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Ion pair potentials-of-mean-force in water

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Abstract

Motivated by the surprising dielectric model predictions of alkali-halide ion pair potentials-of-mean-force in water due to Rashin, we reanalyze the theoretical bases of that comparison. We discuss recent, pertinent molecular simulation and integral equation results that have appeared for these systems. We implement dielectric model calculations to check the basic features of Rashin's calculations. We confirm that the characteristic structure of contact and solvent-separated minima does appear in the dielectric model results for the pair potentials-of-mean-force for oppositely charged ions in water under physiological thermodynamic conditions. Comparison of the dielectric model results with the most current molecular level information indicates that the dielectric model does not, however, provide an accurate description of these potentials-of-mean-force. Since literature results indicate that dielectric models can be helpfully accurate on a coarse, or chemical energy scale, we consider how they might be based more firmly on molecular theory. The objective is a parameterization better controlled by molecular principles and thus better adapted to the prediction of quantities of physical interest. Such a result might be expected to describe better the thermal-level energy changes associated with simple molecular rearrangements, i.e. ion pair potentials-of-mean-force. We note that linear dielectric models correspond to modelistic implementations of second-order thermodynamic perturbation theory for the excess chemical potential of a distinguished solute molecule at infinite dilution. Therefore, the molecular theory corresponding to the dielectric models is second-order thermodynamic perturbation theory for that excess chemical potential. Examination of the required formulae indicate that this corresponding molecular theory should be quite amenable to computational implementation. The second-order, or fluctuation, term raises a technical computational issue of treatment of long-ranged interactions similar to the one which arises in calculation of the dielectric constant of the solvent. Satisfactory calculation of that term will require additional theoretical consideration of those issues. It is contended that the most important step for further development of dielectric models would be a separate assessment of the first-order perturbative term (equivalently the *potential at zero charge*) which vanishes in the dielectric models but is generally nonzero. Parameterization of radii and molecular volumes should then be based on the second-order perturbative term alone. Illustrative initial calculations are presented and discussed.

Key words: Ion pair potentials-of-mean force; Alkali halide; Water

1. Introduction

Potentials describing the average forces on a set of solution constituents can be taken as primitive ingredients in molecular theories of solutions [1]. Biology typically involves aqueous solutions and much of the physics of such solutions requires the treatment of strong electrolytes. Thus,

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the potentials of the average forces among ionic species in aqueous solution are of special relevance to theories of biomolecular structure and dynamics.

Ion pairs form the simplest set of ionic solution constituents for which the potentials of average forces are non-simple. It is quite natural, therefore, that much theoretical and computational effort has been expended in determining those quantities from a molecular basis. Molecularly detailed calculations have been pursued deliberately for the past 15 years [2] and we are nearing the stage of having reliable molecular results for the simplest ion pairs under an important but limited range of solution conditions.

Because of the difficulty of the molecular calculations a simple, physical model of those ionic pair potentials-of-mean-force which reliably captured the important physical features of the known molecular data would be extremely valuable. From this perspective the results of Rashin's application [3] of a dielectric model to the prediction of the potentials of the mean forces between alkali-halide ion pairs in water are especially enticing. Rashin calculated those quantities for a dielectric model and compared the results with integral equation theories for the same quantities. Quite surprisingly, the compared quantities were qualitatively very similar. In particular, the oscillatory features that are often seen in the potentials of the mean forces between atoms or ions in dense liquids appeared in a dielectric model also. The two most significant potential wells were located in about the right place on the basis of a dielectric model and the relative depths of those wells seemed also to be qualitatively correct in the model. A more quantitative analysis was not given.

This paper develops a more current and quantitative analysis. Important new molecular results on ion pair potentials-of-mean-force in water have appeared since Rashin's work. We discuss those recent molecular simulation information which are pertinent to the issue but do not attempt a conventional review. We then implement a dielectric model for the physical circumstances studied by Rashin in order to confirm the essential correctness of those results. There are some technical differences between our model calculation and Rashin's that will check whether the important features of Rashin's results are dependent on minor changes in the model. At that stage we compare the molecular results with those of the model and draw some revised conclusions. We consider how the parameterization of a dielectric model, in particular the size and shape of the molecular cavity, might be modified to bring the predictions of the model more closely into agreement with the molecular results. Finally, we attempt to identify what the qualitative success of a dielectric dielectric model teaches us about how to do more effective molecular calculations and how that lesson helps us in achieving a physically correct parameterization of the model.

2. Molecular results on potentials-of-mean-force between simple ion pairs in water

2.1. Motivation

The explicit molecular modeling of the solvent water in the computation of electrolyte properties gives access to such important quantities as the hydration structure of ions and the dielectric screening of inter-ionic interactions as it depends on solution conditions. In the primitive models the ions are described as rigid spheres that, outside of overlap, interact with the classic long-ranged $1/\epsilon r$ electrostatic interaction screened by the macroscopically measured solvent dielectric constant. In more flexible primitive model descriptions, solvent properties are still simple input parameters, e.g., water molecules might be viewed as forming an impenetrable first hydration layer around the ions whereas bulk water might be modeled as a homogeneous medium with high dielectric constant independent of the actual ionic concentration. But the effects of the molecular "granularity" of the solvent on the potentials-of-mean-force (PMF) between ions require more painstaking approaches. Such effects are expected to be particularly important at short distances. The expected oscillatory behavior of the PMF's is due not only to packing of hydrated ions–perhaps well described in primitive models–

but also due to packing of water molecules that are not explicitly involved in the primitive models.

2.2. Difficulties in the calculation of structural and thermodynamic properties

Compared to the case of simple liquids and primitive model descriptions of electrolytes, reliable theoretical tools for calculating structural and thermodynamic properties of electrolyte models with water included as a molecule are underdeveloped. The well-established methods for atomic liquids are not readily applicable for relatively complex molecular systems. The reference interaction site model (RISM) integral equations, developed to calculate the structure of molecular fluids at an atom–atom correlation level, perform reasonably well for systems with purely repulsive forces. But in the case of aqueous-electrolyte solutions additional difficulties are encountered.

Similarly, the applicability of the computer simulation methodology is limited. One problem that arises is that in low and intermediate concentration electrolyte solutions the number of water molecules exceeds the number of ions by far. This requires the study of very large size systems. The deep electrostatic interaction energies associated with ionic and hydrogen-bonding interactions in addition to the liquid state disorder means that long simulations are necessary to get sufficient statistical accuracy. Moreover, the strong Coulomb interactions also require particular attention because of their long range. However, in primitive model descriptions the implicit high dielectric screening that is appropriate allows the use of less involved methods to compute the Coulomb interactions.

2.3. XRISM integral equation studies of Na–Cl–H_2O electrolytes.

The formulation of Ornstein-Zernike (OZ) type integral equation schemes at the level of atom–atom correlation functions of molecules has been extensively analysed. For reviews see Chandler [4], Cummings and Stell [5], and Monson and Morriss [6]. The reference interaction site model (RISM) is the prototype of these approaches. It adopts an atom–atom Ornstein-Zernike (RISM-OZ) equation that relates total atom–atom correlations $h_{ij}(r)$, atom–atom *direct* correlations $c_{ij}(r)$, and intra-molecular correlations $\omega_{ij}(r)$. This equation defines the $c_{ij}(r)$ in terms of the other quantities that are, in principle, measurable. A second relation, a *closure relation*, is essential to obtaining equations that might be the basis of a numerical solution effort. The discovery of physically motivated, mathematically controlled closures is a serious problem. Well-established closures in the context of Ornstein-Zernike equation theories of atomic liquids have been transfered by analogy to the atom–atom level treatment of molecular liquids. Analogues of the mean spherical approximation, the Percus-Yevick theory, and hypernetted chain (HNC) closure are available. However, applied to the atom–atom level description of molecular liquids, the theoretical justification of all these analogues is more delicate than is the case for atomic liquids. For example, it has been shown that the RISM theory, when viewed from the perspective of graphical cluster expansions series, includes "improper" diagrams. For a discussion, see Chandler, et al. [7], and Monson and Morriss [6]. Therefore, the search for physically motivated, mathematically controlled closures of the RISM-OZ equation is of considerable importance [8].

In the application of the RISM method to polar and ionic systems, additional difficulties arise. For atomic liquids the assumption that the direct correlation functions asymptotically vary like the potential, $c(r) \to -\beta u(r)$ for $r \to \infty$ is well-justified. However, transfered to the atom–atom level for molecular liquids on the basis of the RISM-OZ equation, $c_{ij}(r) \to -\beta u_{ij}(r)$ for $r \to \infty$ results in a seriously wrong dielectric behavior. The dielectric constant assumes an ideal gas value which is too low. Again, the problem may be reduced to finding an appropriate closure to which the asymptotic behavior of $c_{ij}(r)$ is intimately connected.

For special cases such as polar, diatomic molecules, the asymptotic behavior of $c_{ij}(r)$ has been studied carefully [5]. For general molecular structures such an analysis is not currently available. A brute-force method to "improve" the dielectric behavior consists in modifying the k^2 term of the small-k expansion of the atom–atom total correlation functions in Fourier space [9,10] to which the dielectric constant is related. It is clear that this approach contains some arbitrariness and in addition requires *a priori* knowledge about the dielectric behavior. Moreover, these modifications affect the $r \to \infty$ behavior of the atom–atom direct correlation functions requiring corrections, e.g., by simply neglecting the additional terms.

In view of these difficult theoretical issues, the results of practical calculations are enlightening. The RISM method in conjunction with the HNC closure – the XRISM approximation [11] – has been applied to studying aqueous solutions of ions employing interaction site descriptions of water molecules. Pettitt and Rossky [12] analyzed the structure of ion-water and ion-ion correlations at infinite ionic dilution, where the XRISM equations decouple. As a direct manifestation of the wrong dielectric behavior, the infinite dilution ion-ion PMF's behave as $1/\epsilon_{\text{XRISM}}r$ for $r \to \infty$, with ϵ_{XRISM} being approximately 18 instead of the water value of $\epsilon \approx 80$. By subtraction of the $1/\epsilon_{\text{XRISM}}r$ terms and addition of $1/\epsilon r$ terms, Pettitt and Rossky corrected this behavior approximately. In the case of Na^+–Cl^- solutions, the authors observed some remarkable features in the ion-ion PMF's. The $\text{Na}^+ \cdots \text{Cl}^-$ PMF showed a deep contact minimum and a deep, broad solvent-separated minimum. Most interestingly, they also found a very deep contact minimum in the $\text{Cl}^- \cdots \text{Cl}^-$ PMF at about 0.35 nm distance. It is about -1.5 kT deep and followed by a barrier with a PMF value of more than 2.5 kT. The minimum in the $\text{Cl}^- \cdots \text{Cl}^-$ PMF reflects a strong tendency of Cl^- ions to form contact pairs. This astonishing XRISM result has sparked considerable debate. For a discussion see Friedman, et al. [13]. However, recent computer simulation studies [14] have clearly established that this surprising feature of paired anions in the XRISM theory is not correct.

Recently, the XRISM equations for aqueous Na^+–Cl^- solutions were also solved at finite concentration [9], i.e., for ionic concentrations above 0.2 mol/l. (The concentration regime between about 10^{-6} and 0.2 mol/l was observed to be inaccessible to numerical solution. This likely reflects the unphysically weak dielectric screening of the XRISM approximation.) The interaction potentials of Pettitt and Rossky were used, except for a slightly different water model. In view of the experimental decrease of the dielectric constant with increasing salt concentrations, the deficiencies of XRISM due to errors in the description of dielectric screening might become less important under high salt conditions. Indeed, quite reasonable results for the strucure were obtained. However, XRISM predicts strongly paired Cl^- ions under high salt conditions also.

Perkyns and Pettitt studied an XRISM model that was modified in its dielectric behavior [10]. Utilizing a result for the total atom–atom correlation functions h_{ij} by Høye and Stell [15], they modified the small-k behavior of the Fourier transformed solvent atom–atom correlation functions by adding a function $\tilde{\chi}_{ij}(k)$ decaying as $\exp(-\alpha k^2)$ with α an adjustable parameter. Any modification in the total atom–atom correlation functions has its counterpart $\tilde{b}_{ij}(k)$ in the atom–atom direct correlation functions via the RISM-OZ equations. In particular, small-k modifications of the correlation functions affect the long-range behavior of the atom–atom direct correlation functions. To overcome these problems, the authors simply modify the HNC closure relation so that the additional terms are exactly cancelled. In Ref. 10(a), results at 1 mol/l concentration for the $\text{Na}^+ \cdots \text{Cl}^-$ pair correlation function were described using the same model as in Ref. 9. The dielectric constant implicit in their calculation was changed from approximately 18 (the XRISM value) to 78 and they observed a marked diminution of the height of the contact peak. In Ref. 10(b), the authors discuss results for a different interaction site model of aqueous Na^+–Cl^- solutions, again at 1 mol/l concentration. For this model (with ϵ modified to 78.54) they find a very deep contact minimum in the $\text{Na}^+ \cdots \text{Cl}^-$ PMF of approximately -2.6 kT. The $\text{Cl}^- \cdots \text{Cl}^-$ PMF shows a minimum of about -0.7 kT at 0.4 nm distance. Unfortunately, no comparable results for the $Cl^- \cdots Cl^-$ pair correlation had been given in Ref. 10(a). It would be interesting to see the corresponding results of the model of Ref. 10(a) for comparison, in order to disentangle effects of different models and of limitations of the RISM formulation.

Another limitation in the RISM formulation is that intramolecular structure is described only approximately. Thus, some elements of structural consistency between different correlation functions are not obeyed. This unsatisfactory effect is evident in the positions of peaks in the correlation functions of hydrogen with negatively charged sites (water-oxygen and Cl^- ions in aqueous Na^+–Cl^- solutions) and the corresponding results for water–oxygen. For example, the distance between the first peaks of the $H \cdots Cl^-$ and $O \cdots Cl^-$ correlation function significantly exceed the length of the rigid O–H bond. This reflects the difficulty of the RISM scheme with presently used closure relations to correctly transfer the repulsive interaction of the oxygen site with a negatively charged site to the strongly attracted hydrogen site on a rigid water molecule. In the interaction site water models studied extensively by computer simulation, the hydrogen site typically has only a weak or no repulsive shell of its own, but is "protected" inside the van der Waals radius of the oxygen. Such bond constraints violations are also observed in a dielectrically modified XRISM formulation; cf. Fig. 3 of ref. 10(b).

In view of the discussed shortcomings, the XRISM methodology for the calculation of structural and thermodynamic properties of strongly associating, hydrogen bonding liquids such as aqueous electrolytes, is of limited utility. Particular problems are (i) the lack of physically motivated, mathematically controlled closure relations, (ii) the deficiencies in the dielectric screening behavior, so far attacked only by *ad hoc* modifications of the theory; and (iii) the violation of bond constraints in hydrogen bonds, that are essential for describing the hydration of anions and the formation of hydrogen bonds between water molecules correctly. Aside from these arguments, the restricted reliability of presently available XRISM integral equation schemes in describing aqueous electrolytes becomes evident by comparison with extensive computer simulations of two high concentration Na^+–Cl^-–water electrolytes [14]. This comparison clearly shows that XRISM results for ion-ion PMF's should be considered with caution. This now recognized point is clearly of relevance to our reexamination of the comparison presented by Rashin several years earlier.

However, the further development of integral equation schemes describing complex molecular fluids, particularly aqueous solutions, is very important. Many important quantities like solute-solute correlations are not readily accessible with experimental techniques. Computer simulations of aqueous phases are usually very costly with respect to CPU time; and the calculation of thermodynamic quantities is usually subject to very large statistical uncertainties in the case of electrolytes. Integral equation methods such as an improved RISM scheme would open the biologically important low and intermediate ionic concentration regime to the theoretical analysis.

2.4. Computer simulation studies of Na–Cl–H_2O electrolytes.

In a series of computer simulations, two high concentration aqueous sodium-chloride electrolyte systems were analysed, one at room temperature [14(b)], the other at 823 K [14(a)]. In both cases, the SPC model of water was used [16], in conjunction with the parameters of Pettitt and Rossky for the ion-water and ion-ion interaction [12]. The ionic concentration in the room temperature system was 5 mol/l. The high temperature system consisted of 20 mass percent Na^+–Cl^- and had a total mass density of 0.867 g/cm^3, corresponding to an experimentally observed pressure of 2500 bar. We discuss these results particularly rather than review simulation calculations on these problems more broadly for several reasons. These results have appeared very recently, they focused on comparative testing of alternative treatments of long-ranged interactions, and XRISM calculations were performed on the same interaction models. The results should depend on the interaction models used.

The sensitivity of the dependence of the $Cl^- \cdots Cl^-$ and $Na^+ \cdots Na^+$ pair has been observed by Dang, et al. [17].

The results described in the following were obtained with constant energy molecular dynamics simulations of 500 particle systems (416 and 432 water molecules in the room temperature and high temperature simulation, respectively). The standard Verlet integration method was used along with constraints for the rigid water model [18]. A time step of 0.005 ps was employed with the hydrogen masses set to 2 g/mol (heavy water). The electrostatic interactions were treated with Ewald summation [18] using 2×510 k-vectors and a real space damping factor of 5.6/L.

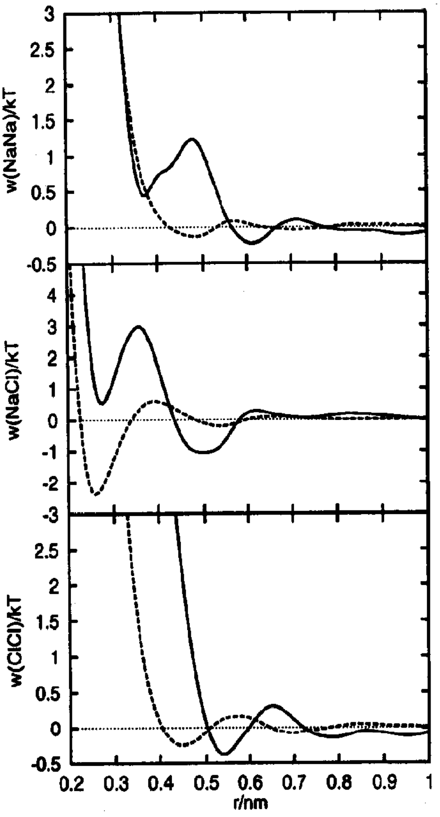

Fig. 1. Potentials-of-mean-force for (top panel) $Na^+ \cdots Na^+$, (middle panel) $Na^+ \cdots Cl^-$, and (lower panel) $Cl^- \cdots Cl^-$ in water as determined from the molecular dynamics calculations of Ref. 14. The solid line in each panel is the result for the room temperature system and the dashed line is the result for the system at $T = 823$ K.

Fig. 1 shows the ion-ion PMF's, calculated as $-kT \log g_{ij}(r)$ for these simulations at finite concentrations of salt. These results are in good agreement with the calculations of Guàrdia, et al., [19] who focused explicitly on infinite dilution conditions by treating only one ion-pair in their simulation volume. Those calculations used the same model for interactions among water (SPC) with the exception that they permitted some internal flexibility of the water molecule structure. We also note that Hummer, et al., [20] have used just the same models and methods to study the concentration dependence of the distribution functions $g_{ij}(r)$ in the range 1 to 5 molar. Our discussions here are consistent with those recent results. As expected, drastic differences between the two thermodynamic states are observed. The high temperature PMF's are generally less structured than the corresponding room temperature curves. This can be understood as a consequence of the comparably weak hydration shell of ions at 823 K, which can easily be disrupted by thermal excitations.

The high temperature $Na^+ \cdots Na^+$ PMF shows very shallow minima at about 0.5 and 0.7 nm distance, whereas the room temperature curve has minima at 0.37 nm (0.5 kT) and at 0.6 nm distance (-0.2 kT), which are clearly separated by a barrier (1.2 kT). Interestingly, in the repulsive region (for distances below 0.37 nm) the two curves are very similar, a behavior that is not found in the case of the $Na^+ \cdots Cl^-$ and $Cl^- \cdots Cl^-$ PMF's. The well-separated minima in the room temperature $Na^+ \cdots Na^+$ PMF can be interpreted as *contact* and *solvent-separated* states. Pairs of positively charged Na^+ ions at small distance can be formed at room temperature, with negatively charged water oxygens mediating the repulsion. However, the *contact* minimum in the $Na^+ \cdots Na^+$ PMF is only weakly populated with a PMF value of 0.5 kT.

We also observe qualitative differences between the PMF's for $Na^+ \cdots Cl^-$ pairs at the two thermodynamic states. At 823 K the contact minimum at 0.26 nm distance is highly populated with a PMF value of -2.35 kT, whereas at room temperature the corresponding PMF value is only 0.56 kT. On the other hand, the room temperature solvent-separated minimum at about 0.5 nm distance is very broad and deep (−1.0 *kT*), in contrast to the shallow minimum in the 823 K curve at 0.53 nm distance. The tendency to form well-separated $Na^+ \cdots Cl^-$ ion pairs at room temperature reflects a high stability of the first hydration shell of the ions. Even large Coulomb energy gains of bringing oppositely charged ions together do not suffice to form a considerable amount of $Na^+ \cdots Cl^-$ pairs in contact.

The shapes of the $Cl^- \cdots Cl^-$ PMF's at room temperature and at 823 K are very similar, with the room temperature curve shifted about 0.1 nm towards larger distances. Both curves show a shallow first minimum (0.54 nm and −0.37 *kT* at room temperature but 0.45 nm and −0.25 *kT* at 823 K) followed by maxima of 0.31 *kT* (room temperature) and 0.16 *kT* (823 K).

A formation of Cl^- pairs in contact is not observed at 823 K, in contradiction to the XRISM prediction [14(a)]. At 823 K, XRISM shows a deep minimum in the $Cl^- \cdots Cl^-$ PMF at approximately 0.36 nm distance with a PMF value of −0.44 *kT*. Even stronger disagreement between the XRISM result and the corresponding simulation data is observed at room temperature. The simulation shows Cl^- ions always well separated. However, the corresponding XRISM curve exhibits a very distinct minimum of almost −1.5 *kT* at 0.34 nm distance [9].

Summarizing the simulation results for ion-ion PMF's at high ionic concentration, at 823 K thermal excitations are able to disrupt the ionic hydration shell. The contact minimum in the $Na^+ \cdots Cl^-$ PMF is well populated. At room temperature Na^+ and Cl^- ions tend to remain independently solvated. They hardly come closer than the diameter of a hydrated ion. Correspondingly, the deepest minima of the PMF's are found at distances of 0.6 nm ($Na^+ \cdots Na^+$), 0.5 nm ($Na^+ \cdots Cl^-$), and 0.54 nm ($Cl^- \cdots Cl^-$). Evidently, the correct description of this behavior is a serious challenge for any theoretical model, since the ion-ion PMF's are the result of a thermal balance of competing strong interactions. All water-water, water-ion and ion-ion interactions give relevant contributions. For instance, severe problems are expected in the case of the $Na^+ \cdots Cl^-$ PMF, which shows a preference for the solvent-separated state, in spite of the huge Coulomb attraction of the two oppositely charged ions. But also the accurate calculation of correlations of like charged ions is far from trivial, as can be seen from the qualitatively and quantitatively wrong results of the XRISM formulation for the $Cl^- \cdots Cl^-$ PMF.

3. Continuum model prediction of the $Na^+ \cdots Cl^-$ potential-of-mean-force in water

Dielectric models can capture gross electrostatic effects with a crude veracity. They can be physical models in the sense that a molecular system, albeit highly idealized, can be identified that would exhibit just the properties ascribed to a dielectric model. In this quality the dielectric models stand in sharp contrast with available integral equation theories. Those integral equation theories offer the potential of fuller incorporation of molecular detail in return for a more tortuous connection to simple physical concepts. They are are also more complicated by their utilization of additional molecular detail. Much of the detail required to implement the molecular calculations is absent in the dielectric models. Thus, Rashin's observation that a dielectric model potential-of-mean-force for alkali-halide ion pairs in water is in good qualitative agreement with the available XRISM results was surprising.

In particular, features of the molecular results which would almost universally be interpreted as due to molecular packing were also predicted by the dielectric model. Since dielectric models depend on empirical parameterization of molecular surfaces, the observed agreement might not seem compelling by itself. However, Rashin's surprising observation raises the possiblity that our understanding of these potentials-of-mean-force can be made more physical and simplified. A confirmation of the principal features of Rashin's result would then focus attention on parameterization and implementation of dielectric models to make the best use of available molecular scale information. Since realistic molecular models are different from the dielectric ones, the dielectric models should be expected to fail when aggressively pushed into more molecular regimes. Even in such cases it can be reasonably hoped that dielectric models would provide a helpfully accurate initial approximation to which molecular scale refinements could be added.

Therefore, we have performed calculations similar to Rashin's for the $Na^+ \cdots Cl^-$ ion pair in water. We solved

$$\nabla \cdot \epsilon(\boldsymbol{r}) \nabla \Phi(\boldsymbol{r}) = -4\pi\rho_f(\boldsymbol{r}), \tag{1}$$

where $\epsilon(\boldsymbol{r})$ is one inside, and the solvent dielectric constant ϵ outside, the bipolar volume depicted in Fig. (2). The free charge $\rho_f(\boldsymbol{r})$ describes δ-function sources of strength $+e$, $(-e)$, at the Na^+, (Cl^-) nucleus. The radii of the solvent exclusion spheres centered on these nuclei were taken from Rashin and Honig [21]: $R_{Na^+} = 0.1680$ nm and $R_{Cl^-} = 0.1937$ nm. The value of the dielectric constant outside the molecular volume was $\epsilon = 77.4$, the measured value of the dielectric constant for water in coexistence with vapor at 301 K. The difference between the model treated here and by Rashin is that in Rashin's case the atom centered spheres are joined by a toroidal surface fragment when the shortest distance between the spherical surfaces is smaller than a van der Waals diameter of a water molecule.

The method of numerical solution was essentially a boundary element approach [22–28] based upon an integral equation formulation of Eq. (1):

$$\epsilon(\boldsymbol{r})G(\boldsymbol{r}, \boldsymbol{r}') = G_0(\boldsymbol{r}, \boldsymbol{r}') + \int_V \nabla'' G_0(\boldsymbol{r}, \boldsymbol{r}'') \cdot \left[\frac{\nabla''\epsilon(\boldsymbol{r}'')}{4\pi\epsilon(\boldsymbol{r}'')}\right] \times \epsilon(\boldsymbol{r}'')G(\boldsymbol{r}'', \boldsymbol{r}')d^3r''. \tag{2}$$

Here $G(\boldsymbol{r}, \boldsymbol{r}')$ is the Green function for the problem, i.e., the electric potential at $\boldsymbol{r}$ due to a unit source at $\boldsymbol{r}'$. $G_0(\boldsymbol{r}, \boldsymbol{r}')$ is the Green function for the $\epsilon(\boldsymbol{r}) = 1$ case. This general equation is correct either for zero boundary data on a surface everywhere distant or for periodic boundary conditions with a system of volume V. The article by Yoon and Lenhoff [26] can be consulted for a statement of the advantages of boundary approaches over alternatives which discretize the three dimensional domain. The present approach was chosen because it is simple to see how the integral equation can be solved by Monte Carlo methods also and that possibility holds some potential for reliable application to much larger systems. In fact, achieving numerical convergence for the solvation free energy on a thermal energy scale is not trivial. The variations of interest here are typically less than 1% of the total solvation free energy of the complex. Similarly accurate results for very much larger systems will provide a computational challenge. The details of the numerical methods used by Rashin are clearly quite different from those used here but those issues are not important for the present discussion. Once this equation is solved the free energy of solvation (excess chemical potential), $\Delta\mu(r)$ which depends on the separation of the sphere centers, is obtained as:

$$\Delta\mu(r) = \tfrac{1}{2}\sum_{i,j} q_i q_j \left[G(r_i, r_j) - G_0(r_i, r_j)\right], \tag{3}$$

where the q_i are the charges associated with $\rho_f(\boldsymbol{r})$. The potential-of-mean-force, $w(r)$, is then composed of this solvation free energy *plus* the bare ion-ion potential energy of interaction. For this latter quantity we used the same function as Rashin did.

The results are shown in Fig. 2. Studies of numerical convergence with respect to the resolution of the sampling of the molecular surface leads us to the conclusion that the curve shown there is accurate to within about 0.3 kT. However, all the features of the model known *a priori* are correctly described in this numerical solution and all qualitative features of the curve are insensitive to further enhancement of that resolution. In particular, the positions and depths of the two wells and the position and height of the barrier are not appreciably changed by changes in the surface density of the boundary sampling by a factor four.

This model result is in good qualitative agreement with that of Rashin except for the height of the free energy barrier between the contact and the outer minima. The barrier is much higher in Rashin's case; that is surely due to the slight differences in definition of the volume of the

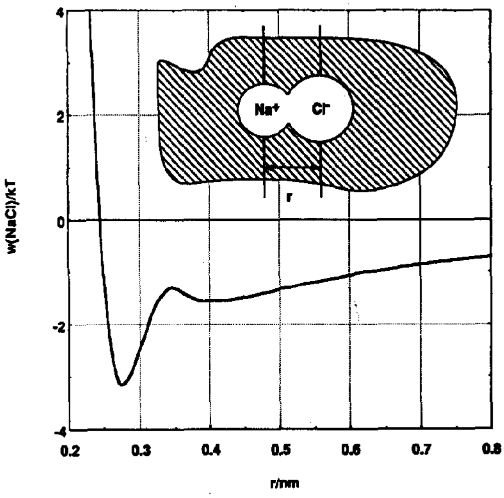

Fig. 2. Potential-of-mean-force for the $Na^+ \cdots Cl^-$ ion pair predicted by a dielectric model for water at its triple point.

ion-pair, particularly the 'neck' between the two atom centered spheres utilized by Rashin but not by us. The molecular volume becomes disconnected within the region of the barrier. The position and depth of the inner-most free energy well is in accurate agreement with Rashin's result. For separations near the contact minimum the neck feature of Rashin's molecular surface is graphically insignificant. The present comparison establishes that it is also insignificant for prediction of the free energy of the contact pair.

It is natural to think that the repulsive portion of this potential-of-mean-force is due principally to van der Waals overlap of the ions. This is not the case for the dielectric model result. Fig. 3 shows the separate contributions, solvation free energy and inter-ionic potential energy, to the potential-of-mean-force. It is clear that the electrostatic solvation, solely, pulls the ions apart for distances larger than about $r \approx 0.23$ nm. The outer minimum probably does not have a general structural explanation. We have found that this minimum can disappear if either the dielectric constant or the radii assumed for the ionic cavities are changed substantially. However, the ions lose stabilizing solvation free energy when they are brought together. The outer minimum is a result of the balancing of solvation stabilization of the separate ions with the bare inter-ionic attraction. This argument clearly does not apply to ions of the same formal charge. In fact, the dielectric model results for those potentials-of-mean-force are qualitatively unlike the results of Fig. (1). For example, the $Cl^- \cdots Cl^-$ pair potential-of-mean-force predicted by the dielectric model is entirely positive. It is strongly repulsive but only after overlap of the separate ionic volumes near $r = 0.39$ nm. At larger distances, that model result is more repulsive than the molecular result of Fig. (1) but the model result conforms accurately to the expected asymptotic form of $q^2/\epsilon r$.

Although the detail obtained from the prediction of the dielectric model is surprising, it is not in accurate agreement with the molecular results discussed in the previous section. Compare Fig. (2) with the middle panel of Fig. (1). The contact well is much too deep relative to the asymptote in the dielectric model. One way to think about the disagreement is the following: The radii which are adopted here for definition of the molecular volume of the ion pair are ones which produce

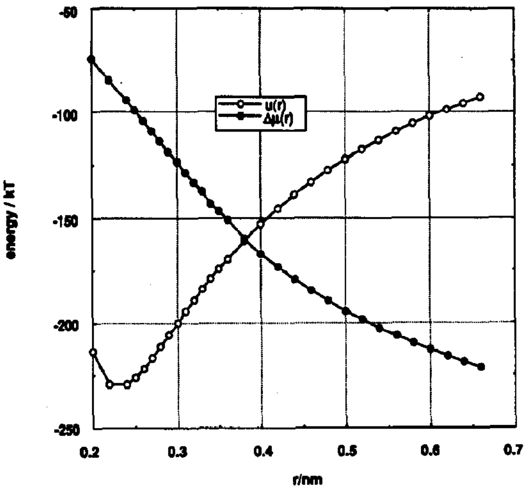

Fig. 3. Separate contributions to the potential-of-mean-force of Fig. (2). The solvation free energy of the ion pair is $\Delta\mu(r)$ and the bare inter-ionic interaction potential energy is $u(r)$.

reasonable values for the solvation free energies of the separated ions. But if one set of radii must be used for all separations r then the way to make the contact well less deep relative to the asymptote is to lower the asymptote by increasing the stabilization of the widely separated ions, i.e., to *decrease* the radii used. But that doesn't seem reasonable. Alternatively, we could adjust the radii for each ion pair separation–increasing the radii as the inter-ionic separation decreases–to get the correct solvation free energy. Much of the utility of the model would then be lost. These comments highlight the fact that the ionic radii are non-trivial parameters of the dielectric model and this parameterization is best considered from the perspective of molecular theory.

In summary, we conclude that the model which produces the result of Fig. 2 fails to reproduce the molecular $Na^+ \cdots Cl^-$ potential-of-mean-force in water, in the absence of further adjustments or theoretical refinements. The most significant failure is in the depth of the contact minimum, or equivalently the free energy of the contact pair relative to the separated ions. Since the present calculation and Rashin's accurately agree in the neighborhood of that contact minimum this most significant error is not due to differences between the two calculations in definition of the molecular surface. Section 4 considers some further steps for the molecular theory which offer some potential for improvement of the present dielectric model approach.

4. What can we learn from comparison of molecular with continuum model results?

On the basis of numerous calculations [29,30] in addition to the results presented here, we conclude that dielectric models provide a physical description of the solvation of charged and polar species in solution but with great crudity. Here we address the question of what we should learn from these comparisons and how we can take advantage of those lessons to obtain more reliable and efficient theoretical predictions.

As a focus for this discussion we use the prediction of the dielectric model for the solvation free energy of a spherical ion:

$$\Delta\mu = -\frac{q^2}{2R}\frac{\epsilon - 1}{\epsilon}. \qquad (4)$$

This is the classic Born model. Here the ion has charge q and a radius value of R is adopted. q and ϵ are parameters that are scarely ever subject to adjustment. This is not true of R, however. A good value for this parameter is not immediately evident. This can be recognized by considering that the solvation free energy of the ion can be determined exactly if the medium is a weakly polar, dilute gas. In that case, R is the distance within which no polarization is ever observed, i.e., a distance of closest approach. But this is not the value of R which works for the ion in liquid water. Similarly, if we consider solvation properties of a particular solute obtained for two different solvents with equal dielectric constants, say methanol and acetonitrile, we must expect that the best molecular volumes will be somewhat different in the two cases. This point was made already by Rashin and Honig [21]. However, it is important to emphasize the obvious and general conclusion that good values of R depend on the solution conditions and are not a property of the ion alone. A corollary of this conclusion is that evaluation of thermodynamic derivatives of the Born model $\Delta\mu$ should account also for variations of R with solution conditions. That R must be considered temperature dependent for the calculation of solvation enthalpies has been pointed-out recently by Roux, et al. [31].

However once a reasonable value of R is established experience suggests that the dielectric model can be helpfully accurate. The calculation of Jayaram, et al. [32], gives contemporary support to this idea. The conclusions we identify on this basis are: (i) that the dependence of the solvation free energy on q^2 is satisfactory; (ii) that the dependence on the solvent dielectric constant ϵ is a simple incorporation of rather sophisticated information about the solvent and a better theory should still take advantage of exactly known properties of the solvent; and (iii) that the most pressing requirement for molecular theory is to treat the molecular scale structure which is historically subsumed in the parameter R. The first two points here lead us directly to second order perturbation theory for the excess chemical potential. The required formula is

$$\Delta\mu \approx \Delta\mu_0 + \left\langle \sum_j \varphi(j) \right\rangle_0 - \frac{\beta}{2} \left\langle \left(\sum_j \varphi(j) - \left\langle \sum_k \varphi(k) \right\rangle_0 \right)^2 \right\rangle_0 . \qquad (5)$$

This approximation has been discussed by Levy, et al [33]. It accounts only for the effects of electrostatic perturbations $\varphi(j)$ in the interactions between an identified solute molecule, e.g., the 0th solute molecule, and the jth solvent molecule; $\Delta\mu_0$ is the excess chemical potential of the designated molecule in the absence of such interactions. The brackets $\langle \cdots \rangle_0$ indicate the average value without the perturbations. It must be remembered that we have some flexibility in definition of $\varphi(j)$ at short range and that such a definition can substantially affect the convergence of a perturbative theory. This idea underlies the WCA approach to the theory of simple liquids.

This formula has the properties sought. First, the computed free energy will be a general quadratic function of partial charges if those quantites are used to describe the electrical charge distribution of the solute. The perturbative approach will supply contributions independent of, and linear in, those charges; those contributions are generally present though absent in the dielectric model. Second, the correlation functions of the solvent, including those correlations which establish the dielectric constant, are exploited directly on the basis of molecular calculations or information not further modeled or approximated. Finally, the solute-solvent molecular structures are treated directly on a molecular level.

Because the first-order term of Eq. (5) stands out as a difference between the molecular and the dielectric approach, the importance of that contribution deserves emphasis. $\Delta\mu$ will include a contribution linear in q which is associated with the electrostatic potential of the phase and is of interest to questions of the electrostatic potential difference between coexisting phases [34]. That contribution is not directly relevant to the local solvation contributions of interest for this discussion. Here we lump that contribution together with $\Delta\mu_0$. Beyond that contribution, the first-order perturbation term is still non-trivial and generally non-vanishing. To the extent that this term is significant in particular cases, merely adjusting radii to bring dielectric and molecular calculations into agreement is physically misleading. The first-order contribution in the molecular approximation serves to discriminate between positive and negative ions of the same physical size; adjusting sizes to accomplish that discrimination in such cases would confuse the origin of that effect. It is possible that the first-order contribution is principally involved in the disagreement noted by Wilson and Pohorille [35] between dielectric model and simulation results for the interaction of monovalent ions with the water liquid-vapor interface. The difference between positive and negative ions of similar size seemed to be basic to their observations.

Although it is quite possible for the first-order term to contribute significantly to the discrepancy between the dielectric model and molecular results for the $Na^+ \cdots Cl^-$ ion pair potential-of-mean-force, that first-order term is even more likely to make an important contribution for the like-ion pair cases $Na^+ \cdots Na^+$ and $Cl^- \cdots Cl^-$. For those cases the current predictions of dielectric models are less satisfactory yet than for the unlike-ion pair $Na^+ \cdots Cl^-$. It would seem natural to ascertain the contribution of the linear term before considering effects which might be ascribed to perturbative contributions beyond second-order. In going beyond second-order, the induced electrostatic interaction with the solvent is a nonlinear function of the solute charges. It is natural to think of these higher-order contributions in terms of the concepts of field-strength-dependent dielectric constant (saturation) and a field-strength-dependent local density (electrostriction). The molecular theory Eq. (5) properly incorporates effects that might be ascribed to a 'local dielectric constant' without addressing broader issues. It will be important to investigate higher order corrections to the simple theory of Eq. (5). In this context, Rashin [3] has suggested that contraction of cavity radii about the incipient double charged ionic solute $Cl^- \cdots Cl^-$, when that pair adopts solvent-excluding configurations, might lead to a minimum in the potential of mean force. Since a minimum is observed in the molecular results for the $Cl^- \cdots Cl^-$ pair potential of mean force only for solvent-separated configurations (see Fig. 1), that argument is not considered further here.

Roux et al. [31] have presented an analysis starting with the XRISM approximation which gives a different perspective on the Born approximation for the solvation free energy of a spherical ion. They helpfully focused particular attention on ions of the same physical size but of opposite charge, i.e Cl^- and the hypothetical 'Cl^+.' That previous analysis did not identify the contribution linear in the charges that the more general discussion here fixes as the primal neglect of the dielectric models.

The calculation of the perturbative contribution of Eq. (5) should be feasible. Such calculations would require simulation of solutions without solute-solvent electrostatic forces for one solute molecule. The mean electrostatic solute-solvent interaction energy and the mean square fluctuation of that quantity must be measured. As might be guessed by the correspondence with Eq. (4) the fluctuation term raises computational issues similar to those that arise in calculation of the dielectric constant of the solvent, namely the result can be sensitive to treatment of long-ranged interactions. A satisfactory calculation of this term will require further theoretical consideration of those issues than we give here. Where the dielectric models are physically correct, the proposed calculation should provide an accurate theory for the solvation free energy because it has a similar physical origin as the dielectric models but augments those models with the proper molecular details.

To the extent that the perturbative approach is valid, it can be worthwhile to reexpress it in alternative ways which are physically equivalent. Indeed, Eq. (5) deserves a fuller theoretical analysis to be more useful for parametrization of dielectric models. We expect to pursue that theoretical analysis at a later date.

The simulation calculations of Jarayam et al., [32] designed to test the Born model of solvation for spherical ions, cast some light on the operation of these formulae. Those calculations gave clear evidence of structural saturation – in the sense discussed by Stell [36] – by the time the charge on the ion was $q \approx e$. See Fig. 3 of Ref. (32) which showed that the change in solvation free energy with respect to charge of the ion was approximately linear for small and for large q but the intercepts and slopes were different in the two regimes. The cross-over between the two regimes was near $q \approx e$. This was just the region where separate structural data began to show saturation; see Fig. (4a) of that work.

On the basis of those results we conclude that the perturbation theory should be satisfactory for simple monovalent inorganic ions. For polar molecules, charge concentrations which exceed $q \approx e$ per atom are unusual; hydrogen-bonding interactions are essentially electrostatic and might offer exceptions to this hypothesis because those charges can be well exposed. Aside from such separate cases, the perturbative approach is expected to be helpfully accurate for solvation of polar solutes. The description of the solvation of multivalent inorganic ions on the basis of this perturbative approach would be expected to incur more substantial inaccuracies. Complex ions of higher formal charge such as CO_3^{2+} might also require additional attention. In both of the latter two cases the chemical nature of the near-neighbor interactions is typically of paramount importance and such interactions have not been considered at all here.

5. Illustrative example

We note again that the calculations called-for by Eq. (5) treat a solution with one solute for which solute-solvent electrostatic interaction are extinguished. It is possible to use a second-order perturbation theory to calculation $\Delta\mu_0$ on the basis of simulation results for the fully coupled solute and that inverse approach is likely to be a helpful technical convenience. The reason for that convenience is that one utility of these theoretical ideas would be the ability to calculate free energies on the basis of a reliable physical theory without intrusive computational devices that are typical of more general calculations of free energies, e.g., umbrellas and stratifiers. The inverse formula will be accurate to the extent that Eq. (5) is quantitatively accurate. In either the direct approach of Eq. (5) or the inverse approach $\Delta\mu_0$ must be separately provided. To present an illustration here, we have adopted the direct approach of Eq. (5) and carried out short molecular dynamics simulations (MD) on a series of systems consisting of 215 water (TIP3P) molecules and one neutral van der Waals solute, denoted by 'M,' with diameters of 0.20, 0.30, 0.325, 0.350, 0.373, 0.40, and 0.45 nm. The van der Waals minimum energy depth for the solute, ϵ, was kept at 0.294 Kcal/mol. Solute-solute interaction parameters are obtained from the relations $A^2_{MM} = 4\epsilon\sigma^{12}$, $C^2_{MM} = 4\epsilon\sigma^6$, the solute-solvent interactions from $A_{OM} = A_{OO}A_{MM}$, – with 'O' indicating the solvent oxygen atom – and $C_{OM} = C_{OO}C_{MM}$, where A_{OO} and C_{OO} are defined by the TIP3P model [37]. The systems were contained in a cubic box of width $L = 1.868$ nm. Constant energy and volume MD simulations were done on each system with average temperatures of 292 ($\pm$10 K) and a water density of 0.99 g/cm^3. Electrostatic forces were evaluated with a generalized reaction field (GRF) [38] and with Ewald summation (ES) [18] approaches. For the GRF all interactions were truncated at $R_c = 0.75$ nm, and the reaction field dielectric constant was taken to be 65.0. For the Ewald sum, 2×510 k-vectors were used in the reciprocal space part of the potential, the screening constant was $5.5/L$, direct interactions were truncated at $L/2$, and the reaction field dielectric constant was 65.0 again. The average potential at the center of the van der Waals solute atom was calculated using the GRF, the Ewald potential, and from integrals over the obtained solute-water pair correlation functions using the bare Coulomb and the GRF potentials. Calculations with the GRF were extended for 125 ps while those with the ES were extended for 50 ps. In order to assess the size dependence of our results, one 50 ps simulation of a system containing 511 waters and one solute atom ($\sigma = 0.373$ nm), using the ES, was done. The box size for this system is 2.484 nm. Unless otherwise indicated, the reported average potentials were calculated with the GRF.

An important route for improvement of the dielectric models is to obtain a separate assessment of the first-order perturbative term and then establish good values for the cavity radii on the basis of the second order term. Fig. 4 shows the dependence of the average electrostatic energy of interaction of the solute and how it depends on solute size. The indicated error bars are $\pm$ one estimated standard deviation. Within these uncertainties a trend with the solute size cannot be confidently established. However, this contribution is positive and substantial in magnitude. The fact that the average potential at the center of the uncharged solute atom is positive has been verified for both the Ewald and the GRF models. These results can be understood in terms of the structure of water near the solute. Fig. 5 shows the distribution functions describing the average radial disposition of the solvent charge about the solute obtained with the Ewald (215 water + solute) model. The first peak of the solute-hydrogen (M-H) rdf is broader than the peak for the

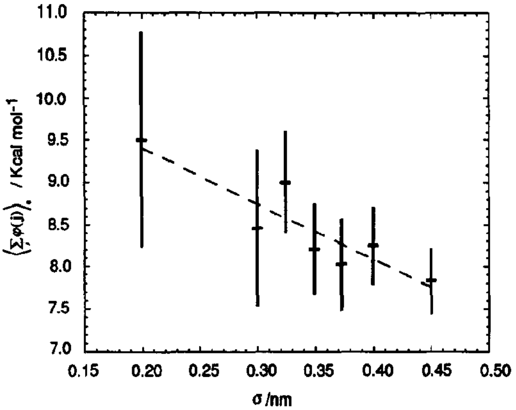

Fig. 4. The average electrostatic potential of the solvent water at the center of spherical van der Waals solute as a function of size of the solute. The error bars indicating one standard deviation were estimated by block averaging over 10 ps segments of the trajectories.

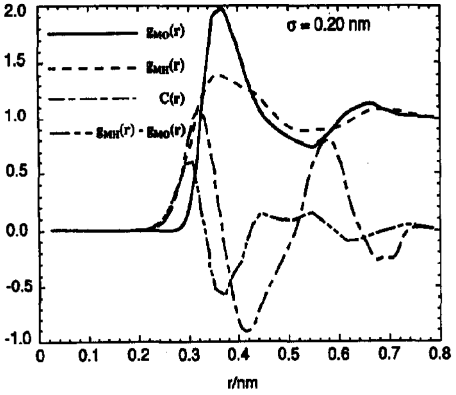

Fig. 5. Radial distribution of solvent (water) atoms from the center of a spherical van der Waals solute with diameter 0.2 nm. The solid curve is the solute-oxygen radial distribution function $g_{MO}(r)$; the dashed curve is the solute-hydrogen radial distribution function $g_{MH}(r)$; the dash-dot curve shows the integrated charge, $C(r)$ of Eq. (6), enclosed in a ball of the specified radius; the dash-dot-dot curve plots the difference function $g_{MH}(r) - g_{MO}(r)$.

solute-oxygen peak, which is located at about the same distance. As a result there is a net positive charge density near the solute. Also shown in Fig. (5) are: the charge density around the solute, defined by $q(r) = 2q_H[g_{MH}(r) - g_{MO}(r)]$ and the integrated charge density,

$$C(R) = 4\pi\int_0^R [g_{MH}(r) - g_{MO}(r)] r^2 \, dr, \qquad (6)$$

as it depends on the radius, R, of included solvent charges from the spherical solute. Fig. 6 shows the contributions to the Coulomb and GRF potentials at the center of the solute atom arising from solvent molecules. This function is obtained by

$$V(R) = 4\pi(2qq_H)\int_0^R r^2 u(r) q(r) \, dr. \qquad (7)$$

Here $u(r) = 1/r$ for the Coulomb potential and

$$u(r) = u_{GRF}(r) = \frac{1}{r}\left(1 - \frac{r}{R_c}\right)^4 \times \left(1 + \frac{8r}{5R_c} + \frac{2r^2}{5R_c^2}\right)\Theta(R_c - r), \qquad (8)$$

with $\Theta(R_c - r)$ the Heaviside step function, for the GRF. Notice that the GRF rapidly converges to the average value, while contributions to the bare Coulomb potential, $1/r$, oscillate with increasing R around the average value even at large distance from the solute. As a result we believe that averages over the bare Coulomb potential in finite size boxes will be sensitive to the system size and simulation parameters.

The average value of the potential obtained by the Ewald sum for two system sizes (215 and 511 water molecules) are shown by the cross and triangle labels in Fig. (6). A positive average potential energy implies that the solvation of a negative ion is lower (more favorable) than the solvation of a positive ion of the same physical size. The radii recommended by Rashin and Honig [21] for the isoelectronic K^+ and Cl^- ions are 0.2172 and 0.1937 nm, respectively. Within

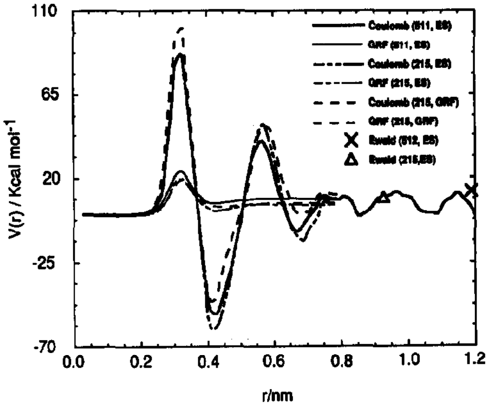

Fig. 6. Electrostatic potential in energy units at the center of a neutral solute atom showing dependence on methods of calculation and system size. The solute is a Lennard-Jones atom with $\sigma = 0.373$ nm as discussed in the text. The designation 'Coulomb' (heavy lines) or 'GRF' (light lines) indicate how the electrostatic potential at the solute was calculated according to Eqs. (7) and (8). In parentheses is given the number of water molecules in the system studied, either 511 or 215, and the method of treatment of the long-ranged electrostatic interactions between water molecules, either Ewald summation (ES) or generalized reaction field (GRF). The cross (plotted at r = 0.9 nm) and triangle (at $r = 1.2$ nm) are the average Ewald potentials (12.8 ± 1.8 and 9.8 ± 1.7 Kcal/mol for the $N = 215$ and $N = 511$ systems, respectively) obtained during the simulations. The corresponding values obtained with GRF are plotted in Fig. (4).

the Born picture, the physical size of the K^+ ion should be slightly smaller than that of the Cl^- ion. Thus, these recommended empirical radii are consistent with our calculation of a *positive* potential at zero charge. This relative ordering of recommended radii is observed for all isoelectronic (alkali metal ion, halide ion) pairs [21]. The present explanation of the ordering of empirical radii for isoelectronic ions is quite different from one of Rashin and Honig [21] which invokes quantum effects and suggests "the electron cloud of the anion is unable to significantly penetrate the empty valence orbital of the cation." [21] The present explanation is consistent with but distinct from the intuitive explanation of Latimer, et al., [39] that anion radii are smaller than isoelectronic cation radii "since the negative ions will have the hydrogens directed in, ...". The present explanation uses quantitative information on the disposition of the water molecules observed about a modelled *neutral* atom of the same physical size. The inference of a *positive* potential at zero charge on the basis of the observed ordering of empirical radii of isoelectronic alkali and halide ions appears to be new.

The evaluation of the second term in the perturbation scheme in Eq. (5) is expected to be sensitive to the modeling of the solvent, both to the assumed molecular structures and forces, and to the treatment of long-ranged (electrostatic) interactions. An important point to be considered is the contribution of electrostatic self-energy terms to the total energy of the system. In adding a charged particle to the system, a constant self-energy contribution proportional to q^2 is added to the energy differences between the charged and uncharged systems. However, different schemes for modeling the long-ranged electrostatic interactions imply different self-energy contributions, even though the resulting energies are the same. It is natural to group these terms together with the fluctuation, $\langle(\Sigma_j\varphi(j) - \langle\Sigma_k\varphi(k)\rangle_0)^2\rangle_0$, because they are both proportional to q^2. As a result, it is expected that the variances in the potential will differ from one approach to another, but when the self-energy terms are correctly included, all models should give similar results for terms proportional to q^2.

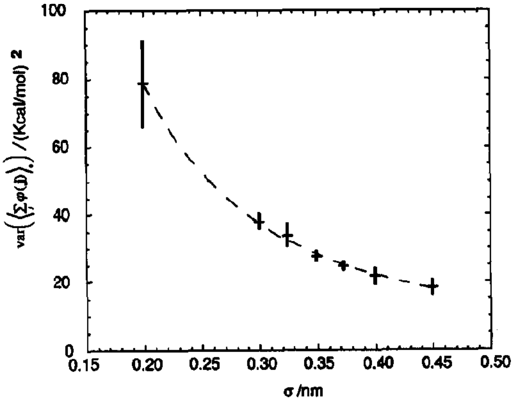

Fig. 7. Mean square fluctuations of the potential at the center of the van der Waals solute as a function of VdW diameters for a set of simulations with N = 215 waters using the GRF approach.

These points deserve more specific theoretical study and will be discussed elsewhere. Fig. 7 shows the dependence of the mean square fluctuations of the potential energy as a function of the size of the solute in our calculations – without the self-energy terms in the GRF model.

Finally, we inquire more specifically about the accuracy of the perturbative approach. In principle, we could calculate succeeding terms in the perturbation series. In practice, such an approach will not avail us here. However, the cumulant expansion to second order in β

$$\begin{aligned}\exp[-\beta(\Delta\mu - \Delta\mu_0)] &= \langle\exp(-\beta[U(q=1) - U(q=0)])\rangle_0 \\ &\sim \exp\left[-\beta\left\langle\sum_j\varphi(j)\right\rangle_0 + \tfrac{1}{2}\beta^2\left\langle\left(\sum_j\varphi(j) - \left\langle\sum_k\varphi(k)\right\rangle_0\right)^2\right\rangle_0\right], \qquad (9)\end{aligned}$$

is exact for a Gaussian distribution of the variable $\Sigma_j\varphi(j)$. We can verify that the perturbation approach is sensible by noting the validity of a Gaussian distribution of the $\Sigma_j\varphi(j)$ when observed in the system for which no solute-solvent electrostatic interactions are expressed. Fig. 8 shows distributions of that variable observed for large (0.373 nm) and small (0.20 nm) solutes con-

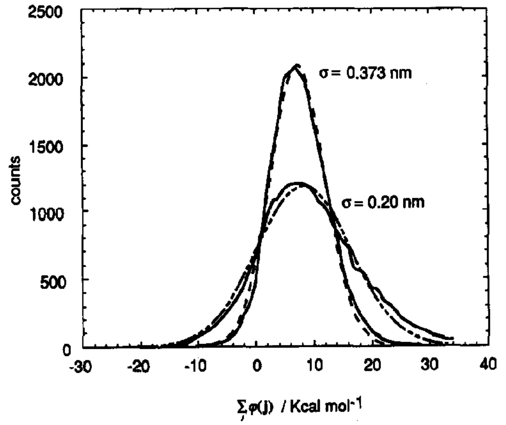

Fig. 8. Distributions of the observed solvent electrostatic potential $\Sigma_j \varphi(j)$ at the center of the van der Waals solute for different size solutes considered. The dashed curves are gaussian distributions fitted to the observed data.

sidered and, in addition, Gaussian model distributions fitted to the observations. The detailed correctness of the perturbation theory will be sensitive to the Gaussian character of these distributions *in the wings* of the distributions and those characteristics are not tested very critically here. However, the agreement with the Gaussian model is satisfactory in the sense that any differences are unlikely to be statistically significant on the basis of the data.

6. Conclusions

This work has confirmed that the surprising qualitative features of Rashin's dielectric model calculations of alkali-halide potentials-of-mean-force in water are correct results of the model. However, the molecular information to which he compared his results were not of sufficient accuracy to conclude that the dielectric model gave a valid description of the free energies of inter-ionic interactions on a thermal scale. Thus, the dielectric model results, although surprising and physical, are not accurate descriptions of the inter-ionic potentials-of-mean-force for alkali-halide/water solution as those quantities are presently known. Other results suggest that a dielectric model can be helpfully accurate on a chemical energy scale. But the accuracy of free energies to thermal levels, i.e., to better than kT for molecular scale rearrangements, has not been broadly tested. It must be emphasized that such tests have been limited by the lack of accurate molecular results as standards for comparison. One exception is the work of Wilson and Pohorille [34] which studied the interaction of monovalent ions with the water liquid-vapor interface. Because of the structural subtlety of those problems they are likely to remain difficult challenges for physical, molecular thermodynamic models.

The extant favorable predictions of dielectric models highlight the most crucial limitation for their application: the definition of molecular volumes or cavity radii. The dielectric model is a modelistic implementation of second-order perturbation theory for the excess chemical potential of the solute. Thus the straightforward theoretical procedure for the study of how that molecular volume should be defined can be based upon thermodynamic perturbation theory evaluated through second-order. The first-order term in that perturbation theory, or equivalently the potential at zero charge, vanishes in the dielectric models but is generally nonzero. Thus an assessment of that first-order contribution is the most important step for further development of dielectric models – of more immediate concern than higher-order perturbative contributions. The *positive* value of this potential at zero charge computed for atomic solutes in water gives a very basic explanation of the observation that empirical radii for halide ions are slightly smaller than the empirical radii for isoelectronic alkali metal ions. With knowledge of this first-order term, parameterization of radii and molecular volumes should then be based of the second-order perturbative term alone.

The second-order perturbative theory can be expressed compactly and is feasible to compute. This fluctuation term raises computational issues similar to those that arises in calculation of the dielectric constant of the solvent regarding treatment of long-ranged interactions. Satisfactory calculation of that term will require additional theoretical consideration of those issues. To the extent that the dielectric approach is reasonable, second-order thermodynamic perturbation theory for the excess chemical potential of the solute, implemented on a molecular basis, should provide a simple and accurate theory of solvation thermodynamics associated with electrostatic interactions.

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Discussion to the paper by L.R. Pratt G. Hummer and A.E. Garcia

Comments

By A. Rashin

It is very gratifying for us, as developers and practitioners of the continuum approach, to see attempts towards rationalization of its apparent success in terms of molecular theories. I completely agree with the thrust of your paper towards providing insights from molecular theories regarding ways to improve the continuum approach. This, however, requires an adequate translation of one language (continuum) to the other (molecular) and vice versa.

One of major faults you seem to find with the continuum approach is that it does not have a term linear in charge that accounts for asymmetry in ion-water interactions in the molecular approach that you advocate. You write "The first-order contribution in the molecular approximations serves to discriminate between positive and negative *ions of the same physical size*; adjusting sizes to accomplish that discrimination in such cases would confuse the origin of that effect". I would claim that "physical size" of an ion is a useful fiction too often treated as reality. Ionic radii are just a useful fiction to provide an additive scheme describing internuclear distances in crystals. There were other measures of the ion size suggested. One of them [1] defines ion radius by the distance from the ion to the minimum in the electron density in the ionic crystal. There are many other definitions (most of them providing additive radii) based on different physical considerations (e.g., see ref. [20] of our paper listed as ref [2] below). In ref. [2] we defined ionic cavity radius based on physical considerations relevant to the problem of polarization of the environment of the ion (asymmetry of the electron density distributions). It seems to be closer to the physical reality than a point dipole in a hard sphere. In reality any dipolar molecule has asymmetry of its charge distribution. Why this reality should not be used in defining asymmetry of cavity sizes for ions with similar ionic radii assigned on the basis of considerations quite irrelevant to the problem of the medium polarization?

The only clear repudiation of our definition, that I can see, may come from the case where there is no real asymmetry in the electron density distribution of solvent molecules, but for which molecular theory will still predict asymmetry between hydration of ions of opposite signs. This could be correct for a solvent of spherically symmetric nonpolar molecules, e.g., liquid argon. However, in such a solvent any electrostatic hydration energy would result from molecular simulations only as a result of polarization of argon molecules. I doubt that any results of this sort are available because integral equation techniques do not handle polarizabilities, and neither do most MM, MC or MD programs. As I understood from our conversation you would not expect a term linear in ionic charge to appear in your formulae for such a solvent. I would appreciate a definitive answer or anything closest to it that you could offer.

Otherwise, I will be very happy if you identified real shortcomings of the continuum approach and found ways to fix them on the basis of information from molecular theories.

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Responses by L.R. Pratt, G. Hummer and A. Garciá to Comments

To A. Rashin

The term arising in perturbation theory that is linear in charge is due to asymmetry in the short-ranged interactions between the solute and the solvent. Thus, we would not expect this linear term to be dominating in cases where the solute–solvent short ranged interactions are about as non-asymmetric as they can be, e.g., the hypothetical case of atomic solute ions in a simple liquid solvent such as liquid argon.

The concept of the physical size of an ion deserves some definition. For our discussion of the importance of the linear term in perturbation theory, we need more specifically a definition which establishes when two solutes have the same physical size. This is an easy conceptual step: two solutes have the same physical size if they experience the same short-ranged interaction with the solvent. We feel that this definition is sufficient for the discussion in our paper. Clearly, an operational definition of physical size of real solutes in water is more difficult and likely to be somewhat arbitrary, as is the definition of a linear scale of physical size.