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Integral equation approaches to structure and thermodynamics of aqueous salt solutions

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Abstract

Results for free energy, entropy, enthalpy and internal energy of solvation for monovalent ions in water have been studied by comparing DRISM theory results to those of RISM and ARISM theories. The greatly improved dielectric behavior in the DRISM case enabled the examination of realistically modeled salts at finite concentrations. The link between solvent structure and the entropy of solvent co-spheres was examined. Finally comparison with the Born free energy equation shows its virtues and flaws due to ignoring cavity formation and asymmetric solvation terms which together always contribute significantly to the free energy of hydration of ions.

Key words: Thermodynamics; Aqueous salt solutions; DRISM theory

1. Introduction

The statistical mechanics and thermodynamics of salt solutions has advanced well beyond the early work of MacMillan and Mayer [1], and Kirkwood and Buff [2], yet an accurate theory applicable to the kinds of biological systems now being examined by molecular dynamics simulations has remained illusive. Despite recent increases in computational speed and availability, there are problems which will remain computationally intractable, even using modern simulation approaches, for some time to come. One general type of system which would benefit greatly by the development of statistical theory is that of biological molecules in physiological (low concentration) salt water solution. An absolute prerequisite to such work is a useful theory of the salt water environment itself. Our recent extension of the reference interaction site model (RISM) [3] theory, which removes the troublesome inherent dielectric inconsistency, is a promising approach at present [4,5].

The main purpose of this paper is twofold. First, we wish to present thermodynamic and structural quantities calculated by the dielectrically consistent RISM (DRISM) theory [4,5] and compare with the results from its predecessors. We wish to examine, in particular, solvation thermodynamical quantities that will prove valuable in further extensions of the theory to more complicated systems. Second, we wish to look at the link between structure and thermodynamics, in particular solvation entropy, in the context of

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some of the older ideas of solvent co-spheres around ions [6,7], and the concepts of structure-making and structure-breaking [8,9].

The remainder of this paper is divided as follows. In section 2 we summarize the DRISM theory and its predecessors as well as the theoretical routes used to retrieve thermodynamic and structural information. In section 3 we compare DRISM results to those of other theories, examine the link between solvent structure and entropy, and finally comment on Born solvation thermodynamics. Section 4 contains a summary and conclusions.

2. Theory

It is our main purpose here to compare the DRISM theory to those previous theories which are most closely related. The DRISM theory has been presented in detail elsewhere [4,5] and need only be summarized here.

Interaction site model (ISM) theories are used to calculate radial distribution functions, $g_{ij}(r)$, which give the probability density of finding site or atom i on one molecule at a distance r from site or atom j on another molecule (possibly of the same species). The distribution functions are sought because, in principle, they can be used to calculate all equilibrium thermodynamic properties of the system while simultaneously yielding a structural perspective. Models for molecules are usually chosen with atom based sites and are defined by the pair potential between sites. Here we choose the common Coulomb plus Lennard-Jones form

$$u_{ij}(r) = \frac{q_i q_j}{r} + 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r}\right)^{12} - \left(\frac{\sigma_{ij}}{r}\right)^{6}\right], \qquad (1)$$

where σ_{ij} and ϵ_{ij} are the usual Lennard-Jones diameter and well depth parameters.

Distribution functions are calculated by simultaneously solving a set of two equations which relate the total correlation functions, $h_{ij}(r) = g_{ij}(r) - 1$, to the direct correlation functions $c_{ij}(r)$. The direct correlation functions can be thought of as defined by one of a related set of site-site Ornstein-Zernike integral equations. The RISM theory can be written as [3]

$$\boldsymbol{\rho}\tilde{\mathbf{h}}\boldsymbol{\rho} = \tilde{\boldsymbol{\omega}}\tilde{\mathbf{c}}\tilde{\boldsymbol{\omega}} + \tilde{\boldsymbol{\omega}}\tilde{\mathbf{c}}\boldsymbol{\rho}\tilde{\mathbf{h}}\boldsymbol{\rho}, \qquad (2)$$

where $\tilde{\mathbf{h}}$ is a matrix whose (i, j)th element is the function $\tilde{h}_{ij}(k)$, which is the Fourier transform of the corresponding total correlation function

$$\tilde{h}_{ij}(k) = 4\pi\int_0^\infty r^2 h_{ij}(r)\frac{\sin(kr)}{kr}\,\mathrm{d}r. \qquad (3)$$

The matrix $\tilde{\mathbf{c}}$ is defined in a similar way. The matrix $\tilde{\boldsymbol{\omega}}$, representing intramolecular correlations, has elements $\tilde{\omega}_{ij}(k) = \rho_i j_0(kd_{ij})$, for rigid molecules, where d_{ij} is the (positive, fixed) distance between site i and site j within the same molecule,and when $d_{ij} = 0$, $\tilde{\omega}_{ij}(k) = \rho_i$. For mixtures, when sites i and j are on different species, $\tilde{\omega}_{ij}(k) = 0$. The matrix $\tilde{\boldsymbol{\rho}}$ is a diagonal matrix with the (i, i)th element being the molecular number density of the species in which site i is located.

The second equation, known as a closure, relates $c_{ij}(r)$ and $h_{ij}(r)$ in a mathematically independent way. For this work we shall use the HNC equation exclusively,

$$c_{ij}(r) = \exp\left[-\beta u_{ij}(r) + t_{ij}(r)\right] - 1 - t_{ij}(r), \qquad (4)$$

where $t_{ij}(r) = h_{ij}(r) - c_{ij}(r)$, and $\beta = 1/k_B T$ with k_B the Boltzmann constant.

Eqs. (2) and (4), when solved together, give distribution functions which have good qualitative behavior yet several well known inadequacies [10]. In the examination of electrolyte solutions, the incorrect dielectric constant, ϵ, which they predict is a problem which must be addressed.

What follows is a summary of the pertinent sections of ref. [5], and the dielectric constants calculated for the various theories and systems discussed are given in Table 1. Dielectric constants can be derived analytically from ISM theories by considering the second moment summation operator [5], $\Sigma^{(2)}$, which extracts the contracted second moment of a matrix or product of matrices such as

$$\Sigma^{(2)}_{u \text{ or } v}(\mathbf{q}\boldsymbol{\rho}\tilde{\mathbf{h}}\boldsymbol{\rho}\mathbf{q}) = 4\pi\beta\sum_{ij} q_i \rho_i \tilde{h}^{(2)}_{ij}(k)\rho_j q_j, \qquad (5)$$

Table 1
Summary of dielectric constants obtained from site-site theories. √ indicate correct, × indicates in general incorrect for the model

		From Eqs. 5, 7a and 7b	From Eqs. 5 and 8
Pure solvent	RISM	$1+3y$ ×	*n/a*
	ARISM	$\dfrac{1+3yA}{1+3y(A-1)}$ √	*n/a*
	DRISM	$1+3y(1+\frac{1}{3}\rho_v\tilde{h}_c(0))$ √	*n/a*
Solvent + ions	RISM	$1+3y$ ×	$1+3y$ ×
	ARISM	$1+3y$ ×	$1+3Ay$ ×
	DRISM	$1+3y(1+\frac{1}{3}\rho_v\tilde{h}_c(0))$ √	$1+3y[1+\frac{1}{3}\rho_v\tilde{h}_c(0)]$ √

where $\tilde{h}_{ij}^{(2)}$ is the coefficient of k^2 in the low k expansion of $\tilde{\mathrm{h}}_{ij}(k)$ given by

$$\tilde{h}_{ij}^{(2)} = -\frac{4\pi}{6}\int_0^\infty r^4 h_{ij}(r)\,\mathrm{d}r, \tag{6}$$

and ρ_i is the density of the species in which site i is situated. In the sum, i and j represent all solvent sites (v) or all solute sites (u) for ionic species. In the former case, asymptotic analysis of distribution functions for pure solvents gives

$$\Sigma_v^{(2)}(\mathbf{q}\rho\tilde{\mathbf{h}}\rho\mathbf{q}) = y\left(\frac{\epsilon-1}{y\epsilon}-3\right), \tag{7a}$$

and for solvents with a finite concentration ionic solute,

$$\Sigma_v^{(2)}(\mathbf{q}\rho\tilde{\mathbf{h}}\rho\mathbf{q}) = y\left(\frac{\epsilon-1}{y}-3\right), \tag{7b}$$

where $y = 4\pi\beta\rho_v\mu^2/9$, ρ_v is the solvent density and μ is the solvent dipole moment. When the sum is taken over ionic solute sites we have

$$\Sigma_u^{(2)}(\mathbf{q}\rho\tilde{\mathbf{h}}\rho\mathbf{q}) = \epsilon. \tag{8}$$

Simultaneously solving Eq. (5) with one of Eqs. (7a), (7b) or (8), where appropriate, yields the value of the dielectric constant. Asymptotic analysis of the functions $h_{ij}(r)$ used in Eq. (5) calculated using a particular theory give the dielectric constant predicted by that theory analytically [5,11].

The RISM/HNC theory predicts, for all systems, a value of $\epsilon = 1 + 3y$ [11,12]. This value is, in general, incorrect for the model in question. For water models in current use in theory and simulation it gives $\epsilon \approx 20$. An arbitrary value for ϵ can be imposed on a pure polar solvent model by solving Eqs. 2 and 4 for an effective system where all the (partial) charges on the solvent sites are scaled by a factor of $A^{1/2}$ in Eq. (1). This results in [13]

$$\epsilon = \frac{1+3Ay}{1+3(A-1)y}, \tag{9}$$

and will be referred to as the ARISM result below. Appropriate values of A, giving $\epsilon \approx 80$, are close to 1. While useful for pure solvents [14] and for ions at infinite dilution [15,16], unacceptable inconsistencies arise in the extension to finite concentration ionic solutes. In particular, Eqs. (7b) and (5) give $\epsilon = 1 + 3y$ for both RISM and ARISM distribution functions. When extending to ionic solutes, a convention must be chosen for the scaling of ionic charges. If only the solvent site charges are scaled, Eqs. (8) and (5) give $\epsilon = 1 + 3y$. If all sites are scaled $\epsilon = 1 + 3Ay$ is retrieved by the solute sum route. A third convention has been used in the infinite dilution ionic case in ref. [16],where solvent sites are scaled in the calculation of solvent–solvent interactions, but unscaled otherwise. Unfortunately, the ARISM route of ref. [16] is not extendable to finite concentration ions because it defies global charge neutrality, which results in the Fourier integrals of distributions diverging. The problem of scaling convention will be discussed below, since it affects ARISM results in a significant way. Our comparison calculations done with the ARISM theory for salt solutions have all interactions scaled. Finally, it should be noted that there is no reasonable value of A in any scaling convention which will give the correct value for the dielectric constant via Eqs. (8) and (5), and further it should be stressed that the (incorrect) value $\epsilon = 1 + 3y$ for solutes with finite concentration ions is a result which is *independent* of the value of A.

A solution to these problems has been presented in refs. [4,5]. If Eq. 2 is replaced by

$$\begin{aligned}(\rho\tilde{\mathbf{h}}\rho-\tilde{\chi}) &= (\tilde{\omega}+\tilde{\chi})\tilde{\mathbf{c}}(\tilde{\omega}+\tilde{\chi})\\ &\quad+(\tilde{\omega}+\tilde{\chi})\tilde{\mathbf{c}}(\rho\tilde{\mathbf{h}}\rho-\tilde{\chi}),\end{aligned} \tag{10a}$$

where $\tilde{\chi}$ is a matrix consisting of elements

$$\tilde{\chi}_{ij}(k) = -j_0(-kd_{ix})j_0(-kd_{iy})j_1(-kd_{iz}) \times j_0(kd_{jx})j_0(kd_{jy})j_1(kd_{jz})\left[\rho_v^2\tilde{h}_c(k)\right], \tag{10b}$$

and d_{ix} is the distance between site i and its molecular center of charge in the x-direction (with the dipolar direction arbitrarily chosen as the z-direction). Also, $j_0(kd)$ and $j_1(kd)$ are zeroth and first-order spherical bessel functions, respectively. The function $\tilde{h}_c(k)$, common to all elements of $\tilde{\chi}$, is given by

$$\tilde{h}_c(k) = \left(\frac{\epsilon - 1}{y\rho_v} - 3\right)\exp(-ak^2), \quad a > 0, \tag{10c}$$

and we use a value of $a = 0.15$ throughout. Eqs. (10a) and (4), when solved together, will be referred to below as the dielectrically consistent RISM, or DRISM theory. The DRISM dielectric constant for all systems discussed here is given by

$$\epsilon = 1 + 3y\left[1 + \tfrac{1}{3}\rho_v\tilde{h}_c(0)\right], \tag{11}$$

and is chosen to give the correct value of ϵ via Eq. (10c).

The solvation free energy for 'growing' a single solute molecule in an infinite solvent bath, in the RISM/HNC formulation, can be written as [16–21]

$$\beta\Delta\mu_{u,\mathrm{sol}}^{(0)} = \rho_v \sum_{i=1}^{n_u}\sum_{j=1}^{n_v}\int \tfrac{1}{2}\left[h_{ij}^{(0)}(r)\right]^2 - c_{ij}^{(0)}(r) - \tfrac{1}{2}h_{ij}^{(0)}(r)c_{ij}^{(0)}(r)\,\mathrm{d}\boldsymbol{r}, \tag{12}$$

where $\Delta\mu$ is the chemical potential (free energy per particle) and the superscript (0) indicates infinite dilution. By a similar derivation to that in ref. [18], because the inclusion of $\tilde{\chi}$ in Eq. (10a) does not explicitly include any additional non-zero terms in the solvent–solute or solute–solute distribution functions for an isotropic solute at infinite dilution, Eq. (12) is directly applicable to results calculated with the DRISM theory. For electrolytes at finite concentration, the change in free energy associated with the 'creation' of the last solute ion can be calculated by regarding the ions already in solution as part of a solvent mixture, and the last (tagged) ion being at infinite dilution. Since this last ion will have the same interaction potential with other sites in the system as all the ions of the same species in solution, the distribution functions between itself and the other species (considering them as part of a solvent mixture) will be identical to those calculated considering the tagged ion as one of the same species at finite concentration. This gives a simple method for calculating the chemical potential of the last ion introduced in the solution,

$$\beta\Delta\mu_{u,\mathrm{sol}} = \sum_{i=1}^{n_u}\sum_{j=1}^{n_v}\rho_j\int \tfrac{1}{2}\left[h_{ij}(r)\right]^2 - c_{ij}(r) - \tfrac{1}{2}h_{ij}(r)c_{ij}(r)\,\mathrm{d}r. \tag{13}$$

3. Results and discussion

The results presented below were calculated for all three theories described above at 298.15 K. Entropy values were calculated via

$$\Delta s_{u,\mathrm{sol},V} = -\left(\frac{\partial\Delta\mu_{u,\mathrm{sol}}}{\partial T}\right)_{\rho_u,\rho_v} \tag{14}$$

and

$$\Delta s_{u,\mathrm{sol},P} = -\left(\frac{\partial\Delta\mu_{u,\mathrm{sol}}}{\partial T}\right)_{P,x_v} \tag{15}$$

by finite difference [15] using related calculations at 296.15 K and 300.15 K. For the DRISM calculations the input dielectric constants for pure water were taken from the cubic polynomial fit to experimental data in ref. [22] as reported in ref. [23]. Dielectric decrements for salt solutions in the HNC approximation are included in the theory (see ref. [5]). For finite concentration constant pressure derivatives the density of the solvent is calculated from the polynomial fit to experimental data in ref. [24]. The solvent model, and the models for the real ions, were taken from the literature and are summarized in Table 2.

In order to compare DRISM results to those of existing theories, and to examine influences of asymmetric solvation, the ions X^+ and X^- as

Table 2
Model potential parameters. The solvent model is SPCE water [44] which has additional geometric parameters $R_{OH} = 1.0$ Å and $\angle_{HOH} = 109.47°$

	ϵ (kcal/mol)	σ(Å)	q(e)
O	0.1554	3.165	−0.8476
H	0.0200	0.040	0.4238
Na^+	1.607	1.897	1.0
Cl^-	0.107	4.446	−1.0
Br^-	0.090	4.624	−1.0
X^+	0.500	5.000	1.0
X^-	0.500	5.000	−1.0

[a] The parameters for Na^+, Cl^-, and Br^- are from refs. [45], [16] and [46], respectively.

Table 3
Solvation thermodynamic properties of X^+ and X^- ions. $\Delta\mu^{(0)}_{u,\mathrm{sol}}$, $\Delta h^{(0)}_{u,\mathrm{sol}}$, and $\Delta\epsilon^{(0)}_{u,\mathrm{sol}}$ are in kcal/mol. $\Delta s^{(0)}_{u,\mathrm{sol},V}$ and $\Delta s^{(0)}_{u,\mathrm{sol},P}$ are in cal/(mol K)

	X^+			X^-		
	RISM	ARISM	DRISM	RISM	ARISM	DRISM
$-\Delta\mu^{(0)}_{u,\mathrm{sol}}$	31.1	30.8	32.7	61.4	61.0	64.0
$-\Delta h^{(0)}_{u,\mathrm{sol}}$	46.1	46.0	45.9	74.7	74.8	74.7
$-\Delta\epsilon^{(0)}_{u,\mathrm{sol}}$	50.7	50.6	50.7	78.8	78.9	79.2
$-\Delta s^{(0)}_{u,\mathrm{sol},V}$	65.8	66.5	60.2	58.5	60.1	51.1
$-\Delta s^{(0)}_{u,\mathrm{sol},P}$	50.2	51.1	44.0	44.6	46.2	36.0

given in Table 2 were used. Because of the extremely low dielectric constants of RISM and ARISM theories (≈ 20), no solution at low finite concentration ($\leqslant 1$ M) for these two theories for any of the real ion models used here are possible. This behavior is due to the phase separation predicted by many theoretical means, including HNC based theories, in low dielectric constant solvents. This behavior has been observed for some time in real systems [25,26],and theoretically [27], and is a subject of much current interest [28–31]. Unfortunately, it must be seen as a severe drawback to RISM and ARISM approaches since it precludes comparison in any meaningful way with the commonly used electrolyte models. It is because of this problem that such large ions with large Lennard-Jones well-depths parameters had to be used. Essentially these models represent large 'hydrophobic' ions which one would expect to dissolve in a low polarity solvent.

3.1. Comparison of theories

Thermodynamic quantities for the ions X^+ and X^+ at infinite dilution are given in Table 3, where $\Delta\mu^{(0)}_{u,\mathrm{sol}}$, $\Delta s^{(0)}_{u,\mathrm{sol},V}$ and $\Delta s^{(0)}_{u,\mathrm{sol},P}$ were calculated as described above, and the other quantities via $\Delta\mu^{(0)}_{u,\mathrm{sol}} = \Delta\epsilon^{(0)}_{u,\mathrm{sol}} - T\Delta s^{(0)}_{u,\mathrm{sol},V}$ and $\Delta\mu^{(0)}_{u,\mathrm{sol}} = \Delta h^{(0)}_{u,\mathrm{sol}} - T\Delta s^{(0)}_{u,\mathrm{sol},P}$. We use the notations $\Delta\mu^{(0)}_{u,\mathrm{sol}}$, $\Delta\epsilon^{(0)}_{u,\mathrm{sol}}$, $\Delta h^{(0)}_{u,\mathrm{sol}}$ and $\Delta s^{(0)}_{u,\mathrm{sol}}$ given in refs. [16,20] to indicate the excess per particle quantities free energy, internal energy, enthalpy and entropy, respectively, and remove the superscript (0) when finite concentration quantities are considered. Several general trends are apparent. For each of the quantities $\Delta\mu^{(0)}_{u,\mathrm{sol}}$, $\Delta s^{(0)}_{u,\mathrm{sol},V}$ and $\Delta s^{(0)}_{u,\mathrm{sol},P}$, for both ions, the ARISM values differed from the

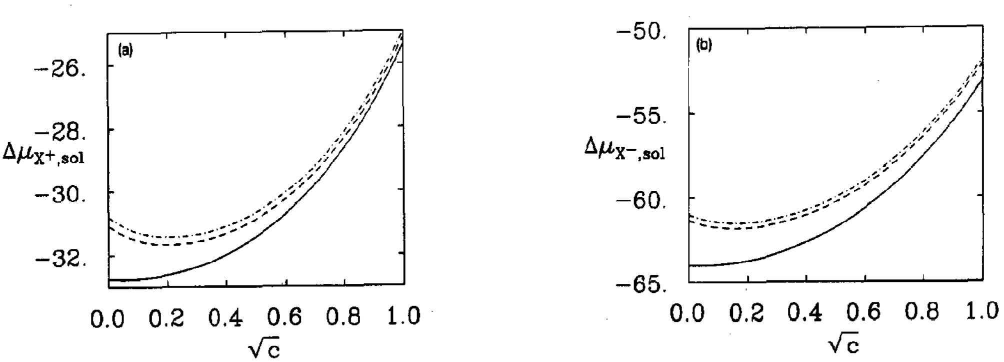

Fig. 1. (a) Excess chemical potential for X^+ ions. The solid, dashed and dot-dashed lines represent the DRISM, RISM and ARISM results, respectively. (b) Excess chemical potential for X^- ions. The lines are as in Fig. 1a.

RISM values in the opposite direction to the DRISM results. The direction in which the ARISM $\Delta\mu_{u,\mathrm{sol}}^{(0)}$ values deviate from the RISM results is opposite to that found previously [16], and is due to the difference in the convention chosen for the extension of the ARISM theory to ionic solutes (see above). Constant pressure entropies of solvation are consistently less negative than the constant volume values for all theories. The DRISM values are consistently and significantly less negative than the values from the other two theories.

The single ion contributions to $\Delta\mu_{u,\mathrm{sol}}$ as a function of square root of concentration (from Eq. (13)) are shown in Figs. 1a and 1b for cations and anions, respectively. The difference in dielectric constant of the solvent, as given by the three theories (see Table 1), is responsible for the difference between, and the order of, the infinite dilution values. As the concentration of ions is increased to 1 M, the difference between the results from the different theories diminishes, mostly due to the dielectric decrement yielded by the DRISM theory but absent from the other two theories. The similarity between the shapes of the respective curves for positive and negative ions is a model dependent result, and not true of more realistic salt models examined below. We note that while the DRISM curves appear to approach zero concentration with a slope of zero, they actually have a negative slope at the infinite dilution limit. This is to be expected since the quan-

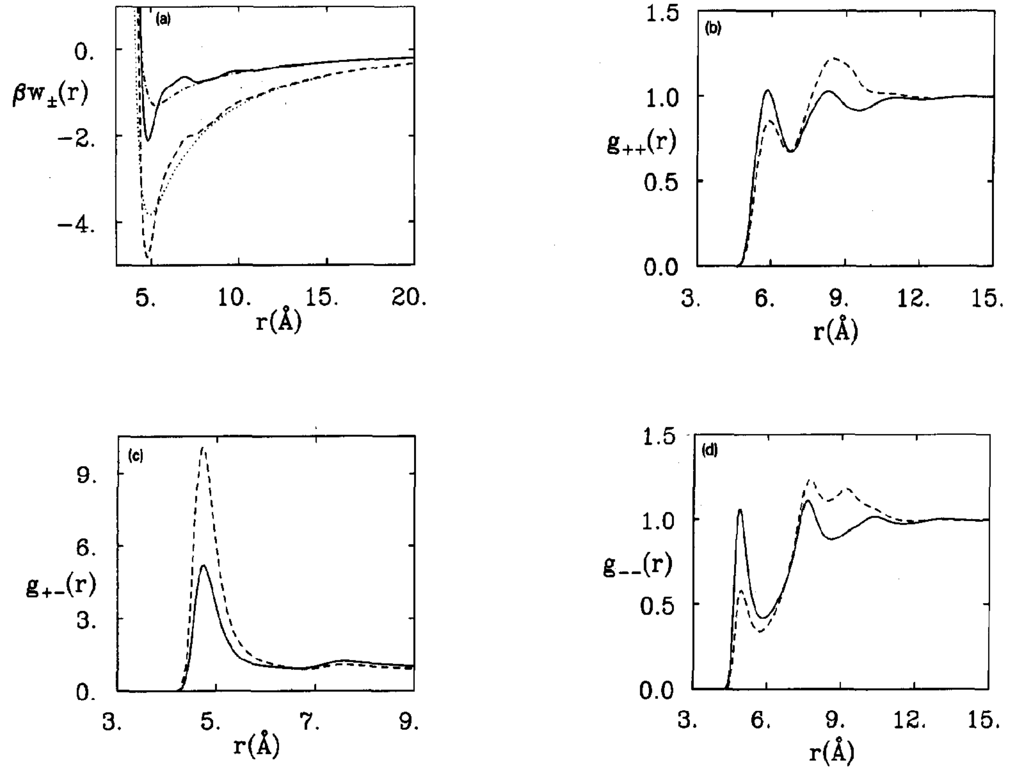

Fig. 2. (a) Potentials of mean force between X^+ and X^- ions at 0.01 M. The solid line and the dashed line are the DRISM and RISM result, respectively. The corresponding results for the same ions in a dielectric continuum with dielectric constant equal to that from the DRISM theory (dot-dashed line) and the RISM theory (dotted line) are also shown. (b) Radial distribution of positive (X^+) ions around a central cation at 1 M. The lines are as in (a). (c) Radial distribution of positive (X^+) ions around a central anion at 1 M. The lines are as in (a). (d) Radial distribution of negative (X^-) ions around a central anion at 1 M. The lines are as in (a).

tity $\Delta\mu_{X^+,\mathrm{sol}} + \Delta\mu_{X^-,\mathrm{sol}}$ is easily related to the Debye–Hückel limiting law. The nature of the difference between the theories at finite salt concentration is easily seen in Fig. 2a, which shows the potential of mean force (PMF) between a positive and negative ion for RISM and DRISM theories at 0.01 M. The ARISM result (not shown) is indistinguishable from the RISM result on the scale of the figure. The difference in well depth of $\approx 5k_BT$/mol (≈ 3 kcal/mol) between RISM and DRISM PMFs shows clearly why at low concentration low dielectric constant solvent are prone to phase instability. The difference in the size of the exponentially decaying 'Debye–Hückel' functional form as $r \to \infty$ is also readily apparent. Figs. 2b–2d show the ion–ion radial distribution functions for X^+ and X^- ions at 1 M, and again demonstrate important differences between RISM and DRISM results. The higher dielectric constant affords a stronger solvation and hence a tendency toward less pairing of oppositely charged ions (Fig. 2c) as well as more stable structures involving like ions in closer proximity as the higher first peaks in $g_{++}(r)$ and $g_{--}(r)$ indicate. Second coordination shells contain correspondingly less like ions in the DRISM case. The difference between Figs. 2b and 2d again demonstrates asymmetric hydration of oppositely charged ions, in this case through the correlations between different pairs of like ions as felt through the intervening or surrounding solvent.

As a more stringent comparison of theories we examine some realistic models of monovalent ions as defined in Table 2. Results of infinite dilution thermodynamic quantities are given in Table 4. Some DRISM quantities, in particular $\Delta s^{(0)}_{u,\mathrm{sol},P}$ for the anions are significantly closer to the experimental results than are the RISM, but it should be noted that there is a significant model dependence of all results, and it would be possible to choose reasonable Lennard-Jones parameters to make both free energies and entropies match experiment exactly for a given theory. The individual ion contributions to the solvation free energy of finite concentration NaCl and NaBr solutions up to 1 M are plotted versus the square root of the concentration in Fig. 3a. The cation contributions for the two cases are not equal, even though the same Na^+ model is used. These single ion contributions are not available from experiment, although they are easily calculated here, and it should be stressed that there is a significant dependence on which counterion is present. This has been inferred qualitatively from computer simulations recently [32]. It is also important to note that unlike the case of the like sized, large X^+ and X^- ion contributions examined above, the solvation of the Na^+ ions is enhanced with increasing ionic strength, whereas Cl^- and Br^-, both reasonably large, have the same general curve shape as the other large ions. The decrease in chemical potential for anions with increased ionic strength overcomes the cation tendency, and they combine into the type of curve associated with the logarithm of the activity coefficient as shown in Fig. 3b. The function values were calculated via

$$\Delta\Delta\mu_{u,\mathrm{sol}} = \Delta\mu_{u,\mathrm{sol},+} + \Delta\mu_{u,\mathrm{sol},-} - \Delta\mu^{(0)}_{u,\mathrm{sol},+} - \Delta\mu^{(0)}_{u,\mathrm{sol},-}, \qquad (16)$$

Table 4
Solvation thermodynamic properties of selected monovalent ions. Energy and entropy units are as in Table 3. Experimental values are from refs. [47–49]

	Na^+			Cl^-			Br^-		
	RISM	DRISM	exp.	RISM	DRISM	exp.	RISM	DRISM	exp.
$-\Delta\mu^{(0)}_{u,\mathrm{sol}}$	81.7	85.2	89.6	80.4	84.0	80.5	75.8	79.2	74.2
$-\Delta h^{(0)}_{u,\mathrm{sol}}$	91.4	91.9	99.9	92.4	92.9	88.8	87.8	88.3	80.8
$-\Delta\epsilon^{(0)}_{u,\mathrm{sol}}$	91.2	92.0	–	94.8	95.8	–	90.5	91.5	–
$-\Delta s^{(0)}_{u,\mathrm{sol},V}$	31.7	22.6	–	48.6	39.5	–	49.4	41.1	–
$-\Delta s^{(0)}_{u,\mathrm{sol},P}$	32.6	22.4	34.5	40.3	29.9	25.8	40.2	30.5	22.1

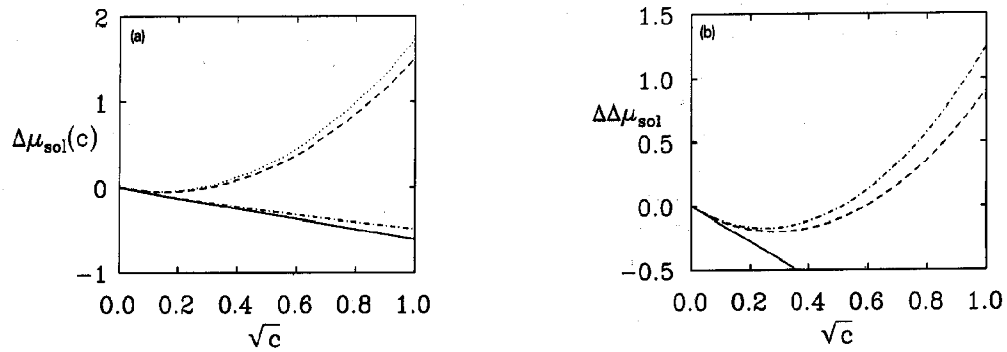

Fig. 3. (a) Single ion contributions to the excess chemical potential for NaCl and NaBr. The solid, dashed, dot-dashed and dotted lines represent Na^+ in NaCl, Cl^-, Na^+ in NaBr and Br^-, respectively. (b) The difference between the excess chemical potential at finite concentration and at infinite dilution for NaCl (dashed line) and NaBr (dot-dashed line). The solid line represents the Debye–Hückel limiting law.

and the corresponding Debye–Hückel limiting law (DHLL) is also shown. It should be noted that the concentration was increased at constant volume, not pressure, to facilitate comparison between model results and alleviate the need for further experimental input in a canonical ensemble calculation. While the DHLL is a true limiting law for both constant V and P, the constant volume results are expected to deviate from the limiting law more rapidly than in the constant pressure case. Kirkwood–Buff (KB) theory [2,33] can be used to find the slope of the curves in Fig. 3b, but numerical integration must be performed to compare the two routes to the same result. The KB results differ from those from Eq. (16) by about 5% for the NaCl calculations. It is not known at present whether this represents a numerical difference or a thermodynamic inconsistency.

3.2. Ideas of solvent structure

The classification of ions into the categories of structure-making and structure-breaking is one that has consequences in several fields [8,9]. It is presumed that each ion has surrounding it a co-sphere of solvent molecules. These co-spheres are regions of high entropy in the case of struc-

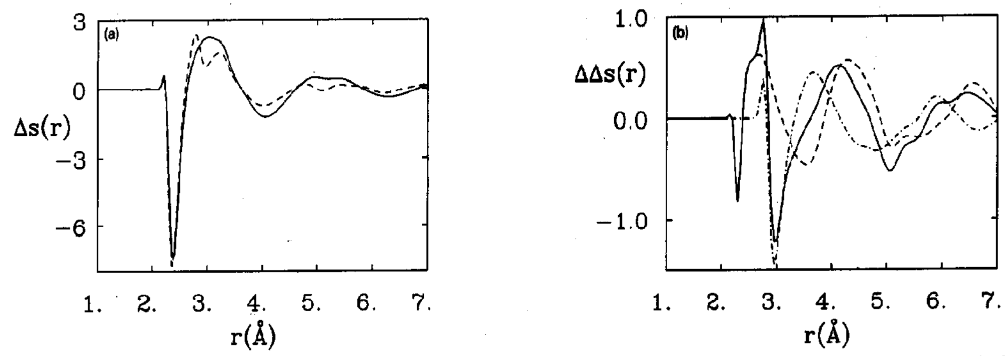

Fig. 4. (a) The function $\Delta s(r)$ (see text for definition) for Na^+ at infinite dilution (solid line) and at 10 M (dashed line). (b) The difference between the function $\Delta s(r)$ for Na^+ at 10 M and at infinite dilution (solid line) as well as the components from ion-solvent interactions (dashed line) and interactions with other ions in solution at 10 M (dot-dashed line). Entropy is in units of k_B.

ture-breaking ions and low entropy in the case of structure-making ions. The co-spheres are presumed to have a strongly held inner shell of water molecules with their orientational structure dominated by the electric field of the ion, and a region outside this shell with structure intermediate between that of the inner shell and the bulk [6,7]. As the concentration of ions is increased, the co-spheres will overlap, decreasing the excess entropy per ion in the structure-breaking case. As an attempt to understand the link between solvent structure and solvation entropy, we have plotted the integrand of the solvation entropy function, defined for the finite difference calculation as

$$\beta\Delta s(r)=\sum_{i=1}^{n_u}\sum_{j=1}^{n_v}\rho_j\frac{1}{T_\mathrm{h}-T_\mathrm{l}}\Big[\Big(\tfrac{1}{2}\big[h_{ij}(r,T_\mathrm{h})\big]^2 - c_{ij}(r,T_\mathrm{h})-\tfrac{1}{2}h_{ij}(r,T_\mathrm{h})c_{ij}(r,T_\mathrm{h})\Big) - \Big(\tfrac{1}{2}\big[h_{ij}(r,T_\mathrm{l})\big]^2-c_{ij}(r,T_\mathrm{l}) - \tfrac{1}{2}h_{ij}(r,T_\mathrm{l})c_{ij}(r,T_\mathrm{l})\Big)\Big], \qquad (17)$$

where T_h and T_l are the upper and lower temperature values surrounding the temperature of interest. This function is plotted for DRISM calculations at infinite dilution and at 10 M for the contributions (values of solvent mixture sites j) to the entropy for Na$^+$ in Fig. 4a. The value of the constant volume entropy (integral of this function) has changed from −22.6 cal/(mol K) to −29.7 cal/(mol K) with the addition of salt, which is not consistent with the trend one would expect with the co-sphere overlap of structure-making ions. However, the situation is elucidated when one looks at lower concentrations of salt. The solvation entropy at first increases, going through a maximum between 1 and 2 M, (the value at 2 M is −20.6 cal/(mol K)) and only when the concentration of salt has become significantly larger does the unexpected trend occur. Differences in the function $\Delta s(r)$ between infinite dilution and finite concentration are too small to notice any simple trends for concentrations below 2 M, but the significant short-range structure in $g_{++}(r)$ at 1 M for X$^+$ ions demonstrates the presence of water-cation structures at relatively low concentrations which account for the low concentration entropy behavior. The formation of such structures, while locally forming a more ordered state, have a smaller amount of influence per ion, and hence results in an overall positive entropy contribution. The solvation entropy function has oscillating positive and negative contributions which decrease in amplitude as the concentration of salt is increased. This again supports the overlapping co-sphere picture. However, if we examine the differences between the the functions $\Delta s(r)$ at 10 M and infinite dilution, $\Delta\Delta s(r)$, (solid line, Fig. 4b) and divide this difference into the contributions from changes in sol-

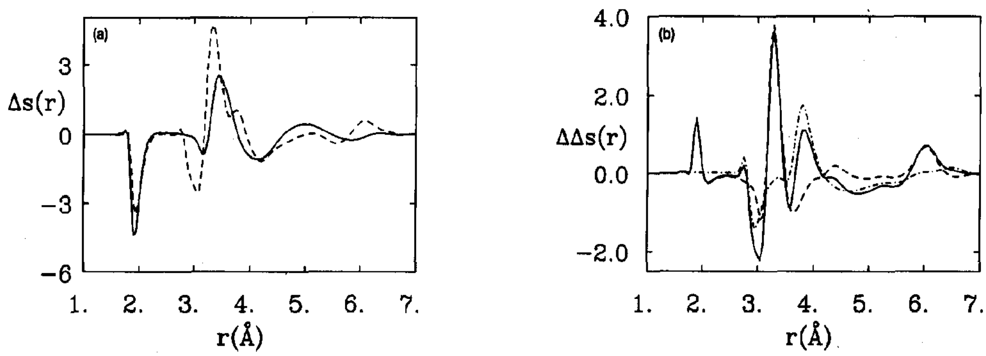

Fig. 5. (a) The function $\Delta s(r)$ (see text for definition) for Cl$^-$ at infinite dilution (solid line) and at 10 M (dashed line). (b) The difference between the function $\Delta s(r)$ for Cl$^-$ at 10 M and at infinite dilution (solid line) as well as the components from ion–solvent interactions (dashed line) and interactions with other ions in solution at 10 M (dot-dashed line). Entropy is in units of k_B.

vent structure (dashed line) and from the other ions already in solution (dot-dashed line, this contribution is zero at infinite dilution), one finds that the two contributions have oscillations which are spatially out of phase, leading to a partial cancellation. The overlapping co-sphere effect seems not to be simply related to the volume of solvent influenced by each molecule, which is decreased. There also seems to be an interference effect at high concentration whereby ions competitively reorder each others' solvation shells, resulting in a much smaller overall decrease in entropy than is seen in the case of Cl^- ions.

The corresponding $\Delta s(r)$ functions for the Cl^- case are shown in Figs. 5a and 5b. Chloride is regarded as a structure-breaking ion. The excess solvation entropy for Cl^- ions is -39.5 cal/(mol K) at infinite dilution, -40.4 cal/(mol K) at 2 M and -61.3 cal(mol K) at 10 M. There is a very small increase in the solvation entropy at very low concentration, but the significant effect seen in the Na^+ case is not seen. There is a more pronounced difference in $\Delta s(r)$ with increased salt concentration which accompanies the larger changes in entropy. The effect of cancellation of contributions seen in the cation case is also missing from Fig. 5b, with the result that the differences are significantly larger (note the scale difference in Fig. 4b versus 5b). This is probably due to the water structure around an anion being more closely related to that in the bulk, so anions in close proximity to each other tend to enhance this structure rather than competing to reorder the solvent. Small anions tend to orient one water hydrogen atom towards their centers rather than orienting the entire dipole of the water molecule as do cations. This is primarily a hydrogen bonding effect which results in hydrated anions presenting both h-bond donors and acceptors to the second solvation shell. In contrast, small hydrated cations present only h-bond donors to the surrounding solvent.

Fig. 6 shows the radial distribution functions of solvent sites around Na^+ (6a) and Cl^- (6b) at infinite dilution and 10 M. The change in solvent structure around a cation with increase in concentration is relatively small, consistent with the small changes in solvation entropy. The large changes in structure seen in the anion case are also consistent with the large solvation entropy changes. We note that using the infinitely dilute pair correlations in McMillan–Mayer thermodynamic theory would result in exaggerated structures (all peaks in radial distributions above 1 at infinite dilution must increase with increasing concentration) unless solvent relaxation triplet correlations are included.

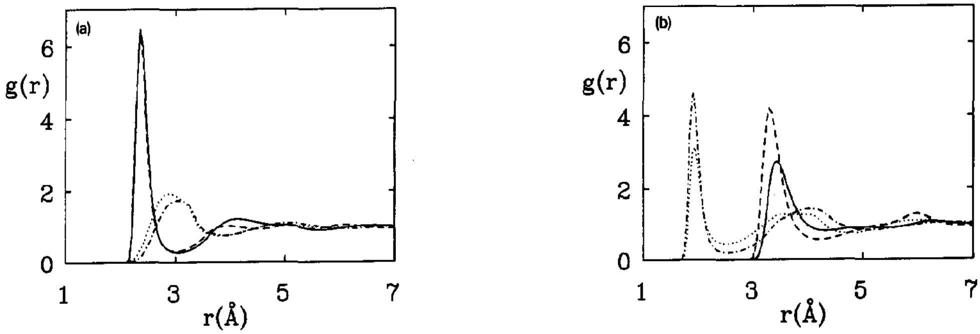

Fig. 6. (a) Radial distributions for solvent sites around a Na^+ ion. The component pairs represented by solid, dashed, dot-dashed and dotted lines are Na^+–O at infinite dilution, Na^+–O in 10 M NaCl, Na^+–H at infinite dilution and Na^+–H in 10 M NaCl, respectively. (b) Radial distributions for solvent sites around a Cl^- ion. The component pairs represented by solid, dashed, dot-dashed and dotted lines are Cl^-–O at infinite dilution, Cl^-–O in 10 M NaCl, Cl^-–H at infinite dilution and Cl^-–H in 10 M NaCl, respectively.

3.3. Comparisons with the born free energy equation

The earliest method for predicting the free energy associated with the transfer of an ion from gas phase (in a vacuum) to a solvated state, modeled as a charged cavity immersed in a dielectric continuum, is due to Born [34] and can be written as

$$\Delta G^{\mathrm{Born}}=\left(\frac{q_i^2}{2d_i}\right)\left(\frac{1}{\epsilon}-1\right), \tag{18}$$

where q_i is the charge on the ion, d_i is the hard-sphere radius of the ion, and ϵ is the dielectric constant of the continuum. This is exactly correct for a hard sphere ion at infinite dilution, and the roughly quadratic relationship between charge and free energy *for a fixed sized ion in an environment of fixed dielectric constant* has been also seen in more exact theories as well as experiments [16,20,35,36]. Reference to this equation is widely made throughout the theoretical chemical literature. Arguments both for and against the applicability of this equation date back to the early part of this century [37–40]. Such continuum methods have been extended to large complex solutes such as proteins and DNA [41]. The merit of wide applicability of such a simple formalism is obvious. However, nearly 30 years ago, H.S. Frank warned in exactly this context that "such a merit can become a fault...when it distracts attention from other features of the system which are really relevant" [6]. The impression that the applicability of Eq. (18) is wide is usually based on 'order of magnitude' or 'first approximation' arguments, which imply that the majority of the solvation free energy can be accounted for by simply charging a cavity, and that more sophisticated treatments will in general make small corrections to the Born value. Evidence that such impressions are largely illusory have appeared in the literature before [20], but the results in the previous sections clearly illustrate some of the assets and liabilities associated with the use of the Born equation.

First we must note that the simplicity and ease of use of Eq. (18) arises from the fact that it is a scalar valued function of ion diameter. However, ion diameter is not only a quantity which has not been uniquely established by experiment, neither is it well defined for soft-sphere ion models which contain other attractive and repulsive terms. Some convention on the amount of space an ion 'takes up' in solution must first be chosen before either experiments or modeled distributions can be interpreted. Unfortunately, there is nothing beyond modeling self-consistency or some sense of reasonableness preventing the choice of 'effective' or 'Born' diameters that result in any value for the free energy desired. Under such circumstances the success of the Born equation should not be surprising. It has been claimed [40] that the simple Born equation agrees well with the experimental data. However, three arbitrary fitting constants are necessary to achieve a reasonable fit. One of these constants is an ionic radius 'adjustment'. A clear case where Eq. (18) can be seen to fail is in the solvation free energies of a symmetric pair such as X^+ and X^- ions. This failure has also been demonstrated with previous theories [16,21] The only difference between the ion models is opposite charge, which Eq. (18) cannot distinguish, yet the results for all three integral equation theories show the difference in this case to be approximately a factor of two. Some authors have attempted to correct the inadequacies of the Born theory by changing the model used until agreement with experiment was reached [40]. Thus, no actual test of the underlying theory was made. Tests such as the one given in this work allow an independent check of theory for a fixed, given model. While it could be claimed that, due to electrostriction, one ion was effectively smaller than the other, the molecular model used captures this difference and *post facto* adjustment of ionic radii is unnecessary.

It has been shown for the mean spherical approximation (MSA) [35,36] and the RISM theory [20] that the functional form for solvation free energy as a function of charge, while generally parabolic, is closer to the form

$$\Delta G(q)=aq^2+bq+c, \tag{19a}$$

where a, b and c are independent of charge but dependent on perhaps many other system properties, rather than the simpler Born form

$$\Delta G(q) = aq^2. \tag{19b}$$

The general form of Eq. (19a) is closely approximated by DRISM and ARISM theories as well. It is the nature of the coefficients b and c, as well as their relative importance with respect to the coefficient a, that we now examine.

The constant term c is clearly the energy required to create an uncharged cavity similar in size to that of the ion. This quantity is available from ISM theories, but not continuum theories, and has been reported [16] for the present Cl^- model with its charge removed, and immersed in a similar water model. Both RISM and ARISM give $\Delta\mu^{(0)}_{u,\mathrm{sol}} \approx 12$ kcal/mol, which is a significant contribution to the corresponding values for Cl^+ and Cl^-, which are in the RISM case −42.0 and −78.3 kcal/mol, respectively. As would be expected, for a given water model, the value of c is almost proportional to the cube of the ion diameter, or proportional to the number of water molecules which must be pushed out of the way, $\frac{1}{6}\pi d^3 \rho_v$. For large ions like X^- and X^+ (or tetraalkylammonium salts, tetraphenylphosphines, etc.) even larger contributions result. A general rule of thumb is that when the size of the ion exceeds the size of a water molecule, the contribution of the constant term in Eq. (19a) will exceed 5% of the total solvation free energy.

The constant term cannot account for the solvation free energy difference between oppositely charged, otherwise identical ions. The b term in Eq. (19a) arises from the asymmetric hydration of anions and cations, discussed above. If the (molecular) solvent model had $\mathrm{C}_{\infty v}$ symmetry, such as a simple dipolar model, the value of b would be zero. Continuum models generally have no b term. The values of a, b and c as derived from DRISM calculations for each ion at charges of $q = 1$, 0 and −1 are given in Table 5. The size of the asymmetry term increases with decreasing ion size, and for Na^+ ions is approximately half the size of the q^2 term. There appears to be no range of ion size where the combined cavity formation and asymmetric solvation terms are not significant. The only case where these terms approximately cancel is for the case of the X^- ion, and in this case Eq. (18) gives a value of −37.8 kcal/mol which differs from the DRISM value by about a factor of two. Both the coefficients b and c seem to take positive values for all ions, indicating that the Born equation should be a significantly worse predictor of cation solvation free energies than for anions. However, the opposite seems to be true. Free energies from Eq. (18) (using model σ values) agree more closely with the DRISM values for cations than for anions. This is because the values of the coefficient of q^2, a, are not close to the coefficients for the Born equation. The free energy change associated with the reorientation of water around a cation is similar in magnitude to the Born energy, both of which take account of the cost of solvent polarization. There is a smaller polarization energy cost for anions because the bulk structure is disrupted less. The Born equation does not make this distinction.

Table 5
DRISM values of the coefficients a (kcal/(mol e^2)), b(kcal/(mol e)) and c (kcal/mol) from Eq. (19a) consistent with calculated values of $\Delta\mu^{(0)}_{u,\mathrm{sol}}$ for each ion at $q = 1$, 0 and −1

	a	b	c
Na	−181.7	96.3	0.2
Cl	−76.7	20.4	13.0
Br	−74.3	19.3	14.3
X	−63.4	15.7	15.0

For a given ion in a given solvent the Born equation seems to predict changes in free energy due to change in dielectric constant well. The differences between ARISM, RISM and DRISM values of $\Delta\mu^{(0)}_{u,\mathrm{sol}}$ are consistent with Eq. (18). This is of extremely limited use, however, because no real system can change its dielectric constant while keeping all other properties fixed.

The universality of the Born equation has been discussed in the context of ignoring explicit solvent effects in continuum electrostatic calculations of free energies of solvation for large biological molecules [41]. Yet, the assignment of a ‘somewhat arbitrary’ cavity radius for such treatments is acknowledged. The free energy cost of forming the uncharged cavity of such molecules must be significant, even measured on a per site basis. Continuum calculations add empirical surface area terms to account for the cavity creation work and related thermodynamic quantities [42,43]. The difference between solvent structures around positive and negative surface sites must also contribute free energy terms of differing magnitudes, and they cannot be expected to cancel even for neutral molecules. This effect is not considered by such treatments. Clearly one should be careful when considering the free energy differences from continuum calculations involving the reversal of charge on surface constituents. Nevertheless, such calculations often do yield useful results when the difference in free energy between two very similar biological molecules is considered.

4. Summary and conclusions

Structural and thermodynamic results for the DRISM integral equation theory for models of both real and idealized models of monovalent ions dissolved in water have been presented and compared to those of RISM and ARISM theories. Numerical solutions for the RISM and ARISM theories were not possible for models of NaCl and NaBr at finite concentrations due to the low dielectric constant inherently associated with these theories. Some infinite dilution DRISM results compared favorably to those of the previous theories but results were found to be model dependent. Evidence of strong asymmetry is apparent in many solvation characteristics including free energies and entropies of solvation as well as solvent distributions about ions. The change in single ion chemical potential as salt concentration is increased, as given by DRISM calculations for NaCl and NaBr solutions, showed that the contribution from the Na^+ depended on which counterion was also dissolved, and that over the range of concentrations up to 1 M the contribution from cations continued to move to a larger negative value whereas the corresponding anion contributions became increasingly less energetically favorable as ionic strength increased. The anion contribution dominated the cation when they were combined to form the total chemical potential for the electrolyte, deviating far from the Debye-Hückel limiting law for constant volume calculations.

The integrand of the expression for solvation entropy, $\Delta s(r)$, was examined with regard to the ideas of ionic structure-making and structure-breaking in surrounding solvent co-spheres. While the general trends in solvation entropy as a function of concentration were found to be consistent with such ideas,it was found that the opposite trend (to higher solvation entropy per molecule) occurred at low concentrations and this was attributed to the net loss of order in the process of changing water structure while forming ion-water structures involving more than one cation. The relatively small change in solvation entropy for Na^+ ions even at high concentration (10 M) was attributed to cations competing with each other to reorder the solvent. The opposite effect was found for anions, which have surrounding water structure more compatible with bulk water, so increasing concentration tends to enhance the structure rather than competing to destroy it.

A close examination of the Born equation for the free energy of solvation of ions was performed in the context of theoretical results for a molecular model of water as solvent. It was argued that the Born equation does not predict solvation free energies accurately or universally. A more accurate quadratic form, containing terms for cavity formation and asymmetry of solvation, was examined and it was discovered that these terms are never negligible. Since electrostatic free energy calculations for biological molecules do not generally consider either cavity formation or asymmetric solvation effects, yet often yield useful results, the argument of the universality of the Born equation as justification for continuum electrostatic models does not follow. In particular care should be taken in the case of free energy changes due to charge reversal on constituent groups.

Acknowledgement

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Discussion to the paper by J. Perkyns and B.M. Pettitt

Comments

By L. Pratt, G. Hummer and A. Garciá

(1) The temperature derivatives of Eqs. (14a), (14b), and (17) are somewhat confusing but these issues are of particular interest because of the recent work of Lazaridis and Paulaitis [J. Chem. Phys. 96 (1992) 3847; Fluid Phase Equilibria 83, (1993) 43; J. Chem. Phys. 97 (1993) 5789; J. Chem. Phys. 98, (1994) 635; see also D.E. Smith, B.B. Laird, and A.D.J. Haymet, J. Phys. Chem.

97 (1993) 5788] that attempts to evaluate directly the partial molar entropy of particular solutes in water. (a) Could you clarify that, at infinite dilution, Eq. (14a) does not give the most commonly considered solvation entropy? Instead it gives

$$\Delta s_{u,\mathrm{sol},P} - v_{\mathrm{s}}^{(0)}\left(\frac{\mathrm{d}p}{\mathrm{d}T}\right)_{v}$$

where the leftmost thermodynamic derivative is a property of the pure solvent and $v_{\mathrm{s}}^{(0)}$ is the partial molar volume of the solute at infinite dilution. The latter quantity is a non-trivial prediction of your theory. (b) What is that prediction? (c) Can you compare or explain the integrand of Eq. (17) in terms of formally more complete theories for entropy densities? [R.L. Stratonovich, Soviet Phys. JETP 1, (1955) 254; R.E. Nettleton and M.S. Green, J. Chem. Phys. 29, (1958) 1365; H.J. Raveche, J. Chem. Phys. 55 (1971) 2242]

(2) Can you explain further the assertion on page 17 that refers to the formula of Eq. (18): "This is exactly correct for a hard sphere ion at infinite dilution, and the roughly quadratic relationship between charge and free energy *for a fixed sized ion in an environment of fixed dielectric constant* has been also seen in more exact theories as well as experiments [16,20,35,36]." Why is the hard-sphere condition important for the exactitude of this relation and what is the significance of "more exact theories as well as experiments" to this "exactly correct" relation?

(3) You comment on page 7 that the ARISM model "defies global charge neutrality." Does the DRISM model satisfy the known moment conditions on ionic correlations?

(4) You comment on page 10 that the impossibility of solutions to the RISM and ARISM theories is "due to the phase separation predicted ... in low dielectric constant solvents." Have you attempted to use those theories to define the other the phases that might be predicted?

(5) You describe your theory as "dielectrically consistent" but it clearly requires a dielectric constant from an external source and as a function of salt concentration. Please explain what you used for this information and why.

By A. Rashin

(1) It is always satisfying to see a theory whose results can be compared to experiment. What worries me is your statement in section 3.1. that "*it would be possible to choose reasonable Lennard-Jones parameters to make both free energies and entropies match experiment exactly for a given theory*". As I understand this is true for RISM, ARISM and DRISM. Then what is the use of comparing their results if your statement seems to imply that they are likely to reflect just (or mostly) results of an incorrect choice of parameters?

(2) Section 3.2 is confusing in a number of places. (a) I do not understand how important it is for the logic of your paper, but in your discussion of solvent co-spheres of ions you state "The cospheres are presumed to have a *strongly held* inner shell of water molecules". 'Co-spheres' do not mean this judging by ref. [1]. Recent NMR studies claim that all surface waters in proteins, even well localized crystallographically, have very short residence times [2]. Thus, I am afraid that your work in this section is cast in not very meaningful terms. (b) Your apparent finding that entropy increases upon addition of an ion at infinite dilution. It never happens to the entropy of water. Theory [3] and experiment [4] show that entropy decreases in transfer of any ion (or even any particle) from a fixed position in gas to a fixed position in the solution. Could your results come from some different reference state (or states) [5], or do you include entropy of 'ionic gas' in your reported entropies? Or may be I misunderstood something?

(3) Section 3.3 presents continuum models in a rather distorted way. (a) A possibility to fit the Born hydration energy to any value by choosing an appropriate radius is no worse than your ability "*to choose reasonable Lennard-Jones parameters*" (see question (1)). In fact, only a single parameter (the same for all solutes) was required to obtain within a few percent experimental hydration enthalpies of three dozens spherical ions from their handbook radii [6]. (b) Symmetry of the Born equation in respect to positive and negative ions is just the result of attempts to characterize ions on the basis of ion–oxygen equi-

librium distance. Its not what the Born equation implies, and not what refs. [6,7] held. 'Born diameter' describes dielectric cavities, and their diameters are not equal to your $\sigma - s$. Attempting to cast your expressions in terms of $\sigma - s$ leads to the necessity of a term linear in charge. It does not mean that your expression is incorrect, it just means that you are likely casting it in irrelevant terms. I apologize for the example, but systems of Copernicus and Ptolemeus are both correct, just one of them is cast in wrong variables and thus made too complicated. (c) The continuum approach allows to account not only for asymmetry of hydration enthalpies of ions with opposite signs but the same σ, but also in their entropies. As discussed in refs. [8,9] agreement of continuum approaches with experiment is at least as good as that of molecular simulations. Thus, I doubt that you point at real weaknesses of the continuum theory. With this I do not deny a possibility of their existence, and rather try to honestly pinpoint them in refs. [8,9].

(4) Recently we have found [3] that in NPT transfer entropy of hydration of positively charged ions and apolar spheres per Å^2 stays almost constant for ion–O $\sigma - s$ larger than 3 Å. Would your method produce a similar result?

(5) We also found [3,9] that the difference between Δs_P and Δs_V is described within ~20% by the formula for gas entropy. For your results in Table 3 it yields $\Delta T \Delta S = 3.8$ kcal/mol (at 298 K). Schmidt and Lee in this issue separately show that 'volume' contributions to entropy strongly depend on the system (L-J or hard spheres). For methane in water we found $\Delta T \Delta S = 1.8$ kcal/mol and experiment gives 1.5 kcal/mol. Does it mean that volume effects in water are much closer to that of ideal gas than any other liquid? It would be interesting to get it from your technique.

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Responses by J. Perkyns and B.M. Pettitt to comments

To A. Rashin

(1) Unfortunately the quoted phrase has been taken out of context as the whole sentence in which it is found makes clear. We are warning the reader not to make too much of the fact that some quantities are very close to experiment because all results are very model dependent, and it would be possible to put any given theory in an artificially positive light by judicious choice (or adjustment) of models. We are careful not to do this by only using models developed by other authors, and feel that deliberate experiment matching is uninteresting and often misleading. See part 3 below.

(2) (a) The term "strongly held" is an energetic one, while residence times are kinetic quantities. They are not simply related, especially for proteins (see V. Lounnas and B.M. Pettitt, Prot. Struct. Funct. and Gen. 18 (1994) 148.) As for definitions we would suggest ref. [8,9] of the original paper. (b) Our results for ionic solvation entropies at infinite dilution are given in Tables 3 and 4. They are all negative. We have checked the text carefully and find no missing negative signs. We assure the reader that there are no hidden reference state problems. Perhaps the confusion arises from the discussion below Eq. (17) in the context of solvation entropies upon dissolving an additional Na$^+$ ion in a finite concentration ionic solution. When this occurs at concentrations of NaCl less than 2 M the change in entropy becomes *less negative*. We feel the text is clear.

(3) There is a strong tendency to embrace the mixing of theory and the model level chosen rather than separating them. While it is not always possible to avoid this, the occasions where such a disentanglement is possible provide us with a clear picture in the path towards quantitative, reliable prediction and interpretation of experiments in this field. What we have attempted to point out is that a model can be adjusted so

that a poor theory can produce an experimental match. Similarly, a good model's agreement with experimental quantities can be ruined by a poor theory. It is here that the interplay of theory, simulation and experiment can be most fruitful. If one has a theory, and if the model used in the theory can be simulated accurately, the quality of the theory can be evaluated. If simulation does not produce numbers which match experiment then it is likely that a model adjustment is warranted.

What we have done is simply extend the ideas from the decorated hard-sphere solvent–hard sphere ion literature [#1] to look for a simple model that contains an artificial symmetry *to test the theories*, not to achieve a possibly meaningless agreement with experiment. This has a long history in the literature and was recently nicely done by Roux, Yu and Karplus (ref. [16] of our contribution) with the $Cl^{\pm}$ models, which we have adopted. Our aim was to separate out model dependence from theoretical technique in considering the origins of the agreement with experiment.

While we agree that neither LJ σs nor ion–oxygen equilibrium distances are an exact measure of the dielectric cavity diameter, the latter are certainly an indication of the cavity size. The use of artificially symmetric ion models was to demonstrate that their solvation chemical potentials are *so different* that any value of cavity diameter that would make their Born values close is completely inconsistent with the structure. The only conclusion is that there is a significant contribution to ionic solvation chemical potentials from reorientation of the solvent. This contribution is not obtainable from continuum theories and *in this case* can only be accounted for in the Born equation by setting cavity diameters to values which could be inconsistent by as much as a factor of 2. Such a solvent reorientation contribution must also be expected for more realistic systems. The use of experimental chemical potentials in the Born equation could yield misleading values of cavity diameter, and continuum theories in this form can discern neither the existence of the problem, nor its origin. The origin of the problem in a field theoretic or perturbative sense is nicely explained in the contribution of Pratt et al.

(4) While entropy-area scaling is not discussed explicitly, we direct the reader to our comment on Ben-Naim's contribution to this issue.

(5) The DRISM values for $\Delta(T\Delta S)$ for the five ion models in our paper are 4.8, 4.5, 0.06, 2.9 and 3.2 kcal/mol at 298 K for X^+, X^-, Na^+, Cl^- and Br^-, respectively. These results agree with the finding that the result depends strongly on system, particularly in the difference between the value for Na^+ and the other ions. The results seem to show that this quantity depends both on ion size and charge, presumably by the way they affect the solvent structure in the corresponding co-sphere.

To L. Pratt, G. Hummer and A. Garciá

(1) Your question is somewhat confusing. We do not know what you have in mind as "the most commonly considered solvation entropy." The reader is referred to ref. [16] for the definitions adopted here. Eq. (17) is simply a finite difference derivative of the Morita and Hiroike expression for chemical potential. As to comparisons with "formally more complete theories", we note that those the author has listed require n-body distributions where our approach would require bridge function contributions to make either formally exact. Neither are available.

(2) A hard-sphere ion at infinite dilution in a dielectric continuum is equivalent to the model conditions of the original (exact) derivation of the Born equation. For most other ionic solution models in common use it is no longer relevant to think in terms of exactness since an effective dielectric cavity diameter must be used to match the Born result. By "more exact theories" we meant theories that come closer to predicting the correct energetics for a given model than those discussed in this paper.

[#1] see for instance P.G. Kusalik and G.N. Patey, J. Chem. Phys. 89 (1988) 5843 where the asymmetric solvation of equal sized positive and negative charged hard spheres is only attributable to solvent model symmetry.

(3) Yes. This is proven in the appendix of ref. [5].

(4) There appears to be a range of ionic concentration for most ion models for which RISM and ARISM results are not possible. It is presumed that the integral equations are predicting a separation into dilute and concentrated liquid phases since this has been seen experimentally for low dielectric constant solvents (refs. [25,26]). RISM and ARISM solutions have been calculated for the more concentrated phase. Since the Debye–Hückel limiting law is correct for all ionic solutions it is presumed that there is a region of low concentration which could yield a numerical solution for low dielectric constant solvents. It is numerically difficult to do this and we have not attempted it for these models, but it has been done in a similar context in ref. [31].

(5) We would, of course, prefer to have a theory which needed no additional parameters and which correctly predicted all properties of a given model, not just the dielectric constant. We are careful to use the term 'consistent' rather than 'predictive'. The motivation for such work is that of application to biological systems, as you mention in your contribution, since useful results in this context rely on many freely adjustable parameters. For the dielectric decrement as a function of salt concentration our theory has the HNC (approximate) result (see ref. [5]) which requires a value of the pure solvent dielectric constant only. We use the experimental value for pure water with a view to biological applications, and realize that the correct value for our water model is slightly lower.