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Molecular Mechanics and Dynamics Studies of Crown Ether–Cation Interactions: Free Energy Calculations on the Cation Selectivity of Dibenzo-18-crown-6 and Dibenzo-30-crown-10

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Abstract: We present a combined molecular mechanics and dynamics study of the complexation of dibenzo crown ethers containing 18 and 30 ring atoms, with alkali cations. The role of solvation was incorporated into the models by studying the complexes and cations surrounded by small (2–6) and large (112–127) clusters of solvent molecules. By using a thermodynamic free energy perturbation method, it was possible to simulate the relatively large K$^+$/Na$^+$ selectivity of the 30-membered ligand and the lower selectivity of the corresponding 18-membered ligand. Although the agreement between experimental and calculated relative free energy is not quantitatively correct, the delicate balance between solvation and binding free energies studied were qualitatively reproduced by our models.

The design of artificial receptor molecules for specific purposes is a fascinating problem not only because of the many possible applications in chemistry but also for the relevance of these receptor molecules to many biochemical processes.

One of the most promising tools for molecular design of receptor molecules is the use of computational models such as molecular mechanics or distance geometry in combination with computer graphics.[1] A number of such studies have been performed on macrocyclic receptor molecules such as crown ethers,[2] cryptands,[3] and (hemi)spherands.[4] However, these calculations were carried out on isolated "gas phase" systems, and only a limited part of the conformational space was examined. Recently, studies have been carried out where in fact a considerable part of the conformational space of crown ethers was investigated, one of them using a diamond lattice approach[5] and one of them using the ellipsoid algorithm combined with molecular dynamics.[6] The effect of the solvent on the relative stability of certain conformations of 18-crown-6 has recently been studied by Ranghino et al. who used Monte Carlo techniques in order to generate ligand-solvent clusters.[7]

Molecular mechanics studies[2a] indicate that the (de)solvation of cations upon complexation is extremely important to the energetics of the process. Therefore it is desirable to incorporate the effect of the solvent in the description of the process. Another issue is that most of the experimentally obtained thermodynamic data on complexation processes is expressed in terms of Gibbs free energies. It is of considerable interest to apply theoretical methods that yield free energies.

One can use results from free energy perturbation theory to calculate relative free energies. The method is based on the generation of ensembles by molecular dynamics or Monte Carlo simulations after which the statistical equilibrium averages such as free energy differences can be obtained.[8] This method has been applied to study a variety of problems, and so far the results are very encouraging. Berendsen and coworkers have studied the free energy of cavity formation in water[9] and the free energy of hydrophobic hydration of noble gases in water.[10] Jorgensen and Ravimohan have calculated differences in the free energies of hydration of methanol and ethane by Monte Carlo simulations.[11] The Kollman and McCammon groups have studied free energy changes in ion-water clusters.[12,13] The method may be regarded as the computational variant of site-specific mutagenesis, as has been illustrated by a number of studies.[14]

So far this method has been used only once for a synthetic macrocyclic receptor. Lybrand et al. have simulated the complexation of the macrotricyclic cryptand SC24 with chloride and bromide anions in water using a united-atom force field in a molecular dynamics approach.[15] For reasons of computational efficiency, in the united-atom force field CH, CH$_2$, and CH$_3$ groups are represented by united atoms, this in contrast with the all-atom force field where all hydrogen atoms are explicitly included.

In this paper we apply free energy perturbation theory in order to simulate a remarkable property of large dibenzo crown ethers. It has been observed that crown ethers with 27–33 ring atoms exhibit a large binding affinity for K$^+$, Rb$^+$, and Cs$^+$ cations

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Table I. Additional Force Field Parameters

bond	K_r (kcal mol^{-1} $Å^{-2}$)	r_{eq} (Å)	
CA–OS	300.0	1.40	
OX–HX	553.0	0.945	
CX–OX	320.0	1.430	
angle	K_θ (kcal mol^{-1} $radian^{-2}$)		θ_{eq} (deg)
CA–CA–OS	70.0		120.0
CA–OS–CT	46.5		113.0
CX–OX–HX	55.0		108.5
dihedral	$V_n/2$	γ	n
X–CA–OS–X	2.0	180.0	2
VDW	R^* (Å)	ϵ (kcal mol^{-1})	
HX	1.00	0.00	
CX	2.118	0.207	
OX	1.723	0.17	
Li^+	1.0	0.01	
Na^+	1.6	0.01	
K^+	2.0	0.03	
Rb^+	2.2	0.035	
Cs^+	2.4	0.06	

relative to Li^+ and Na^+ cations.[16] Since the X-ray structures of a number of complexes of both dibenzo-18-crown-6 (DB18C6) and dibenzo-30-crown-10 (DB30C10) with alkali cations are known as well as the thermodynamics of complexation, these systems are suitable for a computational study. In contrast to the conformationally rigid systems studied at the united-atom level by Lybrand et al., where there was a rather large binding free energy difference of more than 4 kcal mol^{-1} between the ligand-anion complexes[15] and the difference in binding free energy was dominated by ion-SC24 interactions, we aim to study more subtle differences between solvation and intrinsic ion-crown interactions in determining the binding free energies of flexible ligands using the all-atom approach. This is the *first* general application of free energy perturbation methods to a wide series of cation–crown ether complexes, and the ability of the theory to reproduce most of the experimental trends is very encouraging.

Methods

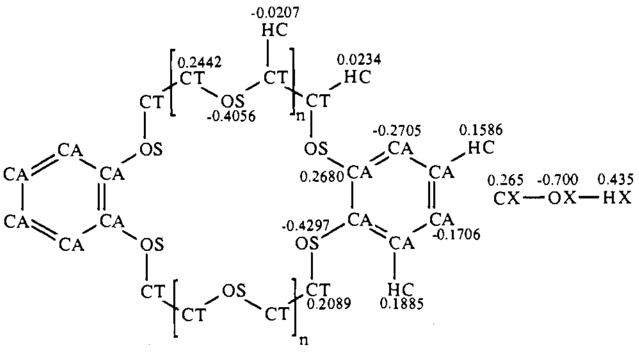
For all molecular mechanics and dynamics calculations the AMBER package was used,[17] in which the energy function is of the form

$$E_{\text{total}} = \sum_{\text{bonds}} K_r (r - r_{eq})^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos (n\phi - \gamma)] + \sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\epsilon R_{ij}} \right] + \sum_{\text{H-bonds}} \left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}} \right] \tag{1}$$

The calculations were carried out on VAX8650 and FPS-264 computers. In general an all-atom force field was used; i.e. all atoms were explicitly represented by the force field, and most of the force field parameters have been previously published.[17b] A complete list of all additional parameters used in the present study is found in Table I. The relation between A_{ij} and B_{ij} on one hand and ϵ and R^* on the other is described in ref 8b.

For the one-half of the dihedral barrier height $V_n/2$ for the CA-CA-OS-CT dihedral a value of 2.0 kcal mol^{-1} was used throughout all calculations. Using the value of 2.0 kcal mol^{-1} leads to an energy difference between the planar and perpendicular conformations of anisole of 2.0 kcal mol^{-1}, in agreement with the value derived from ab initio calculations performed with a 6-31G* basis set.[18] The nonbonded van der Waals parameters for the alkali cations were slightly changed in comparison to the values published earlier for Li^+, Na^+, and K^+.[4b] These parameters

Chart I



were derived in a manner similar to that described in ref 2a, i.e., finding the 6–12 potential energy well depth (ϵ) and the van der Waals radii (R^*) that reproduce best the experimentally determined interaction energy and the minimum energy metal–oxygen distance as calculated by accurate ab initio methods of cation–(TIP3P[19a])water complexes. The maximum deviation between calculated and experimental enthalpies amounted to 0.4 kcal mol^{-1}; the difference between the quantum-mechanically calculated oxygen–metal distance and the van der Waals radii reported here was maximum for Cs^+ being 0.11 Å. In the calculations on solvent models the optimized potentials for liquid simulation (OPLS)[19] parameters for methanol were used. The methyl groups were treated as united atoms, but the hydroxyl hydrogens were included explicitly.

Because of the dominant role of electrostatic interactions in the systems under study, much attention was given to the partial charges at the crown ether atoms. For the $-CH_2OCH_2-$ fragments the charges reported by Howard et al.[20] were used. This set of charges represents a compromise between the different charge sets described by Wipff et al.[2a] for complexed and uncomplexed crown ethers.

In order to obtain partial charges for the aromatic part of the dibenzo crown ethers, a similar procedure was used in which the geometry of 1,2-dimethoxybenzene was refined by using the semiempirical program AM1.[21] The geometry of lowest energy, with the methoxy groups above and below the plane of the benzene moiety,[22] was used for a single point ab initio calculation at the 6-31G* level with the program GAUSSIAN 80 UCSF.[23] By using the electrostatic potential from this calculation the partial atom charges for the fragment $-CH_2O-Ar-OCH_2-$ were obtained by the fitting procedure described earlier.[24] The partial charges are found in Chart I.

As starting geometries for the molecular mechanical calculations on the crown ether–cation complexes, the X-ray data available from the literature were used. For the complexes with the 18- and 30-membered ligands the X-ray structures of, respectively, the DB18C6.NaBr,[25a] DB18C6.KI,[25b] DB18C6.RbSCN,[25c] DB30C10.KI,[25d] DB30C10.KSCN,[25e] and DB30C10.RbSCN[25f] served as input geometries for the various minimizations. The X-ray structures of uncomplexed DB18C6[25c] and DB30C10[25d] were used as starting geometries for the minimizations of the uncomplexed crown ethers. In the case of solvated complexes or cations the solvent molecules were placed in approximate octahedral positions by using the molecular graphics program MIDAS[26] on a Silicon

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Table II. Results of Calculations on the Uncomplexed Crown Ethers

ligand	conformation^a	E_{total}^{b}	internal^c	VdW^d	el^e	rms^f
DB18C6	un	29.0	20.0	5.5	3.5	0.47
DB18C6	co	30.2	6.9	8.1	15.2	0.15
DB30C10	un	37.8	17.2	7.1	13.5	0.18
DB30C10	co	38.9	24.8	2.8	11.3	1.97

^{a}Optimized structures starting with the crystal structures from the uncomplexed ligands (un) and the complexes with K^+ (co). ^{b}Total energy in kcal mol^{-1}; E_{total} = internal + VdW + el. ^{c}Sum of bond length, bond angle, and dihedral angle strain. ^{d}Total van der Waals energy. ^{e}Total electrostatic energy. ^{f}Root-mean-square deviation (Å) for C and O atoms between optimized and X-ray structures.

Graphics system. The geometries of the complexes were optimized until the root-mean-square (rms) energy gradient was less than 0.001 kcal mol^{-1}. Throughout all calculations a constant dielectric with ϵ equal to 1.0 and a scale factor of 0.5 for the 1–4 VDW and 1–4 electrostatic interactions was used (SCNB = SCEE = 2.0).[17b,c] No cutoff value for the nonbonded interactions was maintained.

Starting geometries for the molecular dynamics simulations were the energy-minimized structures from the molecular mechanics studies. In our most realistic solvent model, the crown ethers and cations were placed in the center of a cubic box with dimensions of 20.9 Å originally containing 128 OPLS methanol molecules that had been equilibrated with the Monte Carlo technique, and the methanol molecules with an atom closer than 2.0 Å to a crown/cation atom were removed. Since no periodic boundary conditions were applied during the molecular dynamics calculations, a few OPLS methanol molecules from the outer solvent shells evaporated. However, the inner solvent shells remained intact during the simulations. Before every molecular dynamics run the structures were equilibrated at 300 K for at least 10 ps. In the case of the rather weak association of two methanol molecules to the dibenzo-30-crown-10 complexes, a positional harmonic constraint of 5.0 kcal mol^{-1} was applied to the carbon atom of the two solvent molecules in order to prevent the solvent from "evaporating". In addition, the heating up of these complexes had to be performed slowly in 100 K increments. For the MD runs the windowing technique[8] was used in which 500 equilibration steps and 500 data collection steps were performed with a 0.001 ps timestep. The total length of the runs was 21 ps in which the parameters for the metal were perturbed into the parameters for another metal. All runs were performed forward (λ:1→0) and backward (λ:0→1) with $\Delta\lambda$ = 0.05. Since the ensembles were generated at constant temperature (300 K) and pressure (0 atm), the energies calculated may be regarded as Gibbs free energies. The SHAKE algorithm[27] was applied to the C–H bonds only. The average time for a perturbation calculation, in which 21 ps of molecular dynamics was evaluated for the crown ether–cation complexes with 0–2 solvent molecules, amounted to 1–2 CPU h on a VAX8650 running under the VMS 4.6 operating system. For performing an equivalent calculation with the solvent box models, this time increased to 15 CPU h. The FPS264 running under the SJE 1.0 operating system was about six times faster than the VAX8650 for the Gibbs module in AMBER.

Results

Uncomplexed Crown Ethers. In order to study the conformations of the uncomplexed dibenzo crown ethers, the X-ray structures of the uncomplexed crown ethers served as starting geometries. After minimization the total energies of the DB18C6 and DB30C10 were 29.0 and 37.8 kcal mol^{-1}, respectively, the conformations being essentially unchanged from the ones observed by X-ray analyses (see Table II). When the starting geometries were the conformation adopted by the ligands in the K^+ complexes, the total energies amounted to 30.2 and 38.9 kcal mol^{-1} for the 18- and 30-membered ring systems. The conformation of the 18-membered crown ether without K^+ showed only minor changes after minimization (0.15 Å rms), relative to the experimental structure with the K^+ cation. For the 30-membered ligand the K^+ conformation changed significantly during this minimization (1.97 Å rms), indicating that in the complex unfavorable interactions exist that are compensated by very favorable electrostatic cation–oxygen atom interactions. The conformations of the uncomplexed crown ethers as observed by X-ray crystallography are lower in energy than the conformations adopted by the ligands in the complexes, although the differences are small.

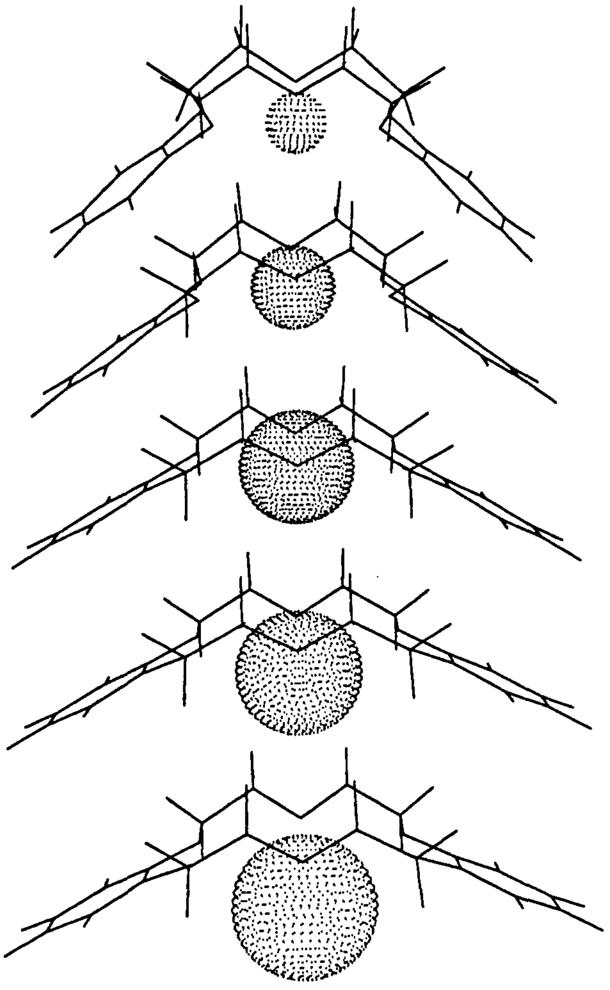

Figure 1. Side view of the molecular mechanics minimized complexes of dibenzo-18-crown-6 with the alkali cations. Top to bottom: the complexes with Li^+, Na^+, K^+, Rb^+, and Cs^+.

Table III. Calculated Interaction Energies^a (kcal mol^{-1}) for (Partially Solvated) Crown Ether–Cation Complexes and Solvent Model–Cation Clusters

cation	1MeOH	6MeOH	DB18C6	DB18C6·2MeOH	DB30C10	DB30C10·2MeOH
Li^+	−79.6	−144.5	−88.3	−138.8	−107.4	−130.5
Na^+	−71.9	−108.7	−72.5	−109.2	−93.3	−105.4
K^+	−62.3	−86.3	−62.4	−90.2	−81.0	−94.3
Rb^+	−55.0	−77.1	−55.1	−79.7	−73.8	−85.6
Cs^+	−46.8	−69.2	−47.0	−68.5	−60.1	−73.6

^{a}Defined as the difference of the total energy of the complex and the total energy of its components in their lowest energy conformation.

Dibenzo Crown Ether–Cation Complexes. The complexes of DB18C6 and DB30C10 with the alkali cations were energy minimized using AMBER. The results of the minimizations are found in Table III and in Figures 1 and 2. All complexes of the 18-membered macrocycle remained in approximately the same conformation as observed in the X-ray structure; only the position of the cation relative to the crown ether changed as the size of the cation changed. This is most obvious for the DB18C6-Li^+ complex, where the Li^+ cation prefers a somewhat asymmetrical position with three short Li^+–oxygen contacts of 1.93 Å each. The oxygens involved in the coordination are two catecholic oxygens belonging to the aromatic moieties at the same side of the polyether chain and the corresponding ether oxygen. In all other cases the

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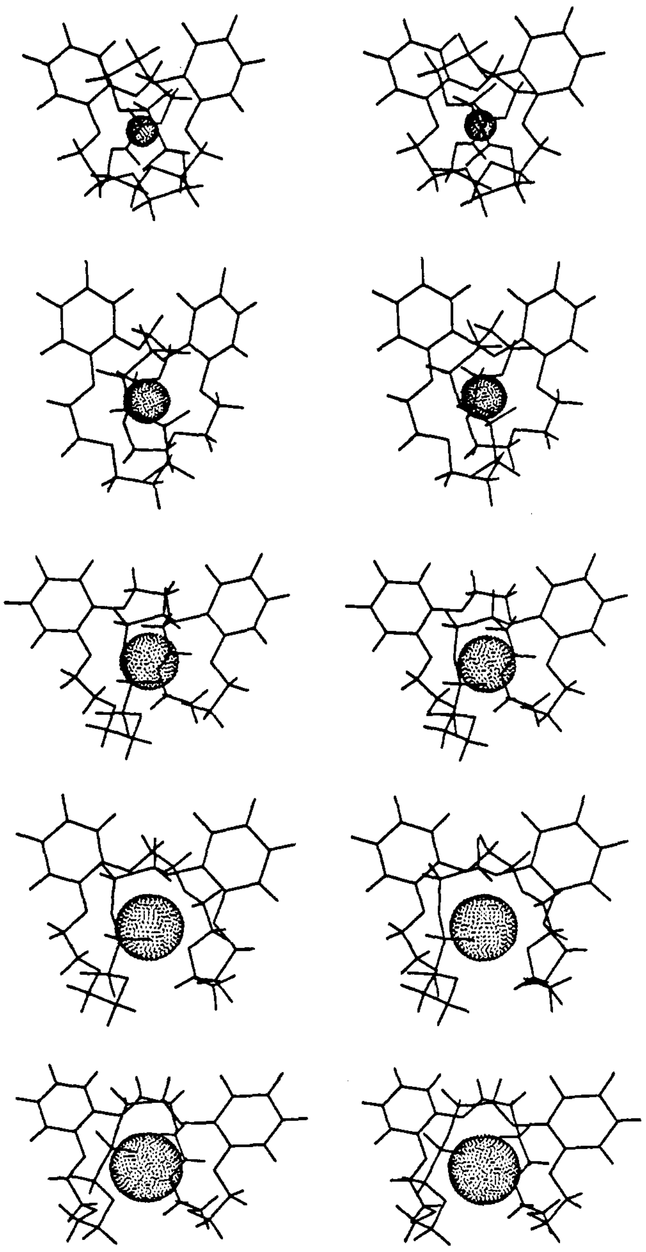

Figure 2. Stereoviews of the molecular mechanics minimized complexes of dibenzo-30-crown-10 with the alkali cations. The order of the cations is the same as in Figure 1.

cation is localized near the center of the cavity. The rms deviation for the C and O atoms between the energy-minimized and X-ray structures[24a–c] for the complexes of DB18C6 with Na^+, K^+, and Rb^+ amounts to 0.43, 0.15, and 0.28 Å, respectively, showing that the conformation stays essentially the same during the minimizations. However, it is clear from looking to the structures in Figure 1 that the conformation of the crown ether is deformed for Li^+ (cavity too big, not suited for tetrahedral recognition) and Cs^+ (cavity too small). In agreement with this, an analysis of all of the components of the energy leads to the conclusion that a minimal conformational energy for the crown ether is observed in the complexes with K^+ and Rb^+. For the 30-membered ligand the situation is different. Here the conformation of the ligand changes somewhat although the ligands wrap around the cation in a way similar to that observed for the complexes with K^+ and Rb^+ cations. For the complexes with K^+ and Rb^+ the rms deviations between calculated and experimental structures[24d,f] with respect to the carbon and oxygen atoms are 0.16 and 0.36 Å. Again the lowest conformational energy for the crown is observed in the complexes with K^+ and Rb^+. From Table III it may be concluded that for both the 18- and 30-membered macrocycles the intrinsically most stable "gas phase" complexes are formed with Li^+. The stability of the complexes gradually decreases going from Li^+ to Cs^+. However, it should be kept in mind that the role of solvation of the cations and complexes has not yet been evaluated.

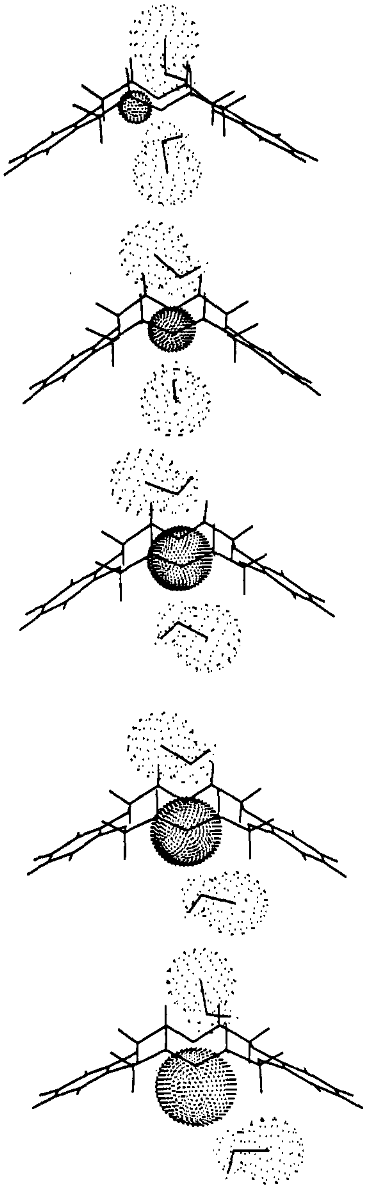

Figure 3. Side views of the molecular mechanics minimized complexes of dibenzo-18-crown-6 with the alkali cations and two OPLS methanol molecules. The order of the cations is the same as in Figure 1.

When two MeOH molecules were added to the crown ether-cation complexes (see Figures 3 and 4) in order to complete the first solvation shell of the cations, the calculated total energies decreased considerably after minimization, the decrease for the DB18C6 complexes being more pronounced than for the complexes with the 30-membered macrocycle. This is in agreement with the observation made in the solid state, for which X-ray studies indicate that the cations are much better encapsulated by the larger relative to the smaller crown ethers.

Upon adding two MeOH molecules to the DB18C6-Li^+ complex the position of the cation changed considerably so that it is tetrahedrally coordinated exhibiting two short (1.91 Å) contacts with the "catecholic" oxygen atoms of one aromatic moiety and two 1.85 Å contacts with the MeOH molecules. A similar phenomenon is observed for the 30-membered macrocycle where in addition to three oxygen atoms from the crown ether one MeOH molecule is involved in the tetrahedral coordination of the cation.

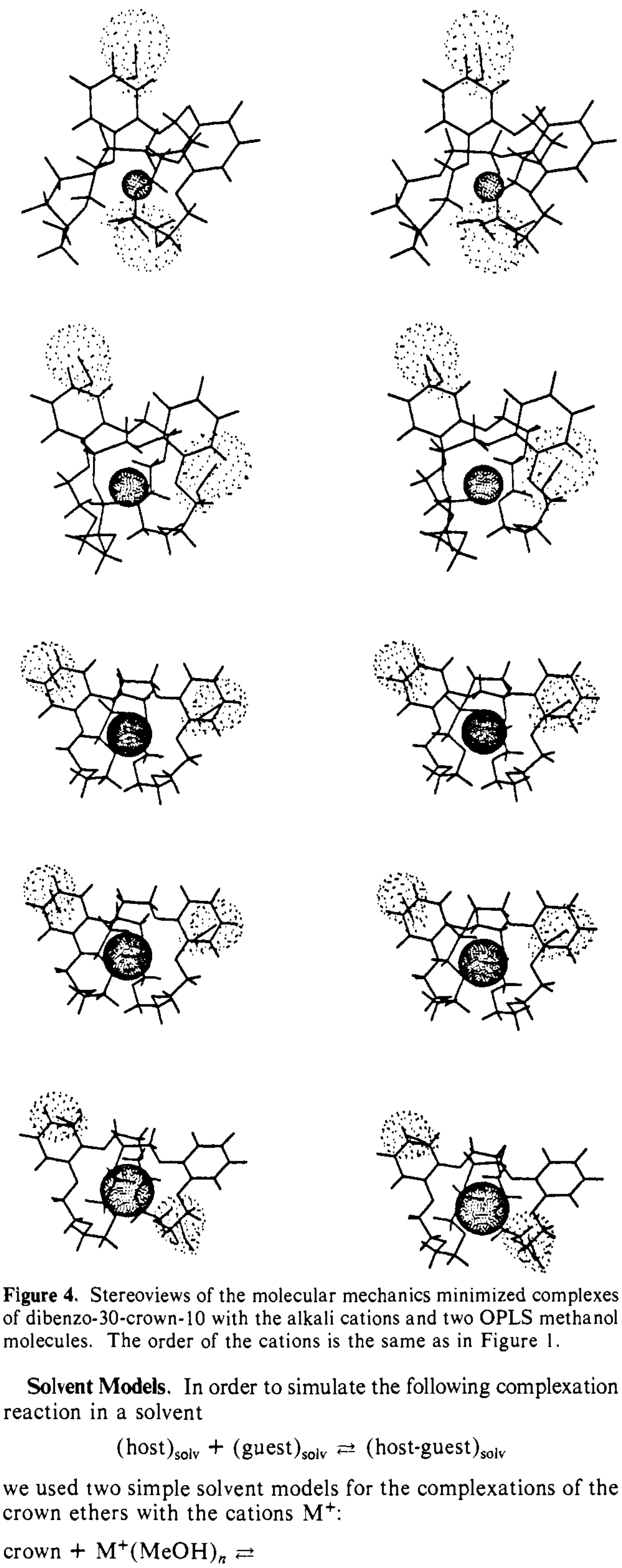

Figure 4. Stereoviews of the molecular mechanics minimized complexes of dibenzo-30-crown-10 with the alkali cations and two OPLS methanol molecules. The order of the cations is the same as in Figure 1.

Solvent Models. In order to simulate the following complexation reaction in a solvent

$$(\text{host})_{\text{solv}} + (\text{guest})_{\text{solv}} \rightleftarrows (\text{host-guest})_{\text{solv}}$$

we used two simple solvent models for the complexations of the crown ethers with the cations M^+:

$$\text{crown} + M^+(\text{MeOH})_n \rightleftarrows \text{crown-}M^+(\text{MeOH})_m + (n-m)\text{MeOH}$$

in which in the simplest case n and m equal 6 and 2, respectively, and in the more complicated case n and m equal 127 and 112–115 (dependent of the crown ether), respectively. We assumed that differences in the solvation of the *uncharged* macrocycles upon complexation were of minor importance relative to the changes in solvation upon complexation of the *charged* species. In our simplest solvent model for the cations, six OPLS methanol molecules were placed in approximate octahedral positions around the cation in order to mimick the first solvation shell, after which the system was minimized. For K^+ and Rb^+ an octahedral coordination of the cation was maintained after minimization, whereas for the Li^+ and Na^+ cations the first coordination sphere consisted of four methanol molecules in a tetrahedral manner surrounding the cation, and the remaining solvent molecules in a second sphere hydrogen bonded to the first one (see Figure 5). For Cs^+ the situation is more complicated; the geometry found here is a sort of flattened tetrahedron of four methanol molecules around the metal cation, the other two solvent molecules again hydrogen bonded to the first shell. The interaction energies between the cation and the six solvent molecules are found in Table III. In general the interaction between the cation and the methanol molecules is somewhat overestimated with respect to the experimental solvation enthalpies (Table IV). However, the qualitative trends are well reproduced.

Table IV. Experimental Gas Phase Enthalpy for a Cation-Methanol Complex and Free Energies of Solvation in Methanol and Complexation[a] with DB18C6 and DB30C10 of the Alkali Cations (kcal mol^{-1})

cation	$\Delta H°$	$\Delta G°_{\text{solv}}$	$\Delta G°_{\text{DB18C6}}$	$\Delta G°_{\text{DB30C10}}$
Li^+	-38.0	-115.0		<1.0
Na^+		-92.0	-5.9	-2.9
K^+	-20.8	-75.0	-6.8	-6.2
Rb^+		-69.0	-5.8	-6.3
Cs^+		-59.5	-4.4	-5.7
ref	27	28	29	16

[a] Determined in methanol, $I = 0.10$, at 298 K.

Table V. Free Energies (kcal mol^{-1}) for Perturbing Guest-1 into Guest-2 in Two Solvent Matrices

guest-1	guest-2	6MeOH	127MeOH	exptl[a]
K^+	Na^+	−19.2 ± 1.0	−21.7 ± 0.2	−17.0
K^+	Rb^+	5.9 ± 0.1	7.6 ± 0.1	6.0
Rb^+	Cs^+	5.0 ± 0.1	7.8 ± 0.2	9.5

[a] Calculated from the experimental data collected in Table IV.

Perturbation Studies. A number of perturbation calculations using molecular dynamics were carried out in order to study the performance of the solvent models and the differences in complexation of the crown ethers toward the alkali cations. In the perturbation calculations the following thermodynamic cycle was used:

$$\begin{tikzcd}
(\text{host})_{\text{solv}} + (\text{guest-1})_{\text{solv}} \arrow[r, "\Delta G_1"] \arrow[d, "\Delta G_3"] & (\text{host.guest-1})_{\text{solv}} \arrow[d, "\Delta G_4"] \\
(\text{host})_{\text{solv}} + (\text{guest-2})_{\text{solv}} \arrow[r, "\Delta G_2"] & (\text{host.guest-2})_{\text{solv}}
\end{tikzcd}$$

The values of ΔG_1 and ΔG_2 have been reported in the literature for DB18C6 and DB30C10 with the alkali cations in MeOH (see Table IV). Although the quantities ΔG_3 and ΔG_4 belong to physically unrealizable processes, they may be used in order to calculate $\Delta G_4 - \Delta G_3$, which should be equal to $\Delta G_2 - \Delta G_1$. First the K^+-6MeOH cluster was perturbed to the corresponding Na^+ and Rb^+ clusters yielding values for ΔG_3 of −19.2 and 5.9 kcal mol^{-1}, respectively (see Table V). These values are in excellent agreement with the differences in solvation free energies calculated from the data in Table IV of K^+ compared to Na^+ and Rb^+ of −17.0 and 6.0 kcal mol^{-1}, respectively. When the solvent model for Rb^+ was perturbed to the corresponding Cs^+ model, the relative free energy difference was found to be 5.0 kcal mol^{-1} which is 4.5 kcal mol^{-1} smaller than the experimental value. A closer look at the experimental data reveals that the differences in solvation free energies between two adjacent alkali metals in the series given in Table IV reaches a minimum between K^+ and Rb^+ after which it increases. This trend is not reproduced by the calculations using our simple solvent model. Since only the first solvation shell is taken into account in the calculations, it is suggested that the effect finds its cause in second or higher order solvation shells. This is confirmed by the calculations using our more complicated solvent model, in which the relative order of the differences in solvation

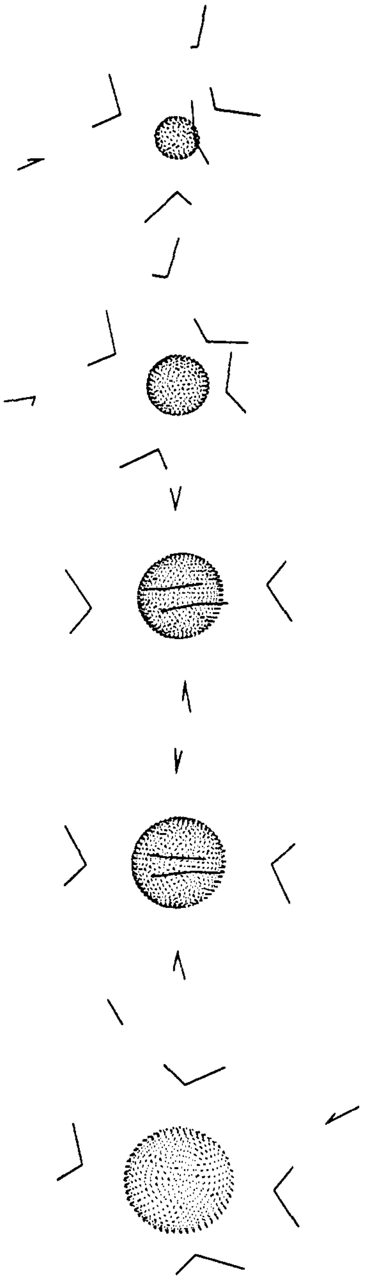

Figure 5. Side views of the molecular mechanics minimized complexes of the alkali cation–OPLS methanol clusters. The order of the cations is the same as in Figure 1.

free energies is reproduced in the perturbation calculations.

Analogous perturbations were carried out for the crown ether·cation complexes in order to calculate ΔG_4. The results are collected in Table VI. It appears that in general the calculated values of $\Delta G_4 - \Delta G_3$ are in qualitative agreement with the experimental values of $\Delta G_2 - \Delta G_1$. The "solvated" complexes apparently give calculated relative free energies closer to the experimental values than the "nonsolvated" complexes. Perturbing K^+ to Na^+ in the complexes is energetically most favorable for DB18C6 and its solvated models, giving ΔG_4 values in the range of −15.6 to −20.4 kcal mol^{-1}. However, when the calculated solvation free energy difference ΔG_3 is taken into account, it turns out that the perturbation is much more unfavourable for DB30C10 than for DB18C6, just as the experimental data indicate. Although the intrinsic complex stability of the Na^+ complexes of both DB18C6 and DB30C10 is greater than the corresponding K^+, Rb^+, or Cs^+ complexes, the relative differences in solvation of the uncomplexed cations seem to dominate the final binding preferences of the ligands. The preference of DB30C10 for Na^+ over K^+ is not enough to compensate for the large preference of the solvent for Na^+ over K^+. This insight differs somewhat from the explanation for the high K^+/Na^+ selectivity of large crown ethers given by Reinhoudt and co-workers.[16]

It is encouraging to see that also more subtle trends such as the experimental ion binding abilities of the dibenzo crown ethers are reflected in the computed data. The binding ability of DB18C6 is a maximum for K^+ and decreases a comparable amount with either Na^+ or Rb^+, with Cs^+ even less tightly bound. The simple "solvated" crown ether model reproduces these trends most accurately. The more complicated solvent model fails to reproduce the difference in complexation between Rb^+ and Cs^+ properly. As one can see from Table VI, the relative size of these $\Delta\Delta G$ values are reproduced by the calculations even though the absolute size of the $\Delta\Delta G$ values are calculated to be a factor of 2–5 larger than experiment. For DB30C10, Rb^+ is slightly better bound than K^+, with Cs^+ less tightly bound, and Na^+ much less tightly bound. With the exception of the small preference of Rb^+ over K^+, the calculations reproduce these trends in a very satisfactory way.

In order to investigate the relation between the force field parameters and the calculated relative free energies, we carried out most of the perturbations shown in Table VI with a different parameter set. We selected the CA–CA–OS–CT dihedral barrier height as a variable in this study since this parameter controls the conformation of the crown ethers around the aromatic moieties to a great deal. By using values for the barrier of 3.5 and 5.0 kcal mol^{-1}, it turned out that the relative free energies were within 2 kcal mol^{-1} of the free energies reported in Table VI. In addition all trends were reproduced as well as with the 2.0 kcal mol^{-1} dihedral barrier. This shows that the reproduction of the trends in the relative free energies in this study is not dependent on subtle differences in torsional parameters.

Discussion

Model Performance. As was pointed out above, the experimental trends found in the relative binding abilities of dibenzo crown ethers toward the alkali cations are reproduced rather well by our calculations. Taking into account that the experimental data were obtained in solution, the very simple model we used for representing a solvent, i.e., only simulating the first solvation shell, performs satisfactorily. The more complicated solvent model seems to give results that in some cases are quantitatively closer to the experimental data, in other cases it is less accurate, and it is computationally much more intensive. The generally good agreement found between calculations and experiment shows that the parametrization of both the crown ethers studied and the OPLS model for methanol are well balanced. This is true for geometrical and energetical data obtained with the molecular mechanics and dynamics calculations.

Although the structural data on the complexes was satisfactorily represented in this study, further improvement of the potential energy functions could make the agreement more quantitative. As has been shown earlier, the addition of both atomic polarizability and nonadditive exchange repulsion terms to the force field leads to a better agreement between computational and experimental values for the total complexation energies of various crown ethers with several cations.[20] Although we used clusters of considerable size in our more complicated solvent study, we plan to use periodic boundary conditions and a constant pressure of 1 atm in order to see if a more quantitative agreement between the computational and experimental free energies can be achieved. We are currently generalizing the AMBER package with respect to its ability to handle arbitrary solvents using periodic boundary conditions.

The good agreement between the free energy differences obtained for systems using different starting geometries is an indication that the sampling was adequate for the systems under study. Nonetheless, we still can only sample a small fraction of allowed conformational space with current computer methodology and resources. However, the dibenzo crown ethers only possess a limited conformational flexibility, and it is far from clear whether for more flexible ligands the sampling would still be representative

Table VI. Results of the Free Energy Calculations (kcal mol^{-1})[a]

host	guest-1	guest-2	ΔG_4	ΔG_3[b]	$\Delta G_4 - \Delta G_3$	$\Delta G_2 - \Delta G_1$[c]
DB18C6	K^+	Na^+	−15.6 ± 1.1	−19.2 ± 1.0	3.6 ± 1.5	0.9
DB18C6	K^+	Rb^+	6.9 ± 0.8	5.9 ± 0.1	1.0 ± 0.8	1.0
DB18C6	Rb^+	Cs^+	7.9 ± 0.2	5.0 ± 0.1	2.9 ± 0.2	1.4
DB18C6-2MeOH	K^+	Na^+	−16.2 ± 1.1	−19.2 ± 1.0	3.0 ± 1.5	0.9
DB18C6-2MeOH	K^+	Rb^+	11.5 ± 1.2	5.9 ± 0.1	5.6 ± 1.2	1.0
DB18C6·2MeOH	Rb^+	Cs^+	10.5 ± 0.7	5.0 ± 0.1	5.5 ± 0.7	1.4
DB18C6-115MeOH	K^+	Na^+	−20.4 ± 1.6	−21.7 ± 0.2	1.3 ± 1.6	0.9
DB18C6-115MeOH	K^+	Rb^+	7.9 ± 1.6	7.6 ± 0.1	0.3 ± 1.6	1.0
DB18C6-115MeOH	Rb^+	Cs^+	7.4 ± 0.3	7.8 ± 0.2	−0.4 ± 0.4	1.4
DB30C10	K^+	Na^+	−11.1 ± 0.3	−19.2 ± 1.0	8.1 ± 1.0	3.3
DB30C10	K^+	Rb^+	6.7 ± 0.1	5.9 ± 0.1	0.8 ± 0.1	−0.1
DB30C10	Rb^+	Cs^+	7.6 ± 0.1	5.0 ± 0.1	2.6 ± 0.1	0.6
DB30C10-2MeOH	K^+	Na^+	−12.1 ± 0.2	−19.2 ± 1.0	7.1 ± 1.0	3.3
DB30C10-2MeOH	K^+	Rb^+	6.3 ± 0.2	5.9 ± 0.1	0.4 ± 0.2	−0.1
DB30C10-2MeOH	Rb^+	Cs^+	8.8 ± 0.1	5.0 ± 0.1	3.8 ± 0.1	0.6
DB30C10-112MeOH	K^+	Na^+	−11.7 ± 1.2	−21.7 ± 0.2	10.0 ± 1.2	3.3
DB30C10-112MeOH	K^+	Rb^+	7.7 ± 0.1	7.6 ± 0.1	0.1 ± 0.1	−0.1
DB30C10-112MeOH	Rb^+	Cs^+	7.8 ± 0.1	7.8 ± 0.2	0.0 ± 0.2	0.6

[a] See the thermodynamical cycle for an explanation of the symbols used. [b] ΔG_3 was calculated by perturbing guest-1·(6MeOH) into guest-2-(6MeOH) or guest-1·(127MeOH) into guest-2·(127MeOH) for the solvent box studies. [c] Calculated from the experimental data collected in Table IV.

using the same equilibration and data collection times. The method described in this paper can be used for designing optimum ligands for certain ions by perturbing both the ligands and the ions. In this paper we focused on ion perturbation, being more simple to carry out and easier to evaluate. Although the absolute error regarding the ionic interactions is large, the error in the relative free energy differences is relatively small.

Structural Results. Although the emphasis throughout this study has been put on the thermodynamical aspects of the complexation and solvation of cations, some interesting structural features also originate from the calculations. In general the deviations between the computed and experimental (X-ray) structures is small, confirming that the force field is well suited for studying crown ether–cation interactions. The prediction that the DB18C6-Li^+ complex is different from the other DB18C6-alkali cation complexes with respect to the position of the cation is interesting. We realize that no extensive search was performed in the conformational space of the structures studied using molecular mechanics. However, we started in most cases from X-ray structures, and therefore we feel that most of the structures are of relatively low energy. In the case of the solvent model studies the calculations give indications of the structure of the first solvation shells of cations in methanol.

What general new insights have come from this study? It has been clear for some time that the strength of interactions between the ions and organic ionophores usually involve a "competition" between the ion–solvent interaction and the ion–ionophore interaction.[2] The smaller the ion with a given charge, the more negative the enthalpy and free energy of solvation in water or methanol. In all of the ionophores studied to date, theoretical studies suggest that the same trend holds for the intrinsic ion–ionophore complexes in vacuo, i.e., the smaller the ion, the more negative the enthalpy and free energy of complexation.

When the smaller ion fits the binding site of the ionophore, i.e., can form ion–ligand interactions of comparable strength to those in the solvent, it will bind more strongly to the ionophore. That is the case with SC24, which binds Cl^- more strongly than Br^-,[15] and the anisole spherand, which binds ions in the order $Li^+ > Na^+ \gg K^+$.[4b] However, 18-crown-6 has its oxygens too far apart to form many optimum oxygen–cation interactions with Li^+ or Na^+. Thus, it binds K^+ optimally because the solvation interactions Li^+ and Na^+ must give up to bind 18-crown-6 are not sufficiently compensated by strong ion–ionophore interactions.

The study presented here has examined this delicate balance between solvation and intrinsic interactions in determining ion specificity of two ionophores, DB18C6 and DB30C10. We have shown that the free energy approach as currently implemented is capable of reproducing the preference for K^+ over Na^+ in both ionophores, with the preference much greater in DB30C10. This greater preference comes about because the extra four oxygen atoms in DB30C10 contribute more to the extra affinity for K^+ than Na^+. The structural basis for this is that, because of the greater size of K^+, it can accomodate more oxygen atoms in an optimum first shell of ligands. In DB18C6, the preference for K^+ over Rb^+ and Cs^+ is qualitatively reproduced in both of the simpler solvation models. Apparently the less effective fit of the larger cations into DB18C6 prevents them from competing well with K^+. In DB30C10, this is not the case; the ability to form many effective ion–ionophore interactions allows the larger cations such as Rb^+ to compete very well with K^+ for the ionophore.

Conclusion

This study has shown that a combination of molecular mechanics and dynamics calculations can qualitatively reproduce experimental trends with respect to binding preferences of receptor molecules like 18-crown-6 to alkali cations in methanol solution. Clusters with a few methanol molecules with alkali cations may serve as computationally inexpensive solvent models. Even with the simple approach presented in this paper, various subtle trends in relative complexation free energies were reproduced. Thus, this study gives confidence in the ability of the theory to make meaningful predictions on design of better ligands/receptors for target guest molecules.

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Note Added in Proof. Very recently two free energy perturbation studies were reported on the complexation of 18-crown-6 with alkali cations in water[31] and methanol.[32] Although somewhat different computational procedures were followed in these studies, the same good agreement between calculated and experimental relative binding free energies was obtained.

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