Enantioselective liquid-liquid extraction in centrifugal contactor separators
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Summary:

Chiral objects do not have an internal mirror plane. A simple example of a chiral object is a (winking) smiley, see Figure S1. If the smiley winks (right) it cannot be superimposed on its mirror image and it is said to be chiral. On the other hand, when the smiley does not wink, it is achiral (left).

Figure S1. Left: achiral smiley. Right: chiral winking smiley.

In chemistry, chirality is an important feature. When a molecule is chiral, the biological activity of the two different mirror images (enantiomers) may differ to a great extent. The consequences may be dramatic. For example, \((S),(S)\)-ethambutol is the active ingredient in a drug against tuberculosis, whereas one of the other enantiomers \((R),(R)\)-ethambutol) causes blindness. Another example is \((S)\)-ketamine. \((S)\)-ketamine is an anaesthetic, while \((R)\)-ketamine is a hallucinogen. Thus, the administration of these (and other) drugs in an enantiopure form to the patients is essential.

Several technologies have been developed for the production of single enantiomers. Racemic production followed by separation is the most common. However, the existing technologies have limitations. This in combination with the rapid increase in the demand for enantiopure compounds has stimulated research and development on alternatives. This thesis describes research on enantioselective liquid-liquid extraction (ELLE), a very promising but not yet commercialized technology. The objective of the research is to demonstrate the use of ELLE in a continuous mode in a bench scale unit. For this purpose, compact centrifugal contactor separators (CCS) were used. Two attractive ELLE-systems for further studies were investigated in batch and the results are described in Chapters 2 and 3. Important characteristics of CCS-equipment were investigated (Chapters
4 and 5) and one of het ELLE-systems was investigated in detail in the continuous CCS-equipment (Chapters 6 and 7).

In ELLE the mixture of enantiomers to be separated is dissolved in a liquid, which is usually water. This solution is called the feed. The feed is contacted with a second, immiscible liquid, usually an organic solvent, containing an extractant (host). The host is chiral and has a high affinity for only one of the solutes. By this selective reaction, one of the guests is extracted to a higher extent to the organic phase than the other, leading to an enantiomeric excess of this enantiomer in the extract phase. A schematic representation of the principles of ELLE is given in Figure S2.

![Figure S2. Schematic representation of ELLE. Symbolen:](image)

High selectivity for the binding between the host and one of the solutes is thus essential. However, it is also important that the interaction between host and solute is reversible. If the reaction between host and guest is irreversible, the host cannot be recycled, leading to unacceptable high manufacturing costs. The host should also be poorly or preferably insoluble in the water phase to avoid losses to the water phase. Finally, versatility is also highly desirable, meaning that a single host is capable of separating a family of compound classes and not only a single component with high selectivity.

In Chapters 2 and 3 research on the equilibrium extraction of an amino acid derivative (3,5-dinitrobenzoyl-(R),(S)-leucine, DNB-R,S-leu) and an aminoalcohol ((R),(S)-phenylglycinol, PGLR,S) is discussed. For the chiral separation of DNB-R,S-leu a chiral cinchona alkaloid extractant (C) was selected from literature. The host (P) for the extraction of PGLR,S was developed by Bas Verkuijl in the group of Prof. dr. Feringa (University of
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Groningen) and consists of a chiral phosphoric acid derivative. Experimental extraction studies were performed in batch and the results could be described well with equilibrium extraction models incorporating homogeneous organic phase complexation of host and guests. For both systems complete separation of the enantiomers could not be achieved in a single equilibrium stage. Multistage countercurrent processing was proposed to increase both the yield and enantioselectivity.

A schematic representation of a multistage countercurrent process is depicted in Figure S3. One of the enantiomers is preferentially extracted into the extract phase in the stages 1 - N by reaction with the chiral host. The other enantiomer leaves the system in the raffinate stream. The extract stream with enantiomer-host complex is transferred to a back-extraction section (stages 1 - M) where the enantiomer is recovered. The host is recycled to the extraction unit.

Figure S3. Countercurrent multistage extraction and back-extraction process.

A multistage countercurrent model was developed for the ELLE of DNB-R,S-leu and used to optimization the chiral separation in terms of yield and enantiopurity.

CINC V02 Centrifugal Contactor Separators (CCS) have been used for the continuous chiral extractions. In this equipment, two immiscible liquids are intensely mixed, leading to exchange of components between the two phases and subsequently separated again. Figure S4 shows a schematic representation (left) and a photograph (right) of the device.
Figure S4. Schematic representation (left) and a photograph of the CCS (right). Dark grey areas in the schematic representation represent the heavy liquid, light grey the light liquid, and the hatched area the dispersion.

Both liquids enter at the sides of the cylindrically shaped device into a tight space between the static wall and the rotating centrifuge. Due to the speed of rotation and the short distance between the static and rotating walls, the liquids are intensely mixed. The dispersion is then transferred to the centrifuge through a hole in the bottom, where the large centrifugal forces cause efficient phase separation. This fast phase separation allows the use of a small centrifuge, making the equipment very compact in size. The unit operations mixing and separation are thus combined in a single device, making it a good example of what is known as process intensification.

Although the use of the CCS for separation purposes has already been known since the late 1960’s, still not much is known about important characteristics of the device like the total interfacial area between two immiscible liquids, the size of the droplets in the system, which of the phases is continuous and which is disperse, and the macro mixing behavior of both phases. An in-depth exploration was performed to gain insights in these features and the results are given in Chapters 4 and 5. This information is of importance for modeling of processes taking place in the CCS.
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The use of the CCS for continuous ELLE of DNB-R,S-leu is reported in Chapter 6. It is shown that the CCS acts as a single equilibrium stage. The possibility of recycling the host was also demonstrated by using a back-extraction step in a single CCS. Essentially quantitative recovery was possible by an extraction with an aqueous pH 9 stream.

The use of a cascade of 7 CCS devices for the enantioselective separation of DNB-R,S-leu including a back-extraction step is given in Chapter 7. The optimum cascade configuration was initially modeled using an equilibrium approach. With this configuration, the production of one of the enantiomers with an ee of 98% and a yield of 55% was proven experimentally. Good agreement between the experimental data and the model was also observed. With the validated model available, it was shown that full separation (ee > 99%) of DNB-R,S-leu in DNB-R-leu and DNB-S-leu should be possible when using a cascade of at least 11 stages. The model also predicts that the separation of 17.7 kg DNB-R,S-leu per week in the individual enantiomers is achievable with only 60g of host.

The research project has demonstrated that it is possible to perform ELLE in a continuous mode using the very compact CCS-equipment. One of the advantages of the CCS devices is that they can be used as bench scale devices for research and development purposes as well as for kilogram scale production. Good insights have been obtained in the characteristics of the CCS equipment, which may be of use not only for ELLE but also for other CCS applications.