Chiral separation of amino-alcohols and amines by fractional reactive extraction

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Chiral separation of amino-alcohols and amines by fractional reactive extraction

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Maria Steensma

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Prof. dr. ir. A.B. de Haan

en de assistent-promotor

Dr. ir. N.J.M. Kuipers

Voorwoord

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Maartje

Contents

Summary

Many naturally occurring substances possess chirality, which is the property that the molecule and its mirror image are not superimposable. Chirality plays an important role in biological systems. For instance, only one enantiomer (mirror isomer) of many pharmaceuticals is the active substance. The availability of optically pure substances is therefore of primary importance in the pharmaceutical and fine chemical industry. Chiral separation is an important, often cost-effective way to obtain these substances. Chiral separation may also be required as final purification step after a selective synthesis. The current industrial separation techniques each have major drawbacks. (Diastereomer) crystallisation is inflexible and involves solid-phase handling. Simulated moving bed (SMB) chromatography is more flexible, but it is very expensive because of the low volumetric productivity and the use of expensive chiral stationary phases (CSP's).

In this thesis, fractional reactive extraction (FREX) is proposed and evaluated as alternative industrial separation technique. In FREX, an enantioselective extractant is applied as chiral selector. The process is versatile if the same extractant can be used with a good selectivity and capacity for a number of different substances from the same chemical class. Both enantiomers can be obtained at the desired purity by application of the fractional extraction scheme. Fractional reactive extraction combines in a liquid process flexibility with lower cost per chiral recognition site and high volumetric capacity. Despite its potential advantages over existing separation techniques, FREX is currently not applied on industrial scale because of a lack of versatile enantioselective extractants and a too low productivity. This thesis is therefore focused on identification of enantioselective extractants, improvement of productivity and technology development.

In chapter 2, the large potential of fractional reactive extraction is demonstrated with an enantioselective extractant for amino acid separation, the copper(II) complex of N-dodecyl-L-hydroxyproline. The selectivity and versatility of this extractant are reported in literature to be good, and the application of the extractant in laboratory scale FREX extractors is also described; however, the productivity was in all cases very low. The influence of process conditions on the selectivity and capacity in a single extraction stage were experimentally determined for this extractant system. Along with the experiments, a predictive model was constructed based on the physical and chemical equilibria in the system. The model could explain all experimental trends. Based on the experiments and the model, it was calculated that the productivity in the lab-scale extractors from literature can be increased by a factor 50-100 by using optimal process conditions, without changing existing chemistry. Thus, the importance of optimisation of process conditions for the economical feasibility of FREX is demonstrated.

A method is developed in chapter 3 to identify potential enantioselective extractants in the vast analytical chiral recognition literature. In this way, selective interactions already known in literature can be exploited for reactive extraction. Because many important chiral intermediates are amines or amino-alcohols, six components with structural variation were selected as model enantiomers from these chemical classes. To test the identification method, a literature database is compiled containing > 100 selectors for amines, amino alcohols and amino acids originating from various (analytical) techniques. 18 systems from this database were experimentally screened for selectivity in extraction. Additional measurements were carried out for the four systems that showed an enantioselectivity > 1.1. The system that gave the best results in the selectivity, an azophenolic crown ether, is a new enantioselective extractant and it is characterised further in later chapters. As for the identification method, the most promising candidate extractants emerge from the database if it is searched for 'selectors originating from a technique with a similar separation mechanism as extraction' in combination with 'high selectivity' and 'versatility'; a successful transfer of selectors from other techniques to extraction is the most likely if the selectors form diastereomeric complexes with the enantiomers in the liquid that differ in complexation constant. The identification method is expected to save a lot of experimental trial and error in future extractant development for enantiomers from other chemical classes.

In chapter 4, the most promising enantioselective extractant is characterised further. This extractant is an azophenolic crown ether that reversibly forms complexes with neutral amines and amino-alcohols, in contrast with a conventional crown ether that complexes with the ammonium form of amines or amino-alcohols. An extraction mechanism is proposed in which the neutral amine or amino-alcohol partitions between the aqueous and the organic phase (physical extraction), followed by complexation with the crown ether in the organic (bulk) phase. The equilibrium between neutral form and ammonium form of the enantiomers in the aqueous phase is governed by the pH. As all equilibrium constants can be obtained from independent measurements, a predictive single stage model can be formulated based on these equilibria and mass balances. Secondly, experiments are carried out with the model amines and amino-alcohols to find the influence of concentrations, pH, temperature and solvent on the selectivity and capacity of extraction. The capacity (distribution ratio) increases with increasing pH, decreasing temperature, increasing excess of extractant and increasing concentration level of enantiomers and extractant. The selectivity increases with increasing extractant concentration until the intrinsic selectivity is approached; to obtain this selectivity, an excess extractant of only 2-3 is required for the investigated systems, whereas in the literature often an excess of > 100 is applied for similar systems. Five out of six model enantiomers could be separated with a selectivity between 1.5 and 9.4 and sufficient capacity. In this way, it has been demonstrated that the new extractant is both versatile and highly selective. The single stage equilibrium model can be used very well to explain all influences of process conditions on the capacity of extraction, and it gives a quantitatively correct

prediction of the operational selectivity. The developed and validated single stage model will be used as basis for a multistage extractor model in chapter 6.

Initial work on determination of the reaction kinetics in reactive extraction systems is described in chapter 5, because it is important to know the mass transfer rates and reaction kinetics separately for a reliable scale-up. To interpret the experimental data from the selected model reactor, the modified Lewis cell, a kinetic model is required. The two-phase 'homogeneous reaction' model was selected over the 'interfacial reaction' model, because the physical extraction is considerable in all systems. The extraction process in the Lewis cell is simulated based on this reaction model. A regime analysis is associated with the homogeneous reaction model. Strictly speaking, it is only valid for an irreversible reaction and a negligible resistance to mass transfer in the non-reactive phase. These conditions are generally not fulfilled in reactive extraction. It was shown by simulations and by theoretical considerations that the regime analysis indeed fails for reactive extraction in a number of regimes. Furthermore, it follows from the simulations that enhancement of mass transfer by reaction may be (partly) invisible. Finally, it becomes clear that the fraction of the species that is in the 'extractable' form should be used in the calculations. As the regime analysis as such cannot be applied to determine the reaction kinetics in the chiral systems, first the mass transfer rate was measured during physical extraction, whereafter the location of the main resistance to mass transfer was determined. Then the enhancement of mass transfer was measured during reactive extraction. By model simulation, it was determined how much enhancement of mass transfer should be observable. In this way, it was concluded that the reaction kinetics of the azophenolic crown ether system are between 'fast' and 'instantaneous', and the reaction kinetics of the Cu(II)-N-dodecyl-L-hydroxyproline system are between 'slow' and 'fast'. The Lewis cell is not the most suitable model contactor to determine reaction kinetics in reactive extraction systems. A more suitable contactor would have lower mass transfer resistances that can be varied independently over a larger range, for instance the rotating diffusion cell or a novel model reactor.

In chapter 6, simulations are carried out for a fractional extractor with a multistage equilibrium model based on the single stage model. A higher pH, lower T, higher concentrations and a higher excess of extractant all result in higher purities in both product streams, but a higher wash stream is required to realise good yield and good purity. The improved purity can be explained from a higher operational selectivity in the single stage, from lower variation of the extraction factors along the extractor, or from a combination of these effects. Application of 'reflux' results in higher product purities at a lower wash stream requirement, but a lower process capacity. The consequences for process design are discussed qualitatively. A specification of 99% yield and 98% enantiomeric excess (e.e.) is defined for the extract, which results in 99% yield and 98% e.e. for the other enantiomer in the raffinate as well. To make the best use of the versatile extractant, the design of a versatile extractor for a multiproduct environment is much more interesting than the design of a 'dedicated'

extractor for a single product. It was shown that various combinations of process conditions result in the desired product specifications, and the more stages available above the minimum number, the larger the process capacity. All systems for which a single stage selectivity of 1.5 was obtained in chapter 4, can be separated in a multiproduct extractor containing 50 stages, evenly distributed over the wash and strip section.

In chapter 7, the predictions from the multistage model are tested experimentally in a set-up consisting of two hollow fiber membrane modules. Almost two equilibrium stages are realised in each module. In this way a partial chiral separation can be obtained. The influence of the flow rate ratios (S/F and W/S) on the enantiomeric excess in the experiments is lower than predicted, possibly because of insufficient residence time. The experimental and predicted trends in the yield are similar. The experimental effect of a temperature decrease was almost nil, probably because the more favourable theomodynamics and the slower kinetics at lower temperature counteracted. A better separation can be obtained if modules are used containing smaller membrane fibers for more interfacial area. Furthermore, the experimental trends can probably be understood better with the help of a non-equilibrium model.

In the last chapter, the overall conclusions are presented and fractional reactive extraction is compared with the main industrial separation techniques, crystallisation and SMB chromatography. Although FREX has some clear advantages over these techniques, more research is required before FREX can be introduced in industry. An economical evaluation should be used to decide if FREX is indeed the best solution for a specific separation problem. More attention is also needed for equipment selection, design and scale-up. For a reliable design, it is in any case required that reaction kinetics and mass transfer in reactive extraction can be described more accurately. For application of FREX as separation technique for enantiomers other than amines or amino-alcohols, identification or design of new affinity extractants is essential. The identification method developed in this thesis is expected to be successful for other classes of enantiomers as well.

Samenvatting

Veel in de natuur voorkomende moleculen bezitten chiraliteit, de eigenschap dat het molecuul in chemische structuur niet gelijk is aan zijn spiegelbeeld. Met name in biologische systemen speelt chiraliteit een grote rol. Er zijn bijvoorbeeld veel geneesmiddelen waarbij de werkzaamheid voornamelijk in één van beide spiegelbeeldisomeren zit. De beschikbaarheid van optische zuivere stoffen is dan ook essentieel voor de farmaceutische en fijnchemische industrie. Een belangrijke, vaak kosteneffectieve route om deze stoffen te verkrijgen is de scheiding van een (racemisch) mengsel, een zogenaamde chirale scheiding. Ook als via een selectieve synthese een niet-racemisch productmengsel is verkregen, is vaak nog een chirale scheiding nodig als laatste zuiveringsstap. De huidige technieken voor chirale scheiding op industriële schaal hebben ieder grote nadelen: (diastereomere) kristallisatie is niet flexibel en vereist bovendien het werken met vaste stof, en het meer flexibele Simulated Moving Bed (SMB) chromatografie is relatief duur vanwege de lage volumetrische capaciteit en het gebruik van een chirale vaste fase (CSP).

In dit proefschrift wordt fractionerende reactieve extractie (FREX) als alternatieve industriële scheidingstechniek voorgesteld en geëvalueerd. Hierbij wordt een enantioselectieve extractant toegepast als chirale selector. Dit scheidingsproces is flexibel indien één extractant beschikbaar is die een voldoende hoge selectiviteit en capaciteit geeft voor een aantal verschillende stoffen uit dezelfde chemische klasse. Beide enantiomeren kunnen dan in de gewenste zuiverheid verkregen worden door gebruik van het fractionerende extractieschema. Fractionerende reactieve extractie combineert aldus in een vloeistofproces flexibiliteit met lagere kosten per ‘chirale site’ en hoge volumetrische capaciteit. Ondanks deze mogelijke voordelen wordt fractionerende reactieve extractie momenteel niet toegepast op industriële schaal, vanwege een gebrek aan veelzijdige, selectieve extractanten voor de belangrijkste verbindingen en vanwege een te lage productiviteit. Dit promotieonderzoek is derhalve voornamelijk gericht op de identificatie van enantioselectieve extractanten, het verbeteren van de productiviteit en de verdere technologieontwikkeling.

Het potentieel van fractionerende reactieve extractie wordt in hoofstuk 2 verder toegelicht met behulp van een enantioselectieve extractant voor het scheiden van aminozuren, het koper(II) complex van N-dodecyl-L-hydroxyproline. Van dit complex is reeds vanuit de literatuur bekend dat de veelzijdigheid en selectiviteit goed zijn, terwijl ook fractionerende reactieve extractie in diverse laboratoriumopstellingen is beschreven; de productiviteit was echter in alle gevallen zeer laag. Met dit extractantsysteem zijn metingen uitgevoerd om de invloed van diverse procesparameters vast te leggen op de selectiviteit en capaciteit in één evenwichtstrap. Tegelijkertijd is een model gemaakt waarin alle evenwichten beschreven worden en waarmee alle experimentele trends kunnen worden verklaard. Op basis van de metingen en het model is berekend dat de capaciteit van de in de literatuur beschreven proefopstellingen met een factor 50-100 verhoogd kan worden door bij optimale procesomstandigheden te werken, zonder de

chemie aan te hoeven passen. Het belang van het optimaliseren van procesomstandigheden voor de economische haalbaarheid van fractionerende reactieve extractie is hiermee aangetoond.

In hoofdstuk 3 is een methode ontwikkeld voor de identificatie van potentiële enantioselectieve extractanten op basis van de uitgebreide analytische literatuur over chirale herkenning. Er kan zo gebruik gemaakt worden van de selectieve interacties die al in de literatuur bekend zijn. Als modelenantiomeren zijn zes componenten met onderlinge variatie in chemische structuur gekozen uit de klassen van amines en amino-alcoholen, omdat veel belangrijke chirale tussenproducten optisch zuivere amines en amino-alcoholen zijn. Voor het testen van de identificatiemethode is een literatuurdatabase gemaakt met > 100 selectoren uit diverse technieken voor amines, amino-alcoholen en aminozuren. Hiervan zijn 18 systemen experimenteel gescreend op het vertonen van selectiviteit in extractie. Voor de vier systemen die een selectiviteit > 1.1 gaven zijn aanvullende metingen verricht. Het systeem dat in deze metingen de beste selectiviteit en veelzijdigheid liet zien, een azofenolische kroonether, is een nieuwe enantioselectieve extractant en wordt in de overige hoofstukken verder onderzocht. Het blijkt dat de meest veelbelovende extractanten uit de database naar boven komen als gezocht wordt op ‘afkomstig uit een techniek met vergelijkbaar scheidingsmechanisme’ in combinatie met ‘hoge selectiviteit’ en ‘veelzijdigheid’: de kans op een succesvolle overdracht van de selector naar extractie is het grootst als er diastereomere complexen in de vloeistof gevormd worden die van elkaar verschillen in complexatieconstante. Met behulp van de ontwikkelde identificatiemethode kan gericht gezocht worden naar potentiële extractanten in de literatuur over chirale herkenning en wordt veel experimentele ‘trial and error’ bespaard.

De meest veelbelovende extractant uit hoofdstuk 3 is in hoofstuk 4 verder gekarakteriseerd. Deze extractant is een azofenolische kroonether, die reversibel complexen vormt met neutrale amines en amino-alcoholen; dit in contrast met een conventionele kroonether, die complexeert met amines in de ammoniumvorm. Er wordt een extractiemechanisme voorgesteld waarbij de neutrale amines of amino-alcoholen vanuit de waterfase naar de organische fase migreren via fysische extractie (partitie) waarna complexatie met de kroonether plaatsvindt in de organische (bulk)fase. In de waterfase heerst een pH-afhankelijk evenwicht tussen de neutrale amines en het geconjugeerde zuur (ammonium). Omdat alle benodigde evenwichtsconstanten uit onafhankelijke metingen te verkrijgen zijn, kan een voorspellend eentraps-evenwichtsmodel geformuleerd worden, gebaseerd op deze evenwichten en de massabalansen. Vervolgens zijn er extractiemetingen uitgevoerd met de amino-alcoholen en amines uit de modelset teneinde de invloed van concentraties, pH, temperatuur en oplosmiddel op de selectiviteit en capaciteit van de extractie vast te leggen. De capaciteit (verdelingscoefficient) blijkt toe te nemen met toenemende pH, afnemende temperatuur, toenemende overmaat extractant en toenemende concentraties enantiomeer en extractant. De selectiviteit neemt toe met toenemende extractantconcentratie tot de intrinsieke selectiviteit bereikt wordt; bij de onderzochte systemen is hiervoor slechts een overmaat extractant van 2-3 nodig, terwijl in de

literatuur (voor andere systemen) vaak een overmaat > 100 gebruikt is. Vijf van de zes amines en amino-alcoholen uit de modelset kunnen gescheiden worden met een selectiviteit tussen 1.5 en 9.4 en met voldoende capaciteit, waarmee aangetoond is dat de nieuwe extractant zowel selectief als veelzijdig is. Het evenwichtsmodel blijkt zeer goed in staat de invloeden van de diverse procesparameters op de capaciteit van extractie te verklaren, en de selectiviteit kwantitatief correct te voorspellen. Het ontwikkelde en gevalideerde model van één evenwichtstrap zal gebruikt worden voor extractorberekeningen in hoofdstuk 6.

In hoofdstuk 5 is een begin gemaakt met het bestuderen van de extractiekinetiek in reactieve extractie-systemen, omdat het voor betrouwbare opschaling van belang is de invloed van stofoverdracht en reactiekinetiek afzonderlijk te kennen. Voor het interpreteren van de meetgegevens uit de gekozen modelreactor, de gemodificieerde Lewis-cel, is het model van de ‘homogene reactie’ verkozen boven de ‘grensvlakreactie’ omdat de fysische extractie in alle systemen aanzienlijk is. Het extractieproces in de Lewis-cel wordt gesimuleerd op basis van deze modelbeschrijving. Bij het homogene reactiemodel hoort een regime-analyse, die strikt genomen alleen geldig is voor irreversibele reactie met een verwaarloosbare weerstand tegen stofoverdracht in de niet-reactieve fase. Bij reactieve extractie wordt in het algemeen aan geen van beide voorwaarden voldaan. Met behulp van simulaties en theorie is dan ook vastgesteld dat deze regime-analyse in een aantal regimes faalt voor reactieve extractie. Verder volgt ook uit de simulaties dat versnelling van stofoverdracht door reactie deels of geheel onzichtbaar kan worden. Tenslotte wordt duidelijk dat gerekend moet worden met de fractie van de stof die in de ‘overdraagbare’ vorm is. Omdat de regime-analyse niet gebruikt kan worden voor het bepalen van de reactiekinetiek, is voor twee chirale systemen eerst de fysische stofoverdrachtssnelheid gemeten en de locatie bepaald van de belangrijkste weerstand; vervolgens is experimenteel bepaald of en hoeveel versnelling van stofoverdracht plaats vond. Modelmatig is bepaald hoeveel versnelling meetbaar zou moeten zijn. Op deze wijze is vastgesteld dat de reactie tussen kroonether en phenylglycinol of phenylethylamine ‘zeer snel’ tot ‘instantaan’ is, terwijl de reactie tussen koper-C_{12}Hyp complex en leucine tussen ‘langzaam’ en ‘snel’ in zit. De Lewis-cel is niet de meest geschikte contactor om reactiekinetiek in dergelijke systemen vast te stellen; beter lijkt een contactor waarin de beide stofoverdrachtsweerstanden kleiner zijn en ieder apart over een grotere range gevarieerd kunnen worden, zoals de roterende membraancel of een nog te ontwikkelen modelreactor.

In hoofdstuk 6 worden berekeningen voor een fractionerende extractor gemaakt met behulp van een meertraps-evenwichtsmodel dat is gebaseerd op het eentrapsmodel. Een hogere pH, lagere temperatuur, hogere concentraties en grotere overmaat extractant resulteren allemaal in een hogere zuiverheid van beide productstromen; echter ook een grotere wasstroom is nodig om in beide productstromen dezelfde hoge zuiverheid en hoge opbrengst te realiseren. De verbeterde zuiverheid kan worden verklaard door een verbeterde operationele selectiviteit per trap, door minder variatie van de extractiefactoren over de extractor of door een combinatie van deze effecten. Verder kan de zuiverheid in beide productstromen verhoogd worden en de

benodigde wasstroom verkleind worden door ‘reflux’ toe te passen. Dit gaat echter wel ten koste van de capaciteit. De gevolgen voor procesontwerp worden kwalitatief besproken. Als specificatie wordt 99% yield en 98% enantiomere overmaat (e.e.) opgelegd aan het extract, met als gevolg 99% yield en 98% e.e. van het andere enantiomeer in het raffinaat. Om optimaal gebruik te maken van de veelzijdige extractant, is het ontwerpen van een extractor voor een ‘multiproduct’ omgeving interessanter dan het ontwerpen van een ‘één-product’ extractor. Uit berekeningen blijkt dat de specificatie voor een bepaalde productzuiverheid en opbrengst op diverse manieren gerealiseerd kan worden, en dat de procescapaciteit toeneemt naarmate er meer evenwichtstrappen dan het minimum aantal beschikbaar zijn. Alle systemen uit hoofdstuk 4 waarvoor een selectiviteit van 1.5 in de enkele trap is bereikt, kunnen gescheiden worden met de gewenste specificatie als er een extractor beschikbaar is met 50 evenwichtstrappen, gelijk verdeeld over de was- en stripsectie.

In hoofdstuk 7 worden de voorspellingen van het multistage model experimenteel getoetst in een opstelling bestaande uit twee holle-vezel membraanmodules. Vrijwel twee evenwichtstrappen worden gerealiseerd per module, waarmee een gedeeltelijke chirale scheiding wordt behaald. De invloed van de stroomverhoudingen (oplosmiddel/voeding) en (wasstroom/oplosmiddel) op de zuiverheid in de experimenten is kleiner dan voorspeld, wellicht doordat de experimentele verblijftijden niet voldoende lang waren. De trends in de experimentele en voorspelde opbrengst (yield) zijn aan elkaar gelijk. Het effect van een temperatuurdaling is in het experiment vrijwel nihil, waarschijnlijk doordat de gunstiger evenwichtsligging en de langzamere kinetiek bij lagere temperatuur elkaars werking opheffen. Een betere scheiding zou kunnen worden gerealiseerd in modules met kleinere membraanvezels door een groter uitwisselend oppervlak. Verder zouden de experimentele resultaten met een tijdsafhankelijk model waarschijnlijk beter verklaard kunnen worden.

In het laatste hoofdstuk worden de conclusies uit het proefschrift op een rijtje gezet en wordt FREX vergeleken met de voornaamste concurrerende industriële scheidingstechnieken, te weten kristallisatie en SMB chromatografie. FREX heeft op papier diverse voordelen ten opzichte van deze technieken. Echter, om FREX in de industriële praktijk in te kunnen voeren is meer onderzoek en ontwikkeling nodig. Een economische evaluatie zal moeten uitwijzen of FREX inderdaad de beste keuze is voor een specifiek scheidingsprobleem. Verder moet er aandacht besteed worden aan apparaatselectie en -ontwerp en methoden voor opschaling. Voor een betrouwbaar ontwerp is in ieder geval vereist dat reactiekinetiek en stofoverdracht in reactieve-extractiesystemen beter beschreven kan worden. Voor toepassing van FREX als scheidingstechniek voor enantiomeren anders dan amines en amino-alcoholen is ontwikkeling van nieuwe extractanten voor andere klassen van chemicaliën essentieel. De ontwikkelde selectiemethode lijkt hiervoor bruikbaar.

1 Introduction

This thesis is concerned with the development of a new separation method for optical isomers, namely fractional reactive extraction. In this chapter, it is explained why optically pure substances are economically interesting, why we aim at separation instead of direct stereospecific synthesis, why fractional reactive extraction is promising as chiral separation technique and which obstacles need to be dealt with for successful application. The chapter is concluded with the outline of the thesis.

1.1 Chirality

Many naturally occurring substances possess chirality, which is the property that a substance and its mirror image are not superimposable[1]. In every-day life, many examples can be found as well: the left and right hand are each other's mirror image, the right foot does not fit in the left shoe, and a screw is always tightened in the same direction (figure 1).

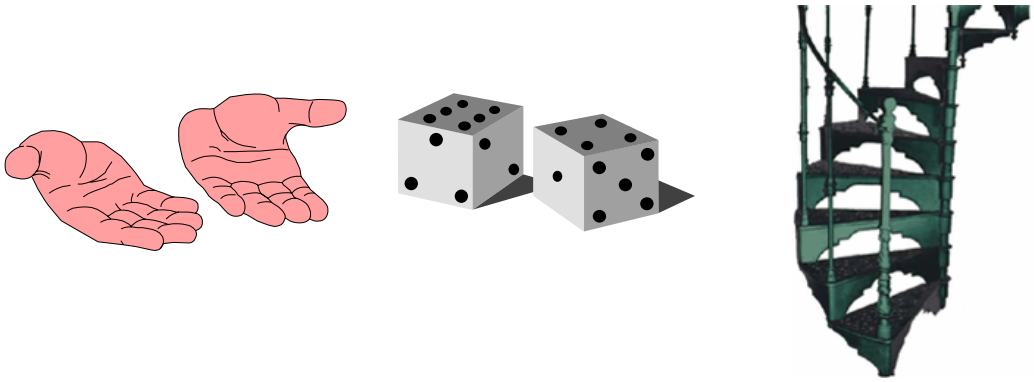


Figure 1: examples of chiral objects in every-day life: hands, dice, spiral staircase

On molecular scale, chirality originates from the three-dimensional orientation of the atoms in the molecule. In many cases, a 'chiral centre' or 'asymmetric carbon atom' can be identified in a chiral molecule: if a carbon atom is connected to four different side groups, the molecule is automatically chiral because of the tetraeder structure (figure 2). But the presence of a chiral centre is not a prerequisite for a molecule to be chiral. A molecule can also possess planar or axial chirality, like a macro-scale screw or a spiral staircase.[2] In this study, the focus will be on chirality that originates from a chiral centre.

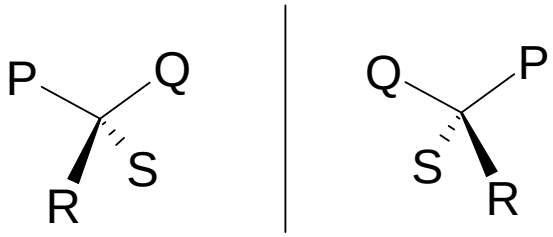


Figure 2: Chirality originating from a chiral centre; the two molecules are each other's mirror image

Mirror isomers are usually referred to as enantiomers or as optical isomers. A 50/50 mixture of two enantiomers is called a racemic mixture. The term 'optical isomer' originates from the rotation effect of chiral molecules on plane-polarised light: one enantiomer will rotate this polarised light to the left-hand side, the other to the right-hand side. Apart from this optical effect, the physical properties such as boiling point, viscosity etc. are in general the same for both enantiomers of a substance. The chemical interaction with achiral reagents is also the same for both enantiomers. Only with reagents that are chiral themselves, enantiomers can show quite different interactions. This may be the reason that the chemical implications of chirality often have been neglected in the past, although the concept of chirality has been known for a long time.

Various nomenclature systems for enantiomers exist. The Cahn-Ingold-Prelog convention is a systematic system, using R and S for designating the three-dimensional structure on each asymmetric carbon in the molecule. The (+) and (-) nomenclature is based on the rotation direction of polarised light. Furthermore, for biological systems the D and L signs are used to distinguish between enantiomers; the designation L or D is based on the structural similarity of the molecule with D-(+)-glyceraldehyde, which serves as a 'benchmark' molecule. For molecules with other types of chirality, other nomenclature systems are in use: helicity and planar chirality is described by P (plus = clockwise) or M (minus = anticlockwise); molecules with axial chirality are also named P and M or Ra and Sa.[2]

1.2 Implications of chirality for the chemical and pharmaceutical industry

Chirality plays an important role in biological systems. For instance, enzymes are chiral biological polymers consisting of solely L-amino acids. They are highly structured compounds: their secondary and tertiary structure is determined by the amino acid constituents. Enzymes function as molecular receptors by binding selectively to specific molecules. As enzymes are chiral, they commonly interact much stronger with one enantiomer of the 'target' molecule: a form of chiral recognition. Enzyme selectivity was explained already in 1894 by Fischer with the 'lock-and-key' concept: one enantiomer 'fits' in the enzyme cavity, the other enantiomer does not (figure 3). The lock-and-key concept was reformulated later as the three-point rule (Easson & Steadman, 1933) and its variations. This rule states that at least three non-coplanar interactions are required for chiral recognition: then all three interactions are present between the 'best-fitting' enantiomer and the receptor, but with the other enantiomer only two interactions are possible. Variations and refinements to this rule have been reported. The most important one is that the interactions may be attractive or repulsive: steric hindrance often plays an important role in chiral recognition.

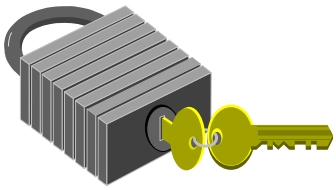


Figure 3: Lock-and-key concept

The therapeutic effect of a pharmaceutical substance is often based on binding with molecular receptors, usually in competition with the 'original' target molecule. Because of the chirality of the molecular receptor, the two enantiomers of a pharmaceutical substance may have a completely different effect. Often, one of the enantiomers is much more active than the other. Moreover, the enantiomers may have effects that oppose each other, or that complement each other. In some cases one of the enantiomers causes serious side effects, all because of the differences in interaction with the molecular receptors. Therefore, it seems logical to study the effects of the enantiomers separately and as a mixture, and to administer only the effective enantiomer, unless there are good reasons to administer the racemate.

A dramatic example of different behaviour of enantiomers from the past is thalidomide (figure 4a). This substance was marketed as Softenon in the 1960s and was administered as a racemate. The S-enantiomer proved to be highly teratogenic, whereas the R-enantiomer was the active ingredient. It is believed nowadays that administering thalidomide as single isomer would not have prevented the problems, because thalidomide is easily racemised within the human body. Nevertheless, a more detailed study of the effect of each enantiomer could have prevented much harm.

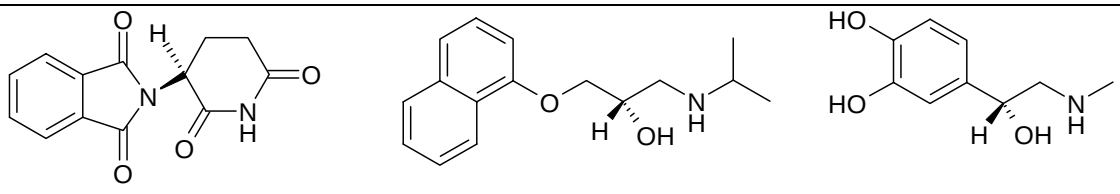


Figure 4: (a) S-thalidomide (b) S-propranolol (c) noradrenaline

Furthermore, it is known that for most beta-blockers the S-enantiomer is the most active enantiomer. The S-enantiomer has the same threedimensional structure as the adrenergic hormone noradrenaline (figure 4b+c). The R-enantiomer of the betablocker does not give serious side-effects, but it does not add to the pharmacological effect either, so it can be considered as 'isomeric ballast'. The most sold beta-blockers (propranolol, atenolol, metoprolol) were developed in the 1970s and are still marketed as racemate. If these substances would have been developed today, it can be expected that they would have been introduced as single enantiomers.

Two developments have intensified the demand for optically pure substances and the search for new manufacturing methods during the past decades: new FDA regulations and the 'racemic switch'. Since 1992, the American Food and Drug Administration (FDA) requires clinical trials with the racemic mixture and each enantiomer separately, before approval can be obtained to use the racemic mixture as a drug. Since then, it has become important to have on a short time-scale kilogram-quantities of optically pure substances at one's disposal, making single-enantiomer production techniques and separation techniques for the industrial production scale to gain in importance. Furthermore, the 'racemic switch' has become fashionable: if a patent on a drug that is marketed as racemic mixture is expiring, it is sometimes possible to obtain a new patent for the active enantiomer.[3,4] In this way, the pharmaceutical company retains the exclusive rights on the substance for another period, but they will have to change their manufacturing method as well. Although only a minority of all racemic drugs has proved to be suitable for a racemic switch, this development has boosted the development of new manufacturing and separation methods. An example of a successful racemic switch is the local anaesthetic bupivacaine (AstraZeneca's Marcain). The S-isomer is now marketed under the trade name Chirocaine. This isomer was found to be substantially less cardiotoxic than the R-isomer, and therefore a new patent was granted. Furthermore, the S-isomer of omeprazole (a proton pump inhibitor by AstraZeneca, known as Losec/Prilosec) is now marketed as a single enantiomer under the trade name Nexium.[3]

Chirality is also important in other fields of chemistry. Large applications are found in agrochemicals and the food and fragrance industry. For example, the S-enantiomer of the compound limonene has lemon odor, and the R-enantiomer orange odor. For chiral herbicides from the class of α-aryloxypropionic acids, the activity is present almost solely in the R-enantiomer. Although currently most herbicides are applied as racemates, the trends is here towards pure enantiomer application as well. Use as single-enantiomer would result in 50% reduction of dosage, which means 50% less environmental pollution.

1.3 Economical importance of single-enantiomer technology

The 'industrial scale' for chiral substances ranges from 'kilos' to 'tens of tons' scale. Rather than expressing the magnitude of the market in volumes, the importance of single-enantiomer products is illustrated well by 'sales'. It will be clear from tables 1-3 that single-enantiomer drugs are big business.

Table 1: Growth: revenues from chiral technology will near $ 15 billion by 2009[5]

	Revenue ($ billions)	Annual growth
1999	4.80	
2000	5.40	12.5 %
2001	6.10	13.0
2002	7.00	14.8
2003	7.74	10.6
2004	8.57	10.8
2005	9.53	11.1
2006	10.61	11.3
2007	11.85	11.7
2008	13.28	12.1
2009	14.94	12.5

Source: Frost & Sullivan

Table 2: Steady share: worldwide sales of single-enantiomer pharmaceutical products approach $ 160 billion[5]

	2001			2002[a]		
		single-enantiomer			single-enantiomer	
$ billions	total market	sales	market share	total market	sales	market share
Cancer	17.0	13.8	81%	18.7	16.8	90%
Antibiotics/antifungal	33.0	26.9	82	33.7	26.8	80
Hematology	16.5	10.7	65	17.8	13.8	78
Hormones/endocrinology	26	18.8	72	29.9	19.4	65
Cardiovascular	50.0	30.0	60	52.5	30.4	58
Vaccines	8.5	4.3	51	9.2	4.5	49
Antiviral	20.0	6.1	31	21.0	6.7	32
Ophtalmic	8.0	2.5	31	8.5	2.7	32
Central nervous system	55.0	10.5	19	56.6	12.0	21
Respiratory	42.0	7.9	19	43.5	9.3	21
Gastrointestinal	50.0	5.4	11	53.0	7.2	14
Dermatology	18.5	1.2	6	18.6	1.1	6
Analgesics	23.5	1.2	5	24.0	1.2	5
Others	42.0	6.8	16	42.2	7.2	17
TOTAL	368.0	139.3	36%	387.0	151.9	37%

[a] *primary estimates. Source: Technology Catalysts International*

Table 3: Blockbusters: top 10 single-enantiomer products belong to billion-dollar club[5]

Brand name	Marketer	Therapeutic area	2002 sales ($ billions)
Lipitor	Pfizer	Cardiovascular	8.0
Zocor	Merck	Cardiovascular	5.6
Pravachol, Mevalotin	Bristol-Myers Squibb and Sankyo	Cardiovascular	4.0
Paxil	GlaxoSmithKline	Central nervous system	3.1
Plavix	Sanofi Synthelabo and Bristol-Myers Squibb	Hematology	2.9
Zoloft	Pfizer	Central nervous system	2.7
Advair, Seretide	GlaxoSmithKline	Respiratory	2.4
Nexium	AstraZeneca	Gastrointestinal	2.0
Augmentin	GlaxoSmithKline	Antibiotic	1.8
Diovan	Novartis	Cardiovascular	1.7
Total			34.2

Source: Technology Catalysts International

1.4 Sources of enantiopure substances

In general, there are three ways to obtain optically pure substances (figure 5):

- from natural sources
- by selective synthesis of the desired enantiomer
- by separation of a racemic mixture

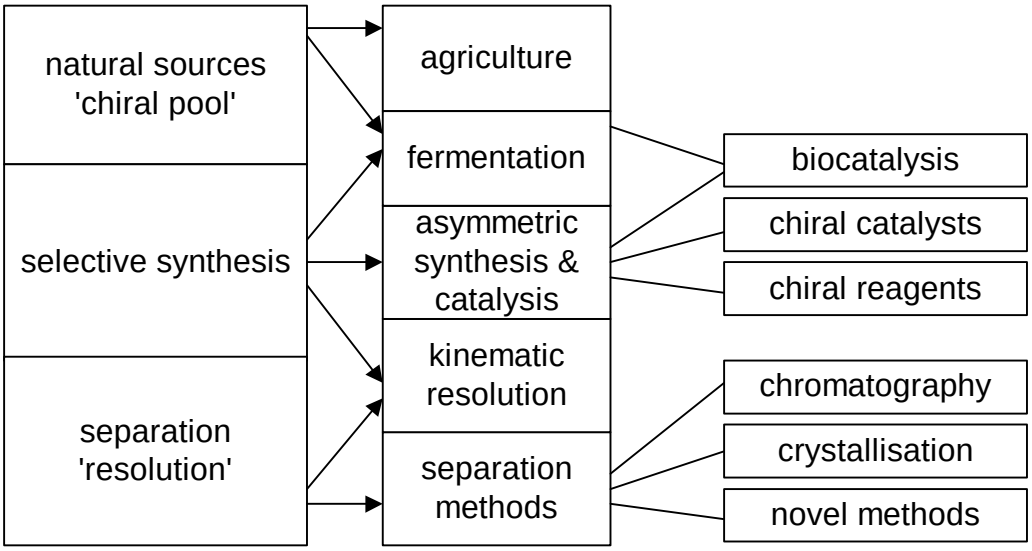


Figure 5: Scheme of most important methods to obtain optically pure substances

Natural sources are often referred to as the ‘chiral pool’. The most important classes of chiral pool substances are amino acids, carbohydrates, hydroxy acids, terpenes and alkaloids.[6]

Examples of applications are found in the fine chemical and pharmaceutical industry. For instance, L-proline is used as key raw material for various ACE-inhibitors, inclusing Captopril, Enalapril and Lisinopril. Terpenes such as pinene, menthol and camphor are used primarily as (raw materials for) chiral auxiliaries, such as resolving agents and chiral ligands for asymmetric catalysis.

Many selective or 'asymmetric' synthesis routes have been developed that yield an enantiopure or an enantio-enriched product.[7,8] In these methods, chirality has to be transferred to the product molecule in one way or another. This can be achieved by using a chiral reagent, yielding a chiral product; the chiral reagent is consumed in the reaction or used catalytically. In these syntheses, a very low reaction temperature (-100 °C) is commonly required, which brings about scale-up problems.[9] Asymmetric synthesis can also be carried out by using a chiral catalyst. For example, catalytic asymmetric hydrogenation can be carried out with a rhodium complex of a monodentate chiral ligands.[7] A variety of chiral ligands is available. A well-tuned reaction may yield an e.e. of > 90%, but 100% conversion and 100% e.e. cannot be obtained.

The technique of fermentation[1] can be classified both under 'natural sources' and 'selective synthesis'. In fermentation, micro-organisms (yeasts, fungi, bacteria) produce optically pure substances usually as a metabolite. Originally, the range of products was restricted to compounds that are produced naturally by various micro-organisms. Nowadays, micro-organisms are also producing a variety of non-natural chemicals, partly after spontaneous mutations, and partly after genetic engineering. Fermentation as production technique has gained importance due to advances in genetics on one hand, and in biochemical engineering on the other hand (micro-organism immobilisation, in situ product removal, use of non-aqueous solvents, etc). Instead of using a complete micro-organism, the active enzyme can also be isolated and used in selective synthesis of compounds. Using such enzymes is sometimes referred to as 'biocatalysis', and this technique may be classified under 'selective synthesis' as well. For example, since 2001 BASF has been operating two plants that produce chiral intermediates such as phenylethylamine under the trademark: ChiPros with a selective lipase.[10]

Separation or resolution of a racemic mixture is the third main technique to obtain enantiopure substances. In direct chiral separations, there is no difference in physical properties and the interaction with a chiral separating agent or 'chiral selector' is required to achieve the separation. The exception to this rule is the separation by crystallisation of so-called conglomerates, which are compounds that form single-enantiomer crystals; 5-10 % of all solids are estimated to be conglomerates. An important class of separation techniques are diastereomer separations; here the enantiomers are first reacted with an optically pure reagent to yield diastereomers, which differ in physical properties and can be separated in various ways.

For direct analytical-scale separations many chromatographic techniques are in use, such as HPLC,[11] GC,[12] TLC and electrophoresis.[13] The chiral selector is either attached to the solid phase or used as additive in the mobile phase. For lab-scale preparative separations, crystallisation and HPLC/liquid chromatography are the main techniques. The majority of industrial-scale separations is carried out by (diastereomer) crystallisation,[14] but simulated moving bed (SMB) chromatography is rapidly advancing.[15] One of the largest applications of SMB is the resolution of the antidepressive agent Celexa (citalopram) by Forest Laboratories, with a capacity of about 50 ton/year (2002). Several other preparative separation techniques are under development. Examples are reactive extraction,[16,17] liquid membrane[18,19] and solid membrane separations,[20,21,22] and various separations of diastereomeric mixtures, for instance by supercritical extraction[23,24] or by distillation[25]. For these techniques, much lab-scale work but no full-scale applications were reported so far. An overview of separation methods is given in figure 6.

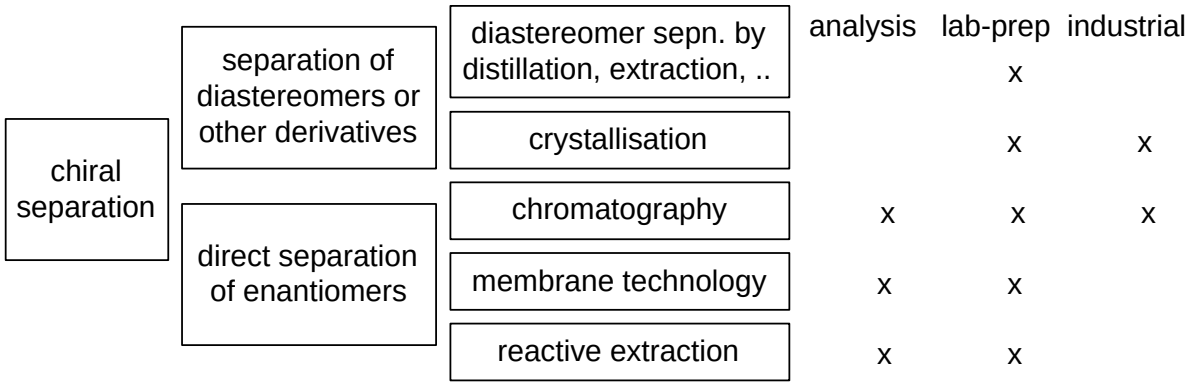


Figure 6: main chiral separation methods and current fields of application

1.5 Importance of chiral separation technology

It should be discussed which of the many routes to obtain optically pure sustances should be selected. If a 'chiral pool' route to enantiopure substances is applicable, this is to be preferred, as these are the most straightforward routes. But, the amount of end products thus obtainable is limited: not each desired compound can be won from natural sources or produced by fermentation. Secondly, if the optical purity is not high enough, a subsequent separation or purification step is still needed.

If the compound cannot be taken from the chiral pool or produced from a chiral pool material, direct production of the desired enantiomer may seem the most attractive. Asymmetric synthesis promises to yield only the desired enantiomer, so there is less waste than in synthesis of a racemic mixture followed by resolution. However, even if an asymmetric synthesis route would be available for each desired compound, there would still be a need for chiral separation methods. First of all, asymmetric synthesis routes often lead to a enantio-

enriched product, which has to be purified further to obtain the desired optical purity: so there is a need for separation. Here a parallel can be seen with non-chiral chemistry: in most processes about 70% of the investment is spent on separations because 100% selectivity and 100% conversion cannot be obtained in the reactor. So, it is important to have chiral separation methods for the final purification step in order to provide the desired product quality to the customer. Secondly, when considering the 'waste' issue the complete processes should be compared. Asymmetric synthesis routes tend to be complicated, with very expensive catalysts, and often consist of multiple steps. If a compound A can be produced as a racemic mixture in a two-step synthesis, and then resolved into its enantiomers, this is probably preferable to an asymmetric synthesis of the desired enantiomer of A in a seven-step selective route, both for environmental reasons and economical reasons. This is even more true if an easy way to racemise to unwanted enantiomer is available. The production of single-enantiomer verapamil (Celltech-Chiroscience) may serve as an example.[5,26] The S and the R-enantiomer of this substance are both interesting, as they can be used to treat hypertension and angina, respectively. The lab-scale asymmetric synthesis routes were complex and therefore impractical for a larger scale synthesis. It was found that verapamilic acid, a precursor of the drug, could be resolved cost-effectively by diastereomer crystallisation using α-methylbenzylamine as resolving agent. As the demand for the S-enantiomer is larger than for the R-enantiomer, the company is currently studying a racemisation method.

It is clear that separation methods are and will remain important.[27] For the industrial scale, only two techniques seem to be used widely at this moment. The majority of large-scale separations is done by diastereomeric crystallisation; the enantiomers first react with an optically pure material, and the resulting diastereomers are separated by crystallisation. If the substance forms conglomerates, direct crystallisation can be used. The major drawbacks of the diastereomer crystallisation method are the need for solid-phase handling and its inflexibility: for each new racemic mixture, a new resolving agent and resolution method has to be devised. Although screening can be speeded up by applying 'Dutch Resolution',[28,29], there is quite some development time needed for each new compound. This is a large disadvantage in the pharmaceutical industry: a company has to sell as much of a new product as possible before the patents expire, so a fast time-to-market is often more important than cost reductions in the production. The second drawback is inherent to crystallisation: the process is relatively slow, difficult to control, and the handling of solids/ slurries is more complicated than the handling of liquids. Finally, in diastereomeric crystallisations a stoichiometric amount of enantiopure reagent is needed, two additional process steps are required, namely derivatization and product recovery, and the enantiopure reagent is either consumed or has to be recovered as well.

A large-scale technique that is gaining importance steadily is simulated moving bed chromatography (SMB), an efficient method to carry out HPLC separation continuously. The separating agent is immobilised as the chiral stationary phase. Simulated moving bed

chromatography is more flexible than crystallisation: only a relatively low selectivity is required because a large number of theoretical stages is present, and therefore the same column material can be used to separate several enantiomers. The chiral separating agent is not consumed. These seem to be the main reasons why SMB is gaining importance over crystallisation. The main drawbacks of SMB are the extremely high cost of the chiral solid phases, and the low productivity per gram of phase per day: the solid phase is easily overloaded. Furthermore, the product streams are diluted considerably in the process because separation and recovery have to be carried out under similar process conditions.

Therefore, an alternative separation process for direct separation of enantiomers should be flexible and suitable for the commercial production scale; the development time for each new pair enantiomers to-be-separated should be lower than in crystallisation, and solid-phase handling should be avoided. Furthermore, the cost of the technique should be lower and the dilution of the products should be less than in SMB.

1.6 Fractional reactive extraction

Fractional reactive extraction is proposed as alternative for diastereomer crystallisation and SMB chromatography. In this method, the well-known conventional liquid-liquid extraction process[30,31] is combined with a reversible enantioselective complexation reaction (figure 7a). To obtain both enantiomers in the desired purity, the fractional extraction scheme is proposed (figure 7b): an additional wash stream will remove the co-extracted undesired enantiomer from the extract.[32,33]

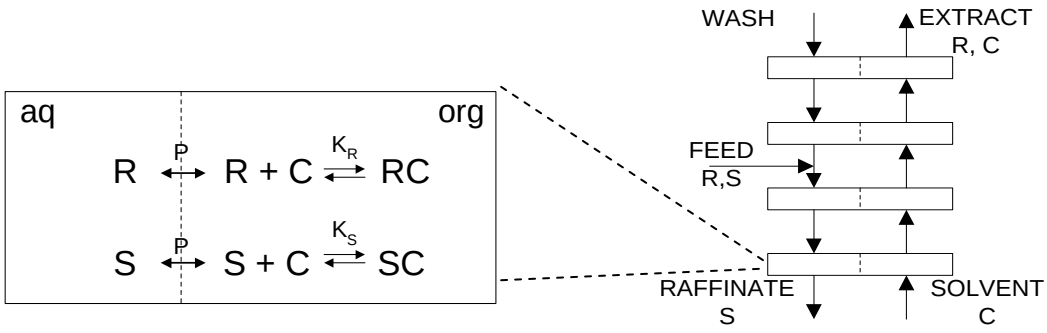


Figure 7: (a) single extraction stage: example of equilibria between enantiomers 'R' and 'S' and enantioselective extractant 'C' (b) fractional extraction scheme, assuming that R is preferentially extracted ($K_R > K_S$)

It is expected that some of the drawbacks encountered in crystallisation and SMB technology may be overcome, or at least reduced by using fractional reactive extraction.[34,35] In extraction, no solid phase handling is involved; the chiral selector (extractant) is not consumed; if a versatile selector is used (i.e. a selector that is selective for various compounds from the same chemical class), the process will be flexible. In comparison with SMB, it is expected that a selector in free solution can be present at larger concentrations than on a surface, resulting in a higher loadability of the selector phase. Because of the higher loadability, the volumetric

capacity of reactive extraction will be higher than in SMB, so the process equipment will be smaller, and a more concentrated feed stream can be handled. A selector in free solution will also be much cheaper than a selector on a support, if the 'price per active site' is compared. Finally, as the 'separation' and 'product recovery' steps do not have to be carried out under the same conditions (in terms of temperature and pH), product recovery is expected to be easier and thus cheaper in reactive extraction, and the dilution of the feed is also expected to be lower, resulting in a better 'product quality'.

To reach these improvements over the existing separation techniques, the following characteristics of the enantioselective extractant can already be stated:

- selectivity should be sufficient
- versatility: the selector should be selective for a number of compounds from the same chemical class; it should preferably be selective for underivatised substances
- reversibility: the complexation reaction should be reversed easily, in order to obtain the product and to recover the extractant for re-use.
- solubility: the selector should be well soluble in one phase (for a high volumetric capacity) and not soluble in the other liquid phase (to avoid losses by leaching)
- other demands, such as acceptable chemical stability, acceptable cost, low toxicity.

Fractional reactive extraction for chiral separations is not new. The process has been demonstrated on lab-scale for various enantiomer separations. Furthermore processes are reported in literature that are essentially fractional liquid-liquid extraction processes, but that appear under other nomenclature. Examples of such related processes are 'counter-current distribution' or 'countercurrent chromatography',[36] 'centrifugal partition chromatography',[37] 'Craig extraction'[38] and 'counter-current droplet chromatography'[39]. A rather large amount of literature is available on single-stage liquid extraction (named 'batch-wise equilibration', 'partitioning experiments' 'distribution', etc) for partial chiral separation.[40,41] Extraction is often used to evaluate new chiral selectors, but most of these references do not consider reactive extraction as preparative separation technique, nor contain information that can be used directly for an extraction process design.

Literature references on FREX for chiral separation go back to the 1960's. Romano *et al.*[42] report the synthesis of 'liquid ion exchangers' based on methylbenzylamine as selectors for chiral separation of sodium mandelate and sodium-N-acetyl-alanate. The selectors were evaluated by batch extraction and by counter-current extraction in a Craig apparatus. Bauer *et al.*[43] report optical enrichment of chiral ferrocene derivates by 'counter-current distribution', employing (+)-diethyltartrate as chiral selector. Bowman *et al.*[44] studied partitioning of racemates between an aqueous phase and a tartaric acid ester phase.

A widely studied, versatile extractant system is based on alkyl derivatives of L-proline or L-hydroxyproline with Cu^{2+} ion. A 1:2 copper-ligand complex is formed in the organic phase, in

which one of the ligands can be exchanged selectively for an amino acid enantiomer. The ligand system originates from chromatography[45,46] and was introduced as enantioselective extractant by Takeuchi *et al.*[47] A number of amino acids and mandelic acid[48] were resolved with this system, with single-stage selectivity ranging from 1.4 to 3. Various lab-scale equipment designs employing the fractional extraction scheme were reported, usually consisting of two separate units representing the wash and strip section. Takeuchi *et al.*[49] use a set-up based on two rotating glass columns to separate DL-valine. The liquid phases are contacted counter-currently and the feed is entered in between (figure 8). The same set-up was also applied for separation of lanthanides with D2EHPA in hexane.[50] Nishizawa *et al.*[48] use a related design called a 'liquid particle extractor' to separate mandelic acid with N-dodecyl-L-proline Cu(II) complex. Ding *et al.*[51] use two hollow fiber membrane modules for separation of leucine. Yokouchi *et al.*[52] carried out fractional reactive extraction in a cascade of small-scale mixer-settlers. All these designs have in common a small scale, a large amount of theoretical stages and long residence times (2-24 hr), resulting in very pure products streams but a low productivity (1-10 mg/hr range).

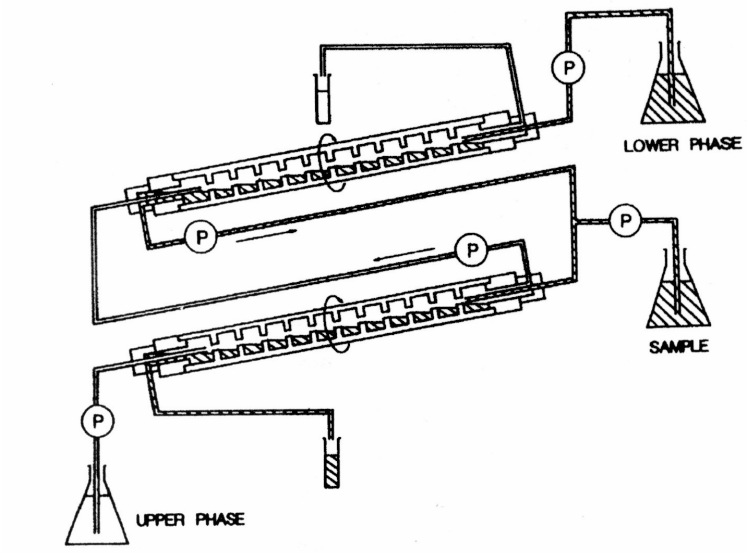


Figure 8: 'Takeuchi' fractional extractor consisting of rotating glass columns[49]

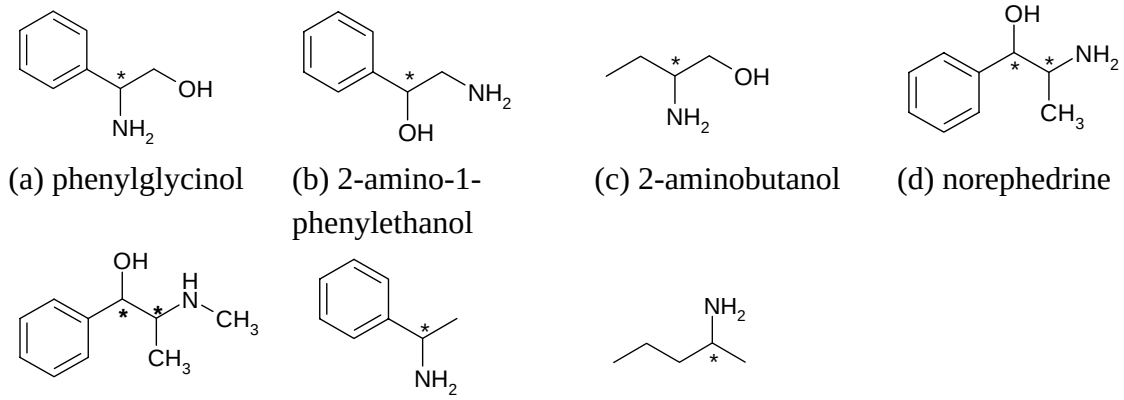
A 'proof-of-principle' of fractional reactive extraction for chiral separation is therefore available, but despite its potential advantages over the other chiral separation techniques, the process has not become common practice in industrial chiral separation. Two main reasons seem to be responsible for this.

Firstly, it is difficult to identify enantioselective extractants that fulfil all requirements listed, especially sufficient selectivity, capacity and versatility, and that can still be used economically. Till now, only for separation of amino acids a significant amount of research on extractants is reported.[47] For introduction of FREX as all-round chiral separation technique, enantioselective extractants need to be available for all major classes of chiral

compounds. For this study, the class of amines and amino-alcohols was selected because many optically pure amines and amino-alcohols are important chiral intermediates.[1] The component phenylglycinol was chosen as archetype model enantiomer. To study the influence of molecular structure, the following model enantiomers were included in the set of model enantiomers (figure 9):

phenylglycinol	archetype
2-amino-1-phenylethanol	phenyl group and chiral centre shifted; '2a1pe'
2-aminobutanol	aliphatic instead of aromatic compound
norephedrine	as 2a1pe, with introduction of second chiral centre
ephedrine	as norephedrine, but secondary amine
phenylethylamine	no hydroxy group. 'α-methylbenzylamine' or 'PEA'
2-aminopentane	aliphatic amine

All studied amino-alcohols have the hydroxyl group and amino group on neighbouring carbon atoms, and all components are primary amines except for ephedrine.



(a) phenylglycinol (b) 2-amino-1-phenylethanol (c) 2-aminobutanol (d) norephedrine

(e) ephedrine (f) phenylethylamine (g) 2-aminopentane

*Figure 9: Structure of amino-alcohols and amines studied. * indicates a chiral centre*

No feasible enantioselective extractant system is available for these substances. One versatile extractant system was developed by Prelog and coworkers,[16] but the selectivity and capacity of this system are too low for commercial application.

Secondly, the productivity was very low in all of the systems as tested in lab-scale / pilot equipment, probably because the emphasis has been on the maximisation of the selectivity and on the design of pilot equipment. Therefore, an economic evaluation study based on these papers will not be positive. A key subject for this thesis is therefore increase of productivity and further development of fractional reactive extraction technology.

1.7 Outline of the thesis

In this first chapter, the importance of industrial chiral separation has been shown, and the disadvantages of current chiral separation processes for the commercial production scale have been listed. The aim of this thesis is to study fractional reactive extraction (FREX) as alternative chiral separation technique for the commercial production scale. Amines and amino-alcohols were selected as model enantiomers. Two main issues were identified that need to be resolved for a successful introduction of fractional reactive extraction:

- identification of enantioselective extractants
- improvement of productivity / technology development

In the second chapter the potential of fractional reactive extraction will be demonstrated in more detail by studying the obtainable productivity increase for leucine separation with N-dodecyl-L-hydroxyproline Cu(II) complex, a reactive extraction system for amino acid separation that has been described in literature by various authors. The high versatility and selectivity of this system are already known.

The third chapter of this thesis will focus on the identification of enantioselective extractant systems. For this purpose, the set of model enantiomers is used containing amino-alcohols and amines with structural variation. It is attempted to exploit the vast amount of analytical and chemical literature on chiral recognition rather than developing new chiral selectors. Chiral recognition is discussed in much chemical literature as a phenomenon in itself,[53] and it is applied in various analytical techniques for a range of chiral substances. It is expected that some of these cases of chiral recognition will provide leads to new enantioselective extractants. An approach for transfer of chiral selectors from other techniques to extraction will be proposed and evaluated.

After that, the selectivity and capacity of the best enantioselective extractant system identified in chapter 3 are experimentally characterised in chapter 4. The influence of process parameters such as pH, temperature and concentrations are studied, as they are expected to have a large influence on the capacity and selectivity. Product and extractant recovery is studied experimentally as well, because efficient product recovery and re-use of the extractant is a prerequisite for an economically feasible process. Along with the experiments, a predictive single-stage model based on the chemical and physical equilibria is developed and validated.

The kinetics of extraction have to be sufficiently fast for an economically feasible process and are therefore discussed in chapter 5. In a reactive extraction system, both the mass transfer and the reaction kinetics may be rate-determining. Therefore, the mass transfer rate and reaction kinetics are studied in the modified Lewis cell for the reactive extraction system from chapter 3/4 and for the C_{12}Hyp-Cu(II) system from chapter 2. The applicability of kinetic models and regime analysis for measuring reaction kinetics in reactive extraction is discussed.

In chapter 6, the single-stage equilibrium model from chapter 4 is expanded to a multistage fractional extractor model, and the influence of changes in flow rates and other process parameters on the selectivity and capacity of the separation is studied by model simulation. The options of recovery of enantiomers and extractant are studied as well. The consequences for conceptual design of a fractional extractor are discussed qualitatively.

In chapter 7, pilot plant tests in a hollow fiber membrane module set-up to test the multistage model predictions are reported.

The thesis is concluded with conclusions and outlook in chapter 8.

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2 Feasibility of fractional reactive extraction as chiral separation technique: improved productivity in the chiral separation of DL-leucine

2.1 Introduction

The concept of fractional reactive extraction has been proposed in chapter 1 as alternative for current large-scale chiral separation techniques. It was stated there that the feasibility of this concept so far is not very promising because of two reasons: the productivity that can be calculated for amino acid separation based on original research papers is very low, and there are no suitable versatile enantioselective extractants to separate components other than amino acids. To justify any further work on fractional reactive extraction for chiral separation, this chapter is concerned with improvement of productivity.

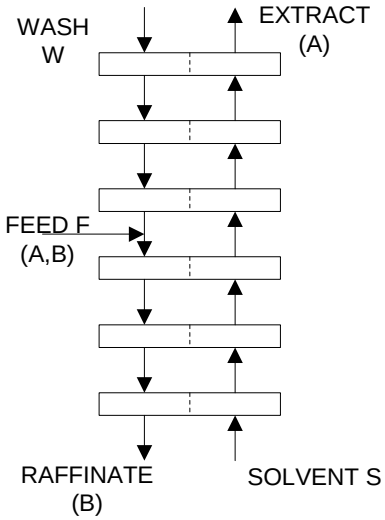


Figure 1: Scheme of FREX, with wash section (upper part) and strip section (lower part); the feed F is introduced in between.

A scheme of the fractional extraction process is given in figure 1. The enantioselective extractant is in general present in the organic solvent (see chapter 1) because chiral recognition tends to be more selective in a hydrophobic environment[1,2]. The enantiomer that complexes most strongly with the extractant is recovered from the extract, and the other enantiomer ends up in the raffinate. The optical purity in a stream is usually expressed as enantiomeric excess[3] (e.e.). For a stream in which enantiomer A is present in the highest concentration, the e.e. is defined in equation 1. If enantiomer B dominates, the e.e. is given in equation 2.

$$e.e. = \frac{[A]-[B]}{[A]+[B]} \qquad (1) \qquad\qquad e.e. = \frac{[B]-[A]}{[A]+[B]} \qquad (2)$$

The yield in a stream is defined as the fraction of the enantiomer in the feed that is present in that stream. For instance, the yield of enantiomer A in the extract is given in equation 3. Similarly, the yield are defined for the other enantiomer and the raffinate.

$$yield_{A,EXTRACT} = \frac{total \quad A \quad extract}{total \quad A \quad feed} = \frac{S \cdot [A]_{out}}{F \cdot [A]_{in}} \tag{3}$$

Initial calculations for the fractional extraction process were carried out in two ways, with the Fenske equation and the Kremser equation[4]. In both equations, a single-stage selectivity α is required as input to calculate the number of stages. The Kremser equation also needs an extraction factor (E) containing the distribution ratio D and the phase ratio. The distribution ratio D represents the capacity in a single stage, and the operational selectivity in a single stage is calculated from the distribution ratios for each enantiomer:

$$D_A = \frac{[A]_{org,allforms}}{[A]_{aq,allforms}} \tag{4}$$

$$D_B = \frac{[B]_{org,allforms}}{[B]_{aq,allforms}} \tag{5}$$

$$\alpha_{op} = \frac{D_A}{D_B} \tag{6}$$

The Fenske equation (eq. 7), which originates from the distillation literature, can be used for a first estimate of the required number of stages N_{min} at a given selectivity (α_{op}) and purity demand for a binary separation. x_{bottom} and x_{top} are mole fractions in bottom product and top product. The minimum number of stages is reached at full reflux, so there is no actual product stream.

$$N_{\min} = \frac{\ln\left[\frac{x_{top}}{1-x_{top}} / \frac{x_{bottom}}{1-x_{bottom}}\right]}{\ln \alpha_{op}} \tag{7}$$

The Kremser equation (eq. 8) is valid for dilute systems with a constant distribution ratio over the extractor and constant flow rates. The value of the extraction factor E determines the direction of mass transfer.

$$N = \frac{\ln\left[\left(\frac{x_{in} - y_{in}/D}{x_{out} - y_{in}/D}\right)\left(1 - \frac{1}{E}\right) + \frac{1}{E}\right]}{\ln E} \tag{8}$$

$$\text{with } E = D \cdot \frac{S}{F} \tag{9}$$

For a reactive system, all information on the reaction can be lumped into an effective distribution ratio D for each substance ($D_A \neq D_B$). If available, experimental values for D can be introduced. To model the fractional extraction scheme (figure 1), the two extraction

sections are each described by a separate Kremser equation[5]. The feed is introduced in between, where it is mixed with the outlet of the wash section.

2.1.1 Selectivity versus number of stages

Both the Fenske equation and the Kremser equation (for fractional scheme) were applied to estimate the number of stages to reach a specified product purity, 98 % e.e. in both raffinate and extract. The results are presented in figure 2. To identify the lowest possible N with the Kremser equation, the simulations had to be done assuming a large solvent-to-feed ratio (S/F=10) and sufficiently large distribution ratios D_A and D_B. (See also figure 3b). The required number of stages calculated with the Kremser equation is a factor 2-2.5 higher than the number calculated with the Fenske equation, because there is a product stream. It can be seen that the number of stages is excessively high if the selectivity is close to 1. For a larger selectivity the amount of stages decreases, and at a selectivity > 2 a small rise in selectivity does not have much effect on the number of stages anymore. The 'minimum' selectivity cannot be determined from this picture, but depends on the overall economics of the process. A value of 1.5 will be used as the minimum value for the time being.

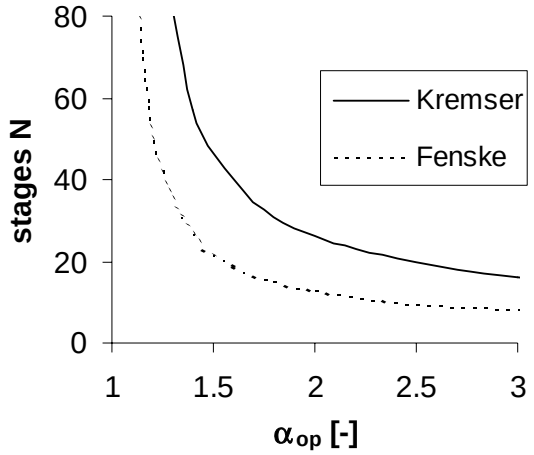
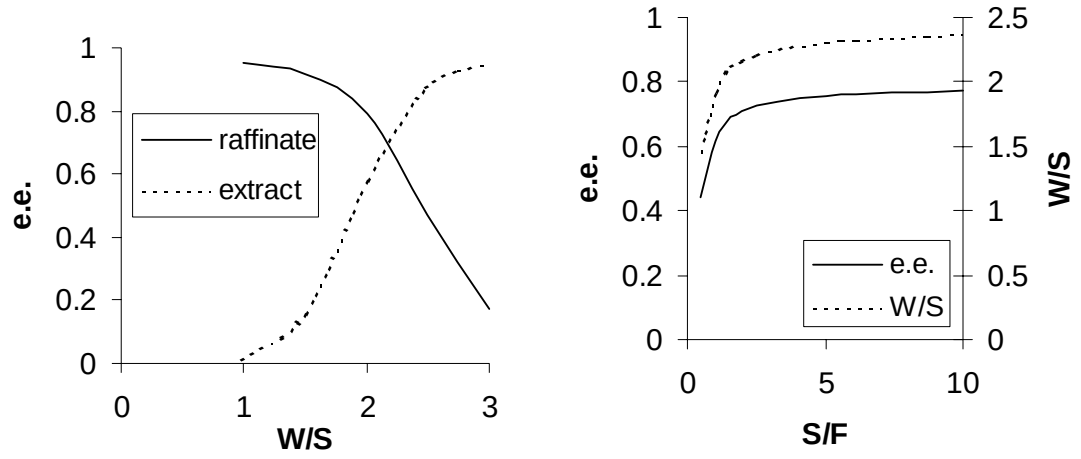


Figure 2: Stages requirement for a product purity (e.e.) of 0.98 in extract and raffinate at a given selectivity (α_{op}) in one stage. Data 'Fenske' with Fenske equation (7). Data 'Kremser': F=1, S=10, W adapted to reach equal e.e. of 0.98, $D_B = 3$, $D_A = \alpha_{op} \cdot D_B$.

2.1.2 Flow rates and distribution ratio

The model of a fractional extractor based on the Kremser equation was used to study the relation between the flow rate ratios, the distribution ratios and the number of stages. The distribution ratios are assumed to be constant over the extractor. The effect of the wash flow rate W on the extraction is given in figure 3a, for constant feed flow F, solvent flow S and distribution ratios D.



(a) (b)

Figure 3: (a) Influence wash-to-solvent ratio (W/S) on product purity e.e., S/F=2, N=20, D_A=3 and D_B=2 (α_{op} =1.5) (b): Influence of solvent-to-feed ratio (S/F), D_A=3 and D_B=2 (α_{op} =1.5), N=20, W/S adapted to find point with equal e.e. in extract and raffinate.

The behaviour in figure 3a is typical for fractional extraction: a small wash flow results in a pure raffinate, and a large wash stream in a pure extract. At one specific W/S ratio, the e.e. in both streams is equal. The influence of solvent flow rate is given in figure 3b. For each value of S, W was adapted to reach equal e.e. in extract and raffinate. It can be seen that at a fixed number of stages and fixed selectivity per stage, the product purity can be improved up to certain limits by increasing S; then also a higher wash stream is required. From a certain S/F, the product purity does not increase anymore and the wash stream requirement increases linearly with S (=W/S constant). There is a trade-off here between product purity (stages requirement) and size of equipment. The economical optimum cannot be found from this plot alone.

The role of 'capacity of extraction' was studied by calculating the solvent requirement to reach a certain product purity, assuming an increase in distribution ratios for both enantiomers, keeping the selectivity constant (table 1).

Table 1: Influence of magnitude of distribution ratios at constant selectivity on flow rates; constant product purity requirement (e.e. = 0.98), 30 stages. Variable S/F, W adapted to reach equal e.e. in extract and raffinate.

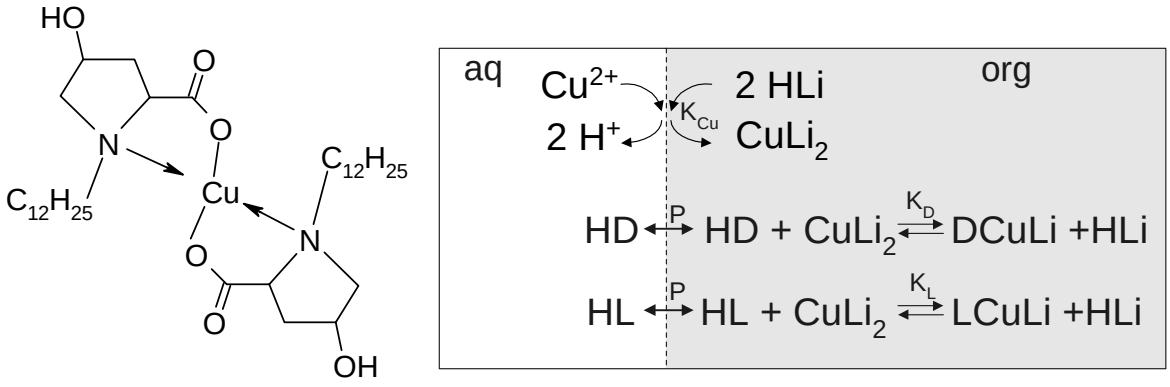
D_A	D_B	S/F	W/F	W/S
1	0.5	10	6.5	0.65
2	1	5	6.5	1.3
4	2	2.5	6.5	2.6
8	4	1.25	6.5	5.2

It can be seen in table 1 that the requirement for the solvent flow rate decreases proportionally with an increase in distribution ratios. Interestingly, the wash stream requirement (W/F) is constant (so W/S increases). With an increase in distribution ratios, the separation can be done with less solvent, but W/S increases, which may pose a hydrodynamical limit in certain extraction equipment.

From these preliminary calculations it is clear that both single stage parameters (distribution ratio D and selectivity α) determine largely the behaviour in the extractor. In literature on FREX at pilot scale[6,7,8,9], the authors all used very small enantiomer concentrations and a very large extractant excess to maximise α_{op}. There seems to be no interest in the role of the distribution ratios, and no attempts to optimise D are reported. This does not seem the optimal approach: the value of D determines the capacity of the extractor and has a substantial influence on the product purity, whereas it follows from figure 2 that a small increase of selectivity α_{op} does not result in a substantial decrease in N. Furthermore, a strongly complexing system would result in strong extraction of both enantiomers (large D's). Theoretically, this can be counteracted by increasing W/S, but in practice there is a hydrodynamical limit. Therefore, the D's should have certain optimal values, and both D and α_{op} need to be studied for a real system in a single extraction stage to see to what extent they can be adapted.

Furthermore, the overal concentration level directly influences the volumetric capacity of an extractor. If the process is operated at 10 times larger concentrations for all components, the volumetric capacity increase will be 10 if the distribution ratios are constant; the distribution ratios may change at this different concentration level as well.

The aim of this chapter is to study experimentally the influence of process parameters (concentrations, T, pH, solvent) on the capacity and selectivity in the single stage for a real reactive extraction system: separation of DL-leucine with the copper(II) complex of N-dodecyl-L-hydroxyproline, in short Cu(II)-C_{12}Hyp (figure 4a), in water/butanol. Simultaneously, the single stage will be modelled based on chemical and physical equilibria in order to improve understanding. The consequences for the productivity of the proposed process parameter changes are discussed in the last paragraph. The complex Cu(II)-C_{12}Hyp is a versatile enantioselective extractant for chiral separation of amino acids. It was selected for this study because the enantioselectivity and the versatility of this system were already demonstrated[10,11] by several research groups. The two neutral enantiomers of leucine will be referred to as 'HL' and 'HD' in the reaction schemes. The chiral ligand N-dodecyl-L-hydroxyproline is abbreviated as 'HLi' (for 'ligand') in the reaction schemes and figures, and as C_xHyp or C_{12}Hyp if the chemical structure is discussed. The copper(II) complex of the chiral ligand is abbreviated as $CuLi_2$ in the reaction schemes and as C_{12}Hyp-Cu(II) in the discussion of the chemistry.



(a) (b)

Figure 4: (a) Chemical structure of 1:2 Cu(II) complex of N-dodecyl-L-hydroxyproline ('$CuLi_2$') (b) Main equilibria in separation of amino acids enantiomers HD and HL. Top part: formation of 1:2 Cu(II)-C12Hyp complex '$CuLi_2$', bottom part: ligand exchange of ligand 'HLi' for neutral enantiomer 'HD' and 'HL' with proton (H^+) transfer.

2.1.3 Chemistry of C_{12}Hyp-Cu(II) extractant

The chiral ligand C_xHyp in combination with Cu^{2+} ion originates from HPLC separation. C_{12}Hyp-Cu(II) was applied as chiral stationary phase for separation of amino acids [10] and aromatic amino-alcohols[12]. The related ligand proline was used as chiral mobile phase[13] to separate amino acids. C_xHyp-Cu(II) complex was introduced as enantioselective extractant by Takeuchi[11]. Takeuchi and coworkers demonstrated that when C_xHyp is present in a water-butanol system, Cu^{2+} ion is extracted to the organic phase by the C_xHyp, and that subsequently enantioselective extraction of amino acid enantiomers can be carried out. They also found that the C_xHyp selector remains in the organic phase if the alkyl tail on the C_xHyp-molecule is larger than octyl (C_8), and they measured the equilibrium constants of the ligand-exchange reaction. The selectivity differs for each amino acid. The C_{12}Hyp-Cu(II) system was applied in a fractional extraction set-up for preparative separation of DL-valine[6]. Several other authors have also used this chemical system to demonstrate fractional reactive extraction for chiral separation of amino acids on preparative scale. Ding *et al.*[9] used two membrane modules as extractor, and Yokouchi *et al.*[8] applied the system in a series of mixer-settlers. The subject of these papers was either maximising the selectivity, or equipment design for lab-scale fractional extraction.

A scheme of the main complexation reactions is given in figure 4b. Cu(II) ion is extracted to the organic phase by two molecules of C_{12}Hyp, releasing two H^+ ions. They form a 1:2 copper-ligand complex '$CuLi_2$' in the organic phase. Then, one of the two chiral ligands can be exchanged for an amino acid enantiomer from the aqueous phase. A mixed-ligand complex is formed and the free chiral ligand remains in the organic phase, as the ligand is not soluble in the aqueous phase. The ligand-exchange reaction is enantioselective if $K_D \neq K_L$. Then, one

enantiomer is extracted to a larger extent, and the overall result is a partial chiral separation in one equilibrium stage.

The copper-ligand equilibrium constant K_{Cu} is defined as:

$$K_{Cu} = \frac{[\overline{CuLi_2}][H^+]^2}{[Cu^{2+}][\overline{HLi}]^2} \qquad (10)$$

An overbar indicated a species in the organic phase. The ligand-exchange equilibrium for enantiomer D is defined in equation 11 (as imilar equation can be given for enantiomer L), and the partitioning ratio P is defined in equation 12. Note that only the neutral amino acid ('HD' or 'HL') partitions between the aqueous and organic phase.

$$K_D = \frac{[\overline{DCuLi}][\overline{HLi}]}{[\overline{HD}][\overline{CuLi_2}]} \qquad (11) \qquad P = \frac{[\overline{HD}]}{[HD]} = \frac{[\overline{HL}]}{[HL]} \qquad (12)$$

Next to these reactions, complexations take place in the aqueous phase between Cu^{2+} ion, acetate (buffer) ions and the cation, anion and/or zwitterions of the amino acids. Koska and Haynes[14] reported an elaborate set of complexation equilibria, for three different amino acids in water/octanol (figure 5). An attempt to measure reaction kinetics was made by Pickering and Chaudhuri[15]. These authors reported the overall extraction rate, which is a function of reaction kinetics and mass transfer rate, so these results are only useful for the specific contactor they used (a Lewis cell), but cannot be used for scale-up to industrial contactors.

$$H_2L^+ \rightleftharpoons H^+ + HL \rightleftharpoons 2\,H^+ + L^-$$
$$Cu^{2+} + L^- \rightleftharpoons CuL^+$$
$$Cu^{2+} + 2\,L^- \rightleftharpoons CuL_2$$
$$Cu^{2+} + Ac^- \rightleftharpoons CuAc^+$$
$$Cu^{2+} + 2\,Ac^- \rightleftharpoons CuAc_2$$

Figure 5: Additional equilibria in aqueous phase for Cu(II)-C_{12}Hyp-leucine system. HL is the neutral L-enantiomer of the amino acid; H_2L^+ cation, L^- anion. Ac^- = acetate ion. All equilibria involving enantiomer 'L' are present for enantiomer 'D' as well.

2.2 Experimental

2.2.1 Materials

L-hydroxyproline (99%) and DL-leucine were obtained from Fluka (Buchs, Switzerland). Octanal (99%) was obtained from Acros. Dodecanal (99%), copper(II) acetate, sodium acetate, butanol and hexane (all analytical grade) were obtained from Merck (Darmstadt,

Germany). The chiral ligands N-dodecyl-L-hydroxyproline (C_{12}Hyp) and N-octyl-L-hydroxyproline (C_8Hyp) were synthesised from dodecanal resp. octanal and L-hydroxyproline according to a slightly adapted method from Takeuchi *et al.*[11] Throughout the study, milli-Q filtered water was used (Millipore, Billerica, MA, USA).

2.2.2 Extraction experiments

Distribution ratios were determined from batch extraction measurements. The aqueous solution was prepared by dissolving copper(II) acetate ($CuAc_2$), sodium acetate (NaAc) and DL-leucine in Q2-filtered water (Millipore) that was presaturated with the organic solvent to obtain a 0.2 M Ac^- solution with $[Cu^{2+}]_{ini}$ ranging from 2.5-50 mM and initial DL-leucine concentrations from 0-10 mM. The organic phase was prepared by dissolving the chiral ligand C_{12}Hyp (0-100 mM) in the appropriate organic solvent, butanol or butanol/hexane, presaturated with water. The batch extractions were carried out in jacketed 25-ml vessels at a constant temperature. 10 ml of both phases were mixed for 1-3 hrs with a magnetic stirrer to reach equilibrium and then allowed to settle. After that, samples were taken from the aqueous phase with a syringe via a septum and analysed by HPLC. In initial experiments, it was confirmed that the mass balance holds within 5 %. The HPLC set-up consisted of a Crownpak (+) chiral column (Daicel, Japan), post-column derivatisation with OPA/MCE reagent and fluorescence detection according to Duchateau *et al.*[16] The Cu(II) concentrations in some of the aqueous samples were determined by AAS (Solaar 939, Unicam, and SpectrAA110, Varian). The pH of the aqueous phase was determined at equilibrium (Inolab pH level 1, WTW) and was between 5.5 and 6, unless stated otherwise.

2.2.3 Determination of copper-ligand equilibrium constant

Rearranging formula 10 yields[14]:

$$\log\frac{[CuLi_2]}{[Cu^{2+}]} = \log D_{Cu} = \log K_{Cu} + 2\cdot(pH + \log[HLi]) \qquad (13)$$

The ratio $[CuLi_2]/[Cu^{2+}]$ is the distribution ratio for copper ion D_{Cu}. Therefore, a graph of log D_{Cu} as a function of log[HLi] + pH should have 2 as slope and log K_{Cu} as intercept. The aqueous and organic Cu^{2+} concentrations can be determined by AAS. The actual ligand [HLi] concentration is calculated from the mass balance as $[HLi]_{ini}$-2·$[CuLi_2]$. The pH is measured with the pH meter.

2.2.4 Determination of ligand exchange equilibrium constant

The equilibrium constants for the enantioselective ligand-exchange reaction were determined[11] from a series of extraction experiments with a varying concentration of Cu(II) ion. Using an additional variable R (equation 14), the observed distribution ratio for the amino acid enantiomer can be expressed by equation 15.

$$R = \frac{[\overline{Cu}]_{total}}{[\overline{HLi}]_0 - 2[\overline{Cu}]_{total}} \qquad (14) \qquad D_L = \frac{[\overline{HL}] + [\overline{LCuLi}]}{[HL]} = P(1 + R \cdot K_L) \qquad (15)$$

$[Cu]_{total}$ denotes the total copper concentration in all forms (overbar: organic phase) and is determined by AAS. The value of the complexation constant K_L can be obtained from a plot of D_L versus R ($R < 0.5$), using a series of extraction experiments with increasing copper concentration. The determination of K_L and K_D has to be done separately with the pure enantiomers.

2.3 Single stage equilibrium model

In a real reactive extraction system, the distribution ratio is a function of the local concentrations. A non-constant distribution ratio can be described by a model of a single equilibrium stage incorporating all relevant physical and chemical equilibria. The performance of such a model is very dependent on the quality of the input data and on the incorporation of all important chemical information. The model is also numerically more complex. The computer program Mathcad (MathSoft, Inc) was found to be a suitable tool to solve the system of non-linear algebraic equations that described the single stage.

Initially, it was attempted to construct a single stage equilibrium model based only on the extraction of Cu^{2+} ion by the chiral ligand and the enantioselective ligand-exchange reactions (reactions in figure 4b). Although this model can be solved easily, the results could not be used to describe or clarify the experimental trends. Apparently, the other complexation reactions in the aqueous phase (figure 5) are essential for a good model prediction, and need to be included. This elaborate model for the closely related system C_{12}Hyp-Cu(II)-phenylalanine-octanol was reported by Koska & Haynes[14]. The formation constants of the aqueous-phase complexes were obtained from literature or measured in titration experiments. The formation constants of the ternary complexes of phenylalanine, leucine and valine were derived from batch extraction data, obtained in the system water/octanol at a pH between 4 and 6. In this way, an equilibrium stage model was constructed which was ‘in good agreement with experimental results’.

The model by Koska & Haynes is reported for phenylalanine/water/octanol and was stepwise adapted to the leucine/water/butanol system. First, the model was implemented in Mathcad and run with the parameters for phenylalanine separation in water/octanol and compared with the data of Koska & Haynes to confirm numerical correctness. Koska & Haynes did not report their experimental data for leucine, but they stated that the model was a good description for their data. Additional extraction experiments for leucine separation in water/octanol were carried out. Our experimental data and the model description with leucine parameters show reasonable agreement between pH 4 and 6 (figure 6). As the formation constants were obtained by regression of data in the pH 4-6 range, it is not surprising that extrapolation above

pH 6 does not give a good result. The deviation may be caused by precipitation of $Cu(OH)_2$ or by partitioning of leucine to octanol. It was also found that the extraction data obtained by Ding, Carr & Cussler[9] for this system do not agree with our experimental data and the model by Koska & Haynes. The data by Ding *et al.* seem to be incorrect. It may be that equilibrium was not reached in their experiments due to insufficient mixing.

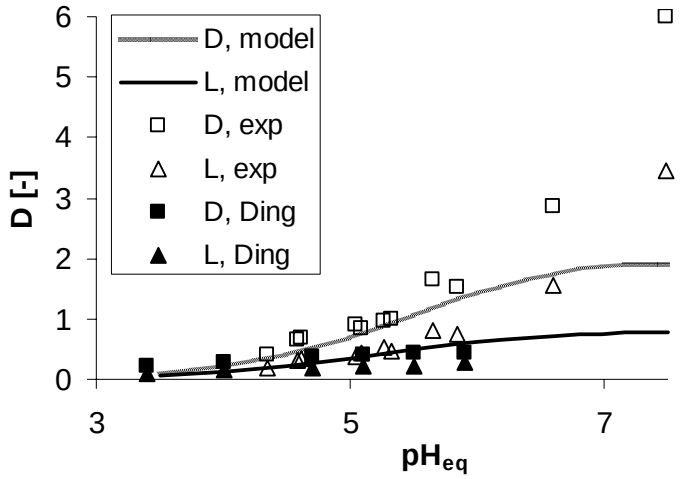


Figure 6: Experimental data (this work and Ding et al.[9]) and model predictions for extraction of 0.9 mM DL-leucine with C_{12}Hyp/Cu(II) complex ($[CuLi_2]_{ini}$ = 10 mM) in octanol, 25 °C.

After converting from phenylalanine to leucine, the model was converted from octanol to butanol. The relevant aqueous-phase complexation constants were taken from literature[15,17]. The equilibrium constant for the extraction of Cu(II) with C_{12}Hyp in butanol, K_{Cu}, was determined experimentally, to be $10^{-3.64}$ [-]. The formation constant of the ternary complexes are assumed to be the same in butanol and octanol. This assumption was done to avoid additional experimental work, although we are aware of the fact that the solvent can have a large influence on equilibria. Because octanol and butanol are related solvents, it was assumed that the selectivity would be similar in both solvents, and that the strength of complexation may be different. Optionally, an electroneutrality condition can be included in the model, in order to account for the pH decrease after extraction of Cu^{2+}. The model predictions for leucine in water/butanol will be discussed along with the experimental results.

2.4 Results

In this part, the influence of process parameters on the single stage extraction is studied experimentally and compared with the single stage model predictions.

2.4.1 Influence of copper-ligand ratio

From the copper-ligand reaction combined with the ligand-exchange reaction, one may expect that an excess of copper ($[Cu^{2+}]_{ini}$ > 0.5 $[HLi]_{ini}$) will result in a very low free ligand

concentration [HLi]. Thus, the enantioselective equilibria are shifted to the right, resulting in formation of more mixed-ligand complexes. However, Takeuchi[6] showed for valine extraction that the optimum copper concentration is $[Cu^{2+}]_{ini}$ = 0.5 $[HL]_{ini}$. From the experimental results in figure 7, the same conclusion is obtained for DL-leucine: an excess of copper (copper present in the aqueous phase) causes a decrease in the distribution ratios and the selectivity for leucine. Therefore, all further extraction experiments were carried out at the 'stoichiometric' copper concentration, and the extractant concentration is given as $[CuLi_2]$.

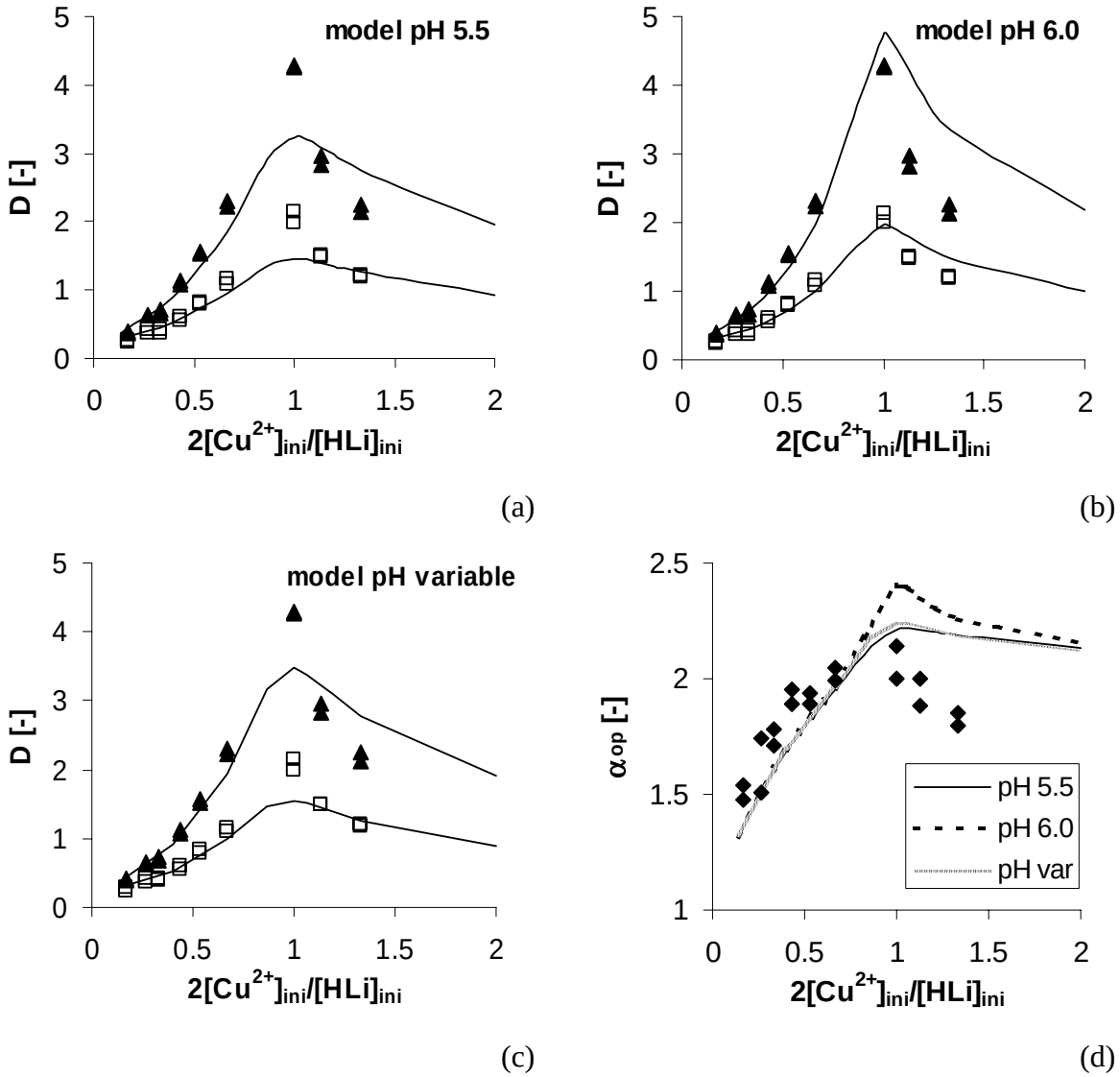


Figure 7. (a-c) DL-leucine separation, influence of Cu^{2+}-ligand ratio on distribution ratio; experimental data (squares: L-leucine, triangles: D-leucine) with (a) model prediction with fixed pH=5.5 (b) model with fixed pH = 6.0 (c) model with variable pH as output; (d) experimental data and model predictions for α_{op}. Water/butanol equal volumes, 25°C, [HLi] = 30 mM, [DL-leucine] = 1 mM, [Cu^{2+}] = 2.5-20 mM.

No simple explanation for the optimal extraction at stoichiometric copper-ligand ratio can be given. The equilibrium stage model is able to reproduce the shape of the curves in figure 7 with reasonably accurate numerical values. Unfortunately, not all pH values in the experiments were recorded exactly; they were all roughly between 5.5 and 6, which was thought to be sufficiently constant at the time. To show the sensitivity of the results for the pH, the experimental data are given with the model predictions at fixed pH 5.5 (figure 7a) and pH 6.0 (figure 7b). Qualitatively, the influence of copper/ligand ratio is represented correctly. The model with variable pH gave somewhat better predictions (fig. 7c), but the experimental values are still not reproduced quantitatively. Finally, all models give very similar predictions for the operational selectivity (fig. 7d). It can be seen that the selectivity at sub-stoichiometric copper-ligand ratio as well as the location of the optimal copper-ligand ratio are predicted correctly, but the selectivity decrease at an excess of copper is only described qualitatively.

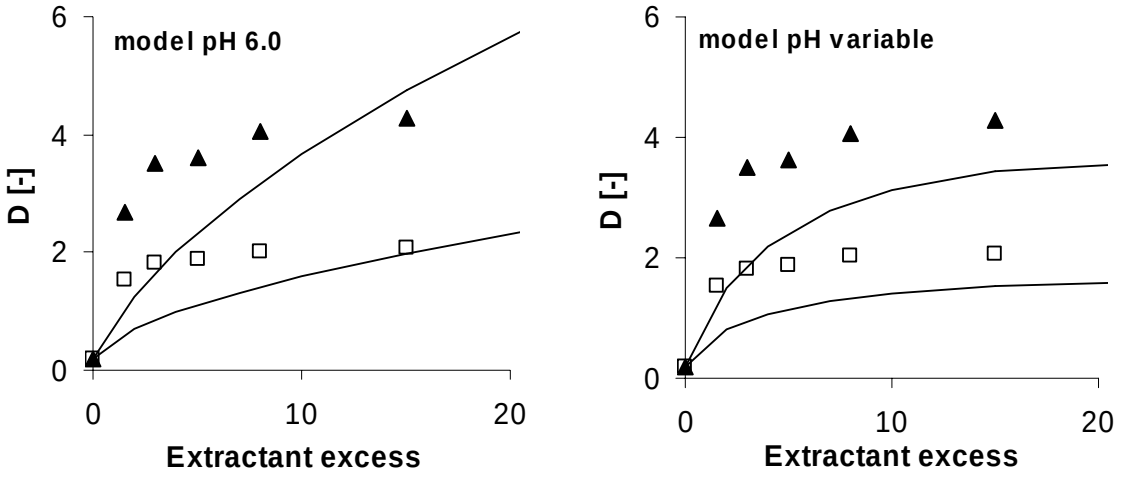
2.4.2 Influence of extractant excess

To study the influence of extractant excess, a series of experiments was carried out at constant enantiomer concentration and increasing '$CuLi_2$' concentration, with $[Cu^{2+}]_{ini} = 0.5\ [HL]_{ini}$. 'Extractant excess' is defined in equation 16. Note that in the present experiments V_{aq} is taken equal to V_{org}.

$$excess \quad extractant = \frac{V_{org} \cdot [CuLi_2]_{ini}}{V_{aq} \cdot [leucine]_{ini}} \tag{16}$$

Figure 8 and 9 show that there is no large increase in D or α once the excess extractant is large enough, i.e. $[CuLi_2]_{ini}/[leucine]_{ini} > 3$. Therefore, the large excess of extractant (10-50) used by a number of authors[9,11] is not necessary under the circumstances studied here.

It must be noted that a part of the effect on D is caused by the pH decrease during extraction. The more extractant and copper is used, the more H^+ is generated. The pH drop results in a lower extent of extraction. The model predictions of the effect of excess of extractant demonstrate this clearly. If the equilibrium pH is assumed to be constant (model with fixed pH, figure 8a), the model predicts that the distribution ratios keep rising with excess selector. The trend from the model with variable pH (figure 8b) is much closer to the experimental result. The numerical values for the distribution ratios are too low, probably because of inaccuracy in formation constants of ternary complexes (which were measured in octanol, not butanol) or in the physical partitioning ratio of leucine. Similarly, the trend for operational selectivity is best represented by the model with variable pH. The actual value of the selectivity is slightly overestimated.



(a) (b)

Figure 8: Influence of excess extractant on distribution ratio at 25 °C; water/butanol, [DL-leucine] = 1 mM, [$CuLi_2$] = 0-15 mM. Solid lines calculated with model 'fixed pH' pH=6 (a) and 'variable pH' (b). Squares: L-leucine, triangles: D-leucine (experimental)

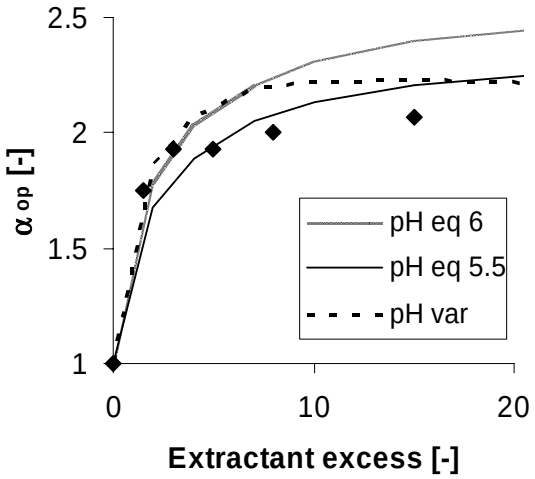


Figure 9: Influence of excess extractant on operational selectivity α at 25 °C; water/butanol, [DL-leucine] = 1 mM, [$CuLi_2$] = 0-15 mM. Dots: experimental, lines: model prediction.

2.4.3 Influence of concentration level

Some of the studies reported in literature were carried out at very low enantiomer concentrations (down to 0.1 mM). Higher concentrations of all components will increase the volumetric process capacity. The concentrations are limited by the solubility. In our system, the leucine solubility decreases from > 50 mM in water to about 10 mM in 0.1 M $Cu(Ac)_2$. Using less concentrated buffer solutions may partially prevent this; pre-extraction of copper(II) to the organic phase also results in a higher leucine solubility. The C_xHyp ligand solubility varies with the solvent and the nature of the organic tail. In butanol, the solubility at 25 °C is about 0.1 M for C_{12}Hyp and 0.5 M for C_8Hyp. It can be concluded from the

experimental data in table 2 that a higher absolute concentration results in an almost unchanged selectivity but higher distribution ratios. Thus, a concentration level 10 times higher results in a 13-14 times higher capacity for forward extraction. The model prediction gives qualitatively the same result, although the actual numbers are not very accurate.

Table 2. Influence of absolute concentrations on extraction, constant concentration ratios, 25 °C, water/butanol/leucine (experimental results)

[DL-leucine] [mM]	[$CuLi_2$] [mM]	D_D [-]	D_L [-]	α_{op} [-]
1	5	3.6	1.9	1.9
5	25	4.4	2.3	1.9
10	50	5.2	2.7	1.95

2.4.4 Influence of temperature

For chiral recognition systems, the enantioselectivity often increases with decreasing temperature[18,19]. To study the effect of temperature on the separation of leucine, D and α_{op} were determined at four temperatures using fixed concentrations (table 3). Secondly, the equilibrium constants K and the physical partitioning ratio P were determined at 5 °C. At higher temperature, both equilibrium constants become higher. This is rather unusual behaviour indicating an endothermic reaction. The intrinsic selectivity α_{int} is slightly higher at the lower temperature. The influence on P is not very clear. In the extraction experiments, it is seen that the distribution ratios for both enantiomers increase with an increase in temperature, whereas the operational selectivity is practically unaffected.

Table 3. Influence of temperature on leucine separation, water /butanol.
D and α: [DL-leucine] = 1 mM, [$CuLi_2$] = 15 mM
K and P: [DL-leucine] = 1 mM, [Cu^{2+}] = 0-8 mM, [HLi] = 30 mM

	D_D [-]	D_L [-]	α_{op} [-]	K_D [-]	K_L [-]	$\alpha_{int}=K_D/K_L$ [-]	P [-]
5 °C	2.6	1.2	2.1	7.9	3.3	2.35	0.17
25 °C	4.3	2.1	2.1	16.2	7.5	2.17	0.15
25 °C [11]				*10.1*	*4.0*	*2.5*	*0.21*
35 °C	5.0	2.5	2.0				
45 °C	5.9	2.9	2.0				

The influence of the operation temperature on the system can be described by the single stage model, although there are many unknown parameters. The temperature may have an influence on the following equilibrium properties:

- the absolute value of the equilibrium constants K in the system, and their ratio
- the partitioning ratio P
- the mutual solubility of the solvents

For leucine in water/butanol, it was found that at 5 °C the values for K_L and K_D are smaller (the reactions are weaker) than at 25 °C and the reaction has a slightly higher intrinsic selectivity; the value for P is hardly affected. A weaker reaction results in smaller distribution ratios (if the partitioning is constant), and this is seen clearly in the experiments. A weaker reaction also results in less formation of ternary complexes, and thus in a lower operational selectivity. On the other hand the intrinsic selectivity is slightly larger at 5 °C, which may result in a larger operational selectivity. So, there are two counter-acting effects on the selectivity, and it is indeed seen in the experiment that the operational selectivity is only slightly affected by T.

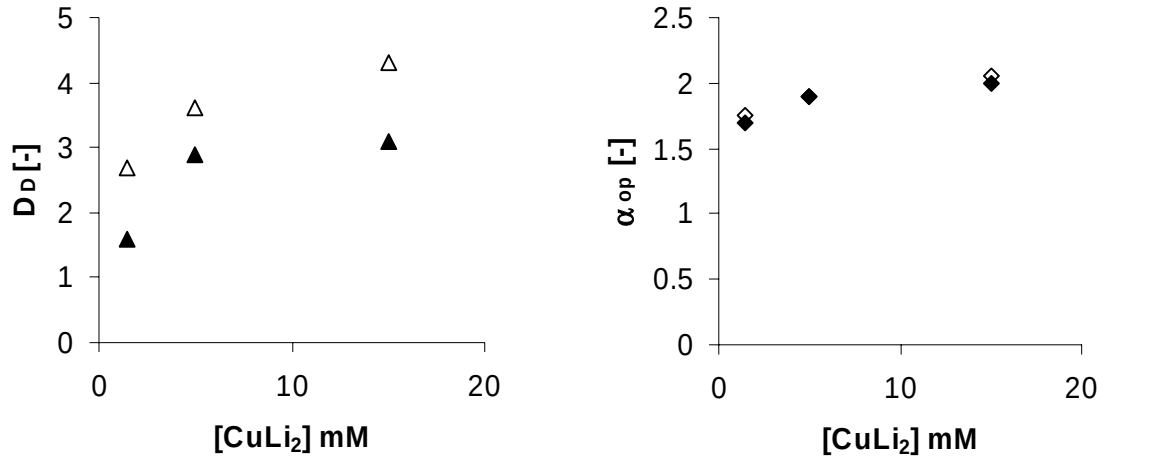
Abe[18] reports for a different extractant system (extraction of beta-blockers with boric acid/didodecyl-L-tartrate in chloroform/water) a decrease in D with increasing temperature. This is in contrast with the trend in the above results, and may have two causes: P may become lower with increasing T in that system, or more likely, the absolute values of K may become smaller with increasing T (exothermic reaction). Concluding, no general rule can be given about the effect of temperature on capacity and selectivity.

2.4.5 Influence of pH

The pH has a complex influence on the performance of this process. From literature[15], it can be concluded that copper extraction by ligand L is favoured by a higher pH (> 5.5) and that the distribution ratios increase about five times when the pH increases from 4 to 6. The operational selectivity α_{op} is not severely affected[6,9]. If the pH becomes too high, precipitation of $Cu(OH)_2$ may become prohibitive. Therefore, all experiments were carried out at pH=5.5-6. No further experiments to study the influence of pH were performed at this stage.

2.4.6 Influence of the solvent

So far, all reported results were obtained with water/butanol as solvents. In the literature, several organic solvents and solvent mixtures have been applied. The solvent influences the solubility of all solutes, the partition ratios and possibly the reaction by acting as a ligand itself. As an illustration of the importance of the solvent, experimental results with two solvent mixtures are represented in figure 10. It can be seen that the operational selectivity (figure 10b) is similar, but that the distribution ratio is lowered considerably in a less polar solvent mixture (figure 10a). From these data alone, it cannot be concluded if the difference is caused by a difference in magnitude of complexation constants, a difference in partitioning ratio, or a combination.



(a) (b)

Figure 10: Influence of solvent on (a) distribution ratio for D-enantiomer and (b) selectivity of leucine extraction. Open symbols: butanol, closed symbols: butanol/hexane 4:1 v/v. [DL-leucine]=1 mM, 25 °C

As a further illustration of the influence of the solvent on equilibrum constants, the equilibrium constant K_{Cu} (equation 10) of copper extraction by C_{12}Hyp in various solvents are listed in table 4. The trend in these data seems to be that the equilibrium constant is higher (so the complex is more stable) if the solvent (mixture) is less polar.

Table 4: Solvent influence on the equilibrium constant for extraction of Cu(II) by C_{12}Hyp

solvent	K_{Cu}, 25 °C [-]	source
butanol	$2.29 \cdot 10^{-4}$	this work
hexanol	$7.08 \cdot 10^{-4}$	[14]
octanol	$7.76 \cdot 10^{-4}$	[14]
decane/hexanol 1:1	$3.09 \cdot 10^{-3}$	[15]

2.4.7 Influence of volume ratio

If in physical extraction the volume ratio S/F is doubled, the distribution ratio is approximately constant, so the capacity of the process roughly doubles due to doubling of the extraction factor. Similarly, with a double distribution ratio and constant S/F the extraction factor also doubles. We wondered if a similar situation exists in reactive extraction. A series of experiments was carried out in which the effect of a variable aqueous /organic phase volume ratio was evaluated. If these experiments are done at constant concentrations, the excess of extractant (equation 16) changes as well; therefore also experiments at different extractant concentrations were included, to study the effect of volume ratio at constant extractant excess. To ensure the optimum copper/ligand ratio of 1:2, the copper was pre-extracted by the ligand; then a fresh aqueous phase containing the amino acid was contacted with the pre-extracted organic phase. In this way, the equilibrium pH was slightly higher than

in the experiments described previously, between 6 and 7. The aqueous/organic ratio was varied between 0.33 and 3.

No simple 'rules', (such as 'doubling the volume at constant concentration results in double capacity or double distribution ratio') could be deduced from the results. It is clear that increasing the amount of solvent (with the same concentration of extractant) results in a higher extracted fraction of amino acid (per volume of aqueous phase), but it is difficult to formulate simple heuristics, because the relations are strongly non-linear. On the other hand, the complete model gives a rather good description of the effect of volume ratio, probably because all reaction equilibria are taken into account. The experimental data and the model results are represented in figure 11 as a parity plot. It can be seen that the fit is rather good.

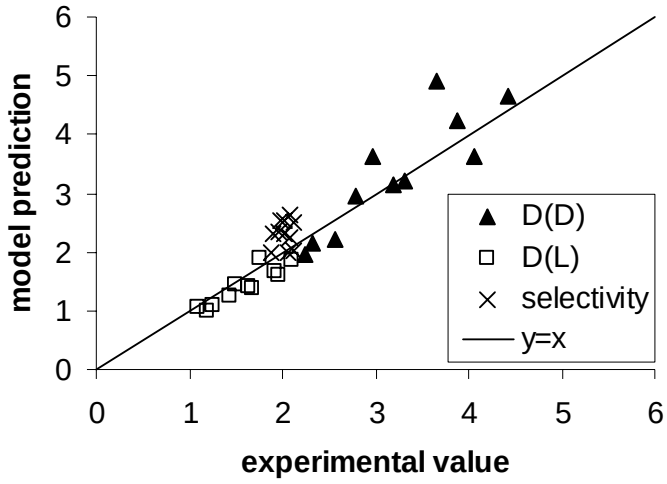


Figure 11: Parity plot for model predictions and experimental data for various DL-leucine extraction experiments, water/butanol, 25 °C, [DL-leucine]= 1 or 2 mM, [$CuLi_2$] = 5 or 10 mM, volume ratio between 0.33 and 3.

As an illustration of the influence of volume ratio in a reactive system, some model results have been compiled in table 5. The results can be compared by 'same concentrations' or 'same extractant excess'. It can be seen that the distribution ratios or yields do not remain constant at constant excess or constant concentrations. To minimise the amount of expensive extractant, a large solvent volume should be used with a low concentration, to reach the largest overall extraction capacity for the amino acid; but to minimise the solvent volume (and thus the equipment size), a high extractant concentration should be used, accepting that the loading of the extractant (effective use) will be lower.

Table 5: effect of extractant concentration and solvent volume according to equilibrium model. Case: water/butanol parameters, pH 6.5, [DL-leucine] = 1 mM, [Ac^-]=0.2 M, $P_{leucine}$=0.2, 25 °C. Extractant 'excess' according to equation 16

V_{org}/V_{aq}	[$CuLi_2$] mM	excess	D_L	D_D	yield L	yield D	% loading
1	10	10	1.31	2.89	78.3	87.2	5.46
2	5	10	1.11	2.44	84.5	91.5	6.16
0.5	20	10	1.56	3.45	71.9	81.7	4.61
1	5	5	0.90	1.75	73.8	81.8	8.29
0.5	10	5	1.07	2.10	67.4	73.6	6.78
1	20	20	2.93	7.87	87.3	94.4	3.825
2	10	20	2.40	6.29	91.4	96.3	4.08

Summarising, it can be stated that all trends in the experimental results are predicted correctly by the single equilibrium stage model for butanol/leucine. The accuracy (quantitative description) is not in all cases very good. At pH 5-7, the predictions are the most accurate, although the predicted selectivity tends to be too high, whereas at lower pH the predicted distribution ratios are too low. The pH effect should be studied further, as well as the lower pH region.

The use of an equilibrium stage model based on the chemical equilibria in the system is very helpful in gaining insight in the extraction system: most of the effects caused by process parameter changes can be explained physically or chemically, and effects of other parameters changes may be predicted in the same way.

2.5 Consequences for design

It has become clear that the choice of process parameters such as concentration level, temperature, solvent and pH have a large effect on the capacity and selectivity obtained in a single reactive extraction stage. The effect of process parameter changes on the dimensions (stages, S/F) of process equipment will now be estimated.

The distribution ratios and operational selectivities that were obtained experimentally are introduced in the Kremser-based fractional extractor model. The calculations could also have been done with a multistage equilibrium model based on the single stage description, but this approach is numerically complex: if the amount of stages exceeds 6, the number of algebraic equations that have to be solved simultaneously becomes too large for the numerical solvers that were attempted (Mathcad, gPROMS). Furthermore, detailed modelling of the separation of amino acids with Cu(II)-C_{12}Hyp is not the ultimate goal of this study.

From the Kremser model or the Fenske equation, the influence of the separation factor on the number of stages was estimated. A minimum α_{op} of 1.5 was stated; furthermore, for $\alpha_{op} > 2$

small changes in α_{op} have a much smaller effect on the number of stages than if $\alpha_{op} < 2$. So, it is unwise to spend much effort on raising α_{op} slightly if α_{op} is already larger than 2. For the separation of leucine at 25 °C, it can be concluded from figure 8 and 9 that using an excess extractant (eq. 16) larger than 3 is not justified. Accordingly, the process should not be carried out at 5 °C but at 25° C or higher temperatures because the larger distribution ratios and the faster extraction kinetics at 25 °C more than compensate for the slightly higher separation factor at 5 °C. However, a too large temperature may cause other problems, such as extractant losses.

The process capacity increases proportionally with the enantiomer concentration and the absolute value of the distribution ratio. Therefore, the process should be carried out at the highest concentrations possible. For the model system, the leucine solubility is limiting (<10 mM at 0.1 M $Cu(Ac)_2$). The solubility of the extractant is in the range of 0.1-0.5 M, which is much higher than applied in lab-scale experiments so far, and non-limiting given the low solubility of leucine. In most of the chiral fractional extraction studies, large wash–to-feed and solvent-to-feed ratios have been applied. This practice has several drawbacks: dilution of the feed stream results in lower distribution ratios (table 1) and a large solvent flow causes much coextraction of the undesired enantiomer, thus requiring also a large wash stream. For two representative literature cases, the effects of parameter changes on the number of theoretical stages (N), the volumetric flow rate of feed (F), solvent (S) and wash fluid (W) and on the extractant inventory (C) have been estimated for a given capacity (kg/hr DL-leucine, product purity 99%) with the Kremser model, using the experimental results from this study (table 6). It can be seen that both the total liquid volume (thus the extractor volume) and the extractant requirements can be decreased considerably at the expense of a small increase in N.

Table 6: Effect of process condition changes for two literature cases

Case	Proposed changes	N/N_0	F/F_0	S/S_0	W/W_0	C/C_0	VR[1]
Takeuchi[6]:	$[valine]_0$ 2.4 → 24 mM						
butanol, pH 6	$[C_{12}Hyp]$ 10 → 100 mM	1	0.1	0.07	0.1	0.7	
$F_0 = 1$, $S_0 =$	4* smaller S (adjust W)	1.15	1	0.25	0.2	0.25	
10, $W_0 = 10$	**Overall effect**	1.15	F=0.1	S=0.18	W=0.2	**0.18**	**38**
Ding[9]:	$[leucine]_0$ 4.9 → 9.8 mM						
octanol, pH 4	$[C_{12}Hyp]$ 20 → 40 mM	1	0.5	0.5	0.5	1	
$F_0 = 1$	pH →6, switch to butanol	1.05	1	0.09	1	0.09	
$S_0 = 40$	3* smaller S (adjust W)	1.15	1	0.333	0.25	0.33	
$W_0 = 10$	**Overall effect**	1.2	F=0.5	S=0.61	W=1.25	**0.03**	**18**

[1)]VR= total extractor Volume Reduction = $[m^3 \text{ liquid } hr^{-1}]_0 \cdot N_0 / [m^3 \text{ liquid } hr^{-1}]_{new} \cdot N$

Concluding, fractional extraction of chiral components with copper-based extractants can be made much more efficient by working with high concentrations of enantiomers, using a stoichiometric amount of copper, working with a slight excess of extractant in a polar solvent,

at a sufficiently high temperature and pH. Compared with literature results reported so far, an extractor volume reduction of 10-50 times maintaining the same productivity can be obtained without changing existing chemistry.

2.6 Conclusion

Process parameters such as concentrations, temperature, solvent and pH have a large influence on the capacity and operational selectivity in reactive extraction, by influencing both the chemistry and the physical properties in the system. It has been demonstrated that for the reactive extraction system based on Cu(II)-C_{12}Hyp the projected productivity can be increased by a factor 10-50 by optimising the process parameters. Study of the influence of process parameters on extraction performance by a combination of experimental work and equilibrium modelling is a good tool to identify the appropriate changes.

With this demonstration, the large potential of the FREX concept for chiral separation has been indicated. In further development of the technique for other classes of enantiomers than amino acids, the identification of suitable enantioselective extractants has the highest priority.

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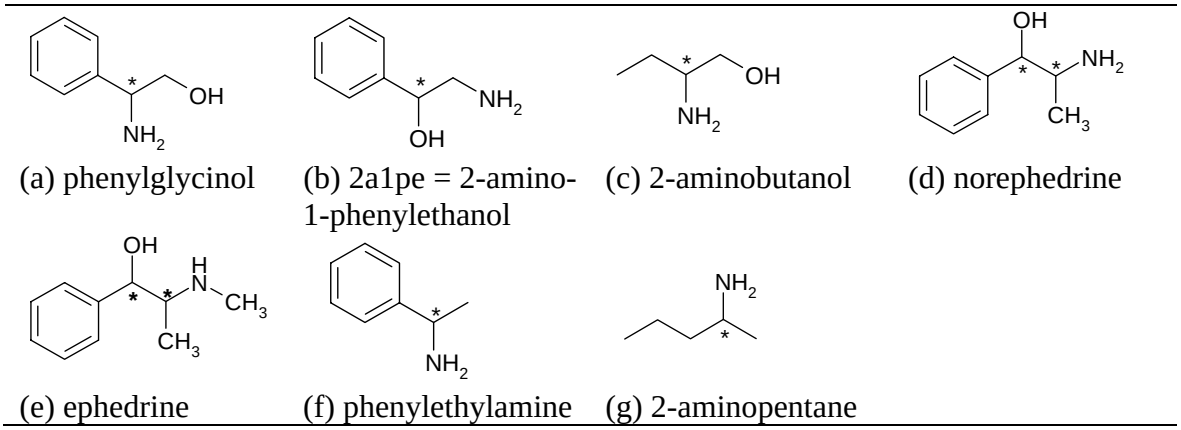
3 Identification of enantioselective extractants for chiral separation of amines and amino-alcohols

3.1 Introduction

Amines and amino-alcohols are important chiral intermediates. The main goal of this chapter is the identification of versatile enantioselective extractants that can be used for chiral separation of a number of chemically related amino-alcohols and amines by reactive extraction. In addition, the influence of the amino-alcohol structure on the extraction behaviour will be studied. To identify enantioselective extractants, a rational approach will be proposed and tested.

The component phenylglycinol has been chosen as archetype model enantiomer for this study. To study the influence of molecular structure, six other model enantiomers were included (figure 1). All studied amino-alcohols have the hydroxyl group and amino group on neighbouring carbon atoms, and all components are primary amines except for ephedrine.



(a) phenylglycinol (b) 2a1pe = 2-amino-1-phenylethanol (c) 2-aminobutanol (d) norephedrine

(e) ephedrine (f) phenylethylamine (g) 2-aminopentane

*Figure 1: Structure of amino-alcohols and amines studied. * indicates a chiral centre*

In the literature, quite some work has been reported on the chiral separation of amino acids by reactive extraction and closely related techniques[1,2,3,4,5,6,7]. Much less attention has been paid to the separation of amino-alcohols and amines by reactive extraction, in particular not to substances with the chiral center next to the amine moiety. Didodecyl-L-tartate with boric acid acted as extractant for four different beta-blockers in a chloroform-water system[8,9]. The selectivity was between 1.5 and 2.9. Beta-blockers belong to a class of amino-alcohols containing a secondary amine group and several other functionalities, with the chiral centre next to the alcohol moiety. A versatile extraction system for chiral separation of amino-alcohols and amines was presented by Prelog[10,11,12]. Various dialkyltartrates and tartrates of bulky alcohols such as menthol were used as extractant at a high concentration in chloroform, typically 1 M. This separation system gave in general somewhat better results for the amino-alcohols with the chiral centre next to the alcohol moiety, but it can also be used for amino-

alcohols with the chiral center next to the amine moiety. Although the versatility of this system is good, the selectivities for most of the tested enantiomers seem too low (1.2-1.6) for commercial application. A second drawback is the need to co-extract a lipophilic counter-ion such as PF_6^-.

There are several strategies to identify potential enantioselective extractants, such as:

1. Design and synthesis of 'new' selectors, usually based on former experience or as a variation on an existing selector. Molecular imprinting[13] or combinatorial chemistry[14] may be used.
2. Molecular modelling can be used as a tool to identify new selectors, or to optimise existing selectors[15].
3. Transferring promising selectors from other separation techniques or ligands from enantioselective catalysis[16] to extraction.

The third method has been selected for this study, because in the chemical and analytical literature a large amount of information on chiral recognition of amino-alcohols and amines is available, and most of this knowledge has not been exploited to develop enantioselective extractants. Examples are analytical techniques for determination of optical purity such as chromatography and electrophoresis, membrane separations and separation by diastereomeric crystallisation. Chiral recognition in liquid systems has also been described.

We have restricted ourselves to chiral selectors used in analytical techniques and separation techniques, excluding the ligands used in asymmetric catalysis. This was done for various reasons: the analytical and separation literature already provides a very large number of potential extractants; secondly, the activity as extractant seems more difficult to predict for ligands from enantioselective catalysts than for selectors from analytical or separation techniques; the catalyst ligands are in general difficult to synthesise, and many enantioselective catalyst ligands are proprietary. However, the literature on enantioselective catalysis ligands may become an additional valuable source for enantioselective extractants besides the analytical chiral separation literature.

To gain more insight in how enantioselective extractants can be selected or adapted from chiral selectors available in other separation techniques, we start with a discussion of the separation mechanism of reactive extraction. Subsequently, the separation mechanisms in the other chiral separation techniques are evaluated to obtain knowledge on the possible transfer of chiral selectors by comparing the similarities and differences with reactive extraction. A literature study will be presented listing many selector systems and results for various analytical separation techniques, featuring mainly selectors for amino-alcohols and amines that can be envisaged as extractants. From this list, a number of the potential extractant systems are selected for experimental evaluation, to test if:
(1) the selector can be kept in one phase (no partitioning/leaching)

(2) the selector is enantioselective for one of the enantiomers (selectivity of extraction)
(3) the enantiomers can be extracted to a sufficient extent (capacity of extraction).

When appropriate, the effect of extraction conditions such as pH, temperature and solvent is determined. The experimental results will be discussed in view of whether chiral selectors show sufficient selectivity and capacity in extraction. Finally, conclusions will be drawn about the suitability of the literature sources to identify enantioselective extractants.

3.2 Theory

3.2.1 Chiral recognition

In molecular recognition, selectors preferentially complex with certain guest molecules. A variety of intermolecular forces can play a role in this process of recognition. The main interactions are dipole-dipole interactions, dipole-induced-dipole interactions, hydrogen bonding, London dispersion forces, π stacking interactions, charge transfer interactions, hydrophobic or solvophobic effects and ionic interactions[17].

In chiral recognition, one of the enantiomers in a racemic mixture is preferred over the other by a selector which has to be chiral itself. For chiral discrimination, in general three bonding sites are required; one of the two enantiomers can coordinate with all three sites, the other enantiomer with only two sites[18]. Alternatively, a combination of two bonding sites and bulky side groups is encountered; one of the two enantiomers cannot coordinate with both bonding sites due to steric hindrance[19]. In principle, all intermolecular forces given above may play a role in chiral recognition[17].

In this chapter, the intrinsic selectivity α_{int} is defined as the ratio of complexation constants: K_R/K_S. The operational selectivity α_{op} is defined in a different way for each technique and can therefore not be compared directly with the operational selectivity in extraction.

3.2.2 Separation mechanism in reactive extraction

A schematic picture of the equilibria important in reactive extraction is given in figure 7a in chapter 1. The most important effects are the complexation reactions between the enantiomers R and S and the extractant C, characterised by equilibrium constants K_R and K_S, and the physical partitioning ratio (P) of the enantiomers and extractant. If extractant C favours complexation with R over S ($K_R > K_S$), more RC than SC is formed, the overall distribution ratio of enantiomer R is larger and a partial separation in one stage is reached. Thus, the complexation reaction in the liquid has to be enantioselective to obtain operational selectivity. Physical partitioning of C will spoil the operational selectivity of the separation[4], because it results in a lower effective concentration of C in the reaction phase and probably also in counter-productive enantioselective complexation in the other phase. Furthermore, physical

partitioning of R and S and the occurence of other complexation reactions such as acid-base disscociation may influence the selectivity and capacity as well. The operational selectivity, which equals the ratio of distribution ratios D for the two enantiomers, is therefore a function of the liquid-phase complexation constants K_R and K_S and the physical partitioning ratio P of enantiomers and selector. For an extraction system in R and S are bases, it can be deduced that:

$$D_R = \frac{[R]_{org,allforms}}{[R]_{aq,allforms}} = \frac{[R]_{org} + [RC]_{org}}{[R]_{aq} + [HR^+]_{aq}} \quad (1)$$

$$D_S = \frac{[S]_{org,allforms}}{[S]_{aq,allforms}} = \frac{[S]_{org} + [SC]_{org}}{[S]_{aq} + [HS^+]_{aq}} \quad (2)$$

$$\alpha_{op} = \frac{D_R}{D_S} = \frac{1 + K_R \cdot [C]}{1 + K_S \cdot [C]} \quad (3)$$

All concentrations are equilibrium concentrations, which need to be solved from the mass balance. The above also shows that the maximum operational selectivity that can be achieved equals the intrinsic selectivity K_R/K_S, which should exceed 1.5.

3.2.3 Separation mechanisms in other chiral separations

From the above, it seems likely to expect that when the operational selectivity in other chiral separation techniques is also determined by the ratio of the complexation constants in solution (K_R/K_S), that this enantioselectivity can be transferred to extraction. Therefore, we will now discuss how the operational selectivity in other chiral (analytical) separation techniques is obtained.

Analytical chiral separations: chromatography and electrophoresis

Direct chiral separation by HPLC can be carried out in two ways: with the chiral selector bound to the column material (chiral stationary phase, CSP) or by adding a chiral selector to the mobile phase (chiral mobile phase, CMP). When a CSP is used, the enantiomers interact with the selector on the solid support and two different diastereomeric complexes are formed. The operational selectivity in the column is given by[20]:

$$\alpha_{op} = \frac{1 + K^S{}_R[C^s]}{1 + K^S{}_S[C^s]} \quad (4)$$

The concentration $[C^S]$ is the 'free selector concentration' at the surface. The selectivity originates from the difference in complexation constants for the reaction on the solid support (superscript ^{S}) and has a maximum value $K^S{}_R/K^S{}_S$. The solid support often has a large influence on the extent of complexation and also on the selectivity (by supplying the 'third

interaction' as steric hindrance, or by blocking access to binding sites). As a result, the ratio K^S_R/K^S_S is often very different from the ratio K_R/K_S for the same selector in solution. Therefore, selectivity obtained with a CSP does not necessarily result in the same selectivity in extraction with the same selector molecule.

In CMP mode, complexation between the chiral selector and enantiomers takes place in the mobile phase. In the ideal case, only the enantiomers partition between mobile phase and stationary (solid) phase, so the chiral selector and the complexes remain in the mobile phase. Then, the selectivity is determined by the complexation in the liquid:

$$\alpha_{op} = \frac{1 + K_R[C]}{1 + K_S[C]} \tag{5}$$

C is the selector concentration in solution; the complexation constants refer to complexation in solution. In this case, the operational selectivity obtained in the HPLC/CMP separation is a direct predictor of selectivity in extraction.

However, this case is very rare. It is much more common that the selector and complexes also partition between mobile and solid (stationary) phase, making the formula for the operational selectivity much more complicated[20]. Moreover, the reactions at the surface and in the eluent may be counterproductive. Therefore, enantioselectivity obtained in a CMP separation may not be a very reliable indicator for selectivity in reactive extraction, although it still seems a better indicator than a CSP separation. For several other chromatographic techniques (GC, SMB, TLC), the same rationale can be applied, since they can be applied in CMP and/or CSP mode.

Capillary electrophoresis is related to chromatography. It is based on differences in solute mobilities μ when a strong electric field E is applied across a separation buffer[21]:

$$v_R = \frac{q}{f} \cdot E = \mu_R \cdot E \tag{6}$$

Gübitz and Schmid[22] reviewed many electrophoretic chiral separations. A chiral separation is usually achieved by adding a chiral selector to the electrolyte solution. The resulting diastereomeric complexes have different mobilities in the buffer phase than the original enantiomers due to mass, shape and/or charge differences[23]:

$$\Delta\mu = \mu_R - \mu_S = \frac{\mu_f + \mu_{RC} K_R[C]}{1 + K_R[C]} - \frac{\mu_f + \mu_{SC} K_S[C]}{1 + K_S[C]} \tag{7}$$

In this formula, [C] is the selector concentration in solution, μ_R and μ_S are the 'overall' resulting mobilities for enantiomers R and S; μ_f is the mobility of the free enantiomer (equal for R and S), and μ_{RC} (μ_{SC}) refers to the mobility of the RC (SC) complex. The difference in complexation constants K_R/K_S in solution is the main origin of enantioselectivity[24]. However, the operational selectivity is also influenced by the mobilities of all components, the electric

field, possible partitioning of the complexes to the capillary surface, and so on. The mobilities of the two diastereomeric complexes may also differ from each other (then $\mu_{RC} \neq \mu_{SC}$). In contrast with chromatography and extraction, the operational selectivity can become even larger than the intrinsic selectivity[23]. As the ratio K_R/K_S is the main origin of enantioselectivity in solution, enantioselectivity obtained in CE is a promising indicator for enantioselectivity in extraction. However, because of the kinetic influences on the operational selectivity, a CE chiral separation is not a direct predictor of success in extraction.

Spectroscopic techniques

Spectroscopic techniques can be used for different purposes. Determination of complexation constants between enantiomers and a chiral complexing agent in solution can be carried out by a titration, using UV-vis spectroscopy, fluorescence or NMR[25,26]. The obtained information on complexation constants between enantiomers and a chiral selector in a certain solvent is of high value, because it means that the intrinsic selectivity of this selector as enantioselective extractant is known. If the partitioning of the substance to the aqueous phase is negligible, the selector can be transferred directly to extraction.

NMR, CD or polarimetry[18] can also be applied for determination of the optical purity (e.e.) of a sample in a single measurement. This type of measurement usually does not provide suitable information on potential selectors, even if a chiral additive is used. For instance, chiral lanthanide shift reagents (LSR) can be applied in NMR to form two diastereomeric complexes that display different chemical shifts. A difference in complexation constants K_R/K_S is not required for the NMR analysis, and therefore NMR shift reagents are not necessarily successful as enantioselective extractants. Nevertheless, the selective extraction system for amino acids reported by Tsukube[5] employs as extractant lanthanide selectors that are similar to the NMR shift reagents.

Laboratory preparative separation techniques

Bulk liquid membranes or U-tubes are sometimes used to evaluate complexing agents for reactive extraction. The complexing agent /chiral selector is usually added as carrier to the liquid membrane phase. The operational enantioselectivity is defined as the relative transport rates of the two enantiomers. The transport rate is influenced by the solubility of the enantiomer in the carrier phase (determined by the interaction with the selector, thus eventually by the ratio K_R/K_S in solution), but also by the transport rate through the liquid membrane[27], the decomplexation rate, etc. The selectivity therefore originates from the ratio K_R/K_S, but there may be a kinetic contribution. If the enantioselectivity is mainly caused by the K_R/K_S ratio, the chiral selector can probably be successfully transferred to reactive extraction.

Crystallisation is a widely used chiral separation technique, both in the laboratory and at industrial scale. Therefore is it important to study if it can be exploited as a source for

enantioselective extractants. Because 90 % of all chiral substances cannot be separated in their enantiomers by direct crystallisation, diastereomeric crystallisation is a commonly used option. In this case enantioselectivity is obtained by a solubility/melting point difference and/or crystallisation rate difference between the formed diastereomers[18]. Although there may be a difference in formation constants of the diastereomers, this does not need to be a large difference. Secondly, enantioselectivity does not originate from a difference in formation constants, but from the difference in physical properties of the resulting diastereomers. Therefore, chiral selectors used in crystallisation are not expected to be successfully transferable to reactive extraction.

3.2.4 Summary

Based on the analysis of separation mechanisms, we expect that selectors used in HPLC/CMP, liquid membranes, electrophoresis, extraction, or selectors from which the complexation constants in solution have been published are the most likely to be selective in extraction as well. In some of these separations, a kinetic effect may be present, and if this effect is dominant, the selectivity may be reduced in extraction. It is expected that selectors from a CSP are more difficult to transfer: because the selector is immobilised onto a solid phase, the enantioselectivity may be decreased or enhanced compared to free solution. Finally, diastereomeric crystallisation and other diastereomeric separations are not expected to have much predictive value, because the origin of enantioselectivity in these separations is not a stability difference in complexation constants.

3.3 Selection of candidate enantioselective extractants for amines and amino-alcohols

In tables 1a-d, the encountered chiral selectors for amino acids, amines and amino-alcohols have been compiled, as applied in various separations and analytical techniques. In table 1a, selectors used in extraction and closely related techniques are included. Table 1b lists selectors applied in chromatography and electrophoresis; table 1c lists selectors for which the complexation constants are reported, and in table 1d selectors are given that have been applied in preparative techniques other than extraction.
Various selectors for amino acids are included in the tables to test if they are applicable for separation of amino-alcohols and amines as well.

Table 1a: chiral selectors for amines, amino-alcohols and amino acids used in extraction

Selector	analyte	technique	operational selectivity	ref	cr1	cr2	cr3	cr4
Carbamoylated quinine derivative	DNB-leucine, DNB-amino acids	extraction	very high, est. 50	[28]	2	1	2	0
Cichona alkaloid derivative	DNB-leucine, protected amino acids	extraction, CPC	2-7	[29]	2	1	2	0
Crown ether, methyl-D-mannopyranoside, naphtyl unit	amino acids and -salts	extraction	2-7 (very low D's)	[6]	2	2	2	0
Crown ether, methyl-D-mannopyranoside, naphtyl unit	amino acids, aromatic	extraction	1.2-2	[30]	2	2	2	0
Dialkyltartrate with $PF6^-$	amino-alcohols (as salts)	extraction	1.2-1.6 up to 2.2	[10,11,12]	2	2	2	1
Didodecyltartrate with boric acid	β-blockers	extraction	1.5-2.9	[8,9]	2	2	2	1
Lanthanide tris(β-diketonate) complexes	amino acids	extraction	2-3	[5,31]	2	2	2	0
N-(1-naphtyl)leucine, octadecyl ester	DNB-leucine	extraction, HF membrane	> 10	[32]	2	0	2	0
N-dodecyl-L-hydroxyproline Cu(II)	amino acids	extraction	1.5-3	[1,4]	2	2	2	1
N-dodecyl-L-hydroxyproline Cu(II)	leucine	extraction, HF membrane	~ 2	[2]	2	0	2	1
N-dodecyl-L-proline Cu(II)	mandelic acid	extraction	~1.6	[33]	1	0	2	1
N-naphtyl-methyl-α-methylbenzylamine and N=octadecyl-α-methylbenzylamine	sodium mandelate and sodium-N-acetyl-alanate	extraction: liquid ion exchanger	1.2-1.4	[34]	0	1	2	0
R-2-aminobutanol	bicyclo[2.2.1]hept-5-ene-2-carboxylic acids	CCC	est. 1.3	[35]	1	1	2	2

abbreviations: DNB dinitrobenzoyl, CCC counter-current chromatography[36], CPC centrifugal partition chromatography[37], HF hollow fiber, est. estimated

cr1, cr2, cr3, cr4 are the scores on criteria for choice of selectors for experimental screening, as explained in the next paragraph and in table 2:

cr1 good operational selectivity

cr2 high versatility

cr3 selector originates from favourable technique

cr4 good availability of selector

Table 1b: chiral selectors used in chromatography and electrophoresis

Selector	analyte	technique	operational selectivity	ref	cr1	cr2	cr3	cr4
Amino acid amides Cu(II) (valine, phenylalanine)	amino acids	HPLC/CMP	most < 1.8, proline up to 5	[38]	1	2	1	1
Amino alcohol Schiff base Cu(II)	amino-alcohols, amino acids	HPLC/CSP	most > 2, some higher	[39]	2	2	0	1
Amylose esters and phenylcarbamates	various	HPLC/CSP	various	[40]	2	2	0	0
Aspartame Cu(II)	α-hydroxy acids, amino acids	CE	1.3 est (R up to 5)	[41]	1	2	1	2
Aspartame Cu(II)	amino acids (DNS)	CE	1.02-1.1	[42]	0	1	1	2
Aspartame Cu(II)	valine	HPLC/CMP	up to 1.4	[43]	1	0	1	2
C_{12}CSP based on phenylethylamine with 2-aminopropanol, Cu(II)	amino acids	HPLC/CSP	up to 5.5, many > 2	[44]	2	2	0	0
Calix[4]arene, S-di-naphtylprolinol-	phenylglycinol, phenylethylamine, norephedrine	CE 'CSP', fluorescence	1.8-2.5 'Stern-Volmer constants'	[45]	2	2	0	1
Camphorsulfonate	β-blockers	HPLC/CMP	~ 1.1	[46]	0	2	1	2
Camphorsulfonate	β-blockers	TLC/CMP	1.3-2.0	[47]	2	2	1	2
Camphorsulfonate	Cisapride, β-amino-alcohols	CE, non-aqueous	1.1 est.	[48]	0	1	1	2
Cellulose esters and phenylcarbamates	various	HPLC/CSP	various.	[40]	2	2	0	1
Cinchona carbamate calix(4)arene (based on quinine and epiquinine)	N-acetylated amino acids	HPLC/CSP	1.5-2.6	[49]	2	1	0	0
Crown ether 1,1-binapthyl	amino alcohols, amines	HPLC/CSP	1.1-2, some up to 3	[50]	2	2	0	0
Crown ether Daicel (proprietary, in CROWNPAK CR)	amines, amino-alcohols, amino acids	HPLC/CSP	1.1-1.8	[51]	2	2	0	0
Crown ether, pseudo-18C6	phenylglycinol, phenylethylamine, naphtylethylamine	HPLC/CSP	2-5	[52]	2	2	0	0
Crown ether tetracarboxylic acid 18C6	amino alcohols, amines	HPLC/CSP	1.2-1.8 up to 3.5	[53]	2	2	0	0
Crown ether tetracarboxylic acid 18C6	amino-alcohols	CE	< 1.2	[54]	0	2	1	0
Cyclodextrin, α, β	various	GC	usually < 1.1	[55]	0	2	0	2

Table 1b, continued

Cyclodextrin, α, β-, various derivatives	amines, amino-alcohols, amino acids, etc, free or as -$COCF_3$ derivatives	GC	1.02-1.08 up to 1.15	[56]	0	2	0	2
Cyclodextrin, α-, 2,3,6-O-methyl	β-blockers, pharmaceuticals	CE	~ 1.05	[57]	0	2	1	1
Cyclodextrin, β-	β-blockers, pharmaceuticals	HPLC/CSP	1.05-1.4, up to 1.7	[58]	1	2	0	2
Cyclodextrin, β- with 18C6 crown ether (non chiral)	primary amino compounds	CE	1.02-1.1	[59]	0	2	1	0
Cyclodextrin, β-, (1-naphtyl)-ethylcarbamate derivative	amines, amino acids, alcohols, carboxylic acids, as 3,5-DNB derivatives	HPLC/CSP	1.1-2, up to 4.3	[60]	2	2	0	0
Cyclodextrin, β-, 2-O-methyl-3,6-di-O-sulfo	2-amino-1-phenylethanol	CE	1.6	[61]	1	0	1	1
Cyclodextrin, β-, carboxymethyl	ephedrine, phenylalanine, propranolol	CE	< 1.1 est.	[62]	0	1	1	2
Cyclodextrin, β-, carboxymethyl	ephedrines	HPLC/CMP	1.07-1.35	[63]	0	1	1	2
Cyclodextrin, β-, carboxymethyl	pharmaceuticals (prim./tert. amine)	CE	~ 1.1 up to 1.3	[64]	0	2	1	2
Dextran	pharmaceuticals	CE	up to 1.1	[65]	0	2	1	2
Dextrin	pharmaceuticals	CE	1.2-1.6	[65]	1	2	1	2
Dibutyltartrate with PF6-	(nor)ephedrine, β-blockers, as salts	HPLC/CMP and CSP	1.05-1.25	[66]	0	2	1	2
Dodecoxycarbonyl-L-leucine and other amino acid carbamates	β-blockers and pharmaceuticals	CE	< 1.06	[67]	0	2	1	1
Hydroxyproline Cu(II)	α-hydroxy acids	CE	1.3 est	[41]	0	2	1	2
Hydroxyproline/ Cu(II)	amino acids	CE	< 1.05	[68]	0	2	1	2
maltodextrin	pharmaceuticals (acids and bases)	CE	1.1 est	[69]	0	2	1	2
Mandelic acid with Cu(II)	amino acids, tertiary amine der.	HPLC/CMP	1.2-2.1	[70]	2	2	1	2
Mandelic acid with Cu(II)	amino-alcohols	HPLC/CMP	1.1-1.2	[70]	0	2	1	2
N,N-dibenzyl-1,2-propanediamine Cu(II)	amino acids (19)	HPLC/CSP	up to 3.2, many > 2	[71]	2	2	0	2
N,S-dioctylpenicillamine, (R,R)-tartaric acid mono-(R)-1-(?-naphtylethyl)-ethyl amide	acids, amines	HPLC/CSP	up to 1.2-1.3	[72]	0	2	0	0

Table 1b, continued

N-(2-hydroxy)-dodecyl-L-4-hydroxyproline Cu(II)	amino-alcohols: norephedrine,	HPLC/CSP	1.5-2.1	[73]	2	2	0	1
N-(2-hydroxy)-octyl-L-4-hydroxyproline Cu(II)	amino acids, DOPA	CE	1.3-2.8	[74]	2	2	1	1
N-(2-hydroxy)-octyl-L-4-hydroxyproline Cu(II)	β-blockers, α-hydroxy acids	CE	most < 1.2, up to 3.1	[75]	1	2	1	1
N-(2-hydroxy)-octyl-L-4-hydroxyproline Cu(II)	norephedrine, sym pathomimetics	CE	1.05/1.8	[76]	2	2	1	1
N-dodecyl-L-hydroxyproline Cu(II)	amino acids (various)	HPLC/CSP	1.2-6 many > 2	[77]	2	2	0	1
N-dodecyl-L-hydroxyproline Cu(II)	norephedrine, 2a1pe, analogues	HPLC/CSP	1.1-1.9; nor=1.77, 2a1pe=1.64	[78]	2	1	0	1
N-dodecyl-L-hydroxyproline Cu(II)	phenylglycinol, 2a1pe	HPLC/CSP	phgly 1.13, 2a1pe 1.98	[79]	1	1	0	1
N-dodecyl-L-hydroxyproline Cu(II) with barbital	amino-alcohols type 1-amino-2-ol, aliphatic	HPLC/CSP	1.2-1.4	[80]	0	2	0	1
N-dodecyl-L-phenylglycinol Cu(II)	amino acids	HPLC/CSP	1.2 est	[81]	1	2	0	1
N-undecyl-L-proline with Cu(II)	(Schiff base of) amino-alcohols	HPLC/CSP	1.2-1.4, highest 2.0	[82,83]	1	2	0	1
Ni(II) complex 'Chirasil-Ni(II)'	free alcohols	GC	1.1 est	[55]	0	2	0	0
Ni(II) tetradentate Schiff base	amines, aliphatic	HPLC/CMP	1.6-2.3 for best ligand	[84]	2	2	1	1
Ni(II) tetradentate Schiff base	amino-alcohols (aromatic)	HPLC/CMP	1.3-1.5	[73]	1	2	1	1
'Pirkle' selectors, various	beta-blockers, underivatised	HPLC/CSP	1.5-4 many > 2	[85,86]	2	2	0	0
Proline with Cu(II)	(aromatic) β-amino-alcohols	HPLC/CMP	na	[87]		2	1	2
Proline, Cu(II)	amino acids	HPLC/CMP	1.3-4.8, many > 2	[88]	2	2	1	2
Proline, with barbital and Cu(II)	amino-alcohols, primary and tertiary amine	HPLC/CMP	primary amine < 1.2, tert. am ~ 4.1	[89]	0	2	1	2
R,R-tartaric acid, mono-amide derivatives of (with Cu(II) ion)	Der. of amino acids, amines, carboxylic acids and alcohols	HPLC/CSP	many between 1.5 and 2.5, up to 3.9	[90]	2	2	0	1
Tartaric acid	β-blockers and related tertiary amines	SFC/CMP	1.1-1.2	[91]	0	2	1	2

Table 1b, continued

Tartaric acid Cu(II) bonded to Kiesel gel	catecholamines, amino acids	HPLC/CSP	1.1-1.2 up to 2	[92]	0	2	0	1
ZGP (=N-benzoxycarbonylglycyl-L-proline)	β-blockers	HPLC/CMP	1.2-1.4	[93]	1	2	1	2
ZGP (=N-benzoxycarbonylglycyl-L-proline)	pharmaceuticals, amine-containing	CE, non-aqueous	1.1	[94]	0	2	1	2

additional abbreviations: DNS dansyl, SFC supercritical fluid chromatography, 2a1pe 2-amino-1-phenylethanol, na not available.
Criteria for choice of selectors for experimental screening as in table 1a.

Table 1c: chiral selectors of which complexation constants (K) have been determined by spectroscopic or other methods

Selector	analyte	technique to determine K	operational selectivity	ref	cr1	cr2	cr3	cr4
Calix[4]arene binaphtyl derivative	phenylglycinol, phenylethylamine, phenylalaninol	UV abs. shift	nd; selective for amino-alcohol only	[95]	1	1	0	0
Crown ether, azophenolic	amines, amino-alcohols	UV	2-5 up to 12	[96]	2	2	2	0
Cyclodextrin, α-	phenylalanine	UF	2.6 (pH 3) 1.2 (pH 11)	[97]	2	0	2	2
Cyclodextrin, α-	threonine	UF	2.1 (pH 3), 1.3 (pH 11)	[97]	2	0	2	2
Cyclodextrin, β-	phenylalanine	UF	1.1	[98]	0	0	2	2
Cyclodextrin, β-	phenylalanine	UF	1.2 (pH 3) 2 (pH 11)	[97]	1	0	2	2
Cyclodextrin, β-	threonine	UF	1.3 (all pH)	[97]	0	0	2	2
Cyclodextrin, β-, copper-6A-(3-aminopropylamino)-6A-deoxy	phenylalanine, tryptophan	pH titration	1.7 (Trp), 2 (Phe)	[99]	2	1	2	0
Cyclodextrin, β-, monomaltosyl	phenylalanine	UF	3.5	[98]	2	0	2	2
Cyclodextrin, β-, nickel-6A-(3-aminopropylamino)-6A-deoxy	phenylalanine, tryptophan	pH titration	10 (Trp) 6.3 (Phe)	[99]	2	1	2	0
Cyclodextrin, β-hydroxypropyl, n=4.6	phenylalanine	UF	2.4	[98]	2	0	2	2
Sapphyrin-based selectors	CBZ-glutamic acid and -aspartic acid	NMR	1.2-2.1, up to 4.5	[100]	2	1	1	0

additional abbreviations: nd not determined; PEA phenylethylamine, UF ultrafiltration, CBZ carbobenzyloxy.
Criteria for choice of selectors for experimental screening as in table 1a.

Table 1d: chiral selectors applied in preparative chiral separation techniques

Selector	analyte	technique	operational selectivity	ref	cr1	cr2	cr3	cr4
BSA	tryptophan	UF	~20	[101]	2	0	1	2
BSA	tryptophan	UF	~10	[102]	2	0	1	2
Camphorsulfonic acid	phenylethylamine, α-p-hydroxy-phenylethylamine	Crystallisation	usually good	[103]	2	1	0	2
Cholesteryl-L-glutamate	phenylalanine	MEUF	1.9	[104]	2	0	1	0
Crown ether derivative	phenylalanine	SLM	up to 8	[105]	2	0	1	0
Crown ether, 1 chiral binaphtyl group, 18C6	amino acid salts, amino ester salts	BLM	many > 3, up to 20	[106]	2	2	1	0
Crown ether, two 1,1'-binaphtyl groups, 18C6	amino ester salts	BLM	1.5; 2.2; 12; 18	[107]	2	2	1	0
Cyclodextrin, α-	tryptophan	electrodialysis/ UF	1.08	[108]	0	0	1	2
Cyclodextrin, β-	pharmaceuticals	BLM	~	[109]			1	2
Dihexyltartrate (with $PF6^-$)	amino-alcohols, amino acids	SLM	< 1.1; norephedrine 1.5 (4°C)	[110]	0	2	1	1
Glutamic acid	2-aminobutanol	Crystallisation	yield 75%	[103]	2	0	0	2
Mandelic acid	amino-alcohols, amines	Crystallisation	usually good	[103]	2	1	0	2
N-3,5-dinitrobenzoyl-L-alanine octylester	alanine, lactic acid	SLM	1.75 alanine 2 lactic acid	[111]	2	1	1	1
N-decyl-L-hydroxyproline Cu(II)	phenylalanine	ELM	1.6	[7]	1	0	1	1
N-hexadecyl-L-hydroxyproline Cu(II)	propranolol, bupranolol	SLM	1.23 (pro) 1.46 (bup)	[112]	1	1	1	1
(S)-N-(1-naphtyl)leucine octadecyl ester	DNB-amino acid derivatives	BLM	2-7	[113]	2	2	1	0
Nopol	amino acids, as hydrochloride	SLM	ca. 1.2; up to 1.5	[114]	1	2	1	1
Poly lactic acid (PLA)	norephedrine	SLM	1.1	[110]	0	0	1	1
Sapphyrin-based selectors	CBZ-glutamic acid and -aspartic acid	K-values (NMR), BLM	1.2-2.1, up to 4.5	[100]	2	1	1	0
Taddols	amines, amino-alcohols, amino acids	Crystallisation (inclusion)	between 0.1 and 1 (yield*ee)	[115,116] [117]	2	1	0	1
Tartaric acid	2-butylamine, 2-aminobutanol, PEA, other amines	Crystallisation	usually good	[103]	2	1	0	2

additional abbreviations: MEUF micellar-enhanced ultrafiltration, SLM supported liquid membrane, BLM bulk liquid membrane, ELM emulsion liquid membrane, ee enantiomeric excess.
Criteria for choice of selectors for experimental screening as in table 1a.

When the literature data compiled in these tables are compared, the following conclusions can be drawn:

- Many chiral selectors exist, but usually the operational enantioselectivity is lower than 1.2.
- A selector that works well for one pair of enantiomers does not necessarily work (well) for a related compound: it is not trivial to find a versatile and highly selective selector. For instance, the dihexyltartrate/PF_6^- selector as applied by Keurentjes *et al*[110] in a supported liquid membrane system displayed an enantioselectivity of 1.5 for norephedrine, and < 1.1 for the other compounds tested (table 1d).
- There are several selectors that are both versatile and sufficiently selective, at least in the technique in which they were applied. Examples are the N-dodecyl-L-hydroxyproline/ Cu(II) system for chiral separation of amino acids[1] (table 1a) and the azophenolic crown ether for chiral recognition of several amines and amino-alcohols in solution[96] (table 1c).
- The same selector applied in different techniques for the same analyte often gives completely different results. More precisely, the differences between chromatography on one hand and 'liquid' techniques on the other hand are sometimes large. For example, N-(2-hydroxy)-alkyl-L-4-hydroxyproline Cu(II) has been applied in HPLC/CSP separations[73] and in CE separations[76] of amino-alcohols (table 1b). Certain components that were well resolved in the HPLC could not be separated well by CE. Secondly, the separation factors that are reported for the azophenolic crown ether system are very high in $CHCl_3$ solution[96] (table 1c), but they drop considerably when the crown ether is immobilised onto a solid support[52] (table 1b). Thus, the enantioselectivity can become larger or smaller in solution. This corresponds well with the expectations presented in the previous paragraph.
- The same selectors applied for the same analytes in the same technique under different circumstances (solvent, pH, T) can give completely different results. For instance, the enantioselectivity reached in HPLC separation with the Crownpak (+) HPLC column (proprietary crown ether CSP) increases very much with decreasing temperature. In the TLC/CMP measurements by Huang *et al*[47], using camphorsulphonate as chiral selector for beta-blockers, the temperature and the solvent composition were crucial to obtain chiral separation.

A selection was made from the literature table for experimental screening. In line with our expectations in the previous paragraph, a selector in the literature table is considered to be a promising enantioselective extractant if it scores well on the following criteria: a high reported enantioselectivity (1), a high versatility (2) and chiral recognition displayed in a 'promising' technique, i.e. chiral recognition in the liquid (3). An important practical point is the availability of selectors (4). In the literature tables 1a-1d, it has been indicated if a certain selector system satisfies one or more of these criteria (table 2):

Table 2: Scores on selection criteria cr1-cr4

Score	cr1: selectivity	cr2: versatility	cr3: suitable technique	cr4: availability
0	$\alpha_{op} < 1.2$	selective for 1 substance	crystallisation, HPLC/CSP	multistep synthesis
1	$1.2 < \alpha_{op} < 1.5$	selective for 2 substances	HPLC/CMP, CE, liquid membranes	1-2 step synthesis
2	$\alpha_{op} > 1.5$	selective for > 2 substances	extraction, reported complexation constants	commercially available

Some selectors did not have a good score on the above criteria but were still included in the experimental study, in order to confirm the expectations presented in the theory paragraph. Furthermore, some additional potential extractants were taken from literature:

- It was shown by Sliwka *et al*[81] that C_{12}-phenylglycinol as CSP can be used for the chiral separation of leucine. Therefore, a selector based on leucine might be selective for phenylglycinol as well (reciprocity principle[18,19]). Leucine can only be used as extractant if its hydrophobicity is increased. Therefore the dodecoxycarbonyl-leucine derivative[67] was selected for the screening experiments.
- Amino acid Cu(II) complexes are much stronger than amino-alcohol Cu(II) complexes at neutral pH[118], so a selector based on a Cu(II) amino acid complex may not exchange its ligand for the target amino-alcohol at neutral pH, whereas a Cu(II) amino-alcohol complex may do so. Therefore, the Cu(II) C_{12}-phenylglycinol complex was tested as extractant for amino-alcohols.
- Considerable effort was spent on testing chiral acids as enantioselective extractants, not only because of their use in crystallisation, but also because it is known that non-chiral hydrophobic acids are very well suited for the extraction of non-chiral amines, and vice versa[119]. Hydrophobic chiral acids are therefore natural candidate enantioselective extractants for chiral amines. Furthermore, Oya and Snyder[35] resolved a bicyclo[2.2.1]hept-5-ene-2-carboxylic acid with R-2-aminobutanol as separating agent using droplet counter-current chromatography (which is an extraction-like technique), thus by reciprocity a chiral acid might function as enantioselective extractant for 2-aminobutanol.
- In initial experiments, it was found that hydrophobic aldehydes are also effective extractants for amines and amino-alcohols. Therefore, a chiral hydrophobic aldehyde, citronellal, was included in the study.

All selected potential extractants are presented in table 3 in the next section. The most prominent selector groups that were excluded from the experiments are certain polysaccharides and other chiral polymers, proteins, cryptands, cyclodextrins and Pirkle-type selectors. The polymers were discarded because they are insoluble or not well soluble. Proteins are usually unstable in organic solvents, and their high molecular weight results in a low loadability per mass and a low process capacity. The various cryptands have a difficult

synthesis in common, so they were excluded for practical reasons. Cyclodextrins are water-soluble selectors, in contrast with most other chiral selector systems in the list. In order to separate a hydrophilic substance by extraction, the cyclodextrin has to be combined with a hydrophobic non-chiral extractant. This more complicated operation will not be discussed further in this paper. Certain Pirkle-type selectors have already been applied as enantioselective extractant[32] for separation of DNB-leucine, and other Pirkle-type selectors are probably applicable as enantioselective extractant as well, especially the selectors designed for direct separation of beta-blockers[85,86]. However, Pirkle selectors have not been included in our 'to-be-screened' list for synthesis constraints.

3.4 Materials and Methods

3.4.1 Chemicals

R- and S-phenylglycinol (99%), R- and S-phenylethylamine (98%), R- and S-2-aminobutanol (97%), L-4-hydroxyproline (99%), 10% Pd on activated carbon 10% (puriss), (+)-camphoric acid, (+)-mandelic acid, citronellal (98%), di-o,o-p-toluyl-L-tartaric acid (98%), Dextran (M_w 500.000) and L-dibutyl-tartrate (98 %) were obtained from Fluka (Buchs, Switzerland). Dibutyl-L-tartrate was dissolved in CH_2Cl_2 and extracted four times with double distilled water prior to use to remove traces of acid. (+)-norephedrine (98%), (-)-norephedrine (99%), (+)-ephedrine hemihydrate (98%), (-)-ephedrine (99%), rac-2-amino-1-phenylethanol (98%), dodecylchloroformate (98%), 1R-(-)-10-camphorsulfonic acid (98%) and L-tartaric acid (99.5 %) were obtained from Aldrich (Milwaukee, Wisconsin, USA). Rac-2-pentylamine (98%) was obtained from Lancaster (Eastgate, England). HCl (32 %), NaOH pellets, dichloromethane, toluene, 1-butanol, methanol and n-hexane (all analytical grade), copper(II)acetate (99%), dodecanal (98%) and sodiumborohydride (96%) were obtained from Merck (Darmstadt, Germany). Methylisobutylketone (99.5 %) was obtained from Acros (Geel, Belgium). Throughout the study, milliQ-filtered water was used (Millipore, Billerica, MA, USA).

4-methylbenzylidene camphor sulfonic acid[120] and anthracenyl camphor sulfonic acid were kindly donated by Dr. J. Nieuwenhuijzen, Syncom bv., Groningen, The Netherlands, as their sulfonate salts. They were converted to free acids by ion exchange over an Amberlite IR-120 (Fluka, Buchs, Switzerland) column with water/methanol 1:1 as eluent. Taddols 'BX' and 'PX'[117] were kindly donated by Dr. S. Müller, University of Nijmegen (KUN), The Netherlands. Aspartame was kindly donated by DSM Research, Geleen, The Netherlands. The azophenolic crown ether was synthesised by Syncom BV (Groningen, The Netherlands), in a custom synthesis[96], estimated purity 90-99 % (HPLC). N-dodecyl-L-hydroxyproline was synthesised according to reference 4, purity > 95% (NMR). N-(2-hydroxydodecyl)-L-hydroxyproline was synthesised according to the method described by Busker *et al*[121]. N-dodecyl-R-phenylglycinol was synthesised according to reference 81. Dodecoxycarbonyl-L-leucine was synthesised according to reference 67.

3.4.2 Extraction experiments and chemical analysis

All extraction experiments were carried out in jacketed 25 mL glass vessels connected to a Julabo F-32 thermostat bath to enable temperature control. Experiments were carried out at 25 °C and/or 5 °C. Water and organic solvent were presaturated in each other. As solvents, butanol, hexane, butanol/hexane mixtures, toluene and in some cases CH_2Cl_2 were considered. If appropriate, the pH of the aqueous phase was controlled with NaOH, HCl or 0.1 M phosphate buffer solutions. In each experiment, 10 mL of aqueous phase containing the enantiomer (ususally as racemic mixture), and if applicable buffer salts or other additives, was mixed with 10 mL of organic phase containing the chiral selector. To determine the (physical) partitioning ratio P, the experiment is carried out without chiral selector present. After agitation for 2 hours, which was found to be sufficient to reach equilibrium, the phases were allowed to settle. Then, the pH of the aqueous phase was determined and a sample of the aqueous phase was taken for analysis by HPLC. The HPLC set-up consisted of a Varian 2510 pump, a Crownpak(+) chiral column (Daicel, Japan), a derivatization coil and a Jasco FP-2020 *plus* fluorescence detector. The eluent, 0.1 M perchloric acid in water, was filtered over a 0.45 μm membrane before use (Millipore, Billerica, MA, USA). Post-column derivatisation with phtalic dialdehyde / mercaptoethanol reagent was carried out according to Duchateau *et al*[122]. Fluorescence detection was carried out at 325 nm excitation and 465 nm emission.

In initial experiments, the mass balance was shown to hold within 5%. After that, the organic phase concentrations were calculated from the aqueous phase concentrations. The distribution ratios (D) and operational selectivity (α_{op}) are calculated from these concentrations. D values between 0.2 and 5 are the most accurate because of their low relative error (5-10%). D values lower < 0.1 or > 10 must be judged with great care, because the relative error easily rises to > 30%. As the operational selectivity is calculated from the ratio of D's, a selectivity lower than about 1.1 cannot be determined accurately by single extraction experiments.

3.5 Results & Discussion

3.5.1 Extractant screening

In table 3 the results of the screening experiments for the separation of *rac*-phenylglycinol have been summarised for 18 potential enantioselective extractants. In about 50 % of the cases some or all of the other model enantiomers were evaluated as well. All potential extractants were tested under various circumstances (pH, T, solvent). The highest enantioselectivity obtained for separation of phenylglycinol is reported for each selector.

Although our aim is a minimal operational selectivity of 1.5 in extraction, all selectors with an enantioselectivity above the experimental error (enantioselectivity > 1.1) in the screening experiments were selected for further experimental study. This was done to test if an operational selectivity of > 1.5 can be reached under more suitable process conditions, and to study if the extractant is enantioselective for the other model enantiomers as well (versatility requirement). Only under the optimal process conditions, the operational selectivity in extraction will approach the intrinsic selectivity and the distribution ratios will be substantial (equation 1-3). For example, the concentrations of enantiomers and selector need to be high enough to obtain sufficient extent of complexation.

For any selector in which the enantioselectivity in all experiments was lower than 1.1, ‘failure mechanisms’ are indicated. Various failure mechanisms can play a role. The selector may partition between the organic and the aqueous phase (1); no enhancement of extraction beyond physical partitioning was observed (2); enhanced extraction was observed, but there was no clear enantioselectivity (3); the selector proved to be chemically unstable (4); a stable emulsion was formed (5); or the enantiomer extracts the selector instead of the other way around (6). Despite the fact that each extractant was tested under various conditions, the possibility remains that enantioselectivity would have been obtained under different process conditions. However, time constraints did not allow further screening.

3.5.2 Performance of non-selective candidate extractant systems

Table 3 shows that many of these selector systems are unable to function as enantioselective extractants, despite the fact that they demonstrated enantioselectivity in a different technique. These unsuccessful experiments may be categorised in three major groups by their failure mechanisms:

I. no enhanced extraction above partitioning was obtained (either by 1, 2 or 6)
II. practical problems, such as unstable compounds (4) or excessive emulsification (5).
III. enhanced extraction, but no enantioselectivity (3)

Failures in category I have two main causes. First, all chiral acid selectors partition between the phases, instead of remaining in one of the two liquid phases. As a result, no clear effect on

Table 3: Results of screening experiments for selected potential extractants for chiral separation of amino-alcohols and amines

Compound	source table	operational selectivity phenylglycinol	failure mechanism
Organic acids and derivatives			
L-tartaric acid	1d	1.0	1, 6
di-p-toluyl-tartaric acid	A	1.0	(1), 3
camphorsulfonic acid	1d	1.0	1, 6
camphorsulfonate sodium salt	1d	1.0	2
4-methylbenzylidene camphorsulfonic acid	A	1.0	1, 3, 5
anthacenyl camphorsulfonic acid	A	1.0	1, 3, 5
mandelic acid	1d	1.0	1, 6
camphoric acid	1d	1.0	1, 6
dibutyl-L-tartrate with boric acid	1a	1.3	☺
Amino acids and derivatives, with Cu(II)			
N-dodecyl-L-hydroxyproline Cu(II) complex	1a,1b	1.0	2
N-(2-hydroxydodecyl)-L-hydroxyproline Cu(II) complex	1b	1.2	☺
N-dodecyl-R-phenylglycinol Cu(II) complex	1b	1.0	2, 5
dodecoxycarbonyl-L-leucine Cu(II) complex	A	1.0	1, 3
aspartame Cu(II) complex	1b	1.0	4
Saccharides			
dextran	1b	1.0	2
Crown ethers			
'Hirose' crown ether	1c	5.0	☺
Miscellaneous			
taddol	1d	1.0	2
citronellal (chiral aldehyde)	A	1.0	3

Symbols: source 1a,1b,1c,1d refers to table 1a,1b,1c,1d, origin A refers to 'included for additional reasons'; ☺enantioselectivity of extraction > 1.1. Failure mechanisms: see text.

amine/ amino-alcohol extraction can be observed. In some cases phenylglycinol extracts the selector to the aqueous phase instead of the other way around. To prevent this type of problems, adaptation of the structure of the selector can be attempted. For instance, Takeuchi

et al[4] connected a dodecyl (C_{12}) tail to L-hydroxyproline to successfully prevent partitioning. Unfortunately, such structural modifications are not possible for all potential selectors in a simple way. In addition, changes in the selector structure may affect the chiral recognition process.
Secondly, some of the potential selectors did not form complexes with the enantiomers in the solution to any appreciable extent. To identify and prevent such problems, it is crucial to study the chemistry of the complexation in solution under the experimental circumstances (pH, solvent, T). For instance, reactions between amines and aldehydes only take place at higher pH, because the uncharged amine group is involved, and the reaction does not take place with an amine present in its ammonium form. Furthermore, reactions between amino-alcohols and Cu(II) are much stronger at higher pH, so they hardly come to expression at neutral pH. In the case of taddols, it was found in literature[117] that these compounds belong to a group of 'inclusion compounds' that only form inclusion complexes in the solid phase, so during crystallisation. Real inclusion complexes do not exist in the liquid, which explains why taddols do not function as extractants.

The behaviour of aspartame is typical for category II. This compound is unstable under the required working conditions (pH neutral or basic). Another practical problem occurred with N-dodecyl-R-phenylglycinol Cu(II) complex and some chiral acids. They could not be studied further because a (fairly) stable emulsion was formed during extraction, which prevented chemical analysis.

In category III, potential extractants are found that did display extraction, but only non-enantioselectively. The chiral acid selectors originate from literature on crystallisation. Their failure as enantioselective extractants is probably due to the need for chiral recognition in the liquid phase. Evidently, the selectors did not selectively form complexes with amino-alcohols in free solution despite the selectivity obtained for amino-alcohols in crystallisation. Another example is the dodecoxycarbonyl-L-leucine selector, which was not selective for phenylglycinol. In this case, we also tried to exploit the reciprocity principle: a CSP selector based on phenylglycinol can be used for separation of leucine[81], so it may work the other way as well. The failure is probably caused here not because the reciprocity principle does not work, but also by a translation failure: a selector that displays an enantioselectivity of 1.2 for leucine as CSP is just not very likely to be a good selector for leucine in free solution. And the same holds for the 'reverse' selector system.

In a few cases, candidate selectors were tested for which enantioselectivity towards amino-alcohols had not been described in literature, only enantioselectivity towards amino acids. Our experiments showed that these systems were unselective for our amino-alcohols: a good selector for amino acids is in many cases not a good selector for amino-alcohols. A good example from literature is C_{12}Hyp/Cu(II) as CSP, which is a good selector for various amino-acids[77], but which was much less selective for several amino-alcohols[79]. A similar effect has

been reported by Yamazaki and coworkers[70] for mandelic acid with Cu(II) as CMP in HPLC: separation factors of 1.2-2.0 were obtained for amino acids, but only separation factors of 1.1-1.2 were found for amino-alcohols (table 1b).

Citronellal and dextran were included in the 'to-be-screened' list although they had not shown a large selectivity for any compound in the literature, and none of them functioned as enantioselective extractant. It can be concluded that testing selectors for reactive extraction is rather pointless if there is no indication of sufficiently large enantioselectivity at all.

3.5.3 Performance of selective candidate extractant systems

Table 3 shows that three systems were successful in the screening experiments, namely dibutyl-L-tartrate with boric acid, N-(2-hydroxydodecyl)-L-hydroxyproline Cu(II) complex and the azophenolic crown ether. With all these systems, enhanced extraction and an enantioselectivity larger than 1.1 were observed. Additional extraction experiments were carried out for these systems to test the versatility of the extractant, and to test if an operational selectivity > 1.5 can be reached by adaptation of the process conditions. Further characterisation, modelling of the extraction behaviour and tests on leaching of extractant and chemical stability are also very important for eventual industrial application, but will be carried out in a later stage of the research.

Dibutyl-L-tartrate (DBT) with boric acid

In all experiments with this system (table 4), equal volumes of water and CH_2Cl_2 phase were used. The concentration of racemic mixture was 2 mM, the initial aqueous boric acid concentration was 100 mM, the dibutyl-L-tartrate concentration in dichloromethane was also 100 mM, the temperature was 5 °C. No buffer salts or other additives were used, resulting in a pH at equilibrium of 6-7, depending on the extent of extraction.

Table 4: Extraction of various amino-alcohols with dibutyl-L-tartrate (DBT) with boric acid. D_1 refers to the strongest extracted enantiomer, which may be S or R.

Chiral compound	D_1 [-]	D_2 [-]	α_{op} [-]	strongest extracted enantiomer
norephedrine	0.43	0.33	1.3	(-)
ephedrine	4.5	3.5	1.3	(-)
2-aminobutanol	< 0.05	< 0.05	nd	
phenylglycinol	0.2	0.16	1.2	S
2-amino-1-phenylethanol	0.21	0.19	1.1	R

nd = not determined because of too low distribution ratio

The dibutyl-L-tartrate with boric acid system was originally developed for chiral separation of β-blockers by reactive extraction, but it has been shown here that the system is also moderately selective for certain other amino-alcohols. Comparison of the extraction of

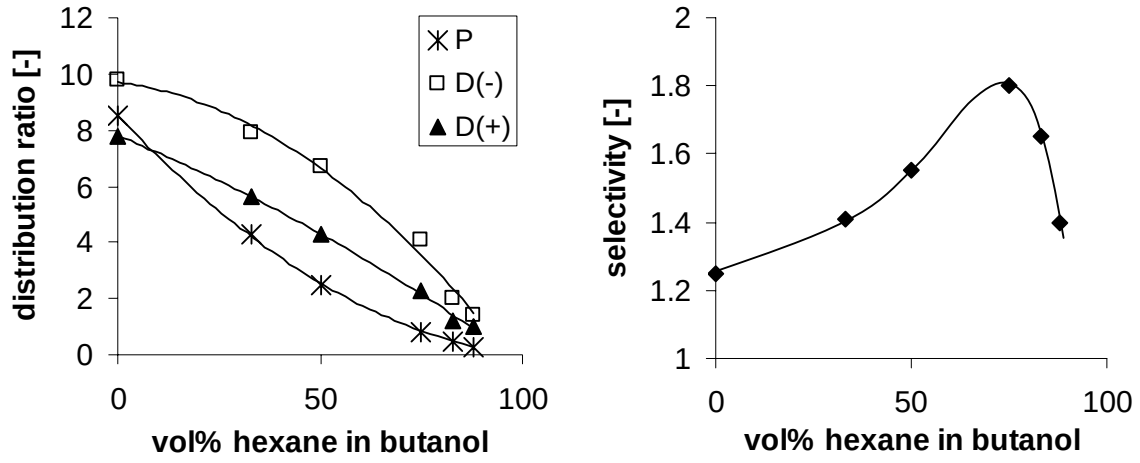
norephedrine and ephedrine results, including literature data, suggests that a secondary amine is more strongly complexed by the DBT system. Although the selector system is rather versatile, further development of this system for the target primary amines and amino-alcohols does not seem justified because of the too low enantioselectivities, namely < 1.3, and the low distribution ratios at high selector concentration (low capacity).

N-(2-hydroxydodecyl)-L-hydroxyproline Cu(II) complex

N-(2-hydroxyalkyl)-L-hydroxyproline Cu(II) complex has been used in CE[76] and as CSP in HPLC[73] for chiral separation of amino-alcohols. To the best of our knowledge, the component has not been used before as extractant for amino-alcohols. From previous work[4,7, 123] with the related selector N-dodecyl-L-hydroxyproline (C_{12}Hyp) for separation of amino acids by reactive extraction, it is known that C_{12}Hyp forms a 2:1 complex with Cu(II) ion in the organic phase. Complexation of an amino acid enantiomer with this selector takes place by ligand-exchange, resulting in a ternary complex of C_{12}Hyp, Cu(II) and amino acid. It is expected that N-(2-hydroxydodecyl)-L-hydroxyproline (OH-C_{12}Hyp) will show similar complexation behaviour. Secondly, it is known[118] that amino-alcohols only form complexes with Cu(II) ion at pH > 9. Therefore, the pH has to be high in order to extract amino-alcohols with this selector system. To prevent copper precipitation at high pH, the pH can be set conveniently by addition of 0.1 M ammonia[76]. It was found that OH-C_{12}Hyp and C_{12}Hyp can only be dissolved to a reasonable extent in an alcohol such as butanol or in a solvent mixture containing > 10 % alcohol; chlorinated solvents were not considered.

In order to study the influence of the 2-hydroxyl group in the side chain on the selectivity, extraction experiments were carried out with both N-(2-hydroxydodecyl)-L-hydroxyproline (OH-C_{12}Hyp) Cu(II) complex and N-dodecyl-L-hydroxyproline (C_{12}Hyp) Cu(II) complex. Initial extraction experiments involved the separation of *rac*-norephedrine with 20 mM OH-C_{12}Hyp / 10 mM Cu(II) in n-butanol. As expected, at low pH only physical partitioning was observed. At high pH the distribution ratios for both enantiomers were very high because of the complexation reaction in combination with the high polarity of the solvent, but the enantioselectivity was only moderate. As a next step, less polar butanol/hexane mixtures were tested as solvent. The extraction results are given in figure 2a and b for chiral separation of *rac*-norephedrine. To demonstrate the influence of the solvent composition on the physical partitioning, the partitioning ratio P at pH 11 is presented as well.

It can be seen that the solvent composition has a large influence on the extent of extraction and on the operational selectivity. A similar strong effect of the solvent on the operational selectivity was described by Huang *et al*[47] for a TLC/CMP separation. Other model enantiomers were tested with both OH-C_{12}Hyp/Cu(II) and C_{12}Hyp/Cu(II) using butanol/hexane solvent mixtures with high hexane content (75 or 83 vol%), under the same circumstances as for the norephedrine separation. The results are given in table 5.



(a) (b)

Figure 2: Extraction of 2.3 mM rac-norephedrine as a function of solvent composition at 25 °C; extractant [OH-C_{12}Hyp] =20 mM, [Cu(II)]=10 mM at pH ~ 9.7 (0.1 M NH_3), equal volumes aqueous phase/organic phase. Lines are trendlines. (a) P = partitioning ratio at pH 11 (NaOH), D = distribution ratios for extraction of norephedrine (b) Selectivity α_{op} = D(-)/ D(+).

Table 5: Extraction of various amino-alcohols (2 mM rac) at 25 °C from water to butanol/hexane mixtures at pH ~ 9.7 (0.1 M NH_3). Extractant: 20 mM C_{12}Hyp or OH-C_{12}Hyp, with 10 mM Cu(II), equal volumes aqueous/organic phase. D_1 refers to strongest extracted enantiomer.

extractant	amino-alcohol	vol% hexane	D_1 [-]	D_2 [-]	α_{op} [-]	strongest extracted enantiomer
OH-C_{12}Hyp	norephedrine	75	4.1	2.3	1.8	(-)
OH-C_{12}Hyp	2-aminobutanol	75	0.5	0.45	1.1	R
OH-C_{12}Hyp	phenylglycinol	83	1.9	1.6	1.2	R
OH-C_{12}Hyp	2-amino-1-phenylethanol	83	1.7	1.45	1.2	R
C_{12}Hyp	norephedrine	75	1.6	1.1	1.5	(+)
C_{12}Hyp	2-aminobutanol	75	< 0.1	< 0.1	nd	
C_{12}Hyp	phenylglycinol	75	0.9	0.9	1.0	
C_{12}Hyp	2-amino-1-phenylethanol	75	1.0	0.7	1.4	S

nd = not determined because of too low distribution ratio

Furthermore, it was observed for OH-C_{12}Hyp that carrying out the extraction at 5 °C results in a similar enantioselectivity, but lower distribution ratios (table 6).

Table 6: Temperature influence on extraction of rac-norephedrine; $[nor]_{ini}$=2.3 mM, 10 mM Cu(II)/20 mM OH-C_{12}Hyp from water to butanol/hexane mixtures at pH ~ 9.7.

vol% hexane	T (°C)	$D_{(-)}$	$D_{(+)}$	$\alpha=D_{(-)}/D_{(+)}$
75	5	1.9	1.1	1.7
75	25	4.1	2.3	1.8
83	5	1.72	0.95	1.8
83	25	2.0	1.2	1.7

The N-(2-hydroxydodecyl)-L-hydroxyproline (OH-C_{12}Hyp) Cu(II) complex has demonstrated a good selectivity of 1.8 for norephedrine under very specific conditions, but only a modest enantioselectivity (≤ 1.2) for other reference enantiomers. The system is therefore not versatile enough to separate various enantiomers from the same chemical class. A further drawback of this system is the presence of ammonia and some Cu(II) in the aqueous phase, which has to be separated from the enantiomer product. Similarly, the C_{12}Hyp/Cu(II) system demonstrates a modest enantioselectivity but in addition much lower distribution ratios.

It is noteworthy that the OH-C_{12}Hyp selector and the C_{12}Hyp selector prefer the opposite enantiomers of norephedrine and 2-amino-1-phenylethanol. Apparently, the presence of the 2-hydroxyl group on the C_{12} side chain has a large effect on the chiral recognition process. N-(2-hydroxydodecyl)-L-hydroxyproline is in fact a mixture of two diastereomers itself; the 2-hydroxyl group on the dodecyl tail introduces a second chiral centre in the molecule. Separation of the two diastereomers of N-(2-hydroxydodecyl)-L-hydroxyproline may result in a pure selector that is more selective towards amino-alcohols than the diastereomeric mixture. However, it was decided not to carry out any further work for this system because of the favourable properties of the next extractant tested.

Azophenolic crown ether

The last selective system to be tested further is the azophenolic crown ether represented in figure 3, which was selected for its high reported enantioselectivity and high binding constants. This crown ether and a number of related crown ethers were developed by Naemura, Hirose and other workers for use in HPLC/CSP systems[52]. In the literature, complexation constants of these compounds with several amino-alcohols and amines in chloroform are reported[96], with enantioselectivities of often > 2, up to 12. In contrast with most other crown ethers, the phenolic crown ethers form inclusion complexes with the *neutral* form of amines and amino-alcohols. Comparison of the enantioselectivities of the various crown ethers shows that the aryl groups on the crown ether ring are very important in the chiral recognition process, by a combination of π-π-interaction, dispersion forces and steric hindrance. If these groups are exchanged for methyl, tert-butyl or adamantyl[124], or if the ring is made more rigid by connecting for instance cyclohexane rings to the sides of the main ring[125], the enantioselectivity drops considerably. The electron-withdrawing 2,4-

dinitrophenylazo group increases the complexation strength[126] and is responsible for the clear colour change of the molecule upon complexation[26].

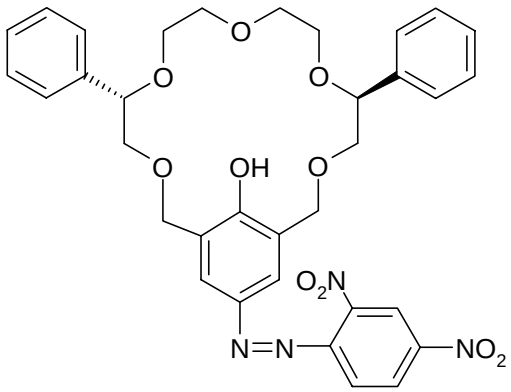


Figure 3: Azophenolic crown ether[96]

Our initial experiments with the crown ether were carried out with CH_2Cl_2 as solvent. Equal volumes of aqueous phase and dichloromethane phase were used. The initial concentration of the racemic mixture in water and of the crown ether in dichloromethane were both 2 mM. The pH was not controlled by buffer salts. It was visually observed and confirmed by UV-Vis spectroscopy that physical partitioning of the crown ether to the aqueous phase is negligible. The extraction results are given in table 7:

Table 7: Chiral separation of various amino-alcohols and amines by reactive extraction with 2 mM azophenolic crown ether in dichloromethane. $[rac]_{ini}$ = 2 mM. D_1 refers to strongest extracted enantiomer.

enantiomer	T [°C]	pH	D_1 [-]	D_2 [-]	α_{op} [-]	strongest extracted enantiomer
phenylglycinol	25	9	4.0	0.8	5.0	R
2-amino-1-phenylethanol	5	10	5.6	4.2	1.3	R
norephedrine	5	8.7	4.5	2.6	1.7	(+)
2-aminobutanol	5	9.9	1.9	0.6	3.2	R
phenylethylamine	5	9.2	20.4	9.9	2.1	S
2-aminopentane	5	9.9	6.2	6.0	1	

The crown ether system shows a good enantioselectivity for 4 out of 6 model compounds, and a modest selectivity for 1 compound. It is therefore a versatile and also very selective extractant system. The distribution ratios are already high at relatively low extractant concentration, which indicates a promising process capacity. According to the literature, the influence of temperature on the complexation constants is high[96] and deserves further study.

By comparing the selectivities, it seems that the compounds bearing the amine group group next to the chiral centre can be separated with the highest enantioselectivity, with exception of 2-aminopentane. This effect seems logical, because the primary interaction between enantiomer and crown ether is inclusion of the (neutral) amine group in the crown ether ring. The difference in selectivity for phenylglycinol and 2-amino-1-phenylethanol (bearing the chiral centre next to the hydroxyl group) is striking. The structure around the chiral centre for the strongest bonded enantiomer is the same for phenylglycinol, phenylethylamine and 2-aminobutanol, despite the difference in R/S designation. This is caused by the priority in the nomenclature of the -C-OH group over the phenyl group in phenylglycinol, and the priority of the phenyl group over the methyl group in phenylethylamine. From the failure to separate 2-aminopentane, it seems that a second functional group is required for chiral recognition; this may be a phenyl group or a hydroxyl group, or possibly a different functionality. The selector may also be enantioselective for other enantiomers that are primary amines with at least one other functionality, such as amino acids, other amino-alcohols and aromatic amines.

3.5.4 Evaluation of the developed identification procedure

In the theoretical part, several chiral separation techniques have been compared, which resulted in the expectation that systems in which the origin of enantioselectivity is the difference in complexation constants in solution, are the most likely to yield enantioselective extractants.

When comparing the three successful systems listed above, it can be concluded that they indeed all originate from 'liquid' systems. OH-C_8Hyp was tested as selector in capillary electrophoresis[76], and proved to be slightly selective for a number of amino-alcohols, and much more selective for norephedrine and some analogues. The same selectivity pattern is found in extraction. OH-C_{12}Hyp was also successfully applied as CSP, but these results[73] are not so similar to the extraction results. The HPLC/CSP separation was carried out at pH 6, which proved to be an unsuitable pH for extraction, and the system was selective for different amino-alcohols. Thus, the results from the 'liquid' technique CE are more predictive of the reactive extraction results than the results from the 'solid' technique HPLC/CSP. The other two selective systems also originate from 'liquid' techniques. DBT was tested as extractant before, for β-blockers. The complexation constants in solution for enantiomer-Hirose crown ether were published, which is a direct indication for a successful transfer to extraction.

If we look at the unsuccessful transfers listed in table 3, we find further confirmation for our expectations. The chiral acids that extracted the amine enantiomers unselectively (failure mechanism 3) originate from the crystallisation literature. According to the hypothesis, selectivity in crystallisation is not predictive for selectivity in extraction. In the literature, we can also find further support for our expectations, such as the azophenolic crown ether system: the separation factors are very high in $CHCl_3$ solution[96], but they drop considerably when the crown ether is immobilised onto a solid support[52]. This confirms that

enantioselectivity obtained with a selector in free solution can differ substantially from the enantioselectivity obtained with the same selector as CSP.

The selection criteria assigned in table 1a-1d are indeed helpful in selection of enantioselective extractants. If the overall scores on the four criteria for all selectors are compared, no good pre-selection of potential extractants is obtained. It seems that the most important criterion is the reported enantioselectivity for the enantiomers of interest, in combination with 'selector originating from a favourable technique'. The literature database which is represented in tables 1a-1d can be searched, and a remarkable result is shown in table 8, obtained with the following criteria:

- selectors for amines and/or amino-alcohols
- score on selectivity has to be 2
- score on versatility and on favourable technique has to be at least 1

Table 8: Search result in literature database (tables 1a-1d) according to criteria above

Selector	analyte	technique	operational selectivity	reference	cr1: α	cr2: versa	cr3: tech	cr4: avai
Crown ether, azophenolic	amines, amino-alcohols	K-values by UV	2-5 up to 12	96	2	2	2	0
Crown ether, methyl-D-mannopyranoside	amino acids, aromatic	extraction	1.2-2	30	2	2	2	0
Camphorsulfonate	β-blockers	TLC/CMP	1.3-2.0	47	2	2	1	2
Dialkyltartrate with PF6-	amino-alcohols (as salts)	extraction	1.2-1.6 up to 2.2	10, 11, 12	2	2	2	1
Didodecyltartrate with boric acid	β-blockers	extraction	1.5-2.9	8, 9	2	2	2	1
N-(2-hydroxy)-octyl-L-4-hydroxyproline Cu(II) complex	norephedrine, sympatho-mimetics	CE	1.05/1.8	76	2	2	1	1
Ni(II) tetradentate Schiff base	amines, aliphatic	HPLC/CMP	1.6-2.3 for best ligand	84	2	2	1	1

In this way, 7 potential extractant systems are selected out of about 100 literature systems, including the three systems that proved to be successful (crown ether, boric acid/dialkyltartrate and N-(2-hydroxy)-octyl-L-4-hydroxyproline Cu(II) complex) and the one successful system from the literature (Prelog system). Camphorsulfonate did not perform well in extraction because of its partitioning to the aqueous phase. The Ni(II) tetradentate Schiff base and the mannopyranoside crown ether were not tested due to synthesis constraints, but may be successful as well. Searching the database with these (or similar) criteria will provide

a good 'priority-of-testing' list, which decreases the amount of experimental work considerably.

It is also noteworthy that only one commercially available system (score '2' on availability) comes up. There is a evidently a trade-off between the performance of the selector system and its ease of availability (i.e. price). For the boric acid system, it was possible to use the commercially available dibutyl-L-tartrate instead of didodecyl-L-tartrate, but this may not be the tartrate that gives optimal selectivity. For the Prelog system, it is reported that tartrates containing more bulky alcohol residues such as menthol are more selective than the simple straight-chain alcohols[12], but they will be more expensive as well.

3.6 Conclusion

Four enantioselective extractant systems for separation of amino-alcohols and amines with the chiral center next to the amino group have been identified, namely dibutyl-L-tartrate with boric acid, N-(2-hydroxydodecyl)-L-hydroxyproline Cu(II) complex, N-dodecyl-L-hydroxyproline Cu(II) complex and azophenolic crown ether. The azophenolic crown ether system is particularly promising, as it displays both a high versatility and high enantioselectivity in extraction. In order to assess the technical and economical feasibility of this extractant, further study is desired to determine the effect of process parameters on selectivity and capacity of the system and to test if recovery of products and extractant is possible. Furthermore, an alternative for the dichloromethane solvent has to be identified.

Secondly, we have proposed an approach to identify potential enantioselective extractants in the chiral recognition literature. For a successful transfer, a certain selector should display chiral recognition towards the components of interest in the liquid phase. Enantioselective extractants are most likely to be found among chiral selectors in the extraction, HPLC/CMP, electrophoresis and liquid membrane literature. Furthermore, the reported enantioselectivity should be large enough, at least 1.5. In this way, a pre-selection or a 'priority-of-testing' list can be made from a database containing chiral selectors from various techniques. Thus, the amount of required batch extraction experiments for identification of a new enantioselective extractant is likely to be reduced drastically. As the process conditions have a large effect on the selectivity and capacity of the extraction, it is important to select them carefully.

We expect that this approach to identify enantioselective extractants in the chiral recognition literature can be applied for other classes of enantiomers as well. In this way, many selectors reported in the chiral recognition research may be transferred to new applications. Finally, the improved availability of enantioselective extractants is an essential step forward for the introduction of reactive extraction as an industrial chiral separation method.

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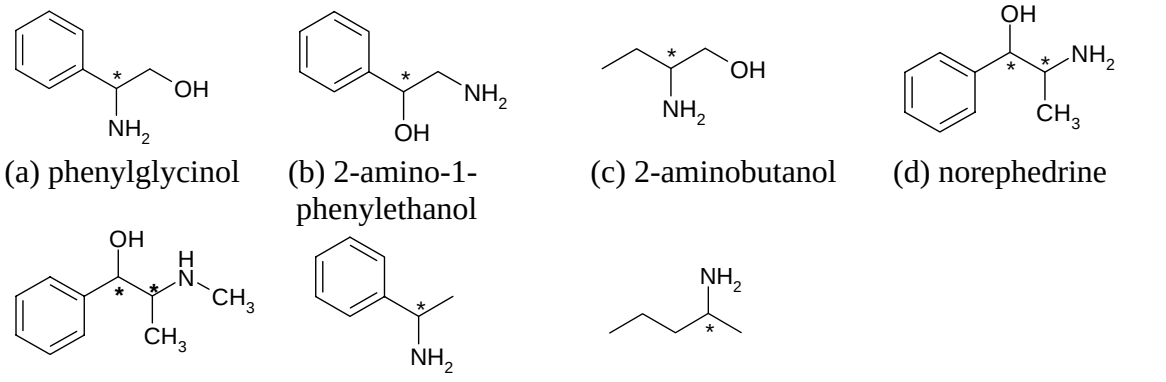
4 Influence of process parameters on extraction equilibria for the chiral separation of amines and amino-alcohols with a chiral crown ether

4.1 Introduction

In the previous chapter, the identification of enantioselective extractants for amines/amino-alcohols was discussed. The set of target enantiomers is given in figure 1. The most promising extractant identified in the screening procedure was the azophenolic crown ether[1,2] presented in figure 2, dissolved in dichloromethane. It could be used to separate 5 out of 7 model enantiomers with enantioselectivities 1.35 - 5.0. The obtained distribution ratios were rather high already at low extractant excess. Because of the structural variations within the group of test enantiomers, the extractant system is expected to be selective for other enantiomers containing primary amine groups as well. Based on the fact that the enantioselectivity of many other chiral crown ethers was determined in extraction experiments, we expect that more chiral crown ethers can be successfully applied as enantioselective extractants in reactive extraction.



(a) phenylglycinol (b) 2-amino-1-phenylethanol (c) 2-aminobutanol (d) norephedrine

(e) ephedrine (f) phenylethylamine (g) 2-aminopentane

*Figure 1: Structure of amino-alcohols and amines studied. * indicates a chiral centre*

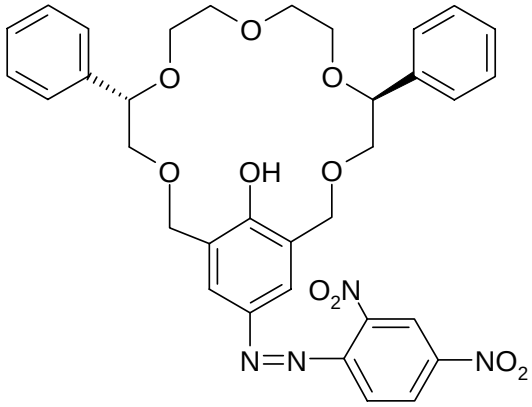


Figure 2: Azophenolic crown ether[1], the enantioselective extractant used in this study

The second obstacle for introduction of FREX is the low process capacity that can be calculated based on the original research papers. This low volumetric productivity seems to be caused by the combination of high excess of chiral selector, very low enantiomer concentrations and by selection of equipment with slow mass transfer characteristics for the laboratory proof-of-principle. To increase the productivity, the required excess of extractant and the role of concentrations and other parameters should be studied, for instance with an equilibrium model of a single extraction stage; for selection and design of equipment, a multistage-stage model and information on the reaction kinetics is required. The final goal of the development procedure is a working extraction system containing the identified versatile enantioselective extractant, which can be used at the commercial production scale and that delivers each enantiomer at the desired purity despite the fact that the enantioselectivity of the crown ether is different for each pair of enantiomers.

The aim of this chapter is to understand and model the behaviour of azophenolic crown ether extraction system in a single equilibrium stage. Firstly, solvent screening experiments will be carried out to identify an environmentally acceptable alternative for dichloromethane, the solvent that was used in all initial experiments. Secondly, the relation between the various process conditions and the capacity and selectivity of the extraction in one stage will be studied experimentally. Process parameters of interest are extractant concentration, extractant excess, temperature and pH. These parameters influence the extent of complexation and the partitioning, and thus the overall extent of extraction and the enantioselectivity. Along with the experimental work, a predictive equilibrium model of the extraction performance in one equilibrium stage will be constructed, based on the chemistry of the system, and validated. The purpose of the model is to improve understanding of the behaviour of the extraction system, to allow extractor modelling and conceptual process design and to study various options for improved productivity of the system. Finally, the recovery of enantiomers and extractant after extraction will be studied by back-extraction experiments and modelling.

4.2 Model description

The azophenolic crown ether is a new enantioselective extractant. Other reactive extraction systems in literature have been modelled successfully by solving equilibrium relations and mass balances simultaneously. Schlichting *et al*[3] reported an equilibrium model for the reactive extraction of salicylic acid and phenylalanine with a secondary and quaternary amine extractant, respectively. The model takes into account acid-base dissociation of the solute in the aqueous phase, physical partitioning and the reaction between target acid and amine extractant in the organic phase. A similar model was reported for extraction of 6-aminopenicillanic acid with a tertiary amine by Bora *et al.*[4] Both authors fitted their model parameters from extraction experiments. The only chiral separation by reactive extraction that was modelled in detail is the separation of DL-phenylalanine, DL-leucine and DL-valine with N-dodecyl-L-hydroxyproline (C_{12}Hyp) Cu^{2+} complex in a water/octanol extraction system, reported by Koska & Haynes.[5] This system functions by a ligand-exchange mechanism. For a good description, a large number of aqueous phase and two-phase complexation reactions had to be included in the model, which resulted in a large set of model equations. Koska & Haynes obtained most of the complexation constants from independent measurements and fitting the remaining complexation constants from extraction data.

According to the literature, the azophenolic crown ether forms 1:1 adducts with amines and amino-alcohols in organic solutions. The complexation constants of the azophenolic crown ether with various amines and amino-alcohols in chloroform were reported.[1] A scheme of this reaction and the other equilibria that play a role in the extraction system is represented in figure 3.

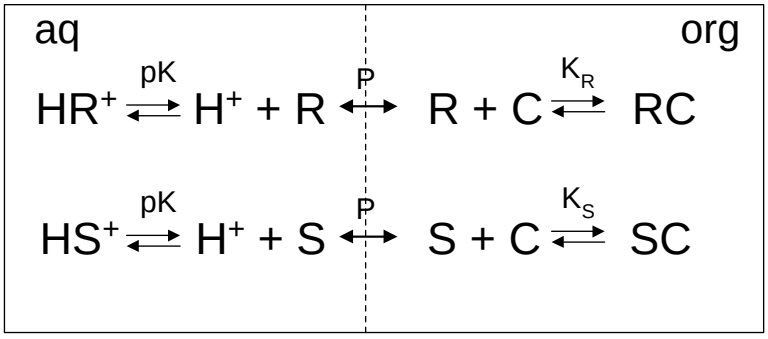


Figure 3: Scheme of equilibria in the reactive extraction system. R,S represent the two enantiomers of the amino-alcohol or amine of interest; HS^+, HR^+: conjugated acid (ammonium form) of this amino-alcohol or amine; C: enantioselective extractant i.e. azophenolic crown ether; SC, RC: diastereomeric complexes of enantiomer and extractant.

Based on this scheme, the behaviour of the extraction system is modelled by combining the following equilibrium conditions and mass balances:

- Acid-base equilibrium in the aqueous phase (neutral amine/ammonium); acid-base dissociation constant K_A is the same for both enantiomers.
- Physical partitioning of the neutral form of the enantiomers between the phases, characterised by partitioning ratio P, which is also the same for both enantiomers.
- Reversible 1:1 complex formation[1] between the crown ether and the neutral amine form of the enantiomers in the organic phase; characterised for the S enantiomer by complexation constant K_S and for the R enantiomer by K_R.
- Mass balances for each enantiomer and for the crown ether to complete the model.
- The resulting pH can be calculated by including an electroneutrality condition in the model. Alternatively, the pH at equilibrium can be used as input parameter.

The physical and chemical equilibria are defined as:

$$P = \frac{[R]_{org}}{[R]_{aq}} \quad (1) \qquad K_R = \frac{[RC]_{org}}{[R]_{org} \cdot [C]_{org}} \quad (2) \qquad \text{and} \qquad K_A = \frac{[R]_{aq} \cdot [H^+]_{aq}}{[HR^+]_{aq}} \quad (3)$$

The formulas are similar for the S-enantiomer. In these formulas, C is the crown ether, R is the uncharged enantiomer, HR^+ is the ammonium form of the enantiomer and RC is the complex between R-enantiomer and crown ether; 'org' refers to the organic phase and 'aq' to the aqueous phase. The distribution ratios D_R and D_S are defined as:

$$D_R = \frac{[R]_{org,allforms}}{[R]_{aq,allforms}} = \frac{[R]_{org} + [RC]_{org}}{[R]_{aq} + [HR^+]_{aq}} = \frac{1 + K_R \cdot [C]_{org}}{1 + [H^+] / K_A} \cdot P \quad (4)$$

$$D_S = \frac{[S]_{org,allforms}}{[S]_{aq,allforms}} = \frac{[S]_{org} + [SC]_{org}}{[S]_{aq} + [HS^+]_{aq}} = \frac{1 + K_S \cdot [C]_{org}}{1 + [H^+] / K_A} \cdot P \quad (5)$$

The operational selectivity α_{op} is defined as the ratio of distribution ratios. It can be deduced from the above that (assuming $K_R > K_S$):

$$\alpha_{op} = \frac{D_R}{D_S} = \frac{1 + K_R \cdot [C]_{org}}{1 + K_S \cdot [C]_{org}} \quad (6)$$

All concentrations in equations 1-6 are *equilibrium* concentrations, which have to be solved using the mass balances.

It can be seen that the distribution ratios D are a strong function of the physical partitioning ratio P, the pH and other parameters of the system. The selectivity reaches an asymptotic value when the product of complexation constant and extractant concentration is large enough. This asymptote is the ratio of the complexation constants, the intrinsic selectivity α_{int}:

$$\alpha_{\text{int}} = \frac{K_R}{K_S} \qquad (7)$$

The most important parameters in this model are the complexation constants for the complexation between crown ether and enantiomers (K_R and K_S), the physical partitioning ratio (P) and the acid dissociation constant of the amine (K_A). All these parameters can be obtained from independent experiments or from literature. In this way, a predictive model can be constructed. For our model, K_R, K_S and P were determined experimentally by UV-titration and partitioning experiments, respectively. Acid dissociation constants were taken from the literature[6,7,8] (table 1). Through equations 4-6, the model predictions can be compared with the experimental results in extraction in terms of D_R, D_S and α_{op}.

Table 1. Literature data for pK_A. NR = not reported

substance	temperature (°C)	pK_A	ref.
2-amino-1-phenylethanol	20	9.0	6
phenylglycinol	20	8.5	7
norephedrine	20	9.4	6
ephedrine	20	9.5	6
2-aminobutanol	NR	9.5	6
phenylethylamine	25	9.4	8
2-pentylamine	NR	10.6	6

4.3 Materials & Methods

4.3.1 Materials

R- and S-phenylglycinol (99%), R- and S-phenylethylamine (98%) and R- and S-2-aminobutanol (97%) were obtained from Fluka (Buchs, Switzerland). (+)-norephedrine (98%), (-)-norephedrine (99%), (+)-ephedrine hemihydrate (98%, (-)-ephedrine (99%) and rac-2-amino-1-phenylethanol (98%) were obtained from Aldrich (Milwaukee, Wisconsin, USA). Rac-2-pentylamine (98%) was obtained from Lancaster (Eastgate, England). HCl (32%), NaOH pellets, dichloromethane, toluene, 1-octanol and n-hexane (all analytical grade) were obtained from Merck (Darmstadt, Germany). Methylisobutylketone (99.5%) was obtained from Acros (Geel, Belgium). The azophenolic crown ether was synthesised by Syncom BV (Groningen, The Netherlands), in a custom synthesis.[1] Throughout the study, milliQ-filtered water was used (Millipore, Billerica, MA, USA).

4.3.2 Determination of complexation constants K_R and K_S

Complexation constants between crown ether and enantiomers in a solvent are determined by UV-vis titration.[9,10] The uncomplexed crown ether exhibits an absorption peak at 400 nm, whereas the complex between crown ether and amine or amino-alcohol shows a peak between 540 and 575 nm, depending on the nature of the amine and the solvent. For each titration experiment, a series of samples is prepared containing a constant concentration of crown ether, typically 0.02 mM, and a varying concentration of one enantiomer of the substance of interest in the solvent, typically between 0.04 and 15 mM. The UV-vis spectrometer is kept at the desired temperature with a Julabo F-25 thermostat bath. All samples are allowed to reach thermal and chemical equilibrium in the spectrometer before the spectrum is recorded. At least six data points were used for each determination; these points were chosen in such a way that they span the 20 % complexation to 80 % complexation range.[10] Naemura *et al*[1] report a 1:1 stoichiometry for complexation of the crown ether with various amines and amino-alcohols in organic solution. This stoichiometry was confirmed by the presence of the characteristic crossing point[9] in the UV titration plots.

Data treatment is done with the Scott plot;[11] this is a straight-line method that gives reliable results if the excess of enantiomer is sufficient (to assume a constant enantiomer concentration) and if a wavelength can be found at which only the complex and the crown ether show absorption of light, and not the enantiomers. The majority of our data could be treated in this way. In a few cases, the K values were so high that a ‘too low’ enantiomer concentration had to be used to be able to span the 20-80% complexation range. As the excess of enantiomer was insufficient to allow the use of straight-line data treatment methods, the more versatile (but more elaborate) Rose-Drago method or a non-linear fitting method was used in these cases[10]. Based on the propagation of experimental error, the accuracy in the obtained K-value is estimated to be 10-20 %. The experimental method was validated by measuring the complexation constant between phenolphtalein and β-cyclodextrin in 0.02 M

Na_2CO_3 buffer at 25°C. The result was $2.3 \cdot 10^4$ M^{-1}, which is consistent with values reported in literature[11,12,13,14]: these values range from $2.0 \cdot 10^4$ M^{-1} to $2.9 \cdot 10^4$ M^{-1} for this buffer composition (not all measurements were performed at isothermal conditions).

4.3.3 Partition and extraction experiments

All partition and extraction experiments were carried out in jacketed 25 mL glass vessels connected to a Julabo F-32 thermostat bath to enable temperature control. In each experiment, 10 mL of aqueous phase containing the enantiomer as racemic mixture, typically at a concentration of 2 mM (rac), and dilute HCl or NaOH if the pH needed to be set, was mixed with 10 mL of organic solvent containing the chiral crown ether as extractant, typically at a concentration of 1-10 mM. To determine the (physical) partitioning ratio P, the experiment is carried out at higher pH (pH 11-12, NaOH) without crown ether present. In the 'base case' extraction experiment 2 mM crown ether and 2 mM rac-enantiomer is used, without addition of acid, base or buffer. After agitation for 2 hours, which was found to be sufficient to reach equilibrium, the phases were allowed to settle. Then, the pH of the aqueous phase was determined and a sample of the aqueous phase was taken for analysis by HPLC. The HPLC set-up consisted of a Varian 2510 pump, a Crownpak(+) chiral column (Daicel), a derivatisation coil and a Jasco FP-2020 *plus* fluorescence detector. Post-column derivatisation with phtalic dialdehyde / mercaptoethanol reagent was carried out according to Duchateau *et al.*[15] Fluorescence detection of the fluorescent derivative was performed at 325 nm excitation and 465 nm emission. From repeated analyses of the same sample, the error in the HPLC concentration determination was found to be ± 3%.

In initial experiments, the mass balance was found to hold within the error of the HPLC determination. After that, the organic phase concentrations were calculated from the aqueous phase concentrations. The distribution ratios (D) and operational selectivity (α_{op}) are calculated from these concentrations, so the error in the concentration propagates in the D and α_{op} values. For D values between 0.2 and 5, the resulting relative error is only slightly higher than the error in the concentrations, 5 - 10%. If the concentration in one of the two phases is very low, the relative error in D easily rises to > 30%, therefore extreme D values (< 0.1 or > 10) must be judged with great care. As the operational selectivity is calculated from the ratio of D's, a selectivity lower than about 1.1 cannot be determined accurately by single extraction experiments.

4.3.4 Experimental approach

For the solvent screening experiments, extraction experiments were carried out as described above, with 2 mM rac-phenylglycinol and 4 mM crown ether dissolved in the solvent under study at 25 °C. After selection of the alternative solvent, the model parameters were obtained and 'base case' extraction experiments were carried out for all test enantiomers. To study the effects of pH, T and concentrations further, additional experiments were carried out with one or two of the test enantiomers.

4.4 Results and discussion: model parameters

In the initial solvent screening experiments that are discussed in the next paragraph, toluene was identified as most promising alternative for dichloromethane. Therefore, all relevant model parameters were obtained with toluene as solvent. For comparison, most of the data were obtained with dichloromethane as well. The influence of temperature, solvent and other process conditions on the model parameters is discussed.

4.4.1 Partitioning ratios

In figure 4, the experimental partitioning ratio P is shown as a function of pH for phenylglycinol in dichloromethane. Similar plots were obtained for other solvent-amine (amino-alcohol) combinations. At low pH, the amino group is charged (ammonium form) and the partitioning to the organic phase is much lower than at high pH. The resulting partitioning ratio (P_{eff}) can be described as a linear combination of contributions of the amine in neutral form (P_{amine}) and charged form ($P_{ammonium}$):

$$P_{\exp} = x_{ammo} \cdot P_{ammo} + x_{amine} \cdot P_{amine} \qquad (8)$$

The mole fractions x ($x_{ammo} + x_{amine} = 1$) of amine and ammonium are governed by the pH of the system and the pK_A of the amine. If the partitioning of the ammonium-form can be neglected (set to zero), the Henderson-Hasselbach equation[3] for amines can be used to describe the resulting effective partitioning P_{eff} as a function of pH:

$$P_{amm} = 0 \quad \Rightarrow \quad P_{eff} = x_{amine} \cdot P_{amine} \equiv x_{amine} \cdot P = P \cdot (1 - \frac{1}{1+10^{pH-pK}}) \qquad (9)$$

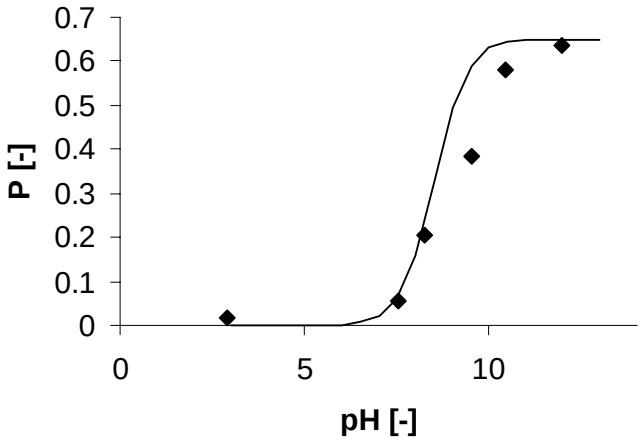


Figure 4: Influence of pH of aqueous phase on partitioning of phenylglycinol into dichloromethane. [PG] = 2 mM, 25 °C. Solid line according to eq. 9 with P= 0.65 and pK_A =8.5.

The partitioning ratio of the ammonium form P_{ammo} is in general very low and will be considered as zero in this work. The value of P_{amine} can be measured at a pH value 2 units higher than pK_A. In the remainder of this chapter, the model parameter 'partitioning ratio P' refers to the value of P_{amine}.

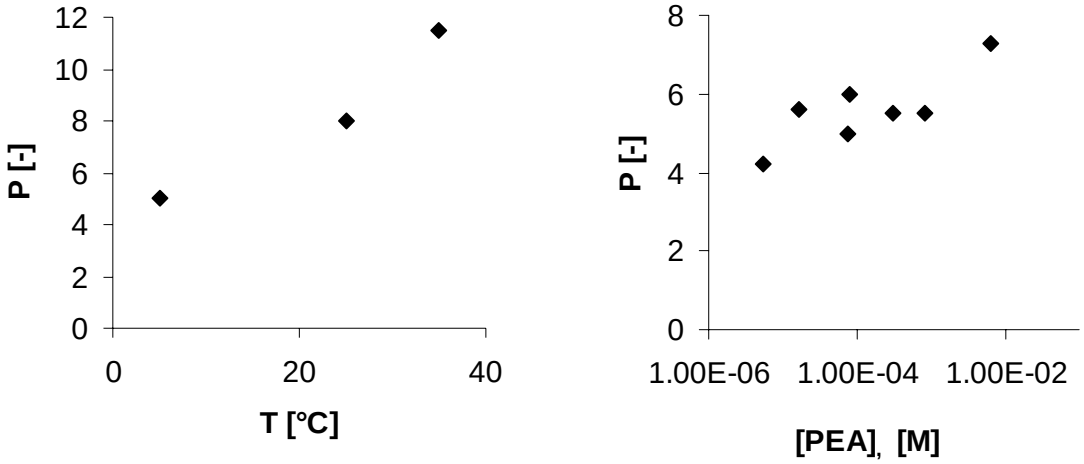
It can be seen in table 2 that in general, the partitioning of the enantiomers is higher in CH_2Cl_2 than in toluene. Apparently the amines and amino-alcohols are solvated better in CH_2Cl_2. Comparison of the amines with the amino-alcohols shows that the presence of the hydroxyl group in the amino-alcohols increases the hydrophilicity of the substances, and thus reduces their partitioning to the organic phase. If the P could not be determined accurately because of the low value, it is denoted as P < x.

Table 2: Partitioning ratios P for CH_2Cl_2 and toluene at two temperatures. [racemic mixture] = 2 mM in all cases. pH set with dilute NaOH.

enantiomer	solvent	T [°C]	P [-] at pH 11-12
2-amino-1-phenylethanol	CH_2Cl_2	25	0.7-0.8
2-amino-1-phenylethanol	toluene	25	< 0.1
2-aminobutanol	CH_2Cl_2	25	< 0.1
2-aminobutanol	toluene	5	< 0.05
2-pentylamine	CH_2Cl_2	5	6.4
2-pentylamine	CH_2Cl_2	25	6.7
2-pentylamine	toluene	5	1.4
norephedrine	toluene	5	<0.05
norephedrine	CH_2Cl_2	5	
norephedrine	CH_2Cl_2	25	1.7
phenylethylamine	CH_2Cl_2	5	> 10
phenylethylamine	CH_2Cl_2	25	> 10
phenylethylamine	toluene	5	5-6
phenylethylamine	toluene	25	8-9
phenylglycinol	CH_2Cl_2	25	0.6
phenylglycinol	toluene	25	< 0.1

To study the influence of temperature and solute concentration on the partitioning ratio in more detail, additional partitioning data were collected for phenylethylamine (PEA). In figure 5a, the results for P at three different temperatures are given. In figure 5b, the variation of P with the PEA concentration at 5 °C is presented. It can be concluded that P increases with increasing temperature, and P also seems to increase slightly with increasing [PEA]. P is probably also temperature dependent for the other amines and amino-alcohols in this study, but accurate experimental determination is more difficult because of the low values of P, and was not attempted. From simulations, it has become clear that it is important to incorporate

the temperature effect on P in the model. The concentration effect is less pronounced and it has less influence on the model results, so P will be considered as independent of amine/amino-alcohol concentration at a given temperature.



(a) (b)

Figure 5: Physical partitioning ratio P of phenyletylamine (PEA) in toluene. (a) temperature dependency; [PEA] = 2 mM. (b) concentration dependency; T = 5 °C.

4.4.2 Complexation constants

A typical example of a UV/Vis titration experiment to determine a complexation constant is represented in figure 6. The colour change upon complexation can be seen clearly: the uncomplexed crown ether is orange-red (peak at 400 nm), and the enantiomer-crown ether complex is purple (peak at ~ 560 nm). The characteristic crossing point present at about 450 nm confirms that the stoichiometry of complexation is 1:1.[9]

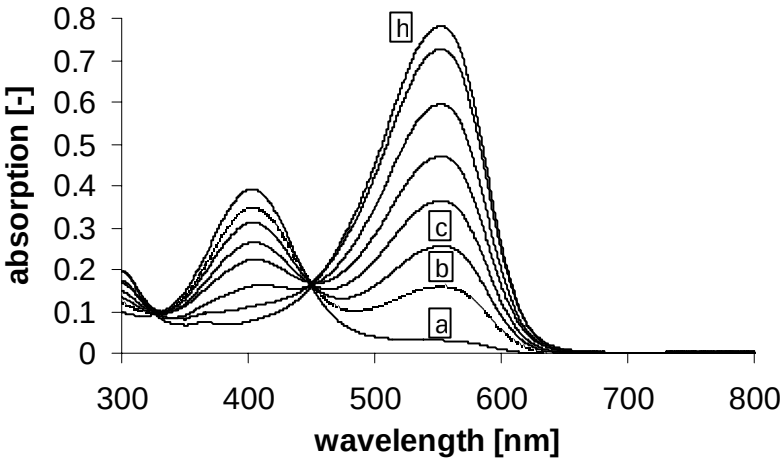


Figure 6: UV-vis titration experiment to the determine complexation constant between crown ether extractant and S-2-aminobutanol in toluene at 25 °C; all samples: [CE] = 0.02 mM, varying amount of S-2-aminobutanol : (a) 0 mM (b) 0.05 mM (c) 0.09 mM (d) 0.18 mM (e) 0.30 mM (f) 0.60 mM (g) 1.43 mM (h) 2.98 mM

The other complexation constants were determined in the same way (table 3).

Table 3: Complexation constants for azophenolic crown ether with amines and amino-alcohol enantiomers, determined by UV-vis titration

enantiomer	solvent	T (°C)	K_1 [l mol^{-1}]	K_2 [l mol^{-1}]	intrinsic selectivity α_{int}	strongest binding enantiomer
2-aminobutanol	toluene	5	50.000	22.000	2.3	R
	toluene	25	9200	4000	2.3	R
ephedrine	CH_2Cl_2	5	350	300	1.2	(+)
norephedrine	CH_2Cl_2	5	60.000	33.000	1.8	(+)
	CH_2Cl_2	25	9000	5000	1.8	(+)
	toluene	5	37.000	29.000	1.3	(+)
	toluene	25	6000	4400	1.4	(+)
phenylethylamine	$CHCl_3$	25	2390	764	3.1	S
	toluene	5	6000	1850	3.2	S
	toluene	25	900	330	2.7	S
	toluene	35	375	180	2.1	S
phenylglycinol	CH_2Cl_2	5	150.000[1]	15.000	10	R
	CH_2Cl_2	25	15.000	1500	10	R
	$CHCl_3$	25	17.400	1410	12	R
	toluene	5	80.000[1]	8200	10	R
	toluene	25	12.000	1200	10	R

[1] *value is minimum value; experimental method does not permit more accurate determination.*

It can be seen in table 3 that the chemical structure of the amine or amino-alcohol has a large influence on the selectivity of the separation. The compounds that bear the chiral centre next to the amine moiety (2-aminobutanol, phenylethylamine and phenylglycinol) are complexed with higher selectivity than the compounds in which the chiral centre is located next to the alcohol moiety (norephedrine, ephedrine). This may be explained by the primary interaction between crown ether and amine: the inclusion of the amine group in the crown ether ring. Secondly, the presence of at least one more functional group next to the amine group seems to be required for chiral recognition, such as a hydroxyl group or a phenyl group. Finally, ephedrine forms a much weaker complex with the crown ether than norephedrine, probably because ephedrine is a secondary amine which does not ‘fit’ very well in the crown ether ring.

It is also clear from table 3 that the solvent has a large influence on the complexation constants and on the intrinsic selectivity. Solvent molecules play an important role in the complexation process, for instance by desolvation of the enantiomers and extractant, solvation of the complex and possibly by acting as a ligand. However, the exact role of the solvent in enantioselective complexation is poorly understood.

The strong influence of temperature on the complexation constants of this extractant that can be observed in table 3 has also been reported in the literature on this crown ether in $CHCl_3$.[1] The temperature dependency of the complexation constants arises from the enthalpy of complexation. For all crown ether-enantiomer combinations tested here, the complexation constant decreases with increasing temperature, which indicates an exothermic reaction. If equilibrium values for at least two temperatures are known, the thermodynamic quantities ΔH and ΔS of complexation can be calculated with the Van 't Hoff equation:[16]

$$\ln(K) = -\frac{1}{RT}\Delta H + \frac{1}{R}\Delta S \qquad (10)$$

In this way, the thermodynamic quantities ΔH and ΔS can be obtained, and complexation constants at intermediate temperatures can be estimated by interpolation. The Van 't Hoff plot for phenylethylamine is shown in figure 7, with experimental data for toluene and literature data for $CHCl_3$. Calculated thermodynamic quantities ΔH and ΔS are reported in table 4.

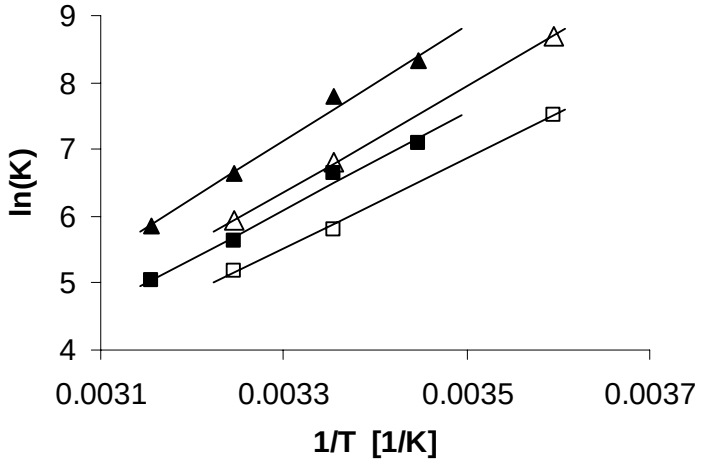


Figure 7: Van 't Hoff plot for complexation constants between crown ether and phenylethylamine in two solvents. Toluene data (open symbols) from table 3. Chloroform data (closed symbols) from reference 10; triangles: S-enantiomer, squares: R-enantiomer.

Table 4: Thermodynamic quantities for complexation of crown ether with model enantiomers, derived from Van 't Hoff plot (figure 7). 'strong' refers to compound that complexes more strongly with CE; ΔΔH and ΔΔS as 'strong' minus 'weak'.

substance	solvent	ΔH (strong) kJ/mol	ΔH (weak) kJ/mol	ΔΔH kJ/mol	ΔS (strong) J/mol/K	ΔS (weak) J/mol/K	ΔΔS J/mol/K
PEA	$CHCl_3$	-71.7	-60.5	-11.2	-177.3	-149.1	-28.2
PEA	toluene	-65.8	-56.0	-9.8	-164.2	-139.1	-25.1
Noreph.	toluene	-62.6	-64.9	2.7	-137.9	-148.2	10.3
PG	toluene	-66.2	-66.2	0	-144.0	-163.1	19.1

It is clear from table 4 that the differences between the R and S enantiomer in enthalpy (ΔΔH) and entropy (ΔΔS) of complexation with the crown ether are rather small, but this small effect is responsible for the observed enantioselectivity. As can be seen in table 3 and 4, with an increase in temperature the enantioselectivity may decrease (i.e. PEA/toluene), increase (norephedrine/toluene) or remain the same (phenylglycinol/ toluene). This behaviour is reflected in the sign and the value of ΔΔH. The entropy effect ΔΔS is important for all combinations. Naemura *et al* reported similar effects for complexation of related crown ether dissolved in chloroform. In general, intrinsic enantioselectivity in reactive extraction is determined by the difference in Gibbs free energy (ΔΔG) of complexation between the enantiomers. The order of magnitude for the required ΔΔG for separation in reactive extraction is only 1-6 kJ/mol, which corresponds with an intrinsic selectivity range of 1.5 to 11.

4.5 Results and discussion: extraction

4.5.1 Influence of solvent

To identify an alternative solvent for CH_2Cl_2, preliminary screening experiments with several solvents were carried out for separation of phenylglycinol. The screening results can be summarised as follows:

- With toluene as solvent, the enantioselectivity and distribution ratios are rather similar, or slighly lower than in dichloromethane.
- Extraction with methylisobutylketone (MIBK) is selective at 25 °C, but the obtained enantioselectivity is lower than with toluene.
- Extraction with 1–octanol as solvent is also effective; the enantioselectivity is again lower than with toluene, but still considerably high (α_{op} ~ 4.2, for 4 mM of crown ether and 2 mM of phenylglycinol at 5 °C). The high viscosity of octanol and the associated slow phase settling is a drawback of this solvent.
- The crown ether cannot be dissolved well in hexane, and the crown ether/amine complex is even less soluble and precipitates. Hexane can therefore not be used as extraction solvent.

The solvent has a clear influence on the enantioselectivity. It takes an active part in the complexation process by solvation/desolvation of the constituents and the complex, and possibly by acting as a ligand. It may be that the more polar solvents (MIBK and 1-octanol) form hydrogen bonds and thus disturb the intermolecular forces that are responsible for the selective complexation between crown ether and phenylglycinol.

Based on this screening, toluene was selected as alternative to dichloromethane. For comparison, both solvents were studied in more detail. In table 5, the results of 'base case' extraction experiments are reported.

Table 5: Base case extraction experiments; [racemic mixture] = 2 mM, no pH buffers. nd = not determined because of too low distribution ratios.

enantiomer	solvent	T	pH_{eq}	$[CE]_{ini}$ mM	D1 [-]	D2 [-]	α_{op} [-]
phenylglycinol	CH_2Cl_2	25	~ 9	2	0.8	3.9	4.9
phenylglycinol	toluene	5	9.3	2	0.3	2.74	9.1
phenylglycinol	toluene	25	9.2	2	0.2	1.14	5.7
2-amino-1-phenylethanol	CH_2Cl_2	5	10	2	5.6	4.2	1.35
2-amino-1-phenylethanol	toluene	5	10	2	1.1	0.7	1.5
2-amino-1-phenylethanol	toluene	25	9.8	2	0.51	0.35	1.5
norephedrine	CH_2Cl_2	5	8.7	2	2.6	4.5	1.7
norephedrine	toluene	5	~9	2	1.1	1.6	1.45
2-aminobutanol	CH_2Cl_2	5	9.9	2	0.6	1.9	3.2
2-aminobutanol	toluene	5	10.9	2	< 0.1	<0.1	nd
2-aminobutanol	toluene	25	~ 10	4	0.12	0.19	1.6
phenylethylamine	CH_2Cl_2	5	9.2	2	20.4	9.9	2.1
phenylethylamine	CH_2Cl_2	25	8.3	2	14.2	9.8	1.5
phenylethylamine	toluene	5	9.7	1.5	7.5	4.0	1.9
phenylethylamine	toluene	25	9.1	1.9	5.9	4.1	1.45
2-aminopentane	CH_2Cl_2	5	9.9	1.9	6.2	6.0	1
2-aminopentane	toluene	5	10.8	1.9	3.0	3.0	1

It was already observed in table 2 and 3 that for most compounds both P and most complexation constants are lower in toluene than in dichloromethane. The intrinsic selectivity is for some of the components lower in toluene than in CH_2Cl_2. This solvent influence on the parameters is reflected in the extraction results (table 5). For all enantiomers, the distribution ratios (D's) are lower in toluene. For norephedrine and 2-aminobutanol, the operational selectivity is lower in toluene, whereas the selectivity seems slightly higher in toluene for 2-amino-1-phenylethanol.

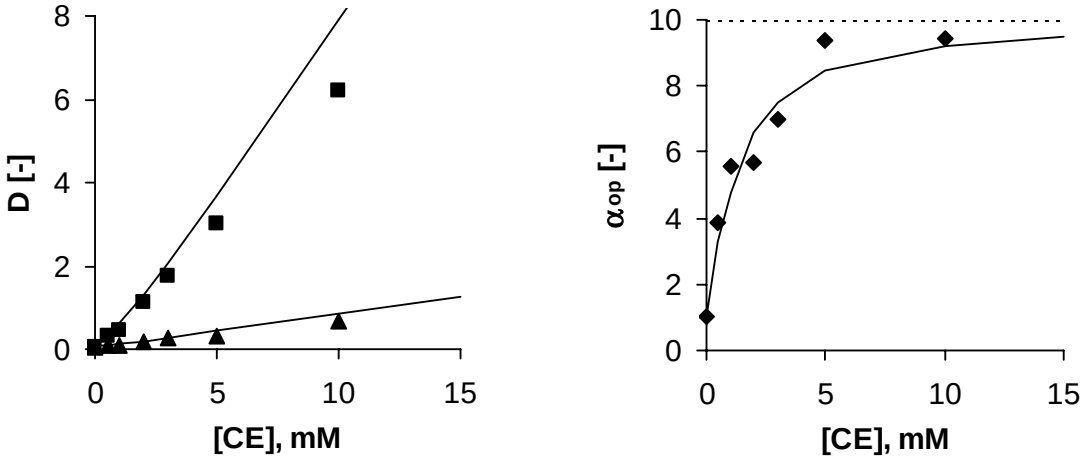
For application of toluene instead of dichloromethane as extraction solvent, a loss in operational selectivity seems to be the largest problem. However, it can be seen that the operational selectivity in toluene is still quite good for most of the test enantiomers, and for separation of 2-amino-1-phenylethanol, toluene is even a better solvent. Furthermore, the distribution ratios are lower in toluene. This is not necessarily disadvantageous in fractional extraction:[17] lower distribution ratios lead to higher solvent flow rates but a lower wash flow rate. Furthermore, the distribution ratios in toluene are not extremely low for most

enantiomers, and it is not expected that the operation will be unfeasible. An exception is the separation of 2-aminobutanol. For this substance, the physical partitioning in toluene is so low that the resulting distribution ratios are too low for accurate determination of selectivity, despite the high complexation constants and intrinsic selectivity (see table 3). We expect these D's to be too low for industrial application as well: a very large extractor would be required. This problem may be less pronounced if the extraction process is carried out at higher concentrations, but the 2-aminobutanol separation is much easier in CH_2Cl_2.

A similar large influence of the solvent on the extent of extraction has been reported for other reactive extractions by other authors, for instance for the reactive extraction of acetic acid with TOPO described by Ricker *et al.*[18] However, it is not clear from this paper if the effect is mainly caused by a difference in physical partitioning or in the complexation constant.

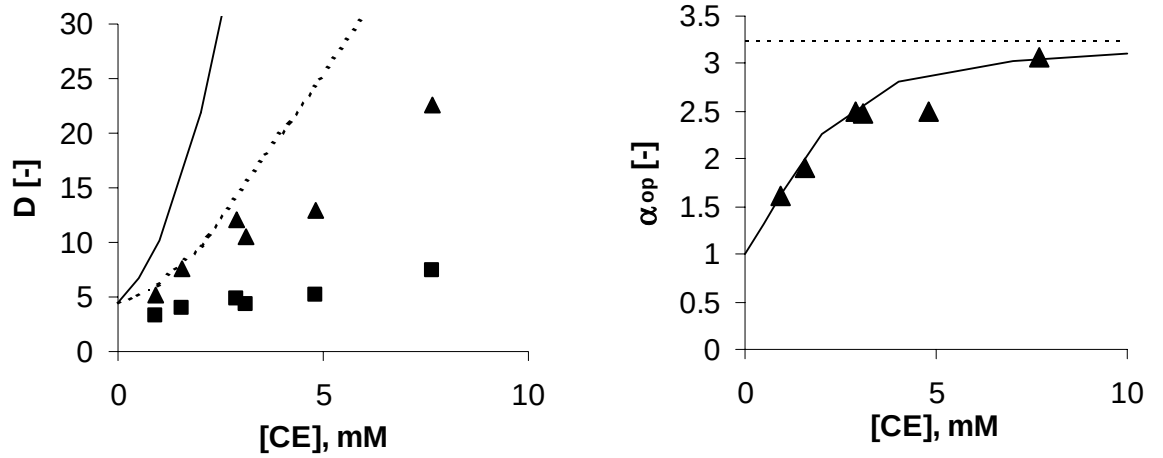
4.5.2 Influence of extractant concentration

The influence of crown ether concentration on the extraction performance has been studied in toluene for two enantiomers, phenylglycinol and phenylethylamine. No buffer salts were used. In figure 8a and b, the observed distribution ratios D and the operational selectivity α_{op} are given for phenylglycinol separation at 25 °C. The model predictions have been presented as solid lines. In figure 9a and b, similar graphs are presented for separation of phenylethylamine at 5 °C in toluene.



(a) (b)

Figure 8: Influence of extractant concentration on extraction of phenylglycinol. [PG] = 2 mM, T = 25°C, solvent: toluene. pH not set, resulting pH 9.0-9.8. Solid lines: model predictions. (a) distribution ratios; triangles: S-enantiomer, squares: R-enantiomer (b) operational selectivity



(a) (b)

Figure 9: Influence of extractant concentration on extraction of phenylethylamine, [PEA] = 2 mM, T = 5°C, solvent: toluene. pH not set, resulting pH 9.2-9.9. Lines: model predictions. (a) distribution ratios, triangles/solid line: S-enantiomer, squares/dotted line: R-enantiomer (b) operational selectivity

It can be seen that a very good operational selectivity is reached for both enantiomers with a relatively low extractant concentration (~ 4 mM) and low extractant excess ([CE]/[rac] ~2-3). The operational selectivity is predicted quite well by the model. This can be explained from equation (6): α_{op} is strongly influenced by the value of K's and the concentration of extractant, and it is only slightly influenced by the partitioning ratio and the acid dissociation constant; therefore small changes in pH or uncertainties in P or pK_A do not have much influence on the predicted operational selectivity. For both enantiomers, the operational selectivity reaches a plateau value if the extractant concentration is sufficient: the intrinsic selectivity α_{int}. At this plateau, the condition holds that $K\cdot[CE] >> 1$ (equation 6 and 7). If the extractant is present in excess, the minimum concentration of extractant to approach the intrinsic selectivity can be estimated from the condition: $K\cdot([CE]_{ini}-[rac]_{ini}) >10$.

For both enantiomers, the distribution ratios increase steadily with increasing extractant concentration. It can be seen that the correct trend is described by the model, but the prediction of the absolute value of D is too high, especially for PEA. For phenylglycinol, it is difficult to obtain experimentally a correct value for P, because P is quite low. In case of a very low P value, it may be better to fit the correct value of P from the experimental extraction data instead of measuring it directly. For phenylethylamine, the deviation of the model prediction from the experimental results seems to be caused mostly by a different effect: the predicted pH was always larger than the experimental pH. The exact value of pH strongly influences the resulting D, as may be clear from figure 3 and equation 4 and 5. With the predicted pH, the distribution ratio is overestimated 2-4 times. To show the large influence of the pH, model predictions were generated by assuming that different amounts of acid were

present in the solution. It was found that a value of 0.15 mM acid results in a correct description of the distribution ratios (figure 10, dashed line), and that with this acid concentration, the equilibrium pH values generated by the model are also close to the experimentally observed values. Thus, this small addition of acid would be a good explanation for the experimental distribution ratios being lower than the model predictions. Likewise, it was calculated for phenylglycinol that assumption of a small amount of acid (0.1 mM) results in a better prediction of the pH at equilibrium. In this case the pH is still substantially above pK and therefore the influence of the pH shift on the distribution coefficients is not so high.

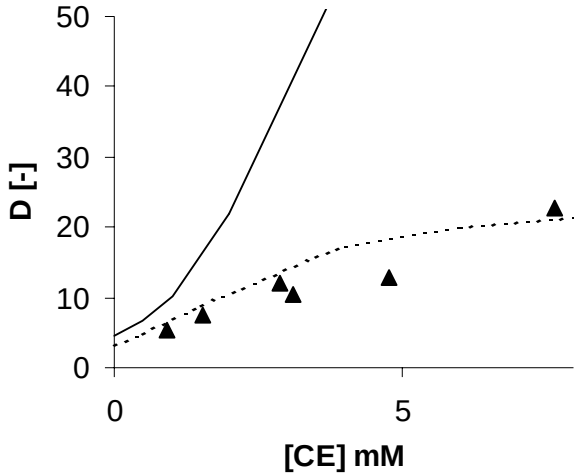


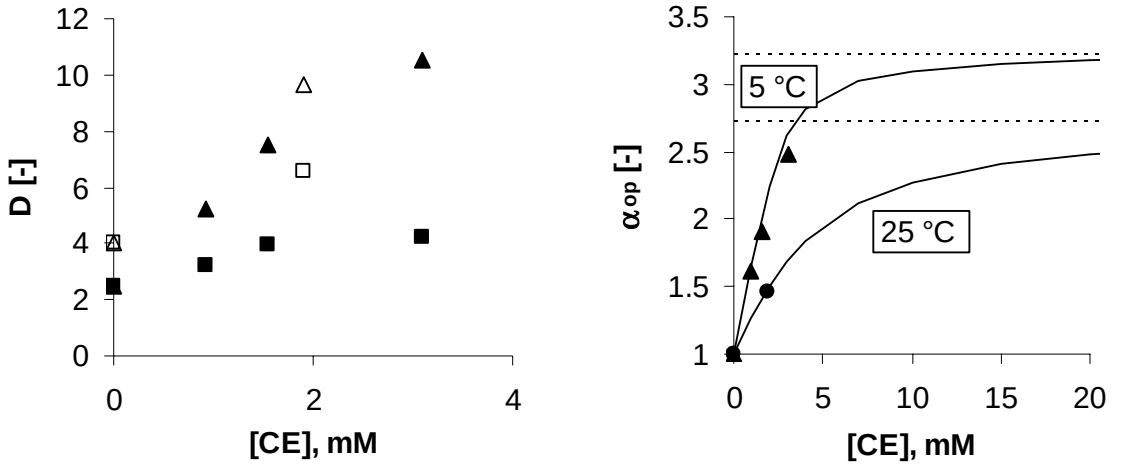
Figure 10: Model prediction of influence of presence of acid on distribution of S-PEA as a function of [CE]. Total [PEA]=2 mM. Trend is the same for R-enantiomer. Solid line: no acid present (=same as figure 9a); dashed line: 0.15 mM acid present.

To provide an explanation for the origin of acid, one portion of a solution of 2 mM phenylethylamine was stirred for two hours under argon atmosphere, while another portion of the same solution was stirred while in contact with air. The resulting pH of the 'open' vessel was about 0.4 pH units lower than the one stirred under argon. This strongly suggests that uptake of CO_2 from air is responsible for the observed lower pH values. As phenylethylamine is a stronger base than phenylglycinol, the CO_2 uptake and the associated pH decrease and deviation from the model prediction is also the strongest with this enantiomer. For correct model predictions for phenylethylamine, the CO_2 uptake should be quantified and included in the model, or CO_2 uptake should be prevented by carrying out the experiments in an inert atmosphere. As for the above result, uptake of 0.15 mM CO_2 by a 2 mM amine solution (~ 7.5% by stoichiometry) during preparation of the solutions seems a realistic value.

4.5.3 Influence of temperature

As can be seen in table 3, the temperature has a strong influence on the absolute values of the complexation constants, and in some cases also on the ratio of complexation constants (intrinsic selectivity). Secondly, it has been found that the partitioning ratio P is also strongly

temperature dependent (figure 5a). The temperature effect on these parameters is clearly reflected in the extraction results. In figure 11, experimental and model results for the separation of PEA at 5 °C and 25 °C have been presented. It can be concluded for the distribution ratios (figure 11a) that the effects of temperature on P and complexation strength counteract, and the overall effect is small. This effect is qualitatively predicted by the model, but because of the large effect of CO_2 uptake on the model results, the prediction was not included in the figure. For the operational selectivity, two effects can be distinguished clearly. The complexation constants are larger at 5 °C than at 25 °C, so the operational selectivity approaches the intrinsic selectivity already at lower extractant excess; and the intrinsic selectivity is higher at 5 °C than at 25 °C, so a larger operational selectivity is reached overall.



(a) (b)

Figure 11: Influence of temperature on (a) distribution ratio and (b) operational selectivity, for phenylethylamine extraction, [PEA] = 2 mM, toluene. In (a), open symbols 25 °C and closed symbols 5 °C, triangles S-enantiomer, squares R-enantiomer. Solid lines in (b) are model predictions.

4.5.4 Influence of pH

The model predicts that the pH has a strong influence on the extent of extraction, the distribution ratio, and a small influence on the operational selectivity (equations 4, 5 and 6). This is caused by a shift in the equilibria: at lower pH, most of the enantiomer is present in the ammonium form, not much free amine is available for transport to the organic phase and subsequent complexation, so the resulting distribution ratios are low. If the pH rises, more enantiomer is present as free amine and more complex can formed; the resulting distribution ratios are higher. Because of the higher loading of the extractant, the operational selectivity decreases slightly. To demonstrate these predictions, experiments were carried out with phenylethylamine and phenylglycinol, using toluene as solvent. For phenylglycinol, the physical partitioning P is so low that the resulting D's approach zero as soon as the pH is lower than 7.5 (figure 12). The solid line in the plot is an independent model prediction, with

the pH at equilibrium as input parameter. It can be seen that the model predicts the behaviour of the system very well. Because of the low values for D, no reliable value for selectivity at lower pH can be given.

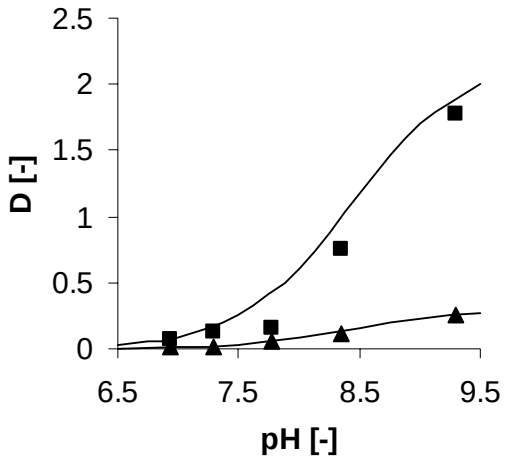
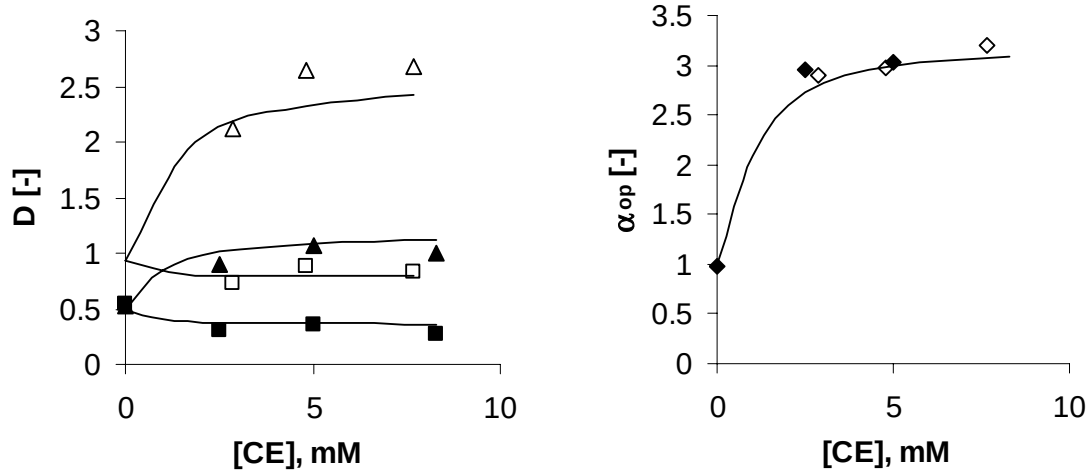


Figure 12: Influence of pH on distribution ratio of PG, [PG] = 2 mM, [CE]= 3 mM, solvent: toluene, 25 °C, pH set with phosphate buffer, triangles S-enantiomer, squares R-enantiomer

For phenylethylamine, similar experimental and model results were obtained: the distribution ratios also drop sharply with a decrease in pH. A second effect was also observed: if some acid is already present in the system, the relationship between D and [CE] changes: the D's no longer rise with [CE] (as in figure 8a and 9a), but the curve flattens off or D even decreases with [CE]. For PEA, experimental data were obtained with 0.8 mM acid and 1.2 mM acid, all with $[PEA]_{ini}$ = 2 mM. The model results and experimental results are given in figure 13.



(a) (b)

Figure 13: Effect of addition of acid (pH decrease) on the extraction of PEA with CE in toluene. [PEA] = 2 mM, [HCl] = 0.8 mM (open symbols) or 1.2 mM (closed symbols); resulting pH 7.5-8.5, T = 5 °C; (a) distribution ratios; triangles S-enantiomer, squares R-enantiomer (b) operational selectivity.

It can be seen that the experimental trends in figure 13 are described well by the model. An explanation for this effect may be that the pH drops when some amine or amino-alcohol is extracted to the organic phase, and the more additional acid is present in the system, the sharper the pH decreases. As the extent of extraction also decreases with decreasing pH, a higher [CE] does not result in higher distribution ratios under these circumstances. It is noteworthy that the predictions for the distribution ratios of PEA in figure 13 are much better than in figure 9a. The presence of the additional acid now dominates the resulting pH in the system.

4.5.5 Extractant and enantiomer recovery by back-extraction

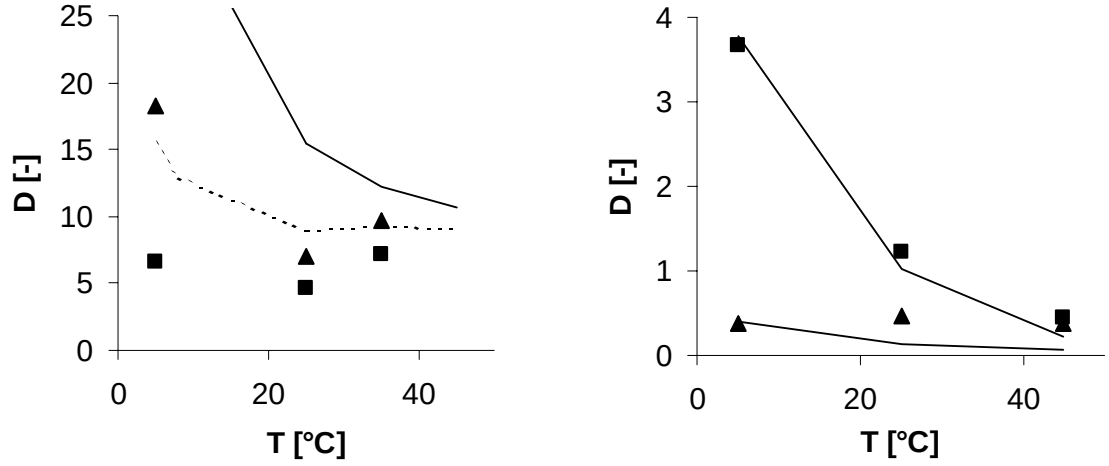
After the chiral separation in the fractional extractor, the enantiomeric product has to be recovered from the loaded organic solution. Back-extraction is a logical operation for this recovery. In the back-extraction unit, the loaded organic phase is treated with an aqueous wash stream of specified temperature and pH. The cleaned organic phase containing the extractant is then recycled to the fractional extractor for re-use.

A decrease in distribution ratio D for both enantiomers may be effected by a temperature increase, a pH decrease or a combination: a temperature rise results in a weaker reaction, and a pH decrease results in lower availability of uncharged amine for complexation. Both back-extraction options, temperature increase and pH decrease, were evaluated experimentally and by model predictions for phenylethylamine and phenylglycinol.

Back-extraction of phenylethylamine and of phenylglycinol by decreasing the pH of the system was successful. If the pH decreases, the distribution ratios decrease as well, as already shown in figure 12 and 13. If pH < 6, the distribution ratios approach zero such that PEA or PG is completely back-extracted to the aqueous phase. The mass balance closed within the measurement error of the HPLC analysis. It is possible to *concentrate* the product stream compared to the feed stream: because of the very low D, all enantiomer can be extracted from the loaded organic phase with a small volume of aqueous wash stream.

The required pH decrease can be effected by addition of dilute acid to the aqueous phase, but salts are produced when the pH is brought back to the original value, so this method is not favoured. A more environmentally friendly method to lower the pH is to dissolve carbon dioxide in the aqueous phase,[19] because the CO_2 can be removed easily by decreasing the CO_2 partial pressure. According to preliminary calculations, a relatively low partial pressure of CO_2 (~ 0.2 bar) is sufficient to reduce the pH in a 2 mM PEA solution to 6. This back-extraction concept was demonstrated to work on labscale by contacting a PEA-loaded CE/toluene solution with water in presence of CO_2. Decomplexation was observed visually from the clear and rapid colour change of the organic layer from deep purple (loaded) to orange (not loaded).

Attempts to back-extract phenylethylamine by a temperature increase failed. A temperature increase results in a weaker reaction, as expected, but also in a larger physical partitioning ratio P, and these effects partly cancel out. The resulting distribution ratio is still quite high (figure 14a).



(a) (b)

Figure 14: Distribution ratios for back-extraction by temperature shift. Both charts: back-extraction with clean milliQ-filtered water, equal volumes aqueous phase/toluene phase, triangles: S-enantiomer, squares: R-enantiomer. (a) Phenylethylamine. Loading conditions: 5 °C, [PEA] = 2 mM, [CE]= 3 mM. Triangles/solid line: S-enantiomer, squares/dotted line: R-enantiomer (b) Phenylglycinol. Loading conditions: 5 °C, [PG] = 2 mM, [CE]=3 mM. Triangles S-enantiomer, squares R-enantiomer. Solid lines: model prediction with P=0.05 (5 °C), P=0.08 (25 °C), P=0.15 (45 °).

Back-extraction of phenylglycinol, which has a much lower physical partitioning ratio than phenylethylamine, could be carried out successfully by a temperature increase. After extraction, portions of the loaded organic phase were contacted with a clean water phase at three different temperatures. In figure 14b, the resulting distribution ratios for back-extraction are reported. It can be seen that the S-enantiomer is already recovered well from the organic phase at a lower temperature than the R-enantiomer; for the R-enantiomer a larger temperature is required to lower the complexation constant sufficiently. For the model fit, it was assumed that the physical partitioning ratio P increases with T, similar to the temperature dependence of P for PEA (figure 5b). It is clear that the temperature dependence of the physical partitioning ratio should be incorporated in the model.

The equilibrium model can be used to describe the back-extraction process, but for a good accuracy of the distribution ratio predictions, the temperature dependence of P should be included in the model. From the experimental data and the model predictions, it can be concluded that a pH decrease is a very effective way to back-extract amines and amino-alcohols from a loaded organic phase. Dissolution of CO_2 in the system is an effective and

'green' way to reduce the pH. For a system with a low physical partitioning ratio P, a temperature shift is also suitable. If a sufficiently large shift in distribution ratio is applied, the product stream is concentrated instead of diluted, compared to the feed composition.

The extractant was recovered successfully as well. After back-extraction with dilute acid, the organic phase was washed at least four times with clean water to remove traces of acid, whereafter the toluene was evaporated, and the extractant was used again for extraction. The performance of the regenerated extractant was the same as of 'fresh' extractant. The extractant could be loaded and recovered several times without loss of activity.

4.6 Direction for optimisation

In the previous paragraphs, it has become clear that both the distribution ratios and operational selectivity can be influenced considerably by adapting the process conditions. From initial calculations with a simple model based on the Kremser equation[20], it is clear that the operational selectivity in one stage is the most important factor in determination of the required number of stages, and that variations in distribution ratios can be compensated (up to certain limits) by adjusting the flow rate ratios. Therefore, the approach seems justified to realise an operational selectivity in one extraction stage close to the intrinsic selectivity by adjusting the process conditions, to adapt the distribution ratios as far as possible and to correct non-optimal distribution ratios with changes in the solvent-to-feed ratio (S/F) and the wash-to-solvent ratio (W/S). The role of distribution ratios and flow rates in a fractional extractor will be the subject of chapter 6.

In table 6, it can be seen that for all components except 2-aminopentane a minimum selectivity of 1.5 could be obtained with toluene as solvent.

Table 6: Highest enantioselectivies measured in this study; [racemic mixture] = 2 mM, no pH buffers, solvent: toluene

Component	T (°C)	$[CE]_{ini}$ mM	D_1 [-]	D_2 [-]	α_{op} [-]
phenylglycinol	25	5	3.0	0.32	9.4
2-aminobutanol	25	4	0.12	0.19	1.6
norephedrine	5	4	2.0	3.0	1.5
2-amino-1-phenylethanol	5	2	1.1	0.7	1.5
phenylethylamine	5	7.7	2.7	0.84	3.2
2-aminopentane	5	1.9	3.0	3.0	1

4.7 Conclusion

The azophenolic crown ether is a versatile and highly enantioselective extractant for chiral separation of amino-alcohols and amines by reactive extraction. The process capacity is good. The influence of process parameters such as temperature, pH and concentrations has been

studied in detail, and these parameters can be used to tune the performance of the extraction system. Toluene and dichloromethane are both suitable solvents. Toluene is preferred to dichloromethane because it is more environmentally acceptable, although the process capacity and versatility is somewhat better in dichloromethane.

Recovery of both enantiomeric products and the extractant has been carried out successfully by back-extraction involving a pH decrease with low-pressure CO_2 or a temperature increase. The extractant could be re-used for chiral separation without loss of activity or selectivity.

The model description based on solving the physical and chemical equilibria in the system is very suitable to understand the system's responses to changes in process conditions. The quantitative description of the operational selectivity is very good, the description of the process capacity is reasonably good if uptake of CO_2 from air is included. The equilibrium model can be used for conceptual design.

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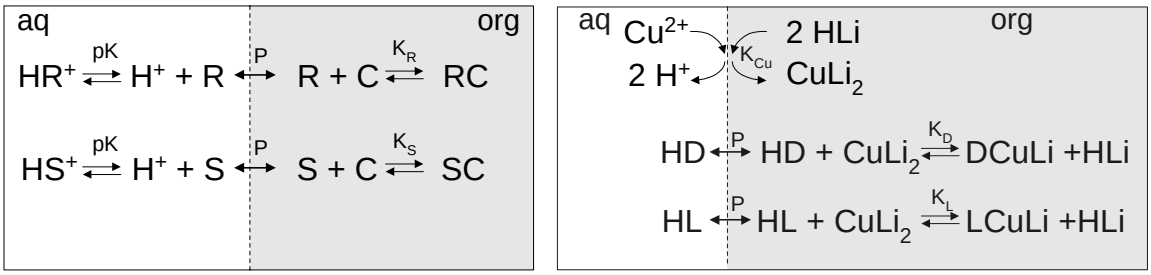
5 Determination of reaction kinetics in reactive extraction for chiral separation of amino acids and amino-alcohols

5.1 Introduction

Two different enantioselective extractants systems were studied in more detail in the previous chapters. For chiral separation of amines and amino-alcohols, an azophenolic crown ether was identified as versatile extractant system. The equilibrium extraction performance was studied experimentally and modelled in chapter 4. A scheme of the reactions is given in figure 1a. Secondly, the Cu(II) complex of N-dodecyl-L-hydroxyproline is a versatile extractant for chiral separation of amino acids. The equilibrium separation of leucine using water/butanol was studied in detail in chapter 2; the main reactions are presented in figure 1b.



(a) (b)

Figure 1: (a) Scheme of physical and chemical equilibria in separation of RS-amine or amino-alcohol with chiral crown ether. HR^+, HS^+: ammonium form of enantiomers; C: crown ether extractant; RC, SC: complexes between crown ether and neutral amine; P; partitioning ratio. (b) main equilibria in separation of DL-leucine. Top part: formation of Cu^{2+}-ligand complex '$CuLi_2$'; bottom part: ligand exchange of ligand 'HLi' for neutral enantiomer 'HD' and 'HL' with proton (H^+) transfer. HLi = N-dodecyl-L-hydroxyproline ligand; DCuLi, LCuLi: ternary complexes.

In both systems, the equilibrium selectivity and capacity are quite good, but for an economically feasible process, the rate of extraction has to be sufficiently large as well. The reaction kinetics and the mass transfer rate may both be rate-determining in a reactive extraction system, and if so, they need to be known separately. The 'true' complexation kinetics are also required for selection and design of process equipment and for a reliable scale-up: a reaction rate that was not limiting in certain bench-scale equipment may become limiting in large-scale equipment with faster mass transfer characteristics. Therefore, knowledge of the 'true' reaction kinetics is important.

5.1.1 Models for extraction kinetics in reactive extraction

Measuring 'true' kinetics in a reactive two-phase system is not trivial. The interpretation of overall extraction rate data in a certain contactor depends strongly on the model that is used to describe mass transfer and reaction kinetics in the system. Basically two fundamentally different model approaches are reported in the literature on reactive extraction: the interfacial reaction model and the homogeneous reaction model.

The interfacial reaction model is used for systems in which each of the reactants is completely insoluble in the other liquid phase. As a result, the location of the chemical reaction is restricted to the interface between the phases. Mass transfer and chemical reaction are described as serial processes: the reactants are transported to the interface, are adsorbed, the reaction takes place at the interface, the products desorb and are transported into the bulk (figure 2a). This model is widely applied for reactive metal extraction processes[1,2] and also for extraction of acids like citric acid[1,3] and penicillin G.[4,5] The reaction rate expressions are typically based on mechanistic considerations. Sometimes the adsorption isotherms are integrated; the resulting rate laws are complex expressions with non-integer reaction orders.

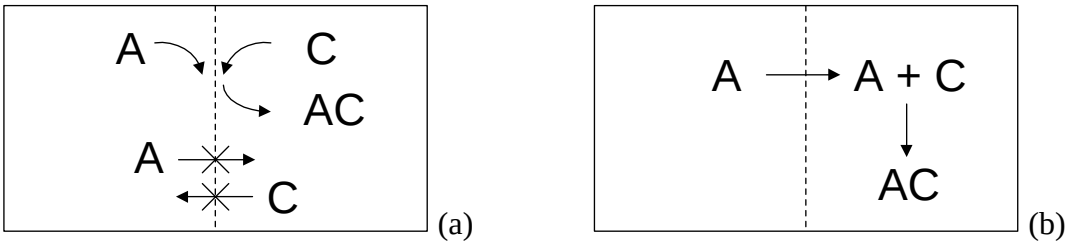


Figure 2: schematic representation of different two-phase reactive extraction systems; compound A is extracted by extractant C. (a) interfacial reaction (b) homogeneous reaction in film and/or bulk

On the other hand, the homogeneous reaction model defined for two-phase reactors ('fluid-fluid' systems, GL or LL) assumes a finite physical solubility of at least one of the reactants in both fluid phases. As a result, the reaction is not located at the interface, but takes place in the film or bulk of one or both of the fluid phases, depending on the relative rates of these processes. Mass transfer and reaction are simultaneous, parallel processes (figure 2b). Preferential adsorption of reagents or products at the interface or the possibility of interfacial reactions is generally not considered. This type of model has been studied extensively for the gas-liquid case, especially for reactive gas absorption.[6,7,8] Although it has not been widely applied to reactive extraction, the extraction of phenyl acetic acid[9] and lactic acid from water by alamine 336 in octanol or decanol[10,11] was studied with this model approach. The reaction rate expressions are typically based on the law of mass action, with integers for the reaction orders.

In fact, the literature on reaction kinetics in reactive extraction systems is not comprehensive. The differences between the two model approaches are not recognised and users of one model do not seem to consider the other approach. This may be caused partly by a difference in background; chemists have a tendency to focus on the chemical reactions without taking into account mass transfer effects quantitatively, whereas engineers tend to simplify reactions and physico-chemical behaviour of the system too much.[12] Users of both types of models apply a regime analysis, in which they vary interfacial area and stirring rate in a model reactor in order to identify the reaction regime. The same experimental result may lead to a completely different interpretation depending on the selected model. For instance, if the extraction rate in a system increases with an increase in interfacial area, but not with an increase in stirrer rate, the interfacial reaction model concludes that the reaction is slow compared to mass transfer[13] ('kinetically controlled', 'plateau zone'), whereas the homogeneous reaction model concludes that the reaction is fast compared to mass transfer[14] ('regime 3', 'E = Ha'). Despite this large difference, both models have been applied to detemine reaction kinetics in chemically related systems, i.e. extraction of organic acids by tertiary amines.[3,9] Finally, although attempts were made to include some 'aqueous phase reaction' contribution in an interfacial reaction mechanism,[15] it does not seem possible to write down the homogeneous reaction model in such a way that the interfacial reaction model is a limiting case, or vice-versa, nor to carry out a simple experiment to distinguish between the two models. The best way to select a model seems therefore to study the physical and chemical properties of the reactive extraction system under study, especially the species solubilities.

In the reactive extraction of the mentioned chiral compounds, there is a clear physical solubility of the enantiomers in the organic phase, and it is therefore not to be expected that the reaction location will be restricted to the interface. The possibility of reaction in the organic bulk phase is correctly described by the homogeneous model. On the other hand, it may be that the enantioselective extractants and/or complexation products show some adsorption at the interface. The chiral ligand N-dodecyl-L-hydroxyproline is an amino acid with a long carbon tail and has a clear surfactant structure, and for crown ethers, surfactant behaviour has also been reported.[16] In that case, the concentration profile near the interface is not described correctly by the homogeneous reaction model. Despite the fact that both these models are not completely applicable to our case, the homogeneous reaction model approach was selected to study the chiral reactive extraction systems further, because it is very unrealistic to locate the reaction at the interface only. If adsorption of the extractant and the products at the interface occurs, it is expected that the contribution of the interfacial reaction will be low compared to the contribution of the homogeneous reaction.

Various model reactors have been developed over the years to study reaction kinetics in two-phase systems.[17] For this study, the modified Lewis cell was selected as model reactor, because the obtained data can be interpreted rather straightforwardly, as the interfacial area and hydrodynamics are known (in contrast with small-scale process extractors, such as the

rotating disc column or the packed bed), and because of its ease of construction and operation (compared to reactors such as the wetted wall column). Finally, the cell can be operated batch-wise, which is advantageous given the small amount of enantioselective extractant that is available.

The regime analysis associated with the homogeneous reaction model[14] is given in the next paragraph (table 2). Regime analysis has proven its usefulness in studies of reaction kinetics in gas-liquid systems, and it was also applied to reactive extraction.[10,11] However, in initial measurements for the chiral reactive extraction systems under study, it seemed that this analysis was not directly applicable. Two possible causes may be stated. The original regime analysis was defined for irreversible reactions, whereas the reactions in reactive extraction systems are generally reversible. Furthermore, the analysis only holds for a case in which the resistance to mass transfer in the non-reactive phase can be neglected. This is also not generally valid in reactive extraction: in contrast with the gas-liquid case, the film layer thicknesses and the diffusion coefficients in both fluid phases are of the same order of magnitude.

The aim of this paper is to study under which circumstances the homogeneous reaction model and regime analysis can be used to describe reactive extraction. Therefore, simulations of the reactive extraction process in a modified Lewis cell are carried out. Secondly, the obtained knowledge will be applied in the experimental study in the Lewis cell of the reaction kinetics in reactive extraction of phenylglycinol and phenylethylamine with the azophenolic crown ether, and the extraction of leucine with Cu(II)-C_{12}Hyp. The scope of this work is to determine the order of magnitude of the reaction kinetics in order to allow equipment selection and conceptual process design.

5.1.2 Homogeneous reaction model and regime analysis

In the homogeneous reaction model, the mass transfer process can be described in various ways. For this work, the two-film model was selected as mass transfer model because of its simplicity, and because the numerical results are similar to those of more realistic models. The two-film model is combined with a definition of the reaction(s) in one or both phases. Here, it is assumed that the reaction of interest takes place in the organic phase only. The mass balance equation for the aqueous stagnant film layer (‘1’) is for each component ‘A’:

$$D_{A,1}\frac{\partial^2[A]_1}{\partial x^2}=0 \qquad (1)$$

in which D denotes the diffusivity. In the organic film ‘2’ (reaction and transport, film model):

$$D_{A,2}\frac{\partial^2[A]_2}{\partial x^2}+R_A=0 \qquad (2)$$

The organic and aqueous bulk phases are assumed to be perfectly mixed, and physical equilibrium is assumed at the interface. In general, this model has to be solved numerically. The resulting expression for the flux J_A is given in equation 3. Note that the enhancement factor E_A is in principle not a constant, but contains information on the reaction rate. For physical extraction, $E_A = 1$. P is the physical partitioning ratio.

$$J_A = K_{ov} \cdot ([A]_{bulk,1} - \frac{1}{P}[A]_{bulk,2}) = \frac{[A]_{bulk,1} - \frac{1}{P}[A]_{bulk,2}}{\frac{1}{k_{L1}} + \frac{1}{Pk_{L2}E_A}} [kmol/m^2/s] \quad (3)$$

Analytical solutions exist for a number of 'limiting regimes', in which specific conditions apply. The dimensionless Hatta number (Ha) and the Hinterland ratio (Al) can be used to characterise these regimes. For a (n,m)-reaction taking place in the organic phase, with rate law $R = -k_{n,m}[A]^n[C]^m$, in which A is the component transported from the other phase and C the organic-phase extractant, Ha_A is given in equation 4; with C present in excess Ha_C is not required.[6] For low conversions, the Hatta number also has this form for a reversible reaction in which the *forward* part of the rate law has the form $R = - k_{n,m}[A]^n[C]^m$.

$$Ha_A = \frac{\sqrt{\frac{2}{n+1} \cdot k_{n,m} \cdot [A]^{n-1} \cdot [C]^m \cdot D_A}}{k_{L2}} \quad (4)$$

The Hinterland ratio (Al) is defined as:

$$Al = \frac{reaction \quad phase \quad volume}{reaction \quad film \quad volume} = \frac{V_2}{O \cdot \delta_2} \quad (5)$$

In this equation, V_2 is the volume of the reactive phase, O is the interfacial area and δ is the thickness of the mass transfer film. For an irreversible (n,m)-reaction, four limiting regimes can be distinguished:[14] very slow reaction, slow reaction, fast reaction and instantaneous reaction. Depending on the regime, the reactive system will respond in a certain way to changes in interfacial area O, mass transfer coefficient k_L (~ stirrer rate) and interfacial concentration $[A]_i$. In a suitable model reactor, the response of the system to these changes can be studied. In this 'regime analysis' it is assumed that the resistance in the non-reactive phase can be neglected ($1/k_{L1} << 1/Pk_{L2}E_A$). The information on the regimes is summarised in table 1. Indicated are the criteria for Ha and Al, the expressions for the volumetric extraction rate N_A ($=J_A \cdot a$), and dependency of extraction rate on specific area a ($=O/V_R$), 'stirrer rate' k_L and interface concentration $[A]_i$.

Table 1: Classical limiting regimes for irreversible reaction[7,14] assuming constant volume.

regime	description	Ha_A	(Al-1)· Ha_A^2	N_A * kmol/m^3/s	dependency on a	stirring	$[A]_i$
1	Very slow reaction	< 0.2	<< 1	$N=V_2 \cdot R_A$	zero	zero	linear
2	Slow reaction	< 0.2	>> 1	$N=J \cdot a= k_{L2} \cdot [A]_i \cdot a$	linear	linear	linear
3	Fast reaction $E_A=Ha$	> 2		$N=J \cdot a= [A]_i \cdot a \cdot \sqrt{(k_{1,1} D_A)}$	linear	zero	linear
4	Instantaneous reaction	> 2		$N=J \cdot a= a \cdot k_{L2,B} \cdot [B]_{org}$	linear	linear	zero

** expression for N_A assuming (1,1)-reaction; other rate laws yield the same dependencies.*

5.2 Simulations with crown ether extractant system

For the simulations, the chemistry of the crown ether system (figure 1a and table 2) was introduced in the homogeneous reaction model equations. The reversible reaction between enantiomer R and crown ether C is known to have 1:1 stoichiometry[18] and is described as R + C ⇔ RC. It is known from previous equilibrium measurements that only R and S partition between the aqueous and the organic phase and that C and RC remain in the organic phase. Therefore, the reaction only takes place in the organic phase (film and bulk). It was assumed that the rate law can be defined according to the law of mass action as a (1,1)-reaction:

$$R_R = k_{1,R} \cdot [R] \cdot [C] - k_{-1,R} \cdot [RC] \qquad [\text{kmol/m}^3\text{/s}] \tag{6}$$

In this equation, $k_{1,R}/k_{-1,R}$ equals the complexation constant K_R. A similar equation is defined for the reaction between the S-enantiomer and the crown ether, with rate constants $k_{1,S}$ and $k_{-1,S}$. From the equilibrium measurements (chapter 4), the complexation constants K_R and K_S of the complexation reactions are known (table 2). The (thermodynamic) intrinsic selectivity is the ratio of the two complexation constants. It is not very likely that there is a kinetic effect in the selectivity, so it is assumed that the ratio of forward reaction rate constants equals the ratio of complexation constants:

$$\alpha_{\text{int}} = \frac{K_R}{K_S} = \frac{k_{1,R}}{k_{1,S}} \tag{7}$$

To find the correct equilibrium compositions, the acid-base dissociation reaction of the amine or amino-alcohol is included in the aqueous phase. The ammonium form of the amine (RH^+) does not partition to the organic phase.

Table 2: chemical data for reactive extraction systems from chapter 2 and 4. Reaction schemes are given in figure 1. All data at 25 °C.

Racemic mixture	phenylglycinol	phenylethylamine	leucine
extractant	crown ether	crown ether	Cu(II)-C_{12}Hyp
solvent	toluene	toluene	butanol
K_1 [m^3/kmol] or [-]	12000 (R)	900 (S)	16.2 * (D)
K_2 [m^3/kmol] or [-]	1200 (S)	330 (R)	7.5 * (L)
α_{int} [-]	10	2.7	2.1
P [-]	0.06	4	0.2
pK [-]	8.5	9.4	I.E.P. 6.0
operating pH	slightly > pK	slightly > pK	5.5-6.0
	no buffer	no buffer	acetate buffer

** ligand-exchange equilibrium*

The Lewis cell geometry was modelled by assuming that the two liquid bulks are ideally mixed, and that all concentration gradients are found in the film layers next to the interface. The film model equations are combined with the reaction rate equation as defined above, boundary conditions and overall mass balances. Experimentally obtained mass transfer coefficients etc. were implemented whenever available. The model was implemented in the gPROMS modelling language (PSE Ltd., London, UK). The numerical solution method is the backward finite difference method (BFDM). The film layer is divided in 10 'slices' for the numerical solution. The concentration profile in time of the transferred component in the non-reactive phase (aqueous bulk) is used for comparison most of the time, because this profile can be obtained experimentally as well.

5.3 Experimental

5.3.1 Materials

R- and S-phenylglycinol (99%), R- and S-phenylethylamine (98%), D- and L-leucine and L-hydroxyproline were obtained from Fluka (Buchs, Switzerland). Toluene, butanol, sodium acetate and copper(II) acetate were obtained from Merck (Darmstadt, Germany). The ligand N-dodecyl-L-hydroxyproline was synthesised according to the method of Takeuchi *et al.*[19] The azophenolic crown ether was manufactured by Syncom b.v. (Groningen, the Netherlands) in a custom synthesis according to Naemura *et al.*[18] Throughout the study, milli-Q filtered water was used (Millipore, Billerica, MA, USA).

5.3.2 Lewis cell design and operation

The modified Lewis cell (figure 3) was manufactured at the glass shop of the University of Twente. The interface is not crossed by any cell internals and is kept flat by the presence of four vertical glass baffles in each phase and by applying moderate stirring rates. Each phase is

stirred by a magnetic stirrer bar, that is mounted between the baffles (Variomag). The mass transfer coefficients at each side of the interface can be influenced separately by changing the stirring rate in that phase. The actual interface of 35 cm^2 can be reduced by floating polymeric balls at the liquid interface[20] (PP, $\rho \approx 900$ kg/m^3, suitable for water/butanol, resulting area ~ 20 cm^2), or by inserting a flexible PP ring at the interface (suitable for water/toluene, resulting area ~ 24 cm^2). The PP balls were kindly donated by Dr. Y. van der Zijpp and Dr. ir. W. Zuiderduin (Artecs, Enschede, The Netherlands). The cell is thermostatted with a Julabo F32 water bath and is equipped with sample ports closed with septa.

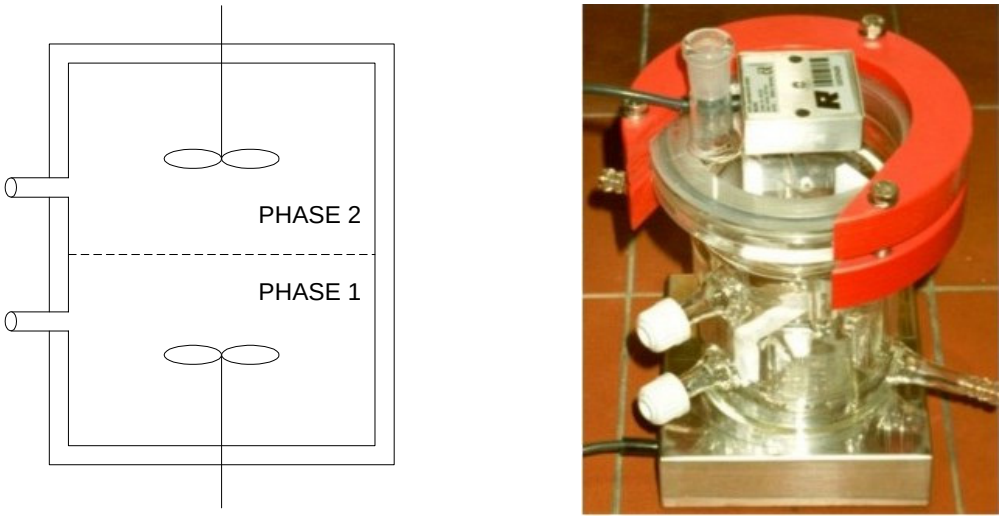


Figure 3: (a) Schematic picture of Lewis cell (b) photo of set-up

To carry out an experiment, 165 mL of the organic phase and 150-155 mL of the aqueous phase are brought in the Lewis cell, containing all reagents except for the compound that is going to be transferred. The solvents are mutually saturated before the measurement. Both liquid phases are stirred at the appropriate temperature (typically 25 °C) for at least 30 minutes, to ensure thermal and physical equilibrium. At t=0, typically 5 mL of the component to-be-transferred dissolved at high concentation in water is entered in the aqueous phase by a syringe. After that, samples are taken from the aqueous phase at appropriate times, usually about 7-10 samples over a time span of 2-3 hours. The amount of samples is limited to avoid substantial volume loss of the aqueous phase. For practical reasons, the pH of the aqueous phase is only determined at the end of the experiment. For reactive extraction of single enantiomers of PEA or PG with the crown ether system, 3 mM of the azophenolic crown ether dissolved in toluene was used as organic phase, and pure water (no buffer) as aqueous phase. At t=0, $[R\text{-}PG]_{ini,aq}$ or $[S\text{-}PEA]_{ini,aq}$ was 0.5 mM. For a physical extraction experiment, the measurement is carried out without extractant present, but otherwise in the same way with $[rac\text{-}enantiomer]_{ini,aq}$ = 2 mM. For reactive extraction of DL-leucine, butanol containing 10 mM $C_{12}Hyp$ is pre-extracted with 0.1 M sodium acetate solution (buffer) containing 5 mM copper(II) acetate. After pre-extraction of Cu(II) to form the Cu(II)-C12Hyp 1:2 complex, the pH of the aqueous phase is 5.5-6.0. At t=0, rac-leucine solution is injected to obtain a concentration of 0.8 mM.

5.3.3 Chemical analysis

The concentrations of both enantiomers of leucine, phenylglycinol or phenylethylamine in aqueous samples were determined by chiral HPLC. As eluent, 0.1 M perchloric acid solution in milli-Q water was used. Post-column derivatization was carried out according to Duchateau *et al.*[21] The HPLC set-up consisted of a Varian 2510 pump, a Crownpak (+) chiral column (Daicel, Japan) cooled in a Varian 510 column oven, an Alltech 301 HPLC pump to deliver post-column derivatization reagent, a reaction coil operating at 40 °C, and a Jasco FP-2020 *plus* fluorescence detector operated at 325 nm excitation and 465 nm emission.
Cu(II) concentrations in water were determined by atomic absorption spectrometry (AAS) on a Varian SpectrAA 110 instrument equipped with SIPS diluter (Varian, Palo Alto, USA). 0.1 M sodium acetate solution saturated with butanol was used as matrix solution.

5.3.4 Data treatment

The outcome of a Lewis cell experiment is a plot of the concentration of the extracted component in the aqueous phase as a function of time. For physical extraction assuming the two-film model, the concentration in the cell of R as a function of time can be found from:

$$-\frac{d[R]_{bulk,1}}{dt} = J_R \cdot \frac{A}{V_{aq}} \qquad (8)$$

The flux J_R follows from the homogeneous reaction model and is given in equation 3. The integrated form of equation 8 combined with equation 3 can be fitted to the experimental results of a physical extraction experiment with K_{ov} as fit parameter. To determine k_{L1} and k_{L2} separately, physical extraction experiments are carried out in the Lewis cell at four different combinations of stirrer speeds in the two phases, namely 140/140, 140/190, 190/140 and 190/190 rpm. The partial mass transfer coefficients ($k_{L1(140)}$, $k_{L1(190)}$, $k_{L2(140)}$ and $k_{L2(190)}$ are obtained by solving the system of four equations for the four K_{ov} values. The diffusion coefficients were estimated with the Wilke-Chang correlation.[22]

The physical extraction of phenylglycinol is so low that it cannot be studied by taking aqueous phase samples, because the concentration decrease in the aqueous phase is almost within the experimental error of the HPLC analysis (~3%), nor by back-extraction of organic-phase samples, because the resulting concentrations are too low to obtain a reliable result. Therefore, the mass transfer coefficients for the physical extraction of PG were estimated from the PEA data, assuming that the film layer thicknesses are the same in both systems.

A reversible reaction is often studied by measuring the initial reaction (extraction) rates, which is only governed by the forward reaction. For a precise determination of the initial extraction rate, it is desirable to use the complete experimental concentration-in-time profile.

Therefore, the experimental results of a reactive extraction run are also fitted to equation 3+8 with K_{ov} as fit parameter. K_{ov} can now be interpreted as '$K_{ov,chem}$' which is the product of $K_{ov,phys}$ and the effective enhancement factor $E_{A,app}$ (see equation 11 in results section). The initial extraction rate can be found from

$$N_{ini,R} = K_{ov,chem} \cdot [R]_{bulk,1} \cdot \frac{A}{V} \tag{9}$$

Fitting of various simulated concentration profiles to this equation resulted in correct results.

5.4 Simulation results

In this paragraph, model simulations of the extraction process in the Lewis cell are presented to study the overall extraction rates that can be expected in this cell for various reaction rate constants under various experimental conditions. The physical and chemical properties of the phenylglycinol-crown ether system (table 2) are used, unless indicated otherwise. The mass transfer resistances are either close to the experimentally obtained values (next paragraph), or they are set to be 'negligible'. First, it is studied under which circumstances enhancement of mass transfer can be observed. Then the applicability of the regime analysis is tested by simulating the effect of changes in interfacial area, 'stirring rate' and interfacial concentration on the extraction rate. Finally, the influence of other reactions such as acid-base dissociation in the system is discussed.

5.4.1 Validation of model

To test if the model results are numerically correct, the simulation model was validated by comparing the model prediction for a case without reaction with the analytical solution for physical mass transfer, using the parameters for phenylglycinol/water/ toluene (table 2). As expected, both concentration profiles were the same. As a next step, the reversible reaction between phenylglycinol and crown ether was incorporated in the model. A set of simulations was carried out with constant mass transfer coefficients and complexation constants, and a increasing reaction rate constant $k_{1,1}$, to pass through the various regimes (table 3). All the trends in the resulting curves were according to the theory in table 3. In further simulations, the parameters in table 3 are used, unless mentioned otherwise.

Table 3: base case parameters for simulations, yielding the four major regimes; $1/k_{L1}$ negligible, k_{L2} (close to) experimentally obtained value, $k_{1,1}$ hypothetical values; reaction R+C= RC with equilibrium parameters for phenylglycinol.

regime	k_{L2} m/s	$k_{1,1}$ m^3/kmol/s	Ha	(Al-1)Ha^2
1	$6.1 \cdot 10^{-5}$	$3 \cdot 10^{-3}$	$2.66 \cdot 10^{-3}$	$6.7 \cdot 10^{-3}$
2	$6.1 \cdot 10^{-5}$	8	0.14	17.9
3	$6.1 \cdot 10^{-5}$	$3 \cdot 10^{3}$	2.66	$6.7 \cdot 10^{3}$
4	$6.1 \cdot 10^{-5}$	$3 \cdot 10^{7}$	266	$6.7 \cdot 10^{7}$

5.4.2 Influence of k_{L1} on effective enhancement factor

The occurrence of enhancement of mass transfer by reaction and the influence of the aqueous-phase mass transfer resistance on the obtained enhancement factor was studied by simulation, leaving out the acid-base dissociation reaction. In each run, the initial extraction rate of component A is calculated from the concentration decrease of A over the first few time intervals. The enhancement factor is determined as the ratio of (initial) reactive extraction rate and the physical extraction rate under the same circumstances:

$$E_A = \frac{N, reactive}{N, physical} \tag{10}$$

The simulations were carried out with and without a substantial aqueous-phase mass transfer resistance, by setting k_{L1} either to $6 \cdot 10^{-5}$ m/s (experimental value) or to a very high value resulting in $1/k_{L1}$ = negligible. To span a range of Ha-numbers, $k_{1,1}$ was varied between $3 \cdot 10^{-3}$ and $3 \cdot 10^{7}$ m^3/kmol/s. The obtained E_A values were plotted as a function of Hatta-number in figure 4.

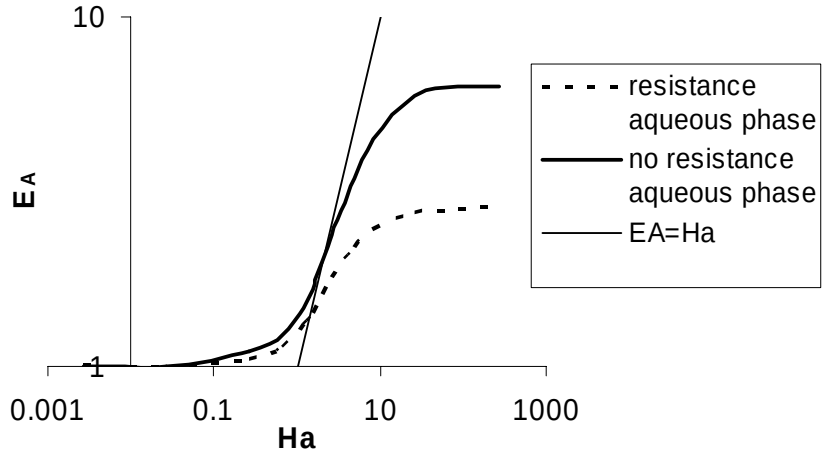


Figure 4: gPROMS simulation; enhancement of mass transfer (E_A) as a function of Hatta number (Ha). Reaction R + C ⇔ RC, $k_{1,1}$ ranges from $3 \cdot 10^{-3}$ and $3 \cdot 10^{7}$ m^3/kmol/s. All cases $k_{L2} = 3 \cdot 10^{-5}$ m/s. 'Resistance': $k_{L1} = 6 \cdot 10^{-5}$ m/s, 'no resistance': $k_{L1} = 1 \cdot 10^{-2}$ m/s.

For the case without aqueous phase mass transfer resistance (solid line in the graph), it can be seen that the characteristic pattern for a reversible reaction[23] is obtained. At low Ha there is no enhancement ($E_A = 1$). A small part of the curve reaches a slope of 1, corresponding with the regime of E_A = Ha (regime 3). At higher Ha values, the enhancement factor reaches a maximum value. Apparently, the maximum enhancement under these circumstances is about 6.5. If there is a substantial aqueous phase mass transfer resistance (dotted line in the graph), it can be seen that the observed enhancement factor is much lower at the same Ha-number, and the maximum enhancement factor is also lower. Furthermore, the dotted E_A vs Ha curve does not reach a slope of 1 anywhere in the graph. In other words, no regime '3' in which E_A = Ha seems to be present. Under these circumstances, there is a difference in the experimentally observable enhancement factor ($E_{A,app}$) and the 'real' enhancement factor E_A which manifests itself only in the reactive phase. The relation between $E_{A,app}$ and E_A can be seen in the following expression for the overall mass transfer coefficient $K_{ov,chem}$ (see also equation 3):

$$K_{ov,chem} = K_{ov,phys} \cdot E_{A,app} = \frac{1}{\frac{1}{k_{L1}} + \frac{1}{P \cdot k_{L2} \cdot E_A}} \qquad (11)$$

If the term containing k_{L1} can be neglected, the effective enhancement factor $E_{A,app}$ equals the 'real' enhancement factor E_A. The larger the influence of k_{L1}, the lower the effect of the 'real' enhancement factor E_A in the overall effective enhancement factor $E_{A,app}$. In a system with a large resistance to mass transfer in the non-reactive phase, the observable enhancement of mass transfer $E_{A,app}$ may disappear altogether.

5.4.3 Influence of k_{L1} and reversibility of reaction on regime analysis

We will now explore the consequences of mass transfer resistance in the aqueous phase and reversibility of the reaction for the results of a classical regime analysis, by simulating the influence of changes in interfacial area, k_{L1} and k_{L2} (stirring rate) and interfacial concentration on the overall initial extraction rate 'N_{ini}' of enantiomer R. This will be repeated for the case with and without a substantial aqueous phase resistance to mass transfer. Unless mentioned otherwise, the parameter values in the simulation have the same values as in the experiments, namely volumes and area of Lewis cell, $k_{L2} = 6.1 \cdot 10^{-5}$, chemical constants from PG system, $[R]_{bulk,1,ini} = 5 \cdot 10^{-4}$ kmol/m^3, $[C]_{bulk,2,ini} = 3 \cdot 10^{-3}$ kmol/m^3. To span all four regimes, the values of the reaction constant $k_{1,1}$ were taken from table 3.

The effects of changes in interfacial area on the initial extraction rate N_{ini} are given in table 4 as the ratio $N_{ini,\ before\ change}/N_{ini,after\ change}$. Similarly, the effects of changes in k_{L1} and k_{L2} are given in table 5 and the effect of changes in $[R]_{bulk,1,ini}$ is given in table 6. For comparison, the effect that is expected based on the conventional regime analysis assuming no resistance in the aqueous phase and irreversible reaction is given as the ratio $N_{ini,\ before\ change}/N_{ini,after\ change}$ this effect is either 'linear' or 'zero' according to table 1.

Table 4: Regime analysis, simulation results: influence of interfacial area change on initial extraction rate N_{ini} (see text). $k_{1,1}$ according to 'regime' in table 3

A, cm^2	k_{L1} m/s	regime	N_{ini}/N_{ini}	Th. ratio*
20 → 35 cm^2	$1 \cdot 10^{-2}$	1	1.67	1
	= no resistance	2	1.72	1.75
		3	1.74	1.75
		4	1.73	1.75
20 → 35 cm^2	$1.1 \cdot 10^{-5}$	1	1.73	1
	= substantial resistance	2	1.73	1.75
		3	1.74	1.75
		4	1.74	1.75

**area factor 35/20 = 1.75; no influence in regime 1.*

Table 5: Regime analysis, simulation results: influence of mass transfer coefficients k_L ('stirring rates') on initial extraction rate N_{ini}. k_L is changed in one phase at a time. 1=aq, 2=org. $k_{1,1}$ according to 'regime' in table 3, A = 35 cm^2

k_{L1}	k_{L2}	regime	N_{ini}/N_{ini}	Th. ratio*
constant, $1 \cdot 10^{-2}$	$6.1 \cdot 10^{-5}$ --> $9.8 \cdot 10^{-5}$	1	1.54	1
= no resistance		2	1.57	1.6
		3	1.18	1
		4	1.57	1.6
constant $1.1 \cdot 10^{-5}$	$6.1 \cdot 10^{-5}$ --> $9.8 \cdot 10^{-5}$	1	1.37	1
= substantial resistance		2	1.38	1.6
		3	1.08	1
		4	1.15	1.6
$1.1 \cdot 10^{-5}$ --> $1.7 \cdot 10^{-5}$	constant, $6.1 \cdot 10^{-5}$	1	1.09	1
	= substantial resistance	2	1.09	1.5
		3	1.15	1
		4	1.28	1.5

**k_{L2} factor = 9.8/6.1 = 1.6; k_{L1} factor 1.7/1.1=1.5; no influence in regime 1 and 3*

Table 6: Regime analysis, simulation results: effect of $[R]_{ini,aq}$ on N_{ini}. All cases $k_{L1} = 1 \cdot 10^{-2}$ m/s, $k_{1,1}$ according to 'regime' in table 3, A= 35 cm^2.

$[R]_{bulk,1,ini}$	regime	N_{ini}/N_{ini}	Th. ratio*
$3 \cdot 10^{-4} \rightarrow 5 \cdot 10^{-4}$ kmol/m^3	1	1.67	1.67
	2	1.67	1.67
	3	1.66	1.67
	4	1.64	1

** $[R]_{ini}$ factor = 5/3 = 1.67; no influence in regime 4*

By comparing the theoretical prediction and the results from the simulation, it is clear that the conventional regime analysis is not directly valid for our system. Some of the deviations can be explained by the reversibility of the reaction and some by the presence of the aqueous phase resistance to mass transfer.

It can be seen in table 5 that the effects of a change in interfacial area by a factor 1.75 are the same for the cases with and without substantial resistance to mass transfer in the aqueous phase. The expected proportional effect of the interfacial area change in regimes 2, 3 and 4 is caused by the fact that mass transfer is a flux-based process in these regimes; if less area is available, the extraction process is proportionally slower, regardless of the location of the main resistance. The unexpected influence of interfacial area on the extraction rate in regime 1 is caused by the use of *initial* extraction rates. In the first part of the extraction process, the bulk of the organic phase becomes physically saturated with A. This part is governed by physical extraction, which is a flux-type process that becomes faster if more area is available. After some time, the bulk is physically saturated and the (slow) reaction determines the overall extraction rate. Now additional area does not influence the extraction rate anymore: both curves are exactly parallel. Along the same line of reasoning, a system in regime 1 will respond *initially* to changes in stirring rate. Therefore, the regime analysis based on *initial* extraction rates cannot be used to identify regime 1. However, in a practical case, regime 1 can be identified easily if the physical and chemical equilibria of the system and the characteristics of the Lewis cell are known.

As for the effect of organic phase stirring rate (k_{L2}), it can be seen in table 5 that the stirring rate has an influence on the initial extraction rate in all regimes, although the magnitude of the effect varies. The unexpected influence of the stirring rate in regime 1 is caused by the use of *initial* extraction rates. For the series with no aqueous phase mass transfer resistance, the influence of k_{L2} is as predicted for regime 2 and 4 (factor 1.57~1.6). This is a logical result, because in this case the resistance is entirely located in the organic phase. The influence of k_{L2} is the smallest in 'regime 3', but the factor is not exactly 1. The system is evidently not exactly on E_A = Ha here (Ha = 2.66 vs. Ea = 2.4), therefore the influence of k_{L2} is small, but k_{L2} is not eliminated completely from the flux expression. In case of substantial aqueous phase mass transfer resistance, no regime E_A=Ha is present (figure 4), so it can be expected

that the influence of k_{L2} is visible everywhere, also in what is supposed to be 'regime 3'. The influence of changes in k_{L2} on the extraction rate in regimes 1, 2 and 4 is smaller here than in the system without mass transfer resistance in the aqueous phase. This is caused by the influence of k_{L1} on the overall resistance. In case of mass transfer enhancement (regime 4), the term ($1/E_A m k_{L2}$) has even less influence on the overall mass transfer resistance. Finally, an improvement in mass transfer in the aqueous film layer (k_{L1}) has an effect in each regime. The largest effect is seen in regime 4, because the organic phase resistance ($1/E_A m k_{L2}$) is the smallest here.

From table 6 it can be seen that the concentration of $[R]_{ini,aq}$ always has an influence on the initial conversion rate, also in regime 4 (note that $[R]_{bulk,1} = [R]_{i,1}$ because of negligible aqueous mass transfer resistance). The deviation from the theoretical behaviour is caused by the reversibility of the reaction: then the maximum enhancement factor is defined by a different equation. For example, for the reversible model reaction R+C = RC, the analytical solution of Olander[6] may be used:

$$E_{A,\infty} = 1 + \frac{D_C}{D_R} \cdot \frac{K_{eq} \cdot [C]_{bulk}}{\frac{D_C}{D_{RC}} + K_{eq} \cdot [R]_i} \qquad (12)$$

It can be seen that even if $E_{A,\infty} >> 1$, $E_{A,\infty}$ is not inversely proportional to $[R]_i$, so $[R]_i$ is not eliminated from the flux equation. As a result, the conventional regime analysis cannot be used to identify regime 4 for a reversible reaction.

Summarising, 'conventional' regime analysis will give erroneous results for reactive extraction in the following cases:

- Regime 1 cannot be found when initial extraction rates are used: the response on area and stirring rate changes are not correct
- For a reversible reaction, regime 4 cannot be identified by studying the response on a $[R]_{ini}$ change
- If mass transfer in aqueous phase is substantial, as is often the case, regime 3 cannot be identified: the response on stirring rate changes is not correct.

5.4.4 Role of acid-base dissociation and other aqueous-phase reactions

Amines and amino-alcohols are bases, and depending on the pH they are present in the aqueous phase as neutral amine or as ammonium ion. Only the neutral amine can partition to the organic phase and react with the extractant, so it can be expected that the extent of acid-base dissociation has an influence on the overall extraction rate. A (very fast) acid-base dissociation reaction of the amine enantiomers was incorporated in the model and simulations of the physical extraction were carried out at pH 8.0-9.4. The pH was kept constant in the model, and the same values for k_{L1} and k_{L2} as in the previous simulations were used. The profiles for $[R]_{tot,1}$ (= $[R]_1 + [RH^+]_1$) have the same shape as the profiles found without acid-

base dissociation, but the lower the pH, the slower the mass transfer process. The profiles were fitted to equation 3 combined with 8 to find the overall mass transfer coefficient $K_{ov,phys}$. It can be seen from the results in table 7 that the $K_{ov,phys}$ determined in this way (as initial flux divided by concentration) is smaller than the $K_{ov,phys}$ used as input in the simulations. This is caused by the lower effective driving force for mass transfer: only the uncomplexed amine or amino-alcohol partitions to the organic phase, but the total aqueous phase concentration is 'measured'. If the initial extraction flux (J_{ini}, kmol/m^2/s) based on the total aqueous amine concentration ($[R_{tot}]_{bulk,1}$) is divided by the neutral amine concentration ($[R]_{bulk,1}$), the correct (input) value for K_{ov} is obtained. The larger the pH, the closer the neutral amine concentration is to the total amine concentration, and the smaller the deviation in $K_{ov,phys}$.

Table 7: Simulation results: influence of pH on determination of $K_{ov,phys}$. Input: $K_{ov,phys}$ = $3.67 \cdot 10^{-6}$ m/s. Total $[R]_{bulk,1,ini}$ = $3 \cdot 10^{-4}$ kmol/m3, pH constant, pK 8.9.

pH	fraction neutral amine $[R]/[R]_{tot}$	J_{ini} for total amine, kmol/m^2/s	$K_{ov,phys}$ as $J_{ini}/[R]_{tot,bulk1,ini}$	$K_{ov,phys}$ as $J_{ini}/[R_{neutral}]_{bulk1,ini}$
8	0.11	$1.2 \cdot 10^{-10}$	$4.1 \cdot 10^{-7}$	$3.6 \cdot 10^{-6}$
9	0.55	$6.0 \cdot 10^{-10}$	$2.0 \cdot 10^{-6}$	$3.6 \cdot 10^{-6}$
9.4	0.76	$8.3 \cdot 10^{-10}$	$2.7 \cdot 10^{-6}$	$3.6 \cdot 10^{-6}$

These model results show that if physical (or reactive) extraction is carried out at a pH near the pK, the actual concentration of the transferred species should be used in calculation of mass transfer coefficients, instead of the total substance concentration (which usually follows from the experiment). If an amine is present in the transferable neutral form for 75%, but the overall amine concentration is used to find $K_{ov,phys}$, the obtained K_{ov} is (1/0.75 = 1.3) times too low.

These results can be extended: other aqueous-phase reactions (such as complexation with metal ions or buffer species, etc.) also have an influence on the fraction of the substance that is present in the transferable form and should also be taken into account. A similar conclusion was drawn by Nymeijer *et al.*[8] for the reactive absorption of ethylene by $AgNO_3$ solution, concerning the availability of Ag^+ ion. If sufficient data are available, the side-reactions may be included in the model. Alternatively, if data are lacking or if the chemistry of the system is complicated, the physical extraction and reactive extraction experiments should be carried out at the same pH and the same concentrations of all additives in the system; then the actual concentration of the transferred species is the same in both experiments, and the initial extraction rates can be compared directly to find the enhancement factor.

5.5 Experimental results

5.5.1 Validation of method & characterisation of Lewis cell

For correct use of the Lewis cell, the range of stirring rates has to be determined in which the interfacial area is constant. To do so, a kinetic experiment has been carried out with a system of which it is known that the reaction is interfacial, a metal ion extraction: the extraction of Cu(II) ion to the organic phase by the extractant C_{12}Hyp in water/butanol. Note that the regime analysis for this system with interfacial reaction is not the same as for a homogeneous reaction: in an interfacial reaction system, any change in interfacial area is visible in the extraction rate. The stirring rates in the organic phase and aqueous phase were set equal. The extraction results are given in figure 5. It can be seen in the plot that the extraction rate is constant for stirring rates below 200 rpm; evidently, the reaction rate is limiting in this case. If the stirring rate is increased to 220 rpm, the extraction rate is increased slightly. At this stirring rate, a small disturbation of the liquid-liquid interface was observed visually as well. From this experiment, it follows that the interface in the cell has a constant area if the stirring rate is kept below 200 rpm. To be on the safe side, a stirring rate of 190 rpm was used as 'high' value, and a stirring rate of 140 rpm as 'low' value. It was assumed that this range of suitable stirring rates can also be used in a water/toluene system.

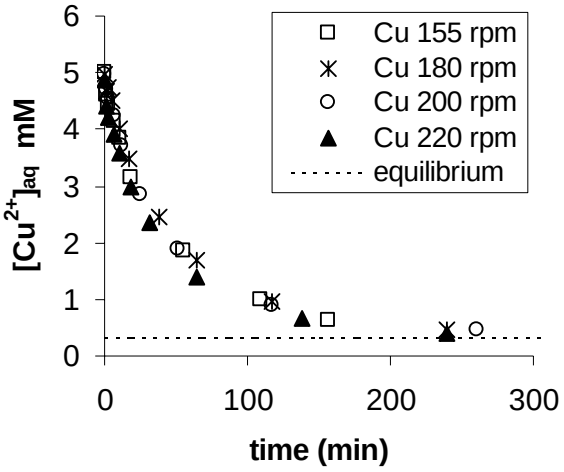


Figure 5: Influence of stirrer speed on copper(II) extraction rate by C_{12}-hydroxyproline (HLi) ligand from water to butanol, Lewis cell; pH = 6.1, 25 °C.

Secondly, it has to be demonstrated that the mass transfer coefficients are indeed increased if the stirring rate is increased from 140 to 190 rpm, as this does not follow from the previous experiment (figure 5). The mass transfer coefficients were measured for the physical extraction of phenylethylamine (PEA) from water into toluene at 25 °C. For further characterisation of the cell, four experiments were carried out at stirrer rates of 140/140, 140/190, 190/140 and 190/190 rpm in the aqueous phase and organic phase respectively. The

resulting graphs are given in figure 6. To show the differences more clearly, the natural logaritm of the concentration decrease was plotted instead of the concentration.

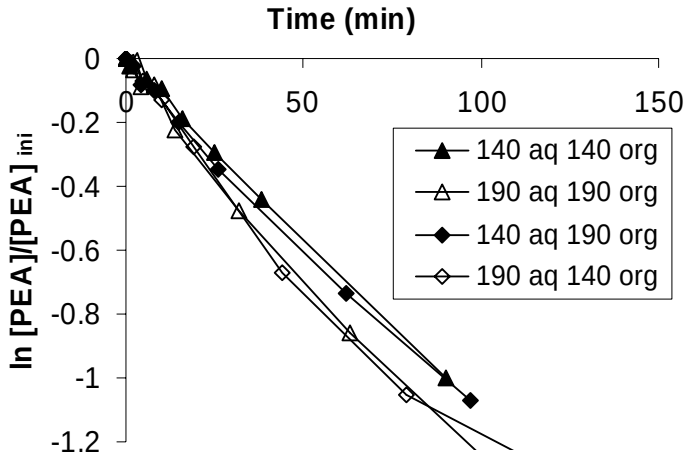


Figure 6: Concentration profiles for physical extraction of PEA from water into toluene, 25 °C. '140' and '190' refer to stirrer rates (rpm) in the respective phases. In axis title, $[PEA]_{tot,bulk,1}$ is abbreviated as [PEA].

It can be seen in figure 6 that the main resistance to mass transfer is located in the aqueous phase: an increase in stirrer speed in the aqueous phase results in an overall larger mass transfer rate, whereas an increase in stirrer speed in the organic phase has hardly any effect. By fitting the concentration profiles to equation 3, the overall mass transfer coefficients for PEA were determined for all four combinations of stirrer rates (table 8). The dissociation degree of PEA and PG was estimated from the experimental pH to be the same in all cases, namely 25 % as ammonium ion and 75 % as free amine. A more precise number could not be obtained, because no data on the pH change during the experiment are available due to practical limitations. It can be seen that the overall mass transfer coefficient is increased with ~ 30% when the stirring rate is increased from 140/140 to 190/190 rpm, which shows that the Lewis cell functions correctly. Based on these overall transfer coefficients, the partial mass transfer coefficients for PEA were estimated as well (table 8). The associated film layer thicknesses (assuming the film model for mass transfer) have been calculated with help of the diffusion coefficients. The mass transfer coefficients of PG are estimated under the assumption that the same film layer thicknesses apply for the physical extraction of PG and PEA (table 9).

Table 8: Experimental overall and partial mass transfer coefficients for physical extraction of PEA in Lewis cell, water/toluene, 25 °C. '1' refers to aqueous phase, '2' to organic phase.

aq. stirring rate (rpm)	org. stirring rate (rpm)	K_{ov}, PEA (m/s)	k_{L1}, PEA (m/s)	k_{L2}, PEA (m/s)	δ_1 (m)	δ_2 (m)
140	140	$1.20 \cdot 10^{-5}$	$1.3 \cdot 10^{-5}$	$6.7 \cdot 10^{-5}$	$5.8 \cdot 10^{-5}$	$4.7 \cdot 10^{-5}$
140	190	$1.23 \cdot 10^{-5}$	$1.3 \cdot 10^{-5}$	$8.5 \cdot 10^{-5}$	$5.8 \cdot 10^{-5}$	$3.6 \cdot 10^{-5}$
190	140	$1.53 \cdot 10^{-5}$	$1.6 \cdot 10^{-5}$	$6.7 \cdot 10^{-5}$	$4.5 \cdot 10^{-5}$	$4.7 \cdot 10^{-5}$
190	190	$1.53 \cdot 10^{-5}$	$1.6 \cdot 10^{-5}$	$8.5 \cdot 10^{-5}$	$4.5 \cdot 10^{-5}$	$3.6 \cdot 10^{-5}$

Table 9: Overall and partial mass transfer coefficients for physical extraction of PG, estimated from data for PEA (table 8) in Lewis cell, water/toluene, 25 °C. '1' refers to aqueous phase, '2' to organic phase.

aq. stirring rate (rpm)	org. stirring rate (rpm)	δ_1 (m)	δ_2 (m)	k_{L1}, PG (m/s)	k_{L2}, PG (m/s)	K_{ov}, PG (m/s)
140	140	$5.8 \cdot 10^{-5}$	$4.7 \cdot 10^{-5}$	$1.2 \cdot 10^{-5}$	$6.4 \cdot 10^{-5}$	$2.89 \cdot 10^{-6}$
140	190	$5.8 \cdot 10^{-5}$	$3.6 \cdot 10^{-5}$	$1.2 \cdot 10^{-5}$	$8.1 \cdot 10^{-5}$	$3.48 \cdot 10^{-6}$
190	140	$4.5 \cdot 10^{-5}$	$4.7 \cdot 10^{-5}$	$1.5 \cdot 10^{-5}$	$6.4 \cdot 10^{-5}$	$3.05 \cdot 10^{-6}$
190	190	$4.5 \cdot 10^{-5}$	$3.6 \cdot 10^{-5}$	$1.5 \cdot 10^{-5}$	$8.1 \cdot 10^{-5}$	$3.71 \cdot 10^{-6}$

The film layer thicknesses are of the same order of magnitude in both phases, which is a result of the similar viscosities and stirring rates. Despite this similarity in film thickness, the resistance to mass transfer of PEA is almost exclusively located in the aqueous film layer (table 8). This effect is caused partly by the smaller diffusion coefficient in the aqueous phase (which results in $k_{L1} < k_{L2}$) and partly by the large partitioning ratio ($m \sim 4$ at this pH). For PG, it can be seen that both phases contribute to the overall resistance to mass transfer with the largest resistance located in the organic phase. This difference with PEA is caused by the much lower value for the physical distribution ratio ($m \sim 0.06$).

5.5.2 Reactive extraction of phenylglycinol with crown ether

The crown ether system was selected for the initial reactive extraction measurements, because the chemistry of the crown ether system is less complicated than the chemistry of the Cu(II)-C_{12}Hyp system. Phenylglycinol was selected over phenylethylamine because the main resistance to mass transfer is located in the reactive phase, so the effect of the reaction with the crown ether is expected to be more clearly visible (equation 11). The concentration profile for the run with 190/190 rpm stirring rate is given in figure 7. Note that the 'fit physical' is based on the mass transfer coefficients from table 9 and the equilibrium distribution ratio for the reactive system. This way of plotting combines the correct *initial* extraction rate for physical extraction (which is not a function of the partitioning ratio) with the correct reactive equilibrium value for a fast comparison, but does not represent any real profile.

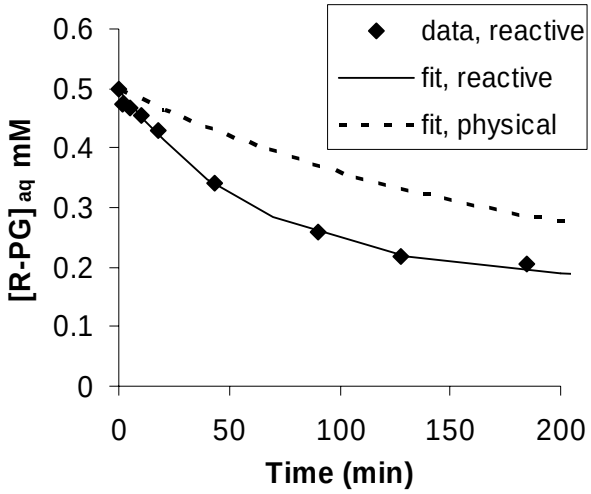


Figure 7: reactive extraction of phenylglycinol; stirrer speed 190/190 rpm in each phase. Prediction of physical extraction from data in table 9.

It can be seen in figure 7 already that the initial reactive extraction rate is larger than the prediction of the rate by physical transport only (at this stirrer rate, for this effective distribution ratio): there is enhancement of mass transfer by reaction. Next, the reactive extraction experiments were repeated with different stirrer rate, a different interfacial area and a different initial PG concentration. In all runs, the experimental data were fitted to the equation 2 to find the fit parameter K_{ov} (equation 1), taking into account that an average 75% of the PG is present as free amine (the transferable form). The results are presented in table 10. The appropriate mass transfer coefficient for physical extraction $K_{ov,phys}$ (from table 9) is indicated as well. In this way, the enhancement of mass transfer by reaction was determined.

Table 10: Reactive extraction of PG at various stirrer rates and interfacial areas.

Case	Stirrers rpm	Area cm^2	$[R\text{-}PG]_{bulk,1,ini}$ $kmol/m^3$	N_{ini} $kmol/m^3/s$	$K_{ov,chem}$ m/s	$K_{ov,phys}$ m/s	E_A
1	140/140	35	$5 \cdot 10^{-4}$	$6.6 \cdot 10^{-8}$	$7.8 \cdot 10^{-6}$	$2.9 \cdot 10^{-6}$	2.7
2	190/190	35	$5 \cdot 10^{-4}$	$8.3 \cdot 10^{-8}$	$1.0 \cdot 10^{-5}$	$3.7 \cdot 10^{-6}$	2.7
3	190/190	24	$5 \cdot 10^{-4}$	$5.7 \cdot 10^{-8}$	$1.0 \cdot 10^{-5}$	$3.7 \cdot 10^{-6}$	2.7
4	190/190	35	$3 \cdot 10^{-4}$	$5.1 \cdot 10^{-8}$	$1.0 \cdot 10^{-5}$	$3.7 \cdot 10^{-6}$	2.7

It is clear from the table that the mass transfer is enhanced by the reaction: in all cases, the initial extraction rate is a factor 2.7 faster than would have been expected for purely physical transport. This result indicates that the reaction is fast or very fast.

Conventional regime analysis is a less suitable tool to study the system, because of the reversible reaction and the non-negligible resistance to mass transfer in the non-reactive phase. Application of conventional regime analysis indeed gives contradictory results. Compare the values for the initial extraction rate (N_{ini}) in table 10 with table 1: the linear

response of the system to a change in stirring rate means that the system is not in regime 1 or 3. A decrease of interfacial area in the cell by 40% resulted in a 40% lower initial extraction rate, which rules out regime 1. Finally, the response of the system to the change in PG-concentration shows that the system is not regime 4 either. So, according to the analysis, the system is in regime 2, but in this regime there is no enhancement of mass transfer. The regime analysis ends in a contradiction, which means that either the regime analysis fails or the system is not in one of the limiting regimes, but somewhere in between.

As the regime analysis alone cannot be used to clarify the behaviour of the PG-crown ether system, the experimental results were compared with simulation results of the homogeneous reaction model. Parameters k_{L1} and k_{L2} from table 9 are used in the simulations. In this way, a maximum enhancement factor of about 3 is predicted. This value is close to the experimentally obtained value for E_A, which indicates that the reaction rate is very fast ('instananeous', regime 4). The almost proportional effect of an increase in stirrer rate (entry 1 and 2 in table 10) also points at 'regime 4' rather than 'regime 3'. For a more direct comparison, an experimental concentration profile is represented in figure 8 along with simulated curves for various reaction rate constants, using the appropriate experimental parameters. The reaction constants were chosen in such a way that they represent all four major regimes (table 3). It can be seen that the experimental data are best represented by the curves with $k_{1,1} > 3 \cdot 10^5$, indicating a very fast reaction. A more precise determination of the reaction rate constants cannot be obtained in this set-up.

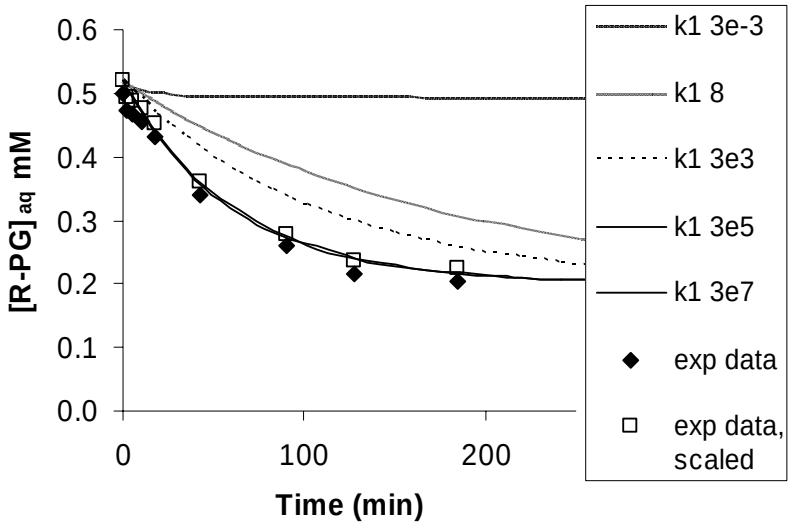


Figure 8: Experimental data and model simulation for reactive extraction of PG, 25 °C, 190/190 rpm, 0.5 mM R-PG, 3 mM crown ether. 'Scaled' experimental data in the figure were scaled slightly to obtain the start and end concentrations from the simulation.

5.5.3 Reactive extraction of PEA

One reactive extraction experiment was carried out with PEA as extracted component. The resulting concentration profile is given in figure 9 along with the (predicted) profile for physical mass transfer only (leading to the same equilibrium value). It can be seen that there is no clear enhancement of mass transfer; E_A is between 1 and 1.2.

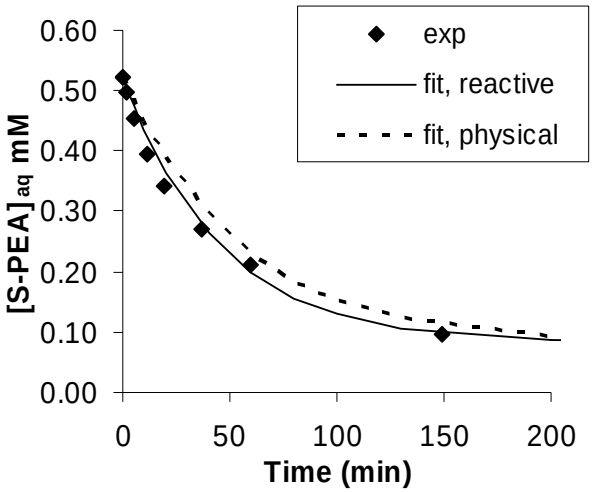


Figure 9: reactive extraction of PEA by crown ether; stirrer speed 190/190 rpm. Prediction of physical extraction from data in table 8.

The absence of mass transfer enhancement suggests regime 1 or 2. However, because the resistance to mass transfer for this system is almost completely located in the aqueous phase, it is just as well possible that the reaction is very fast, but that the enhancement is not observed (equation 11). gPROMS simulations were carried out using the estimated 'acid-base' corrected values for k_{L1} and k_{L2}, the other parameters for PEA and $k_{1,1}$ values from table 3. It can be seen in figure 10 that the experimental concentration decreases faster than the fastest model prediction, which suggests that the acid-base correction was not sufficient. More important, all curves with $k_{1,1} > 8$ (regime 2 and higher) coincide, which means that no (effective) enhancement of mass transfer can be observed in this system anyway.

It can be concluded that the Lewis cell is not a suitable model reactor to study the true reaction kinetics of the PEA system: no conclusion can be drawn on the kinetics because the aqueous phase resistance to mass transfer is too large. These kinetics should be studied in a model reactor in which the aqueous-phase resistance is eliminated or drastically reduced. During the equilibrium experiments of PEA in the highly agigated vessel (chapter 4), it was observed that the colour change which is associated with the complexation reaction took place almost immediately upon addition of the extractant. The colour change was fast both for PG and PEA extraction, and also for the other amines studied. This suggests strongly that the reaction rate for the PEA case is very fast as well.

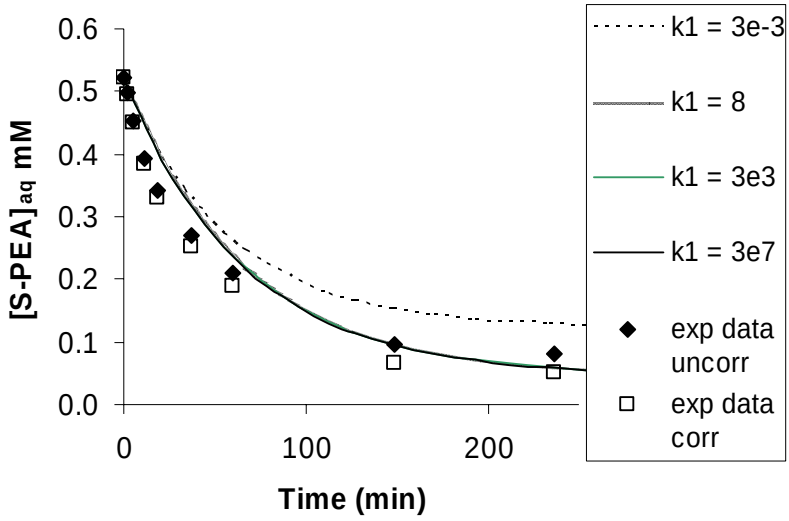


Figure 10: Experimental data and model simulation for reactive extraction of PEA, 25 °C, 190/190 rpm, 0.5 mM R-PEA, 3 mM crown ether. 'Scaled' experimental data in the figure were scaled slightly to obtain the start and end concentrations from the simulation

5.5.4 Reactive extraction of DL-leucine by Cu(II)-C_{12}Hyp

In this part, the reaction kinetics in the reactive extraction of leucine by the Cu(II)-C_{12}Hyp system in water/butanol are studied. The main equilibria in this system are presented schematically in figure 1b. The transferable species is the neutral leucine ion ('HD' and 'HL'), which is a zwitterion. Some of the equilibria involved are presented in figure 2; other side reactions that play a role in this system are aqueous-phase complexations between Cu^{2+} ion, acetate ions (buffer) and leucine anions, zwitterions and cations. More details are reported by Koska & Haynes[24] or can be found in chapter 2. Furthermore, the enantioselective reaction is a ligand exchange reaction, and the liberated ligand HLi will complex again with Cu^{2+} ions from the aqueous phase. It may be clear that the various side reactions in this system complicate the analysis of experimental extraction data: the actual zwitterion concentration cannot be determined. The behaviour of the system may be modelled by assuming that all reactions are instantaneous except for the ligand-exchange reaction, but the resulting model is complicated and suggests a degree of precision that cannot be justified by the available information. Instead, it was decided to carry out physical and reactive extraction experiments under the same circumstances, in terms of buffer concentration, copper concentration and pH, in order to work with equal concentrations of the zwitterion. In this way, an estimate of the reaction rate or regime can be obtained by studying if enhancement of mass transfer is obtained.

The experimental approach was the same as with the crown ether system. The result of a reactive extraction experiment at 140/140 rpm is plotted in figure 11. $K_{ov,phys}$ for leucine in water/butanol at 140/140 rpm stirrer rate was determined to be $6 \cdot 10^{-6}$ m/s. This coefficient

was used to generate the prediction of physical mass transfer rate in figure 12, using the equilibrium distribution ratio of the reactive system.

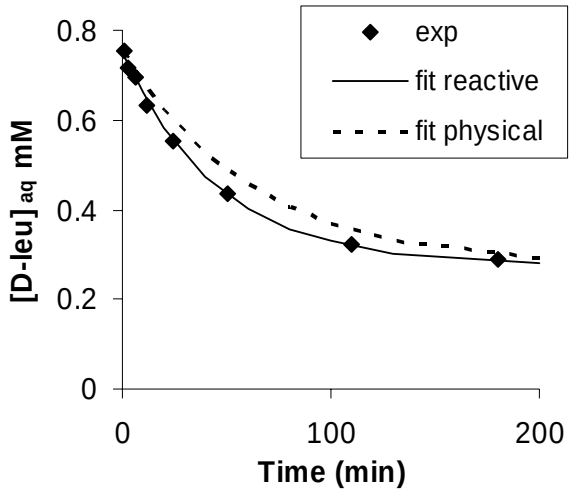


Figure 11: reactive extraction of D-leucine with Cu(II)-C_{12}Hyp system; stirrer speed 140/140 in each phase.

Additional experiments were carried out at larger stirring rates in both phases (190/190 rpm) and with a smaller interfacial area, using the polypropylene balls floating at the interface. The results are presented in tabel 11. As mentioned, the initial flux J_{ini} is based on the total leucine concentration; the presented mass transfer coefficients are therefore uncorrected for the available concentration of neutral leucine. Because the mass transfer coefficients are all the same factor off the correct value, the enhancement of mass transfer can be determined well.

Table 11: reactive extraction results for separation of DL-leucine with Cu(II)-C_{12}Hyp complex, 25 °C, water/butanol.

stirrer (rpm)	area (cm^2)	J_{ini} kmol/m^2/s	N_{ini} kmol/m^3/s	'$K_{ov,phys}$' m/s	'$K_{ov,chem}$' m/s	E_A
140/140	35	$6.2 \cdot 10^{-9}$	$1.3 \cdot 10^{-7}$	$6 \cdot 10^{-6}$	$8 \cdot 10^{-6}$	1.3
140/140	20	$6.2 \cdot 10^{-9}$	$7.7 \cdot 10^{-8}$	$6 \cdot 10^{-6}$	$8 \cdot 10^{-6}$	1.3
190/190	35	$7.9 \cdot 10^{-9}$	$1.7 \cdot 10^{-7}$	$7.8 \cdot 10^{-6}$	$1 \cdot 10^{-5}$	1.3

It can be seen that there is no large enhancement of mass transfer rate under these circumstances, E_A is about 1.3. Given the low value of the physical partitioning (m ~ 0.2) and the about 5 times higher viscosity of butanol compared to toluene, it is very unlikely that the resistance to mass transfer is entirely located in the aqueous phase, as was the case for PEA. With a substantial contribution of both phases to the overall resistance in this system, enhancement of mass transfer by reaction should be clearly visible if the reaction is really fast. It is therefore concluded that the reaction in this system is 'rather slow' compared to the mass transfer: between 'regime 2' and 'regime 3'. The observed response of the system to a change

in area and in stirrer rate is consistent with this conclusion. A more quantitative result in terms of rate constant can only be given if a rate law is assumed, but this was not attempted.

5.5.5 Consequences for equipment design

The reaction rate in the crown ether system is very high. Therefore it is not expected that the reaction rate will be limiting the extraction operation in large-scale equipment. For efficient operation, the aqueous phase mass transfer needs to be promoted, especially for lipophilic enantiomers like phenylethylamine (PEA). This may be done by making an appropriate column design.

On the other hand, the reaction rate in the leucine system may retard the overall extraction rate in a contactor with faster mass transfer characteristics, although no definite conclusions can be drawn based on the available data. Further characterisation of this reaction was not carried out.

5.5.6 Comparison crown ether system-C_{12}Hyp system

The reaction rate in the Cu(II)-C_{12}Hyp system was found to substantially lower than the reaction rate in the crown ether extractant system. This difference may be explained qualitatively by the chemistry of the two systems. The reaction of leucine with the Cu(II)-C_{12}Hyp complex is a ligand-exchange reaction, involving a ligand entering, a ligand leaving and a proton transfer from the entering ligand (leucine) to the leaving ligand (C_{12}Hyp). This is a more complicated reaction scheme than the adduct formation between the amino-alcohol or amine and the crown ether, and may be considerably slower.

5.5.7 Lactic acid/alamine 336 system from literature

It can now be explained why the regime analysis could be used succesfully to study the reactive extraction of lactic acid/alamine 336.[10,11] In these publications, it was observed in the experiments that the extraction rate in this system did not change with stirrer speed. The two phases were stirred with blades mounted on the same stirrer shaft. This means that the resistance to mass transfer in the aqueous phase had to be negligible in this system, although it was not stated explicitely in the original contribution nor determined in a physical extraction measurement. The negligible resistance to mass transfer in the aqueous phase is probably caused by the combination of a very low physical partitioning ratio and a highly viscous organic phase (= octanol or decanol with high concentration of organic extractant). If there is no resistance to mass transfer in the non-reactive phase, regimes 2 and 3 in reactive extraction can be identified with ‘conventional’ regime analysis. In this case, the system turned out to be in regime 3. If the Ha-number and the enhancement factor are estimated from the experimental data, it can be seen that indeed $E_A \sim Ha$. The analysis would have failed in regime 1 (because of the use of initial extraction rates) or in regime 4 (because of the reversibility of the reaction).

5.6 Conclusion

The regime analysis that is used with the homogeneous reaction model fails for reactive extraction in a number of regimes: 'regime 1' cannot be found if initial extraction rates are used; 'regime 3' cannot be identified if the resistance to mass transfer in the non-reactive phase cannot be neglected; and 'regime 4' cannot be identified because of the reversibility of the reaction. However, it is possible to measure if the chemical reaction causes enhancement of mass transfer, by comparing the initial extraction rates with and without reaction. To do so, the physical extraction rate should be high enough to be obtained experimentally, and the fraction of the substance present as the 'transferable' species should be the same in both experiments, i.e. by working at the same pH, additives concentrations and physical properties. After that, information on the chemistry and physical properties of the system (such as partitioning ratio, partial mass transfer coefficients and side reactions) should be used to judge if enhancement of mass transfer would be observable in this system anyway.

This approach was followed for the chiral systems of interest. It was found that the reaction between the chiral azophenolic crown ether and phenylglycinol or phenylethylamine in toluene is very fast in relation to mass transfer. Enhancement of mass transfer was found for phenylglycinol, but could not be observed for phenylethylamine, probably because the main resistance to mass transfer in this system is located in the aqueous phase. The regime of the ligand-exchange reaction applied for the chiral separation of DL-leucine was found to be between 'slow' and 'fast' reaction.

As for the model contactor, it is recommendable in any case to work with equipment in which the partial mass transfer coefficients can be varied separately. In this way, the main resistance to mass transfer can be obtained experimentally. To identify the true reaction kinetics, the Lewis cell is not the most suitable reactor. It would be better to work with equipment in which the resistance to mass transfer in the non-reactive phase is negligible, and in which the resistance in the reactive phase is lower than in the Lewis cell and can be varied over a wider range, such as the rotating diffusion cell or novel, to-be-developed equipment.

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6 Multistage equilibrium modelling of fractional reactive extraction for chiral separation

6.1 Introduction

In the previous chapters, an azophenolic crown ether was identified as a versatile enantioselective extractant for separation of amino-alcohols and amines. The influence of various process parameters on the operational selectivity and distribution ratios in a single stage was studied experimentally for this extractant and a predictive single stage equilibrium model was constructed and validated (chapter 4). The main parameters in this model are the chemical properties of the system (complexation constants K_R and K_S, physical partitioning ratio P and acid-base dissociation constant K_A) and the process conditions (temperature, pH, concentrations of extractant [C] and racemic mixture [rac] and phase ratio Φ). The enantiomer that complexes the most strongly with the crown ether has the largest distribution ratio and is recovered from the extract, whereas the raffinate will contain primarily the less strongly complexed enantiomer. The extent of extraction is characterised by the distribution ratios D_R and D_S for each enantiomer:

$$D_R = \frac{[R]_{org,allforms}}{[R]_{aq,allforms}} = \frac{[R]_{org} + [RC]_{org}}{[R]_{aq} + [HR^+]_{aq}} \tag{1}$$

$$D_S = \frac{[S]_{org,allforms}}{[S]_{aq,allforms}} \tag{2}$$

The operational selectivity α_{op} is defined by the ratio of distribution ratios. Its upper limit is the intrinsic selectivity α_{int}, which is the ratio of the complexation constants:

$$\alpha_{op} = \frac{D_R}{D_S} \qquad \text{assuming } D_R > D_S \tag{3}$$

$$\alpha_{int} = \frac{K_R}{K_S} \tag{4}$$

The equations of the single stage equilibrium model and the experimental validation are already discussed in chapter 4. The influence of the model parameters on D and α_{op} can be summarised as follows:

- The distribution ratios are a complex function of all process parameters. A larger D is caused by larger K_R, K_S, pH, [C], P and (usually) lower T. Especially the pH and [C] influence the D's. The attainable distribution ratios range from <<1 to >>1.

- The selectivity is mainly determined by [C] and K_R and K_S. α_{op} ranges from 1 to α_{int}, α_{int} can be approached closely if $K_R \cdot [C]_{eq} > 10$. The temperature influences the intrinsic selectivity (and the magnitude of K_R and K_S); the other parameters such as [rac] and pH have a small influence on the operational selectivity.

As only a partial separation can be reached in a single stage (figure 1a), staging has to be applied to reach a specified purity and yield. The fractional extraction scheme[1,2] is used to be able to obtain both enantiomers at the required purity (figure 1b). In a fractional extractor, additional degrees of freedom are introduced:

- number of stages N
- location of feed stage
- flow rate ratios S/F and W/S (or W/F), replacing the phase ratio Φ

The influence of the various process parameters on the single stage extraction will be reflected in the behaviour of the multi-stage extractor. To gain insight in the behaviour of a complete extractor, a multistage equilibrium model is constructed in this chapter based on the single stage model developed in chapter 4. Such a model is a rather accurate description of a cascade of mixer-settlers, and can be applied to describe the extraction process in column contactors.

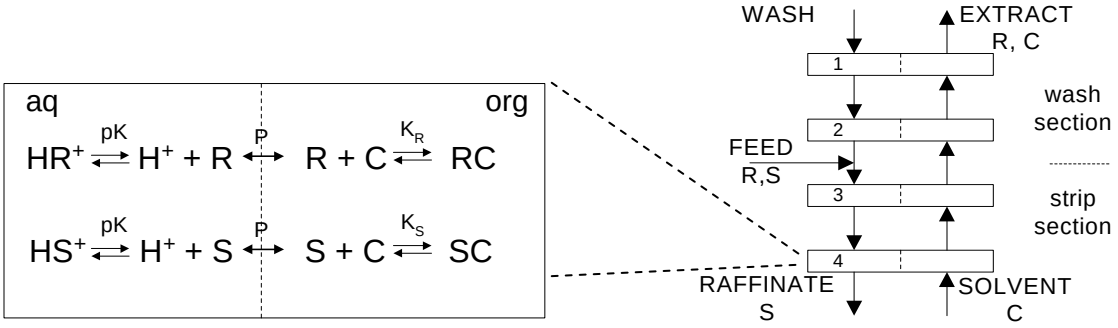
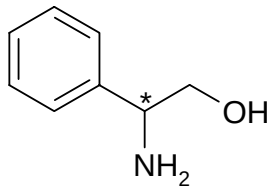
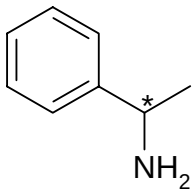


Figure 1: (a) single extraction stage: main equilibria between enantiomers 'R' and 'S' and enantioselective extractant 'C'; (b) fractional extraction scheme, assuming $K_R > K_S$.

From the set of model enantiomers used in previous work (chapter 4), two substances were selected for the multistage modelling study: phenylethylamine and phenylglycinol. These compounds differ in complexation strength with the crown ether (K_R, K_S), in intrinsic selectivity and in physical partitioning. The relevant parameters are presented in table 1.

Table 1: Data on phenylglycinol and phenylethylamine. Partitioning ratios and complexation constants with crown ether in toluene. Parameters at T = 25 °C

Phenylglycinol (PG)		Phenylethylamine (PEA)	
K_R = 12000	[m^3/kmol]	K_R = 330	[m^3/kmol]
K_S = 1200	[m^3/kmol]	K_S = 900	[m^3/kmol]
P = 0.1	[-]	P = 4	[-]
pK_A = 8.5		pK_A = 9.4	
			

From short-cut calculation methods based on the Kremser equation (chapter 2), it is clear that the operational selectivity in one stage mainly determines the required number of stages for a certain product purity. It can be stated that the larger the selectivity, the lower the stages requirement. The capacity of extraction (expressed as distribution ratio) influences the required solvent-to-feed ratio and wash-to-feed ratio, and thus the productivity. This effect is reflected in the extraction factors. In a fractional extractor, the extraction factors in the wash section for each enantiomer ('R' and 'S') are given by:

$$E_R = D_R \cdot \frac{S}{W} \qquad \text{and} \qquad E_S = D_S \cdot \frac{S}{W} \tag{5}$$

and in the strip section:

$$E_R = D_R \cdot \frac{S}{W+F} \qquad \text{and} \qquad E_S = D_S \cdot \frac{S}{W+F} \tag{6}$$

According to literature,[1,2] a 'symmetrical' separation (= equal purity in extract and raffinate) is obtained with the fractional extraction scheme if:

$$\frac{W}{S} = \sqrt{D_R \cdot D_S} \tag{7}$$

This condition implies that the product of the extraction factors E_R and E_S is unity in both sections, with one E larger than unity and the other one smaller than unity, and that the feed is entered in the middle of the extractor. The ratio of E_R and E_S equals the operational selectivity. This condition only leads to a symmetrical separation if E_R and E_S are constant over the extractor, so if the distribution ratios are constant and if the phase ratio is the same in both sections of the extractor, so if W >> F. Under these circumstances, the optimal W/S ratio can be determined directly from the values of D_R and D_S, and extractor design is rather

straightforward. In some literature reports[3,4] on chiral separation by fractional reactive extraction in a pilot set-up, it is attempted to measure the distribution ratios and then set the wash flow to its optimal value by applying equation 7. If the experimental conditions in this literature are considered, the conditions of 'constant D's' and 'constant flow rate ratio in both sections' seem to be fulfilled: a large excess of extractant is used (100-1000), so the variation of D and selectivity from stage to stage is eliminated; and W is large compared to F, so the phase ratio in both sections of the extractor is also more or less constant (W ~ W+F). So, the extraction factors are indeed constant.

However, for a more economical mode of operation than found in the literature cited above, it is desirable to work at higher enantiomer concentrations and minimal excess of extractant (to increase the volumetric capacity, and to limit the inventory of expensive extractant), and to minimise W and S (to allow a larger throughput and/or a better volumetric capacity, and to limit the dilution of the product in the raffinate). In such a real extractor, the extraction factor is determined by the phase ratio in each section, and by the local distribution ratio on each stage; so the local E may vary from section to section and from stage to stage. It is expected that under these conditions the optimal W/S ratio and other process conditions cannot be found from formula (7), but should be deduced from the multistage model.

It is therefore the aim of this chapter to study with the multistage model which combinations of process parameters generate a specified yield and product purity in a multistage extractor. The role of the local operational selectivity and extraction factors are studied in order to understand the deviations from Kremser-like shortcut model predictions. The consequences for the design of a multipurpose extractor will be discussed qualitatively.

6.2 Simulations

Each stage in the multistage model is described by the single stage equilibrium model described in chapter 4. The exiting streams of each stage are assumed to be in equilibrium. The stages in the multistage model are connected countercurrently (fig. 1b): equations of the form eq. 8 and 9 are present for each species i: R, S, HR^+, HS^+, C, RC and SC:

Aqueous stream: $$[i]_{N,out} = [i]_{N+1,in} \tag{8}$$

Organic stream: $$[i]_{N+1,out} = [i]_{N,in} \tag{9}$$

A fractional extractor consists of two sections, a strip section and a wash section. The feed is entered between the sections and is mixed instantaneously with the aqueous stream that exits the wash section. As measure for optical purity of the raffinate and the extract, the enantiomeric excess (e.e.) is used.[5] If enantiomer R predominates in a stream, its e.e. is

defined in equation 10. Note that 'R' and 'S' encompass R and S in all forms (R, HR^+, RC, etc.) in this equation.

$$e.e. = \frac{[R]-[S]}{[R]+[S]} \tag{10}$$

If enantiomer S is present in the largest concentration, the e.e. of the stream is defined by equation 11:

$$e.e. = \frac{[S]-[R]}{[R]+[S]} \tag{11}$$

The yield of the enantiomer R in the extract is given in equation 12. Similarly, the yield of each enantiomer in each stream can be defined.

$$yield_{R,EXTRACT} = \frac{total \quad R \quad extract}{total \quad R \quad feed} \quad \frac{[mol]}{[mol]} \tag{12}$$

The yields and e.e.'s in extract and raffinate are coupled by the mass balance, with two degrees of freedom in steady-state operation. If for instance the optical purity in the extract is specified (such as '0.98 e.e.') as well as the yield (such as '0.99 yield') then the optical purity and the yield of the other enantiomer in the raffinate are fixed as well; and the purity and yield in the raffinate will also be high. Even if one of the two enantiomers is much less interesting than the other one, the optical purity of both enantiomers should be high in their appropriate exit streams, to ensure a good yield of the desired enantiomer. If the purity of the undesired enantiomer is low, it means that much of the desired enantiomer leaves the extractor in this stream. Therefore, the specification for the e.e.'s in extract and raffinate is set to 0.98 each, which results automatically in a yield of 0.99 in each stream of the desired enantiomer.

The process parameters that were studied in chapter 2 and 4 are also studied in these simulations: the temperature, pH and the concentrations of extractant and enantiomer. The concentrations of extractant and enantiomer are expressed as 'extractant excess' (equation 13) and 'concentration level', which is the specific concentration level at a fixed extractant excess.

$$excess \quad extractant = \frac{S \cdot [C]_{solvent}}{F \cdot [rac]_{feed}} \tag{13}$$

Furthermore, the influence of the flow rate ratios S/F and W/S (or W/F; either two ratios are sufficient) are studied. Then, the required number of stages to obtain the required purity of

0.98 e.e. in each stream is studied. The stages are divided evenly over the two sections, unless mentioned otherwise.

Finding process conditions at which the e.e. is 0.98 in each exit stream involves a lot of trial and error. To reduce the simulation time, the influence of process conditions is studied by doing simulations at a fixed number of stages of 4 (2 in each section); the specification of 'e.e. = 0.98 in each stream' is exchanged for 'equal e.e. in each stream'. This specification again ensures the best yield at best purity. It is assumed here that the process conditions which lead to higher e.e. with a fixed number of stages also lead to the lowest stages requirement for a fixed product purity, or at least that all trends observed with four stages hold at higher stage number as well. The validity of this assumption will be demonstrated.

Furthermore, it was seen in the simulations that a single parameter change always results in a lower e.e. in one stream and a higher e.e. in the other stream if all other parameters are kept constant, and there is no unambiguous way to judge if the parameter change results in an improved or deteriorated separation. Therefore, adaptation of the W/S ratio is used after each process parameter change to 'shift' the e.e.'s in extract and raffinate to reach the point where the e.e. in the raffinate equals the e.e. in the extract. This point (new e.e. and new W/S) can be compared with the results for the old parameter setting. In order to explain some of the observed influences of the process parameter changes on the separation, the local operational selectivity and distribution ratios (thus extraction factors) were calculated from the concentration profiles.

After discussing the influence of process parameters on extractor performance, a number of 'combinations of process parameters' are presented which lead to an e.e. of 0.98 in extract and raffinate for separation of phenylethylamine (PEA). This set of 'operating points' will be used as basis for the discussion of an optimal extractor design.

6.2.1 Numerical method

The multistage model is implemented in gPROMS (PSE Ltd., London, UK). All equilibrium conditions and mass balances on all stages are solved simultaneously. This involves solving a large system of non-linear equations. The maximum number of stages that the model can solve is about 80; this number depends slightly on the chosen settings. The pH is assumed to be constant over the extractor and is given as an input value; although calculation of the electroneutrality balance (to identify the pH at equilibrium) is possible, the additional equilibrium condition would result in a larger set of equations for each stage, and therefore in a too severe restriction in the amount of stages that can be calculated.

6.3 Results

6.3.1 Influence of W/S ratio

In figure 2, the influence of a change in W/S ratio on e.e. and yield is presented. It can be seen that at constant S/F, a higher W/S results in a more pure extract stream, but in a less pure raffinate stream. Secondly, the yield of the desired enantiomer in the extract stream decreases with increasing wash stream. With increasing W/S, more of the undesired (less strongly complexed) enantiomer is washed out of the extract, but along with the undesired enantiomer, some of the strongly bound desired enantiomer is also washed back to the aqueous stream. It can be seen from figure 2 that adaptation of W/S can be used to reach the point where the e.e.'s in both streams are equal (indicated with arrows). Because of the mass balance, the yields are equal there as well. As stated, this adaptation of W/S is used after each other process parameter change to find the 'equal e.e.' point which is used to study the influence of the process parameters. Any concentrations indicated are initial concentrations in the respective streams.

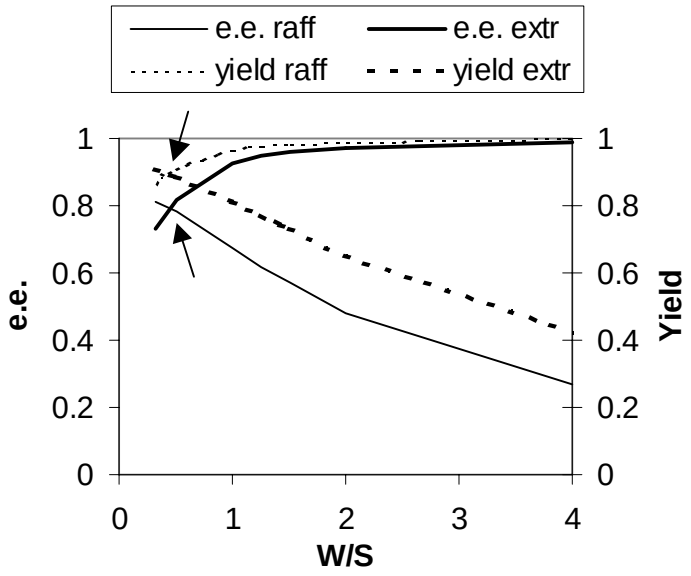
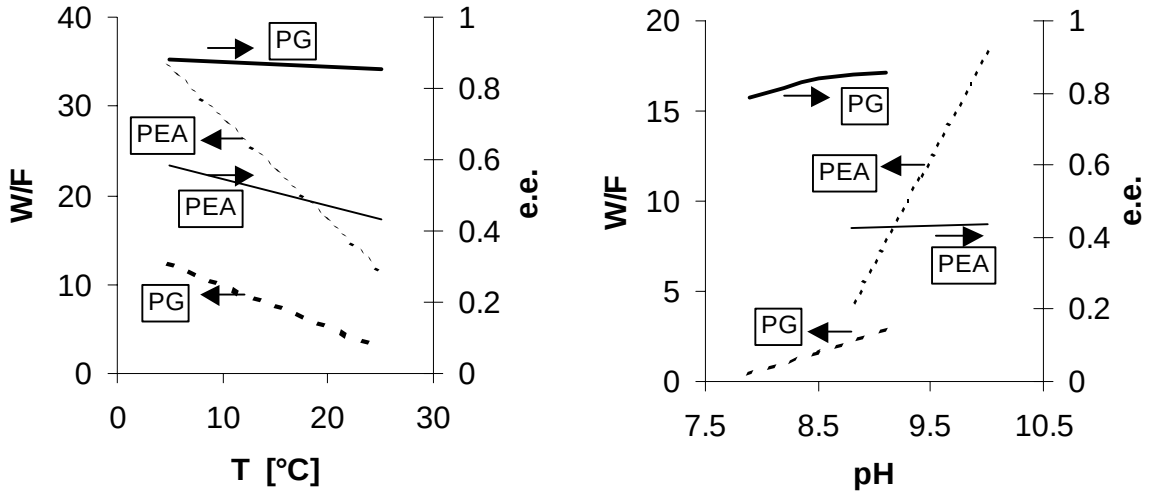


Figure 2: Influence of W/S ratio on e.e. and yield for PG separation, S/F = 1, pH 8.8, T=25 °C, [C]=0.01 M, [rac-PG]=0.01 M, 2+2 stages. Equal e.e./yield point indicated with arrows.

6.3.2 Influence of temperature, pH, extractant excess and concentration level

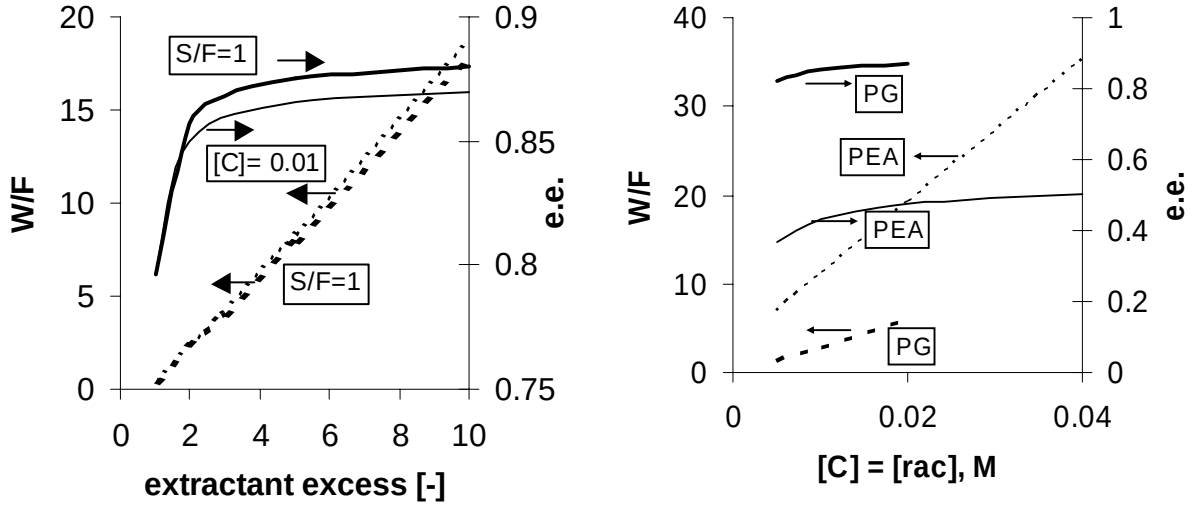
In this paragraph, the effect of various process parameters is presented. Each time, a new process parameter value was used as input, and then W/F was adapted to find the operating point with equal e.e.'s (and equal yields). Only these 'equal e.e.' points are presented in further graphs. The process parameters of interest are resp. temperature (fig. 3a) pH (fig. 3b), extractant excess (either by S/F or by [C]) (fig. 4a) and concentration level (fig. 4b). The

results for S/F and [C] changes are combined in the graph 'extractant excess' to show the similarities.



(a) (b)

Figure 3: (a) influence of temperature on 'equal e.e.' points (W/F, e.e.) for separation of PEA or PG; pH (PEA) =9.4, pH (PG) = 9.1, 2+2 stages, S/F=2 with [rac] =0.01 M and [C]=0.01 M. Lines are trendlines (only two data points were available) (b) influence of pH on 'equal e.e.' points (W/F, e.e.) for separation of PEA or PG, 25 °C, 2+2 stages, S/F=2 with [rac] =0.01 M and [C]=0.01 M.



(a) (b)

Figure 4: (a) influence of extractant excess on separation, PG data only; extractant excess either by increased S/F (then [C]= 0.01) or by increased [C] (then S/F=1), pH 8.8, 2+2 stages (b) influence of concentration level on equal e.e. points (W, e.e.) for separation of PEA or PG, data for 25 °C, 2+2 stages, S/F=2 with [rac] = [C] (= constant extractant excess of 2). pH (PEA) =9.4, pH (PG) = 9.1

Figure 3 and 4 will first be discussed in a general way, because there are many common trends which can all be explained by the same causes. It can be seen in figure 3 and 4 that for both PG and PEA an increase in extractant excess, an increase in pH, a decrease in temperature or a higher overall concentration level all result in an 'equal e.e.' point at a higher e.e. in both streams and at a higher W/S ratio. By each of these changes, the extent of complexation between crown ether and both enantiomers increases: more RC and SC complexes are formed. The yield in the extract increases, but the e.e. decreases; vice-versa, the purity in the raffinate increases, but the yield decreases. If now the wash stream is increased as well, more enantiomer is washed back from the extract, and equal yield and purity are obtained in extract and raffinate. The overall result is a larger W/S requirement to reach this equal e.e. point, and a better e.e. in both exit streams. The increase in e.e. by each of the above process parameter changes can have two main causes.

The first explanation for the increase of e.e. at higher extent of complexation is an increase of operational selectivity in the single stage. This effect can be illustrated by calculating the local operational selectivity for the separation of PEA at three 'concentration levels' for the 'equal e.e.' points from figure 4b. The average operational selectivity over the extractor is given in figure 5 as a function of concentration level. It can be seen that the operational selectivity increases considerably with increasing concentration level. If the extent of complexation increases, the operational selectivity in each stage increases until it approaches the intrinsic selectivity (see also chapter 4). α_{int} is 2.7 under the circumstances given here, indicated by the dotted line. An increase of single-stage operational selectivity from 1.95 to 2.54 has a large effect on the e.e. that can be obtained in a four-stages contactor (figure 4b). Likewise, this selectivity increase will result in a decrease in required number of stages if a product purity is specified.

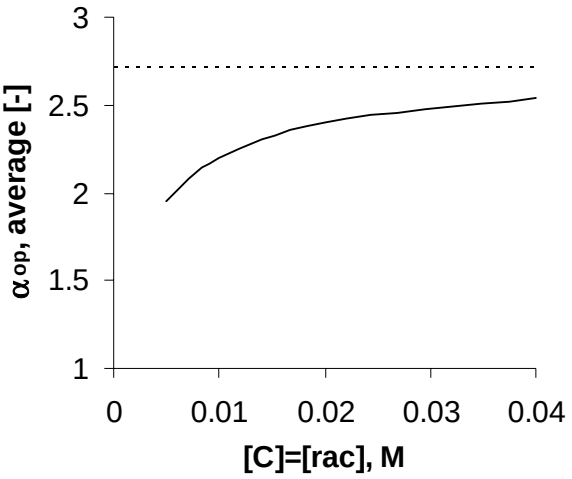


Figure 5: Influence of concentration level ([rac]=[C]) on realised operational selectivity for PEA separation, parameters as in figure 4b. Dotted line: α_{int} = 2.73 (25 °C)

The second cause for an increase of e.e. with certain process parameter changes is the effect of these process parameters on the local extraction factors (equation 5+6) and their variations. The variation of local E's can be demonstrated by comparing the local operational selectivity and extraction factors for separation of PG as a function of pH (figure 3b). In table 2, the local E and α_{op} are presented for two pH values.

Table 2: Local distribution ratios and extraction factors for PG separation, data as in figure 3b. Resulting e.e. = 0.854 for pH 9.1, and e.e. = 0.790 for pH 7.9

pH	9.1				7.9			
section	wash	wash	strip	strip	wash	wash	strip	strip
stage	1	2	3	4	1	2	3	4
D_R	7.32	6.62	5.94	8.03	1.84	1.73	1.66	2.08
D_S	0.80	0.73	0.67	0.87	0.20	0.19	0.18	0.23
α_{op}	**9.11**	**9.02**	**8.92**	**9.18**	**9.11**	**9.05**	**9.02**	**9.20**
Φ	0.70	0.70	0.52	0.52	5.13	5.13	1.44	1.44
E_R	5.12	4.63	3.08	4.16	***9.44***	***8.87***	2.39	2.99
E_S	0.56	0.51	0.34	0.45	***1.04***	***0.98***	0.27	0.33

It can be seen in table 2 that the operational selectivity α_{op} is rather constant along the extractor, whereas α_{op} is even slightly higher for pH 7.9 than for pH 9.1. Therefore, the increase in e.e. at higher pH cannot be explained by an operational selectivity effect. Instead, the local extraction factors should be considered. If on a certain stage both extraction factors are larger or smaller than one, that stage is counter-productive: one of the enantiomers is transported in the wrong direction. If an extraction factor is unity, that stage does not contribute to the purification of that enantiomer. In fact, on each stage for which the product of the extraction factors is not unity, the mass transfer process is not optimal. As a result, the product purity is lowered with each variation in extraction factor and consequently a larger number of stages is required to obtain a certain product purity. The variation of E's with stage number is shown graphically in figure 6.

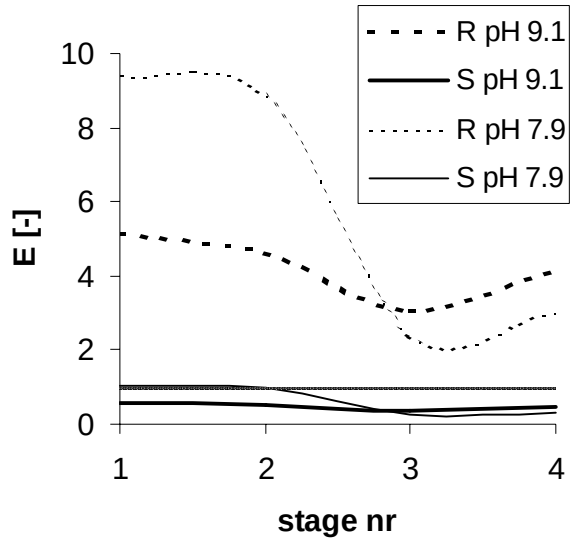


Figure 6: Variation of extraction factor E from stage to stage for PG separation at two pH values. Data from table 2. E=1 indicated by straight line.

In the case of pH 7.9, the variation in local extraction factors is much larger than for pH 9.1. Therefore, some of the local extraction factors have unfavourable values. The large variation in E's is mainly caused by the very small wash flow found at the 'equal e.e.' point for pH 7.9. As a result, the phase ratio in the wash section (=S/W) is very different from the phase ratio in the strip section (=S/(W+F)), and the extraction factors vary largely. This effect is also present at pH 9.1 (W/F=2.86), but much less pronounced. The lower wash flow requirement with lower pH is caused by the lower distribution ratios. Secondly, because of the variation in local concentrations, there is also a variation in distribution ratio from stage to stage (table 2), which adds to the variation in E's. So, variation of E can be caused either by a variation of distribution ratios from stage to stage, or by flow rate ratio variation (i.e. W≠ W+F), or by a combination of both effects. Secondly, the two causes of a change in e.e. (change in operational selectivity and change in local extraction factors) often occur in parallel. Only in some cases one effect is dominant.

It can be concluded from the above that the lowest amount of stages is required if:

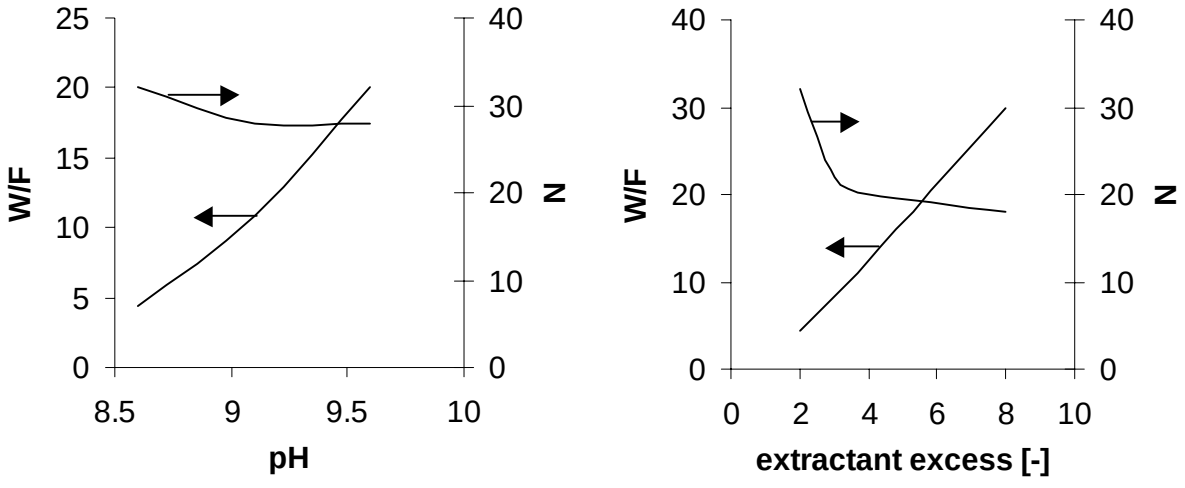
- the operational selectivity is close to the intrinsic selectivity
- there is no variation in extraction factors along the extractor

This situation is approached most closely if the excess of extractant is set high, to ensure high operational selectivity and low variation in E's from stage to stage, and if conditions are chosen that yield high distribution ratios, to ensure a high W/F at operating point and consequently low variation of E between wash and strip section. High distribution ratios can be obtained by choosing a high pH, low T and high extractant excess. On the other hand, operating an extractor at high extractant concentration and high S/F and W/F restricts the process capacity and requires a large inventory of extractant. The issue of designing an 'optimal' extractor will be discussed in the last paragraph.

The differences in physical and chemical properties between PG and PEA are reflected in the main reasons for the e.e. increase with process parameter changes (figure 3 and 4). The complexation between crown ether and phenylethylamine is less strong than between crown ether and phenylglycinol. As a result, for most PG simulations in figure 3 and 4 the operational selectivity is approached within 90% of the intrinsic selectivity, whereas the increase in operational selectivity for PEA upon a process parameter change can be substantial. Vice versa, the distribution ratios tend to be (much) higher for PEA than for PG, mostly because of the large partitioning ratio for PEA. As a result, the required W/F ratio for symmetrical separation is much lower for PG than for PEA. Whereas this lower W/F ratio may be advantageous for the process capacity, it also results in much more variation of the extraction factor in wash and strip section. Therefore, often the increase in PG product purity with a certain change in process conditions can be explained by a reduction of variation in extraction factors over the column, and improved PEA separation can often be explained by an increase in single stage operational selectivity.

6.3.3 Influence of number of stages

An underlying assumption in all of the above is that the process parameter change that causes a higher e.e. in the four-stage extractor will also lead to less stages for a certain product specification. To justify this assumption, it was studied which combinations of process conditions and number of stages yield a product purity of 0.98 e.e. in each exit stream. The influence of pH and concentration level on the W/F ratio and required number of stages are presented in figure 7a and b. A larger list of combinations of process conditions that lead to the same purity result is given in the design paragraph in table 3.



(a) (b)

Figure 7: PEA separation; e.e. = 0.98 in both extract and raffinate, S/F = 2, [rac-PEA] = 0.02 M, 25 °C (a) Influence of pH on W/F ratio and stage requirement N, [C] = 0.02 M (b) influence of extractant excess (via increasing [C], [rac-PEA]=0.02 M), pH 8.6.

It can be seen that the trend observed in figure 3b and 4a for PEA separation in four stages is directly reflected in figure 7a and 7b: lower pH or lower extractant excess results in a lower e.e. in four stages and also in a larger stage requirement to reach e.e. = 0.98. Likewise, the effects of the other process parameter changes as given in the previous paragraph are reflected in table 3. It is therefore concluded that all the effects of process parameter changes predicted for the four-stage extractor can be translated directly to predict the effect on the stages requirement for a given purity specification.

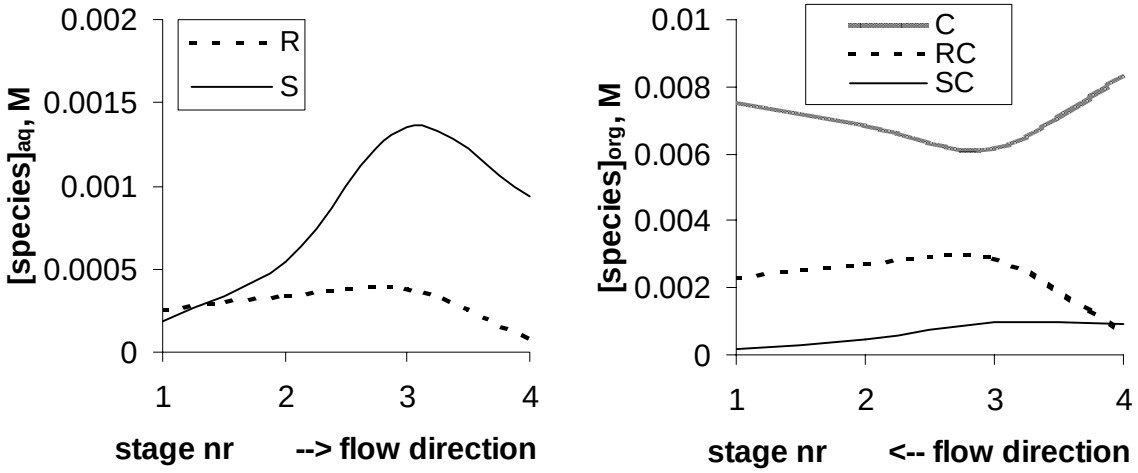
It was observed in the simulations that if there is no excess of extractant over the enantiomers, a full separation can never be obtained in the fractional extractor although a substantial enantiomeric excess may be found in 2+2 stages. Under these circumstances, the extractant will become fully loaded, and adding more stages will not increase the product purity any further. Therefore, the extractant always has to be present in some excess. The minimal excess is around 1.5 for the conditions studied in this paper, but depends on the strength of the interaction and should be studied for each compound separately. This situation differs from conventional (physical) extraction.

6.3.4 Location of feed stage

The location of the feed stage is also a degree of freedom in a fractional extractor. In all simulations so far, the feed stage was located exactly in the middle of the extractor, with an equal amount of stages in the strip section and the wash section. This is the most efficient solution for a symmetrical separation (= e.e. the same in both product streams). However, for a situation in which one enantiomer is the desired product and the other enantiomer is racemised and recycled, an asymmetric product distribution may be preferable, such as 99% e.e. for the desired product and 90% e.e. for the other enantiomer. Such a product distribution can be obtained by using an equal amount of stages in each section and adapting the W/S ratio, or by varying the amount of stages in each section at constant W/S ratio, i.e. by varying the location of the feed stage. Without a detailed economical analysis, it cannot be decided which way (adaptation of feed stage or adaptation of W/S) is most efficient. Therefore no further simulations were carried out.

6.3.5 Reflux

The behaviour of an extractor can be studied in more detail by the concentration profiles. In this way, it was observed that the concentration profile is unfavourable in almost all cases. To illustrate this issue and suggest a solution, concentration profiles for the reactive extraction of PG are given in figure 8. Note that the flow direction for the aqueous phase is from 1 to 4, and for the organic phase counter-currently from 4 to 1. The ammonium ions HR and HS were left out for clarity, [C] is negligible in the aqueous phase and neutral [R] and [S] are negligible in the organic phase.



(a) (b)

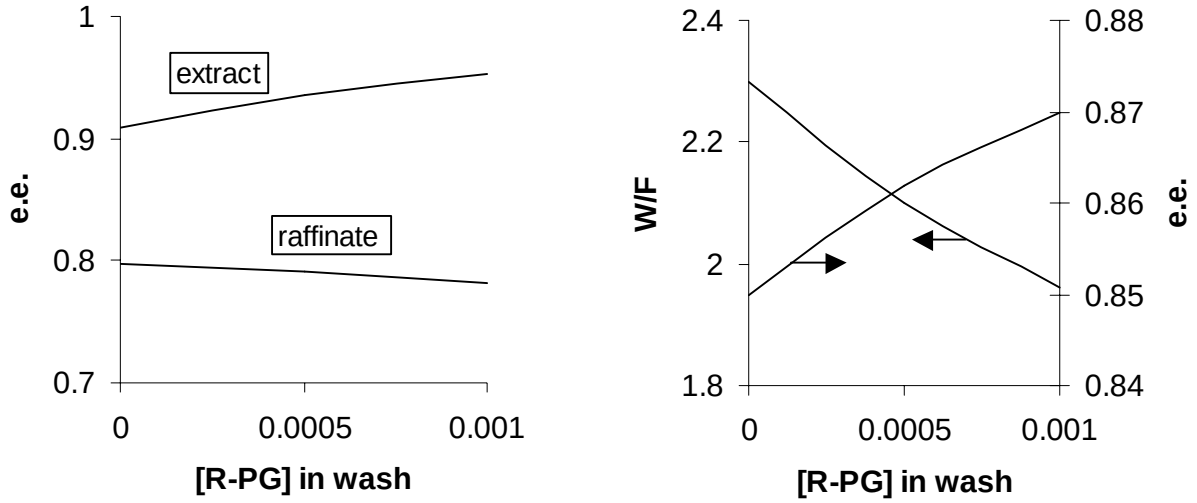
Figure 8: PG separation, concentration profiles over 2+2 stages extractor (a): aqueous phase (b) organic phase. Species: R, S = neutral amine enantiomer, C = extractant, RC and SC = complexes of enantiomer and extractant. S/F=2, W/F=2.3. [C] = 0.01 M, $[rac]_{feed}$ = 0.01 M, 25 °C, pH 8.8

It can be seen in figure 8b that the concentration of complexes RC and SC decreases towards the extract exit (N=1): a considerable fraction of both complexes decomplexes and is washed back from the organic phase to the aqueous phase, inclusing the more strongly complexed enantiomer (R). The entrance of the clean wash stream gives a large driving force for mass transfer towards the aqueous phase, for both enantiomers. This is very inefficient. Introduction of the more strongly bound enantiomer in the wash stream will (partially) prevent the large concentration drop of this enantiomer in the extract, by reducing the driving force for mass transfer for that enantiomer. This mode of operation is called ‘reflux’.

Reflux is a standard part of a distillation design, but in extraction it is not encountered very often. In the FREX operation for chiral separation, the strongest bonded enantiomer is obtained enantiomerically pure in the product stream that exits the back-extraction unit as raffinate 2 (figure 13 in design paragraph), so reflux can be implemented by recycling a small portion of raffinate 2 into the wash stream. The effect of the presence of enantiomer R in the wash stream is that a lower amount of R is washed back from the loaded extract, compared to a clean wash stream. There is no influence on the back-washing of S. As a result, the optical purity in the extract increases. Secondly, the required wash stream flow rate to reach the operating point is reduced slightly, which results in a less dilute raffinate stream.

The effect of reflux on e.e.’s in separation of PG is given in figure 9a for a constant wash stream. It can be seen that the purity in the extract increases, and the purity in the raffinate decreases. So, applying reflux also influences the location of the ‘equal e.e.’ point. New

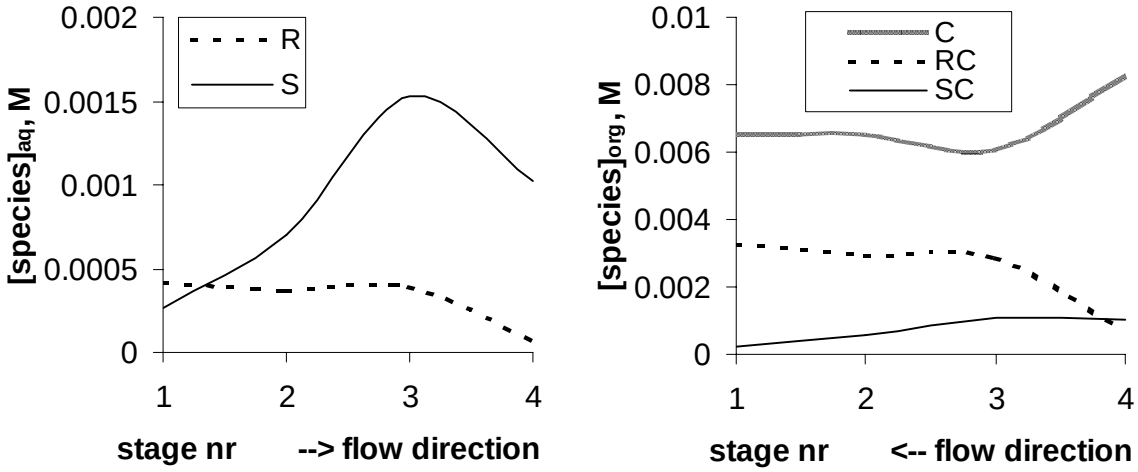
'equal e.e.' points were determined by adapting the wash stream. They are presented in figure 9b.



(a) (b)

Figure 9: (a) Effect of reflux of R-PG in wash stream in PG separation on e.e. in extract and raffinate, fixed W/F =2.3, $[rac]_{feed}$ = 0.01 M, S/F=2 with [C] = 0.01 M, 2+2 stages (b) influence on location of equal e.e. points: W/F and e.e.

The effect of introduction of 0.001 M of [R-PG] in the wash stream on the concentration profiles is shown in figure 10. It can be seen in figure 10b that there is less decomplexation of RC towards the extract exit (stage 1). Because all concentrations are coupled, $[R]_{aq}$ in stage 1 is also higher.



(a) (b)

Figure 10: PG separation, concentration profiles over 2+2 stages extractor (a): aqueous phase (b) organic phase. Species: R, S = neutral amine enantiomer, C = extractant, RC and SC = complexes of enantiomer and extractant. S/F=2, W/F=1.96, [C] = 0.01 M, $[rac]_{feed}$ = 0.01 M, reflux [R-PG]=0.001 M in wash stream.

Because of the improved product purity, it may be expected that the variation in local extraction factors is also reduced by application of reflux. The local D's, α's and E's were calculated from the concentration profiles. It can be seen in figure 11 that although the local E's are influenced by reflux, the variation in E's is not reduced significantly. The most probable cause is the lower actual extractant excess: the same amount of extractant is used for more enantiomer. A lower extractant excess tends to result in more variation of E's over the extractor.

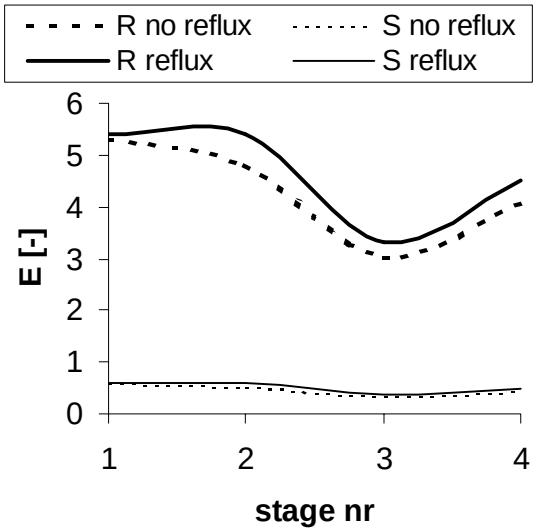


Figure 11: Local extraction factors for PG separation without and with reflux. Data from figure 8 and 10. Refluxed concentration [R-PG] in wash = 0.001 M.

It can be seen in figure 9 that application of reflux indeed results in increased e.e. and decreased W/F, but a rather large fraction of the product has to be refluxed to get an appreciable effect. [R-PG] = 0.001 M in the wash stream at a W/F ratio of 2 means that 40 % of the feed is recycled in the wash stream. For PEA, it was concluded that the effect of reflux is even smaller: for instance recycling of 0.001 M [S-PEA] in the wash stream at a W/F ratio of 4 means recycling 80% of the feed concentration, and it results in an e.e. increase from 0.850 to 0.861 (for 20 stages). The weaker effect of reflux for PEA may be caused by the weaker complexation reaction and stronger physical extraction effect. For PEA separation, the required W/F ratio and number of stages to reach 0.98 e.e. in extract and raffinate are presented as a function of reflux concentration in figure 12. It can be seen that the required number of stages is lowered considerably if reflux is implemented under these circumstances, but note that [S-PEA] = 0.003 in the wash stream at W/F = 3.8 implies that all S-PEA in the feed is recirculated once more through the extractor. Thus, a substantially larger amount of extractant is required to ensure sufficient extractant excess, which may be realised by increasing the S/F ratio.

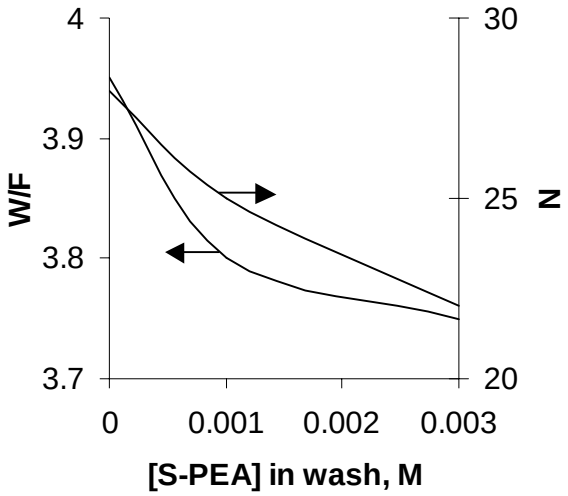


Figure 12: Influence of reflux of S-PEA on W/F ratio and number of stages for specification e.e. = 0.98 in extract and raffinate, S/F=1 with [C]=0.02 M, [rac]=0.01 M, pH 8.6, 25 °C

It is concluded that reflux of the strongly bound enantiomer in the wash stream indeed results in a better e.e. (or lower stage requirement) and lower W/F ratio at the operating point. However, for an appreciable effect a rather large concentration of one enantiomer has to be present in the wash stream, so a large fraction of the product stream (raffinate 2) needs to be refluxed. Especially with a high W/F ratio, application of reflux may be uneconomical. Furthermore, the effective excess of extractant is lowered when reflux is used: the same amount of extractant now has to complex with more enantiomers. Therefore, a sufficient excess of extractant has to be present when reflux is used.

Vice versa, it can be seen in figure 8a or 10a that a large portion of the weakly bound enantiomer is extracted by the fresh organic solution at the bottom stage (N=4). A mode of operation can be envisaged in which an extractant solution partly loaded with the less strongly bound enantiomer enters the system. However, this way of operation was shown by simulation to be ineffective. Loading of the extractant with enantiomer ‘S’ also influences extraction of enantiomer R, because both enantiomers compete for the extractant. The overall result is that a lower excess of extractant is available, so the separation will become worse instead of better.

6.3.6 Back-extraction

To recover the strongly bound enantiomer product and the extractant for re-use, the loaded solvent stream can be treated in a back-extraction unit (figure 13).

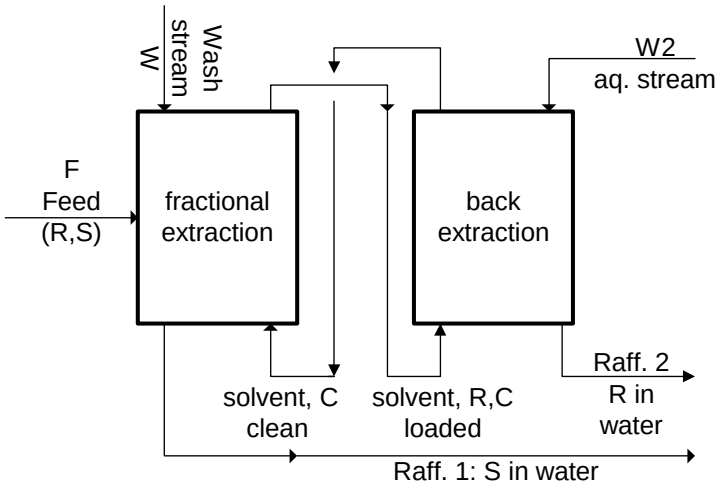
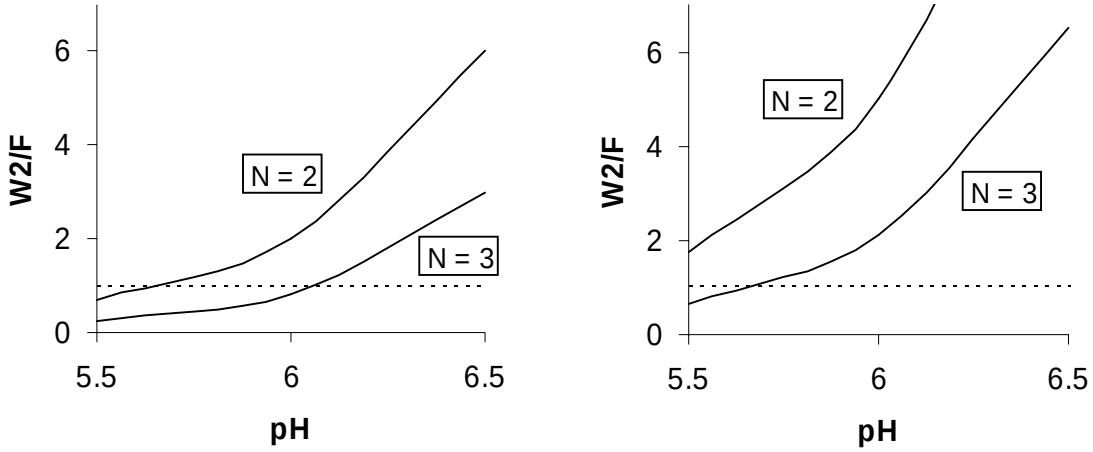


Figure 13: Conceptual flow sheet comprising fractional extraction and back-extraction unit with recycle of solvent stream. Assumption: R is preferentially extracted ($K_R > K_S$)

The extent of back-extraction in the back-extraction unit is determined by the distribution ratios, W2/S ratio and the number of stages. To ensure an efficient back-extraction, the back-extraction unit should be run under process conditions that yield low distribution ratios for both enantiomers: the extraction factor (equation 5) has to be as low as possible, but in any case lower than 1. In chapter 4, it was demonstrated experimentally that (partial) back-extraction in a single stage can be carried out by temperature increase (for components with low physical partitioning) or by pH decrease (for all components). Therefore, back-extraction simulations by pH decrease were done for PEA and PG, and by temperature increase for PG only. The specification was set to a recovery of 99.5 % (sum of enantiomers) from the loaded solvent stream into raffinate 2. The results for back-extraction of PEA and PG by pH shift are presented in figure 14a and b for 2 and 3 equilibrium stages.

It can be seen that the W2/F ratio required for back-extraction decreases with decreasing pH and with increasing number of stages. The lower pH, the lower the resulting distribution ratios for both enantiomers, and the easier the back-extraction. With a higher number of stages, a higher extraction factor (but still E < 1) can be allowed. It is also clear that back-extraction of PEA can be effected at a slightly higher pH than for PG. This is caused by the lower pK_A value for PG and by the stronger complexation between PG enantiomers and the extractant. Finally, a W2/F ratio lower than unity can be used for back-extraction if the pH is sufficiently low in combination with a sufficient number of stages (below dotted line). Under these circumstances, the product in raffinate 2 is concentrated compared to the feed concentration.



(a) (b)

Figure 14: Back-extraction by pH shift, 5 °C, aqueous stream W2 (as ratio to feed F) requirement for 99.5 % recovery. Data for N=2 and N=3 (a) PEA, loading conditions: 5 °C, S/F=1.5, N=21, [C]=[rac]=0.02 M. (b) PG, loading conditions: 5 °C, S/F=1.5, N=8, [C]=[rac]=0.02 M. Below dotted line (W2/F=1), the product is concentrated compared to the feed concentration.

In figure 15, the simulation results for back-extraction of PG by temperature increase is presented. It can be seen that the larger T, the lower the requirement W2/F; however, a considerable W2/F and number of stages is required with temperature shift compared to pH shift. With larger temperature, the contribution of the complexation reaction is eliminated, but the extent of physical extraction increases.

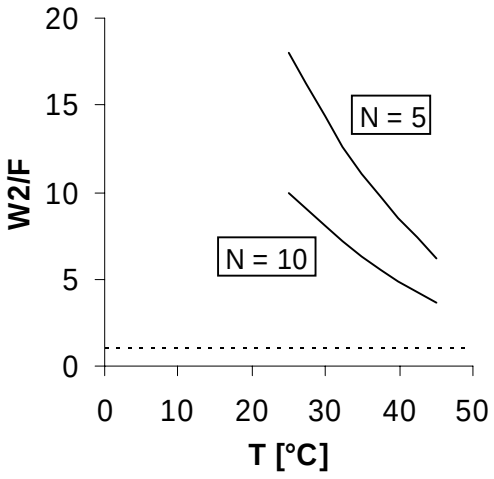


Figure 15: Back-extraction of PG by temperature shift, pH 8.0, aqueous stream W2 (as ratio to feed F) requirement for 99.5 % recovery. Loading conditions: 5 °C, S/F=1.5, N=8, [C]=[rac]=0.02 M. Below dotted line (W2/F=1), the product is concentrated compared to the feed concentration.

For a component in which the physical extraction (partitioning ratio P) is substantial, such as for PEA, back-extraction by temperature shift can only be carried out with a large number of stages and a large W2/F ratio, which is inefficient. From figure 14, it follows that back-extraction by pH shift is very efficient for all amines and amino-alcohols, with high and low physical partitioning. If the pH is sufficiently low, concentration of the product instead of dilution can be realised, which is beneficial for the product quality.

It was estimated and experimentally demonstrated in chapter 4 that the pH shift required for back-extraction (from about 9 to about 6) can be carried out conveniently with low-pressure CO_2. In a process, CO_2 can be removed from raffinate 2 by lowering the CO_2 partial pressure or by stripping with nitrogen. In this way, no salts are produced.

6.4 Design considerations

Conventionally, an extractor is designed to separate one specific compound in the most economical way. According to this method, the overall cost for the extractor is estimated and the various options are compared to find the optimal configuration. For a fractional extractor as described in this chapter, the following can be stated qualitatively: the flow rates determine the 'diameter' size of the extractor; [C] determines the extractant inventory; the number of stages determines the 'height' of the extractor. The flow rate ratio W/S is limited by hydrodynamical constraints. Cooling the system to 5 °C will cost additional money, and lowering the pH may result in salts production.

However, for this process it seems much more interesting to design an extractor that is as flexible as possible instead of optimising the equipment for one specific separation, so to design multipurpose equipment instead of dedicated equipment. In this process, one versatile extractant is used to separate various compounds from the same chemical class (amines and amino-alcohols). The extraction behaviour of all amines and amino-alcohols varies basically in two ways: operational selectivity and capacity (distribution ratio).

As for the capacity (distribution ratios), the extraction factors 'should be average 1' over the extractor, with one extraction factor > 1 and the other < 1, and this can be accomplished by adaptation of the W/S ratio. To work with hydrodynamically acceptable W/S ratios, this means that the distribution ratios should have 'moderate values' (roughly between 0.1 and 10), otherwise, the correct E values cannot be reached. The distribution ratio can be set to these 'moderate' values by adaptation of the process parameters. Especially the pH and the extractant excess are important parameters to set the D's. The influence of process conditions on D and α_{op} is discussed in chapter 4.

The selectivity determines the ease of separation, so the required number of stages. In a given extractor with a fixed number of stages, there is a minimum selectivity to obtain a certain separation; a compound with lower selectivity cannot be separated. This minimum selectivity

can be found from the Kremser equation; and the separation can only be realised if the process conditions are set in such a way that the conditions for the Kremser equation (=constant extraction factors over the extractor) are fulfilled. This can be achieved with high extent of complexation, high W/F and high extractant excess.

Furthermore, it was observed that each variation of the extraction factors over the extractor will decrease the purity in the exit, or result in a higher stages requirement. So, for each case in which the selectivity is larger than the minimum value, conditions can be allowed that result in (more) variation in E's over the column, and these are generally conditions that can be exploited to *increase* the capacity or lower the cost: lower S/F and W/F and/or lower extractant concentration. As illustration, a number of operating points is presented in table 3. Note that the lower S/F and W/F, the larger the possible throughput, and the lower [C], the lower the inventory of expensive extractant. Although this list contains the most important options, it can be extended almost infinitely.

Table 3: Operating points for PEA separation, for a required e.e. = 0.98 in raffinate and extract, [rac-PEA] = 0.02 M. N is total of stages, evenly distributed over the 2 sections.

T (°C)	S/F	W/F	[C] in S	pH	N
5	2	17	0.02	8.6	17
5	1.5	9	0.02	8.6	21
5	1.5	11.8	0.04	8.1	16
5	1.5	3	0.02	8.1	24
5	1.8	4.7	0.02	8.1	20
25	2	20.1	0.02	9.6	28
25	2	10.9	0.02	9.1	28
25	2	4.4	0.02	8.6	32
25	2	57.5	0.04	9.6	19
25	2	12.6	0.04	8.6	20
25	1	3.95	0.04	8.6	28
25	1	18.2	0.04	9.6	26
25	4	61.5	0.02	9.6	20
25	2	30	0.08	8.6	18
25	2	8.4	0.03	8.6	22
25	2	2.8	0.03	8.1	25

Table 3 can be considered as an illustration of the flexibility of FREX. If a fractional extractor with 25 theoretical stages is available, there is still a variety of options to separate PEA with the required purity. If the concentration of crown ether is also already set, still F/S and W/S can be adapted as well as the operating temperature and the pH. If for a certain PEA batch the purity requirement is higher than usual, the process can be run at lower temperature or with higher S and W streams, yielding a better purity at a smaller throughput. And if a different

amine or amino-alcohol has to be treated that shows a lower single-stage selectivity than PEA, the required purity may be reached by decreasing the temperature and increasing the excess of extractant.

The Kremser solution will give the minimal stages requirement for a certain selectivity to reach a required purity (N_{min}). For PEA separation, N_{min} is about 18 stages at 25 °C and about 15 stages at 5 °C. (Note that N is the total of stages; 18 stages means 9 stages in each section). If these numbers are compared with the data in table 3, it can be seen that most options require beween 10 and 60 % more stages than the minimum number predicted by the Kremser equation; the more stages, the lower the S, W or [C] requirement, or, the higher the capacity will be for the same extractor diameter. For an e.e. of 0.98 in both product streams, the number of stages from the Kremser solution, and the range of 10% - 60% as a function of operational single-stage selectivity are given in figure 16.

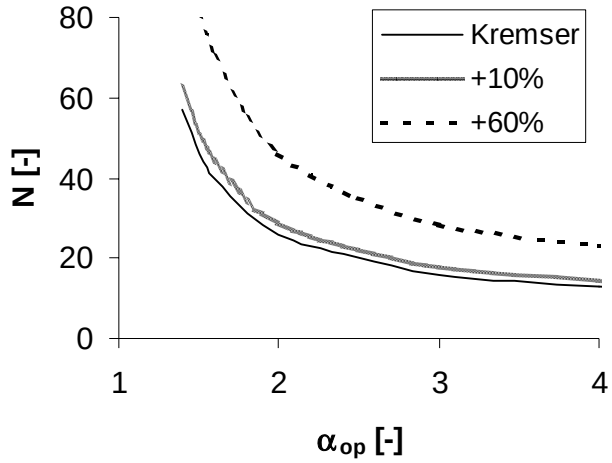


Figure 16: Influence of single stage operational selectivity on required number of stages, for e.e. 0.98 in raffinate and extract. Minimum number by Kremser equation. Ranges of +10% and +60% additional stages (see text). N is divided evenly over the two sections.

So, if 50 stages (total of both sections) are available, all systems with $\alpha_{op} > 1.5$ can be succesfully separated, and if 30 stages are available, all systems with $\alpha_{op} > 2.0$ can be succesfully separated. If a selectivity higher than the minimum value is present, an option with higher stages requirement and 'higher capacity' process parameters can be used to increase the process capacity. If reflux is implemented, the required amount of stages can be decreased by 10-20%. The 'cost' of reflux is a (large) loss in capacity, because a substantial fraction of raffinate 2 has to be refluxed. Therefore, reflux is probably only interesting for a separation in which the specification in purity cannot be met without reflux, and only a reduction of ~ 10% of the stages requirement seems to be feasible. This means that the number predicted by the Kremser model can be considered as a realistic N_{min}. In table 4, ranges for the required number of stages for separation at 0.98 e.e. are presented for the 5

model amino-alcohols/ amines that were successfully separated in chapter 4. The estimation is based on the operational selectivity found in the single stage equilibrium experiments.

Table 4: Ranges for required number of stages N for the target enantiomers, based on experimental α_{op} (chapter 4). N_{min} from Kremser equation; N_{max} is 60% more stages.

substance	T (°C)	solvent	realised α_{op} [-]	N_{min} = $N_{Kremser}$	N_{max}
phenylglycinol	25	toluene	9.4	8	14
2-aminobutanol	25	toluene	1.5	46	81
2-aminobutanol	5	CH_2Cl_2	3.3	15	26
2-amino-1-phenylethanol	5	toluene	1.5	46	81
norephedrine	5	toluene	1.5	46	81
norephedrine	5	CH_2Cl_2	1.8	31	55
phenylethylamine	25	toluene	2.5	20	35
phenylethylamine	5	toluene	3.2	16	28

6.5 Conclusion

The influence of changes in process parameters (pH, T, concentrations) were predicted with the multistage equilibrium model for reactive extraction of phenylglycinol and phenylethylamine. The purity and yield can be improved by each measure that results in a higher extent of complexation, i.e. higher extractant excess (by increasing extractant concentration or higher S/F ratio), higher concentration level, higher pH and lower temperature; but in all cases a higher W/F ratio is required as well to obtain a good yield and purity in both product streams. The increase in product purity can be explained either by an increase in single-stage operational selectivity, or by a reduction of variation in extraction factors along the extractor, or by a combination of these effects.

Implementation of reflux by feeding a portion of the strongly binding enantiomer in the wash stream is advantageous as it results in higher product purities (or less stages) at a slightly smaller W/F ratio. The ‘cost’ of reflux is a loss in capacity and a higher requirement for excess of extractant. Reflux seems the most interesting for compounds that are difficult to separate because of a low single stage selectivity.

Recovery of product and extractant by backextraction can be done by pH shift or temperature shift. A pH decrease results in a (much) lower concentration of the extractable species, and is an efficient back-extraction method for both compounds studied; concentration of the second raffinate instead of dilution can be realised if the pH is lower than about 6. Back-extraction by a temperature increase is much less effective and does not result in concentration of the second raffinate.

The flexibility of the fractional reactive extraction process was demonstrated by presenting the various process options that can be used to yield a certain product specification. The more equilibrium stages are available above the minimum number predicted from the Kremser-based shortcut model, the higher the process capacity. If a fractional extractor is available with 50 stages (25 stages per section), all of the enantiomers that were separated with a minimum single stage selectivity of 1.5 (chapter 4) can be separated with enantiomeric excess 0.98 in each stream.

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7 Fractional reactive extraction pilot experiments in hollow fiber membrane modules

7.1 Introduction

In the previous chapters, an azophenolic crown ether was identified as a versatile enantioselective extractant to separate various chiral amines and amino-alcohols. The single-stage physical and chemical equilibria of this extractant system were studied experimentally and modelled in chapter 4. If a fractional extractor is compared with a single extraction stage, basically three additional degrees of freedom are present: the number of stages, the solvent-to-feed (S/F) ratio and the wash-to-solvent (W/S) ratio. A multistage equilibrium model was constructed based on the single stage description and used to study these degrees of freedom in chapter 6.

The aim of this chapter is the practical demonstration of the chiral separation of phenylglycinol and phenylethylamine by fractional reactive extraction in a pilot set-up, by determination of the number of equilibrium stages that can be realised in the pilot, experimental study of the influence of S/F and W/S ratio on the separation, and comparison of the experimental observations with the predictions of the multistage equilibrium model. The two compounds PEA and PG that are studied in this chapter are presented in figure 1.

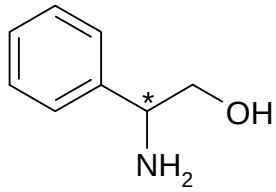
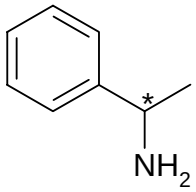
Phenylglycinol (PG)	Phenylethylamine (PEA)
	
Preferentially extracted: R	Preferentially extracted: S
Intrinsic selectivity: 10	Intrinsic selectivity: 2.7

Figure 1: (a) phenylglycinol (b) phenylethylamine

Various types of equipment can be used for liquid-liquid extraction at pilot scale. Column contactors can be constructed with a small diameter and a limited height, containing various internals and various means of energy supply.[1] Secondly, hollow fiber membrane modules have been used to carry out (fractional) extraction.[2,3,4] Centrifugal extractors exist at small scale (for instance, the CINC); furthermore, so-called 'centrifugal partition chromatography' (CPC) or 'counter-current chromatography' (CCC) is also small-scale centrifugal extraction.[5,6] A cascade of mixer-settlers can be operated at small scale[7] or simulated with a series of separatory funnels.[8] Another mixer-settler type design is the Craig extractor[9]. In literature, some custom-made designs for small-scale extraction are reported, such as the

rotating glass column set-up[10] or the 'liquid particle extractor'.[11] With all of these types of equipment, the fractional extraction scheme can be realised by employing two separate extractors for the two sections (wash and strip section); in a column-type contactor, entrance of the feed in the middle of the extractor may be possible, resulting in two extraction sections in one piece of equipment. So far, most authors have employed two separate units for the two sections.[2,10,11]

To carry out the present separation, the following demands to the pilot plant equipment can be listed:

- scale: only a few grams of the extractant, the azophenolic crown ether, are available. The organic phase volume per experiment should be limited to 100-500 mL.
- despite the small scale, multiple equilibrium stages should be realised in the contactor.
- the set-up should represent two sections: a wash and a strip section.
- the contactor should be able to handle various phase ratios.

Because of the particularly small scale of this separation, column equipment and centrifugal extractors could not be used. CCC and CPC equipment, the Craig extractor and the home-made designs were considered too costly and/or too time-consuming to build. The remaining options are a series of mixer-settlers or a membrane module. A cascade of mixer-settlers may be a good contactor to check the model predictions, but the results from this contactor are less useful for design of real contactors; for the present separation, 10-30 stages per section will be required, and mixer-settlers are seldom used for applications with more than three stages. Even if a 50-stage small-volume mixer-settler cascade can be realised, the very long residence time will be prohibitive. The membrane module is a differential contactor and bears more resemblance to multistage real-life extractors; secondly the phases are not dispersed and thus easily separable, and the phase ratio can be set at wish without the risk of flooding. Besides, this contactor has a large interfacial area and promises efficient mass transfer. Therefore, the membrane module was selected as contactor. Two modules are used representing the wash and the strip section. A scheme of the set-up is given in figure 2. More details can be found in the experimental section.

Comparison of the membrane extraction performance with the multistage equilibrium model requires the 'number of equilibrium stages' as input, whereas a membrane module is a differential contactor. Therefore it was decided to determine the NTU that can be realised in one membrane module, and convert this NTU to a number of equilibrium stages for that module. To find NTU, a reactive extraction experiment cannot be used, because the extraction factor is varying along the extractor. Therefore physical extraction of PEA from water to toluene was used to determine NTU, since the physical partitioning ratio of PEA into toluene is sufficiently high to obtain a reliable result.

The obtained 'number of equilibrium stages' (N) is subsequently used to predict the influence of the solvent-to-feed ratio (S/F) on the purities and yield in a single reactive extraction section, without employing a wash section, both for PG and PEA separation. The predicted influence is validated by experiments in a single membrane module, corresponding with one extraction section. After that, simulations are done for the fractional extraction scheme, incorporating the two sections, to model the influence of the W/S ratio on the separation. The predictions are compared with the results of fractional reactive extraction experiments using the two membrane modules for separation of phenylglycinol. Similarly, the influence of temperature is studied for PG extraction.

Finally, the chapter is concluded with a discussion on improvement of the realised separation and on improvement of the model predictions.

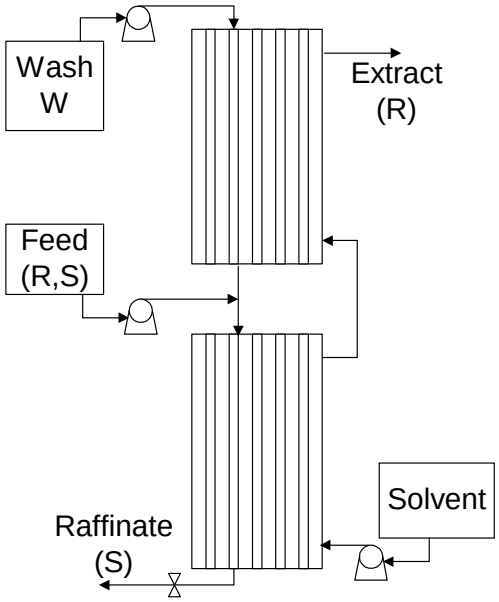


Figure 2: Scheme of fractional reactive extraction pilot set-up consisting of two hollow fiber membrane modules and three pumps. Assumption: R is preferentially extracted.

7.2 Experimental

The enantioselective extractant was manufactured by Syncom BV (Groningen, The Netherlands) in a custom synthesis according to Naemura *et al.*[12] R- and S-phenylglycinol were obtained from Fluka (Buchs, Switzerland). Rac-phenylethylamine was obtained from Sigma-Aldrich (Milwaukee, WI, USA) and toluene was obtained from Merck (Darmstadt, Germany). A scheme of the membrane pilot is given in figure 2. The membrane modules have to be toluene-resistant. Commercially available solvent-resistant modules such as the Liquicel-Extra-Flow modules by Membrana require feed streams of several hundreds of liters

per hour, so they are much too large for this application. Therefore, two small membrane modules were custom-made by SolSep BV (Apeldoorn, The Netherlands). Each module has 15 cm effective membrane length, 16 mm ID and contains 150 polypropylene fibers of 0.33/0.63 mm ID/OD (Membrana, Wuppertal, Germany), that are potted with a proprietary solvent-resistant potting. The resulting specific area is 1090 m^2/m^3 (calculated from log mean fiber diameter). The porosity of the membrane material was determined at 0.78 with a pycnometer[13] and the calculated[14] tortuosity is 1.90. The membrane material is wetted by the toluene phase. To prevent toluene leakage to the aqueous phase, a pressure difference of 50-100 mbar between the aqueous and organic side is maintained by adjusting a valve in the raffinate exit. The modules are jacketed to enable temperature control with a thermostat bath (Julabo F-32). The feed and solvent streams are delivered by a Stepdos 08 S pump (KNF FLODOS AG, Sursee, Switzerland) and the wash stream by a Watson Marlow 101U/R pump (Watson Marlow Limited, Cornwall, UK).

All experiments were carried out with the aqueous phase in the fibers and the toluene phase at the shell side. The feed concentration of the racemic mixture was 2 mM (unbuffered) in MilliQ water (Millipore, Billerica, USA), the extractant concentration was 3 mM in toluene and the wash stream was milliQ water. In each experiment, the module is flushed during 2-5 times the residence time of the solvent flow at the shell side. After that, samples are taken from the aqueous raffinate stream and organic extract stream. The organic phase sample is extracted with dilute acid to obtain an aqueous sample for analysis.

All samples are analysed by chiral HPLC for amine/amino alcohol enantiomer concentration. The HPLC set-up consisted of a Varian 2510 HPLC pump, a Daicel Crownpak (+) chiral column in a column oven, a derivatization coil and a Jasco FP-2020 *plus* fluorescence detector operated at 325 nm excitation and 465 nm emission. Post-column derivatisation with o-phtalic aldehyde /mercaptoethanol reagent is carried out according to Duchateau *et al*.[15] The error in each concentration determined from repeated analysis of the same sample is ± 3%; the back-extraction step for the extract samples introduces an additional experimental error. Based on these error estimations, it was decided to use the data of all experiments for which the mass balance closed within 10% (calculated from feed, extract and raffinate samples).

7.2.1 Data treatment

For a single stage, the capacity is characterised by the distribution ratio D for each enantiomer and the selectivity α_{op} is defined as the ratio of distribution ratios. The intrinsic selectivity α_{int} is determined by the complexation constants (K_R, K_S) between the crown ether and enantiomers. The appropriate formulas can be found in chapter 4. The extraction performance in an extractor is characterised more conveniently by the yield (eq. 1) and the product purity by the enantiomeric excess e.e.[16] (eq. 2 and 3). Similar equations as (1) can be defined for the yield of each enantiomer in the raffinate and extract stream. Note that e.e. is always defined in such a way that its value is between 0 and 1. If [S] is larger than [R], it is defined as in

equation (3). For PG, R ends up in the extract, so e.e.$_{EXTR}$ is calculated with equation 2 and e.e.$_{RAFF}$ with equation 3; for PEA, the situation is reversed.

$$yield_{R,EXTRACT} = \frac{total \quad R \quad extract}{total \quad R \quad feed} \tag{1}$$

$$e.e. = \frac{[R]-[S]}{[R]+[S]} \tag{2}$$

$$e.e. = \frac{[S]-[R]}{[R]+[S]} \tag{3}$$

7.3 Results and discussion

7.3.1 Estimation of number of stages by physical extraction

NTU and N are determined from physical extraction data for transfer of PEA from water to toluene. The formula for NTU in a differential contactor for the raffinate (the non-reactive phase) is presented in equation 4. The number of equilibrium stages N for this separation is given by the Kremser equation. It follows that NTU can be converted to an equilibrium stage number N by applying equation 5.[17] In the equations, P is the physical partitioning ratio and E is the extraction factor (E=P·S/F).

$$NTU = \frac{\ln\left[\left(\frac{[PEA]_{feed} - [PEA]_{solvent}/P}{[PEA]_{raffinate} - [PEA]_{solvent}/P}\right)\cdot\left(1-\frac{1}{E}\right)+\frac{1}{E}\right]}{1-\frac{1}{E}} \tag{4}$$

$$NTU = N\frac{\ln E}{1-1/E} \tag{5}$$

The experimental NTU for phsyical extraction of PEA from water to toluene is presented in figure 3, as well as the number of equilibrium stages N that is calculated with equation 5.

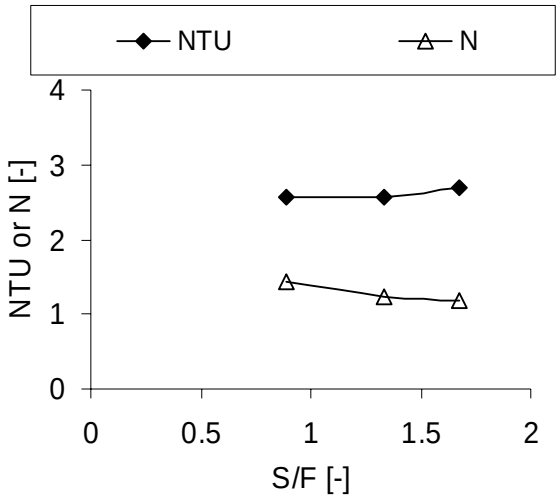


Figure 3: NTU and N for extraction of 2 mM PEA from water to toluene in one membrane module, F = 1.0 ml/min, 25 °C.

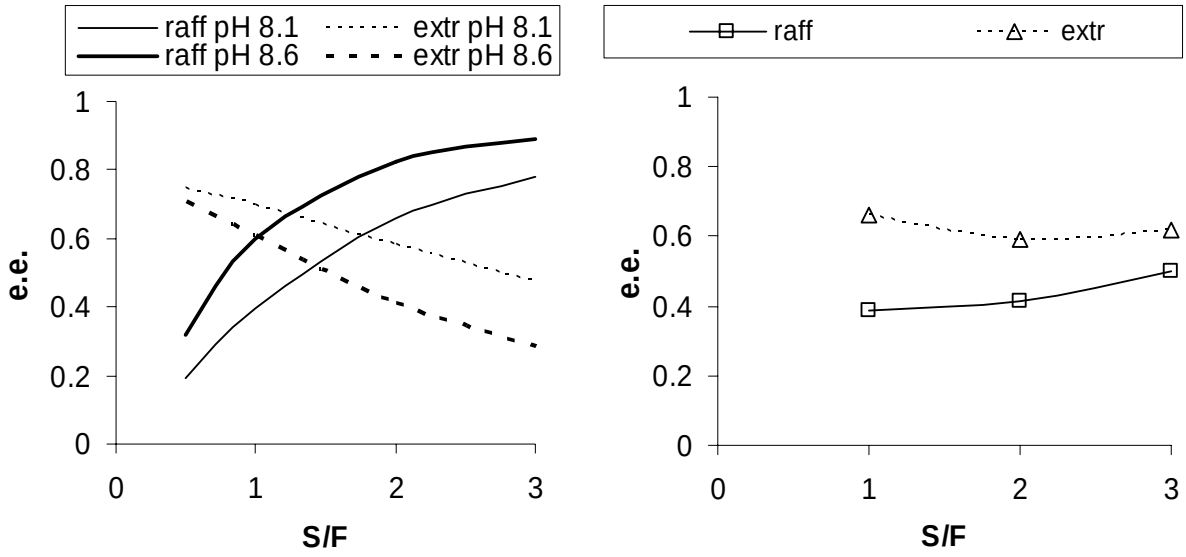
It can be seen that the difference between N and NTU is the most pronounced at high S/F, because the extraction factor E is the largest here. From this figure, it can be concluded that NTU is 2-3 per membrane module, so HTU = L/NTU = 5-7.5 cm. This value of HTU is comparable to the results in literature[4,18] although lower HTU values were also reported (1-3 cm)[19] for lower linear velocities of the liquids and membrane fibers with smaller diameter. The average N that follows from the figure is between 1 and 2, whereas an integer value is required for the model. According to the theory, NTU (and thus N) will be higher if lower flow rates are applied. Because a considerable part of the experiments will be carried out at somewhat lower aqueous and organic flow rates than the flow rates used here, N=2 will be used as 'number of equilibrium stages per section' in all simulations.

7.3.2 Reactive extraction: influence of solvent-to-feed ratio

In the following paragraphs, the results of the reactive extraction experiments are discussed. In all cases, the multistage model prediction is presented next to the experimental result in the same figure. The experimentally used concentrations, pH and temperature are used as input parameters for each model prediction. These values can be found in 'Experimental' unless mentioned otherwise. In a number of cases, the model prediction is very sensitive to the exact value of a model parameter. Then, model predictions for two values of that parameter are indicated in the same figure with 'thin lines' and 'thick lines'. First, the influence of the solvent-to-feed (S/F) ratio for reactive extraction of phenylglycinol and PEA was studied in a single membrane module, corresponding with one extraction section. Note that for PG, enantiomer R is predominant in the extract and for PEA, the R-enantiomer is predominant in the raffinate.

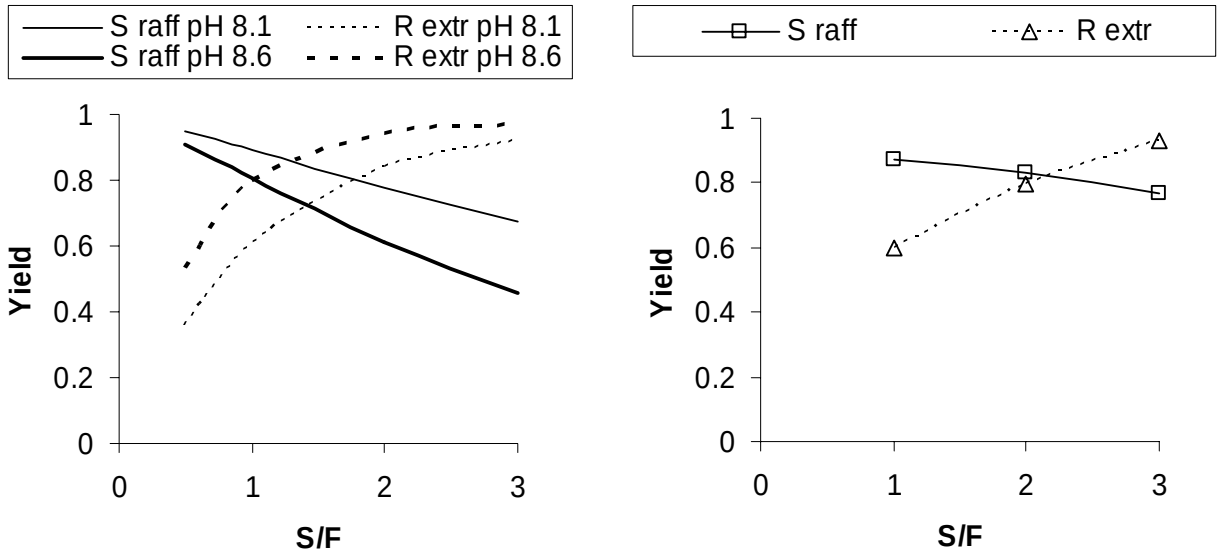
Phenylglycinol

For phenylglycinol, the model predictions and the experimentally observed effect of S/F ratio are presented in figure 4 (enantiomeric excess) and figure 5 (yield). According to the simulations, increasing the S/F ratio results in a higher yield in the extract but a lower extract purity (enantiomeric excess e.e.). Furthermore, model results at different pH values are presented to show the large effect of this process parameter on the product compositions. Because this is an equilibrium simulation, changing the feed flow and solvent flow rate by the same factor while keeping S/F constant does not affect the model result. More details on the model predictions and explanations for the observed behaviour can be found in the previous chapter.



(a) (b)

Figure 4: Influence of S/F ratio on enantiomeric excess in one module for phenylglycinol separation (a) simulation (N=2), pH 8. and pH 8.1 (b) experimental result, feed flow rate F = 0.1 ml/min, pH 8.6, other parameters see 'Experimental'.



(a) (b)

Figure 5: Influence of S/F ratio on yield in one module for phenylglycinol separation. (a) simulation (N=2) pH 8.6 and pH 8.1 (b) experimental results, data for F=0.1 ml/min, pH 8.6.

It can be seen in figure 4b that the effect of S/F on the experimentally obtained e.e is rather small. Secondly, to reach the point in which the e.e. values are the same in raffinate and extract, a higher S/F ratio seems to be required. It was also observed in the experiments that the experimental enantioselectivity (expressed as ratio of distribution ratios according to chapter 4) is larger than the single-stage operational enantioselectivity for this system: under similar circumstances α_{op} = 12 in the module vs. α_{op} = 7 in a single stage. This shows that indeed more than one equilibrium stage is realised in the module. However, the operational selectivity is a poor measure of the quality for this separation, because it presumes that there is equilibrium between the extract and raffinate stream, whereas these streams exit the module at opposite ends and are not in equilibrium at all. Therefore, in the remaining part of this chapter only the enantiomeric excess e.e. will be used as a measure of optical purity in the product streams. For further comparison, the predicted e.e. for a single stage is presented in figure 6 next to the experimental data from figure 4b. The predicted equal e.e. point is located at e.e. = 0.47 for the single stage and at e.e. = 0.60 for two stages (figure 4a), whereas the experimental data tend towards e.e. > 0.55 at the crossing point. Thus, the realised number of stages is indeed close to 2.

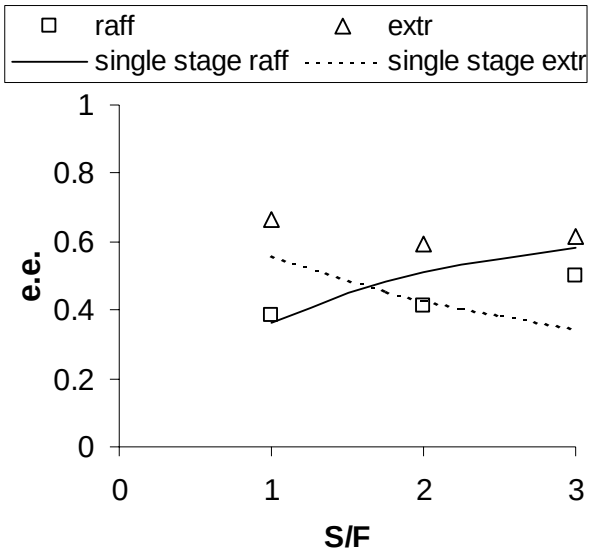
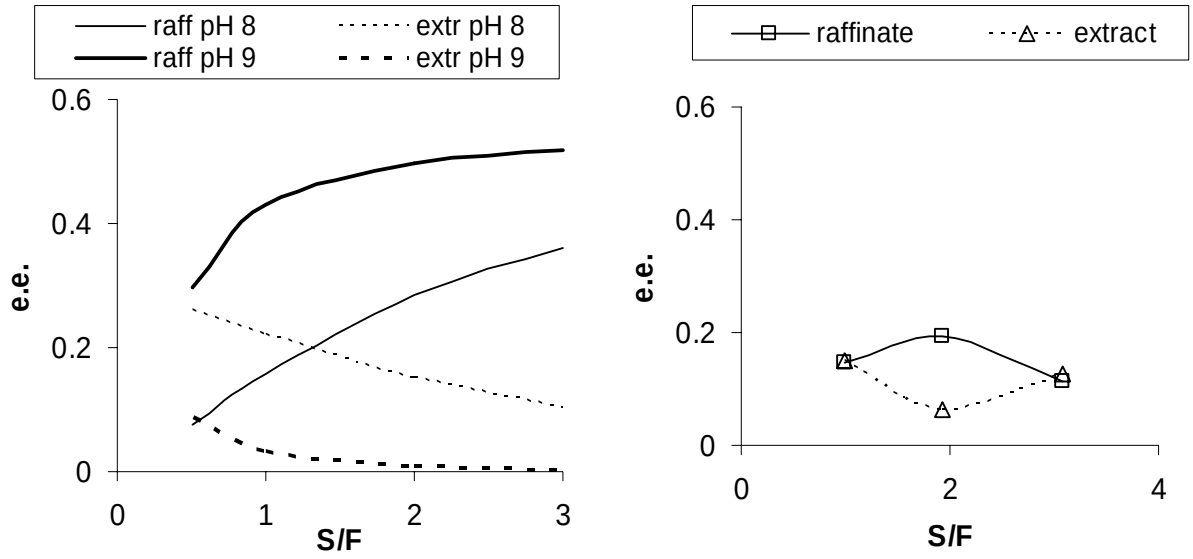


Figure 6: PG separation, experimental e.e. data from figure 4b for one membrane module (open symbols) and e.e for single stage separation by model from chapter 4 (lines).

The experimental result for the yield (fig. 5b) is qualitatively the same as the model prediction: with increasing S/F, the yield in the extract increases and the yield in the raffinate decreases for both enantiomers. The pattern in the experimental results is closer to the prediction with pH 8.1 than pH 8.6, although the experimental pH was 8.6. Alternatively, it may be stated that the 'crossing point' in which the yields of the respective enantiomers in extract and raffinate are equal seems to be located at larger S/F ratio in the experiments than in the simulations. The same was observed for the enantiomeric excess. Thus, it seems that the solvent is not used effectively. This may be due to insufficient residence time for physical extraction and/or complexation. These observations cannot be explained directly from the multistage equilibrium model. It seems that the residence time in the extractor and the mass transfer and/or reaction rate should be taken into account.

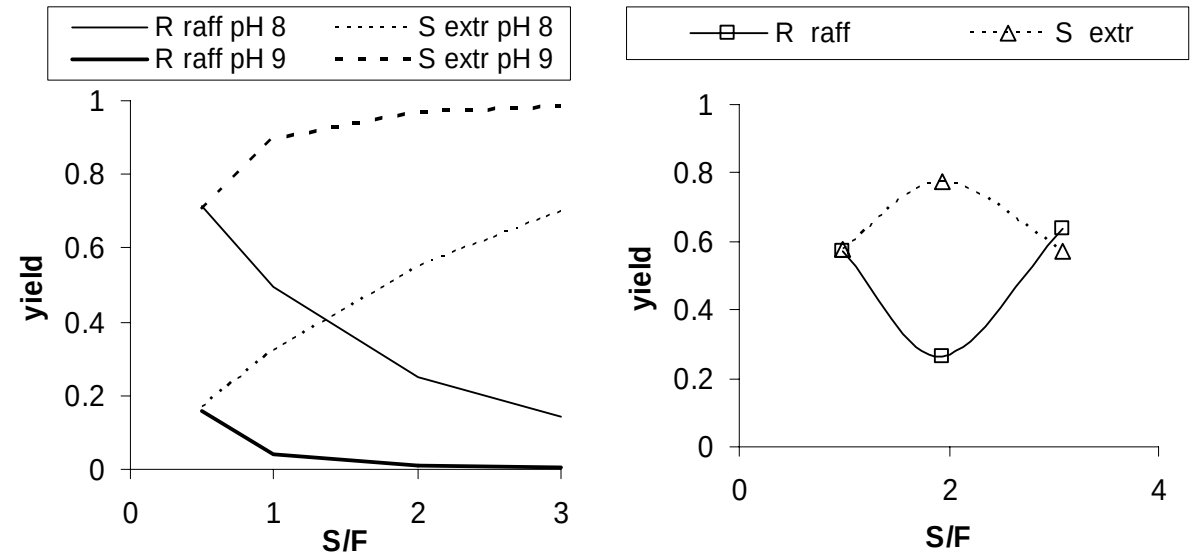
Phenylethylamine

The model predictions and the experimentally observed effect of S/F ratio for phenylethylamine are presented in figure 7 (enantiomeric excess) and 8 (yield). The trends in the model predictions are the same as for phenylglycinol; however, because of the lower selectivity in the single stage for PEA, the enantiomeric excess after 2 stages is also lower. The sensitivity of the model prediction to the value of pH is large, because the pH in the system is close to the pK of phenylethylamine.



(a) (b)

Figure 7: Influence of S/F ratio on e.e. in one module for phenylethylamine separation (a) simulation (2 stages) (b) experimental results, data for F = 0.1 ml/min; lines only indicated for clarity.



(a) (b)

Figure 8: Influence of S/F ratio on yield in one module for phenylethylamine separation (a) simulation (2 stages), pH 8 and pH 9 (b) experimental results, data for F = 0.1 ml/min; lines only indicated for clarity.

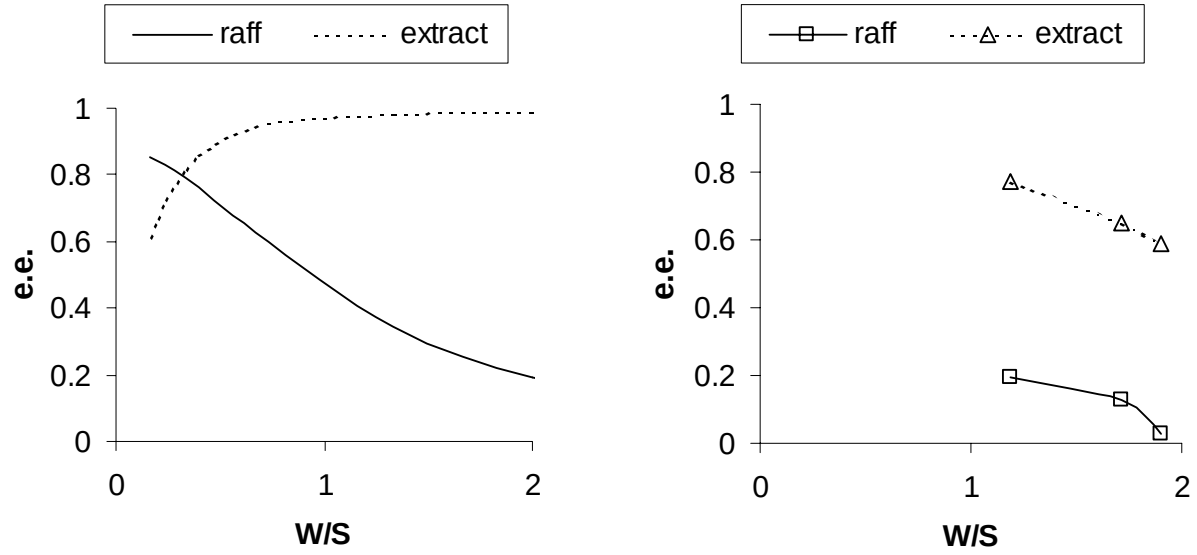
It can be seen that in the experimental results for PEA separation there is no clear trend ('up' or 'down') for e.e. and yield as a function of S/F ratio (figure 7b and 8b). If the order of magnitude of the values for e.e. and yield is compared, it is clear that the model predictions for pH 8 are much better than for pH 9 at this S/F ratio, or alternatively that the predictions for

a low S/F ratio correspond with the experimental results at larger S/F. It seems that again the solvent is only partly used, possibly because of too low residence time. Because there is no clear trend, no conclusion can be drawn on the variation in e.e. and yield with S/F. The variations may be caused by a real effect of S/F ratio but just as well by pH variations. A similar large pH effect caused by CO_2 from air was found for PEA in the single stage extraction experiments (chapter 4).

The remaining experiments with the two membrane modules (fractional extraction scheme) were carried out with PG only, because this substance is a less strong base and proved less prone to CO_2 uptake in the single stage experiments. Therefore PG results are expected to show more clear trends than PEA results.

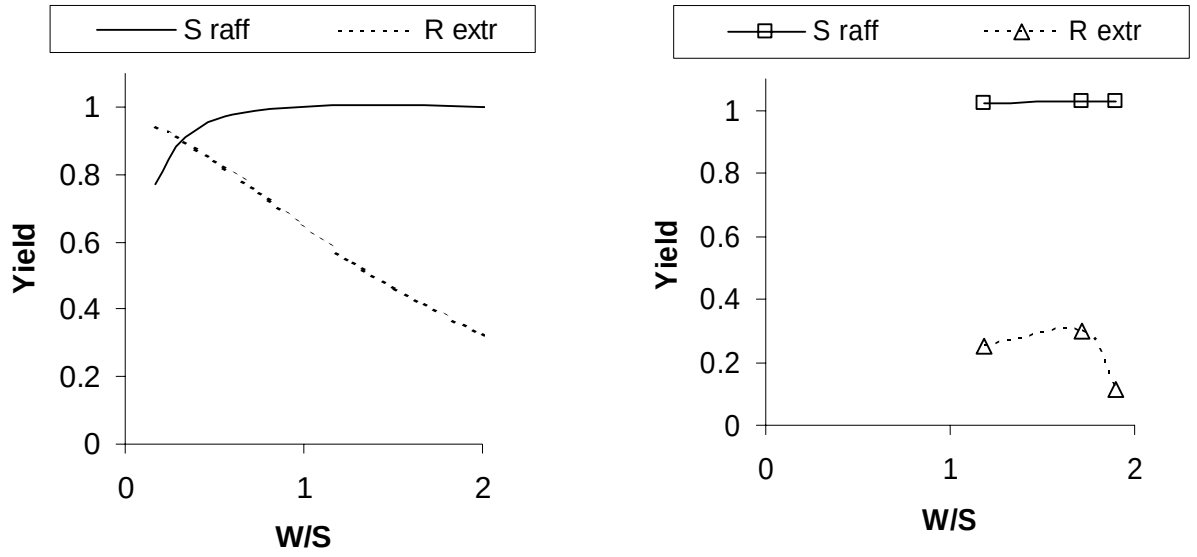
7.3.3 Fractional reactive extraction: influence of wash-to-solvent ratio

Two-module experiments were carried out to identify the influence of the W/S ratio on the chiral separation of phenylglycinol. To our knowledge, this influence was not studied experimentally before, although a number of authors studying fractional reactive extraction estimate the optimal W/S ratio beforehand based on the extraction factors for each enantiomer.[10,11] The simulated and experimental effect on enantiomeric excess is presented in figure 9, the effect on the yield is presented in figure 10. It can be seen that according to the simulation, W/S has a pronounced effect on yield and product purity: an increase in W/S results in a more pure extract, but a lower yield in the extract.



(a) (b)

Figure 9: Influence of W/S ratio on e.e. for phenylglycinol separation. S = 0.6 ml/min, F = 0.2 ml/min, T = 25 °C, pH 8.6 (a) simulation, 2+2 stages (b) experimental data.



(a) (b)

Figure 10: Influence of W/S ratio on yield for phenylglcyinol separation. S = 0.6 ml/min, F = 0.2 ml/min, T = 25 °C, pH 8.6 (a) simulation, 2+2 stages (b) experimental data

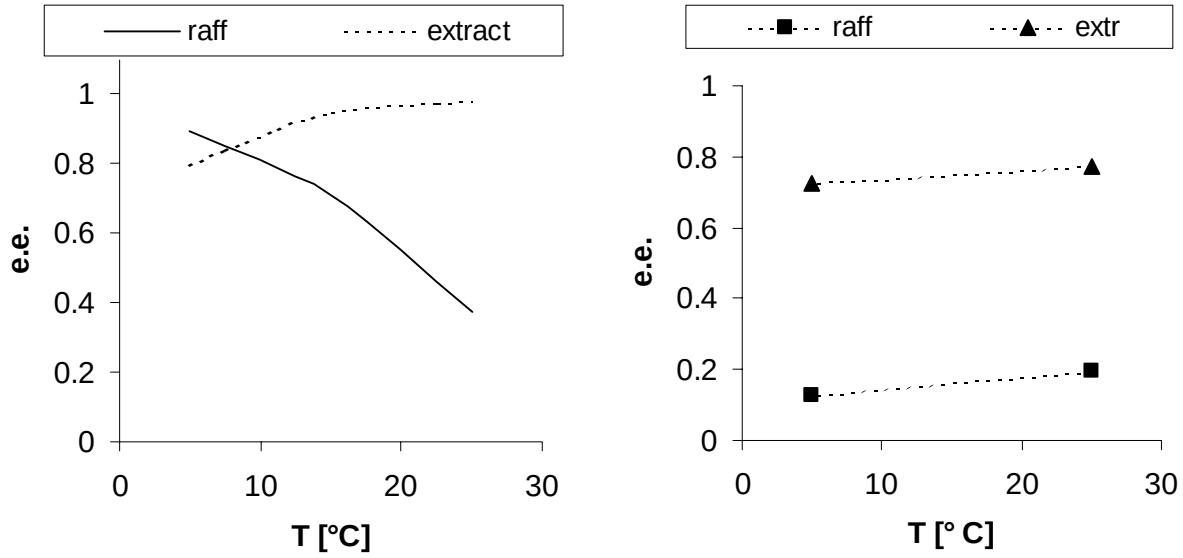
In the experimental results, the influence of the wash stream on the e.e. is clearly visible (compare figure 9b with fig. 4b and 7b). However, the pattern observed in the e.e. in the product streams (fig. 9b) is not expected; the e.e. of the extract is expected to increase further at increasing W/S ratio instead of decrease. The effect in e.e. may be partly caused by the measuring error: because the yield in the extract is low, the concentrations of both phenylglycinol enantiomers are low as well. Under these circumstances it is difficult to monitor the variation of the concentration of the enantiomer present at the lowest concentration (in this case, S), so the e.e. value is not very reliable. Moreover, it may be that the higher aqueous flow rate and thus shorter residence time at higher W/S is detrimental to the separation. Such an effect cannot be described by the equilibrium model.

The experimental and simulated results for the yield (figure 10) are qualitatively similar: with increasing W/S, the yield in the extract becomes very low while the yield in the raffinate approaches 100%. Data points at lower W/S ratio may confirm the patterns found in figure 9a and 10a, but measurements at low W/S could not be carried out because of the limited operating range of the wash flow pump. Finally, an excess of enantiomer R was measured in the aqueous stream exiting the wash section. This excess of R is indeed predicted by the model at a large W/S ratio.

7.3.4 Influence of temperature

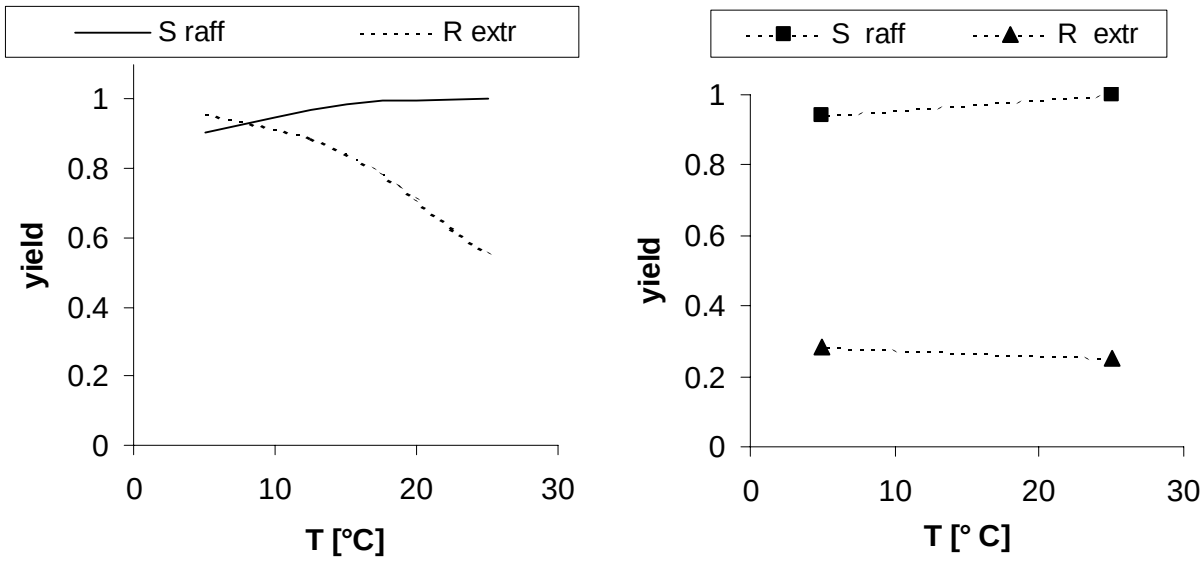
The temperature influences the physical extraction as well as the extent of complexation. For the single stage, a decrease in temperature results in larger distribution ratios and a larger operational selectivity. In line with this result, the multistage model predicts that the point with equal e.e. moves toward larger enantiomeric excess, but is located at larger W/S ratio. If

the same S/F and W/S ratios are used, the yield of the extract will increase with decreasing temperature and its e.e. will decrease (figure 11a and 12a). One experiment was carried out at fixed S/F and W/S. The experimental result is given in figure 11b and 12b.



(a) (b)

Figure 11: Influence of temperature on e.e. in extract and raffinate, PG separation, F = 0.2 ml/min, S = 0.6 ml/min, W = 0.75 ml/min (a) simulation, 2+2 stages (b) experimental results



(a) (b)

Figure 12: Influence of temperature on yield in extract and raffinate, PG separation, F = 0.2 ml/min, S = 0.6 ml/min, W = 0.75 ml/min (a) simulation, 2+2 stages (b) experimental results

It can be seen that the overall influence of the temperature on the separation is almost nil. The most likely explanation is that the temperature change has an opposite effect on the kinetics and thermodynamics of the extraction process. The viscosity of the solvents will be higher at

5 °C, resulting in slower mass transfer rates, and the complexation reaction will be substantially slower at 5 °C; therefore the extent of extraction can be expected to be smaller at lower temperature because of slower kinetics (the residence time is constant). On the other hand, the thermodynamics of the complexation reaction predicts a larger extent of extraction at lower temperature (chapter 4). Apparently, these two effects counteract, and the net result is the same extent of extraction at 5 °C and 25 °C.

7.3.5 Improvement of separation

The number of equilibrium stages / NTU realised in this work was lower than the number realised by other researchers[4,19] and as a result, the extent of separation that was reached in this work is also lower than expected. NTU and HTU are related via NTU=L/HTU. Firstly, some authors used longer membrane modules than 0.15 m or connected several modules in series,[4] which results in a higher NTU than realised in this work. Secondly, a low NTU can also originate from a high HTU (constant L). The specific membrane area in the modules used in this work was lower than the area in commercially available equipment. No solvent-resistant membrane module of this small scale is available as standard module; the custom-made module was constructed from somewhat larger and thicker membrane fibers than used in literature, resulting in a specific area of 1090 m^2/m^3. In comparison with a commercial module with a specific area of about 3000 m^2/m^3, the custom-made module has effectively a 3 times smaller area and thus a three times larger HTU. Finally, the flow rates applied in this research were relatively high, whereas a lower flow rate results in lower HTU in membrane modules. In this work, the operating range of the wash flow pump did not allow the use of lower flow rates.

The thicker membranes also cause a larger phase ratio (shell/fiber volume ~11) than common in membrane extraction: in contrast with the 150 μm membrane thickness in this work, the Celgard membranes (Membrana, Germany) used by most other authors[2,18,19] have a membrane thickness of only 30 μm, and therefore a much more balanced aqueous/organic phase ratio is present when using this fiber.

7.3.6 Improvement of agreement between model and experiment

The agreement between model and experiments is not very good. Firstly, there are some experimental issues that may explain part of the deviations. The most important one is the measuring error: because of the error of ± 3% in the concentration determination by HPLC and the need for back-extraction of organic-phase samples, an overall error up to 10% in the mass balance can occur, and small effects on the yield may become invisible. Next to this effect, determination of a large e.e. value is difficult in general, especially if the concentrations in the sample are low (so in case of low yield). For HPLC separation, it means that the areas of a large peak and a small peak have to be determined from the same chromatogram, so any tailing of the first peak will largely influence the area of the second peak and thus the determined enantiomeric excess. To measure e.e. in a sample precisely by

HPLC, it is best to elute first the enantiomer that is present in the smallest concentration, to minimise the effect of tailing on the second peak area. The company Daicel (Japan) markets two chiral HPLC columns with opposite chirality (Crownpak(+) and Crownpak(-)) for this purpose, but it is an expensive solution.

Secondly, the model prediction is a strong function of all process parameters and in some cases a small process parameter change has a large effect on the prediction. A clear example is the role of the pH on the extent of extraction. It can be seen in the PEA simulations (figure 7a and 8a) that a change in pH determines the behaviour of the system largely. At the same time, the pH cannot be obtained experimentally on each location within the module, so an average value has to be used as model input (for instance, the pH of the raffinate). As a result the model prediction and the experimental result deviate. A sensitivity analysis may be useful for identification of the most influential parameters.

Similarly, a number of equilibrium stages of 2 was determined and used as input in all simulations based on the determination of NTU in the physical extraction experiment. It can be seen in figure 4b and 6 that almost 2 stages are realised; the best value seems to be around 1.8. In the current model, an integer value is required, so N=2 is indeed the best choice. On the other hand, the model results are very sensitive to the value of 'N', so this may explain part of the deviation between model and experiment.

A more fundamental problem is the fact that no time-dependent behaviour is described in the model, whereas it can be expected that the residence time in the membrane module will determine if the equilibrium is approached closely within one 'equilibrium stage' or not. In the experiment at low temperature (figure 11 and 12), the experimental results were explained from a kinetic effect that counteracts the thermodynamic effect, and also in the experiments regarding S/F and W/S influence the residence time may be quite important. A non-equilibrium model of a membrane module may explain the trends observed in the experiments better. With such a model, the need for a 'number of stages' would also be circumvented. On the other hand, a non-equilibrium model requires many input data regarding membrane geometry, mass transfer and reaction kinetics, and it will only give good predictions if all input data are of good quality. The construction of such a model was not carried out because the geometry of these membrane modules cannot be described very well and because the reaction kinetics are not precisely known.

7.4 Conclusion

Fractional reactive extraction for chiral separation of phenylglycinol and phenylethylamine has been performed in a pilot set-up consisting of two membrane modules. Almost two equilibrium stages could be realised in each module. In this way, a partial chiral separation of phenylglycinol and phenylethylamine was obtained. For phenylglycinol separation, it was shown experimentally that the S/F ratio influences the product purity (e.e.) slightly and the

yields substantially, both qualitatively consistent with the multistage model prediction. The effective use of the solvent seemed to be rather low. For phenylethylamine, no clear trend could be found in the experimental data, possibly because of CO_2 uptake and a subsequent pH decrease. Experiments with the two modules representing the fractional extraction scheme for phenylglycinol showed that the W/S ratio influences the yield and purity considerably; the experimental yield was qualitatively similar to the model prediction, but the experimental effect on e.e. showed a deviation from the model predictions, that may be explained with the experimental error or with an influence of residence time. Finally, a temperature decrease from 25 °C to 5 °C had no appreciable effect. The most probable explanation is that the slower kinetics counteracted with the more favourable thermodynamics at lower temperature.

The number of stages realised per module was relatively low, compared to literature values. With a module containing more membrane area, a longer module and lower flow rates, the number of transfer units would have been higher and the separation would have been better.

The experimental error and the sensitivity of the model prediction to the exact values of certain parameters explain some of the deviations between model prediction and experimental results. For better understanding and more accurate predictions, a non-equilibrium model may be developed that takes into account the mass transfer and chemical reaction. In this way, the use of 'number of theoretical stages' is also circumvented. Because the collection of the lacking non-equilibrium data was considered too time-consuming, the construction of such a model was not undertaken.

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8 Conclusions and outlook

In this thesis, fractional reactive extraction is evaluated as alternative industrial chiral separation technique for resolution of amines and amino-alcohols. Two major obstacles for introduction of FREX were identified in the introduction: the lack of enantioselective extractants for all major chemical classes, and the low productivity of current systems. In this final chapter the main conclusions are given, fractional reactive extraction is compared with the current industrial separation techniques and an outlook for further research is presented.

8.1 Conclusions

8.1.1 Development of enantioselective extractants

In this thesis, it has been demonstrated for the chemical classes of amines and amino-alcohols that versatile and selective enantioselective extractants can be identified among known selectors from the chiral recognition literature. Four selective systems for separation of various target amines and amino-alcohols were identified using a systematic selection method. The best system, an azophenolic crown ether, showed an enantioselectivity of 1.3-5.0 for 5 out of 6 target enantiomers in the screening experiments, and a selectivity of 1.5-9.4 for the same enantiomers with improved process conditions. The most promising enantioselective extractants in the chiral recognition literature originate from techniques with a similar separation mechanism as extraction, based on differences in complexation constants for the two enantiomer-extractant complexes in the liquid: liquid membranes, extraction, HPLC/CMP and electrophoresis. To realise an enantioselectivity > 1.5 and versatility in extraction, the enantioselectivity should also be > 1.5 in the original technique, and should be reported for a number of the target analytes or for closely related substances.

8.1.2 Extractant performance

The extraction conditions such as temperature, pH and concentrations of enantiomers and extractant have a large influence on the capacity (distribution ratios) and selectivity in a single stage. The intrinsic selectivity can be approached closely by the operational selectivity if the product of complexation constant and equilibrium extractant concentration is sufficient: $K_R \cdot [C] > 10$. Under the conditions studied, an excess of extractant of 2-3 (mol/mol) was needed to approach this maximum operational selectivity, which is much lower than the extractant excess of 50-100 applied previously in literature. The distribution ratio can be set nearly at wish by adapting pH, excess of extractant, concentration level and temperature. ‘Moderate’ values of distribution ratios should be realised (range 1-10), because they will result in favourable extraction factors in combination with hydrodynamically acceptable phase ratios. A model of the single stage based on the physical and chemical equilibria in the system is valuable to understand and predict the influence of process conditions. For the azophenolic crown ether system, recovery of the extractant and product enantiomer by back-extraction can be carried out by temperature increase, and more effectively by pH decrease: a

pH shift from ~ 9 to ~ 6 is sufficient, which can be realised by dissolving low pressure CO_2. The recovered extractant could be re-used without loss of activity.

By a combination of experiments in the modified Lewis cell and a rate-based model, it was concluded that the reaction kinetics of the azophenolic crown ether system are between 'fast' and 'instantaneous', and the reaction kinetics of the Cu(II)-N-dodecyl-L-hydroxyproline system are between 'slow' and 'fast'. An important conclusion is also that there is no general kinetic model description for reactive extraction including mass transfer in both phases, and no discussion in literature when the 'interfacial reaction model' or the 'homogeneous reaction model' should be applied. Furthermore, the regime analysis derived for reactive gas absorption gives erroneous results for reactive extraction in a number of regimes.

8.1.3 FREX process performance

The multistage equilibrium extractor model based on the validated single stage model was used to determine the required amount of stages, S/F ratio, W/F ratio and process conditions to obtain a specified product yield and purity. The number of stages is primarily determined by the operational selectivity in the single stage; if more stages than the minimum number are available, a larger process capacity can be reached. Various combinations of process conditions can be identified that all yield the same product purity, but differ in capacity. All five model enantiomers with $\alpha_{op} > 1.5$ (chapter 4) can be separated in the same 50-stages fractional extractor. Thus, a fractional extractor is very flexible and suitable for a multi-product environment. Partial chiral separation of phenylethylamine and phenylglycinol by fractional reactive extraction was demonstrated in a pilot set-up consisting of two small-scale membrane modules, each containing almost two equilibrium stages.

8.2 Comparison of FREX with current industrial separation techniques

It has been demonstrated that the main drawbacks of (diastereomer) crystallisation can be overcome by FREX: FREX does not involve solid-phase handling, the chiral selector is not consumed, and with the identified versatile extractant FREX is also more flexible than crystallisation. Crystallisation will probably remain the separation method of choice for those enantiomers that can be separated with very high selectivity in only one or two steps.

As SMB chromatography also has the mentioned advantages compared to crystallisation, outperforming SMB seems to be the real challenge for FREX. SMB seems to be gaining importance over crystallisation[1] mainly because of the better versatility and therefore faster development time. This good versatility is caused by staging: a rather low selectivity is required for full separation compared to crystallisation. For a large-scale SMB separation, a selectivity of 1.3-2.0 is generally aimed at[2] to ensure good productivity, which is comparable to the selectivity required for FREX (1.5-3.0). As a result, a similar process versatility seems possible in FREX. As for cost, enantioselective extractants can be expected to be less expensive than CSP's, compared per mole of selector sites. The selectors for both techniques

are similar in complexity, but only for SMB the selector has to be immobilised onto column material. At this moment SMB beats FREX in development time, because CSP materials are already available for most classes of enantiomers, whereas the availability of enantioselective extractants is very limited.

The main advantage of FREX, compared to SMB, is that the chiral selector (and therefore the enantiomer feed) can be present at a much higher volumetric concentration. As a result, the capacity is higher, which results in smaller process equipment. Additionally, SMB requires high pressures and constant switching of streams. For all these reasons, FREX equipment is expected to be less expensive, both in capital cost, energy input and maintenance. Furthermore, it has been shown in chapter 4 that the extent of complexation is higher at higher concentrations (higher loading at equal excess of extractant), so the selector is used more effectively in FREX and a lower excess is required. As for dilution, the product streams in SMB are in general diluted by a factor 1-3 for the raffinate and 4-10 for the extract compared to the feed.[2,3] Dilution in FREX is less: a FREX process can be designed in such a way that the raffinate will be diluted only 2 times (a W/F ratio lower than about unity is not favourable for the separation), and the extract can even be concentrated compared to the feed by applying different conditions for back-extraction.

Summarising, FREX has clear advantages over other industrial separation techniques such as SMB. However, although the technical feasibility of FREX for amino-alcohol/amine separation has been described, the technology is much less developed than SMB. The major issues that still need to be solved before FREX may be adopted as industrial separation technique are:

- process design, flow sheet, economic evaluation, trials on kg/day scale
- equipment design and scale-up methodology
- identification of extractants for enantiomers from other major chemical classes

8.3 Outlook

8.3.1 Process design

A conceptual process design for a specific amine or amino-alcohol separation may be drafted based on the available data. The capacity and purity requirements should be set and the solubility of enantiomers, extractants and complexes should be determined experimentally to find the maximum concentrations. Then a number of process configurations can be identified using the multistage model, in terms of S/F ratio, stages, process conditions and types of equipment, and be compared by an economical evaluation to find the best alternative. A combination of FREX with other techniques is possible, for instance FREX as main separation with crystallisation as final purification, or purification by FREX of an enantio-enriched product from asymmetric synthesis. For further proof and for marketing purposes, it is essential that pilot tests are carried out on a kg/day scale in industrial extraction equipment.

8.3.2 Equipment design and scale-up

Equipment for FREX differs from most conventional equipment for (reactive) extraction in a number of ways: a large number of stages should be realised in a relatively low volume, two separation sections should be present and a wide range of phase ratios should be allowed. For reliable scale-up and equipment design for FREX, the correct determination of reaction kinetics in reactive extraction deserves more attention. A multidisciplinary approach is recommended, in which both the role of mass transfer and physical extraction is incorporated as well as surfactant behaviour of extractants and complexes. It seems that a combination of experimental techniques will be required, such as experiments in an improved model reactor in combination with analysis of the surface processes by novel spectroscopic techniques.

8.3.3 Extractant development & design

The proposed selection method is expected to be useful to identify enantioselective extractants for other classes of enantiomers than amines/amino-alcohols in the chiral recognition literature. There is a wealth of material on chiral recognition that can be exploited further. Often, the selectors obtained from the literature should be adapted before they can be used as extractants, for instance by connecting an alkyl tail to a molecule to increase hydrophobicity, while preserving the selectivity. Cooperation of chemists and chemical engineers is essential here.

Regarding the design of chiral selectors for chromatography (CSP's), it was stated by Pirkle and Pochapsky[4] that 'the CSP designer should maximise $\Delta\Delta G$ while minimising the absolute value of ΔG to improve chromatographic efficiency'. However, in extraction the strength of the complexation (ΔG) determines the capacity of the forward extraction step, so it should not be minimised at all. Efficient product recovery can be realised under different process conditions. For a selectivity between 1.5 and 3, $\Delta\Delta G$ should be between 1.0 and 2.7 kJ/mol (at ambient temperature), regardless of the strength (ΔG) of the interaction. Therefore, in contrast with the CSP designer, the enantioselective extractant designer should try to realise a sufficiently high $\Delta\Delta G$ for a high selectivity and a high ΔG for a high process capacity, and ensure that a method is available to carry out back-extraction efficiently. Finally, measures to prevent loss of extractant by leaching and/or entrainment should be taken.

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List of symbols

Abbreviations; species may be used as subscripts.

A	acid (in acid-base dissociation constant)
AAS	atomic absorption spectrometry
C, CE	(crown ether) extractant
CD	circular dichroism
CE	capillary electrophoresis
C_{12}Hyp, HLi	N-dodecyl-L-hydroxyproline ligand
CCC	counter-current chromatography
CMP	chiral mobile phase
CSP	chiral stationary phase
Cu(II), Cu	copper(II) ion
FREX	fractional reactive extraction
HR, HR+	ammonium ion of S-enantiomer
HS, HS+	ammonium ion of R-enantiomer
PEA	phenylethylamine
PG	phenylglycinol
PP	polyprolylene
R	R-enantiomer (neutral)
RC	complex of extractant and R-enantiomer
S	S-enantiomer (neutral)
SC	complex of extractant and S-enantiomer
TLC	thin layer chromatography
UF	ultrafiltration

Physico-chemical parameters

A	interfacial area	m^2
Al	Hinterland ratio	[-]
D	diffusion coefficient	m^2/s
E	extraction factor	[-]
E, E_A	enhancement factor (in reaction kinetics)	[-]
E	Electric field (electrophoresis)	
F	feed stream (flow rate)	m^3/s
J	extraction flux	$kmol/m^2/s$
Ha	Hatta number	[-]
K	overall mass transfer coefficient	m/s
K	complexation constant (index: compound)	depends on stoichiometry
[ ]	concentration	$kmol/m^3$
N	volumetric extraction rate	$kmol/m^3/s$

N	number of equilibrium stages	[-]
NTU	number of transfer units	[-]
O	interfacial area (in chapter 5)	m^2
P	partitioning ratio (physical)	org/aq concentration [-]
S	solvent stream (flow rate)	m^3/s
T	temperature	°C
V	volume	m^3
W	wash stream (flow rate)	m^3/s
a	specific interface	m^2/m^3
e.e.	enantiomeric excess	[-]
f	friction factor (electrophoresis)	$J \cdot s/cm^2$
k_L	partial mass transfer coefficient (index L)	m/s
$k_{1,1}$, $k_{n,m}$	reaction rate constant	depends on stoichiometry
q	effective charge (electrophoresis)	C
rpm	rotations per minute	
x, y	mole fraction (Kremser/Fenske)	
y		
α	selectivity	[-]
δ	film layer thickness	m
μ	electrophoretic mobility	$cm^2/V \cdot s$

subscripts

aq	aqueous (phase)
bulk	in the liquid bulk
chem	‘chemical’, refers to reactive system
i	interfacial
ini	initial (at t=0)
int	intrinsic (selectivity)
op	operational (selectivity)
org	organic (phase)
phys	‘physical’, refers to non-reactive system
tot	total (sum of species)
1	‘feed phase’ = aqueous phase
1	strongest extracted enantiomer
2	‘reactive phase’ = organic phase
2	weakest extracted enantiomer
∞	infinite

superscripts

S	surface

List of publications

Reviewed papers & conference proceedings

1. M. Steensma, N.J.M. Kuipers, A.B. de Haan and G. Kwant. Optimisation of process conditions for industrial separation of amino acid enantiomers by fractional reactive extraction. Proceedings of the International Solvent Extraction Conference, ISEC 2002; p. 620-625; South African Institute of Mining and Metallurgy: Johannesburg, 2002
2. A.B. de Haan, N.J.M. Kuipers, M. Steensma. Opportunities for extraction technology in chiral separations. Proceedings of the International Solvent Extraction Conference, ISEC 2002; p. 589-596; South African Institute of Mining and Metallurgy, Johannesburg, 2002
3. M. Steensma, N.J.M. Kuipers, A.B. de Haan and G. Kwant. Identification of enantioselective extractants for chiral separation of amines and amino-alcohols. Submitted to Chirality.
4. M. Steensma, N.J.M. Kuipers, A.B. de Haan and G. Kwant. Influence of process parameters on extraction equilibria for the chiral separation of amines and amino-alcohols with a chiral crown ether. Submitted to the Journal of Chemical Technology and Biotechnology.
5. M. Steensma, R.J.G.W. Stoffele, M.J. Rouhof, N.J.M. Kuipers, A.B. de Haan, G. Kwant. Fractional reactive extraction for chiral separation of amino-alcohols and amines: a pilot plant study. Submitted to International Solvent Extraction Conference, ISEC 2005, Beijing, China.
6. M. Steensma, N.J.M. Kuipers, A.B. de Haan and G. Kwant. Determination of reaction kinetics in reactive extraction for chiral separation of amino acids and amino-alcohols. Manuscript in preparation.
7. M. Steensma, N.J.M. Kuipers, A.B. de Haan and G. Kwant. Multistage equilibrium modelling of fractional reactive extraction for chiral separation. Manuscript in preparation.

Non-reviewed conference proceedings

1. M. Steensma, N.J.M. Kuipers, A.B. de Haan and G. Kwant. Extractant design for the separation of enantiomers by reactive extraction. Proceedings of AIChE annual meeting 2003, p. 396-403; American Institute of Chemical Engineers: New York, 2003.
2. M. Steensma, N.J.M. Kuipers, A.B. de Haan and G. Kwant. Development and optimisation of an enantioselective extractant for chiral separation of amino-alcohols by reactive extraction. Proceedings of CHISA 2004, Prague, Czech Republic, 2004.