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Article

Multiplicativity in Solubility Isotherms

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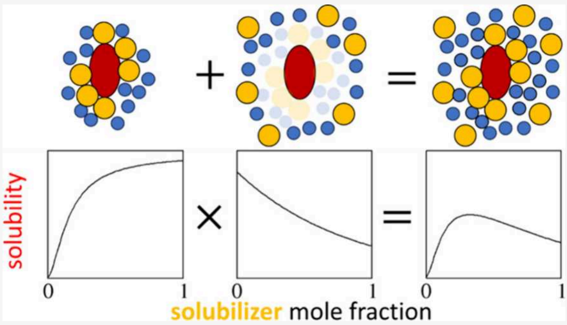
ABSTRACT: With the help of isotherm equations, how solubility changes with solubilizer concentration ("solubility isotherm") can reveal the underlying interactions. However, despite their success in elucidating the mechanisms of hydrotropy (via the cooperative (sigmoidal) isotherm) and synergistic solvation (via the quadratic (bell-shaped) isotherm), these simple statistical thermodynamic isotherm equations alone are insufficient for more complex isotherms that combine their features. Here, we show (i) how simple isotherms can be combined via the isotherm multiplicativity rule founded on the excess number relationship (i.e., solubilizer concentration dependence of the solubilizer excess number around a solute) and (ii) how (i) leads to successful modeling of complex solubility isotherms, capturing that cooperative solute−solubilizer association, in turn, induces the exclusion of solubilizers from the already crowded solute's locality at higher concentrations. Moreover, we will demonstrate that both the cooperative and quadratic solubility isotherms can be derived directly from the excess number relationship, establishing it not only as the basis for the multiplicativity rule but also as the fundamental relationship for simple and complex solubility isotherms.



■ INTRODUCTION

The problem of poor solubility can often be overcome by the addition of solubilizers. Several subcategories of this strategy have been known in the literature (Figure 1): (a) synergistic solvation in the mixture of poor solvents (Figure 1(a); with "poor" being a common terminology signifying low solvation capacity in polymer chemistry[1,2] and the solubility of small molecules[3]),[4−10] (b) hydrotropy by the addition of hydrotropes (i.e., short amphiphilic solubilizers that do not exhibit critical micelle concentration; Figure 1(b)),[11−19] and (c) micellar solubilization by surfactants (Figure 1(c)).[20−24] Across these subcategories, how solubility changes with solubilizer concentration (i.e., "the solubility isotherm"[25]) is the key not only to quantifying the efficacy of a solubilizer (a general term adopted for cosolvents, hydrotropes, and micelles) on a solute but also to understanding the mechanism of solubilization.[25,26]

Our goal is to elucidate the solubilization mechanism underlying a solubility isotherm. As a first step toward this goal, solubility isotherm equations must be derived systematically from the fundamental principles that govern solubilization, with each of their parameters having a clear link to the underlying physical process on a microscopic basis.[25] Let us first summarize the fundamental principles that govern the derivatives of the solubilization isotherm (when plotted against the activity of solubilizers): (i) the first derivative (isotherm gradient) represents preferential solute-solubilizer interaction,[27,28] according to the Kirkwood-Buff theory[29−36] and (ii) the second derivative (isotherm curvature) comes from the change of self-association around the solute, according to the cooperative solubilization theory.[37,38] We emphasize that the derivatives (i) and (ii) result from a statistical (ensemble) average of all the molecular interactions in the solution. In this paper, (i) and (ii) in combination will be referred to as the fluctuation theory.

From the fluctuation theory alone, we have derived the quadratic isotherm, which was successful in capturing the bell-shaped isotherm (Figure 1(a)), with direct mechanistic insights drawn from its parameters that capture (i) and (ii).[25] However, the quadratic isotherm is incapable of modeling sigmoidal-shaped solubility isotherms frequently observed for solubilization by hydrotropes[17,22,39,40] whose signatures are a sudden onset of solubilization (at the minimum hydrotrope concentration) and the subsequent plateau of solubilization around a few molars of hydrotropes (Figure 1(b)).[26] Such a sigmoidal shape can instead be modeled by the cooperative isotherm, successfully applied to hydrotropy.[26]

However, experimental solubility isotherms are sometimes more complex in shape than quadratic or cooperative isotherms.[41−43] As illustrative examples, we have chosen

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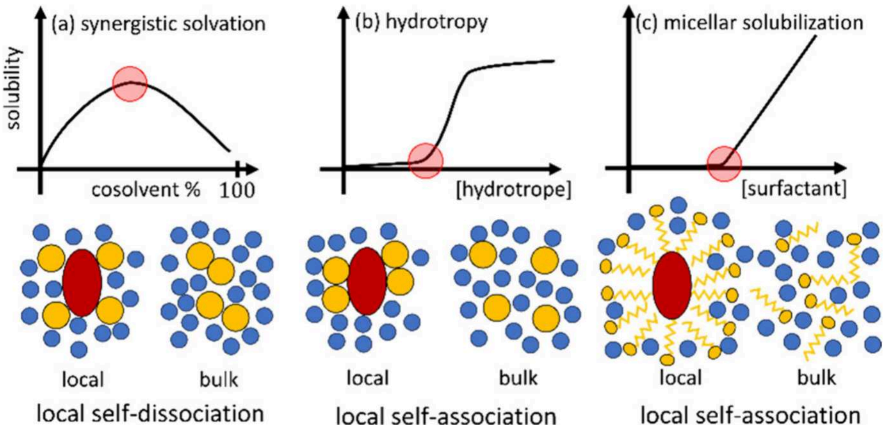

Figure 1. Top. Typical functional shapes for the solubility isotherm (i.e., how solubility changes with solubilizer concentration) of (a) synergistic solvation, (b) hydrotropy, and (c) micellar solubilization. Bottom. The mechanistic insights underlying the isotherms clarified so far: (a) the enhanced self-dissociation in the solubilizer (orange)-solvent (blue) mixture around the solute, (b) the enhanced self-association of the solubilizer (orange) around the solute, and (c) the enhanced self-association in the micelle (orange)-solvent mixture around the solute.

syringic acid solubilization in water by 1,2-alkanediols (Figures 2 and 3)[44] because the functional shape of the isotherm changes as the alkyl group becomes longer, from near-quadratic (ethanediol), through cooperative (propanediol), and finally to a more complex shape (longer alkyls) which combines the features of (1) sigmoidal solubilization at lower solubilizer concentrations and (2) declining solubilization at higher solubilizer concentrations. Neither the cooperative nor quadratic isotherm alone can capture such complex isotherm shapes. The cooperative model[26] can reproduce (1) but not (2), as shown in Figure 2. The quadratic isotherm,[25] when restricted narrowly to low solubilizer concentrations, may fit (1), yet modeling the overall isotherm shape is beyond its capacity (Figure 3).

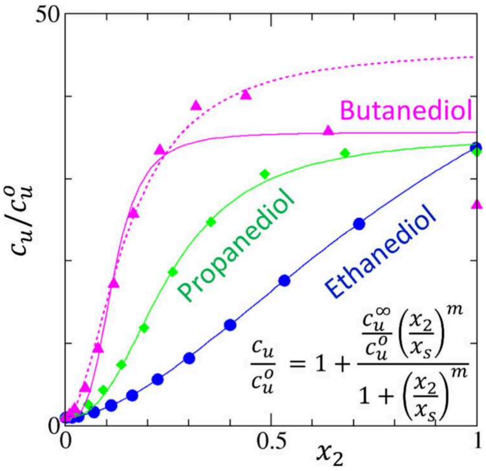

Figure 2. Complex solubility isotherms of syringic acid (solute) in water (solvent) with the concentrations of solubilizers, i.e., 1,2-Ethanediol (blue circles), 1,2-Propandiol (green diamonds), and 1,2-Butanediol (magenta triangles), from the experimental data published by Abranches et al.[44] The solubility (c_u) relative to the pure water value (c_u^o) is expressed as a function of solubilizer mole-fraction (x_2). The fitting by the cooperative solubility isotherm (eq 9, right bottom within the figure) works for 1,2-Ethanediol (blue solid line; (m, x_s, c_u^∞/c_u^o) = (1.7,0.99,66)) and 1,2-Propandiol (green solid line; (2.5,0.25,35)) but fails for 1,2-Butanediol (magenta solid line; (3.4,0.12,36)) or strictly limited to the lower solubilizer concentrations (magenta dotted line; (1.9,0.15,46)).

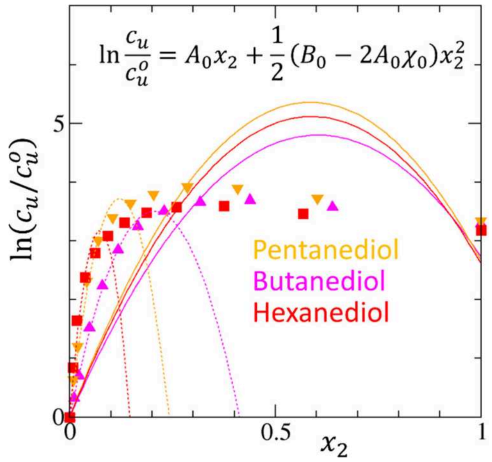

Figure 3. Complex solubility isotherms of syringic acid (solute) in water (solvent) with the concentrations of solubilizers, i.e., 1,2-Butanediol (magenta triangles up), 1,2-Pentanediol (orange triangles down), and 1,2-Hexanediol (red squares), from the experimental data published by Abranches et al.[44] The logarithmic solubilization ($\ln(c_u/c_u^o)$) is expressed as a function of solubilizer mole-fraction (x_2). The global fitting by the quadratic solubility isotherm (eq 5, top within the figure) fails for 1,2-Butanediol (magenta solid line; (A_0, $(B_0 - 2A\chi_0)/2$) = (16,−13)), 1,2-Pentanediol (orange solid line; (18,−16)), and 1,2-Hexanediol (red solid line; (17,−15)). The local fitting for $x_2 \ll 1$ can be done for a strictly limited range ((34,−82), (61,−250), and (87,−590) for the magenta, orange, and red dotted lines).

How can we model complex solubility isotherms that combine the features of simple isotherms? This question is important because isotherms with complex functional shapes are not restricted to alkanediols[44] but are observed also in the wider classes of solubilizers (e.g., glycerol ethers,[42] cyrene,[41,43,45] and ionic liquids[46]). The hint to answer this question comes from a similar problem that was solved recently for *sorption* isotherms: the key was the discovery of the isotherm multiplicativity rule for "conditional" sorption consisting of (1) unconditional (initial) process and (2) conditional process subject to (1).[47] We will demonstrate in this paper that this new approach can be carried over to solubilization through a formal analogy between solvation and sorption,[36,48,49] leading to the discovery of a new class of solubilization phenomenon. To achieve this goal, we need to establish a universal theoretical foundation for simple and complex *solubility* isotherms, based on the statistical thermodynamic fluctuation theory, in a manner parallel to *sorption*. Thus, the objectives of this paper are

I. to derive the cooperative solubility isotherm directly from the fluctuation theory (as was possible for the quadratic isotherm);
II. to show solubility isotherm multiplicativity as the natural consequence of the fluctuation theory;
III. to combine I and II to capture complex isotherms as the conditional solubilization processes.

Achieving these objectives will not only provide mechanistic insights into complex solubility isotherms (objective III) but also furnish a universal theoretical foundation for simple and complex isotherms (objectives I and II). Mirroring the recent progress in sorption,[47,50−52] simple solubility isotherms will be derived systematically by solving differential equations and complex solubility isotherms can be constructed based on a multiplication of simple solubility isotherms,[47] both directly based on the fundamental principles of the statistical thermodynamic fluctuation theory.

■ THEORY

Statistical Thermodynamic Fluctuation Theory. Here, we establish the theoretical foundation for achieving our three objectives (see Introduction). We begin by setting up our system: a solute (which can be a small molecule or a macromolecule; denoted as species u) in a mixture consisting of solvent (species 1, such as water, yet can be used for any solvents) and solubilizer (species 2, which can be electrolytes and nonelectrolytes). The solubilizer has many synonyms (e.g., cosolvents, cosolutes, hydrotropes, osmolytes, denaturants, and stabilizers).[53] Throughout this paper, we adopt a $\{T, P, N_1, \mu_2, \mu_u\}$ ensemble.[54,55] (Note that converting it to the grand canonical ensemble $\{T, V, \mu_1, \mu_2, \mu_u\}$ underlying the Kirkwood-Buff theory[29−36] can be carried out straightforwardly via statistical variable transformation, as outlined in Appendix A of ref 25) The constancy of μ_u emphasizes the phase equilibrium of the solute between solution and its pure phase that underlies eq 1, making it applicable to low and high solubilities alike.[38]

Let us focus on the solubility of a solute (c_u, in the molarity scale[56]) and write down an exact, approximation-free relationship (which was derived as eq 1 of ref 25) as to how it depends on the solubilizer activity (a_2),

$$\left(\frac{\partial \ln c_u}{\partial \ln a_2}\right)_{T,P,N_1;\mu_u} = N_{u2} = \langle N_2\rangle_u - \langle N_2\rangle \tag{1}$$

where N_{u2} is the excess number of solubilizers around a probe solute, which is defined as the difference between $\langle N_2\rangle_u$ (the mean number of the solubilizer molecules in an inhomogeneous ensemble in the presence of a solute molecule whose center of mass is fixed at the origin) and $\langle N_2\rangle$ (in the homogeneous ensemble of bulk solution i.e., a mixture of water, solubilizer, and solute molecules). For electrolyte solutions, N_{u2} refers to the excess number as combined contributions from cation and anion, following the common KB approach to ionic species.[57,58] (Note that cation and anion contributions are combined due to the charge neutrality of the solution system.[57−59]) Hereafter, eq 1, our fundamental equation, will be referred to as the *excess number relationship*.

Not only the gradient (eq 1) but also the curvature is an important signature of an isotherm, such as its concavity or convexity; a sudden onset of solubilization,[37,38] which is an important characteristic of hydrotropy, can also be considered as the isotherm convexity at low solubilizer concentrations.[25] The cooperative solubilization theory links the curvature (second derivative) to the local-bulk difference in solubilizer-solubilizer interaction, via[37,38]

$$\left(\frac{\partial^2 \ln c_u}{\partial [\ln a_2]^2}\right)_{T,P,N_1;\mu_u} = \langle \delta N_2 \delta N_2\rangle_u - \langle \delta N_2 \delta N_2\rangle \tag{2}$$

where $\langle \delta N_2 \delta N_2\rangle_u$ is the local solubilizer number fluctuation around the solute and $\langle \delta N_2 \delta N_2\rangle$ is that in the bulk solution. Through eq 2, how solubilizer-solubilizer number correlation is enhanced locally (around the solute) as compared to the bulk determines the ln-ln curvature of the solubility isotherm.

Thus, the fluctuation theory reveals solubilizer interactions underlying a solubility isotherm (how c_u depends on the solubilizer concentration) through its first and second derivatives.

Deriving the Quadratic Isotherms from the Fluctuation Theory. As an important preparation for achieving Objective I, it is imperative to clarify what it means to derive an isotherm equation directly from the fluctuation theory. To identify the requirements to achieve this goal, we take the quadratic isotherm as an example.

Our theoretical foundation is the *excess number relationship* (eq 1). Here, we rewrite it in a form in closer conformity to an isotherm, using a_2 as its variable instead of $\ln a_2$, as

$$\left(\frac{\partial \ln c_u}{\partial a_2}\right)_{T,P,N_1;\mu_u} = \frac{N_{u2}}{a_2} \tag{3a}$$

This representation of the excess number relationship (eq 3a) is combined with a *characteristic equation*, which expresses how the excess number (N_{u2}) changes along solubilization.[25] Here, we adopt a series expansion around a reference activity, $a_2 = a_r$,

$$\frac{N_{u2}}{a_2} = A_r + B_r(a_2 - a_r) + \cdots \tag{3b}$$

as the characteristic equation, with its coefficients, A_r and B_r, that can be evaluated at that point.[25] (Note that eq 3b is a generalization of our recent expression that was restricted to $a_r = 0$.[25]) To derive a solubility isotherm, it is necessary to combine the excess number relationship (eq 3a) and the characteristic equation (eq 3b),

$$\left(\frac{\partial \ln c_u}{\partial a_2}\right)_{T,P,N_1;\mu_u} = A_r + B_0(a_2 - a_r) + \cdots \tag{3c}$$

and to solve the combination (eq 3c) as a differential equation. Integrating eq 3c yields

$$\ln \frac{c_u}{(c_u)_r} = A_r(a_2 - a_r) + \frac{B_r}{2}(a_2 - a_r)^2 + \cdots \tag{4}$$

which is the quadratic solubility isotherm around $a_2 = a_r$.

Once a solubility isotherm has been derived, the next task is to give each of its parameters a physical interpretation. In the case of the quadratic isotherm (eq 4), its parameters, A_r and B_r, can be interpreted using the fundamental relationships of the fluctuation theory (eqs 1 and 2). As clarified in Supporting

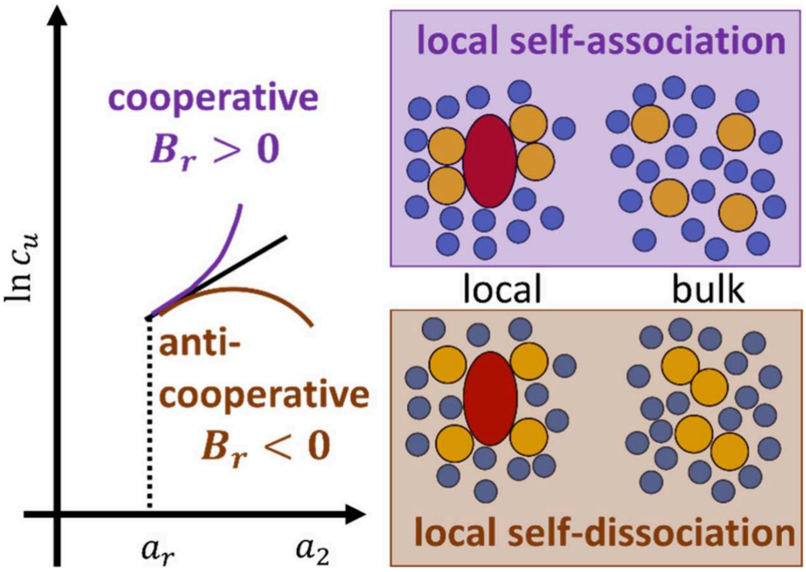

Figure 4. Left. A schematic representation of the second-order gradient of the quadratic isotherm (eq 4). Right. Top: cooperativity ($B_r > 0$) represents the enhancement of self-association of the solubilizer (orange) around the solute compared to the bulk. Bottom: anticooperativity represents the weakening of self-association (=self-dissociation) of solubilizers around the solute compared to the bulk.

Information: Section A, A_r signifies the preferential solute-solubilizer interaction and B_r represents the enhancement of self-interaction by the solute, both defined around $a_2 = a_r$ (Figure 4). We emphasize that the expansion (eq 4), alongside the interpretations of its parameters A_r and B_r, is an exact relationship valid for any solubility isotherms, while truncating eq 4 and using it over a finite range of a_2 is an approximation.

The quadratic isotherm, when expanded around $a_r = 0$ and truncated at a_2^2, is a particularly convenient approximation arising from eq 4. Changing its variable from a_2 to x_2 (see eq 7a of ref 25) leads to

$$\ln\frac{c_u}{c_u^o} = A_0x_2 + \frac{(B_0 - 2\chi_0A_0)}{2}x_2^2 + \cdots \tag{5}$$

with A_0 and B_0 defined at $a_r = 0$, which is also true for χ_0, i.e., the Kirkwood-Buff χ parameter of the bulk solution (see Supporting Information: Section A for its origin and definition). This form of the quadratic isotherm (eq 5) was useful in modeling synergistic solvation isotherms.[25] (In Results and Discussion, in the subsection entitled "Capturing Complex Solubility Isotherms via the Multiplicativity Principle (Objective III)", retaining the first term of eq 5 will be shown to be sufficient for the solubilization of syringic acid by 1,2-alkanediols.)

Thus, with the quadratic isotherm as an example, we have clarified the general procedure of deriving a solubility isotherm from the fluctuation theory, which involves: (i) combining the excess number relationship and the characteristic equation to form a differential equation; (ii) solving the differential equation; and (iii) to provide an interpretation for its parameters.

Deriving the Cooperative Isotherm from the Fluctuation Theory (Objective I). Here, we derive the cooperative isotherm[26] directly from the fluctuation theory. Its original derivation (starting with the partition functions of semi-open ensembles[26]) was achieved with significant mathematical labor, leading to a limited clarity of the physical basis of this isotherm. Here, our novel systematic approach, based on a combination of the excess number relationship and the characteristic equation (see Statistical Thermodynamic Fluctuation Theory), will lead to a clarification of the physical picture underlying the cooperative isotherm.

First, we determine the functional shape of the characteristic equation for the cooperative isotherm. The signatures of the cooperative isotherm are (nearly) zero isotherm gradient before the onset of solubilization and at saturation.[26] This can be captured most succinctly by a quadratic equation which becomes zero at c_u^o (solubility in the absence of solubilizers) and c_u^∞ (saturation solubility), as

$$\left(\frac{\partial c_u}{\partial \ln a_2}\right)_{T,P;\mu_u} = \eta(c_u - c_u^0)(c_u^\infty - c_u) \tag{6a}$$

where η is a constant, whose expression will soon be determined, and why adopting $\ln a_2$ as the variable will be clarified shortly. The constant η must be positive for the isotherm to exhibit a maximum gradient between c_u^o and c_u^∞. Comparing eqs 6a and 1, the simplest functional form for the characteristic relationship of cooperative solubilization is

$$N_{u2} = \eta\frac{(c_u - c_u^o)(c_u^\infty - c_u)}{c_u} \tag{6b}$$

The next step is to solve the differential equation that combines the excess number relationship (eq 1) and the characteristic equation (eq 6b), which is already given as eq 6a.

Second, we determine the precise mathematical form of η, in preparation for solving the differential equation. This can be accomplished by considering the limiting behavior of eq 6a at the onset of solubilization, $c_u \simeq c_u^o$. Expanding the right-hand side of eq 6a in terms of $c_u - c_u^o$ and taking up to its first order, we obtain

$$\left(\frac{\partial c_u}{\partial \ln a_2}\right)_{T,P;\mu_u} = \eta(c_u^\infty - c_u^o)(c_u - c_u^0) \tag{7a}$$

In order for eq 7a to represent the cooperative association of m solubilizer molecules, η must be

$$\eta = \frac{m}{c_u^\infty - c_u^o} \tag{7b}$$

This can be justified easily by integrating eq 7a under eq 7b, namely,

$$\left(\frac{\partial c_u}{\partial \ln a_2}\right)_{T,P;\mu_u} = m(c_u - c_u^0) \tag{7c}$$

which leads, via Supporting Information: Section B, to

$$c_u = c_u^o + K' a_2^m \tag{7d}$$

Indeed, eq 7d expresses the cooperative association of m solubilizers to the solute with K' (originally an integration constant) as the association constant.

Having determined η (eq 7b), the characteristic equation for the cooperative isotherm can be expressed as

$$N_{u2} = m\frac{(c_u - c_u^o)(c_u^\infty - c_u)}{c_u(c_u^\infty - c_u^o)} \tag{8a}$$

which can be solved in combination with the excess number relationship (eq 1). As detailed in Supporting Information: Section B, the separation of variables, followed by partial fraction decomposition, leads to

$$c_u - c_u^o = \frac{(c_u^\infty - c_u^o)Ka_2^m}{1 + Ka_2^m} \tag{8b}$$

which is indeed the cooperative solubility isotherm,[26] previously derived through significant mathematical labor. Note that eq 8b reduces to eq 7d at $c_u \simeq c_u^o$ (Supporting Information: Section B), hence the constant K still signifies the cooperative association constant.

The cooperative solubility isotherm (eq 8b) can be expressed in a more compact form:

$$\frac{c_u}{c_u^o} = \frac{1 + \frac{c_u^\infty}{c_u^o}\left(\frac{a_2}{a_s}\right)^m}{1 + \left(\frac{a_2}{a_s}\right)^m} \tag{8c}$$

with simple algebra, as well as the introduction of the solubilizer activity at the steepest point of the isotherm (see Appendix A of ref 60) via

$$a_s = K^{-1/m} \tag{8d}$$

which is convenient for locating the parameter a_s visually on the isotherm plot.[50,60] Now we make an approximation to facilitate experimental data analysis. When the increase of c_u from c_u^o to c_u^∞ takes place in a relatively narrow range of solubilizer concentration around the solubilizer mole fraction x_s (Supporting Information: Section C), we can express the cooperative isotherm as the function of x_2 as

$$\frac{c_u}{c_u^o} = \frac{1 + \frac{c_u^\infty}{c_u^o}\left(\frac{x_2}{x_s}\right)^m}{1 + \left(\frac{x_2}{x_s}\right)^m} \tag{9}$$

which has been applied to model the sigmoidal solubility isotherms for hydrotropes.[26]

Thus, we have demonstrated that the cooperative solubility isotherm can be derived directly from the excess number relationship (eq 1) in combination with the characteristic relationship (eq 6a or 6b) that captures the cooperative association of solubilizers on the solute (Objective I).

Multiplicativity in Solubility Isotherms (Objective II). So far, the two classes of simple solubility isotherms, quadratic (see Deriving the Quadratic Isotherms from the Fluctuation Theory) and cooperative (see Deriving the Cooperative Isotherms from the Fluctuation Theory (Objective I)), have been derived systematically by combining the excess number relationship (eq 1) and the characteristic equations (eq 3b for the quadratic and eq 8a for the cooperative). The simple isotherms alone (quadratic and cooperative) could not reproduce complex solubility isotherms (see Figures 2 and 3). First, the cooperative isotherm (eq 9) cannot capture post-saturation solubility decreases (Figure 2). Second, the quadratic isotherm (eq 5) cannot reproduce near-plateau isotherm shapes (Figure 3). Third, incorporating higher-order terms of x_2 beyond quadratic results in the fitting coefficients with increasing magnitude, alternating signs, and little physical insights.[26,61] These limitations of simple isotherms necessitate a novel approach to capturing isotherms with complex functional shapes.

Here, we show how complex isotherms, that combine the features of simple isotherms, can be constructed by isotherm multiplicativity. We will show that isotherm multiplicativity can be derived directly from that excess number relationship (eq 1; Objective III). Isotherm multiplicativity manifests when solubilization consists of unconditional and conditional processes, denoted by I and II/I, where the notation II/I signifies "the process II conditional to the occurrence of I". With this preparation, our starting point is the fundamental relationship on the solvation free energy at the completion of process II, μ_u^{*II},

$$\mu_u^{*II} = -RT\ln\frac{Y_u^{II}}{Y} \tag{10a}$$

in terms of the partition functions Y in the $\{T, P, N_1, \mu_2, \mu_u\}$ ensemble and Y_u^{II} in the inhomogeneous ensemble, $\{u\colon T, P, N_1, \mu_2, \mu_u\}$, which contains a solute molecule whose center of mass is fixed at the origin. Through the introduction of Y_u^I (the partition function of the process I), the solvation free energy μ_u^{II*} can be expressed as

$$\mu_u^{*II} = \mu_u^{*I} + \mu_u^{*II/I} \tag{10b}$$

with unconditional and conditional solvation free energies, μ_u^{*I} and $\mu_u^{*II/I}$, defined via

$$\mu_u^{*I} = -RT\ln\frac{Y_u^I}{Y}, \qquad \mu_u^{*II/I} = -RT\ln\frac{Y_u^{II}}{Y_u^I} \tag{10c}$$

by virtue of the basic property of the logarithmic function. The additivity of solvation free energies (eqs 10b and 10c) leads to

$$\left(\frac{\partial \ln c_u}{\partial \ln a_2}\right)_{T,P,N_1;\mu_u} = \left(\frac{\partial \ln c_u^I}{\partial \ln a_2}\right)_{T,P,N_1;\mu_u} + \left(\frac{\partial \ln c_u^{II/I}}{\partial \ln a_2}\right)_{T,P,N_1;\mu_u} \tag{11a}$$

which means that the solubility isotherm is multiplicative

$$c_u = c_u^I c_u^{II/I} \tag{11b}$$

Note that c_u^I carries the concentration units whereas $c_u^{II/I}$ is unitless. The isotherms for the unconditional and conditional processes can be derived by their respective excess number relationships,

$$\left(\frac{\partial \ln c_u^I}{\partial \ln a_2}\right)_{T,P,N_1;\mu_u} = \langle N_2^I\rangle_u - \langle N_2^I\rangle \tag{11c}$$

$$\left(\frac{\partial \ln c_u^{II/I}}{\partial \ln a_2}\right)_{T,P,N_1;\mu_u} = \langle N_2^{II/I}\rangle_u - \langle N_2^{II/I}\rangle \tag{11d}$$

in combination with the appropriate characteristic equations.

Thus, the isotherm multiplicativity principle (eq 11b) has been derived only from the basic mathematical property of logarithm (eq 11a).

■ RESULTS AND DISCUSSION

Capturing Complex Solubility Isotherms via the Multiplicativity Principle (Objective III). We have established the excess number relationship (eq 1) as the common foundation for the quadratic and cooperative isotherms (see Deriving the Cooperative Isotherm from the Fluctuation Theory (Objective I)) and derived the multiplicativity approach to combining simple isotherms (see Multiplicativity in Solubility Isotherms (Objective II)). Here, we focus on the following solubilization mechanism: the cooperative isotherm (eq 9) as the unconditional process (step I in Multiplicativity in Solubility Isotherms (Objective II)) and preferential solute-solubilizer interaction (taking up to Ax_2 in eq 5) as the conditional process (step II/I). Combining eqs 9 and 5 via the multiplicative expression (eq 11b), we obtain

$$\frac{c_u}{c_u^o} = \left[\frac{1 + \frac{c_u^\infty}{c_u^o}\left(\frac{x_2}{x_s}\right)^m}{1 + \left(\frac{x_2}{x_s}\right)^m}\right] e^{Ax_2} \tag{12}$$

as the multiplicative solubility isotherm.

The experimental aqueous solubility isotherms of syringic acid by 1,2-alkanediols have been modeled successfully using eq 12 (Figure 5) via the multiplication of the cooperative and quadratic isotherms as the unconditional and conditional processes (Figure 6). The fitting parameters, summarized in Table 1, provide an insight into the underlying mechanism. Observed for the initial step are (i) mildly cooperative initial association ($m \simeq 2$) for ethanediol, propanediol, and butanediol, (ii) weakened cooperativity ($m < 2$) for pentanediol and hexanediol, (iii) steeper initial association for longer alkyl chains, indicated by the decreasing x_s, and (iv) the maximum solubilization, c_u^∞/c_u^o falls sharply for hexanediol which exhibits weaker local association (i.e., smaller m in Table 1) with reduced association constant ($K = x_s^{-m}$) from pentanediol due probably to an increased molecular size. For the conditional step, the exclusion of solubilizers (except ethanediol) has been observed from the negative A.

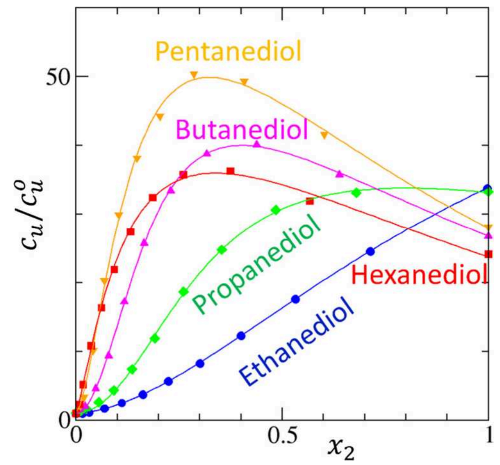

Figure 5. Multiplicative isotherm (eq 12; solid lines) can model complex solubility isotherms of syringic acid (solute) in water (solvent) by 1,2-alkanediols (solubilizers), with the fitting parameters summarized in Table 1. The experimental data, published by Abranches et al.,[44] includes 1,2-Ethanediol (blue circles), 1,2-Propandiol (green diamonds), 1,2-Butanediol (magenta triangles up), 1,2-Pentanediol (orange triangles down), and 1,2-Hexanediol (red squares) as solubilizers.

The physical picture underlying the additivity of N_{u2} (eqs 11a, 11c, and 11d), which leads to the multiplicativity of the solubility isotherm (eq 12), can be expressed schematically in Figure 7 as

1. a cooperative accumulation of solubilizers around the solute (Figure 7(a));
2. the exclusion of further solubilizers from the already crowded solute's locality (Figure 7(b)).

that correspond to c_u^I and $c_u^{II/I}$, respectively. We emphasize that the conditional isotherm, $c_u^{II/I}$, does not contribute to the overall isotherm c_u when multiplied to $c_u^I = 0$; the conditional process kicks in only when the unconditional process is operative. Intuitively speaking, solubilizer exclusion contributes to the overall isotherm only when there is a sufficient number of solubilizers cooperatively associated with a solute already.

Thus, how solubility changes along the solubilizer concentration reflects the conditional solvation processes: solubilizer self-association at lower solubilizer concentrations fills up the solute's locality with the solubilizers, excluding further solubilizers, leading to the reduction of solubility.

Self-Association in Local and Bulk. In the Theory section, we developed the following two approaches to understanding complex solubility isotherms:

A. isotherm multiplicativity (see Multiplicativity in Solubility Isotherms (Objective II)).
B. isotherm derivatives (see Statistical Thermodynamic Fluctuation Theory)

Approach A, such as the combination of the initial cooperative solubilization and the conditional solubilizer exclusion (eq 12), has led to the successful modeling of complex solubility isotherms (Figure 5). Approach B is more general than Approach A because derivatives can always be calculated from any isotherm equations as long as they are differentiable, which provides a more general understanding of the underlying solubilization mechanism, via

- the first-order derivative (isotherm gradient), A_r, representing the solute-solubilizer association;
- the second-order derivative (isotherm curvature), B_r, representing the enhancement of self-association around the solute than in the bulk

that can be calculated at reference solubilizer activity ($a_2 = a_r$) via eq 4 (Figure 4).

Our goal is to reveal the mechanism underlying the solubility peak modeled by multiplicative isotherm (eq 12). To this end, let us calculate the derivative, $\left(\frac{\partial \ln c_u}{\partial x_2}\right)_{T,P,N_1;\mu_u}$, using the

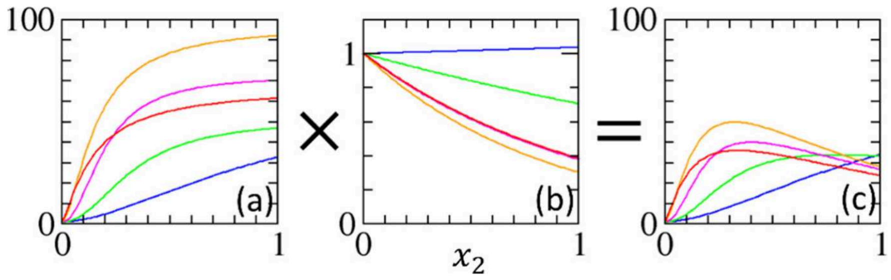

Figure 6. Contributions from (a) the cooperative solubilization and (b) preferential exclusion to (c) the multiplicative solubility isotherms for the solubilizers 1,2-Ethanediol (blue solid lines), 1,2-Propandiol (green solid lines), 1,2-Butanediol (yellow solid lines), 1,2-Pentanediol (orange solid lines), and 1,2-Hexanediol (red solid lines) calculated by eq 12.

Table 1. Fitting Parameters of Equation 12 for the Solubilization of Syringic Acid by 1,2-Alkanediols in Figure 5

solubilizer	ethanediol	propanediol	butanediol	pentanediol	hexanediol
m	1.7	2.1	2.0	1.58	1.3
x_s	0.95	0.33	0.20	0.16	0.15
c_u^{∞}/c_u^{o}	62	52	73	97	67
A	0.037	−0.35	−0.97	−1.2	−0.95

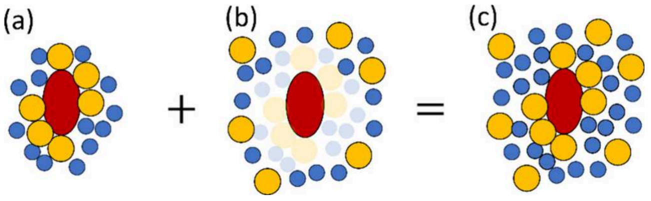

Figure 7. A schematic representation of the additivity of N_{u2} underlying isotherm multiplicativity: (a) initial association between solute (red) and solubilizer (orange), (b) conditional preferential exclusion of solubilizers from the solute, (c) the resultant isotherm as the multiplicative process of (a) and (b).

multiplicative isotherm (eq 12), which can be achieved using the characteristic equations for the unconditional and conditional isotherms (eq 4 with $B_r = 0$ and eq 8a), leading to

$$\left(\frac{\partial \ln c_u}{\partial x_2}\right)_{T,P,N_1;\mu_u} = m\frac{\left(\frac{c_u^{\infty}}{c_u^{o}} - \frac{c_u^{I}}{c_u^{o}}\right)\left(\frac{c_u^{I}}{c_u^{o}} - 1\right)}{\frac{c_u^{I}}{c_u^{o}}\left(\frac{c_u^{\infty}}{c_u^{o}} - 1\right)x_2} + A \tag{13}$$

where c_u^I refers to the cooperative isotherm as the unconditional process, which is the same as c_u in the left-hand side of eq 9. Plotting $\left(\frac{\partial \ln c_u}{\partial x_2}\right)_{T,P,N_1;\mu_u}$ via eq 13 for alkanediols for the entirety of x_2 shown in Figure 8(a) reveals complex functional shapes whose functional behavior in the entire range of x_2 cannot be captured easily via polynomials of x_2 (Supporting Information: Section D). Nevertheless, we can focus around the peak of the isotherm and elucidate its underlying mechanism, i.e., why the solubility peak exists. To do so, we employ the isotherm expansion around $x_2 = x_r$, which has been chosen as the position of the peak of $\ln c_u$, at which $\left(\frac{\partial \ln c_u}{\partial x_2}\right)_{T,P,N_1;\mu_u} = 0$. Incorporating up to $x_2 - x_r$ in eq 12 (Supporting Information: Section E) yields

$$\left(\frac{\partial \ln c_u}{\partial x_2}\right)_{T,P,N_1;\mu_u} \simeq B_r\alpha^2(x_2 - x_r) + \cdots \tag{14}$$

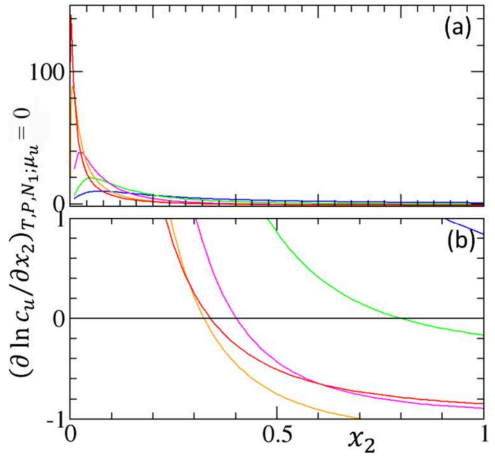

Figure 8. (a) $(\partial \ln c_u/\partial x_2)_{T,P,N_1;\mu_u}$ calculated from the solubility isotherm of syringic acid for the solubilizers 1,2-Ethanediol (blue solid lines), 1,2-Propandiol (green solid lines), 1,2-Butanediol (yellow solid lines), 1,2-Butanediol (magenta solid lines), 1,2-Pentanediol (orange solid lines), and 1,2-Hexanediol (red solid lines) calculated by eq 12, using the parameters in Table 1. (b) The behavior of (a) around $(\partial \ln c_u/\partial x_2)_{T,P,N_1;\mu_u} = 0$.

where the constant $\alpha(>0)$ comes from the activity-mole-fraction conversion via $a_2 - a_r \simeq \alpha(x_2 - x_r)$. Comparing eq 14 with the experimental solubility isotherms around the peak (Figure 8(b)), the sign of B_r can be seen as negative, signifying a weakened self-association of the solubilizer around the solute compared to the bulk (Figure 4 and Supporting Information: Section A). The same behavior was observed previously for bell-shaped isotherms (commonly referred to as the "synergistic" solvation) that were captured successfully by the quadratic isotherm (Figure 1(a)).[25] Here, despite the complexity of the multiplicative isotherm, self-association around the solute is weakened by a combination of saturating cooperative solubilization (that increases the isotherm) and the conditional exclusion of further solubilizers (that decreases the isotherm), driving the solubility to go through a peak.

Thus, the multiplicative isotherm can capture both (i) enhanced self-association at low solubilizer concentration responsible for the onset of solubilization and (ii) weakened self-association of the solubilizer around the solubility maximum.

■ CONCLUDING REMARKS

Insights into the mechanism underlying solubilization can be gained from the shape of a solubility isotherm (namely, how the solubility of a solute changes with solubilizer concentration), with the help of the isotherm equations derived from the statistical thermodynamic fluctuation theory. So far, a simple fitting of cooperative (sigmoidal) and quadratic (bell-shaped) isotherms to experimental solubility data led to mechanistic insights through their fitting parameters. However, these isotherm equations failed to capture more complex solubility isotherms, such as a combination of (i) sigmoidal solubilization at lower solubilizer concentrations and (ii) declining solubilization at higher solubilizer concentrations, that have been observed widely (Figures 2 and 3).

Our goal was to establish a general strategy to model complex solubility isotherms that combine the features of simpler isotherms (such as the cooperative and quadratic), directly from the fundamental relationship for solubility isotherms that link the isotherm gradient exactly to the excess number of solubilizers around the solute. From the excess number relationship alone, we could derive the isotherm multiplication rule when solubilization consists of unconditional and conditional processes. Based on this general principle, we have derived a multiplicative isotherm consisting of (i) initial cooperative association of solubilizers that increase the solubility and (ii) conditional exclusion of further solubilizers from the already crowded solute's locality, leading to solubility decrease. Such a conditional process could capture the complex isotherm shape of solubilizing syringic acid with a series of alkanediols as hydrotropes.

The excess number relationship is useful not only in establishing the isotherm multiplicativity rule but also in deriving isotherm equations directly from it. Combining it with the characteristic equation (i.e., how the excess number changes with solute or solubilizer concentration) leads to a systematic derivation of simple solubility isotherms, as has been demonstrated for the quadratic and cooperative isotherms. Such a twofold efficacy of the excess number equation mirrors the recent progress in sorption isotherms that can be derived systematically by solving differential equations of combined excess number relationship and the characteristic equation,[50,51] as well the discovery of multiplicative sorption phenomena at work in membrane polymers.[47]

The multiplicative solubilization is not limited to hydrotropes; the solubility and stability of proteins in the presence of salts can also be elucidated from this perspective. We emphasize that the solubility maximum (that emerged from the combination of saturating solute-solubilizer association and the exclusion from the already crowded locality) gives rise to the weakening of self-association of the solubilizer around the solute than in the bulk. This underscores the importance of comparing the local and bulk solution structures in the mechanism of solubility isotherms universally across hydrotropy, synergistic solvation, and micellar solubilization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.iecr.4c03215.

Polynomial isotherm around a reference solubilizer activity; deriving the cooperative solubility isotherm; mole-fraction based cooperative isotherm; difficulties of polynomial expansion over the entire range of x_2; and cooperative-exclusion process as viewed from local self-association (PDF)

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Notes

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