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Integrated reaction/separation process for the production of (S)-ibuprofen using supported liquid membranes based on ionic liquids

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A membrane bioreactor containing a supported liquid membrane based on ionic liquids was successfully applied to the kinetic resolution of *rac*-ibuprofen catalysed by a commercial immobilized *Candida antarctica* lipase B (Novozym 435). First of all, different ionic liquids were tested for use as liquid membrane phase supported in a Nylon membrane for the selective transport of the compounds involved in the reaction. The hydrophilic/hydrophobic character of the IL was shown to be a key factor in the selective separation of the substrates and products of the reaction mixture. The influence of the water content of the medium on the synthetic activity, selectivity and enantioselectivity of the enzyme was then analysed in order to establish the optimal amount of water. Finally, the integrated reaction/separation process for the resolution of *rac*-ibuprofen was carried out at the optimal conditions found.

1. Introduction

In recent years, there is an increasing demand for economical and highly efficient methods for commercial synthesis of pure enantiomers which mainly focuses on chiral drugs production. It is because, when racemic mixtures are administered as a drug, very often only one of the enantiomers is biologically active, while the other one might contribute to side-effects, displaying toxicity, or acting as antagonist. As consequence, a number of approaches to prepare it in optically pure form, including resolution of diastereomeric salts, resolution of racemates, and asymmetric syntheses using chiral auxiliaries and chiral catalysts have been proposed over the last two decades. One of these techniques is the kinetic resolution by means of enantioselective catalysts, especially combined with separation systems, such as supported ionic liquids membranes. The combination of the enantioselective properties of the catalyst and the separation properties of the membrane allows the conversion and separation of the enantiomer in a single step. Among membrane-based processes, the use of supported ionic liquid membranes (SILMs) (Fortunato et al., 2006; de los Ríos et al., 2007), porous supports whose pores are filled with a ionic liquid, has numerous advantages. Ionic liquids (ILs) are organic salts that are liquid close to room temperature. They

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usually consist of an organic cation, the most commonly used being dialkylimidazolium and tetraalkylammomium, and a polyatomic inorganic anion (e.g. BF_4^-, PF_6^-). Due to their extremely low vapor pressure, combined with the greater capillary force associated with their relatively high viscosity and the possibility of minimizing their solubility in the surrounding phases by suitable selection of the cation and anion, the use of ionic liquid as liquid phase in SILM make possible to obtain very stable and environmentally friendly supported liquid membranes (Hernández-Fernández et al., 2008).

In this work, a lipase-catalysed reaction has been combined with a supported liquid membrane based on ionic liquids to achieve the selective separation of *rac*-ibuprofen, which is an arylpropionic acid related to the class of non-steroidal, anti-inflammatory drugs. The anti-inflammatory activity of (S)-ibuprofen acid is higher than that of (R)-isomer by 150 times. Moreover, (R)-ibuprofen is easily accumulated in adipose tissues and causes the inhibition of fat metabolism and the destruction of cell membrane function. Thus, it is desired to use only (S)-ibuprofen as the antiinflammatory drugs instead of the racemate. In the present study, the performance of a membrane bioreactor containing a SLM based on ionic liquids for the kinetic resolution of *rac*-ibuprofen by esterification with n-octanol catalysed by *Candida antarctica* lipase B (CALB) was analysed. The effect of various process variables on the separation efficiency was investigated. The cation and anion composition of the ionic liquid was found to be a key parameter for the integrated reaction/separation process.

2. Experimental

2.1. Materials

A commercial lipase (EC 3.1.1.3) was used as catalyst: Candida antarctica lipase B immobilized on a macroporous acrylic resin (Novozym 435), which was a gift from Novo España S.A. (Madrid, Spain).

Hydrophilic Nylon® -polyamide- membranes (25 mm diameter, 0.45 μm pore size, 170μm thickness) were used as supporting membranes, which were supplied by Millipore S.A. (Madrid, Spain).

The ionic liquids 1-butyl-3-methylimidazolium hexafluorophosphate, $[bmim^+][PF_6^-]$ (purity>99%), 1-octyl-3-methylimidazolium hexafluorophosphate, $[omim^+][PF_6^-]$ (purity>99%), 1-butyl-3-methylimidazolium tetrafluoroborate, $[bmim^+][BF_4^-]$ (purity>99%), 1-octyl-3-methylimidazolium tetrafluoroborate, $[omim^+][BF_4^-]$ (purity>99%) were purchased from Solvent Innovation GmbH (Cologne, Germany). 1-Butyl-3-methylimidazolium bis{(trifluoromethyl)sulfonyl}imide, $[bmim^+][NTf_2^-]$ (purity >99%) was purchased from Sigma-Aldrich Chemicals Co. (Madrid, Spain) and 1-octyl-3-methylimidazolium bis{(trifluoromethyl)sulfonyl}imide, $[omim^+][NTf_2^-]$ (purity >99%) from Merck KgaA (Darmstadt, Germany). Other substrates, solvents and chemicals were purchased from Sigma-Aldrich Chemicals Co. (Madrid, Spain), and were of the highest purity available. Solvents and reactants were dehydrated with 3Å molecular sieves before use.

2.2. Preparation of supported liquid membranes

Immobilization was achieved by placing the membrane in a 10 mL AmiconTH ultrafiltration unit and adding 3 mL of ionic liquid. Nitrogen pressure at 2 bar was

applied, and the ionic liquid flowed through the pores of the membrane. The pressure was released once a thin layer of ionic liquid was left on the upper surface of the membrane. This procedure was repeated three times to ensure that all the membrane pores were filled with liquid since the ionic liquids used are quite viscous. Then, the membrane was left to drip overnight to remove the excess ionic liquid from the membrane surface.

2.3. Experimental setup

The experimental setup consisted on a glass diffusion cell with two independent compartments, 30 mL each, separated by the SLM. O-rings were inserted on each side of the SLM. The entire assembly was held together by a threaded connector.

2.4. Transport studies

The transport of *rac*-ibuprofen, n-octanol and n-octyl ester of ibuprofen through the SLMs at 30 ºC was evaluated. In each experiment, the initial solute concentrations in the feed phase were 100 mM in n-hexane. n-Hexane was used as a receiving phase in all cases. The transport experiment was begun by adding 30 mL of each solution to their respective compartments. The solute concentrations were monitored by sampling 100 μL of each compartment at regular time intervals during a 48 h period. An hexane solution of ethyl propionate (internal standard) (100 μL, 60 mM) and n-hexane (800 μL) were added to the sampling vials and the resulting solution (5 μL) was analyzed by GC.

Solute transport was analyzed by the permeability parameter ($\overline{P}$), which was calculated using Eq. (1) (de los Ríos et al., 2008), from the slope of the plot of $\ln [(C_0 - 2 C_r)/ C_0]$ versus t:

$$\ln\left[\frac{(C_0 - 2C_r)}{C_0}\right] = \frac{-2\,\overline{P}\,A}{V}\,t \qquad (1)$$

where C_0 is initial solute concentration in the feed phase (mol · L^{-1}), C_r is the solute concentration in the receiving phase (mol · L^{-1}), A is the membrane area (cm^2) and V is the volume of the compartments (mL).

Furthermore, the average permselectivy ($r\overline{P}$) of the membrane was determined as a numerical criterion to compare the ability of the different membranes to separate the target compounds (Eq. 2).

$$r\overline{P} = \frac{\sum_{i}^{n} rPi}{n} \quad \text{with} \quad rP_i > 1 \qquad (2)$$

where rP_i is the membrane permselectivity between two compounds (e.g. n-octanol and *rac*-ibuprofen) and n is the number of possible pairs of different compounds. rP_i can be expressed as follows:

$$rP_i = \frac{\overline{P}_A}{\overline{P}_B} \quad (3)$$

This parameter indicates the efficiency of the membrane in separating the compounds: the higher $r\overline{P}$, the more selective it is in separating the target compounds.

2.5. Reaction studies

In all the reaction experiments performed, the reaction medium consisted of the stoichiometric mixture of substrates and different percentages of added water. Octanol (1 mmol), *rac*-ibuprofen (1 mmol) and the corresponding amount of water were added to 22 mL screw-capped vials and n-hexane was added up to 10 ml total volume. The water content was controlled by Karl Fisher tritation. The reaction was started by adding 26.6 mg of Novozym 435 and run for 2 h at 30 ºC. At regular time intervals, 30 μL aliquots were taken, diluted with 470 μL n-hexane and cooled in an ice bath. Then, 400 μL of the hexane solution were added to 100 μL 30 mM ethyl propionate (internal standard) in n-hexane and 5 μL of the resulting solution was analyzed by GC. All experiments were carried out in duplicate and the mean values are reported. The efficiency of the catalytic action was measured by three parameters: the synthetic activity (U), defined as the amount of enzyme that produces 1 μmol of ester per minute, the selectivity, defined as the ratio between this parameter and the acyl-donor consumption rate, which takes into account the competitive hydrolitic reaction of the acyl-donor, and the enantiomeric excess of the synthetic product.

2.6. Reaction/separation studies

The reaction/separation experiments were performed at 30ºC using the experimental setup (see section 2.4). Typically, the feed phase consisted of 100 mM rac-ibuprofen and 100 mM n-octanol in n-hexane and the receiving solution was n-hexane. The immobilized enzyme (Novozym 435) was placed into the feed compartment and the experiment was begun by adding 30 mL of each solution to the respective compartments. Both compartments were mechanically stirred. The reaction/separation process was monitored by GC analysis, sampling 100 μL of each compartment at regular time intervals during 72 h. A hexane solution of ethyl butyrate (internal standard) (100 μL, 60 mM) and n-hexane (800 μL) were added to the sampling vials and the resulting solution (5 μL) was analyzed by GC

3. Results and Discussion

In a previous work it was demonstrated that the transport of the compounds through SLM based on IL was mainly regulated by the affinity of the ionic liquid towards each solute, measured as the partition coefficient between feed and received phase (Branco et al., 2002). Furthermore, having in mind that the hydrophilic/ hydrophobic character of the IL was shown to be a key factor in the selective separation of the transesterification reaction products (de los Ríos et al., 2008), ILs with quite different hydrophilic/ hydrophobic character were chosen for the present study. These ionic liquids were based on two 1-alkyl-3-methylimidazolium cations, n-butyl and n-octyl, and three

different anions, namely, hexafluorophosphate (PF_6^-), tetrafluoroborate (BF_4^-) and bis{(trifluoromethyl)sulfonyl}imide (NTf_2^-). For that, in the first set of experiments the hexane/ionic liquids partition coefficient was measured founding that the ionic liquids tested were suitable for the proposed separation and the ionic liquids were immobilized in the Nylon membrane. Then, the permeability of the compounds involved in the kinetic resolution of rac-ibuprofen by transterification with octanol (rac-ibuprofen, n-octanol and n-octyl ester of ibuprofen) through different SLMs based on ionic liquids was analyzed, in order to investigate the influence of the ionic liquid phase on the solute transport. It is important to point that, no significant permeability differences between rac-ibuprofen, n-octanol and n-octyl ester of ibuprofen were observed with the assayed Nylon membrane.

The influence of the ionic liquid on the permeability values was appreciated by comparing the value of this parameter for identical organic molecules. It was observed that an increase in the alkyl chain length of the cation of the ionic liquid involves an increase in the permeability values. One of the most effective supported liquid membrane for separating the selected organic compounds was the one based on $[bmim^+][BF_4^-]$. Comparison with the sequence for the hydrophilic character of the ionic liquids determined in a previous work (de los Ríos et al., 2008), $[omim^+][NTf_2^-] < [omim^+][PF_6^-] < [bmim^+][NTf_2^-] < [omim^+][BF_4^-] < [bmim^+][PF_6^-] < [bmim^+][BF_4^-]$, confirms that an increase in the hydrophilic character of the ionic liquids results in an increase in the permselectivity for the separation of the assayed organic compounds. Since the SLM based on $[bmim^+][BF_4^-]$ was seen to be one the most suitable supporting liquid membrane, the permeability of the compounds involved in the kinetic resolution of rac-ibuprofen with n-octanol through SLMs based on $[bmim^+][BF_4^-]$ was analysed.

The resolution of rac-ibuprofen catalysed by immobilized *Candida antarctica* lipase B (CALB) was also studied using n-octanol at 30 ºC and different water contents. n-Hexane was used as reaction medium because it was the solvent used as feed and receiving phase in the reaction/separation experiments. The synthetic activity exhibited by CALB showed a bell curve, with a maximum at about 100 ppm water content, after which, the activity decreased with increasing amounts of water.

Once the most suitable SLM for the separation process (Nylon with $[bmim^+][BF_4^-]$) and the optimal water content had been selected (100 ppm), the integrated reaction/separation process was carried out.

It was observed that in the feed compartment, the (R)-ibuprofen isomer was consumed by reaction with the alcohol, yielding (R)-n-octyl ester of ibuprofen. The non-reacted (S)-ibuprofen diffused to the receiving phase until their equilibrium concentration was reached. In contrast, the (R)-n-octyl ester of ibuprofen formed in the feed phase found it difficult to cross the supported liquid membrane from feed to receiving phase due the low permeability of these compounds. Therefore, the (S)-ibuprofen isomer could be separated in the receiving phase from the (S)-ibuprofen isomer.

Our investigations demonstrate the exciting potential of coupling the enantioselectivity of lipases with the selectivity of supported liquid membranes based on in ionic liquids for the development of new methodologies for the production of enantiomerically pure or enriched compounds.

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