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ORIGINAL ARTICLE

Influence of polyether chain on the non-covalent interactions and stability of the conformers of calix[4]crown ethers

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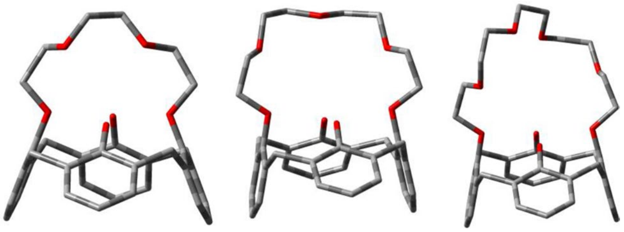
Abstract

Conformational preferences of the calix[4]crown-(4,5,6,7)-ethers were studied utilizing HF/6-31G(d), B3LYP/6-31G(d), B3LYP/6-311G(d), MPWB95/6-31G(d), MPWIPW91/6-31G(d) and M062X/6-31G(d) methods. DFT-D3 (Becke–Johnson) dispersion correction method was also employed. The results acquired from the analysis of the computational data indicated that the stability of conformers of calix[4]crown-(4,5,6,7)-ethers follows the order; cone conformer > partial cone conformer > 1,3-alternate conformer. It was initially assessed, in general, that both hydrogen bond and OH···π interactions play a crucial role in determining the stability of the different conformers. It was further observed that the strength of both H-bond and OH···π interactions, are dependent on the length of the polyether bridge. Hence, in order to comprehend them better, the effect of these interactions was studied systematically on the conformational stability of different isomers. It is found that both intramolecular hydrogen bonds and O–H···π interactions are mainly responsible for relative stabilities of these conformers, which in turn is also dependent on the length of the polyether bridges.

Graphical Abstract

The computational study reported here demonstrate that the size of the polyether bridge along with non-covalent interactions such as hydrogen bond and OH···π interactions play an important role in determining the stability of the conformers of calix[4]crown ethers.



Keywords Calix[4]crown ether · Calixarenes · Computational methods · Calix[4]crown ether conformers · Crown ether

Introduction

Development of synthetic molecular receptors, for selective recognition of important guest molecules, is an area of intense research [1–3]. The recognition of guest species by the synthetic receptor is largely controlled by forces resulting from non-bonding or non-covalent electrostatic and dispersion (intermolecular and intramolecular) interactions. A variety of supramolecular receptors based on calix[n]arene, cyclodextrin, cyclotriveratrylene and crown ethers are available for trapping ionic and molecular species [1–3]. Among a variety of

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available supramolecular receptors, calix[n]arenes are reported as useful building blocks for assembling synthetic receptors, owing to their amenability through simple chemical reactions and comparatively easy control over conformational preference. For better selectivity, several interesting mixed receptors (containing both calix[4]arene and crown ethers moieties) possessing the amalgamation of important features of both crown ethers and calix[4]arene are available in the literature [1–3]. The new family of receptors named as calix[4]crown ethers in general display superior ability as an extractant for various alkali and alkaline earth metal cations. For example, calix[4]crown-5-ether is found to display high selectivity toward K^+/Na^+ extraction [4]. A recent report linked the improved selectivity displayed by calix[4]crown ethers to the conformation preferences of the calix[4]arene ring [5]. Another report described the synthesis of the partial cone and 1,3-alternate conformers of a calix[4]arene, where 1,3-alternate conformer favored the extraction of Ba^{2+} ion extraction, but the partial cone conformer preferred the Ca^{2+} ions extraction [6]. Similarly, Dinake has reported a calix[4]arene derivative, which adopted cone and 1,3-alternate conformer to bind Hg^{2+} ions [7, 8]. The different binding affinities displayed by the conformers of calix[4]arene derivative may be attributed to the variable binding core present in these conformers. Therefore, in order to understand the binding preferences of calix[5]crown ethers at molecular level based on their ring size, it is essential to study and understand the stabilities of different conformations of calix[4]crown ethers [7, 8]. Unlike calix[4]arene that can take any of the four possible conformations (cone, partial cone, 1,2-alternate and 1,3-alternate), the calix[4]crown-(4,5,6,7)-ether due to imposition of intra-annular restriction by polyether bridge between two diametrically opposite OH group can only adopt three conformations i.e. cone, partial cone and 1,3-alternate. To comprehend the selectivity of these receptors and its dependence on conformational preferences of calix[4]crown-(4,5,6,7)-ethers at the molecular level, use of computational methods can be very helpful [9–11]. The structure of the conformer of calix[4]crown-5-ether suggests the presence of potential hydrogen bond and O–H···π interactions. Both hydrogen bond and O–H···π interaction can play an important role in determining the conformational preferences of calix[4]crown-5-ethers. A number of reports are available in the literature related to computations of stabilities of calix[4]arene conformations, which describe the effect of hydrogen bonds using molecular mechanics [3, 8], HF and density functional theory [12]. However, there is no reported study of the conformational stability of calix[4]crown ether detailing the effect of the hydrogen bonds, O–H···π interactions, and size of the polyether bridge. Further, no report is available in the literature, which describes the effect of polyether bridges in calix[4]crown ethers on O–H···π and H-bond interactions Additionally, rarely any report on calix[n]arenes included the effect of dispersive forces in the calculations or utilized the dispersion corrected DFT method. Although, a recent report on the effect of O–H···π, H-bond interactions on the conformation stability of the calix[4]crown-4-ether is available in the literature, however, the report does not describe the effect of polyether bridge on the O–H···π, H-bond, and conformations [13].

Therefore, stabilities of various conformations of calix[4]crown ethers were also investigated by using MPW1PW91 [14] and MPW1B95 [15] methods, which are known to provide a better description of H-bonded systems. To take into account the effect of dispersive forces in the calculation M062X method was also used. The advantage of using such method is to be able to evaluate the effect of various non-covalent intra-molecular interactions in the stability of these conformations. In the present work, the non-covalent interactions were investigated using quantum mechanical calculations at several levels of theory (HF, B3LYP, MPW1B95, MPW1PW91, and M062X) in order to access their effect on the stability of three conformers.

Computational

The starting geometries of the various conformers of calix[4]crown ethers were created using Gauss View 5 [16] and Avogadro [4] programs. Various stable conformations were obtained by using random rotor search method in the Avogadro [4] program. Gaussian 09 Revision A. 02 program suite was employed to carry out the computations [16]. In addition, Orca program ver. 4.0.1 [17] was also used for calculations that involved dispersion-corrected DFT and HF methods [18–20]. The Avogadro program generated conformers were optimized using the AM1 method to get the initial structure for further optimization. The initial AM1 optimized geometries were then optimized with ab initio HF/6-31G(d), DFT B3LYP/6-31G(d), B3LYP/6-311G(d), MPW1B95/6-31G(d) MPW1PW91/6-31G(d) and M062X/6-31G(d) methods using Gaussian 09 to obtain the energies of the conformers using Gaussian Berny's method. The AM1 optimized geometries were also optimized with Orca 4.0.1 program [17] to include dispersion correction using BJ-damped variants of the D3 approach with HF and DFT methods. The local minimum state was corroborated using frequency calculation via the force matrix route through analysis of vibrational spectra.

Results and discussion

The presence of strong intramolecular H-bond in *p-tert*-butylcalix[4]arene was investigated extensively, which as per literature reports renders the cone conformer to be the most stable among the four possible conformers [2, 3]. It is well known that the conformational transition in calix[4]arene takes place either oxygen through annulus or para substituent through annulus rotation. The presence of bulky groups at the upper rim or the lower rim hinders the conformational transition. For example, tetrapropyl-*p-tert*-butylcalix[4]arene is more conformationally rigid in comparison to tetramethyl-*p-tert*-butylcalix[4]arene [2, 3]. The *p-tert*-butycalix[4]crown ethers can take any one of the three possible conformations identified as a cone, partial cone, and 1,3-alternate as shown in Fig. 1. The investigations were generally accomplished with a bulky *p-tert*-butyl group at the *para* position. Therefore, in present investigations, an isomer without *p-tert*-butyl was chosen to investigate, if the absence of bulky group at the *para* position also alters the stability order of the conformer of calix[4]crown-(4,5,6,7)-ethers.

The single point energies of the conformers of calix[4]crown-(5,6,7)-ethers namely cone, partial cone and 1,3-alternate calculated using different quantum chemical methods are listed in Table 1. The energies are listed for the most stable isomer among the various structures, while Table 2 lists the relative energies. The energies of the different conformers of calix[4]crown-4-ether, calculated using the same computational methods were reported earlier [13].

Tables 1 and 2 corroborate the greater stability of the cone conformer over other conformers of calix[4]crown ethers. Partial cone conformer turns out to be more stable in comparison to the 1,3-alternate conformer. All the computational methods provided energies within 0.25% (standard deviation) of each other. The M062X/6-31G(d) afforded the lowest difference between the energies of various conformational isomers in the case of calix[4]crown-(4 [14], 5, 6)-ethers, while it predicted highest energy difference in the case of calix[4]crown-7-ether. However, the MPW1PW91/6-31G(d) and MPW1B95/6-31G(d) methods were within 1 kcal/mol difference in relative energy estimates with respect to each other. The average difference in relative energy ($\Delta E_{\text{relative}}$ (kcal/mol) $= E_{\text{cone}} - E_{\text{partialcone or 1,3-alternate}}$) between cone, partial cone and 1,3-alternate conformers generally decreased with an increase in the crown ether ring size (Table 2). The average total energy, calculated by different computational methods for the cone, partial cone, and 1,3-alternate conformers were plotted against the number of crown ether units and a linear correlation was observed in the case of all the conformers (Figs. 2a, S1, S2). Similarly, the total energies calculated by different computational methods were also plotted against the number of crown ether units, which revealed no significant difference between the different methods and all suggested a decrease in the energy with the increase in the ring size (Figs. S3–S5). However, the difference in energy calculated using M062X/6-31G(d) and HF/6-31G(d) method was found to be ~6950 kcal/mol for the cone, partial cone and 1,3-alternate conformers of the calix[4]crown-5-ether, which may be due to poor ability of the HF/6-31G(d) method to take into consideration the effect of dispersive forces in the calculations (Table S1). In addition, the energy difference increases with the increase in the ring size of the crown ether unit (Fig. S6). The difference in energy calculated by using M062X/6-31G(d) and B3LYP/6-31G(d) methods was found to be around 470–480 kcal/mol for the cone, partial cone and 1,3-alternate conformers of the calix[4]crown-5-ether, which again indicated poor contribution of dispersive forces in the calculation performed using B3LYP methods (Figs. S7, S8). In order to investigate the energy difference between different methods, the B3LYP or HF optimized geometries form Gaussian 09 program were taken. The single point energies of the Gaussian 09 program optimized geometries were calculated by using B3LYP/G, D3(BJ) dispersion corrected B3LYP/G and HF methods (ORCA 4.0.1). The calculations indicated 420–510 kcal/mol energy as the dispersion correction to the HF method, while 118–144 kcal/mol was calculated as the dispersion correction to the B3LYP methods. The dispersion energy increases with the increase in ring size of the crown ether unit, which indicated that the addition of dispersion correction to the B3LYP of HF method improves the estimation of energy (Figs. S9–S11). In order to check whether the optimization of the geometries produce different results, the different geometries were optimized and almost similar results were obtained (Table S2). The average relative energy ($\Delta E_{\text{relative}} = E_{\text{cone}} - E_{\text{partial-cone or 1,3-alternate}}$) calculated for partial cone and 1,3-alternate conformers with respect to the cone conformer was plotted against the number of crown ether units in the polyether chain to yield a linear correlation for both partial cone and 1,3-alternate conformers (Fig. 2b). A drop in the relative energy difference between the cone and partial cone or 1,3-alternate conformer was observed with the increase in the size of the crown ether ring, presumably due to the increase in the flexibility provided to the calix[4]arene skeleton by the crown ether unit. The flexibility provided by the crown ether units influenced the intermolecular interactions present in the calix[4]crown-(4,5,6,7)-ether skeleton. However, the relative energies ($\Delta E_{\text{relative}} = E_{\text{cone}} - E_{\text{partialcone or 1,3-alternate}}$) calculated using Orca program with dispersion corrected methods (BJ) did not follow any particular order, perhaps due to consideration of extra dispersion interaction between the OH of the phenolic ring and oxygen atoms of the crown ether bridge (Table S2).

To investigate the influence of the size of the polyether chain on intermolecular interactions, the hydrogen bonds interactions were estimated using different computational methods. The existence of intramolecular hydrogen bonds in the structure of calix[4]crown-(4,5,6,7)-ether may be expected due to the presence of two OH groups at alternate positions. The presence of intramolecular bonds in calix[4]arene skeleton has a significant influence on the conformational stability [21] as alkylation of the OH groups generally alters the stability order [22]. The stabilization by the

Fig. 1 The structure of different conformers of calix[4]crown-(4,5,6,7)-ether

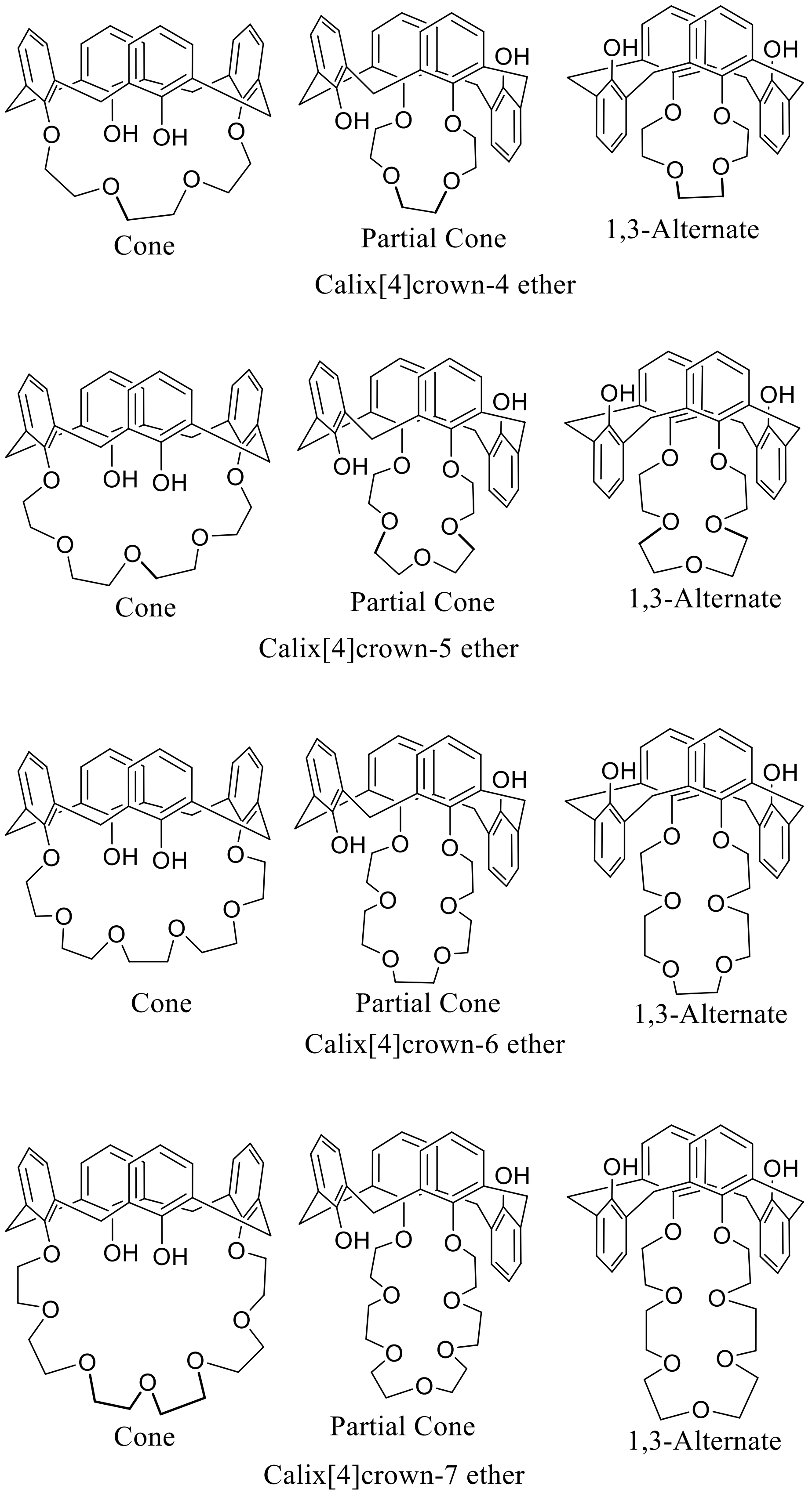

Table 1 Energy (kcal/mol) calculated for different conformers of calix[4]crown-(5,6,7)-ether using different quantum mechanical methods

	HF/6-31G(d)	B3LYP/6-31G(d)	B3LYP/6-311G(d)	MPW1B95/6-31G(d)	MPW1PW91/6-31G(d)	M062X/6-31G(d)	Average
Cone (5)	– 1,198,151	– 1,205,595	– 1,205,865	– 1,205,065	– 1,205,321	– 1,205,114	– 1,204,185
Partial cone	– 1,198,143	– 1,205,586	– 1,205,856	– 1,205,058	– 1,205,313	– 1,205,100	– 1,204,177
1,3-Alternate	– 1,198,136	– 1,205,580	– 1,205,849	– 1,205,052	– 1,205,306	– 1,205,104	– 1,204,171
Cone (6)	– 1,294,102	– 1,302,122	– 1,302,415	– 1,301,550	– 1,301,825	– 1,301,605	– 1,300,603
Partial cone	– 1,294,096	– 1,302,115	– 1,302,408	– 1,301,542	– 1,301,818	– 1,301,599	– 1,300,596
1,3-alternate	– 1,294,090	– 1,302,109	– 1,302,402	– 1,301,536	– 1,301,812	– 1,301,591	– 1,300,590
Cone (7)	– 1,390,057	– 1,398,650	– 1,398,967	– 1,398,033	– 1,398,330	– 1,398,097	– 1,397,023
Partial cone	– 1,390,049	– 1,398,644	– 1,398,961	– 1,398,027	– 1,398,323	– 1,398,087	– 1,397,015
1,3-Alternate	– 1,390,045	– 1,398,640	– 1,398,956	– 1,398,022	– 1,398,318	– 1,398,082	– 1,397,010

Cone (5): calix[4]crown-5-ether; Cone (6): calix[4]crown-6-ether: Cone (7): calix[4]crown-7-ether

Table 2 Relative energies ($\Delta E_{relative}$ (kcal/mol) $= E_{cone} - E_{partialcone\ or\ 1,3-alternate}$) obtained for different conformers of calix[4]crown-(5,6,7)-ether using different methods

Method	Calix[4]crown-5-ether			Calix[4]crown-6-ether			Calix[4]crown-7-ether		
6-31G(d)	Cone	PC	1,3-Alt	Cone	PC	1,3-Alt	Cone	PC	1,3-Alt
HF	0	7.8746	15.0143	0	6.0614	12.0336	0	8.3084	12.6598
B3LYP	0	8.5725	14.8960	0	7.4799	13.1146	0	6.2279	10.4469
B3LYP[a]	0	9.0289	15.9579	0	7.7596	13.8708	0	6.4541	11.3064
MPW1B95	0	7.0564	13.2727	0	8.2184	14.3913	0	6.4389	11.2950
MPW1PW91	0	8.0651	14.6671	0	7.3282	13.5327	0	6.6206	11.3344
M062X	0	5.4244	10.4960	0	5.4442	13.9289	0	10.2540	15.2803
Average	0	7.6703	14.0507	0	7.0486	13.4787	0	7.3840	12.0538

[a] 6-311G(d) was used as the basis set

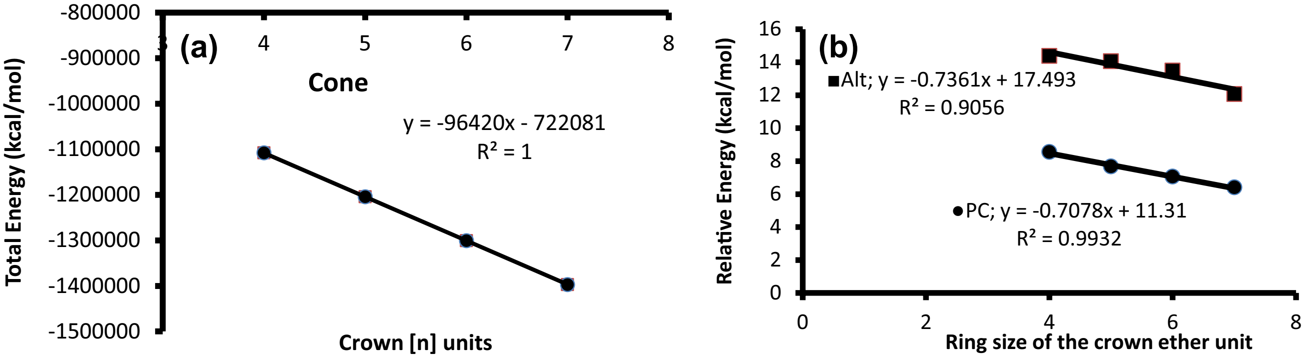

Fig. 2 **a** The change in the average total energy (kcal/mol) of the cone conformer in calix[4]crown ethers with the increase in the crown ring size; **b** A plot of the average relative energy (kcal/mol) of the partial cone and 1,3-alternate conformers of the calix[4]crown ethers with the increase in the crown ring size

O–H hydrogen bonds may also be affected by the size of the crown ether ring due to change in flexibility for the calix[4]arene skeleton, which may influence the H-bond and distances among the atoms leading to the alteration in the stability. Therefore, quantum chemical methods were chosen in a way to provide a better understanding of the effect of hydrogen bonds on the conformer stability in calix[4]crown-(4,5,6,7)-ether and the calculated hydrogen bond parameters are listed in Table 3 and reported for calix[4]crown-4 ether [13].

Figure 3 depicts the MPW1B95/6-31G(d) optimized structures indicating the hydrogen bonding in the cone and partial cone conformers of the calix[4]crown-(4,5,6,7)-ether. The cone conformer calix[4]crown ether having two hydrogen bonds is the most stable conformer, and partial cone conformer having one hydrogen bonds was next in the order. The 1,3-alternate conformer was found to be the least stable conformer, presumably due to the absence of any H-bond in the conformer structure. A short O···O distance (< 3.0 Å) with an O–H···O angle close to 180°, in general, provides strength to the H-bond [13].

Table 3 also lists the H-bond distances of both cone and the partial cone conformers for comparative assessment of the strength of H-bond in the calix[4]crown-(5,6,7)-ether. The average calculated O···O distances (cone: 2.80–2.82 Å and partial cone: 2.76 Å) of the intramolecular hydrogen bonds of the cone and partial conformers of calix[4]crown-5-ether are similar to the experimental crystal structure values (2.692, 2.741 and 2.759 Å) [23] obtained for cone conformer of calix[4]crown-5-ether, which indicated a good correlation between the parameters obtained from optimized geometries and the experimentally obtained parameters. The O···O distances given in Table 3 for calix[4]crown-(5,6,7)-ether and reported for calix[4]crown-4 ether displayed a

Table 3 H-bonding parameters calculated for cone and partial-cone conformers of calix[4]crown-(5,6,7)-ether derivatives

Crown ether ring	Atoms	HF/6-31G(d)	B3LYP/6-31G(d)	B3LYP/6-311G(d)	MPW1B95/6-31G(d)	MPW1PW91/6-31G(d)	M062X/6-31G(d)	Average
Cone (5)	O_2–O_{20}	2.9297	2.7697	2.7697	2.8560	2.7614	2.8674	2.8256
	H_{45}–O_{20}	1.9805	1.8085	1.8049	1.8970	1.7959	1.9046	1.8652
	O_2–H_{45}	0.9504	0.9786	0.9733	0.9707	0.9757	0.9741	0.9705
	O_2–H_{45}–O_{20}	170.53	169.57	170.59	169.05	169.69	168.25	169.61
	O_4–O_1	2.8913	2.7429	2.7429	2.8340	2.729	2.8346	2.7958
	H_{44}–O_4	1.9949	1.7960	1.7993	1.9431	1.7865	1.9348	1.8758
	O_1–H_{44}	0.9512	0.9790	0.9737	0.9731	0.9762	0.9764	0.9716
	O_1–H_{44}–O_4	156.29	161.73	162.31	151.06	161.21	152.06	157.44
Partial cone (5)	O_3–O_{18}	2.8072	2.7492	2.7385	2.7472	2.7277	2.7684	2.7564
	H_{55}–O_3	1.9196	1.8213	1.8143	1.8436	1.7995	1.8733	1.845
	O_{18}–H_{55}	0.9520	0.9790	0.9738	0.9746	0.9764	0.9773	0.9722
	O_{18}–H_{55}–O_3	154.15	156.99	157.29	154.04	157.61	150.92	155.17
Cone (6)	O_{30}–O_{87}	2.8969	2.8091	2.8179	2.7986	2.7981	2.7976	2.8197
	H_{88}–O_{30}	1.9861	1.8793	1.8884	1.9096	1.8690	1.8921	1.9041
	H_{88}–O_{87}	0.9517	0.9786	0.9731	0.97371	0.9757	0.9775	0.9717
	O_{30}–H_{88}–O_{87}	159.53	157.65	158.82	150.52	158.12	152.82	156.24
	O_{16}–O_{82}	2.8477	2.7658	2.7631	2.7489	2.7490	2.7286	2.7672
	H_{83}–O_{16}	1.9125	1.8097	1.8121	1.8078	1.7972	1.7831	1.8204
	H_{83}–O_{82}	0.9517	0.9797	0.9738	0.9749	0.9767	0.9786	0.9726
	O_{82}–H_{83}–O_{16}	166.92	164.37	164.59	161.24	163.93	161.44	163.75
Partial cone (6)	O_{31}–O_{87}	2.9891	2.8859	2.8896	2.8794	2.8681	2.802	2.8857
	H_{88}–O_{31}	2.1011	1.9634	1.9708	1.9714	1.9453	1.9117	1.9773
	H_{88}–O_{87}	0.9510	0.9775	0.9717	0.9726	0.9745	0.9772	0.9707
	O_{31}–H_{88}–O_{87}	154.80	156.43	156.84	154.41	157.10	150.15	154.96
Cone (7)	O_{76}–O_{28}	3.0746	2.9754	2.9600	2.9694	2.9790	2.8961	2.9762
	H_{77}–O_{28}	2.2094	2.0295	2.0276	2.0381	2.0352	1.9332	2.0455
	H_{77}–O_{76}	0.9502	0.9755	0.9703	0.9709	0.9720	0.9747	0.9689
	O_{76}–H_{77}–O_{28}	165.82	162.81	161.28	160.08	163.18	169.09	163.71
	O_{14}–O_{81}	3.0065	2.8556	2.8673	2.8834	2.8460	2.7309	2.8649
	H_{82}–O_{14}	2.0743	1.9132	1.9271	1.9446	1.9054	1.7696	1.9224
	H_{82}–O_{81}	0.9503	0.9771	0.9714	0.9722	0.9741	0.9775	0.9704
	O_{14}–H_{81}–O_{82}	166.48	161.19	162.14	161.58	161.51	166.98	163.31
Partial cone (7)	O_{31}–O_{91}	3.1382	2.9609	2.9822	2.9989	2.9556	2.9086	2.9907
	H_{92}–O_{31}	2.2341	2.0287	2.0518	2.0877	2.0242	2.0150	2.0736
	H_{92}–O_{91}	0.9500	0.9767	0.9708	0.9713	0.9734	0.9759	0.9697
	O_{31}–H_{92}–O_{91}	158.69	158.91	159.91	155.54	159.48	151.22	157.29

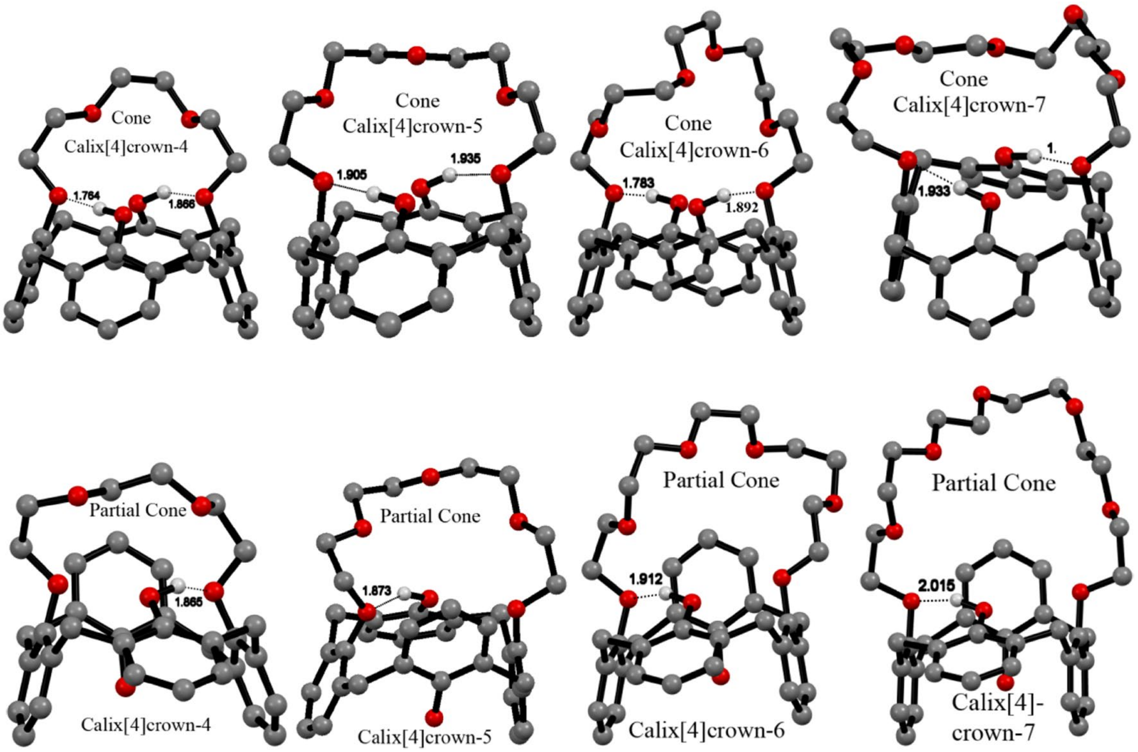

Fig. 3 Cone and partial cone conformers of calix[4]crown-(4,5,6,7)-ether showing H-bond interactions calculated using M062X/6-31G(d) method. Only selected H atoms are shown for clarity

regular increase with the increase in the crown ether ring size. Although the O···O bond distances observed for the calix[4]crown-(4,5,6,7) indicated strong H-bond interactions in the cone conformations [24, 25]. However, the increase in the H-bond distances indicated a decrease in the contribution of the H-bonds in the stability of the cone conformer. The reduction in the strength of the H-bond further indicated the reduction in the average energy difference between the cone conformations and partial cone or 1,3-alternate conformations. A correlation between the average calculated O···O distance and the size of the crown ether unit connected to the calix[4]arene skeleton is shown in the Fig. 4a. Similarly, the O···O bond distance decreases with the decrease in the size of the crown ether unit attached to the calix[4]arene in a partial conformer (Fig. 4a). However, the decrease in the O···O bond distance is less steep in comparison to the decrease in the O···O bond distance calculated in the cone conformer (Fig. 4a). The result indicated that the decrease in the relative energy difference between the cone and partial cone conformer is mainly due to the strength of the H-bond interactions.

The average total energy calculated by different computational methods was also plotted against the O···O distance, which indicated that the energy decreases with the increase in the O···O distance. The results further, suggested that the H-bond plays a major role in stabilization of cone and partial cone conformers (Fig. S12). The O···O distance calculated using different computational methods in the different cone and partial cone conformer was also plotted, which revealed similarity in different methods in predicting the geometry and H-bonds (Figs. S13, S14).

The calculated average (O–H···O) angles of 157°–169° in the case of cone conformer and 155.2° for partial cone conformer (Table 3) was observed in calix[4]crown-5-ether, which was found to correlate with the experimentally observed values in *p-tert*-butylcalix[4]crown-5-ether (152.4°, 1536°, 162.5° and 166.0°) [23]. The calculated value of (O–H···O) angle listed in Table 3, suggests that the hydrogen bonding in the calix[4]crown-5-ether are almost linear and very strong [24, 25]. The B3LYP/6-31G(d) and MPW1PW91/6-31G(d) calculated angles were found to match more closely with experimental values compared to other calculation methods [26]. The results indicated that B3LYP method can also be used for predicting the geometries in similar systems. However, a decrease in the O–H···O bond angle was observed with the increase in the ring size of the crown ether unit. It was further noticed from the calculated data that the strength of the H-bond was controlled by both the O···O bond distance and O–H···O angle (Table 3). A reduction in H-bond strength due to a decrease in O···O bond distance can be adjusted by an increase in an O–H···O angle towards 180°. Therefore, a ratio of O–H···O angle and

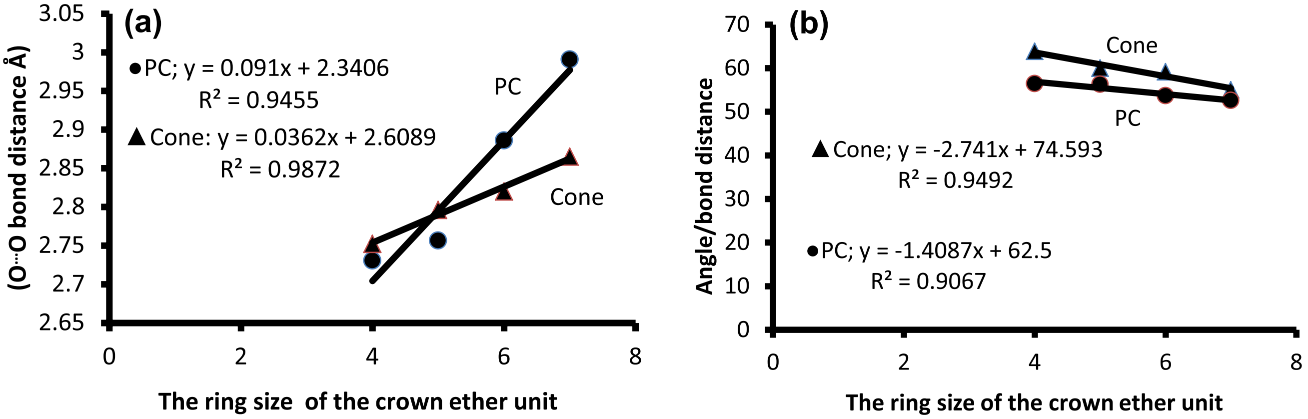

Fig. 4 **a** A correlation between the ring size of the crown ether unit and the O···O bond distance observed in different calix[4]crown-(4,5,6,7)-ether; **b** a correlation between the ring size of the crown ether unit and the bond angle/O···O bond distance observed in different calix[4]crown-(4,5,6,7)-ether

O···O bond distance was plotted against the size of the crown ether unit connected to the calix[4]arene skeleton, which yielded a linear correlation (Fig. 4b). The Fig. 4b also indicated that although the slope of the change in O···O bond distance versus crown ether ring size is different in both cone and partial cone conformer, but the slope of the O–H···O angle/O···O bond distance versus the size of the crown ether unit is almost similar in both cone and partial cone conformer. The results indicated that both the bond angle and bond distance are important parameters that determine the strength of the H-bond in calix[4]crown ethers and in turn determine the stability order of different conformers.

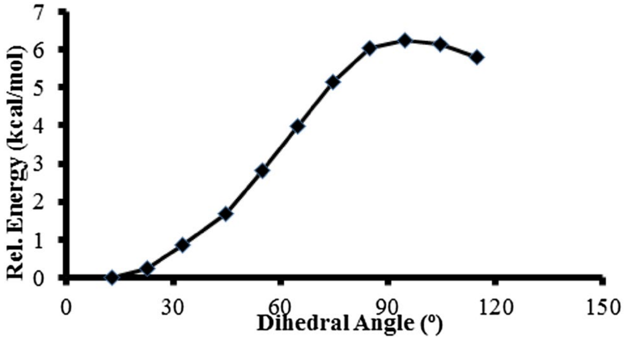

Fig. 5 Ground state potential energy scan for rotation of dihedral (C_{24}–C_{30}–O_1–H_{44}) in the cone conformer of calix[4]crown-5-ether performed using MPW1B95/6-31G(d) method. Energies are given in kcal/mol

To understand and estimate the strength of H-bonds in the cone and partial cone conformer of calix[4]crown-(4,5,6,7)-ether, O–H bond was dihedrally rotated in calix[4]crown-5-ether involved in H-bonding by 10° at each step (Fig. 5). The geometry optimizations were performed using MPW1B95/6-31G(d) level of theory and optimized structures were used to obtain the single point energies of the partial cone and cone conformers. An energy maxima was observed near a dihedral angle of 90° (Fig. 5), which indicated that the H-bond provide minimum stability to the structure at this dihedral angle. Therefore, in the optimized structure of calix[4]crown-(4,5,6,7)-ether, this dihedral angle was constrained to 90° and structure was optimized keeping either one H-bond in the structure or none. In the case of partial cone conformer only one H-bond is present, therefore, it was rotated and the structure was optimized. The energies of the optimized structures were obtained (Table S3) and compared with the energy of the corresponding structure optimized without any constraint (Table 4). An increase in energy of the optimized geometries with the loss of H-bond interaction was observed. For example, an increase in energy of cone conformer by 8.37 kcal/mol or 6.30 kcal/mol was observed in the case of cone conformer of calix[4]crown-5-ether when the geometry was optimized in absence of one of the H-bonds. Since the cone conformer has two O···H–O bonds, while partial cone conformer has one, an average in the energy of all the O···H–O bond present in cone conformer of calix[4]crown-(4,5,6,7)-ethers was taken. Similarly, an average of relative energy of the partial cone conformer of calix[4]crown-(4,5,6,7) was taken. The average relative energy of cone conformer was compared with the average relative energy of the partial conformer reveals that the H-bond provides almost similar stability to both cone and partial cone conformer. The relative data also revealed no clear trend in the energy with respect to the crown ether ring size. However, it indicated that each O–H stabilizes the conformer to ~8.06 ± 1.41 kcal/mol, while the partial cone is stabilized by ~7.66 ± 0.88 kcal/mol. The similar differences were observed within 0–1.5 kcal/mol when calculations were performed with the Orca 4.0.1 program using B3LYP/6-31G(d)/D3BJ method (Table S5). The difference in energy between two hydrogen bonds in the cone

Table 4 The calculated average relative energies of the different conformer of calix[4]arene (4,5,6,7)-ether after restraining either one of the two short contacts or both short contacts (O···H–O–C–C or C$_g$···H–O¯C¯C) with respect to the structure where both the short contacts were present

	O–H···O contact						O–H···π contact		
	Cone			Partial Cone			1,3-Alternate		
	No short contact	One H-bond	One H-bond	No short contact	One H-bond	One C$_g$–H bond	No short contact	One C$_g$–H bond	One C$_g$-H bond
4	13.7481	9.2555	5.1000	18.2477	8.8597	9.9185	16.7851	8.2755	8.5096
5	14.6711	8.3753	6.2959	15.8518	8.1557	9.1089	16.5805	8.0801	8.5004
6	18.0468	9.3812	8.3830	14.7212	7.6719	7.0493	13.4830	7.0002	6.9404
7	17.6856	8.5762	9.1094	14.1324	7.3988	6.9649	12.9875	6.2350	6.9816

The calculations were performed using MPW1B95/6-31G(d) with Gaussian 09 program

conformer is, perhaps, due to the orientation of the crown ether bridge. The difference in the energy between two H-bonds present in the cone conformer decreases with the increase in the size of the crown ether ring, which reduces the effect of the interaction of OH group with the oxygen atom present in the bridge. The data further revealed that the absence of any (O–H···O) H-bond interaction results in the change in stability order in case of calix[4]crown-4 ether to 1,3-alternate > cone > partial cone. However, in the case of calix[4]crown-(5,6,7) crown ethers the stability order changed to 1,3-alternate > partial cone > cone, which indicated that the H-bond plays a significant role in stabilizing the different conformers. In addition, the difference in the relative energy between the cone and partial cone or between 1,3-alternate and cone conformers change almost linearly with the change in the crown ether ring size (Fig. 6a). Further, the difference in energy between cone, partial cone and 1,3-alternate conformers increases with the increase in the ring size of the crown ether unit connected to the calix[4]arene.

During the calculations, the short O–H··· π interactions were also noticed in the partial cone and 1,3-alternate conformer of the calix[4]crown-(4,5,6,7)-ether (Fig. 7). The structure of partial cone conformer allows for the possibility of one O–H···π interaction, while 1,3-alternate conformer allows for the possibility of two short O–H···π interactions. Therefore, the effect of O–H···π interactions on the stability of conformer structures of the calix[4]crown-(4,5,6,7)-ether was also investigated (Table 5; Fig. 7). The average O–H···π distance increases with the increase in the ring size of the crown ether unit attached to the calix[4]arene (Fig. 8a). The calculated results indicated that the energy of the crown ether ring is dependent on the O–H···π distance. The average total energy of the partial cone and 1,3-alternate conformer increases with the increase in the H···π distance (Fig. S15). It was further noticed from the calculated data that the average relative energy of the partial cone and 1,3-alternate conformer with respect to the cone conformer also decreases with the increase in the H···π distance (Fig. 8b). In addition, the average O–H···π angle decreases with the increase in the ring size of the crown ether unit attached to the calix[4]arene (Fig. 9a). The average relative energy of the partial cone and 1,3-alternate conformer with respect to the cone conformer also increases with the increase in the O–H···C$_g$ (centroid of

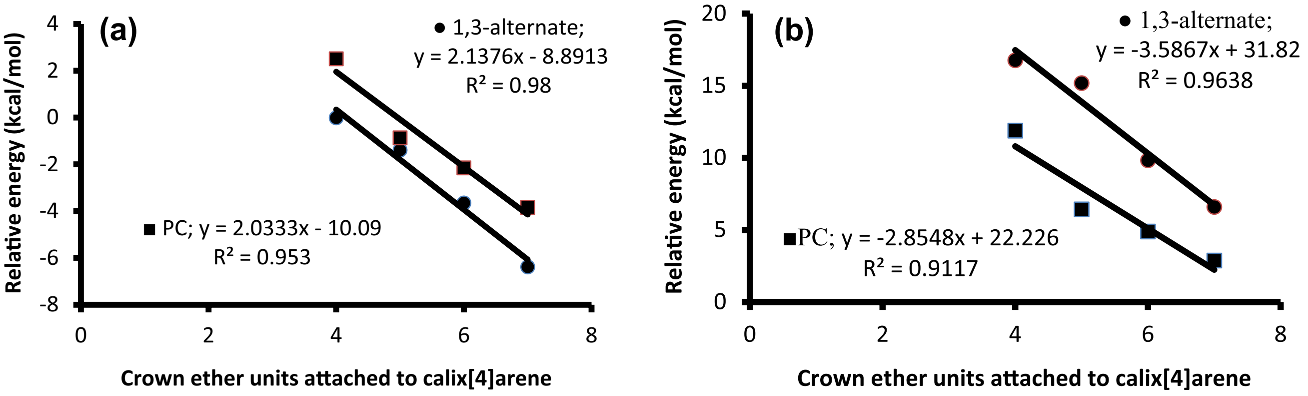

Fig. 6 **a** The calculated change in the relative energy (kcal/mol) of the partial cone and 1,3-alternate conformer in the absence of (O···H–O) H-bond interactions using MPW1B95/6-31G(d); **b** the calculated change in the relative energy (kcal/mol) of the partial cone and 1,3-alternate conformer in the absence of any intramolecular interactions

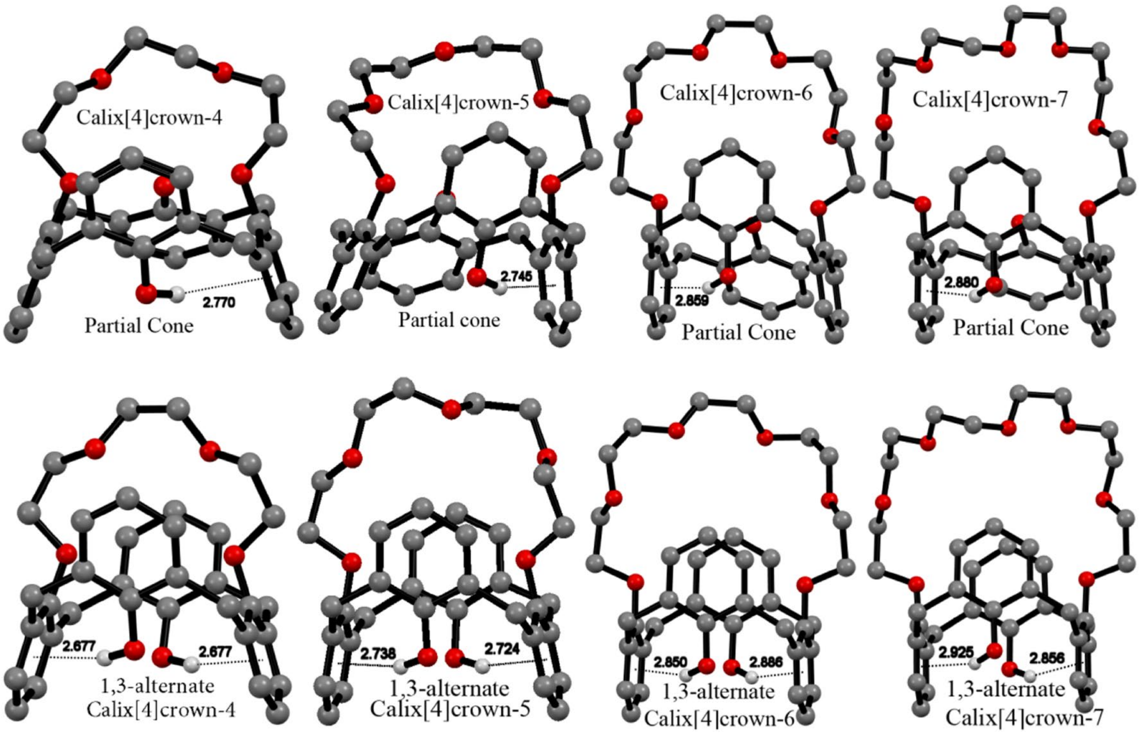

Fig. 7 Short O–H··· π interactions observed in the partial cone and 1,3-alternate conformers of calix[4]crown-5-ethers. Only selected H-atoms are shown for clarity

Table 5 O–H···π bonding parameters calculated for the partial-cone and 1,3-alternate conformers of calix[4]crown-5-ether

	HF/6-31G(d)	B3LYP/6-31G(d)	B3LYP/6-311G(d)	MPW1B95/6-31G(d)	MPW1PW91/6-31G(d)	M062X/6-31G(d)	Average
Partial cone (5)	2.832	2.745	2.734	2.734	2.694	2.747	2.748
	158.35	159.27	159.43	159.65	160.35	161.36	159.73
1,3-Alternate (5)	2.806	2.738	2.702	2.761	2.669	2.760	2.739
	161.6	159.14	159.77	157.68	160.69	160.50	159.90
	2.753	2.724	2.701	2.696	2.651	2.728	2.709
	163.42	159.08	159.67	158.1	160.89	160.40	160.26
Partial cone (6)	2.946	2.859	2.859	2.88	2.829	2.808	2.863
	148.26	156.36	154.14	156.81	155.73	155.98	154.55
1,3-Alternate (6)	2.927	2.85	2.845	2.853	2.883	2.801	2.860
	154.21	155.7	154.91	157.08	153.6	156.41	155.32
	2.955	2.886	2.89	2.862	2.876	2.831	2.883
	152.84	155.08	154.02	156.33	154.15	156.01	154.74
Partial cone (7)	3.014	2.8800	2.874	2.8880	2.844	2.891	2.898
	144.72	153.94	153.23	153.91	154.37	152.87	152.17
1,3-Alternate (7)	3.045	2.925	2.914	2.925	2.878	2.956	2.920
	147.55	153.59	152.82	152.51	154.27	152.31	153.10
	2.966	2.856	2.844	2.865	2.798	2.879	2.848
	149.71	154.88	153.91	153.64	155.83	153.90	154.43

The distances are given between the H and the centroid of the benzene ring, while the angle is for O–H···C_g (centroid)

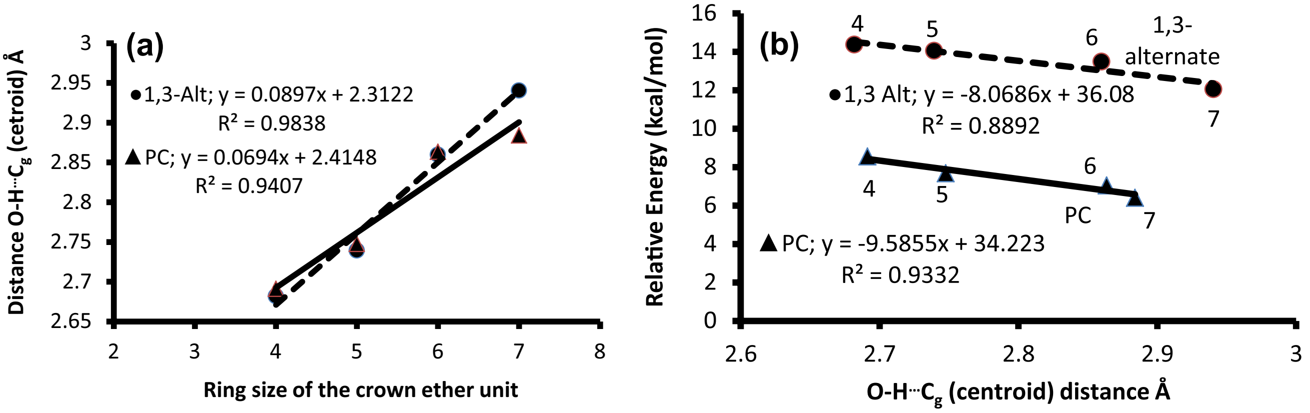

Fig. 8 **a** The calculated O–H···π (C_g centroid of the benzene ring) interaction versus the ring size of the crown ether unit connected to the calix[4]arene skeleton; **b** the calculated O–H···π (C_g centroid versus the relative energy of the 1,3-alternate and partial cone conformer with respect to the cone conformer of the calix[4]crown-(4,5,6,7)-either unit

the π system) angle (Fig. 9b). The results indicated that both H···π distance and O–H···C_g angle are important factors that determine the stability of the 1,3-alternate conformer and partial cone conformers of the calix[4]arene units.

In order to further estimate the effect of the ring size of the crown ether unit and O–H···π interactions on the stability of the different conformer of the calix[4]arene, the H–O–C=C dihedral was rotated stepwise by 10°. The structure corresponding to each step was optimized using MPW1B95/6-31G(d) (Fig. 8). The single point energy corresponding to each step was plotted against the H–O–C=C dihedral angle to observe an energy maxima near 90° (Fig. 10). Therefore, H–O–C=C dihedral angle was constrained at 90 °C in the partial cone and 1,3-alternate conformer and geometries were optimized. The total energies of the optimized geometries are listed in the Table S1. The energies were compared with the energy of the optimized 1,3-alternate and partial cone conformer of the calix[4]crown-(4,5,6,7)-ethers having O–H···π interactions (Table 3). An increase in energy of the partial cone conformer and 1,3-alternate conformer was observed on the elimination of the effect of O–H··· π interaction. A slight decrease in the relative energies of the partial cone and 1,3-alternate conformers of the calix[4]crown-(4,5,6,7) with the increase in the ring size was observed. The two O–H··· π interactions present in the 1,3-alternate conformer produced a slightly different increase in energy, which may be due to the effect of the crown ether moiety interactions with different benzene rings. An average increase in the energy (8.26 ± 0.88 kcal/mol) due to O–H···π interaction present in the partial conformer of calix[4]crown-(4,5,6,7)-ether was observed to be more than the average increase in energy (7.56 ± 0.87 kcal/mol) calculated per O–H···π interaction in the case of 1,3-alternate conformers. The results indicated that the O–H···π interactions also play a significant role in

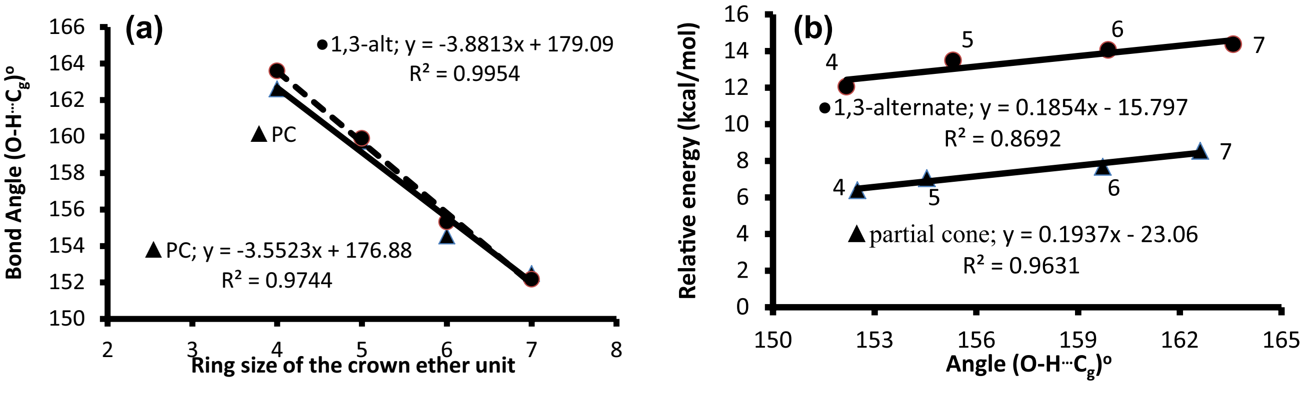

Fig. 9 **a** The calculated O–H···π (C_g centroid of the benzene ring) interaction versus the ring size of the crown ether unit connected to the calix[4]arene skeleton; **b** the calculated O–H···π (C_g centroid versus the relative energy of the 1,3-alternate and partial cone conformer with respect to the cone conformer of the calix[4]crown-(4,5,6,7)-either unit

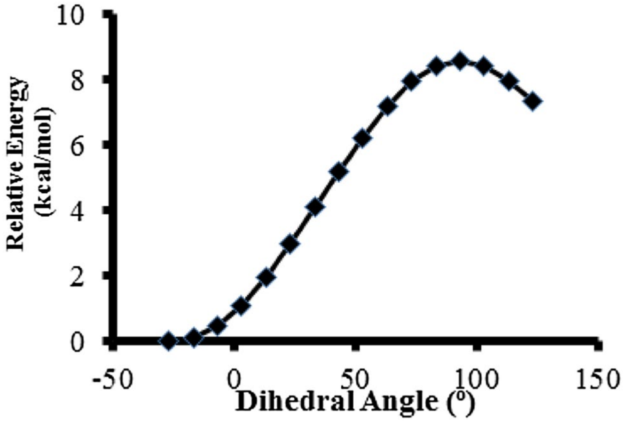

Fig. 10 Ground state potential energy scan for rotation of dihedral (C_1–C_{19}–O_4–H_{45}) in the partial cone conformer of calix[4]crown-5-ether performed using MPW1B95/6-31G(d) method. Energies are given in kcal/mol

the determination of the stability order observed in the calix[4]crown ether, which is a similar order of magnitude as provided by the O···H–O interactions.

Further, when both O–H···π and H-bond interactions are absent, the cone conformer was observed to be more stable than the partial cone conformer, which in turn was more stable than the 1,3-alternate conformer in calix[4]crown-(4,5,6,7) crown ethers. In addition, the difference in stability decreases with the increase in the ring size of the crown ether units (Fig. 6b). The lowest difference in energy between the different conformers was observed for calix[7]crown-7-ether. Therefore, it may be concluded that the stability order in calix[4]crown ethers may not be entirely due to the H-bond (O–H···O), the other factors such as O–H···π interactions and steric hindrance also are other important factors.

Conclusion

In summary, different conformers of calix[4]crown-(4,5,6,7)-ethers were optimized using different computational methods. The study indicated that the cone conformer is more stable than partial cone conformer, which in turn was found to be more stable than the 1,3-alternate conformer. The relative stabilities of the conformers of calix[4]crown-(4,5,6,7)-ether was found to be mainly dependent on the number and strength of the intramolecular short O–H···O and O–H···π interactions. The short O–H···π interactions observed in the partial cone and 1,3-alternate conformers provide similar stability to the conformers as the O–H···O H-bond interactions present in the cone and partial cone conformers. Each short contact contributes 7–9 kcal/mol to the stability of the conformers. In the absence of all such interactions, cone conformer is more stable than the partial cone and 1,3-alternate conformers. The calculated data further indicated that the polyether bridge also plays an important role in the determination of stability order, which acts by providing more flexibility to the structure and influences the short intramolecular interactions. The difference in energy calculated between HF or DFT method without dispersion correction and MO62X increases with the increase in the size of the crown ether ring, which indicated that HF and DFT method does not appropriately reflect the effect of dispersion interaction. The difference in energy reduced in the same order after taking into account dispersion interactions using the D3BJ method. The variation in short intramolecular contacts with the change in crown ether ring size further influences the stability of the conformers of calix[4]crown ethers.

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