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Article

Linear Free-Energy Relationships and Solvation Thermodynamics: The Thermodynamic Basis of LFER Linearity

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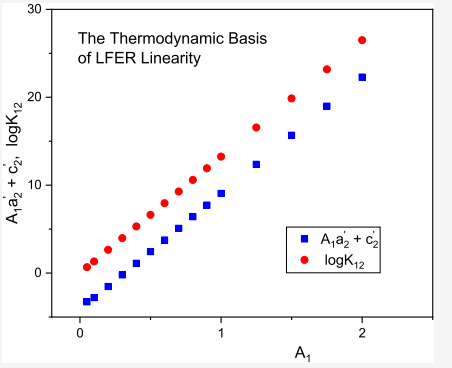
ABSTRACT: The Abraham solvation parameter model, known alternatively as the Linear Solvation Energy Relationships (LSER) model, is widely used in numerous applications in the broader chemical, biochemical, and environmental sector with remarkable success. So far, there is no explanation at the fundamental thermodynamic level for the very linearity of this model. This is, however, essential for the evaluation and exchange of thermodynamic quantities between models and databases. The present work offers such an explanation by combining the equation-of-state solvation thermodynamics with the statistical thermodynamics of hydrogen bonding. It shows what this linearity entails and in what way it is interpreted and handled so far. In addition, it proposes new ways of extending it for estimations over a broad range of external conditions and, eventually, in predicting solvent LFER coefficients from the corresponding molecular descriptors, which are known for thousands of compounds. This would enhance significantly the predictive capacity of the model in practical applications, such as solvent screening, solute partitioning, activity coefficients at infinite dilution, or hydration/solvation energies. Various examples of calculations are reported. A critical discussion of perspectives and challenging emerging issues are also presented.



1. INTRODUCTION

For decades now, the scientific community enjoys the remarkable success of the Abraham solvation parameter model or the linear free energy relationships (LFER) as a predictive tool for obtaining quantitative structure−property relationships (QSPR) for a broad variety of chemical, biomedical and environmental processes.[1−18] In this model, free-energy-related properties of a solute are correlated to its six molecular descriptors, V, L, E, S, A, and B, corresponding to the McGowan's characteristic volume V, the gas−liquid partition coefficient L in n-hexadecane at 298 K, the excess molar refraction E, the dipolarity/polarizability S, the hydrogen bond acidity A, and hydrogen-bond basicity B, respectively. These correlations are done through two basic relationships (LFERs) that quantify solute transfer between two phases. The first LFER quantifies solute transfer between two condensed phases:[2−12]

$$\log(P) = c_p + e_pE + s_pS + a_pA + b_pB + v_pV \quad (1)$$

and the second LFER describes solute transfer from the gas phase:[2−12]

$$\log(K^*) = c_k + e_kE + s_kS + a_kA + b_kB + l_kL \quad (2)$$

where P is the water-to-organic solvent partition coefficient or alkane-to-polar organic solvent partition coefficient and K^* is the gas-to-organic solvent partition coefficient.

The coefficients (lowercase letters) in these equations, which are solvent (phase or system) descriptors, are usually determined by fitting experimental data. This fitting practice is needed, although the coefficients do have a widely accepted physical meaning. The molecular descriptors (E, S, A, B, L, and V) represent the solute influence on various solute−solvent phase interactions. It is, then, considered that the regression coefficients c, e, s, a, b, l, and/or v correspond to the complementary effect of the phases on these interactions. These coefficients are regarded as system characteristic constants, which contain chemical information of the solvent/phase in question. Hence, the LFER constants can be given specific physicochemical meanings.[2−14]

The e coefficient is a measure of the solvent tendency to interact with solutes through π and n-electron pairs. The s coefficient is a measure of the solvent tendency to interact with dipolar/polarizable solutes. The a coefficient is considered to reflect the hydrogen bond basicity of the solvent/phase (acid/base complementarity for interaction), while the b coefficient reflects the hydrogen bond acidity of the solvent/phase. The v

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coefficient is a measure of the hydrophobicity of the solvent/phase. The l coefficient is a measure of the resistance of the solvent for cavity formation. However, although it is widely accepted that these coefficients are not just fitting constants but must obey general chemical principles, their determination remains a fitting process via multiple linear regression until today.[2−18]

The required fitting process does not diminish the value of Abraham's solvation parameter approach. It, however, leaves unanswered the key question: why do the free energies and the free-energy-based properties obey linear eqs 1 and 2? What is most puzzling is why there is such a linearity even for the strong specific hydrogen-bonding or acid−base interactions.[15] For the weaker van der Waals interactions, such as the dispersion and weak polar interactions, one could understand this linearity by simple and widely used arguments such as by considering the cross-interaction energy, ε_{12}, to be given by the classical geometric mean rule of the self-interaction energies ε_{11} and ε_{22},[19] but such a simple rule does not hold true for the strong specific interactions (see discussion in next section). If we could answer the above key question, then we could probably answer a second question: why are there two different measures of the hydrogen-bonding (or acid−base interaction) capacity for the very same molecule depending on whether it is treated as solute or as solvent?[15] With such an answer, we could even derive a fundamental and quantitative relation between the A/B set and the corresponding a/b set of parameters.

There is a rather long history in the development of the LFER approach, but for the purposes of our discussion here, we could confine ourselves to mentioning that in the older but still widely used Kamlet−Taft LFER version,[20−22] the symbols α and β are used for the acidity and basicity molecular descriptors, respectively. It should be stressed, however, that the distinction between these two sets of hydrogen bonding parameters is that those of Abraham (A and B) are determined from free energy data for a molecule acting as a solute, while those of Kamlet and Taft (α and β) are determined in other ways for a molecule, mainly, when acting as a solvent. As expected, there is some correlation between the two LFER sets of scales of hydrogen bonding parameters. Bernales et al[23a] have observed that the acidity descriptors of the two LFER approaches are strongly correlated ($R^2 = 0.94$) through the following equation:

$$A = 0.4098\alpha + 0.0064 \tag{3}$$

A weaker correlation ($R^2 = 0.61$) was found between the basicity descriptors through the equation

$$B = 0.6138\beta + 0.0890 \tag{4}$$

Similarly, it is also expected that there is some correlation between the set of descriptors A and B and the set of the corresponding coefficients, a and b. Indeed, van Noort[13,14] has developed such correlations by hypothesizing that the solvent (system) describing coefficients a and b depend on both Abraham solute solvation parameters, A and B, and should obey the following equations for the solvent/air partitioning:

$$a = n_1 B_{\text{solvent}}(1 - n_3 A_{\text{solvent}}) \tag{5}$$

$$b = n_2 A_{\text{solvent}}(1 - n_4 B_{\text{solvent}}) \tag{6}$$

The coefficients, n_i, in these equations were then determined by fitting to available experimental data for several solutes. Equations 5and 6 attempt to account for self-association, which is not taken explicitly into account by the Abraham model. A more comprehensive discussion on polarity scales and related QSPR-type databases was reported by Katritzky et al.[23b]

To the best of our knowledge, no attempt has been made so far in the open literature to explain, at the fundamental or thermodynamic level, the observed linearity of eqs 1 and 2. As mentioned above, if we had such an explanation, we would probably have a direct and thermodynamically consistent relation between the sets A/B and a/b. This is what we will attempt and report in the present work. This is essential because there is really nothing absolute and universally accepted in the division of intermolecular interactions, and thus, comparison of the strengths of interactions reported by the various polarity scales and QSPR databases is not always easy and meaningful.

Thus, there is a twofold scope in this series of works, with the current work being the first in the series. First, we will examine the basic (LFER) eqs 1 and 2 from a thermodynamic viewpoint in order to extract the physical meaning of molecular descriptors and LFER coefficients and, eventually, quantitative relations between them, with emphasis on hydrogen-bonding contributions. Second, these equations will act as bridges and, eventually, form the basis for the exchange of LFER information with corresponding information from other QSPR-type frameworks, hydrogen-bonding scales, quantum chemical calculations, and molecular dynamics simulations.

The above second task requires additional care in the case of LSER model since hydrogen bonding information may also be extracted through the L descriptor from activity coefficients at infinite dilution in n-hexadecane, but the LSER database was developed without accounting explicitly for self-association in compounds with both proton donor and proton acceptor capacity or even for density and molecular size differences. As will be shown, this step is significantly facilitated by adopting an equation-of-state framework with explicit account of hydrogen bonding for the thermodynamic calculations.[24−27]

In the present work, we will focus on the principles and the thermodynamic basis of LFER linearity, with emphasis on hydrogen-bonding contributions. LSER views hydrogen bonding as a complementary interaction between a (Lewis) acid site and a base site. This contribution, then, will be handled in the classical manner, as a simple quasi-chemical reaction of the form acid + base ⇄ ABcomplex. We will also discuss the issues and challenges associated with the developments of consistent acidity/basicity scales and related molecular descriptor databases. More in-depth equation-of-state developments and the associated Partial Solvation Parameter (PSP) databases will be reported in subsequent parts of this series of papers.

2. SOLVATION THERMODYNAMICS

In this section, we will briefly recall the basic elements of solvation thermodynamics, which will be useful for our discussion. Details may be found elsewhere.[24,28,29]

The solvation free energy of a solute, i, in a mixture, whose composition is shown concisely by $\{N\} = \{N_1, N_2,...,N_t\}$, at temperature, T, and pressure, P, is given by the following defining equation in the mole/mole Ben−Naim's convention:[24,28−30]

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$$\Delta G_i^S(T, P, \{N\}) = \mu_i(T, P, \{N\}) - \mu_i^{IG}(T, P, \{N\}) + RT\ln Z \quad (7)$$

μ_i is the chemical potential of component i, superscript IG denotes the ideal-gas state, and Z is the compressibility factor

$$Z = \frac{PV}{NRT} \quad (8)$$

Equation 7 is a general one and holds true for mixtures as well as for pure fluids (self-solvation). In the limit at infinite dilution of solute 1 in solvent 2 (subscript 1/2), eq 7 leads to the following most useful working equation:[11,29]

$$\frac{\Delta G_{1/2}^S}{RT} = \ln\frac{\varphi_1^0 P_1^0 V_{m2}\gamma_{1/2}^\infty}{RT} \quad (9)$$

where V_{m2} is the molar volume of component 2 and $\gamma_{1/2}^\infty$is the activity coefficient of solute 1 at infinite dilution in solvent 2. $P_1^0$is the vapor pressure of the solute at temperature, T, and is φ_1^0 its fugacity coefficient (typically set equal to 1 at ambient conditions). A more in-depth discussion of solvation thermodynamics may be found in refs 30 and 31 along with a comprehensive databank for solvation quantities.

In order to proceed, we need an expression for $\gamma_{1/2}^\infty$. For this purpose, we will adopt here the versatile statistical thermodynamic LFHB (Lattice Fluid with Hydrogen Bonding) model,[26,32,33] which has been widely tested in the literature and accounts explicitly for hydrogen bonding as a quasi-chemical reaction. This model will be used as a convenient tool here. The key results regarding the LFER linearity of hydrogen-bonding contributions will be independent of any equation-of-state scaling parameters. In this sense, some other analogous model that treats the statistics of hydrogen bonding in a consistent manner may be used as well, and the results are not expected to be much different.

With the LFHB model, eq 9 becomes

$$\frac{\Delta G_{1/2}^S}{RT} = -\ln K^* = -\ln(\omega_1(T)) - \ln(1-\tilde{\rho}_2)^{r_1} - 2r_1\tilde{\rho}_2\frac{\varepsilon_{12}^*}{RT} - \left\{d_1\ln\frac{\nu_{10,0}}{\nu_{10}} + a_1\ln\frac{\nu_{01,0}}{\nu_{01}}\right\}_{x_1\to 0} = \ln\frac{\varphi_1^0 P_1^0 V_{m2}\gamma_{1/2}^\infty}{RT} \quad (10)$$

where, d_i and a_i is the number of donor and acceptor sites, respectively, of molecule i. Equation 10 may be written in the following more illustrative form:

$$\ln K^* = \ln(\omega_1(T)) + r_1\ln(1-\tilde{\rho}_2) + r_1\sqrt{\varepsilon_{11}^*}\left(2\tilde{\rho}_2\frac{\sqrt{\varepsilon_{22}^*}}{RT}\right) + d_1\ln F_{12} + a_1\ln F_{21} \quad (11)$$

or

$$\ln K^* = \ln(\omega_1(T)) + r_1\ln(1-\tilde{\rho}_2) + E_1^*\left(\frac{2\tilde{\rho}_2}{RT}\sqrt{\frac{E_2^*}{E_1^*}\frac{V_1^*}{V_2^*}}\right) + d_1\ln F_{12} + a_1\ln F_{21} \quad (12)$$

where

$$F_{12} = \lim_{x_1\to 0}\frac{\nu_{10,0}}{\nu_{10}} \quad \text{and} \quad F_{21} = \lim_{x_1\to 0}\frac{\nu_{01,0}}{\nu_{01}} \quad (13)$$

The first term on the rhs of eqs 11 and 12 is the conformational−contribution term. It is an "internal" non-configurational term and, as such, thermodynamics cannot tell us much about it. It accounts for conformer distribution and population, flexibility, symmetry, shape, internal restructuring, or changes in the internal degrees of freedom of the solute molecule upon solvation. Quantum mechanics calculations could be more helpful in quantifying this term.[24] Typically, this term is simply neglected in solvation thermodynamics, and for the time being, this is what we will also do here.

The symbols in the remaining terms of the above equations, which are of interest to us here, are as follows: r_1 is the number of segments of the solute (molecule 1). V_i^* and E_i^* are the molar hard-core volume and interaction energy, respectively, of component i (=1,2),$\tilde{\rho}_2 = V_2^*/V_{m2}$ is the reduced density of the solvent (molecule 2) or the probability to find a site occupied by the hard core volume of the solvent molecule. Consequently, $1-\tilde{\rho}_2$ is the probability to find a non-occupied or empty site in the solvent phase. ε_{ij}^* is the interaction energy for the contact of segments i and j. This refers to the non-specific or the weak type of van der Waals (dispersion, weak polar) interactions. For pure component i, we have then, $E_i^* = r_i\varepsilon_{ii}^*$.

The contribution of strong specific interactions is accounted for by the last two terms in eqs 11 and 12. d_1 and a_1 are the number of hydrogen-bond donor and acceptor sites, respectively, of the solute molecule. Typically, when two interacting sites are properly oriented and their interaction strength exceeds a certain energy threshold, the interaction is accounted as a hydrogen-bonding (HB) one. All other interactions of these sites are considered non-hydrogen-bonding (nonHB) interactions. Thus, each donor and acceptor site of the solute molecule is either in an HB or nonHB state. The fraction of donor sites in a nonHB state is indicated by ν_{10}, and that of acceptor sites by ν_{01}. Subscript ij,0 indicates fractions ij in the reference state of zero hydrogen-bonding interaction energy ($K_{ij} = 1$).

Disregarding the first conformational term, all other terms in eqs 11 and 12 have a clear physical meaning with a direct correspondence to the typical solvation (or transfer) steps of the classical solvation process picture of Abraham solvation model[4] and the LFER approach.[20−22] The second term corresponds to the so-called cavitation contribution. It is a measure of the work or the difficulty to accommodate a solute molecule in the solvent phase. One has to find an empty site for the first segment of the solute molecule, and this is successful with a probability equal to $1-\tilde{\rho}_2$. Since there are r_1 segments to be accommodated simultaneously, the overall successful probability is equal to the above probability raised to the r_1th power. This is what this second term in eqs 11 or 12 says. Of course, the solute molecule is accommodated when the r_1 consecutive sites are arranged according to the shape of one of the probable conformers of the molecule. If the particular solvent favors a particular conformation of the solute molecule, it is the first conformational (neglected) term to account for it.

All other terms in eqs 11 and 12 account for the interaction energy or "charging" contribution to the solvation process. The third term accounts for the non-specific or weak intermolecular interactions arising from the molecular polarizability and

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Keesom-type or Debye-type polar interactions. Lewis acid–base or hydrogen-bonding interactions are accounted for by the last two terms in these equations.

3. ON THE LINEARITY OF THE SOLVATION FREE-ENERGY EQUATION

We will examine, now, eq 11 (or 12) more closely and see if there is indeed a linearity in it, like the one claimed or assumed by the LFER approach[1−22] (cf. eqs 1 and 2).

Disregarding again the first conformational term, it is clear from eq 11 that the cavitation term and the first charging term do exhibit the sought linearity. The number of segments, r_1, is a measure of the size of the solute molecule and is independent of the solvent, while $\tilde{\rho}_2$ is an exclusive property of the solvent and is not affected by the solute molecule. Similarly, for the first charging term, the terms in parentheses are exclusive properties of the solvent, while those outside it are exclusive properties of the solute. It is stressed that the plain geometric-mean mixing rule, $\varepsilon_{12}^* = \sqrt{\varepsilon_{11}^*\varepsilon_{22}^*}$, is adopted here. Quite often, especially in engineering applications, the mean geometric mixing rule is corrected by an adjustable empirical factor, ξ_{12}, close to one.

The crucial question now is whether each of the last two terms in eq 11 or 12 also exhibit linearity or not. In order to answer this question, we will recall briefly the very basics of how hydrogen bonding is accounted for in the LFHB model. In the LFER approach, it is typically assumed that each hydrogen-bonding molecule has one type of donor sites and/or one type of acceptor sites. The molecules are also considered monosegmental, and the liquids are incompressible. For simplicity, we will also adopt these assumptions in order to make arguments and presentation more lucid. The full equations without these simplifying assumptions will be recovered later. Some helpful derivations are also reported in the Supporting Information (SI) file.

Let A_i and B_i be the LSER acidity and basicity descriptor, respectively, of component i. We will treat hydrogen bonding in the classical way as a complementarity interaction or as a quasi-chemical reaction: acid + base ⇄ ABcomplex. We do not know how the formation free energy of this reaction is obtained from the corresponding LSER descriptors, and thus, we will proceed by adopting a simple plausible assumption (as we often do in physics). The focus will be on the consistency. After all, our goal is to end up in the simple LFER linearity. Thus, let the free energy change upon formation of such a hydrogen bond i–j be $\Delta G_{ij}^{\mathrm{hb}} = -kA_iB_j$ and the corresponding equilibrium constant of the quasi-reaction be K_{ij}. For simplicity, the proportionality constant, k, is considered to be a characteristic constant of the Abraham solvation model, that is, the same for all types of hydrogen bonds. For the corresponding equilibrium constant, K_{ij}, we may then write

$$\ln K_{ij} = -\frac{\Delta G_{ij}^{\mathrm{hb}}}{RT} = \frac{k}{RT}A_iB_j \tag{14}$$

We must, now, evaluate the fractions ν_{10} and ν_{01} (cf. equation 11–13). This will be done by adopting Veytsman's statistics[32−35] as implemented in LFHB model.[32,33] We stress again the point that LFHB is just a tool here. Any other thermodynamically consistent treatment of the above elementary quasi-chemical reaction may end up in essentially the same results (the same problem may be solved in many equally correct ways). We opted for an equation-of-state model as a tool because we do not want just to show the thermodynamic basis of LFER linearity. Ultimately, we want to develop a sound thermodynamic basis for the transfer of information between diverse polarity scales, QSPR-type databases, and related approaches and thermodynamic studies over a broader range of external conditions. Information on $\Delta G_{ij}^{\mathrm{hb}}$, as an example, could be extracted probably from LSER itself via empirical equations, as shown below, but it could also be obtained by other less empirical means, experimental measurements, or advanced calculations.

For the time being, just to make the presentation more lucid, we will consider the molecules to be monosegmental ($r = 1$) as in the LSER approach. Then, in the limit of infinite dilution ($x_1 \to 0$), the ratios of eq 13 that appear in the last two terms in eqs 11 and 12, take the following simple form (SI, eq S16a):

$$d_1 \ln F_{12} = \ln \frac{\nu_{10,0}}{\nu_{10}} = \ln K_{12} + \ln \frac{\frac{2}{K_{12}} - \frac{1}{K_{22}} + 2\sqrt{\left(1 + \frac{1}{2K_{22}}\right)^2 - 1}}{1 + \sqrt{5}} \tag{15}$$

and

$$a_1 \ln F_{21} = \ln \frac{\nu_{01,0}}{\nu_{01}} = \ln K_{21} + \ln \frac{\frac{2}{K_{21}} - \frac{1}{K_{22}} + 2\sqrt{\left(1 + \frac{1}{2K_{22}}\right)^2 - 1}}{1 + \sqrt{5}} \tag{16}$$

As shown by eqs 15 and 16, each of the hydrogen-bonding terms in eqs 11 and 12 consists of two contributions. Seemingly, only the first of these contributions meets the linearity assumption of the LFER approach. Indeed, replacing from eq. 14, the first terms on the right-hand side of eqs 15 and 16 become

$$\ln K_{12} = A_1\left(\frac{k}{RT}B_2\right) \tag{17}$$

and

$$\ln K_{21} = B_1\left(\frac{k}{RT}A_2\right) \tag{18}$$

Both of these contributions do meet the linearity assumption of the LFER approach: The terms in parenthesis are exclusive properties of the solvent phase. Seemingly, the LFER approach has neglected the second contributions on the right-hand side of eqs 15 and 16. As seen in these equations, this second contribution is not an exclusive property of the solvent/phase but it depends on the solute, as well, through the cross terms K_{12} and K_{21}. We should now examine more closely this second contribution, $\ln(F_{12}/K_{12})$ *or* $\ln(F_{21}/K_{21})$, and see how much is influenced by the hydrogen-bonding capacity of the solute.

Typical calculations of this second contribution for a broad variety of combinations of solute acidity with solvent acidity/basicity descriptors are reported in Table S1 of the Supporting Information (SI) file. Entirely analogous is the effect of solute basicity on the corresponding hydrogen-bonding term in eqs 11 and 12. In Figure 1 is shown graphically the effect of solute acidity on the hydrogen-bonding terms, K_{12} and F_{12}, of the

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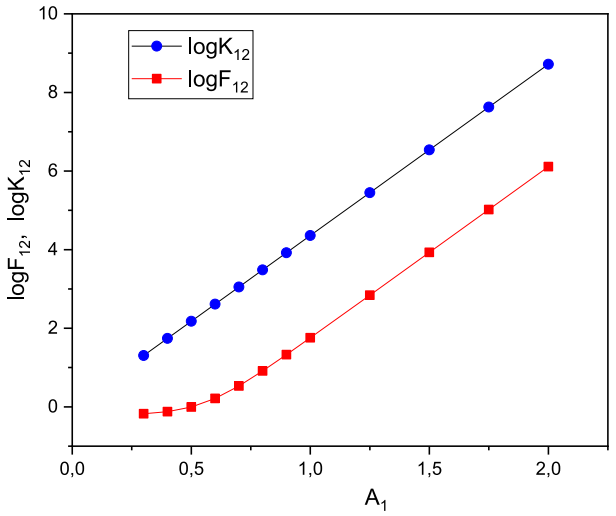

Figure 1. Linearity of $\log K_{12}$ and $\log F_{12}$ terms of the solvation free energy eq 11 when k = 50,000, A_2 = 1.1, and B_2 = 0.5.

equation for the solvation free energy. As observed, the linearity is preserved not only for K_{12} but also for almost all positive $\log F_{12}$ terms. In the LFER framework, one may consider that negative hydrogen-bonding terms have no physical meaning or any discrepancies at weak hydrogen-bonding interactions may be absorbed by the constant or polar term in the LFER eqs 1 and 2. One could consider that these arguments constitute the thermodynamic basis for the LFER linearity. A closer look, however, in Table S1 and in Figure 1 indicates that the above arguments hold true for K_{12} or K_{21} typically larger than 10^3. This condition may not be fulfilled with combinations of small A and/or B descriptors, and thus, more care must be exercised on the hydrogen-bonding contribution of LFER linearity.

Equations 15 and 16 (cf. also eq. S15a of the SI) may be rewritten in the following alternative forms:

$$F_{12} = \frac{2}{1+\sqrt{5}} + \mathrm{K}_{12}\frac{-\frac{1}{K_{22}} + 2\sqrt{\left(1+\frac{1}{2K_{22}}\right)^2 - 1}}{1+\sqrt{5}} \approx 0.618 + K_{12}\frac{0.618}{\sqrt{K_{22}}} \quad (19)$$

and, similarly,

$$F_{21} = \frac{2}{1+\sqrt{5}} + \mathrm{K}_{21}\frac{-\frac{1}{K_{22}} + 2\sqrt{\left(1+\frac{1}{2K_{22}}\right)^2 - 1}}{1+\sqrt{5}} \approx 0.618 + K_{21}\frac{0.618}{\sqrt{K_{22}}} \quad (20)$$

Figure 2 is a graphical representation of eq 19 in its logarithmic form. A larger k factor and a broader range of A_1 values are used in Figure 2. As observed, the linearity is again exhibited for the positive $\log F_{12}$ values. A closer look, however, indicates that this linearity is essentially preserved for K_{12} values typically larger than 10.[5] This is even more severe condition rather hardly met by many combinations of A and B LSER descriptors.[16]

In contrast to the above, Figure 3 is a graphical representation of $\log(F_{12} - 0.618)$, as given by eq. 19, for

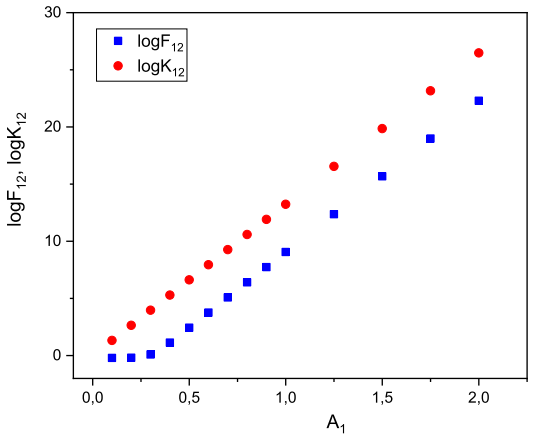

Figure 2. Linearity of $\log K_{12}$ and $\log F_{12}$ terms of the solvation free-energy equation when k = 84,000, A_2 = 0.6, and B_2 = 0.9.

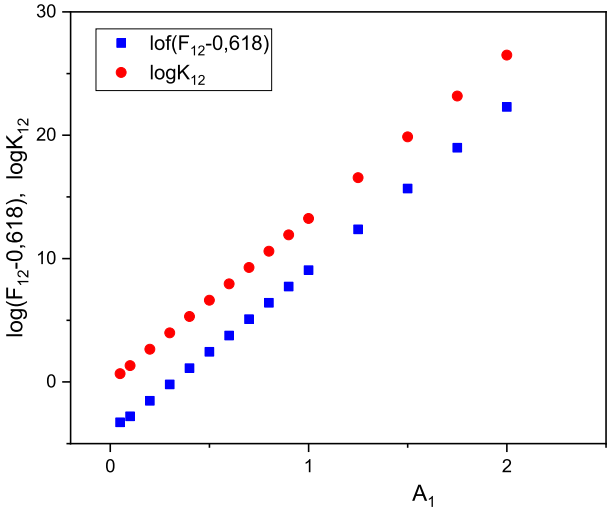

Figure 3. Linearity of $\log K_{12}$ and $\log(F_{12} - 0.618)$ terms of the solvation free-energy equation when k = 84,000, A_2 = 0.6, and B_2 = 0.9.

the very same set of k, A_1, A_2, and B_2 values as the one of Figure 2. In other words, the plotted function is $(c_2'(K_{22}))$, a solvent constant)

$$\log(F_{12} - 0.618) = c_2'(K_{22}) + \log \mathrm{K}_{12} \cong \log\frac{0.618}{\sqrt{K_{22}}} + A_1\left(\frac{kB_2}{2.304RT}\right) \quad (21)$$

Before proceeding further, it is worth pointing out that eq 21 does not contain any equation-of-state-model parameters. As observed in Figure 3, the linearity is now preserved over the full range of A_1 values regardless of the K_{12} values. This is a general observation valid for any physically reasonable combination of LSER hydrogen-bonding descriptors. The implication of this is rather clear: The LFER linearity is indeed preserved but not for the full hydrogen-bonding contribution, F_{12} or F_{21}, to solvation free energy. It is preserved for this hydrogen-bonding contribution reduced by a constant term. This constant term depends on the particularities of the hydrogen-bonding pair and the number of donor and acceptor sites involved, as shown in the Supporting Information (SI). Thus, it contains valuable information for the system. The

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Table 1. Molecular Descriptors and LSER Coefficients of Representative Compounds[9b,16] and Estimated Hydrogen-Bonding (Self-Association) Free Energy, ΔG_{22}^{hb}, and k Constant from Eq 22 and $aA = bB$ from Eq 23

compound	A_2	B_2	a	b	aA_2	bB_2	ΔG_{22}^{hb} (J mol^{-1})	k	$aA = bB$
methanol	0.43	0.47	3.70	1.43	1.591	0.672	−17,211	85,160	1.29
1-pentanol	0.37	0.48	3.78	0.98	1.399	0.470	−15,315	86,233	1.13
1-decanol	0.36	0.49	3.67	0.77	1.321	0.377	−14,622	82,894	1.07
trifluoroethanol	0.57	0.25	2.21	3.81	1.260	0.953	−15,257	107,058	1.12
ethyleneglycol	0.58	0.78	4.58	2.52	2.656	1.966	−29,592	65,413	2.35
ethyl acetate	0.00	0.45	2.95	0					
water	0.763	0.378	3.9	4.81	2.976	1.818	−31,508	109,248	2.51

sought linearity is indeed preserved, but the logarithm of the contribution is not directly proportional to solute's acidity or basicity LSER descriptor, A_1 or B_1 (it is not of the form A_1a_2 but of the form $\alpha + \beta A_1$ or of the more familiar form, $c_2' + A_1a_2'$). The slope and the constant term of this linear equation are independent of the solute and are solvent characteristic parameters, as are the a and b LFER coefficients.

It is important to point out that the hydrogen-bonding interactions contribute also to the constant LFER term, c_2, of the solvent, as eq 21 indicates. This must be taken into account when determining the LFER coefficients.

The above is a general observation and, thus, the LFER linearity assumption even of the hydrogen-bonding terms, does have a sound thermodynamic basis. This is important not only for verifying the validity of LFER approach but also for developing a thermodynamically sound basis for the estimation of LFER coefficients from the acidity/basicity descriptors of the solvent phase. In fact, as we will discuss below and in subsequent parts of this series of papers, the consequences are much broader and affect the very structure of the LFER approach, at least for the overall hydrogen-bonding contribution. It is essential, however, to underline that LFER was not developed on the basis of eq 21 or of Figure 3. It was developed by multiple regression of experimental information and fit to eqs 1 and 2. Thus, in the rest of this work, the focus will be on understanding key features and peculiarities of the LFER approach as currently used and their correspondence to a broader equation-of-state scheme.

4. USE OF LFER LINEARITY AND APPLICATIONS

We will now apply the above findings to real systems and discuss the calculation results. We will focus on systems for which both the solute molecular descriptors (E, S, A, B, V, and L) as well as the corresponding solvent parameters (e, s, a, b, v, and l) are available.

4.1. Calculation of Hydrogen-Bonding Free Energies from the LSER Parameters. In Table 1, the acidity/basicity parameters for a few representative compounds are recalled. We will first apply the above eqs 15 and 16 to the self-solvation of the alcohols of Table 1.

In the case of methanol, (cf. eq 2 and 11): $\log F_{12} = A_2a = 0.43 \times 3.70 = 1.591$ and $\log F_{21} = B_2b = 0.47 \times 1.43 = 0.672$ (cf. columns 6 and 7 in Table 1). Since A and B descriptors are known, the only unknown in eq 15 for F_{12} is the proportionality constant k. In this case of self-solvation, we could replace K_{12} in eq 15 by K_{22} (or K_{11}). For clarity, we write here the equation for F_{12} to be solved for k (cf. equation 15):

$$k = \frac{2RT}{A_2B_2}\ln\frac{10^{a_2A_2}}{0.618} \qquad \text{(self-solvation)} \tag{22}$$

Replacing from Table 1, we obtain k = 101,670 (the exact value without the simplifications shown in eq 22 is 102,500). Thus, the free energy change upon self-association of methanol, from the aA product, is $\Delta G_{22}^{hb} = -101{,}670 \times 0.43 \times 0.47 = -20{,}548$ J/mol (the exact value is −20,715 J/mol). However, this constant may also be obtained from the bB product of the LFER equation. Repeating the above procedure for F_{21}, we obtain, now, k = 49,762 (the exact value is now 48,850), and ΔG_{22}^{hb} = −10,058 J/mol (exact value, −9812 J/mol).

These two drastically different values for the very same free energy change, ΔG_{22}^{hb}, or the very same constant, k, and for self-solvation are indicative of the peculiar way acidity and basicity scales were developed by the LFER approach. It seems that the calculation of an acid−base interaction depends on the "direction" (acid−base or base−acid) of the calculation. As we will see later, part of this discrepancy may be explained by the fact that the LFER coefficients also contain information on the densities and molecular sizes of the solvents. However, in the case of self-solvation, these properties of solute and solvent are also identical and one would expect the equality $aA = bB$ to hold true.

If aA were different from bB on self-solvation, its explanation would be well beyond what our picture of quasi-chemical HB reaction and an equation-of-state model may capture. Other classical hydrogen-bonding models[19] or typical quantum chemical and molecular dynamics calculations would also find it hard to provide an explanation for such a difference. In fact, if aA were indeed different from bB on self-solvation and the LSER model were capturing it correctly, this difference might shed light on novel intermolecular interaction peculiarities and enrich our picture of solvation phenomena. All these are beyond our present approach, and its usefulness, in this case, would be on drawing a line beyond which these eventual peculiarities might be discussed meaningfully.

In any case, the present equation-of-state approach cannot reconcile the above two drastically different k or ΔG_{22}^{hb} values on self-solvation. We may, however, calculate an average proportionality constant, k, in an empirical way, as shown in the SI (eq S20), and obtain an average k = 85,160 or to an average hydrogen-bonding free energy, $\langle \Delta G_{ij}^{hb} \rangle = -k_{ij}A_iB_j = -85{,}160 \times 0.43 \times 0.47 = -17{,}210$ J/mol. This result is also reported in Table 1. This average ΔG value is interesting, but we should stress the point that eq S20 is purely empirical and the result is kept here just for the sake of discussion. The way ΔG_{ij}^{hb} may be obtained by less empirical ways and its incorporation into the LSER calculations will be discussed below.

For the free-energy change upon self-association (hydrogen bonding) of lower alkanols, we have rather good estimations from other thermodynamic properties and or equation-of-state

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considerations.[25,32,33,36] In LFHB,[32,33] the typical hydrogen-bonding interaction enthalpy is about −25,100 J/mol, and the interaction entropy is about −26.5 J K^{-1} mol^{-1} (cf. below), and thus, $\Delta G_{ij}^{hb} = \Delta H_{ij}^{hb} - T\Delta S_{ij}^{hb} = -25{,}100 + 26.5 \times 298.15 = -17{,}200$ J/mol. Thus, the above estimation of the average hydrogen-bonding free energy (−17,210 J/mol) for methanol is rather close to the equation-of-state one. If this will be verified with other classes of compounds as well, then the LFER parameters and molecular descriptors (along with the empirical eq S20) could become a useful set of information for a variety of direct thermodynamic calculations. Before we proceed, however, a diversion is needed in the next subsection.

4.2. On the Prediction of *a* and *b* LFER Coefficients from *A* and *B* Descriptors. Ultimately, what we seek here is an equation for LFER coefficient *a* or *b* of a solvent in terms of its own LSER molecular descriptors, *A* and *B*. Acceptable *a* and *b* values should pass the above simple test, namely, the products *aA* and *bB* should be identical in self-solvation. This is equivalent to expecting one single value for the above constant, *k*, or for ΔG_{ij}^{hb}, regardless of the "direction" of the interaction (acid−base or base−acid). In the above example of methanol, this one single value would be $k = 85{,}160$ with the corresponding ΔG_{ij}^{hb} value of −17,210 J/mol. Then, $K_{22} = \exp(-17{,}210/RT) = 1036$, and eq 22 would give

$$aA = \log F_{12} = \log \frac{1 + 2K_{22}\sqrt{\left(1 + \frac{1}{2K_{22}}\right)^2 - 1}}{1 + \sqrt{5}} = 1.29 \tag{23}$$

From this value, we may now calculate the coefficient *a* to be $a = 1.29/A = 3.0$. In a similar manner, the LFER coefficient *b* from $\log F_{21}$ is equal to $1.29/B = 2.75$. These calculations were made with the assumption that the *A* and *B* values remain the same. Obviously, we cannot change the coefficients *a* and *b* for one compound and leave descriptors and coefficients for all other compounds unchanged. Implementation of the new LFER coefficients requires a concerted effort for the appropriate changes in all compounds. Most likely, the acidity/basicity scales of the current LSER database[16] has to undergo some changes in order to enable the above equations for the LFER coefficients to be predictive.

The above calculations for the average *k* and ΔG_{22}^{hb} values for methanol were also done for the other compounds of Table 1, and the results are shown in the table. In the last column of the table, are shown the corresponding values for the products *aA* or *bB* obtained by eq 23. An empirical way of obtaining the products of the last column in Table 1 is discussed in the SI (eq S21). In fact, eqs S20 and S21 are two independent equations, and in principle, they may be used to predict the LFER coefficients from the *A* and *B* descriptors of any compound, as shown in the SI. Once these principal coefficients are known, the remaining LFER coefficients may be obtained in a rather straightforward manner, as shown in the SI. But, once again, the empirical eqs S20 and S21, although useful, cannot be used for developing a sound thermodynamic basis for LSER calculations. This empirical route, however, may be avoided, and an alternative estimation of ΔG_{ij}^{hb} may be obtained from the activity coefficients at infinite dilution, as discussed in the next section.

5. HYDROGEN BONDING INFORMATION FROM ACTIVITY COEFFICIENTS AT INFINITE DILUTION

In the LSER model, the descriptors *A* and *B* are considered to be the only descriptors that contain the information on solute hydrogen bonding or acidity/basicity character. However, the activity coefficient at infinite dilution, even in inert solvents such as *n*-hexadecane, also contains information on hydrogen-bonding. In the case of *n*-hexadecane and the definition of the descriptor *L*, this activity coefficient is intimately associated with *L*, as shown by eqs 9 and 10. Thus, as we seek thermodynamic consistency, it is important to see what kind of information on hydrogen bonding one may extract from this activity coefficient and the LSER descriptor, *L*, which is known for thousands of compounds.[16] For this purpose, we should return to the key eq 12 for the solvation free energy.

By definition, when the solvent is *n*-hexadecane, we have (cf. eq 9):

$$\gamma_{1/2}^{\infty} = \frac{RT}{K_{1/2}^{*} P_1^0 V_{m2}} = \frac{(RT)10^6}{10^{L_1} P_1^0 294.213} = 8.425\frac{10^{6-L_1}}{P_1^0}(\text{in solvent } n - \text{hexadecane}) \tag{24}$$

In the above equation, $\gamma_{1/2}^{\infty}$ is the activity coefficient of solute (component 1) at infinite dilution in *n*-hexadecane (component 2) and P_1^0 is the vapor pressure of the pure solute (in Pa units). Thus, when the vapor pressure and the descriptor *L* of the solute are known, $\gamma_{1/2}^{\infty}$ is also known and is given by eq 24.

In addition to the above, when the LFHB equation-of-state parameters, *r*, ρ^*, ε^*, for solute and solvent are known, the above equation may be used to extract information on hydrogen bonding (F_{12}, F_{21}) from the descriptor *L* and $\gamma_{1/2}^{\infty}$: One may use eq 12, once for the mixture and once for the self-solvation of the solute, and derive the equation for the activity coefficient at infinite dilution, which in our case reads[24]

$$\ln \gamma_{1/2}^{\infty} = \ln \frac{\omega_{1/2}}{\omega_{1/1}} + r_1 \ln \frac{(1-\tilde{\rho}_1)}{(1-\tilde{\rho}_2)} + \ln \frac{V_{m1}}{V_{m2}} - 2r_1 \frac{\tilde{\rho}_2 \varepsilon_{12}^{*} - \tilde{\rho}_1 \varepsilon_{11}^{*}}{RT} - \{d_1 \ln F_{12} + a_1 \ln F_{21}\}_{x_1=0} + \{d_1 \ln F_{11} + a_1 \ln F_{11}\}_{x_1=1} \tag{25}$$

Of course, in the case of infinite dilution in *n*-hexadecane, only the last term with F_{11} is contributing when the solute is homosolvated or self-associates. In this case, eqs 24 and 25 may be combined in order to extract information on the free energy change upon self-association of the solute.

On the other hand, a combination of eqs 12 and 25 may be used for extracting information on the conformation terms $\omega_{1/i}$. As mentioned already, conformational changes and conformer distributions are outside the realm of the equation-of-state approach. In addition, the ω term in eq 25 contains information for the correction to the second term for the cavitation contribution, namely, the "shape" of the consecutive r_1 empty sites, which must be compatible with the solute conformers. For lack of such specific information and for simplicity, we will also adopt here the classical assumption of a Flory-type combinatorial contribution,[19] or

$$\ln \omega_{1k} = 1 - \left(\frac{r_1}{r_k}\right)^u \tag{26}$$

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Table 2. LFHB Scaling Constants and Hydrogen-Bonding Parameters for 1-Alkanols and Comparison of Experimental [Ref 16 and Eq 24] and Predicted Activity Coefficients at Infinite Dilution in *n*-Hexadecane at 298.15 K by Eq 25

alkanol	ε_h^* (J mol^{-1})	v_{sp0}^* (cm^3 mol^{-1})	ε_s^* (J K^{-1} mol^{-1})	ΔH_{ij}^{hb} (J mol^{-1})	ΔS_{ij}^{hb} (J K^{-1} mol^{-1})	$-\Delta G_{ij}^{hb}$(J mol^{-1})	L	ξ_L	$\gamma_{1/2}^{\infty}$exp	$\gamma_{1/2}^{\infty}$pred
methanol	4162	1.131	1.185	−26,000	−29.5	17,205(17,211)[a]	0.97	0.957	48.5	54.0
ethanol	4134	1.128	−0.107	−24,050	−27.5	15,851	1.50	1.000	33.4	34.0
1-propanol	4072	1.103	0.330	−23,600	−26.5	17,199	2.04	0.997	25.2	27.3
1-butanol	4092	1.097	0.610	−23,400	−26.5	15,499	2.60	0.993	22.9	23.6
1-pentanol	4076	1.088	0.914	−23,380	−27.0	15,330(15,315)[a]	3.10	0.991	20.1	20.1
1-hexanol	4058	1.079	1.090	−23,080	−26.5	15,179	3.61	0.992	17.1	21.3
1-heptanol	4117	1.081	0.730	−23,100	−27.0	15,050	4.11	0.983	22.1	22.1
1-octanol	4086	1.075	1.004	−23,100	−27.5	14,901	4.61	0.988	17.5	18.5
1-nonanol	4088	1.074	1.377	−23,100	−28.0	14,752	5.12	0.985	19.0	19.3
1-decanol	4095	1.072	1.311	−23,100	−28.5	14,603(14,622)[a]	5.62	0.985	16.6	15.8

[a]Values in parenthesis are LFER estimations (cf. Table 1)

The exponent u was set equal to 0.2 for all fluids. Of course, before entering into hydrogen-bonding calculations, the appropriateness of eq 26 could be tested with non-hydrogen-bonded systems. This is done with *n*-alkane solutes, and the results are reported in Table S6. As shown in table S6, the calculated L and activity coefficients are in close agreement with the experimental ones.[16] This agreement could be considered as a preliminary validation of eq 26.

The above calculation scheme could also be applied to homosolvated or self-associated compounds interacting with hydrogen bonds, suffice this hydrogen-bonding capacity be taken properly into account. This is now a crucial step because there is nothing absolute for a precise division of intermolecular interactions into hydrogen-bonding (HB) and non-hydrogen-bonding (nonHB) ones, and thus, some degree of arbitrariness has to be admitted. However, the equation-of-state approach imposes by its very nature some solid criteria, which must be met by any acceptable division of intermolecular interactions into HB and nonHB ones. These divisions should, at least, lead to calculations of key thermodynamic quantities in good agreement with experiment. Thus, apart from the agreement of L and $\gamma_{1/2}^{\infty}$with experiment, the adopted division should also lead to correct calculations of equation-of-state properties such as orthobaric densities, vapor pressures, or heats of vaporization.[37,38] There may be various alternative divisions, but the acceptable ones should meet all the above conditions simultaneously. This reduces significantly the arbitrariness in the above division although it does not remove it entirely. Along these lines, the above calculation scheme was also applied to 1-alkanols, and the results are shown in Table 2.

The LFHB scaling constants were obtained, as with *n*-alkanes, by fitting experimental data on liquid densities, vapor pressures, and heats of vaporization of pure fluids over a broad range of external conditions taken from the DIPPR compilation.[37] The constant v^*_{sp1} was set equal to −0.0001 in this homologous series except for 1-nonanol and 1-decanol, for which this constant was set equal to −0.0003, in better conformity with their long alkane chain, to zero for ethanol and to 0.0002 for methanol. The hydrogen-bonding interaction energy ΔE_{hb} and entropy ΔS_{hb} were also obtained simultaneously with the LFHB scaling constants and are reported in Table 2. These equation-of-state characteristic constants of the fluids were used for the calculation of L and $\gamma_{1/2}^{\infty}$. The cross-interaction term was obtained through the classical geometric mean[32,33,39,40] or $\varepsilon_{12}^* = \xi_L\sqrt{\varepsilon_{11}^*\varepsilon_{22}^*}$. The binary coefficient ξ_L was determined by requiring an exact reproduction of L by eq. 12 and is also reported in Table 2 along with the predicted $\gamma_{1/2}^{\infty}$. Alternatively, one may use L directly, as estimated by the equation of state, and predict $\gamma_{1/2}^{\infty}$, as was done with *n*-alkanes (cf. Table S6). The picture, in fact, does not change very much. It should be kept in mind that often in many practical applications, the required quantity is lnγ, not the plain γ. From this point of view, as seen in Table 2 and Table S6, the predicted ln$\gamma_{1/2}^{\infty}$ are practically identical to the experimental ones.

With the above pair of hydrogen-bonding parameters, one may calculate the free energy change upon hydrogen bond formation over a broad range of temperatures through the classical equation, $\Delta G_{ij}^{hb} = \Delta H_{ij}^{hb} - T\Delta S_{ij}^{hb}$. This free energy change at 25 °C is also reported in Table 2. As we have seen above, this is a key quantity for the new LSER calculations. This encourages an attempt to explore the inverse transfer of information and compare systematically the physicochemical content of LSER molecular descriptors with the equation-of-state scaling constants. This will be done in the subsequent part of this series of works. A major challenge, however, is the case of heterosolvated compounds for which the above predictive scheme cannot be applied. This challenge is examined briefly in the Supporting Information (SI) file, and the results are rather encouraging for undertaking the interconnection of LSER with the equation-of-state approach. As mentioned above, full account of the equation-of-state approach and calculations like those reported in Table 2 will be done in subsequent parts of this series of papers.

6. DISCUSSION

There is a number of important implications of the above calculations that deserve further discussion. First of all, it is rather clear that there is a sound thermodynamic basis of LFER linearity including their hydrogen-bonding contributions. Without such a thermodynamic basis, the evaluation and exchange of thermodynamic quantities would be practically meaningless. The second important implication arises from the equation-of-state formulation of solvation thermodynamics. Once the hydrogen-bonding sum $aA + bB$ (plus a constant) is identified as corresponding to the equation of state term $\log(F_{12}F_{21})$,it may be calculated over a broad range of external conditions. As a result, the solvent screening and other applications may take place over a range of external pressure and temperature conditions. The key quantity for handling hydrogen-bonding contributions is the free energy change

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upon formation of the bond $i-j$, $\Delta G_{ij}^{hb} = \Delta H_{ij}^{hb} - T\Delta S_{ij}^{hb} = -kA_iB_j$. This quantity may be obtained from external sources, including experimental and equation-of-state information, and thus, it may act as a bridging quantity for the exchange of information between diverse databases and approaches.

Thus, the focus in the present work was on the thermodynamic basis of LFER linearity concerning the hydrogen-bonding contribution, which is rather the most difficult to explain. A major portion of this difficulty arises from the way the LFER parameters were historically developed via multiple linear regressions of experimental transfer/partition information. In these regressions, no attempt was made to explicitly account for solute/solvent specificities such as densities or molecular size shapes. All these specificities were assumed to be well described by the set of LSER descriptors. However, as we have seen above, this leads to difficult-to-rationalize peculiarities. It is hard, as an example, to explain the drastic difference of aA and bB products in self-solvated and homosolvated compounds. The above solvation analysis leads to thermodynamically consistent equations, which meet the $aA = bB$ criterion on self-solvation. This could permit the development of predictive equations for a and b coefficients in terms of the corresponding A and B descriptors. As an example, eq 15 and/or 16 could be rewritten in the following predictive form in self-solvation:

$$a \approx \frac{1}{A}\log\frac{1+2\sqrt{K}}{1+\sqrt{5}} = \frac{1}{A}\log\frac{1+2\exp\frac{-\Delta G}{2RT}}{1+\sqrt{5}} = \frac{1}{A}\log\frac{1+2\exp\frac{kAB}{2RT}}{1+\sqrt{5}} \quad (27)$$

and, similarly for b ($=aA/B$).

These equations, however, are not yet useful because the current acidity and basicity A and B scales do not permit, at present, the use of a universal equation of the form $\Delta G_{ij}^{hb} = -kAB$. A concerted effort is required to produce first a critical compilation of ΔG_{ij}^{hb} values, such as those shown on Table 2, and reformulate the A and B scales with a universal proportionality constant, k. Of course, this concerted effort should also account for the discrepancies from the experiment of LSER calculations with solvents, like water and ethylene glycol, which would require excessively large constant LFER terms and which are reported in the Supporting Information (SI) file.

In reformulating the A and B scales, it should be pointed out that even the current A, B, a, and b scales may undergo extensive changes and still preserve their predictive linearity. As an example, the descriptors and LFER coefficients in Table 1 may be shifted without affecting the predictive capacity of LFER linearity, as shown in Table S2. Such shifts are useful when attempting to exchange information from other hydrogen bonding or acidity/basicity scales such as the COSMO-RS databases.[41−45]

In the subsequent parts of this series of papers, we will examine such alternative scales. Exchange of information between these alternative scales is not trivial, however. This effort is facilitated by the introduction of partial solvation parameters (PSP),[24,25,27] which connect the LSER descriptors with equation-of-state quantities. As an example, the dispersive PSP, σ_d, is defined in terms of the LSER descriptors E and V_x as follows:

$$\sigma_d = 100\sqrt{\tilde{\rho}\frac{4V_x+E}{V_m}} = \frac{100}{V_m}\sqrt{V^*(4V_x+E)} = 100\tilde{\rho}\sqrt{\frac{4V_x+E}{V^*}} \quad (28)$$

At 25 °C, this PSP is very close to the dispersive Hansen solubility parameter, δ_d.[38] For non-polar compounds, this PSP is identical to the total Hildebrand solubility parameter.

Eq. 28 is a most useful predictive equation, as V^* is a linear function of V_x. In fact, what will be established in the subsequent parts of this series of papers is that knowledge of LSER descriptors suffice for the calculation of the PSPs of fluids. The advantage of the above connection to the equation-of-state approach is that it may be used for a variety of external conditions, including supercritical ones.[27] On the other hand, E and V_x are well-defined LSER quantities calculated in a straightforward manner[1−5] and available for thousands of compounds.[16]

More pertinent in the present discussion is the hydrogen-bonding PSP, σ_{hb}, which is defined as follows:

$$\sigma_{hb} = \sqrt{\frac{-N_{hb}\Delta H_{ij}^{hb}}{V_m}} \quad (29)$$

$N_{hb} = r\nu_{hb}$ is the number of hydrogen bonds per mol. In the equation-of-state approach, the number of hydrogen bonds in a solvent with d donor and a acceptor sites, per molecule, is obtained by an equation similar to eq S7, or

$$N_{hb} = r\nu_{hb} = \frac{d+a+\frac{r}{\tilde{\rho}K} - \sqrt{\left(d+a+\frac{r}{\tilde{\rho}K}\right)^2 - 4da}}{2} \quad (30)$$

Equation 29 also calculates σ_{hb} over a broad range of external conditions. At 25 °C, this PSP is often close to the Hansen solubility parameter, δ_{hb}.[38] It is worth mentioning that σ_{hb} contains information not only for the enthalpy, ΔH_{ij}^{hb}, but also for the free energy, ΔG_{ij}^{hb}, or the entropy, ΔS_{ij}^{hb}, through the equilibrium constant, K ($-RT \ln K_{ij} = \Delta G_{ij}^{hb}$).

Table 2 contains all needed information for the calculation of σ_{hb}, and the results are shown in Table S7. As shown, the two parameters, σ_{hb} and δ_{hb}, are in rather good agreement at 25 °C. This is important since the Hansen solubility parameter, δ_{hb}, which is also known for a large number of compounds,[38] may be used as a source of information on hydrogen-bonding interaction and comparison with corresponding LSER calculations. As we will see in the subsequent parts of this series of papers, the PSPs could be used for the exchange of information between various databases and QSPR-type frameworks.[23b]

7. CONCLUSIONS

The success of Abraham's LSER model and of the general LFER approach is based on their sound thermodynamic basis. This thermodynamic basis of the LFER linearity has been shown in the present work by combining solvation thermodynamics with a statistical thermodynamic approach to hydrogen-bonding interactions. The equation-of-state model used in this work was just a tool, but the essential results regarding the thermodynamic basis of LFER linearity are of a general character and independent of model details and scaling parameters. By knowing this thermodynamic basis,

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many possibilities are open for a rational expansion of the LSER database, especially the LFER coefficients, which would increase significantly its predictive capacity in various applications, including solvent screening over a broad range of external conditions and solute-partitioning studies in numerous environmental and (bio)chemical applications. Both homosolvated and heterosolvated compounds could be handled, and their hydrogen-bonding capacity could be assessed consistently by meeting basic thermodynamic criteria, such as the equality $aA = bB$ in self-solvation. Of course, our treatment of hydrogen bonding as a quasi-chemical reaction and the equation-of-state approach have limitations, and the above results should be confined to the realm of validity of these approaches. Even there, a number of challenging issues remain to be addressed in this effort. In essence, the full LSER database has to be reworked by making use of refined linearity equations, like eq 21, in order to safely predict LFER coefficients from the corresponding LSER descriptors and, in particular, in order to safely estimate the interaction free energy $\Delta G_{ij}^{hb} = -k_{ij}A_iB_j$ with a universal proportionality constant, k_{ij}. Some of these challenging issues are examined in subsequent parts of this series of papers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.iecr.2c03960.

Essentials of the derivations of the LFHB equations at infinite dilution; examples of the use of linearity of the LSER model in practical calculations; examples of equation-of-state calculations (PDF)

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Notes

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■ LIST OF SYMBOLS

Latin letters

a_i Number of acceptor sites of type i
a_i LFER acidity coefficient for solvent i
A_i LSER acidity molecular descriptor of component i
b_j LFER basicity coefficient for solvent j
B_j LSER basicity molecular descriptor of component j
c Quantities at the infinite-dilution limit in eq. 18−19
d_i Number of donor sites of type i
e LFER solvent refractivity coefficient
E Excess refractivity LSER molecular descriptors
F Hydrogen-bonding contribution term
G Free energy
H Enthalpy
k Proportionality constant
K Equilibrium constant
l LFER coefficient for gas-to-C_{16} partitioning
L LSER molecular descriptor for gas-to-C_{16} partitioning
N Mole number
P Pressure
r Number of molecular segments
R Gas constant
s LFER polarity coefficient
S Entropy
T Temperature
v specific volume
V Volume
V_x McGowan volume
x Mole fraction
Z Compressibility factor

Greek Letters

γ Activity coefficient
δ Solubility parameter
ΔY Change of quantity Y
ΔG_{ij}^{hb} Free energy change on hydrogen-bond formation between donor i and acceptor j.
ε^* Interaction energy
ν Fraction or reduced number of hydrogen bonds
ξ Correction factor to geometric-mean interaction energy
$\tilde{\rho}$ Reduced density
σ Partial solvation parameter
φ Fugacity coefficient
ω Molecular conformation parameter

Superscripts

0 Pure component
∞ Infinite dilution
* LFHB scaling property
hb Hydrogen-bonding quantity
IG Ideal gas
S Solvation quantity

Subscripts

1/2 Property of solute (1) in solvent (2)
0i Fraction of free acceptor sites
i0 Fraction of free donor sites
d Dispersion quantity
hb Hydrogen-bonding quantity
i Quantity pertaining to component i
ij Quantity pertaining to the interacting pair i, j
m Molar quantity
p Polar quantity
sp. Specific

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