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Shimizu, Seishi orcid.org/0000-0002-7853-1683 and Matubayasi, Nobuyuki (2019) Statistical thermodynamics of regular solutions and solubility parameters. JOURNAL OF MOLECULAR LIQUIDS. pp. 626-633. ISSN 0167-7322

<https://doi.org/10.1016/j.molliq.2018.10.024>

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1 Statistical thermodynamics of regular solutions
2 and solubility parameters

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15

16 **ABSTRACT**

17 Solubility parameters, developed originally for regular solutions, have been applied to
18 solutions beyond the presumed weak non-ideality, implying that the true foundation of the
19 solubility parameters may be more general than the regular solution theory. To assess the root

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

33

34 **1. Introduction**

35

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

45

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

$$55 \quad \mu_1 = \mu_1^o + RT \ln x_1 + wx_2^2 \quad (1)$$

$$56 \quad \mu_2 = \mu_2^o + RT \ln x_2 + wx_1^2 \quad (2)$$

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

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

64 (2) The size disparity between the solute and solvent, predicted by Flory [20,21] and Huggins
65 [22], is negligible, hence Eqs. (1) and (2) are applicable regardless of size disparity
66 [1,2,23].

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

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

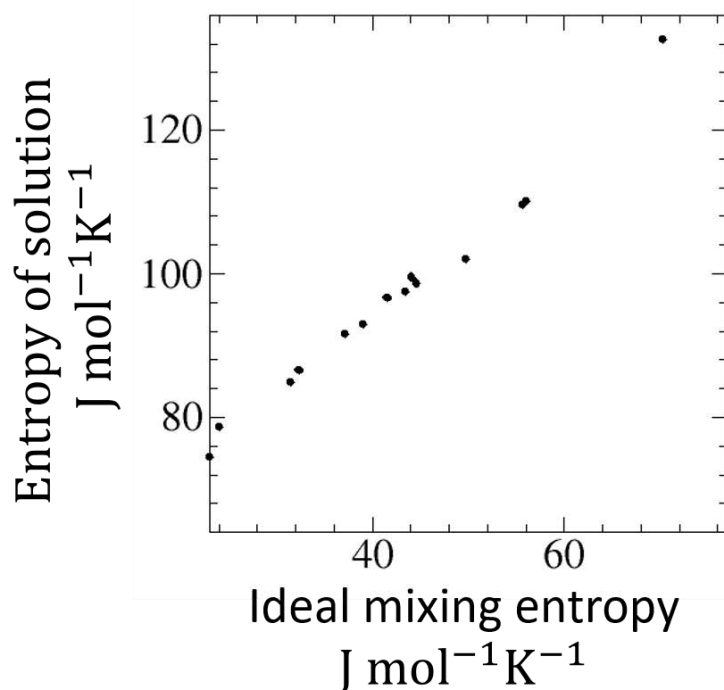
70 (4) w can be calculated from the difference of cohesive energy densities (“solubility
71 parameters”) between the solute and solvent [1,2],

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



82

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-

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]

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

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

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).

134

135 According to the statistical thermodynamics of solvation, the chemical potential of the solute,
 136 μ_2 , can be decomposed into the following manner, in terms of (i) the pseudochemical potential
 137 $\mu_2^{(\alpha)*}$, which signifies the free energy of inserting a solute molecule at a fixed position in the
 138 solvent α , and (ii) the free energy of liberating a solute from a fixed position (which can be
 139 expressed in terms of the molar concentration of the solute $c_2^{(\alpha)}$) as

$$140 \quad \mu_2^{(\alpha)} = \mu_2^{(\alpha)*} + RT \ln c_2^{(\alpha)} \Lambda_2^3 \quad (4)$$

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

144

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

$$150 \quad x_2^{(\alpha)} = \frac{c_2^{(\alpha)}}{c_1^{(\alpha)} + c_2^{(\alpha)}} \simeq \frac{c_2^{(\alpha)}}{c_1^{(\alpha)}} = V_1^{(\alpha)} c_2^{(\alpha)} \quad (5)$$

151 $V_1^{(\alpha)}$ is partial molar volume of the solvent α . Combining Eqs. (4) and (5), we can write down
 152 the transfer free energy of iodine from the solvent α to the solvent β in the following manner:

$$153 \quad \Delta\mu_2^{(\alpha \rightarrow \beta)*} = -RT \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}} + RT \ln \frac{V_1^{(\beta)}}{V_1^{(\alpha)}} \quad (6)$$

154

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)

$$\begin{aligned}
 158 \quad \Delta S_2^{(\alpha \rightarrow \beta)*} &= - \left(\frac{\partial \Delta \mu_2^{(\alpha \rightarrow \beta)*}}{\partial T} \right)_{P,N} = R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}} + \frac{\partial R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} - R \ln \frac{V_1^{(\beta)}}{V_1^{(\alpha)}} - RT \left(\alpha_1^{(\beta)} - \alpha_1^{(\alpha)} \right) \\
 159 \quad &= - \frac{\Delta \mu_2^{(\alpha \rightarrow \beta)*}}{T} + \frac{\partial R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} - RT \left(\alpha_1^{(\beta)} - \alpha_1^{(\alpha)} \right) \approx - \frac{\Delta \mu_2^{(\alpha \rightarrow \beta)*}}{T} + \frac{\partial R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} \quad (7)
 \end{aligned}$$

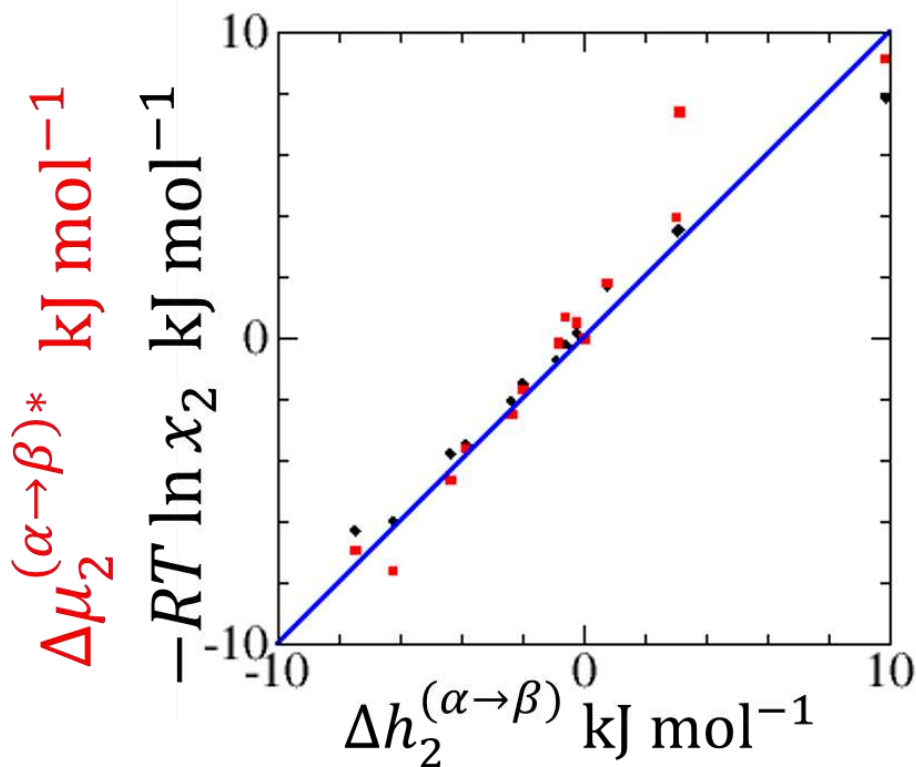
$$\begin{aligned}
 160 \quad \Delta h_2^{(\alpha \rightarrow \beta)*} &= \Delta \mu_2^{(\alpha \rightarrow \beta)*} + T \Delta S_2^{(\alpha \rightarrow \beta)*} = T \frac{\partial R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} - RT^2 \left(\alpha_1^{(\beta)} - \alpha_1^{(\alpha)} \right) \\
 161 \quad &\approx T \frac{\partial R \ln \frac{x_2^{(\beta)}}{x_2^{(\alpha)}}}{\partial \ln T} \quad (8)
 \end{aligned}$$

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

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, $\Delta\mu_2^{(\alpha\rightarrow\beta)*} \simeq \Delta h_2^{(\alpha\rightarrow\beta)}$ and the negligible entropy contribution,
 184 $\Delta s_2^{(\alpha\rightarrow\beta)*} \simeq 0$ (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 $\Delta s_2^{(\alpha\rightarrow\beta)*} \simeq$
 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.



191

192 **Figure 2.** Re-interpretation of iodine dissolution experiments, as a correlation between the

193 enthalpic ($\Delta h_2^{(\alpha \rightarrow \beta)}$, Eq. (8)) and free energy ($\Delta \mu_2^{(\alpha \rightarrow \beta)*}$, Eq. (6), red) contributions, as well as

194 its approximation ($-RT \ln x_2$, black). The blue line corresponds to $\Delta \mu_2^{(\alpha \rightarrow \beta)*} = \Delta h_2^{(\alpha \rightarrow \beta)}$. The

195 reference solvent, α , was chosen to be SiCl_4 . The experimental data were taken from Shinoda

196 and Hildebrand [25–28].

197

198 The above conclusion of ours constitutes a resolution of the paradox, i.e., the apparent

199 independence of the Hildebrand “entropy of solution”, $\Delta \bar{S}_2$, on solute-solvent size ratio,

200 expected from the Flory-Huggins and van der Waals fluid theories [1,2,20–22,30]. This

201 paradox has been revisited in the 1990s in the context of quantifying hydrophobic stabilization

202 of proteins from transfer free energies of amino acids [31,32,41–49,33–40], yet has remained

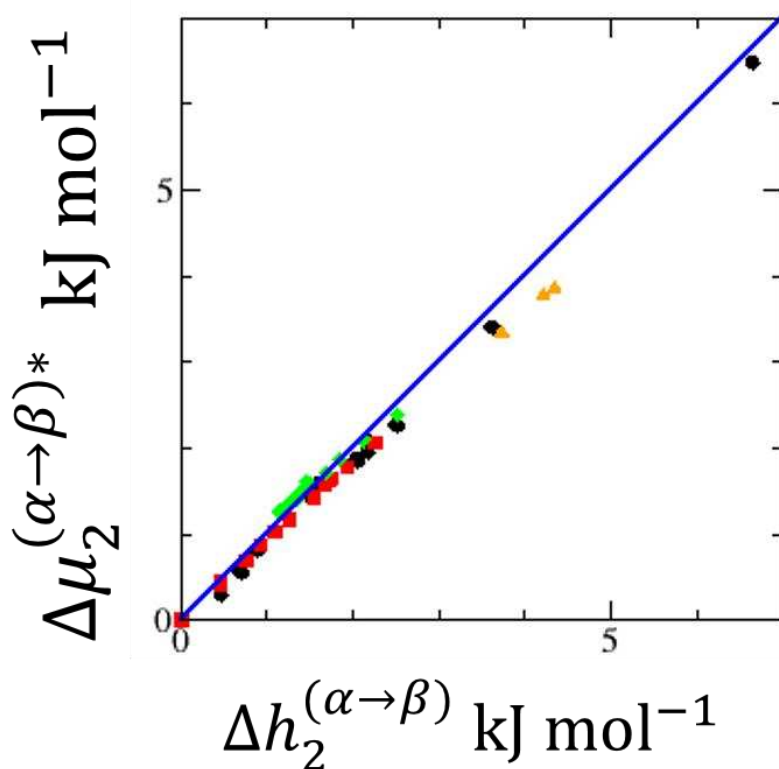
203 unresolved, because of the use of Hildebrand’s “entropy”, $\frac{\partial R \ln x_2}{\partial \ln T}$ as entropy [41,44].

204 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

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.



215

216 **Figure 3.** Correlation between experimental transfer enthalpy ($\Delta h_2^{(\alpha \rightarrow \beta)}$, Eq. (8)) and free
 217 energy ($\Delta \mu_2^{(\alpha \rightarrow \beta)*}$, 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 $\Delta \mu_2^{(\alpha \rightarrow \beta)*} = \Delta h_2^{(\alpha \rightarrow \beta)}$.

220

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]:

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

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 $w = RT \frac{G_{11}^{\infty} + G_{22}^{\infty} - 2G_{12}^{\infty}}{2V_1^0}$ (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 $d\mu_2 = RT \frac{dx_2}{x_2} - 2RT(1 - x_2)dx_2$ (12)

257 whose integration yields

258 $\mu_2 = RT \ln x_2 + wx_1^2 + C$ (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, $x_2 \rightarrow 0$. Taking up to the first order of x_2 ,

261 $\mu_2 = \mu_2^{*\infty} + RT \ln x_2 - 2wx_2 + RT \ln \frac{\Lambda_2^3}{V_1}$ (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 $\Delta\mu_2^{(\alpha \rightarrow \beta)*}$ deviates from its infinite dilution value
 265 $(\Delta\mu_2^{(\alpha \rightarrow \beta)*\infty})$ in the following form

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

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

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

269 (16)

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

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

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

292 **3.1. The regular solution from a statistical thermodynamic perspective**

293

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

296
$$\ln \gamma_1 = Ax_2^2 + \dots \quad (18)$$

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

298
$$A = \frac{G_{11}^\infty + G_{22}^\infty - 2G_{12}^\infty}{2V_1^0} \quad (19)$$

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

302

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

308
$$\ln \gamma_1 = \frac{V_1(c_{11} + c_{22} - 2c_{12})}{RT} \phi_2^2 \quad (20)$$

309 where ϕ_i is the volume fraction the species i . (In the context of the polymer theory, $c_{11} +$
 310 $c_{22} - 2c_{12}$, is related to the Flory χ parameter [21,46].) A comparison of Eq. (20) with Eq. (9)
 311 (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
 312 molar volume of the solute V_2) shows

313
$$A = \frac{G_{11}^\infty + G_{22}^\infty - 2G_{12}^\infty}{2V_1^0} = \frac{V_2^2(c_{11} + c_{22} - 2c_{12})}{RTV_1^0} \quad (21)$$

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

316 $c_{ij} \leftrightarrow \frac{RTG_{ij}}{2V_2^2}$ (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 from $g_{ij}(r)$ 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],

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

344 (23)

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

$$346 A = 2A_{21} - A_{12} \tag{24}$$

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

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

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

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 $\text{cm}^3 \text{mol}^{-1}$) contributions [95]. Based on Eqs. (25) and (26), Eq. (19) can be
 353 rewritten as

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

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,

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

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

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

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

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

380 **Table 1.** Calculation of A (Eq. (24)) from the two-parameter Margules model and from the
 381 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 |

382
 383 ^aBased on Margules parameters A_{12} and A_{21} (see Eq. (24)) compiled by Perry and Green [94];
 384 ^bBased on the Hildebrand solubility parameters [1,23] (see Eq. (29)).
 385

386 Table 2 compares the solute-solute KBI, G_{22}^{∞} , calculated from the regular solution theory in
 387 two different ways (A from the solubility parameters (Eq. (29)) and directly from the solute's
 388 solubility parameter (Eq. (30)) to the experimentally-derived ones from the two-parameter
 389 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

401 **Table 2.** Calculation of G_{22}^{∞} (Eq. (25)) from the two-parameter Margules model and from the
 402 Hildebrand solubility parameters (using Eqs. (29) and (30)) based on the same data as Table
 403 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 |

404

405

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

408

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

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]

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

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]

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

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]

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

472 (A3)

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

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

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

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:

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

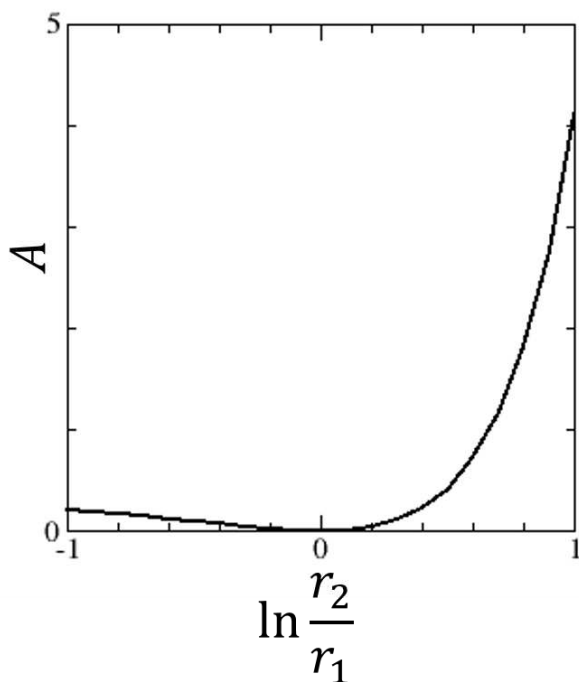
486 (B1)

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

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

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

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

497

498 **Acknowledgements**

499 We are grateful to Charles Hansen, Steven Abbott, Hiroshi Yamamoto, and James Sherwood
500 for discussion. SS thanks the Gen Foundation for travel fund. NM acknowledges support from
501 the Grants-in-Aid for Scientific Research (Nos. JP15K13550, and JP26240045) from the Japan
502 Society for the Promotion of Science, and the Elements Strategy Initiative for Catalysts and
503 Batteries and the Post-K Supercomputing Project from the Ministry of Education, Culture,
504 Sports, Science, and Technology.

505

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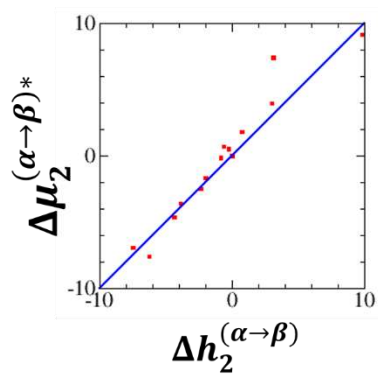
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