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Molecular Dynamics Simulation Study of the Influence of Conformation on the Solvation Thermodynamics of 1,2-Dimethoxyethane and 1,2-Dimethoxypropane in Aqueous Solution

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We have performed atomistic molecular dynamics simulations of 1,2-dimethoxyethane (DME) and 1,2-dimethoxypropane (DMP) in aqueous solution in order to compare the free energy, energy, and entropy of solvation of these ethers as well as to examine the influence of ether conformation on the thermodynamics of solvation. The free energy and energy of solvation were found to be highly favorable for both ethers, whereas the entropy of solvation was highly unfavorable, indicating that the ethers are strongly water-structuring. The free energy of solvation of DMP was found to be slightly more favorable than that of the smaller DME. However, scaling for molecular volume differences reveals that the solvation of DME is intrinsically more favorable than that of DMP. This difference was found to be energetic in origin, resulting from stronger water−ether interactions in the DME solution. DME was found to lead to a larger decrease in entropy upon solvation compared to DMP, indicating that a severe entropic penalty is associated with the stronger ether−water interactions. Similar conformation dependence of the free energy of solvation was observed for DME and DMP. The free energy of solvation for hydrophilic DME conformers was found to be 1.7 kcal/mol more favorable than that for hydrophobic conformers. The corresponding difference for DMP was found to be quite similar at 1.4 kcal/mol. In dilute solution, 88% of DME conformers were found to be hydrophilic, whereas only 78% of DMP conformers were hydrophilic. However, contrary to our previous speculation, only about $^1/_5$ of the difference in DME and DMP solvation thermodynamics can be accounted for by the larger fraction of hydrophilic conformers in DME solutions.

Introduction

At room temperature, poly(ethylene oxide) is consoluble with water for all molecular weights, whereas poly(propylene oxide) is soluble only as low molecular weight oligomers. The reasons for this widely disparate behavior are of great fundamental interest. In a previous work[1], we addressed issues of solvation of 1,2-dimethoxyethane (DME) and 1,2-dimethoxypropane (DMP) by performing atomistic molecular dynamics (MD) simulations on aqueous solutions of these ethers. DME and DMP, illustrated in Figure 1, can be considered as repeat units of poly(ethylene oxide) and poly(propylene oxide), respectively. These simulations revealed a similar hydration structure and the extent of water−ether hydrogen bonding for DME and DMP. One clear difference between the solutions of the two ethers was the population of hydrophilic conformers, i.e., those conformers whose populations increase with increasing dilution of the solution. The most important hydrophilic and hydrophobic conformers of DME and DMP are shown in Figure 1. In dilute solutions at 318 K, 88% of DME conformers were found to be hydrophilic, in contrast to 78% in DMP. Our previous simulations revealed that, energetically, hydrophilic conformers of both DME and DMP have more favorable interaction with water than hydrophobic conformers.[1] We associated the lower hydrophilic fraction in DMP with the intrinsically higher energy of the O−C−C−O gauche conformation[1] in this molecule (see Figure 1) and speculated that the resulting difference in conformational populations could lead to a more favorable free energy of solvation of DME compared to that of DMP and, hence, the difference in PEO and PPO solubility. In this work, we present results of an MD simulation study of the thermodynamics of solvation of DME and DMP in aqueous solution and investigate the roles of energy and entropy in the solvation of these molecules. We also look at the influence of conformation on solvation thermodynamics of both DME and DMP.

Simulation Methodology

We performed MD simulations on solutions of a single DME and a single DMP molecule with 241 water molecules at 318 K. The TIP4P potential[2] was used for water, whereas previously parametrized quantum-chemistry-based potentials were used for DME[3] and DMP[4] as well as interactions between the ethers and water.[4,5,6] The ether−water, water−water, and ether−ether repulsion/dispersion potential functions are the same for DME and DMP solutions. The ether partial atomic charges differ between DME and DMP, having been chosen to best reproduce the quantum chemistry dipole moments of the important conformers of each molecule. Simulations were performed using an NVT ensemble at densities that yield approximately 1 atm pressure. A reversible multiple-time-step integrator[7] was utilized with a 0.7 fs inner time step for bonded interactions, a 1.4 fs time step for nonbonded interactions within 6.0 Å, and a 2.8 fs time step for nonbonded interactions between 6.0 and 9.0 Å as well as the reciprocal space component of the Ewald summation. Bond lengths as well as the TIP4P water geometry were constrained using the standard SHAKE algorithm.[8] Systems were equilibrated for 1 ns followed by sampling trajectories of

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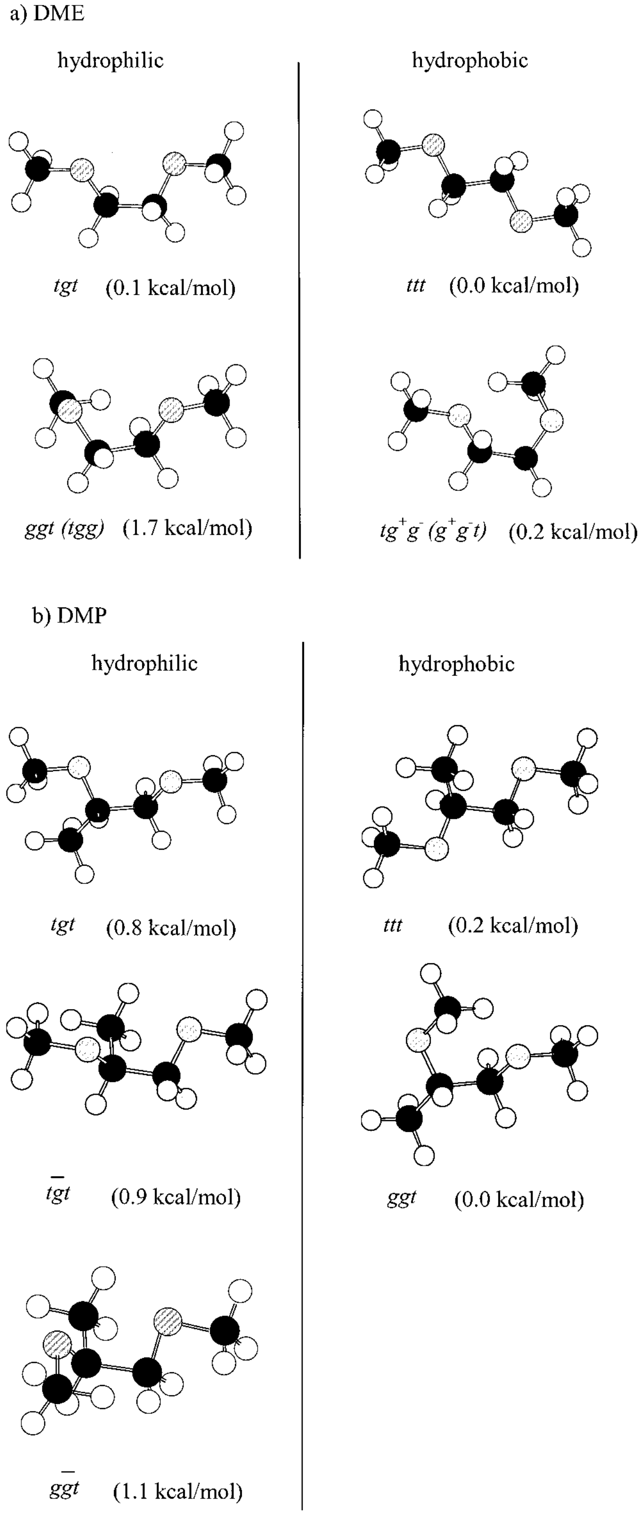

Figure 1. Important hydrophilic and hydrophobic conformers of (a) DME and (b) DMP.

15−20 ns. It was found that sampling sufficient for obtaining order parameter histograms (see below) that yielded free-energy differences to within ± 0.1 kcal/mol could be obtained from 5 ns simulations. In contrast, for many systems, 20 ns simulations were sufficient to yield energies only to within ± 0.3 kcal/mol.

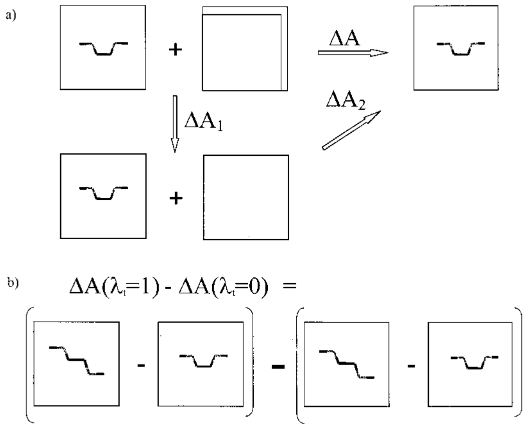

Figure 2. Schematic representation of the solvation of ether molecules: (a) represents the process of solvation of an ideal gas ether molecule divided into two subprocesses involving (1) expansion of the neat liquid water and (2) dissolution of the ether molecule; (b) represents the difference in the free energy of solvation of the conformationally biased and unbiased ether molecules.

For the purpose of determining the free energy of solvation of the ethers (see below) additional simulations were performed on ensembles of pure water (241 molecules) using the same procedure as for ether−water solutions. Ideal gas simulations of ensembles of 100 ether molecules (DME or DMP) were also performed using the stochastic dynamics methodology described elsewhere.[9] Because these simulations involved only intramolecular interactions, for the expediency of insertion attempts of the ideal gas molecules into the water (see below), simulations were performed in periodic cells corresponding to the volume of the ether−water mixtures.

Free Energy of Solvation of DME and DMP

We wish to determine the free energy, energy, and entropy of solvation for DME and DMP in dilute aqueous solution, as is shown schematically in Figure 2a. The free energy of solvation ΔA can be calculated by considering the dissolution of the ideal gas ether molecule in water as the sum of two subprocesses, again shown in Figure 2a. In subprocess 1, the water ($P \approx 1$ atm) is expanded to fill the simulation cell of the final solution (water + ether), whereas in subprocess 2, the ether molecule is inserted into the expanded water, yielding a solution at $P \approx 1$ atm.

Water Expansion. The free-energy change for subprocess 1 can be straightforwardly determined through thermodynamic integration[10]:

$$\Delta A_1 = \int_{V_i}^{V_f} -P \, dV \qquad (1)$$

This requires determination of the pressure of pure water along a path from the initial volume V_i corresponding to a the pure water system at $P \approx 1$ atm to the final volume V_f corresponding to the volume of the ether−water solution at the same pressure (i.e., an equation of state for liquid water). This was obtained by performing NVT simulations of the water system at a series of intermediate volumes and fitting the calculated pressure with a quadratic function in the volume. The resulting values for ΔA_1 (water expansion) for the DME and DMP solutions are given in Table 1. The energy change ΔU for the water expansion process (the difference in potential energy for the expanded and unexpanded water systems) was determined directly from the potential energies yielded by the MD simulations and is also given in Table 1. Uncertainties in the free-energy and potential-energy changes for the water expansion process determined from statistical analysis are ±0.05 and ±0.3 kcal/mol, respectively.

TABLE 1: Thermodynamics of Solvation of DME and DMP

process	ΔA, kcal/mol	ΔU, kcal/mol	$T\Delta S$, kcal/mol	ΔS, kcal/mol/K
Solvation of DME				
[1] water expansion	0.3	9.0		
[2] ether insertion	−9.5	−30.4		
solvation = [1] + [2]	−9.2	−21.4	−12.2	−0.038
Solvation of DMP				
[1] water expansion	0.5	10.5		
[2] insertion	−10.2	−33.6		
solvation = [1] + [2]	−9.7	−23.1	−13.4	−0.042
solvation (volume scaled)	−8.1	−19.2	−11.1	−0.035
Differential Solvation of DMP and DME				
DMP − DME	−0.6	−1.7	−1.1	−0.004
DMP (volume scaled) − DME	1.1	2.3	1.2	0.004

Ether Insertion. In principle, the free-energy change for subprocess 2 can be determined using the Widom insertion method.[11] Here

$$\Delta A_2 = -kT \ln \int \langle \exp(-\Delta E/kT) \rangle_{\text{water}}\, \mathrm{d}s_{\text{ether}} \qquad (2)$$

where ΔE is the interaction energy of the ether with the water, the brackets indicate a canonical ensemble average over the water molecules, and the integral is over the scaled coordinates of the ether. In practice, this calculation involves random insertion of ideal gas-phase configurations of the ether molecule into equilibrium configurations of the water simulated without the presence of the ether. Because the ether molecules (DME and DMP) are much larger than a water molecule, the probability of random insertion of an ether into bulk water without overlap with water molecules, hence, yielding values of ΔE that contribute to the integral in eq 2, is vanishingly small. To overcome this problem, we employed the self-consistent histogram method.[10,12,13] Here, series of NVT simulations were performed for DME/water and DMP/water systems where repulsion/dispersion and electrostatic interactions between the ether and water were scaled by a parameter λ. Simulations were performed with Hamiltonians corresponding to $\lambda = \{1, 0.85, 0.70, 0.50, 0.30, 0.10, 0.05, 0.01, 0.001, 0.0001, 0\}$. The Hamiltonian $\lambda = 1$ yields full ether−water interactions, whereas $\lambda = 0$ corresponds to no interaction. The system volume corresponded to that which yields $P \approx 1$ atm for the ether−water solution (DME or DMP) with full ether−water interaction. Systems were first equilibrated from the next larger λ value for 1 ns before performing 15−20 ns simulations, storing state points every 125 fs. Subsequently, the distribution of interaction energies (order parameter) $\Delta E = E_{\lambda=1} - E_{\lambda=0}$, or histogram was determined from the stored trajectories for each simulation (each value of λ). Here, $E_{\lambda=1}$ and $E_{\lambda=0}$ are the potential energies of the ensemble with full ether−water interaction and no ether−water interaction, determined from the trajectory performed with the Hamiltonian λ. Simulations with the Hamiltonian $\lambda = 1$ yield a histogram corresponding to particle (molecule) removal, whereas the $\lambda = 0$ histogram corresponds to particle insertion. Significant overlap of the order parameter histograms was found as required for accurate determination of ΔA_2. Using the self-consistent histogram method,[10,12,13] values of ΔA_2 were determined for DME and DMP and are given in Table 1. For DME, longer simulations (thereby improving the statistics) and use of additional λ values (e.g., $\lambda = 0.000\,01$) made little difference in the calculated free-energy change. The energy change for the ether insertion process was determined directly from simulation as the difference in potential energy between the ether−water solution ($\lambda = 1$) and the sum of the potential energy of the ideal gas ether molecule and the expanded water system (Figure 2a). Values are given in Table 1. Uncertainties in the free energy and energy of the insertion process are estimated to be ±0.1 and ±0.2 kcal/mol, respectively.

TABLE 2: Contributions to the Energy of Solvation of DME and DMP

ether	ΔU_{ether}, kcal/mol	$\Delta U_{\text{water-water}}$, kcal/mol	$\Delta U_{\text{ether-water}}$, kcal/mol	ΔU_{total}, kcal/mol
DME	0.1	11.0 (43)[a]	−32.5	−21.4
DMP	0.4	11.4 (52)	−34.9	−23.1
DMP (scaled)	0.3	9.4 (43)	−29.0	−19.2
[DMP − DME]	0.3	0.4 (9)	−2.4	−1.7
[DMP (scaled) − DME]	0.2	−1.6 (0)	3.5	2.3

[a] Values in parentheses were determined assuming regular solution behavior based upon interactions in pure water.

Discussion

Thermodynamics of DME and DMP Solvation. In addition to the free energy ΔA and energy ΔU of solvation, Table 1 gives the entropy ($T\Delta S = \Delta U - \Delta A$) of solvation for DME and DMP. Both ethers have large favorable free energies of solvation, consistent with their consolubility with water. For both ethers, ΔU is large and favorable, whereas $T\Delta S$ is large and unfavorable. We have determined the various contributions, namely, intramolecular ether (conformational), intermolecular water−water, and intermolecular water−ether interactions, to ΔU, as is shown in Table 2. These energies are the differences between solution energies and pure water plus ideal gas energies. DMP dissolution results in a 0.4 kcal/mol increase in the conformational energy of the ether; interaction of DMP with water increases the population of hydrophilic conformers that are higher in conformational energy than the preferred gas-phase conformers (see Figure 1). The effect is much smaller in DME where the principal hydrophilic conformer (*tgt*) is comparable in energy to the preferred gas-phase conformers. Ether−water interactions are large and favorable for both DME and DMP, whereas water−water interactions are reduced upon solution formation. Assuming regular solution behavior, we can estimate the expected reduction in water−water interaction energy because of the breaking of water−water contacts upon the introduction of the ethers. These values are given in Table 2 and are much larger than the effects observed from the simulation. As with the unfavorable entropy of solvation for the ethers, the water−water interaction energy in solution is consistent with significant water structuring upon dissolution of the ethers.

Comparison of DME and DMP Solvation. As is shown in Table 1, ΔA for DMP is slightly more favorable than that of DME. This difference is energetic in origin: entropically, DMP solvation is less favorable than that of DME. As is shown in Table 3, this energetic difference is due to more favorable DMP−water interactions compared to those of DME−water. However, any discussion of the relative solubility of DME and DMP, or their respective polymers, should take into account the difference in volume of these molecules. We have therefore scaled ΔA, ΔU, and ΔS of solvation for DMP by the ratio of the molar volumes of DME and DMP (0.83) as determined from simulations of the neat ether liquids. Scaled values are shown in Tables 1 and 2. On this basis, the interaction of DMP with water is less favorable than that of DME, consistent with the relative solubilities of poly(propylene oxide) and poly(ethylene oxide). On the scaled basis, DME solvation is favorable energetically and unfavorable entropically compared to that of DMP. Table 2 shows that the primary contribution to the more favorable DME solvation energetics is from stronger ether−

TABLE 3: Free Energy of Solvation for Important Conformers of DME and DMP

conformation	gas population	solution population	$\Delta\Delta A_i$,[a] kcal/mol	ΔA_i, kcal/mol	P_i(sol)ΔA[b], kcal/mol
		DME			
ttt	21.7	3.3	0.0	−7.6	−0.3
tg^+g^-	31.3	4.9	0.0	−7.6	−0.4
ttg	10.4	2.0	−0.1	−7.7	−0.2
other	4.5	1.7	−0.6	−8.2	−0.1
tgt	27.7	73.4	−1.8	−9.4	−6.9
tgg	4.4	14.6	−1.9	−9.5	−1.4
				total	−9.2
hydrophobic	67.9	11.9	0.0	−7.7	−0.9
hydrophilic	32.1	88.0	−1.7	−9.4	−8.3
				total	−9.2
		DMP (scaled)			
ttt	24.4	4.7	0.0	−6.7	−0.3
ggt	22.6	4.9	−0.1	−6.8	−0.3
gtt	15.5	3.9	−0.1	−6.9	−0.3
other	17.1	8.8	−0.5	−7.2	−0.6
tgt	9.0	16.1	−1.2	−7.9	−1.3
tgg	0.9	2.7	−1.4	−8.2	−0.2
$t\bar{g}t$	6.0	31.3	−1.7	−8.5	−2.6
$g\bar{g}t$	4.5	27.5	−1.8	−8.5	−2.3
				total	−8.1
hydrophobic	79.6	22.3	0.0	−7.0	−1.6
hydrophilic	20.4	77.6	−1.4	−8.4	−6.5
				total	−8.1

[a] Relative to *ttt* or total hydrophobic. [b] Contribution to the free energy of solvation based upon solution populations.

water interactions. These effects may be due to a slightly greater extent of DME−water hydrogen bonding per volume compared with that of DMP, a larger DME dipole moment per unit volume, or intrinsic differences in conformations between DME and DMP. The latter effect is discussed below. The former will be considered in an upcoming paper. It is worth noting that despite the fact that on the scaled basis water−water interactions are energetically less favorable in DME solutions, indicative of a lesser extent of water structuring, the entropy of solvation is still less favorable for DME compared to that of DMP. This indicates that there is an entropic penalty associated with the stronger ether−water interactions in DME solution. Finally, it should be kept in mind that although the differences in ΔA, ΔU, and ΔS of solvation between DME and DMP are not negligible, they are much smaller than these values for the individual ethers. Hence, the solvation of DME and DMP is quite similar, and differences between them are rather subtle.

Influence of Ether Conformation. Table 3 shows the free energy of solvation for important conformers of DME and DMP. The values $\Delta\Delta A_i$ are the free energies of solvation of each conformer i relative to the (nearly) nonpolar *ttt* conformer, determined from the relationship

$$\Delta\Delta A_i = kT \ln \frac{P_{ttt}(\mathrm{sol})}{P_i(\mathrm{sol})} \frac{P_i(\mathrm{g})}{P_m(\mathrm{g})} \tag{3}$$

where P_i(sol) and P_i(g) are the populations of conformer i in dilute solution and in the gas phase, respectively. These populations are given in Table 3 for the DME and DMP conformers. Those conformers whose populations decrease in going from the gas phase to dilute solution are classified as hydrophobic, whereas those whose population increases upon solvation are classified as hydrophilic. For both DME and DMP, all hydrophobic conformers have solvation free energies within about 0.5 kcal/mol of that for the *ttt* conformer ($\Delta\Delta A_i \geq -0.5$ kcal/mol), whereas all hydrophilic conformers have free energies of solvation at least 1.4 kcal/mol more favorable than that for the *ttt* conformer.

The free energy of solvation of DME or DMP (see Table 1) is given by the relationship

$$\Delta A = \sum_i P_i(\mathrm{sol})\Delta A_i = \sum_i P_i(\mathrm{sol})(\Delta A_{ttt} + \Delta\Delta A_i) \tag{4}$$

which can be solved for ΔA_{ttt} for both ethers. The resulting free energy of solvation for each DME and DMP conformer is given in Table 3. Because of the similarity in the free energy of solvation of all hydrophobic and all hydrophilic conformers for both ethers, it is convenient to analyze the influence of conformation on the free energy of solvation of DME and DMP in terms of the total hydrophilic and hydrophobic populations, which are given in Table 3. The contribution of each conformer to the free energy of solvation of the ether, shown in Table 3, reveals that hydrophilic conformers dominate the free energy of solvation for both DME and DMP. Because the total hydrophilic population is lower in the DMP solution compared to DME (77.7% vs 88.0%) solution, it is conceivable that this difference could largely account for the less favorable free energy of solvation for the former (−8.1 vs −9.2 kcal/mol). We repeated the analysis described above but now with the total hydrophobic population as the reference state in order to determine the free energy of solvation of hydrophilic conformers relative to hydrophobic (eq 3) and the free energy of solvation of hydrophilic and hydrophobic conformers (eq 4). These values are given in Table 3.

Table 3 reveals that hydrophilic conformers have a free energy of solvation that is 1.7 (DME) and 1.4 kcal/mol (DMP) more favorable than the respective hydrophobic conformers. In Figure 3, we show the free energy of solvation of DME and DMP as a function of the population of hydrophilic conformers, relative to that for dilute DME solutions (88.0% hydrophilic). It can be seen that reducing the DME hydrophilic fraction to that of DMP reduces the difference in DME and DMP free energy of solvation but not enough to equalize them. It appears differences in conformational populations account for about $^1/_5$ of the difference in solvation between DME and DMP. The remainder

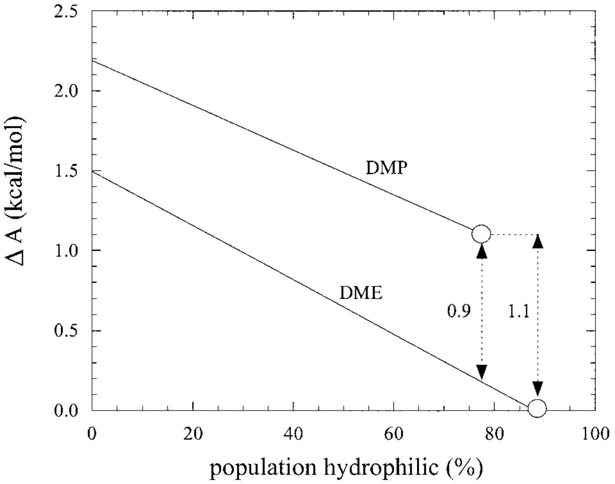

Figure 3. Free energy of solvation of DME and DMP as a function of hydrophilic conformer population relative to dilute DME solution (88.0% hydrophilic).

may be due to differences in hydrogen bonding or polar interactions with the solvent.

Conclusions

The thermodynamics of DME and DMP solvation are very similar. The energy of solvation is highly favorable and the entropy of solvation is highly unfavorable for both DME and DMP. The latter is consistent with the behavior observed for hydrophobic surfaces, bodies, and molecules in aqueous solution and indicates that despite their consolubility with water these ethers are strongly water-structuring. Consistent with the relative solubility of PEO and PPO, DME interacts more favorably with water than DMP because of more energetically favorable (but entropically costly) water−ether interactions. Despite the fact that the variation of the free energy of solvation with conformation is similar for the two ethers, only about $^1/_5$ of the difference in the thermodynamics of solvation between DME and DMP can be accounted for by the intrinsically higher population of hydrophilic conformers for the former, in contrast to our previous speculation that conformational effects may dominate the solution behavior of these ethers and their respective polymers. The influence of polar interactions and hydrogen bonding on the solvation thermodynamics of DME and DMP will be considered in detail in an upcoming paper.

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(15) The free energy of solvation of conformer *i* is the free energy of the solution (water with a single ether in conformation *i*) minus the sum of the free energy of the ideal gas ether in conformation *i* and the free energy of the pure water.