Physico-Chemical Features of Ionic Liquids Solution in Phase Separation of Penicillin(II): Winsor II Reversed Micelle

(Supporting Information)

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This Supporting Information consists of 14 pages of text, 32 equations, with 8 Figures.
The real cosurfactant/surfactant ratio in the interfacial film of W/O microemulsion

Though the mole ratio of cosurfactant (hexanol) to surfactant (ionic liquids) keeps constant in the whole microemulsion system, the actual ratio in the interfacial film would be vary with different experimental condition(such as the salt concentration and W₀) . Hence it’s necessary to investigate the actual ratio of [hexanol]/[ionic liquids] in the interfacial film. We employ the Schulman-Bowcott model[1], which deems the “water core” as well as the interfacial district as an independent region from the residual organic media. When we vary the concentrations of oil and alcohol in the system, but keeping W₀ constant, the characteristic of interfacial film was assumed to be constant, and all of the cost alcohol was supposed to dissolve in the oil phase.

Hence, the amount of alcohol in the microemulsion should be equal to the sum of three parts:

\[ n_\text{a} = n_\text{a}^\text{o} + n_\text{a}^\text{i} + n_\text{a}^\text{aq} \]  

(1)

where n_\text{a} is the total amount of alcohol in the microemulsion, n_\text{a}^\text{o}, n_\text{a}^\text{i} and n_\text{a}^\text{aq} represent the numbers of moles of alcohol in the oil layer, interfacial layer and “water pool”, respectively. Generally, alcohol with relatively long chain shows negligible solubility in water, so n_\text{a}^\text{aq} could be omitted from Equation (1). On the other hand, in order to dilute the system with oil, it’s necessary to maintain a constant alcohol to oil ratio in the continuous phase, i.e.

\[ \frac{n_\text{a}^\text{o}}{n_\text{a}} = K_1 \]  

(2)

Hence we obtain:

\[ \frac{n_\text{a}}{N_\text{al}} = \frac{n_\text{a}^\text{o}}{N_\text{al}} + \frac{n_\text{a}^\text{i}}{N_\text{al}} = \frac{n_\text{a}^\text{i}}{N_\text{al}} + \frac{K_1 n_\text{a}}{N_\text{al}} \]  

(3)

N_\text{al} is the numbers of mole of ionic liquids in the microemulsion. Equation 3 indicates that the microemulsion is diluted with oil(increase the n_\text{a}/N_\text{al}), the necessary alcohol to keep the microemulsion clear would increase proportionally. And we could obtain the actual ratio of alcohol to ionic liquids in the interfacial film from the intercept of Equation 3.
Figure 1~3 show the relationship of \( n_a/N_{ii} \) vs \( n_o/N_{ii} \) in microemulsion with different \( W_0 \) and salinity, where the intercept represents the ratio of alcohol to ionic liquids surfactant in the interfacial film, while the slope refers to the concentration of alcohol in the oil phase. It’s found the mole ratio of alcohol to ionic liquids in the interfacial film maintain within the range of 3.4~4.5, which depends little on the experimental condition. Hence it could draw the conclusion that although the ratio of alcohol to ionic liquids keeps constant at 8 in whole microemulsion system, the actual ratio of alcohol/ionic liquids in the interfacial film is about the half of its original value, and it depends little on \( W_0 \) and salinity. If we consider that some of ionic liquids reside in the “water pool”, over 50% alcohol would retain in the oil phase. In other word, the validity of the conversion factor \( \phi_{il}^\text{inf} (\overline{V}_{il} + \mu_{il}) \) in Equation 3,7 and 8 in the
The actual concentration of ionic liquids surfactant on the interfacial film of W/O microemulsion

To measure the actual concentration of ionic liquids surfactant in the interfacial film, similar method as above could be adopted.

\[ N_{il} = N_{il}^o + N_{il}^i + N_{il}^{aq} \]  \hspace{1cm} (4)

where \( N_{il}^o \), \( N_{il}^i \), \( N_{il}^{aq} \) and \( N_{il} \) are the number of moles of ionic liquids surfactant in the oil, interfacial and “water pool”, respectively. Generally, the concentration of ionic liquids in the hydrocarbon phase is neglectable, i.e, \( N_{il}^o \approx 0 \). Hence, we could suppose a constant concentration of ionic liquids surfactant existing in the “water pool” if the concentrations of salt and ionic liquids surfactant in W/O system could keep constant.

\[ N_{il}^{aq} / n_{aq} = K_2 \]  \hspace{1cm} (5)

where \( n_{aq} \) is the number of moles of water in the “water pool”. We obtain:

\[ \frac{N_{il}}{n_{aq}} = \frac{N_{il}^i}{n_{aq}} + \frac{N_{il}^{aq}}{n_{aq}} = \frac{N_{il}^i}{n_{aq}} + K_2 \]  \hspace{1cm} (6)

i.e

\[ \frac{1}{W_0} = \frac{N_{il}^i}{n_{aq}} + K_2 \]  \hspace{1cm} (7)

In analogy with the above methods to measure the actual alcohol/surfactant ratio in the interface, we adopt a plot of \( 1/W_0 - 1/n_{aq} \) line to explore how much the ionic liquids concentration is required to maintain the W/O microemulsion stable when the water amount in the microemulsion is increased. Figure 4-6 show the relationship between \( 1/W_0 \) and \( 1/n_{aq} \) in various experimental conditions containing different sality and ionic liquids concentration(where the mole ratio of alcohol/ionic liquids keep at 8 in all the works). The intercept \( K_2 \) represents the concentration of surfactant in the “water pool”, while the slope \( N_{il}^i \) refers to the actual concentration of ionic liquids surfactant in the interfacial layer.
Figure 4–6 Relationship between 1/W₀ and 1/n₉ in microemulsion with different nₛ and salt

Figure 4–6 show the relationship between 1/W₀ and 1/n₉ in microemulsion at different W₀ and salt. From their intercept and slope, we could know the amount of ionic liquids surfactant \( N^{li}_i \) in the interfacial film of W/O microemulsion, as well as the concentration of ionic liquids in the aqueous phase. It was found that the ionic liquids concentration in the aqueous solution is relatively small (the intercept in Figure 4–6), while the efficient concentrations of ionic liquids in the interfacial film vary evidently with the salt’s concentration, and the total ionic liquids concentration in the microemulsion(Figure 7).
Figure 7 Interfacial concentrations of ionic liquids at different salt concentration and total ionic liquids concentration.

Figure 7 shows the concentration of ionic liquids in the interfacial films. It’s found that the interfacial concentrations of ionic liquids depend evidently on the total concentration of ionic liquids in the microemulsion $\phi_{il}^{mn}$. When the total concentration increase from 0.15mol/l to 0.3mol/l, the interfacial concentration $\phi_{il}^{inf}$ increase proportionally from 0.065 mol/l to 0.115 mol/l. On the contrary, the salt concentration (i.e the $W_0$) imposes little effect on the interfacial concentrations $\phi_{il}^{inf}$, especially in the low concentration region of ionic liquids. Hence we could approximately assume that the interfacial concentration $\phi_{il}^{inf}$ of ionic liquids keeps proportional with the total concentration of ionic liquids in the microemulsion, i.e.

$$\phi_{il}^{inf} = k \cdot \phi_{il}^{mn}$$

(8)

where k is a constant value between 0.33–0.6, which is independent on the $W_0$ in microemulsion.

Basic thermodynamical expression in ILRM

The curve film in ionic liquids reverse micelle (ILRM) could be looked as a consequence bending from its original state of the planner monolayer, so the chemical potential of penicillin in the interfacial film in ILRM is:
\[\mu_{rm} = \mu_{mo}^0 + RT \ln \frac{\phi_{IL}^{m}}{\phi_{IL}^{inf} \left( \frac{V_{il}}{V_{al}} + \mu_{al} \right)} + \left( \frac{\partial H_{mf}}{\partial n_s} \right)_{N_a} - T \left( \frac{\partial S_{mf}}{\partial n_s} \right)_{N_a} \tag{9} \]

\(\mu_{rm}\) is the chemical potential of solute in the organic phase of ILRM, which comprised of four parts: 1) \(\mu_{mo}^0\) is the standard chemical potential of penicillin in the planar monolayer, which is a reference state without contribution from the conformational entropy and pressure enthalpy due to its infinite large curvature radius[2]. The value of \(\mu_{mo}^0\) can be calculated from regular solution theory as shown in Equation (10)~(12)[3],

\[\frac{\mu_{mo}^0}{k_BT} = z\omega_{ss}/k_BT + \chi_{sc} - g/k_BT \tag{10}\]

\[\chi_{sc} = (z/k_BT) \left[ \omega_{sc} - (\omega_{ss} + \omega_{cc}/2) \right] \tag{11}\]

\[g = \omega_{sc} + \omega_{cc} - \omega_{ss} - \omega_{cc} \tag{12}\]

where \(z\) is the number of nearest neighbors, \(\omega_{xy}\) is the free energy bringing molecules \(x\) and \(y\) from infinite separation to neighboring contact. \(g\) is the excess free energy cost of exchanging a chain/solvent contact with a solute/solvent contact at the interface, where the surface-active penicillin is supposed to locate in the layer 1 near the film/water interface and is likely to be affected by the characters of solvent and ionic liquids chain conformation.

2) The second term in Equation 3 is the mixing entropy of solute, which originates from the actual concentration of solute deviated from its standard state. The term \(\phi_{IL}^{inf} \left( \frac{V_{il}}{V_{al}} + \mu_{al} \right)\) denote as the ratio of volume of interfacial layer to that of whole microemulsion phase (the sum of the volume of the oil, interfacial film and aqueous solution). \(V_{il}\) and \(V_{al}\) are the partial volume of ionic liquids and alcohol molecule. \(u\) is the fixed mole ratio of cosurfactant to ionic liquids surfactant (about 3.4-4.5 despite of its original value at 8). \(W_0\) is the molar ratio of saluted water to ionic liquids.

According to Equation (8), \(\phi_{IL}^{inf}\) could be assumed as a linear function of the bulk concentration of ionic liquids \(\phi_{IL}^{m}\) in the organic layer. Hence Equation (9) could be transferred into:

\[\mu_{rm} = \mu_{mo}^0 + RT \ln \frac{\phi_{IL}^{m}}{k\phi_{IL}^{inf} \left( \frac{V_{il}}{V_{al}} + u\mu_{al} \right)} + \left( \frac{\partial H_{mf}}{\partial n_s} \right)_{N_a} - T \left( \frac{\partial S_{mf}}{\partial n_s} \right)_{N_a} \tag{13}\]

Because \(\phi_{IL}^{m}\) represent the number of mole of ionic liquids in unit volume of microemulsion and it’s measured after the formation of microemulsion system, it will depend on the water concentration in microemulsion (i.e. \(W_0\)). In other word, when the number of mole of ionic liquids keeps constant in microemulsion but \(W_0\) increases, \(\phi_{IL}^{m}\) will
decrease due to the increase in the bulk volume $V_{rm}$ in microemulsion phase.

$$V_{rm} = V_{oil} + V_{int} + V_{aq}$$
$$= V_{oil} + V_{rm} \phi_{IL}^m \left( \bar{v}_d + u \bar{v}_{al} + W_0 \bar{v}_w \right) \quad (14)$$

$$V_{rm} = \frac{V_{oil}}{1 - \phi_{IL}^m \left( \bar{v}_d + u \bar{v}_{al} + W_0 \bar{v}_w \right)} \quad (15)$$

$$\phi_{IL}^m = \frac{N_{il}}{V_{oil}} \left[ 1 - \phi_{IL}^m \left( \bar{v}_d + u \bar{v}_{al} + W_0 \bar{v}_w \right) \right]$$

we obtain:

$$\phi_{IL}^m = \frac{1}{\frac{V_{oil}}{N_{il}} + \bar{v}_d + u \bar{v}_{al} + W_0 \bar{v}_w}$$
$$= \frac{1}{\phi_{IL}^0 + \bar{v}_d + u \bar{v}_{al} + W_0 \bar{v}_w} \quad (16)$$

where $V_{rm}$ is the bulk volume of microemulsion; $V_{oil}$ is the volume of oil phase, which is assumed to keep constant during the formation of reverse micelle(i.e. independent on $W_0$). $N_{il}$ is the total mole of ionic liquids in the microemulsion, which is assumed to be equal to the original number of moles of ionic liquids introduced into the microemulsion. $\phi_{IL}^0$ represents the original concentration of ionic liquids respect to the volume of oil phase $V_{oil}$ (in most case is 0.15mol/l in this work). Equation (16) suggests that $\phi_{IL}^m$ is a function of $W_0$. The larger $W_0$, the smaller $\phi_{IL}^m$ is.
Figure 8 Concentration of ionic liquids (φ<sub>IL</sub><sup>m</sup>) vs W<sub>0</sub> in the microemulsion phase

Figure 8 shows φ<sub>IL</sub><sup>m</sup> as a function of W<sub>0</sub> in the microemulsion system, which decreases with increase in W<sub>0</sub>. When W<sub>0</sub> increase from 20 to 60, φ<sub>IL</sub><sup>m</sup> decreases from 0.142 to 0.125 mol/l. The result is very consistent with the theoretical predication from Equation (16), in which \( \frac{1}{\phi_{IL}^0} \) is 6.66 (1/0.15), \( \bar{v}_w \) is equal to 0.018 (1/55.5) and the volume contribution from the interfacial layer could be ignored. Consequently, the contribution of φ<sub>IL</sub><sup>m</sup> to the increase in log D would be \( \log\left(\frac{0.142}{0.125}\right) = 0.055 \) unit when W<sub>0</sub> increases from 20 to 60. The value is inferior to the contribution from \( -\frac{\kappa_s\bar{\alpha}V_s}{6.909RT\bar{v}_w} \frac{1}{W_0} \) term (about 1.0, see Figure 4-8 in manuscripts). In a simply consideration, we appoint that φ<sub>IL</sub><sup>m</sup> is equal to the original concentration φ<sub>IL</sub><sup>0</sup> in the microemulsion (0.15mol/l in most cases), which allow us to pay out attention in exploring the enthalpic and entropic contribution term. In other word, the second term in Equation 13 keep its original form, and only the fourth term \( -\frac{\kappa_s\bar{\alpha}V_s}{6.909RT\bar{v}_w} \frac{1}{W_0} \) is affected by W<sub>0</sub>. So the meanings of slope and intercept of log D~1/W<sub>0</sub> was explicit now.

\[
\left(\frac{\partial H_{inf}}{\partial n_s}\right)_{N_s}
\]

represents the variation of pressure enthalpy between the solute and interfacial film during the
transfer of the interfacial film from a planar state to a curve one.

4) \( \left( \frac{\partial S_{\text{inf}}}{\partial n_x} \right)_{N_i} \) refers to the entropic cost of the perturbation of chain conformations when the solute is introduced, which is evident as the curvature radius of “water pool” decrease. \( N_i \) and \( n_x \) are molecular number of ionic liquids(include the cosurfactant) and penicillin in reverse micelle [4].

Enthalpy contribution \( \left( \frac{\partial H_{\text{inf}}}{\partial n_x} \right)_{N_i} \) in Equation 13

The interfacial film comprised of surfactant and alcohol can be deemed as an independent zone with constant volume and 2-dimension geometric restriction during the introduction of solutes. The volume of reverse micelle is:

\[
V_{\text{inf}} = A_{\text{inf}} d = 4\pi \left( r + d/2 \right)^2 d = \bar{V}_{i} N_i + \bar{V}_s n_s
\]  

(17)

\( V_{\text{inf}} \) is the volume of interfacial layer in reverse micelle, which has a inner radius of \( r \) (“water pool”) and a thickness \( d \) (close to the side-chain length of ionic liquids), \( \bar{V}_s \) is the partial mole volume of penicillin. \( A_{\text{inf}} \) is the effective area of molecules in the interfacial film.

The partial enthalpy can be calculated from the lattice pressure[3,5]:

\[
\left( \frac{\partial H_{\text{inf}}}{\partial n_x} \right)_{N_i} = \left( \frac{\partial H_{\text{inf}}}{\partial A_{\text{inf}}} \right)_{N_i} \left( \frac{\partial A_{\text{inf}}}{\partial n_x} \right)_{N_i}
\]

(18)

From Equation 17 we can obtain:

\[
\left( \frac{\partial A_{\text{inf}}}{\partial n_x} \right)_{N_i} = \frac{\bar{V}_s}{d}
\]

(19)

According to the curvature modulus theory [6], the interfacial enthalpy of penicillin in reverse micelle is:

\[
H_{\text{inf}} \left( A_{\text{inf}}, N_i \right) = N_i \tilde{H}_{\text{inf}} \left( \alpha_i \right) = N_i \left[ \tilde{H}_{\text{inf}} \left( \bar{\alpha} \right) + \gamma \left( \alpha_i - \bar{\alpha} \right) + \kappa_s \left( \frac{\alpha_i - \bar{\alpha}}{2\bar{\alpha}} \right)^2 \right]
\]

(20)

In Equation 20, \( \tilde{H}_{\text{inf}} \) is the free energy of single ionic liquids surfactant at the interface; \( \gamma \) is the interfacial tension, which is very small in W/O microemulsion and impose little effect on the interfacial enthalpy in comparison with the curvature energy in reverse micelle. So it was omitted from Equation 20[7]. The third term \( \kappa_s \left( \frac{\alpha_i - \bar{\alpha}}{2\bar{\alpha}} \right)^2 \) in
Equation 20 represents the contribution of curvature energy to the partitioning ratio of solute when the interface was bended. $\kappa_\alpha$ is the curvature modulus in the interface, $\alpha_i$ is the equilibrium area per ionic liquids in a curved interface; $\overline{\alpha}$ is the initial area in a planar membrane. From Equation 20 the partial enthalpy in interface is:

$$\frac{\partial \mathcal{H}_{\text{inf}}}{\partial \mathcal{A}_{\text{inf}}}_{N_i} = \kappa_\alpha \left( \overline{\alpha} - \alpha_i \right) \overline{\alpha}$$  \hfill (21)

The relationship between $\alpha_i$ and $\overline{\alpha}$ could be obtained from the geometric restriction in reverse micelle:

$$\alpha_i = \overline{\alpha} \left( 1 - \frac{d}{r} \right)$$  \hfill (22)

Substituting Equation 22 into 23, we obtain:

$$\frac{\partial \mathcal{H}_{\text{inf}}}{\partial \mathcal{A}_{\text{inf}}}_{N_{\text{inf}}} = \frac{d}{r} \kappa_\alpha$$  \hfill (23)

Substituting Equation 23 and 19 into Equation 18, the partial enthalpy during the addition of solutes is obtained:

$$\frac{\partial \mathcal{H}_{\text{inf}}}{\partial \mathcal{n}_s}_{N_i} = \frac{\mathcal{V} \kappa_\alpha}{r}$$  \hfill (24)

Entropy contribution $\frac{\partial S_{\text{inf}}}{\partial \mathcal{n}_s}_{N_i}$ in Equation 13

Contemporarily, the term $\frac{\partial S_{\text{inf}}}{\partial \mathcal{n}_s}_{N_i}$ corresponds to the entropic cost from the disturbance of chain conformation in ILRM as the solute is added, which could be obtained from a lattice model. Each segment in the side-chain of ionic liquids is diametric in order to keep its size equal in any orientation and its length is of 4.6 Å equal to 3.6 methylene groups. Each monomer has a configuration comprised of $n$ lattice segments in any manner, provided it occupies contiguous sites on the lattice. Every segment occupies no more than a single site, and the solute molecule occupies $s$ segments.

$$\frac{\partial \mathcal{S}_{\text{inf}}}{\partial \mathcal{n}_s}_{N_i} = \sum_{i=1}^{s} \sum_{j=1}^{n} \left( \frac{\partial \mathcal{N}_j}{\partial \mathcal{n}_s} \right) \ln q_i = \sum_{j=1}^{n} \left( \frac{\partial \mathcal{N}_j}{\partial \mathcal{n}_s} \right) \ln q_i \langle t_s \rangle$$  \hfill (25)

where $q_i$ is the statistical weight for a segment in layer $i$ (its natural logarithm is the Lagrange multiplier).
refers to the average volume effect based on the mean field theory, and it equals to the unit volume of one segment times the $s$ numbers of segment each solute occupied.

Following the geometrical restriction of reverse micelle, as well as Equation 15, we obtain:

$$N_j = 4\pi / 3 \left[ 3(r + j - 1)(r + j) + 1 \right]$$  \hspace{1cm} (26)

$$\left( \frac{\partial N_j}{\partial n_j} \right) = \left( \frac{\partial N_j}{\partial r} \right) \left( \frac{\partial r}{\partial n_j} \right) = \frac{(2r + 2j - 1)}{2rd}$$  \hspace{1cm} (27)

Substituting Equation 27 into Equation 25, we obtain:

$$\left( \frac{\partial S_{\text{mf}}}{\partial n_j} \right)_{N_j} = \sum_{j=1}^{r} \left[ \frac{2r + 2j - 1}{2rd} \right] \ln q_i \langle l_i \rangle \sim r^0$$  \hspace{1cm} (28)

Equation 28 suggests that the conformational entropy is approximate independent on the radius $r$ of “water pool”. Hence the intercepts of log $D~1/W_0$ line (primarily related to conformational entropy) wouldn’t vary with those factors concerning with the size of “water pool”, while only rely on the factors governing the chain conformation in ILRM (see Equation 30 below).

### Chemical potential $\mu_m$ and partitioning ratio $D$ of penicillin in ILRM

According to Equation 23, 24 and 28, the final expression of the chemical potential of penicillin in ILRM is below:

$$\mu_m = \mu_m^0 + RT \ln \left( \frac{\phi_m}{k_\phi^{m(rm)}(\bar{V}_d + u\bar{V}_al)} \right) + RT \sum_{j=1}^{r} \left[ \frac{2r + 2j - 1}{2rd} \right] \ln q_i \langle l_i \rangle + \frac{\kappa_{al} V_s}{r}$$  \hspace{1cm} (29)

And the partitioning ratio of penicillin in ILRM is:

$$\ln D = \ln \left( \frac{\phi_m}{\phi_s} \right) = - \frac{\left( \mu_m^0 - \mu_s^0 \right)}{RT} - \ln k_\phi^{m(rm)}(\bar{V}_d + u\bar{V}_al) + \sum_{j=1}^{r} \left[ \frac{2r + 2j - 1}{2rd} \right] \ln q_i \langle l_i \rangle - \frac{\kappa_{al} V_s}{RT}$$  \hspace{1cm} (30)

### Correlation of log $D~1/W_0$

According to the geometrical restriction in reverse micelle\(^1\), any radius $r$ could be correlated into the water concentration $W_0 ([\text{H}_2\text{O}]/[\text{Ionic liquids}])$:  

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1. "Geometrical Restriction in Reverse Micelle" by John Doe
\[ r = \frac{3W_0v_w}{\alpha} \]  

(31)

\( v_w \) is the partial volume of H\_2O molecular, \( \alpha \) is the average area of ionic liquids head. So Equation 31 is transformed into 30, in which the partitioning ratio of penicillin is a function of \( W_0 \):

\[ \log D = -\frac{1}{2.303} \left[ \frac{\mu_{m0} - \mu_w^0}{RT} - \ln k\phi_{IL}^m \left( v_d + u\bar{v}_al \right) + \sum_{j=1}^{r} \left[ \frac{2r + 2j - 1}{2rd} \right] \ln q_i \left\langle l_s \right\rangle \right] - \frac{\kappa_a v_s}{2.303RT} \frac{1}{r} \]

(32)

Equation 24 demonstrates a semi-logarithm log D−1/W\_0 plot existing in ILRM. Its slope and intercept are governed by the characteristics of ILRM. The intercept

\[ -\frac{1}{2.303} \left[ \frac{\mu_{m0} - \mu_w^0}{RT} - \ln k\phi_{IL}^m \left( v_d + u\bar{v}_al \right) + \sum_{j=1}^{r} \left[ \frac{2r + 2j - 1}{2rd} \right] \ln q_i \left\langle l_s \right\rangle \right] \]

is dependent on the ionic liquids concentration \( \phi_{IL}^m \), the chain length \( d \), and the species of organic solvent, which interferes the orderliness of chain conformation in ILRM and \( q_i \) in Equation 24. On the other hand, the slope

\[ \frac{\kappa_a v_s}{6.909RTv_w} \frac{1}{W_0} \]

depends on the head area \( \alpha \) and elasticity rigidity \( \kappa_a \), which are affected by the polarity of inorganic salt and the head structure of ionic liquids. Finally, we obtain a semi-logarithm plot of log D vs 1/W\_0 in ionic liquids microemulsion, which is consistent with Equation 8 in the manuscripts.

Reference


