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Self-Assembly Does Not Account for the Hydrophobic Effect

Michael H. Abraham* and Michael J. Blandamer

Contribution from the Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, U.K., and Department of Chemistry, University of Leicester, Leicester, U.K.

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Abstract: Marmur has claimed that large values of activity coefficients for nonelectrolytes, particularly in the context of hydrophobic interactions between solutes in aqueous solution at ambient temperature and pressure, cannot be accounted for by thermodynamics, and has suggested that association (self-assembly) of solute molecules in solution solves this dilemma. We show that the analysis of Marmur is incorrect, specifically because the equilibrium in solution between monomeric solute molecules and associated solute molecules is entirely ignored. We show further that activity coefficients such as that for nitromethane solute in hexane solvent, 39.7, and that for solute hexane in solvent water, 4.48×10^5, can be calculated as 31.9 and 4.71×10^5, respectively, by methods based on well-known molecule−molecule interactions. No assumption of self-assembly is required.

Introduction

The hydrophobic effect can be considered to be the insolubility of certain compounds in water, compared to their solubility in nonaqueous solvents. We consider a component of a binary mixture that is present at low mole fraction, i.e., a component considered to be the "solute". There are a number of measures of "solubility" of the component, one of which is the Raoult's law activity coefficient γ_2. If it is possible to obtain values of γ_2 as a function of the solute concentration (or mole fraction), then extrapolation to zero concentration yields the Raoult's law infinite dilution activity coefficient $\gamma^{\infty}{}_2$. For very insoluble substances that are liquid at 298 K, the most practical way of obtaining γ_2 is as the reciprocal of the mole fraction solubility, but then γ_2 refers not to infinite dilution, but to the mole fraction of the saturated solution, X_2(sat). In Table 1 are given values of γ_2 in water at 298 K for alkanes,[1−3] as typically insoluble or "hydrophobic" compounds, together with a value for ethanol in water,[4] by comparison. The solubility of gaseous solutes can be given in terms of the gas-to-water partition coefficient, K_2, which is the inverse of the Henry's constant. We give in Table 1[1−4] values of $K^x{}_2$, where the standard states are unit pressure in atmospheres and unit mole fraction in solution. The alkanes are characterized by very large values of γ_2, corresponding to very small values of $K^x{}_2$.

Table 1. The Solubility of Some Solutes in Water at 298 K

solute	γ_2	$K^x{}_2$	X_2
methane	$4.49 \times 10^{2\ a}$	$2.55 \times 10^{-5\ b}$	0^c
ethane	$1.22 \times 10^{3\ a}$	$3.40 \times 10^{-5\ b}$	0^c
propane	$4.80 \times 10^{3\ a}$	$2.71 \times 10^{-5\ b}$	$2.7 \times 10^{-5\ d}$
butane	$2.04 \times 10^{4\ a}$	$2.24 \times 10^{-5\ b}$	$2.2 \times 10^{-5\ d}$
pentane	$1.02 \times 10^{5\ a}$	$1.46 \times 10^{-5\ b}$	1.0×10^{-5}
hexane	$4.48 \times 10^{5\ a}$	$1.12 \times 10^{-5\ b}$	2.2×10^{-6}
heptane	$2.06 \times 10^{6\ a}$	$8.08 \times 10^{-6\ b}$	4.8×10^{-7}
octane	$9.48 \times 10^{6\ a}$	$5.75 \times 10^{-6\ b}$	1.1×10^{-7}
decane	$4.0 \times 10^{8\ e}$	1.45×10^{-6}	2.5×10^{-9}
ethanol	3.96^a	3.27^f	0^c

[a] From $\gamma_2 = 1/(K^x{}_2 \cdot f_2)$, where f_2 is the fugacity in atm. [b] Reference 1. [c] At infinite dilution. [d] Reference 2. [e] Reference 3. [f] Reference 4.

Discussion and Results

Marmur[5] has put forward a very novel explanation of the very low solubility of hydrophobic solutes in water. He suggests that the solute forms molecular aggregates in water, and that the concomitant loss in entropy leads to a very large and positive molar excess free energy, defined as $G^E{}_2/RT = \ln \gamma^{\infty}{}_2 \approx -\ln X_2(\text{sat})$. $G^E{}_2$ is also the standard Gibbs energy change, $\Delta G°$(sol), for the process

$$\text{solute (pure liquid)} \rightarrow \text{solute (aqueous solution, } X \text{ mol fraction)} \qquad (1)$$

and is related to the standard Gibbs energy of hydration, $\Delta G°{}_2$(hyd), by

$$\Delta G°{}_2(\text{hyd}) = \Delta G^{o}{}_2(\text{sol}) - \Delta G^{o}{}_2(\text{v}) \qquad (2)$$

where $\Delta G°{}_2$(v) is the standard Gibbs energy of vaporization; $\Delta G°{}_2(\text{hyd}) = -RT \ln K^x{}_2$. Now if a solute, S, is associated in water, giving an "n-mer", we have,

$$\text{S(aq)} \overset{K(\text{ass})}{=} 1/n\text{S}_n(\text{aq}) \qquad (3)$$

$$\Delta G°(\text{ass}) = \Delta H°(\text{ass}) - T\Delta S°(\text{ass}) = -RT \ln K(\text{ass}) \qquad (4)$$

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* Corresponding author. E-mail: m.h.abraham@ucl.ac.uk.

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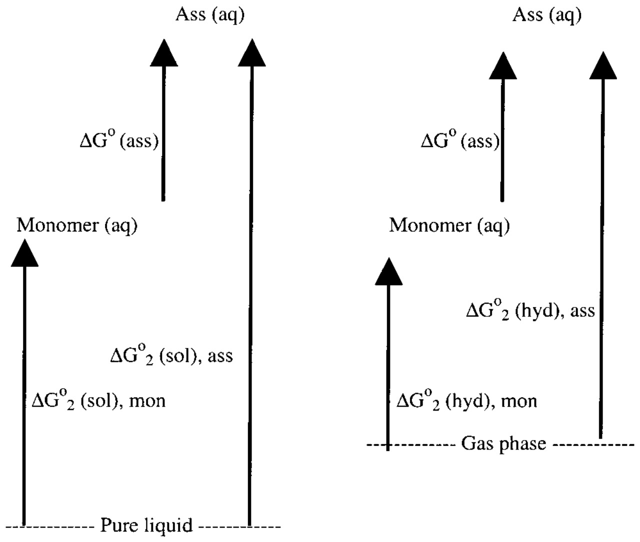

Figure 1.

Table 2. The Fraction of Dimeric Associated Species (n =2) as a Function of Total Solute Mole Fraction and K(ass)

total solute[a]	K(ass)[b]	fraction dimer[c]
2×10^{-4}	1.0	4.0×10^{-4}
1×10^{-4}	1.0	2.0×10^{-4}
5×10^{-5}	1.0	1.0×10^{-4}
1×10^{-5}	1.0	2.0×10^{-5}
2×10^{-4}	0.1	4.0×10^{-6}
1×10^{-4}	0.1	2.0×10^{-6}
5×10^{-5}	0.1	1.0×10^{-6}
1×10^{-5}	0.1	2.0×10^{-7}

[a] Mole fraction. [b] Units of (mol fraction)$^{-1/2}$. [c] Calculated as $2D/(2D + M)$, where D and M are the mole fractions of dimer and monomer.

Then if $\Delta S°$(ass) is very negative, as it is certainly expected to be, and if the contribution of $\Delta H°$(ass) is ignored (as in Marmur's explanation), association will result in a positive $\Delta G°$(ass). This in turn will lead to an increase in $\Delta G°$(sol) and an increase in $\Delta G°_2$(hyd), as postulated by Marmur, because the associated complex is much less soluble than the monomer, see Figure 1.

There is, however, a difficulty in this argument. If $\Delta G°$(ass) is very positive, as it has to be in Marmur's postulate, then in eq 4 the value of the equilibrium constant, K(ass), must be very small, and the fraction of associated solute present must be small. How small can be calculated for various values of K(ass) and various total mole fractions ($S + (1/n)S_n$), where the total mole fraction will be very small, e.g. 10^{-4}, see Table 1. In Table 2 are given the fraction of dimer ($n = 2$) present as a function of total solute mole fraction and K(ass). It can be seen that there is a negligible fraction of solute present as an associate when $K(\text{ass}) < 1$, at a low mole fraction of solute. When $K(\text{ass}) = 0.1$, the fraction of solute present as dimer is 2×10^{-6} at a total mole fraction of solute of 10^{-4}, and 2×10^{-7} at a total mole fraction of solute of 10^{-5}. The fraction present as n-mer when $n > 2$ is even less.

The suggestion of Marmur is physically not possible. In order that the solution process be influenced by the insolubility of the associated species, $\Delta G°$(ass) must be very positive. This means that K(ass) must be much smaller than unity, and this, in turn, means that there is a negligible fraction of associate present at the low total mole fraction of solute in question.

Table 3. Solubilities of Solutes in Hexadecane at 298 K, in Terms of γ^∞_2 and K^x_2

solute	γ^∞_2	$10^3K^x_2$
methane[9]	1.96	5.9
ethane[9]	1.11	37.3
propane[9]	0.96	135.0
water[7]	1250	38.9
methanol[8]	60	10.1

The postulate of Marmur[5] can also be examined through experimental data. If the solubility of a solute in water, expressed as γ_2 or as K^x_2, is influenced by the presence of n-mers, then the solubility should be highly dependent on the total mole fraction of solute in solution (because the fraction of n-mer is highly dependent on the total mole fraction). Rettich et al.[6] have shown that the solubility of methane and ethane in water at 298 K, as K^x_2, is independent of solute partial pressure, contrary to Marmur's postulate.

Marmur also suggested that association, this time of solute water molecules, could be applied to the solubility of water in nonpolar liquids, referred to as "...the low solubility of water in nonpolar liquids." Whether or not water has a low solubility depends on the standard states adopted to describe the solubility. In Table 3 are given solubilities of water,[7] methanol,[8] and alkanes[9] in hexadecane in terms of the two measures we have used, namely γ^∞_2 and K^x_2. Although γ^∞_2 for water is very high, it can be seen that in terms of K^x_2, water is just as soluble in hexadecane as are methane or ethane. It has been pointed out before[10] that a standard state of pure liquid, as used in Raoult's law, is not very useful in the interpretation of solute−solvent interactions in solution, because of intermolecular interactions in the pure liquid. The low solubility of pure liquid water in hexadecane and other nonpolar solvents has almost nothing to do with interactions in the solvent, but is almost entirely the result of interactions between water molecules in the pure liquid water. The use of the gas−liquid partition coefficient as a measure of solubility removes the effects of these pure liquid interactions, to leave only interactions in the solvent. There is therefore no need to postulate association of water in solution to account for the insolubility of water in nonpolar solvents, because gaseous water is actually quite soluble!

Tucker et al.[8] were able to study the association of methanol in hexadecane, and concluded that both trimers and octomers were formed. However, such association cannot account for the large value of γ^∞_2 for methanol in hexadecane. First, near zero methanol mol fraction, the amount of n-mer approaches zero. Second, as the mole fraction of methanol increases, the amount of n-mer increases, but γ_2 decreases. This is as expected if $\Delta G°$(ass) is negative, as found by Tucker et al.[8] Although the entropy of association is negative, the enthalpy of association of methanol in hexadecane is very negative, and this leads to the negative value for $\Delta G°$(ass). Note that Marmur ignored any enthalpic contribution to $\Delta G°$(ass).

Thus for water and methanol in nonpolar solvents, both have large values of γ^∞_2 and both are reasonably soluble, as judged

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by $K^x{}_2$. There is no reason $\Delta G°$(ass) should be positive, as required by Marmur's postulate, and in the case of methanol in hexadecane $\Delta G°$(ass) is actually negative. In any case, as we showed above, if $\Delta G°$(ass) is very positive, then the proportion of associated species will be so low as to be negligible. For water in nonpolar solvents, measurements of association constants are very difficult, but in a detailed review Christian et al.[11] have summarized the experimental evidence that shows water to be monomeric.

All of the above discussion has been in terms of the mole fraction standard state in solution, but we stress that our conclusions in no way depend on this. If the molar standard state is used, exactly the same conclusion follows, namely that association of nonpolar solutes in water or of water or polar solutes in nonpolar solvents cannot account for experimental solubilities.

Marmur goes further than the consideration of solutions of nonpolar solutes in water or of water in nonpolar solvents. He argues that for any solution for which $\ln \gamma_2$ is higher than about 1 (i.e. $\gamma_2 >$ about 3) the formation of molecular aggregates is implied. However, there are numerous nonaqueous binary mixtures for which $\gamma^\infty{}_2 > 3$. Carr et al.[12] have measured values of $\gamma^\infty{}_2$ for 11 aliphatic hydrocarbons in 67 solvents. Of the 737 recorded values of $\gamma^\infty{}_2$, 427 are >3, mostly for the nonpolar solutes in polar solvents. For polar solutes in nonpolar solvents, $\gamma^\infty{}_2$ is also often >3, as shown by Park et al.[13] for the solute nitromethane. We can investigate the origin of large values of $\gamma^\infty{}_2$, and take the example of nitromethane solute in hexane solvent, $\gamma^\infty{}_2 = 39.7$, corresponding to $G^E{}_2 = 2181$ cal mol^{-1}, by comparison with nitromethane in nitromethane, $\gamma_2 = 1$, corresponding to $G^E{}_2 = 0$.

The solution process can be broken down into the vaporization of nitromethane from the bulk liquid to the gas phase, $\Delta G°$(v) = 1813 cal mol^{-1}, followed by solvation of the gaseous nitromethane into hexane or into nitromethane. For the latter process, equations have been constructed in terms of the gas−solvent partition coefficient, as described previously.[14,15] These can be transformed into Gibbs energies for the solvation process, with the standard states we have adopted, viz. unit atm pressure (gas phase) and unit mol fraction (solution phase) as follows.

$$\Delta G°(\text{solvation of gaseous compounds into nitromethane}) = 4088 + 405E - 3668S - 2992A - 701B - 993L \quad (5)$$

$$\Delta G°(\text{solvation of gaseous compounds into hexane}) = 2694 + 230E - 0S - 0A - 0B - 1336L \quad (6)$$

In these equations, our new simplified nomenclature[15] is used. E is the compound excess molar refraction, S is the compound dipolarity/polarizability, A and B are the compound hydrogen bond acidity and basicity, and L is the logarithm of the compound gas−hexadecane partition coefficient. We have these values for nitromethane ($E = 0.313$, $S = 0.95$, $A = 0.06$, $B = 0.31$, and $L = 1.892$)[14] and so all the terms in eqs 5 and 6 can be calculated. The term in L is composed of an unfavorable cavity effect and a favorable general dispersion interaction; the former can be calculated by scaled particle theory (SPT)[16] and the latter obtained from the L-term by difference. The Gibbs energy for creation of a cavity in hexane solvent ($\sigma_1 = 5.97$ Å and $V_1 = 131.6$ cm^3 mol^{-1}) or in nitromethane solvent ($\sigma_1 = 4.31$ Å and $V = 54.0$ cm^3 mol^{-1}) was calculated with Pierotti's version of SPT.[16] The hard sphere diameter and molar volume of the solvent are denoted by σ_1 and V_1, and we take σ_2 as equal to σ_1. Finally, the vaporization Gibbs energy, $\Delta G°(v) = 1813$ cal mol^{-1}, at 298 K must be included in order to start with the bulk nitromethane liquid, rather than with nitromethane in the gas phase. Results of these calculations are in Table 4.

Table 4. Calculation of the Activity Coefficient of Nitromethane in Hexane and of Nitromethane in Nitromethane at 298 K

interaction	nitromethane in hexane	nitromethane in nitromethane
$\Delta G°$(v)	1813	1813
constant	2694	4088
E-term	72	127
S-term	0	−3485
A-term	0	−180
B-term	0	−217
dispersion	−6752	−7428
cavity term	4224	5549
total (G^E)	2051	267
γ_2(calcd)	31.9	1.6
γ_2(obsd)	39.7	1.0

The overall calculation yields G^E (using Marmur's definition) for nitromethane in hexane as 2051 cal mol^{-1}, corresponding to $\gamma^\infty{}_2 = 31.9$ (experimental 39.7),[13] and G^E for nitromethane in nitromethane as 267 cal mol^{-1}, corresponding to $\gamma_2 = 1.6$ (experimental 1.0). Our calculation thus accounts almost quantitatively for the large $\gamma^\infty{}_2$ for nitromethane in hexane, through straightforward chemical interactions, without the need for invoking association of nitromethane at all. Furthermore, inspection of Table 4 reveals exactly the effects that lead to the large $\gamma^\infty{}_2$ and G^E. Solvation of nitromethane in nitromethane is more favorable, i.e., γ_2 and G^E are smaller, mainly because of the very favorable S-term. This is due to dipole−dipole interactions between nitromethane and nitromethane, and counteracts the unfavorable cavity effect in nitromethane. In our view, no extra effects, such as association of nitromethane in hexane solvent, are required to explain the large $\gamma^\infty{}_2$.

Although we can account for the quite large $\gamma^\infty{}_2$ for nitromethane in hexane, values for alkanes in water are orders of magnitude larger (see Table 1). Can a similar type of calculation lead to such very large values? We take the case of hexane in water, $\gamma^\infty{}_2 = 44800$ (Table 1), and for comparison the case of nitromethane in water, where $\gamma^\infty{}_2 = 35.2$ only.[14] Our equation for the solvation of gaseous solutes in water is,[14]

$$\Delta G°(\text{solvation of gaseous compounds into water}) = 6006 - 1121E - 3742S - 5326A - 6567B + 292L \quad (7)$$

and the only extra data we need are the solute parameters for hexane ($E = 0$, $S = 0$, $A = 0$, $B = 0$, and $L = 2.668$),[14] $\Delta G°$(v) for hexane (955 cal mol^{-1}), and the SPT parameters for solvent water ($\sigma_1 = 2.77$ Å and $V_1 = 18.02$ cm^3 mol^{-1}).[16] Details of

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Table 5. Calculation of the Activity Coefficient of Nitromethane in Water and of Hexane in Water at 298 K

interaction	nitromethane in water	hexane in water
$\Delta G°(v)$	1813	955
constant	6006	6006
E-term	−350	0
S-term	−3555	0
A-term	−320	0
B-term	−2036	0
dispersion	−6172	−10995
cavity term	6724	11774
total (G^E)	2110	7740
$\gamma^{\infty}{}_2$(calcd)	35.2	47100
$\gamma^{\infty}{}_2$(obsd)	32.4	44800

the calculations are in Table 5; it can be seen that both calculations lead to excellent agreement with experiment.

Two effects lead to large G^E and hence large γ_2. First, there is a particularly large constant term in eq 5, and second in the special case of water as a solvent, the favorable general dispersion effect does not overcome the very unfavorable cavity effect. Hence values of $\gamma^{\infty}{}_2$ will always be very large unless very favorable solute−water interactions are set up. This is what happens with hexane as solute and, indeed, with nonpolar solutes in general. If the solute is polar or contains groups that can hydrogen bond with water, then various favorable solute−water interactions will be set up. Nitromethane can undergo dipole−dipole interactions (the *S*-term) and hydrogen bond interactions of the type solute base−water acid (the *B*-term) that together total −5591 cal mol^{-1}, and lead to $\gamma^{\infty}{}_2$ values orders of magnitude smaller than that of hexane solute. However, to reduce $\gamma^{\infty}{}_2$ to near unity, solutes that have a greater propensity than nitromethane for favorable solute−water interactions are needed, for example ethylamine ($\gamma^{\infty}{}_2 = 0.5$ in water) or methanol ($\gamma^{\infty}{}_2 = 1.5$ in water).[14]

Thus not only the simpler system of nitromethane in hexane but also the more difficult system of hexane in water can satisfactorily be analyzed without the necessity of postulating effects such as association of solutes.

We have shown that the suggestion of Marmur[5] is physically unreasonable, and that large activity coefficients arise naturally from differences in interaction energies. The question remains as to how Marmur's analysis indicates that large activity coefficients can only be interpreted through some quite unusual phenomenon (such as association of solutes). The original definition of excess Gibbs energy in Marmur's eq 1 is not the same as the Gibbs energy defined in his eq 6; it is the latter quantity that is used in the final key equation, his eq 8. If these two Gibbs energies differ appreciably, then any calculations with his eq 8 will not be valid for his eq 1.

Marmur explains the problem of large activity coefficients through the last term in his eq 8, which we summarize as,

$$(G^E{}_2)a/RT = \ln(\gamma_2)a = [...] - \{\alpha_2(k_2 - 1)/k_2\} \ln x_2 \tag{8,ref.5}$$

In this equation $(G^E{}_2)a$ and $\ln(\gamma_2)a$ are the experimental or observed values, the term in square brackets is irrelevant,[5] α_2 is the fraction of associated species, and k_2 is the association number defined as the number of monomer molecules in the associate. Marmur[5] specifically states that α_2 must be close to unity, so that if k_2 is quite large (22.5 to 119 for example)[5] then for small values of $\ln x_2$, $\ln(\gamma_2)a$ will be a large number.

However, we have already shown that the fraction of molecules that form an aggregate approaches zero as the total solute mole fraction approaches zero, see Table 2 as an example. Thus for the case of $x_2 \rightarrow 0$, the final term in eq 8 from ref 5 will be given by the following: $\{0(k_2 - 1)/k_2\} \ln 0 = 0$. Analysis through eq 8 from ref 5 thus provides no basis for the argument that association of solute molecules is the reason for very high activity coefficients. In particular, the fraction of solute present as an associated complex cannot simply be assigned a given value (i.e. the statement[5] that α_2 must be close to unity). As we have shown, the fraction associated must be calculated from a knowledge of the equilibrium constant for association and the total solute concentration. This is what we show in Table 2, for a monomer−dimer association.

There are two main problems with the analysis of Marmur. First, no account is taken of the equilibrium between the monomer and the associated species. A solution of a "solute" in a solvent is regarded as a three-component system: the solvent, the monomeric species, and the associated species, where the latter is a fixed fraction of the total solute. The fact that the fraction of associated species depends crucially on the total solute concentration is ignored. Second, Marmur refers all interactions to the standard state of the pure liquid solute. It has been pointed out previously[10] that such a standard state obscures solute−solvent interactions, because of the incursion of interactions within the pure liquid. Hence, as we show above in Table 3, water as a bulk liquid is insoluble in alkanes, but water in the gas phase is just as soluble as ethane in hexadecane solvent.

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