

COMMENTS

Comment on “Free Energy of Transfer of a Solute and Its Relation to the Partition Constant”

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In a recent article Goss,¹ stating that “there is an ongoing debate in the literature about the correct relationship between the free energy of transfer of a molecule between two phases and the corresponding partition constant”, proposed that “a discrepancy remains that appears to be related to the free volume in the liquid phase” and that “can be quantified by an empirical linear regression with the surface tension of the liquid phase”. Goss concluded that: “The results of this study should help to improve our thermodynamic understanding of partitioning. They are important for the prediction of equilibrium partitioning from the respective free energy of interaction as well as for a consistent thermodynamic interpretation of equilibrium partition constants”. Actually, there are serious problems with the analysis by Goss, as I will try to show below.

Goss¹ considered the solvation (gas-to-liquid transfer) of *n*-nonane in a lot of solvents at 25 °C and tried to reproduce the experimental ΔG° values as 9 times the transfer Gibbs energy contribution of a CH₂ group, $9 \cdot \Delta G^\circ(\text{CH}_2)$ [the superscript filled circle denotes the unit molar concentration standard state that corresponds to the so-called Ben-Naim standard]. On performing the comparison, a discrepancy emerged that was particularly large in the case of water (see Table 1 in ref 1). Goss assumed that: (a) this discrepancy is entropic in origin, and (b) it “arises from the difference in the accessible free volume of the solvent as compared to its saturated vapor phase”. Obviously the physical basis for this assumption is not at all clear. But, Goss was able to go a step further, finding a linear correlation between the values of this discrepancy in the various solvents and the surface tension of such solvents at 25 °C (see Figure 2 and eq 5 in ref 1). The reliability of this linear relationship was supported by the following statements: “Surface tension is a measure of the cohesive free energy within a solvent. The stronger the cohesive energy between molecules in a solvent the smaller should be the free volume that is accessible for a solute molecule”. Moreover, Goss considered the possibility that “the available free volume of a solvent would decrease for solutes whose size is above a certain threshold”, by repeating the same analysis for *n*-pentane. Since no significant difference with respect to the case of *n*-nonane emerged, Goss concluded that “at least all alkanes smaller than nonane encounter the same free volume in a solvent”.

Let me underscore some points to define the framework in which the analysis by Goss has to be evaluated.

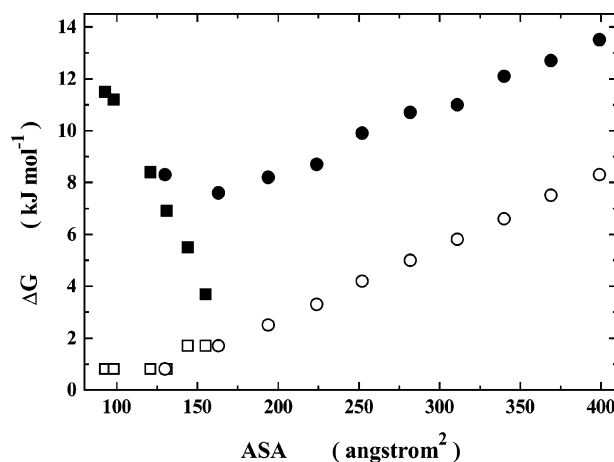


Figure 1. Experimental Ben-Naim standard Gibbs energy of hydration, ΔG° , of noble gases (filled squares) and *n*-alkanes up to *n*-decane (filled circles) at 25 °C as a function of the accessible surface area, ASA, of the solute (data from ref 7 and 8). Estimates of the Gibbs energy of hydration calculated as $n \cdot \Delta G^\circ(\text{CH}_2)$, according to the proposal by Goss, are also shown for noble gases (open squares) and *n*-alkanes (open circles). It has been assumed that He, Ne, Ar, and Kr correspond to a single CH₂ group, while Xe and Rn correspond to two CH₂ groups.

First point. The relationship between the equilibrium partition constant expressed in molar concentrations, $K_2 = C_2(\text{l})/C_2(\text{g})$ [where $C_2(\text{l})$ is the molar concentration of the component 2 in the liquid, and $C_2(\text{g})$ is that in the gas] and the transfer Gibbs energy change, ΔG° , cannot be wrong because it descends from the second principle of thermodynamics and the condition of partition equilibrium of a component between two phases.² This means that the ΔG° values obtained by means of $\Delta G^\circ = -RT \cdot \ln K_2$ have to be considered *experimental data*, measuring the solubility of a compound in a liquid. Therefore, there is no correction to be performed.

Second point. It is important to recognize that a molecular level understanding of the change in a thermodynamic quantity can solely be obtained by resorting to statistical mechanics. Ben-Naim² was able to show, under very general conditions, that ΔG° is the reversible work to transfer a solute molecule from a fixed position in the gas phase to a fixed position in the liquid phase. Moreover, a direct application of statistical mechanics³ shows that the quantity ΔG° takes into account both the excluded volume effect due to solute insertion into the solvent, and the attractive interactions between the inserted solute molecule and the surrounding solvent molecules. Clearly, it is valid to inquire as to what specific solute and solvent properties determine the quantity ΔG° , and, in all probability, this was the aim of the analysis by Goss.

Third point. The discrepancy between the devised additivity model and the experimental ΔG° values (which is very large in the case of gas-to-water transfer) was not considered by Goss as a strong indication of the weakness of the additivity model itself. On the contrary, Goss¹ considered that such a discrepancy is a clear evidence that something is not accounted for in the experimental ΔG° values. This implies that Goss¹ considered the quantity $9 \cdot \Delta G^\circ(\text{CH}_2)$ as the correct measure of the transfer

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TABLE 1: Molar Volume at 20 °C, Cohesive Energy Density at the Same Temperature, c.e.d. = $(\Delta H_{\text{vap}} - RT)/V$, Where ΔH_{vap} Is the Vaporization Enthalpy Change, and Surface Tension at 25 °C of Several *n*-Alkanes and *n*-Alcohols. All Values Are from Ref 6

	v cm ³ mol ⁻¹	c.e.d. J cm ⁻³	γ mN m ⁻¹
<i>n</i> -C ₆ H ₁₄	130.52	220	17.89
<i>n</i> -C ₇ H ₁₆	146.56	230	19.65
<i>n</i> -C ₈ H ₁₈	162.61	240	21.14
<i>n</i> -C ₉ H ₂₀	178.74	245	22.38
<i>n</i> -C ₁₀ H ₂₂	194.92	250	23.37
<i>n</i> -C ₁₁ H ₂₄	211.20	255	24.21
<i>n</i> -C ₁₂ H ₂₆	227.51	260	—
<i>n</i> -C ₁₃ H ₂₈	243.75	260	25.55
<i>n</i> -C ₁₄ H ₃₀	260.09	265	26.13
CH ₃ OH	40.49	875	22.07
C ₂ H ₅ OH	58.37	685	21.97
<i>n</i> -C ₃ H ₇ OH	74.81	600	23.32
<i>n</i> -C ₄ H ₉ OH	91.53	545	24.93
<i>n</i> -C ₅ H ₁₁ OH	108.24	505	25.36
<i>n</i> -C ₆ H ₁₃ OH	125.59	470	25.81
<i>n</i> -C ₇ H ₁₅ OH	141.39	455	—
<i>n</i> -C ₈ H ₁₇ OH	157.47	435	27.10
<i>n</i> -C ₉ H ₁₉ OH	174.37	420	27.89
<i>n</i> -C ₁₀ H ₂₁ OH	190.78	410	28.51
<i>n</i> -C ₁₁ H ₂₃ OH	207.65	400	—

Gibbs energy of *n*-nonane from the gas phase to the various solvents. The physicochemical basis for such an implicit assumption was not discussed at all by Goss. In this respect, I have contrasted the experimental ΔG° values in water, at 25 °C, of noble gases and normal alkanes up to decane, with the estimates calculated as $n\Delta G^\circ(\text{CH}_2)$, where *n* is the number of CH₂ groups in the molecule and $\Delta G^\circ(\text{CH}_2) = 0.83 \text{ kJ mol}^{-1}$, as reported by Goss. A look at this plot emphasizes that the additivity model of Goss, when applied to the solvation of nonpolar solutes in water, does not work. The discrepancy is large due to the existence of nonadditivity effects. In the case of He and Ne, it amounts to more than 10 kJ mol⁻¹, in the assumption that both noble gases correspond to a single CH₂ group. Even though the latter assumption is not so robust, I think it is important to contrast noble gases against the interpretation provided by Goss, because entropy effects related to the free volume in a liquid are expected to become smaller on decreasing the size of the solute molecule.

Fourth point. It is fundamental to distinguish the free volume of a liquid and the volume available for the insertion of a solute molecule of a given size in the same liquid.⁴ Even though the free (not-occupied) volume of a liquid is a large fraction (50–60%) of the total volume, the volume actually available to insert a solute molecule is orders of magnitude smaller. Since the

nonoverlap condition has to be satisfied in the liquid, only the cavities whose size is at least equal to that of the solute molecule are available for the insertion. Therefore, the fundamental issue is the partitioning of the free volume in a liquid. Pratt and Pohorille,⁵ by means of molecular dynamics simulations in an OPLS model of *n*-hexane and in TIP4P water, determined the cavity size distribution in the two liquids at room temperature. They found that: (a) the most probable cavities have a radius of about 0.2 Å in both liquids; (b) the probability of molecular-sized cavities is smaller in water than in *n*-hexane; (c) the probability of molecular-sized cavities becomes smaller on increasing the cavity size in both liquids. Since the results of Pratt and Pohorille should be considered experimental data in view of the adopted procedure, the statements by Goss on the free volume appear approximate and misleading.

Fifth point. It is difficult to understand how a relationship between a supposed entropy term related to free volume effects and the surface tension of the solvent could be considered reliable from a physicochemical point of view. In fact, to the best of my knowledge, there is no direct relationship (a) between the surface tension of a liquid and its cohesive energy and (b) between the cohesive energy of a liquid and the partitioning of its free volume. For instance, at room temperature, along the *n*-alkanes series, from *n*-hexane to *n*-tetradecane, the surface tension increases as does the cohesive energy density; but, along the *n*-alcohols series, from methanol to *n*-undecanol, the surface tension increases even though the cohesive energy density decreases (see Table 1).

In conclusion, the additivity model proposed by Goss is too simplistic, and the advanced empirical relationship does not possess a strong physical basis.

References and Notes

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