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A combined theoretical and simulation study

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Abstract

It has been known for over a century that the presence of cosolvents such as urea and formamide can alter the morphology of NaCl crystals grown from solution. To help understand this effect we have been developing a theoretical approach based on the Kirkwood-Buff (KB) theory of solutions, and have combined this with computer simulations of the interation of urea with different crystal faces of NaCl. In this way one can predict the effect of urea on the thermodynamic stability of different NaCl faces, with atomic level detail provided by the simulations. We observe that urea is preferentially excluded from 100 and 111 crystal faces, but is less excluded from 111 faces which present chloride ions at the surface. The results indicate that the 111 face is stabilized in urea solutions and promotes the formation of octahedral over cubic NaCl crystals. The approach is totally general and can be applied to understand a variety of interfacial properties. Furthermore, we apply KB theory to study several other issues regarding the simulation of crystal growth.

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Introduction

Crystallization from solution is a fundamental phenomenon with important scientific and engineering implications.[1] The growth of pure crystals is often a difficult task, while the absolute control of crystal morphology is rare. Crystals with different morphologies are prime candidates for new materials with interesting and novel properties. However, our ability to understand, especially at the atomic level, exactly why one particular crystal form is favored over another is currently impossible.[2] Crystallization is particularly difficult to understand as it involves both thermodynamic and kinetic issues which affect the growth rate and morphology.[3-5] The focus of this work concerns the crystallization of solids from aqueous solutions. This has additional aspects compared to crystallization from a melt, such as explicit solvation effects,[6] which are also difficult to understand. However, the possibility of adding cosolvents to the solution provides a useful added dimension and a significant opportunity to control crystal morphology.

In principle, computer simulations of crystal growth can provide atomic level detail concerning crystal nucleation, growth, morphology, and the kinetic aspects of the process involved. However, all atom computer simulations are limited to the system sizes and/or simulation times that can be accessed with modern computational resources.[5,7,8] Hence, it is only recently that realistic simulations of crystal formation from aqueous solution have appeared.[5,7] Some of the very recent studies on urea crystallization using kinetic Monte Carlo simulations are the most exciting and promise to dramatically extend the reach of computer simulations.[9,10] Most previous simulations, however, have been limited in their capabilities. An interesting prototype system for crystallization studies in NaCl. Here, several studies of NaCl have been performed for crystal surfaces in contact with a variety of environments including supersaturated solutions.[8,11-13] However, none of these studies have demonstrated crystal formation or growth using all atom simulations.

Another aspect of NaCl crystal morphology is the ability of cosolvents to change the stability of different crystal forms. In particular, urea (and formamide) can stabilize octahedral crystals of NaCl over the usual cubic form. This was first demonstrated in 1783,[14] quantified in 1912,[15] and studied in more detail in 2003.[16] Thermodynamically, urea must lower the chemical potential of the octahedral form in comparison with the cubic form. However, exactly how urea can promote octahedral crystal formation remains a mystery at the atomic level. We believe that the NaCl/urea/water system represents a simple, well characterized, important, and accessible system for the study of crystal growth thermodynamics and kinetics using computer simulation. Unfortunately, a full description of crystal formation and growth, involving the growth the large layers or spiral growth from crystal defects, is still unfeasible. However, one can study the growth and properties of microcrystals and smaller surfaces and investigate the role of cosolvents using presently available computational hardware. This is a focus of the current study.

It is well known that NaCl crystallizes into a FCC lattice (see Figure 1). This lattice represents one of the simplest packing arrangements for spheres and the formation of NaCl crystals is therefore a system which requires understanding before one moves to more complicated arrangements of molecules packing in lower symmetry lattices. An octahedral form of NaCl crystals can be obtained by slicing the cubic crystals along the 111 planes (see Figure 1). On a molecular scale, the 111 surface is rough compared to the 001 surface. Furthermore, the 111 surface can present either sodium or chloride ions to

the nearby solution. The octahedral form is thermodynamically less stable than the cubic form, i.e. it has a higher chemical potential.[15] Consequently, the solubility of octahedral crystals in water is higher than that of cubic crystals, although the difference is small.

On addition of urea, however, two things happen. The solubility of both the cubic and octahedral forms decrease (from 5.4M to around 4.6M in 4.6m urea), and the octahedral form becomes the most thermodynamically stable.[15,16] A similar, but larger, effect is observed for formamide.[15] The reasons behind these changes are largely unknown. More recently, the characteristics of the 111 NaCl surface as grown from solution in the absence and presence of formamide have been investigated using microscopic techniques. It was observed that the detailed morphology of the 111 crystal faces was dependent on the solution composition, with smooth surfaces appearing in the presence of formamide solutions and shallow hillocks appearing from salt solutions.[16] A rigorous methodology designed to understand and use such effects would greatly improve our ability to design new materials.

Here, we use a combined simulation and theoretical approach to study the effect of urea on the morphology of NaCl crystals. The Kirkwood-Buff (KB) theory of solutions is used to help analyze the simulation results and relate solution distributions to changes in the thermodynamics of the crystal or crystal face. The approach is the same as for our studies of changes in surface tension of liquids on the addition of cosolvents.[17] Specifically, we outline the basics of KB theory and our models. Then we describe how these can be used to understand the effect of urea. Finally, we provide evidence for additional applications of KB theory to help define the size of crystal when it is in contact with a saturated solution, and how the chemical potential of a meta stable supersaturated solution may be determined computationally.

Kirkwood-Buff Theory

The current work relies heavily on the use of KB theory.[18,19] We have been using KB theory to help understand cosolvent interactions with proteins in mixed solvent systems.[20-23] However, KB theory is completely general and so we wish to expand our previous applications into the area of crystal growth thermodynamics. We do not know of any other applications of KB theory in this area. There are several advantages of using KB theory over other approaches. First, it is an exact theory with no restriction as to the size or type of molecules that can be studied. Second, it provides a link between the relative distribution of molecules at the atomic level and the corresponding experimental thermodynamics. Third, the required distributions can be obtained rather easily from computer simulations. Fourth, expressions for changes in chemical potentials are easily obtained.

Kirkwood-Buff theory has been outlined in detail elsewhere.[19] Briefly, KB theory expresses several properties of solvent mixtures in terms of KB integrals which are defined by,

$$G_{ij} = 4\pi \int_0^\infty [g_{ij}^{\mu VT}(r) - 1] r^2 dr \tag{1}$$

where $g_{ij}(r)$ is the center of mass radial distribution function (rdf) between i and j in the grand canonical (μVT) ensemble. The above integrals provide a quantitative estimate of

the affinity between species i and j in solution, above that expected for a random distribution. A positive value of the corresponding excess coordination number ($N_{ij} = \rho_j G_{ij}$) indicates an excess number of j molecules around a central i molecule, while a negative value indicates a depletion or exclusion of j molecules from the vicinity of the i molecule. It is important to note that the KB integrals characterize the deviation in the molecular distributions (from a random distribution) over all distances and not just due to the direct interactions such as hydrogen bonds. An approximation to Equation 1 can be used for simulations performed in closed systems, whereby the integral is truncated at some distance (1-1.5 nm) beyond which g_{ij} is essentially unity.[24,25]

The application of KB theory to binary solutions of a solute (2) in a solvent (1) results in a simple expression for the chemical potential derivative of the solute at constant temperature (T) and pressure (P),

$$a_{22} = \beta \left(\frac{\partial \mu_2}{\partial \ln \rho_2} \right)_{P,T} = \left(\frac{\partial \ln a_2}{\partial \ln \rho_2} \right)_{P,T} = \frac{1}{1 + \rho_2 (G_{22} - G_{12})} \tag{2}$$

where a_2 is the activity of the solute, ρ_2 is the solute number density (molar concentration), μ_2 is the solute chemical potential, and $\beta = 1/RT$. If the experimental concentration dependent activity, partial molar volumes, and compressibility are known, then one can determine the above derivative, and therefore the KB integrals which are directly related to the molecular distributions.[26] Alternatively, KB integrals determined from simulation can be used to provide the corresponding solute activity derivatives (and thereby solute activities).[24,27] This approach has be used to fully characterize NaCl solutions using an indistinguishable ion approximation.[20]

KB theory can also be applied to ternary systems and thereby can be used to quantify the interactions between a crystal, a solute, and a solvent. We will consider the case of an infinitely dilute NaCl crystal (2), in a solution of urea (3) and water (1). Here, changes in the pseudo chemical potential of the crystal (or a crystal face) can be expressed as,[20,23]

$$\beta \left(\frac{\partial \mu_2^*}{\partial \ln \rho_3} \right)_{P,T} = -\frac{\rho_3 (G_{23} - G_{21})}{1 + \rho_3 (G_{33} - G_{31})} \tag{3}$$

where μ^* is the pseudo chemical potential of the crystal. The denominator is a property of the urea and water mixture alone and must be positive.[19] The numerator quantifies the difference in affinity of urea and water for the crystal. If urea preferentially binds to the crystal over water, then the numerator is positive and the chemical potential of the crystal is decreased. If urea is excluded from the crystal surface, the numerator is negative and the chemical potential of the crystal is increased. If the urea preferentially binds to a particular face then the chemical potential of this face will be more thermodynamically favorable in the presence of urea. We will use this type of approach to study the effects of urea on NaCl growth thermodynamics.

Kirkwood-Buff Derived Force Fields

The accuracy of computer simulations depends on the quality of the force field and the degree of sampling. We have recently developed force fields for NaCl and urea which reproduce the experimental KB integrals, and therefore the thermodynamics of these solutes in water mixtures.[28,29] We note that this can be achieved without sacrificing the

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agreement with experiment for other properties of the solutions. Furthermore, many current force fields do not naturally provide good agreement with the experimental KB integrals.[25,28,30] Other properties of our models which are important for crystal growth studies are also in good agreement with experiment. The diffusion constants for both ions are well reproduced, the enthalpy of mixing of NaCl and water is in good agreement with experiment, as are the dimensions of the crystal lattice. Finally, our model of NaCl reproduces the solution/vapor surface tension increase observed on the addition of NaCl to solutions,[17] indicating that the model also provides a reasonable description of the interactions at surfaces. Hence, while the model is nonpolarizable, it captures a variety of thermodynamic and structural properties of NaCl solutions. A nonpolarizable model is required to access the timescales of interest in these studies. In summary, we have a high degree of confidence in our simulation models.

Methods

All solution mixtures will be simulated using classical molecular dynamics techniques using the GROMACS code.[31,32] Our own NaCl and urea force fields which are designed for use with the SPC/E model of water were used.[28,29,33] All simulations were performed in the isothermal isobaric ensemble at 300 K and 1 atm. The weak coupling technique was used to modulate the temperature and pressure,[34] with relaxation times of 0.1 and 0.5 ps, respectively. All bonds were constrained using SHAKE[35] and a relative tolerance of 10^{-4}, allowing a 2 fs timestep for integration of the equations of motion. The particle mesh Ewald technique was used to evaluate electrostatic interactions,[36] using a real space convergence parameter of 3.5 nm^{-1} in combination with twin range cutoffs of 1.0 and 1.5 nm, and a nonbonded update frequency of every 10 steps. The reciprocal space sum will be evaluated to ensure 0.1 nm grid resolution.

Two different types of simulations are described here. First, the interactions of urea with the different faces of both cubic and octahedral NaCl crystals were investigated. This involved simulations of the 001 and 111 faces of NaCl with 8M urea solutions. The cubic (001) simulations involved a crystal slab containing a total of 7840 NaCl ions in contact with a urea solution containing 3696 ureas and 16344 water molecules in a box 7.92x7.92x15.28 nm. The octahedral (111) simulations involved a crystal slab containing a total of 8640 NaCl ions in contact with a urea solution containing 3696 ureas and 16344 water molecules in a box 8.30x7.98x15.54 nm. In both simulations the NaCl ions were constrained to their initial positions and there were no free salt ions present in the solution. The simulations were performed for 10 ns each. The second set of simulations involved the growth of an NaCl crystal from a saturated solutions of NaCl. Here, the systems involved a total of 664 ions and 1524 water molecules. The simulations were seeded with a 4x4x4 ion cube to overcome the nucleation step. Simulations were performed for almost 400 ns.

Results

The Effect of Urea of crystal Morphology

One of the major aims of this research is to understand, in a quantitative way, how the addition of other molecules can affect crystal morphology. The addition of urea to NaCl solutions favors the formation of octahedral crystals. Assuming this is a thermodynamic effect, this implies that urea somehow stabilizes the 111 face over the 001 face of the NaCl lattice. Here, we use KB theory to quantify this effect in a way that is general for any crystal in any mixed solvent system. The addition of urea to the solution has two potential effects. First, the chemical potential of bulk NaCl solutions can be altered. This, however, will not affect the relative stability of different crystal faces. Second, the interaction of the urea molecules with the different faces can alter the chemical potentials of the faces. From our analogous work on proteins,[37] it is clear that a favorable interaction of urea with the 111 face over the 001 face will preferentially lower the chemical potential of the 111 face, thus promoting growth.

To investigate this type of effect we have simulated the different faces of a NaCl crystal in contact with a solution of 8M urea. There were no free salt ions in the solution. This approach was adopted in an effort to maintain a regular crystal interface with a predetermined morphology, and to simplify the analysis. When dealing with a crystal face or interface Equation 3 has to be modified slightly. Referring to our work on liquid interfaces,[17] one can write an expression for the change in the chemical potential of a crystal face in the presence of urea (3) and water (1) solutions as,

$$\beta \left(\frac{\partial \mu_2^*}{\partial \ln \rho_3} \right)_{P,T} = -\Gamma_{3,1} a_{33} \tag{4}$$

where μ^* is now the pseudo chemical potential of the crystal face. The excess surface adsorption of solute i per unit surface area is then given by,

$$\Gamma_{i,1} = \rho_i \int_0^R [g_i(r) - g_1(r)] \, dr \tag{5}$$

Here, r and R are the distance away from the interface. As the value of a_{33} must be positive, the sign of the urea affect can be determined from the value of Γ, the excess surface adsorption.

Our initial simulations have probed the interaction of urea with the 001 and 111 faces in water. The preferential interaction (per unit area) of urea with the 001 and 111 (both Na and Cl) faces determined from the simulations is displayed in Figure 2. The results suggest that urea is excluded from both 111 and the two formally identical 001 faces. This is due to the fact that water molecules, being much smaller than urea, can approach closer to the interface. However, the exclusion is greatest for the 111 (Na) face, while urea clearly prefers the 111 (Cl) face. The corresponding surface distributions are displayed in Figure 3. It is clear that water can penetrate the rough 111 surface in comparison to the smooth 001 surface. The urea distribution peaks at much larger distances than water. The urea distribution at the 111 (Cl) surface displays a sizeable first peak in comparison to urea at the 111 (Na) surface.

A snapshot from the trajectory obtained for octahedral faces of NaCl in contact with an 8M urea solution is displayed in Figure 4. The figure suggests a possible reason for the

preference of urea for 111 (Cl) faces lies in the fact that the oxygen of the urea molecules can penetrate the top layer of chloride ions to reach the underlying sodium ions. At the same time the urea hydrogen atoms can form strong interactions with the first layer of chloride ions. Both of these ion-dipole interactions should be favorable. Furthermore, such interactions are not possible, at least simultaneously, for either the 111 (Na) or 001 faces. Formamide, which also promotes octahedral crystal growth, should be able to form similar kinds of interactions as those observed here for urea.

Hence, the presence of urea raises the chemical potentials of all faces, but destabilizes the 111 (Cl) face the least. The simulations described here suggest that the octahedral form should be thermodynamically favored through interaction of urea with the 111 face presenting Cl ions to the solution. This is shown schematically in Figure 5. Experimentally, the growth rate in urea and formamide is observed to be slower than from salt solutions – presumably due to the presence of surface adsorbed cosolvents.[16]

Simulations of Crystal Growth

We have performed preliminary investigations into the feasibility of growing NaCl crystals using all atom (unbiased) molecular dynamics simulations. As expected, crystal growth could not be observed within 100ns from supersaturated solutions (even for very high supersaturations) due to the very slow nucleation processes required.[8] However, we did observed crystal growth after seeding (using a 4x4x4 ion cube) of a supersaturated (12m) solution. The crystal growth was slow but detectable over long simulation times. The crystal size as a function of simulation time is displayed in Figure 6.

After an initial lag time the growth was approximately proportional to time until equilibrium with the remaining solution was obtained after 300 ns. Hence, the direct simulation of crystal growth is feasible and further analysis should provide valuable information on the growth mechanism. A second independent simulation was also performed. After 100 ns, essentially the same growth rate is apparent suggesting consistent and reproducible results can be obtained from the simulations. Several plateau regions appeared periodically during the growth process. Our initial analysis suggests that these correspond to the formation of a complete face. The snapshots displayed in Figure 6 also illustrate that the crystal surface is rough in nature (there are many steps on the surfaces) and some seed atoms do not participate in the growth process. A separate simulation of a perfect cube in contact with a solution at the solubility limit essentially maintains the smooth crystal surfaces. Hence, as step formation should be energetically more unfavorable (fewer crystal contacts),[3] it may well be that the crystal observed after 300ns will rearrange further, while maintaining the same number of ions, to form smoother surfaces. In addition, we have performed simulations using an octahedral seeding crystal. However, the octahedral form is unstable and quickly decomposes to a simple cubic lattice which then proceeds to grow, in agreement with the experimental data.

Determination of NaCl Solubility

To our knowledge, an accurate determination of the solubility of NaCl by simulation has not been reported. Obviously, this is an important property of the force field which needs to be addressed. In principle, one could simply count the number of ions associated with a crystal (and therefore also free in solution) in equilibrium with a saturated solution. This should provide the solution composition at saturation and therefore the solubility. However, from a simulation standpoint there are several technical problems. First, one has to define when an ion is considered a part of the crystal. This sounds easy but is actually quite difficult as many ions from the solution contact the crystal and yet are not necessarily an integral or permanent part of the crystal. Furthermore, the crystal is dynamic and ions associate and dissociate from the surface continuously. These factors also mean that it is very difficult to determine the exact size of crystals observed in simulations. Our initial attempts to determine the solubility of our model involved examining the composition of regions of the solution as far away as possible from the crystal after it has equilibrated with the surrounding solution. Unfortunately, the solution composition fluctuated significantly and many ns of simulation appear to be required.

Given enough simulation time the above approach can be used to accurately determine the solubility limit for the model of choice. However, it does not clearly answer the question of how large is the crystal present in the solution at equilibrium with the saturated solution. In Figure 6 we used a simple geometric measure of whether an ion formed part of the crystal by considering the number of ion-ion contacts an ion made with other ions in the crystal (a cutoff of 3 was used). In our opinion, this is satisfactory to follow crystal growth kinetics. However, we have also pursued a more thermodynamically rigorous definition of the crystal size at equilibrium. This involves a combination of KB theory and a hypothetical equilibrium dialysis experiment.[22] In an equilibrium dialysis experiment a dialysis chamber is used to measure changes in density (composition) of a solution on introduction of a particle (usually a protein) into the chamber. In our case we will consider the introduction of a crystal into a saturated solution of NaCl which is in contact, through a membrane permeable to ions and water but not the crystal, with a bulk NaCl solution also at saturation. If both solutions are at saturation, there will be no net change in the composition of the dialysis chamber as both the NaCl crystal and NaCl solutions have NaCl at the same chemical potential.[19] Experimentally, the change in composition is quantified using the preferential interaction or preferential binding parameter, Γ, which is defined by,

$$\Gamma = \left(\frac{\partial m_3}{\partial m_2} \right)_{T,V,\mu_1,\mu_3} = \rho_3 (G_{23} - G_{21}) \tag{6}$$

where the subscripts 1, 2, and 3 refer to water, crystal and dissolved salt, respectively. For an infinitely dilute crystal the above quantity can be expressed in terms of KB integrals (as shown).[22]

Hence, if a solution is at the solubility limit and a single crystal of salt is added, then the value of Γ should be zero. The only way this can happen is if the two KB integrals cancel. We can use this thermodynamic definition of equilibrium to determine the correct average size of the crystals observed in simulations. For instance, one can select the closest N ions to the center of mass of the NaCl seed cluster. Any other ions therefore belong to the dissolved salt. A subsequent calculation of the value of Γ for the dissolved

salt (and water) around this crystal of N ions can then be determined. If Γ is not zero, then the choice of N is thermodynamically inconsistent with equilibrium between the crystal and a saturated solution. The process can be repeated until a value of N which yields $\Gamma = 0$ is obtained. This is the thermodynamically consistent crystal size. The results are displayed in Figure 7. It is found that the number of ions in the crystal is larger by approximately 10% than that determined by the subjective approach of counting the number of contacts with the crystal.

Chemical Potentials in Supersaturated Solutions

One of the more important parameters used in understanding crystal nucleation and growth involves the chemical potential difference between the aqueous and crystal phases.[3] At saturation these are equal. Growth can only occur from supersaturated solutions where the chemical potential of the supersaturated solution is larger than the crystal. Theoretically, growth rate is expected to be proportional to the degree of supersaturation,[4] although the range of supersaturation is typically much smaller than that initially used here. A slower growth rate is expected for lower degrees of supersaturation.[3]The difference in chemical potential is dependent on the solute concentration in an unknown manner. Simulations of chemical potential differences are possible using thermodynamic integration – but these are generally subject to considerable statistical uncertainty.[2] An alternative is to use KB theory. Here, the slow nucleation problem observed in most solutions can actually help. As nucleation is so slow, one can generate supersaturated solutions of almost any degree by randomly placing ions and water molecules into the simulation box and then equilibrating extensively. The properties of these metastable solutions are generally well defined, reproducible, and stable over many ns of simulation. One can therefore determine the density and KB integrals in such systems in the usual manner. Then, if one requires the chemical potential of NaCl in the supersaturated solution, relative to the crystal, then one simply integrates the value of a_{22} (as defined in Equation 2) from the saturation point to the required supersaturation concentration. To our knowledge this approach has not been used before. However, a similar approach has been used for studying ideality in urea solutions.[38]

Conclusions

In this study we have outlined how to use a combination of simulation and Kirkwood-Buff theory to investigate the effects of cosolvents on the morphology of crystals. Specifically, the effect of urea on NaCl crystals is observed to be in agreement with experiment. The apparent explanation for the increased stability of octahedral NaCl crystals in urea solutions arises from a preferential interaction of urea with the 111 face capped by chloride ions above that for the 001 surface and the 111 surface capped with sodium ions. Other uses of KB theory in this area include an objective (thermodynamic) definition of crystal sizes in contact with saturated solutions, and the determination of chemical potentials for super saturated solutions.

Acknowledgements

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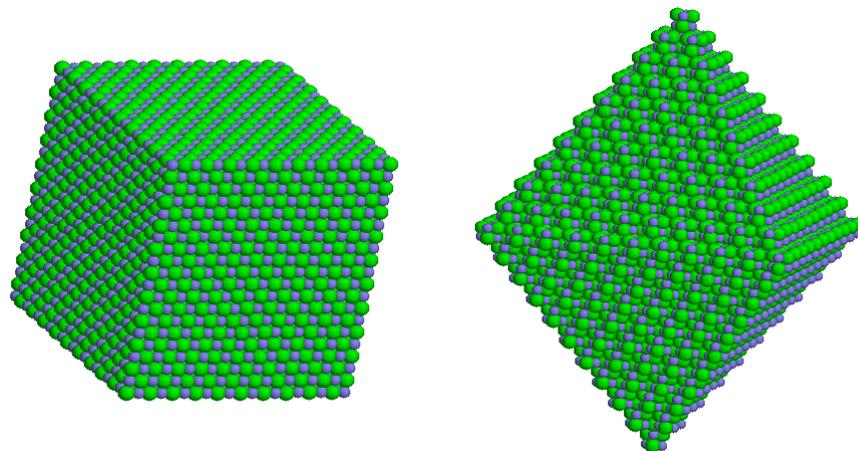
Figure 1. The cubic (left) and octahedral (right) crystal forms of NaCl. Sodium ions are blue, chloride ions are green.
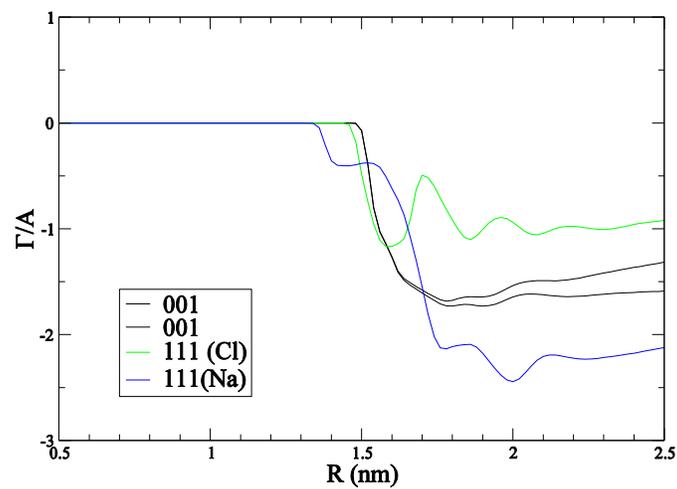
Figure 2. The simulated preferential interaction normalized to unit surface area (Γ/A in molecules per nm^2) of urea with the 001 and 111 faces of NaCl. The preferential interaction is displayed as a function of distance R from the center of the slab geometry used for the two faces. The final value of Γ is obtained from the plateau value reached at large R.
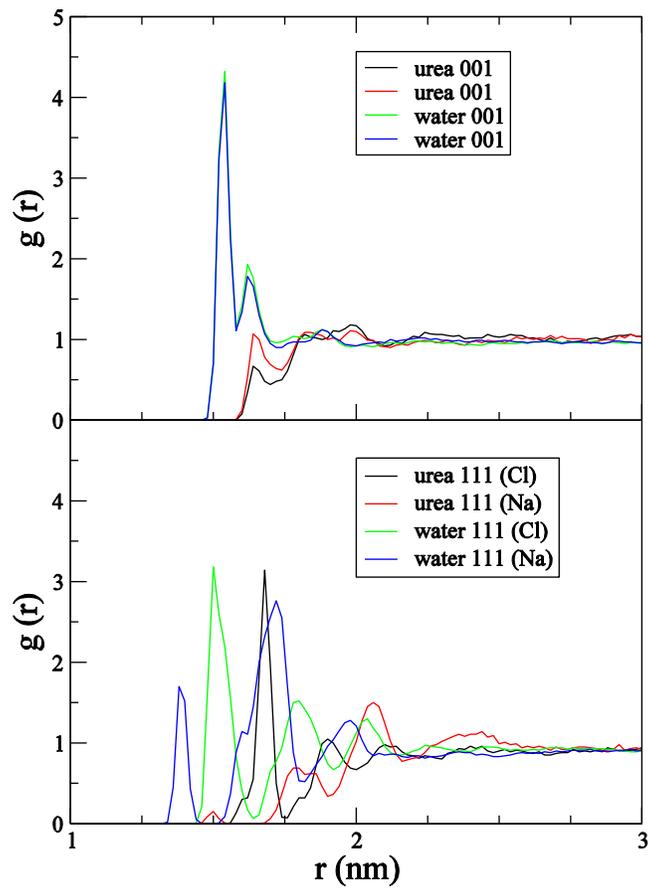
Figure 3. Surface distribution functions for urea and water oxygens as a function of distance r from the center of the NaCl crystal slab. Results for both the 001 (top) and 111 (bottom) surfaces are displayed.
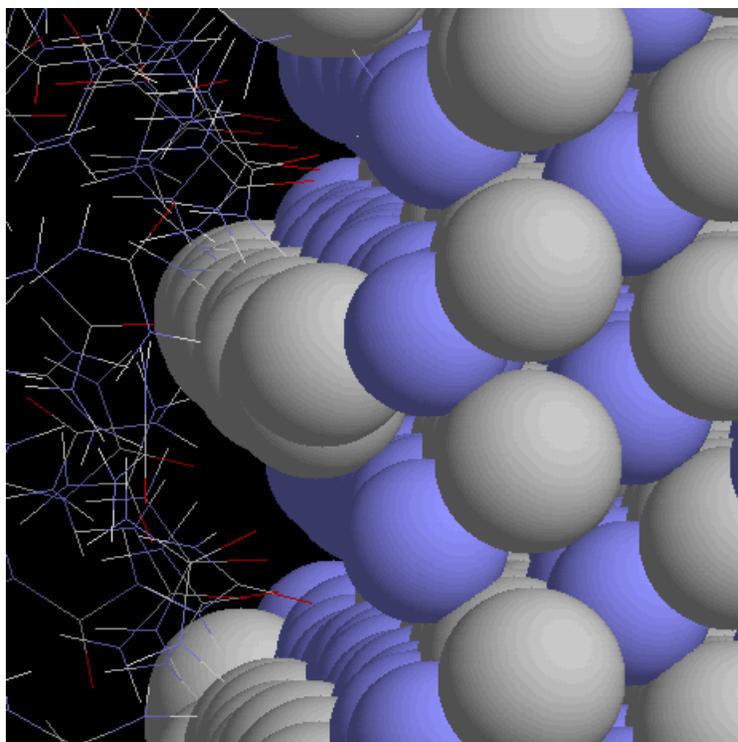
Figure 4. A snapshot of the 111 (Cl) face of a NaCl crystal in contact with an 8M urea solution. Sodium ions are shown as blue, chloride ions as grey, and urea molecules as wireframe. Water molecules have been removed for clarity.
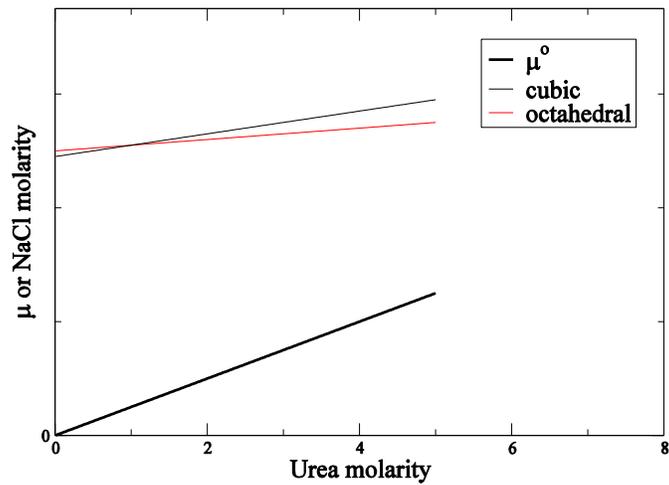
Figure 5. A schematic representation of the effect of urea on the cubic and octahedral NaCl crystals that fits the current experimental and simulation data. The chemical potentials of both the cubic and octahedral forms are increased in the presence of urea. However, the standard chemical potential of the NaCl solution (μ^o) is increased more significantly. Hence, overall solubility is lowered, while the preference of urea for octahedral form makes it more thermodynamically stable in urea solutions.
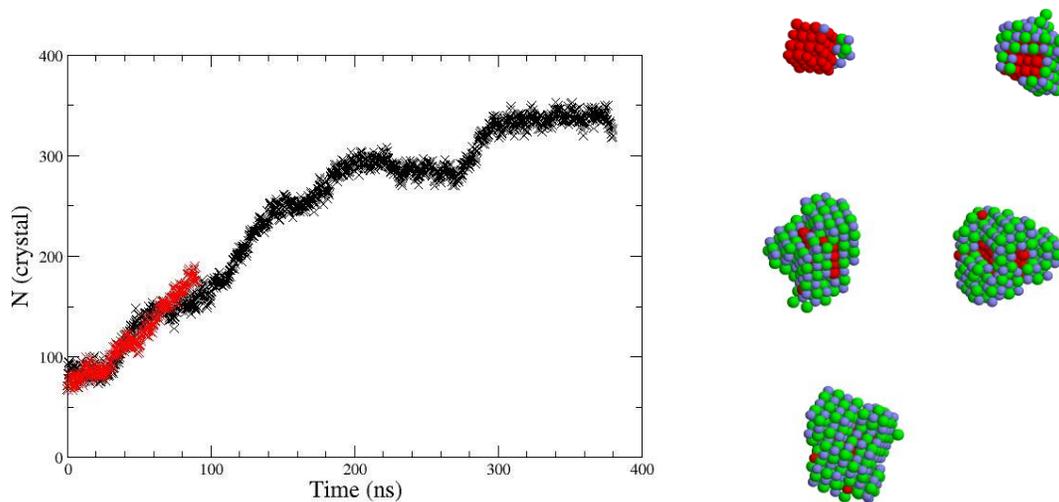
Figure 6. The number of ions (N) in the crystal cluster as a function of time. The black and re5 lines correspond to two independent simulations with different initial ion positions and velocities. The snapshots displayed on the right correspond to the plateau regions in the figure (black line) at times of 10, 70, 160, 250, and 350 ns, respectively. Sodium ions are blue, chloride ions are green, and the seed crystal is colored red. An ion was considered part of the cluster if it made at least 3 ion-ion crystal contacts (< 0.31 nm) with already established members of the cluster.
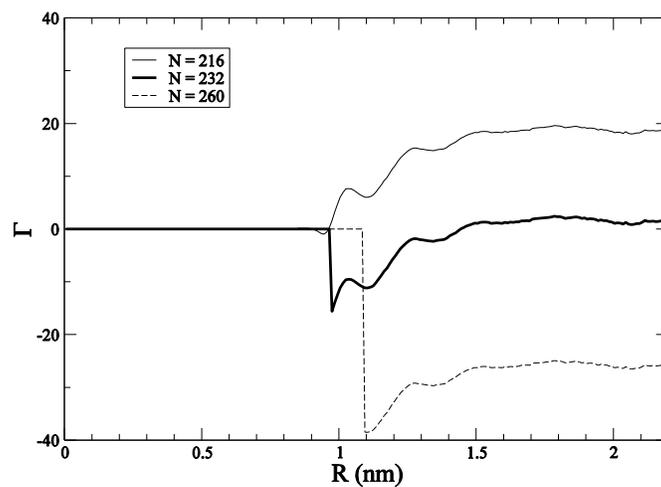
Figure 7. The simulated preferential interaction (Γ) of sodium chloride ions with an (initially) 6x6x6 cube of crystal NaCl at saturation (6.1m) as a function of distance away from the center of the cube. The value of the preferential interaction was determined by assuming different numbers of ions (N) in the crystal. The thermodynamically consistent ($\Gamma = 0$) size of the crystal contains 232 ions.