Selective Anion Complexation by a Calix[4]pyrrole Investigated by Monte Carlo Simulations

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The complexation of anions by octamethylcalix[4]pyrrole **1** and 2,5-dimethylpyrrole has been investigated by energy minimizations in the gas phase and by Monte Carlo (MC) simulations in dichloromethane using the OPLS force field. In agreement with experiment, the 1,3-alternate conformation of **1**, in which adjacent pyrrole rings are pointing in opposite directions, was shown to be the most stable conformation in the absence of a halide anion. The cone conformer of **1**, having all pyrrole units in a parallel orientation, is not stable in the absence of a halide anion, but it is the most stable conformation upon anion binding due to the formation of four NH−halide hydrogen bonds. The relative free energies of binding of chloride, bromide, and iodide with the cone of **1** in dichloromethane are calculated with free energy perturbation (FEP) simulations to be in excellent agreement with experiment. However, the calculations predict a far greater affinity for fluoride ion than was measured. This can be explained by the presence of trace amounts of water. For reference, MC/FEP calculations were also carried out for 2,5-dimethylpyrrole, which was predicted to bind only fluoride ion, consistent with NMR experiments. On the technical side, the MC sampling efficiency of alternative internal-coordinate representations of the complexes was also considered.

Introduction

After being investigated as precursors in the synthesis of porphyrins,[1] and as binding agents for transition metal ions,[2] octaalkylporphyrinogens **1** (Chart 1) have recently been discovered[3−5] as potential host molecules for anion binding.[6] Because the conformational properties of compounds **1** are analogous to calix[4]arenes,[7] as well as the fact that they are not successful porphyrin precursors, Sessler and co-workers have proposed renaming them as calix[4]pyrroles.[3] Calix[4]arenes can adopt four extreme conformations designated the cone, partial cone, 1,2-alternate, and 1,3-alternate, and the same nomenclature is used for the conformations of calix[4]pyrroles (Figure 1). The cone conformation of tetrahydroxycalix[4]arenes is stabilized relative to the other conformations by formation of an array of four intramolecular hydrogen bonds. Because there is no possibility for the formation of such hydrogen bonds between the NH groups, calix-[4]pyrroles adopt the 1,3-alternate conformation in the solid state.[3,8,9] The 1,2-alternate conformation of **1** has been observed in the crystal structure of the dimethyl-
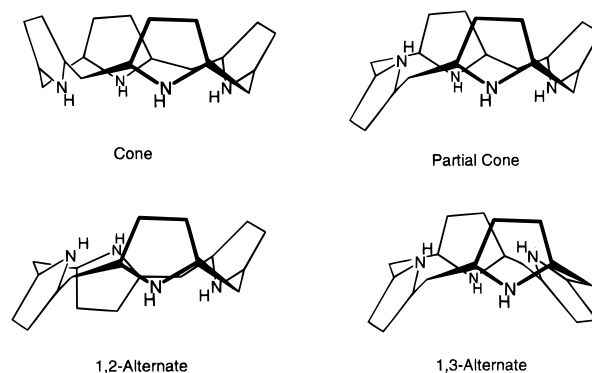
Figure 1. Schematic representations of the four characteristic conformations of calix[4]pyrroles.

Chart 1

1 R = Me   **2**
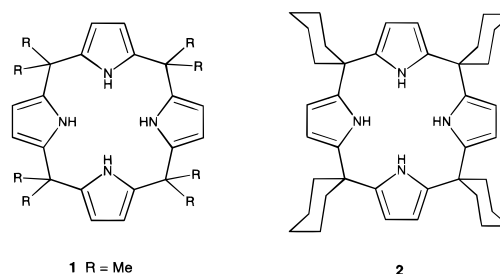
formamide complex.[8] Upon binding of a halide anion, the preferred conformation of **1** is a cone, both in the solid state and in solution, as shown by X-ray crystallography and ^{1}H and ^{19}F NMR spectroscopy.[3,5] The partial cone has not been observed experimentally. In the cone conformation, the four pyrrole units are oriented in the same direction to maximize the number of NH−halide hydrogen bonds. The anions are bound in a 1:1 complex, with a clear preference of binding F^{−} over other anionic guests in dichloromethane.[3] In a control experiment, 2,5-

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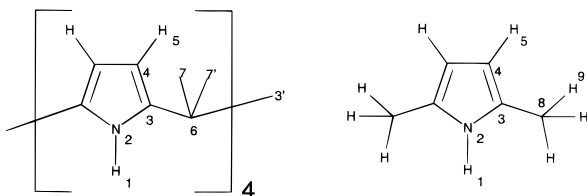
Figure 2. Numbering scheme of calix[4]pyrrole **1** (left) and 2,5-dimethylpyrrole (right). The numbers correspond to the atom types in Supplementary Tables 1−3.

dimethylpyrrole was found to bind fluoride anion only weakly, with an association constant of 9.2 ± 0.9 M^{-1}, with no detectable binding of the other halides.[3]

Computer simulations have been successfully applied to investigate host−guest recognition processes in solution.[10] By carefully sampling the interactions among host, guest, and solvent, structural arrangements and energetic components which determine experimental binding affinities have been elucidated.[11] The binding of anions by calix[4]pyrrole **1** is explored here in a similar manner and complements a recent study of anion binding by a bis(phenylurea) calix[4]arene derivative.[12] Our interest in **1** was particularly stimulated by the conformational change from 1,3-alternate to cone during complexation of an anion. The present simulation methodology is based on Monte Carlo sampling in internal coordinates. In general, sampling of internal coordinates becomes less efficient in the case of long-chain molecules, where changing a central dihedral angle results in large sweeps of the endpoints. Similarly, for macrocyclic molecules, sampling of one dihedral can induce large strains at the closing bond at the opposite side of the molecule. In an earlier paper it was shown that MC is more efficient than MD in sampling the trans/gauche distributions in liquid hexane.[13] It is found here that MC sampling of macrocyclic molecules can be made more efficient with a modified internal coordination representation.

Computational Methodology

Force Field. The OPLS force field[14] implemented in BOSS3.8[15] was used for all energy evaluations. The energy of the system was calculated using harmonic sums for bond stretching and angle bending, a Fourier series for the dihedral angles, and Coulomb and Lennard-Jones terms for atoms separated by three or more bonds (eqs 1−4). The latter two interactions are scaled by a factor of 0.5 for atoms connected by exactly three bonds.

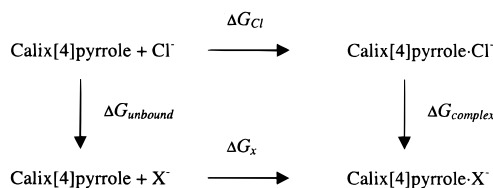$$E_{\text{bond}} = \sum_i k_{b,i}(r_i - r_{0,i})^2 \quad (1)$$

$$E_{\text{angle}} = \sum_i k_{\vartheta,i}(\vartheta_i - \vartheta_{0,i})^2 \quad (2)$$

$$E_{\text{dihedral}} = \sum_i \left\{ \frac{1}{2}V_{1,i}(1 + \cos \varphi_i) + \frac{1}{2}V_{2,i}(1 - 2\cos 2\varphi_i) + \frac{1}{2}V_{3,i}(1 + \cos 3\varphi_i) \right\} \quad (3)$$

$$E_{\text{nonbond}} = \sum_i \sum_{j>i} \left\{ \frac{q_i q_j e^2}{r_{ij}} + 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6} \right] \right\} \quad (4)$$

A combination of united and all-atom representations was used for calix[4]pyrrole **1** (Figure 2). The methyl groups were represented with united atoms, while all other hydrogen atoms were included explicitly. The 2,5-dimethylpyrrole model included all hydrogen atoms. The nonbonded parameters (Supplementary Table 1) were taken from the OPLS parameters for pyrrole,[16] 2-methylpyrrole, halide anions,[12,17] and united and all-atom alkanes.[18] The bond stretch and angle bending parameters in Supplementary Table 2 are mostly adopted from the AMBER force field.[19] The torsional parameters listed in Supplementary Table 3 were not previously parametrized but have been derived by fitting to torsional energy profiles obtained from ab initio molecular orbital calculations. The appropriate torsional profiles were computed for 2-methylpyrrole, 2-ethylpyrrole, and di(2-pyrrolo)dimethylmethane at the HF/6-31G* level using Gaussian95.[20] The same profiles were calculated using the OPLS force field with the missing torsional parameters $V_1 - V_3$ set to zero. Subsequently, the energy differences between the ab initio and the OPLS profiles were used to fit the parameters $V_1 - V_3$ using eq 3. Recalculation of the OPLS profiles with the new $V_1 - V_3$ parameters ensured that the correct fit had been made. Solvated systems were simulated using the OPLS model for dichloromethane.[21]

Monte Carlo (MC) Simulations. The free energies of association in dichloromethane of calix[4]pyrrole **1** and 2,5-dimethylpyrrole with chloride relative to fluoride, bromide, and iodide were calculated with the following thermodynamic cycle.

The difference between the experimental free energies of

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(11) See, for example: (a) Jorgensen, W. L.; Nguyen, T. B. *Proc. Nat. Acad. Sci. U.S.A.* **1993**, *90*, 1194−1200. (b) Carlson, H. A.; Jorgensen, W. L. *Tetrahedron* **1995**, *51*, 449−472. (c) Duffy, E. M.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1994**, *116*, 6337−6343.

(12) McDonald, N. A.; Duffy, E. M.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1998**, *120*, 5104−5111.

(13) (a) Jorgensen, W. L.; Tirado-Rives, J. *J. Phys. Chem.* **1996**, *100*, 14508−14513. (b) Jorgensen, W. L.; Tirado-Rives, J. *J. Phys. Chem. A* **1997**, *101*, 2916−2916.

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binding, $\Delta G_x - \Delta G_{cl}$, is equal to the computed $\Delta G_{complex} - \Delta G_{unbound}$. The latter quantities were calculated by the non-physical transformation of the chloride anion to one of the other halide anions, both bound to the host and free in solution. Free energy perturbation (FEP) theory with Monte Carlo sampling was used to calculate the free energies. The Zwanzig equation[22] was used to evaluate free energy changes:

$$\Delta G(\text{A} \rightarrow \text{B}) = -k_B T \ln \langle \exp[-(E_B - E_A)/k_B T] \rangle_A \quad (5)$$

In this equation, A and B denote the reference and the perturbed states, and $\langle \ \rangle_A$ indicates that sampling has been carried out in the reference state. The actual perturbations were divided into a series of five steps that were coupled to a linear scaling parameter λ running from 0 to 1. Double-wide sampling was used, yielding a stepsize $\Delta\lambda$ equal to 0.1.

Gas-phase energy minimization in combination with a conformational search was applied to find low-energy conformations of **1**, both in the absence and presence of the four halide anions. The lowest-energy cone−Cl⁻ complex was used as the starting point for the bound transformations of chloride to the other halides. Similarly, the lowest-energy cone−F⁻ complex was used as the starting point for a bound fluoride to chloride transformation. The simulations of the calix[4]pyrrole complexes were performed in a simulation box with ca. 33 × 33 × 33 Å dimensions containing 327 dichloromethane molecules. The 2,5-dimethylpyrrole simulations were performed in a ca. 24 × 30 × 32 Å box with 210 dichloromethane molecules. The solvent boxes were subject to periodic boundary conditions and preferential sampling. Moves of either the halide anion or the host molecule were attempted every 50 configurations. Moves of the halide anions consisted of random translations within 0.15 Å in all directions. Both the calix[4]-pyrrole and 2,5-dimethylpyrrole were not rotated or translated; their moves consisted of variations in random subsets of up to 15 internal variables. No internal degrees of freedom were sampled for the solvent molecules. The ranges of the motions of both the solvent molecules and halide anions were adjusted to give acceptance ratios around 40%. The nonbonded interactions were calculated with a 12-Å cutoff. The solute−solute and solute−solvent interactions were quadratically feathered to zero over the last 0.5 Å. If any solute−solvent atom pair was within the cutoff distance, the interactions between that solvent molecule and the entire solute were calculated. The free halide simulations were performed similarly in a cubic box containing 266 dichloromethane molecules, ca. 30 Å on a side. Each window of both the calix[4]pyrrole and 2,5-dimethylpyrrole simulations consisted of 1.5×10^6 configurations of equilibration, followed by 5×10^6 configurations of averaging. The windows during the free halide anion simulations covered 1.5×10^6 and 2×10^6 configurations of equilibration and averaging, respectively. All MC simulations were performed in the isothermal−isobaric (NPT) ensemble at 25 °C and 1 atm.

Z-Matrices. Internal coordinate sampling of macrocyclic molecules such as calix[4]pyrroles can yield low acceptance ratios since small changes in a dihedral angle can result in a large strain on the opposite side of the molecule. This can be illustrated with a hypothetical molecule consisting of four atoms in Figure 3a. A small rotation around the bond between atoms 2 and 3 results in a significant and unfavorable elongation of the bond between 1 and 4. One way of avoiding this unfavorable propagation of changes is depicted in Figure 3b. Each of the four atoms is built independently from the fixed anchor atoms, and changing the position of one atom will not influence the position of the other atoms. A similar Z-matrix has been constructed for calix[4]pyrrole **1** (Supporting Information). In this Z-matrix, each pyrrole ring and each dimethylmethane bridge has been built independently relative to three dummy anchor atoms. Furthermore, rotating around the axis connecting the two ortho carbon atoms enhanced the sampling of the canting of the pyrrole units. The pyrrole units were kept rigid to reduce the degrees of freedom of the system.

(22) Zwanzig, R. W. *J. Chem. Phys.* **1954**, *22*, 1420−1426.
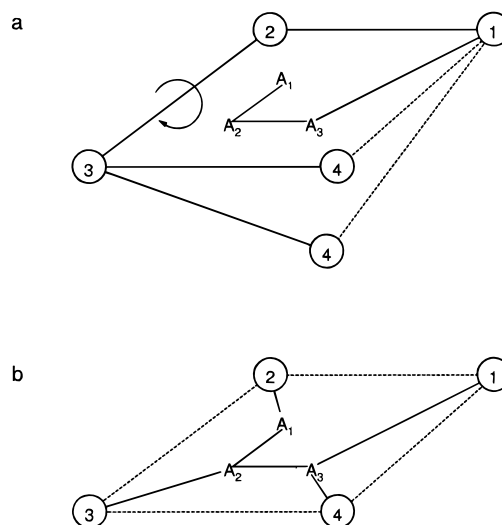
Figure 3. Two ways of building a Z-matrix for a cyclic molecule with four fragments or atoms. In a classic Z-matrix (a), the first atom is built relative to three dummy anchor atoms A_1−A_3, and higher numbered atoms are built relative to the previous. Rotation around the bond between atoms 2 and 3 propagates through the molecule and elongates the bond between atoms 1 and 4. In the fragment Z-matrix (b), each of the atoms 1−4 is built relative to the anchor atoms A_1−A_3 and can move independently.

A second Z-matrix has been constructed in which only the first atom is built from the fixed anchor atoms such as in Figure 3a. In this Z-matrix, changes do propagate and no rotation around a virtual bond is performed (Supporting Information). The Z-matrices will be referred to as the "fragment" and "classic" Z-matrix, respectively. Both Z-matrices have the same total number of degrees of freedom. However, the fragment Z-matrix has 16 variable bonds, 16 variable angles, and 20 variable dihedrals, while the classic Z-matrix has 15, 15, and 22, respectively. For the fragment Z-matrix, the ranges for variations in the dihedral angles were ±10° for dihedral angles determining the tilt angle of a pyrrole unit, ±5° for dihedral angles involving the methyl groups, and ±1° for dihedral angles between the three dummy atoms and an atom of the calix[4]pyrrole. All dihedral angles in the classic Z-matrix were sampled within a range of ±2.5°. Results have been obtained with both Z-matrices and provide a gauge of the sensitivity to the internal coordinate representation.

Results and Discussion

Gas Phase. The results for the gas-phase calculations are presented in Table 1. With both Z-matrices, the cone is not stable upon energy minimization in the absence of a halide anion but yields a 1,3-alternate-like conformation. Subsequently, conformational searches revealed almost the same 1,3-alternate conformation as the most stable conformation (Figure 4a and 4e). The energy difference between the most stable 1,3-alternate conformations from the two Z-matrices is only 0.08 kcal mol⁻¹. Using the fragment Z-matrix, none of the other characteristic conformers known from calix[4]arenes, partial cone or 1,2-alternate, were found as stable conformers. However, other stable conformers were found at 7−16 kcal mol⁻¹ above the 1,3-alternate (Figure 4b−d). They cannot be described by one of the four stable calix[4]arene conformers; they have one or two pyrrole units lying in the plane formed by the four carbon atoms connecting the pyrrole units. A conformation similar to conformer c in Figure 4 has been observed in the solid state for the

Table 1. Results of Gas-Phase Energy Minimizations[a]

anion	ΔE	ΔE_{deform}	ΔE_{inter}	$R(N-X)$[b]
	Cone 1 (Fragment Z-Matrix)			
none	unstable			
F$^-$	−59.10	31.36	−90.46	2.63
Cl$^-$	−23.30	27.00	−50.30	3.31
Br$^-$	−20.89	26.86	−47.75	3.37
I$^-$	−11.45	26.43	−37.88	3.72
	Cone 1 (Classic Z-Matrix)			
none	unstable			
F$^-$	−59.50	31.05	−90.55	2.63
Cl$^-$	−23.58	26.78	−50.36	3.31
Br$^-$	−21.16	26.65	−47.81	3.37
I$^-$	−11.74	26.21	−37.95	3.72
	1,3-Alternate-1 (Fragment Z-Matrix)			
none	0.00	0.00		
F$^-$	unstable[c]			
Cl$^-$	unstable[d]			
Br$^-$	−3.24	2.51	−5.75	3.85
I$^-$	−1.86	1.52	−3.38	4.53
	1,3-Alternate-1 (Classic Z-Matrix)			
none	−0.08	−0.08		
	2,5-Dimethylpyrrole			
F$^-$			−24.67	2.58
Cl$^-$			−13.70	3.26
Br$^-$			−13.09	3.31
I$^-$			−10.84	3.62

[a] ΔE is the net energy difference in kcal mol^{-1}, which consists of the intermolecular interaction energy, ΔE_{inter}, and the deformation energy of the host ΔE_{deform}. The energies ΔE and ΔE_{inter} of the cone are given relative to the uncomplexed 1,3-alternate. [b] Average N−halide ion distance in Å. [c] Yields a cone-like conformation. [d] Yields a partial cone-like conformation.

β-octabromo derivative of **1**.[4] In the search using the classic Z-matrix, a 1,2-alternate was found as a stable conformer (Figure 4g), 8.9 kcal mol^{-1} above the 1,3-alternate. Another stable conformer (Figure 4f) is similar to a structure found in the search with the fragment Z-matrix (Figure 4b). Overall, although the results for the conformational searches differ somewhat depending on which Z-matrix is used, no structure competitive with the 1,3-alternate was found in the gas phase. This is consistent with crystallographic experiments, where the 1,3-alternate has been found for calix[4]pyrrole **1**.[3] Clearly, the 1,3-alternate benefits from antiparallel alignment of the dipoles of adjacent pyrrole fragments, while the cone suffers from parallel dipole alignment and proximity of the amino hydrogens.

The conformational preference is completely altered in the presence of the halide ions (Figure 5). Conformational searches found the cone complex to be the lowest-energy conformer in all cases. The structures are almost identical from both Z-matrices. As was the case for the uncomplexed 1,3-alternate, structures built with the classic Z-matrix have a slightly lower energy; the maximum energy difference is 0.4 kcal mol^{-1} for the cone−fluoride complexes (Table 1). For the 1,3-alternate−halide complexes, energy minimizations have only been performed with the fragment Z-matrix. For fluoride and chloride, no stable 1,3-alternate−halide complex was found in which the halide forms one or more hydrogen bonds with **1**. The 1,3-alternate complexes with bromide and iodide are stable, but hydrogen bond formation is not optimal due to steric interference with the adjacent pyrrole rings.

The deformation energy of the cone with respect to the (empty) 1,3-alternate is 26−31 kcal mol^{-1} (Table 1). This is almost completely due to increases in the intramolecular nonbonded energy of the host by 28.6, 22.9, 22.6, and
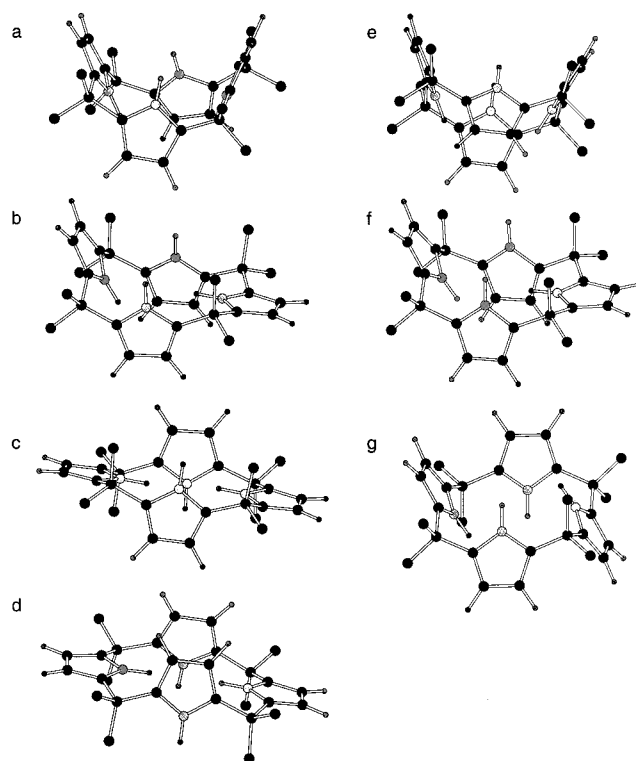

Figure 4. Selected stable conformations found by conformational searches of **1**. Conformations a−d were found with the fragment Z-matrix and e−g with the classic Z-matrix. The 1,3-alternate conformations a and e are the lowest-energy conformations found in the searches. Conformers b to d are 7.13, 12.27, and 14.10 kcal mol^{-1} higher in energy than in a, respectively. Conformations f and g are 6.85 and 8.94 kcal mol^{-1} higher in energy relative to e. Conformation g is a 1,2-alternate.
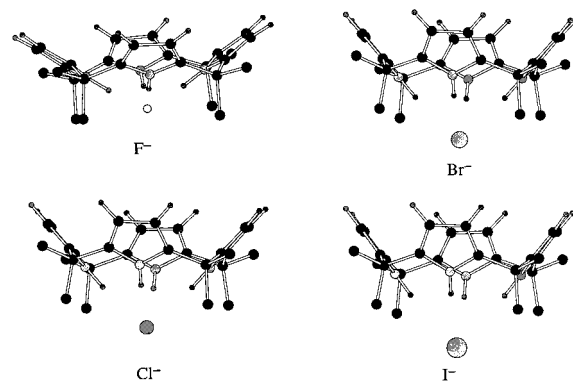
Figure 5. Cone−halide complexes of **1** energy-minimized in the gas phase.

21.4 kcal mol^{-1} for the F$^-$, Cl$^-$, Br$^-$, and I$^-$ complexes, respectively. This is compensated by the intermolecular anion−calix[4]pyrrole interaction of −38 to −90 kcal mol^{-1}. These calculations agree with crystallographic experiments, where for calix[4]pyrrole **1** a cone−Cl$^-$ complex was found.[4] The experimental N−Cl$^-$ distances range from 3.26 to 3.33 Å, in close agreement with the calculated average distance of 3.31 Å. Tetraspirocyclohexyl derivative **2** also adopts the cone conformation when crystallized with F$^-$.[4] The average N−F$^-$ distance is 2.79 Å, slightly more than the calculated 2.63 Å. Compound **2** binds fluoride more weakly in dichloromethane than **1**,[3] so a somewhat larger distance for **2**
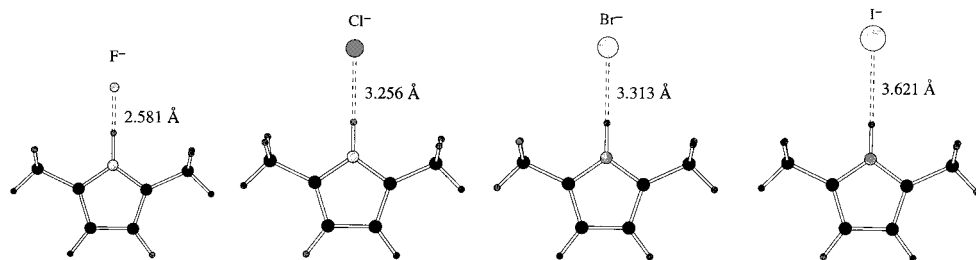
Figure 6. Energy-minimized 2,5-dimethylpyrrole−halide complexes. The N−X$^-$ distance is given.

Table 2. Computed Free Energy Changes (kcal mol^{-1}) for the Halide Anions and Calix[4]pyrrole 1 in Dichloromethane[a]

| transfrmn	$\Delta G_{unbound}$	$\Delta G_{complex}$	$\Delta \Delta G_{calc}$	$\Delta \Delta G_{exp}$[b]
	Cone 1 (Fragment Z-Matrix)			
Cl$^-$ to F$^-$	-21.06 ± 0.16	-38.15 ± 0.17	-17.09 ± 0.23	-2.3
Cl$^-$ to Br$^-$	1.80 ± 0.01	3.07 ± 0.01	1.27 ± 0.01	2.1
Cl$^-$ to I$^-$	8.62 ± 0.07	14.80 ± 0.08	6.18 ± 0.11	>2.1
F$^-$ to Cl$^-$		37.60 ± 0.16		
	Cone 1 (Classic Z-Matrix)			
Cl$^-$ to F$^-$	-21.06 ± 0.16	-36.14 ± 0.18	-15.08 ± 0.24	-2.3
Cl$^-$ to Br$^-$	1.80 ± 0.01	3.04 ± 0.01	1.24 ± 0.01	2.1
Cl$^-$ to I$^-$	8.62 ± 0.07	14.87 ± 0.09	6.25 ± 0.11	>2.1
F$^-$ to Cl$^-$		38.14 ± 0.23		
	2,5-Dimethylpyrrole			
Cl$^-$ to F$^-$	-21.06 ± 0.16	-24.05 ± 0.12	-2.99 ± 0.20	
Cl$^-$ to Br$^-$	1.80 ± 0.01	1.99 ± 0.01	0.19 ± 0.01	
Cl$^-$ to I$^-$	8.62 ± 0.07	9.45 ± 0.05	0.83 ± 0.09	

[a] Statistical uncertainties ($\pm 1\sigma$) were computed via the batch means procedure with batch series of 100 00 configurations. [b] Reference 3.

seems reasonable. In dichloromethane solution, calix[4]pyrrole **1** complexes F$^-$ in the cone conformation as shown by ^{1}H and ^{19}F NMR spectroscopy.[5] The present calculations indicate that the cone is the most stable conformation for all halide complexes in the gas phase.

The model compound 2,5-dimethylpyrrole binds the halides with one NH−anion hydrogen bond (Figure 6). The intermolecular interaction energy of the cone with each of the halide anions is only slightly less favorable than four times the interaction energy of 2,5-dimethylpyrrole with the same halide. This indicates that the cone is flexible enough to position each pyrrole for optimal electrostatic interactions with the anions. Similarly, the N−halide distances are only slightly longer for the cone than for 2,5-dimethylpyrrole.

Free Energies of Binding in Dichloromethane. For the chloride to bromide and iodide transformations, the calculated differences in free energy of binding are almost the same for both Z-matrices (Table 2). For the fragment Z-matrix, the free-energy differences for the chloride to bromide and iodide transformations are 1.27 and 6.18 kcal mol^{-1}, while they are 1.24 and 6.25 kcal mol^{-1} for the classic Z-matrix. These results compare well with the experimental values of 2.1 and >2.1 kcal mol^{-1}, respectively.[3] The free-energy differences are considerably smaller than the corresponding gas-phase energy differences in Table 1. This reflects the damping effect of the solvent environment compared to the gas phase, e.g., both the calix[4]pyrrole and the solvent are better hosts for chloride than for bromide. It also reflects thermal averaging in the MC simulations which includes entropic effects that benefit the weaker complexes.
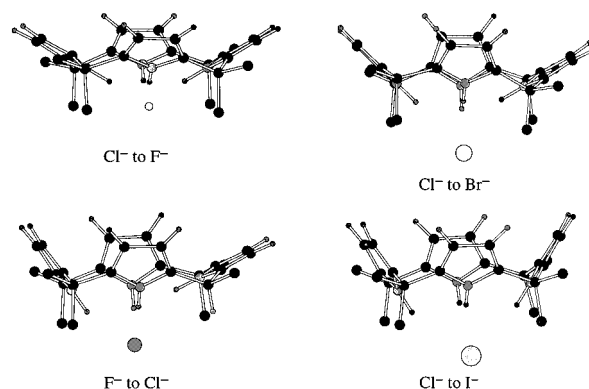
Figure 7. Snapshots of the solutes in the last accepted Monte Carlo configurations for the transformations of the cone−halide complexes with the fragment Z-matrix.

The damping also operates for the fluoride complex, but the calculated $\Delta \Delta G$ between fluoride and chloride is 14.8 kcal mol^{-1} (fragment Z-matrix) and 12.8 kcal mol^{-1} (classic Z-matrix) more negative than the experimental difference. In an earlier paper, we studied the binding of halide anions by a calix[4]arene host in chloroform and also obtained a large $\Delta \Delta G$ favoring binding with fluoride over chloride by 10.4 kcal mol^{-1}.[12] It was shown that complexation of F$^-$ by two water molecules would suffice to overcome binding by the calix[4]arene host. It is likely that water has also interfered in the measurements for calix[4]pyrrole **1** in dichloromethane, since the tetrabutylammonium fluoride salt was added as the trihydrate.[3]

The acceptance ratio of moves sampling the internal degrees of freedom for calix[4]pyrrole **1** was ca. 15% for the fragment Z-matrix and ca. 6% for the classic Z-matrix. Thus the fragment Z-matrix did meet the expectation of a higher acceptance ratio, even with larger ranges for dihedral-angle sampling. For the chloride to bromide and iodide transformations, the conformational change of the cone of **1** is small enough to be sampled equally well with both the fragment and the classic Z-matrix; the maximum free energy difference is 0.07 kcal mol^{-1}. However, when the results for the chloride to fluoride transformation are compared to those for the reverse process, the smaller hysteresis with the fragment Z-matrix (0.55 kcal mol^{-1}) compared to the classic Z-matrix (2.00 kcal mol^{-1}) indicates better convergence for the former. All complexes retained a cone conformation during the MC simulations in dichloromethane. In Figure 7, snapshots of the solutes are presented from the last accepted MC configuration for the transformations from chloride to fluoride, bromide, and iodide, as well as from the chloride end of the fluoride to chloride transformation using the fragment Z-matrix. When these structures are compared to the energy-minimized conformers in Figure 5, the resem-

4.914 Å
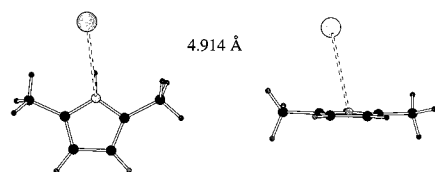
Figure 8. Two views of the complex during the Cl⁻ to I⁻ perturbation showing the halide anion drifting away from 2,5-dimethylpyrrole.

blance is clear. Thus, conversion of the cone conformation adopted in one halide complex to the cone adopted in another was facile. The only exception was in the case of the chloride to fluoride transformation with the classic Z-matrix, which would require extension of the simulation to reach full convergence for the large free-energy changes (Table 2).

For 2,5-dimethylpyrrole, the MC results indicate that the potential single hydrogen bond is not sufficient to bind the halide ions tightly in solution. The computed differences in free energies of binding between chloride and both bromide and iodide are small, indicating that there is no preference for binding these anions (Table 2). In fact, during the chloride to iodide transformation, the anion was observed during part of the simulation at distances as large as ca. 5 Å from the nitrogen atom of 2,5-dimethylpyrrole and out of the plane of the ring (Figure 8). These results are consistent with experimental observations that chloride, bromide, and iodide are at most very weakly bound by 2,5-dimethylpyrrole.[3] If one assumes no binding for chloride, the experimental association constant of 9.2 M⁻¹ for fluoride translates to a $\Delta\Delta G_{binding}$ between fluoride and chloride of -1.3 kcal mol⁻¹. This is consistent with the calculated value of -3.0 ± 0.6 kcal mol⁻¹ in view of the expected influence of trace water.

Conclusions

Energy minimizations in the gas phase and Monte Carlo simulations in dichloromethane have been used to study the anion binding properties of calix[4]pyrrole **1** and 2,5-dimethylpyrrole. The gas-phase calculations

show, in agreement with experiment, that **1** adopts the 1,3-alternate conformation in the absence of halide anions. The cone conformer of **1** is not stable in the absence of a halide anion, but it is the most stable conformation upon anion complexation due to the formation of four NH–halide hydrogen bonds. In dichloromethane solution, the relative free energies of binding of chloride, bromide, and iodide with **1** were calculated to be in excellent agreement with experiment. However, the relative binding free energy for fluoride was calculated to be 14.8 kcal mol⁻¹ more favorable than that from experiment. In an earlier study concerning anion complexation by a neutral urea derivative of calix[4]arene,[12] it was shown that the presence of small amounts of water suffices to explain such discrepancies for fluoride ion complexation. In addition, the reference compound 2,5-dimethylpyrrole was predicted to show significant affinity for only fluoride ion, consistent with NMR experiments. On the technical side, for macrocyclic molecules, Monte Carlo sampling using internal coordinates was found to yield better acceptance ratios if a Z-matrix is constructed in which small dihedral angle changes are not propagated through the molecule. The higher efficiency of such a Z-matrix was noticeable for the interconversion of the complexes of fluoride and chloride ions. Overall, the present results further illustrate the usefulness of computational models including explicit solvation, thermal averaging, and carefully developed force fields for the characterization of host–guest chemistry at an atomic level.[10]

Supporting Information Available: Listings of the force-field parameters and of the fragment and classic Z-matrices for the calix[4]pyrrole **1**–chloride complex in the cone conformation. This material is available free of charge via the Internet at http://pubs.acs.org.

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