Statistical thermodynamics of regular solutions and solubility parameters

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ABSTRACT

Solubility parameters, developed originally for regular solutions, have been applied to solutions beyond the presumed weak non-ideality, implying that the true foundation of the solubility parameters may be more general than the regular solution theory. To assess the root of regularity on rigorous statistical thermodynamics, here we re-examine the classical iodine dissolution experiments by Shinoda and Hildebrand, who concluded that the entropy of mixing is ideal regardless of solute-solvent size ratio. We show that iodine solubility is concerned with the limit of infinite dilution, while the regular solution theory is a scheme to describe the dependence on the solute concentration. This means that the solubility of iodine cannot be a foundation of the regular solution; it is further shown that the differences in the solvation free energy among organic solvents are dominated by enthalpy with negligible role of the entropic component. In addition, the validity of the regular solution concept, i.e., the enthalpic nature of the solution non-ideality, can now be examined quantitatively by expressing the Margules model in terms of the Kirkwood-Buff integrals, which incorporate the excluded volume effects and the potential of mean force nature of interactions that were beyond the reach of the classical thermodynamic models. Such insights into the physical basis of solubility parameters may be useful for improving solubility prediction.

1. Introduction

There has been a resurgence of interest in Hildebrand [1,2] and Hansen [3,4] solubility parameters, due to the need for rational solvent selection and alternative solvent development for greener processes [5–12]. The idea of the solubility parameters originally came from the regular solution theory [1,2], whose applicability is strictly limited to mixtures whose weak deviation from ideality is enthalpic. However, solubility parameters turned out to be useful for mixtures that cannot be considered regular [4], suggesting that it may be more versatile than the regular solution theory itself. This raises a question as to what the solubility parameters really are based upon. We will address this question through rigorous statistical thermodynamics.

Our goal is to establish the physical basis of solubility parameters for improving solubility prediction. As a first step, we will show that the ad-hoc nature of the classical thermodynamic foundation [1,2], upon which the regular solution theory and the solubility parameters are based, is often inconsistent and cluttered, and that their foundation can be made clearer and more transparent based on the modern statistical thermodynamics of solvation by Widom [13], Ben-Naim [14,15], and Gurney [16]. To appreciate this, let us first summarise the classical thermodynamic foundation of the regular solution theory, based upon the following well-known relationships that have arisen from the cell theory of mixing equal-sized solutes and solvents [1,2,17–19]

$$\mu_1 = \mu_1^o + RT \ln x_1 + w x_2^2 \tag{1}$$

$$\mu_2 = \mu_2^o + RT \ln x_2 + w x_1^2 \tag{2}$$

where μ_i, μ_i^o and x_i express the chemical potential, standard chemical potential and mole fraction of the species i, respectively, and $i = 1$ and 2 represent the solvent and solute, respectively. Here, the terms involving w express the deviation from ideality. However, the physical meaning of w, as will be shown, has been dependent on model assumptions; Hildebrand and coworkers have shown that

(1) $RT \ln x_i$ arises from the entropy of mixing, whereas $w x_j^2$ originates from the enthalpy of mixing [1,2].

(2) The size disparity between the solute and solvent, predicted by Flory [20,21] and Huggins [22], is negligible, hence Eqs. (1) and (2) are applicable regardless of size disparity [1,2,23].

These conclusions, when used in conjunction with the following assumptions,

(3) Eqs. (1) and (2) are valid for the entire composition range, hence μ_1^o and μ_2^o are of the pure system [1,2];

(4) w can be calculated from the difference of cohesive energy densities (“solubility parameters”) between the solute and solvent [1,2],

have been considered to be the basis for predicting the solubility ($\ln x_2$) via Eq. (2) from the solubility parameters via w.

The experimental evidence for (1) the ideality of the mixing entropy and (2) the negligibility of size disparity comes from a series of iodine dissolution experiments in which the entropy of solution (i) exhibited a linear correlation to the ideal mixing entropy and (ii) showed no dependence on solvent size, despite the wide variety in the partial molar volume of the solvents (Figure 1) [1,2,23–29]. Thus the seminal work by Hildebrand and coworkers [1,2,23–29] have provided a justification for some of the important pillars of the regular solution theory.

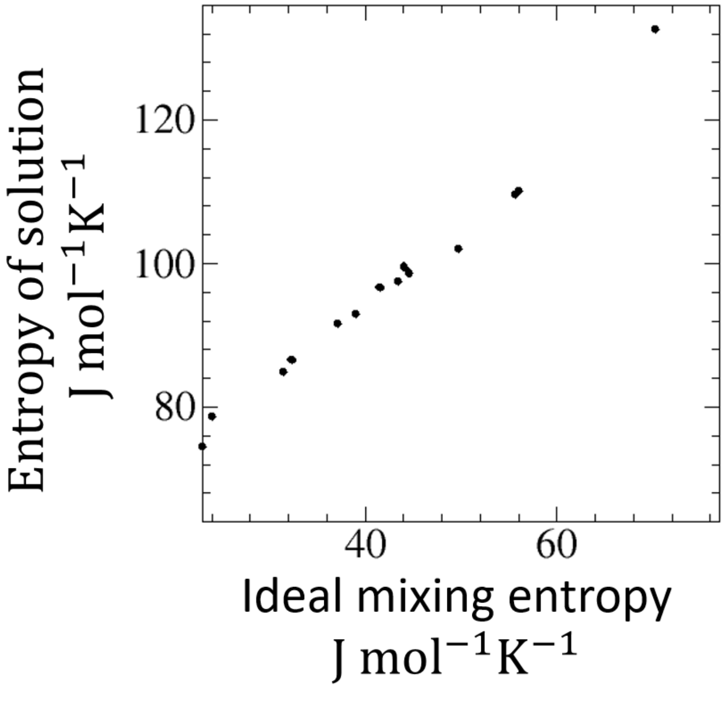

Figure 1. Iodine dissolution experiments in a number of solvents, in which the correlation between the “ideal mixing entropy” ($-R\ln x_2$, where x_2 is the solubility of iodine in mole-

fraction scale) and the “entropy of solution” ($R\frac{\partial \ln x_2}{\partial \ln T}$) has traditionally been interpreted as the basis for (i) neglecting the entropy of mixing arising from solute-solvent size ratio and (ii) the prediction of solubility based on solubility parameters derived from enthalpy. The experimental data were taken from Shinoda and Hildebrand [25–28].

However, that the mixing entropy is independent of solute-solvent size disparity is at odds with the Flory-Huggins lattice model [20–22] and with its re-derivation by Hildebrand based on van der Waals fluids [1,2,30] that have led to the existence of the non-ideal mixing entropy arising from solute-solvent size disparity. Attempts have been made in the 1990s to reconcile the size-independent nature of iodine dissolution with the size-dependent entropy of mixing, motivated largely by the need for quantifying the hydrophobic contribution to protein stability [31,32,41–49,33–40]. However, the paradox has remained unresolved [44].

This paradox on the apparent solvent size independence of iodine dissolution entropy can only be resolved using the rigorous statistical thermodynamics of solvation, as will be demonstrated in the present paper. Statistical thermodynamics becomes particularly helpful through its ability in attributing a molecular-based physical meaning to thermodynamic quantities. This becomes particularly important because the previous analyses were carried out using the following expression for the entropy of solution $\Delta\bar{S}_2$ by Hildebrand (derivation summarised in Appendix A) [1,2]

$$\Delta\bar{S}_2 = R\frac{\partial \ln x_2}{\partial \ln T} \tag{3}$$

which is called the “Hildebrand entropy” and has been acknowledged to be different from the definition of the entropy of solution in other concentration scales [50–52]. As its name indicates, the “Hildebrand entropy” is different from the entropy of dissolution, and we will demonstrate that it is actually enthalpic.

Our statistical thermodynamic re-analysis of the iodine dissolution experiments (Section 2) will show that the iodine dissolution experiments cannot be interpreted as the support for the ideality of mixing entropy regardless of solute-solvent size disparity nor does it have any connection to w. The point of the iodine experiments is instead the dominance of enthalpy in solvation free energy difference. In addition, origin of the deviation from ideality can be identified rigorously by the Kirkwood-Buff (KB) integrals [53,54,63,55–62] that shows not only the enthalpy of mixing [1,2,21,46,64] but also the excluded volume effect and solvent-mediated interactions play an important role (Section 3).

2. Solubility and solubility parameters

The entropy of solution for iodine (according to Eq. (3)) were shown to be ideal even in solvents widely differing in size [1,2,23–29], and has been used as evidence for solubility prediction based on solubility parameters (see assumptions 1-4 and Eqs. (1) and (2)). Based on rigorous statistical thermodynamics, here we examine the validity of this interpretation.

2.1. Iodine dissolution does not support the ideality of mixing entropy

Consider iodine as solute (indexed as $i = 2$), which is in equilibrium with the solvent ($i = 1$). Due to the difficulty of dealing with the solid phase, let us focus on the *difference* in solvation of a single solute between solvents. In the following, the solvent species is distinguished by a superscript (α).

According to the statistical thermodynamics of solvation, the chemical potential of the solute, μ_2, can be decomposed into the following manner, in terms of (i) the pseudochemical potential $\mu_2^{(\alpha)*}$, which signifies the free energy of inserting a solute molecule at a fixed position in the solvent α, and (ii) the free energy of liberating a solute from a fixed position (which can be expressed in terms of the molar concentration of the solute $c_2^{(\alpha)}$) as

$$\mu_2^{(\alpha)} = \mu_2^{(\alpha)*} + RT \ln c_2^{(\alpha)} \Lambda_2^3 \tag{4}$$

where Λ_2 is the momentum distribution function of the solute [15]. The pseudochemical potential $\mu_2^{(\alpha)*}$ is the standard, quantitative measure of solute-solvent interaction in solution chemistry [14].

Iodine solubility, on the other hand, has been reported using the mole fraction concentration scale, $x_2^{(\alpha)}$, instead of molarity required by the statistical thermodynamic theory (Eq. (4)). Hence, we need to link the two solubility scales. Fortuitously, iodine solubility in most solvents are dilute enough such that the approach based on ideal dilute solutions can simplify the theoretical treatment significantly [1,2,23–29]. At this limit,

$$x_2^{(\alpha)} = \frac{c_2^{(\alpha)}}{c_1^{(\alpha)}+c_2^{(\alpha)}} \simeq \frac{c_2^{(\alpha)}}{c_1^{(\alpha)}} = V_1^{(\alpha)} c_2^{(\alpha)} \tag{5}$$

$V_1^{(\alpha)}$ is partial molar volume of the solvent α. Combining Eqs. (4) and (5), we can write down the transfer free energy of iodine from the solvent α to the solvent β in the following manner:

$$\Delta\mu_2^{(\alpha\to\beta)*} = -RT \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}} + RT \ln \frac{V_1^{(\beta)}}{V_1^{(\alpha)}} \tag{6}$$

Since the regular solution theory requires the consideration of entropic and enthalpic contributions to the transfer free energies, the isobaric entropy Δs_u^* and enthalpy Δh_u^* of transfer can be calculated straightforwardly from Eq. (6)

$$\Delta s_2^{(\alpha\to\beta)*} = -\left(\frac{\partial \Delta\mu_2^{(\alpha\to\beta)*}}{\partial T}\right)_{P,N} = R\ln\frac{x_2^{(\beta)}}{x_2^{(\alpha)}} + \frac{\partial R\ln\frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} - R\ln\frac{V_1^{(\beta)}}{V_1^{(\alpha)}} - RT\left(\alpha_1^{(\beta)} - \alpha_1^{(\alpha)}\right)$$

$$= -\frac{\Delta\mu_2^{(\alpha\to\beta)*}}{T} + \frac{\partial R\ln\frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} - RT\left(\alpha_1^{(\beta)} - \alpha_1^{(\alpha)}\right) \approx -\frac{\Delta\mu_2^{(\alpha\to\beta)*}}{T} + \frac{\partial R\ln\frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} \qquad (7)$$

$$\Delta h_2^{(\alpha\to\beta)*} = \Delta\mu_2^{(\alpha\to\beta)*} + T\Delta s_2^{(\alpha\to\beta)*} = T\frac{\partial R\ln\frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} - RT^2\left(\alpha_1^{(\beta)} - \alpha_1^{(\alpha)}\right)$$

$$\approx T\frac{\partial R\ln\frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} \qquad (8)$$

where the minor contributions from the expansivity of the pure solvent $\alpha_1 = \frac{1}{V_1}\left(\frac{\partial V_1}{\partial T}\right)$ have been neglected.

Defining the transfer entropy and enthalpy statistical thermodynamically via Eqs. (7) and (8) has significant advantages. Firstly, as has been shown by one of us that the entropy and enthalpy of solvation defined via Eqs. (4)-(6) can be attributed to the solute-solvent and solvent-solvent interactions around the solute, which converges within finite distance, thereby establishing a link between solvation thermodynamics and its underlying physical picture of the "solvation shell" [65–69]. Secondly, purely thermodynamic approaches based on the mole-fraction scale, when considering entropy and enthalpy, faces significant conceptual difficulties arising from the need for the "mixing" process and its interpretational difficulties on a molecular scale [14,70,71].

Let us now apply Eqs. (6)-(8) to the interpretation of the classical iodine dissolution experiments. According to the regular solution theory, a correlation between $\Delta \bar{S}_2 = \frac{\partial R \ln x_2}{\partial \ln T}$ and $-R \ln x_2$ (ideal mixing entropy, Figure 1) signifies the ideality of the entropy of solution (assumption 1 in Section 1) regardless of the solute-solvent size ratio (assumption 2), in which the deviation from ideality is entirely enthalpic (assumption 1) [1,2,23–29]. However, according to statistical thermodynamics, $\frac{\partial R \ln x_2}{\partial \ln T}$ signifies the enthalpy (Eq. (8)), whereas $-R \ln x_2$ is predominantly the free energy of solvation (Eq. (6)). Thus, according to statistical thermodynamics, iodine dissolution experiments are a direct evidence for the enthalpy-dominated transfer free energy, $\Delta\mu_2^{(\alpha\to\beta)*} \simeq \Delta h_2^{(\alpha\to\beta)}$ and the negligible entropy contribution, $\Delta s_2^{(\alpha\to\beta)*} \simeq 0$ (Figure 2). It should be noted that a solution is always ideal (dilute ideal solution) at dilute conditions [1,2,15,17,19], hence the chemical potential depends on x_2 in the form of $RT \ln x_2$ at small x_2, and thus our focus in the above discussion is not the dependence on x_2 since the x_2 dependence is trivial for dilute solutions. What our analysis revealed is $\Delta s_2^{(\alpha\to\beta)*} \simeq 0$, that is about the excess partial molar entropy, i.e., the entropy change upon dissolution of a single solute molecule; its x_2 dependence does not come into the discussion since iodine was dilute in Figures 1 and 2.

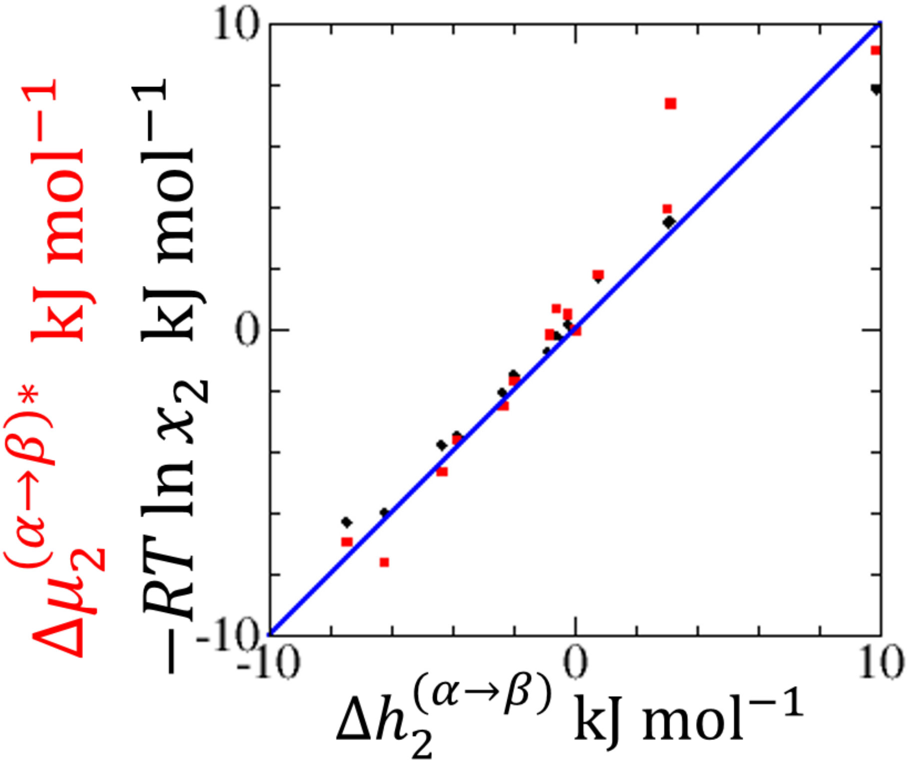

Figure 2. Re-interpretation of iodine dissolution experiments, as a correlation between the enthalpic ($\Delta h_2^{(\alpha\to\beta)}$, Eq. (8)) and free energy ($\Delta\mu_2^{(\alpha\to\beta)*}$, Eq. (6), red) contributions, as well as its approximation ($-RT\ln x_2$, black). The blue line corresponds to $\Delta\mu_2^{(\alpha\to\beta)*} = \Delta h_2^{(\alpha\to\beta)}$. The reference solvent, α, was chosen to be SiCl$_4$. The experimental data were taken from Shinoda and Hildebrand [25–28].

The above conclusion of ours constitutes a resolution of the paradox, i.e., the apparent independence of the Hildebrand "entropy of solution", $\Delta\bar{S}_2$, on solute-solvent size ratio, expected from the Flory-Huggins and van der Waals fluid theories [1,2,20–22,30]. This paradox has been revisited in the 1990s in the context of quantifying hydrophobic stabilization of proteins from transfer free energies of amino acids [31,32,41–49,33–40], yet has remained unresolved, because of the use of Hildebrand's "entropy", $\frac{\partial R\ln x_2}{\partial \ln T}$ as entropy [41,44]. According to Eq. (8), we can see that the correlation between $-R\ln x_1$ and $\frac{\partial R\ln x_2}{\partial \ln T}$ (Figures 1 and 2) has nothing to do with the size-dependent entropy of mixing. The “Hildebrand entropy” is actually an enthalpy, and a conclusion about the entropy is that the solvation entropy is not different among the solvents for dilute iodine.

The dominance of transfer enthalpy on the free energy has been observed also in xenon solubility (Figure 3) in alkanes [72–74], alkanols [75], cyclic alkanes, carboxylic acids, aldehydes [76], and fluoroalkanes [77]. Indeed, the virtual independence of solvation entropy on solvents has been observed widely in gas solubility measurements for many decades [50,72–77]. Instead of being a support for the regular solution theory, the Shinoda-Hildebrand experiments seem to be another example of this common empirical relationship.

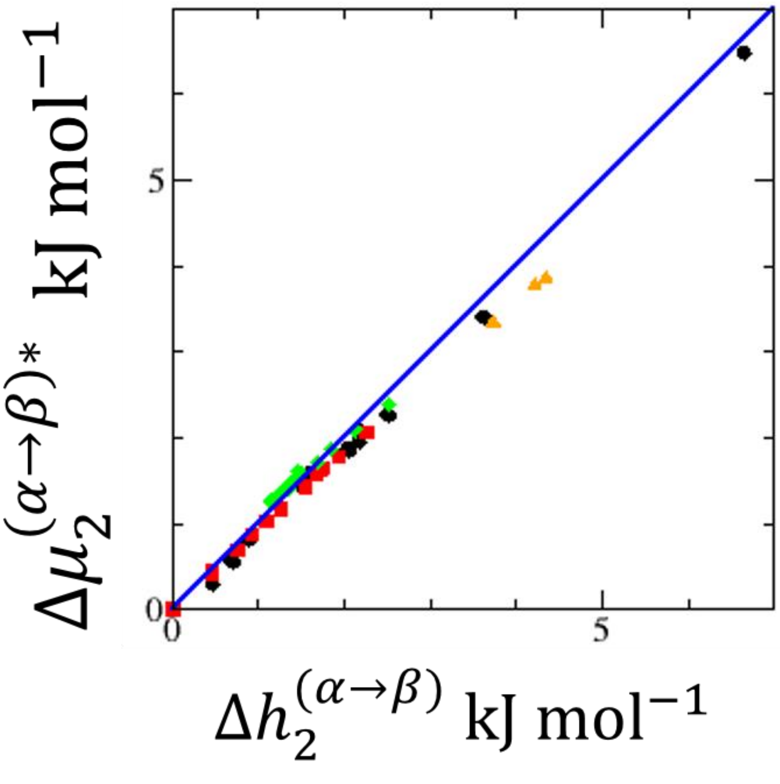

Figure 3. Correlation between experimental transfer enthalpy ($\Delta h_2^{(\alpha\to\beta)}$, Eq. (8)) and free energy ($\Delta\mu_2^{(\alpha\to\beta)*}$, Eq. (6)) of xenon from hexane (as the reference solvent α) to alkanes (red),[72–74] alkanols (green) [75], cyclic alkanes, carboxylic acids, aldehydes (black) [76], and fluoroalkanes (orange) [77]. The blue line corresponds to $\Delta\mu_2^{(\alpha\to\beta)*} = \Delta h_2^{(\alpha\to\beta)}$.

The free energy of solvation also exhibits a linear correlation with enthalpy when various solutes are dissolved in a single organic solvent [1,2,51,52,78], just like the linear free energy relationship (LFER) which has been observed quite universally [79,80]. Thus, enthalpy serves as a predictor of solvation free energy (namely, solute-solvent interaction), which is the true foundation of solubility prediction.

2.2. Solubility, via the regular solution theory, cannot be linked to solubility parameters

Solubility prediction by w (and consequently the solubility parameter difference under the mixing rule) pre-supposes that Eqs. (1) and (2) are valid for all solute-solvent composition range (assumption 3 of Section 1), so that the solubility difference can be attributed to the difference of w via Eq. (2) and to the solubility parameters via the mixing rule (assumption 4). Here we examine the validity of the assumption 3 using statistical thermodynamics [53,54,63,55–62].

Indeed, w was introduced originally for the purpose of quantifying the deviation from ideal mixing (see Eqs. (1) and (2)). The deviation from ideality can in general be quantified by the activity coefficient γ_i of the species i. Our goal therefore is to identify the true origin of non-ideality and how it compares with the perspective of solubility parameters. Let us start from the following statistical thermodynamic relationship, i.e., the Maclaurin expansion of $\ln \gamma_1$ at the infinite dilution of species 2, which can be derived from the Kirkwood-Buff [53] theory [15,81]:

$$\ln \gamma_1 = \left(\frac{G_{11}^{\infty}+G_{22}^{\infty}-2G_{12}^{\infty}}{2V_1^0}\right) x_2^2 + \cdots \qquad (9)$$

where G_{ij} is commonly referred to as the Kirkwood-Buff integral (KBI) defined as

$$G_{ij} = 4\pi \int dr\, r^2 \left[g_{ij}(r) - 1\right]$$

(10)

in which $g_{ij}(r)$ is the radial distribution function between the species i and j. (Note that the superscript, (α), for the solvent species, unless indispensable, will be omitted from this section onwards. See Appendix A of Ref [81] for the derivation of Eq. (9).) The superscript ∞ refers to the infinite dilution of the species 2, and the superscript 0 is for the pure state of the solvent. This means that Eq. (1) is holds true strictly at small x_2, with

$$w = RT \frac{G_{11}^{\infty} + G_{22}^{\infty} - 2G_{12}^{\infty}}{2V_1^0} \tag{11}$$

as the statistical thermodynamic interpretation of w. To write down the expression for μ_2, let us use the Gibbs-Duhem equation, $x_1 d\mu_1 + x_2 d\mu_2 = 0$, which, in conjunction with Eqs. (1) and (11), yields

$$d\mu_2 = RT \frac{dx_2}{x_2} - 2RT(1 - x_2)dx_2 \tag{12}$$

whose integration yields

$$\mu_2 = RT \ln x_2 + w x_1^2 + C \tag{13}$$

where C is a constant. C can be determined by comparing Eqs. (13) with Eqs. (4) and (5), i.e., at infinite dilution condition of solutes, $x_2 \to 0$. Taking up to the first order of x_2,

$$\mu_2 = \mu_2^{*\infty} + RT \ln x_2 - 2w x_2 + RT \ln \frac{\Lambda_2^3}{V_1} \tag{14}$$

This is different in form from Eq. (2) nor it is valid for the entire composition range.

Eq. (14) shows that the transfer free energy $\Delta\mu_2^{(\alpha\to\beta)*}$ deviates from its infinite dilution value ($\Delta\mu_2^{(\alpha\to\beta)*\infty}$) in the following form

$$\Delta\mu_2^{(\alpha\to\beta)*} = \Delta\mu_2^{(\alpha\to\beta)*\infty} - 2\left(w^{(\beta)} x_2^{(\beta)} - w^{(\beta)} x_2^{(\beta)}\right) \tag{15}$$

This, in conjunction to Eq. (6) and the negligibility of its second term, yields

$$\Delta\mu_2^{(\alpha\rightarrow\beta)*\infty} - 2\left(w^{(\beta)}x_2^{(\beta)} - w^{(\beta)}x_2^{(\beta)}\right) = -RT\ln\frac{x_2^{(\beta)}}{x_2^{(\alpha)}}$$

(16)

Taken together with the enthalpy dominance of the transfer free energy, $\Delta\mu_2^{(\alpha\rightarrow\beta)*} = \Delta h_u^{(\alpha\rightarrow\beta)}$, we obtain

$$-RT\ln\frac{x_2^{(\beta)}}{x_2^{(\alpha)}} = \Delta h_u^* + 2(w^{(\beta)}x_2^{(\beta)} - w^{(\alpha)}x_2^{(\alpha)}) \tag{17}$$

The lessons from iodine and gas solubility measurements is now summarised in a compact form by Eq. (17). The solubility difference comes from the enthalpy difference (the first term of the right-hand side). Yet, against the expectation of the regular solution theory, the second term involving w makes a negligible contribution since x_2 is small.

In conclusion, Shinoda-Hildebrand experiments has nothing to do with the regular solution theory; solubility has nothing to do w (assumption 3) nor the presumed enthalpic nature of w (assumption 1).

3. Solubility parameters as the approximate Kirkwood-Buff integrals

Even though the regular solution theory was shown to be irrelevant to the interpretation of solubility experiments by Shinoda and Hildebrand, what really makes a mixture a regular solution should be defined rigorously. As in Section 2.2, this requires us to identify how $\ln\gamma_1$ deviates from 0. Here we show that the lowest-order deviation from ideality (the terms with w), now expressed in terms of the KBIs, which will identify the contributions beyond the reach of the regular solution theory.

3.1. The regular solution from a statistical thermodynamic perspective

Let us start from Eq. (9), which can provide a microscopic interpretation for the well-known empirical formula by Norrish and Margules [81]

$$\ln \gamma_1 = A x_2^2 + \cdots \qquad (18)$$

Comparing Eqs.(9) and (18), the Margules-Norrish parameter can be interpreted as[81]

$$A = \frac{G_{11}^{\infty} + G_{22}^{\infty} - 2G_{12}^{\infty}}{2V_1^0} \qquad (19)$$

Eq. (18), despite its derivation at $x_2 \ll 1$, is often applicable to mixtures far beyond infinite dilution [81], suggesting that KBIs at infinite dilution (Eq. (19)) may play a determining role on non-ideality over a wider concentration range [81].

The rigorous statistical thermodynamic result (Eq. (19)) can now be compared to the regular solution theory [1,2,23]. Based upon the concept of the cohesive energy density of a pure substance, c_{ii} (energy of vaporization of pure species i liquid per molar volume) and its generalization to incorporate the "mutual" term c_{ij} [64], the activity coefficient can be expressed as [1,2]

$$\ln \gamma_1 = \frac{V_1(c_{11} + c_{22} - 2c_{12})}{RT} \phi_2^2 \qquad (20)$$

where ϕ_i is the volume fraction the species i. (In the context of the polymer theory, $c_{11} + c_{22} - 2c_{12}$, is related to the Flory χ parameter [21,46].) A comparison of Eq. (20) with Eq. (9) (which can be done at infinite dilution of the species 2 by exploiting $\phi_2 \approx \frac{V_2}{V_1} x_2$ with the partial molar volume of the solute V_2) shows

$$A = \frac{G_{11}^{\infty} + G_{22}^{\infty} - 2G_{12}^{\infty}}{2V_1^0} = \frac{V_2^2(c_{11} + c_{22} - 2c_{12})}{RTV_1^0} \qquad (21)$$

This reveals the following correspondence between the regular solution theory and the rigorous statistical thermodynamic KB theory:

$$c_{ij} \leftrightarrow \frac{RTG_{ij}}{2V_2^2} \tag{22}$$

This means that

1. G_{ij} comes from the potential of mean force between the species in solution [82–86], whereas c_{ij} focuses exclusively on contact energies;
2. a negative (and often dominant) contribution to G_{ij} from the excluded volume effect [57,58,60,87–93] (Appendix B) is not present in c_{ij}, which focuses exclusively on enthalpy;
3. the long-ranged contribution form $g_{ij}(r)$ to G_{ij} (Eq. (10)) is not considered in the c_{ij} based chiefly on contact energies.

Indeed, a particularly striking consideration that G_{22}^{∞}, which is related to the osmotic virial coefficient by $G_{22} = -2B_{22}$, is generally very different from the interactions between the two solutes in pure phase [82–86], underscoring the importance of the potential of mean force effectively to describe solute-solute interactions. (Note that the distribution function $g_{ij}(r)$ is related to the potential of mean force between the two $\Phi_{ij}(r)$ via $g_{ij}(r) = \exp\left(-\frac{\Phi_{ij}(r)}{kT}\right)$ and that $\Phi_{ij}(r)$ can be substantially different from the pair potential between i and j due to the presence of the solvent molecules).

3.2. Solute-solute potential of mean force: solubility parameters vs statistical thermodynamics

The key differences between the non-ideality from the regular solution theory and statistical thermodynamics have been identified in Section 3.1. Let us compare the predictions from the solubility parameters with experimental data.

Our goal is to compare the Margules-Norrish A and the infinite dilution solute-solute G_{22}^{∞} with the predictions from the solubility parameters. Firstly, A can be obtained from the parameters A_{12} and A_{21} of two-parameter Margules model [94],

$$\ln\gamma_1 = (A_{12} + 2(A_{21} - A_{12})x_1)x_2^2 \simeq (2A_{21} - A_{12})x_2^2 + \cdots \quad (23)$$

which, upon comparison with Eq. (18), yields

$$A = 2A_{21} - A_{12} \quad (24)$$

Secondly, G_{22}^{∞} can be calculated using two well-known KB relationships [15],

$$G_{11}^{\infty} = -V_1^0 + RT\kappa_T \quad (25)$$

$$G_{12}^{\infty} = -V_2^{\infty} + RT\kappa_T \quad (26)$$

where V_1^0 and V_2^{∞} express the partial molar volumes of the pure solvent and the solute at infinite dilution limit, respectively. κ_T, the isothermal compressibility, is neglected due to its small (typically few cm^3 mol^{-1}) contributions [95]. Based on Eqs. (25) and (26), Eq. (19) can be rewritten as

$$G_{22}^{\infty} = (2A + 1)V_1^0 - 2V_2^{\infty} \quad (27)$$

The A and G_{22}^{∞} obtained from experimental data processed through rigorous statistical thermodynamics can now be compared with those obtained from the solubility parameters. Note that solubility parameter model employs the "mixing rule" assumption ($c_{12} = \sqrt{c_{11}c_{22}}$) and defines the Hildebrand solubility parameters, as $c_{ii} = \delta_i^2$ [1]. This will transform Eq. (20) into the fundamental relationship (the Scatchard-Hildebrand equation) [1,2,64,96] in the regular solution theory,

$$\ln\gamma_1 = \frac{V_1}{RT}(\delta_1 - \delta_2)^2\phi_2^2 \quad (28)$$

and Eq. (18) into the following form:

$$A = \frac{1}{RT}\frac{V_2^2}{V_1}(\delta_1 - \delta_2)^2 \tag{29}$$

Within the framework of Hildebrand solubility parameters, there are two possible ways to predict G_{22}^{∞} from the solubility parameters. The first is from A calculated via Eq. (29) combined with Eq. (27), where the latter is a general statistical thermodynamic relationship. The second is from the correspondence Eq. (22) together with the solubility parameter, as

$$G_{22}^{\infty} = \frac{2V_2^2 c_{22}}{RT} = \frac{2V_2^2 \delta_2^2}{RT} \tag{30}$$

Table 1 compares Margules-Norrish A calculated from the solubility parameters (Eq. (29)) to the experimentally-derived ones obtainable from the two-parameter Margules model (Eq. (24)). The generally poor agreement between the two demonstrates that the solution non-ideality, characterized by the Margules constant, cannot be reproduced by the solubility parameters. We also note that, due to the mixing rule, the Margules constant is always predicted to be positive, hence the solubility parameters can only reproduce the positive deviation from ideality.

Table 1. Calculation of A (Eq. (24)) from the two-parameter Margules model and from the Hildebrand solubility parameters (using Eq. (29)).

Solvent (1)	Solute (2)	A Margules[a]	A Hildebrand[b]
Acetone	Chloroform	-0.28	0.04
Acetone	Methanol	0.54	0.90
Benzene	Chloroform	0.10	0.02
Benzene	Ethanol	2.20	0.87
Benzene	Methanol	2.49	0.90
Chloroform	Benzene	0.09	0.02
Chloroform	Acetone	-1.12	0.03
Chloroform	Methanol	2.64	1.00
Ethanol	Benzene	1.11	3.11
Ethanol	Ethyl acetate	0.96	4.22
Ethanol	n-hexane	1.17	15.10
Ethyl acetate	Ethanol	0.64	0.90
Ethyl acetate	Methanol	0.95	0.90
Methanol	Acetone	0.66	5.37
Methanol	Chloroform	-0.07	7.72
Methanol	Benzene	1.44	9.63
Methanol	Ethyl acetate	1.10	12.57
Methanol	Methyl acetate	0.91	7.58
Methyl acetate	Methanol	1.06	1.01
n-hexane	Ethanol	3.47	1.34

[a] Based on Margules parameters A_{12} and A_{21} (see Eq. (24)) compiled by Perry and Green [94]; [b] Based on the Hildebrand solubility parameters [1,23] (see Eq. (29)).

Table 2 compares the solute-solute KBI, G_{22}^{∞}, calculated from the regular solution theory in two different ways (A from the solubility parameters (Eq. (29)) and directly from the solute's solubility parameter (Eq. (30)) to the experimentally-derived ones from the two-parameter Margules model (Eq. (27)). The gross overestimation by Eq. (30) shows that contact energy alone cannot be a good predictor of solute-solute interaction in solution. We observe, quite fortuitously, the mixing rule approximation improves the solubility parameter prediction. Yet the predictions based on the solubility parameters is still poor, with the tendency of grossly overestimating G_{22}^{∞}. The reason for this gross deviation may be multiple, however, note the V_2^2 dependence of α in the Hildebrand model (Eq. (29)), which overrides the second term of Eq. (27) (first order of V_2) when V_2 is large. This means that the larger the solute, the more self-aggregation it predicts in an exaggerated manner, considering that A from the solubility parameters are always positive, even though size-dependent self-aggregation can also be predicted from a purely excluded volume-based perspective (Appendix B).

Table 2. Calculation of G_{22}^{∞} (Eq. (25)) from the two-parameter Margules model and from the Hildebrand solubility parameters (using Eqs. (29) and (30)) based on the same data as Table 1.

Solvent (1)	Solute (2)	G_{22}^{∞} Margules	G_{22}^{∞} Hildebrand (Eq. 29)	G_{22}^{∞} Hildebrand (Eq. 30)
Acetone	Chloroform	-127.9	-81.4	1807
Chloroform	Acetone	-246.6	-62.5	1689
Acetone	Methanol	74.7	124.9	1168
Methanol	Acetone	-49.5	328.9	1689
Chloroform	Benzene	-70.6	-79.1	2255
Benzene	Chloroform	-88.5	-99.9	2436
Chloroform	Methanol	560.1	159.3	1168
Methanol	Chloroform	-199.8	505.8	1807
Ethanol	Benzene	6.6	242.3	2255
Benzene	Ethanol	363.3	127.4	1889
Ethyl acetate	Ethanol	106.4	157.0	1889
Ethanol	Ethyl acetate	-26.9	356.0	2551
n-hexane	Ethanol	925.9	365.4	1889
Ethanol	n-hexane	-71.4	1559.6	3065
Methanol	Benzene	-21.4	641.9	2255
Benzene	Methanol	450.6	168.6	1168
Methanol	Ethyl acetate	-65.7	863.8	2551
Ethyl acetate	Methanol	205.0	191.8	1168
Methyl acetate	Methanol	168.9	158.6	1168
Methanol	Methyl acetate	-44.3	496.3	1776

The comparison above thus points to the importance of considering solute-solute potential of mean force directly in the modelling of mixing.

4. Conclusion

Our goal is to establish the physical basis of solubility parameters for improving solubility prediction. Solubility parameters have been applied with success in wide-ranging applications beyond the remit of their theoretical foundation, i.e., the regular solutions theory [5–12]. This raises a question as to whether the solubility parameters are really based on the regular solution theory or on a more general theoretical basis. Indeed, the ad-hoc nature of the classical thermodynamic foundation [1,2], upon which the regular solution theory and the solubility parameters are based, often led to controversies [31,32,41–49,33–40], which have also motivated us to carry out a clarification based on rigorous statistical thermodynamics.

Statistical thermodynamics has raised questions over the traditional interpretations of iodine dissolution experiments:

(1) The basic relationships for the regular solution theory (Eqs. (1) and (2)) cannot be applied for the entire composition range.

(2) Whether the solution is regular, i.e., that the non-ideality term, wx_2^2, is enthalpic, has nothing to do with solubility prediction.

(3) Whether varying solute-solvent sizes has entropic ramification is irrelevant to the interpretation of iodine dissolution experiments.

Thus, the Shinoda-Hildebrand iodine dissolution experiments does not constitute the support for the basis of the regular solution theory.

Statistical thermodynamics has shown instead that the classical iodine dissolution should be reinterpreted as the dominance of enthalpy in transfer free energies, due to the near-constancy of the solvation entropy over many common organic solvents. We advocate that the classical experiments that have been considered to support the regular solution theory and the solubility parameters should now be reinterpreted as the following:

(1) The linear free energy relationship, i.e., the solvation free energy is linearly correlated with the enthalpy.

(2) The mixing rule applied to the enthalpy of solvation.

These two principles should replace the current foundation for the solubility parameters, which are inaccurate and convoluted.

The origin on the deviation from ideal mixing is understood from KBIs, which can help determine whether the non-ideality is enthalpic and whether the mixing rule is accurate. Such a comparison shows that the regular solution ignores the two major contributions to the KBIs: the excluded volume effect and the potential of mean force nature of interactions in the solution phase.

The rigorous statistical thermodynamic approach is admittedly incapable of predicting solubility at the present stage. However, it has provided a molecular-based interpretation of key experiments free from the historical clutter of the regular solution theory. We believe such a clarification is crucial in overcoming the current limitations and inaccuracies of the solubility parameters [1,4].

Appendix A

Here we outline the derivation of Eq. (3) with the emphasis on the basic assumptions introduced therein.

Consider a solid solute (iodine) in equilibrium with the solvent. According to Hildebrand, the entropy of solution of a solid, $\Delta\bar{S}_2 = \bar{S}_2 - \bar{S}_2^s$, where $\bar{S}_2$ and $\bar{S}_2^s$ express the molar entropies of the solute in solution and in solid, respectively, can be expressed through the chain rule as [1,2]

$$\Delta\bar{S}_2 = -\left(\frac{\partial \Delta G_2}{\partial T}\right)_{P,x_2} = \left(\frac{\partial \Delta G_2}{\partial \ln x_2}\right)_{P,T}\left(\frac{\partial \ln x_2}{\partial T}\right)_{\Delta G_2,P} \qquad \text{(A1)}$$

where $\Delta\bar{G}_2 = \bar{G}_2 - \bar{G}_2^s$ is the change of partial molar Gibbs free energy between the solution phase and the solid phase. Assuming that the solid phase remains unchanged regardless of x_2, the first factor in the r.h.s. of Eq. (A1) [1,2]

$$\left(\frac{\partial \Delta G_2}{\partial \ln x_2}\right)_{P,T} = RT\left(\frac{\partial \ln a_2}{\partial \ln x_2}\right)_{P,T} \qquad \text{(A2)}$$

can be evaluated only in terms of the solution phase activity. Combining Eqs. (A1) and (A2) yields the entropy of solution at saturation [1,2]

$$\Delta\bar{S}_2 = RT\left(\frac{\partial \ln a_2}{\partial \ln x_2}\right)_{P,T}\left(\frac{\partial \ln x_2}{\partial T}\right)_{\Delta G_2,P} = R\left(\frac{\partial \ln a_2}{\partial \ln x_2}\right)_{P,T}\left(\frac{\partial \ln x_2}{\partial \ln T}\right)_{\mathrm{sat},P} \qquad \text{(A3)}$$

For dilute solution, for which the dilute ideal solution is applicable,

$$\left(\frac{\partial \ln a_2}{\partial \ln x_2}\right)_{P,T} = 1 \qquad \text{(A4)}$$

which is satisfied very well by the majority of solvents studied by Shinoda and Hildebrand [1,23–29]. Combination of Eqs. (A3) and (A4) yields Eq. (3).

Appendix B

Here we show that solute-to-solvent size ratio may contribute significantly to the entropic or enthalpic nature of w. To do so, let us calculate the Margules-Norrish A parameter (Eq. (19)) using the effective radii r_1 and r_2 for the solvent and solute, respectively, which leads to the following estimation of the KBI:

$$G_{ij} = -\frac{4}{3}\pi\left(r_i + r_j\right)^3$$

(B1)

Using $V_1^0 \simeq -G_{11}^{\infty}$ in conjunction with Eqs. (20) and (B2), we obtain

$$A = -\frac{(2r_1)^3+(2r_2)^3-2(r_1+r_2)^3}{2(2r_1)^3} = -\frac{1}{2}\left[1+\left(\frac{r_2}{r_1}\right)^3-\frac{1}{4}\left(1+\frac{r_2}{r_1}\right)^3\right] = -\frac{3}{8}\left(\frac{r_2}{r_1}+1\right)\left(\frac{r_2}{r_1}-1\right)^2 \text{(B2)}$$

According to Eq. (B2), Margules-Norrish A parameter depends on solute-to-solvent size ratio r_2/r_1 much more weakly for small r_2/r_1 than larger r_2/r_1 , as shown in Figure 4. Assuming that the radii are not temperature dependent or only weakly so, the entropic contribution to Margules-Norrish A is small for small r_2/r_1 and large for large r_2/r_1.

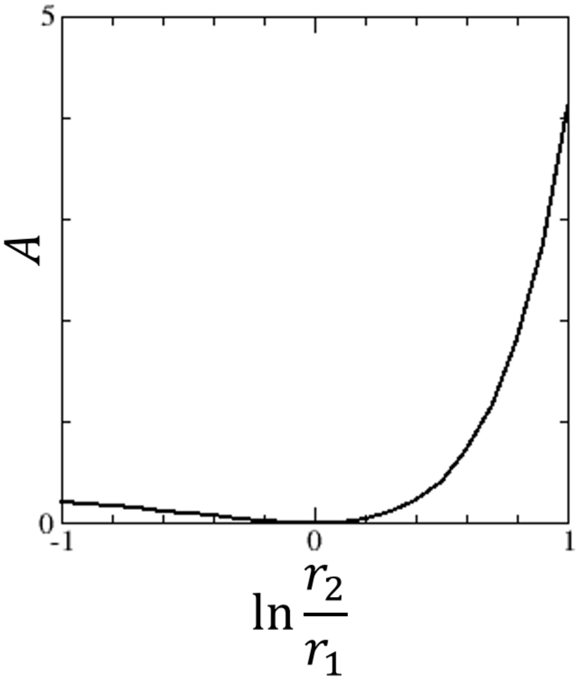

Figure 4. Dependence on the solute-solvent size ratio, $\frac{r_2}{r_1}$, of the excluded volume contribution to the Margules-Norrish A parameter (Eq. (B2)).

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