

Support material

Dependence of viscosity and diffusion on β -cyclodextrin and chloroquine diphosphate interactions

Lenka Musilová ^{1,2}, Aleš Mráček ^{1,2*}, Ana C.F. Ribeiro ^{3,*}, Eduarda F. G. Azevedo ³, M. Melia Rodrigo ⁴, Artur J.M. Valente ³, Miguel A. Esteso ^{4,5}

Estimate of the association constant for solutes in chemical equilibrium

Using theoretical model developed by Paduano et al. [32-35] to adjust the experimental data obtained for the main and cross diffusion coefficients, it was possible to estimate the value for the association constant K , of chloroquine diphosphate (CDP) and β -cyclodextrin (β -CD), considering the kind of complexes formed of the type 1:1. Both this theoretical development, as well as the equations that allow correlating the coefficients of diffusion with the equilibrium constants, are adequately described by these authors and referenced in the bibliography, so that only the most important points will be relevant factors that lead to the determination of the aforementioned equilibrium constants.

This model considers acceptable the approximation that in solutions very diluted the cross-diffusion coefficients, D_{12} and D_{21} , are despicable, and at infinitesimal concentration, these coefficients must be zero, within experimental error. However, when an equilibrium of association occurs these parameters are different from zero.

In addition, to apply the thermodynamics of irreversible processes to coupled Fick equations (Eqs. 1,2),

$$J_1 = -D_{11}\nabla C_1 - D_{12}\nabla C_2 \quad (1)$$

$$J_2 = -D_{21}\nabla C_1 - D_{22}\nabla C_2 \quad (2)$$

where J_1 and J_2 are the molar fluxes of CDP (1) and β -CD (2), respectively, driven by the concentration gradients ∇C_1 and ∇C_2 of each solute 1 and 2, and cross-diffusion coefficients D_{12} and D_{21} give the coupled flux of each solute, driven by a concentration gradient in the other solute, it is necessary to impose some restrictions on the matrix of the coefficients D_{ij} ($(i \neq j)$ and D_{ii} and D_{ij} represent the main and the cross diffusion coefficients, respectively).

That is,

$$\sum D_{ii} > 0 \quad (3)$$

The determinant of the matrix must be greater than or equal to zero (eq. 4). For a ternary system, these restrictions are reduced to eqs (5, 6)).

$$|D_{ij}| \geq 0 \quad (4)$$

$$D_{11} + D_{22} > 0 \quad (5)$$

$$D_{11} D_{22} + D_{12} D_{21} \geq 0 \quad (6)$$

urthmore, for dilute solutions OF component i, the following relation is valid

$$\lim_{C_i \rightarrow 0} D_{ij} = 0 \quad (i \neq j) \quad (7)$$

Generally, positive and high value of D_{ij} ($i \neq j$) are attributed the presence of salting-out effects and negative values, the existence of attractive interactions between the solutes. Relative to the ternary system studied in this work, we have identified these solute species as CDP = 1, β -CD = 2, and CDP- β -CD complexes = 3, respectively, which are in equilibrium according to the equation (eq. 8),



Being the association constant, K , that describes the stability of these complexes, given by expression (9).

$$K = \frac{C_{\text{CDP-}\beta\text{-CD}}}{C_{\text{CDP}} C_{\beta\text{-CD}}} \quad (9)$$

C_{CDP} and $C_{\beta\text{-CD}}$ are the concentrations of free (uncomplexed) CDP and β -CD, respectively, and $C_{\text{CDP-}\beta\text{-CD}}$ is the concentration of the CDP- β -CD complex, which are correlated by the following mass balance equations,

$$-J_1^* = (D_{11}^*) \nabla C_1^* + (D_{12}^*) \nabla C_2^* + (D_{13}^*) \nabla C_3^* \quad (10)$$

$$-J_2^* = (D_{21}^*) \nabla C_1^* + (D_{22}^*) \nabla C_2^* + (D_{23}^*) \nabla C_3^* \quad (11)$$

$$-J_3^* = (D_{31}^*) \nabla C_1^* + (D_{32}^*) \nabla C_2^* + (D_{33}^*) \nabla C_3^* \quad (12)$$

Considering the following relationships, in terms of the constituent species,

$$J_1 = J_1^* + J_3^* \quad (13)$$

$$J_2 = J_2^* + J_3^* \quad (14)$$

$$C_1 = C_1^* + C_3^* \quad (15)$$

$$C_2 = C_2^* + C_3^* \quad (16)$$

However, assuming that in diluted solutions the all cross diffusion terms are negligible ($D_{12}, D_{13}, D_{21}, D_{23}, D_{31}, D_{32} = 0$), and by noting that the total CDP flux (as well as β -CD flux) is the sum of the respective fluxes of free and CDP- β -CD complexes, by inserting this information in the equations (10-12), after some mathematical rearrangement, is it possible to obtain the equations (17) to (20). These equations provide the relations between the mutual diffusion coefficients $D_{11}, D_{12}, D_{21}, D_{22}$ measured for the total CDP(1) + β -CD(2) solute components, and the diffusion coefficients $D_{\text{CDP}}, D_{\beta\text{CD}}, D_{\text{CDP-}\beta\text{CD}}$ which represent the diffusion coefficients of the free CDP, the free β -CD and the corresponding complex, respectively.

$$D_{11} = \frac{1}{2} \{ (D_{CDP} + (D_{CDP-\beta-CD})) + (D_{CDP} - (D_{CDP-\beta-CD})) [1 - K(c_2 - c_1)] R \} \quad (17)$$

$$D_{12} = \frac{1}{2} \{ ((D_{CDP-\beta-CD}) - D_{CDP}) + (D_{CDP} - (D_{CDP-\beta-CD})) [1 - K(c_2 - c_1)] R \} \quad (18)$$

$$D_{21} = \frac{1}{2} \{ ((D_{CDP-\beta-CD}) - D_{\beta-CD}) + (D_{\beta-CD} - (D_{CDP-\beta-CD})) [1 - K(c_2 - c_1)] R \} \quad (19)$$

$$D_{22} = \frac{1}{2} \{ (D_{\beta-CD} + (D_{CDP-\beta-CD})) + (D_{\beta-CD} - (D_{CDP-\beta-CD})) [1 - K(c_2 - c_1)] R \} \quad (20)$$

where

$$R = \{ [1 + K(c_2 - c_1)]^2 + 4Kc_1 \}^{-1/2}$$

K , was chosen in order to obtain the best agreement between these theoretical values (Eqs. (17) to (20)) and the experimental D_{ij} data. In present case, for CDP molar fractions $X_1 \leq 0.5$, an association constant K equal to $30.0 (\pm 0.8) \text{ mol}^{-1} \text{ dm}^3$ was found.