

## Hydrophobicity/Hydrophilicity Index of Solutes in Aqueous Solutions:

Is methyl group always hydrophobic?

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We devised what we call 1-propanol(1P) probing methodology.<sup>1</sup> It is a thermodynamic study of ternary systems, 1P – sample(X) – H<sub>2</sub>O, where X is the test sample, the hydrophobicity or hydrophilicity nature of which is to be indexed. We experimentally determine what we call the 1P-1P enthalpic interaction function,  $H_{1P-1P}^E$ , which is the model-free third derivative of  $G$ . The  $x_{1P}$  (mole fraction of 1P) dependence of  $H_{1P-1P}^E$  pattern takes a peak type anomaly characteristic of a hydrophobic 1P, and this peak marks the onset where the integrity of liquid H<sub>2</sub>O is lost. By the presence of X, the  $H_{1P-1P}^E$  pattern is modified within the respective mole fraction limit where the integrity of H<sub>2</sub>O is retained. The manner in which the pattern is modified gives information about hydrophobicity/hydrophilicity and the strength. For certain ions, their hydration numbers can also be determined.<sup>1</sup>

Figure 1 shows the results plotted in a 2-dimensional map. H<sub>2</sub>O sits at the origin and the probing 1P is necessarily placed at B (-1, 0). The westward direction of the abscissa indicates hydrophobicity and/or hydration number, while the southward direction of the ordinate shows hydrophilicity. The northward direction is therefore negative hydrophilicity. The distance from the origin indicates the strength of each propensity. Amphiphiles spread out in the southwest direction on the map. The west and southward components signify the hydrophobic and the hydrophilic components. This power of distinction became possible since we used the third derivative quantity of  $G$ . Furthermore, the hydration of some ions can now be identified and their hydration numbers can be determined.<sup>1</sup>

The loci of mono-ols span from methanol (ME) at (E) in Fig. 1 to tert-butanol(TBA)(D) monotonously and to 2-butoxyethanol(BE)(S). The distance from the origin points the relative hydrophobicity ranking to be ME < 2P < 1P < TBA < BE in the increasing strength, which is consistent with our suggestion based on the behavior of third derivative quantities in binary aqueous alcohols.<sup>2</sup>

Relative to these alcohol series, the locus for trimethylamine-N-oxide(TMAO) on the map is surprisingly close to the origin (H<sub>2</sub>O). The latter fact was suggested for trehalose as a manifestation of effective “osmolyte” in various organisms at the water-stressed situation.<sup>3</sup> We note there are two more sets of equally surprising results in the map involving the N-methyl groups (attaché to N). Compare the loci of NH<sub>4</sub><sup>+</sup> (M) and N(CH<sub>3</sub>)<sub>4</sub><sup>+</sup> (H). Replacing H- with CH<sub>3</sub>- does not change the resulting N(CH<sub>3</sub>)<sub>4</sub><sup>+</sup> hydrophobic at all, and its hydrophilicity increases! Urea(UR) at (J) on the map, on converting four H's on amino group to four CH<sub>3</sub>-s, moves the locus of resulting tetramethylurea(TMU) to point K. TMU apparently gains hydrophobicity near to but smaller than point C for 2P, while TMU's hydrophilicity is now much larger than UR. On replacing both NH<sub>2</sub>- on UR with CH<sub>3</sub>-, the resulting acetone (AC) shown at point L retains about the same hydrophilicity as UR, while AC's hydrophobicity increases to a little less than that for 2P (point C). This suggests that the hydrophilic effects of NH<sub>2</sub>- in UR is marginal in comparison with that by >C=O.

Thus we point out within our 1P-probing methodology that N-methyl groups do not promote hydrophobicity but rather enhancing hydrophilicity. Although these findings seem surprising at first sight, they may be rationally understood in the following manner. Starting with comparison between NH<sub>4</sub><sup>+</sup> vs. N(CH<sub>3</sub>)<sub>4</sub><sup>+</sup>, H in NH<sub>4</sub><sup>+</sup> is highly acidic due in part higher

electro-negativity of N than C, particularly so in aqueous environment. It is readily neutralized by a single H<sub>2</sub>O as indicated by the hydration number 1±1 as we found experimentally.<sup>1</sup> The influence of a positive charge is thus of short range. N(CH<sub>3</sub>)<sub>4</sub><sup>+</sup>, on the other hand, the central positive charge is protected from direct attacks from H<sub>2</sub>O. The protected charge on N in the hydrophobic pocket induces dipoles on the surrounding H<sub>2</sub>O molecules, which in turn encourages H on methyl groups to form hydrogen bonds with H<sub>2</sub>O. Such weak hydrogen bonds involving N-methyl groups have been known.<sup>4a, 4b</sup> Thus, N(CH<sub>3</sub>)<sub>4</sub><sup>+</sup> acts as purely a hydrophile. For UR(J), our observation suggested that the hydrophilicity of NH<sub>2</sub>- itself is marginal. Thus, on replacing amino group with methyl group, the resulting AC(L) does not lose hydrophilicity, and gain hydrophobicity as much as expected for the one with two methyl groups, in between ME(E) and 2P(C). When H on amino group is replaced by methyl, not only hydrophobicity is lower than expected for containing four methyl groups, but also hydrophilicity increases drastically. The difference between AC and TMU is no doubt due to the difference between C-methyl and N-methyl. In addition to higher electro-negativity of N, the latter has a lone pair on non-bonding π-orbital. This enhances e-donating tendency of N-methyl further resulting in ease in making hydrogen bond to surrounding H<sub>2</sub>O via methyl H's. A similar scenario could be applicable for low hydrophobicity and low hydrophilicity of TMAO. In aqueous media, TMAO is more likely to be in the form (CH<sub>3</sub>)<sub>3</sub>N<sup>δ+</sup>-O<sup>δ-</sup>, and CH<sub>3</sub>-'s e-donating propensity is even more enhanced in addition to the presence of lone pair. Hence, N-methyl groups do not enhance hydrophobicity. The hydrophilicity of O is strong, but overall TMAO turns out to be amphiphilic with weak hydrophobicity and equally weak hydrophilicity. We therefore suggest that N-methyl is not strongly hydrophobic in aqueous solutions. In this regard, we note recent observations on S-methyl groups having the same tendency to donate electron towards S.<sup>5a, 5b</sup> S has indeed a left over lone pairs.

#### References.

- (1) Y. Koga. *Solution Thermodynamics and Its Application to Aqueous Solutions: A Differential Approach*, Elsevier; Amsterdam (2007), Chapter VII and VIII.
- (2) Ref.(1) but Chapter V and VI.
- (3) Y. Koga, K. Nishikawa, P. Westh, *J. Phys. Chem. B* **111**, 13943 (2007).
- (4a) O. Takahashi, Y. Kohno, M. Nishio. *Chem. Rev.*, DOI101021/cr100072x. (4b) L. Brammer. In *Crystal Design: Structure and Function*. G. R. Desiraju, Ed., John Wiley & Sons, Chichester (2003). Chapter I
- (5a) Q. Li, G. Wu, Z. Yu. *J. Am. Chem. Soc.* **128**, 1438 (2006) (5b) H.S. Biswal, P.R. Shirhatti, S. Wategaonker. *J. Phys. Chem. A* DOI101021/jp102346n.

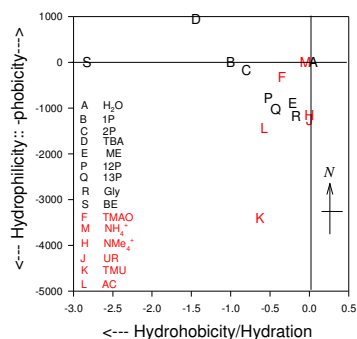


Figure 1 Hydrophobicity/Hydrophilicity Map.