

Enthalpies of Transfer of the $-\text{CH}_2-$ Moiety into Aqueous Amide Solvent Systems; Values from n -Alcohol Solutes

Sedigheh Noban, Paul Donohue, and W. Earle Waghorne*

Department of Chemistry, National University of Ireland, Dublin, Belfield, Dublin 4, Ireland

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The enthalpies of solution of the n -alcohols, ethanol to hexanol, have been measured in aqueous mixtures of formamide, N,N -dimethylacetamide and N -methylpyrrolidinone. The average enthalpy of transfer of the $-\text{CH}_2-$ moiety, $\Delta_t H^\theta(\text{CH}_2)$, from the organic solvents to the mixtures and to pure water are determined from the differences between the enthalpies of transfer of the alcohols. The $\Delta_t H^\theta(\text{CH}_2)$ values pass through maxima in the highly aqueous composition region, with the height of the maximum increasing linearly with the area of the hydrophobic surfaces of the cosolvent. These results are compared to similar data for the aqueous alcohol solvent systems where the maximum in $\Delta_t H^\theta(\text{CH}_2)$ is also sensibly linear in the area of the cosolvent hydrophobic surfaces but increases more rapidly with increasing hydrophobic area.

Introduction

Hydrophobic interactions are central to a wide range of phenomena; thus, the insolubility of nonpolar species in aqueous solutions, formation of a wide range of structures by amphiphiles, and thermally induced structural transitions in polymers such as poly(N -isopropylacrylamide) and their gels are attributed to the hydrophobic interactions of the nonpolar moieties in the molecules. It is also recognized that hydrophobic interactions play a significant role in determining the course of protein folding.

The hydrophobic effect includes two contributions. The first reflects the attractive interactions, through van der Waals or dispersion forces, between the nonpolar entities. For small molecules at least, this is a solute–solute interaction and so disappears at infinite dilution. The second contribution results from the interaction of the nonpolar moieties with the surrounding aqueous solvent; we designate this as hydrophobic solvation (or hydrophobic hydration). Frank and Evans¹ suggested that hydrophobic hydration involved the formation of a region of water with enhanced hydrogen bonding around the nonpolar moiety, which resulted in a lowering of both the enthalpy and the entropy of the system.

The $-\text{CH}_2-$ moiety is the basic building block of many hydrophobic entities, and its interactions are central to the hydrophobic effect. We have previously investigated the enthalpy of transfer of $-\text{CH}_2-$ between water and organic or aqueous organic mixed solvents at 298.2 K.^{2,3} Our approach, also adopted by Sinha and Kundu,⁴ is straightforward; thus, for example, ethanol and propan-1-ol differ by one $-\text{CH}_2-$ moiety, and we can take the enthalpy of transfer of the $-\text{CH}_2-$ group as the difference between those of propan-1-ol and ethanol.

These studies showed that at 298.2 K $\Delta_t H^\theta(\text{CH}_2)$ between organic solvents were close to 0 and were independent of the length of the solute alkyl chain. Moreover, the results are the same for $\Delta_t H^\theta(\text{CH}_2)$ obtained from data for the n -alcohols, where there is a single alkyl chain, and from data for the tetraalkyl ammonium ions, where interactions between chains on a single solute molecule are possible.

For transfers from organic solvents to water, the $\Delta_t H^\theta(\text{CH}_2)$ values obtained from the n -alcohols are also close to 0 but become more endothermic (or less exothermic) with increasing chain length.^{2,3} The $\Delta_t H^\theta(\text{CH}_2)$ values obtained from the tetraalkyl ammonium ions show the same endothermic shift with increasing chain length but are systematically more exothermic, by around 2 kJ mol⁻¹, than those obtained from the alcohol data.³

In the aqueous organic mixed solvents, the $\Delta_t H^\theta(\text{CH}_2)$ values passed through maxima at intermediate solvent compositions, with those from the n -alcohol data being relatively sharp while those from the tetraalkyl ammonium, in aqueous propan-1-ol at least, are quite broad.³

It was found that both the height of the maxima and the composition at which they occur depended on the organic cosolvent. In the aqueous alcohol systems, the maxima became higher and shifted to a lower concentration of the alkyl chain as the alcohol was lengthened (methanol, ethanol, and propan-1-ol). This suggests that the maximum may be related to the hydrophobicity of the cosolvent.^{2–4}

In the present paper, we report enthalpies of solution of n -alcohols in aqueous mixtures of the amides formamide, N,N -dimethylacetamide (DMA), and N -methylpyrrolidinone (NMPy). These, along with literature data for the aqueous N,N -dimethylformamide (DMF) system,⁵ provide $\Delta_t H^\theta(\text{CH}_2)$ for a second series of aqueous mixtures with increasing hydrophobicity of the organic cosolvent.

Experimental Section and Results

The alcohols, ethanol, propan-1-ol, butan-1-ol, pentan-1-ol, and hexan-1-ol (analytical grade) were dried over calcium sulfate and fractionally distilled. Formamide, DMA, and NMPy (analytical grade) were also dried over calcium sulfate and fractionally distilled under a reduced pressure. Distilled water was used throughout.

Enthalpies of solution were measured at 298.2 K (± 0.2 K) using an isoperibol calorimeter running under computer control, as described previously.⁶ The solution enthalpies of the n -alcohols were measured to 10 concentrations, with maximum concentrations ranging from 0.16 to 0.35 mol dm⁻³ (hexanol

* Author to whom correspondence should be addressed. E-mail: earle.waghorne@ucd.ie.

TABLE 1: Enthalpies of Solution of n -Alcohols in Aqueous Formamide Mixtures at 298.2 K^a

X_{Form}	$\Delta_s H^\theta$, kJ mol ⁻¹				
	EtOH	PrOH	BuOH	PeOH	HxOH
0.00	-10.17	-10.10	-9.36	-7.82	-5.77 ^b
	-10.19 ^c	-10.12 ^c	-9.24 ^c	-7.72 ^c	
	-10.12 ^d	-10.18 ^d	-9.36 ^d	-8.08 ^b	
	-10.25 ^e	-10.38 ^e	-9.04 ^e	-6.36 ^f	
	-10.13 ^g	-10.17 ^g	-9.20 ^g	-7.66 ^g	
				-7.82 ^h	
0.1	-6.07	-5.09	-3.65	-2.47	0.20
0.2	-3.69	-2.40	-0.95	0.38	1.76
0.3	-2.25	-0.79	0.55	1.71	2.80
0.4	-1.06	0.21	1.58	2.50	4.18
0.5	-0.11	0.94	2.10	3.29	4.42
0.6	0.46	1.61	2.62	3.51	4.63
0.7	1.01	2.08	2.99	3.59	5.13
0.8	1.43	2.41	3.44	4.15	5.50
0.9	1.91	2.84	3.89	4.61	5.64
1.0	2.34	3.23	4.06	4.82	5.90

^a X_{Form} represents the formamide mole fraction; EtOH, PrOH, BuOH, PeOH, and HxOH represent ethanol, propan-1-ol, butan-1-ol, pentan-1-ol, and hexan-1-ol, respectively. ^b Reference 7. ^c Reference 5. ^d Reference 8. ^e Reference 9. ^f Reference 10. ^g Reference 11. ^h Reference 12.

TABLE 2: Enthalpies of Solution of n -Alcohols in Aqueous DMA Mixtures at 298.2 K^a

X_{DMA}	$\Delta_s H^\theta$, kJ mol ⁻¹				
	EtOH	PrOH	BuOH	PeOH	HxOH
0.1	-2.12	0.56	3.68	6.64	10.84
0.2	1.88	5.15	8.30	11.02	14.22
0.3	2.68	5.64	7.22	10.47	13.09
0.4	2.32	4.60	6.50	8.50	10.53
0.5	1.47	3.34	4.98	6.41	8.24
0.6	0.85	2.36	3.31	4.62	6.23
0.7	0.34	1.56	2.37	3.58	4.48
0.8	0.01	0.96	1.76	2.61	3.74
0.9	-0.18	0.69	1.31	2.37	3.12
1.0	-0.33	0.42	1.02	1.84	2.70

^a X_{DMA} represents the DMA mole fraction; other symbols as in Table 1.

TABLE 3: Enthalpies of Solution of n -Alcohols in Aqueous NMPy Mixtures at 298.2 K^a

X_{NMPy}	$\Delta_s H^\theta$, kJ mol ⁻¹				
	EtOH	PrOH	BuOH	PeOH	HxOH
0.1	-2.06	0.58	3.81	6.83	11.25
0.2	1.87	5.00	8.64	11.04	14.06
0.3	2.41	5.24	7.44	9.83	12.59
0.4	1.94	4.28	5.88	7.63	9.39
0.5	1.11	2.78	4.23	6.05	7.31
0.6	0.59	1.96	3.09	4.42	5.64
0.7	0.16	1.38	2.33	3.36	4.67
0.8	-0.07	0.94	1.8	2.54	3.76
0.9	-0.15	0.66	1.36	2.18	3.22
1.0	-0.17	0.52	1.12	1.86	2.73

^a X_{NMPy} represents the NMPy mole fraction; other symbols as in Table 1.

and ethanol, respectively) and extrapolated to infinite dilution. The precisions of the limiting solution enthalpies were plus or minus the lesser of 0.2 kJ mol⁻¹ or 5%. The limiting enthalpies of solution in the three aqueous amide systems are listed in Tables 1–3. The enthalpies of transfer, $\Delta_t H^\theta$, of the alcohols were calculated from the enthalpies of solution, $\Delta_s H^\theta$, as

$$\Delta_t H^\theta = \Delta_t H_S^\theta - \Delta_t H_R^\theta \quad (1)$$

where $\Delta_t H_S^\theta$ and $\Delta_t H_R^\theta$ are the limiting solution enthalpies in

TABLE 4: Enthalpies of Transfer of $-\text{CH}_2-$ from Formamide to Aqueous Formamide Mixtures at 298.2 K

X_{Form}	$\Delta_t H^\theta(\text{CH}_2)$, kJ mol ⁻¹			
	$\text{C}_3 - \text{C}_2$	$(\text{C}_4 - \text{C}_2)/2$	$(\text{C}_5 - \text{C}_2)/3$	$(\text{C}_6 - \text{C}_2)/4$
0.0	-0.82	-0.45	-0.04	0.21
0.1	0.09	0.35	0.37	0.68
0.2	0.40	0.51	0.53	0.47
0.3	0.57	0.54	0.49	0.37
0.4	0.38	0.46	0.36	0.42
0.5	0.16	0.25	0.31	0.24
0.6	0.26	0.22	0.19	0.15
0.7	0.18	0.13	0.03	0.14
0.8	0.09	0.15	0.08	0.13
0.9	0.04	0.13	0.07	0.04
1.0	0.00	0.00	0.00	0.00

TABLE 5: Enthalpies of Transfer of $-\text{CH}_2-$ from DMF to Aqueous DMF Mixtures at 298.2 K

X_{DMF}	$\Delta_t H^\theta(\text{CH}_2)$, kJ mol ⁻¹		
	$\text{C}_3 - \text{C}_2$	$(\text{C}_4 - \text{C}_2)/2$	$(\text{C}_5 - \text{C}_2)/3$
0.000	-0.86	-0.41	-0.02
0.050	0.39	0.27	1.20
0.100	1.28	1.60	1.81
0.150	1.49	1.86	1.98
0.230	1.83	1.82	1.96
0.350	1.49	1.42	1.43
0.450	1.15	1.01	1.07
0.550	0.89	0.70	0.74
0.675	0.48	0.46	0.44
0.811	-0.01	0.19	0.23
0.940	0.05	0.07	0.10
1.000	0.00	0.00	0.00

TABLE 6: Enthalpies of Transfer of $-\text{CH}_2-$ from DMA to Aqueous DMA Mixtures at 298.2 K

X_{DMA}	$\Delta_t H^\theta(\text{CH}_2)$, kJ mol ⁻¹			
	$\text{C}_3 - \text{C}_2$	$(\text{C}_4 - \text{C}_2)/2$	$(\text{C}_5 - \text{C}_2)/3$	$(\text{C}_6 - \text{C}_2)/4$
0.0	-0.68	-0.27	0.06	0.34
0.1	1.93	2.23	2.20	2.48
0.2	2.52	2.54	2.32	2.33
0.3	2.21	1.60	1.87	1.85
0.4	1.53	1.42	1.34	1.30
0.5	1.12	1.08	0.92	0.94
0.6	0.76	0.56	0.53	0.59
0.7	0.47	0.34	0.36	0.28
0.8	0.20	0.20	0.14	0.18
0.9	0.12	0.07	0.13	0.07
1.0	0.00	0.00	0.00	0.00

the target and reference solvents, respectively; the average $\Delta_t H^\theta(\text{CH}_2)$ values were calculated as

$$\Delta_t H^\theta(\text{CH}_2) = \{\Delta_t H(\text{CH}_3(\text{CH}_2)_n\text{CH}_2\text{OH}) - \Delta_t H(\text{C}_2\text{H}_5\text{OH})\}/n \quad (2)$$

The $\Delta_t H^\theta(\text{CH}_2)$ values, along with those calculated from the literature data for the aqueous DMF system, are listed in Tables 4–7 and are shown as functions of the solvent composition in Figures 1–4.

Discussion

It is clear that the results for aqueous formamide, DMA, and NMPy are similar to those for aqueous DMF. Thus, the $\Delta_t H^\theta(\text{CH}_2)$ values are independent of the alcohol chain length, n , up to around the maximum in the $\Delta_t H^\theta(\text{CH}_2)$ against composition

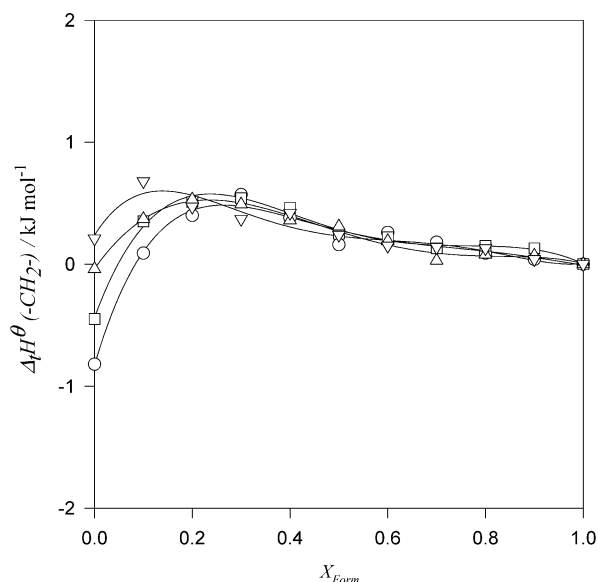


Figure 1. Transfer enthalpies of $-\text{CH}_2-$, $\Delta_t H^\theta(\text{CH}_2)$, in aqueous formamide mixtures: $\text{C}_3 - \text{C}_2$ (O); $(\text{C}_4 - \text{C}_2)/2$ (\square); $(\text{C}_5 - \text{C})/3$ (Δ); and $(\text{C}_6 - \text{C}_2)/4$ (∇).

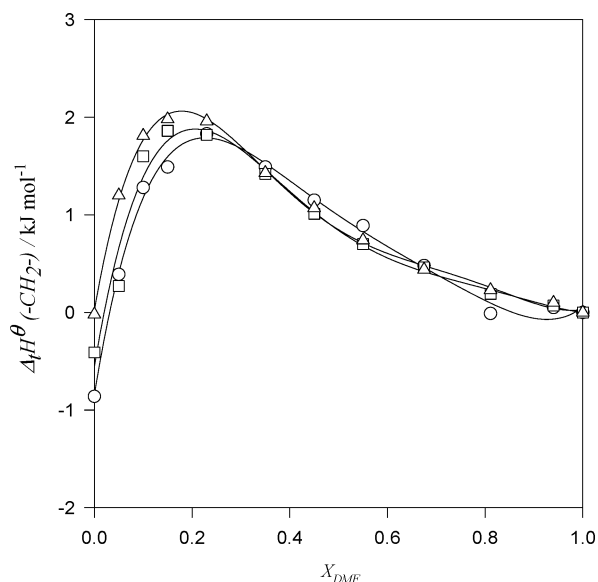


Figure 2. Transfer enthalpies of $-\text{CH}_2-$, $\Delta_t H^\theta(\text{CH}_2)$, in aqueous DMF: $(\text{C}_3 - \text{C}_2)$ (O); $(\text{C}_4 - \text{C}_2)/2$ (\square); $(\text{C}_5 - \text{C})/3$ (Δ); and $(\text{C}_6 - \text{C}_2)/4$ (∇).

TABLE 7: Enthalpies of Transfer of $-\text{CH}_2-$ from NMPy to Aqueous NMPy Mixtures at 298.2 K

X_{NMPy}	$\Delta_t H^\theta(\text{CH}_2)$, kJ mol $^{-1}$			
	$\text{C}_3 - \text{C}_2$	$(\text{C}_4 - \text{C}_2)/2$	$(\text{C}_5 - \text{C}_2)/3$	$(\text{C}_6 - \text{C}_2)/4$
0.0	-0.62	-0.24	0.11	0.37
0.1	1.95	2.25	2.29	2.60
0.2	2.44	2.74	2.38	2.32
0.3	2.14	1.87	1.80	1.82
0.4	1.65	1.33	1.22	1.14
0.5	0.98	0.92	0.97	0.83
0.6	0.68	0.61	0.60	0.54
0.7	0.53	0.44	0.39	0.40
0.8	0.32	0.29	0.19	0.23
0.9	0.12	0.11	0.10	0.12
1.0	0.00	0.00	0.00	0.00

plots but diverge into pure water, with the values calculated from the longer chains lying progressively further above (endothermic of) those from the shorter chains.

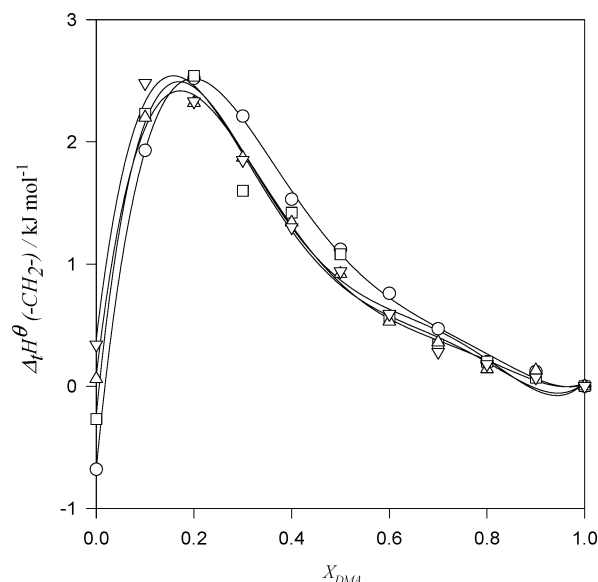


Figure 3. Transfer enthalpies of $-\text{CH}_2-$, $\Delta_t H^\theta(\text{CH}_2)$, in aqueous DMA mixtures: $(\text{C}_3 - \text{C}_2)$ (O); $(\text{C}_4 - \text{C}_2)/2$ (\square); $(\text{C}_5 - \text{C})/3$ (Δ); and $(\text{C}_6 - \text{C}_2)/4$ (∇).

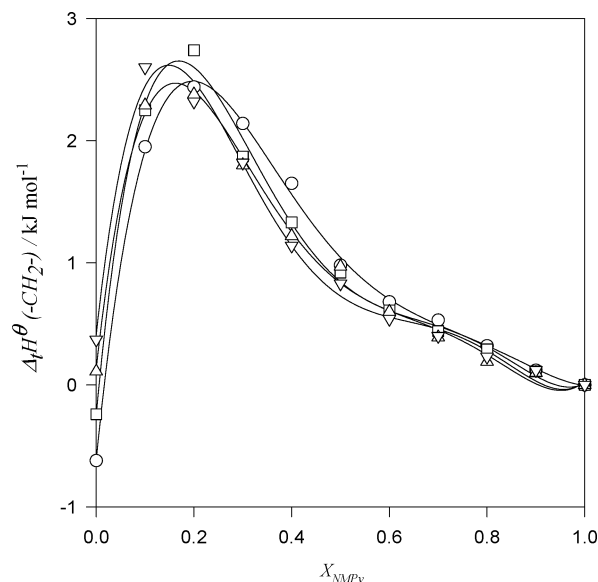


Figure 4. Transfer enthalpies of $-\text{CH}_2-$, $\Delta_t H^\theta(\text{CH}_2)$, in aqueous *N,N*-methylpyrrolidinone mixtures: $(\text{C}_3 - \text{C}_2)$ (O); $(\text{C}_4 - \text{C}_2)/2$ (\square); $(\text{C}_5 - \text{C})/3$ (Δ); and $(\text{C}_6 - \text{C}_2)/4$ (∇).

The $\Delta_t H^\theta(\text{CH}_2)$ values pass through maxima in all of the solvent systems; the same was found in the aqueous alcohol solvent systems, and in both cases, the height of the maximum increases with the size of the nonpolar surfaces of the cosolvent. We have shown previously³ that, for aqueous DMF at least, the variation in $\Delta_t H^\theta(\text{CH}_2)$ can be simply related to the enthalpy of mixing of the solvent system. Mixing enthalpies are not available for the other aqueous amide systems so it is not possible to test whether this holds for them as well. It was also found³ that this simple relationship did not hold for the aqueous alcohol solvents; that is, $\Delta_t H^\theta(\text{CH}_2)$ is not a simple linear function of the mixing enthalpy in these systems.

The increase in the height of the maximum $\Delta_t H^\theta(\text{CH}_2)$ values with the size of the nonpolar surfaces of the cosolvent is interesting. This is shown in Figure 5, where the maximum $\Delta_t H^\theta(\text{CH}_2)$ value, in each mixed aqueous solvent system, is shown as a function of N_{CH} , the number of C-H hydrogen

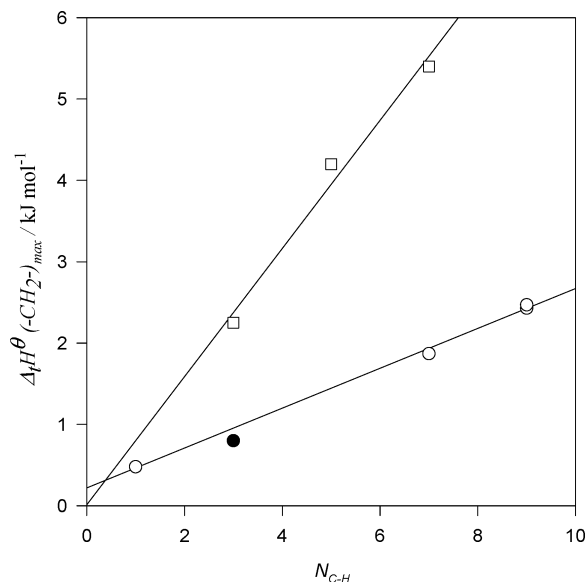


Figure 5. Maximum values of the transfer enthalpy, $\Delta_t H^\theta(\text{CH}_2)_{\text{max}}$, as a function of N_{CH} , the number of $-\text{C}-\text{H}$ hydrogen atoms on the cosolvent; amides (○); n -alcohols (□); and acetonitrile (●). $\Delta_t H^\theta(\text{CH}_2)_{\text{max}}$ are calculated relative to DMF as the reference solvent (see text).

atoms on the amide or alcohol cosolvent. N_{CH} provides a relative measure of the surface area of the nonpolar alkyl surface of the solvent molecule. Remarkably, the $\Delta_t H^\theta(\text{CH}_2)_{\text{max}}$ increase linearly with N_{CH} for both the aqueous amide and the aqueous alcohol solvent systems, although the slopes of the two lines are markedly different. Also shown in Figure 5 is the $\Delta_t H^\theta(\text{CH}_2)_{\text{max}}$ value for the aqueous acetonitrile system, which, perhaps coincidentally, lies close to the line for the amides. To allow comparison between the $\Delta_t H^\theta(\text{CH}_2)_{\text{max}}$ values, they must be calculated relative to a common reference solvent. The values shown in Figure 5 were calculated relative to DMF by adding $\Delta_t H^\theta(\text{CH}_2)$ between DMF and the organic component of the mixture²³ to the observed $\Delta_t H^\theta(\text{CH}_2)_{\text{max}}$.

The differences in the slopes for the normal alcohol and amide cosolvents warrant consideration. The slopes of the two plots provide measures of the effect of the hydrophobicity of the cosolvent on the solvation of neighboring hydrophobic moieties, with the $-\text{CH}_2-$ unit acting as a probe. The difference between the lines for the amide and the n -alcohol may reflect an intrinsic effect of the difference between the configurations of the hydrophobic parts of the cosolvent molecule, those on the amide molecules being relatively rigid while the alkyl chains in the n -alcohols are more flexible. The equality of the maxima for NMPy, with its ring of $-\text{CH}_2-$ groups and DMA, where the hydrophobicity is associated with three $-\text{CH}_3$ groups, suggests that the configuration of the hydrophobic surface may not be critical.

The second possibility is that the differences between the amide and alcohol systems arise from the difference between the interactions of the polar parts of the molecule with the

surrounding water structure. The alcohol OH can fit into the three-dimensional water structure with little disruption of the hydrogen-bonding network. In contrast, the amides form one or two hydrogen bonds to their $\text{C}=\text{O}$ groups but do not act as hydrogen bond donors. Thus, their interactions with water must disrupt the hydrogen bonded water structure. Hydrophobic hydration is generally associated with a caging of the nonpolar surfaces within a cavity, around which the water–water hydrogen bonds are stabilized. Disruption of the water structure by the amides could impede the development of this enhanced hydrogen bonded structure, resulting in the reduced impact of the hydrophobic moieties on the cosolvent.

Whatever the reason for the difference between the effects of the amide and n -alcohol cosolvents on the solvation of the probe $-\text{CH}_2-$, it is clear that the effect depends both on the size of the hydrophobic surface and on the structure of the hydrophilic core of the molecule. This has implications for understanding hydrophobic hydration in complex media, most significantly in biological systems. Thus, the response of a particular hydrophobic entity may depend significantly on the structures of adjacent functional groups in a molecule, so that, for example, the hydrophobicity of a particular side group might well be different when it is attached to an amino acid and when it is attached to the peptide linkage in a protein. There is also the possibility that the hydrophobic hydration of a side group might be influenced by those of neighboring side groups on a protein. These conclusions refer specifically to the hydrophobic hydration of the entity, that is, to its interaction with the surrounding water structure. However, the hydrophobic attraction between hydrophobic moieties may also depend on the chemical environment in which they are located.

These conclusions relate, of course, to the enthalpies of interaction of the hydrophobic surfaces with the surrounding solvent. A large degree of compensation between the enthalpic and entropic contributions to the free energies is the norm and the extent to which the observed differences are transmitted to the free energies is not clear. However, the free energies are not large, and small differences are likely to be significant.

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