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Published in:
Green Chemistry

DOI:
[10.1039/c7gc01700f](https://doi.org/10.1039/c7gc01700f)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Susanti, Meinds, T. G., Pinxterhuis, E. B., Schuur, B., de Vries, J. G., Feringa, B. L., Winkelman, J. G. M., Yue, J., & Heeres, H. J. (2017). Proof of concept for continuous enantioselective liquid-liquid extraction in capillary microreactors using 1-octanol as a sustainable solvent. *Green Chemistry*, 19(18), 4334-4343. [C7GC01700F]. <https://doi.org/10.1039/c7gc01700f>

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An article presented by Prof. Erik H. J. Heeres *et al.* of the University of Groningen, The Netherlands.

Proof of concept for continuous enantioselective liquid-liquid extraction in capillary microreactors using 1-octanol as a sustainable solvent.

The application of capillary microreactors operated in the slug flow regime for liquid-liquid extraction (ELLE) using 1-octanol has been demonstrated. As such, microreactors have great potential for chiral separations as their use allows for continuous operation, precise setting of residence times, fast screening of novel systems and small inventories of expensive host and solvents.

As featured in:

See Hero J. Heeres *et al.*,
Green Chem., 2017, 19, 4334.

rsc.li/greenchem

Registered charity number: 207890

Cite this: *Green Chem.*, 2017, **19**, 4334

Proof of concept for continuous enantioselective liquid–liquid extraction in capillary microreactors using 1-octanol as a sustainable solvent†

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The use of capillary microreactors for enantioselective liquid–liquid extraction (ELLE) was successfully demonstrated using a model system consisting of a buffered aqueous amino acid derivative (3,5-dinitro-benzoyl-(*R,S*)-leucine) solution (phosphate buffer, pH 6.58) and a chiral cinchona alkaloid (CA) host in an organic solvent. It was shown that 1-octanol is a suitable replacement for the commonly used chlorinated solvents like 1,2-dichloroethane. Experiments were conducted in a capillary microreactor set-up (0.8 mm internal diameter) operated in the slug flow regime at 294 K (residence times between 12 and 900 s, 1 : 1 flow ratio of the aqueous to organic phases, 1 mM of host and 1 mM of amino acid derivative). The enantiomeric excess (ee) was shown to be a function of the solvent and residence time and varied between 37% and 49% in 1,2-DCE and 28 and 46% in 1-octanol in the organic phase. The ee values in the organic phase at shorter residence times were higher than the independently determined equilibrium ee values (41% in 1,2-DCE and 31% in 1-octanol at a host concentration of 1 mM). This is an unprecedented observation with large implications for ELLE, as it implies that operation in the kinetic regime may lead to improved enantioseparation performance.

Received 10th June 2017,
Accepted 1st August 2017

DOI: 10.1039/c7gc01700f

rsc.li/greenchem

Introduction

The availability of enantiopure compounds is of great importance for the pharmaceutical,^{1,2} agrochemical,³ flavor and fragrance industries,⁴ as the individual enantiomers may show significant differences in their biological activity. Synthesis of racemic compounds followed by chiral separation is a well-established strategy to obtain enantiopure compounds.^{5,6} Classical resolution for instance by crystallization is the most used technique for racemate separation.^{7–10} However, this approach has a number of limitations, such as excessive solids handling.^{7,11} Alternative methods have been developed such as

kinetic resolution^{12–14} and physical separation. Examples of the latter are membrane separation,^{15–18} chromatographic separation,⁵ capillary electrophoresis,⁷ and enantioselective liquid–liquid extraction (ELLE).^{7,19–40}

ELLE involves the contact of two immiscible liquid phases, one with the racemic mixture to be separated (usually in the aqueous phase) and an organic phase containing a soluble chiral host with a higher affinity to one of the enantiomers. After extraction, the enantio-enriched organic phase is back extracted to recover and recycle the host. The principle of ELLE is schematically shown in Fig. 1.

The advantages of ELLE include the ease of scale-up due to the fact that liquid–liquid extraction is a mature technology and the possibility to use one host family for the separation of multiple racemates.^{7,41,42} Crystallization and filtration, which are the two major unit operations in classical resolutions, are also the two most problematic ones, causing a lot of problems in the plant as a result of too small crystals, blocked filters and long filtration times. These problems are largely avoided by using ELLE. We have recently shown the proof of concept for ELLE in a continuous mode using Centrifugal Contactor Separators (CCS), which are highly process intensified devices that combine mixing and phase

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c7gc01700f

Fig. 1 Schematic representation of ELLE.

separation. By using a countercurrent cascade of multiple CCS devices, good enantioselectivity and yield were obtained for the separation of an aqueous solution of 3,5-dinitrobenzoyl-(*R,S*)-leucine (DNB-(*R,S*)-Leu in Fig. 2) with a cinchona alkaloid host (CA4 in Fig. 2) in 1,2-dichloroethane (1,2-DCE).^{11,29,30} However, due to their relatively low selectivity, many stages are required to obtain both enantiomers in high-enantiopurity,^{41,43} which has a negative effect on capital costs. In addition, there is a clear incentive to minimize the host inventory to reduce the costs. Alternatives for CCS devices are intensified columns, as explored by Kockmann and co-workers,^{22,23} in which a large number of stages are achievable per meter column.

Another possible alternative to intensify enantioseparation by liquid-liquid extraction is the use of microreactors.⁴⁴ The use of microreactors for liquid-liquid extraction has been reported earlier,^{45–55} examples are chip-based microreactors, high capacity mini extractors, and capillary or tubular microreactors (including coil-based flow reactors).⁵³ The use of such capillary microreactors offers good control over temperature and residence time, has led to enhanced mass transfer rates, and is relatively easy to scale up.^{51,54} Moreover, the use of

microreactors may “green-up” ELLE *e.g.*, by being more energy efficient (as compared to CCS) and by reducing solvent use due to the low reactor volume. This applies not only to the production phase, but also to the screening experiments in the lab. Although capillary microreactors are of great interest for ELLE, their use has never been reported in the literature and are an absolute novelty of this paper.

We here present an experimental study on enantioseparation by ELLE in capillary microreactors in the slug flow regime. This flow regime is expected to be advantageous as it is known to enhance the mass transfer rates due to intensified circulation inside slugs and droplets.^{51,56} The experiments were performed in an integrated setup which combines liquid-liquid extraction and separation.⁵⁶ A model system involving the separation of racemic 3,5-dinitrobenzoyl-(*R,S*)-leucine (DNB-(*R,S*)-Leu) using a chiral cinchona alkaloid host¹¹ was used. This reaction was selected as we have ample experience with it in CCS devices^{11,57} and relevant thermodynamic data like complexation constants are available for the reference solvent (1,2-DCE).

Several derivatives of cinchona alkaloid (CA) chiral hosts have been successfully applied for the enantioseparation of DNB-(*R,S*)-Leu (Fig. 2).⁴⁴

In this study, we have used host CA3, the non-oxidized variant of the well-known extractant CA4. It is the precursor for CA4 and as such one synthetic step in the host synthesis may be eliminated. Two solvents were explored, *viz.* 1,2-DCE and 1-octanol. The former has been used extensively for ELLE, though its use has strong drawbacks when considering its environmental performance. As such, the use of the environmentally more benign 1-octanol has also been investigated and its performance will be compared with 1,2-DCE. Higher alcohols are considered as green recommended solvents by a number of solvent selection guides.^{58,59} In addition, 1-octanol is accessible from renewable resources.⁶⁰ Besides solvent effects, the influence of process variables and particularly the residence time on the separation performance was studied by varying the total flow rate and/or the length of the capillary microreactors.

Fig. 2 DNB-(*R,S*)-Leu and examples of cinchona-based chiral hosts for ELLE reported in the literature.⁴⁴

Materials and methods

Materials

The host CA3 was synthesized according to the literature two-step procedure (Fig. S1, ESI†).⁶¹ NMR and elemental analysis data are provided in Fig. S2, S3 and Table S1, ESI†. The amino acid derivative, 3,5-dinitrobenzoyl-(*R,S*)-leucine (DNB-(*R,S*)-Leu), was obtained from DSM. Organic diluents, *viz.* 1-octanol (99.8%) and 1,2-dichloroethane (1,2-DCE) (99.8%), were obtained from Sigma-Aldrich. Disodium hydrogen phosphate ($\geq 99.5\%$) and potassium dihydrogen phosphate ($\geq 99.5\%$) were obtained from Merck. All experiments were performed with Milli-Q water.

Experimental setup

Two set-ups were used for the experimental study reported *i.e.* a batch set-up and a continuous capillary microreactor. Experiments in the batch set-up involved the mixing of an aqueous phase with the racemate and an organic phase with the host in a vial using a Teflon bar (1000 RPM) for a pre-determined amount of time. All continuous experiments were carried out in a capillary microreactor set-up as schematically shown in Fig. 3. The aqueous and organic phases were transferred to the capillary microreactor made of poly(tetrafluoroethylene) (PTFE) tubings (Bola, Germany, 1.6 mm outer diameter and 0.8 mm inner diameter) *via* a Y-junction (120° angle between branches, 1 mm inner diameter, made of polyether ether ketone (PEEK) for the use of 1,2-DCE and polymethyl-methacrylate (PMMA) for 1-octanol) using syringe pumps (model no. LA30, HLL GmbH, Germany). The end of the capillary microreactor was connected to a Y-splitter for the separation of both liquid phases. The outlets of the Y-splitter consist of a PTFE tube and a glass tube of the same dimension (*i.e.*, 1.6 mm outer diameter and 0.8 mm inner diameter). The two tubes were positioned in a prefabricated Y-shaped splitter made from PEEK or PMMA. The separation in the splitter is based on the preferential wettability (aqueous phase: glass, organic phase: PTFE). The composition of the aqueous phase was analyzed (*vide infra*).

Experimental procedures

ELLE experiments in the capillary microreactor. The experiments in the slug flow capillary microreactor were carried out using 1 mM DNB-(*R,S*)-Leu in an aqueous phosphate buffer

Table 1 Experimental conditions for the enantioselective extraction of DNB-(*R,S*)-Leu in a capillary microreactor

	Value	Ranges
Temperature (K)	294	
Buffer concentration (M)	0.1	
Buffer, pH	6.58	
DNB-(<i>R,S</i>)-Leu concentration [mM]	1.01 ± 0.01	
Host, CA3 concentration [mM]	1.03 ± 0.04	
Capillary inner diameter (mm)	0.8	
Capillary length (cm)		10–250
$Q_{\text{aq}}, Q_{\text{org}}$ [mL h ⁻¹]		2.5–15.0
$Q_{\text{aq}}/Q_{\text{org}}$	1.0	

(pH = 6.58) as the feed solution and 1 mM CA3 in 1,2-DCE or 1-octanol as the extractant at room temperature. An overview of experimental conditions is given in Table 1.

For all experiments, a 1 to 1 flow ratio of the aqueous to organic phases was applied. The residence time (τ) is defined using the total flow rate and is given in eqn (1).

$$\tau = \frac{V_c}{Q_{\text{aq}} + Q_{\text{org}}} = \frac{\frac{\pi}{4} d_c^2 L_c}{Q_{\text{aq}} + Q_{\text{org}}} \quad (1)$$

where V_c is the geometrical volume of the microreactor, d_c is the inner diameter, L_c is the length of the capillary microreactor and Q_{aq} and Q_{org} are the volumetric flow rates of the aqueous and organic phases, respectively. In the set-up, residence times between 12 and 900 s are attainable by combining different microreactor lengths and the total flow rates. All experiments were run for at least 2 residence times to ensure that a steady state was obtained. During the experiments, the aqueous phase was collected and analyzed by HPLC. All experiments were performed at least in duplicate. A good reproducibility of the experiments was observed, with a relative standard deviation (RSD) of less than 6%.

ELLE experiments with DNB-(*R,S*)-Leu and CA3 in a batch set-up

To determine equilibrium concentrations and enantioselectivities, the extraction of DNB-(*R,S*)-Leu with CA3 was performed in a batch set-up. Experiments were performed in 20 mL vials, which were loaded with 5 mL of a 1 mM solution of CA3 in 1,2-DCE or 1-octanol and 5 mL of a buffered aqueous phase (pH 6.58) with a racemate concentration of 1 mM. The solution was stirred using a Teflon bar (1000 RPM) for at least 14 h. After extraction, the phases were allowed to settle and

Fig. 3 Schematic representation of the experimental setup.

separate. The pH of the aqueous phase was measured and its composition was analyzed by HPLC. The concentration of the analyte in the organic phase was calculated using an overall mass balance.

Analytical procedures

The concentration of DNB-(*R,S*)-Leu in the aqueous phase was analyzed by reversed phase HPLC (a Shimadzu SIL-20A, with a CTO-20AC column oven and LC-20AD pumps) using a chiral Astec Chirobiotic T column and a UV detector (270 nm). The eluent was a 3 : 1 (v/v) mixture of acetonitrile and methanol with 0.25 vol% triethylamine and 0.25 vol% acetic acid. The flow rate was set at 1 mL min⁻¹ and the injection volume was 15 µL. Before injecting the aqueous phase samples to the column, the samples were filtered using a syringe filter with a pore size of 0.45 µm (Sartorius). A calibration curve using pure DNB-(*R,S*)-Leu was used to determine the concentrations in the samples.

The pH of the aqueous phase was measured using an InoLab pH 730 pH-meter equipped with a SenTix 81 probe (WTW, Germany).

Theory and definitions

The principle of ELLE with the extractant/host in the organic phase (C) and the racemate to be separated in the organic phase (*R* and *S*) is shown in Fig. 4.^{11,32} It involves the transfer of the enantiomers from the aqueous to the organic phase followed by complexation to the chiral host. The complexation constant is different for both enantiomers and this leads to enantioselectivity.

The concentrations of both enantiomers in the water phase were determined experimentally (HPLC). Those in the organic phase were calculated by using overall mass balances (eqn (2) for batch operation and eqn. (3) for continuous operation).^{11,23}

$$V_{\text{aq}}[R]_{\text{aq},0} = V_{\text{aq}}([R]_{\text{aq}} + [R^-]_{\text{aq}}) + V_{\text{org}}([R]_{\text{org}} + [RC]_{\text{org}}) \quad (2a)$$

$$V_{\text{aq}}[S]_{\text{aq},0} = V_{\text{aq}}([S]_{\text{aq}} + [S^-]_{\text{aq}}) + V_{\text{org}}([S]_{\text{org}} + [SC]_{\text{org}}) \quad (2b)$$

$$Q_{\text{aq}}[R]_{\text{aq},0} = Q_{\text{aq}}([R]_{\text{aq}} + [R^-]_{\text{aq}}) + Q_{\text{org}}([R]_{\text{org}} + [RC]_{\text{org}}) \quad (3a)$$

$$Q_{\text{aq}}[S]_{\text{aq},0} = Q_{\text{aq}}([S]_{\text{aq}} + [S^-]_{\text{aq}}) + Q_{\text{org}}([S]_{\text{org}} + [SC]_{\text{org}}) \quad (3b)$$

Fig. 4 Relevant reactions for ELLE.¹¹

Here, $[R]_{\text{aq},0}$ and $[S]_{\text{aq},0}$ represent the inlet (continuous) or initial (batch) concentration of the (*R*)- and (*S*)-enantiomers, V_{aq} and V_{org} represent the volume of aqueous and organic phases in batch operation, Q_{aq} and Q_{org} are the volumetric flow rates of the aqueous and organic phases for continuous operation, and $[RC]$ and $[SC]$ represent the concentration of the host–enantiomer complex.

The operational selectivity (α_{op}) is defined in eqn (4)

$$\alpha_{\text{op}} = \frac{D_S}{D_R}, \quad \text{if } D_S > D_R \quad (4)$$

Here, D is the distribution of the enantiomers between the two liquid phases, which is defined as:

$$D_R = \frac{[R]_{\text{org,all}}}{[R]_{\text{aq,all}}} = \frac{[R]_{\text{org}} + [RC]_{\text{org}}}{[R^-]_{\text{aq}} + [R]_{\text{aq}}} \quad (5a)$$

$$D_S = \frac{[S]_{\text{org,all}}}{[S]_{\text{aq,all}}} = \frac{[S]_{\text{org}} + [SC]_{\text{org}}}{[S^-]_{\text{aq}} + [S]_{\text{aq}}} \quad (5b)$$

The enantiomeric excess, ee , is defined in eqn (6).

$$ee_i = \frac{|[R]_{i,\text{all}} - [S]_{i,\text{all}}|}{[R]_{i,\text{all}} + [S]_{i,\text{all}}} \times 100\%. \quad (6)$$

Here, subscript i represents the organic phase or the aqueous phase.

A good enantioselective extraction process is not only determined by a high ee but also by a high extraction yield, which is defined as the extracted amount into the organic phase compared with the inlet concentration in the aqueous phase.¹¹ The yield of an enantiomer is defined as:

$$Y_R = \frac{[R]_{\text{org,all}}}{[R]_{\text{aq},0}} \cdot \text{SR} = \frac{[R]_{\text{org}} + [RC]_{\text{org}}}{[R]_{\text{aq},0}} \cdot \text{SR} \quad (7a)$$

$$Y_S = \frac{[S]_{\text{org,all}}}{[S]_{\text{aq},0}} \cdot \text{SR} = \frac{[S]_{\text{org}} + [SC]_{\text{org}}}{[S]_{\text{aq},0}} \cdot \text{SR} \quad (7b)$$

Here SR is the solvent ratio, defined as $V_{\text{org}}/V_{\text{aq}}$ for batch operation and $Q_{\text{org}}/Q_{\text{aq}}$ for the continuous microreactor.

Results and discussion

Equilibrium experiments in batch with 1,2-DCE and 1-octanol

Batch experiments were performed in both 1,2-DCE and 1-octanol to determine the equilibrium composition of the enantioselective extraction of DNB-(*R,S*)-Leu with CA3. 1,2-DCE was used as the benchmark and 1-octanol as an example of a greener, environmentally more benign solvent. Experiments were carried out with a fixed phase ratio of the aqueous and organic phase (1 to 1) at room temperature and DNB-(*R,S*)-Leu and host concentrations of 1 mM. To ensure equilibrium, the experiments were performed for at least 14 h. The results for both 1,2-DCE and 1-octanol are given in Table 2.

The value of α_{op} was 3.2 ± 0.2 in both solvents. This value is close to that observed for the well-known extractant CA4 for

Table 2 Batch equilibrium extraction results for DNB-(*R,S*)-Leu with CA3^a

Organic solvent (number of experiments, <i>n</i>)	α_{op} ($\pm$ stdev)	Y_R ($\pm$ stdev)	Y_S ($\pm$ stdev)	ee_{aq} (%) ($\pm$ stdev)	ee_{org} (%) ($\pm$ stdev)
1,2-DCE (<i>n</i> = 6)	3.2 ± 0.2	0.15 ± 0.01	0.36 ± 0.02	14 ± 1	41 ± 2
1-Octanol (<i>n</i> = 5)	3.2 ± 0.2	0.31 ± 0.02	0.58 ± 0.01	25 ± 2	31 ± 3

^a Conditions: $V_{aq}/V_{org} = 1$, phosphate buffer pH 6.58, 294 K, 1 mM DNB-(*R,S*)-Leu, 1 mM CA3.

this extraction system (α_{op} of 3.4) under similar conditions in DCE.¹¹ Thus, non-oxidized CA3 is a good alternative for CA4 with the advantage that one synthetic step in the host synthesis can be eliminated. CA3 is selective for the *S*-enantiomer, as is clear from the yield data in Table 2. When comparing the performance of the two solvents, the data show that the equilibrium *ee* values in the organic phase are higher for 1,2-DCE (41%) than for 1-octanol (31%). However, the yield of the *S* enantiomer is higher in 1-octanol than in 1,2-DCE, which is a promising feature and shows the potential of 1-octanol to replace chlorinated solvents like 1,2-DCE.

Experiments in the continuous microreactor set-up

Experiments in 1,2-DCE. Enantioselective extraction of an aqueous solution of DNB-(*R,S*)-Leu with CA3 in 1,2-DCE was carried out in a slug flow capillary microreactor (Fig. 3) using various residence times, by varying the flow rates and capillary lengths. All experiments were performed at room temperature and a fixed flow ratio of the buffered aqueous to organic phases (1 : 1), see the Experimental section for details.

Initially, three experiments were performed to determine the effect of residence times on the performance. A microreactor with a capillary length of 10 cm was applied and operated at three different flow rates (2.5–7.5 mL h^{−1}, residence times between 12 and 36 s). With these flow settings, the reactor is operated in the slug flow regime (Fig. S4, ESI[†]). All experiments were run for at least 2 residence times to ensure that a

steady state was obtained. The outlet concentrations of DNB-(*R,S*)-Leu in both phases *versus* residence times are shown in Fig. 5.

The results show that the (*S*)-enantiomer is preferentially extracted from the aqueous phase to the organic phase, indeed proving that enantioselective extraction is possible in the microreactor set-up. The *ee* values are calculated from the data presented in Fig. 5 using eqn (6) and are provided in Fig. 6a. The *ee* values are between 41 and 44% for the organic phase, though the error in the values is relatively large. However, the values are within the range for the equilibrium value obtained in batch under similar conditions ($41 \pm 2\%$, Table 2). The operational selectivity is between 2.9 and 3.1 (Fig. 6b) and is also comparable with the operational selectivity obtained in batch experiments (3.2 ± 0.2) under equilibrium conditions.

Though the operational selectivity and the *ee* values seem to be close to the equilibrium values obtained in batch, the concentration in the outlet are not constant and seem to be a function of the residence time, see Fig. 5 for details. This is an indication that the experiments were not solely performed in the equilibrium regime. To further assess this, additional experiments (in total 57, see ESI Table S2[†]) were performed with a wider range of residence times (12–900 s). Residence times were set by changing either the flow rates or the length of the microreactor. The results are given in Fig. 7 and indeed show that the concentrations in the outlet are not constant.

At low residence times, the concentrations are a function of the residence times, whereas the values become constant at higher residence times and about equal to the equilibrium values obtained in batch experiments. This implies that equilibrium is attained at higher residence times, typically above 200 s. A similar trend was found for the *ee* values and the operational selectivity (Fig. 8). The *ee*'s varied between 37% and 49% and of particular interest is the observation that the *ee* values in the organic phase are higher in the kinetic regime than at equilibrium. This implies that higher *ee*'s are possible when operating the microreactor set-up in the kinetic regime at low residence times. This remarkable aspect will be considered further when discussing the experiments with

Fig. 5 Outlet concentrations of DNB-(*R,S*)-Leu in the aqueous phase (a) and organic phase (b) *versus* the residence time in the capillary microreactor (Fig. 3) for 10 cm capillary length. Conditions: see Table 1.

Fig. 6 Enantiomeric excess (a) and operational selectivity (b) of enantioselective extraction of DNB-(*R,S*)-Leu and CA3 in DCE in a microreactor of 10 cm length. Conditions: see Table 1.

Fig. 7 Concentration of DNB-(*R,S*)-Leu in the aqueous phase outlet (a) and organic phase outlet (b) versus residence time after extraction with CA3 in 1,2-DCE in the slug flow capillary microreactor. Conditions: see Table 1.

Fig. 8 Enantiomeric excess (a) and operational selectivity (b) versus the residence time for the enantioselective extraction of DNB-(*R,S*)-Leu with CA3 in 1,2-DCE in the slug flow capillary microreactor. The values are calculated from the data presented in Fig. 7 using eqn (4) and (6). Conditions: see Table 1.

1-octanol, which showed an even more profound effect of residence times on ee.

Continuous experiments in 1-octanol

To find alternatives for 1,2-DCE and to probe the solvent effect on the separation performance, the use of 1-octanol as the organic solvent was explored. A total of 29 experiments were

performed in the continuous set-up in the slug flow regime with a range of residence times by varying the total flow rate and the tube length (Table S3, ESI†). Conditions are shown in Table 1.

The effect of residence times on the outlet concentrations is shown in Fig. 9, and with 1-octanol, the outlet concentrations are a function of the residence time. For residence times

Fig. 9 Aqueous phase outlet (a) and organic phase outlet (b) versus the residence time for the enantioselective extraction of DNB-(*R,S*)-Leu with CA3 in 1-octanol in the slug flow capillary microreactor. Conditions: see Table 1.

beyond 300 s, the concentrations become constant and equilibrium is attained. The outlet concentrations in this regime are indeed equal to those obtained in the batch equilibrium studies (*vide supra*).

Similar trends were observed for the ee values (Fig. 10). The ee's varied between 28 and 46% and are a clear function of the residence time. Values are highest at the shortest residence times and then level off to the equilibrium value (about 30%) at longer residence times. The ee values in the equilibrium regime are similar to those obtained in batch equilibrium studies (31%).

The observation of high ee values at short residence times is more profound in 1-octanol than in 1,2-DCE. This kinetic effect may be explained by considering the intrinsic rates of the complexation reactions in the organic phase (Fig. 1) and the mass transfer rates of both enantiomers from the aqueous to the organic phase. To gain insights into the intrinsic rates of the complexation reactions, a number of batch experiments were performed with DNB-(*R,S*)-Leu and CA3 in 1-octanol. The organic and aqueous phases were in contact intensively for about 6 s and then were separated within 30 s. Analysis of the aqueous phase (HPLC) showed that equilibrium values were attained within this timescale. This implies that the intrinsic kinetics for complexation in the organic phase is faster than

the experimentally observed timescale of the kinetic regime in the microreactor (about 300 s in 1-octanol see Fig. 9). As such the mass transfer rates of the enantiomers from the aqueous phase to the organic phase are also of importance and affect the overall rate of the extraction processes. However, the extraction process in the kinetic regime in the microreactor is not solely governed by mass transfer processes as in this case chiral recognition is not possible and ee values at short residence times are expected to be zero.^{43,62}

This suggests that the experiments were carried out in the intermediate regime where both mass transfer rates and intrinsic kinetics play a role and determine the overall rate of the transfer processes. In this regime, the observed transfer rates of the enantiomers are governed by the physical properties of the system (diffusivities, mass transfer coefficients, *etc.*) which are equal for both enantiomers and by the rates and equilibrium constants of the complexation reactions. The latter are different for both enantiomers and will lead to differences in transfer rates and thus ee values in the experiments performed in the capillary microreactors. We have designated this as the kinetic regime, to make a distinction with the equilibrium regime, but it should be noted that the behaviour of the system is determined not only by the kinetics but also by the mass transfer characteristics. Extensive reactor engineering

Fig. 10 Enantiomeric excess (a) and operational selectivity (b) versus the residence time for the enantioselective extraction of DNB-(*R,S*)-Leu with CA3 in 1-octanol. The values are calculated from the data presented in Fig. 9 using eqn (4) and (6). Conditions: see Table 1.

modeling activities to obtain a better understanding of the complex interplay between the reaction and mass transfer are in progress and will be reported in due course.

Thus, we can conclude that higher ee values are attainable in the capillary microreactors in the kinetic regime. This unprecedented finding has high potential and justifies further studies as it suggests that equilibrium ELLE is not necessarily the best when considering ELLE performance. However, for ELLE, not only the ee is of importance but the yields of the individual enantiomers should also be considered and obviously a high yield is preferred. The yields of the (*R*)- and (*S*)-enantiomer *versus* the residence times for the experiments in 1-octanol are given in Fig. 11. Clearly, the yields are lower in the kinetic regime, for which higher ee values are attainable. As such, a balance between ee and yield should be considered.

Fig. 11 The extraction yields of both enantiomers for enantioselective extraction of DNB-(*R,S*)-Leu with CA3 in 1-octanol. The values are calculated from the data presented in Fig. 9 using eqn (7a) and (7b). Conditions: see Table 1.

In this respect, the development of multistage microreactor concepts in which each individual microreactor is operated in the kinetic mode to obtain high ee values holds great promise.

The results provided above only involve a single extraction step. Higher ee values and yields are possible by performing multistage extractions using various configurations (co-cross and countercurrent operation). Prediction of ee values and yields in the equilibrium regime for such configurations by appropriate (reactor) engineering models is well established.^{32,63} For instance, for an operational selectivity of 3 for a reactive extraction system, about 10 equilibrium stages are required in counter current operation to obtain ee values of 99%.

However, the introduction of non-equilibrium operation (in the kinetic regime) significantly complicates the calculations. Here we want to discuss some preliminary results obtained by operating the system in the kinetic regime, *i.e.* at short residence times, and in combination with a multistage configuration for the system with 1-octanol as the organic solvent. As an example, a multistage concept was applied by taking each time the aqueous outlet to a next ELLE step where it is treated with a fresh organic stream containing only 1 mM of extractant, see Fig. 12. In such a cross flow mode, it is possible to increase the yield of the (*S*)-enantiomer, while at the same time having ee values higher than the equilibrium value for each step, by performing the extraction at a short residence time. Each extraction step then operates in the kinetic regime. However, the ee values at such a short residence time will decrease from each step to the next due to the change in the aqueous inlet concentration of *S* and *R* where the excess of *R* will increase with each step.

Finally, we mention here that by suitably rearranging the inflow and outflow connections, an overall countercurrent flow operation is possible, as illustrated in Fig. 13. Reactor engineering modeling activities to obtain a better understanding of the complex interplay between the reaction and mass transfer and the consequences of various multistep operation modes are in progress and will be reported separately.

Fig. 12 Multistage concept for ELLE using flow reactors applying fresh organic solution to each step.

Fig. 13 Multistage concept for ELLE using flow reactors applying a countercurrent scheme to the feed streams for each step.

Conclusions

We here report the proof of concept for ELLE in a capillary microreactor operated in the slug flow regime. 1-Octanol was shown to be a good, environmentally more benign alternative for conventionally used chlorinated solvents like 1,2-DCE. The use of microreactors holds great potential for future exploration as it allows for continuous operation, precise setting of residence times and small inventories of expensive hosts and solvents. Furthermore, for new chemistry systems, it allows for fast screening and optimization of process conditions. Of high interest is also the observation that ee is higher in the kinetic regime than in the equilibrium regime for particularly 1-octanol, indicating that non-equilibrium ELLE may have high potential. Process studies are in progress to demonstrate the use of microreactors for multistage operation, including a host recycling step (back-extraction), to separate racemates and to give both enantiomers in high yields and purity.

Acknowledgements

The authors thank the technical staff of the Department of Chemical Engineering, University of Groningen, The Netherlands, for the design of the experimental setup. Financial support from STW through project no. 11404 (Chiral Separations by Kinetic Extractive Resolution in Microfluidic Devices) and input from all user committee members of the project are gratefully acknowledged.

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