Toward Understanding the Hofmeister Series. 3. Effects of Sodium Halides on the Molecular Organization of H_2O As Probed by 1-Propanol

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We investigated the effects of NaF, NaCl, NaBr, and NaI on the molecular organization of H_2O by a calorimetric methodology developed by us earlier. We use the third derivative quantities of *G* pertaining to 1-propanol (1P) in ternary 1P−a salt−H_2O as a probe to elucidate the effects of a salt on H_2O. We found that NaF and NaCl worked as hydration centers. The hydration numbers were 19 ± 2 for NaF and 7.5 ± 0.6 for NaCl. Furthermore, the bulk H_2O away from the hydration shell was found unaffected by the presence of Na^+, F^-, and Cl^-. For NaBr and NaI, in addition to the hydration to Na^+, Br^- and I^- acted like a hydrophilic moiety such as urea. Namely, they formed a hydrogen bond to the existing H_2O network and retarded the fluctuation nature of H_2O. These findings were discussed with respect to the Hofmeister ranking. We suggested that more chaotropic anions Br^- and I^- are characterized as hydrophiles, whereas kosmotropes, F^- and Cl^-, are hydration centers.

Introduction

The Hofmeister series ranks the relative influence of anions and cations on the properties and functions of biopolymers.[1−3] It also applies to ion effects on a wide range of other processes in aqueous environments, particularly so within colloid sciences. The generality of this ion ranking has sparked a massive interest in the possible underlying mechanism. However, the molecular level understanding of the Hofmeister effect is still fragmentary. The recent interest is spearheaded by its relevance in biotechnology. Thus, the physical instability, which is inherent to most biotechnological products, is alleviated by the addition of the so-called excipients chosen according to their positions in the Hofmeister series. Also, problems associated with precipitation during fermentation or purification is addressed by the modification of the solvent based on Hofmeister arguments.[4,5]

Basic studies on Hofmeister mechanisms are dominated by investigations of binary aqueous solutions of the respective salts. This approach has provided important advances through analysis of various factors including surface tension increment, lyotropic number, viscosity *B*-coefficient, etc.[1−3] However, not all of these physical properties of binary aqueous salts carry the hallmark of the Hofmeister effect. In particular, information obtained by modern experimental techniques is not converging. For example, a classical Raman study showed that the intensities of both the bending and stretching vibrations increase in the order of $F^- < Cl^- < Br^- < I^-$, hinting that the strength of hydrogen bonding between the halide ion and H_2O weakens in this order.[6] On the other hand, recent dielectric relaxation studies revealed that the effects of halide ions together with NO_3^-, ClO_4^-, and SCN^- on H_2O dynamics were surprisingly similar and the connection to the Hofmeister series is not apparent.[7−10] Another recent study by the K-edge X-ray absorption spectroscopy of aqueous NaCl, NaBr and NaI demonstrated that these ions perturb the electronic structure of adjacent H_2O molecules, and the magnitude of this effect followed the trend $I^- \approx Br^- > Cl^-$.[11] The femtosecond pump−probe IR studies showed that the dynamics of the hydration shell of Cl^-, Br^-, or I^- in H_2O is much slower than that of the bulk H_2O outside of the hydration shell,[12,13] hence supporting the existence of the hydration shell. The hydration shell of Cl^- was suggested to be smaller than that of Br^- or I^-. It also suggested that the dynamics of bulk H_2O outside the hydration shell is not affected at all by the presence of not only halides[12,13] but also SO_4^{2-} and ClO_4^-.[14] The latter two are positioned at the both extremes in the Hofmeister ranking; SO_4^{2-} near to the kosmotropic (salting-out, structure making) and ClO_4^- near to the chaotropic (salting-in, structure breaking) ends.[1,2]

After all, the Hofmeister effect manifests itself in the presence of a third component; biopolymers, colloids etc. Hence it appears fruitful to investigate simple ternary systems containing the target salts and probe the effects of the salt on the molecular organization of H_2O in the presence of a third component. To this end, we have initiated experiments on ternary systems using the third component 1-propanol and use its thermodynamic behavior as a probe.[15−17] 1-Propanol (abbreviated as 1P) is convenient in that its effect on H_2O has been extensively studied,[18,19] and it has a balance of polar to nonpolar surface area that is comparable to that of many biomolecules.[40−42] The results of the first paper in the series[16] suggested that ClO_4^- and SCN^- from the chaotropic end of the series form hydrogen bonds to H_2O and reduce the degree of fluctuation in the hydrogen bond network of H_2O, as a typical hydrophile such as urea.[30] Conversely, a kosmotropic ion, SO_4^{2-}, was shown to be hydrated by about 16 molecules of H_2O and to promote the entropy-volume cross fluctuations in the system. Though these findings are not inconsistent with some of the earlier conjectures on the Hofmeister mechanism,[2] other anions such as acetate

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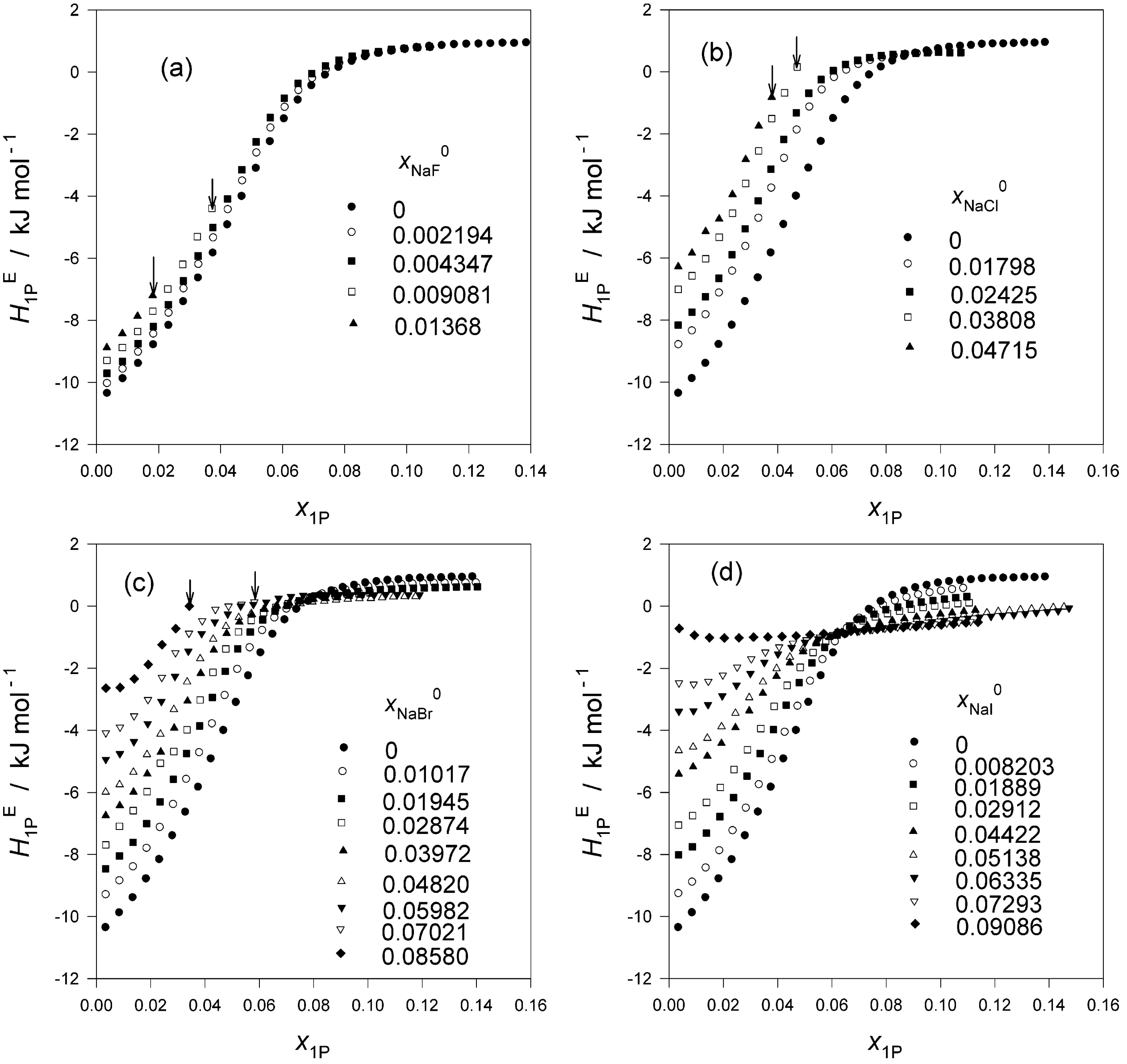

Figure 1. Excess partial molar enthalpy of 1-propanol (1P), H^E_{1P}, against the mole fraction of 1P, x_{1P}, in 1P−Na halide−H_2O at 25 °C: (a) NaF; (b) NaCl; (c) NaBr; (d) NaI. The initial mole fraction of aqueous Na halide to which 1P is successively titrated is shown within each panel.

showed a qualitatively different (structure-making) behavior due likely to the methyl group. Thus, to further investigate the potential of the methodology, we apply the same methodology to homologous halide ions, F^-, Cl^-, Br^- and I^-, which span the series from strongly kosmotropic (F^-) to strongly chaotropic (I^-) effects, and seek more direct relationship to the accepted Hofmeister ranking.[1,2]

Methodology

Our methodology has been described earlier.[15,16,20−25] Briefly, we experimentally determine the excess partial molar enthalpy of 1P, H^E_{1P}, in ternary 1P−a salt−H_2O, by perturbing the amount of 1P, n_{1P}, keeping all the other variables constant. Namely,

$$H^E_{1P} \equiv \left(\frac{\partial H^E}{\partial n_{1P}}\right) \tag{1}$$

which signifies the actual enthalpic contribution of 1P toward the entire system, or the actual enthalpic situation of 1P in the mixture. We stress that it is only the target component, 1P for the present case, that is perturbed, and thus we can isolate the enthalpic situation of 1P among all the other components. We measure this quantity accurately with 4 significant figures and in small increments in the mole fraction of 1P, x_{1P}. Hence it is possible to take one more derivative with respect to n_{1P} graphically without resorting to any fitting function. We thus obtain purely experimentally, without resorting to any fitting function, what we call the 1P−1P enthalpic interaction, H^E_{1P-1P}, defined as

$$H^E_{1P-1P} \equiv N\left(\frac{\partial H^E_{1P}}{\partial n_{1P}}\right) = (1 - x_{1P})\left(\frac{\partial H^E_{1P}}{\partial x_{1P}}\right) \tag{2}$$

Because eq 2 shows the effect of an infinitesimal addition of 1P on H^E_{1P}, H^E_{1P-1P} is naturally interpreted as the enthalpic measure of the 1P−1P interaction. Here again, we perturb only the amount of 1P, and thus H^E_{1P-1P} pertains strictly to 1P regardless of the presence of the salt. The effect of salt could appear in the resulting value of H^E_{1P-1P} or its x_{1P}-dependence, which will be used as a probe to elucidate the effect of the

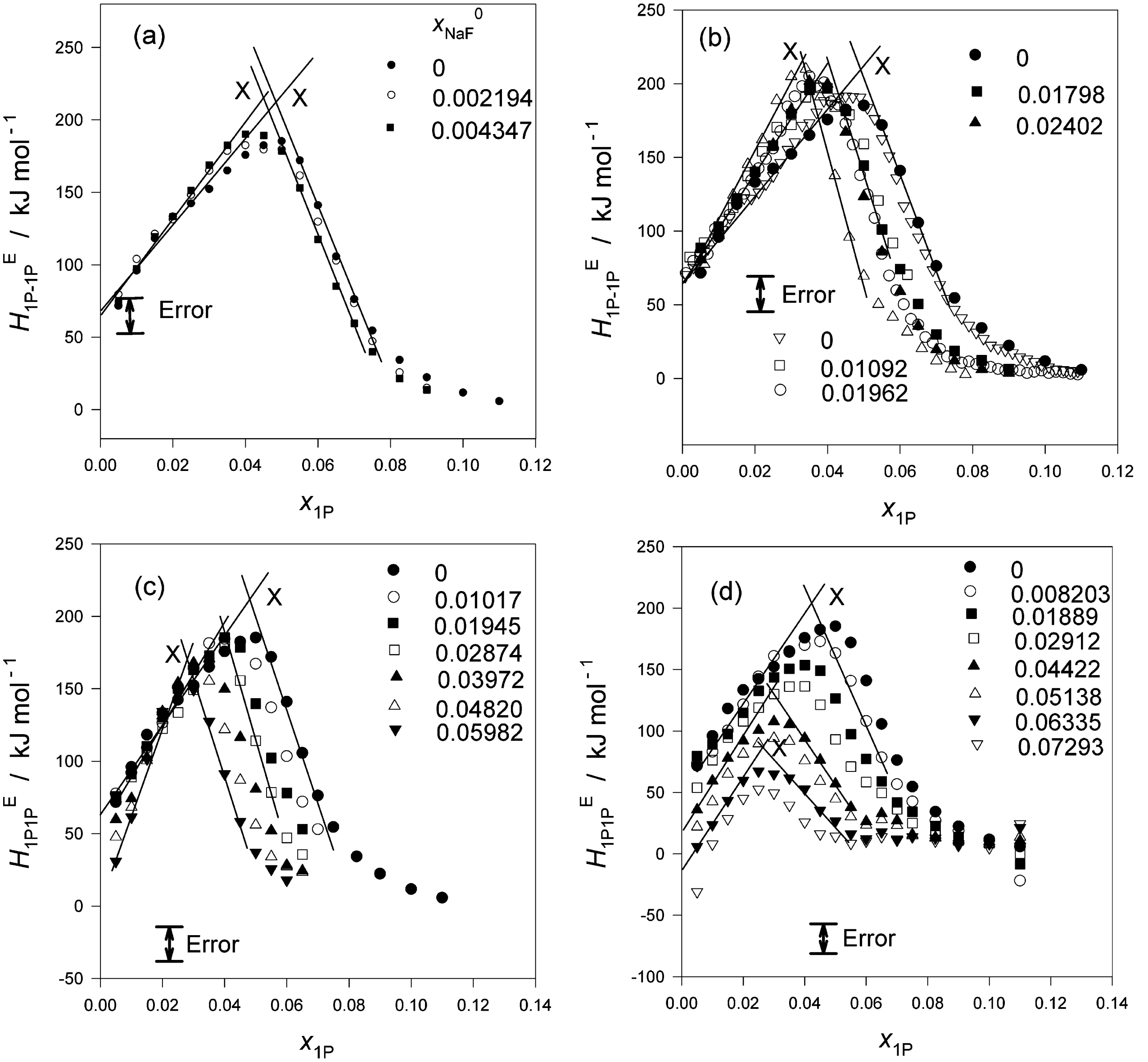

Figure 2. Enthalpic interaction between 1-propanol (1P), H_{1P-1P}^E, against the mole fraction of 1P, x_{1P}, in 1P−Na halide−H_2O at 25 °C: (a) NaF; (b) NaCl; (c) NaBr; (d) NaI. The initial mole fraction of Na halide of the mixed aqueous solvent is indicated in each panel. For (b) NaCl, the data from the earlier work[3] were included, shown by hollow symbols. For clarity only a few straight lines determining point X are shown in each panel.

chosen salt. Because H^E in eq 1 contains a first derivative of G, H_{1P}^E has a second and H_{1P-1P}^E a third derivative of G.

We earlier devised the normalized entropy−volume cross fluctuation, ${}^{SV}\Delta$, using thermal expansivity, α_p, which is a second derivative of G, and molar volume.[26] Namely,

$$ {}^{SV}\Delta \equiv RT\alpha_p/V_m \tag{3}$$

where V_m is the molar volume. ${}^{SV}\Delta$ contains information about the peculiarity of liquid H_2O. Unlike normal liquids, in which fluctuation with volume increase is consistently associated with entropy increase, H_2O molecules fluctuate in part with the volume increase associated with entropy decrease due to hydrogen bond formation. Thus the behavior of ${}^{SV}\Delta$ reflects the well-known peculiarity of H_2O. We then define and evaluate graphically the partial molar normalized fluctuation of 1P as

$$ {}^{SV}\Delta_{1P} \equiv (1 - x_{1P})(\partial^{SV}\Delta/\partial x_{1P}) \tag{4}$$

This quantity, a third derivative of G, shows the effect of 1P on the entropy−volume cross fluctuation in aqueous solution. It thus reflects how the peculiarity of H_2O is modified as the concentration of 1P increases. We showed that the x_{1P}-dependence pattern of H_{1P-1P}^E matches exactly with that of ${}^{SV}\Delta_{1P}$ on scaling the ordinate.[26] Hence we concluded that the 1P−1P enthalpic interaction and that the effect of 1P on the cross fluctuation share the same cause and the interaction between 1P molecules is mediated via the bulk H_2O. Thus, the x_{1P} dependence of H_{1P-1P}^E as well as that of ${}^{SV}\Delta_{1P}$ represents the state of partially modified H_2O.

Using these quantities, we found that the 1P−H_2O system is not a simple mixture. Generally, for aqueous nonelectrolytes including 1P−H_2O, we found[15,16,18−26] that there are three distinctively different mixing schemes operating depending on the composition. We call them mixing schemes I, II and III from the H_2O-rich side. In mixing scheme I in the H_2O-rich region, H_2O protects its “integrity” (i.e., the hydrogen bond network is retained) against the invading solute. The manner in which H_2O does this depends on the characteristics of the solute. A more hydrophobic solute such as 1P enhances the hydrogen bond network of H_2O in its immediate vicinity—

classically referred to as iceberg formation—but the hydrogen bond probability of bulk H_2O away from the "icebergs" is reduced.[18,19,27] However, the long-range hydrogen bond connectivity is still intact though in a lesser degree. As the composition of solute increases and the bulk hydrogen bond probability decreases to a threshold value, the hydrogen bond percolation and thus the "integrity" of H_2O is lost. Thereupon mixing scheme II pertinent to the intermediate composition region sets in. The solution then consists of two kinds of clusters, one rich in H_2O and the other in solute. The process of reaching this crossover point is depicted by the increase in H^E_{1P--1P}, among other third derivative quantities, as will become evident in Figure 2 above. Point X in the figure, as will be explained below, marks the onset of the transition of mixing scheme.

We stress that in mixing scheme 1 the solute−solute interaction is bulk H_2O mediated.[15,16,18−27] It is the somewhat modified but still hydrogen-bond percolated H_2O that dictates the solute−solute interaction. This is true between different solute molecules for multicomponent aqueous solutions[24,25] as well as the same solutes. These findings contribute to the basis of the present methodology. Namely, the changes induced in the pattern of H^E_{1P-1P} vs x_{1P} on addition of a salt reflect what the added salt does to H_2O, and are used as a probe to elucidate its effects on H_2O, as long as the system remains within mixing scheme 1.

Experimental Section

For the calorimetric measurements, NaF (>99%, Merck, Darmstadt, Germany), NaCl (>99.5%, Sigma, St. Louis, MO), NaBr (>99%, BHD, Poole, UK), NaI (>99.5%, Merck) and 1-propanol (>99.8%, Fluka, Buchs, Switzerland) were used as supplied. Due care was exercised not to contaminate these chemicals with moisture. Stock aqueous solutions of salts were made with fresh MilliQ water (Millipore, Bedford, MA) immediately after breaking the seals. The stock solutions were gravimetrically diluted as required. For NaI, the measurements were carried out in a dry nitrogen atmosphere so that I^- was not oxidized during the experiments. The lack of oxidation at the end of measurement was checked by colorimetry after extracting possible oxidation product, I_2, into chloroform. For the determination of the three-component phase boundary, chemicals were treated in the same manner as above, except they were all Wako, Special Grade and quoted purities are NaF (99.0%), NaCl (99.5%), NaBr (99.5%), NaI (99.5%), and 1P (99.5%).

The excess partial molar enthalpy of 1P, H^E_{1P}, was determined by using a TAM-2277 titration calorimeter (Thermometric, Järfälla, Sweden). Six hundred microliters of water or salt solution was quantified by weight in a 1 mL stainless steel cell and mounted on a type 2250 calorimeter (Thermometric). The solution was subsequently titrated with 4.17 μL aliquots of 1P delivered by a Lund Pump (Thermometric) with a 500 μL glass syringe. The experimental temperature was 25.00 ± 0.01 °C. The ratio of titrant over titrate was shown sufficiently small so that the result could be approximated as H^E_{1P}.[28] The uncertainty is estimated as ±0.003 kJ mol^{-1}. The phase separation boundary of 1P−salt−H_2O was determined within 0.1% by the method developed by us recently.[29] The temperature of the observation cell was controlled at 25.0 ± 0.1 °C.

Results

Figure 1 shows the results of the excess partial molar enthalpy of 1P, H^E_{1P}, in the respective ternary aqueous solutions. The arrows in the figure indicate phase separation. Figure 1a suggests that the effect of NaF is qualitatively similar to that by NaCl, Figure 1b, which is a complete replica of our earlier study.[20] On the other hand, the effects of NaBr and NaI, Figure 1c,d, are qualitatively different from the above two. NaI, in particular, alters the x_{1P} dependence of H^E_{1P} in the same manner as urea, a typically hydrophilic solute that was argued to form hydrogen bonds directly with the H_2O network and retard the degree of fluctuation inherent in liquid H_2O.[30] The x_{1P} dependence on H^E_{1P} is more conspicuous in the next derivative, H^E_{1P-1P}, eq 2. As described in detail in the previous paper,[16] we drew smooth curves through all the data points by aid of a flexible ruler. We then read the value of H^E_{1P} off the drawn curve at the interval of 0.04 in x_{1P}. The derivative of eq 2 is approximated as $\delta H^E_{1P}/\delta x_{1P}$ with $\delta x_{1P} = 0.08$. This approximation was earlier shown to be acceptable.[23] The results are shown in Figure 2. The maxima in the figure correspond to the inflection points in Figure 1 that represent the onset of the transition from mixing scheme I to II.[18,19] Due to an inevitable uncertainty of ±10 kJ mol^{-1} introduced through the graphical differentiation, we determined the maximum of H^E_{1P-1P} in the following manner. We linearly extended both sides of a peak and take point X, the intersection, as the maximum of H^E_{1P-1P}, as shown in Figure 2. For NaF, NaCl, and NaBr, the series that prematurely ended at the respective phase separation points are omitted from Figure 2. For NaI, the case for $x^0_{NaI} = 0.09086$ does not display an inflection point in Figure 1d and was not included in Figure 2d, because at this high NaI composition the system is already out of mixing scheme I.

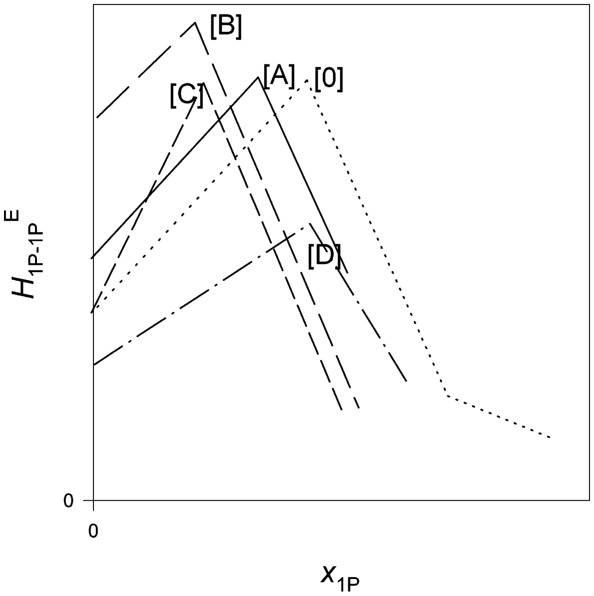

Figure 3. Schematic presentation of the H^E_{1P-1P} pattern changes induced by the presence of various types of a third component in 1P−third component−H_2O, we have studied so far. Key: [0], for a binary 1P−H_2O; [A], the third component is equally hydrophobic as the probing 1P; [B], the third component is more hydrophobic than 1P; [C], the third component is a hydration center; [D], the third component is hydrophilic.

Discussion

Effects of a Third Component on the H^E_{1P-1P} Pattern. The effect of the added salt on the changes of the H^E_{1P-1P} pattern is the key information used in elucidating the effect of the salt on H_2O. To facilitate comparisons, we briefly review how various types of the chosen third component modifies the x_{1P} dependence

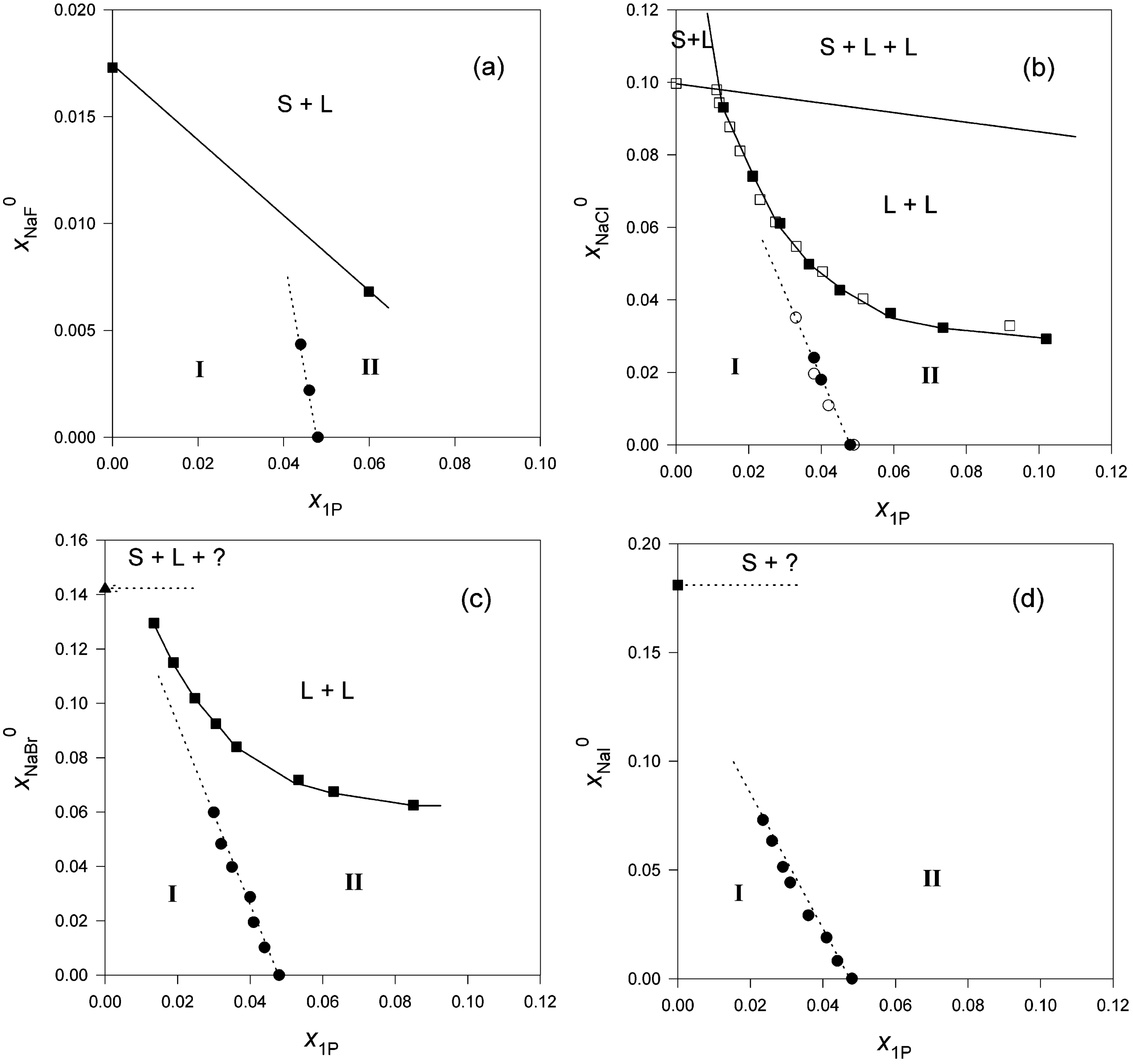

Figure 4. Mixing scheme and phase boundaries for ternary 1-propanol (1P)−Na halide−H$_2$O at 25 °C: (a) NaF; (b) NaCl; (c) NaBr; (d) NaI. Key: I, region for mixing scheme I; II, region for mixing scheme II; S, region for solid phase; L, region for liquid phase. For (d) NaI, no phase separation was observed even for $x^0_{NaI} = 0.09956$ and up to $x_{1P} = 0.1780$.

pattern of H^E_{1P-1P} that we have studied so far. Figure 3 is a schematic representation. In this figure, the dotted line (marked [0]) represents H^E_{1P--1P} for binary aqueous 1P. Characteristic changes in the interaction function for different categories of solutes are illustrated by the four other curves, [A], [B], [C] and [D]. Thus, case [A] represents the effect of 2-propanol (2P),[31,32] which is almost equally hydrophobic as the probing 1P.[18,19,33] Because the existing 2P has already modified H$_2$O in a manner similar to that for 1P and in proportion to its concentration, 1P then further modifies H$_2$O for the rest of way to point X. Hence the H^E_{1P-1P} pattern of case [0] shifts parallel to left, toward a smaller value of x_{1P}. Thus, the value of x_{1P} at point X decreases, the value of H^E_{1P-1P} at point X remains the same, and the value of H^E_{1P-1P} at $x_{1P} = 0$ increases. The effect of acetate was of this type, indicating phenomenologically that acetate is equally hydrophobic as 1P, as shown in the previous paper.[16] Case [B] was observed for *tert*-butyl alcohol (TBA),[32] which is more hydrophobic than 1P.[18,19,33] Hence, the existing TBA modifies H$_2$O more strongly than 2P, so that the iceberg-clad 1P interaction with another iceberg-clad solute (TBA or 1P) is higher than for case [A]. Thus, point X ends up with a higher value of H^E_{1P-1P} and a smaller value of x_{1P}. The fact that the slopes of both sides of the peak remain almost the same as for [0] confirms that the 1P−1P interaction is H$_2$O-mediated. We note that SO$_4{}^{2-}$ was of this type.[16] Case [C] was found for the effect of NaCl.[20] Because the value of x_{1P} at point X decreases proportionally to the initial mole fraction of NaCl, x^0_{NaCl}, we concluded that a number of H$_2$O molecules are hydrated with Na$^+$ and Cl$^-$ ions and make them unavailable to 1P to interact. That such a hydration shell exists and the hydrated H$_2$O stays in the shell was supported by the femtosecond pump spectroscopy studies.[12−14] The fact that the value of the H^E_{1P-1P} at $x_{1P} = 0$ as well as that at point X remains the same suggests that the bulk H$_2$O away from the hydration shell remains unaffected, which corroborates the findings for NaCl.[13] A first principle simulation study indicated that a Na$^+$ ion hydrates 5.2 molecules of H$_2$O and leaves the bulk H$_2$O away from the hydration shell unperturbed.[34] If we assume the hydration of Na$^+$ and that of Cl$^-$ are independent, it follows then that a Cl$^-$ ion is hydrated

TABLE 1: H^E_{1P-1P} Pattern Changes Induced by Addition of a Third Component in 1-Propanol (1P)−Third Component−H_2O System

case	H^E_{1P-1P} at $x_{1P} = 0$	at point X x_{1P}	 H^E_{1P-1P}	third comp. examples	ref
[A]	increase	decrease	constant	2-propanol	31, 32
[B]	increase	decrease	increase	*tert*-butyl alcohol	32
[C]	constant	decrease	constant	NaCl	20
[D]	decrease	constant	decrease	urea	30

by two molecules of H_2O without affecting H_2O outside the hydration shell. There are a number of estimates for the hydration numbers of ions in the literature.[35−38] The individual definitions for the hydration number are not identical on the basis of a different method with different assumptions. It is not immediately obvious that one method is superior to the others. Here we use the hydration number determined by the present methodology for comparative purposes. As shown below, we recover the hydration number for Na^+, ensuring the self-consistency of the present method. Case [D] shows the results of a typical hydrophilic solute such as urea.[30] Our interpretation is that urea forms hydrogen bonds directly to the existing hydrogen bond network of H_2O and consequently retards the degree of fluctuation inherent in liquid H_2O but does not change the hydrogen bond connectivity nature. This suggestion is consistent with the conclusion of a simulation study that urea leads to stiffening of the short-time dynamics of both urea and H_2O.[39] The effects of ClO_4^- and CNS^-, typical chaotropes in the Hofmeister series,[1,2] are of this type.[16] The behavior of the locus of point X and the intercept at $x_{1P} = 0$ are summarized in Table 1 for each case.

Hydration Number. In comparison with Figure 3, Figure 2a shows that NaF belongs to case [C] together with NaCl, Figure 2b. Namely, the value of H^E_{1P-1P} at point X remains the same within the estimated uncertainty, whereas that of x_{1P} decreases on addition of the salt. The loci of point X, the onset of transition to mixing scheme II, are shown in relation to the respective phase diagrams in Figure 4a,b. The mixing scheme boundary seems to form a straight line, the slope of which is related to the hydration number, if the mechanism discussed above is correct. In other words, the x^0_{salt} intercept of the boundary gives the putative value of salt at which all the H_2O molecules are hydrated and are made unavailable for 1P to interact. Accordingly, the hydration number of NaF is estimated as 17.5−20.5. Or with that of Na^+ assumed to be 5.2,[21] the hydration number of F^- becomes about 13 ± 2. The hydration number for NaCl is 7.5 ± 0.6 from the present measurements, the same as the previous evaluation.[20] In passing, we suggested the hydration number of SO_4^{2-} is 16 in the previous paper,[16] by the same methodology.

Br^- and I^-, on the other hand, show effects similar to those for case [D]. The effect of the countercation Na^+ is that of case [C], as discussed above, which may be responsible for point X to move to the left in Figure 2c,d. The loci of point X in terms of x_{1P} as NaBr and NaI are added are shown in Figure 4c,d. Both mixing scheme boundaries may be regarded as straight lines, whose slopes (or the x^0_{salt} intercept) give 5.3 and 5.6 hydration numbers, respectively, for NaBr and NaI. The match of these numbers to the theoretical estimate, 5.2,[34] for Na^+ provides the self-consistency of the present method of estimating the hydration number. We conclude therefore that what is observed in Figure 4c,d is the sum of the two effects: one by Na^+, which shifts point X to the left without changing the value of H^E_{1P-1P}, and the other by Br^- and I^-, which reduce the value of H^E_{1P-1P}.

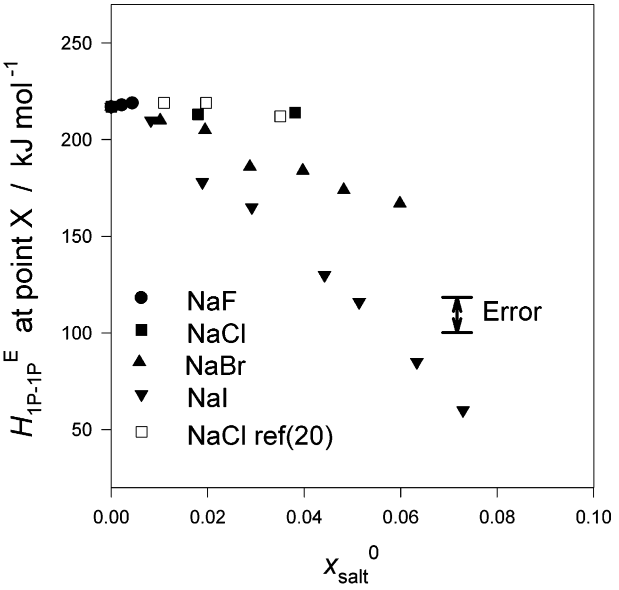

Figure 5. Loci of point X in terms of H^E_{1P-1P} against the initial mole fraction of Na halide, and other Na salts from paper I.[2]

Relation to the Hofmeister Series—Conclusion

We limit our attention to the halide ions studied here and to their relationship to the Hofmeister effect. The more general discussion including other anions as well as cations will be forthcoming. The Hofmeister ranking for the halides is more or less established as, from the kosmotropic (salting-out, structure-making, stabilizing) to the chaotropic (salting-in, structure-breaking, destabilizing) end,[1,2]

$$F^- > Cl^- > Br^- > I^- \tag{5}$$

As mentioned above, the hydration numbers are 13 for F^- and 2 for Cl^-, which is in accordance with the ranking (5). Namely, F^- makes more H_2O molecules unavailable by hydration and hence has a stronger tendency for salting out proteins. The hydrogen bonding of F^- toward H_2O is known to be the strongest of halides from Raman study.[6] Hence F^- could form a tight hydration shell with many H_2O molecules, whereas Cl^- forms a very modest hydration shell. Br^- and I^-, on the other hand, form a weaker hydrogen bond to H_2O,[6] such that the inherent hydrogen bond network of H_2O is not disrupted, or rather Br^- and I^- connect onto the existing hydrogen bond network of H_2O. By so doing, they retard the characteristic fluctuation of H_2O by breaking H donor/acceptor symmetry, as urea.[30] The degree of such an effect can be monitored by the decrease in the value of H^E_{1P-1P} or equivalently that of $^{SV}\Delta_{1P}$. Figure 5 shows the plots of the value of H^E_{1P-1P} at point X as each salts are added. As is evident from the figure, this "hydrophilic" effect is in the same order as ranking (5). Thus, we suggest within the halide ions that the kosmotropes are acting as hydration centers, much more so for F^- in comparison with Cl^-. The chaotropes, on the other hand, act as fluctuation retarders, and its effect is stronger for I^- than for Br^-. How the characteristics of the chaotropes, salting-in or destabilizing propensities, come about from retardation of fluctuation nature is yet to be elucidated.

We stress that the present methodology is limited to what the moderately hydrophobic probe, 1P, can detect. Although 1P has a balance of hydrophobic and hydrophilic surfaces roughly similar to those of most biomolecules,[40−42] there must be hydrophobic or hydrophilic specific effects that dictates the overall behavior of biopolymers in aqueous solutions. Thus we need similar information probed by a more hydrophobic or a more hydrophilic solute than the present 1P.

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Supporting Information Available: Table S1 of the excess partial molar enthalpies of 1P in 1P−salt−H_2O, for salt = NaF, NaCl, NaBr and NaI; Table S2 of phase boundaries in 1P−salt−H_2O. This material is available free of charge via the Internet at http://pubs.acs.org.

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