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Conformational Features and Anion-Binding Properties of Calix[4]pyrrole: A Theoretical Study

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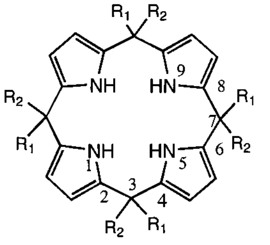
The conformational preference of calix[4]pyrrole and its fluoride and chloride anion-binding properties have been investigated by density functional theory calculations. Geometries were optimized by the BLYP/3-21G and BLYP/6-31G* methods, and energies were evaluated with the BLYP/6-31+G** method. To model the effect of medium, the SCIPCM solvent model was also employed. Four typical conformations of the parent substituent-free calix[4]pyrrole were studied. Both in the gas phase and in CH_2Cl_2 solution, the stability sequence is predicted to be 1,3-alternate > partial cone > 1,2-alternate > cone. The cone conformation is predicted to be about 16.0 and 11.4 kcal/mol less stable in the gas phase and CH_2Cl_2 solution, respectively. This is mainly due to electrostatic repulsions arising from the all-syn pyrrole/pyrrole/pyrrole/pyrrole arrangement present in this conformer. The existence of possible 1:1 and 1:2 anion-binding modes were explored in the case of fluoride anion, and the factors favoring the 1:1 binding mode are discussed. The calculated binding energy for fluoride anion is about 15 kcal/mol larger than that for chloride anion. The calculated binding energy for chloride anion agrees with the experimental value very well. The presence of *meso*-alkyl substituents destabilizes the cone conformer with respect to the 1,3-alternate conformer and, therefore, reduces the anion-binding affinity by 3−4 kcal/mol. The strength of N−H- - -anion hydrogen bonds in the various structures subject to study were estimated on the basis of the calculated anion-binding energies and the predicted structural deformation energies of substituent-free calix[4]pyrrole.

Introduction

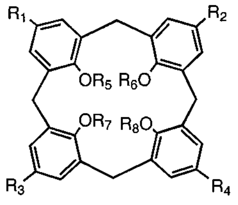
Anion binding plays an important role in the chemistry of biological processes, as evidenced by the fact that the substrates of structurally characterized enzymes are anionic in nature.[1] Although the chemistry of anion binding has developed more slowly than that of cation binding, there has been a boom in the design and synthesis of receptors for specific anionic substrates in the past decade.[2−6] Recently, it was found that alkylated analogues of porphyrinogen (1), the so-called calix[4]pyrroles (e.g., **14** and **15**),[7] act as easy-to-make anion-binding agents, especially for spherical species such as fluoride and chloride anions.[8,9] In analogy to the calix[4]arenes **2**, which have received extensive attention in recent years,[10] calix[4]pyrroles also are macrocyclic systems that can adopt a range of limiting conformations. They contain, however, four pyrroles rather than four phenol units.

calix[4]pyrrole



1, R_1=R_2=H (porphyrinogen)
14, R_1=R_2=Me
15, R_1,R_2= -$CH_2(CH_2)_4CH_2$-

calix[4]arene



2

While there have been many theoretical studies on the conformational features of calix[4]arenes,[11−13] there is only one theoretical investigation of calix[4]pyrrole, which was reported recently by van Hoorn and Jorgensen.[14] In their study, they used a Monte Carlo force field simulation to investigate the anion binding selectivity evidenced by calix[4]pyrrole. It is still useful to understand more detailed conformational features and anion-binding properties of calix[4]pyrrole and its analogues.

In this paper, we report a quantum mechanics density functional theory study of the conformational preference of the parent porphyrinogen form of calix[4]pyrrole (**1**). We also present an analysis of the potential anion-binding modes expected for the four predicted conformations of this model calix[4]pyrrole. The anion-binding energy and hydrogen-bonding strength of putative complexes formed as the result of both 1:1 and 1:2 complexation are discussed. Also considered are the effects of *meso*-alkyl groups such as are present in bona fide

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calix[4]pyrroles (e.g., **14**, **15**), on conformational stability and anion binding.

Computational Methodology

An initial conformational analysis of unsubstituted calix[4]pyrrole (**1**) was first performed with Monte Carlo conformational search method using the Macromodel 6.0 (MM2* force field).[15] Stable conformations were then optimized by the PM3 semiempirical method[16] and density functional method (BLYP, Beck 88 exchange and Lee−Yang−Parr correlation) with the 3-21G basis set first.[17] Selected structures were also optimized with the BLYP/6-31G** methods. All these calculations used Gaussian 94 program.[18] For a proper description of the anion and interactions with it, it is necessary to supplement the basis set with a set of diffuse s- and p-functions for heavy atoms.[19] So, single-point energies in the gas phase and solution were evaluated with the BLYP/6-31+G** method using BLYP/3-21G geometries. To investigate the effect of solvent on the conformational preference and the anion binding energies, the self-consistent isodensity polarization continuum model, SCIPCM, was used.[20] If not otherwise mentioned, the isodensity value was 0.0004, while a dielectric constant of 8.0 was used to model dichloromethane (CH_2Cl_2) solvent. Except for some special cases, only the BLYP/6-31+G** energies will be discussed.

Results and Discussion

1. Conformational Feature of Calix[4]pyrrole. It has been known for some time that calix[4]arenes **2** have four conformations:[10a] a cone (all phenyl rings oriented in the same direction), a partial cone (three phenyl rings pointing up or down, the fourth adopting an intermediate orientation), a 1,2-alternate structure (two neighboring phenyl rings pointing up, and the other two down), and a 1,3-alternate conformation (with opposite phenyl rings pointing up or down, respectively). Due to the geometrical resemblance between calix[4]pyrrole and calix[4]arene, it was expected that calix[4]pyrrole could also adopt four major conformations. Indeed, all four calixarene-like conformations were obtained when calix[4]pyrrole was subjected to an MM2* Monte Carlo conformation search. On the other hand, PM3 calculations lead to the prediction that only three of four conformations are stable, with the partial cone being the one that is absent; it converts readily to the 1,3-alternate conformation. All four conformations can also be located using the BLYP/3-21G method.

As shown in Figure 1, the predicted orders of stabilities are the same for the gas phase and CH_2Cl_2 solution, namely 1,3-alternate **3** > partial cone **5** > 1,2-alternate **4** > cone **6**. This order of stability is quite different from that for calix[4]arenes, where the cone conformation is the most stable while the 1,3-alternate conformation is seldom observed.[10] While the high stability of the cone conformation of calix[4]arene may be rationalized in terms of internal hydrogen bonds, it nonetheless important to note that the 1,3-alternate conformer **3** is predicted to be the most stable for calix[4]pyrrole, which is in agreement with experiment. In the absence of bound anions, neutral substrates, or perturbing substituents, it is this conformer that is observed in diffraction analysis of calix[4]pyrrole.[7]

Molecular mechanics calculations indicate that the 1,3-alternate conformation has a torsional interaction of about 1−2 kcal/mol smaller than that of the other conformations. The most significant factor for the conformational preference is electrostatic interaction. Each pyrrole ring carries a dipole pointing toward the nitrogen atom. Accordingly, as will be discussed later (see Table 6), each set of adjacent pyrrole rings has an inherent propensity to exist in an anti rather than syn orientation. In the 1,3-alternate conformation, **3**, each adjacent pyr-

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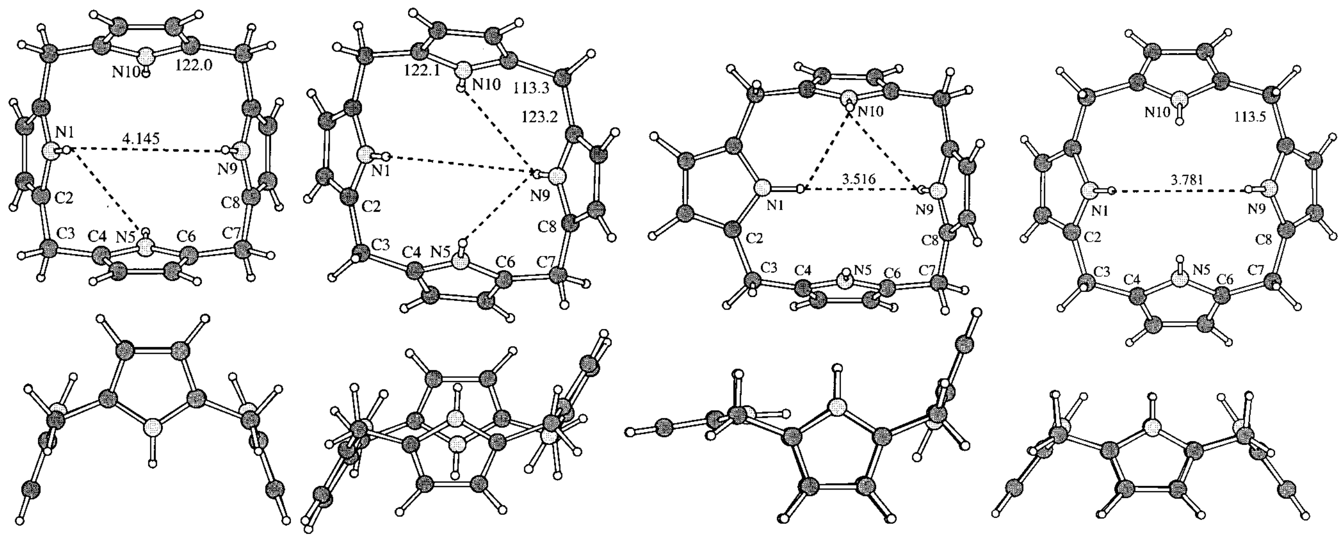


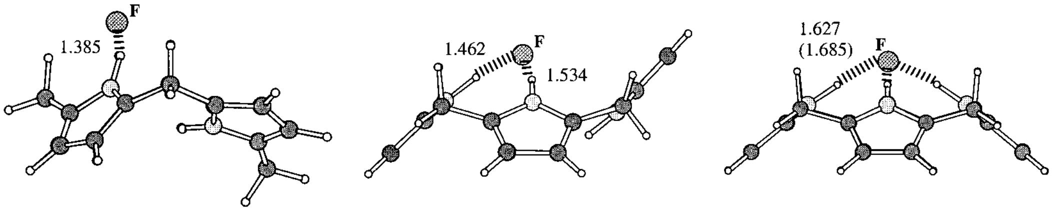
1,3-alternate (S4)
3
0.0 [0.0]

1,2- alternate (C2h)
4
6.7 [4.4]

partial cone (Cs)
5
4.8 [3.7]

cone (C4v)
6
16.0 [11.4]

Figure 1. Four typical conformations of calix[4]pyrrole and their relative energies at the BLYP/6-31+G** level (kcal/mol, the values in brackets are for CH_2Cl_2 solution).



1,2- alternate (Cs)
7
22.0 [20.4]

partial cone (Cs)
8
10.6 [9.4]

cone (C4v)
9
0.0 [0.0]

Figure 2. Calculated structures of calix[4]pyrrole−F^- complexes with 1:1 binding mode and their relative energies at the BLYP/6-31+G** level (kcal/mol, the values in brackets are for CH_2Cl_2 solution). The F- - -H distances are in angstroms. For **9**, the F- - -H distance calculated by the BLYP/6-31G** method is given in parentheses.

role pair is anti. As a result, this particular conformation benefits the most from this electrostatic effect. On the other hand, the pyrroles in the cone conformation, **6**, all point to the same direction, and as a result, this conformation suffers the most from electrostatic repulsion. Meanwhile, the pyrroles in the 1,2-alternate (**4**) and in partial cone conformation (**5**) are subject to a modest level of electrostatic destabilization.

2. Comparison with X-ray Crystallographic Structure of Calix[4]pyrrole. A comparison between the calculated geometrical parameters of the 1,3-alternate conformation (**3**) of unsubstituted calix[4]pyrrole (**1**) using the BLYP/3-21G and BLYP/6-31G** methods with the X-ray crystal structure of octamethylcalix[4]pyrrole (**14**) is provided in Table S1 of the Supporting Information. The calculated structures agree with the X-ray structure very well. While the calculated bond lengths are generally longer than the X-ray values by 0.03 Å, the calculated bond angles are within 3° of experimental values.[8] In analogy to the case of porphyrin isomers,[21] the geometries calculated using the BLYP/3-21G and BLYP/6-31G** methods are very similar. Therefore, on this basis it was considered justified to optimize most of the other structures using only the BLYP/3-21G method. Presumably as the result of steric interactions involving the *meso*-methyl groups, the X-ray structure of octamethylcalix[4]pyrrole (**14**) reveals some distortion within the N_4 core; indeed, the twist angle is about 9.5°. When ethyl groups replace the methyl groups, this distortion becomes more severe, and the twist angle increases to 15.1°.[22]

3. Analysis of Anion-Binding Modes of Calix[4]pyrrole. The 1:1 Calix[4]pyrrole−Anion-Binding Mode. Experimental results indicate that *meso*-alkyl-substituted calix[4]pyrroles (e.g., **14** and **15**) form 1:1 complexes with fluoride and chloride anions. In these anion complexes, the calix[4]pyrrole macrocycles are observed to adopt the cone conformation with the anion sitting above the cone and forming four hydrogen bonds with the four pyrrole N−Hs.[8a] On the other hand, neutral molecules such as alcohols and amides form 2:1 complexes with calix[4]pyrroles. Depending upon the nature of the neutral guest, actually calix[4]pyrroles can exist

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Table 1. Four Typical Dihedral Angles (Deg, See 1 for Numbering) for the Calculated Structures 3−13

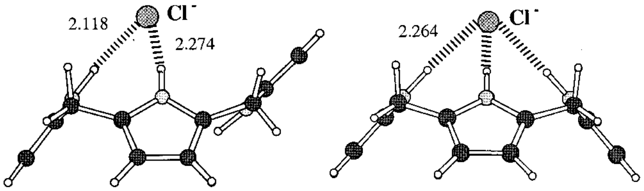
	ϕ(N1−C2−C3−C4)	χ(N5−C4−C3−C2)	ω(N5−C6−C7−C8)	ψ(N9−C8−C7−C6)
3	−53.6	−53.4	53.5	53.5
4	−82.4	82.4	−44.8	−44.8
5	−36.4	88.3	−57.5	−50.8
6	−75.7	75.7	−75.7	75.7
7	−75.9	75.9	−73.9	17.0
8	−66.1	67.0	−36.3	−36.7
9	−64.8	64.8	−64.8	64.8
10	−73.6	76.9	−48.4	−31.9
11	−72.7	72.7	−72.7	72.7
12	−30.0	−32.8	30.0	32.8
13	−80.2	80.2	−43.8	−43.8

in either the most stable 1,3-alternate conformation (in alcohol complexes) or the 1,2-alternate conformation (in amide complexes).[8b]

As a first step toward understanding on a theoretical basis the nature of anion and neutral substrate binding by calix[4]pyrrole, we studied the calix[4]pyrrole−fluoride anion complexation process in detail. Here, both 1:1 and 1:2 complexation modes were considered. For 1:1 complexation, we attempted to optimize all the putative anion-binding structures for all the four limiting conformations. However, stable structures were found for only three conformers. In particular, it was observed that the 1,3-alternate structure is unstable and is converted into the cone structure **9** upon geometry optimization. The three calculated minimal structures are shown in Figure 2. The cone structure, **9**, has four equivalent NH- - -F$^-$ bonds of about 1.68 Å. Due to the short NH- - -F$^-$ hydrogen bonds, the calix[4]pyrrole is flattened. This is indicated by the decrease of ∠N1−C2−C3−C4 dihedral angles from −76° in F$^-$−free cone structure **6** to −64.8° in cone−F$^-$ complex **9** as given in Table 1. In contrast to the cone complex **9**, the partial cone complex **8** forms three NH- - -F$^-$ hydrogen bonds. These hydrogen bonds are slightly shorter than those in structure **9**, indicating that the hydrogen bonds in **8** might be somewhat stronger than those in **9**. There is a considerable change in geometry observed upon fluoride anion binding (compare the dihedral angles of **5** with **8** in Table 1). The flat pyrrole in **5** tilts upward while the other three pyrroles become relatively flattened. For the 1,2-alternate complex **7**, the two upward pyrroles form two NH- - -F$^-$ bonds with the fluoride anion. Consequently, this structure is severely distorted. The two pyrroles involved in hydrogen bonding are tilted up while the other two are flattened out relative to the mean atom plane. Moreover, the two hydrogen bonds in this structure are calculated as being much stronger than those in **9** and **8**, as indicated by a short NH- - -F$^-$ distance of 1.38 Å.

The cone complex **9** is calculated to be most stable. The partial cone complex **8** is predicted to be the second most stable. In the gas phase, it lies about 10.6 kcal/mol higher in energy than the cone complex **9**. When the solvent effect by dichloromethane is accounted for, the destabilization of **8** as compared to **9** is decreased to 9.3 kcal/mol.

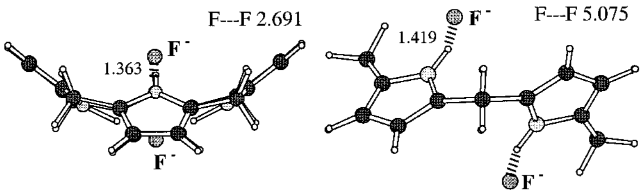
The 1,2-alternate complex **7** is predicted to be less stable than the cone structure **9** by 25.4 and 20.4 kcal/mol in the gas phase and in CH_2Cl_2 solution, respectively. The relative stabilities reflect the number of hydrogen bonds in these complexes, indicating that the inonic hydrogen bonds in these complexes are very strong.



partial cone 10
7.5 [8.1]

cone 11
0.0 [0.0]

Figure 3. Calculated structures of calix[4]pyrrole−Cl$^-$ complexes with the 1:1 binding mode and their relative energies at the BLYP/6-31+G** level (kcal/mol, the values in brackets are for CH_2Cl_2 solution). Cl- - -H distance is in angstroms.



1,3-alternate 12
18.9 [16.1]

1,2-alternate 13
0.0 [0.0]

Figure 4. Calculated structures of calix[4]pyrrole−2F$^-$ complexes with the 1:2 binding mode and their relative energies at the BLYP/6-31+G** level (kcal/mol, the values in brackets are for CH_2Cl_2 solution).

We also calculated the 1:1 calix[4]pyrrole−Cl$^-$ complexes for comparison. The calculated structures **10** and **11** are shown in Figure 3. The related dihedral angles ϕ, χ and ω in **10** and **11** are about 8° larger than those in the fluoride anion complexes **8** and **9** (Table 1). The calculated relative energies further demonstrate that the cone complex **11** is more stable than the partial cone **10**, both in the gas phase (by 7.5 kcal/mol) and CH_2Cl_2 solution (by 8.1 kcal/mol).

The 1:2 Calix[4]pyrrole−Anion-Binding Mode. Two energetically reasonable 1:2 fluoride anion complexes were calculated for unsubstituted calix[4]pyrrole **1**, as shown in Figure 4. In these putative complexes, one fluoride binds above the host and the other binds below. Surprisingly, our calculations reveal that the 1,2-alternate structure **13** is more stable than 1,3-alternate complex **12** by about 19 and 16 kcal/mol at the BLYP/6-31+G** level in the gas phase and in CH_2Cl_2 solution, respectively. Several factors cause the destabilization of **12**. (1) The formation of NH- - -F$^-$ hydrogen bonds by the 1,2-alternate structure of calix[4]pyrrole does not require much geometrical change. This is clearly apparent when the dihedral angles of **13** and **4** are compared (Table 1). By contrast, binding of two fluoride anions by the 1,3-alternate structure requires significant ring flattening. Thus, the absolute values of the dihedral angles (ϕ, χ, ω, ψ) are reduced from about 54° in **3** to about 30° in **12**. This causes considerable destabilization (see section 6 for

Table 2. Binding Energy and Structural Deformation Energy (kcal/mol) of 1:1 and 1:2 Fluoride Anion Binding Modes of Calix[4]pyrrole Calculated at the BLYP/6-31+G Level**

	1,2-F^- (**7**)		paco−F^- (**8**)		cone−F^- (**9**)		1,3−2F^- (**12**)		1,2−2F^- (**13**)		$Bu_4N^+-F^-$
	$\Delta E_{binding}$	ΔE_{deform}	$\Delta E_{binding}$	ΔE_{deform}	$\Delta E_{binding}$	ΔE_{deform}	$\Delta E_{binding}$	ΔE_{deform}	$\Delta E_{binding}$	ΔE_{deform}	$\Delta E_{binding}$
gas phase	−44.6	13.0	−56.0	12.3	−66.6	20.9	−6.0	19.0	−24.9	6.9	−95.9
CH_2Cl_2, 0.0003	−7.0	9.9	−17.5	9.5	−27.6	16.5	13.5	18.2	−0.9	4.1	−6.0
CH_2Cl_2, 0.0004	−2.8	10.4	−13.7	9.7	−23.1	17.1	20.0	18.8	3.9	4.8	−1.6

Table 3. Binding Energy and Structural Deformation Energy (kcal/mol) of 1:1 Chloride Anion Binding Mode of Calix[4]pyrrole Calculated at the BLYP/6-31+G Level**

	paco−Cl^- (**10**)		cone−Cl^- (**11**)		$Bu_4N^+-Cl^-$
	$\Delta E_{binding}$	ΔE_{deform}	$\Delta E_{binding}$	ΔE_{deform}	$\Delta E_{binding}$
gas phase	−29.9	10.1	−37.4	16.5	−79.5
CH_2Cl_2, 0.0003	−3.2	6.9	−10.1	10.8	−3.7
CH_2Cl_2, 0.0004	1.4	7.1	−6.7	11.8	−1.7

further discussion). (2) The two fluoride anions in **12** are separated by about 2.7 Å, and there should be a significant electrostatic repulsion between them, while in **13**, the two fluoride anions are far away from each other (5.1 Å). (3) In structure **12**, each fluoride anion is sandwiched by two pyrrole rings that are not involved in hydrogen bonding. Since there is also considerable π-electron density above and below the electron-rich pyrrole ring, this should also cause significant destabilization.

On the basis of the above analysis, it becomes possible to predict roughly just which binding mode should be dominant when calix[4]pyrrole binds a guest. This can be summarized as follows: there are two critical factors controlling the binding mode of calix[4]pyrrole. One is the strength of the NH- - -X hydrogen bonds, which is the major driving force for complexation. The other is the thermodynamic stability of the specific conformation in question. The cone conformation is about 11 kcal/mol less stable than the 1,3-alternate conformation in CH_2Cl_2 solution, but it allows the formation of four hydrogen bonds with an anion. The cone conformation is thus favored for binding of anions since the energy gain associated with the formation of four strong hydrogen bonds overcomes the energy penalty associated with adopting what otherwise would be an unstable conformation. In contrary, the binding of neutral molecules leads only to the formation of weak hydrogen bonds. In this instance, the gain in energy produced by substrate binding is insufficient to overcome the instability of the cone conformation. Therefore, more stable 1,3-alternate and 1,2-alternate conformations are favored.

4. Anion-Binding Energy. From Sessler's experiments, the affinity constant $K_{binding}$ (or K_a) for F^- and Cl^- complexation by *meso*-octamethylcalix[4]pyrrole (**14**) in CH_2Cl_2 solution at room temperature (tetrabutylammonium countercation) is about 17 170 and 350 mol^{-1}, respectively.[8a] Therefore, the $\Delta G°$ for F^- and Cl^- binding is calculated to be about −5.8 and −3.5 kcal/mol, respectively, from $\Delta G° = -RT \ln K$. From a theoretical perspective, the anion-binding energy can be accessed by eq 1. For our calculations, the relative anion binding energies of both calix[4]pyrrole and Bu_4N^+ were calculated (eqs 2−3). The binding energy ΔE of eq 1 was then derived by subtracting ΔE_2 from ΔE_1. Tables 2 and 3 give the binding energy values (ΔE_1 and ΔE_2) calculated for the binding of F^- and Cl^- to calix[4]pyrrole, respectively. Limitations in computer power precluded calculations of vibration frequencies. As such, the binding entropies were not evaluated, meaning that it was ΔE for binding, rather than $\Delta G°$. On the other hand, it is expected that the binding entropy for the reaction in eq 1 is small.

$$\text{calix[4]pyrrole} + Bu_4N^+F^- \xrightarrow{\Delta G° \text{ or } \Delta E} \text{calix[4]pyrrole}-F^- + Bu_4N^+ \quad (1)$$

$$\text{calix[4]pyrrole} + F^- \xrightarrow{\Delta E_1} \text{calix[4]pyrrole}-F^- \quad (2)$$

$$Bu_4N^+ + F^- \xrightarrow{\Delta E_2} \text{calix[4]pyrrole}-F^- + Bu_4N^+ \quad (3)$$

To confirm the reliability of our predictions for gas-phase reactions, we calculated the binding energy of the F^-- - -H−F system in the gas phase. This system has been studied previously by experiment and the G2 calculation.[23] Our results indicate that both the BLYP and B3LYP methods give results similar to those obtained by the experiment and from G2 calculations, as long as a 6-31+G* basis set or better is used.[24]

For the binding of F^- by calix[4]pyrrole, several relevant findings are summarized as follows: (1) The gas-phase binding energy is very large. (2) The highest binding is observed for the 1:1 complex from the cone conformation **9** **(**about 66 kcal/mol). (3) The binding energy is significantly reduced in CH_2Cl_2 solution. For the three 1:1 complexes represented by structures **7**−**9**, the reduction in binding energy is about 37−39 kcal/mol (isodensity value of 0.0003). (4) The binding energy is substantially reduced for structures corresponding to 1:2 complexes (**10** and **11**), with the extent of this reduction being about 20−24 kcal/mol. On the basis of these results, the 1:2 binding mode for this substrate can be ruled out.

Compared to F^-, the binding energies for Cl^- are much smaller (Table 3). The solvent effect is also reduced. This is due to the larger size of Cl^- than F^- and the related fact that Cl^- acts as a much weaker hydrogen bond acceptor.

In the literature, most SCIPCM calculations employ an isodensity value of 0.0004.[24] As can be seen in Tables 2 and 3, we found that the binding energies of $Bu_4N^+-F^-$ and $Bu_4N^+-Cl^-$ calculated with this isodensity value are quite small, −1.6 and −1.7 kcal/mol, respectively. The reported binding energy of $Bu_4N^+-Cl^-$ is about 3.5 kcal/mol in acetone solution.[26] It is expected that the binding energy of $Bu_4N^+-Cl^-$ in CH_2Cl_2 solution should be somewhat larger. Thus, the absolute binding energy calculated by using an isodensity value of 0.0004 may be underestimated. This is because the solvent stabilization effect for the anion itself, which is quite small, is

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[23] Wenthold, P.; Squires, R. *J. Phys. Chem.* **1995**, *99*, 2002−2005.

[24] The BLYP/6-31+G** gives an F−H- - -F^- hydrogen bond energy of about 46.2 kcal/mol, compared to 45.8 ± 1.6 kcal/mol by experiment and 43.4 kcal/mol by G2 calculation (see ref 23)

[25] (a) Pan, Y.; McAllister, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 166. (b) Miaskiewicz, K.; Smith, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 1872. (c) Lecea, B.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1997**, *62*, 6485. (d) Wu, Y.-D.; Wang, D.-P. *J. Am. Chem. Soc.* **1998**, *120*, 13485.

[26] Bianchi, A.; Garcie-Espana, E. In ref 2, Chapter 6.

Scheme 1

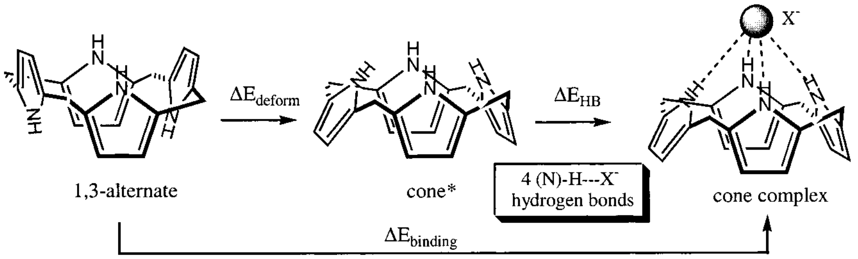

Table 4. Calculated Binding Energy (kcal/mol) of Calix[4]pyrrole (Cone Complex) with Fluoride and Chloride Anions and Anion Selectivity (kcal/mol) at the BLYP/6-31+G Level**

	$\Delta E(\mathrm{F}^-)$	$\Delta E(\mathrm{Cl}^-)$	$\Delta E = \Delta E(\mathrm{F}^-) - \Delta E(\mathrm{Cl}^-)$
gas phase	29.3	42.1	−12.8
CH_2Cl_2, 0.0003	−21.6	−6.4	−15.2
CH_2Cl_2, 0.0004	−21.6	−5.0	−16.4

overestimated with respect to the bound complex in which the negative charge is more delocalized. When an isodensity value of 0.0003 is used, the calculated anion binding energies for calix[4]pyrrole and Bu_4N^+ with F^- and Cl^- are increased. In addition, the binding energy for $Bu_4N^+{-}F^-$ (−6.0 kcal/mol) becomes larger than that of $Bu_4N^+{-}Cl^-$ (−3.7 kcal/mol) by about 2.3 kcal/mol, a finding that is viewed as being more reasonable since F^- binds more strongly than Cl^- under CH_2Cl_2 solution phase condition. Therefore, an isodensity value of 0.0003 seems to be more reasonable for anion calculations.

It is interesting that the calculated fluoride and chlorideanion binding energies of Bu_4N^+ are larger than those of calix[4]pyrrole in the gas phase. However, they are smaller than those of calix[4]pyrrole in CH_2Cl_2 solution. Thus, as shown in Table 4, the reaction energy of calix[4]pyrrole$-X^-$ with Bu_4N^+ is positive in the gas phase and negative in solution. We also note that the reaction energies in Table 4 are not overly dependent upon the choice of isodensity value. This is understandable, because the errors associated with anion binding by calix[4]pyrrole and Bu_4N^+ serve to cancel each other out, at least to a first approximation.

Tables 2 and 3 also include entries for the calculated deformation energies, $\Delta E_{\mathrm{deform}}$. This value represents the energy difference between the calix[4]pyrrole in the anion bound structure and the fully optimized 1,3-alternate conformation **3**. These deformation energies are larger than those associated with the same conformations in the anion-free form. In particular, deformation of the bis-fluoride complex **12** is quite large. This is likely one of the reasons why this particular 1:2 anion binding motif is not observed. It is also noted that the deformation energies for Cl^- binding are several kilocalories smaller than those for F^- binding. Since Cl^- is much larger than F^-, binding of Cl^- does not induce as much geometric deformation as does F^- binding.

Although the anion selectivity of calix[4]pyrrole anion binding is reproduced qualitatively by the calculations, the difference in the binding energy between Cl^- binding and F^- binding, which is about 15−16 kcal/mol, is too large compared to the experimental value of about 2.3 kcal/mol. This feature was also found by van Hoorn and Jorgensen in their MC simulation using the molecular mechanics force field.[14] They reported an energy difference of about 17 kcal/mol and attributed the large discrepancy between the calculation and experiment to the fact that a small amount of water is likely present in the experiment[27] used to obtain affinity constants.[8a] Other factors may also contribute to the "too large" calculated anion selectivity.[28] One is the exclusion of entropy. However, PM3 calculations for eq 1 indicate that entropy factor may not be important. We note that the calculated anion selectivity is actually smaller in the gas phase than in the CH_2Cl_2 solution (Table 4). This raises two questions: (1) whether the SCIPCM is good enough to account for the solvent effect and (2) whether eq 1 represents the real situation well enough. Unfortunately, we do not have answers for these questions right now.

5. Estimations of Hydrogen Bond Strengths. Although it is generally known that hydrogen bonds involved in anion complexation are strong, it is usually difficult to determine an unequivocal value for such bonds experimentally.[29−31] Our current study provides an opportunity to evaluate the average strength of the $N{-}H{\cdots}F^-$ hydrogen bonds occurring in calix[4]pyrrole−halide complexes. The method we used to determine these values is illustrated in Scheme 1. It assumes that anion binding involves two steps. Using the cone structure as an example, the first step is presumed to involve deformation of calix[4]pyrrole to a cone* structure, which, in geometric terms, is essentially identical to the one found in the anion-bound cone structures. The second step is the anion binding. The cone* structure was generated by the removal of the anion from the cone−X^- complex, followed by partial geometry optimization with the ring frame dihedral angles constrained. The energy difference between the cone* and 1,3-alternate structure (**3**) is defined as the deformation energy, $\Delta E_{\mathrm{deform}}$.

Thus, the anion-binding energy, $\Delta E_{\mathrm{binding}}$, contains two energy items. One is the structural deformation energy and the other is the hydrogen bond energy. The binding and structural deformation energies are tabulated in Tables 2 and 3. With these values in hand, the average hydrogen bond energy in a particular structure can be evaluated by deviding $\Delta E_{\mathrm{binding}} - \Delta E_{\mathrm{deform}}$ by the number of hydrogen bonds in the structure. The estimated hydrogen bond strengths are collected in Table 5.

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[27] In experiment, $Bu_4N^+F^-$ was added as the trihydrate (ref 8a).

[28] We thank one of the reviewers for raising the issue.

[29] Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.

[30] Chen, J.; McAllister, M. A.; Lee, J. K.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 4611.

[31] The understanding of anionic hydrogen bonding is important to the study of enzymatic catalysis. See selected references: Warshel, A.; Papazyan, A.; Kollman, P. A. *Science* **1995**, *269*, 102. (b) Cleland, W. W.; Kreevoy, M. M. *Science* **1995**, *269*, 104. (c) Fray, P. A. *Science* **1995**, *269*, 105. Gerlt, J. A.; Kreevoy, M. M.; Cleland, W. W.; Fray, P. A. *Chem. Biol.* **1997**, *4*, 259. (d) Shan, S.-O.; Loh, S.; Herschlag, D. *Science* **1996**, *272*, 97.

Table 5. Estimated Average Hydrogen Bond Strength (kcal/mol) in the Complexes of Calix[4]pyrrole with Fluoride and Chloride Anions by the BLYP/6-31+G Method**

	ΔE_{HB}[a]						
method	1,2-F^- (**7**)	paco−F^- (**8**)	cone−F^- (**9**)	paco−Cl^- (**10**)	cone−Cl^- (**11**)	1,3−2F^- (**12**)	1,2−2F^- (**13**)
gas phase	28.8	22.8	21.9	13.3	13.5	6.3	8.0
CH_2Cl_2, 0.0003	8.5	9.0	11.0	3.4	5.2	1.2	1.3
CH_2Cl_2, 0.0004	6.6	7.8	10.1	2.8	4.6	/	/

[a] $\Delta E_{HB} = (\Delta E_{deform} - \Delta E_{binding})/Z$, Z is the number of hydrogen bonds formed in the anion complexes.

For the 1:1 calix[4]pyrrole−F^- binding mode analyzed in the gas phase, the hydrogen bonds in the 1,2-alternate complex **7** (28.8 kcal/mol) are much stronger than those in the partial cone **8** (22.8 kcal/mol) and cone structures **9** (21.9 kcal/mol). These findings are in accord with the NH- - -F distances calculated for these structures (Figure 2). However, this trend in hydrogen bond strength is reversed in dichloromethane solution. In this solvent, the hydrogen bond strength in complex **9** was calculated to be stronger than those in the complexes **8** and **7**. On the other hand, due to the effect of solvent, the net bond strengths are drastically reduced (to 10.1 kcal/mol with an isodensity value of 0.0004 and only 1 kcal/mol change with an isodensity value of 0.0003). Therefore, we believe that the hydrogen bond strength should be 10 ± 1 kcal/mol in CH_2Cl_2 solution and about 22 kcal/mol in the gas phase, in the cone structure. To the extent analyses are correct, the NH- - -F^- hydrogen bonds can be classified as strong. Estimates of the NH- - -F^- interactions for the 1:2 calix[4]pyrrole−2F^- systems reveals that the relevant hydrogen bonds in these complexes are much weaker than those in the 1:1 calix[4]pyrrole−F^- systems, probably due to the fact that the anions are sandwiched between two pyrroles.

For the cone structure of 1:1 calix[4]pyrrole−Cl^- complex **11**, the calculated NH- - -Cl^- hydrogen bonds are about 14 and 5 kcal/mol in the gas phase and in CH_2Cl_2 solution, respectively. Thus, the NH- - -Cl^- hydrogen bond is weaker than the NH- - -F^- hydrogen bond. Once again, in CH_2Cl_2 solution, the partial cone complex is found to display weaker hydrogen bonds than the corresponding cone complex.

6. The Effect of Meso Substituents on the Anion-Binding Energy. In the above discussion, the calix[4]pyrrole in the calculations lacks the *meso*-alkyl groups as in the experimental cases. Sessler et al. observed that different alkyl groups at the bridging, meso-like carbons can affect the anion-binding affinity.[8a] To investigate the effect of substituents on anion binding, we carried out PM3 calculations for the binding of fluoride anion by *meso*-octamethylcalix[4]pyrrole **14** and *meso*-tetraspirocyclohexylcalix[4]pyrrole **15**. Due to limitations in computer power, DFT calculations were not carried out for these larger systems. The PM3 calculations indicated that the binding free energy of the parent calix[4]pyrrole **1** (−66.1 kcal/mol) is larger than those substituted ones, **14** (−62.8 kcal/mol) and **15** (−62.6 kcal/mol), by over 3 kcal/mol. In addition, structure **14** displays a slightly larger binding free energy than structure **15**. While the calculated difference between **14** and **15** is smaller than is observed by experiment, the trend in affinity constant, **14** > **15**, is nonetheless gratifying.[8a]

To obtain more detailed insights in the effect of substituents, we carried out calculations on a key constituent of calix[4]pyrrole, that is, dialkyl-2,2′-dipyrrolemethane. We reason that in the 1,3-alternate conformation there are four *anti*-dipyrrole units, while in the cone conformation there are four *syn*-dipyrrole units. The meso substituents influence the relative stabilities of the two conformations via mainly steric effects and consequently change the anion-binding affinity. As shown in Table 6, the calculations predict that the energy difference between the syn and anti conformations of alkyl-free 2,2′-dipyrromethane is about 4.2 and 2.3 kcal/mol in the gas phase and in CH_2Cl_2 solution, respectively. These energy differences are about one-fourth of those between the 1,3-alternate and cone structures (16.0 and 11.4 kcal/mol in the gas phase and solution, respectively (see Figure 1)). This also indicates that the cone structure is mainly destabilized by unfavorable dipole interactions involving four pairs of syn dipyrrole units. In the case of dimethyl-2,2′-dipyrrolemethane, the energy difference between the syn and anti conformations increases to 5.5 and 3.7 kcal/mol in the gas phase and CH_2Cl_2 solution, respectively. This means that the methyl groups disfavor the syn conformation more than they do the anti conformation by about 1.3 kcal/mol. The results are in accord with those from the PM3 calculations for the parent calix[4]pyrrole **1** and octamethylcalix[4]pyrrole **14**. For the cyclohexyl-substituted dipyrrolemethane, the energy difference between the syn and anti conformations is also increased compared to the nonsubstituted case. However, the calculated substituent effect of the “larger” cyclohexyl substituent seems to be slightly smaller than that of the “smaller” methyl substituents. This counterintuitive result indicates that factors such as entropy and ring strain may also have a small influence on the relative stabilities of calix[4]pyrrole conformations. The general conclusion is that the cone structure of calix[4]pyrrole is destabilized by the *meso*-alkyl substituents by about 3−4 kcal/mol.[32] Assuming that the *meso*-alkyl substituents in question have little electronic effect on anion binding, we predict that octamethylcalix[4]pyrrole should display a binding energy of about 2−3 kcal/mol for Cl^- binding, in good agreement with experiment.[8a]

Table 6. Energy Difference (ΔE, kcal/mol) between the Syn and Anti Conformers of 2,2′-Dipyrrolemethane and Its *meso*-Dialkyl Derivative Calculated at the BLYP/6-31+G Level[a,b]**

	$\Delta E = E_{syn} - E_{anti}$		
	$R_1 = R_2 = H$	$R_1 = R_2 = Me$	$R_1, R_2 = (CH_2)_5$
gas phase	4.0	5.1	4.6
CH_2Cl_2, 0.0003	2.5	3.4	3.1
CH_2Cl_2, 0.0004	2.3	3.4	3.1

[a] Anti conformers were fully optimized. When $R_1 = R_2 = H$ or Me; $\angle N_1-C_2-C_3-C_4 = \angle N_5-C_4-C_3-C_2 = 56.8°$ or 48.8°, respectively. When $R_1, R_2 = (CH_2)_5$, $\angle N_1-C_2-C_3-C_4 = 76.4°$ and $\angle N_5-C_4-C_3-C_2 = 33.9°$. [b] Syn conformers were partially optimized by constraining two dihedral angles, $\angle N_1-C_2-C_3-C_4$ and $\angle N_5-C_4-C_3-C_2$, with −75.7° and 75.6°, respectively.

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Conclusion

We have studied the conformational preferences and fluoride and chloride anion binding properties of calix[4]pyrrole by PM3 and density functional theory methods in the gas phase and in dichloromethane solution. Several conclusions are summarized as follows: (1) In agreement with experimental observations, the 1,3-alternate conformation is calculated as being most stable. The stability sequence is predicted to be 1,3-alternate > partial cone > 1,2-alternate > cone, either in the gas phase or in CH_2Cl_2 solution. The cone conformation, which is observed in the solid-state structure of the calix[4]pyrrole$-F^-$ complex, is about 16.0 and 11.4 kcal/mol less stable in the gas phase and CH_2Cl_2 solution, respectively, when analyzed at the BLYP/6-31+G** level. (2) Anion binding analysis reveals that the 1:1 calix[4]pyrrole$-F^-$ binding mode with the cone conformation is more favorable than a possible 1:2 binding mode involving a 1,2-alternate conformation. (3) A rough estimate of an average F^-- - -H$-$N hydrogen bond strength in the cone structure resulted values of about 22 and 11 kcal/mol in the gas phase and in CH_2Cl_2 solution, respectively. (4) Our analysis of the effect of meso substituents, specifically methyl and cyclohexyl groups, on the conformational and anion-binding properties revealed that the steric hindrance of these groups disfavors the cone conformer more than the 1,3-alternate conformer and that it is this difference that accounts for the experimental difference in anion affinity.

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Supporting Information Available: Tables of calculated total energies and Cartesian coordinates of structures **3**−**13** and structural comparison between **3** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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