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Organic Solvent Nanofiltration: fundamentals and application to Dynamic Kinetic Resolution

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ABSTRACT

The separation of molecules present in organic solvents by nanofiltration has great potential in a variety of industries from refining to pharmaceutical synthesis. Suitable organic solvent stable nanofiltration membranes have recently become available, thus starting a rapidly growing research field. However, there is still little information available on the processes controlling solvent fluxes and solute rejections in solvent nanofiltration and there is a multitude of applications waiting to be discovered. This thesis is divided into two sections.

In the first section, the transport properties of organic solvent nanofiltration (OSN) membranes have been investigated. The current state of knowledge in the field of OSN has been assessed: the membranes' structure, characterisation & manufacture, results of experimental investigations into their behaviour and their practical applications. Preliminary experiments were conducted to probe the membranes' basic behaviour and trends of flux and rejection with pressure were established. Mathematical descriptions of the transport processes controlling organic solvent nanofiltration were evaluated. Using this information along with the preliminary experimental results, the membranes were characterised using three simple pore models. A model combining the solution-diffusion model for membrane transport with the film theory for mass transfer limitations and allowing deviation from ideality, was derived and verified experimentally, with satisfactory results. The data suggests that due attention should be given to the governing thermodynamics and mass transfer effects, not just the membrane transport mechanism.

In the second section, the application of OSN to Dynamic Kinetic Resolution (DKR) was studied. Many molecules are inherently chiral and biological activity is highly dependent on enantiomeric purity. Generation of chirally pure species is important, especially in the pharmaceutical industry. One method for producing enantiomerically pure species is DKR. In this process an enantiospecific resolution is combined with a racemisation, thereby converting the unresolved enantiomer into the reacting enantiomer. Such systems are subject to the limitation that the two catalytic systems must be compatible in order to allow the convenience of a “one-pot” process, rather than a two stage process. This severely limits the scope of DKRs to a small number of compatible catalysts. OSN membranes have the potential to separate incompatible catalytic systems. Two DKR systems were identified and the chemistries of the systems in terms of the individual racemisation and resolution reactions were studied. The resolution was found to be the simpler of the two steps. The ‘one-pot’ reactions gave poor results in all cases. A continuous rig was designed to enable DKRs to be performed as a single process but with the two catalytic environments kept separate by an OSN membrane, thus removing the need for the resolution and racemisation systems to be compatible. This process, Membrane Enhanced Dynamic Kinetic Resolution (MEDKR), should allow an 100% conversion of reactant into an enantiomerically pure product. MEDKR experiments were performed in the rig using the two chemical systems already studied. In all cases, conversions were low and no successful MEDKR was achieved. This is thought to be due to negative interactions between the reactants and products of the resolution and racemisation systems and problems with membrane stability. Further work is required to discover DKR systems where this is not the case, whereby MEDKR could be achieved.

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CHAPTER 1

INTRODUCTION

The separation of molecules present in organic solvents by nanofiltration has great potential in a variety of industries from refining to fine chemical and pharmaceutical synthesis. Suitable organic solvent stable nanofiltration (NF) membranes have recently become available, thus starting a rapidly growing research field. However, there is still little information available on the processes controlling solvent fluxes and solute rejections in solvent nanofiltration and there is a multitude of applications waiting to be discovered. This thesis is divided into two distinct sections.

In the first section, the transport properties of organic solvent nanofiltration (OSN) membranes have been investigated. The current state of knowledge in the field of organic solvent nanofiltration has been assessed: the membranes' structure, characterisation & manufacture. The results of experimental investigations into their behaviour have been assessed including the effects of temperature, pressure and solvent on solute rejection and solvent flux. The practical applications of OSN membranes have been assessed. Currently, they are mainly employed for the retention and recycling of catalysts and solvents in chemical synthesis processes. Following this, preliminary experiments were conducted to probe the membranes' basic behaviour in terms of solute rejection and solvent flux. Model solute molecules were used along with solvents common in synthetic organic chemistry. Mathematical descriptions of the transport processes controlling organic solvent nanofiltration were evaluated. Simple models were used to estimate the pore size of the membranes, giving physically realistic values. A suitable transport model was selected and developed and a model to describe membrane transport was derived. Model parameters were obtained and the model was verified experimentally and was found to describe the data reasonably well.

In the second section, the application of OSN to the dynamic kinetic resolution (DKR) process was studied. Many biological molecules are inherently chiral and

biological activity is highly dependent on enantiomeric purity. Generation of chirally pure species is important, especially in the pharmaceutical industry. One method for producing enantiomerically pure species, DKR, has been studied. In this process an enantiospecific resolution is combined with a racemisation process, thereby converting the unresolved enantiomer into the reacting enantiomer. Such systems are subject to the limitation that the two catalytic systems (racemisation and resolution) must be compatible in order to allow the convenience of a "one-pot" process, rather than a two stage process. This severely limits the scope of such DKRs to a small number of compatible catalysts. The potential for the application of OSN membranes to separate incompatible catalytic systems has been investigated. This is the novel concept of Membrane Enhanced Dynamic Kinetic Resolution (MEDKR). The work divides into three parts. First, model DKR systems were chosen and the individual DKR reaction systems, the resolution and racemisation and the 'one pot' DKR were studied. Then suitable membranes to retain the resolution and racemisation catalysts were identified. Finally a MEDKR rig was designed and constructed and continuous MEDKRs were performed. The systems were found to be more complex than initially suspected and an inherent problem, that is the interference of the components of the two catalytic systems, was discovered. Also, the membranes, thought to be stable under the reaction conditions were found to degrade with time, thus losing their integrity. Although no successful DKR was achieved, much insight into the MEDKR process has been gained and it is hoped that MEDKR will be possible with different chemistries.

CHAPTER 2

ORGANIC SOLVENT NANOFILTRATION: LITERATURE REVIEW AND PRELIMINARY INVESTIGATIONS OF FLUX AND REJECTION

2.1 INTRODUCTION

Membranes are semi-permeable barriers capable of great selectivity, and can offer substantial savings in separations operations. In all membrane processes, separation is achieved because the membrane has the ability to transport one component of a feed mixture more readily than the others. The applicability of membranes is expanding rapidly, covering separations from the atomic or ionic range (solutes <1nm in size), to biological molecules with high molecular weights in the region 100 000 – 500 000 and particulate matter separations of macroparticles of size 1000 – 10 000nm. Membrane processes now include [1]: microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), reverse osmosis (RO), dialysis, pervaporation (PV), vapour permeation (VP) and membrane contactors. Table 2.1 summarises the basic types of membrane processes.

Membranes are available in various forms: flat sheets, tubes, fibres, in plate and frame configurations and spiral wound elements. Most laboratory scale work is performed using flat sheet membranes.

Nanofiltration [1] is a pressure driven process between reverse osmosis and ultrafiltration. A nanofiltration membrane has a looser structure than a reverse osmosis membrane allowing higher flux, but has a tighter structure than an ultrafiltration membrane, allowing the rejection of smaller organic molecules. The nanofiltration process is believed to occur through a combination of charge interaction and size exclusion [1].

Table 2.1: Details of membrane processes [1].

Process	Pressure range Bar	Pore size μm	MWCO range Da	Typical solutes separated
MF	0.1-2	1-0.1	> 1000000	yeast cells, bacteria
UF	1-5	0.1-0.01	1000000 – 10000	proteins, microsolute, colloidal silica, viruses, proteins, bacteria
NF	5-20	0.01-0.001	800-50	aqueous salts, metal ions sugar, proteins, microsolute
RO	10-100	N/A	100-50	aqueous salts, metal ions, sugar

The pressure driven membrane processes detailed in Table 2.1 are essentially confined to the treatment of aqueous solutions due to materials difficulties: membranes are found to be unstable in organic solvents. Recently, organic solvent stable membranes have been developed. The field of organic solvent nanofiltration (OSN) is rapidly expanding. However, there is little information on the behaviour of these membranes in non-aqueous systems. The work to date in this field broadly consists of:

1. Manufacture, structure and characterisation of organic solvent stable membranes
2. Experimental investigations into their behaviour
3. Their applications

These aspects of organic solvent stable membranes will be discussed in turn.

2.2 STRUCTURE, CHARACTERISATION & MANUFACTURE OF ORGANIC SOLVENT STABLE MEMBRANES

2.2.1 Basic membrane types

The choice of membrane material [1] is based on specific properties originating from structural factors. Membranes may be organic or inorganic. Organic membranes are polymeric. All polymers may be used as barrier or membrane materials, but chemical or physical properties vary so much that only a limited number are useful in practice. Various factors affect their properties: the polymeric repeat unit, chain configuration, interactions and flexibility, molecular weight distribution, the glass transition temperature, T_g , and melting temperature, T_m , and mechanical properties. The requirement for polymers to be solvent resistant is that they are insoluble in the solvent and do not swell detrimentally. The presence of certain groups like imide in the backbone can help to achieve this [2]. Co-polymerisation leads to rigid segments which impart solvent resistance, as does the presence of highly cross-linked sections. Membranes containing imide and siloxane linkages particularly exhibit chemical stability. Some of the organic polymers developed for solvent resistant applications comprise modified silicone rubber, methacrylates, polyimide and polyamides. Organic membranes can be *porous*, or *non-porous*. Porous membranes have an open structure and are often used for microfiltration and ultrafiltration. The selection of membrane material is normally determined by process requirements such as fouling tendency and chemical or thermal stability. Examples of polymers used to make porous membranes are polypropylene (PP), polytetrafluoroethylene (PTFE) and aromatic polyamides. Non-porous or dense membranes are often used for gas separation and pervaporation. Polyoxadiazoles may be used to make non-porous membranes. Selection of membrane material is normally governed by intrinsic material properties. Membranes may be composite (more than one polymeric material) or integral (one polymeric material only) and symmetric or asymmetric. Asymmetric composite membranes may be required because diffusion across the membrane is very slow. This necessitates a very thin active layer ($\sim 0\text{-}1.0\mu\text{m}$), in order to increase the flux, which may be mounted on a porous

support ($\sim 20\text{-}200\mu\text{m}$). Biological membranes [1] may also be used which have highly specific carrier mediated transport mechanisms. Inorganic membranes, often superior to organic membranes in terms of chemical and thermal stability, are limited in their use. There are four main types: ceramics (e.g. Al_2O_3), glasses (e.g. pyrex), metallic membranes (e.g. stainless steel) and zeolitic membranes. Inorganic membranes are often multi-layered with the advantage that each layer may be optimised independently.

2.2.2 Membrane characterisation

In order to understand the behaviour and differences between membranes, it is necessary to find some method of characterisation. The aim of membrane characterisation [1] is to relate structural properties to separation performance, so that an informed choice of membrane may be made for a given specific application. Note that there are differences between *intrinsic* and *actual* membrane properties: actual membrane properties are affected by phenomena such as fouling and concentration polarisation. Types of characterisation are shown in Figure 2.1. Details of structure related characterisation techniques are shown in Table 2.2.

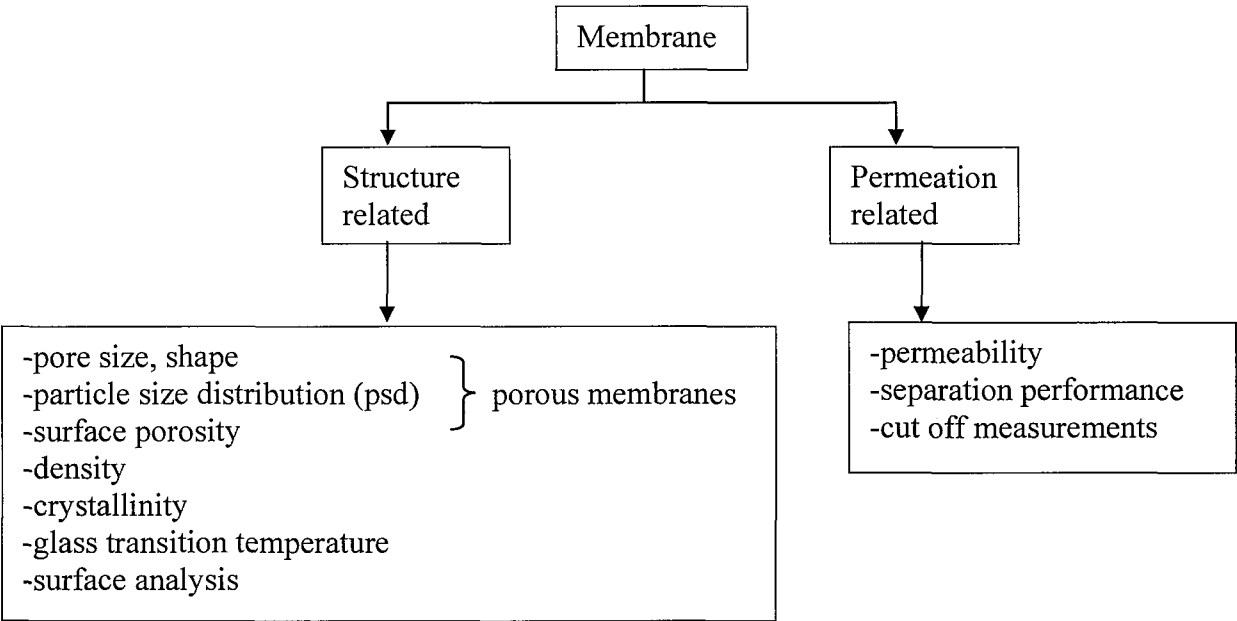


Figure 2.1: Types of membrane characterisation

Table 2.2: Structure related membrane characterisation techniques

Technique	Details	Ref.
Atomic force microscopy (AFM)	Topographical image of membrane surface generated; sizes of peaks and troughs measured.	[3,4]
Contact angle measurements	Measures surface energy of membrane.	[5,6]
Differential scanning calorimetry / thermal analysis	Chemical transitions / reactions in membrane polymer measured by quantifying energy required to counteract temperature change. Leads to information of crystallinity and T_g .	[1]
Liquid displacement	Liquid is used to displace a second, immiscible liquid already present in pores of porous membrane material. Allows calculation of particle size distribution, psd.	[1]
Plasma etching	Reaction between plasma and membrane surface allows measurement of thickness of active layer.	[1]
Spectroscopy	Characterises chemical groups on surface of membrane. For example, x-ray photoelectron or auger electron spectroscopy, scanning electron microscopy (SEM) and secondary ion mass spectroscopy.	[1]
Thermoporometry	Calorimetric measurement of solid-liquid transition of water in pores of porous membrane material allows pore size to be inferred.	[1]
X-ray diffraction	X-rays scattered by the membrane can give information about size and shapes of crystallites and degree of crystallinity.	[1]

Any type of membrane may also be characterised by its permeation behaviour. If a mixture is fed to a membrane (the feed) some components of the mixture will pass through the membrane (the permeate) and others will be retained (the retentate), as illustrated by Figure 2.2.

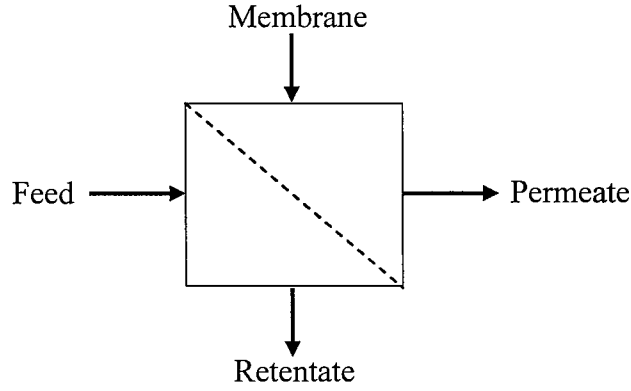


Figure 2.2: Schematic of basic membrane process

A membrane's separation properties [1] for a given solute may be determined experimentally and expressed as rejection (R) or retention (Rt). For a batch system:

$$R = 1 - \frac{c_p}{c_r} \quad (2.1)$$

$$Rt = \frac{c_r V_r}{c_0 V_0} \quad (2.2)$$

Where c is the concentration and V is the volume. The subscripts 0 , p and r the initial (feed), final permeate and final retentate conditions.

For a batch system, the flux or permeation rate is defined as the volume flowing through the membrane per unit area and time.

$$J = -A \frac{dV}{dt} \quad (2.3)$$

Membrane performance can change over time, for example due to fouling, concentration polarisation, adsorption, pore blocking and gel layer formation, and this may result in flux decline. Flux decline is a disadvantage of membrane processes, since at a lower

flux, less feed can be processed, thus increasing the overall cost. As a result, caution should be taken in defining the solvent flux through a membrane since it is not necessarily a constant.

The molecular weight cut off (MWCO) is the solute molecular weight at which a defined rejection is achieved, often taken as 90%. For some OSN membranes this can give a good first approximation, but the rejection is affected by the presence of a non aqueous solvent, due to swelling. The effect will be different for different solvents and will be affected by the properties of the solute molecule – chemical structure, charge and polarity. The MWCO is a good indication of the membrane's separation performance in aqueous solution but not such a good measure in organic solvents [7], which have been less widely researched. In addition, membranes may be unstable in more aggressive solvents which could cause swelling and / or cracking.

Various models exist to predict the rejection from membrane physical properties. These models necessarily make assumptions about the membrane structure, that is whether it is porous or non-porous. These will be discussed in Chapter 3.

Quantities frequently used in the characterisation of porous membranes [1] are the ratio of effective membrane thickness (Δx) to effective porosity (A_k) and the reflection coefficient (σ). If the membrane is charged, the charge density, X_d , [8],[9], surface charge density (q_w) and the ratio of charge density to electrolyte concentration (ξ), [9] may be used. Merieles *et al.* also use sieving coefficients [10] which are functions of diffusive and convective transport through the membrane and can be evaluated using hydrodynamic models of the flow in the pores, which may or may not exist in nanofiltration membranes. The performance of a porous membrane can be quantified by the permeability (L_p) [1], based on models of the flow through the pores. The Hagen Poisseuille model assumes that the flow occurs through parallel cylindrical pores, although, few membranes are actually like this. It expresses the flux (J) and hence the permeability as:

$$J = \frac{\varepsilon r^2}{8\mu\tau} \frac{\Delta P}{\Delta x} \quad \text{that is,} \quad L_p = \frac{\varepsilon r^2}{8\mu\tau} \quad (2.4)$$

ε is the surface porosity, given by $n\pi r^2$ /surface area and τ is the tortuosity.

Alternatively, the Carmen Kozeny model, which works well for organic and inorganic sintered membranes, assumes the membrane is formed of close packed spheres. The flux and permeability are given by:

$$J = \frac{\varepsilon^3}{K\mu s^2 (1 - \varepsilon^2)} \frac{\Delta P}{\Delta x} \quad \text{that is,} \quad L_p = \frac{\varepsilon^3}{K\mu s^2 (1 - \varepsilon^2)} \quad (2.5)$$

K is a constant which depends on pore shape and tortuosity and s is the internal surface area.

As mentioned earlier, many membranes, particularly nanofiltration membranes, may be asymmetric, consisting of an active surface layer, a porous support and often an ultrafiltration sublayer. Machado *et al.* have overcome the problem of the differing properties of the different layers by characterizing the membrane using a resistances in series model [11] which contains three experimentally determined parameters which characterise the transport process. Two of these characterise the membrane properties and the third characterises the solvent-membrane interactions.

2.2.3 Membrane manufacture

The preparation of synthetic membranes will be discussed in general, for organic and inorganic membranes. Then the preparation of specific nanofiltration membranes relevant to this study will be discussed.

2.2.3.1 Organic membranes

Synthetic organic membranes may be symmetric or asymmetric. Symmetric membranes, with a homogeneous structure, may be produced by the methods [1] outlined in Table 2.3.

Table 2.3: Methods for preparing symmetric organic membranes.

Method	Details	Pore Size	Porosity	Use
<i>Sintering</i>	A compressed powder is sintered at elevated temperatures so that the ‘interfaces’ between the particles disappear.	0.1-10 μ m	10-20%	MF
<i>Stretching</i>	An extruded film or foil is stretched. An applied stress causes the material to rupture, producing a porous structure.	0.1-3 μ m	Up to 90%	MF, UF, NF, dialysis
<i>Etching</i>	A film is subjected to high energy particle radiation which creates tracks in the film. The film is chemically etched away along the tracks, creating the pores.	0.02-10 μ m	<10%	
<i>Leaching</i>	One component is chemically leached out of a film.	Large range, Minimum of 0.005 μ m		

Asymmetric membranes are required when diffusion across the membrane is very slow, necessitating a very thin active layer, in order to increase the flux, on a porous support. The structure of such an asymmetric membrane is shown in Figure 2.3. Note that an asymmetric membrane may be integral or composite.

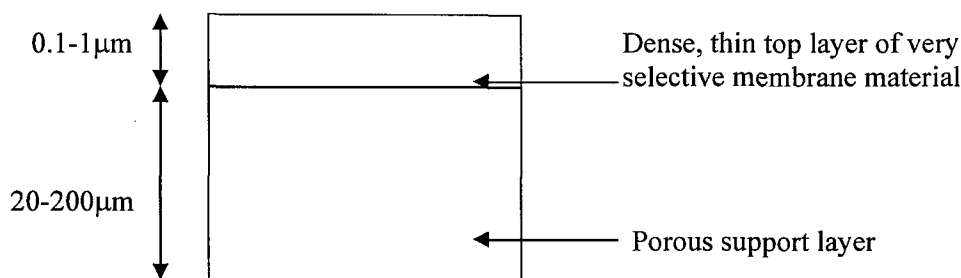


Figure 2.3: Schematic of basic structure of an asymmetric membrane.

Asymmetric integral membranes may be produced by phase inversion [1] from a single polymer: the polymer is dissolved in a solvent and coated onto a support. The solid matrix is then formed. Solidification can be achieved by precipitation by controlled evaporation, thermal precipitation from the vapour phase and immersion precipitation, where the wet supported film is immersed into a coagulation bath of non-solvent. By controlling the initial stage of phase transition the membrane morphology can be controlled. Most commercially available membranes are produced by immersion precipitation. The membrane structure ultimately obtained results from a combination of mass transfer and phase separation. Porous as well as non porous membranes can be formed by this method.

Alternatively, the membrane can be formed as a composite structure where the active layer is deposited on a thicker support matrix by spray coating, in-situ polymerisation (where the polymerisation reaction occurs at the interface between two immiscible solvents) or grafting. Grafting (e.g. radiation induced grafting) is a means of modifying dense membranes which allows a number of different kinds of groups to be introduced into the polymer resulting in membranes with completely different properties. A polymer film is irradiated with electrons which lead to the generation of radicals. The film is immersed in a monomer bath where the monomer diffuses into the film. Polymerisation is initiated at the radical sites in the polymeric substrate and a graft polymer is covalently bound to the basic polymer.

2.2.3.2 Inorganic membranes

Inorganic membranes are multi-layered with the advantage that each layer may be optimised independently. Figure 2.4 shows details of the manufacture methods [1] for each layer of a typical inorganic membrane.

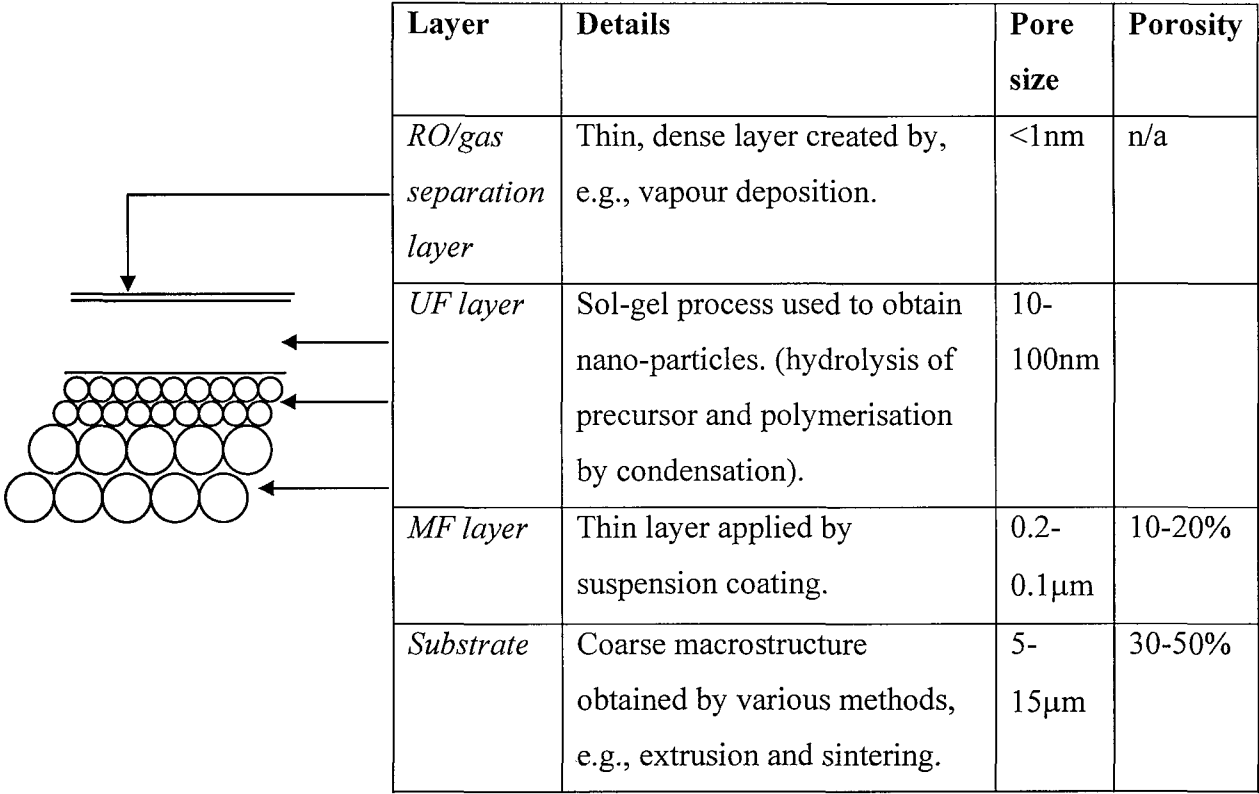


Figure 2.4 Methods for preparing inorganic membranes.

2.2.4 Manufacture of OSN membranes

Organic solvent nanofiltration membranes are polymeric materials, frequently based on silicone or polyimide structures. Table 2.4 shows details of commercially available OSN membranes. MPF membranes are supplied by Koch Membrane Systems inc. USA. Desal, membrane D and YK membranes are supplied by Osmonics, Switzerland. The STARMEM TM series of membranes are supplied by W.R. Grace, Columbia, M.D., USA. The N30F, NF-PES-10 membranes are supplied by Celgard, Germany. The UTC-

20 membrane is supplied by Toray, UK. Some further details are available about the manufacture of specific OSN membranes.

Table 2.4: Details of commercially available OSN membranes.

Membrane	Structure	Affinity	MWCO	Ref.
MPF 44	Negative silicone membrane	Hydrophilic	250	[7]
MPF 50, 60	Uncharged silicone membrane	Hydrophobic	700 ¹ , 400	[5, 7, 12-14]
Desal	Composite polyamide membrane	Hydrophilic	Not supplied	[5]
Membrane D	Composite PDMS membrane			[15]
YK	AP-based charged membrane			[15]
Starmem TM 120, 122, 228, 240	Integral asymmetric polyimide membranes	Hydrophobic	200, 220, 280, 400 ²	[16-18]
N30F, NF-PES-10	Polyethersulfone membranes	Hydrophilic	400, 1000	-
UTC-20	Positively charged polyimide	Hydrophilic	180	-

White *et al.* [16] use an asymmetric polyimide membrane formed by condensation of 2,4-diisocyanato methylbenzene and 1,1'-methylene bis[4-isocyanatobenzene] with 5,5'-carbonyl bis[1,3]-isobenzofurandione. In later work, White and Nitsch [17] use a polyimide formed from a condensation of diamino phenylindane with benzopenone tetra carboxylic dianhydride. The StarmemTM series of membranes from W.R. Grace consist

¹ Measured by the manufacturer using water as the solvent based on 95% solute rejection

² These are values from the manufacturer, calculated using toluene as the solvent and based on 90% solute rejection of n-alkanes.

of an active skin layer of less than 0.2 μm and pore size $< 5\text{ nm}$ covering a polyimide membrane body [16,17]. The structure of StarmemTM122 is shown in Figure 2.5. The polyimide used to manufacture the '2' series of Grace membranes, StarmemTM 228 and 240, Matrimid 5218, is shown in Figure 2.6. The membranes are made by dissolving the polymer in a solvent to give a viscous solution, spreading the solution upon a non-woven polyester support fabric, 'Hollytex 3329', partially evaporating the solvent to form a film and quenching the film in water. This precipitates the polymer and forms an asymmetric membrane by the phase inversion process.

MPF50 [19], from Koch membrane systems, is a polysiloxane composite OSN membrane with an outer layer of cross linked polydimethyl siloxane. It is supplied preserved in 50% ethanol solution. It is formed by dissolving the polymer in a solvent and applying the resulting solution to a polyacrylonitrile support by a technique such as dipping or spraying. The wet supported film may be immersed immediately or after a partial drying step in a gelling bath of a non-solvent such as water. This step removes the leachable material and results in a porous membrane.

No information is available about the manufacture about the Desal membranes.

Details of the manufacture of other non-commercial membrane can be found by consulting patents in the area. Kumar *et al.* [20] have patented a method for manufacturing a composite nanofiltration membrane. The membrane comprises a substrate ultrafiltration membrane formed from a nitrile polymer such as polyacrylonitrile and substituted polyacrylonitrile. The substrate is coated with a hydrophilic polymer, such as chitosan, containing reactive functional groups (e.g. amino groups) formed from an aqueous solution of the polymer. The functional groups are crosslinked with a cross linking reagent. The substrate membrane may be supported on a porous support fabricated from non-woven or woven polyethylene, glass fibres, graphite or inorganic supports based on alumina or silica. Miller *et al.* [21] have patented a method for manufacturing a membrane from a copolyimide produced by

solution-spinning or casting of the product of a condensation reaction in a solvent of at least three reactants selected from

1. a diamine A or A'
2. a dianhydride B or B'

The reactants are selected so that the polymer has a suitable glass transition temperature and degree of solvent resistance.

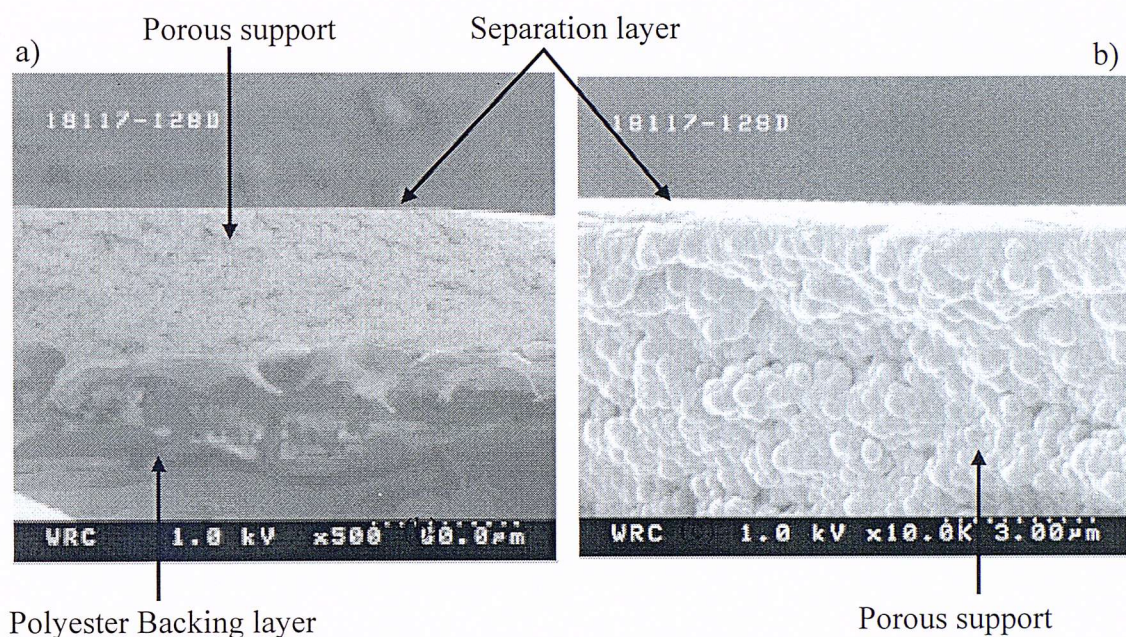


Figure 2.5: Electron micrograph picture of cross section of StarmemTM 122; a) 500x magnification, b) 10 000x magnification. Pictures courtesy of W.R. Grace, USA.

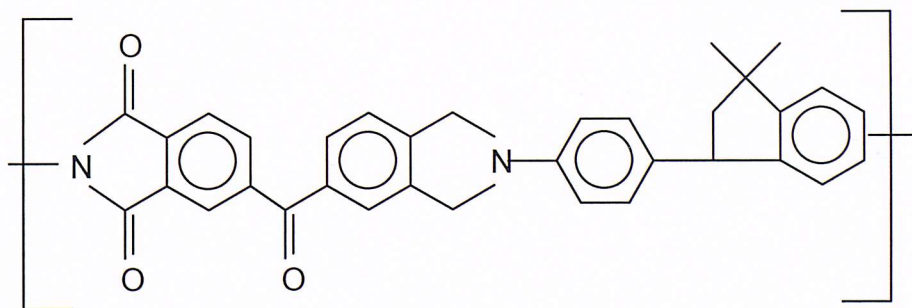


Figure 2.6: Structure of Matrimid 5218 used in the manufacture of StarmemTM '2' series membranes.

2.3 Experimental investigations into OSN

The first membranes used for organic systems were developed for aqueous systems, and the aqueous characteristics were assumed to apply also to organic systems. This, however, is not always valid, as it has been shown that some membranes can have widely different performances in different solvents [17]. Separation performance in one solvent cannot necessarily be transferred to another and characterisation experiments should be conducted in the solvent medium in which the membrane will be applied. For polymeric membranes this can be attributed to the tendency of the polymer to swell, to differing degrees, in different solvents.

Results of experiments probing the basic behaviour of OSN membranes reported in the literature are varied and inconclusive, as is to be expected in any new field, since no standardised protocols have been established. Table 2.5 summarises the work done in this field to date.

Table 2.5: Experimental results for OSN membranes.

Author [ref]	Membrane	Solute	Solvent	Results
Bhanushali <i>et al</i> [5]	MPF 50 Osmonics membranes	Dyes, triglycerides	Alcohols, alkanes	Correlation with solvent properties, e.g., sorption of solvent by membrane Rejection = function of MW.
Bhanushali <i>et al</i> [15]	Membranes D and YK	Dyes	Alcohols, alkanes	Rejection dependent on solvent and membrane. Solvent and solute fluxes are coupled.
Gibbins <i>et al</i> [22]	MPF 50 Starmem TM Desal	Quaternary alkyl ammonium bromide salts	Toluene, methanol	High rejections reported, MWCO and need for pre- treatment identified.

Author [ref]	Membrane	Solute	Solvent	Results
Machado <i>et al</i> [13]	MPF	-	Water, methanol, ethanol, propanol, acetone	Temperature and pressure effects reported. Correlation with solvent properties, within homologous series. Solvent mixtures investigated.
Linder <i>et al</i> [19]	MPF	Homogeneous catalysts	Ethyl acetate	High rejections observed.
Miller <i>et al</i> [21]	MPF	Rhodium organo-phosphite	But-aldehyde, acetone	Rejection >93% observed.
Raman <i>et al</i> [23]	MPF	Free fatty acids, vegetable oil	Methanol	Rejection >90% observed.
Robinson <i>et al</i> [24]	PDMS composite membrane	-	n-alkanes, i-alkanes, cyclic compounds	Differences between solvents attributed to swelling differences – Hildebrand solubility parameter. Positive intercept in graph of J vs P.
Robinson <i>et al</i> [24]	PDMS composite membrane	-	n-hexane, n-heptane, cyclohexane xylene	At high P, transport governed by hydraulic mechanism, low pressure, 2 nd mechanism (sorption, diffusion).
Scarpello <i>et al</i> [26]	Starmem TM Desal MPF	Organometallic catalysts	DCM, THF, Ethyl acetate	High rejections obtained (>78% for all solutes). Rejection trend follows trend in solvent flux. Effect of temperature and pressure noted.
Stafie <i>et al</i> [27]	PDMS supported on PAN	Sunflower oil, polyisobutylene	Hexane	Swelling and osmotic phenomena observed. Trends with pressure observed.

Author [ref]	Membrane	Solute	Solvent	Results
Tarleton <i>et al</i> [28]	PDMS composite membrane	Low polarity, sulphur bearing organometallic and polynuclear aromatic solutes	Alkyl / aromatic solvents	Rejection = f(trans membrane pressure, cross flow rate, solute size, degree of solvent induced swelling). MWCO of membrane characterised.
Van der Bruggen <i>et al</i> [29]	MPF, Celgard hydrophilic membranes	Maltose, raffinose, plus organic soluble compounds of similar MWs	Water Ethanol hexane	Results correlated with membrane affinity. Pretreatment shown to be important.
Vankelecom <i>et al</i> [30]	MPF50, Lab PDMS membrane	Dyes, Ru- BINAP	Acetone, MeOH, IPA, EA, toluene, DCM	Physio-chemical properties of membranes characterised by SEM and elemental analysis of top layer. Compaction of membrane observed.
White <i>et al</i> [17, 18]	Polyimide membrane	6 organic markers (aromatic / aliphatic, branched / unbranched)	toluene	Trends observed corresponding with solute structure.
Whu <i>et al</i> [14]	MPF	Dyes	methanol	Rejection increases with time.
Yang <i>et al</i> [7]	MPF	Dyes	Methanol, Ethyl acetate, toluene	High rejections obtained. Flux decrease over time. Stability and pre-treatment identified as areas for further work.

Generally, the membrane performance, which is less predictable in organic solution than in aqueous media depends on a number of different effects, as outlined below:

Polymer characteristics [13, 30]

Hydrophobicity, Hydrophilicity, polymer-solvent interactions

Solute parameters [7, 13]

Molecular size, aromaticity, solubility parameters, charge, polarity

Solvent parameters [7, 30]

Molecular size, viscosity, air-liquid surface tension, contact angle, polarity, dielectric constant, dipole moment

Physical parameters [30]

Pressure, concentration, stirring

The collection of reproducible data seems difficult, for example, Machado *et al.* [13] and Whu *et al.* [14] report contradictory flux data (150 and 40 L/m²h respectively for permeation of methanol through MPF50 at 30 bar pressure) due to differing pre-treatment methods. Data suggest a compaction effect under pressure [22], reaching a maximum level after which the flux and separation properties are steady. A pre-treatment method should be employed such that it is ensured that the membrane is operating at steady state. Authors also report stability problems and, as mentioned earlier, that the concept of MWCO seems an insufficient indicator of separation capabilities when organic solvents are used.

2.4 Applications of OSN

Table 2.6 summarises the work published on the application of OSN membranes to industrial or chemical processes.

Table 2.6: Practical applications of OSN membranes.

Author	Membrane	Process	Solvent	Other details
Aerts <i>et al</i> [31]	MPF60, lab. silicone membrane	Recycling of homogeneous Co- Jacobsen catalysts for hydrolytic kinetic resolution of epoxides.	Methanol	Catalyst successfully recycled.
Datta <i>et al</i> [32]	Dense PDMS layer on PAN support	Recycling of Heck catalysts, enlarged by phosphinated polymers, in coupling reactions of aryl halides.	THF, DMS, dioxane, DMA, DEE, toluene, cyclohexane	Retention of >99.95% of catalysts, enabling catalyst recycle up to 9 times.
De Smet <i>et al</i> [12]	MPF 60	Reactions catalysed by chiral compounds.	Methanol	High enantioselectivity achieved.
Ebart <i>et al</i> [33]	Polyamide / cellulose active layer, on porous polyamideimide support	Edible oil recovery. (proven at lab. and pilot plant scale).	Acetone	Advantages compared with conventional methods in terms of energy savings, solvent usage and waste disposal.
Giffels <i>et al</i> [34]	Polystyrene gel.	Production of chiral alcohols from ketones in membrane reactor with Polymer enlarged oxazoboralides.	THF, Methanol, Toluene	High enantioselectivity and catalyst recycling achieved.
Nair <i>et al</i> [35]	MPF 50 / 60	Homogeneous Heck catalysis.	Ethyl acetate, THF, water acetone, MTBE	Membranes used to improve reactor productivity.

Author	Membrane	Process	Solvent	Other details
Kataro <i>et al</i> [36]	MPF 50 /60	Multistage membrane process for recovery of solvents / solutes in chromatographic systems.	Acetonitrile, acetone, methanol ethanol	Application to pharmaceuticals.
Koris <i>et al</i> [37]	Mavibran FP055A, SP15A	Removal of phospholipids from crude vegetable oil,	Ethanol, propanol	
Luthra <i>et al</i> [38]	Starmem TM series	Catalyst separations in continuous, homogeneous phase transfer reactions.	Toluene	
Raman <i>et al</i> [23]	Several commercial and prototype membranes	Solvent recovery and partial deacidification of vegetable oils.	Hexane	Free fatty acids and triglycerides separated from oils.
White [17]	Polyimide membranes	Recovery of solvent from lube oil filtrates.	MEK, Toluene	Used to debottleneck refrigeration and recovery sections of solvent lube plant.

As can be seen from the table, the membranes' application is very limited, with only one example of bench to commercial scale OSN process scale up [17]. Whu *et al.* [14] have also performed a theoretical study into the use of OSN membranes coupled with an organic synthesis reactor, showing that the use of membranes could significantly enhance reaction conversion, speed up reaction time and improve selectivity. Clearly there is still a great opportunity for the application of OSN membranes in real industrial situations.

An important aspect of this research area highlighted by this chapter is that the collection of reproducible data is difficult, which seems to be due to differing pre-

treatment methods. This leads to the conclusion that a standardised pre-treatment method should be employed in order to ensure that the membrane has equilibrated at the experimental conditions and is operating at steady state. The first experimental work to be conducted will therefore aim to establish such a standardised pre-treatment protocol and using this protocol, collect reliable and repeatable data for membrane transport properties using various solvents, solutes and membranes. It is hoped that this data will provide insight into the potential mechanisms of membrane transport, which can then be investigated further.

Following on from the work reviewed in Table 2.5, experimental observations of solvent flux and solute retention by OSN membranes were made using various solutes, solvents and membranes. The aim of this work is to give some insight into the membrane transport mechanisms before more detailed modelling work is carried out.

2.5 PRELIMINARY INVESTIGATIONS: MATERIALS AND METHODS

Experiments were conducted using several membranes in a stainless steel, SEPA ST (Osmonics, USA) dead end nanofiltration cell with an effective membrane area of 14cm^2 . The experimental setup is shown in Figure 2.8. The membranes employed were those commonly used in organic solvent systems: StarmemTM 122, from W.R.Grace, MPF50, from Koch Membrane Systems and Desal DL, from Osmonics. The driving force for the filtration was pressure applied with nitrogen gas. The experiments were conducted at 20°C .

Solvents commonly employed in organic synthesis reactions were chosen: methanol and toluene. Solvents were used as supplied from Aldrich chemical co., Dorset, U.K. The flux of pure solvent through the membrane was measured until it became steady. Once the contents of the SEPA cell had permeated through the membrane, the pressure was

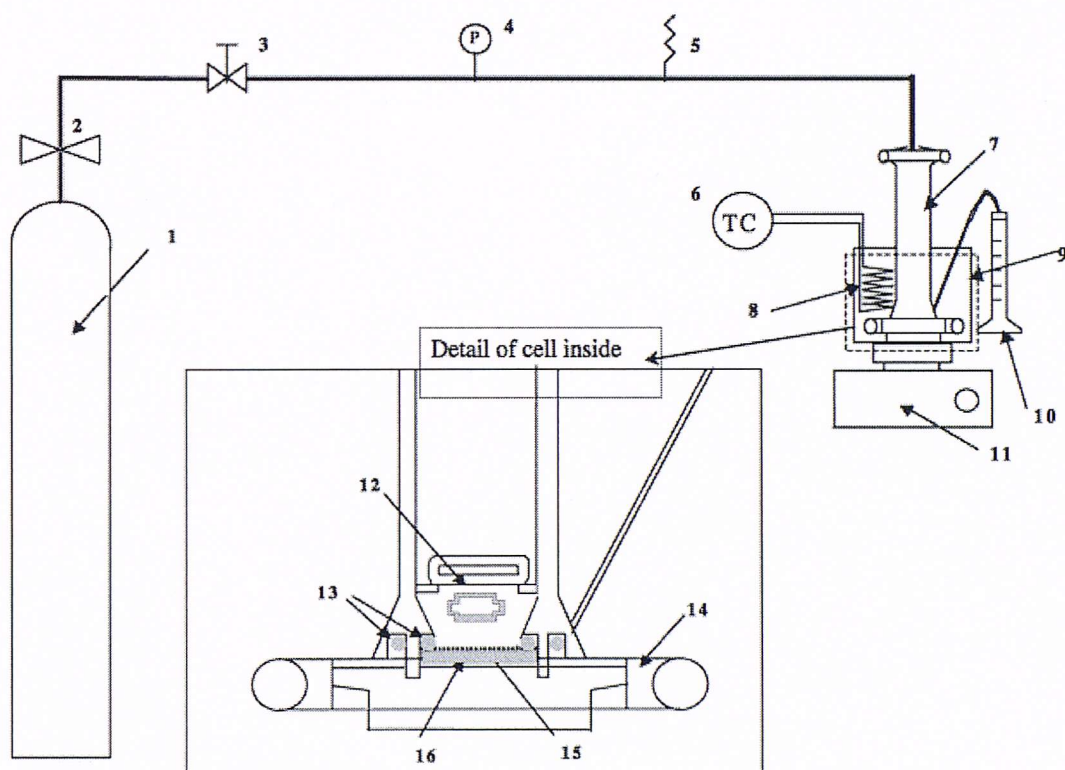
released, the cell refilled with solvent and the permeation repeated. This was done three times (run 1, run 2 and run 3). It is assumed that the final flux at the end of run 3 is the 'steady state flux'. In most cases, an absolutely steady flux will never be achieved, the flux will continue to decline indefinitely, but for the purposes of this work, the flux change after the 3 pre-conditioning runs changes only negligibly and therefore can be assumed 'steady'. The initial and final fluxes, and time taken to reach a 'steady' flux were noted for each pressure tested. Separation properties of the membranes were investigated for well-conditioned membranes, that is, membranes for which a steady flux had been obtained. The separation properties were obtained by loading the cell with a feed solution containing a range of symmetric quaternary alkyl ammonium bromide salts (quats), supplied by Aldrich, each at 0.005M in the solvent of choice and applying pressure until half the feed volume had permeated. These quats were chosen because of their similarity to the organometallic complexes which catalyse a variety of reactions for synthesising pharmaceutical intermediates, such as palladium organic complexes used in Heck couplings [35]. The feed, permeate and retentate concentrations were measured using gas chromatography. A new membrane disc was used at each pressure to avoid the influence of polymer memory [13]. Experiments were conducted in quick succession to prevent reversible compaction affecting the results.

2.6 SOLVENT FLUX RESULTS

The solvent flux properties of membranes were measured with methanol and toluene. For methanol, one of the polyimide StarmemTM series of membranes, StarmemTM 122 (MWCO = 220) was compared with the silicone membrane MPF50. Comparing two membranes made of different polymeric materials will make it clear whether the material of the membrane itself has a part to play in determining its flux properties. It is interesting that both the membranes used are hydrophobic, yet it is still possible to permeate methanol, suggesting a porous transport mechanism.

Figure 2.9 shows that for successive uses of the StarmemTM 122 membrane and methanol, at all pressures, the initial flux decline of solvent decreased and stable fluxes

could be achieved more quickly. The solvent flux converges towards a constant final flux characteristic of the membrane at a given pressure. The flux decline can be attributed to membrane compaction under pressure, reaching a critical level beyond which no further compaction can occur and a steady flux is achieved. The fluxes show a positive relationship with pressure, which is consistent with other data reported in the literature, and consistent with the two main mathematical models used to describe permeation through this type of membrane, the pore flow model and the solution diffusion model. Mathematical modeling will be discussed in further detail in chapter 3.



KEY: 1. nitrogen cylinder, 2. pressure regulator, 3. isolation valve, 4. pressure gauge, 5. pressure relief valve, 6. heater/cooler, 7. Osmonics Sepa ST pressure cell with high pressure couplings, 8. copper cooling coil connected to 6., 9. water bath, 10. measuring cylinder for permeate collection, 11. magnetic stirrer, 12. magnetic stirrer bar, 13. Viton seals, 14. Sepa ST high pressure coupling, 15. membrane disk, 16. permeable stainless steel disk.

Figure 2.8: Dead end cell configuration.

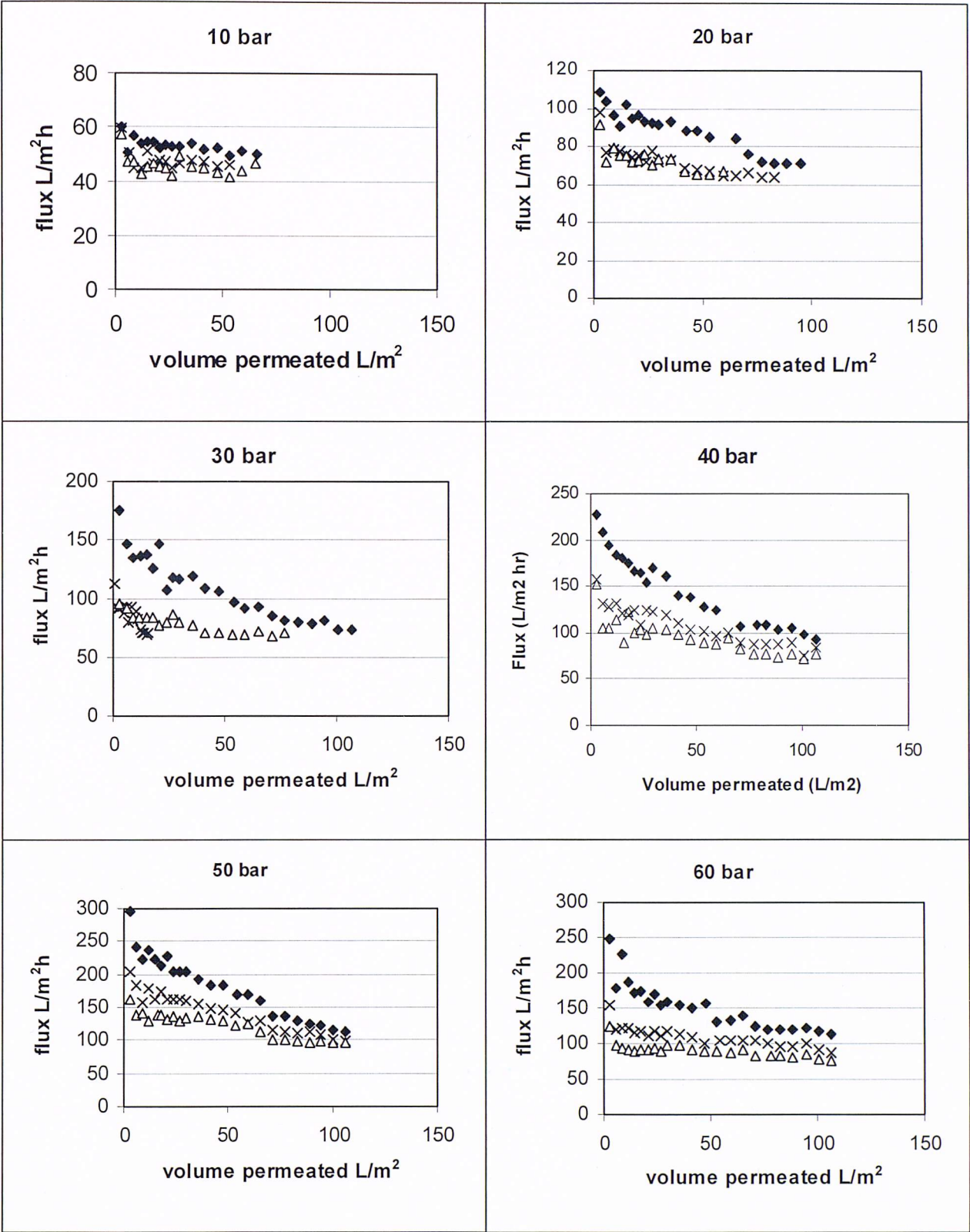


Figure 2.9: Pure methanol flux decline across StarmemTM 122 at various applied pressures. ♦ Run 1 △ Run 2 x Run 3.

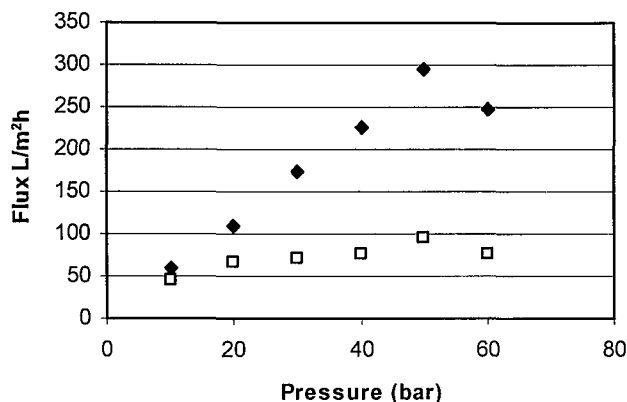


Figure 2.10: Effect of pressure on pure methanol flux across Starmem™ 122.

The graphs in Figure 2.9 also show that the flux decline effect becomes more pronounced at higher pressures. This could be because the membrane experiences a greater compaction at higher pressures. This effect is shown more clearly by Figure 2.11, where the percentage flux decline over the three permeation runs is shown as a function of pressure. The flux decline reaches a steady value of 70% as pressure is increased, taking longer to equilibrate to its final compaction level at higher pressures. The data suggests a critical pressure of around 40 bar, beyond which the percentage flux decline is constant, and further increases in the pressure have no effect in terms of speed of equilibration of the membrane.

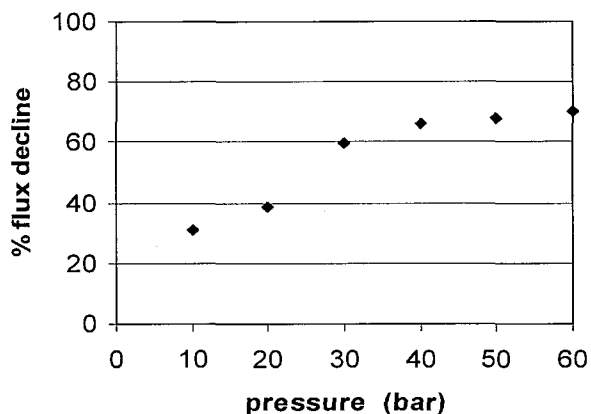


Figure 2.11: Effect of pressure on percentage flux decline over three runs for pure methanol across Starmem™ 122.

The methanol flux decline at various pressures was also measured across the MPF50 membrane. MPF50 behaves in a very different way from StarmemTM 122. It responds very quickly to pressure, reaching steady state almost immediately, that is, there is virtually no flux decline at any pressure, an example of which is shown in Figure 2.12, for 40 bar. The same phenomenon is observed for the other pressures investigated. Another interesting difference between the two membranes investigated is the behaviour between successive runs. For StarmemTM 122, the compaction is partially reversible, that is the flux at the beginning of a run is greater than that at the end of the previous run. Whereas, for MPF50, as shown in Figure 2.12, the flux at the end of the run 1 is almost identical to that at the start of run 2, about 60 L/m²h, indicating that any compaction that has occurred (albeit a small effect) is permanent and is not reversed by releasing the pressure before the subsequent runs. This difference can be attributed to different physical properties of the polymers from which the two membranes are manufactured.

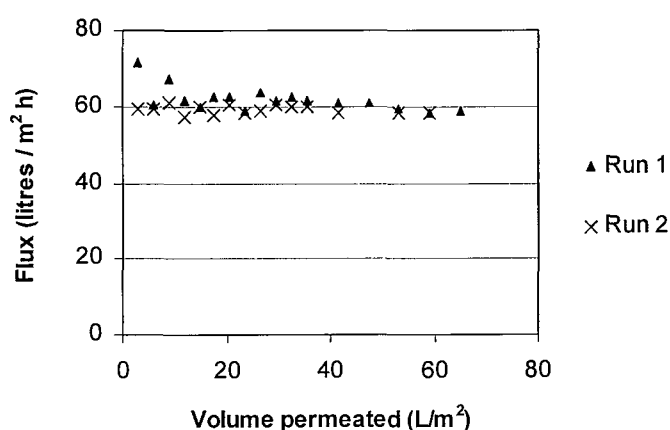


Figure 2.12: Pure methanol flux decline across MPF50 at 40 bar.

As for StarmemTM 122, the relationship between pressure and pure methanol flux for MPF50, shown in Figure 2.13, is positive, as expected.

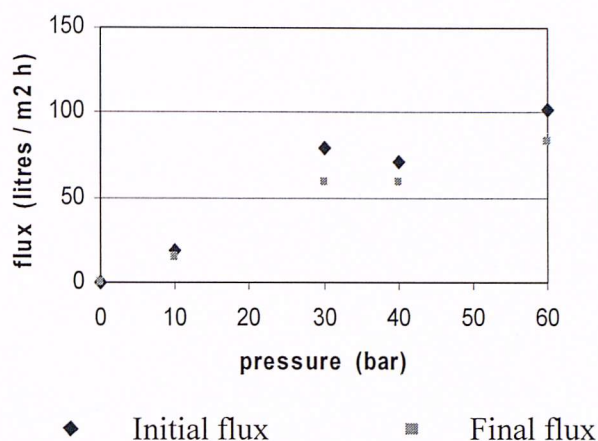


Figure 2.13: Effect of pressure on pure methanol flux across MPF50.

Figure 2.14 shows that for StarmemTM 122, and toluene, the flux decline effect is much less pronounced than with methanol, especially at low pressures where there is a negligible flux decline. What compaction effect exists is irreversible, as the flux at the start of a run is the same as that at the end of the previous run. Therefore, it seems that, in a toluene environment, the polymeric material of StarmemTM 122, is less susceptible to compaction and the consequent flux decline. Figure 2.15 shows that, as in all the previous cases the relationship between pressure and flux is found to be linear.

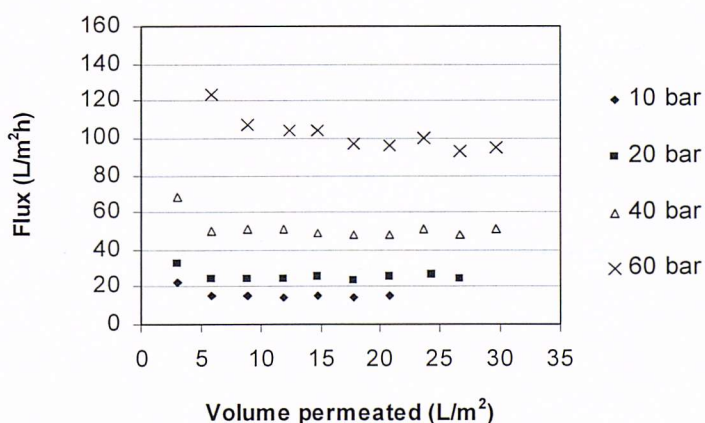


Figure 2.14: Pure toluene flux decline across StarmemTM 122, at various applied pressures.

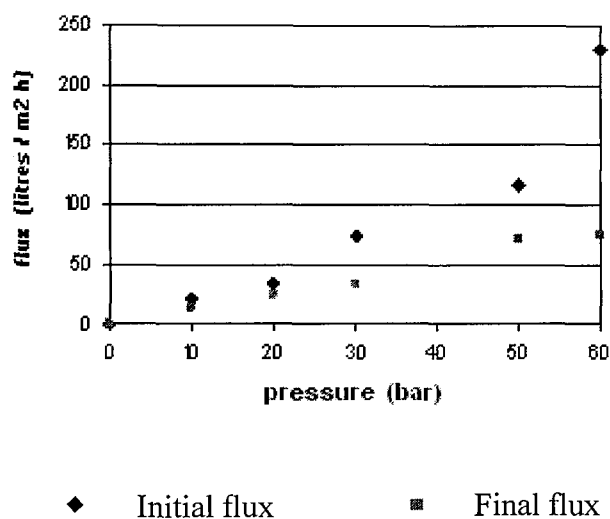


Figure 2.15: Effect of pressure on pure toluene flux across Starmem™ 122.

It is interesting to compare the behaviour of the same membrane with the two different solvents. A comparison of Starmem™ 122 with methanol and toluene is shown in Figure 2.16. As expected, the general trend for both solvents is the same, that is, a linear increase in flux with pressure. The toluene flux is greater than the methanol flux. This indicates that there is a greater affinity between the membrane material of Starmem™ 122 and toluene than methanol since it allows a greater permeation of the former. Given that differences were also found between the behaviour of the same membrane with different solvents, it seems that interactions between the membrane material and the solvent will be important in characterising the relationship between solvent and flux. It is likely that each new membrane and solvent combination will behave differently and should be investigated prior to commencing work. This will be considered further in the Chapter 3, where the modeling of transport processes is investigated. The conclusion from this is that the choice of solvent is crucial for any given membrane in order to obtain a reasonable flux. High fluxes are necessary in real applications to ensure an adequate throughput of material.

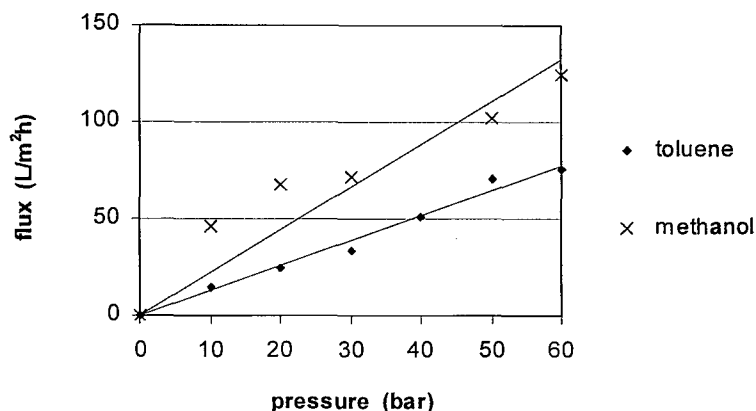


Figure 2.16: Effect of pressure on pure solvent flux across Starmem™ 122.

2.7 SOLUTE REJECTION RESULTS

The effect of pressure on the rejection of the membrane was studied for a range of quats using well-conditioned membranes. A clear positive dependence is observed for Starmem™ 122 with both methanol and toluene, as shown in Figures 2.17 and 2.18. A higher rejection for larger molecular weight quats at a given pressure is consistent with a size exclusion mechanism of membrane transport, and, as discussed earlier, higher rejection at higher pressures is consistent with compaction: at higher pressures, the membrane is more compacted. This forces the polymer chains in the membrane closer together, thus making it more difficult for the solute molecules to pass. Higher rejections are found with methanol at all pressures, with a rejection of around 100% being observed at the highest pressure, 50 bar. As discussed previously, the interaction between the membrane and the membrane polymer will be important in these processes. The polymer will behave differently with different solvents, for example, swelling to different degrees, which will change its separation characteristics for a given solute. The data sets for both solvents suggest the presence of a molecular weight cutoff (MWCO) of 200-250, above which high rejections, greater than 90%, are obtained at all pressures. This is consistent with the nominal MWCO of 220 for Starmem™ 122, as stated by the manufacturer. Note that in Figure 2.18, the rejection of a lower molecular weight

species, stilbene (MW = 180.24) is shown to demonstrate that a molecule of size less than the MWCO is retained poorly by the membrane.

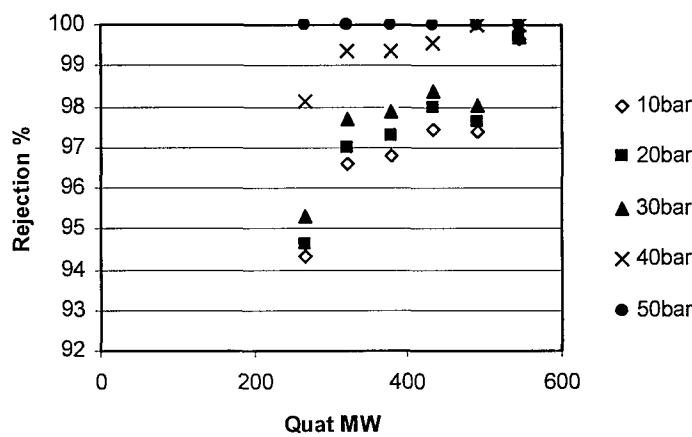


Figure 2.17: Influence of MW and applied pressure on rejection of a molecular weight spread of quats in methanol with StarmemTM 122.

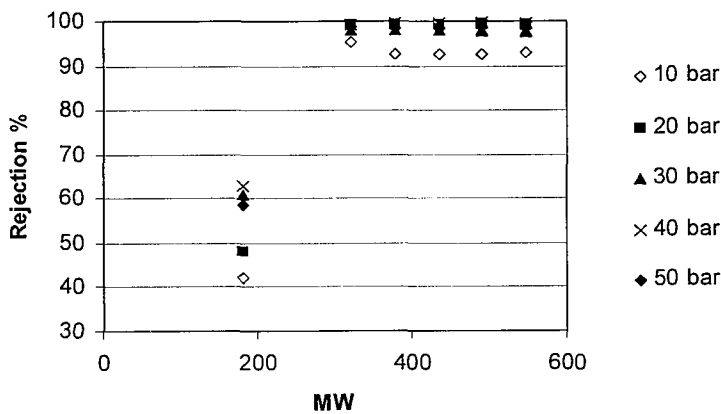


Figure 2.18: Influence of MW and applied pressure on rejection of a molecular weight spread of quats in toluene with StarmemTM 122.

A clear positive dependence of rejection on molecular weight and pressure was also observed for MPF50 using methanol as the solvent, as seen in Figures 2.19. The rejections are slightly lower than with StarmemTM 122, suggesting that MPF50 has a

looser structure. This is as expected since the nominal MWCO for MPF50, as stated by the manufacturer is 700, much greater than that of StarmemTM 122. The data shown in Figure 2.19 suggests a MWCO of around 300, which is not consistent with the value of 700 quoted for this membrane. This can be attributed to the fact that the manufacturer value was measured using water as the solvent and the response of the membrane in an organic rather than an aqueous system is likely to be very different.

It was demonstrated that as the amount of solvent permeated across the membrane prior to quat filtration was increased, the rejection improved; the underlying effect causing flux decline seems to have a positive effect on rejection. This suggests membrane compaction under pressure resulting in constant flux and rejection after a critical volume of solvent is permeated, for example, 200mls of solvent for StarmemTM 122 at 30 bar, as shown in Figure 2.20. This demonstrates the need for pre-conditioning treatment prior to measuring separation performance. Inconsistency in the literature data [13, 14] can be explained by different pre-conditioning methods since membrane performance is highly dependent on the volume with which the membrane is pre-conditioned. For all future membrane experiments, the membrane will be pre-conditioned before use by permeating the pure solvent in which the experiments will be conducted until the flux has stabilised to a constant value.

In the case of a solution, as in the case of the quat solutions, flux decline could also be attributed to the formation of a secondary membrane or gel layer, where the solute builds up at the surface of the membrane during permeation as a result of the fact that it has a higher rejection than the solvent.

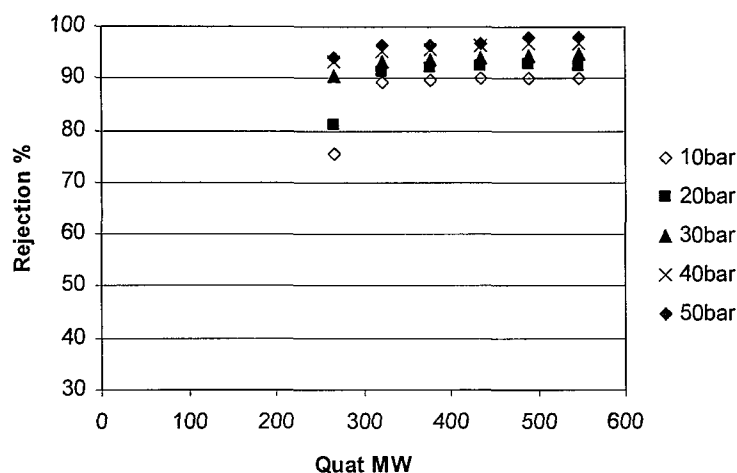


Figure 2.19: Influence of MW and applied pressure on rejection of a molecular weight spread of quats in methanol with MPF50.

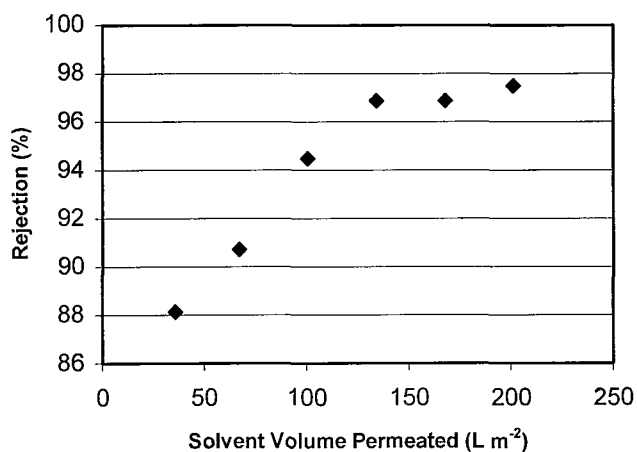


Figure 2.20: Influence of preconditioning volume on rejection of 0.005M tetra butyl ammonium bromide (MW=322) in methanol, using StarmemTM 122.

2.8 CONCLUSIONS

The work in this section has allowed a better understanding of the basic behaviour of OSN membranes using solvents typical in organic synthesis reactions. A standard preconditioning protocol has been established which will help to obtain good results from a

given membrane and will allow better comparison of different experiments. The data collected shows that there are substantial differences between the behaviour of one membrane in different solvents and equally, between different membranes in the same solvent. Therefore, it is clear that the interactions between the polymer material of the membrane and the solvent are important. More insight will be gained into the behaviour of these membranes by studying the transport mechanisms and their mathematical description in more detail.

CHAPTER 3

TRANSPORT PROCESSES: LITERATURE REVIEW and MODELLING

The conclusion from the experiments described in Chapter 3 indicated that the interactions between the membrane material and the solvent used may have an important effect on the performance of the membrane. In order to understand the behaviour of OSN membranes more fully, their transport mechanisms need to be studied. This will allow the transport mechanism to be modelled and a mathematical description of the transport to be derived.

3.1 INTRODUCTION

Although the application of OSN membranes is becoming more widespread, the mechanism by which nanofiltration membranes work in organic solution is still not well understood. Various models exist to predict the permeation properties of a membrane. The models fall into two categories [39]: those which make no assumptions about the membrane structure or transport mechanism (thermodynamic or phenomenological, ‘black box’ models) and those assuming a structure (either porous or homogeneous). The different types of models will now be discussed.

3.2 PHENOMENOLOGICAL METHODS

The thermodynamics of irreversible processes [39] indicate that the flow of each component in a solution is linked to the flows of other components. The Spiegler Kedem irreversible thermodynamics model [40] describes the system in terms of a reflection coefficient, σ . $\sigma = 0$ represents no rejection; $\sigma = 1$ represents 100% rejection. Note that when $\sigma = 1$, the model reduces to the solution diffusion model (which will be discussed in further detail later).

For the solvent $J_v = L_p (\Delta P - \Delta \Pi)$ (3.1)

For the solute $J_s = -P \Delta x \frac{dc}{dx} \pm (1 - \sigma) J_v c$ (3.2)

The rejection can be calculated from these equations as:

$$R = \frac{\sigma(1 - F)}{1 - \sigma F} \quad (3.3)$$

where $F = \exp(-J_v a_2)$ (3.4)

and $a_2 = \frac{1 - \sigma}{P_m}$ (3.5)

where J_v = solvent flux (L/m²h), L_v = hydraulic permeability coefficient (m/s kPa), P_m = overall permeability (m/s), σ = reflection coefficient, $\Delta \Pi$ = osmotic pressure different (bar), ΔP = pressure difference (bar).

Therefore, the transport is characterised by the three parameters L_p (solvent permeability), σ (reflection coefficient) and P (solute permeability).

3.3 POROUS MEMBRANES

In pore models, the membrane is assumed to be porous and the transport takes place through the pores under the influence of pressure. Pore models relate the rejection of the membrane to its main intrinsic physical property: pore size or pore size distribution. In general, the flux (J), is proportional to the pressure gradient across it:

$$J \propto \frac{dp}{dx} = \frac{k(p_0 - p_l)}{l} \quad (3.6)$$

Where k = mass transfer coefficient (m/s), l = membrane thickness (m), p_0 and p_l are the upstream and downstream pressures.

The profiles across the membrane are shown in Figure 3.1.

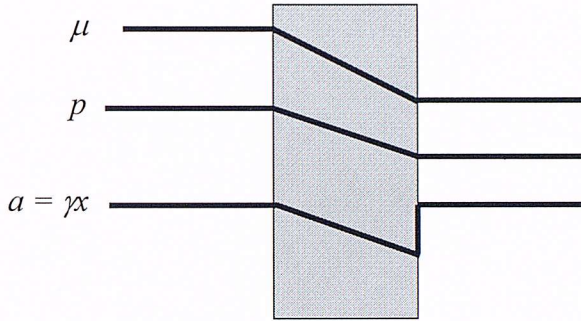


Figure 3.1. Gradients across the membrane, assuming pore flow model: chemical potential (μ), pressure (p) and activity (a). Note: activity is the product of the activity coefficient (γ) and the concentration (x).

Mathematical details of some of these models are given below. All of the models discussed neglect the effect of osmotic pressure. The validity of this assumption will be discussed in section 3.9.1, when the pores models are applied to the data collected in Chapter 2.

Sieve constant model of Ferry and steric hindrance pore model [41]

The model assumes that the membrane works under ‘normal’ filtration conditions, that is, without pore blocking. The pores are cylindrical and perpendicular to the surface. The direction of flow is perpendicular to the surface. Solute molecules have a constant diameter and permeate only within the pores. The sieve constant is defined as the ratio of the permeate concentration to the feed concentration:

$$\phi = c_p/c_f \quad (3.7)$$

If d_p is the pore diameter and d_s is the solute diameter, the following inequalities are assumed:

$$\begin{aligned} d_p < d_s & \quad \phi = 0 \\ d_p > d_s & \quad 0 < \phi < 1 \\ d_p \gg d_s & \quad \phi = 1 \end{aligned}$$

Solutions being filtered follow streamlines which, in the plane of the membrane, are distributed according to the Poiseuille formula. This allows calculation of the velocity at the mouth of the pore, the volume of the solution entering the pore and the number of particles entering the pore. The concept of statistical sieving due to steric limitations is built into the model: a solute molecule has a certain probability of entering a pore depending on how close it passes to the mouth of the pore. This probability is 1 where the solute falls within the pore radius, that is, where the solute centre falls within a circle of diameter $(d_p - d_s)$. This model leads to the *Ferry formula*:

$$\phi = 1 - 2(1 - \eta)^2 + (1 - \eta)^4 \quad (3.8)$$

where $\eta = d_s/d_p$ = ratio of the solute diameter to the pore diameter

Hence the retention properties of the membrane, in the form of the sieving constant can be predicted from a simple relationship between the solvent and pore dimensions.

The model has the following limitations:

1. Restricted condition for solute penetration: a solute may strike the edge of the pore and be conveyed into the pore by the flux of the solvent.
2. Electrical charge is neglected
3. Penetration of a solute into a pore does not guarantee its emergence on the permeate side: solutes may become caught inside the pores.

Various authors have developed the model. Renkin [42] includes viscous forces in the pore to allow for friction between the solute and pore wall. Pappenheimer [39], Kamide and Manabe [42] build membrane pore size distributions into the model, Kamide and Zeman and Wales [39] express the Ferry formula in terms of the reflection coefficient, $\sigma = 1 - \phi$, which can in term be expressed in terms of the permeate and feed concentrations, c_p and c_f .

$$\sigma = 1 - \phi = 1 - \frac{c_p}{c_f} = 1 - 2(1 - \eta)^2 + (1 - \eta)^4 = 1 - (\eta(\eta - 2))^2 \quad (3.9)$$

Zeman and Wales [39] also include a factor to account for steric hindrance which causes hydrodynamic lag during the convective flow in the pores. Based on experimental results, the factor is assumed to have an exponential dependence on the ratio, η :

$$\text{Factor} = v_{\text{molecule}}/v_{\text{water}} = K_2/K_1 = \exp(-\alpha\eta^2) \quad (3.10)$$

Where α , K_1 and K_2 are constants and v is the velocity.

The reflection coefficient therefore becomes,

$$\sigma = 1 - [(\eta(\eta - 2))^2] \exp(-\alpha\eta^2) \quad (3.11)$$

The steric hindrance pore (SHP) model [40] uses the parameter, σ , and accounts for interactions with the pore wall. The reflection coefficient is given by

$$\sigma = 1 - H_F S_F \quad (3.12)$$

Where H_F represents the effect of the pore wall and S_F represents the steric hindrance:

$$H_F = 1 + (16/9)\eta^2 \quad (3.13)$$

$$S_F = (1 - \eta)^2 [2 - (1 - \eta)^2] \quad (3.14)$$

The SHP model gives acceptable results but due to the idealised modelling of the membrane the results could be improved upon. Note also that the model ignores pressure dependent diffusion limitations.

Log normal model [43]

A log normal distribution is assumed for the pore size distribution, characterised by two parameters, $\underline{r}$, the mean pore size, which is the size of molecule that has a retention of 50% retention, and S_p the standard deviation. Steric hindrance and hydrodynamic lag are ignored and the diffusive contribution to transport is considered negligible. It is assumed that a molecule permeates through every pore that is larger than its diameter. The reflection coefficient is the sum of the fraction of pores that are smaller than the molecular diameter, r^* .

$$\sigma(r^*) = \int_0^{r^*} \frac{1}{S_p \sqrt{2\pi}} \frac{1}{r} \exp\left(-\frac{[\ln(r) - \ln(\underline{r})]^2}{2S_p^2}\right) dr \quad (3.15)$$

This gives a good estimation of the reflection coefficient but the results could be optimised by accounting for hydrodynamic lag in the pores, using the velocity ratio of Zeman and Wales given in equation (3.10). It is assumed that solutes are completely retained if their diameter is larger than the pore. If their diameter is smaller than the pore, they are partially retained to the extent that the velocity in the pores is lower than the water velocity.

σ = sum of fraction of pores that are smaller than the molecular diameter

+

term representing fraction of molecules retained by larger pores

Thus the reflection coefficient is expressed in terms of $\underline{r}$, S_p and α .

The experimental results of Van de Bruggen et al. [40] showed that the hydrodynamic lag was unimportant. Therefore, although the adapted model is theoretically the 'best' model, no significant advantage is seen from taking the lag into account and the simple log normal model has the advantage of only two parameters.

Note that these models should be checked for physical and experimental consistency:

1. the retention should increase with molecular diameter

$$\text{i.e. } dR/dr > 0 \text{ for } r > 0$$

2. a molecule of ∞ diameter should be retained completely.

$$\text{i.e. } \lim_{\eta \rightarrow \infty} R(r) = 1$$

The log normal models were found to comply with these physical observations as long as $\alpha > 0$.

Pore model of Verniory [43, 44]

Of the three parameters of the irreversible thermodynamics model, L_p , σ and P , defined earlier in equations 3.1- 3.5, the solvent permeability can be found from pure solvent flux (J_v) experiments, the other two parameters can be found by simple curve fitting, using the pore theory of Verniory:

$$J_s = P(c_m - c_p) + J_v c_f (1 - \sigma)$$

$$J_s = Df(\eta)S_D \frac{A_k}{\Delta x} (c_m - c_p) + J_v c_f g(\eta)S_F \quad (3.16)$$

Where, D = diffusivity (m^2/s), η = ratio of solute diameter to pore diameter, A_k = membrane porosity, Δx = membrane thickness (m), c_m = concentration in the membrane, c_p = permeate concentration, c_f = feed concentration

g and f are analytic functions of η , which have been calculated by Haberman and Sayre. S_D and S_F are steric hindrance factors accounting for diffusive and filtration flow, also analytic functions of η , with the same form as the Ferry formula:

$$S_D = (1 - \eta)^2 \quad \text{and} \quad S_F = 2(1 - \eta)^2 - (1 - \eta)^4 \quad (3.17)$$

The membrane parameters can be expressed as:

$$\sigma = 1 - g(\eta)S_F \quad \text{where} \quad g(\eta) = \{1 - 2/3\eta^2 - 0.2\eta^5\}/(1 - 0.76\eta^5) \quad (3.18)$$

$$P = Dg(\eta)S_D \left(\frac{A_k}{\Delta x} \right) \quad (3.19)$$

These equations allow the calculation of the pore radius, r_p and the ratio of membrane porosity, A_k to membrane thickness, Δx . As the porosity of a given membrane is a constant, this allows calculation of the pore thickness. Equally, with the rejection data of a given membrane, the equations can be used to calculate the physical parameters defining the membrane.

Surface force pore flow model [39]

The surface force pore flow model (SFPPF) was first reported by Matsuura and Sourirajan in 1985. It is a quantitative expression of the preferential sorption capillary flow model (PSCF) and characterises the flow on the basis of the pore size distribution (or, more simply, average pore size) and a measure of the surface forces between the solute, solvent and pore walls.

The assumptions of the model are as follows:

1. transport is governed by interaction, friction and driving forces
2. pores are cylindrical
3. as in the PSCF model, a layer of pure water is preferentially sorbed onto the membrane surface
4. a solute potential field exists in the pore which controls the radial distribution of the solute

The basic elements of the model are:

The velocity profile in the pore is written in dimensionless form which is solved with appropriate boundary conditions to give the intrinsic rejection of the membrane:

$$R = 1 - \frac{\int_0^1 c_s(r_p^+) v_p^+(r_p^+) r_p^+ dr_p^+}{\int_0^1 v_p^+(r_p^+) r_p^+ dr_p^+} \quad (3.20)$$

where

$v_p^+(r_p^+)$ is the dimensionless velocity as a function of the dimensionless radial position (r/r_p) .

$$c_s(r_p^+) = \frac{\exp[v_p^+(r_p^+)]}{1 + (b(r_p^+)/\exp[-\Phi(r_p^+)])\{\exp[v_p^+(r_p^+)] - 1\}} \quad (3.21)$$

b is the friction parameter which is the ratio of the frictional force on the solute in the pore to that in the bulk. It is a function of $\underline{d}/r_p$ where $\underline{d}$ is the characteristic distance of steric hindrance which can be approximated by the Stokes radius of the solid.

In accounting for the sorbed water layer adjacent to the membrane surface, the pore radius is defined as $r_p = r_a + d_w$ where d_w , the diameter of a water molecule, is taken to be 0.87 Å and r_a is the effective pore radius. r_a should therefore be used in the equations rather than r_p .

The above model assumes that the pore radius is a constant. A more realistic model uses a pore distribution with an extra term, $Y_i(r_p)$ representing the frequency of the distribution. This model can be solved numerically [45].

Extended Nernst Plank model [46, 47]

Bowen *et al.* use the extended Nernst-Planck equation for uncharged solutes, that is, neglecting electric potential in the following form:

$$J_s = -D_{s,p} \frac{dc_s}{dx} - K_{s,c} c_s J_v \quad (3.22)$$

where J_s = solute flux

$D_{s,p}$ = hindered diffusivity = $K_{s,d} D_{s,\infty}$

$D_{s,\infty}$	= bulk diffusivity
C_s	= concentration in membrane
V	= velocity
$K_{s,d}$ and $K_{s,c}$	= hindrance factors for diffusion and convection
J_v	= solvent flux

The hindrance factors incorporate details about the membrane's pore size, as they are functions of η , the ratio of solute radius to pore radius. They are related to the hydrodynamic drag coefficients K^l and G , the enhanced drag and the lag coefficient for a spherical solute moving in an infinitely long cylindrical pore. K^l and G (and hence the hindrance factors) are defined as analytic functions of η and are also dependent on the velocity profile in the pore.

For porous nanofiltration membranes, for the solvent, the steric pore flow model is used where the velocity profile is assumed to be parabolic, described by the Hagen Poiseuille equation:

$$J_v = \frac{r_p^2 \Delta P}{8\mu(\Delta x / A_k)} \quad (3.23)$$

thus, if r_p is known, for example from atomic force microscopy, the value of $\Delta x / A_k$ can be calculated from the solvent flux data.

The value of $\Delta x / A_k$ can be used to enable the rejection properties of the membrane to be calculated by integrating the Nernst-Planck equation across the membrane with concentrations at the membrane surface expressed in terms of the bulk permeate and feed concentrations using equilibrium partition coefficients, Φ_s :

$$R_s = 1 - \frac{K_{s,c} \Phi_s}{1 - \exp(-Pe_m)[1 - \Phi K_{s,c}]} \quad (3.24)$$

$$\text{The Peclet number is } Pe_m = \frac{K_{s,c}}{K_{s,d}} \frac{V \Delta x}{D_{s,\infty} A_k} \quad (3.25)$$

$$\text{And } \Phi = \frac{c_{s,x=0}}{C_{s0}} = \frac{c_{s,x=\delta}}{C_{sp}} \quad (3.26)$$

where c = concentration at membrane surface

C = concentration in bulk

δ = membrane thickness

When the interactions between the solute and the pore wall are purely steric, Φ_s accounts for the finite size of the solute and $\Phi_s = (1-\eta)^2$.

Bowen *et al.* [46-48] have also done considerable investigation into the characterisation of nanofiltration membranes used with charged solutes, using parameters determined experimentally and from the Donnan-steric-pore-model (DSPM) [46]:

r_p average pore radius, obtained by atomic force microscopy

$\Delta x/A_k$ ratio of effective membrane thickness to effective charge, obtained from water flux and the Poiseuille equation:

$$J_w = \frac{r_p^2 \Delta P}{8\mu(\Delta x / A_k)} \quad (3.27)$$

X_d effective membrane charge density, obtained by fitting rejection and flux data using the DSPM model.

The DSPM model (for charged solutes) defines concentrations, fluxes, potentials and velocities in terms of radially averaged quantities and applies the conditions of electroneutrality with expressions for electric potential gradient.

Hindered transport model of Deen [49]

Rates of transport through membranes are often lower than expected because transport is hindered due to the fact that the constrained space of the membrane's pores causes

molecular friction to increase with respect to an unbounded solution. Steric restrictions and long-range intermolecular forces also play a part causing interactions between the solutes and the pore wall. In his hindered transport model, Deen, accounts for these factors. The basic assumptions of the model are:

1. pore radius (r_0) and solute radius (r_s) $\gg$ solvent radius
2. pore length $\gg$ pore radius (ignore end effects; velocity profile fully developed)
3. dilute (no solute-solute interactions)

The driving force for transport is the gradient in chemical potential which leads to a body force on the molecules being transported, or a hydrodynamic force. Ignoring pressure contributions, the diffusional force = hydrodynamic force (Stokes):

$$kT \frac{\partial \ln c}{\partial z} = -6\pi\eta r_s K(U - Gv) \quad (3.28)$$

K = enhanced drag coefficient

U = velocity

G = lag coefficient

V = unperturbed velocity

The solute flux, N is given by

$$N = Uc = -\frac{D_\infty}{K} \frac{\partial c}{\partial z} + Gvc \quad (3.29)$$

where D_∞ is given by the Stokes formula:

$$D_\infty = \frac{kT}{6\pi\eta r_s} \quad (3.30)$$

The coefficients K and G , which account for effects of finite pore size, depend on η as in previous models. Assuming cylindrical pores, the velocity, as function of β (the dimensionless pore size, r/r_0), is given by:

$$v = 2 \langle v \rangle (1 - \beta^2) \quad (3.31)$$

Since radial variations of the concentration are important, c , v , K and G all vary with β . Therefore, N varies with β too. It is more useful to use $\langle N \rangle$, the flux averaged over the pore cross section. Therefore, $\langle N \rangle$ can be expressed in terms of $\langle c \rangle$, the mean concentration, as the local flux equation:

$$\langle N \rangle = -K_d D_\infty \frac{d\langle c \rangle}{dz} + K_c \langle v \rangle \langle c \rangle \quad (3.32)$$

K_c and K_d are integrals of the inverse drag and lag coefficients. Equation (3.32) can be integrated over the pore length with appropriate boundary conditions derived from the equilibrium between the material just inside and outside the pores to give:

$$\langle N \rangle = \frac{W \langle v \rangle c_0 [1 - (c_l / c_0) e^{-Pe}]}{[1 - e^{-Pe}]} \quad (3.33)$$

Pe is the Peclet number defined by $Pe = \frac{W \langle v \rangle L}{H D_\infty}$ (3.34)

H and W are hindrance factors for convection and diffusion which are defined mathematically. Their evaluation is affected by lack of complete hydrodynamic information. They can be determined analytically using the centre-line approximation, that is, that β is zero. Note that the transport is dominated by diffusion and convection for $Pe \ll 1$ and $Pe \gg 1$ respectively. The reflection coefficient can thus be determined from $\sigma_f = 1 - W$ (3.34)

Of course this model does have limitations. It can be extended using extra terms accounting for, for example:

- electric field (affects hindrance factors)
- electrostatic interactions (need an extra length scale – the Debye length)
- differing pore shapes
- non spherical solutes (by using a mean projected molecular dimension)
- solute-solute interactions (likely to be important at high concentrations) which cause deviations in the radial distributions and hydrodynamic interactions.

Summary of pore models

A number of models have been discussed, all of which assume that material passes through a membrane as a result of pore flow. In order for the models to be practical, they necessarily simplify the structure of the membrane, normally confining the pore shape to be cylindrical and the pore orientation to be perpendicular to the membrane surface and often assuming that the pore size is uniform. Some of the models are derived mathematically from analysing the transport of the solute such as the hindered transport model of Deen and the Nernst-Planck model. Others are more empirically derived based such as the Pappenheimer extension to the Ferry formula or statistically based like the log normal model. Although the models necessitate assumptions and simplifications about the structure of the membrane, many give adequate descriptions of membrane transport.

3.4 NON POROUS MEMBRANES

The main transport model for homogeneous membranes is the solution diffusion model [50]. This states that solute / solvent molecules dissolve into the membrane material, diffuse across the membrane under a concentration gradient and emerge at the other side. It is assumed that fluid on either side of the membrane is in equilibrium with the material at the interface, that is, there is a continuous chemical potential gradient from one side of the membrane to the other. The flux of any component through the membrane is proportional to the chemical potential gradient. Separation is achieved because of differences in the amount of different species that dissolve in the membrane and their diffusion rate.

It is assumed that the pressure across a membrane is uniform and that the chemical potential gradient is expressed as a concentration gradient. Note how this is different from pore-flow models which assume that the concentration gradients in the membrane are constant and the chemical potential gradient is expressed as a pressure gradient. The

membrane gradients for a solution diffusion membrane are shown in Figure 3.2 (compare Figure 3.1 for pore flow models).

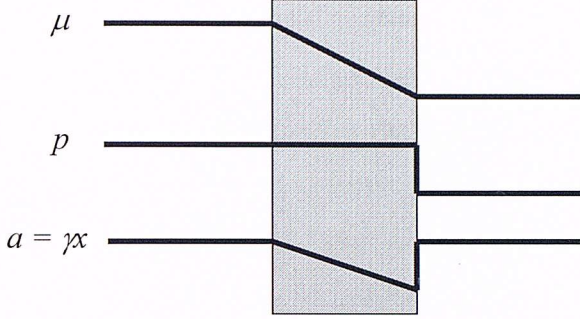


Figure 3.2: Gradients across the membrane, assuming solution diffusion model: chemical potential (μ), pressure (p) and activity (a). Note: activity is the product of the activity coefficient (γ) and the mole fraction(x).

A derivation of the solution diffusion model follows, as reported by Wijmans and Baker [50]. The flux of any component, i , is proportional to the chemical potential gradient:

$$J_i = -L_i \frac{d\mu_i}{dz} \quad (3.35)$$

In general, the chemical potential gradient consists of pressure and concentration driving forces:

$$d\mu_i = RT d \ln(\gamma_i x_i) + v_i dp \quad (3.36)$$

where v_i is the molar volume of species i , R is the ideal gas constant and T is the temperature, x_i is the mole fraction of species i .

Assuming incompressibility, and integrating equation (3.36) with $p_{iF} = p_{isat}$ gives an expression for chemical potential:

$$\mu_i = \mu_i^o + RT \ln(\gamma_i x_i) + v_i (p - p_{iF}) = \mu_i^o + RT \ln(\gamma_i x_i) + v_i (p - p_{isat}) \quad (3.37)$$

A chemical potential balance on each side of the membrane will be conducted, as indicated by Figure 3.3.

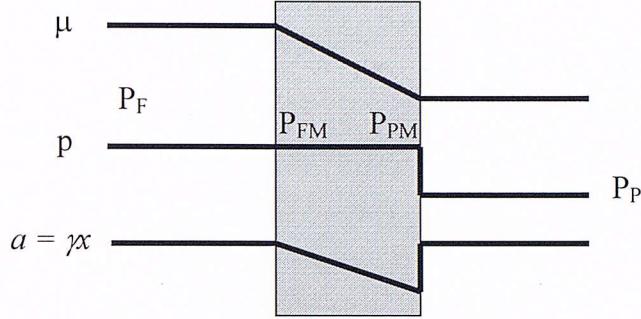


Figure 3.3: Details of chemical potential balance across membrane.

Performing chemical potential balance on the feed side for any species, i , gives,

$$x_{iFM} = \frac{\gamma_{iF}}{\gamma_{iFM}} x_{iF} = K x_{iF} \quad \text{where } K = \gamma_{iF} / \gamma_{iFM} \quad (3.38)$$

And on the permeate side,

$$x_{iPM} = \frac{\gamma_{iFM}}{\gamma_{iF}} \frac{\gamma_{iF}}{\gamma_{iFM}} \frac{\gamma_{iP}}{\gamma_{iPM}} x_{iP} \exp\left(-\frac{\nu_i (p_{PM} - p_P)}{RT}\right) \quad (3.39)$$

Then Wijmans and Baker make the assumption that $\frac{\gamma_{iFM}}{\gamma_{iPM}} = 1$ and $K_i = \gamma_{iF} / \gamma_{iFM}$, as defined in equation (3.38), and assume that the ratio between the upstream and downstream activity coefficients are equal,

$$x_{iPM} = K_i x_{iP} \exp\left(-\frac{\nu_i (p_{PM} - p_P)}{RT}\right) \quad (3.40)$$

Fick's law, states that $J_i = -D_{iM} \frac{dx_i}{dz}$. Now assuming a constant diffusion coefficient and integrating gives:

$$J_i = \frac{D_{iM}(x_{iF} - x_{iPM})}{l} \quad (3.41)$$

Comparing this with equation (3.35), it can be seen that the chemical potential gradient is $(x_{iF} - x_{iPM})/l$ and the proportionality factor is D_{iM} .

$$\text{So, } J_i = \frac{D_{iM}K_i}{l} \left[x_{iF} - x_{iP} \exp\left(-\frac{\nu_i(p_{PM} - p_P)}{RT}\right) \right] \quad (3.42)$$

For the **solvent**, for which osmotic pressure is important, this can be simplified using the assumption that the activity coefficients are equal and the fact that the flux is zero when the pressure difference is equal to the osmotic pressure, $\Delta\Pi$:

$$J_i = 0 = \frac{D_{iM}K_i}{l} \left[x_{iF} - x_{iP} \exp\left(-\frac{\nu_i(\Delta\Pi_i)}{RT}\right) \right]$$

$$\text{which gives } x_{iP} = x_{iF} \exp\left(\frac{\nu_i\Delta\Pi_i}{RT}\right) \quad (3.43)$$

Substituting equation (3.43) back into equation (3.42) gives the expression for flux:

$$J_i = \frac{D_{iM}K_i}{l} \left[x_{iF} - x_{iF} \exp\left(\frac{\nu_i\Delta\Pi_i}{RT}\right) \exp\left(-\frac{\nu_i(p_{PM} - p_P)}{RT}\right) \right]$$

$$J_i = \frac{D_{iM}K_i x_{iF}}{l} \left[1 - \exp\left(\frac{\nu_i(\Delta p - \Delta\Pi_i)}{RT}\right) \right] \quad (3.44)$$

This can be simplified further for easier mathematical manipulation using the following assumption: $1 - \exp(x) \rightarrow x$ as $x \rightarrow 0$, which gives:

$$J_i = \frac{D_{iM}K_i x_{iF} \nu_i (\Delta p - \Delta\Pi_i)}{lRT} \quad (3.45)$$

Note that by letting $\frac{D_{iM} K_i c_{iF} v}{lRT} = B$, equation (3.45) reduces to the osmotic pressure model where the coefficient, B, is the membrane permeability or resistance. Note that this is for the solvent only.

$$J_i = B(\Delta P - \Delta \Pi_i) \quad (3.46)$$

Similarly for the **solute**, equation (3.42) becomes:

$$J_i = \frac{D_i K_i}{l} (c_{i0} - c_{i1}) = B(c_{i0} - c_{i1}) \quad (3.47)$$

where B is the solute permeability.

There is no exponential term because it is assumed that the pressure difference of the solute across the membrane is negligible.

Equations (3.46) and (3.47) are the most commonly used simplified forms of the solution diffusion model. Note that if the membrane permeability is constant and the solute rejection ~100%, a plot of solvent permeate flux against applied pressure should be a straight line with an intercept equal to the osmotic pressure. In many cases, this equation is accurate enough to describe experimental data. However, as Bhanushali *et al* [5] point out, this version of the solution diffusion equation makes an approximation based on the relatively small molar volume of their solvent, water (18 cm³/mol). This approximation is good enough for aqueous systems, however, it may not be valid in the case of systems where the solvent is a large hydrocarbon. Bhanushali [5] *et al.* have calculated the error for pure decane as 21% at 47 bar pressure. The same argument can be applied to the simplifications made by Wijmans and Baker for the solute transport. If the solute molar volume is significant and / or the rejection different from 100%, this simplification could generate considerable error.

But if we want to be able to predict the permeate side concentration, x_{iP} , but don't have information on osmotic pressure, we cannot use equations (3.43) and (3.44). Starting

again with equation (3.42), we can eliminate x_{ip} by calculating the mole fraction in terms of fluxes rather than concentrations. So for component i,

$$x_{ip} = \frac{J_{ip}}{J_{ip} + J_{jp}} \quad (3.48)$$

Which gives:

$$J_i = \frac{D_{iM}K_i}{l} \left[x_{iF} - \frac{J_i}{J_1 + J_2} \exp\left(-\frac{v_i(p_{PM} - p_P)}{RT}\right) \right] \quad (3.49)$$

Now let, the constant $D_{iM}K_i/l = P_{iM}$, the membrane permeability and the pressure difference across the membrane be the applied pressure, p . This gives the following equations, for components 1 and 2:

$$J_1 = P_{1m} \left(x_{1F} - \frac{J_1}{J_1 + J_2} \exp\left(-\frac{v_1 p}{RT}\right) \right) \quad (3.50)$$

$$J_2 = P_{2m} \left(x_{2F} - \frac{J_2}{J_2 + J_1} \exp\left(-\frac{v_2 p}{RT}\right) \right) \quad (3.51)$$

It is interesting to note that the solution diffusion model reduces to the V'ant Hoff equation under certain conditions. Starting with equation (3.42) as before, again for the solvent (component i), and setting the conditions to osmosis, that is, $\Delta\Pi_i = \Delta P$ and $J = 0$, gives:

$$c_{iF} = \frac{\gamma_{iP}}{\gamma_{iF}} c_{iP} \exp\left(\frac{-v_i \Delta\Pi_i}{RT}\right)$$

$$\Delta\Pi_i = \frac{RT \ln \gamma_{iP} c_{iP} - RT \ln \gamma_{iF} c_{iF}}{v_i} \quad (3.52)$$

Component i is the solvent, and if we assume high solute rejection, then the permeate side is essentially pure solvent. Therefore, $c_{iP} \sim 1$ and $\gamma_p \sim 1$ and equation (3.52) becomes:

$$\Delta\Pi_i = \frac{-RT \ln \gamma_{iF} c_{iF}}{v_i} \quad (3.53)$$

Now, letting component j be the solute: $c_{iF} + c_{jF} = 1$ so, $c_{iF} = 1 - c_{jF}$. Also, $\ln(1-x) \sim -x$ and with the fact that the V'ant Hoff equation is valid only for ideal solutions, that is, those where $\gamma = 1$, equation (3.53) becomes:

$$\Delta\Pi_i = \frac{RTc_{jF}}{v_i} \quad (3.54)$$

The mole fraction of the solute divided by the molar volume of the solvent can be rewritten as the molar concentration of j, the solute, [j], thus giving the V'ant Hoff equation, which is valid for ideal solutions and at high rejections:

$$\Delta\Pi_i = RT[j] \quad (3.55)$$

Several authors have used the solution diffusion model to explain and describe their experimental data. For example, White *et al.* [17] experimentally determine the parameter in equation (3.49), D_iK_i/L for the permeation of mixtures of toluene, lube oil and methyl ethyl ketone through polyimide membranes and successfully use the solution diffusion model to describe their experimental results.

The solution diffusion model as presented by Wijmans and Baker has a number of shortcomings:

1. Assumes constant ratio of activity coefficients
2. Requires information about the osmotic pressure, which may not be available
3. Does not provide any description of mass transfer limitations on the feed side
4. Assumes equal equilibrium partition coefficients on both sides of the membrane
5. Assumes low solvent molar volume, which may not be valid in organic systems
6. Assumes low swelling of the membrane (<10-15%), which may not be valid in organic systems

In order to overcome some of these problems, various authors have made attempts to extend the solution diffusion model. Bhanushali et al. [5] relate the solvent diffusivity in the membrane to the solvent viscosity as:

$$\frac{D_i}{T} \propto \frac{1}{\mu}.$$

Combining this with the expression for the solvent permeability, equation (3.45) and using the solvent molar volume, V_m gives:

$$J_i \propto A_i \propto \frac{V_m}{\mu}$$

The model can be further extended by including membrane properties such as factors accounting for sorption and cluster formation and surface energy, γ ,

$$J_i \propto A_i \propto \left(\frac{V_m}{\mu} \right) \left(\frac{1}{\gamma} \right) \quad (3.56)$$

The solution diffusion model assumes that both solvent and solute transport occur by diffusion, with no absorption of solute and / or solvent into the membrane material. Williams *et al.* [51] report that Rautenbach and Gröschl suggested that a better assumption for potentially absorbed organics is that the total solute and solvent concentration in the membrane is constant. This implies that there is a finite number of sites in the membrane that may be occupied by both the solvent and solute molecules. Mathematically, this conservation is: $x = x_i + x_j$ where x is the total concentration in the membrane. They use this assumption in conjunction with the Langmuir isotherm, equation (3.57), to substitute for the concentration in equation (3.44) to generate a new form of the solution diffusion model.

$$\frac{x_i}{x} = \frac{b_0 x_0}{1 + b_0 x_0} \quad (3.57)$$

Paul *et al.* [52] investigate the use of the solution diffusion model for binary liquid mixtures and highly swollen rubber membranes. They establish that the two most important factors in hydraulic membrane transport are the viscosity and degree of

swelling due to the solvent. They describe a method for extending the solution-diffusion model for multi-component systems. First expressions relating the up and downstream membrane surface concentrations to the bulk feed and permeate concentrations are derived. Without details, they state that the following are needed to complete the model:

1. activity data (relating activity to bulk concentrations)
2. thermodynamic model relating activity and concentrations in the membrane)
3. multicomponent diffusion equation (equivalent to Fick's law for a single component system)

Experimentally, they note that the ratio of fluxes of the two components is equal to the proportion of the two components in the feed mixture. The feed mixture is treated as a pseudo-pure liquid with the properties of the mixture. This is justified by the fact that the large osmotic pressure effect ensures that the two components move through the membrane together as one fluid, without any separation. They conclude that the single component solution-diffusion model can be applied to the binary system. This assertion is further justified by experimental calculation of the diffusion coefficient of each mixture.

The final point in the list of limitations of the solution diffusion model is the assumption of low membrane swelling. The degree of swelling of a membrane is dependent on the membrane polymer and the solvent. Beerlage [53] reported swelling ratios of Lenzing P84 polyimide, from which the StarmemTM series of membranes is made, of 12.2 wt% in methanol, 2.7wt% in toluene and 2.8wt% in ethyl acetate. Tarleton *et al.* [54] measured a range of degrees of swelling of PDMS nanofiltration membranes in a variety of alkane, aromatic and alcohol solvents. They found that more polar solvents showed less swelling and that the swelling could be reduced by the application of pressure. Membrane swelling can be reduced by selecting the optimum polymer-solvent combination and therefore need not be a significant effect.

3.5 ASYMMETRIC MEMBRANES

All the above models, both solution-diffusion based and pore flow based, assume that the membrane is symmetric. In fact, most nanofiltration membranes consist of an active surface layer, a porous support and often an ultrafiltration sublayer. Machado *et al.* have overcome the problem of the differing properties of the different layers by using semi-empirical resistances in series model [11], which combines viscous and surface resistances. The model predicts the flux given the composition of a binary mixture. Constants characterising the intrinsic properties of the membrane and a single solvent parameter, characterising the solvent-membrane interactions, are used. The model showed a good fit to experimental data for a number of different solutions, except in the cases of low dielectric constants.

3.6 CONCENTRATION POLARISATION

It should be noted that the conditions at the membrane surface are not necessarily the same as those in the bulk feed or permeate. There may be concentration gradients at both sides of the membranes, which will impose mass transfer limitations on the system. Concentration gradients at the feed side are more likely due to gel layer formation or concentration polarisation. The phenomenon of concentration polarisation is well-known and there are several studies on the subject, mainly concerning ultrafiltration [55-59]. The theory of concentration polarisation states that retained solutes in the feed accumulate at the membrane surface to form a boundary layer of thickness, δ . Concentration build up generates a diffusive back flow of feed back into the bulk which eventually reaches steady state, as shown in Figure 3.4.

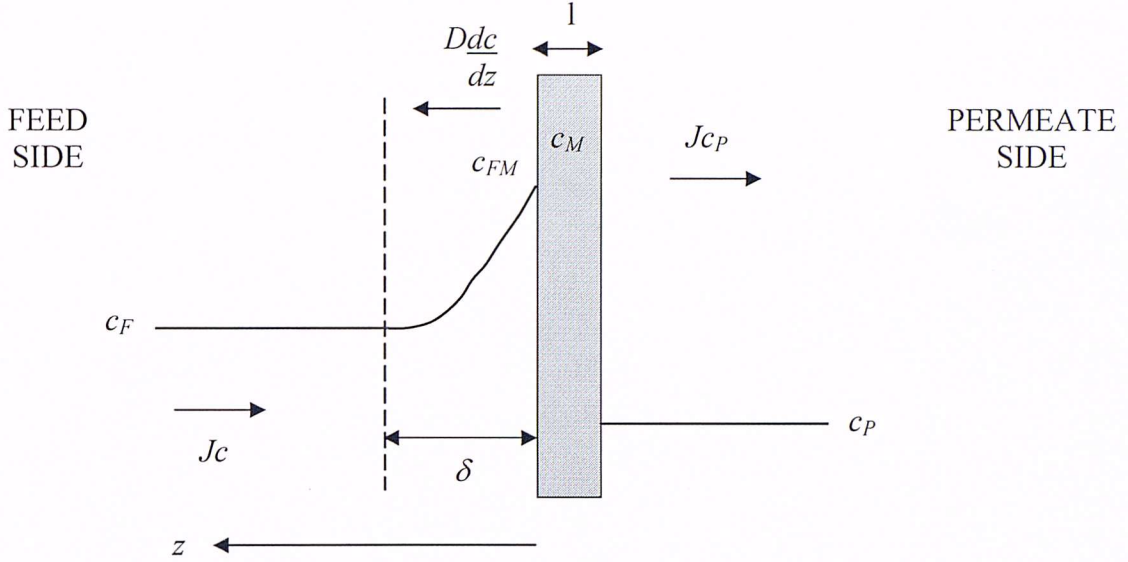


Figure 3.4: Schematic of concentration profiles across membrane with concentration polarisation.

The concentration, c , can be described mathematically by the film theory, which states that, at steady state, the transport of the solute is comprised of the sum of the permeate flow and the diffusive back flow, with a diffusion coefficient, D_i . So, for component i ,

$$Jc_i = Jc_{ip} - D_i \frac{dc_i}{dz} \quad (3.58)$$

The molar flux through the membrane is equal to the flux multiplied by the molar permeate concentration, $J_i = Jc_{ip}$. Letting component 1 be the *solute* and component 2 be the *solvent*, the film theory gives:

$$Jc_1 - D_1 \frac{dc_1}{dz} - J_1 = 0 \quad Jc_2 - D_2 \frac{dc_2}{dz} - J_2 = 0 \quad (3.59)$$

For the solute (component 1):

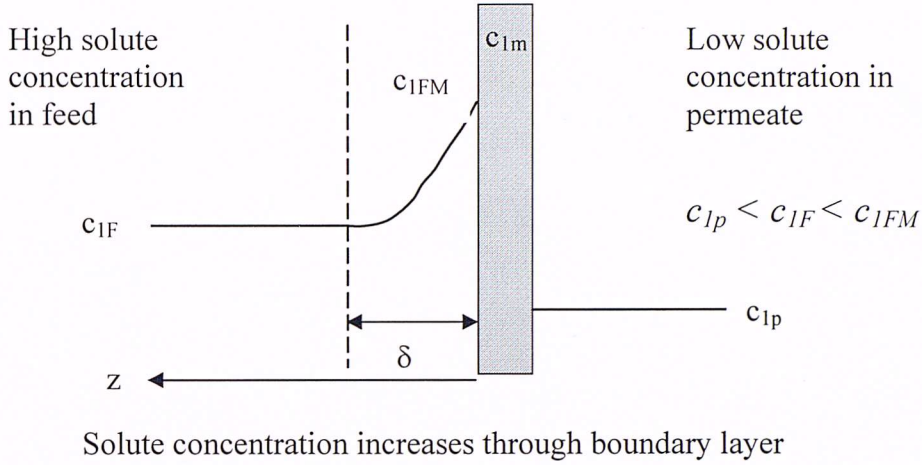


Figure 3.5: Schematic of concentration polarisation for solute.

Integrating equation (3.59) across the boundary layer, from $z = 0$ to $z = \delta$:

$$\int_0^\delta \frac{-1}{D_1} dz = \frac{1}{J} \int_{c_{1FM}}^{c_{1F}} \frac{1}{c_1 - c_{1p}} dc_1$$

$$\frac{-J\delta}{D_1} = \ln \left(\frac{c_{1FM} - c_{1p}}{c_{1F} - c_{1p}} \right) \quad (3.60)$$

Similarly for the solvent (component 2),

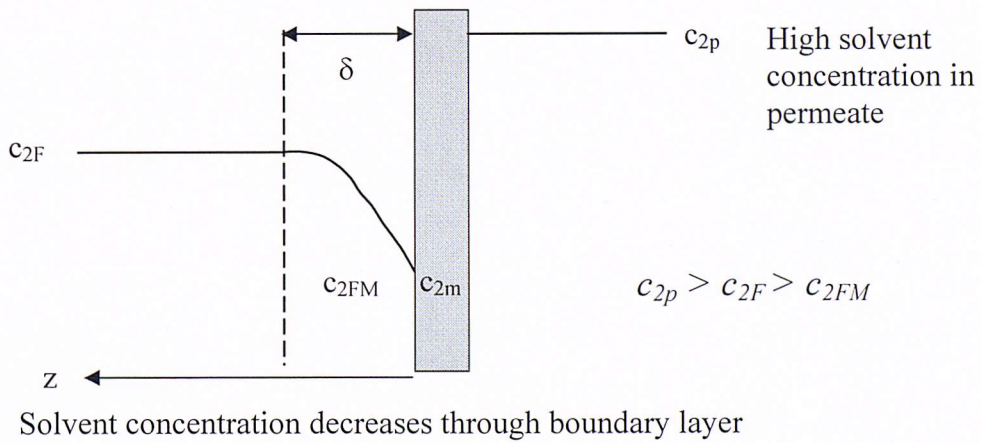


Figure 3.6: Schematic of concentration polarisation for solvent.

$$\frac{-J\delta}{D_2} = \ln\left(\frac{c_{2p} - c_{2FM}}{c_{2p} - c_{2F}}\right) \quad (3.61)$$

The constant D/δ is equal to the mass transfer coefficient, k . Therefore, equations (3.60) and (3.60) may be re-written as:

$$-\frac{J}{k_1} = \ln\left(\frac{c_{1FM} - c_{1p}}{c_{1F} - c_{1p}}\right) \quad -\frac{J}{k_2} = \ln\left(\frac{c_{2p} - c_{2FM}}{c_{2p} - c_{2F}}\right) \quad (3.62)$$

Note that the film theory may be solved using either the differential equations (3.59) or the two algebraic equations (3.62).

Various authors combine the film theory with a membrane transport model. Murthy and Gupta [60, 61] combine the simplified form of the solution diffusion model, equations (3.46) and (3.47), with the film theory to give a non linear membrane transport model in terms of the rejection (R) and observed rejection (R_o):

$$\frac{R_o}{1 - R_o} = \frac{J_v}{D_{AM}K/\delta} \exp\left(\frac{-J_v}{k}\right) \quad (3.63)$$

where D_{AB}/l is k , the mass transfer coefficient:

The problem with this method is that it requires detailed experimental flux and rejection data in order to find the parameters by non-linear parameter estimation. Such data may not always be available and so it is difficult to apply the model for predictive purposes.

Wijmans and Nakao [55] present a combined solution diffusion and film theory model. However, it is severely by the assumption that the rejection of the solute is always 100%, and therefore will not be discussed in this study.

3.7 WHICH MODEL IS CORRECT?

The question of which transport mechanism is the most appropriate is much debated, with data supportive of both models presented in the literature. It is particularly problematic that the two models reduce to the same form under some conditions (equations 3.6 and 3.46): Both models state that the flux is proportional to the pressure difference across the membrane when there is no osmotic pressure.

Some interesting evidence is reported by Ebra-Lim and Paul [52, 62]. They study the transport of organic solvents across a stack of several swollen rubber membranes under pressure. After a period of time, the membranes were removed and separated rapidly, allowing the concentration profile across the composite membrane to be measured, which they claim is proof of a diffusional mechanism, as the pore flow mechanism states that there is no concentration gradient across the membrane, as in Figure 3.1. However, the effect of the surfaces of the membranes could be responsible for this effect, with solute building up at the interfaces.

Since it is not known whether organic solvent nanofiltration membranes are porous or homogeneous, it is predicted that a transition region [50] between the two mechanisms might be more satisfactory. In a solution-diffusion membrane free volume elements (pores) that exist in the membrane are statistical fluctuations that appear and disappear in the same time scale as the permeation. In a pore-flow membrane, the free volume elements are relatively fixed and do not fluctuate in position or volume on the time scale of permeation. The larger the free volume element, the more likely they are to be present long enough to produce pore-flow characteristics in the membrane. The transition between permanent pore flow and transient solution diffusion flow appears to be in the range 0.5-1nm. Of course, the mathematics of such a transitional model will be complex and numerical methods will need to be employed. One such example, is the model of Gerald *et al.* [63], which combines pore flow, diffusion mechanisms, membrane-solvent interactions, osmotic pressure and mass transfer using computational fluid

dynamics. Unless the influence of one or other of the transport models can be quantified experimentally, a transitional mechanism should be considered.

3.8 INTERIM CONCLUSIONS

There are many models applicable to nanofiltration membranes. However, due to the fact that there are so many competing effects in the process, it seems that none of the models tells the whole story; the process is complicated. A combined model, taking all the different possible mechanisms and effects into account should be aimed for. Experimental data should be collected in order to try to elucidate which parameters are the most relevant for modelling. The following quotation from a recent article by Straatsma *et al.* entitled “Can nanofiltration be fully predicted by a model?” [64] sums up the current level of knowledge in this field succinctly:

“At the current state of science the knowledge of the nanofiltration process...is not sufficient to make a model fulfilling the requirements...”

There is much work to be done!

The first part of this chapter has examined the various mathematical models available for describing transport through OSN membranes. Pore flow models from the literature review will be selected and used to describe the experimental data already collected, as detailed in Chapter 2. Following this, further investigations into the solution diffusion model will be performed.

3.9 PORE FLOW MODELLING

3.9.1 Methods

Some of the pore models reviewed are straightforward and can be solved analytically or by simple numerical methods. They express the reflection coefficient, σ , which may be related to the rejection, as a function of η only, where η is the ratio of the solute size to the pore size. So, $\sigma = f(\eta) = f(\text{solute size} / \text{pore size})$, for example, the ratio of the radii, $\sigma = f(r_s/r_p)$. Table 3.1 shows details of three of these models, chosen for further work. There are two ways of using these models:

1. Given the solute and pore sizes, prediction of the reflection coefficient
2. Given data of the reflection coefficient as a function of solute size, least squares fit to estimate the pore size

Table 3.1: Details of three simple pore models to be used in this study.

Model	Formula	Equation
Ferry formula	$\sigma = 1 - \frac{c_p}{c_f} = 1 - 2(1 - \eta)^2 + (1 - \eta)^4$	(3.9)
SHP	$\sigma = 1 - H_F S_F$	(3.12)
	$H_F = 1 + (16/9)\eta^2$	(3.13)
	$S_F = (1 - \eta)^2 [2 - (1 - \eta)^2]$	(3.14)
Verniory	$\sigma = 1 - g(\eta) S_F$	(3.18)
	$g(\eta) = \{1 - 2/3\eta^2 - 0.2\eta^5\} / (1 - 0.76\eta^5)$	(3.18)
	$S_F = (1 - \eta)^2 [2 - (1 - \eta)^2]$	(3.17)

Note that all of the models chosen neglect osmotic pressure. This is valid in this system, since the concentrations of the solutes are small enough that the contribution of osmotic pressure is negligible. For example, for 0.005M tetra octyl ammonium bromide (MW = 546.81), the osmotic pressure is 0.12 bar. This is 1% of the minimum operating

pressure, 10bar, so it is valid to neglect osmotic pressure in these calculations. The models will be used to estimate the pore size of the membranes given a set of rejection data. This is useful because, if OSN membranes are indeed porous, their pore size is very difficult to measure, since the size of the pores is at the resolution limit of the analytical equipment available, such as atomic force spectroscopy [3]. In addition to this the roughness of the surface of a membrane is of the same order of magnitude as the pore dimensions, making it difficult to distinguish between genuine pores and surface fluctuations.

First it was necessary to obtain an estimate of the molecular sizes of the solutes used. This was done by assuming the solutes were spherical with an equivalent diffusion coefficient and using the Stokes-Einstein equation:

$$r_s = \frac{RT}{6\pi\mu DN_A} \quad (3.64)$$

The equation is valid, providing that the solute size is much greater than the solvent size.

The diffusivity of the solute, D , in equation (3.64) was estimated using Polson's equation [65]:

$$D = \frac{9.4 \times 10^{-15} T}{\mu_s M_1^{1/3}} \quad (3.65)$$

where μ_s is the viscosity of the solvent and M is the molecular weight of the solute, in kg/mol.

It was assumed that the viscosity of the solution was equal to that of the pure solvent, which is valid since the solution concentration is low, $< 0.01M$. The viscosity of methanol was taken to be 0.00058 Nsm^{-2} . Table 3.2 shows the calculated diffusivities and molecular sizes of the solutes investigated. The radius of the solvent, methanol is approximately 0.2nm which is smaller than the solute radii, therefore the use of the Stokes-Einstein equation can be considered acceptable for these calculations.

Table 3.2: Parameters calculated for solutes under investigation.

Solute	MW	Solute diffusivity D	Solute radius r_s
		$\times 10^{-10} \text{ m}^2 \text{ s}^{-1}$	nm
Tetrabutyl ammonium bromide	322.28	6.93	0.53
Tetrapentyl ammonium bromide	378.47	6.57	0.56
Tetrahexyl ammonium bromide	434.6	6.28	0.59
Tetraheptyl ammonium bromide	490.17	6.03	0.61
Tetraoctyl ammonium bromide	546.81	5.81	0.64

3.9.2 Results

The models were applied, using a numerical method where necessary (Newton-Raphson), to data for the six different solutes listed in Table 3.2, in methanol, at a range of different pressures from 10 to 50 bar. The membranes used were StarmemTM 122 and MPF50. Figure 3.7 shows the variation of the estimated pore size with the molecular weight of the quat used and with pressure for StarmemTM 122. The estimated pore radii are of the order 0.5 – 0.7nm in all cases. This seems a reasonable estimate for a membrane expected to effect separations for solutes in the nanometer size range. The results are also consistent with the results of Bowen *et al.* [46] who calculate the pore radius of a polyethersulphone nanofiltration membrane as 0.72nm. For all models, there is a clear positive dependence of the estimated pore size on the molecular weight of the quat used to generate the data from which the pore size was estimated. There is also a clear downwards trend for the estimated pore size as pressure increases for the Ferry and SHP models, indicative of compaction as discussed in Chapter 2. The Verniory model gives consistent results across the pressure range.

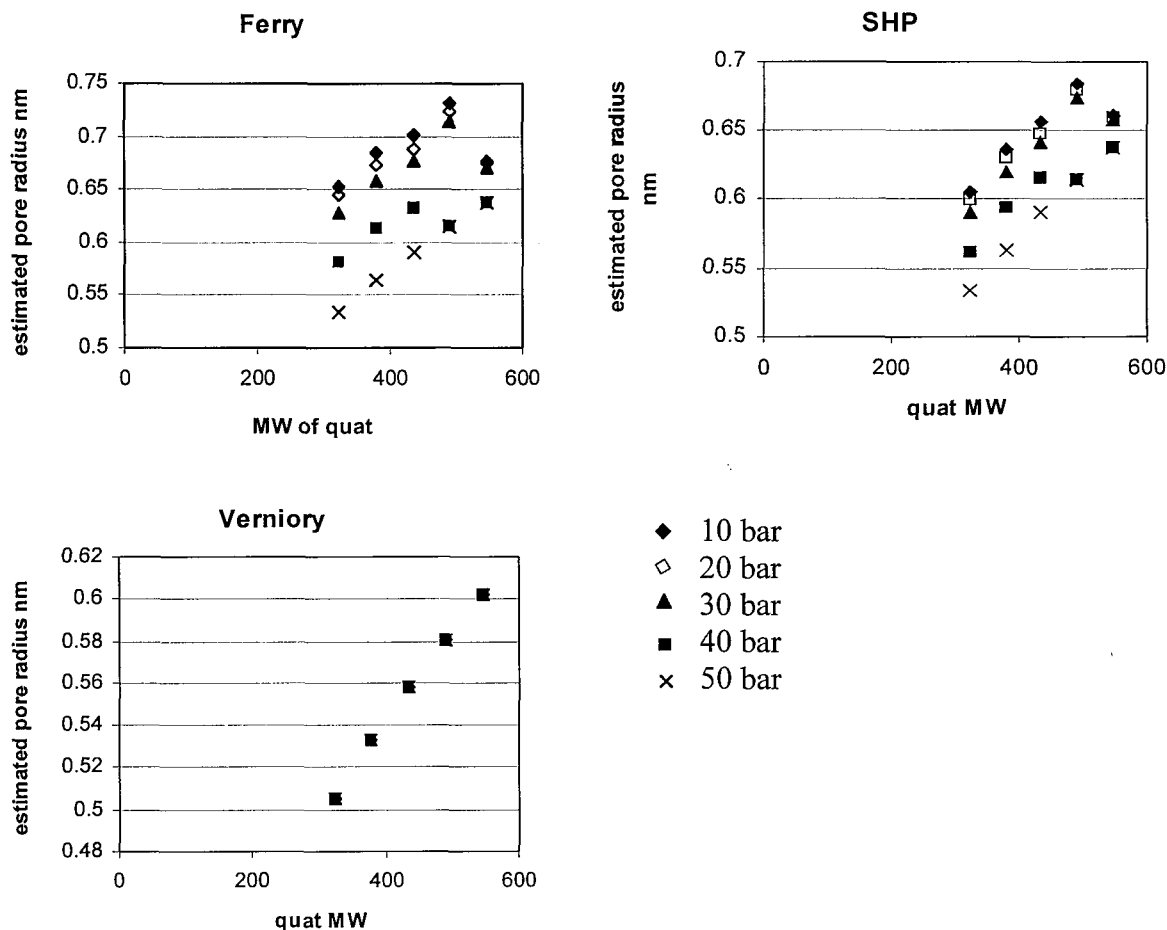


Figure 3.7: Effect of quat MW and pressure on estimated pore size of StarmemTM 122 with methanol for the three models used.

Figure 3.8 shows the variation of the estimated pore size with the molecular weight of the quat used and with pressure for MPF50. The results are very similar to those for StarmemTM 122, with estimated pore radii in the range 0.5 – 0.95nm in all cases. The spread of the data is slightly greater and the average pore size slightly larger, which is consistent with the fact that MPF50 has a larger nominal MWCO (700 compared with 220 for StarmemTM 122).

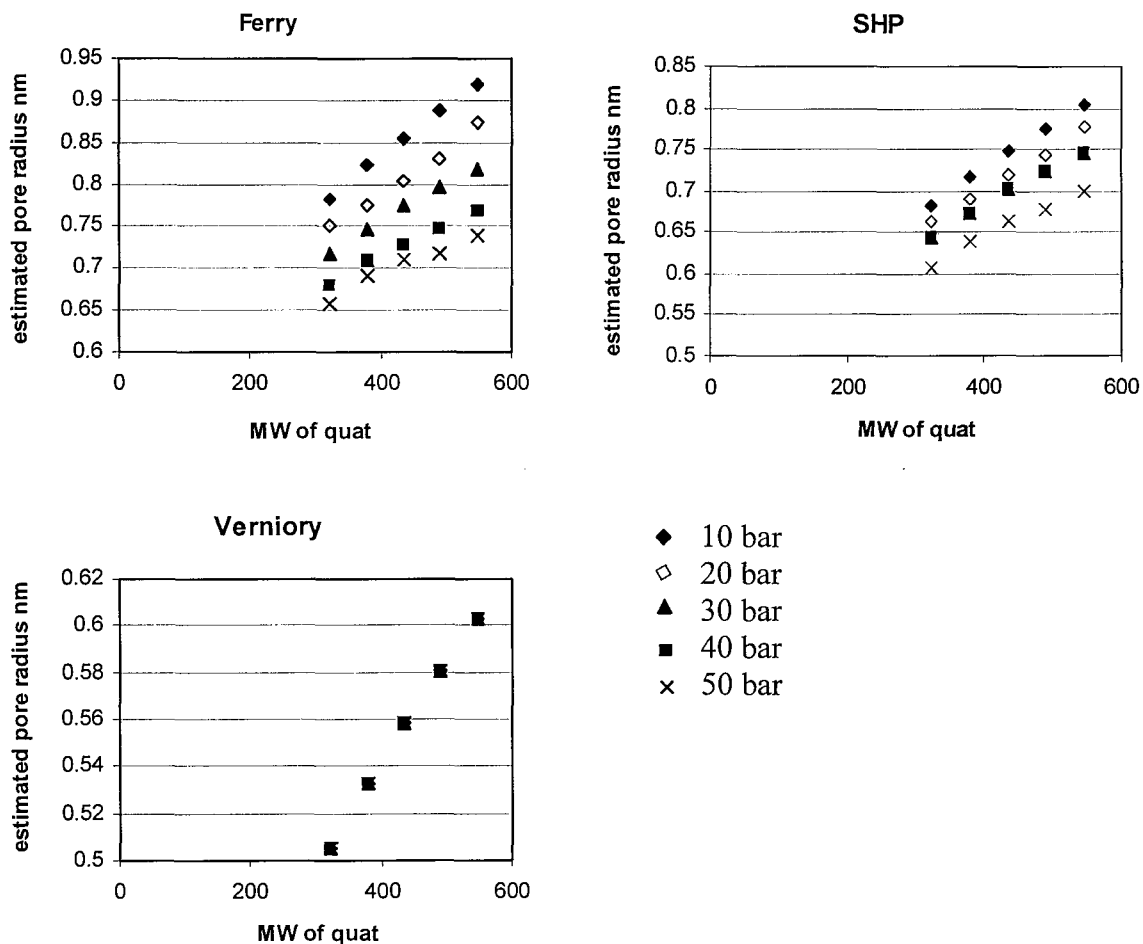


Figure 3.8: Effect of quat MW and pressure on estimated pore size of MPF50 with methanol for the three models used.

In some cases the models give pore sizes smaller than the largest solute size (0.64 nm). If the membrane transport mechanism was truly pore flow and the pore size uniform, 100% rejection would be expected for all solutes larger than the pore size. This is not the case for these experimental results, suggesting errors in the pore size calculations, the presence of a pore size distribution, or that the assumption that the membrane is porous is not valid: a solution diffusion mechanism or transitional mechanism is possible. It should be noted that the fact that an effective pore size can be calculated does not necessarily indicate that geometrically well defined pores exist [46].

Generally, the variations of predicted pore radius with pressure and solute size are small, suggesting that it is valid to estimate the pore size based on one solute size and pressure alone. The results, therefore, were averaged over all pressures and solute sizes to give one prediction of the pore size for each membrane. These results are shown in Table 3.3.

Table 3.3: pore radii (nm) calculated from three simple pore models, averaged over all pressures and solute sizes.

Model	StarmemTM 122		MPF50	
	Pore radius nm	Standard deviation	Pore radius nm	Standard deviation
Ferry	0.65	4.0×10^{-5}	0.77	5.4×10^{-2}
SHP	0.52	2.0×10^{-5}	0.58	2.7×10^{-2}
Verniory	0.56	4.5×10^{-5}	0.56	2.2×10^{-5}

The models all give very similar results. The Ferry model gives the highest estimate of the pore radius for both membranes. The Verniory model gives identical results for both membranes. The results suggest that MPF50 has a larger pore size than StarmemTM 122, which, as mentioned earlier, is consistent with the higher MWCO of MPF50. The spread of the results is greater for MPF50 (larger standard deviation) which is due to the fact that the initial rejection has more spread.

Figures 3.9 and 3.10 indicate which factors are most important in determining the pore size of the membrane by this method. The data is for StarmemTM 122. Figure 3.9 shows that the effect of pressure is small for all the models, because they are derived from the Spiegler Kedem model which suggests that the pressure has no effect on the transport of the solute. A small variation with pressure is observed in some cases, which can be attributed to compaction of the membrane under pressure, which reduces the pore size.

Figure 3.10 shows that the molecular weight of the quat used has a much greater influence on the predicted pore size.

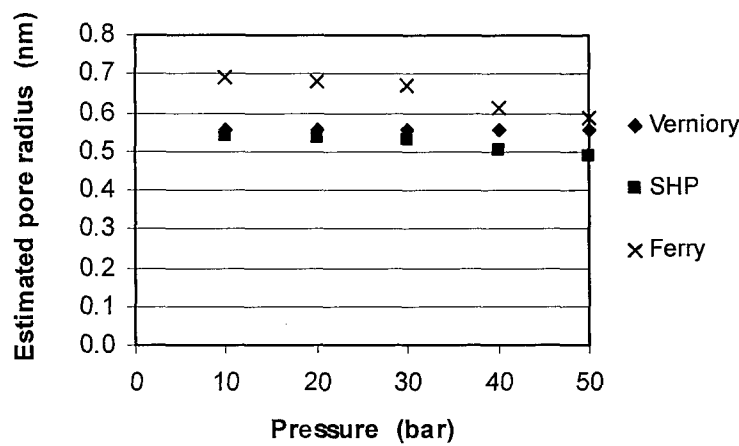


Figure 3.9: Effect of pressure on estimated pore size of StarmemTM 122 with methanol for the three models used. Data averaged over all quat molecular weights.

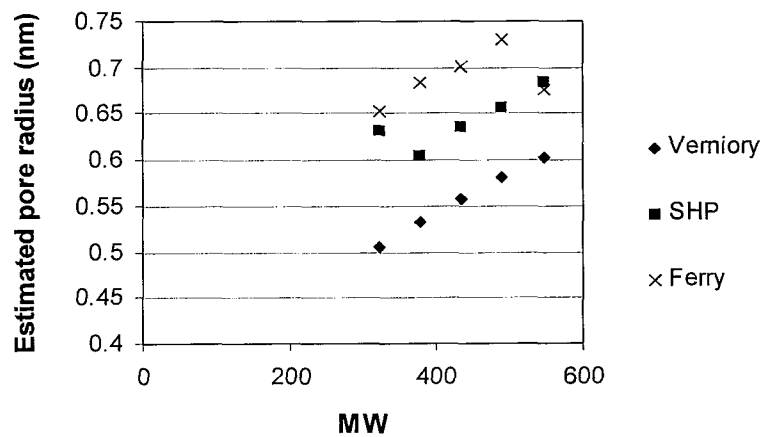


Figure 3.10: Effect of quat molecular weight on estimated pore size of StarmemTM 122 with methanol for the three models used. Data averaged over all pressures.

Using the pore size data, an estimation of the membrane effective thickness, solvent flux data and the Hagen-Poiseuille equation, the surface porosity of the membrane (if it were

porous) can be calculated. Note that this porosity is for the active layer of the membrane, the part which offers all the resistance.

$$J_v = \frac{A_k r_p P}{8\mu x} \quad (3.66)$$

White and Nitsch [17] measure the active layer thickness of a polyimide OSN membrane as 400 nm, which value will be used in these calculations along with flux data from the filtrations. The results are shown in Table 3.4 for three different pressures, 10, 20 and 30 bar.

The estimated surface porosities range between 0.01 – 0.02 over the pressures studied, which are quite low, suggesting that the membranes may not really be porous. As discussed earlier, the precise nature of these OSN membranes is not known, and they could be homogenous, dense films rather than porous. The values given at different pressures and with the different models are all similar showing that the models are consistent with each other.

Table 3.4: Surface porosity of the membranes based on estimated pore radii (averaged over all molecular weights), flux data and an estimation of the thickness of the active layer of the membrane. Values calculated at three different pressures.

Model	Starmem™ 122			MPF50		
	10 bar	20 bar	30 bar	10 bar	20 bar	30 bar
Ferry	0.010	0.011	0.011	0.008	0.007	0.010
SHP	0.013	0.011	0.013	0.015	0.013	0.018
Verniory	0.019	0.015	0.020	0.019	0.015	0.020

The three models used are, of course, very simplistic and have limitations due to the assumptions they make:

1. pore blocking may occur
2. pores may not be uniform – a pore size distribution may exist

3. pores may not be cylindrical
4. pores may not be perpendicular to the membrane surface
5. direction of flow may not be perpendicular to the surface

The presence of a non-uniform pore size distribution could be accounted for by using the log normal distribution [40, 66].

The modelling has also assumed that the solute size is much larger than the solvent size, which may be true in this system, but is not necessarily applicable to all systems. In the case where the solute and solvent have similar sizes, a correction to the Stokes-Einstein equation can be used [67]:

$$r_s = \left(1.5 \frac{a}{b} + \frac{1}{1 + a/b} \right) r_{s(Stokes)} \quad (3.67)$$

a = solute radius; b = solvent radius

The smallest solute used in this study is tetrabutyl ammonium bromide, which has a molecular weight of 322. This is significantly larger than the nominal MWCO of StarmemTM 122, which is 220. If the MWCO value is to be believed, then 100% rejection of all the quaternary salts should be obtained at all pressures. The data presented in chapter 2 shows that this is not the case. In order to characterise the membranes better, a solute with a molecule size smaller than the MWCO should be used. Stilbene was chosen for this experiment. Stilbene's details are given in Table 3.5. Rejection results for 0.005M stilbene in methanol with StarmemTM 122 are shown in Figure 3.11. As expected, the rejections are much lower than for the quats due to the fact that the size of stilbene is below the MWCO of StarmemTM 122. The pore modelling results are shown in Figure 3.12.

Table 3.5: Parameters calculated for stilbene.

Solute	MW	Solute diffusivity D	Solute radius r_s
		$\times 10^{-10} \text{ m}^2 \text{ s}^{-1}$	nm
Stilbene	180	8.2	0.44

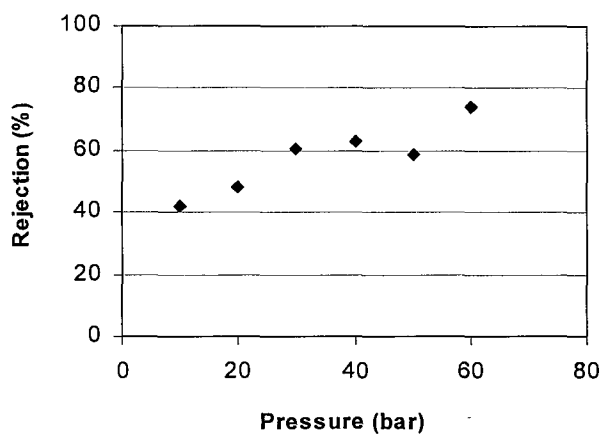


Figure 3.11: Effect of pressure on rejection of 0.005M stilbene in methanol with Starmem™ 122.

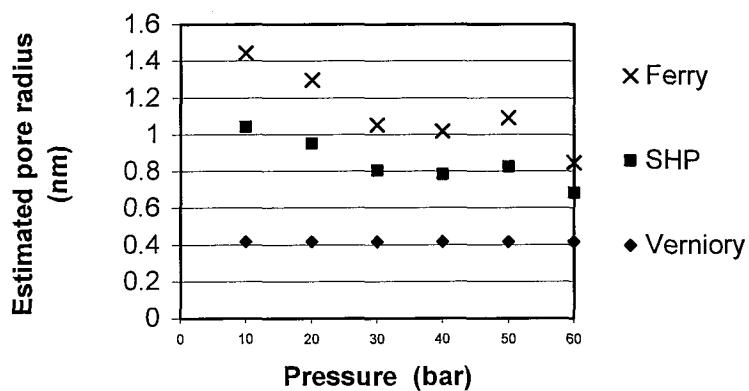


Figure 3.12: Effect of pressure on estimated pore size of Starmem™ 122 with methanol and stilbene.

The values predicted using stilbene as the solute are higher for the Ferry and SHP models. As for the quats, pressure has a reasonably small effect on the pore size estimation. The Verniory model gives consistent results across the pressure range, as found for the quats, although the pore radius is 0.42nm, compared with 0.56nm with the quats. As before, the estimated pores size allows a membrane porosity to be calculated. These values are shown in Table 3.6. The porosity values are consistently lower than when calculated using quat rejection data. For the Ferry and SHP models, this effect is due to the fact that the pore sizes estimated using stilbene are larger so fewer pores are required to allow a given level of transport through the membrane.

Table 3.6: Porosity of StarmemTM 122 based on pore radii estimated using stilbene as the solute in methanol, flux data and an estimation of the thickness of the active layer of the membrane. Values calculated at three different pressures.

Model	StarmemTM 122		
	10 bar	20 bar	30 bar
Ferry	0.001	0.001	0.002
SHP	0.002	0.002	0.003
Verniory	0.014	0.012	0.012

3.9.3 Conclusions

The membranes have been characterised using three pore flow models in terms of an equivalent (uniform) pore size. The predicted pore size varies with solute size, although the variation is small. The effect of the applied pressure is negligible. Thus, the membrane pore size can be quoted on the basis of an average over all pressures and solutes. Reasonable estimates are obtained using quat data for a nanofiltration membrane (0.5 - 0.8 nm pore radius, corresponding to a porosity of 0.02 - 0.04) which is expected to effect separations for solutes in the nanometer size range. The results are also consistent with the results of Bowen *et al.* [46] who calculate the pore radius of a polyethersulphone nanofiltration membrane as 0.72nm.

Limitations of the models have been discussed. Of course, the biggest assumption made in this work is that the membranes are indeed porous. As discussed earlier, this is a matter of some controversy. The possibility that the membrane is homogenous should also be considered, for example, by using the solution diffusion type models. There is also the possibility that there is some sort of transitional mechanism between pore flow and solution diffusion. The possibility that the membrane is non-porous will be investigated in the next section.

3.10 SOLUTION DIFFUSION MODELLING¹

3.10.1 Introduction

Experiments will be performed in a cross flow rig in which nanofiltration is carried out in a continuous mode, in order to improve the understanding of organic solvent nanofiltration phenomena [68]. Description of the experimental data, including prediction of the rejection of a highly rejected solute, will be performed using the solution diffusion model for membrane transport and the film theory for liquid mass transfer effects (these are reviewed earlier in this chapter). The solution diffusion model was chosen because it is the only adequate model for describing non-porous membranes and it has been successfully used to model the StarmemTM membranes before [17].

3.10.2 Model

In some cases, some of the simplifying assumptions of the solution diffusion model, as presented by Wijmans and Baker [50], as discussed in Chapter 3.4, are not valid. A set of equations has been derived combining the original, unsimplified, form of the solution diffusion equation with the film theory. A binary (that is solvent-solute) system has

¹ This section of work was done in collaboration with Ludmilla Peeva.

been assumed, although the equations could be generalised for a system of n components. In the following derivation, component 1 is the solute and component 2 is the solvent. A schematic of the membrane transport process is shown in Figure 3.13.

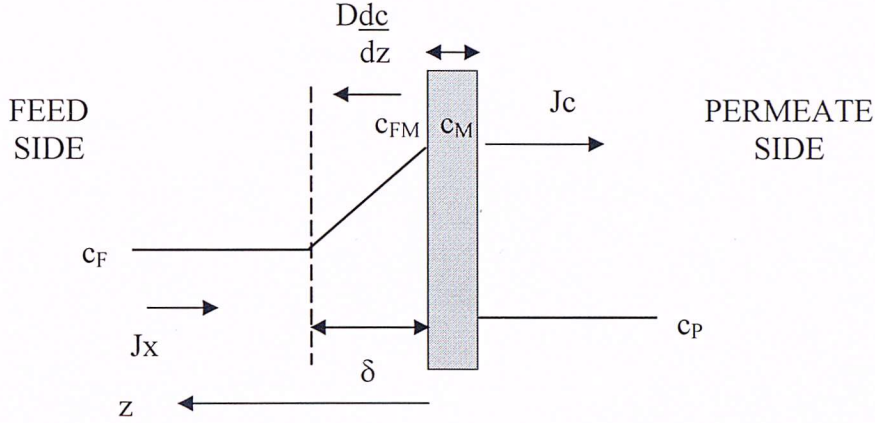


Figure 3.13: Schematic of concentration profiles across membrane.

A concentration gradient is assumed on the feed side, but not on the permeate side, as the permeate side solute concentration is low in this case. The membrane is assumed to be a homogeneous layer for simplicity.

The film theory of mass transfer, as discussed earlier, is used for components 1 and 2,

$$J_v c_1 - D_1 \frac{dc_1}{dz} - J_v c_{1,p} = 0 \quad J_v c_2 - D_2 \frac{dc_2}{dz} - J_v c_{2,p} = 0 \quad (3.68)$$

where J_v is the total volumetric flux, c is the concentration and D is the diffusivity.

The following boundary conditions are used:

$$z = 0 \quad c_1 = c_{1,FM} \quad c_2 = c_{2,FM}$$

$$z = \delta \quad c_1 = c_{1,F} \quad c_2 = c_{2,F}$$

giving:

$$\frac{J_v}{k_1} = \ln \left(\frac{c_{1,FM} - c_{1,p}}{c_{1,F} - c_{1,p}} \right) \quad \frac{J_v}{k_2} = \ln \left(\frac{c_{2,p} - c_{2,FM}}{c_{2,p} - c_{2,F}} \right) \quad (3.69)$$

A mass balance in the system gives:

$$J_v = J_1 v_1 + J_2 v_2 \quad (3.70)$$

It will be assumed that the mass transfer coefficients for components 1 and 2 are equal, that is, that there is no separation across the membrane, since the liquid diffusion coefficients are equal and $k_i = D/\delta_i$:

$$D_1 = D_2 \quad (3.71)$$

This is justified [69] by assuming that the partial molar volumes of the species are constant (true for most of the liquid solutions), that is, $\bar{V}_1 = \text{constant}$ and $\bar{V}_2 = \text{constant}$. So, starting with the original flux equations,

$$Jc_{1,F} - D_1 \frac{\partial c_{1,F}}{\partial z} - Jc_{1,P} = 0 \quad Jc_{2,F} - D_2 \frac{\partial c_{2,F}}{\partial z} - Jc_{2,P} = 0 \quad (3.72)$$

and multiplying both equations by the partial molar volume and adding together:

$$J(c_{1,F}\bar{V}_1 + c_{2,F}\bar{V}_2) - D_1\bar{V}_1 \frac{\partial c_{1,F}}{\partial z} = D_2\bar{V}_2 \frac{\partial c_{2,F}}{\partial z} + J(\bar{V}_1c_{1,P} + \bar{V}_2c_{2,P}) = 0 \quad (3.73)$$

Conducting a mass balance on the system per unit volume gives:

$$\Sigma \{ \text{molar concentration } (mol/m^3) \times \text{molar volume } (m^3/mol) \} = 1$$

So for the retentate and permeate, respectively:

$$c_{1,F}\bar{V}_1 + c_{2,F}\bar{V}_2 = 1 \quad \text{and} \quad c_{1,P}\bar{V}_1 + c_{2,P}\bar{V}_2 = 1 \quad (3.74)$$

$$\text{So, } J(\cancel{c_{1,F}\bar{V}_1 + c_{2,F}\bar{V}_2}) - D_1\bar{V}_1 \frac{\partial c_{1,F}}{\partial z} = D_2\bar{V}_2 \frac{\partial c_{2,F}}{\partial z} - J(\cancel{\bar{V}_1c_{1,P} + \bar{V}_2c_{2,P}}) = 0$$

$$\Rightarrow D_1\bar{V}_1 \frac{\partial c_{1,F}}{\partial z} = -D_2\bar{V}_2 \frac{\partial c_{2,F}}{\partial z} \quad (3.75)$$

However, as $\bar{V}_1$ and $\bar{V}_2$ are constant,

$$\bar{V}_1 \frac{\partial c_{1,F}}{\partial z} + \bar{V}_2 \frac{\partial c_{2,F}}{\partial z} = \frac{\partial \bar{V}_1 c_{1,F}}{\partial z} + \frac{\partial \bar{V}_2 c_{2,F}}{\partial z} = \frac{\partial (\bar{V}_1 c_{1,F} + \bar{V}_2 c_{2,F})}{\partial z}$$

$$\frac{\partial(V_1 c_{1,F} + V_2 c_{2,F})}{\partial z} = 0 \quad (\text{derivative of a constant is zero}) \quad (3.76)$$

So this leads to the conclusion that $D_1 = D_2$ and hence $k_1 = k_2$, since $k_i = D_i / \delta_i$ and assuming that the hydrodynamic boundary layers are the same, that is $\delta_1 = \delta_2$.

The membrane transport is modelled with the solution diffusion model, as discussed earlier, equations (3.35)–(3.51). However, the simplifying assumption that the ratio of activity coefficients is equal to 1 is not made, meaning that the activity coefficients remain in the equations.

As before, on the feed side:

$$x_{i,MF} = \frac{\gamma_{i,FM}}{\gamma_{i,MF}} x_{i,FM} = K_i x_{i,FM} \quad \text{where } K_i = \gamma_{i,FM} / \gamma_{i,MF} \quad (3.38)$$

And on the permeate side:

$$x_{i,MP} = \frac{\gamma_{i,FM}}{\gamma_{i,FM}} \frac{\gamma_{i,MF}}{\gamma_{i,MF}} \frac{\gamma_{i,P}}{\gamma_{i,MP}} x_{i,P} \exp\left(-\frac{v_i(p_{MP} - p_P)}{RT}\right) \quad (3.39)$$

Assuming that there is no change in activity across the membrane, that is: $\frac{\gamma_{i,MF}}{\gamma_{i,MP}} = 1$, and

using the fact that $K_i = \gamma_{i,FM} / \gamma_{i,MF}$, as defined in Equation (3.38),

$$x_{i,MP} = \frac{\gamma_{i,P}}{\gamma_{i,FM}} K_i x_{i,P} \exp\left(-\frac{v_i(p_{MP} - p_P)}{RT}\right) \quad (3.77)$$

Fick's law, states that $J_i = -D_{i,M} \frac{dx_i}{dz}$

Assuming a constant diffusion coefficient and integrating across the membrane gives

$$J_i = \frac{D_{i,M}(x_{i,MF} - x_{i,MP})}{l} \quad (3.78)$$

Comparing this with Equation (3.35), $J_i = -L_i \frac{d\mu_i}{dz}$, it can be seen that the chemical potential gradient is $(x_{i,MF} - x_{i,MP})/l$ and the proportionality factor is D_{iM} .

So by substituting in for $x_{i,MF}$ and $x_{i,MP}$ from Equations (3.38) and (3.77), the following equation is obtained:

$$J_i = \frac{D_{i,M}K_i}{l} \left[x_{i,FM} - x_{i,P} \frac{\gamma_{i,P}}{\gamma_{i,FM}} \exp\left(-\frac{v_i(p_{MP} - p_P)}{RT}\right) \right] \quad (3.79)$$

In the case where the activity coefficients are equal, the model reduces to the form of the solution diffusion model presented by Wijmans and Baker [50].

By calculating the mole fraction in terms of fluxes rather than concentrations, x_{iP} can be eliminated. So for component i,

$$x_{i,P} = \frac{J_i}{J_i + J_j} \quad (3.80)$$

which substituted into (3.79), along with letting $D_{i,M}K_i/l = P_{i,M}$, the membrane permeability and the applied pressure across the membrane = p ,

$$J_i = P_{i,M} \left[x_{i,FM} - \frac{J_i}{J_i + J_j} \frac{\gamma_{i,P}}{\gamma_{i,FM}} \exp\left(-\frac{v_i p}{RT}\right) \right] \quad (3.81)$$

In summary the combined solution diffusion – film theory model consists of the following system of seven non-linear algebraic equations which allow the prediction of the permeate flux and solute rejection, when the membrane permeability for a given component and the mass transfer characteristics of the equipment are known.

$$\frac{J}{k_1} = \ln \left(\frac{c_{1,FM} - c_{1,p}}{c_{1,F} - c_{1,p}} \right) \quad (3.82)$$

$$\frac{J}{k_2} = \ln \left(\frac{c_{2,p} - c_{2,FM}}{c_{2,p} - c_{2,F}} \right) \quad (3.83)$$

$$J = J_1 v_1 + J_2 v_2 \quad (3.84)$$

$$J_1 = P_{1,M} \left(x_{1,FM} - \frac{\gamma_{1,p}}{\gamma_{1,FM}} \frac{J_1}{J_1 + J_2} \exp \left(-\frac{v_1 p}{RT} \right) \right) \quad (3.85)$$

$$J_2 = P_{2,M} \left(x_{2,FM} - \frac{\gamma_{2,p}}{\gamma_{2,FM}} \frac{J_2}{J_2 + J_1} \exp \left(-\frac{v_2 p}{RT} \right) \right) \quad (3.86)$$

$$\gamma_1 = f(x_1), \quad \gamma_2 = f(x_2) \quad \text{or} \quad \gamma_1 = \gamma_2 = 1 \quad (3.87)$$

$$R_{calc} = 1 - \frac{J_1}{Jc_{1,F}} \quad (3.88)$$

Equations (3.82) and (3.83) describe the diffusion in the liquid film adjacent to the membrane, while Equations (3.84) to (3.87) describe membrane transport and Equation (3.88) defines the rejection. The equations were solved using gPROMS, a process modelling package from Process Systems Enterprises, UK. The code can be found in Appendix I.

3.10.3 Experimental procedure

The solvent used in this study was toluene. Two solutes were used, the quaternary ammonium salt, tetraoctylammonium bromide, TOABr, used in the pore flow modelling work in Chapter 3.9, and docosane. Both solutes have been previously used in toluene with this membrane [17, 38]; this preliminary information was a good starting point for further studies and modelling. For the salt-water experiments NaCl 99% was used.

The membrane used was StarmemTM 122. The same membrane discs were used for the whole set of experiments with each solute. Readings were taken after at least two hours, from each change of experimental conditions, to allow the membrane to equilibrate to the new conditions. The membrane used for salt-water experiments was a commercially available reverse osmosis membrane Desal SE High Rejection Brackish Water from Osmonics, USA. The membrane has an average NaCl rejection ~99% (as measured by the manufacturer for 2 g/l NaCl solution at 2930 kPa).

A cross-flow filtration rig, shown in Figure 3.14, was used in all the experiments. The membrane discs, of area 78 cm², were placed into dual cross flow test filtration cells (Osmonics, U.S.A). The stage cut was between 0.01 and 0.3% over the whole concentration and pressure range. Ideal mixing within the cell is assumed. The feed solution was circulated from a 5 L feed tank through the cross flow unit using a diaphragm pump, Hydra-Cell, Wanner, USA, which had a maximum flow rate of 200 L h⁻¹. The apparatus can be run in a batch mode (solid lines in Figure 3.15) or continuous mode (dashed lines). The flow rate was measured, in the continuous mode, by collecting the flow in calibrated measuring vessels located above the main feed tank. Each filtration cell was equipped with an individual backpressure regulator and a pressure gauge. Two sets of glycerin filled pressure gauges (WIKA Instruments Ltd, UK) with different ranges were used: 0-10 ± 0.5 bar for the lower readings, and 0-60 ± 2 bar for the higher readings. The temperature of the circulating fluid was controlled at 30°C with a heating/cooling coil immersed into the reservoir. Samples of the retentate and permeate fluids were taken from sampling ports placed in the retentate and permeate lines.

Two groups of experiments were performed. One set of experiments with toluene solutions of TOABr was performed to study the influence of the feed flow rate (cross-flow velocity) on the permeate flux at a constant pressure of 30 bar. The other set studied the influence of solute concentration and applied pressure on the permeate flux and solute rejection. A wide range of experiments was performed using toluene solutions of docosane (molecular weight of 310) and TOABr (molecular weight of 546) using a

range of pressures: 0-50 bar, and concentrations: 0-20 wt% (0-0.35M, 0-0.04 mole fraction) for TOABr in toluene and 0-20wt% (0-0.67M, 0-0.09 mole fraction) for docosane in toluene. The construction of the cross-flow rig made it difficult for exactly the same flow rate to be maintained through the cells at different pressures, however it was always kept in the range of 40-80 L/h for the low flow rate scenario and 120-150 L/h for the high flow rate scenario.

3.10.4 Analytical methods

Concentrations of TOABr were determined using a Perkin-Elmer Gas Chromatograph with a flame ionisation detector and a Megabore column 25m long and with 0.23mm i.d. with BP1 (SGE, Australia) as the stationary phase. The temperature programme ran from 80°C to 300°C at a rate of 25°C.min⁻¹. The coefficient of variation was 5% for 3 independent measurements. Concentrations of docosane were measured using a Perkin Elmer FT-IR Spectrometer. Absorbance at 2928 cm⁻¹ was monitored. The coefficient of variation was within 4% for 3 independent measurements, at the 0.1M level.

The freezing point of the TOABr toluene solutions was measured with a Differential Scanning Calorimeter (DSC): Pyris 1 – Perkin Elmer. The kinematic viscosities of TOABr and docosane solutions in toluene were measured with a Poulten Selfe&Lee Ltd, UK, scientific capillary viscometer at 25°C. The coefficient of variation was 1% for 3 independent measurements.

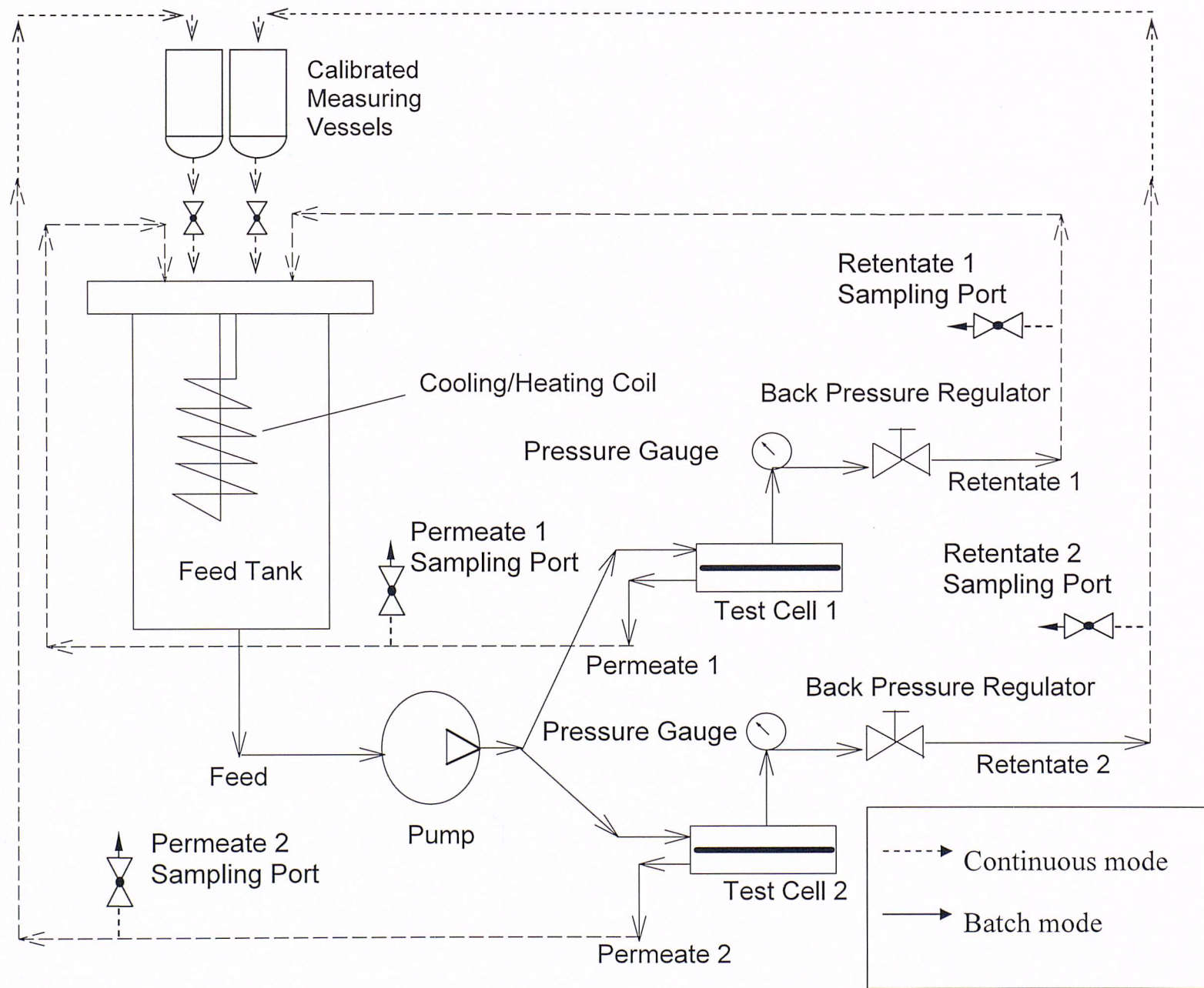


Figure 3.14: Schematic of the cross-flow filtration unit.

3.10.5 Parameter estimation

The molar volumes of toluene and docosane were taken from the literature [17]. The molar volume of TOABr was estimated based on Fedors method [70].

The mass transfer coefficients in the cross flow cell were determined from independent measurements of dissolution of a plate of benzoic acid into water at two different cross flow rates: 50 L/h and 120 L/h, at 30°C. To prepare this test, a layer of molten benzoic acid was poured into the cross flow cell and allowed to solidify. Water, with kinematic viscosity near to that of the docosane solutions, was circulated through the cell at flow rates 50 L/h and 120 L/h, dissolving the benzoic acid. The benzoic acid concentration in the water was monitored as a function of time, allowing calculation of the mass transfer coefficient.

The mass transfer coefficients for docosane and TOABr were estimated based on the benzoic acid values and mass transfer coefficient correlations available in the literature. In general, the Sherwood number is related to the Schmidt and Reynolds numbers as follows [1]:

$$Sh = \frac{k d_h}{D} = a Re^b Sc^c \left(\frac{d_h}{L} \right)^d \quad (3.89)$$

where d_h , the hydraulic diameter, depends on the geometry of the system. The values, a , b , c , d depend on the system geometry, type of fluid (Newtonian or non-Newtonian) and flow regime. By assuming that the system's hydrodynamic and geometric conditions are constant, the correlation can be reduced to:

$$k \propto \eta^{(c-b)} D^{(1-c)} \quad (3.90)$$

Therefore the ratio of the solute mass transfer coefficient to the benzoic acid mass transfer coefficient can be expressed as [65]:

$$\frac{k_{solute}}{k_{benzoicacid}} \propto \left(\frac{\eta_{solute}}{\eta_{benzoicacid}} \right)^{(c-b)} \left(\frac{D_{solute}}{D_{benzoicacid}} \right)^{(1-c)} \quad (3.91)$$

Several correlations are available in the literature for cross flow cells [69]. The correlations have Reynolds number exponents (b in the above equations) ranging from 0.65 to 0.875. The Schmidt number exponents (c in the above equations) range from 0.25-0.6. One widely used correlation is the Chilton-Colburn correlation:

$$Sh = 0.023 Re^{0.8} Sc^{0.33} \quad (3.92)$$

A correlation specific to the cell used in this study, where the flow is tangential, is not available, however the benzoic acid data from this study suggested an exponent for Re of around 0.8. For that reason the Chilton-Colburn correlation was used as a basis for calculating the mass-transfer coefficients for docosane and TOABr. Note that it was necessary to assume that the contents of the cross flow cell are well mixed and that turbulent flow correlations are valid in order to perform these calculations.

The diffusion coefficient for benzoic acid ($0.8 \times 10^{-9} \text{ m}^2/\text{s}$) was taken from the literature [71]. The diffusion coefficients for docosane and TOABr in toluene were calculated theoretically using the Siddiqi-Lucas Equation [72].

This correlation applies for ‘dilute’ solutions. The diffusion coefficient of toluene in the boundary layer was assumed to be equal to the diffusion coefficient of the corresponding solute [73] and thus $k_1 = k_2$ was used in the equations. There is also a variety of theoretical and empirical correlations for the diffusion coefficient in concentrated solutions, most of which are likely to either over-predict or under-predict the results [73]. However, as will be shown later, the theoretically calculated values from the model correspond reasonably well to experimental data, so it is not considered necessary to use more complex correlations at this stage.

The mass transfer coefficient values, measured using the dissolution of benzoic acid method, were $1.4 \times 10^{-5} \text{ m/s}$ and $4 \times 10^{-5} \text{ m/s}$ for 50 L/h and 120 L/h flow rates respectively. The mass transfer coefficients calculated for docosane and TOABr, using the Chilton-Colburn correlation, are presented in Table 3.7.

Table 3.7: Summary of the mass-transfer coefficient values used in the model.

Compound	Concentration [mol/L]	Mass-transfer coefficient at 120-150 L/h flow rate $\times 10^5$ [m/s]		Mass-transfer coefficient at 40-80 L/h flow rate $\times 10^5$ [m/s]	
		From Chilton- Colburn	Best fit of experimental data	From Chilton- Colburn	Best fit of experimental data
Docosane	0.33	5.3	5.3	1.9	1.9
	0.67	4.8	4.8	1.7	1.7
TOABr	0.21	2.2	1.1	0.8	0.8
	0.33	1.7	1.7	0.6	0.9

It is interesting to compare these values with values in the literature for similar systems. Although all of the data available are for aqueous systems and most are for ultrafiltration, it is useful to verify whether similar values are obtained. Some literature data are shown in Table 3.8 [74-77]. The values are in the same order of magnitude as our values: $\sim 10^5$ m/s, indicating that the estimates in Table 3.7 are reasonable.

Table 3.8: Mass transfer coefficient data from the literature.

Author [ref]	Membrane	Solvent	Solute	Cross Flow rate ($\text{m}^3\text{m}^{-2}\text{s}^{-1}$)	Pressure	$k \times 10^5$ (ms^{-1})
Prádamos <i>et al.</i> [74]	Ultrafiltration membrane: Aromatic polyamide on porous poly- sulfone support	water	0.1 wt% PEGs (300- 12000Da)	0.02-4.62	650kPa	0.02-3.5
Um <i>et al.</i> [75]	Ultrafiltration membrane: Polysulfone, MWCO = 100000	water	5wt% emulsion oil (oil, surfactants, additives)	2.5×10^{-5}	1 bar	0.23-1.7
Yeh <i>et al.</i> [76]	Dialysis with microfiltration membrane: Microporous polypropylene	Water, xylene	Acetic acid	$0.5-1 \times 10^{-5}$	atmospheric	1.6
Platt <i>et al.</i> [77]	Dialysis with ultrafiltration membrane: Cellulose, MWCO = 5000- 10000	water	0.1 wt% PEGs (1500- 10000Da)	2×10^{-5}	atmospheric	$1.6-3^5$
This study	Starmem TM 122	toluene	TOABr, docosane	0.001- 0.005	0-60 bar	0.6-5.3

The activity coefficients for docosane and toluene were calculated applying the modified UNIFAC method² [78]. The results for docosane are presented in Figure 3.15. From these results it was possible to develop a simple algebraic function describing the activity coefficient as a function of mole fraction of docosane and toluene respectively:

$$\text{Toluene: } \gamma_T = 0.99 + 0.30x_T - 0.29x_T^2 \quad (3.93)$$

$$\text{Docosane: } \gamma_D = 3.57 - 2.63x_D / (0.01 + x_D) \quad (3.94)$$

Where x_T and x_D are the mole fractions of toluene and docosane respectively.

This function was applied to both the permeate and retentate sides in the model.

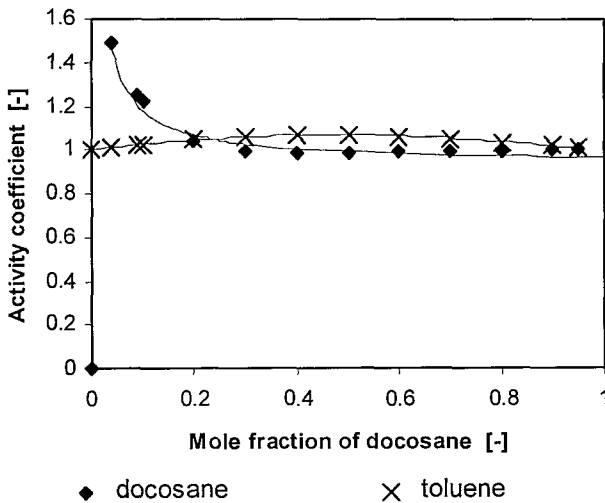


Figure 3.15: Activities of toluene in toluene-docosane system, calculated from UNIFAC, data fitted using equations (3.93) and (3.94).

The activity coefficients for toluene in the TOABr-toluene system at different mole fractions of TOABr were calculated using a model which combines a modified Debye-Huckel term, accounting for the long-range (LR) electrostatic forces, with the original UNIFAC [79] group contribution method for the short-range (SR) physical interactions:

² Generation of activity coefficient data was performed by Roumiana P. Strateva at the Institute of Chemical Engineering at the Bulgarian Academy of Science, Sofia 1113, Bulgaria.

$$\ln \gamma_{\text{solvent}} = \ln \gamma_{\text{solvent}}^{\text{LR}} + \ln \gamma_{\text{solvent}}^{\text{SR}} \quad (3.95)$$

The LR term was calculated as described by Macedo *et al.* [80]. The SR term was calculated according to:

$$\ln \gamma_{\text{solvent}}^{\text{SR}} = \ln \gamma_{\text{solvent}}^{\text{C}} + \ln \gamma_{\text{solvent}}^{\text{R}} \quad (3.96)$$

where $\ln \gamma_{\text{solvent}}^{\text{C}}$ and $\ln \gamma_{\text{solvent}}^{\text{R}}$ represent the UNIFAC combinatorial and residual contributions [79]. The UNIFAC group interaction parameters between the solvent groups were taken directly from the literature [81]. The interaction parameters between ion and solvent groups, where not available in the literature, for example [82], have been estimated using a standard optimisation procedure. The results for toluene are shown in Figure 3.16.

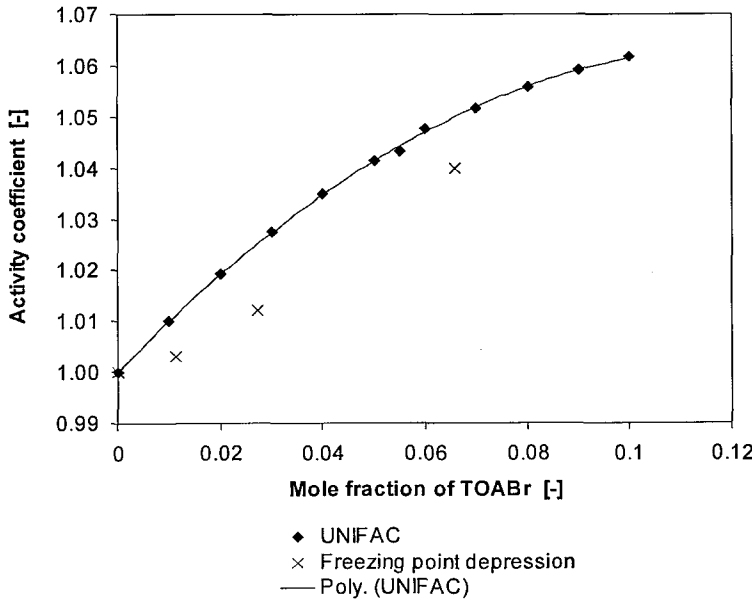


Figure 3.16: Activities of toluene in toluene-TOABr system, calculated using equation (3.95) and from freezing point depression data.

Again, a function describing the data was developed:

$$\text{Toluene: } \gamma_T = -4.16x_T^2 + 7.29x_T - 2.13 \quad (3.97)$$

This activity coefficient function was applied to toluene on the retentate/feed side in the model. The activity coefficient of toluene on the permeate side was assumed to be unity, because the solute mole fraction is sufficiently low. For simplicity, all the TOABr activity coefficients were assumed to be unity since the solute mole fraction on the permeate side is close to zero and so this term does not contribute significantly to the results.

For comparison, the activity coefficients of toluene in the TOABr-toluene system were also calculated from freezing point depression data according to the following relation using the freezing point of the pure solvent (T_0) and the freezing point of the solvent containing solute (T) [83]:

$$\ln(x_A) = -\frac{\Delta H_{fus}^0}{R} \left(\frac{1}{T_0} - \frac{1}{T} \right) \quad (3.98)$$

It should be pointed out that a variety of different values for the enthalpy of fusion are cited in the literature. The DSC analysis gave a value of 5.45 kJ/mol, however the most often cited value is ~ 6.6 kJ/mol [84-87]. The latter value has been used in all further calculations. A comparison of results obtained from freezing point depression data with those calculated according to Equation (3.95) is shown in Figure 3.16. The activity coefficients calculated using the equation are similar but not identical to those estimated from freezing point depression data, with the former values being consistently higher. The discrepancy is not unexpected and most probably is due to uncertainty in the value of ΔH_{fus}^0 and experimental error in the measurement of freezing point depression: the technique is difficult and additional problems are encountered due to the evaporation of toluene. However, the trends are in agreement.

The membrane permeability for toluene was determined from independent measurements of the pure toluene flux at different applied pressures. Docosane and TOABr membrane permeabilities were determined from the nanofiltration data assuming a concentration driving force (using Equation 3.41) and a solute flux experimentally determined at a low applied pressure of 4 bar, to avoid the influence of the exponential term in the solution diffusion model and, the effect of concentration polarisation. The experimental results for 0.33M docosane and 0.21M TOABr solutions were used. It is interesting at this stage to compare the values for the membrane permeabilities with those calculated by White [17] for toluene and docosane using similar polyimide nanofiltration membranes. White also uses the solution diffusion equation, which seems to describe the experimental data well. The comparison is shown in Table 3.9.

Table 3.9: Comparison of parameters estimated in this study with values from the literature.

Permeability ($=D_iK_i/l$) ($\text{molm}^{-2}\text{s}^{-1}$)	This study	White [17]
Toluene	1.1	0.8
Docosane	0.0007	0.007

The values are of the same order of magnitude for toluene, but there is a factor of 10 difference for docosane. This can be attributed to a different experimental setup, including higher temperature (50°C in [17] compared with 30°C in this study), the fact that the data in [17] was taken after 24 hours, whereas the data in this study was taken after 2 hours, differences between the membranes (the newer membranes used in this study are tighter MWCO), and the fact that White's experiments involve a mixture of six hydrocarbons in toluene rather than a binary system.

The model parameter values are summarised in Table 3.10.

Table 3.10: Summary of the model parameters values.

Compound	Docosane	TOABr	Toluene – Docosane	Toluene - TOABr
Diffusion coefficient [m ² s ⁻¹]	1.23x10 ⁻⁹	0.88x10 ⁻⁹	1.23x10 ⁻⁹	0.88x10 ⁻⁹
Molar volume [m ³ mol ⁻¹]	398x10 ⁻⁶	766x10 ⁻⁶	106x10 ⁻⁶	106x10 ⁻⁶
Membrane permeability [molm ⁻² s ⁻¹]	0.0007	3.10 ⁻⁵	1.1	1.1
Activity coefficient [-]	See Figure 3.15	1	See Figure 3.15	See Figure 3.16

In conclusion, one of the advantages of this model are that the only parameters to be estimated, other than physical properties, are the mass transfer coefficients, which may be measured, and the permeabilities, P_{IM} , which may be calculated from flux data.

3.10.6 Results and discussion

3.10.6.1 Nanofiltration of salt-water solutions

In order to illustrate the implications of the simplified version of the solution diffusion model discussed earlier (Equation 3.46), experiments were performed using salt-water solutions with a reverse osmosis membrane. The results for the water permeate fluxes are shown in Figure 3.17. Straight lines are obtained and the intercept corresponds well to the osmotic pressure calculated from the Van't Hoff equation:

$$\Pi = RTc \quad (3.99)$$

These results show that this is a nearly ideal system, in contrast with the behaviour of TOABr, which will later be shown to be highly non-ideal. The results also suggest that concentration polarisation is not important for the salt-water solutions within these concentration and cell flowrate ranges. A detailed analysis of these experimental results will not be presented, since reverse osmosis of salt-water solutions is a well known and

widely studied process. These data are presented for the purposes of comparison with the results obtained with organic solvents. Specifically, since the salt-water and docosane-toluene systems have similar molarities and viscosities, we expect the mass transfer effects will not be very significant in the docosane-toluene system either.

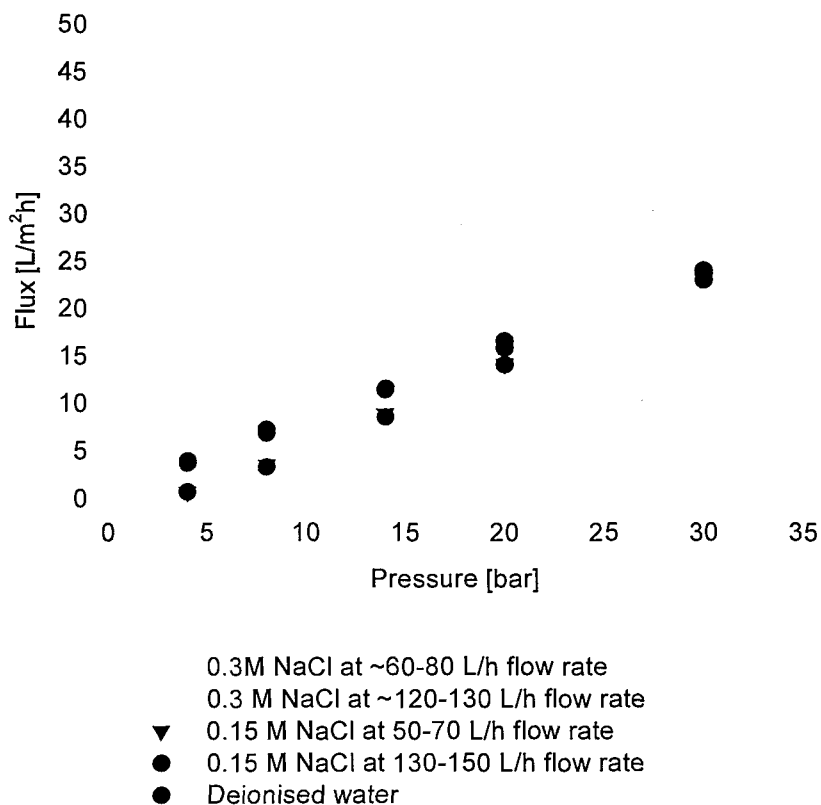


Figure 3.17: Deionised water volumetric flux and permeate volumetric flux for water solutions with various NaCl concentrations versus pressure for reverse osmosis membrane Desal-SE.

3.10.6.2 Viscosities of Toluene Solutions of Docosane and TOABr

The viscosities, measured as described in Section 3.10.4, are presented in Figure 3.18. The viscosity of the docosane solutions is almost constant across the concentration range, and is similar to the viscosity of water. The viscosity of the TOABr solutions varies significantly with concentration, and increases by an order of magnitude as the

concentration rises from 0.005 to 0.4 M. As a result of this, the TOABr-toluene system is more difficult to describe from the mass-transfer point of view and the existence of significant mass transfer limitations might be expected.

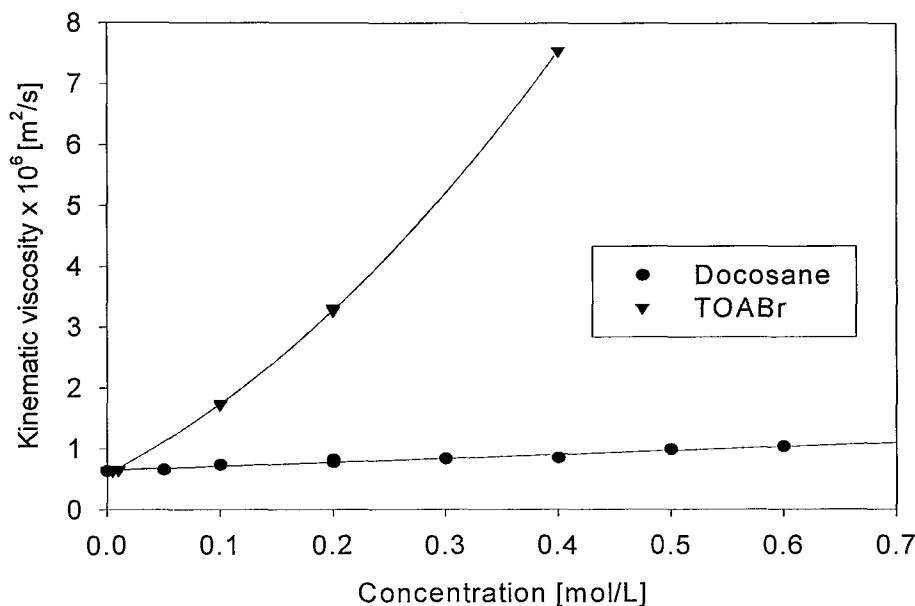


Figure 3.18: Kinematic viscosity of TOABr and docosane solutions in toluene.

3.10.6.3 Nanofiltration of Docosane – Toluene solutions

The first experiments were conducted with the docosane-toluene system. This is considered an ‘easy’ binary system with which to verify the model due to the fact that nanofiltration data are available in the literature for comparison [17], and as mentioned above, the change in viscosity with concentration is negligible.

Two concentrations of docosane (0.33M and 0.67M) in toluene were tested at various pressures and flow rates. The results for the permeate flux and docosane rejection are presented in Figures 3.19 and 3.20. As can be seen from the figures, both docosane rejection and permeate flux decrease with decreasing pressure at both concentrations. The fluxes and rejections are lower at the higher docosane concentrations. This type of

result is not surprising and has been observed previously with other systems [55, 56]. Experimentally, the flow rate through the cross-flow cell does not have a significant effect on the flux or the rejection performance.

The suggested model was then applied to the docosane system. The results were calculated for two cases: (i) assuming that the activity coefficients of the solvent and solute were equal to unity, and, (ii) by applying the activity coefficient functions derived from the UNIFAC data (Equations 3.93 and 3.94). The comparisons of the model results with the experimental values for the permeate flux and docosane rejection are shown in Figures 3.19 and 3.20.

For the flux data (Figures 3.19A and 3.20A), the calculated values correspond better with the experimental data at higher pressures. When activity coefficients are taken as unity, the model predicts almost no flux at pressures lower than 8 bar for 0.33M concentration, and ~18 bar for 0.67 M concentration whereas, experimentally, flux is seen at all pressures. Since the predicted rejection corresponds reasonably well with the experimental values over this pressure range, the existence of flux experimentally suggests that the effective osmotic pressure is lower than predicted and that the system deviates from ideality. Introduction of the activity coefficient ratios improves the fit of the model to the permeate flux data. At pressures higher than 20 bar the model predicts some influence of the flow rate on the permeate flux, however none is seen experimentally. This could be the influence of membrane compaction at higher pressures, which contributes to the membrane performance as follows: if the mass transfer is considered from the resistances in series point of view, the overall resistance for nanofiltration consists of 3 components: the liquid boundary layer resistance, the top layer resistance and the porous support resistance. However, if due to membrane compaction, the membrane resistance increases as a result of pore size reduction in the porous support and/or decrease in the free volume in the top active layer, then the influence of the boundary layer resistance will be minimised compared with these increased resistances. This effect is difficult to quantify for use in the model. An alternative explanation is that our mass transfer coefficients values were estimated

considering diffusion coefficient in dilute conditions: at the high concentrations that we are working with, the variation of the mass transfer coefficients at different flow rates could be less significant. The diffusion coefficient is a more complicated function depending on concentration, pressure, viscosity and activity of the components of the system [88]. Therefore it is not surprising that a discrepancy is observed between experimental results and the results calculated from the model on the basis of a single value of the diffusion coefficient, and this is an interesting area for further study.

For the rejection data (Figures 3.19B and 3.20B), no influence of the mass transfer coefficient (i.e. flow rate) is predicted for 0.33M docosane. For 0.67M docosane, a slight variation is predicted due to a more significant concentration polarisation effect at higher concentrations. As for the flux data, the shape of the predicted curve improves when the activity coefficient ratios are not constrained to unity, but the model values are higher than the experimental values, especially at high pressures. This discrepancy could be due to the simplified approach used to estimate the membrane permeability for docosane. It should also be noted that the membrane permeability is assumed to be constant, independent of pressure and concentration of the components. However, a detailed analysis of the factors contributing to the membrane permeability term suggests that this assumption is not always true. The three contributing terms are the component diffusion in the membrane, the partition coefficient and the membrane thickness. The diffusion coefficient in the membrane is unlikely to change with pressure and concentration. However, the partition coefficient is the ratio between the activities of the component in the feed and the membrane, which is not necessarily a constant independent of concentration. The membrane thickness may also vary due to membrane compaction, or membrane swelling. A more detailed study on the nanofiltration process is required to understand the influence of these parameters on the membrane performance.

Since most of the thermodynamic parameters used in the model are estimated theoretically based on existing correlations, the fit of the experimental data is considered quite satisfactory at this stage.

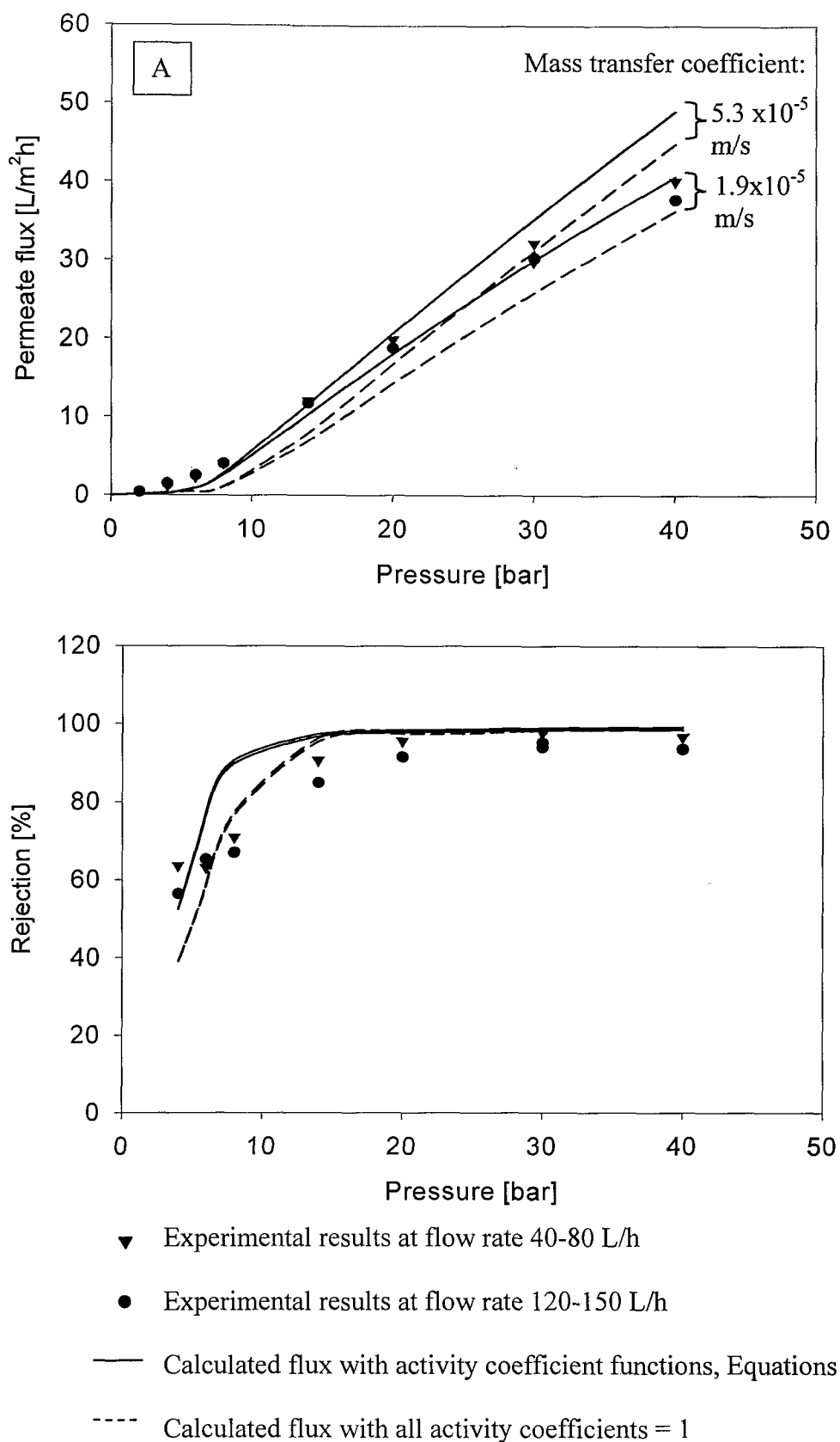
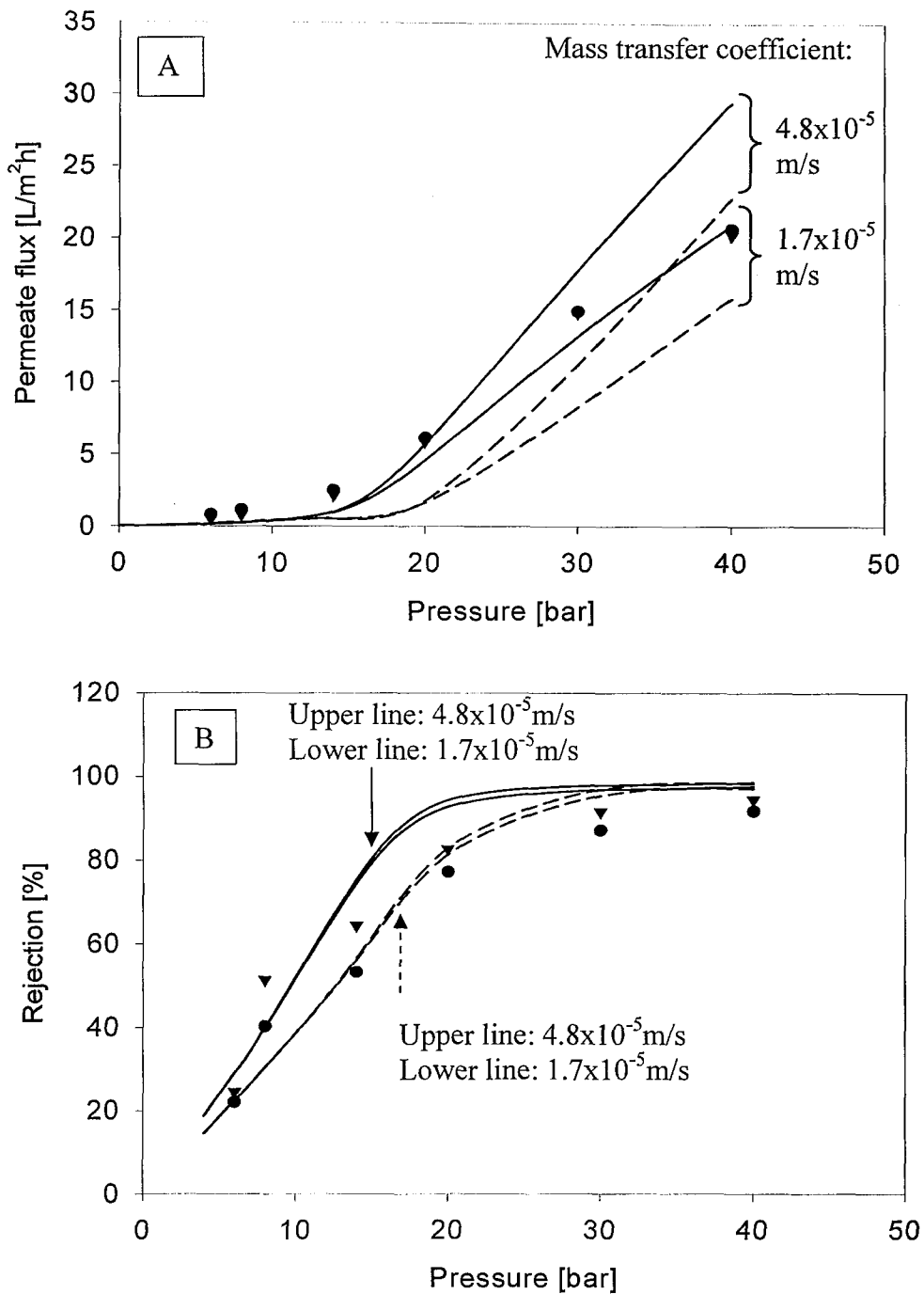


Figure 3.19:

A. Experimental and calculated values for permeate flux of 0.33M docosane solution.
 B. Experimental and calculated values for rejection of 0.33M docosane solution.



- ▼ Experimental results at flow rate 40-80 L/h
- Experimental results at flow rate 120-150 L/h
- Calculated flux with activity coefficient functions, Equations (3.93), (3.94)
- Calculated flux with all activity coefficients = 1

Figure 3.20:

A. Experimental and calculated values for permeate flux of 0.67M docosane solution.

B. Experimental and calculated values for rejection of 0.67M docosane solution.

3.10.6.4 Nanofiltration of TOABr – Toluene Solutions

Following the work with the docosane-toluene system, a more “difficult” binary mixture was chosen, TOABr-toluene, in which system there are significant changes in viscosity with concentration of TOABr (Figure 3.18).

The results of the influence of the flow rate on the permeate flux are presented in Figure 3.21. These experiments were performed in order to understand whether concentration polarisation is important in this process, and also its range of influence. As can be seen from the figure, the effect of concentration polarisation is significant at all except very low concentrations $\sim 0.005\text{M}$. This behaviour is markedly different from that observed in the docosane-toluene system, where the flow rate has a negligible effect on the permeate flux. The difference could be attributed to two factors. Firstly, the diffusion coefficient of docosane in toluene is higher than that of TOABr ($1.23 \times 10^{-9} \text{m}^2 \text{s}^{-1}$ compared with $0.88 \times 10^{-9} \text{m}^2 \text{s}^{-1}$) when calculated at infinite dilution, but in concentrated solutions, considering the viscosity change, this difference could be even higher. Secondly, the rejection of TOABr remains in the range 98-99% (unlike docosane), which increases the build up of solute in the boundary layer.

After performing several experiments varying pressure, flow rate and solute concentrations an attempt was made to fully describe the process. Experimental data are shown in Figure 3.22. Although the solute rejection was very high ($\sim 99\%$) over the whole pressure range, the shapes of the permeate flux versus applied pressure were completely different from those for the salt-water solutions (Figure 3.18) of the same concentrations.

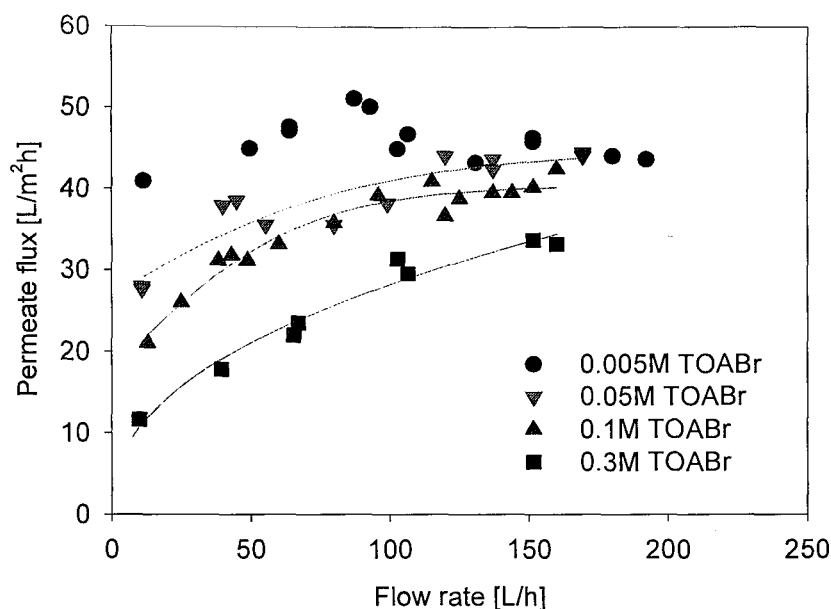


Figure 3.21: Permeate flux dependence on the feed flow rate at different TOABr concentrations. The cross flow unit was operated at 30°C and 30 bar pressure.

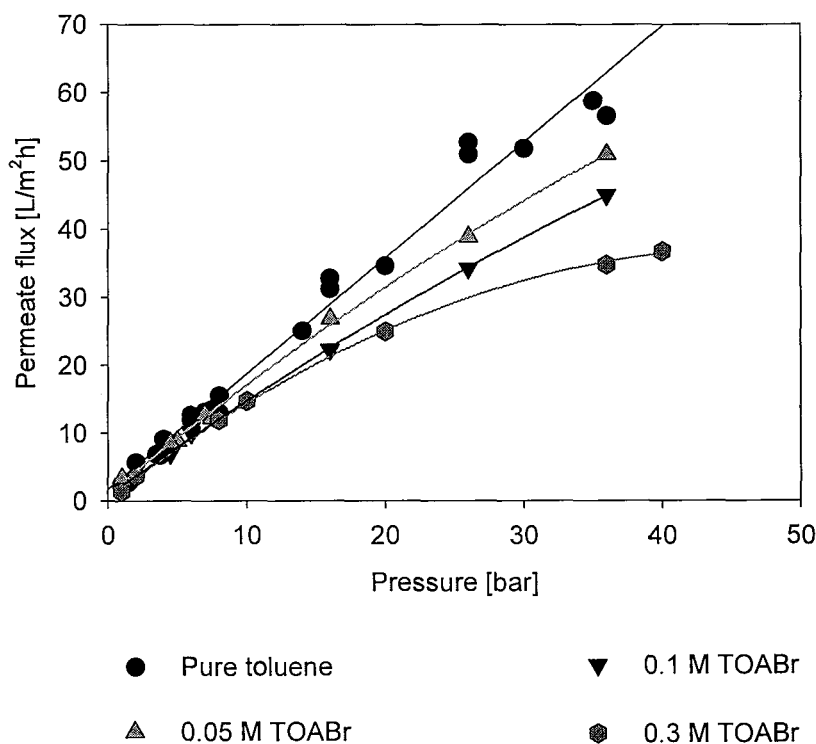
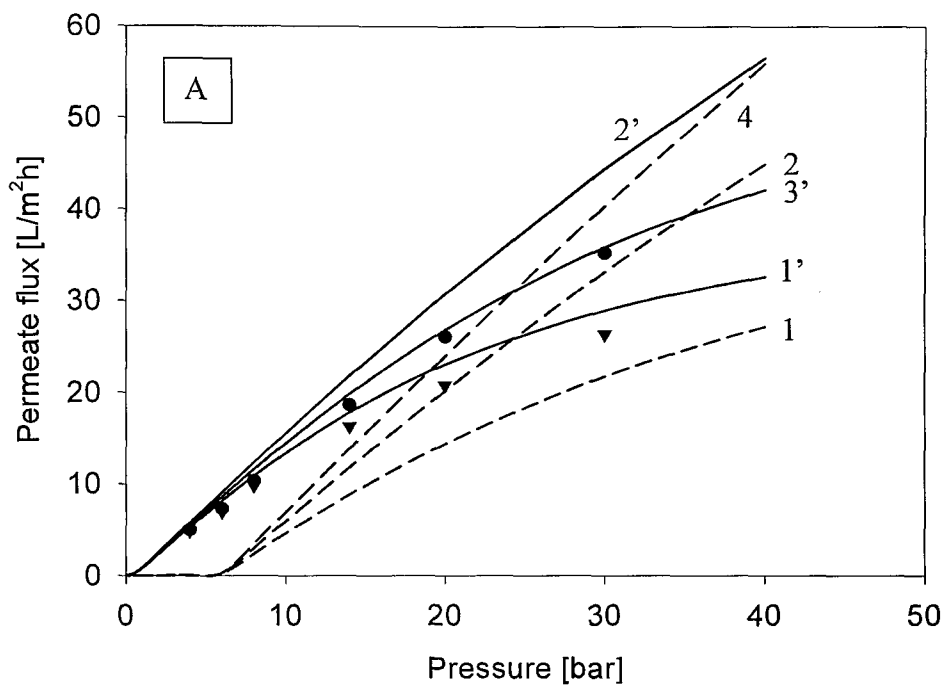


Figure 3.22: Permeate flux for various concentrations of TOABr in toluene, as a function of pressure: pure toluene, 0.05M, 0.1M and 0.33M at cross flow rate 120-150L/h.

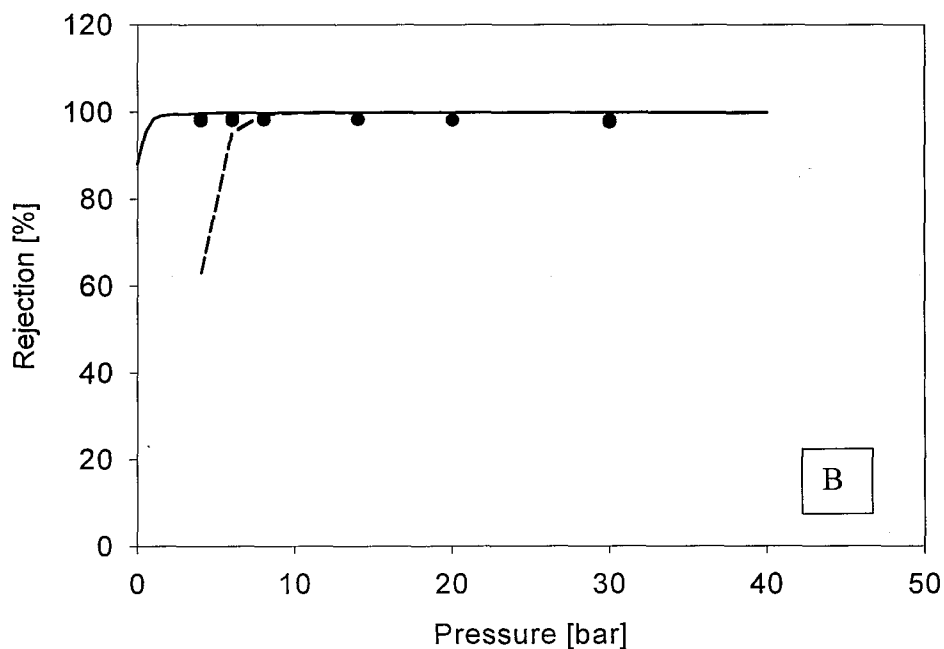
The results suggest that the osmotic pressure differs from that given by the Van't Hoff equation, and it was obvious that the data could not be described with the simplified solution diffusion model (Equation 3.46). Similar types of curves have been reported in the literature with macromolecular solutions [57] where the activity of the system components differs from unity. The observed divergence of the dependence of flux on pressure from linearity at higher concentrations also suggests the existence of concentration polarisation.

Initially, the influence of the mass transfer coefficient, k , on the permeate flux was investigated, assuming all the activity coefficients were unity. However, as shown in Figure 3.23A, for 0.21M TOABr in toluene, (dashed lines), the data could not be described in this way, no matter what the mass transfer coefficient values were. Even when the mass-transfer coefficient value $\rightarrow \infty$ (line 4 on Figure 3.23A), the model predicts an osmotic pressure of around 6 bar, at a concentration of 0.21M, which is not observed experimentally.



Mass transfer coefficient values [m/s] :

$$\begin{aligned}
 1 &= 0.8 \times 10^{-5} & 1' &= 0.8 \times 10^{-5} \\
 2 &= 2.2 \times 10^{-5} & 2' &= 2.2 \times 10^{-5} \\
 4 &= \infty & 3' &= 1.1 \times 10^{-5}
 \end{aligned}$$



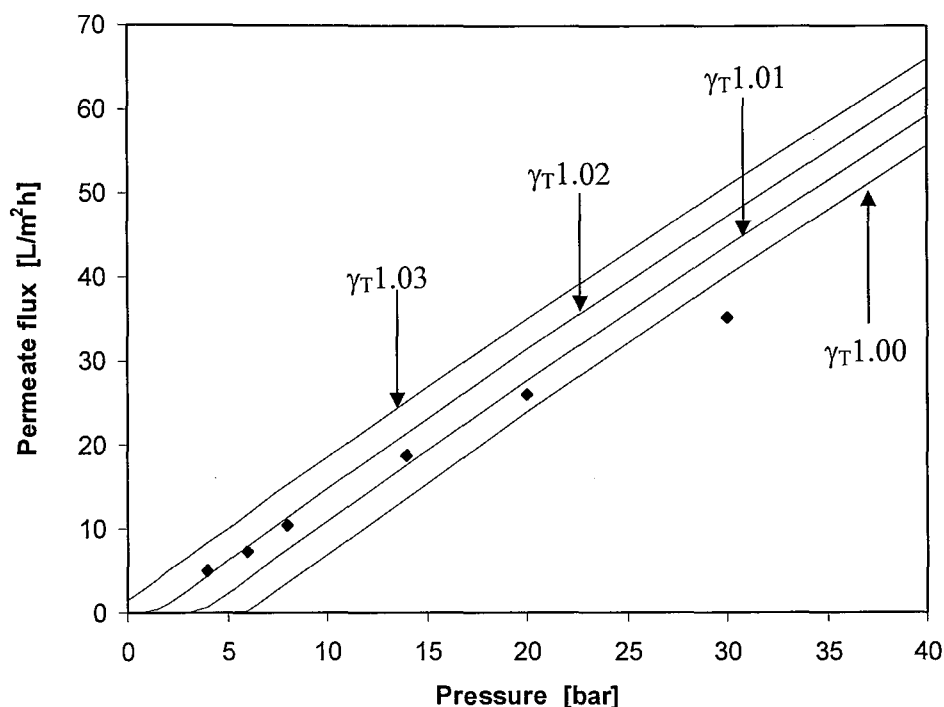
- ▼ Experimental results at flow rate 40-80 L/h
- Experimental results at flow rate 120-150 L/h
- Calculated flux with activity coefficient function, Equation (3.97)
- Calculated flux with all activity coefficients = 1

Figure 3.23:

A. Experimental and calculated values for permeate flux of 0.21M TOABr solution.

B. Experimental and calculated values for rejection of 0.21M TOABr solution.

Activity differences could be responsible for this difference. Figure 3.24 demonstrates that the activity coefficient of toluene in the boundary layer has an important effect in this system. The permeate flux in the system was calculated using values for the activity coefficient of toluene between 1 and 1.04 (the range predicted by applying Equations 3.95 and 3.96), and for the case where mass transfer limitations were negligible. With negligible mass transfer limitations, the concentration and activity coefficients at the membrane-liquid interface are the same as those in the bulk liquid. As can be seen from the data in Figure 3.24, even a very small change in the activity coefficient has a significant effect. The results show that, for 0.21M TOABr in toluene, $\gamma_{\text{TFB}} = 1.02$ gives the most accurate description of the experimental data, at low pressures. The inclusion of mass transfer limitations is necessary in order to describe the high pressure behaviour, as will be discussed later. Interestingly, the model suggests the existence of a probably purely hypothetical case where the activity coefficient is so high that there is some permeate flux, (albeit small, $\sim 2 \text{ L/m}^2\text{h}$), at zero applied pressure difference across the membrane. As these curves represent hypothetical situations and physical systems corresponding to these activities have not been observed, this should not be seen as a matter for concern.



- Experimental toluene flux for 0.21M TOABr in toluene, flow rate 120-150L/h

Lines represent calculated flux for various toluene activity coefficients (as shown on graph). All other activity coefficients = 1.

Figure 3.24: Effect of toluene activity coefficient on model data for 0.21M TOABr solution.

Since the activity coefficient has been shown to have an important role in this system, the activity coefficient function (Equation 3.97) was included in the model. Figure 3.23A shows a comparison of the experimental and model data. The Figure demonstrates that it is only possible to describe the low pressure flux behaviour of the system with the inclusion of activity coefficients, indicating that the system is not ideal. Other parameters in the model, such as the permeability of the solvent and the solute, were varied to check whether they could be responsible for this effect. However, it was found to be impossible to describe the data by alteration of the two permeabilities or the mass transfer coefficient. Equally, it is only possible to describe the high pressure, concentration polarisation effect with the inclusion of mass transfer effects. The overall system requires both activity coefficients and mass transfer coefficients in order to

obtain a satisfactory description of the experimental data. The mass-transfer coefficient values estimated from Chilton-Colburn correlation (see Table 3.7) describe the experimental data reasonably well at lower flow rate (40-80 L/h), corresponding to a mass transfer coefficient of 0.77×10^{-5} m/s. However, the flux values at the higher flow rate range 120-180 L/h, are over predicted, corresponding to a mass transfer coefficient of 2.2×10^{-5} m/s. The experimental data at this higher range are better described by a mass transfer coefficient of 1.1×10^{-5} m/s, as shown in Figure 3.23A. This difference can be attributed to the fact that the Chilton-Colburn correlation, as for many other mass transfer correlations is developed for non-porous smooth duct flow and its application to membrane operations may be limited [69]. It does not account for the change of physical properties such as viscosity and diffusivity across the boundary layer. Also, as mentioned earlier, the true flow in the cell is tangential, which makes hydrodynamics difficult to describe. Therefore, the values estimated from the Chilton-Colburn correlation should be considered an approximation.

The model predicts very high rejection (Figure 3.23B) for both the ideal and non-ideal cases above about 10 bar, as observed experimentally. The mass transfer coefficient seems to have a negligible effect on the rejection, as observed for docosane. There is a discrepancy between non-ideal and ideal model data for pressures under 10 bar. If activity coefficients are included, the model predicts ~100% rejection for nearly all pressures, only deviating slightly from 100% at very low pressures (~2 bar). If activity coefficients are not included, the rejection begins to deviate from 100% at around 8 bar and decreases to ~60% as the pressure decreases to 4 bar, where the total flux becomes nearly zero. This behaviour for the ideal solution case is due to the fact that the model predicts that the solvent flux drops considerably at pressures lower than 6 bar, while the solute flux does not change so dramatically, thus causing the decrease in rejection. This is more obvious from the equations of the simplified solution-diffusion model (Equations 3.46 and 3.47) where the solvent flux is clearly affected by the osmotic pressure, while the solute flux is not. However this ideal case is very different from the actual behaviour of the non-ideal TOABr-toluene system.

The divergence of the system from ideality increases at higher concentrations of TOABr, as illustrated for the flux data in Figure 3.25, for 0.33M TOABr in toluene.

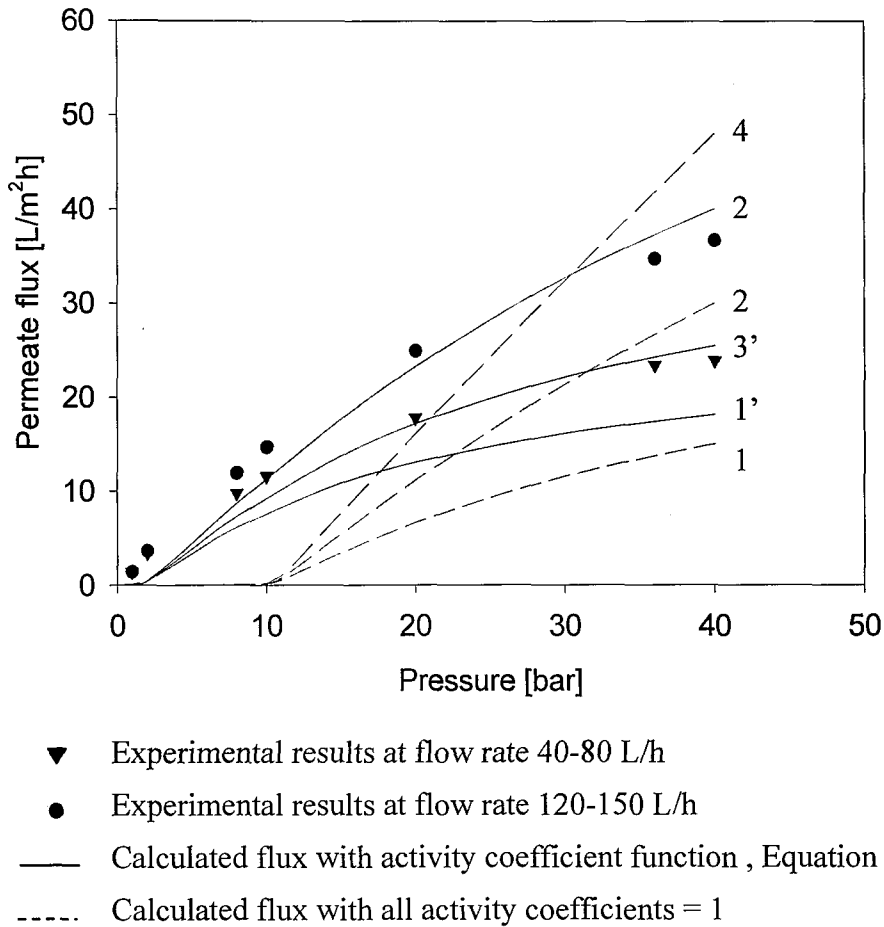


Figure 3.25: Experimental and calculated values for permeate flux of 0.33M TOABr solution.

Note that, as for the 0.21M case, the model without activity coefficients also predicts an osmotic pressure, this time about 10 bar, even at infinite mass transfer coefficient (line 4 on Figure 3.26). As before, this phenomenon is attributed to activity differences. Again the mass transfer correlation slightly under predicts the permeate flux values, but this time at the lower flow rate (40-80 L/h), with a mass-transfer coefficient value of 0.6×10^{-5} m/s versus 0.9×10^{-5} m/s as estimated by comparing the model to the experimental data. More surprising is the fact that the mass-transfer coefficient values describing the

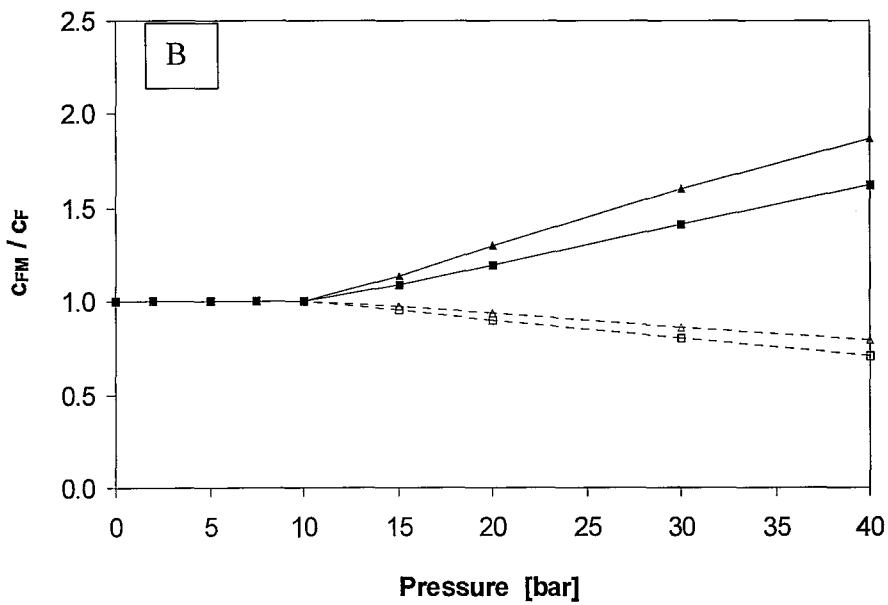
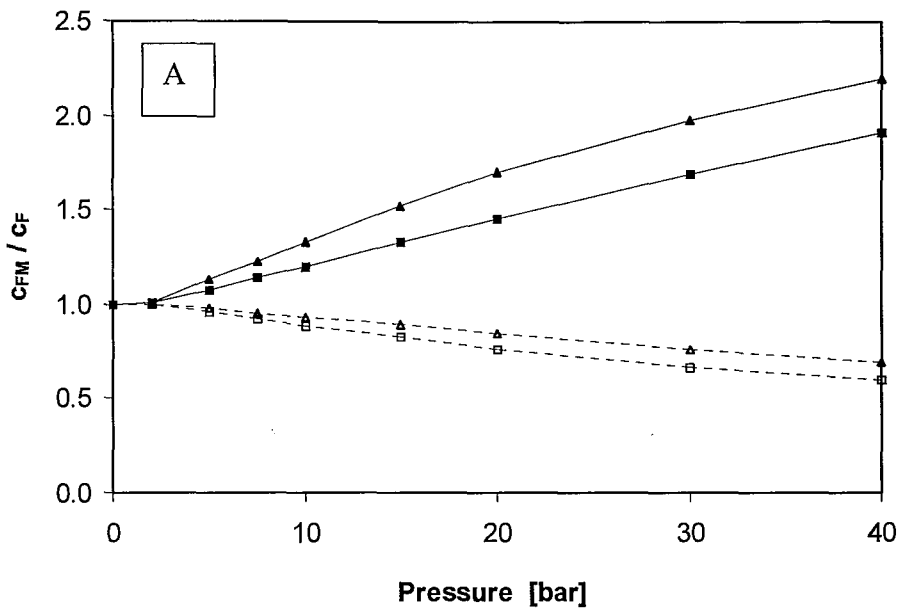
experimental data at 0.33M TOABr are slightly higher than those describing 0.21M TOABr solutions. This could be due to non-ideality of the system, the unpredictable changes of the diffusion coefficient with concentration or the build up of a gel-layer at the membrane surface. The latter is investigated further below.

The extent of concentration polarisation at 0.33M is demonstrated by Figure 3.26, which shows the ratio of the predicted concentration at the membrane-liquid interface to the bulk liquid concentration.

At 40bar pressure, the TOABr concentration at the membrane-liquid interface is over twice the bulk concentration (Figure 3.26A, for the non-ideal case), illustrating that the mass transfer limitation in the system is severe. This represents a concentration of over 0.72M at the membrane surface, causing concern that a gel-layer might be formed. The solubility of TOABr in toluene at 30°C was measured to be 0.76M. Hence, the TOABr should not precipitate out of solution at the membrane surface, but clearly is approaching the range where this might occur. At low pressures, this effect is much less significant due to the lower solvent flux. When non-ideality is not accounted for (Figure 3.26B), the mass transfer limitation is less severe (the solvent flux is lower due to the higher osmotic pressure effect): the concentration at the membrane surface is about 1.9 times the bulk concentration at 40bar. For both the ideal and the non-ideal case, the concentration polarisation effect appears over the whole pressure range, up to the point where the permeate flux becomes ~ 0 .

If the concentrations at the membrane surface really are as high as 0.72M, the viscosity at the membrane surface may also be high due to solute build up (concentration polarisation), thus inhibiting mass transfer even further. This questions whether it is valid to use a constant mass transfer coefficient in the system. An extension of this study could be to include variation of the diffusion coefficient (and thus the mass transfer coefficient) with position in the boundary layer.

An interesting comparison is the variation in the solvent flux for the two different systems under exactly the same conditions: 40 bar, 0.33M, and cell flow rate 120-150 L/h. The toluene flux in the docosane-toluene system is 20.7 L/m²h and in the TOABr-toluene system is 36.7 L/m²h. This is in spite of the higher viscosity and lower mass transfer in the TOABr-toluene system. Thus it can be seen that the non-ideality of the TOABr-toluene system actually assists the filtration process by reducing the osmotic pressure difference across the membrane and thus allowing a higher flux. This creates an interesting opportunity for organic solvent nanofiltration. By choosing carefully, based on thermodynamic predictions, an effective solute-solvent combination, the solvent flux could be improved significantly.



- 1.72x10⁻⁵ m/s TOABr
- ▲— 0.9x10⁻⁵ m/s TOABr
- - -■- - 1.72x10⁻⁵ m/s tol
- - -▲- - 0.9x10⁻⁵ m/s tol

Figure 3.26:

A. Ratio of concentration at membrane surface to bulk concentration for 0.33M TOABr solution, $\gamma_T = -4.16x_T^2 + 7.29x_T - 2.13$, $\gamma_{TOABr} = 1$.

B. Ratio of concentration at membrane surface to bulk concentration for 0.33M TOABr solution, $\gamma_T = \gamma_{TOABr} = 1$.

3.10.7 Conclusions

In many industrial applications of nanofiltration, the solute needs to be concentrated significantly. At higher concentrations, concentration polarisation becomes important. Osmotic pressure effects also become significant. Concentrated organic solutions may deviate substantially from ideality. Hence the ratio of the activity coefficients on the permeate side and feed side of both the solvent and the solute should be taken into account. Accounting for these, for example, for a 0.33M TOABr solution (Figure 3.26, lines 2 and 2'), gives a 75% improvement in the prediction.

The suggested mathematical model combines the solution diffusion model for membrane transport with the film theory for mass transfer. It also allows for system non-ideality, by incorporating the ratio of the activity coefficients on the permeate and feed sides. Data, collected with StarmemTM 122, toluene and TOABr and docosane as solutes, can be described reasonably well with the model. The model does not allow for any coupling of the fluxes of the system components, but still describes the data sufficiently well. While much previous work has focused on the exact nature of the membrane permeation [50-52, 55, 58], this work suggests that due attention should also be given to the governing thermodynamics and to mass transfer effects.

CHAPTER 4

DYNAMIC KINETIC RESOLUTION: LITERATURE REVIEW

As mentioned in Chapter 1, there are two parts to this study. The first part comprises an investigation into the fundamentals of membrane transport including the description of experimental data using a mathematical model. The second part is an investigation into the applicability of OSN membranes to a separation problem arising in industry. There are many separation processes in industrial contexts to which membrane technology could be applied. In this study, the application of OSN membranes to dynamic kinetic resolution (DKR) processes will be assessed. A summary of the current state of research into DKR follows.

4.1 BACKGROUND

As many essential biological molecules are inherently chiral, biological activity is highly dependent on enantiomeric purity [89]. Synthesis of a racemic compound is inefficient, as one enantiomeric form has low or no activity. Furthermore, the presence of the inactive enantiomer may have adverse side effects. Therefore, enantiomerically pure chiral compounds are essential for several industries such as pharmaceuticals, agrochemicals and food.

Enantiomerically pure compounds can be produced by asymmetric synthesis [90], but this is often difficult and, due to the use of expensive reagents, not economic. Alternatively, enantiomerically pure compounds can be generated by resolution of the racemic mixture, although, as enantiomers have identical physical properties and differ only in optical activity, this is also difficult. Some of the approaches are as follows:

1. *Kinetic resolution* (biological separation)
2. *Chemical separation* (often using a chiral metal complex as a catalyst)
For example, Jacobsen's chiral Salen Co or Cr^{III} complexes for resolving epoxides [91]
3. *Chromatography*
4. *Diastereomic resolution* [92]

Kinetic resolution uses the selectivity of enzymes to resolve, for example, alcohols using lipases. A schematic showing this process for a model secondary alcohol is shown in Figure 4.1 [89]. If $k \gg k_{\text{ent}}$ both the unchanged alcohol *ent*-1 and the product acetate **2** can be obtained in high enantiomeric purity (>99%). However, each product is obtained with a *maximum yield of 50%*. In addition the alcohol and acetate must be separated from each other as well as from the catalyst.

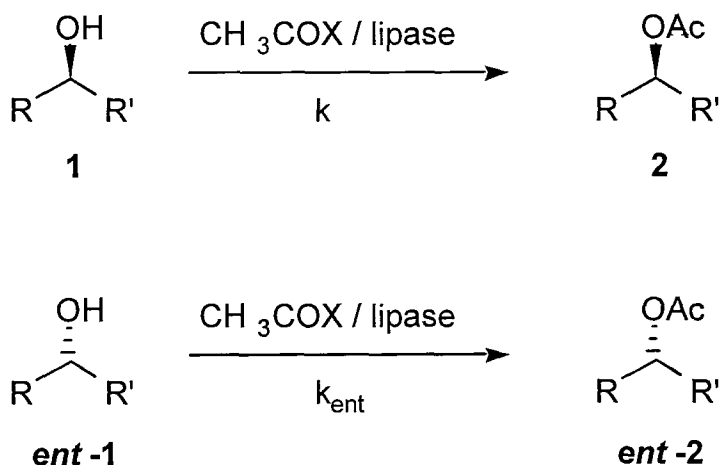


Figure. 4.1: Scheme for kinetic resolution of secondary alcohol.

4.2 CONCEPT OF DYNAMIC KINETIC RESOLUTION

The maximum possible yield of a kinetic resolution can be raised from 50% to 100% by converting the process to a Dynamic Kinetic Resolution (DKR), as shown in Figure 4.2, which combines the resolution with a racemisation process, thus converting the non-

reacting enantiomer into the reacting enantiomer. This process is governed by the continuous equilibrium of both enantiomers and driven by an increase in entropy [93, 94]. DKR is only possible when the chiral starting material racemises rapidly and the racemisation of the product is very slow ($k_{\text{rac}} \gg k \gg k_{\text{ent}}$). Note that the only separation required is of the product from the catalyst.

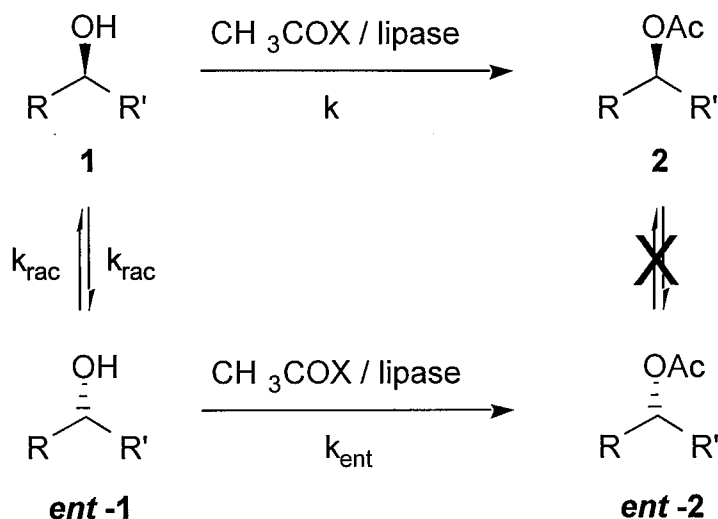


Figure 4.2: Scheme for Dynamic Kinetic Resolution of secondary alcohol.

Hence, in general, two catalysts are required for DKR: an enantioselective resolution catalyst (often an enzyme) and a racemisation catalyst. Racemisation catalysts may be, for example, transition metal complexes or bases. Problems are encountered when the conditions required for the two catalytic systems are incompatible.

4.3 EXPERIMENTAL DKR LITERATURE REVIEW

A number of recent reviews and accounts have highlighted the growing importance of DKR. Caddick and Jenkins [95] and Pellisier [96] have provided comprehensive general accounts of DKR following the earlier fundamental review by Ward [97]. Results can be divided into three main sections: DKRs with 1) enzyme mediated resolution, and 2)

non-enzyme mediated resolution, and 3) one stage DKRs (crystallisation induced). Authors report their results in terms of reaction yield and enantiomeric excess (ee) which is defined as the excess of one enantiomer over racemic material:

$$ee = (\%enantiomer_1 - \%enantiomer_2) \times 100\% \quad (4.1)$$

Most of the work published in this field involves an enzyme mediated resolution and chemically catalysed racemisation. For this reason, this study will focus on such methods, although alternative methods will be mentioned for the sake of completeness.

4.3.1 Enzyme mediated resolution

4.3.1.1 DKR involving spontaneous racemisation

A number of efficient DKRs exploit spontaneous racemisation of the substrate, without any additional reagent [94], which are often thermally induced. Suitable substrates are compounds which racemise by rotation or deformation of bonds [94], such as biaryls, by pyramidal inversion or by bond rearrangement. This method has great industrial advantage, being simple and economic and not requiring extra reactants which may interfere with the enzymes. However, suitable examples are rare, control of the process may be difficult and decomposition of the substrate may occur in cases where high temperatures are required. An example of such a DKR is the enantioselective hydrolysis of racemic mandelonitrile, reported by Yamamoto *et al.* [98, 99], using cells from *Alcaligenes faecalis* to yield (R)-mandelic acid in 91% yield.

4.3.1.2 DKR using chemically catalysed racemisation

There are many examples of the use of enzymes in combination with chemical catalysts in the literature. The main chemical methods are base catalysts and transition metal catalysts (TMC). Other less widely used methods include acid catalysed mechanisms [94, 100], Schiff-base mechanisms [93], redox mechanisms, nucleophilic substitutions and mechanisms proceeding via a-chiral meso-compounds [101].

(i) Base catalysed

Base catalysed racemisation is well known and probably the most frequently used method [94]. It can be applied to any species with an acidic hydrogen at the chiral centre, and hence, has a large scope. The acidic hydrogen is removed from the chiral centre to form a carbanion, which must be stabilised in one of two ways. Firstly, it can be stabilised by adjacent groups, as shown in Figure 4.3. These groups can be keto, nitrile or nitro functionality groups. Alternatively, it can be stabilized by reversible elimination of a β -substituent, as shown in Figure 4.4.

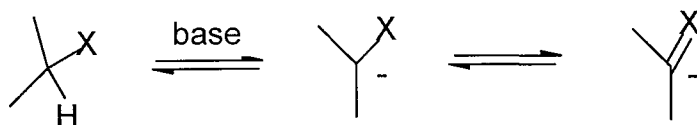


Figure 4.3: Stabilisation of species for base catalysed racemisation by adjacent groups, $X = C(O), CN, NO_2$ etc.

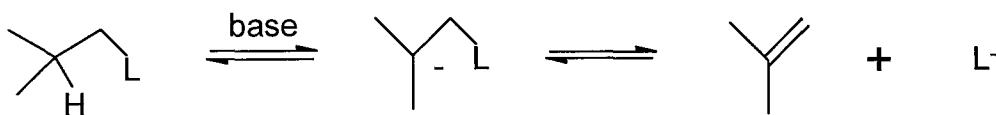


Figure 4.4: Stabilisation of species for base catalysed racemisation by elimination.

The disadvantage of such base catalysed racemisations is that preparation of a derivative with enhanced acidity is often required, introducing additional steps which may not be feasible in situ. Another problem is that removal of a hydrogen in an apolar solvent results in an intimate ion pair. In this case, re-addition of the proton often occurs predominantly at the same side from which it was removed ('retention'), resulting in, at best, very slow racemisation or in the worst case, no racemisation. Compare the case of a protic polar solvent, where the ion pair is separated and re-addition occurs predominantly from the opposite side resulting in an 'inversion' and fast racemisation. For these reasons, the choice of solvent is important.

Bases used for racemisation include hydroxides, metal alcoholates, metal amides and amines. Suitable substrates are amino acids and related compounds, α -alkyl or -aryl or hydroxy substituted carboxylic acids, ester, ketones and related compounds and compounds containing a nitrogen or oxygen at the chiral centre. Table 4.1 summarises the literature on enzymatic resolutions with base catalysed racemisations.

Table 4.1: Base-catalysed racemisation coupled with enzymatic resolutions.

Author [Ref.]	Enzyme	Base	Substrate	Product	Other reactants	Solvent	Yield %	Ee %	Conditions
Inagaki <i>et al.</i> [102]	Pseudomonas Ceacia Lipase	Basic anion exchange resin (Amverlite IRA- 904)	Aldehyde	Cyanohydrin acetates	Acylation agent: isopropenyl acetate, acetone	Di- isopropyl ether	63-100	Up to 94	40°C
Um <i>et al.</i> [103]	Various Hydrolases	Triethyl amine	Thioesters	Carboxylic acids		PIPES buffer	95-97	80- 83	pH 7
Um <i>et al.</i> [103]	PCL (PS-30)	Triethyl amine	Thioester of 2,4- dichlorophenoxy -propionate	Carboxylic acids	Acyl acceptor: n-butyl alcohol	Toluene	81	93	pH >8 room temp.
Xin <i>et al.</i> [104]	Candida Rugosa lipase	NaOH	Naproxen methyl ester	Naproxen	Tris-HCl buffer	Biphase: isooctane / water	60	>96	32°C pH 7.5

In addition to this, there are many examples of base catalysed racemisations (without enzymatic resolutions), which may be useful from the point of view of examining and selecting the individual reactions which make up the DKR process. Some examples which illustrate the variety of bases that may be used are shown in table 4.2.

Table 4.2: Base catalysed racemisations.

Author [ref]	Base	Substrate	Time	Yield %	ee %
Brown <i>et al.</i> [105]	Sodium methoxide	Hemiesters of lactones	Several hours	-	-
Ebbers <i>et al.</i> [94]	Sodium	α -hydroxy carboxylic acids	5 hours	44%	100%
“	Alkali metal hydroxides	α -hydroxy carboxylic acids	-	-	100%
“	Catalytic NaNH_2 or NaH	Aromatic amines	-	~100%	100%
“	NaOH / NaOMe / NaHCO_3 / Na_2CO_3 / DABCO	Amines containing –OH group at chiral centre	-	-	100%
Tsujino <i>et al.</i> [106]	Various e.g. K-t-Bu	Nicotine	Various	Various e.g. 95%	-

(ii) Transition Metal Catalysed

The application of transition metal catalysts (TMC), as the racemisation catalyst, to DKR is a growing field. Table 4.3 summarises the work to date. Further details of the most commonly investigated substrates, secondary alcohols, are given below.

Table 4.3: Transition metal-catalysed racemisation coupled with enzymatic resolution.

Author [Ref.]	Catalyst	Co-catalyst	Enzyme	Substrate	Product	Other reactants	Solvent	Yield %	Ee %	Time	Con- ditions
Allen <i>et al.</i> [107]	$\text{PdCl}_2(\text{MeCH})_2$	-	PFL and various hydrolases	Allylic acetates	Allylic alcohols	-	Phosphate buffer	68- 96	85- 96	19- 23 days	37-40 °C, pH 7.0,
Choi <i>et al.</i> [108]	Aminocyclo- pentadieny ruthenium chloride	Na_2CO_3	Novozym 435	Secondary alcohols	Secondary Acetates	dry toluene, Acyl donor: alkenyl acetate	t-BuOH	?	>99	30 hrs.	Argon 25°C
Choi <i>et al.</i> [109]	$\text{Pd}(\text{PPh}_3)_4$	-	Novozym 435, PCL	Allylic acetates	Allylic alcohols	Acyl acceptor: 2- propanol	Dry THF, IPA	86- >99	97- 99	1.5-3 days	Argon, Room temp.
Dijksman <i>et al.</i> [110]	$\text{RuCl}_2(\text{PPh}_3)$ or Achiral Ru.complex	TEMPO, KOH	Novozym 435	Secondary alcohols	Secondary acetates	4 chloro- phenyl acetate	Toluene	61- 91	55- 76	48 hrs.	N_2 , 70°C
Dinh <i>et al.</i> [111]	Ir, Al, Rh complexes	Ir require KOH	PSL, PFL	Secondary alcohols	Secondary Acetates	Vinyl acetate	C_6H_{12} CH_2Cl_2	60- 91	2-98	72- 144 hrs.	20- 80°C

Author [Ref.]	Catalyst	Co-catalyst	Enzyme	Substrate	Product	Other reactants	Solvent	Yield %	Ee %	Time	Con- ditions
Huerta <i>et al.</i> [112]	Dimeric Ru complexes	-	PCL: lipase PS-C	α - hydroxy esters	Acetates	Acyl donor: <i>p</i> -chloro- phenyl acetate	Cyclohexane	> 40	30- 98	24- 72 hrs.	Argon, 60 °C
Huerta <i>et al.</i> [113]	Dimeric Ru complexes	-	PCL	β -hydroxy esters	Acetates	4-chloro- phenyl acetate	<i>t</i> -butyl methyl ether	-	70- 99	6 days	60 °C
Kim <i>et al.</i> [114]	Dimeric Ru complexes	-	PCL	β - hydroxy- butyrate with protective group	Acetates	4 chloro- phenyl acetate	Toluene	97- >99	86- >99	4-5 days	Argon, 70°C
Kim <i>et al.</i> [114]	Dimeric Ru complexes	-	PCL	Diols	Acetates	2,6-dimethyl- 4-heptanol	Toluene	95	95- 99	6-8 days	Argon, 70°C
Kim <i>et al.</i> [114]	Dimeric Ru complexes	-	PCL, CALB	Hydroxyl aldehydes with 1,2- benzenedi methanol	Acetates	Acyl donor: AcOPh- <i>p</i> -Cl	Toluene	90- 95	35- 98	3 days	Argon, 70°C

Author [Ref.]	Catalyst	Co-catalyst	Enzyme	Substrate	Product	Other reactants	Solvent	Yield %	Ee %	Time	Con- ditions
Koh <i>et al.</i> [115]	Indenyl Ru complex	-	-	Secondary alcohols	Secondary Acetates	KOH	CH ₂ Cl ₂	0	0	20 mins	25°C
Koh <i>et al.</i> [116]	Indenyl Ru complex	Trimethyl- amine	PCL	Secondary alcohols	Secondary Acetates	4 chloro- phenyl acetate, oxidant	CH ₂ Cl ₂	60- 98	82- 99	43 hrs.	60°C
Lee <i>et al.</i> [117]	Ruthenium cymene complexes	Trimethyl- amine	PCL	Allylic alcohols	Allylic acetates	4 chloro- phenyl acetate	CH ₂ Cl ₂	94- >99	95- >99	48 hrs.	Argon, 20- 25°C
Pàmies <i>et al.</i> [118]	Dimeric Ru complexes	-	PCL, lipase PS-C	δ-hydroxy esters	Acetates	4 chloro- phenyl acetate, H ₂ donor	Toluene	52- 92	95- 99	24- 92 hrs.	60- 70°C

Author [Ref.]	Catalyst	Co- catalyst	Enzyme	Substrate	Product	Other reactants	Solvent	Yield %	Ee %	Time	Conditions
Pàmies <i>et al.</i> [119]	Dimeric Ru complexes	-	Novozym 435	Amines	Acetamide Amines	Ethyl acetate Hydrogen donor: 2,4- dimethyl-3- pentanal,	Toluene	11-100	92-> 99	1- 48 hrs.	2 steps: 40°C for enzymatic KR, 110°C for racemisation.
Persson <i>et al.</i> [89]	Dimeric Ru complexes	-	Novozym 435	Secondary alcohols	Secondary Acetates	4 chloro- phenyl acetate	Toluene	>99	>99	46 hrs.	Argon, 70°C
Persson <i>et al.</i> [89]	(PPh ₃) ₃ RuCl ₂	-	Novozym 435	Secondary alcohols	Secondary Acetates	Various acyl donor, Aceto- phenone	t-BuOH	100	>99	87 hrs.	Argon, 70°C
Persson <i>et al.</i> [89]	Dimeric Ru complexes	NaOH	Novozym 435	Secondary alcohols	Secondary Acetates	Various acyl donor, Aceto- phenone	t-BuOH	Very low	Very low	4 hrs.	Argon, 70°C

Author [Ref.]	Catalyst	Co- catalyst	Enzyme	Substrate	Product	Other reactants	Solvent	Yield %	Ee %	Time	Conditions
Reetz <i>et al.</i> [120]	Pd on carbon	-	Novozym 435	Amines Phenethyl- amine	Acetamide N-acylated	Ethyl acetate	Triethyl amines	75-77	99	8 days	Argon, 50-55°C
Runmo <i>et al.</i> [121]	Dimeric Ru complexes	-	PCL, lipase PS-C	γ - hydroxy esters	Acetates	4 chloro- phenyl acetate, H ₂ / 2,4dimethyl -3-pentanol as H donor	Toluene	43-93	94- 98	72 hrs.	H ₂ , 60-70°C

Where

Dimeric ruthenium complex: $[\text{Ru}_2(\text{CO})_2(\mu\text{-H})(\text{C}_4\text{Ph}_4\text{COHOCC}_4\text{Ph}_4)]$

Indenyl ruthenium complex: $[(\eta^5\text{-Indenyl})\text{RuCl}(\text{PPh}_3)_2]$

DKR of SECONDARY ALCOHOLS

The acylation of secondary alcohols is a popular reaction for study. Authors report variable results, demonstrating the difficulties involved in the process.

The Williams group was the first to employ TMC complexes as racemisation catalysts in a DKR process. *Pseudomonas fluorescens* lipase (PFL) coupled with a rhodium catalyst and vinyl acetate as the acyl donor was used for the DKR of secondary alcohols. A yield of only 76% with an ee of 80% was obtained [111].

More satisfactory results have been reported by the Bäckvall group [89]. The substrate secondary alcohols were racemised in the presence of the dimeric ruthenium complex catalyst, $[\text{Ru}_2(\text{CO})_4(\mu\text{-H})(\text{C}_6\text{H}_4\text{COHOCC}_6\text{H}_4)]$. This reaction was combined with an enzyme-catalysed transesterification by immobilised *Candida antarctica* lipase, Novozyme 435, at 70°C. Various acyl donors were tested, including 4-chlorophenyl acetate, vinyl acetate and isopropenyl acetate. The best results were obtained with 4-chlorophenyl acetate because it does not interfere with the ruthenium catalyst or form the by-products which may oxidise the substrate. A particularly good example reported is the DKR of 1-phenylethanol using 4-chlorophenyl acetate, which gave high a yield (100% conversion, 92% isolated yield) and an excellent optical purity (>99% ee). This reaction is shown in Figure 4.5. However, an obvious drawback of this procedure is the requirement for a ketone, acetophenone, as a hydrogen mediator, to minimise the oxidation of starting material, that is to suppress the side reaction.

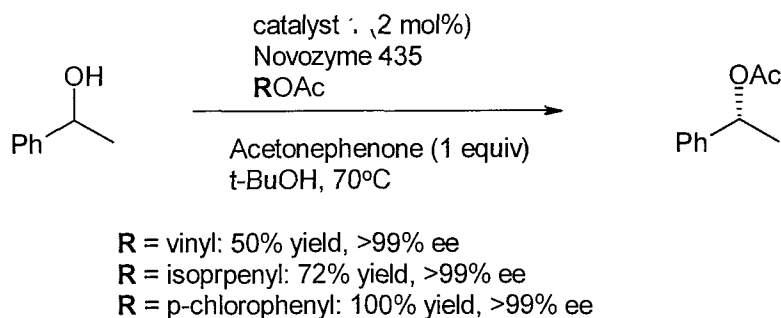


Figure 4.5: The DKR of 1-phenylethanol using a lipase and ruthenium catalyst.

The Park group has reported a highly efficient racemisation reaction using an indenyl-ruthenium complex catalyst, η^5 -IndenylRuCl(PPh₃)₂, in the presence of a strong base at room temperature [115]. However, the coupling of the catalytic racemisation with lipase-catalysed acetylation for the DKR was unsuccessful because the strong base caused chemical acetylation of the alcohol. An exception was found, still using the indenyl catalyst, that did not need a hydrogen mediator. Instead, a weak base, and a high reaction temperature were required. DKRs of various secondary alcohols were carried out at 60°C with an immobilised *Pseudomonas cepacia* lipase (PCL) [116].

The Park group has also reported the DKR of secondary alcohols using a novel aminocyclopentadienyl ruthenium chloride catalyst, which can racemise the substrate efficiently at room temperature without the aid of a hydrogen mediator. In addition, this new catalyst was compatible with the acyl donor isopropenyl acetate. The DKR of 1-phenylethanol using this system gave a yield of 97% and an optical purity of >99% ee [108]. They also found that (*p*-cymene)-ruthenium complexes catalysts can also be used for the DKR of secondary alcohol at room temperature, but with the presence of triethylamine and hydrogen mediators such as the ketone equivalent of the substrate alcohol [117]. DKRs of allylic alcohols can be carried out at room temperature with such systems. Other ruthenium catalysts were not suitable for these reactions, because allylic alcohols are prone to ruthenium-catalysed isomerisation at elevated temperatures resulting in the corresponding saturated ketones.

The Sheldon group [110] has reported the use of a catalyst system involving [TosN(CH₂)₂NH₂]RuCl(*p*-cymene), Novozym 435, and the base, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), for the racemisation of secondary alcohols. The DKR of 1-phenylethanol using this catalyst system gave 61% yield an optical purity of >99% ee which is much lower than those reported by the Park and Bäckvall groups.

As discussed earlier, the choice of solvent can be important in DKR. A wide range of solvents have been used in DKRs of secondary alcohols, including, toluene, hexane,

tetrahydrofuran, dichloromethane, 1-butanol and 1,4-dioxane. The choice of solvent may dictate the success of both the resolution and racemisation reaction.

Equally, the choice of acyl donor can dictate the success of the resolution. Much work has been done into identifying suitable acyl donors. Persson *et al.* [89] report problems with oxidation of the starting material when using alkenyl acetates, such as vinyl acetate and propenyl acetate. Activated esters such as trichloroethyl esters are also unsuitable due to the alcohol released interfering with the ruthenium catalyst. Aryl esters seem to be the only solution, as they are more reactive than alkyl esters. They also have the advantage that the reactivity can be tuned with electron withdrawing or donating substituents. Phenyl acetate is not found to be sufficiently active, but 4-chlorophenyl acetate, shown in Figure 4.6, is found to be an excellent acyl donor in many reactions [109, 114-116, 122].

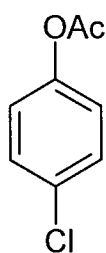


Figure 4.6: 4-chloro-phenyl acetate.

A deeper understanding of the process can be gained from studying the mechanism of the racemisation reactions in further detail. For example, for the DKR of secondary alcohols to form acetates, authors agree that the transformation proceeds through a base mediated hydrogen abstraction from a hydrogen donor, forming an intermediate alkoxy species as shown in Figure 4.7. Subsequent re-addition of the hydrogens to the ketone completes the catalytic cycle.

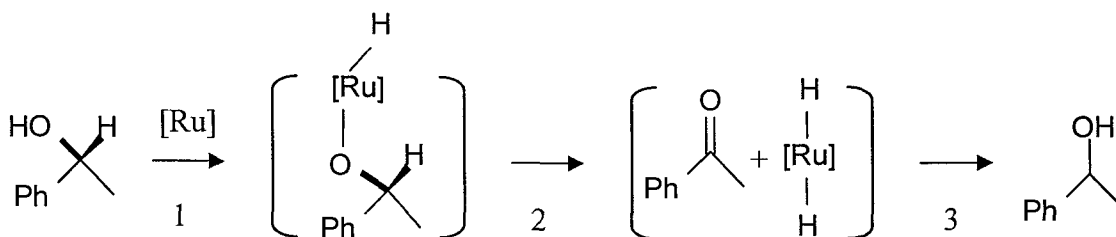


Figure 4.7: Mechanism for racemisation of 1-phenyl ethanol [89].

That is, the reaction proceeds via an oxidation of the alcohol to the ketone, and subsequent reduction to regenerate the racemic alcohol. This reaction, known as a hydrogen transfer mechanism, has been widely studied [123, 124], with TMC catalysts, and further DKR mechanistic details can be inferred from the mechanisms reported for this hydrogen transfer step.

In addition, there are various papers in the literature investigating transition metal catalysed racemisations, without a resolution step. Wuyts *et al.* [125] report the use of a ruthenium hydroxypatite catalyst for the racemisation of various secondary alcohols under mild conditions, with various degrees of success – ee's ranging from 6-100%. Ito *et al.* [124] report the use of a ternary catalyst system for the racemisation of various secondary alcohols, with good ee's of less than 1% in all cases. The catalyst system comprises a ruthenium complex, $\eta^5\text{-C}_5(\text{CH}_3)_5\text{-Ru}$ with phosphine amine ligands and a base such as KOt-Bu. Ratovelomanana-Vidal and Genêt [126] use a commercial chiral ruthenium (II) catalyst modified *in situ* to hydrogenate prochiral olefins and keto groups in various substrates such as itaconic acid. Good ee's are obtained in all cases. Other reports of racemisations are available which could be investigated for further ideas about how to perform the racemisation stage of a DKR process.

(iii) Enzyme catalysed

This method has the obvious advantage that the substrate racemising conditions are not detrimental to the enzyme performing the kinetic resolution [97]. A number of enzymes and related biocatalysts can effect racemisation. However, the scope of racemisation by racemases is limited, and mainly restricted to amino acid derivatives and α -hydroxy-carboxylic acids and their derivatives [94]. The common features of these substrates are that the chiral centre bears a proton and a carbonyl group or a related acidity enhancing substitute situated adjacent to the chiral centre. Recently, there has been significant development in a methodology for large scale production of a stable crude enzyme preparation of mandelate racemase from the *Pseudomonas putida* strain ATCC 12633 [127]. In this approach, the enzyme-catalysed *in situ* racemisation could be coupled with the traditional enzymatic resolution step in a two-enzyme DKR system. Another industrial example [128] is the production of D-*p*-hydroxyphenylglycine using D-hydantoin racemases isolated from *Arthrobacter aurescens* and D-N-carbamoylases for the resolution.

4.3.1.3 Photochemically induced racemisation

Circularly polarised light has been shown to effect chiral enrichment in the cyclisation of various stilbene derivatives to hexahelicenes [95, 96]. The method seems to be of very little value however, as the enantiomeric excesses obtained are very low, and it is applicable to only a small number of substrates.

4.3.2 Non enzyme mediated resolution

There are numerous chemical resolutions of chiral compounds. The combination of these with racemisation is difficult however [93]. Typically, chiral auxiliaries or chiral organometallic complexes are used to effect the desired resolution. The most successful

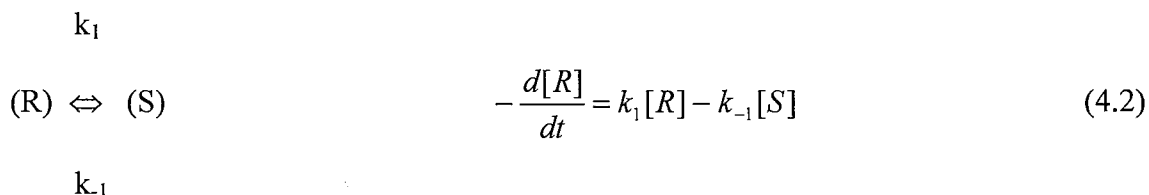
substrates for resolution by chiral metal catalysts usually contain a carbonyl function with an adjacent acidic C-H centre. Noyori *et al.* [129] established that the use of appropriate chiral diphosphanes, particularly BINAP compounds, and chiral diamines resulted in rapid asymmetric hydrogenation of a range of aromatic and heteroaromatic ketones with consistently high yields of 90-100% and ee's of up to 90-100%. The same group has also explored DKR coupled with transfer hydrogenation, which allowed them to widen their substrate range. By employing a diamino-type ruthenium(II) complex in a transfer hydrogenation process, benzil was selectively reduced to 100% enantiomerically pure hydrobenzoin [130]. Another example is the DKR which achieves asymmetric transfer hydrogenation of 1-aryl-substituted cyclic ketones reported by Alcock *et al.* [131]. A range of 1-aryl-2-tetranols and 1-phenyl-2-indanol were generated in high yields with high % ee values from the corresponding racemic ketones. The catalyst system used was Ru(II)(*p*-cymene)-TsDPEN in formic acid and triethylamine in a ratio of 5:2. (TsDPEN: N-tosyl-1,2-diphenylethylenediamine). This method benefits from practical simplicity and cost effectiveness due to low catalyst loading.

4.3.3 Crystallisation induced DKR

Selective crystallisation is a practical and efficient DKR [94]. The first reported examples (crystallisation of glucose) were reported by Dubrunfaut in 1846. Since then, many examples of auto-induced and seeded crystallisation have been reported. One example, is the DKR of narwedine, carried out by Shieh and Carlson with a yield of 84% [132].

4.4 MODELLING

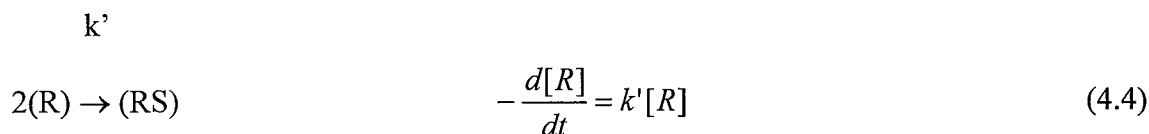
The driving force for racemisation is predominantly an increase in entropy caused by the mixing of the two enantiomers. The rate of racemisation [94], defined as the rate of interconversion of enantiomers, can be described by first order kinetics:



Initially, when one of the enantiomers dominates, $k_1 \neq k_2$, but the difference in a solution can be considered negligible, i.e. $k_1 = k_2 = k$. If the racemisation starts from a pure enantiomer, say R, with conditions $[R]_0 - [R]_t = [S]_t$, equation (4.2) is elaborated to:

$$\ln \left[\frac{[R]_0}{2[R]_t - [R]_0} \right] = 2kt \qquad (4.3)$$

Alternatively the rate of racemisation can be defined as the forming of a racemate (RS) from a pure enantiomer in an irreversible first order reaction:



with the condition, $[R]_0 - [R]_t = 2[RS]_t$, this becomes:

$$\ln \left[\frac{[R]_0}{[R]_0 - 2[RS]_t} \right] = 2k' t \qquad (4.5)$$

Another variable often used to describe racemisation is the racemisation half life. When calculated from equation (4.3), this is defined as:

$$t_{1/2} = \frac{\ln 2}{2k} \qquad (4.6)$$

And when calculated from equation (4.4), this is defined as:

$$t_{1/2} = \frac{\ln 2}{k'} \quad (4.7)$$

The enzyme resolution step may be modelled as a simple first order reaction, as in equation 4.2 or by using an enzyme kinetic model such as the Michaelis Menten model [133]. The reaction scheme for the enzyme reaction is shown in Figure 4.8, assuming the enzyme is active on the R enantiomer and proceeds via an enzyme-substrate complex, 'ER'.



Figure 4.8: Michaelis Menten enzyme reaction scheme.

The rate of formation of product, P, is:

$$\frac{d[P]}{dt} = \frac{V_{\max} [R]}{K_M + [R]} \quad (4.8)$$

Where K_M is the Michaelis constant and $V_{\max}$ is the maximum rate of reaction, both of which can be found experimentally by plotting a graph of the reciprocal of the reaction rate against $1/[R]$.

Racemisation kinetics can be combined with resolution kinetics to give an overall description of the whole DKR process. The kinetic parameters controlling the efficiency of DKR have been determined experimentally by Kitamura *et al.* using an oxoester – ruthenium BINAP system [134] and quantitatively analysed [135]. A schematic is shown in Figure 4.9. S denotes the substrates and P denotes the products. P_R is the prevailing product.

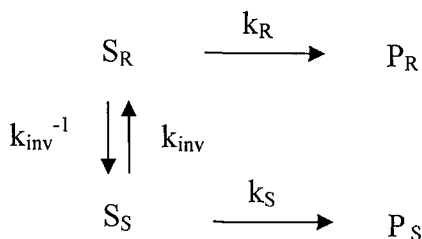


Figure 4.9: Schematic of model used by Kitamura *et al.*

The model assumes first order, reversible reactions, stable products, that is, $k_{inv} = k_{inv}^{-1}$ and $k_R > k_S$. Kinetic expressions for the rates of consumption of the substrates, along with expressions for the substrate quantities as a function of time are derived and integrated to give the quantity of each component at any time. These values can be computed to predict the enantiomeric excess and conversion, having derived the model parameters from experimental data.

4.5 CONCLUSIONS

This chapter demonstrates that there is a great variety of DKRs. All the examples are, however, subject to the limitation that the two catalytic systems (racemisation and resolution) must be compatible. The experimental results in the field are variable, which demonstrates that the DKR process has several problems associated with it. The following points outline the five major problems with DKR:

1. *Racemisation of product, which is clearly undesirable*
2. *Catalyst instability*

Certain ruthenium catalysts are so sensitive to oxygen that they are unstable in air. For example, chlorobis(triphenylphosphine) Ruthenium(II) is inherently unstable under atmospheric conditions due to the detachment of the triphenylphosphine ligands from

the ruthenium centre. In such a case the catalyst must be handled under oxygen free conditions.

3. *Resolution catalyst system incompatibility with enzyme due to requirement for strong base in TMC cycle* [89, 110, 122]

A particular problem [123] is the requirement of some, more simple, catalysts for a strong base to activate the catalytic cycle. For example, Persson *et al.* report that the use of $(PPh_3)_3RuCl_2$ in the DKR of 1-phenyl ethanol requires 10 mol % of sodium hydroxide. Authors overcome this problem by using more complex catalysts, shown in Figure 4.10 which are active without the presence of a base. Note that use of these catalysts may be limited due to lack of commercial availability and difficulty of synthesis.

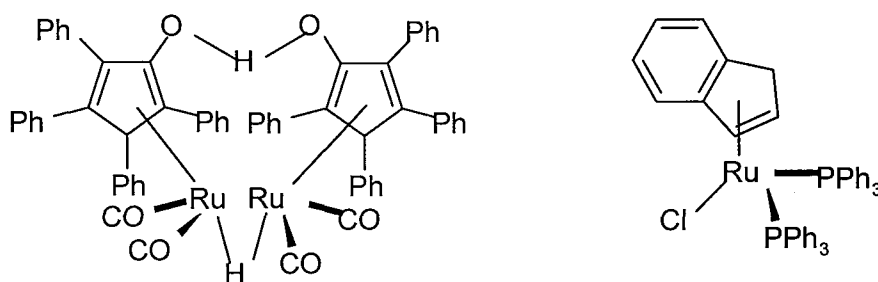


Figure 4.10: More complex ruthenium catalysts, not requiring base:

(a) used by Persson, Pàmies, Runmo [89, 118, 121]

(b) used by Koh [115, 116]

It is interesting to note that Stürmer [136] reports a high base tolerance for the enzyme, *pseudomonas fluorescens*, used in the DKR of secondary alcohols and acetates; up to 20 mol% at elevated temperatures.

4. *Lack of thermal stability of the enzyme* [109, 122]

5. *Oxidation of starting material* [89, 108, 122, 123]

The risk of undesired oxidation of the starting material is removed by shifting the equilibrium of the reversible reaction by adding the oxidation product to the reaction mixture, for example, Persson *et al.* [89] add 1 equivalent of the ketone, acetophenone, to the DKR of phenethyl ethanol, as shown in Figure 4.11.

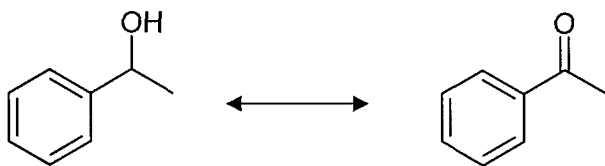


Figure 4.11: Reversible oxidation of phenethyl ethanol to acetophenone.

Likewise, Runmo *et al.* add a hydrogen source, such as molecular hydrogen, to re-hydrogenate the ketone back to the starting material, a γ -hydroxy acid derivative [121]. In all cases, the accidental oxidation of starting material is increased by increasing the reaction temperature; so there is a trade off between producing unwanted oxidation products and improving the racemisation rate.

There is such a vast array of resolution and racemisation systems that there is a variety of alternatives available for synthesis many of which will allow good stereocontrol, despite the problems outlined in the five points above. The use of an OSN membrane in the DKR system will help to combat the above problems.

CHAPTER 5

DYNAMIC KINETIC RESOLUTION: REACTION SYSTEMS

5.1 MEDKR CONCEPT

As discussed in Chapter 4, an extensive array of different DKR systems has been reported in the literature. Of these systems, enzymatic resolutions and chiral transition metal catalysts combined with bases are especially well studied and there are a variety of alternatives available for synthesis which should allow good stereocontrol. All such examples are, however, subject to the limitation that the two catalytic systems, the racemisation and the resolution, must be compatible in order for the convenience of a “one-pot” DKR process, rather than a two stage process, to be possible. In many cases, the strong base required in order to initiate the transition metal catalytic cycle may interfere with the enzyme, rendering the one-pot process unfeasible. This severely limits the scope of such DKRs to a small number of compatible catalysts.

Consequently, there is potential for the application of membranes in order to separate incompatible catalytic systems, thus increasing the scope of one-pot DKRs. The membrane should allow free permeation of products, substrates and any other reactants, whilst retaining the catalysts. The basic principle of this process, *Membrane Enhanced DKR*, or MEDKR is shown in Figure 5.1.

The concept of Membrane Enhanced DKR is novel in that it:

- (i) removes the need for the enantioselective and racemisation DKR catalysts to tolerate each other
- (ii) allows facile separation of enantiomerically enriched products from both the DKR catalysts

Thus the proposed concept could substantially increase both the scope and applicability of DKR processes.

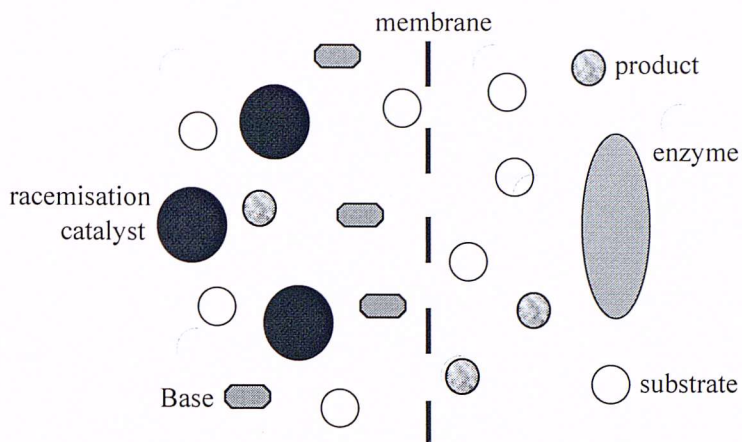


Figure 5.1: Principle of Membrane Enhanced DKR.

In Chapters 2 and 3, the fundamental properties and behaviour of organic solvent nanofiltrations were investigated. The second motivation of this study concerns the application of these organic solvent nanofiltration membranes to DKR in the Membrane Enhanced DKR (MEDKR) process. It has already been demonstrated in Chapter 2 that these membranes may be applied to the field of organic synthesis, allowing facile separation of products from unreacted substrate, catalyst and by-products. Hence, the possibility of their application to the synthesis of chirally pure compounds via MEDKR will be investigated. The aims of this section of work are as follows:

- I. To prove the feasibility of MEDKR
- II. To construct and commission membrane reactor systems in which two catalysts can act independently on the same substrate, and to optimise operation of these reactor systems.
- III. To show that such reactor systems can be used to generalise the scope of DKR.

The strategy to be used for achieving these aims is outlined below:

1. Examination of the enzyme resolution processes and transition metal racemisations already reviewed in Chapter 4.
2. Identification of suitable DKR systems for further investigation.

3. Experiments to gain understanding of the individual chemical reaction steps, resolution and racemisation, for the identified systems.
4. Testing of “one-pot” DKR reaction.
5. Identification of a suitable membrane to separate the two catalyst systems
6. Design, construction and commissioning of the MEDKR rig
7. Testing of the MEDKR of the identified systems.
8. Development of a mathematical model to describe the MEDKR process.
9. Extension of MEDKR to further DKR systems.

The rest of the thesis follows this progression towards realising the MEDKR concept. Chapter 5 addresses points 1 to 4, the identification and investigation of the individual DKR reactions. Chapter 6 addresses point 5, the membrane studies and Chapter 7 addresses MEDKR. Although the work is presented in these three distinct chapters, work on the individual DKR reactions, the membrane and MEDKR was carried out simultaneously.

5.2 IDENTIFICATION OF SUITABLE SYSTEMS

Following the literature review in Chapter 4, two potential reaction systems have been identified from the literature for further work. Details of the systems are given below along with schematics for the processes.

Transition metal catalyst - enzyme system for DKR of secondary alcohol [89]

The substrate secondary alcohol, 1-phenyl ethanol, will be converted to the secondary acetate, α -methylbenzylacetate (styrallyl acetate). A schematic of this process is shown in Figure 5.2. This is a commonly studied reaction in the literature and hence is a good starting point for this study, since there is considerable information available. The resolution system will consist of the lipase, novozyme 435 along with various acyl donors: vinyl acetate, isopropenyl acetate and 4-chloro phenyl acetate. The possibility of alternative enzymes will also be investigated. The racemisation will be effected by a ruthenium catalyst which may require the presence

of a base in order to initiate the catalytic cycle. Additional reactants may be required in order to suppress the side reaction which oxidises the substrate alcohol to the corresponding ketone, acetophenone. Such reactions have been performed in various solvents. The solvent used for this study will be toluene for both the racemisation and resolution steps since it has already been proven that the available OSN membranes have a good compatibility with this solvent.

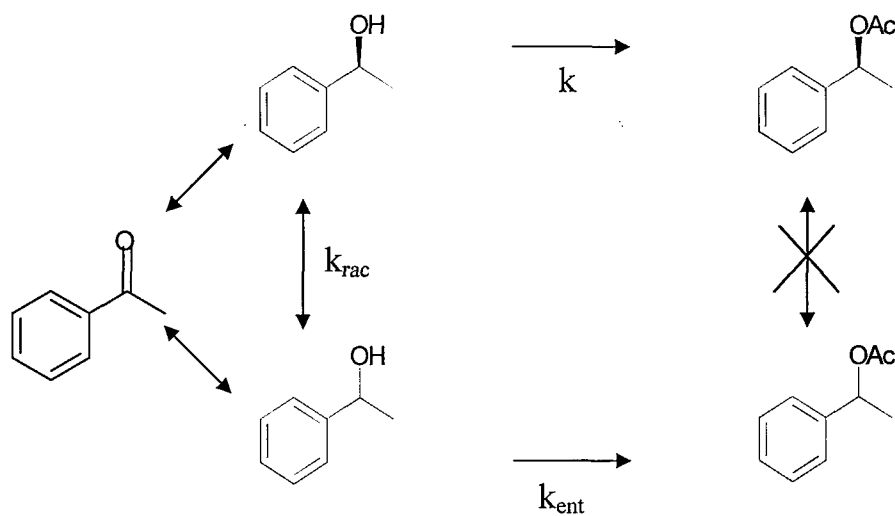


Figure 5.2: Schematic of DKR of 1-phenyl ethanol.

Transition metal catalyst - enzyme system for DKR of allylic alcohol [117]

The substrate allylic alcohol, 4-phenylbut-3-ene-2-ol will be converted to the secondary acetate, 4-phenylbut-3-ene-2-acetate. A schematic of this process is shown in Figure 5.3. Although this is a less commonly studied reaction than 1-phenyl ethanol, there is evidence that the racemisation is easier and less susceptible to unwanted oxidation and therefore may be an easier substrate for first attempts at MEDKR. The resolution system will be the same as for 1-phenyl ethanol, that is, novozyme 435 along with various acyl donors. Likewise, the racemisation will be effected by a ruthenium catalyst. Since 4-phenylbut-3-ene-2-ol should be less susceptible to oxidation, it is unlikely that side-reaction suppressing additive will be required. Again, the both reaction steps will be performed in toluene.

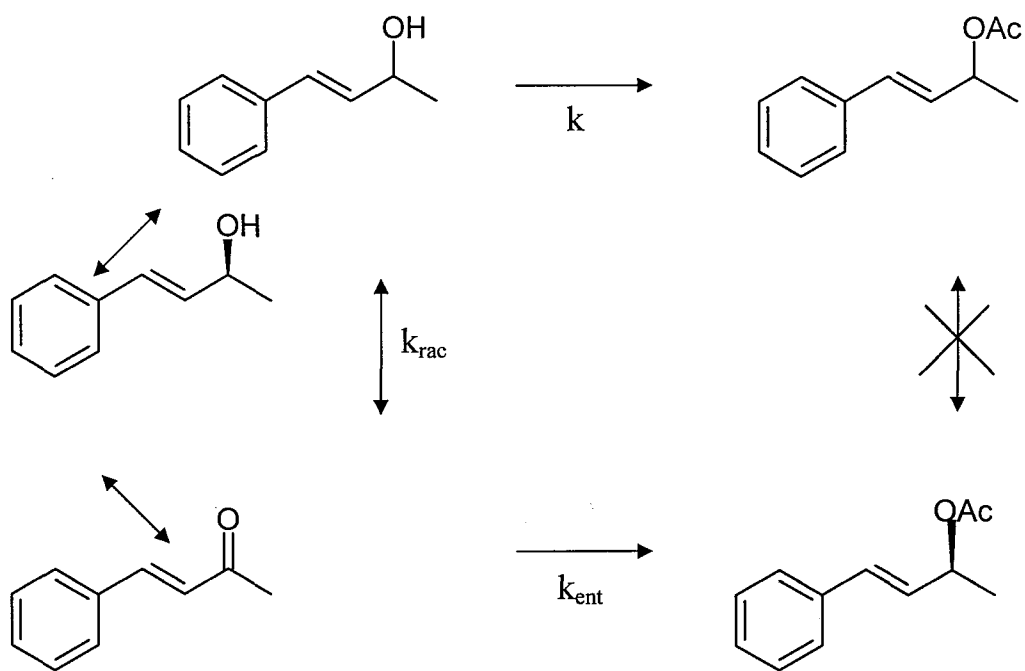


Figure 5.3: Schematic of DKR of 4-phenylbut-3-ene-2-ol.

Ruthenium catalysts

A variety of ruthenium catalysts will be investigated, all of which have been reported in the literature. Figure 5.4 gives details of the catalysts chosen.

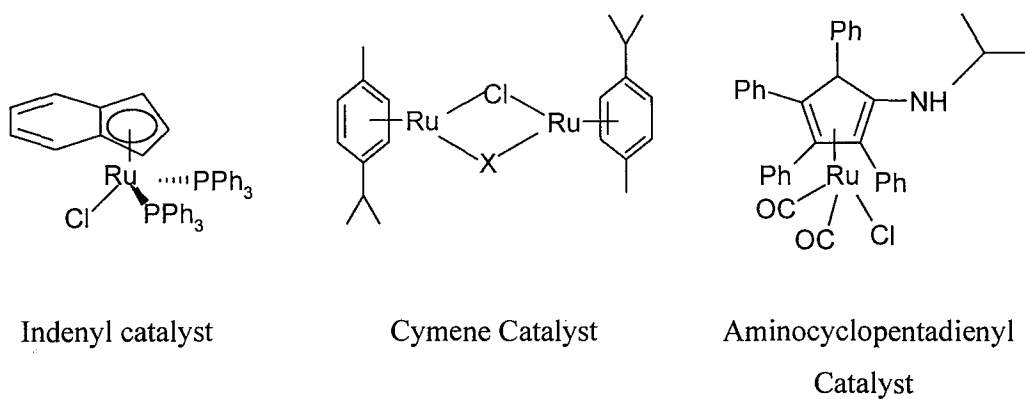


Figure 5.4: Ruthenium catalysts chosen for MEDKR studies, where $X=Cl$

Bases

The ruthenium catalysts require the presence of a base in order to initiate the catalytic cycle [89]. Two classes of bases will be investigated. The first class is strong phosphazene bases [137]. These are uncharged bases built on a nitrogen basic centre, double bonded to a pentavalent phosphorous. The two monomeric bases shown in Figure 5.5 will be used, P₁-t-Bu-tris(tetramethylene), abbreviated to P1 tris and P₁-t-oct, abbreviated to P1 oct. These bases have a basicity about 2-3 units beyond the basicity range of more commonly used organic bases such as DBU and DBN. The relative basicities of various common bases are shown in Figure 5.6. These bases have been chosen since they are very strong and should therefore racemise the substrates easily, and they have a high solubility in apolar solvents such as toluene, which is the intended solvent for this study. They also have the potential to enhance reaction rate [132] and due to their large molecular weights (312.4 for P1 tris and 290.43 for P1 oct), should be easily retained by the membranes. It should be noted that the base should not be *too* strong in order to avoid the problem of unwanted racemisation of the product.

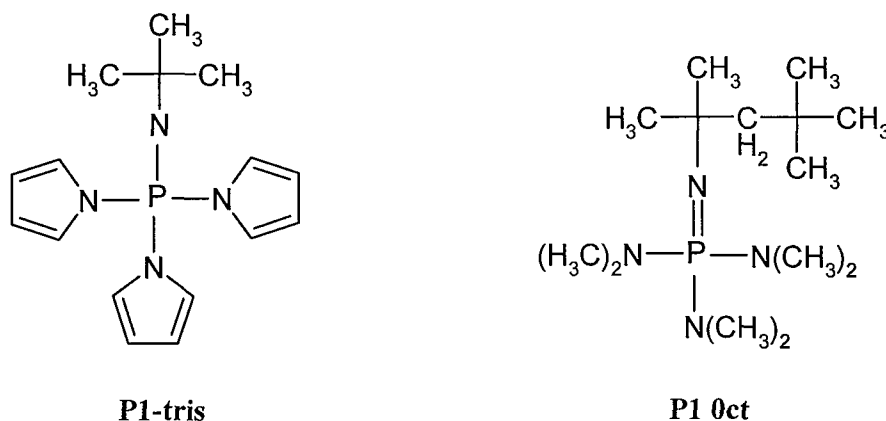


Figure 5.5: Phosphazene bases chosen for this study [137].

A variety of examples in the literature use triethyl amine to activate the TMC in DKR processes [110, 115-117]. Consequently, tertiary amine bases will also be employed. A range of these bases exists, allowing the molecular size to be chosen to suit the needs of the experiment. The bases used are: triethyl amine (TEA), trihexyl amine (ThexA), triheptyl amine (TheptA), trioctyl amine (TOA) and tridodecyl

amine (TDDA). The position of triethyl amine (Et_3N , on the Figure) is shown on the basicity scale in Figure 5.6. As the figure shows, triethyl amine is considerably less basic than the phosphazene bases. The other amine bases have a similar basicity to triethyl amine

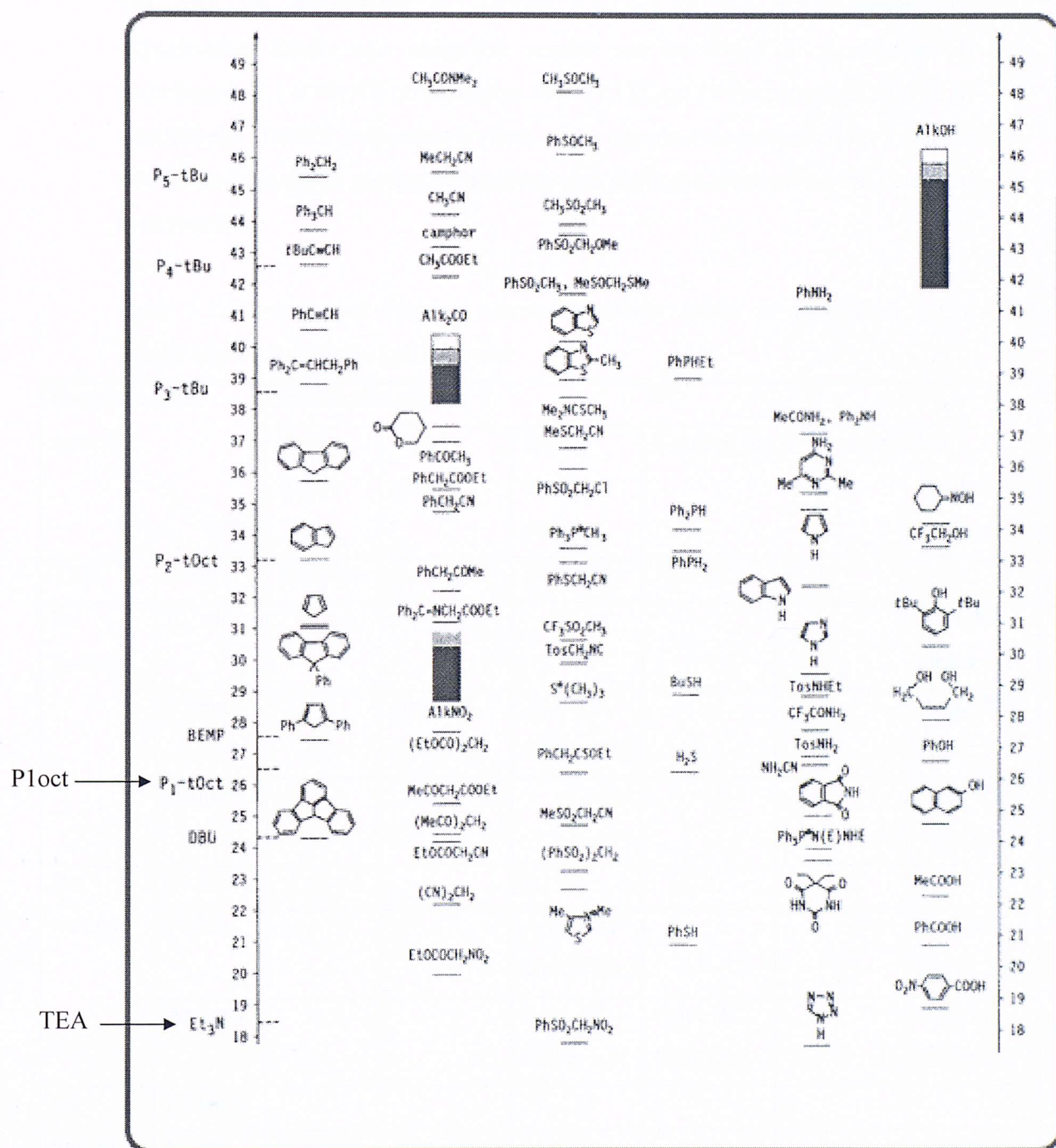


Figure 5.6: Basicity scale [137].

5.3 MEDKR INDIVIDUAL REACTIONS

As discussed in section 5.1, the individual enzyme resolutions and transition metal racemisations will be examined and then the “one-pot” DKR reaction will be tested. The data are summarised in sections 5.3.1, 5.3.2 and 5.3.3 respectively. Experimental details and numerical results can be found in Appendices II (experiments 1.1-9.14), III (experiments 10.1-21.11) and IV (experiments 22.1-25.6) respectively. Table 5.1 shows overviews of the experiments performed for 1-phenyl ethanol and for allylic alcohol respectively and show the locations of the details of each reaction.

Table 5.1: Overview of 1-phenyl ethanol reactions: tables in appendices where details of the experiments can be found.

Racemisation system		Resolution system					
		Acyl donor	Vinyl acetate	Iso-propenyl acetate	4 chloro phenyl acetate		No resolution catalysts
TMC	Base	Enzyme	Nov 435	Nov 435	Nov 435	PCL	
Ru cymene	PI tris						App. III, tables 1,2
	PI oct		App. IV, tables 1,2	App. IV, tables 1,2			App. III, tables 3-5
	Amines						App. III, table 6
Ru indenyl	PI tris						
	PI oct			App. IV, tables 1,2			App. III, tables 7,8
	Amines			App. IV, tables 1,2	App. IV, tables 1,2		App. III, tables 7,8
Ru amino cpd	PI tris						
	PI oct		App. IV, tables 1,2				App. III, table 9
	Amines						

No racemisation catalysts		App. II, tables 3-6	App. II, tables 7-10	App. II, Tables 1,2	App. II, tables 3-6	
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Table 5.2: Overview of allylic alcohol reactions: tables in appendices where details of the experiments can be found.

Racemisation system		Resolution system		
		Acyl donor	Vinyl acetate	No resolution catalysts
TMC	Base	Enzyme	Nov 435	
Ru cymene	PI oct		App. IV, tables 3,4	App. III, tables 11,12
	Amines		App. IV, tables 5,6	App. III, table 13
No racemisation catalysts			App. IV, tables 12,13	

5.3.1 Enzyme resolution

5.3.1.1 1-phenyl ethanol: analytical methods

Concentrations of all the solutes were determined using a Perkin-Elmer Gas Chromatograph with a flame ionisation detector and a Megabore column 25m long and with 0.23mm i.d. with BP1 (SGE, Australia) as the stationary phase. The temperature programme ran from 80°C to 300°C at a rate of 25°C / min. The coefficient of variation was 5% for 3 independent measurements. Enantiomeric excesses were measured using a Chiralcel OD-H HPLC column from Daicel, consisting of a cellulose tris(3,5-dimethylphenylcarbamate) / macroporous silica gel stationary phase. The mobile phase was 95:5 hexane:IPA at a flow rate of 500µL/min. The species were detected by UV at 254nm and the analysis time was 20 minutes.

5.3.1.2 1-phenyl ethanol: results

Biotransformations of 1-phenyl ethanol were performed with novozyme 435, in toluene with different concentrations of various acyl donors: 4 chlorophenyl acetate (4 CPA), isopropenyl acetate (IPPA) and vinyl acetate (VA). Details of the experiments and numerical results are given in Appendix II. Reactant concentrations were chosen according to literature methods [88]. All reactants were used as supplied by Aldrich chemical co., Dorset, U.K. Catalysts were used as supplied by Strem Chemicals, Rouston, U.K. The reactions were performed in a Radleys reaction carousel, as shown in Figure 5.7. This apparatus, from Radleys Discovery Technologies, Essex, U.K., allows multiple reactions to be performed simultaneously under closely controlled conditions. The substrate and acyl donor were added to the solvent in the carousel vessel. All reactions throughout this chapter were performed in 25mL of toluene. The mixture was stirred at the reaction temperature in the carousel and the enzyme added at $t = 0$. All reactions were well stirred to ensure adequate contact between the substrate and enzyme active site.

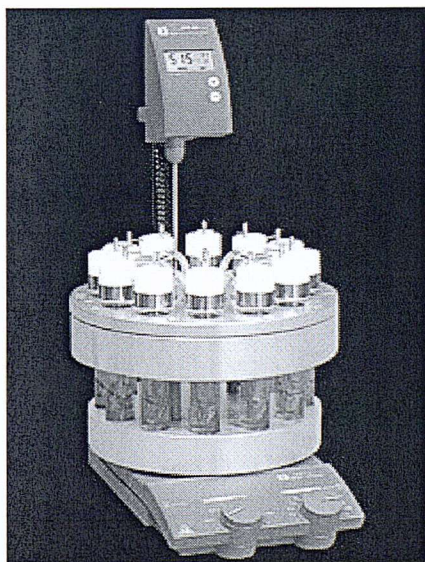


Figure 5.7: Radleys Reaction Carousel.

Results are reported in terms of yield of product acetate, yield of ketone, ee of product acetate and ee of remaining alcohol. The yields are calculated using equations (5.1) and (5.2). The ee's are calculated according to equation (4.1).

$$\text{product yield} = \frac{\text{moles product formed}}{\text{moles substrate}} \times 100\% \quad (5.1)$$

$$\text{ketone yield} = \frac{\text{moles ketone formed}}{\text{moles substrate}} \times 100\% \quad (5.2)$$

Acyl donor: 4 Chlorophenyl acetate

Biotransformations were performed using varying numbers of equivalents of 4 CPA as the acyl donor and at variable temperatures. The results are variable, with the conversion ranging between ~ 20% and ~70%. The best results are obtained at 40°C with 20mM 1-phenyl ethanol and 3 equivalents of 4 CPA and 0.03g of novozyme 435. For the ee data, if the reaction is working correctly, the enzyme should convert all the R alcohol to R acetate leaving 100% S alcohol behind. It was not possible to measure the ee in all the experiments. The measured values range from 30% to 80% indicating a poor purity of the remaining alcohol, and showing that the biotransformation has not been successful.

The progress of some of the biotransformations was monitored over time. This allowed graphical comparisons of the different experiments. Figure 5.8 shows the effect of varying the number of equivalents of acyl donor in the reaction, using 49mM substrate at room temperature. This data indicates that the optimum results for phenyl ethanol at 49mM with 4 CPA are obtained with an equimolar mixture of substrate alcohol and acyl donor. For the other results, 0.5, 5 and 10 equivalents of 4 CPA, higher yields are obtained for higher numbers of equivalents.

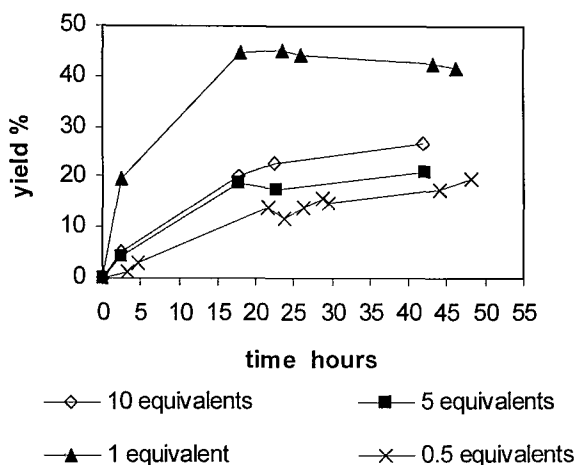


Figure 5.8: Effect of varying equivalents of 4 CPA in biotransformation of 49mM 1-phenyl ethanol with 0.03g novozyme 435 at room temperature.

The effect of temperature was also investigated. Enzymatic reactions, like chemical reactions, will normally show an increase in rate at higher temperatures, but care must be taken not to exceed the maximum temperature limit for the enzyme in question, beyond which it will denature and lose its catalytic activity. Figure 5.9 shows the effect of temperature on the biotransformation of 49mM 1-phenyl ethanol with 0.5 equivalents of 4 CPA and 0.03g novozyme 435. The graph shows that the end result seems to be unaffected by the temperature – the end product yields are very close. However, the rate at which this end yield is attained is faster at the higher temperature. From this, it can be concluded that higher temperature improves the rate but not the extent of the biotransformation reaction.

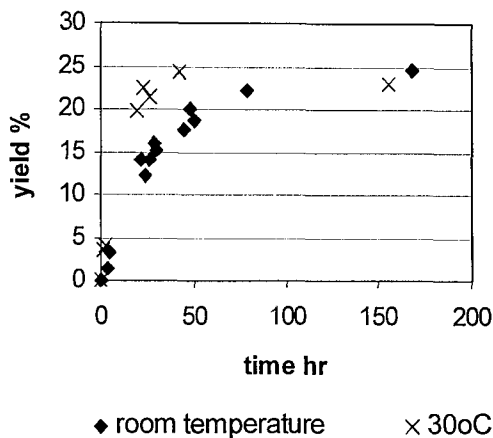


Figure 5.9: Effect of temperature on the biotransformation of 49mM 1-phenyl ethanol with 0.5 equivalents of 4 CPA.

Acyl donor: vinyl acetate

Experiments were performed using 20mM 1-phenyl ethanol, varying numbers of equivalents of vinyl acetate as the acyl donor and 0.03g novozyme 435, at various temperatures. High yields of product (>50%), no conversion to ketone and 100% ee of the remaining alcohol were obtained for 1 and 1.5 equivalents of VA. Poor results were obtained with 0.5 equivalents of VA – a low yield (<15%) and an unexpectedly high ketone yield of around 40%. The product yield improves as the number of equivalents of VA is increased, with the best results, 61% yield, being obtained with 1.5 equivalents.

It is important for this study to prove that the individual steps of the DKR process work well independently. But it is also crucial that, when the two steps, the biotransformation and racemisation are combined, that they do not interfere with each other. Hence biotransformations have been performed ‘spiked’ with doses of reagents used in the racemisation system, that is, with the ruthenium catalyst and the base (either a phosphazene base or an amine base) required to activate the catalytic cycle of the ruthenium catalyst. The effect of the base will be particularly interesting since it is known that enzymes work in a limited pH range. Of course, the whole point of the MEDKR process is that the membrane prevents contact between

elements of the two catalytic systems. However, it may not be possible to obtain a perfect separation with the membrane, so there may be some 'leakage' of components of either system across the membrane.

Standard biotransformations of 1-phenyl ethanol with VA were spiked with 20 mol % Ru cymene and 8 mol% P1 tris. The 'spiked' reactions were compared with an equivalent 'unspiked' benchmark experiment with a conversion of 52.4% and no conversion to ketone. It is clear that the presence of both the ruthenium catalyst and the phosphazene base affect the biotransformation. Lower product yields are achieved with both spikes, an average of 20.0% with the ruthenium and an average of 8.4% with the phosphazene base. The enzyme is denatured by the basicity of the P1 tris, although why the ruthenium catalyst should affect the enzyme is not clear and further research is required to investigate this. Interestingly, the spikes cause more ketone to be formed in the reaction which may be a disadvantage of the combined system.

Acyl donor: isopropenyl acetate

Biotransformations were performed using 33.5mM 1-phenyl ethanol, 1.4 equivalents of isopropenyl acetate (IPPA) as the acyl donor and 0.03g of novozyme 435. Reactant ratios were adapted from the literature. High product yields are obtained in all the experiments, ranging from 47% to 87%. The average product yield for this run of experiments is 70.0%. These results suggest that after the enzyme has turned over the R isomer, it then continues to metabolise the S isomer. Unfortunately, no ee data is available for the acetate product to confirm this. The ee data available for the remaining alcohol is variable and is both contrary to expectations and hard to interpret. The effect of 'spikes' of species from the racemisation systems on this biotransformation was investigated using 4 mol% Ru cymene, 22.4 mol% P1oct, and 3 equivalents of TEA and TOA. Additionally, spikes of the reaction products, 1-phenyl acetate and acetone (the reaction product of the acyl donor, IPPA), at 1 equivalent were also investigated to test whether novozyme 435 is susceptible to product inhibition in this system.

Figure 5.10 shows a graphical summary of the averaged results of the ‘spiked’ experiments. Clearly, all the spikes affect the overall product yield at the end of the resolution reaction negatively; all the spiked experiments show a lower yield than the equivalent, unspiked benchmark experiment. The biggest negative effect is found in the case of TOA. It is expected that TOA will impede the enzyme more than TEA, since it is a stronger base. However, P1 oct, which is significantly stronger base than any of the amine base series, shows the lowest decrease in yield of any of these spiked experiments. Although the differences in product yield between the different spikes is difficult to explain, and of dubious statistical significance, the conclusion is clear: the enzyme in this system is unable to tolerate a basic pH and the resolution reaction suffers from product inhibition.

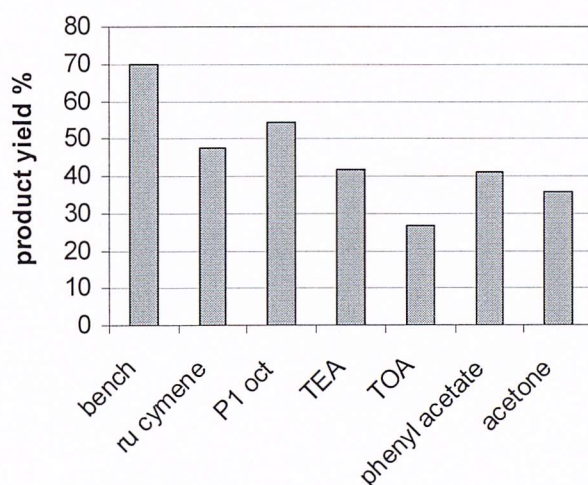


Figure 5.10: The effect of ‘spikes’ of species from the racemisation catalyst system and product species on the resolution of 33.5mM 1-phenyl ethanol with 1.4 equivalents of IPPA, by novozyme 435, in toluene at 25°C.

There is also a possibility of using different enzymes to perform the biotransformation stage of the MEDKR. From the literature, pseudomonas cepacia lipase (PCL) seems to be another potential enzyme for this acylation reaction [108, 116]. Reactions were performed with 49mM 1-phenyl ethanol with 1 equivalent of 4 CPA, and 0.04g of PCL in 40mL of toluene and room temperature. The benchmark,

unspiked run, gives a good yield of over 50% with no conversion to ketone indicating that it is a possibility in this system. The experiments were also performed with spikes of the amine bases (TEA, TOA and TDDA), all at 3 equivalents and with 2 mol% ruthenium indenyl. The results are shown in Figure 5.11. The spikes all affect the product yield negatively, reducing the yield by about 20% compared with the benchmark, except for the case of TEA where there is a negligible effect.

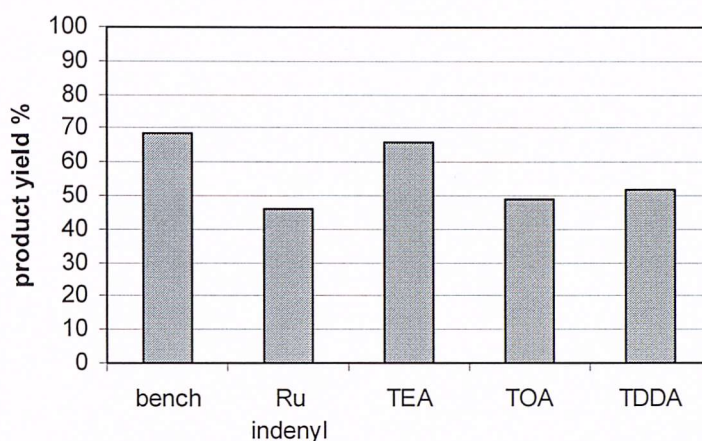


Figure 5.11: The effect of 'spikes' of species from the racemisation catalyst system on the resolution of 49mM 1- phenyl ethanol with 1 equivalent of 4 CPA, by PCL, in toluene at room temperature.

5.3.1.3 Allylic alcohol: analytical methods

Solute concentrations were measured by gas chromatography using an Agilent 6850 series GC system. A capillary column ATTM-5 from Alltech was used, with length 30m, ID 0.53mm and a 0.25µm film thickness. The Temperature programme began at 100°C, rising at 10°C/min to 140°C, then at 5°C/min to 200°C, and then at 20°C/min to 250°C. The final temperature was held for 5 minutes to ensure all the material had passed out of the column. Enantiomeric excesses were measured using a Chiralcel OJ HPLC column from Daicel, consisting of a cellulose tris(4-methylbenzoate) stationary phase. The mobile phase was 97.5:2.5 hexane:IPA at a flow rate of 500µL/min. The species were detected by UV at 254nm and the analysis time was 45 minutes.

5.3.1.4 Allylic alcohol: results

Several biotransformations were performed using 40mM AA, 1.5 equivalents of VA and 0.03g of novozyme 435 in 25mL of toluene and at 25°C. The reactions were performed in the Radleys reaction carousel shown in Figure 5.7 and the experimental procedure followed was as for the 1-phenyl ethanol reactions. Details of the reactions and numerical results are given in Appendix II. The results are promising: product yields of over 50% are obtained in most cases with low conversion to ketone (<10 %) and quite high enantiomeric excesses of both the product acetate and remaining unreacted alcohol. The average product yield for these experiments was 52.0%. As discussed in chapter 4, the ruthenium catalyst in the MEDKR system is likely to be sensitive to oxygen and the reaction may need to be performed in air free conditions. The biotransformation part of MEDKR is unlikely to be affected by the atmosphere in which the reaction is performed, but the effect of a different atmosphere will be investigated. AA resolutions were performed with exactly the same experimental set-up as the above experiments, but in the presence of a nitrogen atmosphere, that is, with no oxygen present. The reactions were continued for 24 hours and attained yields of 68.6 and 62.1%, with no conversion to ketone. The acetates were formed with ee's of 85.6 and 91.7% and the remaining alcohol had ee's of 98.4 and 99.7%. Again, this is very promising and indicates that the resolution is not negatively affected by a change of atmosphere, if anything, the nitrogen atmosphere produces better results.

The effect of 'spikes' of species from the racemisation systems on this biotransformation was investigated as for 1-phenyl ethanol. The phosphazene base, P1 oct (at 22.4 mol%), amine bases (at 1 equivalent) and Ru cymene catalyst (at 4 mol%) were tested, as well as spikes of the product of the reaction, that is allylic acetate (at 1 equivalent), to test whether novozyme 435 is susceptible to product inhibition in this system. As for the benchmark, unspiked experiments, all the tests were performed with 40mM AA, 1.5 equivalents of VA and 0.03g of novozyme 435 in 25mL of toluene, at 25°C and under atmospheric conditions since it was shown earlier that there is little effect of change of atmosphere.

There is a large spread of results and since great trouble was had in obtaining experimental repeatability, the differences between experiments may not be statistically significant. Figure 5.12 shows a graphical summary of the averaged results of the 'spiked' experiments. Only the Ru cymene, P1 oct and acetone spikes have a noticeable effect on the product yield. The product yield for the allylic acetate and amine base spikes is around 50%, the same as the benchmark experiments. The data for the ee of the remaining alcohol is difficult to interpret. The P1 oct has an extreme negative impact on the ee of the product acetate formed, reducing it to around 50%. All the amine bases have a negative impact on the ee of the product acetate formed, compared with the benchmark experiments, but to varying extents. The amine bases also affect the ee of the remaining S alcohol. It should be noticed that all the amine base runs achieve a product yield of approximately 50%, so the expected ee's at the end of the reactions are 100% R acetate and 100% S alcohol. Figures 5.13 and 5.14 show the effect of the amine bases on the end acetate and alcohol ee's.

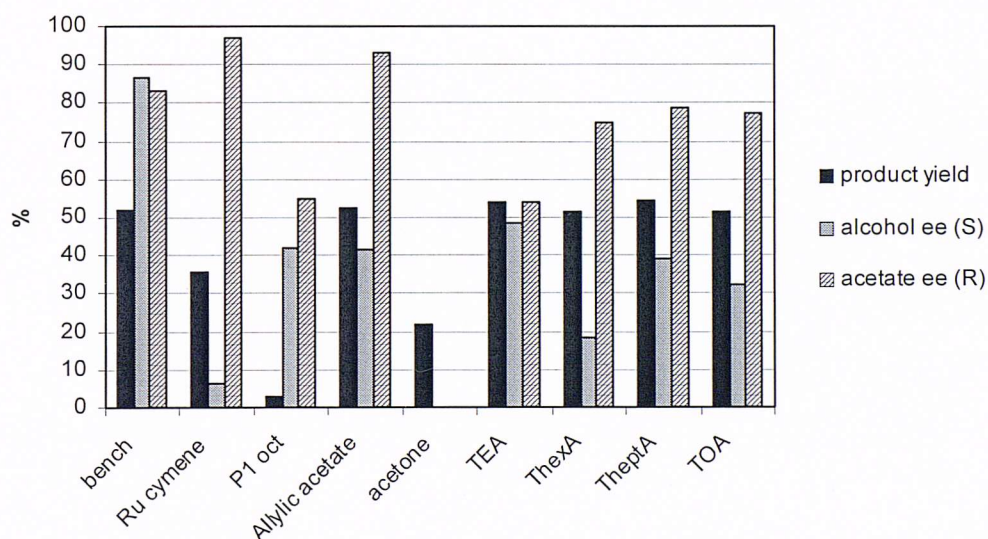


Figure 5.12: The effect of 'spikes' of species from the racemisation catalyst system and product species on the resolution of 40mM allylic alcohol with 1.5 equivalents of VA, by novozyme 435, in toluene at 25°C, under atmospheric conditions.

The best product ee's are obtained with the larger amine bases. Contrary to this is the result for the remaining alcohol: the best ee is obtained with TEA. Of course, if a good separation between the racemisation and resolution systems is to be obtained,

TEA cannot be used as the base in the racemisation system, due to its small size preventing it from being retained by the OSN membranes available. The results indicate that the chemical behaviour of the hexyl, heptyl and octyl amine bases is very similar. Therefore, the decision of which base to use should be made based on the rejection test results. The best rejection results, as will be shown in Chapter 6, were obtained for trihexyl amine. Therefore, this base will be used in all further amine base experiments.

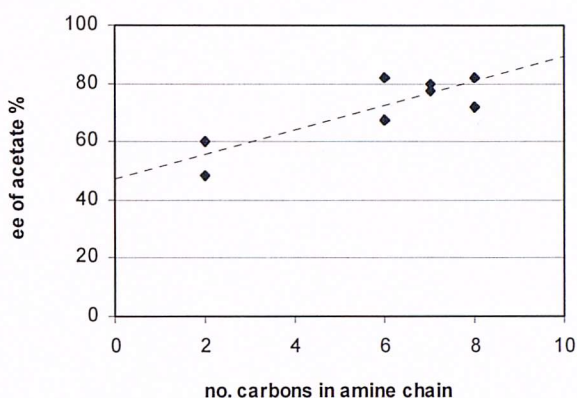


Figure 5.13: Effect on ee of product acetate of amine base 'spikes' in the resolution of 40mM allylic alcohol with 1.5 equivalents of VA, by novozyme 435, in toluene at 25°C. ee's measured at the end of the 24 hour reaction, under atmospheric conditions.

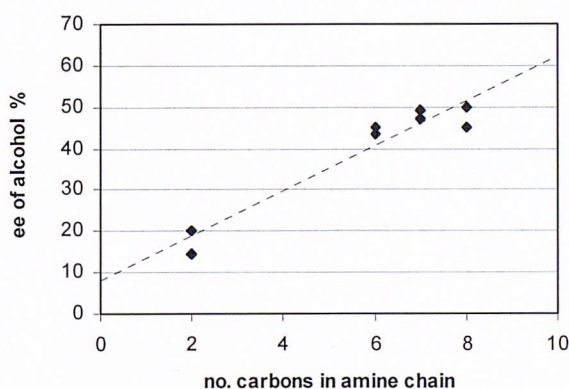


Figure 5.14: Effect on ee of remaining unreacted alcohol of amine base 'spikes' in the resolution of 40mM allylic alcohol with 1.5 equivalents of VA, by novozyme 435, in toluene at 25°C. ee's measured at the end of the 24 hour reaction, under atmospheric conditions.

Allylic alcohol resolutions spiked with Ru cymene and P1 oct were performed with exactly the same experimental set-up as the above experiments, but in the presence of a nitrogen atmosphere, that is, with no oxygen present. The reactions were continued for 24 hours. The 4mol% Ru cymene spiked run produced 60.7% of the product acetate with an ee of 96.1%, leaving alcohol with an ee of 96.0%. This is a more reasonable result than for the equivalent runs under atmospheric conditions (experiments 8.1-8.4) where a large spread of product yields and ee's of remaining alcohols was found. The two P1oct runs produced 10.5 and 7.4% product acetate with ee's of 97.1 and 87.0%, leaving alcohol with ee's of 9.3 and 5.5%. These are slightly higher yields than in the equivalent run under atmospheric conditions (experiments 8.6 and 8.7) suggesting that the presence of oxygen does have an effect in this system.

It is also important to check whether the enzyme catalyses the back reaction, that is conversion of the product acetate back into the alcohol. This will answer the important question of whether the acetate formed will remain as acetate in the system. All experiments were performed with 40mM R allylic acetate, 1.5 equivalents of VA and 0.03g of novozyme 435 in 25mL of toluene and at 25°C. The results indicate that the enzyme is unable to metabolise the allylic acetate and therefore no back reaction is catalysed. No ketone was generated in any of these experiments and the ee of the allylic acetate remains high. This proves that any acetate formed in the MEDKR process will remain as acetate and will not be degraded by or react with any of the other components of the MEDKR system.

5.3.2 Racemisation

5.3.2.1 1-phenyl ethanol

Racemisations of 1-phenyl ethanol were performed in toluene with different concentrations of ruthenium catalysts, ruthenium cymene, indenyl and aminocyclopentadienyl (Figure 5.4). The reactions were performed in the Radleys reactions carousel. The transition metal catalyst and base were dissolved in the solvent, toluene, at the reaction temperature first in order to ensure that the active

catalyst had been formed. The substrate was then added at $t = 0$. All reactions were well stirred to ensure adequate contact between the substrate and catalysts. Two classes of bases were used, at different concentrations, to activate the ruthenium catalytic cycle: phosphazene bases, P1 oct and P1 tris, and a range of trialkyl amine bases. Analyses were performed as detailed in Section 5.3.1.1. Details of the experiments and numerical results are given in Appendix III.

Several racemisations of 33.5mM 1-phenyl ethanol were performed with various concentrations of ruthenium cymene (4, 8 12 and 16 mol%) and 20 or 40 mol% P1 tris at 25°C. These experiments aimed to test the effect of the concentration of both the ruthenium catalyst and the phosphazene base. All reactions were performed at room temperature. The results are summarised in Figure 5.15. The benchmark experiments have been performed on the S enantiomer. This is because it has been shown that the enzyme, novozyme 435, is active on the R isomer of 1-phenyl ethanol [140]. Hence, in a MEDKR system, following a successful biotransformation of the R isomer, the S isomer will be left unreacted, as the substrate for the racemisation reaction.

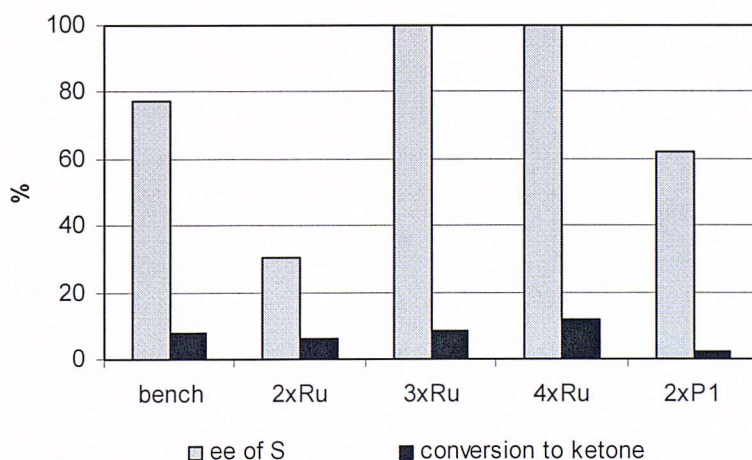


Figure 5.15: Summary of average results for racemisations of 1-phenyl ethanol with ruthenium cymene and P1 tris.

The benchmark experiments had an average ee of 77.7% S isomer with a standard deviation of 23.1: there is a lot of scatter in the data. The aim of the racemisation is to generate the racemic mixture (ee = 0%) from the individual isomer (ee = 100%). These racemisations have not worked successfully. A possible reason for this is the fact that the reactions were performed at room temperature and under air. Elevated temperature might allow the activation energy of the reaction to be exceeded more easily, thus producing a better result. The presence of oxygen has been shown to oxidise ruthenium catalysts of this sort causing them to lose their catalytic activity. Doubling the ruthenium concentration produces a much better ee of around 30%, but no racemisation occurred at all with three and four times the benchmark ruthenium concentration. Doubling the concentration of the P1 tris base produces a slightly better racemisation. The conversion to ketone in all the reactions is low, less than ~10%, as required. Experiments were also performed using the R enantiomer rather than the S enantiomer as the substrate to check whether the catalysts are capable of racemising both enantiomers equally. These experiments began with an ee of the S enantiomer of -100% (that is 100% R enantiomer). The final ee measured is around 85% S, suggesting that it has gone from being 100% R enantiomer, through the racemic mixture though to being largely S enantiomer. This indicates that there are analytical problems with these analyses and so the results should probably be neglected.

Given that the combination of ruthenium cymene and P1 tris has not produced good results, different ruthenium TMC and base combinations will be tested. Experiments were performed with 33.5mM 1-phenyl ethanol runs with ruthenium cymene and Ploct. The benchmark experiments contained 4 mol% Ru cymene and 30 mol% Ploct. Better temperature control was used than with the cymene / P1 tris runs in order to establish more accurately the effect of temperature and the reactions were performed under different gases (atmospheric atmosphere, argon and nitrogen) in order to establish the effect of the atmosphere under which the reaction takes place. As before, the effect of doubling the concentrations of the catalysts was measured. It might be possible that the concentration of the substrate has an effect on the reaction due to steric factors as a result of how the substrate and catalysts interact before they react. In order to test this, runs with higher (ten times) the benchmark substrate concentration were performed. The results are summarised in Figure 5.16.

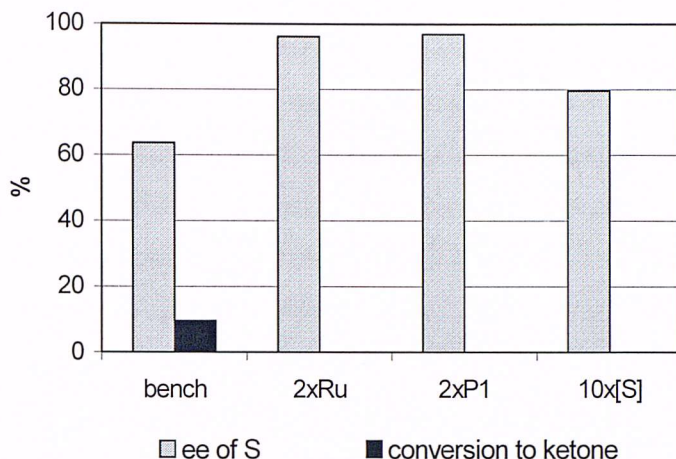


Figure 5.16: Summary of average results for racemisations of *S* 1-phenyl ethanol with ruthenium cymene and P1 oct.

The average ee of the benchmark experiments is 64% with a standard deviation of 21.0. This is a slight improvement on the result using P1 tris, which was 77.7%, although the scatter in the data is still considerable. These results suggest that the P1 oct base will be more effective for MEDKR. The results when the concentrations of the catalysts are doubled are worse: less racemisation occurs. The same is found when the initial substrate concentration is increased by a factor of ten. The ketone formation is low or zero in all cases, indicating that a side-reaction suppressing reagent is not necessary, as suggested by Bäckvall *et al.* [89]. The effect of the atmosphere under which the reactions take place, shown in Figure 5.17, is interesting. The best result is obtained under argon. The result under air is slightly worse than under argon and the least racemisation is obtained under nitrogen. This could be due to the formation of some sort of di-nitrogen complex. For this reason, subsequent reactions with ruthenium cymene and P1 oct will be performed under argon.

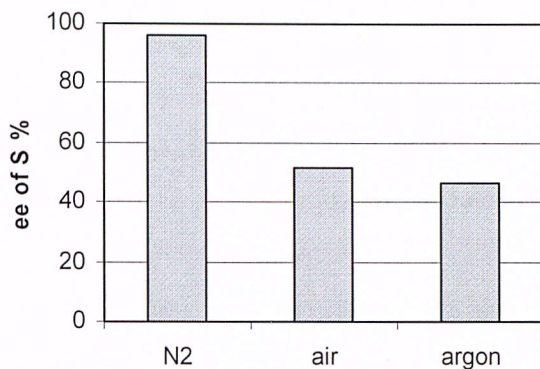


Figure 5.17: Effect of atmosphere on the racemisation of *S* 1-phenyl ethanol with ruthenium cymene and P1 oct.

It is important that the species from the racemisation system do not affect the resolution reaction negatively. Equally, it is important to check that the components of the resolution system do not affect the racemisation. For this reason, reactions of phenyl ethanol with ruthenium cymene and P1 oct were performed ‘spiked’ with the resolution product, phenyl acetate, one potential acyl donor, IPPA and the reaction product of IPPA, acetone. The racemisations were performed with 33.49mM *S* 1-phenyl ethanol, 4 mol% ruthenium cymene and 20 mol% P1 oct, in 25mL of toluene at 25°C under argon. Phenyl acetate and acetone spikes were at 1 equivalent and IPPA spikes were at 1.4 equivalents. The results are shown in Figure 5.18.

Compared with the benchmark racemisation under argon all the ‘spikes’ effect the racemisation negatively. The spike producing the most significant decrease in racemisation is phenyl acetate, the resolution product. This suggests that in a MEDKR process the resolution product will impede the racemisation, thus slowing the whole DKR down. This could be a severe limitation of MEDKR. The requirement will be that the substrate, 1-phenyl ethanol in this case, should move freely around the MEDKR system, whereas, ideally, the product, phenyl acetate, should be retained in the resolution reactor, however, it is not possible to differentiate between the substrate and product of the reaction with the membranes available, since their molecule sizes are too similar.

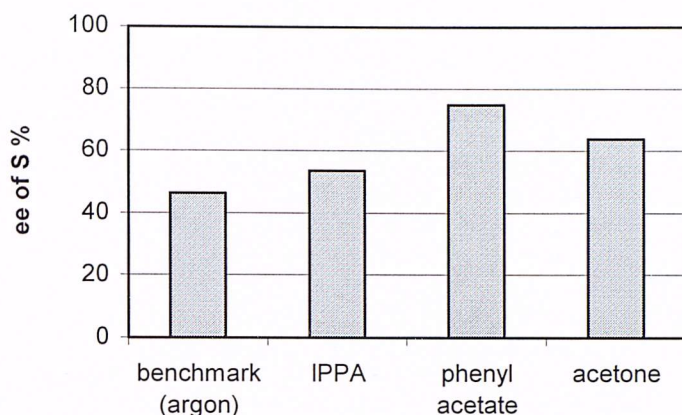


Figure 5.18: Results for 'spiked' racemisations of 33.49mM S 1-phenyl ethanol with 4 mol% ruthenium cymene and 20 mol% P1 oct, in 25mL of toluene at 25°C under argon.

With the ruthenium cymene and P1 oct system, the best racemisation obtained produces an ee of 40%, where an ee of 0% would indicate that a complete reaction had occurred. This clearly needs to be improved upon. There is also the potential for using amine bases instead of phosphazene bases, which might give a better racemisation. Racemisations with 33.49mM 1-phenyl ethanol and 4 mol% Ru cymene were performed with 3 equivalents of the following amine bases: TEA TOA and TDDA. The results are shown in Figure 5.19, and compared with the benchmark P1 oct racemisation.

Less racemisation occurs with the amine bases, compared with P1 oct. This is because the amine bases are weaker than the phosphazene bases and 1-phenyl ethanol is a difficult substrate to racemise. A base stronger than the amine bases will be required. Similar racemisations occur with TEA and TOA, around 60% ee. The racemisation with TDDA is significantly worse. This may be because of the large size of TDDA, (molecular weight of 522, compared with 101.2 and 353.7 for TEA and TOA, respectively and 290.43 for P1 oct) which may sterically prevent it from interacting with the ruthenium catalyst and initiating the catalytic cycle properly.

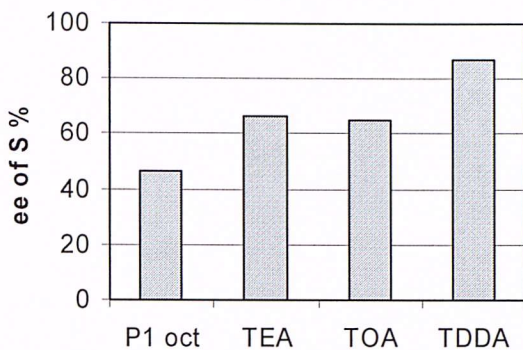


Figure 5.19: Results for racemisations of 33.49mM S 1-phenyl ethanol with 4 mol% ruthenium cymene and various amine bases in 25mL of toluene at 25°C under argon. The benchmark result for P1 oct is also shown for comparative purposes.

From these experiments, it is concluded that out of those tested, P1 oct, P1 tris, TEA, TOA and TDDA, the best base for MEDKR with ruthenium cymene is P1 oct.

Other ruthenium catalysts were tested for their applicability to the MEDKR of phenyl ethanol. Experiments using ruthenium indenyl were performed using 33.49mM S 1-phenyl ethanol with 1.34mM ruthenium indenyl in 25mL of toluene under atmospheric conditions and at 25°C. 3 equivalents of TEA and TOA and various concentrations of P1 oct (2.5, 5, 10 and 20 mol%) were used as the bases to initiate the catalytic cycle. The results show very little racemisation with any of the bases: the ee of the phenyl ethanol remains around 100% in all cases with 2-10% conversion to ketone. In conclusion, the ruthenium indenyl catalyst is not suitable for the racemisation of 1-phenyl ethanol in toluene at 25°C.

Another potential catalyst is ruthenium amino cyclopentadienyl (amino cpd). Experiments were performed using a benchmark 33.49mM S 1-phenyl ethanol with 4 mol% ruthenium amino cpd and 20 and 20 mol% P1oct, under argon at 25°C. The effect of the substrate concentration was also investigated using 10 times the benchmark concentration of 1-phenyl ethanol. The results showed ee's of around 70% at the lower concentration (33.49mM) and 50-60% at the higher concentration (334.9mM). This shows promise, especially at the higher concentration. However, it

is expensive to buy the Ru amino cpd catalyst, and if MEDKR is to be applied industrially, the reactants should be easily affordable. For this reason, no further experiments using this catalyst will be performed. It is not really feasible to perform all experiments at the higher concentration, again for economical reasons, therefore, it is better to try to find a catalyst system which can operate at low concentration.

The possibility of the resolution product, 1-phenyl acetate, in this case interfering with the racemisation of the substrate alcohol, 1-phenyl ethanol, may be important. Therefore, it is important to test how the racemisation works on a resolution product mixture, which will contain the product acetate, the acyl donor as well as the unreacted substrate alcohol, that is how the racemisation catalysts works under “real” conditions. These tests were performed with P1oct and two ruthenium catalysts, ruthenium cymene and ruthenium amino cyclopentadienyl. First standard biotransformations at low and high substrate concentrations were performed at room temperature using 33.49mM 1-phenyl ethanol, 1.5 equivalents of VA and 0.03g of novozyme 435 in 25mL of toluene for the low concentration experiments and 335.9mM 1-phenyl ethanol, 1.5 equivalents of VA and 0.3g of novozyme in 4mL of toluene for the high concentration experiments. All reactions were performed at room temperature for 24 hours. The reactions were stopped by filtering out the enzyme using a paper filter and the reaction products combined to give the feed for the racemisations. The average product yield at low concentration was 57.4%, resulting in a feed for the racemisation consisting of 14.3mM 1-phenyl ethanol and 19.2mM 1-phenyl acetate. The average product yield at high concentration was 56.5%, resulting in a feed for the racemisation consisting of 146mM 1-phenyl ethanol and 190mM 1-phenyl acetate. The 1-phenyl acetate was formed at an ee of 100% R isomer for both the low and high concentration cases. Racemisation catalysts were then added to give an overall Ru catalyst concentration of 4 mol%, and a P1 oct concentration of 20 mol%. The cymene catalyst was used for high and low substrate concentrations. The amino cyclopentadienyl catalyst was used for low substrate concentration only. The racemisations were performed under argon and at 25°C for 30 hours. No ketone was produced in any of the reactions. Unfortunately, no alcohol ee data was obtained. The ee data for the acetate shows that some racemisation of the product occurred, particularly noticeable in the case of the amino cyclopentadienyl catalysts, where the ee of the product, 1-phenyl acetate, dropped

from 100% at the end of the resolution step to around 40% after the racemisation step. This is clearly unacceptable, as an enantiomerically pure product is necessary in this DKR process. It can be concluded that the amino cyclopentadienyl catalyst is unsuitable for MEDKR. The cymene catalyst requires further work to confirm its applicability to MEDKR.

5.3.2.2 Allylic alcohol

Experiments were performed as for 1-phenyl ethanol to investigate the racemisation of the allylic alcohol. Analyses were performed as in section 5.3.1.3. First benchmark experiments were performed with 33.49mM allylic alcohol, 4 mol% ruthenium cymene and 20 mol% P1 oct in 25mL toluene, at 25°C. The effect of an argon atmosphere was compared with normal atmospheric conditions. The effects of spikes of product, allylic acetate (1 equivalent), side products, acetaldehyde and acetic acid (each at 1 equivalent) and the acyl donor, vinyl acetate (1.4 equivalents) from the resolution system were also investigated. Details for all the experiments and the numerical results are given in Appendix III. The results are summarised in Figure 5.20.

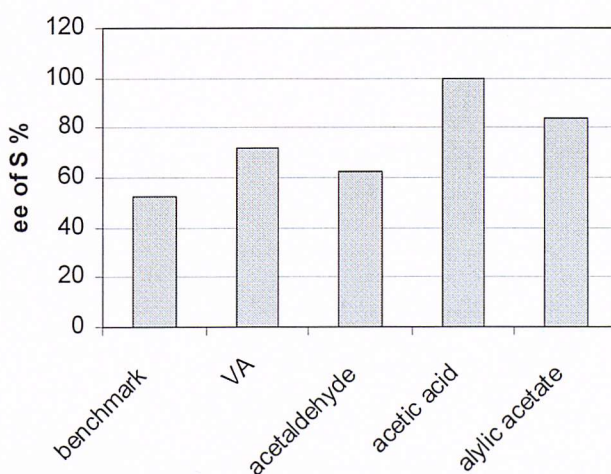


Figure 5.20: Results for racemisations of 33.49mM *S* allylic alcohol with 4 mol% ruthenium cymene and P1 oct in 25mL of toluene.

The average ee obtained for the benchmark reactions was 52%, that is, a racemisation of only half the total starting material. In these reactions, the conversion to ketone was less than or equal to 16%. Given that a complete racemisation under these conditions is very difficult to achieve, this is an acceptable result. Interestingly, virtually no racemisation or ketone production occurred for any of the reactions under argon. It is known that the racemisation of secondary alcohols of this type proceeds in a catalytic cycle via the ketone species [89] and some ruthenium catalysts require the presence of oxygen to initiate the catalytic cycle [116]. Evidently, in the case of the allylic alcohol, the catalytic cycle cannot be initiated in the complete absence of oxygen. For this reason, all future reactions with Ploct and ruthenium cymene will be performed under normal atmospheric conditions. This result is different from the equivalent for the 1-phenyl ethanol, where similar racemisations occurred under air and argon, and the worst racemisation was found under nitrogen. This could be because of different reactivities of the different alcohol species, possibly due to different steric configurations and thus different accessibilities of the alcohol to the catalytic site of the ruthenium catalyst molecule.

By far the best racemisation occurs for the benchmark experiments. All the 'spikes', VA, acetaldehyde, acetic acid and allylic acetate decrease the rate of racemisation, with acetic acid preventing any racemisation from occurring. This result agrees with the results found for 1-phenyl ethanol - the best racemisation occurs for the 'pure' system. Again, this poses a potential problem for the MEDKR result as the membranes available are not capable of distinguishing between the reactant molecules which are all of a similar size.

Since there are evident problems of product inhibition when using Ploct in combination with ruthenium cymene as the racemisation catalyst system, the possibility of using the amine bases will be investigated. Reactions were performed with 33.49mM S allylic alcohol with 4 mol% ruthenium cymene and various number of equivalents of TEA, ThexA, TheptA and TOA, under air and at 25°C using different concentrations of base. The results are shown in Figures 5.21 and 5.22.

The effect of the amine base used can be seen in Figure 5.21. Clearly, the best racemisation occurs with TEA, where an average ee of 17% is achieved, which is the

optimum result obtained with any base / ruthenium catalyst combination. However, as the aim of MEDKR is to maintain two separate catalytic environments, TEA cannot be used as its molecular weight, 101.2, makes it too small to be retained by any of the OSN membranes available and experiments 8.15 and 8.16 show that it has a negative impact on the ee of the product acetate in the resolution of the allylic alcohol. The graph suggests that the racemisation power of the amine bases in the catalytic cycle with ruthenium cymene increases with the length of the carbon chain in the base, and suggests the presence of some sort of molecular weight cutoff, shown by the vertical line in the figure, above which the racemisation power ceases to increase, given that the racemisations obtained with the C₆, C₇ and C₈ amine bases are all very similar, producing an ee of around 45%. Further work on a larger selection of amine bases would be required to confirm this hypothesis. The C₆ amine base, trihexyl amine, produces a marginally better racemisation than the two larger bases. Therefore trihexyl amine will be used for all further amine base experiments with the allylic alcohol and ruthenium cymene.

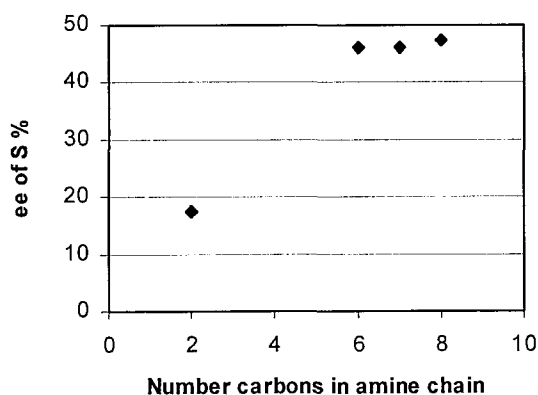


Figure 5.21: Results for racemisations of 33.49mM S allylic alcohol with 4 mol% ruthenium cymene and different sizes of amine bases, all at 1 equivalent concentration in 25mL toluene.

The effect of the concentration of the amine base is shown in Figure 5.22 for TEA and TOA. The effect of concentration follows the same trend for both bases. Similar ee's are obtained for 0.5, 1 and 2 equivalents of base and a significantly worse racemisation is obtained in the case of 3 equivalents. The results suggest therefore that the optimum concentration for the amine base in this racemisation is

between 1 and 2. 1 equivalent seems an adequate concentration, and since most of the previous experiments have used 1 equivalent, further experiments will also use this concentration to enable comparisons.

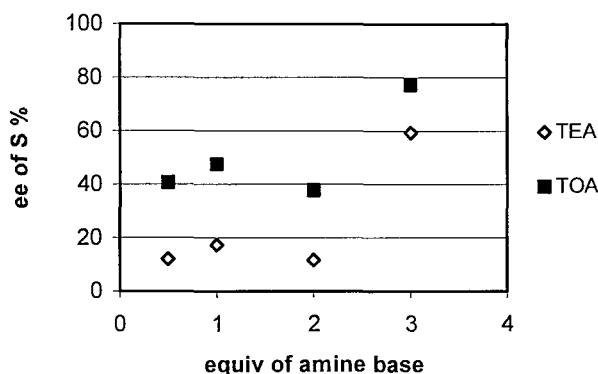


Figure 5.22: Effect of concentration of amine bases TEA and TOA on the racemisation of 33.49mM S allylic alcohol with 4 mol% ruthenium cymene in 25mL of toluene.

It is interesting that TEA and TOA have not produced ketone in any of the experiments whereas, ThexA and TheptA produced 15-20% ketone in these experiments, a possible disadvantage.

A series of experiments were performed to test whether the combination of amine bases or Ploct and ruthenium cymene was capable of racemising the product of the allylic alcohol resolution system, the allylic acetate. The reactions contained 33.49mM allylic acetate with 4mol% ruthenium cymene in 25mL of toluene, under atmospheric conditions and 25°C. Various bases were used: TEA, TOA, ThexA, (all at 1 equivalent and 2 equivalents), Ploct (40mol%). The effect of 'spikes' from the resolution system were also added to confirm that the product is not racemised even in the presence of the resolution system components. The spikes tested were: VA, acetaldehyde, acetic acid (all at 1 equivalent) and the enzyme, novozyme 435, 0.03g. Virtually no racemisation was obtained in any case, ee's greater than 98.6% were obtained for all the experiments. There was no conversion to ketone in any of the

reactions. This proves that the product acetate, once formed, as the pure R species will remain enantiomerically pure, as required.

The possibility of the resolution product, allylic acetate, in this case interfering with the racemisation of the substrate alcohol, allylic alcohol, may be important. Therefore, it is important to test how the racemisation works on a resolution product mixture, which will contain the product acetate, the acyl donor as well as the unreacted substrate alcohol. These tests were performed with a range of bases, P1oct, TEA, TOA, ThexA and TheptA. First standard biotransformations were performed at room temperature using 33.49mM allylic alcohol, 1.5 equivalents of VA and 0.03g of novozyme in 25mL of toluene at room temperature for 24 hours. The reactions were stopped by removing the enzyme by paper filtration and the reaction products combined to give the feed for the racemisations. The overall yield was 52% of R acetate with an ee of 87%. The remaining S alcohol had an ee of 94%. This meant that the racemisation feed consisted of 16.1mM alcohol and 17.4mM acetate. The racemisation catalysts were then added to give an overall Ru cymene concentration of 4 mol%, a P1 oct concentration of 20 mol% and amine base concentrations of 1 equiv. The racemisations were performed under atmospheric conditions and at 25°C for 30 hours. The bases used were 1 equivalent of TEA, and ThexA and 20mol% of P1oct. The results are shown in Figure 5.23.

Before discussing these results, it is important to recall the desired outcome of the reactions are. At the end of the resolution reaction, it is expected that the reaction mix should consist of:

50% acetate (100% R isomer)

50% alcohol (100% S isomer)

Following addition of the racemisation catalysts, it is expected that the reaction mix should consist of:

50% acetate (100% R isomer)

50% alcohol (50% S isomer, 50% R isomer)

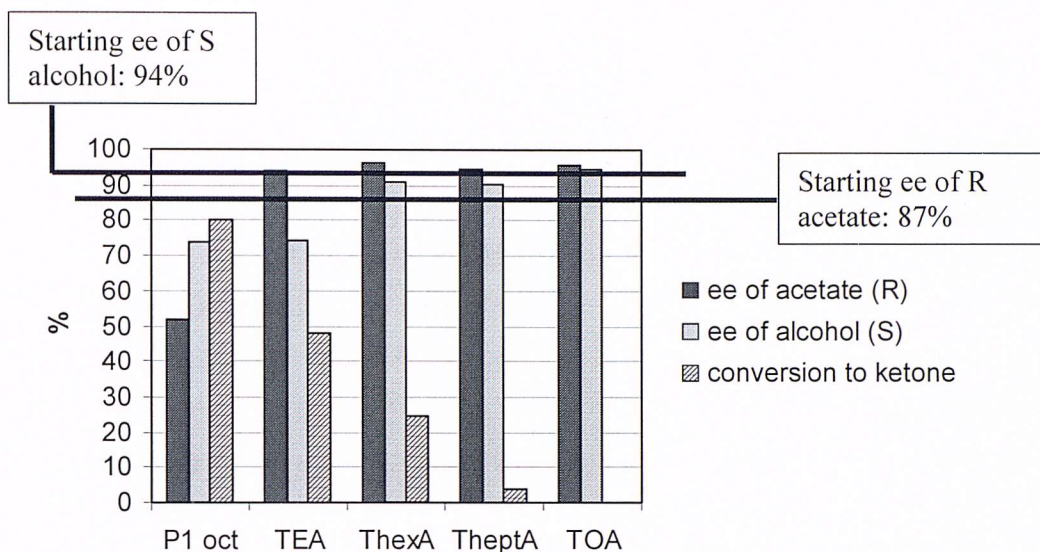


Figure 5.23: Summary of results for racemisations of product from resolution. Feed contains 16.1mM allylic alcohol and 17.4mM allylic acetate. Reactions performed with 4 mol% ruthenium cymene and various bases in 25mL of toluene, under atmospheric conditions and at 25°C.

Therefore, now looking at Figure 5.23, if the ee of the acetate is less than the starting value (87%), this indicates that the racemisation catalysts have racemised the product as well as the substrate, thus resulting in the generation of a non-pure product – a failure from the point of view of the DKR process. This has occurred in the case of P1oct. This is contrary to earlier results where, when the acetate was tested on its own with P1 oct, no racemisation occurred. The ee of the acetate for all the amine bases is > 90%, higher than the starting value, which is difficult to explain. How the two catalytic systems interact with each other is clearly not yet understood fully. As stated above, if the addition of the racemisation catalysts has had some effect, a 50:50 mixture of the S and R isomers of the allylic alcohol is expected, that is an ee of 0%. The Figure shows that none of bases have succeeding in racemising the alcohol well, although, some decrease in ee has occurred compared with the initial value of 94%. The lowest ee obtained, with P1 oct, was still as high as ~70%. This proves that the racemisation is not working well *in situ* on a real reaction mixture and is further evidence to support the assertion that the two catalytic systems interfere

with each other. The ketone production is low for TOA, ThexA and TheptA, higher for TEA and very high for P1oct. This is clearly bad for MEDKR, as, in the case of P1oct, most of the substrate allylic alcohol will be ‘wasted’, being converted to by-product ketone rather than useful product acetate.

These results are not very promising for a successful MEDKR. Literature [138-140] suggests that the acetic acid formed as a by-product from the acyl donor of the resolution reaction inhibits the racemisation. One possibility for solving this problem is adding a base, such as sodium carbonate, Na_2CO_3 , to soak up the acetic acid and prevent it stopping the racemisation reaction. Therefore the previous racemisations of resolution reaction products were repeated exactly but with the addition of 1 equivalent of powdered Na_2CO_3 , at the same time as the racemisation catalysts. The racemisations were performed under argon and at 25°C for 30 hours, as before. The results of these racemisations are shown in Figure 5.24. The ee of the R acetate is maintained at a higher level in the presence of sodium carbonate and the level of ketone production is lower, although why this should be is unclear. The racemisation of the S isomer is still poor however, with the lowest ee (that is most racemisation) being found with TEA, although it is still an ee of above 50% which is not entirely promising.

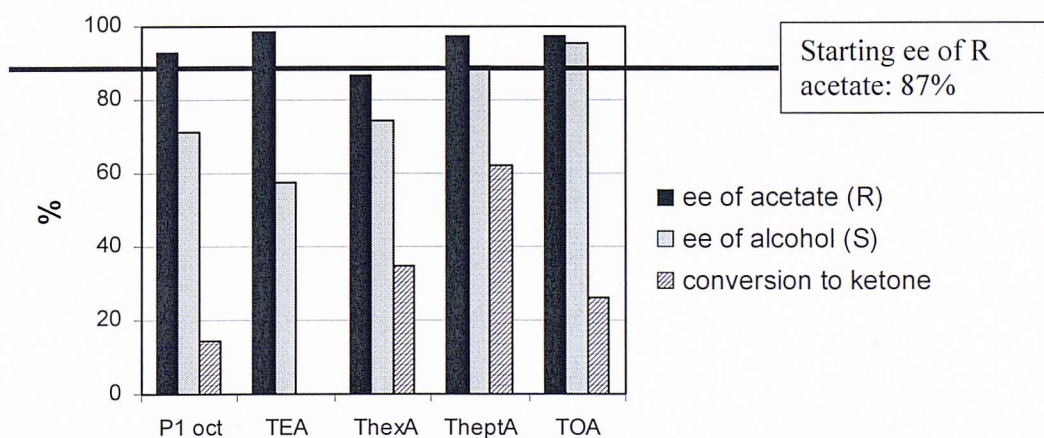


Figure 5.24: Summary of results for racemisations of product from resolution. Feed contains 16.1mM allylic alcohol and 17.4mM allylic acetate. Reactions performed with 4 mol% ruthenium cymene, various bases and 1 equivalent of Na_2CO_3 in 25mL of toluene, under atmospheric conditions and at 25°C.

The conclusion from these racemisation experiments is that the racemisation is the more challenging of the two steps of a DKR. Even when the racemisation is performed alone, it is still difficult to obtain good results. When other reaction components are added to the racemisation, the success of the reaction drops in nearly all cases, showing that interference between the two systems is likely to be a serious issue. Of course, interference between the resolution and racemisation systems is expected and this is why the concept of MEDKR has been suggested in order to introduce separation of the two systems. However, it was initially expected that the major problem in a one-pot DKR would be the base from the racemisation system interfering with the enzyme and preventing the resolution from working properly, hence, large bases such as the Ploct or TOA have been suggested for MEDKR which can be adequately retained by the membranes available, preventing them from contacting the enzyme. However, these racemisation results indicate that the products of the resolution are likely to have as great an effect on the racemisation as the base has on the resolution. This is a substantial problem for the MEDKR process, since at present, it is not possible to separate the substrates and products of these acylation reactions since their molecular weights are so similar (122.17 and 164.17 respectively for the phenyl ethanol system and 148 and 190 for the allylic alcohol system) and the membranes available work by size exclusion.

Further information about how the two reactions of DKR work together can be gained by investigating the one-pot reactions and establishing how the two reactions work together *in-situ*.

5.3.3 “One-pot” DKR

“One-pot” DKR reactions were performed in order to

- a) Establish how the two reactions of DKR work together *in-situ*
- b) Provide a benchmark against which to measure any improvement due to the membrane in MEDKR

5.3.3.1 1-phenyl ethanol

Reactions were performed in the reaction carousel, as for the individual biotransformation and racemisation reactions. The racemisation catalysts (ruthenium species and base) were premixed at the reaction temperature to ensure they were well dissolved and that the active catalyst had been generated. All other ingredients were then added (acyl donor, enzyme). Finally, the substrate alcohol was added, at time $t = 0$. Various combinations of catalysts were used. Analyses were performed as in section 5.3.1.1. Results are reported in terms of yield of product and ketone (calculated using equations 5.1 and 5.2 respectively), ee's of product acetate and remaining alcohol (calculated using equation 4.1) and overall mass balance, to check conservation of reaction species in the system (equation 5.3). The details of the experiments and numerical results can be found in Appendix IV.

$$\text{Overall mass balance} = \frac{(\text{mol alcohol} + \text{mol acetate} + \text{mol ketone})^{t=\text{end}}}{(\text{mol alcohol})^{t=0}} \times 100\% \quad (5.3)$$

The first experiments were performed with 20mM 1-phenyl ethanol, 2 mol% ruthenium indenyl, 3 equivalents of TEA, TOA or TDDA as the racemisation catalyst system and 0.03g PCL and 1.5 equivalents of 4 chloro phenyl acetate as the resolution system, in 25mL toluene at 40°C under nitrogen. Low yields of significantly under 50% were obtained and no trend with type of base was observable due to scatter in the data. The best result was obtained with TOA, a yield of just under 40%. The worst yield was with TDDA, around 20%. Previously, TDDA failed to racemise phenyl ethanol well in a straight racemisation reaction, so it is no surprise that the result is poor for a one-pot DKR. The conversion to ketone in these reactions was reasonably low, between 10 and 15%. These reactions have a lower product yield than the straight biotransformation which is expected to reach the maximum yield of 50% in this time scale. From this, it is concluded that combining the two catalytic systems prevents both systems from working properly and indicates that separation of the two systems, which appear to work reasonably individually, as in MEDKR, should provide some benefits.

Experiments were performed with 33.49mM 1-phenyl ethanol with 0.03g novozyme 435 and 1.5 equivalents of IPPA as the resolution system, various racemisation catalyst combinations were investigated: the ruthenium catalysts (cymene and indenyl) were used at 4 mol%, the phosphazene base P1 oct was used at 20mol% and the amine bases (TEA and TOA) were used at 3 equivalents. The results are shown in Table 5.3.

Table 5.3: Results for one-pot DKRs of 1-phenyl ethanol with a resolution system consisting of novozyme 435 and IPPA. All results based on average of two experiments.

Ru catalyst	Base	Yield	Ketone yield	Overall mass balance	Ee of alcohol (S)
		%	%	%	%
Cymene	P1 oct	49.6	11.1	104.9	71.4
Indenyl	P1 oct	0.7	5.6	104.0	89.2
Indenyl	TEA	27.4	1.3	113.7	51.4
Indenyl	TOA	36.6	0.0	93.5	100.0

For ruthenium cymene and P1 oct, product yields of around 50% were obtained, equivalent to the straight biotransformation. The presence of the racemisation catalysts seems to have made no difference, suggesting that they are not working *in-situ*. By comparison, when P1 oct is used with ruthenium indenyl rather than cymene, virtually no product is made, suggesting that this catalyst combination interferes with the resolution system to the extent that it prevents any resolution occurring. This effect is also shown, to a lesser degree, when amine bases, TEA and TOA are used with the indenyl catalyst instead of P1 oct. Low yields are seen of 20-30% showing that the presence of the racemisation catalysts prevents the biotransformation from going to completion. The conversion to ketone in all the indenyl reactions is low: < 6%. Although the poor product yield results suggest that no ketone is seen in the reactions due to the fact that the catalytic cycle never starts. If the racemisation is working, it is expected that a racemic mixture of the substrate alcohol will be found at all points in the reaction, that is, an ee of 0%. However, for

all the reactions using IPPA as the acyl donor, ee's much greater than 0% are observed, proving that the racemisation catalysts are unable to work *in-situ*.

Experiments were performed with 33.49mM 1-phenyl ethanol with 0.03g novozyme 435 and 1.5 equivalents of VA as the resolution system. The racemisation system was 4 mol% ruthenium amino cpd or cymene and 20mol% P1oct. The reactions were performed in 25mL toluene, at 25°C and under argon due to the sensitivity of the ruthenium catalyst to oxygen. One reaction was also performed at a substrate concentration ten times higher, to test the effect of the concentration of 1-phenyl ethanol. Each experiment was performed twice and the averaged results are shown in Figure 5.25. The conversion to ketone in all cases was low, < 15%. The product formed was 100% R isomer, as required. Interestingly, for both catalysts, ruthenium cymene and ruthenium amino cpd, the results are significantly better, around 20% higher product yield, at higher concentrations. The product yield at low substrate concentration for both catalysts is around 50%, that is, no improvement compared with the straight biotransformation, leading to the conclusion, that the racemisation catalysts are having no effect at low concentration, but offering a significant improvement at high concentration.

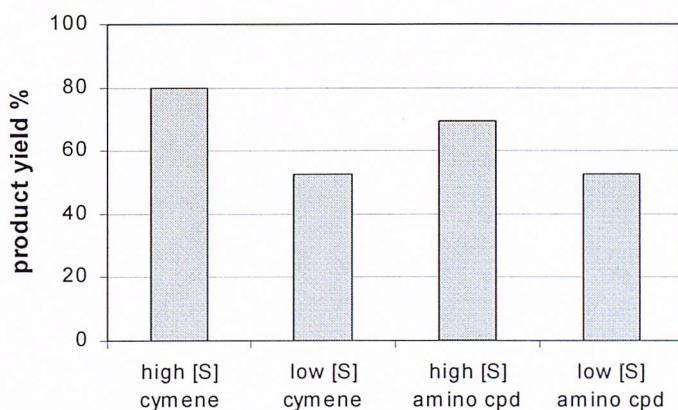


Figure 5.25: Results for one-pot DKRs of phenyl ethanol with novozyme 435, P1oct and VA. Reactions use different substrate concentrations and ruthenium catalysts. Reactions were performed under argon and 25°C for 48 hours.

The conclusion from these phenyl ethanol reactions is that there is a significant problem with interaction between the two catalytic systems in a one-pot DKR. This is consistent with findings of other authors such as Verzijl *et al.* [141]. They report that when using isopropenyl acetate to resolve a secondary alcohol in a DKR process with novozyme 435 in toluene, the IPPA acts as a hydrogen source creating reductive conditions in the presence of a redox racemisation catalyst, a di-ruthenium complex in their case. This leads to problems with the reversibility of the transesterification part of the mechanism causing the reaction to end in equilibrium. Therefore they conclude that the racemisation system prevents the resolution system from working properly, as is suggested by the data in this study. Verzijl *et al.* overcome this problem by continuously removing the acyl donor residue during the reaction by selective distillation. For situations where this is not possible, there is a real need for the advantages of MEDKR in separating resolution system from the racemisation system.

5.3.3.2 Allylic alcohol

One-pot DKR reactions were performed with allylic alcohol using VA and novozyme 435 as the resolution system. Ruthenium cymene and various bases were used as the racemisation system. The effect of the concentrations of the enzyme, ruthenium and bases and substrate allylic alcohol were tested. The acyl donor was always used at a concentration of 1.5 equivalents and all the reaction were performed in 25mL toluene and at 25°C. The effect of varying the initial alcohol substrate by a factor of 10 was also studied. Analyses were performed as in section 5.3.1.3. Further experimental details and numerical results can be found in Appendix IV.

The benchmark reactions (33.75mM AA, 1.5 equivalents VA, 0.03g novozyme 435, 20mol% PI oct, 4 mol% Ru cymene) have only low product yields, an average of around 16.3% with a standard deviation of 4.6%. The purity of the allylic acetate formed is variable, but the unreacted allylic alcohol left behind has a low ee, with an average of 2.4%, indicating that it is close to racemic and that, therefore, the racemisation is working. There is a very variable conversion to ketone ranging from

8% to 52%. Clearly, the one-pot DKR of allylic alcohol with ruthenium cymene and P1oct is not a feasible reaction, giving opportunity for improvement using MEDKR. The effect of changing the concentrations of the catalysts, using low substrate concentration is summarised in Figure 5.26. The effect of increasing the concentrations of the racemisation catalysts is negligible. A large increase in product yield is seen when the quantity of the enzyme is increased to double and a further, but smaller, increase is seen when it is increased to quadruple the benchmark quantity. This is demonstrated clearly in Figure 5.27. Clearly, the quantity of enzyme is the limiting factor in this reaction. This does imply problems for the MEDKR rig, however. If a MEDKR is to produce a significant quantity of product acetate, a rig with a volume much larger than the reaction carousel tubes will be required, say, a volume of 2 litres compared with 25mL which would require 2.4g compared with 0.03g of enzyme, which may be prohibitively expensive. Also, a larger mass of enzyme may pose problems from the point of view of mass transfer due to the high level of particulates in the reaction mixture and problems may be caused with the resolution reactor clogging up.

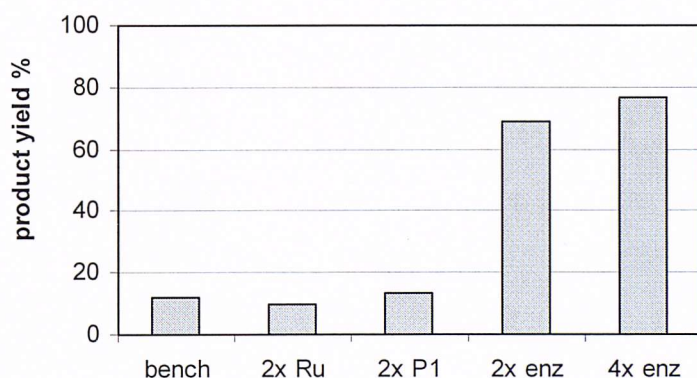


Figure 5.26: Summary of product yields for one-pot DKRs of low concentration allylic alcohol with 1.5 equivalents of VA as the acyl donor, ruthenium cymene, novozyme 435 and P1oct.

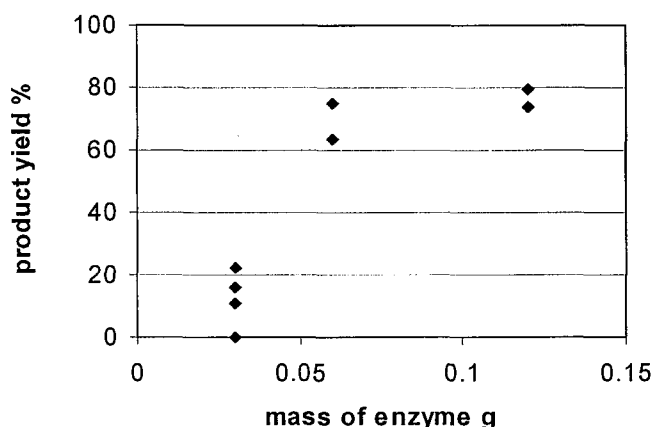


Figure 5.27: Summary of effect of quantity of enzyme on product yields for one-pot DKRs of low concentration allylic alcohol with 1.5 equivalents of VA as the acyl donor, ruthenium cymene, novozyme 435 and P1oct.

For the high concentration substrate benchmark reactions, where the concentration of the substrate 1-phenyl ethanol was 337.5mM, an average product yield of 63.4% is obtained. Although this is higher than previous reactions, it is still not significantly higher than the straight enzyme resolution showing that the racemisation process is still not working sufficiently well. The ketone conversion is low for all the experiments: less than 3%. As Figure 5.28 shows there is little effect of changing the enzyme concentration, suggesting that the enzyme concentration is only limiting at low substrate concentration. This implies that the issue of how the substrate reaches the enzyme and interacts with the active site is important. The ee of the product acetate is above 75% in all the reactions. The ee of the unreacted alcohol is also high, showing that, once again, the racemisation is not working properly. This is consistent with the sequential resolution then attempted racemisation experiments, Table 5.31.

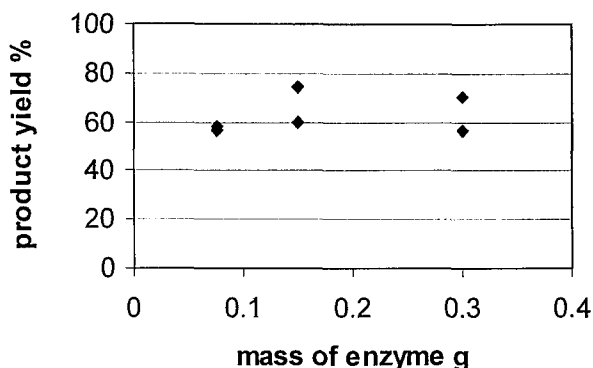


Figure 5.28: Summary of effect of quantity of enzyme on product yields for one-pot DKRs of high concentration allylic alcohol with 1.5 equivalents of VA as the acyl donor, ruthenium cymene, novozyme 435 and P1oct.

One-pot DKR reactions were also performed with allylic alcohol with VA as the acyl donor and ruthenium cymene as the catalyst, novozyme 435 and amine bases instead of P1oct. Previous racemisation experiments have suggested that the optimum amine base in terms of racemisation power and retention by the membrane is trihexylamine. Therefore, the first experimental runs will use ThexA. The experiments were performed using 33.75mM allylic alcohol with 1.5 equivalents of VA and 0.03g of enzyme. All reactions were in 25mL of toluene under atmospheric conditions, at 25°C for 24 hours and were well stirred to ensure adequate contact between substrates and catalysts and thus provide the best opportunity for reaction. Different concentrations of ruthenium cymene and ThexA were used.

The yields in all cases are low, around 30%, which is significantly less than the equivalent biotransformation on its own, which would reach a product yield of 50%. The relationship between the product yield obtained and the concentration of catalyst used is shown in Figure 5.29. The concentration of the ThexA has little effect, as expected if the racemisation is not actually working. The results indicate a slight increase in product yield as the concentration of the ruthenium catalyst is increased. The acetate formed is of reasonable purity in all cases, with an ee > 88%. The unreacted alcohol also has a high ee, greater than 88%, which is not really consistent with the fact that the yields of product are all significantly below 50% and the yields

of ketone are low in most cases. Given this fact, the observed effect of increasing yield with increasing ruthenium cymene concentration should not be taken too seriously. The conversion to ketone is low in most cases, below 6%.

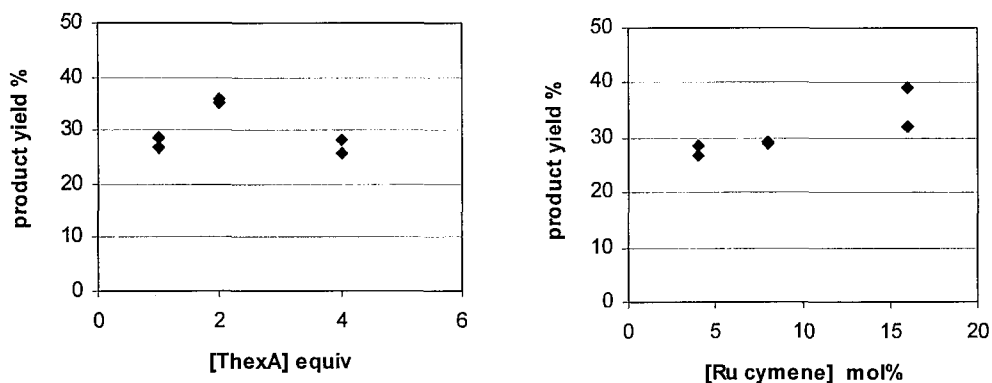


Figure 5.29: Effect of varying catalyst concentration for one-pot DKRs of 33.75mM allylic alcohol with 1.5 equivalents of VA as the acyl donor, ruthenium cymene, novozyme 435 and ThexA.

For comparison, runs using different amine bases were performed using both low (33.75mM) and high (337.5mM) substrate concentrations. The acyl donor, VA was used at a concentration of 1.5 equivalents. TEA and TOA were used as the bases, both at 1 equivalent with ruthenium cymene at 4 mol%.

At high substrate concentration, with TEA a high yield, of around 70% is obtained, with less than 3% conversion to ketone. This is still not a significant improvement compared with the individual biotransformation. The product ee is only around 70%, when 100% is expected and the ee of the remaining alcohol is high, suggesting that in this case little racemisation has occurred. DKRs with low concentration substrate and TEA and TOA produced reasonably high product yields of 60-75%, with an enantiopurity of 100%, of course, this is still not significantly higher than the yield in the individual resolutions.

Another interesting aspect of these reactions is their time profiles. Figure 5.30 shows how the product yield varies as a function of time for two identical one-pot DKRs with 33.75mM allylic alcohol with 1.5 equivalents of VA, 4 mol% ruthenium cymene, 0.03g novozyme 435 and 1 equivalent of TEA. The product yield increases from $t=0$ as expected, reaching a maximum in the first experiment around 3 hours and in the second experiment around 2 hours. In both cases, after the product yield peaks, it then drops. This is another potential problem for MEDKR, if, *in-situ*, the product formed in the resolution reaction degrades. If this is the case, then the product would need to be removed from the reaction system before it is degraded in order to maximise the product yield of the overall reaction.

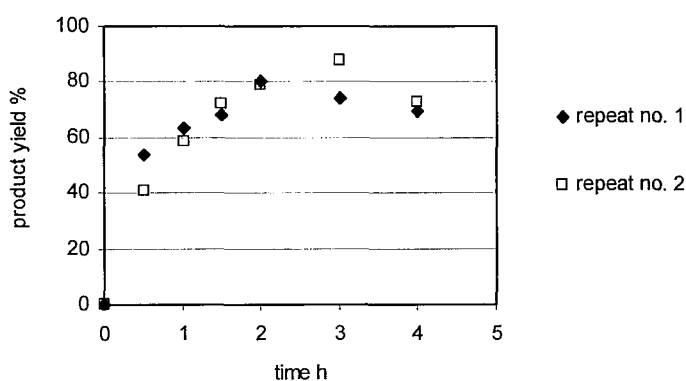


Figure 5.30: Time profile for one-pot DKRs of 33.75mM allylic alcohol with 1.5 equivalents of VA, 4 mol% ruthenium cymene, novozyme 435 and 1 equivalent of TEA

The conclusion from these allylic alcohol reactions is, as for the case of 1-phenyl ethanol, that there is a significant problem with interaction between the two catalytic systems in a one-pot DKR. It has not been possible with either substrate to obtain a good DKR result. This shows that there is a real need for the advantages of MEDKR in separating resolution system from the racemisation system. It is hoped, therefore, that MEDKR will allow a successful DKR to take place.

5.3.4 Summary and Conclusions

Resolutions

For 1-phenyl ethanol with 4-chloro phenyl acetate, a large scatter in the data was found with a range of product yields from 20-70%. The best results were obtained using one equivalent of 4-chloro phenyl acetate. The rate of reaction but not the end conversion was affected by the reaction temperature. With vinyl acetate, high yields were obtained, greater than 50%, with 100% product ee's. The best results were obtained with 1.5 equivalents of vinyl acetate. For isopropenyl acetate, yields of around 50% were obtained. 'Spikes' of racemisation catalysts were found to affect the yield and ee negatively.

For allylic alcohol and vinyl acetate, high yields, greater than 50% were obtained and all 'spikes' were found to have a negative effect, especially Ploct. For the amine base spikes, the best results were found for the larger bases. The enzyme is not capable of catalysing the back reaction.

Resolutions

For both 1-phenyl ethanol and allylic alcohol, there was a large amount of scatter in the data; reproducibility was poor. The best results were found for 1-phenyl ethanol using ruthenium amino cyclopentadiene with a high substrate concentration, although, this combination is likely to be prohibitively expensive. For all the ruthenium catalysts, better racemisations were obtained using the stronger phosphazene bases than the amine bases. All 'spikes' were found to affect the racemisation negatively and the systems were found to be susceptible to product inhibition. The catalysts were found to be capable of racemising the product acetate as well as the alcohol substrate.

One-pot reactions

Low yields were found in all cases: the yields were less than 50% proving that the DKR process offers no improvement compared with the simple enzyme resolution.

Better results were found using increased concentrations of substrate and enzyme, although operating at these conditions at a large scale would prove prohibitively expensive and large concentrations of enzyme could create problems in terms of mass transfer and fluid mechanics.

Conclusions

The poor one-pot reaction results leave more potential for improvement using MEDKR. The following chapters discuss the study of the MEDKR process. The experiments in this chapter assist in choosing the chemical systems for preliminary DKR experiments.

For 1-phenyl ethanol, reasonable resolution results were found using novozyme 435, vinyl acetate and isopropenyl acetate. Poor results were found for 4-chloro phenyl acetate. Therefore MEDKR experiments will proceed using vinyl acetate and isopropenyl acetate only. In terms of the racemisation, the best combination of racemisation power and cost is the ruthenium cymene catalyst. The amine bases will be abandoned at this stage since they produce poor racemisations and are smaller than the phosphazene bases and so will be retained by the membranes in MEDKR less well. Therefore MEDKR experiments will proceed using ruthenium cymene, P1tris and P1oct.

For allylic alcohol, vinyl acetate and novozyme 435 will be used for the resolution system. The best results for the racemisation were obtained with ruthenium cymene and P1oct, therefore these will be used for the racemisation system.

CHAPTER 6

DYNAMIC KINETIC RESOLUTION: MEMBRANE INVESTIGATIONS

As discussed in Section 5.1, the aim of the MEDKR is to use membranes to separate the two DKR catalysts, which for the systems identified for this study, are an enzyme and a transition metal catalyst. The MEDKR process will separate the two chemical reaction systems, the racemisation and the resolution, using an OSN membrane to retain the enzyme retained in a resolution reaction vessel and the transition metal catalyst in a racemisation reaction vessel. In this section, suitable membranes will be chosen and their separation properties with respect to all the components of the 1-phenyl ethanol and allylic alcohol systems will be measured.

6.1 ANALYTICAL METHODS

Concentrations of the components of the 1-phenyl ethanol system were analysed as in section 5.3.1.1. Concentrations of the components of the allylic alcohol system were analysed as in section 5.3.1.3. The concentrations of the transition metal catalysts were measured by UV spectroscopy, detecting at 278nm, using a UV-2101PC UV-vis scanning spectrophotometer from Shimadzu. Concentrations of the phosphazene bases were measured by gas chromatography using the Agilent GC as detailed in section 5.3.1.3. The Temperature programme began at 100°C, rising at 10°C/min to 140°C, then at 5°C/min to 200°C, and then at 20°C/min to 250°C. The final temperature was held for 5 minutes to ensure all the material had passed out of the column.

6.2 MATERIALS AND METHODS

To retain the enzyme, a microporous *Millipore Durapore*® membrane was chosen. It is a solvent stable, hydrophilic, symmetric porous polyvinylidene fluoride (PVDF) membrane, with a pore size of 0.65nm and a porosity of 70%. The porous structure

of the membrane is shown in Figure 6.1. It was chosen because it has a lower protein binding than other microporous membranes made of nylon, nitrocellulose or PTFE, and thus the pores should be less susceptible to clogging.

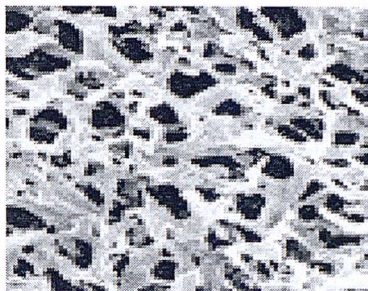


Figure 6.1: Millipore Durapore® membrane.

Preliminary tests showed that the membrane shows so little resistance to toluene that an average flux of toluene through the membrane in the absence of pressure was 163 L/m²h, based on three measurements with a standard deviation of 7.4. With 1 bar of pressure, the flux increased dramatically to larger than 1300 L/m²h. Visual inspection of the membrane following permeation of toluene showed it to be intact, and thus solvent stable as the manufacturers claimed. For the filtrations of the reactants for the two chosen system, the membrane showed zero rejection of all the components, including the catalysts. Hence this membrane will provide no resistance to the flow of the substrates and products in the MEDKR process, as desired.

To retain the racemisation catalyst, a separation at the molecular level is required, since the catalysts are in homogeneous solution. Hence, one of the Starmem™ series of membranes will be chosen. The sizes, that is, molecular weights, of the components of the systems need to be considered, and a membrane with a suitable molecular weight cut-off chosen accordingly. The potential transition metal catalysts for the system are:

Ruthenium cymene

MW = 612.39

Ruthenium indenyl

MW = 861.16

Aminocyclopentadienyl ruthenium MW = 619.12

The potential classes of bases are

1) Phosphazene bases

PI-oct MW = 290.43

PI-tris MW = 321.44

2) Amine bases

Ranging from: triethyl amine MW = 101.20

to: trihexyl amine MW = 269.51

and: tridodecyl amine MW = 522.00

The main substrates are

1-Phenyl ethanol MW = 122.17

Allylic alcohol MW = 148.00

Therefore, a membrane capable of retaining the ruthenium species and phosphazene bases, but allowing permeation of the secondary alcohols is required. Any amine base used in the system would need to have a molecule weight greater than that of the alcohol substrate. Starmem™ 122 was chosen for preliminary test work. Its MWCO of 220 should ensure a good retention of the catalysts and good permeation of the substrates.

The rejections and compatibility with the membrane of all the components of both systems must be measured in toluene, the solvent of interest. Rejections were measured in the dead-end cell, as detailed in Section 2.4. Concentrations were chosen so as to replicate “real” reaction mixtures. 30 bar of nitrogen gas provided the pressure for filtration in all cases. All components were tested at 25°C. 1-phenyl ethanol was also tested at 40°C. The compatibility with the membranes was established firstly by visual inspection following soaking of the membrane in solutions of the components, and then by testing the rejection of a highly rejected marker compound, tetraoctyl ammonium bromide, before and after filtration of the component in question.

6.3 RESULTS

The results for all the filtrations of the 1-phenyl ethanol and allylic alcohol system components and catalysts are shown in Appendix V. Each filtration was repeated several times and the results averaged. These results are summarised in Table 6.1.

Table 6.1: Summary of filtration results for components of allylic alcohol and 1-phenyl ethanol systems, with Starmem™ 122, in toluene and at 30bar and 25°C.

Component	Solvent Flux			Solute Rejection		
	Av	Standard dev	Coeff of variance	Av	Standard dev	Coeff of variance
	Lm ⁻² h ⁻¹	%	%	%	%	%
Allylic alcohol	41.55	1.05	2.65	20.18	0.09	0.04
Allylic acetate	42.38	1.13	2.99	28.98	4.67	75.26
Phenyl ethanol	49.64	1.12	2.51	5.33	1.93	70.19
Phenyl acetate	51.98	0.62	0.73	13.18	1.82	25.13
Acetophenone	49.64	1.12	2.51	10.48	1.52	22.09
VA	49.24	1.67	5.69	5.42	1.91	67.03
IPPA	121.12	6.18	31.53	16.16	1.90	22.34
4 CPA	44.61	0.91	1.86	25.54	0.40	0.63
Ruthenium cymene	36.34	2.56	18.1	98.17	1.00	1.02
Aminocyclopentadienyl ruthenium	n/m	n/m	n/m	100.00	0	0
Ruthenium indenyl	n/m	n/m	n/m	85.53	2.81	9.20

The data at 25°C shows good solvent fluxes for all the reaction components: 40-50 Lm⁻²h⁻¹ in most cases. The flux with IPPA was particularly high. Why this should be is not clear. The flux with the TMCs was lower in all cases and very low for the aminocyclopentadienyl and indenyl catalysts, suggesting some sort of pore blocking

mechanism or the build up of a filtration cake at the membrane surface. As previously discussed, these types of membranes do not necessarily have pores. However, the spaces between polymer chains through which permeating species diffuse may be blocked by large TMCs. The filtration flux with 1-phenyl ethanol at 40°C was slightly higher than at 25°C: an average of 53.39 compared with 49.64 Lm^2h^{-1} . This could be because the polymer chains of the membrane have a greater mobility at higher temperatures thus allowing more solvent molecules to permeate. Alternatively it could be due to the solvents having a lower viscosity at higher temperatures.

The data at 25°C shows low rejections of the substrates, products and reactants, less than 25%, and high rejection of the TMCs, as required for MEDKR. It is interesting that the largest catalyst, the ruthenium indenyl catalyst, is the least well retained. This is further evidence, as already discussed, that the mechanism for nanofiltration is not simply size exclusion. Some of the solute molecules are charged and thus charge interactions could be important, both in solution and with the membrane. The repeatability of the filtration measurements is reasonable, with the coefficient of variation not exceeding 35% in most cases. It seems that better repeatability is not feasible with this apparatus. The poor repeatability for species like vinyl acetate and 1-phenyl ethanol is due to the fact that they are volatile, thus making analysis difficult. The membrane has an extremely low rejection of 1-phenyl ethanol at 40°C. It is known that membranes lose their integrity at higher temperatures ($>70^\circ\text{C}$) [142] so it is possible that partial degradation of the membrane is occurring in this instance. Thus it is essential for a fully continuous MEDKR process that the individual chemical steps have sufficiently high reaction rates and conversions at lower temperatures, to be compatible with the membrane filtration process.

Another important factor to investigate is the effect the components have on each other in a filtration of a 'real' reaction mixture. All of the above data were calculated from filtrations of the components individually. It is advantageous if these components show the same filtration characteristics in a mixture as they do individually. This was investigated for all the components of each of the two systems. The comparison of the rejections and retentions individually with those for

the reaction mixtures, at the same concentrations are shown in Figure 6.2, A and B for the 1-phenyl ethanol and allylic alcohol systems respectively.

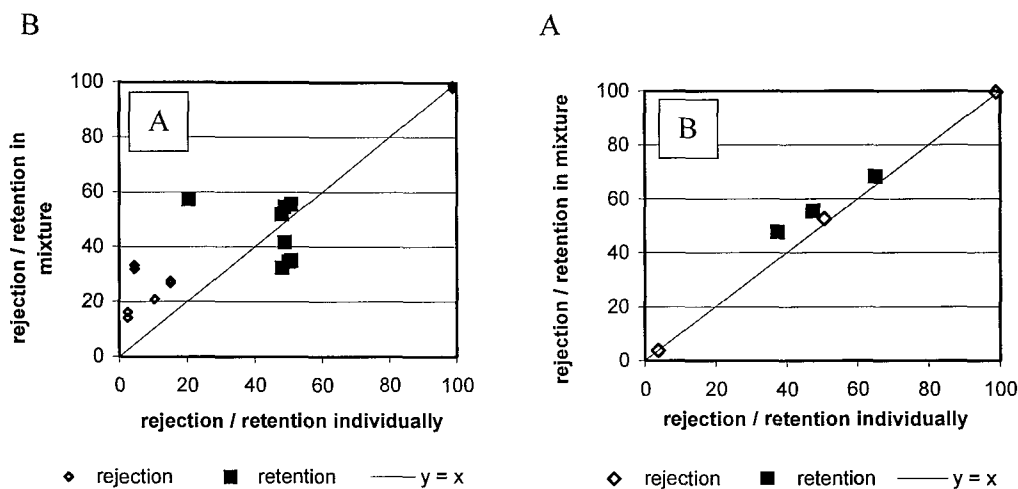


Figure 6.2: Comparison of rejection and retentions of reaction systems' components individually with those in the reaction mixture.

A: 1-phenyl ethanol system [33.75mM 1-phenyl ethanol, 5mM acetophenone, 33.75mM 1-phenyl acetate, 5mM 33.75mM 4 chlorophenyl acetate, 33.75mM IPPA, 49.95mM VA, 1.68mM ruthenium cymene]

B: allylic alcohol system [25mM allylic alcohol, 25mM allylic acetate, 49.95mM VA, 1.68mM ruthenium cymene]

Visually, the correlation between the two data sets is better for the allylic alcohol system than for the phenyl ethanol system, which is quite scattered, although the data set is smaller for the allylic alcohol system. To quantify this, a least squares regression was performed on the data set, allowing the calculation of the correlation coefficient r^2 . For the allylic alcohol system, the r^2 value is 0.93 and for the 1-phenyl ethanol system, the value is 0.70. This confirms that the correlation is better for the allylic alcohol system and justifies the conclusion that the components do not affect each other in a mixture. Although the correlation for the 1-phenyl ethanol system is not as good, there is no obvious alternative trend to the data, it is just scattered. Therefore, it can be concluded that there is no definite effect of the reaction components on each other in this system.

Since it has been shown that the base used in the racemisation system has a severe effect on the resolution system, due to the limited pH tolerance of the enzyme, special attention has been paid to the filtration characteristics of the bases.

Two phosphazene bases are of interest: Ploct and Pltris. For both bases, visual inspection of Starmem™ 122 after soaking in a solution of the PI base in toluene showed no noticeable degradation. Details of the phosphazene base filtrations are given in Appendix II and summarised in Table 6.2. The data show that both the phosphazene bases, Ploct and Pltris, have good rejections with Starmem™122. It is expected that the rejection will be higher for Pltris since it has a higher molecular weight than Ploct (312.44 compared with 290.43) however the reverse is seen. MEDKR experiments are required in order to investigate whether this small amount of permeation will affect the enzyme's activity detrimentally. The presence of the P1 base as a solute reduces the solvent flux through the membrane greatly, for instance, for Ploct, from a steady state toluene flux of around 40 L/m²h to an average of 11 L/m²h with Ploct. A possible reason for this is pore blocking by the large solute molecules. This is consistent with the fact that the large transition metal catalyst molecules also slow the solvent flux, although not as significantly as the phosphazene bases (compare Table 6.1). The rejection of a marker compound, TOABr, was maintained at >99%, after treatment with both P1 bases for 24 hours showing that the membrane remains intact.

Table 6.2: Summary of filtration results for phosphazene bases with Starmem™ 122, in toluene and at 30bar and 25°C.

Component	Flux			Rejection		
	Av	Standard dev	Coeff of variance	Av	Standard dev	Coeff of variance
	Lm ⁻² h ⁻¹	%	%	%	%	%
Ploct	11.21	1.10	10.70	99.63	0.06	3.6x10 ⁻³
Pltris	9.11	0.34	1.23	95.84	4.17	18.10

Since phosphazene bases are known to be strong, it was suspected that the membranes, although stable with the base at low concentrations and for short periods of time, might loose their integrity if exposed to a higher concentration of the base.

Figure 6.3 shows the effect of Ploct concentration on the membranes integrity. The graph, which displays the rejection of TOABr after soaking the membrane in solutions of Ploct for 48 hours, demonstrates that at higher concentrations, the integrity of the membrane is lost. However, since the concentration at which the integrity of the membrane is lost is somewhere between 25 and 50mM, and given that the Ploct base is generally used at a concentration of 22mol% of the substrate concentration, that is, <10mM, the stability is considered to be adequate for this application.

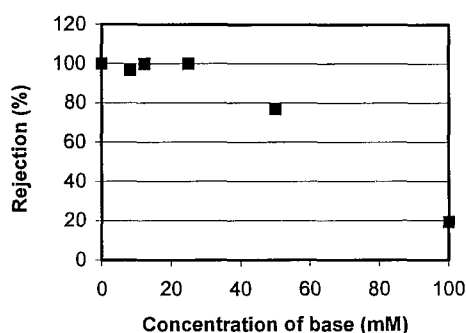


Figure 6.3: Effect on integrity of Starmem™ 122 of treatment with solutions of Ploct in toluene for 48 hours: rejection of TOABr for various pre-treatment concentrations.

A number of measurements of the rejections and filtration fluxes for the homologous series of amines bases were made. The results are shown in Figures 6.4 and 6.5. The repeatability for most of the bases is excellent (coefficient of variation < 4%). The error bars on the graph show the largest error for the smallest base, triethyl amine base, MW = 101.2, which is because of a larger analytical error in measuring the feed, permeate and retentate concentrations due to the volatile nature of this base.

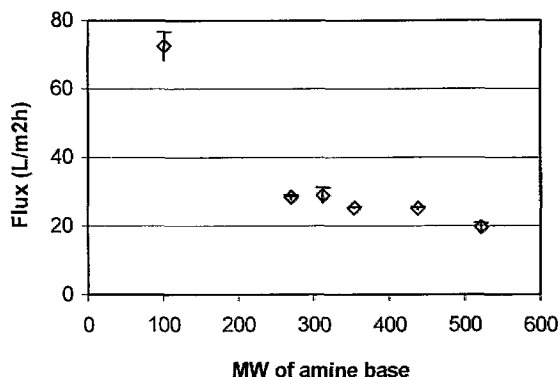


Figure 6.4: Filtration flux for 101.25mM amine bases (3 equivalents of the substrate alcohol) with Starmem™ 122, in toluene, at 30bar and 25°C. Filtration feed volume was 40mL, permeate volume was 20mL.

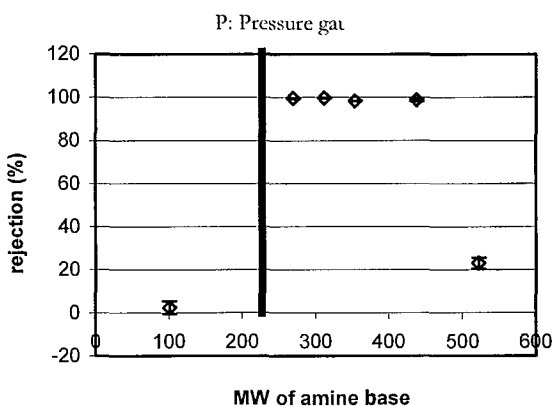


Figure 6.5: Rejection of 101.25mM amine bases (3 equivalents of the substrate alcohol) with Starmem™ 122, in toluene, at 30bar and 25°C. Filtration feed volume was 40mL, permeate volume was 20mL.

The results show a similar, moderate flux for all the larger amine bases (20-30 L/m²h for bases with molecular weight greater than 300 – that is trihexyl amine and larger). The flux with TEA is around three times larger, because it is a smaller molecule and has virtually no retention by the membrane, as expected since its molecular weight (101.2) is below the MWCO of Starmem™ 122, which is 220. As TEA passes through the membrane easily, there will be no effect of retarding the solvent flow due

to flux coupling, hence the higher filtration flux. The next four bases in the homologous series, trihexyl, triheptyl, trioctyl and tridecyl amines (molecular weights 269.51, 311.59, 353.68 and 437.83 respectively) are highly rejected, >98%, with excellent repeatability. However, tridodecyl amine has a rejection of only 23.11%, with coefficient of variation 6.73%, based on six independent measurements. This is further evidence that factors other than simple size exclusion are important in the mechanism of nanofiltration. For the purposes of MEDKR any of the trihexyl, triheptyl, trioctyl and tridecyl amines would be suitable.

A possible approach to try to explain the anomalous rejection result of tridodecyl amine is to examine the configuration of the amine base molecules in solution using molecular modelling packages. This might give some information about the shape, orientation or mobility of the molecules in solution and thus explain how a large molecule such as tridodecyl amine is able to pass through the membrane relatively unhindered, whereas the smaller trihexyl and tri heptyl amines display a very high rejection. A further discussion of this is given in Appendix VI since it is not central to this study.

6.4 FURTHER LONG TERM TESTING

Although initial tests showed a good resistance of Starmem™ 122 to P1oct and a high rejection of P1oct in toluene, it is important to investigate further the long term effect of P1oct on the membrane. The long term *in-situ* stability of the Starmem™ 122 membrane to P1oct was tested in a continuous rig similar to that which will be used for performing MEDKR experiments. The membranes were pre-conditioned prior to use according to the usual protocol. The integrity of the membrane was tested using the highly rejected marker compound, TOABr, before and after exposure of the membrane to P1oct. The continuous rig used for these experiments, as shown in Figure 6.6. The operating conditions were: pressure = 30bar, temperature = 25°C, pump flow rate = 10mL/min. At the start of the experiment, the nanofiltration cell was filled with 150mL of 7.7mM P1oct in toluene and the pump reservoir contained

100mL of pure toluene. The experiment was run for 48 hours. The results for three identical tests are shown in Table 6.3.

Table 6.3: Results for stability tests with Starmem™ 122 and P1oct in toluene in the continuous rig.

Experiment	Unit	1	2	3
Pure solvent flux	L/m^2h	48.9	40.8	46.4
TOABr rejection before exposure to P1oct	%	44.9	99.6	52.0
TOABr retention before exposure to P1oct	%	37.6	87.9	25.6
Mass balance on TOABr before exposure to P1oct	%	60.0	88.4	70.4
TOABr filtration flux before exposure to P1oct	L/m^2h	37.9	36.7	34.8
Overall P1oct rejection	%	60.2	99.6	48.6
Overall mass balance on P1oct	%	98.9	73.3	127.0
Average P1oct filtration flux	L/m^2h	11.1	6.7	12.7
Average loop flow rate	mL/min	4.2	4.7	4.5
TOABr rejection after exposure to P1oct	%	85.3	87.3	68.2
TOABr retention after exposure to P1oct	%	71.8	75.5	66.6
Mass balance on TOABr exposure to with P1oct	%	83.5	84.0	91.9
TOABr filtration flux after exposure to P1oct	L/m^2h	10.3	25.1	27.3

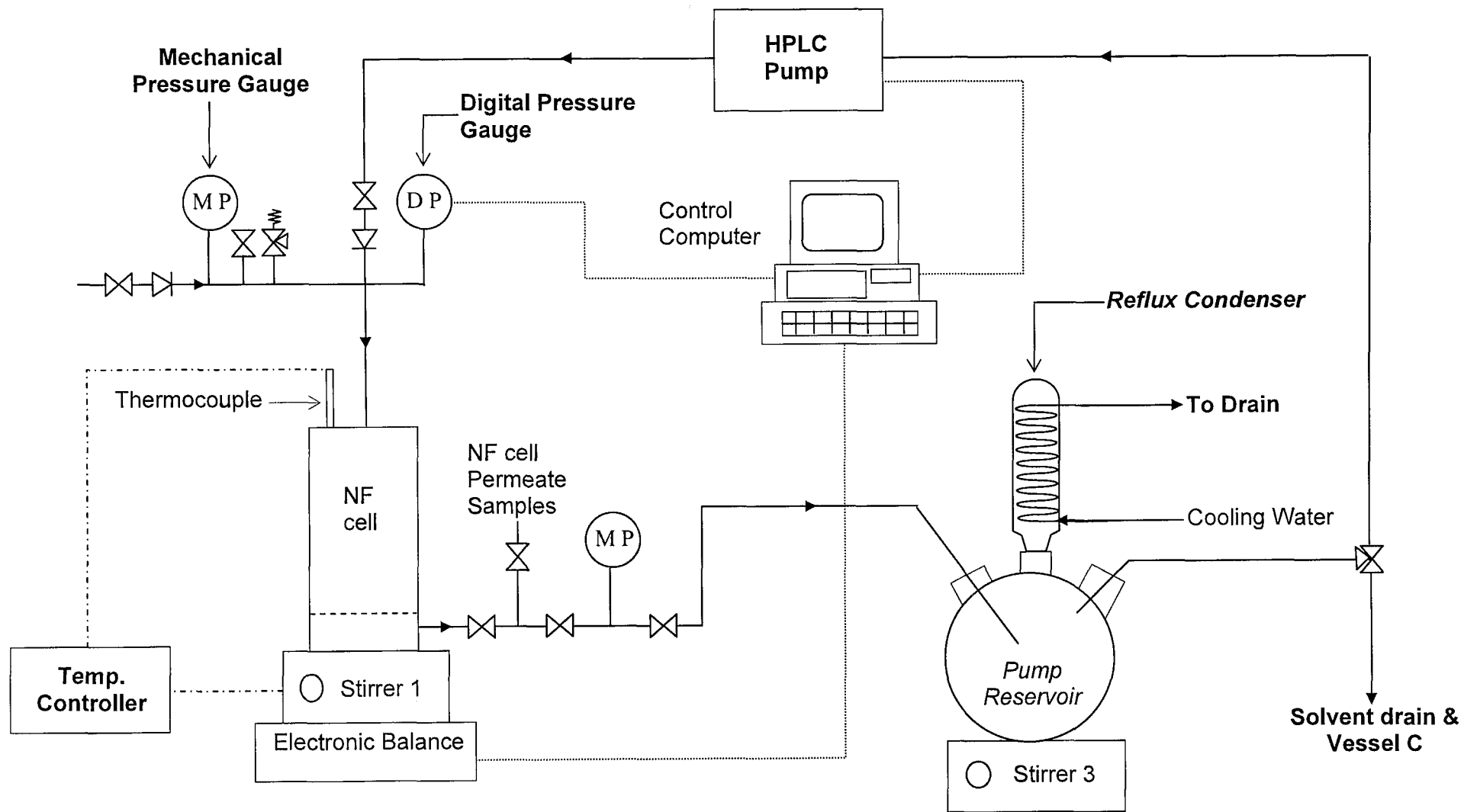


Figure 6.6: Continuous rig, for long-term membrane stability tests.

The data shown in Table 6.3 highlight the fact that there is a severe repeatability problem with these membranes in the dead end cell mode; there is a large amount of scatter in the data. For Experiments 1 and 3, in Table 6.3, the initial rejection of TOABr is very poor (the value is expected to be >95%), which suggests that there may have been a fault with the membranes in these experiments. The initial rejection of TOABr in Experiment 2 is good, hence this experiment should be considered the most significant. In this experiment, a good overall rejection of P1oct is found (99.6%), however, after treatment with the P1oct, the rejection of TOABr dropped to 87.3% indicating that some sort of degradation of the membrane has occurred causing it to lose its integrity. Curiously, the rejection of TOABr measured after exposure of the membrane to P1oct, in Experiments 1 and 3, is higher than before. The filtration flux with P1oct is substantially lower than the pure solvent flux ($\sim 10\text{L/m}^2\text{h}$ compared with $\sim 45\text{L/m}^2\text{h}$). This could be due to some sort of pore blocking mechanism due to the large size of P1oct (MW = 290.43), or due to the build up of a gel layer at the surface of the membrane, as discussed in Chapter 3.

It is widely accepted that the data obtained from dead-end cell nanofiltration experiments is less reliable than those obtained from cross flow [13, 14]. This is due to better hydrodynamic control in cross flow mode and a lower susceptibility to concentration polarisation and gel layer formation. Therefore, it was decided to run long term stability tests on Starmem™ 122 with P1oct in a general usage cross flow rig, shown in Figures 6.7 and 6.8. Although this is less similar to the kind of rig that the MEDKR experiments will be performed in, it allows four membranes to be tested simultaneously, thereby increasing the rate at which data can be collected, which is important in long term experiments such as these. There are four cross flow nanofiltration cells in series, with an area of 69.4 cm^2 and a tangential flow pattern. Exactly the same hydrodynamic conditions are obtained in all four cells, thus allowing measurement of the repeatability and uniformity of the membranes. 1 litre of feed solution containing 7.7mM P1oct was circulated at a flow rate of 75L/h, over the four separate discs of Starmem™ 122, following a pre-treatment step with pure toluene. The feed also contained 5mM TOABr (expected rejection $\sim 100\%$) in order to check the integrity of the membranes. The pressure was maintained at 30bar and the temperature at 25°C. The rig was run for 74 hours. Permeate samples were taken periodically for analysis.

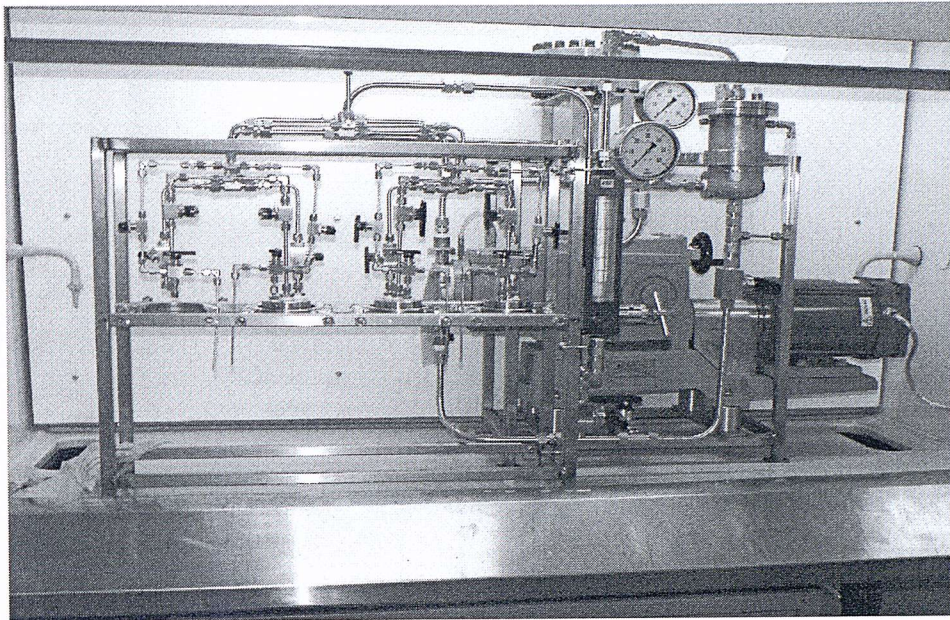


Figure 6.7: Nanofiltration cross flow rig.

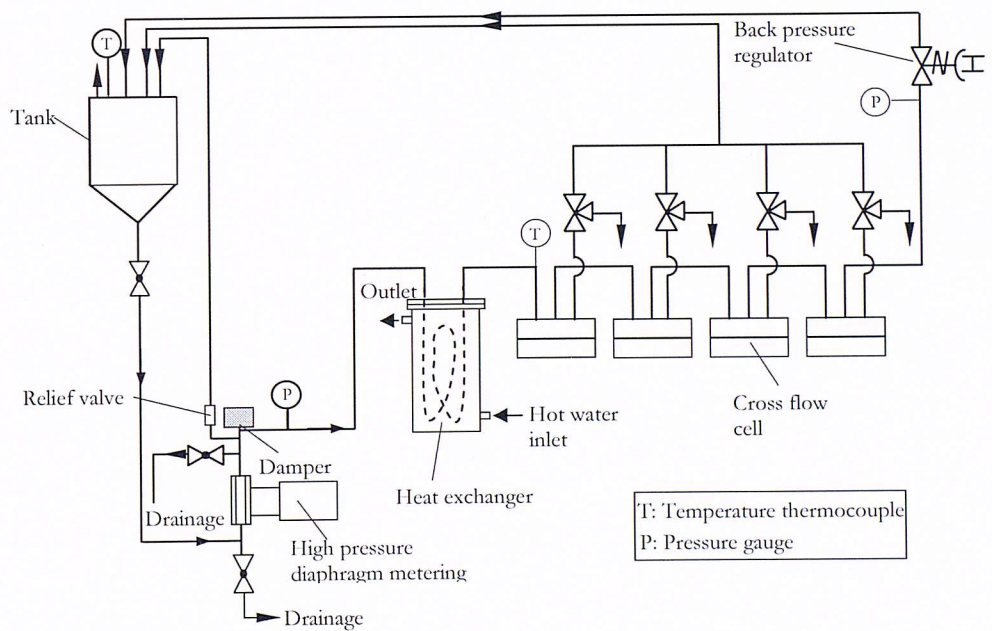


Figure 6.8: Schematic of nanofiltration cross flow rig.

The results are shown in Figure 6.9. The conclusion is that the integrity of the membrane is not maintained at high concentrations of Ploct over a long time period for the following reasons:

1. permeate concentration of Ploct and TOABr increases gradually with time
2. rejection of Ploct and TOABr decreases gradually with time
3. solvent flux increases dramatically with time

Since the permeate concentrations increase and the rejections decrease only gradually, and the data does not suggest a breakthrough point in the experiment. It is concluded that the membrane's integrity is gradually reduced rather than experiencing a sudden attack by the base. To understand how this degradation of the membrane occurs, it is necessary to know how the polymer and Ploct interact. An adsorption isotherm experiment, was performed to establish the uptake rate of the Ploct into the polymer: a 25mL sample of a solution of Ploct in toluene was loaded with Lenzing P84 polyimide powder, the polymer from which StarmemTM 122 is manufactured, at low and high loadings (0.3 and 0.6g respectively) and stirred well for 48 hours. The concentration of the Ploct was 7.7mM. The concentration of Ploct in solution was measured after 24 and 48 hours. The percentage decreases in concentration of Ploct at these times are shown in Table 6.4.

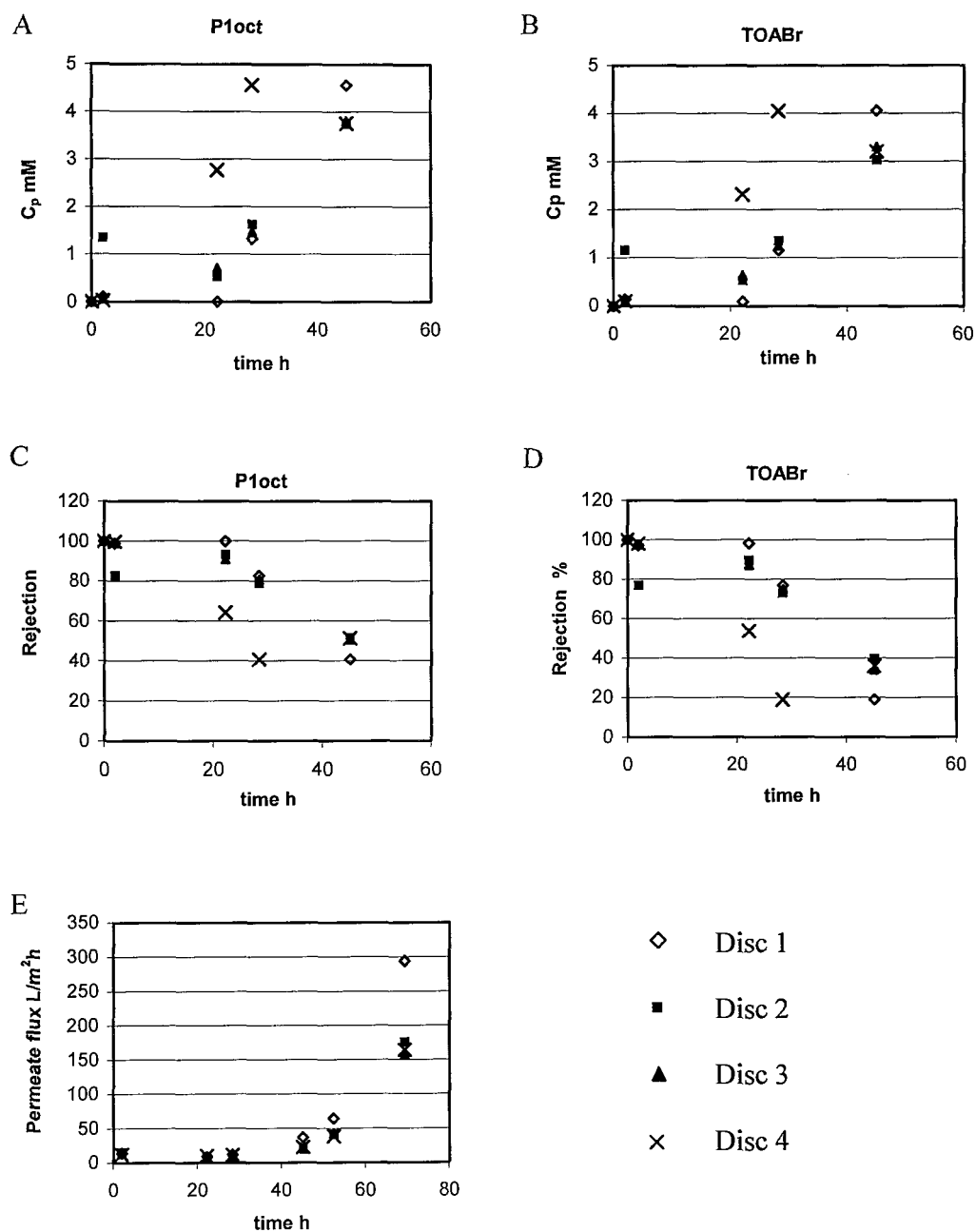


Figure 6.9: Results for cross flow stability tests of Starmem™ 122 in toluene with P1oct, using TOABr as a marker: A. Permeate concentration for P1oct, B. Permeate concentration for TOABr, C. Rejection for P1oct, D. Rejection for TOABr, E. Permeate flux.

Table 6.4: Adsorption isotherm experiment results for P1oct: percentage decrease in concentration of P1oct in solution.

	Low loading	High loading
t = 24 hours	50.7%	82.8%
t = 48 hours	61.1%	92.4%

The data show that there is a substantial uptake of the P1oct into the polymer material. Either it is simply absorbed into the voids between the polymer chains, thus pushing the chains apart, causing a larger flux and lower rejection, or it undergoes some chemical reaction or interaction with the polymer molecule. A possible explanation involves the fact that an important functional group in the polymer is the carbonyl group. Due to the high electronegativity of the oxygen atom, the carbonyl bond, $C=O$, is very polarised, with a highly electrophilic region and a highly nucleophilic region, as demonstrated in Figure 6.10. Hence it can react either as a nucleophile or an electrophile.

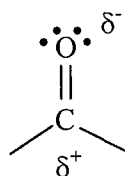


Figure 6.10: Polarised nature of the carbonyl bond

The δ^+ , electrophilic region of the carbonyl bond would have the capacity to react via nucleophilic attack with ‘normal’ bases, as shown in Figure 6.11.

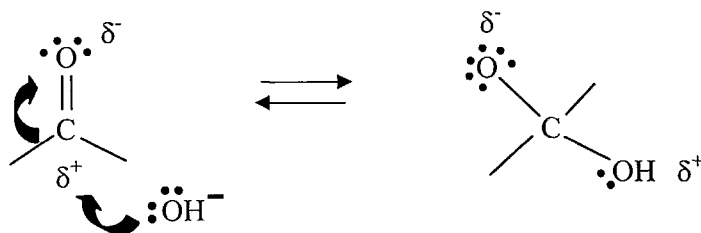
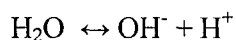


Figure 6.11: Nucleophilic attack on carbonyl bond in polymer

The phosphazene bases [137, 144 - 146] are strong and uncharged bases, built on a nitrogen basic centre double bonded to a pentavalent phosphorous. They are not nucleophilic and so do not undergo the normal basic S_N1 and S_N2 and substitution reactions. However, they do have the ability to strip off acidic hydrogens. So, for instance, if there is a small impurity of water in the solvent, the following reaction might occur:



Then nucleophilic attack by the OH^- species could then occur, as in Figure 6.11, causing degradation of the membrane material. Another important factor is that the basicity, which can be measured by the pK_A value (see Figure 5.6), for a given solute will change according to the solvent in which it is dissolved [145]. Therefore, it was decided to perform preliminary tests to investigate whether the base resistance of Starmem™ 122 can be improved by changing the solvent. Solvents common in organic synthesis reactions were chosen for further investigation. The membranes were first soaked in the various solvents overnight and visually checked for signs of degradation. The membrane was not noticeably affected in any case. The membranes were preconditioned in the deadend nanofiltration cell with the pure solvent at 30 bar and at 25°C, and the membranes' integrity determined by measuring the rejection of TOABr. The long term stability with 7.7mM P1oct was tested continuously using the continuous MEDKR-type rig, as detailed earlier in Figure 6.6. The pump flow in the rig was set at 10mL/min. The solvents investigated were: iso-octane, dioxane, methanol and ethyl acetate.

The flux of iso-octane was found to be too slow to be practical for this application: less than 3 L/m²h. The flux with dioxane was reasonable: a steady state flux of around 11 L/m²h was obtained after three preconditioning runs, as shown by Figure 6.12.

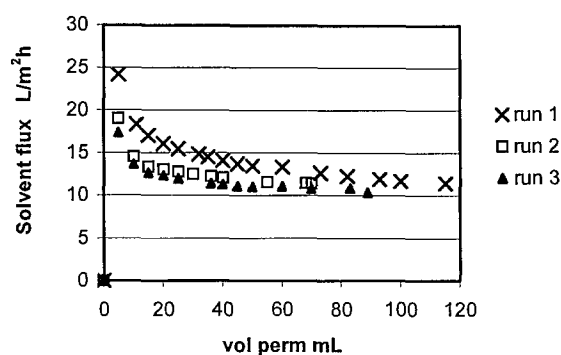


Figure 6.12: Preconditioning of Starmem™ 122 with dioxane, at 30 bar and 25°C.

Despite being visually stable following overnight soaking in dioxane, after the first filtration of TOABr, the solvent flux suddenly increased to greater than 3000 L/m²h. On removal from the cell, the membrane was found to be covered in cracks and ‘bubbles’ where the active top layer had become detached from the support layer and the top layer flaked and fell off when touched. In conclusion, Starmem™ 122 is not stable in dioxane.

The flux of methanol was high: around 70 L/m²h, as shown in Figure 6.13 and a high initial rejection of TOABr was measured: 98.0%.

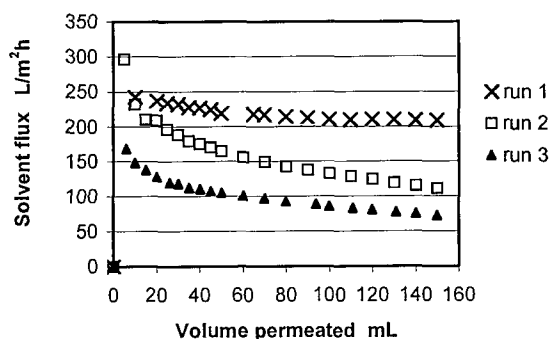


Figure 6.13: Preconditioning of Starmem™ 122 with methanol, at 30 bar and 25°C.

However, upon addition of Ploct, the membrane immediately failed and all the contents of vessel A passed through the membrane into vessel C. One explanation for this is that the phosphazene base strips the acidic hydrogen from the methanol leaving a methoxy species ($\text{MeOH} \rightarrow \text{MeO}^-$) which is a very strong nucleophile and

can attack the carbonyl bond in the polymer molecule. In conclusion, using methanol instead of toluene reduces the membrane's stability to Ploct.

A very high flux of around 150 L/m²h was obtained with ethyl acetate, as shown by Figure 6.14 and a good TOABr rejection of 99.4% was measured prior to exposure of the membrane to Ploct.

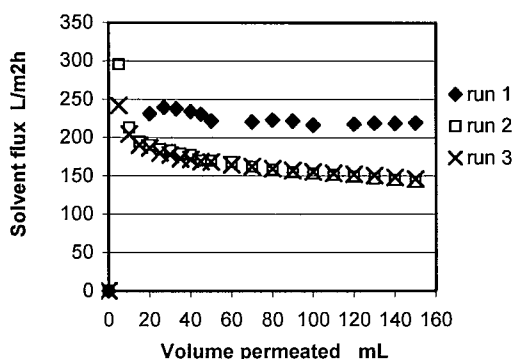


Figure 6.14: Preconditioning of Starmem™ 122 with ethyl acetate, at 30 bar and 25°C.

This system, since the membrane seems to be stable in ethyl acetate, was run in the modified MEDKR rig for 12 hours. The progress of the Ploct was monitored over time. The planned pressure of 30bar had to be reduced to 10bar since the flux through the membrane at 30bar was too high for the pump to be able to control the system. The results are shown in Figure 6.15. The overall rejection of Ploct was 76.6% with a mass balance of 104.4%. The rejection of TOABr after exposure to Ploct had decreased to 71.9%, indicating that some degradation of the membrane had probably occurred. In conclusion, although better than the other solvents tested, ethyl acetate does not significantly improve the resistance of Starmem™ 122 to Ploct compared with toluene.

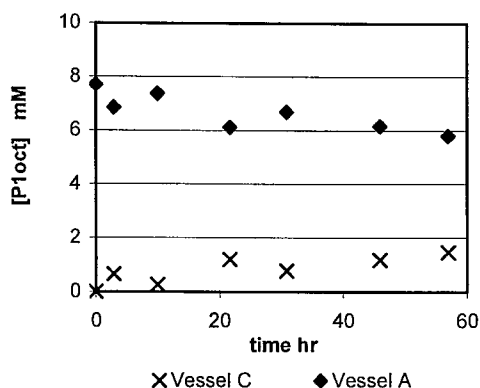


Figure 6.15: Progress of Ploct around continuous MEDKR-type rig during stability test of Starmem™ 122 in ethyl acetate.

Another possible idea for improving the membrane's resistance to Ploct, rather than using a completely different solvent, is to use a 'sacrificial' impurity. The basis of this idea is that a small spike of a second solvent will preferentially react with the Ploct, thus removing the Ploct from the solution and preventing it from attacking the membrane. To test this idea, the membrane was first preconditioned in the usual way with pure toluene. A 98.1% rejection of TOABr was measured prior to the addition of Ploct. The stability test was then run for 12 hours under 30bar pressure in the modified MEDKR rig, using 7.7mM Ploct in toluene containing 5% ethyl acetate. The results are shown in Figure 6.16.

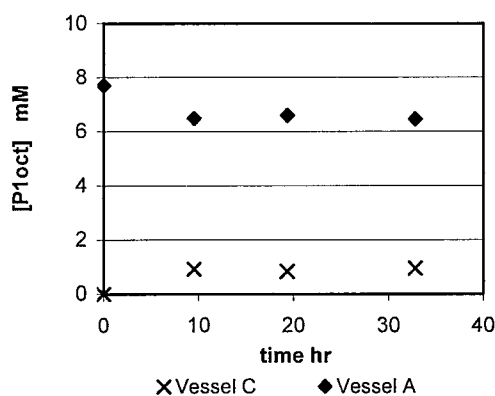


Figure 6.16: Progress of Ploct around continuous MEDKR-type rig during stability test of Starmem™ 122 in toluene with 5% "sacrificial" ethyl acetate.

The overall rejection of Ploct was 74.3% with a mass balance of 106.8%. Following exposure of the membrane to Ploct, the rejection of TOABr was measured to be 98.9%. In conclusion, the addition of ethyl acetate allowed the integrity of the membrane to be maintained over this time scale. However, the rejection of the Ploct is too low to be useful in this application.

The results for the different solvent systems are summarised in Table 6.5.

Table 6.5: Effect of different solvents on the stability of Starmem™ 122 with Ploct.

Solvent system	Result
Toluene	Membrane degrades over longer time period, losing integrity
Iso-octane	Flux too slow to be practical
Dioxane	Membrane not stable in solvent
Methanol	Immediate failure on addition of Ploct
Ethyl acetate	Membrane degrades over longer time period, losing integrity
Toluene with 5% ethyl acetate	Integrity maintained over long time period, but rejection of Ploct too low

In conclusion, what is really required for this study, is a new membrane with a high tolerance to the base chosen for the racemisation step of MEDKR and a high rejection of the base. A number of other commercial nanofiltration membranes are available for testing.

Alternative Starmem™ series membranes are available, such as Starmem™ 240 (MWCO of 400) and Starmem 120 (MWCO of 200). A cutoff of 400, in the case of Starmem™ 240 is obviously larger than the size of Ploct (290.43), but since it has already been shown in this study that factors other than simple size exclusion drive the nanofiltration process, it is worth trying. Samples of both membranes appeared to be stable after soaking for 24 hours in a solution of 7.7mM Ploct. The membranes were preconditioned in pure toluene, at 30bar and 25°C in the deadend

cell, giving steady state fluxes of around 18 and 150 L/m²h for Starmem™ 120 and 240 respectively, as shown in Figure 6.17.

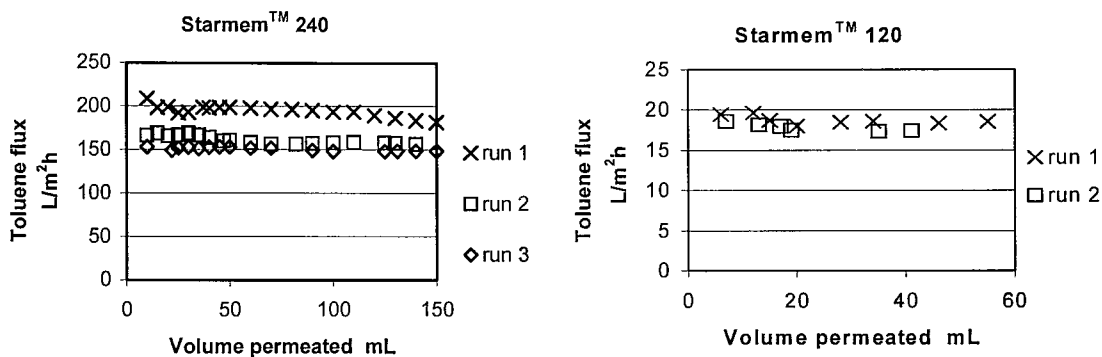


Figure 6.17: Preconditioning of Starmem™ membranes with toluene, at 30 bar and 25°C

The integrity of the membranes was then tested by soaking in a 7.7mM solution of P1oct for different lengths of time and then measuring the rejection of the marker compound, TOABr. The results, shown in Figure 6.18, indicate that Starmem™ 120, for which >99.5% rejection of TOABr is maintained, is stable and Starmem™ 240, which shows a marked decrease in rejection of TOABr, is not stable.

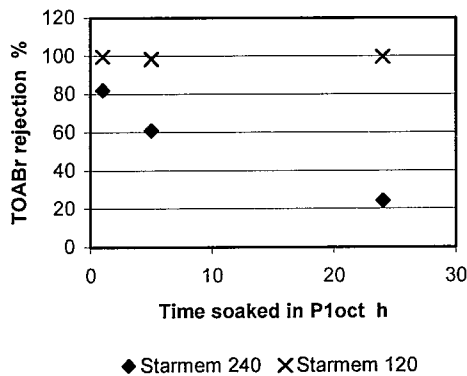


Figure 6.18: Effect on rejection of TOABr of pre-treating Starmem™ membranes in solutions of 7.7mM P1oct in toluene.

Despite the high tolerance to Ploct, the rejection of Ploct with Starmem™ 120 was only 57.14%, with a mass balance of 98.11% and a filtration flux of 5.93 L/m²h. Both the rejection and flux are too low to be practical in the MEDKR process. In conclusion, neither Starmem™ 120 or 240 is suitable for this application.

MPF50, as used earlier in Chapter 2, was also investigated. The membrane has a nominal MWCO of 700, which again is larger than the size of Ploct, but for the same reasons as for Starmem™ 240 it is worth trying. The membrane was first washed with pure methanol to wash out the storage solution of ethanol and water from the pores. It was then preconditioned in the normal way with pure toluene, giving a steady state flux of around 40 L/m²h. Rejections of 69% of TOABr were found both before and after a straight batch filtration of 7.7mM Ploct in toluene, indicating that in the short term, MPF50 is unaffected by Ploct. However, the rejection of Ploct was only 21.1% with a mass balance of 86.4%, showing that MPF50 is unsuitable for this application, where a very high rejection of the phosphazene base is required.

A number of commercial composite membranes based on polydimethyl siloxane (PDMS) are available from GKSS Forschungszentrum (Germany) [147]. These membranes, designed for gas separations, consist of a 2µm active layer of nonporous PDMS on a 70µm microporous support, cast on a 130µm non-woven backing sheet of polyester or polypropylene. The supports readily available are hydrophilic polyacrylonitrile (PAN), hydrophobic polyvinylidene fluoride (PVDF), hydrophobic polyetherimide (PEI) and polyphenylsulfone (PPSu). No information on the nature of PPSu is available. Of these PVDF has a poor solvent resistance and PEI has a good solvent resistance. PAN has a moderate to good base resistance [148], PEI has a good resistance [149], PPSu can withstand strong acid and base attack [150] and the resistance of PVDF to NaOH varies from 10wt% to only pH 13 in the literature [151-153]. The PAN supported membrane was chosen for further investigation as it seemed the most promising in terms of solvent and base resistance. The membrane was preconditioned in toluene in the usual way at 30bar and 25°C, as shown in Figure 6.19. It is interesting to note that this GKSS membrane does not undergo the

reversible compaction exhibited by the Starmem™ series of membranes; the compression of the PDMS polymer chains is permanent.

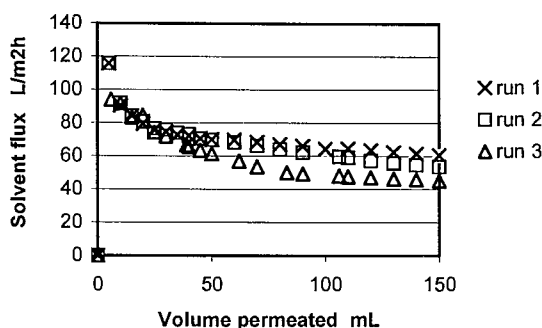


Figure 6.19: Preconditioning of PDMS and PAN membrane from GKSS with toluene, at 30 bar and 25°C.

The initial rejection of TOABr was 97.97%. The rejection of 7.7mM P1oct was then measured by straight batch filtration. The rejection was found to be 70.4% with a mass balance of 80.7%. The rejection of TOABr after permeation of P1oct was 91.6% with a mass balance of 90.4%. The TOABr filtration flux changed from 55.7 to 67.4 L/m²h after permeation of P1oct. During the filtration of P1oct, the permeate became very cloudy and small particles and droplets of a second liquid phase seemed to be permeating the membrane. From this observation, the drop in TOABr rejection (small, but suggestive of a slow degradative process as in the case of toluene and Starmem™ 122) and the increase in solvent flux, it is concluded that the membrane is not stable to P1oct. Also, the rejection of P1oct is too low for the membrane to be useful in this application where a very high rejection is required.

Finally, it is concluded that, what is really required for this project is a new membrane with the required base and solvent stability and filtration characteristics, since none of the commercial membranes readily available has perfect characteristics. On a laboratory scale, to date, investigations into the use of membranes in corrosive environments, such as highly acidic or highly basic conditions, have only been conducted in aqueous media [154, 155]. So, the only solution is to prepare solvent stable membranes with a high base resistance specifically for the MEDKR process. One possibility is the preparation of composite membranes via a dip-coating procedure [156]. The polymer used for coating could be

chosen in order to fine-tune the solvent and base resistance. Preparation of base and solvent stable membranes would be a major part of any extension of this study.

Another possible alternative in this process is to combine the membrane stage with the separation stage. Various authors have reported the use of enantioselective membranes to effect chiral separations [92, 157]: solid membranes made of chiral polymers or liquid membranes. If problems continue with non-chiral membranes, chiral membranes might be investigated.

Although, the work reported in this chapter suggest that the membranes readily available are not perfect for use in this study, StarmemTM 122 seems to offer the best combination of filtration characteristics and solvent / base resistance. As the preparation of new organic stable membranes is outside the scope of this project, at the present time, StarmemTM122 is the only available solution to the membrane problem. Therefore, work will continue using this membrane.

CHAPTER 7

DYNAMIC KINETIC RESOLUTION: MEMBRANE ENHANCED

7.1 MEDKR-I CONFIGURATION

The individual reactions and membrane transport properties for the components of the two chosen systems have now been investigated and it has been showed that, at low concentrations, the yield of product in the one-pot DKR process does not exceed 50%. The MEDKR process can now be employed using these two systems to determine whether the presence of the membrane to separate the catalysts of the racemisation and resolution processes can indeed allow the DKR to reach the maximum yield of 100%.

A continuous rig was designed and constructed for the MEDKR process. A schematic and photograph of the MEDKR rig are shown in Figures 7.1 and 7.2. The main components of the MEDKR rig are the racemisation and resolution reactors. The racemisation reactor, vessel A, is the standard SEPA cell used previously for performing batch nanofiltration experiments, shown in Figure 2.8. Vessel A contains the nanofiltration membrane in order to retain the racemisation catalysts. Vessel A is pressurised using nitrogen gas, which provides the driving force for filtration. The permeate from vessel A (at atmospheric pressure) flows into the resolution reactor, vessel B. Vessel B is a modified SEPA cell, operating at atmospheric pressure, and containing a microfiltration membrane to retain the enzyme for the resolution. Due to the high pressure in vessel A, the permeate will contained some dissolved gas which may come out of solution when back at atmospheric pressure. To prevent build up of this gas in Vessel B, this vessel is operated full and 'upside-down', with the microfiltration membrane at the top so that the gas can pass out of the vessel along with the permeate liquid stream. To ensure good mixing at the surface of the membrane, a shaft was added to the stirrer of the standard SEPA cell so that a second stirring paddle could be added at the top of the cell. This modification is shown in Figure 7.3. The permeate from vessel B flows into vessel C, the solvent reservoir

which is open to the atmosphere in order to allow any gas that has built up in the system to escape. Vessel C is fitted with a condenser to prevent the loss of solvent. All three vessels are stirred with electronic stirrers. Vessels A and B are fitted with thermocouples and the temperature controlled with external temperature controllers.

It is important that the nanofiltration membrane in vessel A is not allowed to dry out, since this will result in cracking, loss of separating power and potential failure. In order to maintain the level of solvent inside vessel A, it is placed on an electronic balance, a Sartorius CP 16001, which monitors the drop in weight as permeation of the liquid inside vessel A through the membrane occurs. This information is transferred to the control computer which turns the pump, a Gilson 305 HPLC pump, on in order to replace the liquid from the solvent reservoir, vessel C. The pump can provide a maximum flow rate of 10mL/min. The computer control system is HPVEE, version 5.01, from Hewlett-Packard. The software samples the balance reading every 0.1 seconds and maintains the weight of vessel A between two limits, the upper and lower setpoint values which are usually set at a spacing of 0.1g.

In order to account for any sort of system failure, the rig is equipped with pressure relief valves. In addition to this, the capacity of vessel C is sufficiently large to hold the entire system volume in the eventuality of membrane failure by cracking or rupturing.

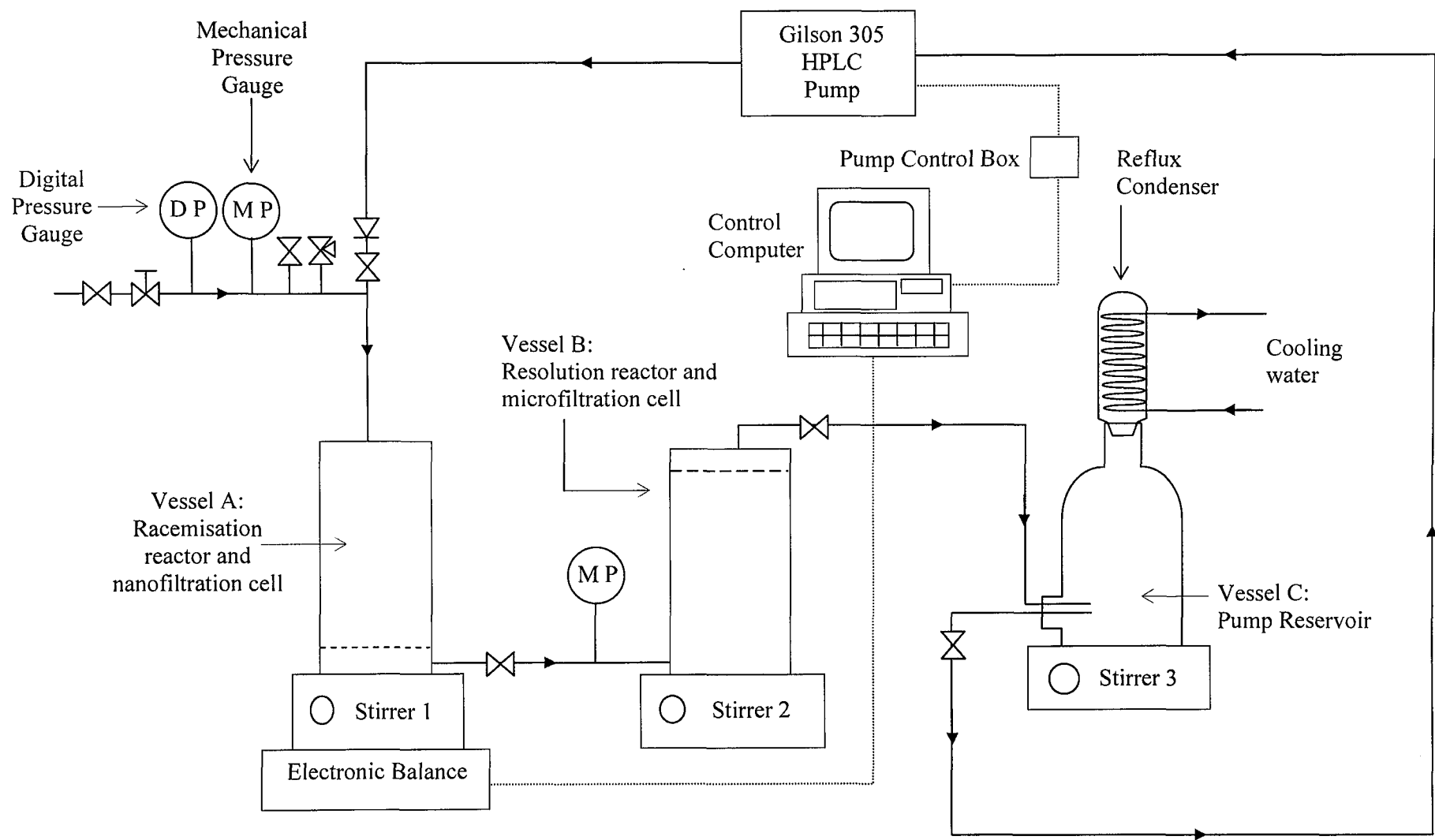


Figure 7.1: Schematic of MEDKR-I rig

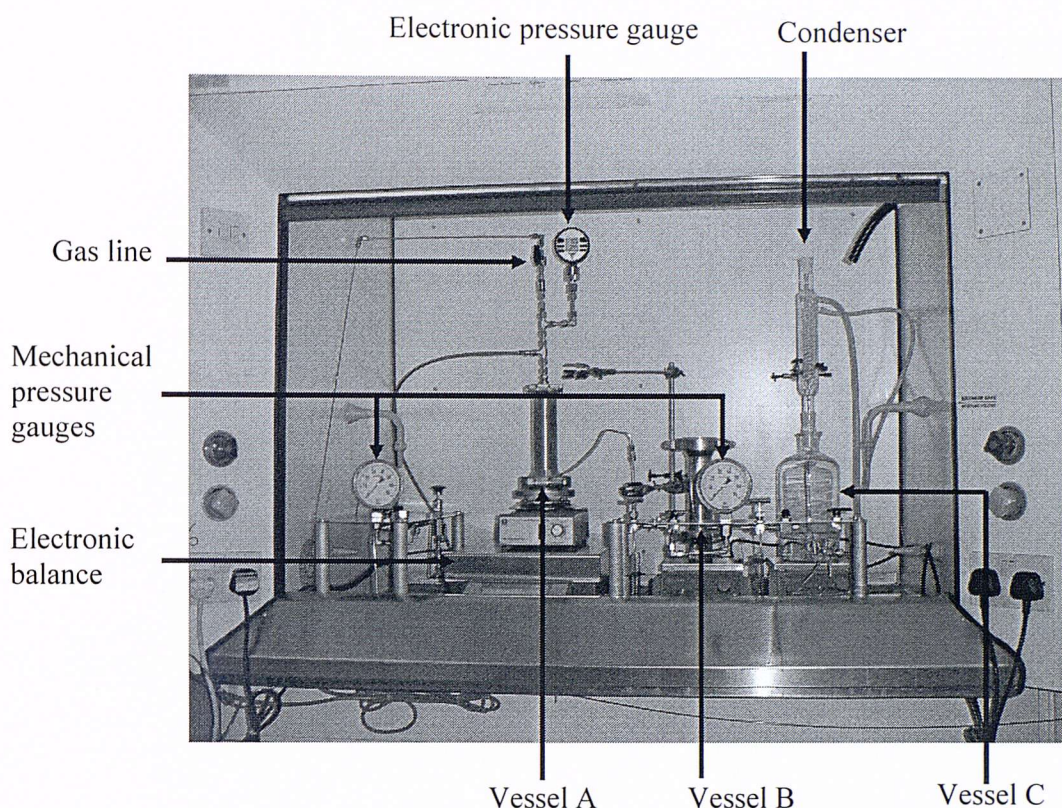


Figure 7.2: Photograph of MEDKR-I rig

The MEDKR rig allows a “one-pot” DKR reaction to be performed continuously with separation of the two catalytic systems. Valves either side of all the vessels allow isolation of the vessels if required. Downstream sampling ports are present on all three vessels so that samples can be taken periodically during the reaction for analysis, so that the progress of the reaction can be monitored. The flux through the nanofiltration membrane was measured during sample collection from vessel A. The computer control system log files give a read out of the balance reading against time. From these files, the average flow rate around the loop can be calculated for each run, thus giving an estimate of the hold up in the rig and the number of passes through the rig per experiment. Details of the method used to calculate the loop flow rate from the computer log files can be found in Appendix VII.

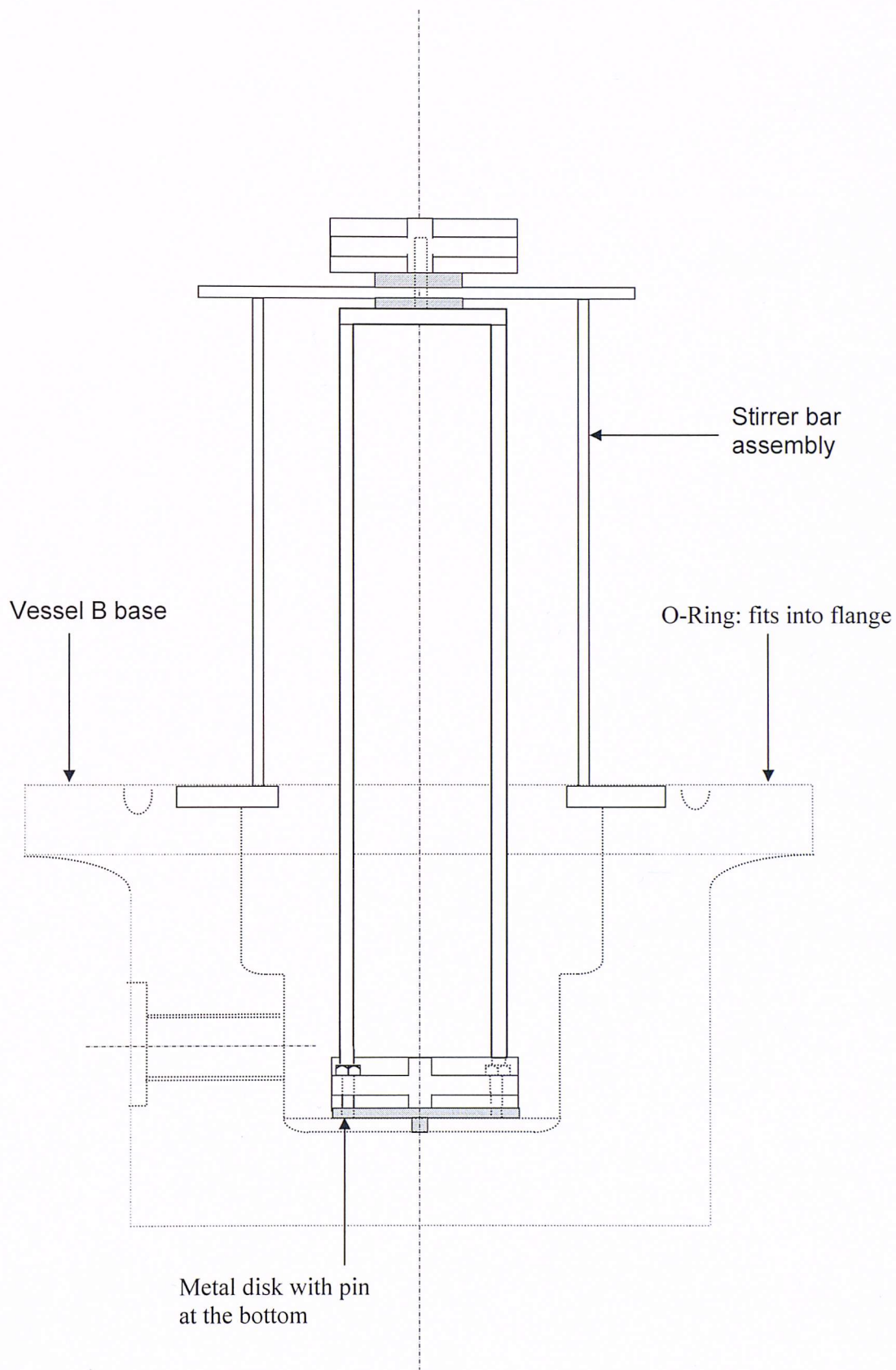


Figure 7.3: Schematic of modified SEPA cell: vessel B.

A number of MEDKR experiments were performed in the MEDKR rig. Details of the experiments are shown in Table 7.1. Concentrations were chosen according to model reactions in the literature. The table shows the initial concentrations, that is at time, $t=0$, of all the reaction species in the three vessels, A, B and C. Since it has been shown already that the rejection of the substrate is very low, it will be assumed that these molecules will be equally distributed around the whole rig, that is, their concentrations are based upon the volume of the whole rig, not just on the volume of the vessel in which they are initially present at the start of the run. Hence, the concentrations of the catalysts (calculated in mole percent of the substrate concentration) are based on this diluted concentration. Experiment 26.2 is an exact repeat of experiment 26.1. Experiment 26.4 was performed 'staggered'. That is, rather than adding all the reactants at the start of the run in the vessels indicated, the biotransformation alone was performed first, before the racemisation catalysts were added, the aim being that a product yield of 50% would be attained with the biotransformation, and then with regeneration of the active isomer of the substrate as a result of the addition of the racemisation catalysts, the yield would increase above 50%.

The reactions were run to completion, that is, until no further change in product yield was observed. The concentrations of the organic species were monitored by gas chromatography, using methods described in sections 5.3.1.1 and 5.3.3.1, during the reaction allowing calculation of the product yield and conversion to unwanted ketone by-product. Some ee's of the substrate alcohol and product acetate were also monitored using HPLC.

Figure 7.4 shows the results of these experiments. The graphs show the product yield (%), yield of ketone (%) and overall mass balance on 1-phenyl ethanol at each sampling time. These were calculated according to equations (5.1), (5.2), (4.1) and (5.3). The graphical results and ee data are summarised in Table 7.2.

Table 7.1: Details of MEDKR-I experiments.

Expt	Vessel	Toluene volume	Stirring speed	T	Substrate	Acyl donor	Additives	Enzyme, novozyme 435	Ru catalyst	Phosphazene base
26.1	A	200ml	4	25 °C				0.3g	1.77mM Ru cymene	4.41mM P1 tris
	B	250 ml	3	25 °C		52.94mM VA (2.4 equiv)				
	C	400 ml	1	N/A	22.06mM 1-phenyl ethanol		22.06mM acetophenone			
26.2	A	200 ml	4	25 °C				0.3g	1.77mM Ru cymene	4.41mM P1 tris
	B	250 ml	3	25 °C		52.94mM VA (2.4 equiv)				
	C	400 ml	1	N/A	22.06mM 1-phenyl ethanol		22.06mM acetophenone			
26.3	A	200 ml	4	25 °C				0.3g	1.77mM Ru cymene	22.1mM P1 oct
	B	250 ml	3	25 °C		43.69mM IPPA (1.30 equiv)				
	C	400 ml	1	N/A	33.61mM 1-phenyl ethanol					

Expt	Vessel	Toluene volume	Stirring speed	T	Substrate	Acyl donor	Additives	Enzyme, novozyme 435	Ru catalyst	Phosphazene base
26.4	A	200 ml	4	25 °C				0.3g	1.77mM Ru cymene	22.1mM P1 oct
	B	250 ml	3	25 °C		43.69mM IPPA (1.30 equiv)				
	C	400 ml	1	N/A	33.61mM 1-phenyl ethanol					
26.5	A	200 ml	4	25 °C				0.3g	1.77mM Ru cymene	22.1mM P1 oct
	B	250 ml	3	25 °C		49.95mM VA (1.48 equiv)				
	C	400 ml	1	N/A	33.75mM allylic alcohol					

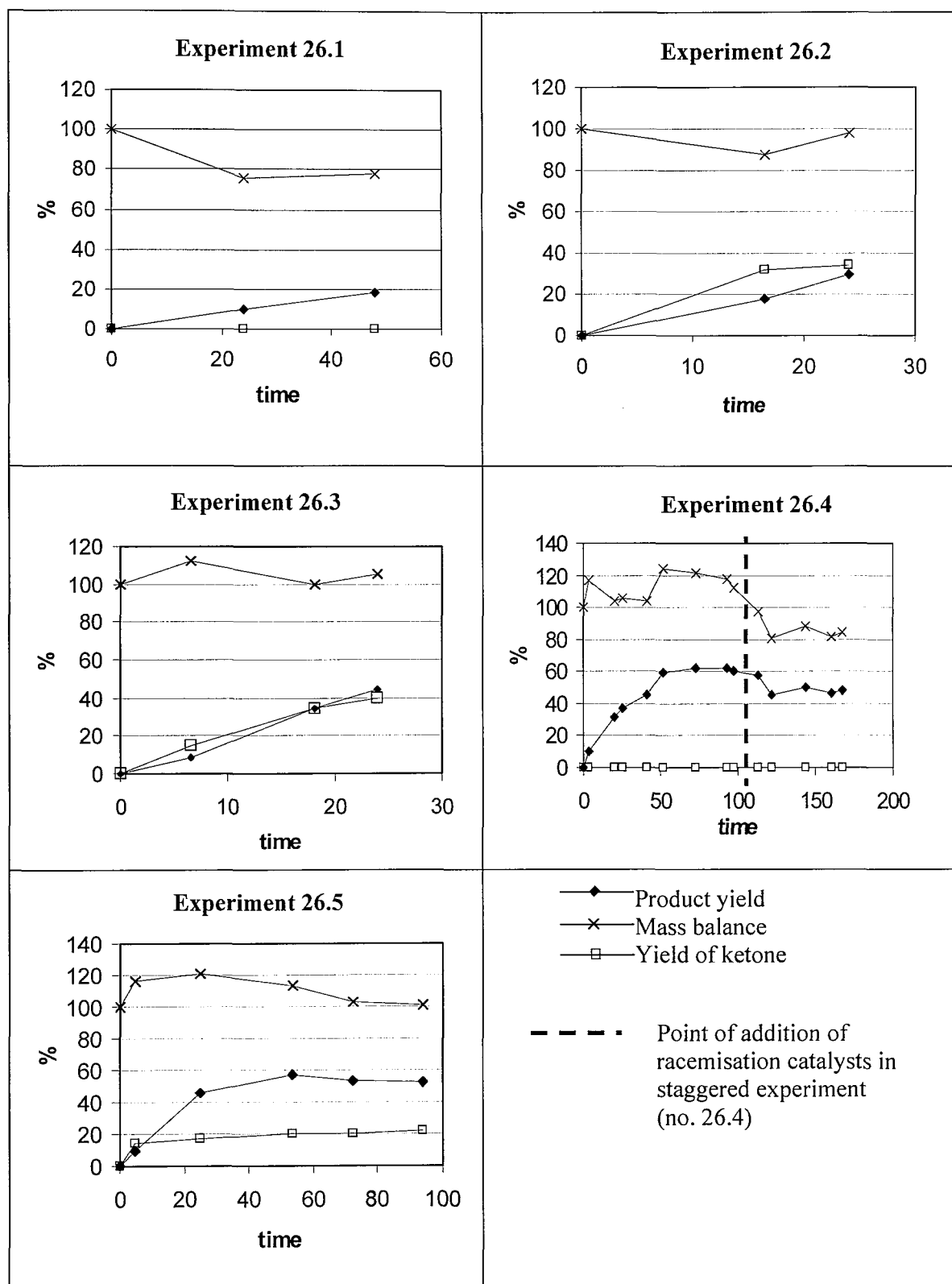


Figure 7.4: Overall results of first configuration rig experiments; experimental details given in Table 7.1.

Table 7.2: Summary of Results of MEDKR-I experiments: first configuration.

	Duration	Final yield of product	Final yield of ketone	Final ee
	Hours	%	%	%
26.1	48	18.3	0	-
26.2	25	29.1	34.2	-
26.3	24	44.8	39.9	See Table 7.3
26.4	90 hr biotransformation	62.2	0	See Table 7.3
	75 hr racemisation	No improvement	0	See Table 7.3
26.5	94	52.3	21.0	See Table 7.3

For Experiments 26.1 and 26.2, 1-phenyl ethanol with vinyl acetate (identical reaction set-ups), low final product yields of ~20% and ~30% were achieved respectively. Despite the identical feeds, no ketone was formed in Experiment 26.1, and ketone was formed to about the same degree as the product acetate in Experiment 26.2. In both cases, the mass balance drops below 100% meaning that there is some material unaccounted for. Experiment 26.3, 1-phenyl ethanol with IPPA, like Experiment 26.2, produces the same quantity of ketone as acetate, around 40%, although in this case, the mass balance stays between 100% and 110%. These results agree with the one-pot reactions discussed in section 5.3.3, supporting the theory that there is some interference between the racemisation and resolution catalysts, preventing either system from working properly. Experiment 26.4, 1-phenyl ethanol with IPPA, run in a staggered mode, achieves a good product yield in the biotransformation stage (>50%), with the mass balance remaining at 100-120%. However, on addition of the racemisation catalysts, no improvement is seen, in fact, the measured product yield deteriorates to below 50% and the mass balance decreases to 80%, indicating that some of the reaction species have been consumed by some unexpected mechanism. Experiment 26.5, allylic alcohol with vinyl acetate produces a 50% yield of product with 20% ketone formed. The mass balance in all cases is between 100-120%.

No enantiomeric excess data is available for Experiments 26.1 and 26.2. The enantiomeric excesses of the remaining alcohol were measured in the three reaction vessels at the end of Experiments 26.3, 26.4 and 26.5. Note the results for Experiment 26.4 are for the end of the whole reaction, that is, after the racemisation catalysts have been added. The ee of the product alcohol was measured in Experiment 26.5. These results are shown in Table 7.3.

Table 7.3: Final ee data for Experiments 26.3, 26.4 and 26.5.

Reaction	Ee of (R) acetate (%)			Ee of (S) alcohol (%)		
	Vessel A	Vessel B	Vessel C	Vessel A	Vessel B	Vessel C
26.3	n/m	n/m	n/m	10.9	18.2	19.9
26.4	n/m	n/m	n/m	97.5	94.7	92.8
26.5	93.0	100.0	100.0	60.5	72.2	56.3

The results indicate that in Experiment 26.5, all the product acetate that is formed is enantiomerically pure, as required. The expected result for the alcohol, is that the ee should be 0% (that is both the R and S isomers are present in equal amounts), if the racemisation catalysts are working properly. That is, the enzyme converts the R alcohol into the R acetate, leaving behind an excess of the S alcohol which should then be racemised immediately resulting in a 50:50 mixture of the R and S isomers again. Experiment 26.3 shows a low alcohol ee, 10-20% in all three vessels. This shows that the racemisation catalysts are having some effect. Experiment 26.4 shows that the alcohol at the end of the reaction is almost entirely the S isomer. Given that for this reaction, a product yield of over 60% was achieved, this is further evidence that the racemisation catalysts in this reaction were completely inactive. The racemisation catalysts in Experiment 26.5 seem to have had some effect – ee's of around 55-70% were measured, but a complete racemisation has not occurred.

In none of the experiments performed in the MEDKR-I rig, has a yield significantly greater than 50% been achieved, indicating no improvement compared with the straight biotransformation or a one-pot DKR reaction. It is possible that the reasons for this are not purely chemical, but more linked to the mechanical set-up of the

MEDKR-I rig, that is poor mixing in the rig might mean that the catalysts and reactants are not exposed to each other sufficiently meaning that a complete reaction is not able to occur. It was therefore decided to alter the rig with the aim of improving the mixing and mass transfer, and ultimately improving the product yields.

7.2 MEDKR-II CONFIGURATION

The MEDKR rig was altered following the reaction results discussed in section 7.1, in order to try to improve the MEDKR reaction. Table 7.4 shows the alterations made, along with justifications for the changes. The racemisation reactor, vessel A, has been scaled up to give a larger membrane area, 54cm^2 compared with 14cm^2 in the old SEPA cell. This larger membrane area allows a higher flux and throughput of material. The resolution reactor, vessel B, has been redesigned to have a smaller volume and good kinetics for the reasons outlined in Table 7.4. A schematic of the new vessel B, the spider cell, is shown in Figure 7.5. The cell, which is like a ‘truncated’ dead end cell with smaller volume, has been designed for numerous potential applications and has eight inlets/outlets. In this application, only one inlet and one outlet are being used, along with one outlet for the thermocouple to allow good temperature control. The other ports are all blocked. The flow in the cell is tangential and the cell contains a large magnetic stirrer bar which should enable good mixing inside the cell. Note that a large vessel C is still used, as in the first configuration rig, although it not operated full but with a volume of only 100mL. It is necessary for vessel C to be capable of containing the entire system volume ($\sim 350\text{mL}$), so that in the eventuality of a nanofiltration membrane failure by, for example, rupture, all the liquid in the system is safely contained. A photograph and schematic of the MEDKR rig are shown in Figures 7.6 and 7.7.

Table 7.4: Differences between the two configurations of the MEDKR rig.

MEDKR-I	MEDKR-II	Justification
Vessel A = SEPA cell	VESSEL A = METCELL	Increases throughput of vessel A by: - increasing cell volume - increasing membrane area
Vessel B = modified SEPA cell, volume = 280mL	Vessel B = “spider cell”, volume = 83mL, good mixing	1. Gives better mixing in vessel B since enzyme kinetics are very dependent on stirring speed 2. Reduces volume of system in order to: - decrease recirculation rate around loop - reduce equilibration time - improve overall system mixing - improve yield and reaction rate
Vessel C run at volume of 300-400mL	Vessel C run at volume of 100mL	Reduces volume of system in order to: - decrease recirculation rate around loop - reduce equilibration time - improve overall system mixing
No control of oxygen levels	Nitrogen line into vessel C for nitrogen blanket	Possibility of running system under oxygen free conditions where air sensitive catalysts are used
Excessively long piping	Pipe volume reduced	Reduces dead volume in system to improve mixing

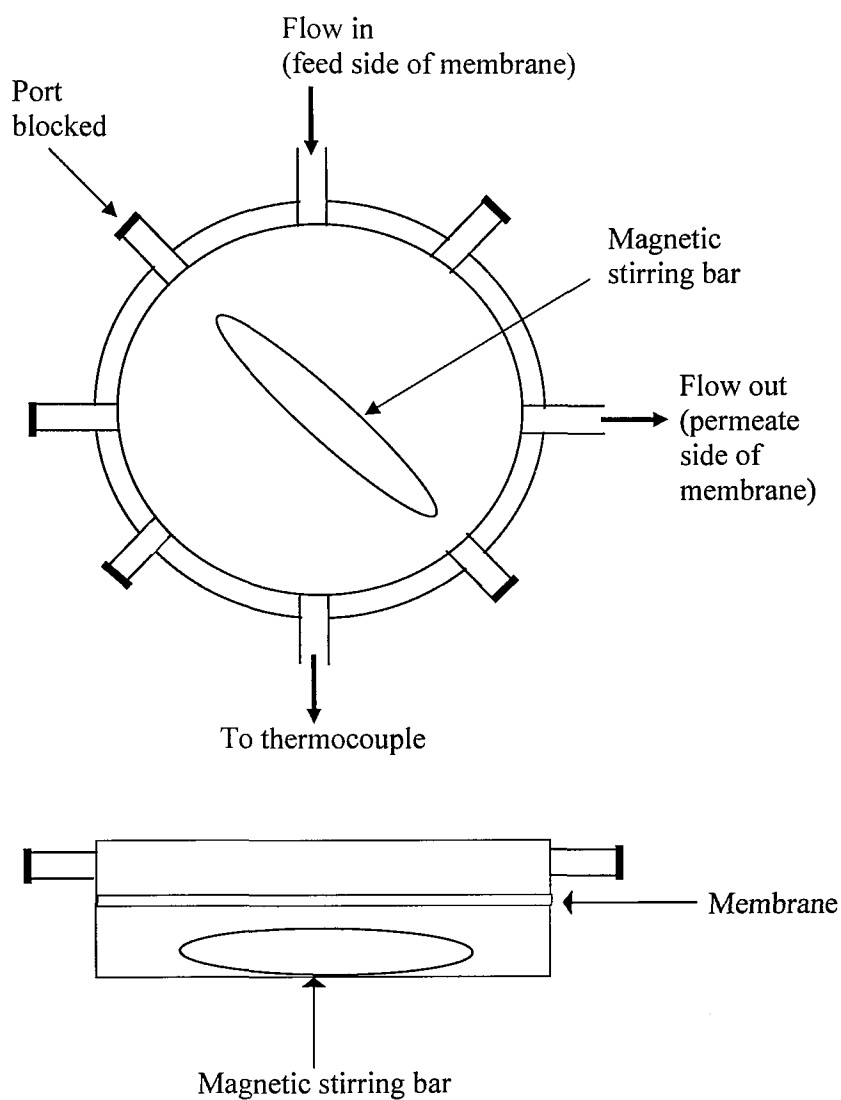


Figure 7.5: Schematic of new resolution reactor, spider cell, vessel B.

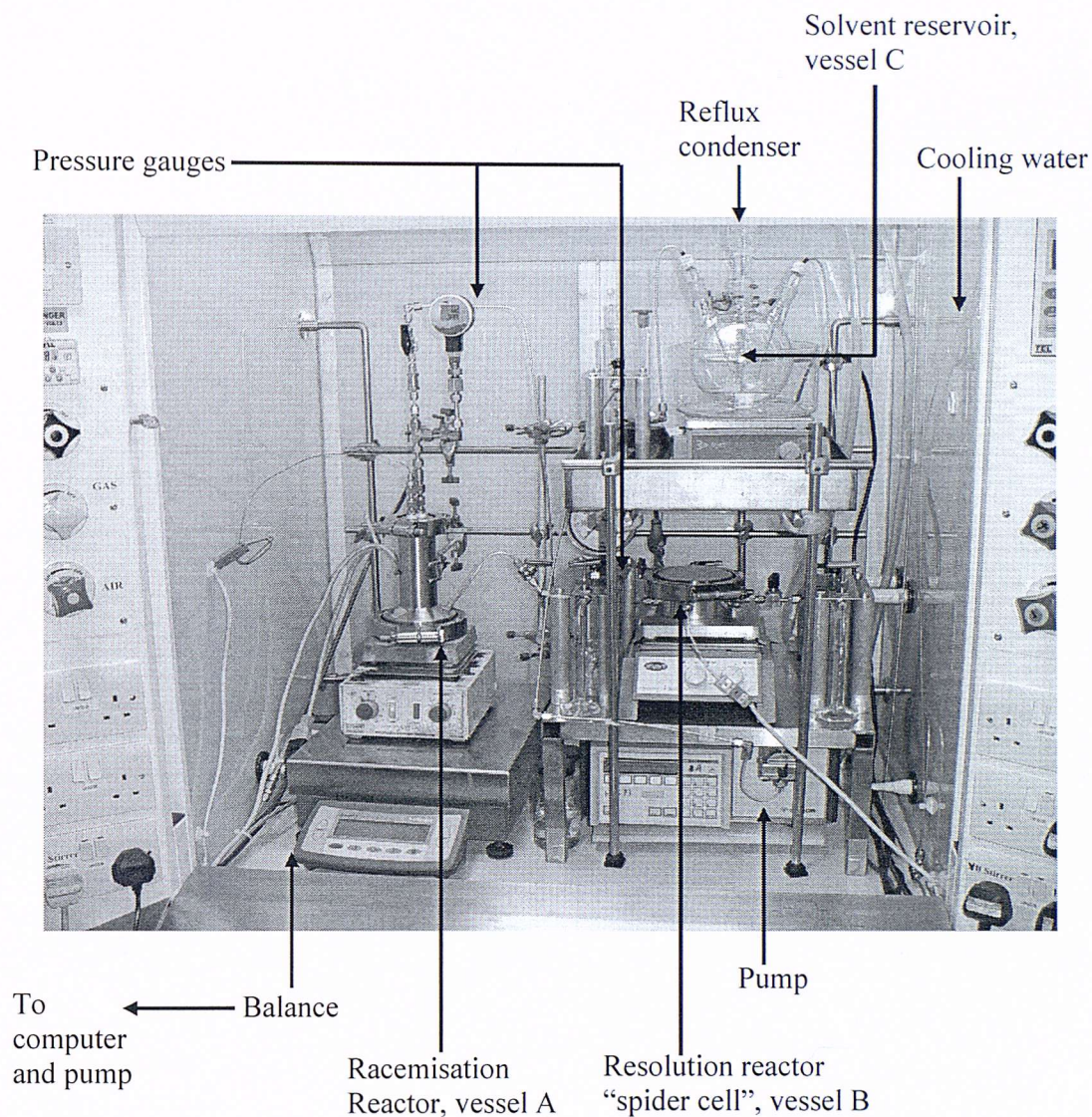


Figure 7.6: Photograph of MEDKR-II rig.

A number of MEDKR experiments were performed in this new, redesigned MEDKR rig. Details of the experiments are shown in Table 7.5. As earlier, the table shows the initial concentrations, that is at time, $t=0$, of all the reaction species in the three vessels, A, B and C, based on a diluted concentration, assuming zero rejection for the organic species. The reactions were run to completion, that is, until no further change in product yield was observed. The concentrations of the organic species were monitored during the reaction allowing calculation of the product yield and conversion to unwanted ketone by-product. Some ee's of the substrate alcohol and product acetate were also monitored.

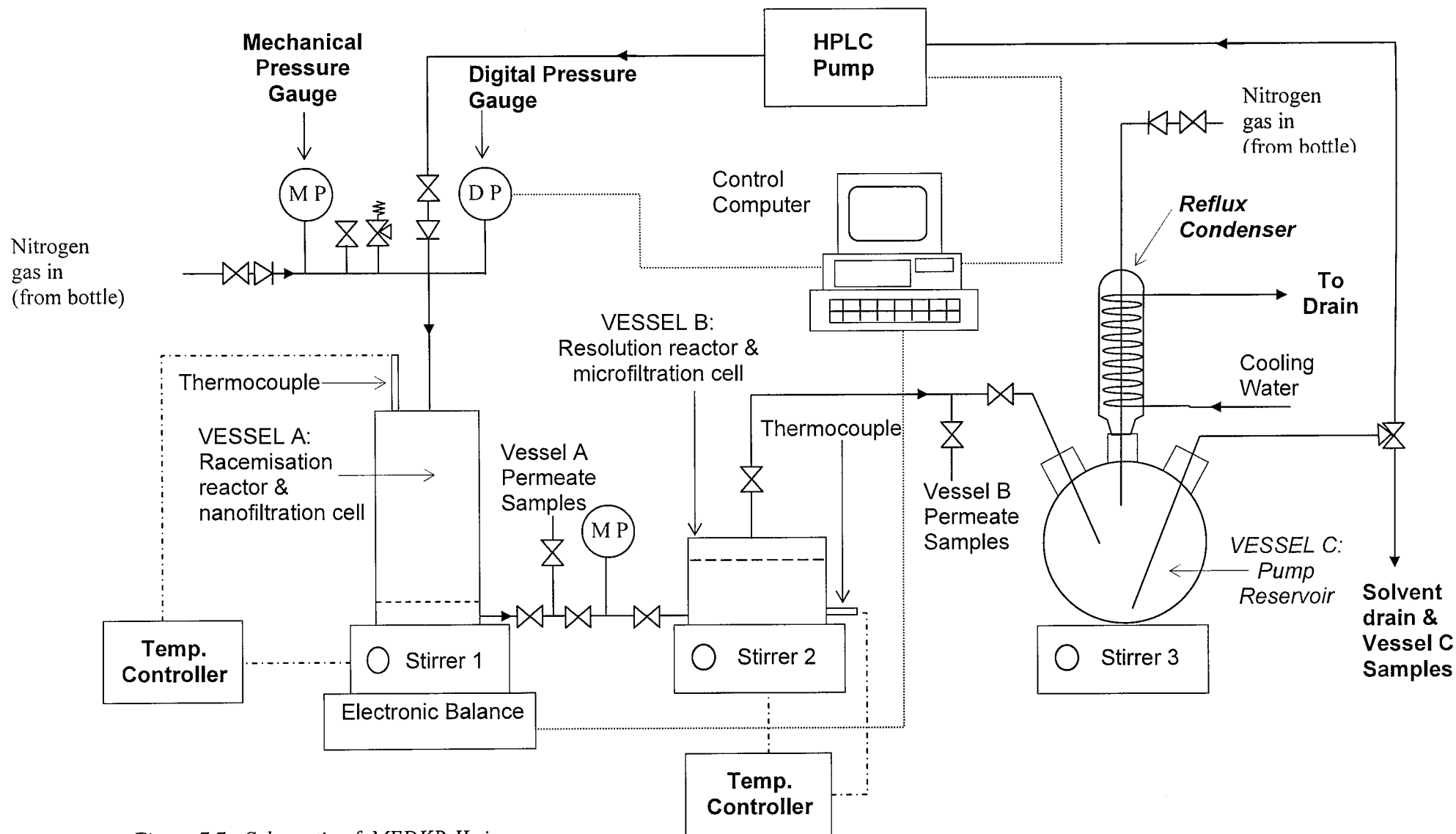


Figure 7.7: Schematic of MEDKR-II rig

Table 7.5: Details of MEDKR-II rig experiments.

Expt	Vessel	Toluene volume	Stirring speed	T	Substrate	Acyl donor	Enzyme, novozyme 435	Ru catalyst	Phosphazene base
27.1	A	150ml	4	25 °C				1.4mM Ru cymene	7.7mM P1 oct
	B	83 ml	3	25 °C		46.9mM VA (1.3 equiv)	0.1g		
	C	100 ml	1	N/A	35.0mM phenyl ethanol				
27.2	A	150ml	4	25 °C				1.4mM Ru cymene	7.7mM P1 oct
	B	83 ml	3	25 °C		46.9mM VA (1.3 equiv)	0.1g		
	C	100 ml	1	N/A	35.0mM phenyl ethanol				
27.3	A	150ml	4	25 °C				1.4mM Ru cymene	7.7mM P1 oct
	B	83 ml	3	25 °C		46.9mM VA (1.3 equiv)	0.9g		
	C	100 ml	1	N/A	35.0mM phenyl ethanol				

Expt	Vessel	Toluene volume	Stirring speed	T	Substrate	Acyl donor	Enzyme, novozyme 435	Ru catalyst	Phosphazene base
27.4	A	50 ml	4	25 °C				0.97mM Ru amino cpd	5.34mM P1 oct
	B	83 ml	3	25 °C		36.44mM IPPA (1.50 equiv)	0.3g		
	C	150 ml	1	N/A	24.3mM phenyl ethanol				
27.5	A	150 ml	4	25 °C				0.97mM Ru cymene	5.34mM P1 oct
	B	83 ml	3	25 °C		36.44mM VA (1.50 equiv)	0.16g		
	C	200 ml	1	N/A	24.3mM allylic alcohol				
27.6	A	150 ml	4	25 °C				0.97mM Ru cymene	5.34mM P1 oct
	B	83 ml	3	25 °C		36.44mM VA (1.5 equiv)	0.16g		
	C	200 ml	1	N/A	24.3mM allylic alcohol				

Expt	Vessel	Toluene volume	Stirring speed	T	Substrate	Acyl donor	Enzyme, novozyme 435	Ru catalyst	Phosphazene base
27.7	A	50 ml	4	25 °C				3.79mM Ru amino cpd	20.85mM P1 oct
	B	83 ml	3	25 °C		142.2 VA (1.5 equiv)	0.48g		
	C	150 ml	1	N/A	94.7mM allylic alcohol				

Experiments 27.1 and 27.2 (identical set-up) are the ‘benchmark’ runs with ruthenium cymene and P1oct. Experiment 27.3 was performed in a four stage ‘staggered’ mode: first the biotransformation was performed in the rig, giving a product yield of 50%, racemisation catalysts were then added, since no improvement was seen, more enzyme and then more racemisation catalysts were added in two subsequent stages. Experiment 27.3 uses three times as much enzyme, to test whether all the catalytic activity of the enzyme had been exhausted. Experiment 27.4 is a benchmark run with ruthenium amino cyclopentadienyl and P1oct. Experiments 27.6 and 27.7 (identical) are further ruthenium cymene and P1oct runs. Experiment 27.7, with Ru amino cyclopentadienyl and P1oct, uses three times the concentrations of all the reactants, compared with the benchmark, Experiment 27.4. This high concentration run was performed with amino cyclopentadienyl rather than ruthenium cymene since the high concentration one-pot reactions with ruthenium cymene produced a high product yield (>90%) anyway, so it would be unlikely that any improvement would be noticed by performing the reaction in the rig.

Figure 7.8 shows the results of these experiments. The graphs show the product yield (%), ketone yield (%) and overall mass balance at each sampling time, calculated as in section 7.2. The graphical results and ee data are summarised in Table 7.6.

Experiments 27.1 and 27.2 (identical runs with ruthenium cymene and P1 oct give similar results: around 20% product yield and a low conversion to ketone, although no ketone was detected at all in Experiment 27.2 compared with a low, but still detectable amount in Experiment 27.1. It seems likely that the ketone measured in experiment 27.1 is due to analytical error, especially since no ketone is detected in any of the subsequent runs. The low yield in Experiment 27.2 may be explained by the poor mass balance for this experiment, which drops to around 60%, indicating that some material was not accounted for in these analyses. Experiment 27.3 shows a 50% conversion in 40 hours for the straight resolution stage. This should be compared with the equivalent resolution stage in the staggered run in the first configuration rig (Experiment 26.4). In this experiment, a 50% product yield was achieved after around 50 hours. Therefore it can be concluded that the combination of a higher enzyme loading with the modified rig increases the reaction rate for the

biotransformation stage to some extent, but only by around 20%. No further improvement in yield is seen on addition of the resolution catalysts in stage 2 or in the subsequent stages. This suggests that the racemisation catalysts are not working *in situ*, confirming the equivalent result in the first configuration rig set-up. Experiments 27.5 and 27.6, also with ruthenium cymene and P1 oct, but with a slightly lower initial substrate concentration produced very different results, 0.5% and 33% product yields respectively. For some reason the enzyme seems to have been deactivated in Experiment 27.5. Experiment 27.6 has a higher product yield compared with Experiments 27.1 and 27.2 (higher substrate concentration), suggesting that concentration effects are important in this system, as found in the one pot systems (see Tables 5.33 and 5.35). This is confirmed with the ruthenium amino cpd system, where a lower yield (about half) of product is obtained in Experiment 27.7 compared with the benchmark Experiment 27.4, in which the concentrations of all the reactants are one third of those in Experiment 27.7.

Table 7.6: Summary of Results of MEDKR-II experiments.

Expt	Duration	Final yield of product	Final yield of ketone	Final ee
	Hours	%	%	%
27.1	30	25	3	See table 7.7
27.2	45	18	0	See table 7.7
27.3 *	40 biotransformation	50	0	See table 7.7
	60 + resolution catalysts	33	0	See table 7.7
	20 + further enzyme	31	0	See table 7.7
	90 + further resolution catalysts	24	0	See table 7.7
27.4	65	33	0	See table 7.7
27.5	45	0.5	0	n/m *
27.6	40	35	0	See table 7.7
27.7	34	17	0	See table 7.7

* It was not possible to measure any product ee's for this experiment since the product yield was so low (<1%) as to be undetectable by HPLC.

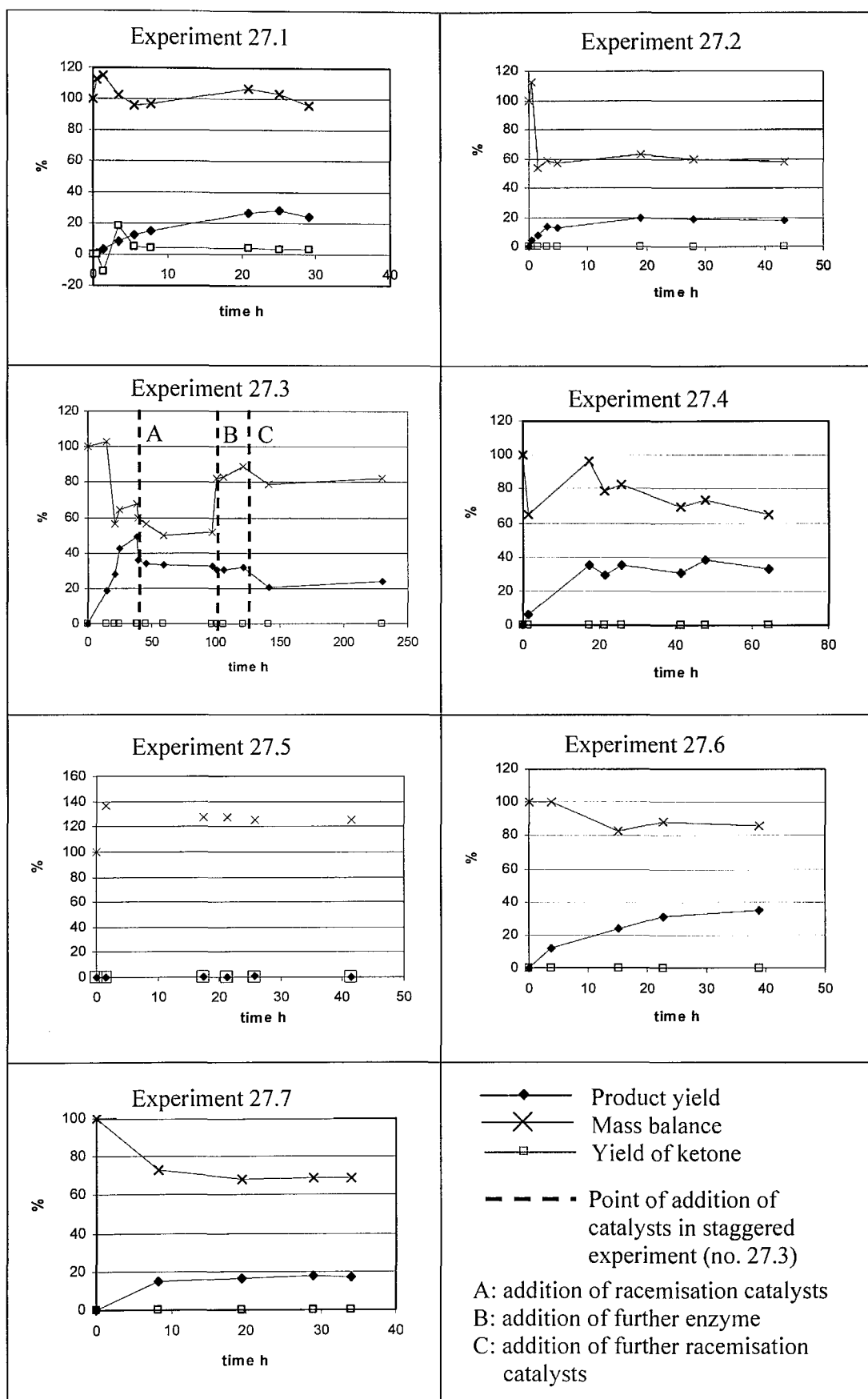


Figure 7.8: Results of MEDKR-II experiments; experimental details are given in Table 7.5

The ee data for these reactions is shown in Table 7.7. As discussed earlier, the expected result for the alcohol, is that the ee should be 0% (that is both the R and S isomers are present in equal amounts), if the racemisation catalysts are working properly. The acetate should be formed in its pure, 100% R form, since the enzyme should only metabolise the R alcohol, converting it to the R acetate.

Table 7.7: Final ee data for reactions 27.1-4, 27.6, and 27.7.

Reaction		Ee of (S) alcohol (%)			Ee of (R) acetate (%)		
Vessel		A	B	C	A	B	C
27.1		36	0	28	49	15	25
27.2		54	43	7	82	94	0
27.3	Stage 1 Biotransformation	0	46	97	78	91	99
	Stage 2 + resolution catalysts	14	15	76	95	100	97
	Stage 3 + further enzyme	64	n/m	n/m	97	n/m	n/m
	Stage 4 + further resolution catalysts	100	n/m	n/m	100	n/m	n/m
27.4		3	n/m	100	93	100	100
27.6		32	100		100	100	100
27.7		0	n/m	69	100	100	100

The data shows that, with the exception of Experiment 27.1, the product R acetate is formed at a high enantiomeric purity, >90% in most cases. Experiment 27.1 is very different from the other experiments suggesting a problem with the analysis in this case. The S alcohol data seems somewhat random. After vessel A, the racemisation reactor, the ee should be zero, yet the results show it varying from 3% to 100%. After vessel B, the resolution, the composition of the alcohol should be 100% S isomer, yet the results show the ee varying from 15% to 100%. These results indicate that, either the racemisation is not working correctly, or that there is a problem with the analysis.

The possibility of the phosphazene base leaking out of vessel A and contaminating vessels B and C was considered in Experiment 27.1. The concentration of Ploct in vessel C was measured throughout the Experiment. The results are shown in Figure 7.9. The figure clearly demonstrates that the Ploct is not being well contained within vessel A since at the end of the experiment a concentration of 5.5mM was measured in vessel C. This is contrary to the results in Chapter 6 where an average rejection of 99.6% was obtained for Ploct (Table 6.2). This suggests that the strong base could be causing the membrane to loose its integrity over the course of the experiment, hence the increasingly poor rejection. The permeation of Ploct around the MEDKR rig will affect the resolution reaction by interfering with the enzyme in vessel B. This will require further investigation.

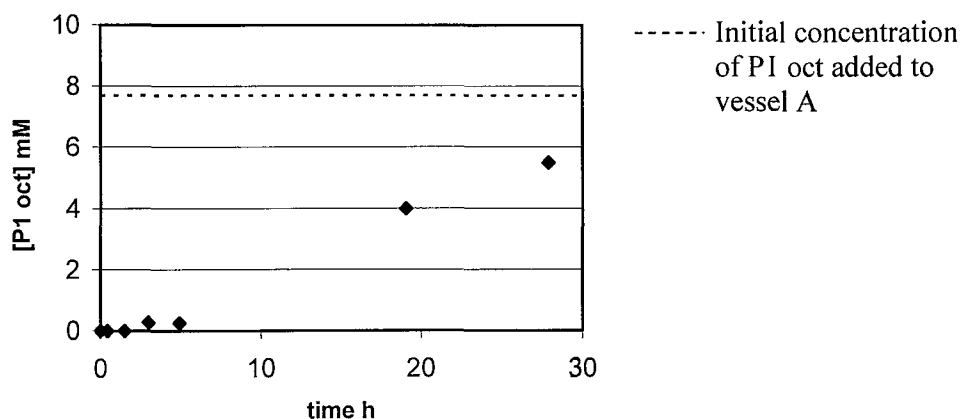


Figure 7.9: Concentration of Ploct in vessel C in experiment 27.1: MEDKR of phenyl ethanol with VA, novozyme 435, Ru cymene and Ploct in toluene.

7.3 Further investigations

The chemical problems with MEDKR have been discussed in Chapters 5 and the earlier parts of this chapter. The conclusion from the MEDKR rig reactions is that none of the experiments produced a product yield significantly greater than 50%, indicating no improvement compared with the straight biotransformation or a one-pot DKR reaction. Initially, it was thought that this might have been linked to the mechanical set-up of the MEDKR rig, that is, poor mixing in the rig might have

prevented the MEDKR from going to completion. However, the rig was altered to improve the mixing, and the results were not improved. From this, it is concluded that the catalysts are not working *in situ*, since in most cases, a yield of not even 50% is achieved, which would be expected in the benchmark individual resolution.

Examination of the individual reactions (section 5.3) shows that the racemisation is the more challenging of the two steps of a DKR. Even when the racemisation is performed alone, it is still not always possible to obtain good results, whereas good results are obtained when the resolution is performed alone. Initially, it was expected that the major problem in a one-pot DKR would be the base from the racemisation system interfering with the enzyme and preventing the resolution from working properly, hence the fact that large bases such as the Ploct or TOA have been used which can be adequately retained by the membranes available. However, the racemisation results indicate that the products of the resolution are likely to have as great an effect on the racemisation as the base has on the resolution. This is likely to be an unsolvable problem, since the current state of materials science means that it is not possible to create membranes which have such a finely tuned selectivity that they are capable of separating species with molecular weights as close as the substrates and products of these DKR reactions. The only option with these systems would be to find some way of extracting the product from the resolution reactor as soon as it is formed so that it cannot pass back into the racemisation reaction. The chemical reactivities and physical properties of the secondary alcohols and acetates are similar, so this is unlikely to be possible.

Although interference from the resolution system is the most likely explanation for the racemisation not working *in-situ*, other factors have been changed in the MEDKR rig compared with the individual reactions in the reaction carousel. The presence of the membrane itself, the change of vessel (from small glass reaction tubes in the carousel to larger stainless steel METcell in the MEDKR rig) and the application of pressure in the MEDKR rig. These will be investigated in order to eliminate them as potential problems in this process.

Firstly, standard 'benchmark' racemisations of S 1-phenyl ethanol were performed in the reaction carousel, containing small pieces (27x29mm) of the membrane,

StarmemTM 122. This is to test whether the racemisation is affected by the presence of the membrane. Since the racemisation reactant P1 oct is observed to degrade the membrane polymer, there is a possibility that one of the degradation products of this mechanism could be inhibiting the racemisation reaction. The reactions were performed in duplicate, under argon and at 25°C with 25mL toluene, 33.49mM S 1-phenyl ethanol, 4mol% Ru cymene and 20mol% P1 oct. The reactions were allowed to continue for 24 hours. The results are given in Table 7.8.

Table 7.8: Results for racemisations of S 1-phenyl ethanol with ruthenium cymene and P1 oct in the presence of membrane StarmemTM 122.

Experiment	Ee of alcohol	Conversion to ketone
	S %	%
31.1	22.0	7.9
31.2	17.8	4.1

In both repeats of this experiment, a reasonable racemisation was observed with a low conversion to ketone. In conclusion the membrane does not affect the racemisation and therefore can be eliminated as a potential reason for the racemisation not working in the MEDKR rig.

Next the possibility of the change of reaction vessel being responsible for the racemisation not working *in-situ* will be investigated. There are two possibilities here: that the stainless steel material of the METcell interferes with the reaction or that the hydrodynamic conditions / different stirring regime in the METcell and the scale up in terms of reaction volume (150mL in the METcell compared with 25mL in the reaction carousel) prevent the reaction going to completion. A racemisation of S 1-phenyl ethanol was performed in the METcell (with no membrane present) under argon and 25°C using 150mL toluene, 33.48mM S 1-phenyl ethanol, 4mol% Ru cymene and 20mol% P1 oct. The reaction was allowed to continue for 24 hours. No ketone was formed in the reaction and the final ee of S alcohol was 72.3%. Some racemisation occurred, but at a slower rate than in the reaction carousel tubes where the volume is smaller and the stirring is better. This suggests that the system suffers from mass transfer limitations when scaled up. The rig could be modified to use

smaller volumes, but this would limit the scope severely to a very small throughput of material, which since the reaction times are so long, would be inconvenient if one wished to synthesise a reasonable quantity of product.

The final factor to be tested is whether the application of pressure in the MEDKR rig affects the racemisation. It is possible that there is a pressure effect since pressure effects on asymmetric hydrogenation reactions have been reported [158] and the racemisation in the systems investigated in this study is suspected to proceed via a hydrogenation step. A racemisation of S 1-phenyl ethanol was performed in the METcell, as detailed above, but under a pressure of 30bar. Again the reaction was allowed to continue for 24 hours. As before, no ketone was formed in the reaction and the final ee of S alcohol was 93.5%: virtually no racemisation has occurred. This suggests that a major factor contributing to the failure of the racemisation in the MEDKR rig is application of high pressure. This is a major problem, since the filtration through the OSN membrane will not occur under atmospheric pressure. The only solution would be to perform the racemisation under atmospheric pressure and then after a complete racemisation had occurred, perform the separation under pressure. However, this would prevent the process operating continuously. Instead a multi-stage process of sequential racemisations, filtrations and resolutions would be required, which would be very labour intensive and slow.

7.4 Basic MEDKR rig model (both rig configurations)

A mathematical model to describe the system in terms of basic flow rates will be developed. This will allow predictions of parameters such as the basic loop flow rate, equilibration times to reach steady state and hold up times, all of which are important for experimental design for the full MEDKR reactions. The model will be verified with experimental data.

Figure 7.10 shows a simplified diagram of the MEDKR rig which will form the basis of a model to describe how the system components move around the system in the absence of chemical reaction. Note that vessel C is neglected in this analysis on the

grounds that the microfiltration membrane causes no resistance to the permeation of any of the components of the system (except for the enzyme, which it retains), hence the volumes of vessels B and C can be combined mathematically. This is a valid assumption since the rejection of the components of the system through the microfiltration membrane is negligible.

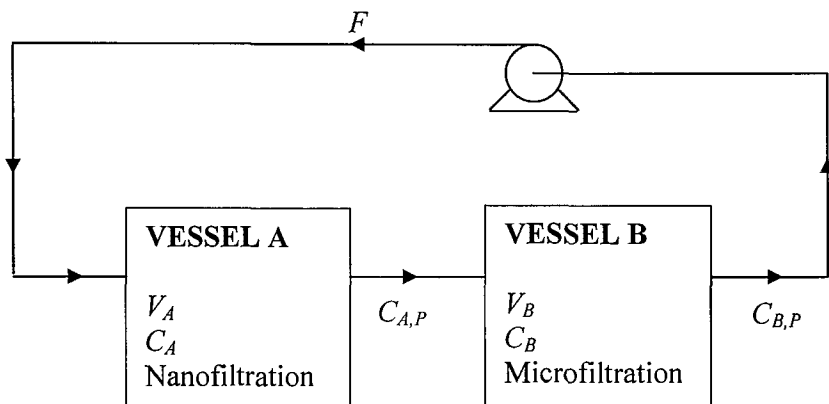


Figure 7.10: Simplified diagram of MEDKR rig.

The model will be based on a ‘pulse’ of a single reactant component added to vessel A at the start of the experiment, that is, the system’s initial conditions are:

$$t = 0 \quad C_A = C_{A0}$$

$$t = 0 \quad C_B = C_{B0} = 0$$

The following assumptions are made:

1. Rejection is constant with time
2. The flow around the loop is constant with time
3. Vessel B is well mixed
4. Connecting pipes have negligible volume
5. There are no interactions between the system components

Mass balances are performed overall and separately on vessels A and B and expressions for the membrane rejection are incorporated. Details of the model derivation are given in Appendix VIII. The model consists of the set of equations (7.1) to (7.4) in the following parameters V_A , V_B , M_{total} , $C_{A,0}$, F , R_A , and R_B .

$$M_{total} = C_{A,0}V_A + C_{B,0}V_B = C_A V_A + C_B V_B \quad (7.1)$$

$$R_i = 1 - \frac{C_{i,P}}{C_i} \quad (7.2)$$

where i corresponds to vessel A or B.

$$C_A = \frac{1}{x} \left[y + (xC_{A,0} - y) \exp \left\{ -\frac{Ftx}{V_A} \right\} \right] \quad (7.3)$$

$$C_B = \frac{M_{total} - V_A C_A}{V_B} \quad (7.4)$$

The concentration in vessel C, as discussed above, can then be assumed to be equal to the concentration in vessel B.

7.4.1 MEDKR-I

1-Phenyl ethanol was used as the test compound for this basic model. The parameters for the system are given in Table 7.9. The results are shown in Figure 7.11.

Table 7.9: Parameters for basic MEDKR model, for 1-phenyl ethanol.

Parameter	Value	Unit
V_A	100	mL
$V_B (=V_B+V_C)$	250+400 = 650	mL
M_{total}	0.0036	Moles
$C_{A,0}$	33.6	mM
F	3.8	mL/min
R_A	2.9	%
R_B	1.0	%

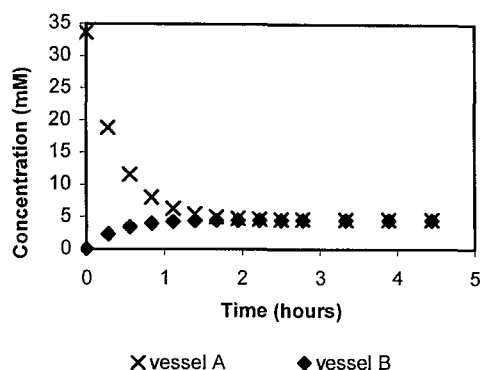


Figure 7.11: Concentration profile in vessels A and B for 1-phenyl ethanol around MEDKR-I rig following initial condition $[1\text{-phenyl ethanol}]_{\text{vessel A}} = 33.6\text{mM}$ and $[1\text{-phenyl ethanol}]_{\text{vessel B}} = 0$.

The figure shows that the concentrations should equilibrate after around 2 hours. The equilibrium concentration is 4.5mM which is the diluted concentration of 1-phenyl ethanol accounting for the increase in volume in the rig compared with vessel A, due to the presence of vessels A and C.

7.4.2 MEDKR-II

As for the MEDKR-I, the basic model can be used to predict the mass transfer characteristics of the system. As before, phenyl ethanol was used as the test compound. The parameters for the system are given in Table 7.10. The results are shown in Figure 7.12. Because of the volume reduction, the model should predict a faster equilibration time.

Table 7.10: Parameters for basic MEDKR model, for 1-phenyl ethanol.

Parameter	Value	Unit
V_A	100	mL
$V_B (=V_B+V_C)$	83+200 = 283	mL
M_{total}	0.0036	Moles
$C_{A,0}$	33.6	mM
F	3.8	mL/min
R_A	2.9	%
R_B	1.0	%

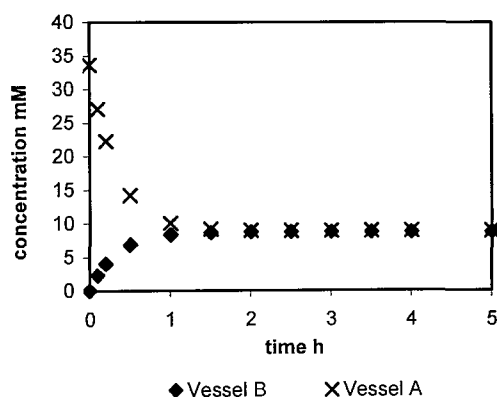


Figure 7.12: Concentration profile in vessels A and B for 1-phenyl ethanol around MEDKR rig following initial condition $[1\text{-phenyl ethanol}]_{\text{vessel A}} = 33.6\text{mM}$ and $[1\text{-phenyl ethanol}]_{\text{vessel B}} = 0$.

The figure shows that the concentrations should equilibrate after around 2 hours. The equilibrium concentration is 8.8mM, compared with 4.5mM (see Figure 7.11) in the first configuration rig. This difference is due to the difference in overall volume of the two rigs: 383mL compared with 750mL.

In order to check that the model gives sensible results, simulations using a different test molecule were run: a hypothetical catalyst molecule of rejection $R_A = 99\%$ and

$R_B = 50\%$. The results, shown in Figure 7.13, as expected, show that the catalyst should remain in vessel A throughout the experiment.

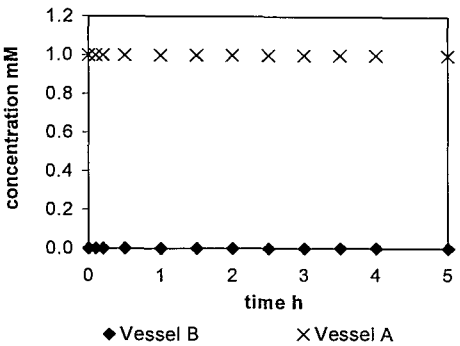


Figure 7.13: Concentration profile in vessels A and B for hypothetical catalyst molecule around MEDKR rig following initial condition $[catalyst]_{vessel\ A} = 1\text{mM}$ and $[catalyst]_{vessel\ B} = 0$.

Single component “pulse” tests using the standard concentrations of phenyl ethanol ($33.6\text{mM} = 0.00336\text{g/L}$) were run in the rig in order to establish the validity of the mathematical model. The rig set-up is shown in Table 7.11. The pump flow rate was set at 10mL/min . The nanofiltration membrane was preconditioned prior to use, as usual. The test was performed twice (experiments 28 and 29) to determine the repeatability of the data. The results are shown in Figures 7.14 and 7.15.

The data shows for both experiments 28 and 29 that the rig should be well mixed (that is equilibrated concentration profiles for the three vessels) in under two hours, as predicted by the model. The overall average loop flow rate was 3.93mL/min for the first experiment and 5.34mL/min for the second. These values are quite different suggesting that the system is not stable yet. The model describes the data reasonably well except for the initial start up period. An initial ‘surge’ in the concentrations in vessels B and C is observed at in the first hour of the experiment (especially pronounced in the first experiment, Figure 7.14), which is not predicted by the model. This is due to an initial holdup in vessel A at start up. The solutes pass through the membrane after this initial time lag, causing the surge in concentration in

vessels B and C which then falls again to the steady state equilibrium value due to dilution in vessels B and C. However, further experiments could be done, since the repeatability is not good between experiments 28 and 29.

Table 7.11: MEDKR rig set-up for mass transfer model verification.

Vessel	Type	Vol. mL	T °C	P Bar	Stirring speed	Solution	Membrane
A	METcell	150	20	30	4	“Feed”: 0.034M 1-phenyl ethanol + 0.00145M Ru cymene* in toluene	Starmem TM 122
B	Spider cell	83	20	N/A	3 / 4.5	Pure toluene	MF
C	Glass vessel	100	N/A	N/A	1	Pure toluene	N/A

* Ruthenium cymene was required to reduce the flux through the nanofiltration membrane which, otherwise, would be too high to allow the pump to control the loop flow.

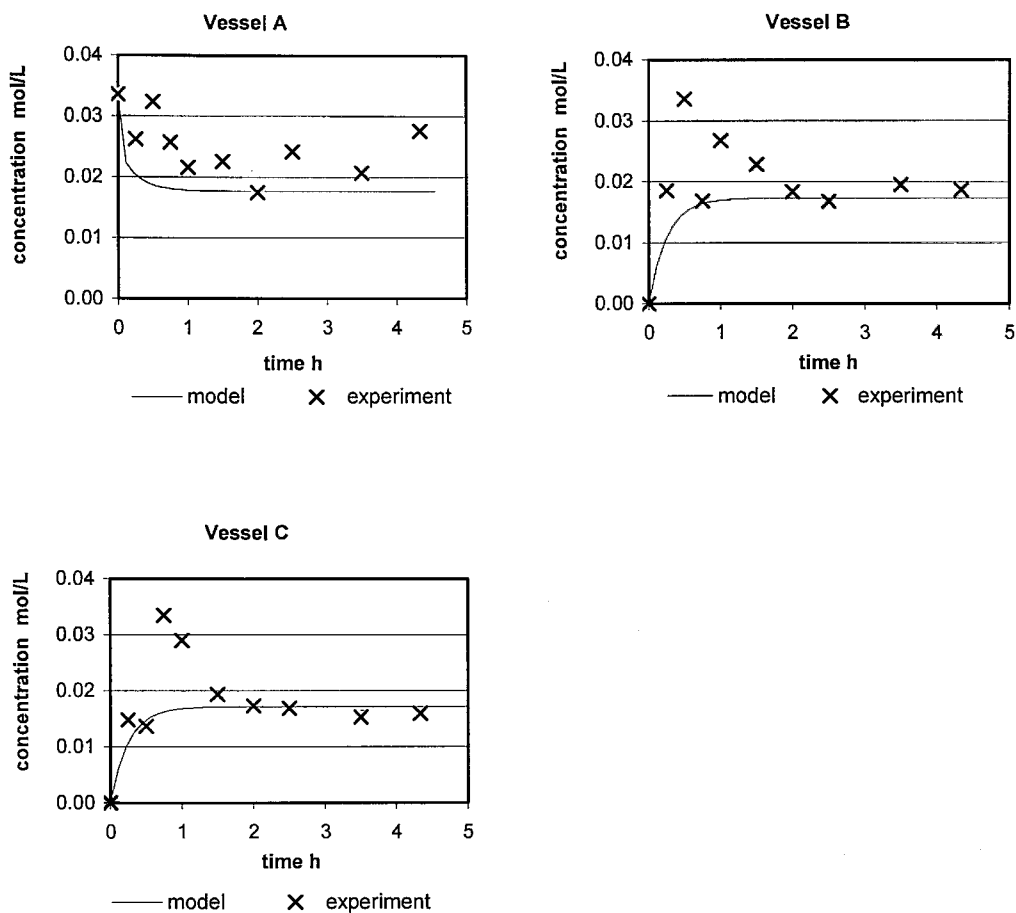


Figure 7.14: Comparison of model and experimental data for 1-phenyl ethanol “pulse” experiment. Experiment 28.

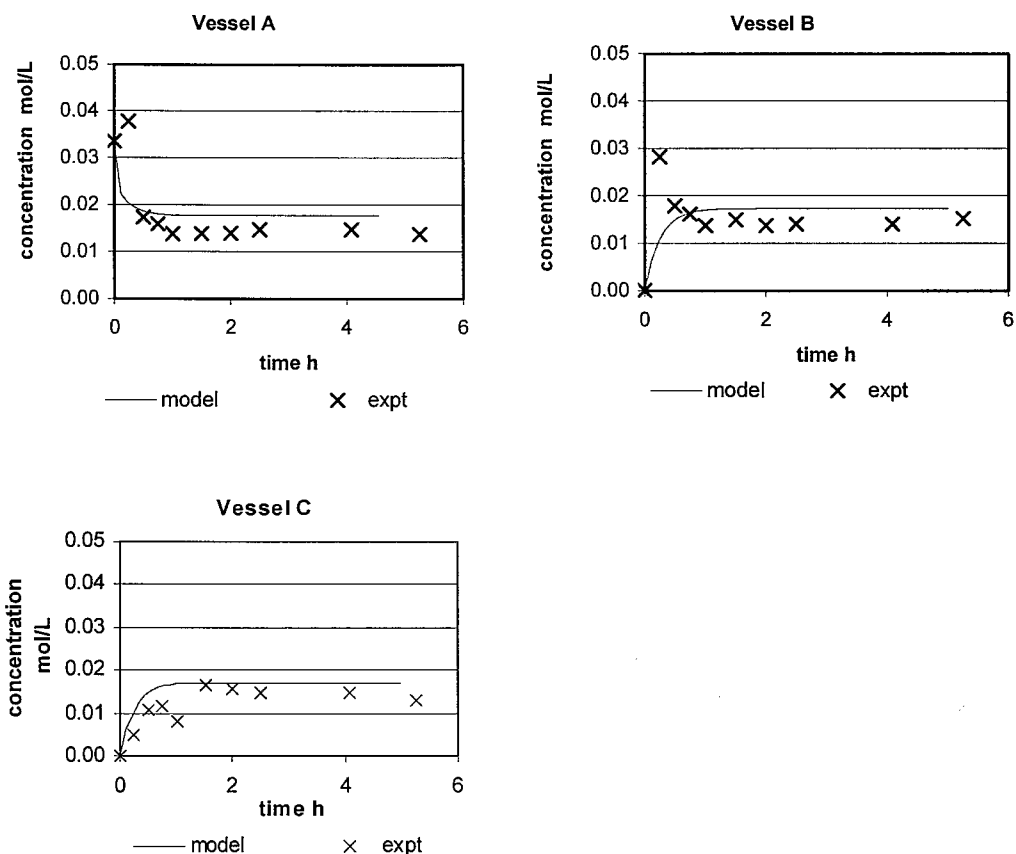


Figure 7.15: Comparison of model and experimental data for 1-phenyl ethanol “pulse” experiment. Experiment 29: repeat of 28.

Another useful modelling exercise for comparison with real data from the MEDKR rig is to calculate the basic hold-up in the rig and the number of passes through the rig that occur during an average experiment. For the MEDKR-I configuration (total volume = 750mL), for a loop flow rate of 3.8mL/min, the hold up in the rig is 3.3 hours, and in an average experiment of length 48 hours, there are 14.6 passes through the rig. For the MEDKR-II configuration (total volume = 433mL), for the same flow rate of 3.8mL/min, the hold up is 1.9 hours and the number of passes through the rig is 25.3. These figures demonstrate the advantages of the second rig configuration – better mixing will be achieved and hence faster reaction rates due to the higher number of passes through the rig during the experiment.

7.5 Full MEDKR rig model

Mathematical modelling can be used in order to describe and predict the behaviour of the MEDKR rig in terms of concentration profiles. The model will consist of the modelling of the mixing behaviour along with the chemical kinetics of the DKR process. Before, combining the physical and chemical models, the chemical behaviour will be examined separately, that is the one-pot reaction kinetics only, with no mass transfer effects. Initially, a one-pot system is assumed to describe the DKR process, characterised following variables and parameters. Later the MEDKR process with its three vessels will be described.

Variables:

C	concentration
t	time

Parameters:

V	reactor volume
k	rate constant

The following subscripts will be applied:

S	S isomer of racemic substrate
R	R isomer of racemic substrate
P	product
rac	racemisation
enz	enzymatic reaction

The following assumptions are made:

1. Reaction vessel is well mixed
2. Components of the system do not interact
3. Enzyme obeys first order kinetics

This is justified so long as the substrate concentration is low, that is, $[S] \ll K_m$.

4. Product is stable: reaction forming product is irreversible; product is not itself racemisable
5. There are no side products
(likely to be untrue, but model can be extended to account for side products later)

6. Enzyme is active only on the R isomer
7. Forward and backward rate constants for racemisation are equal

The initial conditions, at $t = 0$, are

$$C_S = C_{S,0} \quad \text{For a racemic feed, } C_{S,0} = C_{R,0}$$

$$C_R = C_{R,0}$$

$$C_P = 0$$

For simplicity, the system will be considered as a single reactor, as shown in Figure 7.16.

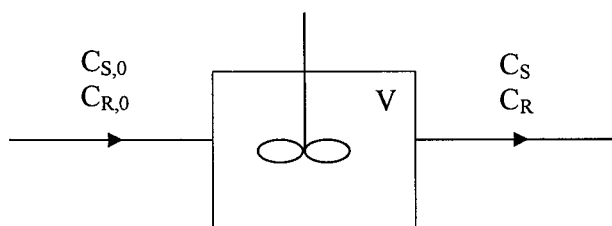


Figure 7.16: Schematic of simple one-pot DKR

A simplified chemical reaction scheme is used, assuming that no side products are formed, as shown in Figure 7.17.

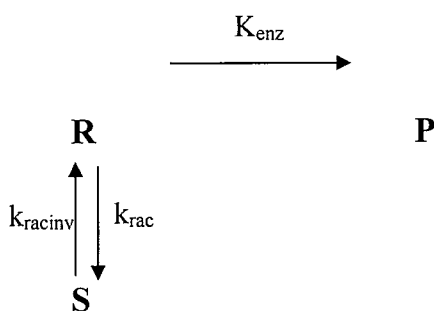


Figure 7.17: Simplified chemical reaction scheme for one-pot DKR

The model is derived by performing mass balances on each component (R and S enantiomers of the substrate and product) over the reactor, shown in Figure 7.16 and applying the chemical kinetics, outlined in Figure 7.17.

Mass balance on component S:

rate of accumulation = flow in – flow out + generated – consumed

$$\frac{dC_S}{dt} = k_{rac}C_R - k_{racinv}C_S \quad (7.5)$$

Mass balance on component R:

$$V \frac{dC_R}{dt} = V k_{racinv}C_S - V k_{rac}C_R - V k_{enz}C_R \quad (7.6)$$

Mass balance on component P:

$$\frac{dC_P}{dt} = k_{enz}C_R \quad (7.7)$$

This given a solvable system of 3 equations (7.5 - 7.7) and 3 unknowns C_S , C_R , and C_P , subject to the parameters k_{rac} , k_{racinv} and k_{enz} .

For preliminary simulations, the 1-phenyl ethanol, IPPA, ruthenium cymene, Pl oct, novozyme 435 system was chosen. Data from individual racemisation and resolution experiments were used in order to estimate the parameters required for the model: the racemisation and resolution rate constants.

For the resolution, for simplicity, first order enzyme kinetics, with no back reaction were assumed. k_{enz} can be found using the half life for the reaction. For a first order reaction of substrate, denoted S,

$$-\frac{d[S]}{dt} = k_{enz}[S] \quad (7.8)$$

$$\ln\left(\frac{S_t}{S_0}\right) = -k_{enz}t \quad (7.9)$$

At the point at which the conversion is equal to 50%, the time is $t_{0.5}$, the half life of the reaction:

$$\ln\left(\frac{S_0}{2}\right) = \ln S_0 - k_{enz} t_{0.5}$$

$$k_{enz} = \frac{\ln 2}{t_{0.5}} \quad (7.10)$$

Taking the time profiles of conversions to product for four typical 33.6mM biotransformation of 1-phenyl ethanol with IPPA and novozyme 435, as detailed in Table 5.7, gave an average value of $k_{enz} = 6.39 \times 10^{-5} \text{ s}^{-1}$, with standard deviation, $\sigma^2 = 3.07 \times 10^{-9}$. Unfortunately, it has not been possible to find any values for k_{enz} for this enzyme and substrate combination in the literature for comparison. Likewise for the racemisation, first order kinetics, that is, the validity of equations (7.8) – (7.10), was assumed. Taking the time profiles of four typical 1-phenyl ethanol racemisations with ruthenium cymene and Ploct, as detailed in Table 5.17, gave an average value of $k_{rac} = 1.44 \times 10^{-5} \text{ s}^{-1}$, with standard deviation, $\sigma^2 = 2.03 \times 10^{-11}$. Again it has not been possible to find any literature data on reaction rate for this reaction.

Thus the model was applied using the following benchmark parameters:

$$\begin{aligned} k_{rac} & 1.44 \times 10^{-5} \text{ s}^{-1} \\ k_{racinv} & 1.44 \times 10^{-5} \text{ s}^{-1} \\ k_{enz} & 6.39 \times 10^{-5} \text{ s}^{-1} \end{aligned}$$

This ‘benchmark’ case gives the results shown in Figures 7.18 and 7.19.

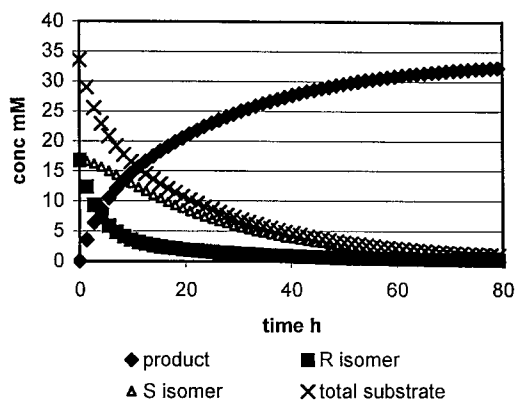


Figure 7.18: Concentration profiles for benchmark case for one-pot DKR..

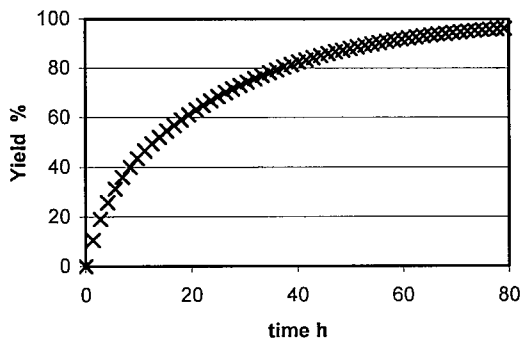


Figure 7.19: Yield profile for benchmark case for one-pot DKR..

One major use of such a model could be to examine, prior to experimental work, how variation in the system parameters will effect the performance of the system. Figures 7.20 and 7.21 demonstrate how this could be done. The parameters were varied by powers of ten.

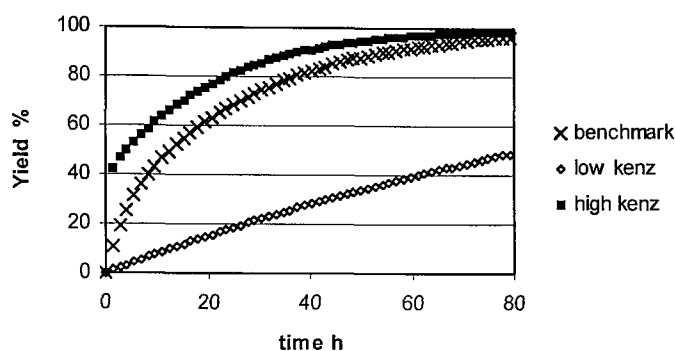


Figure 7.20: Effect of varying the enzymatic rate constant.

Benchmark $k_{enz}=6.39 \times 10^{-5} \text{ s}^{-1}$, low $k_{enz}=6.39 \times 10^{-6} \text{ s}^{-1}$, high $k_{enz}=6.39 \times 10^{-4} \text{ s}^{-1}$.

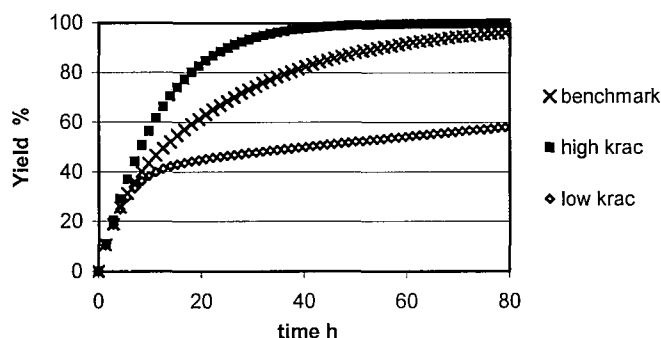


Figure 7.21: Effect of varying the racemisation rate constant.

Benchmark $k_{rac}=1.44 \times 10^{-5} \text{ s}^{-1}$, low $k_{rac}=1.44 \times 10^{-6} \text{ s}^{-1}$, high $k_{rac}=1.44 \times 10^{-4} \text{ s}^{-1}$.

Note: in all cases, $k_{rac}=k_{racinv}$.

The figures clearly demonstrate the important effect the rate constants have on the speed at which the maximum yield is attained. The rate constants only control how long it takes to reach the maximum yield and do not effect the value of the maximum yield, which is 100% in all cases. In a real experiment, the rate constants could be varied and optimised by varying parameters such as pressure, temperature and concentration. Thus, an optimised parameter set for these simulations can be identified, as shown in Figure 7.22, which indicates that the maximum yield of 100% can be achieved in under 10 hours.

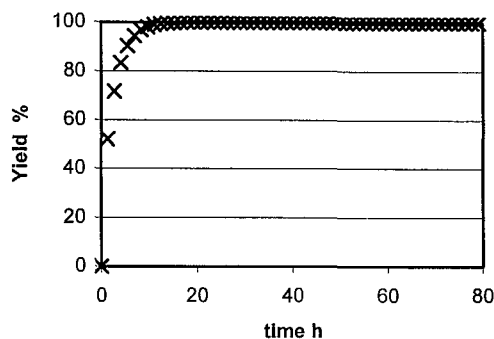
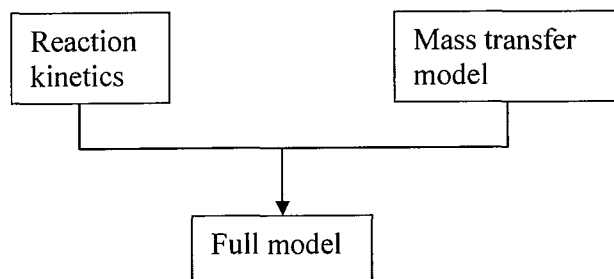


Figure 7.22: Optimised system parameters to achieve fastest conversion:

$$k_{rac}=1.44 \times 10^{-4} \text{ s}^{-1}, k_{enz}=6.39 \times 10^{-4} \text{ s}^{-1}.$$

However, the data in Chapter 5.3.3 shows that no successful one-pot DKRs were achieved, so this model cannot be verified. This is due to the fact that factors more complex than those accounted for in this simplified model are affecting the system. The two catalytic systems interact preventing either catalyst from working efficiently, whereas the model assumes total independence of the two catalysts.

Combining these chemical reaction kinetics with the mass transfer model already developed in Chapter 3, allows the whole MEDKR system to be described mathematically.



The full derivation of the full MEDKR model is in Appendix VI. Figure 7.23 shows the simplified process diagram for the MEDKR rig. The reaction scheme is as for the one-pot DKR model, as shown in Figure 7.17.

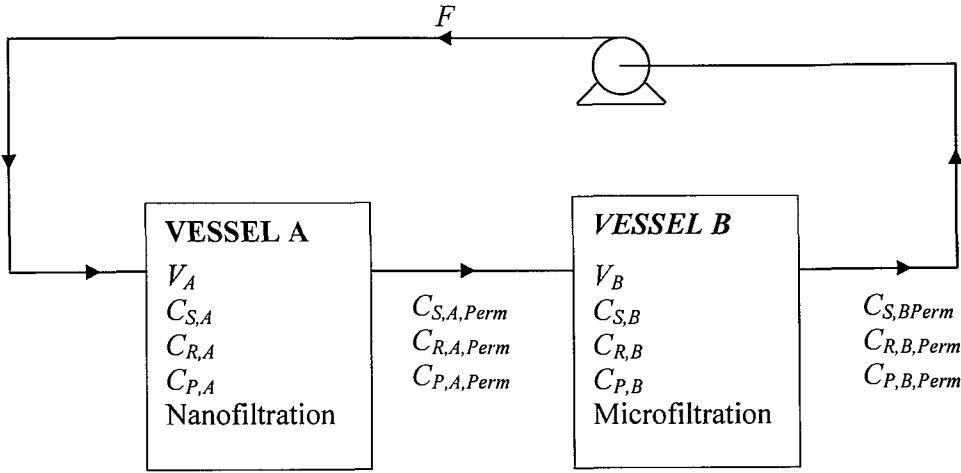


Figure 7.23: Simplified process diagram for model of the MEDKR rig.

Nomenclature:

F	loop flow rate
V	vessel volume
C	concentration
t	time
k	rate constant

Subscripts:	A	in vessel A
	B	in vessel B
	S	S isomer of racemic substrate
	R	R isomer of racemic substrate
	P	product
	E	enzyme
	$perm$	permeate, i.e. downstream of membrane at reactor outlet

In order to simplify this complex system, the following assumptions have been made:

1. Rejection is constant with time
2. Loop flow rate is constant
3. Vessels B and C are well mixed
4. Connecting pipes have negligible volume
5. System components do not interact
6. Enzyme obeys first order kinetics
7. Product is stable: reaction forming product is irreversible
8. Enzyme is active only on the R isomer
9. Forward and backward rate constants for racemisation are equal
10. Resolution occurs only in vessel B, i.e. rejection of enzyme in vessel B is 100%
11. Racemisation occurs only in vessel A, i.e. rejection of racemisation catalysts in vessel A is 100%. This is probably an erroneous simplification. The model can be altered later to account for permeation of racemisation catalyst around the system

The following initial conditions are used: at $t = 0$,

$$C_{S,A} = C_{S,A,0} \quad \text{For a racemic feed, } C_{S,A,0} = C_{R,A,0}$$

$$C_{R,A} = C_{R,A,0}$$

$$C_{P,A} = 0$$

$$C_{S,B} = 0$$

$$C_{R,B} = 0$$

$$C_{P,B} = 0$$

$$C_{S,C} = 0$$

$$C_{R,C} = 0$$

$$C_{P,C} = 0$$

The model consists of the following set of equations (details in Appendix IX)

$$R_i = 1 - \frac{C_{i,P}}{C_i} \quad (7.2)$$

$$V_A \frac{dC_{S,A}}{dt} = FC_{S,B}(1 - R_{S,B}) - FC_{S,A}(1 - R_{S,A}) + V_A(k_{rac}C_{R,A} - k_{rac}^{-1}C_{S,A}) \quad (7.11)$$

$$V_B \frac{dC_{S,B}}{dt} = FC_{S,A}(1 - R_{S,A}) - FC_{S,B}(1 - R_{S,B}) \quad (7.12)$$

$$V_C \frac{dC_{S,C}}{dt} = FC_{S,B}(1 - R_{S,B}) \quad (7.13)$$

$$V_A \frac{dC_{P,A}}{dt} = FC_{P,B}(1 - R_{P,B}) - FC_{P,A}(1 - R_{P,A}) \quad (7.14)$$

$$V_B \frac{dC_{P,B}}{dt} = FC_{P,A}(1 - R_{P,A}) - FC_{P,B}(1 - R_{P,B}) + V_B k_{enz} C_{ER,B} \quad (7.15)$$

$$V_C \frac{dC_{P,C}}{dt} = FC_{P,B}(1 - R_{P,B}) \quad (7.16)$$

$$V_A \frac{dC_{R,A}}{dt} = FC_{R,B}(1 - R_{R,B}) - FC_{R,A}(1 - R_{R,A}) + V_A(k_{rac}^{-1}C_{S,A} - k_{rac}C_{R,A}) \quad (7.17)$$

$$V_B \frac{dC_{R,B}}{dt} = FC_{R,A}(1 - R_{R,A}) - FC_{R,B}(1 - R_{R,B}) - k_{enz} C_{R,B} V \quad (7.18)$$

$$V_C \frac{dC_{R,C}}{dt} = FC_{R,B}(1 - R_{R,B}) \quad (7.19)$$

Therefore the model consists of 9 equations (7.11 – 7.19) in 9 unknowns: $C_{S,A}$, $C_{S,B}$, $C_{S,C}$, $C_{R,A}$, $C_{R,B}$, $C_{R,C}$ and $C_{P,A}$, $C_{P,B}$, and $C_{P,C}$, with the following set of parameters:

V_A , V_B , V_C

F

$R_{i,A}$, $R_{i,B}$ where i = the component, R , S or P

k_1 , k_2 , k_{-1}

k_{rac} , r_{rac}^{-1}

$C_{E,B,0}$

The equations were solved using gPROMS ModelBuilder, 2.2.4 from Process Systems Enterprise Limited. The coded equations are given in Appendix X.

For preliminary benchmark simulations, the 1-phenyl ethanol, IPPA, ruthenium cymene, Ploct, novozyme 435 system was chosen. Estimations for the rate constants were used as for the one-pot DKR simulations, that is, $k_{enz} = 6.39 \times 10^{-5} \text{ s}^{-1}$ and $k_{rac} =$

$1.44 \times 10^{-5} \text{ s}^{-1}$. A racemic feed of concentration 33.6mM was assumed for vessel A, with all other starting concentrations equal to zero. The system's physical parameters were taken as:

$$V_A = 200 \text{ mL} = 2 \times 10^{-4} \text{ m}^3$$

$$V_B = 83 \text{ mL} = 0.83 \times 10^{-4} \text{ m}^3$$

$$V_C = 100 \text{ mL} = 1 \times 10^{-4} \text{ m}^3$$

$$F = 3.93 \text{ mL/min} = 6.55 \times 10^{-8} \text{ m}^3/\text{s}$$

$$R_{R,S,P,A} = 2.9\% = 0.029 \quad (\text{average value from previous dead end cell experiments})$$

$$R_{R,S,P,B} = 1\% = 0.01 \quad (\text{average value from previous dead end cell experiments})$$

The results of the benchmark simulation are shown in Figure 7.24, which shows the concentration profiles in the three MEDKR rig vessels (A, B and C) and the overall product yield. With the benchmark parameters, the maximum theoretical yield of 100% is reached in about 150 hours. The concentration of the S isomer at any time is greater than that of the R isomer. This is due to the fact that the R isomer is metabolised by the enzyme, whereas, the S isomer has to be converted to the R isomer via the racemisation reaction before it can be metabolised. The concentration profiles in the three vessels are very similar, indicating that the mixing in the model is close to ideal.

As for the one-pot system discussed earlier, the effect of variation in the system parameters can be investigated using the model. The effect of the system's physical and chemical parameters is shown in Figures 7.25 and 7.26.

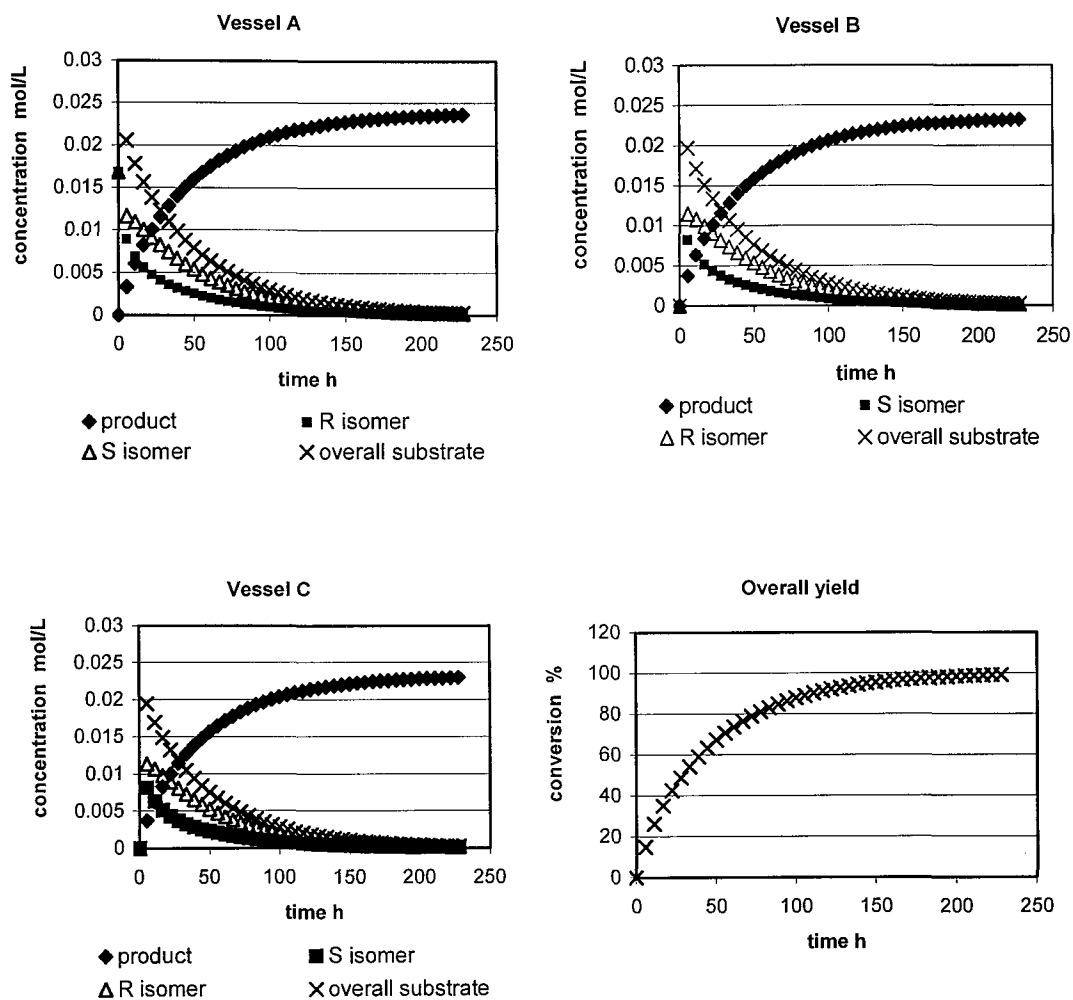


Figure 7.24: Graphical results for simulation of MEDKR of 1-phenyl ethanol with IPPA, ruthenium cymene, Ploct and novozyme 435.

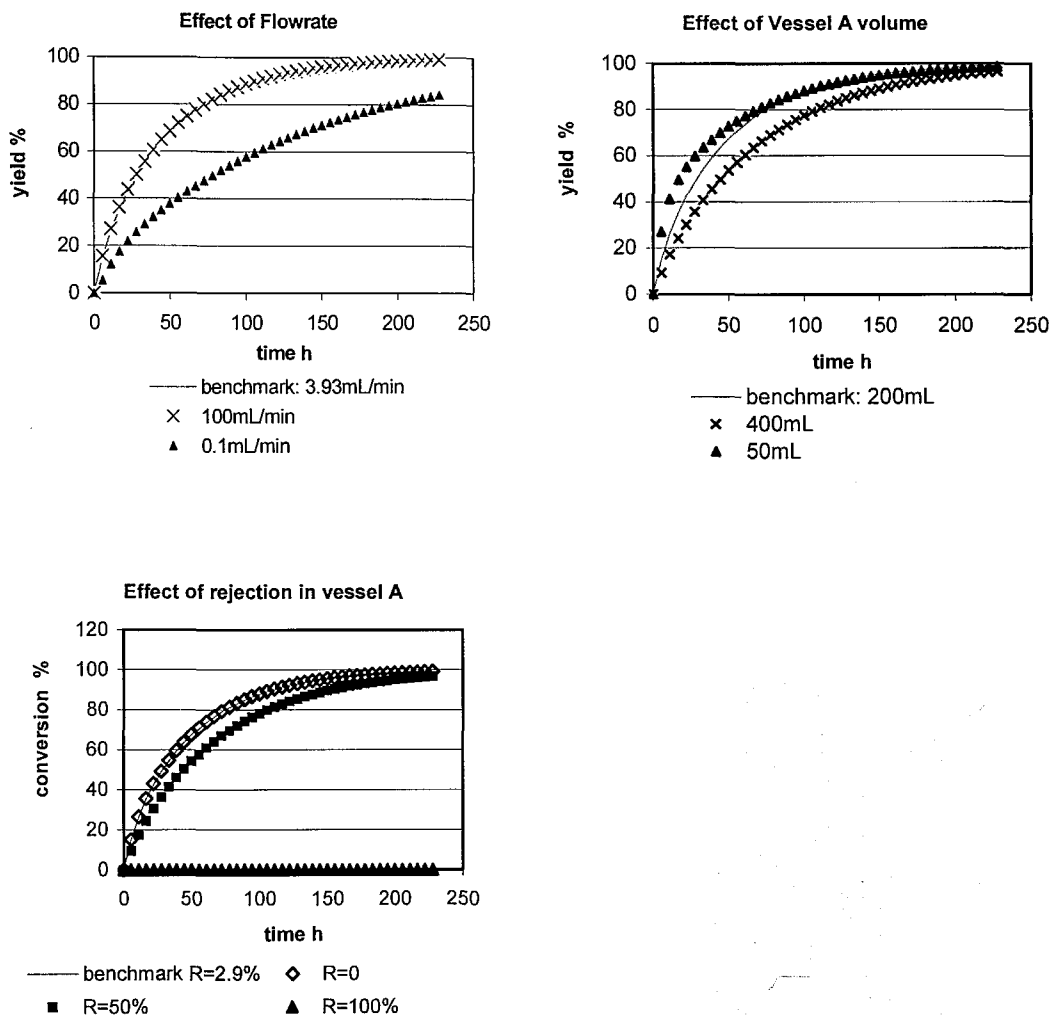


Figure 7.25: Effect of system physical parameters.

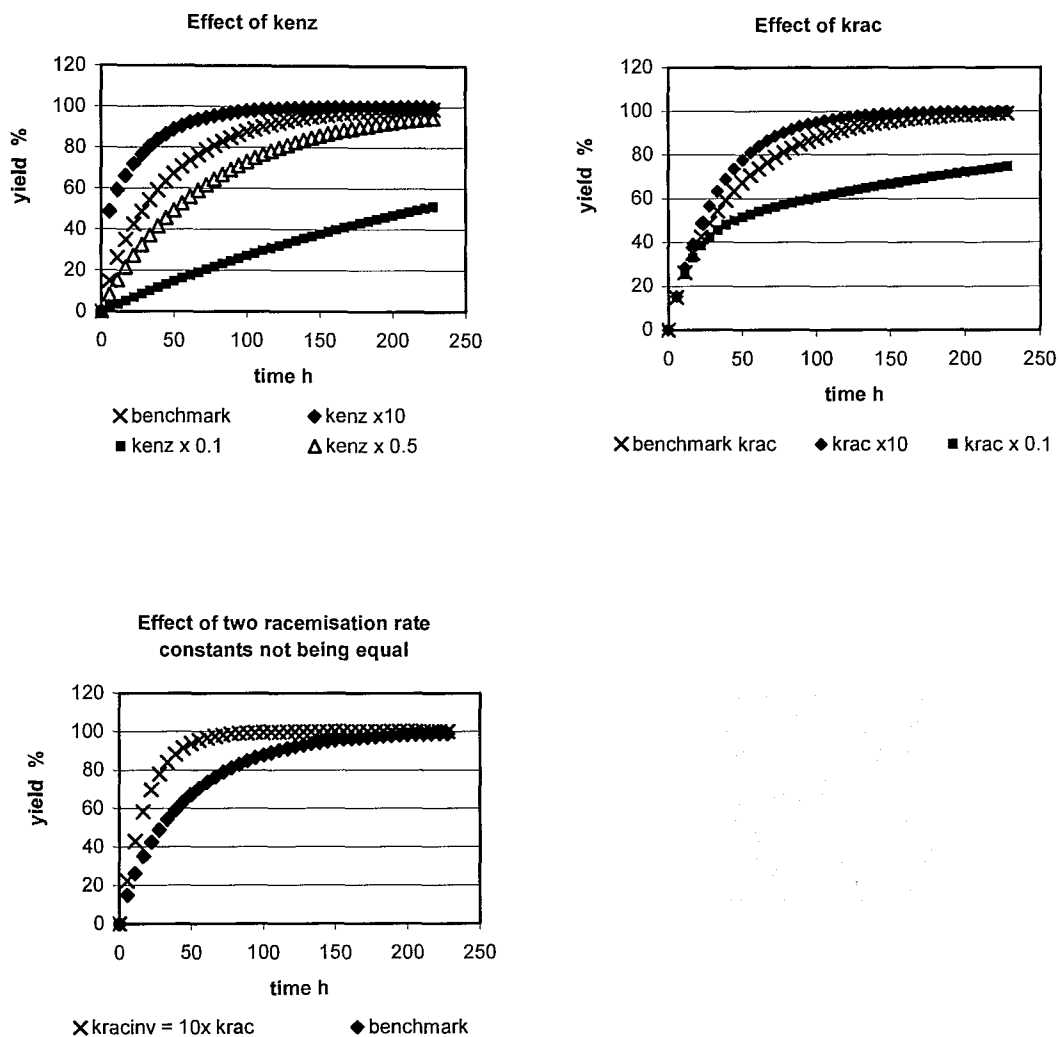


Figure 7.26: Effect of system chemical parameters.

Another interesting scenario is the case where no chemical reactions occur, that is, $k_{\text{rac}} = k_{\text{racinv}} = k_{\text{enz}} = 0$. In this case, the concentration profiles in the system should reduce to the simple mass transfer model. Obviously the concentration of the product acetate is zero throughout. The model predicts equal concentrations of the R and S isomers at all points, indicating that the racemisation is instantaneous. Comparing Figure 7.27 and Figures 7.15 and 7.16, shows that the simple mass transfer model gives the same results as the full MEDKR model. It is interesting to note that, for the case of no reaction, equilibrium is reached within two hours, whereas, with chemical reaction, equilibrium is reached after a much longer period,

in excess of 100 hours for the benchmark case. The instability caused by the changing chemical nature of the system obviously causes the longer equilibration time.

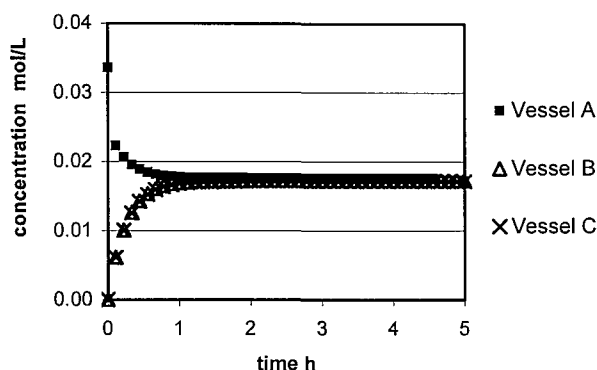


Figure 7.27: MEDKR model with no chemical reaction: overall concentration of substrate (that is, the sum of R and S enantiomers) in the three rig vessels.

The final parameter variation to be investigated is the effect of the initial feed concentration. Figure 7.28 shows that there is no effect of altering the feed concentration by a factor of 10 larger or smaller. This is due to the fact that the model assumes that the catalysts work equally well, regardless of the substrate concentration they are fed with. Individual reactions in Section 5.3 have indicated that this is not the case – the reaction is affected by the initial substrate concentration. This is due to simple collision theory – at low concentration the molecules are further apart in the solution and so the chance to two molecules colliding and then reacting is lower, hence the reaction rate / overall conversion is lower. Therefore, in order to optimise the experimental system completely, a range of feed concentrations should be run to establish the effect of concentration.

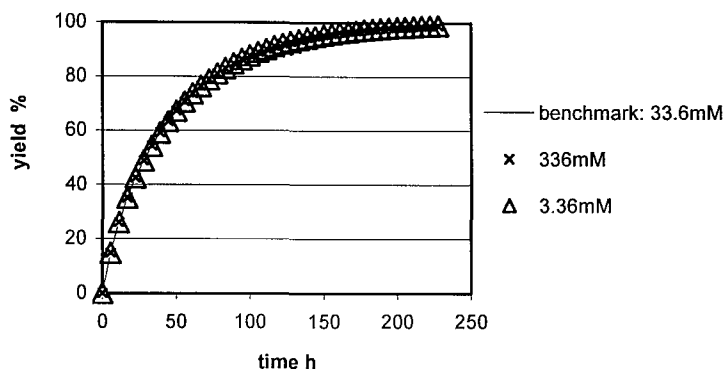


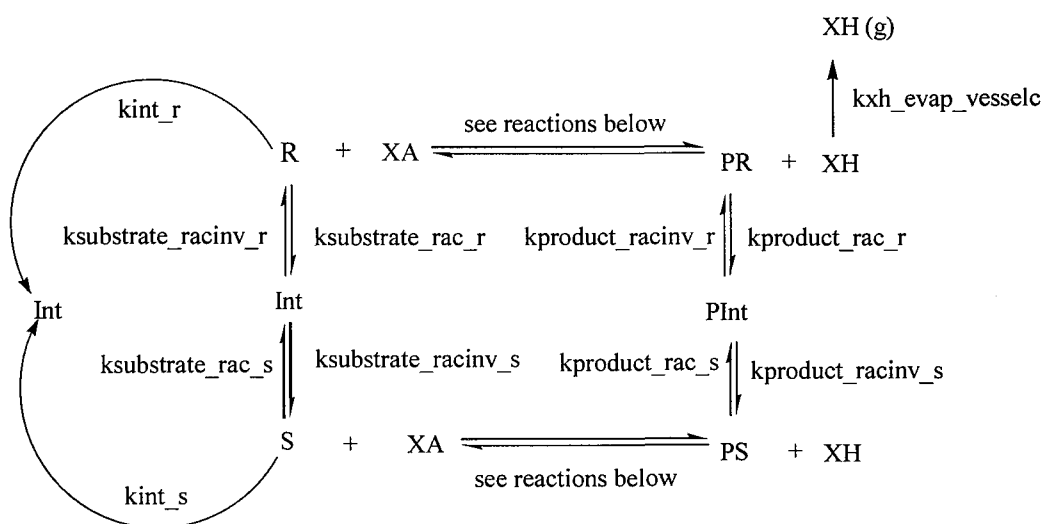
Figure 7.28: Effect of initial feed concentration on MEDKR.

In conclusion, a model has been devised which could be used to predict the concentration profiles in the MEDKR process. The model cannot be validated with experimental data at this stage since no successful MEDKR process has been identified, due to various problems. It should be noted the model suggested here is a simplification which could easily be extended to account for more complex reaction schemes. Of course, this might not be necessary, the current model might be adequate, but it is not possible at this stage to establish this since it has not been possible to generate any suitable data with which to verify the model. Possible ways of making the model more sophisticated are:

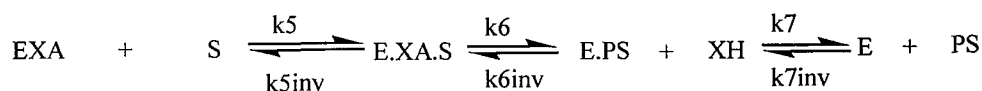
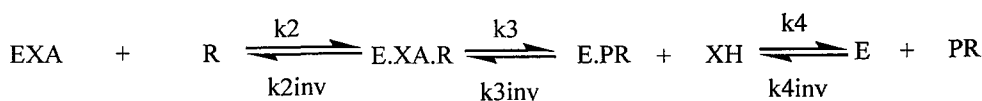
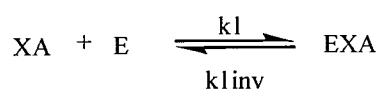
- Allowing for the equilibrium nature of the enzyme reaction, that is, by accounting for the back reaction from product to substrate
- Allowing the enzymatic resolution to occur by a mechanism other than first order kinetics, such as, Michalis Menten kinetics or an ordered bi-bi ternary complex enzyme kinetics (ternary complex mechanism) [143].
- Including terms for the acyl donor, its product in the biotransformation, and potential evaporation of this product, which may be highly volatile, from vessel C
- Allowing for racemisation of the product
- Allowing for racemisation elsewhere in the system other than vessel A, to account for the fact that the racemisation catalysts are not completely retained by the nanofiltration membrane

- Accounting for the ketone intermediate in the racemisation reaction
- Accounting for intermediate in enzymatic transformation

Figure 7.29 shows a potential modification of the reaction schematic including the enzymatic mechanism on which an improved model might be based, which allows for these additional factors.



Enzyme reaction



Inhibition

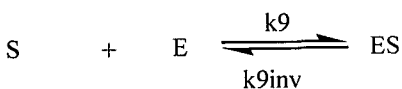
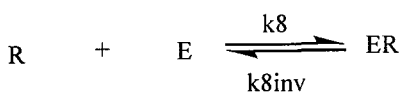


Figure 7.29: Modification of MEDKR reaction scheme, including ordered bi-bi ternary complex enzyme kinetics [143].

CHAPTER 8

CONCLUSIONS AND FURTHER WORK

The application of organic stable membranes in industrial processes is very limited, yet, membranes have great potential in a variety of industries. This thesis has studied the fundamental behaviour of organic solvent nanofiltration (OSN) membranes and their application to an organic chemical synthesis process, one that could potentially be useful in the pharmaceutical industry.

The first section of the thesis reviewed the work done to date on the basic behaviour of OSN membranes. An important issue highlighted by this review is that the collection of reproducible data is difficult, which seems to be due to differing pre-treatment methods. A standardised pre-treatment method should be employed in order to ensure that the membrane has equilibrated at the experimental conditions and is operating at steady state. Experimental observations of solvent flux and solute retention by OSN membranes were made using various solutes (quaternary ammonium bromide salts), membranes (StarmemTM and MPF50) and two solvents common in organic chemistry processes, toluene and methanol. The solutes chosen were a range of quaternary ammonium bromide salts. The work allowed a better understanding of the basic behaviour of OSN membranes which will provide a useful basis for choosing the best membrane for application in a given chemical process. A standard pre-conditioning protocol has been established which will ensure the best possible results from a membrane and will allow better comparison of different experiments. The data collected showed that there are substantial differences between the behaviour of one membrane in different solvents and equally, between different membranes in the same solvent. Therefore, interactions between the polymer material of the membrane and the solvent are important. Some insight into the potential mechanisms of membrane transport was gained from these experiments.

The question of the transport mechanism for OSN membranes is much debated; data supportive of the two main models, the pore flow model and the solution diffusion model, are presented in the literature. A major problem is that the two models reduce

to the same form under some conditions: a linear relationship of flux with pressure, providing that the osmotic pressure term can be neglected. Since it is not known whether organic solvent nanofiltration membranes are porous or homogeneous, it is possible that some sort of transitional mechanism might be more satisfactory.

Membranes (StarmemTM 122 and MPF50) were characterised using three pore flow models in terms of an equivalent (uniform) pore size. The models used were the Ferry formula, the steric hindrance pore model and the Verniory model. The predicted pore size varied with solute size slightly. The effect of the applied pressure on the predictions was negligible. Membrane pore sizes have been quoted on the basis of an average over all pressures and solutes. Reasonable estimates were obtained using quat data for a nanofiltration membrane (0.5 - 0.8 nm pore radius, corresponding to a porosity of 0.02 - 0.04) which is expected to effect separations for solutes in the nanometer size range. The results were consistent with the findings of other authors in the field. This section of work assumes that OSN membranes are indeed porous, which is a matter of some controversy.

If OSN membranes are homogeneous, a pore model is not appropriate. A mathematical model was derived to describe and predict the behaviour of OSN membranes which are non-porous. The model combined the solution diffusion model with the film theory to account for mass transfer limitations. The model also allowed for system non-ideality, by incorporating the ratio of the activity coefficients on the permeate and feed sides. Data, collected with StarmemTM 122, toluene and one of the quaternary ammonium bromide salts, tetra octyl ammonium bromide (TOABr) and docosane as solutes, were described reasonably well with the model. The model does not allow for any coupling of the fluxes of the system components, but still describes the data sufficiently. While much previous work has focused on the exact nature of the membrane permeation, this work suggests that due attention should also be given to the governing thermodynamics and to mass transfer effects

Dynamic kinetic resolution (DKR) was chosen as a potential process where membranes could be useful. DKR allows the generation of an enantiomerically pure product from a racemic substrate, and thus has applicability in the pharmaceutical,

agricultural and food industries. The concept of membrane enhanced dynamic kinetic resolution (MEDKR) allows a membrane to separate the catalytic environments for the two processes in DKR, the resolution and the racemisation. These two processes are, in many cases, incompatible due to interaction of the catalysts. This means that DKRs cannot always be performed as a single 'one pot' process, but have to be split into a two step process which requires more lengthy processing. Two DKRs were chosen for further investigation: the conversion of 1-phenyl ethanol to 1-phenyl acetate. The individual chemical steps in the DKRs, the resolution, racemisation and then the one-pot reaction were first examined, using a variety of different catalysts in order to find the optimum experimental conditions.

The resolution was found to be the easier of the two steps. Several enzyme and acyl donor combinations produced good yields of the acetate product, over 50% with good enantiomeric purity. Good racemisation results were hard to obtain. Ruthenium cymene with a phosphazene base was found to be the most reliable racemisation catalyst system. Resolutions were found to be affected negatively by 'spikes' of reactants from the racemisation system. Equally, racemisations were found to be affected negatively by 'spikes' of reactants from the resolution system. A particular problem was that the racemisation was inhibited by the presence of the reaction product, the acetate. This presents problems for MEDKR since the membranes available are not capable of distinguishing between the alcohol substrate and product acetate. Low yields were found for all the one-pot reaction: the yields were less than 50% proving that the DKR process offers no improvement compared with the simple enzyme resolution. This means that there is great potential for improvement using MEDKR. The best racemisation and resolution systems from this section of work were chosen to be investigated using MEDKR.

An MEDKR rig was designed and constructed allowing the resolution and racemisation reactions to be carried out in separate vessels, each in a separate catalytic environment. Membranes suitable for retaining the catalysts in each vessel were chosen. A simple mass transfer model to predict the movement of species around the rig was derived and verified experimentally. A more sophisticated model including all the chemical reactions was also derived and reaction yield predictions were made. MEDKR experiments were run with 1-phenyl ethanol and allylic

alcohol with various catalyst combinations. As a result of the findings from the first batch of experiments, the rig was modified to improve the mass transfer properties. Even with the modified rig, no successful MEDKR was achieved. Out of all the experiments, the maximum product yield achieved was less than 40%, which is significantly lower than the equivalent simple resolution. This shows that, MEDKR offers no improvement compared with a kinetic resolution. It is thought that this is because the individual DKR steps are not working properly *in-situ*. This is due either to the resolution reaction product interfering with the racemisation. This is likely to be an unsolvable problem, since the current state of materials science means that it is not possible to create membranes which have such a finely tuned selectivity that they are capable of separating species with molecular weights as close as the substrates and products of these DKR reactions. The only option with these systems would be to find some way of extracting the product from the resolution reactor as soon as it is formed so that it cannot pass back into the racemisation reaction. The chemical reactivities and physical properties of the secondary alcohols and acetates are similar, so this is unlikely to be possible. Alternatively, the poor MEDKR results could be due to the base required in the racemisation reaction interfering with the enzyme and deactivating it, thus preventing the resolution from taking place. Although MEDKR should retain the base in the racemisation reactor, over an extended period, problems were encountered with membrane stability on contact with the basic racemisation reaction feed, causing the base to pass through the membrane, contrary to the aims of MEDKR.

Finally, it is concluded that, what is really required for the MEDKR of 1-phenyl ethanol or allylic alcohol, is a new membrane with the required base and solvent stability and filtration characteristics, since none of the commercial membranes readily available has ideal characteristics. On a laboratory scale, to date, investigations into the use of membranes in corrosive environments, such as highly acidic or highly basic conditions, have only been conducted in aqueous media [154, 155]. So, the only solution is to prepare solvent stable membranes with a high base resistance specifically for the MEDKR process. One possibility is the preparation of composite membranes via a dip-coating procedure [156]. The polymer used for coating could be chosen in order to fine-tune the solvent and base resistance.

Preparation of base and solvent stable membranes would be a major part of any extension of this study.

Another possible alternative in this process is to combine the membrane stage with the separation stage. Various authors have reported the use of enantioselective membranes to effect chiral separations [92, 157]: solid membranes made of chiral polymers or liquid membranes. If problems continue with non-chiral membranes, chiral membranes might be investigated.

Instead of modifying the membrane to suit the chemistry, another possibility is to choose a different chemistry that required less corrosive catalyst, so that the current available membranes are still useable. A different chemistry from the secondary alcohols used in this study might be less complex and the interactions between the individual reactions might be less difficult to predict and rationalise.

Therefore, if the concept of MEDKR is to be proven, potential other reactions systems should be investigated. Three possible systems will be discussed. The substrates of all the systems are of a suitable molecular size for separation by the membranes already used in this study. The first example is the base and enzyme catalysed DKR of thioesters [159, 160]. Various thioesters can be resolved using lipases and esterases to form carboxylic acids, as shown in Figure 8.1. Literature examples use triethyl amine as the racemisation catalyst. However, TEA cannot be retained by the OSN membranes available due to its small size (MW = 107.31). Larger amine bases, which would have a better retention by the membrane, could be investigated instead. It has also been shown that the membranes have a good tolerance towards the amine base series. The reaction should be performed in the presence of an acyl acceptor, such as n-butanol and a solvent system consisting of toluene and a buffer, such as PIPES can be used.

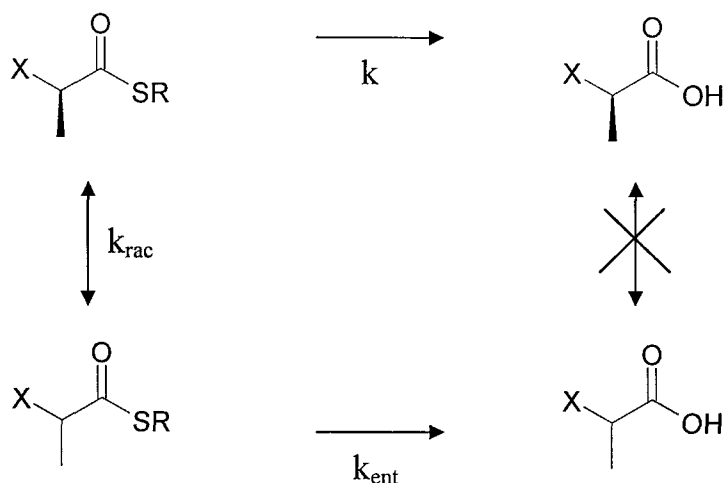
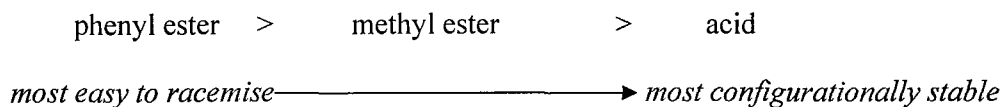


Figure 8.1: Schematic of DKR of thioesters.

Another example is the base and enzyme catalysed DKR of esters [161]. Phenyl and methyl esters of 2-phenylpropionic acid might be a good place to start. For this scheme, shown in Figure 8.2, the ester is converted to 2-phenylpropionic acid using *candida cylindracea* lipase. DBU, DABCO or other similar large bases can be used for the racemisation. Again, as for the potential thioester systems, the substrate should be racemised by a weak base, avoiding the problems of poor membrane stability. The reaction should be performed in a solvent system of an organic solvent such as CH_2Cl_2 , DMSO or H_2O and a phosphate buffer. In this system, the acid product is more chirally locked than the esters, and so less susceptible to racemisation, as required for DKR. The relative rates of racemisation can be summarised as follows:



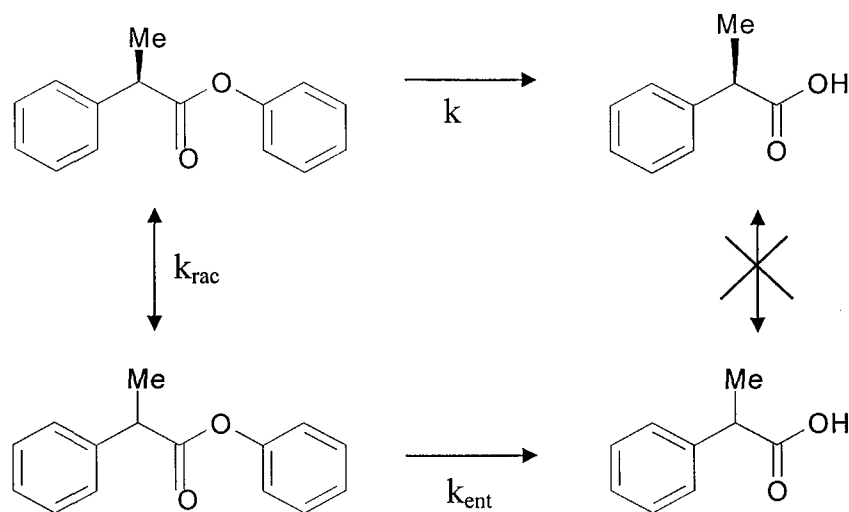


Figure 8.2: Schematic of DKR of the phenyl ester of 2-phenylpropionic acid.

Another ester substrate that could be used in the same way as in the scheme shown in Figure 8.2, is naproxen methyl ester to produce naproxen [162]. One possible system is to use *Candida rugosa* lipase to effect the resolution and sodium hydroxide as the racemisation catalyst in an aqueous-organic biphasic system consisting of iso-octane and tris-HCl buffer. There is some literature evidence [162] already of attempts to use this system in conjunction with a membrane separation, although, in this case, a tubular silicone membrane is used rather than a flat sheet OSN membrane. An alternative [163] is a strong base such as a phosphazene species to effect the racemisation of fluoro-esters of naproxen in a non-polar solvent such as isooctane, cyclohexane or *n*-hexane. The only potential disadvantage of naproxen systems is that naproxen ester will be quite difficult to racemise, hence strong bases will be required which may not be compatible with the membranes.

In conclusion, it has not been possible to prove the concept of MEDKR due to the reasons discussed above. It is still believed, that the concept could be of great value in a variety of industries. An extension of this study would seek to find a combination of reactants and membranes which allows MEDKR to be achieved.

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NOMENCLATURE

a	Activity	-
A_k	Membrane porosity	-
B	Membrane permeability (eq 3.46)	m / s bar
B	Solute permeability (eq 3.47)	L m /s kg
c	Concentration	M, kg/m ³
d_h	Hydraulic diameter	m
d_p	Pore diameter	m
d_s	Solute diameter	m
D	Diffusivity	m ² /s
ee	Enantiomeric excess	%
F	MEDKR rig loop flow rate	L/h
G	Lag coefficient	-
H	Convection hindrance factor	-
J	Flux	L/m ² h
k	Mass transfer coefficient	m/s
k	Rate of reaction	s ⁻¹
K	Hindrance factor	-
K	Partition coefficient	-
K^{-1}	Enhanced drag coefficient	-
l	Membrane thickness	m
L_v	Hydraulic permeability coefficient	m/s kPa
M	Number of moles	-
N	Solute flux	mol/m ² s
p	Pressure	bar
P_m	Overall permeability	m/s
q_w	Surface charge density	C/m ²
r	Pore radius	m
$\bar{r}$	Average pore radius	m

r_a	Effective pore radius	m
r^*	Molecular radius	m
r^+	Dimensionless pore radius	-
R	Rejection	%
Re	Reynolds number	-
Rt	Retention	%
s	Internal surface area	m ²
S	Steric hindrance factor	-
Sc	Schmidt number	-
Sh	Sherwood number	-
S_p	Standard deviation of pore sizes	-
t	Time	s
$t_{1/2}$	Reaction half life	s
T	Temperature	K or °C
T_0	Freezing point of pure solvent	K or °C
U	Velocity	m/s
v	Velocity	m/s
v^+	Dimensionless velocity	-
V	Volume	m ³
V	Unperturbed velocity (Deen model)	m/s
$\bar{V}$	Partial molar volume	m ³ /mol
V_m	Molar volume	m ³ /mol
W	Diffusive hindrance factor	-
x	Concentration (mole fraction)	-
X_d	Charge density	C/m ²

Greek characters:

β	Dimensionless pore size	-
γ	Activity coefficient	-
γ	Surface energy	N m
δ	Membrane thickness	m
ΔH_{fus}^0	Enthalpy of fusion	kJ/mol
ΔP	Pressure difference	bar
Δx	Membrane thickness	m
$\Delta \Pi$	Osmotic pressure difference	bar
ε	Surface porosity	-
η	Ratio of solute diameter to pore diameter	-
μ	Viscosity	N s/m ²
v	Molar volume	m ³ /mol
ξ	Electrolyte concentration	kg/m ³
σ	Reflection coefficient	-
τ	Tortuosity	-
ϕ	Sieving coefficient	-
Φ_s	Equilibrium partition coefficient	-

Subscripts / Superscripts:

A	Vessel A (racemisation) in MEDKR rig
B	Vessel B (resolution) in MEDKR rig
D	Docosane
E	Enzyme
f	Feed
i	Species, i
m	Membrane
p	Permeate
P	Product
perm	Permeate
r	Retentate
R	R isomer
S	S isomer
T	Toluene
FM	In membrane, on feed side
LR	Long range (activity coefficient models)
PM	In membrane, on permeate side
rac	Racemisation
res	Resolution
SR	Short range (activity coefficient models)
0	Initial / feed
1	Species, 1, of binary system
2	Species, 2, of binary system

Other symbols:

[]	Concentration
-----	---------------

APPENDIX I **gPROMS CODE FOR** **SOLUTION DIFFUSION / FILM THEORY MODEL**

Parameter

D1,D2	as	real
D1m, D2m	as	real
Delta	as	real
R	as	real
T	as	real
Molarvol1, Molarvol2	as	real
C1b, C2b	as	real
visco	as	real

Distribution_domain

zdomain	as (0:delta)
---------	--------------

Variable

C1	as Distribution (zdomain)	OF	concentration
C2	as Distribution (zdomain)	OF	concentration
J1	as	concentration	
J2	as	concentration	
J	as	concentration	
JL	as	concentration	
press	as	pressure	

Rejection	as	concentration
y	as	concentration
x	as	concentration
gammaratio	as	gammaratio
a	as	concentration
b	as	concentration

Boundary

$$C1(0) = C1b;$$

$$C2(0) = C2b;$$

Equation

COMPONENT 1 = TOABr, COMPONENT 2 = toluene

for z:= 0|+ to delta DO

$$J*C1(z)-D1*partial(C1(z),zdomain)-J1 = 0;$$

$$J*C2(z)-D2*partial(C2(z),zdomain)-J2 = 0;$$

end#z

$$gammaratio=1/((1+(1.03*(C1(delta)/(C1(delta)+C2(delta))))+(4.16*(C1(delta)/(C1(delta)+C2(delta)))^2)));$$

$$J1 = D1m * (C1(\text{delta}) / (C1(\text{delta}) + C2(\text{delta})) - (J1 / (J1 + J2))) * \exp(-\text{molarvol1} * \text{press} / (R * T));$$

$$J2 = D2m * (C2(\text{delta}) / (C1(\text{delta}) + C2(\text{delta})) - (J2 / (J1 + J2))) * \text{gammaratio} * \exp(\text{molarvol2} * \text{press} / (R * T));$$

$$J = J1 * \text{molarvol1} + J2 * \text{molarvol2};$$

$$JL = J * 3600e3 ;$$

$$\text{Rejection} = 1 - J1 / (J * C1b);$$

#permeate concentrations

$$a = J1 / J;$$

$$b = J2 / J;$$

#boundary layer - membrane interface concentrations

$$y = C2(\text{delta});$$

$$x = C1(\text{delta});$$

APPENDIX II

RESULTS OF ENZYME RESOLUTION REACTIONS

SUBSTRATE: phenyl ethanol, **ACYL DONOR:** 4 chlorophenyl acetate

Table 1: Experimental conditions for biotransformations of 1-phenyl ethanol with 4 CPA as the acyl donor and novozyme 435.

Expt	[1-phenyl ethanol]	[acyl donor]	Toluene volume	T	Enzyme mass	Duration
	mM	Equiv	ML	°C	g	Hours
1.1	49	0.5	25	Room	0.03	50
1.2	49	0.5	25	30	0.03	50
1.3	20	0.67	25	50	0.03	27
1.4	49	1	25	Room	0.03	45
1.5	49	1	25	Room	0.03	48
1.6	20	3	25	40	0.03	7
1.7	20	3	25	40	0.03	7
1.8	49	5	25	Room	0.03	45
1.9	49	10	25	Room	0.03	45

Table 2: Results for biotransformations of 1-phenyl ethanol with 4 CPA as the acyl donor and novozyme 435 . “n/m” = not measured.

Expt	Product yield	Ketone yield	Ee of remaining alcohol	Ee product acetate
	%	%	% ee of S	% ee of R
1.1	24.7	None	29.7	n/m
1.2	23.0	None	33.3	n/m
1.3	47.5	None	79.8	n/m
1.4	42.0	None	N/m	n/m
1.5	42.0	None	N/m	n/m
1.6	68.4	None	N/m	n/m
1.7	29.3	None	N/m	n/m
1.8	18.1	None	N/m	n/m
1.9	28.4	None	N/m	n/m

SUBSTRATE: phenyl ethanol, ACYL DONOR: vinyl acetate

Table 3: Experimental conditions for biotransformations of 1-phenyl ethanol with VA and novozyme 435.

Expt	[1-phenyl ethanol]	[acyl donor]	Toluene volume	T	Enzyme mass	Duration
	mM	Equiv	mL	°C	g	Hours
2.1	20	0.5	25	50	0.03	50
2.2	20	0.5	25	50	0.03	50
2.3	20	1	25	50	0.03	26
2.4	20	1.5	25	25	0.03	74
2.5	20	1.5	25	25	0.03	74

Table 4: Results for biotransformations of 1-phenyl ethanol with VA and novozyme 435.

Expt	Product yield	Ketone yield	Ee of remaining alcohol	Ee product acetate
	%	%	% ee of S	% ee of R
2.1	5.9	42.2	n/a	n/m
2.2	11.6	39.5	n/a	n/m
2.3	52.4	None	100	n/m
2.4	61.6	None	100	n/m
2.5	61.2	None	100	n/m

Table 5: Experimental conditions for 'spiked' biotransformations of 1-phenyl ethanol with VA and novozyme 435.

Expt	[1-phenyl ethanol]	[acyl donor]	Tol. Vol.	T	Enz. Mass	Spike		Duration
	mM	equiv	mL	°C	g	Type	Conc	Hours
3.1	20	1	25	50	0.03	Ru cymene	4mM (20mol%)	50
3.2	20	1	25	50	0.03	Ru cymene	4mM (20mol%)	50
3.3	20	1	25	30	0.03	P1 tris	1.6mM (8mol%)	50
3.4	20	1	25	50	0.03	P1 tris	1.6mM (8mol%)	50

Table 6: Results for 'spiked' biotransformations of 1-phenyl ethanol with 4 VA and novozyme 435.

Expt	Spike	Product yield	Ketone yield	Ee of remaining alcohol	Ee product acetate
		%	%	% ee of S	% ee of R
3.1	Ru	0	37.8	n/m	n/m
3.2	Ru	41.1	0.8	n/m	n/m
3.3	P1 tris	16.7	49.4	n/m	n/m
3.4	P1 tris	0	53.4	n/m	n/m

SUBSTRATE: phenyl ethanol, ACYL DONOR: isopropenyl acetate

Table 7: Experimental conditions for biotransformations of 1-phenyl ethanol with IPPA and novozyme 435.

Expt	[1-phenyl ethanol]	[acyl donor]	Toluene volume	T	Enzyme mass	Duration
	mM	Equiv	mL	°C	g	Hours
4.1	33.5	1.4	25	25	0.03	26
4.2	33.5	1.4	25	25	0.03	26
4.3	33.5	1.4	25	25	0.03	26
4.4	33.5	1.4	25	25	0.03	26
4.5	33.5	1.4	25	25	0.03	74
4.6	33.5	1.4	25	25	0.03	74
4.7	33.5	1.4	25	25	0.03	49

Table 8: Results for biotransformations of 1-phenyl ethanol with IPPA and novozyme 435.

Expt	Product yield	Ketone yield	Ee of remaining alcohol	Ee product acetate
	%	%	% ee of S	% ee of R
4.1	72.0	0	n/m	n/m
4.2	86.3	0	n/m	n/m
4.3	80.5	0	n/m	n/m
4.4	78.2	0	n/m	n/m
4.5	69.5	0	30.4	n/m
4.6	56.5	0	26.4	n/m
4.7	61.6	0	53.0	n/m

Table 9: Experimental conditions for 'spiked' biotransformations of 1-phenyl ethanol with IPPA and novozyme 435.

Expt	[1-phenyl ethanol]	[acyl donor]	Toluene volume	T	Enzyme Mass	Spike		Duration
	mM	Equiv	mL	°C	g	Type	Conc	Hours
5.1, 5.2	33.5	1.4	25	25	0.03	Ru cymene	1.3mM (4mol%)	49
5.3, 5.4	33.5	1.4	25	25	0.03	P1 oct	7.5mM (22.4mol%)	49
5.5, 5.6	33.5	1.4	25	25	0.03	TEA	3 equiv	30
5.7, 5.8	33.5	1.4	25	25	0.03	TOA	3 equiv	30
5.9- 5.12	33.5	1.4	25	25	0.03	Phenyl acetate	1 equiv	20
5.13- 5.16	33.5	1.4	25	25	0.03	Acetone	1 equiv	25

Table 10: Results for 'spiked' biotransformations of 1-phenyl ethanol with IPPA and *novozyme 435*.

Expt	Spike	Product yield	Ketone yield	Ee of remaining alcohol	Ee product acetate
		%	%	% ee of S	% ee of R
5.1	Ru cymene	51.6	n/a	81.1	n/a
5.2	Ru cymene	43.3	n/a	100.0	n/a
5.3	P1 oct	62.5	n/a	89.9	n/a
5.4	P1 oct	46.5	n/a	42.7	n/a
5.5	TEA	42.7	n/a	100.0	n/a
5.6	TEA	40.7	n/a	70.1	n/a
5.7	TOA	26.5	2.6	23.5	n/a
5.8	TOA	26.4	2.7	16.2	n/a
5.9	Phenyl acetate	45.0	n/a	n/a	n/a
5.10	Phenyl acetate	37.5	n/a	100.0	n/a
5.11	Phenyl acetate	51.2	n/a	66.8	n/m
5.12	Phenyl acetate	30.5	n/a	86.9	n/m
5.13	Acetone	43.8	n/a	100.0	n/m
5.14	Acetone	48.6	n/a	63.4	n/m
5.15	Acetone	16.2	n/a	82.2	n/m
5.16	Acetone	34.0	n/a	47.8	n/m

Table 11: Results for 'spiked' biotransformations of 1-phenyl ethanol with IPPA and PCL. Reaction performed with 33.5mM 1-phenyl ethanol, 1.4 equivalents of IPPA and 0.04g PCL.

Expt	Spike		Duration	Product yield	Ketone yield	Alcohol ee	Acetate ee
	Type	Conc	Hours	%	%	% ee of S	% ee of R
6.1	None	-	7	68.4	None	n/m	n/m
6.2	TEA	3 equiv	7	62.7	None	n/m	n/m
6.3	TEA	3 equiv	7	69.1	None	n/m	n/m
6.4	Ru indenyl	2 mol%	7	40.1	2.7	n/m	n/m
6.5	Ru indenyl	2 mol%	7	51.5	None	n/a	n/a
6.6	TOA	3 equiv	7	34.6	None	n/m	n/m
6.7	TOA	3 equiv	7	63.7	None	n/m	n/m
6.8	TDDA	3 equiv	7	47.5	None	n/m	n/m
6.9	TDDA	3 equiv	7	56.0	None	n/m	n/m

SUBSTRATE: allylic alcohol, ACYL DONOR: vinyl acetate

Table 12: Results for biotransformations of 40mM allylic alcohol with 1.5 equiv VA, 0.03g novozyme 435 in 25mL toluene at 25°C, under atmospheric conditions. Experiments 7.1-7.10 are identical.

Expt	Duration	Product yield	Ketone yield	Ee of remaining alcohol	Ee product acetate
	hours	%	%	% ee of S	% ee of R
7.1	19	53.3	10.0	n/m	n/m
7.2	19	58.0	9.1	n/m	n/m
7.3	19	52.5	8.7	n/m	n/m
7.4	19	63.3	8.1	n/m	n/m
7.5	24	15.1	None	84.7	96.4
7.6	24	34.7	None	68.4	93.0

Expt	Duration	Product yield	Ketone yield	Ee of remaining alcohol	Ee product acetate
	hours	%	%	% ee of S	% ee of R
7.7	24	52.0	None	94.4	87.0
7.8	24	74.7	None	n/m	60.2
7.9	24	71.9	None	n/m	73.6
7.10	24	45.5	None	100.0	89.0

Table 13: Results for 'spiked' biotransformations of 40mM allylic alcohol with 1.5 equiv VA, 0.03g nov 435 in 25mL toluene at 25°C, under atmospheric conditions.

Expt	Spike		Duration	Product yield	Ketone yield	Alcohol ee	Acetate ee
	Type	Conc	Hours	%	%	% ee of S	% ee of R
8.1	Ru cymene	4 mol%	30	1.4	24.4	-6.5	97.4
8.2	Ru cymene	4 mol%	30	1.4	23.9	-3.6	95.1
8.3	Ru cymene	4 mol%	24	67.9	None	41.4	96.1
8.4	Ru cymene	4 mol%	24	72.8	None	-6.5	100.0
8.5	Ru cymene	8 mol%	24	80.7	None	89.7	18.8
8.6	P1 oct	22.4 Mol%	30	3.1	8.3	42.9	51.1
8.7	P1 oct	22.4 Mol%	30	2.9	8.1	41.2	59.1
8.8	Allylic acetate	1 equiv	24	19.8	1.6	n/a	n/a
8.9	Allylic acetate	1 equiv	24	22.7	1.7	n/a	n/a

Expt	Spike		Duration	Product yield	Ketone yield	Alcohol ee	Acetate ee
	Type	Conc	Hours	%	%	% ee of S	% ee of R
8.10	Allylic acetate	1 equiv	24	86.0	None	79.3	91.0
8.11	Allylic acetate	1 equiv	24	80.8	None	86.9	95.3
8.12	Allylic acetate	2 equiv	24	80.7	None	-77.7	n/a
8.13	Acetone	1 equiv	24	19.6	1.5	n/a	n/a
8.14	Acetone	1 equiv	24	24.2	1.7	n/a	n/a
8.15	TEA	1 equiv	24	52.7	None	79.7	60.0
8.16	TEA	1 equiv	24	55.4	None	17.3	48.3
8.17	ThexA	1 equiv	24	47.8	None	29.3	67.3
8.18	ThexA	1 equiv	24	55.5	None	71.1	82.0
8.19	TheptA	1 equiv	24	54.6	None	37.0	77.8
8.20	TheptA	1 equiv	24	53.5	None	41.1	79.9
8.21	TOA	1 equiv	24	40.5	None	53.5	82.3
8.22	TOA	1 equiv	24	62.4	None	11.1	71.8

Table 14: Results for 'spiked' biotransformations of 40mM R allylic acetate, 1.5 equivalents of VA and 0.03g of novozyme 435 in 25mL of toluene, at 25°C and under atmospheric conditions.

Expt	Spike		Duration	Conversion to alcohol	Ketone yield	Alcohol ee	Acetate ee
	Type	Conc	Hours	%	%	% ee of S	% ee of R
9.1	None	-	24	None	None	None present	98.0
9.2	None	-	24	None	None	None present	97.0
9.3	Ru cymene	4 mol%	24	None	None	None present	96.3
9.4	Ru cymene	4 mol%	24	None	None	None present	97.4
9.5	Pl oct	22.4 mol%	24	None	None	None present	97.1
9.6	Pl oct	22.4 mol%	24	None	None	None present	93.1
9.7	TEA	1 equiv	24	None	None	None present	95.9
9.8	TEA	1 equiv	24	None	None	None present	96.7
9.9	ThexA	1 equiv	24	None	None	None present	96.2
9.10	ThexA	1 equiv	24	None	None	None present	95.5
9.11	TheptA	1 equiv	24	None	None	None present	95.3
9.12	TheptA	1 equiv	24	None	None	None present	94.7
9.13	TOA	1 equiv	24	None	None	None present	93.6
9.14	TOA	1 equiv	24	None	None	None present	93.7

APPENDIX III

RESULTS OF RACEMISATION REACTIONS

SUBSTRATE: phenyl ethanol, catalyst: ruthenium cymene

Table 1: Experimental conditions for racemisations of 33.5mM 1-phenyl ethanol with ruthenium cymene and P1 tris. 1.3 equivalents of the additive acetophenone were added to each reaction to suppress the ketone forming side reaction.

Expt	Type of substrate	[Ru cymene]	[P1 tris]	Toluene volume	T	Duration
		Mol%	Mol%	mL	°C	hours
10.1	S	4	20	25	25	48
10.2	S	4	20	25	25	48
10.3	S	4	20	25	25	48
10.4	S	4	20	25	25	48
10.5	S	4	20	25	25	48
10.6	S	4	20	25	25	24
10.7	S	4	20	25	25	24
10.8	S	4	20	25	25	52
10.9	S	4	20	25	25	52
10.10	S	8	20	25	25	48
10.11	S	8	20	25	25	24
10.12	S	12	20	25	25	24
10.13	S	12	20	25	25	24
10.14	S	16	20	25	25	24
10.15	S	16	20	25	25	24
10.16	S	4	20	25	25	24
10.17	S	4	40	25	25	48
10.18	S	4	40	25	25	48
10.19	R	4	40	25	25	48
10.20	R	4	40	25	25	48

Table 2: Results for racemisations of 1-phenyl ethanol with ruthenium cymene and P1 tris and acetophenone.

Expt	Reaction type	Ee of alcohol	Ketone yield
		S %	%
10.1	Benchmark	-16.0	0
10.2	Benchmark	94.4	0
10.3	Benchmark	-1.2	0
10.4	Benchmark	-11.5	0
10.5	Benchmark	-28.2	59.8
10.6	Benchmark	49.4	1.5
10.7	Benchmark	44.5	1.2
10.8	Benchmark	100.0	2.8
10.9	Benchmark	100.0	8.2
10.10	2x [Ru]	39.3	3.9
10.11	2x [Ru]	21.4	4.8
10.12	3x [Ru]	100	8.5
10.13	3x [Ru]	100	8.6
10.14	4x [Ru]	100	12.8
10.15	4x [Ru]	100	11.1
10.16	2x [P1 tris]	42.2	2.4
10.17	2x [P1 tris]	43.5	3.3
10.18	2x [P1 tris]	100	1.9
10.19	R isomer	84.1	3.5
10.20	R isomer	88.7	17.0

Table 3: Experimental conditions for racemisations of *S* 1-phenyl ethanol with ruthenium cymene and P1 oct.

Expt	[1-Phenyl ethanol]	[Ru cymene]	[P1 oct]	Atmosphere	Toluene volume	T	Duration
	mM	Mol%	Mol%		mL	°C	hours
11.1	33.49	4	20	N2	25	40	5
11.2	33.49	4	20	N2	25	40	5
11.3	33.49	4	20	Room	25	25	73
11.4	33.49	4	20	Room	25	25	73
11.5	33.49	4	20	Room	25	25	24
11.6	33.49	4	20	Argon	25	25	39
11.7	33.49	4	20	Argon	25	25	39
11.8	334.9	4	20	Argon	25	25	39
11.9	334.9	4	20	Argon	25	25	39
11.10	33.49	8	20	N2	25	40	5
11.11	33.49	8	20	N2	25	40	5
11.12	33.49	4	40	N2	25	40	5
11.13	33.49	4	40	N2	25	40	5

Table 4: Results for racemisations of *S* 1-phenyl ethanol with ruthenium cymene and P1 oct.

Expt	Explanation	Ee of alcohol	Ketone yield
		S %	%
11.1	Benchmark (N ₂)	97.2	12.5
11.2	Benchmark (N ₂)	95.6	1.2
11.3	Benchmark (air)	50.0	0
11.4	Benchmark (air)	53.6	0
11.5	Benchmark (air)	46.1	0
11.6	Benchmark (argon)	46.6	0
11.7	Benchmark (argon)	56.4	53.4
11.8	10x [substrate]	59.2	0
11.9	10x [substrate]	100.0	0
11.10	2x [Ru cymene]	95.7	-19.8
11.11	2x [Ru cymene]	96.5	-10.5
11.12	2x [P1 oct]	96.4	-21.1
11.13	2x [P1 oct]	97.2	-18.3

Table 5: Results for racemisations of 33.49mM *S* 1-phenyl ethanol with 4 mol% ruthenium cymene and 20 mol% P1 oct, in 25mL of toluene at 25°C under argon.

Expt	Spike		Ee of alcohol	Ketone yield
	Type	conc	S %	%
12.1	IPPA	1.4 equiv	51.2	None
12.2	IPPA	1.4 equiv	56.2	10.8
12.3	Phenyl acetate	1 equiv	65.5	3.0
12.4	Phenyl acetate	1 equiv	84.4	1.9
12.5	Acetone	1 equiv	60.5	5.1
12.6	Acetone	1 equiv	38.7	6.5
12.7	Acetone	1 equiv	87.5	None
12.8	Acetone	1 equiv	69.3	3.1

Table 6: Results for racemisations of 33.49mM S 1-phenyl ethanol with 4 mol% ruthenium cymene and various amine bases in 25mL of toluene at 25°C under argon.

Expt	Base		Ee of alcohol	Ketone yield
	Type	Conc	S %	%
13.1	TEA	3 equiv	56.0	19.3
13.2	TEA	3 equiv	76.4	10.4
13.3	TOA	3 equiv	60.8	6.2
13.4	TOA	3 equiv	69.8	0
13.5	TDDA	3 equiv	87.6	0
13.6	TDDA	3 equiv	86.8	0

SUBSTRATE: phenyl ethanol, catalyst: ruthenium indenyl

Table 7: Experimental conditions for racemisations of 33.49mM S 1-phenyl ethanol, with 1.34mM ruthenium indenyl, in 25mL of toluene, under atmospheric conditions and 25°C

Expt	Base		Spike		Duration
	Type	Conc	Type	Conc	hours
14.1	P1 oct	20 mol%			25
14.2	P1 oct	20 mol%			25
14.3	P1 oct	10 mol%			25
14.4	P1 oct	10 mol%			25
14.5	P1 oct	5 mol%			25
14.6	P1 oct	5 mol%			25
14.7	P1 oct	2.5 mol%			25
14.8	P1 oct	2.5 mol%			25
14.9	P1 oct	20mol%	IPPA	1.4 equiv	24
14.10	TEA	3 equiv			30
14.11	TEA	3 equiv			30
14.12	TOA	3 equiv			30
14.13	TOA	3 equiv			30

Table 8: Results of racemisations of 33.49mM *S* 1-phenyl ethanol, with 1.34mM ruthenium indenyl, in 25mL of toluene.

Expt	Explanation	Ee of S	Ketone yield
		%	%
14.1	20mol% P1 oct	100.0	2.2
14.2	20mol% P1 oct	99.0	7.2
14.3	10mol% P1 oct	99.5	7.0
14.4	10mol% P1 oct	95.6	5.7
14.5	5mol% P1 oct	99.4	10.4
14.6	5mol% P1 oct	97.8	4.4
14.7	2.5mol% P1 oct	97.2	9.7
14.8	2.5mol% P1 oct	99.9	7.6
14.9	20mol% P1 oct + IPPA	81.6	None
14.10	3 equiv TEA	99.2	9.7
14.11	3 equiv TEA	96.3	6.3
14.12	3 equiv TOA	100.0	6.2
14.13	3 equiv TOA	100.0	2.0

Table 9: Experimental set-up for racemisations of *S* 1-phenyl ethanol with 4 mol% ruthenium amino cpd with 20 mol% P1 oct, in 25mL of toluene, under argon and at 25°C.

Expt	1-Phenyl Ethanol	Toluene volume	Ru amino cpd	P1 oct	Duration	Ee of S	Ketone yield
	mM	mL	mol%	mol%	hours	%	%
15.1	334.9	4	4	20	39	48.7	14.0
15.2	334.9	4	4	20	39	60.3	None
15.3	33.49	25	4	20	39	69.0	None

Table 10: Results for racemisations of product from resolution at high and low initial 1-phenyl ethanol concentrations. See text for exact composition of racemisation feed. Reactions performed with 4 mol% ruthenium catalyst and 20mol% P1 oct in 25mL of toluene, under atmospheric conditions and at 25°C.

Expt	Catalyst	[1-phenyl ethanol]	Ee of R acetate	Ee of S alcohol	Ketone yield
			%	%	%
16.1	cymene	High	99.8	n/m	None
16.2	cymene	High	68.1	n/m	None
16.3	cymene	Low	96.4	n/m	None
16.4	cymene	Low	87.9	n/m	None
16.5	Amino cpd	Low	39.4	n/m	None
16.6	Amino cpd	Low	47.6	n/m	None

SUBSTRATE: allylic alcohol, catalyst: ruthenium cymene

Table 11: Experimental conditions for racemisations of 33.49mM S allylic alcohol with 4 mol% ruthenium cymene and P1 oct in 25mL of toluene.

Expt	[P1oct]	'Spike'		Atmosphere	T	Duration
	Mol%	Type	Conc		°C	hours
17.1	20			Room	25	24
17.2	20			Room	25	30
17.3	20			Room	25	30
17.4	20			Argon	40	6
17.5	20			Argon	40	6
17.6	20	VA	1.5 equiv	Room	25	24
17.7	20	VA	1.5 equiv	Room	25	24
17.8	20	VA	1.5 equiv	Room	25	30
17.9	20	Acetaldehyde	1 equiv	Room	25	24
17.10	20	Acetaldehyde	1 equiv	Room	25	24
17.11	20	Acetic acid	1 equiv	Room	25	24
17.12	20	Allylic acetate	1 equiv	Room	25	24
17.13	20	Allylic acetate	1 equiv	Room	25	24

Table 12: Results for racemisations of 33.49mM *S* allylic alcohol with 4 mol% ruthenium cymene and P1 oct in 25mL of toluene.

Expt	Explanation	Ee of S	Ketone yield
		%	%
17.1	Benchmark	77.2	16.1
17.2	Benchmark	49.4	9.1
17.3	Benchmark	30.8	10.4
17.4	Benchmark, argon	98.3	0
17.5	Benchmark, argon	97.7	0
17.6	VA spike	79.2	12.5
17.7	VA spike	84.2	16.7
17.8	VA spike	52.8	13.9
17.9	Acetaldehyde spike	78.8	26.2
17.10	Acetaldehyde spike	46.5	20.2
17.11	Acetic acid spike	100.0	0
17.12	Allylic acetate spike	100.0	21.6
17.13	Allylic acetate spike	67.4	18.8

Table 13: Experimental conditions and results for racemisations of 33.49mM *S* allylic alcohol with 4 mol% ruthenium cymene and amine bases in 25mL of toluene. Reactions were performed for 24 hours, under air and 25°C

Expt	Base	Concentration	Ee of S	Ketone yield
		Equiv	%	%
18.1	TEA	0.5	16.9	None
18.2	TEA	0.5	7.2	None
18.3	TOA	0.5	49.9	None
18.4	TOA	0.5	31.6	None
18.5	TEA	1	14.6	None
18.6	TEA	1	20.1	None
18.7	TOA	1	45.2	None
18.8	TOA	1	49.7	None

Expt	Base	Concentration	Ee of S	Ketone yield
		Equiv	%	%
18.9	ThexA	1	45.2	12.3
18.10	ThexA	1	46.9	19.8
18.11	TheptA	1	43.3	16.8
18.12	TheptA	1	48.9	18.6
18.13	TEA	2	12.2	None
18.14	TEA	2	10.8	None
18.15	TOA	2	40.4	None
18.16	TOA	2	35.2	None
18.17	TEA	3	59.4	None
18.18	TEA	3	59.3	None
18.19	TOA	3	80.2	None
18.20	TOA	3	74.5	None

Table 14: Experimental conditions and results for 'spiked' racemisations of 33.49mM S allylic acetate with 4 mol% ruthenium cymene in 25mL of toluene, under atmospheric conditions and 25°C and for a duration of 24 hours.

Expt	Base		Spike		Ee of R alcohol	Ketone yield
	Type	Conc	%	%	%	%
19.1	TEA	1 equiv			99.0	None
19.2	TEA	1 equiv			99.5	None
19.3	TOA	1 equiv			99.6	None
19.4	TOA	1 equiv			99.6	None
19.5	ThexA	1 equiv			99.8	None
19.6	ThexA	1 equiv			99.9	None
19.7	TEA	2 equiv			99.6	None
19.8	TEA	2 equiv			99.4	None
19.9	TOA	2 equiv			99.4	None
19.10	TOA	2 equiv			99.5	None

Expt	Base	Spike	Ee of R alcohol	Ketone yield		
	Type	Conc	%	%	%	%
19.11	Ploct	20mol%	VA	1 equiv	99.4	None
19.12	Ploct	20mol%	VA	1 equiv	98.6	None
19.13	Ploct	20mol%	Acetaldehyde	1 equiv	99.3	None
19.14	Ploct	20mol%	Acetaldehyde	1 equiv	99.3	None
19.15	Ploct	20mol%	Enzyme	0.03g	100.0	None
19.16	Ploct	20mol%	Enzyme	0.03g	100.0	None
19.17	Ploct	20mol%	Acetic acid	1 equiv	99.4	None
19.18	Ploct	20mol%	Acetic acid	1 equiv	99.6	None

Table 15: Results for racemisations of product from resolution. Feed contains 16.1mM allylic alcohol and 17.4mM allylic acetate. Reactions performed with 4 mol% ruthenium cymene and various bases in 25mL of toluene, under atmospheric conditions and at 25°C.

Expt	Base		Ee of R acetate	Ee of S alcohol	Ketone yield
	Type	Conc	%	%	%
20.1	Ploct	20 mol%	38.4	61.2	68.4
20.2	Ploct	20 mol%	65.4	86.1	92.0
20.3	TEA	1 equiv	94.5	69.5	28.0
20.4	TEA	1 equiv	93.3	79.3	68.3
20.5	ThexA	1 equiv	95.8	89.6	27.9
20.6	ThexA	1 equiv	96.4	92.4	21.5
20.7	TheptA	1 equiv	95.5	93.8	7.4
20.8	TheptA	1 equiv	93.9	87.2	None
20.9	TOA	1 equiv	95.2	93.1	None
20.10	TOA	1 equiv	96.4	95.9	None

Table 16: Results for racemisations of product from resolution. Feed contains 16.1mM allylic alcohol and 17.4mM allylic acetate. Reactions performed with 4 mol% ruthenium cymene and various bases in 25mL of toluene, under argon and at 25°C. All reactions contain 1 equivalent of sodium carbonate.

Expt	Base		Ee of R acetate	Ee of S alcohol	Ketone yield
	Type	Conc	%	%	%
21.1	Ploct	20 mol%	95.3	64.2	2.9
21.2	Ploct	20 mol%	84.9	73.3	None
21.3	Ploct	20 mol%	98.2	76.5	40.7
21.4	TEA	1 equiv	99.6	21.5	None
21.5	TEA	1 equiv	96.9	93.2	None
21.6	ThexA	1 equiv	97.7	96.8	28.2
21.7	ThexA	1 equiv	75.8	52.3	41.6
21.8	TheptA	1 equiv	97.6	82.7	64.2
21.9	TheptA	1 equiv	97.3	95.4	60.4
21.10	TOA	20 mol%	98.1	93.1	28.1
21.11	TOA	20 mol%	97.2	98.1	24.3

APPENDIX IV

RESULTS OF ONE POT REACTIONS

Table 1: Experimental conditions for one-pot DKRs of 1-phenyl ethanol with various catalysts and acyl donors. All reactions are in 25mL of toluene and are well stirred to ensure adequate contact between substrates and catalysts and thus provide the best opportunity for reaction.

Expt	[1-Phenyl ethanol]	Acyl donor		Ruthenium catalyst		Base		Enzyme		T	Atmosphere	Duration
	mM	Type	equiv	Type	mol%	Type	Conc	Type	g	°C		hours
22.1	20	4 CPA	1.5	Indenyl	2	TEA	3 equiv	PCL	0.03	40	Nitrogen	8
22.2	20	4 CPA	1.5	Indenyl	2	TEA	3 equiv	PCL	0.03	40	Nitrogen	8
22.3	20	4 CPA	1.5	Indenyl	2	TOA	3 equiv	PCL	0.03	40	Nitrogen	8
22.4	20	4 CPA	1.5	Indenyl	2	TOA	3 equiv	PCL	0.03	40	Nitrogen	8
22.5	20	4 CPA	1.5	Indenyl	2	TDDA	3 equiv	PCL	0.03	40	Nitrogen	8
22.6	20	4 CPA	1.5	Indenyl	2	TDDA	3 equiv	PCL	0.03	40	Nitrogen	8
22.7	33.49	IPPA	1.5	Cymene	4	Ploct	20 mol%	Nov 435	0.03	25	room	73
22.8	33.49	IPPA	1.5	Cymene	4	Ploct	20 mol%	Nov 435	0.03	25	Room	73
22.9	33.49	IPPA	1.5	Indenyl	4	Ploct	20 mol%	Nov 435	0.03	25	Room	30
22.10	33.49	IPPA	1.5	Indenyl	4	Ploct	20 mol%	Nov 435	0.03	25	Room	30

Expt	[1-Phenyl ethanol]	Acyl donor		Ruthenium catalyst		Base		Enzyme		T	Atmosphere	Duration
	mM	Type	equiv	Type	mol%	Type	Conc	Type	g	°C		hours
22.11	33.49	IPPA	1.5	Indenyl	4	TEA	3 equiv	Nov 435	0.03	25	Room	30
22.12	33.49	IPPA	1.5	Indenyl	4	TEA	3 equiv	Nov 435	0.03	25	Room	30
22.13	33.49	IPPA	1.5	Indenyl	4	TOA	3 equiv	Nov 435	0.03	25	Room	30
22.14	33.49	IPPA	1.5	Indenyl	4	TOA	3 equiv	Nov 435	0.03	25	Room	48
22.16	334.9	VA	1.5	Cymene	4	PlOct	20 mol%	Nov 435	0.3	25	Argon	48
22.17	33.49	VA	1.5	Cymene	4	PlOct	20 mol%	Nov 435	0.03	25	Argon	48
22.18	33.49	VA	1.5	Cymene	4	PlOct	20 mol%	Nov 435	0.03	25	Argon	48
22.19	334.9	VA	1.5	Amino cpd	4	PlOct	20 mol%	Nov 435	0.3	25	Argon	48
22.20	33.49	VA	1.5	Amino cpd	4	PlOct	20 mol%	Nov 435	0.03	25	Argon	48
22.21	33.49	VA	1.5	Amino cpd	4	PlOct	20 mol%	Nov 435	0.03	25	Argon	48

Table 2: Results for one-pot DKRs of 1-phenyl ethanol with various catalysts and acyl donors. All reactions are in 25mL of toluene and are well stirred to ensure adequate contact between substrates and catalysts and thus provide the best opportunity for reaction.

Expt	[1-phenyl ethanol]	Acyl donor	Ru	Base	Enzyme	Yield	Ketone yield	Overall mass balance	Ee of alcohol (S)	Ee of acetate (R)
						%	%	%	%	%
22.1	Low	4 CPA	Indenyl	TEA	PCL	21.0	None	112.4	n/a	n/a
22.2	Low	4 CPA	Indenyl	TEA	PCL	42.9	18.4	120.5	n/a	n/a
22.3	Low	4 CPA	Indenyl	TOA	PCL	45.8	None	174.4	n/a	n/a
22.4	Low	4 CPA	Indenyl	TOA	PCL	31.5	None	146.2	n/a	n/a
22.5	Low	4 CPA	Indenyl	TDDA	PCL	16.8	10.8	128.9	n/a	n/a
22.6	Low	4 CPA	Indenyl	TDDA	PCL	23.4	14.7	139.1	n/a	n/a
22.7	Low	IPPA	Cymene	Pl oct	Nov 435	52.7	None	107.8	75.0	n/a
22.8	Low	IPPA	Cymene	Pl oct	Nov 435	46.5	22.1	102.0	67.8	n/a
22.9	Low	IPPA	Indenyl	Pl oct	Nov 435	1.4	3.3	103.9	88.4	n/a
22.10	Low	IPPA	Indenyl	Pl oct	Nov 435	0.0	5.8	104.0	90.0	n/a
22.11	Low	IPPA	Indenyl	TEA	Nov 435	28.1	None	113.4	43.9	n/a
22.12	Low	IPPA	Indenyl	TEA	Nov 435	26.6	2.5	114.0	58.9	n/a
22.13	Low	IPPA	Indenyl	TOA	Nov 435	48.9	None	100.4	100.0	n/a

Expt	[1-phenyl ethanol]	Acyl donor	Ru	Base	Enzyme	Yield	Ketone yield	Overall mass balance	Ee of alcohol (S)	Ee of acetate (R)
						%	%	%	%	%
22.14	Low	IPPA	Indenyl	TOA	Nov 435	24.2	None	86.5	100.0	n/a
22.16	High	VA	Cymene	Ploct	Nov 435	79.8	None	188.4	59.2	100.0
22.17	Low	VA	Cymene	Ploct	Nov 435	49.9	None	98.4	100.0	100.0
22.18	Low	VA	Cymene	Ploct	Nov 435	54.7	3.0	161.9	100.0	100.0
22.19	High	VA	Amino cpd	Ploct	Nov 435	69.3	14.1	115.4	35.5	100.0
22.20	Low	VA	Amino cpd	Ploct	Nov 435	47.8	10.2	121.4	20.7	100.0
22.21	Low	VA	Amino cpd	Ploct	Nov 435	57.1	None	155.5	42.1	100.0

Table 3: Experimental conditions for one-pot DKRs of allylic alcohol with 1.5 equivalents of VA as the acyl donor, ruthenium cymene, novozyme 435 and P1oct. All reactions are in 25mL of toluene at 25°C for 24 hours and are well stirred to ensure adequate contact between substrates and catalysts and thus provide the best opportunity for reaction.

Expt	[allylic alcohol]	[Cymene]	[P1 oct]	Enzyme Mass	Atmosphere
	mM	mol %	mol %	g	
23.1	33.75	4	20	0.03	Room
23.2	33.75	4	20	0.03	Room
23.3	33.75	4	20	0.03	Nitrogen
23.4	33.75	8	20	0.03	Nitrogen
23.5	33.75	8	20	0.03	Nitrogen
23.6	33.75	4	40	0.03	Nitrogen
23.7	33.75	4	40	0.03	Nitrogen
23.8	33.75	4	20	0.06	Argon
23.9	33.75	4	20	0.06	Argon
23.10	33.75	4	20	0.12	Argon
23.11	33.75	4	20	0.12	Argon
23.12	337.5	4	20	0.3	Argon
23.13	337.5	4	20	0.3	Argon
23.14	337.5	4	20	0.15	Argon
23.15	337.5	4	20	0.15	Argon
23.16	337.5	4	20	0.075	Argon
23.17	337.5	4	20	0.075	Argon

Table 4: Results for one-pot DKRs of allylic alcohol (AA) with 1.5 equivalents of VA as the acyl donor, ruthenium cymene, novozyme 435 and Ploct.

Expt	Description	Yield	Ketone yield	Overall mass balance	Ee of alcohol (S)	Ee of acetate (R)
		%	%	%	%	%
23.1	Bench	22.1	25.1	172.6	3.7	66.1
23.2	Bench	16.0	51.5	69.4	3.5	80.9
23.3	Bench	10.9	7.9	92.8	0.0	91.6
23.4	2x Ru	9.1	19.3	138.1	0.0	87.7
23.5	2x Ru	10.8	5.1	60.3	0.0	91.6
23.6	2x Ploct	14.3	12.9	83.4	0.0	89.5
23.7	2x Ploct	12.4	4.5	57.3	0.0	95.6
23.8	2x enzyme	75.1	16.6	110.8	21.7	86.5
23.9	2x enzyme	63.2	2.7	119.0	61.5	34.1
23.10	4x enzyme	73.8	2.1	151.7	39.6	72.4
23.11	4x enzyme	79.7	0.6	196.8	24.0	74.5
23.12	High [S]	70.1	3.0	102.6	98.2	99.3
23.13	High [S]	56.6	2.6	76.3	93.6	89.3
23.14	High [S], 0.5x enzyme	59.7	13.4	89.6	89.9	99.5
23.15	High [S], 0.5x enzyme	74.3	9.5	100.6	99.3	100.0
23.16	High [S], 0.25x enzyme	56.1	11.2	83.8	n/a	n/a
23.17	High [S], 0.25x enzyme	57.8	9.2	86.0	64.7	75.8

Table 5: Experimental conditions and results for one-pot DKRs of 33.75mM allylic alcohol with 1.5 equivalents of VA as the acyl donor, ruthenium cymene, novozyme 435 and ThexA. All reactions are in 25mL of toluene under atmospheric conditions, at 25°C for 24 hours and are well stirred to ensure adequate contact between substrates and catalysts and thus provide the best opportunity for reaction.

Expt	Cymene	ThexA	Yield	Ketone yield	Overall mass balance	Ee of alcohol (S)	Ee of acetate (R)
	mol %	Equiv	%	%	%	%	%
24.1	4	1	28.5	2.7	67.5	97.9	90.2
24.2	4	1	26.9	3.5	75.2	97.9	93.9
24.3	8	1	28.9	18.4	88.1	95.9	92.9
24.4	8	1	29.2	5.9	94.4	97.0	92.0
24.5	4	2	35.2	25.1	93.1	95.8	89.6
24.6	4	2	36.0	46.1	101.6	88.3	87.4
24.7	16	1	39.0	3.5	68.6	n/a	100.0
24.8	16	1	32.1	4.7	106.8	95.3	90.0
24.9	4	4	28.3	3.8	90.6	98.5	97.7
24.10	4	4	25.9	3.1	86.2	98.0	92.6

Table 6: Experimental conditions and results for one-pot DKRs of allylic alcohol with 1.5 equivalents acyl donor, 4 mol% ruthenium cymene, novozyme 435 and 1 equivalent of base. All reactions in 25mL of toluene under argon, at 25°C for 4 hours and well stirred to ensure adequate contact between substrates and catalysts and thus provide the best opportunity for reaction.

Expt	[allylic alcohol]	Acyl donor	Base	Yield	Ketone yield	Overall mass balance	Ee of alcohol (S)	Ee of acetate (R)
	mM			%	%	%	%	%
25.1	337.5	VA	TEA	75.2	2.9	84.9	90.9	69.2
25.2	337.5	VA	TEA	67.3	1.6	74.5	95.8	72.1
25.3	33.75	VA	TEA	64.9	n/a	n/a	76.7	100.0
25.4	33.75	VA	TEA	65.5	n/a	n/a	67.2	100.0
25.5	33.75	VA	TOA	69.7	n/a	n/a	n/a	100.0
25.6	33.75	VA	TOA	72.5	n/a	n/a	n/a	100.0

APPENDIX V

DETAILS OF FILTRATION EXPERIMENTS

The details of the filtration experiments for the 1-phenyl ethanol, allylic alcohol system components and catalysts are shown below. Table 1 gives details of the substrates and products, Table 2, the acyl donors, Table 3, the transition metal catalysts and Table 4 the phosphazene bases. The results are reported as solvent flux (calculated from equation 2.3), solute rejection (equation 2.1), retention (equation 2.2) and mass balance, the ratio of solute measured at the end of the experiment to that in the feed, which should, of course, be 100%. C_f is the feed concentration and V_f is the feed volume. The filtrations were continued until half the feed volume had been permeated.

Table 1: Filtration results for substrates and products, with Starmem™ 122, in toluene and at 30bar.

Component	C_f	V_f	T	Flux	Rejection	Retention	Mass balance
	mM	mL	°C	L/m ² h	%	%	%
Allylic alcohol	25	40	25	42.60	20.09	53.13	92.75
Allylic alcohol	25	40	25	40.50	20.27	49.03	85.39
Allylic acetate	25	40	25	43.50	33.65	58.44	94.50
Allylic acetate	25	40	25	41.25	24.31	56.51	98.65
1-Phenyl ethanol	33.75	40	25	48.10	6.59	48.28	95.62
1-Phenyl ethanol	33.75	40	25	50.13	2.6	48.01	97.12
1-Phenyl ethanol	33.75	40	25	50.70	6.81	51.11	98.74
1-Phenyl ethanol	33.75	40	40	58.68	-0.92	53.04	103.21
1-Phenyl ethanol	33.75	40	40	48.10	-0.98	51.76	101.54
Acetophenone	5	40	25	50.13	9.10	54.07	100.87
Acetophenone	5	40	25	50.70	9.74	52.73	107.85
Acetophenone	5	40	25	43.92	12.6	51.66	91.79
1-Phenyl acetate	33.75	40	25	52.59	15.00	50.70	93.79
1-Phenyl acetate	33.75	40	25	51.36	11.36	49.50	93.38

Table 2: Filtration results for acyl donors, with Starmem™ 122, in toluene and at 30bar.

Component	C _f	V _f	T	Flux	Rejection	Retention	Mass balance
	mM	mL	°C	L/m ² h	%	%	%
4 CPA	33.75	40	25	43.70	25.94	41.54	78.90
4 CPA	33.75	40	25	45.52	25.14	41.38	78.98
IPPA	33.75	40	25	114.94	18.06	52.94	96.31
IPPA	33.75	40	25	127.30	14.26	51.30	106.25
Vinyl acetate	49.95	40	25	50.13	3.07	49.50	95.19
Vinyl acetate	49.95	40	25	50.70	5.46	48.89	92.90
Vinyl acetate	49.95	40	25	46.90	7.74	43.81	84.23

Table 3: Filtration results for transition metal catalysts, with Starmem™ 122, in toluene and at 30bar.

Component	C _f	V _f	T	Flux	Rejection	Retention	Mass balance
	mM	mL	°C	L/m ² h	%	%	%
Ruthenium cymene	1	40	25	34.60	96.76	84.01	87.75
Ruthenium cymene	1	40	25	39.96	98.88	70.10	70.91
Ruthenium cymene	1.68	40	25	34.45	98.88	70.10	70.86
Aminocyclopentadienyl ruthenium	1.35	40	25	n/m	100.0	101.85	101.85
Aminocyclopentadienyl ruthenium	1.35	40	25	n/m	100.0	108.9	103.7
Ruthenium indenyl	1.35	40	25	n/m	88.33	99.94	95.19
Ruthenium indenyl	1.35	40	25	n/m	82.72	84.39	80.37

Table 4: Filtration results for phosphazene bases, with Starmem™ 122, in toluene and at 30bar.

Base	C _f	V _f	T	Flux	Rejection	Retention	Mass balance
	mM	mL	°C	L/m ² h	%	%	%
Ploct	5	40	25	12.30	99.57	90.65	91.04
Ploct	5	40	25	10.11	99.69	78.62	78.84
Pltris	1	40	25	9.44	100.00	87.75	97.75
Pltris	1	40	25	8.77	91.67	76.16	82.50

APPENDIX VI

MOLECULAR MODELLING OF AMINE BASES [1,2]

Computational chemistry simulates chemical structures numerically, based on fundamental laws of physics, allowing the study of chemical phenomena by running simulations rather than by experiment. There are two broad areas devoted to the structure of molecules and their reactions: *molecular mechanics* and *electronic structure theory*, which both perform the same basic types of calculations:

- 1) computing the energy of a molecule
- 2) geometrical optimisation - locating the structure with the lowest energy
- 3) computing vibrational frequencies of molecules resulting from interatomic motion within the molecule

1. Molecular mechanics

Molecular mechanics simulations use classical physics to predict the structures and properties of molecules. The methods are characterised by *force fields* which consist of

- a set of equations defining how the potential energy of the molecule varies with the positions of its component atoms
- a set of *atom types* defining the characteristics of an element in its chemical context
- *parameter sets* that fit the equations and atom types to experimental data.

Molecular mechanics calculations analyse interactions between nuclei in a molecule and neglect the individual electrons. Electronic interactions are implicitly included in the force field parameters. The limitations of this method are that the force fields used are very system specific and cannot be generalised. Also, due to neglecting the electrons, systems where electronic effects, such as bond breaking / bond formation, are important cannot be analysed.

2. Electronic structure theory

Electronic structure theory uses quantum mechanics, assuming that the energy of a molecule can be calculated from the Schrödinger equation, subject to appropriate boundary conditions:

$$\left\{ \frac{-h^2}{8\pi^2m} \nabla^2 + V \right\} \Psi(r,t) = \frac{ih}{2\pi} \frac{\partial \Psi(r,t)}{\partial t} \quad (1)$$

where	Ψ	=	wavefunction
	m	=	mass of particle
	h	=	Planck's constant
	V	=	potential field in which particle is moving

If V is not a function of time, the equation may be simplified by separation of variables, giving $H\Psi(r) = E\Psi(r)$, where H is the Hamiltonian operator. Solutions of this equation correspond to different stationary states of the particle, or molecule, the lowest energy of which is the ground state. Since exact solutions to the Schrödinger equation are not computationally possible in most cases, mathematical approximations must be used:

- *semi-empirical methods* AM1, MINDO/3 and PM3, as used by programs like *Gaussian*, using parameters extracted from experimental data to simplify the computation, generating an approximate form of the Schrödinger equation.
- *Ab initio methods*, also used by *Gaussian*, based purely on the first principles of quantum mechanics, a few fundamental physical constants (speed of light, Planck's constant etc.) but no experimental parameters.

The choice of method depends on the trade-off between computational cost and accuracy of result: *Ab initio* methods may require super computers but generate highly quantitative predictions, whereas semi-empirical solutions may be generated quickly, but give more qualitative descriptions (reasonable quantitative predictions can be obtained only if a good parameter set exists).

A molecular modelling package such as *Gaussian* is capable of predicting a range of properties: optimised molecular energy and structure, energy and structure of transition states, bond and reaction energies, molecular orbitals, dipole moments, atomic charges and electrostatic potentials, vibrational frequencies, IR and raman spectra, NMR properties, polarizabilities, thermochemical properties, reaction pathways

Gaussian uses a model chemistry for predicting the properties of a molecule or system. The model chemistry consists of a theoretical method and a basis set, the combination each of which represents a different approximation to the Schrödinger equation.

In this work the theoretical model used is the default ground state (rather than electronically excited) Hartree-Fock method. This is useful for providing initial predictions of structures of stable molecules in many systems. It does not, however, account for interactions between electrons.

A basis set is the mathematical description of the orbitals in a molecule, which combine to approximate the overall electronic wavefunction. A larger basis set is more accurate as it imposes fewer restrictions on the spatial locations of the electrons. A minimal basis set contains the minimum number of basis functions for each atom. In this work a larger (and thus more accurate) basis set will be used, the 321G (split valence basis set) method will be used. It is an intermediate method in terms of computational cost, range of applicability and error in calculation of molecular energy.

For solvent systems, *Self-consistent Reaction Field (SCRF)* methods are used, which model the solvent as a continuum of uniform dielectric constant, ϵ , the reaction field. The solute is placed into a cavity within the solvent. There are various approaches to defining the cavity and the reaction field, two of which are shown in Figure 1. The simplest, the Onsager model, allows the solute to occupy a fixed spherical cavity of a given radius, r , in the solvent field. A dipole in the solute molecule induces a dipole in the medium; the electric field thus applied interacts with the solute dipole. However, this model is not applicable to systems having a zero dipole moment – the

result will be equivalent to a gas phase calculation. In this work, the default SCRF is used: Tomasi's Polarised continuum model (PCM). This defines the cavity as the union of a series of interlocking atomic spheres. The effect of polarisation of the solvent continuum is represented numerically and computed by numerical integration.

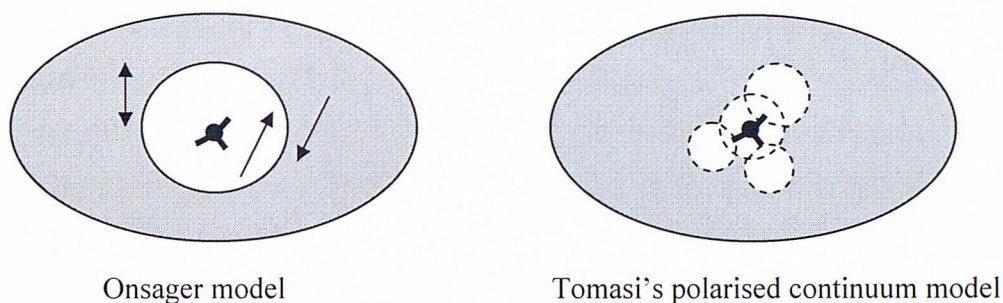


Figure 1: Self-consistent Reaction Field (SCRF) models for simulating solvent continuum.

Details of packages used:

Gauss View 3.0

Gaussian Inc, Pittsburgh, USA, www.gaussian.com

CS Chem 3d Ultra, version 7.0.0, Molecular modelling and analysis

Cambridgesoft, Cambridge, USA, www.cambridgesoft.com

The molecular structures of the amine bases under investigation were submitted to Gaussian for optimisation. The ground state Hartree-Fock method was used with default spin, with a 3-21G basis set. The PCM method was used to describe the solvation effects, with toluene as the solvent. Figure 2 shows the optimised chemical structures.

The following parameters for the optimised amine base molecules were extracted using Chem 3D: Bend Energy¹ (kcal/mol), boiling point (K), Connolly solvent excluded volume² (Å³), critical volume (cm³/mol), diameter, ovality³, shape attribute and total energy (kcal/mol). The results are displayed graphically in Figure 3.

The diameter (based on spherical molecule) of the molecules increases uniformly with the number of carbons in the amine chain, thus, if a size exclusion mechanism for permeation through the membrane, a higher rejection is expected for the amines with longer carbon chains, taking into account the molecular weight cutoff of the membrane. This is also reflected in the volume parameters, which also increase uniformly with increasing carbon chain. This clearly does not help to explain the anomalous low rejection of TDDA. The ovality (that is deviation in shape from a perfect sphere) increases as the carbon chain increases, as is to be expected based on the molecular structure of the species. The smallest amine base, triethyl amine, is expected to be a more 'globular', spherical molecule. The total energy of the molecules increases with the size of the carbon chain, again as expected due to the increase in the number of atoms present. The bend energy follows an unexpected trend, with the values for the heptyl and octyl amines being much lower than the others. The simulations predict an increasing boiling point with molecular size, which is not found in practice: the simulated values predict the actual values well for the smaller amines, but the error becomes significant for the larger amines. This suggests that more complex molecular interactions exist than are accounted for in these simple simulations.

¹ BEND ENERGY: Sum of angle bending terms in the force field equation. Larger values mean that more energy is required to deform the angles from their equilibrium positions.

² CONNOLLY SOLVENT EXCLUDED VOLUME: Volume contained in within the contact molecular surface.

³ OVALITY: Ratio of molecular surface area to the minimum surface area, that is, a sphere with the same volume as the solvent excluded volume.

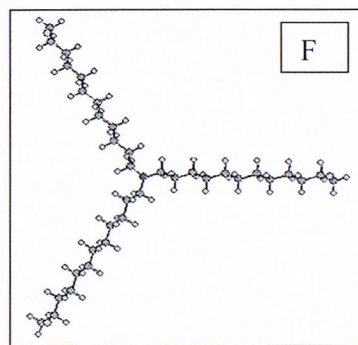
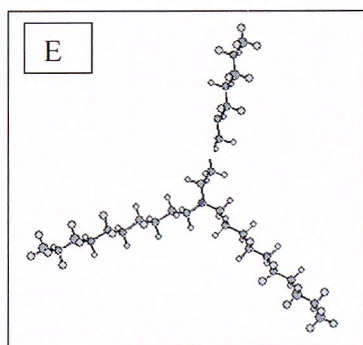
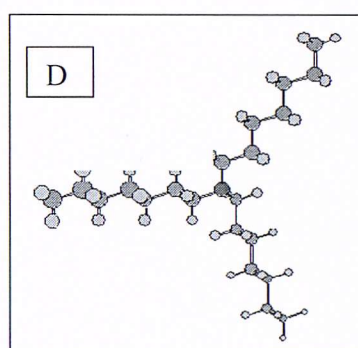
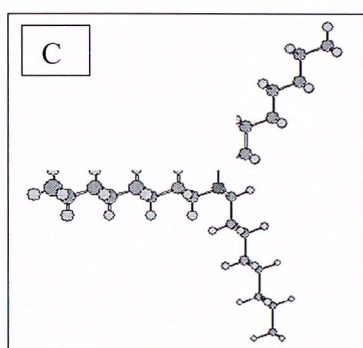
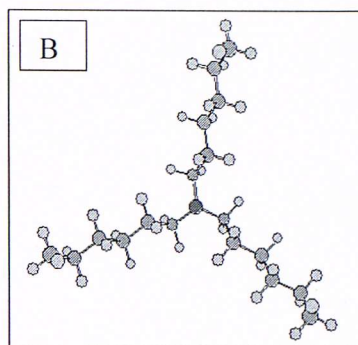
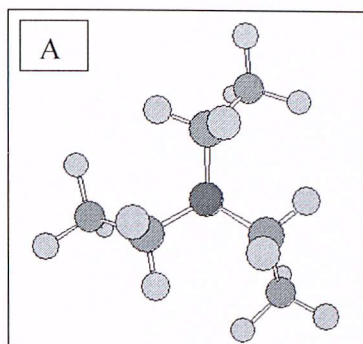


Figure 2: Optimised structures for amine bases:

<i>A</i>	<i>TEA</i>	<i>B</i>	<i>ThexA</i>
<i>C</i>	<i>TOA</i>	<i>D</i>	<i>TheptA</i>
<i>E</i>	<i>TDA</i>	<i>F</i>	<i>TDDA</i>

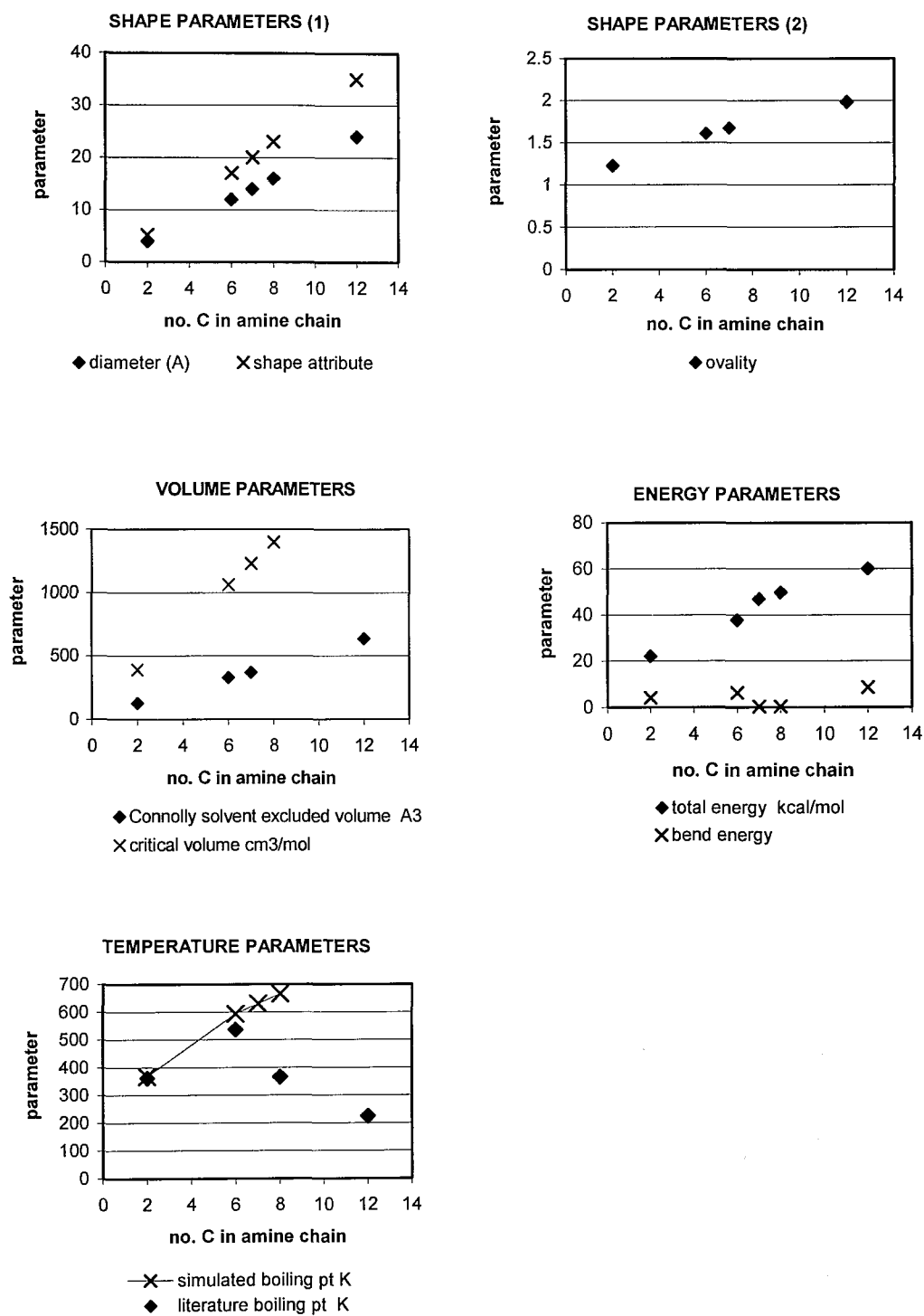


Figure 3: Parameters derived from molecular modelling simulations for amine bases.

In order to investigate this further, dynamic molecular simulations were run with an increasing temperature, up to 1000°C. Although this is well above the range of temperatures to be used in this study, it will be useful to observe how the movement of the alkyl chains changes as the temperature is increased. The chains in the larger amines become more mobile and flexible as the temperature is increased. This increased mobility at highly elevated temperatures might reduce “tangling” of the carbon chains. This increased flexibility of the carbon chains for the larger amines may help explain the anomalous filtration results. Conceivably, for the larger amines, the flexible chains could fold back on themselves allowing the molecular to take a more linear form, whereas, for the smaller amines, the chains are not long enough to fold back on themselves causing a more ‘globular’ shape which cannot permeate the membrane pores as easily. A schematic demonstrating this mechanism is suggested in Figure 4. There is also evidence in the literature [3] that long chain molecules may, in liquid state, keep some of the order they possessed in the solid state – the chains may be orientated one along the other in order to maximise the Van der Waals interaction along the chains.

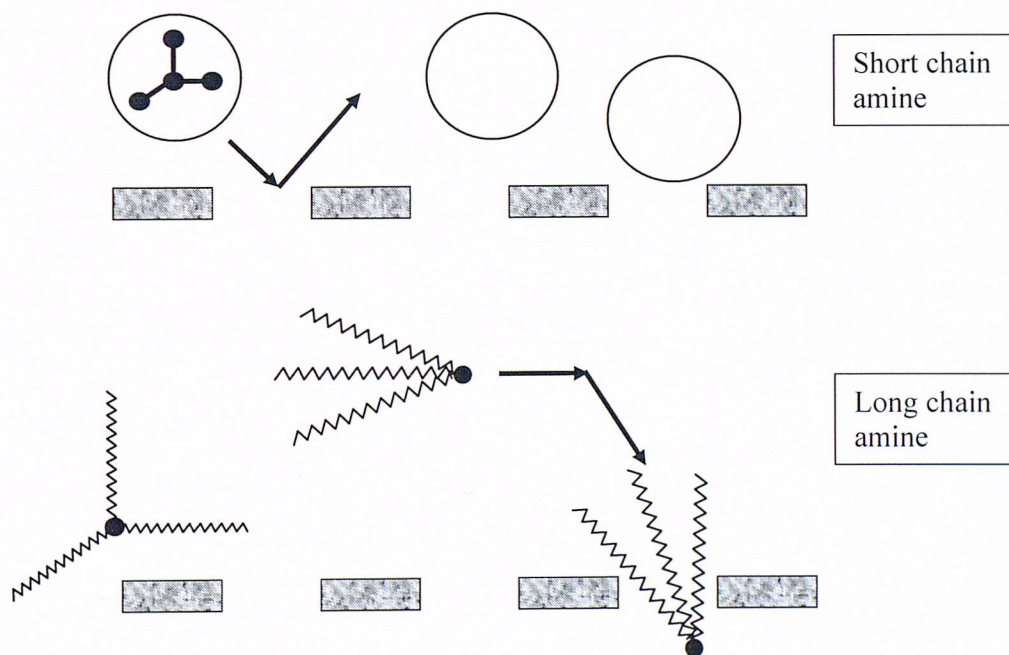


Figure 4: Schematic rationalising amine base results.

References:

1. Exploring Chemistry with electronic structure methods, 2nd ed, James B. Foresman, Aeleen Frisch, Gaussian Inc., Pittsburgh, PA, USA, (1993).
2. A. Frisch, R. D. Dennington, T.A. Keith, Gauss View Reference manual, Gaussian Inc (2003).
3. R. Phillipe, G. Delmas, P.N. Hong, Excess heats of tri-*n*-alkanes and tetraalkyl compounds in linear and branched alkanes: correlations of molecular orientations and steric hindrance effect, *Canadian J. Chem.* **57** (1979) 517-525.

APPENDIX VII
LOOP FLOW CALCULATIONS FOR MEDKR
RIG

The computer control software for the MEDKR rig generates a log of the balance reading as a function of time, an example of which is shown in Figure 1. The control system operates by maintaining the balance reading between two values, the upper set-point and lower set-point. In an ideal situation, the balance reading will oscillate periodically between the two values. Figure 2 shows this, in an expanded section of Figure 1.

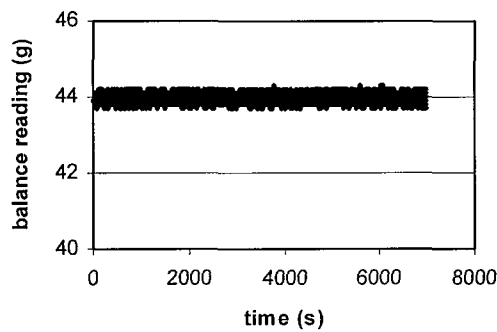


Figure 1: MEDKR experiment computer log file displayed graphically.

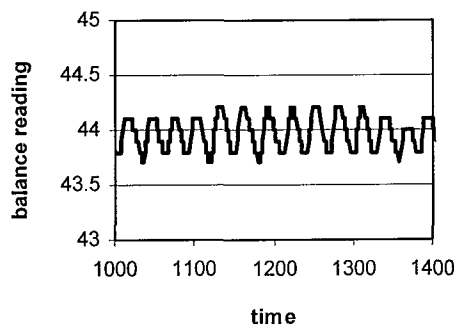


Figure 2: Expansion of Figure 1 indicating the oscillation of the signal between the two set-point values, in this case, 44.1 and 43.9g.

For each data point, a value of “0” or “1” is assigned to signify whether the pump is “off” or “on”, that is, whether the balance reading is decreasing or increasing. These values are summed over the time range, thus allowing the calculation of the percentage of the duration of the experiment that the pump is on. This percentage multiplied by the pump flow rate (10mL/min for most experiments) gives the average loop flow rate for the run.

Figure 3 gives the Excel spreadsheet details for the assignment of the values, “0” and “1” to each data point. The data in Figure 3 is displayed graphically in Figure 4.

	A	B	C	D	E
1	Time	Time interval	Balance reading	Difference	Assigned value
2		S	G		
3	09:56:40	1	43.9		
4	09:56:41	1	43.9	0	0
5	09:56:42	1	43.8	-0.1	0
6	09:56:43	1	43.8	0	0
7	09:56:44	1	43.8	0	0
8	09:56:45	1	43.7	-0.1	0
9	09:56:46	1	43.7	0	0
10	09:56:47	1	43.8	0.1	1
11	09:56:48	1	43.8	0	1
12	09:56:49	1	43.8	0	1
13	09:56:50	1	43.9	0.1	1
14	09:56:51	1	43.9	0	1
15	09:56:52	1	43.8	-0.1	0
16	09:56:53	1	43.8	0	0
17	09:56:54	1	43.7	-0.1	0
18	09:56:55	1	43.7	0	0
19	09:56:56	1	43.8	0.1	1
20	09:56:57	1	43.8	0	1
21	09:56:58	1	43.9	0.1	1
22	SUM = 20			SUM =8	

Figure 3: Excel spreadsheet for determining MEDKR rig loop flow rate.

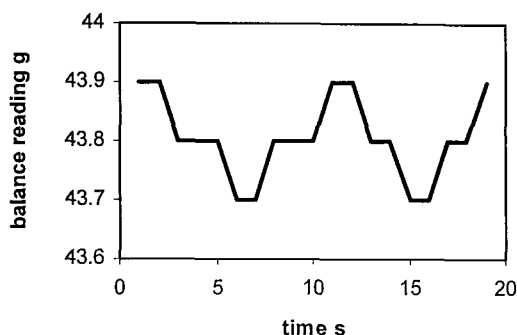


Figure 4: Graphical display of data in Figure 3.

In Figure 3, the value in column D, the 'difference', is equal to the difference between the balance reading for that row and the balance reading for the previous row, for instance, the value in cell D9 is equal to C9 – C8. If the difference is positive, the data point is assigned a value of "1" in column E. If the difference is negative, the assigned value is "0". If the difference is zero, indicating no change in the status of the pump, the assigned value is the same as the previous row. The excel formula used to assign the value according to these criteria, for example, for cell E9 is as follows:

IF(D9>0, 1, IF(E9=0), E8, 0)

The sum of these assigned values is computed in cell E22, in Figure 3, along with the total run time of the experiment (cell B22). Thus the percentage of the time that the pump is on = $\frac{\text{sum of assigned values}}{\text{duration of experiment}} \times 100\%$, which is 40% for this example.

duration of experiment

Given a pump speed of 10mL/min, the overall average loop flow rate is equal to:

loop flow rate = $\frac{40}{100} \times 10\text{mL/min} = 4\text{mL/min}$.

100

APPENDIX VIII

BASIC MEDKR MODEL

Figure 1 shows a simplified diagram of the MEDKR rig which will form the basis of a model to describe how the system components move around the system in the absence of chemical reaction. Note that vessel C is neglected in this analysis on the grounds that the microfiltration membrane causes no resistance to the permeation of any of the components of the system (except for the enzyme, which it retains), hence the volumes of vessels B and C can be combined mathematically. This is a valid assumption since the rejection of the components of the system through the microfiltration membrane is negligible.

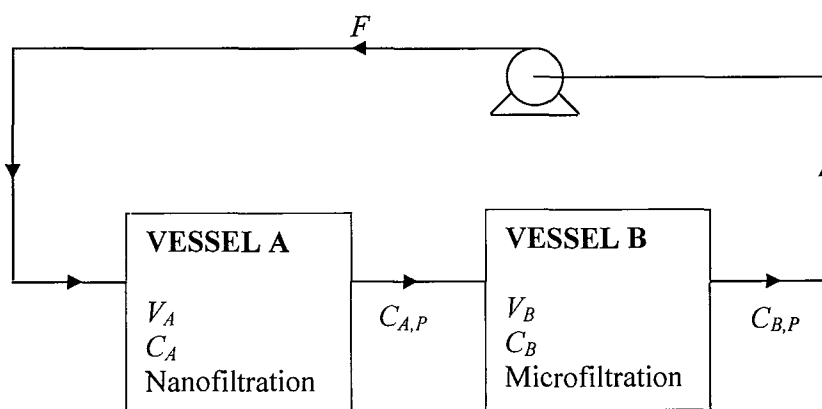


Figure 1: Simplified diagram of MEDKR rig.

The model will be based on a 'pulse' of a single reactant component added to vessel A at the start of the experiment, that is the system's initial conditions are:

$$t = 0 \quad C_A = C_{A0}$$

$$t = 0 \quad C_B = C_{B0} = 0$$

The following assumptions are made:

1. Rejection is constant with time
2. The flow around the loop is constant with time
3. Vessel B is well mixed
4. Connecting pipes have negligible volume

5. There are no interactions between the system components

An overall mass balance on the system gives:

$$M_{total} = C_{A,0}V_A + C_{B,0}V_B = C_A V_A + C_B V_B \quad (1)$$

The rejection is defined as (where i is the vessel – A or B):

$$R_i = 1 - \frac{C_{i,P}}{C_i} \quad (2)$$

$$\text{So, } C_{A,P} = C_A (1 - R_A) \quad \text{and} \quad C_{B,P} = C_B (1 - R_B)$$

Mass balances are performed separately on vessels A and B and the rejection expressions incorporated, giving

Performing mass balances on vessels A and B:

$$\text{Vessel A: } -V_A \frac{dC_A}{dt} = F(C_{A,P} - C_{B,P}) \quad (3)$$

$$\text{Vessel B: } -V_B \frac{dC_B}{dt} = F(C_{B,P} - C_{A,P}) \quad (4)$$

For vessel A, substituting the rejection definitions into equation (2):

$$-V_A \frac{dC_A}{dt} = F(C_A(1 - R_A) - C_B(1 - R_B)) \quad (5)$$

And substituting for C_B from equation (1) gives:

$$\begin{aligned} -V_A \frac{dC_A}{dt} &= F \left(C_A(1 - R_A) - \frac{M_{total} - V_A C_A}{V_B} (1 - R_B) \right) \\ -V_A \frac{dC_A}{dt} &= C_A(1 - R_A) - \frac{M_{total}(1 - R_B)}{V_B} + \frac{V_A}{V_B} (1 - R_B) \\ -V_A \frac{dC_A}{dt} &= C_A \left[(1 - R_A) + \frac{V_A}{V_B} (1 - R_B) \right] - \frac{M_{total}(1 - R_B)}{V_B} \end{aligned}$$

$$\int_0^t -\frac{F}{V_A} dt = \int_{C_{A,0}}^{C_A} \frac{1}{C_A \left[(1-R_A) + \frac{V_A}{V_B} (1-R_B) \right] - \frac{M_{total}(1-R_B)}{V_B}} dC_A \quad (6)$$

$$\text{Let } (1-R_A) + \frac{V_A}{V_B} (1-R_B) = x \quad \text{and} \quad \frac{M_{total}(1-R_B)}{V_B} = y$$

Substituting x and y (combinations of physical parameters of the system, that is constants) into equation (6) and integrating from time, $t = 0$ to time, t , gives:

$$\begin{aligned} \int_0^t -\frac{F}{V_A} dt &= \int_{C_{A,0}}^{C_A} \frac{1}{xC_A - y} dC_A \\ \left[\frac{\ln(xC_A - y)}{x} \right]_{C_{A,0}}^{C_A} &= -\frac{Ft}{V_A} \\ \frac{xC_A - y}{xC_{A,0} - y} &= \exp\left\{-\frac{Ftx}{V_A}\right\} \\ C_A &= \frac{1}{x} \left[y + (xC_{A,0} - y) \exp\left\{-\frac{Ftx}{V_A}\right\} \right] \end{aligned} \quad (7)$$

Therefore the system is described by the following two equations:

$$C_A = \frac{1}{x} \left[y + (xC_{A,0} - y) \exp\left\{-\frac{Ftx}{V_A}\right\} \right] \quad (8)$$

$$C_B = \frac{M_{total} - V_A C_A}{V_B} \quad (9)$$

The concentration in vessel C, as discussed above, can then be assumed to be equal to the concentration in vessel B.

Thus the mass transfer in the system is characterised by the following set of parameters: V_A , V_B , M_{total} , $C_{A,0}$, F , R_A , and R_B .

APPENDIX IX

FULL MEDKR MODEL

Figure 1 shows the simplified process diagram for the MEDKR rig. The reaction scheme is as for the one-pot DKR model, as shown in Figure 7.16.

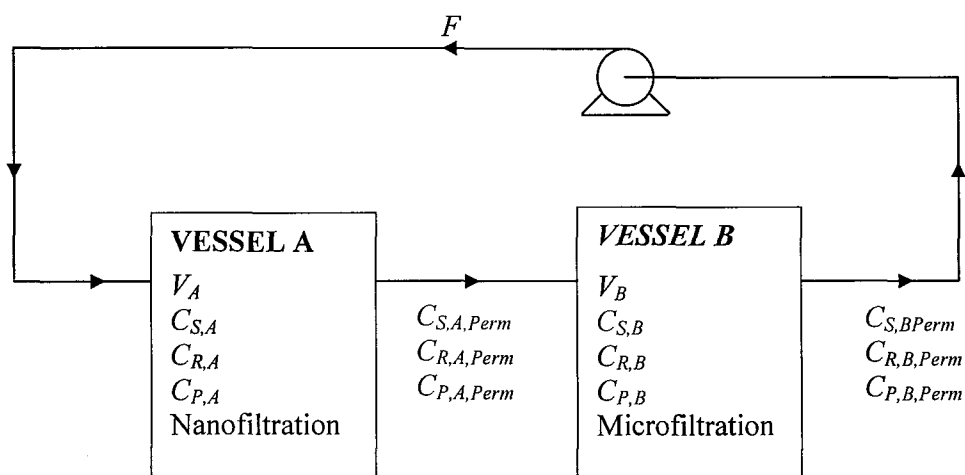


Figure 1: Simplified process diagram for model of the MEDKR rig.

Nomenclature:

F	loop flow rate
V	vessel volume
C	concentration
t	time
k	rate constant

Subscripts:	A	in vessel A
	B	in vessel B
	S	S isomer of racemic substrate
	R	R isomer of racemic substrate
	P	product
	E	enzyme
	$perm$	permeate, i.e. downstream of membrane at reactor outlet

In order to simplify this complex system, the following assumptions have been made:

1. Rejection is constant with time
2. Loop flow rate is constant
3. Vessels B and C are well mixed
4. Connecting pipes have negligible volume
5. System components do not interact
6. Enzyme obeys first order kinetics
7. Product is stable: reaction forming product is irreversible
8. Enzyme is active only on the R isomer
9. Forward and backward rate constants for racemisation are equal
10. Resolution occurs only in vessel B, i.e. rejection of enzyme in vessel B is 100%
11. Racemisation occurs only in vessel A, i.e. rejection of racemisation catalysts in vessel A is 100%. This is probably an erroneous simplification. The model can be altered later to account for permeation of racemisation catalyst around the system

The following initial conditions are used: at $t = 0$,

$$C_{S,A} = C_{S,A,0}$$

$$\text{For a racemic feed, } C_{S,A,0} = C_{R,A,0}$$

$$C_{R,A} = C_{R,A,0}$$

$$C_{P,A} = 0$$

$$C_{S,B} = 0$$

$$C_{R,B} = 0$$

$$C_{P,B} = 0$$

$$C_{S,C} = 0$$

$$C_{R,C} = 0$$

$$C_{P,C} = 0$$

Definition of rejection:

$$R_i = 1 - \frac{C_{i,P}}{C_i} \quad (7.2)$$

So, for example, $C_{S,A,perm} = C_{S,A} (1 - R_{S,A})$

Mass balance on component S, in vessel A:

rate of accumulation = flow in – flow out + generated – consumed

$$V_A \frac{dC_{S,A}}{dt} = FC_{S,B,perm} - FC_{S,A,Perm} + V_A (k_{rac} C_{R,A} - k_{rac^{-1}} C_{S,A})$$

$$V_A \frac{dC_{S,A}}{dt} = FC_{S,B} (1 - R_{S,B}) - FC_{S,A} (1 - R_{S,A}) + V_A (k_{rac} C_{R,A} - k_{rac^{-1}} C_{S,A}) \quad (1)$$

Mass balance on component S, in vessel B:

rate of accumulation = flow in – flow out + generated – consumed

But, no racemisation occurs in vessel B, so both the ‘generated’ and ‘consumed’ terms are zero.

$$V_B \frac{dC_{S,B}}{dt} = FC_{S,A,perm} - FC_{S,B,Perm}$$

$$V_B \frac{dC_{S,B}}{dt} = FC_{S,A} (1 - R_{S,A}) - FC_{S,B} (1 - R_{S,B}) \quad (2)$$

Mass balance on component S, in vessel C:

rate of accumulation = flow in – flow out + generated – consumed

$$V_C \frac{dC_{S,C}}{dt} = FC_{SB} (1 - R_{S,B}) \quad (3)$$

Mass balance on component P, in vessel A:

rate of accumulation = flow in – flow out + generated – consumed

But, no resolution occurs in vessel A, since the enzyme is entirely retained in vessel B, hence the ‘generated’ term is zero. The product is assumed to be stable (see assumption number 7), hence the consumed term is zero.

$$V_A \frac{dC_{P,A}}{dt} = FC_{P,B,perm} - FC_{P,A,Perm}$$

$$V_A \frac{dC_{P,A}}{dt} = FC_{P,B}(1 - R_{P,B}) - FC_{P,A}(1 - R_{P,A}) \quad (4)$$

Mass balance on component P, in vessel B:

rate of accumulation = flow in – flow out + generated – consumed

The product is assumed to be stable (see assumption number 7), hence the consumed term is zero.

$$V_B \frac{dC_{P,B}}{dt} = FC_{P,A,perm} - FC_{P,B,Perm} + V_B k_{enz} C_{ER,B}$$

$$V_B \frac{dC_{P,B}}{dt} = FC_{P,A}(1 - R_{P,A}) - FC_{P,B}(1 - R_{P,B}) + V_B k_{enz} C_{ER,B} \quad (5)$$

Mass balance on component P, in vessel C:

rate of accumulation = flow in – flow out + generated – consumed

$$V_C \frac{dC_{P,C}}{dt} = FC_{P,B}(1 - R_{P,B}) \quad (6)$$

Mass balance on component R, in vessel A:

rate of accumulation = flow in – flow out + generated – consumed

$$V_A \frac{dC_{R,A}}{dt} = FC_{R,B,perm} - FC_{R,A,Perm} + V_A (k_{rac^{-1}} C_{S,A} - k_{rac} C_{R,A})$$

$$V_A \frac{dC_{R,A}}{dt} = FC_{R,B}(1 - R_{R,B}) - FC_{R,A}(1 - R_{R,A}) + V_A (k_{rac^{-1}} C_{S,A} - k_{rac} C_{R,A}) \quad (7)$$

Mass balance on component R, in vessel B:

rate of accumulation = flow in – flow out + generated – consumed

$$V_B \frac{dC_{R,B}}{dt} = FC_{R,A,perm} - FC_{R,B,Perm} - k_{enz} C_{R,B} V_B$$

$$V_B \frac{dC_{R,B}}{dt} = FC_{R,A}(1 - R_{R,A}) - FC_{R,B}(1 - R_{R,B}) - k_{enz} C_{R,B} V_B \quad (8)$$

Mass balance on component R, in vessel C:

$$V_C \frac{dC_{R,C}}{dt} = FC_{R,B}(1 - R_{R,B}) \quad (9)$$

Therefore the model consists of 9 equations (1-9) in 9 unknowns: $C_{S,A}$, $C_{S,B}$, $C_{S,C}$, $C_{R,A}$, $C_{R,B}$, $C_{R,C}$, and $C_{P,A}$, $C_{P,B}$, and $C_{P,C}$, with the following set of parameters:

V_A, V_B, V_C

F

$R_{i,A}, R_{i,B}$ where i = the component, R, S or P

k_1, k_2, k_{-1}

k_{rac}, r_{rac}^{-1}

$C_{E,B,0}$

APPENDIX X

gPROMS CODE FOR FULL MEDKR MODEL

Parameter

Va, Vb	as	real
F	as	real
krac, kracinv	as	real
kenz	as	real
Rra, Rrb	as	real
Rsa, Rsb	as	real
Rpa, Rpb	as	real

Variable

Cra	as	concentration
Crb	as	concentration
Crc	as	concentration
Csa	as	concentration
Csb	as	concentration
Csc	as	concentration
Cpa	as	concentration
Cpb	as	concentration
Cpc	as	concentration

Equation

Component S, vessel A

$$V_a * \$C_{sa} = ((F * C_{sb} * (1 - R_{sb}))) - (F * C_{sa} * (1 - R_{sa})) + (V_a * k_{rac} * C_{ra}) - (V_a * k_{racinv} * C_{sa});$$

Component S, vessel B

$$V_b * \$C_{sb} = (F * C_{sa} * (1 - R_{sa})) - (F * C_{sb} * (1 - R_{sb}));$$

Component S, vessel C

$$C_{sc} = C_{sb} * (1 - R_{sb});$$

Component P, vessel A

$$V_a * \$C_{pa} = (F * C_{pb} * (1 - R_{pb})) - (F * C_{pa} * (1 - R_{pa}));$$

Component P, vessel B

$$V_b * \$C_{pb} = (F * C_{pa} * (1 - R_{pa})) - (F * C_{pb} * (1 - R_{pb})) + (k_{enz} * C_{rb} * V_b);$$

Component P, vessel C

$$C_{pc} = C_{pb} * (1 - R_{pb});$$

Component R, vessel A

$$V_a * \$C_{ra} = (F * C_{rb} * (1 - R_{rb})) - (F * C_{ra} * (1 - R_{ra})) + (V_a * k_{racinv} * C_{sa}) - (V_a * k_{rac} * C_{ra});$$

Component R, vessel B

$$V_b * \$C_{rb} = (F * C_{ra} * (1 - R_{ra})) - (F * C_{rb} * (1 - R_{rb})) - (k_{enz} * C_{rb} * V_b);$$

Component R, vessel C

$$C_{rc} = c_{rb} * (1 - R_{rb});$$

APPENDIX XI

LIST OF ACRONYMS / ABBREVIATIONS

AA	Allylic alcohol: 4 phenylbut-3-ene-2-ol
Acetate	Allylic acetate: 4 phenylbut-3-ene-2-acetate
CALB	Candida antarctica lipase B
4 CPA	4-chlorophenyl acetate
DABCO	Di-aza-[2.2.2]bicyclo-octane
DBU	1,8-diazabicyclo[5,4,0] undec-7-ene
DMSO	Dimethyl sulfoxide
DKR	Dynamic kinetic resolution
EE	Enantiomeric excess
IPA	Isopropyl alcohol
IPPA	Isopropenyl acetate
KR	Kinetic resolution
MEDKR	Membrane enhanced dynamic kinetic resolution
n/m	Not measured
Nov 435	Novozyme 435
OSN	Organic solvent nanofiltration
PCL	Pseudomonas cepacia lipase
PFL	Pseudomonas fluorescens lipase
PSL	Pyruvate sialate lyase
Ploct	P ₁ -t-oct
Pltris	P ₁ -t-Bu(tetramethylene)
Ru aminocyclopentadienyl ¹	Dicarbonylchloro-1[(1-methylethyl)amino]- 2,3,4,5-Tetraphenyl-2,4-cyclopentadien-1-yl ruthenium I
Ru cymene ¹	Dichloro(<i>p</i> -cymene) ruthenium (II) dimer

¹ See Figure 5.4.

Ru indenyl ¹	chloro(indenyl)bis(triphenylphosphine) ruthenium (II) dichloromethane adduct
TDA	Tridecyl amine
TDDA	Tridodecyl amine
TEA	Triethyl amine
ThexA	Trihexyl amine
TheptA	Theptyl amine
THF	Tetra hydrofuran
TMC	Transition metal catalyst
TOA	Trioctyl amine
VA	Vinyl acetate