THE JOURNAL OF PHYSICAL CHEMISTRY B
A JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/JPCB
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Synergistic Solvation as the Enhancement of Local Mixing

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Cite This: https://doi.org/10.1021/acs.jpcb.4c01582
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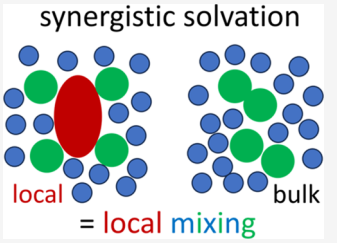
ABSTRACT: Mixing two solvents can sometimes make a much better solvent than expected from their weighted mean. This phenomenon, called synergistic solvation, has commonly been explained via the Hildebrand and Hansen solubility parameters, yet their inability in other solubilization phenomena, most notably hydrotropy, necessitates an alternative route to elucidating solubilization. While, recently, the universal theory of solubilization was founded on the statistical thermodynamic fluctuation theory (as a generalization of the Kirkwood−Buff theory), its demand for experimental data processing has been a hindrance for its wider application. This can be overcome by the solubility isotherm theory, which is founded on the fluctuation theory yet reduces experimental data processing significantly to the level of isotherm analysis in sorption. The isotherm analysis identifies the driving force of synergistic solvation as the enhancement of solvent mixing around the solute, opposite in behavior to hydrotropy (characterized by the enhancement of demixing or self-association around the solute). Thus, the fluctuation theory, including its solubility isotherms, provides a universal language for solubilization across the historic subcategorization of solubilizers, for which different (and often contradictory) mechanistic models have been proposed.



1. INTRODUCTION

Low solubility is a major hindrance to formulation processes.[1] This can be overcome, however, by adding solubilizer molecules. The "solubilizer" is a general terminology adopted in this paper, which encompasses different subcategories, commonly referred to as (a) cosolvents, which can mix with solvents at high concentrations (Figure 1a),[2−4] as well as (b) hydrotropes (Figure 1b)[5−7] and (c) surfactants (Figure 1c)[7−14] that are usually added in dilution to water.

Our goal is to establish a universal theory of solubilization. So far, we have clarified how hydrotropes[1,7] and surfactants[15] work, based on the statistical thermodynamic fluctuation theory, whose applicability ranges from solutions,[16−18] macromolecules and colloids,[1,19] and interfaces.[20] However, an important class of solubilization phenomena, synergistic solvation, remains to be elucidated beyond the current limitations, as summarized below.

1.1. Synergistic Solvation. When the solubility in a binary solvent mixture is higher than expected from those in pure solvents (shown schematically in Figure 1a), synergistic solvation takes place. Its mechanism, according to the regular solution model,[21] is the matching of solubility parameters: the solubility parameter for the mixed solvent (calculated via weighted averaging of the pure solvent values) matches that of the solute.[22−24] This approach was adopted later by the three-dimensional solubility parameters by Hansen.[24] However, such an approach is not only dependent on a series of model assumptions (as will be made clear in Section 3) but also limited only to the positive deviation from ideality.[25]

This necessitates a renewed quest for understanding the mechanism of synergistic solvation on a molecular basis. To do so, the key is the solubility isotherm (i.e., a plot of solubility against solubilizer concentration, Figure 1), whose shape contains information on the underlying solubility mechanism.[1,7,15] In the following, we will survey the two modern theoretical tools available for elucidating solubility isotherms.

1.2. Kirkwood−Buff Theory. Hydrotropes are a loosely defined class of solubilizers, most commonly small molecules with weak amphiphilicity, which do not exhibit critical micelle concentrations (CMC).[1,5,6] Classically, hydrotrope preaggregation (i.e., self-association in the bulk) was considered to be the driving force for solubilization.[6,26] Despite the lack of micelle formation, an analogy between the threshold hydrotrope concentration for solubilization (i.e., the minimum hydrotrope concentration) and micellar solubilization has been invoked by some authors.[27,28] However, the Kirkwood−Buff (KB) theory of solutions,[16−19,29] an exact, model-free theory from classical statistical thermodynamics, has shown that the hydrotrope self-association in the bulk decreases solubilization efficiency,[30−32] contrary to the classical hypothesis.

Before the application of the KB theory, it was necessary to classify solubilizers into subcategories (such as hydrotropes, cosolvents, and surfactants) and to develop a different model for each.[30−32] The KB theory was game-changing in its ability to quantify the interactions between every pair of species in the

Received: March 11, 2024
Revised: May 2, 2024
Accepted: May 21, 2024

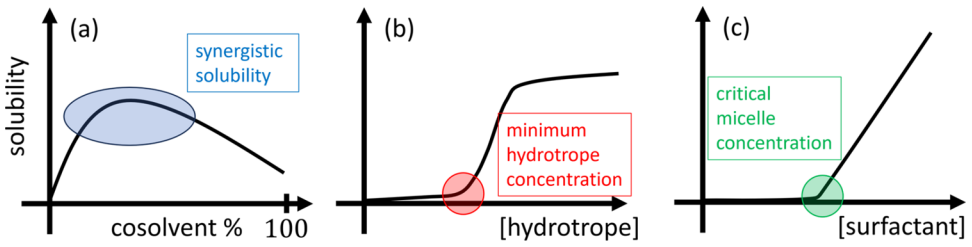


Figure 1. Schematic diagram showing the solubility isotherms in the presence of (a) cosolvents, (b) hydrotropes, and (c) surfactants. (a) Synergistic solubility is the existence of a solubility peak above the solubilities in pure solvent and cosolvent. (b) Minimum hydrotrope concentration is a sudden onset of solubility increase, typically around 0.5 M. (c) Around CMC, a sudden onset of solubilization is observed, above which solubility increases linearly.

solution, based directly on experimental data,[16−19,29] to identify the interactions that influence solubilization dominantly and to achieve the above quantification and identification without introducing any model assumptions.

Need for Simplification. The rigorous nature of the KB theory has also been the source of difficulty, which can be appreciated by considering solubility in a binary mixture. For this system, six KB integrals (KBIs; solute−solvent, solute−solubilizer, solvent−solvent, solubilizer−solubilizer, solubilizer−solvent and solute−solute) need to be evaluated, requiring 6 different sets of thermodynamic data as an input; not only solubility but also density, activity coefficients, and compressibility measured extensively as a function of composition. Focusing on dilute solutes reduces the number of KBIs only by one.[32] Because of such difficulty, a full determination of KBIs in concentrated ternary solutions has rarely been performed.[33−37] However, only a few KBIs (such as the solute−solubilizer and solubilizer−solubilizer) turned out to be the key to understanding solubilization.[15,32] This implies that the solubilization mechanism could be revealed via a simpler route. Such a simplification will be carried out in this work.

1.3. Cooperative Solubilization. Understanding the origin of the abrupt solubilization onset at the "minimum hydrotrope concentration"[27,28] necessitated us to go beyond the KB theory. We have developed a theory of cooperative solubilization,[30−32] which was successful in attributing the onset of solubilization to the enhancement of hydrotrope self-association around the solute. This has led to replacing the classical hydrotrope preaggregation hypothesis with the cooperative hydrotrope association around the solute.[30−32] This conclusion applies not only to hydrotropes alone but also to surfactants, for which the sudden onset of solubilization comes from the enhanced surfactant aggregation around CMC.[15]

Need for Simplification. The application of the cooperative solubilization theory, despite its universality, has been limited to the onset of solubilization (such as the minimum hydrotrope concentration and CMC) because of its theoretical complexity. To overcome this limitation, we have developed the cooperative solubility isotherm for hydrotropes,[38] expressed via a simple analytical equation for capturing solute-induced hydrotrope association, which can be used to fit experimental solubility data.[30−32] However, its success has been limited to hydrotropes.[39,40] A solubility isotherm based on the statistical thermodynamic fluctuation theory, which can be applicable to synergistic solubility, is not available until now.

1.4. Need for a Solubility Isotherm. Our goal is to reveal the mechanisms of solubilization via solubility isotherms as a novel, simpler alternative to the KB and cooperative solubilization theories that are exact yet complicated for applications.[38] To achieve this goal, important lessons come from sorption isotherms. First, the recently established analogy between solvation and sorption enables the application of the theoretical tools for sorption to solubilization, across their difference in the thermodynamic degrees of freedom.[19,41,42] Second, our recent sorption isotherms enable a statistical thermodynamic interpretation (such as number fluctuations and KBIs) of experimental data through only a few parameters.[43−45] Such an approach is less demanding in data acquisition and processing than the KB theory.[20,43,46,47] Third, cumbersome thermodynamic variable transformation, indispensable for converting experimental data to KBIs, has been made more efficient by statistical variable transformation.[48,49]

1.5. Our Aims. Armed with the modern theoretical tools summarized above, we will implement our aims (see the opening paragraph) with the following objectives:

a. To establish an isotherm approach to elucidating solubilization mechanisms as a facile alternative to the KB theory.

b. To derive the polynomial solubility isotherm to capture solute−solubilizer preferential interaction and the enhancement or reduction of self-association around the solute.

c. To show that synergistic solvation and cooperative solubilization have the opposite behavior in terms of the solute's role in solubilizer self-association.

To quantify the self-association of solubilizers and solvents, we will employ the Kirkwood−Buff χ (KB χ) parameter, which we introduced recently as the generalization of the Flory χ and employed to elucidate sorption.[43,44]

2. THEORETICAL METHODS

2.1. Fluctuation Theory. Consider the solubility of a solute (denoted as species u) in a mixture consisting of a solvent (species 1) and a solubilizer (species 2). (Note that the terms "solvent" and "solubilizer" have been introduced to facilitate comparison across different classes of solubilization. For synergistic solvation, the "solubilizer" simply refers to the component whose concentration is increased when plotting the solubility isotherm.) Let N_i be the number of species i molecules, $\langle N_i \rangle$ be its ensemble average, and $\delta N_i = N_i - \langle N_i \rangle$ be its deviation from the mean. Our starting point is the fundamental relationship from the fluctuation solution theory on how the solvation free energy of a solute (μ_u^*, i.e., pseudochemical potential) depends on the chemical potential of the solubilizer (μ_2),

https://doi.org/10.1021/acs.jpcb.4c01582
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$$-\left(\frac{\partial \mu_u^*}{\partial \mu_2}\right)_{T,P,N_1;\mu_u} = \frac{\langle \delta N_u \delta N_2 \rangle}{\langle N_u \rangle} \tag{1a}$$

which is linked to the solute−solubilizer number correlation. (For the derivation of eq 1a, see eq 35 of ref 48 with the indexes 1 and 2 swapped.) Note that eq 1a, derived under phase equilibrium between the solute in its pure phase and in solution (constant μ_u in equilibrium with the pure solute phase), is valid for any solute concentration.[15] (This means that the equation of the same form applies to solutes with sparse solubility, including the examples analyzed in this paper.) Here, for mathematical simplicity, we adopt a $\{T, P, N_1, \mu_2, \mu_u\}$ ensemble,[50,51] yet converting to the grand canonical ensemble $\{T, V, \mu_1, \mu_2, \mu_u\}$, commonly adopted for the KB theory,[16−18] is straightforward via statistical variable transformation (Appendix A).[48,49]

Here, we rewrite eq 1a in the format suitable for solubility isotherms. This can be achieved using the well-known relationships, first between the solvation free energy and solubility c_u, $d\mu_u^* = -RTd \ln c_u$,[52] which can be derived straightforwardly from the basic relationship between μ_u and μ_u^* (see Appendix A), and second between the chemical potential and solubilizer activity, $d\mu_2 = RTd \ln a_2$, through which we obtain

$$\left(\frac{\partial \ln c_u}{\partial \ln a_2}\right)_{T,P,N_1;\mu_u} = \frac{\langle \delta N_u \delta N_2 \rangle}{\langle N_u \rangle} \tag{1b}$$

See Appendix A for its derivation.

Improved clarity can be attained in the application of eq 1b by introducing an inhomogeneous ensemble, which contains a fixed solute molecule at the origin as the source of an external field for the solution mixture.[53,54] The ensemble average in the inhomogeneous ensemble, $\langle\rangle_u$, is the conditional mean in the presence of a fixed solute molecule, which is related to $\langle\rangle$ (i.e., the "homogeneous" mean), via

$$\langle N_2 \rangle_u = \frac{\langle N_u N_2 \rangle}{\langle N_u \rangle} \tag{2}$$

Through eq 2, eq 1b can be expressed in the following simple form

$$\left(\frac{\partial \ln c_u}{\partial \ln a_2}\right)_{T,P,N_1;\mu_u} = \langle N_2 \rangle_u - \langle N_2 \rangle \tag{3}$$

Equation 3, being a rigorous relationship, is the theoretical foundation for solubility isotherms that will be derived in this paper.

2.2. Solubility Isotherms. Our aim is not only to derive solubility isotherm equations for fitting experimental data but also to quantify the interactions underlying solubilization through the fitting parameters. Just like sorption isotherms,[43−45] there may be multiple isotherm equations serving different subclasses of solubilization. Indeed, our previous theory of cooperative solubilization[38] is in fact a solubility isotherm for hydrotropes that exhibit a sigmoidal functional shape. In this paper, we will derive the polynomial isotherm, founded on the a_2-dependence of $\langle N_2 \rangle_u - \langle N_2 \rangle$ and thereafter employ x_2 (solubilizer mole fraction) as the variable, to conform to the experimental practice. The polynomial isotherms will reveal the molecular interactions underlying nonlinear solubilization (Section 3) and will serve as facile alternatives to the KB theory.[19,29,30,32]

2.2.1. Polynomial Isotherm. Here, we derive the polynomial isotherm by expanding $\langle N_2 \rangle_u - \langle N_2 \rangle$ in terms of solubilizer activity, a_2, as

$$\langle N_2 \rangle_u - \langle N_2 \rangle = A_0 a_2 + B_0 a_2^2 + \cdots \tag{4a}$$

where the parameters A_0 and B_0 are defined at the $a_2 \to 0$ limit as

$$A_0 = (A)_{a_2 \to 0} = \left(\frac{\langle N_2 \rangle_u - \langle N_2 \rangle}{a_2}\right)_{a_2 \to 0} \tag{4b}$$

$$B_0 = (B)_{a_2 \to 0} = \left(\frac{\partial}{\partial a_2}\frac{\langle N_2 \rangle_u - \langle N_2 \rangle}{a_2}\right)_{a_2 \to 0} \tag{4c}$$

where the subscript 0 is the shorthand for $a_2 \to 0$, which will be used throughout this paper. Note that the lowest-order term in eq 4a is $A_0 a_2$ because $\langle N_2 \rangle - \langle N_2 \rangle_u$ tends to 0 as $a_2 \to 0$. Combining eqs 3 and 4a yields

$$\left(\frac{\partial \ln c_u}{\partial a_2}\right)_{T,P,N_1} = A_0 + B_0 a_2 + \cdots \tag{5a}$$

and integrating eq 5a (Appendix B) yields

$$\ln \frac{c_u}{(c_u)_0} = A_0 a_2 + \frac{B_0}{2} a_2^2 + \cdots \tag{5b}$$

where $(c_u)_0$ is the molar solubility in the absence of the solubilizer at $a_2 = 0$. Equation 5b will be referred to as the polynomial isotherm.

In the above, the polynomial isotherm was truncated at the second order of a_2, and the second-order expansion with respect to the mole fraction of the solubilizer x_2 will be discussed in Section 3.2.2. Synergistic solvation is typically expressed in the form of quadratic dependence of the solubility on a_2 or x_2, in which case eq 5b is enough to capture the physical meanings of the coefficients involved in the quadratic form. If a quadratic fit is insufficient, our formulation can be straightforwardly extended to incorporate higher-order terms beyond the quadratic in eq 5b.

2.2.2. Interpreting A_0 and B_0. The fluctuation theory provides an interpretation of the isotherm parameters, A_0 and B_0. Statistical variable transformation[48,49] enables a straightforward conversion between different ensembles (see Appendices B and C), through which A_0, defined via eq 4b in the $\{T, P, N_1, \mu_2, \mu_u\}$ ensemble,[50,51] can be expressed in the grand canonical ($\{T, V, \mu_1, \mu_2, \mu_u\}$) ensemble as

$$A_0 = [c_1(G_{u2} - G_{u1})]_0 \tag{6a}$$

where c_1 is the mole per volume of the pure solvent, V is the volume of the system, and G_{u2} and G_{u1} are the solute−solubilizer and solute−solvent KBIs. The subscript 0 expresses the $a_2 \to 0$ limit. The parameters for the polynomial solubilization isotherm are defined and evaluated at this limit, just like the ones for the statistical thermodynamic sorption isotherms.[43,44,46,55] As is clear from eq 6a, A_0 is the difference between the solute−solubilizer and solute−solvent KBIs, commonly referred to as the preferential interaction of solubilizers.[50,51]

https://doi.org/10.1021/acs.jpcb.4c01582
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Likewise, B_0, defined via eq 4c in the $\{T, P, N_1, \mu_2, \mu_u\}$ ensemble, can be transformed into the grand canonical ensemble $\{T, V, \mu_1, \mu_2, \mu_u\}$ as (Appendix C)

$$B_0 = K_e^2\langle N_1\rangle_u(\chi_u + 1) - \langle N_1\rangle(\chi_0 + 1) \tag{6b}$$

where K_e is the equilibrium constant for swapping "a solvent at the vicinity of the solute" with "a solubilizer in the bulk," and χ_u and χ_0, the KB χ parameters around the solute and in the bulk,[44] are defined as

$$\chi_u = \left[\frac{\langle N_1\rangle_u}{V}(G_{u,11} + G_{u,22} - 2G_{u,12})\right]_0,$$
$$\chi_0 = \left[\frac{\langle N_1\rangle}{V}(G_{11} + G_{22} - 2G_{12})\right]_0 \tag{6c}$$

χ_u and χ_0 signify the net self-interaction (solvent−solvent and solubilizer−solubilizer, as compared to solubilizer−solvent) around the solute and in the bulk, respectively. Both χ_u and χ_0 have been defined at the $a_2 \to 0$ limit. The KB χ (eq 6c) was introduced as the generalization of the Flory χ.[25,44] While the Flory χ has been derived in the framework of the lattice model of solutions under mean-field approximation, the KB χ parameter is model- and approximation-free. Using the KB χ, B_0 can be interpreted as the solute-induced enhancement of the self-interaction. (Note that B_0/A_0 will later be employed for fitting and interpretation, which will be shown shortly to be free of $\langle N_1\rangle_u$ and $\langle N_1\rangle$ as found in eq 6b, which sharpens its character as the extent of the solute-induced enhancement of the self-interaction).

The KB χ for the bulk solution (eq 6c) appears also in the conversion of a_2 to the mole fraction x_2 (see Appendix C), via

$$a_2 = x_2 - \chi_0 x_2^2 + \cdots \tag{6d}$$

which shows that the KB χ captures the nonideality of binary solution mixtures in a manner analogous to the Flory χ.[25] However, the common adoption of the mixing rule (especially in the solubility parameters) has prevented the Flory χ-based approaches from recognizing the importance of the solute-induced enhancement or reduction of self-interactions (eq 6c).

Combining eqs 5b and 6d, we obtain the following logarithmic solubility isotherm as a function of x_2

$$\ln\frac{c_u}{(c_u)_0} = A_0 x_2 + \frac{A_0}{2}\left(\frac{B_0}{A_0} - 2\chi_0\right)x_2^2 + \cdots \tag{7a}$$

which can also be expressed in the (linear-)solubility representation as

$$\frac{c_u}{(c_u)_0} = 1 + A_0 x_2 + \frac{A_0}{2}\left(\frac{B_0}{A_0} + A_0 - 2\chi_0\right)x_2^2 + \cdots \tag{7b}$$

The parameters A_0 and χ_0 have already given interpretations (eqs 6a and 6c). Combining eqs 6a and 6b, $\frac{B_0}{A_0}$ can be expressed (Appendices C and D) as

$$\frac{B_0}{A_0} = \frac{K_e K_2(\chi_u + 1) - (\chi_0 + 1)}{K_2 - 1} \tag{7c}$$

where K_2 is the bulk−solute vicinity partition coefficient of the solubilizer. Based on eq 7c, $\frac{B_0}{A_0}$ is interpreted as the solute-induced enhancement of self-association (from χ_0 in the bulk to χ_u around the solute).

Thus, the two representations of the polynomial isotherm, $\ln c_u/(c_u)_0$ and $c_u/(c_u)_0$, will both be useful in the analysis and interpretation of experimental isotherms, as will be discussed in Section 3. The polynomial solubilization isotherm bears similarity to the polynomial sorption isotherm in its parameters and interpretation.[44] To summarize, we have established the polynomial solubility isotherm (eqs 7a and 7b), whose parameters contain contributions from the preferential solute−solubilizer interaction (A_0), the enhancement of self-interaction around the solute (B_0/A_0), and the bulk χ.

2.2.3. Significance of the Polynomial Isotherm. The polynomial solubility isotherm, in its two representations (eqs 7a and 7b), is founded on the a_2-expansion of solubilization (eq 5b) and the x_2-expansion of a_2 (eq 6d). While these expansions are exact, truncating the expansion leads to approximation. The parameters of the expansions (eqs 5b and 6d), as well as of the polynomial solubility isotherm (eqs 7a and 7b), are defined at the $x_2 \to 0$ limit. This is not an approximation but is a logical consequence of the Maclaurin expansions (eqs 5b and 6d) underlying the solubility isotherm. In this way, our theory can be considered as the generalization of the McMillan−Mayer theory of osmotic pressure, which involves a series expansion of the osmotic pressure in terms of the solute concentration.[56] Its parameters (i.e., the virial coefficients) are defined at the zero solute concentration, analogous to our polynomial solubility isotherm. Approximation can be made via the truncation of the expansion, whose sufficiency can be informed through fitting experimental data.

The novelty of the solubility isotherm is threefold. First, in contrast to the conventional KBI calculations at each concentration,[30] the solubility isotherm synthesizes the predictive nature of an isotherm equation and the capability for a rigorous molecular interpretation via its parameters. Note that the concept of solute-induced self-association (which is contained in B_0) was beyond the reach of the traditional KBIs (which are, by definition, binary). This novel concept was introduced by us initially via the inhomogeneous solution theory,[14] thereafter through the cooperative solubilization model applicable for hydrotropes at low concentration,[38] and finally as one of the characteristic parameters for the sorption isotherms.[44] Second, how the solute-induced self-association affects the shape of the solubility isotherm over a wide composition range has now been clarified, which was not possible with our previous approach.[14] Third, our solubility isotherm constitutes a part of a universal approach spanning from solution to sorption, founded on the mathematical analogy between solvation and sorption, which has only recently been formulated rigorously.[19,41,42]

3. RESULTS AND DISCUSSION

3.1. Synergistic Solvation. *3.1.1. Synergy via Quadratic Isotherm.* Our goal is to reveal the mechanism of synergistic solvation and clarify how it differs from hydrotropy. Our theoretical foundation is the polynomial isotherm derived from the fluctuation solution theory (eqs 7a and 7b). The strict definition of synergistic solvation has not been established, yet "a binary solvent mixture exhibits a higher solubility than either of the component solvents alone" may be the most general one at this stage.[4] Note that synergistic solvation is "also known as parabolic solubility"[4] due to the ubiquitousness of the parabolic solubility isotherms.[3,57,58] Hence, the present paper

https://doi.org/10.1021/acs.jpcb.4c01582
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focuses on the quadratic isotherm as the simplest and most common class of synergistic solvation as the first step. (For the solubility isotherms with more complex functional shapes, cubic or higher-order terms in x_2 may be incorporated.)

3.1.2. Logarithmic versus Linear Plots of Solubility. Here, we show that the logarithmic representation (eq 7a) of the polynomial isotherm is superior to the linear representation (eq 7b) in fitting experimental solubility data. To demonstrate this, we have chosen the solubility of benzoin in ethyl acetate−methanol and ethyl acetate−ethanol mixtures[57,59] and the solubility of rivaroxaban in methanol−dichloromethane mixtures.[58,60] While the logarithmic representation leads to an excellent fit incorporating up to x_2^2 (Figure 2), the linear

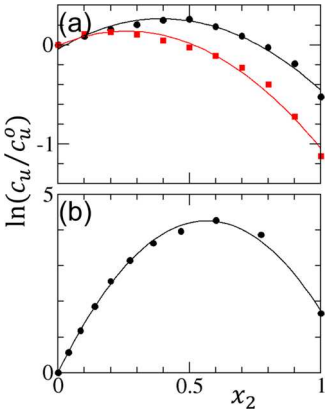

Figure 2. Application of the quadratic solubility isotherm (eq 8) to fit the logarithmic scale solubility data ($\ln c_u/(c_u)_0$), plotted against the mole fraction x_2. (a) Solubility of benzoin (species u) in the mixtures of ethyl acetate (species 1) and alcohol (species 2) at 298.15 K (black circles for methanol and red squares for ethanol), based on the data reported by Yang et al.,[57] in combination with the density data of alcohol−ethyl acetate mixtures published by Nikam et al.[59] (b) Solubility of rivaroxaban (species u) in the mixture of methanol (species 1) and dichloromethane (species 2) at 293.15 K, based on the data reported by Jeong et al.,[58] in combination with the density data by Damyanov and Velchev.[60] The fitting parameters are summarized in Table 1.

representation exhibited fitting difficulties, requiring higher-order terms (Figure 3). Note that a minor adjustment was involved for the logarithmic representation (eq 7a) with an adjustable constant, ϵ, as

$$\ln\frac{c_u}{(c_u)_0} = A_0 x_2 + \frac{1}{2}(B_0 - 2A_0\chi_0)x_2^2 + \epsilon \tag{8}$$

leading to a good fit over the entire range of x_2 with a negligibly small ϵ (see Appendix B for its necessity). The fitting parameters are summarized in Table 1, from which the interaction parameters have been calculated (Table 2). Although the linear representation has been adopted widely to report experimental solubility isotherms, we advocate for a logarithmic representation based not only on the facility for fitting but also on its directness in interpreting the fitting parameters.

3.1.3. Conditions for Synergy. According to its definition, higher solubility in the mixture is observed for synergistic solvation than is expected from the weighted averaging of solubilities in pure solvents. Based on the logarithmic representation of the polynomial isotherm (eq 7a), here we

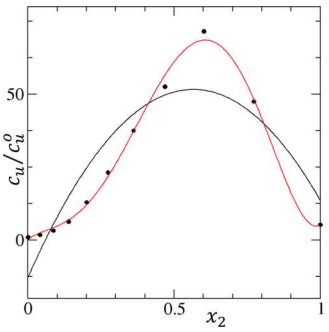

Figure 3. Linear solubility isotherm, $c_u/(c_u)_0$ against x_2, of rivaroxaban (species u) in the mixture of methanol (species 1) and dichloromethane (species 2), to be compared with the logarithmic isotherm in Figure 2b. A quadratic isotherm ($c_u/(c_u)_0 = -12.969 + 228.27x_2 - 201.65x_2^2$, black line) was insufficient to fit the experimental data (black circles), and the fifth-order polynomial was required for a reasonable fit (red line; $= 0.2061 + 70.076x_2 - 523.91x_2^2 + 3304.7x_2^3 - 5355.1x_2^4 + 2509.2x_2^5$). This complication contrasts with the ease of fitting by the logarithmic isotherm (Figure 2b).

clarify the mechanism underlying the solubility maximum. As a first step, we rewrite eq 7a as

$$\ln\frac{c_u}{(c_u)_0} = -\frac{A_0}{2}\left(2\chi_0 - \frac{B_0}{A_0}\right)\left(x_2 - \frac{1}{2\chi_0 - \frac{B_0}{A_0}}\right)^2 + \frac{A_0}{2}\frac{1}{2\chi_0 - \frac{B_0}{A_0}} + \cdots \tag{9}$$

For eq 9 to exhibit a maximum, $A_0\left(2\chi_0 - \frac{B_0}{A_0}\right)$ must be positive. (This is in line with the negative $\frac{B_0}{A_0} - 2\chi_0$ in Table 2). Under this condition, the maximum solubility, c_u^{max}, is expressed as

$$\ln\frac{c_u^{max}}{(c_u)_0} = \frac{A_0}{2}\frac{1}{2\chi_0 - \frac{B_0}{A_0}} \tag{10a}$$

For c_u^{max} to be greater than $(c_u)_0$, $A_0/\left(2\chi_0 - \frac{B_0}{A_0}\right)$ must be positive. This condition is equivalent to the above positiveness condition for $A_0\left(2\chi_0 - \frac{B_0}{A_0}\right)$. In addition, the maximum solubility at

$$x_2 = x_2^{max} \equiv \frac{1}{2\chi_0 - \frac{B_0}{A_0}} \tag{10b}$$

must be located between $x_2 = 0$ and 1. $x_2^{max} > 0$ leads to $2\chi_0 - \frac{B_0}{A_0} > 0$. Consequently, $A_0 > 0$ results in combination with the maximum and synergy conditions. The other end, $x_2^{max} < 1$, leads to $2\chi_0 - \frac{B_0}{A_0} > 1$. Taking all together, we can summarize the conditions following for synergistic solubilization as

$$A_0 > 0, \quad 2\chi_0 - \frac{B_0}{A_0} > 1 \tag{10c}$$

which is indeed satisfied by all of the examples (Table 2).

https://doi.org/10.1021/acs.jpcb.4c01582
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Table 1. Fitting Parameters for the Logarithmic Representation of the Quadratic Solubility Isotherm (Equation 8)

solute	solvent	cosolvent	A_0	$B_0 - 2A_0\chi_0$	ϵ
benzoin	ethyl acetate	methanol	1.56	−3.93	−0.044
benzoin	ethyl acetate	ethanol	1.14	−4.34	−0.011
rivaroxaban	methanol	dichloromethane	15.1	−26.6	−0.0036

Table 2. Interaction Parameters Evaluated Based on Table 1

solute	solvent	cosolvent	χ_0	A_0	B_0	$\frac{B_0}{A_0} - 2\chi_0$
benzoin	ethyl acetate	methanol	1.91[a]	1.56	2.03	−2.52
benzoin	ethyl acetate	ethanol	1.32[a]	1.14	−1.33	−3.80
rivaroxaban	methanol	dichloromethane	1.06[a]	15.1	5.42	−1.76

[a]Calculated from Table 13−4 of ref 71 and ref 72 which can be transformed to $\chi_0 = 2\alpha$ via eq C8.

3.1.4. Mechanism of Synergy. Having identified the range of parameters that exhibit synergistic solvation (eq 10c), here we clarify its significance on a mechanistic basis. To do so, let us start by summarizing the interpretations of the parameters involved:

a. A_0 for preferential solute−solubilizer interaction (eq 6a)
b. $\frac{B_0}{A_0}$ for the self-association (KB χ) enhancement around the solute (eq 7c)
c. χ_0 for bulk-phase self-association (eq 6c).

The interpretation of the parameters (a−c) will now reveal the mechanism of synergistic solubilization (eq 10c). First, $A_0 > 0$ in eq 10c signifies preferential solute−solubilizer interaction compared to solute−solvent. Second, $2\chi_0 - \frac{B_0}{A_0} > 1$ in eq 10c signifies sufficiently stronger bulk-phase self-association (χ_0) compared to the self-association enhancement around the solute (B_0/A_0). This can be rephrased more intuitively by rewriting it as $-\frac{B_0}{A_0} - 2(-\chi_0) > 1$. Now, $-\frac{B_0}{A_0}$ signifies the enhancement of solvent−solubilizer mixing (self-dissociation), whereas $-\chi_0$ means the solvent−solubilizer mixing in the bulk. The rephrased inequality shows that mixing, enhanced around the solute, is stronger than the bulk-phase mixing of solvent and solubilizer.

3.1.5. Synergy versus Cooperative Solubilization by Hydrotropes. We have shown above that synergistic solvation takes place under preferential solute−solubilizer interaction and enhanced solvent−solubilizer mixing around the solute. The above signatures of synergistic solvation, expressed schematically via Figure 4a, are contrasted with the cooperative solubilization by hydrotropes[14,38,61] and surfactants (Figure 4b),[15] both of which involve enhanced solubilizer self-association around the solute. We emphasize that solubilizer self-association (in the case of hydrotropes and surfactants) is synonymous with solvent−solubilizer demixing, opposite to solvent−solubilizer mixing underlying synergistic solvation (Figure 4).

In the case of hydrotropy (surfactancy), the accumulation of hydrotropes (surfactants) around the solute leads to a further increase in the gradient of the solubility isotherm (Figures 4b and 1b,c). In contrast, solvent−solubilizer mixing weakens the effect of solubilizer accumulation (Figures 4a and 1a), leading to a decreased gradient in the solubility isotherm.

3.2. Choices for Interpretive Clarity in Solubility Isotherms. The solubility isotherm, founded on the fluctuation solution theory, is capable not only of drawing mechanistic insights into solubilization directly from experimental data but also of unifying solubilization phenomena that were classified previously into different subcategories. In the following, we will show how mechanistic interpretation could be facilitated by an appropriate choice in reporting experimental solubility isotherm data.

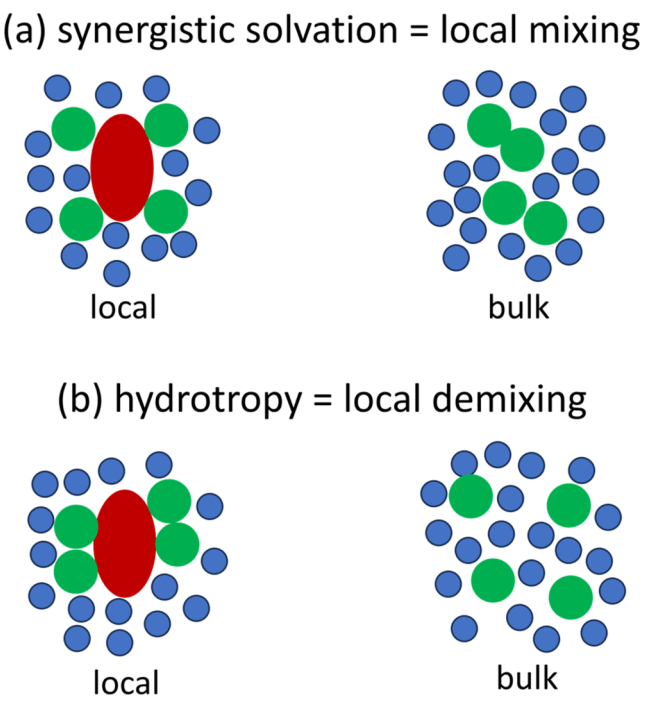

Figure 4. Difference between (a) synergistic solvation and (b) hydrotropy as clarified by our theory. (a) Synergistic solvation is driven by local mixing, i.e., the mixing of solvent (blue) and solubilizer (green) is enhanced around the solute (red) compared to the bulk solution. (b) Hydrotropy is driven by local demixing, i.e., the enhancement of self-association around the solute compared to the bulk solution. Synergistic solvation and hydrotropy exhibit opposite behaviors.

3.2.1. Linear versus Logarithmic Solubility Isotherms. Solubility isotherms have traditionally been the linear representation (eq 7b), i.e., the plot of solubility itself against composition. However, the logarithmic representation (eq 7a) is superior for the following reasons. First, the logarithmic representation offers a better fitting capability of experimental isotherms (compare Figure 2b with Figure 3). Second, while the logarithmic scale involves two parameters ($\frac{B_0}{A_0}$ and χ_0, eq 7a) in the quadratic term, the linear scale involves three ($\frac{B_0}{A_0}$,

https://doi.org/10.1021/acs.jpcb.4c01582
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A_0, and χ_0, eq 7b); hence, interpreting the logarithmic scale isotherm is easier than the one in the linear scale.

3.2.2. Mole-Fraction versus Molarity Solubility Scales. The superiority of the molarity scale for solubility over the mole-fraction scale was established decades ago,[52] with its direct interpretation as the solute insertion process. This generality contrasts with the mole-fraction scale, which either requires activity coefficients or its restriction to dilute solubility.[52] However, the mole-fraction scale is still used today for reporting solubility. Here, we add another reason as to why the mole-fraction scale adds complications. To this end, let us start with the following definition of the mole-fraction solubility in the constant N_1 ensemble (to be consistent with eqs 1a and 1b)

$$x_u = \frac{\langle N_u \rangle}{N_1 + \langle N_2 \rangle + \langle N_u \rangle} \tag{11}$$

Our goal is to derive a mole-fraction counterpart to eq 3, which is the foundation of solubility isotherms. The first step is to carry out a μ_2-derivative of eq 11 (Appendix E), which yields

$$\left(\frac{\partial \ln x_u}{\partial \ln a_2}\right)_{T,P,N_1;\mu_u} = (1 - x_u)\frac{\langle \delta N_u \delta N_2 \rangle}{\langle N_u \rangle} - x_u \frac{\langle \delta N_2 \delta N_2 \rangle}{\langle N_2 \rangle} \tag{12}$$

Let us examine eq 12 as the potential generating relationship for isotherms (i.e., x_u as a function of x_2). There are two contributions: (i) $\frac{\langle \delta N_u \delta N_2 \rangle}{\langle N_u \rangle}$ as the measure of solute−solubilizer interaction via their number correlation and (ii) $\frac{\langle \delta N_2 \delta N_2 \rangle}{\langle N_2 \rangle}$ as the bulk property. This contrasts with the molarity scale counterpart (eq 1b), which only contains (i), without any contributions from the bulk properties, (ii). Thus, the molarity scale is superior, which enables us to focus on solute−solubilizer interactions without any involvement of the bulk property.

3.3. Comparison to Solubility Parameters. *3.3.1. Solubility Parameters are Founded on the Regular Solution Theory.* Synergistic solubility is conventionally explained by solubility parameters.[24] According to this approach, solubility maximum takes place when the solubility parameter of the solute matches that of the solvent mixture, calculated as the weighted average of the parameters for the pure solvent and solubilizer.[24] This explanation is founded on the regular solution theory.

Our objective here is to show the advantages of our new theory over the classical approach. This task is made complicated due to the gulf in foundations between the modern statistical thermodynamics of solvation (founded on the pseudochemical potential, μ_u^*, in eq 1a) and the classical solution thermodynamics (founded on the "ideal solubility" and the solute activity coefficient). The regular solution theory aims to provide an approximate model for the contribution of a solute's activity coefficient to solubility.

However, in contrast to the directness afforded by modern statistical thermodynamics in achieving the aims a−c set out in Section 1.5, the regular solution model not only complicates its link to solubility via a series of assumptions but also is incapable of achieving these aims, as will be clarified in the following.

3.3.2. Regular Solution Theory as the Deviation from the Ideal Solubility. The regular solution theory[21] considers the free energy of transferring one mole of solute from the pure liquid to a regular solution

$$\mu_u - \mu_u^{\circ} = RT \ln a_u \tag{13a}$$

where μ_u° is the chemical potential of the solute at its pure state. The regular solution theory divides this into the following two steps. The first is the transfer from the pure liquid to the ideal solution (denoted by the superscript i),

$$\mu_u^i - \mu_u^{\circ} = RT \ln x_u \tag{13b}$$

The second is the transfer "from the ideal solution to a regular solution"[62]

$$\mu_u - \mu_u^i = RT \ln \frac{a_u}{x_u} = RT \ln \gamma_u \tag{13c}$$

For eq 13c, the regular solution theory assumes the following functional form

$$RT \ln \gamma_u = b x_1^2 \tag{14}$$

and assumes the parameter b to be of enthalpic origin. The regular solution theory, in its traditional form, expresses b in eq 14 in terms of the "solubility parameters," under a series of model assumptions, most notably the mixing rule, the solvent mixtures as the weighted mean of the pure solvents, and the lattice model with mean-field approximation or the van der Waals fluid model.[21] Based on these assumptions, the solubility parameter models of Hildebrand[21] and Hansen[24] provide b via one- and three-dimensional distances between the solubility parameters of solute and solvent for the solubilities in pure solvents. For mixed solvents, their solubility parameters are estimated as the weighted mean of the constituent solvents.

What does the parameter b signify in eq 14? To answer this question, the following expansion from the fluctuation theory (derived by swapping the indexes 2 and u eq B4 in Appendix B) is useful

$$\ln \gamma_u = \chi_R x_1^2 + \cdots \tag{15a}$$

where χ_R is expressed via the KBIs,[25] as

$$\chi_R = \frac{\langle N_u \rangle}{V}(G_{uu} + G_{11} - 2G_{u1}) \tag{15b}$$

Due to the mathematical analogy between eqs 14 and 15a, χ_R in eq 15b constitutes the statistical thermodynamic interpretation for b/RT in eq 14, signifying the relative strength of the self-interactions ($1 - 1$ and $u - u$) over mutual ($1 - u$).

3.3.3. Difficulties of the Solubility Parameters in Deriving Solubility Isotherms. We have rewritten the fundamental relationship for the regular solution theory (eq 14) in the language of the statistical thermodynamic fluctuation theory (eqs 15a and 15b; without adopting any of the assumptions for deriving solubility parameters). Here, we show that it is not straightforward to derive solubility isotherms from the regular solution theory (Cf. Aim b in Section 1.5). Combining eq 14 (or eqs 15a and 15b) with eq 13b and 13c, we obtain

$$\mu_u - \mu_u^{\circ} = RT \ln x_u + b x_1^2 \tag{16a}$$

Under phase equilibrium, $\mu_u = \mu_u^{\circ}$, eq 16a leads to

$$RT \ln x_u = -b x_1^2 \tag{16b}$$

which is the solubility isotherm derived from the regular solution theory. (Noting that $\ln \gamma_u = -\ln x_u$ under $\mu_u = \mu_u^{\circ}$, eq

https://doi.org/10.1021/acs.jpcb.4c01582
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16b for the binary mixture of the species 1 and u is parallel in form to eq B4 in Appendix B, expressed for the mixture of the species 1 and 2.) However, when applying eq 16b to the solvation of the solute u in the binary solvent mixtures (consisting of the species 1 and 2) via the solubility parameters, the following two assumptions have been introduced.[21,24] First, b in eq 14 (which is used as the model approximation for χ_R in eq 15b) is the squared "distance" of solubility parameters between the solute and the binary mixture. Second, the solubility parameters for the binary mixture are assumed to be the composition-weighted mean of the pure (bulk) solvent values. These two assumptions have made it impossible to identify the fact that solubilization is linked to the local solution structure around the solute, which, by contrast, is captured by the fluctuation theory and its polynomial isotherm.

Thus, the solubility parameters cannot capture the microscopic basis of solvation, i.e., the local solution structure around the solute. Nevertheless, the Hansen solubility parameters have been used widely as a handy tool for solvent selection and screening.[24] Their true foundation, applicability, and limitations should be identified via modern statistical thermodynamics.[25] (As a preliminary step, the historic iodine dissolution experiments,[63−65] previously taken as the supporting evidence for regular solution theory,[21] have been reinterpreted as the dominance of enthalpy on the solvation free energy difference between solvents).[25]

3.4. Comparison to the Kirkwood−Buff Theory and Its Generalizations. Our quadratic isotherm marks a departure from a direct application of the KB theory[16−18] and cooperative solubilization theory.[7,14,61,66] Our isotherm focuses exclusively on how solubility changes with solubilizer concentration, leading to a facile identification of a few key parameters (e.g., A_0 and B_0, together with χ_0) that can describe the overall functional shape of an isotherm.[43,46,55] Such an ease contrasts with the calculation of KB integrals at every solubilizer concentration, for which measurements other than solubility (e.g., activity, density, and compressibility) are indispensable. The simplification here owes itself to the mathematical simplicity of the isotherm, which can nevertheless capture (a) solute−solubilizer interaction and (b) solute-solubilizer mixing enhancement around the solute that would require significantly more work on data processing when approached via a direct application of the KB theory.[7,14,15] Thus, the solubility isotherm, despite its simplicity in form, captures the salient mechanisms of solubilization. However, a direct application of the KB theory will remain a powerful approach when an exhaustive quantification is needed for all interactions.

4. CONCLUSIONS

Our goal was twofold: (i) to elucidate the mechanism underlying synergistic solvation (i.e., the maximum solubility in binary solvent mixtures being larger than the weighted mean of the solubilities in pure solvents) and (ii) to achieve (i) via the solubility isotherm theory as a simpler alternative to the Kirkwood−Buff and the cooperative solvation theories. This was made possible by combining our recent theoretical progress: capturing solution structure and its change around the solute via molecular distribution functions and number correlations,[14,15,32,61] a systematic approach for deriving isotherm equations directly from the principles of the fluctuation theory,[19,20,29,41,42] and the ability to generalize our approach to isotherms to solvation via the mathematical analogy between solvation and sorption isotherms.[19,41,42]

Synergistic solvation is caused by the enhancement of solvent mixing around the solute. This behavior is opposite to hydrotropy, which involves the demixing of water and hydrotropes (i.e., self-association) around the solute. This conclusion was reached via the solubility isotherm derived from the statistical thermodynamic fluctuation theory. While the solubility isotherm provides a clear interpretation of its parameters that are rooted in the molecular distribution functions and the Kirkwood−Buff integrals, its application to experimental solubility isotherms is far less demanding than the evaluation of the Kirkwood−Buff integrals via cumbersome data analysis involving additional experimental data (e.g., density, compressibility, and osmotic data).[14,15,32,61]

Historically, the study of solubilizers has relied on classifying them into subcategories (e.g., cosolvents, hydrotropes, and surfactants) that involved challenging outliers and misleading mechanistic hypotheses. Instead, our simple, isotherm-based approach provides a universal language of solubilization.[20,43,44]

APPENDIX A STATISTICAL VARIABLE TRANSFORMATION AND A LINK TO SOLUBILITY

First, we carry out a statistical variable transformation[48,49] to link solubility measurements to KBIs. If approached thermodynamically, converting thermodynamic fluctuation expressed in one ensemble (e.g., $\{N_1, \mu_2, \mu_u, P, T\}$, abbreviated as $\{N_1\}$ below) to another (e.g., $\{\mu_1, \mu_2, \mu_u, V, T\}$, abbreviated as $\{\mu_1\}$) involves a cumbersome change of variables that need to be carried out for the elements of the fluctuation Hessian matrix.[49] In contrast, significant simplification comes from statistical variable transformation.[48,49] The starting point is the invariance of the solubilizer−solvent mole ratio, $C_2 = N_2/N_1$, and its deviation from the mean, as

$$\frac{N_2 + (\delta N_2)_{\{N_1\}}}{N_1} = \frac{N_2 + (\delta N_2)_{\{\mu_1\}}}{N_1 + (\delta N_1)_{\{\mu_1\}}} \tag{A1}$$

The Maclaurin expansion of eq A1 yields

$$(\delta N_2)_{\{N_1\}} = (\delta N_2)_{\{\mu_1\}} - C_2(\delta N_1)_{\{\mu_1\}} \tag{A2}$$

Likewise, from the invariance of $C_u = N_u/N_1$, we can also derive

$$(\delta N_u)_{\{N_1\}} = (\delta N_u)_{\{\mu_1\}} - C_u(\delta N_1)_{\{\mu_1\}} \tag{A3}$$

Equations A2 and A3 are the relationships for statistical variable transformation between $\{N_1, \mu_2, \mu_u, P, T\}$ and $\{\mu_1, \mu_2, \mu_u, V, T\}$ that will be used throughout this paper.

Now, we use eqs A2 and A3 to carry out a $\{N_1, \mu_2, \mu_u, P, T\} \rightarrow \{\mu_1, \mu_2, \mu_u, V, T\}$ transformation of eq 1a, which yields

$$\frac{\langle (\delta N_u)_{\{N_1\}} (\delta N_2)_{\{N_1\}} \rangle}{\langle N_u \rangle_{\{N_1\}}} = \frac{\langle (\delta N_u)_{\{\mu_1\}} (\delta N_2)_{\{\mu_1\}} \rangle}{\langle N_u \rangle_{\{\mu_1\}}} - C_2 \frac{\langle (\delta N_u)_{\{\mu_1\}} (\delta N_1)_{\{\mu_1\}} \rangle}{\langle N_u \rangle_{\{\mu_1\}}} \tag{A4}$$

where $C_u \rightarrow 0$ has been used. To simplify eq A4 further, we will introduce the Kirkwood−Buff integrals,[16,48,49]

https://doi.org/10.1021/acs.jpcb.4c01582
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$$G_{u1} = V\frac{\langle(\delta N_u)_{\{\mu_1\}}(\delta N_1)_{\{\mu_1\}}\rangle}{\langle N_u\rangle_{\{\mu_1\}}\langle N_1\rangle_{\{\mu_1\}}}$$

$$G_{u2} = V\frac{\langle(\delta N_u)_{\{\mu_1\}}(\delta N_2)_{\{\mu_1\}}\rangle}{\langle N_u\rangle_{\{\mu_1\}}\langle N_2\rangle_{\{\mu_1\}}} \tag{A5}$$

through which eqs 1a and A4 can be expressed as

$$-\left(\frac{\partial\mu_u^*}{\partial\mu_2}\right)_{T,P,N_1} = c_2(G_{u2} - G_{u1}) \tag{A6}$$

Note that eq A6 is a well-known relationship in the Kirkwood−Buff theory.[19,29] When solute molecules are under phase equilibrium, a generalization of eq A6 to arbitrary solute concetrations can be carried out as shown in Appendix A of ref 15.

Second, we link the solvation free energy (pseudochemical potential), μ_u^*, to solubility. This can be carried out by decomposing the chemical potential of the solute in the solution phase, μ_u, into the following two contributions: (i) the pseudochemical potential μ_u^*, which has a clear physical meaning as the free energy of inserting a solute molecule at a fixed position and (ii) the free energy of liberating a solute from positional fixation, via[52,67]

$$\mu_u = \mu_u^* + RT\ln\rho_u\Lambda_u^3 \tag{A7}$$

where the contribution (ii), i.e., the second term of eq A7, involves ρ_u (the number density of the solute) and Λ_u (the momentum distribution function of the solute).[52,68] Equation A7 is valid for multiple-component solutions regardless of solute concentration and solvent composition.[52,68] Differentiating eq A7 under constant temperature yields

$$\mathrm{d}\mu_u = \mathrm{d}\mu_u^* + RT\,\mathrm{d}\ln c_u \tag{A8}$$

In deriving eq A8, we have exploited the fact that the only difference between ρ_u (number density) and c_u (molarity concentration) are their units, which leads to $\mathrm{d}\ln\rho_u = \mathrm{d}\ln c_u$. When the solute in the solution phase is at phase equilibrium with the pure solute phase, $\mu_u = \mu_u^\circ$, where μ_u° is the chemical potential of the solute in its pure phase. Under constant temperature and pressure, μ_u° is a constant. Consequently, μ_u remains a constant, which leads to $\mathrm{d}\mu_u = 0$. Thus, under phase equilibrium (i.e., constant μ_u),

$$\mathrm{d}\mu_u^* = -RT\,\mathrm{d}\ln c_u \tag{A9}$$

Combining eqs A6 and A9, we obtain

$$RT\left(\frac{\partial\ln c_u}{\partial\mu_2}\right)_{T,P,N_1;\mu_u} = c_2(G_{u2} - G_{u1}) \tag{A10}$$

Note that the newly appeared subscript, μ_u, signifies that the partial derivative is defined under constant μ_u, reflecting the derivation of eq A9. From eq A10, eq 3 can be derived straightforwardly from the elementary relationship between μ_2 and a_2.

We emphasize here that the use of the molarity (or number density) scale is advantageous because its foundation, eq A7, is "valid for any composition of the mixture."[52] This is in contrast to the use of the mole-fraction solubility scale whose fundamental equation has been derived "only in the limit of extremely dilute solution."[52]

APPENDIX B INTERPRETING THE PARAMETERS OF THE POLYNOMIAL ISOTHERM

Activity Scale

Let us attribute to the parameters A and B a statistical thermodynamic interpretation. To facilitate the derivation, we specify the $a_2 \to 0$ limit at the end. As a first step, we rewrite A, defined via eq 4b, as

$$A = \frac{\langle N_2\rangle_u - \langle N_2\rangle}{a_2} = \frac{\langle N_1\rangle}{V}V\frac{\langle N_2\rangle_u - \langle N_2\rangle}{\langle N_2\rangle} = c_1V\frac{\langle N_2\rangle_u - \langle N_2\rangle}{\langle N_2\rangle} \tag{B1a}$$

where $c_1 = \langle N_1\rangle/V$ is the concentration of pure solvent. Note that $V\frac{\langle N_2\rangle_u - \langle N_2\rangle}{\langle N_2\rangle}$ in eq B1a is reminiscent of the definition of KBI. However, the ensemble adopted for eq B1a is $\{T, P, N_1, \mu_2\}$ instead of the grand canonical ensemble ($\{T, V, \mu_1, \mu_2\}$) for KBIs. Consequently, $V\frac{\langle N_2\rangle_u - \langle N_2\rangle}{\langle N_2\rangle}$ may be considered as the *pseudo*-KBI in $\{T, P, N_1, \mu_2\}$, defined as

$$G'_{u2} = V\frac{\langle N_2\rangle_u - \langle N_2\rangle}{\langle N_2\rangle} \tag{B1b}$$

through which A has the following interpretation

$$A = c_1G'_{u2} \tag{B1c}$$

Thus, the parameter A signifies solute−solubilizer interaction in the framework of the $\{T, P, N_1, \mu_2\}$ ensemble. In Appendix C, we have carried out a $\{T, P, N_1, \mu_2\} \to \{T, V, \mu_1, \mu_2\}$ transformation, using the statistical variable transformation (Appendix A),[48,49] and express A in eq B1c in the framework of the conventional KB theory.

Now, we move onto B, defined via eq 4c. Carrying out the differentiation, we obtain

$$B = \frac{\partial}{\partial a_2}\frac{\langle N_2\rangle_u - \langle N_2\rangle}{a_2} = \frac{\frac{\partial[\langle N_2\rangle_u - \langle N_2\rangle]}{\partial\ln a_2} - [\langle N_2\rangle_u - \langle N_2\rangle]}{a_2^2} = \frac{(\langle\delta N_2\delta N_2\rangle_u - \langle N_2\rangle_u) - (\langle\delta N_2\delta N_2\rangle - \langle N_2\rangle)}{a_2^2} \tag{B2a}$$

Note that eq B2a is under the $\{T, P, N_1, \mu_2\}$ ensemble (instead of the grand canonical ensemble for the KB theory). Introducing the pseudo-KBI in the $\{T, P, N_1, \mu_2\}$ ensemble via

$$G'_{22} = V\frac{\langle\delta N_2\delta N_2\rangle - \langle N_2\rangle}{\langle N_2\rangle^2} \tag{B2b}$$

$$G'_{u,22} = V\frac{\langle\delta N_2\delta N_2\rangle_u - \langle N_2\rangle_u}{\langle N_2\rangle_u^2} \tag{B2c}$$

and noting $a_2 \simeq x_2 \simeq \langle N_2\rangle/\langle N_1\rangle$ at $a_2 \to 0$, we obtain

$$B_0 = \left(\frac{\partial}{\partial a_2}\frac{\langle N_2\rangle_u - \langle N_2\rangle}{a_2}\right)_{a_2\to 0} = \left[\frac{1}{a_2^2}\left(\frac{\langle N_2\rangle_u^2}{V}G'_{u,22} - \frac{\langle N_2\rangle^2}{V}G'_{22}\right)\right] \tag{B2d}$$

https://doi.org/10.1021/acs.jpcb.4c01582
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for eq 4c. B_0, according to eq B2d, signifies the change of solubilizer−solubilizer interaction induced by the presence of a solute molecule. This, again, is the interpretation of the $\{T, P, N_1, \mu_2\}$ ensemble. Transformation to the grand canonical ensemble will be carried out in Appendix C via statistical variable transformation (Appendix A).

Conversion to the Mole-Fraction Scale

Here, we convert the variable a_2 of the polynomial isotherm to the mole fraction, x_2, in the form of

$$a_2 = x_2 + \lambda x_2^2 + \cdots \tag{B3}$$

where we have chosen the dilute-ideal standard state, which has made the coefficient for the first-order term 1. We are going to determine the parameter λ. This can be achieved by using the simplest activity model, the Margules model, which has the following form

$$\ln \gamma_1 = \alpha x_2^2 + \cdots \tag{B4}$$

Connecting γ_1 to a_2 requires the Gibbs−Duhem equation under constant temperature and pressure

$$x_1 \mathrm{d}\mu_1 + x_2 \mathrm{d}\mu_2 = 0 \tag{B5a}$$

which can be rewritten as

$$\left(\frac{\partial \ln a_2}{\partial \ln x_2}\right)_{T,P} = (x_2 - 1)\left(\frac{\partial \ln \gamma_1}{\partial x_2}\right)_{T,P} + 1 \tag{B5b}$$

Combining eqs B4 and B5b yields

$$\left(\frac{\partial \ln a_2}{\partial \ln x_2}\right)_{T,P} = 1 - 2\alpha x_2 + 2\alpha x_2^2 + \cdots \tag{B6}$$

The corresponding expression from eq B3 is

$$\left(\frac{\partial \ln a_2}{\partial \ln x_2}\right)_{T,P} = \frac{1 + 2\lambda x_2 + \cdots}{1 + \lambda x_2 + \cdots} \simeq 1 + \lambda x_2 + \cdots \tag{B7}$$

Comparing eqs B6 and B7 yields $\lambda = -2\alpha$; hence, we obtain the following activity expansion using the Margules constant, α, as

$$a_2 = x_2 - 2\alpha x_2^2 + \cdots \tag{B8}$$

whose parameter will be given a statistical thermodynamic interpretation in Appendix C.[25]

Our theory is applicable when species 2 is a salt consisting of several ions. In this case, following the well-established method in the KB theory, x_2 is taken as the mole fraction of total ions, a_2 is the activity of the average ion, and all of the resultant KBIs refer to the interactions with the average ion.[69] Indeed, we emphasize that salt concentrations, instead of individual ion concentrations, are controlled when changing the composition of the mixture experimentally.

Application to Data Fitting

When we use eq 7a directly to fit the data, $(c_u)_0$, i.e., the solubility at $x_2 = 0$, is taken as the value without any errors. To prevent this, we introduce

$$\ln c_u = A_0 x_2 + \frac{1}{2}(B_0 - 2A_0\chi_0)x_2^2 + \ln(c_u)_0 + \epsilon \tag{B9}$$

such that the solubility at $x_2 = 0$, $\ln(c_u)_0 + \epsilon$, is also a fitting parameter. Consequently, ϵ signifies the difference between experimental and fitted logarithmic solubility at $x_2 = 0$.

APPENDIX C INTERPRETATION OF THE POLYNOMIAL ISOTHERM PARAMETERS IN THE GRAND CANONICAL ENSEMBLE

Ensemble Transformation: $\{T, P, N_1, \mu_2\} \rightarrow \{T, V, \mu_1, \mu_2\}$

To interpret parameters A and B in the grand canonical ($\{T, V, \mu_1, \mu_2\}$) ensemble, here we carry out a $\{T, P, N_1, \mu_2\} \rightarrow \{T, V, \mu_1, \mu_2\}$ transformation via statistical variable transformation (Appendix A).

To carry out the statistical variable transformation on A, the inhomogeneous ensemble average must first be expressed in terms of the homogeneous,[14] i.e.

$$G'_{u2} = V\frac{\langle N_2\rangle_u - \langle N_2\rangle}{\langle N_2\rangle} = V\frac{\langle \delta N_u \delta N_2\rangle}{\langle N_u\rangle\langle N_2\rangle} \tag{C1a}$$

Carrying out the statistical variable transformation on δN_u and δN_2 (Appendix A), we obtain

$$G'_{u2} = G_{u2} - G_{u1} \tag{C1b}$$

Hence, the parameter A, in the grand canonical ensemble, can be rewritten as

$$A = c_1(G_{u2} - G_{u1}) \tag{C2}$$

This means that A signifies the preferential solute−solubilizer interaction compared to solute−solvent.

To carry out statistical variable transformation on B, we need to convert G'_{22} and $G'_{u,22}$. The key is the following statistical variable conversion (Appendix A)

$$\begin{aligned}
&\langle \delta N_2 \delta N_2\rangle_{\{N_1\}} - \langle N_2\rangle_{\{N_1\}} \\
&= \langle (\delta N_2 - C_2 \delta N_1)^2\rangle_{\{\mu_1\}} - \langle N_2\rangle_{\{\mu_1\}} \\
&= \langle \delta N_2 \delta N_2\rangle_{\{\mu_1\}} - \langle N_2\rangle_{\{\mu_1\}} - 2C_2\langle \delta N_1 \delta N_2\rangle_{\{\mu_1\}} \\
&\quad + C_2^2\langle \delta N_1 \delta N_1\rangle_{\{\mu_1\}}
\end{aligned} \tag{C3a}$$

Here, we introduce the conventional KBI in the grand canonical ensemble, defined as

$$G_{ij} = V\frac{\langle \delta N_i \delta N_j\rangle_{\{\mu_1\}} - \delta_{ij}\langle N_i\rangle_{\{\mu_1\}}}{\langle N_i\rangle_{\{\mu_1\}}\langle N_j\rangle_{\{\mu_1\}}} \tag{C3b}$$

Using eq C3b, eq C3a can be expressed as

$$\begin{aligned}
&\langle \delta N_2 \delta N_2\rangle_{\{N_1\}} - \langle N_2\rangle_{\{N_1\}} \\
&= \frac{\langle N_2\rangle^2}{V}\left(G_{11} + G_{22} - 2G_{12} + \frac{V}{\langle N_1\rangle}\right)
\end{aligned} \tag{C3c}$$

This leads to the following transformation rule between the pseudo-KBI in $\{T, P, N_1, \mu_2\}$ (eq B2b) and the conventional KBI in $\{T, V, \mu_1, \mu_2\}$

$$G'_{22} = G_{11} + G_{22} - 2G_{12} + \frac{V}{\langle N_1\rangle} \tag{C4a}$$

This can easily be generalized as

$$G'_{u,22} = G_{u,11} + G_{u,22} - 2G_{u,12} + \frac{V}{\langle N_1\rangle_u} \tag{C4b}$$

Thus, when expressed in the grand canonical ($\{T, V, \mu_1, \mu_2\}$) ensemble, the pseudo-KBI signifies the net self-interaction, i.e., the difference between the self (solvent−solvent, G_{11}, and solubilizer−solubilizer, G_{22}) and mutual (solvent−solubilizer,

https://doi.org/10.1021/acs.jpcb.4c01582
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G_{12}) interactions. The presence of $V/\langle N_1\rangle$ in eq C4a (or $V/\langle N_1\rangle_u$ in eq C4b) can be justified by considering a system in which species 2 interacts weakly with itself as well as with species 1, such that $G_{22} \simeq 0$ and $G_{12} \simeq 0$. Since $G_{11} \simeq -V/\langle N_1\rangle$ for pure solvent,[19] this non-interacting solubilizer example leads to $G'_{22} = G_{11} + G_{22} - 2G_{12} + V/\langle N_1\rangle \simeq 0$.

Kirkwood–Buff χ

Following our previous papers,[43,44] here we introduce the Kirkwood–Buff (KB) χ parameter as the measure of self-interaction as

$$\chi = \frac{\langle N_1\rangle}{V}(G_{11} + G_{22} - 2G_{12}) \tag{C5a}$$

through which eq C3c can be expressed as

$$\langle \delta N_2 \delta N_2\rangle_{\{N_1\}} - \langle N_2\rangle_{\{N_1\}} = \frac{\langle N_2\rangle^2}{N_1}(\chi + 1) \tag{C5b}$$

Through eqs C5a and C5b, together with their inhomogeneous counterparts and the $a_2 \simeq x_2 \simeq \frac{\langle N_2\rangle}{\langle N_1\rangle}$ at $a_2 \to 0$, B_0 in eq B2a can be rewritten as

$$B_0 = K_e^2\langle N_1\rangle_u(\chi_u + 1) - \langle N_1\rangle(\chi_0 + 1) \tag{C6a}$$

where K_e is the equilibrium constant for the swapping of "a solubilizer in bulk" and "a solvent in solute's vicinity", defined as

$$K_e = \frac{K_2}{K_1}, \quad K_1 = \frac{\langle N_1\rangle_u}{\langle N_1\rangle}, \quad K_2 = \frac{\langle N_2\rangle_u}{\langle N_2\rangle} \tag{C6b}$$

where K_1 and K_2 are the bulk-to-solute vicinity exchange constant of the solvent and solubilizer, respectively. Consequently, B_0 contains the effect of solute-induced enhancement of self-interaction, but the presence of $\langle N_1\rangle_u$ and $\langle N_1\rangle$ complicates its interpretation.

A simpler interpretation can be obtained for $\frac{B_0}{A_0}$. Combining eq C6a with eqs B1a and C6b yields

$$\frac{B_0}{A_0} = \frac{K_e K_2(\chi_u + 1) - (\chi_0 + 1)}{K_2 - 1} \tag{C7}$$

Now, eq C7 does not contain $\langle N_1\rangle_u$ and $\langle N_1\rangle$. It signifies the enhancement of self-interactions (i.e., KB χ) around the solute from the bulk.

The Margules parameter, α, has also been given a statistical thermodynamic interpretation. Leaving the derivation to our recent papers,[25,70] here we emphasize that α can also be expressed in terms of the bulk Kirkwood–Buff χ parameter as

$$\alpha = \frac{\chi_0}{2} \tag{C8}$$

through which the expansion of a_2 in the power series of x_2 (eq B8) can be rewritten as

$$a_2 = x_2 - \chi_0 x_2^2 + \cdots \tag{C9}$$

Thus, the Kirkwood–Buff χ plays a central role in the nonlinear term of solubilization isotherms.

APPENDIX D ALTERNATIVE EXPRESSION FOR B/A

This appendix provides an alternative expression for B/A in the homogeneous ensemble. Our starting point is the fluctuation expressions of A and B (eqs B1a and B2a), from which we obtain

$$\frac{B}{A} = \left(\frac{1}{a_2}\frac{(\langle \delta N_2 \delta N_2\rangle_u - \langle N_2\rangle_u) - (\langle \delta N_2 \delta N_2\rangle - \langle N_2\rangle)}{\langle N_2\rangle_u - \langle N_2\rangle}\right)_{a_2\to 0} \tag{D1a}$$

with

$$\langle N_2\rangle_u - \langle N_2\rangle = \frac{\langle \delta N_2 \delta N_u\rangle}{\langle N_u\rangle} \tag{D1b}$$

based on the definition of the mean in the inhomogeneous ensemble, $\langle N_2\rangle_u = \langle N_2 N_u\rangle/\langle N_u\rangle$. Our goal is to simplify eq D1a. The first step is to use (for derivation, see below)

$$\langle \delta N_2 \delta N_2\rangle_u - \langle \delta N_2 \delta N_2\rangle = \frac{\langle \delta N_2 \delta N_2 \delta N_u\rangle}{\langle N_u\rangle} - \left(\frac{\langle \delta N_2 \delta N_u\rangle}{\langle N_u\rangle}\right)^2 \tag{D2}$$

through which eq D1a can be rewritten with the help of eq D1b, as

$$\frac{B}{A} = \left(\frac{1}{a_2}\frac{\langle \delta N_u \delta N_2 \delta N_2\rangle - \langle \delta N_u \delta N_2\rangle}{\langle \delta N_u \delta N_2\rangle} - \frac{1}{a_2}\frac{\langle \delta N_2 \delta N_u\rangle}{\langle N_u\rangle}\right)_{a_2\to 0} \tag{D3}$$

Combining eqs D3 and 4b, we obtain

$$\frac{B}{A} + A = \left(\frac{1}{a_2}\frac{\langle \delta N_u \delta N_2 \delta N_2\rangle - \langle \delta N_u \delta N_2\rangle}{\langle \delta N_u \delta N_2\rangle}\right)_{a_2\to 0} = c_1^\circ V\left(\frac{\langle \delta N_u \delta N_2 \delta N_2\rangle - \langle \delta N_u \delta N_2\rangle}{\langle \delta N_u \delta N_2\rangle\langle N_2\rangle}\right)_{a_2\to 0} \tag{D4}$$

Proof of Equation D2

From the definition of δ, the left-hand side of eq D2 can be rewritten as

$$\langle \delta N_2 \delta N_2\rangle_u - \langle \delta N_2 \delta N_2\rangle = \langle N_2^2\rangle_u - \langle N_2\rangle_u^2 - \langle N_2^2\rangle + \langle N_2\rangle^2 \tag{D5a}$$

Using the definition of the inhomogeneous mean

$$\langle N_2^2\rangle_u - \langle N_2\rangle_u^2 = \frac{\langle N_u N_2^2\rangle}{\langle N_u\rangle} - \left(\frac{\langle N_u N_2\rangle}{\langle N_u\rangle}\right)^2 \tag{D5b}$$

Combining eqs D5a and D5b, we obtain

$$\langle \delta N_2 \delta N_2\rangle_u - \langle \delta N_2 \delta N_2\rangle = \frac{\langle N_u N_2^2\rangle}{\langle N_u\rangle} - \left(\frac{\langle N_u N_2\rangle}{\langle N_u\rangle}\right)^2 - \langle N_2^2\rangle + \langle N_2\rangle^2 \tag{D5c}$$

The first term of the right-hand side of eq D2 becomes

$$\frac{\langle \delta N_2 \delta N_2 \delta N_u\rangle}{\langle N_u\rangle} = \frac{1}{\langle N_u\rangle}\langle (N_2 - \langle N_2\rangle)(N_2 - \langle N_2\rangle)(N_u - \langle N_u\rangle)\rangle = \frac{\langle N_u N_2^2\rangle}{\langle N_u\rangle} - 2\frac{\langle N_u N_2\rangle\langle N_2\rangle}{\langle N_u\rangle} - \langle N_2^2\rangle + 2\langle N_2\rangle^2 \tag{D6}$$

From eqs D5c and D6, straightforward algebra yields

https://doi.org/10.1021/acs.jpcb.4c01582
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$$\langle \delta N_2 \delta N_2 \rangle_u - \langle \delta N_2 \delta N_2 \rangle - \frac{\langle \delta N_2 \delta N_2 \delta N_u \rangle}{\langle N_u \rangle} = -\left(\frac{\langle N_u N_2 \rangle}{\langle N_u \rangle} - \langle N_2 \rangle \right)^2 \quad \text{(D7)}$$

which, via eq D1b, is equivalent to eq D2.

APPENDIX E LOCAL FLUCTUATION IN THE MOLE-FRACTION SOLUBILITY SCALE

Here, we demonstrate that the use of the mole-fraction solubility scale leads to a more complicated version of eq 1b. Let us start with the definition of solubility in the mole-fraction scale, written as eq 11. Here, we adopt the constant N_1 ensemble (to be consistent with eq 1b). Our goal is to derive a mole-fraction version of eq 1b. The first step is to carry out a μ_2-derivative of eq 11, which yields

$$\begin{aligned} \frac{\partial x_u}{\partial \mu_2} &= \frac{1}{(N_1 + \langle N_2 \rangle + \langle N_u \rangle)^2} \times \left[(N_1 + \langle N_2 \rangle + \langle N_u \rangle) \frac{\partial \langle N_u \rangle}{\partial \mu_2} - \langle N_u \rangle \left(\frac{\partial \langle N_2 \rangle}{\partial \mu_2} + \frac{\partial \langle N_u \rangle}{\partial \mu_2} \right) \right] \\ &= \frac{1}{(N_1 + \langle N_2 \rangle + \langle N_u \rangle)^2} \left[(N_1 + \langle N_2 \rangle) \frac{\partial \langle N_u \rangle}{\partial \mu_2} - \langle N_u \rangle \frac{\partial \langle N_2 \rangle}{\partial \mu_2} \right] \\ &= \frac{1}{k_B T} \frac{(1 - x_u)\langle \delta N_u \delta N_2 \rangle - x_u \langle \delta N_2 \delta N_2 \rangle}{N_1 + \langle N_2 \rangle + \langle N_u \rangle} \end{aligned} \quad \text{(E1)}$$

This leads to eq 12.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This study originated as "homework" from Charles Hansen about a decade ago; S.S. apologizes for the time taken while thanking him for his insights. The authors are grateful to Steven Abbott for his helpful comments on their manuscript. The authors thank Julie Lynch, Will Heamen, and Aro Nugawela for the discussions. S.S. acknowledges the travel fund from the Steven Abbott TCNF Ltd. N.M. is grateful to the Fugaku Supercomputer Project (Nos. JPMXP1020230325 and JPMXP1020230327) and the Data-Driven Material Research Project (No. JPMXP1122714694) from the Ministry of Education, Culture, Sports, Science, and Technology and to Maruho Collaborative Project for Theoretical Pharmaceutics.

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