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Simple Model for Nonassociative Organic Liquids and Water

Peter Buchwald*,† and Nicholas Bodor

Contribution from the Center for Drug Discovery, Health Science Center, University of Florida,
P.O. Box 100497, Gainesville, Florida 32610-0497

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Abstract: A simple model that has been derived from molecular-level considerations (*J. Phys. Chem. B* **1998**, *102*, 5715) is revisited and extended. It is shown that it gives a unified and adequate description of a variety of properties related to intermolecular interactions, including boiling point, enthalpy of vaporization, vapor pressure, surface tension, and a number of partition and solubility data for organic liquids that do not contain associative or strongly polar substituents. All corresponding equations were derived from the same free energy expression that forms the basis of the model. For the organic liquids considered here that include haloalkanes, aromatics, haloaromatics, esters, and ketones, molecular size as the sole descriptor (characterized here by molecular volume) can account for 80−90% of the variance. Furthermore, water, which is a highly abnormal liquid, seems to be integrable within the model by a simple modification of the interaction-related constant. This modification is consistent with the modified hydration-shell hydrogen-bond model of Muller, with data on partition and solubility in water, and with the large surface tension value of water. Within this approach, the controversy related to different macroscopic/microscopic free energies of interactions per surface area that was raised by Tanford and has recently resurfaced in the work of Honig, Sharp, and co-workers is also avoided.

Introduction

One of the most frustrating facts facing physical chemists is that while most of the relevant chemical and biochemical processes take place in or at the interface of liquid phases, we still seem to be unable to grasp the essence of this phase.[1−4] Our ability to describe quite well gas and crystalline solid phases at the molecular level only makes this even more frustrating, because liquids are obviously somewhere "between" these two phases. Nevertheless, neither lattice gas and compressed gas nor defective crystal models have yet provided real solutions. Pictures obtained from Monte Carlo and molecular dynamics calculations are promising, but such calculations can provide only computation-expensive simulations and not physicochemical theories that relate bulk properties to intermolecular forces in a more direct way. Because chemistry itself was once defined as the study of solutions (the alchemist experience could be summed up as "*corpora non agunt nisi soluta*" that is, compounds do not react unless dissolved),[5] and because life on Earth is intimately liquid-based, the frustration is understandable. Furthermore, life as we know it is water-based and so are most of our everyday liquid-related experiences. This only complicates matters, because water is quite unique, even among liquids.

The present paper intends to prove that our recently introduced molecular-size-based, unified, approximate model[6,7] can give reasonable descriptions of essentially all intermolecular-interactions-related properties in simple organic liquids that have no functional groups that are strongly polar or susceptible to associative (e.g., hydrogen bonding) behavior. Moreover, even water can be accommodated within this model, and many unusual properties of water are correctly accounted for. Admittedly, this is an oversimplified model that is somewhat in the phenomenological style of the van der Waals equation of state or the Hildebrand solubility model, but for the liquids considered, which include haloalkanes, aromatics, haloaromatics, esters, and ketones, its predictions are consistent with a variety of intermolecular-interactions-related properties, including boiling point, enthalpy of vaporization, vapor pressure, surface tension, and a number of partition and solubility data.

Experimental Data

The database includes haloalkanes ($n = 39$), aromatics and alkylaromatics ($n = 48$), haloaromatics ($n = 31$), and monofunctionalized esters ($n = 28$) and ketones ($n = 22$) [also monofunctionalized alcohols ($n = 49$) and amines ($n = 36$) for octanol−water partition and water solubility data] with at least one experimental data available. We attempted to include as varied structures as possible. Molecular volumes used here are effective van der Waals volumes and were computed with a radii set[6,8,9] and an essentially analytical algorithm[8] that have been described elsewhere. Enthalpies of vaporization, boiling points, densities, and molecular weights are from recent collections.[10,11] Surface tension values are from the compilation of Jasper.[12] Gas−hexadecane Ostwald absorption coefficients are from Abraham and co-workers.[13,14] Water solubilities are from articles published by Hine and Mookerje,[15]

[†] Present address: IVAX Corp., 4400 Biscayne Blvd., Miami, FL 33137. Phone: (305) 575−4021. Fax: (305) 575−6027. E-mail: Peter_Buchwald@ivax.com.

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Valvani and co-workers,[16] and from the recent collection by Abraham and Le.[17] Hexadecane−water partition coefficients are from Abraham and co-workers.[13,18] Octanol−water partition coefficients are mainly recommended values from compilations by Hansch and co-workers[19] and Sangster.[20] Detailed data are included in the Supporting Information. Statistical analyses were performed using a standard spreadsheet program (Microsoft Excel 97).

Molecular-Size-Based Model for Simple Organic Liquids

To describe liquid properties and solvation processes, one must have some molecular-level model of the liquid state. On the basis of specific, molecular-level assumptions, we recently introduced a simple molecular-size-based model that allows a unified description of important properties such as enthalpies of vaporization, boiling points, Ostwald absorption coefficients, vapor pressures, partition coefficients, and water solubilities for simple organic liquids.[6,7] For such liquids, around 90% of the variance in these properties is accounted for by molecular size as measured by the computed van der Waals molecular volume (υ). Because for most organic molecules differently defined (e.g., van der Waals, solvent accessible, contact), surface areas or molecular volumes tend to correlate strongly,[8,21,22] and because any of these quantities represents a reasonable measure of three-dimensional size, we designated our model as molecular-size-based and not as molecular-volume-based. The model in its present form works only for simple organic liquids whose molecules have no hydrogen bonding or strongly polar substituents. However, by changing the interaction-related constant, a simplified but consistent description is obtained for the properties of water and for the hydrophobic effect[7] that is also in agreement with the modified hydration-shell hydrogen-bond model of Muller.[23,24] A previously derived, fully computerized method (QLogP)[8,25,26] that estimates octanol−water partition properties for a large variety of organic solutes could also be integrated within this unified approach, and the value obtained for the interaction constant of octanol is also consistent with the present model.

Chemical Potential. The present model was obtained starting with a chemical potential (μ) form obtained in a statistical mechanics formalism that is essentially identical to that used by Ben-Naim:[27,28]

$$\mu_i = kT \ln\left(\frac{N_i \Lambda_i^{3}}{V q_i}\right) + W_i \qquad (1)$$

Here k is the Boltzmann constant, T is the absolute temperature, N represents particle number, and Λ is the thermal de Broglie wavelength. The internal partition function q_i was considered to be independent of the environment, and thus it was disregarded. The first term on the right-hand side of the above equation, $kT \ln(\Lambda_i^3 N_i/V)$, represents the translational contribution to the chemical potential μ_i. The second term on the right-hand side can be regarded as the average work, W_i, of coupling a molecule located at some fixed position to its environment.

The following additional molecular-level assumptions were introduced:[6,7]

(1) The total volume of the liquid phase (V) is a linear function of molecular numbers (N_i) and molecular volumes (υ_i). Hence, for a pure liquid, the molar volume (V^0) will be considered as $V^0 = aN_0\upsilon$. For the effective van der Waals molecular volumes used in this work (υ), we obtained V^0 (L) $= 0.00123\upsilon$ (Å^3) ($n = 260$, $r^2 = 0.87$).[6] Only flat, fused aromatics, such as perylene or fluoranthrene, were strong deviants. For mixtures of different compounds, the volume of the liquid phase will be considered as determined by the number and the size of its constituent molecules, $V = n_iV_i^0 + n_jV_j^0 = a(N_i\upsilon_i + N_j\upsilon_j)$. These are reasonable, but undeniably rough approximations. When molecules of unequal size are mixed, these assumptions introduce an additional term in the corresponding equations.

(2) The volume available for translation in a liquid can be considered as a fraction, $f < 1$, of the total volume of the liquid, $V^{\text{free}} = fV$. Consequently, the translational contribution to the chemical potential is also modified. Molecules in a liquid are free to move throughout the medium, but their volume obviously represents a major fraction of the total volume. Hence, the average volume accessible to a molecule in a liquid phase (V^{free}) is only part of the total volume. At any given time, a considerable portion of the total volume is inaccessible owing to the size of the molecules present, as was the case even for a van der Waals gas.[6,29] Introduction of each solute molecule into the liquid produces a free volume increase proportional to the size of the introduced solute that will be available to all the other molecules present in the liquid phase. Assumptions 1 and 2 are practically those introduced in the Hildebrand model.[30,31] The present model was consistent with a value of $f = 0.023$, suggesting that about 2−3% of the total liquid volume can be considered as available for translation.

(3) In simple liquids, the binding energy and, hence, the coupling work of a molecule to its environment (W) are linearly related to molecular volume, $W_i = -w_0 - w\upsilon$. In liquids, dispersion forces are clearly dominant among attractive van der Waals forces,[32−34] and they are to a good extent size-related. This potential should account for most nonspecific intermolecular interactions in liquids where they are, at least to a reasonable extent, orientation averaged. The interaction-related constants $w_0 = \omega_0 kT_0$ and $w = \omega kT_0$ ($T_0 = 298.15$ K) should have similar values in similar liquids, and indeed, the model that was derived for all of the above-mentioned data (e.g., enthalpy of vaporization, boiling point, Ostwald absorption coefficient, vapor pressure) was consistent with $\omega_0 = 5.39$ and $\omega = 0.082$. The alkane data required a different ω_0 (2.52) and a similar but slightly modified ω (0.089). For essentially all

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examined properties, alkanes seem to be in a class of their own, and they will not be included in the present discussion.

The chemical potential $\mu_i^{sol,j}$ obtained from these assumptions for solute i in solvent j was[6]

$$\mu_i^{sol,j} = kT \ln\left(\frac{\rho_i}{f}\Lambda_i^{3}\right) - \left(w_{ij} + \frac{kT}{v_j}\right)v_i - w_0 + kT \qquad (2)$$

where $\rho_i = N_i/V$ represents particle density. Different molecular sizes and volume additivity introduce in this expression a $kT(1 - v_i/v_j)$ term.[6] Similar terms, obtained (or not) by different authors using different assumptions, generated considerable controversy recently.[31,35−58] In addition to the Hildebrand model, formally similar terms can be obtained[31] within the framework of the Flory−Huggins theory of polymer mixing[59−61] or within the theory proposed by Sharp and co-workers.[45] In the present model, as in that of Hildebrand, this term appears as a consequence of the larger increase in the volume of the liquid phase and, hence, the larger increase in the volume available for translation produced by introduction of larger molecules.

The present model indicates the presence of a ln f factor in gas−liquid transfer free energy expressions, a factor that is not obtained in the Flory−Huggins or Sharp models as shown by Chan and Dill.[31] The f fraction introduced here equals $c/(c + 1)$, where c, as defined by Chan and Dill,[31] is assumed to be constant and represents the ratio between the free volume associated with a solute and the hard core volume of the solute. No such term appears in the Sharp model in which the full volume of the liquid phase is considered accessible in a sort of compressed ideal gas approximation.[31,45] This, however, cannot be a good choice, because most of the volume of a liquid is that excluded by the molecules themselves, and the excluded volume cannot be neglected, even for van der Waals gases.[6,29] Despite a similar mathematical form, the Flory−Huggins model is obtained from very different physical considerations (lattice model approximation). The corresponding Flory−Huggins equation, instead of the ln f term, contains an m_a term, where m_a denotes the hard-core volume of the corresponding (polymeric) unit relative to the monomer (essentially the length of the polymer). It should be noted here that all equations derived for gas−liquid transfers from the present model that contained this ln f (= ln 0.023 = −3.76) term gave satisfactory numerical agreement with the experimental data.[6] They included equations for the Ostwald absorption coefficient in hexadecane for simple organic compounds (γ_{hd}, $n = 49$), the Ostwald absorption coefficient in liquid alkanes for xenon (γ_{Xe}, $n = 12$), and data on vapor−liquid equilibrium (ρ^{gas}, $n = 42$). However, the quality of the experimental data is not sufficiently good enough to clearly distinguish among these models, because, in most cases, there are only small differences between their predictions.

The chemical potential of pure liquids can be obtained from eq 2 by considering the solute and solvent molecules as identical: $i = j$, $v_i = v_j = v$, $w_{ij} = w_{ii} = w$.

$$\mu^{liq} = kT \ln\left(\frac{\rho}{f}\Lambda^{3}\right) - wv - w_0 \qquad (3)$$

The chemical potential of (perfect) gases, $\mu^{gas} = kT \ln(\rho\Lambda^3)$, can also be obtained by taking $w_0 = w = 0$ (no interaction) and $f = 1$ (whole volume available for transition). The present model is essentially a background potential model, but although a van der Waals gas model is obtained with $W = -aN/V$ (and $V^{free} = V - Nb$), here we assume $W = -w_0 - wv$ (and $V^{free} = fV$).

For a pure liquid, a number of properties, such as boiling point, enthalpy of vaporization, vapor pressure, and surface tension, are directly related to intermolecular forces. Hence, the most direct tests of any model of intermolecular forces are its predictions for these properties, and we will look at them in the following.

Boiling Point. The f value used here (0.023) was obtained so as to give a molar entropy of vaporization, $\Delta S° = R(1 + \ln RT_b/p_0fV^0)$ with the present model, in agreement with the crude Trouton rule ($\Delta S° \approx 87$ J/K mol).[6] From the condition that $\Delta\mu^{liq\to gas}$ is 0 at the boiling point (T_b), we obtained

$$T_b = \frac{w_0 + w_{ii}v_i}{k \ln\left(\frac{RT_b}{p_0 fV_i^{0}}\right)} = T_0\frac{\omega_0 + \omega_{ii}v_i}{\ln\left(\frac{RT_b}{p_0 fV_i^{0}}\right)} \approx \frac{298.15}{9.46}(5.39 + 0.082v)\ (\mathrm{K}) \qquad (4)$$

which is in good agreement with the experimental data (omitting the small, fluoro-substituted compounds). The linear dependence on the rightmost side was obtained by assuming that T_b/V^0 is constant, which is a reasonable first approximation ($3.63 \pm 0.6\ 10^6$ K/m^3, $n = 95$). As Figure 1 and eq 5 illustrate, the agreement between experimental and model-predicted data (both in °C) is reasonably good, even for compounds containing nonassociative functional groups, such as esters or ketones

$$t_b^{exp}\ (°\mathrm{C}) = 0.961(\pm 0.037)t_b^{mod} + 6.667(\pm 6.875) \qquad (5)$$

$$n = 135,\ r^2 = 0.838,\ \sigma = 35.145,\ F = 687.2$$

Enthalpy of Vaporization. Considering that for vaporization, $\Delta\mu = \mu^{gas} - \mu^{liq}$, the model gives for the molar enthalpy of vaporization (ΔH^0)

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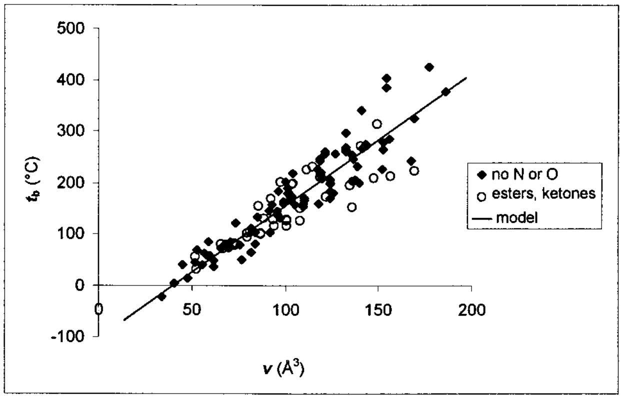

Figure 1. The boiling point (t_b, °C) of 135 molecules as a function of molecular size as measured by the computed van der Waals molecular volume (in Å^3). The line represents the prediction of the present model (eq 4).

$$\Delta H^0 = N_0\left(\frac{\partial(\Delta\mu/T)}{\partial(1/T)}\right)_p = RT_0\left(\frac{T_b}{T_0} + \omega_0 + \omega v\right) = 2.48\left(\frac{T_b\ (\mathrm{K})}{298.15} + 5.39 + 0.082v\right)\ (\mathrm{kJ/mol}) \quad (6)$$

which is in very good agreement with available experimental data (Figure 2).[6] In fact, this equation was used in the original publication[6] to derive the values for the ω (w) interaction-related constants. By using eq 4 for T_b, one can directly relate ΔH^0 to v

$$\Delta H^0\ (\mathrm{kJ/mol}) = 14.78 + 0.225v\ (\text{Å}^3) \quad (7)$$

As Figure 2 illustrates, despite all the estimations made, the agreement is also good even for nonassociative liquids such as esters and ketones

$$\Delta H^{0,\mathrm{exp}}\ (\mathrm{kJ/mol}) = 0.911(\pm 0.059)\Delta H^{0,\mathrm{mod}} + 2.846(\pm 1.870) \quad (8)$$

$$n = 47,\ r^2 = 0.842,\ \sigma = 1.794,\ F = 241.1$$

Gas−Liquid Equilibrium. Considering that the Ostwald absorption coefficient (γ) is defined as the ratio of liquid and gas number densities (molar concentrations) at equilibrium, and that at equilibrium the chemical potentials are equal ($\mu_i^{\mathrm{gas}} = \mu_i^{\mathrm{sol},1}$), we obtained for the present model[6]

$$\log \gamma_i^1 = \log\left(\frac{\rho_i^{\mathrm{sol},1}}{\rho_i^{\mathrm{gas}}}\right) = \frac{1}{\ln 10}\left[(-1 + \omega_0 + \ln f) + \left(\omega + \frac{1}{v_1}\right)v\right] \quad (9)$$

For gas−hexadecane partition ($v_1 = 232$ Å^3), the corresponding equation

$$\log \gamma_{hd} = 0.274 + 0.0375v \quad (10)$$

was in very good agreement with the experimental data measured by Abraham and co-workers[13,14]

$$\log \gamma_{\mathrm{hd}} = 0.161(\pm\ 0.127) + 0.0378(\pm\ 0.0014)v \quad (11)$$

$$n = 49,\ r^2 = 0.943,\ \sigma = 0.264,\ F = 770.3$$

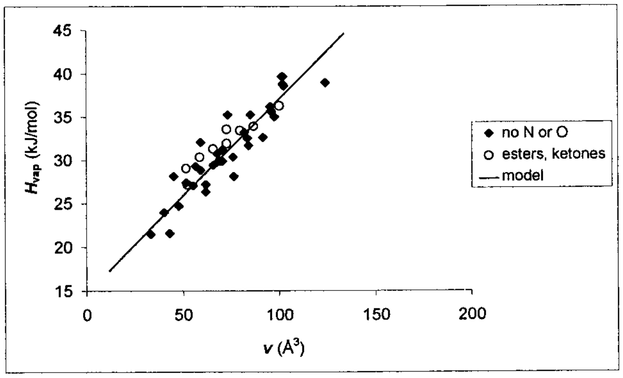

Figure 2. Molar enthalpy of vaporization (H^0_{vap}) as a function of molecular volume. The line represents the prediction of the present model (eq 6 using predicted T_b).

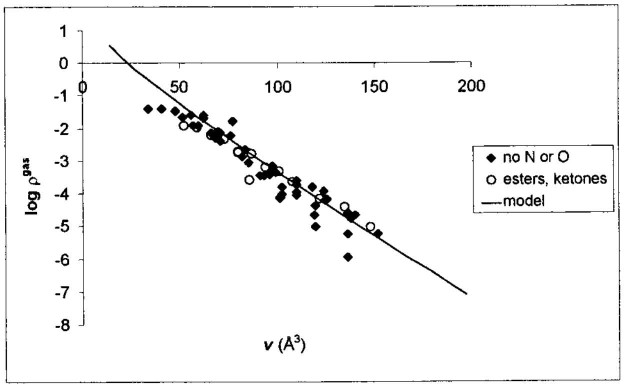

Figure 3. Molar gas concentration (ρ^{gas}) at equilibrium between a liquid and its vapor. The continuous line represents the predicted value (eq 13).

Equation 9 also can be used to describe the equilibrium between a pure liquid and its vapor (vapor pressure) if this is considered simply as solvation of a molecule by its own liquid. Taking 1 = i (solvent = solute) and using $\rho = 1/V_i^0$ for the molar density of a pure liquid in eq 9, one obtains[6]

$$\log \rho^{\mathrm{gas}} - \log \frac{1}{V_i^0} = -\frac{1}{\ln 10}(\omega_0 - \ln f + \omega v) = -0.708 - 0.0356v \quad (12)$$

Using the approximation V^0 (L) = $0.00123v$ (Å^3) for the molar volume, this gives

$$\log \rho^{\mathrm{gas}} = 2.202 - 0.0356v - \log v \quad (13)$$

which is in reasonable agreement with available experimental vapor pressure data of 67 liquids (haloalkanes, aromatics, alkylaromatics, haloaromatics, esters, and ketones excluding the fluoro-containing and the larger rigid aromatics such as naphthalene and anthracene) (Figure 3)

$$\log \rho^{\mathrm{gas,exp}} = 0.962(\pm 0.038) \log \rho^{\mathrm{gas,mod}} - 0.301(\pm 0.125) \quad (14)$$

$$n = 67,\ r^2 = 0.908,\ \sigma = 0.357,\ F = 637.8$$

Surface Tension. The surface tension is one of the most striking manifestations of intermolecular forces in liquids. Molecules at or near the surface are attracted inward, creating a force that tends to minimize the surface so that the maximum number of molecules are in the bulk where they are surrounded by a maximum number of neighbors. The surface tension σ is defined as the free energy per unit surface area, which also equals the force per unit length on the surface

$$\sigma = \left(\frac{\partial G}{\partial A}\right)_{p,T} \tag{15}$$

Becasue this is clearly a free-energy-related property, we should be able to obtain an expression for it starting from eq 3 for pure liquids. Molecules in the surface layer of the liquid phase will have a raised potential, because part of the molecule is exposed to the much less dense gas phase and cannot participate in the attractive interactions characteristic for the liquid phase. We will assume that only a quasi-monomolecular layer is perturbed, because it is customary to assume that any molecule at a distance greater than 10^{-9} m (10 Å) is in the bulk liquid. For the present purposes, we can assume that for molecules in this surface layer, only a fraction $v' = cv$ ($c < 1$) of their volume can be used in the -wv term of the attractive potential of eq 3 (because only part of the molecule can participate in the corresponding interactions). Because the interactions with the other molecules that are within this layer or bellow it in the liquid phase are essentially the same, and only the interactions with the molecules that should be in the layer above it (in the gas phase, where the density can be neglected in the present conditions of room temperature T_0 and atmospheric pressure p_0) are "missing", one can assume that about one-fourth to one-third of the interactions are lost, and hence, $c = 0.66-0.75$. For perfectly packed spheres, only 3 out of the 12 nearest neighbors are "missing"; hence, only one-fourth of the near-neighbor interactions are lost in this ideal case.

It is also likely that the translational motion in the surface layer is more restricted than in the bulk. Because molecules cannot leave the liquid phase, one translational direction is lost out of the six possible ones, and one may consider $f' \approx 5f/6$. However, compared to the interaction term, this produces only a negligible effect, and this will not be considered here. The change in chemical potential in moving from the bulk to the surface layer is, therefore

$$\Delta\mu^{\text{bulk}\rightarrow\text{surface}} = \mu^{\text{surface}} - \mu^{\text{bulk}} = -wv' - w_0 + wv + w_0 = wv(1-c) \approx 0.3wv \tag{16}$$

The free energy needed to create an additional dA surface (which will affect dN_{aff} molecules within a dV_{aff} volume of depth h_{aff} at surface) can be written as

$$\mathrm{d}G = \Delta\mu\, \mathrm{d}N_{\text{aff}} = \Delta\mu\, \rho\, \mathrm{d}V_{\text{aff}} = \Delta\mu\, \rho\, h_{\text{aff}}\, \mathrm{d}A \tag{17}$$

By comparing this with d$G = \sigma$ dA (from eq 15), we have $\sigma = \Delta\mu\ \rho\ h_{\text{aff}}$. Because $\rho = N_0/V^0 = 1/av$, and $w = \omega kT_0$, we have

$$\sigma = \frac{kT_0}{a}\omega(1-c)h_{\text{aff}} \tag{18}$$

With the present model, this gives

$$\sigma\ (\text{mN/m}) = 16.53\ (1-c)h_{\text{aff}}\ (\text{Å}) \tag{19}$$

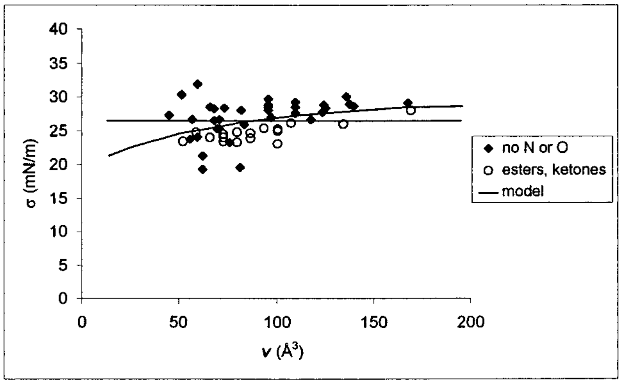

Figure 4. Surface tension (σ) of 53 molecules as a function of molecular size. Some larger values corresponding to ring structures that have a polar substituent (e.g., chlorobenzene, bromobenzene, dichlorobenzene, chlorotoluene, cyclohexanone, and acetophenone) have been omitted. The lines represent the predictions of the present model (eq 20 and 21, respectively).

Assuming that the affected layer at the surface has about the same height in different liquids, one obtains a constant value for σ, an assumption that bears out for most of the considered liquids (Figure 4) that have an average surface tension of 26 mN/m (26.17 ± 2.68 mN/m, $n = 54$). Some compounds having a more rigid ring structure with a polar substituent have slightly higher values (most likely because of ordering effects in the surface layer) and have been omitted from this calculation. They include chlorobenzene, bromobenzene, dichlorobenzene, chlorotoluene, cyclohexanone, acetophenone, and propiophenone; chloromethane also was omitted as an outlier. Compared with eq 19, this value indicates

$$\sigma\ (\text{mN/m}) = 16.53 \times 1.583\ (\text{Å}) \tag{20}$$

$$n = 53,\ \sigma = 2.680$$

This gives 1.58 Å for $(1-c)h_{\text{aff}}$. By using the previously derived value for c (0.66−0.75), we have $h_{\text{aff}} \approx 4.75-6.25$ Å, which is just about the perfect value for a monomolecular layer. Therefore, the present size-based model of intermolecular interactions in organic liquids can also give a correct, approximate picture of surface tension.

One could argue that the affected height should increase with size. For spherical molecules, one could expect proportionality to $v^{1/3}$. However, as already mentioned, for most organic molecules, molecular volumes and surface areas tend to correlate strongly,[8,21,22] indicating a more elongated, cylindrical-type and not a spherical shape. Hence, a constant or maybe very slightly increasing h_{aff} seems to be a more reasonable choice. In fact, allowing for proportionality with an arbitrary power of v makes the fit somewhat better, but only marginally so, and the power coefficient is, indeed, much smaller than 1/3 (Figure 4)

$$\sigma\ (\text{mN/m}) = 16.53 \times 0.925v^{0.120}\ (\text{Å}^3) \tag{21}$$

$$n = 53,\ \sigma = 2.470$$

In fact, the quasi-independence of the surface tension measured at room temperature (T_0) and atmospheric pressure (p_0) from molecular size is not surprising. Macleod's empirical formula[62] expresses the surface tension of a liquid in equilibrium with its vapor as a function of the molar densities of liquid and vapor (ρ_l, ρ_v). As modified by Sugden to introduce the parachor ($\mathcal{P}$),[63] this equation is

$$\sigma = \mathcal{P}^4(\rho_l - \rho_v)^4 \tag{22}$$

The success of this empirical equation prompted a number of

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attempts to justify it on the basis of theoretical considerations.[64,65] The parachor P, introduced on the basis of this formula, became the first really successful descriptor of molecular size, because it was thought to be volume-related, was very nearly temperature-independent, and could be well-estimated using additive contributions.[66] On the basis of these considerations, it is, therefore, not surprising that at normal conditions in which the density of the gas phase can be neglected, $\rho_l - \rho_v \approx \rho_l = 1/V^0$, the surface tension, $\sigma \approx P^4/(V^0)$,[4] is approximately constant, because both P and V^0 are strongly molecular-size-related.

Water

An important aspect of biologically and chemically relevant liquid modeling is related to water, which is the most common solvent and has an overriding importance in biological systems, but which is a highly anomalous liquid.[7,67] A whole literature is dedicated to the description of water structure and of so-called hydrophobic interactions,[24,27,67−92] yet relatively few things are known with certainty. As we showed earlier,[6,7] despite its highly anomalous nature, water could also be included in the present model if a different interaction-related constant, ω, is used to describe water as a solvent. It has also been shown that this $\Delta\omega$ change, which is most likely related to the changes that the solute produces in the hydrogen-bonded structure of water, agrees very well with the value that can be derived from the modified hydration-shell hydrogen-bond model of Muller.[7]

Hydrogen-Bond Model. The Muller model[23,24] assumes that in bulk water, intact and broken hydrogen bonds are in an equilibrium described by molar enthalpies and entropies [$\Delta H_b^0 = 9.80$ kJ/mol, $\Delta S_b^0 = 21.60$ J/(mol K)] that are independent of temperature. Hydrogen bonds in the hydration shell around a nonpolar solute molecule are assumed to be in a similar equilibrium, but described by modified enthalpy and entropy parameters [$\Delta H_{hs}^0 = 10.70$ kJ/mol, $\Delta S_{hs}^0 = 27.36$ J/(mol K)] so that H-bonds in the hydration shell are somewhat more broken than those in bulk water but have higher bond-breaking enthalpies and entropies (Figure 5). The Muller model accounts quite well for the hydrogen bond contribution to the heat capacity of bulk water ($C_{p,b}^h$), for the excess molar heat capacity of nonpolar solutes in water (ΔC_p^0), and for the water proton NMR chemical shift displacement ($\Delta\delta$) produced by nonpolar solutes (Figure 5). A number of recent molecular dynamics simulations gave results that agreed very well with this model.[89,93−95] For example, Mancera obtained the same qualitative picture with somewhat modified parameter values: $\Delta H_b^0 = 11.76$ kJ/mol, $\Delta S_b^0 = 26.32$ J/(mol K) and $\Delta H_{hs}^0 = 13.37$ kJ/mol, $\Delta S_{hs}^0 = 32.76$ J/(mol K), respectively.[95]

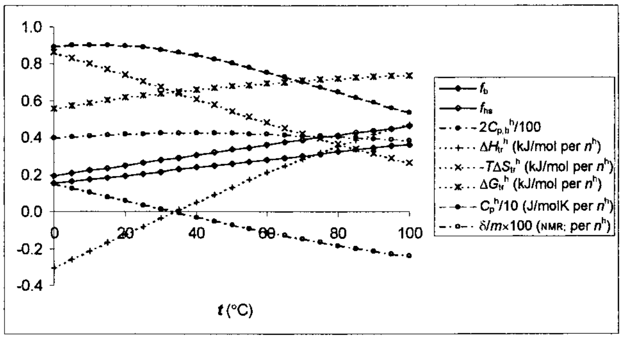

Figure 5. Temperature dependence of various properties as obtained from the modified hydration-shell hydrogen-bond model of Muller. Notation is as follows: f_b, f_{hs} fraction of broken hydrogen bonds in bulk and hydration-shell water; $2C_{p,b}^h$ hydrogen bond contribution to the heat capacity of bulk water; ΔH_{tr}^h, ΔS_{tr}^h, ΔG_{tr}^h, hydrogen-bonding contribution to changes in the entropy, enthalpy, and Gibbs free energy upon hydration (per one affected hydrogen bond); $C_p^h = C_{p,hs}^h - C_{p,b}^h = \Delta C_p^0/n^h$ excess molar heat capacity (per one affected hydrogen bond); δ/m water proton NMR chemical shift displacement (δ) produced by a solute at molality m in water (per one affected hydrogen bond).[7,24]

The change of the solute−solvent interaction coefficient, $\Delta\omega = \omega_{iw} - \omega = -0.070 - 0.082 = -0.152$, required in our model when water is the solvent, produces for a solute of molecular volume v a corresponding change in the molar free energy: $\Delta G° = -N_0\Delta wv = -RT_0\Delta\omega v = 0.377v$ (kJ/mol).[7] During solvation in water, the size-dependent attractive part of the potential that is present for other solvents $-N_0wv = -RT_0\omega v = -0.203v$ (kJ/mol) has to be corrected with this (repulsive) $0.377v$ (kJ/mol) value to account for the effects caused by disruption of hydrogen bonding, which is assumed to be homogeneously distributed through the (water) solvent. This allowed good quantitative description of water solubility, alkane−water and octanol−water partition, and also agreed with data on the gas−water Ostwald absorption coefficient and the Muller model of hydrogen bonding.[6,7] By assuming that this $\Delta\omega$ change is entirely due to the disruption of hydrogen bonding, which is considered as having a uniform density through the aqueous solvent, and by using the corresponding free energy obtained in the Muller model at room temperature, $\Delta G^h = \Delta H^h - T_0\Delta S^h = 0.6294n^h$ (kJ/mol), we obtained the number of affected

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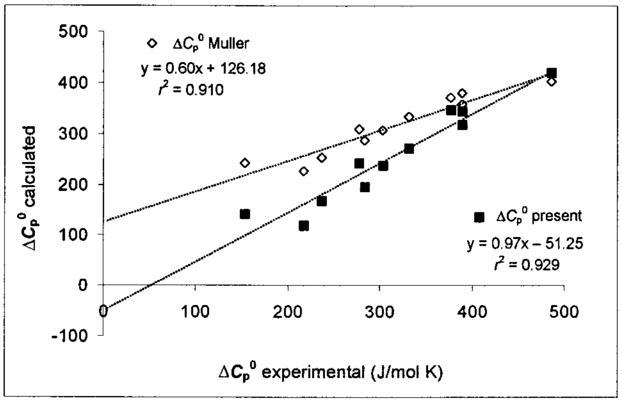

Figure 6. Calculated versus experimental excess molar heat capacity ΔC_p^0 for 11 nonpolar solutes in water. Calculated values are shown both as estimated originally by Muller[23] and as obtained with the n^h estimate (eq 23) derived from $\Delta\omega$ of the present model.

hydrogen bonds, n^h, as[7]

$$n^h = 0.599v \qquad (23)$$

These n^h values gave an even better overall agreement for the 11 experimental ΔC_p^0 data used by Muller than the original n^h values used by him, which were estimated as $3N_w^h/2$,[23] with N_w^h being an estimated number of water molecules in the hydration shell taken from the work of Dec and Gill (Figure 6).[96] The agreement, as indicated not only by the correlation coefficient but also by the slope and intercept values, is satisfactory, especially considering that the ΔC_p^0 data are for alkanes and alkenes. Alkenes were not included in our model, and as mentioned, alkanes tended to behave somewhat different from the other compounds.

Surface Tension. The above assumptions also agree with the unusually high surface tension value of water (71.99 mN/m at 25 °C). For water molecules, movement into the surface layer is unfavorable not only because of the disruption of attractive interactions, but also because of the disruption of hydrogen bonding. Hence, the ω value used in eq 18 has to be increased with $|\Delta\omega| = 0.152$ for water to account for the additional unfavorable effect produced in hydrogen bonding. With this correction, we obtain for water 74.7 and 60.3 mN/m from the adjusted versions of eq 20 and 21, respectively, which are in very good agreement with the experimental value of σ for water (71.99 mN/m). This indicates again that many unusual properties of water may be accounted for even by the present, admittedly oversimplified, model through a combination of nonspecific interactions as extrapolated from other liquids, considerations for the unusually small size of water molecules, and a reasonable model of hydrogen bonding.

From similar considerations, the interfacial free energy of hydrocarbon−water surfaces can be obtained as the part responsible for the disruption of hydrogen bonding by using this time only $|\Delta\omega| = 0.152$ instead of ω, because the attractive interactions themselves are not disrupted (they are considered to be similar between water and hydrocarbon molecules). The obtained value of 48.5 mN/m (from eq 20 with the modified ω value) is in excellent agreement with the experimental value of about 51 mN/m (erg/cm^2).[97] It is important to note that within this formalism, the entire controversy of different macroscopic/microscopic free energy of interactions per surface area that has been raised by Tanford[97] and has resurfaced recently in the work of Honig, Sharp, and co-workers[45−47] is also avoided. The same $\Delta\omega$ that was used to describe the "microscopic" hydrophobic effect, as modeled, for example, by water solubility, and that was in good agreement with the Muller model, can also account for the large surface tension of water and for the "macroscopic" hydrophobic effect, as modeled by the water−hydrocarbon interfacial surface tension.

Honig, Sharp, and co-workers have recently raised the issue that although the hydrophobic effect, as measured from the surface area dependence of the solubilities of hydrocarbons in water, is generally estimated to be about 25 cal/mol/Å^2, which would correspond to a surface-tension-type value of 25 × 4.18 J/(6.023 × 10^{23})/(10^{-20} m^2) = 17.4 mN/m, the surface tension at a hydrocarbon−water surface used earlier is almost three times higher, about 72 cal/mol/Å^2 (51 mN/m with the same conversion). In an attempt to bring the two values closer, they introduced a revised microscopic value of 47 cal/mol/Å^2.

The solvent-accessible surface areas (SASA) used by them are proportional to the volumes used by us as a measure of molecular size ($A_{SASA} = 85.31 + 2.122v$, $r^2 = 0.999$), indicating again that both volume and surface area can serve as a reasonable measure of molecular size. We can use this relationship to rescale values from the present model as surface-dependent values for comparison purposes. With this conversion, the size-dependent attractive interaction ($-RT_0\omega$) among simple organic solutes is −22.9 cal/mol/Å^2 (and this is also present between water−solvent molecules). The total solvent−water interaction, which would be referred to as the "hydrophobic effect", is 19.6 cal/mol/Å^2 (24.0 for alkanes) because the unfavorable hydrogen bond disruption opposes the previous attractive interaction with a 42.5 cal/mol/Å^2 value (48.9 for alkanes). As larger solutes introduce a larger accessible free volume into the solvent, there is also a $-RT_0/v_{solvent}$ term that favors solvation, which for water as solvent gives a −19.1 cal/mol/Å^2 term. These terms were calculated here only to provide a basis for comparison with other, previous models and not because we assign any special physicochemical meaning to them.

Partition into Water. For two immiscible solvents, the corresponding interaction coefficients must have considerably different values, $\omega_{i1} \neq \omega_{i2}$. Otherwise, the two solvents would be miscible to some reasonable degree. A solute that partitions between these two solvents will be in equilibrium when its chemical potential in the two phases is equalized, $\mu_i^{sol,1} = \mu_i^{sol,2}$. From here, within the present model, the partition coefficient $P_{1/2}$, which is defined as the ratio of the molar concentrations of the solute i in the two different phases, is obtained as

$$\log P_{1/2} = \log \frac{\rho_1}{\rho_2} = \frac{1}{\ln 10}\left(\omega_{i1} - \omega_{i2} + \frac{1}{v_1} - \frac{1}{v_2}\right)v_i \qquad (24)$$

Hexadecane−water partition data ($n = 69$, $r^2 = 0.956$) for solutes that are not subject to specific interactions gave a somewhat more negative intercept (−0.550 ± 0.107) than expected (0.000), but a slope (0.0394) that agrees very well with that which was predicted by this equation (0.082 + 0.070 + 1/232 − 1/14.6)/2.303 = 0.0381.[6] Octanol−water partition data gave an even better agreement (Figure 7), and for these data, imposing a zero intercept did not worsen the correlation giving[6]

$$\log P_{o/w} = 0.0327(\pm 0.0002)v \qquad (25)$$

$$n = 118,\ r^2 = 0.973,\ \sigma = 0.242,\ F = 4219.6$$

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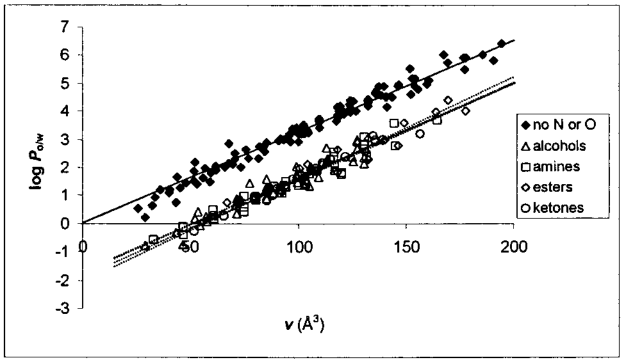

Figure 7. Log octanol−water partition coefficient as a function of molecular volume for 118 compounds having no strongly polar or hydrogen-bonding substituents (no N or O) and a total of 130 alcohols, amines, esters, and ketones. The continuous line is the trendline obtained using an imposed zero intercept for compounds with no N or O. Oxygen- or nitrogen-containing aliphatic monofunctionalized molecules show a very similar size-dependence, as illustrated here by the four separate trendlines for alcohols, amines, esters, and ketones (dashed).

However, the slope of the above equation, when compared to that of eq 24, indicates a value of $\omega_{io} = 0.066$ for solute−octanol ($v_o = 127.5$ Å^3) interactions, which is somewhat smaller than the values used until now (0.082) to describe nonspecific solute−solvent interactions (none of these solvents was, however, an alcohol). In fact, by assuming that this deviation is also due to disruption of hydrogen bonding in wet (water saturated) octanol, one can almost quantitatively account for it. As shown earlier, the disruption of hydrogen bonding in water caused a $\Delta\omega = -0.152$ change in the size-related interaction coefficient. Although a (formal) density of hydrogen bonds in water (two H-bonds per molecule, $v_w = 14.6$ Å^3) can be calculated as $2/14.6 = 0.137$ Å^{-3}, in water-saturated octanol (one H-bond per molecule, $v_o = 127.5$ Å^3; mole fraction of water in octanol, 0.275), the same density can be estimated as $(1 \times 0.725 + 2 \times 0.275)/(127.5 \times 0.725 + 14.6 \times 0.275) = 0.013$ Å^{-3}. Accordingly, as compared to water, one might expect a proportionally smaller change in the interaction coefficient of octanol: $\Delta\omega = -0.152 \times 0.013/0.137 = -0.014$. This makes the total solute−octanol interaction coefficient $\omega_{io} = 0.082 - 0.014 = 0.068$, which is in almost perfect numerical agreement with the value obtained from the slope of the experimental data (0.066).

As Figure 7 indicates, the size-dependence (the slope of log $P_{o/w}$ versus v) is essentially the same for oxygen- or nitrogen-containing aliphatic monofunctionalized molecules (e.g., alcohols, amines, esters, ketones). This indicates the similarity of the nonspecific interactions and the possibility to generalize the model. In fact, the generalization already has been achieved for log octanol−water partition coefficients by the introduction of a new, quantified parameter N (the shift of ~1.5 log units between the two essentially parallel trendlines of Figure 7 corresponds to an $N = 2$ value for alcohols, amines, esters, and ketones).[8,25,26] This N parameter is most likely related to the changes in hydrogen bonding at the acceptor sites of the solute produced by the octanol → water transfer. This assumption is supported by the agreement between the related Gibbs free energy change ($G_N{}^0 = 0.723RT_0 \ln 10 = 4.2$ kJ/mol) and that accepted for hydrogen bonds in water (4−6 kJ/mol),[34,68,98] by the correlation between N values and the solvatochromic hydrogen bond acceptor basicity (β),[99] by the agreement of N values with the similar N_I values derived for acceptor sites by Edward from the total N_H number of hydrogen bonds from the volume decrement caused by the polar function i in the partial molal volume V'^0 of organic solutes in water,[100] and by the general agreement between this model and that which was obtained recently from molecular dynamics simulations by Duffy and Jorgensen.[101]

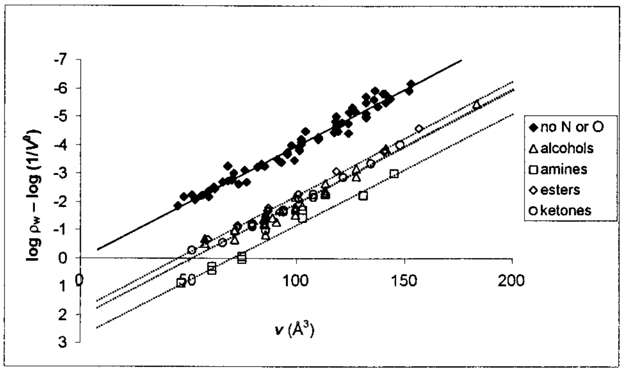

Figure 8. Log water solubility as a function of molecular volume for 68 compounds having no strongly polar or hydrogen-bonding substituents (no N or O) and a total of 55 alcohols, amines, esters, and ketones. The continuous line is the trendline for compounds with no N or O. Oxygen- or nitrogen-containing aliphatic monofunctionalized molecules show a very similar size-dependence, as illustrated here by the four separate trendlines for alcohols, amines, esters, and ketones (dashed). To illustrate the similarity between the problem of solubility and partition as treated here, log $1/V^0$ (eq 26) is subtracted, and the vertical axis is inverted.

Solubility in Water. The problem of solubility (for liquids) can be approached as the partitioning of a solute between a solvent and the solute itself because the two phenomena are identical at the molecular level. Therefore, for the present model, as long as the solubility is not very high, an expression for the solubility can be obtained by simply using 2 = i (solvent 2 = solute) in eq 24. Based on these considerations, for water solubility (ρ_w) one obtains

$$\log \rho_w - \log \frac{1}{V_i^0} = \frac{1}{\ln 10}\left[-1 + \left(\omega_{iw} - \omega_{ii} + \frac{1}{v_w}\right)v_i\right] = -0.434 - 0.0361v \quad (26)$$

Here ρ refers again to molar concentrations (mol/L), and $\rho_2 = 1/V_i{}^0$ was used for the solute when in pure liquid phase. Water solubility data on nonfunctionalized solvents gives a slightly more positive intercept and a slightly more negative slope than predicted, but an excellent general agreement with this equation (Figure 8)[6]

$$\log \rho_w - \log 1/V^0 = 0.036(\pm\, 0.097) - 0.0400(\pm\, 0.0009)v \quad (27)$$

$$n = 68,\ r^2 = 0.966,\ \sigma = 0.221,\ F = 1848.1$$

Furthermore, in a manner very similar to that of log $P_{o/w}$, the size-dependence (the slope versus v) is essentially the same for oxygen- or nitrogen-containing aliphatic monofunctionalized molecules (e.g., alcohols, amines, esters, and ketones) (Figure 8). The vertical axis of Figure 8 is inverted to further emphasize

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[101] Duffy, E. M.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2000**, *122*, 2878−2888.

the analogy between the treatment of the problem of partitioning and solubility, which now becomes evident through the similarity of Figures 7 and 8. It is hoped, therefore, that the development of a general predictive method for aqueous solubility within the present, unified framework in a manner similar to that developed for log $P_{o/w}$ will be possible. Because the shift between the essentially parallel trendlines of nitrogen- or oxygen-containing monofunctionalized molecules and nonfunctionalized molecules in log ρ_w − log $1/V^0$ (1.96 ± 0.04 without the amines, Figure 8) is close to the similar shift in log $P_{o/w}$ (1.61 ± 0.03, Figure 7), the adequacy of a similar approach is even more likely.

Conclusions

The general agreement between experimental data for a wide variety of properties related to intermolecular interactions and the predictions of the present, admittedly oversimplified, size-based model for organic liquids suggests that the molecular-level picture that forms its basis is, at least to a reasonable degree, correct. Molecules in the liquid phase can be considered as moving in a completely disordered and essentially free manner in a small fraction of the total volume that is not excluded by their own size and under the influence of an average attractive potential of the surrounding molecules that can be described by molecular volume through a simple, linear relationship. Furthermore, many unusual properties of water may be accounted for by a proper combination of the nonspecific interactions as extrapolated from other liquids, the unusually small size of its molecules, and an adequate model of hydrogen bonding.

Supporting Information Available: Table listing data included in the present study. This material is available free of charge via the Internet at http://pubs.acs.org.

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