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Dissolution and Self-Assembly: The Solvophobic/Hydrophobic Effect

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The hydrophobic effect,[1−12] namely, the very limited solubility in water of nonpolar substances that are soluble in organic solvents, is the key to the existence of life as we know it. It is also an essential element in many chemical processes in daily life and industry that rely on phase separation between either "oil" or gases and water. Thermodynamically, the hydrophobic effect is an extreme case of solution non-ideality. This is expressed by the very high values of the molar excess free energy of the solute (i.e., the difference between the chemical potential of the solute and its chemical potential had the solution been ideal). For systems with very limited solubility, the molar excess free energy of a solute i at its saturation composition is well-described[6] by the simple approximation $G_i^{Es}/RT \approx -\ln(x_i^s)$. Here, x_i^s is the mol fraction of the solute at saturation, R is the universal gas constant, and T is the absolute temperature. For example, x_i^s for octane in water is of the order of magnitude of 10^{-7} at room temperature and pressure; hence, $G_i^{Es}/RT \approx 16$. Such values of the molar excess free energy have been considered very high simply by comparison with other solutions (e.g., 6). However, it will be shown below that RT is an upper bound on the molar excess free energy, so that values higher than RT pose a fundamental problem.

Although studied for many years, the hydrophobic effect is incompletely understood.[1−12] So far, it has been explained by the formation of an ordered structure of water (an "iceberg") around the nonpolar molecules of the solute.[11,12] The high value of the molar excess free energy was attributed, according to one line of thought,[11,12] to entropy loss due to the formation of such ordered structure of the solvent. Another hypothesis was that enthalpy was gained due to this formation.[9] In any case, the "iceberg" approach mainly emphasizes the role of water as a solvent; therefore, one of its main shortcomings is the lack of explanation of the low solubility of water in nonpolar liquids. Here it is shown that entropy loss due to self-assembly of solute molecules into molecular aggregates is sufficient to account for the hydrophobic effect. This is shown to be true regardless of the type of the solute molecule, so that it holds for aqueous solutions of nonpolar liquids as well as for solutions of water in nonpolar liquids. Moreover, it is shown that the formation of molecular aggregates is not limited to aqueous solutions or even to systems of low solubility. Rather, it is a universal phenomenon associated with appreciably non-ideal solutions.

The central argument that is developed and used in the present discussion is the theoretical observation that the molar excess free energy of a solute cannot assume such high values as are characteristic of the hydrophobic effect or, in fact, of any appreciably non-ideal solution. This observation stems from an order-of-magnitude analysis of the following equation for the molar excess free energy of a component i, by which it may (in principle) be calculated from equation-of-state data:[13]

$$G_i^E/RT = \ln \gamma_i = (1/RT) \int_0^P (\bar{V}_i - V_i)dP \tag{1}$$

In this equation γ_i is the activity coefficient, P is the pressure, $\bar{V}_i$ (which depends on x_i, P, T) is the partial molar volume of component i in solution (at the mol fraction x_i, for which G_i^E is calculated), and V_i (at the same P,T) is the molar volume of the pure component i. The difference $(\bar{V}_i - V_i)$ is the molar volume change of component i due to mixing. The integration is performed at constant T. Equation 1 is a standard thermodynamic equation; however it is not frequently used, since available equations of state (in terms of $\bar{V}_i(x_i,P,T)$ and $V_i(P,T)$) are not sufficiently accurate to describe the liquid state. Nonetheless, it is a valid thermodynamic equation.

To make eq 1 more transparent for the analysis to follow, the integral can be replaced by the product of the average of $(\bar{V}_i - V_i)$ and the pressure range: $(\Delta V_i)_{av}P$. This average is defined by $(\Delta V_i)_{av} \equiv 1/P\int_0^P(\bar{V}_i - V_i)dP$. Obviously, this replacement does not change the content of eq 1, which can now be rewritten as

$$G_i^E/RT = (\Delta V_i)_{av}P/RT = (\Delta V_i)_{av}/V^{ig}(P,T) \tag{2}$$

where $V^{ig}(P,T)$ is the molar volume of an ideal gas at T and P. Thus, the molar excess free energy is given by the ratio of the average molar volume change of component i due to mixing to the molar volume of an ideal gas at P and T.

Now, eq 2 can be subjected to a simple order-of-magnitude analysis, to show that G_i^E/RT cannot be a large number. The idea is to show that, over the whole pressure range from 0 to P, all contributions to $(\Delta V_i)_{av}$ are small compared with V^{ig}. At very low pressures, that is, at the ideal gas state, $(\bar{V}_i - V_i) \rightarrow 0$, by definition. At somewhat higher pressures, the gaseous mixture may not be an ideal gas anymore, but the approximation of an ideal *solution* holds, so that $(\bar{V}_i - V_i)$ still remains vanishingly small (this difference is zero for an ideal solution). This may not be true for extremely high pressures, but the present discussion refers mainly to solutions at mild pressures, not too far away from atmospheric pressure. Since the present discussion deals with mixtures that are in the liquid state at T and P, the transition from the gaseous state to the liquid state occurs over some pressure range below P. In the liquid state $(\bar{V}_i - V_i)$ may be positive or negative; however, typical data show that this difference is less (usually much less) than V_i. Moreover, under mild pressures, the molar volume of a liquid, V_i, is much smaller than that of an ideal gas under such pressures. Therefore, it can be concluded that the average molar volume change of component i due to mixing is small compared with V^{ig}, the molar volume of an ideal gas at P and T. Hence,

$$G_i^E/RT = \ln \gamma_i = (\Delta V_i)_{av}/V^{ig} < 1 \tag{3}$$

Thus, to understand non-ideal dissolution in general, and explain the hydrophobic effect in particular, one must answer the

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question: how can experimentally derived values of the molar excess free energy of the solute be so much higher than allowed by thermodynamics? Since the principles of thermodynamics are taken for granted, and since the relevant experimental data (such as solubilities or liquid−vapor equilibrium concentrations) are measured by simple and accurate methods, the answer should be pursued in the domain of the assumptions underlying the definition of the system. The main implicit assumption in the thermodynamics of solutions is that the solute is dispersed in the solvent as single molecules. Therefore, it is interesting to check the implications of the possibility of the solute molecules being dispersed as molecular aggregates. Indeed, it will be shown in the following that the formation of molecular aggregates of the solute solves the above dilemma. The self-assembly of the solute molecules decreases their entropy and, consequently, increases the molar excess free energy.

To quantitatively substantiate this claim, an equation for ΔG, the molar free energy change due to mixing, needs to be developed in a way that takes molecular aggregation into account. For molecularly dispersed components, the well-known expression for ΔG is

$$\Delta G = \sum_i x_i(\mu_i - \mu_i^p) = RT\sum_i x_i \ln \gamma_i x_i \qquad (4)$$

where μ_i is the chemical potential of component i in solution, dispersed as single molecules, and μ_i^p is the chemical potential of the pure component i under the same temperature and pressure. To account for molecular aggregation, this expression has to be modified. It is assumed that the fraction of molecules of component i that form aggregates is α_i, and, for simplicity, as a first approximation, that all aggregates consist of the same number of molecules k_i. Then,

$$\Delta G = \sum_i (1 - \alpha_i)x_i(\mu_i - \mu_i^p) + (\alpha_i x_i / k_i)(\mu_{k_i} - k_i\mu_i^p) \quad (5)$$

where μ_{k_i} is the chemical potential of a molecular aggregate, treated as a separate component. The first term in the summation is the contribution of the molecularly dispersed components, the mol fraction of which is $(1 - \alpha_i)x_i$. The second term describes the contribution of the molecular aggregates. Their mol fraction is $\alpha_i x_i/k_i$ (since k_i molecules of component i form one "molecule" of the aggregate), and the reference chemical potential is that of k_i single molecules of the pure component.

To relate eq 5 to experimental data, the *actual* activity coefficient, $(\gamma_i)_a$, is defined, similarly to eq 4 as

$$\Delta G \equiv RT\sum_i x_i \ln(\gamma_i)_a x_i \qquad (6)$$

This definition is based on the nominal mol fractions of the components, x_i, regardless of molecular aggregation. Therefore, the *actual* activity coefficient is, in fact, the one calculated from experimental data. This is so, since in these calculations molecular aggregation is not explicitly accounted for. By comparing eqs 5 and 6 one gets

$$RT \ln(\gamma_i)_a x_i = (1 - \alpha_i)(\mu_i - \mu_i^p) + \frac{\alpha_i}{k_i}(\mu_{ki} - k_i\mu_i^p) \quad (7)$$

To get the final equation, the differences in chemical potentials are now related to mol fractions and activity coefficients by the usual thermodynamic relationship. $(\mu_i - \mu_i^p)$ is given by $RT \ln \gamma_i(1 - \alpha_i)x_i$. Similarly, considering the molecular aggregates as a separate component, $(\mu_{ki} - k_i\mu_i^p)$ is given by $RT \ln \gamma_{ki}\alpha_i x_i/k_i$, where γ_{ki} is the activity coefficient of the aggregates. Introducing these two expressions into eq 7 one gets

$$(G_i^E)_a /RT \equiv \ln(\gamma_i)_a = [(1 - \alpha_i)\ln(1 - \alpha_i)\gamma_i + \alpha_i /k_i \ln(\alpha_i\gamma_{ki} /k_i)] - \alpha_i(k_i - 1)/k_i \ln x_i \quad (8)$$

where the *actual* molar excess free energy, $(G_i^E)_a$, is also defined. The term in square brackets in this equation must be smaller than one (the expressions α_i/k_i, $(1 - \alpha_i)$, $(\alpha_i/k_i) \ln(\alpha_i/k_i)$, and $(1 - \alpha_i) \ln(1 - \alpha_i)$ are always smaller than 1 based on their mathematical definitions; $\ln \gamma_i$ and $\ln \gamma_{k_i}$ are smaller than 1 by virtue of eq 3). Therefore, eq 8 shows that for $(G_i^E)_a$ to be large (e.g., of the order of magnitude of $(-\ln x_i)$ as is experimentally observed for solutes of very low solubility), the extent of aggregation must be large: k_i must be bigger than 1 and α_i must be close to 1.

It should be emphasized that the present conclusion is not limited to cases of very low solubility. It applies in general to all situations for which $(\gamma_i)_a$ is high. It will be shown elsewhere, that $(\gamma_i)_a$ data for aqueous solutions of alcohols, for example, follow eq 8 over a wide concentration range. Values of k_i calculated from eq 8 range from ∼2.5 for ethanol to ∼119 for 1-butanol. Thus, the present theory proves that appreciable non-ideality of a solution implies the formation of molecular aggregates of the component for which $\ln(\gamma_i)_a$ is higher than about 1. The decrease in entropy that is associated with this self-assembly process is the cause of the high actual molar excess free energy or activity coefficient. In particular, the present theory shows that the hydrophobic effect is due to self-assembly of *solute* molecules into molecular aggregates. This is so, since the activity coefficient of the solute is extremely high, while that of water (the mol fraction of which is almost 1) is very close to one ($\ln(\gamma_i)_a \approx 0$). This explanation is intuitively appealing, considering the well-known empirical rule that "like dissolves like" and vice versa: it shows that non-polar molecules prefer to aggregate in an aqueous environment rather than be dispersed as single molecules. The present theory is independent of the type of solute and solvent, and, in particular, applies to the dissolution of non-polar molecules in water as well as to the dissolution of water in non-polar liquids. Therefore, the phenomenon of self-assembly into molecular aggregates should be associated with the more general term "solvophobic effect" rather than with the term "hydrophobic effect."

The idea of molecular aggregates is, of course, well-known for surfactant systems. For systems that do not include surfactants it was also suggested long time ago.[14] The novel point in the present communication is the realization that (a) there is a theoretical upper limit to the actual excess free energy that is much lower than experimentally derived values for appreciably non-ideal solutions and (b) that this contradiction can be solved only by admitting self-assembly into molecular aggregates. Thus, the existence of molecular aggregates in appreciably non-ideal solutions is shown to be a must rather than an option. The present analysis, being based on classical thermodynamics, cannot offer a mechanism for the formation of the molecular aggregates; what it does is prove their existence. Specifically, regarding the hydrophobic effect, the present theory does not exclude an explanation based on the structuring of water, but shows that the self-assembly of solute molecules into aggregates is sufficient to explain the experimental data. Moreover, it may be speculated that it is the structuring of water that leads to the molecular aggregation of the non-polar solutes.

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