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Correlating solvation free energies and surface tensions of hydrocarbon solutes

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Abstract

A simple equation relating ratios of transfer free energies and solvation free energies to surface tension is derived. When applied to hydrocarbons in water, experimental values for macroscopic surface tension yield remarkably accurate predictions of a ratio involving microscopic quantities, if one uses transfer free energies which have been adjusted for the effects of solute/solvent volume differences. The results support the validity of applying macroscopic concepts such as interfacial free energy at the molecular level. They further suggest that molecular volume as well as surface area contributes to the solubility of hydrocarbons in water.

Key words: Solvation free energy; Surface tension; Hydrocarbon; Alkane

1. Introduction

The free energies of transfer of nonpolar solutes into water, and the interfacial free energies (surface tensions) between nonpolar liquids and water provide alternate measures of the free energy per unit area of creating an oil/water interface. Based on published data, however, the two measures appear mutually inconsistent since the transfer free energies yield values of the microscopic surface tension, γ^{ow}, of about 25 cal/mol/Å^2, considerably smaller than the macroscopic value of 72 cal/mol/Å^2, which characterizes alkane/water surface tension (Γ^{ow}) [1]. Macroscopic interfacial free energies can be measured directly. The standard procedure used to extract interfacial free energies from partition coefficients is to set

$$\Delta G^{\circ}(\mathrm{ow}) = -RT \ln K(\mathrm{ow}), \qquad (1)$$

where K is the partition coefficient, and to obtain γ^{ow} from the expression

$$\Delta G^{\circ}(\mathrm{ow}) = \gamma^{ow} A, \qquad (2)$$

where A is the accessible surface area of the solute. The preference for accessible surface area over, say, molecular surface area is based on the fact that the former is related to the number of water molecules that can be packed around a given solute [2]. That surface area terms provide the largest contribution to the transfer free energy has been widely assumed, and is consistent

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with scaled particle theory if atmospheric pressure is used in all volume dependent terms [3]. On the other hand, Neff and McQuarrie have argued that hard sphere pressures should be used in scaled particle theory which leads to volume as well as area dependent contributions to solubility [4]. The question as to whether molar volume makes a significant contribution to solubility at 1 atm pressure has not to our knowledge been definitively resolved.

The issue has recently resurfaced with the suggestion that partition coefficents depend on differences in molar volume between solute and solvent as well as on surface area, implying that Eq. (2) should not be used to obtain interfacial free energies [5–8]. If solubility is dependent on volume as well as on area, Eq. (2) should be replaced by

$$\Delta G^{\circ}(\mathrm{ow}) = \gamma^{\mathrm{ow}} A + f(\bar{V}_1, \bar{V}_2), \tag{3}$$

where $\bar{V}_1$, $\bar{V}_2$ are the molar volumes of solute and solvent, respectively. As dicussed above, neither the magnitude nor the exact functional form of $f(\bar{V}_1, \bar{V}_2)$ is known. However, use of the Flory–Huggins (FH) expression [9,10]

$$f(\bar{V}_1, \bar{V}_2) = RT(1 - \bar{V}_1/\bar{V}_2) = RT(1 - r) \tag{4}$$

in conjunction with Eq. (3) yields values of γ^{ow} for alkanes of approximately 45 cal/mol/Å^2 [5–7]. The remaining discrepancy with the macroscopic value has been attributed to curvature differences between microscopic and macroscopic interfaces [7,8].

There has been considerable controversy surrounding the suggestion that FH theory should be used to analyze solubility data. Some of the discussion has focused on semantic issues rather than on the substantive question concerning the contribution of molar volume to solubility. The source of confusion appears to be the statement that it is incorrect to use free energies extracted from Eq. (1) to derive a value for hydrophobic surface tension [7]. In that study, a set of transfer free energies were introduced in which transfer free energies obtained from Equation (1) were 'corrected' with the FH expression, using

$$\Delta G^{\mathrm{FH}}(\mathrm{ow}) = -RT \ln K(\mathrm{ow}) - RT(1 - r), \tag{5}$$

where the $\Delta G^{\mathrm{FH}}(\mathrm{ow})$ denotes a free energy from which combinatorial, volume-dependent terms have been removed using FH theory. Thus if FH theory accurately accounts for volume effects, $\Delta G^{\mathrm{FH}}(\mathrm{ow})$ will depend on surface area alone. The rationale for using Eq. (5) to define free energies is that all terms arising from the combinatorial entropy of mixing are placed on the right side of the equation [7]. Of course one can move the $1 - r$ term to the left side of the equation and write

$$\begin{aligned}\Delta G^{\circ}(\mathrm{ow}) &= \Delta G^{\mathrm{FH}}(\mathrm{ow}) + RT(1 - r) \\ &= -RT \ln K(\mathrm{ow}),\end{aligned} \tag{6}$$

where in this formulation the only term that appears on the right-hand side of the equation involves the experimental partition coefficient, while FH theory is used to break down standard state free energies that appear on the left side of the equation into area and volume dependent terms.

The formal issue as to whether deviations from ideality due to size differences should appear on the left- or right-hand side of the equation should not divert attention from more substantive questions such as: (a) are there significant volume-dependent contributions to solubility?, and (b) if such contributions do exist are they adequately represented by FH theory? It thus seems preferable, as argued by Holtzer [11] and Ben-Naim and Mazo [12], to abandon the definition of free energies suggested by Sharp et al., i.e. use Eq. (1) exclusively, and then focus discussion on what physical properties of the solute contribute to free energies defined in the standard way.

To date, there has been no definitive argument offered as to whether alkane solubility in water is or is not dependent on molar volume. The improved agreement between macroscopic and microscopic surface tensions mentioned above supports the existence of volume effects close to those predicted by FH theory, but it is also possible to argue that the entire difference is due to curvature effects, and that no volume-dependent contributions need be invoked. In order to remove the uncertain effects of curvature, we derive here a simple relationship between transfer free energies and macroscopic surface tensions which assumes no specific functional form for the curvature dependence of interfacial free energies. When FH adjusted free energies are used in the equation, a remarkable correlation between macroscopic and microscopic surface free energies is found.

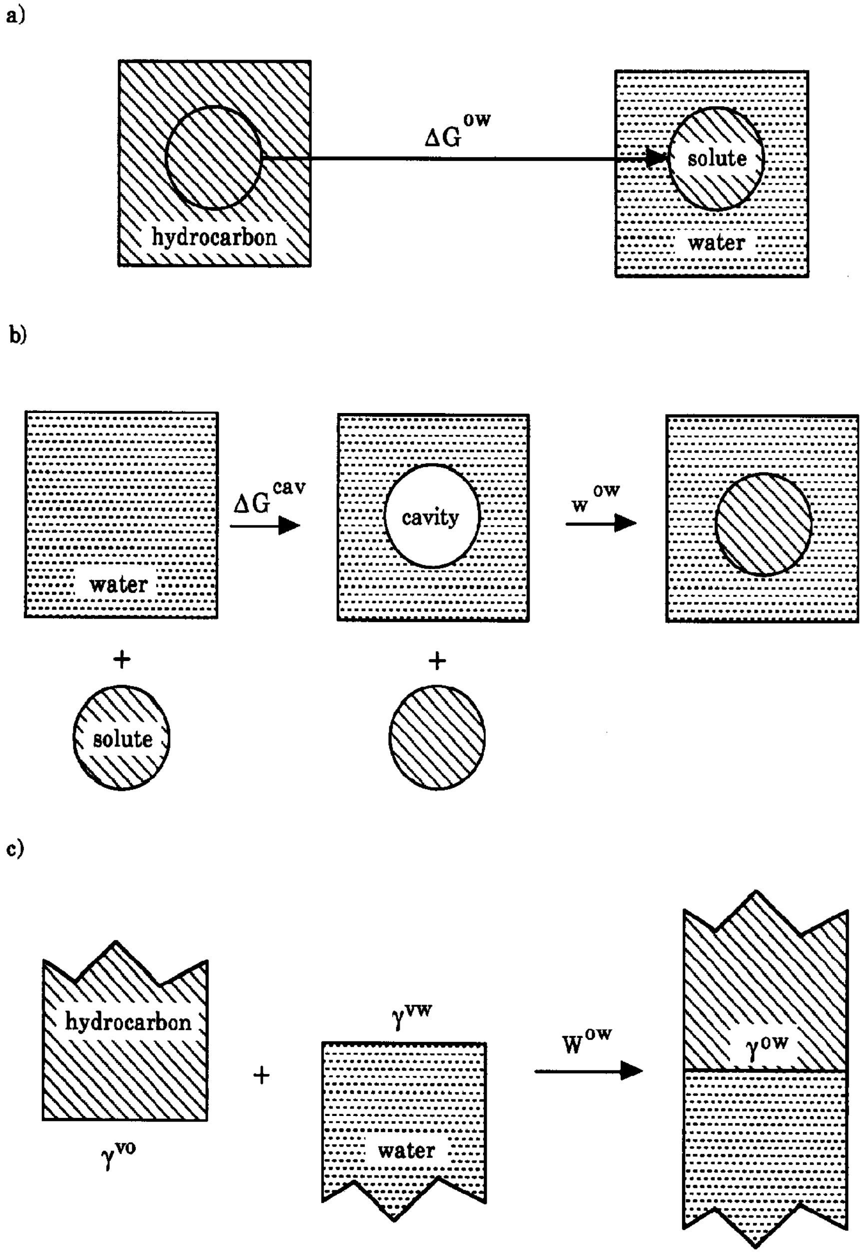

Fig. 1. Interaction of hydrocarbon solutes with water. Diagonal hatching indicates the hydrocarbon phase or hydrocarbon solute, stippling indicates the aqueous phase. (a) Solute transfer from its pure liquid phase into water. (b) Solute transfer from the vapor phase into water. (c) Formation of a macroscopic planar interface between liquid hydrocarbon and water. Symbols are defined in the text.

2. Theory and methods

We assume that the microscopic surface tension, defined alternatively by Eq. (2) or (3) (see also Fig. 1a), is related to the macroscopic value by the expression:

$$\gamma^{ow} = C\Gamma^{ow}, \tag{7}$$

where C is a factor which accounts for curvature differences between molecular and macroscopic interfaces (see e.g. Nicholls et al. [8] and Sharp et al. [6]).

Consider now the transfer, in two stages, of a solute from the gas phase into water (Fig. 1b). In the first step a cavity of the size and shape of the solute is formed in water. The vacuum/water interface has the same area and curvature as the solute/water interface, and hence differences in the free energy of cavity formation can be written as

$$\Delta G^{cav} = A\gamma^{vw} = AC\Gamma^{vw}, \tag{8}$$

where Γ^{vw} is the vacuum/water surface tension. In the second step the solute is introduced into the cavity, which involves a work of interaction between the solute and water (due, e.g. to dispersion and induction interactions between them). For two macroscopic liquid surfaces the work of interaction (or work of adhesion) between them is related to the surface tensions by the Dupré equation [13]

$$W^{ow} = \Gamma^{ow} - \Gamma^{vw} - \Gamma^{vo}, \tag{9}$$

where Γ^{vo} is the nonpolar oil/vapor interfacial tension (Fig. 1c). We now introduce the assumption that the relationship between the macroscopic and microscopic work of adhesion is the same as that between the macroscopic and microscopic interfacial free energies. In other words, the geometric factor C that describes the curvature dependence of the surface tension is assumed to be identical to the one that describes solute/solvent attractive interactions. This is entirely reasonable since the same interface is involved in both cases. With this assumption we may write, in analogy with Eq. (7), a microscopic work of adhesion, w^{ow}, as

$$w^{ow} = CW^{ow}, \tag{10}$$

which is the work of placing the solute in the preformed cavity.

Vacuum to water solute transfer free energies are now written as the sum of the cavity formation, and solute introduction free energies,

$$\Delta G^{vw} = AC(\Gamma^{vw} + W^{ow}) = AC(\Gamma^{ow} - \Gamma^{vo}), \tag{11}$$

where Eq. (9) is used to eliminate W^{ow}. Dividing Eq. (11) by Eq. (2) yields

$$\Delta G^{vw}/\Delta G^{ow} = 1 - \Gamma^{vo}/\Gamma^{ow}, \tag{12}$$

where Eq. (7) is used to eliminate γ^{ow}.

Eq. (12) was used to analyze the solvation free energies of four groups of liquid hydrocarbons: linear alkanes (pentane through decane), branched alkanes (isohexane, 3 methyl pentane, neohexane, 2,4 dimethyl pentane, isooctane and 2,2,5 trimethyl hexane), cyclic alkanes (cyclopentane, cyclohexane, methyl cyclopentane, methyl cyclohexane and 1,2 dimethyl cyclohexane), and aromatics (benzene, toluene, ethylbenzene, 1,2-, 1,3- and 1,4-dimethyl benzene). Liquid to vapor transfer (vaporization) free energies and vapor to water transfer free energies were taken from Ben-Naim and Marcus [14] and from Cabani et al. [15]. The molar volume of water is taken as 18 ml/mol. Hydrocarbon molar volumes were obtained by dividing the molecular weight by the pure liquid density obtained from the CRC handbook [16]. Hydrocarbon liquid to water transfer free energies were obtained by adding the free energy of vaporization to vapor to water transfer free energies. The water/vapor interfacial tension was taken as 104 cal/(mol Å^2) [16]. Hydrocarbon liquid/vapor and liquid/water interfacial free energies were obtained from Girifalco and Good [17] except for isooctane/water, which was taken from Aveyard and Hayden [18]. Microscopic transfer free energies on the left-hand side of Eq. (12) were obtained using either Eq. (1), referred to as unadjusted values, or from Eq. (5), for volume adjusted values. It should be emphasized again that the term adjusted (applied here in place of the term 'corrected' used previously) refers not to the validity of Eq. (1), which is general, but to the elimination of putative volume dependent contributions to the transfer free energy.

The transfer free energy and surface tension data used in the calculations are collected in Table 1. For the linear alkanes, the interfacial tension data for heptane and octane are representative of this group and the average was used in the calculations. Similarly for the aromatics, the average of the interfacial tension data for benzene, toluene and ethylbenzene were used. Liquid/water surface tensions for some of the branched and cyclic compounds could not be found in the literature, so we used the values for iso-octane for all the branched alkanes, and cyclohexane for all the cyclic alkanes. As is evident from Table 1, liquid hydrocarbon/water interfacial tensions are fairly constant, even between different groups of alkanes, so that variation within groups is likely to be of secondary importance. We have assumed, for simplicity of discussion, that the linear relationship between free energy and surface area (Eq. (2)) has a zero intercept. Allowing for non zero intercepts has only a marginal effect on the conclusions of this study.

3. Results and discussion

Inserting the values for the interfacial free energies, Γ^{ov} and Γ^{ow}, from Table 1 into Eq. (12) the *macroscopic* prediction for the ratio of *micro-*

Table 1
Transfer energy and interfacial free energy data for hydrocarbons [a]

Group	Solute [b]	SA	V	Γ^{ov}	Γ^{ow}	$-W^{ow}$	ΔG° (vw)	ΔG° (ow)	ΔG^{FH} (vw)	ΔG^{FH} (ow)	$\frac{\Delta G^{FH}(vw)}{\Delta G^{FH}(ow)}$	$1-\Gamma^{ov}/\Gamma^{ow}$
linear alkanes	pentane	255	115				2.34	5.74	5.57	8.97	0.62	
	hexane	284	130				2.55	6.60	6.29	10.35	0.61	
	heptane	313	146	29.4	72.3	61.1	2.63	7.32	6.90	11.59	0.59	0.59
	octane	341	162	31.4	73.8	61.6	2.89	8.21	7.70	13.02	0.59	0.58
	nonane	370	178				3.04	9.02	8.38	14.36	0.58	
	decane	399	195				3.22	9.85	9.10	15.73	0.58	
branched alkanes	isohexane	277	132				2.53	6.38	6.27	10.12	0.62	
	3 m-pentane	276	130				2.51	6.43	6.17	10.09	0.61	
	neohexane	267	133				2.60	6.20	6.37	9.97	0.64	
	2,4 m-pentane	299	149				2.89	7.12	7.18	11.41	0.63	
	isooctane	314	165	27.1	71.6	59.5	2.85	7.43	7.68	12.26	0.63	0.62
	2,2,5 m-hexane	347	181				2.72	7.89	8.09	13.26	0.61	
cyclic alkanes	cyclopentane	224	94				1.21	5.02	3.70	7.51	0.49	
	cyclohexane	245	108	36.7	72.3	68.4	1.24	5.66	4.19	8.62	0.49	0.49
	m-cyclopentane	250	112				1.60	5.80	4.70	8.90	0.53	
	m-cyclohexane	270	128				1.69	6.56	5.29	10.16	0.52	
	1,2 m-cyclohexane	292	141				1.57	6.92	5.60	10.95	0.51	
aromatic	benzene	236	89	41.5	50.4	95.1	−0.88	3.66	1.48	6.03	0.25	0.18
	toluene	263	106	41.0	52.0	93.0	−0.77	4.37	2.17	7.30	0.30	0.21
	ethylbenzene	288	122	42.0	55.3	90.7	−0.60	5.13	2.82	8.56	0.32	0.24
	1,2 m-benzene	289	123				−0.91	5.13	2.55	8.50	0.30	
	1,3 m-benzene	285	123				−0.84	5.05	2.60	8.41	0.31	
	1,4 m-benzene	289	120				−0.81	4.97	2.56	8.34	0.31	

[a] SA: accessible surface area (Å^2) calculated using a carbon radius of 1.9 Å and a hydrogen radius of 0.0 Å; V: molar volume (ml/mol); Γ^{ov}, Γ^{ow}: hydrocarbon liquid/vapor, hydrocarbon liquid/water surface tensions (cal/mol · Å^2); W^{ow}: hydrocarbon solute/water work of adhesion, calculated from Eq. (9) (cal/mol Å^2); ΔG°(vw), ΔG°(ow): standard vapor → water and hydrocarbon liquid → water transfer free energies, calculated using Eq. (1) (kcal/mole); ΔG^{FH}(vw), ΔG^{FH}(ow): Flory–Huggins volume adjusted vapor → water and hydrocarbon liquid → water transfer free energies, calculated using Eq. (5) (kcal/mol).
[b] m: methyl.

scopic transfer free energies, $\Delta G^{\mathrm{vw}}/\Delta G^{\mathrm{ow}}$, is 0.58 for linear alkanes, 0.62 for branched alkanes, 0.49 for cyclic alkanes and 0.21 for aromatics. Table 1 and Fig. 2 show the experimental transfer free energy ratios for the four hydrocarbon groups, using the unadjusted literature values, ΔG°, and values obtained from Eq. (5), ΔG^{FH}. The first point to note is that within each hydrocarbon group the free energy ratios are very similar even though individual transfer free energies vary substantially. The unadjusted transfer ratios, however, fall well below those expected from the interfacial free energies. The values even have the wrong sign for the aromatic compounds. When the volume adjusted transfer free energies are used, the ratios all lie quite close to the expected values (most within 5%). Even the very minor difference in the surface tension based prediction for the linear and branched alkanes (0.58 versus 0.62) is reflected in the transfer free energy ratios. The largest discrepancies between macroscopic and microscopic quantities are for the benzene derivatives. Because aromatic groups have some polar character, their works of adhesion are fairly large (see Table 1). Consequently the ratio of hydrocarbon liquid/vapor to liquid/water surface tensions is close to one. As is apparent from Eq. (12), this will magnify any error in the

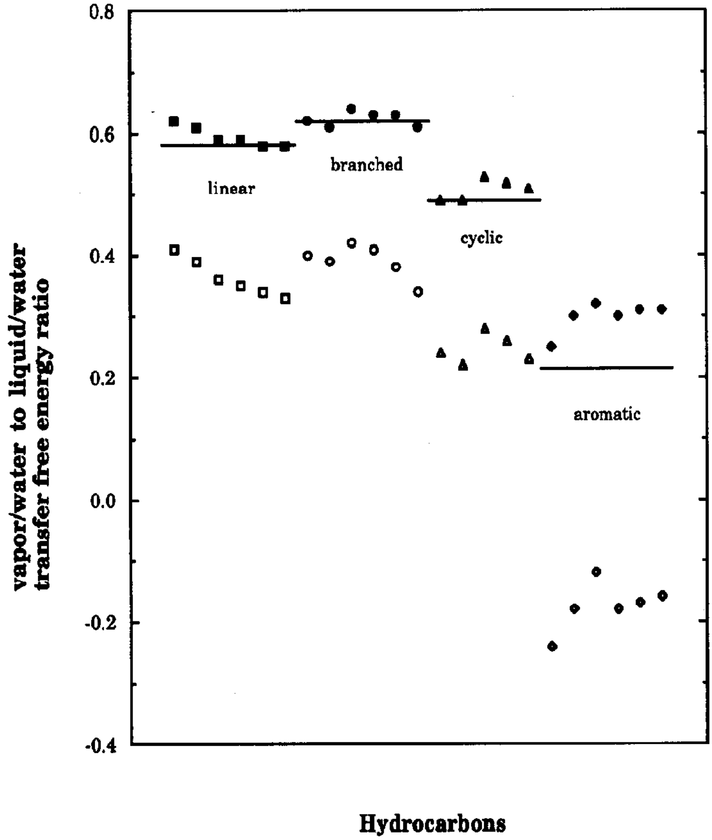

Fig. 2. Comparison of experimental vacuum → water/liquid → water transfer free energy ratios to those calculated from interfacial free energies. Linear alkanes: (■), (□). Branched alkanes: (●), (○). Cylic alkanes: (▲), (△). Aromatics: (◆), (◇). Open symbols: unadjusted transfer free energy data. Filled symbols: transfer free energy data adjusted for the solute/water size difference using Eq. (5). The order of data points within groups corresponds to the order of individual molecules in Table 1. Horizontal lines indicate the expected transfer ratios for each group calculated from interfacial free energy data using Eq. (12).

calculated transfer free energy ratio. Using volume adjusted transfer free energies also reduces the variation within each group of compounds. The variation in transfer ratio between the saturated hydrocarbon groups arises primarily from the difference in hydrocarbon liquid/vapor interfacial tension, since there is not much variation in the liquid/water surface tensions.

It is notable that Eq. (12) is satisfied for each of the four classes of hydrocarbons when Eq. (5) is used. This success says nothing about the source of variability among classes, but rather that whatever interactions are present in the macroscopic regime are present at the level of individual molecules as well. It should be emphasized that the right side of Eq. (12) is calculated from experimental values for interfacial free energies while the left side is calculated from experimental partition coefficients. Thus the two sets of measurements are completely independent. Eq. (12) was derived by assuming that microscopic interfacial free energies are proportional to their macroscopic counterparts. The coefficient C which relates the microscopic and macroscopic scales is never defined, but it is assumed that a single value of C is appropriate whether the transfer is from the gas phase or the oil phase, into water.

Whether one expects, *a priori*, that Eq. (12) be satisfied is to some extent a matter of intuition, but there is ample precedent to expect a relationship between macroscopic and microscopic surface tensions [19–21]. That the equation is satisfied only if FH adjusted free energies are used supports the suggestion that transfer free energies obtained from Eq. (1) are not proportional to surface area alone. In addition, it suggests that FH theory is capable of describing volume dependent contributions to solubility which, when removed from the total transfer free energies as in Eq. (5), yield true microscopic interfacial free energies.

Of course it is possible that the correlations found in this work are fortuitous and that they do not prove that FH theory can be used to account for volume dependent contributions to hydrocarbon solubility. On the other hand, the results of this work constitute the third independent observation that solubility data can be better rationalized with FH adjusted than with unadjusted free energies. The other two examples are the study of De Young and Dill [5] on benzene partitioning between the alkane and aqueous phases and the observation that microscopic and macroscopic surface tensions can be reconciled if Flory–Huggins adjusted oil/water transfer free energies are used [6].

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Discussion to the paper by D. Sitkoff, K. Sharp and B. Honig

Comments

By A. Ben-Naim

(1) There is no theoretical basis for a relation between ΔG and γ (Eq. 2). Therefore γ values obtained from Eq. (2) need not be related to the macroscopic surface tension of water – hence no "inconsistency" exists between the so-called "microscopic" and the macroscopic surface tension.

(2) "The formal issue as to whether deviations from ideality due to the size differences should appear on the left- or right-hand side of the equation...".

In my opinion there is no issue of "deviation from ideality", in the first place, and secondly a correction term should not be added neither to the right- nor to the left-hand side of the equation.

By A. Rashin

We have started our studies of the entropy of hydration [1] at about the same time as you [2]. We encountered the problem of the ideal gas entropy about 1.5 years ago as we computed hydration entropies at constant pressure and constant volume [3]. I spent many hours discussing the problem with a number of colleagues (see Acknowledgements in ref. [3]). A number of discussions of our results with you indicated that you had reached on your own at least some of our conclusions. However, our discussions have never been conclusive, and your paper does not clearly state a resolution to the controversy started in ref. [2] regarding volume terms in the free energies of transfer. Therefore my comments are aimed on a clarification of whether we have reached any consensus.

In our review [4] and in ref. [3] we demonstrate that free energy of transfer of a solute impenetrable for the solvent can behave very differently for solvents with no (or weak) cohesive interaction between its molecules and solvents wilh a strong cohesive interaction between its molecules. I will not repeat all the line of arguments of refs. [3,4] here and only summarize them. To this summary I add evidence from other contributions in this Issue that seems to support our reasoning.

(1) The conclusions of refs. [3,4] can be formulated as follows. We can model solvent with no cohesive interactions between its molecules as a compressed ideal gas. A transfer to such solvent of a solute with its partial molecular volume impenetrable to the gas leads to the increase in its free energy which is proportional to the solute's partial molecular volume. In the case of constant VT transfer it originates in the compression entropy of the solvent, and in the case of constant PT transfer it originates in exactly equal $P\Delta V$ work against a high pressure required to keep the ideal gas in liquid's volume [3,4].

(2) Liquids with strong cohesion between their molecules can be modeled by ideal gas in a mean field that keeps solvent together and has different magnitudes near the solute and in the bulk. In such model solvents entropy of insertion of the solute described above leads to effects around the solute, that result in entropy changes roughly proportional to solutes accessible areas, plus the compression entropy identical to that of ideal gas [3,4]. In the case of constant PT transfer there is no change in the compression entropy because the solvent is not compressed. Therefore, only terms nearly proportional to the accessible surface area contribute to the fransfer entropy. $P\Delta V$ work against an atmospheric pressure outside of the liquid with strong cohesion between its molecules is negligible for molecular size solutes [5–7]. Thus, for PT transfer no terms proportional to solute's volume will contribute appreciably to the free energy of transfer [3,4]. In VT transfer the decrease in entropy of the solvent due to its compression should be compensated by decrease in solvent's internal energy upon its compression [4] This assures equivalence of free energies of transfer for both ensembles. Only terms that are nearly proportional to the surface will appear for these solvents with strong cohesion.

(3) This shows that derivations in which effects are derived from a stage utilizing a compressed ideal gas [2] cannot be transferred to at least some model cohesive solvents [3,4] and, therefore, do not possess generality. Thus, they [2]

cannot be considered as a proof of anything as long as the counter-example [3,4] is not excluded by some qualifiers. Also, effects observed for hard spheres (another non-cohesive solvent) cannot be transferred to at least some model cohesive solvents [3,4]. In principle, real cohesive solvents may behave in a way intermediate between the extremes of model non-cohesive and cohesive solvents and somehow retain part of the volume effects. This, however, cannot justify the derivation of ref. [2] which remains faulty.

Now we turn to evidence from other contributions in this Issue that seems to indicate that main conclusions of refs. [3,4] reproduced above may be generally correct.

(4) If to accept arguments of refs. [6,7] that in *all known* cases the volume term is only $P\Delta V$ then, because its always small for molecular size solutes in strongly cohesive liquids, there are no appreciable volume terms for transfer of molecular size solutes to such liquids. This should be correct as long as *no other cases contrary to the known ones are found.*

(5) Everybody seems to agree that for large enough solutes volume terms will dominate and, thus, free energy of transfer asymptotically behaves as solute's volume. Ref. [8] shows that with increasing cohesiveness of the solvent the size of the solute for which the asymptotic behavior is approached shifts to increasingly larger solutes. Our results suggest that for strongly cohesive solvents the asymptote will be reached only for macroscopic solutes while for non-cohesive solvents it is reached at microscopic solute sizes. Thus, the trend observed in ref. [8] agrees with our conclusions. However, the range of the cohesion magnitudes studied in ref. [8] is too narrow and close to the low cohesion to prove that volume effects may become negligible.

(6) Ref. [9] supports our expectation that larger negative entropy change upon transfer at VT conditions is compensated by the decrease in the internal energy.

(7) A demonstration that volume terms may be negligible for highly cohesive solvents for, say, solutes of 30–40 Å radius with methods of refs. [8,9] would provide a strong support to our general conclusion [3,4] and its consequences.

(8) Considerations of transfers between two solvents are not required to prove our point. First, we here deal with hydration and this limits our interest to other liquid phases as any transfer between two liquid phases can be considered as two transfers between a liquid and a gas. Second, all of our discussion above applies to any solvent. Thus, according to our line of reasoning, volume effects from the second liquid phase could be appreciable only if this phase represents a low cohesion liquid at experimental conditions.

As far as the polymer theory is concerned I would suspect that cohesiveness should be decisive there as well. But I prefer to limit myself to the subject of this Issue, hydration, and to leave the polymer theory to its practitioners.

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By Y. Marcus

(1) The difference between the observed ΔG°(ow) and that calculated from the surface tension, Eq. (3), is ascribed in Eq. (4) exclusively to the ratio of molar volumes of solute and solvent, according to the Flory–Huggins expression. Could not an alternative explanation in terms of solute molar volume and the difference in the internal pressures of the solvents between which the solute transfers do as well?

(2) The surface areas and the volumes of solutes with relative molecular masses between 60 and 600 are well linearly correlated (whether or not the exclusion area and volume are taken into accoun. cf. Pearlman in ref. [1]. Hence it is impossible to answer the question posed as to which of these quantities contributes to the thermody-

namic function by a fit to experimental data given their realistic accuracies.

(3) The assumption made, that the curvature parameter C is independent of the medium in which a solute is situated (water, a hydrocarbon, or vacuum), ought to be stated explicitly at the place where C is introduced, Eq. (8). It is difficult to justify concerning condensed phases on the one hand and the gas phase on the other, since no cavity is formed in the latter.

[1] R.S. Pearlman, in: Partition coefficient determination and estimation, eds. W.J. Dunn, J.H. Block and R.S. Pearlman (Pergamon Press, Oxford, 1985).

By B.K. Lee

Eq. (10), and Eq. (11) which is derived from it, implies that the free energy of an isolated non-polar molecule in vacuum is not zero, as is conventionally assumed, but is given by $A\gamma^{vo}$, where is γ^{vo} the "microscopic surface tension" of the non-polar molecule in vacuum. Since absolute value of the free energy is never defined, there is no problem here. However, is it reasonable to assume that γ^{vo} is also given by $C\Gamma^{vo}$? Γ^{vo} is the free energy required to form a unit area of oil–vacuum interface by bringing the non-polar molecules from the bulk oil phase to the interface. How realistic is it to imagine that a non-polar molecule in vacuum is created by a similar process? For one thing, Γ^{vo} must involve a significant entropic component since a molecule in the bulk has a different entropy than one in the interface. But how can one imagine an entropic component for a single molecule in vacuum? (Clearly internal degrees of freedom is not at issue here.)

By L. Pratt.

(1) The broadest conclusion suggested by this work and its predecessors feels paradoxical to me. Therefore, I would like to paraphrase that conclusion in terms that makes the apparent paradox evident and to request a physical explanation of the apparent paradox: The idea is that an adjustment of the measured partition coefficient should be made to account for molecular volumes (and thus packing effects) of solute and solvent. A consequence of this adjustment is that the adjusted quantity is better fit by a surface area model with a larger tension parameter, now somewhat closer to the measured surface tension of water–oil interfaces. The apparently paradoxical point is that the packing adjustment reduces the solvation free energy and thereby raises the contribution required from the surface area model. This is apparently paradoxical because, if any one phase is considered, excluded volume interactions with the solvent generally *raise* the chemical potential or the solvation free energy. But this excluded volume adjustment *lowers* the chemical potential. One way around this point is to note that the adjustment should include contributions from both phases involved. Thus, perhaps the excluded volume adjustment raises the chemical potential of the oil phases more than it raises the chemical potential of the solute in water. Then the difference would be lowered. But this is not the situation that would be most commonly guessed. Moreover, the formula for the adjustment is not obviously a difference. Please explain.

(2) This paper notes that Neff and McQuarrie (Ref. [4] in the original paper) have argued that the pressure of the hard sphere liquid should be used in the scaled particle model of solubilities in hydrophobic molecules in water. The general discussion due to Stillinger (Ref. [21] in the original paper) of the scaled particle approach identifies on a molecular basis the role in determining the solvation free energy of the experimental pressure of the solvent and the experimental surface tension. Is the hard sphere perturbation theory of Neff and McQuarrie as applied to hydrocarbon solubility in water inconsistent with the Stillinger's formulation?

(3) Temperature dependences of the solvation free energies of hydrophobic solutes are of particular interest. For macroscopic models that feature the surface tension that temperature dependence is closely tied to the separately known temperature dependence of surface tensions. How do the temperature variations of the parameters γ^{OW} of Fqs. (2) and (3) compare to the measured temperature variations of the macroscopic surface tensions?

(4) The fundamental molecular theory for the

calculation of solubilities appears to be completely understood; molecular sizes and volumes will certainly play an essential role but the details will be different in different cases. However, $\bar{V}_1$ (the molar volume of the coexisting oil phase) is only an indirect indicator of an intuitive molecule size. For example, if the coexisting phase is a dilute gas, e.g., the oil phase is gaseous methane, then $\bar{V}_1 \rightarrow \infty$. As another example, suppose the case considered is the transfer of a solute species A at dilute concentrations between two liquids B and C. Then the $\bar{V}_A$ is typically unknown in either phase but a subtle function of the solvation structure, not necessarily positive, and not in a trivial way the volume of an A molecule. For inert gases in water it is known that these volumes are substantially smaller, by factors of 2 or 3, than the geometric volumes of the solutes. For a discussion and calculation, see ref. [1]. How would your adjustment workout if these quantities were used rather than $\bar{V}_1$.

[1] L.R. Pratt and A. Pohorille, Proceedings of the EBSA (Association of European Biophysical Societies) 1992 International Workshop on Water-Biomolecule Interactions, Eds. M.U. Palma, M.B. Palma-Vittorelli and F. Parak (Societa' Italiana di Fisica, Bologna, 1993): Hydrophobic Effects from Cavity Statistics (1992). LA-UR-92-3260.

Responses by D. Sitkoff, K. Sharp and B. Honig to Comments

Many of the comments on our manuscript really pertain to our earlier papers where we argued first that (ref. [6] of our paper in this Issue) the use of Flory–Huggins theory to analyze the partition of solutes between the *alkane* and *aqueous* phases led to microscopic surface tensions that were close to the macroscopic value. In the second paper (ref. [7]) we used a partitioning of the free energy through an ideal gas step to argue that the result was quite general and was applicable as well to transfers from the gas phase into water. The papers generated considerable controversy, most of it positive in the sense that researchers began to consider the possibility that molar volume makes a contribution to solubility; a possibility that had been effectively ignored for 20 years. Most of the criticism has focused on a few points. Ben-Naim argues that the derivation in the Biochemistry (ref. [7]) paper is wrong, but seems to agree with our conclusion that volume is important. Lee in this volume argues that our derivation is correct, but whether it is important or not can be judged only from criteria based on utility. Some of Pratt's and Rashin's comments are based to some extent on scaled particle theory considerations where use of 1 atm in the volume term effectively removes all volume dependent contributions to solubility for small solutes. The original question which motivated us to investigate these issues, alkane to water transfers, has been addressed only indirectly in the questions.

We have collaborated with a number of other scientists, particularly Sanat Kumar and Peter Rossky in an attempt to resolve these and many other questions. We are currently preparing two papers for publication which hopefully will clarify much of what is going on. Since our response to the questions posed in this journal is contained in these papers which involve other authors, we will only respond briefly in the following paragraphs.

As a final introductory comment, we are surprised that a number of the questions imply that a relationship between macroscopic and microscopic surface tension is not to be expected. We expect a relationship simply because the underlying forces are the same. Moreover, our intuition seems to be shared by others. Eyring and Sinanoglu considered this issue in some detail in the 1970s and Stillinger argues in the paper referred to by Pratt that the large radius limit should be reached for solutes of the dimension of 3 or 4 water molecules. It is important to emphasize that understanding how surface tension scales with size and curvature is crucial if surface area concepts are to be applied to very large molecules such as proteins. For example, should one treat the surface area of a protein as microscopic or macroscopic when estimating binding free energies of substrates? These are important and interesting questions which we would hope that modern theoretical and experimental approaches can address. We believe that our work has been a step in this direction. The fact that so many different opinions have emerged about the issues we have raised demonstrates that they are not as well understood as some might have imagined.

To B.K. Lee

Eq. (10) just states that the attractive forces between oil and water on the microscopic and macroscopic scales are related. We never define the free energy of an isolated molecule in vacuum. Rather we are always concerned with free energy differences.

Regarding the extent to which it is realistic to assume a relationship between microscopic and macroscopic values, for example between Γ^{vo} and γ^{vo}, in our view it is reasonable because the relevant forces are similar. Bringing molecules from the bulk to an interface, or the process of bringing molecules from the bulk to the gas phase both involve replacing solute surface area that was previously in contact with other molecules with area that is in contact with the gas phase. If the dominant effect in both cases is the loss of van der Waals interactions, then the two coefficients should be related. If entropic effects at the interface are significant we agree that no relationship should be expected. That a correlation is found between microscopic and macroscopic values is suggestive that our assumptions are reasonable, but of course it does not prove them.

To A. Ben-Naim

(1) Ben-Naim categorically dismisses Eq. (2) despite its widespread use. From his paper we understand that he accepts Eq. (3) or at least the notion that solubility depends on volume. Since our intention was to determine which equation is more appropriate, and we concluded as we had previously, that Eq. (2) is in fact incorrect, then Ben-Naim apparently agrees with us on this point.

(2) Ben-Naim appears to be saying that there are no deviations from ideal mixing behaviour due to volume differences between molecules, which would then contradict his paper in this Issue. Since we doubt that this was his intention, we can only conclude that he has again failed to understand that the goal of our work has been to attempt to extract the contribution of molar volume to solubility.

For a detail critique of Ben-Naim's thinking on these issues, see our comments to his paper in this Issue.

To L. Pratt

(1) Excluded volume does indeed lower the chemical potential. However, at constant pressure, the excluded volume does not increase. (More about this in our response to Rashin). Nevertheless, Pratt is correct in surmising that volume effects raise the chemical effects more in the alkane phase than in the aqueous phase. As we will show this effect is the true source of Flory–Huggins theory as applied in polymer theory (Kumar et al., in preparation). The form of the expressions will become obvious when we present its derivation.

(2) Yes, there is an apparent contradiction between Neff and McQuarrie and the general discussion due to Stillinger. However, if one uses hard sphere pressure for the entropy in scaled particle theory, it is possible that the corresponding terms are canceled in the free energy by attractive interactions between the solvent molecules. This might well result in the use of the ambient pressure in the expression for the free energy. In collaboration with Rossky and Kumar, we shortly expect to have quantitative data on an appropriate model liquid which should definitively answer this question.

(3) We have not looked into this issue. It is worth pointing out, however, that for small solutes, the enthalpy and entropy are very temperature dependent while the free energy exhibits little temperature dependence. Indeed the classical hydrophobic effect becomes enthalpic in origin as temperature is increased. Macroscopic surface tension also appears to involve an increase in energy. Thus it may be that the temperature dependence of surface tension at room temperature resembles that of "microscopic surface tension" at much higher temperatures. Nevertheless, since the same forces are involved we expect that the two phenomena are closely related.

(4) We disagree (see above) that the fundamental theory is completely understood although it well may be for spheres. The properties of chain molecules are certainly not understood within the context of liquid state theory nor for

that matter are issues of entropy and enthalpy compensation raised above. Regarding hydrocarbons in water, the molar volumes are about 70% larger than the van der Waals volumes and are quite similar in either the aqueous or alkane phase.

To A. Rashin

(1) and (2): We have discussed these points extensively with Dr. Rashin in the last few years and are in complete agreement with most of them. There are, however, additional volume dependent contributions to the entropy and enthalpy at both constant pressure and constant volume that we will be discussing in a forthcoming publication.

(3) Nothing in comments 1 and 2, which never invokes an ideal gas state, can be used as counter examples to a thermodynamic cycle that does. To argue that the straightforward derivation in ref. [7] is faulty would require some evidence of error. None is provided so it is difficult to respond. We do agree that the derivation may have missed the true source of volume effects in that there may be canceling terms to those we derived. This would imply, in Peter Rossky's words, that the derivation is uninteresting, but not incorrect. This issue as well will be discussed in our forthcoming publication.

(4) We will demonstrate that volume contributions to the entropy do not come from *PV* ambient work. There may be other *PV* type terms that may enter into the entropy and enthalpy but specific identification of *P* and *V* still needs to be established.

(5) The role of cohesive forces is certainly of great interest, as we have been discussing for some time.

(6) and (7): See above.

(8) See above for the effects of the alkane phase.

To Y. Marcus

Taking the points in order (1) What is meant by the term "internal pressure"? If this means the pressure that an ideal gas has at the solvent density then the difference in internal pressure between solvents is just given by the difference in density (i.e. molar volume). In fact the cycle that we described in our Biochemistry paper, Sharp et al. (1991), involving compressed ideal gas mixing steps provides the PV work (entropy) arising from just this effect, and leads to the Flory–Huggins expression.

(2) The fact that area and volume are both linearly dependent on the number of carbons within a homologous alkane series is just the problem: It means that volume and area terms cannot be distinguished by any single set of experimental measurements, such as transfer into a single solvent. It is only by comparing sets of measurements where area and volume terms contribute differently that one can separate them; e.g. solvation versus surface tension, as we do here, or varying the size of the solvent, as de Young and Dill did. The ability to match small differences between linear, branched and cyclic alkanes shows that accuracy is not the issue.

(3) We do assume that the curvature correction is the same for the oil water and vacuum water interface (In Eqs. (7) and (8)), also that the work of adhesion (Eq. (9)) has the same curvature dependence. This is because all involve interactions at the water interface. Our thermodynamic cycle never involves the energy of cavity formation in vacuum for precisely the reason that it is ill defined.