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Belen Altava[a]; Antonio Bianchi[b]; Carla Bazzicalupi[b]; M. Isabel Burguete[a]; Enrique García-Espanña[c]; Santiago V. Luis[a]; Juan F. Miravet[a]
[a] Departamento de Química Inorgánica y Orgánica, Universitat Jaume I, caslón, Spain [b] Dipartimento di Chimica, Università di Firenze, Firenze, Italy [c] Departamento de Química Inorgánica, Universitat de València, Burjassot, Valencia, Spain

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Structural Studies on Polyaza[n]paracyclophanes. A Molecular Mechanics and Crystallographic Study

BELEN ALTAVA[a], ANTONIO BIANCHI[b], CARLA BAZZICALUPI[b], M. ISABEL BURGUETE[a], ENRIQUE GARCÍA-ESPAÑA[*,c], SANTIAGO V. LUIS[*,a] and JUAN F. MIRAVET[a]

[a]*Departamento de Química Inorgánica y Orgánica, Universitat Jaume I, 12080, Castellón, Spain;*
[b]*Dipartimento di Chimica, Università di Firenze, Via Maragliano 75/77, 50144, Firenze, Italy;*
[c]*Departamento de Química Inorgánica, Universitat de València, C/Doctor Moliner 50, 46100 Burjassot (Valencia), Spain*

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Structural analysis of polyaza[n]paracyclophanes **1-5** has been carried out by the use of molecular mechanics and other techniques. NMR data and molecular mechanics calculations show that conformations in which the polyamine chain is arching above the aromatic ring are prevalent in solution. The crystal structure of triprotonated durene derivative **2b** agrees with those studies. Crystals of $3H^+$.**2b** are triclinic, space group $P\bar{1}$, with $a = 11.758(4)$ Å, $b = 13.870(5)$ Å, $c = 17.181(3)$ Å, $\alpha = 96.66(2)°$, $\beta = 106.02(2)°$, $\gamma = 104.87(3)°$, $Z = 4$, $R_1 = 0.072$, $wR_2 = 0.18$. Three different conformations are present in the crystal. Good agreement between the crystal structures and calculated conformations is observed, results being more accurate for AMBER* and OPLS* force fields which seem to be the force fields of choice for calculations involving those compounds. Consideration of solvent (GB/SA approach) improves results obtained in calculations.

INTRODUCTION

Preorganization represents an essential structural feature for the design of novel synthetic receptors.[1] We have recently developed a series of polyaza[n]paracyclophanes as water-soluble receptors being able to interact with metal cations as well as with anionic guests.[2-4] One of the most interesting features of these ligands is the potential convergence of the aromatic ring and the nitrogen atoms into the cavity of the free hosts. Such a preorganization would provide a very specific site for the coordination of substrates. NMR and X-ray crystallography are the most relevant techniques to get structural information for these type of compounds. Molecular modelling could also provide interesting information in this respect. The use of molecular mechanics, even for relatively complex molecules, has been made possible by recent advances in computer technology and has become an essential tool for conformational studies.[5] Molecular mechanics studies have been very useful in the analysis of macrocyclic receptors as well as supramolecular

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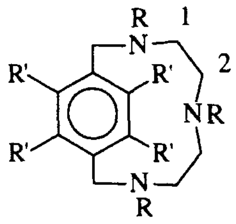
*Corresponding author



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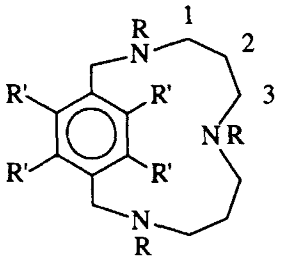

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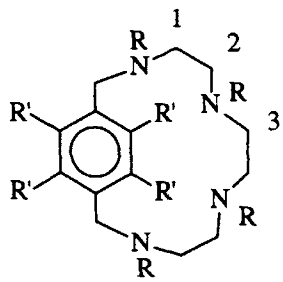

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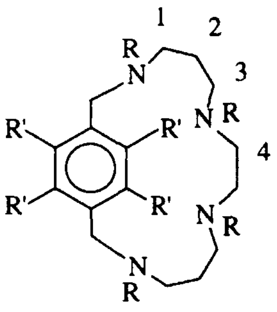

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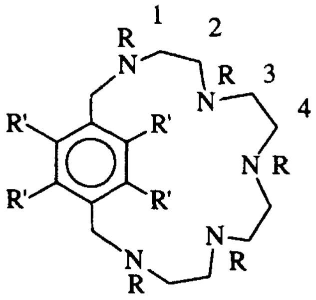

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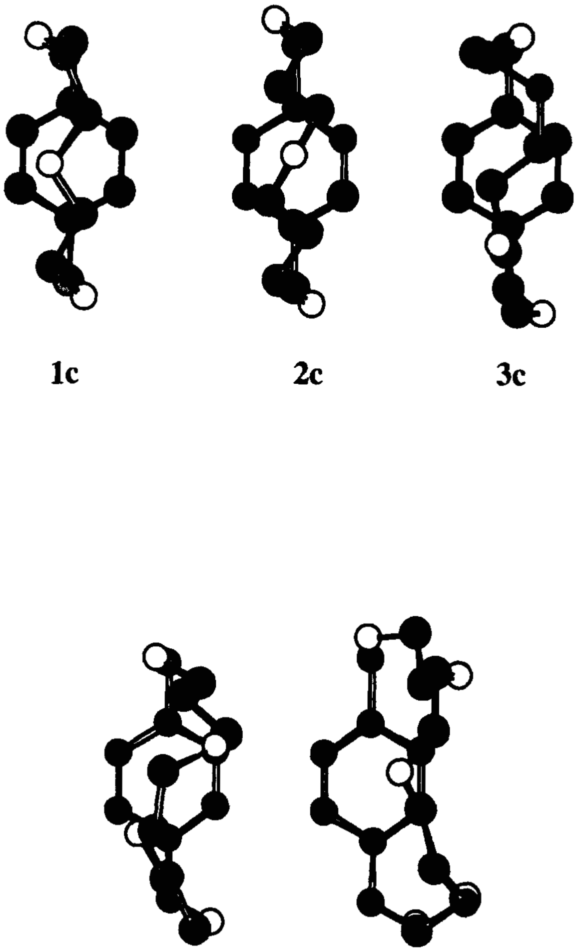
a $R = R' = H$

b $R = H, R' = CH_3$

c $R = Ts, R' = H$

d $R = Ts, R' = CH_3$

complexes.[6-8] In general, macrocyclic structures have a high conformational mobility which hampers localization of minimum energy geometries. However, development of different methodologies for conformational searching has allowed efficient study of conformations of highly flexible molecules, as is the case of cycloheptadecane for which 262 conformations having MM2 energies within 13 kJ mol^{-1} of the global minimum were discovered.[9] Although the small paracyclophanes here considered would not probably have such a high mobility, they present additional structural features, like the presence of several nitrogen atoms or the strain provided by the aromatic spacer, which could difficult molecular modelling. Additionally results have to be applicable



1c 2c 3c

4c 5c

FIGURE 1 Minimum energy conformers for pertosylated polyaza[n]paracyclopanes 1c-5c. Tosyl groups have been omitted for clarity.

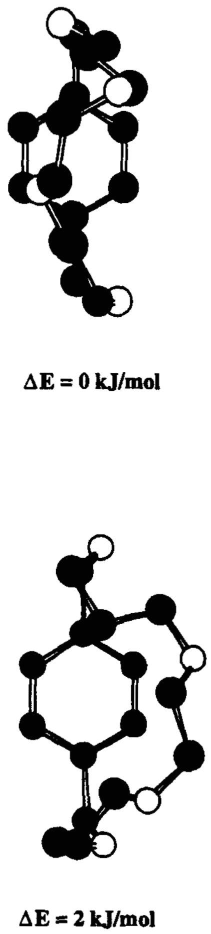


FIGURE 2 Comparison between the lower energy conformer for 4c and the first one showing a displacement of the aliphatic chain from the plane perpendicular to the aromatic ring and containing both benzylic carbon atoms. Energies are relative to the one for the minimum energy conformer.

for analyzing conformations in aqueous solutions where these ligands present high degrees of protonation. Therefore, the use of molecular mechanics calculations to understand the conformational preferences of polyaza[n]paracyclophanes requires a careful study of the different force fields available and their ability to reproduce experimental or crystallographic data. Here we report on the results obtained from molecular mechanics calculations for polyaza[n]paracyclophanes **1–5** (R=H) and their pertosylated analogs (**1–5**, R=Ts). The crystal structure of triprotonated cyclophane **2b** (R=H, R′=CH_3), here reported, has allowed us to check the validity of the modellization results.

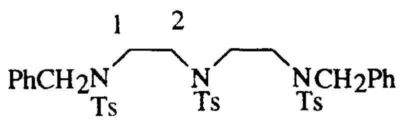
RESULTS AND DISCUSSION

In the first step, we carried out molecular mechanics calculations on pertosylated polyaza[n]paracyclophanes **1–5** (R=Ts). We applied the torsional Monte Carlo method exploited by the BATCHMIN V3.5 molecular mechanics

TABLE I More relevant upfield shifts for cyclophanes **1–4** relative to polyamines **6–9**

Proton	Compound	δ(ppm)	Compound	δ(ppm)	Δδ(ppm)
1	**1c**	2.5	**6**	2.71	0.21
2	**1c**	2.5	**6**	3.15	0.65
1	**2c**	3.03	**7**	2.92	-0.11
2	**2c**	1.19	**7**	1.39	0.20
3	**2c**	2.71	**7**	3.12	0.41
1	**3c**	2.85	**8**	2.77	-0.08
2	**3c**	2.91	**8**	3.26	0.35
3	**3c**	2.95	**8**	2.50	0.45
1	**4c**	3.08	**9**	2.87	-0.21
2	**4c**	1.47	**9**	1.62	0.15
3	**4c**	2.96	**9**	3.10	0.14
4	**4c**	2.74	**9**	3.04	0.30

program, as a part of the MACROMODEL package.[10] Results obtained using the MM2* force field[11] showed that conformations in which the aliphatic chain is arching above of the aromatic ring are prevalent in vacuum or in chloroform (GB/SA approach)[12] solution. Figure 1 shows the minimum energy conformers found in chloroform for pertosylated polyaza[n]paracyclophanes **1c–5c** having chain lengths ranging from 9 to 15 atoms. For the [9], [11] and [12] paracyclophanes all the conformers found within 20 KJ mol^{-1} of the most stable one show similar relative arrangements of the bridge and the aromatic ring. For the larger [14] and [15]paracyclophanes, the conformational search showed the presence of conformations, within a few kJ mol^{-1} of the minimum energy conformer, having the aliphatic chain displaced from the plane perpendicular to the aromatic ring which contains both benzylic carbon atoms. This is illustrated in Figure 2 for the pertosylated tetraaza[14]paracyclophane **B323** (**4c**).



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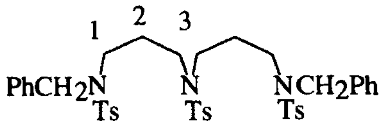

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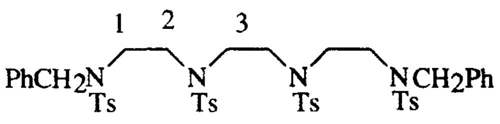

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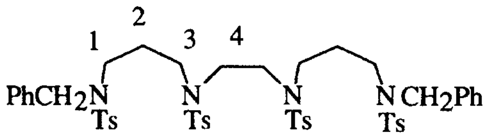

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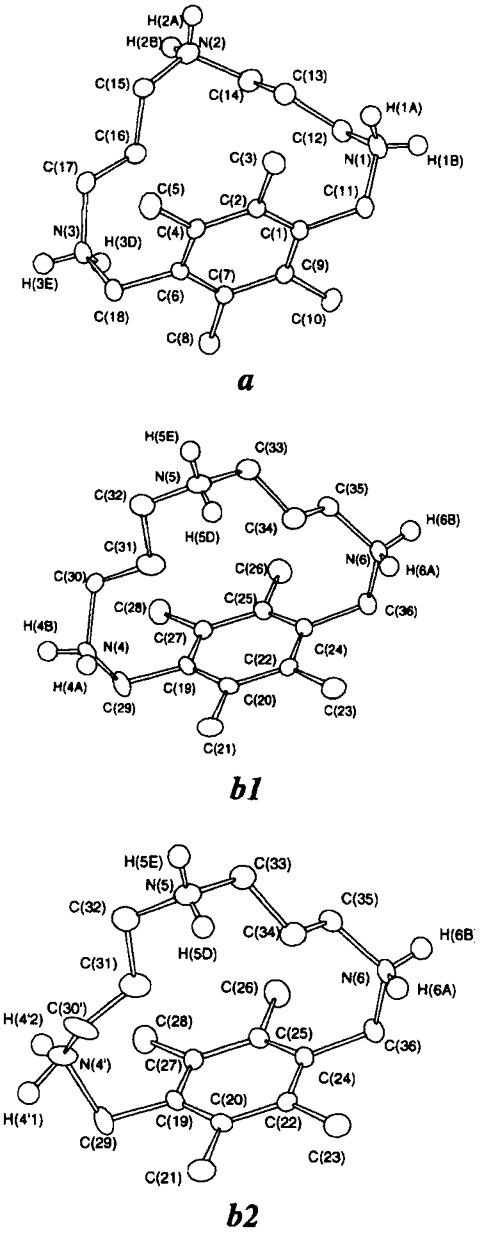
These results are in good agreement with ^1H NMR data that show an important shielding effect of the aromatic ring on the central protons of the chain.[13] As expected, the upfield shift is larger for smaller cyclophanes (see Table 1). Thus, for instance, the central methylene in **1c** is shifted 0.65 ppm upfield relative to the related tosylated dibenzylated open chain polyamine **6**. For **3c** the central ethylene is shifted 0.45 ppm relative to the open chain analogue **8**, and for **4c** the shift is 0.3 ppm. Structural analysis of the minimum energy conformers also reveals the reason for the relatively more effective shielding observed for the central methylene in propylene subunits (in **2c** and **4c** for instance), since these protons are always found at shorter distances from the aromatic ring than other methylene groups of the subunit.

Molecular Mechanics analysis of the non-tosylated polyaza[n]paracyclophanes **1–5 a** and **b** would be more significant in order to understand recognition capabilities of these receptors. This is, however, a more difficult target since these hosts are essentially designed to act in aqueous solutions. So, the solvent can play a fundamental role in determining the most stable conformations and calculations in vacuum could be of little significance. On the other hand polyamines such as **1–5 a** and **b** can be extensively protonated in water which add new difficulties to the achievement of reliable data from molecular mechanics calculations.[4a,6,8]

Comparison of molecular mechanics derived structures with X-ray diffraction structures represents the most general approach for checking the validity of the methodology used in the calculations. In this sense, crystals suitable for X-ray analysis were obtained for the perchlorate salt of the triprotonated derivative of D33.



a

b1

b2

FIGURE 3 ORTEP drawing for conformations present in the X-ray structure of $3H^+{\cdot}2b$.

The molecular structure consists of $H_3(D33)^{3+}(3H^+.2b)$ cations, disordered perchlorate anions and lattice water molecules. Two independent cations *a* and *b* have been found in the asymmetric unit, whose ORTEP [14] drawings are shown in Figure 3. The cation labelled *b* shows two different conformations *b1* and *b2* (Figures 3 and 4) which share the same position (ratio *b1*/*b2* = 57/43) and differ only for the position of the

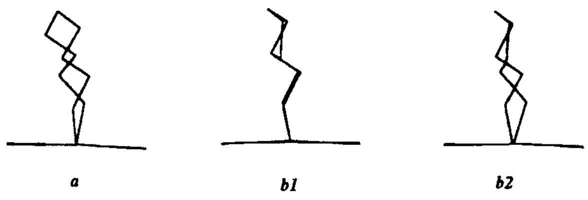


FIGURE 4 Schematic view of conformations present in the X-ray structure of $3H^{+}\cdot 2b$.

N(4),N(4′), C(30), C(30′) atoms. The most important differences between the three conformers are due to the disposition of the aliphatic chain and are schematically shown in Figure 4: the trends of torsional angles (PARST)[15] are approximately consistent in *a* with the presence of a non-crystallographic C_2 axis, through the N(2) atom and the baricenter of the aromatic ring and in ***b1*** with a non-crystallographic symmetry plane passing through the N(2) atom and bisecting the C(20)-C(22), C(25)-C(27) bonds.

Similar strain is present in the three cations, as demonstrated by the bond-angle values (mean values 113.8°, 114.7°, 114.1° for ***a, b1*** and ***b2***, respectively), and it is mostly localized on the nitrogen atom (min/max bond angle values 115.7(4)° for C(17)-N(3)-C(18) in *a* and 129.8(1)° for C(29)-N(4)-C(30) in ***b1***) and on the methylenic carbon atoms adjacent to the aromatic rings (107.6(10)° for C(19)-C(29)-N(4′) in ***b2*** and 116.4(7)° for N(4)-C(29)-C(19) in ***b1***). The angles between the best fit planes described by the three nitrogen atoms and the aromatic ring are 78.7(3)°, 84.6(3)° and 78.8(3)° for ***a, b1*** and ***b2***, respectively.

A systematic MM study was carried out on the structure of triprotonated **D33**, using the different force fields implemented in the Macromodel package: MM2*,[11] MM3*,[16] AMBER*[17] and OPLS*.[18] The torsional Monte Carlo method was applied and results were compared with structures in the crystal. Results are summarized in Table 2. As can be observed molecular mechanics derived struc-

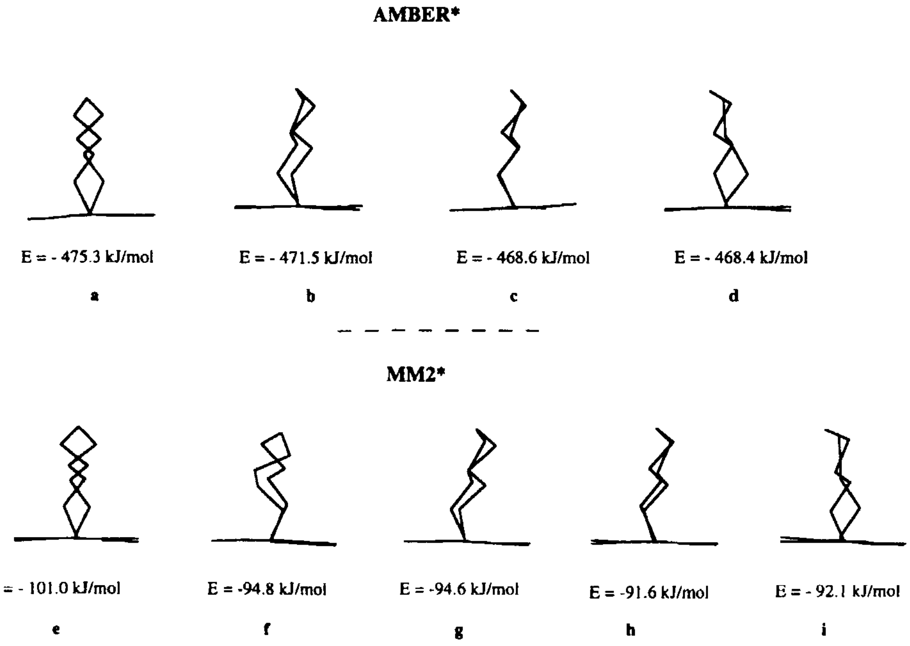


FIGURE 5 Schematic view for the four lower conformers found in the conformational search for $3H^{+}\cdot 2b$. a–d: AMBER* (H_2O); e–i: MM2* (H_2O).

TABLE II Summary of results obtained from molecular mechanics calculations

X-ray structure	Force field	Solvent	Confomer position	Relative energy (kJ/mol)	Superimposition coefficient(Å)
a	MM2*	H_2O	1st	0	0.208
b1	MM2*	H_2O	3rd	6.4	0.292
b1	MM2*	H_2O	4th	9.3	0.259
b2	MM2*	H_2O	5th	9.5	0.245
a	MM2*	vacuum	1st	0	0.217
b1	MM2*	vacuum	2nd	7.8	0.306
b2	MM2*	vacuum	3rd	10.9	0.244
a	MM3*	H_2O	1st	0	0.175
b1	MM3*	H_2O	3rd	7.4	0.271
b2	MM3*	H_2O	4th	14.8	0.196
a	MM3*	vacuum	1st	0	0.180
b1	MM3*	vacuum	2nd	6.91	0.288
b2	MM3*	vacuum	4th	15.25	0.201
a	AMBER*	H_2O	1st	0	0.180
b1	AMBER*	H_2O	2nd	4.79	0.255
b1	AMBER*	H_2O	3rd	6.68	0.247
b2	AMBER*	H_2O	4th	6.94	0.215
a	AMBER*	vacuum	1st	0	0.197
b1	AMBER*	vacuum	2nd	5.68	0.263
b1	AMBER*	vacuum	3rd	7.52	0.274
b2	AMBER*	vacuum	4th	7.83	0.220
a	OPLS*	H_2O	1st	0	0.160
a	OPLS*	H_2O	2nd	2.8	0.185
b1	OPLS*	H_2O	3rd	6.9	0.264
b2	OPLS*	H_2O	4th	12.8	0.205
a	OPLS*	vacuum	1st	0	0.193
a	OPLS*	vacuum	2nd	1.5	0.190
b1	OPLS*	vacuum	3rd	6.2	0.349
b2	OPLS*	vacuum	4th	12.9	0.231

tures reproduce well the crystallographic structures. First of all it is worth mentioning that conformations ***a*, *b1*** and ***b2*** were always found among the most stable families of conformers obtained from calculations. For all force-fields studied, the X-ray structure conformations were present within the five most stable conformers, and the calculated structures reproduced well the folding trends observed in the crystal for the polyamine strand (see Figures 4 and 5). Additionally, correlation coefficients calculated for the aliphatic chain are, in general, below 0.25 for the most stable conformers. For algorithms used by Macromodel, a value below 0.25 is considered an indication that both structures are essentially superimposable, complete superimposition being reflected by a value of 0.[19]

In order to analyze the optimal conditions for molecular mechanics calculations for polyaza[n]paracyclophanes, several points have to be considered. For AMBER* and OPLS* forcefields the four most stable conformers calculated

TABLE III Mean deviations for lengths and angles

X-ray structure	Force Field[a]	Bond angle mean deviation (°)	Bond length mean deviation (Å)
a	MM2*	2.2	0.018
b1	MM2*	2.1	0.031
b2	MM2*	2.0	0.042
a	MM3*	2.5	0.021
b1	MM3*	2.6	0.045
b2	MM3*	3.1	0.045
a	OPLS*	1.0	0.021
b1	OPLS*	1.6	0.035
b2	OPLS*	2.2	0.043
a	AMBER*	1.2	0.019
b1	AMBER*	1.6	0.033
b2	AMBER*	2.0	0.041

a) Water was considered as solvent (GB/SA) approach.

in the conformational search correlate with one of the conformers found in the crystal. The situation is slightly different for MM2* and MM3* force fields, in particular for the first one, as the second conformer in energy is calculated to have folding trends in the polyamine chain that are not related with the ones found in the X-ray structures (see, for instance, structure **f** in Figure 5).

No big structural differences were found when calculations were carried out in vacuum or in water (GB/SA approach), but superimposition coefficients for the structures calculated in water were always better than those calculated in vacuum, so that consideration of the solvent has a positive effect on calculations.[8a]

As can be observed in Table 3, structures of the first calculated conformer of each conformational family found in the crystal (***a***, ***b1*** and ***b2***) reproduce well bond lengths and angles. The mean deviations for bond angles are ca. 2° while mean deviations for bond lengths are in the order of 0.02 Å for conformers ***a*** and 0.03–0.04 Å for conformers ***b1*** and ***b2***.

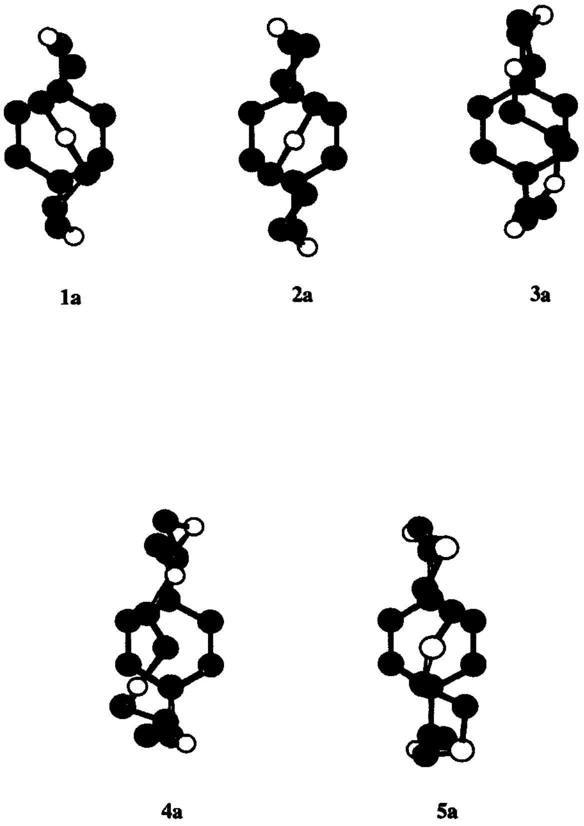
Additional information can be obtained from an analysis of individual bond lengths and angles. As was previously mentioned, X-ray structures showed the presence of a similar strain in all three conformers, ***a***, ***b1*** and ***b2***, strain being mainly localized at the nitrogen atoms and at the benzylic carbon atoms. Relatively similar strain trends were also observed in the calculated structures, the bond-angle mean values being 113.1° (MM2*), 115.2° (MM3*), 114.2° (OPLS*) and 113.8° (AMBER*) for conformer ***a*** (X-ray value 113.8°), 113.6° (MM2*), 115.6° (MM3*), 114.4° (OPLS*) and 114.2° (AMBER*) for ***b1*** (X-ray value 114.7°) and 113.8° (MM2*), 115.9° (MM3*), 114.6° (OPLS*) and 114.5° (AMBER*) for ***b2*** (X-ray value 114.1°). However the four force fields seem to fail partially trying to locate strain, as larger bond angle deviations between observed and calculated structures are found for positions involved in strain in the crystallographic structures. In particular, molecular mechanics calculations do not correctly predict the values of the smallest bond angles found in the crystal structure. This is the case for C(19)-

C(29)-N(4′), for which a value of 107.6(10)° was found in the crystal. The most important deviations are observed for this bond angle, the values calculated ranging from 112.7° for OPLS* force field to 116.2° for MM3*, being this (8.6°) the largest deviation found in the comparison between calculated and X-ray structures. Important differences were also observed for those bond angles which present maximum values in the crystal structures. Thus, for instance, bond angle C(29)-N(4)-C(30) in ***b1*** which presents the maximum observed bond angle value (119.8(1)°) gives place to deviations in the calculated structures ranging from 2.5° for OPLS* to 3.8° for MM3*.

In this respect, MM3* seems to be less accurate in reproducing bond angles. On the contrary, OPLS* andAMBER* force fields reproduce slightly better bond angles, showing a wider range of values. Results are particularly favorable for OPLS* and AMBER* calculations of conformer ***a*** for which deviations are always below 3°. Some larger deviations are observed for ***b1*** and ***b2***.

For bond length values, deviations from the observed structure are similar for the different force fields. Again, maximum deviations occur for positions where strain seems to be present. Comparable deviations are obtained for all distances in conformer ***a***, deviations being smaller for OPLS* and AMBER*. The larger mean value in bond length deviations observed for conformers ***b1*** and ***b2*** originates mainly from bonds C(29)-N(4) in ***b1*** and C(29)-N(4′) in ***b2*** which show the minimum and maximum C-N bond length values and from bond C(30′)-C(31) for ***b2***, the shortest distance observed in the crystal. For these bonds, deviations in the calculated structures are in the order of 0.1 Å.

Most likely the former considerations reflect the limitations of the different force fields to model strain and, probably, the presence of charged nitrogen atoms. Several works have suggested that AMBER* and OPLS* force fields can be superior for calculations involving polyazamacrocyclic species.[6,8]


1a **2a** **3a**

4a **5a**

FIGURE 6 Minimum energy conformers for fully protonated polyaza[n]paracyclophanes 1a–5a.

According to results obtained in calculations involving triprotonated **D33** (***2b***), molecular mechanics calculations were carried out for polyaza[n]paracyclophanes **1–5** (**a** and **b**, R=H, R′=H, CH_3) as well as for the different protonated forms of these compounds using the AMBER* force field and selecting water as the solvent (GB/SA approach). For both, protonated and unprotonated macrocycles, MM calculations showed, as for N-tosylated analogues **1–5** (**c** and **d**, R=Ts), that minimum energy conformers are always those having the aliphatic chain arching above the aromatic ring. Figure 6 shows the minimum energy conformers obtained in this way for fully protonated polyazamacrocycles **1a–5a** (R=R′=H), and can be compared with Figure 1.

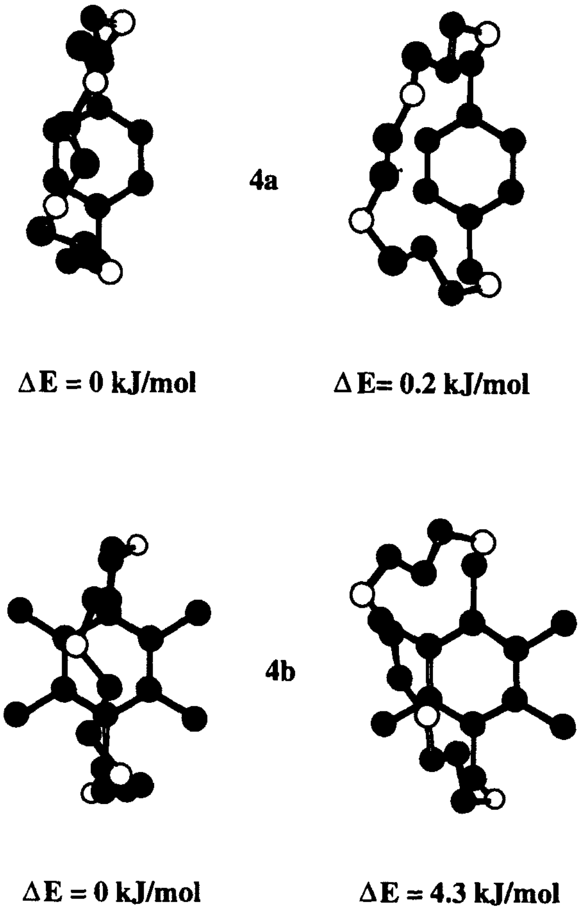


FIGURE 7 Comparison between the lower energy conformers for 4a and 4b and the first ones showing a displacement of the aliphatic chain from the plane perpendicular to the aromatic ring containing both benzylic carbon atoms. Energies are relative to the one for the minimum energy conformer.

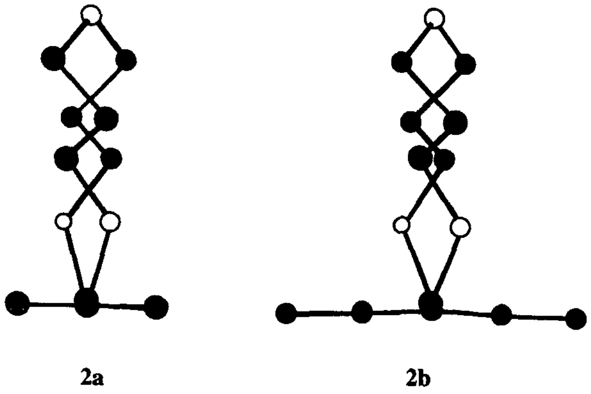


FIGURE 8 Comparison between minimum energy conformers for fully protonated 2a and 2b (AMBER*, H_2O).

However, an important difference with the tosylated compounds is the higher flexibility observed for the polyamine strand, as had to be expected for the absence of the bulky tosyl groups. In this sense, the total number of conformers found for a given energy interval was always larger for polyaza[n]paracyclophanes **1–5** (**a** and **b**) than for their pertosylated analogues. Thus, for instance, 75 conformations were obtained for **3b** (**D222**) within 20 kJ mol^{-1} of the lower energy conformer but only 20 conformations were detected for the pertosylated compound **3d**. Protonation seems to reduce conformational flexibility of the chain, and accordingly the number of conformers detected within the 20 kJ mol^{-1} energy interval was lower: 60 conformations were only detected for tetraprotonated **3b**. The higher degree of preorganization obtained upon protonation of the nitrogen atoms can be important in order to understand the potential of these compounds to act as selective anion receptors.[2,3a,20]

Again, for the larger macrocycles, the conformational search found, within the energy range considered (20 kJ mol^{-1}), the presence of conformers with the aliphatic chain displaced from the plane perpendicular to the aromatic ring which contains both benzylic carbon atoms, but in this case, the energy difference between both types of conformers can be very low. This is the case of tetraprotonated **B323** (**4a**) (see Figure 7 a and b), for which the energy difference between the most stable conformer and the first one having the aliphatic chain almost completely displaced from above the aromatic ring was calculated to be only 0.2 kJ mol^{-1}. Very similar trends were obtained for benzene and durene derivatives, and minimum energy conformers found by calculations have almost identical conformations of the aliphatic chain as is illustrated in Figure 8 for fully protonated **B33** (**2a**) and **D33** (**2b**). The presence of the methyl groups in durene derivatives plays, however, an important role reducing the mobility of the chain in order to avoid unfavorable steric interactions. This is clearly shown in Figure 7 in the comparison between fully protonated **B323** (**4a**) and **D323** (**4b**). For the durene derivative, the energy difference between the minimum energy conformer and the first one having the polyamine strand out of the mean plane perpendicular to the aromatic ring is much higher (4.3 kJ mol^{-1}) than that observed for the case of **B323** (**4a**) (0.2 kJ mol^{-1}). In good agreement with these results, the total number of conformers detected for durene derivatives was always smaller than that for benzene derivatives for a given energy interval.

CONCLUSIONS

Molecular Mechanics calculations represent a very useful tool in order to predict conformations in polyaza[n]paracyclophanes **1–5**. For the cases considered, the aliphatic chain of these compounds is predicted to occupy, in the minimum energy conformers, the plane perpendicular to the aromatic ring which contains both benzylic carbon atoms. This situation is similar for tosylated and non-tosylated cyclophanes as well as for protonated macrocyclic polyamines and confirms structural factors considered for the design of these receptors. The X-ray structure of the triprotonated **D33** allows one to check the validity of the molecular mechanics calculations for these compounds. The X-ray structure confirms that the polyamine strand is situated above the aromatic ring. OPLS* and AMBER* force fields seem to give more accurate results than MM2* and MM3*. The poor modelling of ammonium groups by MM2* and MM3* can be important in order to understand these results. The minimum energy conformers calculated with the MM2*, MM3*, AMBER*, and OPLS* force fields, as implemented in the Macromodel package, reproduce appropriately the experimental structures found in the crystal, in terms of folding tendencies of the chain and values of bond distances and angles. In general, consideration of the solvent, using the GB/SA approach gives better results as can be observed by the use of superimposition coefficients. Similar results are obtained for benzene and durene derivatives, but the presence of the methyl groups on the aromatic ring produces a higher degree of preorganization, limiting the mobility of the polyamine chain, and a similar decrease of mobility seems to be produced upon protonation of the nitrogen atoms. The highest degree of preorganization is always observed for pertosylated systems **1–5** (**c** and **d**).

EXPERIMENTAL SECTION

Crystal Data for $[H_3 2b](ClO_4)_3 \cdot 0.5H_2O$.

$C_{18}H_{35}Cl_3N_3O_{12.5}$, M = 543.74. Triclinic, a = 11.758(4)Å, b = 13.870(5)Å, c = 17.181(3)Å, α = 96.66(2)°, β = 106.02(2)°, γ = 104.87(3)°, V = 2550(1)$Å^3$ (by least-squares refinement of diffractometer setting angles of 25 carefully centered reflections, λ = 0.71069Å), space group $P\bar{1}$, Z = 4, Dc = 1.42 Mg/m^3. Prismatic colorless crystals. Crystal dimensions 0.6 × 0.5 × 0.5 mm, μ(Mo-Kα) = 4.20 cm^{-1}.

Data Collection and Processing

Enraf-Nonius CAD4 diffractometer, $\theta/2\theta$ scan mode with θ scan width = 0.6 + 0.34 tgθ, \theta speed 4.1 deg min^{-1}, graphite monochromatized Mo-Kα radiation, T 298 K; 8184 reflections measured ($2.52 < \theta < 24.97°$, + h, + k, l), 5969 unique with $I > 2.0\sigma(I)$. Two standard reflections monitored: no loss of intensity observed. Lorentz and polarization effects correction applied.

Structure Analysis and Refinement

Direct method. Absorption correction applied once the structure was solved. Two independent molecules found in the asymmetric unit. Fullmatrix least-squares refinement with all non-hydrogen atoms anisotropic and the hydrogen atoms in calculated position with overall, fixed temperature factors U = 0.103Å^2 for the methylic and U = 0.067Å^2 for the methylenic ones. The ΔF map did not allow to localize the hydrogen atoms bound to the oxygen of the solvent and to the nitrogen atoms of the ligand. These ones have been introduced in calculated position with overall, fixed thermal parameters U = 0.067Å^2. For both N4 and C30 two different position found and refined with partial population parameters (0.57 and 0.43 for N4, C30 and N4′,C30′, respectively). Disorder found in some perchlorate molecules. Double position with population parameter 0.5 refined for the O42, O42′, O44, O44′ and O51, O51′ oxygen atoms belonging to the fourth and fifth perchlorate molecule, respectively, and with population parameters 0.58 and 0.42 for the C16, O62, O63 and C16′, O65, O66 atoms, respectively, of the sixth perchlorate molecule, while the O61 and O64 atoms have been refined with whole population parameter. Function minimized: Σ $w(|Fo|^2 - |Fc|^2)^2$, with the weighting scheme calculated in agreement to the resolution program (weighting factors 0.1121 and 2.25). Final R and wR^2 values are 0.072 and 0.18 for 742 refined parameter. Programs used and sources of atomic scattering factors and anomalous dispersion corrections are given in Reference 21.

The crystal cell contains two indenpendent cations ***a*** and ***b1*** or ***b2***. The planes containing the aromatic rings of both independent cations ***a*** and ***b*** are nearly coplanar, the dihedral angle being 6.25°. The aromatic groups belonging to symmetry related cations are 4.7 Å and 5.3 Å apart from each other for ***a*** and ***b***, respectively. An extensive H-bonding network relates the cations, the counterions and the water molecules.

Molecular Modelling Calculations

The calculations with the MM2*, MM3*, AMBER* and OPLS* force fields were performed with version 3.5X of MACROMODEL on a HP7000 or a Indy Workstation of Silicon Graphics.[10] These force fields were used as implemented in Macromodel without modification of any of the parameters. Standard parameters, cut-off distances and charges were used as present in MACROMODEL. The GB/SA solvation treatment was considered, when necessary, for chloroform or water.[12] Starting geometries were drawn manually in the Input mode of the program and the torsional Monte Carlo method exploited by the BATCHMIN V3.5 molecular mechanics program was used for the conformational search. Structures were minimized using the conjugate gradient minimization with the Polak-Ribiere first derivative method and the convergence criterion was a value of 0.05 kJ mol^{-1} Å^{-1} for the root-mean-square of the gradient. All structures were characterized as true minima. For each conformational search 500 to 1000 structures were generated and minimized to yield, in general, a high number of unique conformers. The energy interval was selected from 20 to 50 kJ mol^{-1}. The number of unique conformers was dependent on the nature of the structure under study, and was much lower for tosylated compounds **1–5** (**c** and **d**) (293 conformers for **D33** (**2b**) and 183 for its tosylated analogue (**2d**) within 50 kJ mol^{-1} of the lower energy conformer). Some differences, at this respect, were also observed between neutral and protonated polyamines (212 conformations were obtained for 3H$^+$.**D33** in the 50 kJ mol^{-1} interval) and between benzene and durene derivatives (276 conformations found for tosylated **B323** (**4c**) and 182 for tosylated **D323** (**4d**) within 50 kJ mol^{-1} of the most stable conformer). For the more significant energy interval of 20 kJ mol^{-1} the number of conformers ranged from 10–20 for tosylated compounds and smaller cyclophanes to ca. 150 for large untosylated macrocycles. Conformational searches were carried out in duplicate, in most cases, starting from different geometries, a good convergence of results being obtained for all cases.

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