

Thesis Summary

Name of Student: Mr. Amit Zodge

Name of Supervisor: Dr. Edit Szekely

Thesis Title: Enantioselective diastereomeric salt crystallisation based optical resolution of selected mandelic acid derivatives using supercritical carbon dioxide.

Today, the increasing demands for product purity, environmental regulations and guidelines will pose serious problems for industry professionals, thus continuous upgrade is needed for an industrial ecosystem. With this objective, this research work used the environmentally friendly supercritical carbon dioxide for the diastereomeric salt precipitation and purification of the racemic salts into enantiopure salt.

The focus of this thesis is the improvements of resolutions of racemates by Gas Anti-solvent (GAS) system; using supercritical carbon dioxide with this objective, the resolution of two racemic compounds were done using two different resolving agents. The following mention scientific contributions is achieved.

Resolution of α -methoxyphenylacetic acid with (*R*)-cyclohexylethyl amine is possible using gas antisolvent precipitation with carbon dioxide. Half-equivalent amount of resolving agent is optimal for maximizing selectivity while keeping the amount of resolving agent as low as possible. Both the temperature and pressure influence the resolution significantly, and the optimal setting was found to be 40°C and 12 MPa. The results obtained by this method show a good perspective for development of a semicontinuous process. Successfully grown the two single crystals in the laboratory, (*S*)- α -Methoxy phenyl acetic acid and (*S*)-Cyclohexylethylamine - (*S*)- α -Methoxy phenyl acetic acid salt. Single crystal X-ray structure of two compounds of this system has been determined and reported.

Detailed analytical features using X-ray powder diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), and Differential scanning calorimetry (DSC) of all pure substances are compared. Structural implications are drawn for salts without known structures based on analytical features. Binary and ternary eutectic phase diagrams in the resolution system are constructed for pure, racemic and salt form of 2-Methoxy phenyl acetic acid, Cyclohexylethylamine.

Gas antisolvent precipitation was presented as the separation method in the chiral resolution of racemic 4-chloromandelic acid using the half-molar equivalent of (*R*)-1-phenylethylamine as the resolving agent. Detailed investigations on the effect of pressure, temperature and solvent ratio (the mass ratio of the organic solvent and carbon dioxide) were conducted in the ranges of 12-20 MPa, 35-45 °C and carbon dioxide to methanol mass ratio of 7.5-25 respectively. Although the solvent mass ratio had an effect on yield an enantiomeric excess, selectivity remained unaffected by this parameter as well. The 72% enantiomeric excess (ee) was achieved in the raffinate at 16 MPa, 40 °C and 7.5 solvent ratio, while a 65% ee acid was purified to over 90% by another resolution step with half molar equivalent of the amine. The repetition of resolution (dissolution of salty samples with a fresh amount of resolving agent base and re-precipitation) resulted in a substantial increase in diastereomeric excess.