Searching the Conformational Space of Cyclic Molecules: A Molecular Mechanics and Density Functional Theory Study of 9-Crown-3

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Received: April 14, 1999; In Final Form: September 14, 1999

The conformational space of 1,4,7-trioxacyclononane (9-crown-3) was studied using Conflex-AMBER and ab initio calculations at the density functional level of theory (DFT). The Conflex-AMBER calculations predict that the $[225]^{100}$ conformation with C_2 symmetry is the global minimum with the $[144]^0$ conformation being 0.9 kcal mol^{-1} above the global minimum and these two conformations exist in a deep conformational well. The next lowest energy structure is 3.3 kcal mol^{-1} above the global minimum. The DFT studies show that the stability order is inverted. The C_2 symmetry conformation $[225]^{100}$ is 0.9 kcal mol^{-1} higher in energy than the global minimum $[144]^0$ conformation and the next lowest energy conformer is 4.8 kcal mol^{-1} above the global minimum. The study highlights the flexibility of 9-crown-3 and the suitability of Conflex-AMBER program for conformational space searching of macrocyclic ligands.

Introduction

The knowledge of conformational behavior is expected to provide insight into biologically important phenomena such as molecular recognition. Though structural data can be obtained from NMR and X-ray diffraction, reliable interpretations of experimental data can be better achieved using theoretical methods.[1] Exploration of conformational space is a difficult problem, which is especially acute for cyclic molecules due to the interdependence of torsion angles.[2] Considerable progress has been made in the development of computational methods for searching the conformational space of cyclic molecules, and it has become possible to produce all the significantly populated conformers.[3−6]

Since the first synthesis of crown ethers by Pedersen in 1967,[7] many crown ethers have been synthesized and extensively studied.[8] High conformational flexibility of crown ethers allows them to act selectively as receptors to various guests (cations, anions, and small organic molecules).[8−10] There is an increased interest in the coordination chemistry of crown ethers due to their importance in analytical chemistry,[11]medicine,[12] and environmental monitoring.[13] The crown ethers are also interesting from a molecular modeling point of view as they share with enzymes specificity in their selective binding to ions. In the present article, the results of a conformational space search, carried out on 1,4,7-trioxacyclonane [9-crown-3, 9C3], using different theoretical techniques are reported. Crystal structure studies have not been reported for free 9C3 or any 9C3 metal-coordinated complexes. A Cambridge Structure Database search[14] of the 9C3 fragment yielded only one hit: [cyclohexyl-9-crown-3: ref code PEWMIN].[15] In contrast, for 1,4,7-trithiacyclononane ([9]aneS$_3$) CSD search yielded 119 hits comprising 164 fragments.

Low temperature ^{13}C NMR and IR studies suggested that 9C3 exist predominantly with an unsymmetrical conformation.[16] Molecular mechanics calculations[17,18] and ab initio molecular orbital studies carried out at various levels of theory[18] have been reported for 9C3. We have been interested in the development of molecular modeling techniques for generating low-energy conformations (LECs) of cyclic molecules.[19] This paper addresses the generation of LECs of 9C3 starting from an arbitrarily chosen conformation. The results obtained have been assessed using density functional theory (DFT).[20,21] We have chosen to work at this level of theory due to the large number of conformations to be studied and since DFT includes some correlation.

Methodology

The LECs of 9C3 were determined using the program Conflex-AMBER (CA) developed in our group.[19] For the evaluation of energy gradients, the AMBER 4.0 force field,[22] supplemented with the parameters developed by Billeter et al. for crown ethers,[23] was used. A dielectric constant of $\epsilon = 1$ was used with no cutoff for nonbonded interactions. Coulombic interactions involving third neighbor atoms were not scaled, but the 1−4 van der Waals interactions were scaled by a factor of 0.5. The conformations were minimized until the root-mean-squared (rms) value of the energy gradient was less than 0.001 kcal/(mol Å). The initial arbitrarily chosen conformation was subjected to minimization. This structure was then perturbed sequentially, by a series of flips and flaps of the atoms and bonds of the endocyclic backbone to generate additional starting or probe structures.[24] These starting structures were then minimized. The process of perturbation and minimization enables the molecule to cross high-energy barriers and relax to LECs. The reservoir filling strategy ensures that conformational search is directed toward LECs.

The minimized starting structures were compared with those already stored. The criterion of rms difference between the corresponding dihedral angles was calculated. Because of the symmetry of the molecule, these comparisons also included reflection and rotation of the atom numbering of the cyclic backbone. If in one of the comparisons, the rms deviation is

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10.1021/jp991201w CCC: $18.00

TABLE 1: Torsion Angles and Energies Using Conflex-AMBER (CA)

	conformation[b]											
torsion angle[a]	$[225]^{100}$	$[144]^{0}$	$[9]^{0}$	$[225]^{010}$	$[333]^{0}$	$[9]^{1}$	$[234]^{001}$	$[144]^{100}$	$[234]^{110}$	$[144']^{100}$	$[234]^{0}$	$[333]^{3}$
O1−C2	−64.9	−112.7	93.9	−58.2	128.4	58.3	−44.2	−90.2	−59.8	89.2	−127.5	−54.6
C2−C3	68.3	70.0	−104.4	109.9	−51.8	−79.5	−42.7	118.4	54.7	−60.2	56.5	124.0
C3−O4	62.1	68.4	132.5	−84.4	−63.4	128.9	139.5	−90.2	64.3	89.2	61.2	−54.0
O4−C5	−107.9	−117.1	−88.4	100.0	128.4	−118.5	−64.4	80.6	−138.0	−139.2	−83.2	−54.6
C5−C6	81.2	65.5	44.7	−49.4	−51.7	89.7	−62.6	−118.0	93.5	115.0	−35.8	124.0
C6−O7	−107.9	−86.6	−88.1	−78.6	−63.4	−40.3	51.6	62.0	−27.9	−37.3	136.0	−54.6
O7−C8	62.1	136.4	151.6	76.3	128.9	−58.7	57.3	62.0	−55.7	−37.3	−59.8	−54.6
C8−C9	68.2	−86.3	−54.4	60.9	−51.8	148.3	−133.3	−118.0	138.0	114.9	−38.7	124.0
C9−O1	64.9	65.4	−51.1	−62.4	−63.4	−97.7	105.7	80.6	−56.6	−139.2	103.6	−54.6
RE[c]	0.0	0.9	3.3	4.8	4.9	5.6	6.0	6.3	7.3	7.6	8.9	9.2
frequency[d]	19	61	31	33	20	42	24	18	22	9	20	16
point group symmetry	C_2	C_1	C_1	C_1	C_3	C_1	C_1	C_2	C_1	C_1	C_1	D_3

[a] The torsion angles in degrees with respect to the indicated central bond. [b] Conformations using Dale nomenclature. Atom C9 is connected to atom O1 in the ring. [c] Relative energy in units of kcal mol^{-1}. [d] Frequency of occurrence of the particular conformation.

larger than 15°, the structures being compared are considered to be different. Duplicate structures are also eliminated by the precheck feature during minimization. This prevents the search from repeatedly visiting the same conformational space defined by a set of torsion of angles. The CA program also calculates the point group symmetry for a given tolerance limit. The computer program SYMMOL[25] was modified and incorporated into the CA program. Conflex-AMBER calculations described in this article were performed on a Micron-Millenia Pentium II (400 MHz) based personal computer.

There is an increasing use of DFT in computational chemistry.[21] An important feature of this method is that it takes into account electron correlation while requiring less computational time and computer resources when compared to correlated methods such as MP2 calculations. All the DFT calculations reported in this paper were carried out using the DMOL program[26] running on an Octane SGI workstation. These calculations employed the BLYP functional (B = Becke[27] gradient corrected exchange correlational functional and LYP = Lee, Yang, and Parr[28] gradient corrected correlational functional). We employed a double numerical plus polarization (BNP) basis set with a FINE mesh. The inner core orbitals were treated by the frozen core approximation.

Results and Discussions

In the following, the conformers are designated by the nomenclature devised by Dale.[29] Two adjacent gauche bonds of the same sign are called as genuine corners and corners with adjacent gauche bonds of opposite sign are termed as pseudocorners. The number of bonds between corners are written between square brackets. The nomenclature was further modified by Anderson et al.[18] and this numbering scheme was used in this paper. The OCCO, CCOC, and COCC dihedral angles are designated[30] as g^+, g^-, or anti if the angle is respectively 60° ± 60°, −60° ± 60°, and 180° ± 60°.

Conflex-AMBER

Using an arbitrarily chosen starting conformation, a CA calculation was carried out, which required the generation of 320 trial structures within an energy window of 15 kcal mol^{-1} to generate 12 symmetry-unique conformations. The calculations took less than 2 min on the personal computer. The choice of the arbitrary starting conformation was also used to assess the conformational search capability of the CA method. The torsion angles involving heavy atoms and energies for the 12 conformations are summarized in Table 1 and the conformations are shown in Figure 1.

The global energy minimum (GEM) is the $[225]^{100}$ conformation with C_2 symmetry, and the $[144]^{0}$ conformation with C_1 symmetry is 0.9 kcal mol^{-1} higher in energy. The energy difference between the two LECs is small and is not enough to indicate with certainty the preference of one conformation over the other. The next low-energy conformer $[9]^{0}$ with C_1 symmetry is 3.3 kcal mol^{-1} higher in energy. The $[333]^{0}$ and $[333]^{3}$ conformers are 4.9 and 9.2 kcal mol^{-1} higher in energy than GEM. Because of the attractive gauche effect, OCCO angles generally prefer gauche torsion angles and the CCOC angles are generally anti.[31] The two low-energy conformations are characterized by having all the OCCO torsion angles gauche like the geometry of the larger crown ethers.[32]

Early molecular mechanics calculations by Bovill et al.[17] have considered six structures in their analysis. Their study showed that the GEM is the $[225]^{100}$ followed by a twist−chair−chair conformation $[144]^{0}$, which is 0.8 kcal mol^{-1} higher in energy. Three twist−boat−chair conformations with C_1 symmetry $[234]^{001}$, $[234]^{101}$, and $[234]^{0}$, and a structure with C_3 symmetry $[333]^{0}$ were also considered. These conformations were reproduced in the CA calculations with a stability order similar to Bovill et al. More recently, a comprehensive conformational analysis of 9C3 using the MMX molecular mechanics force field was reported.[18] The conformational space search strategy involved the usage of multiple starting geometries. To exhaustively search for all the LECs of 9C3, six known LECs of cyclononane were used for generating the structures. The CH_2 groups were substituted with oxygen at various 1, 4, and 7 positions and minimized. The conformational analysis generated 12 LECs with $[144]^{0}$ conformation as the GEM followed by $[225]^{100}$conformation, which was 1.7 kcal mol^{-1} higher in energy. The 12 conformations were subjected to minimization using semiempirical molecular orbital calculations. Five of the conformers converged to different geometries. The authors also studied the structures and energies of the seven conformers of 9C3 at 6-31G** HF and MP2 levels of theory. Though the order of the LECs was nearly the same as the MMX calculations, the energy difference between the LECs in the HF study and MP2 investigation was respectively 1.8 and 0.7 kcal mol^{-1}. The CA conformational space search could generate all 12 of the structures obtained using the MMX method, and the results differed only in the stability ordering. It also has to be noted that the 12 conformations in the CA search were generated using an arbitrarily chosen starting structure. In the case of the MMX study, multiple starting geometries were required.

The number of duplicates gives the number of times a particular conformation has been visited. This also provides

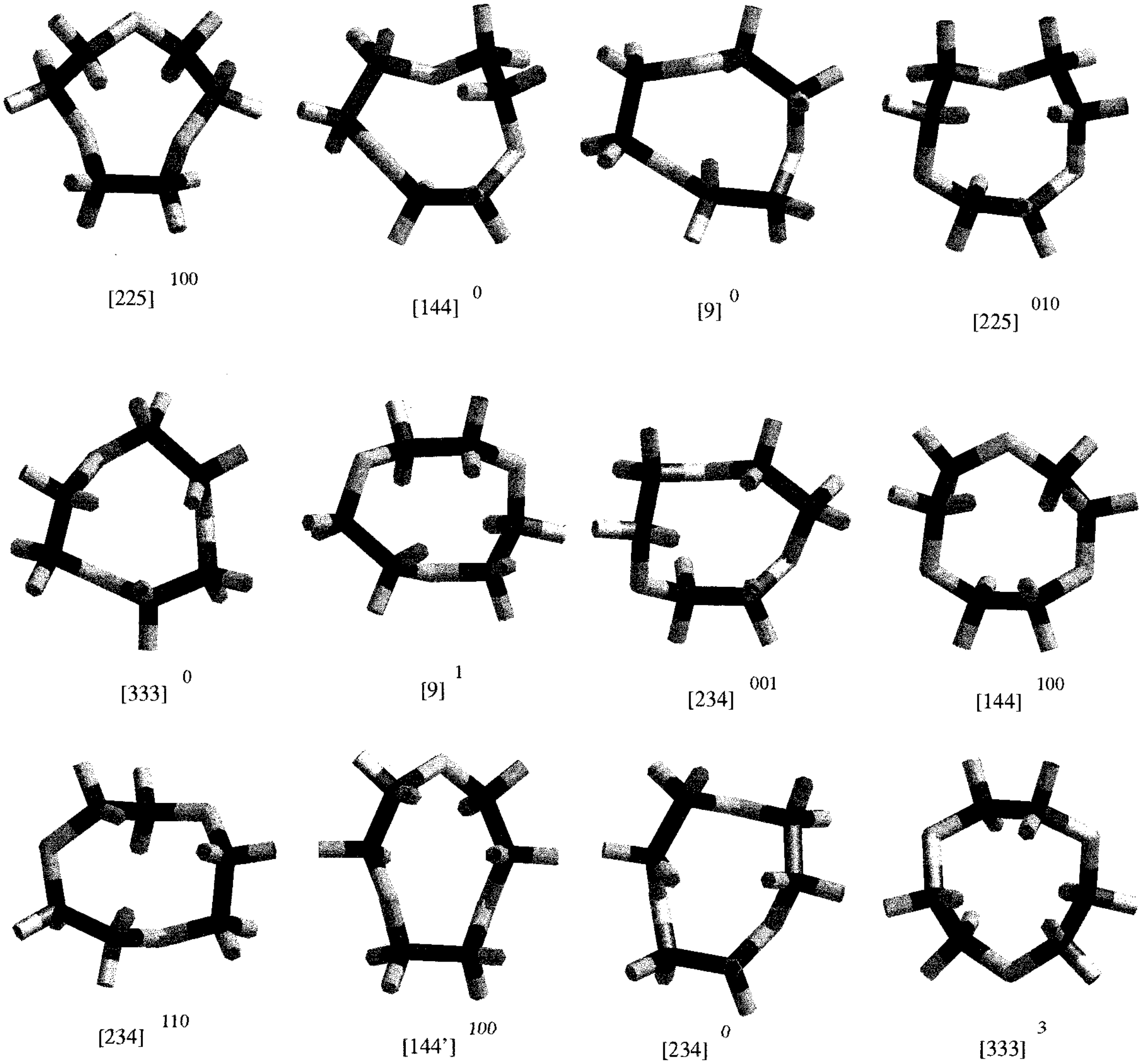

Figure 1. Conflex-AMBER minimized low-energy conformations.

evidence for the extent of the conformational space search.[4] The numbers of duplicates are given in Table 1, and the values ranging from 9 to 61 are indicative of the search capabilities of CA method. A recent publication has highlighted the criteria for judging the quality of conformational search; the method should be thorough, while efficiency is secondary in importance.[6] The small size of 9C3 (21 atoms and 9 rotatable torsion angles) allowed testing the effect of starting geometry on conformational search. When two other structures $[225]^{100}$ and $[333]^{0}$ were used as starting geometries for the CA conformational space search, no additional structures were obtained within 10 kcal mol^{-1} of the global minimum. We believe that the conformational space search is complete and no conformations have been missed.

Small, odd membered, cyclic molecules are characterized by ring strain, and this is reflected in the anomalous torsion angles. Perusal of Table 1 shows that a large number of torsion angles are around ±120°. The 9C3 conformations are determined by the 1,4 CH···CH and 1,5 CH···O interactions. Although C−H···O hydrogen bonds are relatively weaker than conventional hydrogen bonds, they have been shown to be of importance in stabilizing organic and biological structures.[33−35] Anderson et al.[18] have observed that the lowest energy conformers of 9C3 are characterized by having two C−H···O interactions and the conformers $[225]^{010}$, $[234]^{001}$, and $[9]^{1}$ have one C−H···O. The CA minimized geometries of $[234]^{0}$ and $[234]^{110}$ also have one C−H···O interaction each. These intramolecular hydrogen bonding interactions are energetically significant and it was concluded from ab initio HF study of 18C6 that each 1,5 C−H O would contribute 0.6 kcal mol^{-1}.[36] The internal hydrogen bonding interactions account for 1.2 kcal mol^{-1} of the energy differences between conformers. It is seen from Table 1 that there is a large energy gap of 2.4 kcal mol^{-1} between conformers 2 and 3 and a gap of 1.34 kcal mol^{-1} between conformers $[144']^{100}$ and $[234]^{0}$. It appears that energies of 9C3 are distributed in a three "well" system. Similar energy gaps were not observed in the larger crown ethers of 18C6[19] and 12-crown-4.[37]

DFT Calculations

The 12 LECs generated from the CA study were used as starting geometries for full optimization by DFT. Of the 12 structures, $[9]^{0}$ and $[144']^{100}$ converged to the $[144]^{0}$ and $[9]^{1}$ structures, respectively. The torsion angles involving the nonhydrogen atoms and relative energies of the 10 conformers are given in Table 2. The DFT study inverted the stability ordering of the two lowest energy conformers obtained from CA. Global energy minimum is the $[144]^{0}$ structure and the $[225]^{100}$ is only 0.9 kcal mol^{-1} higher in energy. The order of local minima obtained from DFT reproduces the HF study using 6-31G** basis set and the MP2 study.[18]

TABLE 2: Torsion Angles and Energies Using DFT

	conformation[b]									
torsion angle[a]	$[144]^0$	$[225]^{100}$	$[225]^{010}$	$[333]^0$	$[9]^1$	$[144]^{100}$	$[234]^0$	$[234]^{001}$	$[234]^{110}$	$[333]^3$
O1−C2	−118.2	−63.1	−55.9	126.6	62.5	−87.9	−118.2	−38.4	−62.7	−54.2
C2−C3	67.9	67.8	104.7	−55.9	−77.4	108.9	52.4	−49.9	−60.3	123.3
C3−O4	64.6	62.7	−82.1	−57.7	127.1	−88.8	66.8	139.9	62.1	−55.1
O4−C5	−118.6	−106.9	100.8	126.5	−122.5	84.6	−82.8	−61.1	−136.5	−54.1
C5−C6	76.2	75.4	−52.1	−56.5	87.0	−117.1	−46.4	−65.8	87.0	122.7
C6−O7	−80.3	−105.4	−76.4	−57.6	−34.8	59.3	−58.5	57.3	−22.1	−54.5
O7−C8	126.5	64.6	76.0	126.2	−64.0	60.7	−33.7	52.1	−60.3	−54.6
C8−C9	−95.3	66.4	60.8	−56.3	144.9	−118.6	−58.5	−127.6	134.9	123.3
C9−O1	71.1	−66.7	−63.9	−58.1	−97.9	84.0	105.1	103.2	−55.1	−54.8
R. E.[c]	0.0	0.9	4.8	5.5	6.5	7.7	8.2	8.8	9.7	12.7
point group symmetry	C_1	C_2	C_1	C_3	C_1	C_2	C_1	C_1	C_1	D_3

[a] The torsion angles in degrees with respect to the indicated central bond. [b] Conformations described using Dale nomenclature. Atom C9 is connected to atom O1 in the ring. [c] Relative energy in units of kcal/mol.

TABLE 3: Comparison of Structural Parameters for the $[144]^0$ Conformation

	CA		DFT		6-31G**[c]		experimental[d]	
bond	*r*[a]	*t*[b]	*r*[a]	*t*[b]	*r*[a]	*t*[b]	*r*[a]	*t*[b]
O1−C2	1.423	−112.7	1.456	−118.2	1.400	−117.0	1.432	−122.3
C2−C3	1.544	70.0	1.541	67.9	1.519	62.2	1.514	58.8
C3−O4	1.425	68.4	1.452	64.6	1.399	74.3	1.425	76.6
O4−C5	1.423	−117.1	1.455	−118.6	1.399	−118.6	1.438	−120.5
C5−C6	1.540	65.5	1.540	76.2	1.515	62.9	1.532	67.6
C6−O7	1.421	−86.6	1.452	−80.3	1.398	−96.2	1.427	−96.1
O7−C8	1.424	136.4	1.463	126.5	1.406	132.8	1.416	127.5
C8−C9	1.540	−86.3	1.538	−95.3	1.517	−77.4	1.500	−78.1
C9−O1	1.421	65.4	1.456	71.1	1.398	74.4	1.435	78.3

[a] *r* is the distance in angstrom between the indicated atoms. [b] *t* is the torsion angle in degrees with respect to the indicated central bond. [c] HF 6-31G** (ref 18). [d] Cyclohexyl-9-crown-3 (ref 15). The signs of the torsion angles have been reversed for conformity with theoretical studies.

All the theoretical studies have indicated $[144]^0$ and $[225]^{100}$ as the low-energy conformations, but with different energy ordering. The unsymmetrical conformation $[144]^0$ is particularly important as the crystal structure of a 9C3 derivative has this structure, and it is also the most sampled CA conformation. The structural parameters obtained for this conformation is compared from different studies are given in Table 3. A significant difference between the HF 6-31G** and the DFT structures is the increase in bond lengths. The C−O bond lengths are 0.053 Å longer and the C−C bond lengths are longer by 0.022 Å. Such a systematic increase in bond lengths has also been observed previously.[38] In Figure 2 the nine membered ring system of cyclohexyl-9-crown-3 is superimposed over the $[144]^0$ conformation obtained from CA calculations. To compare the two structures, the mirror image of the calculated CA conformation was taken. The rms superimposition deviation is 0.063 and clearly there is a good agreement between the two structures. It is also seen that all the methods are in good agreement with the experimental data. The $[225]^{100}$ structure with approximate C_2 symmetry was not observed experimentally for 9C3, though these conformations are observed in Au−([9] aneS$_3$) and Ag−([9] aneS$_3$) complexes.[39,40]

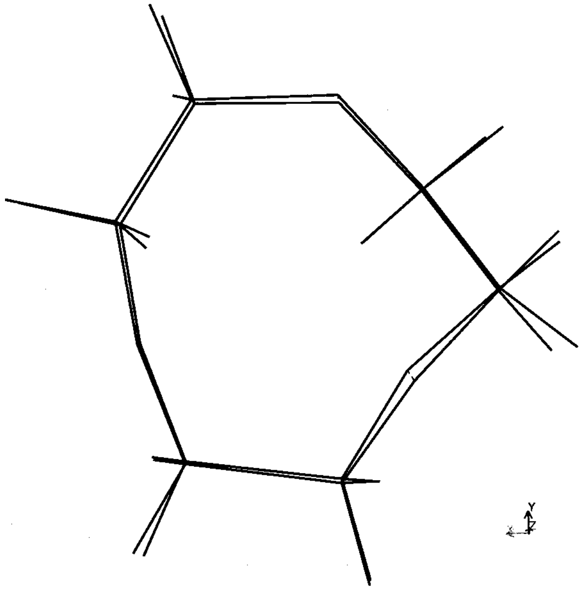

Figure 2. Superposition of calculated $[144]^0$ (CA) minimum and the X-ray crystal structure of cyclohexyl-9-crown-3.

Concluding Remarks

Crown ethers are flexible molecules and some of the conformers are separated by high-energy barriers. To surmount the barriers, long MD simulations or special sampling techniques such as high-temperature dynamics or other modifications, such as umbrella sampling are required. In the present study, low-energy conformations were generated by the program CA using an arbitrarily chosen initial conformation and without using any experimental restraints. The program CA samples many conformations and generates the distinct and unique LECs. The program is fast and can be used for conformational sampling of macrocycles. Duplication rates and convergence of results demonstrate the efficiency and thoroughness of the conformational search. The purpose of the Conflex-AMBER method is not to generate the global minimum, as it is dependent on many factors, but the enumeration of low-energy conformers. The program requires only an arbitrarily chosen starting structure to generate all the known low-energy conformers unlike other molecular mechanics studies that used multiple starting geometries.

The low-energy conformations were also evaluated using DFT calculations. The conformational energies and relative structural ordering obtained using DFT theory are comparable with the MP2 results. The study shows that ab initio calculations at the DFT level of theory can be used for determining the conformational preferences of crown ethers.

The CA program has been extensively tested for symmetric crown ethers. The program is being presently evaluated for the conformational analysis of cyclic pentapeptides. It is expected that the LECs generated by CA method can be used to explain the NMR observables (NOE and coupling constants).

Acknowledgment. We thank Dr. K. V. Raghavan and Dr. J. S. Yadav for support and encouragement, Dr. A. C. Kunwar for critical reading of the manuscript, and the anonymous referees for valuable suggestions. Acknowledgment is also made to Profs. P. A. Kollman, E.Osawa, and T.Pilati for providing copies of the programs AMBER 4.1, Conflex, and SYMMOL and their help in implementing the modules in the Conflex-AMBER program.

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