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ARTICLE *in* JOURNAL OF COMPUTATIONAL CHEMISTRY · JULY 2010

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Thermodynamic Stability of Hydrogen-Bonded Systems in Polar and Nonpolar Environments

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Received 22 September 2009; Accepted 1 December 2009
DOI 10.1002/jcc.21491
Published online 1 February 2010 in Wiley InterScience (www.interscience.wiley.com).

Abstract: The thermodynamic properties of a selected set of benchmark hydrogen-bonded systems (acetic acid dimer and the complexes of acetic acid with acetamide and methanol) was studied with the goal of obtaining detailed information on solvent effects on the hydrogen-bonded interactions using water, chloroform, and *n*-heptane as representatives for a wide range in the dielectric constant. Solvent effects were investigated using both explicit and implicit solvation models. For the explicit description of the solvent, molecular dynamics and Monte Carlo simulations in the isothermal–isobaric (*NpT*) ensemble combined with the free energy perturbation technique were performed to determine solvation free energies. Within the implicit solvation approach, the polarizable continuum model and the conductor-like screening model were applied. Combination of gas phase results with the results obtained from the different solvation models through an appropriate thermodynamic cycle allows estimation of complexation free energies, enthalpies, and the respective entropic contributions in solution. Owing to the strong solvation effects of water the cyclic acetic acid dimer is not stable in aqueous solution. In less polar solvents the double hydrogen bond structure of the acetic acid dimer remains stable. This finding is in agreement with previous theoretical and experimental results. A similar trend as for the acetic acid dimer is also observed for the acetamide complex. The methanol complex was found to be thermodynamically unstable in gas phase as well as in any of the three solvents.

 J Comput Chem 31: 2046–2055, 2010

Key words: hydrogen-bonded systems; complexation in solution; thermodynamic properties; explicit and implicit solvation models; molecular dynamics and Monte Carlo simulations

Introduction

Hydrogen bonds are found ubiquitously in nature and play an essential role in numerous chemically and biochemically relevant processes such as base pairing in DNA and protein folding.[1–3] Beyond these applications, processes such as transport, fixation, accumulation and allotment of pollutants in the environment are controlled by adsorption processes, to which hydrogen bonding contributes essential structural features as well. In soil systems, humic substances provide a multitude of sites for adsorption processes.[4] The reactivity and chemical behavior of humic substances are primarily related to the abundance and dis-

Additional Supporting Information may be found in the online version of this article.

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Contract/grant sponsor: Austrian Science Fund; contract/grant number: P20893-N19

Contract/grant sponsor: Deutsche Forschungsgemeinschaft (SPP 1315); contract/grant number: GE1676/1-1

tribution of various functional groups (e.g., COOH, NH_2, and OH) within their structure. The accessibility of these groups depends on the microstructure of humic substances which can be strongly affected by the surrounding environment. Aqueous environments play a prominent role, but they are not the only ones to be considered since in many of the afore-mentioned cases also nonpolar or hydrophobic regions exist, which can be characterized by a wide range of local dielectric constants.

There are basically two approaches—implicit and explicit solvation models—available for the theoretical treatment of solvent effects. The first class describes the solvent as a polarizable continuum whereas the latter explicitly includes solvent molecules. Implicit solvation models are commonly used in quantum chemically based methods, for example, in the form of polarizable continuum models (PCM)[5] and have found a large number of successful applications. Their main drawback is found in the fact that they are not able to properly reflect specific interactions (such as hydrogen bonds) between solute and solvent molecules. For the explicit description of the solvent, only a quite limited number of solvent molecules can be included directly into the quantum chemical calculations for reasons of computational efficiency. Quantum mechanical/classical mechanics (MM) embedding schemes[6] or purely classical (MM)[7] calculations have been used successfully in extending the size of the solvent environment.

In the assessment of adsorption processes thermodynamical data are of highest interest beyond standard structural and purely energetic information. For the gas phase standard procedures based on the harmonic oscillator, rigid rotator and ideal gas are common practice. However, calculation of solvent contribution to Gibbs free energies beyond the PCM approach is still a challenge. Statistical mechanical simulations based on classical potentials (force field methods) are most commonly applied using free energy perturbation (FEP)[8] or thermodynamical integration[7,9] techniques. Monte Carlo (MC) or molecular dynamics (MD) methods can be used for generating the required statistical ensembles. Even though these approaches are computationally significantly more involved than PCM methods, they have been used quite frequently and successfully in detailed mechanistic simulations of solvent processes (see e.g., refs. 7, 10–13).

The motivation of the present work is derived from the above-mentioned adsorption processes involving polar moieties in environmental processes and the need for respective contribution of solvent free energies. Analysis of the chemical composition of humic substances shows that the carboxyl group plays a major role for the formation of hydrogen bonds. Moreover, experience with the investigation of different molecular model systems[14–17] indicates that acetic acid represents, for example, the hydrogen-bonded interaction of the herbicides 2,4-dichlorophenoxyacetic acid and (4-chloro-2-methylphenoxy) acetic acid very well. Therefore, acetic acid was chosen as the key compound in our investigations and complemented by two other polar compounds (acetamide and methanol). Thus, the hydrogen-bonded complexes of the acetic acid dimer and the interaction of acetic acid (AcOH) with acetamide ($AcNH_2$) and methanol (MeOH) form an interesting benchmark set for studying the influence of the environment on the thermodynamic stability of these complexes. The variation in the environment is taken into account by choosing three different solvents, water, chloroform and *n*-heptane, characterized by a wide range in the dielectric constant. The thermodynamical stability of the acetic acid dimer has already been studied intensively before.[10,11,13,18,19] The thermodynamical properties of the other two compounds (acetamide and methanol) as partner in hydrogen-bonded interactions in condensed phase have been investigated much less.[20] Previous extensive experiences with MC simulations and FEP calculations obtained in one part of our group[21–26] are used in performing the thermodynamical calculations with explicit solvation models. Previously, variations of free energy were calculated to study proton transfer reactions[21,23] and intramolecular torsions caused by charge transfer[24] in aqueous solution, redox reactions in several solvents[25,26] and also confinement and hydrophobic effects due to inclusion of water molecules in a cyclodextrin cavity.[22] In the study of redox reactions, also the enthalpy of solvation was calculated for phenol and the phenoxy radical in benzene, acetonitrile and aqueous solution.[25,26] MD simulations are used together with FEP as well. Extensive comparison is made with two implicit solvation models (PCM and conductor-like screening model (COSMO)[27,28]).

Computational Methods

The thermodynamic cycle (see Scheme 1) was used to compute Gibbs free complexation energies ΔG^{sol} in solution[29] as

$$\Delta G^{sol} = \Delta G^{gas} + \Delta\Delta G_{solv}, \tag{1}$$

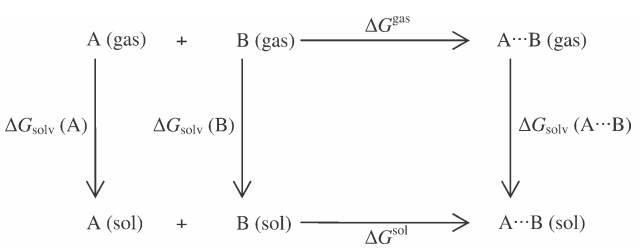
where

$$\Delta\Delta G_{solv} = \Delta G_{solv}(\text{complex}) - \sum \Delta G_{solv}(\text{monomers}), \tag{2}$$

is the differential solvation of the monomers as compared to the complex and

$$\Delta G_{solv} = \Delta G^{0}_{solv} + RT\ln(24.46), \tag{3}$$

the free energy of solvation of the monomers or the complex in a concentration of 1 mol/L. The last term in eq. (3) takes into account the change of the reference state of the ideal gas[30,31] from the standard gas phase at 1 atm to a gas phase concentration of 1 mol/L. At 298 K this term is equal to 1.9 kcal/mol.



Scheme 1. Thermodynamic cycle.

This thermodynamic cycle was used within MC simulations to compute the complexation enthalpy ΔH^{sol} in aqueous solution applying Eqs. (1) and (2), where the free energy (G) was substituted by the enthalpy (H). As before[25,26] the enthalpy of solvation of the monomers or the complex was calculated as

$$\Delta H_{solv} = E_{SX} + \Delta H_R - RT. \quad (4)$$

E_{SX} is the solute–solvent interaction energy and ΔH_R is the contribution of the solvent relaxation to the enthalpy, given by

$$\Delta H_R = \Delta E_R + p\Delta V_R, \quad (5)$$

where ΔE_R is the solvent relaxation energy and ΔV_R the solvent relaxation volume, which is negligible under normal conditions in the liquid phase. These relaxation terms are calculated as the difference in the solvent–solvent energy, E_{SS}, and the volume, V, with and without the presence of the solute. The estimation of solvation enthalpies from Eq. (4) is difficult due to the slow convergence of the solvent relaxation energy ΔE_R, which is calculated as the difference between two strongly fluctuating numbers. Nonetheless, by carrying out very long simulations it is possible to get reliable values.[25,26]

After calculating the Gibbs free energy and the enthalpy, the entropic contribution ($T\Delta S$) was obtained as ΔH–ΔG and analyzed for the solvation of the monomers and complexes as well as for the complexation process in gas phase and aqueous solution.

For all molecular species investigated in this work, free energies of solvation (vertical paths in Scheme 1) were calculated by means of the explicit and implicit solvation models. Within the discrete solvation model, MD and MC statistical mechanical simulations with the FEP technique[8] were performed. Since the MD and MC methods are only used as different sampling methods it is expected that both should give equivalent results. In the implicit solvation model approach PCM[32–34] and COSMO[27,28] were used. In both the cases a solute is placed into a cavity surrounded by an infinite polarizable continuum representing the solvent. It should be noted at this point that in COSMO only electrostatic interactions are taken into account whereas nonelectrostatic contributions are included additionally in the PCM approach.

In gas phase, full geometry optimizations of the investigated hydrogen-bonded complexes and their individual constituents were performed at the density functional theory (DFT) level of theory using the hybrid B3LYP[35,36] functional and the TZVPP[37] basis set. Only the most stable complexes in gas phase with two cyclic hydrogen bonds were considered. The computed energy minima were verified by vibrational frequency analysis. Harmonic vibrational frequencies as well as thermodynamical quantities were calculated within the standard harmonic oscillator—rigid rotator—ideal gas approximation. For all gas phase complexes, the final stabilization energies were corrected for the basis set superposition error (BSSE) using the counterpoise method.[38] Within the implicit solvation models, the three investigated solvents are characterized by their relative dielectric constants ε_r of 78.39 (water), 4.90 (chloroform), and 1.92 (*n*-heptane). For all examined complexes and their respective monomers in solution, full geometry optimizations were performed at the B3LYP/TZVPP level using PCM and COSMO, respectively, starting at the optimized gas phase structures. Within the PCM approach, the atomic radii of spheres used to build the molecular cavities were taken from the united atom model for Hartree-Fock model.[39] The DFT/COSMO and DFT/PCM calculations were performed using the Turbomole[40] and Gaussian 03[41] program packages, respectively.

In the explicit solvation approach, empirical force field MD and MC simulations were carried out in the isothermal–isobaric (NpT) ensemble at $p = 1$ atm and $T = 298$ K. The simulated systems consisted of the solute embedded in 518 water, 115 chloroform, or 64 *n*-heptane molecules. The solute was kept fixed in these simulations. All investigated systems were arranged in a cubic box with initial dimensions $25 \times 25 \times 25$ Å leading to the experimental densities of the three solvents, 0.997, 1.492, and 0.684 g/cm^3 for water, chloroform and *n*-heptane, respectively.[42] A spherical cutoff radius equivalent to half of the box length was employed for nonbonded interactions. Periodic boundary conditions combined with the image method were applied. Molecular geometries of the solutes were obtained from DFT/COSMO calculations. For MD simulations, the AMBER force field parameters[43] were used to describe the intramolecular interactions. The intermolecular interactions, in both MD and MC simulations, were described by the Lennard-Jones plus Coulomb potential with three parameters for each atom i (ε_i, σ_i, and q_i). These parameters were taken from the optimized parameters for liquid simulations (OPLS) force field.[44] For water, the SPC/E[45] model was used. The standard combination rules $\varepsilon_i = (\varepsilon_i\varepsilon_j)^{1/2}$ and $\sigma_i = (\sigma_i\sigma_j)^{1/2}$ were applied for computing pairwise interatomic parameters.

In the MD simulations, the Newton's equations of motion were integrated with the Beeman algorithm[46] using a time step of 1 fs. The temperature was held constant at $T = 298$ K applying a Nosé-Hoover thermostat.[47] Long-range electrostatic interactions were corrected by application of the Ewald sum method.[48] The total simulation time was 1 ns.

MC simulations were also performed at $T = 298$ K. Standard procedures[49] together with the Metropolis sampling technique[50] were used. Long-range corrections to the Lennard-Jones interactions were included using the pair distribution function procedure.[49] One MC step was concluded after selecting a molecule randomly and trying to translate it in all directions and to rotate it around a randomly chosen axis. Then, after performing N MC steps a MC cycle was completed. In total, a simulation was performed with an equilibration phase of 2×10^5 cycles and a production phase of 4×10^5 cycles for the free energy calculations and 8×10^5 cycles for the enthalpy calculations. Therefore, the largest simulation was performed with 4.1×10^8 MC steps ($=N \times 8 \times 10^5$ MC cycles $= 519 \times 8 \times 10^5$) in the case of water.

The solvation free energies were calculated using a hypothetical process[51] in which the solute is annihilated in solution by stepwise reduction of the intermolecular potential of the solute to zero. These computations were performed using the FEP technique.[8] As in previous studies[21–26] the annihilation process was divided into three stages where the Lennard-Jones (ε_i and σ_i) and Coulomb (q_i) potentials were separately scaled to zero. To

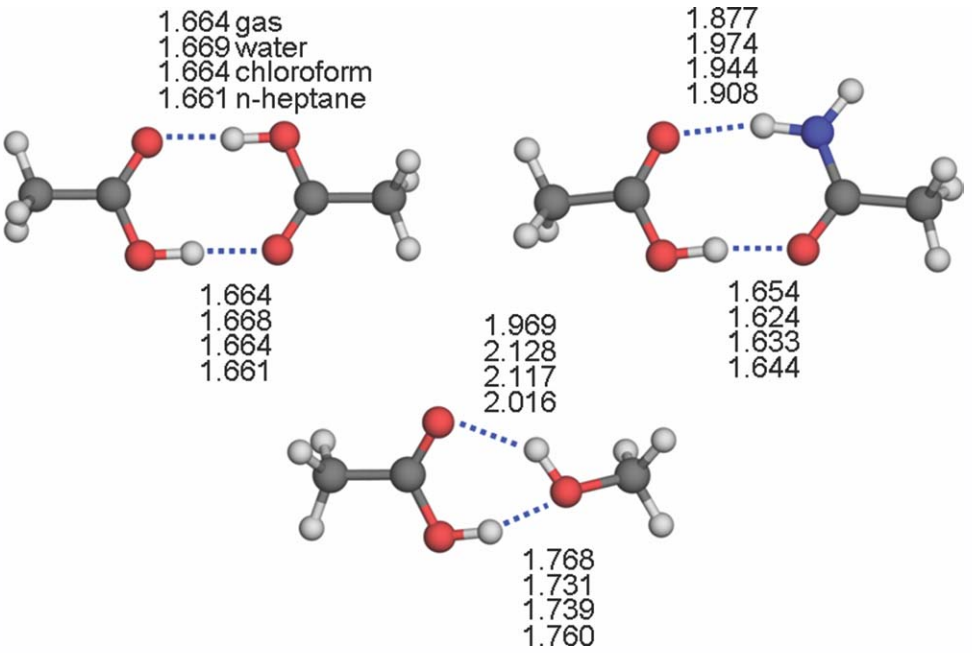


Figure 1. B3LYP/TZVPP optimized structures of the acetic acid dimer and the complexes of acetic acid with acetamide and methanol, with hydrogen bond distances (Å) in, top down, gas phase, aqueous, chloroform and *n*-heptane solution (COSMO).

make the solute gradually disappear double-wide sampling[52] was applied. All statistical mechanical simulations were carried out using the programs Tinker[53] and Dice[54] for MD and MC computations, respectively.

Results and Discussion

Enthalpy and Free Energy in Gas Phase

The three investigated complexes are displayed in Figure 1. All of them form cyclic structures in gas phase where the monomers are bound through two hydrogen bonds. B3LYP/TZVPP calculated hydrogen bond lengths in gas phase as well as in aqueous, chloroform and *n*-heptane solution (COSMO) are presented in Figure 1. Respective Cartesian coordinates and total energies are found in the Supporting Information. Two equivalent, relatively strong hydrogen bonds are observed for the acetic acid dimer whereas the two other complexes form a stronger and a weaker hydrogen bond. An extensive discussion of the geometric parameters of the studied complexes can be found in our previous work.[20]

The calculated complexation energies (ΔE^{gas}), enthalpies (ΔH^{gas}) and Gibbs free energies (ΔG^{gas}) of the complexes are summarized in Table 1. A direct correlation between hydrogen bond lengths and stabilization energies is evident. The calculated stabilization energy for the acetic acid dimer of −15.3 kcal/mol corresponds to the formation of relatively strong hydrogen bonds. This result agrees very well with previous theoretical studies using DFT (BLYP/SVP + sp value of −15.3 kcal/mol)[20] and other high level quantum chemical methods (MP2/aug-cc-pVTZ value of −15.8 kcal/mol).[10] Similar agreement is also observed for the complexation enthalpy (ΔH^{gas}). Our ΔH^{gas} value of −14.1 kcal/mol conforms well with earlier investigations reporting complexation enthalpies of −14.2 kcal/mol (MP2/aug-cc-pVTZ)[10] and −14.7 kcal/mol (BLYP/SVP + sp).[20] The experimental values for the enthalpy of complexation in the gas phase range between −14.2 and −15.3 kcal/mol.[55] Both the complexation energy and enthalpy for the acetamide complex are only about 1 kcal/mol lower than the value for the acetic acid dimer (in absolute values). Differently, the methanol complex has a relatively low stabilization energy (see Table 1) corresponding to a system with weaker hydrogen bonds.

Enthalpy and Free Energy in Solution

The solvation free energies (ΔG_{solv}) of the investigated complexes and their respective monomers are collected in Table 2. This table also reports the solvation contributions to the complexation reac-

Table 1. Interaction Energies (ΔE^{gas}), Enthalpies (ΔH^{gas}) and Gibbs Free Energies (ΔG^{gas}) at T = 298 K for the Complexation Reactions in Gas Phase Determined by the B3LYP/TZVPP Method Including BSSE Corrections.

	ΔE^{gas}	ΔH^{gas}	ΔG^{gas}
AcOH + AcOH → AcOH···AcOH	−15.3	−14.1	−4.0
AcOH + $AcNH_2$ → AcOH···$AcNH_2$	−14.3	−12.9	−1.6
AcOH + MeOH → AcOH···MeOH	−9.1	−7.6	1.9

All the values are given in kcal/mol.

Table 2. Free Energies of Solvation in Water, Chloroform, and *n*-Heptane for the Monomers ($\Delta G_{solv}^{(m)}$), Respective Complexes with Acetic Acid ($\Delta G_{solv}^{(c)}$), $\Delta\Delta G_{solv}$ Values (Eq. 2) and Available Experimental $\Delta G_{solv}^{(m)}$ Values.

		AcOH			$AcNH_2$			MeOH		
Solvent	Method	$\Delta G_{solv}^{(m)}$	$\Delta G_{solv}^{(c)}$	$\Delta\Delta G_{solv}$	$\Delta G_{solv}^{(m)}$	$\Delta G_{solv}^{(c)}$	$\Delta\Delta G_{solv}$	$\Delta G_{solv}^{(m)}$	$\Delta G_{solv}^{(c)}$	$\Delta\Delta G_{solv}$
Water	MD–FEP	−7.8	−4.1	11.5	−9.7	−7.9	9.6	−3.8	−3.9	7.7
	MC–FEP	−7.8	−4.5	11.1	−10.0	−8.7	9.1	−4.1	−4.0	7.9
	PCM	−5.2	0.0	10.4	−8.0	−4.1	9.1	−3.1	−0.8	7.5
	COSMO	−7.4	−6.3	8.5	−12.6	−11.1	8.9	−4.4	−6.0	5.8
	Exp.	−6.7[a]			−9.7[a]			−5.1[b]		
Chloroform	MD–FEP	−4.9	−9.3	0.5	−6.7	−11.4	0.2	−2.1	−7.4	−0.4
	MC–FEP	−6.3	−12.4	0.2	−8.2	−17.0	−2.5	−3.0	−10.9	−1.6
	PCM	−0.3	1.9	2.5	−1.9	0.3	2.5	0.2	1.9	2.0
	COSMO	−4.1	−3.5	4.7	−6.9	−6.2	4.8	−2.2	−3.3	3.0
	Exp.	−4.5[c]		1.7[c]	−7.1[d]			−3.3[d]		
n-Heptane	MD–FEP	−2.9	−7.4	−1.6	−2.9	−7.5	−1.7	−0.1	−4.4	−1.4
	MC–FEP	−2.7	−9.6	−4.2	−2.9	−9.6	−4.0	0.0	−3.6	−0.9
	PCM	−0.3	0.2	0.8	−1.4	−0.7	1.0	0.1	0.3	0.5
	COSMO	−0.9	−0.7	1.1	−1.9	−1.8	1.0	0.0	−0.5	0.4
	Exp.							−1.3[d]		

All the values are given in kcal/mol.
[a]Ref. 57.
[b]Ref. 58.
[c]Ref. 10.
[d]Ref. 59.
MD, molecular dynamics; MC, Monte Carlo; FEP, free energy perturbation; PCM, polarizable continuum model; COSMO, conductor-like screening model.

tion [$\Delta\Delta G_{solv}$, Eq. (2)] as well as available experimental solvation data for the monomers for comparison. Calculated free energies of solvation were obtained by means of the explicit and implicit solvation models. In aqueous solution, the experimentally measured value for the solvation free energy of acetic acid is −6.7 kcal/mol.[56] Both our results obtained from the discrete solvation model (−7.8 kcal/mol) are larger in absolute value by approximately 1 kcal/mol than the experimental value. Another study using MC–FEP reports ΔG_{solv} values for acetic acid in the range of −5.4 to −8.0 kcal/mol.[10] The implicit PCM approach gives a value of −5.2 kcal/mol, which is lower than the one obtained from explicit solvent models. This result is in agreement with other theoretical estimates reporting values between −5.6 and −7.8 kcal/mol.[10,11,20] The second implicit solvation model (COSMO) gives also a value for ΔG_{solv}, which is in good agreement with the experimental one. Therefore, all calculated solvation free energies for acetic acid in aqueous solution are similar and agree well with the experimental value.

A similar trend as for acetic acid in water is observed for the second monomer, acetamide (see Table 2). The solvation free energy obtained from the PCM approach (−8.0 kcal/mol) is in good agreement with the experimental value of −9.7 kcal/mol[56] and with the result from our previous calculations (−10.2 kcal/mol).[20] However, the COSMO result seems to overestimate the solvation effect in the case of acetamide. All calculated solvation free energies for methanol in aqueous solution (including COSMO) are similar and agree well with the experimental value[57] (see Table 2).

In chloroform solution, the MD–FEP and COSMO approaches give similar ΔG_{solv} values for all monomers and are in good agreement with the experimental values.[10,58] In contrast to aqueous solution, the PCM approach clearly underestimates the free energies of solvation for all three monomers (see Table 2). A similar underestimation by PCM ($\Delta G_{solv}^{(m)} = -2.2$ kcal/mol) has been found for acetic acid in chloroform in previous theoretical investigations (B3LYP/6-31G**).[11]

In *n*-heptane the different approaches give roughly the same results of around 0 kcal/mol for methanol (see Table 2), which is not far from the experimental value of −1.3 kcal/mol.[58] For acetic acid and acetamide the PCM and COSMO results are smaller in absolute value than the FEP data. Unfortunately, there are no experimental data available to compare with our results.

Analysis of the solvation free energies of the monomers in water, chloroform and n-heptane as shown in Table 2 indicates the expected result that there is a direct correlation between the ΔG_{solv} values and the polarity of the solvent. The more polar the solvent the more energy is gained upon solvation.

$$\Delta G_{solv}(\text{water}) < \Delta G_{solv}(\text{chloroform}) < \Delta G_{solv}(n-\text{heptane})$$

For all investigated cases in aqueous solution the sum of the solvation free energies of the monomers is larger in absolute value than the solvation free energies of the respective complexes. This fact is mainly related to the dipole moments of the investigated species and to the loss in solvent accessible surface

Table 3. Individual Contributions to the Solvation Free Energy (ΔG_{solv}) of the Acetic Acid Monomer and Dimer in Water, Chloroform, and *n*-Heptane.

	AcOH			AcOH···AcOH		
	MD–FEP	MC–FEP	PCM	MD–FEP	MC–FEP	PCM
Water						
ΔG_{el}	−8.8	−8.6	−8.4	−3.0	−3.0	−5.2
ΔG_{cav}	4.3	4.5	10.0	7.3	7.4	18.6
ΔG_{rep}			2.3			2.9
ΔG_{disp}	−5.2	−5.6	−11.0	−10.3	−10.8	−18.2
RT ln (24.46)	1.9	1.9	1.9	1.9	1.9	1.9
ΔG_{solv}	−7.8	−7.8	−5.2	−4.1	−4.5	0.0
Chloroform						
ΔG_{el}	−1.2	−1.3	−2.7	−0.6	−0.6	−1.8
ΔG_{cav}	1.9	2.3	7.2	2.9	2.3	13.4
ΔG_{rep}			1.2			1.6
ΔG_{disp}	−7.5	−9.2	−7.9	−13.5	−16.0	−13.2
RT ln (24.46)	1.9	1.9	1.9	1.9	1.9	1.9
ΔG_{solv}	−4.9	−6.3	−0.3	−9.3	−12.4	1.9
n-Heptane						
ΔG_{el}	0.0	0.0	−1.4	−0.1	0.0	−0.9
ΔG_{cav}	2.1	2.4	6.7	2.9	1.5	12.5
ΔG_{rep}			1.8			2.2
ΔG_{disp}	−6.9	−7.0	−9.3	−12.1	−13.0	−15.5
RT ln (24.46)	1.9	1.9	1.9	1.9	1.9	1.9
ΔG_{solv}	−2.9	−2.7	−0.3	−7.4	−9.6	0.2

All the values are given in kcal/mol.
MD, molecular dynamics; MC, Monte Carlo; FEP, free energy perturbation; PCM, polarizable continuum model.

due to the complex formation. Each monomer has a large dipole moment as it possesses a polar functional group (i.e., COOH, NH_2, and OH), which strongly interacts with polar solvents. Thus, all monomers have relatively high free energies of solvation. On the other hand, the hydrogen-bonded complexes are less solvated than the corresponding monomers, which can be explained by the compensation of individual monomer dipole moments leading to complete annihilation or strong reduction of the total dipole moment and by the loss of hydrogen bond capabilities with the solvent upon complexation. The strongly positive $\Delta\Delta G_{solv}$ values for aqueous solution agree quite well between different methods in spite of the discrepancies in the ΔG_{solv} values for the individual species. Chloroform has a smaller, but still significant destabilizing effect on the complexation for the implicit solvent models. For the explicit solvent models it has a negligible or even a small stabilizing effect upon complexation. In *n*-heptane solution, a similar trend is observed. The implicit solvent models present a small destabilization of the complex, but the explicit solvent models present a stabilization of the complex.

To rationalize this global comparison, the contributions to the solvation free energy were analyzed in more detail. Table 3 reports the individual contributions to ΔG_{solv} for the acetic acid monomer and dimer in water, chloroform and *n*-heptane. The other systems show a similar behavior and are, therefore, not discussed further in this context. As the COSMO free energy of solvation is only of electrostatic nature it is not included in Table 3. However, the obtained COSMO results given in Table 2 are similar to the electrostatic terms in PCM. The electrostatic contributions ΔG_{el} agree well between the different solvent models. The remaining contributions (ΔG_{cav}, ΔG_{rep}, ΔG_{disp}, cavitation, repulsion and dispersion, respectively) of the PCM method can be directly related to the ε_i and σ_i parameters of the Lennard-Jones potential. For reasons of comparison, the sum of the repulsive contributions to the solvation free energy (ΔG_{cav} and ΔG_{rep}) within PCM is compared to the repulsive contribution of the Lennard-Jones potential described by σ_i. This contribution turned out to be the most sensitive one (see Table 3). The FEP simulations show that in all cases investigated here PCM strongly overshoots this term. In water the repulsive contributions approximately double when comparing the monomer and the dimer. Their effect thus cancels in computing $\Delta\Delta G_{solv}$. The dispersion contribution to ΔG_{solv} for water is significantly more negative for PCM than for the explicit solvation models. Again,

Table 4. Gibbs Free Energies (ΔG^{sol}) at $T = 298$ K for the Complexation Reactions in Water (H_2O), Chloroform ($CHCl_3$), and *n*-Heptane (C_7H_{16}) (Eq. 1) Determined from Different Free Energy Estimates.

	Solvent	MD–FEP	MC–FEP	PCM	COSMO
AcOH + AcOH → AcOH···AcOH	H_2O	7.5	7.1	6.5	4.5
	$CHCl_3$	−3.5	−3.8	−1.5	0.7
	C_7H_{16}	−5.6	−8.0	−3.1	−2.9
AcOH + $AcNH_2$ → AcOH···$AcNH_2$	H_2O	8.0	7.5	7.5	7.3
	$CHCl_3$	−1.8	−2.1	0.9	3.2
	C_7H_{16}	−3.3	−5.6	−0.6	−0.6
AcOH + MeOH → AcOH···MeOH	H_2O	9.6	9.8	9.4	7.7
	$CHCl_3$	1.1	2.3	3.7	4.9
	C_7H_{16}	0.5	1.0	2.5	2.3

All the values are given in kcal/mol.
MD, molecular dynamics; MC, Monte Carlo; FEP, free energy perturbation; PCM, polarizable continuum model; COSMO, conductor-like screening model.

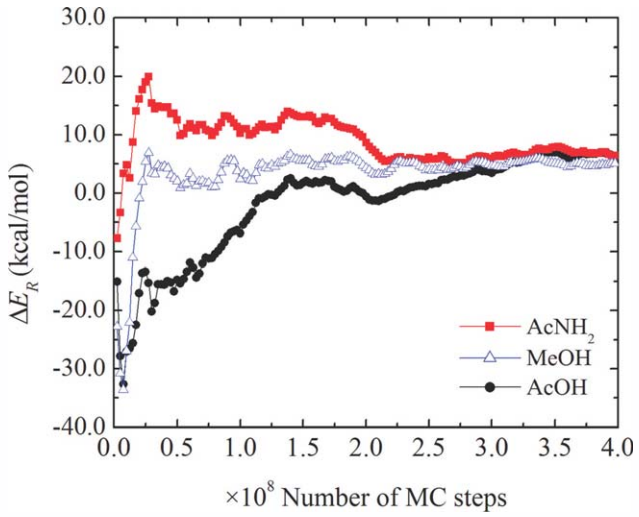


Figure 2. Convergence of the solvent relaxation energy ΔE_R as a function of the number of MC steps for acetic acid, acetamide, and methanol in aqueous solution.

roughly a factor of two is observed between monomer and dimer leading to an approximate cancellation in $\Delta\Delta G_{solv}$. Thus, finally the overall values for $\Delta\Delta G_{solv}$ are quite similar for all methods in spite of the differing amount of individual contributions.

In chloroform and *n*-heptane solution the electrostatic term ΔG_{el} is significantly smaller in absolute value than for water. The dispersion contributions are quite similar for all methods, and cancel again approximately in the computation of $\Delta\Delta G_{solv}$. The repulsive contributions are strongly reduced (by a factor of two and more) in the explicit models as compared to values for water whereas in PCM respective reductions in comparison to water are much smaller percentage-wise. Changes between dimer and monomer contributions of the repulsive terms to $\Delta\Delta G_{solv}$ cancel for PCM. The values for the repulsive contribution computed by the explicit models are much smaller and cancellation in $\Delta\Delta G_{solv}$ is found also. The small differences observed for the repulsive contribution in the MC results have no significant meaning and can be related to statistical fluctuations. In any case, the overall effect is quite small.

This analysis shows that for association reactions the changes in the electrostatic terms dominate the solvent contributions $\Delta\Delta G_{solv}$ and that the substantial variation between different methods in the remaining contributions practically cancels.

Combination of gas phase results with the results obtained from different free energy estimates using the thermodynamical cycle [Eq. (1)] allows the determination of the total complexation free energy in solution and thus to obtain information about the thermodynamical stability of the investigated hydrogen-bonded complexes. The final free energies of complexation in solution (ΔG^{sol}) considered in this work are summarized in Table 4. It can be seen that independent of the method for the free energy calculation the acetic acid dimer is not stable in aqueous solution. The calculated complexation free energy is clearly positive ranging from 4.5 kcal/mol (COSMO) to 7.5 kcal/mol (MD–FEP). This result is in agreement with previous theoretical studies which also report positive ΔG^{sol} values between 3.5 kcal/mol[10] and 7.5 kcal/mol.[20] Experimental studies of the acetic acid dimerization in water have suggested ΔG^{sol} values ranging from 0.0 to 2.0 kcal/mol.[18,59,60] One likely explanation for the rather large differences of computed ΔG^{sol} values to the experimental ones could be that the experimentally observed dimer in aqueous solution does not correspond to the double hydrogen-bonded gas phase structure. Experimental[60,61] as well as theoretical[10,62] investigations have proposed an open chain structure in aqueous solution. Chocholoušová et al.[11] have investigated five additional (more likely) open chain structures in aqueous solution and concluded that at low acetic acid concentrations no dimer structure exists. Potential of mean force calculations for aqueous solution allowing relative rotation of the acetic acid molecules confirm this view.[13] Based on the CHARMM22 force field, in that work a ΔG^{sol} value of 0.05 kcal/mol is reported, which is located within the experimental window.

According to the calculated ΔG^{sol} results obtained from the discrete solvation models, the acetic acid dimer is stable in chloroform. The values of −3.5 kcal/mol (MD–FEP) and −3.8 kcal/mol (MC–FEP) are in good agreement with the experimentally estimated value of −3.4 kcal/mol obtained from the dimerization constant of 300 L/mol.[19] Our result agrees well with earlier theoretical investigations[10] where complexation free energies in chloroform solution ranging form −3.1 to −3.9 kcal/mol were obtained. The PCM approach also correctly predicts the stable dimer (see Table 4) whereas the COSMO method gives a slightly positive ΔG^{sol} value of 0.7 kcal/mol.

In *n*-heptane the complexation free energies determined from all computational methods used in this work are negative (Table 4) supporting the stability of the double hydrogen bond acetic acid dimer. Our result is in agreement with previous calculations in which a negative ΔG^{sol} value of −1.8 kcal/mol is reported.[20] The explicit models give more negative values. Unfortunately, there are no experimental results for comparison, but there is an experimentally estimated value of −4.8 kcal/mol obtained from the dimerization constant of 3200 L/mol[18] in n-hexane which is similar to *n*-heptane. For the acetic acid–acetamide complex, a similar trend as for the acetic acid dimer is observed. The complex is not stable in aqueous solution whereas a stable complex is predicted in less polar solvents from explicit solvation calculations. In chloroform, both implicit solvation models produce positive ΔG^{sol} values of 0.9 (PCM) and 3.2 kcal/mol (COSMO). As shown before, both the acetic acid dimer and the acetamide complex are relatively strongly bound systems. Thus, the similar trend observed for both complexes is not unexpected.

As the methanol complex is not stable in gas phase (see Table 1) it is not expected to be stable in any solvent independently of its polarity. Indeed, the results obtained in this work confirm this assumption (see Table 4). For all free energy estimates used, all ΔG^{sol} values are positive ranging from 0.5 kcal/mol (MD–FEP) for *n*-heptane to 9.8 kcal/mol (MC–FEP) for water.

In the case of aqueous solution, the solvation and complexation enthalpies were calculated by means of MC simulations using Eq. (4). 3.2×10^8 MC steps were computed to obtain a properly converged solvent relaxation enthalpy (ΔH_R) for all investigated solutes. In Figure 2, this convergence is shown for

Table 5. Individual Contributions to the Solvation Enthalpy (ΔH_{solv}) of the Monomers and Complexes in Aqueous Solution. Corresponding Differences for the Complex Formation are also Shown.

				AcOH···		
	AcOH	$AcNH_2$	MeOH	AcOH	$AcNH_2$	MeOH
E_{SX}	−23.9	−31.2	−18.8	−22.5	−29.4	−21.4
ΔH_R	6.3	6.4	5.1	3.5	5.0	5.9
$-RT$	−0.6	−0.6	−0.6	−0.6	−0.6	−0.6
ΔH_{solv}	−18.2	−25.4	−14.3	−19.6	−25.0	−16.1
ΔE_{SX}				25.3	25.7	21.3
$\Delta\Delta H_R$				−9.1	−7.7	−5.5
$\Delta\Delta H_{solv}$				16.8	18.6	16.4

All the values are given in kcal/mol.

the monomers. It is interesting to note that although the monomers induce significant solvent reorganization energies of 6.3, 6.4, and 5.1 kcal/mol for acetic acid, acetamide, and methanol, respectively, the contribution to the differential solvation enthalpy is small, as these molecules have approximately the same size. The calculated solvation enthalpy (ΔH_{solv}) values of the investigated complexes and their respective monomers are presented in Table 5. This table also reports the individual contributions to ΔH_{solv}, the solute–solvent interaction (E_{SX}) and the solvent relaxation ($\Delta H_R \approx \Delta E_R$) energies as well as the constant term [see Eq. (4)]. All monomers and complexes present an energetically favorable solvation in aqueous solution. The dominant contribution, however, comes from the solute–solvent interaction energy (see Table 5). The solvent relaxation enthalpy requires around 15–30% of this interaction energy to accommodate the solute, an amount that cannot be neglected.

Analyzing the complexation in aqueous solution, the sum of the solute–solvent interaction energies for the monomers is larger in absolute value than for the respective complexes. This trend was already observed for the solvation free energies and can directly been related to the dipole moments of the investigated species. Analysis of hydrogen bonds between the water molecules and the monomers during MC simulations reveals on average 3, 4, and 2.5 hydrogen bonds for acetic acid, acetamide, and methanol, respectively. For the complexes, on average 2, 3.5, and 2.5 hydrogen bonds were observed for the acetic acid dimer, acetamide, and methanol complexes, respectively, in aqueous solution. These values show that 4 (acetic acid dimer), 3.5 (acetamide-), and 3 (methanol-complex) hydrogen bonds were lost upon complexation. These two factors contribute to the large difference in the solute–solvent energies (ΔE_{SX}) that destabilizes the complexes. Large positive ΔE_{SX} values (see Table 5) ranging from 21.3 kcal/mol for the methanol complex to around 25.7 kcal/mol for the acetamide complex were obtained. On the other hand, the energetic cost to accommodate the solute in the network of hydrogen bonds of liquid water is larger for the sum of the monomers than for the complexes. As shown in Table 5, the differences in solvent relaxation energies ($\Delta\Delta H_R$) stabilizing the complexes are −9.1 kcal/mol for acetic acid dimer, −7.7 kcal/mol for acetamide- and −5.5 kcal/mol for the methanol-complex. Therefore, combining these two differential contributions and the RT term, the differential enthalpy of the monomers as compared to the complex ($\Delta\Delta H_{solv}$) were obtained [see Eq. (2), changing G for H, and Eq. (4)]. The $\Delta\Delta H_{solv}$ values are presented also in Table 5. The energetic cost to bring the separated monomers together in aqueous solution ranges from around 16.4 kcal/mol for the methanol complex to around 18.6 kcal/mol for the acetamide-complex mostly due to the loss of solute–solvent interactions (positive ΔE_{SX}) and the gain of solvent reorganization (negative $\Delta\Delta H_R$). Using the thermodynamic cycle presented in Scheme 1 and the corresponding Eq. (1) for the enthalpy (H), the total complexation enthalpy in solution (ΔH^{sol}) was computed and is listed in Table 6 for each complex. As can be seen by comparing the $\Delta\Delta H_{solv}$ values given in Table 5 with ΔH^{gas} presented in Tables 1 and 6, the energetic cost to form the complexes in solution is larger than the energetic gain to form the hydrogen bonds in the complexes. Therefore, the obtained values of ΔH^{sol} show that the formation of all investigated complexes is energetically unfavorable in aqueous solution, 2.7 kcal/mol for the acetic acid dimer, 5.7 kcal/mol for the acetamide complex and 8.8 kcal/mol for the methanol complex.

Entropic Contribution

The entropic contribution $T\Delta S$ to solvation and complexation in gas phase and aqueous solution were obtained using the calculated MC-FEP Gibbs free energies and enthalpies of solvation and complexation as reported in Tables 1, 2, 4, and 5. All these values and the entropic contributions are summarized in Table 6. Inspection of this table reveals that the entropic contributions $T\Delta S$ to the solvation and complexation processes are substantial and unfavorable for both processes.

The computed $T\Delta S^{gas}$ value of −10.1 kcal/mol for the acetic acid dimer is in good agreement with the experimental value of about −10.7 kcal/mol.[55,63] The present result agrees also very well with previous theoretical calculations (MP2/aug-cc-pVTZ

Table 6. Summary of the Solvation and Complexation Gibbs Free Energies (ΔG), Enthalpies (ΔH) and Entropy Terms ($T\Delta S$), at T = 298 K for the Complexation Reactions in Gas Phase and Aqueous Solution.

Formation in gas phase	ΔG^{gas}	ΔH^{gas}	$T\Delta S^{gas}$
AcOH + AcOH → AcOH···AcOH	−4.0	−14.1	−10.1
AcOH + $AcNH_2$ → AcOH···$AcNH_2$	−1.6	−12.9	−11.3
AcOH + MeOH → AcOH···MeOH	1.9	−7.6	−9.5
Aqueous solvation	ΔG_{solv}	ΔH_{solv}	$T\Delta S_{solv}$
AcOH	−7.8	−18.2	−10.4
$AcNH_2$	−10.0	−25.4	−15.4
MeOH	−4.1	−14.3	−10.2
AcOH···AcOH	−4.5	−19.6	−15.1
AcOH···$AcNH_2$	−8.7	−25.0	−16.3
AcOH···MeOH	−4.0	−16.1	−12.1
Formation in aqueous solution	ΔG^{sol}	ΔH^{sol}	$T\Delta S^{sol}$
AcOH + AcOH → AcOH···AcOH	7.1	2.7	−4.4
AcOH + $AcNH_2$ → AcOH···$AcNH_2$	7.5	5.7	−1.8
AcOH + MeOH → AcOH···MeOH	9.8	8.8	−1.0

All values are given in kcal/mol.

value of −10.2 kcal/mol).[10] This large loss of entropy accompanying the complexation reaction in gas phase is a generally known phenomenon that occurs for associative reactions[64] and was observed in other studies as well.[11,20] The unfavorable $T\Delta S^{gas}$ factor is the reason that only the strongly bound complexes such as the acetic acid dimer and the acetamide complex are stable in gas phase at room temperature while the weakly bound methanol complex is not stable.

For the solvation process (see Table 6), the $T\Delta S_{solv}$ values range from −10.2 (methanol) to −16.3 kcal/mol (acetic acid–acetamide complex). They are of comparable size for the monomers and the complexes, but they are not large enough to destabilize the solvation in water due to the strong solute–solvent interaction that generates a large favorable solvation enthalpy.

In case of the complexation process (see Table 6), the $T\Delta S^{sol}$ values are not so large in absolute value as compared to $T\Delta S_{solv}$ values ranging from −1.0 kcal/mol for the methanol complex to −4.4 kcal/mol for the acetic acid dimer. However, the situation is different from the solvation process of individual systems discussed just above. As the formation enthalpies are already unfavorable, and by adding an even larger unfavorable entropic contribution the entire complexation process is strongly destabilized. In consequence, the three investigated complexes are unstable in aqueous solution at room temperature.

Conclusions

In this work, benchmark hydrogen-bonded systems (acetic acid dimer and the acetic acid–acetamide and –methanol complexes) in water (polar), chloroform (less polar), and *n*-heptane (nonpolar) have been investigated. For the study of solvation effects on interaction energies two completely different approaches, explicit (MD–, MC–FEP) and implicit (PCM, COSMO) solvation models were used. In the first step, free energies of solvation of the complexes and their respective constituents were calculated. With increasing polarity of the solvent an increase in solvation free energy (absolute value) is observed. Both explicit solvation approaches give similar results demonstrating that the statistical sampling methods were adequate. Comparison to experimental values for the monomers indicates that both MD– and MC–FEP present very good results for the solvation free energies. Regarding the Gibbs free energies of complexation in solution, the differences between the MD and MC approaches are found to be smaller than 0.5, 1.5, and 2.5 kcal/mol for water, chloroform, and *n*-heptane, respectively. This can be attributed to statistical fluctuations that are larger for smaller systems (518 water, 115 chloroform, and 64 *n*-heptane). The PCM model is found to reproduce well the experimental ΔG_{solv} for acetic acid in aqueous solution while in chloroform it clearly underestimates the free energies of solvation. COSMO, on the other hand, shows a good performance for solvation free energies of the monomers. In *n*-heptane all methods give similar results. For the hydrogen-bonded complexes, the solvation free energies are significantly more negative for the methods using explicit solvation with respect to the PCM result. The large repulsive contribution (mainly cavitation energy) to the solvation free energy within the implicit PCM model is responsible for this result. COSMO lacks this contribution leading to ΔG_{solv} values, which are systematically more negative than the PCM results. However, computing the solvation contributions to total complexation Gibbs free energy ($\Delta\Delta G_{solv}$) the discrepancies are largely compensated.

A detailed analysis of individual contributions to $\Delta\Delta G_{solv}$ leads to the conclusion that for association reactions of polar molecules the electrostatic contribution dominates. Repulsive terms and dispersion interactions cancel approximately, even though varying considerably between explicit and implicit solvent models for monomers and complexes. These results give a justification for concentrating on electrostatic terms, which can be computed in a straightforward way. Nevertheless, more investigations have to be performed in order to investigate the influence of the molecular size and a larger complexity in the polar substituents.

Owing to the large influence of water, the double hydrogen-bonded acetic acid dimer is not stable in aqueous solution. The calculated complexation Gibbs free energy is computed as significantly more positive (∼7 kcal/mol) than experimental estimates (0–2 kcal/mol).[18,59,60] This discrepancy points to a more basic reason than eventual inaccuracies in the calculations or the experiments. Therefore, for the acetic acid dimerization in water, other mechanisms, eventually through a chainlike structure, have been suggested previously.[10,11,62] In weak polar or apolar solvents such as chloroform and *n*-heptane, the dimerization of acetic acid is favorable, in good agreement with available experimental results. Similar to the gas phase, the cyclic acetic acid dimer is the most stable structure. The strongly bound acetic acid–acetamide complex shows the same behavior as the acetic acid dimer. It is not stable in aqueous solution but shows stability in less polar solvents. The weakly bound methanol complex is thermodynamically not stable at room temperature in all of the investigated solvents. This result is not surprising since even in gas phase the methanol complex is not stable.

Enthalpic (ΔH) and entropic contributions ($T\Delta S$) were computed for both the solvation process and the complexation in aqueous solution using MC simulations. It is important to note that not only the free energies ΔG^{sol} of complexation in solution are positive but also the respective ΔH^{sol} values. Implicit solvation models give only the solvation contribution to the free energy but not to the enthalpy. Thus, the present results nicely complete the entire thermodynamic picture of the present benchmark association complexes in solution.

Acknowledgments

H.L. acknowledges support by the grant from the Ministry of Education of the Czech Republic (Center for Biomolecules and Complex Molecular Systems, LC512) and by the Praemium Academiae of the Academy of Sciences of the Czech Republic, awarded to Pavel Hobza in 2007. This work was part of the research project Z40550506 of the Institute of Organic Chemistry and Biochemistry of the Academy of Sciences of the Czech Republic. We are grateful for the technical support and the computer time on the Linux-PC cluster III of the University of

Vienna. H.C.G., T.F.M., K.C., and S.C. acknowledge the Brazilian agencies CNPq, CAPES, and FAPESP.

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