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A van der Waals Model of Solvation Thermodynamics

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Abstract: Exploiting the van der Waals model of liquids, it is possible to derive analytical formulas for the thermodynamic functions governing solvation, the transfer of a solute molecule from a fixed position in the ideal gas phase to a fixed position in the liquid phase. The solvation Gibbs free energy change consists of two contributions: (a) the high number density of all liquids and the repulsive interactions due to the basic fact that each molecule has its own body lead to the need of spending free energy to create a cavity suitable to host the solute molecule; (b) the ubiquitous intermolecular attractive interactions lead to a gain in free energy for turning on attractions between the solute molecule and surrounding liquid molecules. Also the solvation entropy change consists of two contributions: (a) there is an entropy loss in all liquids because the cavity presence limits the space accessible to liquid molecules during their continuous translations; (b) there is an entropy gain in all liquids, at room temperature, due to the liquid structural reorganization as a response to the perturbation represented by solute insertion. The latter entropy contribution proves to be balanced by a corresponding enthalpy term. This scenario emerged from the van der Waals model is in qualitative agreement with experimental results.

Keywords: van der Waals model of liquids; solvation; number density; molecular size; repulsive and attractive interactions

1. Introduction

Water and aqueous solutions play a fundamental role on the Earth and for living organisms. All the biochemical processes occur in aqueous solutions, taking advantage of the extraordinary properties of water [1,2]. For instance, the ability of polypeptide chains to fold and assume a unique 3D structure, the native, functionally active one, is strictly connected to the gain in translational entropy of water molecules for the increase in accessible configurational space associated with chain collapse [3]. The quantitative study, by both experimental approaches and theoretical methods, of phenomena related to the hydrophobic effect pointed out the need of a profound change in the way to analyze data in order to arrive at correctly defined thermodynamic quantities [1]. Most of the needed work has been done by Arieh Ben-Naim, as it can readily be recognized on looking at the three books he published in 1974, 1980 and 1987 [4–6]. Following the Ben-Naim's statistical mechanical analysis, solvation refers to the transfer of a solute molecule from a fixed position in the ideal gas phase to a fixed position in the liquid phase (the latter can be a pure liquid or a solution, without restrictions on the concentration of the components). The transfer of a species from a liquid to another liquid is defined in the same way. This definition allows the elimination of the effects coming from the difference in molar volume of the two phases, that can be large [7,8] (i.e., for the transfer from the ideal gas phase to water, the Gibbs free energy contribution coming from the simple difference in molar volume amounts to 17.87 kJ mol^{-1}, at 25 °C and 1 atm; for the transfer from n-hexane to water, it amounts to 4.92 kJ mol^{-1} at 25 °C and 1 atm). Ben-Naim showed that the effects due to the difference in molar volume and thermal motion can be eliminated not only in theoretical approaches, but also in analyzing experimental data by simply using the molar concentration scale [5,6].

Now the use of the so-called Ben-Naim standard is almost universally accepted, but, at the beginning, several scientists raised a lot of concerns. In particular, in the nineties, it was erroneously claimed that a volume correction term should be added to the transfer Gibbs free energy values based on the molar concentration scale [9–12]. In retrospect, these erroneous claims were motivated by a wrong understanding of the deep analysis performed by Ben-Naim [13–16].

In the present study, we want to use the van der Waals model of real gases and liquids to develop a statistical mechanical approach to solvation thermodynamics. In 1873, in his PhD thesis, van der Waals proposed the famous and successful equation of state, named after him [17]. He was able to account in a very simple manner of: (1) the volume possessed by each molecule that leads to the non-accessibility of the space occupied by the other molecules, as a consequence of strongly repulsive and short-ranged intermolecular interactions; (2) the long-ranged intermolecular energetic attractions. These two corrections take the form of the two van der Waals constants: the repulsive one, b, and the attractive one, a, which are specific for each chemical species. The van der Waals equation of state, even though very simple, is able to describe the gas-liquid phase transition, to reproduce the existence of the critical point and of the law of corresponding states, and to lead to a virial series expansion [18,19]. The van der Waals model is correct from a qualitative point of view, not from the quantitative one. It may be useful to describe solvation thermodynamics because the treatment is entirely analytic [20–22], and the various formulas have a transparent physical meaning.

2. A van der Waals Binary Solution

In all this study, we consider monoatomic particles to eliminate the subtleties associated with the presence of internal degrees of freedom. The canonical partition function for a binary solution of monoatomic van der Waals fluids is given by **[20,21]**:

$$Q(N_1,N_2,V,T) = [V^{(N1+N2)}/N_1!\Lambda_1^{3N1}\cdot N_2!\Lambda_2^{3N2}]\cdot[V - (b_1N_1+b_2N_2)/V]^{(N1+N2)}\cdot \exp[(a_1N_1+a_2N_2)^2/kTV] \quad (1)$$

where V is the volume of the system; $\Lambda_i \equiv h/(2\pi m_i kT)^{1/2}$ is the thermal de Broglie wavelength of particles i; N_i is the number of particles i; the parameter b_i measures the repulsive interactions of particles i, and the parameter a_i measures the attractive interactions of particles i (i.e., a_i and b_i are positive and constant, because they are considered to be temperature-independent); *k* is the Boltzmann constant and T is the absolute temperature. The quantity $[V - (b_1N_1+b_2N_2)]$ represents the free volume of the system, and, according to van der Waals, the particles move independently of one another in this volume, where there is a constant attractive potential energy given by $-(a_1N_1+a_2N_2)^2/V$ (i.e., the absence of a potential energy gradient implies the absence of attractive intermolecular forces). Knowledge of the canonical partition function allows the straightforward calculation of the Helmholtz free energy, and then of the chemical potential of component 2 in the solution:

$$\mu_2 \equiv (\partial A/\partial N_2)_{T,V,N1} \quad (2)$$

Performing the calculations, one arrives at [**21**]:

$$\mu_2(vdW) = kT\cdot\ln\varrho_2\Lambda_2^3 - kT\cdot\ln[V-(b_1N_1+b_2N_2)/V] + kT\cdot\{(N_1+N_2)b_2/[V-(b_1N_1+b_2N_2)]\} + - 2a_2(a_1N_1+a_2N_2)/V \quad (3)$$

where $\varrho_2 = N_2/V$ is the number density of component 2. Equation (3) represents the chemical potential of component 2 in a binary solution of monoatomic van der Waals fluids. The expression indicates that the classical translational degrees of freedom are separated from the terms accounting for all the interactions of a component 2 particle with the surroundings. Therefore, the chemical potential can be rewritten as:

$$\mu_2(vdW) = kT\cdot\ln \varrho_2\Lambda_2^3 + \mu_2^\bullet \quad (4)$$

where $\mu_2^\bullet$ is the so-called Ben-Naim standard chemical potential (Ben-Naim standard quantities are denoted by a superscript filled circle); it represents the coupling work of the solute molecule to the solution, or the interaction free energy of a component 2 particle, fixed at any position in the solution, with its entire surroundings, with no restriction on the solute concentration. This interpretation comes directly from the statistical mechanical derivation. There is no need to define a standard state, in contrast to what happens in the framework of classical thermodynamics. The quantity $\mu_2^\bullet$ depends upon the composition of the solution, exactly because the coupling work changes with the composition of the solution **[6–8]**. This is a fundamental feature of the so-called Ben-Naim standard chemical potential in order to address the role of solvation thermodynamics in basic biochemical processes, such as protein folding, protein-protein and protein-DNA recognition because the latter occur in crowded media [**23**].

It is well established that the chemical potential of the monoatomic component 2 in the ideal gas phase is [**19**]:

$$\mu_2(ig) = \mathrm{kT}\cdot\ln\varrho_2\Lambda_2^3 \tag{5}$$

Solely the classical translational degrees of freedom contribute to $\mu_2(ig)$ because there are no interactions among molecules, and so $\mu_2^\bullet = 0$. Statistical thermodynamics unequivocally indicates that the number density is the concentration unit to be used in the chemical potential formulas.

3. Solvation Thermodynamics

The knowledge of the chemical potential of the component 2 in the van der Waals binary solution and in the ideal gas phase allows us to study solvation thermodynamics, in the assumption that the van der Waals binary solution represents the liquid state. At thermodynamic equilibrium, the chemical potential of the component 2 has to be the same in the two phases:

$$\mu_2(ig) = \mu_2(vdW) \tag{6}$$

The use of Eqs (4) and (5) into Eq. (6) leads to:

$$k\mathrm{T}\cdot\ln\varrho_2(ig)\cdot\Lambda_2^3 = \mu_2^\bullet(vdW) + k\mathrm{T}\cdot\ln\varrho_2(vdW)\cdot\Lambda_2^3 \tag{7}$$

The de Broglie wavelength term is identical in the two phases and cancels out, and one has:

$$\Delta G^\bullet = \mu_2^\bullet(vdW) = k\mathrm{T}\cdot\ln[\varrho_2(ig)/\varrho_2(vdW)] \tag{8}$$

where $\Delta G^\bullet$ is the Ben-Naim standard Gibbs free energy change associated with the solvation process. The first equality on the right-hand-side of Eq. (8) shows that $\Delta G^\bullet$ is given by the solute-solvent coupling work; the second equality on the right-hand-side of Eq. (8) shows that the ratio of the number densities of component 2 in the two phases allows the evaluation of the Gibbs free energy change associated with the transfer from a fixed position in the ideal gas to a fixed position in the liquid, at constant temperature and pressure (i.e., $\Delta G^\bullet$ values are readily obtained from experimental data) **[6,7]**.

Now we consider an infinitely dilute solution of the component 2 in the monoatomic van der Waals fluid 1. The $\Delta G^\bullet$ expression is readily obtained by making the limit in Eq. (3), noting that for $N_2 \rightarrow 0$, $N \cong N_1$ and $V \cong N_1 v_1$, where v_1 is the molecular volume of component 1. Thus, $\Delta G^\bullet$ is given by [**21**]:

$$\Delta G^\bullet = \mu_2^\bullet(vdW) = -\,k\mathrm{T}\cdot\ln[(v_1 - b_1)/v_1] + k\mathrm{T}\cdot[b_2/(v_1 - b_1)] - 2(a_1 a_2/v_1) \tag{9}$$

To make a step forward, it is mandatory to assign a physical meaning to the contributions making up Eq. (9). The first two represent the reversible work to create a cavity suitable to host the component 2 particle in the monoatomic van der Waals fluid 1:

$$\Delta G_C(vdW) = -k\mathrm{T}\cdot\ln[(v_1 - b_1)/v_1] + k\mathrm{T}\cdot[b_2/(v_1 - b_1)] \tag{10}$$

In fact, one has:

$$-k\mathrm{T}\cdot\ln[(v_1 - b_1)/v_1] = -k\mathrm{T}\cdot\ln[(v_{1,free})/v_1] = -k\mathrm{T}\cdot\ln(1 - \xi_1) \tag{11}$$

$$k\mathrm{T}\cdot[b_2/(v_1 - b_1)] \cong P(vdW)\cdot b_2 \tag{12}$$

where Eq. (11) represents the decrease in the configurational space useful to insert the component 2 particle (note that ξ_1 is the volume packing density of fluid 1), and Eq. (12) represents the pressure-volume work done to insert the component 2 particle in the van der Waals fluid 1. They should correspond to the first and fourth terms in the ΔG_C formula provided by the classic scaled particle theory **[24,25]**. The latter accounts for the mutual correlations among the positions occupied by individual particles, in order to fulfill the non-overlap requirement holding in real liquids, and so works quantitatively better than Eq. (10).

On the other hand, according to the physical meaning of the parameters a_1 and a_2, the third term on the right-hand-side of Eq. (9) is the average interaction Gibbs free energy of the component 2 particle with all the particles of the van der Waals fluid 1:

$$\Delta G_a(\mathrm{vdW}) = -2a_1a_2/v_1 \qquad (13)$$

Equation (9) confirms that the solvation process can be decomposed in two sub-processes [4–7,24–29]: (a) creation of a cavity in the liquid, suitable to host the solute molecule; (b) turning-on the solute-solvent attractive potential. Both the solvent-excluded volume effect due to the finite size of real molecules, and the attractive interactions due to the charge distribution of real molecules play a role in solvation [4–7], and are accounted for by the quantity $\Delta G^{\bullet}$, as obtained in the van der Waals model [20,21].

We can calculate the enthalpy and entropy contributions associated with the two sub-processes, under the constant pressure condition **[21]**. For the cavity creation step, one readily obtains:

$$\Delta H_C = -T^2[\partial(\Delta G_C/T)/\partial T] = kT^2[\alpha_{P,1}/(v_1-b_1)]\cdot\{b_1+ [v_1b_2/(v_1-b_1)]\} \qquad (14)$$

$$\Delta S_C = -(\partial\Delta G_C/\partial T) = k\cdot\ln[(v_1-b_1)/v_1] - k\cdot[b_2/(v_1-b_1)] + (\Delta H_C/T) =$$
$$= \Delta S_X + (\Delta H_C/T) \qquad (15)$$

where $\Delta S_X = -\Delta G_C/T$, and represents the solvent-excluded volume entropy contribution due to cavity creation; and $\alpha_{P,1}$ is the isobaric thermal expansion coefficient of the van der Waals fluid 1. A liquid structural reorganization occurs upon cavity creation; this contribution is directly proportional to $\alpha_{P,1}$, and affects the enthalpy and entropy changes in a totally compensating manner. The creation of a cavity, under NPT conditions, causes a small change in the volume of the system, which, in turn, determines an enthalpy change (remember that the internal energy of a van der Waals fluid is inversely proportional to the volume). This enthalpy change has to come from the liquid structural reorganization since there is no other source, and is totally balanced by a corresponding entropy change; look at Eq. (14) and Eq. (15). For the attractive potential turning-on step, one obtains:

$$\Delta H_a = -T^2[\partial(\Delta G_a/T)/\partial T] = -(2a_1a_2/v_1)\cdot(1+\alpha_{P,1}T) \qquad (16)$$

$$\Delta S_a = -(\partial\Delta G_a/\partial T) = -2a_1a_2\alpha_{P,1}/v_1 \qquad (17)$$

where again the liquid structural reorganization upon turning-on the solute-solvent attractive potential proves to be directly proportional to $\alpha_{P,1}$, and to affect the enthalpy and entropy changes in a totally compensating manner. The finding that the liquid structural reorganization is proportional to the isobaric thermal expansion coefficient of the liquid is reliable because α_P is a measure of the ensemble correlations between enthalpy fluctuations and volume fluctuations: $\alpha_P \equiv \langle\delta H\cdot\delta V\rangle/kT^2\langle V\rangle$, where $\delta H = H - \langle H\rangle$ and $\delta V = V - \langle V\rangle$ represent the enthalpy and volume fluctuations with respect to their ensemble average values [19].

Such results are in line with the analysis by Qian and Hopfield aimed at explaining the occurrence of enthalpy-entropy compensation in many processes **[30]**. They showed that the action of a small perturbation on a thermodynamic system can be dissected into two contributions: a direct interaction between the perturbation and the unperturbed system; and a response of the system by means of a redistribution among its subsystems, which are in thermal equilibrium, following the Le Chatelier principle. The redistribution is ruled by the environmental constraints applied to the system, or better by the microscopic fluctuations that the thermodynamic system can make. A perfect enthalpy-entropy compensation holds for that redistribution, and the Gibbs free energy change comes from the direct interaction between the perturbation and the unperturbed system. For the solvation process, the perturbation is represented by the insertion of the solute molecule at a fixed position into the solvent. The direct part of the perturbation consists of both cavity creation and turning on solute-solvent attractive potential; the liquid structural reorganization is the system's response to the direct perturbation.

4. Some Calculations

It may be instructive to make some calculations with the van der Waals model of solvation thermodynamics. In particular, we calculate the reversible work to create a cavity suitable to host a xenon atom (i.e., its van der Waals diameter $\sigma = 4$ Å) in water, c-hexane and benzene, at 25 °C and 1 atm. This choice is dictated by the understanding that it is the cavity creation step to distinguish water from the other common liquids **[4,7,25,27]**. To perform calculations it is necessary to modify Eq. (10), passing to molar quantities and rearranging the terms **[22]**:

$$\Delta G_C(\mathrm{vdW}) = -RT \cdot \ln(1 - \varrho_1 b_1) + RT \cdot [\varrho_1 b_2/(1 - \varrho_1 b_1)] \qquad (18)$$

where $\varrho_1 = N_{Av}/v_1$ is the liquid number density, v_1 is its molar volume, $b_i = (\pi \cdot \sigma_i^3/6)/0.64$, σ_i is the effective hard sphere diameter of liquid molecules or of the solute particle, and the factor 0.64 in the denominator accounts for the basic fact that the random close packing of spheres corresponds to 64% of system volume occupancy **[31]**. The cavity enthalpy and entropy changes, expressed as ΔG_C(vdW) in Eq. (18), are:

$$\Delta H_C(\mathrm{vdW}) = RT^2 \cdot \alpha_{P,1} \cdot [\varrho_1/(1 - \varrho_1 b_1)] \cdot \{b_1 + [b_2/(1 - \varrho_1 b_1)]\} \qquad (19)$$

$$\Delta S_C(\mathrm{vdW}) = R \cdot \ln(1 - \varrho_1 b_1) - R \cdot [\varrho_1 b_2/(1 - \varrho_1 b_1)] + \Delta H_C(\mathrm{vdW})/T \qquad (20)$$

To perform calculations, we have used the experimental values of v_1 and $\alpha_{P,1}$ for the three liquids, and their effective hard sphere molecular diameters **[32]** (see the 2-4 columns of Table 1). The calculated values are reported in the 5-9 columns of Table 1. It results that: (a) the ΔG_C(vdW) value in water is significantly larger than in c-hexane and benzene; (b) the reverse holds for ΔH_C(vdW); (c) the ΔS_C(vdW) value is large and negative in water, but small and positive in the two organic liquids.

Table 1. Effective diameters, and experimental values, at 25 °C and 1 atm, of the molar volume and isobaric thermal expansion coefficient for the three reported liquids [**32**]. Gibbs free energy change, enthalpy and entropy change for the creation in the three reported liquids of a cavity of 4 Å diameter, using the van der Waals model, Eqs (18)-(20).

	σ_1 Å	v_1 cm^3 mol^{-1}	$\alpha_{P,1} \cdot 10^3$ K^{-1}	ΔG_C kJ mol^{-1}	ΔH_C kJ mol^{-1}	ΔS_C J K^{-1}mol^{-1}	ΔS_X J K^{-1}mol^{-1}	$\Delta H_C/T$ J K^{-1}mol^{-1}
water	2.80	18.07	0.257	13.03	2.27	-36.1	-43.7	7.6
c-hexane	5.63	108.75	1.214	7.85	11.10	10.9	-26.3	37.2
benzene	5.26	89.40	1.240	8.43	11.62	10.7	-28.3	39.0

Since the calculations have been done in the same way, regardless of the liquid identity, the differences have to come from the physico-chemical properties of the three liquids. The ΔG_C(vdW) magnitude depends on the liquid number density, and water has the largest ϱ_1 value because it has the smallest molar volume, which reflects the very small diameter of water molecules **[32]**. The ΔS_C(vdW) formula consists of two contributions: (a) the first $\Delta S_X = -(\Delta G_C/T)$ is a measure of the solvent-excluded volume effect associated with cavity creation, and is always negative in all liquids; (b) the second $\Delta S_{nx} = (\Delta H_C/T)$ is a measure of the liquid structural reorganization upon cavity creation, is proportional to $\alpha_{P,1}$, and is always positive at room temperature in all liquids. The contribution of the liquid structural reorganization is larger in c-hexane and benzene than in water due to the $\alpha_{P,1}$ magnitude; in addition, it is able to overwhelm the ΔS_X contribution in the two organic liquids, rendering ΔS_C(vdW) positive. In contrast, the contribution of the liquid structural reorganization is not large in water, and cannot counterbalance the large and negative ΔS_X contribution, so that ΔS_C(vdW) is negative.

5. Conclusions

The present analysis and calculations emphasize that the van der Waals model of solvation works in a qualitatively correct manner because it recognizes the need, in liquid phases, to account for the short-ranged repulsive interactions that produce the solvent-excluded volume effect on solute insertion **[33,34]**. The latter, however, is treated in a rough manner, because the van der Waals model accounts only for the liquid free volume $(1 - \rho_1 b_1)$. The latter is a large quantity in real liquids (50-60% of the total volume), whereas the volume available to insert a molecular-sized cavity is smaller by orders of magnitude, because the non-overlap requirement has to be fulfilled **[35]**. A very small fraction of the entire free volume of a liquid is available for the insertion of a real solute (i.e., only the cavities large enough to accommodate the solute molecule). This reasoning emphasizes that the partitioning of the free volume is a fundamental property of a liquid that is not be accounted for by the van der Waals model. Anyway, the latter, using the experimental values of ρ_1 and $\alpha_{P,1}$, leads to a clear difference between water and the two organic liquids for the cavity entropy change, in line with scaled particle theory results **[7,25,27]**.

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Dedication by Giuseppe Graziano. The article is dedicated to Arieh Ben-Naim in the occasion of his ninethieth birthday; Arieh was born July 11, 1934 in Jerusalem and is still very active. I think that the book "Water and Aqueous Solutions. An Introduction to a Molecular Theory", published by Ben-Naim in 1974, has had a profound impact on all those interested in water and the hydrophobic effect. Of course, over the years, he did other important contributions to solvation thermodynamics. His lasting friendship is an honor to me.

References

1. Blokzijl, W.; Engberts, J.B.F.N. Hydrophobic Effects. Opinions and Facts. *Angewandte Chemie International Edition in English* **1993**, *32*, 1545–1579, doi:10.1002/anie.199315451.
2. Ball, P. Water as an Active Constituent in Cell Biology. *Chem. Rev.* **2008**, *108*, 74–108, doi:10.1021/cr068037a.
3. Merlino, A.; Pontillo, N.; Graziano, G. A Driving Force for Polypeptide and Protein Collapse. *Phys. Chem. Chem. Phys.* **2016**, *19*, 751–756, doi:10.1039/C6CP07397B.
4. Ben-Naim, A. *Water and Aqueous Solutions*; Springer US: Boston, MA, 1974; ISBN 978-1-4615-8704-0.
5. Ben-Naim, A. *Hydrophobic Interactions*; Springer US: Boston, MA, 1980; ISBN 978-1-4684-3547-4.
6. Ben-Naim, A. *Solvation Thermodynamics*; Springer US: Boston, MA, 1987; ISBN 978-1-4757-6552-6.
7. Lee, B. Solvent Reorganization Contribution to the Transfer Thermodynamics of Small Nonpolar Molecules. *Biopolymers* **1991**, *31*, 993–1008, doi:10.1002/bip.360310809.
8. Lee, B. [25] Analyzing Solvent Reorganization and Hydrophobicity. In *Methods in Enzymology*; Energetics of Biological Macromolecules; Academic Press, 1995; Vol. 259, pp. 555–576.
9. Sharp, K.A.; Nicholls, A.; Fine, R.F.; Honig, B. Reconciling the Magnitude of the Microscopic and Macroscopic Hydrophobic Effects. *Science* **1991**, *252*, 106–109, doi:10.1126/science.2011744.
10. Sharp, K.A.; Kumar, S.; Rossky, P.J.; Friedman, R.A.; Honig, B. Size Dependence of Transfer Free Energies. 2. Hard Sphere Models. *J. Phys. Chem.* **1996**, *100*, 14166–14177, doi:10.1021/jp960668t.
11. De Young, L.R.; Dill, K.A. Partitioning of Nonpolar Solutes into Bilayers and Amorphous N-Alkanes. *J. Phys. Chem.* **1990**, *94*, 801–809, doi:10.1021/j100365a054.
12. Chan, H.S.; Dill, K.A. Solvation: Effects of Molecular Size and Shape. *The Journal of Chemical Physics* **1994**, *101*, 7007–7026, doi:10.1063/1.468327.
13. Ben-Naim, A.; Mazo, R.M. Size Dependence of the Solvation Free Energies of Large Solutes. *J. Phys. Chem.* **1993**, *97*, 10829–10834, doi:10.1021/j100143a050.
14. Ben-Naim, A. Solvation of Large Molecules: Some Exact Results on the Dependence on Volume and Surface Area of the Solute. *Biophysical Chemistry* **1994**, *51*, 203–216, doi:10.1016/0301-4622(94)00041-7.
15. Ben-Naim, A.; Mazo, R. Size Dependence of Solvation Gibbs Energies: A Critique and a Rebuttal of Some Recent Publications. *J. Phys. Chem. B* **1997**, *101*, 11221–11225, doi:10.1021/jp970257s.

16. Graziano, G. On the Partitioning of Benzene between Water and *n*-Alkanes. *Chemical Physics Letters* **2010**, *486*, 44–47, doi:10.1016/j.cplett.2009.12.086.
17. J.D. van der Waals, On the continuity of the gaseous and liquid states, PhD Thesis, Leiden University, 1873.
18. T.H. Hill, *Introduction to Statistical Thermodynamics*, Addison-Wesley, Reading, 1960.
19. McQuarrie, D. *Statistical Mechanics*, Harper & Row, New York, NY, USA, 1976.
20. Ashbaugh, H.S.; Truskett, T.M.; Debenedetti, P.G. A Simple Molecular Thermodynamic Theory of Hydrophobic Hydration. *The Journal of Chemical Physics* **2002**, *116*, 2907–2921, doi:10.1063/1.1436479.
21. Graziano, G. Solvation Thermodynamics in a van Der Waals Liquid. *Thermochimica Acta* **2003**, *399*, 181–187, doi:10.1016/S0040-6031(02)00457-4.
22. Graziano, G. A van Der Waals Approach to the Entropy Convergence Phenomenon. *Phys. Chem. Chem. Phys.* **2004**, *6*, 406, doi:10.1039/b313021e.
23. Lee, B. Relation between Volume Correction and the Standard State. *Biophysical Chemistry* **1994**, *51*, 263–269, doi:10.1016/0301-4622(94)00047-6.
24. Reiss, H. Scaled Particle Methods in the Statistical Thermodynamics of Fluids. In *Advances in Chemical Physics*; John Wiley & Sons, Ltd., 1965; pp. 1–84 ISBN 978-0-470-14355-1.
25. Pierotti, R.A. A Scaled Particle Theory of Aqueous and Nonaqueous Solutions. *Chem. Rev.* **1976**, *76*, 717–726, doi:10.1021/cr60304a002.
26. Tomasi, J.; Persico, M. Molecular Interactions in Solution: An Overview of Methods Based on Continuous Distributions of the Solvent. *Chem. Rev.* **1994**, *94*, 2027–2094, doi:10.1021/cr00031a013.
27. Graziano, G. Shedding Light on the Hydrophobicity Puzzle. *Pure and Applied Chemistry* **2016**, *88*, 177–188, doi:10.1515/pac-2015-1003.
28. Graziano, G. Contrasting the Hydration Thermodynamics of Methane and Methanol. *Phys. Chem. Chem. Phys.* **2019**, *21*, 21418–21430, doi:10.1039/C9CP03213D.
29. Silverstein, T.P. The Hydrophobic Effect: Is Water Afraid, or Just Not That Interested? *ChemTexts* **2020**, *6*, 26, doi:10.1007/s40828-020-00117-8.
30. Qian, H.; Hopfield, J.J. Entropy-enthalpy Compensation: Perturbation and Relaxation in Thermodynamic Systems. *The Journal of Chemical Physics* **1996**, *105*, 9292–9298, doi:10.1063/1.472728.
31. Torquato, S.; Truskett, T.M.; Debenedetti, P.G. Is Random Close Packing of Spheres Well Defined? *Phys. Rev. Lett.* **2000**, *84*, 2064–2067, doi:10.1103/PhysRevLett.84.2064.
32. Graziano, G. Scaled Particle Theory Study of the Length Scale Dependence of Cavity Thermodynamics in Different Liquids. *J. Phys. Chem. B* **2006**, *110*, 11421–11426, doi:10.1021/jp0571269.
33. Widom, B. Intermolecular Forces and the Nature of the Liquid State. *Science* **1967**, *157*, 375–382, doi:10.1126/science.157.3787.375.
34. Chandler, D.; Weeks, J.D.; Andersen, H.C. Van Der Waals Picture of Liquids, Solids, and Phase Transformations. *Science* **1983**, *220*, 787–794, doi:10.1126/science.220.4599.787.
35. Tang, K.E.S.; Bloomfield, V.A. Excluded Volume in Solvation: Sensitivity of Scaled-Particle Theory to Solvent Size and Density. *Biophysical Journal* **2000**, *79*, 2222–2234, doi:10.1016/S0006-3495(00)76470-8.