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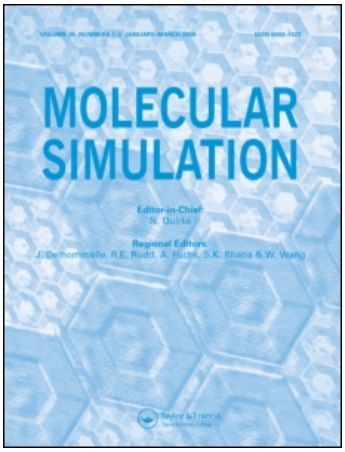

Molecular Simulation
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713644482

The importance of polarisability in the modelling of solubility: quantifying the effect of charged co-solutes on the solubility of small non-polar solutes

Hugh Docherty[a]; Peter J. Dyer[a]; Peter T. Cummings[ab]
[a] Department of Chemical and Biomolecular Engineering, Vanderbilt University, Nashville, TN, USA [b] Oak Ridge National Laboratory, Center for Nanophase Materials Sciences, Oak Ridge, TN, USA

Online publication date: 28 March 2011

To cite this Article Docherty, Hugh , Dyer, Peter J. and Cummings, Peter T.(2011) 'The importance of polarisability in the modelling of solubility: quantifying the effect of charged co-solutes on the solubility of small non-polar solutes', Molecular Simulation, 37: 4, 299 — 309
To link to this Article: DOI: 10.1080/08927022.2011.553225
URL: http://dx.doi.org/10.1080/08927022.2011.553225

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Molecular Simulation
Vol. 37, No. 4, April 2011, 299–309

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The importance of polarisability in the modelling of solubility: quantifying the effect of charged co-solutes on the solubility of small non-polar solutes

Hugh Docherty[a], Peter J. Dyer[a] and Peter T. Cummings[a,b]*

[a]*Department of Chemical and Biomolecular Engineering, Vanderbilt University, Nashville, TN 37235-1604, USA;* [b]*Oak Ridge National Laboratory, Center for Nanophase Materials Sciences, Oak Ridge, TN 37831-6494, USA*

(*Received 26 April 2010; final version received 4 January 2011*)

In a recent work (Dyer et al., J. Chem. Phys. 129 (2008), 024508), we demonstrated that by accounting for the polarisability of small non-polar solutes, in an explicit manner, it is possible to approach quantitative agreement with experimental values of the excess chemical potential of the molecules in pure water. Here, we continue this line of research by considering the effects of ionic co-solutes (i.e. salts) on the solubility of an explicitly polarisable model suitable for a variety of small non-polar solutes. In doing so, we calculate the excess chemical potential that is related to the solubility of the solute in the solution, and investigate how the solubility of hydrophobic solutes varies with ion concentration, i.e. salting-out/salting-in effects, as measured by the Setchenow parameter. In particular, we consider the solubility of Ne, Ar, Kr, Xe and CH_4 in aqueous NaCl solutions for the TIP3P, TIP4P-Ew and TIP4P/2005 models of water. Using these models, we discover that the addition of explicit polarisability to the solute models decreases the excess chemical potential, but fails to obtain quantitative agreement with experimental values. In addition, we determine that explicit polarisation has minimal effect on the Setchenow parameter and, in turn, minimal effect on salting-out. Instead, we show that the over-prediction of the excess chemical potential is due to an inaccurate ion–solute interaction potential. Further to this, we demonstrate that, by accounting for polarisability explicitly, it is possible to obtain pair interaction potentials from *ab initio* calculations that perform as well as, or better than the models commonly used to study these systems.

Keywords: polarisability; solubility; salting-out; hydrophobic hydration; molecular dynamics

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1. Dedication to Ed Smith

We dedicate this paper to the memory of Ed Smith, who advised the PhD dissertation of one of us (PTC) between 1976 and 1980. I (PTC) began working with Ed in 1975 as an undergraduate in the Mathematics Department at the University of Newcastle, and was his second PhD student (after Colin Hoskins). When Ed moved to Melbourne University in 1977, I followed him there and eventually received my PhD under his guidance from the University of Melbourne. Both the Universities of Newcastle and Melbourne were great places to be a student of statistical mechanics: at Newcastle, I took courses from Ed, Tony Guttmann and Clive Croxton; at Melbourne, in addition to Ed and Tony Guttmann (who also moved to Melbourne), I sat in on Colin Thompson's Mathematical Statistical Mechanics course. I learned from all of these individuals and from their steady stream of visitors (e.g. a short course on Monte Carlo simulation by Stu Whittington at Newcastle and a short course on Mellin transforms by D. John Mitchell at Melbourne).

Ed stimulated in me a life-long interest in understanding water – as my first project, he assigned to me the task of solving the mean spherical approximation (MSA) analytically for a model for water (hard sphere + dipole + quadrupole). While I did not succeed in this (after several months of trying to understand the relevant papers on rotational invariants by Lesser Blum, I had to admit defeat) and instead focused on analytically solving the MSA and/or Percus-Yevick approximation for a model for nucleation, a model for liquid metals and the hard-core and soft-core Yukawa fluid. Ed's style was to encourage his students to be self-sufficient – he was a hands-off adviser – and to this day I believe this was the best thing for me: I learned to be an independent thinker and researcher from my years of working with Ed.

I had the pleasure of meeting Ed several times since I finished my PhD, at La Trobe and when he visited me at the University of Tennessee and Oak Ridge National Laboratory. He was the same old Ed on every occasion: he immediately went to the board (black or white, as available!) and started filling it with equations for my reaction and to see if I could notice some error he was missing. His enthusiasm for life and for science remained intact and infectious. We as a community of scholars are poorer for his untimely passing. We dedicate this paper on the role of polarisability in modelling the solubility of hydrophobic solutes in water to his memory.

*Corresponding author. Email: peter.cummings@vanderbilt.edu

ISSN 0892-7022 print/ISSN 1029-0435 online
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DOI: 10.1080/08927022.2011.553225
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2. Introduction

This is the second in a series of work aimed at elucidating the role of polarisability in the calculation of solubility. In the first work [1], we demonstrated that, by explicitly accounting for the polarisability of small non-polar solutes, it is possible to approach quantitative agreement with experimental values of the excess chemical potential for the solute in pure water for a range of temperatures. In this work, we consider the related question of whether or not the addition of explicit polarisability to the solute model is sufficient to account for the qualitative and quantitative disagreements between experimental and simulation values in the modelling of the excess chemical potential for solutes in solutions containing charged co-solutes.

Understanding the solubility of hydrophobic compounds in aqueous solutions is important in traditional engineering situations, such as the formation of hydrates in oil pipelines [2,3], in various geological systems [4], as well as more contemporary applications such as the denaturing of proteins [5–7]. The effect of the addition of charged species to aqueous solutions containing hydrophobic solutes has long been well known, but the mechanism is still subject to debate. Typically, the addition of salt results in either a decrease in the solubility of hydrophobic compounds, known as salting-out, or an increase in solubility known as salting-in. Applications of salting-out effects include the separation of proteins [8], based on the principle that hydrophobic proteins are less soluble at higher salt concentration. Thus, the ability to reproduce these effects is important in the modelling of biological systems. Given this, it is perhaps unsurprising that a number of interesting simulation studies have been undertaken which provide an insight into ion–protein interactions [9–11]. However, despite this, the models typically employed in simulating solubility are unable to provide a quantitative description for even simple small spherical non-polar solutes. A commonly cited explanation for this inability to describe accurately even the simplest systems is that the models used fail to account for polarisability in an explicit manner [12,13].

Salting effects (i.e. salting-out and salting-in) follow what is known as a Hofmeister series [14]. The Hofmeister series was developed from observation of the differing impact of various ions on the solubility and stability of proteins [15,16] and has long been thought to be primarily due to the effect of the ions on the surrounding water structure [17,18], i.e. the chaotropic (structure breaking) and kosmotropic (structure making) nature of the ions. However, in a recent work, Zhang and Cremer [19] challenged this explanation, concluding that changes in the bulk water structure and density do not explain specific ion effects. Their reasoning is based on there being a negligible change in the water structure around an ion after the second solvation shell, as revealed in the work of Omta et al. [20]. As a result, they postulated that salting effects are predominantly due to direct interactions between the solute and the ions. Here, we attempt to clarify the underlying causes of salting-out by examining the effect of charged co-solutes on different regions of aqueous solutions, and the individual contributions of these regions to the excess chemical potential. These regions are described in Section 6 of this article.

In terms of modelling the salting-out of methane and other similar small solutes, Docherty et al. [12] demonstrated that the salting-out effect can be rationalised in terms of a single parameter, the packing fraction, highlighting the role of volume exclusion. They proceeded to show that even a non-polarisable model capable of reproducing accurately the solubility of methane in pure water [21] is unable to capture the effect of salt concentration on solubility, i.e. salting-out. Specifically, they observe an over-prediction of the salting-out effect and given the importance of polarisation of the solute molecule for the solubility of methane in pure water; they logically suggest this may be due to neglecting the effect of the charged co-solutes' contribution to the electric field. In this work, we test this hypothesis using point polarisable models for a variety of solutes (Ne, Ar, Kr, Xe and CH_4), and show that although polarisability plays a role in the salting-out effect, the dominant force is once again volume exclusion. We show that accounting for polarisability explicitly in the solute model is insufficient to account for the discrepancy between simulation and experimental values for the excess chemical potential and salting-out. In doing so, we highlight the importance of an accurate representation of the ion–water system, i.e. solute free, for accurately reproducing the experimental excess chemical potential as well as demonstrate the importance of explicit polarisability in developing intermolecular potentials from *ab initio* calculations.

3. Theory

3.1 The Setchenow parameter

In studying the effect of the addition of salts on the solubility of hydrophobic molecules, the Setchenow coefficient is a commonly used indicator of the degree of salting-out. The Setchenow parameter may be written as

$$k_{\mathrm{Salt}} M_{\mathrm{Salt}} = \ln\left(\frac{x^0_{\mathrm{Sol}}}{x_{\mathrm{Sol}}}\right), \tag{1}$$

where x^0_{Sol} and x_{Sol} are the mole fraction solubility of the solute in pure water and aqueous salt solution, respectively, k_{Salt} is the Setchenow coefficient; and M_{Salt} is the molarity of the aqueous solution. It is worth noting that, while we used molarity and molality, in the literature,

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a variety of concentration scales appear to have been used, often without specification, making comparison difficult.

Unfortunately, in its current form, Equation (1) does not lend itself readily to the calculation of the Setchenow parameter, since mole fraction solubility is not the most intuitive or easy value to calculate directly from molecular simulation. Because of this, we would like to rephrase the Setchenow equation in terms of more easily accessible variables. To start, the mole fraction x_{Sol} can be related to Henry's coefficient

$$x_{\mathrm{Sol}} = \frac{y_{\mathrm{Sol}}P}{H_{\mathrm{Sol}}}, \tag{2}$$

where H_{Sol} is Henry's constant and $y_{\mathrm{Sol}}P$ is the partial pressure of the solute in the gas phase. Assuming that the solvent does not form a significant fraction of the vapour phase, which is a reasonable assumption for the systems considered here at ambient condition, $y_{\mathrm{Sol}}P$ is constant and Equation (1) may be written in terms of Henry's coefficients

$$k_{\mathrm{Salt}}M_{\mathrm{Salt}} = \ln\left(\frac{x^0_{\mathrm{Sol}}}{x_{\mathrm{Sol}}}\right) = \ln\left(\frac{H_{\mathrm{Sol}}}{H^0_{\mathrm{Sol}}}\right). \tag{3}$$

In turn, Henry's coefficients can be determined from the excess chemical potential of the solute at infinite dilution

$$H_{\mathrm{Sol}} = k_{\mathrm{B}}T\rho\exp\left(\frac{\mu^{\mathrm{ex}}_{\mathrm{Sol}}(\infty)}{k_{\mathrm{B}}T}\right), \tag{4}$$

where k_{B} is the Boltzmann constant, T is the temperature and ρ is the number density of the solution. As in previous work, we calculate the excess chemical potential using the Widom insertion method [22] which can be expressed as

$$\mu^{\mathrm{ex}}_{\mathrm{Sol}}(\infty) = -k_{\mathrm{B}}T\ln\left\langle\exp\left(\frac{-U_{\mathrm{Sol}}}{k_{\mathrm{B}}T\rho}\right)\right\rangle. \tag{5}$$

Thus,

$$H_{\mathrm{Sol}} = \frac{k_{\mathrm{B}}T\rho}{\left\langle\exp\left(-U_{\mathrm{Sol}}/k_{\mathrm{B}}T\right)\right\rangle} \tag{6}$$

and the Setchenow coefficient may now be written in terms of a change in internal energy U_{Sol}, caused by the addition of a solute particle

$$\begin{aligned} k_{\mathrm{Salt}}M_{\mathrm{Salt}} &= \ln\left(\frac{x^0_{\mathrm{Sol}}}{x_{\mathrm{Sol}}}\right) = \ln\left(\frac{H_{\mathrm{Sol}}}{H^0_{\mathrm{Sol}}}\right) \\ &= \ln\left(\frac{\rho\left\langle\exp\left(-U^0_{\mathrm{Sol}}/k_{\mathrm{B}}T\right)\right\rangle}{\rho^0\left\langle\exp\left(-U_{\mathrm{Sol}}/k_{\mathrm{B}}T\right)\right\rangle}\right). \end{aligned} \tag{7}$$

The contribution of the solute to the internal energy of the system maybe considered as the sum of van der Waals and polarisability components

$$U_{\mathrm{Sol}} = U^{\mathrm{vdW}}_{\mathrm{Sol}} + U^{\mathrm{Pol}}_{\mathrm{Sol}}, \tag{8}$$

where $U^{\mathrm{vdW}}_{\mathrm{Sol}}$ is the energy due to the van der Waals interactions and $U^{\mathrm{Pol}}_{\mathrm{Sol}}$ is the contribution to the system energy from the polarisability of the solute molecule and is given by

$$U^{\mathrm{Pol}}_{\mathrm{Sol}} = -\frac{1}{2}\alpha\left|\left(\vec{E}\right)^2\right|, \tag{9}$$

where $\vec{E}$ is the electric field at the polarisation site and α is the polarisability of the solute. For full details of the calculation of the electric field, see our previous work [1].

3.2 *Molecular models*

In this section, we describe in more detail the molecular models used for each of the species considered in this work, namely water, NaCl and solute molecules (Ne, Ar, Kr, Xe and CH_4). We begin by noting that all cross-species interactions are approximated using the Lorentz–Berthelot combining rules

$$\sigma_{ij} = \left(\frac{\sigma_{ii} + \sigma_{jj}}{2}\right), \quad \varepsilon_{ij} = \sqrt{\varepsilon_{ii}\varepsilon_{jj}}. \tag{10}$$

3.2.1 *Water potential*

In this work, we consider three popular models of water. The TIP4P-Ew [23] and TIP4P/2005 [24] models are chosen due to their superior performance in predicting the solubility of small non-polar solutes in water [1]. In addition to these, the TIP3P [25] model is evaluated due to its extensive use in the study of biological systems in which polarisability and hydrophobic hydration are believed to play an important role. All of these are rigid non-polarisable water models consisting of a single Lennard-Jones site located at the centre of the oxygen, together with a number of point charges to account for the charged nature of the hydrogen and oxygen atoms. The parameters for these models are shown in Table 1.

3.2.2 *Co-solute potential*

Non-polarisable Na^+ and Cl^- ions were modelled using the Smith and Dang [26] potential model for ions, i.e. they are considered as dissociated ions, described by charged single-site Lennard-Jones spheres. This model was chosen as it has previously been shown to reproduce, with a high level of accuracy, the density of NaCl solutions [12]. The parameters for the ions are presented in Table 1.

Table 1. Model parameters for the aqueous solution.

	TIP3P	TIP4P/2005	TIP4P-Ew	Na	Cl
σ	3.1506	3.1589	3.1644	2.35	4.40
ε	76.546	93.240	81.910	65.42	50.32
Q	q_h 0.4170 q_o −0.8340	q_h 0.5564 q_o −1.1128	q_h 0.52422 q_o −1.04844	q_i 1.0	q_i −1.0

3.2.3 *Solute potential*

Following our previous work, we consider two models for the solute molecules. In the first, the molecules are described by the single Lennard-Jones site of Hirschfelder et al. [27], while in the second, in addition to the Lennard-Jones site for the first model, the molecules have a polarisable site located at their centre of mass. The solute polarisability is taken from experimental values [28,29], and is shown together with the Lennard-Jones parameters for each solute in Table 2.

4. Computational method

4.1 *Methodology*

Our calculation of the excess chemical potential of each solute in solutions of NaCl of varying concentration consisted of three steps. In all steps, for all models and systems, interactions were truncated at 9 Å and standard tail corrections applied. In the first two steps, i.e. Steps 1 and 2, simulations were performed using the LAMMPS [30] computational software with long-ranged Coulombic interactions calculated via the particle–particle, particle–mesh (PPPM) [31] technique. Finally, in Step 3, we used our in-house code with the Wolf method [32] to account for the long-range nature of electrostatic interactions, i.e. the calculation of the electric field. Following the work of Demontis et al. [33], and Avendano and Gil-Villegas [34], in the Wolf method we chose a damping factor (β) of $2/R_C$, where R_C is the Coulombic truncation distance (9 Å). For an explanation of our use of the Wolf method, as well as a justification of the choice of the PPPM method in our LAMMPS simulations, we refer the reader to our previous work [1].

Table 2. Solute potential Lennard-Jones parameters and polarisability (α).

	σ (Å)	ε (K)	α (Å^3)
Neon	3.035	18.6	0.40
Argon	3.415	125	1.64
Krypton	3.675	169	2.48
Xenon	3.975	214.7	4.044
Methane	3.730	147.5	2.56

4.2 *Step 1: Aqueous solution simulations*

In the first step of our calculations, the density, as predicted by each model at a variety of concentrations, was determined from isothermal–isobaric molecular dynamics simulations (NPT) at a pressure of 1 bar and a temperature of 298 K. These simulations consisted of 278 water molecules together with 1, 2, 5, 10, 15, 20 or 25 NaCl molecules, corresponding to concentrations of 0.200, 0.399, 0.998, 1.997, 2.995, 3.993 and 4.992 mol/kg (mol of solute/kg solvent) molality, respectively. Starting with a randomly orientated and transitionally distributed configuration at a density close to experimental, each system was first subjected to a simulation period of 300 ps in order to obtain an equilibrated configuration. A 1-ns production run was then performed in which the mean density was calculated. These densities are shown together with experimental values in Figure 1.

4.3 *Step 2: Generation of sample configurations*

Starting with the final configuration from Step 1, each system was adjusted in volume to the average density for each system (a minor adjustment) and subjected to an equilibration period of 5 ps of constant volume, constant temperature molecular dynamics simulation (NVT)

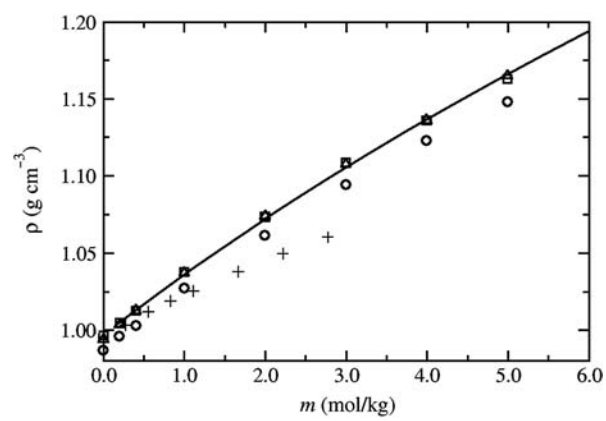

Figure 1. System density as a function of salt concentration for aqueous NaCl systems at 298 K and 1 bar for the TIP4P/2005, TIP4P-Ew and TIP3P water models. The solid line represents experiment densities [41], squares are TIP4P/2005, triangles are TIP4P-Ew, circles are TIP3P and pluses are the values of Holzmann et al. [13].

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in order to relax the system following the volume change. Sample configurations were then generated by performing 7 ns of NVT molecular dynamics simulations, recording a configuration every 70 fs for a total of 100,000 configurations for each water model and ion concentration.

4.4 Step 3: Calculation of the excess chemical potentials

The third and final step was the calculation of the chemical potential of the solute via the Widom insertion technique [22] using in-house code. In this method, a phantom solute molecule is inserted 100,000 times into each configuration, resulting in 10^{10} insertions for every water model and ion concentration.

5. Is explicit polarisability sufficient?

5.1 Density of the solvent

First, given the importance of the solution density for the solubility of hydrophobic molecules, as shown in our previous work [1], as well as work by Paschek [35] and Docherty et al. [12], we test the ability of each water model to reproduce the density–concentration relationship for NaCl solutions. In Figure 1, we show solution density as a function of ion concentration, as predicted by each water model at 298 K and 1 bar, calculated from isothermal–isobaric molecular dynamics simulations. We note that the TIP4P/2005 and TIP4P-Ew models provide essentially identical values and an excellent description of the density of NaCl solutions. TIP3P, however, significantly under-predicts the densities of the solutions considered in this work and this will have a fairly dramatic effect on solute solubility, which will be demonstrated later. Finally, we have also plotted data from the recent work of Holzmann et al. [13] for comparison. Note that their choice of models (TIP4P-Ew water and Heinzinger ion potentials [36]) significantly under-predicts the solution densities. As for the TIP3P model, this will affect the calculation of the excess chemical potential and raises doubts as to the models accuracy in describing the underlying physics of salting-out.

5.2 Chemical potential

As in previous work [1], we begin by showing the effect of polarisability on the excess chemical potential of each solute species considered. We note that all the solutes considered here exhibit a similar trend and, to this end, Figure 2 shows the excess chemical potential for krypton using both the polarisable and non-polarisable models (figures for the other solutes may be found in the accompanying supplementary material). As expected, the inclusion of explicit polarisability reduces the excess

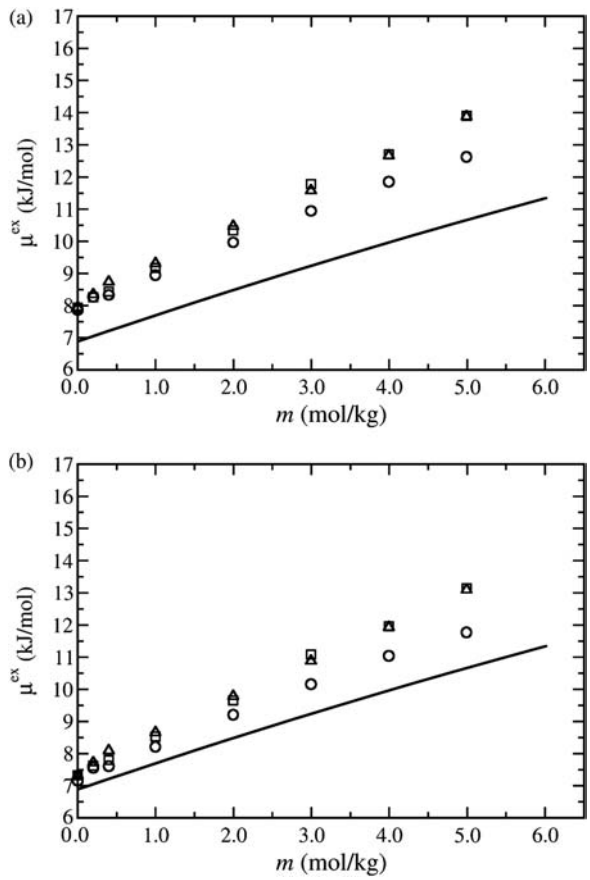

Figure 2. Excess chemical potential as a function of salt concentration for krypton in aqueous NaCl solutions: (a) a non-polarisable krypton model and (b) a polarisable krypton model. See Figure 1 for the explanation of symbols.

chemical potential, i.e. increases solubility, although it does not provide enough of a decrease to achieve quantitative agreement with experiment. Interestingly, in contrast to the temperature dependence of solubility, the TIP3P model gives the best agreement with experiment. However, it is important to note that this is not due to the TIP3P model providing a better description of the physics of the system but is rather a fortuitous cancellation of errors. As mentioned previously in this work, TIP3P greatly under-predicts the density of NaCl solutions. This results in a lower excess chemical potential and, since the models used in this work typically over-predict this value, leads to improved agreement with experiment. Proof of this is given in Figure 3, which contains values for the excess chemical potential of krypton for the TIP3P model calculated at solution densities predicted by the TIP4P-Ew model, as opposed to those predicted by the TIP3P model. For comparison, results for the TIP4P-Ew model are also shown. We note that in the case of the solution densities being equal, agreement between the models is good. In addition to demonstrating the dominant role of volume exclusion in solubility, this highlights the need to

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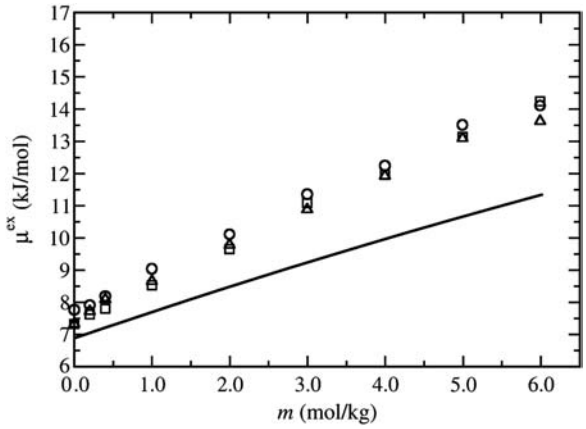

Figure 3. Excess chemical potential as a function of salt concentration for polarisable krypton model in aqueous NaCl solutions. Squares are TIP4P/2005, triangles are TIP4P-Ew and circles are TIP3P at the corresponding TIP4P-Ew system density.

understand the physics behind the values calculated using these models, which is one of the key aims of this work.

5.3 *Setchenow parameter*

In Figure 4, the Setchenow coefficient for krypton (for other solutes see Supplementary Material) is the gradient as a function of molarity and is over-predicted with respect to the experimental value (solid line). The effect of explicitly accounting for polarisability is shown in Figure 4, using krypton as demonstrative of all the systems studied here. As hoped, the addition of explicit point polarisability to the solute model leads to a reduction in the Setchenow coefficient (see Table 3), improving agreement with experiment and corresponding to improved qualitative agreement for the concentration dependence of the excess chemical potential. However, the decrease is relatively minor and is far from being sufficient to obtain quantitative agreement. This should be of interest to a number of workers, such as Docherty et al. [12] and, more recently, Holzmann et al. [13] who have suggested that the lack of accounting for polarisability explicitly is the cause of the over-prediction of the Setchenow coefficient. However, it is clear from the work presented here that this is not the case.

Given that this hypothesis is incorrect, the question now is what causes the over-prediction in the Setchenow coefficient? In answering this, our attention returns to the excluded volume of the system and, since the water–ion potentials attain the correct density for the TIP4P/2005 and TIP4P-Ew models and the water–solute potential approaches quantitative agreement, our focus is on the ion–solute potential. We postulate that the over-prediction of the excess chemical potential and, in turn, the Setchenow parameter is due to an inaccurate ion–solute interaction potential due to assumptions implicit in the use of the Lorentz–Berthelot mixing rules.

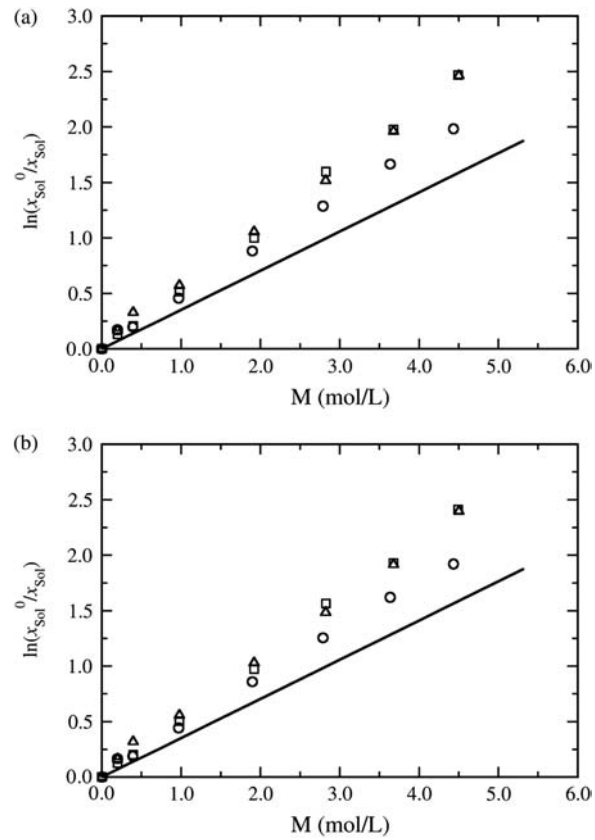

Figure 4. Setchenow relationship for krypton in aqueous NaCl solutions: (a) a non-polarisable model and (b) a polarisable model. The solid line represents experiment values [42], squares are TIP4P/2005, triangles are TIP4P-Ew and circles are TIP3P.

Finally, it is interesting that while the inclusion of explicit polarisation improves quantitative agreement of the temperature dependences of solubility at a cost of reduced qualitative agreement [1], it results in an improvement of both qualitative and quantitative agreements for the salt concentration dependence of solubility.

6. Understanding the causes of salting-out

In order to gain a better understanding of the causes of salting-out, we divide the solvent into three regions in a manner similar to that of Holzmann et al. [13,37] using the TIP4P/2005 model as a representative example. These regions are defined in relation to the ion–oxygen radial distribution functions. Specifically, in terms of the Widom method, an insertion is considered to be in Region 1 (first hydration layer) if the distance from the insertion point to the centre of mass of the nearest ion is less than the distance to the first minima in the corresponding ion–oxygen radial distribution function. In a similar manner, a Region 2 insertion (second hydration layer) occurs if the distance to the nearest ion is less than the distance to the second minima but greater than the distance to the first

Table 3. Setchenow coefficients.

		TIP3P		TIP4P-Ew		TIP4P/2005	
	EXP	NP	P	NP	P	NP	P
Neon	0.277	0.310	0.306	0.358	0.354	0.355	0.351
Argon	0.336	0.400	0.391	0.475	0.464	0.477	0.467
Krypton	0.353	0.455	0.442	0.544	0.530	0.549	0.534
Xenon	0.378	0.526	0.503	0.627	0.612	0.633	0.615
CH_4	0.335	0.469	0.455	0.558	0.544	0.559	0.547

Note: NP and P refer to the non-polarisable and polarisable solute models, respectively and EXP to experimental values.

minima. Finally, if an insertion is neither first nor second hydration shell, it is considered a bulk region insertion. For clarity, this is shown below

$$\text{region} = \left\{ \begin{array}{ll} \text{1st} & r_{\text{ion-solute}} < d_{\text{firstmin}} \\ \text{2nd} & d_{\text{firstmin}} < r_{\text{ion-solute}} < d_{\text{secondmin}} \\ \text{Bulk} & r_{\text{ion-solute}} > d_{\text{secondmin}} \end{array} \right\},$$

where $r_{\text{ion-solute}}$ is the distance from the solute insertion point to the nearest ion and d_{firstmin} and $d_{\text{secondmin}}$ are, respectively, the distances to the first and second minima in the appropriate ion–oxygen radial distribution function.

The excess chemical potential of a solute in an aqueous solution, as calculated in this work using the Widom insertion method, is a function of the number of insertions into each region (first, second or bulk) and the chemical potential obtained for each region. Figure 5 shows the composition of the system, in terms of these regions, as a function of concentration. We note that at low concentrations insertions into the bulk fluid decrease rapidly, being replaced by an increasing number of first and second hydrations layer insertions and that the number of second layer insertions initially increases faster than the first layer due to the larger volume of the second hydration layers. However, the number of second layer insertions peaks and then declines, as second hydration layer volume is replaced by first hydration layer since, if an insertion is in the second layer of one ion, but the first layer of another, it is considered as a first layer insertion.

We now consider the excess chemical potential associated with each region of the solvent. Given the importance of density in the calculation of excess chemical potential, we begin by investigating the density of each region. The density in each region was determined during the widom insertion calculation as follows: first, the volume of each region was obtained by considering the fraction of insertions into each and the total system volume. Second, each molecule in the system was analysed to determine the number (and hence mass) in each region. From this information, the density of each region is readily obtained and is shown in Figure 6 as a function of concentration together with the overall system density. From this figure, it is clear that the increase in the system density is not due to an increase in the density of the bulk water from induced structural changes, but is rather due to an increasing fraction of the system being composed of first hydration layers. Also, of particular interest in terms of the chemical potential is the reduction in density of the bulk and second hydration layers, which

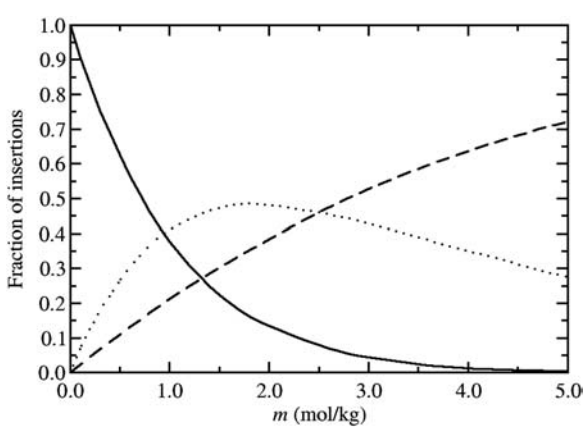

Figure 5. Probability of attempted solute insertion, by region, as a function of salt concentration: first hydration shell (dashed line), second hydration shell (dotted line) and bulk fluid (solid line).

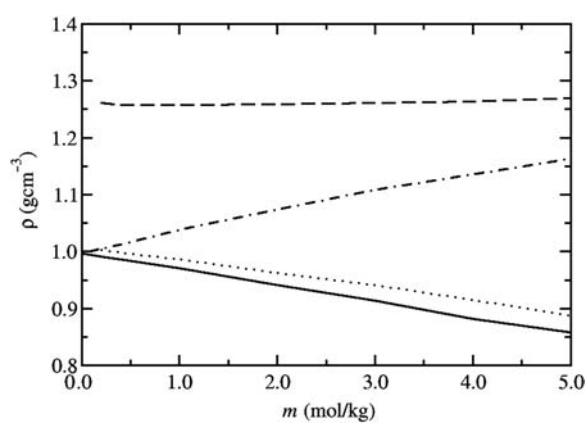

Figure 6. Regional densities as a function of concentration for aqueous NaCl solutions: first hydration shell (dashed line), second hydration shell (dotted line), bulk fluid (solid lines) and the overall density of the solution (dot-dashed line).

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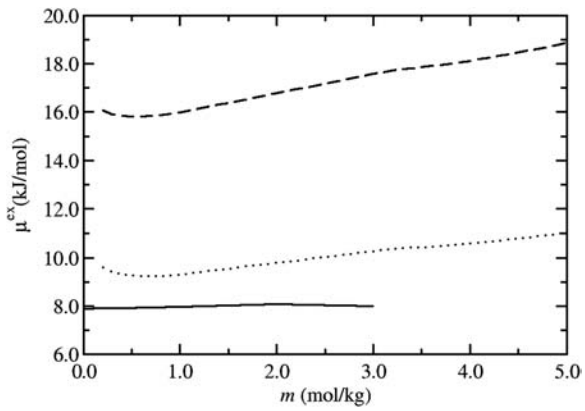

Figure 7. Excess chemical potential of a non-polarisable krypton model in each region. See Figure 5 for the explanation of symbols.

one might expect to result in a decrease in the chemical potential in these regions.

Figure 7 shows the excess chemical potential for insertions into each of the three regions together with the overall system value. We begin by noting that although the density of the bulk and second hydration layer regions decreases, the chemical potential does not. This means that the hydrated ions are more repulsive in nature than the water molecules they replace. This is confirmed by the higher excess chemical potential of the first hydration layer. The conclusion we draw from this figure is that the increase in overall chemical potential, caused by the addition of salt, occurs because hydrated ions are relatively repulsive compared to an equivalent volume of bulk water. This in turn leads to our hypothesis that the over-prediction of the salting-out of systems studied here is due to the use of a relatively repulsive, or insufficiently attractive, ion–solute potential.

In summary, salting-out occurs because hydrated ions have a larger excluded volume than bulk water. This observation is consistent with the work of Docherty et al. [12] who demonstrated a direct relationship between solvent packing fraction and solubility, and the work of Graziano [38] who showed that for a quantatively accurate scaled particle theory method, the salting-out of methane via the addition of NaCl is dominated by the work of cavity creation. It follows from this that the models considered in this work over-predict the salting-out effect as they fail to capture accurately the nature of the ion–solute interaction.

7. A better ion–solute potential

Having shown that the over-prediction of salting-out is due to the ion–solute potential, it seems logical that the next step in attempting to correctly reproduce the salting-out effect is the development of an improved solute–ion potential. Perhaps the most obvious and straightforward method of accomplishing this would be to fit the solute–ion potential to experiment. However, this requires experimental solubility data that, even for a common molecule like CH_4, are very limited. As an alternative to this, we have chosen to fit the ion–solute potentials to *ab initio* calculations as this requires no experimental data and, as such, is a fully predictive method.

In an attempt to more accurately capture the repulsive nature of the ion–solute interaction, we choose to model short-range interactions via the Buckingham exp-6 potential

$$U(r) = \frac{\varepsilon_{ij}}{1 - 6/\gamma_{ij}} \left(\frac{6}{\gamma_{ij}} \exp\left(\gamma_{ij} \left(1 - \frac{r_{ij}}{\sigma_{ij}} \right) \right) - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right), \tag{11}$$

which contains an exponential repulsive wall that is less steep than the r^{-12} of the Lennard-Jones. σ_{ij} is the location of the minimum energy, ε_{ij} is the minimum energy and γ_{ij} controls the gradient of the repulsive wall. The Buckingham exp-6 potential obtains a better approximation of the potential wall, which is important for Monte Carlo simulations as the wall potential is frequently sampled. The Buckingham exp-6 parameters σ_{ij}, ε_{ij} and γ_{ij} are optimised to reproduce the appropriate *ab initio* MP2 energy for each ion–solute dimer, using a gradient descent optimisation for the energy.

7.1 Force field parameterisation

In this work, we have developed ion–solute potentials by fixing the polarisability of the solute molecule to an appropriate experimental value and then fitting the sum of this polarisable contribution (Equation (9)) and a Buckingham exp-6 potential (Equation (11)) to the MP2 point energy of the ion-solute interaction for separations ranging from approximately 0.6 Å closer than the overall energy minima to 3.3 Å past it at intervals of 0.1 Å. In all cases, the *ab initio* calculations were performed using the computational package NWCHEM [39]. The 6-311 + + G(3df,3pd) basis set was used for the calculation of the Hartree–Fock energy and basis set superposition error was corrected for via the half counterpoise method [40,41]. For comparison, Figure 8 shows the fit of the proposed potential to the MP2 point energy for the neon–sodium dimer, together with the pair potential obtained by applying the Lorentz–Berthelot mixing rules to the Smith and Dang ion potential [26] and the Hirschfelder et al. solute potential [27]. Given that polarisability plays an important, but highly system dependent, role in the system energy, the ability to decouple the van der Waals and polarisability contributions is a major advantage of using explicit polarisability. For example, in the case of an isolated pair interaction, such as that used here, the

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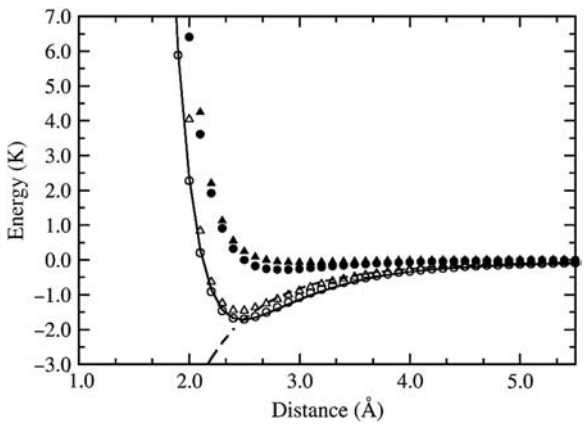

Figure 8. Neon–sodium dimer energy from *ab initio* MP2 point energy calculations (solid line). Symbols correspond to the ion-solute potentials used in this work: triangles are obtained by applying the Lorentz–Berthelot mixing rules to the Smith and Dang ion potential [26] and the Hirschfelder et al. solute potential [27], and circles are the exponential-6 fit to the *ab initio* data proposed in this work. Hollow and solid symbols represent values for polarisable and non-polarisable solute models, respectively, and the dashed line corresponds to the polarisable contribution to the ion–solute potentials (Equation (9)).

Table 4. Solute potential exp-6 parameters and polarisability (α), from fitting to MP2 point energies.

	σ (Å)	ε (K)	λ	α (Å^3)
Neon				
Na^+	2.833	142.666	12.765	0.40
Cl^-	5.228	1.516	16.750	
Argon				
Na^+	3.414	161.691	12.783	1.64
Cl^-	4.326	105.278	12.620	
Krypton				
Na^+	3.597	300.777	11.741	2.48
Cl^-	4.597	59.927	13.904	

electrostatic shielding typical of bulk systems is absent and, as such, accounting for polarisability in an implicit manner, e.g. fitting only the exp-6 potential to the MP2 energy, would significantly overestimate the polarisability contribution in a condensed phase calculation. The values of the new ion–solute interaction potentials are shown in Table 4. As before, the electrostatic charges on the ions and solutes are set to their isolated value (+1e for Na^+ and −1e for Cl^-) and the polarisability was set to their relevant experimental value [28,29,35].

7.2 *Results from new potentials*

The new potentials were tested by comparing values for the excess chemical potential and the Setchenow coefficients (Table 5) to those calculated using the original parameters, as well as experiment. For brevity, we show only figures of the Setchenow coefficients; however, due to their close relationship, similar trends are seen for the chemical potentials. Specifically, Figures 9–11 show the Setchenow coefficient for both the new and original potentials using both the TIP4P/2005 and TIP4P-Ew water models. We note that for the argon and krypton solutes, shown in Figures 10 and 11, respectively, a significant improvement over the Lennard-Jones parameters taken

Table 5. Comparison of Setchenow coefficients obtained using a polarisable exponential-6 solute model fitted to *ab initio* calculations.

	EXP	LJ	Exp-6
Neon	0.277	0.351	0.393
Argon	0.336	0.467	0.378
Krypton	0.353	0.634	0.410

Notes: EXP, experimental values; LJ, polarisable Lennard-Jones potential; Exp-6, *ab initio* parameterised potential. For both models, the TIP4P/2005 water model was used.

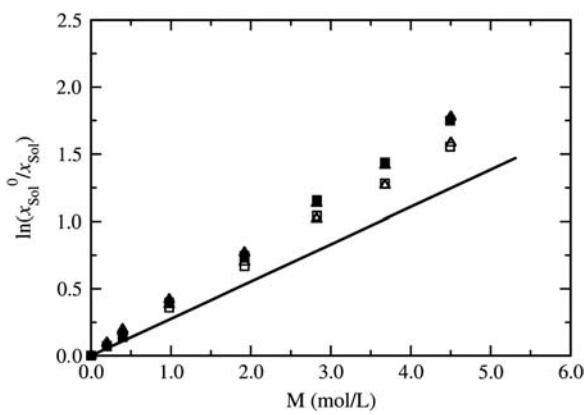

Figure 9. Setchenow relationship for a polarisable neon model in aqueous NaCl solutions. The solid line represents experiment values, squares are TIP4P/2005 and triangles are TIP4P-Ew. Hollow symbols correspond to the Lennard-Jones model and solid symbols correspond to the exponential-6 potential fitted to *ab initio* calculations of this work.

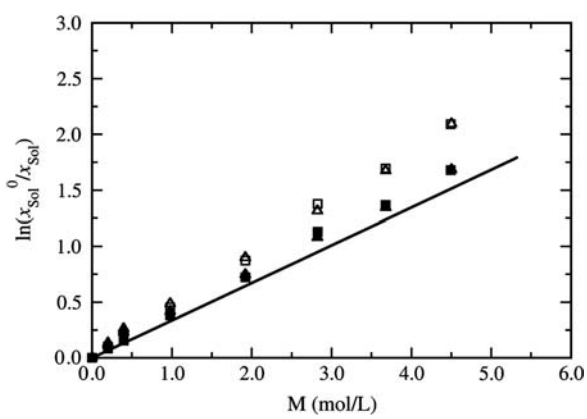

Figure 10. Setchenow relationship for a polarisable argon model in aqueous NaCl solutions. See Figure 9 for the explanation of symbols.

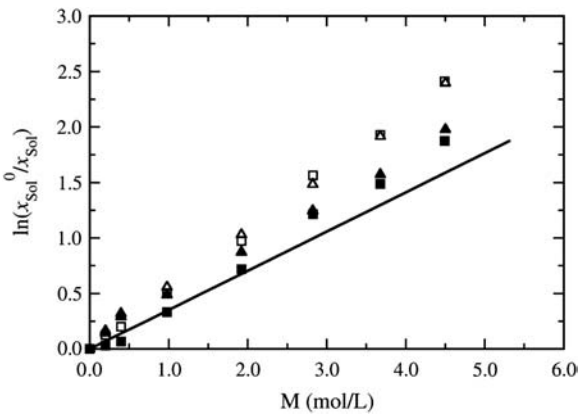

Figure 11. Setchenow relationship for a polarisable krypton model in aqueous NaCl solutions. See Figure 9 for the explanation of symbols.

from the literature is observed. Conversely for neon, shown in Figure 9, agreement with experiment is slightly worse with the new potential suggesting that other factors are not being accounted for. However, as a proof of concept, the new potentials work well.

8. Conclusions

In this work, we began by showing that, when coupled with common rigid molecules, single-site non-polarisable models of small non-polar solutes fail to capture either qualitatively or quantitatively the effect of charged co-solutes on solubility. Given that in our previous work, we showed that such models fail to reproduce the temperature dependence in pure water, this is unsurprising. In fact, these models over-predict salting-out effects. Here, we have investigated the common hypothesis that this over-prediction is due to not accounting for solute polarisability explicitly. We have shown that, with respect to salting-out, explicit polarisability improves both the qualitative and quantitative agreements with experiment, but is not sufficient to provide the desired agreement with experiment. In fact, we present evidence to suggest that disagreement with experiment is largely due to inadequacies in ion–solute interactions. Further to this, we have demonstrated that, by accounting for polarisability explicitly, it is possible to obtain pair interaction potentials from *ab initio* calculations that perfom as well as, or better than, the models commonly used to study these systems.

Acknowledgements

This research was supported as follows: P.J.D. was supported by the Chemical Sciences, Geosciences and Biosciences Division, Office of Basic Energy Sciences, Office Of Science, US Department of Energy through Grant No. DE-FG02-03ER15385; H.D. was supported by the National Science Foundation through Grant No. CHE-0626259. PTC was supported in part by the Fluid Interface Reactions, Structures and Transport (FIRST) Center, an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences under Award Number ERKCC61.

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