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Conformational Study of the Structure of Free 18-Crown-6

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A conformational search was performed for 18-crown-6 using the CONLEX method at the MM3 level. To have a more accurate energy order of the predicted conformations, the predicted conformations were geometry optimized at the HF/STO-3G level and the 198 lowest energy conformations, according to the HF/STO-3G energy order, were geometry optimized at the HF/6-31+G* level. In addition, the 47 nonredundant lowest energy conformations, according to the MP2/6-31+G* energy order at the HF/6-31+G* optimized geometry, hereafter the MP2/6-31+G*//HF/6-31+G* energy order, were geometry optimized at the B3LYP/6-31+G* level. According to the MP2/6-31+G*//B3LYP/6-31+G* energy order, three conformations had energies lower than the experimentally known C_i conformation of 18c6. At the MP2/6-31+G*//B3LYP/6-31+G* level, the S_6 lowest energy conformation is more stable by 1.96 kcal/mol than this C_i conformation. This was confirmed by results at the MP2/6-31+G* level with an energy difference of 1.84 kcal/mol. Comparison between the structure of the S_6 conformation of 18c6 and the S_4 lowest energy conformation of 12-crown-4, as well as other important conformations of both molecules, is made. It is concluded that the correlation energy is necessary to have an accurate energy order of the predicted conformations. A rationalization of the conformational energy order in terms of the hydrogen bonding and conformational dihedral angles is given. It is also suggested that to have a better energy order of the predicted conformations at the MM3 level, better empirical force fields corresponding to the hydrogen bond interactions are needed.

Introduction

Although crown ethers were first discovered by Pedersen at du Pont in 1967,[1,2] cyclic polyethers were known long before[3−5] and Pedersen was only the first to indicate their outstanding binding properties. Since their discovery, there has been an immense increase in the interest and research of the chemistry of crown ethers and their applications. For example, a new field in chemistry called molecular design[6] was opened with a large variety of molecules, e.g., cavitands, cryptands, cyclidenes, cryptophanes, etc. Much of the interest in crown ethers is due to their various solubility capability and therefore different binding properties to cations.

Crown ethers have numerous applications. They are used in cancer treatment,[7] treatment of nuclear waste,[8] catalysis,[9] control of reaction mechanisms,[10] second-sphere coordination,[11] ion transport,[12] macrocyclic liquid crystals,[13] zeolite synthesis,[14] and ion-selective electrodes.[15] Also, the ability of crown ethers to form complexes with biologically important cations makes them good models as enzyme-binding sites[16] and as ionophores in membrane transport.[17] They are also used in anion activation,[18] cation inhibition, and nucleophilic addition reactions.[19]

Crown ethers are composed of two parts, the core part and the side chain attached to the core part. Thus, because of the side chain, crown ethers are called armed crown ethers. The most important core parts are 12-crown-4 (12c4), also known as 1,4,7,10-tetraoxacyclododecane; 15-crown-5 (15c5), known also as 1,4,7,10,13-pentaoxacyclopentadecane; and 18-crown-6 (18c6), known as 1,4,7,10,13,16-hexaoxacycloocatdecane, Figure 1.Because of the widespread applications of crown ethers, there has been a great interest in their conformational analysis.

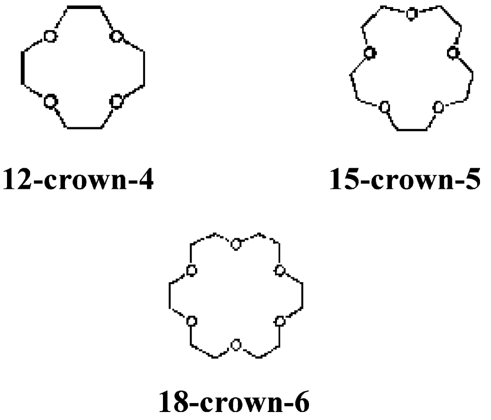

Figure 1. Structure of some of the crown ethers.

Conformational analysis has been reported for 9-crown-3 (9c3),[20,21] 12c4,[22−24] 15c5,[25] and 18c6.[26−42] In a recent report, a full conformational search of 12c4 has been performed using the CONFLEX method.[22] The search led to the prediction of 180 conformations at the MM3 level. To get a more accurate energy order of the predicted conformations and to study the dependence of the conformational energy order on the method used, computations were performed at HF/STO-3G level for all conformations and at the HF/4-31G and HF/6-31+G* levels for the 100 lowest energy conformations, according to HF/STO-3G energy order. In addition, optimized geometries were computed at the B3LYP/6-31+G* and MP2/6-31+G* levels for the 20 lowest energy conformations, according to the MP2/6-31+G*//HF/6-31+G* energy order. The function of this study was to be used as a guide in the conformational analysis of the larger 18c6, which has a much larger number of possible

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conformations. For the 20 conformations considered at the B3LYP level, it was concluded that the relative energies, with respect to the lowest energy conformation, at the MP2/6-31+G* and MP2/6-31+G*//B3LYP/6-31+G* levels are too close to each other to within 0.1 kcal/mol. There is the exception of only two conformations where the difference was as large as 1.13 kcal/mol. This is a quite important observation since geometry optimization at the MP2/6-31+G* level is considerably expensive especially for molecules as large as 18c6. It was shown that this observation is merely a reflection of the closeness of the MP2 and B3LYP optimized geometries. In larger differences in the structure of the optimized geometries, the difference in the relative energies was larger. It was also concluded that consideration of the correlation energy is necessary to get an accurate energy order of the predicted conformations. The hydrogen-bonding interaction was one of the important factors, but not the only factor, in the determination of the relative conformational stability.

There are many reports of the conformational analysis and simulation of 18c6 at the molecular dynamics,[26−33] Monte Carlo,[34−38] molecular mechanics,[39−42] and ab initio[43−45] levels. The majority of these studies was performed at the beginning and middle of the past decade. It is clear from these studies that the conformation of 18c6 depends on the medium it exists in, and the C_i and D_{3d} conformations are two of the most important conformations of 18c6. Molecular dynamics simulations predict that 18c6 has a C_i symmetry in vacuo and in apolar solvents,[26,30] although other low-energy conformations also exit.[30] In aqueous solutions, the D_{3d} conformation is of lower energy by 5.0 kcal/mol than the C_i conformation.[29] Straatsma et al.[31] also concluded that the lowest energy conformation of 18c6 in vacuo is not necessarily the most populated conformation in the solution phase. The authors estimated that the D_{3d} conformation is higher by 2.6 kcal/mol than the unconstrained 18c6. Monte Carlo simulation was in agreement with the molecular dynamics simulation. It was concluded that in apolar solvents, 18c6 adopts a C_i structure while in polar solvents it assumes a D_{3d} structure.[34−38] It was estimated that the potential energy of solvation in aqueous solutions is 23 kcal/mol lower for the D_{3d} conformation than for the C_i conformation.[38] Molecular mechanics[39−42] studies agreed in principle with the molecular dynamics and Monte Carlo simulations. In a recent conformational search report, the CONFLEX algorithm using the AMBER force field was applied to 18c6.[42] It was shown that the new routine was able to locate the experimentally known conformations of 18c6 and other conformations predicted through molecular dynamics simulations. Comparison between this report and the results presented in the current work will be made in the Results and Discussion section.

Ab initio results were reported by Feller and co-workers[43−45] that included a study of the nature of the complexes formed between 18c6 and different alkali and alkaline earth metal cations. It was concluded that the C_i conformation is more stable by 4.2, 4.4, and 5.4 kcal/mol than the D_{3d} conformation at the AM1, HF/6-31+G*, and MP2/6-31+G*//HF/6-31+G* levels, respectively.[43] Vibrational spectra of 18c6, free and its metal complexes, have been the focus of many studies.[46]

The experimental structure of 18c6, in the free and in the metal-complex state,[47−50] has been reported. X-ray structural data of free 18c6 at room temperature[47] and at 100 K[48] indicated that free 18c6 in the solid phase has a C_i structure. X-ray diffraction and Raman measurements of aqueous 18c6 were interpreted as 18c6 in aqueous solution having C_1 or D_{3d} symmetry.[49] It was concluded consequently that the molecule is flexible and in the aqueous solutions it may exit as a mixture of two conformations. X-ray measurement of 18c6−alkali metal cations showed that 18c6−alkali metal cations have structures ranging from D_{3d}, for the K^+ complex, C_{3v} for the Rb^+ and Cs^+ complexes, and C_1 for the Na^+ complex, depending on the size of the alkali metal cation.[50]

In the present publication, we report the results of the conformational analysis of one of the most important crown ethers, 18c6. The function of this conformational analysis report is to predict the lowest energy conformations of 18c6, to obtain an accurate energy order of the predicted conformations, and to study the factors affecting the relative conformational stability. This study is guided by the previous conformational analysis study of the similar and smaller 12c4.[22]

Computational Details

18c6 is a large ring molecule with 18 rotatable bonds and consequently many different possible combinations of dihedral angles and large number of possible conformations. In the conformational search of 18c6, an efficient method of the conformational search of ring molecules, the CONFLEX[51] method, was used. The method as implemented in the CAChe program[52] has the additional advantage of being fully programmed, making a conformational search of a large molecule such as 18c6 a simple procedure. The method was also used for the conformational search of the smaller 12c4.[22] The details of the conformational search, using the CONFLEX method, are described in detail elsewhere[22] and are mentioned here briefly for completeness. Starting from a given initial conformation, the conformational search method uses the edge flip, corner flap, and dihedral rotation perturbation options to generate possible conformations of 18c6. The generated conformations are geometry optimized, compared with the stored conformations, if available, in the conformational storage space and nonredundant conformations are stored. In the comparison step, permute, reverse, and reflect options were used. The perturbation step is repeated, in a cyclic manner, using each of the stored conformations in the conformational storage until all conformations in the conformational storage are exhausted. The located conformations are again geometry optimized and the vibrational frequencies are calculated. Conformations with imaginary vibrational frequencies are then eliminated. In the geometry optimization step, the CAChe MM3 augmented force field was utilized along with the conjugate gradient geometry optimization method.

There are only two differences between the conformational search procedures performed for 12c4 and 18c6. The first is that the program has the limitation of storing only the 5000 lowest energy conformations. These are the predicted conformations and not the conformations stored in the conformational storage which are to be subjected to the perturbation step for the generation of new conformations as will be described shortly. The number of the conformations in the conformational storage and in awaiting perturbation did not exceed 2060 conformations at any time, although the number of predicted conformation reached the limit of 5000 conformations at the early stages of computations. The second is that the conformational search of 12c4 was performed twice and the predicted conformations were geometry optimized at the HF/STO-3G level. It was found that the predicted conformations in both search steps resulted in the same conformations. Consequently, no additional conformational search steps were tried. For 18c6, because of the large number of the conformations predicted, the conformational search step was performed only once. In addition, as will be described shortly, about half of the predicted conformations were considered redundant. The CAChe program reports MM3 steric energy rather than MM3 strain energy usually reported by most of the other programs, a reason that no MM3 energies are given in this report.

The number of conformations located by the conformational search procedure described above, after exclusion of the conformations with imaginary frequencies from the 5000 conformation, was 3136 conformations. Geometry optimization was performed for these 3136 MM3 predicted conformations at the HF/STO-3G level and for the 250 lowest energy conformations, according to the HF/STO-3G energy order, at the HF/6-31+G* level. This is with the exception of 52 conformations which had equal energies, at the HF/STO-3G level, and steric energy differences of less than 0.02 kcal/mol to some of the other 198 conformations. These 52 conformations were considered redundant. This step was followed to reduce the number of conformations need to be computed at the HF/6-31+G* level. Although the number of conformations considered at the HF/6-31+G* level was still considerably high, 198 conformations, as will be described in the Results and Discussion section, some of the HF/STO-3G high-energy conformations were among the lowest energy conformations at higher levels of theory. In addition, it was found that 59 conformations, compared to the other 139 conformations, had equal energies at the HF/STO-3G and HF/6-31+G* levels and steric energies next to each other. These conformations were also considered as redundant and were excluded. Thus, the number of conformations was reduced to 139 conformations.

To recover some of the correlation energy, MP2 energies were calculated at the HF/6-31+G* geometry for the 139 above-mentioned conformations. This calculation is referred to as the MP2/6-31+G*//HF/6-31+G* level. Optimized geometries were also calculated at the B3LYP/6-31+G* level and the correlation energy was determined at the MP2/6-31+G*//B3LYP/6-31+G* level for the 60 lowest energy conformations, according to the MP2/6-31+G*//HF/6-31+G* energy order. This is with the exception of 12 conformations which had equal energies at the HF/STO-3G, HF/6-31+G*, and B3LYP/6-31+G* levels but had different steric energies. These 12 conformations were excluded since they may correspond to redundant conformations. Problems of locating minima of conformations or convergence of a conformation to another have been reported for the smaller 12c4.[22,24,55]

The ab initio computations were performed using the Gaussian 98[53] and Gaussian 03[54] programs. The Gaussian program default parameters were used in all computations. Optimized geometries were calculated at any step starting form the MM3 optimized geometry. The additional diffuse function in the 6-31+G* basis set was used to minimize the basis set superposition error and for the possible future calculation of the binding energies between 18c6 and different metal cations where the diffuse function is necessary for accurate prediction of energies and geometries of cation complexes.[56] The MP2 computations were performed with the full-direct algorithm of handling the two-electron integrals and the fixed core option of neglecting the core electrons.

Results and Discussion

The relative energies of the 47 predicted conformations, as was described in the Computational details section, of 18c6 at the HF/STO-3G, HF/6-31+G*, MP2/6-31+G*//HF/6-31+G*, B3LYP/6-31+G*, and MP2/6-31+G*//B3LYP/6-31+G* levels are given in Table 1. The relative energies were calculated with respect to conformation **2** since it is the lowest energy conformation at the correlated MP2/6-31+G*//HF/6-31+G* and MP2/6-31+G*//B3LYP/6-31+G* levels. Conformation **1**, of C_i symmetry, is the experimentally observed conformation of free 18c6 in the solid phase and has been sampled, to the best of out knowledge, as the lowest energy conformation of free 18c6 in almost all previous studies[26−45] and is the lowest energy conformation at the HF/STO-3G, HF/6-31+G*, and B3LYP/6-31+G* levels in the current study. To further clarify the energy order of conformation **1**, hereafter the C_i conformation, and conformation **2**, hereafter the S_6 conformation, optimized geometries were computed for both conformations at the MP2/6-31+G* level. The computations were in fact quite time demanding, although facilitated by symmetry, and therefore could not be performed for a larger number of conformations, except for the D_{3d} conformation. As shown in Table 1, the S_6 conformation is more stable by 1.84 kcal/mol than the C_i conformation, which justifies it to be considered as the lowest energy conformation of 18c6. Also for comparison, optimized geometry was computed at the MP2/6-31+G* level for conformation **26**, of D_{3d} symmetry, hereafter the D_{3d} conformation, utilizing its high symmetry, since this conformation is observed in some of the 18c6 cation metal complexes.[47−50] The relative energy of this conformation at the MP2/6-31+G* level is shown in Table 1. A conformation number, according to the HF/STO-3G energy order, symmetry, according to the HF/ STO-3G geometry, and a qualitative description of the dihedral angles of the four C−O−C−C−O−C groups, on the basis of the MM3 optimized geometry, of each of the 47 conformations considered of 18c6 are also given in Table 1. The structure of the 12 lowest energy conformations, according to the MP2/6-31+G*//B3LYP/6-31+G* energy order, is depicted in Figure 2.

In the next two subsections, the relative energy order at the different levels considered in this work and the factors governing this order, mainly, the CH···O interactions and dihedral angles, will be discussed.

Relative Energy Order. The calculated relative energies at the MP2/6-31+G*//HF/6-31+G* level, Table 1, show that there exist two conformations of lower energy than the known lowest energy C_i conformation of free 18c6.[47,48] These are the S_6 conformation and conformation **122** with C_2 symmetry, hereafter the C_2 conformation. In addition, the calculated relative energies at the MP2/6-31+G*//B3LYP/6-31+G* level show that the energy order of the predicted conformations is S_6, C_2, **115**, and C_i. The first three conformations have lower energy than the C_i conformation only after the inclusion of the electron correlation at the HF or B3LYP levels. The S_6 and C_i energy order is further supported by the calculated energies at the MP2/6-31+G* level. This indicates the importance of inclusion of the electron correlation for the accurate prediction of the energy order concluded for 12c4.[22] This is in contradiction to what was reported earlier by Anderson et al.[21] and Bultanic et al.[24] that the electron correlation is not necessary for accurate predication of order of the relative conformational energies. Also, because of the known accuracy of the optimized geometries predicted at the B3LYP level compared to those at the HF level, according to the MP2/6-31+G*//B3LYP/6-31+G* energy order, it is reasonable to assume that conformation **115** has lower energy than the C_i conformation.

The C_2 conformation, the second lowest energy conformation according to the MP2/6-31+G*//HF/6-31+G* and MP2/6-31+G*//B3LYP/6-31+G* energy orders, has the energy order of 1056 according to the MM3 steric energy and the order of

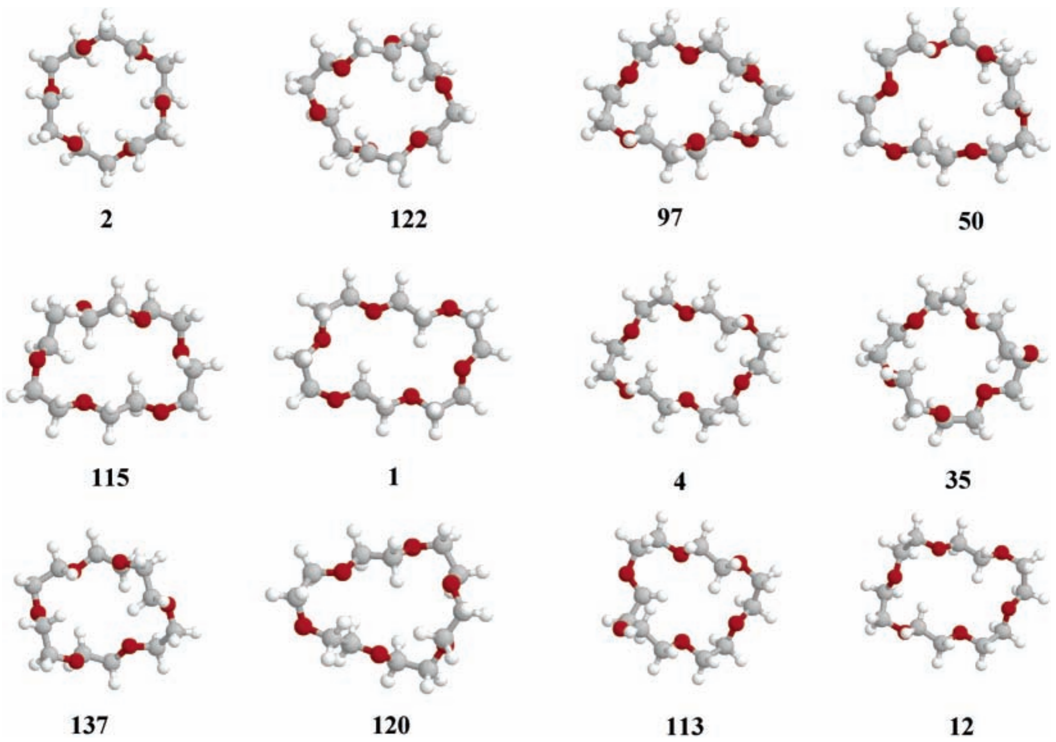
TABLE 1: Relative Energies of the 47 Unique Lowest Energy Conformations, According to the MP2/6-31+G*//HF/6-31+G* Energy Order, of 18c6[a]

		HF		MP2/HF[b]	B3LYP	MP2/B3L3YP[c]	MP2						
no.	sym.	STO-3G	6-31+G*	6-31+G*	6-31+G*	6-31+G*	6-31+G*	conformation description of the dihedral angles[d]					
1	C_i	−0.67	−3.55	1.62	−0.78	1.96	1.84	− 0 0	0 0 +	0 0 −	+ 0 0	0 0 −	0 0 +
2	S_6	0.00	0.00	0.00	0.00	0.00	0.00	0 − +	0 + −	0 − +	0 + −	0 − +	0 + −
3	C_3	0.21	−1.54	3.89	1.27	4.10		− 0 0	0 0 +	− 0 0	0 0 +	− 0 0	0 0 +
4	C_2	0.45	−1.03	2.31	0.26	2.66		0 0 +	0 0 +	0 + −	0 0 +	0 0 +	0 + −
7	C_1	0.68	−1.84	3.91	0.78	4.29		− 0 0	0 0 +	0 0 −	0 0 +	− 0 0	0 0 +
8	C_1	0.68	0.75	2.73	3.99	5.39		0 0 −	0 0 −	0 0 +	0 0 −	+ 0 −	0 0 −
12	C_1	0.74	−1.15	2.61	0.54	2.90		0 0 +	0 0 −	+ 0 0	0 + +	0 0 −	+ 0 +
13	C_1	0.74	−1.15	2.61	0.54	2.90		0 0 +	0 0 −	− 0 0	0 − +	0 0 −	0 0 −
16	C_1	0.81	−0.60	3.03	0.92	3.32		0 − +	0 + +	0 0 0	0 − +	0 0 −	0 0 −
25	C_1	0.91	0.22	3.00	1.43	3.19		0 − 0	0 − +	0 0 −	0 0 −	0 − +	0 + −
26	D_{3d}	1.03	0.80	7.22	1.88	7.63	7.90	0 0 −	0 0 +	0 0 −	0 0 +	0 0 −	0 0 +
33	C_1	1.18	−0.10	3.31	2.80	4.71		0 + 0	0 − +	0 0 −	0 0 0	0 + −	0 − +
34	C_1	1.18	0.02	3.18	1.33	3.31		0 + −	0 − +	+ 0 +	0 − +	0 0 −	0 0 +
35	C_1	1.19	1.30	2.63	1.83	2.81		0 0 −	0 − +	0 + −	0 0 +	0 0 +	− − +
37	C_1	1.26	−0.13	2.88	1.28	3.00		− 0 −	+ 0 0	0 + −	0 0 +	0 0 −	+ 0 +
40	C_1	1.52	−0.61	2.97	1.10	3.32		0 − +	0 0 +	0 + −	0 0 +	0 0 +	0 + 0
43	C_1	1.53	1.02	2.94	2.07	3.32		0 + −	0 − +	0 + −	0 0 +	0 0 +	− − 0
48	C_1	1.73	2.29	3.68	5.08	7.40		0 0 +	0 0 +	0 + −	− 0 −	0 0 +	0 + −
49	C_1	1.73	−0.89	3.15	1.52	3.36		0 0 0	0 + −	0 0 +	0 0 0	0 + −	− 0 −
50	C_1	1.74	−0.50	2.26	1.17	2.46		− 0 −	+ 0 +	0 0 −	+ 0 0	0 0 −	+ 0 +
52	C_2	1.74	−0.27	3.59	1.91	3.86		0 0 +	+ 0 +	− 0 0	0 0 +	+ 0 +	− 0 0
53	C_1	1.75	1.30	2.63	1.83	2.81		0 + −	0 − +	0 + −	0 0 −	+ + −	0 0 +
54	C_1	1.75	1.39	3.06	2.25	3.13		0 0 −	0 − +	+ 0 +	0 − +	0 0 +	− − +
63	C_1	1.85	1.26	3.41	2.26	3.61		0 − 0	0 − +	0 0 +	0 + −	0 − +	0 + −
65	C_1	1.86	0.51	3.81	2.43	4.04		0 0 0	− − +	0 0 0	0 − +	0 0 +	0 + −
66	C_1	1.86	0.06	3.87	2.21	4.23		+ 0 0	+ 0 +	− 0 0	0 0 +	− 0 −	0 0 −
69	C_1	1.91	−0.54	3.14	1.33	3.37		0 0 0	0 + −	0 0 +	0 0 −	0 − +	0 + −
73	C_1	1.93	0.69	3.53	1.59	3.82		0 0 +	0 0 −	0 0 +	0 + −	0 − +	0 + −
77	$\mathrm{C_s}$	1.96	1.08	3.33	2.41	4.64		0 0 +	0 0 +	0 + −	0 0 +	0 0 +	− − +
82	C_1	2.03	−0.10	3.31	2.00	3.41		− 0 −	+ 0 0	0 + −	0 0 +	− 0 0	+ 0 +
85	C_1	2.07	−0.60	3.03	2.50	5.10		0 + −	0 − −	0 − 0	0 + −	0 0 +	0 0 +
86	C_1	2.10	−0.54	3.14	1.50	3.09		− 0 −	+ 0 +	0 0 −	0 0 +	− + 0	0 0 +
90	C_1	2.13	−3.55	1.62	3.78	6.05		+ 0 0	0 − +	0 0 −	0 0 0	0 + −	0 0 +
97	C_1	2.13	1.84	2.52	2.42	2.37		− − +	0 − +	0 + −	0 0 +	0 0 +	0 + +
108	C_2	2.18	-0.44	3.63	1.67	4.01		0 − 0	0 − +	0 0 −	0−0	0 − +	0 0 −
111	C_1	2.20	1.29	3.88	2.40	4.04		0 − 0	0 + −	− 0 −	0 0 −	0 − +	0 + −
113	C_1	2.21	1.54	2.42	2.95	2.87		0 − +	0 0 +	0 + −	0 0 +	0 0 +	− − −
114	C_1	2.23	0.04	3.87	2.22	3.97		− 0 0	0 − −	− 0 −	+ 0 0	0 0 −	0 0 +
115	C_1	2.23	−0.50	2.26	2.02	1.81		0 0 −	+ 0 +	− 0 −	+ 0 +	− 0 −	+ 0 0
118	C_1	2.24	−0.17	3.54	1.58	3.80		0 0 0	0 + +	0 + −	0 0 +	0 0 +	0 + −
120	C_1	2.27	−0.16	2.15	1.81	2.20		0 0 0	−+−	0 0 0	0 + −	0 − +	0 + −
122	C_2	2.27	1.71	1.56	1.75	1.79		0 − −	0 − +	0 + −	0 − −	0 − +	0 + −
124	C_1	2.31	2.51	3.32	2.61	3.44		0 − +	0 + +	0 0 +	0 + −	0 − +	0 + −
130	C_1	2.32	0.88	3.36	2.46	3.50		0 0 +	+ 0 +	− 0 0	0 0 +	0 0 −	+ 0 +
132	C_1	2.33	1.40	3.05	2.03	3.38		0 0 +	0 0 +	0 + +	0 + −	0 − +	0 + −
137	C_1	2.37	1.67	2.02	2.20	2.18		0 + −	0 − +	0 + −	0 0 −	0 − +	0 + +
138	C_1	2.38	1.37	3.59	2.47	3.75		+ 0 +	− 0 −	0 0 −	+ + −	0 0 −	+ 0 0

[a] Relative energies with respect to conformation **2**, see text. No. is the conformational number according to the HF/STO-3G energy order, see text. For conformation **2**, the energies at the HF/STO-3G, HF/6-31+G*, MP2/HF/6-31+G*, B3LYP/6-31+G*, B3LYP/MP2/6-31+G*, and MP2/6-31+G* levels are −905.95750, −917.50589, −920.14623, −923.02003, −920.15426, and −920.15948 kcal/mol, respectively. [b] MP2/6-31+G*//HF/6-31+G* relative energy. [c] MP2/6-31+G*//B3LYP/6-31+G* relative energy. [d] Qualitative description of the dihedral angles of the four C−O−C−C−O−C groups on the basis of the MM3 geometry. Angles between 0 and 2/3π are designated as (+), angles between 0 and −2/3π are designated as (−), and angles between 2/3π and 4/3π are designated as (0).

224 according to the HF/STO-3G energy order out of the 3136 MM3 predicted conformations. This rationalizes the method used in this work and the consideration of 250, or rather 198, conformations at the HF/6-31+G* level to locate the lowest energy conformations of 18c6. It can then be concluded that the MP2/6-31+G*//HF/6-31+G* level is the lowest reliable level for the accurate prediction of the conformational energy order.

As was mentioned before, it was concluded for 12c4 that the relative energy order at the MP2/6-31+G*//B3LYP/6-31+G* level is quite close to that at the MP2/6-31+G* level to within 0.1 kcal/mol with the exception of only two conformations out of the 20 conformations considered. For 18c6, MP2/6-31+G* optimized geometries were computed only for the S_6, D_{3d}, and C_i conformations. The differences between the relative energies at the MP2/6-31+G* and MP2/6-31+G*//B3LYP/6-31+G* levels for the C_i and D_{3d} conformations, Table 1, are 0.12 and 0.37 kcal/mol, respectively. It is clear that this conclusion is almost respected by the S_6 conformation but not by the D_{3d} conformation. Clearly, more optimized geometries of conformations of 18c6 need to be computed at the MP2/6-31+G* level to derive a more reliable conclusion of the relation between the MP2/6-31+G* and MP2/6-31+G*//B3LYP/6-31+G* energy orders of 18c6. Assuming that the closeness of the relative energies at the MP2/6-31+G*//B3LYP/6-31+G* and MP2/6-31+G* levels is a reflection of the closeness of the optimized geometries at both levels, because of the larger ring of 18c6 compared to that of 12c4, it is expected that the relative energy



2 **122** **97** **50**

115 **1** **4** **35**

137 **120** **113** **12**

Figure 2. Structure of the 12 lowest energy conformations according to the MP2/6-31+G*//B3LYP/6-31+G* energy order of 18c6.

differences between the MP2/6-31+G*//B3LYP/ 6-31+G* and MP2/6-31+G* levels are larger for 18c6 than for 12c4. In fact, this is the case for the S_6 and D_{3d} conformations.

The C_i conformation has been considered, to the best of our knowledge, to be the lowest energy conformation of 18c6 in almost all reports of 18c6 at the MD,[26−33] MC,[34−38] MM,[39−42] and ab initio[43−45] levels and also observed experimentally in the solid phase of 18c6.[47,48] It was consequently considered as the lowest energy conformation of 18c6 in calculating the binding energies between free 18c6 and different alkali and alkaline earth metal cations.[43,44] To get more accurate binding energies, it is then interesting to recompute these binding energies relative to the S_6 lowest energy conformation of 18c6 rather than to the C_i conformation. This study in fact is being planned in our lab.[56] According to the data in Table 1, a rough correction of the binding energies, with respect to the S_6 conformation of 18c6, reported in refs 43 and 44, is about 3.55 and 1.62 kcal/mol at the HF/6-31+G* and MP2/6-31+G*//HF/6-31+G* levels, respectively.

In fact, this is not the first time to report the S_6 and C_2 conformations of 18c6. In an earlier conformational search report by Jagannadh et al.,[42] which also used an earlier version of the CONFLEX routine and the AMBER force field rather than CAChe MM3 augmented force field, as is the case in the current report, the S_6 conformation was also predicted but as the second lowest energy conformation after the C_i conformation. A complete comparison between the conformations predicted in ref 42 and those predicted in the current work is not possible since the MM3 energy orders in both reports are different as will be shown shortly. It is not clear whether the MM3 relative energies in Jagannadh's results correspond to MM3 steric or strain energies, as is the case in this report. In fact, the only means of comparing conformations predicted in this report and those predicted in Jagannadh's work is through the qualitative description of the dihedral angles. Also in Jagannadh's report, the D_{3d} and C_3 conformations were predicted to be the 13th and 14th lowest energy conformations, respectively. In this report, the C_i, S_6, C_3, and D_{3d} conformations are predicted to have the order of 8, 473, 168, and 1 out of 3136 conformations predicted at the MM3 level. It is clear then that the MM3 energy orders in this report and that in Jagannadh's report are different. On the other hand, on the basis of the dihedral angle description, no conformation similar to conformation **115** predicted in this work can be related to any of the conformations predicted in Jagannadh's work. It is worth mentioning here that conformational search using the newly developed MM4 method for oxygen-containing molecules, as alcohols and ethers,[57] did not predict the S_6 conformation as the lowest energy conformation of 18c6.[58]

It can be seen from Table 1 that at the MP2/6-31+G*//B3LYP/6-31+G* level, the lowest energy S_6 conformation is more stable by about 1.8, 1.8, and 2.0 kcal/mol than the second C_2, the third **115**, and the fourth C_i conformations, respectively. This is followed by nine conformations, conformations **137**, **120**, **97**, **50**, **4**, **35**, **53**, **113**, and **12**, with differences of the relative energies of less than 1.0 kcal/mol from the C_i fourth lowest energy conformation. It is clear that the energy gap between the lowest energy S_6 conformation and the other conformations of 18c6 is large. Computations at the MP2/6-31+G* level, to get more accurate energies, of these conformations are in fact not reasonable at the present time especially for conformations with C_1 symmetry, the floppiness of the 18c6 ring, and the consequent large number of iterations required to achieve convergence, as was tried by us, compared to those of higher symmetry and to the large CPU time required by the MP2 method.

It was reported for 12c4 that the energy order at the HF/STO-3G, HF/4-31G, HF/6-31+G*, and B3LYP/6-31+G* levels is in good agreement with that at the MP2/6-31+G* level, but the agreement is better at the correlated MP2/6-31+G*//HF/6-31+G* and MP2/6-31+G*//B3LYP/6-31+G* levels, especially at the later level.[22] For 18c6, the 10 lowest energy conformations at the HF/6-31+G* level are conformations **1**, **90**, **92**, **7**, **9**, **10**, **3**, **12**, **13**, and **4**. At the B3LYP/6-31+G* level, the 10 lowest energy conformations are **1**, **2**, **4**, **12**, **13**, **7**, **16**, **40**, **50**, and **3**. At the MP2/6-31+G*//HF/6-31+G* level, the order is **2**, **122**, **123**, **1**, **90**, **92**, **137**, **120**, **121**, and **50** and at the MP2/6-31+G*//B3LYP/6-31+G* level is **2**, **122**, **115**, **1**, **137**, **120**, **97**, **50**, **4**, and **35**. Notice that the conformation number assigned to each conformation is according to the HF/STO-3G energy order. It is clear that the energy order at the HF/6-31+G* is close to that at the HF/STO-3G level, but this similarity is less at the B3LYP/6-31+G* level. With the exception of conformations **1** and **2**, the order at the correlated MP2/6-31+G*//HF/6-31+G* and MP2/6-31+G*//B3LYP/6-31+G* levels is quite different from that at the HF/6-31+G* and B3LYP/6-31+G* levels, which are in turn similar to each other. In other words, inclusion of the electron correlation had a significant effect on the energy order. As was mentioned above, this is in a clear agreement to what was concluded for 12c4[22] but in contradiction to what was observed for 9c3[21] and in a previous report of 12c4.[24] It is not clear the reason of this disagreement between 12c4 and 18c6 on one hand and 9c3 on the other hand, but this may be attributed to the small number of the possible conformation of 9c3. Notice that the agreement between the energy order at the HF/6-31+G* and B3LYP/6-31+G* levels and that at the correlated MP2/6-31+G*//HF/6-31+G* and MP2/6-31+G*//B3LYP/6-31+G* levels is worse in the case of 18c6 than in the case of 12c4.[22]

It was reported that the C_i conformation is more stable by 4.4 and 5.4 kcal/mol than the D_{3d} conformation at the HF/6-31+G* and MP2/6-31+G*//HF/6-31+G* levels, respectively.[43] The data in this report of 4.4 and 5.6 kcal/mol at the above two mentioned levels, respectively, are in agreement with these previous values. The small difference in the values of the relative energies at the MP2/6-31+G*//HF/6-31+G* level, between that obtained in the current work and that reported in ref 43, is most probably due the small difference between the basis sets used in both reports. In the current report, the 6-31+G* basis set was used for all atoms and in ref 43 the 6-31+G* basis set was used for all atoms except the carbon atoms where the 6-31G* basis set was used instead. At the MP2/6-31+G* level, the highest level used in this report, the energy difference between the C_i and D_{3d} conformations is high at 6.06 kcal/mol. At the B3LYP/6-31+G* level, the difference is lower at only 2.66 kcal/mol, which is a significant difference from that at the MP2/6-31+G* level.

The D_{3d} conformation is the conformation assumed by 18c6 in polar solvents and in the crystalline state in some of its metal complexes.[47−50] Interestingly, it is predicted to be the lowest energy conformation at the MM3 level. At the HF/STO-3G, HF/6-31+G*, and B3LYP/6-31+G* levels, this conformation is predicted to have the order of 26, 65, and 24, respectively. At the correlated MP2/6-31+G*//HF/6-31+G* level, the D_{3d} conformation is predicted to be the 136 highest energy conformation, and at the MP2/6-31+G*//B3LYP/6-31+G* level, it is predicted to be the highest energy conformation considered. Notice that except for the MP2/6-31+G* level, the MP2/6-31+G*//B3LYP/6-31+G* energy order is expected to be more accurate than any of the levels considered in this work. Notice also that 139 conformations were considered at the HF/6-31+G* level and only 47 conformations were considered at the B3LYP/6-31+G* level.

For 12c4, the S_4 conformation was predicted to be the lowest energy conformation at the MM3 level and also at the higher levels of ab initio methods.[22] For 18c6, the S_6, C_2, C_i, C_3, and D_{3d} conformations are predicted to have the order of 473, 1056, 8, 168, and 1, according to the MM3 energy order, out of the 3136 conformations predicted at the MM3 level. Computations had to be done at the MP2/6-31+G*//HF/6-31+G* level to have a more reliable and accurate estimate of the energy order. It is clear that the amount of computations done in this work is quite significant. In fact, the number of conformations of 18c6, as was mentioned in the Computational Details section, was significantly larger than 5000, the maximum number of the stored conformations by the CAChe program in the conformational storage space. For 24c8, it is clear that a similar methodology of locating the lowest energy conformations, as the one used in the current report, may not be successful. This suggests that more efficient methods of conformational search need to be developed to reach the lowest energy conformations of a molecule as large as 24c4. A simple possible solution, as will be detailed in the next subsection, is to include more accurate forces to account for the hydrogen-bonding interactions in the MM3 force field. Contrary to what might be concluded from the previous discussion, the MM3 energy order is in good qualitative agreement with that obtained at the highest level of computations considered in this report, the MP2/6-31+G*//B3LYP/6-31+G* level. For example, conformations **1** and **8** are predicted to be two of the lowest energy conformations of 18c6, as is the case at the MP2/6-31+G*//HF/6-31+G* level. Definitely, this agreement between the MM3 and the MP2/6-31+G*//B3LYP/6-31+G* energy orders is worse than all other levels used in this report.

CH···O Interactions. An important point which needs to be addressed now is what factors affect the conformational stability. A second question is why the S_6 conformation is the most stable conformation of 18c6. The same question can be addressed to the smaller 12c4. Of course, these questions might be difficult to answer but the advantage of the current report is that there exists data for two similar molecules, 12c4 and 18c6, which probably with a closer inspection of their conformational analysis results can offer an answer to these two questions.

It is apparent that the stability of a given conformation depends on the steric, or structural, and electronic effects. Resonance, hyperconjugation, and hydrogen bonding are the main factors of electronic effects. Only the latter may play a significant role for the present molecule. For example, it is believed that the 1,5-CH···O interactions somehow are one of the factors which affect the conformational stability of crown ethers.[21] It was concluded for 12c4 that hydrogen bonding is one of the main factors that affect the relative conformational stability.[24] Concerning the steric effects, with the presence of too many ring dihedral angles especially for 18c6, it is rather complicated and not simple to judge how these may affect the conformational stability especially for small angle changes. In comparing these factors, which is not clear exactly how they may affect the relative conformational stability, it is preferable, in order not to have fortuitous conclusions, to depend on solid features.

To facilitate the study of the factors affecting the conformational stability, the dihedral angles, OCCO and COCC, the CH···O distances of less than 3.0 Å, and the conformational order of some selected conformations optimized at each level are given in Table 2. No conformational order number is given at the MP2/6-31+G* level since this has been calculated only for the S_6, C_i, and D_{3d} conformations, but the energy order of these conformations is clear from Table 1. Notice that the MM3 energy order is according to the MM3 energy rather than to the HF/STO-3G energy order as is the case at the other levels. Table 3 shows a comparison between the structures of the S_6, C_i, and D_{3d} conformations of 18c6 at the MP2/6-31+G* level and the

TABLE 2: Comparison between the Dihedral Angles and CH···O Interaction Distances of Some Selected Conformations of 18c6[a]

conformation		MM3	HF/STO-3G	HF/6-31+G*	B3LYP/6-31+G*	MP2/6-31+G*	n
S_6	OCCO	84	81	74	76	76	
	COCC	72	75	86	83	83	
		174	176	174	176	176	
	CH···O	2.47	2.39	2.52	2.49	2.49	6
	order	473	2	46	2		
C_2	OCCO	67	62	64	66		
		86	84	76	78		
		−84	−78	−72	−74		
	COCC	−71	−72	−79	−77		
		−173	−174	−168	−170		
		70	78	89	85		
		171	179	179	178		
		82	79	78	77		
		−177	−179	−179	−178		
	CH···O	2.49	2.32	2.48	2.45		2
		2.50	2.43	2.54	2.52		2
	order	1056	122	106	20		
1041	OCCO	−168	−167	−177	−164		
		88	93	65	87		
		−75	−68	−77	−68		
		82	78	72	74		
		−93	−97	77	−76		
		72	66	68	65		
	COCC	174	171	163	176		
		−72	−70	−93	−70		
		−172	−176	178	−173		
		97	93	165	104		
		−167	−173	−176	−171		
		−68	−73	−96	−80		
		171	171	168	169		
		67	67	77	70		
		177	175	176	174		
		−103	−93	−96	−101		
		−173	−174	−166	−171		
		172	173	173	169		
	CH···O	2.38	2.43	2.42	2.51		
		2.55	2.42	2.63	2.70		
		2.51	2.37	2.60	2.51		
		2.98	2.75	2.52	2.69		
		2.68	2.39		2.59		
		2.63					
	order	1041	115	25	26		
C_i	OCCO	79	77	72	71	70	
		−72	−69	−70	−74	−74	
		174	175	177	177	179	
	COCC	−176	−176	−171	−168	−165	
		165	167	169	171	164	
		170	173	167	168	171	
		178	177	176	179	174	
		−175	−176	−179	−174	−180	
		83	77	84	81	80	
	CH···O	2.33	2.25	2.45	2.42	2.37	2
	order	8	1	1	1		
C_3	OCCO	171	170	170	170		
		−80	−77	−73	−74		
	COCC	171	173	161	163		
		−171	−173	−177	−176		
		−170	−168	−172	−172		
		83	78	88	86		
	CH···O	2.32	2.21	2.43	2.40		3
	order	168	3	7	10		
D_{3d}	OCCO	73	74	75	76	76	
	COCC	178	176	177	176	177	
	CH···O						
	order	1	26	65	24		

[a] Angles in degrees. Distances in Å. Order is the conformational order at the specified level, except at the MM3 level where the order is with respect to the 3136 MM3 predicted conformations, see text. *n* is the number of CH···O interactions due to symmetry.

experimental X-ray data of the C_i conformation.[47,48] Also, the MP2/6-31+G* optimized geometry of the S_4 lowest energy and C_i conformations of 12c4, in addition to the X-ray determined structure of the C_i conformation,[59] have been added to Table 3.

TABLE 3: Comparison between the Structures of Some Selected Conformations of 12c4 and 18c6 Calculated at the MP2/6-31+G* Level[a]

molecule	12c4	18c6	12c4	18c6	18c6	12c4/C_i	18c6/C_i	18c6/C_i
coord.[b]	S_4	S_6	C_i	C_i	D_{3d}	exp.[c]	exp.[d]	exp.[e]
C−O	1.430	1.423	1.431	1.425	1.420	1.423	1.414	1.425
	1.432	1.427	1.429	1.424		1.429	1.408	1.423
			1.428	1.422		1.430	1.403	1.421
			1.431	1.422		1.431	1.405	1.418
				1.427			1.407	1.422
				1.435			1.426	1.430
C−C	1.513	1.522	1.511	1.514	1.508	1.502	1.506	1.511
			1.514	1.508		1.505	1.509	1.506
				1.514			1.505	1.512
COC	114.4	115.4	112.7	114.5	111.9	113.1	113.3	113.0
			114.6	113.9		114.1	114.0	112.8
				112.3			113.3	112.7
OCC	108.3	109.7	106.7	113.0	108.5	108.5	114.6	114.1
	111.6	114.7	111.3	108.1		112.3	111.0	110.2
			110.8	107.3		111.9	109.6	109.6
			109.0	107.6		110.3	107.9	108.3
				106.7			106.4	105.5
				105.8			109.1	108.3
OCCO	72.5	75.6	76.9	77.5	75.7	74.5	75.4	74.7
			74.0	−70.1		75.4	−67.6	−65.1
				179.3			174.7	173.7
COCC	92.2	82.8	153.2	−80.3	176.8	140.2	−79.7	−80.3
	157.3	175.5	97.1	−164.3		102.7	−155.2	−154.9
			−163.3	165.3		−173.6	165.8	165.1
			−91.2	171.4		−85.2	175.5	175.2
				179.4			174.7	172.4
				174.3			170.1	169.2

[a] Bond lengths in Å and angles in degrees. [b] Conformational symmetry for the columns and coordinate for the rows. [c] Reference 59. [d] Reference 47. [e] Reference 48.

A clear feature in Table 2 is that the S_6 conformation has the largest number of CH···O interactions, one for each of the six oxygen atoms of the molecule, at distances of only about 2.5 Å. This is in fact quite similar to the case of the S_4 conformation of 12c4 which has four CH···O interactions, with also one CH···O interaction for each oxygen atom, and also at about the same distances at all levels as for the S_6 conformation of 18c6.[22] Clearly, the S_4 structure of 12c4 and the S_6 structure of 18c6 allow each conformation to have the highest number of CH···O interactions for each molecule. This clearly rationalizes their highest stability relative to the other conformations. Notice that the S_6 conformation of 18c6 has six of the CH···O interactions, the C_2 conformation has four, the C_i conformation has two, the C_3 conformation has three, and interestingly the D_{3d} conformation has none of these CH···O interactions.

The D_{3d} conformation, the lowest energy conformation at the MM3 level, is the 10th lowest energy conformation at the HF/STO-3G level and has the order of 65 and 24 at the HF/6-31+G* and B3LYP/6-31+G* levels, respectively. This can be attributed to that the MM3 method does not accurately account for the weak hydrogen-bonding interactions. This in fact may rationalize that the S_6 conformation is not the lowest energy conformation at the MM3 level. Consequently, at the ab initio level, where these weak forces are accounted for, other conformations became more stable than the D_{3d} conformation. It is reasonable then to assume that the MM3 geometry of the D_{3d} conformation is the lowest energy conformation at the ab initio level if the hydrogen-bonding interactions are to be excluded.

To further clarify the effect of the CH···O interactions, some of the high-energy conformations were also examined. Although the data of these conformations are not shown in Table 2, it is noticed that the high-energy conformations do not possess CH···O interactions, defined as CH···O distances of less than 3.0 Å, nor have any of the dihedral angles less than 60°. For a large ring molecule as 18c6, small dihedral angles are needed to bring the CH and O groups close to each other for the hydrogen bonding. On the other hand, low-energy conformations, of energy higher than those in Table 2, contain CH···O interactions and have at most one of the dihedral angles in the 50−60° range. Definitely, for strain reasons, a dihedral angle of about 80 or 180° (or −80 or −180), as is the case for most of the low-energy conformations of 18c6, is more favorable than an angle of less than 60°. It can be concluded that CH···O interactions play a role in the stabilization of conformations, but it is difficult or unclear how it affects the relative energy order of certain conformations especially in relation to the dihedral angles.

The stability of the C_2 conformation can be rationalized similarly to the S_6 conformation. It also has four of the CH···O interactions compared to six for the S_6 conformation, the CH···O distances are comparable to those of the S_6 conformation, and the dihedral angles of both conformations are similar too. On the other hand, although the C_3 conformation has three of the CH···O interactions, it is not one of the most stable conformations at the correlated MP2/6-31+G*//HF/6-31+G* and MP2/6-31+G*//B3LYP/6-31+G* levels. It is noticed that this conformation is as planar as the high-energy D_{3d} conformation unlike the low-energy S_6 and C_2 conformations.

Finally, the data in Table 3 show an excellent agreement between the calculated and experiment geometry of the solid phase of the C_i conformation of 18c6.

Conclusion

In the present report, a conformational analysis of one of the most important crown ethers, 18c6, is presented. In this conformation analysis, an efficient method of conformational search of cyclic molecules, the CONFLEX method,[51] was used to locate the lowest energy conformations of 18c6. The conformational search methodology was performed similarly to that followed for the smaller 12c4,[22] although complicated by the large size of 18c6. The conformational search resulted in the identification of 3136 conformations as the lowest energy conformations of 18c6 at the MM3 level. To have a more accurate energy order of the predicted conformations, computations were performed at the HF/6-31+G* level for the 198 lowest energy conformations, according to the HF/STO-3G energy order, and at the B3LYP/6-31+G* level for the 47 unique lowest energy conformations, according to the MP2/6-31+G*//HF/6-31+G* energy order.

The amount of computations performed in this report is in fact quite significant, especially for a molecule as large as 18c6, and resulted in the prediction of three conformations of lower energy than the known C_i lowest energy conformation of 18c6. The predicted S_6 lowest energy conformations of 18c6 was calculated to be more stable by 1.84 kcal/mol at the MP2/6-31+G* level than the C_i conformation. Interestingly, this S_6 conformation is quite similar to the S_4 lowest energy conformations of 12c4. It is quite probable that a similar S_8 conformation will be among the lowest energy conformations of the larger 24c8.

The study showed that the electron correlation is necessary to get an accurate energy order of the predicted conformations. It was also concluded that the MP2/6-31+G*//HF/6-31+G* level is the lowest reliable level for the accurate prediction of the conformational energy order. The same result was observed for 12c4.[22] Similar to the case of 12c4, it is concluded that hydrogen bonding is an important factor for the determination of the relative conformational stability, but the effect of the dihedral angles is still not clear. The large amount of computations done in this report suggests that more efficient methods of conformational search still need to be developed to have a faster and more accurate prediction of the low-energy conformations. A possible solution is to improve the energy order of the predicted conformations at the MM3 level by developing better empirical force fields corresponding to the hydrogen bond interactions.

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Supporting Information Available: The relative energies of the 139 predicted conformations, as was explained in the Computational Details section, of 18c6 at the HF/STO-3G, HF/6-31+G*, and MP2/6-31+G*//HF/6-31+G* levels and the relative energies of the 47 unique lowest energy conformations, according to the MP2/6-31+G*//HF/6-31+G* energy order, at the B3LYP/6-31+G* and MP2/6-31+G*//B3LYP/6-31+G* levels are provided as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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