УДК 541.18.045:546.426

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MEMBRANE-BASED PROCESSES OF CHIRAL SEPARATION

The state of the art in membrane-based separation ofoptical isomers has been reviewed.A molecular recognition in such processes is provided by chiral environment in a membrane phase or by soluble chiral selector (CS) preferentially binding one of isomers. The principles and potentialities of chiral separations based on CS rejection by membrane (complexation/ultrafiltration), CS transportation through the membrane (membrane extraction), and CS inclusion into the membrane phase (liquid membrane) have been discussed. Data on development of membranes for the molecular recognition of optical isomers and membrane mass-transfer during enantiomer separation have been analysed. The chiral separation in membrane reactors with CS as a catalyst of enantiomer transformation has been discussed.

The importance of chiral separations in a number of fields cannot be overemphasised. Enantiomerically pure compounds are desirable and, in many cases, vital in the food, agrochemical, and pharmaceutical industries. Numerous examples of different biological activities of enantiomeric drug substances, herbicides, vitamins and food components are well decribed [1]. The growing need for pure chiral compounds is demonstrated by the increase of the chiral drug market from USS18 billion in 1990 to USS45.2 billion in 1994 and an estimated USS300 billion in the year 2000.

Enantiomerically pure compounds can be produced by asymmetric synthesis, but it can become uneconomic if numerous steps and the use of expensive enantiomeric reagents are needed. In some cases, it is less expensive to separate the racemic mixture by physical methods as diastereomeric crystallisation or chromatography. Conventional methods of optical resolution have the common drawback that only a small amount of material can be treated in one operation. On the other hand, the optical resolution using the membrane separation processes is very promising for large-scale separations.

Enantiomers are identical to each other not only in size but also in all physical and chemical properties except for optical rotation, so their separation composes one of the most complicated problems in chemical technology. Separation of enantiomers is possible only in chiral surrounding. Thus, the use of chiral selector is basic principle of chiral separation. Free or bound chiral selectors can be used for membrane-based processes of enantiomer resolution.

Membrane-based enantiomer separation with mobile chiral selector

Enantiomer separation with free chiral selector is a process of kinetic resolution. It is based on the ability of chiral selector (CS) reacts with enantiomers of a racemic mixture at different rates:

$$\text{L-isomer} + \text{CS} \underset{k'_L}{\overset{k_L}{\rightleftharpoons}} \text{L-isomer} - \text{CS}$$

$$\text{D-isomer} + \text{CS} \underset{k'_D}{\overset{k_D}{\rightleftharpoons}} \text{D-isomer} - \text{CS} \qquad (1)$$

Both enantiomers bind competitively with CS and selectivity of enantiomer binding depends on ration of binding constants of enantiomers. Concentrations of free and bound enantiomers are determined by low of mass action. The aim of membrane use is a separation of complex of substance with CS containing preferentially bound isomer from free isomers enriched by second isomer. It should be note that CS can transform specific isomer. In this case CS is a chiral reagent or catalyst. Chiral separation based on the enantiomer transformation does not belong to transport-mediated separation and will be considered in a chapter "Membrane reactors in chiral resolution".

The principle of kinetic resolution with mobile chiral selector have been realised in ultrafiltration, liquid membranes and membrane-based solvent extraction. Of course, the search for suitable CS was dominated task in such research.

Complexation/ultrafiltration

Chiral resolution by ultrafiltration is based on the retention of substance/CS complex by porous membrane with free transport of unbound enantiomers. Additionally to high enantiospecificity CS has to satisfy to a size criterion, namely the size of diastereomeric complex of substance/CS has to be sufficient to be retained by a membrane.

The principle could be realised, first of all, for well described systems of optically active substance and

CS. Studies of the enantiomer resolution by complexation/ultrafiltration published so far [2—10] are practically restricted by using serum albumin as CS which high affinity to L-amino acid is well known. The enrichment of enantiomer mixture by D-amino acid in permeate is reached as a result of preferential binding ofL-isomer with bovine serum albumin (BSA) which are rejected by ultrafiltration membranes.

F. Garnier et al. [6] considered three models of amino acid complexation with BSA: a binding of D- and L-isomers with sites of two types that are specific to one isomers; dominant binding ofL-isomers by high stereospecific site with concurrent binding ofboth isomers by secondary less selective site; concurrent binding ofboth isomers by site with different complexation constant. A comparison of experimental data with the proposed models showed that the competitive binding ofD- and L-isomers is a complexation mechanism between amino acid and BSA. This mechanism was early postulated by Japanese researchers [3, 4]. In general ultrafiltration can be considered as supplemental method for evaluation of complexation parameters and mechanism including systems with optically active substances. For example, this approach is used for studies of plasma protein binding and consequently pharmacokinetics and pharmacodynamics of drug substances [11]. Although this method seems simple it should take into consideration the phenomena of concentration polarisation and gel formation complicating processes of ultrafiltration. So, A.Highuchi et al. obtained different rates of binding constants of L- and D-phenylalanin to BSA with using ofhollow fibre and flat membranes. The cause of that can be the different levels of concentration polarisation that leads to variation of complex concentration at membrane surface and can influences on the equilibriums (1).

Like as any chemical reaction the equilibriums (1) depend on different parameters as pH, temperature, concentration etc. Moreover system parameters can also influence on the structure of binding sites changing binding selectivity. So, the complexation of amino acid and consequently enantioselectivity depends on pH [6—8]. The authors assumed that the complexation occurs between the zwitter-ionic amino acid form and the unprotonated BSA site. The variations of the apparent binding constants versus pH are the result of the protonation ofboth the amino acid and the binding site. It was established that apparent complexation constants for both D- and L-enantiomer show a maximum in the pH range from 9 to 10. Thus experiments of earlier works [2—4] on amino acid separation at pH 7 were carried out at non-optimal conditions. As a result to reach high separation factors concentrations of CS have to be more than 10 times higher than optically active substances being separated. At the same time, ultrafiltration at pH 9.5 allowed obtaining an enantiopurity above 80% at BSA: amino acid rations closed to equimolar [6—8]. The total flux ofD-isomers during complexation/ultrafiltration reached 2.2 mol/m^2 hour. It seems, that such fluxed are barely reachable by other membrane methods.

Practically complete dissociation of amino acid/BSA complex in acid solutions allows the regeneration ofBSA for other cycles of the purification and a recovery of enriched L-isomer. Thus in two-stage chiral separation by complexation/ultrafiltration solution enriched by weakly complexated isomers is produced at the first stage whereas solution enriched by strongly bound isomers is obtained at the second stage (complex dissociation/ultrafiltration).

Probably there was only one attempt [9] to use other CSs in addition to BSA for chiral separation using ultrafiltration. In this work it was established that glucosyl- maltosyl- and hydroxypropyl-P-cyclodextrins stronger includes L-phenylalanine than D-isomers that allowed the separation of this pair of enantiomers by ultrafiltration.

Obviously broadening of the method of compexation/ultrafiltration is restrained by the difficulties of CS choosing. Fortunately, search of soluble CSs is dynamic in other applications of CSs for chiral separation. So, chiral separation in capillary electrophoresis is performed, as a rule, with using of mobile CSs [12]. The use only cyclodextrins as CS provides the resolution of more than 700 compounds in capillary electrophoresis; these include P-blockers, sympathomimetic, antipsychotics, antidepressant, hypnotic, barbiturates, local anaesthetic, bronchodilators, etc. It seems that the use of these knowledge should promote a development of chiral separation by compexation/ultrafiltration.

In general using two-stage principle of chiral separation by complexation/ultrafiltration should provide two streams that are enriched by one enantiomer but not enantiopure. And additional enrichment can be necessary. To consider the use of complexation/ultrafiltration for further enrichment (cascade scheme) the CS has to preferentially bind a target isomer. In this case further enrichment is possible in accordance of the low of mass action; isomer which concentration is less will be bond by CS in less degree. CS towards to optical antipode of target isomers does not allow enhancing of enantiopurity of the target enantiomer. As a result, the enantiomer enrichment that reaches on the first stage of ultrafiltration (target isomer in permeate) is maximally possible.

If both isomers are useful, two types of CSs towards to each isomer will be necessary. It should be note that biding enantioselectivity for CS can be significantly varied. So, A.Highuchi et al. [4] observed changing of enantioselectivity for the phenylalanine/BSA system. For binary system BSA preferentially binds L-isomer, but in the presence of phosphatidylcholine or sodium palmitate it stronger binds D-isomer. Thus one substance can serve as CS for both enantiomer.

Ultrafiltration for chiral separation can be used also in colloid systems containing micelles formed by chiral amphiphilic substances. Micellar-enhanced ultrafiltration is used to remove organic molecules from aqueous solutions by solubilization in the hydrophobic core of the micelle. An amphiphilic amino acid derivatives, L-5-cholesterol-glutamate (L-5-CSG) and L-N-n-decylhistidine (5L-DH), together with non-ionic surfactant forms micelles that preferentially bind D-phenylalanine over L-isomer [11]. For formation of ternary complexes of amino acid with micelles the system has to contain cooper-ions and the best enantio-separation is reached at equimolar ration of amphiphilic cosurfactant to cooper-ions. The highest degree of enantioselectivity was observed at concentration of amphiphilic CS in two times higher than racemate concentration. The maximal purity of L-phenylalanine in permeate reached about 75%.

Thus all published works on application of complexation/ultrafiltration for chiral resolution were connected with separation of amino acid. They practically did not include data on mass transfer, an influence of permeate recovery on enantioselectivity and a consideration of concentration polarisation and gel polarisation phenomena. The last play important role in ultrafiltration and, of course, should significantly influence on chiral separation.

Liquid Membranes

Liquid membranes (LM) are triphasic systems composed of aqueous-organic-aqueous solutions utilising carriers for transportation of target substance from feed solution in receiving phase. To separate enantiomers an optically active substance is used as chiral selector and carrier. The organic solvent in which the carrier is diluted does not have optical resolution capacity, and both enantiomer can diffuse through it. In order to reach a good optical resolution through LM, it is advisable to use a highly stereoselective carrier dissolved in an organic solvent through which non-carrier mediated diffusion of isomers does not occur or is very low.

In general, the parameters that influence on the mass transport through a LM are primarily the viscosity of organic solvent; the viscosity, molecular size and concentration of the organic carrier and solute to be transported; the temperature; and solubility of the solute in the different phases.

There are numerous publications on chiral separation by LM with abundance of tested CS. So, in review [13] about 50 different CS are considered. Crown ethers were the first CS and the most frequently utilised in LM. They include binaphtyl crown ethers, biphenanthryl crown ethers, helicene-based crown ethers, crown ether based on the 2,3,6,7-dibenzobicyclo[3.3.1]nona-2,6-diene subunit, tetrahydrofuran- and cyclohexanediol-based crown ethers. Methyl-l-butanol [14], N-decyl-(L)-hydroxyproline [15], derivatives of L-leucine [16] are the samples of CS so fo thertypes.

Using the LM high enantiomeric enrichment was reached for various racemates. As a result of selective transport of one isomer the source phase will enrich by other enantiomer. Increase of this enantiomer in source phase relatively to isomer, which is better transported, will result in increasing of this enantiomer binding by CS in accordance of equilibriums (1). This causes an increased transport of undesired isomer and enantioselectivity decrease. For most resolution by LM, the enantioselectivities reported at low degrees of solute transport in receiving phase (3% to 5% transport is typical). The entire system will ultimately come to equilibrium with an essentially racemic mix of solute in each aqueous phase. The greatest enantioenrichment can be obtained only at the early stages of transport.

The elegant solution of this problem was proposed by Cram's group [18]. The possibility of enantiomer separation by LM at high degrees of solute recovery system is based on simultaneous enantioselective transport of two isomers from the feed solution into two different receiving phases. Their system consists of two U-tubes (Fig. 1). The organic phases in different

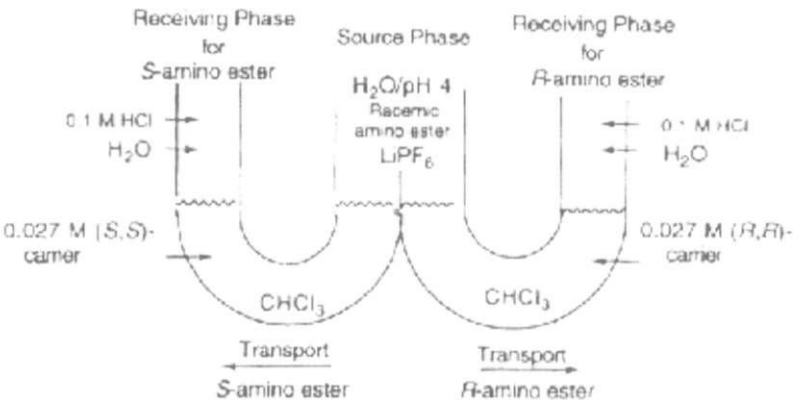


Fig. 1. Cram's "double U-tube" system for continuous enantiomer resolution

tubes contain different CS for each enantiomer but feeding is performed from the same source. Consequently, the source phase does not become enriched by one of the enantiomers, and the ratio of the fluxes of the solute enantiomer is the same. In such system D.J.Cram et al. reached stable enantiomeric enrichment up to 85% in each receiving phases.

Thus, there is a principal possibility of racemate resolution by LMs at high levels of enantiomer recovery with using of CS for both enantiomers. However, the processes of chiral resolution with LMs have not yet been developed beyond the laboratory scale, analytical quantities and batch configurations. The deterioration of resolution with time is the major problem of that process. This is mainly caused by the washing out of chiral carrier to the feed and/or receiving phases.

The several methods are developed which are able to improve considerably the lifetime of LMs, e.g. a gelation of the LM-phase and the application of a polymeric stabilising layer between the carrier phase and the aqueous phases by interfacial polymerisation or ion exchange layers on the surface of porous support.

The second method has been used for modified system with a mobile CS in liquid phase entrapped into porous support (membrane) [19]. Apoenzymes were entrapped in pores of microfiltration membranes by two layers of electropolymerised polypyrrole (on both membrane side). Thus, high molecular weight apoenzymes cannot diffuse through enough tight polypirrole layers and retain mobility in liquid phase filled in pores. In this work membrane separate two aqueous mediums and is soaked by aqueous solution, consequently, it is not a true LM. But the CS is mobile within the membrane pores.

D-amino acid oxidase apoenzyme used as CS preferentially binds D-amino acid. The enantioselective transport is supposed to be a result of facilitated transport of D-isomer. The maximal enantioselectivity value of 4.9 was reached. Because the pore volume is filled by aqueous solution the transport of isomers not mediated by CS should be equal for both ones. This worsens the enantioselectivity. An increase of apoenzyme concentration in pore volume (in membrane with smaller pore sizes) improves the enantioselectivity due domination of the transport mediated by CS.

Membrane-based solvent extraction

In devices for a membrane-based solvent extraction the membrane separate two miscible liquid phases. Solutes are distributed between the two phases according to their thermodynamic distribution coefficients. If complex enantiomer/CS is preferentially distributed in one phase compared with single enantiomer it will be possible to separate the enantiomers by the membrane-based solvent extraction. Thus, racemates of underivatised leucine and dinitrobenzoyl derivative of leucine were separated with using N-dodecylhydroxyproline [20] and ester or amide derivatives N-(1-naphtyl)leucine [21] respectively as CS. In both works evidences ofhigh enantiomeric enrichment in organic receiving phase is observed.

Membrane-based solvent extraction in chiral separation can be designed for a simultaneous extraction of target-transported enantiomer into second aqueous phase by a passing of the receiving phase through an additional membrane element [21]. In the second membrane element enantiomer is extracted in aqueous phase and CS become free. This principle was realised with using of hollow fibre elements. In case of flat membrane, three-channel configuration of membrane module could be used for this purpose. In such device organic receiving phase is situated between aqueous source phase and aqueous receiving phase separated by two membranes.

Maintenance oflow levels of target enantiomers in receiving organic phase promotes to high fluxes as a result ofhigh driving force (concentration gradient). But, the enantiospecificity will decrease with solute recovery due to increase of concentration of second enantiomer in aqueous source solution. It is obviously, that due to use of two CSs towards to both enantiomers the transport of each isomer in different receiving phases is possible like as above mentioned Cram's scheme. Thus, it is desirable for there to be two CSs for each enantiomer for this membrane-based method of chiral separation.

Membrane based enantiomer separation with fixed chiral selector

Membranes with fixed chiral substances

In membrane-based processes of chiral separation with mobile CSs they can be excluded from the membrane phase (complexation/ultrafiltration), transported through the membrane (membrane-based solvent extraction) and included in the membrane phase (LMs). Only in the last case the membrane phase possesses by chiral recognizing properties due CS. But loss of CS is the main disadvantage ofLMs. A feasible alternative is fixed site carrier membranes. Their principal advantage over liquid membranes is a potentially much longer lifetime.

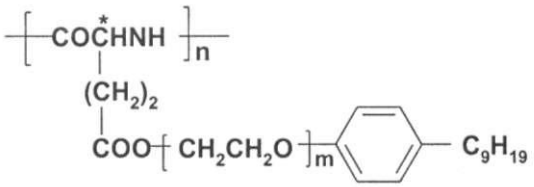
Principally membranes with fixed CS can be porous and nonporous. The main efforts on development of enantioselective membranes were logically directed to nonporous membranes to exclude a non-selective transport through the membrane pores. But porous membrane with fixed CS can provide enantioselective sorption by membranes. This property can be obviously used in other chiral separation processes like as membrane chromatography [22, 23].

Fixed CS can assure a higher partition coefficient of one isomer as compared with its antipode in a membrane phase. It is obvious that obtaining of ideal mem-

brane (full exclusion of penetration of second enantiomer in membrane phase) is difficultly reachable because the content of CS in the membrane phase, as a rule, is limited. For the non-porous membranes it is possible to analyse the permeation by the solution-diffusion mechanism, i.e. $P^c = DxS$ where P^c is the permeability coefficient, D — the diffusion coefficient, and S — the solubility coefficient.

A role of fixed chiral centres in trans-membrane transport is not still clear. Depending on strength of solute/CS interaction CS can obviously retard or promote a diffusivity of selective enantiomers. There are a few publications [24, 25] on the facilitated transport by fixed sites, but this mechanism demands still more detailed experimental confirmations. On the other hand, a strong interaction between CS and one isomer can result in saturation of CS by this isomer with following non-selective transport ofboth isomers in achiral environment. Thus the best enantioselective separation during trans-membrane transport should be reached at both preferential binding one of isomers (solubility factor) and CS-mediated increased diffusivity of this enantiomer. Obviously enantioseparation can be reached as a result of diffusivity or solubility enhancing.

Membranes with fixed chiral centres can be obtained from chiral polymers or surface of membranes from achiral materials (organic or inorganic) can be modified by chiral substances. The earliest attempts to develop the solid membranes containing the fixed chiral selector are based on using ofpoly(L-glutamate) derivatives [26, 27]:



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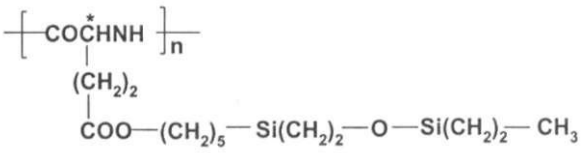
These membranes demonstrated practically complete separation of some amino acids with stable enantioselectivity during more than 500 hours. D-tryptophan, D-serine and D-tyrosine are preferentially transported through the membrane as compared to L-enantiomers. It should be note that a direct observation of selective binding by sorption experiment can be often difficult because of a small volume of membrane samples. The authors studied the binding of amino acid enantiomers by chiral polymers using monolayers obtained by LB technique and quartz microbalance covered by polymeric film. In these experiments they used (1) obtained from both poly(L-glutamate) and poly(D-glutamate) and shown that D-isomer was absorbed more than L-isomer by derivative of poly(L-glutamate), while the reverse adsorption behaviour occurred in poly(L-glutamate) derivative. Thus, binding enantioselectivity correspond to transport one.

The poly(L-glutamate) derivative has chiral centres in the main chain and amphiphilic side chains with hydrophobic and hydrophilic segments. A well-ordered self-organized structure ofhelix and amphiphilic side chains was shown by CD spectra and X-ray analysis [27]. Well-ordered structure of alternating hydrophilic and hydrophobic blocks prevents non-selective transport through this achiral medium and only isomer preferentially bonded by CS can penetrate through membrane. But solute fluxes through the membrane are extremely low (about $4x1^{-4}$ mmol/m^2hour) because of a significant part of practically impermeable achiral domains.

In order to obtain a more highly permeable membrane Aoki et al. [28] obtained a membrane from po - ly[y-{3-(pentamethyldisiloxanyl)propyl)-l-glutamate] **(2),** a poly(L-glutamate) derivative containing the chiral backbone and flexible siloxane short side chain:



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The authors tested the membranes in separation by reverse osmosis. The membranes showed enantioselective permeability for L-tryptophan with enantiomeric enrichment up to 16% in permeate. This transport enantioselectivity is opposite to observed for membrane based on **1** in diffusion experiments. Moreover polymer **(2)** as particles better absorbs D-isomer that agrees with sorption selectivity by polymer **(1)** [27]. The authors supposed that the enantioselectivity is caused by a suppression ofD-isomer transport by the relatively higher interaction with CS resulting in the selective permeation of(L)-isomer. However, there is a high possibility of solute transport through non-selective achiral domains formed by flexible side chains. This "appeared" enantioselectivity could be observed until CSs are saturated. Although the stable enantioselectivity was reported for transport duration about 160 hours, this time can be not sufficient for saturation. Additional information about polymer sorption capacity, degree of solvent recovery is needed to discuss these results. However, such data are absent in the work.

The enhanced trans-membrane fluxes can testify about the possibility of non-selective transport. The permeation rates of the membranes based on **(2)** were 10^5 higher than that of the membranes from poly-

mer **(1).** The authors assumed that the siloxane regions constitute highly continuous domains and form an important permeation route. Therefore, the aqueous tryptophan solution mainly permeates these siloxane domains, which have no asymmetric centres. It seems that this permeation route can barely provide enantioselective recognition and transport.

In general, derivatives of poly (amino acid) have in their chiral main chain amide-groups that are able to H-binding. It is possible to suppose that participation of these groups in interactions of CS with amino acid transported through the membrane makes these interactions enough strong. That can significantly restrict diffusivity of enantiomer preferentially bonded by CS in the membrane phase. It can contribute to low solute permeability in case of the high enantioselective membrane based on the polymer **(1)** and can cause preferential transport of enantiomer that are more weekly bonded in case of the membrane from the polymer **(2).** In the last case the enantioselectivity should disappear after reaching of CS saturation.

This saturation mechanism was demonstrated in liquid-liquid separation of oxprenolol racemate through membrane from cellulose tris(3, 5-dimethylphenylcarbamate) (CTPC), well-known polymer for preparation of chiral stationary phases (CSP) in HPLC separation [29]. This membrane provides a high enantioselective adsorption of (S)-oxprenolol that corresponds to results on optical resolution of oxprenolol on the CTPC column by HPLC: (R)-isomer elutes before the (S)-isomer. During concentration-driven diffusional separation at initial time the (R)-oxprenolol permeates preferentially and enantiomer enrichment reaches about 18%. But after that, the enantiomer enrichment in the receiving phase decreases rapidly and became nearly racemic within 1 hour. So, after adsorption of oxprenolol in the CTPC membrane comes to equilibrium, both isomers probably diffuse through the membrane without interactions with the chiral centres.

It is probably the similar situation could be realised for a membrane prepared from graft-copolymer of acrylonitrile containing D-glucitol during amino acid separation [30]. The authors reported preferential transport ofD-isomers of phenylglycine, phenylalanin and tryptophan when the quantities of permeated amino acid did not exceed 5%. While the copolymer more strongly bind of L-isomers than D-isomer. With increasing of solute recovery the enantioselectivity could probably decrease or even disappear.

At the same time the saturation of chiral centres is probably possible for very strong their interaction with solutes. In case of more week interactions a competitive interactions of both enantiomers will influence both enantioselective binding and diffusivity of enantiomers. So, the binding enantioselectivity observed in paper [30] reached only 5.8%. This fact can testify enough high binding competition. Taking into consideration that the highest enantiomeric purity of transported amino acid was much more (about 75%) the authors concluded that the enantioselective permeation is caused by difference in diffusion between the D- and L-isomers. But, to prove the possibility of this mechanism the high enantioselectivity has to be demonstrated at higher degrees of solute recovery. In any case, an opposite action of solubility and diffusivity factors decreases a separation potential.

Group of Japanese authors considered this situation for enantiomer separation under a pressure gradient [31—33]. They obtained different membranes containing fixed naturally occurred optically active substances. L-phenylglycine containing membranes were obtained by a casting of solutions that contain L-phenylglycine condensate with glutaraldehyde as a source of chiral substance and polysulphone as a membrane-forming polymer [31]. Other group of membranes was obtained by plasma polymerisation of different terpenes (L-menthol, R-limonene, [(lS)-endo]-borneol, S-(-)-p-citronelol) on the surface of porous cellulose acetate membranes [32, 33].

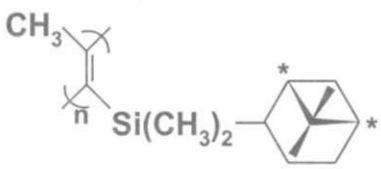
For all these membranes they observed the preferential permeation ofD-amino acid during diffusion experiments with the solutions of racemic mixture. The enantioselectivity towards to D-isomers retains at volume flux under pressure gradients and, at low transmembrane fluxes, the separation factor is even higher than in diffusional experiments. The authors supposed that the difference in the solute permeability at diffusion is attributed to the difference in the interaction between chiral centres and enantiomers. In case of volume fluxes the solute permeability composes of a diffusion flow based on a concentration gradient and a viscous flow based on a pressure gradient.

They attempted to estimate a contribution of viscous flow in the enantioselectivity. From the results of the diffusion experiments the partition and diffusion coefficients for each enantiomers were calculated. Taking into consideration that these results were obtained at very small amounts of transported solutes their use seems to be questionable. Basing on these coefficients the authors concluded that even in the range of the viscous flow the L-isomers interact more strongly with the membrane than D-isomers and thus the enantioselectivity becomes better at low transmembrane fluxes. The enantioselectivity factor up to 10 was observed experimentally at volume flux about 4.7×10^{-8} m/s. However, it is not clear from experiment description could be these data considered as steady-state results.

Nevertheless if this mechanism can really work its application promises some advantages, first of all, a higher solute flux than in diffusion separation. Moreover an additional enrichment of permeate in cascade scheme with the use of the same membrane is possible. It is obvious that for such separation distribution of CS

through the membrane volume is preferential than surface allocation. Additionally to strength of CS/enantiomer interaction the membrane pore sizes have to effect on the separation effectiveness.

T. Aoki's group used intensively complex polymers and copolymers of silylpropyne **(3)** [34—36], **(4)** [37] and norbornadiene [38] containing (-)- or (+)-P-pinene as optically active pendant groups.



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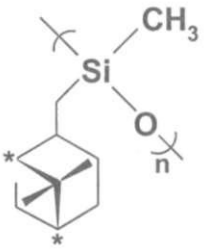

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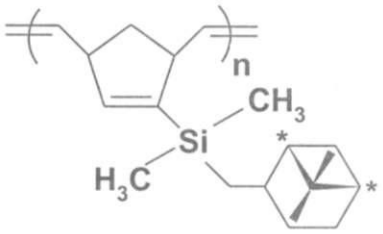

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These (co)polymers have a good film-forming property that allows obtaining of self-standing membranes. The authors used the membranes for the separation of different racemates including amino acids, 1,3-budanediol, 2-butanole and their acetate esters, propranolol by using dialysis as well pervaporation for volatile substances. For these membranes almost complete optical resolution occurred at the initial period and stable permeations with moderate enantioselectivity were observed after the initial period.

The main difference of membranes based on polymers **(3)** and **(5)** from above mentioned ones is an absence of enantioselective sorption. Taking into consideration that chiral pendant pinanyl groups do not contain functional groups the strong interactions between chiral centres and solutes seem to be unlikely. Therefore, the enantioselective permeation is achieved not by selective dissolution at the membrane surface but by selective diffusion. These membranes are dense and non-porous. The authors of paper [36] supposed that bulky chiral pinanyl groups should be packed densely. Enantiomers obviously permeate through a space surrounded by the bulky chiral pinanyl groups. Since permeants should contact strongly with the bulky chiral pinanyl groups during the permeation through the space, enantioselectivity is thought to occur in this diffusion process. The reason for the enantioselective permeation for the wide range of the size of compounds may be the variability in size of the space among the chiral groups by molecular motion of the pendant groups. Accordingly, when suitable conditions are selected so as not to enlarge the space, optical resolution is achieved by the membrane.

The tryptophan permeability through the membrane based on norbornadiene polymer **(5)** was about 15 times higher than that of the membrane based on silylpropyne polymer **(3)** having higher selectivity. This may be caused by higher flexibility of the main-chain of polymer **(5)** than that of polymer **(3).** The high stability of enantioselectivity is observed during enough long period (up to 2000 h) [36, 38]. Relatively high permeability of these membranes, long transport enantioselectivity with simultaneous absence of binding enantioselective allow to exclude with high degree reliability a possibility of contribution of the CS saturation to enantioselectivity. Thus, the enantioselective transport based on the selective diffusion is probable. An advantage of using of such separation is a possibility of the chiral resolution of many kinds of racemates by one membrane.

Because CSs do not bind selectively one isomer this factor does not effect the enantioselectivity with increasing of one isomer recovery as it is observed in LM or membrane-based solvent extraction. However, decreasing of enantioselectivity with the increase of one isomer recovery should be observed as a result of decreasing of this isomer concentration in the membrane phase. So, for membrane chiral separation based on enantioselective diffusion the Cram's scheme can be also useful. This scheme should allow maintaining a composition of feed solution close to racemic. Thus, the membranes of two types with enantioselective transport towards the both isomers are desirable. The searching of chiral polymers for membrane formation is the most important task for research in this direction.

The polymers, containing chiral groups, are obtained, as a rule, through multi-step reactions and are difficultly available and expensive. The use of natural chiral polymers and their derivatives as membrane forming materials can decrease the cost of membranes. The natural polysaccharides, for example, cellulose triacetate, above-mentioned CTPC etc., are the main candidates. Attractive possibility to decrease a consumption of expensive optically active polymers is an approach of membrane surface modification by chiral compounds.

Elegant example of surface-modified membrane was reported by Aoki et al [37]. They used hydrophobic optically active siloxane oligomer **(4)** in blend with a more polar poly(methylmethacrylate). As a result during the casting of the blend solution containing a small amount (10—12 wt%) of oligomer **(4)** the siloxane compound is accumulated at the surface owing to its lower surface energy. The accumulation of

siloxane oligomer at the membrane surface is confirmed by comparison of spectrums in attenuated total reflection IR and transmittance IR. In the concentration-driven permeation of mandelic acid, valine and phenylalanine racemates through the membranes in all cases (+)-isomers predominantly permeated and the enantioselective permeation continued for more than 1800 h. In all three racemic bodies, (+)-isomers are selectively adsorbed and mandelic acid adsorbed with a high enantioselectivity permeates with a higher enantioselectivity. These findings indicate that the enantioselectivity in the permeation is caused by the facilitated solution process at the membrane surface of the (+)-isomer, which interacted more strongly with oligomer **(4).**

It is interesting that oligomer **(4)** having the chiral pinanyl pendant groups shown enantioselective adsorption in contrast to polymers **(3)** and **(5)** with the same chiral groups. A closeness of siloxane main chain obviously provides interaction with solutes due the siloxane bonds. The main chains of polymers **(3)** and **(5)** consist of extremely hydrophobic silylpropyne and norbornadiene.

It seems that potentialities of membrane surface modification for development of enantioselective membranes were used very weakly. Besides of the above-mentioned surface modification by plasma polymerisation of terpenes [32, 33] and BSA binding on the surface of ultrafiltration membranes [2,3] an another Japanese group studied hollow fibres with bound BSA [39, 40], as well as ceramic membranes with sorbed P-cyclodextrin on the pore surface have been developed [41]. All these membranes including modified by plasma polymerisation after modification remain rather porous than dense. At the same time, interfacial polycondensation, graft copolymerisation, covering by polyelectrolyte complexes, LB method can allow obtaining of dense surface layers based on chiral substances. For example, chiral polymerised surfactants or high-molecular-mass surfactants [42] can be used for formation of thin layers with well organised structure by graft-copolymerisation, LB technique etc.

Porous membranes containing CS should be considered, first of all, as a solid medium for selective sorption. After selective sorption of one enantiomer by such materials, the enantiomer can be eluted by a solution, which assures dissociation of CS/solute complexes. As it was mentioned early the binding of amino acid by BSA depends on the pH rate. At the acid condition BSA does not bind amino acid. That allows an eluating and collecting of pre-sorbed L-amino acid during filtration ofbuffer solution with pH 3.0 through the membrane with immobilised BSA [2, 3]. This principle is similar to chromatographic separation with alternating cycles of sorption and eluation.

The same principle was used for separation of oxprenolol with the use of CTPC membrane [29]. To exclude non-selective transport through the membrane it was contacted only with source phase by one side during the sorption. The other side of membranes was in contact with air. In such situation only the enantioselective sorption is realised and membrane enriches by one enantiomer. During the eluation membrane does not contact with source phase, non-selective transmembrane transport is absent and enantioenriched solute is washed out from the membrane by extraction solvent. In such way enough high enantiomeric enrichment (36.2% and 22.9% in receiving and source phases respectively) was obtained at high degree of solute recovery (38%).

An alternative method of membrane chromatography is based on a simple injection of solution of racemate being to be separated into the system. It also principally differs from the concentration- or pressure-driven separation using enantioselective membranes. The volume of membrane pores can be significantly filled with protein as a result of multilayer binding by grafted reactive chains [39, 40]. For such multilayered hollow fibres containing BSA the effective separation of DL-tryptophan was reached in a filtration mode. Such membrane chromatography can be used for preparative resolution of enantiomers. For scaling-up of these processes to preparative levels the system that provide a uniform loading of enantioselective membranes by injectable solution have to be developed.

Molecularly imprinted membranes

Thus, many approaches were realised for development of enantioselective membranes. Materials for membrane preparation or modification are optically pure substances and, as a rule, are obtained through multi-stage chemical transformation and are expensive. So, development of new approaches for obtaining of enantioselective membranes is still actually.

A creation of enantioselective surroundings in polymeric materials by technique of so-called molecular imprinting [43] is a new promising and elegant route for the development of enantioselective membranes. The imprinting polymerisation consists of cross-linking of the functional monomer or monomers in the presence of a template substance by radical polymerisation. After polymerisation, the target molecules are washed out leaving the selective cavities due strong orientation of functional groups and correspondence of the shape and size of cavity to the target substance. Imprinted polymers were developed for the purpose of enantiomer separation as well [44—47]. The formation of solid materials from the polymer solution containing template molecules [48—51] or imprinting polymerisation at presence of second polymer [52] can be considered as an alternative method of formation of imprinted polymers.

To provide a high selectivity the imprinted polymers should be posses the following main properties:

stiffness of the polymer structure that enables the cavities to retains their shape corresponding to template; good accessibility of the specific cavities; high number and strength of the interactions between complementary functional groups of the template and polymer [43].

Some of these properties contradict the principles of design of polymeric membranes. The stiffness of the structure of imprinted membranes is reached due high degree of cross-linkage. As a result these materials are fragile. This is a main problem for obtaining of membranes based on imprinted polymers. The membranes should be as thinner as possible but have good mechanical properties at this thickness.

There are a few reports in literature dealing with molecularly imprinted membranes. Membranes were prepared, as a rule, by imprinting polymerisation in the solutions impregnated into the pores of support materials [53—55]. Membrane formation by dry method [56—63] or phase inversion [53—55] from polymer solutions containing template substances was developed as alternative molecular imprinting technique. In this approach the binding sites are created due functional groups of polymers.

Among of mentioned attempts on development of imprinted membranes only several ones are directed on design of membranes for enantiomer separation. Three-dimensional polymerisation in a porous support [47, 55] results in thick membranes with a possibility of heterogeneous distribution of cross-linked domains and micro-phase separation on the interface pore surface/cross-linked domain. The later can be a source of non-selective transport.

The membrane imprinted towards CBZ-L-tyrosine shown more fast diffusion of CBZ-L-tyrosine than CBZ-D-tyrosine [55]. This is opposite to chromatographic system with column loaded with the same polymer: D-isomer eluted more rapidly than L-isomer. The cause of such behaviour is not clear. Moreover the authors did not observe the enantioselective transport with using of racemate solution in source phase. The paper contains too less results on transport data for correct discussion.

In research series M.Yoshikawa et al. [56—63] used polymers containing chiral groups (oligopeptides) [56—61], derived natural polymers (cellulose acetate) [62] and achiral synthetic copolymers [63] for preparation of imprinted membranes by dry method from polymer solution containing amino acid derivatives as template. The enantioselectivity was confirmed in sorption experiments, diffusion transport and electrodialysis. It should be note that such membranes act not only as molecularly imprinted. The highest enantioselectivity (up to 6.0) were obtained for membranes based on polymer with bond chiral oligopeptides. The moderate enantioselectivity (about 2.5) was obtained for cellulose acetate, derivative of natural chiral polymer. Membranes based on achiral carboxylated polysulfone demonstrated maximal enantioselectivity factor of 1.2. So, polymer chirality contributes significantly in membrane enantioselectivity.

Enantioselectivity in diffusion experiments is opposite to sorption enantioselectivity and membrane selectivity during electrodyalisys. As it was mentioned under discussion of separation result on membranes with chiral groups, to conclude the possibility and potentialities of chiral separation the thorough transport experiments are necessary. Unfortunately, these works do not contain data on the degrees of solute recovery or time of transportation. The data on membrane performance during the time are especially important because these membranes are not cross-linked and stability of their structure and consequently enantioselectivity can be changed with time.

Thus, in spite of numerous data on enantioselective imprinting polymers the self-standing enantioselective membranes based on molecularly imprinted polymers with high degree of cross-linking are not still developed. Moreover the imprinting polymerisation can be performed as graft-copolymerisation on the surface of polymeric membranes [64]. That should allow obtaining of thin enantioselective layers based on achiral substances. For formation of enantioselective layers on membrane surface can be used polymerisation of aniline. When polyaniline is doped with optically pure substances it adopts a chiral structure able to recognise enantiomers [65].

Membrane reactors in chiral separation

CSs can not only selectively bind one enantiomer but also induce its chemical transformation. Chiral agent can act in stoichiometric or catalytic fashion to favour the formation of desired enantiomer as a result of asymmetric synthesis from prochiral substrate or the chiral resolution due the transformation of one enantiomer in racemate. Both asymmetric synthesis and chiral resolution can be integrated with membrane separation in membrane reactors. Their use promises a lot of advantages in large-scale processes of enantiomer production and separation.

It seems that synthetic chiral reagents and catalyst have not yet been used in membrane reactors. Although a progress in polymer supported chiral reagents and catalyst [66, 67] allows anticipating an advances in development and application of synthetic chiral agents in membrane system for production of optically pure substances.

In recent years, several types of membrane reactors have been explored to conduct enzyme-catalysed bioconversions for purpose of enantiomer production or separation [68]. Ultrafiltration, membrane extraction, supported liquid membranes, and electrodialysis are the most common membrane separation processes

combined with biotransformation in realizing enantiospecific biocatalytic membrane reactors.

Among the simplest is an enzyme continuous stirred tank reactor (CSTR) combined with ultrafiltration (UF) reactor wherein an aqueous enzyme solution confined within CSTR is continuously circulated through an ultrafiltration module, from which enzyme-free ultrafiltrate is continuously removed while fresh substrate for the enzymatic conversion is continuously fed to the reactor in aqueous solution. This results in continuous generation and isolation of the enzymatically transformed product, without loss of enzyme. A number of nutritionally important amino acids and 2-hydroxy acids have been synthesized or optically resolved, some on an industrial scale, in Japan and Germany via enzymatic reactions that are conducted in homogeneous, single-phase CSTR/UF membrane reactors [69—72].

Nano- and ultrafiltration membranes can also assure maintenance of cofactor in reaction zone for cofactor-dependent enzymatic reactions. So, the production of L-phenylalanine out of the racemic mixture of D,L-phenyllactate was carried out in an enzyme membrane reactor, where enzyme and cofactor (NADH/H) were compartmentalised behind an ultrafiltration membranes [73]. To reject cofactor by ultrafiltration membranes it was covalently bound to polyethyleneglycol with molecular weight of 20000. The production of L-phenylalanine out of the racemic mixture of D,L-phenyllactate is an example of two-stage biotransformation under action of two enzymes. The L-phenylalanine is obtained by consecutive reaction catalysed by D,L-hydroxyisocaproate dehydrogenase and L-phenylalanine dehydrogenase.

In general, it is sometimes preferentially to utilize the entire catalytic system of the whole cell rather than an individual enzyme to effect a biological conversion. The enantioselective hydrolysis of 5-p-hydroxyphenylhydantoin into corresponding N-carbamyl was studied in biocatalytic membrane reactors realized by segregation the whole cell of *Agrobacterium* in the lumen circuit of a hollow-fibre reactor [74]. During ultrafiltration the D-isomer of N-carbamyl was recovered in permeate while the biocatalyst remained in the retentate and could be reused for further reaction by adding fresh substrate. The same sample of biomass was reused for five subsequent experiments with a 20% decrease of activity per experiment.

In a variant of membrane reactor based on ultrafiltration, continuous enzymatic transformations have been carried out within a membrane ultrafiltration cell by allowing an enzyme to concentrate by polarization on the upstream membrane surface [75—78]. Upon continuous ultrafiltration of an aqueous solution of substrate, the latter is transformed to product during transportation through the enzyme gel layer residing atop the membrane. The product is in the permeate.

A somewhat different membrane/immobilized enzyme reactor concept involves the loading of a concentrated aqueous solution of enzyme to the shell-side of a hollow-fibre-bundle of ultrafiltration membranes, while the aqueous substrate solution passed continuously through the lumens of the fibres [79]. Kinetically limited conversions were achieved in this manner. Additionally, biocatalysts have been covalently attached to high-internal-surface-area microporous membranes or entrapped in a membrane structure by phase inversion for the purpose of effecting enzyme-catalysed reactions of aqueous-phase reactants to aqueous-phase products [74, 80].

Above-mentioned enantioselective hydrolysis of 5-p-hydroxyphenylhydantoin was carried out in continuous mode during ultrafiltration through the biocatalytic membrane obtained from polymer solution containing whole cells of *Agrobacterium* by phase inversion [74]. It was shown that organic solvents do not deactivate the microorganism. The initial reaction rate was higher when using biomass segregated in the hollow-fibre reactor than biomass entrapped in the flat sheet membrane.

Membrane bioreactors with reactants and products in aqueous phase are not practically able to change passing ofbiocatalytic reaction. As far as, many enzymatic reactions can by inhibited by reaction products, a degree of substrate conversion is restricted. So, for enzymatic reaction a continuous separation of reactants and products is very desirable. It could be realised in two-phase extractive reactors if the reactants and products possess the different solubility. For chiral separation in membrane bioreactors of such type the product of enzymatic reaction are badly dissolved in medium used for reactants and extracted through the membrane in other immiscible liquid medium.

Such extractive membrane reactors can also work in combination with CSTR and as one-stage process with enzymatic reaction and extraction in membrane module. Using of CSTR is possible even in case of enzymatic reaction inhibited by products. For example, oxidation of alcohols by alcohol dehydrogenases are characterised by low conversions and slow reaction rates due to severe product inhibition. This can be overcome when only a small amount of product is formed in CSTR. The product is extracted through hollow fibre membrane. This results in an increase of the relative activity of the dehydrogenase at a given degree of conversion. The product extraction is not enantioselective process but enantioselectivity is provided by enzymatic reaction. This principle allowed a kinetic resolution of racemic l-phenyl-l,2-ethanediol by glycerol dehydrogenase (GDH) [82]. A conversion of 50% with respect to the racemate and enantiomeric excess more than 99% of the (S)-enantiomer was reached.

CSTR with embedded dialysis tube have been used for the continuous production of (S)-(+)-2-(6-

raethoxy-2-naphthyl) propionic acid (Naproxen) [82]. The process consists of a stereoselective hydrolysis of the racemic Naproxen methyl ester by *Candida rugosa* lipase in an aqueous-organic biphasic system. A continuous flow ofbuffer solution through the loop ofdialysis membrane provided the extraction of product. The hydrolysis reaction yielded (S)-(+)-Naproxen with more than 90% enantiomeric excess and overall conversion of 30%. The CSTR was allowed to operate continuously for 60 days at 30^0C with a 30% loss of activity.

In continuous mode ofoperation membrane separates two miscible phases, one of which contents biocatalyst and reactants. The products are continuously extracted into the second medium due their good solubility. The several systems have been studied with using of enzymes and whole cells [83, 84]. It should be note that biocatalyst can be found both in organic and aqueous solution. But biocatalyst localisation in membrane seems to be preferential because of stability enhancing, increase ofbiocatalyst concentration in reaction zone etc.

The most ofwork in multiphase reactor were carried out with immobilised biocatalyst. Of course, for this application the method of biocatalyst immobilisation are similar that use for above described CSTR/ultrafiltration systems and the simplest method of immobilisation is a gel layer precipitation on the membrane surface and biocatalyst loading in porous supporting layer of membrane due filtration [85—87]. However, the methods of covalent immobilisation are also used.

Lipase from *Pseudomonas sp.* was covalently immobilized in a porous polyamide membrane (flat sheet as well as hollow-fibres) via glutaraldehyde [88]. Enzymatic stereoselective hydrolysis of (R,S)-1-phenylethyl propionate was performed in a biphasic enzyme membrane reactor with counter-current circulation ofboth organic and aqueous phases on both sides of the membrane. At a conversion degree lower 55—60%, pure enantiomer of the remaining ester (i.e. > 98%) was obtained. But hydrolysis product exhibits a moderate or low enantiomeric purity. Using the similar system with immobilised Lipase from *Pseudomonas sp.* authors reached high enantiomeric purity of product (enantiomeric excess > 97%) due performing of transesterification with vinyl acetate [89].

The possibility to influence on the reaction equilibrium due selective substance transport through the membrane creates great possibilities to change strategy of production of enantiopure substances. Impressive example is a production of diltiazem, a highly useful cardiovascular product [86, 87].

The original synthesis illustrated on the left site of Figure 2, uses a tin-catalysed epoxide ring opening of racemic methyl p-methoxyphenylglycidate with o-nit-

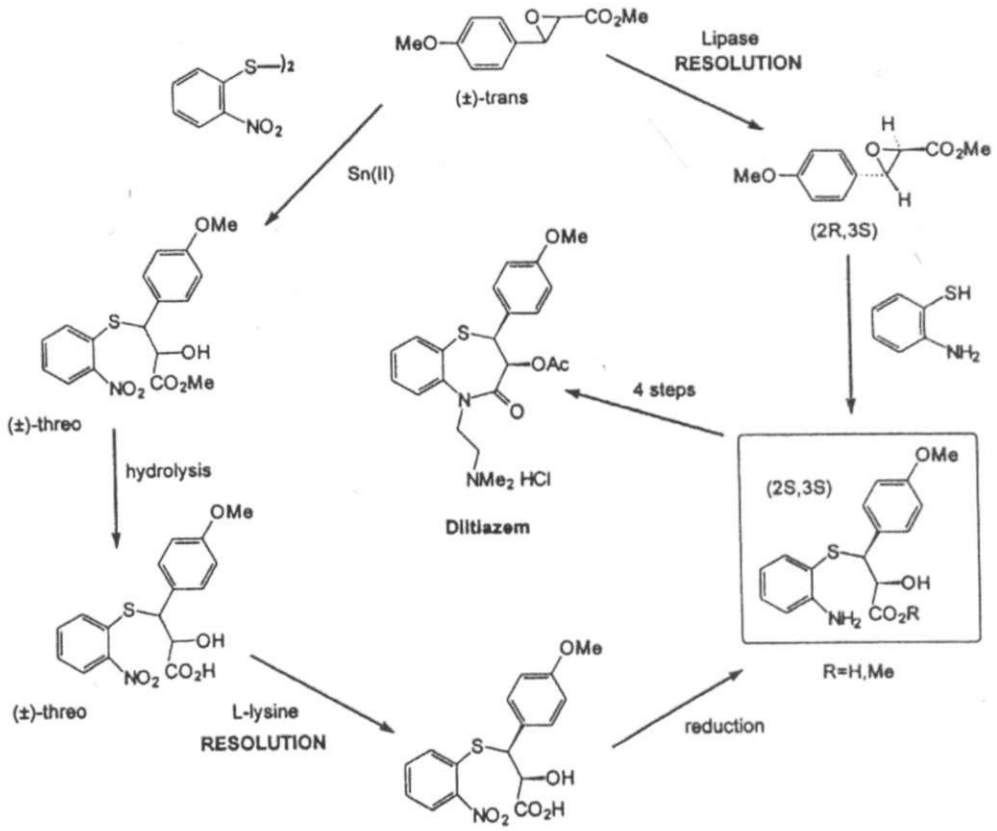
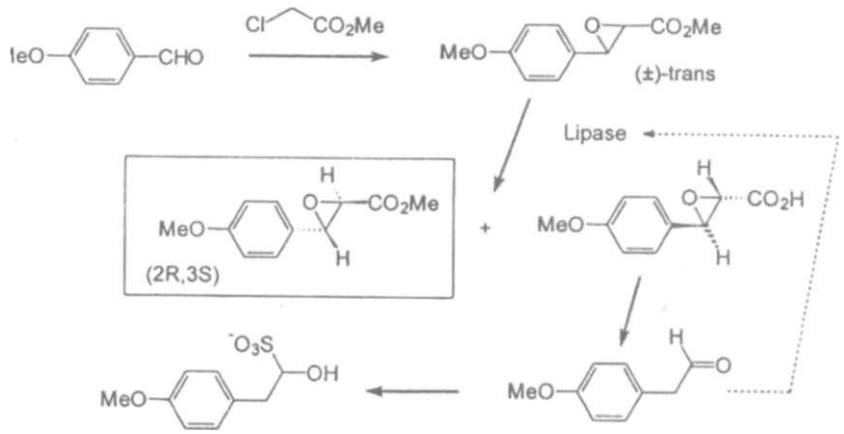


Fig. 2. Routes for Diltiazem production

rophenol. Elaboration of the adduct yields an a-hydroxy acid derivative, which is resolved by using L-lysine. Since there is no practical way to recycle the unwanted enantiomer, it is discarded. Reduction of the nitro group followed by further elaboration yields diltiazem. The sequence is characterised as a racemic synthesis with resolution occurring relatively late.

A key element in the new route is the efficient resolution of racemic methyl p-methoxyphenylglycidate. The process is based on the discovery of a series of lipases that preferentially catalyse the hydrolysis of the unwanted (2S, 3R)-glycidate ester:



Introduction of enzymatic reaction into the chemical synthetic route of diltiazem reduces the number of processes from nine to five. An interesting feature of the reaction is that the hydrolysis product undergoes spontaneous decarboxylation and rearrangement to the aldehyde, which is a powerful inhibitor of the enzyme. To overcome this drawback, sodium bisulphite is added to the reaction mixture to bind the aldehyde and prevent the inhibition. In the practical implementation of this process at scale, two additional issues needed to be addressed. First, the enzyme had to be recovered, since it is relatively expensive. Second, the reaction mixture consists of two liquid phases — an organic ester-containing phase and an aqueous bisulphite adduct containing phase — which must be separated at the end of reaction.

The requests easily satisfied by using of multiphase membrane reactor. Enzyme is loaded into the spongy matrix of the hollow fibre membranes. It is retained in the membrane by flowing the ester containing toluene phase, in which the enzyme is not soluble, from one side, and dense layer of asymmetric membrane from other side. This commercial membrane reactor installation has now been operating for years and produces over 75 metric tonnes per year of the resolved intermediate of diltiazem.

Conclusions and prospects

Among membrane-based processes of chiral separation biocatalytic enantiomer resolutions in membrane reactors have demonstrated the most promising results. There are examples of industrial applications of membrane bioreactors for the production of pure enantiomers. It is not surprisingly taking into a consideration a success in application of biotechnological methods for chiral resolution. The membrane processes allow a rationalization of the biocatalytic processes. The variety of membrane methods is a base to effect on a passing of such processes. A growing number of applications of membrane bioreactors could be expected in the field of chiral separation.

So far different types ofhydrolases have been preferentially used in membrane bioreactors for chiral resolution. To produce a pure enantiomer with these enzymes an additional stage of obtaining of racemic derivatives is required. It seems that a direct chiral synthesis in membrane bioreactors should be extensively developed with the use ofother types ofbiocatalysts. Moreover, membrane systems should be integrated with asymmetricsynthesis based on synthetic reagents and catalysts.

In membrane-based systems with mobile CSs a membrane plays an auxiliary role providing separation of enantiomers, which are preferentially bounded and unbounded with CS. A search of effective CSs is certainly a predominated task. On the other hand, known CS shows, as a rule, cross-selectivity for related chemical substances. That allows using of CS for various pairs ofenantiomers. Membrane-based chiral separation with mobile CSs is promising for large-scale applications. The comprehensive studies of mass-transfer during complexation/ultrafiltration and membrane-based solvent extraction are necessary to understand the potentialities and cost effectiveness of these methods.

Despite enough extensive research on development of membranes with fixed chiral selector a possibility of the chiral separation by such membranes is still controversial especially in case of porous membranes. Studies of possible mechanisms of chiral separation by the membranes should be continued. Development of membranes with chiral recognizing properties and different structures is important for both mechanism studies and application of chiral separation.

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НАПІВПРОНИКНІ МЕМБРАНИ В РОЗДІЛЕННІ ОПТИЧНИХ ІЗОМЕРІВ

В огляді проаналізовано стан досліджень мембранного розділення оптичних ізомерів. Молекулярне розпізнавання в таких процесах забезпечується власне мембраною, молекулярна структура якої включає центри структурної асиметрії, чи розчиненою оптично-активною речовиною-селектором (РС), що переважно зв'язує один з ізомерів. Обговорюються основні принципи та можливості розділення, що ґрунтуються на затримці рухливої РС мембраною (комплексутворення/ультрафільтрація), її транспорті крізь мембрану (мембранна екстракція) та включення РС у фазу мембрани (рідинні мембрани). Проаналізовано також праці, присвячені розробці мембран для молекулярного розпізнавання оптичних ізомерів та масопереносу крізь них при розділенні енантіомерів. Розглядається розділення оптичних ізомерів у мембранних реакторах, в яких РС каталізує енантіоселективне перетворення оптично активних речовин.