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Continuous Chiral Separation of Amino Acid Derivatives by Enantioselective Liquid−Liquid Extraction in Centrifugal Contactor Separators

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Abstract:

The continuous enantioselective liquid−liquid extraction of aqueous 3,5-dinitrobenzoyl-D,L-leucine (DNB-d,l-leu) by a cinchona alkaloid extractant (CA) in 1,2-dichloroethane using a centrifugal contact separator (CCS) was studied at 294 K. Typical concentrations were in the order of 1 mM for both DNB-d,l-leu and CA. The best results were found at a pH of 6, with 61% yield for DNB-l-leu and an enantiomeric excess of 34%. Back-extraction studies at different pH values showed that the host can be recovered efficiently in a single CCS, provided that pH > 9. Experimental studies indicate that the CCS behaves as an equilibrium extraction stage, even at total throughputs exceeding 50% of the equipment capacity (1.9 L min^{-1}). A previously developed equilibrium stage extraction model was successfully applied to describe the data for both the extraction and the back-extraction experiments.

Introduction

The growing demand for enantiopure compounds[1] is evoking the development of new competitive technologies.[2–4] A promising technique is enantioseparation by liquid−liquid extraction.[5] Although a number of studies have shown the potential of this technique,[5–22] translations into processes for industrial practice are scarce.[16] To the best of our knowledge, processes making use of enantioselective liquid−liquid extraction have not been commercialized yet. In the pharmaceutical and fine chemical industries, batch processing in multipurpose batch reactors and separators is state of the art. Although highly flexible, batch operation has a number of inherent drawbacks such as batch-to-batch product variation when multiple batches are required, relatively large equipment sizes and limited process control options.[23] The development of continuous, highly intensified processes is a major research topic in the field.[24]

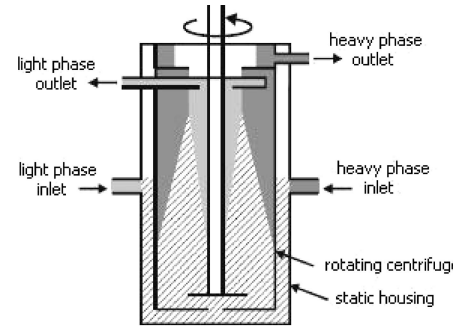

Figure 1. **Sketch of the CINC (hatched: dispersion, darker gray: heavy phase, lighter gray: light phase).**

The centrifugal contact separator (CCS) is an example of a compact continuous flow device that seems ideally suited for continuous operation in the pharmaceutical and fine chemical industry. A CCS combines efficient mixing of two immiscible liquids with fast phase separation. An example of such a CCS is the CINC device.[25] It is available in sizes with maximum liquid throughput ranging from 1.9 L min^{-1} to 757 L min^{-1}. The device was originally invented for oil−water separation.[26] We recently demonstrated that the device can also be used for process intensification by combining continuous biphasic (bio) catalytic reactions and separation.[27] The V02 is the smallest,

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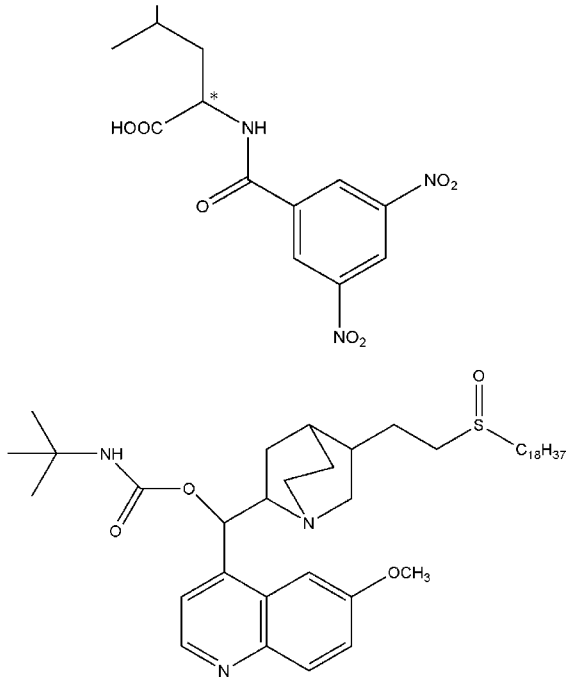

Figure 2. **Chemical structures of DNB-d,l-leu (top) and extractant CA (bottom).**

table-top scaled version with a maximum total throughput of 1.9 L min^{-1}. Due to large centrifugal forces (up to 900*g*), the apparatus is very compact but still capable of separating two immiscible liquids efficiently, even when their densities differ only by 10 kg m^{-3}. The CINC basically consists of a rotating hollow centrifuge in a static housing, see Figure 1. The liquids enter the device in the annular zone between the static wall and the rotating centrifuge, where they are intensely mixed. Next, they are transferred into the centrifuge where separation occurs by the centrifugal forces.

To investigate the potential of the CINC for continuous enantioselective liquid−liquid extraction and subsequent back-extraction of the host (extractant), we studied the enantioselective extraction of aqueous 3,5-dinitrobenzoyl-D,L-leucine (DNB-d,l-leu, see Figure 2, top) using *O*-(1-*tert*-butylcarbamoyl)-11-octadecylsulfinyl-10,11-dihydroquinine (CA, see Figure 2, bottom) as the host. This system was selected from the open literature for its promising selectivity.[28,29] In earlier studies in batch equipment, the effect of the operating variables such as concentrations, volume ratio and pH on the extraction and back-extraction performance was quantified, and an equilibrium model was formulated.[30] In this contribution, reactive extraction experiments in the CCS will be reported. The experimental data are modeled using the previously developed equilibrium model.

Results and Discussion

Proof of Principle for Enantioselective Extraction in the CINC V02. To proof the suitability of the CINC for enantioselective extraction, an experiment was performed with flow rates of 30 mL min^{-1} for both phases and a rotational frequency of 50 Hz. Initially, the CINC was fed with pure 1,2-dichloroethane as organic solvent and a buffered aqueous solution of racemic DNB-d,l-leu (1 mM). After several minutes steady-state was achieved (Figure 3). Subsequently, the organic feed was switched from pure 1,2-dichloroethane to a 0.5 mM CA solution in 1,2-dichloroethane.

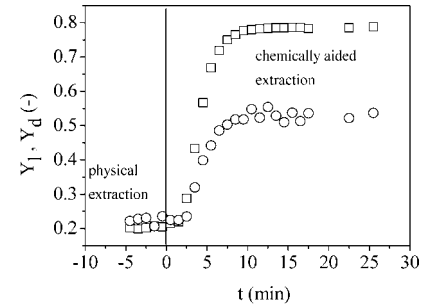

Figure 3. **Extraction yield profiles. $F_{aq} = F_{org} = 30$ mL min^{-1}, $N = 50$ Hz, pH = 5.12, $c_{DNB\text{-}d,l\text{-}leu,aq,0} = 1$ mM, $c_{CA,org,0} = 0.5$ mM. □: Y_l, ○: Y_d.**

As expected, the enantiomeric excess (ee) is negligible when applying 1,2-dichloroethane without host ($t < 0$). At $t > 0$, the extraction yields of both enantiomers increase dramatically due to the complexation with CA in the organic phase. Steady-state operation is achieved in less than 10 min. With a total liquid hold-up in the CCS of 180 mL and a total throughput of 60 mL min^{-1}, this corresponds with just over three average residence times. The steady-state yield of DNB-l-leu is 0.78, and that of DNB-d-leu is 0.53. Here, the yields are defined as:

$$Y_i = \frac{F_{org}}{F_{aq}} \frac{c_{i,org,tot}}{c_{i,aq,in}} \quad [i = l,d] \tag{1}$$

Furthermore, it is clear that the host has a preference for the L-enantiomer, leading to an organic phase ee of 19%. The ee in the aqueous phase is 37%. This experiment clearly illustrates the suitability of the CINC device for enantioselective liquid−liquid extraction.

Influence of Flow Rates and the Rotational Frequency. Experiments with different liquid flow rates were conducted to investigate the effects on the steady-state yields of the enanti-

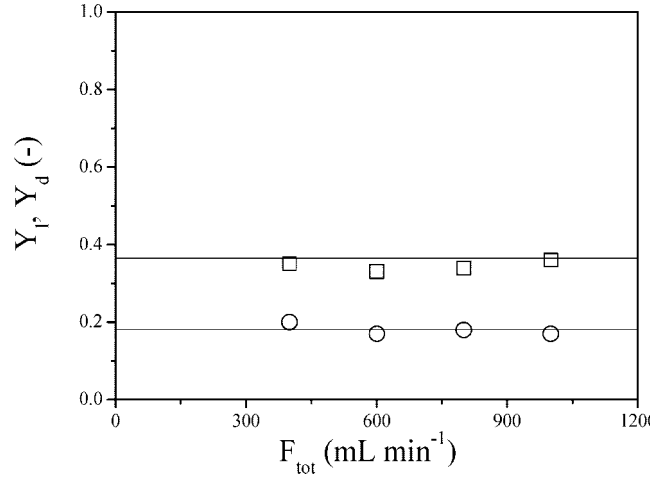

Figure 4. **Extraction yields at different flow rates. $N = 50$ Hz, pH = 5.73, $c_{DNB\text{-}d,l\text{-}leu,aq,0} = 1$ mM, $c_{CA,org,0} = 0.3$ mM, $F_{aq} = F_{org}$. □ = Y_l, ○ = Y_d, lines are equilibrium model predictions.**[30]

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Table 1. **Experimental data for continuous extractions in the CINC[a]**

expt	$c_{DNB\text{-}d,l\text{-}leu,aq,0}$ (mM)	$c_{CA,org,0}$ (mM)	pH	F_{aq} (mL min^{-1})	F_{org} (mL min^{-1})	Y_d (−)	Y_l (−)	ee_{org}	ee_{aq}
1	1.01	0.326	5.74	26.0	32.5	0.29	0.57	33	25
2	0.995	0.274	5.73	26.0	34.1	0.29	0.49	26	16
3[b]	1.01	0.274	5.76	25.7	37.7	0.25	0.52	35	22
4[c]	1.00	0.478	5.94	29.0	30.2	0.28	0.57	34	25
5[d]	0.994	0.478	5.96	46.8	50.2	0.22	0.51	40	23
6	1.16	1.068	6.03	30.0	30.0	0.30	0.61	34	28
7	0.992	0.286	5.73	200	200	0.20	0.35	28	11
8	0.992	0.286	5.73	300	300	0.17	0.33	32	11
9	0.993	0.287	5.73	400	400	0.18	0.34	31	11
10	0.993	0.287	5.73	500	500	0.17	0.36	36	13

[a] 294 K, rotational frequency 50 Hz, ionic strength 0.11 M. [b] Rotational frequency 40 Hz. [c] Ionic strength 0.10 M. [d] Ionic strength 0.13 M.

Table 2. **Parameters of the equilibrium model**

parameter	definition[a]	value	dimensions
K_a	$\gamma^2[H^+]_{aq}[DNB\text{-}leu^-]_{aq}/[DNB\text{-}leu]_{aq}$	1.92×10^{-4}	mol L^{-1}
m	$[DNB\text{-}leu]_{org}/[DNB\text{-}leu]_{aq}$	8.04	−
$K_{eq,d}$	$[CA\cdot DNB\text{-}d\text{-}leu]_{org}/[CA]_{org}[DNB\text{-}d\text{-}leu]_{org}$	2.71×10^4	L mol^{-1}
$K_{eq,l}$	$[CA\cdot DNB\text{-}l\text{-}leu]_{org}/[CA]_{org}[DNB\text{-}l\text{-}leu]_{org}$	9.31×10^4	L mol^{-1}

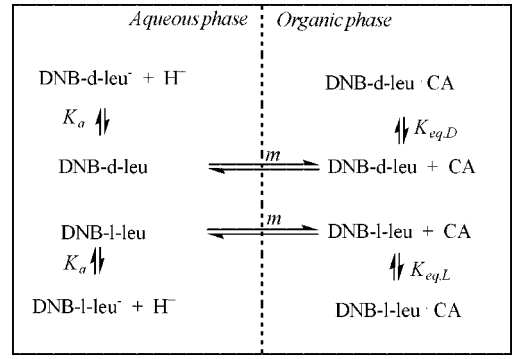
[a] The definitions of the parameters K_a and m are valid for both enantiomers.

omers (experiments 7−10, Table 1). The yield is essentially independent of the flow rates (Figure 4). This implies that the chemical composition of the outlet streams is at equilibrium for all experiments. The liquid residence time at the highest flow rate is about 12 s, meaning that the time needed for chemical and physical equilibrium to establish is very short. This conclusion is strengthened by comparison of experiments 2 and 3 (Table 1). These experiments were carried out at different rotational frequencies but otherwise under comparable conditions. The results are very similar. From this it can be concluded that differences in hydrodynamic conditions (e.g., mass transfer coefficients and liquid hold-up) by changing the rotational frequency do not affect the yields. This again justifies the statement that the overall rate of the complexation reactions is very fast and that the outlet streams are at chemical equilibrium.

Equilibrium-Stage Modeling of the Continuous Extraction Experiments in the CCS. We have previously developed an equilibrium model for the enantioselective extraction of DNB-d,l-leu with CA based on batch experiments.[30] The model was validated at 294 K for concentrations up to 3 mM and 3.5 < pH < 11. The model is based on a homogeneous extraction mechanism (Scheme 1).[15] Here, complexation between host and enantiomer takes place in the organic phase. The values for the parameters in the model were determined earlier in our group[30] and are given in Table 2.

The experimental data in Table 1 were modeled using the equilibrium model. The correlation between the model predictions and the experimental data is depicted in Figure 5. The mean absolute relative error between model prediction and experiments is 11.5%. It may thus be concluded that the equilibrium model is very well suited to predict the CCS

Scheme 1. **Extraction model for DNB-d,l-leu by CA**



extraction performance and that chemical equilibrium was achieved in all experiments, even those with total flow rates as high as 1 L/min, corresponding to residence times as low as 12 s.

With the use of the model, the observed experimental trends (Table 1) may be rationalized. Experiments 4 and 5 have comparable conditions (i.e., flow ratio, intake concentrations, pH), except for the ionic strength in the aqueous phase. The ionic strength in experiment 4 is 0.10 mol L^{-1} compared to 0.13 mol L^{-1} in experiment 5. The higher yields in experiment 5 are a direct result of the lower ion activities due to the higher

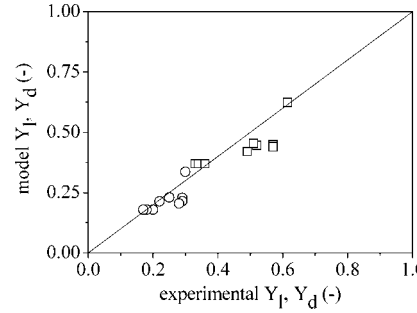


Figure 5. **Parity plot of the experimental and modeled yields. □: Y_l, ○: Y_d**

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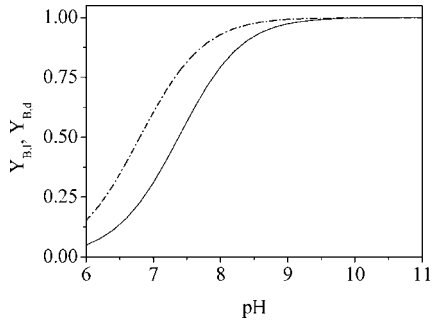

Figure 6. **Predicted back-extraction yields as function of aqueous phase pH at constant ionic strength of 0.12 M. Organic phase input concentrations are 0.5 mM for both enantiomers and 3 mM for the host, $F_{org}/F_{aq} = 3.3$. solid line: $Y_{B,l}$, dashed line: $Y_{B,d}$**

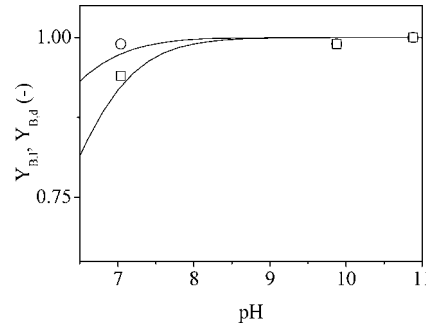

Figure 7. **Back-extraction yields at an ionic strength of 0.2 M, $R = 1.06$, and organic phase intakes of racemate and host of 0.9 and 0.3 mM, respectively. Lines are model predictions. □: $Y_{B,l}$, ○: $Y_{B,d}$.**

buffer concentration. This comparison shows that the ionic strength has a profound effect on the extraction process.

The equilibrium extraction model may also be used to determine the optimum experimental conditions for the extraction process. For this purpose, the performance factor PF is very helpful. The PF is determined as the product of the organic phase ee and the yield of the preferred enantiomer:[8]

$$\mathrm{PF} = Y_l \mathrm{ee}_{org} \tag{2}$$

With the yield ranging from 0 to 1 and the ee from 0 to 100%, the PF ranges from 0 to 100%. The equilibrium extraction model was used to determine the optimum PF. The highest PF value was 19% at experimental conditions as given for experiment 6 (Table 1). The experimental Y_l and Y_d for experiment 6 were 0.61 and 0.30 respectively, leading to an organic phase ee of 34%. The experimental PF according to eq 2 is 21%, which is in good agreement with the model prediction.

Optimization of the Back-Extraction Using Model Predictions. The equilibrium model may also be used to optimize the efficiency of the back-extraction process. In the back-extraction, organic streams containing the host−DNB-d,l-leu complexes are brought in contact with an aqueous buffer to back-extract the DNB-d,l-leu and hereby recover the host solution. Particularly for expensive host compounds, efficient host recovery is of major importance. If the back-extraction has a high efficiency, the organic host solution may be returned to the extraction stage without further treatment. The efficiency of the back-extraction is expressed in yield terms. The yields in the back-extraction step are defined as:

$$Y_{B,i} = \frac{F_{aq}}{F_{org}} \frac{c_{i,aq,tot}}{c_{i,org,in}} \quad [i = l, d] \tag{3}$$

The equilibrium model predicts that the back-extraction efficiency is very sensitive to the pH of the aqueous phase. With increasing pH, the equilibrium in the aqueous phase shifts towards the dissociated form of the amino acid derivative, leading to higher back-extraction yields (Scheme 1). This is demonstrated in Figure 6 for a model simulation at a high host concentration (3 mM), a flow ratio F_{org}/F_{aq} of 3.3, inlet concentrations of both enantiomers of 0.5 mM and an aqueous phase ionic strength of 0.12 M. Clearly, at pH > 9 the model predicts that the back-extraction of both enantiomers is quantitative in a single equilibrium stage.

A number of experiments were carried out in the CCS using an organic phase containing racemic DNB-d,l-leu and the host (0.9 mM DNB-d,l-leu, 0.3 mM CA) and an aqueous phase with a buffer of appropriate concentration, typically $I > 0.1$ M ($F_{org}/F_{aq} = 1.06$, 59 mL min^{-1} total flow). The back-extraction yields at different pH values of the aqueous phase were measured to verify the model predictions. The experimental results and the model predictions are compared in Figure 7. Agreement between model and experiment is good. Thus, it can be concluded that the back extraction of the organic phase may be conveniently carried out using an aqueous solution with pH > 9. Hereafter, the recovered host solution can be recycled without further treatment for a new extraction step.[12]

Conclusions and Outlook

In this paper, the proof of principle for the application of CCS equipment for the continuous separation of racemates is provided. The concept was demonstrated for a model system composed of a racemic mixture of protected amino acids (DNB-d,l-leu) with a chiral cinchona alkaloid host. Under optimum conditions, the ee_{org} was 34% and the L-enantiomer yield, Y_l was 0.61, leading to a PF of 21%. It was shown that the application of a single CCS for the back extraction is sufficient for efficient recovery of the host, provided that pH > 9. Experiments and subsequent modeling activities indicate that both the extraction and the back-extraction step in the CCS may be modeled as an equilibrium extraction stage. This statement was proven for total flow rates not exceeding 1 L min^{-1}. Full separation of the enantiomers (ee_{org} and $ee_{aq} > 0.99$; PF > 98%) in a single extraction stage is not possible with the DNB-d,l-leu/CA system. Multistage countercurrent extraction with a cascade of CCSs is envisaged to achieve this objective. A schematic representation of the proposed countercurrent process with a single back-extraction step for efficient host recycle in the extract phase is depicted in Figure 8.

Considering the operational limits of the bench-scale CCS (up to 1 L min^{-1} was verified experimentally in this study, equipment capacity 1.9 L min^{-1}) and the solubility of the species to be separated, a typical separation capacity of 10 kg racemate

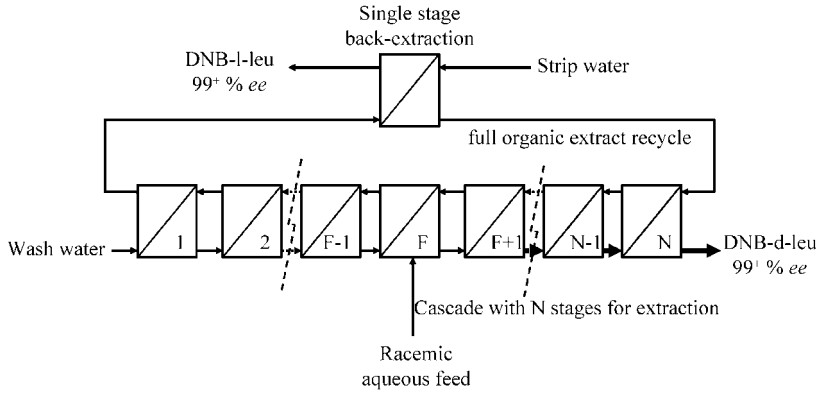

Figure 8. **Schematical representation of a countercurrent setup of N CCSs for chiral separation with full recycle of the extract stream**

per week should be possible. Further scale-up may easily be achieved by application of larger (commercially available) CCS equipment.

Experimental Section

Chemicals. Water was obtained by reverse osmosis followed by deionization using a deionization apparatus from Labconco, 1,2-dichloroethane (99%) from Sigma-Aldrich, potassium dihydrogen phosphate (pa), disodium hydrogen phosphate dodecahydrate (pa) and triethyl amine (99%) from Merck, glacial acetic acid from Acros, methanol (AR) and acetonitrile from Labscan.

O-(1-*tert*-Butylcarbamoyl)-11-octadecylsulfinyl-10,11-dihydroquinine, 3,5-dinitrobenzoyl-L-leucine, 3,5-dinitrobenzoyl-D-leucine and 3,5-dinitrobenzoyl-L-leucine were kindly provided by DSM Research.

Experimental Setup. All experiments were carried out in a CINC V02 (a table-top version with a maximum total throughput of 1.9 L min^{-1} (3.2×10^{-5} m^3 s^{-1}) and maximum rotational frequency of 100 Hz) made from Hastelloy and equipped with a heating/cooling jacket. Both liquids were transferred to the reactor using Verder VL1000 Control peristaltic tube pumps equipped with double pump heads (1.6 × 1.6 × 8R). Glass supply and receive vessels were used. Cooling the jacket with tap water enabled a constant temperature of 294 K, this was monitored using temperature sensors (CMA, Amsterdam) connected with a PC via a CoachLab II interface (CMA, Amsterdam).

Experimental Procedures. Typical extraction experiments were started after calibration of the pumps by feeding the CINC with 1,2-dichloroethane (the heavier of the two liquids) and starting the centrifuge. When the reactor was filled with the heavy phase and the heavy phase outlet started running, the pump of the buffered aqueous DNB-d,l-leu solution (the light phase) was started. After achieving steady-state operation, the feed of heavy phase was switched from pure 1,2-dichloroethane to a CA solution in 1,2-dichloroethane, thereby switching from pure physical distribution of DNB-d,l-leu over the phases to an enantioselective reactive liquid−liquid extraction. After achieving steady-state in the enantioselective process, the experiments were continued for several minutes. Samples for analysis were taken from the aqueous phase at regular time intervals, starting directly after the aqueous reactor outlet had started running.

Back-extraction experiments were performed similarly, but now the DNB-d,l-leu and the CA were fed as solution in 1,2-dichloroethane. After the heavy phase exit started running, the aqueous feed, containing a phosphate buffer to set the pH was started. Samples for analysis were taken from the aqueous phase.

Analytical Procedures. The concentrations of the DNB-leu enantiomers in the aqueous phase were determined with an accuracy of 3% by HPLC using an Agilent LC 1100 series apparatus, equipped with an Astec Chirobiotic T column (now Supelco, Sigma-Aldrich). Detection was done using 270 nm UV light. The eluent was a 3:1 (v/v) mixture of acetonitrile and methanol, to which 0.25% (vol) triethyl amine and 0.25% (vol) acetic acid were added. The flow rate was set at 1 mL per minute. Before injecting the aqueous phase samples to the column, 0.10 mL of each of the samples was diluted with 1.0 mL eluent and filtered over a syringe filter with pore size 0.45 μm (Waters Chrom). Quantitative analysis was enabled using calibration curves.

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List of Symbols

c	concentration (M = mol L^{-1})
CA	cinchona alkaloid (extractant), see Figure 2
DNB-d,l-leu	3,5-dinitrobenzoyl-D,L-leucine, see Figure 2
ee	enantiomeric excess (-)
F	flow (mL min^{-1})
I	ionic strength (M)
K	equilibrium constant, various dimensions
m	partition coefficient (-)

N	rotational frequency (Hz)
PF	performance factor (%)
T	temperature (K)
Y	yield (-)
γ	activity coefficient for ionic species, determined using $^{10}\log(\gamma_i) = [-0.5115(z_i)^2 I^{1/2}]/[1 + (1.316)I^{1/2}]$

SUBSCRIPTS

0	initial or feed
a	acidity
aq	aqueous
B	back-extraction
d	D-enantiomer
eq	equilibrium
i	index
l	L-enantiomer
org	organic
t	total

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