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Chiral Resolution by Thin Layer Extraction

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An approximate design method for the resolution of a racemate by thin layer extraction identifies a range of operation parameters that promise good separation. Its predictions are substantiated by a detailed dynamic simulation. It is concluded that chiral resolution by thin layer extraction is feasible, potentially providing a simple and economical separation method.

1. Introduction

Enantiomers play an important role in the pharma, flavors and fragrances, agrochemicals and food industries. They are presently obtained by one of several methods, including asymmetric synthesis, crystallization and chromatography. Impediments in the present methods such as low versatility, high cost and limited economical production volumes have attracted in recent years interest in chiral resolution by liquid-liquid extraction. However, conventional liquid-liquid extraction is also impeded by bulky and/or costly equipment and by the high cost of the chiral hosts used in the extractant. Thin Layer Extraction, a relatively new, versatile version of liquid-liquid extraction promises a simple and economical solution.

2. Thin Layer Extraction Brief

Thin Layer Extraction (TLX) is an intensive, periodic reactive liquid-liquid extraction method [Lavie R., 2008] that implements a compact extraction/back-extraction cycle using little extractant. The species of interest react with the extractant or with a host present therein to form a complex and are then released later in the cycle into strip liquids at appropriate conditions (pH and/or temperature) that favor such release.

The counter-current multistage TLX process (figure 1) is particularly effective. The advantages of TLX derive from its minimum extractant inventory, simplicity of operation, compactness and extraction efficiency. In TLX, mass transfer resistance is negligible: with a molecular diffusivity in the order of 10^{-9} m^2/s, the characteristic time for diffusion through a 20μ thick layer is of the order of 0.4 s which is shorter than that of the complexation reaction. Unlike resin based processes, TLX is not limited to the processing of dilute aqueous feeds thanks to frequent switching. It is versatile in its allowing manipulation in situ of process parameters that are ordinarily fixed in conventional liquid-liquid extraction. In particular, TLX permits in situ adjustment of either the organic to aqueous ratio or of the number of ideal stages. Its qualities make of it an attractive candidate for difficult separations such as chiral resolution.

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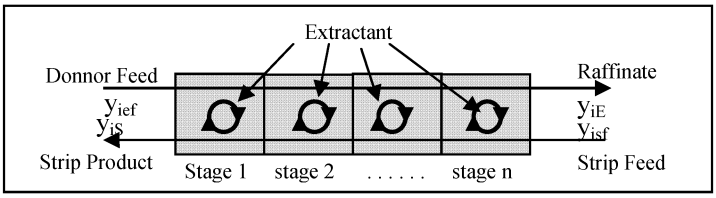

Figure 1: The Thin Layer Extraction scheme

A material balance over the entire extraction scheme yields for a solute-free strip feed:

$$R_i = \frac{y_{iE}}{y_{ef}} = \frac{D_{ie} - D_{is}}{D_{ie}\left(\frac{D_{ie}+1}{D_{is}+1}\right)^n - D_{is}} \text{ , dimensionless} \quad (1)$$

$D_{i,j}$ is the extraction or striping factor:

$$D_{ij} = \left(\frac{S}{F_j}\right) K_{ij}, \text{ dimensionless} \quad (2)$$

S/F_j is the extractant to aqueous ratio in the extraction or stripping step.
Equation (1) permits the evaluation of the D and L guest compositions in the raffinate and the strip products, relative to the racemate feed composition, as a function of the extraction factors $\mathbf{D_{ie}}$, the stripping factors $\mathbf{D_{is}}$ and the number of stages **n**.

3. Chiral Resolution

Chiral resolution by liquid-liquid extraction requires a liquid extractant being, or containing, the chiral host. Data concerning liquid hosts are relatively scarce but can be inferred by analogy with chiral chromatography [Steensma M., 2006, Schurig V., 2009, Schuur B. et al, 2011]. In HPLC, the host is attached chemically to a substrate forming the CSP (chiral stationary phase). It is however not obvious that the chemically immobilized host will be as effective as the virgin host. Indeed, it has been suggested [Besenius P. et al, 2008] that its effectivity may decrease significantly upon immobilization. It is tempting to speculate that in TLX, where the liquid host is held on a substrate in pure or concentrated form by capillary forces without tinkering with the molecule itself, one may obtain better results. Moreover, in a CSP, the active sites are accessible through convection and diffusion into and out of tiny pores where they are confined to a monomolecular film, whereas the relatively thicker liquid extractant layer in TLX is fully and directly accessible, thereby providing both enhanced mass transfer and capacity. Using a concentrated host will facilitate the processing of a correspondingly concentrated aqueous feed.

3.1 The equilibrium model

The equilibrium homogeneous organic phase ligand addition mechanism for a dilute extraction/stripping cycle is modelled in figure 2 [B.Schuur, 2010].
The fundamental parameters $\mathbf{K_a}$, $\mathbf{K_{eqD}}$, $\mathbf{K_{eqL}}$ are related to the compositions through:

$$K_{a\,i,j} = \left(\frac{\gamma^2 [H^+][A_i^-]}{[A_i]}\right)_{aq\,j} \text{ , mol/lit} \quad (3)$$

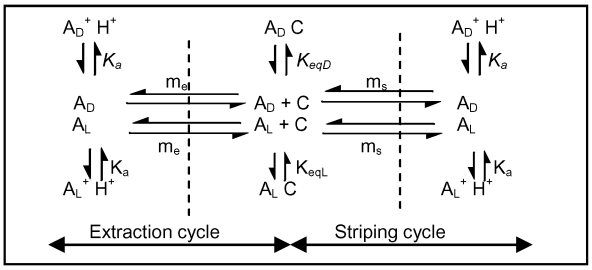

Figure 2 – The equilibrium model

$$m = \frac{[A_i]_{org}}{[A_i]_{aq}}, \ (\text{mol/lit})_{org}/(\text{mol/lit})_{aq} \tag{4}$$

$$K_{eq\,i} = \left(\frac{[A_iC]}{[A_i][C]}\right)_{org}, \ \text{lit/mol} \tag{5}$$

Where i= D, L (the two enantiomers) and j = e, s (the extraction and stripping steps)
An apparent overall distribution coefficient K_{ij} may be defined as the ratio of all forms A in the organic phase to all forms A in the aqueous phase:

$$K_{ij} = \frac{[A]_{org} + [AC]_{org}}{[A]_{aq} + [A^-]_{aq}} = \frac{m_j(1 + K_{eq\,i}[C])}{\left(1 + \frac{K_{a\,ij}}{\gamma^2[H^+]_j}\right)}, \ \text{mol/mol} \tag{6}$$

3.2 Fundamental parameters

The most critical choice to be made is that of an appropriate host. It is characterized by the operational selectivity

$$\alpha = \mathbf{max}\left\{\frac{K_{Le}}{K_{De}}, \frac{K_{De}}{K_{Le}}\right\} \cong \mathbf{max}\left\{\frac{K_{Ls}}{K_{Ds}}, \frac{K_{Ds}}{K_{Ls}}\right\} \quad . \tag{7}$$

The K_{ij}'s and therefore the selectivity depend on the chosen host more than on anything else.

The design decisions concern the choice of host, its concentration[C], the mobile phase composition and the number of necessary ideal stages n.

As, in TLX, the operating conditions (S/F_j), pH_j and T_j, j = e, s may be changed, within limits, in situ, those may be considered as control variables. They, together with given K_D and K_L data, fully define four interrelated extraction/stripping factors D_{ij}:

Firstly, equations (2) and (7) relate D_{Lj} to D_{Dj}. Then, equation (4) relates D_{ie} to D_{is} as

$$\beta = \frac{D_{Ds}}{D_{De}} \cong \frac{D_{Ls}}{D_{Le}} \ , \tag{8}$$

On the basis of equations (7) and (8), all four D_{ij} can be represented by a single parameter Δ, say $\Delta = D_{De}$.

Given α, it is possible to decompose a search for optimal operating conditions into: first finding promising combinations of n and Δ, while exploring a range of values for β, and then translating Δ and β into corresponding control variables values.

Approximating α and β as constants, even though they may vary somewhat with temperature and pH, is a small sacrifice simplifying the analysis. This, together with the assumptions of linearity and equilibrium, label the results as being approximate.

4.1 Process outputs

The raffinate composition y_{iE} and the strip product composition y_{iS} are related to the reduction ratio R and to the racemate donor feed composition y_{if} through:

$$y_{iE} = R_i y_{ief}, \qquad y_{iS} = E_i y_{ief} = \frac{F_s}{F_e}(1 - R_i) y_{ief} = \beta(1 - R_i) y_{ief} \tag{9}$$

4.2 Performance

Given a host with characteristic selectivity α, our objective is now narrowed to selecting operating conditions that define the extraction/stripping factors represented in β and Δ and then choosing a number of stages n that will provide a satisfying performance.
Relevant performance criteria are:

1. The enantiomer product purity, expressed as an enantiomer excess ee:

$$ee = max\{ee_i\} = max\left[\frac{R_D - R_L}{R_D + R_L}, \frac{R_L - R_D}{R_D + R_L}\right] \tag{10}$$

2. The yield Y, that is the fraction of the enantiomer in the feed that is recovered in the raffinate or in the strip product, whichever has the higher purity.

$$Y = \left\{ \begin{array}{ll} \text{either} & Y_E = R = \dfrac{y_{iE}}{y_{ief}} \\ \text{or} & Y_S = E = \beta(1 - R) \end{array} \right\} \tag{11}$$

3. The performance factor is a combined measure of yield and enantiomer purity.

$$pf = ee \cdot Y \tag{12}$$

While advocated by some, *pf* is a useful measure only when both purity and yield are sufficiently high.

5. Results

5.1 Design for performance – a direct method

Equations (1) and (10) are used to generate plots (figure 3) of ee, first (a) as a function of n and Δ at fixed α and β then (b) as a function of α and β at fixed n and Δ, for a solute-free strip feed. Thus, we may explore the range of parameters that provide a performance of interest. Those are displayed in figures 3 and 4, indicating a reasonably wide range of parameter values that place the enantiomer excess on a plateau where the purity is close to 100%. As expected, a high purity engenders a lower yield. A purity exceeding 90% requires no less than four TLX stages. As a generalization, it can be stated on the basis of figure 3 (a) and (b) that, given a host and host concentration providing $\alpha > 2$, operating conditions corresponding to $\Delta > 2$, $\beta \leq 0.2$ and $n > 4$ define a region of the design and operation parameter space that is likely to produce an enantiomer excess of interest.

5.2 Simulation

A detailed dynamic simulation for n = 4 and n = 8 stages TLX, for selectivities of $\alpha = 4$ and $\alpha = 10$ was carried out to verify the validity of the direct approach. The product

composition converged within minutes of operation time to steady state values yielding the enantiomer excess plotted in figure 4. Those turned out to match closely the equilibrium values obtained by the direct method in figure 3. The consistent data used: S/F_e= 0.1, S/F_s= 0.02, y_{def} = 10mMol/L, [C]=0.6 (mMol/lit), m=10 (Mol/lit)/(Mol/lit), pK_a=4, pH_e=7, pH_s=9 and a nominal mass transfer resitance.

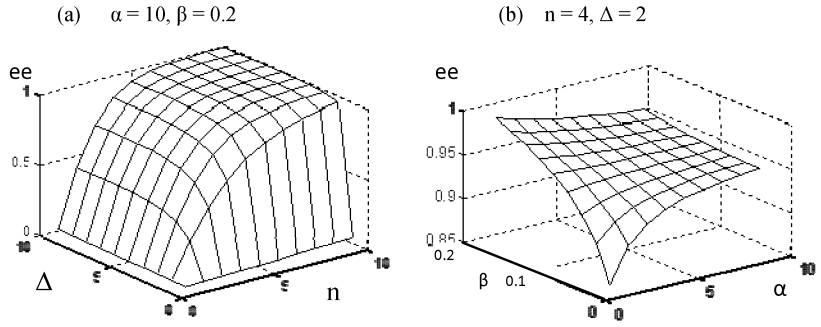

Figure 3- Direct method enantiomer excess:(a) ee=ee(n,Δ), (b)ee=ee(α,β).

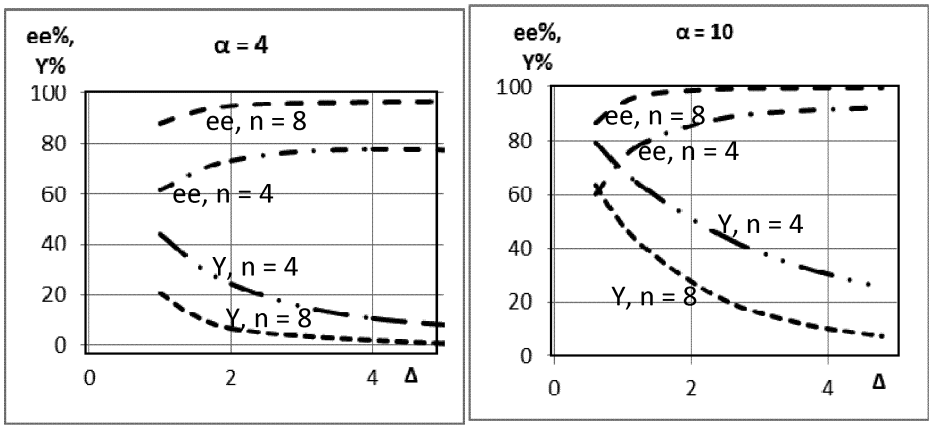

Figure 4 –Predicted purity and yield for α=4 and α=10, n=4 and n=8 .

5.3 Discussion

A pure product and a high yield are obviously both desirable. In a single TLX train, like in any other comparable, single pass liquid-liquid extraction/stripping pair of trains, there is an inherent conflict between purity and yield as purity engenders a reduced concentration of both enantiomers. Faced with a choice, purity is mostly preferred as it is the harder to reach.

A separation process seldom consists of a single separation unit but is mostly preceeded and/or followed by additional processing steps, with possible recycles, up to obtaining the final product. The choice of a performance compromise for the particular chiral resolution component impacts on the costs and other considerations concerning the entire separation system. The versatility of TLX that allows the shaping and adjustment

of parameters, some in situ, provides a flexibility in the design of the overall system that will impact the details and cost of the overall separation system.

6. Conclusions

Chiral resolution by TLX appears to be feasible, potentially providing a simple and economical chiral resolution method. A direct scheme proposed to guide the design of a TLX process predicts well the expected performance in comparison with a more detailed simulation. Increasing the number of stages engenders higher purity. Indications are that a host providing a selectivity of $\alpha > 2$ will be capable, under certain conditions, to provide a high purity product using no more than 8 TLX stages.

Notation

[C] – Host concentration, mmol/L.
ee – Enantiomer excess, equation (10),%.
D, Δ – Extraction factor, equation (2, 8).
E – Enrichment ratio.
F – Aqueous batch size, L.
K – Distribution coef, (mol/L)/(mol/L).
m – Phase distrib. coef, (mol/L)/(mol/L)
R – Reduction ratio.
S – Organic batch size, L.
Y – Yield, %.
y – Aqueous phase composition, mmol/L.
α – Selectivity, equation (7).
β – Extraction factor ratio, equation (8).

Subscripts:
i – Enantiomer, D or L.
j – Aqueous phase identity, e or s.

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