

## Soluble 1:1 Complexes and Insoluble 3:2 Complexes

Understanding the Phase-Solubility Diagram of Hydrocortisone and  $\gamma$ -Cyclodextrin

Schönbeck, Jens Christian Sidney; Madsen, Tobias Løvgren; Peters, Günther H.; Holm, René; Loftsson, Thorsteinn

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# **Soluble 1:1 Complexes and Insoluble 3:2 Complexes – Understanding the Phase-Solubility Diagram of Hydrocortisone and $\gamma$ -Cyclodextrin**

Christian Schönbeck, Tobias L. Madsen, Günther H. Peters, René Holm, and Thorsteinn Loftsson

Supplementary material

## General construction of theoretical phase-solubility diagrams

Phase-solubility diagrams are plots of the solution-phase concentrations of solute at equilibrium,  $S_{eq}$ , as a function of the initial concentration of ligand,  $L_t$ , in the dissolution medium. Less common, the solution-phase concentration of ligand at equilibrium,  $L_{eq}$ , can also be plotted as a function of  $L_t$ . Theoretical phase-solubility diagrams are constructed by calculating  $S_{eq}$  and/or  $L_{eq}$  from the known quantities  $L_t$  and  $S_t$  (the total amount of added solute). Such calculations involve solving a set of equations expressing the relevant mass balances (eq. 1, 2, 5 and 6 in the manuscript) and laws of mass action (eq. 3 and 4 in the manuscript). These equations contain various equilibrium constants such as the solubility of solute ( $S_0$ ) and complex ( $S_{XY}$ ) and the equilibrium constants for the formation of complexes ( $K_{XY}$ ). These equilibrium constants must be determined experimentally.

Theoretical expressions for  $S_{eq}$  and/or  $L_{eq}$  are derived for each of the regions in the phase-solubility diagrams. The transitions between the regions can be found as the intersections of these expressions, *i.e.* the transition between region I and II can be found as the intersection between the expression for  $S_{eq}$  in region I and the plateau in region II.

### Solving the 3:2 model

The relevant mass balances are (adapted from eq. 1 and 2 in the manuscript):

$$S_{eq} = [S] + [LS] + 2[L_3S_2]$$

$$L_{eq} = [L] + [LS] + 3[L_3S_2]$$

The relevant laws of mass action are (adapted from eq. 3 and 4 in the manuscript):

$$[LS] = K_{11} * [L] * [S]$$

$$[L_3S_2] = K_{32} * [L]^3 * [S]^2$$

#### **Region I:**

Since no ligand precipitates:

$$L_{eq} = L_t$$

Since solid S is present:

$$[S] = S_0$$

From the mass balances and the laws of mass action:

$$L_{eq} = [L] + [LS] + 3[L_3S_2]$$

$$= [L](1 + K_{11} \cdot S_0) + 3K_{32}[L]^3 S_0^2$$

This 3. order equation can be solved for [L], which can be inserted into:

$$S_{eq} = [S] + [LS] + 2[L_3S_2]$$

$$= S_0 + [L] \cdot K_{11} \cdot S_0 + 2K_{2:3}[L]^3 S_0^2$$

Now  $S_{eq}$  is expressed as a function of  $S_0$ ,  $L$ ,  $K_{11}$ , and  $K_{23}$ .

### **Region II:**

Since solid solute and solid 3:2 complex is present:

$$[S] = S_0$$

$$[L_3S_2] = S_{32}$$

$$[L]^3[S]^2 = K_{32}^S$$

Rearranging the latter equation:

$$[L] = \sqrt[3]{K_{32}^S / S_0^2}$$

which can be inserted into:

$$[LS] = K_{11} * [L] * [S]$$

to give:

$$[LS] = K_{11} \cdot \sqrt[3]{K_{32}^S \cdot S_0}$$

The solubility product can be expressed in terms of  $S_{32}$  and  $K_{32}$ :

$$K_{32}^S = S_{32} / K_{32}$$

so

$$[LS] = K_{11} \cdot \sqrt[3]{S_{32} / K_{32} \cdot S_0}$$

This can be inserted into the mass balances:

$$S_{eq} = [S] + [LS] + 2[L_3S_2] = S_0 + [LS] + 2S_{32} = S_0 + K_{11} \cdot \sqrt[3]{S_{32} / K_{32} \cdot S_0} + 2S_{32} = constant$$

$S_{eq}$  is hereby expressed as a function of  $S_0$ ,  $S_{32}$ ,  $K_{11}$ , and  $K_{23}$ .

$$L_{eq} = [S] + [LS] + 3[L_3S_2] = [LS] \left( 1 + \frac{1}{K_{11} \cdot S_0} \right) + 3[L_3S_2]$$

$$= K_{11} \cdot \sqrt[3]{S_{32} / K_{32} \cdot S_0} \cdot \left( 1 + \frac{1}{K_{11} \cdot S_0} \right) + 3S_{32} = constant$$

$L_{eq}$  is hereby expressed as a function of  $S_0$ ,  $S_{32}$ ,  $K_{11}$ , and  $K_{23}$ .

### **Region III:**

Adaptation of eq. 7 in the manuscript:

$$2 \cdot L_t - 3 \cdot S_t = 2 \cdot L_{eq} - 3 \cdot S_{eq}$$

Insertion of the mass balances:

$$\begin{aligned} 2 \cdot L_t - 3 \cdot S_t &= 2 \cdot [L] + 2 \cdot [LS] + 6 \cdot [L_3S_2] - 3 \cdot [S] - 3 \cdot [LS] - 6 \cdot [L_3S_2] \\ &= 2 \cdot [L] - 3 \cdot [S] - [LS] \end{aligned}$$

Two out of the three molecular species ([L], [S], and [LS]) may be eliminated by the use of:

$$[L]^3[S]^2 = K_{32}^S$$

$$[LS] = K_{11} \cdot [L] \cdot [S]$$

The last molecular species may be obtained as the appropriate solution to the resulting polynomial which, however, must be solved numerically. Alternatively, a solver function can be used to numerically solve the system of 3 equations with 3 unknowns.

Once [L], [S], and [LS] are determined  $S_{eq}$  and  $L_{eq}$  can be calculated as:

$$S_{eq} = [S] + [LS] + 2 \cdot S_{32}$$

$$L_{eq} = [L] + [LS] + 3 \cdot S_{32}$$

$S_{eq}$  and  $L_{eq}$  are hereby calculated as a function of  $S_{32}$ ,  $K_{11}$ ,  $K_{32}^S$ ,  $L_t$ , and  $S_t$ . Using the relation  $K_{32}^S = S_{32} / K_{32}$ ,  $S_{eq}$  and  $L_{eq}$  can instead be calculated as a function of  $S_{32}$ ,  $K_{11}$ ,  $K_{32}$ ,  $L_t$ , and  $S_t$ .

### **Transitions:**

To construct the phase-solubility diagram it is also necessary to know the location of the transitions between the regions.

The transition from region I to region II is found as the intersect between the functions for  $L_{eq}$  in region I and region II. Setting these two expressions equal to each other yields:

$$L_{eq}(I) = L_{eq}(II)$$

$$L_t = K_{11} \cdot \sqrt[3]{S_{32}/K_{32} \cdot S_0} \cdot \left(1 + \frac{1}{K_{11} \cdot S_0}\right) + 3S_{32}$$

It is seen that this transition does not depend on  $S_t$ .

In principle, the transition from region II to region III can be found as the intersect between the functions for  $L_{eq}$  in region II and region III but since no analytical expression is available for  $L_{eq}$  in region III another strategy is used. For notational simplicity the transition between region I and II is called point A, and the transition from region II to III is called point B. Region II starts when the 3:2

complex starts precipitating from the solution and ends when all solid S is converted to complex. Since L and S is converted to complex in a 3 to 2 ratio the length of region II can be calculated as:

$$L_t(B) - L_t(A) = 1.5 \cdot S_{\text{solid}}(A) = 1.5 \cdot (S_t - S_{\text{eq}}(A))$$

where  $S_{\text{solid}}(A)$  is the amount of solid S at point A which in turn is equal to the total amount of S minus the amount of S in solution.

Replacing  $L_t(A)$  with the already derived expression for  $L_{\text{eq}}$  in region II and replacing  $S_{\text{eq}}(A)$  with the expression for  $S_{\text{eq}}$  in region II allows for  $L_t(B)$  to be isolated as:

$$L_t(B) = 1.5 \cdot (S_t - S_0) \cdot K_{11} \cdot \sqrt[3]{S_{32}/K_{32} \cdot S_0} \cdot \left( \frac{1}{K_{11} \cdot S_0} - 0.5 \right)$$

It is seen that the location of this transition depends on  $S_t$ .

## Construction of reverse phase-solubility diagrams for the 3:2 model

The equilibrium constants that govern the shape of the normal phase-solubility diagram also govern the shape of the reverse phase-solubility diagram. Further, the equations that apply to the various regions in the normal phase-solubility diagram also apply to the reverse phase-solubility diagram. Only the location of the transitions between the regions are different in the reverse phase-solubility diagram. Also the equations in the new region IV needs to be derived for the reverse phase-solubility diagram but this is a trivial problem as no precipitate is formed and therefore  $S_{\text{eq}} = S_t$  and  $L_{\text{eq}} = L_t$ .

### ***Transition from region IV to region III:***

Transition from region IV to region III occurs when the product  $[L]^3[S]^2$  exceeds the solubility product  $K_{32}^S$  and the 3:2 complex starts precipitating. No analytical expression can be found for this transition which can be found by numerically solving the following systems of equations, assuming that the concentration of 3.2 complexes in solution is negligible:

$$S_t = [S] + [LS]$$

$$L_t = [L] + [LS]$$

$$[LS] = K_{11} \cdot [L] \cdot [S]$$

$$[L]^3[S]^2 = K_{32}^S$$

This system of equations can be solved to provide the total amount of added solute,  $S_t$ , at which the transition occurs. This is a function of  $K_{11}$ ,  $K_{32}^S$ , and also the total concentration of cyclodextrin in the medium,  $L_t$ . As  $L_t$  goes up the value of  $S_t$  at which the transition occurs decreases.

***Transition from region III to region II:***

The starting point for deriving an expression for the transition from region III to region II is the previously derived relation:

$$2 \cdot L_t - 3 \cdot S_t = 2 \cdot [L] - 3 \cdot [S] - [LS]$$

which is valid in region III but not in region II. Region II starts when  $[S]$  reaches  $S_0$  so the transition occurs when  $[S] = S_0$ .

The remaining molecular species,  $[L]$  and  $[LS]$ , are then substituted. First,  $[L]$  is substituted with:

$$[L] = [LS]/K_{11} \cdot S_0$$

Then  $[LS]$  is substituted with the previously derived relation:

$$[LS] = K_{11} \cdot \sqrt[3]{K_{32}^S \cdot S_0}$$

This results in the final expression for the transition:

$$S_t = K_{11} \cdot \sqrt[3]{K_{23}^S \cdot S_0} \cdot \left( \frac{1}{3} - \frac{2}{3 \cdot K_{11} \cdot S_0} \right) + S_0 + \frac{2}{3} \cdot L_t$$

It is seen that the transition depends on  $L_t$  but in a simple linear way.