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Effect of solute aggregation on solubilization

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ABSTRACT

Strong self-association of hydrophobic solutes takes place in water. However, solute self-association has often been neglected in understanding the aqueous solubility of drugs as well as their solubilization by excipients, cosolvents and hydrotropes. Based on a rigorous statistical thermodynamic foundation, here we show how to estimate the contribution from solute self-association to solubility and solubilization, based on experimental data such as solubility and the osmotic second virial coefficients. Such data show that solute self-association can indeed be negligible in most common cases of hydrotropic solubilization, Setschenow coefficients and the hydrophobic hydration.

Key Words: solubilization; hydrotrophy; salting-in; salting-out; statistical thermodynamics; Kirkwood-Buff

1. Introduction

Poor solubility of drugs poses a serious challenge to drug development. However, this problem can be overcome by the use of weakly amphiphilic organic molecules called hydrotropes [1–5]. Hydrotropes, when added to water, increase the solubility of hydrophobic drug molecules up to several orders of magnitude [6–8]. Yet how hydrotropes work on a molecular level long remained a puzzle, until a rigorous statistical thermodynamics theory has rationalized the increase of solubility in terms of the interplay between solute-hydrotrope affinity (which increases solubility) and bulk-phase hydrotrope self-association (which reduced the per-solute solubilization efficiency) [9–13], solving this long standing problem.

Due to the extremely low solubility of hydrophobic solutes, the statistical thermodynamic approach to hydrotrophy initially focused at the infinite dilution of solutes, neglecting solute-solute interactions [9–13]. However, uses of hydrotropes are not limited to solutes with extremely low solubility; they are also used with concentrated solutes. For high solute concentrations, “pre-structuring” (or hydrotrope self-association in the bulk solution) was proposed to promote solubilization, in stark contrast with our statistical thermodynamic theory [14–18]. According to the pre-structuring hypothesis, solubilization inefficiency is the artefact of infinite dilution limit [17]. However, a subsequent generalization of our theory to concentrated solutes has shown that the original conclusion is valid regardless of solute concentration and the degree of hydrotrope pre-structuring; hydrotrope self-aggregation still

makes solubilization inefficient [19]. However, the theory of hydrotrophy incorporating solute-solute interaction is still qualitative [19].

The importance of quantifying solute self-association has wider ramifications outside of hydrotrophy, because solubility and solubilization is crucial universally, to answer questions in wide-ranging problems:

- a. How salts and electrolytes affect the solubility, which can be quantified via the Setschenow coefficients [20–22]. These have been correlated to other physical properties of drugs such as partition coefficients towards their prediction [23–25].
- b. How partition coefficients ($\log P$) of amino acids, peptides, and hydrophobic drugs, between water and hydrophobic solvents or membrane, serve as a quantitative basis for hydrophobicity scales and membrane permeability, these are determined with the utmost care, in purpose to prevent self-aggregation of solutes [26–29].
- c. Solubility determinations of drugs, amino acids and peptides, for which quantitatively dissecting solute-solvent and solute-solute interactions is crucial for their uses in estimating solvation contributions in biomolecular stability and drug binding as a key step towards prediction.

Thus, this paper aims to establish

1. the contribution of solute's self-aggregation to solubilization;
2. how 1. can be estimated based on experimental data.

Theoretical analysis, based on the first principles of statistical thermodynamics, will lead to establishment of a simple criterion upon which the negligibility of solute self-association on solubilization can be determined, which, despite extensive studies conducted on solute self-association in binary and ternary mixtures [30–33], has not been addressed previously. We will

show that the solute's self association indeed makes negligible contributions in the hydrotrope solubilization of hydrophobic solutes studied in our previous papers [9–13], while it may not be negligible in less hydrophobic solutes, such as caffeine [23,34,35].

2. Quantifying solute self-association

Consider a solute molecule (denoted by $i = u$) in a mixture of water ($i = 1$) and cosolvent ($i = 2$). The cosolvent can be hydrotrope (Section 3) or salts (Section 4), or can be absent (Section 5).

According to the inhomogeneous solvation theory [12], the chemical potential of a solute fixed in its centre-of-mass position, μ_u^* , can be expressed under constant pressure (P) and temperature (T) in the following manner:

$$-d\mu_u^* = \sum_i (\langle N_i \rangle_u - \langle N_i \rangle) d\mu_i \quad (1)$$

where μ_i is the chemical potential of the species i and $\langle N_i \rangle_u$ and $\langle N_i \rangle$ respectively express the average numbers of the species i in the presence and absence of a fixed solute. In the inhomogeneous solvation theory [36–38], the fixed solute molecule acts as the source for an external field for all the species in solution [12], in contrast to the standard statistical thermodynamics of solutions, referred to as the homogeneous theory, in which the solute molecule can freely move around [12]. The advantage of the inhomogeneous solution theory over the homogenous theory is its ease in establishing a link between the solution structure around the solute and the free energy of solvation [38]. Note that the inhomogeneous and homogeneous theories give equivalent results; Eq. (1) can also be derived from the homogeneous theory based on a pair of the Gibbs-Duhem equations, one around the solute, the other far away from the solute in the bulk region. See Refs [39,40] for such an alternative

derivation and Ref [12] (Appendices B and C in that paper) for the demonstration of the equivalence between the two.

When interpreting solubility data in terms of the affinity between different molecular species, it is convenient to introduce the Kirkwood-Buff integrals (KBIs) between the species i and j

$$G_{ij} = \frac{V(\langle N_j \rangle_i - \langle N_j \rangle)}{\langle N_j \rangle} \quad (2)$$

where V is the volume of the system. KBIs have an interpretation of the net excess distribution of the species j around i relative to the normalized bulk concentration. The equivalence between the inhomogeneous (Eq. (2)) and homogeneous definitions of KBI are shown in Appendix A.

Via KBI thus defined, Eq. (1) can be rewritten for the three-component mixture as

$$-d\mu_u^* = c_1 G_{u1} d\mu_1 + c_2 G_{u2} d\mu_2 + c_u G_{uu} d\mu_u \quad (3)$$

where $c_i = \langle N_i \rangle / V$ is the bulk number density of the species i . Eq. (3) can also be derived from the homogeneous theory by a pair of Gibbs-Duhem equations, one around the solute, the other in the bulk phase [41], which underscores the equivalence between the inhomogeneous (Eq. (2)) and homogeneous (Ref [12], Eq. (23)) definitions of the KBIs.

Our goal is to express how the solvation free energy of a solute, μ_u^* , is affected by the addition of hydrotropes and by the self-association of solutes. To do so, we use the following rigorous relationships to supplement Eq. (3). The first is the relationship between μ_u^* and μ_u [38],

$$d\mu_u = d\mu_u^* + \frac{RT}{c_u} dc_u \quad (4)$$

where R is the gas constant. Eq. (4) expresses the free energy of liberating a solute molecule from a fixed centre-of-mass position. The second is the Gibbs-Duhem equation [12,38]

$$c_u d\mu_u + c_1 d\mu_1 + c_2 d\mu_2 = 0 \quad (5)$$

First, eliminating $d\mu_1$ from Eq. (3) using Eq. (5), we obtain

$$-d\mu_u^* = c_2(G_{u2} - G_{u1})d\mu_2 + c_u(G_{uu} - G_{u1})d\mu_u \quad (6)$$

Using Eq. (4), Eq. (6) can be rewritten as

$$-[1 + c_u(G_{uu} - G_{u1})]d\mu_u^* = c_2(G_{u2} - G_{u1})d\mu_2 + RT(G_{uu} - G_{u1})dc_u \quad (7)$$

A straightforward algebra leads to

$$-d\mu_u^* = \frac{c_2(G_{u2} - G_{u1})}{1 + c_u(G_{uu} - G_{u1})} d\mu_2 + \frac{RT(G_{uu} - G_{u1})}{1 + c_u(G_{uu} - G_{u1})} dc_u \quad (8)$$

which serves as the foundation of all our subsequent discussions.

Eq. (8) is the generalization of our previous theory of hydrotropy derived at the infinitely dilute limit of the solute [9–13]. Our previous theory can be derived straightforwardly from Eq. (8) at the $c_u \rightarrow 0$ limit. The new insights that Eq. (8) provides are:

1. solute self-association, G_{uu} , contributes to increase solubility ($d\mu_u^* < 0$);
2. solute self-association, G_{uu} , weakens the contribution from preferential hydrotrope-solute interaction ($G_{u2} - G_{u1}$) to solubilization.

Indeed, 1. can be understood by noting that a larger positive G_{uu} makes the second term of Eq. (8) larger, which drives $-d\mu_u^*$ towards a larger positive, which means the solvation free energy of the solute, μ_u^* , becomes more negative and the solubility is increased. Point 2. can be appreciated in a similar manner by looking at the first term of Eq. (8); a larger positive G_{uu} in the denominator works to reduce the positive contribution from $G_{u2} - G_{u1}$ which would contribute to increase solubility. Both contributions can be estimated quantitatively using the experimental data for G_{uu} , as will be demonstrated in the subsequent sections.

3. Estimating solute self-association contribution to hydrotrophy

Here we estimate the contribution from solute self-association to solubilization based on Eq. (8) and the experimental data available in the literature. Due to their low solubility in water, experimental data on solute self-association have limited availability. However, we have obtained the examples tabulated in Table 1. To estimate the solute self-association contribution to solvation free energy μ_u^* , we first approximate the total differentials in Eq. (8) by differences denoted by δ , such that

$$-\delta\mu_u^* = \frac{c_2(G_{u2}-G_{u1})}{1+c_u(G_{uu}-G_{u1})}\delta\mu_2 + \frac{RT(G_{uu}-G_{u1})}{1+c_u(G_{uu}-G_{u1})}\delta c_u \quad (9)$$

which is valid over small differences $\delta\mu_2$ and δc_u . The contribution due to solute self-association arises in the denominator of the first term, as well as the second term. When the solute concentration changes by $\delta c_u = c_u$, from $c_u = 0$, the second term of Eq. (9), can be simplified as

$$(G_{uu} - G_{u1})\delta c_u \approx G_{uu}c_u \quad (10)$$

because $|G_{uu}|$ is one order of magnitude larger than $G_{u1} \approx -V_u$ [39,42], where V_u is solute's partial molar volume [43,44]. Such an approximation made in Eq. (10) can be justified in the following manner. Firstly, the subsequent tables will show that $G_{uu}(= -2B_{uu})$ is in the order of $10^3 \text{ cm}^3 \text{ mol}^{-1}$, whereas the majority of the solutes have V_u between 50–150 $\text{cm}^3 \text{ mol}^{-1}$ according to the extensive compilation [43,44]. Secondly, shows that $G_{u1} \approx -V_u$ comes from a rigorous relationship, $G_{u1} = -V_u + RT\kappa_T$, where κ_T is the isothermal compressibility of water. Using $\kappa_T = 0.45 \times 10^{-9} \text{ Pa}^{-1}$ for pure water at 298 K [45], we obtain $RT\kappa_T \approx 1.2 \text{ cm}^3 \text{ mol}^{-1}$ which is indeed much smaller than V_u [39,42].

Hence the contribution from solute self-association to solvation free energy can be estimated using Eq. (10). For G_{uu} , we use (i) the well-known relationship between G_{uu} and the second virial coefficient B_{uu} , $G_{uu} = -2B_{uu}$, [46] and (ii) B_{uu}^∞ , at the infinite dilution limit, as the upper limit of B_{uu} , because solubility increase by hydrotrope means favourable solvation of the solute, which reduces its self-association [39,40]. Thus a comparison between the maximum solubilization $-\frac{\delta\mu_u^*}{RT} = \ln \frac{c_u^{max}}{c_u^0}$ versus $-2B_{uu}^\infty \delta c_u^{max}$ (where c_u^{max} is the maximum solubility attained by hydrotrope addition) in Table 1 shows that the latter is much smaller than the former. This means that solute self-association contributes negligibly to solubilization by hydrotropes, supporting our previous theory [9–13] and underscoring the approximation taken in Eq. (10). And indeed, the errors arising from Eq. (10) does not change the conclusion that solute self-association is negligible.

Note that our theory assumes that the solute-solute self-association in the presence of solubilizers (hydrotropes and salts) remains as strong as in pure water. However, in the presence of solubilizers, solute-self association can be weakened dramatically. This is why the B_{uu} at $c_2 = 0$, B_{uu}^∞ , is the upper bound of solute-solute interaction. It follows that when the upper bound evaluation of solute-solute interaction is negligible, then solute-solute interaction at finite c_2 is automatically negligible. However, in the case of riboflavin in the presence of nicotinamide [47], not previously analysed statistically thermodynamically, $-2B_{uu}^\infty \delta c_u^{max}$ is about a quarter of $-\frac{\delta\mu_u^*}{RT}$, meaning that solute self-association still makes a minor contribution. Yet due to the exceptionally high self-aggregation and solubilization exhibited in this case, a precise quantification of solute self-aggregation would require a direct evaluation of G_{uu} in the presence of nicotinamide instead of its upper limit. This can be achieved by a rigorous evaluation of KBIs using in ternary mixture [48]. However, in the cases of benzene,

ethylbenzene and cyclohexane, the negligibility of $-2B_{uu}^{\infty} \delta c_u^{max}$ will simplify the inversion process of KB theory drastically (Appendix B).

4. Solute self-aggregation in Setschenow coefficients for salting-in and -out

Estimating contributions from solute self-association can be made more straightforward when the free energy of hydration, μ_u^* , increases linearly with the concentration of cosolvents, such as salts, still in dilution [20–22,49]. This linearity is related to the Setschenow coefficient [20,23–25] defined as

$$\ln \frac{c_u}{c_u^0} = s c_2 \quad (11)$$

where the superscript 0 in c_u^0 signifies the value at $c_2 = 0$. Note that s , when defined in terms of log, can be converted straightforwardly to Eq. (11) by multiplying 2.303. Using Eq. (11), together with the diluteness of cosolvents leading to $\left(\frac{\partial \mu_2}{\partial c_2}\right)_{T,P,c_2 \rightarrow 0} = \frac{RT}{c_2}$ [12,38], Eq. (8) can be simplified as

$$s = \frac{(G_{u2} - G_{u1})}{1 + c_u(G_{uu} - G_{u1})} + \frac{(G_{uu} - G_{u1})}{1 + c_u(G_{uu} - G_{u1})} \frac{dc_u}{dc_2} \quad (12)$$

By differentiating Eq. (12), $\frac{dc_u}{dc_2} = s c_u$, which transforms Eq. (12) into the following form

$$s \left[1 - \frac{c_u(G_{uu} - G_{u1})}{1 + c_u(G_{uu} - G_{u1})} \right] = \frac{(G_{u2} - G_{u1})}{1 + c_u(G_{uu} - G_{u1})} \quad (13)$$

This reduces back to the infinite-dilution expression of the Setchenow coefficient, $s = G_{u2} - G_{u1}$ [20,40], under the condition that

$$|(G_{uu} - G_{u1})c_u| \approx |G_{uu}^{\infty} c_u^0| \ll 1 \quad (14)$$

in which we have used G_{uu}^{∞} as in Section 3 and by the use of its upper bound G_{uu}^{∞} , as has been done in Section 2.

Table 2 demonstrates that Eq. (14) is satisfied for common hydrophobic liquid solutes, which means that the solute self-association contribution to the Setschenow coefficients is negligible. Note that caffeine is the only solute which is in crystalline form (hence $\Delta\mu_u^*$ cannot be calculated) and for which Eq. (14) is not satisfied due to their strong self-association. To deal with the dissolution of caffeine, previous studies used the isodesmic model for caffeine aggregation [34,35,50,51] or a direct calculation of caffeine-caffeine KBI [52]. However, we emphasise that all the other solutes in Table 1 (n-alkanes, cycloalkanes and aromatic hydrocarbons) exhibit $G_{uu}^0 c_u^0$ negligible compared to 1, increasingly so for longer n-alkanes much more than cycloalkanes and aromatics. This conclusion our conclusion again shows that the Setchenow coefficients can be attributed entirely to the competition between solute-salt and solute-water interactions, $s = G_{u2} - G_{u1}$, and a direct link between solubility measured under isothermal-isobaric conditions and G_{u1} and G_{u2} can be determined from a simpler inversion process in Appendix B.

5. Hydrophobicity scales and solute self-aggregation

The effect of solute self-association on solubility and partitioning has long been considered crucial [53–58] and solubility and partitioning experiments have been conducted extensively due to the need for accurately quantifying solute-solvent interactions [59–63]. To this end, we consider a binary mixture consisting of solute and solvent, by eliminating the cosolvent from Eq. (6) by putting $c_2 = 0$. This yields the following:

$$-d\mu_u^* = \frac{RT(G_{uu}-G_{u1})}{1+c_u(G_{uu}-G_{u1})} dc_u \quad (15)$$

Now we apply Eq. (15) to evaluate the contribution of solute self-association on the free energy of solvation, for which we must calculate the free energy difference arising from $\delta c_u = c_u$,

which is the difference between the infinite dilution of solute ($c_u = 0$) and the finite, experimental concentration, c_u . Since we mainly deal with dilute solutes, we take up to the first order of c_u , to obtain

$$\delta\mu_u^* = RT(G_{uu} - G_{u1})c_u \simeq RTG_{uu}c_u \quad (16)$$

in which we have used G_{uu}^∞ as an estimate of G_{uu} and the small contribution, G_{u1} , has been neglected.

Whether self-association is negligible can now be examined quantitatively by comparing the solvation free energy $\Delta\mu_u^*$ and the self-association contribution $RTG_{uu}^\infty c_u$, which has been carried out in Table 3 for common hydrophobic solutes frequently used in solubility and partitioning measurements. For all aliphatic, cyclic and aromatic hydrocarbons in Table 3 (except caffeine), $RTG_{uu}^\infty c_u$ is negligibly small compared to $\Delta\mu_u^*$, and is particularly the case as the aliphatic chain length increases. For benzene, $RTG_{uu}^\infty c_u$ is larger than other hydrocarbons but is still negligible. For caffeine, for which $\Delta\mu_u^*$ cannot be determined due to its solid form at room temperature, $RTG_{uu}^\infty c_u$ is much larger than hydrocarbons, supporting again the significance of its self-aggregation in water. Thus, the comparison in Table 3 shows that the infinite dilution approximation for the hydrocarbons, which neglects the contribution of solute-solute interaction on solvation free energy, is an excellent approximation.

6. Conclusion

Aqueous solubility of hydrophobic solutes, and their solubilization in the presence of hydrotropes and salts, so far have been rationalized and analyzed under the infinite dilution of solutes, neglecting the contribution from solute-solute interactions. However, different views

on the origin of hydrotrophy, arising from the realm of concentrated solutes, prompted evaluation of solute-solute interaction on solubility and solubilization [14,17–19].

We have developed a simple theoretical framework upon which the contribution from solute self-association can be estimated. The only required information is solubility and the osmotic second virial coefficient. Our analysis have shown that hydrophobic solute self-association indeed contributes negligibly to solubility and solubilization, thereby providing a strong support for the infinite dilution approximation adopted throughout in the study of hydrophobic drugs [9–13]. These conclusions advocate the unified picture of hydrotrophy, driven by the balance between solute-hydrotrope affinity as the dominant contribution and hydrotrope self-association as the source of per-hydrotrope inefficiency [19].

Appendix A

Here we briefly show that the definition of KBI via the inhomogeneous solvation theory (Eq. (3)) is equivalent to the standard definition, i.e., via the homogeneous theory. A full discussion is found in a recent paper by one of us [38]. Let us focus on the solute-solute KBI, which, in the inhomogeneous solvation theory, involves a solute molecule, whose centre of mass position has been fixed, which makes the fixed solute distinguishable from the rest. The KBI, according to Eq. (3), is

$$G_{uu} = \frac{V(\langle N_u \rangle_u - \langle N_u \rangle)}{\langle N_u \rangle} \quad (\text{A1})$$

where $\langle N_u \rangle_u$ and $\langle N_u \rangle$ express the ensemble averages in the inhomogeneous and homogeneous systems, respectively [12,38]. Through the following relationship that links the homogeneous and inhomogeneous ensemble averages, the difference in solute distinguishability [12,38] can be taken into account

$$\langle N_u \rangle_u = \frac{\langle N_u(N_u-1) \rangle}{\langle N_u \rangle} \quad (\text{A2})$$

Combining Eqs. (A1) and (A2), we obtain

$$G_{uu} = \frac{V(\langle N_u^2 \rangle - \langle N_u \rangle^2 - \langle N_u \rangle)}{\langle N_u \rangle^2} \quad (\text{A3})$$

which is the well-known definition of KBI in the homogeneous system [12,38].

Appendix B

Here we discuss the implication of our present paper to the inversion of the KB theory [19,30,64,65]. The inversion procedure determines the KBIs through the elements of matrix \mathbf{B} ,

$$B_{ij} = c_i c_j G_{ij} + c_i \delta_{ij}$$

$$(\text{B1})$$

which can be determined from the following matrix inversion

$$\mathbf{B} = \mathbf{A}^{-1} \quad (\text{B2})$$

in which the elements of \mathbf{A} , defined as

$$A_{ij} = \frac{1}{RT} \left(\frac{\partial \mu_i}{\partial c_j} \right)_{T, c_{j' \neq j}}$$

$$(\text{B3})$$

can be accessible from thermodynamic measurements [19,30,64,65]. Note that the right-hand side of Eq. (B3) cannot be evaluated directly from the experimental data taken in isothermal-isobaric ensembles and a cumbersome change of variables is required to process the experimental data [19,30,64,65].

We have established in this paper how the condition $|c_u G_{uu}| \ll 1$ for dilute hydrophobic solutes can be guaranteed using the experimental data. Under this condition, the KB inversion procedure for the determination of G_{u1} and G_{u2} can be drastically simplified and can be linked directly to experiments under the isobaric-isothermal conditions [19,39,40] through a simple

matrix transformation [38]. This well-established procedure have been applied successfully to protein stability [40,42], hydrotrophy [9–11,13], kosmotropy and chaotropy [20].

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References

- [1] A.M. Saleh, L.K. El-Khordagui, Hydrotropic agents: a new definition, *Int. J. Pharm.* 24 (1985) 231–238. doi:10.1016/0378-5173(85)90023-7.
- [2] J.Y. Kim, S. Kim, M. Papp, K. Park, R. Pinal, Hydrotropic solubilization of poorly water-soluble drugs, *J. Pharm. Sci.* 99 (2010) 3953–3965. doi:10.1002/jps.22241.
- [3] R.E. Coffman, Self-association of nicotinamide in aqueous solution: light-scattering and vapor pressure osmometry studies, *J. Pharm. Sci.* 85 (1996) 848–853. doi:10.1021/js9505197.
- [4] Y. Cui, C. Xing, Y. Ran, Molecular dynamics simulations of hydrotropic solubilization and self-aggregation of nicotinamide, *J. Pharm. Sci.* 99 (2010) 3048–3059. doi:10.1002/jps.22077.
- [5] S.A. Damiati, L.G. Martini, N.W. Smith, M.J. Lawrence, D.J. Barlow, Application of machine learning in prediction of hydrotrope-enhanced solubilisation of indomethacin, *Int. J. Pharm.* 530 (2017) 99–106. doi:10.1016/j.ijpharm.2017.07.048.
- [6] P. Bauduin, A. Renoncourt, A. Kopf, D. Touraud, W. Kunz, Unified concept of solubilization in water by hydrotropes and cosolvents, *Langmuir.* 21 (2005) 6769–6775. doi:10.1021/la050554l.

- [7] C. Neuberg, Hydrotropie, *Biochem. Z.* 76 (1912) 107–176.
- [8] S.E. Friberg, Hydrotropes, *Curr. Opin. Colloid Interface Sci.* 2 (1997) 490–494. doi:10.1016/S1359-0294(97)80096-9.
- [9] J.J. Booth, S. Abbott, S. Shimizu, Mechanism of hydrophobic drug solubilization by small molecule hydrotropes, *J. Phys. Chem. B.* 116 (2012) 14915–14921. doi:10.1021/jp309819r.
- [10] S. Shimizu, J.J. Booth, S. Abbott, Hydrotropy: binding models vs. statistical thermodynamics., *Phys. Chem. Chem. Phys.* 15 (2013) 20625–20632. doi:10.1039/c3cp53791a.
- [11] J.J. Booth, M. Omar, S. Abbott, S. Shimizu, Hydrotrope accumulation around the drug: the driving force for solubilization and minimum hydrotrope concentration for nicotinamide and urea, *Phys Chem Chem Phys.* 17 (2015) 8028–8037. doi:10.1039/C4CP05414H.
- [12] S. Shimizu, N. Matubayasi, Hydrotropy: Monomer-micelle equilibrium and minimum hydrotrope concentration, *J. Phys. Chem. B.* 118 (2014) 10515–10524. doi:10.1021/jp505869m.
- [13] S. Abbott, J.J. Booth, S. Shimizu, Practical molecular thermodynamics for greener solution chemistry, *Green Chem.* 19 (2017). doi:10.1039/c6gc03002e.
- [14] M.L. Klossek, D. Touraud, W. Kunz, Eco-solvents--cluster-formation, surfactantless microemulsions and facilitated hydrotropy., *Phys. Chem. Chem. Phys.* 15 (2013) 10971–7. doi:10.1039/c3cp50636c.
- [15] T.N. Zemb, M. Klossek, T. Lopian, J. Marcus, S. Schöetl, D. Horinek, S.F. Prevost, D. Touraud, O. Diat, S. Marčelja, W. Kunz, How to explain microemulsions formed by solvent mixtures without conventional surfactants, *Proc. Natl. Acad. Sci. U. S. A.* 113 (2016) 4260–4265. doi:10.1073/pnas.1515708113.

- [16] S. Schöttl, D. Touraud, W. Kunz, T. Zemb, D. Horinek, Consistent definitions of “the interface” in surfactant-free micellar aggregates, *Colloids Surfaces A Physicochem. Eng. Asp.* 480 (2015) 222–227. doi:10.1016/j.colsurfa.2014.11.029.
- [17] T. Buchecker, S. Krickl, R. Winkler, I. Grillo, P. Bauduin, D. Touraud, A. Pfitzner, W. Kunz, The impact of the structuring of hydrotropes in water on the mesoscale solubilisation of a third hydrophobic component, *Phys. Chem. Chem. Phys.* 19 (2016) 1806–1816. doi:10.1039/C6CP06696H.
- [18] W. Kunz, K. Holmberg, T. Zemb, Hydrotropes, *Curr. Opin. Colloid Interface Sci.* 22 (2016) 99–107. doi:10.1016/j.cocis.2016.03.005.
- [19] S. Shimizu, N. Matubayasi, Unifying hydrotropy under Gibbs phase rule, *Phys. Chem. Chem. Phys.* 19 (2017) 23597–23605. doi:10.1039/c7cp02132a.
- [20] S. Shimizu, W.M. McLaren, N. Matubayasi, The Hofmeister series and protein-salt interactions, *J. Chem. Phys.* 124 (2006) 234905. doi:10.1063/1.2206174.
- [21] K.D. Collins, M.W. Washabaugh, The Hofmeister effect and the behaviour of water at interfaces., *Q. Rev. Biophys.* 18 (1985) 323–422. <http://www.ncbi.nlm.nih.gov/pubmed/3916340> (accessed June 4, 2018).
- [22] B. Hribar, N.T. Southall, V. Vlachy, K.A. Dill, How ions affect the structure of water., *J. Am. Chem. Soc.* 124 (2002) 12302–11. doi:10.1021/JA026014H.
- [23] A. Al-Maaieh, D.R. Flanagan, Salt effects on caffeine solubility, distribution, and self-association, *J. Pharm. Sci.* 91 (2002) 1000–1008. doi:10.1002/jps.10046.
- [24] N. Ni, S.H. Yalkowsky, Prediction of Setschenow constants., *Int. J. Pharm.* 254 (2003) 167–72. <http://www.ncbi.nlm.nih.gov/pubmed/12623192> (accessed June 4, 2018).
- [25] R. Sanghvi, D. Evans, S.H. Yalkowsky, Stacking complexation by nicotinamide: A useful way of enhancing drug solubility, *Int. J. Pharm.* 336 (2007) 35–41. doi:10.1016/j.ijpharm.2006.11.025.

- [26] A. Radzicka, R. Wolfenden, Comparing the polarities of the amino acids: Side-chain distribution coefficients between the vapor phase, cyclohexane, 1-octanol, and neutral aqueous solution, *Biochemistry*. 27 (1988) 1664–1670. doi:10.1021/bi00405a042.
- [27] R. Wolfenden, C.A. Lewis, Y. Yuan, C.W. Carter, Temperature dependence of amino acid hydrophobicities, *Proc. Natl. Acad. Sci.* 112 (2015) 7484–7488. doi:10.1073/pnas.1507565112.
- [28] R. Wolfenden, Experimental measures of amino acid hydrophobicity and the topology of transmembrane and globular proteins, *J. Gen. Physiol.* 129 (2007) 357–362. doi:10.1085/jgp.200709743.
- [29] F. Glaab, M. Kellermeier, W. Kunz, E. Morallon, J.M. García-Ruiz, Formation and evolution of chemical gradients and potential differences across self-assembling inorganic membranes, *Angew. Chemie - Int. Ed.* 51 (2012) 4317–4321. doi:10.1002/anie.201107754.
- [30] E. Matteoli, L. Lepori, Solute–solute interactions in water. II. An analysis through the Kirkwood–Buff integrals for 14 organic solutes, *J. Chem. Phys.* 80 (1984) 2856–2863. doi:10.1063/1.447034.
- [31] J.J. Kozak, W.S. Knight, W. Kauzmann, Solute-solute interactions in aqueous solutions, *J. Chem. Phys.* 48 (1968) 675. doi:10.1063/1.1668700.
- [32] E. Ruckenstein, I. Shulgin, Effect of a third component on the interactions in a binary mixture determined from the fluctuation theory of solutions, *Fluid Phase Equilib.* 180 (2001) 281–297. doi:10.1016/S0378-3812(01)00365-X.
- [33] E. Ruckenstein, I. Shulgin, Solubility of drugs in aqueous solutions: Part 4. Drug solubility by the dilute approximation, *Int. J. Pharm.* 278 (2004) 221–229. doi:10.1016/j.ijpharm.2004.03.007.
- [34] S. Shimizu, Caffeine dimerization: effects of sugar, salts, and water structure, *Food*

- Funct. 6 (2015) 3228–3235. doi:10.1039/C5FO00610D.
- [35] T.H. Lilley, H. Linsdell, A. Maestre, Association of caffeine in water and in aqueous solutions of sucrose, *J. Chem. Soc. Faraday Trans.* 88 (1992) 2865. doi:10.1039/ft9928802865.
- [36] T. Lazaridis, Inhomogeneous fluid approach to solvation thermodynamics. 1. Theory, *J. Phys. Chem. B.* 102 (1998) 3531–3541. doi:10.1021/jp9723574.
- [37] T. Lazaridis, Inhomogeneous fluid approach to solvation thermodynamics. 2. Applications to simple fluids, *J. Phys. Chem. B.* 102 (1998) 3542–3550. doi:10.1021/jp972358w.
- [38] S. Shimizu, N. Matubayasi, A unified perspective on preferential solvation and adsorption based on inhomogeneous solvation theory, *Phys. A Stat. Mech. Its Appl.* 492 (2018) 1988–1996. doi:10.1016/j.physa.2017.11.113.
- [39] S. Shimizu, Estimating hydration changes upon biomolecular reactions from osmotic stress, high pressure, and preferential hydration experiments., *Proc. Natl. Acad. Sci. U. S. A.* 101 (2004) 1195–1199. doi:10.1073/pnas.0305836101.
- [40] S. Shimizu, N. Matubayasi, Preferential solvation: Dividing surface vs excess numbers, *J. Phys. Chem. B.* 118 (2014) 3922–3930. doi:10.1021/jp410567c.
- [41] D.G. Hall, Kirkwood-Buff theory of solutions. An alternative derivation of part of it and some applications, *Trans. Faraday Soc.* 67 (1971) 2516–2524. doi:10.1039/TF9716702516.
- [42] S. Shimizu, C.L. Boon, The Kirkwood-Buff theory and the effect of cosolvents on biochemical reactions, *J. Chem. Phys.* 121 (2004) 9147–9155. doi:10.1063/1.1806402.
- [43] L. Lepori, P. Gianni, Partial molar volumes of ionic and nonionic organic solutes in water: A simple additivity scheme based on the intrinsic volume approach, *J. Solution Chem.* 29 (2000) 405–447. doi:10.1023/A:1005150616038.

- [44] S. Cabani, P. Gianni, V. Mollica, L. Lepori, Group Contributions to the Thermodynamic Properties of Non-Ionic Organic Solutes in Dilute Aqueous Solution Sergio Cabani , 1 Paolo Gianni , 1 Vincenzo, J. Solution Chem. 10 (1981) 563–595. doi:10.1007/BF00646936.
- [45] R.A. Fine, F.J. Millero, Compressibility of water as a function of temperature and pressure, J. Chem. Phys. 59 (1973) 5529–5536. doi:10.1063/1.1679903.
- [46] T.W.J. Nicol, N. Matubayasi, S. Shimizu, Origin of non-linearity in phase solubility: solubilisation by cyclodextrin beyond stoichiometric complexation, Phys. Chem. Chem. Phys. 18 (2016) 15205–15217. doi:10.1039/C6CP01582D.
- [47] R.E. Coffman, D.O. Kildsig, Effect of nicotinamide and urea on the solubility of riboflavin in various solvents, J. Pharm. Sci. 85 (1996) 951–954. doi:10.1021/js960012b.
- [48] E. Matteoli, L. Lepori, Kirkwood–Buff integrals and preferential solvation in ternary non-electrolyte mixtures, J. Chem. Soc., Faraday Trans. 91 (1995) 431–436. doi:10.1039/FT9959100431.
- [49] A. Burant, G. V. Lowry, A.K. Karamalidis, Measurement and modeling of Setschenow constants for selected hydrophilic compounds in NaCl and CaCl₂ simulated carbon storage brines, Acc. Chem. Res. 50 (2017) 1332–1341. doi:10.1021/acs.accounts.6b00567.
- [50] A. Cesaro, E. Russo, V. Crescenzi, Thermodynamics of caffeine aqueous solutions, J. Phys. Chem. 80 (1976) 335–339. doi:10.1021/j100544a026.
- [51] A. Cesaro, E. Russo, D. Tessarotto, Thermodynamics of caffeine in aqueous denaturant solutions, J. Solution Chem. 9 (1980) 221–235. doi:10.1007/BF00648328.
- [52] M. Żółkiewski, Kirkwood-Buff integrals and density fluctuations in aqueous solution of caffeine, J. Solution Chem. 16 (1987) 1025–1034. doi:10.1007/BF00652586.

- [53] A. Marmur, An upper bound on the theoretical activity coefficient of non-electrolytes, *ChemPhysChem.* 3 (2002) 952–956. doi:10.1002/1439-7641(20021115)3:11<952::AID-CPHC952>3.0.CO;2-Y.
- [54] A. Marmur, Dissolution and self-assembly: The solvophobic/hydrophobic effect, *J. Am. Chem. Soc.* 122 (2000) 2120–2121. doi:10.1021/ja9929281.
- [55] S. Shimizu, H.S. Chan, Statistical mechanics of solvophobic aggregation: Additive and cooperative effects, *J. Chem. Phys.* 115 (2001) 3424–3431. doi:10.1063/1.1386420.
- [56] S. Shimizu, The hydrophobic effect and the excess free energy of solvation, *Chem. Phys. Lett.* 392 (2004) 456–459. doi:10.1016/J.CPLETT.2004.04.124.
- [57] M.J. Blandamer, M.H. Abraham, A critique of a thermodynamic description of hydrophobic aggregation in aqueous solution, *Thermochim. Acta.* 403 (2003) 219–222. doi:10.1016/S0040-6031(03)00037-6.
- [58] M.H. Abraham, M.J. Blandamer, Self-assembly does not account for the hydrophobic effect, *J. Am. Chem. Soc.* 124 (2002) 7853–7856. doi:10.1021/ja0255599.
- [59] H.S. Chan, K.A. Dill, Solvation: How to obtain microscopic energies from partitioning and solvation experiments, *Annu. Rev. Biophys. Biomol. Struct.* 26 (1997) 425–459. doi:10.1146/annurev.biophys.26.1.425.
- [60] B. Moeser, D. Horinek, Unified description of urea denaturation: Backbone and side chains contribute equally in the transfer model, *J. Phys. Chem. B.* 118 (2014) 107–114. doi:10.1021/jp409934q.
- [61] B. Moeser, D. Horinek, The role of the concentration scale in the definition of transfer free energies, *Biophys. Chem.* 196 (2015) 68–76.
- [62] B. Moeser, D. Horinek, Unified description of urea denaturation: Backbone and side chains contribute equally in the transfer model, *J. Phys. Chem. B.* 118 (2014) 107–114. doi:10.1021/jp409934q.

- [63] S. Shimizu, M. Ikeguchi, S. Nakamura, K. Shimizu, Size dependence of transfer free energies: A hard-sphere-chain-based formalism, *J. Chem. Phys.* 110 (1999) 2971–2982. doi:10.1063/1.477940.
- [64] A. Ben-Naim, Inversion of the Kirkwood–Buff theory of solutions: Application to the water–ethanol system, *J. Chem. Phys.* 67 (1977) 4884–4890. doi:10.1063/1.434669.
- [65] P.E. Smith, On the Kirkwood-Buff inversion procedure, *J. Chem. Phys.* 129 (2008) 124509.
- [66] H. Liu, E. Ruckenstein, Aggregation of hydrocarbons in dilute aqueous solutions, *J. Phys. Chem. B.* 102 (1998) 1005–1012. doi:10.1021/jp972793q.
- [67] R.H. Wood, P.T. Thompson, Differences between pair and bulk hydrophobic interactions., *Proc. Natl. Acad. Sci. U. S. A.* 87 (1990) 946–949. doi:10.1073/pnas.87.3.946.
- [68] C. Marimuthu, C. Jayakumar, N.N. Gandhi, A Study on hydrotropy —Petroleum and petrochemical products, *Pet. Sci. Technol.* 29 (2011) 337–348. doi:10.1080/10916460903330106.
- [69] A.B. Morais, C. Jayakumar, N.N. Gandhi, Hydrotropic effect and thermodynamic analysis on the solubility and mass transfer coefficient enhancement of ethylbenzene, *Korean J. Chem. Eng.* 30 (2013) 925–930. doi:10.1007/s11814-012-0213-y.
- [70] K.K. Jayakumar, N.N. Gandhi, Enhancement of solubility and mass transfer coefficient of salicylic acid through hydrotropy, *Int. J. Chem. Anal. Sci.* 3 (2012) 1348–1352.
- [71] S.F. Baranovskii, P.A. Bolotin, Association of riboflavin, caffeine, and sodium salicylate in aqueous solution, *J. Appl. Spectrosc.* 74 (2007) 211–218. doi:10.1007/s10812-007-0033-8.
- [72] C. McAuliffe, Solubility in water of paraffin, cycloparaffin, olefin, acetylene, cycloolefin, and aromatic hydrocarbons, *J. Phys. Chem.* 70 (1966) 1267–1275.

doi:10.1021/j100876a049.

- [73] M. Goral, B. Wisniewska-Gocłowska, A. Skrzecz, I. Owczarek, K. Blazej, M.C. Haulait-Pirson, G.T. Hefter, Z. Maczynska, A. Szafranski, C.L. Young, IUPAC-NIST solubility data series. 81. Hydrocarbons with water and seawater - Revised and updated. Part 3. C₆H₈-C₆H₁₂ hydrocarbons with water and heavy water, *J. Phys. Chem. Ref. Data*. 34 (2005) 657–708. doi:10.1063/1.1796631.
- [74] A. Ben-Naim, Y. Marcus, Solvation thermodynamics of nonionic solutes, *J. Chem. Phys.* 81 (1984) 2016–2027. doi:10.1063/1.447824.

Table 1

Solute	G_{uu}^{∞} $\text{cm}^3 \text{mol}^{-1}$	Best hydrotrope	c_u^{max} mol cm^{-3}	$\frac{c_u^{max}}{c_u^0}$	$c_u^{max} G_{uu}^0$	$\ln \frac{c_u^{max}}{c_u^0}$
benzene	662 ^a	urea ^c	7.7×10^{-5} ^c	6.9 ^c	5.1×10^{-2}	1.9
ethylbenzene	1244 ^a	sodium salicylate ^d	4.3×10^{-5} ^d	28 ^d	5.4×10^{-2}	3.3
cyclohexane	1192 ^b	urea ^e	8.4×10^{-5} ^e	21 ^e	1.0×10^{-1}	3.0
riboflavin	1.25×10^5 ^f	nicotinamide	8.0×10^{-6} ^g	36.2	1	3.58

^aData taken from Liu & Ruckenstein [66], Wood and Thompson [67], ^eMarimuthu et al.[68],
^dMorais et al.[69], ^eJayakumar and Gandhi [70], ^fBaranovskii and Bolotin [71], and ^gCoffman
& Kildsig [47].

Table 2

Solute	$c_u^0 \text{ mol cm}^{-3}$	$B_2^\infty \text{ cm}^3 \text{ mol}^{-1}$	$G_{uu}^\infty c_u^0$
n-pentane	5.3×10^{-7}	-1276.4	1.3×10^{-3}
n-hexane	5.5×10^{-7}	-1620.8	1.8×10^{-3}
2,3-dimethylbutane	3.8×10^{-7}	-1306.3	1.0×10^{-3}
n-heptane	2.9×10^{-8}	-1968.9	1.2×10^{-4}
n-octane	5.8×10^{-9}	-2477.9	2.9×10^{-5}
n-decane	6.1×10^{-9} ^a	-3407.2	4.1×10^{-5}
n-dodecane	2.9×10^{-10} ^a	-4533.6	2.7×10^{-6}
cyclopentane	2.2×10^{-6}	-833.5	3.7×10^{-3}
cyclohexane	6.5×10^{-7}	-997.1	1.3×10^{-3}
cycloheptane	3.1×10^{-7}	-1094.7	6.7×10^{-4}
benzene	2.3×10^{-5}	-331.0	1.5×10^{-2}
toluene	5.6×10^{-6}	-471.0	5.3×10^{-3}
ethylbenzene	1.4×10^{-6}	-672.6	1.9×10^{-3}
caffeine	1.1×10^{-4} ^b	-4500 ^c	1.0

Osmotic second virial coefficient data are taken from Liu & Ruckenstein [66] and solubility data are from McAuliffe [72], except for ^aGoral et al. [73], ^bCesaro et al. [50], ^cŻółkiewski [52].

Table 3

Solute	$B_2^\infty \text{ cm}^3 \text{ mol}^{-1}$	$c_u \text{ mol cm}^{-3}$	$RTG_{uu}^\infty c_u \text{ J mol}^{-1}$	$\Delta\mu_u^* \text{ J mol}^{-1}$
n-pentane	-1276.4	5.3×10^{-7}	3.4	2.4×10^4
n-hexane	-1620.8	5.5×10^{-7}	4.5	2.8×10^4
n-heptane	-1968.9	2.9×10^{-8}	0.29	3.1×10^4
n-octane	-2477.9	5.8×10^{-9}	0.071	3.4×10^4
cyclopentane	-833.5	2.2×10^{-6}	9.2	2.1×10^4
cyclohexane	-997.1	6.5×10^{-7}	3.2	2.3×10^4
benzene	-331	2.3×10^{-5}	37.4	1.4×10^4
caffeine	-4500 ^a	1.0×10^{-4} ^b	2510.8	-

Osmotic second virial coefficient data are taken from Liu & Ruckenstein [66] solubility data are from McAuliffe [72], and liquid \rightarrow water transfer free energy are from Ben-Naim [74], except for ^aŻółkiewski [52], ^bCesaro et al.[50].