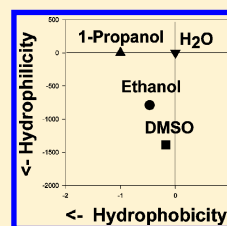


Effects of Ethanol and Dimethyl Sulfoxide on the Molecular Organization of H₂O as Probed by 1-PropanolTakeshi Morita,[†] Peter Westh,[‡] Keiko Nishikawa,[†] and Yoshikata Koga^{*,§}[†]Graduate School of Advanced Integration Science, Chiba University, Chiba 263-8522 Japan[‡]NSM Research for Functional Biomaterials, Roskilde University, Roskilde DK-4000 Denmark[§]Department of Chemistry, The University of British Columbia, Vancouver, BC Canada V6T 1Z1

Supporting Information

ABSTRACT: We characterized the effects of ethanol (ET) and dimethyl sulfoxide (DMSO) on H₂O within a limited H₂O-rich region by the 1-propanol (1P)-probing methodology developed by us earlier. The results are displayed on a two-dimensional map with twin coordinates: one pertaining to hydrophobicity and the other to hydrophilicity. The locus of ET on this map was at a point in between methanol (ME) and 2-propanol (2P) as expected from our earlier findings by thermodynamic studies. That for DMSO, however, was surprisingly more hydrophilic than ME. Similar to N-methyl groups discussed recently (*J. Phys. Chem. B* **2011**, *115*, 2995), it was argued that the methyl groups attached to the S atom are made susceptible for direct hydrogen bonding to the surrounding H₂O molecules due possibly to the electronegativity of the S atom. In view of these findings, we suggest caution to be exercised for the conventional general trend of taking any methyl groups to be “hydrophobic.”



1. INTRODUCTION

We have devised a thermodynamic methodology for characterizing the effect of solute on the molecular organization of H₂O in the limited H₂O-rich concentration region.¹ While the methodology, which we call the 1-propanol (1P)-probing methodology, was also described to some detail in more recent publications;^{2–4} a brief description is given here. We study a ternary system 1P–S–H₂O, where S is the test sample for which the effect is to be examined. In this complex ternary system with many-body interactions, we perturb the system by an infinitesimal increase in the molar amount of 1P, n_{1P} , and determine the response of the system in terms of its excess enthalpy, H^E , in order to reveal the effect of the target component 1P on the property of the whole system. This is equivalent to measuring the excess partial molar enthalpy of 1P, H_{1P}^E , defined as

$$H_{1P}^E \equiv \left(\frac{\partial H^E}{\partial n_{1P}} \right)_{p, T, n_i \neq 1P} \quad (1)$$

for a given initial mole fraction of S, $x_S^0 = n_S / (n_S + n_W)$, where n_S and n_W are the molar amounts of S and H₂O (W), respectively. Since $H^E = G^E - T(\partial G^E / \partial T)$, H_{1P}^E is a second derivative of G together with the entropy and volume analogues. The definition, eq 1, indicates that H_{1P}^E signifies the effect of 1P on H^E of the whole system, or the actual enthalpic situation of 1P in the mixture. We then perturb the system again to evaluate the effect of 1P on H_{1P}^E , which is defined as

$$H_{1P1P}^E \equiv N \left(\frac{\partial H_{1P}^E}{\partial n_{1P}} \right) = (1 - x_{1P}) \left(\frac{\partial H_{1P}^E}{\partial x_{1P}} \right) \quad (2)$$

where $N = n_{1P} + n_S + n_W$ and $x_{1P} = n_{1P} / N$. H_{1P1P}^E thus defined is a third derivative and shows the effect of 1P on the actual enthalpic situation of 1P in the mixture. Hence we call this the enthalpic 1P–1P interaction. We evaluate H_{1P1P}^E by graphically or numerically calculating the partial derivative of the far right of eq 2 without resorting to any fitting function.^{5,6} Thus H_{1P1P}^E is model-free and experimentally accessible.

Without the presence of S, the x_{1P} -dependence pattern of H_{1P1P}^E is sketched as case [A] in Figure 1. We learned from previous works that the peak type anomaly in H_{1P1P}^E is a hallmark of hydrophobic 1P in aqueous solution and that the integrity of liquid H₂O is maintained up to the top of the peak, point X. By the integrity of liquid H₂O we mean that the latter is a highly fluctuating hydrogen bonding system, but at any given instance the hydrogen bonds are bond percolated throughout of the entire bulk.^{7,8} Beyond point Y in the figure, the hydrogen bond network is no longer connected throughout the entire bulk of H₂O. The region from point X to point Y is the transient, with X being the onset and Y being the end of the transition in the mixing scheme (molecular level scenario) to that operative in the intermediate concentration range. We named these Mixing Schemes I and II from the H₂O-rich end.⁵ This peak type of anomaly in H_{1P1P}^E was found to be common for other hydrophobes. Or rather, we call a given solute i (in binary i -H₂O) a hydrophobe if its H_{ii}^E pattern shows a peak type anomaly as in Figure 1, case [A]. From extensive studies on aqueous hydrophobes using the second and the third derivative thermodynamic quantities, we suggested that a hydrophobe on entering in H₂O forms a hydration shell around it, within which

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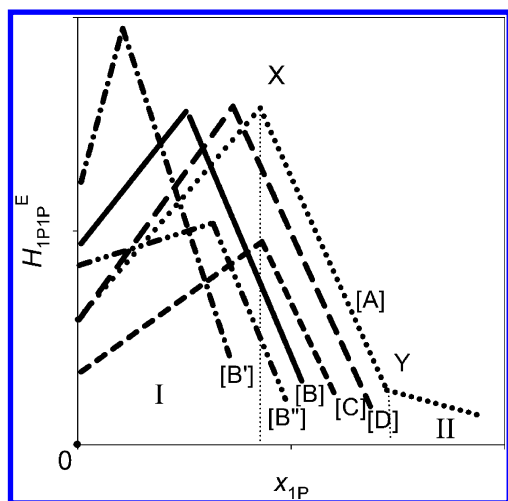


Figure 1. The induced changes of H_{1PIP}^E pattern in the presence of various kinds of S: [A] without S. See text for X, Y, I and II. [B] S = an equally hydrophobic solute as the probing 1P. [B'] S = a stronger hydrophobe than 1P. [B''] S = a weaker hydrophobe than 1P. [C] S = a hydrophile. [D] S = a hydration center.

the hydrogen bond probability of H_2O is enhanced, but more importantly we argued that the hydrogen bond probability of bulk H_2O away from hydrations shells is reduced gradually, using various experimental evidence.⁵ The transition to Mixing Scheme II is regarded as a loss of bond-percolation when the hydrogen bond probability is reduced to the percolation threshold.^{5,7,8}

A hydrophile i shows a different H_{ii}^E pattern in that it decreases sharply to point X, and thereupon H_{ii}^E turns gradually to point Y. After point Y, H_{ii}^E decreases linearly with a smaller slope than that prior to point X. Its slope is about the same as that for hydrophobic H_{ii}^E in Mixing Scheme II. The mole fraction region before point X for a hydrophile is also named Mixing Scheme I where the integrity of liquid H_2O is retained. Within Mixing Scheme I, although the integrity of liquid H_2O is retained, the detail manner by which the bulk H_2O is modified is different from hydrophobe. We suggested that a hydrophile forms hydrogen bonds directly to a momentarily existing hydrogen bond network of H_2O . By so doing, it exists as an impurity in the network and hence retards the degree of fluctuation inherent in H_2O .^{5,7} When the mole fraction of a hydrophilic i reaches about 0.1, the availability of bulk H_2O becomes limited, solutes start to aggregate, and Mixing Scheme II sets in.

For an amphiphilic i , the initial behavior of the H_{ii}^E pattern is between the above two. Instead of showing an initial increase as hydrophobes, H_{ii}^E either stays constant or decreases with much smaller slopes than that for hydrophiles up to point X and then drops sharply to point Y. We observed the former kind for aqueous 2-butanone and iso-butyric acid, while we observed the latter for 1,2-propanediol and DMSO.⁵ Here, we use “hydrophobicity, hydrophilicity, or amphiphilicity” to describe what such a solute does to H_2O within Mixing Scheme I in the respective manner described above.

How then do we quantify the strength of “hydrophobicity, hydrophilicity, and amphiphilicity”? An answer evidently lies on the behavior of the x_{1P} -dependence pattern of H_{1PIP}^E (Figure 1). In the presence of an almost equally hydrophobic S, (e.g., 2-propanol (2P)), the H_{1PIP}^E pattern shifts parallel toward lower x_{1P} (i.e., to the west) as shown as case [B] in Figure 1.^{1,4} This

westward shift was found to be proportional to x_s^0 . Its slope is therefore used as an index of hydrophobicity. It also indicates the hydration number n_{H_2O} since S makes a number of H_2O molecules unavailable for 1P to interact, resulting in a lesser value of x_{1P} to drive the system to point X. If a stronger (weaker) hydrophobe as *tert*-butanol (methanol) is present, the westward shift shows a larger (smaller) slope than that for case [B]. In addition, the value of H_{1PIP}^E at the top of the peak, point X, is larger (smaller) as sketched as [B'] ([B'']). In the presence of hydrophiles, such as urea (UR) and glycerol (Gly), the H_{1PIP}^E patterns are suppressed southward as case [C] in Figure 1, without showing westward shift. This southward shift was also found linear to x_s^0 , and its slope was taken to show the index of hydrophilicity. Amphiphiles shift point X in a southwestern direction with two composite components: the westward hydrophobic and the southward hydrophilic contributions. Thus, in this manner the distinction of the effect of a given solute on H_2O could be expressed by a set of two indices, instead of the conventional linear scale: a hydrophobe at one end, a hydrophile at the other, and an amphiphile in the middle. Its relative strength is given by the distance from a chosen null point on the linear scale. Instead, we have advanced the idea¹⁻⁴ to characterize the nature of a solute by a two-dimensional map with two diagonal axes; hydrophobicity and hydrophilicity determined by the present 1P-probing methodology. Hence characterization of the amphiphile will be more detailed identifying its hydrophobic and hydrophilic contribution separately.

The probable reasons behind the induced changes of the H_{1PIP}^E pattern by the respective type of test sample S shown in Figure 1 were discussed extensively earlier in relation to what we learned about the effect of a hydrophobe or hydrophile on H_2O .^{1-5,7} We stress that all the above discussion is limited within the H_2O -rich concentration range where the integrity of liquid H_2O is retained as a highly fluctuating hydrogen bonding system with its network bond-percolated at any given instance. In particular, it was argued that the north/south shift of point X is closely related to the net increase/decrease of the entropy-volume cross fluctuation of the system,^{1-5,7,9} using our finding that the enthalpic 1P–1P interaction and the effect of 1P on the S–V cross fluctuation share the same fundamental cause.^{5,7,9} Here we simply catalogue the effects of each type of solute on the H_{1PIP}^E pattern and use them to identify what ethanol (ET) and dimethyl sulfoxide (DMSO) do to H_2O .

We add the effects of another group of solutes, electrolytes, in Figure 1, for convenience of later discussion. NaCl induces the change illustrated as case [D].^{1,10} The westward shift of point X is naturally interpreted as forming a hydration shell as in the case of hydrophobes (case [B]). The total number of hydrating H_2O molecules was found to be 7.5 from the linearity of the westward shift against x_s^0 (S = NaCl). However, we note that the values of H_{1PIP}^E at the start, $x_{1P} = 0$, and at point X remain the same as case [A] without the presence of S (= NaCl). This suggests that while the $\{Na^+, Cl^-\}$ ion pair form hydration shells, they leave the bulk H_2O away from the hydration shells unperturbed. Furthermore, our extensive thermodynamic studies indicated that Na^+ forms its hydration shell with 5.2 molecules of H_2O and leaves the bulk H_2O away from the hydration shells unperturbed.^{1,10} This finding has support from *ab initio* molecular dynamics (MD) calculations^{11,12} and an anomalous X-ray and neutron diffraction study.¹³ Hence we suggested that Cl^- has 2.3 molecules of H_2O in its hydration shell and leaves the bulk H_2O away from

hydration shells unperturbed. This provides a convenient counterion in identifying the effect of a test individual ion. Namely, we use an appropriate counterion, Na^+ or Cl^- , and apply the same methodology in order to characterize the effect of the test ion on H_2O . In this manner we found some ions, Br^- and I^- , act as a hydrophile (case [C]), while others such as acetate and propionate ions behave as a “hydrophobe”.¹² The latter surprising issue will be discussed later relative to the findings of the present work.

2. EXPERIMENTAL SECTION

ET (Kemetyl, Koge, Denmark, anhydrous 99.9%+) and DMSO (Sigma, 99.9%+) were used as supplied. Stock solutions were made using them from a freshly opened bottle and Milli-Q H_2O . Stock solutions were diluted to a desired concentration immediately before measurement using the same H_2O . 1P (Sigma-Aldrich, 99.9%+) was used as supplied. Due care was exercised not to contaminate with moisture from the atmosphere. The excess partial molar enthalpy of 1P, H_{1P}^E , is determined by using a TAM-2277 Thermal Activity Monitor (Thermometric, Jarfalla, Sweden) with 2250 type calorimeters. The experimental temperature was controlled at 25.00 ± 0.01 °C. The ratio of titrant over titrate was on the order of 10^{-5} and is well within the acceptable range for approximating the differentiation on the right of eq 1.¹⁴ The uncertainty in the resulting H_{1P}^E was estimated as $\pm 0.01 \text{ kJ} \cdot \text{mol}^{-1}$.

RESULTS AND DISCUSSION

The data of H_{1P}^E are deposited as Supporting Information and plotted in Figure 2a and 2b against x_{1P} for a given initial mole fraction of ET and DMSO, respectively, x_S^0 ($S = \text{ET or DMSO}$). A sigmoid increase in H_{1P}^E with an inflection point is evident as long as x_S^0 is not too high. Our previous thermodynamic studies for binary ET– H_2O ^{5,15} and DMSO– H_2O ^{5,16} indicated that ET is a weak hydrophobe, and in the range $x_{\text{ET}} < 0.06$, the system ET– H_2O is in the Mixing Scheme I where the present 1P-probing methodology is applicable. DMSO was found to be an amphiphile, and the region for Mixing Scheme I is in the range $x_{\text{DMSO}} < 0.21$.^{5,16} The loci of point X for hydrophiles and amphiphiles are generally found to be about 0.1 mol fraction (see the table on p. 159 of ref 5). DMSO is therefore unique with the value 0.21 at point X. This fact was interpreted as DMSO molecules form small aggregates, perhaps as dimers or trimers even in Mixing Scheme I, which had a support from our X-ray diffraction study on binary DMSO– H_2O .^{5,17} [Of course, in Mixing Scheme II, $x_{\text{DMSO}} > 0.35$ DMSO molecules cluster together and form DMSO-rich clusters. The “small DMSO aggregates” are meant to be much smaller than the “DMSO-rich clusters” in Mixing Scheme II.] In any case, in binary DMSO– H_2O ($x_{\text{DMSO}} < 0.21$), the integrity of liquid H_2O is retained. For ET, Figure 2a, it is apparent that up to x_S^0 ($S = \text{ET}$) = 0.048, H_{1P}^E shows a sigmoid increase, but at $x_S^0 = 0.078 > 0.06$, no such behavior is shown. This indicates that the probing 1P identifies that the integrity of liquid H_2O is retained up to $0.048 < 0.06$. For DMSO (Figure 2b), however, already at x_S^0 ($S = \text{DMSO}$) = 0.08 < 0.21 , there is hardly any sign of an inflection point. To see these features more clearly (of course it was our original plan), we evaluate H_{1P}^E by eq 2.

With a good set of H_{1P}^E raw data at hand, we use the raw H_{1P}^E data themselves for evaluating the derivative on the far right of eq 2, rather than reading the H_{1P}^E values of a smoothly drawn curve through all the data points, as normally exercised.⁶ We

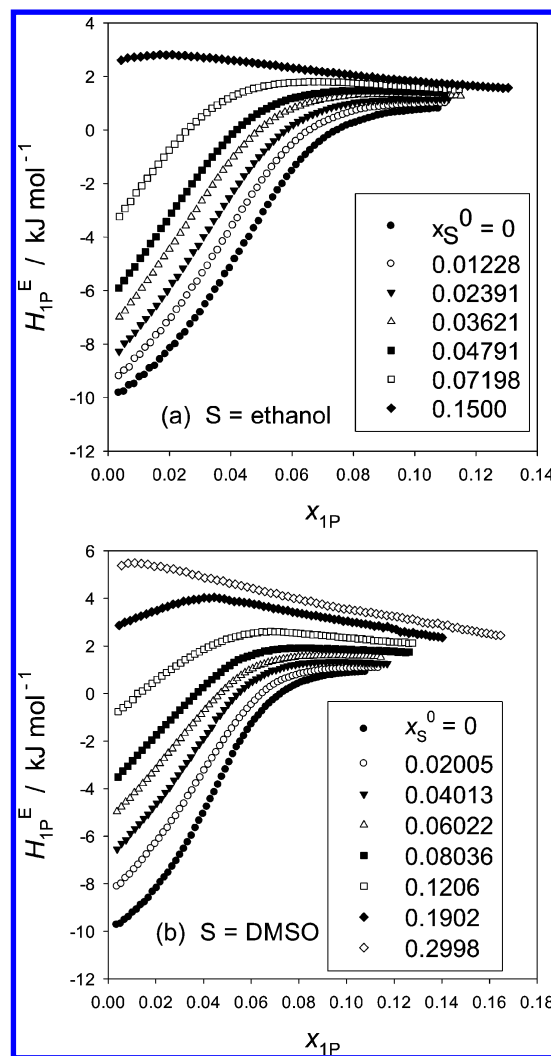


Figure 2. (a) The excess partial molar enthalpy of 1P in 1P–ET– H_2O at 25 °C at given x_S^0 , $S = \text{ET}$. (b) The excess partial molar enthalpy of 1P in 1P– S – H_2O at 25 °C at given x_S^0 , $S = \text{DMSO}$.

averaged slopes of neighboring data points with the x_{1P} interval, $\delta x_{1P} \approx 0.004$ for an approximate slope at the x_{1P} value of the midpoint. As we discussed extensively earlier, the x_{1P} increment $\delta x_{1P} \approx 0.008$ was found to be appropriate for approximating the derivative in eq 2 with the quotient $\delta H_{1P}^E / \delta x_{1P}$.⁶ The resulting values of H_{1P}^E are plotted in Figure 3a and 3b, respectively.

For $S = \text{ET}$, as long as $x_S^0 < 0.06$, all H_{1P}^E patterns show peaks, indicating that the mixture ET– H_2O retains the integrity of liquid H_2O as expected. There is still room for the probing 1P to drive the system to point X, thereupon the system changes into the Mixing Scheme II regime. For $S = \text{DMSO}$ (Figure 3b); however, already at $x_S^0 = 0.08$ (filled square symbols in Figure 3b), less than the threshold value 0.21 for the binary DMSO– H_2O , the H_{1P}^E pattern loses the peak, although a break in slope is apparent. Since the peak type H_{1P}^E pattern is the prerequisite for the present 1P-probing methodology, we should limit ourselves within x_S^0 ($S = \text{DMSO}$) < 0.08 . We point out, however, that the H_{1P}^E pattern for x_S^0 ($S = \text{DMSO}$) = 0.08, 0.12, and 0.19 < 0.21 resembles that of H_{1P}^E ($i = \text{DMSO}$) in binary DMSO– H_2O . This hints that for $0.08 < x_S^0 < 0.21$, the probing 1P acquires an amphiphilic nature as DMSO itself in this range in the ternary 1P–DMSO– H_2O . It could well be that the probing 1P is trapped within the small aggregates of

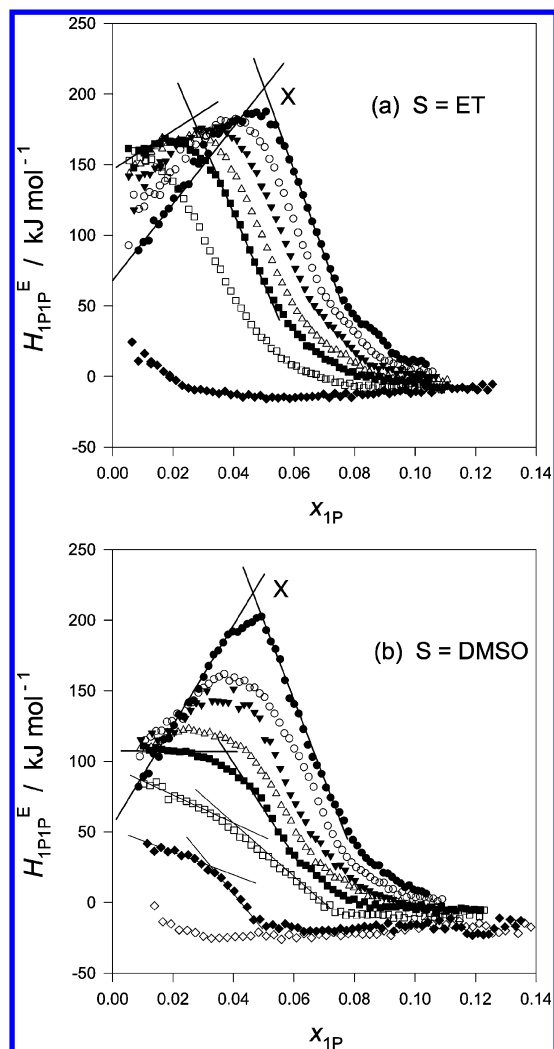


Figure 3. (a) The enthalpic 1P–1P interaction, H_{1P1P}^E , in 1P–S–H₂O at 25 °C, for a given x_S^0 (S = ET). Symbols are the same as in Figure 2a. (b) The enthalpic interaction, H_{1P1P}^E , in 1P–S–H₂O at 25 °C for a given x_S^0 (S = DMSO). The symbols are the same as in Figure 2b.

DMSO discussed above, and hence the H_{1P1P}^E pattern resembles that of H_{ii}^E (i = DMSO) in binary aqueous solution.

The induced changes in the loci of point X on addition of S (S = ET and DMSO) are now plotted in Figure 4. Figure 4a shows the induced changes in the x_{1P} -loci and Figure 4b those in the H_{1P1P}^E -loci of point X against x_S^0 (S = ET and DMSO). For S = DMSO, the loci of the break points for amphiphiles, which are equivalent to the peak top for hydrophobes, are also plotted for reference. Since there is a qualitative difference and the present 1P-probing is not applicable at these high DMSO concentrations, we limit ourselves with $x_S^0 < 0.08$. Since in the applicable range both plots are evidently linear within an estimated uncertainty given in each figure captions, the slope of Figure 4a provides the hydrophobicity index of the solute, and that of Figure 4 provides its hydrophilicity index. These indices are listed in Table 1 and used to construct the two-dimensional hydrophobicity/hydrophilicity map probed by 1P. They are shown in Figure 5 together with those for other solutes evaluated in the same manner earlier.

H₂O defines the origin of the map, and the probing 1P is necessarily plotted at (−1, 0), point H. Relative to these points, more hydrophobic solutes span to the west, and more

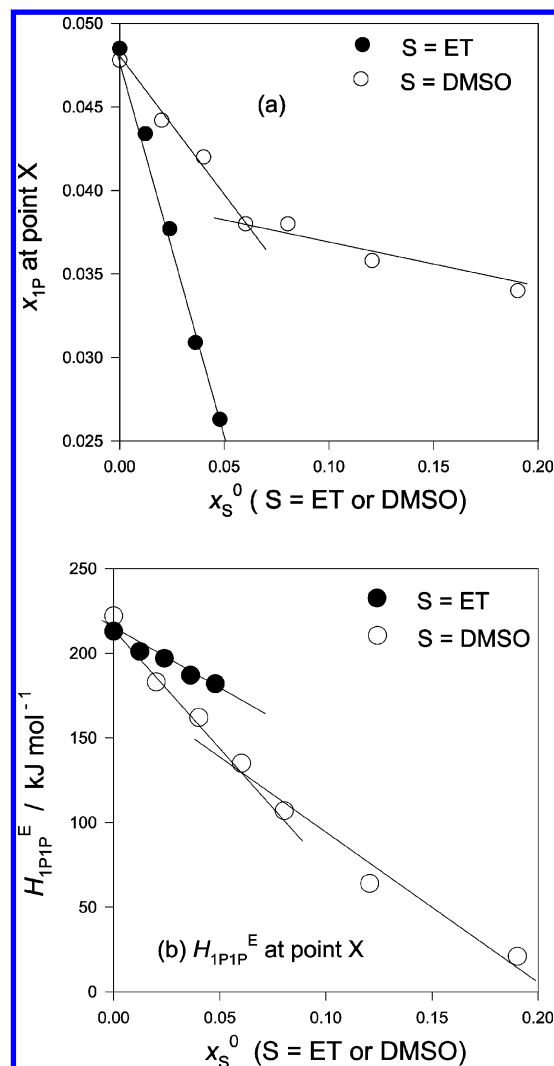


Figure 4. (a) The westward shift of point X against x_S^0 for (S = ET or DMSO). The slope is the index for hydrophobicity of S, and also indicates the hydration number, n_{HV} , of the hydration shell surrounding S in dilute aqueous solution. The uncertainty of the x_{1P} loci of point X is estimated as ± 0.001 . (b) The southward shift of point X against x_S^0 for S = ET or DMSO. The slope indicates the hydrophilicity of S, which is related the net effect of S on the S–V cross fluctuation of the system by S. The uncertainty for H_{1P1P}^E is estimated as ± 10 kJ·mol^{−1}.

hydrophilic ones span to the south. For hydrophobes, in addition, a stronger (or weaker) hydrophobe than the probing 1P shows a northward (or southward) shift. This is additional information about the characteristics of the effect of each solute on H₂O. The present result for ET is shown at F on the map. This completes the plots for a series of mono-ols from methanol (ME) to tert-butanol (TBA), and they are lined up smoothly from point E(ME) to J(TBA) in the order of the size of alkyl groups, although not linearly. Our previous thermodynamic studies for aqueous mono-ols indicated that the hydrophobicity rank among mono-ols was shown as BE > TBA > 1P > 2P > ET > ME from the values of H_{ALAL}^E (AL = mono-ols) and those of x_{AL} loci at the peak point of H_{ALAL}^E . It is in line with the size of alkyl group. 2-Butoxyethanol (BE) at point K on the map is clearly an exception in terms of the north/south-ward shift, which could be due to the presence of an ether group in BE molecule. We confirmed recently that the H_{ALAL}^E pattern for AL = BE is quite different from those of other

Table 1. Hydrophobicity/Hydrophilicity Indices as Probed by 1P

solute (abbr.)	symbol in Figure5	hydrophobicity slope of Figure4a	n_H hydration#	hydrophilicity slope of Figure4b	applicable x_s^0 range
ET	F	-0.47	8.6 ± 0.6	-790	<0.06
DMSO	P	-0.17	2.6 ± 0.5	-1390	<0.08

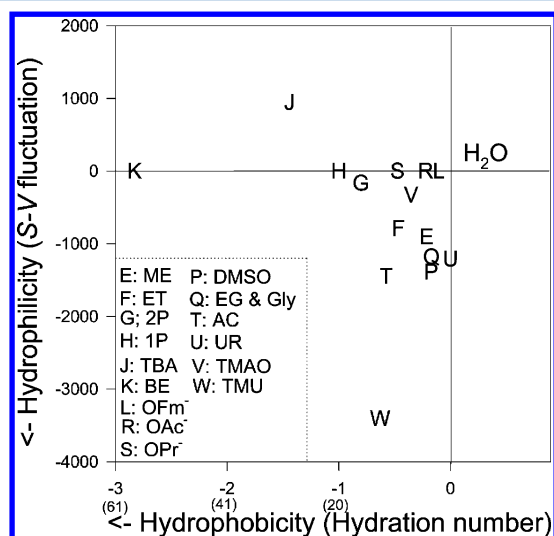


Figure 5. Hydrophobicity/hydrophilicity map for various solutes. See text for discussion. Abbreviations: ME, methanol; ET, ethanol; 2P, 2-propanol; 1P, 1-propanol; TBA, tert-butanol; BE, 2-butoxyethanol; DMSO, dimethyl sulfoxide; EG, ethylene glycol; Gly, glycerol; 12P, 1,2-propane-diol; 13P, 1,3-propane-diol; AC, acetone; UR, urea; TMAO, trimethylamine-*N*-oxide; TMU, tetramethyl urea; OFm⁻, formate ion; OAc⁻, acetate ion; OPr⁻, propionate ion. ET and DMSO, this work; OFm⁻, OAc⁻, and OPr⁻,² all the rest are from ref 4.

mono-ols, in that the initial increase in H_{ALAL}^E up to point X does not show linearity, but it breaks at a half way to a steeper increase to point X.¹⁸ Another recent MD study on a BE–H₂O system suggested that at a very low mole fraction range before the BE–BE aggregation starts (for Mixing Scheme II), the BE molecule displays intramolecular association involving –O– and the end –OH.¹⁹ If so, the –OH is then hidden from surrounding H₂O molecules, and the hydrophobicity could increase at this point. Thus, for BE, the hydrophobicity in terms of hydration number (the value in brackets on the abscissa) is related to the size of the alkyl group but in terms of the effect on the S–V cross fluctuation does not show an appropriate northward shift. This suggests that the size of alkyl group alone does not fully indicate its effect on H₂O. Indeed, the loci of ethylene glycol (EG) and Gly are almost identical at Q in the map. This suggests that nonmethyl alkyl and hydroxyl groups seem to mutually compensate. ME at point E is less hydrophilic in terms of north/south scale and also slightly hydrophobic as signified by a westward shift than Q (EG or Gly). This indicates that the methyl group is stronger in its hydrophobicity than a nonmethyl alkyl moiety. Comparison between 1P (H) and 2P at G may hint that multiple methyl groups in a branched configuration are not as hydrophobic as the normal propyl group. And yet TBA is clearly a stronger hydrophobe than 1P, 2P, ET, and ME according to the map.

Other surprising results involving N-methyl groups (methyl groups attached to a N atom) were found and discussed extensively earlier in terms of relative loci of UR, acetone (AC), tetramethyl urea (TMU) and trimethylamine-*N*-oxide (TMAO).⁴ It was suggested that the electro-negativity of the

N atom is responsible for making CH₃– groups more susceptible for direct hydrogen bonding to the surrounding H₂O molecules. A similar interpretation about S-methyl was reached on the basis of spectroscopic studies showing similar electron donating propensity from methyl to S.^{20,21} The present result shows the locus for DMSO is P for x_s^0 ($S = \text{DMSO}$) ≤ 0.06 , more hydrophilic than Q for EG and Gly. The southward component of DMSO suggests more hydrophilic than UR, in spite of having two methyl groups! Clearly, the number of methyl group alone does not dictate the solute's hydrophobicity/hydrophilicity. The intramolecular arrangement, and particularly the nature of neighboring atoms also, seems important in this regard.

In our recent publication,² we applied the same methodology to formate (OFm⁻), acetate (OAc⁻), and propionate (OPr⁻). The results are reproduced as L, R, and S on the map. For OFm⁻, the westward shift corresponded to $n_H \approx 1$, and it showed the characteristics of a hydration center, case [D] in Figure 1. It was interpreted as hydration of a single H₂O molecule to the carboxylate end. For OAc⁻ and OPr⁻, including presumably a single H₂O molecule at the carboxylate end, a total of 3.7 and 9 molecules of H₂O hydrate the alkyl group, respectively. Moreover, the latter hydration showed the H_{IP1P}^E pattern change of the hydrophobe (case [B] in Figure 1). We therefore suggested that hydration on an alkyl group is of hydrophobic nature. As such, the relative locus R and S on Figure 5 shows that OPr⁻ is more hydrophobic than OAc⁻ in terms of hydration number, n_H . As is evident from the map, the westward loci of ET (F) and ME (E) are about the same as S (OPr⁻) and R (OAc⁻). In terms of n_H , they are 8.6 for ET and 3.5 for ME,⁴ while they are 9 and 3.7 for OPr⁻ and OAc⁻. However, for the former carboxylate ions, there are no north/southward shifts, indicating that their effects on the S–V cross fluctuation remain the same as that of the probing 1P! The difference between the mono-ol and the carboxylate pairs is of course the neutral –OH versus carboxylate anion adjacent to the alkyl groups in question. Here again, what moiety is present adjacent to the alkyl group is important in dictating the solute's overall effect on the molecular organization of H₂O. Further investigation is obviously required. The present results together with those from earlier studies^{1–4} could serve for pointing toward the direction at which future investigation should aim.

In closing, we comment on recent criticisms or controversies^{22–25} about the “iceberg” formation by “hydrophobic solutes”. While these and other studies^{26–28} support the existence of a hydration shell that has a slower dynamics than that of bulk H₂O, they conclude that the hydrogen bond probability of H₂O in the hydration shell is not particularly enhanced. However, the samples that were used as an example of hydrophobe for all these studies are either TMU or trimethyl-*N*-oxide or both. In view of the present findings and the earlier similar works,^{2,4} the existence of methyl groups in the solute molecules does not guarantee hydrophobicity at least in terms of the present methodology. The nature of the neighboring atoms dictates the hydrophobicity/hydrophilicity of methyl groups. One must therefore be careful in choosing the appropriate solute. The map presented here could provide a

guide for such a purpose. Certainly, benzene and cyclohexane are *bona fide* hydrophobes, and MD calculations on their aqueous solutions support the existence of organized hydration shells in their vicinity.^{29,30} Unfortunately, they are only sparingly soluble in H₂O for experimental studies. We showed by thermodynamic studies using the higher order derivative quantities that a series of mono-ols turned out to be convenient systems to reveal the effect of alkyl groups on H₂O. Further experimental studies using a series of mono-ols are awaited.

■ ASSOCIATED CONTENT

■ Supporting Information

Supplemental table containing the raw data of H_{TP}^E for ternary 1P–S–H₂O at 25 °C. This material is available free of charge via Internet at <http://pubs.acs.org>

■ AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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