the level of statistical uncertainties in the MC simulation data; e.g., the shoulders at $R_{C-O2} = 2.4$ and 2.6 Å. Also in accord with the MC results, the HNC–RISM theory predicts a shift of the transition state from $R_{C-O2} = 2.39$ Å in the gas phase to 2 Å in water. Another advantage of the HNC–RISM theory is that temperature and density derivatives can be used to decompose the free energy into enthalpic and entropic contributions. It shows that the enthalpy provides the dominant solvent effect.

It is important to note also that the HNC–RISM calculation requires ~2 orders of magnitude less computer time than the MC simulation; an equivalent of 180 days of VAX 11/780 time was needed for the latter. Therefore, it seems clear that, given a set of quantum mechanical potentials (which are themselves vey time consuming to determine by ab initio methods, particularly for reactions), it is desirable to employ the analytic integral equation theory to make a preliminary exploration of the reaction mechanism in aqueous solution or do other more extensive searches of the conformational space that are not possible by simulations. Moreover, the HNC–RISM free energy profiles can provide guidelines for the construction of a biasing function for the umbrella sampling scheme used in simulation studies.

A disadvantage of the HNC–RISM theory is that it is approximate, even for a given set of parameters, and that there are possible inaccuracies in the results. In the present case, molecular dynamics simulations with the same model potential show some quantitative deficiencies in the radial distribution functions from the HNC–RISM theory. The accuracy of the thermodynamic values for the reaction path presumably involves some cancellation of errors. In part, this is due to the fact that differences in rather than absolute values of the solvation free energy are used. However, the nature of the error cancellation is not fully understood, so that it is not yet possible to predict a priori when the HNC–RISM theory can be applied with confidence. Experience from a number of studies, including the present one, suggests that it is best for polar or charged solutes with net charge no larger than unity. More studies are needed to clarify the situation. Also it would be useful to have better closures that retain the simplicity of the HNC–RISM calculations while at the same time improve the accuracy of the thermodynamic and structural results.[58]

Acknowledgment. We thank Dr. Jiin-yun Liang for contributing to our interest in this system. We also thank Drs. Jiali Gao and Jiin-yun Liang for helpful discussions. This research was supported in part by a grant from the National Science Foundation.

Registry No. OH^-, 14280-30-9; H_2CO, 50-00-0.

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Free Energy of Association of the 18-Crown-6:K$^+$ Complex in Water: A Molecular Dynamics Simulation

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Abstract: We study a cation–crown association process in aqueous solution, using thermodynamic perturbation theory[1] and molecular dynamics simulations. The process studied is the association of K$^+$ with 18-crown-6. The results obtained in these simulations give both structural and energetic insight. The potential of mean force for the association of K$^+$ to 18-crown-6 in water displays a minimum significantly different from the crystal structure. This result can be rationalized by the greater solvation of K$^+$ in this configuration, compared to the crystal structure. The structures of 18-crown-6 during the dynamics simulations were studied by examining the values of the dihedral angles; the structure is in the D_{3d} conformation found in the crystal when the K$^+$ is in the center of the crown. However, at K$^+$ distances greater ~1 Å from the center of the crown, the crown changes conformation and remains in a relatively high energy (~5 kcal/mol higher internal energy than D_{3d}) conformation throughout the rest of the simulation. The calculated ΔG_b for the association of the complex in water is -3.5 ± 0.4 kcal/mol, in good agreement with the experimental value of -2.9 kcal/mol.

I. Introduction

One of the recent exciting developments in computational chemistry has been the ability to calculate free energies for complex processes in solution. These include the application of free-energy perturbation methods to study solvation,[2] enzyme catalysis,[3] and ligand binding.[4] This approach typically is used to compare properties, e.g., the relative solvation or binding free energy of two molecules.

On the other hand, it is well-known that one can calculate the free energy as a function of coordinate or potentials of mean force (PMF), and applications of the latter approach have been extremely interesting as well. A knowledge of the PMF allows one to examine in detail the effect of solvent on the solute–solute or ion–ion interactions, and to determine various thermodynamic properties such as the location of the barrier height, the equilibrium constant, and the binding free energy. Many of these properties can be compared directly to experimental measurements. These calculations are typically even more time consuming than the free-energy perturbation calculations because one is attempting to calculate the relative free energy over a large range of coordinates. The PMF's of two ions,[5] two Lennard-Jones solutes,[6] two amides,[7] or two nucleic acid bases[8] in water have been de-

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termined by computer simulations or by statistical mechanical theory. The PMF's for the reaction of $Cl^- + CH_3Cl$[9] and hydrolysis of amides[10] by the serine proteases have been determined using a combination of quantum and molecular mechanical methods.

In general, the agreement with experiment achieved when doing such PMF simulations has been good. But the opportunity to make direct and meaningful agreement with experimental free energies of association has been limited to a few cases.

We present here simulations of the free energy of association of K$^+$ to 18-crown-6 in water. This system is a prototype of ion–neutral noncovalent association. Our calculations are one of the first to directly study noncovalent association in an ion–neutral system using the thermodynamic perturbation theory.[1] Furthermore, our system is among the largest and most complex molecular systems (18-crown-6) studied with PMF methods to date. Recently, a different approach has been proposed by van Eerden et al.[11] to determine the PMF of this system. Many of the results presented in this report are in qualitative agreement with those of van Eerden et al.[11] with the exception that we are able to reproduce the experimental binding free energy, ΔG_b.

Although the near-quantitative agreement of our calculated ΔG_b with experiment[12] may be fortuitous, the fact that the agreement is good lends support to both the potential functions and the methodology we have used to determine ΔG_b. The simulations presented support the importance and usefulness of general applications of the PMF approach to macromolecular systems.[13,14] In section II we briefly outline the computational methodology and the potential functions. The results are presented and discussed in section III. Section IV summarizes our conclusions.

II. Methodology

The calculations employed the thermodynamic perturbation theory[1] to determine the potential of mean force. The approach used here is similar to the previous study of the PMF of two nucleic acid bases in water,[8] which is based on the equation

$$A_1 - A_0 = -kT \ln \langle \exp(-\beta(U_1 - U_0)) \rangle_0 \qquad (1)$$

in which the free-energy difference between a reference system, 0, and a perturbed system, 1, is given as a function of the average energy difference between two systems. Here, $\langle ... \rangle_0$ indicates the average is calculated corresponding to the potential energy describing state 0, k is the Boltzmann constant, T is the absolute temperature, and $\beta = 1/kT$. By performing a series of such calculations along the reaction coordinate, the resulting accumulated free-energy changes yield the potential of mean force.

Subsequently, the PMF is used to estimate the ion–crown association constant and the binding free energy via the following equations[15]

$$K_a = N \int_0^{r_c} 4\pi r^2 \exp(-W(r)/kT)\, dr \qquad (2)$$

and

$$\Delta G_b = -kT \ln K_a \qquad (3)$$

in which $W(r)$ is the ion–crown potential of mean force, r_c is the geometric limit for association, and N is the Avogadro number. These equations have been used successfully recently in the calculations of the association constants for amides[7] and base pairs[8] in solution.

The model consists of an 18-crown-6:K$^+$ complex immersed in a periodic box of 907 water molecules with the box lengths of 29, 29, and 37 Å in the x, y, and z directions, respectively. The initial coordinates of the complex were taken from the X-ray data[16] where the K$^+$ is located at the center of the 18-crown-6 with perfect D_{3d} symmetry. The potential function describing the interactions of the system has the following form:

$$U_{\text{total}} = \sum_{\text{bonds}} K_r(r - r_{\text{eq}})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{\text{eq}})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j} \left\{ \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} \right] + q_i q_j / \epsilon R_{ij} \right\} + \sum_{\text{H bonds}} \left\{ \frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}} \right\} \qquad (4)$$

In this equation U_{total} is the potential energy of the system; K_r and r_{eq} are the bond stretching constant and the equilibrium bond distance; K_θ and θ_{eq} are the bond angle stretching constant and the equilibrium bond angle; V_n, n, and γ are the torsional force constant, the periodicity of the torsional term, and the phase angle; A_{ij} and B_{ij} are the nonbond (Lennard-Jones) repulsion and attraction coefficients; R_{ij} is the interatomic distance between atoms i and j; q_i and q_j are the atomic partial charges on atoms i and j; and ϵ is the dielectric constant (=1 in the present case). The all-atom force field of Billeter et al.[17] was used to model the interactions of 18-crown-6 and 18-crown-6:K$^+$ complex while the TIP3P[18] model was used for the water–water interactions.

In calculating the PMF's, we have approximated the reaction coordinate as the distance between 18-crown-6 center of mass and K$^+$, which is along the z direction in this study. This approximation may not agree with the description of the reaction coordinate resulting from a steepest path calculation.[19] We started out the simulations in which both solutes were perturbed with a distance of ±0.250 Å. Although the position of the minimum in the PMF was acceptable, however, these simulations predicted a minimum free energy which is deeper than that presented here, and the PMF did not level off at long distances. Consequently, we reduced the perturbation distance to ±0.125 Å and carried out the simulations from $r = 0$ Å to the near-contact minimum. We then used a perturbation distance of ±0.250 Å for distances larger than the contact minimum. We found this approach gave more acceptable results for the free energy.

The simulations were carried out with a time step of 1.5 fs, and the SHAKE[20] procedure was adapted to constrain all the bond lengths to their equilibrium values. A nonbonded cutoff of 9 Å was used for water–water interactions, and no cutoff was imposed on the water–crown, water–ion, and crown–ion interactions. The simulations use periodic boundary conditions with a constant pressure (1 atm) and constant temperature (T = 300 K) algorithm with coupling constants $\tau_p = 0.5$ ps^{-1} and $\tau_t = 0.2$ ps^{-1}. The canonical ensemble was employed using a temperature of 300 K. A total of 19 simulations were carried out to cover a total distance of 7 Å; each simulation consisted of 7.5-ps equilibration followed by 15 ps of data collection for each ion–crown center of mass separation. All the simulations were carried out using a modified version of AMBER 3.0.[21]

Finally, we note here that the preliminary results using the protocol outlined above indicated there were two minima on the PMF. One was located at 0.65 Å and the other one at 1.5 Å. They were separated by a small barrier height of 0.65 kcal/mol. The binding free energy (−3.2 kcal/mol) estimated from these simulations was in excellent agreement with experimental data (−2.9 kcal/mol). However, we felt the occurrence of two minima with such a small barrier between them was probably due to inadequate sampling. We reequilibrated the system at various positions near these minima using the last coordinates of the previous simulations as starting points and then carried out further perturbation calculations. We found that the first minimum disappeared and the second one remained in the same location, with a ΔG_{bind} of −3.5 kcal/mol. We present these results below.

III. Results and Discussion

We present in Figures 1a and 1b the potential energy of the 18-crown-6:K$^+$ complex in the gas phase as a function of ion–crown center of mass distance and the PMF for association of the K$^+$ to 18-crown-6 in solution. In displaying the PMF in the Figure

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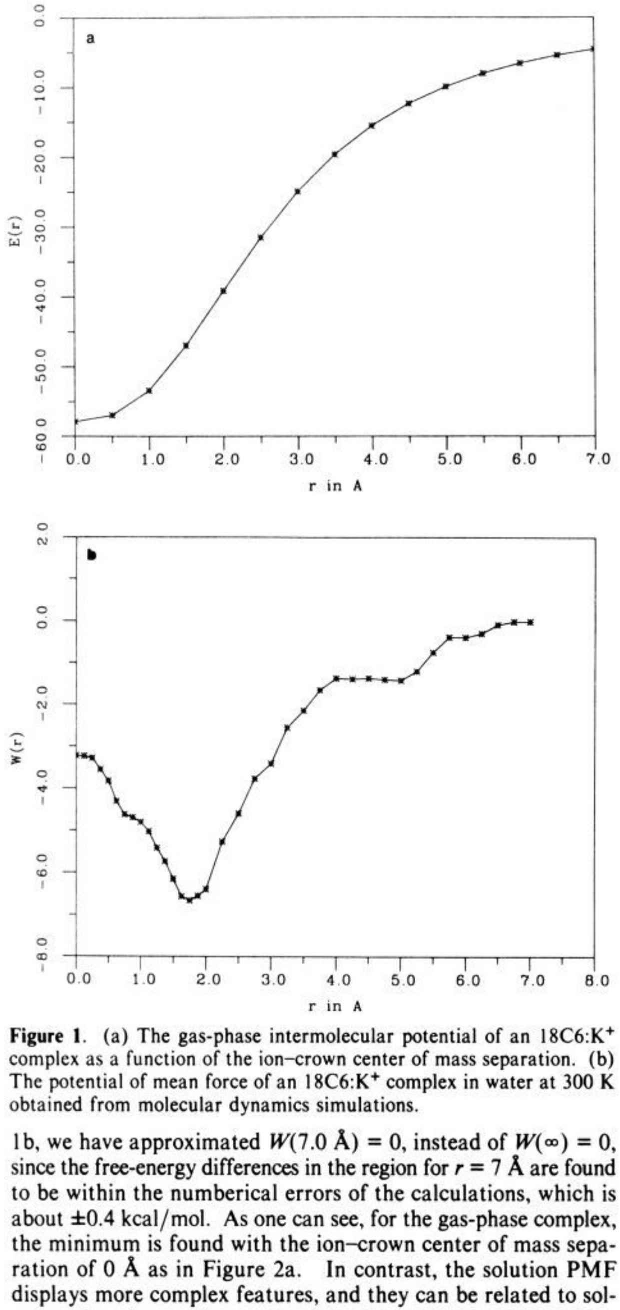

Figure 1. (a) The gas-phase intermolecular potential of an 18C6:K$^+$ complex as a function of the ion–crown center of mass separation. (b) The potential of mean force of an 18C6:K$^+$ complex in water at 300 K obtained from molecular dynamics simulations.

1b, we have approximated $W(7.0\ \text{Å}) = 0$, instead of $W(\infty) = 0$, since the free-energy differences in the region for $r = 7$ Å are found to be within the numberical errors of the calculations, which is about ±0.4 kcal/mol. As one can see, for the gas-phase complex, the minimum is found with the ion–crown center of mass separation of 0 Å as in Figure 2a. In contrast, the solution PMF displays more complex features, and they can be related to solvent–solute interactions.

On examining the PMF of the complex, we find the contact minimum corresponds to the ion–crown center of mass separation of 1.7 Å instead of the 0 Å found in the crystal. At this separation (Figure 2b and 3), the potassium ion moves out of the pocket and interacts favorably with water and with the 18-crown-6. We found three water molecules interact strongly with K$^+$ on one side, and the crown oxygens interact with K$^+$ on the other side. In the early molecular dynamics simulations by van Eerden et al.,[11] they found a contact minimum corresponding to the K$^+$-crown center of mass separation near 1 Å. For this region, they found two water molecules interacting strongly with K$^+$ at one side and another one at the other side of the 18-crown-6.

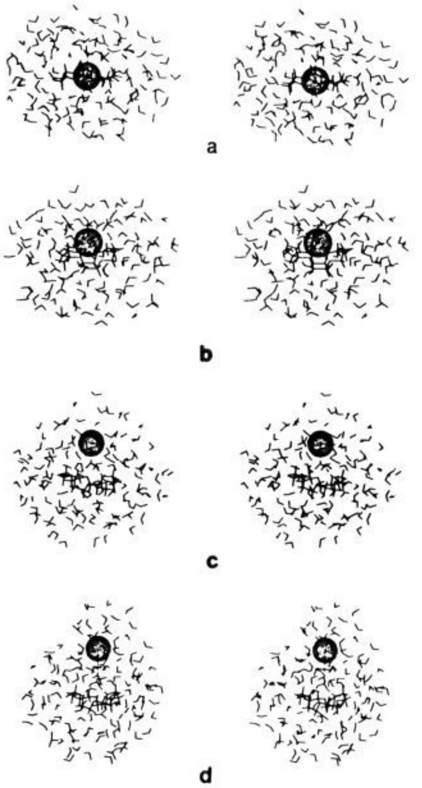

Figure 2. A snapshot of water molecules within 6 Å of the complex in water (a), equilibrated at $r = 0$ Å, (b) at the contact region $r = 1.75$ Å, (c) the ion–crown center of mass separation of 5.0 Å, (d) the ion–crown center of mass separation of 7.0 Å.

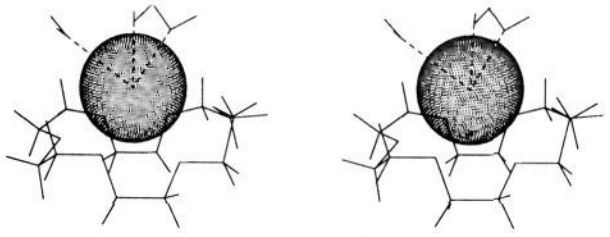

Figure 3. A snapshot of the crown, the K$^+$, and the three waters coordinating to the K$^+$ from Figure 2b.

The regions beyond 4.0 Å can be described as the solvent-separated regions, where the 18-crown-6:K$^+$ complex is separated by a water molecule (e.g., water–crown–water–ion–water). In this regions, the water oxygen is interacting with the ion, and its hydrogens are interacting with the oxygens of the 18-crown-6 as shown in Figure 2c. These features are similar to those found by van Eerden et al.[11] in their molecular dynamics simulations. The so-called "bridging solvation" of crown–water–ion observed in regions of 4.0–5.3 Å is very interesting and is analogous to what is found in the PMF for two unlike ion pairs in water.[5a] It may be one of the reasons why the free energies in this regions are lower than in the regions of 5.4–7.0 Å.

In Figure 2d, we presented a "snapshot" of the complex corresponding to the K$^+$-crown center of mass separation of 7 Å. The potassium ion has been fully surrounded by water molecules, and no water molecules are found to interact simultaneously with the 18-crown-6 and the ion.

We examined the conformations of the 18-crown-6 during the association by examining their dihedral angles and their corresponding minimized energy of the crown ether as a function of ion–crown center of mass separation. We only focus on the final structures of the crown ether at the end of each simulation distance, since these will be representative of the conformational mix. We then minimize each of these structures in the absence of solvent or cation. As one can see in Table I, the conformation of the crown changes from D_{3d} to different conformations beyond the ion–crown center of mass separation of 0.7 Å. In the contact minimum regions, the crown conformation is not of D_{3d} symmetry. In the regions beyond the contact minimum, crown conformations are mainly of C_1 and C_2 symmetry, and the calculated conformation is similar in the remainder of the simulations. This is in contrast to the crystallographic conformation for the uncomplexed crown

Table I. The Conformation[a] of 18-Crown-6 as a Function of Ion–Crown Center of Mass Separation

X-ray[b]																		
D_{3d} (18.3 kcal/mol)[c]	a	g^-	a	a	g^+	a	a	g^-	a	a	g^+	a	a	g^-	a	a	g^+	a
C_i (18.1 kcal/mol)[c]	a	g^+	a	a	g^-	g^+	a	a	a	a	g^-	a	a	g^+	g^-	a	a	a
MD[d] (r, Å; E, kcal/mol)																		
0.000; 18.3	a	g^-	a	a	g^+	a	a	g^-	a	a	g^+	a	a	g^-	a	a	g^+	a
0.125; 18.3	a	g^-	a	a	g^+	a	a	g^-	a	a	g^+	a	a	g^-	a	a	g^+	a
0.375; 18.3	a	g^-	a	a	g^+	a	a	g^-	a	a	g^+	a	a	g^-	a	a	g^+	a
0.625; 21.7	a	g^-	a	a	g^-	a	a	g^+	a	a	g^-	a	a	g^-	a	a	g^+	a
0.875; 24.1	a	g^+	a	a	g^-	a	a	g^-	a	g^-	g^-	a	a	g^-	a	a	g^+	a
1.125; 23.8	a	g^-	a	a	g^-	a	a	g^+	a	a	g^+	g^+	a	g^+	a	a	g^+	a
1.375; 23.2	a	g^-	a	a	g^-	a	a	g^+	a	a	g^+	g^+	a	g^+	a	a	g^+	a
1.625; 26.8	g	g^-	a	a	g^+	a	a	g^-	a	a	g^+	g^+	a	g^-	a	a	g^+	a
1.875; 22.0	g	g^-	a	a	g^-	a	g^-	g^-	a	a	g^+	g^+	a	g^-	a	g^-	g^-	a
2.250; 23.4	a	g^+	g^+	a	g^-	a	g^-	g^-	a	a	g^+	g^+	a	g^-	a	g^-	g^-	a
2.750; 23.4	a	g^+	g^+	a	g^+	a	g^-	g^-	a	a	g^+	g^+	a	g^+	a	g^-	g^-	a
3.250; 23.4	a	g^+	g^+	a	g^+	a	g^-	g^-	a	a	g^+	g^+	a	g^+	a	g^-	g^-	a
3.750; 23.4	a	g^+	g^+	a	g^+	a	g^-	g^-	a	a	g^+	g^+	a	g^+	a	g^-	g^-	a
4.250; 23.4	a	g^+	g^+	a	g^+	a	g^-	g^-	a	a	g^+	g^+	a	g^+	a	g^-	g^-	a
4.750; 26.2	a	g^-	g^+	a	g^+	a	g^-	g^-	a	a	g^+	g^+	a	g^+	a	g^-	g^-	a
5.250; 23.4	a	g^+	g^+	a	g^+	a	g^-	g^-	a	a	g^+	g^+	a	g^+	a	g^-	g^-	a
5.750; 23.4	a	g^+	g^+	a	g^+	a	g^-	g^-	a	a	g^+	g^+	a	g^+	a	g^-	g^-	a
6.250; 23.4	a	g^+	g^+	a	g^+	a	g^-	g^-	a	a	g^+	g^+	a	g^+	a	g^-	g^-	a
6.750; 23.4	a	g^+	g^+	a	g^+	a	g^-	g^-	a	a	g^+	g^+	a	g^+	a	g^-	g^-	a
7.250; 23.4	a	g^+	g^+	a	g^+	a	g^-	g^-	a	a	g^+	g^+	a	g^+	a	g^-	g^-	a

[a] Dihedral angle ranges for the 18 different single bonds of 18-crown-6. The values at positions 2, 5, 8, 11, 14, and 17 correspond to OCCO bonds; the others to COCC. [b] X-ray structures in the presence of K$^+$ (D_{3d}) and absence of cation (C_i). [c] Energy after in vacuo energy minimization to a gradient of 0.1 kcal/mol Å^2. [d] Structures after MD windows. The K$^+$–crown center of mass distance and energy after in vacuo energy minimization to a gradient of 0.1 kcal/mol Å^2 are listed, and the conformation of the last configuration in the window is presented.

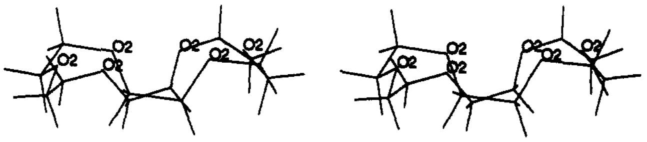

Figure 4. The minimized structure of the C_2 conformation of the crown ether at the K$^+$–crown center of mass separation of 7 Å.

ether, which is of C_i symmetry. In the recent study of the conformations of the uncomplexed 18-crown-6 in solution by Straatsma and McCammon,[22] they found the most populated conformations are of D_{3d} and C_1 symmetry, and no C_i symmetry was observed.

Table I also contains the conformational energies of the crown ether after molecular mechanics minimization starting with the structure at the end of each simulation distance. The significance of the conformation a g^+ g^+ a g^+ a g^- g^- a a g^+ g^+ a g^+ a g^- g^- a, which is observed in 10 simulations is not clear. It contains g^+ or g^- at each OCCO linkage, but has, in addition, four g^+ or g^- COCC linkages, which is energetically costly in vacuo. The net destabilization of this conformation, 5 kcal/mol compared to D_{3d}, can be easily compensated for by better interactions with the K$^+$ and H_2O molecules. In fact, one can see that this conformation (Figures 3 and 4) has all six oxygens on one side of the crown ether molecule, optimizing K$^+$...crown interactions, so it makes sense that, as K$^+$ is pulled away from the crown, this conformation is favored. These results are in qualitative accord with the study of the complexation of Na$^+$ with 18-crown-6 by Hase et al.,[18] in which the "oxygen planes" merge upon association with Na$^+$ (Figure 7 in ref 18).

IV. Conclusion

We have presented an extensive computer simulation on a complex molecular system, involving approximately 2800 atoms for nearly 500 ps of total simulation. In this study, we have computed the PMF for the association of K$^+$ to 18-crown-6 in water. We found the PMF of the complex in water displays a minimum which appears to have very favorable crown–cation–water interactions. We found that the minimum energy distance of the K$^+$-crown complex in water is not at the center of the crown ether as found in X-ray structures, but is 1.7 Å away from the center. These results indicate that the potassium ion prefers to move out the pocket to interact with water molecules at the same time it interacts with the crown ether. Furthermore, we found the symmetry of the crown during the association process is mainly of C_1 and C_2 symmetry.

We estimated the binding free energy for the 18-crown-6:K$^+$ complex in solution via eq 2 and 3. The calculated ΔG_b for the association of the complex in water is −3.5 ± 0.4 kcal/mol, in good agreement with the experimental value of −2.9 kcal/mol. (See Note Added in Proof.) This result suggests that our approach is reasonable and well-balanced. This balance may seem somewhat surprising, given that the TIP3P model is an "effective" two-body potential, with dipole moment enhanced to reproduce the enthalpy of vaporization of liquid water and the 18-crown-6 charges have been fit to gas-phase quantum mechanical calculations. However, the 6-31G* basis set used in that fit leads to dipole moments larger than experiment typically by 10–20%, comparable to the enhancement of the water dipole in the TIP3P model. Thus, the electrostatic charges in water and 18-crown-6 are likely to be well-balanced, and this will lead to a reliable relative attraction of these molecules to K.$^+$ It is not clear why our ΔG_b is much more reasonable than that found by van Eerden et al.,[11] but a possible explanation lies in our use of no cutoff for ion–crown interactions with each other and with water. This avoids possible cutoff artifacts when the K$^+$ and crown separate. We have studied the PMF with only one set of potential function parameters, and there are others that could be used for water–water, water–ion, crown–water, and crown–ion interactions. But it is highly unlikely that good results would be achieved unless the sets of interaction potentials are *balanced*, i.e., have been derived in closely analogous ways.

We plan to use same approach to obtain the PMF's for the ion–crown complex in a nonaqueous solvent such as methanol. Thus, we will be able to examine the effects of the different solvents on the PMF's of ion–crown complexes immersed in solution. We will report these results in a forthcoming communication.

Note Added in Proof. In view of the fact that eq 2 is rigorously correct only for spherical molecules, we have examined the consequence of considering the K$^+$/18-crown-6 association as a function of both r and θ (the angle the K$^+$ makes with the axis through the center of the crown). Unfortunately, it is computationally prohibitive to calculate W as a function of both r and θ. If we assume there is essentially no attraction at $\theta = 90$, where the K$^+$ approaches in the plane of the crown, $W(r,\theta{=}90°) = 1/(e^r - e^{-r})$, $W(r,\theta{=}0)$ as in Figure 1b. We then assume $W(r,\theta) =$

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[22] Staatsma, T. P.; McCammon, J. A. *J. Chem. Phys.* **1989**, *91*, 3631.

$W(r,\theta{=}0°)\cos\theta + W(r,\theta{=}90°)\sin\theta$. We can evaluate eq 2 as follows

$$K_a = \int_0^{2\pi} d\phi \int_0^{\pi} \int_0^{r_c} e - \frac{W(r,\theta)}{kt} r^2\, dr \sin\theta\, d\theta$$

$$\text{and } \Delta G = -RT \ln K_a$$

With these approximations, $\Delta G = -2.0$ kcal/mol, still in very respectable agreement with the experimental $\Delta G = -2.9$ kcal/mol.

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Activation Hardness: New Index for Describing the Orientation of Electrophilic Aromatic Substitution

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Abstract: The *activation hardness* concept is defined and used to predict the orientation of electrophilic aromatic substitution. With the transition state defined much in the manner of Wheland, it is shown that the activation energy is the negative of twice the change in hardness in going from reactant to transition state (called the activation hardness). The smaller the activation hardness is the faster the reaction is; the harder the transition state is the better. Calculations presented show that the activation hardness is an excellent index for predicting orientation effects. Several new principles of maximum hardness or softness are stated and discussed.

I. Introduction

The ultimate goal of quantum chemistry is molecule design. The exploration of chemical reactions is one of the ingredients of which the path to this goal is made. As early as in the 1930's there was devised the absolute rate theory,[1] which is still considered as one of the most sophisticated theories to predict reaction rate. For most practical problems the value of sophisticated theories is limited by their tractabilities. Hence simpler model theories have been developed over the years. A simple reactivity index is attractive not only because it can be easily calculated but also because a simple index can provide general chemical insights. In this paper we define and demonstrate the utility of a new reactivity index.

The molecular orbital theory as formulated by Mulliken and Hund has been very successful in explaining and predicting chemical behaviors for an enormous number of molecules. It was Fukui who first noticed the prominent role played by the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) in governing chemical reactions.[2] The energy difference between the LUMO of an electron acceptor and the HOMO of an electron donor has long been used as a reactivity index.[3] Recent investigations have been revealing that the HOMO–LUMO gap is an important stability index for the individual species concerned.[4–7] A large HOMO–LUMO gap implies high stability. High stability of a molecule reflects its low reactivity toward chemical reactions in some sense.

There exists a semiempirical principle, the hard and soft acids and bases (HSAB) principle, that encapsulates both thermodynamic and kinetic propensities of numerous molecules.[8] The concept of hardness, first emphasized by Pearson as an index of reactivity,[8] was quantified in 1983 by Parr and Pearson.[9] The quantified "absolute hardness" concept has been shown to be useful in chemistry.[4,10–13] For example, for organic molecules the property conventionally called aromaticity has been shown to parallel hardness,[10] and an index called relative hardness has been introduced to distinguish aromatic from antiaromatic species.[11]

In the present paper we show how the hardness concept can be employed to predict the orientation of electrophilic aromatic substitution, a problem area in which there is a large literature.[2,15–25] We introduce the concept of *activation hardness*, and

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