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Investigation of the Salting Out of Methane from Aqueous Electrolyte Solutions Using Computer Simulations

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We calculate the excess chemical potential of methane in aqueous electrolyte solutions of NaCl using Monte Carlo computer simulations. In a recent work [Docherty et al. *J. Chem. Phys*. **2006**, *125*, 074510], we presented a new potential model for methane in water which is capable of describing accurately the excess chemical potential of methane in pure water over a range of temperatures, a quantity that can be related to the solubility and which is commonly used to study the hydrophobic effect. Here, we use the same potential model for the water−methane interactions and investigate the effect of added salt on the chemical potential of methane in the solution. The methane molecules are modeled as single Lennard-Jones (LJ) interaction sites, and the water molecules are modeled with the TIP4P/2005 model. A correcting factor of $\chi = 1.07$ for the energetic Berthelot (geometric) combining rule of the methane−water interaction is also used, which mimics the polarization of methane in water. We consider NaCl as the salt and treat the ions with the Smith and Dang model (i.e., as charged LJ interaction sites). Ion−water, ion−ion, and ion−methane interactions are treated using Lorentz−Berthelot combining rules. In addition, the Coulombic potential is used to model charge−charge interactions which are calculated using the Ewald sum. We have carried out isobaric−isothermal (*NpT*) simulations to determine the equilibrium densities of the solutions. The simulation data is in excellent agreement with experimental densities of aqueous NaCl solutions of different concentration. Hydration numbers are also obtained and found to be in agreement with reported data. Canonical (*NVT*) simulations at the averaged densities are then performed using the Widom test-particle insertion method to obtain the excess chemical potential of methane in the saline solutions. An increase in the chemical potential of methane, corresponding to a salting out effect, is observed when salt is added to the solution. We investigate different concentrations and ion sizes. An overprediction of the salting out effect as compared with experimental data is observed, which we believe is due to the polarizing effect of the ions in the solution, which is not taken into account by the model. We also find a direct correlation between the increase in the chemical potential and the packing fraction of the solution and argue that the main cause of the observed salting out effect (as represented by an increase in the excess chemical potential) is the increase in the packing fraction of the solutions due to the added salt. Together, with this, we put forward an argument toward explaining the anomalous Hofmeister effect of Li^+.

I. Introduction

The effect of ions in solutions is of widespread interest in fundamental and applied sciences, in the design of industrial processes such as antisolvent salt crystallization or water desalination, in geochemical systems such as the formation and inhibition of gas hydrates,[1] and throughout biological and chemical systems. The presence of ions affects the phase behavior of pure solvents and solutions and is of special interest when determining the partitioning of hydrophobic molecules in aqueous phases. Adding salt to an aqueous solution of a hydrophobic molecule can result in either a decrease (salting out) or an increase (salting in) of the solubility of the hydrophobe. As may be expected, different salts result in different effects.

Hofmeister ranked the effect of different salts on the solubility of proteins, compiling the so-called Hofmeister series, where ions are ordered by the effect they cause to the solubility of the molecule.[2] A general rule of thumb indicates that the larger the charge, or the smaller the size of the ion (i.e., the larger the charge density), the larger the salting out caused. There are, however, notable exceptions, such as the fact that Li^+, although smaller than Na^+, has a weaker Hofmeister effect. Hofmeister effects occur in a wide range of phenomena, from the simplest salt solubilities to complex biological systems including, for example, bacterial growth.[3] The reviews of Grover and Ryall[4] and Kunz et al.[3,5] give excellent overviews of the current knowledge regarding the mechanisms leading to salting out and of its impact and relevance in chemical and biological applica-

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tions. Dill et al.[6] have reviewed the key findings from simplified models for water, which can be used in analytical frameworks and which are proving invaluable in providing a complete understanding of the hydrophobic and salting out phenomena.

Here, we are interested in the change in the chemical potential of methane with salt concentration in aqueous saline solutions. Although involving relatively simple molecules, the interactions between water and hydrocarbons remain an important challenge. These systems provide a perfect case study to examine the hydrophobic effect,[2,7−10] exhibiting a characteristic increase in solubility at low temperatures, and unexpected trends in infinite dilution properties at high temperatures and pressures (see ref 11 and references therein). It is also known that the temperature-dependent solubilities of small nonpolar molecules mimic the main aspects of those of protein unfolding,[12] and as many denaturing agents involve ionic species (urea is a common one), investigations such as that presented here can be of importance for these more complex systems.

Many studies have concentrated on the calculation of the potentials of mean force and radial distribution functions of simple nonpolar solutes in water (see for example refs 13−15 and references therein). From these, much is believed to be known of the phenomena underlying the hydrophobic effect, which is usually explained in terms of a tendency of the solute to aggregate within the water phase as a mechanism to compensate the decrease in the entropy of water provoked by the introduction of the hydrophobic molecule. Such an aggregation is expected to have a temperature dependence such that aggregation increases as the temperature is increased (resulting in lower solubility of the hydrophobe), until a maximum is reached when the trend is reversed. Co-solvents and, in particular, salts have been considered only relatively recently. Wallqvist et al.[15] have calculated the potential of mean force in solutions of methane in water in the presence of urea, which has led them to propose a new mechanism for the chemical denaturation of globular proteins. Jönsson et al.[9] have carried out Monte Carlo simulations of water/methane/salt solutions using a TIP4P model for water, a simple Lennard-Jones (LJ) site for methane, and the Smith and Dang[16] models for the ions. Previous molecular dynamics calculations by Mancera[17−19] had shown that the aggregation of methane molecules in water is enhanced in the presence of an added salt, and that the maximum aggregation temperature is shifted to higher temperatures when salt is present. Jönsson et al.[9] have compared model monovalent and divalent salts and confirm that the potential of mean force between the methane molecules is more attractive in the case of the divalent salt (higher charge density), and Gosh et al.[20] were able to quantify the effect of NaCl on the methane−methane potential of mean force. In the same theme, Zangi and Berne[21] have carried out molecular dynamics calculations with the SPC/E model of water and investigate the effect of ionic strength on hydrophobic interactions by considering charges of fixed size but increasing charge.

In the case of a simple gas solute such as methane, the excess chemical potential at infinite dilution can be directly understood as an inverse measure of solubility: the more positive the chemical potential, the lower the solubility. It is important to mention that the excess chemical potential at infinite dilution should not, in general, be used on its own as a measure of solubility when conditions are such that the solute is not in a gas state; note that, in the case of complex molecules such as proteins, this would be the case for standard ambient conditions. The recent publication of Deschamps et al.[22] and the book of Dill and Bromberg[2] are useful detailed sources of information on how to treat more complex solutes.

Ostwald's solubility coefficient γ_{CH_4} and Henry's constant K_{CH_4} for methane in an aqueous solution are defined as[23]

$$\gamma_{CH_4} = \lim_{x_{CH_4} \to 0} \frac{\rho^{liq}_{CH_4}}{\rho^{g}_{CH_4}} \tag{1}$$

and

$$K_{CH_4} = \lim_{x_{CH_4} \to 0} \frac{p_{CH_4}}{x_{CH_4}} \tag{2}$$

where $\rho^{liq}_{CH_4}$ and $\rho^{g}_{CH_4}$ are the number densities of methane in the liquid (an aqueous solution) and in the gas phase, respectively, p_{CH_4} is the partial pressure of methane in the gas phase, and x_{CH_4} is the mole fraction of methane in the aqueous solution. Notice that these properties are defined at infinite dilution of methane in the aqueous solution. From a molecular point of view, the chemical potential of methane can be written as

$$\mu_{CH_4} = \mu^{ideal}_{CH_4} + \mu^{ex}_{CH_4} = k_B T \ln(\rho_{CH_4}/q) + \mu^{ex}_{CH_4}, \tag{3}$$

where q contains the internal degrees of freedom (vibration, electronic, nuclear) plus the integration over translational and rotational momenta. By equating the chemical potential of the methane molecule in the gas and in the liquid phase as given by the previous equation and taking the limit of infinite dilution (so that the gas phase behaves as an ideal gas), it can be shown that

$$\mu^{ex}_{CH_4}(\infty) = k_B T \ln\left(\frac{K_{CH_4}}{k_B T \rho}\right), \tag{4}$$

or

$$\mu^{ex}_{CH_4}(\infty) = k_B T \ln\left(\frac{1}{\gamma_{CH_4}}\right) \tag{5}$$

where $\mu^{ex}_{CH_4}(\infty)$ is the excess chemical potential of a methane molecule in the aqueous solution at infinite dilution and $\rho = (N_{H_2O} + N_{salt})/V$ is the total number density of the aqueous solution. From the previous equations, it is clear that the excess chemical potential of methane at infinite dilution can be obtained from experimental values of the solubility coefficient, from Henry's constant, or from both. Henry's constants of methane in NaCl solutions have been reported by O'Sullivan and Smith.[24] They report values of 0.544×10^5 atm in pure water, 0.728×10^5 atm for a 1 molal solution, and 1.570×10^5 atm for a 4 molal one at a temperature of 51.5 °C. Since the number density is affected only slightly by the presence of salt, such an increase in Henry's constant suggests an increase in the chemical potential of methane as the salt is added. In other words, the solubility of methane decreases as salt is added, so that salting out occurs. A similar conclusion is drawn from the measurements of Ben Naim and Yaacobi,[25] who have measured Ostwald's solubility coefficients at room temperature for methane in several water solutions with different concentrations of NaCl. They also observe a decrease in the solubility of methane in water as NaCl is added (i.e., salting out). The magnitude of the salting out can be rationalized using the empirical Setchenow equation,[23] which can be written as

$$\ln\left(\frac{x^0_{CH_4}}{x_{CH_4}}\right) = k_{salt}m_{salt}, \tag{6}$$

where $x^0_{CH_4}$ and x_{CH_4} are the molar fractions of methane in pure water and in the aqueous solution, respectively, m_{salt} is the salt molality, and k_{salt} is the Setchenow salting out coefficient. Note that according to eq 6 the molar fraction of methane in water decreases exponentially with the molality of the salt. Although often reported in the literature, the units of concentration are not always provided explicitly, and thus, inconsistencies in the values of k_{salt} coefficients are often found. A useful discussion regarding these discrepancies and the equations relating the coefficients in different concentration scales is given by Masterton et al.[26]

Besides the measurements of Henry's constant and Ostwald's coefficient for NaCl solutions, Ben Naim and Yaacobi[25] have also measured the Ostwald coefficient for other salts. Measurements for KCl and CsCl show the expected trend of a decrease in the salting out effect as the cation size increases. For this reason, one should, in principle, expect the salting out effect of LiCl to be stronger than that of NaCl. However, the experimental measurements of Ben Naim and Yaacobi showed the opposite trend; that is, LiCl presents a smaller salting out effect than NaCl. Understanding these trends represents a major challenge from a theoretical point of view. Another set of experimental measurements of solutibilities of methane in aqueous saline solutions has been reported by Kiepe et al.,[27] although unfortunately NaCl was not considered in their study.

As for the case of experimental studies of the salting out effect of methane in water, theoretical works are scarce. Although the chemical potential of methane in water has been evaluated by computer simulation in a number of papers,[14,28,29] the effect of adding salt has been considered in just a few cases. One of these is the work of Smith[12] who computed the chemical potential of methane in water and in salt−water solutions using computer simulations with the SPC/E model to describe water. He found an increase in the excess chemical potential of methane from 9.4 kJ/mol to 10.7 kJ/mol (i.e., a change of 1.3 kJ/mol) when going from pure water to a 1 M solution of NaCl in water, predicting correctly a decrease in the solubility of methane as the salt is added. Unfortunately, the prediction of the chemical potential of methane in pure water was not accurate (the value of 9.4 kJ/mol is approximately 1 kJ/mol above the experimental value), which means that it is difficult to draw definite conclusions on the salting out on the basis of the calculations. Lyubartsev et al.[30] have also determined the chemical potential of methane in pure water and in NaCl solutions (see Table 3 in their work) using the SPC model of water. A salting out effect is also observed, although unfortunately the error bars in the excess chemical potential are too large to establish quantitative conclusions. It is also useful to mention the work of Hummer et al.,[8] who report molecular dynamics simulation data for the change in the excess chemical potential of a hard sphere of the typical size of methane models. They report an increase of about 10 kJ/mol when increasing the NaCl concentration from 0 to 5 M (this figure can be roughly compared with an expected experimental increase of 4 kJ if the data of Ben Naim and Yaacobi is extrapolated to 5 M concentrations). Following recent works, which have pointed toward the importance of treating the polarization of the hydrophobe in a water-rich phase,[31,32] we have proposed a new potential model for methane and water solutions in which polarization effects are treated effectively and have calculated the excess chemical potential of methane in water at various temperatures, observing excellent agreement with experimental data. Thus, we have now a model able to reproduce quantitatively the excess chemical potential of methane in pure water. Here, we use this model to carry out Monte Carlo computer simulations to study the changes in chemical potential with the addition of NaCl and consider the effect of changes in the sizes of the ions. Our calculations confirm the expected salting out of methane when NaCl is added and provide useful information as to phenomena associated with Hofmeister effects.

TABLE 1: Intermolecular Potential Model Parameters for the Water−Water (TIP4P/2005),[33] Methane−Methane,[37] and Ion−Ion[16] Interactions[a]

model	ϵ/k_B (K)	σ (Å)	q_H/e
water TIP4P/2005	93.19	3.1589	0.5564[b]
CH_4	147.5	3.730	0
Na^+	65.42	2.35	1.0
Cl^-	50.32	4.40	−1.0

[a] In the TTP4P/2005 model, the distance between the oxygen and the *M* site where a charge of -2_{qH} is placed is 0.1546 Å. All unlike interactions are obtained using the Lorentz−Berthelot combining rules, except the water−methane interaction for which a correcting parameter $\chi = 1.07$ is used for the unlike energy. [b] Charge of one hydrogen atom.

II. Molecular Models and Simulation Details

The water molecules are modeled using the TIP4P/2005 potential of Abascal and Vega,[33] which was parametrized to give a correct description of the liquid density of water up to 373 K, including the maximum density at 4 °C. The model yields good phase diagram predictions[33,34] and critical properties.[35] The model is identical to the TIP4P potential of Jorgensen[36] in relation to the positions of the oxygen and hydrogen atoms but differs from it in terms of the values of the partial charges and their position (see ref 33 for details and comparisons to other models, and see Table 1 for numerical values of the parameters). For the methane molecules, we have used a single Lennard-Jones site with the molecular parameters proposed by Hirschfelder[37] (see Table 1). In a recent work, following Paschek,[32] we have highlighted the importance of having a correct estimation of the water density in order to represent accurately the excess chemical potentials in solution.[31] Furthermore, we found that a correcting factor $\chi = 1.07$ incorporated in the Berthelot (geometric) combining rule for the energy parameter of the water−methane interaction can be used to account for polarization effects, albeit in an effective way. We use the same correcting factor here. For the ions, we use the model of Smith and Dang,[16] in which the ions are modeled as charged Lennard-Jones spheres. In this work we consider NaCl (the parameters are given in Table 1), with water−ion and ion−methane interactions treated following the Lorentz−Berthelot combining rules exactly; that is, no corrections are used. As in previous work, the Lennard-Jones potentials are truncated at 9 Å in all simulations, and a standard long-range correction to the energy is added.[38] The Coulombic interactions are calculated using the Ewald-summation technique with a real-space cutoff of 9 Å and a screening parameter of 0.33/Å, and the reciprocal space is restricted to the vectors **h** such that the modulus of the vector is $|\mathbf{h}|^2 < 60$.

We determine the excess chemical potential of methane in water and NaCl solutions at 298 K and 0.1 MPa by following a two-step procedure. We first carry out isothermal−isobaric *NpT* Monte Carlo simulations with 270 water molecules, and a number of ions as corresponding to a given molality, for example, 5 Na^+ and 5 Cl^- ions for a 1 molal solution

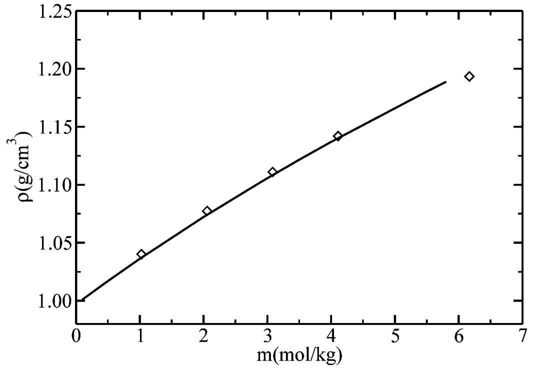

Figure 1. H_2O + NaCl solution densities at 298 K and 0.1 MPa as a function of molality *m*. The curve corresponds to experimental data,[40,41] and the symbols correspond to the simulated data of this work. Details of the potential model are given in the text and in Table 1.

(approximately) and 10 Na^+ and 10 Cl^- ions for a 2 molal solution (approximately). The molecules are placed in a cubic box and 10^5 equilibrium cycles and 10^6 averaging cycles are performed, each cycle consisting of a trial move per particle and a trial isotropic volume change. In this way, the densities of the solutions are obtained quite accurately. The equilibrium density obtained from the *NpT* runs is used in a second step in which canonical *NVT* simulations together with the Widom[39] test-particle insertion method is used to obtain the excess chemical potential of methane in the solutions. In our recent calculation of the excess chemical potential of methane in pure water,[31] an average of 5×10^9 attempted insertions where performed. In order to get a similar accuracy when salt is present in the solution, we find that we need of the order of 10×10^9 attempted insertions (20 000 insertions are attempted every 10 cycles, over 14 independent runs of 4×10^5 cycles). We estimate the average error in our calculation of the excess chemical potential of methane in the solution to be of ±0.15 kJ/mol.

III. Results and Discussion

As a starting point for our investigation, we consider a solution of NaCl in water at 298 K and 0.1 MPa, using the models described in the previous section. It is useful to address the validity of the model parameters before discussing the salting out effect. We confirm the validity of our choice of water−salt intermolecular interaction parameters by studying the increase in the density of the solution upon the addition of salt, comparing our simulated data to experimental values[40,41] at 298 K and 0.1 MPa, for concentrations up to $m \simeq 6$, approaching the solubility limit for NaCl in water at these conditions. The comparison is presented in Figure 1. We have also calculated the hydration number for Na^+ and Cl^- in water at the same conditions by integrating the water−ion radial distribution function up to the first minimum. For a concentration of 1 molal, we estimate a hydration number for Na^+ of 6.0 and for Cl^- of 7.2, which are in good agreement with published data.[42] The water−methane intermolecular potential parameters were presented and validated in a previous work,[31] in which we showed that the excess chemical potential of methane in water is obtained very accurately with the TIP4P/2005 model for water and the Hirshfelder potential for methane, together with a correcting factor of 7% for the water−methane energy parameter. Here, we show again these calculations for completeness (Figure 2). Specifically, at 298 K and 0.1 MPa, the excess chemical potential of methane was calculated to be 8.27 kJ/mol, which corresponds to an error of −0.07 kJ/mol when compared with experimental data.[32] We have also performed a simulation at the same temperature and density with a larger number of water molecules (540 as compared with 360 in ref 31) and find an excess chemical potential for methane of 8.33 kJ/mol; that is well within the statistical uncertainty of the simulation. It is useful to recall that the positive value of the excess chemical potential of methane in water immediately points to the hydrophobic nature of methane.

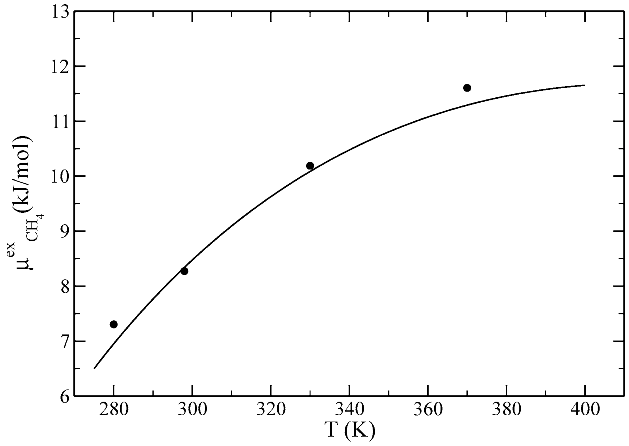

Figure 2. Comparison of calculated excess chemical potential $\mu^{ex}_{CH_4}$ of methane in water at infinite dilution with experimental data. The curve corresponds to experimental data,[32,47] and the symbols correspond to data from computer simulations carried out in a previous work.[31] Details of the intermolecular potential models are given in Table 1. A correction factor of $\chi = 1.07$ is used to calculate the methane−water unlike energy parameter.

TABLE 2: Calculated Excess Chemical Potential μ^{ex} (at Infinite Dilution) of Methane in Aqueous NaCl Solutions[a]

solution	σ_+ (Å)	σ_- (Å)	*m* (mol/kg)	η	μ^{ex} (kJ/mol)
			0	0.5505	8.27
NaCl	2.35	4.40	1.03	0.5724	9.67
NaCl	2.35	4.40	2.06	0.5918	11.22
NaCl(15%)	2.35	3.74	2.06	0.5944	11.41
Na(15%)Cl	1.998	4.40	2.06	0.5968	11.75
NaCl(30%)	2.35	3.08	2.06	0.6009	11.75
Na(30%)Cl	1.645	4.40	2.06	0.5932	11.25
Na(30%)Cl(30%)	1.645	3.08	2.06	0.6036	11.92
NaCl	2.35	4.40	4.11	0.6250	13.76
NaCl[b]	2.35	4.40	4.11	0.6250	13.67

[a] First line corresponds to the excess chemical potential in pure water; it is given for comparison. The σ_+ and σ_- correspond to the diameters of the anion and cation. The model parameters of Smith and Dang (see also Table 1) are first used and are later modified to investigate the effect of ion size. The variable *m* corresponds to the molality, and η corresponds to the packing fraction. The error in the calculation of the chemical potential is estimated to be of ±0.15 kJ/mol. [b] A larger system of 540 water molecules and 40 ions was used.

In order to study the effect of salt concentration, we calculate the excess chemical potential of methane at infinite dilution for various concentrations of NaCl−water solutions. The excess chemical potentials are calculated using the Widom test-particle insertion method in an *NVT* ensemble, where the fixed density is obtained for each concentration from an *NpT* run. The values of the calculated excess chemical potentials are presented in Table 2. Two interesting observations can be made on first inspection of the data. First, the addition of 1 molal of NaCl to the solution clearly results in an increase of the chemical potential of methane. This reflects the expected salting out effect, since the solubility of a gaseous solute can be related to its excess chemical potential in the solvent as obtained using the Widom test method. The more positive the chemical potential,

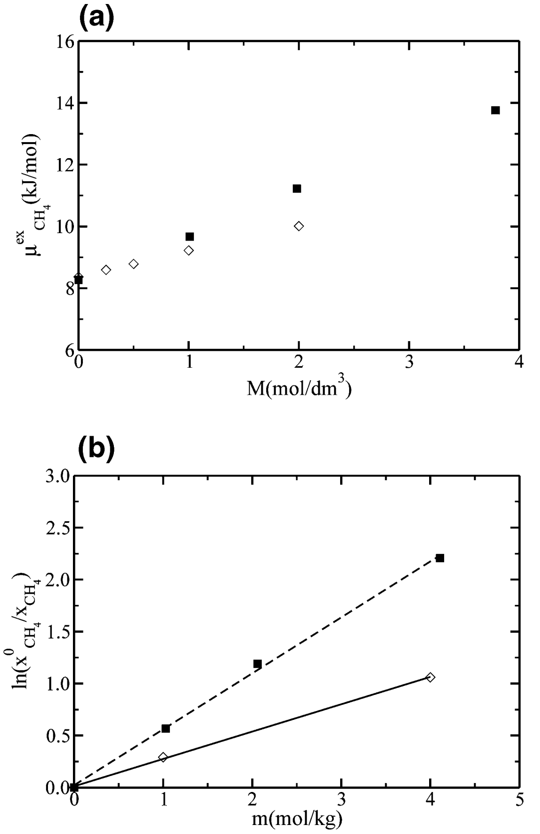

Figure 3. (a) Calculated excess chemical potential of methane at infinite dilution in H_2O + NaCl solutions of varying concentration compared with experimental data. The filled squares correspond to computer simulation data obtained in this work, and the empty diamonds correspond to the experimental data of Ben-Naim and Yaacobi.[25] (b) Salting out constant in terms of the ratio of logarithms of concentrations as obtained from the computer simulations of this work and the relations presented in the introductory section, compared with the solubility data of O'Sullivan and Smith.[24] The filled squares correspond to the simulated data of this work, and the empty diamonds correspond to the experimental data. The lines correspond to linear fits of the data.

the lower the solubility of a given compound. Second, larger molalities result in larger chemical potentials; that is, the salting out effect is more noticeable in more concentrated solutions, as suggested by the Setchenow relation mentioned in the introduction. For the case of the most concentrated solution, we have also carried out simulations following the same procedure but using a larger system of 540 water molecules and 40 ions (20 cations and 20 anions). In this case, we obtain an excess chemical potential of methane in solution of 13.67 kJ/mol as compared with 13.76 kJ/mol obtained for the smaller system. This suggests that the system size chosen is large enough for the calculations performed and that the Widom-test method is adequate for the calculation of the chemical potential in these systems; note that the insertion of more complex solutes, such as larger alkanes, would require more sophisticated sampling techniques.[32]

In Figure 3, we present a comparison of the calculated effect of salt concentration on the salting out, both in terms of the actual excess chemical potential and in terms of the Setchenow equation. In Figure 3a, the excess chemical potentials are compared to the experimental data of Ben Naim and Yaacobi,[25] who measured Ostwald solubility coefficients at 298 K. The concentration is presented in units of molarity (M = moles per liter of solution). It is clear that our calculations overpredict the chemical potential of methane in the solutions; that is, we overpredict the salting out. This is also reflected in a comparison of the salting out constant, as seen in Figure 3b, where we compare our computer simulation data with the experimental data of O'Sullivan and Smith.[24] A linear dependency is expected, as described by eq 6, where the slope corresponds to the salting out constant. Our calculations present the expected linear behavior, although the Setchenow salting out constant is overpredicted. Note that, in this figure, following the experimental data, we report the concentration in units of molality (m = mol/kg of solvent). It should also be taken into account that the experimental data correspond to a temperature of 51.5 °C, instead of 25 °C (298 K) used in our work. However, as illustrated in the work of O'Sullivan and Smith,[24] the salting out effect is hardly affected by small variations of temperature, so that the variation of the Setchenow constant with temperature is very small. We found it useful to validate our calculations using two separate experimental sources, as there are few data available. Both sets of experimental results yield similar results and point out clearly that the salting out effect is overestimated significantly by our model. It is important to note also that the difference between the calculated and the experimental data cannot be explained in terms of the uncertainty range of the simulation data: approximately ±0.15 kJ/mol.

The question we may now consider is as follows: What is the reason for the overprediction of the salting out effect seen in the simulation results? A quick answer may simply be that the parameters of the model are not adequate to describe the salting out effect (with the hope that other potential parameters will do). Although, it is also possible that the origin of the discrepancy could have a more fundamental origin and may be suggesting that it is not possible to describe quantitatively the salting out effect with the type of model proposed in this work or in related studies. We believe this second reason is the cause of the discrepancy. In a previous work, we argued the importance of having accurate densities of the solvent in order to obtain accurate estimates of the excess chemical potential of a solute. Here, we have shown that our calculations provide excellent descriptions of solution densities for various salt concentrations, which suggests that the potential model for water and salt interactions is valid. In addition, the intermolecular potential model between water and methane has been validated in a previous work.[31] The model used in this work is the only one proposed so far which is able to describe simultaneously the density of water in a broad range of temperatures, the density of the NaCl solution up to ~6 m, and the chemical potential of methane in pure water in a broad range of temperatures. Even so, it fails to describe quantitatively (although the qualitative description is correct) the salting out effect. Why?

Guillot and Guisani[14] and Paschek[32] have illustrated the fact that methane molecules can be polarized when inserted in pure water. This polarization yields an important contribution to the insertion energy of a methane molecule. In a previous work, we have shown that an approximate way of accounting for this polarization is to increase the methane−water interaction energy and were able to describe with quantitative accuracy the chemical potential of methane in water. It seems clear that not only the water (dipoles) but also the ions of the salt (monopoles) can polarize the molecule of methane provoking an induced dipole moment on the methane molecule. The model used in this work is nonpolarisable. Although the polarizing effect of water on the methane molecule has been taken into account in an effective way by increasing the strength of the methane−water Lennard-Jones interaction, no correction has been included to account for the fact that the ions can also further polarize the methane and water molecules. The importance of

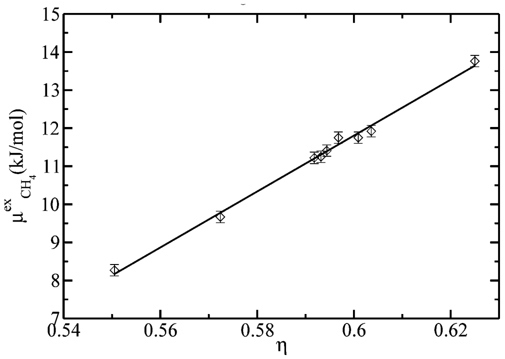

Figure 4. Excess chemical potential at infinite dilution for methane in aqueous saline solutions as a function of the packing fraction η. The data presented here is shown numerically in Table 2. The symbols correspond to the simulation data of this work, and the line corresponds to a linear correlation of this data.

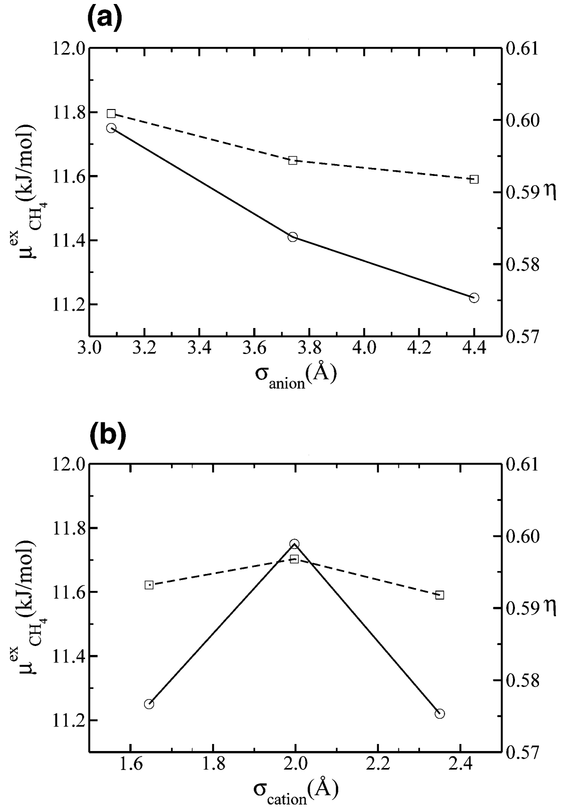

Figure 5. (a) Effect of anion size on the excess chemical potential, at infinite dilution, of methane in aqueous saline solutions 2 molal (circles, left *y* axis) and on the packing fraction (squares, right *y* axis). (b) Effect of cation size on the excess chemical potential, at infinite dilution, of methane in aqueous saline solutions (circles, left *y* axis) and on the packing fraction (squares, right *y* axis). In both cases, the same data is presented numerically in Table 2. The lines are guides to the eye.

such polarization will increase as the number of ions increases in the mixture, which would explain why the discrepancy between simulation and experiment increases with salt concentration. The message appears to be that nonpolarizable models cannot describe quantitatively the salting out of methane in water (maybe one could account for such polarization in an effective way by increasing the Lennard-Jones interaction between the methane and the ions of the mixture, but it is likely that the increase would need to be very large in order to account for the strong polarization generated by the ions, so that the final parameters would be of limited value). Taking into account that methane is one of the simplest hydrophobic molecules, we suggest that nonpolarizable models will, in general, fail in describing the change in the chemical potential of a hydrophobic molecule because of the addition of salt to the water solution. We believe that the behavior of methane in water in the presence of salt highlights this important issue.

Aside from the concentration effects discussed in detail above, we focus now on the effect of ion size (the Hoffmeister effect). In order to gain insight into this effect, we have calculated the excess chemical potential of methane in solutions where the same ion parameters given in Table 1 are used but where the sizes (i.e., the value of σ) of Na^+ and Cl^- are reduced by 15% and 30%, first independently and finally together. The resulting excess chemical potentials corresponding to concentrations of 2 molal for these model solutions are given in Table 2. In a previous paper, we noted that the value of the excess chemical potential of methane in pure water was strongly determined by the density of the water (the solvent). Following this idea, we consider the packing fraction of the solutions in the presence of salt as the ion sizes are changed. In order to calculate the packing fraction of the solution, we use the diameters as given in Table 2 and the following:

$$\eta = \frac{\pi}{6}\frac{1}{V}\sum_i N_i \sigma_i^3, \tag{7}$$

where V is the total volume and the sum is over all components i. We do, indeed, find a direct correlation between an increase in the packing fraction of the solution and an increase in the excess chemical potential (see Figure 4). This result is in agreement with a recent comment of Hribar et al.[43] who have already pointed out that Hofmeister effects are more closely related to solvation volume effects than to charge densities. It is, of course, difficult to separate the two, as larger charge densities will lead to larger electrostriction[2,44] (i.e., larger volume contraction) and hence to larger salting out (or chemical potential). In any case, Figure 4 shows that the salting out effect can be rationalized in terms of a single parameter, the packing faction of the solution η, and one can simply state that methane is less soluble in an aqueous electrolyte solution than in pure water because the packing fraction of the electrolyte solution is higher.

Taking NaCl as a reference, it is useful to focus in more detail on the effect of the reduction of the cation and anion sizes separately. In Figure 5a, the effect of a decrease of the size of the anion (Cl^-) on the chemical potential and packing faction is presented. As can be seen, a reduction of the size of the anion leads to an increase in packing fraction and, as discussed above, to the related increase in the chemical potential or to more salting out. In Figure 5b, the effect of decreasing the size of the cation (Na^+) is shown. Initially, the behavior is similar to that found for the anion; that is, decreasing the size of the cation increases the packing fraction, the excess chemical potential, and hence leads to more salting out. However, when the ion becomes very small, the trend is reversed. In fact, as can be seen in Figure 5b, there is a particular size of the cation that results in the highest packing fraction, the highest chemical potential, and maximum salting out. Further decreases of the size of the cation lead to a decrease in the packing fraction, in the excess chemical potential, and in the salting out effect. These results should be interpreted with a degree of care as an error of ±0.15 kJ/mol is estimated for all of our chemical potential calculations, but the existence of such a maximum can be stated with confidence. To understand the molecular origin of such a maximum, we have studied the ion−water radial distribution functions. In the case of a 30% cation diameter reduction, we find a reduction from six neighboring water molecules to five, which would lead to a lesser electrostriction since there are fewer water−ion close-range interactions or, in our calculations, lead to the fact that the packing fraction is not reduced further. Similar effects have been reported by Rempe et al.[45] who have used ab initio quantum mechanical calculations and the quasichemical solution theory to conclude that Li^+ has four inner-shell water ligands at normal conditions, while in a following publication a larger number of five ligands for Na^+ has been reported.[46] Our calculations may be pointing toward the same conclusion of less electrostriction in the case of very small ions. Of course that would explain why LiCl provokes a smaller salting out effect than NaCl. The message is that if an ion is very small, a lower coordination number of water molecules can be expected, and hence, the increase in the packing fraction provoked by the presence of the ion is not as effective as in the case of ions with a higher coordination number.

IV. Conclusions

We have calculated the excess chemical potential of methane at infinite dilution in aqueous NaCl solutions and have considered salt concentration and ion size effects. These calculations are of interest as they point toward solubility, hydrophobicity, and salting out effects. We have used Monte Carlo computer simulations, carrying out first isobaric−isothermal (*NpT*) simulations to determine the equilibrium densities of the solutions, and then applied the Widom test-particle insertion method in *NVT* ensembles, at the equilibrium densities, to determine the excess chemical potentials. We have used the TIP4P/2005 model for water, and LJ spheres for methane, Na^+, and Cl^-, although in the case of the ions, the LJ spheres are also charged.

In respect of the effect of salt concentration, we find that the addition of salt leads to an increase of the chemical potential of methane, corresponding to the salting out effect observed experimentally. Moreover, increases of salt concentration lead to increases in salting out. A comparison with experimental data suggests, however, that our calculations overpredict the extent of salting out in the system and that the effect is more pronounced the higher the concentration. We noted in a previous work[31] that methane is polarized in water and that it is necessary to treat this effect in order to reproduce the excess chemical potential of methane in water. In this work, we use the correction proposed earlier so that this polarization is accounted for, albeit, effectively. We noted in the same work that it is crucial to have an accurate description of the density of the solvent in order to be able to reproduce chemical potentials at infinite dilution. In this work, we have shown that we reproduce the experimental solution densities for varying concentrations well, which would suggest that the water−ion models are reasonable. From this, we conclude that the overestimation of the salting out effect is due to errors in the methane−ion interactions. Indeed, it can be expected that methane and water are further polarized because of the presence of ions. The forces resulting from this polarization effect will be attractive and, hence, stabilizing, leading to lower chemical potentials. Our findings suggest that, in addition to electrostriction (volume contraction) effects, polarization plays an important role, so that polarizable models may need to be considered in the future.

The study of concentration and ion size effects has also led to an interesting finding. We report a direct relation between the value of the excess chemical potential of methane in solutions and the packing fraction of the solution. Therefore, salting out effects can be rationalized in terms of a single and simple parameter, the packing fraction of the solution. The smaller solubility of methane in salt−water solutions as compared with water can be explained in terms of the higher packing fraction of the mixture. As well as explaining the occurrence of salting out effects, the packing fraction η allows us to understand both the effect of salt concentration and the effect of ion size. The correlation between the excess chemical potential and the packing fraction of the mixture is clear, and all of the results of this paper follow within the same trend: increasing the concentration of the salt always increases the packing fraction of the mixture, which leads to increases of the excess chemical potential of the methane molecule and thus to more salting out. More salt, more salting out, there is no exception to this rule. The relation between the size of the ion and the volume fraction of the mixture is however less straightforward.

We find that reducing the size of the anion provokes an increase in the volume fraction, excess chemical potential, and salting out. Reducing the size of the cation by a small amount provokes the same effect, however, and this is the key difference, making the cation very small leads to a decrease in the packing fraction and hence of the excess chemical potential and the salting out. This explains quite nicely why LiCl is less effective than NaCl in reducing the solubility of methane in water, as was shown experimentaly by Ben Naim and Yaacobi more than 30 years ago. This effect is related to the ion size, not to the nature of the ion (i.e., an anion small enough could be expected to also show a reverse in the salting out trend).

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