Novel Binding Modes in Tetramethoxycalix[4]arene: Implications for Ligand Design

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Abstract: Calixarenes are used as molecular scaffolds for the preparation of novel receptors for cations, anions, and neutral molecules. Although widely studied, the nature of the host−guest interactions within these molecules remains obscure. We present a combined density-functional theory and second-order perturbation theory study of the complexation of the alkali cations Na^+ and Cs^+ with tetramethoxycalix[4]arene. The results show that the host−guest interactions of this simple system are much more complex than previously thought and suggest new approaches for the design of selective cation receptors.

Introduction

Molecular recognition phenomena play a central role in biochemistry and in the quickly emerging field of supramolecular chemistry.[1] Macrocyclic architectures with conformationally preorganized and electrostatically favorable binding sites provide ideal systems to study the nature of host−guest interactions. Of particular interest are the calixarene macrocycles that are widely used as hosts for cations, anions, and neutral molecules.[2−11] The most well-studied member of this class of compounds, calix[4]arene, is composed of four phenol units connected by ortho-methylene bridges (Figure 1). The 16-membered macrocycle ring of calix[4]arene exhibits only four distinct conformations (see Figure 2 for nomenclature), an unusual property for a ring of this size. Each conformer presents a unique binding cavity for the metal to occupy. Synthetic methods allow for the selective addition of different functional groups either at the hydroxyl site or at the arene carbons para to the hydroxyls, which results in a wide variety of calix[4]arene derivatives. Placement of bulky substituents at the hydroxyl positions can be used to immobilize calix[4]arene in one of its four conformations, designated here as CONE; partial cone (PACO); 1,3-alternate (13ALT); and 1,2-alternate (12ALT).

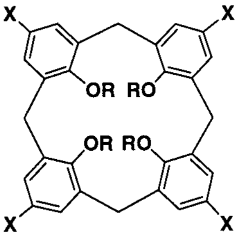

Figure 1. Calix[4]arene macrocycle.

The alkali cations are a class of guests that have received considerable attention both because of their use as templating agents in calixarene syntheses[2−10] and because of the selectivity shown by particular calixarenes in alkali cation coordination.[2−16] In the absence of structural modifications, the calix[4]arene scaffold itself exhibits a relatively weak affinity for these cations.[17] The challenge we now confront is how to modify calix[4]arene in such a way as to yield the most efficient and selective receptor for any specified guest. Current receptor design strategy involves the introduction of additional binding sites, typically through O-alkylation, to yield cavities with increased denticity. Although this strategy has inspired the preparation of a large number of calix[4]arene derivatives,[2−17] few of these exhibit enhanced selectivity for specific alkali metal cations. Currently, this Edisonian approach remains the dominant mode of investigation. Effective criteria for the rational design of enhanced calix[4]arene receptors, even for these simple, spherically symmetric guests, are not available. A vital step in the development of such criteria is the determination of how the alkali cations interact with the calix[4]arene scaffold, and we have adopted this goal for the present work.

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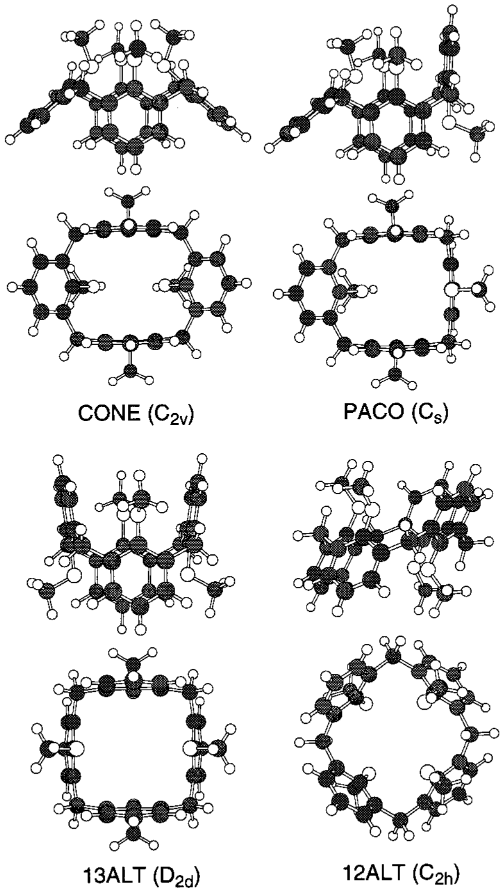

Figure 2. CONE; partial cone (PACO); 1,3 alternate (13ALT); and 1,2 alternate (12ALT) conformations of tetramethoxycalix[4]arene (TMC) (Figure 1, R = Me, X = H).

Tetraalkoxycalix[4]arenes (Figure 1, R = alkyl) are the simplest derivatives containing the binding sites found in more elaborately functionalized calix[4]arenes. All four conformations of tetraalkoxycalix[4]arenes are known to coordinate with the alkali cations.[18] However, structural information on the actual mode(s) of coordination is limited,[11] and thermodynamic data on the stability of such complexes is not available.[17] Although it was originally assumed that cation coordination to calixarenes would occur only through the oxygens, crystal structure data shows that the electron-rich arene rings can provide alternative binding sites.[11,19−24] Acting upon evidence that benzene forms relatively stable complexes with the alkali cations,[25−30] we recently established[31] that the calix[4]arene building block, methoxybenzene, is an ambidentate ligand capable of coordination through either the oxygen or the arene (Figure 3). Comparison of the calculated binding energies revealed that the two binding modes yield complexes of approximately equal strength for the Li^+ through Cs^+ series of cations. The similarity of these binding energies suggests the possibility for multiple cation binding modes in each calix[4]arene conformation.

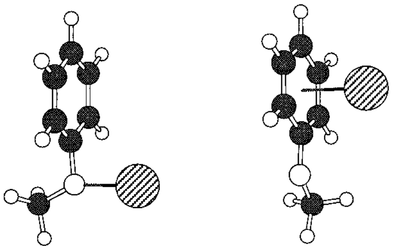

Figure 3. Two stable geometries for Na^+ complexes with methoxybenzene are a representative example of the two possible binding modes for alkali cations.[11]

Due to major advances in computational hardware and software, we can now apply reliable electronic structure methods to molecules the size of calix[4]arenes. Herein we report the use of density functional theory[32] and second-order perturbation theory to identify the binding modes of Na^+ and Cs^+ with tetramethoxycalix[4]arene (TMC), the simplest derivative in which all four hydroxyl groups are alkylated (Figure 1, R = methyl, X = H).

Methods

Initial geometries for 12 tetradentate binding conformations of M^+:TMC, M = Na and Cs, were obtained from molecular mechanics calculations using a modified MM3(96) force field.[33] The cation−oxygen and cation−arene centroid distances were constrained to values observed in methoxybenzene ($C_6H_5OCH_3$) complexes, namely $r_{NaO} \cong 2.24$ Å, $r_{NaX} \cong 2.48$ Å, $r_{CsO} \cong 3.10$ Å, and $r_{CsX} \cong 3.61$ Å.[31] Further optimization was then done at the restricted Hartree−Fock (RHF) level of theory using a combination of Dunning−Hay[34] [3s,2p/2s] contractions for carbon, oxygen, and hydrogen, and effective core potentials (ECPs) and their associated valence basis sets for sodium and cesium.[35] The cesium ECP included the dominant relativistic effects. In the Gaussian program, this collection of ECPs and basis sets is referenced by the keyword LANL2DZ.[36]

Although all of the initial optimizations were performed in C_1 symmetry, in many cases additional symmetry elements appeared during the course of the optimization. In such cases, the calculations were halted, and explicit symmetry was imposed. Normal mode calculations were used to verify that the optimized geometries represented minima on the RHF/LANL2DZ potential energy surface. These geometries were used as input for final geometry optimizations using the BLYP exchange-correlation functional.[37,38] The BLYP/DFT calculations used

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the 6-31G** basis set[39,40] on H, C, O, and Na, and LANL2DZ/ECP on Cs. Cation binding energies were corrected for the undesirable effects of basis set superposition error (BSSE) by the counterpoise method of Boys and Bernardi.[41] All of the RHF and DFT electronic structure calculations were performed with Gaussian 94, Revision E.2.[36]

Finally, refined energetics were obtained at the BLYP/DFT geometries from second-order Møller−Plesset perturbation theory (MP2)[42] calculations with the diffuse function augmented correlation consistent valence double-ζ basis set (aug-cc-pVDZ) for H, C, and O.[43,44] Sodium was described by a [5s,4p,2d] contracted basis set and the (2s,2p) shell of electrons was explicitly correlated. Cesium was described by a [4s,4p,2d] basis set and the (n−1) Hay-Wadt ECP.[35]

Previous studies of M^+(ether), M = Na and Cs, complexes with basis sets as large as quadruple-ζ with extra diffuse functions (aug-cc-pVQZ) demonstrated that the relatively modest aug-cc-pVDZ basis set was fortuitously capable of yielding results within 1 kcal/mol of the complete basis set limit for sodium and within 1.5 kcal/mol for cesium.[45] Very recent studies of M^+(benzene) complexes with equally large basis sets, show that the same aug-cc-pVDZ basis set is able to reproduce estimated complete basis set MP2 binding energies to within 0.3 (Na) and 1.1 (Cs) kcal/mol.[46,47] Thus, both the ether oxygen and arene binding modes should be well-represented at the MP2/aug-cc-pVDZ level of theory. Application of the BSSE correction actually worsens agreement between the MP2/aug-cc-pVDZ and complete basis set results, and therefore, was not applied in this part of the study. Investigation of the importance of higher-order correlation effects in the cases of M^+(ether) and M^+(benzene) complexes, such as through couple cluster calculations, showed such effects to be unimportant.

All MP2 calculations were performed using the NWChem[48] program running on the 512-node IBM SP in the Molecular Science Computing Facility. The default threshold of 10^{-5} was used for eliminating linearly dependent eigenvectors of the overlap matrix. In practice, the number of basis set vectors eliminated remained relatively constant (at approximately 25) across the various complexes. The largest MP2 calculation performed in this study involved 1015 basis functions.

Results and Discussion

The DFT and MP2 calculations produced slightly different energy orderings for the bare TMC molecule. At the BLYP/DFT level of theory, the CONE conformation lies a mere 0.1 kcal/mol lower in energy than the PACO structure, whereas at the MP2 level of theory, these conformations are reversed and the PACO structure is 0.9 kcal/mol lower. This difference in the nature of the TMC global minimum is reflected in the binding energies, ΔE, shown in Table 1. ΔE is defined as the total energy of the complex minus the sum of the total energies of the cation and the most stable free ligand conformation, that is, the CONE structure for BLYP/DFT and the PACO structure for MP2. Both BYLP/DFT and MP2 qualitatively agreed on the highest-lying TMC conformation (12ALT), but MP2 found this conformation to be more than 3 kcal/mol less stable than DFT.

Table 1. Energetic Data for TMC Complexes with Na^+ and Cs^{+a}

		Na^+			Cs^+		
binding mode	method	ΔE	ΔE_{rel}	ΔE_{comp}	ΔE	ΔE_{rel}	ΔE_{comp}
CONE 4O	MP2/aVDZ	−67.3	8.6	9.1	−22.6	19.1	20.1
	BLYP/6-31G**	−76.2	0.0	0.2	−17.9	8.3	10.7
CONE 2O+2A	MP2/aVDZ	−75.6	0.4	0.9			
	BLYP/6-31G**	−72.6	3.6	3.8			
CONE 4A	MP2/aVDZ				−35.1	6.5	7.5
	BLYP/6-31G**				−22.7	3.6	5.7
PACO 4O	MP2/aVDZ	−67.1	8.8	10.3			
	BLYP/6-31G**	−70.0	6.2	6.3			
PACO 3O+1A	MP2/aVDZ	−69.4	6.6	8.0	−31.1	10.5	12.5
	BLYP/6-31G**	−72.9	3.3	3.4	−21.0	5.3	7.5
PACO 2O+2A	MP2/aVDZ	−75.9	0.0	6.6			
	BLYP/6-31G**	−72.1	4.0	4.2			
PACO 1O+3A	MP2/aVDZ				−41.6	0.0	1.9
	BLYP/6-31G**				−26.3	0.0	2.2
13ALT 4O	MP2/aVDZ	−67.4	8.5	6.6			
	BLYP/6-31G**	−68.6	7.6	5.0			
13ALT 2O+2A	MP2/aVDZ	−69.2	6.8	4.9	−37.1	4.6	3.1
	BLYP/6-31G**	−68.9	7.3	4.7	−24.2	2.1	1.6
12ALT 4O	MP2/aVDZ	−67.8	8.1	0.0			
	BLYP/6-31G**	−70.1	6.1	0.0			
12ALT 2O+2A	MP2/aVDZ				−34.0	7.7	0.0
	BLYP/6-31G**				−22.3	4.0	0.0

[a] aVDZ = aug-cc-pVDZ. Binding energies, ΔE, and relative binding energies, ΔE_{rel} and ΔE_{comp}, are given in kcal mol^{-1}. MP2 ΔE values are given with respect to the PACO conformation of bare TMC (the lowest-energy MP2 structure) and are not corrected for BSSE. BLYP ΔE values are with respect to the CONE conformation of bare TMC (the lowest-energy BLYP structure) and are corrected for BSSE.

We restricted our attention to tetradentate complexes in which each of the four methoxybenzene components of the macrocycle ring was coordinated to the cation. The various cation binding modes are differentiated by the conformation of the macrocycle and the number and type of binding sites. For example, the notation "CONE 2O+2A" indicates that TMC is in the cone conformation and the metal is bonded to two ether oxygens and 2 arenes.

Methoxy rotamers of isolated calix[4]arenes, that is, with unoccupied cavities, have previously been examined with force field methods.[49] It should be noted that when the metal cation is coordinated to arene donor groups, it may be possible for uncoordinated methoxy groups to rotate into the macrocycle cavity. However, X-ray crystal structures provide no evidence of such conformations when metal cations are present within a calix[4]arene, and these methoxy rotamers were not examined in the current study. There are also binding modes in which the cation binds to the "outside" of the calixarene cavity and, thus, to *less* than four binding sites. These binding modes are necessarily weaker and are also not considered. Due to steric restrictions, there do not appear to be any binding modes in which *more* than four binding sites are able to coordinate with the cation.

There are 12 physically achievable ways that tetradentate M^+-(TMC) complexes can form. These are designated as the CONE 4O, CONE 2O+2A, CONE 4A, PACO 4O, PACO 3O+1A, PACO 2O+2A, PACO 1O+3A, 13ALT 4O, 13ALT 2O+2A,

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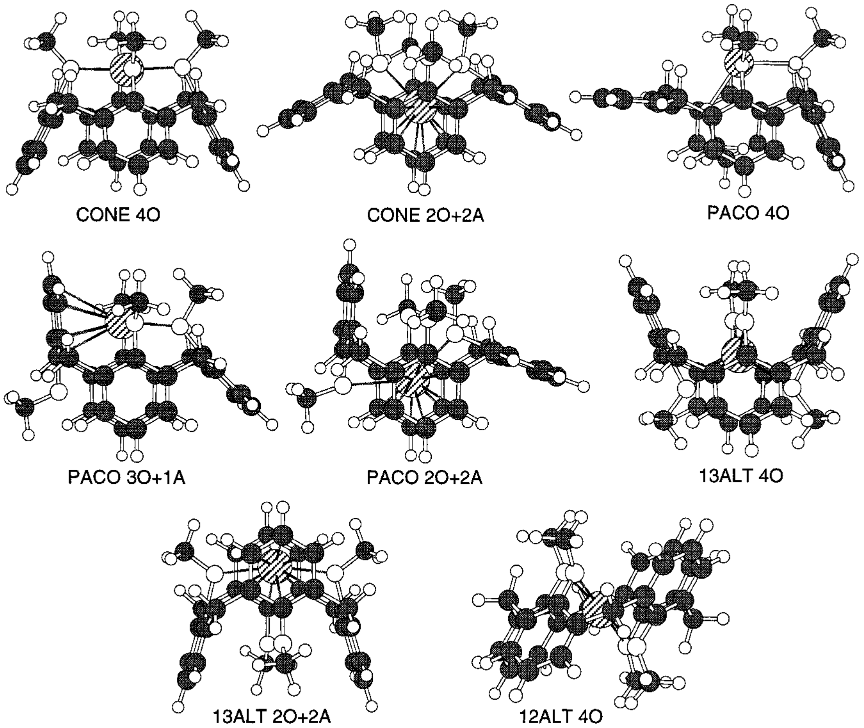

Figure 4. Tetradentate binding modes for the coordination of Na^+ by TMC located at the BLYP/6-31G** level of theory.

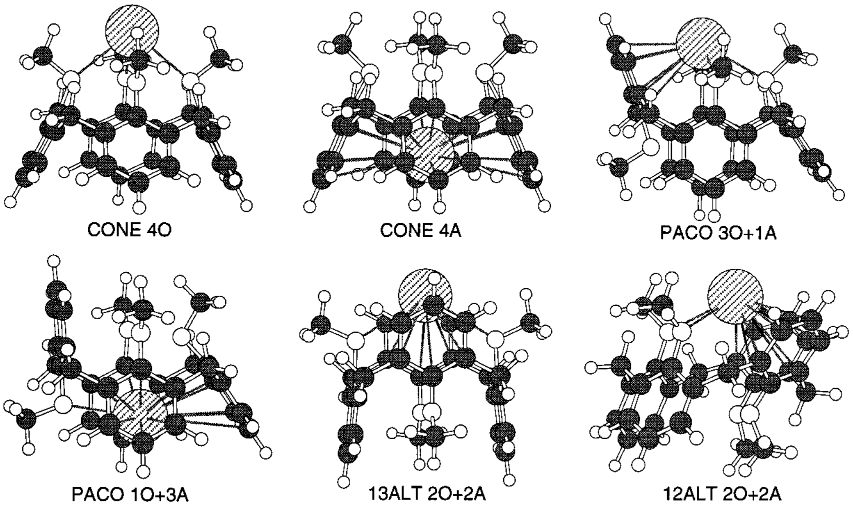

Figure 5. Tetradentate binding modes for the coordination of Cs^+ by TMC located at the BLYP/6-31G** level of theory.

13ALT 4A, 12ALT 4O, and 12ALT 2O+2A. In practice, the BLYP calculations yielded eight distinct binding modes for Na^+ (Figure 4) and six distinct binding modes for Cs^+ (Figure 5).

Of the three possible ways the CONE conformation could bind Na^+, only two resulted in stable complexes. The CONE 2O+2A binding mode is one of the most stable of all of the Na^+ complexes, as can be seen from the relative binding energies, ΔE_{rel}, shown in Table 1. The reference point for ΔE_{rel} is the lowest-energy conformation, which is the CONE 4O structure for MP2 and the PACO 2O+2A structure for BLYP. The CONE 2O+2A binding mode is found in a crystal structure of a Na^+ calixarene complex (Figure 1, R = OMe, OH, X = *tert*-butyl).[50] The calculations also predict that Na^+ forms a less stable CONE 4O complex. This binding mode has been observed in a Na^+ calixarene complex (Figure 1, R = OMe, X = *tert*-butyl).[51] The remaining CONE 4A geometry with Na^+ collapses to the CONE 2O+2A complex. Unlike Na^+, the larger Cs^+ does adopt a CONE 4A structure. This binding mode has been observed in a crystal structure of a Cs^+ calixarene complex (Figure 1, R = H, X = *tert*-butyl).[19] The CONE 4O conformation also binds Cs^+, but in contrast to the results for Na^+, it is the least stable of all of the Cs^+ complexes. The CONE 2O+2A geometry with Cs^+ collapses into the CONE 4A complex.

The PACO conformation has four possible binding modes, three of which result in stable Na^+ complexes. The most stable of these is the PACO 2O+2A, with PACO 3O+1A and PACO 4O being less stable. Optimizations of the PACO 1O+3A geometry with Na^+ give the PACO 2O+2A complex. For Cs^+, only two of the four possible PACO binding modes yield stable complexes. The PACO 1O+3A binding mode is the most stable of all the Cs^+ complexes, whereas the PACO 3O+1A mode binds Cs^+ weakly. Attempted optimizations of the PACO 4O

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Table 2. Comparison of BLYP and MP2 Results for M^+/Dimethyl Ether and M^+/Benzene[a]

		Na^+/DME		Na^+/benzene		Cs^+/DME		Cs^+/benzene	
basis set	method	ΔE	r_{NaO}	ΔE	r_{NaX}	ΔE	r_{CsO}	ΔE	r_{CsX}
6-31G**	BLYP	−30.0	2.197	−28.1	2.387	−11.6	3.130	−9.3	3.584
	BLYP(CP)	−26.8		−25.6		−9.9		−7.5	
aug-cc-pVDZ	MP2	−25.8	2.218	−25.3[b]	2.420[b]	−13.2	3.090	−13.0[c]	3.406[c]
aug-cc-pVTZ	MP2	−26.2	2.204	−24.7[b]	2.393[b]	−15.0	3.023	−15.3[c]	3.309[c]
aug-cc-pVQZ	MP2	−26.3	2.212	−25.0[b]	2.390[b]			−14.2[c]	3.313[c]

[a] Electronic binding energies (ΔE) are given in kcal/mol. For M^+/benzene complexes, r_{MX} is the distance between the metal cation and the center of the carbon ring. For the MP2 calculations on Na^+/DME and Na^+/benzene, the frozen core approximation the 1s pair of electrons on C, O, and Na, that is, the sodium (2s,2p) electrons were active. [b] Feller, ref 46. [c] Feller, et al., ref 47.

and 2O+2A geometries yield the 3O+1A and 1O+3A geometries, respectively. There are as yet no crystal structures of alkali cations bound to PACO conformations of simple tetraalkoxy-substituted calix[4]arenes. However, precedent for the PACO 4O and PACO 3O+1A modes is found in crystal structures of calix[4]crown ethers and calix[4]spherands with Na^+, K^+, and Rb^+.[52−55]

There are three possible binding modes for the 13ALT conformation. Of these, Na^+ forms the more stable 13ALT 2O+2A complex and the less stable 13ALT 4O complex. All attempts to optimize a 13ALT 4A geometry with Na^+ gave the 13ALT 2O+2A geometry. In contrast, the calculations predict that Cs^+ forms only a stable 13ALT 2O+2A complex. There are as yet no crystal structures of alkali cations with 13ALT conformations of simple tetraalkoxy-substituted calixarenes. However, precedent for the 13ALT 2O+2A binding mode is found in crystal structures of calix[4]crown ethers with cesium[12,13,56−59] and in a Na^+ complex (Figure 1, R = $CH_2C(=O)OEt$, X = *tert*-butyl).[60]

Finally, of the two possible binding modes of the 12ALT conformation, Na^+ forms only the 12ALT 4O complex, and Cs^+ forms only the 12ALT 2O+2A complex. There are as yet no crystal structures of alkali cation complexes with 12ALT conformations of any calix[4]arene. In summary, crystal data demonstrates the existence of several of our predicted binding modes, although others await experimental verification. In addition, there are no crystal data for either Na^+ or Cs^+ which show binding modes that the computations indicate are not stable.

Binding energies, ΔE, obtained at the BLYP and MP2 levels are listed in Table 1. When comparing ΔE values from the two methods, one should keep in mind that different TMC reference conformations were used for BLYP and MP2. Furthermore, although the BLYP binding energies have been corrected for BSSE, the MP2 values are without adjustment because, as previously mentioned, the raw MP2 binding energies for prototype systems were in better agreement with complete basis set estimates than the BBSE-adjusted values. In light of the previous calibration of MP2 binding energies with respect to higher-level coupled cluster theory results for similar chemical systems,[45−47] the MP2/aVDZ method applied here is expected to yield reliable binding energies. In comparison, the BSSE-corrected BLYP ΔE values are, on average, overestimated by 1.5 kcal/mol for Na^+ and underestimated by 11.2 kcal/mol for Cs^+. This behavior is consistent with calculations on smaller prototype systems, as illustrated by results for M^+/dimethyl ether (DME) and M^+/benzene shown in Table 2. When compared with the MP2/aVDZ method, the BSSE-corrected BLYP method yields Na^+ binding energies for the prototype complexes that are too strong by 1.0 kcal/mol with DME and 0.3 kcal/mol with benzene and yields Cs^+ binding energies that are too weak by 3.3 kcal/mol with DME and 5.5 kcal/mol with benzene.

Binding energies relative to that of the most strongly bound complex, ΔE_{rel}, are also reported in Table 1. Despite the fact that the BLYP method significantly underestimates the strengths of the Cs^+−oxygen and Cs^+−arene interations, the relative stability order for all Cs^+ complexes is the same at both levels of theory, with the PACO 1O+3A complex being the most stable. In contrast, the relative stabilities for the Na^+ complexes are dramatically altered at the two levels of theory. For example, BLYP finds the CONE 4O to be the most stable, whereas MP2 finds the PACO 2O+2A to be most stable, which represents a change in relative binding energy of 12.6 kcal/mol! Only 1.0 kcal/mol of this difference can be attributed to changes in the relative energies of the bare TMC conformers (vide supra). Moreover, because the origin of this difference does not appear to lie with the fundamental Na^+−oxygen and Na^+−arene interactions, we speculate that BLYP may not properly account for repulsive nonbonded interactions[61,62] induced within TMC upon metal ion binding.

The ΔE_{rel} values include the cost of conformational reorganization and, thus, reflect the relative stabilities of the TMC complexes when the ligand is conformationally mobile. After correction for entropic contributions arising from rotational and conformational degeneracy,[63] we can use the ΔE_{rel} values to predict the gas-phase populations (%) that would result if TMC were completely saturated with either cation. If the vibrational entropy is assumed to be constant, relative free energies of the cation complexes are obtained from ΔE_{rel} after correction for conformational and rotational degeneracy with $\Delta G_{rel} = \Delta E_{rel} + RT \ln(\sigma/n)$, where T is 298 K, σ is the symmetry number, and n is the conformational degeneracy.[63] The theoretical results predict that Na^+ would be a mixture of two binding modes, the PACO 2O+2A (88%) and the CONE 2O+2A (12%), and Cs^+

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would be predominantly (99.99%) in the PACO 1O+3A mode with a minor contribution (0.01%) from the 13ALT 2O+2A mode.

These predictions are consistent with NMR studies of the effect of added salts on the conformational equilibria of calix[4]arenes. In the absence of salts, CD_3Cl:CD_3CN solutions of tetramethoxycalix[4]arenes (Figure 1, R = methyl, X = H or *tert*-butyl) contain mixtures of conformers in which the major forms are the CONE (15−35%) and the PACO (60−80%), and the minor forms are the 13ALT (0−5%) and the 12ALT (0−5%).[64−66] Addition of $Na^+ClO_4^-$ to CD_3Cl:CD_3CN (9:1, v/v) solutions of TMC causes a decrease in PCONE concentration and an increase in the CONE conformation with the appearance of new peaks that can be assigned to a Na^+−CONE complex.[64] With addition of the more soluble $Na^+BF_4^-$ to CD_3Cl:CD_3CN (1:1, v/v), it is possible to drive the equilibrium completely to a single Na^+ CONE species (Figure 1, R = methyl, X = *tert*-butyl).[65] Our results indicate this species to be the CONE 2O+2A structure. Although the calculations predict that the Na^+ PACO 2O+2A complex would be populated in the gas phase, the failure to observe this species in solution is consistent with a stabilization of the more polar CONE over the less polar PACO complex expected in dielectric media.[64] The addition of $Cs^+I_3^-$ to a CD_3Cl:CD_3CN (1:1, v/v) solution containing calix[4]arene (Figure 1, R = methyl, X = *tert*-butyl) results in the disappearance of all free calix[4]arene and the formation of two Cs^+ complexes, a PACO form (∼80%) and a 13ALT form (∼20%).[66] Our theoretical results indicate these species to be Cs^+ complexes in the PACO 1O+3A and 13ALT 2O+2A binding modes.

The ability of a set of donor groups to interact with a metal ion is, to a large extent, controlled by the structure of the host.[67−71] Therefore, an important aspect of the effort to design metal ion receptors with enhanced binding affinity is the identification of host structure that provides the strongest interaction with the targeted guest. The effort to increase selectivity of the receptor for one metal ion over another involves the identification of a structure that provides strong interaction with the targeted metal and prevents strong interaction with competing metals. As has been demonstrated in a number of prior examples,[72−84] it is possible to evaluate the degree to which a host structure complements a metal ion through an analysis of isolated, that is, gas phase, structures and, on the basis of such analyses, to rationalize the influence of host structure on metal ion binding affinities in solution.

So far, we have considered the binding energy of each M^+(TMC) complex relative to the optimal geometry of bare TMC. Because the addition of appropriate functional groups to the macrocycle often is used to synthesize TMC derivatives that are preorganized for binding, another quantity of interest is the binding energy relative to TMC when locked in the conformation it possesses in the complex. These values, denoted ΔE_{comp} in Table 1, provide a quantitative measure of the degree of cation *complementarity*[85] associated with each binding mode. More specifically, ΔE_{comp} is defined as the total energy of the complex minus the energy of the cation and the *binding* conformer of the free ligand and is reported relative to the most strongly bound complex. Examination of Table 1 reveals that the three most complementary receptor sites for Na^+ are provided by the 12ALT 4O, CONE 2O+2A, and 13ALT 2O+2A binding modes, whereas the three most complementary receptor sites for Cs^+ are provided by the 12ALT 2O+2A, PACO 1O+3A, and 13ALT 2O+2A binding modes.

Experimental evidence to support our theoretical ranking of binding mode complementarity is provided by a study of 1,3-dimethoxycalix[4]crown-6.[13] In the absence of cations, this molecule exists as a mixture of three conformers in $CDCl_3$: 60% CONE, 25% PACO, and 15% 13ALT. There are only three calixarene binding modes that allow a large cation such as Cs^+ to simultaneously contact the crown ether oxygen donors and the calixarene donor groups: CONE 4O, PACO 3O+1A, and 13ALT 2O+2A. Of these three modes, only the 13ALT 2O+2A provides a complementary architecture for Cs^+ (see Table 1). In full agreement with the theoretical results, the ^{1}H NMR reveals a shift in conformational equilibria to >95% 13ALT form when Cs^+ is present. Moreover, when this architecture is modified to obtain the conformationally inert 1,3-dipropoxycalix[4]crown-6 in the form *with the lowest* Cs^+ *complementary*, CONE, Cs^+ complexation is too weak to measure. When this same structure is isolated as the conformationally inert conformation *with the highest* Cs^+ *complementary of the three possible binding modes*, 13ALT, the Cs^+ binding constant increases by 2 orders of magnitude in comparison to the conformationally mobile form.

A strategy for the rational design of more effective and selective calixarene hosts is to choose structural modifications that (1) constrain the macrocycle to a conformation that favors binding, (2) provide additional binding sites to augment the interactions of the targeted binding mode, and (3) weaken or eliminate any alternate binding modes that may be preferred by competing guests. The results herein suggest how this strategy could be used in the development of new calix[4]arene receptors that are selective for Cs^+ in the presence of Na^+. For example, with the proper choice of substituents, such as replacing two adjacent −OR groups with −R groups, it should be possible to prepare a 12ALT conformation that is preorganized to the most complementary binding mode for Cs^+, 12ALT 2O+2A, and that does not adopt the 12ALT 4O binding mode

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preferred by Na^+. Replacement of $-OR$ groups with $-R$ groups should result in only slightly reduced cation−arene binding. Preliminary calculations of Na^+ binding the arene ring of methoxybenzene and toluene give binding energies of −26.7 and −26.3 kcal/mol, respectively, a difference of only about 2%. Modifications to the two $-OR$ substituents could be explored to introduce additional donor sites that are complementary to the geometry of the Cs^+ 12ALT 2O+2A binding mode. Similar strategies could be pursued with other conformers, for example, enhancement of the PACO 1O+3A mode while eliminating the PACO 2O+2A mode or enhancement of the CONE 4A mode, while eliminating the CONE 2O+2A modes.

Summary

Our theoretical analysis of the alkali cation binding modes of a simple calix[4]arene scaffold shows that the coordination chemistry of calix[4]arene is considerably more complex than previously recognized. Of 12 potential tetradentate binding modes, 11 have been verified by theoretical calculations and ranked in terms of their relative stability and complementarity for Na^+ and Cs^+. The structures and relative binding energies are fully consistent with available data from crystallographic and ^1H NMR studies. In a number of cases, conformer binding modes with predominant arene coordination form stronger complexes than those with predominant oxygen coordination, which further confirms the importance of the arene as a donor for the alkali cations. The results reveal that a rational approach to the design of a calixarene-based receptor must not only account for the selection of macrocycle conformation, but also must account for the different ways that a given conformation can interact with the guest. The contrasting binding modes observed for Na^+ and Cs^+ suggest new approaches for designing cation selective calix[4]arenes.

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Supporting Information Available: Two tables giving total energies, relative energies, BSSE, and BSSE-corrected relative energies at the BLYP/6-31G** level of theory. Two tables giving total energies and relative energies at the MP2/aVDZ level of theory. Cartesian coordinates (Å) and point-group symmetry for the BLYP/6-31G**-optimized structures of the Na^+ and Cs^+ TMC complexes and the bare TMC conformers. This material is available free of charge via the Internet at http://pubs.acs.org.

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