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Conformational Analysis of [12]aneN_4 (1,4,7,10-Tetraazacyclododecane) and [14]aneN_4 (1,4,8,11-Tetraazacyclotetradecane) Using Molecular Mechanics and ab Initio Methods

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The macrocyclic polyamines [12]aneN_4 and [14]aneN_4 have been investigated using molecular mechanics (MM3) and ab initio quantum chemical methods. Molecular mechanics conformational searching was performed using two schemes, and the lowest energy minima were submitted to HF/6-31G** ab initio calculations. Differences between molecular mechanics and ab initio results are discussed, with emphasis on intramolecular interactions, most notably intramolecular hydrogen bonding and electrostatic interactions. MM3 gives structures that agree well with the ab initio structures but is unable to reproduce subtle effects governing the ab initio energetic order of rotamers. Basis set dependence and influence of electron correlation is also investigated for [12]aneN_4.

Introduction

Since the discovery by Pedersen[1] of crown ethers as interesting agents for selective complexation of metal ions, a large number of macrocycles have been synthesized. Not all of these are based on the ether functional group, and a large number of other functional groups are now used for selective metal ion complexation.[2,3] Well-known examples of nitrogen donor macrocycles are [12]aneN_4 and [14]aneN_4, whose conformational properties in the free (uncomplexed) state are reported in this study.

Despite the large interest in these macrocycles and the number of applications of its derivatives, there has been relatively little research to investigate the conformational properties of the macrocycles. Most of it is done using molecular mechanics, and ab initio work is largely limited to those structures that are found in metal complexes. Earlier ab initio work by Hannongbua and Rode and co-workers[4,5] is mostly limited to the geometries of [12]aneN_4 that are found in metal complexes or is limited to only partial geometry optimizations. Ribeiro-Claro et al.[6] have published ab initio work on the present macrocycles.

The rather limited number of structures considered and the relatively small basis set used make a reinvestigation of the conformational properties of the macrocycle necessary, and this is the scope of the present article.

Methods and Computational Details

Molecular Mechanics. Locating the lowest lying minima of molecules such as [12]aneN_4 or [14]aneN_4 is not straightforward due to the high number of degrees of freedom. This makes scanning the potential surface for minima quite difficult using ab initio methods. Several approaches toward locating different minimum energy structures are possible. Ribeiro-Claro et al.[6] chose to use information obtained for smaller systems as input for obtaining initial guesses at low energy minima for the larger macrocycles. We have chosen, in an attempt to get a better picture of the position of different low energy minima and stability determining effects, to use a systematic as well as a stochastic method for locating different minima on the molecular potential energy hypersurface.

Extensive conformational searching for molecules such as the ones discussed here is not yet feasible on ab initio level using sufficiently large basis sets. A method that combines high computational speeds with relatively good results (although bypassing the subtleties governing the conformational properties of macrocycles[6]) is molecular mechanics. In this work, extensive conformational searching was done using the MM3 force field and using the MM3(94) and MM3(96) releases of the MM3 program.[7,8]

In a first approach, we used a systematic method to locate different minima. A Z-matrix for the ring atoms was constructed, where each atom x ($x > 1$) was connected to atom (x-1); for $x > 2$ a valence angle x_(x-1)_(x-2) and for $x > 3$ a dihedral angle x_(x-1)_(x-2)_(x-3) is given. All bond lengths in the ring, as well as the valence angles were given standard values. Dihedral angles were developed in a grid with step size of 60°. By checking if the distance between the first and the last atom in the ring is smaller than 1.5 times a standard value for a bond of that type, we checked if the chain of atoms obtained using this method still represents a cyclic structure. This criterion was found to be a good balance between overlooking too many possibly interesting structures and taking into account too many structures that do not yield cyclic structures when further optimized. When a certain structure was found to fall within the criterion of being cyclic, the carbon atoms in the ring were saturated with hydrogen atoms. For each ring geometry, different spatial arrangements are possible for the hydrogen atoms on the nitrogen atoms. For a certain ring geometry, a best fit plane was calculated through the four nitrogen atoms, and each amine hydrogen atom was placed above (+) or under (−) the plane. All combinations of + and − for the four hydrogen atoms were constructed, and for each a specific complete macrocyclic structure was made. This geometry was then submitted to MM3 geometry optimization. The resulting minimum (if one was

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found) was kept in a structure file, together with energy, symmetry point group, and atomic coordinates.

As was stated by Saunders,[9] the quality of the potential hypersurface scan depends quite strongly on the step size used in systematic methods (here 60°). If this step size is too large, minima can be overlooked. Smaller step sizes make conformational searching for molecules as the ones considered here too computationally demanding. To alleviate this problem, we supplemented our list of minima with those obtained using the stochastic method of Saunders.[9] With this method, the structure of the molecule was optimized, obtaining one stationary point, after which the atoms were kicked randomly, and the structure obtained was reoptimized. The MM3 program automatically produces a library of structures. The number of kick-optimized sequences was limited to 200, using step sizes of maximally 2 Å. First a structure in which all ring atoms (C and N atoms) lie in the same plane was drawn. On the basis of this structure, we then made all possible structures differing in the relative amine hydrogen atom positions toward the ring. These geometries were then used as starting points for stochastic searches. For each of these series of optimizations, after a first stochastic search, the number of minima was examined, together with the number of times every minimum was found. After each search, the lowest energy minimum that was found only once was used as a starting geometry for a new stochastic search. For [12]aneN_4, conformational searching was considered converged if all minima were found at least twice, and for [14]aneN_4 we considered the conformational search converged if all minima with relative energy under 10 kcal/mol were found at least twice. For both molecules, all minima found in the different searches were combined in one large structure library together with the results of the systematic search. Redundant minima were removed by inspecting interatomic distance matrixes.

Ab Initio Calculations. Ab initio calculations were performed using the GAMESS[10] and BRABO[11] ab initio programs. These were compiled on a set of three IBM RS/6000 machines working in parallel using TCGMSG[12] for GAMESS and PVM[13] for BRABO. Hartree−Fock level calculations were carried out using different basis sets, each on geometries fully optimized using that same basis set. Basis set primitive exponents and coefficients were taken directly from the built-in values of GAMESS.

The BRABO program was used for the geometry optimizations. GAMESS was used for calculations of natural population charges with the NBO 4.0 package[14] linked to it. Gaussian94[15] was used for the calculation of normal modes.

The BRABO program is especially useful for calculations involving a high number of basis functions, since it includes the MIA approach.[11] This approach is a combination of Direct SCF[16] and the Multiplicative Integral Approximation.[17] The result of an SCF calculation using the MIA approach is systematically of equal quality as a classic SCF calculation, whereas the speed of a MIA-SCF calculation is much higher than that of a classic calculation.

Results and Discussion

A. [12]aneN_4. *1. Molecular Mechanics Calculations.* Earlier ab initio studies on [12]aneN_4 considered only a few geometries of the free macrocycle, mostly geometries that allow formation of complexes with metal ions (e.g., Hannongbua et al.[4,5]). The study by Ribeiro-Claro et al.[6] focused among other macrocycles on free [12]aneN_4. No intensive conformational searching was done in their study, since knowledge of the conformational preferences of smaller macrocycles was used as input to find interesting (meaning low-energy) conformers of the larger macrocycles. Furthermore, only relatively small basis sets (3-21G quality) were used, and we previously found the 3-21G and similar basis sets to be severely lacking for ethylenediamine and 1,3-propanediamine.[18] These molecules may be seen as building blocks of macrocycles such as [12]aneN_4.

TABLE 1: MM3 Relative Energies (RE, in kcal/mol) of the 25 Lowest Energy Minima of [12]aneN_4 Together with the Description of Their Geometry and Symmetry Point Group of the MM3 Optimized Structure

no.	conformation	sym	RE	no.	conformation	sym	RE
1	0++ 0++ 0++ 0++	C_2	0.00	14	+0+ +- - 00+ +0+	C_1	4.33
2	0-- 00+ +- - 0- -	C_1	2.27	15	-0- 00+ 0++ 00-	C_s	4.34
3	00+ +0+ +0+ +- -	C_1	2.37	16	00- 0- - 00+ +0+	C_1	4.34
4	+0+ +0+ +0+ +0+	C_1	2.40	17	+- - 00+ +- - 00+	C_{2v}	4.53
5	-0- -0- -0- -0-	C_1	2.72	18	+0+ 00- 0- - 00+	C_1	4.54
6	0++ 00- -0- -++	C_s	3.21	19	-++ 00- -++ 00-	C_s	4.59
7	0++ 00- -++ 0++	C_1	3.24	20	00+ 0++ 00- -0-	C_s	4.69
8	00+ +- - 0- - 0- -	C_1	3.31	21	-0- -0- -++ 00-	C_1	4.69
9	00+ +- - 0- - 0- -	C_1	3.37	22	0++ 00- -0- -++	C_s	4.70
10	00+ 0++ 00- -0-	C_s	3.97	23	+0+ +0+ +0+ 00-	C_1	4.81
11	0- - 0- - 0- - 0- -	C_1	4.07	24	-0- -0- -++ 00-	C_1	5.04
12	+0+ +0+ 00- +0+	C_1	4.27	25	00- -++ 00- -++	C_{2v}	5.11
13	00+ +- - 0- - 0- -	C_1	4.31				

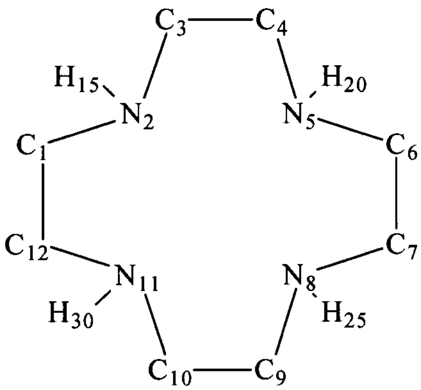

Figure 1. Atom numbering in [12]aneN_4 (hydrogen atoms on carbon not displayed).

MM3 conformational searching, using 79 stochastic searches and the systematic search yielded a set of 992 minima. Table 1 presents the results of the MM3 calculations for the 25 minima with lowest relative energy. The MM3 relative energies of all these minima are within 5 kcal/mol, except for minima 24 and 25 which have a relative energy of just above 5 kcal/mol. The conformation description of the geometries is based on that introduced by Hay et al.[19] The first code letter (a +, −, or 0) is used for the dihedral angle about the C1−N2 bond, the second is for the C1−N2−C3−C4 angle, and so on. A + means that the dihedral angle has a value between 0 and 120 degrees, a − means between 240 and 360 degrees, and 0 refers to a dihedral angle between 120 and 240 degrees. Atom numbering is shown in Figure 1.

Table 1 reveals a C_2 symmetry geometry as the global minimum of the molecule. A probable reason for the stability of this structure is the presence of four N···H interactions in which the distance between the noncovalently bonded nitrogen and hydrogen atoms is less than the sum of the van der Waals radii. Internuclear N···H distances in this C_2 structure are 2.44 and 2.56 Å, respectively, whereas the sum of van der Waals radii is 2.70 Å. The presence of these interactions is reminiscent of the smaller polyamines, such as ethylenediamine.[18] All this may indicate hydrogen bonding, but a more in depth study of the intramolecular interactions, and the ability of MM3 to

TABLE 2: Experimental, MM3, and HF/6-31G Values (in deg) for the Dihedral Angles around the Bonds in the Macrocyclic Ring of the Global Minimum of [12]aneN$_4$ (C_2 Symmetry)**

	C1−N2	N2−C3	C3−C4	C4−N5	N5−C6	C6−C7
exp	−160	71	62	−165	81	62
MM3	−160	77	60	−165	80	60
HF/6-31G**	−160	82	62	−164	74	59

reproduce these, will be presented below. All other rotamers of [12]aneN$_4$ have relative energies higher than 2 kcal/mol.

Similar to ethylenediamine is the presence of gauche NCCN conformations, meaning the preference of the NCCN chains to adopt dihedral angles of approximately 60 or −60°. The "Gauche-effect"[20] often stabilizes the gauche conformation of XCCY dihedral angles (where X and Y are both electronegative elements). We previously found it to be an important stabilizing term in ethylenediamine.[18] In case of a macrocycle such as [12]aneN$_4$, it is not possible to assess the importance of the gauche effect as a leading reason for the presence of gauche NCCN conformations. One cannot simply change the conformation of the NCCN angle from gauche to trans, keeping bond distances and valence angles in the rest of the molecule equal, and as a consequence the energy difference between the two possible conformations cannot be attributed to the gauche effect. The preference for gauche NCCN orientations may simply be a consequence of larger steric strain induced in the ring when trans NCCN arrangements are present. It should be noted in this context that trans NCCN arrangements were found only in higher energy conformations (the lowest energy rotamer with a trans NCCN dihedral angle has a relative energy of 7.6 kcal/mol. Trans NCCN angles are moderately abundant only in rotamers with relative energies over 12.5 kcal/mol).

Few experimental results could be found that focus on the conformational properties of the free macrocycle. Searching of the Cambridge Structural Database (CSD)[21] revealed several crystallographic studies in which the 1,4,7,10-tetraazacyclododecane entity is found. Most of these studies, however, deal with molecules containing this entity but with functionalized groups attached to the entity. These functional groups clearly influence the conformational properties of the free macrocycle and can as such not be used to investigate the agreement between experiment and calculation. Reibenspies et al.[22,23] published two studies in which they used crystallography to identify the structure of the free macrocycle (CSD codes, respectively, VUCGEF and SEFREA). Only the VUCGEF structure qualifies for a direct comparison with the calculated structures. The SEFREA structure was found for the macrocycle in salt-form and is a tetracation. The VUCGEF structure (found for 1,4,7,10-tetraazacyclododecane trihydrate) agrees not only qualitatively with the MM3 calculated global minimum, but Table 2 shows that there is very good quantitative agreement between the experimental values for the dihedral angles in the macrocyclic ring and the MM3 calculated ones.

2. *Ab Initio Calculations.* Starting from the MM3 optimized geometries HF/6-31G** geometry optimizations were performed. No symmetry restrictions or other restrictions on the molecular geometry were employed, thus yielding fully optimized structures. The energetic order of the different minima obtained using the HF/6-31G** geometry optimizations is given in Table 3. The global minimum is still the C_2 geometry. The MM3(2) structure remains the second lowest energy minimum on the HF/6-31G** level, but the agreement in the rest of the energetic order is worse [MM3(x) denotes the xth minimum in the MM3 determined energetic ranking of rotamers, see Table 1]. The most pronounced differences are for the MM3(12) and MM3(20) geometries which are highly stabilized. On the other hand, we find that the MM3(4) structure has a much higher relative energy on the HF/6-31G** level than on the MM3 level. Also remarkable is the lowering of the relative energy of the MM3(25) geometry. For most other minima, the relative energies with respect to the global minimum do not change more than 2 kcal/mol between the MM3 and the HF/6-31G** calculations. The poorer performance (as compared to the agreement in structural features, see below) of the MM3 calculations in obtaining the energetic order of minima is the reason 25 minima were chosen for the ab initio calculations. Including fewer could possibly result in too biased conclusions drawn from the ab initio calculations. Further inclusion of MM3 minima results in too large computational requirements.

At this stage, it is interesting to compare structural features between the MM3 and the HF/6-31G** levels of calculation. Valence angles and dihedral angles are compared directly, but for bond distances, care should be taken because MM3 and ab initio calculations use different types of bond lengths. MM3 optimizations are done in r_g, whereas ab initio calculations yield r_e values (see e.g., Hargittai[24] for the definition of different types of bond lengths). The MM3 program, used in full matrix optimization of the molecular geometry, also calculates $r_{e,MM3}$ values from the $r_{g,MM3}$ values used in the actual optimization. Tables 4−5 show the MM3 and ab initio determined structural parameters for the five lowest energy minima. Analysis of both tables shows that there is fine agreement between the MM3 and HF/6-31G** calculated values. r_e bond distances differ on average 0.009 Å for N−C bonds and 0.006 Å for C−C bonds. CCN and CNC valence angles differ 1.29° and 1.82° on average, and even the dihedral angles show a very good agreement (2.86 ° and 1.55° differences on average for CNCC and NCCN dihedral angles). At least for the calculation of molecular geometries, we may conclude that the MM3 force field is very well parametrized.

Experiments do not yield r_e values but often give r_g values. The latter are also used in MM3. Ma et al.[25] have proposed a method that allows us to obtain $r_{g,ai}$ (the subscript ai refers to "ab initio") values from the $r_{e,ai}$ values using a simple, yet empirical formula. They studied several small molecules at high levels of theory and using extended basis sets. These yielded "converged" $r_{e,ai}$ distances. Using an empirical constant C, they derived the following simple formula to obtain $r_{g,ai}$ distances from MP2/6-31G* calculated $r_{e,ai}$ values:

$$r_{g,ai} = r_{e,ai} + (r_{g,MM3} - \mathrm{r}_{e,MM3}) + C \qquad (1)$$

$r_{g,ai}$ is obtained from $r_{e,ai}$ by adding the MM3 difference in r_g and r_e. The empirical constant C accounts for the differences in basis set truncation and treatment of electron correlation between the MP2/6-31G* calculated r_e values and the "converged" r_e values (calculated at CCSD level with extended basis sets). Since our work yielded HF/6-31G** r_e values, we have used the same formula (eq 1) but have re-derived a value for C by adding to it an extra term, accounting for differences in basis set truncation and treatment of electron correlation between the HF/6-31G** and MP2/6-31G* levels. This extra term was evaluated from calculations on ethane, methylamine, and dimethylamine (i.e., the same molecules as used by Ma et al.[25] for their determination of C). Using our values for C, knowledge of $r_{e,MM3}$ and $r_{g,MM3}$ from our MM3 calculations, and the $r_{e,ai}$ values, we calculated $r_{g,ai}$ values. Depending on the type of bond involved, the following values of C were used: 0.008 (N−H), 0.007 (N−C), 0.000 (C−H), and −0.006 (C−C). Tables 4−5

TABLE 3: Relative Energies (in kcal/mol) Calculated at the Different Levels of Theory[a]

conformation	HF/6-31G**	HF/3-21G(N*)	MP2/6-31G**	MM3 position	configuration
0++ 0++ 0++ 0++	0.00[b]	0.00[b]	0.00[b]	1	$(2+2)_D$
0- - 00+ +- - 0- -	1.50	1.89	0.67	2	$(2+2)_D$
+0+ +0+ 00- +0+	2.47	3.24	2.06	12	$(2+2)_D$
00+ 0++ 00- -0-	2.85	3.42	1.84	20	$(2+2)_D$
00+ +0+ +0+ +- -	3.00	3.12	3.05	3	$(2+2)_D$
0++ 00- -0- -++	3.23	3.62	2.92	6	$(2+2)_D$
00- -++ 00- -++	4.02	4.72	2.89	25	$(2+2)_D$
-0- -0- -0- -0-	4.55	5.36	4.98	5	$(2+2)_{ND}$
0++ 00- -++ 0++	4.56	5.23	3.45	7	(3+1)
+0+ 00- 0- - 00+	4.68	5.72	4.43	18	$(2+2)_{ND}$
00+ +- - 0- - 0- -	4.88	6.06	4.70	8	$(2+2)_{ND}$
+0+ +0+ +0+ 00-	5.02			23	(3+1)
+0+ +0+ +0+ +0+	5.12	other	5.27	4	(3+1)
00+ 0++ 00- -0-	5.17	6.03	4.72	10	(3+1)
00+ +- - 0- - 0- -	5.37	1.89	4.95	9	(3+1)
+0+ +- - 00+ +0+	5.48			14	$(2+2)_{ND}$
00- 0- - 00+ +0+	5.71			16	$(2+2)_{ND}$
-++ 00- -++ 00-	5.95			19	(3+1)
0- - 0- - 0- - 0- -	5.99	other	7.29	11	(3+1)
+- - 00+ +- - 00+	6.06			17	$(2+2)_D$
-0- -0- -++ 00-	6.07			24	(3+1)
00+ +- - 0- - 0- -	6.32			13	$(2+2)_{ND}$
0++ 00- -0- -++	6.55			22	(3+1)
-0- 00+ 0++ 00-	7.05			15	(3+1)
-0- -0- -++ 00-	7.54			21	(3+1)

[a] HF/3-21G(N*) and MP2/6-31G**//HF/6-31G** calculations were carried out on a subset of conformations (see text). “Other” means that the optimization, using the level of calculation indicated, converges to another minimum than the MM3 of HF/6-31G** optimized geometry from which it was started (see text). MM3 position refers to the energetic ranking of a specific geometry on the MM3 level (see Table 1). Configuration refers to the orientation of Lone electron pairs and amine hydrogen atoms in the macrocyclic cavity of [12]aneN_4. See Figure 2 for abbreviations and their meaning. MM3(17) has a favorable configuration, but high steric strain. [b] Energies for the global minimum: −532.373068 Hartree (HF/6-31G**), −529.542014 Hartree (HF/3-21G(N*)), and −534.259400 Hartree (MP2/6-31G**//HF/6-31G**).

give $r_{g,ai}$ and $r_{g,MM3}$ values for the five lowest minima. We found that the $r_{g,ai}$ values agree very well with the $r_{g,MM3}$ values, with differences in C−N and C−C bond lengths 0.003 Å on average, which is still better than the agreement between the r_e values calculated on both levels of theory.

As already stated, the differences in the energetic order of minima between the MM3 and HF/6-31G** levels of calculation are more pronounced. Different effects can play a role in this. The gauche effect cannot readily explain this, since all minima exhibit the same number of gauche NCCN arrangements. Intramolecular hydrogen bonding may play a role in [12]aneN_4, together with differences in the extent of hydrogen bonding at both levels of theory. We will therefore first discuss the presence of intramolecular interactions using the ab initio calculations. Unfortunately, for intramolecular interactions, one cannot split the large molecule in monomers and calculate interaction energies or use energy decomposition schemes to identify intramolecular interactions. Neither can one simply control the possibility of hydrogen bonding by changing some geometrical parameter, as is the case in intermolecular interactions, where one can also investigate the interactions by studying the influence of increasing or decreasing distances or changing orientations between monomers. On the other hand, hydrogen bonds, intermolecular as well as intramolecular ones, are often characterized through their effect on vibrational frequencies, or by the (N-)H···N distances that are shorter than the sum of van der Waals distances. Other effects are their preference for linear (N-)H···N angles, the larger atomic charges on the hydrogen atoms involved in the hydrogen bond, and longer N−H bond lengths when the hydrogen atom is involved in a hydrogen bond.

We investigated whether these effects are found in [12]aneN_4, using the HF/6-31G** calculations. We found that there are indeed several (N-)H···N distances that are shorter than the sum of the van der Waals radii. Such short distances occur in many of the rotamers of the macrocycle, but this by itself did not allow us to conclude the presence of hydrogen bonding. These shorter distances may simply be a byproduct of the molecular geometry, which is then caused by other factors. To investigate that these shorter distances are indeed associated with hydrogen bonds, we calculated NPA charges. We found that the charges on the hydrogen atoms involved in such an interaction are indeed somewhat higher. In the lowest energy rotamers, we found that charge differences between the hydrogen atoms involved in a possible hydrogen bond and those that are not, amount to 0.016e and 0.013e, respectively. On the other hand, the MM3(12) and MM3(20) structures, which are highly stabilized when going from MM3 to HF/6-31G** calculations, do not exhibit these differences [respectively, 0.006e and 0.005e for MM3(12) and MM3(20)]. These are quite small numbers and do not prove that their small (N-)H···N distances are in any way due to hydrogen bonding. Furthermore, we did not find the expected trends in N−H bond lengths. Considering all rotamers, we found only a few rotamers where N−H bond lengths are longer when the hydrogen atom is involved in a short-distance (N-)H···N interaction. Another argument against hydrogen bonding are the N−H···N angles. A preference for linear arrangements is expected, with some variation allowed, but in most rotamers the N−H···N angles in the possible hydrogen bonds are as small as 120°. In most rotamers, no vibrational shifts for the N−H stretches were found. Only four rotamers were found where the geometrical conditions are favorable for hydrogen bonding. The MM3(7), MM3(18), MM3(10), and MM3(8) structures exhibit N−H···N angles over 149° and N−H···N distances below the sum of van der Waals radii. These are not among the very lowest energy minima, so we conclude that hydrogen bonding plays only a secondary role.

We then performed a geometrical analysis for all minima studied at the HF/6-31G** level and found a rationale explaining the energetic order of the different minima. Each nitrogen atom in the macrocycle can point its hydrogen atom or its lone pair

TABLE 4: MM3 Optimized Molecular Geometries for the Five Lowest Energy Structures of [12]aneN$_4$[a]

Nr.		C1	N2	C3	C4	N5	C6	C7	N8	C9	C10	N11	C12	
1	r_e		1.4609	1.4606	1.5238	1.4592	1.4591	1.5236	1.4609	1.4606	1.5238	1.4592	1.4591	1.5236
1	r_g		1.4697	1.4693	1.5336	1.4679	1.4678	1.5335	1.4697	1.4693	1.5336	1.4679	1.4678	1.5335
1	a	111.382	114.477	112.068	111.627	114.153	112.660	111.382	114.477	112.068	111.627	114.153	112.660	
1	t		-160.816	76.991	59.719	-164.751	79.826	60.370	-160.816	76.991	59.719	-164.751	79.826	60.370
2	r_e		1.4607	1.4613	1.5262	1.459	1.4571	1.5218	1.464	1.4661	1.5236	1.4581	1.4598	1.5234
2	r_g		1.4694	1.4700	1.5361	1.4677	1.4657	1.5315	1.4729	1.4750	1.5334	1.4667	1.4685	1.5332
2	a	111.438	115.432	112.420	111.386	113.814	111.226	114.232	116.950	113.861	112.154	114.823	113.711	
2	t		154.693	-69.109	-52.928	159.101	-165.436	55.192	71.749	-93.640	-57.296	175.276	-71.440	-57.767
3	r_e		1.4571	1.4589	1.5252	1.4597	1.4598	1.5248	1.4623	1.4599	1.525	1.4623	1.4602	1.5213
3	r_g		1.4657	1.4676	1.5351	1.4684	1.4685	1.5347	1.4710	1.4686	1.5348	1.4711	1.4689	1.5310
3	a	111.100	114.750	110.900	112.801	114.620	111.683	113.047	114.763	112.223	114.011	117.142	114.279	
3	t		163.236	-157.493	52.051	72.091	-157.604	56.761	69.698	-173.238	57.982	96.100	-72.956	-54.879
4	r_e		1.4586	1.4625	1.5259	1.4603	1.4591	1.5242	1.4612	1.4617	1.5242	1.4593	1.4601	1.5261
4	r_g		1.4673	1.4713	1.5358	1.4691	1.4678	1.5341	1.4700	1.4704	1.5341	1.4680	1.4689	1.5360
4	a	114.311	115.312	113.106	113.941	114.694	111.528	111.991	114.273	111.412	112.541	113.732	113.151	
4	t		70.807	-154.169	66.030	76.855	-165.014	59.901	78.075	-159.526	59.676	78.986	-167.726	61.562
5	r_e		1.4597	1.4599	1.524	1.4621	1.4601	1.5238	1.4597	1.4617	1.5242	1.4588	1.4609	1.5265
5	r_g		1.4684	1.4686	1.5338	1.4708	1.4689	1.5336	1.4683	1.4705	1.5341	1.4675	1.4696	1.5364
5	a	114.133	114.853	111.434	111.891	114.122	112.254	112.596	114.401	111.409	112.390	113.942	112.957	
5	t		-74.302	158.367	-60.318	-78.663	165.540	-62.476	-77.093	160.327	-57.932	-78.359	164.595	-63.844

[a] r_e and r_g are distances in Å between the indicated atoms, *a* are bond angles (in deg) in the ring, centered on the atom indicated, and *t* are the torsion angles in degrees with respect to the indicated central bond. Atom numbering is shown in Figure 1.

toward the cavity of the ring. Suppose a simple model, namely, a square in the macrocyclic cavity, where the corners of the square are hydrogen atoms or lone pairs. When the corner is a lone pair, it carries a negative charge; if it is a hydrogen atom, it carries a positive charge. Figure 2 shows different possible arrangements of charges on this square and introduces the nomenclature used. The electrostatically optimal combination of the charges is one where two positive charges and two negative charges form the four corners in a geometry where equal charges are on opposing corners. This is the $(2+2)_D$ geometry (see Figure 2). Less favorable is the $(2+2)_{ND}$ geometry, and least favorable are both (3+1) combinations. (4+0) combinations were not found in the rotamers of [12]aneN$_4$. We then checked if the energetic order could be explained through the order of preference for the electrostatic interaction $[(2+2)_D > (2+2)_{ND} > (3+1)]$, bearing in mind that the view of a true square is only an idealized picture for illustrating our ideas. All lowest energy minima are characterized by a $(2+2)_D$ configuration of the charges. Still in agreement with the electrostatic considerations, higher energy rotamers exhibit a $(2+2)_{ND}$ configuration, which is electrostatically less favorable. Still other rotamers with even higher relative energies have three hydrogen atoms or three lone pairs pointing inside the macrocyclic cavity. The energetic order of the minima on the HF/6-31G** level can thus be explained. Table 3 shows the agreement between energetic order and the configuration of hydrogen atoms and lone pairs. Moreover, the simple model also explains the differences between the MM3 and HF/6-31G** energetic rankings of MM3(12), MM3(20), and MM3(25). These rotamers are stabilized by a $(2+2)_D$ geometry. It is clear that MM3 is unable to reproduce such subtle effects, despite its good performance in yielding macrocyclic structures. The MM3(4) geometry is highly destabilized when going from MM3 to ab initio level, which is because this geometry has an unfavorable (3+1) configuration.

On the other hand, the MM3(7), MM3(18), MM3(8), and MM3(10) still have a relatively low relative energy on the HF/6-31G** level, despite their less favorable hydrogen-lone pair configurations. These geometries were found to be stabilized by hydrogen bonding. The (N-)H•••N distances are below the sum of the van der Waals radii, and the N−H•••N angle is above 149°. Furthermore, the NPA charge on the hydrogen atom involved in the hydrogen bond is larger than those on the other amine hydrogen atoms. For example, for MM3(18), we find that the (N-)H•••N distance is 2.2105 Å, with a N−H•••N angle of 149.00°. The charge on the hydrogen atom involved in the hydrogen bond is 0.022e higher than that of the other hydrogen atoms. Its N−H distance is 0.003 Å longer than the other N−H bond distances. Clearly, the main factor governing the energetic order of the minima is the electrostatic interaction within the macrocyclic cavity. Hydrogen bonding plays a secondary role.

When using molecular mechanics for coordination compounds, quite often charges are put on the donor atoms. These charges are fixed and usually not allowed to vary with conformation. This amount of variation could be especially important for the C, N, and (N)-H atoms, since these are most likely to be given a charge in molecular mechanics calculations. From HF/6-31G** NPA charges, we find that the charges on the (N)-H atoms and the N atoms are only slightly scattered and that the scattering is likely to yield only minor errors when using fixed charges [standard deviations for the charges on C, N and (N-)H are 0.006e, 0.009e, and 0.010e, respectively].

TABLE 5: HF/6-31G Optimized Molecular Geometries for the 5 Lowest Energy Structures of [12]aneN$_4$[a]**

Nr.		C1	N2	C3	C4	N5	C6	C7	N8	C9	C10	N11	C12
1	r_e	1.4537	1.4557	1.5263	1.4479	1.4478	1.5324	1.4537	1.4557	1.5263	1.4479	1.4478	1.5324
1	r_g	1.4695	1.4714	1.5301	1.4635	1.4635	1.5363	1.4694	1.4714	1.5301	1.4635	1.4635	1.5363
1	a	110.739	116.318	111.697	110.247	115.923	115.033	110.737	116.318	111.697	110.248	115.923	115.032
1	t	-159.547	81.986	61.660	-164.055	74.142	59.286	-159.547	81.988	61.660	-164.055	74.142	59.287
2	r_e	1.4528	1.4549	1.5289	1.4445	1.4438	1.5265	1.4558	1.4587	1.5280	1.4482	1.4481	1.5348
2	r_g	1.4685	1.4707	1.5328	1.4602	1.4595	1.5302	1.4716	1.4745	1.5317	1.4639	1.4638	1.5386
2	a	110.953	117.150	111.856	110.594	115.437	110.706	113.234	118.133	112.988	110.276	116.172	115.935
2	t	156.795	-75.058	-54.245	157.644	-160.846	55.156	75.756	-98.994	-59.717	170.478	-66.022	-55.425
3	r_e	1.4490	1.4513	1.5353	1.4477	1.4483	1.5276	1.4558	1.4518	1.5321	1.4492	1.4468	1.5330
3	r_g	1.4646	1.4670	1.5393	1.4634	1.4640	1.5315	1.4715	1.4675	1.5359	1.4650	1.4625	1.5368
3	a	110.725	117.604	110.406	114.787	116.020	110.508	112.441	116.219	110.871	116.313	119.010	117.308
3	t	161.857	-154.403	53.435	70.089	-157.829	56.819	73.522	-172.793	57.346	92.157	-72.407	-55.066
4	r_e	1.4500	1.4536	1.5328	1.4513	1.4484	1.5261	1.4572	1.4557	1.5322	1.4493	1.4520	1.5324
4	r_g	1.4657	1.4694	1.5367	1.4670	1.4640	1.5300	1.4729	1.4715	1.5361	1.4650	1.4678	1.5363
4	a	116.641	117.666	112.084	116.496	116.520	110.272	111.574	116.080	110.696	114.699	115.817	111.292
4	t	68.397	-150.355	68.950	70.419	-163.371	62.086	82.137	-158.753	58.256	74.703	-166.588	65.646
5	r_e	1.4517	1.4477	1.5269	1.4547	1.4490	1.5286	1.4500	1.4522	1.5328	1.4487	1.4530	1.5327
5	r_g	1.4674	1.4634	1.5308	1.4704	1.4647	1.5325	1.4656	1.4681	1.5367	1.4644	1.4687	1.5366
5	a	116.189	116.449	110.213	111.485	115.869	112.716	113.390	116.911	109.954	114.105	115.740	111.121
5	t	-70.788	159.628	-59.814	-80.346	162.582	-63.173	-77.536	161.346	-56.604	-77.842	160.900	-67.263

[a] r_e and r_g are distances in Å between the indicated atoms, *a* are bond angles (in deg) in the ring, centered on the atom indicated, and *t* are the torsion angles in degrees with respect to the indicated central bond. Atom numbering is shown in Figure 1.

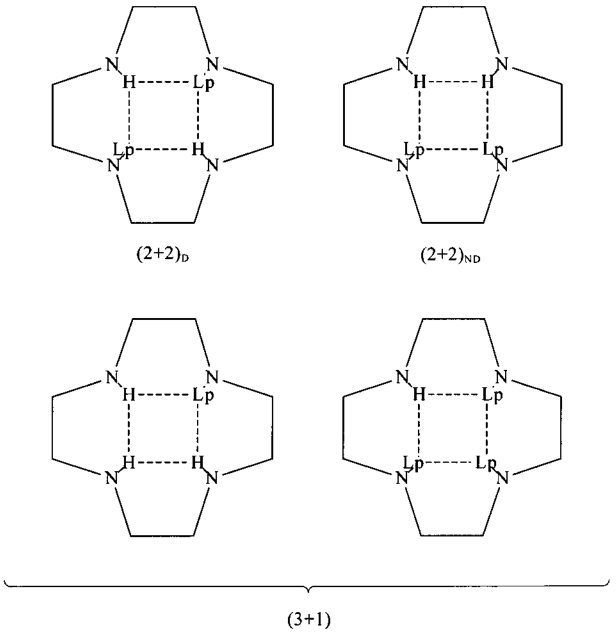

Figure 2. Different configurations of lone electron pairs (Lp) and amine hydrogen atoms in the macrocyclic cavity (illustrated for [12]aneN$_4$). Only the lone pairs and hydrogen atoms pointing toward the cavity are shown.

Given the size of the molecule studied and the number of relatively low energy conformers, quite often ab initio calculations are restricted to relatively small basis sets. In a study by Ribeiro-Claro et al.,[6] basis sets of 3-21G quality were used, including a nitrogen d-type polarization function [exponent 0.8, this basis set will be abbreviated as 3-21G(N*) in what follows]. Another approach is to use effective core potentials to reduce the number of basis functions. The applicability of this approach was examined by Ribeiro-Claro et al.[6] It is of course necessary to find which level of basis set is appropriate to study compounds such as macrocycles, since the quality of studies on macrocyclic complexes and complexation reactions will depend not only on calculations on the complexes but also on the quality of the study of free macrocycles (to study for example preorganization effects). Use of smaller basis sets decreases the computer time, which is especially important for molecules such as [12]aneN$_4$ where ab initio calculations should always be performed for many rotamers. We took the 10 lowest energy minima on molecular mechanics level and supplemented these with the 10 lowest energy minima found on the HF/6-31G** level (given redundancies, this yields 14 structures) and re-optimized their geometry using HF/3-21G(N*) calculations.

On the basis of the 0,+,− conformation descriptions for all minima (except MM3(4) and MM3(11), these structures optimize toward different minima) located using the different basis sets, we found that each minimum has the same qualitative geometry when optimized with the two basis sets. The smaller basis set performs relatively well for the geometries of the different minima. Taking numeric values of the dihedral angles in the ring as a measure of the agreement between the optimized geometries for the different basis sets and taking the HF/6-31G** geometries as reference, we found that the HF/3-21G-(N*) CNCC and NCCN dihedral angles differ on average 3.12° and 1.71°. The agreement between the energetic ordering is worse. Table 3 shows the relative energies obtained for the different minima using the 3-21G(N*) and 6-31G** basis sets. From this table, we see that the smaller basis set yields results that are different from those obtained with the larger basis set. The HF/3-21G(N*) level of calculation tends to yield a low relative energy for MM3(9), whereas this structure is strongly destabilized on the HF/6-31G** level. Furthermore, when using smaller basis sets like 3-21G(N*), some minima optimize to previously located minima, resulting in the loss of some minima. The smaller basis set does exhibit strong stabilization of the MM3(12) and MM3(20) structures, which agrees with the results of the HF/6-31G** calculations. As a general conclusion, one should take care in using small basis sets to do conformational analysis of macrocycles, since the energetic ordering of minima can differ strongly from the ones obtained using the larger basis sets, and some minima cannot be found using the smaller basis sets.

Not only is the size of basis sets of importance, but we also investigated the importance of electron correlation. Given the size of the molecule and of the basis sets used, we restricted ourselves to investigating what the effect is of electron correlation by doing MP2(full)/6-31G** level calculations using the HF/6-31G** optimized geometries. Previous calculations of similar quality on 12-crown-4 by Bultinck et al.[26] and work by Anderson et al.[27] on 9-crown-3 revealed that electron correlation has a minor effect on the energetic ordering of the minima in crown ethers. Taking 15 minima [comprising the 10 lowest energy minima on the MM3 and HF/6-31G** levels and MM3-(11)] Table 3 shows that MP2 electron correlation generally lowers the relative energy of all minima and that the qualitative ordering largely remains the same as on the HF/6-31G** level. The most prominent differences are for the MM3(5) structure, which has a higher relative energy on the MP2 level, and the MM3(7), MM3(20), and MM3(25) structures, which are more than average stabilized upon going from the HF/6-31G** to the MP2/6-31G** level. On average, the difference between the relative energies calculated on these two levels is less than 0.5 kcal/mol.

As noted previously, only a few experimental structure determinations are known for [12]aneN$_4$. As was already discussed above, Reibenspies identified two different crystal structures, of which only one can be used for direct comparison to the calculated structures.[22,23] The VUCGEF structure resembles the structure of the global minimum. Table 2 gives the values for the dihedral angles in the macrocyclic ring, showing that there is very good agreement between the experimental structure and the HF/6-31G** global minimum.

B. [14]aneN$_4$. *1. Molecular Mechanics Calculations.* The cyclam macrocycle differs from [12]aneN$_4$ in the presence of two propylene alkylbridges instead of two ethylene bridges. As was the case for [12]aneN$_4$, little theoretical work has focused on the conformational properties of the free molecule. Most of these studies deal with few structures of the macrocycle or consider only those geometries of the free macrocycle that are found in the complexes.[6] On the other hand, the number of experimental studies is quite high, although not all qualify for a comparison with the calculated structural features (see below).

A systematic search was performed, together with a total of 35 stochastic searches. This number may seem relatively small for this macrocycle (as compared with the 79 such searches for [12]aneN$_4$) and is a consequence of the very high number of higher-energy minima found for [14]aneN$_4$. We therefore required the searches to yield not all minima at least twice but only those minima with a relative energy under 10 kcal/mol. Requiring that all minima should be found at least twice would give rise to too high a number of searches to be conducted. In total, the MM3 searches give rise to 41 minima having a relative steric energy under (or only slightly above) 6 kcal/mol. Table 6 gives the conformation description, MM3 relative energy, and symmetry point group for the 41 minima. The four-letter codes describe the geometries of the NCCCN alkyl chains, while the three-letter codes describe the structures of the NCCN type bridges. Table 6 shows that the global MM3 minimum exhibits a C_i structure. All minima from Table 6 were further optimized using the 6-31G** basis set. Table 6 indicates that the agreement between the MM3 and HF/6-31G** is fair, not only for the energetic order but also for the values of the relative energies.

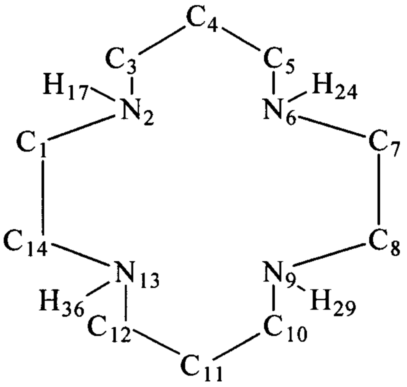

Figure 3. Atom numbering in [14]aneN$_4$ (hydrogen atoms on carbon not displayed).

In case of [12]aneN$_4$, we found that intramolecular hydrogen bonds play only a secondary role in the stabilization of certain minima over other minima. The presence of these interactions was investigated by checking the (N)-H···N distances and by calculating the NPA charges on the hydrogen atoms, among other methods. In case of [14]aneN$_4$, we also found relatively small such distances in the lower energy minima. Care should be taken however in concluding the presence of these interactions, since almost every minimum (irrespective of its steric energy) exhibits relatively small interaction distances. We previously found that the main reason for the stabilization of the lowest energy minima is the electrostatic interaction inside the macrocyclic cavity, with a clear preference for a $(2+2)_D$ configuration. We can now check if this observation holds for other nitrogen-containing macrocycles as well. We found that indeed the energetic order of minima in [14]aneN$_4$ is explained by the strength of the electrostatic interaction in the macrocyclic cavity, with the lowest energy minima having a $(2+2)_D$ configuration. In the higher energy rotamers, we find less favorable $(2+2)_{ND}$ configurations, while still higher energy rotamers exhibit (3+1) type structures. Noteworthy also is that the order in electrostatic configuration also explains the stabilization and destabilization of rotamers when going from the MM3 to the HF/6-31G** level. A good example is MM3-(7). This structure exhibits a (3+1) configuration and is destabilized. On the other hand, a structure such as MM3(25) is stabilized in the energetic order because it has a $(2+2)_D$ structure. Note that stabilization is hereby defined as ranking lower in the energetic order, not necessarily having a lower relative energy on HF/6-31G** level than on MM3 level [e.g., the relative energy of MM3(25) is similar on both levels of theory, but on HF/6-31G** level it is the tenth lowest energy minimum.].

The agreement between the structural features of the MM3 optimized structures and the corresponding HF/6-31G** optimized structures exhibits the same characteristics as in [12]-aneN$_4$. There is good agreement in all geometrical parameters.

TABLE 6: Conformation Description, Symmetry Point Group, and Relative Energy (in kcal/mol) for All [14]aneN_4 Minima Calculated at the MM3 and HF/6-31G Levels[a]**

conformation				MM3	HF	sym	conformation				MM3	HF	sym
0-+0	0-0	0+-0	0+0	0.00	0.00[b]	C_i	0+-0	0+0	+++0	+-0	5.51	5.74	C_1
0+-0	--0	0+-0	--0	2.05	1.94	C_2	0-++	0+0	0+- -	0-0	4.12	5.83	C_i
0+-0	0++	0++0	0-0	2.08	2.15	C_1	0+- -	0-0	0-+0	0-0	5.63	6.06	C_1
0+-0	0+0	0--0	--0	2.00	2.35	C_1	0++0	++0	0-+0	0-0	4.82	6.11	C_1
0--0	0++	0+-0	0+0	2.93	3.00	C_1	0-+0	0- -	0--0	0+0	5.11	6.16	C_1
0++0	0-0	0+-0	--0	3.07	3.30	C_1	0-++	0+0	++-0	0+0	5.40	6.24	C_1
0-+0	0-0	0+-0	0+0	2.32	3.92	D_2	0-+0	0-0	0+-0	0+0	4.07	6.44	C_1
0+-0	0++	0+-0	--0	3.34	4.51	C_1	0+- -	0-0	0+-0	0+0	5.01	6.52	C_1
0-+0	+++	0++0	0- -	3.83	4.57	C_1	0++0	++0	0+- -	0-0	5.20	6.76	C_1
0+-0	0+0	++-0	0-0	4.87	4.64	C_1	0+-0	--0	0+-0	--0	4.67	6.89	C_1
0++0	++0	0-+0	0-0	5.73	4.85	C_1	0+-0	--0	0++0	+++	5.27	6.94	C_1
0-++	0+0	0-+0	0-0	4.54	4.85	C_1	0+-0	0+0	0--0	--0	5.44	6.95	C_1
0++0	+++	0+-0	--0	4.38	4.96	C_1	0-+0	0- -	0-+0	0- -	4.95	7.10	C_1
0--0	0+0	0-+0	++0	5.08	4.99	C_1	0+- -	0-0	0-++	0+0	5.67	7.39	C_1
++-0	0+0	0-+0	0+0	3.53	5.03	C_1	0-+0	0-0	0+- -	0-0	5.17	7.51	C_1
+++0	+-0	0+-0	0+0	5.11	5.07	C_1	0++0	+++	0+-0	--0	5.33	7.51	C_1
0-++	0+0	0-++	0+0	2.46	5.36	C_1	0--0	0++	0++0	++0	5.96	7.51	C_1
0+-0	0+0	++-0	0-0	3.67	5.38	C_1	0+- -	0-0	0-+0	0-0	4.17	7.65	C_1
- -+0	0+0	++-0	0-0	3.37	5.43	C_1	0+- -	0-0	- -+0	0-0	4.51	8.41	C_2
0+-0	0++	0+-0	0++	3.42	5.50	C_1	0+- -	0-0	0+-0	0+0	5.32	8.45	C_1
0-−0	0++	0++0	++0	5.91	5.58	C_1	0-++	0+0	0-++	0+0	5.89	8.93	C_1
++-0	0-0	0+-0	0+0	4.30	5.61	C_1	0+-0	0-0	- -+0	0-0	5.76	9.40	C_1
0+-0	0+0	0+- -	0-0	2.92	5.63	C_1	- -+0	+++	0+- -	0-0	5.47	10.02	C_2
0--0	0+0	0-++	0+0	5.56	5.68	C_1	++-0	0+0	++-0	0+0	5.43	12.00	C_1
0+-0	-+0	++-0	0++	5.41	5.69	C_1							

[a] See Figure 3 for atom numbering. [b] HF/6-31G** energy for the global minimum: −610.455005 Hartree.

For the NCCC dihedral angles the difference amounts to 4.1° on average, which is also good. Since differences are small and were discussed in detail for [12]aneN_4, we do not repeat the entire discussion for [14]aneN_4.

The structure of cyclam has been studied experimentally numerous times. Most entries in CSD are for [14]aneN_4 carrying extra functional groups. Since we cannot readily assess the influence of these groups, we have to discard these entries in our comparison for structural data obtained experimentally and using ab initio calculations. Other CSD entries are for structure determinations in solutions where [14]aneN_4 is protonated, yielding a dication or tetracation. Especially for the tetracations, we find that the NCCN angles usually have a trans orientation, which is easily explained since protonated ethylenediamine fragments are similar to *n*-butane. Given the fact that experimental structure determinations are for another species than our ab initio calculations, no assessment of the agreement between experimental and theoretical structures can be given.

Conclusions

Using molecular mechanics methods and by doing extensive conformational searching of the potential energy hypersurface, we located 25 minima with MM3 relative energy under 5 kcal/mol for [12]aneN_4 and 41 minima for [14]aneN_4. HF/6-31G** geometry optimizations starting from these minima revealed that ab initio calculations can yield different energetic orderings of these minima. MM3 optimized geometries on the other hand agree well with the HF/6-31G** ones. Since macrocycles exhibit numerous different minima, conformational searching using ab initio techniques is too computationally demanding at present. Conformational searching using force field methods yields a high number of minima with values for the structural parameters that agree well with ab initio determined values. Since the agreement in energetic order is less favorable, ab initio calculations should always involve a fairly large number of the lower energy minima found using the force field calculations. In this study, we considered all minima with relative energies under 5 kcal/mol.

The global minima for [12]aneN_4 and [14]aneN_4 exhibit a C_2 and C_i geometry, respectively. The stability of the lowest lying geometries is mainly due to favorable electrostatic interactions inside the macrocyclic cavity. A simple model explains the energetic order obtained for the different minima. Stabilizing (N)-H•••N interactions are only of secondary importance. The MM3 force field geometries agree very well with the HF/6-31G** geometries, but force field calculations are unable to reproduce the subtle effects governing the energetic order of the minima.

A small basis set dependence study shows that small basis sets, such as 3-21G(N*), can be used for qualitative geometries but are too small to be used for obtaining relative energies of different minima and tend to discard some minima. Electron correlation has only a minor influence on the qualitative energetic ordering.

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References and Notes

(1) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495.
(2) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *98*, 1875.
(3) Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Vol. 1−6, Plenum Press: New York, 1974.
(4) Rode, B. M.; Hannongbua, S. V. *Inorg. Chim. Acta* **1985**, *96*, 91.
(5) Hannongbua, S. V.; Rode, B. M. *Inorg. Chem.* **1985**, *24*, 2577.
(6) Ribeiro-Claro, P. J. A.; Amado, A. M.; Marques, M. P. M.; Teixeira-Dias, J. J. C. *J. Chem. Soc., Perkin Trans. II* **1996**, 1161.
(7) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.
(8) MM3 versions 1994, 1996; obtained from QCPE.
(9) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.

(10) Schmidt, M. W.; Balridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

(11) Van Alsenoy, C.; Peeters, A. *J. Mol. Struct. (THEOCHEM)* **1993**, *286*, 19.

(12) Harrisson, R. J. *TCGMSG Message Passing Toolkit*; Battelle Pacific Northwest Laboratory.

(13) Beguelin, A. L.; Dongarra, J. J.; Geist, G. A.; Jiang, W. C.; Manchek, R. J.; Moore, B. K.; Sunderam, V. S. *PVM version 3.3: Parallel Virtual Machine System*, University of Tennessee, Knoxville, TN, Oak Ridge National Laboratory, Oak Ridge, TN, Emory University, Atlanta, GA.

(14) Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO 4.0*, Theoretical Chemistry Institute, University of Wisconsin, Madison, WI, 1994.

(15) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision C.1; Gaussian, Inc.: Pittsburgh, PA, 1995.

(16) Almlöf, J.; Faegri, K.; Korsell, K. *J. Comput. Chem.* **1982**, *3*, 385.

(17) Van Alsenoy, C. *J. Comput. Chem.* **1988**, *9*, 620.

(18) Bultinck, P.; Goeminne, A.; Van de Vondel, D. *J. Mol. Struct. (THEOCHEM)* **1995**, *339*, 1.

(19) Hay, B. P.; Rustad, J. R.; Zipperer, J. P.; Wester, D. W. *J. Mol. Struct. (THEOCHEM)* **1995**, *337*, 39.

(20) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102.

(21) Allen, F. H.; Bellard, S. A.; Brice, M. D.; Cartwright, B. A.; Doubleday: A.; Higgs, H.; Hummelink, T.; Hummelink-Peters, B. G.; Kennard, O.; Motherwell, W. D. S.; Rodgers, J. R.; Watson, D. G. *Acta Crystallogr.* **1979**, *B35*, 2331. The authors wish to thank the CAOS/CAMM department of the University of Nijmegen for providing access to this database.

(22) Reibenspies, J. H.; Anderson, O. P. *Acta Crystallogr.* **1990**, *C46*, 163.

(23) Reibenspies, J. H. *Acta Crystallogr.* **1992**, *C48*, 1717.

(24) Hargittai, M.; Hargittai, I. *Int. J. Quantum Chem.* **1992**, *44*, 1057.

(25) Ma, B.; Lii, J.-H.; Schaefer III, H. F.; Allinger, N. L. *J. Phys. Chem.* **1996**, *100*, 8763

(26) Bultinck, P.; Goeminne, A.; Van de Vondel, D. *J. Mol. Struct. (THEOCHEM)* **1999**, *467*, 211.

(27) Anderson, W. P.; Behm, P.; Glennon, T. M.; Zerner, M. C. *J. Phys. Chem. A* **1997**, *101*, 1920.