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On the Theory of Solute Solubility in Mixed Solvents

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Abstract

A series of equations are developed for the study of the effects of cosolvents on the solubility of a solute in mixed solutions where the solute displays a finite solubility. The equations differ depending on the scale used for the solute (and cosolvent) concentrations. The expressions use Kirkwood-Buff integrals to relate the changes in solubility to changes in the local solution composition around the solute, and can be applied to study any type of ternary system including electrolyte cosolvents. The expressions provided here differ from previous approaches due to the use of a semi open ensemble, and the extension to finite solute solubilities.

Introduction

Cosolvents (anything other than the primary solvent) are well known to affect the solubility of solutes in solution. A rigorous theory of the effects of cosolvents is desirable in order to understand the molecular level interactions responsible for the changes in solubility, and therefore improve our ability to manipulate the properties of solutions. Recently, the Kirkwood-Buff (KB) theory of solutions[1] has been used to rationalize the effects of cosolvents on the solubility of sparingly soluble solutes in terms of intermolecular distributions.[2–13] KB theory is an exact theory of solution mixtures and therefore provides a solid foundation for the understanding of such effects.

Previous studies have investigated many aspects and applications of the theory, from small molecules to large biomolecule solutes. The general idea is to use KB fluctuation theory to extract information about the local microscopic distribution of molecules from macroscopic experimental results. The theory has nothing directly to say about the interactions that bring about the microscopic structure; but, of course, it is the intermolecular interactions which are ultimately responsible for them. Apparently, Hall and O'Connell were the first to suggest the use of KB theory to study changes in solubility in ternary systems with a finite solute solubility.[2,14] In particular, KB theory has been applied to study low solute solubility in water by deriving KB based expressions for Henry's constant.[2,4] These studies typically used closed ensembles, sparingly soluble solutes, with solubilities and cosolvent concentrations expressed using mole fractions. Lee studied finite solubilities using KB theory and closed ensembles.[3] However, Hall and more recently Mazo recognized that the most appropriate ensemble for these studies was one where T, P, and the chemical potential of the solute are held constant.[7,14]

The approach presented here builds on the ideas of Hall and Mazo.[7,14] We extend the range of applicability to include solutes with finite solubilities in ternary systems of any type. The observed relationships differ from previous approaches primarily due to the use of an open

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system ensemble in the current study. Futhermore, we investigate in detail the differences observed when solubilities and cosolvent concentrations are defined using different concentration scales, and argue that the molarity scale provides the simplest and clearest picture of the cosolvent effect.

General Theory of Solubility

We will adopt the convention of a primary solvent (1), solute of interest (2), and cosolvent (3) at a fixed temperature (T) and pressure (P), together with the approach previously outlined by Mazo.[7] The chemical potential of the solute (μ_2) can be expressed by the statistical mechanical relationship,[15]

$$\beta\mu_2=\beta\mu_2^*+\ln(\Lambda_2^3\rho_2) \tag{1}$$

where Λ is thermal de Broglie wavelength, μ^* is the pseudo chemical potential, ρ_2 is the solute number density (n_2/V), and $\beta = 1/RT$. The pseudo chemical potential (pcp) was introduced by Ben-Naim and its uses have been discussed in detail.[15] The current use of the pcp, and thereby the molar concentration scale for the solute solubility, represents one of the major differences from previous studies and the consequences of this choice will be discussed later. At saturation, the chemical potential of the solute is the same as the pure solid (or gaseous) solute at the same T and P for any solvent and cosolvent mixture. Hence, if we follow the saturation equilibrium ($\rho_2 = \rho_2^{sat} = S_2$) for a particular system then we have,

$$\beta d\mu_2^*= - d\ln S_2 \tag{2}$$

for all solvent and cosolvent solution compositions. To relate changes in the solubility to changes in the cosolvent concentration (ρ_3) it will prove convenient to define the following derivative,

$$K_{23}^c= -\left(\frac{\partial \ln S_2}{\partial\rho_3}\right)_{T,P,\mu_2} =\beta\left(\frac{\partial\mu_2^*}{\partial\rho_3}\right)_{T,P,\mu_2} \tag{3}$$

The superscript c for K_{23} indicates that the solubility and cosolvent concentration are measured in terms of number densities (molarities). The value of K_{23}^c clearly depends on the solution composition and represents the slope of the saturation (solubility versus cosolvent molarity) curve. In general, if the solute solubility is increased on addition of a cosolvent then the value of K_{23} will be negative for most compositions, and vice versa. Experimentally, this slope is often determined to be independent of cosolvent concentration. However, we do not make that assumption here. The objective is to determine an expression for K_{23}^c in terms of the distribution of both the cosolvent and solvent molecules around the solute.

Kirkwood-Buff Theory

In order to relate the thermodynamics of the salting in/out process to changes in the distribution of cosolvent and solvent molecules in solution we will use the Kirkwood-Buff theory of solutions.[1,15] KB theory relates integrals over radial distribution functions (g_{ij}) to properties of the solution. The main components are the KB integrals between the different species,

$$G_{ij}=G_{ji}=4\pi\int_0^\infty [g_{ij}^{\mu VT}(r) - 1]\, r^2 dr \tag{4}$$

and the number densities or molar concentrations of each species ($\rho_i = n_i/V$). An excess coordination number can be defined ($N_{ij} = \rho_j G_{ij} \neq N_{ji}$) which characterizes the excess number of *j* molecules around a central *i* molecule in an open system above that observed within an equivalent volume of a bulk solution. It is a measure of how the addition of a single *i* molecule affects the distribution of *i* and *j* molecules around it compared to the bulk reference distribution. Generally, a positive value of N_{ij} indicates an increase in the local density of *j*

around *i* above that of their bulk ratios. This can be viewed as the result of some favorable net interaction or affinity between the two species. However, fluctuation theory is mute about specific details of the nature of these interactions.

Combinations of KB integrals can be used to provide information on solution properties in either open or closed systems. Before doing so it will be useful to define several expressions which appear repeatedly in the following analysis. In particular, the previous notation introduced by Smith for binary and ternary solutions will be used.[16,17] We define,

$$a_{33}(\rho_2)=\frac{1}{1+\rho_3(G_{33}-G_{13})} \tag{5}$$

with,

$$\eta_{13}(\rho_2)=\rho_1+\rho_3+\rho_1\rho_3(G_{11}+G_{33}-2G_{13}) \tag{6}$$

and,

$$A_1(\rho_2)=1+\rho_1(G_{11}+G_{23}-G_{12}-G_{13}) \tag{7}$$

Note that we have emphasized that the above expressions depend on the solute concentration even though the expressions themselves do not explicitly contain the solute concentration. There is no requirement that the G_{ij} values be independent of concentration.

Many interesting cosolvents are salts. KB theory can be applied to salt solutions as long as one does not treat the individual ions as independent thermodynamic variables.[18] There are several approaches to this problem.[19–24] We will use the indistinguishable ion approach in the case that the cosolvent is a salt.[25] This involves treating the salt as a collection of ions, without acknowledging the differences between anions and cations. This has particular advantages when analyzing computer simulation data (see the Discussion).[25] Therefore, we will distinguish between the traditional molar salt concentration c_s and the total ion number density ρ_3. The following relationships then hold: $\rho_3 = n_{\pm}\, c_s$, $n_{\pm}d\mu_3 = d\mu_s = n_+ d\mu_+ + n_- d\mu_-$, and $\gamma_3 = \gamma_{\pm}$, etc, where $n_{\pm} = n_+ + n_-$ is the total number of ions produced on dissolving the salt. In our opinion, this is the simplest approach for salts and provides equivalent expressions to other methods.[20,21,26] However, care must be taken when using the mole fraction concentration scale for salts (see Appendix 1).

Kirkwood-Buff Theory of Semi Open Ternary Systems

One can express several properties of semi open ternary solutions using the above definitions. The following expressions were determined using the approach of Smith.[17] The change in cosolvent activity with cosolvent molarity is provided by,

$$\beta\left(\frac{\partial\mu_3}{\partial\ln\rho_3}\right)_{T,P,\mu_2}=\left(\frac{\partial\ln a_3}{\partial\ln\rho_3}\right)_{T,P,\mu_2}=a_{33}(\rho_2) \tag{8}$$

where a_3 is the cosolvent activity. Alternatively, using the molality and mole fraction concentration scales one finds,

$$\beta\left(\frac{\partial\mu_3}{\partial\ln m_3}\right)_{T,P,\mu_2}=\frac{\rho_1}{\eta_{13}(\rho_2)} \tag{9}$$

and,

$$\beta\left(\frac{\partial\mu_3}{\partial\ln x_3}\right)_{T,P,\mu_2}=\frac{\rho_1}{\eta_{13}(\rho_2)}\frac{1}{1-x_3-x_2\rho_3A_1(\rho_2)/\eta_{13}(\rho_2)} \tag{10}$$

respectively. The last equation was obtained from Equation 9 using an expression for the required derivative $(\partial x_3/\partial m_3)_{T,P,\mu_2}$ which was derived using a similar approach to that in Appendix 1, together with previously existing expressions.[17] All three equations reduce to the expected binary system results when n_2 tends to zero. In the case of the molarity and molality derivatives the expressions themselves do not change, whereas the mole fraction derivative expression simplifies considerably. The additional complexity in Equation 10 arises from the fact that n_2 can vary in a system open to the solute and this directly affects the cosolvent mole fraction, whereas it does not directly affect the cosolvent molarity or molality.

Throughout this paper we will refer to molalities according to $m_i = n_i/n_1$. Hence, our molalities are dimensionless. They are related to the standard experimental definition of molality by a simple conversion factor of $1000/M_1$ or 55.5 mol/kg for water. In real applications this conversion factor has to be included.

Kirkwood-Buff Theory of Closed Binary Solutions

In the limit that the solute concentration approaches zero the above expressions are related to properties of the binary solvent and cosolvent solution. In this case, Equation 8 and Equation 9 adopt the same functional form but are now applicable to a closed binary system of 1 and 3 at constant T and P. Therefore, we can then use several additional established relationships derived for binary systems under constant T and P conditions. For instance, the partial molar volumes (pmv) in the binary solution can be written as,[1,15]

$$\overline{V_3}=\frac{1+\rho_1(G_{11}-G_{13})}{\eta_{13}(0)} \quad \text{and} \quad \overline{V_1}=\frac{1+\rho_3(G_{33}-G_{13})}{\eta_{13}(0)}=\frac{1}{a_{33}(0)\eta_{13}(0)} \tag{11}$$

Alternatively, the cosolvent pmv can be expressed by,[14,17]

$$\overline{V_3}=RT\kappa_T-\rho_1 G_{31}\overline{V_1}-\rho_3 G_{33}\overline{V_3} \tag{12}$$

where κ_T is the isothermal compressibility of the solution. The above equation can then be used to eliminate G_{13} from Equation 5 to generate,[27]

$$a_{33}(0)=\frac{\phi}{1+\rho_3(G_{33}-RT\kappa_T)} \tag{13}$$

and $\phi_1=\rho_1\overline{V_1}$ is the volume fraction of solvent. Furthermore, the pmv of an infinitely dilute solute in a cosolvent and solvent mixture is given by,[15]

$$\overline{V_2}^{\infty}=RT\kappa_T-\rho_1 G_{21}\overline{V_1}-\rho_3 G_{23}\overline{V_3} \tag{14}$$

Finally, we note that,

$$A_1(0)=\rho_1(G_{23}-G_{21})+\eta_{13}(0)\overline{V_3} \tag{15}$$

All of the above relationships can be used when the solute concentration is low.

General Kirkwood-Buff Theory of Solubility

Having provided a variety of background information we return to Equation 3, which is the starting equation for the present discussion. An expression for the first derivative in Equation 3 in terms of KB integrals has been determined previously for semi open ternary mixtures.[17] Therefore, using this expression (Equation 17 of Reference 17 with an appropriate change of indices) for the required derivative one finds,

$$K_{23}^{c}=-\frac{G_{23}-G_{21}}{1+\rho_3(G_{33}-G_{31})}=-(G_{23}-G_{21})a_{33}(\rho_2) \tag{16}$$

The above expression holds for any concentration of solvent or cosolvent, and also any solubility of the solute. It also holds for electrolyte cosolvents. The G_{ij} values depend on the particular solute, solvent, and cosolvent composition. All the above KB integrals should be evaluated at saturation of the solute.

Many studies use molality (m) and not molarity for both the solubilities and the cosolvent concentration. In this case one obtains a different expression for K_{23} given by Equation 20 of Reference 17 with an appropriate change of indices. The result is,

$$K_{23}^{m} = -\rho_1 \frac{1+\rho_1(G_{11}+G_{23}-G_{12}-G_{13})}{\rho_1+\rho_3+\rho_1\rho_3(G_{11}+G_{33}-2G_{13})} = -\rho_1 \frac{A_1(\rho_2)}{\eta_{13}(\rho_2)} \tag{17}$$

where we have used the definitions provided by Equation 6 and Equation 7. The above equation is essentially that suggested by Hall but derived using a different approach.[14] In addition, concentrations may be measured using mole fractions (x). To derive an expression on this concentration scale we use the following thermodynamic relationship,

$$\left(\frac{\partial x_2}{\partial x_3}\right)_{T,P,\mu_2} = \frac{-x_2+(1-x_2)m_{23}}{1-x_3-x_3 m_{23}} \tag{18}$$

where $m_{23} = (\partial m_2/\partial m_3)_{T,P,\mu 2}$ and which was derived from the corresponding mole fraction definitions using a similar manner to the approach outlined in Appendix 1. From the above relationship, and the molality derivative used to develop Equation 17, one finds that the correct expression when the solute and cosolvent concentrations are measured using mole fractions is given by,

$$K_{23}^{x} = -\frac{-1+(1-x_2)\rho A_1(\rho_2)/\eta_{13}(\rho_2)}{1-x_3-x_2\rho_3 A_1(\rho_2)/\eta_{13}(\rho_2)} \tag{19}$$

where $\rho = \rho_1 + \rho_2 + \rho_3$ is the total number density of the solution. The above expression is applicable to salts. However, care has to be taken with the mole fraction definition using the indistinguishable ion approach. In particular, $dx_3 \neq n_{\pm}\, dx_s$ and the exact relationship between the two approaches is somewhat complex for ternary systems open to one component (see Appendix 1).

Equation 16, Equation 17, and Equation 19 represent the primary results from the application of KB theory to quantify the effects of cosolvents on the solubility of solutes where all concentrations are finite. The difference between Equation 16 and Equation 17 or Equation 19 arises from two factors. The numerator is different due to the different solubility scales adopted for the solute. The denominators are different due to the change in cosolvent concentration scale and thereby the corresponding derivative. The latter difference disappears as ρ_3 decreases, while the former does not. The reasons for this will be discussed later. We will focus primarily on the molarity based expression in the subsequent sections.

Sparingly Soluble Solutes

The above expressions are valid for any stable ternary mixture with the solute component 2 at saturation. Many solubility studies involve a solute that is sparingly soluble in both the pure solvent and the cosolvent-solvent mixtures. In this case one can take the limit that ρ_2 tends to zero. This does not change the expressions provided in Equation 16 or Equation 17. However, in this limit the previous ensemble (T, P, μ_2) now approaches that of a constant T and P ensemble. Therefore, using Equation 16 one finds that,

$$K_{23}^{c} = -(G_{23}-G_{21})a_{33}(0) \tag{20}$$

where the activity derivative a_{33} is now a property of the binary solution mixture alone. It should be noted that although the above expression is identical in form to Equation 16, the KB integrals themselves will be different as the presence of a solute at finite concentrations can alter (both directly and indirectly) the intermolecular distributions. For K_{23}^c to be constant over all cosolvent concentrations one requires $G_{23} - G_{21}$ to be proportional to $1/a_{33}$. Whether or not K_{23}^c is constant, the value of a_{33} is always positive.[14] Hence, the difference in KB integrals ($G_{23} - G_{21}$) determines the sign of K_{23}^c and therefore the direction of the salting in/out effect.

In many cases one can replace some of the (often unknown) KB integrals with corresponding properties of the solution which are known or can be easily approximated. Elimination of G_{21} using Equation 14 provides,[27]

$$K_{23}^c = -\frac{G_{23} + \overline{V_2}^{\infty} - RT\kappa_T}{\phi_1} a_{33}(0) \tag{21}$$

where the infinity superscript indicates the pmv of the solute corresponds to that at infinite dilution in the solution mixture. Additional elimination of G_{13} via Equation 12 then gives,

$$K_{23}^c = -\frac{G_{23} + \overline{V_2}^{\infty} - RT\kappa_T}{1 + \rho_3(G_{33} - RT\kappa_T)} \tag{22}$$

The above equations are exact for an infinitely dilute solute. In the final expression the value of G_{33} is a property of the mixture in the absence of solute and is the same for all solutes. The value of G_{23} quantifies the distribution of cosolvent molecules around an infinitely dilute solute molecule. The latter can be obtained from the slope of the solubility curve if the corresponding properties (pmv of the solute and G_{33}) of the solution mixture are known.

When one expresses the solubility and cosolvent concentrations using molalities the sparingly soluble solute limit provides an identical expression to that of Equation 17, although one can now use the properties of the cosolvent and solvent mixture to provide,

$$K_{23}^m = -\rho_1 \left[\rho_1(G_{23} - G_{21})/\eta_{13}(0) + \overline{V_3}\right] \tag{23}$$

or equivalently,

$$K_{23}^m = -\rho_1 \left[(G_{23} - G_{21})a_{33}(0)\phi_1 + \overline{V_3}\right] \tag{24}$$

Alternatively, the sparingly soluble solute approximation for the mole fraction concentration scale provides,

$$K_{23}^x = -\frac{1}{x_1}\left[-1 + \rho\frac{A_1(0)}{\eta_{13}(0)}\right] \tag{25}$$

or using the properties of the solution mixture,

$$K_{23}^x = -\rho \left[\rho(G_{23} - G_{21})a_{33}(0)\overline{V_1} + \overline{V_3} - \overline{V_1}\right] \tag{26}$$

The last two equations can be used for electrolytes. Again, care has to be taken with the mole fraction definition using the indistinguishable ion approach. In particular, one finds that $dx_3 = (x_3/x_s)(1-x_3)/(1-x_s)\, dx_s \neq n_{\pm}\, dx_s$ for a closed binary system (see Appendix 1). This differs from the much simpler molarity and molality based cases.

Electrolyte Cosolvents

The above equations refer to sparingly soluble solutes in any type of cosolvent solution. In the case of electrolytes the KB integrals are related to the individual ion integrals through a series of electroneutrality conditions. For the cosolvent we have,[21,28]

$$\rho_3 G_{33} = \rho_3 G_{+-} - 1 \tag{27}$$

and,

$$G_{13} = G_{1+} = G_{1-} \tag{28}$$

In addition, for the salt distribution around the solute one can write,

$$\rho_3 G_{23} = \rho_+ G_{2+} + \rho_- G_{2-} \tag{29}$$

which combined with the electroneutrality constraint equation,

$$z_+ \rho_+ G_{2+} + z_- \rho_- G_{2-} = 0 \tag{30}$$

provides,

$$G_{23} = \frac{1}{\rho_3}\left(\rho_+ - \frac{z_+}{z_-}\rho_+\right) G_{2+} = \left(\frac{n_+}{n_\pm} - \frac{z_+}{z_-}\frac{n_+}{n_\pm}\right) G_{2+} = G_{2+} = G_{2-} \tag{31}$$

Ben-Naim has pointed out that the above expressions for salts are not due to the ionic nature of the interactions per se, but the fact that the cation and anion concentrations cannot be varied independently.[18] Hence, combining Equation 22, Equation 27, and Equation 31 provides,

$$K_{23}^c = -\frac{G_{2+} + \overline{V_2}^\infty - RT\kappa_T}{\rho_3 (G_{+-} - RT\kappa_T)} \tag{32}$$

which holds for any solvent and cosolvent concentration, and where we have focused on the cation as the single independent species.

To relate our expressions to the salting out constants commonly presented in the literature one can integrate Equation 3 using the assumption that K_{23}^c (= K_S^c) is independent of cosolvent concentration (as observed for many salts) to give,

$$\ln\left(\frac{S_2^o}{S_2}\right) = K_s^c \rho_3 \tag{33}$$

where S_2^o is the molar solubility of the solute in pure solvent. Traditionally, experimental solubility curves have used the common logarithm for the solute solubility, and often the ionic strength in place of concentration. The ionic strength on the molarity scale is defined by,

$$I_3^c = \frac{1}{2}(n_+ z_+^2 + n_- z_-^2)\, c_3 = \lambda\, c_3 \tag{34}$$

where z_+ and z_- are the charges on the cation and anion, respectively, and c_3 is the cosolvent molarity. Consequently, the use of the indistinguishable ion approach provides,

$$\log\left(\frac{S_2^o}{S_2}\right) = \frac{n_\pm}{2.303\lambda} K_s^c I_3^c \tag{35}$$

which can be directly compared to the experimentally observed slope.[7]

The interpretation of G_{23} provided by Equation 32 and Equation 35 depends on the treatment of the salt. For the present indistinguishable ion approach, the value of G_{23} quantifies the deviation in the ion distribution around the solute. Alternatively, one could use the traditional molarity (c_3) of the salt solution and set $n_\pm = 1$ during the analysis. The corresponding value of G_{23} then quantifies the deviation in the distribution of salt “molecules” around the solute.

Salting Out Constants

Salting out constants are usually defined by the slope of the solubility curve as the solute and cosolvent concentrations tend to zero. Applying the zero cosolvent concentration limit for the case of sparingly soluble solutes we have,

$$K_S^c = -(G_{23} - G_{21}) \tag{36}$$

where it is implied that the KB integrals correspond to the distributions observed at infinite dilution of both solute and cosolvent. Using our relationships for the solute pmv and the properties of salt solutions (Equation 14 or Equation 32) this can be expressed in an equivalent form,

$$K_S^c = -(G_{2+}+\overline{V_2}^{\infty} - RT\kappa_T^{\mathrm{o}}) \tag{37}$$

where we have used the fact that $\rho_3 G_{+-} \rightarrow 1$ as $\rho_3 \rightarrow 0$,[28] and the zero superscript indicates a property of the pure solvent. Alternatively, using the molality concentration

$$K_S^m = -\left[1+\rho_1^{\mathrm{o}}(G_{23} - G_{21}+G_{11} - G_{13})\right] \tag{38}$$

which can be written,

$$K_S^m = -\rho_1^{\mathrm{o}}(G_{2+}+\overline{V_3}^{\infty}+\overline{V_2}^{\infty} - RT\kappa_T^{\mathrm{o}}) \tag{39}$$

Equation 38 and Equation 39 were previously derived by Mazo.[7] Finally, the solubility can also be measured in mole fraction units in which case,

$$K_S^x = -\rho_1^{\mathrm{o}}(G_{23} - G_{21}+G_{11} - G_{13}) \tag{40}$$

or,

$$K_S^x = -\rho_1^{\mathrm{o}}(G_{2+}+\overline{V_3}^{\infty} - \overline{V_1}^{\mathrm{o}}+\overline{V_2}^{\infty} - RT\kappa_T^{\mathrm{o}}) \tag{41}$$

Hence, a series of limiting expressions are obtained which depend on the concentration units adopted for measuring the solubility of the solute. We note that Equation 38–Equation 41 involve properties of the cosolvent even at infinite dilution of both the solute and cosolvent.

The Relationship Between Expressions for K_{23} Using Different Concentration Scales

The expressions for the salting out constants derived using the different solubility scales are clearly similar. A general relationship can be developed for sparingly soluble solutes. Equating the solute chemical potentials using the different concentration scales one can write,

$$\beta\mu_2^{\mathrm{o,m}}+\ln\gamma_2 m_2=\beta\mu_2^{*}+\ln\Lambda_2^3\rho_2=\beta\mu_2^{\mathrm{o,x}}+\ln f_2 x_2 \tag{42}$$

for the molality scale, the pcp (or molarity) scale, and the mole fraction scale, respectively. Here, γ_2 and f_2 are the molal and mole fraction activity coefficients and the standard states correspond to the infinitely dilute solute and the pure solute for the molality and mole fraction scales, respectively. Taking derivatives with respect to the cosolvent molality at infinite dilution of the solute one obtains,

$$\left(\frac{\partial[\beta\mu_2^{\mathrm{o,m}}+\ln\gamma_2]}{\partial m_3}\right)_{T,P}^{\infty}=\beta\left(\frac{\partial\mu_2^{*}}{\partial m_3}\right)_{T,P}^{\infty} - \rho_1\overline{V_3}=\left(\frac{\partial\ln f_2}{\partial m_3}\right)_{T,P}^{\infty} - x_1 \tag{43}$$

Using the standard thermodynamic relationships of $(\partial\rho_3/\partial m_3)_{T,P} = \rho_1\varphi_1$ and $(\partial x_3/\partial m_3)_{T,P} = x_1^2$ for binary mixtures of 1 and 3 provides,

$$\left(\frac{\partial[\beta\mu_2^{o,m}+\ln\gamma_2]}{\partial m_3}\right)_{T,P}^{\infty}=\rho_1\phi_1\beta\left(\frac{\partial\mu_2^*}{\partial\rho_3}\right)_{T,P}^{\infty}-\rho_1\overline{V_3}=x_1^2\left(\frac{\partial\ln f_2}{\partial x_3}\right)_{T,P}^{\infty}-x_1 \tag{44}$$

Therefore, replacing the corresponding derivatives with the appropriate K_{23}, defined in analogous fashion to Equation 3, one finds the final relationship,

$$K_{23}^m=\rho_1(\phi_1K_{23}^c-\overline{V_3})=x_1(x_1K_{23}^x-1) \tag{45}$$

which is general for any cosolvent concentration. The above relationship (Equation 45) relates the mole fraction based approach of Shulgin and Ruckenstein,[6] to the molality based approach of Mazo,[7] and the pseudo chemical potential approach presented here – all for an infinitely dilute solute. An alternative (more general) derivation is also provided in Appendix 2. The corresponding salting out constants are therefore related by,

$$K_s^m=\rho_1^o(K_s^c-\overline{V_3}^{\infty})=K_s^x-1 \tag{46}$$

which only involves properties of the pure solvent and an infinitely dilute cosolvent.

Symmetric Ideal and Ideal Dilute Solutions

Symmetric ideal (SI) and ideal dilute solutions provide a useful reference point and so we will briefly discuss the results obtained from Equation 16, Equation 17, and Equation 19 when the cosolvent mixture is ideal. Ideal solutions display unit activity coefficients for all compositions. However, the conditions for ideal behavior depend on the concentration scale for finite cosolvent concentrations. Ideality arises when the lhs of Equation 8, Equation 9, and Equation 10 equals unity. On the molar concentration scale an ideal dilute solution is characterized by $a_{33}=1$ or $G_{33}-G_{13}=0$ for all compositions. Alternatively, ideal dilute behavior on the molality scale is provided when $\eta_{13}=\rho_1$ or $\rho_1(G_{11}+G_{33}-2G_{13})=-1$ for all compositions. These are the same conditions for ideal behavior in closed binary systems of 1 and 3. Consequently, Equation 16 and Equation 17 reduce to,

$$K_{23}^c=-(G_{23}-G_{21}) \tag{47}$$

and,

$$K_{23}^m=-A_1(\rho_2) \tag{48}$$

respectively. Both are valid for finite solute concentrations.

The condition for ideality on the mole fraction scale is more involved. Ben-Naim has shown that symmetric ideal solutions are characterized by $\Delta G_{ij}=G_{ii}+G_{jj}-2G_{ij}=0$ for all i-j pairs.[18] In this case, one has $\eta_{13}=\rho_1+\rho_3$ with $A_1=1$ and therefore $K_{23}^x=0$, as expected. If we restrict ourselves to just symmetric ideal solutions of 1 and 3 then Equation 19 reduces to,

$$K_{23}^x=-\frac{\rho_1+\rho_3}{\rho_1}(-1+A_1(\rho_2)) \tag{49}$$

for any solute concentration. Hence, for symmetric ideal and ideal dilute solvent and cosolvent solutions the expressions involve only the terms in the numerators of Equation 16, Equation 17, and Equation 19.

Comparison with the Hall Approach

Hall derived the equations of KB theory using a totally different approach from Kirkwood and Buff. In doing so Hall produced two primary equations from which many of the expressions presented here can be generated. These have the advantage of being directly applicable to semi open systems and are relatively simple to use for binary and ternary systems. His approach,

however, was still somewhat involved. Here we present a simpler derivation of the Hall equations. The first focuses on changes in the molar concentrations of any component. If we consider the species molarities in the grand canonical ensemble to be functions of T and all chemical potentials then we can write,

$$d\rho_i = \sum_{j=1}^{n_c} \left(\frac{\partial \rho_i}{\partial \mu_j} \right)_{T, \mu_{k \neq j}} d\mu_j \tag{50}$$

for any component *i* at constant T. The summation is over all n_c components of the solution. The above derivatives in terms of KB integrals are provided directly from the fact that,[15]

$$\left(\frac{\partial \rho_i}{\partial \mu_j} \right)_{T, \mu_{k \neq j}} = \beta \rho_i (\delta_{ij} + \rho_j G_{ij}) \tag{51}$$

which is the starting equation for KB theory. Here, δ_{ij} is the Kroenecker delta function. From the these two equations one finds,

$$d \ln \rho_i = \beta \sum_{j=1}^{n_c} (\delta_{ij} + N_{ij}) d\mu_j \tag{52}$$

which is valid for composition changes of any component in any multicomponent system and any thermodynamically reasonable ensemble with T constant. This is the equation derived by Hall but using a much longer route. From this equation one easily finds,

$$\left(\frac{\partial \ln \rho_2}{\partial \rho_3} \right)_{T, P, \mu_2} = N_{21} \beta \left(\frac{\partial \mu_1}{\partial \rho_3} \right)_{T, P, \mu_2} + N_{23} \beta \left(\frac{\partial \mu_3}{\partial \rho_3} \right)_{T, P, \mu_2} \tag{53}$$

and,

$$\left(\frac{\partial \ln \rho_3}{\partial \mu_3} \right)_{T, P, \mu_2} = N_{31} \beta \left(\frac{\partial \mu_1}{\partial \mu_3} \right)_{T, P, \mu_2} + \beta (1 + N_{33}) \tag{54}$$

for our semi open ternary system. These expressions, when combined with the Gibbs-Duhem derived relationships,

$$\left(\frac{\partial \mu_1}{\partial \mu_3} \right)_{T, P, \mu_2} = -\frac{\rho_3}{\rho_1} \quad \text{and} \quad \left(\frac{\partial \mu_1}{\partial \rho_3} \right)_{T, P, \mu_2} = -\frac{\rho_3}{\rho_1} \left(\frac{\partial \mu_3}{\partial \rho_3} \right)_{T, P, \mu_2} \tag{55}$$

provide Equation 16. This procedure replaces many of the thermodynamic transformations required by other approaches,[1,15,17] with relatively simple algebraic manipulations.

In addition, Hall also provided the following general expression for changes in molal concentrations at constant T and P,

$$d \ln m_i = \beta \sum_{j=2}^{n_c} (\delta_{ij} + N_{ij}^{+}) d\mu_j \tag{56}$$

where $N_{ij}^{+} = N_{ij} + m_j (1 + N_{11} - N_{i1} - N_{j1})$. Equation 56 can be generated from Equation 52 by noting that $d \ln m_i = d \ln \rho_i - d \ln \rho_1$, and then eliminating $d\mu_1$ via the corresponding Gibbs-Duhem relationship at constant T and P,

$$\sum_{j=1}^{n_c} \rho_j d\mu_j = 0 \tag{57}$$

Hence, the additional constraint of constant P. Using Equation 56 one immediately finds,

$$\left(\frac{\partial \ln m_2}{\partial m_3}\right)_{T,P,\mu_2} = N_{23}^{+}\beta\left(\frac{\partial \mu_3}{\partial m_3}\right)_{T,P,\mu_2} \tag{58}$$

and,

$$\left(\frac{\partial \ln m_2}{\partial \mu_3}\right)_{T,P,\mu_2} = \beta(1+N_{33}^{+}) \tag{59}$$

for our semi open ternary system which, after combining and rearranging, provide Equation 17. We note that $\eta_{1i} = \rho_1(N_{ii}^{+} + 1)$ and $A_1 = \rho_1 N_{23}^{+}/\rho_3$.

The primary advantage of the Hall approach is that it can be applied to any number of solution components in any constant T ensemble (molarity version) or constant T and P ensemble (molality version). However, Hall did not provide a starting expression for mole fractions. This can be achieved by noting that,

$$d\ln x_i = d\ln \rho_i - \sum_{j=1}^{n_c} x_j d\ln \rho_j \tag{60}$$

Therefore using Equation 52 we have,

$$d\ln x_i = \beta\sum_{j=1}^{n_c}(\delta_{ij}+N_{ij})d\mu_j - \beta\sum_{j=1}^{n_c} x_j \sum_{k=1}^{n_c}(\delta_{jk}+N_{jk})d\mu_k \tag{61}$$

which is somewhat involved but very useful as it applies to any number of components in any constant T ensemble. The above equation leads to the mole fraction results for our ternary system, although the algebra involved makes it no more efficient than our previous approach. It does confirm the relationships derived in the present manuscript, as well as many of those derived earlier.[16,17]

The Direct Correlation Function Approach

In several previous applications of KB theory the direct correlation approach has been used.[29,30] The expressions provided here in terms of KB integrals, based on the total correlation function, can be converted to equivalent expressions using the direct correlation function (c_{ij}). The direct correlation functions are defined by the relationship,

$$(\mathbf{1}+\rho\mathbf{G}) = (\mathbf{1}-\rho\mathbf{C})^{-1} \tag{62}$$

This is merely the Ornstein-Zernike (OZ) equation in matrix form in wave number space evaluated at zero wave number. Here, **G** is the matrix (G_{ij}), **C** is the matrix (C_{ij}), and **ρ** is a diagonal matrix with diagonal elements (ρ_1, ρ_2, …). The C_{ij} integrals are given by,

$$C_{ij} = 4\pi\int_0^\infty c_{ij}(r) r^2 dr \tag{63}$$

Equating the elements of the two resulting matrices in Equation 62 provides expressions for the G_{ij} integrals in terms of the C_{ij} integrals,

$$\begin{aligned}
1+\rho_1 G_{11} &= [(1-\rho_2 C_{22})(1-\rho_3 C_{33}) - \rho_2\rho_3 C_{23}^2]/\,|1-\rho C| \\
1+\rho_2 G_{22} &= [(1-\rho_1 C_{11})(1-\rho_3 C_{33}) - \rho_1\rho_3 C_{13}^2]/\,|1-\rho C| \\
1+\rho_3 G_{33} &= [(1-\rho_1 C_{11})(1-\rho_2 C_{22}) - \rho_1\rho_2 C_{12}^2]/\,|1-\rho C| \\
G_{21} &= [C_{12}(1-\rho_3 C_{33}) + \rho_3 C_{13} C_{32}]/\,|1-\rho C| \\
G_{31} &= [C_{31}(1-\rho_2 C_{22}) + \rho_2 C_{21} C_{32}]/\,|1-\rho C| \\
G_{32} &= [C_{32}(1-\rho_1 C_{11}) + \rho_1 C_{12} C_{31}]/\,|1-\rho C|
\end{aligned} \tag{64}$$

for a ternary system. If necessary, the $|1-\rho C|$ determinant appearing on the rhs of the above expressions can also be evaluated. However, this factor will cancel in the majority of expressions we have provided here. The above set of equalities can then be used to transform any of the present expressions into equivalent expressions involving just the C's.

For example, the major result of this study is Equation 16. In terms of the direct correlation function integrals this can be written,

$$K_{23}^{c}=-\frac{C_{23}(1-\rho_1C_{11}-\rho_3C_{31})-C_{21}(1-\rho_3C_{33}-\rho_1C_{31})}{(1-\rho_2C_{22})(1-\rho_1C_{11}-\rho_3C_{31})-\rho_2C_{12}(\rho_1C_{12}+\rho_3C_{32})} \tag{65}$$

For sparingly soluble solutes one then has,

$$K_{23}^{c}=-\frac{C_{23}(1-\rho_1C_{11}-\rho_3C_{31})-C_{21}(1-\rho_3C_{33}-\rho_1C_{31})}{1-\rho_1C_{11}-\rho_3C_{31}} \tag{66}$$

and the corresponding salting out constant is then provided by,

$$K_{s}^{c}=-\frac{C_{23}(1-\rho_1^{o}C_{11})-C_{21}(1-\rho_1^{o}C_{31})}{1-\rho_1^{o}C_{11}}=-(C_{23}-C_{21}\rho_1^{o}\overline{V_3}^{\infty}) \tag{67}$$

where we have used previously derived expressions for the solution properties in terms of the direct correlation function integrals.[30] We have not provided a complete set of expressions in terms of the direct correlation function for reasons outlined in the Discussion.

Discussion

In the previous sections we have outlined a general approach for understanding solubility curves in terms of KB integrals. The primary result is Equation 16 where all concentrations are measured on the molarity scale. This equation can be applied to small solutes (He, Ne, CH_4, etc) or large molecules such as peptides and proteins at any level of solubility. In addition, the KB approach allows one to isolate G_{23} (or G_{2+}) at infinite dilution, and other concentrations if a_{33} is known. A more physical picture of the difference in KB integrals can be obtained by reference to a similar thermodynamic property which is used to quantify cosolvent effects in biological systems.[31] In particular, Timasheff and coworkers have used preferential binding to understand equilibrium dialysis experiments and the thermodynamics of transfer of proteins from pure solvent to cosolvent mixtures.[32] The preferential binding at infinite dilution of a protein solute is given by,[16]

$$\Gamma_{23}=\left(\frac{\partial m_3}{\partial m_2}\right)_{T,\mu_1,\mu_3}=\rho_3(G_{23}-G_{21})=N_{23}-\frac{\rho_3}{\rho_1}N_{21} \tag{68}$$

The last equality indicates that when the ratio of cosolvent to water molecules in the vicinity of the solute is greater than the bulk cosolvent to solvent ratio (ρ_3/ρ_1) the value of Γ_{23} is positive. This is equivalent to a negative value of K_{23}^{c} and a salting in effect. When the ratio of the local cosolvent to solvent concentrations is less than the bulk ratio one observes a salting out effect. In the case of hydrophobic solutes and ionic cosolvents, it is expected that the ions will be excluded from the solute surface due to their strong solvation shells. Here, the solutes are preferentially hydrated and Γ_{23} will be negative. KB theory provides a way to quantify these changes in the ion and solvent distributions. The use of Equation 14 to relate G_{23} and G_{21} physically states that the solvent and cosolvent distributions are linked through a constraint on the volume surrounding the solute. Therefore, if a cosolvent is excluded from the vicinity of a solute then an equal volume of water must replace the cosolvent to maintain a constant overall volume.

Our presentation has been given in terms of the KB integrals and not direct correlation function integrals. Indeed, when KB theory was first published the direct correlation function $c_{ij}(r)$ was rarely used in statistical mechanics. Since that time, however, several authors have preferred to express the results of KB theory in terms of these integrals.[3,29,30] Presumably, the rationale for using the C's is that their integrands (c_{ij}) have a shorter spatial range than do the integrands ($g_{ij} - 1$) of the G's. Although it is not difficult to use Equation 64 to express Equation 16, Equation 17, and Equation 19 in terms of the C's rather than the G's, we have not pursued this approach for two main reasons. First, the G's have a clear physical meaning in terms of the excess particle numbers, or concentration fluctuations.[18] The C's have no such direct physical meaning. Second, the c's are *defined* by Equation 62. They are not measurable experimentally nor calculable theoretically by any method of which we are aware that does not use Equation 62 or something equivalent to it. The G's, on the other hand, are measurable (at least in principle) by radiation scattering and have been successfully calculated by simulation.[19,33,34] In addition, the resulting expressions in terms of the G's are much simpler. When any of the g_{ij} functions become really long range, such as near a critical point,[30] then it becomes advantageous to use the C's instead of the G's. But, barring such exceptional circumstances, we advocate the present formulation in terms of the G's.

The value of $G_{23} - G_{21}$ is central to the discussion of the salting in or out effect. Other KB integrals correspond to properties of the solution mixture and are not measures of the effect of a specific cosolvent on a specific solute (they are the same for all solutes in that particular cosolvent solution). This is precisely why the pseudo chemical potential approach is to be preferred. If a cosolvent displays a positive value of $G_{23} - G_{21}$ then K_{23}^c is negative and the solute solubility is increased (salting in effect). Conversely, if $G_{23} - G_{21}$ is negative then K_{23}^c is positive and the solute solubility is decreased (salting out effect). If one measures the solute solubility using molalities or mole fractions, then additional terms appear in the numerator of the expressions for K_{23} which refer to properties of the solution. These terms have nothing to do with the solute under investigation. Hence, the molarity or pcp based approach is much simpler and easier to interpret, especially when the cosolvent and water pmvs are unknown. For example, if a cosolvent displays no preference for the solute ($G_{23} - G_{21} = 0$) then an increase in cosolvent molarity leads to no change in the solute solubility (Equation 16) as K_{23}^c is zero. However, if one uses the molality or mole fraction scale results (Equation 17 and Equation 19) then the values of K_{23}^m and K_{23}^x are non zero and there will be a change in solubility even though there is no preference of the cosolvent for the solute. Let us be clear about what this sentence means. We are certainly not asserting that the physical amount of solute in a solution changes when one changes the units of measurement. The point is that the definition of solubility is dependent on these units. The molal and mole fraction based equations are perfectly correct, but they do not, in our opinion, provide the simplest and clearest interpretations of the experimental data.

Recently, Mazo presented an analysis of the effects of salts on the solubility of benzene based on the experimental data of McDevit and Long.[7,35] Here, we have reanalyzed the same experimental data. The new analysis is presented in Table 1 and is different to that of Mazo for several reasons. First, Mazo analyzed the molarity based data of McDevit and Long using the molality based Equation 39. In principle, this is incorrect but is numerically not serious at these low concentrations. Second, Mazo used the pmv of the salt rather than the indistinguishable ion $(n_{\pm}\overline{V}_3 = \overline{V}_s)$ – but this is also not serious. Third, a misplaced decimal point in the original calculations led to the most serious error in the construction of the previous table. Therefore, R.M.M. would like to withdraw Table 2 of Reference 7 and substitute for it Table 1 of the present paper.

The results presented in Table 1 demonstrate a decrease in salt exclusion for sodium salts as the anion becomes larger. This is exactly the trend predicted on simple solvation principles.

The same trend is observed for alkali metal chlorides as the cation size increases, with the noticeable exception of LiCl. If LiCl were incompletely dissociated in dilute solution this would decrease the salting out effect and explain the anomaly at least qualitatively. On the other hand, we are not aware of any evidence for incomplete dissociation. In conductance studies it appears to be a typical strong electrolyte. An alternative conjecture involves the possibility of significant cation interactions with the benzene pi system. This would favor an increase in G_{2+} for Li^+ over other cations. However, this remains quite speculative at present.

In the above analysis the value of $G_{21} = -89.4\ cm^3/mol$ is the same for all cosolvents at infinite dilution. The corresponding excess coordination number N_{21} is then −4.9. This can be interpreted as benzene, at infinite dilution, occupies the same space as 4.9 water molecules would occupy in pure water.

The results obtained from Equation 39 and presented in Table 1 should not be interpreted as favoring a picture of cation dominated interactions. The anions play an equally important role. The deviations in the distribution of both cations and anions around a benzene molecule, from the bulk solution distributions, must be the same due to the electroneutrality constraint (Equation 31). It is possible that only one ion interacts directly with the solute. However, exactly which of the ions provides the driving force for the association with, or exclusion from, the solute cannot be deduced from the KB approach. In our opinion, this kind of information can only be obtained from accurate computer simulation data.

There have been several computer simulation studies aimed at understanding the changes in small molecule solubility by different cosolvents.[33,36,37] These approaches are often based on Widom particle insertion calculations.[38] In this case the excess chemical potential (μ_2^{ex}) of the solute is the property to be determined and is defined by the following expression,

$$\beta\mu_2=\beta\mu_2^{ex}+\ln(\Lambda_2^3\rho_2 q_2^{-1}) \tag{69}$$

where q_2 is the internal partition function of the solute. It should be noted that the above excess chemical potential is different to the traditional experimental definition for mixtures on the mole fraction scale. Clearly, the pcp and the excess chemical potential differ by a factor of ln q_2, which in most cases can be safely assumed to be reasonably independent of solution composition. Hence, the particle insertion calculations essentially probe changes in the pcp of the solute. In addition, one of the main advantages of using the indistinguishable ion approach is observed when analyzing computer simulation data concerning the distribution of salt ions around a solute. While it is relatively easy to count the number of ions (either anions or cations) observed around a central solute, it is quite difficult to count salt “molecules” when the salt is fully dissociated.

Many of the relationships provided for finite solute concentrations in our open ensemble take on exactly the same form as those for sparingly soluble solutes in closed ensembles, especially for the molarity and molality cases. They are different because the KB integrals will adopt different numerical values under different compositions. The similarities are immediately understood if one examines the Gibbs-Duhem relationship for these ternary systems. Namely,

$$n_1 d\mu_1+n_2 d\mu_2+n_3 d\mu_3=0 \tag{70}$$

at constant T and P. Clearly, our open ensemble ($d\mu_2 = 0$) and the low solute concentration closed ensemble ($n_2 \to 0$) provide the same relationship ($n_1 d\mu_1 + n_3 d\mu_3 = 0$) between the chemical potentials of the solvent and cosolvent. This relationship generally appears in the expressions occurring in the denominator of Equation 16 and Equation 17 (compare with Equation 8 and Equation 9). From the point of view of the solute, as the solute concentration tends towards that of an infinitely dilute solute ($n_2 \to 1$), the properties of the solution tend towards that of a simple binary solution of 1 and 3 at the same composition, and therefore

$n_2 d\mu_2 \rightarrow 0$. This provides the expressions that occur in the numerator of Equation 16 and Equation 17.

The current approach is different from that of other studies which have primarily focused on sparingly soluble solutes.[2,4,10] In particular, the majority of previous approaches have adopted the KB expressions for ternary systems in closed ensembles, even for finite solute solubilities.[3] Hence, their expressions differ from the semi open ensemble results developed here. In particular, the finite concentration results quoted here are generally simpler and do not involve G_{22}. Both the open and closed ensemble approaches provide the same results for sparingly soluble solutes. Equation 16 and Equation 19 are new, while Equation 17 was originally derived by Hall.[14] They are the only ones that should be applied to study changes in solubility where the solute appears at a finite concentration.

The equations presented here provide a solid foundation for the analysis and interpretation of solubility in mixed solvents. The required KB integrals can be obtained from theory, simple models, or experimental data where available. The latter is relatively simple to obtain for sparingly soluble salts as one only requires properties of the binary solvent and cosolvent solution (G_{33} and G_{13}), from which knowledge of the solubility curve provides values for $G_{23} - G_{21}$. The required experimental data is more extensive for semi open ternary systems where all species appear at finite concentrations. Fortunately, the KB integrals can be obtained from studies of the corresponding closed ternary system at the same composition, i.e the solute solubility limit, using existing equations for closed ternary systems.[17,39,40] This is the same process as used previously.[3] Performing such an analysis will generate all the G_{ij} values. Hence, one does not require the slope of the solubility curve to provide $G_{23} - G_{21}$ in this case, and therefore one could use knowledge of the solubility curve as a consistency check. In either case, we argue that the correct expressions for the interpretation of the solubility data involve Equation 16, Equation 17, or Equation 19.

Conclusions

Solubility may be quantitatively defined in several ways using different measures of the relative amounts of solute and solvent(s) present in solution. We have discussed the three most common measures in this paper - molarity, molality, and mole fraction. From the point of view of logic, these are all equivalent, merely involving a (nonlinear) change of scale. From the point of view of interpretation in terms of molecular distributions, we have argued that the molarity scale of solubility is the most convenient one. We have given formulae for solubilities and salting out coefficients for all three concentration scales. All of these rely on the Kirkwood-Buff integrals to express the local structure of the solution, particularly near a solute molecule, as well as auxiliary thermodynamic properties of the solution. It appears that the molarity scale formulae emphasize the structural information, and deemphasize the ancillary part to a greater extent than do the other two scales. We therefore recommend that, as far as possible, the molarity scale be used when measuring and reporting solubilities. Certainly, molalities and mole fractions have their advantages as concentration measures. Nevertheless, for interpretive purposes we recommend molarities.

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Appendix 1. The Indistinguishable Ion Approach for Mole Fractions

The use of the indistinguishable ion approach is relatively straight forward for the molarity and molality concentration scales. In this case we find $d\rho_3 = n_\pm\, dc_s$ and $d \ln \rho_3 = d \ln c_s$ for the cosolvent molarity, and similarly for molality. Both are independent of the ensemble. However, the same is not true for the mole fraction scale in both closed and, especially, open ensembles. There are two possible definitions for the cosolvent mole fraction in ternary systems,

$$x_s = \frac{n_s}{n_1+n_2+n_s} \quad \text{and} \quad x_3 = \frac{n_\pm n_s}{n_1+n_2+n_\pm n_s} \tag{A1.1}$$

where n_s is the number of salt "molecules" and the latter refers to the indistinguishable ion definition. Note that the particular definition also affects the solvent and solute mole fractions. Let us consider our ensemble with T, P, and μ_2 constant and therefore n_2 can vary. Using the first expression one can write,

$$\left(\frac{\partial x_s}{\partial n_s}\right)_{T,P,\mu_2} = \frac{1}{n_1+n_2+n_s} - \frac{n_s(1+dn_2/dn_s)}{(n_1+n_2+n_s)^2} = \frac{1}{n_1+n_2+n_s}[\,1 - x_s(1+n_\pm m_{23})] \tag{A1.2}$$

where m_{23} was defined earlier in the text. If we apply the same procedure to x_3 then we have,

$$\left(\frac{\partial x_3}{\partial n_s}\right)_{T,P,\mu_2} = \frac{n_\pm}{n_1+n_2+n_\pm n_s}[\,1 - x_3(1+m_{23})] \tag{A1.3}$$

Hence, we find that,

$$\left(\frac{\partial x_3}{\partial x_s}\right)_{T,P,\mu_2} = \frac{x_3[\,1 - x_3(1+m_{23})]}{x_s[\,1 - x_s(1+n_\pm m_{23})]} \tag{A1.4}$$

and therefore it is clear that $d \ln x_3 \neq d \ln x_s$ and also $dx_3 \neq n_\pm\, dx_s$ for this ensemble. The corresponding relationship in a closed ternary system is recovered when $m_{23} = 0$, for which one also has $dx_3 \neq n_\pm\, dx_s$ for the cosolvent. The relationship in a closed binary system of 1 and 3 is provided by setting $n_2 = 0$ and $m_{23} = 0$, but one still finds $dx_3 \neq n_\pm\, dx_s$ for the cosolvent. Only when x_3 tends to zero do we find that $dx_3 = n_\pm\, dx_s$ is valid. Hence, the determination of K_S^x is relatively straight forward, but the determination of K_{23}^x is more involved. One can still use the indistinguishable ion approach in all cases, but care should be taken that the required transformations are performed correctly.

Appendix 2. The Sechenov Constant for Different Concentration Measures – A Unified Approach

The object is still to express the slope of the solubility curves in terms of Kirkwood-Buff integrals. In this appendix we show how all three cases can be treated on a common basis. This is neither more nor less correct than the previous approach, it is merely a way of emphasizing the common idea behind all three representations. The Sechenov coefficient (K_S^z) is defined by,

$$K_s^z = \lim_{c_s \to 0}\left(\frac{d}{dc_s}\log\left(\frac{S_0^z}{S^z}\right)\right)_{T,P,\mu_2} \tag{A2.1}$$

where S is the solubility of a solute in a salt solution of salt concentration c_s, measured in concentration units z. The units of z can be either molality (m_2), molarity (c_2), or mole fraction (x_2). From now on, we drop the T and P subscripts on partial derivatives, since these will be held constant throughout. We first write,

$$\left(\frac{\partial \log z_2}{\partial c_s}\right)_{\mu_2} = -\frac{n_\pm}{2.303 z_2}\left(\frac{(\partial\mu_2/\partial c_3)_{z_2}}{(\partial\mu_2/\partial z_2)_{c_3}}\right) \tag{A2.2}$$

where $n_\pm$ is the total number of ions resulting from the dissociation of one formula unit of the salt, and $c_3 = n_\pm c_s$ (see text). All we have to do is calculate the derivatives on the rhs. It is the derivatives $(\partial\mu_i/\partial N_j)_{N'}$ that are easily computed in terms of KB integrals, so we must express the derivatives appearing in Equation A2.2 in terms of the latter. That can be done as follows,

$$\left(\frac{\partial\mu_2}{\partial N_j}\right)_{N'} = \left(\frac{\partial\mu_2}{\partial z_2}\right)_{c_3}\left(\frac{\partial z_2}{\partial N_j}\right)_{N'} + \left(\frac{\partial\mu_2}{\partial c_3}\right)_{z_2}\left(\frac{\partial c_3}{\partial N_j}\right)_{N'} \qquad j=1,2 \tag{A2.3}$$

These are two linear equations in the two unknowns. These can be solved, say by Cramer's rule, for the two unknowns, $\partial\mu_2/\partial z_2$ and $\partial\mu_2/\partial c_3$. It only remains to place the solutions in Equation A2.2 and then pass to the limit $c_3 \to 0$.

The $\partial z_2/\partial N$ and $\partial c_3/\partial N$ derivatives are easy to calculate. Since we are computing a ratio and then taking a limit, a lot of cancellation occurs. In particular, we may safely set $c_3 = 0$ everywhere except where it multiplies G_{33} or where it occurs in a denominator. When the cosolvent is an electrolyte it is not completely obvious that $c_3G_{33} = 0$ at infinite dilution of electrolyte since $c_3G_{+-} = 1$ in this limit.[21] However, Equation 27 of this paper shows that, in fact, there is no problem.

When c_3 occurs in a denominator, the dangerous looking poles get tamed when taking the ratio but this must be done carefully. It is not necessary to compute the KB determinant since it will cancel on taking the ratio. Similarly, in solving Equations A2.3 using Cramer's rule it is not necessary to compute the determinant of the coefficients as this will also cancel. These rules greatly simplify the algebra of the computation.

Finally, the results obtained from Equation A2.2 yield Equation 38, Equation 39, and Equation 41 of the main text.

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Table 1

KB analysis of the effects of different salts on benzene solubility at 298 K.

Salt	k_s M^{-1}	$G_{23} - G_{21}$ cm^3/mol	G_{2+} (= G_{2-}) cm^3/mol
NaF	0.254	−292	−382
NaCl	0.195	−225	−314
NaBr	0.155	−179	−268
NaI	0.095	−109	−199
LiCl	0.141	−162	−252
NaCl	0.195	−225	−314
KCl	0.166	−191	−281
RbCl	0.140	−161	−251
CsCl	0.088	−101	−191

Salting out constants ($k_S = K_S^C = K_{23}^C$) were taken from Reference 35. All values correspond to infinite dilution of both solute and cosolvent. Data in column three were obtained using Equation 35 and Equation 36. Data in column four were obtained from Equation 37 using a value of $\overline{V_2}^{\infty} - RT\kappa_T = -G_{21}^{\infty} = 89.4\ \mathrm{cm}^3/\mathrm{mol}$ taken from Reference 35.