

Reply to the Comment on "Entropy of Hydrophobic Hydration: A New Statistical Mechanical Formulation"

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This note is in response to a comment by Smith et al. regarding the correct expression for the solvation entropy of a simple, hydrophobic solute at infinite dilution in water. They argue that the expression given in Lazaridis and Paulaitis¹ should be supplemented by a term describing the change in water-water pair correlations upon insertion of the solute. On the basis of the work of Yu and Karplus,² they also assert that this contribution to the solvation entropy will be large and therefore cannot be neglected. We acknowledge the argument given in ref 1, that led us to neglect such contributions, is flawed. However, we wish to emphasize the important difference between solute insertion at constant volume, as was considered in ref 2, and at constant pressure, as was considered in ref 1, and offer possible reasons why this "solvent reorganization" contribution is apparently small in the system we studied.

The correlation expansion for the entropy of a binary mixture in the canonical ensemble is¹

$$S = N_w \left(\frac{3}{2} k - k \ln(\rho_w \Lambda^3) \right) + N_s \left(\frac{3}{2} k - k \ln(\rho_s \Lambda^3) \right) - N_w \frac{2k}{2V} \int g_{ww} \ln g_{ww} \, dr - N_s \frac{2k}{2V} \int g_{ss} \ln g_{ss} \, dr - N_s N_w \frac{k}{V} \int g_{sw} \ln g_{sw} \, dr + \text{higher order terms} \quad (1)$$

where subscripts s, w denote the two components of the mixture; N_w , N_s are the number of molecules of each component; ρ_w , ρ_s are number densities; and g_{ww} , g_{sw} , g_{ss} are pair correlation functions. For simplicity of notation we consider two monatomic species. The analysis can, however, be trivially extended to molecules with orientational degrees of freedom. The terms in parentheses in eq 1 are essentially the partial molar entropies of an ideal gas mixture except for an additional term equal to Boltzmann's constant, which arises from the fact that the integrals in eq 1 do not vanish for an ideal gas in the canonical ensemble. We can easily factor this term out of the integrals,³ but this will not be necessary in the present analysis.

The partial molar entropy of the solute is obtained by differentiating eq 1 with respect to N_s at constant T , P , and N_w , or by differentiating the molar entropy with respect to x_s (mole fraction) at constant T and P :

$$\bar{S}_s = \left(\frac{\partial S}{\partial N_s} \right)_{T,P,N_w} = \underline{S} + x_w \left(\frac{\partial \underline{S}}{\partial x_s} \right)_{T,P} \quad (2)$$

In ref 1, we obtained the partial molar entropy at infinite dilution by approximating the first derivative as $S(T,P,N_w,N_s=1) - S(T,P,N_w,N_s=0)$ in the limit $N_w, V \rightarrow \infty$. In this analysis, we incorrectly maintained that integrals of water-water correlation functions in the mixture and in pure water were equal in the limit of infinite dilution; thus, we neglected contributions due to changes in the water-water pair correlation function. The partial molar entropy, obtained by differentiating eq 1 directly and then taking

the infinite dilution limit, is

$$\bar{S}_s^\infty = \lim_{x_s \rightarrow 0} \bar{S}_s = \left(\frac{3}{2} k - k \ln(\rho_s \Lambda^3) \right) - k(1 - \rho_w \bar{v}_s^\infty) - k \rho_w \int g_{sw} \ln g_{sw} \, dr + \frac{k}{2} \rho_w^2 \bar{v}_s^\infty \int g_{ww} \ln g_{ww} \, dr - \frac{k}{2} \rho_w \left(\frac{\partial}{\partial x_s} \int g_{ww} \ln g_{ww} \, dr \right)_{T,P} \quad (3)$$

where \bar{v}_s^∞ is the partial molar volume of the solute at infinite dilution. The term $k(1 - \rho_w \bar{v}_s^\infty)$ arises from the derivative of the ideal partial molar entropies in eq 1 and has been recently derived⁴ on the basis of Flory-Huggins theory. The third term in eq 3 accounts for solute-water pair correlations and is the contribution evaluated in ref 1. The last two terms follow from "solvent reorganization" upon solute insertion at constant pressure. The first accounts for volume expansion of the solution and the second for changes in the water-water pair correlations.

The change in entropy upon particle insertion at constant volume is obtained by differentiating eq 1 with respect to N_s at constant T , V , and N_w and then taking the limit of infinite dilution,

$$\hat{S}_s^\infty = \lim_{\rho_s \rightarrow 0} \left(\frac{\partial S}{\partial N_s} \right)_{T,V,N_w} = \left(\frac{3}{2} k - k \ln(\rho_s \Lambda^3) \right) - k - k \rho_w \int g_{sw} \ln g_{sw} \, dr - \frac{k}{2} \rho_w^2 \left(\frac{\partial}{\partial \rho_s} \int g_{ww} \ln g_{ww} \, dr \right)_{T,V,N_w} \quad (4)$$

The last term in this expression accounts for changes in water-water pair correlations when the solute is inserted at constant volume. It is the term identified by Smith et al. and evaluated by Yu and Karplus,² although within the context of an entirely different statistical mechanical formulation. This term is related, but not equal, to the last term in eq 3.

The difference between \hat{S}_s^∞ and \bar{S}_s^∞ can be estimated from experimental data using standard thermodynamic relations:

$$\left(\frac{\partial \hat{S}_s^\infty}{\partial N_s} \right)_{T,P,N_w} - \left(\frac{\partial \bar{S}_s^\infty}{\partial N_s} \right)_{T,V,N_w} = \left(\frac{\partial S}{\partial V} \right)_T \bar{v}_s = \left(\frac{\partial P}{\partial T} \right)_V \bar{v}_s \quad (5)$$

For methane at infinite dilution in water, we use the measured partial molar volume at infinite dilution⁵ and volumetric data for pure water⁶ to calculate a difference of nearly +5 e.u. For comparison, the residual solvation entropy at 25 °C is approximately -16 e.u.⁷ Thus, the quantity \hat{S}_s^∞ is substantially more negative than the partial molar entropy, \bar{S}_s^∞ . The physical reason behind this difference is the increase in density that accompanies solute insertion at constant volume; i.e., the solvent cannot expand to accommodate the solute as it can when solute insertion takes place at constant pressure. It is evident from the magnitude of this difference and from a term-by-term comparison of eqs 3 and 4 that one must use caution in comparing the results of ref 2 to those of ref 1. In addition, the results of ref 2 with regard to hydrophobic solvation cannot be considered quantitatively reliable, since their predictions are quite disparate from experimental values.

According to Yu and Karplus, the "solvent reorganization" entropy is equal to the corresponding contribution to the solvation energy.² This result can be shown to hold for the solvation enthalpy and entropy upon solute insertion at constant pressure as well. Normally, this contribution is positive, as the calculations in ref 2 confirm. However, the comparison between our calculated values of \bar{S}_s^∞ and experimental data suggests that this contribution is small for methane at infinite dilution in water, at least at room temperature. This could be explained if the last term in eq 3 were negative and about the same magnitude as the fourth term. This is consistent with the concept of "water structure enhance-

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ment" in the vicinity of the hydrophobic solute, if we associate this concept with the last term in eq 3, rather than the sum of the two last terms. We note, however, that our results deviate considerably from experiment at higher temperatures. We now suspect that this deviation may be due, at least in part, to the above solvent contributions, rather than the inadequacy of the interaction potentials. It is imperative, of course, that these issues be analyzed beyond the present level of speculation. This is a demanding task, considering the difficulty of calculating the terms involving water-water pair correlation functions and their derivatives by computer simulations, which we feel at present to be the most reliable approach.

Finally, we agree with the point made by Smith et al. regarding the need to test the entropy expansion, independent of the interaction potentials, by comparing our results with model data, rather than experiment. Unfortunately, current alternative methods for calculating solvation entropies by simulations suffer from such statistical uncertainty that any comparison would be precarious. Comparisons of this nature have been reported, however, for hard-sphere and Lennard-Jones fluids.^{3,8,9} As for

the use of the ensemble invariant expression for the entropy, we refer the reader to our discussion of this issue in another publication.¹⁰

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References and Notes

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