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Assessing the hydration free energy of a homologous series of polyols with classical and quantum mechanical solvation models

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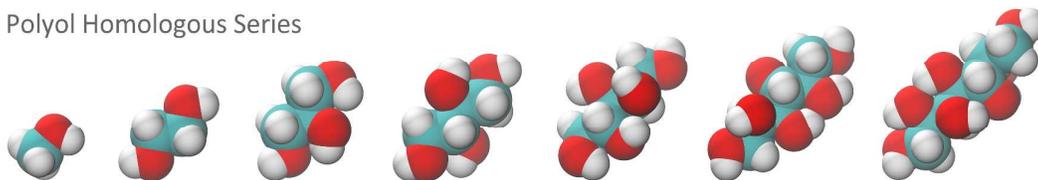
Abstract

Molecular dynamics (MD) simulations associated with the thermodynamic integration (TI) scheme and the polarizable continuum model (PCM) in combination with the SMD solvation model were used to study the hydration free energy of the homologous series of polyols, $C_nH_{n+2}(OH)_n$ ($1 \leq n \leq 7$). Both solvation models predict a nonlinear behavior for the hydration free energy with the increase of the number of hydroxyl groups. This study also indicates that there is a sizable solute polarization in aqueous solution and that the inclusion of the polarization effect is important for a reliable description of the free energy differences considered here.

Keywords: Polyols, molecular dynamics, DFT, PCM, hydration free energy

TOC

Polyol Homologous Series



1. Introduction

The modeling of molecular properties in different environments has been of great importance for elucidating various aspects of biological, chemical and physical processes.^{1,2} The study of the hydration free energy of nonpolar molecular systems, for example, has allowed a better understanding of the hydrophobic effect and the explanation for several physicochemical phenomena in aqueous environment.³⁻¹⁰ It is well known that most of the thermodynamic functions of homologous series of organic compounds in gaseous, liquid or solid phase can have a remarkable linear dependence with the number of carbon atoms.¹¹⁻¹³ It has been shown, for example, that for n-alkanes (C_nH_{2n+2} , $n > 0$) the change in enthalpy, entropy and free energy of hydration varies linearly with the number of carbon atoms (except for $n = 1$; the methane molecule has a higher value than expected on a linear extrapolation).¹⁴⁻¹⁶ In particular, the contribution of each n additional to the hydration free energy has been estimated to be of the order of 0.7 kJ mol^{-1} .

Hydration free energy of polar systems, such as iso-alcohols, may also display a linear dependence with the number of carbons, similarly that shown for n-alkanes. In fact, homologous alcohols obey a linear pattern with increase of the number of methylene groups ($-CH_2-$). However significant deviations from linearity can be found. The most common refers to members of any homologous series with a low number of carbon atoms. Cyclic compounds may also exhibit a behavior that deviates from linearity due to the differences in geometry and energy for each carbon ring.¹⁴ Acyclic polyalcohols (systems which contain multiple polar sites) represent a class of compounds to which is also expected deviation from linearity. Since the thermodynamic properties of a compound depend on its chemical neighborhood, in this case OH groups,

interactions with the nearest neighbors may lead to a nonlinear dependence on the number of hydroxyl groups.

In this work we report the dependence of the hydration free energy with the number of hydroxyl groups for polyhydric alcohols (or polyols, $C_nH_{n+2}(OH)_n$, $1 \leq n \leq 7$). Figure 1 shows a series of seven polyols (methanol, ethylene glycol, glycerol, D-threitol, D-arabitol, D-glucitol, D-volemitol) that are investigated. This class of molecules besides having multiple hydroxyl groups plays an important role in biochemistry.¹⁷⁻¹⁹ Besides its importance as metabolic precursors for many cellular molecules and biologically important processes also play a central role in cellular osmotic regulation.²⁰ Here we have used MD simulations based on additive CHARMM force field associated with the thermodynamic integration approach to study systematically the hydration free energy for all members of the homologous series of polyols. Additive force fields have been successfully applied in the modeling of complex molecular systems over the past two decades, despite being a relatively simple model.²¹ However, some limitations of the additive model emphasize the need to take into account explicitly the polarization effects.^{17,22} To estimate the importance of polarization effect, we have also calculated the hydration free energy of each polyol as well as the contribution of the polarization energy using the PCM method in combination with the SMD solvation model. In addition, dipole moment and dipole polarizability were obtained in both vacuum and aqueous environment, and an estimate of degree of polarization of each polyol molecule in solution has been evaluated from the solvent effect on these electric properties.

<< FIGURE 1 >>

2. Computational Details

The hydration free energy of the homologous series of polyols was determined in this study using two different methodologies. The first considers the solvent explicitly through the use of classical additive models in the atomistic molecular dynamics framework, while the second one considers the solvent implicitly through the self-consistent reaction field with the SMD model. Below we present the computational details employed in both methods.

Molecular Dynamics and Thermodynamic Integration

The molecular dynamics simulations were performed in the *NPT* ensemble with $T = 298\text{ K}$ and $P = 1\text{ atm}$ for a system composed by one polyol molecule and 1000 water molecules in a cubic box with periodic boundary condition employing the minimum image convention.²³ The TIP3P potential²⁴ was used for the water molecule. Polyol solute was modeled using and CHARMM36 force field.^{17,25,26} Properties were calculated from simulations considering a time-step of 2 fs with data collected at each 0.01 ps. The cubic cells were equilibrated for 500 ps and for the equilibration process we have performed a running length of 5 ns, both in the *NPT* ensemble. The system was kept at the appropriate temperature and pressure via velocity rescaling²⁷ and Parrinello-Rahman²⁸ schemes, with a constant coupling of 0.1 and 1.0, respectively. All bond lengths were constrained via the LINCS algorithm.²⁹ A cutoff distance of 1.2 nm for LJ interaction was employed, whereas the Coulomb interactions were treated by using the PME algorithm.³⁰

The elucidation of free energy differences due to changes in intermolecular interactions is an important issue in solution chemistry^{4,31,32} and could be used here to describe the thermodynamics solvation of polyols. Hydration free energy was calculated

using stochastic molecular dynamics associated with the thermodynamic integration scheme²³ by decoupling a solute molecule from the solvent using the identity:³³

$$\Delta G = \int_{\lambda=0}^{\lambda=1} \left\langle \frac{dH(\lambda)}{d\lambda} \right\rangle d\lambda$$

where H is the parameterized Hamiltonian, for which the coupled state ($\lambda = 1$) corresponds to a simulation with the fully interacting solute with the solvent and the uncoupled state ($\lambda = 0$) corresponds to a simulation with non-interacting solute with the solvent. For the purpose of avoiding singularities, we have used the soft-core interactions for the LJ interactions.³⁴⁻³⁶

The decoupling of both terms, Coulomb and van der Waals, can lead the system to instabilities during the process of thermodynamic integration.³³ Therefore, first, we decouple the electrostatic interactions of the solute, retaining only the van der Waals interactions, and then we decouple the van der Waals interactions, transforming the solute in a set of completely non-interacting atoms. For each polyol, two series of simulations were performed: one to decouple the Coulomb interactions and the other to decouple the van der Waals interactions. In each series 26 values for λ were used, from 0 to 1. For the van der Waals interactions the $\Delta\lambda$ increments was uniformly separated by 0.04 while for electrostatic interactions a non-uniform $\Delta\lambda$ set was employed: from 0.00 to 0.20 at intervals of 0.04; from 0.22 to 0.38 at intervals of 0.02; and from 0.40 to 1.00 at intervals of 1.00. For each simulation, the system was equilibrated for 1 ns followed by running length of 5 ns. The solvation free energy was then obtained by summing the energies of each process, ie: $\Delta G = \Delta G_{\text{Coul}} + \Delta G_{\text{vdW}}$. All stochastic and molecular dynamics simulations have been performed with the GROMACS 4.5 program.^{35,36}

Electronic Properties and SMD solvation method

In first step, the ground state geometry of each polyol molecule was fully optimized with the second-order Møller–Plesset perturbation theory (MP2) using the 6-311+G(2d) basis set in vacuum and in water without any symmetry constraint. The solvent dependence of the geometry has been obtained by employing the integral equation formalism polarizable continuum model (IEF-PCM),³⁷ as implemented in the Gaussian 09 program.³⁸ PCM-MP2/6-311+G(2d) calculations of the dipole and dipole polarizabilities were performed numerically through the finite field (FF) method. We found that the FF method with field strength of 0.001 a.u. is suitable for numerical evaluation of these electric properties.³⁹ Free energy of hydration were calculated at the MP2/6-311+G(2d) and B3LYP/6-311+G(2d) levels with the IEF-PCM method combined with the SMD solvation model. The SMD model predicts solvation free energies of neutral and ionic solutes in solutions.^{40,41} This model separates the solvation free energy into two main components. The first component is based on a self-consistent reaction field treatment of bulk electrostatics that involves an integration of the nonhomogeneous Poisson equation. The second component is the nonbulk-electrostatic contribution between the solute and the surrounding solvent treated by using the cavity-dispersion-solvent-structure term.⁴² This assumption does not account for specific interactions (such as hydrogen bonds) between the solute and the solvent molecules, which are expected for the protic solvent considered, and may be important for an appropriate description of solvent effects. All quantum calculations were performed using Gaussian 09 program.³⁸

3. Results and Discussions

In Table 1 we present a comparison between the vacuum and in-water results for the permanent dipole moment, μ , and dipole polarizability, σ , of polyols obtained at the MP2/6-311+G(2d) level. The in-water results were calculated with the PCM method. An estimate of the solvent effect can be obtained from the difference between the results obtained in solution and in vacuum ($\Delta\mu$, $\Delta\sigma$). One can see that values of μ are dependent on the molecular geometry, the largest value (in vacuum) occurs to glycerol molecule, 3.68D, while ethylene glycol and D-threitol molecules no exhibit dipole nor in water and nor in vacuum by symmetry requirement. Solvent effects are mild for the four smallest polyols but particularly important for the three largest polyols with increments of the in-water μ values between 60-85%, as compared with the vacuum results. This evidences the fact that polyols when are transferred from vacuum to a solvent can be polarized due to the electric field of the solvent, affecting the description of solute-solvent interactions. The polarizability is an additive property and our results show that the solvent effect is remarkable for this series of molecules. For this property, the increments of the in-water α values are between 19-28%, indicating that polyols are high polarizable in water and that the polarization is important for the appropriate description of solute-solvent interactions. One can see that $\Delta\alpha$ is also proportional to the volume, and that large polyols are also more polarizable. Notice that D-volemitol ($\Delta\alpha \sim 32$ u.a.) is 9 times more polarizable than the methanol ($\Delta\alpha \sim 3.5$ u.a.). This behavior has direct consequences for the hydration properties of the polyols, particularly for the free energy.

<< TABLE 1 >>

Table 2 shows the B3LYP/6-311+G(2d) and MP2/6-311+G(2d) results for the hydration free energy, ΔG_{PCM} , and the solute polarization energy, U_{pol} , of polyols both obtained with the SMD/PCM method. This table also contains the hydration free energy

values obtained by using the TI/MD-CHARMM model, ΔG_{CHARMM} , and previous experimental results, ΔG_{EXP} .^{32,40,43} These findings are depicted in graph form in Figure 2. Experimental data for hydration free energy were found only for methanol,⁴³ ethylene glycol³² and glycerol⁴⁰ molecules. Comparing with the experimental results, the magnitudes of free energy obtained with the TI/MD-CHARMM model for methanol, ethylene glycol and glycerol molecules differ by around 3-18%, in good concordance with experiment. Similarly, the corresponding SMD/PCM-B3LYP magnitudes vary between between 3-12% whereas SMD/PCM-MP2 magnitudes are slightly larger, varying between 10-26%. In addition, we can observe (Figure 2) that for the four smallest polyols both classical and quantum mechanical solvation models give an almost linear shape for ΔG , in agreement with the experiment. However, the SMD/PCM results clearly indicate that the behavior of both ΔG and U_{pol} undergoes an inflection in $n=4$ (D-threitol), affecting significantly the linear behavior of the curve with increasing polyol size. Unlike what has been reported for the homologous series of n-alkanes, for which each added ethylene group increases the hydration free energy by nearly same amount,¹⁴ one can see for the polyol series that the magnitude of the hydration free energy increases with the number of hydroxyl groups but not linearly. Thus, simple group contribution based methods¹⁴ for predicting thermodynamic properties should be used with caution for this homologous series.

<< TABLE 2 >>

<< FIGURE 2 >>

Due to the presence of multiple hydroxyl groups, polyols can form hydrogen bonds (HBs) with water molecules. In Table 2 (last column) are also presented the number of hydrogen bonds formed with water for each polyol. Our simulation results show, in addition, that the number of HBs increases with the size of the polyol and is

closely related to the hydration free energy. From Table 1 we can estimate a value of -8 to -10 kJ mol^{-1} as the contribution of each hydrogen bond to the hydration free energy. However, it should be stressed that this estimate may be affected by the polarization effect.^{44,45}

Connections between variations of hydration free energy and changes on dipole moment due to solvent effect are observed for this series of molecules. Table 2 also displays the differences in the energy of hydration, $\Delta\Delta G$, for the series of polyols considered. For the four smallest polyols, in which the solvent effect on dipole moment is mild, the free energy differences obtained with both TI/MD-CHARMM and SMD/PCM-B3LYP models are essentially equivalent, with discrepancies between the corresponding values of $\Delta\Delta G$ which do not exceed 13%. In contrast, for the three largest polyols, in which the impact of the solvent effect has a remarkable influence on dipole moment, the corresponding discrepancies can be very significant. For example, for D-arabitol and D-threitol the magnitude of $\Delta\Delta G$ obtained with the TI/MD-CHARMM model is around 80% smaller than that obtained with the SMD/PCM-B3LYP model. This suggests that in the case of polyols not only variation of polarizability but also variation of dipole moment in going from vacuum to water can influence the behavior of the free energy of hydration. These later results for the larger polyols indicate limitations of the pairwise additive force field (employed here), emphasizing the need to take into account explicitly the polarization effects to predict free energy differences for polyhydric alcohols. In fact, the polarization has significant impact on the determination of the thermodynamic properties of these systems, especially for the free energy of hydration even for the smaller polyols.¹⁷ The magnitude of this contribution is directly related to dipole polarizability of the solute and is not treated by potential additives. In addition, calculations of $\Delta\Delta G$ obtained using the

SMD/PCM-MP2 model displays a performance similar to that of the SMD/PCM-B3LYP model. This suggests that a quantitative reproduction of the variation of hydration free energy for polyols can be obtained using the SMD/PCM method.

Finally we draw attention to the methodological aspect since the accurate prediction of the solvation free energy is one of the most complex problems in computational chemistry. Here we employed both robust methods for determination of hydration free energies based on the thermodynamic integration scheme and on the SMD solvation model. These methods can provide results with a degree of accuracy that is sufficient for all practical purposes, depending on the system under investigation. In this work we see that the methods showed consistent values for the hydration free energy of each polyol, especially for the smaller ones, and also for the general description of the behavior of free energy in relation to the number of hydroxyl groups present in the solute. Differences between the results obtained by the methodologies are expected and become more evident for the larger polyols due to the high polarization of the system. In the case of the classic model, the additivity of the potential can suppress important contributions to the free energy of solvation, thus polarizable models may become necessary for a more accurate description. In the case of the quantum model, the choice of functional or theoretical level can have profound impact on the determination of the electronic properties in a solvent; in particular for the energetic cost to polarize the solute.

4. Conclusions

The dependence of the hydration free energy with the number of hydroxyl groups for a homologous series of hydrophilic molecules [$C_nH_{n+2}(OH)_n$, $n > 0$] has been determined systematically using the TI/MD method with additive CHARMM force field

and the SMD/PCM method at the B3LY/P6-311+G(2d) and MP2/6-311+G(2d) levels. Both TI/MD and SMD/PCM methods predict for the series of polyols considered a nonlinear dependence of the magnitude of the hydration free energy with the number of hydroxyl groups. These methods give hydration free energy values for methanol, ethylene glycol and glycerol in good agreement with the experimental results. It is found that the solvent dependence of dipole moment can affect the behavior of hydration free energy with the size of polyol. For the larger polyols, the discrepancies for the free energy differences obtained with the TI/MD and SMD/PCM methods can be marked, indicating limitations of additive force field.

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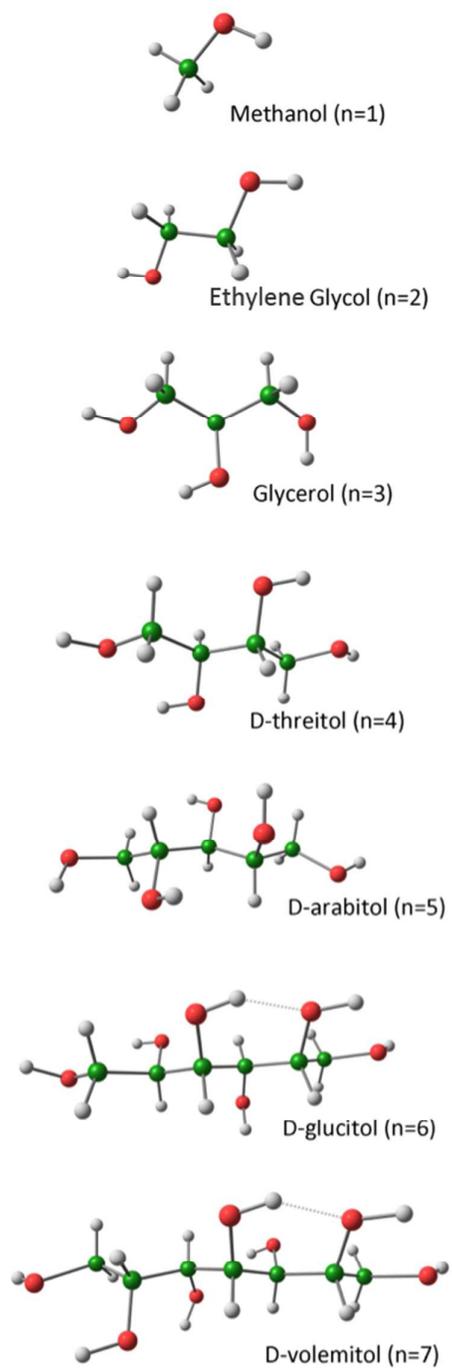


Figure 1: Homologous series of polyols $[C_nH_{n+2}(OH)_n]$ with n ranging from 1 to 7.

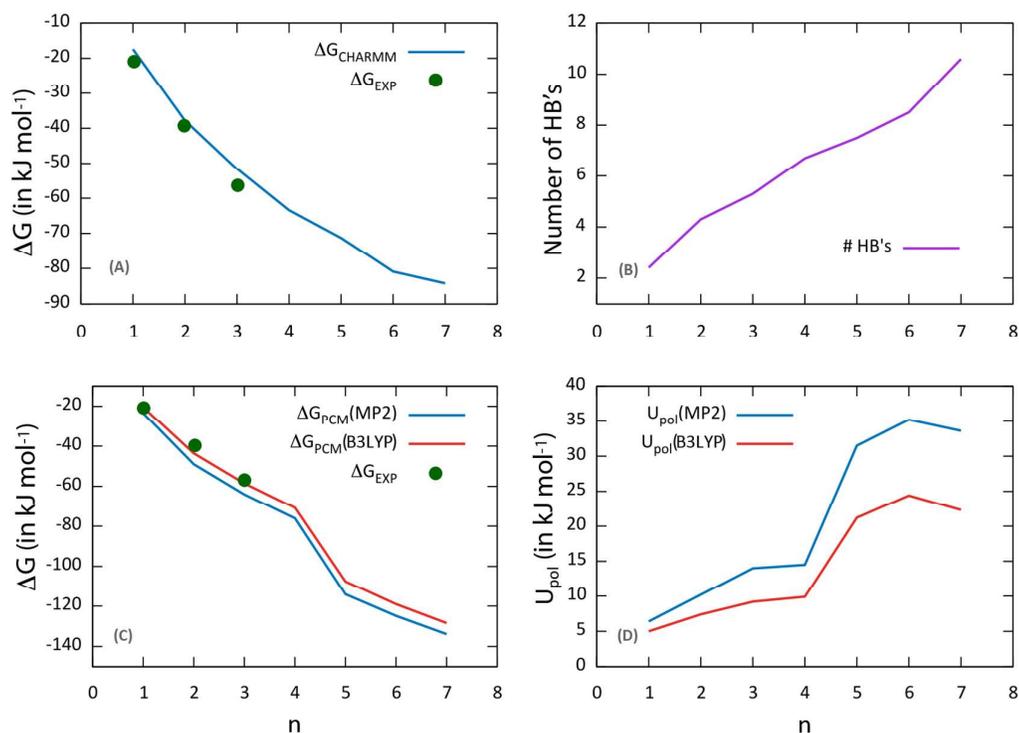


Figure 2: Classical and quantum results with increasing polyol size are presented at A/B and C/D plots, respectively. A and C present the behavior of the hydration free energy. B presents the average number of hydrogen bond between each polyol and water obtained from classical simulations. D present the polarization energy obtained from the difference between the total energy in vacuum and total energy in PCM. The statistical error for ΔG_{CHARMM} was obtained using block averaging and is of the order of 2% for all the polyols.

Table 1: Changes in dipole moment ($\Delta\mu$, in D) and dipole polarizability ($\Delta\alpha$, in a.u.) in going from vacuum to water obtained at the MP2/6-311+G(2d) level. The in-water results were obtained with the PCM method.

Polyol	μ (VACCUM)	$\Delta\mu$	α (VACUUM)	$\Delta\alpha$
Methanol	1.92	0.38	18.65	3.47
Ethylene Glycol	0.00	0.00	34.32	7.70
Glycerol	3.68	-0.12	50.62	12.65
D-Threitol	0.00	0.00	66.57	17.35
D-Arabitol	3.35	2.00	82.31	22.30
D-Glucitol	2.63	1.76	98.90	26.86
D-Volemitol	2.70	2.29	114.32	31.55

Table 2: Hydration free energy (ΔG_{CHARMM} , in kJ mol^{-1}) computed with the TI/MD-CHARMM model. Hydration free energy (ΔG_{PCM} , in kJ mol^{-1}) and solute polarization energy (U_{pol} in kJ mol^{-1}) computed with the SMD/PMC method at the MP2/6-311+G(2d) and B3LYP/6-311+G(2d) levels. Number of hydrogen bonds formed between solute-solvent obtained from classical simulations. Free energy differences are in parenthesis. Experimental values for methanol, ethylene glycol and glycerol are taken from references^{30, 37, 40} respectively.

Polyol	ΔG_{CHARMM}	$\Delta G_{\text{PCM(B3LYP)}}$	$\Delta G_{\text{PCM(MP2)}}$	$U_{\text{pol(B3LYP)}}$	$U_{\text{pol(MP2)}}$	ΔG_{Exp}	# HBs
Methanol	-17.4 (0.0)	-20.5 (0.0)	-23.5 (0.0)	5.0	6.4	-21.2	2.4
Ethylene Glycol	-37.8 (-20.4)	-43.6 (-23.1)	-49.0 (-25.5)	7.4	10.2	-38.9	4.3
Glycerol	-51.6 (-13.8)	-58.5 (-14.9)	-64.0 (-15.0)	9.2	14.0	-56.1	5.3
D-Threitol	-63.4 (-11.8)	-70.8 (-12.3)	-76.1 (-12.1)	9.9	14.5	--	6.7
D-Arabitol	-71.3 (-7.9)	-107.6 (-36.8)	-114.1 (-38.0)	21.2	31.5	--	7.5
D-Glucitol	-80.9 (-9.6)	-119.0 (-11.4)	-124.8 (-10.7)	24.4	35.2	--	8.5
D-Volemitol	-84.2 (-3.3)	-128.4 (-9.4)	-133.9 (-9.1)	22.3	33.6	--	10.6