



Conformational study of the structure of 18-thiacrown-6



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ABSTRACT

Conformational analysis was performed for 18-thiacrown-6 (18t6) using the CONFLEX method and the MMFF94s force field. Computations were performed for some of the low energy conformations at the HF, B3LYP, CAM-B3LYP, M06, M06L, M062x, M06HF and MP2 levels. The computations were also performed using the DFT-D3 method along with the TPSS and PBE functionals. The study predicted a new C_2 conformation as the ground state conformation of 18t6. This new C_2 conformation is more stable than the experimentally known solid state conformation by 4.7 kcal/mol at the MP2/6-311G** level. This conformation has all of the SCCS dihedral angles adopt exodentate structure. However, the experimentally known conformation of the solid phase has two of the SCCS dihedral angles violating this exodentate rule. It was concluded that for 18t6 stability a linear dihedral SCCS angle requirement is more important than a gauche CCCC dihedral angle requirement.

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1. Introduction

Since the discovery of crown ethers, [1,2] there has been a deal great of interest and research in the their chemistry and applications. For example a new field of chemistry called molecular design [3] 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 high selectivity in binding to different metal cations. One of the most important crown ethers is 18-crown-6 (18c6). Although 18c6 has been the subject of many studies, less interest has been shown in its sulfur analogue 18t6.

We have been actively involved in conformational and vibrational analysis studies of different crown ethers, such as 12-crown-4 (12c4) 18c6 and 12-thiacrown-4 (12t4) and some of their cation metal complexes [4–10]. The aim of these studies is to determine in what conformation different crown ethers and some of their metal complexes exist. The conformational analysis is done through the conformational search to predict the lowest-lying conformations of the studied crown ether and to perform computations at higher levels of the ab initio and DFT theories to determine their lowest energy conformations. This is followed by measuring the vibrational spectrum of the studied crown ether and through the comparison between the measured and calculated scaled vibrational frequencies to conclude in what conformation the considered crown ether exists. In the conformational study of 12c4 it was predicted that the S_4 conformation is the ground state conformation [4]. Although there have been experimental studies to determine

the lowest-lying conformation of 12c4 [11–18], there was an ambiguity concerning what is the conformation of 12c4. However, a vibrational study of 12c4 conducted by us showed that IR active modes are Raman inactive and IR inactive modes are Raman active [6]. This led to the conclusion that 12c4, at least in the phases we considered, exists in the C_i conformation. Similar conformational analysis of 18c6 concluded that a new S_6 conformation characterizes the ground state of 18c6 [5]. It was rationalized, similar to our understanding of the ground state S_4 conformation of 12c4, that the reason for the stability of the S_6 conformation of 18c6 is that it has one hydrogen bond per oxygen atom with distances shorter than for any other conformation of 18c6. This indicates that hydrogen bonding controls the structure of crown ethers. This is contrary to the original unexplained observation that crown ethers have endodentate structure, with the oxygen atoms directed to the ring plane.

For 12t4, in agreement with the X-ray results [19,20] the D_4 conformation was predicted to be the ground state conformation [10]. Comparison between the dihedral angles of some of the low and high energy conformations concluded that for the stability of 12t4, an SCCS dihedral angle of 180° requirement is more important than having a gauche CCCC dihedral angle requirement.

Although there have been many conformational analysis studies of the smaller 9t3 [21–23] and 12t4 [21,24,25] thiacrown ethers, there is only one conformational analysis report for 18t6 [21]. This is due to the large size of 18t6 and consequent increased floppiness of the crown ether ring, which leads to a large number of possible conformations and consequently requires a very significant amount of computational time. In the previous conformational analysis study of 18t6 [21], the conformational search was performed using molecular dynamics simulation at high temperature. Subsequently,

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the optimized geometries of the 12 lowest MM energy conformations were calculated at both the HF/3-21G and HF/6-31 + G* levels plus correlation energy corrections were calculated at the MP2 level at the HF/6-31 + G* optimized geometry. It was concluded that the experimentally known C_2 conformation [19,26,27] is the second lowest energy predicted conformation.

The aim of current publication is to perform a detailed conformational analysis of 18t6. The conformational search was performed using the CONFLEX conformational search method for cyclic molecules. This was followed by HF, MP2 and DFT calculations to predict the ground state conformation of 18t6. The report aims also to study the factors that affect the conformational stability of 18t6. This can be done by comparing the structures of some of the low and high energy conformations.

2. Computational details

Conformational search of 18t6 was done using the CONFLEX [28,29] method implemented in the CONFLEX program [30] utilizing the MMFF94s force field [31–35]. The MMFF94s force field has the advantage that it combines the good features of the MM3 force field while being applicable to a wide range of sizes for organic molecules. The parameters of the MMFF94s force field have been derived from computational data obtained from quantum chemical (ab initio) calculations at the HF/6-31G* and MP2/6-31G* levels. This method is in contrast to other force fields that use parameters derived from experimental data. The problem with deriving parameters from experimental data is that they may not be accurate enough and needed values for some molecules may be missing. Thus the MMFF94s force field is known for its consistency. The CONFLEX method starts from an initial geometry, and new conformations are generated by edge flip, corner flap and stepwise rotation. Each new conformation is considered as an initial geometry and is subjected to the same type of perturbation steps. The process is repeated till no new conformations are generated. Vibrational frequencies are calculated for the predicted conformations, and those conformations that have imaginary vibrational frequencies are excluded. For 18t6, due to the large number of generated conformations (>100,000), the search for low-lying structures was not finished after several months. However, the number of new predicted conformations decreased greatly with time. Most importantly, the 15,000 lowest energy conformations had an MMFF94s relative energy of about 4.78 kcal/mol, remained unchanged for a long period of time. It was then concluded that hardly any of the new predicted conformations will have an MMFF94s energy less than the energy of these 15,000 lowest energy conformations. Optimized geometries were then calculated at the HF/3-21G level for these 15,000 lowest energy conformations, according to the MMFF94s energy ordering.

Further computations for the 500 lowest HF/3-21G energy conformations were then performed at the HF/6-311G** level with the correlation energy recovered at the MP2/6-311G** level using the HF/6-311G** optimized geometries. The energy computations at the MP2/6-311G** level for the HF/6-311G** optimized geometries will be referred hereafter as the MP2/6-311G**//HF/6-311G** level. In addition, computations were performed for the 50 lowest MP2/6-311G**//HF/6-311G** energy conformations at the B3LYP, CAM-B3LYP, M06, M06L, M062x, and M06HF levels with correlation energy calculated at the MP2 level, at the corresponding B3LYP, CAM-B3LYP, M06, M06L, M062x, and M06HF optimized geometries, using the same 6-311G** basis set. Optimized geometries were also calculated at the MP2/6-311G** level for those conformations having symmetry higher than C_1 among these 50 conformations. This is in addition to the lowest energy C_1 conformation, according to the MP2/6-311G**//HF/6-311G** level energy order. This is to investigate the energy of this C_1 conformation

relative to the other conformations of higher symmetry. Also, optimized geometries were calculated for the 15,000 lowest MMFF94s conformations of symmetries other than the C_1 , C_s and C_3 symmetries at the HF, B3LYP, CAM-B3LYP, M06, M06L, M062x, M06HF and MP2 levels using the 6-311G** basis set. The correlation energy was also estimated at the MP2 level for the above seven, i.e. HF, B3LYP, CAM-B3LYP, M06, M06L, M062x, M06HF, optimized geometries using the same 6-311G** basis set. Optimized geometries were also calculated using the DFT-D3 method along with the TPSS and PBE functionals using the 6-311G** basis set. The resolution of the identity (RI) method was used in all of the DFT-D3 computations along with the Becke's and Johnson's (BJ) rational damping function. This computations were performed for all of the conformations for which MP2/6-311G** optimized geometry was calculated. It is significant to add here that the choice of these DFT functionals, B3LYP, CAM-B3LYP, M06, M06L, M062x, M06HF, TPSS and PBE, is arbitrary. Basically most of these DFT functional are relatively new in addition to the traditional B3LYP functional.

The MP2 computations were done with the frozen core option of the inner electrons. The ab initio computations were done using the Gaussian 09 program [36], except at the TPSS and PBE levels where the Turbomol program [37] was used.

3. Results

The HF/3-21G relative energies of the 15,000 lowest energy conformations, according to the MMFF94s energy order, for space reason are not presented here. Instead, the HF/3-21G, HF/6-311G** and MP2/6-311G**//HF/6-311G** relative energies of the 500 lowest HF/3-21G energy conformations among these 15,000 conformations are listed in Table S1. Each conformation is given a number typed in bold face according to its MMFF94s energy order.

Table 1 lists the relative energies at the B3LYP, MP2/6-311G**//B3LYP/6-311G**, M06, MP2/6-311G**//M06/6-311G**, TPSS, MP2/6-311G**//TPSS/6-311G** and MP2/6-311G** levels for the above mentioned 38 selected conformations for which optimized geometries were calculated at the MP2/6-311G** level. The relative energies of all of the considered conformations and levels of theory considered in the current study are listed in Table S2. The relative energies are calculated with respect to the energy of conformation **9485**. However, at the B3LYP/6-311G**, M062x/6-311G** and M06HF/6-311G** levels convergence was not achieved for conformation **9485** after a specified number of geometry optimization steps. Consequently the relative energies at these computational levels were calculated with respect to the next most stable conformation, according to the MP2/6-311G** energy order, conformation **9492**. In a different publication we report the vibrational analysis of 12t4 and 18t6 [38]. For these, harmonic force fields were calculated for a total of 17 conformations which are more stable, according to the MP2/6-311G** energy order, than the experimentally known conformation of 18t6, i.e. conformation **6222**. This enabled the calculation of the free energies of these 17 conformations. The vibrational frequencies were calculated at the HF, B3LYP and CAM-B3LYP using the 6-311G** basis set and at the MP2 level using the 6-31G* basis set. The calculated free energies of these 17 conformations at the HF, B3LYP, CAM-B3LYP and MP2 levels are listed in Table S4, and those at the CAM-B3LYP and MP2 levels only are in Table 2. Fig. 1 depicts the structures of the 9 lowest energy conformations of 18t6, according to the MP2/6-311G** energy ordering, in addition to the experimentally known conformation, corresponding to conformation **6222** [19,26], the lowest MMFF94s energy conformation, conformation **1**, and one of the highest MP2/6-311G** energy conformations, conformation **4109**. Fig. 2 shows the atom numbering of the ground state conformation, conformation **9485** and the experimentally observed

Table 1
Relative energies, in kcal/mol, of 18t6 conformations.^{a,b}

No.	Sym	B3LYP	MP2// B3LYP	M06	MP2// M06	TPSS	MP2// TPSS	MP2	Conformation description of the torsion angle ^c					
9485	C ₂	ftc		0.00	0.00	0.00	0.00	0.00	0+0	0++	0++	0+0	0++	0++
8603	C ₁	−1.42	−0.15	3.41	2.54	1.82	1.82	3.21	0++	0−0	0++	0++	0−0	0++
78	C ₂	−1.44	−0.10	3.56	2.38	1.36	1.36	2.17	0+0	0+0	0++	0+0	0−0	0++
9492	C ₂	0.00	0.00	1.21	0.81	0.81	0.81	0.91	00+	0++	0+0	0+0	0++	0++
1446	C ₂	−0.78	0.20	2.68	1.76	1.44	1.44	1.71	0+0	0+0	0−−	00+	00+	0++
5611	C _{2h}	−0.35	0.24	1.93	1.25	0.93	0.93	1.36	000	0++	0++	000	0−−	0−−
6222	C ₂	1.79	0.03	−0.96	1.36	−1.40	−0.78	4.67	0++	00−	++−	0++	00−	++−
7874	C _i	−0.26	0.82	4.13	2.71	2.29	2.29	2.82	0++	0+0	0+0	0−−	0−0	0−0
12214	C ₂	ftc		3.72	2.57	2.24	2.66	2.61	00−	0−+	00−	00−	0−+	00−
13958	C _i	1.78	0.53	2.51	1.58	1.16	1.16	1.66	0+0	+++	0+0	0−0	−−−	0−0
3127	C ₂	3.10	4.42	8.27	6.36	5.02	5.62	6.48	00−	0−0	0−0	00−	+−0	00−
3157	C ₂	ftc		3.48	3.98	0.42	0.60	3.58	0+0	00−	−++	0+0	00−	−++
8516	S ₆	−0.23	1.54	6.85	4.10	3.72	3.96	4.28	0+0	0−0	0+0	0−0	0+0	0−0
5620	C ₂	2.24	1.78	2.16	2.40	1.19	0.52	2.50	000	00+	−+0	000	0++	0++
949	C ₂	4.24	1.48	0.45	1.95	−0.42	−0.45	1.73	0++	0++	0++	−+0	+0+	−++
6962	C ₂	2.02	2.85	2.08	2.85	ftc		2.64	0++	00−	+0−	0++	0+−	+0−
2670	D ₂	2.08	2.64	5.78	6.25	2.52	3.62	4.85	0++	00−	+−0	0++	00−	+−0
9486	C ₂	2.08	2.64	ftc		2.74	2.74	5.34	0+0	0++	0++	0+0	0++	0++
3156	C ₂	2.59	2.56	4.33	5.11	2.91	2.91	3.76	00+	−−0	0+−	00+	−−0	00−
6716	C _i	2.19	2.75	3.71	4.21	2.37	2.37	4.67	0+0	+−0	0++	0−0	+−0	0−−
7009	C ₂	2.02	2.85	ftc		ftc		2.64	0++	00−	+0−	0++	00−	+0−
5608	C _i	2.97	3.45	5.69	4.66	2.60	2.60	4.66	000	++0	0−−	000	−−0	0++
3355	C ₂	1.49	3.92	6.29	6.05	3.60	3.60	6.00	0++	00−	+−0	0++	0++	0++
2903	C ₂	2.70	3.84	5.96	5.58	4.33	4.33	5.62	00+	0++	0+0	0+0	+00	+0+
8926	C ₂	3.33	3.53	5.75	5.53	2.97	2.97	5.52	00+	0+0	0+0	+−0	00−	+0+
71	C ₂	3.07	4.16	6.66	5.57	3.66	3.66	5.44	0+0	++0	0−0	0+0	++0	0−0
12970	C _i	5.37	3.73	3.38	5.13	2.15	2.15	5.07	0+0	+0−	+−−	0−0	−0+	−++
2024	C ₂	3.38	4.43	5.45	5.83	4.25	4.25	6.66	00−	−0−	00−	0−0	0−0	−−0
3378	C ₂	5.63	3.63	3.00	4.41	2.52	2.52	4.38	0−+	−+−	00−	−++	0++	−−0
13064	C _i	4.43	4.14	4.16	4.86	3.83	3.83	4.81	000	0−−	++0	000	0++	−−0
2030	C ₂	4.27	4.44	4.71	6.04	4.25	4.22	6.05	00−	+−+	000	0+−	+−0	0++
12304	C _i	5.67	5.16	5.54	7.04	3.83	3.83	6.93	000	+−+	+−−	000	−+−	−++
2556	C ₂	4.50	5.90	3.61	5.29	3.15	3.15	ftc	0−+	+0+	0+−	0+−	0+0	++−
8078	C _i	5.90	5.38	7.90	8.09	4.62	4.62	7.65	00+	0++	−00	00−	0−−	+00
2118	C ₂	6.47	6.01	5.68	6.15	4.88	4.88	5.94	0−−	−00	0−−	0−−	0−0	−−−
2314	C ₂	8.55	5.03	4.75	5.82	2.68	0.63	5.86	00−	−−0	−++	00−	−−0	−++
974	C ₂	6.42	7.15	10.27	9.39	1.32	1.32	9.26	00+	−00	−0−	00+	−00	−0−
4109	C ₂	7.70	7.57	8.95	9.70	7.77	7.77	9.80	00+	+0+	−0−	−−0	−+0	++0

^a Relative energies are calculated with respect to conformation **9485**, the ground state conformation according to the MP2/6-311G**//HF/6-311G** energy. At the B3LYP level, since convergence of conformation **9485** was not achieved, relative energies were calculated with respect to the following higher energy conformation, conformation **9492**.

^b No stands for conformational number. Sym stands symmetry. MP2//B3LYP stands for MP2/6-311G**//B3LYP/6-311G**. ftc stands for failed to converge after a specified number of geometry optimization steps. For energies of the lowest energy conformation, see Table S3.

^c Qualitative description of the torsion angles of the six C–S–C–S–C groups based on the MP2/6-311G** geometry. Angles between 0 and 2/3 π are designated as (+), angles between 0 and −2/3 π are designated as (−) and angles between 2/3 π and 4/3 π are designated as (0).

Table 2
Relative free energies, in kcal/mol, of some selected conformations of 18t6.^{a,b}

No	CAM	MP2
9485	0.00	0.00
9492	0.88	0.66
5611	0.37	0.59
13958	2.27	1.92
1446	−0.64	0.66
949	4.32	3.25
78	−1.29	0.14
5620	2.72	2.29
6962	2.02	0.72
7009	2.02	0.63
7874	0.02	1.02
3157	1.80	1.00
3156	2.61	2.36
8516	0.03	1.76
3378	4.67	4.56
5608	2.66	3.21
6222	2.38	0.63

^a No stands for conformational number and CAM stands for the CAM-B3LYP functional. The 6-311G** basis set was used at the CAM-B3LYP level and the 6-31G* basis set was used at the MP2 level. Relative energies are calculated with respect to that for conformation **9485**.

^b Free energy of conformation **9485** at the CAM-B3LYP/6-311G** level is −2860.52198 au and at the MP2/6-31G* level is −2855.46198 au.

conformation, conformation **6222**. Table 3 lists the bond length and dihedral angles of conformations **9485** and **6222** at the HF, B3LYP, TPSS and MP2 levels using the 6-311G** basis set. Table S5 lists the same bond length and dihedral angles of conformations **9485** and **6222** at all levels considered in the current study.

4. Discussion

4.1. Predicted conformations

From the data in Table 1 and S2, it is clear that conformation **9485** is the ground state conformation of 18t6. Recall that the predicted conformations by the CONFLEX method are given numbers according to their MMFF94s energy order and in the initial computation at the HF/3-21G level 15,000 conformations were considered. This justifies the large number of conformations considered in the initial computation at the HF/3-21G level as the 9485th lowest energy conformation, according to the MMFF94s energy order, is the ground state conformation. This indicates problems with predicting the ground state conformation for a molecule of similar or larger size than 18t6 as the need for more accurate force fields may decrease this computational time.

Table 3Geometry of conformation **6222**, corresponding to the experimental conformation, and the ground state conformation, conformation **9485**, of 18t6.^a

Coordinate	HF	B3LYP	M06	TPSS	MP2	Exp ^b
Conf. 6222						
S ₁ –C ₂	1.824	1.841	1.828	1.828	1.817	1.797
C ₂ –C ₃	1.528	1.529	1.516	1.530	1.529	1.486
C ₃ –S ₄	1.823	1.841	1.829	1.830	1.818	1.817
S ₄ –C ₅	1.821	1.841	1.826	1.831	1.813	1.900
C ₅ –C ₆	1.525	1.526	1.513	1.526	1.523	1.364
C ₆ –S ₇	1.821	1.840	1.826	1.829	1.815	1.954
S ₇ –C ₈	1.822	1.842	1.828	1.831	1.814	1.812
C ₈ –C ₉	1.525	1.526	1.513	1.525	1.521	1.446
C ₉ –S ₁₀	1.831	1.850	1.837	1.841	1.820	1.845
C ₁₈ S ₁ C ₂ C ₃	–96.1	–94.4	–92.4	–90.1	–96.6	–93.5
S ₁ C ₂ C ₃ S ₄	68.3	70.9	70.2	67.0	61.6	75.3
C ₂ C ₃ S ₄ C ₅	100.1	99.9	98.3	95.0	97.2	99.6
C ₃ S ₄ C ₅ C ₆	–72.4	–71.0	–69.7	–74.3	–65.2	–77.74
S ₄ C ₅ C ₆ S ₇	–173.2	–173.9	–175.4	–177.0	–176.3	–174.8
C ₅ C ₆ S ₇ C ₈	78.9	81.2	76.4	75.3	61.3	83.7
C ₆ S ₇ C ₈ C ₉	76.4	79.0	77.6	73.6	59.3	73.7
S ₇ C ₈ C ₉ S ₁₀	177.2	177.1	177.0	176.5	179.4	179.1
C ₈ C ₉ S ₁₀ C ₁₁	121.7	111.9	112.6	119.7	154.5	116.3
Conf. 9485						
S ₁ –C ₂	1.821	ftc ^c	1.826	1.831	1.815	
C ₂ –C ₃	1.524		1.513	1.525	1.523	
C ₃ –S ₄	1.819		1.825	1.829	1.814	
S ₄ –C ₅	1.824		1.830	1.833	1.817	
C ₅ –C ₆	1.525		1.513	1.526	1.524	
C ₆ –S ₇	1.818		1.823	1.827	1.812	
S ₇ –C ₈	1.821		1.829	1.831	1.816	
C ₈ –C ₉	1.524		1.511	1.524	1.522	
C ₉ –S ₁₀	1.821		1.827	1.831	1.816	
C ₁₈ S ₁ C ₂ C ₃	64.6		58.8	58.6	59.6	
S ₁ C ₂ C ₃ S ₄	172.4		176.4	174.3	177.1	
C ₂ C ₃ S ₄ C ₅	68.7		72.7	68.7	73.4	
C ₃ S ₄ C ₅ C ₆	165.8		178.9	175.6	180.0	
S ₄ C ₅ C ₆ S ₇	173.9		173.2	179.2	178.7	
C ₅ C ₆ S ₇ C ₈	67.2		66.2	68.6	65.3	
C ₆ S ₇ C ₈ C ₉	64.8		58.3	63.8	59.9	
S ₇ C ₈ C ₉ S ₁₀	169.6		173.5	174.0	170.8	
C ₈ C ₉ S ₁₀ C ₁₁	63.4		58.0	58.3	57.1	

^a Bond lengths in Å and angles in degrees. Atom numbering of conformations **6222** and **9485** is given in Fig. 2.^b Refs. [19,26].^c ftc stands for failed to converge after a specified number of geometry optimization steps.

Comparison between the conformations predicted in this work and those reported in Ref. [21] can be made by comparing the relative HF/3-21G energies only after taking symmetry into consideration. This is because for a given predicted conformation in Ref. [21], too many conformations are predicted in the current work with the same energy. Note that the ground state conformation in Ref. [21] is not the same as the ground state conformation in the current work and that conformation 2 in Ref. [21] and conformation **6222** in the current report correspond to the experimentally known conformation of 18t6. Then conformation 2 in Ref. [21] of relative energy of 2.3 kcal/mol at the HF/3-21G level corresponds to conformation **6222** in the current report at the same HF/3-21G level of relative energy of 0.93 kcal/mol, it is concluded then that the ground state conformation, conformation 1, predicted in Ref. 21 corresponds to conformation **78** in the current work. According to the MP2/6-311G** energy this **78** conformation is the seventh lowest energy conformation. Thus conformations 1, 2, 3, 4, 5, 9 and 11 in Ref. [21] correspond to conformations **78**, **6222**, **7874** (or **14438**, since both are of C_i symmetry and have the same energy), **8516** (predicted in the current work with S₆ symmetry), **12214**, **9298** and **6962** (or **7009**, since both are of C_i symmetry and of the same energy), respectively. It is not possible to locate the conformation in the current work that corresponds to conformation 12 in Ref. [21]. This is because about 200 conformations in the current work were predicted with the same relative energy of

4.3 kcal/mol with not enough variables to differentiate them and it is also possible that this conformation might be higher in the MMFF94s energy than the 15,000 conformations considered in the current study for computation at the HF/3-21G level. The case is similar for conformations 6, 7, 8 and 10 predicted in Ref. [21]. On the other hand, the ground state predicted conformation in this work, conformation **9485**, is more stable by 2.17 kcal/mol at the MP2/6-311G** level than the ground state predicted conformation in Ref. [21], which corresponds to conformation **78** in the current work.

The most important predicted conformations of 18c6 are the S₆, C_i and C₂ conformations [5]. Geometry optimization of these three conformations were performed at the HF/3-21G level, after replacing the oxygen atoms by the sulfur atoms. The calculated relative energies of these S₆, C_i and C₂ conformations were 9.45, 9.70 and 8.77 kcal/mol, respectively. None of the 15,000 conformations considered for computation at the HF/3-21G level in the current report had the same symmetry and relative energy. We located conformation **58920** of S₆ symmetry and did the geometry optimization for this conformation at the HF/3-21G level. The relative energy was 9.45 kcal/mol, the same as that of the above-mentioned S₆ conformation constructed similar to 18c6. A similar search was not tried for the other two C_i and C₂ conformations as too many conformations were predicted with the same symmetry.

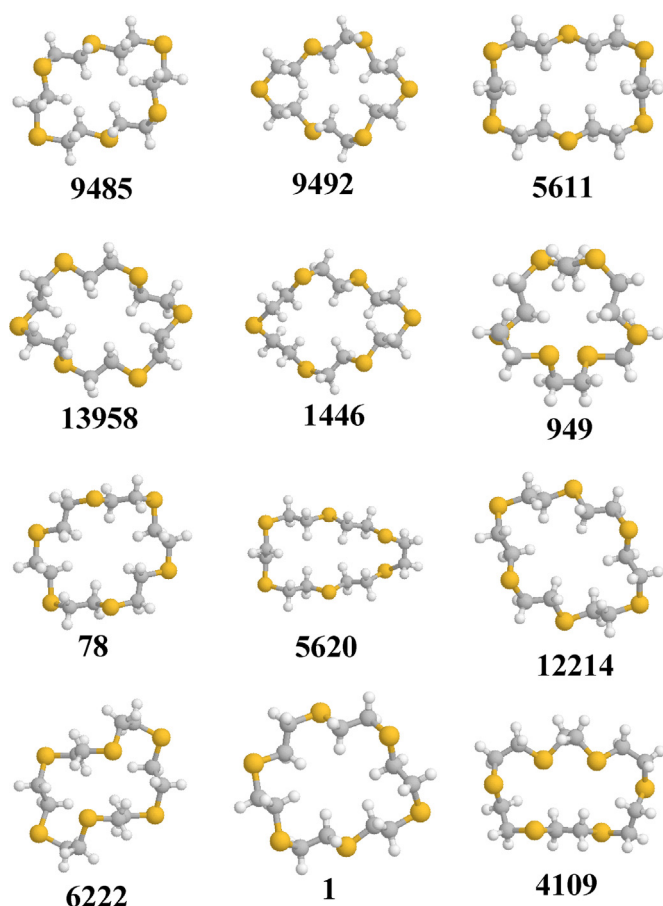


Fig. 1. Structure of the 9 lowest energy conformations, according to MP2/6-311G** energy order, of 18t6, in addition to the conformation corresponding to the experimentally known conformation, conformation 6222 [19,26]. This is in addition to the lowest MMFF94s energy conformation, conformation 1, and one of the highest MP2/6-311G** energy conformation, conformation 4109.

4.2. The structure of the ground state conformation of 18t6 and the factors affecting its stability

One of the most important and critical points to be addressed here is the structure of the ground state conformation, conformation 9485, and the reason behind its stability. The same discussion was performed for 12t4. It is useful here to summarize some of the points about the structure of 12c4 and 18c6 first. In both molecules, the oxygen atom can form a hydrogen bond. As a result the ground state structure of 12c4 has S_4 symmetry and the ground state

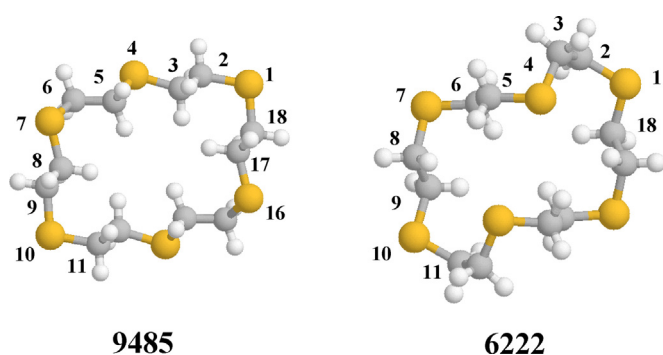


Fig. 2. Atom numbering of the ground state conformation, conformation 9485, and the conformation corresponding to the experimentally known conformation, conformation 6222.

structure of 18c6 has S_6 symmetry. The S_4 and S_6 conformations of 12c4 and 18c6, respectively, are the ground state conformations, which occur due to each conformation having the largest number of hydrogen bonds, and at distances shorter than any other predicted conformation of each molecule. Consequently, crown ethers, the oxygen analogues of thiacycrown ethers, adopt an endodentate structure. Notice that a more accurate statement about the structure of crown ethers, because their structure is controlled by hydrogen bonds, is that they have an endodentate-like structure since an endodentate structure implies that they have a structure similar to their metal complexes. For thiacycrown ethers, the hydrogen bond is absent and the C–S bond is longer than the C–O bond. Consequently thiacycrown ethers adopt an exodentate structure. For 18t6, it was reported that two of the sulfur atoms violate this exodentate rule [19]. There is a slight misunderstanding about this point. The low energy structures of these molecules should be judged by their gas phase and not solid phase properties, since crystal packing forces may change their structure. The reported structure of 18t6, which has two sulfur atoms violating the exodentate rule, is that of the solid state, which corresponds to conformation 6222, while the ab initio computations reported here correspond to the gas phase, isolated molecule which has a predicted ground state structure corresponding to conformation 9485, and not conformation 6222. As detailed below, all of the SCCS angles in conformation 9485 adopt the exodentate structure. Unlike 18t6, the calculated ground state conformation [10] of 12t4 is the same as the solid state conformation, determined by X-ray [19,20].

Table 4 lists the dihedral angles of some selected conformations of 18t6. According to the MP2/6-311G** energy, Table 1 and S2, conformations 9485, 9492, 1446, 949 and 78 are the five lowest energy conformations, conformations 974 and 4109 are the two highest energy conformations and conformations 3156, 3378, 6222 and 2314 have energies between both groups of conformations. Note that all of these conformations have C_2 symmetry. It is clear from the data in Table 4 that the five lowest MP2/6-311G** energy conformations, conformations 9485, 9492, 1446, 949 and 78, have all three SCCS angles the closest to the 180° linear angle requirement and all of the CSCC dihedral angles, among all of the conformations listed in Table 4, are the closest to the 60° gauche angle requirement, with the exception of only one CSCC angle which is close to 180.0° , within 7° . Notice that conformation 9485 is the lowest energy conformation since it has the closest agreement to these SCCS linear angle and CSCC gauche angle requirements, while the other four conformations, conformations 9492, 1446, 949 and 78, have different variations from these two requirements. Conformations 1446 and 78 have two CSCC angles close to 180.0° , within 15° , while all of the three SCCS angles are close to 180° . This is clearly a reflection that maintaining a linear 180° SCCS angle is more important than having gauche CSCC angles. The same result was also concluded for 12t4 [10]. The two highest energy conformations considered in the current work, according to the MP2/6-311G** energy, conformations 4109 and 974, have only one SCCS angle closest to 180° , within 5° , while the other two SCCS angles are closest to 60° , within 17° . Both conformations have three of the six CSCC angles close to 180° , within usually less than 13° . Conformation 6222 which is of average energy between the low and high energy conformations, and corresponds to the experimentally observed conformation, has one SCCS angle of 61.6° . This also the case for the other 3156, 3378 and 2314 conformations of close relative energy.

4.3. Comparison between the experimental and calculated geometry

For 12t4, with ground state conformation of D_4 symmetry, the experimental S–C and C–C bond lengths determined by X-ray are 1.816 and 1.512 Å, respectively, [19,20] and the calculated

Table 4
MP2/6-311G** dihedral angles, in degrees, of some selected conformations of 18t6^a.

No	Sym	MP2	SCCS	CSCC
9485	C ₂	0.00	177.1, 170.8, –178.7	65.3, 59.9, 57.1, 59.6, 73.4, 180.0
9492	C ₂	0.91	165.7, 174.7, –176.8	74.5, 55.0, 61.5, 60.8, 65.6, –177.6
1446	C ₂	1.71	179.7, –176.9, 177.8	78.6, 59.3, –57.7, –165.0, 81.4, –175.9
949	C ₂	1.73	152.6, 175.4, –68.9	99.5, 93.5, 72.9, 63.0, 48.2, –171.9
78	C ₂	2.17	178.6, –178.3, –177.7	–78.2, 176.9, 76.8, 77.4, 75.4, 173.1
3156	C ₂	3.76	178.5, 174.4, –66.3	–79.6, –155.4, 91.0, –66.5, –165.1, 163.4
3378	C ₂	4.38	178.4, 83.7, 67.8	81.3, –119.1, –78.8, –101.2, 64.8, –149.9
6222	C ₂	4.67	179.4, 61.6, –176.3	97.2, –65.2, 61.3, 59.3, 154.5, –96.6
2314	C ₂	5.86	–49.2, –91.8, 173.4	152.9, –65.8, –57.5, 174.3, 61.7, 67.6
974	C ₂	9.26	178.6, –73.3, –76.4	175.3, 154.1, 129.8, –75.3, –177.6, 90.8
4109	C ₂	9.80	76.9, 70.3, –175.2	80.3, 178.4, –97.5, 167.2, –71.1, –178.7
Exp ^b	C ₂		–179.1, –174.8, 75.3	73.7, 83.7, –77.7, 99.6, –93.5, 116.3

^a No, sym and MP2 stand for conformational number, symmetry and MP2/6-311G** relative energies, respectively.

^b Refs. [19,26].

S–C and C–C bond lengths at the MP2/6-311G** level are 1.816 and 1.525 Å, [10] respectively. For 18t6, there are two reports of the X-ray experimental structure [19,26]. Both report a C₂ structure of 18t6 with the same geometrical parameters. The reported experimental S–C bond lengths in Ref. [19] (or Ref. [26]) are quite diverse, ranging between 1.797 and 1.954 Å, but the calculated S–C bond lengths are tightly grouped, ranging between 1.813 and 1.820 Å, as shown in Table 2 and S4. These calculated values of the S–C bond lengths are comparable to those calculated for 12t4. It is clear that the longest C₆–S₇ bond length of 1.954 Å found experimentally is not reflected in the calculation at the MP2 level or at any other level considered in this work. The calculated dihedral angles at the MP2 level have the worst agreement with the experimental dihedral angles followed by those obtained at the M06HF level. The other levels perform almost equal and better than that at the MP2 or M06HF level.

4.4. Energy order of the predicted conformations

For 12t4, the energy ordering of the predicted conformations at the different levels of theory used was compared to that at the G3MP3 level [10]. For 18t6, computation at the G3MP2 level is quite costly. Consequently, the highest level of theory used in the current study is the MP2 level. Computation at the MP2/6-311G** level was performed only for conformations of symmetry other than the C₁, C_s and C₃ symmetries for the 15,000 lowest MMFF94s energy conformations. This is in addition to only one conformation of C₁ symmetry, conformation **8603**. Thus a total of 38 conformations were considered for calculation at the MP2/6-311G** level. It is quite interesting to notice that the lowest energy conformation at the M06, M062x, M06L, TPSS and PBE levels is the experimental solid state conformation, conformation **6222**, Table 1 and S2. It is also the lowest energy conformation at the TPSS and PBE levels after the inclusion of the electron correlation at the MP2 level, i.e. at the MP2/6-311G**/TPSS/6-311G** and MP2/6-311G**/PBE/6-311G** levels. Also, at the M06HF level, conformation **6222** is the fourth lowest energy conformation. Compared to the energy order at the MP2/6-311G** level, it is interesting also to notice that conformation **6222** became more stable at all of the other correlated levels. The same observation was reported in Ref. 21. In general, qualitatively the same energy order was preserved at the correlated MP2 levels. The agreement between the energy order at all the uncorrelated levels and that at the MP2/6-311G** level is worse than that at the other correlated levels. The calculated free energy at the MP2/6-311G* level, Table 2 and S4, also predicted conformation **9485** to be the ground state conformation. However, conformation **6222** became more stable with a relative energy of only 0.63 kcal/mol.

The calculated free energies at the HF and CAM-B3LYP levels predict that conformation **78** to be the ground state conformation and still conformation **9485** to be more stable than conformation **6222**.

4.5. Polarizable continuum model (PCM)

The computations in the current report correspond to gas phase isolated molecule. These computations indicate that 18t6 exists in conformation **9485**. Experimentally by X-ray 18t6 exists in conformation **6222**. In a recent vibrational study of 18t6 we have shown that the best agreement between the experimental and calculated vibrational frequencies of 18t6 in the solid phase is obtained assuming the structure of conformation **6222** of 18t6 [38]. It is not simple to measure the vibrational spectra of 18t6 in the gas phase due to experimental complications in getting a high enough concentration (pressure) of gaseous 18t6 without the sample condensing on the cell windows. Even if possible, the broadness of the vibrational bands in the gas phase and especially for a large molecule as 18t6 with 120 fundamental vibrations will make it very difficult to distinguish in what conformation 18t6 exists. In the current study we use the PCM method [39] to explore properties of various 18t6 conformations in the aqueous phase. The computations were performed for the same 17 conformations for which free energies were calculated. The computations were performed at two different levels, the CAM-B3LYP/6-311G** and MP2/6-311G* levels. The

Table 5
Relative energies, in kcal/mol, of some selected conformations of 18t6 in water as a solvent using the PCM method^{a,b}.

No	CAM	MP2
9485	0.00	0.00
9492	0.57	0.72
5611	1.16	1.69
13958	1.35	0.84
1446	0.71	1.24
949	6.23	4.02
78	0.09	0.93
5620	4.43	4.11
6962	4.79	4.96
7009	4.79	4.96
7874	1.09	1.74
3157	4.98	4.49
3156	4.06	3.91
8516	1.63	2.78
3378	6.65	5.25
5608	3.49	3.77
6222	3.62	2.00

^a See corresponding footnote in Table 2.

^b Free energy of conformation **9485** at the CAM-B3LYP/6-311G** level is 2860.83649 au and at the MP2/6-311G* level is –2855.78492 au.

computations were not performed at the MP2/6-311G** level because geometry optimization of conformation **9485** failed to converge at this level, after a specified number of geometry optimization steps. Notice that computations failed also to converge at some levels of theory used in the current study as shown in Table 1 and S2. The calculated relative energies using the PCM method are listed in Table 5. The results indicate that the conformation **8516** is the most stable conformation and that of conformation **6222** is higher in energy by 2.00 kcal/mol, at the MP2/6-31G* level.

5. Conclusion

Unlike 12c4 [4] and 12t4 [10], the number of the predicted conformations of 18c6⁵ and 18t6, due to the larger more flexible ring, was quite huge, more than 100,000 conformations. This necessitated a huge amount of computations as the ground state conformation of both of 18c6 and 18t6 was not among the lowest MM energy conformations. This suggests that an improved force field than the available MM force fields is needed for faster prediction of the ground state and low energy conformations, especially if larger systems is to be studied. The intensive computations performed in the current report predicted a new C₂ conformation of 18t6 that is more stable by 4.67 kcal/mol, according to the MP2/6-311G** level, than the experimentally known C₂ conformation. It is known that thiocrown ethers adopt exodentate structure and that two of the SCCS angles of 18t6 violate this rule. The problem with this definition is now clear; it is based on solid state data although the structure of molecules should be judged by that of the gas phase data, as that predicted from the ab initio computations. In fact, for this new gas phase, low energy C₂ conformation, all of the SCCS dihedral angles without exception comply with this exodentate rule. By comparison between the structure of the low and high energy conformations, it is concluded for the stability of 18t6, similar to 12t4, that having a linear SCCS angle requirement is more important than having a gauche CSCC angle.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jmngm.2013.08.004>.

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