Solvation Free Energies of Methane and Alkali Halide Ions. An Expanded Ensemble Molecular Dynamics Simulation Study

A.P.Lyubartsev [†*], O.K.Førrisdahl [††] and A.Laaksonen [†]

[†] Division of Physical Chemistry, Arrhenius Laboratory,
Stockholm University, S-106 91 Stockholm, Sweden.
[††] Telemark Institute of Technology, Kjølnes, N-3914, Porsgrunn, Norway

ABSTRACT

Solvation free energy for methane, dissolved both in pure water, water/methane mixture (14 mole % methane) and in aqueous NaCl solution, is calculated using the expanded ensemble molecular dynamics method. Dependencies due to system size and potential model are investigated. Results, using a simple one-site methane model, together with large enough system size, are found in very good agreement with experimental data, while calculations using a flexible five-site methane model give too high free energies. Also, the solvation energy for 20 different ion pairs of alkali halides is calculated in a systematic study. Very good overall agreement is found for the solvation energies of all the ion pairs. Calculations of solvation free energies provide a sensitive test of the used potential models.

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[*] Also affiliated with Scientific Research Institute of Physics, St.Petersburg State University, 198904, St.Petersburg, Russia.

1. INTRODUCTION

Solubility, lack of solubility and other solvation properties of atoms, molecules and ions in aqueous solutions play an important role in biological processes and industrial applications. One of the most important solvation properties is the free energy of solvation, controlling solubilities and association of solutes, phase equilibria and nucleation processes.

The solvation free energy is determined as the Gibbs free energy change in a process to transfer a solute molecule from ideal gas phase into a solvent. To obtain a reliable free energy from theoretical calculations is still difficult and behind a tedious work. During the last decade several schemes have been suggested in literature to calculate free energies using computer simulations [1-5]. Most of these methods require a considerable number of repeated computer runs and face difficulties or even fail for systems with strong coupling parameters or at high densities.

The solvation free energy is closely related to the chemical potential of the solute molecule. The standard procedure to calculate chemical potential is to use the Widom particle insertion method [1]. However, direct application of this method becomes inefficient at liquid densities. Various techniques, such as, *f-g* sampling [6], umbrella sampling [7] and biased simulations [8] have been suggested in order to improve the applicability of the Widom formula at higher densities.

A new efficient approach which allows calculations of absolute free energies with a high precision for arbitrary systems, called the expanded ensemble (EE) method, was recently introduced within Monte Carlo (MC) [9] and molecular dynamics (MD) [10] simulations. The basic idea in the method is to construct an expanded ensemble as a sum of conventional (e.g. canonical) ensembles with pre-weighted ("balancing") factors. A probability distribution over subensembles is obtained as a stochastic walk by means of Metropolis Monte Carlo [11]. This quantity is directly related to the ratio of corresponding partition functions and, hence, to the free energy differences. The free energy can be readily obtained for any of the subensembles if it is already known for one subensemble (the reference system). Related approaches have been suggested in literature quite recently: multicanonical ensemble [12], simulated tempering [13], force balance method [14]. An overview and evaluation of these methods can be found in recent papers by Smith and Bruce [15] and Hansmann and Okamoto [16].

In this work we have applied the EE method to calculate the solvation free energy of two completely different systems dissolved in water solution: the sparsely soluble methane and readily soluble ions of alkali halides. To calculate the free energy difference due to insertion of a molecule into a solution we have used the technique of gradual particle insertion within the EE method, in which the (N+1):th particle is slowly mutated from a real particle into a "ghost" (non-interacting) particle. The EE method has proven to be very efficient in calculations of chemical potentials [17-19], including studies of dense polymer systems [20,21].

2. OUTLINE OF THE EXPANDED ENSEMBLE METHOD

The details of the EE method together with the underlying theory are already given in our previous papers [9,19]. For a convenience, we outline the basic formalism and computational features and clarify the gradual particle insertion in some more details.

Consider a limited volume of a liquid or a solution consisting of N particles. Assume that an additional ($N+1$):th particle is gradually inserted into the solution. Somewhat arbitrarily, we call the original N-body system a *solvent* and the inserted particle a *solute*. At each arbitrary point m, while the insertion is in progress, the configurational partition function for the system can be given as:

$$Z_m = \int_V \prod_{i=1}^{N+1} dq_i \exp(-\beta(H_{\mathrm{N}}(q_i) + \alpha_{\mathrm{m}} h_{N+1}(q_i))) \tag{1}$$

where H_{N} is the Hamiltonian of the system of N particles (solvent), $h_{\mathrm{N+1}}$ is the interaction energy of the ($N+1$):th particle with all the other particles, α_{m} is a set of values, gradually changing from 0 to 1, while m changes from 0 to M (the number of subensembles). In the case of a complex (polyatomic) solute, the intramolecular interaction term for the solute can be added into H_{N}.

The partition function of the expanded ensemble is given as:

$$Z = \sum_{m=0}^{M} Z_m \exp(\eta_m) = \sum_{m=0}^{M} \int_V \prod_{i=1}^{N+1} dq_i \exp(-\beta(H_{\mathrm{N}}(q_i) + \alpha_{\mathrm{m}} h_{N+1}(q_i)) + \eta_{\mathrm{m}}) \tag{2}$$

where η_m parameters are "balancing factors". The 0:th subensemble, with $\alpha_0=0$, corresponds to the system with N interacting particles and one single "ghost" particle. Since the ghost particle does not interact with the other particles, it can be assumed to be in an ideal gas phase. Subensembles with an increasing m correspond to a gradual insertion of the ($N+1$):th particle, while the M:th subensemble with $\alpha_{\mathrm{M}}=1$ corresponds to the true ($N+1$) particle system (solution).

A Monte Carlo walk in the expanded space of ($\{q_{\mathrm{i}}=1,\ldots,N+1\},m$), consisting of both particle displacements and changes of m, produces a probability distribution over the subensembles p_{m}. The probability ratio of the two extremes, $m=0$ and $m=M$, can be given as:

$$\frac{p_{\mathrm{M}}}{p_{\mathrm{o}}} = \frac{Z_{\mathrm{M}}}{Z_{\mathrm{o}}} \exp(\eta_{\mathrm{M}} - \eta_0) = \exp(-\beta(F(M) - F(0)) + \eta_{\mathrm{M}} - \eta_0) \qquad (3)$$

where $F(M)$ is the free energy of the solvent including the inserted solute particle and $F(0)$ is the sum of the free energies of the pure solvent and the solute molecule in the ideal gas phase. The difference $F(M)$-$F(0)$ is the "excess" solvation free energy μ_{ex}, corresponding to the free energy of a transfer from ideal gas at a given density to a solution with the maintained density. The excess solvation energy μ_{ex} is given:

$$\mu_{ex} = -\ln\left(\frac{p_{\mathrm{M}}}{p_0}\right) + \eta_{\mathrm{M}} - \eta_0 \qquad (4)$$

Experimental values of the solvation free energies often refer to the "standard molar free energies". These correspond to a transfer of a solute particle from gas state at 1 atm to 1M solution. The standard molar free energies differ from the excess free energies by a term kT *ln* (P_M/P_0), where P_M=1 atm and P_0 is the pressure of an ideal gas at 1M concentration [22]. This quantity has a value: -7.92 kJ/M.

3. COMPUTATIONAL DETAILS

3.1 Molecular models

The flexible SPC water model by Rahman and Toukan [23] is used in all the simulations as a solvent. Two potential models are used for methane. In the first model, proposed by Jorgensen *et al*.[24], methane consists of a single Lennard-Jones sphere. The second one is a flexible five-site model [25] with AMBER force-field [26] parameters. Rigid ion models are used for the monovalent ions: alkali metal cations ranging from Li^+ to Cs^+ and for the halide anions ranging from F^-

to I^-. The Lennard-Jones parameters σ and ε for the ions are taken from the work of Heinzinger [27]. The potential parameters for all the simulated specii are listed in Table 1. Lorentz-Berthelot combination rules are applied to all cross-interactions.

3.2 Simulation set up

Molecular dynamics version of the expanded ensemble method [10] is used in the present work, moving the system in the phase space along the NVT or NPT trajectories, while the changes of subensembles are generated according to Metropolis Monte Carlo rules.

The simulations are carried out using periodic boundary conditions together with the minimum image convention. The Ewald method [11] is used for the treatment of the electrostatic interactions. The method of double time steps is applied in the simulation. The short time step of 0.2 fs is used for the fast fluctuating intramolecular degrees of freedom and for the close range intermolecular interactions and the large time step of 2.0 fs is employed for the rest of the interactions. The multiple time step method is that of Tuckerman *et al.*[28]. The NVT and NPT ensembles are maintained using the Nose-Hoover method [29-31]. The length of final molecular dynamics trajectories (after optimizing the balancing factors) was 200 ps for calculations of methane solvation free energies (300 ps for the case of 512 molecules) and 500 ps for ion pairs. All simulations are carried out at 300 K.

3.3 Setting up the expanded ensemble sampling

The use of the expanded ensemble method requires a number of parameters to be determined in advance for each particular system or a specific application.

The number of subensembles, M, must be specified together with the points α_m, distributed within the interval [0,1]. The intermediate α_m points should be chosen so that a reasonably high probability is provided for transitions between subensembles in order to obtain a fast exploration of the expanded configurational space. Furthermore, the balancing factors, η_m, have to be chosen so that the probabilities p_M do not become too small. The strategy for choosing the intermediate α_m points and for optimizing the balancing factors is discussed in detail in our previous papers [9,19].

In the present simulations transitions among the subensembles are induced after each 6 fs. The number of intermediate subensembles was 18 in all simulation runs. The intermediate α-points were chosen more frequently close to 0, because the effective size of a Lennard-Jones particle decreased very slowly upon decreasing the α parameter. This particular choice of subensembles gave an acceptance ratio for transitions between subensembles of 40-50% throughout the whole interval. The balancing factors η_m were fitted in several trial runs before each simulation run.

4. SOLVATION FREE ENERGY: RESULTS AND DISCUSSION

4.1 Methane dissolved in pure water

We have carried out a series of MD simulations of methane dissolved in pure water, corresponding to infinitely diluted aqueous methane solutions in order to study the effect of system size and potential models to the results. Two conceptually very different methane models have been tested: a single-site and a five-site model. In addition, the effect of using two different sets of fractional charges for the five-site model of methane has been investigated. Also, possible differences from using NVT and NPT ensembles are studied. All the results are gathered in Table 2, together with a reported experimental value at infinite dilution. For a comparison, Table 2 also contains some results, carried out by other workers using other water models and other computational schemes for free energy calculations.

<u>Size dependence</u>: We have carried out calculations of solvation free energy of the simple methane model in water by successively increasing system size from 108 molecules to 256 and then to 512 and obtained μ_{ex}=10.5kJ/M, 8.9 kJ/M and 8.5 kJ/M, respectively (see Table 2). The fairly large difference in results between the first two simulations can be explained to originate from a too small size of the simulation cell for the case of 107 H_2O and 1 CH_4, with the side length of the cell, L_{box}=14.7Å. In such a small box the hydration shell of the methane molecule may overlap with itself in the neighboring periodic cells. Moreover, for Lennard-Jones particles, the long-range corrections become negligible if the used cut-off distance $L_{box}/2$ exceeds 3 σ. This is fulfilled in the case for 255 water molecules (L_{box}=19.8Å), but not for the smaller system. A further increasing of the system size to 511 water molecules (L_{box}=24.8Å) does not give any significant changes in the results.

<u>NVT vs NPT</u>: Some of the calculations of the solvation free energies are carried out in the expanded NPT ensemble. Details on the expanded ensemble algorithm in NPT ensemble are given in our previous work [19]. The main purpose was to study whether the NPT calculations would provide a more effective route since the system volume in NPT is adjusted at each insertion step and the whole process of insertion or deletion would go more smoothly. This turns out not to be the case. We do not find any noticeable differences, neither in the results, nor in the effectiveness even in the smallest system (108 molecules). The solvation free energies, from the simulations at constant pressure and constant volume, are well within the statistical error. Any differences between other simulation results, such as internal energies, distribution functions, etc, are not observed. From the users point of view, the NVT algorithm is more straightforward to implement.

In summary, our result from the simulation of the infinitely diluted methane solution with the larger system, using the simple single-site Lennard-Jones model for methane, μ_{ex}=8.5 $\pm$0.7 kJ/M, agrees very well with the experimental value 8.4 kJ/M at 298K [32]. Calculations of the solvation free energy using this methane model have been reported in literature: Jorgensen *et al*.[33] calculated the free energy of hydration for methane in TIP4P water to be μ_{ex}=10.5 $\pm$1.7 kJ/M, using MC simulations and perturbation method. Using the test particle method, Guillot et al. [34] obtained μ_{ex}=9.5 kJ/M for methane in rigid SPC water. Hummer et al. [22] report μ_{ex}=10.2 $\pm$0.9 kJ/M, using the same potential models and method as Guillot and coworkers. All these results, calculated for systems of 256 molecules, are slightly higher than our free energy result. One possible explanation could be that we have used a flexible water model, which, due to the flexibility can lead to configurations with lower energy in the vicinity of the methane molecule compared to the corresponding rigid SPC model. These lower-energy configurations will lower even the solvation free energy.

Model dependence: The single-site Lennard-Jones model for methane provides seemingly a very significant simplification of a five-atomic molecule to a sphere with an effective mass and size of methane. What may seem particularly serious is the complete lack of rotational degrees of freedom.

We have used a more “realistic” methane model in attempt to improve our results. A five-site methane molecule, with AMBER force field parameters for the carbon and hydrogen atoms is created. Furthermore, two sets of point charges are used to study the role of the electrostatic interactions. One set is taken from mulliken population analysis, the other set consists of ESP charges (see Table 1). This methane model has been previously used by Sun *et al*.[24]. After dissolving one five-site methane in 255 water molecules, we obtain 11 ±1 kJ/M for the set of Mulliken charges and 11.6 ±1 kJ/M for the ESP charges. The difference of solvation free energies between the two models with ESP and Mulliken charges is below the statistical error. This difference was also calculated directly by perturbation method by Sun *et al*[25] to be 0.25kJ/M. The same difference (0.25kJ/M) was observed between the uncharged five-site methane model and the model with ESP charges[35]. We conclude that the charges on the all-atom methane model have only a small influence on the solvation free energy.

Calculations of the solvation free energy for the five-site methane model with ESP charges are also reported previously. An earlier result by Bash et al.[36] using TIP3P water was 8.9 ±3.8 kJ/M. Later the same group obtained, using a more precise dynamically modified windows perturbation technique[35], quite different results: 15.35 ±0.6 or 14.7 ±0.9 kJ/M depending on how the bond stretching contributions were treated. We would like to stress that in using the expanded ensemble method, contributions due to changing of the covalent bond lengths and angles in a process of transformation from a real molecule to a ghost molecule are automatically taken into account.

Our results are 3 – 4 kJ/M lower than those reported by Pearlman and Kollman[35] and can be explained partly by the use different water models (flexible SPC *vs* rigid TIP3P) and partly depending on the way how the bond stretching contribution is treated.

Our results from using the five-site flexible methane models are lower than previous theoretical results but still consistently higher than the corresponding experimental result and our theoretical results using the simple single-site methane model. A possible reason is that we have used standard AMBER force field hydrocarbon parameters, developed primarily for macromolecular systems. By reducing the Van der Waals diameter σ or increasing the potential well depth ε, one can adjust the value of the solvation free energy to better agree with the experimental value. However, it is not our purpose to refine force field parameters in the present work. We simply conclude that free energy calculations provide a rigorous test of the used potential models.

4.2 Methane dissolved in water/methane mixture

The solvation free energy of inserting one methane molecule into a water-methane mixture, containing 14% molar ratio of methane, at 300 K and density 0.92g/cm^3 was calculated. This mixture was chosen because both the density and the molar ratio are equal to that for methane clathrate hydrates with 100% cage occupancy [37]. Detailed knowledge of both favorable and unfavorable thermodynamical conditions to a formation of clathrate hydrate phase is important in solving technical problems connected to construction of gas pipelines.

Our simulation results (see Table 3) are 14.1 $\pm$0.5 kJ/M for the system of 92 H_2O + 16 CH_4 molecules and 13.1 $\pm$0.8 for 184 H_2O + 32 CH_4 molecules, respectively. Again, the obtained difference between these two results is due to a too small simulation cell in the former case. In fact, this difference is of the same magnitude as was found previously in testing the size dependence for methane dissolved in pure water. We do not expect that the solvation free energy for methane in water/methane mixture would change markedly as a result of further increasing the system size.

The solvation free energy of methane in the 14 mole % water/methane mixture is about 4 kJ/M higher than that in pure water. This means that it is much more difficult to dissolve additional methane molecules in water/methane mixture as the methane concentration increases and the system should overcome a rather high "free energy" barrier in order to dissolve enough methane molecules in water to create a clathrate hydrate phase. In fact, formation of the hydrate phase is a slow process, taking time from a few minutes to several weeks.

4.3 Methane dissolved in salt water

Simulations are carried out for methane dissolved in an ionic solution, with sodium chloride as a salt using the simple single-site model for methane. Two salt concentrations, comparable to salt water in oceans are used. In the first case we have used a mixture of 251 H_2O and 2 Na^+Cl^- and in the second case a mixture of 237 waters and 9 sodium chloride pairs. The results, quoted in Table 3, show that the presence of ions in water has only a small effect on the solvation free energies when compared to the case of pure water (see Table 2).

4.4 Ions of alkali halides in water solution .

Determination of solvation free energy for ionic hydration is still very much an open question. To simulate electrolyte solutions is complicated due to the long-range electrostatic interactions. It has been shown by Straatsma *et al*.[38] that truncation of the Coulombic potential affects the results for charged systems considerably. Account for the long-range part of the electrostatic interactions in free energy calculations can be made by using the reaction field[39,40] or by the Ewald summation[41] methods. These methods have been shown to work well for electroneutral systems. However, there are still some problems in calculations of an energy change due to addition of a charged particle to the system. Within periodic boundary conditions, addition of a charge into the basic simulation cell means introduction of a net charge into the system, which consequently gives an infinite contribution to the electrostatic energy. Omitting the periodic boundary conditions makes the treatment of the electrostatics self-consistent, but it is difficult to perform simulations of liquids and solutions without applied periodicity.

We have calculated the solvation free energies for a complete set of alkali halide ion pairs in aqueous solution, by converting the two opposite charged ions into ideal (ghost) particles. In this way the system is kept electroneutral, allowing us to apply the Ewald summation method to treat the long-range part of the electrostatic interactions and to avoid difficulties arising typically in cases when only one single ion is present in solution. The number of water molecules was 254, corresponding to 0.2M salt concentration.

It should be pointed out that the solvation free energy of an ion pair is not exactly equal to the sum of hydration energies of the both ions. The ion-ion interaction gives a small contribution to the free energy, leading to a non-additivity in solvation free energies for ion pairs. For example, our results for $F_{solv}(K^+,Cl^+)$-$F_{solv}(K^+,F^+)$ differs from $F_{solv}(Na^+,Cl^+)$-$F_{solv}(Na^+,F^+)$ approximately by 5 kJ/M. For ions at a fixed distance, the contribution from the ion-ion interactions is equal to the potential of mean force between the ions at the same distance. If the distance is not fixed, this contribution is equal to the mean value of the potential of mean force. Reported potential of mean force studies show that this contribution can be of the order of a few kJ/M [42], much less than the corresponding solvation free energies and of the order of statistical errors.

Calculations of the solvation free energy for the ion pairs turned out to be a more time-consuming procedure compared to the corresponding methane study, mainly due to very large free energy differences of hundreds of kJ/M. Typically, 200-300 ps longer simulations were needed to properly adjust the balancing factors. Also, longer time was needed for the system to walk between the extreme sub-ensembles and to evaluate probabilities P_0 and P_M. That is why the final *absolute* statistical errors are higher than in the simulation of methane. On the other hand, when the free energy differences are large, the main contribution to the final result comes from the fixed difference η_M-η_0 (see eq. (4)). The term $ln\,(P_M/P_0)$, obtained from the simulation, is only a small correction to this difference. Now, if we adjust the balancing factors properly in such a way that the system is able to walk between the extreme sub-ensembles, the *relative* statistical error will be small: about 0.2 – 0.3 % after 500 ps of production simulation for the case of ionic hydration. This is one of the advantages of using the expanded ensemble method.

The solvation free energies for the various ion pairs are summarized in Table 4, together with the corresponding experimental values from the work of Marcus[43]. There is a very good overall agreement between the simulated and the experimental values, with exception of the Li^+ salts, for which the free energies are found to be about 55 kJ/M higher than the experimental results. Of course, the rigid ion model may be too crude and for the smallest ions such as Li^+, *ab initio* type of potentials may be preferable.

The ions in the simulations differ only by their Lennard-Jones parameters σ and ε. These parameters were derived empirically[27] to reproduce some experimental data. There exist several sets of potential parameters in literature for the alkali halide ions. In comparing various ion-ion potentials, it can be seen that differences between the Lennard-Jones parameters for a specific ion taken from different works, are often larger than differences in the same parameter for different ions in the same set of parameters. Because of the strong sensitivity of the solvation free energies to potential parameters, free energy calculations should provide a very effective test of potential models.

5. CONCLUSIONS

Solvation free energies for methane are calculated, using the expanded ensemble method [9,19], by inserting one methane molecule into three very different solutions: pure water, concentrated methane solution corresponding to a methane hydrate chlathrate and ionic water solution, corresponding typical salt contents in oceans. In addition, the solvation free energies are calculated for a complete set of monovalent alkali halide salts dissolved in water in a systematic study. The choice of solutes ranges from highly hydrophobic particles to readily soluble ions.

The main conclusions from this work are:

- The expanded ensemble method provides an efficient scheme for solvation free energy calculations, giving accurate values in a single MD simulation run of a few hundred ps. The initial work of adjusting the parameters of the algorithm is, however, important.
- The simple, single-site Lennard-Jones model by Jorgensen and coworkers for methane gives results for the solvation energy in very good agreement with the experiment. This is a somewhat astonishing observation, since a polyatomic methane molecule is modeled as a sphere completely without rotational degrees of freedom. Methane, of course, is effectively spherical and makes water behave in the same way as the noble gas atoms do in aqueous solution. Attempts to use a realistic flexible five-site model did not improve further the results. A similar observation was made previously by

Laaksonen and Stilbs [44] in their study of methane in water solution using several rigid methane models.

- System sizes should be large enough, even when a non-polar molecule like methane is dissolved in water.
- To dissolve methane in an electrolyte solution of moderate salt concentration is almost equally expensive as in pure water, while attempt to dissolve methane in a solution, already containing a high concentration of methane is much more expensive compared to the case with pure water.
- The solvation energy for alkali halide ion pairs increases with the ionic radii for both cations and anions and is in a very good agreement with the experimental results. Only for the two smallest ions, Li^+ and F^-, there are some noticeable deviations from the experimental results.
- Calculations of solvation free energies appear to be a very sensitive test of molecular models.

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Table 1. Interaction parameters, used in the simulations.

Site	σ (Å)	ε(kJ/M)	charge	
	SPC water model [1)]			
O	3.1656	0.65	-0.82	
H	0.	0.	0.41	
	Methane			
a) 1-site L-J model [2)]				
	3.73	1.231	0	
b) 5-site model [3)]				
C	3.207	0.251	-0.66 [a)]	-0.464 [b)]
H	2.744	0.042	0.165 [a)]	0.116 [b)]
	Ions [4)]			
Li^+	2.37	0.149	1	
Na^+	2.73	0.358	1	
K^+	3.36	0.568	1	
Rb^+	3.57	1.602	1	
Cs^+	3.92	2.13	1	
F^-	4.0	0.05	-1	
Cl^-	4.86	0.168	-1	
Br^-	5.04	0.27	-1	
I^-	5.4	0.408	-1	

[1)] - ref. [23] [2)] - ref. [24] [3)] - ref. [25], [a)] - Mulliken charges, [b)] - ESP charges, bonds and angles interaction parameters are taken from ref. [26]

[4)] Lennard-Jones parameters for all ions from ref. [27].

Table 2 . Summary of results of solvation free energy for methane molecule in water solution. For details, see the text.

Water	Methane	Ensemble	Method	μ_{ex}(kJ/M)	Ref.
511 SPC (flex)	1 Jorgensen	NVT	EE	8.5 ±0.7	This work
255 SPC (flex)	1 Jorgensen	NVT	EE	8.9 ±0.6	-“-
255 -“-	1 -“-	NPT	EE	9.0 ±0.6	-“-
107 -“ -	1 -“-	NVT	EE	10.4 ±0.5	-“-
107 -“ -	1 -“-	NPT	EE	10.6 ±0.5	-“-
255 SPC (rigid)	1 -“-	NVE	test particle	9.5	ref. [34]
255 SPC (rigid)	1 -“-	NVT	test particle	10.2 ±0.9	ref. [22]
255 TIP4P	1 -“-	NVT	perturbation	10.5 ±1.7	ref. [33]
255 SPC(flex)	1 5-site [a)]	NVT	EE	11 ±1	This work
255 -“ -	1 5-site [b)]	NVT	EE	11.6 ±1	-“-
400 TIP3P	1 -“-	NPT	perturbation	8.9 ±3.8	ref. [36]
295 TIP3P	1 -“-	NPT	perturbation	15.35 ±0.6	ref. [35]
-“- -“-	-“- -“-	-“-	-“-	14.7 ±0.9	ref. [35]
Experiment			infinite dilution	8.4	ref. [32]

[a)] - Mulliken charges , [b)] - ESP charges.

Table 3. Summary of results of solvation free energy for methane molecule in methane/water mixture and in ionic solution. All calculations are carried out using the expanded ensemble method and in NVT ensemble. For details, see the text.

Water		Methane		Ions		μ_{ex}(kJ/M)
92	SPC(flex)	16	Jorgensen	-		14.1 $\pm$0.5
184	-" -	32	-"-	-		13.1 $\pm$0.8
251	-" -	1	-"-	2	Na^+Cl^- [a)]	8.6$\pm$0.5
237	-" -	1	-"-	9	Na^+Cl^- [b)]	9.2$\pm$0.6

[a)] salt concentration 0.45M, [b)] salt concentration 1.9 M

Table 4. Calculated and experimental solvation free energies for ion pairs (in kJ/M). The statistical error in the simulations is 2 kJ/M or less. The experimental results are given as a sum of free energies of the anion and cation from ref. [43].

		Li^+	Na^+	K^+	Rb^+	Cs^+
F-	calc.	-895	-850	-782	-755	-734
	exp.	-940	-830	-760	-740	-715
Cl-	calc.	-754	-704	-639	-614	-596
	exp.	-815	-705	-635	-615	-590
Br -	calc.	-728	-676	-613	-590	-570
	exp	-770	-680	-610	-590	-565
I-	calc.	-696	-646	-576	-556	-534
	exp.	-750	-640	-570	-550	-525