

Selective complexation of alkali metal ions using crown ethers derived from calix[4]arenes: a computational investigation of the structural and energetic factors

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Abstract A systematic analysis of the structural, energetic, and thermodynamic factors involved in alkali metal (i.e., Na⁺, K⁺, Rb⁺, and Cs⁺) complexation by four calix[4]arene crown-6 ethers in the 1,3-alternate conformation is presented here. The ligands (or hosts) in this work are identical to, or closely related to, the four molecules whose selectivity towards complexing Na⁺, K⁺, Rb⁺, and Cs⁺ from aqueous solutions was studied experimentally by Casnati et al. (Tetrahedron 60(36):7869–7876, 2004). By dividing the complexation process into three different contributions, namely, the binding energy of the ion to the crown, the elastic energy of the crown, and the solvation effect, it becomes clear that the primary factor that determines ion selectivity in crown-6-ethers is not the size of the crown, as currently believed. All four crown ethers preferentially complex with the smallest ion (Na⁺) in the gas phase. In the condensed phase, these crown-6 ethers preferentially complex with the larger ions *only because the aqueous solvation energies of the alkali metal ions make it*

thermodynamically less favorable to extract the smaller ions from aqueous solutions. This suggests that the current understanding of the factors influencing the selectivity of metal ion complexation by crown ethers may be in need of revision.

Keywords Calixarenes · Crown compounds · Computational chemistry · Density functional methods · Alkali metal ions

Introduction

Calix[*n*]arenes are an important class of molecules in macrocyclic chemistry. The chapters and the large number of references cited in a recent monograph [1] attest to the wide range of work that has been directed at understanding their properties, especially the interactions in which the calixarene plays the role of ligands (hosts) for metal ions (guests). The crown ethers derived from calix[4]arenes are among the most widely studied ligands for selective complexation of alkali metal ions from aqueous solutions [2]. Practical interest in their complexation chemistry and the structural factors that contribute to selectivity is driven to a large extent by potential applications in nuclear waste management. According to Arnaud-Neu et al. [3], the widely used PUREX process [4] and its variants for extracting and purifying uranium and plutonium from spent nuclear waste leaves behind highly acidic aqueous solutions containing almost all of the non-gaseous fission products such as ¹²⁹I ($t_{1/2} = 1.7 \times 10^7$ year), ¹⁰⁷Pd (7×10^6 year), ¹³⁵Cs (3×10^6 year), ²³⁷Np (2.4×10^6 year), ⁹³Zr (1.5×10^6 year), ¹³⁷Cs (30 year), and ⁹⁰Sr (27.7 year). One widely adopted strategy is to vitrify these high level wastes for storage. Recovery of ¹³⁷Cs and ⁹⁰Sr would remove 90 % of the thermal emissions from high activity wastes, permitting great reductions in the vitrified volume [3].

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It is a major challenge to selectively complex the Cs^+ ion from solutions produced by the PUREX process, which have high concentrations of Na^+ and K^+ ions. In a detailed study of the efficiency of nuclear waste treatments by supported liquid membranes (SLM), Hill et al. concluded that classical crown ethers “such as the widely used 21C7 derivatives” had poor stability and low efficiency, but calix[4]arene crown-6 ethers “in the so-called 1,3-alternate conformation led to very stable (over 50 days), highly selective (concentration factor >100) and efficient (decontamination factor = 20) SLMs, for the removal of cesium from high salinity and acidity media” [5].

Experimental evidence shows that crown-5 ethers are selective to the smaller K^+ ion while crown-6 ethers are selective to the larger Cs^+ [1, 2]. This leads to the seemingly logical conclusion that the size of the crown determines the selectivity. In 2004, Casnati et al. published the results of a study in which they enlarged the crown of two calix[4]arene crown-6 ethers by adding a methylene group to the crown [6]. This helped enlarge the cavity available for cation coordination while keeping the number and nature of the coordination sites constant. Based on existing experimental evidence, it was expected that the enlarged crowns would show enhanced selectivity towards the larger Cs^+ ion compared to the K^+ ion. Therefore, it was rather surprising that the selectivity measurements showed that the enlarged crowns were actually *less selective* towards the larger ion than the original crowns. The study, reported here, was motivated by the desire to understand the factors responsible for this behavior using computational chemistry.

Due to the relatively large size of the host molecules and the heavier elements as the guests, quantum chemical studies to date have not fully addressed the main questions of interest in this field. Many researchers have used semi-empirical methods [7] which have yielded reasonably accurate structures in some cases but have also led to incorrect predictions of relative stability of complexes [8]. Those employing *ab initio* (wave function theory or density functional theory) methods have either studied model systems that are considerably smaller than the calix[4]arene crown ethers used in

experiments, focusing either on the calixarenes without the crown ether [9], or on crown ethers without the calixarene [10, 11], limited calculations to Hartree–Fock level of theory (no electron-correlation) [6], or have focused on gas phase structural aspects rather than the experimental results on complexation thermodynamics [12, 13]. The extensive molecular dynamics studies of Wipff and coworkers are also notable [14–18], although the force fields underlying these calculations were not specifically designed for the molecules studied. The assumption that crown size is the main factor in selectivity has not been contested to this day, neither by experiments or simulations, and results such as those obtained by Casnati et al. [6], remain unexplained.

In this paper, a systematic analysis of the structural, energetic, and thermodynamic factors involved in alkali metal (i.e., Na^+ , K^+ , Rb^+ , and Cs^+) complexation by four calix[4]arene crown-6 ethers in the 1,3-alternate conformation is presented. The ligands (or hosts) studied here are identical to, or closely related to, the four molecules whose selectivity towards complexing Na^+ , K^+ , Rb^+ , and Cs^+ from aqueous solutions was studied by Casnati et al. [6]. The success of these calculations in reproducing many of the qualitative aspects of the experiments justify the use of computational modeling as a tool for dissecting the factors that contribute to the observed trends in the alkali metal ion complexation by calix-crowns. This analysis suggests that some of the long-standing “conventional wisdom” in this field may benefit from closer examination.

The remainder of this paper is organized as follows. In Sect. 2, the molecules studied and the computational approaches adopted are described. In Sect. 3 results of the calculations and the comparisons to the experimental results of Casnati et al. [6] are discussed. Section 4 provides a summary and concluding remarks.

Calculations

The four calix[4]arene crown-6 molecules studied by Casnati et al. [6] and in this work are shown in Fig. 1. The

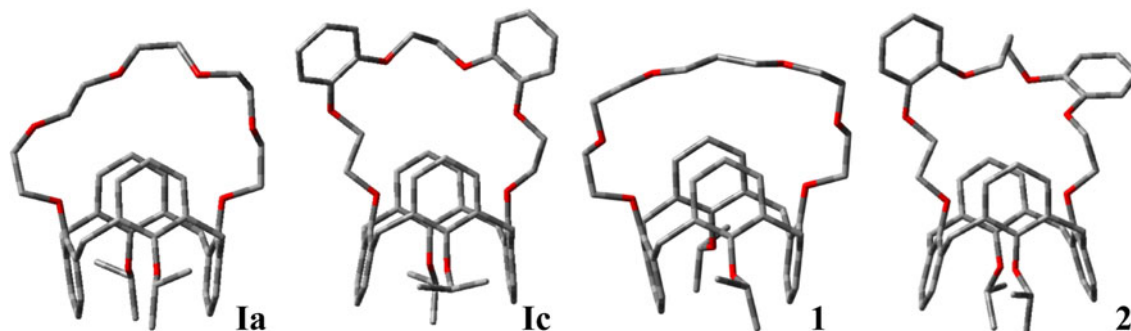


Fig. 1 The four crown ether molecules studied in this work. In this work the *O*-*n*Oct used in Ref [6] is replaced by *O*-*i*Pr (isopropyl)

numbering scheme of these authors was also adopted here, and thus the molecules are identified as **Ia**, **Ic**, **1**, and **2**. The only difference between molecules **Ia** and **1** is that the crown of the latter contains an extra methylene group between the two upper most O atoms in the crown. An identical relationship exists between the molecules **Ic** and **2**. Thus, **1** is obtained by enlarging the crown of **Ia**, and **2** by enlarging **Ic**. A difference exist between the molecule **Ic** studied here and the one synthesized and studied by Casnati et al. Ref. [6], the aromatic rings of the calyx that are not attached to the crown have the *-O-n*Oct groups as substituents. In this work, as shown in Fig. 1, *-O-iPr* groups were used instead to keep the molecules computationally more manageable but mainly so the only difference between **Ia** and **Ic** respectively from **1** and **2** is the size of the crown, which makes the factors that influence the ion selectivity more evident.

The term “model chemistry” is used to refer to a specific combination of computational methods and basis sets. The model chemistry for this work is the following: density functional theory (DFT) is used for the structure and energy calculations in this work. The calculations utilize the B3PW91 hybrid functional resulting from the 3-parameter exchange functional of Becke [19] and the 1991 correlation functional of Perdew and Wang [20, 21] DFT. Geometry optimizations and frequency calculations are done using the LANL2DZ [22–25] basis set. These are followed by single point energy calculations in which larger basis sets that include diffuse and polarization functions are placed on the O atoms and the alkali metal atoms, whose interactions are of central interest here. In these single point calculations, the def2-tzvpp basis sets and the effective core potentials (ECP) of Ahlrichs et al. [26] are used for the alkali metal ions, while the O atoms are described by Dunning’s augmented correlation-consistent polarized valence double zeta basis set (aug-cc-pVDZ) [27, 28]. The structures shown in Fig. 1 are the optimized “gas phase” structures from this particular model chemistry. To the best of our knowledge, these are the largest calculations to date on the complexes studied or similar molecules. The energies of the host-metal complexes were corrected for basis set superposition errors using the counterpoise correction method of Boys and Bernardi [29].

Solvent effects are taken into account using continuum solvation models within the theoretical framework of the self-consistent reaction field (SCRF) approach. The integral equation formalism version of the polarized continuum model (IEFPCM) of Tomasi et al. [30] is used here. The experimental determination of complexation equilibrium constants made use of the mildly hydrophilic nature of the crown ether which makes it a good phase transfer agent. The alkali metal ions are initially present in an aqueous layer, and are extracted into a chloroform layer which contains the calix-crowns. To approximate the different solvent

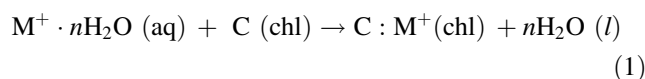
environments in these experiments, the solvation free energy of the uncomplexed alkali metal ions are calculated in the aqueous phase and the solvation of the hosts and the guest-host complexes in the organic (chloroform) phase.

All calculations were done using Gaussian 09 [31]. The SCRF calculations with the IEFPCM used Universal Force Field (UFF) radii for the atoms and keywords for incorporating the solute–solvent dispersion [32, 33] and repulsion interactions [32, 33], and the solute cavitation energy [34] were included. No other changes to the Gaussian 09 defaults were made in treating continuum solvation.

All free energy calculations were corrected to account for the change in standard states in going from the gas phase (the default in quantum chemistry calculations) to the condensed phase. Specifically, a correction term $RT \ln(c^\circ RT/P^\circ)$ must be added per mole of each species in the reaction under consideration, which represents the change in free energy involved in compressing the system from standard pressure P° (or a concentration of P°/RT) used in gas phase calculations to the standard concentration of $c^\circ = 1$ mol/L commonly used for solutions. This term is numerically equal to +1.89 kcal/mol at 298.15 K [35, 36].

The effect of ion solvation was also studied using explicit hydration of the alkali metal ions in the aqueous phase. In this case, to be consistent with the model chemistry described above, the def2-tzvpp basis set was used for the alkali metal ions, LanL2DZ for the H atoms, and aug-cc-pVDZ for the O in the water molecules. The number of water molecules in the first solvation sphere was used as a parameter and was varied from 2 to 6 to evaluate the effect on the free energy of complexation. The secondary and tertiary solvation spheres of the explicitly hydrated ionic species and all solvation of free water itself were taken into account using one or the other of the two continuum solvation methods mentioned above.

When the hydrated ion is complexed by the crown and extracted into the organic layer, the hydration spheres including the explicitly represented water molecules are assumed to be released into the aqueous layer. The thermodynamics in these cases is based on the process



where “C” stands for the crown ether host, “aq” indicates continuum solvation in water and “chl” represents continuum solvation in chloroform. An additional standard state correction is necessary in such instances to account for the second term in the free energy expression.

$$\Delta G^\circ = -RT \ln \frac{[C:M^+]}{[C][M^+ \cdot nH_2O]} - nRT \ln \frac{[H_2O]}{c^\circ} \quad (2)$$

This correction accounts for the fact that the concentration of pure water at 298.15 K is 55.51 mol/L

while the standard concentration c° is 1 mol/L. This correction is -2.38 kcal for each mole of water released from the primary hydration sphere [29].

Casnati et al. used Cram's method [37] to determine the association constants from which the free energies were calculated. The multi-phase complexation in Eq. (1) is a simplification of the competing equilibria considered in Ref. [37] which neglects the presence of the counterions (picrates, in typical laboratory work). While Eq. (1) is closer to the "real-life" applications in which Cs^+ ions are complexed from aqueous solutions using SLM nanofiltration devices, the neglect of counterion effects in the computational model used here precludes quantitative comparisons with experimental results. However, as shown below, comparisons of *relative* free energy changes appear not to be affected by neglecting this factor and thus the results presented here provide the necessary elements to understand the factors that influence complexation and ion selectivity among this class of host molecules.

Results and discussion

It appears that there is considerable uncertainty in the complexation free energy of the crowns with Na^+ ions. Casnati et al. chose to discuss the thermodynamics of complexation using $-\Delta G^\circ$ as the metric. So, a large positive value for $-\Delta G^\circ$ indicates that the process is more favorable at constant temperature and pressure. For the complex with **1a**, a value of $-\Delta G^\circ = 29.2$ kJ/mol (6.98 kcal/mol) is reported in an earlier work [38] but for **1c**, the best experimental estimate [39] is that $-\Delta G^\circ < 29.0$ kJ/mol, i.e., a definite number has not been reported, and only the upper limit for $-\Delta G^\circ$ is available. In Ref. [6], the same upper limit estimate is provided for the complexation free energies of Na^+ with the enlarged crowns **1** and **2**. Given these uncertainties, Casnati et al. have assumed that $-\Delta G^\circ$ for Na^+ complexation is ~ 29 kJ/mol for all four crown molecules, as reflected in Fig. 5 of Ref. [6]. In this work the same approach is taken, but for convenience, the origin of the free energy axis is chosen to be the calculated complexation free energy for each crown with Na^+ .

The explicitly hydrated ions with $n = 2, 4,$ and 6 were studied in anticipation that such a treatment may increase the accuracy of the model. The equilibrium structures of the hydrated ions are provided in the Supporting Information. The secondary solvation spheres of the hydrated ions were represented by the IEFPCM approach as described above.

As noted above, we set the $-\Delta G^\circ$ values for complexation of Na^+ to zero, and report all other $-\Delta G^\circ$ values *relative* to these values for a given crown. The relative free energies calculated using these modes are compared with

experimental free energies in Fig. 2. For completeness, the actual values of the calculated $-\Delta G^\circ$ values are given in the Supporting Information.

As anticipated, there are considerable numerical differences between the calculated and measured values. Some of these differences can be attributed to the neglect of counterion effects, as noted earlier. However, the qualitative similarities between the calculated and experimental *relative* free energies are readily apparent from the four panels of Fig. 2. In each case, the saturation of the first hydration sphere with explicit water molecules brings the calculated results into better agreement with the experimental observations. The thermodynamic favorability for complexation by all crown molecules, measured by $-\Delta G^\circ$, follow the order $\text{Rb}^+ > \text{K}^+ > \text{Na}^+$ in both calculations and experiments. As noted in the Introduction, the experimental results indicate that the enlargement of the crowns by adding the methylene group *does not* lead to increasingly favorable complexation thermodynamics for K^+ , Rb^+ , or Cs^+ .

Another quantity of great interest is the selectivity of the calix crowns for complexing Cs^+ relative to K^+ , defined as $\alpha_{\text{Cs}/\text{K}} = \Delta G_{\text{K}}^\circ - \Delta G_{\text{Cs}}^\circ$. The selectivities of the four crowns with respect to complexation with K^+ , as a function of the number of explicit water molecules in the primary solvation shell, are compared with the experimental results of Casnati et al. in Fig. 3. It is clear that the calculations achieve excellent qualitative agreement with the measured $-\Delta G^\circ$ values. Furthermore, when the primary hydration sphere of the alkali metal ions are well-represented ($n = 4$ and 6) by explicit water molecules, the results also show very good quantitative agreement. In fact, the calculated values may well be within the overlap region of the error bars of the experiments and the error bars that could be assigned to the calculated results to account for finite basis set size, use of ECP, etc. Consistent with the experimental results, our calculations show that enlarging the crowns by introducing an extra $-\text{CH}_2-$ group to generate **1** from **1a**, and **2** from **1c** actually made complexation with the larger ions less favorable and decreased the selectivity towards Cs^+ relative to K^+ .

The results presented above suggest that greater insights into the factors responsible for the trends observed experimentally may be obtained by further dissection of the calculated results. In order to do so, three different contributions to the interaction energy are identified and each contribution studied separately. The three contributions are, gas phase binding energy, elastic energy involving the re-shaping of the crown, and solvation energies.

We begin by examining the free energies of complexation in the gas phase. The gas phase free energies of alkali metal ion complexation by the four calix crowns, calculated using the model chemistry described in the previous

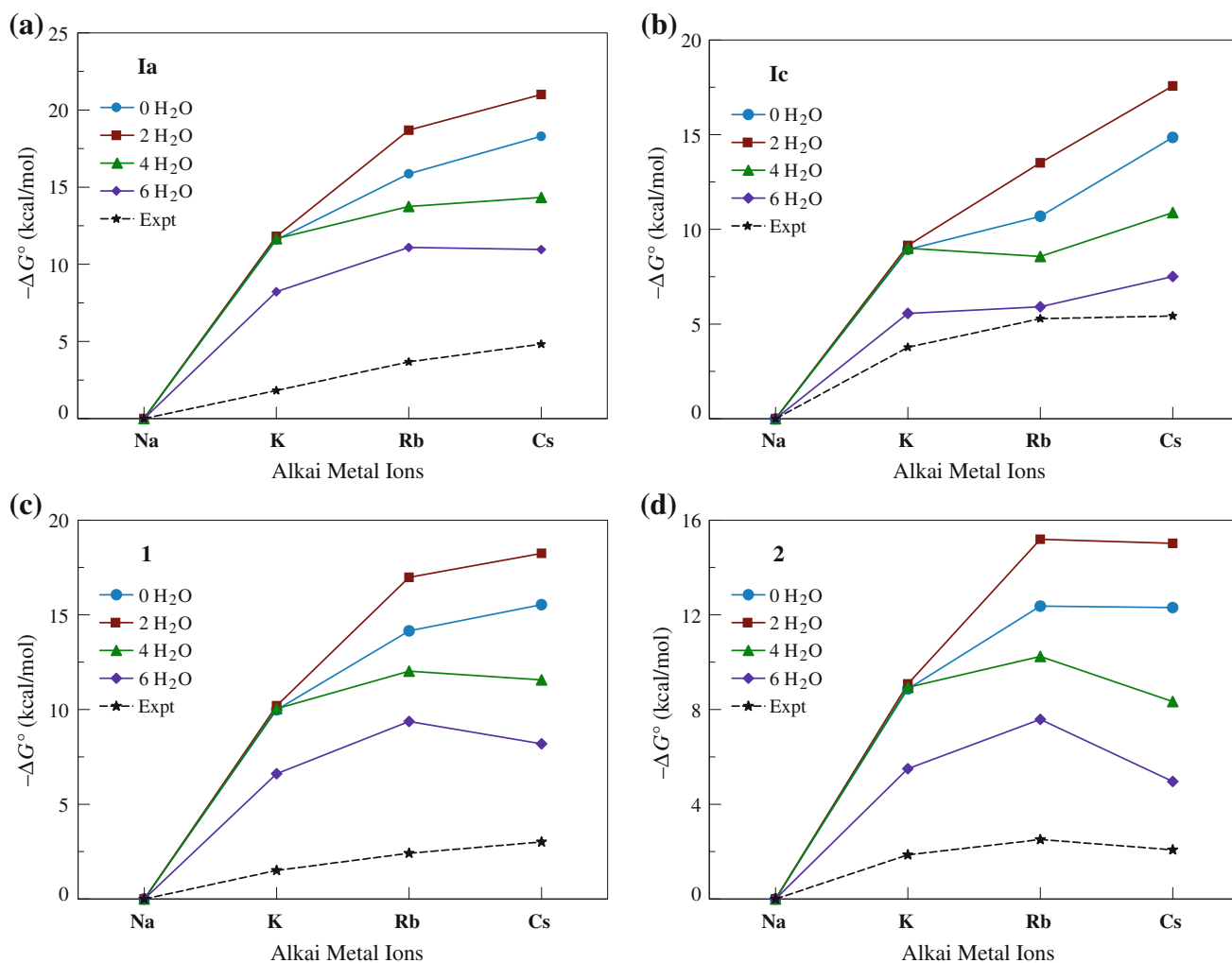


Fig. 2 Comparison of $-\Delta G^\circ$ for the complexation of alkali metal ions by the four calix crown ethers according to Eq. (1), with $n = 0, 2, 4$, and 6 (with n the number of explicit water molecules) with the experimental results of Casnati et al.

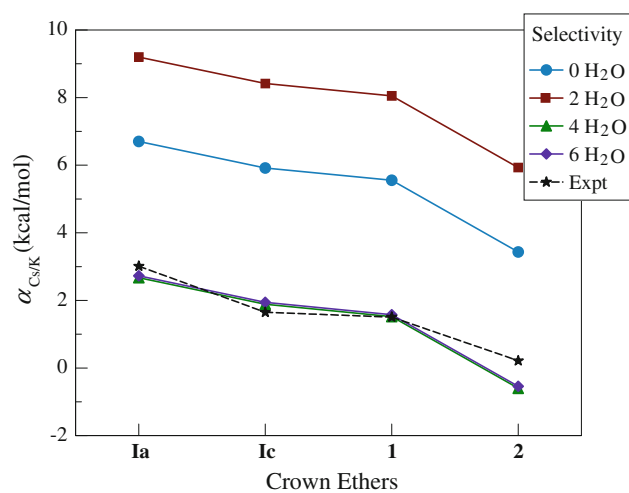


Fig. 3 Calculated selectivities of Cs^+ complexation with respect to K^+ for the four crown ethers compared with experimental results from Ref. [6]

Sect., are shown in Fig. 4. The largest $-\Delta G^\circ$ for all four crown ethers are for complexation with Na^+ while complexation with Cs^+ is the least favorable. This is true even for the enlarged crowns **1** and **2** which, it was expected, would complex more readily with the larger ions because of the larger dimensions of the crown. The assumption underlying this expectation is that the cavity size of the crown **6** most closely matches the size of the larger ion and thus the crowns would have to undergo only minor structural changes to accommodate those. By the same token, significant structural deformations will be required in order to accommodate the smaller ions, and it is reasonable to expect that there would be an energy penalty to be paid for these structural changes. Results presented here clearly contradict this assumption, and suggests that the elastic energy, i.e., the energy required for structural deformations, may not be as significant a factor as has been assumed.

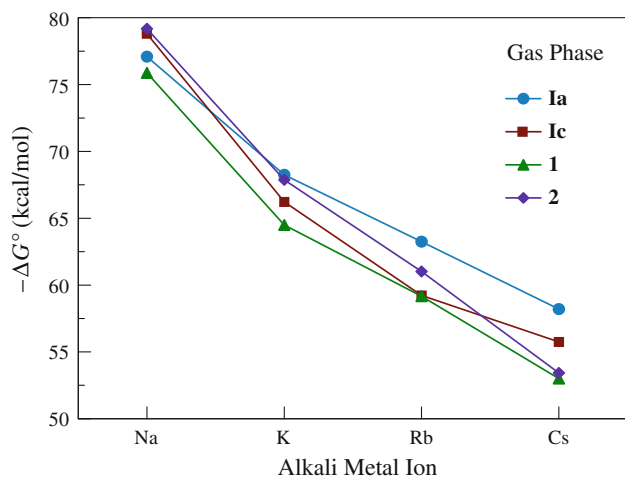
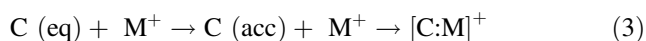


Fig. 4 The $-\Delta G^\circ$ values for the gas phase complexation of alkali metal ions by the four crown ethers studied, calculated using the model chemistry described in Sect. 2

A quantitative way to examine the energy penalty for structural accommodation is to consider the complexation as a two-step process. In the first step, the host crown ether distorts from its equilibrium geometry so as to accommodate the incoming guest, M^+ . In the second step, the distorted host complexes with the guest, resulting in the complex. This can be represented as follows:



where “C (eq)” represents the equilibrium structure of the host, and we designate the structurally deformed crown as “C (acc).” Figure 5 schematically illustrates this idea. The energy change encountered in the first step is a measure of the structural strain energy required to accommodate the metal ion. This is calculated as

$$\begin{aligned} \Delta E_{\text{strain}} &= (E_C - E_A) - (E_C - E_B) \\ &= \Delta E_{\text{adiabatic}} - \Delta E_{\text{vertical}} \end{aligned} \quad (4)$$

Figure 6a shows the equilibrium structure (A in Fig. 5) for the crown **Ia**, and the equilibrium structures (C in Fig. 5) resulting from complexation with Na^+ (Fig. 6b) and Cs^+ (Fig. 6c). It is easy to see that greater structural deformations are required in order to accommodate the Na^+ ion which has a van der Waals radius of 95 pm than to accommodate the Cs^+ ion which has a vdW radius of 169 pm.

The results of the analysis of strain energy is presented in Fig. 7 for the crown **Ia** and the corresponding enlarged crown **1**. Note that each of the terms in Eq. (4) are negative (Fig. 7a) but the difference is positive (Fig. 7b). For both **Ia** and **1**, the greatest strain energy is for complexation with Na^+ . However, this does not prevent complexation with Na^+ because the stabilization resulting from complexing with the ion, given by $\Delta E_{\text{vertical}}$, is so great that the energy cost of structural deformation is easily recovered. Interestingly,

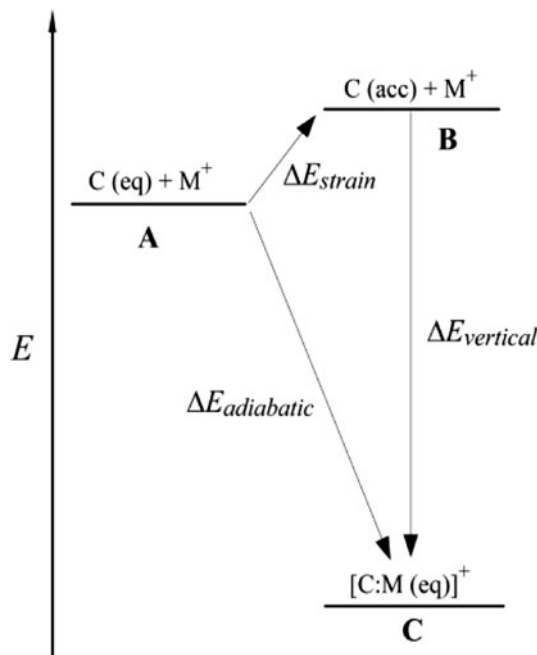


Fig. 5 Schematic representation of the calculation of “strain” energy involved in alkali metal complexation by crown ethers

Fig. 7b reveals that the strain energy for the enlarged crown **1** for complexing with K^+ , Rb^+ , and Cs^+ are roughly comparable. This suggests that the structural changes of the type shown in Fig. 6 in the crown skeleton to accommodate the ions take place over a fairly flat energy landscape, especially for the enlarged crowns. Specifically focusing on the Cs^+ – K^+ competition, there is virtually no contribution from the deformation energy of the crown. Figure 7b can also be used to understand the trend in Fig. 3 where, consistent with experimental results, results presented here show that increasing the size of the crown actually decreases selectivity towards Cs^+ over K^+ . The gas phase binding energy is larger for K^+ than for Cs^+ in the case of **Ia** as well as the enlarged crown ether **1**, but for **Ia** there is a larger strain penalty for K^+ than the Cs^+ while in the case of **1**, the penalty seems to be approximately the same for both ions. Therefore, it appears that **Ia** is able to better discriminate between K^+ and Cs^+ than **1**. The relative insensitivity of the strain energy to ion size in the case of the enlarged crown is clearly due to the greater flexibility of the crown ether as a result of the additional methylene group.

This discussion still leaves open the question of why complexation with the smallest ion is most favorable in the gas phase, even for the enlarged crowns. We performed a rather simplistic analysis of the electrostatic potential energy of interaction as

$$V_{es} = \sum_{i=1}^6 \frac{q_M q_{O_i}}{r_i} \quad (5)$$

Fig. 6 The equilibrium structures of the crown **1a** in **a** uncomplexed state, **b** complexed with Na^+ (ionic radius 96 pm) and **c** Cs^+ (ionic radius 169 pm)

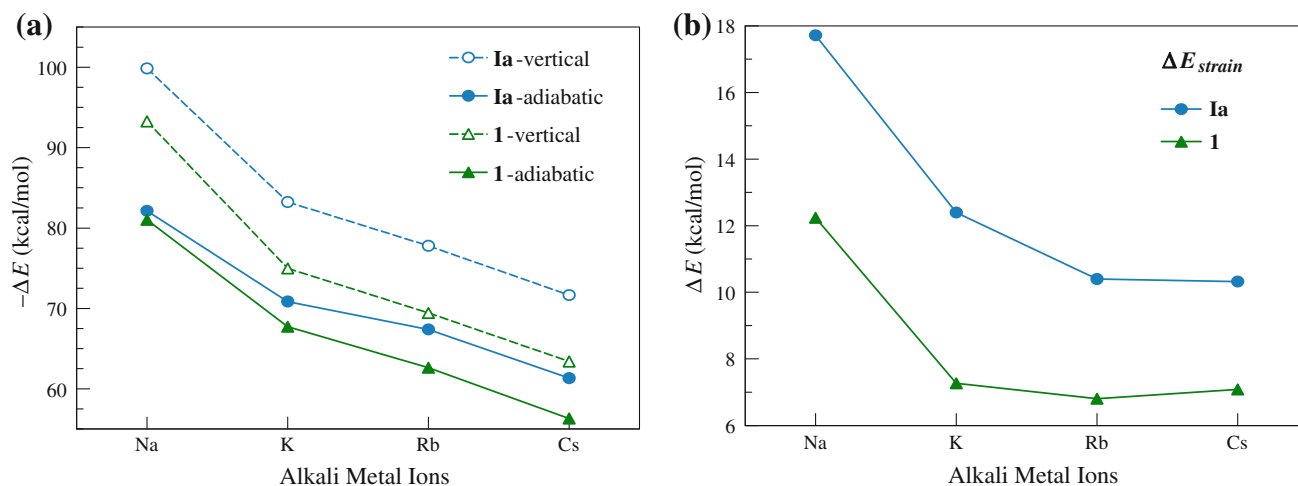
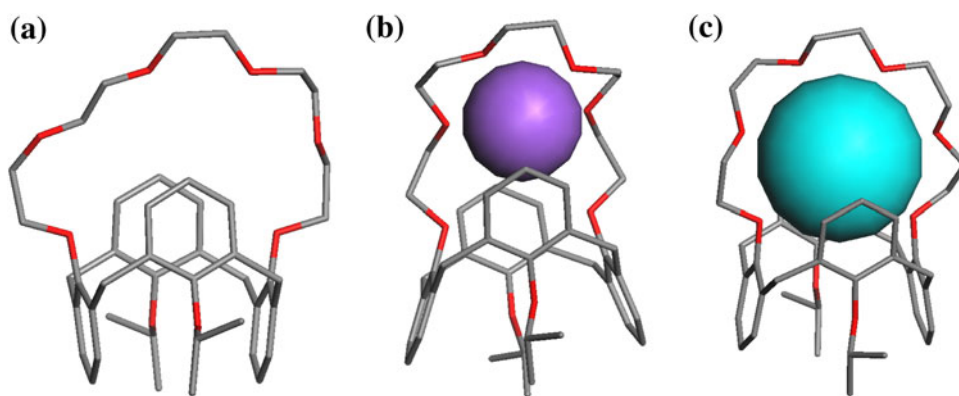


Fig. 7 Calculation of the strain energy for the crowns **1a** and the corresponding enlarged crown **1** complexing with the four alkali metal ions using Eq. (5)

where q_M is the charge on the metal ion in the complex, and the q_O 's are charges on the six oxygens in the crown, which are at distances r_i from M. Using atomic charges obtained by fits to the electrostatic surface potential using the Merz–Singh–Kolman algorithm [40, 41], the electrostatic contribution amounts to -139.8 , -127.7 , -128.8 , and -116.1 kcal/mol for the crown ether **1a** complexing with Na^+ , K^+ , Rb^+ , and Cs^+ , respectively. The average of the six $\text{M}-\text{O}_i$ distances are 2.89, 3.14, 3.23, and 3.28 Å for Na^+ , K^+ , Rb^+ , and Cs^+ , respectively. This strongly suggests that the complexation of crown ethers with alkali metal ions is driven by electrostatic attraction between the positive metal ion and the negatively charged oxygens. As long as the crown ether skeleton is sufficiently flexible, the distances between the metal ion and the oxygens are smallest for the smallest ion, and this determines the trends in the gas phase complexation thermodynamics. These conclusions are consistent with the experimental findings of More et al. [42] from mass spectrometric determinations of the bond dissociation energies of crown-ether: M^+ complexes in the gas phase.

Interactions between the π electron clouds of the phenyl rings and the cation also play a role in facilitating the complexation. These interactions are evident from the tendency of the two phenyl rings with O-*i*pr substituents to lean “outwards” by a small amount when complexing Na^+ and considerably more when complexing the larger Cs^+ , evident from Fig. 6b, c. Such cation- π interactions drive the complexation of metal ions by calix[*n*]arenes [9, 43] but, in the case of calix[*n*]arene-based crown ethers, the positions of the cations in Fig. 6b, c suggest that the cation is complexed primarily by the interactions with the oxygen atoms. Having established that the preference of the crown ethers towards the alkali metal ions in the gas phase is exactly the reverse of the trends observed in the experimental trends established by Cram’s method, we now examine the solvation energetics of the metal ions, the host crowns, and the complexed crowns.

The continuum solvation energy of the neutral crowns (H) and the positively charged crown-metal ion complex $[\text{C}:\text{M}]^+$ in chloroform, calculated using the IEFPCM method as implemented in Gaussian 09, is shown in

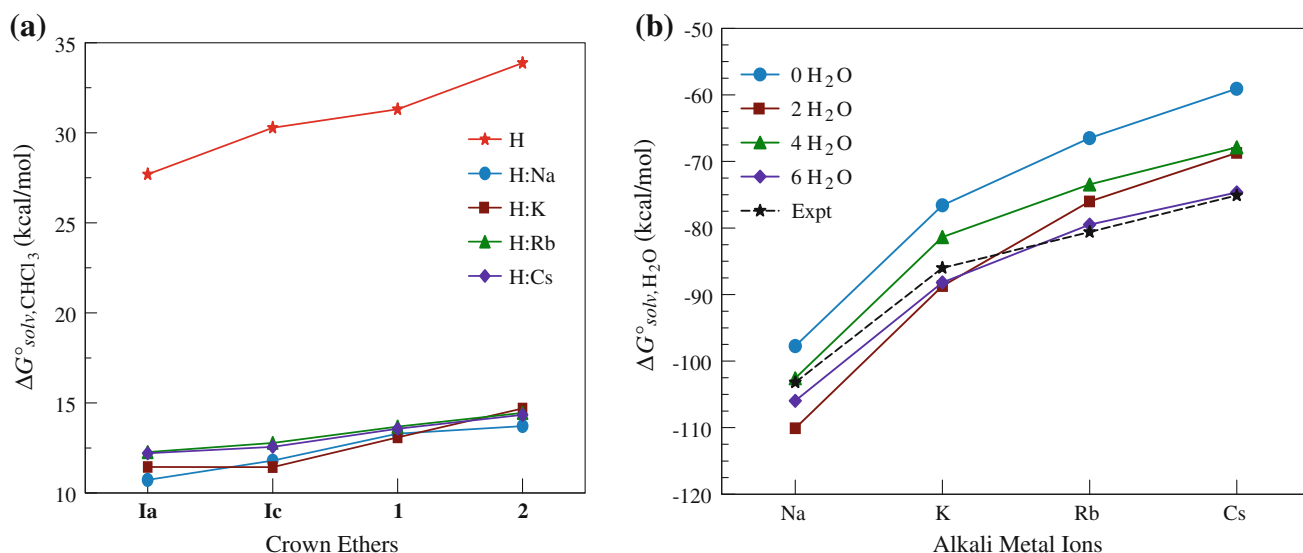


Fig. 8 Free energies of solvation for **a** the host molecules (H) and the H:M complexes with alkali metal ions in chloroform, and **b** the alkali metal ions in aqueous medium with and without explicit hydration by

Fig. 8a. IEFPCM predicts positive solvation free energies for all four host molecules. The solvation energies of the neutral host molecules vary between 27.7 kcal/mol for **Ia** to 33.9 kcal/mol for **2**, a range of 6.2 kcal/mol. The solvation free energies for the $[\text{C}:\text{M}]^+$ complexes are less positive, but all complexes have very similar values. The average solvation energy and the range for the $[\text{C}:\text{M}]^+$ in chloroform are (11.7, 1.5), (12.1, 1.3), (13.4, 0.6), and (14.3, 1.0) kcal/mol, respectively, for **Ia**, **Ic**, **1**, and **2**. It is clear that the solvation free energies of the $[\text{C}:\text{M}]^+$ complexes in chloroform cannot account for the reversal of the trends in complexation free energies between the gas phase and condensed phases. Figure 8b, shows the solvation free energy for the alkali metal ions M^+ when solvated as $\text{M}:\text{nH}_2\text{O}^+$ ($n = 0, 2, 4, 6$) in aqueous medium, which is calculated as the *total* free energy change for the process

$$\text{M}^+(\text{g}) + n\text{H}_2\text{O}(\text{l}) \rightarrow \text{M} \cdot n\text{H}_2\text{O}^+(\text{aq}), \quad (6)$$

where “aq” indicates IEFPCM solvation in water. With the standard state corrections already discussed in Sect. 2, this is equivalent to one side of the thermodynamic cycle (cycle 3) considered by Kelly, Cramer, and Truhlar [44] for obtaining the solvation energies of monovalent ions in aqueous solutions. The experimental absolute aqueous solvation energies for the ions [45, 46], calculated on the basis of assigning -265.9 kcal/mol to the solvation energy of the proton [44], are also given in this panel.

We make two important observations based on the results shown in Fig. 8b. First, the calculated solvation energies achieve increasingly good agreement with the experimental values as the primary solvation sphere is progressively saturated with explicit water molecules.

coordinated water molecules. The experimental solvation energies from Refs. [45] and [46] are also shown on panel (b)

Second, and most important for the present work, *the aqueous solvation energies of the alkali metal ions are large enough to overcome and reverse the free energy trends for the formation of $[\text{C}:\text{M}]^+$ complexes in the gas phase.*

Summary and conclusion

In this work, the structural, energetic, and thermodynamic factors involved alkali metal (i.e., Na^+ , K^+ , Rb^+ , and Cs^+) complexation by four calix[4]arene crown-6 ethers in the 1,3-alternate conformation is presented. The calculated complexation free energies and selectivities are compared to experimental measurements reported by Casnati et al. [6] The structural and energetic aspects of the complexation are analyzed by breaking up the process into distinct steps: (a) structural deformation of the crowns to accommodate the ions, (b) stabilization resulting from the complexation of the positive ion by the electronegative oxygens in the crown, and (c) solvation effects. It is found that in the gas phase all crown-6 ethers studied preferentially bind with the smallest ion, Na^+ as its smaller size allows O atoms to be closer to this ion leading to a smaller electrostatic energy. Cation- π interactions between the metal ion and the phenyl rings may also play a minor role in driving the complexation. Figure 7b shows that the structural deformation needed to accommodate the smaller ions require only moderately greater (~ 6 kcal/mol) strain energy than the larger Rb^+ and Cs^+ ions for the crown **Ia** while there is practically no difference in the strain energy of the enlarged crown **1** for complexing with K^+ , Rb^+ , or

Cs⁺. Thus the potential energy surface over which these structural deformations occur is relatively flat, especially when the crown ether is enlarged by the insertion of a methylene group what makes it more flexible. This also explains the lower selectivity of the enlarged **1** and **2** compared to the regular size **1a** and **1c**. The relatively small energy penalty for structural deformation allows the electrostatic contribution to drive the complexation. The last contribution to the process is given by the solvation energy. The solvation energies of the neutral crowns as well as the [C–M]⁺ complexes are practically independent of the ion size (Fig. 8a). However, the aqueous solvation energy of the uncomplexed M⁺ changes significantly from ion to ion, with solvation energy increasing as the ion size decreases. The magnitude and the variation in aqueous solvation energy is enough to reverse the trend in the gas phase so that the overall process of extracting the ions from the aqueous media into the crown is more favorable for larger ions than for smaller ones.

Thus the main conclusions to emerge from this study are:

1. The crowns of calix[*n*]arene crown-6 ethers are flexible enough to accommodate alkali metal ions of various sizes from Na⁺ to Cs⁺, and the structural distortions needed to accommodate the different ions occur over a relatively flat energy landscape.
2. Because of this, in the gas phase, calix[*n*]arene crown-6 ethers *preferentially complex with the smaller ions*, driven by the structural stabilization resulting from stronger electrostatic interactions between the oxygens in the crown and the positive metal ion.
3. In condensed phase, calix[*n*]arene crown-6 ethers preferentially complex with the larger ions rather than the smaller ions *only because the aqueous phase solvation energy of the smaller ions are large enough to overcome and reverse the trends in gas phase complexation*.

Thus, the operating assumption in such guest–host interactions, that achieving the perfect match between the cavity of the host and the size of the guest is the key to high selectivity, is called into question. Given a sufficiently flexible molecule that can deform over a relatively flat energy landscape, the electrostatic interactions between the oxygens of the crown ether and the metal ions favor the complexation of the smaller ions. Although the role of the solvation of the species has been cited by authors as a factor in determining guest–host chemistry [43], to the best of our knowledge, this is the first report that clearly identifies the central and decisive role played by the aqueous solvation energies of the alkali metal ions in the complexation thermodynamics of calix crown ethers.

As any computational research, some simplifications have been adopted. The most significant one is probably

the neglect of the effect of counter ions. Also, continuum solvation neglects the effects of the phase boundary. Both of these simplifications are necessary to keep the size of the molecular systems manageable so that relatively high levels of theory and adequate basis sets can be used. However, in spite of these omissions, the major conclusions of our study listed above are well-supported and justified. The factors neglected do not change the conclusion that the coulombic interaction between the ion and the O atoms in the crown is responsible for the complexation in the gas phase, which favors the smaller ions. It is also well established that the crowns are very flexible and thus elastic energy is not responsible for reversing the gas phase trends. This indicates that aqueous solvation energy of the metal ions is responsible for the free energy trends and selectivity behavior observed in the experiments.

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