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Solubility of Urea in Acetonitrile−Water Mixtures and Liquid−Liquid Phase Separation of Urea-Saturated Acetonitrile−Water Mixtures

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ABSTRACT: The solubility of urea in mixtures of acetonitrile (MeCN) and water was measured in terms of mole fraction over the entire range of MeCN/water compositions. With respect to mole fractions of the three components, it was found that in water-rich mixtures the mole fraction of urea in urea saturated solutions showed almost no decline even after 25 mole percent water was replaced with MeCN. In the MeCN range of (77 to 86) % (v/v), the mixtures divided into two liquid phases after urea saturation. The more dense layer contained a roughly 2:2:1 mole ratio of water/MeCN/urea, while the less dense layer was primarily MeCN with small amounts of water and urea. Changing the MeCN content within the (77 to 86) % (v/v) range caused the volume ratio of the two layers to vary, but the composition of the upper and lower layers remained essentially constant. This behavior suggests that the water-rich phase is saturated in both urea and MeCN. The driving force for the phase separation is explained as the tendency for urea to promote self-association of the individual water and MeCN components. In MeCN-rich mixtures close to the limit of pure MeCN, urea solubility varied in a roughly linear fashion with water content. This behavior is explained qualitatively by the ability of water to act as a hydrogen-bond donor to urea, an interaction which is not possible with a nonprotic solvent such as MeCN.

INTRODUCTION

Acetonitrile (MeCN) is an organic solvent which is widely used as a mobile phase component in reversed phase liquid chromatography (RP-LC). Although MeCN is miscible with water in all proportions, MeCN/water mixtures will separate into two liquid phases under certain conditions. One way to induce phase separation of a MeCN/water mixture is by reducing the temperature.[1,2] Phase separation can also be induced by the addition of salts which has been studied in detail.[3,4] On the other hand, the phase separation of MeCN/water mixtures induced by the addition of nonelectrolytes has received only limited attention. We are aware of only one such study, which describes the observed phase separations of MeCN/water mixtures induced by sugars.[5]

We recently studied the solubility of urea in MeCN/water mixtures, as part of an RP-LC study.[6] Knowledge of the solubility behavior was required to allow mathematical modeling of the partitioning behavior of urea between the MeCN/water mobile phase and the adsorbed layer of MeCN on the stationary phase of the RP-LC column. We found only one literature report describing the MeCN−water−urea system, in which a ternary phase diagram was presented.[7] The phase diagram indicated a boundary between homogeneous solution and liquid + excess solid domains, which we assumed was an indicator of the solubility limit. However, lacking density values, the conversion of weight ratio values from the phase diagram into molar or weight per unit volume concentrations would be difficult without numerous assumptions. Therefore, we elected to make our own solubility measurements of urea in MeCN/water mixtures. As expected, the solubility of urea decreased substantially as the mixture changed from water-rich to MeCN-rich, which is not surprising when considering that urea has a high solubility in water[8] compared to a low solubility in MeCN.[9] However, at a composition of about 4:1 (v/v) MeCN/water, we observed separation of the mixture into two liquid phases after saturation with urea. Since we were unaware of any previous accounts of this phenomenon, we investigated it further by experimentally examining the mole fractions of the three components within the region of phase separation as presented in this report.

EXPERIMENTAL SECTION

Chemicals, Apparatus, and Methods. Water was purified using a Purelab Ultra system (Elga Labwater, Lowell, MA, USA). Solvents were high-performance liquid chromatography (HPLC) grade (99.9 %, Fisher Scientific, Fair Lawn, NJ, USA). Urea (> 99.5 %) was from Invitrogen (Carlsbad, CA, USA).

Twelve different mixtures of MeCN/water were prepared on a v/v basis, by combining volumes of the two components together. Saturated urea solutions were prepared by stirring an excess of solid urea in approximately (2 to 3) mL of MeCN/water mixture overnight (∼16 h) in 4 mL glass vials equipped with magnetic stirring, tightly covered with Teflon lined plastic screw caps to prevent solvent evaporation. The vials were then placed in a constant temperature water bath maintained at 25 ± 1 °C for about 4 h before filtering through a 0.22 μm membrane filter.

The weight fraction of urea was determined gravimetrically from an accurately weighed aliquot of each filtrate. Results of duplicate gravimetric determinations of urea were generally within ± 1 % for the most concentrated solutions, and the variation increased to about ± 5 % for the most dilute solutions. For samples which separated into two liquid phases, the

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Table 1. Mole Fractions of Urea, Water, and MeCN in Urea-Saturated Solutions of Different MeCN/Water Mixtures[a]

initial % MeCN (v/v)	X_{Ai}		urea (X_U)	water (X_W)	MeCN (X_A)
0	0		0.270	0.730	-
20	0.079		0.265	0.677	0.058
40	0.185		0.260	0.603	0.138
50	0.255		0.254	0.556	0.190
60	0.339		0.234	0.507	0.259
70	0.444		0.198	0.446	0.356
77	0.533	upper	0.078	0.251	0.670
		lower	0.187	0.425	0.388
80	0.577	upper	0.077	0.241	0.682
		lower	0.190	0.426	0.384
83	0.625	upper	0.074	0.243	0.683
		lower	0.186	0.423	0.390
86	0.677	upper	0.073	0.248	0.680
		lower	0.186	0.424	0.389
90	0.755		0.066	0.229	0.704
94	0.843		0.033	0.152	0.815
96	0.891		0.020	0.106	0.873
98	0.944		0.011	0.056	0.933
99	0.971		0.0067	0.028	0.965
99.5	0.986		0.0052	0.014	0.980
100	1.00		0.0037	-	0.996

[a] Mole fraction of MeCN in the initial binary MeCN/water mixture (X_{Ai}, column 2) prior to saturation with urea are calculated for the different MeCN/water (v/v) mixtures (column 1) based on density values of 0.9970 for water[10] and 0.7756 for MeCN.[11] Mole fractions of the three components ($X_{U,W,A}$) refer to the final equilibrium ternary mixture after saturation with urea. For mixtures which separated into two layers, upper and lower refers to the MeCN-rich and water-rich layers, respectively. The uncertainty of mole fraction values is ± 1 % (for $X > 0.2$), ± 2 % (for $0.1 < X < 0.2$), and ± 5 % (for $X < 0.1$).

experiments were run on a larger scale with 20 mL of solvent in 50 mL screw cap glass tubes. The entire volume was filtered into a 25 mL graduated cylinder so that the relative volumes of the two phases could be recorded. Each layer was then subjected to gravimetric analysis for urea content and a separate analysis for water content. Water content was measured using a model DL35 Karl Fischer titrator (Mettler-Toledo, Columbus, OH, USA) with a precision of ± 0.3 % (w/w).

Calculation of Mole Fractions in Urea-Saturated Solutions. To obtain mole fractions of the three components in the MeCN/water solutions after saturation with urea, the method for calculation was different depending on whether the mixture remained as a single liquid phase or if it divided into two liquid phases. For single liquid-phase mixtures, the weight fraction of urea was first calculated on the basis of the weight of urea determined in a known weight of solution. The remaining nonurea fraction was assumed to consist of the same MeCN/water weight ratio as was present in the initial solution (calculated from literature values for density of water and MeCN).[10,11] For mixtures which separated into two phases, the assumption of a constant MeCN/water ratio was no longer valid. In these cases, the weight fractions of both urea and water were measured experimentally, and the balance was assumed to be the weight fraction of the third component (MeCN). The weight fraction values could then be used to calculate mole fractions ($X_{U,W,A}$) which are shown in Table 1.

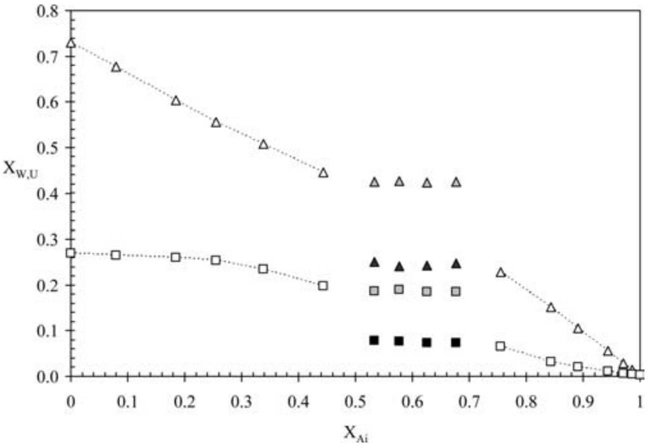

Figure 1. Mole fractions in urea-saturated solutions as a function of the initial mole fraction of MeCN (X_{Ai}) in the original binary MeCN/water composition prior to saturation with urea. For clarity, only X_U (squares) and X_W (triangles) are shown. In region of $0.53 < X_{Ai} < 0.68$, the mole fractions of both the upper layer (black symbols) and lower layer (gray symbols) are shown.

Literature values obtained in pure water ($X_U = 0.265$)[8] and in pure MeCN (0.079 M)[9] showed reasonable agreement to our own experimental values of $X_U = 0.270$ in water and 0.070 M in pure MeCN. For MeCN/water mixtures, the agreement of experimental values with the earlier reference[7] was within 6 % relative in the water-rich composition range (up to about 50 % v/v MeCN), but for increasingly MeCN-rich mixtures the deviation increased, differing by a factor of 4 or higher in some cases with respect to the urea fraction. On the basis of the much closer agreement of our own urea solubility value in 100 % MeCN with that of another reference,[9] we suspect the values from the earlier reference[7] are biased toward higher urea fraction values within the MeCN-rich milieu. Also, no mention was made in the earlier reference[7] of any observed liquid—liquid phase separation in the MeCN—water—urea ternary system. However, this is understandable when considering that the described experimental method consisted of visually observing the point of turbidity when adding a third component to a binary mixture,[7] meaning that cloudiness due to the phase separation could have been interpreted as solid precipitation.

■ RESULTS AND DISCUSSION

Urea Solubility in Water-Rich Mixtures and Comparison with EtOH/Water Mixtures. In each solubility determination, a binary mixture of known MeCN/water composition was used as a starting point. Therefore, the data are presented in Figure 1 according to the initial mole fraction of MeCN in the binary MeCN/water mixture along the horizontal axis, represented by X_{Ai}, where the subscript indicates the mole fraction of MeCN (A) in the initial (i) binary MeCN/water mixture. After saturation with urea, a ternary mixture is obtained. The mole fractions of water (X_W, triangles) and urea (X_U, squares) in the resulting ternary mixture are shown on the same plot using the same vertical scale (Figure 1). In the region $0 < X_{Ai} < 0.44$ [(0 to 70) % v/v MeCN], the mixture remained as a single liquid phase. As X_{Ai} was increased from 0 to 0.25, X_U showed almost no decline in this

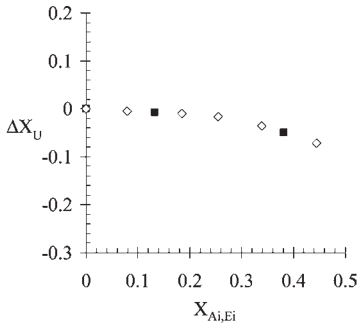

Figure 2. Change in X_U (ΔX_U) as the initial mole fraction of organic solvent in binary solvent/water mixture ($X_{Ai,Ei}$) is increased from pure water ($X_{Ai} = 0$). Data shown for MeCN/water (white diamonds) from current study, calculated by subtracting the X_U values in MeCN/water from the X_U value in pure water from Table 2. For EtOH/water (black squares), values were calculated by subtracting the X_U values in 33 % and 67 % (v/v) EtOH/water mixtures (calculated from literature values)[8] from the X_U value in pure water obtained from the same literature report.[8] Values of X_{Ei} were calculated based on the literature density value for EtOH.[12]

region (Figure 1, Table 1). This suggests that, in water-rich mixtures, replacing up to about 25 % of the water molecules with MeCN molecules has very little impact on the number of urea molecules which can be dissolved, although it is important to recognize that solution volume will increase in accordance with the higher molar volume of MeCN relative to water.

By using literature values for urea solubility in mixtures of ethanol (EtOH) with water,[8] it was possible to compare the behavior between the nonprotic solvent MeCN with a protic solvent of similar molecular size. This is shown in Figure 2, where the change in the mole fraction of urea from the initial value in pure water ΔX_U is shown, as the amount of MeCN or EtOH in the initial binary mixture was increased. The amount of organic solvent in the initial binary mixture is represented along the horizontal axis as described previously for Figure 1, with the symbols X_{Ai} for MeCN/water and X_{Ei} for EtOH/water. (X_{Ei} was calculated using the literature value for EtOH density.)[12] The term ΔX_U was used instead of X_U itself to remove the slight bias (of 0.005) observed between our own experimental X_U value and the X_U value from the literature[8] obtained in pure water. Note that ΔX_U for EtOH/water at (33 and 67) % (v/v) shows very similar behavior relative to the MeCN/water system, despite the much higher urea solubility in pure EtOH (~0.7 M) compared to pure MeCN (~0.07 M). It appears that, with respect to altering the ability of water to accommodate urea as solute, both solvents show very similar behavior within the water-rich region of composition ($0 < X_{Ai} < 0.25$), and MeCN does not appear to impact the equilibrium of urea between dissolved state and solid state differently than EtOH does.

The mole ratio X_W/X_U declined from about 2.7 in pure water to a value of 2.2 at X_{Ai} 0.25 and remained approximately constant at 2.2 within the range of $0.25 < X_{Ai} < 0.44$. This behavior suggests that a small population of "free" water molecules[13] can be replaced by solvent molecules, leaving a hydrogen-bonded network of about two water molecules per one urea molecule intact. This approximate 2:1 ratio correlates with recent dielectric spectroscopy studies of aqueous urea solutions,[14] which seem to indicate that concentrated aqueous solutions of urea consist of coclusters of one urea molecule which is on average bonded strongly with two water molecules.

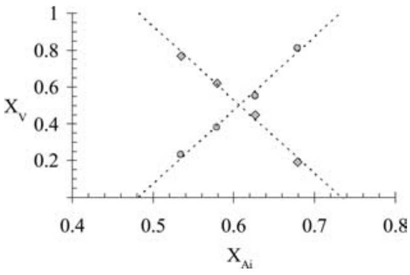

Figure 3. Volume fractions $X_{V(lower)}$ (diamonds) and $X_{V(upper)}$ (circles) and linear regressions (dotted lines) used to determine critical X_{Ai} values defining the between one liquid phase versus two liquid phase domains. Critical X_{Ai} values obtained using x-intercepts of extrapolated regression lines. Water-rich boundary defined by x-intercept of $X_{V(upper)}$ regression (slope 3.99, y-intercept −1.92, r^2 0.991) and MeCN-rich boundary defined by x-intercept of $X_{V(lower)}$ regression (slope −3.99, y-intercept 2.92, r^2 0.991).

MeCN/Water Composition Range Where Liquid−Liquid Phase Separation Occurs in Urea-Saturated Solutions. Within the range $0.53 < X_{Ai} < 0.68$ [(77 to 86) % v/v MeCN], the solutions formed two liquid phases after saturation with urea. Figure 1 shows $X_{W,U}$ values for both the higher density water-rich layer and the lower density MeCN-rich layer. The compositions of each layer remained approximately constant, but the relative volumes of the water-rich and MeCN-rich phases changed as X_{Ai} was varied, as shown in Figure 3. The critical X_{Ai} values, which defined the lower and upper boundaries at which the mixture transitioned between one and two liquid phases, were calculated by two different methods. The first method was based on the change in volume fractions as a function of X_{Ai} (Figure 3), which shows experimental volume fractions $X_{V(upper)}$ and $X_{V(lower)}$ and corresponding linear regressions. The x-intercepts of the extrapolated regression lines were assumed to represent the lower and upper X_{Ai} limits of the liquid−liquid domain, for which values of 0.48 and 0.73 were obtained. The second method to determine the critical X_{Ai} values was to evaluate the mole fraction X_A relative to the total $X_A + X_W$ within each of the two liquid phases. The resulting $X_A/(X_A + X_W)$ values (based on the average of all four phase separations at X_{Ai} = 0.53, 0.58, 0.63, and 0.68) were 0.48 and 0.73, respectively, for the lower and upper layers, in agreement with the first method. Thus, both methods indicate that the two-phase domain exists within $0.48 < X_{Ai} < 0.73$ (Figure 3).

The driving force for the urea-induced phase separation can be explained by the ability of urea to interact preferentially with water relative to the solvent component, promoting water self-association and solvent self-association in water/solvent mixtures. This tendency has been studied using a different solvent, *n*-propanol (*n*-PrOH). In mixtures of *n*-PrOH/water, urea appears to form a hydrogen-bonded network with water of increased rigidity,[15] and as urea is added to a mixture of *n*-PrOH/water it interacts preferentially with water while increasing self-association of *n*-propanol.[16] When further considering that an MeCN/water binary mixture itself shows a pronounced tendency toward self-association of the individual water and MeCN components, even in the absence of a third component,[17] it is evident that urea need only impart a moderate enhancement of water self-association to produce the phase separation effect in MeCN/water mixtures. Arguably, the unusually strong deviations from ideal behavior in MeCN/water mixtures are most likely a requirement for a urea-induced phase separation to occur, and the relatively

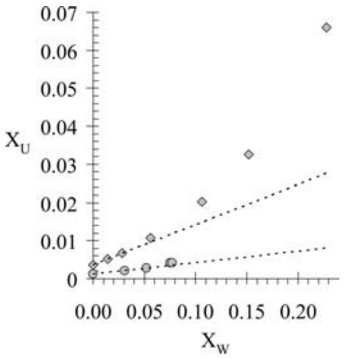

Figure 4. X_U as a function of X_W within the solvent-rich composition range. Data from current study for MeCN ($1.0 > X_{Ai} > 0.75$) are shown as diamonds, also shown for the solvent EtOAc from literature values[22] as circles. The regression line for the limit approaching $X_W = 0$ is shown for first three data points only (MeCN slope 0.11, int. 0.0037, $r^2 > 0.999$, EtOAc slope 0.031, int. 0.0012, $r^2 > 0.998$).

weak water-structuring effect of urea is probably insufficient to produce phase separations for most other water-miscible solvents. We tested this hypothesis experimentally by investigating another solvent, acetone, and found that urea did not produce any phase separations in acetone/water mixtures. This was checked carefully across the entire range of composition, particularly in the range of (65 to 95) % (v/v) acetone, which was checked in 3 % (v/v) increments. In no case was a liquid−liquid phase separation observed in any of the acetone/water solutions after saturation with urea. Thus, although acetone does exhibit moderate deviations from ideal mixing behavior with water,[17] the inherent tendency for self-association of the individual water and solvent components in an acetone/water mixture is not nearly as strong as in MeCN/water mixtures. Consequently, the relatively weak water-structuring effect of urea is insufficient to induce phase separations in acetone/water mixtures, even though solutes having a stronger interaction with water, such as salts and sugars, are known to induce acetone/water mixtures to separate into two liquid phases.[4,18]

Urea Solubility in MeCN-Rich Mixtures. For $X_{Ai} > 0.73$, urea-saturated solutions remained as a single liquid phase, and no liquid−liquid phase separation was observed. Similar behavior was reported for MeCN/water phase separations induced by NaCl.[3] NaCl-induced separations occurred as high as X_A 0.7, but when X_A was 0.84 or higher, only a single liquid phase existed in equilibrium with solid NaCl, and no evidence of significant microheterogeneity in the MeCN-rich domain could be observed using X-ray and neutron scattering techniques.[3] This was interpreted as the lack of tendency toward water-rich cluster formation in the MeCN-rich domain. The likely reason for this change in behavior at higher X_{Ai} is the competition from MeCN as hydrogen-bond acceptor toward water, thereby interfering with water−water interactions. Infrared spectroscopy studies have shown that MeCN-rich aqueous solutions consist of individual water molecules which are presumably isolated from each other and are hydrogen-bonded on average to one MeCN molecule.[19] Thus, the occurrence of water dimers or larger water-rich aggregates is very low in the MeCN-rich domain, probably because the competition from the large population of MeCN molecules prohibits water aggregation, and subsequently the coalescence of water-rich aggregates necessary for phase separation is prevented, even when solutes such as salts, sugars, or urea are present.

In 100 % MeCN, the low solubility of urea (Table 1) is not surprising when considering MeCN's lack of a hydrogen-bond donor group, which greatly limits its ability to compensate for the substantial bond enthalpy which is lost during transfer of urea from the solid to dissolved state,[20,21] in contrast to protic solvents such as water or alcohols which are capable of acting as hydrogen-bond donors. As water is added to MeCN, the solubility of urea begins to increase. For the limit approaching $X_{Ai} = 1$ ($X_W = 0$), it appears that $\Delta X_U/\Delta X_W$ approaches a constant value (Figure 4). This linear relationship between X_W and X_U occurred only under extremely MeCN-rich conditions of $X_W < 0.05$. Similar behavior has been reported for the solvent ethyl acetate (EtOAc), where it was shown that urea solubility in EtOAc also increased in an approximately linear fashion with regard to water content up to X_W of about 0.05.[22] These data have also been shown in Figure 4. The observed linear relationship between water and urea concentrations suggest that, in addition to the dissolved urea which is solvated by organic solvent alone, a second form of solvated urea is produced by a concentration-driven equilibrium involving a rather specific 1:1 urea−water interaction. The most likely interaction is the carbonyl oxygen of urea acting as H-bond acceptor, an interaction which can occur with water but cannot occur with the nonprotic solvents MeCN or EtOAc. Since water molecules in MeCN-rich solution are known to exist predominantly as 1:1 hydrogen-bonded water−MeCN complexes,[19] this means that the formation of a water−urea hydrogen-bonded complex will be competitive with water−MeCN complex formation. However, the hydrogen-bond basicity parameters (0.82 for urea compared to values of only 0.32 or 0.45 for MeCN or EtOAc,[23,24] respectively) indicate that a hydrogen-bond interaction between water and urea, where water acts as donor, will be thermodynamically favored over an interaction between water and MeCN or EtOAc solvent. A description of a similar competitive process, in which a water molecule replaces an organic solvent molecule in the solvation shell of a urea molecule, has also been described by others to explain the dissolution enthalpy behavior of urea in mixtures of water with another nonprotic solvent, dimethoxyethane, in the low X_W range.[25]

The likely reason for the increase in slope of $\Delta X_U/\Delta X_W$ for $X_W > 0.05$ (Figure 4) is the growing number of water−water interactions as X_W increases,[19] leading to an increased population of urea molecules solvated by more than one water molecule, where each additional water molecule provides more compensation for the lost bond enthalpy during transfer of urea from solid to liquid and consequently shifts equilibrium from solid to dissolved state. Such behavior is reasonable considering theoretical studies of urea−water interactions, which predict an almost linear increase in interaction energy as a urea molecule is successively hydrated with up to three water molecules.[26]

■ CONCLUSIONS

The solubility of urea in MeCN/water mixtures was measured on a mole fraction basis. In water-rich composition ($0 < X_{Ai} < 0.3$), X_U was relatively insensitive to the substitution of water with MeCN. Similar behavior was found for EtOH, based on X_U values calculated from literature solubility values. This suggests that a small population of "free" water molecules, which are not actively engaged in a water-urea hydrogen-bonded network, can be substituted with MeCN molecules while having little impact on X_U, even for a solvent such as MeCN which by itself is a poor solvent of urea.

In the region $0.48 < X_{Ai} < 0.73$, the mixture divided into two liquid phases. The denser layer contained a roughly 2:2:1 mole ratio of water/MeCN/urea, while the less dense layer was primarily MeCN with small amounts of water and urea. This behavior suggests that the composition of the water-rich layer is saturated in both urea and MeCN. The phase separation is rationalized on the basis of a strong interaction between urea and water, which form a strongly hydrogen-bonded network, and which enhances the well-known inherent tendency toward self-association of the individual water and MeCN components in MeCN/water mixtures. When MeCN content was above a critical amount, a single liquid phase was observed in equilibrium with solid urea, and no phase separation occurred. This lack of phase separation for $X_{Ai} < 0.73$ is assumed to be caused by the large population of MeCN molecules effectively competing for hydrogen-bond donor sites of water molecules, having the effect of isolating water molecules from each other and prohibiting the growth of large water−urea coclusters.

In extremely MeCN-rich compositions, the slope of $\Delta X_U/\Delta X_W$ approached a near constant value, within the range of about $0.95 < X_{Ai} < 1$. This suggests a concentration-driven equilibrium in which a hydrogen bond is formed between a hydrogen atom from water and an oxygen atom from urea, an interaction which is not possible in the nonprotic solvent MeCN. As X_{Ai} decreased to 0.95, the slope of $\Delta X_U/\Delta X_W$ began to increase substantially, suggesting that, when moving toward a lower MeCN content, the number of water molecules interacting with urea increases due to decreased competition from MeCN, having an increasingly favorable effect on the solvation of urea.

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