

Process Design for the Separation of (*R,S*)-1-Phenylethanol Enantiomers

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Lipase-catalyzed acylation of the chiral alcohol (*R,S*)-1-phenylethanol with several acylating agents in supercritical carbon dioxide (scCO₂) media was studied. Phase equilibrium measurements were performed at temperatures from 313 K to 333 K and at pressures from 10 MPa to 14 MPa for the ternary system *rac*-1-phenylethanol / *rac*-1-phenylethyl laurate / CO₂. The experimental data was correlated using the program package PE2000. The complete process (reaction and separation of the products) was carried out in a continuous high pressure apparatus.

INTRODUCTION

The need of technologies that allow separating optical isomers is increasing. Enzymes can distinguish substances on the molecular level very efficiently. They can catalyze a biotransformation, where basically one of the enantiomers is preferably chemically modified. As a result, the reaction products differ in their physical behaviour more than the educts. This difference can be adjusted to the needs of subsequent separation processes by choosing appropriate compounds for modification of the enantiomers. Using supercritical carbon dioxide as a reaction medium would be advantageous to utilize the solvent power of carbon dioxide to separate the reaction products immediately after the reaction. [1,2]

MATERIALS AND METHODS

The (*R,S*)-1-phenylethanol was supplied by Fluka and has a purity of 98%. Vinyl decanoate, vinyl laurate, vinyl stearate, methyl decanoate and methyl laurate and methyl stearate were supplied by Sigma-Aldrich with a purity between 96% and 99.9%. CO₂ was supplied by KWD Kohlensäurewerk Deutschland GmbH (Bad Hönningen) and has a purity of 99.95%.

The experimental apparatus used for the reaction experiments and phase equilibrium measurements is already described elsewhere [3].

The apparatus used for the continuous experiments (Figure 1) consists of two main sections, the reaction section and the separation section. The reaction section consists on a tubular packed-bed reactor immersed in a water bad. The separation section consists on three single

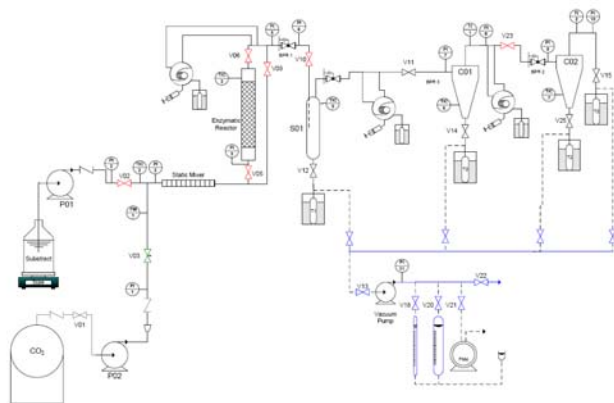


Figure 1 - Three-dimensional representation of the high pressure apparatus

separators (one gravimetric separator and two cyclones) operated at different pressure and temperature conditions.

RESULTS

For this work lipase-catalyzed acylation of the chiral alcohol (*R,S*)-1-phenylethanol with several acylating agents in supercritical carbon dioxide (scCO₂) media were studied. Different vinyl esters and methyl esters with alkyl chain lengths from 10 to 18 were considered.

All reactions were carried out at 313 K and 15 MPa using Novozyme 435.

Batch experiments were performed in a 1:1 initial molar ratio of racemic alcohol to ester. This means that in reality the ester is in excess. Because only the (*R*)-enantiomer reacts with the ester an initial molar ratio of 1:2 of (*R*)-enantiomer to ester can be considered.

In Figure 2 is shown the enantiomer consumption with time for the three acylating agents.

The reaction rate increases with the increasing of the chain length of the acylating ester. This

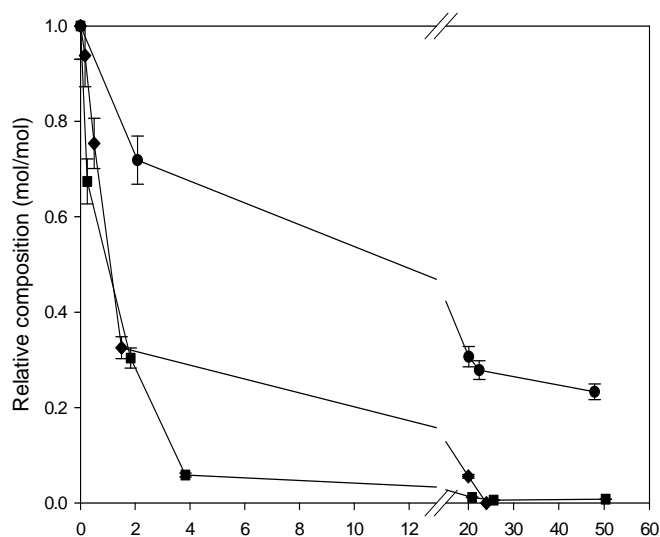


Figure 2 -Comparison of the (*R*)-Phenylethanol consumption with time and with the three acylating agents at 313 K and 15 MPa. ● (*R*)-1-Phenyl-ethyl decanoate; ◆ (*R*)-1-Phenyl-ethyl laurate; ■ (*R*)-1-Phenyl-ethyl stearate

can be explained by the fact that the longer the alkyl chain, the more flexible it is, making it able to fold and to adjust itself better to the space available in the active site of the enzyme. In another hand, the shorter the chain length, the more stiff it is. Not being able to fold in a way that allows the ester group of the molecule to easily reach the active site of the enzyme slows down the reaction rate. Obviously, if the alkyl chain is short enough the conformational limitations cease to be relevant.

In the reaction with vinyl decanoate the conversion is not complete. It can also be observe that the rate of reaction for the other two esters is very similar. Contrary to vinyl stearate, vinyl laurate is liquid at room temperature which avoids

problems with handling and product precipitations. For this reason all further experiments were done using vinyl laurate as the acylating agent.

For the comparison between using methyl esters instead of vinyl esters as acylating agents two esterification reactions using methyl decanoate and methyl laurate were carried out.

The efficiency of these esters is much lower than the vinyl esters. The conversion of (*R*)-1-phenylethanol is much slower than with any of the vinyl esters and the conversion is always under 40%.

The ability of scCO₂ to separate (*S*)-1-phenylethanol and (*R*)-1-phenyl-ethyl laurate was determined using phase equilibria as the starting point.

For the separation studies, isothermal vapor-liquid phase equilibrium was measured at temperatures between 313 and 333 K for the ternary systems (*R,S*)-1-phenylethanol / (*R,S*)-1-phenyl-ethyl laurate / CO₂, in the pressure range of 10 – 14 MPa.

Three different feed compositions were studied; 0.25, 0.50, and 0.75 mass fraction of (*R,S*)-1-phenylethanol.

To evaluate the selectivity of CO₂ towards (*R,S*)-1-phenyl-ethyl laurate the separation factor α , was analyzed and the capability of CO₂ to separate these two compounds at the determined conditions of temperature, pressure and feed composition evaluated.

This parameter is calculated from the compositions of the vapor and liquid phase of (*R,S*)-1-phenyl-ethyl laurate and (*R,S*)-1-phenylethanol:

$$\alpha = \frac{y_{PhEtOH} / x_{PhEtOH}}{y_{PhEtLau} / x_{PhEtLau}} \quad (1)$$

Where y represents the vapor composition and x represents the liquid phase composition of each compound. *PhEtLau* stands for (*R,S*)-1-phenyl-ethyl laurate and *PhEtOH* stands for (*R,S*)-1-phenylethanol.

The effect of pressure and feed composition in the separation factor at 323 K is presented in Figure 3, for pressures between 10 – 13 MPa and (*R,S*)-1-phenylethanol mass feed compositions of 0.50 and 0.75.

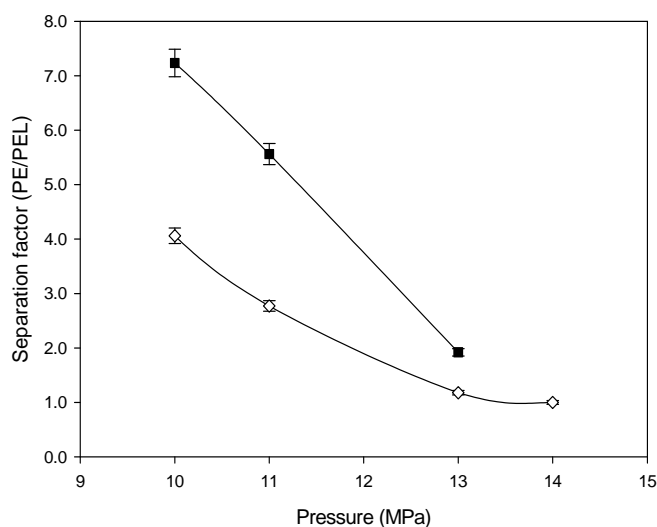


Figure 3 - Separation factor between (*R,S*)-1-phenylethanol (PE) and (*R,S*)-1-phenyl-ethyl laurate (PEL) as a function of pressure for several mass feed (*R,S*)-1-phenylethanol (PhEtOH) compositions (solvent free basis): ◇ 0.50 mass fraction of PhEtOH, ■ 0.75 mass fraction of PhEtOH

feed mass composition (in a solvent free basis) of 0.5.

By analysis of the previous figures, the boundary conditions for pressure and temperature to be used in a separation process can be determined.

For the separation of a 0.5 mass feed mixture (in a solvent free basis), that is expected to be the composition of the liquid mixture at the outlet of the reactor, the separation process should be operated at a temperature above 323 K and at pressures above 11 MPa. Some caution needs to be taken with the upper limits of operation. At pressures higher than 14 MPa a much

As it can be observed the separation factor decreases with increasing pressure. Due to the increase of the CO₂ density and corresponding solvent power there is an increase of the most soluble component in the gas phase and correspondent decrease in the separation factor. At 10 MPa is possible to achieve separation factors close to 8. The separation factor values drops rapidly to a value close to one at pressures higher than 13 MPa.

Also, as the mixture becomes richer in (*R,S*)-1-phenyl-ethyl laurate the separation factor decreases which means that the separation will be more difficult.

In Figure 4 is presented a comparison between the separation factor values and the liquid solubility as a function of temperature at a constant pressure of 13 MPa and with a (*R,S*)-1-phenylethanol

higher temperature is necessary to achieve a successful separation and to still have enough liquid dissolved in the gas phase to make the process viable. This high temperature brings additional energy costs to the process.

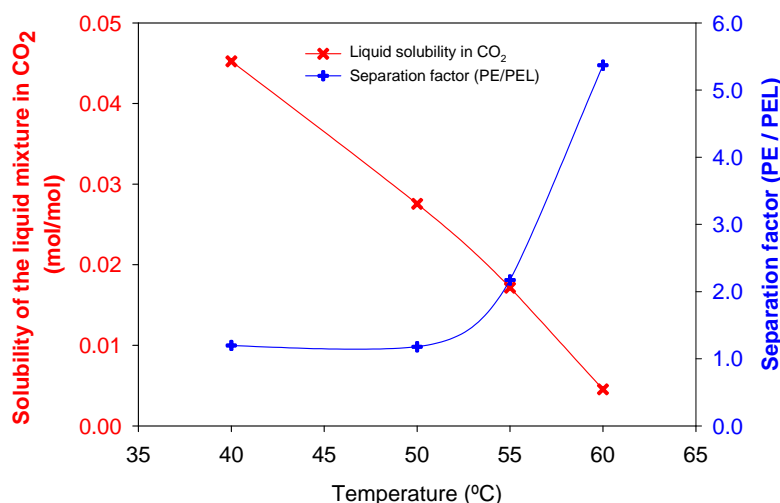
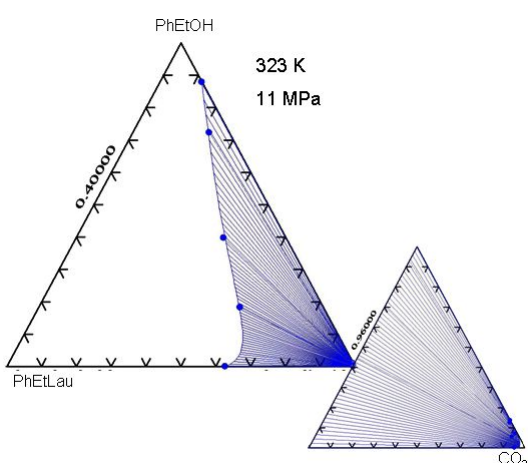


Figure 4 - Separation factor between (*R,S*)-1-phenylethanol (PE) and (*R,S*)-1-phenyl-ethyl laurate (PEL) against the liquid solubility in CO₂ as a function of temperature at 13 MPa with a mass feed (*R,S*)-1-phenylethanol composition (solvent free basis) of 0.5

The $pTxy$ experimental phase equilibrium data was correlated with the program package PE2000 [4] using the Peng-Robinson equation of state (PR-EOS) [5] with the Mathias-Klotz-Prausnitz mixing rule (MKP-MR) [6].

In Figure 5 is presented a comparison between the EOS predictions for the liquid and gas phases for the ternary system (*R,S*)-1-phenyl-ethyl laurate / (*R,S*)-1-Phenylethanol / CO₂. The optimum set of values obtained for the ternary system (*R,S*)-1-phenyl-ethyl laurate / (*R,S*)-1-Phenylethanol / CO₂ at 323K and the absolute average deviation (AAD) between the experimental and the correlated data are also presented.

As it can be seen the method was able to give very good predictions for the liquid phase but some small deviations from the experimental data are observed in the gas phase.



| | 1-2 | 1-3 | 2-3 |
|----------------|---------|---------|---------|
| k_{ij} | -0.1591 | 0.1348 | -0.3483 |
| λ_{ij} | -0.0440 | 0.0033 | -0.1765 |
| l_{ij} | -0.0020 | -0.1445 | 0.6518 |
| AAD < 2% | | | |

Figure 5 - Comparison between the correlation of the $pTxy$ experimental data with the Peng-Robinson EOS and Mathias-Klotz-Prausnitz mixing rule using the program package PE at 323K for the liquid and gas phases. Points represent experimental data.

The complete continuous process for the separation of (*R,S*)-1-phenylethanol enantiomers was carried out via an enzymatic transesterification reaction in scCO₂ media followed by the products separation and purification.

The reaction conditions were maintained constant at 16 MPa and 318 K.

The separators were operated at pressures between 10 - 13 MPa and temperatures in the range of 313 – 333 K.

The best results were obtained for the conditions presented in Table 1.

| | Reaction | Separator 1 | Separator 2 | Separator 3 |
|-----------------|----------|-------------|-------------|-------------|
| Temperature (K) | 318.15 | 325.65 | 325.65 | 325.65 |
| Pressure (MPa) | 16.0 | 13.3 | 11.0 | 10.1 |

The compositions at the outlet of each separator for the first experiment are presented in Figure 6.

At the end on the three separations steps it can be observed that practically all (*R*)-1-phenyl-ethyl laurate has been removed from the mixture and the (*S*)-1-phenylethanol can be recovered with a purity of 86.3% (mol/mol). Because 10% (mol/mol) of the liquid mixture is still composed by vinyl laurate this purity can still be improved. A further analysis of this value assuming a total consumption of the acylating agent gives a theoretical final purity of 96.5% (mol/mol) of (*S*)-1-phenylethanol.

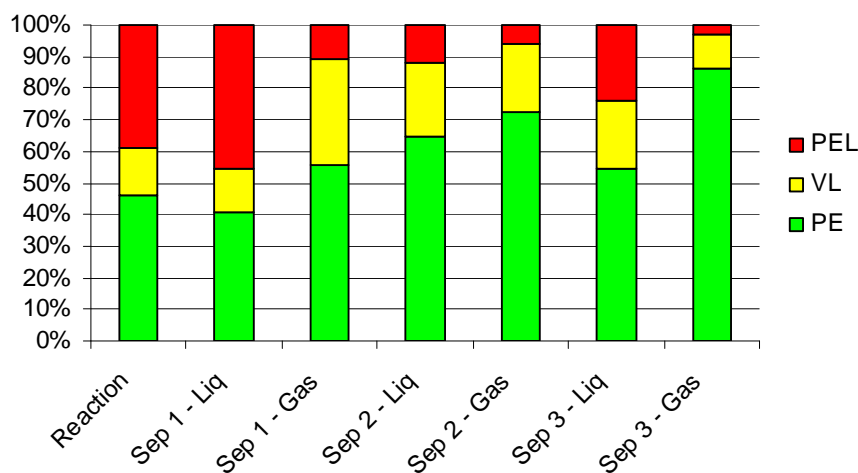


Figure 6 - Molar compositions on each of the process outlet streams for the conditions of Table 1. PEL, (*R*)-1-phenyl-ethyl laurate; VL, vinyl laurate; PE, (*S*)-1-phenylethanol

At the first separator it was possible to remove 71% (mol/mol) of (*R*)-1-phenyl-ethyl laurate from the liquid mixture. As it was expected the separation becomes more difficult as the mixture enriches in (*S*)-1-phenylethanol and in the second separator it was only possible to remove 47% (mol/mol) from the gas stream coming from the previous separator.

At the end of the process it is possible to recover about 1% (mol/mol) of the total feed, which means that if the reaction is complete and no vinyl laurate is present at the end of the reaction an effective recovery of about 2% of the racemic mixture can be recovered as a pure enantiomer with a purity of over 95%.

CONCLUSION

A complete process for the separation of (*R,S*)-1-phenylethanol was proposed by means of an enzymatic reaction in scCO₂ followed by the products separation with the scCO₂ as a separation agent.

Reaction experiments were carried out to determine the best acylating agent in this transesterification.

Between vinyl esters and methyl esters, it was concluded that the best acylating agent was vinyl laurate.

After analyzing the separation factor between (*R,S*)-1-phenylethanol and (*R,S*)-1-phenyl-ethyl laurate it was concluded that CO₂ was likely to be able to separate them with separation factor values reaching 8 at 10 MPa and 323 K.

The experimental data was accurately correlated with the PR-MKP with an absolute average deviation between the experimental data and the calculated one of less than 2% at 323K and a pressure range of 10 – 14 MPa.

The complete process was carried out in a newly build high pressure apparatus constituted by a continuous reaction section and a separation section. For the separation section three separators operated at different conditions were used to ensure an effective separation.

We were able to collect an 86.3% pure (*S*)-1-phenylethanol at the end of the process at a rate of 1% of pure product per amount of loaded racemic mixture.

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