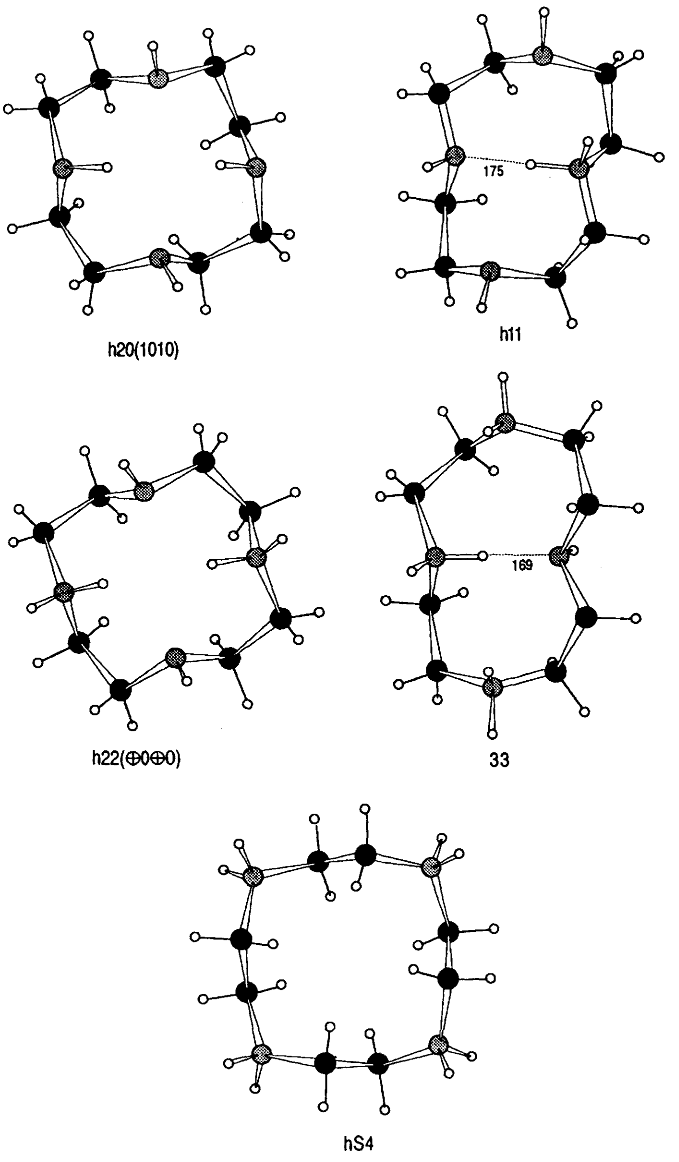
1,4,7,10-Tetraazacyclododecane ([12]aneN_4). Table 3 presents the torsion angles of the most stable conformers found for the tetraazamacrocycle [12]aneN_4 in its different protonation states. The lowest energy geometry for each degree of protonation is represented in Fig. 4.

Analogous to [9]aneN_3, a larger number of minima are found for the unprotonated state of this amine, for which the absolute minimum configuration contains an equal number of NH bonds and nitrogen lone pairs pointing 'inwards', stressing

Table 3 Torsion angles for the optimized geometries of the conformers of [12]aneN$_4$ with a population higher than 10% at 25 °C [3-21G(N*) level of calculation]

	Torsion angles[a]/°											
Conformer	CNCC	NCCN	CCNC	CNCC	NCCN	CCNC	CNCC	NCCN	CCNC	CNCC	NCCN	CCNC
h20(1010)	161.9	−62.2	−84.3	166.4	−56.9	−74.6	161.9	−62.2	−84.3	166.4	−56.9	−34.6
h11	−163.3	−40.5	−77.7	134.5	−62.9	−89.7	−163.6	−39.9	−75.5	134.1	−66.6	−84.9
h22(⊕0⊕0)	160.3	−55.2	−91.9	173.8	−51.8	−81.4	160.3	−55.2	−91.9	173.9	−51.8	−81.3
33	116.9	−77.4	−93.9	−165.5	−53.8	−51.6	107.1	−76.5	177.3	167.0	64.7	−80.8
h33[b]	−50.5	−56.6	−166.9	−82.4	−74.0	122.5	−53.4	−50.2	−162.7	−87.5	−71.8	118.0
hS4	−67.6	155.7	−67.6	−67.6	155.7	−67.6	−67.6	155.7	−67.6	−67.6	155.7	−67.6

[a] For the unsymmetrical geometries, the torsion angles are defined according to the following priority of nitrogen atoms: NH$_2$, NH$_{in}$, NH$_{out}$. [b] Higher energy minimum by 1.6 kJ mol^{-1} relative to the lowest minimum in the same protonation state.



h20(1010)

h11

h22(⊕0⊕0)

33

hS4

Fig. 4 Perspective views of the 3-21G(N*) structures of the lowest energy conformers for the [12]aneN$_4$ amine in its different protonation states. The four nitrogen atoms are nearly in the same plane.

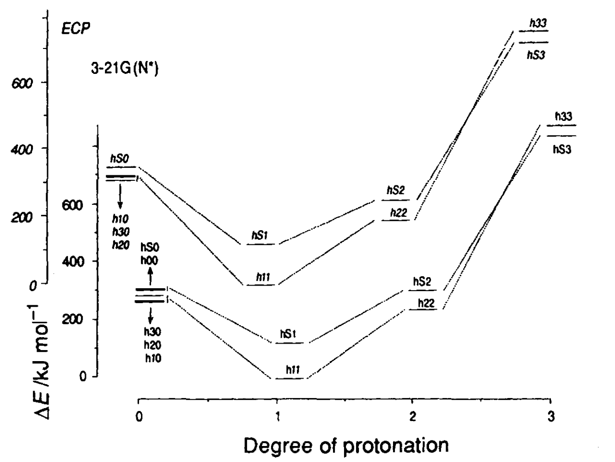


Fig. 5 Representation of the energy difference between the different conformers found for the [9]aneN$_3$ amine through the corresponding protonation process. Comparison between the ECP and the 3-21G(N*) results.

the importance of the balance between these closely spaced positive and negative charges.

For the $n = 1$ protonation state, the interaction between NH bonds and nitrogen lone pairs leads to a clear distortion of the quadrangular shape of this 12-membered ring, which is associated with the formation of a strong intramolecular hydrogen bond that overcomes the steric repulsions occurring within the macrocycle (Fig. 4). The strength of this interaction can be evaluated by the short NH • • • N distance, *ca.* 175 pm, which is smaller than that observed in the monoprotonated form of [9]aneN$_3$ (*ca.* 200 pm). Also the angle NH • • • N (θ) can determine the efficiency of these hydrogen interactions within the macrocycle, their degree of colinearity being higher for [12]aneN$_4$ ($\theta = 170°$) than for [9]aneN$_3$ ($\theta = 120°$).

The lower energy structure of the diprotonated form is closely related to the structure of the unprotonated molecule. In fact, the distorted structures found for $n = 1$ do not yield minima for $n = 2$. However, for $n = 3$ the distorted structures with a strong intramolecular hydrogen bond are preferred again. The lower energy minima, labelled 33 for simplicity, is not really a helical structure, as it presents three NH bonds above and one below the molecular plane. The helical geometry h33, also distorted by strong hydrogen bonding, lies only 1.6 kJ mol^{-1} above.

In the case of the fully protonated form ($n = 4$), hS4 is the most stable conformer. In fact, the relative energies of the hSn structures follow the same trend found for [9]aneN$_3$: they decrease with an increasing degree of protonation, becoming the lowest energy geometry for the maximum value of n. This kind of conformational preference is in agreement with the X-ray data available for the similar system [12]aneN$_1$-hydrochloride, in which the positively charged NH$_2$ group is located at one 'corner' of the square.[21]

ECP Calculations

The ECP approach has been chosen mainly in view of a future extension of the present calculations to larger systems and/or to complexes of these macrocyclic molecules with different metal ions, as they provide a significant reduction of computation time without losing the quality of the results. In fact, this has been confirmed in the present work by comparing the results

Table 4 Torsions angles for the optimized geometries of the conformers of [10]aneN_3 with a population higher than 10% at 25 °C (ECP level of calculation)

Conformer	Torsion angles/° CNCC	NCCN$_I$′	CCN$_I$′C	CN$_I$′CC	N$_I$′CCC	CCCN$_{II}$′	CCN$_{II}$′C	CN$_{II}$′CC	N$_{II}$′CCN	CCNC
h20(101)	131.2	−58.9	−79.5	140.0	−18.6	−24.5	−70.1	162.3	−58.7	−56.8
h20(110)[a]	128.8	−60.0	−79.8	139.9	−17.8	−27.0	−66.9	161.0	−60.6	−54.5
h11(0⊕0)	137.6	−49.0	−93.5	151.1	−28.9	−6.6	−88.1	171.5	−49.4	−69.2
h11(00⊕)[a]	135.4	−48.6	−91.1	149.1	−25.4	−11.3	−86.7	173.3	−49.9	−68.2
h22(⊕0⊕)	131.5	−51.7	−86.5	146.0	−28.0	−8.5	−84.9	172.4	−53.5	−63.0
hS3	−42.4	123.9	−55.8	−84.1	74.0	66.5	−68.6	−59.2	141.3	−65.5

[a] Higher energy minima by 0.4 kJ mol^{-1} [h20(110)] and 0.2 kJ mol^{-1} [h11(00⊕)] relative to the lowest minimum in the same protonation state.

Table 5 Torsion angles for the optimized geometries of the conformers of [11]aneN_3 with a population higher than 10% at 25 °C (ECP level of calculation)

Conformer	Torsion angles/° CNCC	NCCC	CCCN$_I$′	CCN$_I$′C	CN$_I$′CC	N$_I$′CCN$_{II}$′	CCN$_{II}$′C	CN$_{II}$′CC	N$_{II}$′CCC	CCCN	CCNC
h20(101)	125.2	33.0	−64.2	−68.1	157.5	−57.1	−70.0	139.5	−13.7	−62.1	−58.7
h11(⊕00)	136.7	31.5	−61.9	−60.2	155.2	−63.8	−72.2	143.9	−13.8	−55.8	−64.9
h22(⊕⊕0)	−168.1	−81.2	51.1	−86.4	145.8	−51.9	−117.0	156.6	−61.8	40.7	−141.1
h22(⊕0⊕)[a]	175.3	−42.0	−6.1	−81.2	−177.8	−47.5	−68.6	142.0	−92.4	35.1	−98.3
h23(0⊕⊕)	89.9	−168.8	85.4	−69.9	139.4	−66.8	−56.3	123.1	−160.1	89.8	−32.1

[a] Higher energy minimum by 1.5 kJ mol^{-1} relative to the lowest minimum in the same protonation state.

obtained for the [9]aneN_3 and [12]aneN_4 systems using both the all-electron [3-21G(N*)] and the ECP methods.

[9]aneN_3 and [12]aneN_4. Fig. 5 compares the energies of the different conformers found for the [9]aneN_3 system, using both the all-electron and the ECP methods. A rather good agreement is clearly observed between these two types of results, both in the number of minima found and in their relative energies. Furthermore, the calculated geometries for each conformer are identical in the two methods, apart from the systematic difference in bond lengths [*e.g.* 3-21G(N*) bond lengths are always shorter than the corresponding ECP values; the scaling factor is 0.95 for skeleton bonds and 0.98 for CH and NH bonds]. Both methods stress the importance of the orientation of the NH bonds and predict the hs*n* geometry to be the most stable one in the fully protonated state of the macrocycle. The same type of agreement is also found for the [12]aneN_4 system.

The only noticeable exception to the general agreement between the ECP and the 3-21G(N*) results is in the lowest energy minimum found for the unprotonated state of [9]aneN_3, h20 for ECP and h10 using the 3-21G(N*) basis function. This difference shows that the repulsions inside the macrocycle are weighted differently by these two methods: the all-electron method emphasizes the repulsions between hydrogen atoms bound to the ring nitrogens (*e.g.* favouring the h10 geometry over h20), while ECP results reflect stronger repulsions between the nitrogen lone pairs (*e.g.* favouring h20 over h10 and not yielding h00 as a minimum energy geometry). The overweighting of the lone pair–lone pair repulsions, however, is not exclusive of the ECP method, as in published results on acyclic diamines, using the 6-31G* basis set, the energy of the H–H and lone pair–lone pair repulsions is evaluated to be 2 and 10 kJ mol^{-1}, respectively.[22] In addition, at the ECP level the energy difference between the h10 and h20 conformers is equal to 9.9 kJ mol^{-1}, in accordance with the experimental observation of a single and sharp NMR resonance signal in aqueous solution at high pH values.[7] Thus, in the absence of additional experimental data we have no means of deciding the relative importance of these two distinct geometries (h10 and h20).

1,4,7-Triazacyclodecane ([10]aneN_3) and 1,4,8-triazacycloundecane ([11]aneN_3). Tables 4 and 5 present the torsion angles of the minimum energy conformations found for the [10]aneN_3 and [11]aneN_3 in their different protonation states. The lowest energy geometries for each degree of protonation are represented in Figs. 6 and 7.

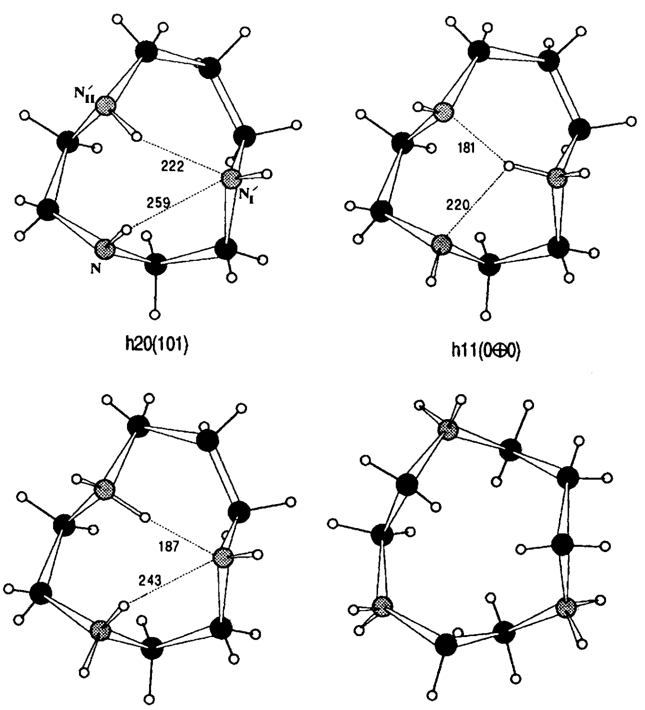
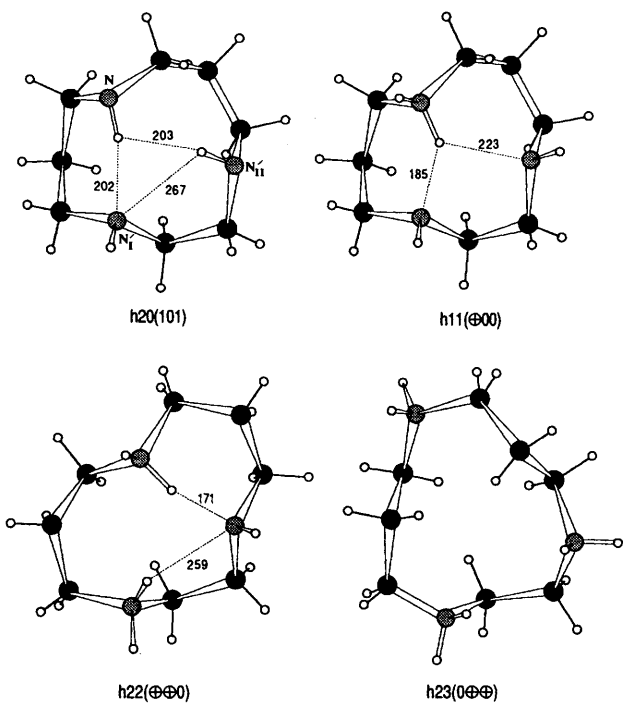


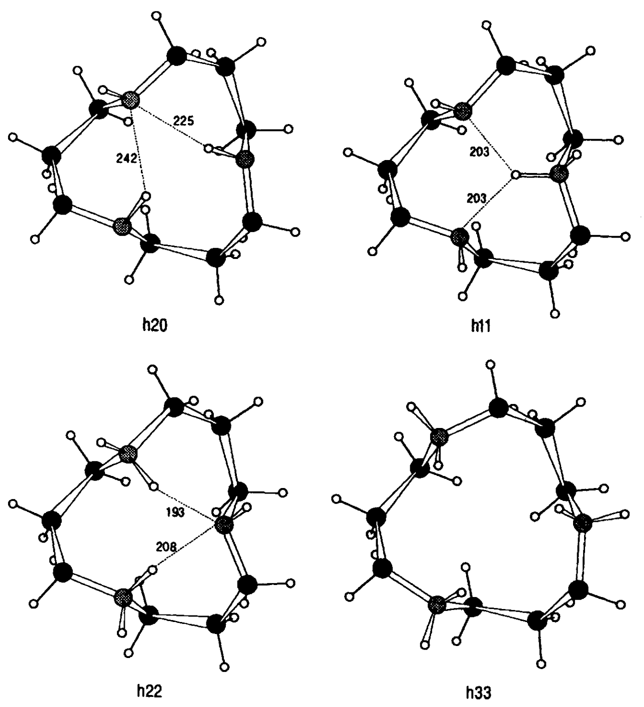
Fig. 6 Perspective views of the ECP structures of the lowest energy conformers for the [10]aneN_3 amine in its different protonation states

The presence of the propylenediamine bridges in these asymmetric amines is responsible for their higher conformational freedom. This additional flexibility allows the macrocycle to maximize the hydrogen-bond-type interactions, lowering the total steric energy strain. In particular, it was found that the lowest energy conformers correspond to geometries in which the intramolecular hydrogen bonds give rise to six-membered



h20(101) h11(⊕00) h22(⊕⊕0) h23(0⊕⊕)

Fig. 7 Perspective views of the ECP structures of the lowest energy conformers for the [11]aneN_3 amine in its different protonation states



h20 h11 h22 h33

Fig. 8 Perspective views of the ECP structures of the lowest energy conformers for the [12]aneN_3 amine in its different protonation states

rings within the macrocycle that are expected to be more stable than the five-membered rings formed in systems containing only ethylenediamine bridges. These six-membered intramolecular structures display a rather distorted, roughly chair-like conformation, probably caused by the tendency of the macrocycle to adopt a helical geometry. In the lowest energy geometries, the consecutive dihedral NCCC and CCCN angles in the ring were found to adopt either a *cis–cis*, a *cis–gauche*, a *gauche–gauche* or a *gauche–skew* conformation.

These conformational preferences can be compared with the crystal structure of related molecules. For instance, cyclam ([14]aneN_4) presents alternating propylenediamine and ethylenediamine bridges. The crystal structure of the diprotonated form[23] clearly shows the presence of intramolecular hydrogen bonds and the preferential formation of six-membered rings instead of five-membered ones. The NCCC and CCCN angles adopt a *gauche–gauche* conformation, which is seldom found in the most stable forms of [10]aneN_3 and [11]aneN_3 (Tables 5 and 6).

The most stable structures found for the monoprotonated forms of the [10]aneN_3 and [11]aneN_3 amines agree well with previously obtained NMR spectroscopy results (in aqueous solution) that proved the existence of preferential protonation sites for these macrocyclic asymmetric systems.[7] Thus, the preferential sites relative to the first protonation step are the nitrogen atoms N' and N for the [10]aneN_3 and [11]aneN_3 amines, respectively (see Figs. 6 and 7). The calculated structures found for these systems show that these protonation preferences are determined by the possibility of formation of a maximum number of intramolecular six-membered rings, through NH ··· N type interactions within the macrocycles. In fact, in the [10]aneN_3 amine, the higher stability detected for conformers h11(0⊕0) and h11(00⊕) relative to geometry h11(⊕00) results from the orientation of the hydrogen atom pointing inwards that does not allow the formation of a six-membered intramolecular ring within the system, yielding five-membered rings instead. The same arguments apply to the [11]aneN_3 system, for which structure h11(0⊕0) was not found to be a minimum unlike geometries h11(⊕00) and h11(00⊕). This extra stabilization of the monoprotonated conformers of the asymmetric triamines explains the high value of their first protonation constant (pK_1) relative to the corresponding value for the [9]aneN_3 amine (Table 2).

The presence of two closely spaced minima in both the unprotonated and monoprotonated species of the [10]aneN_3 and [11]aneN_3 systems is a consequence of the non-equivalence of the nitrogen atoms of their propylenediamine and ethylenediamine groups. This non-equivalence, that arises from the different conformation adopted by these bridges, is not expected to hold in a dynamic situation such as an aqueous solution at room temperature. In this way, the results now obtained are consistent with the observation of a single set of resonances for each protonation state by NMR spectroscopy in solution.

As for the fully protonated species, [10]aneN_3 and [11]aneN_3 present distinct situations. In the case of [10]aneN_3, the most stable form for $n = 3$ is hS3, following the behaviour already found for [9]aneN_3. However, for [11]aneN_3, the h23(0⊕⊕) is *ca.* 18.6 kJ mol^{-1} below the hS3 form.

1,5,9-Triazacyclododecane ([12]aneN_3). Table 6 presents the torsion angles of the minimum energy conformations found for the [12]aneN_3 system in its different protonation states. For this twelve-membered symmetric amine, two conformers were found for its deprotonated form, h10 and h20, the former being much less stable ($\Delta E = 0.9$ kJ mol^{-1}) due to the steric repulsion between the two electron lone-pairs of the nitrogen atoms oriented to the centre of the ring (Fig. 8). In fact, this destabilizing effect overcomes the repulsive interaction between the two hydrogen atoms pointing to the centre of the macrocycle in the h20 geometry (in accordance with the observations made for the [9]aneN_3 system). The high stability of the h20 conformer is due to the presence of three six-membered intramolecular rings, thanks to the formation of a tricentred hydrogen bond between the nitrogen electron lone-pair and the two protons bound to the adjacent heteroatoms.

Only one conformer was found for the monoprotonated species of this amine, h11 (Fig. 8, Table 6), also displaying a stable, tricentred hydrogen bond, the proton pointing to the centre of the ring being practically equidistant to the two nitrogen atoms involved in that bond. Once more, the stabilizing effect due to the formation of several six-membered intramolecular rings overcomes the steric repulsion between

Table 6 Torsion angles for the optimized geometries of the conformers of [12]aneN_3 with a population higher than 10% at 25 °C (ECP level of calculation)

	Torsion angles[a]/°											
Conformer	CNCC	NCCC	CCCN	CCNC	CNCC	NCCC	CCCN	CCNC	CNCC	NCCC	CCCN	CCNC
h20	171.7	−35.6	−43.5	−47.4	168.4	−34.7	−38.5	−59.1	179.5	−29.1	−40.0	−50.9
h11	−175.9	−23.6	−36.6	−61.0	179.3	−25.8	−43.4	−55.1	172.5	−26.5	−39.0	−66.8
h22	177.5	−35.0	−41.6	−50.7	164.1	−32.9	−35.2	−68.9	−175.4	−21.8	−33.2	−61.5
h33	154.4	−49.7	−52.0	−23.2	154.4	−49.7	−52.0	−23.3	154.4	−49.7	−52.0	−23.2

[a] For the unsymmetrical geometries the torsion angles are defined according to the following priority of nitrogen atoms: NH_2, NH_{in}, NH_{out}.

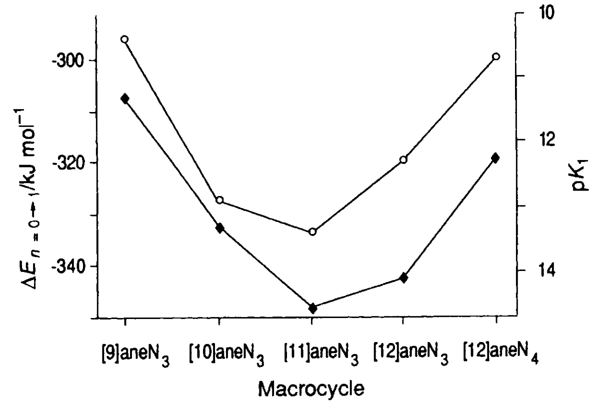


Fig. 9 Representation of the energy difference between the deprotonated and monoprotonated forms of the macrocyclic amines [x]aneN_3 (x = 9–12) and [12]aneN_4, $\Delta E_{n=0\to1}$ (◆), and of the corresponding pK_1 values (○)

the nitrogen electron lone-pairs. The h21 structure, in turn, is unstable, for there are repulsive interactions between the protons bound to the heteroatoms and oriented to the inside of the ring.

For the higher protonation states, $n = 2$ and $n = 3$, only one stable geometry was found for this amine, respectively h22 and h33 (Fig. 8, Table 6). Conformer h22 is particularly stable, for, as in geometry h20 previously discussed, it presents a tricentred hydrogen bond between a nitrogen electron lone-pair and two protons bound to the adjacent heteroatoms, yielding two intramolecular six-membered rings.

Much attention has been paid in the literature to the question of amine basicities for several types of amines.[24–26] Most of the factors affecting the relative stability of unprotonated and protonated species (and consequently their protonation constants), such as intramolecular hydrogen bonding and steric energy strain, are expected to be correctly evaluated by the calculations performed here. Fig. 9 compares the experimental pK_1 values for this series of amines[4–7] with the calculated energies of the protonation process, $\Delta E_{n=0\to1}$ [reaction (1)], where L represents the amine.

$$L + H_3O^+ \longrightarrow HL^+ + H_2O \qquad (1)$$

The agreement between the sets of data is quite reasonable, especially keeping in mind that entropy effects are not included and the experimental data refers to the aqueous solution. The trends in pK_1 variation along the series are correctly reproduced by the calculations, which predict [11]aneN_3 to be the easiest system to monoprotonate and [9]aneN_3 to be the hardest.

From the present work two main conclusions may be drawn. First, the reliability of the ECP approach when compared with the all-electron calculations allows the possibility of further quantum mechanical calculations in larger polyazamacrocycles as well as in their complexes. Secondly, the quantum mechanical calculations are able to provide relevant structural information on these systems, even for condensed phase studies.

In fact, the results herein reported are in excellent agreement with the experimental NMR and X-ray data available, suggesting that, in these kinds of systems, the intramolecular interactions play a much more significant role than intermolecular interactions.

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