

Article

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 leading to the need to spend free energy to produce an appropriate cavity to contain the solute molecule; (b) the ubiquitous intermolecular attractive interactions lead to a gain in free energy for switching-on attractions between the solute molecule and neighboring 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 addition. The latter entropy contribution is balanced by a corresponding enthalpy term. The scenario that 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



Citation: Tortorella, A.; Graziano, G. A van der Waals Model of Solvation Thermodynamics. *Entropy* **2024**, *26*, 714. <https://doi.org/10.3390/e26080714>

Academic Editor: Arieh Ben-Naim

Received: 29 June 2024

Revised: 19 August 2024

Accepted: 20 August 2024

Published: 22 August 2024



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1. Introduction

Water and aqueous solutions play a fundamental role on the Earth and for living organisms. All 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 for 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 performed 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 Ben-Naim’s statistical mechanical analysis, solvation describes the process of transferring 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 asserted that a correction term, accounting for the difference in molar volume between solute and solvent, 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 for: (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-range intermolecular interactions; (2) the long-range 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 this study, we consider monoatomic particles to eliminate the subtleties associated with the presence of internal degrees of freedom. Starting from the physico-chemical ideas of van der Waals for a binary solution of monoatomic species, it is possible to write down the corresponding classical partition function [20,21]:

$$Q(N_1, N_2, V, T) = \left[\frac{V^{(N_1+N_2)}}{N_1! \Lambda_1^{3N_1} \cdot N_2! \Lambda_2^{3N_2}} \right] \cdot \left[\frac{V - (b_1 N_1 + b_2 N_2)}{V} \right]^{(N_1+N_2)} \cdot \exp \left[\frac{(a_1 N_1 + a_2 N_2)^2}{kTV} \right] \quad (1)$$

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 independent of temperature); k is the Boltzmann constant and T is the absolute temperature. The quantity $[V - (b_1 N_1 + b_2 N_2)]$ 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 $-(a_1 N_1 + a_2 N_2)^2 / V$ (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:

$$\mu_2 \equiv \left(\frac{\partial A}{\partial N_2} \right)_{T, V, N_1} \quad (2)$$

Performing the calculations, one arrives at [21]:

$$\mu_2(vdW) = kT \cdot \ln \rho_2 \Lambda_2^3 - kT \cdot \ln \left[\frac{V - (b_1 N_1 + b_2 N_2)}{V} \right] + kT \cdot \left[\frac{(N_1 + N_2) b_2}{V - (b_1 N_1 + b_2 N_2)} \right] - \frac{2a_2(a_1 N_1 + a_2 N_2)}{V} \quad (3)$$

where $\rho_2 = N_2/V$ 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:

$$\mu_2(vdW) = kT \cdot \ln \rho_2 \Lambda_2^3 + \mu_2^\bullet \quad (4)$$

where μ_2^\bullet consists of the three remaining terms in Equation (3) and represents the standard chemical potential according to Ben-Naim (we denote the Ben-Naim standard quantities by means of 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 surroundings, without accounting for special limits to the concentration of the solute. This physical interpretation is a direct consequence of the adopted statistical mechanical procedure. It is not necessary to define a special state, the so-called standard state, in contrast to what happens in the framework of classical thermodynamics. The quantity μ_2^\bullet is affected by the solution composition, precisely because the coupling work magnitude depends on the solution composition [6–8]. This is a fundamental feature of the so-called Ben-Naim standard chemical potential, and its advantage 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].

As it is well known, the expression of the chemical potential of the monoatomic component 2 in the ideal gas phase is [19]:

$$\mu_2(ig) = kT \cdot \ln \rho_2 \Lambda_2^3 \quad (5)$$

There are no interactions among ideal gas molecules, and so only the classical translational degrees of freedom contribute to $\mu_2(ig)$, and $\mu_2^\bullet = 0$. 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, assuming that the liquid state can be described as a van der Waals binary solution. At thermodynamic equilibrium, the chemical potential of the component 2 has to be the same in the two phases:

$$\mu_2(ig) = \mu_2(vdW) \quad (6)$$

Inserting Equations (4) and (5) into Equation (6) leads to:

$$kT \cdot \ln \rho_2(ig) \Lambda_2^3 = \mu_2^\bullet(vdW) + kT \cdot \ln \rho_2(vdW) \Lambda_2^3 \quad (7)$$

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

$$\Delta G^\bullet = \mu_2^\bullet(vdW) = kT \cdot \ln \left[\frac{\rho_2(ig)}{\rho_2(vdW)} \right] \quad (8)$$

where ΔG^\bullet is the Ben-Naim standard Gibbs free energy change associated with the solvation process. There are two equalities in Equation (8); the first indicates that ΔG^\bullet is given

by the solute–solvent coupling work; the second indicates that ΔG^\bullet can be calculated by determining the ratio of the number densities of component 2 in the two phases, at constant temperature and pressure (i.e., ΔG^\bullet values are readily obtained from experimental data) [6,7].

Now, we consider a solution of the component 2 in the monoatomic van der Waals fluid 1, at infinite dilution. The ΔG^\bullet expression is readily obtained by making the limit in Equation (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, ΔG^\bullet is given by [21]:

$$\Delta G^\bullet = \mu_2^\bullet(vdW) = -kT \cdot \ln \left[\frac{v_1 - b_1}{v_1} \right] + kT \cdot \left[\frac{b_2}{v_1 - b_1} \right] - 2 \left(\frac{a_1 a_2}{v_1} \right) \quad (9)$$

To proceed with our analysis, it is helpful to assign a physical meaning to the contributions making up Equation (9). The first two terms correspond to the reversible work to produce an appropriate cavity to contain the component 2 particle in the monoatomic van der Waals fluid 1:

$$\Delta G_c(vdW) = -kT \cdot \ln \left[\frac{v_1 - b_1}{v_1} \right] + kT \cdot \left[\frac{b_2}{v_1 - b_1} \right] \quad (10)$$

For the first term of Equation (10), we can write:

$$-kT \cdot \ln \left[\frac{v_1 - b_1}{v_1} \right] = -kT \cdot \ln \left[\frac{v_{1,free}}{v_1} \right] = -kT \cdot \ln(1 - \xi_1) \quad (11)$$

and for the second term:

$$kT \cdot \left[\frac{b_2}{v_1 - b_1} \right] \cong P(vdW) \cdot b_2 \quad (12)$$

where Equation (11) represents the decrease in the configurational space that occurs when inserting the component 2 particle (note that ξ_1 is the volume packing density of fluid 1), and Equation (12) represents the pressure–volume work done to insert the component 2 particle in the van der Waals fluid 1. The two terms in Equation (10) should correspond to the first and fourth terms in the ΔG_c formula provided by the classic scaled particle theory [24–26]. This theory uses geometric criteria to take into account the spatial correlations existing between the particles in any liquid phase for the simple fact that each particle has its own body and so two particles cannot stay in the same position, at the same instant of time (i.e., non-overlap requirement). Scaled particle theory gives quantitative predictions that are more accurate than those from Equation (10) [22,27].

The physical interpretation of the parameters a_1 and a_2 leads to state that the third term on the right-hand-side of Equation (9) is the attraction Gibbs free energy of the component 2 particle with all the particles of the van der Waals fluid 1:

$$\Delta G_a(vdW) = -\frac{2a_1 a_2}{v_1} \quad (13)$$

Equation (9) shows that the solvation process can be decomposed in two sub-processes [4–7,24–29]: (a) production of an appropriate cavity in the liquid to contain the solute molecule, Equations (10)–(12); (b) switching-on the attractive potential energy between the solute molecule and the neighboring solvent molecules, Equation (13). Solvation thermodynamics is ruled by the effect of the solvent-excluded volume associated with cavity production in the liquid, and by the solute–solvent energetic attractions [4–7]; the quantity ΔG^\bullet accounts for both such contributions, as obtained in the van der Waals model [20,21].

It is straightforward to calculate the enthalpy and entropy changes associated with the two sub-processes under the constant pressure condition [21]. For cavity production, the following relationships are obtained:

$$\Delta H_c = -T^2 \left[\frac{\partial \left(\frac{\Delta G_c}{T} \right)}{\partial T} \right] = kT^2 \left[\frac{\alpha_{P,1}}{v_1 - b_1} \right] \cdot \left\{ b_1 + \left[\frac{v_1 b_2}{v_1 - b_1} \right] \right\} \quad (14)$$

$$\begin{aligned} \Delta S_c &= - \left(\frac{\partial \Delta G_c}{\partial T} \right) = k \cdot \ln \left[\frac{v_1 - b_1}{v_1} \right] - k \cdot \left[\frac{b_2}{v_1 - b_1} \right] + \left(\frac{\Delta H_c}{T} \right) \\ &= \Delta S_x + \left(\frac{\Delta H_c}{T} \right) \end{aligned} \quad (15)$$

$$T \cdot \Delta S_c = T \cdot \Delta S_x + \Delta H_c \quad (16)$$

where $\Delta S_x = -\Delta G_c/T$, and represents the solvent-excluded volume entropy contribution due to cavity production; and $\alpha_{P,1}$ is the isobaric thermal expansion coefficient of the van der Waals fluid 1. A liquid structural reorganization occurs upon cavity production; this contribution is directly proportional to $\alpha_{P,1}$. We see from Equation (14) that ΔH_c is proportional to $\alpha_{P,1}$ and from Equation (16) that $T \cdot \Delta S_c$ increases with ΔH_c , hence any increase in $\alpha_{P,1}$ yields the same increment in both ΔH_c and $T \cdot \Delta S_c$, and thus no change in ΔG_c . We can conclude that, in terms of liquids with different $\alpha_{P,1}$, cavity production yields compensating enthalpy and entropy changes. The production 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. For switching-on the attractive potential, the following relationships are obtained:

$$\Delta H_a = -T^2 \left[\frac{\partial \left(\frac{\Delta G_a}{T} \right)}{\partial T} \right] = - \left(\frac{2a_1 a_2}{v_1} \right) \cdot (1 + \alpha_{P,1} T) \quad (17)$$

$$\Delta S_a = - \left(\frac{\partial \Delta G_a}{\partial T} \right) = \frac{-2a_1 a_2 \cdot \alpha_{P,1}}{v_1} \quad (18)$$

$$T \cdot \Delta S_a = \left(\frac{-2a_1 a_2}{v_1} \right) \cdot T \cdot \alpha_{P,1} \quad (19)$$

$$\Delta H_a = \left(\frac{-2a_1 a_2}{v_1} \right) + T \cdot \Delta S_a \quad (20)$$

where again the liquid structural reorganization upon switching-on the solute–solvent attractive potential depends linearly on $\alpha_{P,1}$, and affects the enthalpy and entropy changes in a totally compensating manner. The finding that the liquid structural reorganization depends linearly on the isobaric thermal expansion coefficient of the liquid cannot be a surprise because α_P comes from 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 performed by Qian and Hopfield with the aim to rationalize the presence, in several and different processes, of a large enthalpy–entropy compensation [30]. It was shown that the thermodynamic effect of a small perturbation on a system consists of two contributions: (1) one accounting for the direct interaction of the perturbation with the untouched system; (2) the other accounting for the system's response to the perturbation, by realizing a redistribution among its different microstates, which are in thermal equilibrium, in accord with the Le Chatelier principle. The external constraints imposed to the system determine the allowed microscopic fluctuations, and govern the redistribution. The latter proves to be characterized by a complete enthalpy–entropy compensation, and the Gibbs free energy change comes from the direct interaction

between the perturbation and the untouched system. The perturbation, in the case of the solvation process, is given by the addition of the solute molecule to a fixed position of the solvent. The direct part of the perturbation consists of both cavity production and switching-on solute–solvent attractive potential; the structural reorganization of the liquid is the response of the system to the 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 produce an appropriate cavity to contain a xenon atom (i.e., its hard sphere diameter $\sigma = 4 \text{ \AA}$) in water, methanol, ethanol, carbon tetrachloride, n-hexane, n-decane, c-hexane and benzene, at 25 °C and 1 atm. This choice is dictated by the understanding that it is the cavity production step that distinguishes water from the other common liquids [4,7,25,27]. To perform calculations, it is necessary to modify Equation (10), converting to molar quantities and rearranging the terms [22]:

$$\Delta G_c(\text{vdW}) = -RT \cdot \ln(1 - \rho_1 b_1) + RT \cdot \left[\frac{\rho_1 b_2}{1 - \rho_1 b_1} \right] \quad (21)$$

where $\rho_1 = N_{Av}/v_1$ 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 $\Delta G_c(\text{vdW})$ in Equation (21) in terms of molar quantities, are:

$$\Delta H_c(\text{vdW}) = RT^2 \cdot \alpha_{P,1} \cdot \left[\frac{\rho_1}{1 - \rho_1 b_1} \right] \cdot \left\{ b_1 + \left[\frac{b_2}{1 - \rho_1 b_1} \right] \right\} \quad (22)$$

$$\Delta S_c(\text{vdW}) = R \cdot \ln(1 - \rho_1 b_1) - R \cdot \left[\frac{\rho_1 b_2}{1 - \rho_1 b_1} \right] + \frac{\Delta H_c(\text{vdW})}{T} \quad (23)$$

To perform calculations, we have used the experimental values of v_1 and $\alpha_{P,1}$ for the eight liquids, and their effective hard sphere molecular diameters [16,32] (see the columns 2–4 of Table 1). It is important to recognize that it is a very rough approximation to consider as simple spheres the molecules of n-hexane or n-decane, but also those of ethanol and benzene. The calculated values are reported in the columns 6–10 of Table 1. It results that: (a) the $\Delta G_c(\text{vdW})$ value in water is significantly larger than in the other liquids; (b) the $\Delta H_c(\text{vdW})$ value in water is significantly smaller than in the other liquids; in addition, $\Delta H_c(\text{vdW})$ is markedly smaller than $\Delta G_c(\text{vdW})$ in water, but the reverse holds in the other liquids, with the exception of methanol; (c) the $\Delta S_c(\text{vdW})$ value is large and negative in water, but small and positive in the other liquids, again with the exception of methanol.

Since the calculations have been performed in the same way, regardless of the liquid identity, the differences have to come from the physico-chemical properties of the considered liquids. The $\Delta G_c(\text{vdW})$ 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 $\Delta S_c(\text{vdW})$ 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 the organic liquids than in water due to the $\alpha_{P,1}$ magnitude (i.e., the latter depends on the strength of the intermolecular attractions in the liquid, 3D H-bonds in water versus dispersion attractions in hydrocarbons); in addition, it is able to overwhelm the ΔS_x contribution in the organic liquids, rendering $\Delta S_c(\text{vdW})$ 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 $\Delta S_c(\text{vdW})$ is negative. It is worth underscoring that the $\Delta G_c(\text{vdW})$ values in all the considered liquids are markedly smaller than those calculated by means of scaled particle theory or computer simulations, because the van der Waals model accounts in a very approximate manner for the solvent-excluded volume effect [22,27,32]. This reflects in the $\Delta S_x = -(\Delta G_c/T)$ magnitude, that proves to be too small in all the considered liquids [32,33]. As a consequence, one cannot expect that the van der Waals model can reproduce in a quantitative manner the solvation thermodynamics of xenon or other solutes in the considered liquids. Its merits consist in the possibility to arrive at analytical, and qualitatively correct relationships for all the relevant thermodynamics quantities.

Table 1. Effective diameters, experimental values, at 25 °C and 1 atm, of the molar volume and isobaric thermal expansion coefficient, and b_1 values for the eight considered liquids [32]. Gibbs free energy change, enthalpy and entropy change for the creation in the considered liquids of a cavity of 4 Å diameter, using the van der Waals model, Equations (21)–(23). The two contributions of the cavity entropy change are reported in the last two columns. For xenon, $b = 52.4 \text{ \AA}^3$.

	σ_1 Å	v_1 $\text{cm}^3 \text{ mol}^{-1}$	$\alpha_{P,1} \cdot 10^3$ K^{-1}	b_1 \AA^3	ΔG_c kJ mol^{-1}	ΔH_c kJ mol^{-1}	ΔS_c $\text{J K}^{-1} \text{ mol}^{-1}$	ΔS_x $\text{J K}^{-1} \text{ mol}^{-1}$	$\Delta H_c/T$ $\text{J K}^{-1} \text{ mol}^{-1}$
water	2.80	18.07	0.257	18.0	13.0	2.3	−35.9	−43.6	7.7
methanol	3.83	40.73	1.189	46.0	8.8	8.5	−1.0	−29.5	28.5
ethanol	4.44	58.68	1.089	71.6	8.3	8.4	0.4	−27.8	28.2
CCl ₄	5.37	97.09	1.226	126.7	7.6	9.7	7.0	−25.5	32.5
n-hexane	5.92	131.62	1.390	169.7	6.5	8.8	7.7	−21.8	29.5
n-decane	7.08	195.94	1.020	290.3	9.2	16.5	24.4	−30.9	55.3
c-hexane	5.63	108.75	1.214	146.0	7.9	10.9	10.1	−26.5	36.6
benzene	5.26	89.40	1.240	119.1	8.5	12.0	11.7	−28.5	40.2

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-range repulsive interactions that produce the solvent-excluded volume effect on solute addition [34,35]. The latter, however, is treated in an approximate manner, because the van der Waals model accounts only for the liquid free volume $(1 - \rho_1 b_1)$. In real liquids, the free volume represents 50–60% of the total volume, whereas the appropriate volume to contain a molecular-sized solute is smaller by orders of magnitude, because the solvent-excluded volume effect is operative (i.e., the non-overlap requirement holds) [36]. Only a very small part of the liquid's free volume is available to host a real solute (i.e., only the cavities large enough to contain the solute molecule). These sentences underscore that the free volume division is a fundamental feature of a liquid (largely dependent on the size and shape of the liquid molecules), that is totally neglected by the van der Waals model. In any case, the latter, using the experimental values of ρ_1 and $\alpha_{P,1}$, leads to a clear difference between water and the organic liquids for the cavity entropy change, in line with scaled particle theory results [7,25,27].

Author Contributions: Conceptualization, G.G.; formal analysis and investigation, A.T. and G.G.; writing—original draft preparation, A.T. and G.G.; writing—review and editing, A.T. and G.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by internal funds of the University of Sannio; it has not received external funding.

Data Availability Statement: All the relevant data are reported in the article.

Acknowledgments: This article is dedicated to Arieh Ben-Naim on the occasion of his ninetieth birthday; Arieh was born 11 July 1934 in Jerusalem and is still very active. I believe 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 made other important contributions to solvation thermodynamics. His lasting friendship is an honor to me.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Blokzijl, W.; Engberts, J.B.F.N. Hydrophobic Effects. Opinions and Facts. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1545–1579. [[CrossRef](#)]
2. Ball, P. Water as an Active Constituent in Cell Biology. *Chem. Rev.* **2008**, *108*, 74–108. [[CrossRef](#)] [[PubMed](#)]
3. Merlino, A.; Pontillo, N.; Graziano, G. A Driving Force for Polypeptide and Protein Collapse. *Phys. Chem. Chem. Phys.* **2016**, *19*, 751–756. [[CrossRef](#)]
4. Ben-Naim, A. *Water and Aqueous Solutions*; Springer: Boston, MA, USA, 1974; ISBN 978-1-4615-8704-0.
5. Ben-Naim, A. *Hydrophobic Interactions*; Springer: Boston, MA, USA, 1980; ISBN 978-1-4684-3547-4.
6. Ben-Naim, A. *Solvation Thermodynamics*; Springer: Boston, MA, USA, 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. [[CrossRef](#)] [[PubMed](#)]
8. Lee, B. Analyzing Solvent Reorganization and Hydrophobicity. In *Methods in Enzymology*; Energetics of Biological Macromolecules; Academic Press: Cambridge, MA, USA, 1995; Volume 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. [[CrossRef](#)] [[PubMed](#)]
10. Sharp, K.A.; Kumar, S.; Rosicky, P.J.; Friedman, R.A.; Honig, B. Size Dependence of Transfer Free Energies. 2. Hard Sphere Models. *J. Phys. Chem.* **1996**, *100*, 14166–14177. [[CrossRef](#)]
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. [[CrossRef](#)]
12. Chan, H.S.; Dill, K.A. Solvation: Effects of Molecular Size and Shape. *J. Chem. Phys.* **1994**, *101*, 7007–7026. [[CrossRef](#)]
13. Ben-Naim, A.; Mazo, R.M. Size Dependence of the Solvation Free Energies of Large Solutes. *J. Phys. Chem.* **1993**, *97*, 10829–10834. [[CrossRef](#)]
14. Ben-Naim, A. Solvation of Large Molecules: Some Exact Results on the Dependence on Volume and Surface Area of the Solute. *Biophys. Chem.* **1994**, *51*, 203–216. [[CrossRef](#)]
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. [[CrossRef](#)]
16. Graziano, G. On the Partitioning of Benzene between Water and *n*-Alkanes. *Chem. Phys. Lett.* **2010**, *486*, 44–47. [[CrossRef](#)]
17. van der Waals, J.D. On the Continuity of the Gaseous and Liquid States. Ph.D. Thesis, Leiden University, Leiden, The Netherlands, 1873.
18. Hill, T.H. *Introduction to Statistical Thermodynamics*; Addison-Wesley: Reading, MA, USA, 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. *J. Chem. Phys.* **2002**, *116*, 2907–2921. [[CrossRef](#)]
21. Graziano, G. Solvation Thermodynamics in a van Der Waals Liquid. *Thermochim. Acta* **2003**, *399*, 181–187. [[CrossRef](#)]
22. Graziano, G. A van Der Waals Approach to the Entropy Convergence Phenomenon. *Phys. Chem. Chem. Phys.* **2004**, *6*, 406. [[CrossRef](#)]
23. Lee, B. Relation between Volume Correction and the Standard State. *Biophys. Chem.* **1994**, *51*, 263–269. [[CrossRef](#)]
24. Reiss, H. Scaled Particle Methods in the Statistical Thermodynamics of Fluids. In *Advances in Chemical Physics*; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 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. [[CrossRef](#)]
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. [[CrossRef](#)]
27. Graziano, G. Shedding Light on the Hydrophobicity Puzzle. *Pure Appl. Chem.* **2016**, *88*, 177–188. [[CrossRef](#)]
28. Graziano, G. Contrasting the Hydration Thermodynamics of Methane and Methanol. *Phys. Chem. Chem. Phys.* **2019**, *21*, 21418–21430. [[CrossRef](#)]
29. Silverstein, T.P. The Hydrophobic Effect: Is Water Afraid, or Just Not That Interested? *ChemTexts* **2020**, *6*, 26. [[CrossRef](#)]
30. Qian, H.; Hopfield, J.J. Entropy-enthalpy Compensation: Perturbation and Relaxation in Thermodynamic Systems. *J. Chem. Phys.* **1996**, *105*, 9292–9298. [[CrossRef](#)]
31. Torquato, S.; Truskett, T.M.; Debenedetti, P.G. Is Random Close Packing of Spheres Well Defined? *Phys. Rev. Lett.* **2000**, *84*, 2064–2067. [[CrossRef](#)]

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. [[CrossRef](#)]
33. Graziano, G. Solvation Thermodynamics of Xenon in *n*-Alkanes, *n*-Alcohols and Water. *Biophys. Chem.* **2003**, *105*, 371–382. [[CrossRef](#)]
34. Widom, B. Intermolecular Forces and the Nature of the Liquid State. *Science* **1967**, *157*, 375–382. [[CrossRef](#)]
35. Chandler, D.; Weeks, J.D.; Andersen, H.C. Van Der Waals Picture of Liquids, Solids, and Phase Transformations. *Science* **1983**, *220*, 787–794. [[CrossRef](#)] [[PubMed](#)]
36. Tang, K.E.S.; Bloomfield, V.A. Excluded Volume in Solvation: Sensitivity of Scaled-Particle Theory to Solvent Size and Density. *Biophys. J.* **2000**, *79*, 2222–2234. [[CrossRef](#)]

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