A QM/MM Molecular Dynamics Study of the Potential of Mean Force for the Association of K^+ with Dimethyl Ether in Aqueous Solution

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Abstract: We present a hybrid Quantum Mechanical/Molecular Mechanical (QM/MM) molecular dynamics study of the free energy profile for the association of K^+ with dimethyl ether (DME) in H_2O. The QM/MM method employs the semiempirical AM1 method to describe DME, the MM parametrization of Dang for K^+, and the SPC/E model for H_2O. The electrostatic and van der Waals parameters for the QM/MM coupling terms, which describe the interaction of K^+/DME and H_2O/DME, have been previously described.[1] We calculate a potential of mean force and find a weak solvent separated ion–dipole pair (SSIDP) at 5.4 Å separation and a contact ion–dipole (CIDP) free energy minimum at 2.7 Å separation of the K^+ with the oxygen of DME. The latter distance agrees well with the gas-phase optimized K^+/DME structure. There is a 3-kcal/mol barrier separating the CIDP and SSIDP which is centered at 3.8 Å K^+/DME separation. The estimated ΔA_{bind} for the CIDP is 0.9 ± 0.1 kcal/mol which predicts that K^+/DME is not a strongly bound complex in aqueous solution. The SSIDP has only a 0.2-kcal/mol barrier separating it from completely uncomplexed K^+/DME, and it also does not represent a stable bound structure. K^+ and its first solvation shell waters exert an opposite effect on repolarizing the wave function of DME when the latter is inside the 3.8-Å barrier. However, outside this barrier, both the solvent and the cation act to enhance the induced dipole moment of DME. This study demonstrates the nonadditive interactions of a solvated cation with a simple monodentate organic ligand. These results are useful for interpreting K^+ complexation by multidentate ligands, such as the crown ethers.

I. Introduction

The interaction between metal cations and neutral organic ligands is of considerable importance to environmental chemistry. For example, crown ethers show a remarkable range of specificity for a wide variety of cations that depends, in part, on the number and type of the donor atoms in the crown (e.g. oxygen, nitrogen, sulfur) as well as the polarity of the solvent.[2–4] Theoretical studies of cation–ligand association have done much to elucidate the mechanisms for the selectivity of 18-crown-6 (18c6) for K^+ in polar solvents.[5–9] To date, these studies have all employed molecular mechanics (MM) force fields. However, it is clear that the charge distribution of the ligand is a sensitive function of both the instantaneous conformation of the ligand and solvent and the proximity and charge of the cation.[5,8] For this reason, we recently began to study crown ether/cation interactions for gas-phase and hydrated clusters, using *ab initio* quantum mechanical methods, and the condensed phase, using a hybrid quantum mechanical/molecular mechanical (QM/MM) approach.[1,10,11] Hybrid QM/MM methods treat part of the system with QM (typically the solute(s) of interest) and the remainder of the system with MM (such as the solvent). The two motifs are then coupled by a QM/MM interaction Hamiltonian.[12] In prior QM/MM studies, we have shown the importance of QM polarization in treating cation–neutral interactions for 18c6/K^+ in bulk H_2O.[1,10]

While much has been said about cation/crown complexation free energies, a detailed structural and energetic description of this process is lacking, especially for a nonadditive force field that employs some description of polarization. The process of the ligand complexing the cation can be viewed as the donor atoms of a multidentate ligand (i.e., oxygens for 18c6) replacing part or all of the first solvation shell of the solvated cation. 18-Crown-6 can be thought of as 6 polarizable dipoles (each consisting of $-H_2C-O-CH_2-$) interacting with the cation guest. We assert that a detailed understanding of the process of solvent replacement with ligand donor atoms must necessarily begin with a study of the simplest crown ether subunit, the monodentate ligand, dimethyl ether (DME). In this paper, we present results of molecular dynamics simulations of the free energy of association of K^+ and DME in H_2O by calculating the potential of mean force (pmf).[7,13,14] Our approach is unique in that we employ a quantum mechanical treatment of DME, and hence can describe QM polarization effects and assess their role in the complexation process.

II. Methods

Hybrid QM/MM methods have been described several times in the literature.[1,10,12,15–20] Our QM/MM parametrization, including all elec-

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trostatic and van der Waals parameters used here, has been described previously.[1] Briefly, DME is treated by Hartree–Fock molecular orbital theory, while the solvent and K^+ are described with MM. Specifically, we use the AM1 parametrization[21] of the semiempirical neglect of diatomic differential overlap model Hamiltonian[22] to represent the QM solute while H_2O and K^+ are treated with the SPC/E 3-site model for H_2O[23] and the parameters of Dang,[24] respectively. Wave function polarization effects in the QM motif arise from inclusion of the MM-atom/QM-electron term in the one-electron matrix used in the Fock equations. We treat the AM1 implementation of the QM/MM electrostatic terms in a fashion similar to Field *et al.*,[12] but we fit the actual values of these parameters to MP2/6-31+G* (CP corrected) binding energies and structures.[1]

All calculations employed the Argus computer program version 3.0.[25] MD simulations were carried out in the NVT ensemble in a periodic system using the minimum image convention.[26] The periodic box size was 25 Å. SHAKE constraints[27] were used for rigid SPC/E H_2O and DME (C–H bonds, 1.121 Å). Velocities were scaled by the method of Berendsen to simulate contact with an infinite thermal bath.[28] The MM/MM and QM/MM nonbond lists were generated with a 12.0 Å cutoff while the actual interactions were truncated at 9.0 Å. The nonbonded lists employ neutral group cutoffs and were rebuilt every 10 steps. Initial configurations for solutes embedded in a box of H_2O were obtained using the Insight molecular modeling program 2.2 (Biosym Technologies[29]). These files were then converted to input files for subsequent simulations with Argus. The system was first energy minimized by steepest descents then annealed to 10 K using a temperature coupling constant of $\tau = 0.01$ ps, then slowly warmed up to 300 K. A time step of 2.0 fs was employed for all simulations. For the pmf, we used a temperature coupling constant of $\tau = 0.20$ ps.

The reaction coordinate for the pmf was defined as the distance between K^+ and the oxygen of DME (O_D). The pmf profile consists of a series of equilibrium molecular dynamics simulations and was generated in the following fashion: (1) The initial K^+/O_D distance was set at 2.316 Å. (2) The system was equilibrated to 300 K as described above. The K^+/O_D distance was constrained in a fashion similar to that used by Dang and Kollman.[7] DME is allowed to freely rotate during the simulation. (3) The pmf consisted of a series of equilibrium molecular dynamics simulations, each with 4 ps of equilibration, at the new K^+/O_D separation, followed by 50 ps of data collection. The relative free energy values were calculated with the free energy perturbation technique[7,13,14,30] and employed a step size of 0.125 Å with double-wide sampling. Configurations were saved every 100 fs to disk for later analysis. The entire pmf profile required a total of 17 simulations each 54 ps in length for a total of 918 ps of simulation time. Simulations were carried out on an IBM Model 590 Power2 workstation.

The association constant for K^+/DME complexation can be calculated by the following equation.[31]

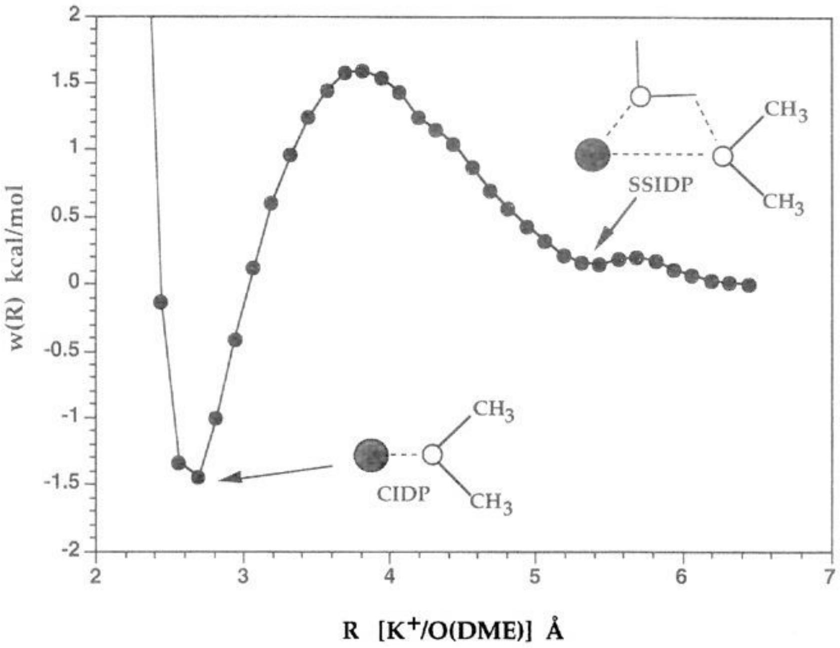

Figure 1. PMF profile for K^+ with DME in H_2O. Also shown schematically are structures for the solvent separated ion–dipole pair (SSIDP) with the bridging water and the contact ion–dipole pair (CIDP).

$$K_a = N \int_0^{r_c} 4\pi r^2 \exp[-w(r)/kT]\, dr \tag{1}$$

K_a is the association constant, N is Avagadro's number, r_c is the cutoff distance for the association, $w(r)$ is the value of the pmf, k is Boltzmann's constant, and T is the temperature. Note, eq 1 is derived assuming that the associating species are spherical, and hence provides only an approximation to the true association constant for K^+/DME. However, we note that eq 1 has been used to obtain reasonable values of K_a for K^+/18c6 association in aqueous solution by a pmf procedure similar to ours.[7] The calculated value of K_a can be used to obtain the Helmholtz free energy of binding.

$$\Delta A_{\text{bind}} = -RT \ln K_a \tag{2}$$

Note, we have assumed ideal activity coefficients for the solutes in eq 2. Our simulations are run under NVT conditions, and thus provide an estimate of the Helmholtz free energy (ΔA_{bind}) rather than the Gibbs free energy (ΔG_{bind}). For liquid systems, such as the one studied here, values of ΔA_{bind} should be comparable to ΔG_{bind}. The uncertainties we report for ΔA_{bind} were obtained by integrating the pmf using uncertainties obtained by a block averaging procedure over 10 separate subintervals within each simulation.[32]

III. Results and Discussion

A. Potential of Mean Force. The K^+/O_D pmf curve is shown in Figure 1. We set the value of the pmf to zero at 6.44 Å as the pmf does not change beyond this point. There is a minimum at 2.7 Å which we label the contact ion–dipole pair (CIDP). This structure agrees with the gas-phase minimized structure for K^+/DME that we previously reported as having a K^+/O_D distance of 2.546 Å.[1] The K^+/O_D distance of 2.7 Å is close to the maximum in the first peak in the K^+/O_{water} (O_w) radial distribution function located at 2.8 Å.[1,7] At 5.4 Å there is a small minimum which represents the solvent separated ion–dipole pair (SSIDP). This minimum is very shallow with a barrier of only ~0.2 kcal/mol separating it from the unbound region of the pmf. There is a 3-kcal/mol barrier for dissociating the CIDP to the SSIDP, with the maximum at 3.8 Å K^+/O_D separation. The well depth of the SSIDP is very shallow, and it may be sensitive to the parametrization employed. We originally parametrized the DME–K^+ and DME–H_2O QM/MM interactions to gas-phase MP2/6-31+G* (CP-corrected) binding energies and structures.[1] We note here the caveat that

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slight changes in parameters could change weakly interacting portions of the pmf such as the SSIDP.

The coordination number for free K^+ in bulk H_2O is 7.0 (obtained by integrating the K^+/O_w radial distribution function to 3.5 Å).[1] We perform a similar analysis for K^+ at selected points along the K^+/DME pmf profile. At K^+/O_D distances larger than the SSIDP, K^+ has a coordination number of 7.0. At the CIDP/SSIDP barrier maximum, the coordination number for K^+ is reduced only slightly to a value of 6.7. At the CIDP, the K^+ coordination number is 5.7. Thus, as expected, DME displaces one water from the first solvation shell of K^+.

Integration of the pmf (eqs 1 and 2) from 2 Å to the maximum at 3.8 Å gives the ΔA_{bind} for the CIDP as 0.9 ± 0.1 kcal/mol. Thus, the K^+/DME complex is not strongly bound in aqueous solutions. This is reasonable since our previously reported binding energies for K^+/H_2O and K^+/DME were −17.9 and −17.5 kcal/mol, respectively, using the present QM/MM model. For comparison, we also reported MP2/6-31+G* hybrid (CP corrected) binding energies of −18.8 and −18.9 kcal/mol, respectively.[1] Given the uncertainties in our hand-fit QM/MM potential parameters, the sampling uncertainties present in any simulation approach, and the assumptions in the derivation of eq 1,[31] we can conclude that K^+/DME might be, at most, weakly bound. We expect the methyl groups of DME to be sterically unfavorable for packing with the other waters of the first hydration shell of K^+ and they will not form good hydrogen bonds with the second-shell solvation waters of K^+. It is intriguing that 18c6 forms a thermodynamically stable complex, despite the fact that each of its 6 "electrostatic" subunits ($-CH_2-O-CH_2-$) cannot, by themselves, stably bind K^+ in H_2O. This is the so-called "chelate effect" for monodentate vs polydentate ligands which has been successfully used to design ligands that strongly bind cations.[33-36]

The K^+/DME SSIDP is a weak interaction. We define a bridging water as simultaneously having a K^+/O_w distance less than 3.5 Å (minimum after the first peak in the K^+/O_w radial distribution function[1]) and an O_D/H_w distance <2.5 Å (minimum after the first peak in O_D/H_w rdf[1]). Given this criteria, we calculate the simulation average number of bridging waters for the SSIDP as 0.7. This compares to 1.5 bridging waters recently reported by Smith and Dang for the much stronger SSIP in the NaCl pmf in SPC/E water.[32] In Figures 2 and 3 we show the O_D/H_w distribution for both hydrogens of the bridging water in the SSIDP and the distribution of the $O_w-H_w-O_d$ angle for only the H_w nearest O_D. We see the characteristic bimodal distribution for the two H_w-O_D distances (Figure 2). The nearer H_w shows a peak at ~2.0 Å that is very similar in position and shape to the first solvation shell of O_D seen in our previous DME/H_2O simulations.[1] The other H_w distribution shows a peak at ~3.3 Å and is slightly broader than the nearer H_w; we would expect the near-H_w peak to be more constrained due to its more direct interaction with O_D. In Figure 3, we see that the majority of the $O_w-H_w-O_D$ angles are ~50°, with only a small percentage having a more linear H-bonding arrangement greater than 120°. This attests to the weakness of the SSIDP complex. The interaction of the bridging water with DME is not strong enough to rotate the bridging water significantly away from its orientation with K^+ (in which the water dipole and the vector connecting the O_w and K^+ are essentially collinear). Not surprisingly, this observation contrasts with the NaCl SSIP reported by Smith and Dang, which was observed to be a much stronger and more stable structure than the SSIDP reported here. They observed that Cl^- significantly rotated the bridging H_2O away from its optimal orientation with Na^+.[32]

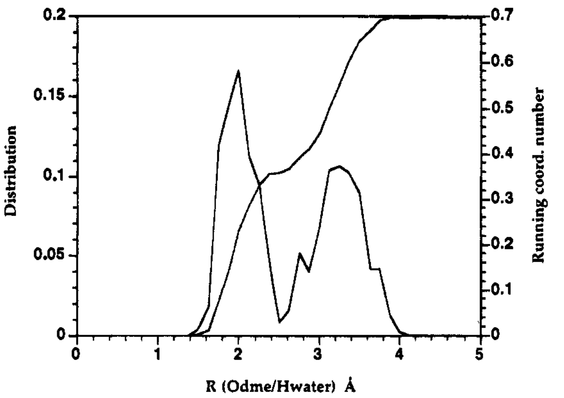

Figure 2. Distribution of the O_D-H_w distances for the bridging water from the SSIDP structure (Figure 1). The distribution for both hydrogens is shown. Running coordination numbers integrate to 0.7 waters, the simulation average number of bridging waters. A total of 500 configurations were analyzed from the 50 ps collection phase for this window in the pmf.

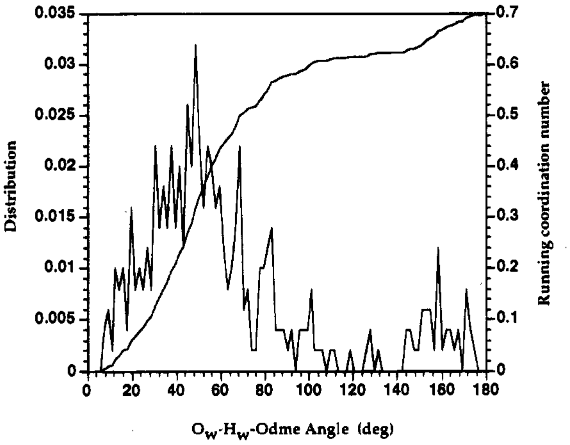

Figure 3. Distribution of the angle for $O_w-H_w-O_D$ from the bridging water molecule from the SSIDP (Figure 1). Only the angle distribution for the H_w nearest to O_D is shown. Running coordination numbers integrate to 0.7 waters, the simulation average number of bridging waters. A total of 500 configurations were analyzed from the 50 ps collection phase for this window in the pmf.

B. Polarization of DME. In the gas phase, K^+ presents a large electric field perturbation to DME. We previously reported an induced dipole moment ($|\mu_{\mathrm{ind}}|$) of 1 D for DME in the energy minimized complex with K^+, relative to isolated DME.[1] Here, we present the simulation average induced dipole moment of DME at selected points along the pmf reaction coordinate. This is done to ascertain the relative effects of K^+, its first solvation shell waters, and bulk water on the QM wave function of DME. We define $|\mu_{\mathrm{ind}}|$ as the dipole moment of solvated DME minus isolated DME (at the same geometry). The results of this analysis are presented in Table 1. When we include the effects of both K^+ and H_2O (Table 1, column 3), we observe that the $|\mu_{\mathrm{ind}}|$ of 0.49 D, at the CIDP, is only about half of that observed in the gas-phase K^+/DME minimized structure.[1] Furthermore, the increase in $|\mu_{\mathrm{ind}}|$ from the SSIDP to the CIDP is only about 0.1 D, despite the much closer distance to K^+ in the latter. To examine the separate effects of K^+ and the solvent on $|\mu_{\mathrm{ind}}|$, we repeat the above analysis, but include only the effects of K^+ (column 4) and the H_2O (column 5) achieved by setting the charges of all H_2O (column 4) and K^+ (column 5) to zero, respectively. When just K^+ is considered (column 4), we

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Table 1. Induced Dipole Moment for DME at Selected Points on the PMF Profile

PMF	K^+/O_D	DME $\lvert\mu_{ind}\rvert$, D[a]		
window	sep, Å	solv = K^+,H_2O[b]	solv = K^+[c]	solv = H_2O[d]
CIDP	2.7	0.49	0.93	−0.39
barrier	3.8	0.36	0.51	−0.01
SSIDP	5.4	0.37	0.27	0.17

[a] Simulation average of $\mu_{solv} - \mu_{gas}$ for dimethyl ether. [b] Electrostatic effects of both K^+ and H_2O retained in calculating μ_{solv}. [c] Electrostatic effects of only K^+ retained in calculating μ_{solv} (Charges of all H_2O set to zero). [d] Electrostatic effects of only H_2O retained in calculating μ_{solv} (Charge of K^+ set to zero).

observe a $|\mu_{ind}|$ of 0.93 D for the CIDP, which is nearly the same as the gas-phase energy-minimized value. The $|\mu_{ind}|$ gets progressively smaller as the K^+/O_D distance is increased. When we examine the effects of just H_2O (column 5), we observe the strong effect that the first solvation shell of K^+ has on the QM polarization of DME. The first solvation shell waters actually diminish the dipole moment of DME ($|\mu_{ind}| = -0.39$ D) at the CIDP. This is clearly understood, since the molecular dipoles of the waters in the first solvation shell for K^+ are oriented unfavorably relative to DME. In the absence of the cation's electrostatic field, these water dipoles will dominate the local electric field effect on DME. The effect of just these waters at the barrier peak, at 3.8 Å, is diminished where $|\mu_{ind}|$ is now only −0.01 D. As DME moves outside the first solvation shell we observe an enhanced polarization in DME ($|\mu_{ind}| = 0.17$ D). Here, the dipoles of the cation's first solvation shell waters, closest to DME, are favorably oriented to enhance the DME dipole and, as well, the effects of bulk H_2O are more important. Thus, inside the barrier peak, we see that the solvent and K^+ exert opposite electrostatic effects on the QM polarization of DME, while outside 3.8 Å, their effects reinforce the induced polarization of DME. It is evident that this interplay of opposing effects, which change along the pmf profile, requires a polarizable method to be even qualitatively correct. Lastly, notice that the effects of K^+ and H_2O, taken separately, are not strictly additive (i.e., Table 1, column 4 and 5 do not add to give column 3). By including QM in our solute, we no longer have a strictly additive force field.

While we feel our description of polarization is a fundamental improvement over traditional pairwise-additive MM techniques, we note two caveats about our present QM/MM approach: (1) Charge transfer from the ligand to the cation, which we do not treat, may be important,[1] especially for the alkaline earth dications. (2) The solvent and cation are presently treated with pairwise additive MM potentials. We previously noted the problems of obtaining consistent structure and energetics when part of the system included polarizability (QM) and another part did not (MM).[1] Recently, we have presented a QM/MMpol method in which the MM atoms now include atom-centered polarizabilities.[20] Further work along these lines is in progress.

C. Orientation of DME. Last, we examine the effect of K^+ on the orientation of the DME molecular axis relative to the K^+/O_D axis. This shows how strongly the cation orients DME, relative to thermal fluctuations that would cause DME to tumble. Since we constrain only the K^+/O_D distance in our simulations, DME is free to rotate under the influence of the solvent and the cation. In Figure 4, we show the distribution of cos (θ), where θ is the angle between the K^+/O_D axis and the C−O−C bisector axis of DME. We show this distribution at four selected points on the pmf curve: the CIDP, barrier peak at 3.8 Å, SSIDP, and 5.8 Å K^+/O_D separation (outside the SSIDP). As expected, DME is strongly oriented at the CIDP with the K^+/O_D and C−O−C bisector distributed close to a collinear orientation (cos (θ) = 1). At the CIDP/SSIDP barrier peak, DME begins to show a broadening of this distribution, though the effects of K^+ can still be seen. The distribution broadens only slightly at the SSIDP at 5.4-Å separation. The effects of K^+ and its first solvation shell, relative to random thermal fluctuations, are essentially gone by the K^+/O_D separation of 5.8 Å where the cos (θ) distribution is distributed over all angles.

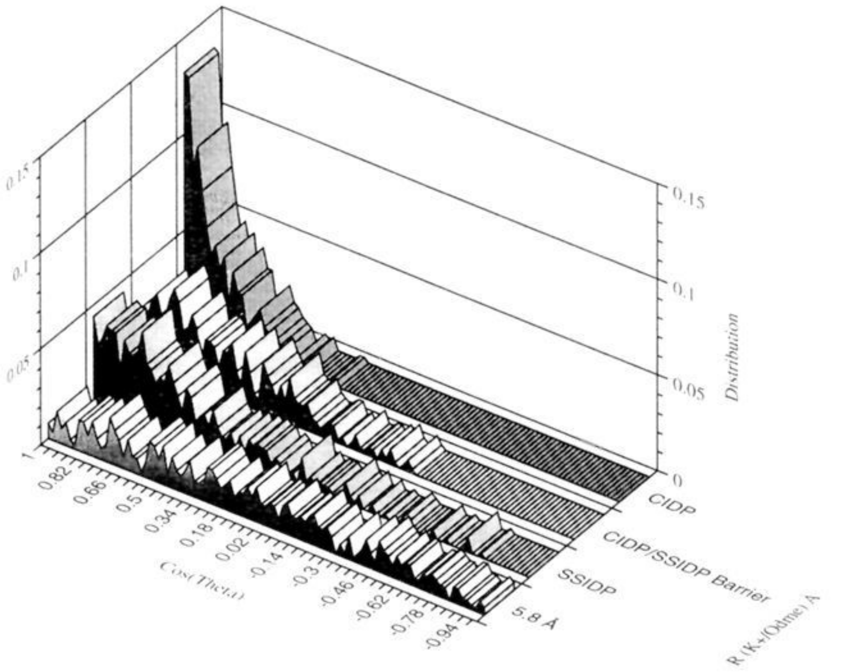

Figure 4. Distribution of cos (θ) between the axis connecting K^+/O_D and the C−O−C molecular dipole axis for DME. A value of cos (θ) = 1 indicated that the DME methyl groups are oriented directly away from the $K^+ \rightarrow O_D$ axis. Distributions for four selected points of the pmf profile are shown (Figure 1).

IV. Summary

We have presented a QM/MM study of the free energy of association for K^+ with a monodentate ligand, dimethyl ether (DME) in H_2O: DME does not form a strongly bound complex with K^+, having a calculated ΔA_{bind} of 0.9 ± 0.1 kcal/mol. By treating the ligand with a QM method, we are able to describe the differential effects of the cation, its first solvation shell waters, and bulk water on the induced polarization of an organic ligand. These effects cannot be accounted for in effective pair potentials and further emphasize the need to use polarizable methods to treat interactions of cations with neutral organic ligands. These observations should be important to better understanding QM/MM pmf results of K^+/18c6 association.

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