

CHIRAL RESOLUTION IN SUPERCRITICAL CARBON-DIOXIDE: A BACKGROUND STUDY ON TWO CARBOXYLIC ACIDS

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B. Simándi, E. Fogassy and their coworkers recognized that the selectivity of a resolution using half molar equivalent of the resolving agent to the racemic compound can be highly improved by using supercritical carbon dioxide extraction to remove the unreacted amount of the racemic compound. [1-2] Our research work focused on two resolution-systems: the (\pm)- α -methoxyphenylacetic acid – (R)-(-)-1-cyclohexylethylamine (MPAA–CEA) system and the cis-chrysanthemic acid – (S)-(+)-2-benzylamino-butanol (CCA–BAB) system.

When using the *in situ* technique, both the racemic acid and the resolving agent (in half molar quantity) are measured into an autoclave without the use of any organic solvent. The autoclave is then pressurized with carbon dioxide, which acts as a solvent for the heterogeneous-phase chemical reaction. Both CCA and MPAA could be resolved using this technique. While the reaction was fast in the case of CCA (completed within an hour) MPAA–CEA system required nearly a week to approach the equilibrium separation. The course of these chemical reactions could also be followed by taking samples from the reaction mixture.

Using antisolvent precipitation, an enantiomeric excess of 45% could be reached in the case of MPAA using a 1:1 mixture of toluene and acetonitrile as an organic solvent. The raffinate yield was slightly under 90% and the extract yield was above 90% relative to their theoretical values. In the case of CCA the diastereomeric salt could not be precipitated.

To understand the driving forces of the above separations, we developed a new measurement method using a high pressure view cell to determine the solubilities of the diastereomeric salts. We found that the dissolution of the diastereomeric salts in supercritical carbon dioxide can be described with the solubility product, similar to that of inorganic salts in water. In an *in situ* system of the CCA and BAB compounds, a great difference between the solubilities of the two pure diastereomeric salts was found: $1,77 \cdot 10^{-6}$ and $2,85 \cdot 10^{-5} \left(\frac{\text{mmol}}{\text{ml}}\right)^2$ for the stable and the unstable diastereomer, respectively. It can be assumed that the thermodynamic control of the heterogeneous-phase reaction is favourable to achieve high enantioselectivity. In the MPAA–CEA system, in the case of gas antisolvent technique, the obtained values of the two diastereomers were very similar $\left(7 \cdot 10^{-9} - 3 \cdot 10^{-8} \left(\frac{\text{mmol}}{\text{ml}}\right)^2\right)$. Thus, we assumed that the chiral separation is determined by the kinetics of either the nucleus formation or the crystal growth under CO₂ pressure.

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