

Efficient conformational sampling of multiconformational cyclic molecules: application to 1,4,7,10,13-Pentaoxacyclopentadecane

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Abstract The result of an exhaustive search of low-energy conformers of 1,4,7,10,13-Pentaoxacyclopentadecane is presented. The search method combines the generation of large number of trial conformers using local nonstochastic deformations known as the Conflex method, which is coupled to AMBER force field as the minimizer. The extent of the conformational space sampled was evaluated from the view point of the number of duplicates of each conformer, generation of inclusion type structures without considering the substrate and the spread of the allowed torsion angles visited during the search. It is shown that the conformational search is exhaustive and efficient as conformers, which the metal coordinated crown ether complexes adopt, were generated. Free energies using the AMBER structures were calculated using the model of Cramer and Truhlar. The study suggests that 1,4,7,10,13-Pentaoxacyclopentadecane exists as a mixture of conformers in solution. The results show the efficiency of the method and could be the method of choice in the design of synthetic macrocyclic receptors.

Keywords Conformational space search · Computational sampling and preferences · Cyclic molecules · Multiple minima · Solvation energies

Introduction

Macrocyclic crown ethers are known for their ability to coordinate metal ions including alkali cations and organic

molecules [1]. This characteristic feature has led to crown ethers finding applications in separating nuclear wastes [2] in the design of photo switchable molecular devices [3], as contrast enhancing agents in magnetic resonance imaging [4] and in the understanding molecular recognition in biological systems [5]. Numerous crown ether hosts have been synthesized and their complexation properties with various substrates investigated [6, 7]. Though a variety of factors are responsible for the crown ether-substrate interactions, it was observed from experimental and theoretical studies that crown ethers due to their cyclic nature, multiple oxygen sites and symmetry are structurally flexible and adopt many conformations appropriate to the substrate and the environment [1, 8, 9].

Although the chemical structure of crown ethers might suggest that they are rigid, in the absence of a metal or a substrate they can exist in multiple conformations. In order to design tailor made crown ethers for a specific metal, the complete conformation profile of the uncomplexed molecule must be known. Numerous theoretical studies have been reported for the conformational analysis of crown ethers using *ab initio* quantum mechanical methods, molecular mechanics, molecular dynamics and Monte Carlo simulations [10–14]. These studies have emphasized the conformational flexibility of crown ethers.

The conformational space of crown ethers involves a large number of minima, which are separated by high energy barriers. Molecular dynamics (MD) simulation samples only those regions of the conformational space, which do not require transitions over high energy barriers. Straatsma and McCammon [8, 9] from MD simulations have shown that a few conformational transitions take place and that the geometry of crown ethers stayed around the starting geometry. Sun and Kollman [14] sampled the conformational space of 18-Crown-6 by 6 ns MD simula-

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tion at 500 K to achieve conformational equilibrium. The incomplete sampling of MD simulation has been attributed to a symmetry related degeneracy factor. It was also observed from theoretical studies that to obtain inclusion type structure from crown ethers, the metal ion must be implicitly considered in the MD simulation [15].

Even for small systems like 9-crown-3 and its thia analogue 9-[Ane]-S3 that it was not trivial to find all the low-energy conformers. Multiple starting geometries had to be considered for generating all the low-energy conformers for these molecules [16, 17]. Hill & Feller [18] commented that accurate prediction of low-lying conformations in floppy molecules is a challenging task, and the presence of intermolecular C—H—O interactions in the title compound, though weak, could well alter computational energy rankings derived for isolated molecules. We have shown earlier that it was possible to generate the inclusion type structures for 18C618C6 [19] and 9-[Ane]-S3 [20] without considering the host metal ions which the MD simulations have missed. There is an ongoing research program to design cyclic molecules which self-assemble to form nanotubes [21]. As a part of this program, we have been working to develop a reliable conformational space search methodology for studying cyclic molecules. In this communication, we present the results of a conformational search carried out for 1,4,7,10,13, Pentaoxacyclopentadecane (15C5). The high flexibility and symmetry lead to the existence of a large number of low-energy conformers. It will be an ideal test case for the Conflex method to generate all the relevant conformations.

Computational methods

We have used the CONFLEX program [22, 23] for the conformational space, which was modified to use the AMBER force field [24] as the minimizer supplemented by parameters by Billter *et al.* [25] (henceforth referred to as CA). The starting geometry was built using the PLEP suite of programs and was chosen for the conformational search calculations. The conformational search involves a three step cycle. An arbitrarily chosen starting geometry is chosen and then minimized. The minimized structure is then subjected to perturbation to produce more starting conformers, which are also minimized. Thirdly the resulting structures are compared with previously stored conformers. The choice of an arbitrarily generated starting structure is also used to show the conformational sampling capability of CA program. Redundancy is a well-known problem in conformational search programs. Duplicates were detected and eliminated using the RMS difference of all the possible pairs of torsion angles between the current structure and with the previously stored structures. If the value of the

RMS difference is greater than 15° the two conformers are judged to be different. The numbering of the atoms was permuted in both the directions and also the signs of the torsion angles were changed to allow for the symmetry of the molecule. The symmetry equivalent structures are counted as one conformer. Reservoir filling and a gradual increase in the search limits ensure an efficient coverage of the conformational space and that the direction of the search is from high energy to low-energy regions. Conformational searches were carried out for 15 kcal mol⁻¹ above the local minimum. The notation used for describing the endocyclic torsion angles are *gauche*⁺ (60°±60°), *gauche*⁻ (-60° ± 60°) and *anti* (180°±60°). The conformers are designated according to Dale nomenclature [26]. Two successive *gauche* angles are termed as a corner and the number of corners are written between square brackets. The direction of the numbering and the starting point are chosen so as to give the smallest number.

The CA program was further modified to calculate the maximum symmetry group for a given tolerance [27]. The solvation energy was calculated using the Omnisol program [28] for predicting solvation energies using only geometry-dependent atomic surface tensions developed for organic solvents was used [29] and integrated into the CA program. The method is based on gas-phase geometries and exposed atomic surface areas; electrostatics being treated implicitly. A combination of Ortep III [30] and Povray was used to prepare the figures.

Results and discussion

Conformational search calculations were carried out for 15C5 using the CA program. The dielectric constant (ϵ) used in the CA calculations was $\epsilon=4$ and required 7659 trial structures to generate 195 symmetry-unique conformers within an energy span of 12 kcal mol⁻¹. Still and co-workers have defined D_{\min} , the smallest times a conformer is found as an indicator of search efficiency [31]. The molecule structure can be described *via* the 15 torsion-angle sequence. This sequence, number of times a conformer is found, CA relative energies, point group symmetry is given in Table 1. The 12 conformations of Raithby *et al.* and two crystal structures recently reported for 15C5 have been compared with the 195 conformers obtained from CA calculations. Fourteen conformers which match the reported torsion angles are listed in Table 1 and the conformers are shown in Fig. 1.

The extent to which the conformational search has been sampled is an important question and this was addressed by using the distribution about the three contiguous torsion angles (-O-C-, -C-C- and -C-O-), the radius of gyration (Rg) and the ability to sample experimentally observed

Table 1 Torsion angle sequence, symmetry and relative energies of LECs of 15C5

S.No.	Torsion Angle sequence ^a	Conformation ^b	Symmetry ^c	CA ^d		Solvation energy	Total energy
				R.E	D _{min}		
1	O-O --O O+O O-O O+O	Uniangular-1	C ₁	0.18	151	-8.38	-8.20
2	O-O O-O O+O O-O O+O	Anangular	C ₂	1.21	38	-7.62	-6.40
3	O-O --O O++ O++ O+O	[348]	C ₁	1.44	88	-10.36	-8.92
4	O-O ++O ++O O-- O-O	[411]	C ₁	1.72	66	-10.44	-8.72
5	--O --O O+O O-O --O	[339]	C ₁	2.39	59	-10.62	-8.22
6	O+O --O O+O O-O O++	[510]	C ₁	2.58	48	-8.25	-5.67
7	O-O --O O+O O++ O+O	[78]	C ₁	2.72	36	-8.25	-5.53
8	O-O --O O++ --O O+O	[249]	C ₁	3.02	31	-9.86	-6.84
9	+O --O O+O O+ OOO	Uniangular -2 ^e	C ₁	3.26	53	-10.53	-7.27
10	--OO ++O O+O O -O -O	Uniangular-3 ^e	C ₁	3.30	32	-11.85	-8.55
11	++O ++O O-- O-- O-O	[3435]	C ₁	3.89	23	-11.92	-8.02
12	O++ --O O++ O++ O++	[23334]	C ₁	3.99	35	-11.78	-7.79
13	--O -O -O -O --O	[33333]	C ₅	4.18	15	-13.37	-9.19
14	O++ --O O-O -O-O	[2436]	C ₁	4.57	21	-9.27	-4.70

^a Torsion angles of 15C5 given as a sequence with the C-C bonds at positions 2,5,8, 11 and 14.

+ are for angles ($60^\circ \pm 60^\circ$), - for angles ($-60^\circ \pm 60^\circ$) and O for angles ($180^\circ \pm 60^\circ$)

^b Conformation according to Dale nomenclature used in reference [26]. Uniangular-1 structure is from reference [33].

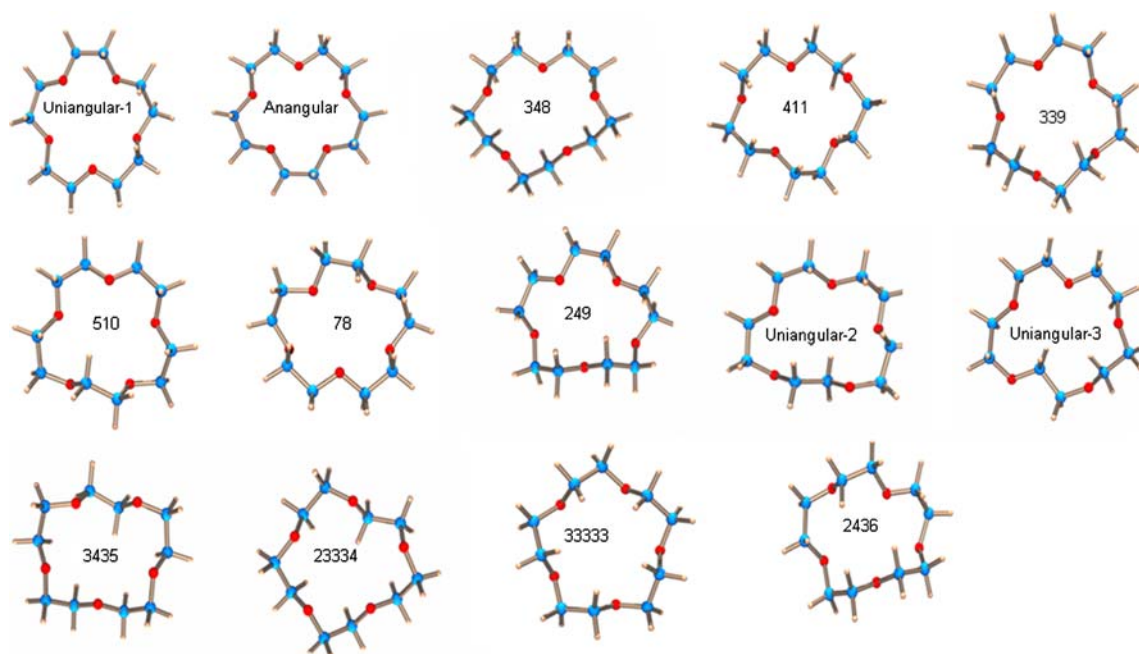
^c Point group symmetry

^d Relative energy, solvation energy and total energy are given in kcal mol⁻¹.

^e Crystal structures for reference [34]

conformers. The one dimensional scatter plots for the three angles shown in Fig. 2(a–c) and the plot of the radius of gyration for the various minimized structures is shown in Fig. 3. Features to note from Fig. 2(a–c) is that the

sampling of the torsion angles is widely distributed and torsion angles below 40° are not found in the conformation space search of 15C5 and angles around $\pm 50^\circ$ are observed at higher energy conformers ($2.5 \text{ kcal mol}^{-1}$ above the

**Fig. 1** Low-energy conformers of 15C5

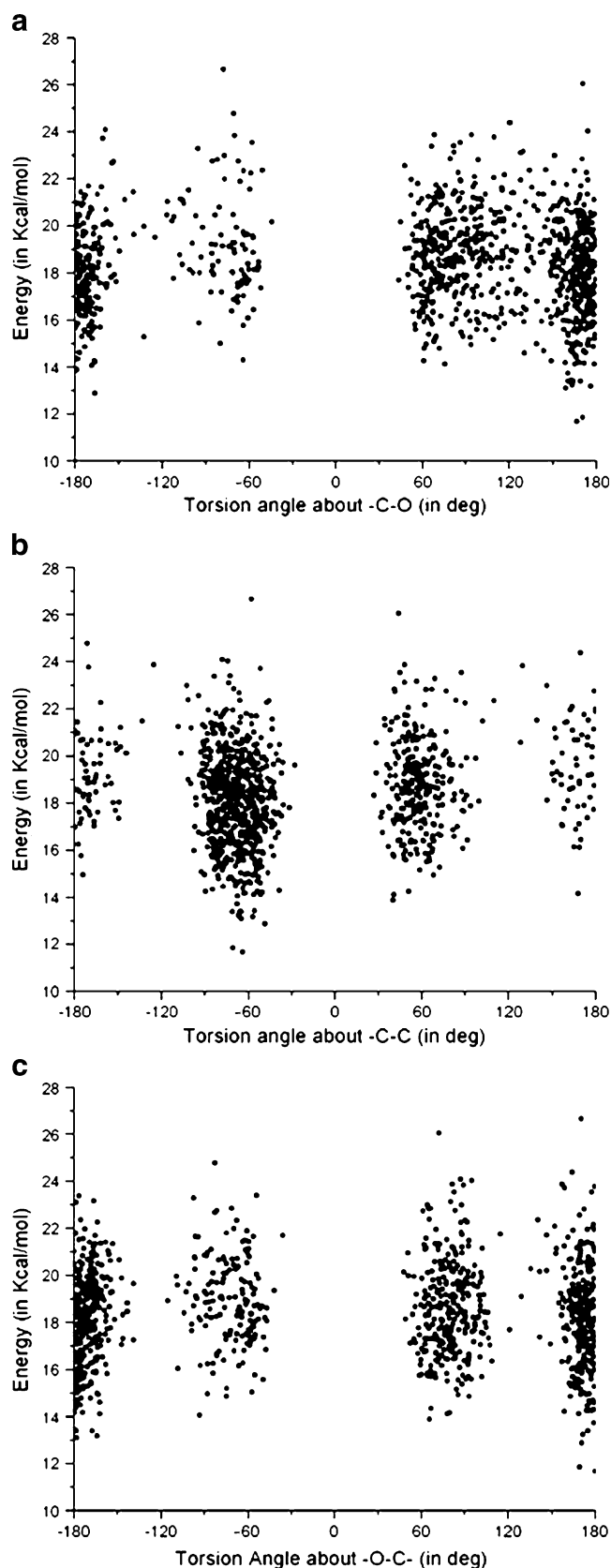


Fig. 2 Scatter plots for the three torsion angles (a) $-C-C-O-C$ (b) $O-C-C-O$ and (c) $C-O-C-C$

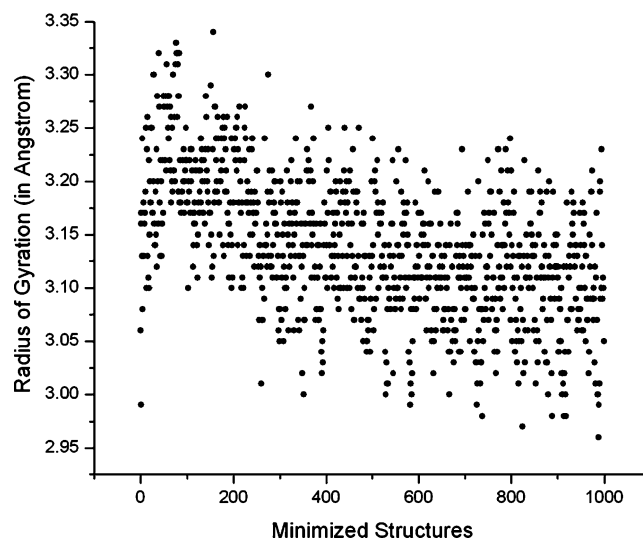


Fig. 3 Scatter plot of the radius of gyration for the minimized structures

lowest energy). The torsion angles are distributed chiefly in the ranges $[50^{\circ}-100^{\circ}]$, $[150^{\circ}-180^{\circ}]$. Radius of gyration can be used as a measure of the conformational diversity of the structures generated. The values of R_g spans from 2.95 Å to 3.25 Å and from the R_g values it can be inferred that the conformational space search contains structurally diverse conformations. Repeated deformation of atoms and bonds by corner flipping and flapping by the Conflex technique enables the system to cross over energy barriers and minimize to conformers that are lower in energy.

Dale has carried out pioneering work in the conformational analysis of cycloalkanes [32]. He suggested that the structure of cyclopentadecane will possess a quinquangular [33333] structure. Crystallographic results retrieved from Cambridge Structure Database and their subsequent minimization using molecular mechanics (MM3) showed that the conformational preferences of 15C5 are dictated by the coordination environment [33] and identified 15 low-energy conformers (LECs). It was observed that the unangular, triangular [348] and anangular conformations predominate in the CSD data and are adopted by a wide range of metals. Recently, the crystal structure of 15C5 was reported, which is liquid at room temperature [34]. It crystallizes, using in situ methods, with two different conformers in the asymmetric unit, which differs from those identified in conformational searches based on data. A RMSD comparison was made between structures obtained from the CA studies and the 17 structures generated from crystallographic data. Two of the three conformations that the search missed are I_{383} , I_{14} , which are characterized by a planar OCCO torsion angles and are transition state structures in the 15C5 energy landscape. The third conformation missed by CA is the [357] which has a CCOC angle

of 7°. The I_383 conformer relaxes to the [78] conformation on minimization, which the present search could generate.

Most of the CA generated structures were the unsymmetrical conformers the search could also generate structures with point group symmetry of C_5 , C_2 and C_s . All the OCCO torsion angles are close to the expected *gauche* conformation and all of the CCOC angles are close to *trans* conformation. The frequency of occurrence for the 14 LECs given in Table 1 ranged from 15 to 158, which is indicative of the thoroughness of the conformational space search. Goodman and Still have suggested that a value of 5 for the number of times a conformation is found to represent search efficiency [31]. The conformational space study of 15C5 was comprehensive as the study could generate the previously reported experimentally observed structures and theoretical LECs. Many of the conformation of the 15-crown-5 moiety have the (O+O O-O)₂ O+ torsion angle sequence which is similar to the (O+O O-O O+O)₂ conformation of the 18-Crown-6.

The conformational preferences of 15C5 are determined by the 14,CH...CH interactions [35]. Due to these interactions, the OCCO torsion angle prefers to be *gauche* and the COCC angles *anti* such that the oxygen lone pairs are oriented toward the cavity and are appropriately placed for complexation with metals. The twelve 15C5 conformers obtained from CSD and the conformers obtained from CA have all the five OCCO torsion angles *gauche*. A combination of MD simulations using the CVFF force field and the *ab initio* calculations were used to identify the LECs of 15C5 by Hill and Feller [18]. Of the 16 LECs (Table 2 in reference [18]) only conformer 4 and 16 matched the experimental data. The other conformers were endodentate as at least one of the OCCO torsion angles was *anti*. These conformations are not ideal coordination geometries due to lone pair placement is not suited for metal binding. The conformational search carried out by Paulsen *et al.* [36] using the MM3 force field has reported 35 conformers within 2.5 kcal mol⁻¹ above GEM. Of these only three are representative of the crystal structures and in 18 of the conformers at least one of the OCCO torsion angles is *anti*. The present study shows that CA method can generate the conformers which have been observed in crystal structures.

The conformers of 15C5 that are present in solution have not been unambiguously been identified. We have analyzed the conformer relative energies in solution and the interactions within the crown ether-solvent system is described approximately by $E_{tot} = E_{AMBER} + E_{SOL}$ where E_{AMBER} is the energy of the AMBER force field and E_{SOL} is the solvation energy calculated using Omnisol [28]. The results suggest that 15C5 exists as a mixture of conformers with major contributions from the conformers uniaxial,

[348], [411], [339], [33333]. This is in agreement with the report of Paulsen *et al.* [36]. Though the conformational space search indicates many conformers, only some of them predominate both in the crystal and solution. These results demonstrate that the Conflex-AMBER method is well suited for studying the conformational preferences of crown ethers in the absence of substrates and metals.

Conclusions

Extensive conformational sampling is an important issue to obtain accurate molecular modeling results in the design of new molecules for practical applications. The conformational flexibility of 15C5 has been investigated using Goto-Osawa algorithm based conformational search method. The system studied is a cyclic molecule with 15 variable torsion angles. The method was able to generate inclusion-type structures without explicitly considering the metal ion. These structures were obtained from an arbitrary chosen starting conformation and without using experimental constraints. This demonstrates the efficiency and thoroughness of the conformational search using Conflex method. The generation of all the LECs is mandatory for deconvoluting NMR data into viable multiple conformations, which are populated and can be used to explain the solution data. The goal of the study is to develop search methods and protocols for analyzing and interpreting NMR data of cyclic peptides making extensive use of the generated low-energy structures, which are populated and which are chemically meaningful. Presently investigation is being carried out in these lines in the design of novel amphi-ionophores, which have affinities for cation and anions. The experience in studying the conformations of crown ethers reveal that in order to improve the speed of the calculations duplicate conformer detection and removal has to be improved. Research is in progress in this direction.

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