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Article

Enantioseparation of Racemic α-Cyclohexyl-Mandelic Acid across Hollow Fiber Supported Liquid Membrane

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Este artigo trata da separação enantiomérica do ácido α-cicloexilmandélico contendo cobre(II) N-dodecil-(L)-hidroxiprolina (CuN_2) como um carregador quiral, usando uma membrana líquida suportada em fibra oca. Um modelo matemático de transporte e separação enantiomérica de compostos quirais foi deduzido; o coeficiente de partição observado entre a fase de alimentação e a membrana, a fase de eluição e a membrana, a resistência à transferência de massa na interface na fase de eluição dentro das fibras ocas, interface na fase de alimentação e a difusão na membrana foram levados em consideração nas equações do modelo. Usando os resultados experimentais, vários parâmetros do modelo proposto foram obtidos pelo método de ajuste não linear. Esse é um modelo matemático simples, que pode ser usado facilmente para predizer a concentração dos enantiômeros e o fator de separação do processo de separação enantiomérica; o modelo pode ser usado também para planejar e promover o aumento de escala do processo de separação enantiomérica.

This paper deals with the enantioseparation of racemic α-cyclohexyl-mandelic acid containing copper(II) N-dodecyl-(L)-hydroxyproline (CuN_2) as a chiral carrier using hollow fiber supported liquid membrane. A mathematical model of transport and enantioseparation of chiral compounds was deduced, the observed partition coefficient between the feed phase and the membrane phase, the stripping phase and the membrane phase, mass transfer resistance of boundary layer in strip phase inside the hollow fibers, boundary layer in feed phase and the diffusion in the membrane phase are taken into account in the model equations. Using the experimental results, several parameters of the proposed model have been achieved by nonlinear fitting method. It is a simply mathematical model which can be easily used to predict the concentration of the enantiomers and the separation factor of the enantioseparation process, and it can also be used to design and scale up the enantioseparation process.

Keywords: enantioseparation, hollow fiber supported liquid membrane, α-cyclohexyl-mandelic acid, model

Introduction

It is widely known that different enantiomers of a drug can have vastly different pharmacological activities. So it is imperative to separate these closely related chiral isomers to obtain stereochemically pure drugs.[1-3] Separation techniques such as crystallization, kinetic resolution, chiral chromatography and membrane technology have been used for the production of pure drugs. Over recent years, attention has increased in the use of liquid membrane as selective enantioseparation barriers.[4-6] Hollow fiber supported liquid membrane (SLM) is a kind of liquid membrane which offers many advantages such as high selectivity, high efficiency of separation, high enrichment efficiency and less use of the organic phase than in the classical solvent extraction process.

Optical pure α-cyclohexyl-mandelic acid (HCHMa) is a kind of important precursor of chiral drugs and can be used to synthesize multiple chiral drugs with vital biological activity and good healing effect such as oxybutynin.[7] Chiral extraction for enantioseparation of enantiomers has great potentialities, and it has been highly regarded in recent years.[8-10] So it is necessary to resolve racemic HCHMa into R- and S-enantiomers.

In this work, a hollow fiber supported liquid membrane is used to resolve the racemic HCHMa and a new

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mathematical model is presented for analyzing the transport of enatiomers. It is a simple mathematical model which can be easily used to simulate the concentration of the enantiomers and the separation factor of the enantioseparation process.

Theory

In this paper it was proposed a mechanism for the transport of HCHMa enantiomers through a hollow fiber SLM. Consider a porous carrier-facilitated SLM used for separating R- and S-α-cyclohexyl-mandelic acid of the racemic mixtures. The membrane consists of a chiral carrier dissolved in a water immiscible organic diluent.

In the system of chiral ligand exchange extraction, property of extraction mainly depends on two types of reaction in the organic phase. At first, transition metal ions, often Cu^{2+} in aqueous phase, partition into organic phase (octanol) containing N-*n*-dodecyl-*L*-hydroxyproline (HN) by forming binary complexes (CuN_2) with the free ligands in organic phase at the two phases boundary where the ligand can release one or more protons into the aqueous phase.

$$2\overline{HN} + Cu^{2+} \rightleftharpoons \overline{CuN_2} + 2H^+ \quad (1)$$

After Cu^{2+} in aqueous phase form binary complexes with chiral ligands in organic phase, HCHMa enantiomers form two ternary complexes with the binary complexes in organic phase.

$$HCHMa_j + \overline{CuN_2} \rightleftharpoons \overline{CuNCHMa_j} + \overline{HN} \quad (2)$$

The subscript "*j*" is used to denote the enantiomer concerned (*S*- or *R*-). The overbar notation is used to describe a species in the organic phase. The partition coefficients for *S*, *R*-enantiomer is expressed as follows

$$P_j = \frac{[\overline{CuNCHMa_j}]}{[HCHMa_j]} \quad (3)$$

In order to simplify the mathematics and model development for enantioseparation process of HCHMa using supported liquid membrane, several assumptions are made in this paper: (*i*) An ideal system exists under complete mixing and constant temperature operation; (*ii*) constant physical and transport properties; (*iii*) the membrane phase is completely immiscible with the aqueous phase and (*iv*) the volume of the liquid membrane phase is neglected relative to the volume of the feed phase and the strip phase.

In this enantioseparation process, the following steps are necessary:

First, transport of the solute from the bulk of the feed phase to the interface with the liquid membrane, the flux of the solute is expressed by

$$j_f = k_f(C_f - C_f') \quad (4)$$

Second, partition of the enantiomers at the interface of the feed phase and the membrane phase, the flux of the solute is expressed by

$$j_1 = p_1 C_f' - p_{-1} C(0,t) \quad (5)$$

Third, diffusion of the complex through the liquid membrane phase to the interface with the strip phase, the flux of the solute is expressed by

$$j_{m1} = -D_e[\partial C(0,t)/\partial x] \quad (6)$$

$$j_{m2} = -D_e[\partial C(x_0,t)/\partial x] \quad (7)$$

Fourth, partition of the enantiomers at the interface of the membrane and the strip phase, the partition flux of the solute is expressed by

$$j_2 = p_{-2} C(x_0,t) - p_2 C_s' \quad (8)$$

Fifth, transport of the solute from the interface to the bulk of the strip phase, the flux of the solute is expressed by

$$j_s = k_s(C_s' - C_s) \quad (9)$$

Where x_0 is the thickness of the membrane, x is the distance in the membrane, t is the time, c is the concentration of the enantiomers, $p_{1j}(p_{2j})$ and $p_{-1j}(p_{-2j})$ refer to the forward interfacial enantioselective partition rate constants and the backward interfacial enantioselective partition rate constants, respectively, k_f and k_s refer to the mass transfer coefficients in extraction boundary layer and strip boundary layer respectively. In the present work a Lévèque type equation will be used to correlate both the tube side and the shell side mass transfer coefficients:

$$Sh_f = a_f Sc_f^{b_f} Re_f^{c_f} (d_o/L)^{d_f} \quad (10)$$

$$Sh_s = a_s Sc_s^{b_s} Re_s^{c_s} (d_o/L)^{d_s} \quad (11)$$

Where Sh, Sc and Re are the dimensionless numbers of Sherwood, Schmidt and Reynolds, respectively, a, b,

c and d are the unknown parameters. The dimensionless numbers are defined as:

$$Sh = kd/D \tag{12}$$

$$Re = du\rho/\mu \tag{13}$$

$$Sc = \mu/(\rho D) \tag{14}$$

Where k, d, u, ρ, μ, D are the mass transfer coefficient, dimension, liquid velocity, liquid viscosity and diffusion coefficient, respectively.

D is the free bulk diffusion coefficient for the solute calculated using the Wilke-Chang equation,[11] and De is the effective diffusivity in the membrane and is defined as:

$$D_e = D\varepsilon' / \tau' \tag{15}$$

$$D = 7.4\times10^{-8}(\varphi M_B)^{0.5} T/(\mu_B V_A{}^{0.6}) \tag{16}$$

Where ε' is the porosity of the membrane, and τ' is the tortuosity factor which takes into account the difference between the effective thickness and the physical thickness.

If the time is enough for these processes to reach a steady-state, the solute concentration of the feed phase, the liquid membrane phase and the strip phase will come to a state of homeostasis. The mass-conservation equation and the concentration expression are given by:

$$V_f C_{f0} + V_s C_{s0} = V_f C_f + V_s C_s + V_m C_m \tag{17}$$

$$C_m = C_f P_1 = C_s P_2 \tag{18}$$

Then, for this pseudo steady-state assumption, the solute concentration expression of the feed phase (c_f), the liquid membrane phase (c) and the strip phase (c_s) can be obtained as:

$$C_m = \frac{V_f C_{f0} + V_s C_{s0}}{V_f/P_1 + V_s P_2} \tag{19}$$

$$C_f = \frac{V_f C_{f0} + V_s C_{s0}}{V_f + V_s P_1/P_2} \tag{20}$$

$$C_s = \frac{V_f C_{f0} + V_s C_{s0}}{V_s + V_f P_2/P_1} \tag{21}$$

As for transitional state, equations describing the concentrations of the solute in the supported liquid membrane (SLM), the feed phase (FP), and the strip phase (SP) are as follows.

SLM:

$$\frac{\partial C_j}{\partial t} = D_e \frac{\partial^2 C_j}{\partial x^2} \quad (0 < x < x_0) \tag{22}$$

$$t = 0,\ C_j = 0 \quad (0 < x < x_0) \tag{22a}$$

$$t \to \infty \quad C_j = \frac{V_f C_{f0j} + V_s C_{s0j}}{V_f/P_{1j} + V_s P_{2j}} \quad (0 < x < x_0) \tag{22b}$$

$$x = 0 \quad D_e \frac{\partial C_j(0,t)}{\partial x} = k_f\left[C_j(0,t) P_{1j} - C_{fj}\right] \quad (t > 0) \tag{22c}$$

$$x = x_0 \quad D_e \frac{\partial C_j(x_0,t)}{\partial x} = k_s\left[C_{sj} - C_j(x_0,t) P_{2j}\right] (t > 0) \tag{22d}$$

FP:

$$V_f \frac{dC_{fj}}{dt} = AD_e \frac{\partial C_j(0,t)}{\partial x} \tag{23}$$

$$t = 0, C_{fj} = C_{f0j} \tag{23a}$$

$$t \to \infty, C_{fj} = \frac{V_f C_{f0j} + V_s C_{s0j}}{V_f + V_s P_{1j}/P_{2j}} \tag{23b}$$

SP:

$$V_s \frac{dC_{sj}}{dt} = -AD_e \frac{\partial C_j(x_0,t)}{\partial x} \tag{24}$$

$$t = 0,\ C_{sj} = C_{s0j} \tag{24a}$$

$$t \to \infty, C_{sj} = \frac{V_f C_{f0j} + V_s C_{s0j}}{V_s + V_f P_{2j}/P_{1j}} \tag{24b}$$

where A is the liquid membrane area, V_f and V_s are the volumes of the feed phase and the strip phase, respectively, c (x, t) is the solute concentration within the supported liquid membrane and is defined as the moles *per* unit membrane volume, subscript "j" refer to the enantiomeric form.

The equations can be cast into dimensionless form by defining:

$$y = x/x_0, \tau = D_e t/x_0{}^2, E_{fj} = C_{fj}/C_{f0}, E_{sj} = C_{sj}/C_{f0}, E_{mj} = C_j/C_{f0} \tag{25a}$$

$$\beta = C_{s0j}/C_{f0j}, K_f = k_f x_0/D_e, K_s = k_s x_0/D_e \tag{25b}$$

$$\gamma_f = Ax_0/V_f, \gamma_s = Ax_0/V_s, \gamma_f/\gamma_s = V_s/V_f \tag{25c}$$

Then, using Laplace transform techniques, the dimensionless concentration of the enantiomers in the feed phase, strip phase and membrane phase can be obtained as:

$$E_{fj} = \frac{P_{2j}(\gamma_s + \beta\gamma_f)}{\gamma_f P_{1j} + \gamma_s P_{2j}} + \frac{\gamma_f (P_{1j} - \beta P_{2j})}{\gamma_f P_{1j} + \gamma_s P_{2j}} \exp(-\lambda_j \tau) \quad (26)$$

$$E_{sj} = \frac{P_{1j}(\gamma_s + \beta\gamma_f)}{\gamma_f P_{1j} + \gamma_s P_{2j}} + \frac{\gamma_s (P_{1j} - \beta P_{2j})}{\gamma_f P_{1j} + \gamma_s P_{2j}} \exp(-\lambda_j \tau) \quad (27)$$

Where λ_j is defined as:

$$\lambda_j = \frac{\gamma_f P_{1j} + \gamma_s P_{2j}}{1 + P_{1j}/K_f + P_{2j}/K_s} \quad (28)$$

For enantioselective separation process with selectivity for the S-isomer, the separation factor α is defined by

$$\alpha = \frac{j_S}{j_R} = \frac{E_{sS} - E_{sS0}}{E_{sR} - E_{sR0}} \quad (29)$$

Then, combined with the equation (22), it can be obtained as:

$$\alpha = \{ \frac{P_{1S}(\gamma_s + \beta\gamma_f) - \gamma_s (P_{1S} - \beta P_{2S}) \exp(-\lambda_S \tau)}{\gamma_f P_{1S} - \gamma_s P_{2S}} - E_{sS0} \} \Big/ \{ \frac{P_{1R}(\gamma_s + \beta\gamma_f) - \gamma_s (P_{1R} - P_{2R}) \exp(-\lambda_R \tau)}{\gamma_f P_{1R} - \gamma_s P_{2R}} - E_{sR0} \} \quad (30)$$

Since the solvent system of the feed phase is the same as that of the strip phase for the resolution of racemic mixtures, then equations (27), (28) and (29) can be simplified as:

$$\lambda_j = \frac{\gamma_f + \gamma_s}{1/P_{1j} + 1/K_f + 1/K_s} \quad (31)$$

$$E_{sj} = \frac{\gamma_s}{\gamma_f + \gamma_s} + \frac{\gamma_s}{\gamma_f + \gamma_s} \exp(-\lambda_j \tau) \quad (32)$$

$$\alpha = [1 - \exp(-\lambda_S \tau)] / [1 - \exp(-\lambda_R \tau)] \quad (33)$$

Experimental

Materials

Racemic HCHMa was purchased from Synergetica Changzhou, Ltd. in China. *L*- hydroxyproline was obtained from Xinghu Biology of Science and Technology Zhaoqing Ltd. in China, $[\alpha]_D^{20}$ = -85.2º, the purity was above 98%. Aldehyde C-12 lauric was purchased from Fluka Chemical Company, the purity was above 97%. Palladium on carbon catalyst was from Shanghai Chemical Reagent Company in China. All other reagents are of analytical grade and purchased from different suppliers. The polyvinylidene fluoride (PVDF) hollow fiber membrane modules were purchased from Mo-tian Membrane Engineering and Technology Co. Ltd.(Tianjin, China).

Analytical method

HPLC was performed with a LC-2010A SHIMADZU system controller (Kyoto Japan), a sample loop injector of 20 μL, a Shimadzu C-R3A Chromatopac, a Kromasil RP-18, 5 μm, 4.6 mm × 150 mm column was used for the analysis.

Copper ion concentrations in aqueous phase were determined by volumetric titration with EDTA using 1-(2-pyriclylaze)-2-naphthol (PAN) indicator dye. The copper concentration in the organic phase was determined by first diluting the sample with ethanol and then titrating with EDTA using PAN. HN was synthesized in our lab.[12]

The concentrations of enantiomers in the aqueous were measured by chiral mobile phase HPLC. Chromatographic conditions:[13] concentration of β-cyclodextrin, 9.5mmol L^{-1}; 0.075 mol L^{-1} aqueous solution KH_2PO_4 : ethanol : acetonitrile (65: 20: 15, V/V/V), pH 4.8, flow rate 1 mL min^{-1} and room temperature.

Enantioseparation of HCHMa

The experiments were carried out on the resolution of racemic HCHMa using copper(II) N-dodecyl-(L)-hydroxyproline (CuN_2) as a chiral carrier by a membrane solvent (octanol). The optimal operation conditions were determined by chiral extraction studies detailed in Feipeng Jiao and Kelong Huang.[14] The organic phase was prepared by adding HN (10 mmol L^{-1}) to octanol, and was then contacted with an equal volume of aqueous copper acetate solution (Cu^{2+}: 5 mmol L^{-1}) at pH 4.0. The aqueous copper acetate solution was prepared by adding cupric sulfate to acetate buffer. The organic and aqueous solutions were contacted for 48 h. The membrane was soaked in the resulting organic phase for at least 3 h.

The whole solution was immobilized in the pores of the polyvinylidene fluoride polymeric membrane separating two tube- and shell-side aqueous phases. The solution of chiral selectors in the membrane pores was immobilzed by pumping the solution of chiral selectors into the tube-side

of the hollow fiber module. This solution was circulated for 24 hours in order to distribute the dissolved CuN_2 molecules into the membrane pores.

The feed and strip solutions were prepared by adding perchloric acid to deionized water until the solution pH was 4.0. A racemic mixture of the HCHMa was dissolved in the feed solution (solute concentration: 10 mmol L^{-1}). The feed phase was pumped into the shell-side while the strip solution into the tube-side. At various times, 100 μL samples were removed from the strip solution and the R and S-enantiomers concentrations were determined using HPLC.

Results and Discussions

Experimental result of enantiomers concentration and separation factor

The experimental data of the enantiomers dimensionless concentration and separation factor of enantioseparation process are shown by dot in Figures 1 and 2. It can be seen that both enantiomer concentrations of the strip solution increase rapidly in the first few hours, and the S-HCHMa concentration is higher than that of the R-HCHMa. The slope of S-HCHMa is steeper than the slope for R-HCHMa. The concentration difference between the S- and the R-HCHMa in the strip solution shows a maximum. This maximum concentration difference is determined by the ratio of the observed partition coefficients of the two enantiomers. In this case, the maximum was shown at the time of 20 h. This result can be used as a guideline to determine the optimum operation conditions for the enantioseparation process.

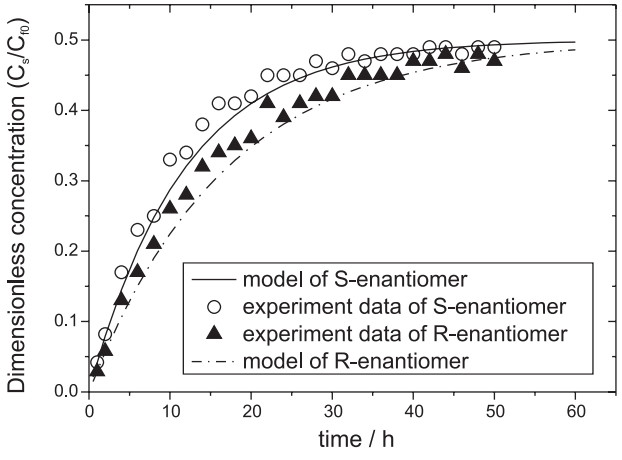

Figure 1. Dimensionless concentration profiles of enantiomers in the stripping phase. Experimental data: ▲ and ○; solid line: model prediction of dimensionless concentration of the S-enantiomer; dot line: model simulation of dimensionless concentration of the R-enantiomer.

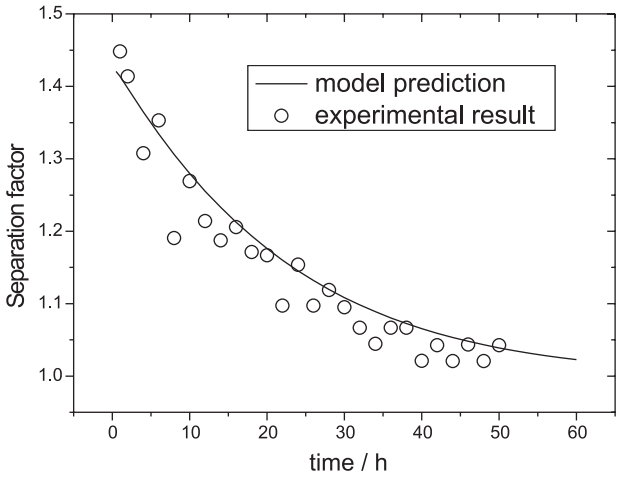

Figure 2. Separation factor of the enantioseparation process. ○ Experimental data of separation factor; solid line: results computed by equation (33).

Model simulation of enantiomers concentration profiles

There are eight unknown constants of a, b, c and d in the stripping phase and feed phase. According to the research of many workers,[15-17] there are some semi-experiential formulas about the equations (10) and (11), and some constants of them are the same:

$$b_f = b_s = 0.33, d_s = 0.33, d_f = 1 \tag{34}$$

Then equations (10) and (11) will be expressed as a function of four unknown parameters:

$$k_f(d_o/D) = a_f Sc_f^{0.33} Re_f^{c_f} (d_o/L) \tag{35}$$

$$k_s(d_i/D) = a_s Sc_s^{0.33} Re_s^{c_s} (d_i/L)^{0.33} \tag{36}$$

Using the experimental data of enaniomers dimensionless concentration which are shown in Figure 1, the four unknown parameters can be obtained by nonlinear fitting method as:

$$a_f = 4.75; a_s = 1.42; c_f = 2.23; c_s = 0.33 \tag{37}$$

The simulation curves of the enantiomers dimensionless concentration are shown by line in Figures 1, and the correlation coefficients of curve simulation of S-enantiomer concentration and R-enantiomer concentration are 0.995 and 0.996 respectively.

Model prediction and experimental result of separation factor

Substituting the parameters obtained by nonlinear fitting method into equations (31) and (33), the

mathematical model of separation factor can be obtained.

Figure 2 shows the experimental result and model prediction of the separation factor of enantioseparation process. It can be seen that the computational results of separation factor are shown by a solid line which is in good agreement with the experimental data. Therefore, it can be concluded that equation (33) can simulate the enantioseparation process well. It also indicates that the initial separation factor is the highest one achieved during the run, and it declines rapidly in the first few hours, then it approaches the value of 1 as time goes on. According to the equation (33), the initial separation factor is defined as:

$$\lim_{\tau \to 0} \alpha = \frac{\lambda_S}{\lambda_R} \tag{38}$$

It means that the ratio of the overall mass transfer coefficient for the S and R- enantiomers may be used to predict the maximum degree of separation that could be expected under ideal conditions. For this case, the initial separation is calculated to be 1.45.

Conclusions

Enantioseparation of racemic α-cyclohexyl-mandelic acid containing copper(II) N-dodecyl-(L)-hydroxyproline (CuN2) as a chiral carrier using hollow fiber supported liquid membrane was carried out successfully.

A mathematical model has been developed to analyze the mass transfer and the separation factor of R- and S-HCHMa across hollow fiber supported liquid membranes containing a chiral carrier. The observed partition coefficient between the feed phase and the membrane phase, the stripping phase and the membrane phase, mass transfer resistance of boundary layer in strip phase inside the hollow fibers, boundary layer in feed phase and the diffusion in the membrane phase are taken into account in the model equations.

Using the experimental results of the enantiomers concentration, several parameters of the proposed model have been obtained by nonlinear fitting method. The mathematical model was used to predict the separation factor of the enantioseparation process and the computational results of separation factor are in good agreement with the experimental data. It is a simple mathematical model which can be easily used to predict the concentration and the separation factor of the enantioseparation process, and it also can be used to design and scale up the enantioseparation process.

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References

1. Rosa, H. H.; Pilar, C. F.; *J. Chromatogr., B* **2000**, *740*, 169.
2. Bonato, P. S.; Paias, F. O.; *J. Braz. Chem. Soc.* **2004**, *15*, 318.
3. Jiao, F. P.; Huang, K. L.; Ning, F. R.; Hu, W. G.; Yu, J. G.; *Sep. Sci. Technol.* **2006**, *41*, 1893.
4. Pawel, D.; Piotr, W.; Pawel, K.; *J. Sep. Sci*. **2003**, *26*, 1050.
5. Miyako, E.; Maruyama, T.; Kubota, F.; Kamiya, N.; Goto, M. S.; *Langmuir* **2005**, *21*, 4674.
6. Maximini, A.; Chmiel, H.; Holdik, H.; *J. Membr. Sci*. **2006**, *276*, 221.
7. Vladimir, P. ; Zarko, S.; Krunoslav, K.; *Helv. Chim. Acta* **1982**, *65*, 377.
8. Cen, Z.; Cai, S.; *Journal Chemical Industry and Engineering (China)* **2000**, *51*, 418.
9. Vladimir, P.; Mi¿e, K.; Martin, E.; *Angew. Chem., Int. Ed.* **1989**, *28*, 1147.
10. Jérôme, L.; Catherine, G. G.; Sonya, T. H.; Jonathan, J. J.; *Angew. Chem., Int. Ed.* **2000**, *39*, 3695.
11. Reid, R. C.; Prausnitz, J. M.; Sherwood, T. K.; *The Properties of Gases and Liquids*, 3rd ed., McGraw-Hill: New York, 1977.
12. Ding, H. B.; Carr, P. W.; Cussler, E. L.; *AIChE J.* **1992**, *38*, 1493.
13. Shanshan, H.; Yizu, W.; Meiren, S.; *Fine Chemical* **2004**, *21*, 731.
14. Feipeng, J.; Kelong, H.; Xia, Y.; Xuehui, Z.; Jingang, Y.; *J. Bio. Sci.* **2006**, *9*, 1149.
15. Ortiz, I.; Galan, B.; Roman, F. S.; Ibanez, R.*; AIChE J.* **2001**, *47*, 895.
16. Gawronski, R.; Wrzesinska, B.; *J. Membr. Sci.* **2000**, *168*, 213.
17. Wu, J.; Chen, V.; *J. Membr. Sci.* **2000**, *172*, 59.

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