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Conformational preferences of 1,4,7-trithiacyclononane: a molecular mechanics and density functional theory study

Abstract Conformational preferences of 1,4,7-trithiacyclononane were studied using a highly efficient sampling technique based on local nonstochastic deformations and the MM2(91) force field. The results show that conformers that the molecule adopts in the crystal state were found to be low-energy conformers (LECs) within 5 kcal mol^{-1} of the global minimum. A conformation with C_1 symmetry was the global minimum and the C_3 and C_2 conformations were calculated to be 0.03 and 1.78 kcal mol^{-1} higher in energy, respectively. The structures were further minimized using Density Functional Theory (DFT) calculations with two different functionals. The C_2 and the C_1 conformations were found to be LECs with the C_3 conformation more than 4.0 kcal mol^{-1} above the global minimum. The relative energies and structural ordering obtained using the BP86 functional are in agreement with the previously reported relative energies calculated using second-order Moller–Plesset (MP2) ab initio calculations. With the energy ordering being dependent on the molecular mechanics force field used, the approach of MM→DFT (searching exhaustively the available conformational space at the MM level followed by generating the energy ordering through DFT calculations) appears to be appropriate for thiacrown ethers.

Keywords Conformational space sampling · Molecular mechanics · Density functional theory

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Introduction

The synthesis of crown ethers by Pedersen in 1967 [1] marked the beginning of host–guest chemistry. This has become an active area of research mainly due to the ability of the highly flexible crown ethers to adopt different conformations for optimal binding, depending on the substrate and environment. [2] Crown ethers have also found widespread chemical, biological and industrial applications (e.g. ion-transfer catalysis, environmental protection, photoswitchable devices and various medicinal uses). [3, 4, 5] They also serve as model systems for studying molecular recognition in biological systems. [6] There are many aspects of crown ethers that determine selectivity, such as the size of the macrocycle and the nature and arrangement of the donor groups. [2] Information on the conformation that the crown ether adopts in the absence of the ligand is important in the engineering of macrocycles with predetermined selectivity for binding with specific substrates.

Crown ethers are highly flexible molecules and determining their conformational preferences has proved to be a computational challenge. A major problem in the modeling studies of crown ethers and other macrocycles is to obtain structures which are preorganized for complexation. [7, 8] Due to the difficulties in the conformational space search, inclusion-type structures are not obtained easily. In prior studies, detailed conformational analysis of 18-crown-6 (18C6) [9] and 9-crown-3 (9C3) [10] were reported as a part of a research program for the development of efficient conformational sampling techniques for cyclic molecules. In this paper, the methodology is extended to thiacrown ethers, which show increased selectivity over crown ethers for binding with second and third row transition metal ions. [11] The present paper describes the conformational analysis of the smallest thiacrown ether, 1,4,7-trithiacyclononane (9S3), using a combination of Molecular Mechanics and Density Functional Theory (DFT) methods.

Methodology

An exhaustive conformational search was carried out using the Conflex program [12] at the molecular mechanics level using the MM2(91) force field. The search was done using the Conflex algorithm, which has been described in detail elsewhere [13, 14] and will be given briefly. The method uses a three-step procedure: structure generation, minimization and duplicate detection, for generating the low-energy conformers (LECs). Reservoir filling and a gradual increase in the energy window ensures that the conformational space search is directed towards LECs. Duplicates were detected and eliminated using root-mean-squared difference (RMSD) of the torsion angles. This method was found to be fast and effective when compared to other methods. [15] A structure was judged to be different if the RMSD between the structures being compared is more than 15°. [9] All possible equivalent structures were checked for symmetry to generate unique conformers. The Conflex program was modified to calculate the point group symmetry for a given tolerance. [16] The conformations are described using the point group symmetries (C_1, C_2, C_3 and D_3). The notation used refer to *gauche*$^+$ 60°±60°, *gauche*$^-$ −60°±60° and *anti* 180°±60°. Conflex calculations were performed on a Pentium II computer.

Conformational preferences were also studied at the DFT level of theory and the calculations were performed with the program DeFT developed by St-Amant. [17] For the DFT calculations, double-ζ plus polarization and triple-ζ plus polarization orbital basis sets were placed, respectively, on the hydrogen and heavy atoms. According to Huzinaga's notation, [18] the H atoms had a (41/1*) contraction pattern, the C atoms had a (7111/411/1*) and the S atoms a (73111/6111/1*). Auxiliary fitting basis sets for S, C and H atoms were (5,4; 5,4), (4,4; 4,4) and

(3,1; 3,1) respectively. All DFT calculations were carried out on an SGI Origin 200 computer.

Results and discussion

Molecular mechanics studies

The initial structure of 9S3 was constructed using an arbitrarily chosen geometry. The default dielectric constant of 1.5, which is standard for gas phase calculations was used and the convergence limit for energy gradient was set to be less than 10^{-4} kcal mol^{-1} Å^{-1}. Twelve symmetry-unique LECs were located within an energy span of 5 kcal mol^{-1}. The execution time was approximately 6 min. The structures were characterized by computing second derivatives. [19] The absence of negative frequencies confirmed the structures to be minima. Table 1 shows the results of the Conflex search. The torsion angles not involving hydrogen atoms, relative energies for the twelve conformations, frequency of occurrence of each conformer and their point group symmetries are shown. The 12 structures are drawn in order of increasing relative energy in Fig. 1.

Conflex calculations generated 348 trial structures within a energy search window of 5 kcal mol^{-1} while accessing many regions of the conformational space. Each torsion angle assumed a range of value *gauche*$^+$, *gauche*$^-$ and *anti*. The calculations show that conformer **1** with C_1 symmetry is the global energy minimum (GEM) and the conformer **2** with C_3 symmetry virtually isoenergetic in which sulphur atoms are in the all *endo* conformation. The other important conformers of 9S3 are **4** and **5** with C_2 and D_3 symmetries, respectively. Thiacrown ethers generally prefer an exodendate orientation of the sulphur atoms because of the preference of

Table 1 Torsion angles and relative energies of 9S3 obtained using Conflex

Torsion angle[a]	Conformation[b]											
	1	2	3	4	5	6	7	8	9	10	11	12
S1–C2	134.0	133.8	153.6	73.8	61.0	−153.9	84.0	−115.8	133.7	−76.6	109.3	54.7
C2–C3	−96.7	−51.9	−54.0	−70.0	−140.8	94.9	−136.9	111.9	−51.8	−65.3	−146.0	−149.7
C3–S4	74.8	−62.5	−53.2	−58.8	61.2	−57.2	68.5	−47.1	−64.0	77.0	56.0	57.1
S4–C5	−124.7	133.9	101.8	111.3	61.0	98.5	68.3	−61.8	82.2	53.8	64.6	35.8
C5–C6	62.0	−52.0	−116.8	−92.9	−140.8	−138.3	−137.0	163.3	41.5	−123.9	−69.3	−108.8
C6–S7	73.8	−62.4	128.4	111.4	61.0	107.2	84.2	−99.5	−138.2	96.1	−57.4	140.9
S7–C8	−122.1	133.9	−95.7	−58.5	61.1	−103.5	−92.6	59.4	53.7	−105.6	144.1	−58.4
C8–C9	82.2	−52.1	72.0	−70.2	−140.8	49.9	136.5	−99.8	43.9	50.7	−48.8	−58.4
C9–S1	−92.8	−62.5	−96.4	73.6	61.1	63.8	−92.8	125.2	−114.6	79.0	−37.3	76.8
R.E.[c]	0.0	0.03	1.24	1.98	2.37	2.66	2.76	3.19	3.23	3.47	3.84	5.00
Freq.[d]	40	21	37	19	19	26	24	4	24	36	33	12
Symm.[e]	C_1	C_3	C_1	C_2	D_3	C_1	C_2	C_1	C_1	C_1	C_1	C_1
Conformation Beech et al.[f]	b	a	c	g	d	l	j	h	e	f	i	k

[a] The torsion angles in degrees with respect to the indicated central bond
[b] Designations of conformations as used in Fig. 1
[c] Relative energy in units of kcal mol^{-1}
[d] Number of times a conformer is found
[e] Point group symmetry
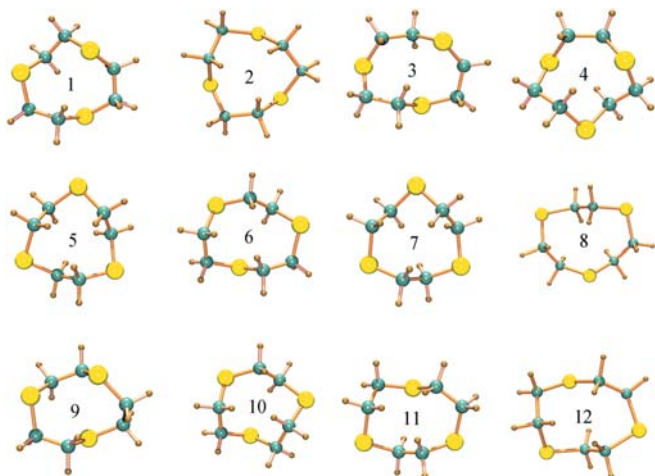[f] Conformation notation used in [26]

Fig. 1 Low-energy conformations of 9S3 obtained using Conflex

C–S bonds to adopt *gauche* torsion angles and C–C bonds *anti* torsion angles. [20] The exodendate conformation must switch to the endodendate orientation of sulphur atoms with SCCS torsion angles *gauche* for complexation to take place. The X-ray structure of 9S3 in the metal-free state displays the C_3 symmetry [21] preorganized for metal complexation. An analysis of structures with the 9S3 backbone was carried out using the Cambridge Structure Database (Version 5.15, April 1998, 182513 entries). [22] The search yielded 119 hits and the results show that the metal-free 9S3 adopts the C_3 conformation preferentially and that this conformation is predominant even upon complexation. A smaller number of conformations have also been observed with C_2 symmetry (9S3–Au complex [23] and 9S3–Cu^2 complex [24]). Conformer **4** is in agreement with the crystal structure of 9S3–Au complex (CSD code: KAMXOL)

The gas-phase GEM and the LECs of 9S3 was found to be dependent on the force field and methodology used. Blom et al. [25] have studied the four representative forms for 9S3 (C_1 (**1**), C_3(**2**), C_2 (**4**) and D_3 (**5**)) using molecular mechanics and reported that the C_1(**1**) and C_2(**4**) conformers best explain the electron diffraction data. An extensive conformational space search have been reported by Beech et al. [26] who have used the CHARMm force field, 1,000 structures and three different search procedures to identify 13 LECs for 9S3. Thus, previous attempts in the conformational space search have shown that the determination of the GEM and all the LECs is not trivial even for a small cyclic system such as 9S3. They have observed that the C_3 conformer was the global minimum and the C_1 conformer was found to be 0.3 kcal mol^{-1} higher in energy. The LECs generated also served as a valuable source for verifying the capability of Conflex for conformational sampling. The present Conflex calculations could also generate 12 of the 13 conformers identified as LECs by Beech et al. without using multiple starting geometries. The thirteenth conformer, which could not be generated, was shown by Beech et al. [26] to be dependent on the protocol and the optimization method used. Conflex calculations and the CHARMm force field studies predict the C_3 conformation observed in the solid state as a low-energy conformer. Recently, Hill and Feller [27] have reported the conformational analysis of 9S3 using the CVFF force field. They carried out a high temperature (2,000 K) Molecular Dynamics (MD) simulations and produced eight conformers within a 5 kcal mol^{-1} energy window and predicted a different conformational energy ordering. The C_1 and C_2 conformers were the most stable ones and the C_3 conformer was calculated to be 4.0 kcal mol^{-1} higher in energy. The calculations did not find the D_3 conformer. The relative energies obtained from Conflex calculations are compared with the results obtained using the CVFF and CHARMm molecular mechanics force fields (Table 2). It appears that different force fields produce low-energy conformers with differing energy ordering.

9S3 being a small and odd-numbered ring system can be expected to have considerable strain. [27] Due to this strain, the energy barriers of transformation exodendate→endodendate will be high. Molecular dynamics simulations are not efficient in searching the conformational space of molecules due to kinetic traps and rarely interconvert conformations. This was highlighted in the MD simulations reported for 18-crown-6 (18C6). [7] The

Table 2 Relative conformational energies (in kcal mol^{-1}) for 9S3 from different theoretical studies

Conformer	Symmetry	Molecular mechanics			DFT		MP2[b]
		Conflex	CHARMm[a]	CVFF[b]	VWN	BP	
1	C_1	0.0	0.3	0.0	–	0.7	0.3
2	C_3	0.0	0.0	4.0	5.2	4.9	4.5
3	C_1	1.2	0.9	–	1.3	–	–
4	C_2	1.8	0.6	0.0	0.0	0.0	0.0
5	D_3	2.4	1.5	–	1.4	2.3	–
6	C_1	2.7	2.3	–	4.3	–	–
7	C_2	2.8	2.8	4.6	3.7	3.3	3.4
8	C_1	3.2	3.6	4.2	4.5	3.9	4.0
9	C_1	3.2	3.0	5.1	7.7	6.9	7.1
10	C_1	3.5	3.0	3.3	2.0	1.9	1.9
11	C_1	3.8	2.9	–	5.2	5.2	–
12	C_1	5.0	4.0	4.3	4.6	4.9	5.2

[a] [26]
[b] [27]

Table 3 Experimental and theoretical geometries for the C$_3$ conformer of 9S3

Structural parameters	Crystal structure[a]	Present study			MP2[b]
		Conflex	VWN	BP86	
S–C	1.822	1.821	1.813	1.844	1.832
C–C	1.510	1.542	1.511	1.534	1.533
C–C–S	115.1	114.3	116.9	118.1	116.7
C–S–C	102.8	101.5	101.2	102.3	103.4
C–S–C–C	131.1	133.9	131.5	129.7	−130.4
S–C–C–S	58.6	52.0	56.2	56.3	56.8
C–S–C–C	55.1	62.5	57.7	57.1	58.2
S⋯S[c]	3.454	3.308	3.428	3.526	3.525

[a] [21]
[b] [27]
[c] Cross ring S⋯S distance

important conformers of 18C6, C$_i$ (in the free state) and D$_{3d}$ symmetry (when complexed to K), are only 1.9 kcal mol^{-1} apart, yet MD simulations could not sample both the conformations in a single search. In spite of the significant energy barriers between the C$_3$ and D$_3$ conformers of 9S3, the Conflex studies enabled interconversions between them, thereby overcoming the limitations of MD simulations. The effect of starting geometry on the LECs was also studied and Conflex calculations were carried out from two other starting geometries No new conformers were generated within an energy window of 5 kcal mol^{-1}. This shows that Conflex procedure is not biased by the best starting structure, unlike MD simulations. [28]

Chang et al. have defined D_{min}, the number of times a conformer is found as an indicator of search efficiency. [29] It was suggested that D_{min} of at least 5 for each conformer is an indication of the thoroughness and the efficiency of the conformational search. [30] The frequencies of occurrence observed for each structure, shown in Table 1, varies between 4 and 40 and provides further evidence that Conflex calculations can search the available conformational space of 9S3 efficiently. The number of starting geometries can also be considered as a measure of efficiency. The Conflex study required the generation of 348 trial structures for obtaining the 12 symmetry unique conformations.

DFT studies

The calculations were carried out using the DeFT package. [31] The choice of the density functional is critical to reliably predict the geometries and conformational energy of organic molecules. Two functionals were used in the study, first local density approximation DFT calculations were performed using the Vosko–Wilk–Nusair (VWN) correlation functional. [32] The second functional used the combination of Becke exchange functional [33] and Perdew correlation functional [BP86]. [34]

Full geometry optimization of the 12 Conflex generated structures was performed using these functionals, yielding structures that are close to the starting struc-

tures[1]. During DFT optimization, some of the geometries converged to other structures: using the VWN functional, conformer **1** converged to **3** and for the BP86 functional conformers **3** and **6** converged to **1**. Table 2 lists the relative energies obtained using the VWN and BP86 functionals and these are compared with the relative energies obtained from the MP2 level of theory reported by Hill and Feller. [27] There was also reordering of the conformations. Of the two DFT methods used, both functionals predicted conformation **4** with C$_2$ symmetry as the GEM. The BP(86) functional showed that **1** with C$_1$ symmetry was 0.7 kcal mol^{-1} higher in energy. These conformers are lower in energy than other conformations. The relative energy ordering for the conformers common to VWN and BP86 show a similar trend. Ab initio calculations at the MP2 level of theory using the 6-31+G* basis set have been reported for eight of the conformers and the relative energies are also shown in Table 2. Density Functional calculations are able to reproduce the conformational energy trend of MP2 calculations. The DFT-BP86 calculations are better suited to produce the MP2 energy trend than the DFT-VWN calculations.

Table 3 provides a comparison of the bond lengths, bond angles and torsion angles of the C$_3$ conformer obtained from the X-ray crystal structure, Conflex, MP2, and DFT theoretical studies. Taking the absolute differences it appears that the DFT–VWN calculations reproduce the C–C and C–S bond lengths and the transannular S.....S cross ring distance better than other methods. On the other hand, the gradient corrected DFT–BP86 calculations overestimate the C–C and C–S bond lengths by 0.02 Å and the S....S distance by 0.07 Å when compared with the crystal structure. When the bond lengths obtained from MP2 calculations are compared to the DFT studies, BP(86) gives better agreement than the VWN DFT functional. The bond angles and torsion angles obtained from the VWN and BP86 density functionals are indistinguishable and are within 1 to 3° of the experimental value. It appears that the local density approximation (VWN) is able to reproduce the structural parameters of

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[1] RMSD of the nine torsion angles of the Conflex and the corresponding DFT geometries was within 15°.

9S3, although the energies are not in good agreement with the MP2 studies.

Conclusion

In this study the conformational preferences of 9S3 were studied by the combined use of molecular mechanics and DFT calculations. Conformational-space sampling was carried out for 9S3 using the Conflex algorithm. Previously reported structures were obtained from an arbitrarily chosen starting conformation and without using experimental data as constraints. It was not possible through MD simulations to cross the conformational barrier between exodendate C_3 and endodendate D_3 conformations, but the Conflex sampling allowed the interconversions. The ligand has a preorganized conformation for complexation in the conformational properties of 9S3. The generation of inclusion type structures without explicitly considering the metal ion and the high frequency of occurrence of each conformer also demonstrates the efficiency and the extent of the conformational sampling by the Conflex method. It appears that combining molecular mechanics with DFT calculations was successful in obtaining relative conformational energies comparable to high-level MP2 calculations and can be extended to other molecules of biochemical interest. The generation of all the LECs is mandatory for deconvoluting NMR data into viable multiple conformations, which when considered together can explain the solution data. This will be future application of Local Perturbation Method of conformational space sampling being developed.

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