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Molecular Recognition in Nonaqueous Solvents: Na^+, K^+, and 18-Crown-6 in Methanol

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Abstract: Molecular dynamic simulations are used to predict the binding affinity in host–guest systems by the thermodynamic cycle–perturbation method. The relative free energy of solvation of Na^+ and K^+ in methanol (19.6 kcal/mol) and the relative free energy of binding of Na^+ and K^+ to 18-crown-6 in methanol (−3.5 kcal/mol) are calculated by thermodynamic integration in the canonical ensemble. These results are in reasonable agreement with the experimental values, 17.3 and −2.47 kcal/mol, respectively.

The ability of host molecules to discriminate among various guests is widely known.[1] A theoretical technique, the thermodynamic cycle–perturbation method,[2] has recently been introduced that should be useful in the interpretation and prediction of binding affinity in host–guest systems. The first application of this technique helped to rationalize the relative affinities of Cl^- and Br^- for the cryptand SC24 in liquid water.[3] In the present article, we describe initial results of a series of new calculations designed to explore the recognition of alkali cations by crown-type receptors in liquid methanol. More specifically, the present results include estimates of the relative free energy of solvation of Na^+ and K^+ in methanol as well as of the relative free energy of binding of these ions to 18-crown-6 in methanol.

Theory

In the thermodynamic cycle–perturbation method, one considers a cycle that comprises two binding reactions and two hypothetical perturbation reactions. This allows the relative free energy of binding of guests G and g to host H to be expressed as $\Delta\Delta A = \Delta A_4 - \Delta A_3 = \Delta A_2 - \Delta A_1$. The free energies of perturbation, ΔA_3 and ΔA_4, are calculated to obtain $\Delta\Delta A$. ΔA_3 is the change in free energy upon exchanging guest g with G in the solvent. This quantity is the relative free energy of solvation between the two guests in the particular solvent.[4,5] ΔA_4 is the change in free energy for the same exchange, while the guest is bound to the host.

$$\begin{tikzcd} \text{g} + \text{H} \arrow[r, "\Delta A_1"] \arrow[d, "\Delta A_3"'] & \text{g:H} \arrow[d, "\Delta A_4"] \\ \text{G} + \text{H} \arrow[r, "\Delta A_2"'] & \text{G:H} \end{tikzcd} \tag{1}$$

The calculations discussed in this article were used to obtain the relative free energy of binding of Na^+ and K^+ to the polyether 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctane) in liquid methanol. The relevant cycle is given by (1) with $g \equiv Na^+$, $G \equiv K^+$, and $H \equiv$ 18-crown-6. ΔA_3 and ΔA_4 were calculated by thermodynamic integration[6] and were compared with experimental estimates for $\Delta A_2 - \Delta A_1$ and for ΔA_3.

Thermodynamic integration allows for the calculation of the free energy difference between two states A and B. In the canonical ensemble, this is given by

$$\Delta A_{BA} = A_B - A_A = -\beta^{-1} \ln (Q_B/Q_A) \tag{2}$$

Here, A_i is the Hemholtz free energy of state i, and β is the reciprocal of the product of Boltzmann's constant and absolute temperature. Q_i is the partition function for state i and is defined as

$$Q_i = \frac{1}{N!h^{3N}} \int\int \exp\,[-\beta\{V_i(\mathbf{q}) + T_i(\mathbf{p})\}]\;\mathrm{d}\mathbf{p}\,\mathrm{d}\mathbf{q} \tag{3}$$

where T_i and V_i are, respectively, the kinetic and potential energies of state i, N is the number of particles in the system, and h is Planck's constant. If the potential energy $V_i(\mathbf{q})$ is made a function of a perturbation parameter λ, such that $V_A = V(\mathbf{q}, \lambda_A)$ and $V_B = V(\mathbf{q}, \lambda_B)$, then the free energy difference between the two states can be expressed as the integral from state λ_A to state λ_B of the derivative of eq 2 with respect to λ

$$\Delta A_{BA} = \int_{\lambda_A}^{\lambda_B} \frac{\partial A(\lambda)}{\partial\lambda}\,\mathrm{d}\lambda \tag{4}$$

or with (3)

$$\Delta A_{BA} = \int_{\lambda_A}^{\lambda_B} \left\langle \frac{\partial V(\mathbf{q},\lambda)}{\partial\lambda} \right\rangle_{\lambda} \mathrm{d}\lambda \tag{5}$$

By slowly changing λ during a molecular dynamics simulation, the free energy difference can be calculated from eq 5.

In this study, the term being averaged is

$$\frac{\partial V(\mathbf{q},\lambda)}{\partial\lambda} = \frac{\partial}{\partial\lambda}\,[(\epsilon_i(\lambda)\cdot\epsilon_j)^{1/2}\cdot(r^*_i\,(\lambda) + r^*_j)^{12}\cdot r_{ij}^{-12} - 2\cdot(\epsilon_i(\lambda)\cdot\epsilon_j)^{1/2}\cdot(r^*_i(\lambda) + r^*_j)^{6}\cdot r_{ij}^{-6}] \tag{6}$$

where r_{ij} is the distance between the cation (ith atom) and the jth atom, $\epsilon_i(\lambda) = (1 - \lambda)\cdot\epsilon_i^A + \lambda\cdot\epsilon_i^B$, and $r^*_i\,(\lambda) = (1 - \lambda)\cdot r^{*A}_i + \lambda\cdot r^{*B}_i$. Ion solvation in methanol has also been studied by integral equation methods by Levy et al.[7]

Computational Methods

All molecular dynamics simulations in this article were done in the NVT ensemble in a box of equilibrated methanol 28.52 Å on a side with periodic boundary conditions at 300 K. The volume was chosen so as to correspond to the experimental volume[8] of 343 methanol molecules at 1 atm and 300 K. The molecular dynamics package AMBER version 3.0[9] was used for all calculations. It employs the leap frog algorithm to integrate the equations of motion and the SHAKE[10] routine to constrain all bonds to their equilibrium lengths. A time step of 1fs was maintained throughout the calculations. The united atom model[11] was used with

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Table I. Relative Free Energy of Solvation Na^+ to K^+ in Methanol

simulation time (ps)	time step (fs)	ΔA (kcal/mol)	direction[a]
20	1	19.7	r
20	1	19.0	r
20	1	19.3	r
20	1	20.4	f
20	1	20.1	f
20	1	19.9	f
20	1	19.5	f
20	2	19.4	r
20	2	19.7	r
20	2	19.7	f
20	2	19.4	f

[a] f indicates a forward transformation from sodium to potassium, and r the reverse. The sign of ΔA always corresponds to the forward direction.

Jorgensen's OPLS parameters[12] for methanol. The hydrogen atom on methanol was assigned a mass of 10 amu so as to reduce the frequency of molecular librations; this leads to increased sampling efficiency. The nonbonded parameters for the 18-crown-6 atoms were from Jorgensen's OPLS for proteins,[13] while the bond, angle, and dihedral parameters were from Kollman et al.[11] Charges for 18-crown-6 ($q_{c2} = 0.17$, $q_{os} = -0.34$) were selected so as to reproduce the dipole moment of dimethyl ether. A second set of charges was also investigated by Kollman[14] ($q_{os} = -0.6$) for the complexed crown ether in vacuum. Sample runs using these charges for our system yielded results that were qualitatively similar but quantitatively in poorer agreement with experiment, compared to the first set of charges. The parameters for the cations were from Lybrand et al.[15] and were calculated so as to reproduce the energy of interaction of the particular cation and water. The K^+ parameters are $r^* = 1.70$ Å and $\epsilon = 0.10$ kcal/mol. The Na^+ parameters are $r^* = 1.28$ Å and $\epsilon = 0.10$ kcal/mol. A 9 Å cutoff was used in calculating the nonbonded interactions.

In total, calculations were done on four different cases, viz., one corresponding to the forward calculation of ΔA_3 ($Na^+ \rightarrow K^+$), one for the reverse, one corresponding to the forward calculation of ΔA_4 (Na^+:C6 $\rightarrow$ K^+:C6), and one for the reverse. Starting configurations for each case were arrived at as follows. In the two calculations of ΔA_3, the cations were immersed in separate though identical boxes of methanol by removing one methanol molecule. The systems were then allowed 40 ps of equilibration before starting the perturbation experiments. A similar procedure was used to create the starting configurations for the calculation of ΔA_4, the only difference being that eight methanol molecules were removed from the solvent bath to form a cavity for the cation:18-crown-6 complex. Again, 40 ps of equilibration on the cation:18-crown-6 methanol systems were performed prior to the start of the perturbation simulations.

The perturbation experiments consisted of molecular dynamics thermodynamic integration runs of 20, 30, or 50 ps in length in which λ changed linearly over the runs. In order to establish the convergence of the calculations, different configurations of the initial states were used as starting points for the molecular dynamics perturbation runs. These configurations were removed from a standard NVT molecular dynamics run at 10 ps intervals.

Table II. Relative Free Energy of Complex Formation Na^+ to K^+ Bound to 18-Crown-6 in Methanol

simulation time (ps)	time step (fs)	ΔA (kcal/mol)	direction[a]
20	1	16.3	f
20	1	16.6	f
20	1	17.0	f
30	1	17.0	f
50	1	16.8	f
20	1	15.6	r
20	1	15.0	r
30	1	15.1	r
50	1	15.4	r
20	2	16.2	f
20	2	16.9	f
20	2	15.6	r

[a] f indicates a forward transformation from sodium to potassium, and r the reverse. The sign of ΔA always corresponds to the forward direction.

Results and Discussion

Results for the various runs can be found in Tables I and II. The simulations yielded a relative free energy of solvation of potassium cation versus sodium cation in methanol, $\Delta A_3 = 19.6 \pm 0.4$ kcal/mol. This is in accord with the experimental value of 17.3 kcal/mol.[16] The calculated value of ΔA_4, the free energy difference between bound K^+ and bound Na^+, is 16.1 ± 0.8 kcal/mol. These results yield a relative free energy of binding of K^+ versus Na^+ to 18-crown-6 in methanol, $\Delta\Delta A = \Delta A_4 - \Delta A_3 = -3.5 \pm 1.3$ kcal/mol. This value is in reasonable agreement with the experimental value of −2.47 kcal/mol.[17] The simulations also show that the substantial unfavorable free energy of interaction of K^+ versus Na^+ for the 18-crown-6 in methanol is more than compensated for by the fact that K^+ is more readily desolvated than Na^+. Preliminary investigation also shows that the complexed $Na^+ \rightarrow K^+$ perturbation is accompanied by a $C_1 \rightarrow D_{3d}$ conformational change of the crown ether, as observed experimentally.[14]

The methods outlined in this article are also being applied to study the effects of changes in the composition of the receptor molecule. This work and additional details on the simulations described here will be described elsewhere.

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Registry No. Na, 7440-23-5; K, 7440-09-7; methanol, 67-56-1; 18-crown-6, 17455-13-9.

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