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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.

2

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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]

$$\mu_1 = \mu_1^o + RT \ln x_1 + w x_2^2 \qquad (1)$$

$$\mu_2 = \mu_2^o + RT \ln x_2 + w x_1^2 \qquad (2)$$

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];

3

70   (4) w can be calculated from the difference of cohesive energy densities ("solubility

71   parameters") between the solute and solvent [1,2],

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

73   solubility parameters via w.

74

75   The experimental evidence for (1) the ideality of the mixing entropy and (2) the negligibility

76   of size disparity comes from a series of iodine dissolution experiments in which the entropy of

77   solution (i) exhibited a linear correlation to the ideal mixing entropy and (ii) showed no

78   dependence on solvent size, despite the wide variety in the partial molar volume of the solvents

79   (Figure 1) [1,2,23–29]. Thus the seminal work by Hildebrand and coworkers [1,2,23–29] have

80   provided a justification for some of the important pillars of the regular solution theory.

81

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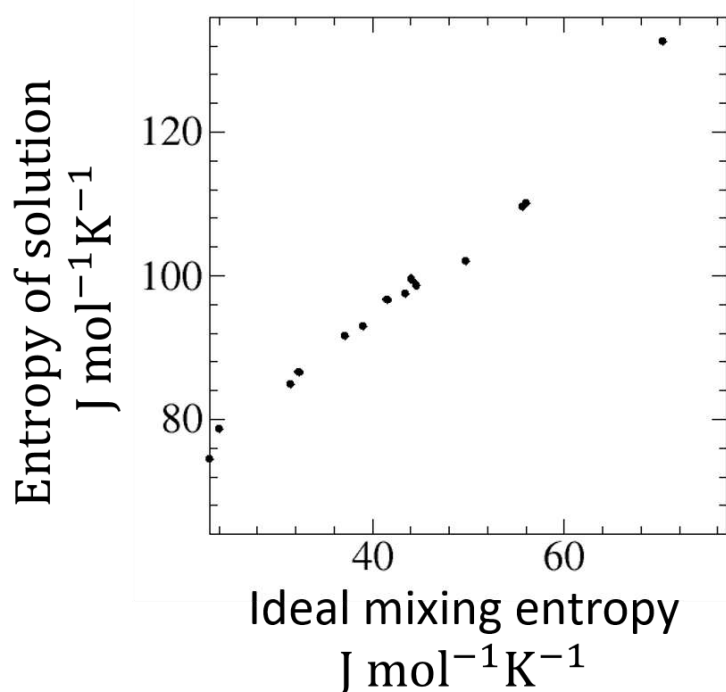
83   **Figure 1.** Iodine dissolution experiments in a number of solvents, in which the correlation

84   between the "ideal mixing entropy" ($-R \ln x_2$, where x_2 is the solubility of iodine in mole-

4

85 fraction scale) and the "entropy of solution" ($R \frac{\partial \ln x_2}{\partial \ln T}$) has traditionally been interpreted as the

86 basis for (i) neglecting the entropy of mixing arising from solute-solvent size ratio and (ii) the

87 prediction of solubility based on solubility parameters derived from enthalpy. The experimental

88 data were taken from Shinoda and Hildebrand [25–28].

89

90

91 However, that the mixing entropy is independent of solute-solvent size disparity is at odds

92 with the Flory-Huggins lattice model [20–22] and with its re-derivation by Hildebrand based

93 on van der Waals fluids [1,2,30] that have led to the existence of the non-ideal mixing entropy

94 arising from solute-solvent size disparity. Attempts have been made in the 1990s to reconcile

95 the size-independent nature of iodine dissolution with the size-dependent entropy of mixing,

96 motivated largely by the need for quantifying the hydrophobic contribution to protein stability

97 [31,32,41–49,33–40]. However, the paradox has remained unresolved [44].

98

99 This paradox on the apparent solvent size independence of iodine dissolution entropy can

100 only be resolved using the rigorous statistical thermodynamics of solvation, as will be

101 demonstrated in the present paper. Statistical thermodynamics becomes particularly helpful

102 through its ability in attributing a molecular-based physical meaning to thermodynamic

103 quantities. This becomes particularly important because the previous analyses were carried out

104 using the following expression for the entropy of solution $\Delta \bar{S}_2$ by Hildebrand (derivation

105 summarised in Appendix A) [1,2]

106 $$\Delta \bar{S}_2 = R \frac{\partial \ln x_2}{\partial \ln T} \tag{3}$$

107 which is called the "Hildebrand entropy" and has been acknowledged to be different from the

108 definition of the entropy of solution in other concentration scales [50–52]. As its name

5

109　indicates, the "Hildebrand entropy" is different from the entropy of dissolution, and we will

110　demonstrate that it is actually enthalpic.

111

112　　Our statistical thermodynamic re-analysis of the iodine dissolution experiments (Section 2)

113　will show that the iodine dissolution experiments cannot be interpreted as the support for the

114　ideality of mixing entropy regardless of solute-solvent size disparity nor does it have any

115　connection to w. The point of the iodine experiments is instead the dominance of enthalpy in

116　solvation free energy difference. In addition, origin of the deviation from ideality can be

117　identified rigorously by the Kirkwood-Buff (KB) integrals [53,54,63,55–62] that shows not

118　only the enthalpy of mixing [1,2,21,46,64] but also the excluded volume effect and solvent-

119　mediated interactions play an important role (Section 3).

120

121　**2. Solubility and solubility parameters**

122

123　The entropy of solution for iodine (according to Eq. (3)) were shown to be ideal even in solvents

124　widely differing in size [1,2,23–29], and has been used as evidence for solubility prediction

125　based on solubility parameters (see assumptions 1-4 and Eqs. (1) and (2)). Based on rigorous

126　statistical thermodynamics, here we examine the validity of this interpretation.

127

128　**2.1. Iodine dissolution does not support the ideality of mixing entropy**

129

130　Consider iodine as solute (indexed as $i = 2$), which is in equilibrium with the solvent ($i = 1$).

131　Due to the difficulty of dealing with the solid phase, let us focus on the *difference* in solvation

132　of a single solute between solvents. In the following, the solvent species is distinguished by a

133　superscript (α).

6

134

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

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

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,

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

$V_1^{(\alpha)}$ 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:

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

154

7

155   Since the regular solution theory requires the consideration of entropic and enthalpic

156   contributions to the transfer free energies, the isobaric entropy Δs_u^* and enthalpy Δh_u^* of

157   transfer can be calculated straightforwardly from Eq. (6)

158
$$\Delta s_2^{(\alpha \to \beta)*} = -\left(\frac{\partial \Delta \mu_2^{(\alpha \to \beta)*}}{\partial T}\right)_{P,N} = R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}} + \frac{\partial R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} - R \ln \frac{V_1^{(\beta)}}{V_1^{(\alpha)}} - RT \left(\alpha_1^{(\beta)} - \alpha_1^{(\alpha)}\right)$$

159
$$= -\frac{\Delta \mu_2^{(\alpha \to \beta)*}}{T} + \frac{\partial R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} - RT \left(\alpha_1^{(\beta)} - \alpha_1^{(\alpha)}\right) \approx -\frac{\Delta \mu_2^{(\alpha \to \beta)*}}{T} + \frac{\partial R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} \qquad (7)$$

160
$$\Delta h_2^{(\alpha \to \beta)*} = \Delta \mu_2^{(\alpha \to \beta)*} + T \Delta s_2^{(\alpha \to \beta)*} = T \frac{\partial R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} - RT^2 \left(\alpha_1^{(\beta)} - \alpha_1^{(\alpha)}\right)$$

161
$$\approx T \frac{\partial R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} \qquad (8)$$

162   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

163   neglected.

164

165   Defining the transfer entropy and enthalpy statistical thermodynamically via Eqs. (7) and (8)

166   has significant advantages. Firstly, as has been shown by one of us that the entropy and enthalpy

167   of solvation defined via Eqs. (4)-(6) can be attributed to the solute-solvent and solvent-solvent

168   interactions around the solute, which converges within finite distance, thereby establishing a

169   link between solvation thermodynamics and its underlying physical picture of the "solvation

170   shell" [65–69]. Secondly, purely thermodynamic approaches based on the mole-fraction scale,

171   when considering entropy and enthalpy, faces significant conceptual difficulties arising from

172   the need for the "mixing" process and its interpretational difficulties on a molecular scale

173   [14,70,71].

174

8

175   Let us now apply Eqs. (6)-(8) to the interpretation of the classical iodine dissolution

176   experiments. According to the regular solution theory, a correlation between $\Delta \bar{S}_2 = \frac{\partial R \ln x_2}{\partial \ln T}$ and

177    $-R \ln x_2$ (ideal mixing entropy, Figure 1) signifies the ideality of the entropy of solution

178   (assumption 1 in Section 1) regardless of the solute-solvent size ratio (assumption 2), in which

179   the deviation from ideality is entirely enthalpic (assumption 1) [1,2,23–29]. However,

180   according to statistical thermodynamics, $\frac{\partial R \ln x_2}{\partial \ln T}$ signifies the enthalpy (Eq. (8)), whereas

181    $-R \ln x_2$ is predominantly the free energy of solvation (Eq. (6)). Thus, according to statistical

182   thermodynamics, iodine dissolution experiments are a direct evidence for the enthalpy-

183   dominated transfer free energy, $\Delta \mu_2^{(\alpha \to \beta)*} \simeq \Delta h_2^{(\alpha \to \beta)}$ and the negligible entropy contribution,

184    $\Delta s_2^{(\alpha \to \beta)*} \simeq 0$ (Figure 2). It should be noted that a solution is always ideal (dilute ideal solution)

185   at dilute conditions [1,2,15,17,19], hence the chemical potential depends on x_2 in the form of

186    $RT \ln x_2$ at small x_2, and thus our focus in the above discussion is not the dependence on x_2

187   since the x_2 dependence is trivial for dilute solutions. What our analysis revealed is $\Delta s_2^{(\alpha \to \beta)*} \simeq$

188   0, that is about the excess partial molar entropy, i.e., the entropy change upon dissolution of a

189   single solute molecule; its x_2 dependence does not come into the discussion since iodine was

190   dilute in Figures 1 and 2.

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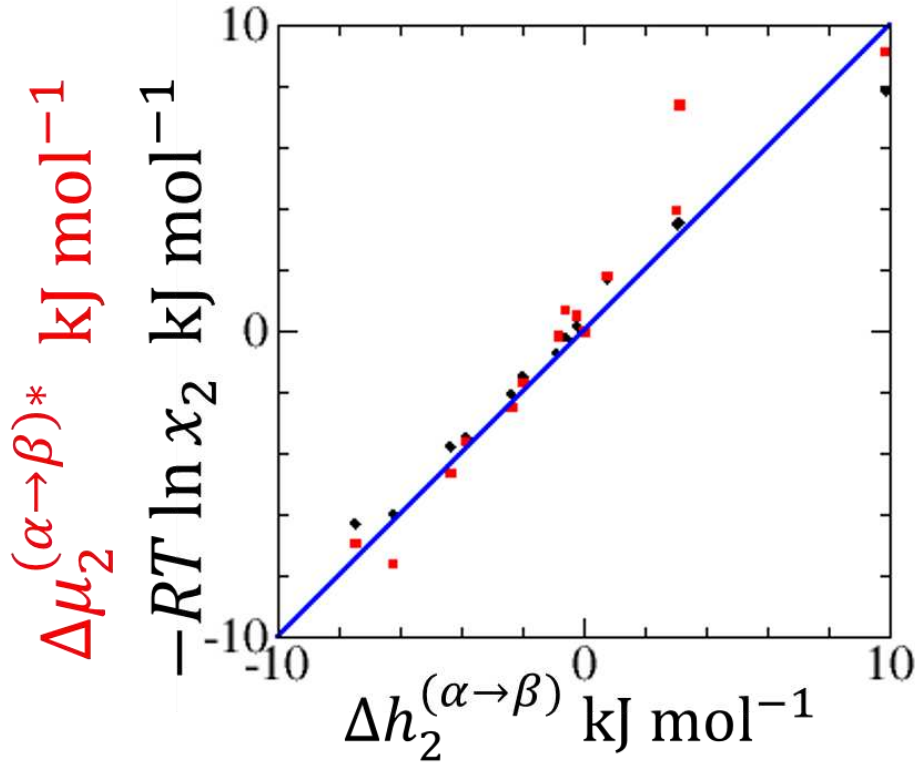
Figure 2. Re-interpretation of iodine dissolution experiments, as a correlation between the enthalpic ($\Delta h_2^{(\alpha \to \beta)}$, Eq. (8)) and free energy ($\Delta \mu_2^{(\alpha \to \beta)*}$, Eq. (6), red) contributions, as well as its approximation ($-RT \ln x_2$, black). The blue line corresponds 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

10

205 and 2) has nothing to do with the size-dependent entropy of mixing. The "Hildebrand entropy"

206 is actually an enthalpy, and a conclusion about the entropy is that the solvation entropy is not

207 different among the solvents for dilute iodine.

208

209 The dominance of transfer enthalpy on the free energy has been observed also in xenon

210 solubility (Figure 3) in alkanes [72–74], alkanols [75], cyclic alkanes, carboxylic acids,

211 aldehydes [76], and fluoroalkanes [77]. Indeed, the virtual independence of solvation entropy

212 on solvents has been observed widely in gas solubility measurements for many decades [50,72–

213 77]. Instead of being a support for the regular solution theory, the Shinoda-Hildebrand

214 experiments seem to be another example of this common empirical relationship.

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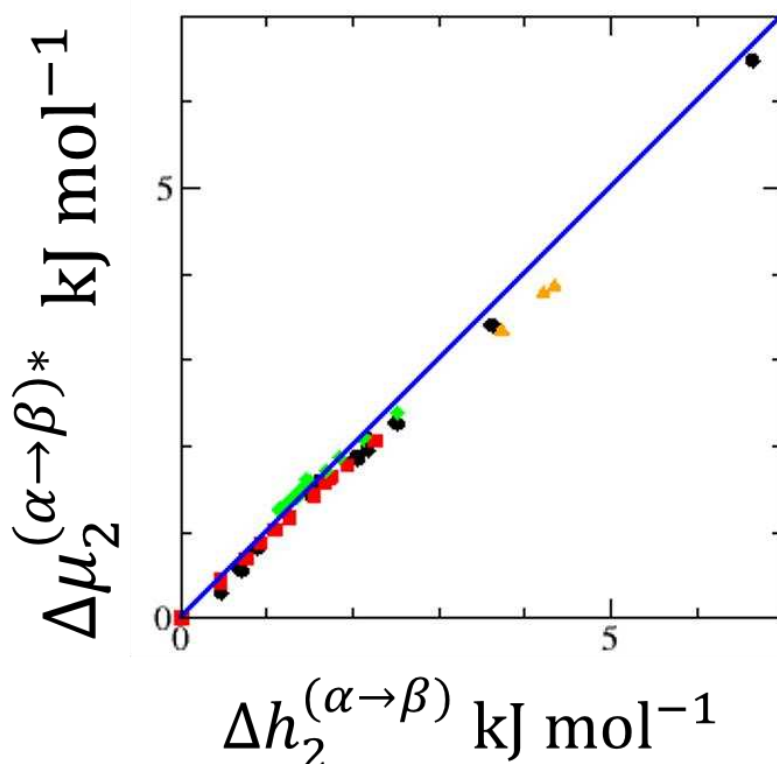
216 **Figure 3.** Correlation between experimental transfer enthalpy ($\Delta h_2^{(\alpha\to\beta)}$, Eq. (8)) and free

217 energy ($\Delta\mu_2^{(\alpha\to\beta)*}$, Eq. (6)) of xenon from hexane (as the reference solvent α) to alkanes

218 (red),[72–74] alkanols (green) [75], cyclic alkanes, carboxylic acids, aldehydes (black) [76],

219 and fluoroalkanes (orange) [77]. The blue line corresponds to $\Delta\mu_2^{(\alpha\to\beta)*} = \Delta h_2^{(\alpha\to\beta)}$.

11

221   The free energy of solvation also exhibits a linear correlation with enthalpy when various

222   solutes are dissolved in a single organic solvent [1,2,51,52,78], just like the linear free energy

223   relationship (LFER) which has been observed quite universally [79,80]. Thus, enthalpy serves

224   as a predictor of solvation free energy (namely, solute-solvent interaction), which is the true

225   foundation of solubility prediction.

226

227   **2.2. Solubility, via the regular solution theory, cannot be linked to solubility parameters**

228

229   Solubility prediction by w (and consequently the solubility parameter difference under the

230   mixing rule) pre-supposes that Eqs. (1) and (2) are valid for all solute-solvent composition

231   range (assumption 3 of Section 1), so that the solubility difference can be attributed to the

232   difference of w via Eq. (2) and to the solubility parameters via the mixing rule (assumption 4).

233   Here we examine the validity of the assumption 3 using statistical thermodynamics

234   [53,54,63,55–62].

235

236   Indeed, w was introduced originally for the purpose of quantifying the deviation from ideal

237   mixing (see Eqs. (1) and (2)). The deviation from ideality can in general be quantified by the

238   activity coefficient γ_i of the species i. Our goal therefore is to identify the true origin of non-

239   ideality and how it compares with the perspective of solubility parameters. Let us start from

240   the following statistical thermodynamic relationship, i.e., the Maclaurin expansion of $\ln \gamma_1$ at

241   the infinite dilution of species 2, which can be derived from the Kirkwood-Buff [53] theory

242   [15,81]:

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

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

245 $G_{ij} = 4\pi \int dr\, r^2 [g_{ij}(r) - 1]$

246   (10)

247 in which $g_{ij}(r)$ is the radial distribution function between the species i and j. (Note that the

248 superscript, (α), for the solvent species, unless indispensable, will be omitted from this section

249 onwards. See Appendix A of Ref [81] for the derivation of Eq. (9).) The superscript ∞ refers

250 to the infinite dilution of the species 2, and the superscript 0 is for the pure state of the solvent.

251 This means that Eq. (1) is holds true strictly at small x_2, with

252 $w = RT \dfrac{G_{11}^{\infty} + G_{22}^{\infty} - 2G_{12}^{\infty}}{2V_1^0}$ (11)

253 as the statistical thermodynamic interpretation of w. To write down the expression for μ_2, let

254 us use the Gibbs-Duhem equation, $x_1 d\mu_1 + x_2 d\mu_2 = 0$, which, in conjunction with Eqs. (1)

255 and (11), yields

256 $d\mu_2 = RT \dfrac{dx_2}{x_2} - 2RT(1 - x_2)dx_2$ (12)

257 whose integration yields

258 $\mu_2 = RT \ln x_2 + w x_1^2 + C$ (13)

259 where C is a constant. C can be determined by comparing Eqs. (13) with Eqs. (4) and (5), i.e.,

260 at infinite dilution condition of solutes, $x_2 \to 0$. Taking up to the first order of x_2,

261 $\mu_2 = \mu_2^{*\infty} + RT \ln x_2 - 2w x_2 + RT \ln \dfrac{\Lambda_2^3}{V_1}$ (14)

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

263

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

265 $(\Delta\mu_2^{(\alpha \to \beta)*\infty})$ in the following form

266 $\Delta\mu_2^{(\alpha \to \beta)*} = \Delta\mu_2^{(\alpha \to \beta)*\infty} - 2\left(w^{(\beta)} x_2^{(\beta)} - w^{(\beta)} x_2^{(\beta)}\right)$ (15)

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

13

268 $\Delta\mu_2^{(\alpha\to\beta)*\infty} - 2\left(w^{(\beta)}x_2^{(\beta)} - w^{(\beta)}x_2^{(\beta)}\right) = -RT\ln\frac{x_2^{(\beta)}}{x_2^{(\alpha)}}$

269   (16)

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

271 we obtain

272 $-RT\ln\frac{x_2^{(\beta)}}{x_2^{(\alpha)}} = \Delta h_u^* + 2(w^{(\beta)}x_2^{(\beta)} - w^{(\alpha)}x_2^{(\alpha)})$ (17)

273

274   The lessons from iodine and gas solubility measurements is now summarised in a compact

275 form by Eq. (17). The solubility difference comes from the enthalpy difference (the first term

276 of the right-hand side). Yet, against the expectation of the regular solution theory, the second

277 term involving w makes a negligible contribution since x_2 is small.

278

279   In conclusion, Shinoda-Hildebrand experiments has nothing to do with the regular solution

280 theory; solubility has nothing to do w (assumption 3) nor the presumed enthalpic nature of w

281 (assumption 1).

282

283 **3. Solubility parameters as the approximate Kirkwood-Buff integrals**

284

285 Even though the regular solution theory was shown to be irrelevant to the interpretation of

286 solubility experiments by Shinoda and Hildebrand, what really makes a mixture a regular

287 solution should be defined rigorously. As in Section 2.2, this requires us to identify how $\ln\gamma_1$

288 deviates from 0. Here we show that the lowest-order deviation from ideality (the terms with

289 w), now expressed in terms of the KBIs, which will identify the contributions beyond the reach

290 of the regular solution theory.

291

14

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]

$$\ln \gamma_1 = A x_2^2 + \cdots \tag{18}$$

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

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

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]

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

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

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

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

15

316 $$c_{ij} \leftrightarrow \frac{RTG_{ij}}{2V_2^2} \qquad (22)$$

317 This means that

318 1. G_{ij} comes from the potential of mean force between the species in solution [82–86],

319   whereas c_{ij} focuses exclusively on contact energies;

320 2. a negative (and often dominant) contribution to G_{ij} from the excluded volume effect

321   [57,58,60,87–93] (Appendix B) is not present in c_{ij}, which focuses exclusively on

322   enthalpy;

323 3. the long-ranged contribution form $g_{ij}(r)$ to G_{ij} (Eq. (10)) is not considered in the c_{ij}

324   based chiefly on contact energies.

325 Indeed, a particularly striking consideration that G_{22}^{∞}, which is related to the osmotic virial

326 coefficient by $G_{22} = -2B_{22}$, is generally very different from the interactions between the two

327 solutes in pure phase [82–86], underscoring the importance of the potential of mean force

328 effectively to describe solute-solute interactions. (Note that the distribution function $g_{ij}(r)$ is

329 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

330 that $\Phi_{ij}(r)$ can be substantially different from the pair potential between i and j due to the

331 presence of the solvent molecules).

332

333 **3.2. Solute-solute potential of mean force: solubility parameters vs statistical**

334 **thermodynamics**

335

336 The key differences between the non-ideality from the regular solution theory and statistical

337 thermodynamics have been identified in Section 3.1. Let us compare the predictions from the

338 solubility parameters with experimental data.

339

340   Our goal is to compare the Margules-Norrish A and the infinite dilution solute-solute G_{22}^{∞}

341   with the predictions from the solubility parameters. Firstly, A can be obtained from the

342   parameters A_{12} and A_{21} of two-parameter Margules model [94],

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

344   (23)

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

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

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

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

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

350   where V_1^0 and V_2^{∞} express the partial molar volumes of the pure solvent and the solute at infinite

351   dilution limit, respectively. κ_T, the isothermal compressibility, is neglected due to its small

352   (typically few cm^3 mol^{-1}) contributions [95]. Based on Eqs. (25) and (26), Eq. (19) can be

353   rewritten as

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

355

356   The A and G_{22}^{∞} obtained from experimental data processed through rigorous statistical

357   thermodynamics can now be compared with those obtained from the solubility parameters.

358   Note that solubility parameter model employs the "mixing rule" assumption ($c_{12} = \sqrt{c_{11}c_{22}}$)

359   and defines the Hildebrand solubility parameters, as $c_{ii} = \delta_i^2$ [1]. This will transform Eq. (20)

360   into the fundamental relationship (the Scatchard-Hildebrand equation) [1,2,64,96] in the

361   regular solution theory,

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

363   and Eq. (18) into the following form:

364 $$A = \frac{1}{RT}\frac{V_2^2}{V_1}(\delta_1 - \delta_2)^2 \qquad\qquad (29)$$

365 Within the framework of Hildebrand solubility parameters, there are two possible ways to

366 predict G_{22}^∞ from the solubility parameters. The first is from A calculated via Eq. (29) combined

367 with Eq. (27), where the latter is a general statistical thermodynamic relationship. The second

368 is from the correspondence Eq. (22) together with the solubility parameter, as

369 $$G_{22}^\infty = \frac{2V_2^2 c_{22}}{RT} = \frac{2V_2^2 \delta_2^2}{RT} \qquad\qquad (30)$$

370

371   Table 1 compares Margules-Norrish A calculated from the solubility parameters (Eq. (29))

372 to the experimentally-derived ones obtainable from the two-parameter Margules model (Eq.

373 (24)). The generally poor agreement between the two demonstrates that the solution non-

374 ideality, characterized by the Margules constant, cannot be reproduced by the solubility

375 parameters. We also note that, due to the mixing rule, the Margules constant is always predicted

376 to be positive, hence the solubility parameters can only reproduce the positive deviation from

377 ideality.

378

379

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

390 alone cannot be a good predictor of solute-solute interaction in solution. We observe, quite

391 fortuitously, the mixing rule approximation improves the solubility parameter prediction. Yet

392 the predictions based on the solubility parameters is still poor, with the tendency of grossly

393 overestimating G_{22}^∞. The reason for this gross deviation may be multiple, however, note the V_2^2

394 dependence of α in the Hildebrand model (Eq. (29)), which overrides the second term of Eq.

395 (27) (first order of V_2) when V_2 is large. This means that the larger the solute, the more self-

396 aggregation it predicts in an exaggerated manner, considering that A from the solubility

397 parameters are always positive, even though size-dependent self-aggregation can also be

398 predicted from a purely excluded volume-based perspective (Appendix B).

399

400

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.

21

409 **4. Conclusion**

410

411 Our goal is to establish the physical basis of solubility parameters for improving solubility

412 prediction. Solubility parameters have been applied with success in wide-ranging applications

413 beyond the remit of their theoretical foundation, i.e., the regular solutions theory [5–12]. This

414 raises a question as to whether the solubility parameters are really based on the regular solution

415 theory or on a more general theoretical basis. Indeed, the ad-hoc nature of the classical

416 thermodynamic foundation [1,2], upon which the regular solution theory and the solubility

417 parameters are based, often led to controversies [31,32,41–49,33–40], which have also

418 motivated us to carry out a clarification based on rigorous statistical thermodynamics.

419

420   Statistical thermodynamics has raised questions over the traditional interpretations of iodine

421 dissolution experiments:

422   (1) The basic relationships for the regular solution theory (Eqs. (1) and (2)) cannot be

423   applied for the entire composition range.

424   (2) Whether the solution is regular, i.e., that the non-ideality term, wx_2^2, is enthalpic, has

425   nothing to do with solubility prediction.

426   (3) Whether varying solute-solvent sizes has entropic ramification is irrelevant to the

427   interpretation of iodine dissolution experiments.

428 Thus, the Shinoda-Hildebrand iodine dissolution experiments does not constitute the support

429 for the basis of the regular solution theory.

430

431   Statistical thermodynamics has shown instead that the classical iodine dissolution should be

432 reinterpreted as the dominance of enthalpy in transfer free energies, due to the near-constancy

433 of the solvation entropy over many common organic solvents. We advocate that the classical

22

434 experiments that have been considered to support the regular solution theory and the solubility

435 parameters should now be reinterpreted as the following:

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

437   with the enthalpy.

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

439 These two principles should replace the current foundation for the solubility parameters, which

440 are inaccurate and convoluted.

441

442   The origin on the deviation from ideal mixing is understood from KBIs, which can help

443 determine whether the non-ideality is enthalpic and whether the mixing rule is accurate. Such

444 a comparison shows that the regular solution ignores the two major contributions to the KBIs:

445 the excluded volume effect and the potential of mean force nature of interactions in the solution

446 phase.

447

448   The rigorous statistical thermodynamic approach is admittedly incapable of predicting

449 solubility at the present stage. However, it has provided a molecular-based interpretation of

450 key experiments free from the historical clutter of the regular solution theory. We believe such

451 a clarification is crucial in overcoming the current limitations and inaccuracies of the solubility

452 parameters [1,4].

453

454 **Appendix A**

455

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

457 therein.

458

459   Consider a solid solute (iodine) in equilibrium with the solvent. According to Hildebrand,

460   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

461   of the solute in solution and in solid, respectively, can be expressed through the chain rule as

462   [1,2]

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

464   (A1)

465   where $\Delta\bar{G}_2 = \bar{G}_2 - \bar{G}_2^s$ is the change of partial molar Gibbs free energy between the solution

466   phase and the solid phase. Assuming that the solid phase remains unchanged regardless of x_2,

467   the first factor in the r.h.s. of Eq. (A1) [1,2]

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

469   can be evaluated only in terms of the solution phase activity. Combining Eqs. (A1) and (A2)

470   yields the entropy of solution at saturation [1,2]

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

472   (A3)

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

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

475   (A4)

476   which is satisfied very well by the majority of solvents studied by Shinoda and Hildebrand

477   [1,23–29]. Combination of Eqs. (A3) and (A4) yields Eq. (3).

478

479   **Appendix B**

480

24

481   Here we show that solute-to-solvent size ratio may contribute significantly to the entropic or

482   enthalpic nature of w. To do so, let us calculate the Margules-Norrish A parameter (Eq. (19))

483   using the effective radii r_1 and r_2 for the solvent and solute, respectively, which leads to the

484   following estimation of the KBI:

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

486   (B1)

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

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

489

490   According to Eq. (B2), Margules-Norrish A parameter depends on solute-to-solvent size

491   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.

492   Assuming that the radii are not temperature dependent or only weakly so, the entropic

493   contribution to Margules-Norrish A is small for small r_2/r_1 and large for large r_2/r_1.

494

25
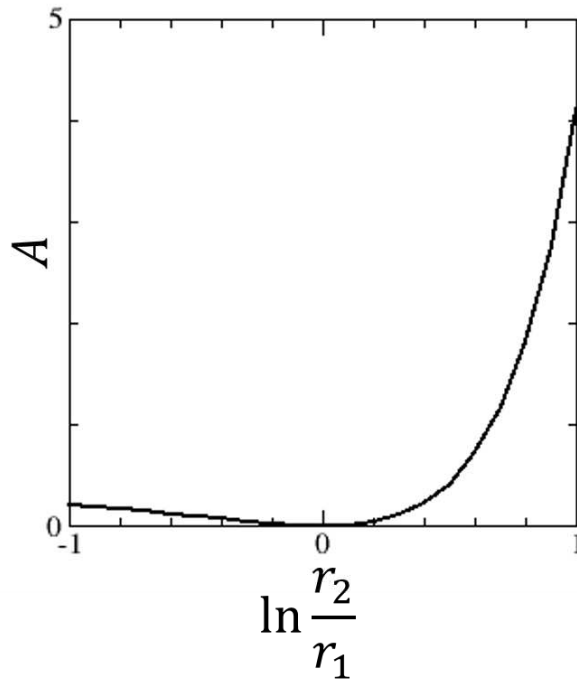
Figure 4. Dependence on the solute-solvent size ratio, $\frac{r_2}{r_1}$, of the excluded volume contribution to the Margules-Norrish A parameter (Eq. (B2)).

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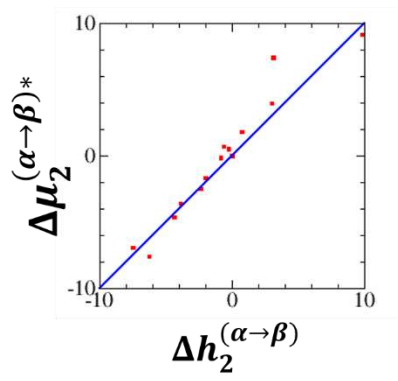
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