

COMMENTS

Comment on “Reevaluation in Interpretation of Hydrophobicity by Scaled Particle Theory”

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In a recent letter (L),¹ Kodaka tried to provide an interpretation of the results from scaled particle theory,² SPT, using calculations different from the usual ones.^{3,4} This matter is important in reaching a molecular-level understanding of the origin of hydrophobicity.⁵ In the present comment, I would like to show that the Kodaka's reasoning is not correct.

It is well established that the transfer from the gas phase to the liquid phase of a nonpolar molecule is governed by the balance between the work expended to create a suitable cavity in the solvent, ΔG_c , and the work needed to turn on the solute–solvent attractive interactions, ΔG_a .^{6–11} The first term is a large positive quantity that contrasts the transfer in all solvents. The second term is a negative quantity that favors the transfer and is quantitatively similar in all solvents. What distinguishes water from the other common solvents is that ΔG_c is significantly larger in such a solvent. This became clear after Pierotti first applied SPT to water in the mid-1960s.¹² The problem is to clarify why ΔG_c is so large in water.

Inspection of the SPT equation for ΔG_c indicates that the latter, at a given temperature for a given cavity diameter, is a function of the size of the solvent molecules, σ , and the volume packing density of the solvent, $\xi = \pi\sigma^3 N_A/6v$, where v is the molar volume of the solvent itself. The two variables act in opposite directions: for a given ξ , ΔG_c rises on decreasing σ , and for a given σ , ΔG_c rises on increasing ξ . Such a dependence can easily be rationalized in geometric terms. The value of $(1 - \xi)$ represents the empty space of a liquid, so on increasing ξ , the empty space diminishes and ΔG_c rises. However, the quantity $(1 - \xi)$ is not the sole determinant of ΔG_c . The size of the molecules determines the length scale of the liquid and thus the size of the pieces in which the empty space is partitioned. For a given ξ , the smaller the solvent molecules, the smaller the pieces in which the empty space is divided and the smaller the fraction of the empty volume that is actually available for solute insertion. In other words, more work has to be done to exclude solvent molecules from the region in space that should be occupied by the solute molecules.

Lucas³ and Lee,⁴ by recognizing these facts, pointed out that water is anomalous in having the smallest values of σ and ξ among all common solvents: $\sigma = 2.75$ Å and $\xi = 0.363$, with $v = 18.07$ cm³ mol^{−1},¹³ at 25 °C. Therefore, they concluded that ΔG_c is larger in water because water molecules are smaller

than other solvent molecules (the size of a water molecule should correspond to that of an oxygen atom).

Kodaka,¹ however, emphasized that even though ΔG_c seems to depend on σ and ξ the latter quantity is actually a function of the internal pressure, P_{int} , of the solvent (see the solid curves in Figure 2 of L). In general, $P_{\text{int}} = (\partial U/\partial V)_T$, and for nonpolar liquids, P_{int} practically corresponds to the cohesive energy density (*ced*),^{14,15} which is the ratio of the internal energy change upon vaporization to the molar volume of the liquid, $\text{ced} = (\Delta_{\text{vap}}H - RT)/v$. Kodaka pointed out that, for homologous series of nonpolar liquids, σ and P_{int} are independent of each other on the basis of the independence of the experimental P_{int} values with regard to the molecular weight of cycloalkanes (see Figure 1 in L). Then he suggested that σ and P_{int} should be better variables than σ and ξ in analyzing the SPT formula of ΔG_c , implicitly claiming that σ and P_{int} are independent of each other for all liquids. Calculations using the SPT equation of state to evaluate P_{int} showed that the two variables act in the same direction: for a given P_{int} , ΔG_c rises on increasing σ , and for a given σ , ΔG_c rises on increasing P_{int} . Because water has the smallest value of σ and the greatest value of P_{int} among those of all common solvents (note that he did not refer to the experimental values of P_{int} but to those calculated using the SPT equation of state, eq 4 in L), it is the great value of P_{int} that renders ΔG_c so large in water. Then, by considering $P_{\text{int}} \cong \text{ced}$ also in the case of water, which is a strongly polar liquid, Kodaka took the final step. Because the large *ced* of water is due to the presence of strong H-bonds with respect to weak van der Waals interactions, Kodaka concluded that the strength of the H-bonds should be the ultimate cause of hydrophobicity (note, however, that the large *ced* of water is in part due to the small molar volume of this liquid, which is strictly related to the small size of its molecules).

The line of reasoning followed by Kodaka is not very transparent, probably because of the conciseness of his work. I suggest a possible step-by-step way to analyze his arguments and to point out the conceptual flaws. First, σ and P_{int} are not independent of each other for all liquids; the sizes of the molecules depend on the types of interactions in which they are involved. Second, one cannot assume that $P_{\text{int}} \cong \text{ced}$ for all liquids. Third, it is not correct to consider the pressure calculated using the SPT equation of state, P_h , to be equal to P_{int} and, in turn, to *ced* of a real liquid. Fourth, the role played by H-bonds in determining the magnitude of ΔG_c is derived in an indirect manner that cannot be considered reliable or accepted. We will develop these arguments in the following discussion by using available experimental data.

The values of σ , v , ξ , $\Delta_{\text{vap}}H$, and *ced* at 25 °C for several liquids are collected in Table 1. The ξ values listed in Table 1 are larger than those shown in Figure 2 of L because Kodaka used the σ values determined by Reiss,² which are smaller than those determined by Wilhelm and Battino.^{16,17} The latter should be preferred because they have been extracted from gas solubility data by means of a consistent and robust procedure. The values of *ced* agree well with those reported by Dack.¹⁵ The SPT estimates of ΔG_c to create a cavity of 5.0-Å diameter at 25 °C in the same liquids are listed in the last column of

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TABLE 1: Values of σ , v , ξ , $\Delta_{\text{vap}}H$, and ced at 25 °C for Several Liquids^a

	σ , Å	v , cm ³ mol ⁻¹	ξ	$\Delta_{\text{vap}}H$, kJ mol ⁻¹	ced , atm	ΔG_c , kJ mol ⁻¹
<i>n</i> -hexane	5.92	131.62	0.497	31.6	2184	20.9
<i>n</i> -heptane	6.25	147.46	0.522	36.6	2284	22.0
cyclohexane	5.63	108.75	0.517	33.0	2770	25.2
benzene	5.26	89.41	0.513	33.8	3437	27.5
toluene	5.64	106.86	0.529	38.0	3281	26.9
carbon tetrachloride	5.37	97.09	0.503	32.8	3082	25.2
carbon disulfide	4.53	60.65	0.483	27.5	4125	29.6
acetone	4.76	74.01	0.459	31.0	3803	24.0
dimethyl sulfoxide	4.91	71.37	0.523	52.9	6972	32.5
water	2.75	18.07	0.363	43.9	22623	34.8
methanol	3.69	40.73	0.389	37.8	8559	24.6
ethanol	4.34	58.68	0.439	42.5	6731	24.9
2-methyl-1-propanol	5.29	92.88	0.503	50.8	5134	25.8
cyclohexanol	5.75	105.94	0.566	62.0	5545	32.2
ethylene glycol	4.36	55.98	0.467	67.8	11669	28.9
hydrazine	3.62	31.94	0.468	44.8	13077	39.6

^a All of the values of σ , v , and ξ come from ref 16, except those of carbon disulfide (ref 6), water (ref 12), and ethylene glycol (ref 23b); the values of $\Delta_{\text{vap}}H$ come from ref 29 for the first six liquids; ref 30 for water and hydrazine; ref 31 for methanol and ethanol; ref 32 for 2-methyl-1-propanol and cyclohexanol; ref 33 for carbon disulfide, acetone, and dimethyl sulfoxide; and ref 34 for ethylene glycol. Values for ced have been calculated using the relation $ced = (\Delta_{\text{vap}}H - RT)/v$. In addition, the SPT estimates of ΔG_c to create a cavity of 5.0-Å diameter at 25 °C in such liquids are listed in the last column.

Table 1. Such a cavity diameter has been selected solely to elucidate the differences among the various solvents; the results are qualitatively similar for other cavity diameters. The SPT calculations were performed using the equation reported in ref 6, with the pressure equal to 1 atm, as suggested by Pierotti,¹² Stillinger,¹⁸ and others.¹⁹

Let us consider the first point. The van der Waals diameter of an oxygen atom is 3.16 Å;²⁰ this number is greater than the effective size of a water molecule, 2.75 Å, as extracted from gas solubility data^{12,17} and determined from the first maximum in the oxygen–oxygen radial distribution function of liquid water at room temperature, which was obtained from both X-ray and neutron scattering experiments.²¹ This happens because the H-bonds, because of their strength, are able to keep the molecules closer than their van der Waals dimensions. This point was well emphasized by the computer simulation results of Madan and Lee.²² Such a situation occurs also in the case of methanol and ethanol. For CH₃OH, the van der Waals diameter is 4.10 Å,²³ whereas the effective diameter $\sigma = 3.69$ Å; for C₂H₅OH, the van der Waals diameter is 4.66 Å,²³ whereas the effective diameter $\sigma = 4.34$ Å (note that the effective diameter σ of methanol and ethanol correspond to those of methane and ethane, respectively¹⁶). Even though the alcohol molecules are not spheres, the σ values extracted from gas solubility data agree with the distance at which the first peak of the respective radial distribution functions obtained from X-ray scattering experiments occurs.²⁴ Therefore, the H-bonds render the interacting molecules significantly smaller than expected on the basis of van der Waals dimensions. To the extent that $P_{\text{int}} \cong ced$, such a result contrasts with Kodaka's claim that P_{int} and σ are independent of each other for all liquids. The molecules considered in Figure 1 of L are all examples of what Kodaka classified as type b solvents—liquids with weak intermolecular interactions. The above analysis emphasizes that σ cannot be considered independent of ced in liquids with strong intermolecular interactions such as water. Thus, it is not legitimate to use σ and P_{int} as independent variables to explore the implications of the SPT equation of ΔG_c for H-bonded liquids.

TABLE 2: Values at 25 °C of the Thermal Expansion Coefficient, α , Isothermal Compressibility, β , Internal Pressure, $P_{\text{int}} = T\alpha/\beta$, P_h , and ced for the Same Liquids Listed in Table 1^a

	$\alpha \times 10^3$, K ⁻¹	$\beta \times 10^5$, atm ⁻¹	P_{int} , atm	P_h , atm	ced , atm
<i>n</i> -hexane	1.407	16.27	2578	2546	2184
<i>n</i> -heptane	1.276	14.43	2636	2725	2284
cyclohexane	1.214	11.55	3134	3300	2770
benzene	1.240	9.80	3773	4204	3437
toluene	1.086	9.34	3467	3959	3281
carbon tetrachloride	1.226	10.81	3381	3603	3082
carbon disulfide	1.170	9.86	3538	5005	4125
acetone	1.509	12.55	3585	3480	3803
dimethyl sulfoxide	0.880	5.32	4932	5672	6972
water	0.257	4.63	1655	7828	22 623
methanol	1.189	12.75	2780	4055	8559
ethanol	1.089	11.53	2816	3849	6731
2-methyl-1-propanol	1.1	7.80	4205	3769	5134
cyclohexanol	1.0	6.70	4450	5328	5545
ethylene glycol	0.663	3.77	5243	4863	11 669
hydrazine	0.893	2.54	10482	8572	13 077

^a The values of α come from refs 4, 6, 35, and 36 (those of 2-methyl-1-propanol and cyclohexanol have been estimated on the basis of data in ref 36); the values of β come from refs 2, 33, and 37. P_h is calculated by means of eq 4 in L using the σ and ξ values reported in Table 1.

Now we consider the second and third points. Kodaka calculated ΔG_c by considering ξ as a function of P_{int} (see eq 7 in L), and the latter was estimated by means of the SPT equation of state using the assumption that $P_{\text{int}} \cong P_h$ (see eqs 4 and 5 in L). Then he analyzed the results from the assumption that $P_{\text{int}} \cong ced$ (see eq 6 in L). In this respect, one has to consider the fact that ced , P_{int} , and P_h are different quantities; their equality cannot be taken for granted but should be verified for each liquid. The statistical mechanical relationships for ced and P_{int} reported by Dack¹⁵ indicate that the two quantities do not reflect the same physical property of the liquids (strictly, P_{int} should not be a component of ced).

To clarify the situation, the values of the three quantities at 25 °C are reported in Table 2 for the same liquids that are listed in Table 1. Although there is some agreement between the values of ced , P_{int} , and P_h for nonpolar liquids, there is no relationship between these quantities for H-bonded liquids. For instance, in the case of *n*-hexane, $ced = 2184$ atm, $P_{\text{int}} = 2578$ atm, and $P_h = 2546$ atm; in the case of benzene, $ced = 3437$ atm, $P_{\text{int}} = 3773$ atm, and $P_h = 4204$ atm. However, in the case of water, $ced = 22\,623$ atm, $P_{\text{int}} = 1655$ atm, and $P_h = 7828$ atm; in the case of methanol, $ced = 8559$ atm, $P_{\text{int}} = 2780$ atm, and $P_h = 4055$ atm. The differences between ced , P_{int} , and P_h are particularly striking in the case of water. (The difference between the first two quantities amounts to an order of magnitude!) The above numbers point out that the calculation procedure adopted by Kodaka (i.e., ΔG_c calculated using the SPT equation of state to relate ξ to P_h for the assumption that $P_h \cong P_{\text{int}} \cong ced$ for all liquids) cannot be considered reliable, especially for H-bonded liquids. Therefore, the behavior of the latter liquids, water in particular, with respect to ΔG_c cannot be rationalized by such an approach.

In addition, according to the SPT equation of state, on increasing σ and keeping ξ constant, P_h would decrease (see eq 4 in L). Thus, as σ is raised, P_h can be kept constant only by increasing ξ (see the solid curves in Figure 2 of L). Such an increase in ξ is the real cause of the increase in ΔG_c as σ is raised at constant P_h , as shown by the solid curves in Figure 3 of L. (Note that for Kodaka constant P_h means constant P_{int} and constant ced .) This is the technical explanation of the results obtained by Kodaka.

A comparison between the experimental values of ced and the SPT estimates of ΔG_c may be of further usefulness (see the last two columns of Table 1). Hydrazine has a ced that is significantly lower than that of water (13 077 atm vs 22 623 atm) but a ΔG_c that is significantly larger than that of water (i.e., to create a cavity of 5.0-Å diameter at 25 °C, $\Delta G_c = 39.6$ kJ mol⁻¹ in hydrazine and 34.8 kJ mol⁻¹ in water). This result is confirmed by the experimental finding that helium, argon, and nitrogen are less soluble in hydrazine than in water.²⁵ The work of cavity creation is very large in hydrazine because even though its molecules are larger than those of water ($\sigma = 3.62$ Å) and its ced is smaller, its packing density is high ($\xi = 0.468$, close to that of large hydrocarbons). Similarly, ΔG_c is larger in dimethyl sulfoxide than in ethylene glycol (32.5 vs 28.9 kJ mol⁻¹) even though the former liquid has a ced that is lower than that of the latter (6972 vs 11 669 atm). The same situation occurs for the couples benzene and toluene versus methanol and ethanol (see Table 1). The ced values of benzene and toluene are half of those of methanol and ethanol, but the ΔG_c estimates in the former liquids are larger than those in the latter ones. Therefore, it is not true that a large ced , or the presence of H-bonds, implies large ΔG_c values, as claimed by Kodaka.

We consider now the fourth point. Because there are no relationships among ced , P_{int} , and P_h in the case of water, the role of H-bonds in determining the large positive ΔG_c in water cannot be addressed by Kodaka's approach. In addition, the experimental values of P_{int} and ced of water are the smallest and the largest, respectively, among those reported in Table 2. (This is also true for the values compiled by Dack.¹⁵) Kodaka claimed, on the basis of the solid curves reported in Figure 2 of L, that the ξ value of water (0.363 at 25 °C) has to be considered large in view of the small size of water molecules, which is a consequence of the large ced of liquid water (always with the wrong assumption that $P_h \cong P_{int} \cong ced$ for all liquids). He expects that if water had a lower ced ξ would be smaller than 0.25 and ΔG_c would be smaller than in the other solvents. Kodaka explicitly wrote "Water would never give large positive ΔG_c if it had smaller ced (viz., lower packing density)." In other words, if the H-bonds were turned off, water would not be hydrophobic. However, this notion requires closer scrutiny.

One can try to single out the role played by H-bonds in determining the large positive ΔG_c in water by studying what happens on removing the H-bonds. This thought experiment, however, has to be done with care. Water would not be in the liquid state if the H-bonds were turned off, and hypothetical water without H-bonds would have to be under high pressure to behave as a liquid. Thus, the H-bonds should be turned off by keeping the volume of the system fixed to preserve the number density of real water. The latter is a fundamental requirement because ΔG_c is exactly related by a statistical mechanical equation to the probability that the region in space of interest is devoid of solvent molecules.^{2,6} In contrast, by using eq 7 even for water, Kodaka effectively turns off the H-bonds by keeping the pressure of the system low so as to maintain the validity of the assumption of eq 5. In this manner, the volume of the system would increase, and the number density would decrease toward that of a gas. (Consider that for water the ϵ parameter value in the Lennard-Jones potential is smaller than that of argon.⁶)

A system having $\xi < 0.25$ is not in the liquid state, as can be shown using the values of σ and ν listed in Table 1. Common organic solvents in which the H-bonds are absent or do not play a dominant role have $\xi \cong 0.50$ at 25 °C (half of the molar volume is empty). This result is consistent with the observations

that²⁶ (a) no organic crystals have $\xi < 0.65$ and (b) a volume expansion of about 10% occurs on melting. Water, methanol, and ethanol have the lowest ξ values because of their strongly directional H-bonds, but their ξ values are still significantly larger than 0.25. It seems grossly inappropriate to compare liquid water with a system having $\xi < 0.25$, as Kodaka suggests, because only a gaseous system can be made to have a packing density as low as 0.25.

Therefore, because the H-bonds should be turned off by keeping the volume of the system fixed, the molar volume of water would not change, and σ would increase up to the van der Waals diameter of an oxygen atom. At 25 °C, whereas real water has $\sigma = 2.75$ Å, $\nu = 18.07$ cm³ mol⁻¹, and $\xi = 0.363$, hypothetical water without H-bonds would have $\sigma = 3.16$ Å, $\nu = 18.07$ cm³ mol⁻¹, and $\xi = 0.551$. Such hypothetical water, with ξ close to that of common liquids, would be "dense". (This is what Madan and Lee²² found in their computer simulations on passing from TIP4P water to the corresponding Lennard-Jones liquid.)

Another possibility that would preserve the number density of liquid water without increasing the pressure would be to remove the H-bonds by increasing the ϵ parameter of water molecules in the Lennard-Jones potential so as to have a ced close to that of common nonpolar liquids (i.e., the procedure adopted by Pratt and Pohorille²⁷ in their computer simulations). What would be the molecular size and molar volume of such a liquid? We have pointed out that H-bonds render the interacting molecules smaller, thus σ should increase upon their removal. However, it can be simply shown that the molar volume of a liquid does not depend significantly upon the nature of the intermolecular interactions.²⁸ Consider, for instance, that a mole of particles having the size of an oxygen atom ($\sigma = 3.16$ Å) and the volume packing density of common liquids at room temperature ($\xi = 0.51$) would occupy a volume of 19.5 cm³. The latter number is close to the experimental molar volume of water at 25 °C. Therefore, in this case, the hypothetical water without H-bonds would also be dense.

The important result is that ΔG_c would be larger in the hypothetical dense water than in the real water. For instance, to create a cavity of 5.0-Å diameter at 25 °C, $\Delta G_c = 34.8$ kJ mol⁻¹ when $\sigma = 2.75$ Å and $\xi = 0.363$, but $\Delta G_c = 81.3$ kJ mol⁻¹ when $\sigma = 3.16$ Å and $\xi = 0.551$. This comparison, in conjunction with the ΔG_c estimates for the other solvents reported in the last column of Table 1, confirms the fundamental role played by the small size of water molecules in contrast to the H-bonds in determining the large positive ΔG_c values. Actually, the bunching-up effect due to H-bonds causes an increase in the empty space into which a molecular-sized cavity can be inserted. One could therefore say that the H-bonds reduce ξ and cause a decrease in ΔG_c , thus favoring the transfer of a nonpolar molecule from the gas phase to water. Such a conclusion was previously reached by Lee⁴ and does not agree with Kodaka's arguments.

In conclusion, the present analysis confirms the assertion that σ and ξ are the correct variables to use to analyze the SPT formula of ΔG_c because they represent the length scale and the occupied space of the liquid, respectively (i.e., the two features that determine the probability of cavity occurrence). In addition, it is re-stated that ΔG_c is larger in water than in other common solvents because of the smallness of the water molecules themselves, as originally claimed by Lucas and Lee.

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- (28) Considering that a water molecule contains 3 atoms whereas a cyclohexane molecule contains 18 atoms, one could estimate that v of the latter is 6 times that of the former. In fact, $6(18.07) = 108.42 \text{ cm}^3 \text{ mol}^{-1}$ against $108.75 \text{ cm}^3 \text{ mol}^{-1}$ at 25°C . In the case of *n*-heptane, one obtains $(^{23}/_3)18.07 = 138.54 \text{ cm}^3 \text{ mol}^{-1}$ against $147.46 \text{ cm}^3 \text{ mol}^{-1}$ at 25°C . Similarly, considering that a methanol molecule contains 6 atoms whereas a *n*-hexane molecule contains 20 atoms, one obtains $(^{20}/_6)40.73 = 135.77 \text{ cm}^3 \text{ mol}^{-1}$ against $131.62 \text{ cm}^3 \text{ mol}^{-1}$ at 25°C . In the case of benzene, the result is $2(40.73) = 81.46 \text{ cm}^3 \text{ mol}^{-1}$ against $89.41 \text{ cm}^3 \text{ mol}^{-1}$ at 25°C ; in the case of toluene, the result is $(2.5)(40.73) = 101.83 \text{ cm}^3 \text{ mol}^{-1}$ against $106.86 \text{ cm}^3 \text{ mol}^{-1}$ at 25°C . An additivity principle appears to hold for v regardless of what interactions exist among the molecules in the liquid state. This simple approach demonstrates that H-bonds do not significantly affect the molar volume.
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