

Molecular Size-Based Model To Describe Simple Organic Liquids

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Received: January 6, 1998; In Final Form: March 6, 1998

A simple, molecular size-based model is presented that allows unified description of solubilities, partition coefficients, vapor pressures, enthalpies of vaporization, and boiling points for a variety of simple organic liquids where no specific interactions are present. A free energy expression obtained from specific, molecular-level assumptions is used. This makes it unnecessary to rely on standard state and activity concepts, and it also leads to relations that cannot be obtained from purely thermodynamic arguments. Molecules in the liquid phase are considered as moving in a fraction of the volume not excluded by their own size and in an average attractive potential of the surrounding molecules that can be described by molecular volume through a simple, linear relationship. These assumptions allow the development of a model that gives unified and reasonably good description of organic liquids that have no hydrogen bonding or strongly polar substituents. In practically all of the individual correlations presented, molecular size alone as measured by computed van der Waals molecular volume, accounts for more than 90% of the variance in these properties. In addition, interaction constants derived from enthalpies of vaporization can describe not only boiling points but partition and solubility properties as well. A previously described, fully computerized method that estimates octanol–water partition properties for a large variety of organic solutes (Bodor, N.; Buchwald, P. *J. Phys. Chem. B* 1997, 101, 3404) can also be integrated within this approach.

Introduction

The present work explores the possibilities of a simple, molecular size-based model that allows a unified description and estimation of solubilities, partition coefficients, vapor pressures, enthalpies of vaporization, and boiling points for a variety of simple organic liquids where no specific interactions are present. The free energy expression used is obtained within a statistical mechanics approach using a number of clearly stated molecular-level assumptions. This makes it unnecessary to rely on often misused concepts of standard states and activities, and it leads to relations that cannot be obtained from purely thermodynamic arguments.^{1–3} In addition, by considering different molecular size-dependent effects and by assuming the existence of a simple, size-determined, attractive interaction potential in the liquid phase, unified and reasonably good descriptions are achieved for the above-mentioned properties of organic liquids that have no hydrogen bonding or strongly polar substituents. In practically all of the individual correlations presented, just one structure-determined parameter, computed van der Waals molecular volume, accounts for more than 90% of the variance in these properties. In addition, interaction constants derived from enthalpies of vaporization can describe not only boiling points, but partition and solubility properties as well. Within certain limits, description of properties related to water solubility is also possible by using the same model with a different interaction constant to characterize solute–water nonspecific interactions. Furthermore, a previously derived model^{4,5} to estimate log octanol–water partition coefficient (log $P_{o/w}$) for a wide range of compounds, including large, multi-functionalized molecules,^{4–8} can also be integrated within this

approach by inclusion of only one additional parameter that might describe changes in hydrogen bonding during octanol–water transport.

Model

Statistical mechanic theory incorporates all information about the thermodynamic properties of a system into the partition function, which represents a sum over all possible microstates l of energy E_l

$$Q = \sum_l e^{-E_l/(kT)} \quad (1)$$

A simple connection to usual thermodynamic quantities can be made, for example, through the Helmholtz free energy, $A = -kT \ln Q$. Thus, the chemical potential, our main interest here, is obtained for a given component i as

$$\mu_i = \left(\frac{\partial A}{\partial N_i} \right)_{T,V,N_j} = -kT \left(\frac{\partial \ln Q}{\partial N_i} \right)_{T,V,N_j} \quad (2)$$

Usual notation is used: k , Boltzmann constant; T , temperature; N_i , number of i type molecules. To obtain a model that is of any use for liquids, a few simplifying assumptions have to be made. Most of the following assumptions already have been explored in other models. To clarify the background and to ensure consistency, we will briefly outline main ideas and major consequences.

(a) *The translational degrees of freedom of the molecules are essentially classical.* This condition should be satisfied by most liquids, except maybe those that form only at very low temperatures, like liquid hydrogen.

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(b) *The internal degrees of freedom are essentially the same in the liquid as in the gas.* We assume, therefore, that molecular rotation and intramolecular vibration are unaffected by the presence of neighbor molecules in the liquid. This is a reasonable approximation, even if it is strictly true for hard spheres only.

These two assumptions are fairly general and common.⁹ They allow the factoring out of the internal degrees of freedom and the integration of the translational part. We omit details of the derivation and only briefly summarize the translation-related part for a nondegenerate system of indistinguishable molecules. If Boltzmann statistics applies, the canonical ensemble partition function can be written as^{10,11}

$$Q_t = \frac{q_t^N}{N!} = \frac{V^N e^N}{\Lambda^{3N} N^N} \quad (3)$$

In this equation, V denotes the volume, q_t is the translational part of the molecular partition function, and Λ^3 is the momentum partition function obtained from integration over all possible translational momenta of the molecule. Λ is also referred to as the thermal de Broglie wavelength, and it equals $(h^2/2\pi mkT)^{1/2}$ (m , mass of molecule; h , Planck constant).

If interactions are present, some assumptions concerning the interaction potential must also be made. A crude approximation, introduced originally by Guggenheim,¹² is obtained from the following frequently used assumption:

(c) *The interaction potential may be replaced by its value averaged over all accessible configurations.* This value is denoted here W_i .

This last assumption introduces an additional NW_i term in the equation for the Helmholtz free energy

$$A_t = -kT \ln Q_t + NW_i = -NkT - NkT \ln \left(\frac{V}{\Lambda^3 N} \right) + NW_i \quad (4)$$

Through eq 2, this leads to a chemical potential that is essentially identical with that used by Ben-Naim^{2,3}

$$\mu_i = kT \ln \left(\frac{N_i \Lambda_i^3}{V q_i} \right) + W_i = kT \left[\ln \left(\frac{N_i \Lambda_i^3}{V q_i} \right) - \ln \langle e^{-B_i/(kT)} \rangle \right] \quad (5)$$

Here B_i is the binding energy of one molecule i at a fixed position to all the other molecules at a specified configuration, and $\langle \rangle$ denotes an ensemble average over all the possible configurations of all other molecules in the system. Furthermore, q_i is the internal partition function of a single molecule i . As stated in (b), it is considered independent of the environment; therefore, it will be disregarded (considered 1) from now on.

The first term in 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 , and within classical limits, it is always negative. In the formalism used by Ben-Naim, it is referred to as "liberation" free energy and represents the change due to the release of the molecule from a fixed position. In the qualitative picture given by Ben-Naim,³ the translational kinetic energy acquired in this process contributes the $kT \ln \Lambda_i^3$ term, the availability of the volume V introduces the $-kT \ln V$ term, and the loss of distinguishability from all other similar molecules is responsible for the $kT \ln N_i$ term. The second term on the right-hand side of eq 5 can be regarded as the average work W_i of coupling a molecule located at some fixed position to its environment.

For perfect gases, the volume occupied by molecules is negligible, and there are no intermolecular forces ($B_i = 0$, $W_i = 0$). All familiar expressions for perfect gases can be obtained from these conditions, including

$$\mu^{\text{gas}} = kT \ln \left(\frac{N}{V \Lambda^3} \right) = kT \ln(\rho \Lambda^3); \quad \Lambda = \sqrt{\frac{h^2}{2\pi mkT}} \quad (6)$$

Here ρ represents particle density. If neither the size nor the interactions are negligible, one may assume that the free volume available for translation is the total volume less that excluded by the molecules regarded as hard spheres, $V^{\text{free}} = V - Nb$, and the interaction is simply proportional to particle density, $W = -a\rho = -aN/V$. Introducing these expressions in eq 4, the well-known van der Waals equation of state for gases can be obtained

$$p = -\left(\frac{\partial A}{\partial V} \right)_{T,N} = -\frac{aN^2}{V^2} + \frac{NkT}{V - Nb} \quad (7)$$

Despite an overwhelming need, no thoroughly good model exists for liquids, especially for those of chemical interest. The situation is more difficult here as noncovalent intramolecular forces play a major role, and their complex nature makes it practically impossible to describe all effects. Development of simple models was also impeded by the complexity of the involved quantum mechanic calculations.¹³ Nevertheless, a limited number of parameters may account for a large majority of the variance in liquid properties. A study by Cramer¹⁴ suggested that two variables suffice to explain ~95% of the variance in several physical properties of the 114 liquids considered. Since molecular size clearly plays a major role, and a good number of evidence suggests linearity between size and free energies of transfer, we will explore the following assumptions accounting for different size-related effects:

(d) *In simple liquids, the binding energy and hence the coupling work of a molecule to its environment are linearly related to molecular volume.*

This should account for most nonspecific intermolecular interactions in liquids where they are, at least to a reasonable extent, orientation averaged. Therefore, for most molecules, among attractive van der Waals forces, including dipole–dipole, dipole–induced dipole, and dispersion forces, dispersion forces are clearly dominant.^{9,11,15} As they strongly depend on polarizability, and polarizability is to a good extent size related, molecular size as measured by molecular volume should be a good predictor for the interaction potential of these nonspecific forces. There are indeed many studies proving not only good correlation between free energies of transfer (as measured, for example, by log partition coefficients or log solubilities) and molecular size, but also a quite similar slope within different classes of compounds.^{16–23} Therefore, instead of focusing on pairwise interactions, we introduce an average interaction energy between a molecule and its environment that is linearly related to molecular volume v : $W_i = -w_0 - wv$. We expect w_0 and w to be interaction-related constants that are about the same for similar liquids. Size alone cannot account for more specific interactions, such as hydrogen bonding or interactions between strongly polar substituents (not to mention problems related to association and/or dissociation); therefore, in a complete treatise W should contain additional terms. However, since our purpose here is to show that the present form can account for most nonspecific effects in several liquids, we will let such additional terms be absorbed in w_0 for now.

Among the assumptions made here, this one is the only one that has not been explored in previous models. However, Ben-Naim already derived models suggesting the use of a solute volume (V) and surface area (A) dependent, $W = aV + bA$, form, which for large (spherical) solutes should have the R^3 proportional volume as leading term.^{24–26} He found these results consistent with the scaled-particle theory²⁷ predictions that W is a cubic polynomial in R_{cav} .²⁶

For organic compounds such as those included here it has been shown that molecular volume and surface area are well-correlated, even if computed with somewhat different radii sets.^{4,22,28} We, therefore, prefer to designate our potential and the resulting model simply as size-based, and we will use volume, which is somewhat more convenient and was also used in our previous partition model.^{4–8} Considering the empirical success of the van der Waals radius concept and the fact that contours of constant electronic density (0.001–0.002 electrons/ \AA^3) that contain over 96% of the total electronic charge gave good representations of the molecular van der Waals surfaces or of the smoother contact surfaces,²⁹ the van der Waals volume computed as described in our previous publication⁴ should give a good description of molecular size.

(e) *The volume of the liquid phase is a linear function of molecular numbers and molecular volumes.*

Hence, for a pure liquid, the molar volume will be considered as $V^0 = aN_0v$. This is a simplifying assumption but represents a reasonable estimate for most organic molecules, and it makes possible estimates starting from molecular structure alone. For our data (part of which is presented in Table 1), even if not all densities were determined at the same temperature (many included compounds do not even condense to liquids around room temperature and normal pressure), we found V^0 (L) = 0.001 23 v (\AA^3) ($n = 260$, $r^2 = 0.87$). Only flat, multiring aromatics, such as perylene or fluoranthrene, were strong deviants.

For mixtures of different compounds, the volume of the liquid phase will be considered as $V = n_iV_i^0 + n_jV_j^0 = a(N_iv_i + N_jv_j)$. Thus, it is determined by the number and the size of its constituent molecules, an assumption similar to that used by Hildebrand.³⁰ When molecules of unequal size are mixed, these assumptions introduce an additional term in the corresponding equations. Such terms, obtained (or not obtained) by different authors within different models, generated considerable controversy recently, much of which we were unaware of during the development of the present model.^{24–26,31–45}

(f) *The volume available for translation in a liquid can be considered as a fraction f of the total volume of the liquid, $V^{\text{free}} = fV$.* This changes the translational contribution to the chemical potential in eq 5 into $kT \ln(N\Lambda^3/fV)$, where $f < 1$.

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 (eq 7). Therefore, to maintain the advantages of Ben-Naim's approach,^{1–3} we will introduce a factor f in the form $kT \ln(N\Lambda^3/fV)$ and assume that it is approximately the same for the considered liquids. Assumptions (e) and (f) are practically those introduced in the Hildebrand model.^{30,44} The f fraction introduced here equals $c/(c + 1)$, where c , as defined in eq 5.7 in the review of Chan and Dill,⁴⁴ 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. Introduction of each solute molecule in 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. No temperature dependence is included in formulas used for the free volume or in the interaction potential, but certainly both are temperature dependent to some extent. This is again a simplification that might affect some derived properties later, even if polarizability, for example, is nearly temperature independent.¹⁵

The above assumptions give for a pure liquid

$$\mu^{\text{liq}} = kT \ln\left(\frac{N\Lambda^3}{fV}\right) - wv - w_0 = kT \ln\left(\frac{\rho\Lambda^3}{f}\right) - wv - w_0 \quad (8)$$

For a liquid mixture of i and j , the total Gibbs free energy is $G = N_i\mu_i + N_j\mu_j$. Since the volume V is a function of N_i as stated in (e), after performing the partial derivative, we obtain for the chemical potential of component i (considered here as the solute)

$$\mu_i^{\text{sol},j} = \left(\frac{\partial G}{\partial N_i}\right)_{p,T,N_j} = kT \ln\left(\frac{N_i\Lambda^3}{fV}\right) - w_{ij}v_i - w_0 + kT\left(1 - \frac{N_iv_i + N_jv_j}{N_iv_i + N_jv_j}\right) \quad (9)$$

The term w_{ij} accounts for the interaction of solute i with solvent j , and to get a model of any use it should be about the same for similar organic solvents as already stated in (d). For sufficiently dilute solutions, all i molecules are surrounded by j molecules only. No i – i interactions have to be considered justifying the use of only a w_{ij} term. Meanwhile, $N_j \gg N_i$, and thus

$$\mu_i^{\text{sol},j} = kT \ln\left(\frac{\rho_i\Lambda_i^3}{f}\right) - \left(w_{ij} + \frac{kT}{v_j}\right)v_i - w_0 + kT \quad (10)$$

Compared to eq 8, different molecular sizes and volume additivity introduce here an additional $kT(1 - v_i/v_j)$ term. As mentioned in (e), such terms, obtained (or not obtained) by different authors using different assumptions, generated considerable controversy recently.^{24–26,31–45} In addition to the Hildebrand model, formally similar terms can be obtained⁴⁴ within the framework of the Flory–Huggins theory of polymer mixing or within the theory proposed by Sharp and co-workers. In the present model, it 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.

To summarize, we will consider molecules in simple liquids as moving in a fraction of the volume not excluded by their own size and in an average attractive potential of the surrounding molecules that can be described by molecular volume through a simple, linear relationship as long as no strongly specific interactions are present. It may be worthwhile to compare the chemical potential form obtained in eq 10 with the general form (eq 5) written in the formalism of Ben-Naim as

$$\mu_i = kT \ln \rho_i \Lambda_i^3 + W(i|I) \quad (11)$$

Here $W(i|I)$ is referred to as the coupling work of i to the system and denotes the average Gibbs energy of interaction of i with its entire surroundings.³ It can be seen now that in the present model we have

TABLE 1: Experimental Data for Compounds Included in the Present Study^a

compound	formula	v (Å ³)	M_W	density (kg/L)	V^0 (L)	ΔH^0_{vap} (kJ/mol)	T_b (°C)	$\log \gamma_{\text{hd}}$	$\log \rho^{\text{gas}}$ (mol/L)	$\log \gamma_w$	$\log P_{\text{hd/w}}$	$\log P_{\text{o/w}}$	$\log \rho_w$ (mol/L)
bromotrifluoromethane	C ₁ BrF ₃	51.61	148.91	1.5800	0.0942		-57.80			-1.31		1.86	-2.70
chlorotrifluoromethane	C ₁ ClF ₃	43.99	104.46				-81.40			-1.85		1.65	-3.24
dichlorodifluoromethane	C ₁ Cl ₂ F ₂	52.00	120.91				-29.80			-1.24		2.16	-2.63
tetrachloromethane	C ₁ Cl ₄	67.98	153.82	1.5940	0.0965	29.82	76.80	2.82	-2.15	-0.06	2.88	2.83	-2.22
tetrafluoromethane	C ₁ F ₄	35.98	88.00	3.0340	0.0290		-128.00			-2.29	1.49	1.18	-3.71
chlorodifluoromethane	C ₁ H ₁ ClF ₂	40.40	86.47	1.4909	0.0580		-40.70			-0.08		1.08	-1.47
trichloromethane (chloroform)	C ₁ H ₁ Cl ₃	56.58	119.38	1.4832	0.0805	29.24	61.17	2.48	-1.87	0.79	1.69	1.97	-1.12
trifluoromethane	C ₁ H ₁ F ₃	32.31	70.01				-82.10			-0.59		0.64	-1.98
bromochloromethane	C ₁ H ₂ BrCl	53.05	129.38	1.9344	0.0669		68.00					1.41	-0.89
dichloromethane	C ₁ H ₂ Cl ₂	45.17	84.93	1.3266	0.0640	28.06	40.00	2.02			1.06	1.25	-0.65
difluoromethane	C ₁ H ₂ F ₂	28.99	52.02	0.9600	0.0542		-51.60					0.20	
bromomethane	C ₁ H ₃ Br	40.57	94.94	1.6755	0.0567	23.91	3.50	1.63		0.60	1.03	1.19	-0.81
chloromethane	C ₁ H ₃ Cl	33.76	50.49	0.9110	0.0554	21.40	-24.09	1.16		0.40	0.76	0.91	-1.00
fluoromethane	C ₁ H ₃ F	25.66	34.03	0.5660	0.0601		-78.40			0.16		0.51	-1.23
iodomethane	C ₁ H ₃ I	51.63	141.94	2.2790	0.0623	27.34	42.55	2.11	-1.66	0.65	1.46	1.51	-1.01
halothane	C ₂ H ₁ BrClF ₃	77.02	197.38	1.8710	0.1055	28.08	50.20			0.08	2.10	2.30	
1,1,1-trichloroethane	C ₂ H ₃ Cl ₃	70.80	133.40	1.3390	0.0996	29.86	74.09	2.73	-2.14	0.14	2.59	2.49	-2.00
1,1-dichloroethane	C ₂ H ₄ Cl ₂	59.43	98.96	1.1757	0.0842	28.85	57.40	2.32	-1.91	0.62	1.70	1.79	-1.29
1,2-dichloroethane	C ₂ H ₄ Cl ₂	59.31	98.96	1.2351	0.0801	31.98	83.50	2.57	-2.32		1.26	1.48	-1.05
1,1-difluoroethane	C ₂ H ₄ F ₂	43.29	66.05	0.8960	0.0737	21.56	-24.95			0.08		0.75	-1.31
bromoethane	C ₂ H ₅ Br	55.77	108.97	1.4604	0.0746	27.04	38.50	2.12	-1.58	0.54	1.58	1.61	-1.07
chloroethane	C ₂ H ₅ Cl	47.95	64.51	0.8902	0.0725	24.65	12.30	1.68	-1.48	0.46	1.22	1.43	-1.02
iodoethane	C ₂ H ₅ I	65.84	155.97	1.9358	0.0806	29.44	72.50	2.57	-2.13	0.54	2.03	2.00	-1.60
1,3-dichloropropane	C ₃ H ₆ Cl ₂	73.30	112.99	1.1876	0.0951	35.18	120.90	3.10	-2.99		1.71	2.00	-1.60
1-bromopropane	C ₃ H ₇ Br	69.82	122.99	1.3537	0.0909	29.84	71.10	2.62	-2.12	0.41	2.21	2.10	-1.71
1-chloropropane	C ₃ H ₇ Cl	61.96	78.54	0.8899	0.0883	27.18	46.50	2.20	-1.72	0.24	1.96	2.04	-1.46
2-chloropropane	C ₃ H ₇ Cl	62.00	78.54	0.8617	0.0911	26.30	35.70	1.97	-1.59	0.18	1.79	1.90	-1.41
1-bromobutane	C ₄ H ₉ Br	83.84	137.02	1.2758	0.1074	32.51	101.60	3.11	-2.66	0.29	2.82	2.75	-2.36
1-chlorobutane	C ₄ H ₉ Cl	75.96	92.57	0.8862	0.1045	30.39	78.60	2.72	-2.22	0.12	2.60	2.64	-2.12
1-bromopentane	C ₅ H ₁₁ Br	97.58	151.05	1.2182	0.1240	35.01	129.80	3.61	-3.15	0.07	3.54	3.37	-3.08
1-fluoropentane	C ₅ H ₁₁ F	81.72	90.14	0.7907	0.1140		62.80					2.33	
hexachlorobenzene	C ₆ Cl ₆	169.58	284.78	2.0440	0.1393		325.00					5.73	
hexafluorobenzene	C ₆ F ₆	84.32	186.06	1.6184	0.1150	31.66	80.26					2.55	
pentachlorobenzene	C ₆ HCl ₅	152.85	250.34	1.8342	0.1365		277.00					5.18	-5.28
1,2,3,4-tetrachlorobenzene	C ₆ H ₂ Cl ₄	135.95	215.89				254.00	6.17		0.98	5.19	4.64	-4.25
1,2,3,5-tetrachlorobenzene	C ₆ H ₂ Cl ₄	136.28	215.89					5.92		1.19	4.73	4.66	-4.77
1,2,4,5-tetrachlorobenzene	C ₆ H ₂ Cl ₄	136.28	215.89	1.8580	0.1162		244.50	5.93		0.92	4.95	4.60	-4.96
1,3,5-tribromobenzene	C ₆ H ₃ Br ₃	143.87	314.80				271.00					4.51	
1,2,3-trichlorobenzene	C ₆ H ₃ Cl ₃	119.04	181.45	1.4533	0.1249		218.50	5.42		0.91	4.13	4.14	-3.76
1,2,4-trichlorobenzene	C ₆ H ₃ Cl ₃	119.37	181.45	1.4590	0.1244		213.50	5.25		0.82	4.43	4.02	-3.57
1,3,5-trichlorobenzene	C ₆ H ₃ Cl ₃	119.62	181.45				208.00	5.05		0.57	4.48	4.19	-4.44
<i>o</i> -dibromobenzene	C ₆ H ₄ Br ₂	117.71	235.91	1.9843	0.1189		225.00					3.64	-3.50
<i>p</i> -dibromobenzene	C ₆ H ₄ Br ₂	118.59	235.91	2.2610	0.1043		218.50					3.79	-4.01
<i>m</i> -dichlorobenzene	C ₆ H ₄ Cl ₂	102.45	147.00	1.2884	0.1141	38.62	173.00	4.41	-3.80	0.72	3.69	3.53	-3.08
<i>o</i> -dichlorobenzene	C ₆ H ₄ Cl ₂	102.12	147.00	1.3059	0.1126	39.66	180.00	4.52	-4.13	1.00	3.52	3.43	-3.13
<i>p</i> -dichlorobenzene	C ₆ H ₄ Cl ₂	102.40	147.00	1.2475	0.1178	38.79	174.00	4.44	-4.02	0.74	3.70	3.44	-3.28
bromobenzene	C ₆ H ₅ Br	93.28	157.01	1.4950	0.1050		156.06	4.04	-3.46	1.07	2.97	2.99	-2.39
chlorobenzene	C ₆ H ₅ Cl	85.22	112.56	1.1058	0.1018	35.19	131.72	3.66	-3.00	0.82	2.84	2.89	-2.26
fluorobenzene	C ₆ H ₅ F	70.72	96.10	1.0225	0.0940	31.19	84.73	2.79	-2.37	0.59	2.26	2.27	-1.79
iodobenzene	C ₆ H ₅ I	101.55	204.01	1.8308	0.1114		188.40	4.50	-4.15	1.28	3.22	3.25	-2.87
benzene	C ₆ H ₆	68.03	78.11	0.8765	0.0891	30.72	80.09	2.79	-2.31	0.63	2.15	2.13	-1.66
bromocyclohexane	C ₆ H ₁₁ Br	102.81	163.06	1.3359	0.1221		166.20					3.20	
trifluoromethylbenzene	C ₇ H ₅ F ₃	91.96	146.11	1.1884	0.1229	32.63	102.10				2.71	3.01	
<i>m</i> -chlorotoluene	C ₇ H ₇ Cl	99.24	126.59	1.0750	0.1178		161.80	4.16				3.28	
<i>o</i> -chlorotoluene	C ₇ H ₇ Cl	99.14	126.59	1.0825	0.1169		159.00	4.17	-3.37	0.84	3.33	3.42	-2.53
<i>p</i> -chlorotoluene	C ₇ H ₇ Cl	99.14	126.59	1.0825	0.1169		159.00	4.16				3.33	-2.53
toluene	C ₇ H ₈	82.00	92.14	0.8669	0.1063	33.18	110.63	3.26	-2.80	0.65	2.68	2.73	-2.24
1-bromoheptane	C ₇ H ₁₅ Br	125.68	179.10	1.4000	0.1279		179.00	4.66	-4.18	-0.25	4.91	4.36	-4.43
1-chloroheptane	C ₇ H ₁₅ Cl	118.04	134.65	0.8758	0.1537		159.00	4.28	-3.79	-0.21	4.49	4.15	-4.00
1-iodoheptane	C ₇ H ₁₅ I	136.13	226.10	1.3791	0.1639		204.00	5.09	-4.61	-0.20	5.29	4.70	-4.81
styrene	C ₈ H ₈	91.16	104.15	0.9060	0.1150		145.00	3.86		0.91	2.95	2.95	-2.54
ethylbenzene	C ₈ H ₁₀	96.00	106.17	0.8670	0.1225	35.57	136.19	3.78	-3.26	0.58	3.20	3.15	-2.81
<i>m</i> -xylene	C ₈ H ₁₀	95.99	106.17	0.8642	0.1229	35.66	139.12	3.84	-3.41	0.61	3.23	3.20	-2.82
<i>o</i> -xylene	C ₈ H ₁₀	95.78	106.17	0.8802	0.1206	36.24	144.50	3.94	-3.42	0.66	3.28	3.12	-2.76
<i>p</i> -xylene	C ₈ H ₁₀	96.04	106.17	0.8611	0.1233	35.67	138.37	3.84	-3.36	0.59	3.25	3.15	-2.77
1-bromooctane	C ₈ H ₁₇ Br	140.06	193.13	1.1080	0.1743		200.00	5.09	-4.68	-0.38	5.47	4.89	-5.06
1 <i>H</i> -indene	C ₉ H ₈	96.33	116.16	0.9960	0.1166		182.00					2.92	
allylbenzene	C ₉ H ₁₀	105.03	118.18	0.8920	0.1325		156.00					3.23	
cyclopropylbenzene	C ₉ H ₁₀	103.82	118.18	0.9317	0.1268		173.60					3.27	
indan	C ₉ H ₁₀	101.53	118.18	0.9639	0.1226	39.63	177.97	4.59		1.07	3.52	3.18	-3.04
1,2,4-trimethylbenzene	C ₉ H ₁₂	110.15	120.19	0.8758	0.1372		169.38	4.44	-3.95	0.63	3.81	3.63	-3.32
1,3,5-trimethylbenzene	C ₉ H ₁₂	110.11	120.19	0.8652	0.1389		164.70	4.34	-3.90	0.66	3.68	3.42	-3.40
isopropylbenzene	C ₉ H ₁₂	109.97	120.19	0.8618	0.1395		152.40	4.08	-3.60	0.22	3.86	3.66	-3.38
propylbenzene	C ₉ H ₁₂	110.00	120.19	0.8620	0.1394		159.24	4.23	-3.73	0.39	3.84	3.72	-3.34
azulene	C ₁₀ H ₈	100.46	128.17									3.20	
naphthalene	C ₁₀ H ₈	104.37	128.17	1.0253	0.1250		217.90	5.16		1.76	3.41	3.30	-3.57
1,2,3,4-tetramethylbenzene	C ₁₀ H ₁₄	124.12	134.22	0.9052	0.1483		205.00					3.98	

TABLE 1. (continued)

compound	formula	v (Å ³)	M_W	density (kg/L)	V^0 (L)	ΔH_{vap}^0 (kJ/mol)	T_b (°C)	$\log \gamma_{\text{hd}}$	$\log \rho^{\text{gas}}$ (mol/L)	$\log \gamma_w$	$\log P_{\text{hd/w}}$	$\log P_{\text{o/w}}$	$\log \rho_w$ (mol/L)
1,2,3,5-tetramethylbenzene	C ₁₀ H ₁₄	124.26	134.22	0.8903	0.1508		198.00					4.04	
1,2,4,5-tetramethylbenzene	C ₁₀ H ₁₄	124.28	134.22	0.8380	0.1602		196.80					4.00	−4.34
butylbenzene	C ₁₀ H ₁₄	124.16	134.22	0.8601	0.1561		183.31	4.73	−4.23	0.29	4.44	4.38	−3.94
tert-butylbenzene	C ₁₀ H ₁₄	124.08	134.22	0.8665	0.1549		169.10	4.41	−3.92	0.32	4.09	4.11	−3.60
adamantane	C ₁₀ H ₁₆	123.60	136.24	1.0700	0.1273							4.24	
1-bromodecane	C ₁₀ H ₂₁ Br	167.85	221.18	1.0702	0.2067		240.60					6.00	
1-methylnaphthalene	C ₁₁ H ₁₀	118.39	142.20	1.0202	0.1394		244.70	5.80		1.79	4.05	3.87	
2-methylnaphthalene	C ₁₁ H ₁₀	118.42	142.20	1.0058	0.1414		241.10					3.86	−3.84
n-pentylbenzene	C ₁₁ H ₁₆	137.65	148.25	0.8585	0.1727		205.40	5.23	−4.76	0.17	5.06	4.90	−4.59
pentamethylbenzene	C ₁₁ H ₁₆	138.45	148.25	0.9170	0.1617		232.00					4.56	
decachlorobiphenyl	C ₁₂ Cl ₁₀	270.53	498.66									8.27	
2,3,4,5-PCB	C ₁₂ H ₆ Cl ₄	194.59	291.99									6.41	
2,4,5-PCB	C ₁₂ H ₇ Cl ₃	177.79	257.55									5.90	
2,2'-PCB	C ₁₂ H ₈ Cl ₂	159.89	223.10									4.97	−5.35
2,4'-PCB	C ₁₂ H ₈ Cl ₂	160.87	223.10									5.10	−5.07
2-PCB	C ₁₂ H ₉ Cl	143.37	188.66	1.1499	0.1641		274.00					4.53	−4.84
1,1'-biphenyl	C ₁₂ H ₁₀	127.06	154.21	1.0400	0.1483		256.10	6.01		1.95	4.08	4.01	−4.33
1,3-dimethylnaphthalene	C ₁₂ H ₁₂	132.42	156.23	1.0144	0.1540		263.00	6.24		1.81	4.51	4.42	−4.30
1,4-dimethylnaphthalene	C ₁₂ H ₁₂	132.46	156.23	1.0166	0.1537		268.00	6.34		2.07	4.27	4.37	−4.16
1-ethylnaphthalene	C ₁₂ H ₁₂	132.43	156.23	1.0082	0.1550		258.60	6.14		1.76	4.38	4.39	−4.20
2,3-dimethylnaphthalene	C ₁₂ H ₁₂	132.47	156.23	1.0030	0.1558		268.00	6.29		2.04	4.25	4.40	−4.70
2,6-dimethylnaphthalene	C ₁₂ H ₁₂	132.42	156.23	1.0030	0.1558		262.00	6.23		1.93	4.30	4.31	−4.89
hexamethylbenzene	C ₁₂ H ₁₈	152.48	162.27	1.0630	0.1527		263.40					4.61	
n-hexylbenzene	C ₁₂ H ₁₈	151.95	162.27	0.8575	0.1892		226.10	5.72	−5.23	0.03	5.69	5.52	−5.20
9H-fluorene	C ₁₃ H ₁₀	132.64	166.22	1.2030	0.1382		295.00	6.92		2.46	4.40	4.18	
diphenylmethane	C ₁₃ H ₁₂	141.39	168.24	1.0010	0.1681		265.00					4.14	−4.70
1,4,5-trimethylnaphthalene	C ₁₃ H ₁₄	146.40	170.25									4.90	
anthracene	C ₁₄ H ₁₀	140.71	178.23	1.2800	0.1392		339.90	7.57		2.90	4.67	4.50	
phenanthrene	C ₁₄ H ₁₀	140.79	178.23	0.9800	0.1819		340.00	7.63		2.85	4.74	4.52	−5.05
9H-fluorene, 9-methyl	C ₁₄ H ₁₂	146.75	180.25	1.0263	0.1756							4.97	
dibenzyl	C ₁₄ H ₁₄	155.77	182.27	0.9780	0.1864		284.00					4.79	
fluoranthrene	C ₁₆ H ₁₀	154.34	202.26	1.2520	0.1615		384.00					5.16	
pyrene	C ₁₆ H ₁₀	154.45	202.26	1.2710	0.1591		404.00	8.83		3.32	5.51	4.88	
decylbenzene	C ₁₆ H ₂₆	207.83	218.38	0.8555	0.2553							7.35	
naphthacene	C ₁₈ H ₁₂	177.06	228.29									5.90	
triphenylene	C ₁₈ H ₁₂	177.29	228.29				425.00					5.49	
p-terphenyl	C ₁₈ H ₁₄	185.89	230.31				376.00					6.03	
perylene	C ₂₀ H ₁₂	190.74	252.32	1.3500	0.1869							5.82	
methane	C ₁ H ₄	22.34	16.04	0.4228	0.0379	8.19	−161.48	−0.32		−1.46	1.14	1.09	−2.82
ethane	C ₂ H ₆	36.36	30.07	0.5446	0.0552	14.69	−88.60	0.49		−1.34	1.83	1.81	−2.70
cyclopropane	C ₃ H ₆	44.24	42.08	0.6170	0.0682	20.05	−32.81	1.31		−0.55	1.86	1.72	
propane	C ₃ H ₈	50.45	44.10	0.4930	0.0895	19.04	−42.10	1.05		−1.44	2.49	2.36	−2.85
butane	C ₄ H ₁₀	64.55	58.12	0.5730	0.1014	22.44	−0.50	1.62		−1.52	3.13	2.89	−2.97
isobutane	C ₄ H ₁₀	64.59	58.12	0.5510	0.1055	21.30	−11.73	1.41		−1.70	3.11	2.76	−3.07
cyclopentane	C ₅ H ₁₀	70.10	70.13	0.7457	0.0940	27.30	49.30	2.48	−1.77	−0.88	3.40	3.00	−2.65
2,2-dimethylpropane	C ₅ H ₁₂	78.52	72.15	0.5852	0.1233	22.74	9.48	1.82		−1.84	3.66	3.11	−3.34
n-pentane	C ₅ H ₁₂	78.42	72.15	0.6262	0.1152	25.79	36.06	2.16	−1.56	−1.70	3.87	3.51	−3.27
cyclohexane	C ₆ H ₁₂	84.19	84.16	0.7785	0.1081	29.97	80.73	2.96	−2.17	−0.90	3.91	3.44	−3.07
2,2-dimethylbutane	C ₆ H ₁₄	92.66	86.18	0.6444	0.1337	26.31	49.73	2.35	−1.71	−1.84	4.19	3.82	−3.61
2,3-dimethylbutane	C ₆ H ₁₄	92.78	86.18	0.6616	0.1303	27.38	57.98	2.50		−1.72	4.22	3.85	−3.62
n-hexane	C ₆ H ₁₄	92.48	86.18	0.6548	0.1316	28.85	68.73	2.67	−2.14	−1.82	4.49	3.90	−3.96
cycloheptane	C ₇ H ₁₄	98.27	98.19	0.8098	0.1213		118.40			−0.59		4.00	
methylcyclohexane	C ₇ H ₁₄	98.15	98.19	0.7694	0.1276	31.27	100.93	3.32		−1.25	4.49	3.61	−3.85
n-heptane	C ₇ H ₁₆	106.53	100.20	0.6837	0.1466	31.77	98.50	3.17	−2.61	−1.96	5.14	4.50	−4.53
octane	C ₈ H ₁₈	120.63	114.23	0.6986	0.1635	34.41	125.67	3.68	−3.12	−2.11	5.79	5.18	−5.24
n-dodecane	C ₁₂ H ₂₆	176.54	170.34	0.7487	0.2275		216.32					6.80	
n-tetradecane	C ₁₄ H ₃₀	204.33	198.39	0.7628	0.2601		253.58					8.00	

^a Values in italic have not been used in correlations (see text).

(1) an additional factor f that describes the fraction of the total volume available for translation in a liquid,

(2) a simple, molecular size-related attractive potential $-w_{ij}v_i - w_0$ to describe the coupling work, and

(3) an additional $kT(1 - v_i/v_j)$ term to account for different volume contributions of differently sized molecules.

To test the validity of the model, expressions for measurable properties will be derived from the chemical potentials obtained in eqs 6, 8, and 10, and they will be compared to available experimental data. The present approach relies on clearly stated assumptions regarding molecular interactions, avoids the need for often hypothetical standard states or related activities, leads to relations that cannot be obtained from purely thermodynamic

arguments, and gives a unified view of all these processes as related to equilibrium distributions of molecules between two different phases. As the model is based on computed molecular size, it makes possible reasonable property estimates from three-dimensional molecular structures.

If a molecule partitions between two phases that are at the same temperature and pressure, equilibrium is reached when the chemical potential is the same in both phases

$$\mu_i^\alpha = \mu_i^\beta \quad (12)$$

Equations obtained from such conditions link equilibrium concentrations to different intermolecular interactions in the two

phases. As solubility and partitioning data used here are mainly at room temperature (T_0), for convenience, we will introduce interaction constants $\omega = w/kT_0$.

Experimental Data

The database collected contains more than 400 molecules with at least one piece of experimental data available. Enthalpies of vaporization, boiling points, densities, and molecular weights are from recent collections;^{46,47} water solubilities are from articles published by Hine and Mookerje,⁴⁸ Valvani and co-workers,⁴⁹ and Bodor and Huang;⁵⁰ gas–water Ostwald absorption coefficients are from Hine and Mookerje⁴⁸ with some additions from Abraham and co-workers;^{51,52} gas–hexadecane Ostwald absorption coefficients are from Abraham and co-workers;^{51,52} hexadecane–water partition coefficients are from Abraham and co-workers;^{51,53} octanol–water partition coefficients are mainly recommended values from compilations by Hansch and co-workers^{54,55} and Sangster;⁵⁶ gas–*n*-alkane Ostwald absorption coefficients for xenon are those published by Pollack and Himm;^{57,58} Most correlations presented here were performed on a set of 134 molecules having no strongly polar or hydrogen-bonding substituents including a group of 115 haloalkanes, haloaromatics, and unsubstituted aromatics and a separate group of 19 alkanes and cycloalkanes (Table 1). Regressions were performed with a standard spreadsheet program (Microsoft Excel 5.0).

Molecular volume was computed with an algorithm and a radii set (H 1.08, C 1.53, N 1.40, O 1.36, F 1.29, Cl 1.60, Br 1.83, I 2.05, S 1.70, P 1.75, Si 2.10—all values in Å) that has been described earlier.⁴ These radii are about 10% smaller than those used after Bondi⁵⁹ and are practically identical with the effective van der Waals radii^{60,61} that represent the distance of closest approach and describe the atoms' own volume into which other atoms cannot intrude. A radii set⁶² similar to that of Bondi was also tested. All conclusions were quite similar as obtained volumes correlate well enough to affect correlation coefficients with experimental data at most in the third significant figure. In general, different van der Waals molecular volumes and surface areas correlate well enough to not allow clear selection of a best descriptor based on available experimental data, as already mentioned.

For haloaromatics, somewhat better correlations for enthalpies of vaporization, boiling points, and solubility properties were obtained after a small increase in the atomic radii of the halogen atoms attached to aromatic rings. As this was not true for molar volume, it might reflect a change in the interaction ability of these halogen atoms. The van der Waals radii of these larger atoms are known to be more environment and direction sensitive.⁶³ A clear distinction would have required data for polyhalogenated compounds, but enough data for this class were available only for octanol–water partition, where a similar but, because of the involvement of water, probably even more significant trend is present. Not being able to make a clearly justified choice, we simply used the halogen radii set introduced in the log $P_{o/w}$ study to account for such effects (arom. F 1.25, Cl 1.80, Br 2.00, I 2.15).⁴

Results and Discussion

Enthalpy of Vaporization. When vaporization occurs at the boiling point, the vapor pressure equals the atmospheric pressure p_0 ; thus, $\mu^{\text{gas}} = kT_b \ln \rho = kT_b \ln(p_0/kT_b)$, and using eqs 6 and 8 we obtain for the free energy of transfer per molecule

$$\Delta\mu = \mu^{\text{gas}} - \mu^{\text{liq}} = kT \ln \left(\frac{p_0 f}{kT \rho^{\text{liq}}} \right) + w_0 + w_{ii} v_i \quad (13)$$

From here, using the Gibbs–Helmholtz equation, we obtain a molar enthalpy of vaporization that is linearly related to molecular volume

$$\Delta H^0 = N_0 \left(\frac{\partial(\Delta\mu/T)}{\partial(1/T)} \right)_p = N_0 (kT_b + w_0 + w_{ii} v_i) = RT_0 \left(\frac{T_b}{T_0} + \omega_0 + \omega_{ii} v_i \right) \quad (14)$$

Indeed, there is a very good correlation between enthalpy of vaporization and molecular volume, even if no temperature dependence for the binding energy was included in the model. Certainly, T_b also depends on size, but the available experimental data can already be used to obtain a first estimate for ω . For the compounds having no strongly polar or hydrogen-bonding substituents

$$\Delta H^0 = RT_0 (T_b/T_0 + 5.386(\pm 0.445) + 0.0815(\pm 0.0058)v) \\ n = 35, \quad r^2 = 0.855, \quad \sigma = 0.681, \quad F = 195.0 \quad (15)$$

Compared with eq 14, this gives $\omega_0 = 5.39$ and $\omega_{ii} = 0.082$. As it will turn out, these values can be used practically unaltered to describe all following properties (boiling point, solubility, vapor–liquid, and liquid–liquid partition). Values for alkanes and slightly deviating cycloalkanes are on a line with a similar slope but a clearly different intercept

$$\Delta H^0 = RT_0 (T_b/T_0 + 2.251(\pm 0.619) + 0.0887(\pm 0.0078)v) \\ n = 16, \quad r^2 = 0.902, \quad \sigma = 0.809, \quad F = 128.7 \quad (16)$$

suggesting $\omega_0 = 2.25$ and $\omega_{ii} = 0.089$ for this group of compounds (Figure 1).

Boiling Point. From the condition of equilibrium that $\Delta\mu$ as expressed in eq 13 is zero at the boiling point ($T = T_b$), using $\rho^{\text{liq}} = N_0/V_0^{\text{liq}}$ for the number density, we obtain after some rearranging

$$kT_b \ln \left(\frac{kT_b N_0}{p_0 f V_i^0} \right) = w_0 + w_{ii} v_i \quad (17)$$

Even with the simple assumption that $V_i^0 = aN_0 v_i$, this equation gives a complex, nonlinear dependence between boiling point (T_b) and molecular volume (v_i). Nevertheless, as a reasonable first estimate, T_b/V_0 can be considered constant, especially that only its logarithm appears in the equation. We have thus

$$T_b = \frac{w_0 + w_{ii} v_i}{k \ln \left(\frac{RT_b}{p_0 f V_i^0} \right)} = T_0 \frac{\omega_0 + \omega_{ii} v_i}{\ln \left(\frac{RT_b}{p_0 f V_i^0} \right)} \quad (18)$$

Repeating this after first adding kT_b to both sides in eq 17, and using eq 14 to introduce the enthalpy of vaporization, we get

$$T_b = \frac{kT_b + w_0 + w_{ii} v_i}{k \left(1 + \ln \frac{RT_b}{p_0 f V_i^0} \right)} = \frac{\Delta H^0}{R \left(1 + \ln \frac{RT_b}{p_0 f V_i^0} \right)} \quad (19)$$

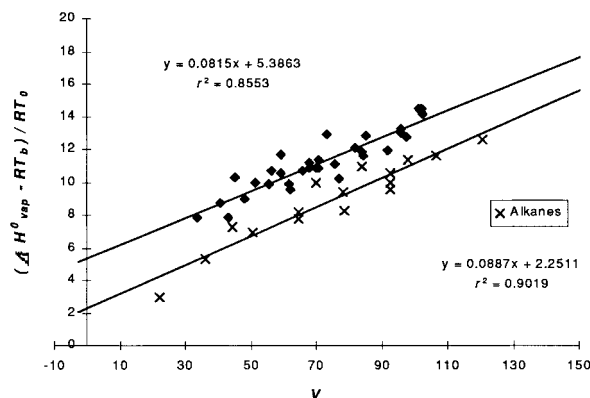


Figure 1. Molar enthalpy of vaporization scaled according to eq 14 as a function of molecular volume (in Å³) to obtain estimates for ω . Continuous lines are trendlines.

The denominator is, of course, the molar entropy of vaporization at the standard boiling point, and it also can be obtained directly from $\Delta\mu$ (eq 13)

$$\Delta S^0 = -N_0 \left(\frac{\partial(\Delta\mu)}{\partial T} \right)_{p,N} = R \left(1 + \ln \frac{RT_b}{p_0 V_i^0} \right) \quad (20)$$

According to the crude Trouton rule, for most liquids this is the same constant and has a value around 88 J/K mol.¹⁰ For our data its average is 86.91(±1.16) J/K mol ($n = 35$), while the average for T_b/V^0 is 3.63(±0.6) × 10⁶ K/m³ ($n = 95$). The value of T_b/V^0 is not significantly changed even by the inclusion of functionalized molecules: 3.69(±0.9) × 10⁶ K/m³ ($n = 252$). These values give $\ln(RT_b/p_0 V^0) = 5.70$ and thus an estimate for f around 2.3% ($\ln f = -3.76$). The present work suggests, therefore, 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 in the eqs 5.18a–5.18c of Chan and Dill.⁴⁴

It would be hard to predict exactly what portion of the total volume in a liquid can be considered as available for *free* translation; estimates are usually of the order of a few percent.^{9,11,64} A considerable portion of the total volume is anyway “lost”: even the closest packing of spheres leaves about 26% of the volume unfilled.⁶⁵ Estimates of free volume within cell models range somewhere between 0.1 and 10%.⁹ The speed of sound in liquids can also be used for such an estimate.¹¹ For most liquids, this speed is about 5–10 times the speed of sound in gas. Roughly, this is so because in a liquid, where molecular size cannot be neglected, a molecule of radius r_i has to travel only a $d - 2r_i$ distance instead of the whole intermolecular distance d before hitting its nearest neighbor. The ratio of the two speeds is $(d - 2r_i)/d$; therefore, the ratio of free and total volume should be somewhere around $(d - 2r_i)^3/d^3$, that is, around 0.1–1%. The value obtained here (~2%) seems therefore reasonable.

Omitting nine small fluoro-substituted compounds, where other more specific interactions are likely to be present, we have for the unsubstituted molecules (Figure 2)

$$T_b/T_0 = 0.570(\pm 0.0386) + 0.00876(\pm 0.00034)v \\ n = 93, \quad r^2 = 0.877, \quad \sigma = 0.111, \quad F = 649.7 \quad (21)$$

The equation of the trendline is only slightly changed by inclusion of other molecules, such as unsaturated hydrocarbons, esters, ethers, amines, nitro- and nitrile compounds, and others, excluding well-known outliers such as alcohols, acids, and

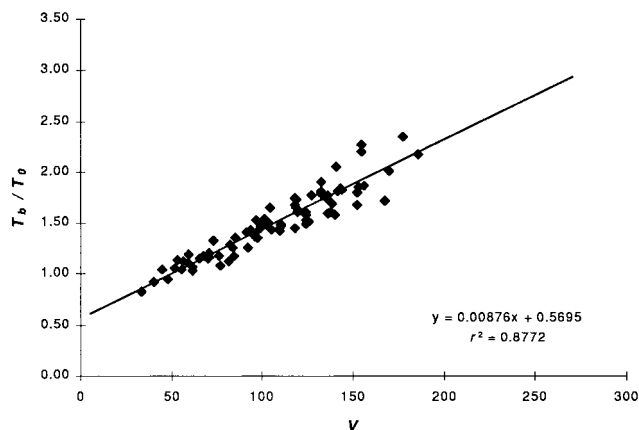


Figure 2. Boiling point (T_b/T_0) for 93 molecules as a function of molecular size as measured by computed van der Waals molecular volume (in Å³).

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$$T_b/T_0 = 0.569(\pm 0.0317) + 0.00855(\pm 0.00032)v \\ n = 220, \quad r^2 = 0.766, \quad \sigma = 0.154, \quad F = 714.0 \quad (22)$$

Alkanes are again on a separate line with

$$T_b/T_0 = 0.295(\pm 0.0594) + 0.00934(\pm 0.00074)v \\ n = 17, \quad r^2 = 0.914, \quad \sigma = 0.078, \quad F = 159.5 \quad (23)$$

Using the above derived f , we have from eq 18 $\omega_0 = 5.38$ and $\omega_{ii} = 0.0827$ (respectively, $\omega_0 = 2.79$ and $\omega_{ii} = 0.088$ for the alkanes)—in excellent accord with values obtained from enthalpies of vaporization ($\omega_0 = 5.39$, $\omega_{ii} = 0.082$). Since more data are available here, but the expected relationship is less linear, one can consider $\omega_0 = 5.39$, $\omega_{ii} = 0.082$ (respectively, $\omega_0 = 2.52$, $\omega_{ii} = 0.089$ for alkane–alkane interactions) as reasonable estimates.

Gas–Liquid Solubility (Ostwald Absorption Coefficient). Again, at equilibrium the chemical potentials are equal

$$\mu_i^{\text{gas}} = \mu_i^{\text{sol},1} \quad (24)$$

The Ostwald absorption coefficient (γ) is defined as the ratio of liquid and gas number densities (molar concentrations) at equilibrium. Using the corresponding chemical potential forms (eq 6 and 10), we obtain for its logarithm

$$\log \gamma_i^1 = \log \left(\frac{\rho_i^{\text{sol},1}}{\rho_i^{\text{gas}}} \right) = \frac{1}{2.303} \left[(-1 + \omega_0 + \ln f) + \left(\omega_{i1} + \frac{1}{v_1} \right) v_i \right] \quad (25)$$

The equation was already converted to decimal logarithms more commonly used in practical applications. Index i denotes the solute; index 1 refers to the solvent. According to this equation, solubility on the molar scale is enhanced in solvents of smaller size where v_i/v_1 is larger, if all other terms can be considered equal. Such a tendency, without a quantitative description, was indeed noted for solvation of some small molecules.^{66,67} The difference of two such terms ($v_i/v_1 - v_i/v_2$) will appear later in the partition equation as well, and it is exactly the correction introduced by De Young and Dill in describing benzene partition between water and different alkane solvents.⁶⁸ White and Wimley also found that the partitioning

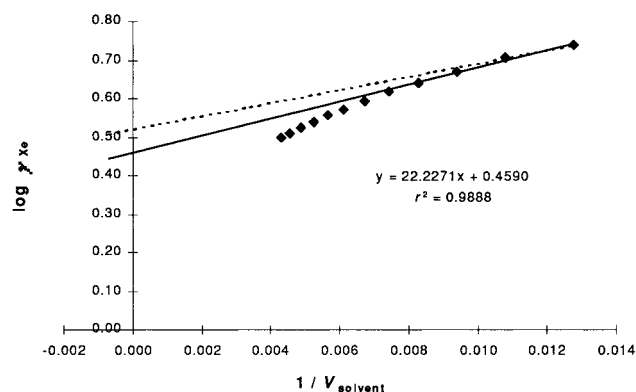


Figure 3. Gas-alkane Ostwald absorption coefficient for xenon at 20 °C as a function of the molecular size of the alkane solvent. The continuous line is the trendline obtained from the experimental data of the four smallest alkane solvents (*n*-pentane–*n*-octane); the dashed line is obtained from the model using the coefficients obtained from alkane enthalpies of vaporization and $r_{Xe} = 2.1$ Å.

of peptides into lipid bilayers is better explained by a Flory–Huggins theory that introduces a similar type of correction.⁴³ On the other hand, the classical study of Shinoda and Hildebrand^{69,70} for iodine as solute in solvents of different size and a more recent work by Giesen and co-workers³¹ seem to suggest no need for such volume corrections. In a more recent theory,³⁹ Sharp and co-workers were, however, able to account for the Shinoda–Hildebrand data, but not all aspect have been completely clarified yet.⁴⁵ It seems to become clear that some correction is needed if long-chain molecules are involved, but the situation of spherical molecules is less clarified.^{31,39,45}

Detailed measurements of Ostwald absorption coefficients of xenon in a series of liquid *n*-alkanes have been published.^{57,58} As Figure 3 indicates, there is a slight curvature for larger alkanes (smaller $1/v_{\text{solvent}}$), but the experimental data measured at 20 °C confirms the general trend predicted by eq 25 and is, indeed, to a good extent linearly related to $1/v_{\text{solvent}}$ ($1/v_1$ in eq 25). Considering that data are for *n*-alkanes, a tendency for nonlinearity for longer-chain alkanes is not surprising at all. These highly flexible molecules can more easily surround small solutes than predicted by size. This makes the apparent volume “seen” by a solute molecule smaller than the calculated volume shifting the corresponding points in Figure 3 to the right (toward larger $1/v_{\text{solvent}}$), as is indeed the case. Solvated xenon atoms mainly interact with methyl and methylene groups in their immediate surrounding; these interactions tend to a limiting value as chain length, and hence molecular volume, becomes large.²¹ The trendline obtained for the four smallest alkane solvents (*n*-pentane–*n*-octane) gives

$$\log \gamma_{Xe} = 0.459(\pm 0.018) + 22.227(\pm 1.674)1/v_{\text{solvent}} \\ n = 4, \quad r^2 = 0.989, \quad \sigma = 0.006, \quad F = 176.4 \quad (26)$$

The obtained slope, $v_{Xe}/2.303$ according to eq 25, gives a size for the xenon dissolved in *n*-alkanes that agrees well with the expected value, being maybe somewhat larger. Considering spherical xenon atoms, the above equation gives a van der Waals radius of $r_{Xe} = 2.30$ Å, whereas it is usually considered to be somewhere in the 2.00–2.27 Å range.⁶⁶ Nevertheless, this is still more realistic than the volume ratio of 5.5 obtained by Chan and Dill between xenon and methylene groups.⁴⁵ The dashed line in Figure 3 illustrates the prediction according to our model. As a first estimate, we can use coefficients derived earlier for alkanes ($\omega_0 = 2.52$, $\omega_{i1} = 0.089$) in eq 25, even if alkane–xenon interactions may not be the same as alkane–alkane

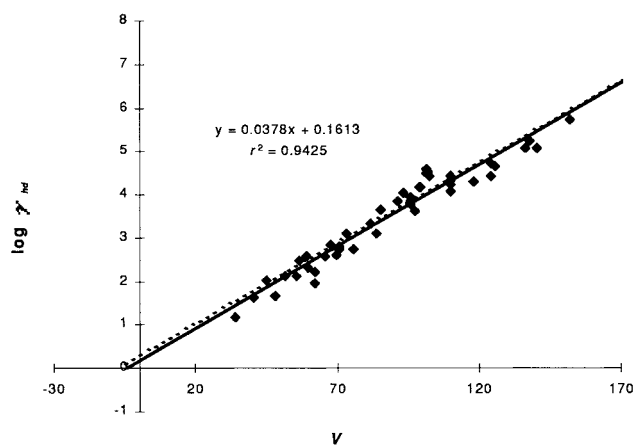


Figure 4. Gas-hexadecane Ostwald absorption coefficient as a function of molecular volume (in Å³) for molecules included in the present database. The continuous line is the trendline, while the dashed line is that predicted by the unified model having coefficients obtained from enthalpies of vaporization.

interactions, and a volume $v_1 = 38.8$ Å³ for xenon, obtained with a choice⁶⁶ of $r_{Xe} = 2.1$ Å that agrees reasonably well with our van der Waals radii scale. These lead to an intercept of $(-1 + 2.5 - 3.76 + 0.089 \times 38.8)/2.303 = 0.527$ and a slope of $38.3/2.303 = 16.85$, giving the correct trend, but a somewhat less steeper slope than expected, as illustrated in Figure 3. However, even the alkanes used for regression (*n*-pentane–*n*-octane) are already quite long-chain and flexible alkanes, and this might be responsible for a part of the deviation.

Good, and even numerical, agreement is obtained for Ostwald coefficient data of simple organic molecules measured by Abraham and co-workers^{51,52} in hexadecane with the exception of some large, rigid aromatics (naphthalenes, anthracene, tri- and tetrachlorobenzenes) that seem to be scattered along a somewhat steeper line

$$\log \gamma_{hd} = 0.161(\pm 0.127) + 0.0378(\pm 0.0014)v \\ n = 49, \quad r^2 = 0.943, \quad \sigma = 0.264, \quad F = 770.3 \quad (27)$$

This is in very good agreement (Figure 4) with that predicted by eq 25 by using coefficients obtained from enthalpies of vaporization and $v_1 = 232$ Å³ for hexadecane: intercept $(-1 + 5.39 - 3.76)/2.303 = 0.274$, slope $(0.082 + 1/232)/2.303 = 0.0375$. For alkanes

$$\log \gamma_{hd} = -0.840(\pm 0.256) + 0.0385(\pm 0.0033)v \\ n = 16, \quad r^2 = 0.909, \quad \sigma = 0.337, \quad F = 140.1 \quad (28)$$

compared to $(-1 + 2.52 - 3.76)/2.303 = -0.973$ and $(0.089 + 1/232)/2.303 = 0.0405$. The excellent agreement, obtained this time for a process that at first sight seems completely unrelated—partition between hexadecane and gas—is good proof favoring the hypothesis that our model and unified interaction constants can be useful in obtaining first estimates of various properties as long as no specific interactions are present.

Vapor–Liquid Equilibrium. As already pointed out by Ben-Naim and Marcus,²¹ an additional advantage of such statistical mechanics-based approaches is that the equilibrium between a pure liquid and its vapor can be included simply by considering it 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 25, one obtains after a sign inversion

$$\log \rho^{\text{gas}} - \log \frac{1}{V_i^0} = -\frac{1}{2.303}(\omega_0 - \ln f + \omega_{ii}v_i) \quad (29)$$

For 42 liquids (haloalkanes, haloaromatics, unsubstituted aromatics) where vapor pressure data was available⁴⁸

$$\log \rho^{\text{gas}} - \log 1/V^0 = -1.109(\pm 0.153) - 0.0324(\pm 0.0016)v$$

$$n = 42, \quad r^2 = 0.910, \quad \sigma = 0.277, \quad F = 406.2 \quad (30)$$

If one compares the values obtained here with the predicted intercept, $-(5.39-3.76)/2.303 = -0.708$, and slope, $-0.082/2.303 = -0.0356$, agreement with the model is quite satisfactory (Figure 5). No regression was performed for alkanes since their behavior is less regular and only limited data are available (smaller alkanes do not condense to liquids around room temperature).

Water. Water is certainly a special, more ordered, strongly hydrogen-bonded liquid. A whole literature is dedicated to the description of its structure and to the description of so-called hydrophobic interactions,^{2,64,71-74} yet only few things are known with certainty. Extrapolation of the H_2Te , H_2Se , H_2S series to H_2O gives melting and boiling temperatures of -100°C and -80°C ,⁷⁵ respectively—a clear indication of the extraordinary nature of water. Our size-based equation derived for simple organic liquids (eq 21) gives an estimated boiling temperature around -62°C for water ($v_{\text{water}} = 14.6 \text{ \AA}^3$), still far from its normal boiling point (100°C). The abnormally high boiling point of water is also indicated by the value of $20.6 \times 10^6 \text{ K/m}^3$ for T_b/V^0 , whereas, as already mentioned, its average for other molecules in this study is $3.6 \times 10^6 \text{ K/m}^3$. Hydrogen bonding is certainly responsible for most of these deviations. Each H_2O molecule having two donor and two acceptor sites, the structure of water is kept remarkably open. The coordination number, which for spherical, nonpolar molecules is near 12 at the melting point, starts at only 4 for liquid water and increases somewhat with temperature.⁷⁵ At room temperature, the overwhelming majority of water molecules seems to be in a state that still has four or three hydrogen bonds.⁷³ Accordingly, only about 10–15% of OH groups are free of hydrogen bonding, as it is indeed suggested by spectroscopic evidence^{71,75} contrary to somewhat higher earlier estimates.⁶⁴ It is also not clear to what extent are the translational degrees of freedom of a water molecule separable or to what extent can they be treated classically.³

Therefore, it would be of no surprise if the interaction between a solute and an aqueous solvent could not be included within this model. Indeed, size dependence is quite ambiguous when describing gas–water solubility.^{66,76} The correlation between molecular size and gas–water Ostwald absorption coefficient is much worse than those obtained earlier indicating that other, not properly described effects may also be important here. Omitting small fluoroalkanes and large, rigid aromatics that are scattered away, we are left with practically no size dependence at all

$$\log \gamma_w = 0.577(\pm 0.187) - 0.00072(\pm 0.00190)v$$

$$n = 51, \quad r^2 = 0.003, \quad \sigma = 0.391, \quad F = 0.1 \quad (31)$$

With such nonexistent correlation, both the slope and the intercept depend strongly on the data included, but a negative, very small (almost 0) slope seems likely here. As the slope is close to zero, using a practically 0 value for $\omega_{iw} + 1/v_w$ (-0.001) to describe water–solute interactions in the equations to be derived for water/organic solvent partition and for water solubility might be a reasonable idea ($\omega_{iw} = -0.070$ instead of

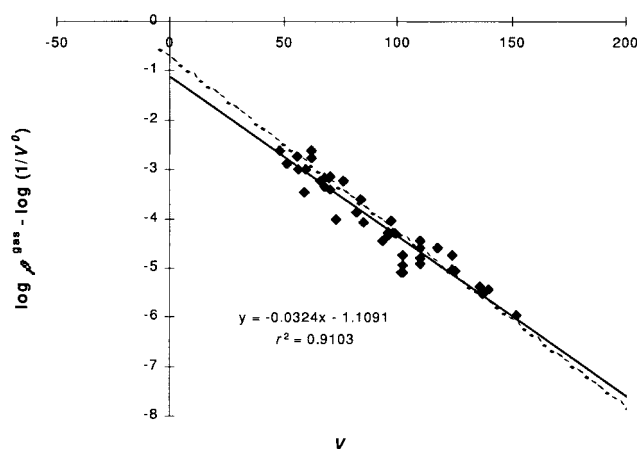


Figure 5. Molar gas concentration at equilibrium between a liquid and its vapor. The continuous line is the trendline, while the dashed line is that predicted by the unified model having coefficients obtained from enthalpies of vaporization.

$\omega_{ii} = 0.082$ used for other solvents). The goodness of the correlations to be obtained in the followings suggests that, at least for this purpose, water can be included within the model by using only a different interaction constant. Within this context, the above correlation is so poor mainly because ω_{iw} and $1/v_w$ compensate each other giving a practically 0 slope and annihilating volume dependence. This idea is also reinforced by the fact that the standard deviation obtained here in eq 31 for $\log \gamma_w$ ($\sigma = 0.391$) is only somewhat larger than those obtained in the similar but much better correlated equations for $\log \gamma_{\text{hd}}$ (eq 27, 0.263) and $\log \rho^{\text{gas}} - \log 1/V^0$ (eq 30, 0.277).

Alkanes (excluding cycloalkanes) give again a significantly different intercept and this time a more negative slope

$$\log \gamma_w = -1.148(\pm 0.075) - 0.0074(\pm 0.0009)v$$

$$n = 12, \quad r^2 = 0.862, \quad \sigma = 0.089, \quad F = 62.3 \quad (32)$$

Compared to eq 25, the slope of this equation, $(\omega_{iw} + 1/v_w)/2.303 = -0.0074$, suggests that for alkane–water interactions $\omega_{iw} = -0.086$ should be used instead of $\omega_{ii} = 0.089$ used for alkane–alkane interactions ($\omega_{iw} + 1/v_w = -0.017$). Solvation of longer chains is less favorable, probably owing to restricted flexibility in water. Larger alkanes are more likely to have longer chains. This makes the above slope more negative, and the difference between the slope obtained for alkanes and that obtained for other compounds more significant than those obtained for other properties where water was not involved. The role of restricted flexibility is also indicated by the fact that the more rigid cycloalkanes are scattered away: inclusion of five cycloalkanes does not alter considerably the intercept and the slope (-0.984 and -0.0061 , respectively) but worsens the correlation significantly: r^2 decreases from 0.862 to 0.117. The obtained negative intercept agrees reasonably well with that predicted by the model: $(-1+2.52-3.76)/2.303 = -0.973$.

Partition between Two Solvents. If the two solvents are immiscible or solute partitioning is performed without allowing solvent mixing, equilibrium is reached when the corresponding chemical potentials are equal:

$$\mu_i^{\text{sol},1} = \mu_i^{\text{sol},2} \quad (33)$$

The partition coefficient P is defined as the ratio of the molar concentrations of i in the two different phases. Since this equals the ratio of number densities, we can use eq 10 for both sides and obtain

$$\log P = \log \frac{\rho_1}{\rho_2} = \frac{1}{2.303} \left(\omega_{i1} - \omega_{i2} + \frac{1}{v_1} - \frac{1}{v_2} \right) v_i \quad (34)$$

This equation predicts a zero intercept if $\log P$ is represented as a function of molecular volume. Our earlier studies on octanol–water partition, chosen because of its pharmaceutical/biological/environmental relevance and because of the large number of available experimental data, proved not only this (even for noble gases) but also found similar slopes for different classes of monofunctionalized compounds.^{4,5} These studies gave us the original impetus to further explore the hypothesis that molecular size is a good descriptor for nonspecific interactions in organic liquids.

Within the limits of experimental error, most alkanes (e.g., hexane, heptane, octane, decane, hexadecane) seem to give similar $\log P$ values in alkane–water partition studies.⁷⁷ This agrees with the prediction of eq 34 that only relatively small differences are present owing to the different molecular sizes of the involved solvents. Data available for the hexadecane–water system give

$$\log P_{\text{hd/w}} = -0.550(\pm 0.107) + 0.0394(\pm 0.0010)v$$

$$n = 69, \quad r^2 = 0.956, \quad \sigma = 0.268, \quad F = 1452.7 \quad (35)$$

The intercept is more negative than the expected 0; this is the most significant deviation observed in the present work. Even if one solvent is water and the other one is an alkane, the obtained slope agrees well with that predicted by the model being slightly larger: $(0.082 + 1/232 + 0.001)/2.303 = 0.038$ (Figure 6).

For alkane partition we also have a good correlation

$$\log P_{\text{hd/w}} = 0.055(\pm 0.102) + 0.0466(\pm 0.0013)v$$

$$n = 16, \quad r^2 = 0.989, \quad \sigma = 0.133, \quad F = 1313.8 \quad (36)$$

Here the intercept is very close to 0, and the slope agrees well with the expected one: $(0.089 + 1/232 + 0.017)/2.303 = 0.047$. Certainly, a model that adequately describes gas–water and gas–hexadecane solubility should also work well here, since water–hexadecane partition coefficient can be determined as the ratio of these two solubility coefficients.⁵¹ However, the good correlations obtained prove that despite the small r^2 obtained for gas–water partition, water can be included within this description using only a different ω_w .

The log *n*-octanol–water partition coefficient ($\log P_{\text{o/w}}$) also fits within this description. It represents an important parameter, widely used in quantitative structure–activity relationships (QSAR) developed for pharmaceutical, environmental, or biochemical applications. Large amounts of experimental data are available^{54–56} since most compounds of interest have $\log P_{\text{o/w}}$ values that are in a range where experimental determinations using standard (e.g., shake-flask) methods are relatively simple.^{56,73,78} This is a consequence of the fact that octanol still retains some of the hydrogen-bonding ability of water and it even contains a considerable amount of solvated water: at room temperature the saturation mole fraction of water in octanol is around 0.275.⁷⁸ In very nonpolar solvents, like hexadecane, structural variations can cause large variations and solute association can easily become a problem. There are a number of studies indicating that two parameters may account for a large part of the variance in $\log P_{\text{o/w}}$: a principal component analyses by Dunn et al.,⁷⁹ Cramer's already mentioned study on liquid properties,¹⁴ the finding that only two of the six so-called TLSE parameters are significant when correlating with log

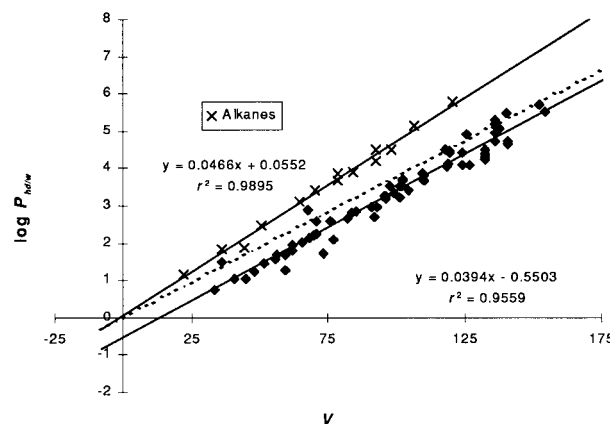


Figure 6. Log hexadecane–water partition coefficient as a function of molecular size as measured by computed effective van der Waals molecular volume (in Å³). The dashed line is that predicted by the unified model with the coefficients derived in the text.

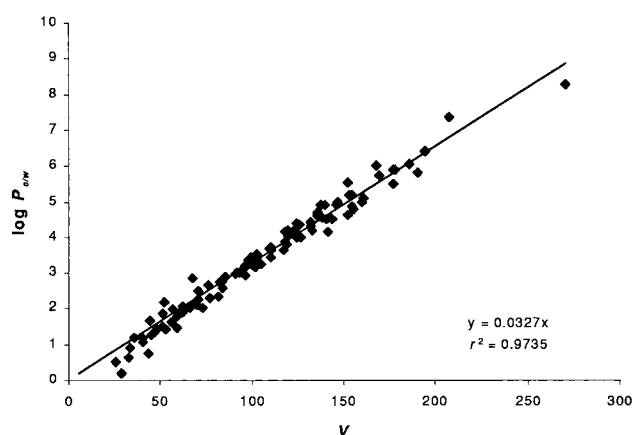


Figure 7. Log octanol–water partition coefficient as a function of molecular volume for 115 compounds having no strongly polar or hydrogen-bonding substituents. The continuous line is the trendline obtained with an imposed 0 intercept.

$P_{\text{o/w}}$,⁸⁰ and studies^{81,82} related to Taft and Kamlet's solvatochromic model.^{83,84}

Since the solvents involved in this partition are water and an alcohol, different ω 's and hence different slopes are expected, but the very good correlations obtained prove again the advantages of the present approach. In the present database, for molecules containing no strongly polar or hydrogen-bonding substituents, we have a very good fit, a zero intercept, and a slightly smaller slope than that obtained for the hexadecane–water system

$$\log P_{\text{o/w}} = -0.140(\pm 0.060) + 0.0338(\pm 0.0005)v$$

$$n = 115, \quad r^2 = 0.974, \quad \sigma = 0.239, \quad F = 4351.8 \quad (37)$$

The intercept is slightly negative, but imposing a zero intercept as predicted by eq 34 does not worsen the correlation (Figure 7)

$$\log P_{\text{o/w}} = 0.0327(\pm 0.0005)v$$

$$n = 115, \quad r^2 = 0.974, \quad \sigma = 0.243, \quad F = 4183.0 \quad (38)$$

Similar results, suggesting zero intercepts, were also obtained for noble gases,⁵³ as both McGowan's characteristic volume (-0.016 ± 0.039) and that computed with the radii from Bondi's 1964 paper (0.059 ± 0.126) give practically zero intercepts.⁴ By accepting the previously derived $(\omega_{\text{iw}} + 1/v_w) = -0.001$

for water and a $(\omega_{io} + 1/\nu_o) + 0.001 = 0.0327 \times 2.303$ value indicated by eq 38 for octanol, a model for a large variety of molecules can be developed. Since for octanol $\nu_o = 127.5 \text{ \AA}^3$, we have $\omega_{io} = 0.066$ for solute–octanol interactions. Strangely enough, the weighted average of the coefficients used to describe solute–water (-0.070) and solute–solvent (0.082) nonspecific interactions gives a very similar value if one consider that octanol has 8 $-\text{CH}_2$ groups and 1, about similarly sized, $-\text{OH}$ group: $(-0.070 \times 1 + 0.082 \times 8)/9 = 0.065$.

As water and octanol have similar hydrogen bond acceptor abilities, by introducing only one additional parameter, a fully computerized model could be developed that predicts $\log P_{o/w}$ from three-dimensional molecular structure for a large variety of compounds,⁴ including even nonzwitterionic peptides.⁵ The value of this novel, quantified parameter (N) is determined by oxygen- and nitrogen-containing functional groups present in the solute molecule. It correlates well with solvatochromic hydrogen bond acceptor basicity (β)⁸⁴ and describes a free energy change ($\sim 4.2 \text{ kJ/mol}$) that agrees well with that accepted for hydrogen bonds in water,^{15,64,85,86} suggesting that it is a parameter related to changes occurring in hydrogen bonding during octanol–water transport.

The final model was obtained by linear regression on a set of 320 different molecules.⁴ Since the radii set used gave a practically 0 intercept, we imposed a 0 intercept and obtained a consistent model with only three adjustable parameters

$$\log P_{o/w} = 0.0318(\pm 0.0002)\nu - 0.723(\pm 0.007)N + 0.0103(\pm 0.0007)\nu I_{\text{alk}}$$

$$n = 320, \quad r^2 = 0.978, \quad \sigma = 0.214, \quad F = 4760.1 \quad (39)$$

Here, I_{alk} is an alkane indicator introduced to account for the increase in slope observed for alkanes. This previously obtained increase, $0.010(\pm 0.0007)$, agrees well with the constants derived in this work from enthalpies of vaporization and from eq 32 for water–solute interactions: $((0.089 - 0.082) + (0.017 - 0.001))/2.303 = 0.010$. The slope describing size dependence obtained after inclusion of structures containing functional variety (eq 39, 0.0318) is close to that obtained earlier for the set of simple organic molecules (eq 38, 0.0327). We believe that this is a good proof for the consistency of the $\log P$ model.

Solubility (Liquid–Liquid). A major advantage of the present approach is the possibility to treat solubility as partitioning between a solvent and the solute itself—as this is what actually happens at molecular level. As long as solubility is not very high, we can simply use eq 34 with $2 = i$ (solvent 2 = solute); thus

$$\log \rho_1 - \log \frac{1}{V_i^0} = \frac{1}{2.303} \left[-1 + \left(\omega_{i1} - \omega_{ii} + \frac{1}{\nu_1} \right) \nu_i \right] \quad (40)$$

Here ρ_1 refers again to molar concentrations, and $\rho_2 = 1/V_i^0$ was used for the solute when in pure liquid phase. Therefore, to correctly relate solubility and solute–environment interactions connected here to molecular size, we need to consider the molar (or number) density of the pure solute, $\rho_i = n_i/V = 1/V_i^0$, a relation unobtainable from purely thermodynamic arguments.² When looking for connections between solubility and partition, such purely thermodynamic approaches have to rely on additional assumptions regarding the activity in one or the other solvent.^{15,82}

Except for five small, fluoro-substituted compounds, even water solubility data gives good agreement with this equation (Figure 8) as indicated by a comparison with values from the

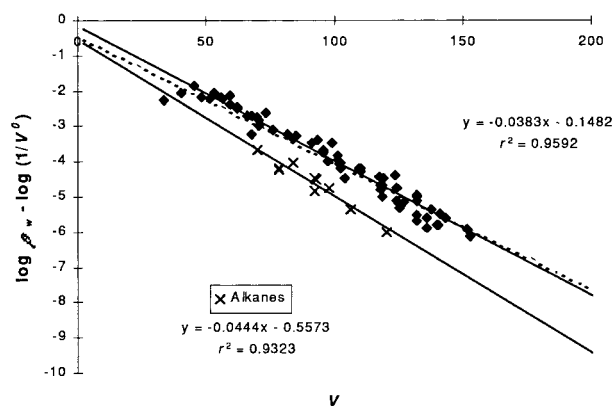


Figure 8. Water solubility scaled according to eq 40 as a function of molecular volume (in \AA^3). The dashed line is that predicted by the unified model.

unified model: $-1/2.303 = -0.434$ for intercept and $(-0.082 + 0.001)/2.303 = -0.0361$ for slope

$$\log \rho_w - \log 1/V^0 = -0.148(\pm 0.102) - 0.0383(\pm 0.0010)\nu$$

$$n = 67, \quad r^2 = 0.959, \quad \sigma = 0.247, \quad F = 1529.4 \quad (41)$$

The model clearly does not work for smaller alkanes, but for those bigger than butane the agreement is good again with a slope close to that predicted, $(-0.089 - 0.017)/2.303 = -0.046$

$$\log \rho_w - \log 1/V^0 = -0.557(\pm 0.391) - 0.0444(\pm 0.0042)\nu$$

$$n = 10, \quad r^2 = 0.932, \quad \sigma = 0.188, \quad F = 110.1 \quad (42)$$

Conclusions

A consistent model relying on free energy expressions obtained from clearly stated molecular-level assumptions was presented. By incorporating two assumptions regarding molecular interaction and motion in liquid phase, it gives a unified treatment for various processes in simple organic liquids where no strongly specific interactions are present. An important achievement is that molecular volume-based interaction coefficients (ω) obtained from the enthalpies of vaporization can be used in subsequently derived equations to adequately describe solubility and partition properties for this group of molecules. The obtained individual equations rely only on computed molecular volume and account for 90–95% of the variance in the corresponding properties. Undoubtedly, the present model gives a crude, oversimplified description; its predictions may not be always accurate. Nevertheless, it represents a unique, unified approach, and it could serve as starting point for a more general model describing properties even for compounds where more specific interactions are also present. Such an extension already has been achieved for $\log P_{o/w}$ with a remarkably simple and fully computerized model that works for many large and multifunctionalized molecules.

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