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Molecular recognition of ammonium ion by tetrahomodioxacalix[4]biscrown

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Abstract—The first theoretical study on the conformational features and the complexation behaviors upon ammonium ion binding of tetrahomodioxacalix[4]biscrown-4 has been performed using molecular dynamic simulations and density functional theory. The conformational analyses show that the relative stability and the geometry of the ammonium ion complexes are directly contributed by the number of putative hydrogen bonds between oxygen lone pairs and ammonium hydrogens.

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Calixarene has been one of the key players in the host–guest chemistry due to its potential accessibility for molecular recognition, ion transport phenomena, enzyme model building, and the construction of sensors for a wide variety of applications.[1,2] Tetrahomodioxacalix[4]arene (**1**), incorporating two –CH_2OCH_2– groups in the macrocyclic ring, can provide larger cavity, greater flexibility, and extra coordination sites for guest complexation compared to calix[4]arene (**2**, Fig. 1).[3–5] Only limited studies have been reported on the syntheses, conformational analyses, and complexation of tetrahomodioxacalix[4]arenes due to the synthetic difficulties.[6–8] Recently, tetrahomodioxacalix[4]arene derivatives have been synthesized and several experimental attempts have been made to determine the conformational preference depending on the substituents.[9–15] Among these derivatives, considerable interest has been drawn to the tetrahomodioxacalix[4]biscrowns in that crown ether loops attached to the calix[4]arene framework provide extra binding sites increasing guest recognition ability and complex stability. Last year, No et al. [14] reported the syntheses, X-ray structures, and metal binding abilities of five tetrahomodioxacalix[4]biscrowns with crown rings varying from crown-2 to crown-6. Among these ligands, it was observed that the tetrahomodioxacalix[4]biscrown-4 (**3**–**5**) showed the best extraction ability for the guest ions, in particular, the highest binding affinity for ammonium ion. Molecular recognition of ammonium compounds by a variety of host molecules has attracted much interest due to its biological applications.[16] The study of complex formation with ammonium ions by their receptions may provide valuable information for the understanding of the mechanism, for example, in the recognition process of acetylcholine and related biological systems.

Despite the novel synthesis and complexation studies of tetrahomodioxacalix[4]biscrowns, no theoretical studies on the origin of the conformational stability or complexation affinity for tetrahomodioxacalix[4]biscrowns have yet been born out. Herein, we report the first theoretical investigation on the conformational preference of tetrahomodioxacalix[4]biscrown-4 and its ammonium ion complex by using molecular dynamic (MD) simulations and density functional theory (DFT) method. The aim of this work is threefold. First, it is to provide the thermodynamic stability sequence of parent tetrahomodioxacalix[4]biscrown-4 in a gas phase by computational methods and to compare the results with the available experimental data. Secondly, it is to determine the relative binding affinity among different conformations of the hosts toward ammonium ion guest that may provide the chemical origin and physical nature of the complexation behavior for tetrahomodioxacalix[4]biscrown-4. Lastly, the result of this work can be applied to design the calixcrown-based host molecules for ammonium ion selectivity with varying structural characteristics.

The conformational preference of tetrahomodioxacalix[4]arenes with three different *p*-substituents on the phenolic ring was investigated by density functional

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Keywords: Calix[4]biscrown; Molecular recognition; DFT calculation.

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theory (DFT) and the stability order was predicted to be cone > C-1,2-alternate > partial cone > 1,3-alternate > COC-1,2-alternate.[17] Due to the restriction by two crown ether linkages in tetrahomodioxacalix[4]biscrown-4 (**3**–**5**), only three isomers are available and the stability sequence is predicted to be C-1,2-alternate (**4**) > 1,3-alternate (**5**) > cone (**3**).[18] The lowest energy structures located at the B3LYP/6-31G* level for three different isomers are shown in Figure 2.

When tetrahomodioxa *p*-phenylcalix[4]arene (**1**) was reacted with triethylene glycol ditosylate, two isomers of tetrahomodioxacalix[4]biscrown-4 were isolated.[14] From their NMR spectra, two isomers were assigned to be C-1,2-alternate and 1,3-alternate with C-1,2-alternate higher in yield. From the Molecular Dynamics simulations followed by DFT computations, C-1,2-alternate (**4**) was optimized to be the most stable conformer that is in agreement with the experimentally observed thermodynamic stability. While calix[4]arene and tetrahomodioxacalix[4]arene prefer a cone conformation, the most stable conformation for tetrahomodioxacalix[4]biscrown-4 is a C-1,2-alternate, which is 6.3 and 3.4 kcal/mol more stable in energy than that of **3** and **5**, respectively, as listed in Figure 2. Crown ether linkages in **4** try to avoid steric repulsion with adjacent benzene rings pointing outward from the cavity. It is noted that the ether oxygens of the –CH_2OCH_2– groups in the macrocycle of **4** also pointed out from the cavity. This particular conformation favors the most from the electrostatic effect and dipole preference, resulting in thermodynamic stability for **4**. The computed geometry of **4** is in close similarity to the crystal structure in Ref. 14. On the basis of the excellent agreement between geometrical parameters by X-ray and B3LYP/6-31G* herein, B3LYP/6-31G* optimized structure was considered to be relevant to characterize physical nature and chemical origin for the conformations of **1**. Compound **3** exhibits the highest energy among three isomers by computation and it was not experimentally observed. Two crown ether linkages facing each other create steric congestions and electrostatic repulsions destabilizing the conformation of **3** as shown in Figure 2. In all three isomers, the ether oxygens in the –CH_2OCH_2– groups in the macrocycle pointed away from the cavity in order to release the electrostatic repulsion between crown ether oxygens.

Recent complexation study determined by NMR provides that tetrahomodioxacalix[4]biscrown-4 forms a 1:1 complex with ammonium ion, albeit the crystal structure for a complex has not been obtained.[14] To understand the origin of the molecular recognition phenomena, we optimized the geometries of NH_4^+ binding complexes for all three possible isomers. Energy minimum structures are shown in Figure 2 and the relative energies are listed in Table 1. The 1,3-alternate complex (**8**) is computed to be most stable among the three complexes. The cone complex (**6**) is predicted to be the second most stable, which is 4.2 kcal/mol higher in energy than **8**. The C-1,2-alternate complex (**7**) is computed to be the least stable, which is the most stable without ammonium ion guest.

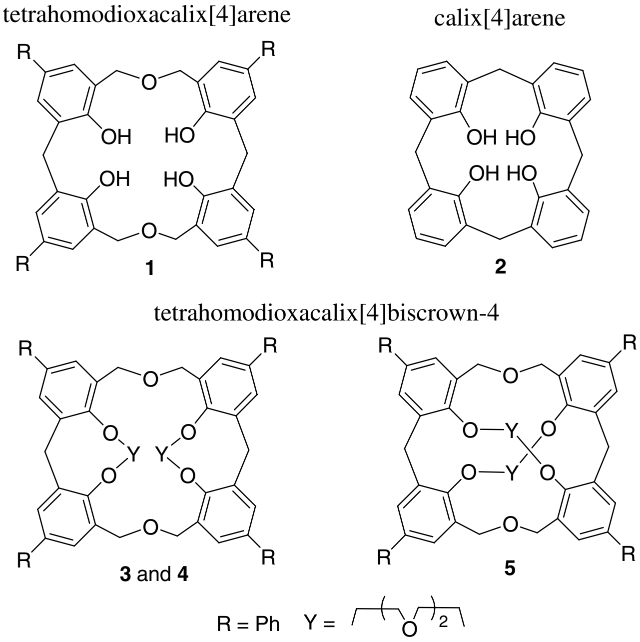
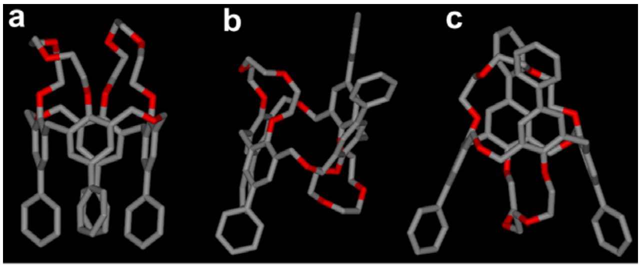


Figure 1. Schematic representation of calix[4]arenes.



Cone
3
6.3

C-1,2-alternate
4
0.0

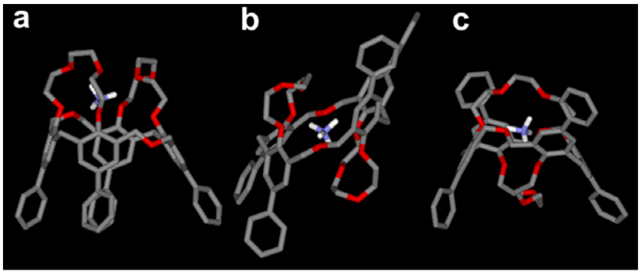
1,3-alternate
5
3.4

Figure 2. Three available conformations of tetrahomodioxa *p*-phenylcalix[4]biscrown-4 and their relative energies (in italic) at the B3LYP/6-31G* level (in kcal/mol). Hydrogen atoms are omitted for clarity.

Table 1. Relative energy (kcal/mol), binding energy (kcal/mol), dipole moment (debye), and the number of hydrogen bonding (HB) for ammonium ion complexes of **1** computed at the B3LYP/6-31G* level are listed

	6	**7**	**8**
Relative energy	4.2	7.7	0.0
Binding energy	−77.8	−70.0	−79.1
Dipole	20.5	23.0	4.0
# of HB	4	3	7

For the most stable complex **8** (Fig. 3), there are considerable geometry changes in the process of ammonium ion binding. The most distinctive geometrical change upon complexation is the nucleation of the guest binding sites (all possible oxygen atoms) to pre-organize the molecular cavity to adopt the guest molecule (Fig. 4). Due to the geometrical constrain of the crown ether linkages to maximize the hydrogen bonding with NH_4^+ guest, *p*-substituted phenyl groups are propagated

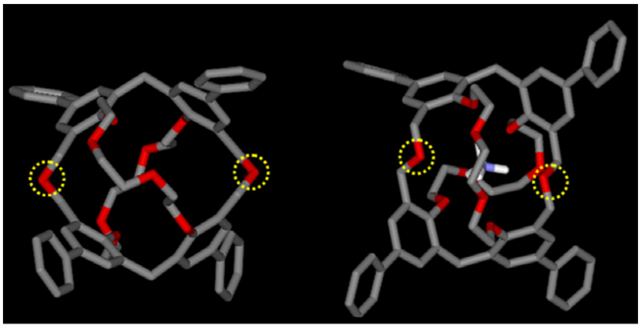


$3+NH_4^+$
6
4.2

$4+NH_4^+$
7
7.7

$5+NH_4^+$
8
0.0

Figure 3. Calculated structures of ammonium ion complexes of tetrahomodioxa *p*-phenylcalix[4]biscrown-4 and their relative energies (in italic) at the B3LYP/6-31G* level (kcal/mol). Hydrogen atoms in host are omitted for clarity.



5 **8**

Figure 4. Conformational changes upon complexation with ammonium ion. Top views are shown. The distance between two ether oxygens in the macrocycle shown in a yellow dotted circle to be 9.12 Å in **5** is decreased upon ammonium ion complexation to be 5.68 Å in **8**. Hydrogen atoms in host are omitted for clarity.

outward from the cavity increasing the radius of gyration. It is notable that two ether oxygens of the $-CH_2OCH_2-$ group in the macrocycle are now located inward to form hydrogen bonds with two hydrogens of ammonium ion, consequently, the distance between two ether oxygens in the macrocycle is to be 5.68 Å in **8**, which is 9.12 Å in **5**. The homooxacalix[4]arene cavity indeed offers extra binding sites in recognizing the guest ammonium ion. A total of seven hydrogen bonds are detected in **8** with the average distance of 2.17 Å. The dipole moment also contributes to the relative stability of **8** (Table 1). The binding energy is computed to be the highest for **8**, which is −79.1 kcal/mol.[23]

The putative cone complex (**6**) also exhibits a notable change in geometry upon complexation. There are two possible binding sites in **6** for guest ion. The *exo*-complex is formed with the guest ion surrounded by the crown ether linkages and *endo*-complex with guest ion surrounded by the phenyl groups.[24] The ammonium ion in **6** was computed to locate around the ether oxygens to form *exo*-complex rather than *endo*-complex. This indicates that the electrostatic interactions between oxygen lone pairs and NH_4^+ hydrogens are stronger than the cation–π interaction in **6**. Also, it is observed that the oxygen of the $-CH_2OCH_2-$ group in the macrocycle of **6** participates to form H-bond to the NH_4^+ hydrogen. In order to maximize the hydrogen bonding between crown ether oxygens and NH_4^+ hydrogens, the macrocycle cavity in **6** is severely distorted. There are four hydrogen bonds found in **6** with the average distance of 1.97 Å. The C-1,2-alternate complex (**7**) is computed to be 7.7 kcal/mol less stable than **8**. In **7**, the distinctive difference between before and after complexation is the geometry of two crown ether linkages pointed inward to form three hydrogen bonds with NH_4^+ hydrogens with the average distance of 1.87 Å. Here, we found that the relative stability and the geometry of the ammonium ion complexes are directly contributed by the number of putative hydrogen bonds and electrostatic interactions between oxygen lone pairs and NH_4^+ hydrogens, while the cation–π interaction does not play a major role.

In conclusion, the first theoretical study on the conformational features and the complexation behaviors upon ammonium ion binding of tetrahomodioxacalix[4]biscrown-4 has been performed using molecular dynamics simulations and density functional theory in a gas phase. The C-1,2-alternate (**4**) is computed to be the most stable, which is in agreement with the experimental observations by X-ray and NMR. The most stable ammonium ion complex is to be 1,3-alternate (**8**), which also exhibits the highest binding energy. The most distinctive conformational feature upon complexation is the nucleation of the oxygen binding sites to pre-organize the molecular cavity to adopt ammonium ion. The conformational analyses show that the most important factor to determine the geometry and stability of the complex is the intramolecular hydrogen bonding pattern displayed by the crown ether oxygens and ammonium hydrogens.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.127.

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18. To search the global minima structures for each isomer and for its complex with ammonium ion, the following procedure was executed. An initial conformational analysis for each molecular system was first performed by molecular dynamics (MD) simulation using SANDER module of AMBER program employing parm99 force field.[19] From the MD simulation trajectory, total 200 structures were collected, which were then subjected to the following optimization procedure using AM1 semi-empirical method[20] to find the energy minim that would be used as initial structures for the density functional theory (DFT) calculations. The DFT calculations were performed at the B3LYP/3-21G and B3LYP/6-31G* level[21] using the *Gaussian 03* package.[22] Frequency calculations were performed to verify the identity of each stationary point as a minimum. All energies discussed here are at the B3LYP/6-31G* level.
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23. The binding energy was calculated as the following equation. $\mathrm{BE} = E(\mathrm{complex}) - \{E(\mathrm{host}) + E(\mathrm{ammonium\ ion})\}$.
24. The *exo*- and *endo*-complex of **6** are drawn in Figure S1 in Supplementary data.