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Chiral ligand exchange countercurrent chromatography: Equilibrium model study on enantioseparation of mandelic acid

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ABSTRACT

The equilibrium model in enantioseparation of mandelic acid by chiral ligand exchange countercurrent chromatography was investigated using *N*-n-dodecyl-L-proline as chiral ligand and cupric ion as central metal. Important parameters, including physical partition coefficient and formation constants of binary and ternary coordination complexes in the two-phase solvent system, were determined. This equilibrium model could give an excellent prediction of distribution ratio and enantioseparation factor of the analyte in the biphasic solvent system, which was further verified by experiments. All the average relative deviations were less than 12%, indicating that the established model could provide a simple computational approach for optimization of enantioseparation conditions in chiral ligand exchange countercurrent chromatography.

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1. Introduction

The availability of pure enantiomers is of primary importance in the pharmaceutical industries because of their different bioactivities in human body [1]. To obtain an enantiopure compound, a series of methods have been developed, such as crystallization [2,3], membranes technology [4], electrophoretic technique [5], simulated moving bed [6], enantioselective liquid-liquid extraction [7] and various kinds of chromatographic techniques [8]. Chiral ligand exchange chromatography has been applied to separate chiral compounds for nearly 40 years since it was first reported by Hare and Gil-Av [9]. Compared to other chiral chromatographic methods, chiral ligand exchange chromatography has competitive advantages for enantioseparation of α-amino acids, α-hydroxy acids, and amino alcohols because the chemical structure of these compounds has a tendency to form an intermediate diastereomeric complex. Chiral ligand exchange is one of the most powerful chiral recognition methods for chiral separation in countercurrent chromatography, which depends on the formation of diastereomeric coordination ternary complex among enantiomer, transitional metal and chiral ligand. D,L-Isoleucine and D,L-valine were enantioseparated by chiral ligand exchange countercurrent chromatography [10,11]. In our previous studies, five mandelic acid derivatives were successfully enantioseparated by high speed countercurrent chromatography using the chiral ligand exchange method [12].

Theoretical model of countercurrent chromatography could be used to predict and optimize the two-phase solvent system before carrying out the separation experiments. Several countercurrent chromatography mathematical models have been reported in literature to predict retention behavior of the analyte in countercurrent chromatography through modeling the mass transfer and partition behavior in two immiscible liquid phases [13–15]. However, no literature is so far available to model the distribution ratio and enantioselectivity factor through analyzing complex equilibria in the chiral ligand exchange countercurrent chromatography. The complex equilibria and partitioning performance which occur in liquid-liquid chiral extraction can be modeled by describing them in terms of global reaction equilibria equations [16–18]. Modeling the complex formation and partitioning performance in a two-phase solvent system is helpful to determine the distribution ratios and enantioselectivity factors. Generally the two-phase solvent system in countercurrent chromatography can be optimized by enantioselective liquid-liquid extraction experiments in order to obtain a suitable distribution ratio and a high enantioseparation factor. Enantioselective liquid-liquid extraction is an attractive alternative for chromatography and resolution by crystallization that, based on the scientific literature, still needs development towards commercialization. Numerous literatures are available about modeling study on enantioselective liquid-liquid extraction,

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Nomenclature

K_{f1}	The complexation equilibrium constant of cupric binary complex
$K_{f\pm,2}$	Complexation equilibrium constant of ternary complex
K_a	Dissociation constant of mandelic acid in aqueous phase
$[H^+]$	The concentration of hydrogen ion in aqueous phase
$[LH]_{org,0}$	The concentration of chiral ligand in organic phase in the first stage
$[LH]_{org}$	Equilibrium concentration of chiral ligand in the organic phase in the second stage
$[Cu^{2+}]_{aq}$	The concentration of cupric ion in aqueous phase
$C_{MH\pm}$	The initial concentration of mandelic acid in aqueous phase.
C_{CuL_2}	The initial concentration of cupric ion binary complex after equilibrium in organic phase.
$C^i_{Cu^{2+}}$ and C^i_{LH}	The initial concentrations of cupric ion and chiral ligand
P_0	Physical partition coefficient of molecular mandelic acid
P_i	Partition coefficient of ionic mandelic acid
$[MH_\pm]_{org}$ and $[MH_\pm]_{aq}$	The concentration of molecular mandelic acid in organic stationary phase and aqueous mobile phase
$M^-_{\pm org}$ and $M^-_{\pm aq}$:	The concentration of ionic mandelic acid in the organic stationary phase and the aqueous mobile phase
$[M_\pm CuL]_{org}$	Concentration of ternary complex in organic phase
$[CuL_2]_{org}$	Equilibrium concentration of cupric ion binary complex
$D_\pm$	Distribution ratio of mandelic acid enantiomer
D_{Cu}	Distribution ratios of cupric ion
P	Apparent partition coefficient
ARD	Average relative deviations

in which most of them were used for prediction and optimization of the enantioseparation conditions [19–21]. Basically two different models for enantioselective liquid-liquid extraction have been proposed in literature, namely interfacial reaction model and homogeneous reaction model [7]. The main differences between these two models are the locus of the complexation reaction. The interfacial model is used for systems in which enantiomers are only soluble in one phase of the two-phase solvent system, where the location of chemical reaction is restricted to the interface between the two phases. The homogeneous model is suitable for enantiomers that have solubility in both phases, in which the reaction takes place in one of the two phases.

In our previous paper [12], chiral ligand exchange countercurrent chromatography has been applied in enantioseparation of five racemic aromatic α-hydroxyl acids, in which the separation mechanism for countercurrent chromatography was proposed based on the experimental results. The separation mechanism showed that, for a given two-phase solvent system at constant temperature, distribution ratio of enantiomer was largely dependent on partition coefficient of the analyte, pH value of the aqueous phase, binary and ternary complex formation constant, concentration of transition metal ion and concentration of chiral ligand in the organic phase, whereas the enantioseparation factor was critically dependent on several parameters such as the difference between two ternary complex formation constants, concentration of transition metal ion and chiral ligand and pH value of the aqueous phase. However, modeling and optimization of separation conditions had not been developed in our previous work yet. Hence, the aim of our present paper is to model the complex equilibria and provide a simple computational approach for equilibria model in chiral ligand exchange countercurrent chromatography.

2. Experimental section

2.1. Chemicals

Mandelic acid was purchased from J&K Scientific Ltd. (Shanghai, China). Hydroxypropyl-β-cyclodextrin was purchased from Qianhui Fine Chemical & Co. Inc. (Shandong, China). Acetonitrile used for HPLC analysis was of chromatographic grade. Ultra-pure water was used for HPLC. All other chemicals used for separation were of analytical grade. The chiral ligand *N*-*n*-dodecyl-L-proline was synthesized by one-step reductive N-alkylation of the amino acid, according to the method described in our previous paper [12].

2.2. Determination of physical distribution coefficient P_0 and P_i

The physical distribution coefficients of molecular and ionic mandelic acid (P_0 and P_i) in the *n*-butanol-aqueous two-phase solvent system were each determined in a water bath at 10 °C. The two phases were prepared as following: (1) 0.1 mol L^{-1} phosphate buffer solutions with series of pH values in the range 3.0–7.0 were prepared from *n*-butanol-saturated water. Then mandeilc acid was dissolved in the aqueous phase at the concentration of approximately 2 mmol L^{-1}. (2) The equal volumes of above prepared aqueous solution and the water-saturated *n*-butanol solution (each 2 mL) were delivered into a 10 mL glass-stoppered test tube in a water bath at 10 °C followed by vigorous shaking for 10 min to reach equilibrium. After phase equilibrium was established, the concentration of enantiomers in the aqueous phase was determined by HPLC, while that in the organic phase was calculated by the subtraction method. The analytical method for mandelic acid enantiomers can be found in the literature [22].

2.3. Enantioselective liquid–liquid extraction experiments

The biphasic solvent system for enantioselective liquid-liquid extraction was *n*-butanol-saturated water and water-saturated *n*-butanol prepared according to our previous study [12]. The chiral ligand *N*-*n*-dodecyl-L-proline was dissolved in water-saturated *n*-butanol and cupric acetate monohydrate was dissolved in *n*-butanol-saturated water, and then these two liquids were mixed. The upper phase was used as the organic phase for the biphasic solvent system.

The equilibrium experiments were performed in 10 mL glass-stoppered tube. Equal volumes (each 2.0 mL) of the above prepared organic phase and *n*-butanol-saturated water containing mandelic acid were delivered into a stoppered glass tube in a water bath (20 min) at a constant temperature followed by vigorous shaking for 10 min to reach equilibrium. The concentration of mandelic acid in the aqueous phase was determined by HPLC, while the concentration in the organic phase was calculated by the subtraction method. Investigation on the concentration of chiral ligand and transition metal ion was similarly conducted, except that the pH value of aqueous phase was investigated in the second step (2) instead of the first step (1) as described in our previous work.

2.4. Determination of equilibrium constant of binary complexation (K_{f1})

The concentration of copper ion in different pH of aqueous solution was measured by the titration method. The experiments were

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