CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200903063

The Nature of Aqueous Solutions: Insights into Multiple Facets of Chemistry and Biochemistry from Freezing-Point Depressions

Andreas A. Zavitsas*[a]

Abstract: Contrary to current widely held beliefs, many concentrated aqueous solutions of electrolytes and nonelectrolytes behave ideally. For both, the same simple equation yields mole fractions of water that are equal to the theoretical activities of water. No empirical activity coefficients or ad hoc parameters are needed. Thermodynamic hydration numbers and the number of particles produced per mole of solute are found by searching freezing-point depression measurements, as if asking the water, "How much available water solvent is left and how many solute particles are there?" The results answer questions currently under debate: Do solutes alter the nature of water outside their immediate surroundings? What is the number of ion pairs formed by various electrolytes and what affects extents of their formation? What are some factors that cause precipitation of proteins, latexes, and so forth from aqueous solutions upon addition of other solutes (Hofmeister series)? Which nonelectrolytes form aggregates in water and what are the implications? Why do different solutes affect viscosity differently? How do ion-selective channels in cell membranes function at the molecular level?

Keywords: hydration number · ion channels · ion pairs · salt effect · water chemistry

Introduction

Water may be ideal for life, but it does not behave "ideally." Not much fundamental research is being carried out currently on the colligative properties of aqueous solutions, apparently with good reason. Accurate measurements are available for the important hydrophilic nonelectrolyte solutions and those of common strong electrolytes. Virtually all measurements indicate deviations from "ideal" behavior, and such deviations have been accurately expressed by activity coefficients, γ, usually described by high-degree polynomials obtained by empirical fitting of the observed deviations. Often activity coefficients of solute are reported, even though it is the activity of water solvent that is relevant to colligative properties because it is water that freezes, evaporates, and so forth. Although activity coefficients are accurate measures of deviations from ideality, there is another equally valid description: γ is an accurate measure of our inability to describe quantitatively the phenomenon being observed in terms of physically meaningful effects. This work attempts to address that problem, or at least ameliorate the current state of affairs. The results have a direct bearing on topics of current research interest: the influence of solutes on the properties of bulk water not in the immediate vicinity of solute; factors that affect ion-pair formation; some causes of the Hofmeister series and salting out; electrolyte effects on solution viscosity; limiting conductivities; ion-selective channels in cell membranes; "solventbergs" of amphiphiles; aggregates of urea; and so on.

Ideal behavior is one that adheres to theoretically expected relationships between solute concentration and the water property affected. For freezing-point depressions, the relationship is van Laar's Equation (1). T_0 and T_f in K are the freezing temperatures of pure water and of pure water–ice out of the solutions, respectively. The cryoscopic constant k_c is equal to R/L_0, in which R is the gas constant and L_0 is the enthalpy of fusion of water at 273.15 K; $k_c = 1.987/1436.2 = 1.384 \times 10^{-3}\ \mathrm{K}^{-1}$. The natural logarithm of the theoretical activity of water in the solution at T_f is denoted by $\ln(a_w)$.

$$(1/T_f - 1/T_0) = -k_c \ln(a_w) \qquad (1)$$

For ideal behavior, a_w must be equal to the mole fraction of water, x_w, which is conventionally calculated by Equa-

---

[a] Prof. Dr. A. A. Zavitsas
Department of Chemistry and Biochemistry
Long Island University, University Plaza
Brooklyn, New York 11201 (USA)
Fax: (+1) 718-488-1465
E-mail: zavitsas@liu.edu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903063.

tion (2), in which 55.509 denotes moles of water per kilogram, m is the molality (moles of solute per kilogram of water), and i is the van 't Hoff index, the stoichiometric number of particles produced per mole of solute: 1 for nonelectrolytes, 2 for NaCl, 3 for $CaCl_2$, 4 for $AlCl_3$, and so on. The quantity $(T_0-T_f)/m=K_f=1.86\,\mathrm{K\,kg\,mol^{-1}}$ is often also called the cryoscopic constant, but this approximation is valid only at high dilutions and the definition of Equation (1) is used in this work.

$$x_w = 55.509/(55.509+im) \qquad (2)$$

At realistic concentrations, x_w calculated by Equation (2) is not equal to a_w and plots of $(1/T_f-1/T_0)$ versus $\ln(a_w)$ are curved. Hence, aqueous solutions are not considered to be ideal. When the mole fraction of water is multiplied by the empirically derived activity coefficient, γ_w, at each concentration, ideal behavior is forced, so that $x_w \times \gamma_w = a_w$.

Debye–Hückel (D–H) theory is used to rationalize nonideal behavior for electrolyte solutions, but the theory is applicable only to extremely dilute solutions. "Extended" D–H theory for higher concentrations essentially also uses empirical parameters to fit the data. Also, D–H theory only refers to various interionic interactions and does not address possible ion–solvent interactions or the behavior of solutions of nonelectrolytes, which are also nonideal.

An earlier publication reported hydration numbers, h, of various solutions of nonelectrolytes and strong electrolytes, as deduced from measurements of colligative properties.[1] The term "hydration number" was defined as the number of water molecules per mole of solute that are bound sufficiently strongly to solute as to be removed from the water available as solvent for additional solute(s). This hydration number is a dynamic weighted average and was the single number that removed curvatures from plots of colligative properties over wide ranges of solute concentration. The mole fraction of water was calculated by Equation (3), in which hm was the amount of water strongly bound to solute and not available to act as solvent. The amount of water available to act as solvent for additional solute(s) will be diminished,[2,3] but the number of solute particles remains the same because strongly hydrated species act as a single entity.[3]

$$x_w = (55.509-hm)/(55.509-hm+im) \qquad (3)$$

The hydration numbers found[1] for electrolytes were quite similar to those reported for chlorides, bromides, iodides, and perchlorates by Stokes and Robinson,[2a] who obtained them by fitting empirically determined activity coefficients using two constants: the number of water molecules "bound" per mole of solute and a parameter $\mathring{a}$ denoting "the closest distance to which the center of the unhydrated anion can approach that of the hydrated cation." For nonelectrolytes, Stokes and Robinson used two essentially empirical coefficients, K and n, with n described as being related to the hydration number; for sucrose, $K=0.994$ and $n=11$; for glucose, $K=0.786$ and $n=6$, and so forth.[2b] Scatchard also used the concept of bound water for rationalizing colligative property measurements for aqueous solutions of a few nonelectrolytes.[2c] Lewis also noted[2d] in his discussion of glycine solutions in 1.0 M aqueous sucrose, "On general grounds one would expect that the water bound by the sucrose would be unavailable as solvent for the glycine." The importance of such hydration in describing the behavior of aqueous solutions was also emphasized recently.[2e] Although it was understood that strongly bound water molecules are removed from the total water available to act as solvent,[2,3] no specific value for what constitutes "sufficiently strong" binding was available. Qualitatively, it is water adhering to solute more strongly than to more water molecules. A value of binding energy necessary for removing a water molecule from the solvent was estimated for the first time as a minimum of about 13.3 kcal mol^{-1}.[1] Although previous approaches used different equations for electrolytes and nonelectrolytes, Equation (3) was applied to both and is simpler than previous efforts to account for bound water. The previous work assumed that the cryoscopic constant remained fairly constant at the temperatures of freezing-point measurements.[1]

Confusion has subsequently arisen because of terminology. For example, a recent review[4] questioned the reported[1] hydration numbers on the grounds that neutron diffraction studies showed clearly different numbers of water molecules arranged around the solutes. Diffraction techniques (neutron, X-ray, extended X-ray absorption fine structure (EXAFS)) and molecular dynamics simulations often use the term "hydration number" for the number of water molecules that surround the solute at a particular distance and generally provide firm information about the first hydration shell, those molecules immediately adjacent to the solute particle. The term "coordination number" or "solvation number" is also used in such studies, which generally do not report quantitative information about specific binding energies, even though small Debye–Waller factors in EXAFS can suggest stronger bonds when comparing isostructural coordinated ions in solution. Diffraction and molecular dynamics studies find that the number of water molecules immediately surrounding the solute generally increases with the size of the solute both for cations and anions.[5] It is not surprising that solutes dissolved in water will have water around them and that the larger the solute the more water molecules can fit immediately around it. The focus of the present work is not on how many water molecules surround the immersed particles and their geometric arrangement, but on how many of those are bound more strongly to the particle rather than to other water molecules. To avoid confusion, the term used in the present work for the number of strongly bound water molecules is "thermodynamic hydration number," or H_T. Diffraction studies and molecular dynamics simulations provide information about the structure of the solvation shells, whereas h of Equation (3) did not provide such structural information and did not distinguish between first-, second-, or higher-shell water molecules. On the other hand, h was found to correlate with many phenomena: the number of water molecules coextracted with various cations from water into nitrobenzene, charge density of the ions, theoretical calculations of sequential binding energies of water to solute, experimental gas-phase ion–water cluster sequential binding energies, ionic conductivities, some viscosities of ionic solutions, and so forth.[1] Diffraction measurements have not been reported to show any such correlations. Hydration numbers obtained from colligative properties and those from diffraction measurements bear no direct relation to each other. This had been also succinctly stated by Stokes and Robinson:[2a] "We wish to emphasize that our hydration number is not the same thing as the conventional number of water molecules in the first layer around the ion." Hydration numbers of zero were attributed[1] to Cl^-, Br^-, and I^-, as was also done by Stokes and Robinson.[2a] For Cl^-, $h=0$ was found by dielectric relaxation measurements of Buchner et al.,[6a] by many NMR spectroscopic studies,[5] and by size-exclusion chromatography measurements of Kiriukin and Collins,[7] among others. A hydration number of zero does not mean that the anion is not solvated by water. Sequential, sometimes called differential, binding energies of water to chloride ion, $Cl(H_2O)_n^-$, have been determined experimentally and are for $n=0\rightarrow1$, $\Delta H_r=-13.1$ kcal mol^{-1}; for $n=1\rightarrow2$, -12.7 kcal mol^{-1}; for $n=2\rightarrow3$, -11.7 kcal mol^{-1}; and for $n=3\rightarrow4$, -11.1 kcal mol^{-1}.[8] All are less exothermic than the minimum requirement of 13.3 kcal mol^{-1}. Cl^- is definitely solvated but not sufficiently strongly as to remove water from the bulk solvent. Corresponding exothermicities for Br^- and I^- are even smaller. Kaatze assigns hydration numbers of zero to Cl^-, Br^-, and I^- in his review of dielectric relaxation measurements,[9] as do Wachter et al.[6b]

Diffraction measurements, molecular dynamics simulations, quantum mechanical calculations of sequential binding energies, dielectric relaxation measurements, NMR and IR spectroscopic measurements, gas-phase ion–water cluster measurements, colligative property measurements, and so forth, are all valid but all do not address the same subject. Which approach is preferable depends on what aspect of water behavior one is seeking to understand.

The following peculiarities were noted in a previous work on colligative properties.[1] All solutions of the hydrophilic nonelectrolytes then examined gave linear plots of $(1/T_f-1/T_0)$ versus $\ln(x_w)$ with slopes essentially equal to the theoretical value of the cryoscopic constant, 1.384×10^{-3} K^{-1}. However, solutions of strong electrolytes gave slopes somewhat lower than theoretical by up to 20% for some linear plots of various strong electrolytes of chlorides, bromides, and iodides.

The linearities of the plots obtained over wide ranges of electrolyte concentration led to the conclusion that ion pairs were not evident, because the extent of ion-pair formation, if any, would increase with increasing salt concentration according to the law of mass action.[1] This would have made linear plots impossible over wide ranges of concentration. However, ion pairs have now been experimentally observed by various techniques.[10]

The present work establishes a model and procedure for describing accurately freezing-point depressions, without the use of empirical activity coefficients or of ad hoc parameters. The method is the same for both electrolytes and nonelectrolytes. It is found that the concentrated solutions treated here exhibit ideal behavior in all respects over wide ranges of concentration, contrary to currently common beliefs. The peculiarities noted previously[1] are addressed and explained by searching freezing-point depression data for their causes, which are found in the measurements.

Ion pairing: Determining the extent of ion-pair formation in aqueous solutions is not a straightforward task. As noted by Lewis and Randal:[11] "It would be necessary to know how far apart the constituent atoms of a molecule must be, to warrant our calling the molecule dissociated. But such a decision would be arbitrary, and according to our choice of this limiting distance, we should find one or another degree of dissociation." In the present work, this problem is eliminated by not assigning any specific distances, but by examining measurements of freezing-point depression to determine how many particles the observed depression indicates.

Ion-pair formation is generally depicted as in Equation (4), for example, for MX, in which M^+ and X^- denote the "free" ions and $^+M||X^-$ denotes ion pairs of all kinds.

$$M^+ + X^- \rightleftharpoons {}^+M||X^-; \qquad K_A = [{}^+M||X^-]/([M^+][X^-]) \tag{4}$$

The law of mass action requires that the degree of association to ion pairs increases as the concentration of the solute increases. However, there have been several reports that the degree of association is relatively independent of concentration over wide ranges. For example, in 1912 G. N. Lewis[12] noted that, "As a matter of fact, it is well known that in the case of the so-called strong electrolytes this ratio [of K_A] varies enormously with concentration." The law of mass action appears not to hold for Equation (4)! Bancroft and Davis[13] found that the degree of dissociation of KCl, KBr, and KI into free ions at 25 °C "was practically constant at about 80 percent over a considerable range of concentrations." The wide concentration ranges examined were 1.0 to 4.4m KCl, 0.03 to 7.0m KBr, and 0.07 to 7.0m KI. Recent work by Heyrovska[14] proposed detailed lists of the degree of dissociation of strong electrolytes that gave fairly constant values generally between 0.1 and 5.0m for HCl, HBr, HI, $HClO_4$, $LiClO_4$, NaCl, $NaClO_4$, NaCNS, and KCNS. Fluorides and hydroxides did not exhibit similar constancies. As Lewis remarked 88 years ago:[11] "To those who have not examined this question closely it may be surprising to learn how far K_A is from being constant." Activity coefficients, γ, were introduced specifically for this reason so that molalities multiplied by their corresponding empirical γ would produce activities, or "effective concentrations," so that "K_A is an exact constant."[12]

The problem of violating the law of mass action is due to the formulation of Equation (4). To describe realistically ion-pair formation, account must be taken of the fact that ions are hydrated by strongly bound water. For a strong 1:1 electrolyte MX, the reaction-forming ion pairs are as in Equation (5), assuming four water molecules bound to M^+ and none to X^-. Ion-pair formation would replace at least one of the water molecules strongly bound to M^+ by X^- to form ion pair $M(H_2O)_3X$:

$$\begin{aligned} &M(H_2O)_4{}^+ + X^- \rightleftharpoons M(H_2O)_3X + H_2O;\\ &K_e = [M(H_2O)_3X][H_2O]/([M(H_2O)_4{}^+][X^-]) \end{aligned} \tag{5}$$

The law of mass action holds according to Equation (5) and requires that the degree of dissociation remains constant over wide concentration ranges, as found experimentally. The remaining water is "spectator." Even if introduced in Equation (5), it would appear on both sides and cancel. The equilibrium constant K_A of Equation (4) has units of M^{-1}, whereas K_e of Equation (5) is dimensionless. It does not appear that the equilibrium expression of Equation (5) has ever been proposed previously for ion-pair formation. Many types of ion pairs have been postulated or detected by various techniques: intimate ion pairs, contact ion pairs, solvent separated, solvent shared, double solvent separated, and so forth, as described in a recent review of the subject,[10] which also describes the extensive work that has been done to establish the extent of ion pairing and the elaborate procedures involved. In the present work, ion pairs are defined as only those species that affect colligative properties, that is, the total number of individual particles, ions, and ion pairs that affect the behavior of the solvent (depression of freezing point, and so on). It is emphasized that the definition used here is not the same thing as the ones used by various other techniques.[10] Specifically, if $1.00\,m$ electrolyte MX is dissociated to the extent of 80% into "free" ions, the total number of particles present will be the molality of solute multiplied by $(0.80+0.80+0.20=1.80)$, rather than the stoichiometric 2.00. The calculated x_w with Equation (2) and 80% dissociation will be 0.96859; with 100% dissociation, x_w will be 0.96522. The difference is only 0.35%. Calculated by Equation (3) with $h=4.0$ and 80% dissociation, $x_w=0.96624$; with 100% dissociation, $x_w=0.96262$, for a difference of only 0.38%. At $2.0\,m$ MX, the differences would still be less than 0.8%. Such small differences would not have affected much the linearities of the previously reported plots of Equation (1),[1] but may affect the slopes of such plots.

The cryoscopic constant: To establish how an ideal solution is expected to behave according to theory, account must be taken of any variations of k_c in Equation (1). Because freezing-point depressions are measured over a range of temperatures, the cryoscopic constant is not truly a constant. Only for small freezing-point depressions, $\Delta T < 6\,°C$, can it be approximated as such. For treating accurately measurements of greater ΔT, knowledge of the temperature dependence of the enthalpy of fusion, L_f, is required to use the correct L_f at each T_f. An early estimate of L_f as a function of ΔT was provided by Lewis as $L_f = L_0 - 4.5\Delta T$.[15] Several other approaches are available for obtaining L_f at various T_f. Hildebrand and Scott provide Equation (6) for relating a_w to ΔT to account for the variability of L_f.[16] $\Delta T = (T_0 - T_f)$ and ΔC_p is the difference between the heat capacities of water and of ice at atmospheric pressure at 273.15 K. The value $\Delta C_p = 9.2495\ \text{cal mol}^{-1}\,\text{K}^{-1}$.

$$\ln(a_w) = -(L_0\Delta T)/(RT_0T_f) + (\Delta C_p/R)[\Delta T/T_0 - \ln(T_f/T_0)] \tag{6}$$

When the ideal value of $\ln(a_w)$ from Equation (6) is inserted in the ideal Equation (1), the value of L_f is obtained at any T_f by $L_f = -R[\ln(a_w)/(1/T_f - 1/T_0)]$. Other similar type relations between ideal a_w and ΔT are available from, for example, Glasstone,[17] Scatchard,[18] Robisnson and Stokes,[19] and Blandamer et al.[20]

Plots of enthalpies of fusion of water at atmospheric pressure obtained from the above six relationships are shown in Figure 1 up to $\Delta T = 70\,°C$. All yield essentially the same results up to about $\Delta T = 20\,°C$. The change in L_f is significant. The fractional change is greater from 0 to −70 °C than the change in the enthalpy of vaporization of water from 0 to 100 °C. The relation of ref. [14], Equation (6), is adopted for this work. It is near the average of all six and does not make the approximation of $T_0T_f \approx T_0^2$.

Somewhat greater declines of L_f of Figure 1 have been estimated from freezing-point depressions of various solutions up to $\Delta T = 20\,°C$,[21] greater by about 3% at $\Delta T = 10\,°C$ and by 7% at $\Delta T = 20\,°C$ per mole of total water. If account had been taken of the amount of water that is not "freezable" because it is tightly bound to solute, the L_f values ob-

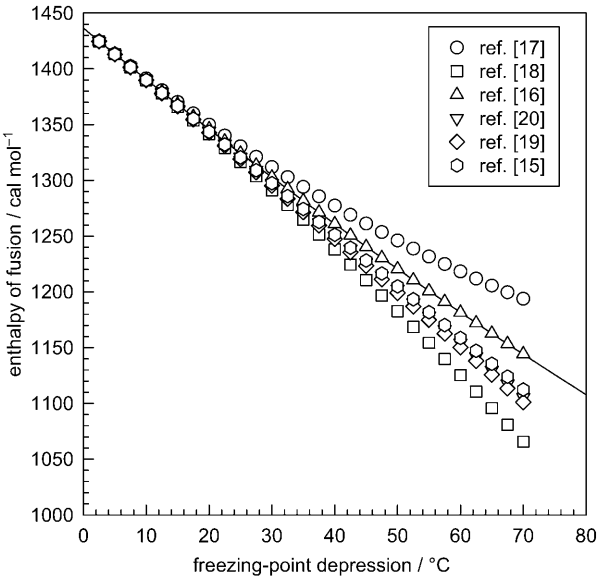

Figure 1. Enthalpy of fusion of water versus freezing-point depression obtained from the references indicated. The second-order regression line is shown for the relation of Equation (6): $L_f = 1436.4 - 4.6668(\Delta T) + 7.0213\times10^{-3}(\Delta T)^2\ \text{cal mol}^{-1}$.

tained[21] per mole of water available for freezing would have been somewhat greater and more in line with the results of Figure 1. No account was taken of the fraction of water that is not "freezable" because it is tightly bound to solute. Greater declines of L_f with decreasing temperature have been reported for supercooled pure water.[22] However, the changes that occur in solution will be different as the solutes interact with the water and there will be heat changes as the concentration of solute is altered on ice melting (heat of dilution). In addition, supercooled pure water is in a metastable state, whereas it is in a stable state in solutions below 273.15 K.

Despite the significant deviations in L_f shown for $\Delta T > 20\,°C$ in Figure 1 for the six relations, the effect is not great on the quantities of interest in this work, the calculated activities of water for ideal behavior, a_w. Figure 2 shows plots of a_w versus ΔT, in which the selected relation of Equation (6) is shown with filled symbols. The six relations are essentially equivalent up to about $\Delta T = 40\,°C$. All measurements treated in this work have $\Delta T < 40\,°C$, except for two (of H_2O_2 and of NH_3 solutions), so that the particular choice among the six is not critical.

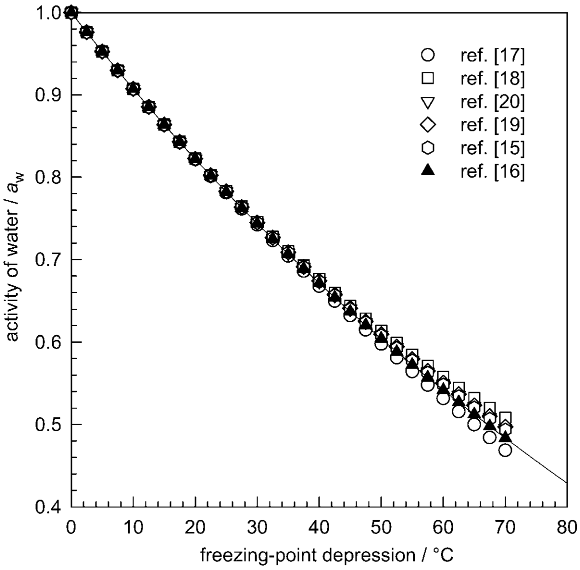

Figure 2. Ideal activity of water versus freezing-point depression obtained from the references indicated in the inset. The selected Equation (6) is shown as filled symbols and the third-order regression line for it is shown: $a_w = 1.0000 - 9.6605\times10^{-3}(\Delta T) + 4.0673\times10^{-5}(\Delta T)^2 - 1.1512\times10^{-7}(\Delta T)^3$.

An expedient way often used for obtaining a_w from ΔT is through the osmolality per kilogram commonly obtained by $\mathrm{Osm} = \Delta T/1.8598$ for extended ranges of ΔT so that $-\ln(a_w) = \mathrm{Osm}/55.509$. The variation of L_f with temperature renders this approach invalid by a significant amount for $\Delta T > 10\,°C$. Expressing osmolality per kilogram as $\mathrm{Osm} = \Delta T/Y$ allows the calculation of Y by $Y = -\Delta T/[55.509\times\ln(a_w)]$, with the values of ideal a_w established above. This is the Y value needed for obtaining the correct a_w. The results are shown graphically in Figure 3. At $\Delta T = 10\,°C$, $Y = 1.849$; at 20 °C, 1.830; at 30 °C, 1.826; at 50 °C, 1.787; and at 70 °C, 1.736.[23] The plot shows a "wiggle" near $\Delta T \approx 0$, but the Y intercept of the curve of a second-order regression is 1.858. The above results are different from those proposed by Scatchard, whose Y is essentially constant at 1.86 ± 0.02.[18]

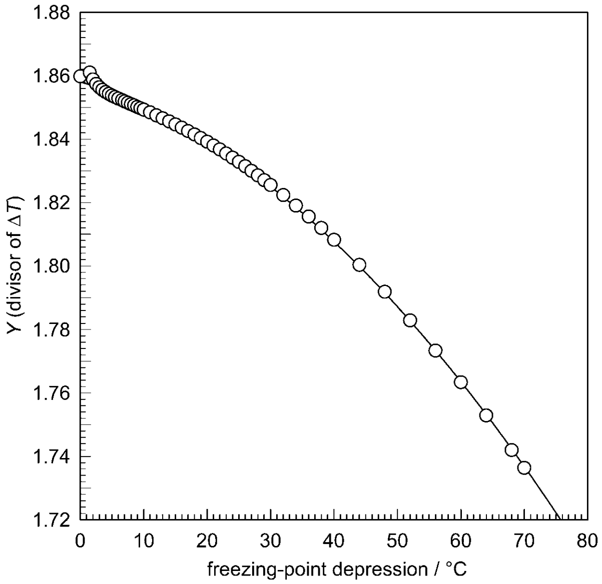

Figure 3. Plot of Y versus freezing-point depression. Y is the value by which ΔT must be divided to obtain the activity of water by $a_w = \exp[-\Delta T/(Y\times55.509)]$.

The model: A model for describing behaviors of aqueous solutions must include expected physically meaningful effects. Effects influencing colligative properties include: a) the thermodynamic hydration number, H_T, and b) the extent of dissociation, or ion-pair formation, as quantified by i_e, the number of particles per mole of solute that are effective in depressing the freezing point.

H_T should be fairly constant when a very large excess of water is available. H_T is a weighted average of various distributions of waters of hydration, which exchange with the bulk water and with the variously hydrated ions. At very high solute concentrations, less "free" water will be available and eventually there will a competition for water, as in Equation (7), in which M^+ denotes an ion. This will result in the onset of a decrease of the average thermodynamic hydration number H_T.

$$M(H_2O)_4{}^+ + M^+ \rightleftharpoons M(H_2O)_3{}^+ + M(H_2O)^+ \rightleftharpoons 2\,M(H_2O)_2{}^+ \tag{7}$$

The extent of ion-pair formation should also be constant in the presence of a large excess of water, as required by the equilibrium expression of Equation (5).

Equation (8) incorporates effects a and b. The van 't Hoff stoichiometric index i of Equation (3) does not account for formation of ion pairs. Equation (8) uses the number of particles per mole of solute that are effective in lowering the freezing point, i_e, thus accounting for all particles including any ion pairs that act as a single entity in affecting colligative properties.

$$x_w = (55.509 - mH_T)/(55.509 - mH_T + mi_e) \qquad (8)$$

The answer as to whether and to what extent H_T and i_e are constant should be lying hidden in the freezing-point depression measurements. Also, the measurements should contain information about the extent to which inclusion of these two effects in the model of Equation (8) is sufficient for describing reality accurately and about the concentration range of the validity of the model.

The procedure: The information about H_T and i_e contained in the experimental measurements is found as follows. For each point in the data set of a particular solute, the theoretical a_w is obtained by solving Equation (1) at each T_f of the data set with the corresponding value of L_f. Then H_T is assigned sequentially from $H_T = -2.0$ up to, if necessary, 26.0, by increments of 0.1 H_T unit. At each H_T value, Equation (8) is solved at each T_f for the value of i_e needed to produce $x_w = a_w$. At first, different values of i_e result for each T_f point with the same H_T, until at a particular H_T the procedure yields essentially identical numbers of effective particles, i_e, for all points in the set, or for a large portion of them. There is some leeway in obtaining good agreement with theory, a higher H_T being compensated by a lower i_e, but this is usually a small effect of about ±0.15 units of H_T (±0.4 units for small $H_T < 1.0$). In this way the information contained in the data is found regarding the thermodynamic hydration number, the extent of ion-pair formation, and the range of concentration over which H_T and i_e are constant. The procedure is a computer-aided heuristic approach for finding information contained in the data, but not obviously apparent. "Mining the data" in current parlance. H_T and i_e are not arbitrary fitting parameters, but describe physical phenomena known to affect colligative properties. The data thus provide a clear, quantitative answer as to the validity of the model and to the magnitude of each effect a and b.

Demonstration of the application of the procedure is simplest for hydrophilic nonelectrolytes. Measurements of freezing-point depressions of maltose solutions[24] yield a constant $H_T = 5.8$ and $i_e = 1.00$ up to 42 wt% (724 g of maltose per 1000 g of water) and maximum ΔT of 4.878 °C. Figure 4 is a plot of Equation (1) with x_w obtained by Equation (8) (solid circles). The solid line is the theoretical line of $-\ln(a_w)$, not the best fit to the data. The open circles are calculated with x_w obtained by the conventional Equation (2). The inset values in the figure are the ratios of theoretical a_w to x_w, from 2 to 42 wt% in steps of 4 wt%. This ratio is the activity coefficient, γ_w, of "free" or bulk water, not strongly bound to solute. All activity coefficients are within 0.06% of 1.0000, as required by ideal behavior. Plots of $(1/T_f - 1/T_0)$ versus $-\ln(a_w)$ remain quite linear for $\Delta T < 6$ °C. Linear regression through the origin yields a slope of 1.388×10^{-3} K^{-1}, compared to the cryoscopic constant $k_c = 1.384 \times 10^{-3}$ K^{-1} at 273.15 K.

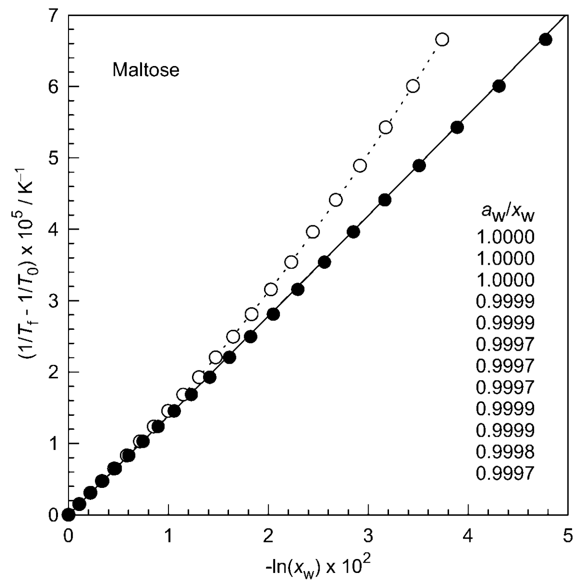

Figure 4. Plot of Equation (1) for maltose solutions, up to 42 wt% (2.116 m) and $\Delta T = 4.878$ °C. The solid line is a plot of the theoretical $\ln(a_w)$. Open circles: x_w obtained by conventional Equation (2); solid circles: x_w obtained by Equation (8), with $H_T = 5.8$ and $i_e = 1.00$. Inset: activity coefficients of "free" water (solid circles), in steps of 4 wt%, $a_w/x_w = \gamma_w$.

The procedure for strong electrolytes is demonstrated in Figure 5, which shows four plots of Equation (1) using different ways of treating measurements of NaCl solutions[24] up to 23.00 wt% (5.111 m) and $\Delta T = 20.667$ °C. The solid line is a plot of the theoretical $-\ln(a_w)$ and shows a noticeable curvature as a result of varying L_f. The open circles represent calculation of x_w by the conventional Equation (2), which disregards bound water and assumes complete dissociation; a substantial curvature is obtained, not matching the theoretical line. The squares represent x_w calculated by Equation (3), which assumes complete dissociation; a straight line is obtained with $H_T = 3.8$, but the line does not match the theoretical line and the slope is only 1.194×10^{-3}, 14% lower than the theoretical value. The triangles represent the best possible fit to the theoretical line that can be obtained by using Equation (3) ($H_T = 1.6$), which assumes complete dissociation; the points thus obtained curve around the theoretical line, first to the right and then to the left of it. The filled circles represent x_w obtained by Equation (8), with $H_T = 3.4$ and $i_e = 1.69$, the values obtained by the procedure described. Now there is an excellent match with the ideal solid line.

At saturation in Figure 5, $mH_T = 5.111 \times 3.4 = 17.3$ moles of water are strongly bound and there are $mi_e = 5.116 \times 1.69 = 8.64\,m$ particles in solution. The value of $i_e = 1.69$ represents 69% separate ions and 31% ion pairs (0.69 + 0.69 +

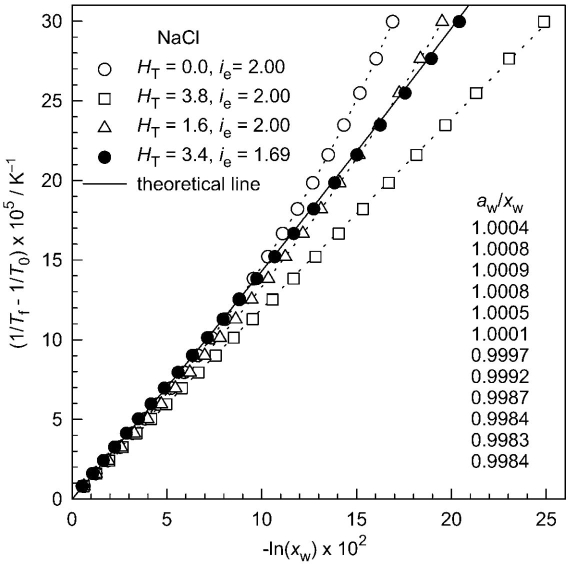

Figure 5. Plot of Equation (1) up to 5.111 m NaCl. The solid line is the theoretical $\ln(a_w)$. Open circles: x_w obtained by using conventional Equation (2). Squares: x_w obtained by using Equation (3), complete dissociation. Triangle values were obtained by using Equation (3), complete dissociation, with $H_T = 1.6$ providing the best possible, but poor, match to the theoretical line. Filled circles: x_w obtained by using Equation (8), with $H_T = 3.4$ and $i_e = 1.69$. Inset values: $a_w/x_w = \gamma_w$ of solid circles (alternate points).

0.31). The fraction of ion pairs represents pairs of all kinds that are affecting the freezing point. The data show that H_T and i_e remain constant throughout the solubility domain of NaCl. The equilibrium constant for ion-pair formation by Equation (5) is $K_e = 0.31^2/0.69^2 = 0.20$, and the Gibbs free-energy change is $\Delta_r G = 0.84$ kcal mol^{-1} at 263 K, the average of the temperature range of the measurements. The values of $a_w/x_w = \gamma_w$ inset in Figure 5 pertain to the solid circles and $\gamma_w = 0.9997 \pm 0.0006$ (unsigned average deviation of alternate points). The activity coefficients of "free," unbound water remain throughout at $\gamma_w = 1.00$, the activity coefficient of pure water by definition. The solid circles in Figure 5 are accurately[25] described by $(1/T_f - 1/T_0) = 1.393 \times 10^{-3} [-\ln(x_w)] + 3.344 \times 10^{-4} [-\ln(x_w)]^2$. The leading coefficient on the right-hand side of the equation is essentially the value of the theoretical cryoscopic constant at 273.15 K, as required for ideal behavior.

Results

Results for some nonelectrolyte solutions are presented in Table 1. Measurements of ammonia solutions show the greatest range treated successfully, $\Delta T = 60.77$ °C. Data from

Table 1. Summary of results by Equation (8) for nonelectrolyte solutions that exhibit stoichiometric dependence of the number of particles produced per mole of solute, $i_e = 1.00$.

Compound	H_T[a]	i_e[b]	wt %[c]	m[c]	ΔT[c]	c_1[d]	γ_w[e]	Ref.
NH_3	1.53	1.00	26.00	20.63	60.77	1.377	0.9981	[24]
NH_3	1.53	1.00	25.41	19.68	58.00	1.352	0.9978	[26]
NH_3	1.53	1.00	25.41	20.00	58.00	1.413	1.0006	[26]
H_2O_2	0.91	1.00	40.49	20.00	43.00	1.422	1.0013	[26]
H_2O_2[f]	0.93	1.00	45.00	24.05	53.40	1.416	0.9999	[26]
methanol	0.73	1.00	30.00	13.38	25.91	1.406	1.0003	[24]
methanol	0.93	1.00	24.26	10.00	20.00	1.362	0.9997	[26]
ethanol	1.48	1.00	32.00	10.21	22.44	1.341	0.9989	[24]
ethanol	1.44	1.00	31.54	10.00	22.00	1.371	0.9993	[26]
$(HOCH_2CH_2)_2$	1.49	1.00	36.00	9.06	19.82	1.359	0.9995	[24]
glycerol	1.94	1.00	28.00	4.22	8.77	1.401	1.0002	[24]
glycerol	2.17	1.00	18.72	2.50	5.00	1.399	1.0000	[26]
mannitol[g]	2.00	1.00	15.00	0.97	1.84	1.383	1.0000	[24]
glucose	2.50	1.00	30.00	2.38	4.79	1.394	0.9999	[24]
glucose[g]	2.51	1.00	24.47	1.80	3.55	1.396	1.0000	[27]
fructose[g]	2.10	1.00	28.00	2.16	4.20	1.386	0.9998	[24]
sucrose[g]	6.00	1.00	42.00	2.12	4.93	1.393	0.9999	[24]
sucrose	6.00	1.00	40.64	2.00	4.60	1.393	1.0000	[26]
sucrose[g]	6.30	1.00	29.07	1.20	2.54	1.393	1.0000	[27]
maltose	5.80	1.00	42.00	2.12	4.88	1.388	0.9998	[24]
lactose[g]	6.10	1.00	39.61	1.92	4.34	1.400	1.0002	[28]
raffinose[g]	11.90	1.00	16.80	0.40	0.81	1.383	1.0000	[27]
$H_2NCH_2CH_2OH$[h]	1.50	1.00	24.40	5.28	10.81	1.397	1.0011	[29]
$HN(CH_2CH_2OH)_2$[i]	2.55	1.00	32.87	4.66	10.41	1.399	0.9995	[29]
$N(CH_2CH_2OH)_3$[j]	2.75	1.00	40.46	4.55	10.29	1.412	1.0003	[29]
DEANOL	3.40	1.00	29.92	4.79	11.50	1.370	1.0003	[29]
DGA[k]	4.00	1.00	29.07	3.90	9.59	1.391	0.9995	[29]
$H_2NC(CH_2OH)_3$[l]	0.70	1.00	20.00	2.06	3.85	1.384	0.9999	[24]
tartaric acid[g]	2.93	1.00	40.00	4.44	10.20	1.396	1.0000	[24]
tartaric acid	2.94	1.00	42.87	5.00	11.75	1.407	1.0000	[26]

[a] Thermodynamic hydration number. [b] Number of particles per mole that are effective in reducing the freezing point. [c] From zero up to the value indicated. [d] Coefficient of the leading term ($\times 10^3$) of the polynomial fit through the origin to the points obtained by Equation (8). [e] Average ratio of ideal a_w to calculated x_w over the concentration range indicated. [f] Up to the eutectic. [g] All available data. [h] Ethanolamine. [i] Diethanolamine. [j] Triethanolamine. [k] Diglycolamine. [l] Tris-hydroxymethylaminomethane.

three available sets[24,26] are shown together in Figure 6. The extent of ionization to produce two particles is negligible in concentrated solutions of ammonia ($pK_b = 4.75$). The curvature of the theoretical solid line is clear and the applicability of the method is evident over a very wide range of ΔT and molality. At the highest concentration (26 wt %, 20.63 m) treated successfully by Equation (8) with $H_T = 1.53$ and $i_e = 1.00$, 57 % of the total water is bound. At the next available measurement at 28 wt % and 22.83 m, the point deviates from the ideal line and is not plotted. Competition as outlined in Equation (7) evidently sets in and the thermodynamic hydration number begins to decline. The ratio $a_w/x_w = \gamma_w$ by Equation (8) for all 36 points in Figure 6 is 0.9991 ± 0.0012 (unsigned average deviation).

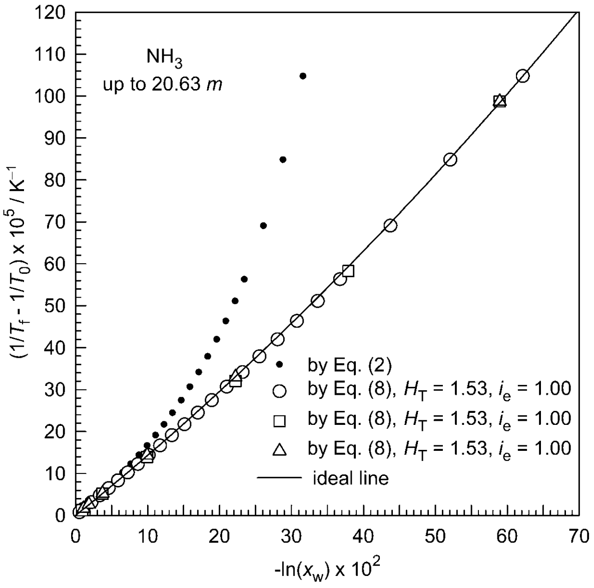

Figure 6. Plot of Equation (1) for NH_3 solutions. The solid line is the theoretical $\ln(a_w)$. Dots represent x_w obtained by using conventional Equation (2) (data of ref. [24]); open circles by Equation (8) (ref. [24]); open squares by Equation (8) (ref. [26], p. 261); and open triangles by Equation (8) (ref. [26], p. 254).

Results of additional measurements of freezing-point depression of nonelectrolyte solutions that exhibit $i_e = 1.00$, the stoichiometric value, are summarized in Table 1 for hydrogen peroxide, methanol, ethanol, ethylene glycol (ethane-1,2-diol), glycerol (propane-1,2,3-triol), D-mannitol ((2*R*,3*R*,4*R*,5*R*)-hexane-1,2,3,4,5,6-hexol), D-glucose (6-(hydroxymethyl)oxane-2,3,4,5-tetrol), D-fructose ((2*R*,3*S*,4*R*,5*R*)-2,5-bis(hydroxymethyl)oxolane-2,3,4-triol), sucrose, maltose, lactose (4-*O*-β-D-galactopyranosyl-β-D-glucopyranose), raffinose (maltotriose), ethanolamine (2-aminoethanol), diethanolamine (2,2′-iminodiethanol), triethanolamine (2,2′,2″-nitrilotriethanol), DEANOL (2-(dimethylamino)ethanol), diglycolamine (2-(2-aminoethoxy)ethanol), tris-hydroxymethylaminomethane (2-amino-2-hydroxymethylpropane-1,3-diol), and D-tartaric acid (2,3-dihydroxybutanedioic acid).

In Table 1 and subsequent tables, the columns headed by c_1 and γ_w indicate the following. Results of the calculations of x_w by Equation (8) were fitted to polynomials: $a = c_1 b + c_2 b^2 + c_3 b^3$, in which $a = (1/T_f - 1/T_0)$ and $b = -\ln(x_w)$. For maximum $\Delta T < 6.0\,^\circ C$, plots of Equation (1) are very nearly linear and only the first term is needed to represent the results accurately; for ΔT up to 40 °C, two terms are needed; for $\Delta T > 40\,^\circ C$, a third-degree polynomial is needed. For ideal behavior, the coefficient of the leading term, c_1, should be equal to the value of the cryoscopic constant at 273.15 K, $1.384 \times 10^{-3}\,K^{-1}$. The average of all c_1 entries in Table 1 is 1.389×10^{-3}. The ratio of the theoretical activity of water to mole fraction of water calculated by Equation (8), $a_w/x_w = \gamma_w$, should be unity if the solute does not affect the properties of bulk, unbound water. This ratio remains at 1.00 throughout the concentration ranges of all entries in Table 1.

Results of nonelectrolyte solutes that exhibit $i_e < 1.00$ are presented in Table 2 for 1-propanol, 2-propanol, 2-butanol, methylamine, dimethylamine, ethylamine, diethylamine, urea, urethane (ethyl carbamate), acetamide, 2-pyrrolidone, acetic acid, lactic acid (2-hydroxypropanoic acid), glycine (2-aminoacetic acid), and glutamine (2-amino-4-carbamoylbutanoic acid). In these cases, i_e is generally between 0.90 and 0.98, thereby indicating some small aggregation of solute molecules in the range of concentration for which treatment by Equation (8) matches theoretical expectations. The acids and bases included have small ionization constants and formation of ions does not contribute significantly to the number of particles in concentrated solutions. Activity coefficients of water, γ_w, remain at 1.00, thereby indicating no effect of the solutes on the structure of bulk water. Figure 7 is a plot of Equation (1) for diethylamine as an example of solutions treated successfully up to the eutectic point.

Results for solutions of strong electrolytes are presented in Table 3 for HCl, HBr, HI, LiCl, NaCl, NaBr, NaI, NaSCN, KCl, KBr, KI, KSCN, RbCl, CsCl, NH_4Cl, $MgCl_2$, $CaCl_2$, $SrCl_2$, $SrBr_2$, $BaCl_2$, $BaBr_2$, $AlCl_3$, $FeCl_3$, $MnCl_2$, $CoCl_2$, $NiCl_2$, and $CuCl_2$. The thermodynamic hydration numbers found here are ascribed only to the cations. $H_T = 0$ for Cl^-, Br^-, and I^-, consistent with data already cited. Additional support comes from a study of the residence time of a water molecule around Cl^- and around other water molecules.[36a] The two are the same and there is no preference for water to adhere to chloride rather than to bulk water. Diffusion studies also find that the best fit to the data is obtained with $H_T = 0$ for Cl^- and for ClO_4^-.[36b] Solvation of Cl^- and Br^- has also been studied and it was found that the water molecules in the first shell around the anions maintain water–water interactions that "greatly resemble those formed in the bulk liquid."[37]

Activity coefficients of "free" water remain at $\gamma_w = 1.00$ throughout the range of solute concentrations treated in Table 3, indicating no significant effect of these strong electrolytes on the structure of bulk water.

As an example of absence of ion pairing, Figure 8 shows the plot of Equation (1) for HI solutions. The ratio of effec-

Table 2. Summary of results by Equation (8) for nonelectrolyte solutions with $i_e < 1.00$ and the hydrophobic effect.

Compound	H_T[a]	i_e[b]	wt %[c]	m[c]	ΔT[c]	c_1[d]	γ_w[e]	Ref.
1-propanol	0.60	0.97	20.00	4.16	7.55	1.382	1.0004	[24]
1-propanol	0.80	0.96	19.38	4.00	7.28	1.374	1.0000	[26]
2-propanol	2.10	0.97	20.00	4.16	8.52	1.393	1.0000	[24]
2-propanol	2.50	0.87	23.10	5.00	9.90	1.374	0.9998	[26]
2-butanol	4.90	0.98	10.59	1.60	3.30	1.397	1.0000	[30]
$MeNH_2$	2.70	0.94	21.62	8.88	23.68	1.390	1.0000	[31]
Me_2NH[f]	4.16	0.90	21.79	6.18	17.35	1.399	1.0007	[31]
$EtNH_2$[f]	3.87	0.89	19.25	5.29	12.70	1.409	1.0000	[31]
Et_2NH[f]	6.10	0.89	20.98	3.63	9.51	1.371	0.9999	[31]
urea	0.00	0.96	20.00	4.16	7.00	1.414	0.9998	[24]
urea	0.00	0.94	16.83	3.40	5.59	1.390	1.0000	[32]
urethane	0.00	0.95	5.79	0.69	1.19	1.386	1.0000	[32]
acetamide[g]	0.00	0.97	17.42	3.57	6.18	1.394	0.9998	[32]
pyrrolidone[f]	0.00	0.98	41.60	8.37	13.70	1.400	0.9999	[33]
acetic acid	0.00	0.96	10.00	1.85	3.23	1.399	1.0001	[24]
lactic acid	0.00	0.91	18.00	2.44	3.96	1.381	0.9998	[24]
glycine[g]	0.00	0.978	10.12	1.50	2.68	1.396	1.0000	[34a]
glutamine[g]	0.00	0.977	2.62	0.184	0.333	1.384	1.0000	[35]

[a] Thermodynamic hydration number. [b] Number of particles per mole that are effective in reducing the freezing point. [c] From zero up to the value indicated. [d] Coefficient (×10^3) of the leading term of polynomial regression through the origin to the points obtained by Equation (8). [e] Average ratio of ideal a_w to calculated x_w over the concentration range indicated. [f] Up to the eutectic point. [g] All available data.

tive number of particles to stoichiometric value is $i_e/i = 1.00$ up to 4.00 m hydrogen iodide (8.00 m ions), at which point 51 % of the total water is bound.

Figure 9 shows the plot of Equation (1) for $FeCl_3$ solutions, which show extensive ion-pair formation with $i_e/i = 0.75$.

At the highest point successfully treated (1.3533 m $FeCl_3$), there are 4.07 moles of effective particles in solution (1.3533×3.01). Of the total water, 46 % is strongly bound (1.3533×19.0/55.509).

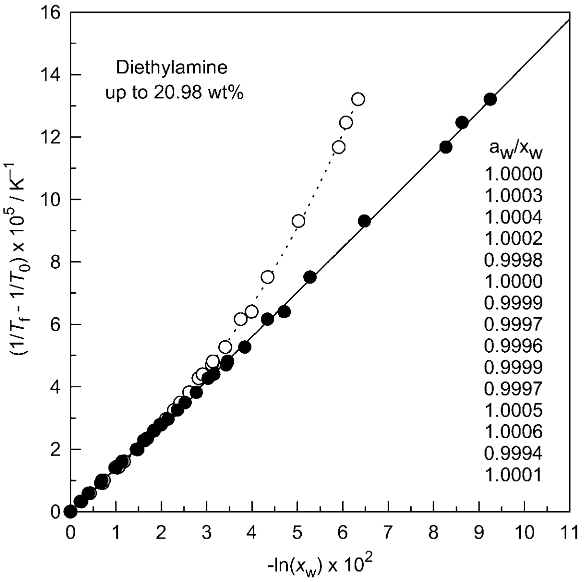

Figure 7. Plot of Equation (1) for diethylamine, up to 3.63 m and $\Delta T = 9.51\,°C$. The solid line plots the theoretical $\ln(a_w)$. Open circles: x_w obtained by conventional Equation (2). Filled circles: x_w obtained by Equation (8), $H_T = 6.1$, $i_e = 0.89$. Inset values: $a_w/x_w = \gamma_w$ (of solid circles, alternate points). Data from ref. [31].

Plots of Equation (1) with mole fractions obtained by Equation (8) are given in the Supporting Information for the 92 entries of Tables 1–3, with the values of a_w/x_w for each point, and of c_1, c_2, and c_3 for each entry as required by the maximum ΔT.

Discussion

Evaluation: Evaluation of the validity of modeling mole fraction of water by Equation (8) should include the following facts.

The model describes accurately all data up to saturation or to the eutectic point (when known) in eleven cases. They are, with the percent of bound water, $mH_T/55.509$, at the maximum concentration in parentheses: H_2O_2, 39 % of the total water is bound (45 wt % solute); dimethylamine, 46 % (22 wt % solute); ethylamine, 37 % (22 wt % solute); diethylamine, 40 % (19 wt % solute); 2-pyrrolidone, 0.0 % (41.60 w % solute); NaCl, 32 % (23 wt % solute); KCl, 6 % (20 wt % solute); KBr, 8 % (31 wt % solute); KI, 17 % (52 wt % solute); NH_4Cl, 11 % (20 wt %); and $BaCl_2$, 23 % (22 wt % solute).

For glucose, the eutectic occurs at 31 wt % and the model used here remains valid to 30 wt % with 11 % bound water. For $SrCl_2$ the eutectic occurs at 26.2 wt % and the model used remains valid to 24.1 wt % with 42 % bound water.

Not all measurements in Tables 1–3 are available to the saturation point or to the eutectic. For those that are, the method used does not always cover the entire available range. Some such examples of limits of validity in terms of the amount of bound water are the following: HCl, valid up to 40 % bound water; LiCl up to 36 %; $MgCl_2$ up to 51 %; $CaCl_2$ up to 46 %; $AlCl_3$ up to 41 %; $FeCl_3$ up to 50 %. It is not possible to model all solutes up to saturation or to the

Table 3. Summary of results by Equation (8) for strong electrolyte solutions.

Compound	H_T[a]	i_e[b]	wt %[c]	m[c]	ΔT[c]	c_1[d]	γ_w[e]	Ref.
HCl	6.60	1.90	11.00	3.39	17.89	1.409	0.9997	[24]
HCl	6.60	1.91	6.80	2.00	8.86	1.372	0.9998	[26]
HBr	7.00	2.00	24.45	4.00	26.00	1.374	0.9995	[26]
HI	7.10	2.00	33.85	4.00	26.20	1.369	0.9994	[26]
LiCl	6.70	1.89	12.00	3.21	16.59	1.374	0.9993	[24]
LiCl	6.70	1.88	11.28	3.00	15.12	1.368	0.9997	[26]
NaCl	3.40	1.69	23.00	5.11	20.67	1.393	0.9997	[24]
NaCl[f]	3.40	1.69	23.31	5.20	21.12	1.388	0.9998	[26]
NaBr[g]	3.50	1.79	17.00	1.99	7.32	1.380	1.0000	[24]
NaBr	3.50	1.80	17.07	2.00	7.36	1.386	1.0001	[26]
NaI	3.90	1.87	13.03	1.00	3.66	1.387	0.9999	[26]
NaSCN[g,h]	3.40	1.76	10.00	1.37	4.71	1.393	1.0000	[24]
KCl	1.30	1.74	13.00	2.00	6.45	1.421	1.0003	[24]
KCl[i]	1.00	1.74	19.74	3.30	10.69	1.381	0.9999	[26]
KBr	1.10	1.75	32.00	3.95	12.98	1.397	1.0001	[24]
KBr[i]	1.20	1.74	31.34	3.84	12.60	1.381	1.0001	[26]
KI	1.40	1.82	40.00	4.01	13.97	1.364	0.9997	[24]
KI[i]	1.40	1.80	52.21	6.58	23.03	1.407	1.0000	[26]
KCN[h,g]	1.50	1.75	31.31	7.00	24.57	1.370	1.0000	[26]
KSCN[h]	1.30	1.72	12.00	1.40	4.45	1.394	1.0000	[24]
KSCN[h,g]	1.10	1.69	23.07	3.09	9.78	1.386	1.0000	[26]
RbCl[g]	0.60	1.77	8.82	0.80	2.61	1.394	1.0001	[26]
CsCl[g]	0.00	1.69	20.00	1.48	4.49	1.390	1.0000	[24]
NH_4Cl[g]	1.60	1.76	13.00	2.79	9.47	1.373	0.9999	[24]
NH_4Cl[i]	1.30	1.76	19.68	4.58	15.36	1.409	1.0001	[26]
$MgCl_2$	14.00	2.57	5.00	0.55	3.01	1.384	0.9999	[24]
$MgCl_2$	14.00	2.61	16.00	2.00	17.60	1.400	0.9997	[26]
$MgCl_2$	14.00	2.65	16.18	2.03	18.39	1.386	1.0000	[38]
$CaCl_2$	12.00	2.56	19.00	2.11	16.70	1.387	1.0003	[24]
$CaCl_2$	12.10	2.52	18.16	2.00	15.36	1.368	0.9999	[26]
$SrCl_2$	12.10	2.52	22.00	1.78	12.74	1.367	1.0000	[24]
$SrCl_2$	11.70	2.53	24.08	2.00	15.08	1.373	1.0000	[26]
$SrBr_2$	12.00	2.87	19.84	1.00	6.65	1.364	1.0002	[26]
SrI_2[j]	13.70	3.00	4.61	0.70	4.61	1.393	0.9996	[26]
$BaCl_2$[g]	9.30	2.40	16.00	0.92	4.67	1.397	1.0000	[24]
$BaCl_2$[i]	9.40	2.40	21.89	1.34	7.50	1.370	1.0000	[26]
$BaBr_2$	9.60	2.55	37.28	2.00	13.44	1.381	0.9999	[26]
$AlCl_3$	23.00	2.97	12.17	1.00	9.45	1.391	0.9998	[26]
$FeCl_3$	19.00	3.01	18.00	1.35	13.08	1.379	0.9998	[24]
$FeCl_3$	18.60	3.04	19.57	1.50	15.45	1.398	0.9996	[26]
$MnCl_2$	12.00	2.63	11.18	1.00	6.05	1.396	0.9996	[26]
$CoCl_2$	14.80	2.56	16.30	1.50	11.22	1.372	0.9999	[26]
$NiCl_2$	13.00	2.68	16.27	1.50	11.02	1.366	1.0004	[26]
$CuCl_2$	10.20	2.58	21.19	2.00	13.90	1.371	0.9994	[26]

[a] Thermodynamic hydration number. [b] Number of particles per mole that are effective in reducing the freezing point. [c] From zero up to the value indicated. [d] Coefficient of the leading term ($\times 10^3$) of polynomial regression through the origin to the points obtained by Equation (8). [e] Average ratio of ideal a_w to calculated x_w over the concentration range indicated. [f] Up to the limit of solubility. [g] All available data. [h] Assigning $H_T(CN^-)$ and $H_T(SCN^-) = 0.0$. [i] Up to the eutectic point. [j] One point at 12.02 wt % was omitted; it is far off the line of all other points, apparently because of a typographical error.

eutectic by Equation (8). The reason can be understood in terms of HCl solutions, as an example. At the eutectic, 8.83 m,[26] the amount of bound water with constant $H_T = 6.6$ of Table 3, would be $8.83 \times 6.6 = 58.278$ mol, but there are only 55.509 total available. This is an impossibility. The hydration number has to start dropping at some point according to Equation (7).

For measurements not available to saturation or to the eutectic, the method used treats successfully all available data for 18 of the entries of Tables 1–3 (see footnotes therein).

The validity of the model used should also be judged by considering some of the high amounts of solute (grams of solute per 1000 g water) treated successfully: up to 684.6 g sucrose, up to 657.2 g lactose, up to 750.5 g tartaric acid, up to 678.8 g triethanolamine, up to 511.6 g HI, up to 1,092.3 g KI, and up to 594.3 g $BaBr_2$.

It is also worth noting that Equation (8) is the simplest of any proposed for accounting for strongly bound water. Unlike previous efforts in this direction, it accounts for ion pairs and formation of aggregates of amphiphiles, and it is applicable to both electrolytes and nonelectrolytes.

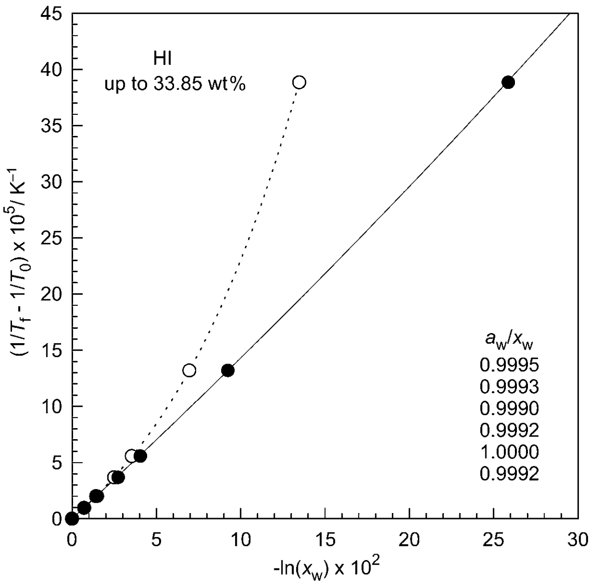

Figure 8. Plot of Equation (1) up to 4.00m HI and $\Delta T = 26.20\,°C$. The solid line is the theoretical $\ln(a_w)$. Open circles: x_w obtained by conventional Equation (2). Filled circles: x_w obtained by Equation (8) with $H_T = 7.1$ and $i_e = 2.00$. Inset values: $a_w/x_w = \gamma_w$ (of solid circles). Data of ref. [26].

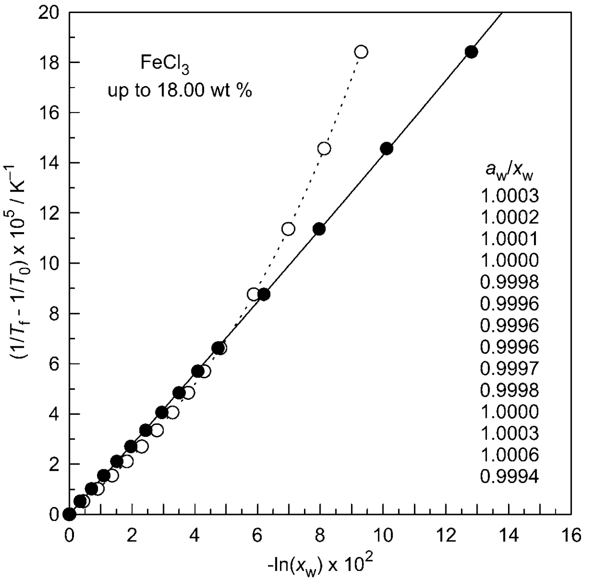

Figure 9. Plot of Equation (1) up to 1.3533m FeCl$_3$ and $\Delta T = 13.08\,°C$. The solid line is the theoretical $\ln(a_w)$. Open circles: x_w obtained by the conventional Equation (2). Filled circles: x_w obtained by Equation (8), $H_T = 19.0$, $i_e = 3.01$. Inset values: $a_w/x_w = \gamma_w$ (of solid circles). Data of ref. [24].

Peculiarities: Peculiarities in the previous work[1] included the finding that the nonelectrolytes then examined (ammonia, hydrogen peroxide, methanol, ethanol, urea, ethylene glycol, glycerol, glucose, and sucrose) showed slopes nearly equal to the cryoscopic constant of 1.384×10^{-3} K^{-1} at 273.15 K. On the other hand, virtually all strong electrolytes showed somewhat lower slopes, except for HBr and HI. The present work establishes the reason for this. Deviations of strong electrolytes from the theoretical slope are now demonstrated to have been due to previously neglected ion-pair formation. The initial slope of plots of Equation (1), c_1, should be equal to $k_c = 1.384 \times 10^{-3}$ K^{-1} at 273.15 K. The average of all 44 c_1 values in Table 3 is 1.383×10^{-3} and the largest deviation is 0.025×10^{-3}. The previous[1] peculiarity of the wrong slopes of strong electrolytes is thus understood. HBr and HI, which had given the correct slope, are now shown to have $i_e = 2.00$, the stoichiometric value assumed previously.

The previous conclusion that there was no evidence of ion-pair formation was due to the assumption that the law of mass action would make linear plots impossible according to Equation (4), which is the conventional way of expressing ion-pair formation. It is now clear that the law of mass action expressed more realistically by Equation (5) requires that the extent of ion-pair formation be constant, as is also found experimentally, when a large excess amount of unbound water is available.

All the nonelectrolytes previously treated produced the stoichiometric number of particles, $i_e = 1.00$. No aggregation of solute occurs, as was assumed, and the correct slope was obtained. Urea was the only nonelectrolyte with a value near zero, but negative $h = -0.2$, which is not acceptable in the context of the work. The present work finds $H_T = 0.0$ and $i_e = 0.96$ up to 20.00 wt % (4.16m), whereas the previous work assumed $i_e = 1.00$. Urea is now known to form aggregates, dimers, and so forth.[39] No aggregates were detected by IR spectroscopy below 1 M, but as much as 20 % of the total at 11 M was found as aggregates, dimers, and oligomers. At the maximum concentration of adherence to theory found in this work, about 4m, the average extent of dimer formation can be obtained from the value of $i_e = 0.95 \pm 0.01$, which indicates that about 0.90 ± 0.02 molecules per mole on average in the range up to 4m are "free" and about 0.10 are probably dimers $[0.90 + (0.10/2) = 0.95]$. The value of $H_T = 0.0$ is consistent with reports that "the presence of urea molecules in water has almost no influence on the structure of the H$_2$O molecules that surround the urea molecules,"[39] and that for water molecules in close proximity to urea "the hydrogen bonds are similar to those in pure water."[40]

Different hydration numbers were reported previously[1] for strong electrolytes of chlorides, bromides, and iodides, which is inconsistent with the attribution of all strongly bound water to the cation. This would require identical hydration numbers for all three halides with the same cation. It is now found that the average H_T value must be different, if there is a difference in the tendency of X$^-$ to form ion pairs. Ion pairs have a smaller number of water molecules bound to them than "free" hydrates, because the halide replaces bound water in forming ion pairs [Eq. (5)]. This is demonstrated by the results for NaX (Table 3), for which i_e(NaCl) = 1.69, i_e(NaBr) = 1.80, and i_e(NaI) = 1.87; 31 % of

NaCl is in the form of ion pairs, 20% of NaBr, and 13% of NaI.[41] The smaller the fraction of ion pairs, the greater the H_T value per mole of solute, the dynamic average of water molecules strongly bound to "free" hydrated cation and to ion pairs. The same is seen on comparing HCl, HBr, and HI, for which $i_e = 1.90$, 2.00, and 2.00, respectively. In the HCl solutions in Table 3, 10% is in the form of ion pairs; in those of HBr and HI no ion pairs are found. Hence, $H_T = 6.6$ for HCl, whereas H_T is higher and essentially the same for HBr and HI: 7.0 and 7.1, respectively. For KCl, KBr, and KI, the first two have essentially identical $i_e = 1.74$ and essentially identical $H_T = 1.15$ (average of the entries in Table 3), whereas KI shows a higher $i_e = 1.81$, fewer ion pairs, and higher $H_T = 1.40$. The values of H_T for chlorides, bromides, and iodides can be different, as has been found. The charge density of I^- is lower than that of Br^- and of Cl^-, and thus I^- is generally less prone to be attracted by the cations to form ion pairs. The same trend is observed in the comparison of i_e values of $BaCl_2$ (2.40) to $BaBr_2$ (2.55). The former has the lower i_e, that is, more ion pairs formed with Cl^- because of its higher charge density. The much higher charge densities of F^- and HO^- cause them to be strongly hydrated[1,42] and the expectation is that they would form extensive ion pairs with cations.

Hydrophilic nonelectrolytes: The hydrophilic nonelectrolytes in Table 1, except for ammonia, have OH groups and are characterized by a high ratio of hydroxyl groups relative to aliphatic carbons. Hydrogen peroxide exhibits the highest molality range treated successfully, up to 24*m*. In general, H_T values tend to increase with the number of hydroxyl groups present in the molecule. The monosaccharides glucose and fructose have similar H_T values: 2.5 and 2.1, respectively. The disaccharides, sucrose, maltose, and lactose, show about the same $H_T = 6 \pm 0.2$, whereas the trisaccharide raffinose is considerably higher at 11.9. An estimate that each sucrose "holds" six water molecules was made 78 years ago for mixed glycine–sucrose aqueous solutions, with the authors adding "this quantity is unavailable as solvent" for glycine.[2d] Variations among the saccharides of the same class are probably due to different extents of strong, internal hydrogen bonding. The alkanolamines are of interest as scrubbers to remove CO_2 from flue gases, H_2S from natural gas, and so forth. Their values of $i_e = 1.00$ indicate that they do not form micelles or other aggregates up to high concentrations in the range of 20–40 wt%. D-Tartaric acid, unlike acetic acid, does not form dimers up to about 40 wt% ($\approx 5m$), probably because of internal hydrogen bonding of the two carbonyl groups with the two OH groups at the α positions forming stable five-membered rings.

Methanol is hydrated on average by less than one water molecule per mole. In solutions of methanol, water has been reported to be bridging neighboring methanol hydroxyl groups.[43a] Such a case would result in $H_T \approx 0.5$, in fair agreement with 0.73 and 0.93 in Table 1. Alcohols, including the sugars, generally cannot be modeled successfully with a constant H_T beyond about 10*m* hydroxyl groups. At higher concentrations, the alcohols and sugars apparently start bonding to each other, which is consistent with reports of aggregates of fructose at high concentrations.[43b]

One of the consequences of disregarding the amount of bound water is demonstrated by examining the data for maltose as an example (Figure 4 and Table 1). At the highest concentration, the experimental ΔT is 4.878 °C and m is 2.116. To attain this value of ΔT, Equation (1) requires that the mole fraction of water be 0.95304 and that of solute, x_s, 0.04696, or 2.735*m* solute. This is 29% greater than the actual amount of maltose in solution and implies 29% more particles produced per mole of maltose. Maltose neither ionizes nor decomposes to produce that many additional particles. The absurd result is due to disregard of bound water removed from the total solvent. Using the mole fraction calculated by Equation (8) ($H_T = 5.8$ and $i_e = 1.00$), Equation (1) leads to calculated $x_w = 0.95335$ and $x_s = 0.04665$, or 2.716*m*, which is only 0.7% lower than the theoretical 2.735*m*. When the mole fraction of water is calculated by the conventional Equation (2) the value of x_w obtained is 0.9633. Solving Equation (1) for T_f with this value of x_w yields 3.809 °C instead of the actual 4.878 °C.

Nonelectrolytes with $i_e < 1.00$: Nonelectrolytes with $i_e < 1.00$ (Table 2) have higher ratios of aliphatic-type carbon atoms relative to hydroxyl groups than the solutes of Table 1 or are lacking hydroxyl groups. Amphiphilic molecules have hydrophobic groups and they tend to immobilize water in their vicinity as found, for example, by femtosecond mid-infrared pump–probe spectroscopy and many other techniques.[44] Results from Table 2 shed light on what has been called the hydrophobic effect. Langmuir suggested that the folding of proteins into compact structures in water is due to hydrophobicity.[45] Frank and Evans suggested that observed large entropy losses on dissolution of such particles in water is due to the formation of highly structured water around them, a quasisolid structure, "iceberg," and that the effect increases with the size of the solute molecule.[46] The term "solventberg" is also used. The subject has received widespread attention by many techniques[47] and there are recent reviews that describe methods used to investigate hydrophobicity and its relevance in understanding biological functions.[48] An account of recent research is also available, and the hydrophobic effect appears to be due primarily to loss of translational degrees of freedom of associated water.[49] Water is immobilized around hydrophobic groups. Results from Table 2 demonstrate the effect in terms of the amount of water strongly bound and immobilized. H_T of 2-butanol is higher than H_T of 2-propanol. The same is seen with methylamines: H_T of dimethylamine is higher than H_T of methylamine. The same is also found with the two ethylamines treated successfully up to the eutectic point: diethylamine shows a higher H_T than ethylamine. The model used here finds that there is "immobilized" bound water around the amphiphile, that the hydrophobic effect increases with the size of solute, and that this water is not available to act as solvent. The hydrophobic effect can also be seen with methanol and ethanol (Table 1), in which ethanol has a higher H_T than methanol.

In the solubility domains of Table 2, urea, urethane, acetamide, 2-pyrrolidone, and acetic and lactic acids do not show strongly bound water, $H_T = 0$, with i_e values between 0.91 and 0.98, thereby indicating some extent of association. Aggregation has been demonstrated independently for urea.[37] Acetic acid is known to form hydrogen-bonded dimers.

The action of urea in denaturing proteins has long been a mystery extensively discussed. Does urea affect the structure of water or does its interaction with solute cause the protein to unfold? Does urea bind more strongly to water or to protein? A recent work poses these questions, reviews support for both alternatives, and finds that, at 7.0 M, urea is binding to the solute, thereby causing it to unfold, and that this preferential binding is the key to the protein denaturing mechanism.[50] The freezing-point depression measurements answer the questions directly. Urea does not affect the structure of water; $\gamma_w = 1.000$ up to 4.2 m urea. $H_T = 0$ shows that urea does not bind strongly to water. It binds more strongly to itself (dimerizes, and so forth), $i_e = 0.95 \pm 0.01$, or an average of 10% in the form of aggregates, as it would bind to carbonyl or amino groups in the proteins, perhaps disrupting the hydrogen bonds that hold the coiled structure together or act as a surfactant. 2-Pyrrolidone is a five-membered ring lactam with functional groups similar to urea. The value of $H_T = 0.0$ and only 5% of the molecules are in aggregate form up to the eutectic at 8.37 m.

Urethane is treated successfully only up to 0.69 m; the onset of substantial amounts of aggregates occurs very early with $H_2NCO_2CH_2CH_3$. Acetamide conforms to ideal behavior up to all available data, 3.572 m, and shows a small average extent of association, $i_e = 0.97$.

The dimerization of acetic acid in water is still a subject of active research.[51] The equilibrium constant for aqueous $2\,CH_3CO_2H \rightleftarrows (CH_3CO_2H)_2$ is $K_D \approx 0.05$.[52] This K_D value leads to a fraction of 0.915 in the monomeric form and 0.085 in dimers: $(0.085/2)/(0.915)^2 = 0.05$. In the concentration domain covered in Table 2, up to 1.85 m, the value of $i_e = 0.96$ indicates that an average fraction of 0.92 is in the monomeric form, in excellent agreement with the reported K_D.

Lactic acid shows an average of about 82% in the monomeric form up to 2.44 m and substantial deviations beyond.

Glycine and glutamine, whether in the zwitterionic form or not, also show no evidence of strong binding to water and little association: $i_e = 0.978$ and 0.977, respectively. This is consistent with the report that no glycine dimers are detectable below 0.2 M.[2d] There is continuing current interest in the extent of dimer formation in aqueous glycine solutions, with conflicting views regarding high or low extents of aggregation. Two recent reports indicate that dimers are "only observed infrequently"[34b] and that only "25% of the glycine molecules form dimers" in supersaturated solutions.[34c] The results of Table 2 demonstrate a small extent of association up to 1.5 m, $i_e = 0.978$.

Strong electrolytes: The strong electrolytes in Table 3 show some general trends. With extensively hydrated univalent cations, the higher the extent of hydration the less likely is formation of ion pairs, as if the cation were insulated by the bound water. This is seen in comparing LiCl ($H_T = 6.7$) to NaCl ($H_T = 3.4$). The former forms ion pairs to the extent of 11% and the latter to 31%. With 1:2 and 1:3 strong electrolytes it is not possible to calculate the percent of ion-pair formation from the i_e values, because more than one kind can exist, for example, $Al(H_2O)_nCl^{2+}$, $Al(H_2O)_{n-1}Cl_2^{+}$, and so forth. The i_e values lump together all ion pairs that affect the freezing point.

The overall extent of formation of ion pairs of all kinds that affect the freezing point is given by the ratio of particles found (i_e of Table 3) to the stoichiometric number, i_e/i, with a lower value indicating a greater extent of ion pairing. The values are $i_e/i = 1.00$ for HBr, HI, and SrI_2; 0.96 for $SrBr_2$; 0.95 for HCl and LiCl; 0.94 for NaI; 0.91 for KI; 0.90 for NaBr; 0.89 for RbCl and $NiCl_2$; 0.88 for NaSCN, KBr, NH_4Cl, and $MnCl_2$; 0.87 for KCl and $MgCl_2$; 0.86 for NaCl, KSCN, and $CuCl_2$; 0.85 for CsCl, $CaCl_2$, and $BaBr_2$; 0.84 for $SrCl_2$ and $CoCl_2$; 0.80 for $BaCl_2$; 0.76 for $FeCl_3$; and 0.74 for $AlCl_3$.

In comparing i_e/i values of the 1:2 extensively hydrated chlorides of Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+}, the values decrease from 0.87 to 0.85, to 0.84, to 0.80, respectively. The more hydrated species form fewer ion pairs with the same anion, as found with LiCl and NaCl.

The extent of complete ionization for KCl, KBr, and KI is 74, 75, and 82%, respectively, from freezing points. This is in line with the 1929[13] estimate of "about 80% complete dissociation" at 25 °C for concentrated solutions of the three salts, keeping in mind that extent of hydration can vary with temperature.[53]

The equilibrium constants for association of 1:1 electrolytes can be calculated by Equation (5) from their i_e values of Table 3 by $K_e = (2-i_e)^2/(i_e-1)^2$. The values of K_e are HCl, 0.012; HBr $\approx$ 0.0; HI $\approx$ 0.0; LiCl, 0.015; NaCl, 0.20; NaBr, 0.063; NaI, 0.022; NaSCN, 0.10; KCl, 0.12; KBr, 0.12; KI, 0.06; KCN, 0.11; KSCN, 0.15; RbCl, 0.09; CsCl, 0.20; and NH_4Cl, 0.10. It is emphasized that K_e values found here by Equation (5) are not to be compared to any that have been determined by Equation (4).[10]

The negative value ($h = -0.2$) for hydration of CsCl reported previously[1] can now be seen to have been due to ion-pair formation, $H_T = 0$ and $i_e = 1.69$, and 31% of the solute is in the form of ion pairs. Dielectric relaxation measurements found that the water molecules surrounding Cs^+ interact with the cation too weakly to cause any irrotational binding of H_2O,[54] consistent with $H_T = 0$.

The assignment of $H_T = 0$ to cyanide is supported by the finding that $H_T(KCN) = 1.5$ is similar to $H_T(KCl) = 1.30$ and $H_T(KI) = 1.4$, and by the viscosity B value of CN^- (see below). The assignment of $H_T = 0$ to thiocyanate is supported by the finding that the H_T values of NaSCN and KSCN are essentially the same as those of the corresponding chlorides and by the location of SCN^- in the Hofmeister series (see below).

The order of ion association by vapor-pressure measurements of transition-metal chlorides has been reported to increase in the order $NiCl_2 < MnCl_2 < CuCl_2$.[55a] $CoCl_2$ showed the most extensive degree of association.[55b] The i_e/i values of the four transition-metal chlorides decrease in the same order, which shows that the fraction of solute in the form of ion pairs (decreasing i_e/i) increases in the order $Ni^{2+} < Mn^{2+} < Cu^{2+} < Co^{2+}$: $i_e/i = 0.893$, 0.878, 0.860, 0.853, respectively. Disregarding ion-pair formation, Stokes and Robinson reported hydration numbers of 13 for Ni^{2+} and 11 for Mn^{2+} at 25 °C, compared with $H_T = 13.0$ and 12.0, respectively.[2a] Price et al. reported cation hydration numbers obtained from diffusion coefficients at 25 °C as 12 for $MgCl_2$, 12 for $NiCl_2$, 19 for $FeCl_3$, and 22 for $AlCl_3$, assuming no hydration contribution from the anions (Cl^- and ClO_4^-).[36b] The corresponding H_T values are 14.0, 13.0, 19.0, and 23.0 from freezing points and confirm the very high hydration of Fe^{3+} and Al^{3+}. The predominant structure of hydrated calcium ions is $Ca^{2+}(H_2O)_{12}$ by infrared laser-action spectroscopy of electrospray clusters,[56a] in agreement with $H_T = 12.0$ from freezing points. The weighted average of relative abundances of gas-phase $H(H_2O)_n^+$ clusters from $n = 1$ to 11 is 6.9 (zero abundance at $n = 1$ and very near zero at $n = 11$),[56b] in excellent agreement with $H_T = 6.6$ for HCl, 7.0 for HBr, and 7.1 for HI. The most abundant gas-phase $Cu^{+2}(H_2O)_n$ cluster by mass spectrometry is at $n = 10$, with detected distributions from $n = 7$ to 11,[56c] consistent with $H_T = 10.2$. Dielectric relaxation measurements at 25 °C have been reported to yield a constant value of about 10 irrotationally bound water molecules to Cu^{2+} above 0.4 M. For Na^+, the same technique gave 4.2 ± 0.3[6a] compared with $H_T = 3.9$ for NaI, which is the least ion-paired sodium salt in Table 3.

H_T values found in this work are somewhat different from those reported previously.[1] Variations do not exceed 0.5 units of H_T for univalent cations, up to 1.3 units for the divalent $SrCl_2$, and 1.2 units for the trivalent $AlCl_3$. However, the ordering of the cations by their H_T values remains the same as previously reported and so do the correlations with various physical properties reported.[1]

The issue as to whether various strong electrolytes affect the structure of bulk, unbound water has been much debated and the subject has been reviewed recently by Marcus.[57] He states, "Whether and how much influence an ion has beyond the hydration shell(s) is still an open question." The freezing-point measurements show that the mole fraction of "free" water is equal to the theoretical activity of water, $a_w/x_w = \gamma_w = 1.00$, throughout the extensive range of concentrations treated in Tables 1–3, thus clearly showing the absence of significant effects on the structure of bulk unbound water. Recent reports indicate the same. In concentrated $NaClO_4$ and $Mg(ClO_4)_2$ solutions studied by femtosecond spectroscopy, the presence of ions does not lead to an enhancement or a breakdown of the hydrogen-bond network in liquid "bulk" water.[58] X-ray and X-ray Raman scattering finds that only water molecules in close vicinity to the ions (NaCl, KCl, and $AlCl_3$) are affected.[59] Raman spectroscopy and computer simulations find that hydrogen-bond strengths are only weakly modified beyond the solvation shell of KF, KCl, KBr, and KI.[60] The freezing-point measurements show that all solutes treated do not significantly affect the structure of bulk water, by the most direct method: γ_w(bulk water) = 1.00.

It is worth noting that the thermodynamic hydration numbers of Table 3 are generally in the same order as reported residence times of water around the cations.[5] The residence time of water around Cs^+ and Cl^- has been reported to be the about the same: 9.5 and 9.0 ps, respectively;[61a] their $H_T = 0.0$ are also the same. Mean ligand residence time of water around Cs^+ has been reported as smaller than that of pure water.[61b] A very short residence time of water, 2.0 ps, has also been calculated for the first solvation shell of Rb^+ ,[61c] consistent with the low $H_T = 0.6$. Reorientation times of water around Cl^-, Br^-, and I^- are shorter than those of pure water by dielectric relaxation;[42,61d] water does not bind to these anions more strongly than pure water binds to more water molecules.

Hydration numbers of cations, h_0 at 0 °C, have been estimated recently from electrostricive and intrinsic volumes.[62] The correlation of such estimates, obtained by a method quite different from freezing-point measurements, with H_T of the alkali and alkaline earth metals is shown in Figure 10. By size-exclusion chromatography,[7] the "apparent dynamic hydration numbers" of biologically important cations follow the same trend as H_T of Table 3.

Judging qualitatively, it is expected that the H_T values reported in Tables 1–3 are accurate to about 0.5 units up to $H_T = 7$ and to about 1.0 unit above this, in the concentration domain covered therein and at the specified temperatures.

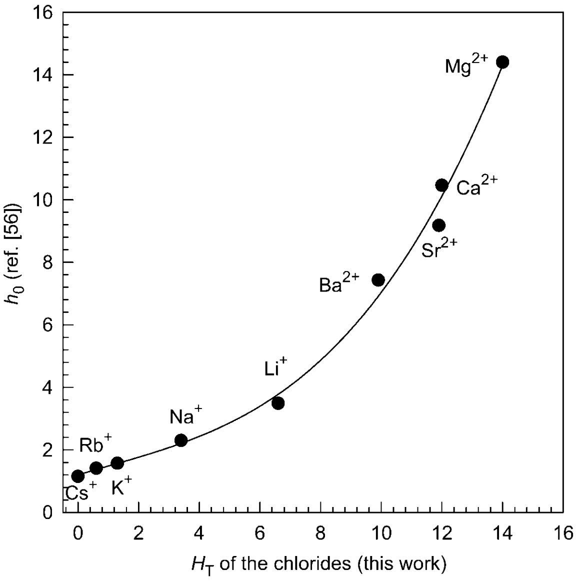

Figure 10. Estimates of hydration numbers of ref. [62] versus H_T values of the chlorides of cations in common with this work.

Sequential binding energies: The sequential binding energies from some experimental gas-phase ion–water cluster studies from the compilation of ion-clustering data of the NIST database[63] are shown below as illustrative examples of the correlation with H_T of some ions. ΔH_r is the sequential binding energy for a water molecule that adheres strongly to the ion or to hydrated ion. The ΔH_r values below are the average of values listed in the database[63] in $\mathrm{kcal\,mol^{-1}}$. In all cases, the estimate that a minimum of $(13.3 \pm 1.0)\ \mathrm{kcal\,mol^{-1}}$ biding energy is required to remove water from the solvent and become part of the H_T of the solute is consistent with the reported exothermicity values of the reactions [Eqs. (9)–(28)]:

$$\mathrm{Na^+ + H_2O \rightarrow Na(H_2O)^+},\ \Delta H_r = -22.8 \pm 3 \tag{9}$$

$$\mathrm{Na(H_2O)^+ + H_2O \rightarrow Na(H_2O)_2{}^+},\ \Delta H_r = -19 \pm 2 \tag{10}$$

$$\mathrm{Na(H_2O)_2{}^+ + H_2O \rightarrow Na(H_2O)_3{}^+},\ \Delta H_r = -15.9 \pm 1 \tag{11}$$

$$\mathrm{Na(H_2O)_3{}^+ + H_2O \rightarrow Na(H_2O)_4{}^+},\\ \Delta H_r = -13.1 \pm 0.9;\ H_T = 3.4 - 3.9 \tag{12}$$

$$\mathrm{Na(H_2O)_4{}^+ + H_2O \rightarrow Na(H_2O)_5{}^+},\ \Delta H_r = (-11.5 \pm 1) \tag{13}$$

$$\mathrm{K^+ + H_2O \rightarrow K(H_2O)^+},\ \Delta H_r = (-17.6 \pm 1.6) \tag{14}$$

$$\mathrm{K(H_2O)^+ + H_2O \rightarrow K(H_2O)_2{}^+},\ \Delta H_r = -16 \pm 3;\ H_T = 1.3 - 1.4 \tag{15}$$

$$\mathrm{K(H_2O)_2{}^+ + H_2O \rightarrow K(H_2O)_3{}^+},\ \Delta H_r = (-13.4 \pm 3) \tag{16}$$

$$\mathrm{K(H_2O)_3{}^+ + H_2O \rightarrow K(H_2O)_4{}^+},\ \Delta H_r = -12.4 \pm 0.6 \tag{17}$$

$$\mathrm{Cs^+ + H_2O \rightarrow Cs(H_2O)^+},\ \Delta H_r = -12.8 \pm 0.9;\ H_T = 0.0 \tag{18}$$

$$\mathrm{Cs(H_2O)^+ + H_2O \rightarrow Cs(H_2O)_2{}^+},\ \Delta H_r = -11.9 \pm 0.4 \tag{19}$$

$$\mathrm{Cs(H_2O)_2{}^+ + H_2O \rightarrow Cs(H_2O)_3{}^+},\ \Delta H_r = -10.5 \pm 0.7 \tag{20}$$

$$\mathrm{CN^- + H_2O \rightarrow CN(H_2O)^-},\ \Delta H_r = -13.7 \pm 0.7;\ H_T = 0.0 \tag{21}$$

$$\mathrm{CN(H_2O)^- + H_2O \rightarrow CN(H_2O)_2{}^-},\ \Delta H_r = -11.7 \tag{22}$$

$$\mathrm{CN(H_2O)_2{}^- + H_2O \rightarrow CN(H_2O)_3{}^-},\ \Delta H_r = -9.8 \pm 1.0 \tag{23}$$

$$\mathrm{Br^- + H_2O \rightarrow Br(H_2O)^-},\ \Delta H_r = -13 \pm 2;\ H_T = 0.0 \tag{24}$$

$$\mathrm{Br(H_2O)^- + H_2O \rightarrow Br(H_2O)_2{}^-},\ \Delta H_r = -12.1 \pm 0.7 \tag{25}$$

$$\mathrm{I^- + H_2O \rightarrow I(H_2O)^-},\ \Delta H_r = -10.4 \pm 0.7;\ H_T = 0.0 \tag{26}$$

$$\mathrm{I(H_2O)^- + H_2O \rightarrow I(H_2O)_2{}^-},\ \Delta H_r = -9.7 \pm 0.4 \tag{27}$$

$$\mathrm{I(H_2O)_2{}^- + H_2O \rightarrow I(H_2O)_3{}^-},\ \Delta H_r = -9.2 \pm 0.6 \tag{28}$$

Although gas-phase ion–water clusters may not be thought to correlate with liquid-phase behavior, the fact is that the cutoff for incorporation of a water molecule into H_T is about $13.3\ \mathrm{kcal\,mol^{-1}}$, within the uncertainties in measured ΔH_r values. Mass spectra of ion–water clusters show a distribution of hydrated ions around the most abundant mass number, consistent with the noninteger values of H_T.

Hofmeister series: The thermodynamic hydration numbers of the ions correlate with the Hofmeister series,[64] which orders the relative effectiveness of ions in precipitating out of aqueous protein-containing solutions, latexes, colloidal suspensions, and so on; the "salting out" effect. Even though specific ion effects with various substrates can change some ordering in the series, the general order is usually preserved. The order of the Hofmeister series for ions in common with this work is generally as follows, listed from the least destabilizing (more stabilizing) to the most destabilizing: $\mathrm{I^- < Br^- < Cl^- < Cs^+ < Rb^+ < K^+ < NH_4{}^+ < Na^+ < Li^+ < H^+ < Ba^{2+} < Sr^{2+} < Ca^{2+} < Mg^{2+} < Al^{3+}}$. The order of $\mathrm{K^+}$ and $\mathrm{NH_4{}^+}$ and of $\mathrm{Ca^{2+}}$ and $\mathrm{Sr^{2+}}$ in the series is reversed sometimes, depending on the literature source. $\mathrm{CN^-}$, $\mathrm{SCN^-}$, and $\mathrm{ClO_4{}^-}$ also appear in different locations among the halide anions listed above. For the above anions in the Hofmeister series, the thermodynamic hydration number found is zero. H_T for the cations increases in the same order as their position in the Hofmeister series. The reported occasional reversal of $\mathrm{K^+}$ and $\mathrm{NH_4{}^+}$ can be understood in terms of their almost identical H_T values and similarly for $\mathrm{Ca^{2+}}$ and $\mathrm{Sr^{2+}}$. The order of the common metal cations in the series also follows, and can be quantified by, their known enthalpies of hydration: $\mathrm{Cs^+}$, −66.0; $\mathrm{Rb^+}$, −71.0; $\mathrm{K^+}$, −77.0; $\mathrm{Na^+}$, −97.0; $\mathrm{Li^+}$, 124.3; $\mathrm{Ba^{2+}}$, −311.9; $\mathrm{Sr^{2+}}$, −344.9; $\mathrm{Ca^{2+}}$, −376.9; $\mathrm{Mg^{2+}}$, −459.1; and $\mathrm{Al^{3+}}$, $-1{,}115.0\ \mathrm{kcal\,mol^{-1}}$. The assignment of $H_T(\mathrm{SCN^-}) = 0$ in Table 3 is consistent with its location in the Hofmeister series.

The correlation of previously reported hydration numbers with the Hofmeister series was not noted at the time.[1] It was subsequently noted by others and has been of interest to biochemists and biologists who examine such issues as, for example, the effect of solutes on growth rates of *Staphylococcus aureous* and *Pseudomonas aeruginosa*,[65] the stability of the acidic protein *Desulfovibrio desulfuricans* apoflavodoxin,[66] the osmoregulation of enderotoxin expression by *Escherichia coli*,[67] actions of biologically important ions,[7] kidney function and urology,[68] effect of solutes on helix–coil transitions of macromolecules,[69] formation of α-synuclein fibrils,[70] and so forth. Solvation, coordination, or hydration numbers obtained from diffraction experiments have not been reported to correlate with the Hofmeister series. The underlying causes for the Hofmeister series are still being investigated[71] and a correlation with charge density of ions has been reported recently,[72] in agreement with previous similar findings.[1,7]

One aspect of the action of electrolytes in precipitating proteins is clear. If a protein is dissolved to a concentration just below Hofmeister's cloud point and then the solution is made 2 molal in $MgCl_2$, the following will happen. The electrolyte will bind $mH_T = 2 \times 14.0 = 28$ moles of water, thereby "stealing" half the solvent. The concentration of protein in the remaining available solvent is doubled and it precipitates. This effect will always be present, in addition to any other ion-specific or protein-specific effects.

Jones–Dole viscosity *B* coefficients: The Jones–Dole equation[73] [Equation (29)] is an empirical relation between concentration of a solute and viscosity of the solution. Viscosity of aqueous solutions, η, relative to that of water, η_0, is described as a function of concentration expressed in mol L^{-1}, M, and A and B are empirical coefficients. A correlation of hydration numbers with viscosity B coefficients was not noted previously.[1]

$$\eta/\eta_0 = 1 + A\text{M}^{1/2} + B\text{M} \tag{29}$$

Equation (29) has been used widely and a review of such work and its applications is available.[74] Data pertaining to concentrations greater than 0.1 M were not included because such is the limitation of Equation (29). There is extensive literature that correlates the B coefficient with many other phenomena, thereby indicating that B is a physically meaningful quantity. The review discusses various efforts made to rationalize the values of the B coefficients. They are known to provide information concerning the ion–solvent interaction and its effect on the structure of water near the environment of the solute particles. One of many proposals is that the magnitude of the B coefficients is proportional to the molar "hydrated volume" of the ion, but this is not universally accepted.[74] There is general agreement that the B coefficient is related to ion–solvent interactions and that small or negative B values indicate a weak interaction.[74] Table 4 lists B values at 25 °C[74] and H_T values found in this work. The negative B values of I^- through NH_4^+ clearly show weak interactions with solvent, consistent with zero or small H_T values found. Omitting the tentative values in Table 4, Figure 11 shows that there is a good correlation of B with H_T from Na^+ to Mg^{2+} in the table. As usual, H^+ misbehaves and is shown but not included in the second-order regression line. An exact correlation with H_T is not expected because of uncertainties in both values plotted and because the hydrated volume of the ion should include the volumes of the ions and only the volume of water is reflected in H_T. The viscosity results prove two things: 1) viscosity depends on the size of solute particles, but this was known from the beginning of the last century;[75] 2) the ions and their strongly bound water, as quantified by H_T, move through the solvent as a single entity. Solvation, coordination, or hydration numbers from diffraction studies have not been reported to correlate with B. The plot in Figure 11 is not linear because the B coefficients describe viscosities only up to 0.1 M solute. For higher concentrations, a term in M^2 must be added. The H_T values apply to high concentrations.

Table 4. Jones–Dole B coefficients and H_T values.

Ion	B[a]	H_T[b]
I^-	−0.073	0.0
Br^-	−0.033	0.0
Cl^-	−0.005	0.0
CN^-	(−0.024)	0.0
SCN^-	(−0.022)	0.0
Cs^+	−0.047	0.0
Rb^+	−0.030	0.6
K^+	−0.009	1.2
NH_4^+	−0.008	1.4
Na^+	0.085	3.4
H^+	0.086	6.6
Li^+	0.146	6.7
Ba^{2+}	0.216	9.2
Sr^{2+}	0.261	11.9
Ca^{2+}	0.284	12.0
Mg^{2+}	0.385	14.0
Fe^{3+}	(0.690)	18.9
Al^{3+}	(0.744)	23.0

[a] Values in parentheses are designated "tentative" in ref. [74]. [b] Of the chlorides of the cations.

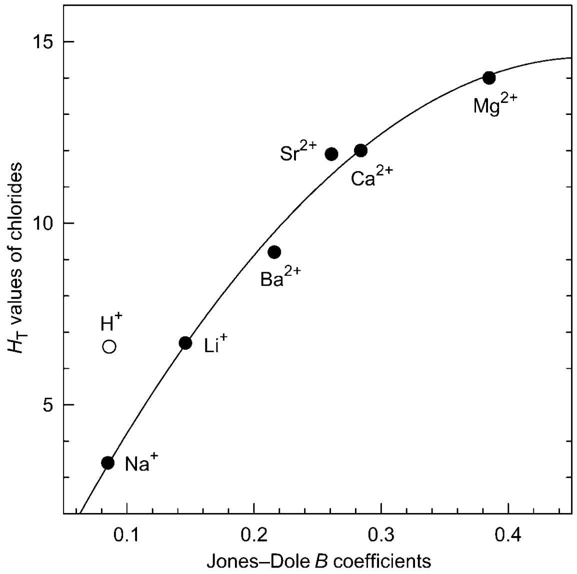

Figure 11. Plot of the thermodynamic hydration numbers of cation chlorides (H_T) versus Jones–Dole B coefficients of viscosity of the cation.

Ionic conductivities: Ionic conductivities should be related to the charge and size of the ion. Smaller ions should diffuse through the solvent faster, that is, with higher mobilities. They do not. The only way to understand this apparently strange phenomenon is by considering not only the size of the ion, but the size of its hydrated species that moves through the solvent as an entity with the ion. Also to be considered is the extent of association of the salt involved, because ion pairs would not respond to the electric field. This has all been known for a long time in a qualitative fashion,[76] but no commonly agreed extents of hydration and ion-pair formation had been available. Figure 12 shows plots of H_T values of the metal chlorides from Table 3 and the

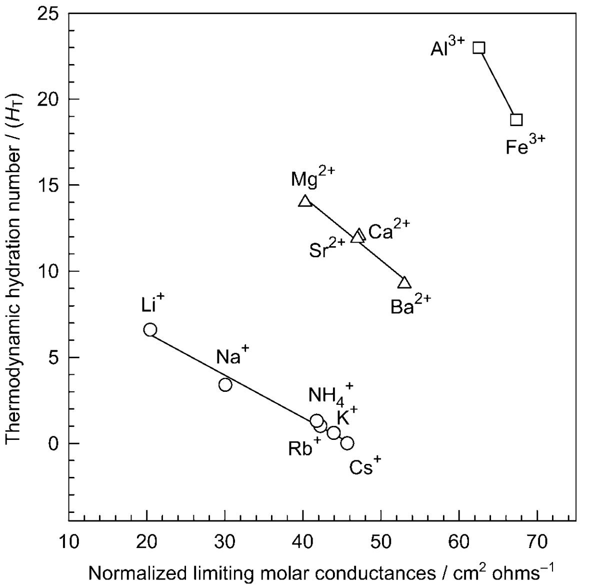

Figure 12. Thermodynamic hydration numbers of the chlorides (H_T) versus limiting molar conductance of the cation normalized by the extent of ion pairing (also units of 10^{-4} S m^2 mol^{-1}).

molar conductances of the ions,[24] the latter normalized by dividing the conductance by the i_e value; the more ion pairs, the lower the conductance. The correlation with the number of bound water molecules and the extent of ion-pair formation is clear, even when only the strongly bound water molecules are being considered, disregarding the size of the ion itself. Three straight lines are obtained and the slopes become steeper with increasing ionic charge. Cs^+, Cl^-, Br^-, I^-, and CN^- all have $H_T = 0$ and virtually identical limiting molar conductances: 77.2, 76.3, 78.8, 76.8, and 78.0 S m^2 mol^{-1}, respectively.[24]

Ion-selective channels in cell membranes: These have been the subject of extensive interest, because K^+ permeates the narrow channel of potassium-selective pores at least 10000 times faster than the smaller Na^+. Since the discovery of aquaporin channels[77] and the crystal-structure resolution to 2 Å of the potassium-selective channel from *Streptomyces lividans* (KcsA),[78] interest has intensified and various rationalizations have been used to explain the known facts. A narrow pore constitutes the entrance to the channel, followed by a wider site (S2) with carbonyl functions in it, followed by a mostly hydrophobic narrow pore. Coordinating ligands (oxygen atoms of carbonyl groups) in the selective site S2 of KcsA are positioned to precisely fit K^+, but not Na^+, presumably because they are too far apart to do so with the smaller Na^+.[79] This appears inconsistent with the protein being sufficiently flexible and capable of shrinking enough to coordinate with the smaller Na^+.[80] Results from freezing-point depression measurements are relevant to understanding the function of ion-selective channels. A fact whose significance has not been emphasized often is that Li^+ and Na^+ are excluded by the KcsA filter, but Rb^+ and Cs^+ are not.[79] In the context of the present work, one characteristic difference among these ions is that Li^+ and Na^+ have significantly higher H_T values (NaCl, 3.4; LiCl, 6.6) than the other three univalent cations (KCl, 1.1; RbCl, 0.6; and CsCl, 0.0). To enter the narrow opening of the channel that separates the selectivity cavity from the extracellular solution, hydrated ions have to shed some associated water molecules.[79,81] Water molecules, above and beyond the H_T number, solvating the ions can easily be shed to extracellular water molecules at the entrance to the channel. The energy cost of shedding strongly bound water is greater for Na^+ than K^+. Conservatively assuming that K^+ sheds two strongly bound water molecules, the required energy is about 34 kcal mol^{-1}, as indicated from its sequential binding energies. For Na^+ to shed three water molecules, about 58 kcal mol^{-1} are required.[82] The energy loss is much greater for Na^+ dehydration or partial dehydration, thus favoring K^+. Energy losses of dehydration are compensated by formation of bonds to the carbonyl ligands of the S2 site. The larger size of K^+ allows it to coordinate with more (up to eight) carbonyl functions at the site.[82] From the crystal radii of the ions, the surface area of K^+ is 2.75 times greater than that of Na^+. It is not surprising that more water molecules can fit around a larger area, and scattering studies of solvation of the two ions by water show that more water molecules can be arranged immediately around K^+, thereby solvating it, than around the smaller Na^+. This will also be true for carbonyl oxygen atoms immediately surrounding the two ions in the S2 site in emulation of water. This is a second advantage for K^+. A third is present at the mainly hydrophobic lining of the pore beyond the S2 site.[79] The smaller charge density of the larger ions K^+, Rb^+, and Cs^+ makes them less likely to interact with dipoles in this part of the channel and they pass through, whereas Li^+ and Na^+ will bind more strongly, thereby decreasing their permeability at this site as well. The high selectivity for K^+ over Na^+ then is understood in terms of the thermodynamic hydration number of the ions, sequential binding energies to water, size, and charge density, which are the same characteristics as those found to affect colligative properties in the present work.

In contrast to the KcsA ion-selective channel, the NaK channel is nonselective for Na^+ and K^+. The two channels are generally similar according to crystallographic determinations to a resolution of 2.4–2.8 Å, but the NaK selectivity filter contains fewer cation-binding sites, estimated to be only two.[83] The S2 site of the NaK channel is also estimated to be able to accommodate approximately up to three water molecules.[82a] Thus, neither K^+ nor Na^+ have to be extensively dehydrated and the energetic advantage of K^+ in dehydration for the KcsA channel is substantially diminished. Also, both K^+ and Na^+ can bind to all of the fewer available ligands at the S2 of the NaK channel. The size-dependent, higher-coordination or solvation advantage of K^+ in KcsA is eliminated. In addition, Na^+ binds to carbonyl groups more strongly than K^+,[81] thereby leading to an advantage for Na^+. The net result is loss of selectivity.

Proof that the values obtained for H_T and i_e are not just arbitrary parameters to fit freezing-point data but instead describe known physical phenomena is the fact that these values correlate with the Hofmeister series, the B coefficients of viscosities, ionic conductivities, hydration numbers obtained from electrostrictive and intrinsic volumes, dielectric relaxation measurements, diffusion measurements, and sequential binding energies of gas-phase ion–water clusters. H_T and i_e were not obtained from fitting to all of these apparently unrelated physical properties and experimental measurements.

Conclusion

Thermodynamic hydration numbers of aqueous solutions of nonelectrolytes and of strong electrolytes of chloride, bromide, iodide, cyanide, and thiosulfate describe accurately freezing-point depression behavior to high concentrations, often to the limit of solubility or to the eutectic. Account is taken of the extent of ion pairing, which is understood on the basis of a new, more realistic equilibrium expression for their formation. Ideal behavior is demonstrated to high concentrations. No recourse is made to empirical activity coefficients or other ad hoc parameters. The solutes treated do not affect the structure of "free" bulk water. The minimum ion–water binding energy required to remove water from the solvent is estimated. There is a good correlation of the thermodynamic hydration numbers with the Hofmeister series and the results have a bearing on the causes of denaturing of proteins and the "salting out" effect. Correlation is also good with the Jones–Dole B coefficients of viscosity. Ionic conductivities are related to the hydration numbers reported and to the extent of ion-pair formation of the various metal chlorides. The function of ion-selective channels of cell membranes at the molecular level is rationalized in terms of effects shown to be common with those that affect colligative properties.

Acknowledgements

Support from the Intramural Research Program of Long Island University is gratefully acknowledged.

---

[1] A. A. Zavitsas, *J. Phys. Chem. B* **2001**, *105*, 7805–7817.

[2] a) R. H. Stokes, R. A. Robinson, *J. Am. Chem. Soc.* **1948**, *70*, 1870–1878; b) R. H. Stokes, R. A. Robinson, *J. Phys. Chem.* **1966**, *70*, 2126–2131; c) G. Scatchard, *J. Am. Chem. Soc.* **1921**, *43*, 2406–2418; d) W. C. M. Lewis, *Chem. Rev.* **1931**, *8*, 81–165; e) J.-P. Simonin, S. Krebs, W. Kunz, *Ind. Eng. Chem. Res.* **2006**, *45*, 4345–4354.

[3] J. Bockris, A. Reddy, *Modern Electrochemistry*, 2nd ed., Plenum Press, New York, **1998**.

[4] M. J. Blandamer, J. B. F. M. Engberts, P. T. Gleeson, J. C. R. Reis, *Chem. Soc. Rev.* **2005**, *34*, 440–458.

[5] H. Ohtaki, T. Radnai, *Chem. Rev.* **1993**, *93*, 1157–1204.

[6] a) R. Buchner, G. T. Hefter, P. M. May, *J. Phys. Chem. A* **1999**, *103*, 1–9; b) W. Wachter, W. Kunz, R. Buchner, G. Hefter, *J. Phys. Chem. A* **2005**, *109*, 8675–8683.

[7] M. Y. Kiriukhin, K. D. Collins, *Biophys. Chem.* **2002**, *99*, 155–168.

[8] M. Arshadi, R. Yamdagni, P. Kebarle, *J. Phys. Chem.* **1970**, *74*, 1475–1482.

[9] U. Kaatze, *J. Solution Chem.* **1997**, *26*, 1049–1112.

[10] Y. Marcus, G. Hefter, *Chem. Rev.* **2006**, *106*, 4585–4621.

[11] G. N. Lewis, M. Randall, *J. Am. Chem. Soc.* **1921**, *43*, 1112–1154.

[12] G. N. Lewis, *J. Am. Chem. Soc.* **1912**, *34*, 1631–1644.

[13] W. D. Bancroft, H. L. Davis, *J. Phys. Chem.* **1929**, *33*, 591–604.

[14] R. Heyrovská, *Electroanalysis* **2006**, *18*, 351–361.

[15] G. N. Lewis, *J. Am. Chem. Soc.* **1908**, *30*, 668–683. There seems to be a typographical error in the published equation, but the meaning is clear.

[16] J. H. Hildebrand, R. L. Scott, *Regular Solutions*, Prentice-Hall, Engelwood Cliffs, **1962**.

[17] S. Glasstone, *Thermodynamics for Chemists*, Van Nostrand-Reinhold, New York, **1947**: $-\ln(a_w) = [L_0(\Delta T)]/(RT_0^2) + [(\Delta T)^2/(RT_0^2)] \times (L_0/T_f^2 - \Delta C_p/R)$.

[18] G. Scatchard, B. Vonnegut, D. W. Beaumont, *J. Chem. Phys.* **1960**, *33*, 1292–1298. $\ln(a_w) = -\text{Osm}/55.509$, with osmolality per kilogram being obtained by $\text{Osm} = \Delta T/[1.8598 - 9.94\times10^{-4}(\Delta T) + 9.32\times10^{-6}(\Delta T)^2 + 7.88\times10^{-8}(\Delta T)^3]$.

[19] R. A. Robinson, R. H. Stokes, *Electrolyte Solutions*, Butterworths, London, **1955**. Quoted in: H. T. Chang, M. Posey, G. T. Rochelle, *Ind. Eng. Chem. Res.* **1993**, *32*, 2324–2335. $-\ln(a_w) = L_0\Delta T/(RT_0^2) + (\Delta T^2/T_0^2)(L_0/RT_0 - \Delta C_p/2R)$.

[20] From Equation (88) of reference [4]. $\ln(a_w) = -9.687\times10^{-3}(\Delta T) - 4.84\times10^{-6}(\Delta T)^2$. Equation (87) appears to have a typographical error.

[21] H. Kumano, T. Asaoka, A. Saito, S. Okawa, *Int. J. Refrigeration* **2007**, *30*, 267–273. From Figure 3a and b.

[22] A. Kostinski, W. Cantrell, *J. Atmos. Sci.* **2008**, *65*, 2961–2971, and references therein.

[23] The value of Y may be obtained at any temperature between $\Delta T =$ 0.0 and 70.0 °C by $Y = 1.8580 - 6.304\times10^{-4}(\Delta T) - 1.575\times10^{-5}(\Delta T)^2$.

[24] *CRC Handbook of Chemistry and Physics*, 70th ed. (Ed.: R. C. Weast), CRC, Boca Raton, **1992**.

[25] A quadratic expression is sufficient for providing an accurate description of results with maximum $\Delta T < 40\,^{\circ}\mathrm{C}$.

[26] *International Critical Tables of Numeric Data, Physics, Chemistry and Technology, Vol. 4* (Ed.: E. W. Washburn), McGraw-Hill, New York, **1928**.

[27] K. Kiyosawa, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 633–642.

[28] E. O. Whittier, *J. Phys. Chem.* **1933**, *37*, 847–849.

[29] H.-T. Chang, M. Posey, G. T. Rochelle, *Ind. Eng. Chem. Res.* **1993**, *32*, 2324–2335.

[30] K. Ochi, T. Saito, K. Kojima, *J. Chem. Eng. Data* **1996**, *41*, 361–364. A change in scattered light intensity is reported at small ΔT, consistent with formation of 2-butanol aggregates.

[31] W. C. Somerville, *J. Phys. Chem.* **1931**, *35*, 2412–2433.

[32] H. M. Chadwell, F. W. Politi, *J. Am. Chem. Soc.* **1938**, *60*, 1291–1293.

[33] L. J. Lohr, *J. Phys. Chem.* **1958**, *62*, 1150–1151.

[34] a) J. Y. Cann, *J. Phys. Chem.* **1932**, *36*, 2813–2816; b) S. Hamad, C. E. Hughes, C. R. A. Catloe, D. M. Harris, *J. Phys. Chem. B* **2008**, *112*, 7280–7288; c) J. Huang, T. C. Stringfellow, L. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 13973–13980.

[35] C. R. Keener, G. D. Fullerton, I. L. Cameron, J. Xiong, *Biophys. J.* **1995**, *68*, 291–302.

[36] a) R. W. Impey, P. A. Madden, I. R. McDonald, *J. Phys. Chem.* **1983**, *87*, 5071–5083, residence time study; b) W. E. Price, R. Mills, L. Woolf, *J. Phys. Chem.* **1996**, *100*, 1406–1410, diffusion study.

[37] A. Grossfield, *J. Chem. Phys.* **2005**, *122*, 024506.

[38] H. F. Gibbard, A. F. Crossman, *J. Solution Chem.* **1974**, *3*, 385–393.

[39] J. Grdadolnik, Y. Maréchal, *J. Mol. Struct.* **2002**, *615*, 177–189.

[40] A. Panuszko, P. Bruździak, D. Wyrzykowski, J. Stangret, *J. Phys. Chem. B* **2009**, *113*, 14797–14809.

[41] For example, particles produced per mole of NaCl: 0.69 not ion-paired hydrated $Na^+ + 0.69\ Cl^- + 0.31$ ion pairs $= 1.69 = i_e$. Particles produced by NaBr: 0.80 not ion paired Na^+ hydrate $+ 0.80\ Br^- +$

0.20 ion pairs = 1.80 = i_e. Particles produced by NaI: 0.87 not ion paired Na^+ hydrate + 0.87 I^- + 0.13 ion pairs = 1.87 = i_e.

[42] Y. Marcus, *J. Phys. Chem. B* **2009**, *113*, 10285–10291.

[43] a) S. Dixit, J. Crain, W. C. K. Poon, J. L. Finney, A. K. Soper, *Nature* **2002**, *416*, 829–832; b) M. H. H. Pomata, M. T. Sonoda, M. S. Skaf, M. D. Elola, *J. Phys. Chem. B* **2009**, *113*, 12999–13006.

[44] Y. L. A. Rezus, H. J. Bakker, *Phys. Rev. Lett.* **2007**, *99*, 148301; Y. L. A. Rezus, H. J. Bakker, *J. Phys. Chem. A* **2008**, *112*, 2355–2361; H. J. Bakker, Y. L. A. Rezus, R. L. A. Timmer, *J. Phys. Chem. A* **2008**, *112*, 11523–11534.

[45] I. Langmuir, *Proc. R. Soc. London Ser. A* **1939**, *170*, 1–39.

[46] H. S. Frank, M. W. Evans, *Chem. Phys.* **1945**, *13*, 507–532; F. Franks, *Water: A Comprehensive Treatise*, Plenum Press, New York, **1972**.

[47] C. Tanford, *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*, Wiley, New York, **1973**.

[48] C. Hansch, A. Kurup, R. Garg, H. Gao, *Chem. Rev.* **2001**, *101*, 619–672; L. Pratt, A. Pohorille, *Chem. Rev.* **2002**, *102*, 2671–2692.

[49] A. A. Bakulin, C. Liang, T. La Cour Jansen, D. A. Wiersma, H. J. Bakker, M. S. Pshenichnikov, *Acc. Chem. Res.* **2009**, *42*, 1229–1238.

[50] R. Zangi, R. Zhou, B. J. Berne, *J. Am. Chem. Soc.* **2009**, *131*, 1535–1541.

[51] L. Pu, Y. Sun, Z. Zhang, *J. Phys. Chem. A* **2009**, *113*, 6841–6848; T. Nakabayashi, H. Sato, F. Hirata, N. Nishi, *J. Phys. Chem. A* **2001**, *105*, 245–250.

[52] G. C. Pimentel, A. L. McClellan, *The Hydrogen Bond*, W. H. Freeman, San Francisco, **1960**, pp. 368–369.

[53] A. A. Zavitsas, *J. Phys. Chem. B* **2005**, *109*, 20636–20640; P. Lindqvist-Reis, R. Klenze, G. Schubert, T. Fanghänel, *J. Phys. Chem. B* **2005**, *109*, 3077–3083.

[54] T. Chen, G. Hefter, R. Buchner, *J. Phys. Chem. A* **2003**, *107*, 4025–2031.

[55] a) T. E. Moore, F. W. Burtch, C. E. Miller, *J. Phys. Chem.* **1960**, *64*, 1454–1458; b) T. E. Moore, E. A. Gootman, P. C. Yates, *J. Am. Chem. Soc.* **1955**, *77*, 298–304.

[56] a) M. F. Bush, R. J. Saykally, E. R. Williams, *J. Am. Chem. Soc.* **2008**, *130*, 15482–15489; b) X. Yang, A. W. Castleman, Jr., *J. Am. Chem. Soc.* **1989**, *111*, 6845–6846; c) A. J. Stace, N. R. Walker, S. Firth, *J. Am. Chem. Soc.* **1997**, *119*, 10239–10240; d) C. Akilan, G. Hefter, N. Rohman, R. Buchner, *J. Phys. Chem. B* **2006**, *110*, 14961–14970.

[57] Y. Marcus, *Chem. Rev.* **2009**, *109*, 1346–1370.

[58] A. W. Omta, M. F. Kropman, S. Woutersen, H. J. Bakker, *J. Chem. Phys.* **2003**, *119*, 12457–12461.

[59] L.-Å. Näslund, D. C. Edwards, P. Wernet, U. Bergmann, H. Ogasawara, L. G. M. Pettersson, S. Myneni, A. Nilsson, *J. Phys. Chem. A* **2005**, *109*, 5995–6002.

[60] J. D. Smith, R. J. Saykally, P. L. Geissler, *J. Am. Chem. Soc.* **2007**, *129*, 13847–13856.

[61] a) S. H. Lee, J. C. Rasaiah, *J. Phys. Chem.* **1996**, *100*, 1420–1425; b) C. F. Schwenk, T. S. Hofer, B. M. Rode, *J. Phys. Chem. A* **2004**, *108*, 1509–1514; c) T. S. Hofer, B. R. Randolf, B. M. Rode, *J. Comput. Chem.* **2005**, *26*, 949–956; d) W.-Y. Wen, U. Kaatze, *J. Phys. Chem. A* **1977**, *81*, 177–181.

[62] Y. Marcus, *J. Phys. Chem. B* **2009**, *113*, 10285–10291; Y. Marcus, G. Hefter, *J. Solution Chem.* **1999**, *28*, 575–592.

[63] National Institute of Standards and Technology (NIST) Chemistry WebBook, NIST Standard Reference Database Number 69, Thermochemistry of cluster ion data compiled by M. Meot-Ner (Mautner), S. G. Lias: http://webbook.nist.gov/chemistry/.

[64] a) F. Hofmeister, *Arch. Exp. Pathol. Pharmakol.* **1888**, *24*, 247–260; b) B. Lonetti, P. Lo Nostro, B. Ninham, P. Baglioni, *Langmuir* **2005**, *21*, 2242–2249; c) W. Kunz, P. Lo Nostro, B. W. Ninham, *Curr. Opin. Colloid Interface Sci.* **2004**, *9*, 1–18; d) D. T. Bowron, J. L. Finney, *J. Chem. Phys.* **2003**, *118*, 8357–8372; e) J. L. Finney, D. T. Bowron, *Phil. Trans. R. Soc. A* **2005**, *363*, 469–492; f) J. M. Broering, A. S. Bommarius, *J. Phys. Chem. B* **2005**, *109*, 20612–20619; g) M. Chaplin provides a good description of Hofmeister effects at http://www.lsbu.ac.uk/water/hofmeist.html; h) T. López-León, M. Santander-Ortega, J. L. Ortega-Vinuesa, D. Bastos-González, *J. Phys. Chem. B* **2008**, *112*,16060–16069; i) F. Franks, *Water: A Matrix of Life*, 2nd ed., RSC, London, **2000**.

[65] P. Lo Nostro, B. W. Ninham, A. Lo Nostro, G. Pesavento, L. Fratoni, P. Baglioni, *Phys. Biol.* **2005**, *2*, 1–7.

[66] E. Sedlák, L. Stagg, P. Wittung-Stafshede, *Arch. Biochem. Biophys.* **2008**, *474*, 128–135.

[67] J. D. Trachman, M. Yasmin, *Curr. Microbiol.* **2004**, *49*, 353–360.

[68] H. E. Corey, *Kidney Int.* **2003**, *64*, 777–787; P. K. Grover, R. L. Ryall, *Chem. Rev.* **2005**, *105*, 1–10.

[69] X. Shi, R. B. Macgregor, *Biophys. Chem.* **2007**, *130*, 93–101.

[70] L. A. Munishkina, J. Henriques, N. Uversky, A. L. Fink, *Biochemistry* **2004**, *43*, 3289–3300.

[71] R. Zangi, J. B. F. N. Engberts, *J. Am. Chem. Soc.* **2005**, *127*, 2272–2276; R. Vácha, R. Zangi, J. B. F. N. Engberts, P. Jungwirth, *J. Phys. Chem. B* **2008**, *112*, 7689–7692.

[72] R. Zangi, M. Hagen, B. J. Berne, *J. Am. Chem. Soc.* **2007**, *129*, 4678–4686; R. Zangi, B. J. Berne, *J. Phys. Chem. B* **2006**, *110*, 22736–22741.

[73] G. Jones, M. Dole, *J. Am. Chem. Soc.* **1929**, *51*, 2950–2964.

[74] H. D. Jenkins, Y. Marcus, *Chem. Rev.* **1995**, *95*, 2695–2724.

[75] A. Einstein, *Ann. Phys.* **1906**, *324*, 289–306; A. Einstein, *Ann. Phys.* **1911**, *339*, 591–592.

[76] S. Glasstone, *The Elements of Physical Chemistry*, Van Nostrand, New York, **1946**.

[77] P. Agre, G. M. Preston, B. L. Smith, J. S. Jung, S. Raina, C. Moon, W. B. Guggino, S. Nielsen, *Am. J. Physiol.-Renal Physiol.* **1993**, *265*, F463–F476, and references therein.

[78] a) Y. Zhou, J. H. Morais-Carbal, A. Kaufman, R. MacKinnon, *Nature* **2001**, *414*, 43–48; b) E. Gouaux, R. MacKinnon, *Science* **2005**, *310*, 1461–1465.

[79] D. A. Doyle, J. Morais-Cabral, R. A. Pfuetzner, A. Kuo, J. M. Gulbis, S. L. Cohen, B. T. Chait, R. MacKinnon, *Science* **1998**, *280*, 69–77.

[80] S. Y. Noskov, B. Roux, *Nature* **2004**, *431*, 830–834.

[81] M. Thomas, D. Jayatilaka, B. Corry, *Biophys. J.* **2007**, *93*, 2635–2643.

[82] A similar argument in terms of total free energies of solvation of K^+ and Na^+ has been made by: a) S. Y. Noskov, B. Roux, *J. Gen. Physiol.* **2007**, *129*, 135–143; b) H. Yu, S. Y. Noskov, B. Roux, *J. Phys. Chem. B* **2009**, *113*, 8725–8730.

[83] N. Shi, S. Ye, A. Alam, L. Chen, Y. Jiang, *Nature* **2006**, *440*, 570–574.

Received: November 6, 2009