

Computational Study on the Conformational Characteristics of Calix[4]pyrrole Derivatives

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The comparative study of three calix[4]heterocycles (calix[4]pyrrole, calix[4]furan, and calix[4]thiophene) has been theoretically performed by using high-level density functional theory (DFT) at the MPWB1K/6-311G**//B3LYP/6-311G** level. The effect of different hetero-atoms (nitrogen, oxygen, and sulfur) placed in the heterocycles on the conformational flexibility, thermodynamic stability order, cavity sizes, charge distributions, and binding propensities are examined. The thermodynamic stability differences between the conformers are found to be much greater in calix[4]pyrrole compared to those in calix[4]furan and calix[4]thiophene. Relatively larger NH group and higher dipole of a pyrrole ring in calix[4]pyrrole contribute to the higher energy barrier for the conformational conversions and relatively rigid potential energy surface compared to the case of calix[4]furan and calix[4]thiophene. The computational results herein provide theoretical understanding of the conformational flexibility and the thermodynamic nature which can be applied to understand the complexation behavior of the three calix[4]heterocycles.

Key Words: Calix[4]pyrrole, Calix[4]furan, Calix[4]thiophene, Conformational flexibility, Binding property

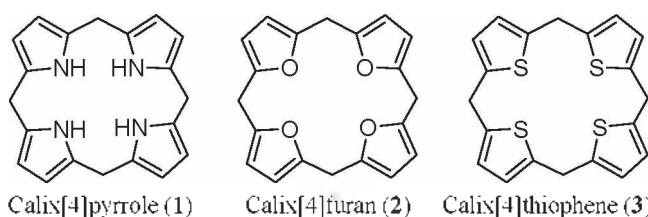
Introduction

Calixarene, methylene bridged cyclic oligomer of phenols, is one of the most studied host molecules in supramolecular chemistry. Recently, calixarene family has been extended to the compounds with similar aromatic units due to its conformational flexibility, diverse binding affinity, and easiness for the applications.^{1,5} One of the extended calixarene families is the calixheterocycle with various aromatic units instead of phenol. Calix[4]pyrrole (**1**), porphyrinogen-like macrocycle, has been drawn much attention due to its significant anion recognition properties.³⁻¹⁶ Although the first synthesis of **1** was initially reported in 1886,³ the guest binding properties had not been extensively investigated until late 1990's.^{4,5} Calix[4]pyrrole adopts four major conformations as in the case of calix[4]arene.⁶ While 1,3-alternate conformation of **1** was found to be preferred in the absence of a guest determined by theory^{6,12} and X-ray method,⁴ the cone conformation was observed to be dominant in the presence of an anionic guest by the formation of hydrogen bonding between pyrrolic NH and an anion.^{4,6} Among various anionic guests, the fluoride ion was observed to bind most strongly to **1** in the gas phase^{5,6,12} and the neutral substrates were also detected to weakly bind to **1**.^{18,20}

On the other hand, calix[4]furan (**2**), methylene bridged cyclic oligomer of furan, was first taken as the product of furan condensation reaction in the presence of ketones and HCl catalysis by Ackman and coworkers in 1955 as the name of tetraoxaporphyrinogen.²¹ After the first synthesis, many other methods to make calix[4]furan and extended calix[n]furan ($n = 6, 8, \text{ and } 10$) have been reported.²²⁻²⁸ Calix[4]furan also allows four main conformations and the predominant conformer is the 1,3-alternate determined by X-ray²⁴ and theoretical methods.¹² Since the oxygen atom in a furan ring provides the electron abundant nature, calix[4]furan is expected to bind cationic guest molecules.^{25,26}

Calix[4]thiophene (**3**), constituting four thiophene rings in the macrocycle, has been scarcely synthesized compared to the other members in the family due to its synthetic difficulty. The first synthesis was not reported until 1989 that it was obtained from calix[4]furan in the presence of H₂S and HCl.²⁹ Among various conformations of calix[4]thiophene, 1,3-alternate was found to be the most stable conformer by theoretical method.¹² It was suggested that the sulfur atom in a thiophene ring acts as a soft donor and consequently interacts with soft metal cations.³⁰ Although there have been many reports on the various calix[4]pyrroles and their binding properties, there exists only one theoretical report on the comparative study of **1-3** by Wang and Wu, which compared seven calix[4]aromatics by executing BLYP/6-31G**//BLYP/3-21G level calculations in the gas phase and in CH₂Cl₂ phase.¹² It is still useful to investigate more detailed conformational characteristics as well as the binding propensities of **1-3** by using high-level density functional theory (DFT) method.

Here, we report the comparative study on three calix[4]heterocycles (calix[4]pyrrole, calix[4]furan, calix[4]thiophene) to understand their structural homogeneity and heterogeneity by performing high-level DFT calculations at the MPWB1K/6-311G**//B3LYP/6-311G** level. We also report the predicted guest binding propensities of **1-3** by employing atomic charge calculations. We focus on the effect of different hetero-atoms (nitrogen, oxygen, and sulfur) placed in the heterocycles to the conformational flexibility, thermodynamic stability



Scheme 1. Three calix[4]heterocycles are presented.

order, cavity shape and size, and binding propensities of **1**–**3**. The results described here thus render the inherent guest binding properties of three calix[4]heterocycles attributed from the conformational flexibility that plays an important role in modulating the recognition properties of those chemical receptors. Finally, the result of this theoretical work may provide useful insight for the desirable host design based on calix[4]heterocycle.

Computational Methods

All energy calculations and geometry optimizations were performed using the *Gaussian 03* package.³¹ To search the global minima structure for each conformer, several starting geometries for all conformers were constructed. An initial conformational analysis for each molecular system was performed by using AM1 semi-empirical method³² to find the low energy structures that would be used as initial structures for the DFT calculations. The DFT calculations were performed by using B3LYP functional³³ with 3-21G*, 6-31G**, and 6-311G** basis sets followed by vibrational analysis to verify the identity of each stationary point as a minimum. Single point energy calculation was executed at the MPWB1K/6-311G**³⁴ level using B3LYP/6-311G** optimized geometry. All energies in the main text are at the MPWB1K/6-311G**//B3LYP/6-311G** level unless otherwise noted. The atomic charge calculations were executed by using CHelpG algorithm at the B3LYP/6-311G** level.³⁵

Results and Discussion

Conformational characteristics of calix[4]pyrrole (1**).** Four distinctive conformations of **1** are located at the B3LYP/6-311G** level of theory and the optimized structures are shown in Figure 1. The relative energies and dipole moments are summarized in Table 1. The thermodynamic stability order for **1** is computed to be 1,3-alternate > partial cone > 1,2-alternate > cone at the MPWB1K/6-311G**//B3LYP/6-311G** level. This energy order is in agreement with the previous

calculation at the BLYP/6-31G**//BLYP/3-21G level.¹² While the 1,3-alternate conformation is hardly observed for calix[4]arene, the 1,3-alternate (**1a**) is found to be the most stable conformer among the four. Furthermore, whereas the cone of calix[4]arene is the most stable, the cone (**1d**) is found to be the most dominant for **1**. The thermodynamic preference for the conformers of **1** is rationalized mainly by the electrostatic interaction. Each pyrrole ring has a dipole moment of 1.94 D pointing toward the nitrogen atom computed at the same level of theory. Subsequently, **1a** with each adjacent pyrrole to face opposite direction to each other is favored by the electrostatics with a dipole moment of zero. In contrast, **1d** is observed to be 18.9 kcal/mol higher in energy than **1a**. Four pyrrole rings are placed to point one direction in **1d** and the energy penalty from the electrostatics is notable with the subsequent dipole moment of 4.5 D. Moreover, the distance between two hydrogens from the confronting pyrrole rings in **1d** is only 3.84 Å. The unfavorable electrostatic interactions between pyrrole rings subjected by the molecular shape make the cone (**1d**) the least probable conformer for **1**.

The second most stable conformer for **1** is computed to be partial cone (**1b**) with 5.0 kcal/mol higher in energy than **1a**. The dipole moment of **1b** is found to be 1.9 D. The next probable conformer is detected to be the 1,2-alternate (**1c**) and the shape is shown in Figure 1. Although the dipole moment for **1c** is zero due to the two-fold symmetry, closer proximity between the pyrrolic hydrogens of the adjacent pyrroles

Table 1. Relative energies (in kcal/mol) computed at the B3LYP/6-311G** and MPWB1K/6-311G**//B3LYP/6-311G** levels of theory are listed for **1**. Dipole moments (in D) at the B3LYP/6-311G** level are listed.

	B3LYP/ 6-311G**	MPWB1K/ 6-311G** ^a	Dipole moment
1,3-Alternate (1a)	0.0	0.0	0.017
Partial cone (1b)	4.7	5.0	1.885
1,2-Alternate (1c)	6.8	7.4	0.003
Cone (1d)	16.4	18.9	4.521

^aGeometry optimized using the B3LYP/6-311G** level

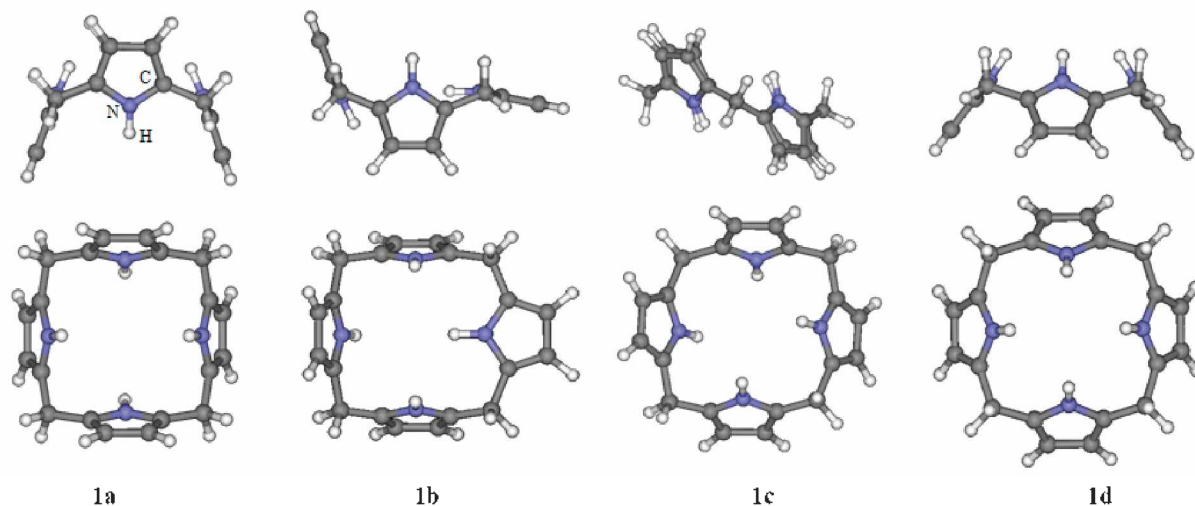


Figure 1. Four main conformations of calix[4]pyrrole (**1**) located at the B3LYP/6-311G** level are shown. (a) 1,3-alternate, (b) partial cone, (c) 1,2-alternate, and (d) cone. For each structure, side (upper panel) and top (lower panel) views are displayed.

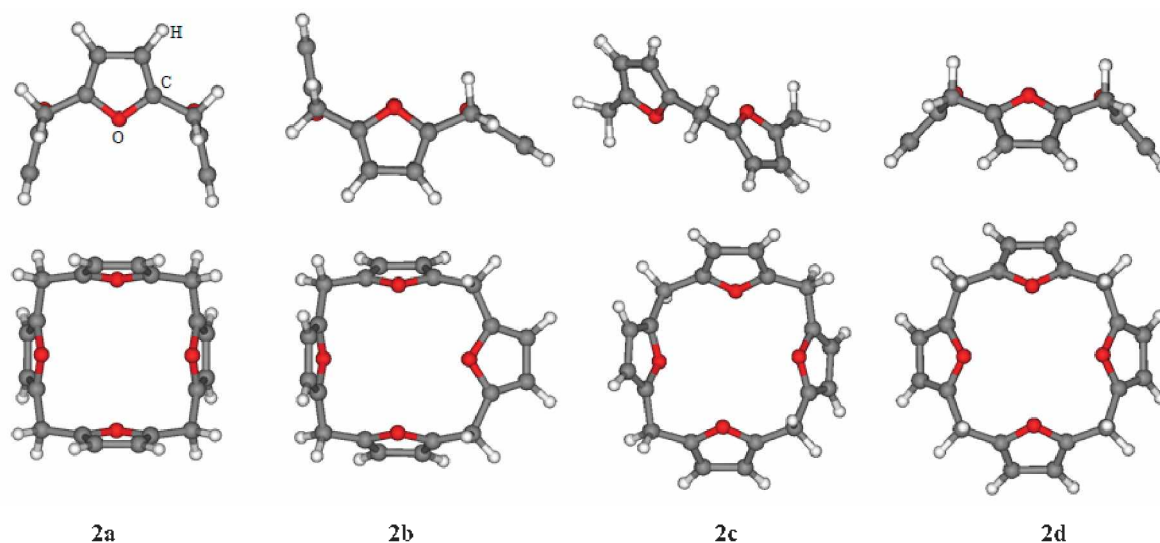


Figure 2. Four main conformations of calix[4]furan (**2**) located at the B3LYP/6-311G** level are shown. (a) 1,3-alternate, (b) partial cone, (c) 1,2-alternate, and (d) cone. For each structure, side (upper panel) and top (lower panel) views are displayed.

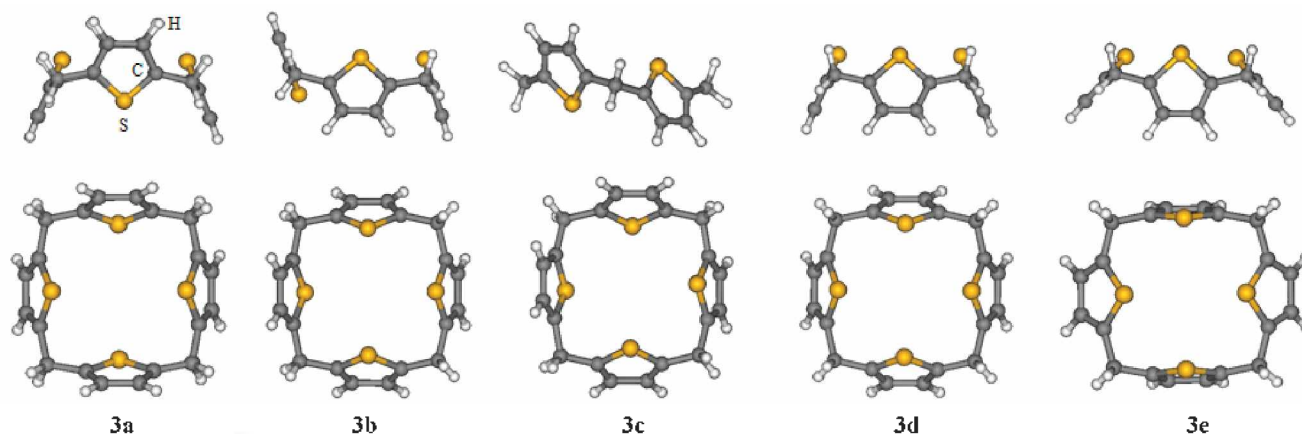


Figure 3. Four main conformations of calix[4]thiophene (**3**) located at the B3LYP/6-311G** level are shown. (a) 1,3-alternate, (b) 1,2-alternate, (c) partial cone, (d) cone, and (e) pinched cone. For each structure, side (upper panel) and top (lower panel) views are displayed.

facing the same direction renders the steric congestion. As a result, **1c** is computed to be 7.4 kcal/mol higher in energy than **1a**. The computational results is in excellent agreement with the X-ray diffraction data⁴ that the differences between X-ray and B3LYP/6-311G** optimized geometry in bond distances and in angles are within 0.01 Å and 1°, respectively.

Conformational characteristics of calix[4]furan (2). Four main conformations as in the case of **1** are placed at the B3LYP/6-311G** level for **2**. The optimized geometries are shown in Figure 2 and the calculated thermodynamic stabilities are listed in Table 2. The thermodynamic stability order for **2** is 1,3-alternate > partial cone > cone > 1,2-alternate. This is slightly different from the case of **1** that the relative order for cone and 1,2-alternate is reversed. The most stable conformer is found to be the 1,3-alternate (**2a**) as in the case of **1**. The electrostatic interaction also contributes to the thermodynamic stability of **2a** resulting a zero dipole moment. The second most stable conformer is the partial cone (**2b**) which is located to be 1.2 kcal/mol higher than **2a**. The next stable conformer is the cone (**2d**) to be 1.8 kcal/mol higher in energy than **2a**. The dipole moment of **2d** is computed to be only 0.96 D which is

much smaller than 4.5 D for **1d**. Since the dipole moment of a single furan ring is computed to be 0.62 D which is much smaller than 1.94 D for a single pyrrole ring at the same level, **2d** carries much smaller dipole than **1d**. Moreover, an oxygen atom in the furan is smaller in size compared to a NH group in the pyrrole. As a consequence, the distance between the facing oxygens in **2d** is 4.70 Å which is much longer than 3.84 Å for the facing pyrrolic hydrogens in **1d**. Taken together, the energy difference between **2a** and **2d** is much smaller than that between **1a** and **1d**. The least probable conformer for **2** is the 1,2-alternate (**2c**) which is 4.0 kcal/mol higher in energy than **2a**.

It is noted that the relative energy differences in **2a**–**2d** are much smaller than those in **1a**–**1d**. Smaller dipole of each furan ring as well as the smaller size of an oxygen in **2** compared to each pyrrole ring and a NH group in **1** contribute to the relative easiness of the conformational conversions and the relatively smaller energy gap between the conformers in **2**. Notably, the energy difference between the cone (**2d**) and the 1,3-alternate (**2a**) is only 1.8 kcal/mol implying that the conformational conversions might be easily obtained upon slight

Table 2. Relative energies (in kcal/mol) computed at the B3LYP/6-311G** and MPWB1K/6-311G**//B3LYP/6-311G** levels of theory are listed for **2**. Dipole moments (in D) at the B3LYP/6-311G** level are listed.

	B3LYP/ 6-311G**	MPWB1K/ 6-311G** ^a	Dipole moment
1,3-Alternate (2a)	0.0	0.0	0.002
Partial cone (2b)	0.9	1.2	0.567
1,2-Alternate (2c)	3.5	4.0	0.001
Cone (2d)	1.3	1.8	0.959

^aGeometry optimized using the B3LYP/6-311G** level

perturbations from the microenvironmental changes such as solvent polarity or guest binding.

Conformational characteristics of calix[4]thiophene (3). By introducing a sulfur atom instead of an O or a NH in a heterocycle, **3** is found to adopt two different cone conformations, a conventional cone (**3d**) with four-fold symmetry and a pinched cone (**3e**) with two-fold symmetry. As a result, total five conformations are located as displayed in Figure 4. The theoretically predicted order of stability for **3** is to be 1,3-alternate > 1,2-alternate > partial cone > pinched cone > cone as shown in Table 3. As in the case of **1** and **2**, the 1,3-alternate (**3a**) is the most dominant conformer for **3** due to the electrostatics (dipole). The second most stable conformer is the 1,2-alternate (**3c**) with 3.5 kcal/mol higher in energy than that of **3a**. The dipole moment for **3c** is also computed to be zero. The next stable conformer is the partial cone (**3b**) which is located to be 3.6 kcal/mol higher than **3a**. Finally, **3d** and **3e** are 7.4 and 6.5 kcal/mol higher in energy, respectively, compared to **3a**. The dipole moment of a single thiophene ring is computed to be 0.56 D which is smaller than 1.94 D for a pyrrole. Consequently, the energy penalty to form the cone conformation with unfavorable electrostatics is not as severe for **3** compared to that for **1**.

The distance between two facing sulfur atoms in **3d** is 5.16 Å that is much longer than that between two facing oxygen atoms of 4.70 Å in **2d**. Since the sulfur in the thiophene ring is bigger than the oxygen in the furan ring, **3d** displays a deeper cavity in a macrocycle than **2d** due to maximize the distances between facing sulfur atoms. The distances between the facing sulfur atoms in **3e** are observed to be 4.56 Å and 5.68 Å. It is noted that the C-S-C angle in the thiophene ring in **3a** is 92.1° which is much smaller than the C-N-C angle (110.6°) and the C-O-C angle (107.5°) in **1a** and **2a**, respectively. Consequently, the C-S bond distance in **3a** is computed to be 1.748 Å which is much longer than the C-N bond (1.378 Å) and the C-O bond (1.369 Å) in **1a** and **2a**, respectively. The energy differences between the conformers of **3** are slightly greater than those of **2** but smaller than those of **1**. The sulfur atom is larger than the oxygen atom and smaller than the NH group. Since there is no distinct hydrogen bonding available in **1**–**3**, the electrostatic interaction along with the size of the hetero atoms play a dominant role in determining the relative thermodynamic stability and the conformational flexibility between the conformers of **1**–**3**.

Guest binding modes of 1–3. To investigate the guest

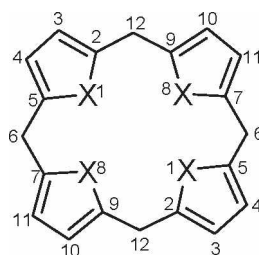
Table 3. Relative energies (in kcal/mol) computed at the B3LYP/6-311G** and MPWB1K/6-311G**//B3LYP/6-311G** levels of theory are listed for **3**. Dipole moments (in D) at the B3LYP/6-311G** level are listed.

	B3LYP/ 6-311G**	MPWB1K/ 6-311G** ^a	Dipole moment
1,3-Alternate (3a)	0.0	0.0	0.000
Partial cone (3b)	3.2	3.6	1.168
1,2-Alternate (3c)	3.0	3.5	0.000
Cone (3d)	6.2	7.4	2.337
Pinched cone (3e)	6.0	6.5	2.224

^aGeometry optimized using the B3LYP/6-311G** level

binding modes, we computed the atomic charges using CHelpG algorithm³⁵ for the unsubstituted calix[4]heterocycles, **1**–**3**. Since the most dominant conformer is the 1,3-alternate for all three heterocycles and the most probable conformer upon the guest complexation may be the cone due to the molecular shape, we here focus on the atomic charges for those two conformations of **1**–**3**. As seen in Table 4, the charge of a hydrogen in a pyrrole ring of **1d** is 0.308e, whereas the charge of an oxygen in a furan ring of **2d** is -0.211e and the charge of sulfur in a thiophene ring of **3d** is -0.043e. The computed charges agree well with the experimental observations that the cone of calix[4]pyrrole acts as an efficient anion platform by providing the electrostatic interactions between the electropositive pyrrolic H and a guest anion.⁴ It is noted that the charge of a pyrrolic hydrogen in **1d** (0.308e) is more positive than that in **1a** (0.239e). Although 1,3-alternate is the most probable conformation for **1**, the cone is more prone to adapt the anion guest due to its molecular shape as well as the charge distribution. Consequent equilibrium shift from **1a** to **1d** may be readily occurred when the energy gain provided by the anion complexation or the microenvironmental changes could compensate the energy penalty to overcome the unfavorable electrostatics employed in **1d**.

On the other hand, **2d** carries the negative oxygen atoms (-0.211e) in a macrocycle and the subsequent cation binding property is predicted. This is also in accord with the experimental observation.^{25,26} The differences in charge distributions and the dipole moment between **2a** and **2d** are not as distinctive as in the case of **1**. Since the thermodynamic stabilities and the charge distributions are not largely different among the conformers of **2** due to the flexible potential energy surface, the energy penalty attributed to the conformational conversion from **2a** to **2d** may be easily overcome by the relatively weak binding energy upon guest complexation. For calix[4]thiophene, the atomic charges of the sulfur atoms are computed to be -0.073e and -0.043e in **3a** and in **3d**, respectively. Since the sulfur in **3** is not as negative as the oxygen in **2**, calix[4]thiophene is expected to be not as effective cation platform as calix[4]furan. Compared to the case of **1**, in the case of **2** and **3**, the charges are more delocalized in the macrocycle and the atomic charge differences between the cone and the 1,3-alternate are smaller than those in the case of **1**. As a consequence, the kinetic contributions may be relatively more important to determine the preferential confor-

Table 4. CHelpG atomic charges of 1,3-alternate and cone conformations of 1~3 computed at the B3LYP/6-311G** level.

	calix[4]pyrrole		calix[4]furan		calix[4]thiophene		
	1a	1d	2a	2d	3a	3d	3e
1	-0.242	-0.373	-0.238	-0.211	-0.073	-0.043	-0.044
1(H)	0.239	0.308					
2	0.065	0.115	0.273	0.231	0.003	0.020	-0.012
3	-0.217	-0.255	-0.254	-0.253	-0.188	-0.183	-0.205
4	-0.263	-0.255	-0.280	-0.253	-0.172	-0.205	-0.205
5	0.077	0.115	0.302	0.231	-0.006	-0.012	-0.011
6	0.069	0.055	-0.308	-0.194	0.256	0.241	0.274
7	0.068	0.115	0.273	0.231	0.064	-0.018	-0.060
8	-0.240	-0.373	-0.239	-0.211	-0.073	-0.043	-0.030
8(H)	0.239	0.308					
9	0.079	0.115	0.302	0.231	-0.008	-0.014	-0.061
10	-0.236	-0.255	-0.279	-0.253	-0.171	-0.204	-0.155
11	-0.247	-0.255	-0.255	-0.253	-0.189	-0.184	-0.156
12	-0.061	0.055	-0.308	-0.194	0.260	0.240	0.275

mation upon the guest binding in the case of 2 and 3 compared to the case of 1.

Conclusions

The conformational features and the binding propensities of three calix[4]heterocycles (calix[4]pyrrole, calix[4]furan, and calix[4]thiophene) have been theoretically investigated by performing high-level density functional theory calculations at the MPWB1K/6-311G**/B3LYP/6-311G** level. The most probable conformations for all three cases are computed to be the 1,3-alternate with the dipole moment of zero due to the molecular shape. Notably, the thermodynamic stability differences between the conformers are found to be much greater in 1 compared to those in 2 or 3. Moreover, the differences in charge distributions and the dipole moment between the 1,3-alternate and the cone are observed to be most distinctive in 1 compared to those in 2 and 3. Relatively larger NH group compared to O and S as well as the higher dipole of the pyrrole ring for 1 contribute to the higher energy barriers for the conformational conversions and relatively more rigid potential energy surface compared to the case of 2 and 3. Based on the atomic charge calculations, the predicted binding modes of 1~3 upon guest complexation are in accordance with the observed experimental data. More negative N and more positive H in 1d compared to those in 1a make 1d more susceptible to the anion recognition than 1a. In the case of 2 and 3, the charges are more delocalized in the macrocycle and the atomic charge differences between the cone and the

1,3-alternate are smaller than those in the case of 1. As a consequence, in the case of 2 and 3, the kinetic contributions may be relatively more important to determine the preferential conformation upon the guest recognition as in the case of 1. The computational results described here provide to understand the inherent guest binding properties of three calix[4]heterocycles attributed from the conformational flexibility, thermodynamic nature, and atomic charge distributions. The result of this theoretical work may provide useful insight for the desirable host design based on calix[4]heterocycle.

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Supporting Information. Cartesian coordinates of all conformers for 1~3 optimized at the B3LYP/6-311G** level are available at the bkcs website (<http://www.kcsnet.or.kr/bkcs>).

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