Tetrahedron: *Asymmetry* 20 (2009) 1052–1056

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Chiral separation of *trans*-stilbene oxide through cellulose acetate butyrate membrane

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ARTICLE INFO

Article history:
Received 24 January 2009
Accepted 3 March 2009
Available online 6 May 2009

ABSTRACT

An enantioselective membrane was prepared using cellulose acetate butyrate as a membrane material. The flux and permselective properties of membrane using 50% ethanol solution of (*R*,*S*)-*trans*-stilbene oxide as feed solution were studied. The top surface and cross-section morphology of the resulting membrane were examined by scanning electron microscopy. The resolution of over 92% enantiomeric excess was achieved when the enantioselective membrane was prepared with 15 wt % cellulose acetate butyrate and 30 wt % *N*,*N*-dimethylformamide in the casting solution of acetone, 10 °C temperature of water bath for the gelation of the membrane, and the operating pressure and the feed concentration of the *trans*-stilbene oxide were 3 kgf/cm^2 and 5.2 mmol/L, respectively. Since the cellulose acetate butyrate contained a large amount of asymmetric carbons on the backbone structure, it was possible to form helical structure, this was considered to be the reason for the enantioselectivity of the membrane.

1. Introduction

Chirality is a phenomenon which is of great importance to some biological and chemical processes. Many pharmaceutical and flavoring compounds are racemic mixtures with chiral isomers having nearly identical physical and chemical properties. Under many circumstances, only one enantiomer could meet specific needs while the other one possessed a lesser or even a negative effect. The increasing need for single enantiomers in pharmaceutical and chemical industries has stimulated a significant demand for efficient processes to resolve racemic mixtures. However, the separation of enantiomers is an arduous and challenging task because of extremely similar physiochemical properties in nature with respect to enantiomers.[1]

Currently, enantioseparation is typically performed by fractional crystallization, microbiological methods, kinetic enzymatic resolution technology, asymmetric catalysis, chromatographic and membrane separation.[2] Due to an incomparable preponderance over traditional methods, such as low energy and time saving, set-up simplicity, large processing capacity and the possibility to be used in continuous mode, membrane separation systems are well established and have potential to be applied in large-scale industrious enantiomer separation processes.[3]

Cellulose derivatives have been widely used for the preparation of polymer membranes for reverse-osmosis, nanofiltration, ultrafiltration, microfiltration, etc.[4] Various membrane configurations have already been proposed for separating a large number of chiral species, including aminoacids, drugs and their derivatives.[5] Cellulose acetate butyrate (CAB) possesses many asymmetric carbon atoms in its molecular structure unit and has been used as a chiral stationary phase in high performance liquid chromatography.[6] It has also been used in the enantioselective membrane preparation with good resolution for (*R*,*S*)-2-phenyl-1-propanol because the high content of chiral active sites in the membrane is very useful to separate the stereoisomers.[7]

trans-Stilbene oxide enantiomer is an important intermediate reagent for the synthesis of chiral compounds, such as medicines, pesticides, and chiral selectors. Herein, the CAB membrane was prepared by the phase inversion method and enantioselective separation of racemic *trans*-stilbene oxide was investigated. To the best of our knowledge, until now there is no example describing enantiomer separations through a CAB membrane except for (*R*,*S*)-2-phenyl-1-propanol.

2. Results and discussion

2.1. Morphological analyses

Figure 1 shows the SEM images of the top surface and cross-section morphological structure of the CAB membrane prepared with 15 wt % CAB and 30 wt % DMF. Clearly, the top surface, namely the active layer, was smooth and had a homogeneous structure, but it was noticeable that there were macrovoids in the cross-section of membrane, because during the phase separation process, a one-phase casting solution was converted into two-phase system consisting of a solid phase (CAB-rich) that formed the membrane

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doi:10.1016/j.tetasy.2009.03.032

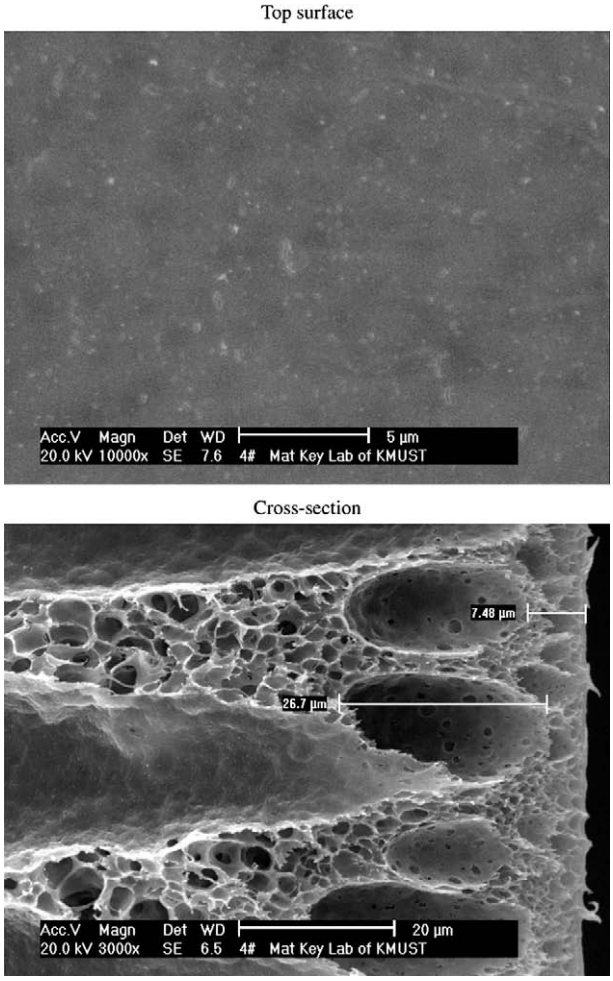

Figure 1. Scanning electron microscopy images of the membrane prepared with 15 wt % CAB and 30 wt % DMF.

structure and a liquid phase (CAB-poor) that formed the pores in the final membrane.

2.2. Influence of CAB concentration on the properties of the membrane

Polymeric membranes of CAB were formed by interpenetrating cellulose acetate butyrate. It is known that the polymer concentration in the casting solution strongly influences the structure of the asymmetric membrane. With 10 wt %, 15 wt %, and 20% wt % CAB casting solution, respectively, three CAB membranes were prepared by the same preparation method. The racemic mixture of *trans*-stilbene oxide was separated through these CAB membranes using 3 kgf/cm^2 of operating pressure and 5.2 mmol/L of feed concentration. Figure 2 shows the flux and enantiomeric excess in the enantioseparation. When the CAB concentration increased from 10 wt % to 20 wt %, the flux through the membrane decreased. Whereas a high enantioselectivity was obtained for 15 wt % CAB membrane, low enantioselectivity was observed for 10 wt %. The reason is the tighter membrane structure for a higher CAB concentration.

2.3. Influence of DMF content on properties of membrane

The effect of DMF content in the casting solution on flux and enantioselectivity of the membrane was able to be given due to the difference in solution rates and diffusion rates of the acetone and DMF in the membrane formation. With an increase of DMF content in the casting solution, an increase in flux can be seen from Figure 3. However, the membrane in this case (30 wt % DMF) exhibited good enantioselective ability. From this result, it became evident that the DMF content in the casting solution is important for the enantioseparation ability of membrane.

2.4. Influence of the coagulation bath temperature on the properties of the membrane

Figure 4 shows the effect of the coagulation bath temperature on properties of membrane for the resolution of *trans*-stilbene oxide. Increasing the temperature of the water coagulation bath from 10 °C to 30 °C, resulted in an increase of the flux, but in a decrease of the percentage enantiomeric excess. This was due to the fact that with a higher temperature of the water coagulation bath, the solvent of the membrane casting solution was diffused faster into the water. Thus, the membrane prepared under these conditions was porous, which resulted in high flux and low selectivity.

2.5. Influence of the operation pressure on the properties of the membrane

Under different operation pressures, the Q and %ee through CAB membrane were measured (Fig. 5). It can be seen that there was an increase in flux and a decrease in percentage enantiomeric excess while operating pressure increased from 3 kgf/cm^2 to 5 kgf/cm^2.

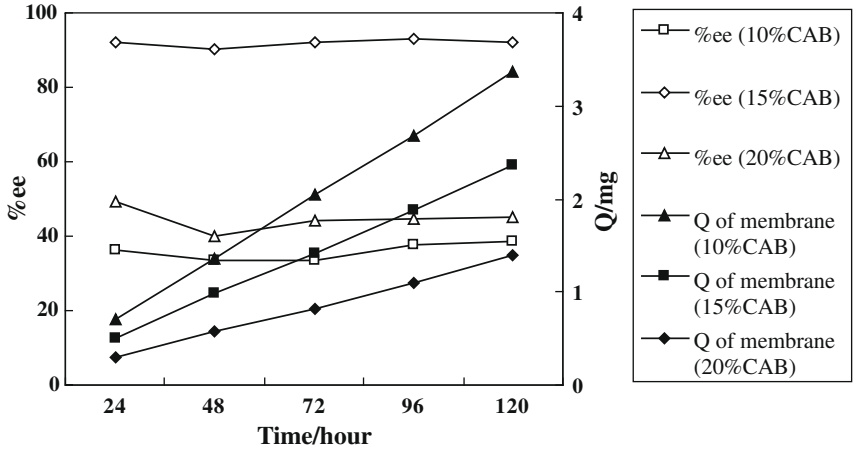

Figure 2. Q and %ee in the enantioseparation of *trans*-stilbene oxide racemates through CAB membrane prepared at different CAB concentrations. Operating pressure, 3 kgf/cm^2; feed concentration, 5.2 mmol/L.

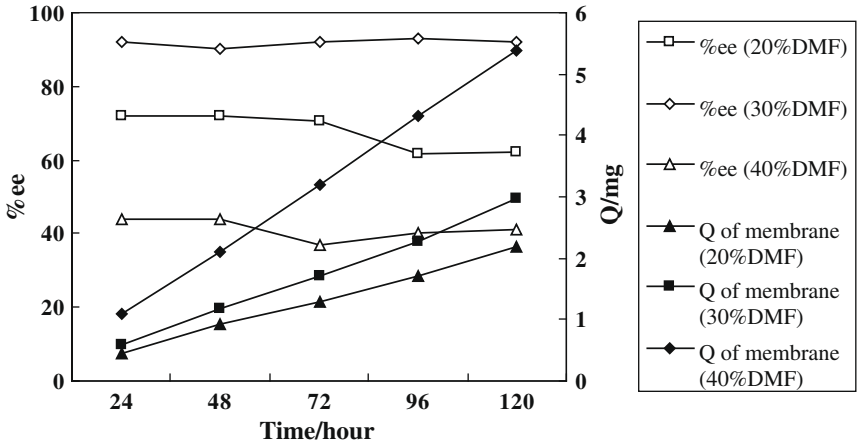

Figure 3. *Q* and %ee in the enantioseparation of *trans*-stilbene oxide through CAB membrane prepared at different DMF contents. Operating pressure, 3 kgf/cm^2; feed concentration, 5.2 mmol/L.

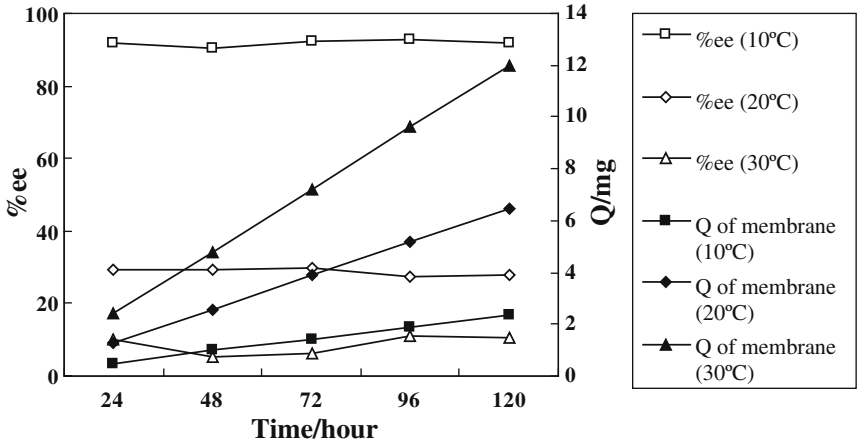

Figure 4. *Q* and %ee in the enantioseparation of *trans*-stilbene oxide through CAB membrane prepared at different coagulation bath temperatures. The coagulation bath temperatures were 10 °C, 20 °C, and 30 °C, respectively. Operating pressure, 3 kgf/cm^2; feed concentration, 5.2 mmol/L.

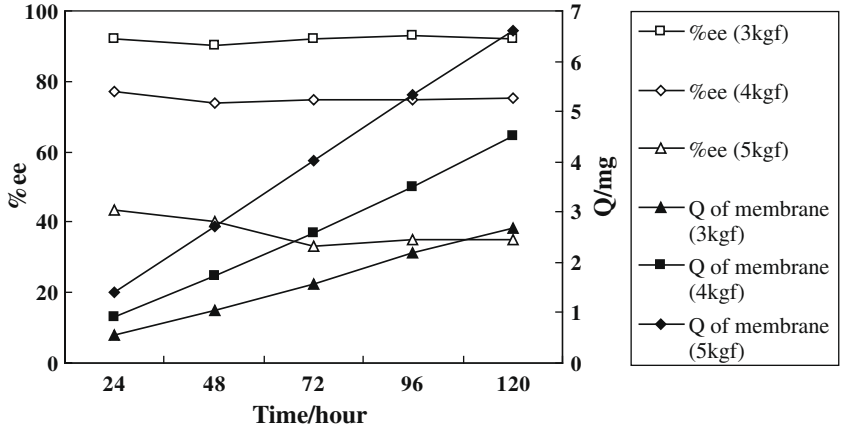

Figure 5. *Q* and %ee in enantioseparation of *trans*-stilbene oxide through CAB membrane with 5.2 mmol/L of feed concentration. The operating pressures were 3 kgf/cm^2, 4 kgf/cm^2, and 5 kgf/cm^2, respectively.

This behavior could be explained by the interaction between membrane and solutes, because with an increase of operating pressure, the movement of the solution accelerated, leading to decreasing diffusion selectivity and sorption selectivity. Consequently, the flux increased and enantiomeric excess decreased.

2.6. Influence of feed concentration of the racemate on the properties of membrane

Increasing the feed concentration, too much of both the isomers (*R* and *S*) were absorbed into the membrane, the enantioselectivity

of membrane decreased when the active sites of membranes were limited. Figure 6 shows that the effect of feed concentration on the flux and enantiomeric excess. As the feed concentration increased from 5.2 mmol/L to 7.8 mmol/L, the amount of the *trans*-stilbene oxide that penetrated through the CAB membrane increased dramatically, while decreasing the enantioselectivity of the membranes. For the 5.2 mmol/L of feed concentration, a high enantioselectivity and moderate flux were obtained.

In order to identify that the chiral separation in the membranes was not generated by a simple adsorption mechanism of one side of the isomer, one piece of membrane with a diameter of 3 cm was dipped in 15 mL of 5.2 mmol/L of *trans*-stilbene oxide solution (ethanol/water = 1:1) with stirring for 24 h. The membrane was taken out from the solution and washed with pure water, then placed in 2 mL of ethanol for 24 h. The *trans*-stilbene oxide solution and ethanol were analyzed by chiral HPLC with CHIRALPAK OD, equal areas of two peaks were shown for each sample.

The solubility selectivity of (*R*)-isomer and (*S*)-isomer was also studied. Therefore, 1 mg, 4 mg, 7 mg, and 10 mg of *trans*-stilbene oxide were dissolved in 1 mL of mixture solvent (ethanol/water = 1:1) with an ultrasonic bath, respectively, they still exhibited equal area for the two peaks when those solutions were analyzed.

3. Conclusions

Chiral separation of *trans*-stilbene oxide is possible through CAB membrane by a pressure driven-process because CAB contains a large amount of asymmetric active carbons on the backbone structure. Chiral recognition was a result of the steric fit of the enantiomers in the chiral space of the membrane, and of dispersion, dipole–dipole, and hydrogen-bond interactions with the glucopyranose units in the CAB. The properties of the membrane can be influenced by changing the CAB and DMF concentration in casting solution, coagulation bath temperature, operating pressure, and feed concentration, respectively.

4. Experimental

4.1. Reagents

The cellulose acetate butyrate, with an acetyl content of 29.5%, a butyryl content of 16.5–19.0%, and a MW of 200,000, was purchased from Acros (Belgium). *trans*-Stilbene oxide was supplied by Acros (USA). All the chemicals were of analytical grade and used without further purification. Pure water was used as solvent of feed solution.

4.2. Preparation of CAB membranes

The CAB membranes were prepared through the phase inversion technique. So, 2 g of the CAB was dissolved in mixed solvent of acetone (9.3 mL) and *N*,*N*-dimethylformamide (DMF, 4.2 mL) to obtain a cellulose acetate butyrate solution. An ultrasonic bath was applied to help the free up of the air bubbles that were entrapped in it. Under the conditions of 40% humidity and 10 °C temperature, the resulting homogeneous solution was cast on the surface of a glass plate using an adjustable casting knife. After evaporating the CAB membrane on the glass plate for 5 min, the nascent membrane was immersed into a water coagulation bath at 10 °C for at least 30 min. The membrane was washed in pure water at 10 °C for 24 h to remove the DMF and acetone. Finally, the membrane was prepared and stored in pure water until use.

4.3. Characterization of membranes

Scanning electron microscopy (XL30ES-EM-TMP, Holland) was used to characterize the morphologies and the structures of CAB membranes. The wet samples of CAB membrane prepared according to the experimental method were first immersed in propanol and subsequently treated with heptane to retain their original structures, and then snapped in liquid nitrogen to give a generally clear break of the cross-section for the cross-section scan. Before scanning analysis, the surface and cross-section of resulting membrane were coated with gold.[8]

4.4. Permeation experiment

Permeation experiments were conducted at room temperature by using a membrane cell which could hold one piece of membrane with an effective diameter of 3 cm and the capacity of the cell is about 100 mL.[7] For the permeation test, 50 mL of 5.2 mmol/L of *trans*-stilbene oxide solutions containing 50% ethanol was used as feed solutions. Constant pressure was applied through nitrogen gas to apply the required pressure. The operating pressure was controlled by adjusting the regulator attached to a gas container. All membranes were used once only.

4.5. HPLC analysis

The HPLC system was equipped with a LabTech LC600 liquid delivery pump, UV–vis detector (USA). The chiral analysis was performed using a chiral column CHIRALPAK OD (4.6 mm i.d. × 250 mm, Daicel, Japan) and a mixture of *n*-hexane/isopropanol (90/10, v/v) as mobile phase at 30 °C. The detection was exam-

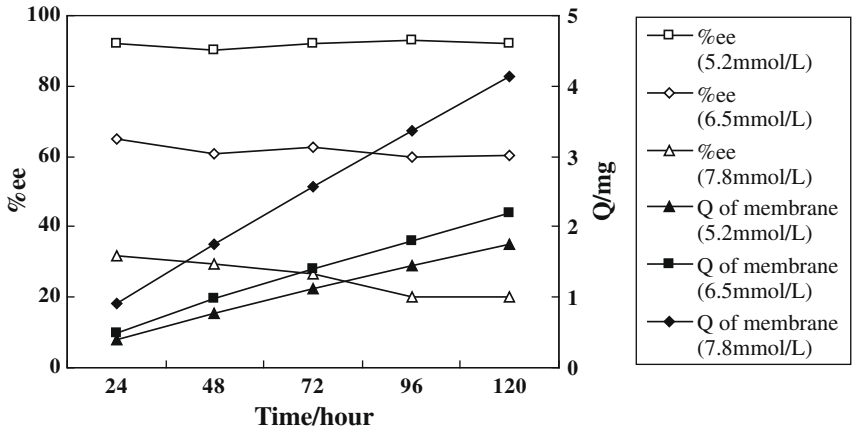

Figure 6. Q and %ee in enantioseparation of *trans*-stilbene oxide through CAB membrane at 3 kgf/cm^2 of operating pressure. The feed concentrations were 5.2 mmol/L, 6.5 mmol/L, and 7.8 mmol/L, respectively.

ined at 254 nm, and the flow rate of the mobile phase was 0.5 ml min^{-1}. Each sample was introduced by injector with 20 μl. A personal computer equipped with a LabTech HPLC Workstation for the LC system was used to process the chromatographic data. The (−)-isomer was selectively permeated.

4.6. Membrane performance definitions

Membrane performance was evaluated by the flux and the percentage enantiomeric excess (%ee). Their equations are as follows:

$$\text{Flux } (\text{mg/m}^2\text{h}) = \frac{Q}{At}$$

$$\text{ee } (\%) = \frac{A_R - A_S}{A_R + A_S} \times 100$$

where Q is the mass of the solute permeated for a given time, A is the effective membrane area, and t is the permeation time. A_S and A_R are the peak area of (R)- or (S)-isomer in the permeation, respectively.

Acknowledgments

The authors acknowledge the experimental guidance of Professor S.C. Wang of Tianjin University of China. The work is supported by National Natural Science Foundation (No. 20775066) and Yunnan Province's Natural Science Foundation (No. 2005E0006Z) of China.

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