The Effect of Donor Atoms on the Complexation of Alkali Cations With Spherands: A Density Functional Investigation

SHABAAN A. K. ELROBY
Department of Chemistry, Faculty of Science, Beni-Suef University, Egypt

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ABSTRACT: Spherands are highly preorganized hosts composed of methoxy 1, fluoro 2, and cyano 3 benzene units attached to one another at their 2,6-positions. Density functional theory calculations were used to investigate the complexation between these spherands and alkali metal ions (Li⁺, Na⁺, and K⁺) to understand the intrinsic factors affecting cation complexation. A comparison of binding energies for these spherands shows that, this order O–Me ⪪ F ⪪ CN. Although anisyl units are basically poor ligands for metal ions, the rigid placements of their oxygen during synthesis rather than during complexation are undoubtedly responsible for the enhanced binding and selectivity of the spherand. The ion–dipolar moiety interactions are found to be the main factors affecting the preference of external binding in the CN-spherands. © 2009 Wiley Periodicals, Inc. Int J Quantum Chem 109: 1515–1521, 2009

Key words: spherands; DFT; complementarity; preorganization; donor group orientation

Introduction

In host–guest complexation, the concave surface of a host complements the convex surface of a guest. Similarly, the receptor sites of enzymes frequently contain rigid cavities whose internal surfaces complement the convex surfaces of substrates or inhibitor [1]. To imitate nature’s complexes, hosts that contain enforced concave surfaces of substantial dimensions must be designed and synthesized. The spherands [2], exemplified by Chart 1 are a specific type of cavitand. Unlike the chorands (crowns) or cryptands, they contain rigid cavities formed during their syntheses rather than during their complexation. The spherands’s preorganization resulted in the highest binding and selectivity yet observed for the alkali metal ions [3, 4]. Much has been done and written with respect to understanding the factors that control metal ion
binding affinity with ligands [5–14]. Ligand design consists essentially of selecting appropriate donor atoms for the target metal ion, and then connecting that number of them appropriate for the coordination number of the metal ion in an architecture that satisfies the geometric requirements of the metal ion. The principle of size-match selectivity was first proposed based on the behavior of 18-membered ether macrocycles such as 18-crown-6 [15]. However, subsequent studies have established this be-
A comparison of the conformations of the 24-membered cyclic hosts, octafluorocavitand [20], octamethoxyspherand [21], and octacyanospherand [22], is instructive. The nonbinding octafluoro compound (2) exists in the conformation (u-m-d-m), with D_{2d} symmetry (evidence from ^19F NMR), which minimizes its cavity size. The octamethoxy host 1 has the square-antiprismatic oxygen arrangement (u-d)_x with its methoxy methyls at 12 and 6 o’clock turned inward to partially fill its cavity and provide C_{2v} symmetry. From this studies, the authors concluded that, for the maintenance of conformational stability of 24-membered carbocycles of this type, CN > OCH3 > F as inward-oriented substituents.

The present work addresses a comparison of the binding energies of the metacyclophane ring spheras towards alkali metals (Li^+, Na^+, and K^+) in the gas phase.

An ab-initio studies concerning the spheras compounds are very rare [23–25], presumably due to the large size of these hosts. Furthermore, ab-initio studies in gas phase would give a zero-order yet valuable opportunity to understand the intrinsic factors affecting the complexation without including the effects of solvation.

To understand the complexation of the spheras, we have undertaken a density functional theory (DFT) study of the effect of donating groups on the behavior of the spheras upon complexation with Li^+, Na^+, and K^+ ions.

**Computational Method**

All DFT calculations were carried out using the G03 suite of programs [26]. We used the standard B3LYP/6-31G^{**} (5d) [27] model. All structures were fully optimized. Basis set superposition error corrections (BSSEC) [28] were used to obtain more reasonable binding energies. All the calculations were done using KIST teraflops linux cluster.

**Results and Discussion**

As detailed in our previous papers [24, 25] we have presented theoretical studies about the behavior of Spherands 2 and 3 toward Li, Na, and K ions. In the present study, we compared shortly the effect of donor-atom (Me–O, CN, and F) type and ring size on the complexation of spheras 1, 2, and 3 (see Chart 1) with alkali cation Li^+, Na^+, and K^+. Because of the importance of Li^+, Na^+, and K^+ in physiological chemistry, the ability of hosts to differentiate between these ions in complexation is interesting.

Upon complexation with cations, the spheras have two binding sites: one at the center, internal binding, (D_{3d}, D_{2d}, and D_{4d}) and the other out of the cavity, external binding, (C_{2v} or C_{4v}) see Figure 1. All binding energies with BSSE correction are listed in Table I. The results indicate that, all hosts prefer the external binding for the alkali metals.

The binding energies of Li^+ ion are 134.16, 97.17, and 30.90 kcal/mol for spheras 1, 2, and 3, respectively. These results indicate that the small ions strongly bind toward all the studied compounds except 1B (Me–O8). The cavity presented by an array of donor atoms is too large, and then the possibility exists that not all of the donor atoms will be able to make contact. In fact, the flexible 1B is a reasonably good size match for all of the host cations, although it is optimum for K^+. In contrast, there is a clear tendency that the absolute value of binding energy is inversely proportional to the ionic radius with other ligands 1A, 2, and 3. Comparisons of Na^+–O distance of spherand 1A complexes with standard value of 2.35 (These values were obtained by adding the ionic radii of the metal ions to the van der Waals radii of the ligating atoms. [29]) show that spherand 1A has strong interactions with all metal than host 2 and host 3 (see Table II). The spheras 1B and 2 appear beautifully preorganized to bind all guests. The rigid placements of their oxygen during synthesis rather than during complexation are undoubtedly responsible for the enhanced binding and selectivity of the spherand.

In case of CN-Spheras, Upon complexation with cations, CN8-spheras are highly preorganized. The binding energy values (kcal/mol, Table I) are highest at 30.9 and 80.8 kcal/mol with Li^+ of the internal and external binding, respectively. On the other hand, the lowest binding energies are 4.6 and 34.7 kcal/mol for K^+ internal and external binding, respectively. There is a clear tendency that the absolute value of the binding energy is inversely proportional to the ionic radius. The most interesting results obtained in the present theoretical study of spherand 3 are that although the size of the host cavity encompasses the size of the guest...
FIGURE 1. Different conformations of the studied spherands upon complexation with Li, Na, and K ions.

Oxygen atom
Nitrogen atom
Florin atom
carbon atom

$2B\cdot Li^+(D_{4d})$
$2B\cdot K^+(C_4v)$

$3B\cdot K^+(C_{3v})$
$3A\cdot K^+(D_{3d})$

$1A\cdot Na^+(D_{3d})$
perfectly, the central binding with higher coordination number is much lower favorable than the external binding with less coordination number. The final conclusion reported is that the important rule of ion–dipolar orientations as well as the host–guest size complementarity must be considered in a study these compounds.

Interactions between covalently bonded fluorine atoms (C—F) and metal cations have been observed in the solid state and discussed based on crystallographic data [30]. Theoretical studies also predict such interactions in solution [31]. On the other hand, few reports are available of experimental elucidation of these interactions [32]. The first attempt to obtain experimental evidence was made in 1984 by Cram et al. [20]. However, the fluorinated spherands did not show any complexation phenomena toward alkali metal cations. Plenio et al. synthesized several types of macrocyclic compounds which contain oxygen and fluorine as the donor atoms [20]. On the basis of 13C and 19F NMR spectral data, X-ray crystallographic analyses, and determinations of stability constants, they concluded that the fluorine atom plays an important role in the complexation of alkali and alkaline earth metal cations.

One of the criteria for optimal complementarity is that the metal ion be able to contact all the donor atoms of the ligand at an optimal M-L distance. The distances between Li⁺, Na⁺, and K⁺ and the fluorine atoms are 2.062, 2.0209, and 2.543 Å, respectively. To the best of our knowledge, the value of 2.56 Å for F-K⁺ is among the shortest reported [33]. If the cavity presented by an array of donor atoms is too large, then the possibility exists that not all of the donor atoms will be able to make contact. The converse is also true, that if the cavity is too small, then the metal ion cannot enter and cannot contact the donors at an optimal distance. In case of F6-Spherand, upon complexation with Li⁺ or Na⁺, we could only obtain internal binding mode; i.e., when externally attached, the cation spontaneously goes inward during structure optimization. In contrast, with K⁺, external binding (C₃v), as well as internal binding structures could be obtained.

In conclusion, the host–guest size complementarity is obviously an important factor to achieve highest affinity for any cations. However, there appears to be more tolerance to the larger cavity than to the smaller one. This may come from a need to avoid steric bumping. The favorable host should have a cavity that has a suitable size, i.e., a little bigger than, but not too much bigger than, the incoming guest.

### Conclusion

Three types of spherands and their alkali cation complexes have been investigated by DFT calculations. The results of our investigations can be summarized as follows:

1. For all structures investigated, there is a clear tendency for the binding energy to be in-

<table>
<thead>
<tr>
<th>Structures</th>
<th>Host</th>
<th>Compound/X</th>
<th>Eₜₜₜ_bind (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OMe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CN</td>
</tr>
<tr>
<td>X₆-spherand (A)</td>
<td>D₃d</td>
<td>A-Li⁺</td>
<td>−134.16</td>
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<tr>
<td></td>
<td></td>
<td>A-Na⁺</td>
<td>−106.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A-K⁺</td>
<td>−62.75</td>
</tr>
<tr>
<td></td>
<td>C₃v</td>
<td>A-Li⁺</td>
<td>−80.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A-Na⁺</td>
<td>−56.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A-K⁺</td>
<td>−38.96</td>
</tr>
<tr>
<td>X₈-spherand (B)</td>
<td>D₂d</td>
<td>B-Li⁺</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-Na⁺</td>
<td>−7.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-K⁺</td>
<td>−162.16</td>
</tr>
<tr>
<td></td>
<td>C₄v</td>
<td>B-Li⁺</td>
<td>−89.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-Na⁺</td>
<td>−66.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-K⁺</td>
<td>−41.97</td>
</tr>
</tbody>
</table>

*Eₜₜₜ_bind, binding energy with basis set superposition error correction. The missing values represent conformations that were not stationary points.
versely proportional to the ionic radius of the cation.

2. The spherands 2 and 3 appear beautifully pre-organized to bind all guests

3. The host–guest size complementarity is obviously an important factor to achieve highest affinity for any cations.

4. In the case of CN-spherands, the important rule of ion-dipolar orientations as well as the host-guest size complementarity must be considered in a study of these compounds

5. A good agreement is observed between theoretical predictions and experimental data for studied spherands

ACKNOWLEDGMENT

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TABLE II
Distance in the geometric structures of the spherands and their complexes.

<table>
<thead>
<tr>
<th>Point group</th>
<th>Compound</th>
<th>MeO-spherand</th>
<th>F-spherand</th>
<th>CN-spherand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Spherical diameter (Å)</td>
<td>O—M⁺</td>
<td>Spherical diameter (Å)</td>
</tr>
<tr>
<td>D₃d</td>
<td>1A</td>
<td>4.458</td>
<td>4.172</td>
<td>6.529</td>
</tr>
<tr>
<td></td>
<td>A-Li⁺</td>
<td>4.312</td>
<td>2.156</td>
<td>5.888</td>
</tr>
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<td></td>
<td>A-Na⁺</td>
<td>4.593</td>
<td>2.296</td>
<td>2.062</td>
</tr>
<tr>
<td></td>
<td>A-K⁺</td>
<td>5.201</td>
<td>2.600</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>6.536</td>
</tr>
<tr>
<td></td>
<td>A-Li⁺</td>
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<td>6.254</td>
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<td></td>
<td>A-Na⁺</td>
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<td>6.399</td>
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<td></td>
<td>A-K⁺</td>
<td></td>
<td></td>
<td>6.454</td>
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<tr>
<td>Cᵥ</td>
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<td></td>
<td></td>
<td>2.706</td>
</tr>
<tr>
<td></td>
<td>B-Li⁺</td>
<td>6.163</td>
<td>2.105</td>
<td>5.646</td>
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<tr>
<td></td>
<td>B-Na⁺</td>
<td>5.992</td>
<td>3.096</td>
<td>5.948</td>
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<td></td>
<td>B-K⁺</td>
<td>6.002</td>
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<td>L</td>
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<td>5.948</td>
</tr>
</tbody>
</table>

a The diameter of the spherical cavity that comprises oxygen, fluorine, and nitrogen atoms.

References