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Cation Affinities of [1_6]Starand Model. Comparison with 12-Crown-4: Crucial Role of Dipolar Moiety Orientations

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[1_6]Starand appears to be a promising ionophore because of its rigid structure with the spherical cavity into which Li^+ can fit perfectly. Using ab initio calculations, we investigated if the starand model has strong affinity as well as high selectivity for Li^+, compared to 12-crown-4 of almost the same cavity size. Li^+ favors the external binding (binding outside of the cavity) for the [1_6]starand model. The ion−dipolar moiety interactions are found to be the main factors affecting the preference of external binding in the starand model. When a cation is located at the center of the starand model, the out-of-plane bending angle of a cation from the plane of the ketal moiety is more than 90°, resulting in unfavorable energetics. By the same reasoning, the somewhat flexible 12-crown-4 structure, upon complexation with Li^+ and Na^+, drastically orients itself into a volcano structure with four oxygen atoms on the top so as to have favorable ion−dipolar moiety orientations with the cation located above the volcano. Therefore, in addition to the host−guest size complementarity, the ion-dipolar moiety orientations should be very important in designing novel ionophores.

I. Introduction

The study of cation−ionophore binding is one of the fundamental subjects for understanding molecular recognition.[1] In the last few decades, numerous hosts have been synthesized, and their complexation with various cations has been investigated.[2] It is well-established that host−guest size complementarity is very important.[3] In an evolutionary course of metal cation−ionophore chemistry, diverse hosts were extensively investigated starting from crown ethers to cryptands to spherands, and the structural rigidity of the hosts has been considerably increased. As for these ionophores, more rigid ionophores have stronger affinities as well as higher selectivities in general.[4] Recently, Lee et al. synthesized unexpected polyketals with 2*n*-crown-*n* moieties, which are named as starands, though their target molecules were polyketones, so-called ketonands.[5] The starands should not be categorized as crown ethers, because the two systems are quite different chemically.[6] Starands can be considered as one of the most rigid ionophores with the most spherical cavity. Li^+ fits perfectly into the cavity of [1_6]starand.[7] Therefore, one may anticipate that this molecule would show high affinity and high selectivity for Li^+.

In general, strong affinity and high selectivity are very desirable characteristics for various applications of ionophores. One of the most important factors for high selectivity would be high structural rigidity of a host molecule. For better complexation, the binding sites and steric barriers in potential host−guest partners must be complementary to one another in electronic character and geometric arrangement.[3a] However, besides the host−guest size complementarity, factors affecting affinity are not well-studied due to complicated environmental effects which are associated with most experimental conditions.[8]

There have been a number of theoretical studies about ionophores such as ab initio calculations, molecular mechanics, molecular dynamics, and Monte Carlo simulations.[9−11] As yet, a simple but clear concept beyond the host−guest size complementarity and structural rigidity has not been exploited significantly in designing ionophores. In this regard, the interaction potentials used in molecular mechanics have been useful. For example, carbonyl orientations toward a cation have been noted in various studies such as membrane channels. Recently, Hay et al.[12a,b] studied aliphatic ether complexes of alkali and alkaline earth cations (M) using MM3 force field and Hartree−Fock (HF) calculations using the STO-3G basis sets. They found that Hartree−Fock calculations on $M-O(Me)_2$ and $M-O(Me)(Et)$ revealed a preference for trigonal planar geometry when aliphatic ether oxygens are coordinated to alkali and alkaline earth cations. The study implied that a ligand structure satisfying its preference for trigonal planar geometry has a greater effect on complex stability than a structure satisfying its preference for the optimized M−O distances. More, Ray, and Armentrout[12c,e] reached similar conclusions in studies of the dissociation energies of Na^+ complexes of dimethyl ethers, 1,2-dimethoxyethane, and 12-crown-4. In the past, electrostatic interactions of cations with negatively charged atoms (O or N) in ionophores have been harnessed extensively as the main criteria for designing novel ionophores, while the energetically favored orientations of the dipoles toward the cation have not been seriously exploited. In the case of rigid ionophores such as starands, the reorientations of their ketal moieties toward a cation are not feasible, so the cation has to orient itself into an energetically favorable binding site. Particularly the electrostatic interaction energy between the ketal moieties in the [1_6]starand was surprisingly negative (i.e., attractive force) due to the head-to-tail dipole orientations.[6] In this regard, we investigated the affinity and selectivity of [1_6]starand model for alkali metals (Li^+ and Na^+) in comparison with those of 12-crown-4, because both [1_6]starand and 12-crown-4 have nearly the same cavity size. To understand the interaction between cation and ionophore independent of environmental effects (i.e., solvent effect, counterion effect, etc.) with modest reliability, we employed quantum mechanical methods as a tool to investigate the intrinsic

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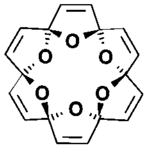
TABLE 1: Interaction Energies and Geometries of the Ionophores and Complexes[a]

		HF/{6-31+G*}		MP2/6-31+G*//HF					
		Δ*E*	BSSEC	Δ*E*	BSSEC	(Ct−O) M···O	M···O	(ϕ°) ϕ	ϕ'
1	D_{3d}	0.0				(1.883)		(96.0)	
1·Li$^+$	D_{3d}	−79.9	−76.6			1.883		92.5	
1·Li$^{+\prime}$	C_{3v}	−92.6	−90.4			1.904[b]	2.986	41.2	125.8
1·Na$^+$	D_{3d}	10.3	13.8			1.986		95.7	
1·Na$^{+\prime}$	C_{3v}	−66.3	−64.2			2.278[b]	3.484	30.7	130.5
2	S_4	0.0				(1.986)		(97.8)	
2·Li$^+$	D_{2d}	−90.1	−86.7	−98.9	−82.4	1.855		60.0	
2′·Li$^{+\prime}$	C_4	−91.3	−88.8	−97.8	−86.8	2.001		47.8	
2·Na$^+$	D_{2d}	−29.3	−26.3	−36.8	−21.6	2.080		79.2	
2′·Na$^{+\prime}$	C_4	−65.4	−63.4	−70.7	−61.4	2.341		42.9	

[a] Energies are in kcal/mol, distances in angstroms, angles in degrees. **M** denotes **Li**$^+$ or **Na**$^+$. **Ct** denotes the center of the ionophore. **M···O/Ct···O** is the distance between the metal ion/center and oxygen. $\phi/\phi°$ is the supplementary angle between the **M···O/Ct···O** vector and the **C−O−C** plane; ϕ' is the supplementary angle only for the lower three O atoms in the starand. **MP2** calculations were done at the **HF**-optimized geometries. See the text for the basis set. [b] **M···O** distances for the upper three **O** atoms. The **M···O** distances for the lower three **O** atoms are 2.986 Å for **1·Li**$^{+\prime}$ and 3.484 Å for **1·Na**$^{+\prime}$.

factors affecting the cation affinity as well as selectivity using a Gaussian 94 suite.[13]



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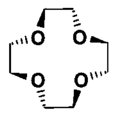

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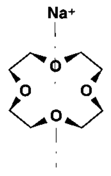

2′

II. Calculation Method

All the structures were fully optimized by HF calculations. The 6-31+G* basis set was employed for all the atoms except for the double-bonded carbon atoms situated on the rim of the model starand for which a 6-31G* basis set was used. This mixed basis set will be denoted as {6-31+G*}. In the cases of crown ethers and their complexes, Möller−Plesset second-order perturbation (MP2) calculations were also performed on the HF/6-31+G*-optimized geometries. Basis set superposition error correction (BSSEC) was also considered.[14]

The predicted binding energies and geometrical parameters of the metal−oxygen distances (M···O) and the out-of-plane bending angles (ϕ^o/ϕ) of the Ct···O/M···O vectors from the C−O−C planes of the dipolar moieties are listed in Table 1, where Ct denotes the ionophore center. The MP2 energies are found to be consistent with the HF energies.[15] In the following discussion, for comparative purpose, binding energies (−Δ*E*) are reported with the HF/{6-31+G*} values with BSSEC.

III. Results and Discussion

In the present study, we investigated the starand model (**1**), since we have already reported that this model can well represent [1_6]starand.[6] Upon complexation with cations, the starand model is found to have two binding sites: one at the center (internal binding) and the other out of the cavity on the C_3 axis (external binding). These two complexes will be denoted as **1·M** and **1·M′** (Figure 1), respectively, where M denotes Li$^+$ or Na$^+$. Seidl and Schaefer[16] studied various configurations of 12-crown-4, reporting that S_4 conformation (**2**) is the global minimum energy structure at the DZ+d self-consistent-field level. Thus, we optimized the structures of the neutral 12-crown-4 and its cation complexes under S_4 symmetry using the 6-31+G* basis set. Upon complexation with cations, the structures changed to D_{2d} symmetry, which will be denoted as **2·M**. To study the influence of the dipole moiety orientations to the binding site of the 12-crown-4 with cation, we also studied the case of the external binding under C_4 symmetry because crystal structures of many cation complexes of 12-crown-4 show C_4 symmetry. Ray[12e] et al. also reported an ab initio structure of the Li$^+$ complex of 12-crown-4 under C_4 symmetry. Indeed, we find that the 12-crown-4 of S_4 symmetry and Li$^+$-complexed 12-crown-4 of C_4 symmetry are the most stable conformers. The geometrical parameters of 12-crown-4 and its complex with Li$^+$ are very close to those of Ray's results. This metal-complexed structure of C_4 symmetry will be denoted as **2′·M′**, which have a volcano shape with four oxygen atoms on the top and the cation located above the volcano (Figure 1).

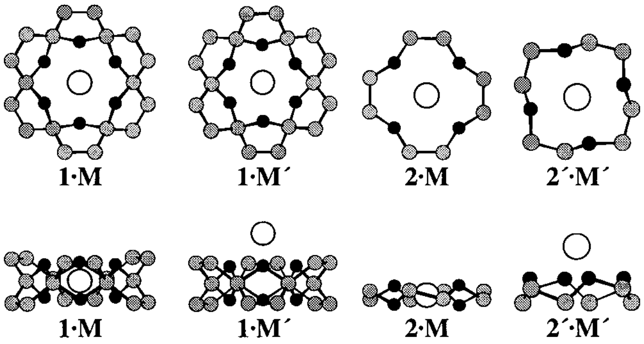

Figure 1. Selected structures of starand, 12-crown-4 and their cation complexes (top views in 1st row and side views in second row). All H atoms are removed to improve visualization. Black solid circles denote O atoms; shaded circles, C atoms; unfilled circles, cations.

For **1** and **2**, the distances from the center to the oxygen atoms (Ct···O) are 1.883 and 1.986 Å, respectively, and the out-of-plane bending angles ϕ^o of the center from the plane of the ether moiety are 96° and 98°, respectively.

The binding energies for **1·Li**$^+$ and **1·Na**$^+$ are 77 and −14 kcal/mol, respectively. The negative binding energy for **1·Na**$^+$ is partly attributed to the exchange repulsions between Na$^+$ and O atoms (i.e., the cavity size of **1** is small to accommodate Na$^+$, which can be noted from the Ct···O distance (1.986 Å) enlarged by 0.103 Å). When Li$^+$ is bound at the center of cavity, the Ct···O distance is reduced by 0.0003 Å. Therefore, Li$^+$ perfectly fits into the cavity. The binding energy of Li$^+$ with **2** (i.e., **2·Li**$^+$) is 89 kcal/mol. The binding energy for the internal binding of **1·Li**$^+$ (77 kcal/mol) is small compared to crown ethers against our expectation. Therefore, we tried to locate other binding sites, as addressed earlier. At the distance of 0.89 Å from the upper plane of the three oxygens along the C_3 axis, Li$^+$ is bound externally to **1**. The binding energy of this external binding of **1·Li**$^{+\prime}$ is 90 kcal/mol. Then, the binding

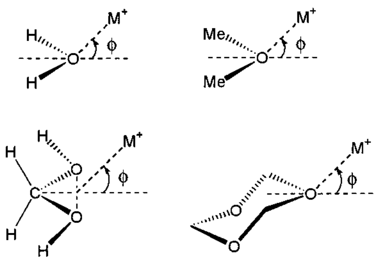

Figure 2. Out-of-plane bending angles ϕ between cations and dipole moieties of the model compounds.

affinity of **1** for Li^+ has a value comparable to those of **2** and 18-crown-6. Similarly, the binding energy of **1·Na**$^{+\prime}$ is 64 kcal/mol. Although the binding energies of Li^+ and Na^+ bound to the center of **1** are small and even negative, those to the external bindings are reasonably large. This is a surprising result, not only because Li^+ fits the starand model cavity size perfectly, but also because Li^+ is coordinated by six negatively charged O atoms at the center of cavity, but only by three ones at the outside of the cavity. Even though the size of the host cavity encompasses the size of the guest perfectly, the central binding with more coordination number is much less favorable than the external binding with less coordination number. Therefore, the complexation of **1** with Li^+ cannot be explained satisfactorily by the principle of host−guest size complementarity. Then, it is natural to investigate the contribution of the electronic effects on the model starand system. In this regard, the energetics based on various existing molecular mechanics potential parameters[17] as well as Hay's HF/STO-3G energy profiles for the M−O(Me)$_2$ and M−OMeEt are very helpful.

To elucidate the effect of the dipole orientations, we investigated the complexation energies of Li^+ and Na^+ with 1,3,5-trioxane ($C_3H_6O_3$) whose C−O−C moiety was taken into account as a building unit of the starand, and with Me_2O, H_2O, and $CH_2(OH)_2$ using the 6-31+G* basis set for comparative purpose. The out-of-plane bending angle of a cation from the C−O−C plane (for trioxane and dimethyl ether) or H−O−H plane (for water) is defined as the angle ϕ, and the corresponding definition of angle ϕ for gem-diol is shown in Figure 2. For trioxane, we fully optimized the neutral structure first, then optimized only the M···O distance to estimate the metal−trioxane interaction energies at the corresponding fixed angle ϕ, and for others, the structures were fully optimized in the constraint of C_s symmetry at the corresponding fixed angle ϕ. Figure 3 shows the variation of the energy against the angle (ϕ) relative to the energy of the planar structure ($\phi = 0°$). For $CH_2(OH)_2$, the relative energies are taken as half the real value in order to obtain the interaction energy due to only one oxygen, because there are two oxygen atoms in $CH_2(OH)_2$. At $\phi = 0°$, the interaction energies of Li^+ and Na^+ with 1,3,5-trioxane are −31.4 and −20.5 kcal/mol, respectively; those of $CH_2(OH)_2$ due to one oxygen atom are −27.9 and −21.0 kcal/mol; those of Me_2O are −39.6 and −26.8 kcal/mol; those of H_2O are −36.6 and −26.2 kcal/mol, respectively. Although the interaction energies of model compounds with Li^+ and Na^+ are quite different, their interaction energy changes against the angle ϕ are somewhat similar. Since for all model compounds in the current study the interaction energies at $\phi = 0°$ are at least 13 kcal/mol more stable than those at $\phi = 90°$ and there are six dipolar moieties in [1_6]starand model and four dipolar moieties in 12-crown-4, the dipolar moiety orientations should play a very important role in the binding.

To elucidate the role of dipolar moiety orientations, it is necessary to decompose the total interaction energy (ΔE_{HF}) into a few important components. Many studies have been done to derive the atom−atom pair interaction potentials for various systems. For example, Smith et al. successfully reproduced the ab initio complex energies for the ion−single-ligand complexes using a simple atomistic force field with two body potential functions.[18] In our study, the total interaction energy is approximately estimated from the decomposed components: $\Delta E_{HF} \doteqdot \Delta E_{sum} = \Delta E_{dipole} + \Delta E_{exch} + \Delta E_{deform}$. Here, ΔE_{dipole} is the interaction energy between the dipolar moieties and cation, ΔE_{exch} is the exchange repulsion energy, and ΔE_{deform} is the energy difference between the original fully optimized host and the deformed host upon complexation with a cation. The short-range exchange repulsion energy is approximately expressed as inversely proportional to the 12th power of distance r. By combining these results with additional ab initio calculations, the exchange energy of ΔE_{exch} between the metal cation and the oxygen atom was estimated.[19] The electrostatic energy is governed dominantly by the interactions between the dipolar moiety and the cation, due to negligible monopole−cation interactions in neutral ionophores. But, it is difficult to estimate the pure ΔE_{dipole} from the cation complex of model starand (**1**)

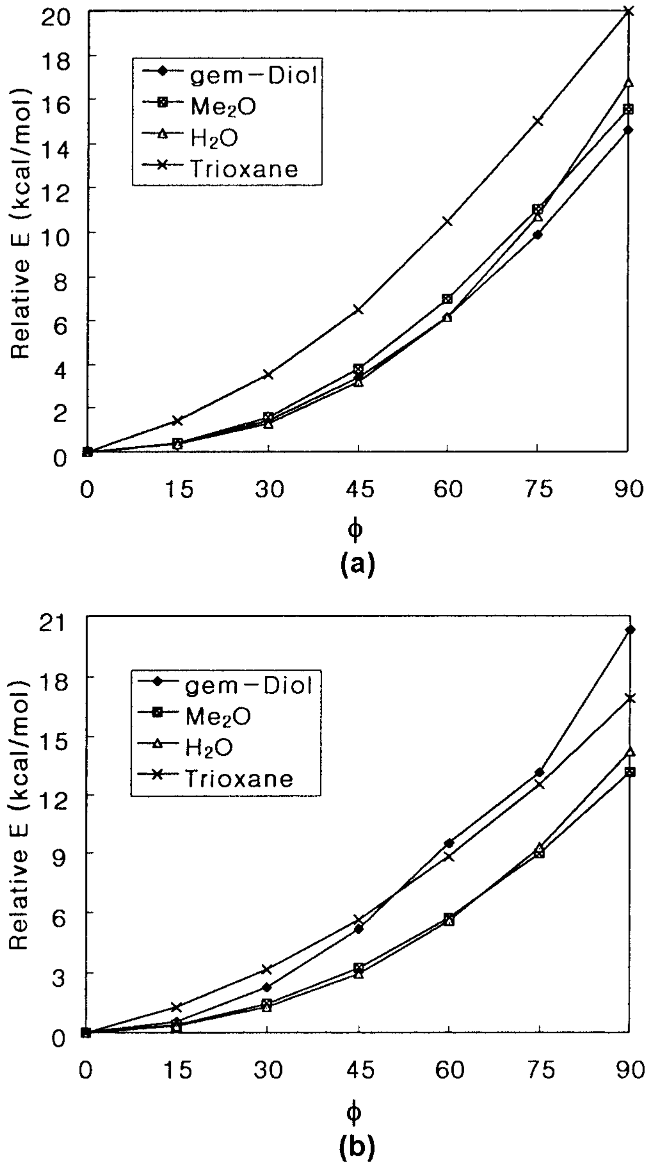

Figure 3. HF/6-31+G*-predicted relative energy vs the out-of-plane bending angle ϕ in the complexes of the model compounds with Li^+ (a) and Na^+ (b).

TABLE 2: Energy Components for the Interaction Energies[a]

	ΔE_{HF}	ϕ	$\Delta E_{\mathrm{align}}$	ΔE_{bend}	(E_{dipole})	ΔE_{exch}	$\Delta E_{\mathrm{deform}}$	(ΔE_{sum})
1·Li$^+$	−79.9	92.5	−188	122	(−66)	7	8	(−51)
1·Li$^{+\prime}$	−92.6	41.2	−94	17	(−77)	3	4	(−70)
1·Na$^+$	10.3	95.7	−123	102	(−21)	34	22	(+35)
1·Na$^{+\prime}$	−66.3	30.7	−62	10	(−52)	3	2	(−47)
2·Li$^+$	−90.1	60.0	−158	28	(−130)	5	13	(−112)
2′·Li$^{+\prime}$	−91.3	47.8	−158	16	(−142)	2	16	(−124)
2·Na$^+$	−29.3	79.2	−107	41	(−66)	13	12	(−41)
2′·Na$^{+\prime}$	−65.4	42.9	−107	12	(−95)	3	11	(−81)

[a] Energies are in kcal/mol. ΔE_{HF} is the HF/{6-31+G*}-predicted ΔE. See the text for notations.

or 12-crown-4; thus, we estimated the $\Delta E_{\mathrm{dipole}}$ of model starand complexes from the interaction energy of the metal cation with trioxane and the $\Delta E_{\mathrm{dipole}}$ of 12-crown-4 complexes from the interaction energy of the cation with ether (Me_2O) (i.e., trioxane was taken as the building unit of model starand, and Me_2O was taken as the building unit of 12-crown-4). Consequently, as a simple approach, $\Delta E_{\mathrm{dipole}}$ can be obtained from the product of interaction energy of each cation per building unit with the number of the C−O−C moietites directly bound to the cation; $\Delta E_{\mathrm{dipole}}$ is estimated from $\Delta E_{\mathrm{align}}$ and ΔE_{bend}, which are respectively the interaction energy of the cation with the aligned dipolar moiety ($\phi = 0°$) and the energy required to bend the dipolar moiety orientation by ϕ ($\Delta E_{\mathrm{dipole}} = \Delta E_{\mathrm{align}} + \Delta E_{\mathrm{bend}}$). The ΔE_{bend} is estimated directly from the energy profile in Figure 3. The estimated values are shown in Table 2.

As shown in Table 2, the estimated interaction energy (ΔE_{sum}) between the cation and host molecule shows overall consistency with the HF-predicted interaction energy (ΔE_{HF}). Table 2 clearly shows that, although $\Delta E_{\mathrm{deform}}$ and ΔE_{exch} become significant when the size complementarity is important, $\Delta E_{\mathrm{dipole}}$ plays the dominating role in describing ΔE_{HF}. Therefore, the preference of the external binding is clearly noted from the values of $\Delta E_{\mathrm{dipole}}$. For example, in the case when the Li^+ ion fits well in the ionophore cavity, the difference in ΔE_{HF} or that in ΔE_{sum} between **1·Li**$^+$ and **1·Li**$^{+\prime}$ arises mostly from that in $\Delta E_{\mathrm{dipole.}}$ In the case when the Na^+ ion is slightly larger than the cavity size, the difference in ΔE_{HF} or that in ΔE_{sum} between **1·Na**$^+$ and **1·Na**$^{+\prime}$ arises from those in $\Delta E_{\mathrm{dipole}}$ and ΔE_{exch}. In both Li^+ and Na^+ cases, the interal complexation has very large ΔE_{bend} due to large ϕ, while the external complexation has very small ΔE_{bend} due to small ϕ.

The 12-crown-4 also shows a similar trend as shown in the model starand. Since the Li^+ ion fits well for the 12-crown-4 cavity and the ether moieties are somewhat flexible, the internal complex has slightly larger ΔE_{bend} (due to slightly larger out-of-plane bending angle ϕ) than the external complex (i.e., 60° vs 48° for ϕ). In the case when the Na^+ ion is slightly larger than the cavity size, the structural change required for 12-crown-4 is beyond the limits of its flexibility, so that the internal complex has energetically unfavorable distortion angle ϕ (79°). Thus, the external complex is favored. In particular, in this case, since the 12-crown-4 is somewhat flexible, it changes the S_4 symmetry structure to the C_4 symmetry structure by transforming its conformation into a volcano-like shape so as to make favorable dipolar moiety orientations ($\phi = 43°$). These results vividly demonstrate the crucial role of the dipolar moiety orientations in the conformational energetics of ionophores upon complexation with cations. Thus, to design ionophores with large affinities for cations, favorable orientations of dipolar moieties toward the cation binding site are highly desirable.

The binding energy difference between **1·Li**$^{+\prime}$ ($-\Delta E = 90$ kcal/mol) and **1·Na**$^{+\prime}$ ($-\Delta E = 64$ kcal/mol) is only 26 kcal/mol, and that between **2′·Li**$^{+\prime}$ ($-\Delta E = 89$ kcal/mol) and **2′·Na**$^{+\prime}$ ($-\Delta E = 63$ kcal/mol) is 26 kcal/mol. Therefore, the affinity and selectivity of [1_6]starand model for Li^+ is not so high as we expected because the alkali metals cannot bind at the center. Nevertheless, the affinties and selectivities of the starands model toward cations are yet still similar to those of 12-crown-4, as long as we are concerned with the intrinsic interaction energy. Then, in comparing the affinities and selectivities of starands with crown ethers in solvents, the solvent effect would be important in comparing with starand and crown ether systems, because the starand is a peculiar ionophore with almost spherical rigid structure having head-to-tail dipolar moiety orientations. This interesting study is in progress in this laboratory.

IV. Concluding Remarks

Despite the promising features of the starands model which have most spherical compact cavities and rigid structures, their internal complexes with cations do not show large affinities for cations due to unfavorable dipolar moiety orientations. Thus, the external complexes are more stable. For external complexations, the starand model behaves as a reasonably good ionophore which is equivalent to the crown ethers. In 12-crown-4, to have better favorable dipolar moiety orientations, the structure transforms itself from the S_4 symmetry to C_4 symmetry structure. This concretely validates the trend of ion−dipole orientations toward a coplanar structure in molecular mechanics. In conclusion, the ion−dipolar moiety orientations can play a dominant role in conformational energetics of ionophores upon complexation with ions, and somewhat flexible ionophores can change even its own structure to have better dipolar moiety orientations when the out-of-plane bending angle ϕ is very large. Therefore, in addition to the host−guest size complementarity, the utilization of the ion−dipolar moiety orientations should be very important in designing novel ionophores. Indeed, this concept has been applied to design novel amphi-ionophores having large affinities for both cations and anions.[20]

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Supporting Information Available: HF/{6-31+G*} optimized geometries and energies of **1** and **2**, as well as these complexes with Li^+ and Na^+ (5 pages). Ordering information is given on any current masthead page.

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(7) The diameters of Li$^+$ and O$^-$ are 1.3 and 2.6 Å, respectively, and the distances between two diagonal oxygen atoms for 12-crown-4 (S$_4$) and model starand (D_{3d}) are 4.0 and 3.8 Å, respectively. Furthermore, the presence of Li$^+$ dose not alter the size of the cavity of the model starand (the actual change is only 0.0003 Å decrease). This discussion follows in the text.

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