

Gas Antisolvent Approach for the Precipitation of α -Methoxyphenylacetic Acid – (*R*)-1-Cyclohexylethylamine Diastereomeric Salt



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One of the major drawbacks of diastereomeric salt precipitation based enantioseparation is the time and solvent requirement of crystallization. In the gas antisolvent (GAS) approach, supercritical carbon dioxide is applied as an antisolvent, and the precipitation takes place in a couple of minutes. By setting the process parameters diastereomeric excess, yields, and selectivity can be controlled. Applicability of the process is demonstrated on the resolution of racemic 2-methoxyphenylacetic acid with enantiopure (*R*)-(-)-1-cyclohexylethylamine. Diastereomeric excess values over 55 % along with 80 % yields were achieved at optimal conditions in a single step.

Key words:

supercritical CO₂, optical resolution, α -methoxyphenylacetic acid, capillary electrophoresis

Introduction

The chemical industry market for enantiopure chemicals exhibits a great demand and it is increasing day by day. The preparation technique plays a key role in its economics. While several chiral catalytic processes are already industrialized, the conventional manufacturing technique mainly includes diastereomeric salt formation followed by fractionated crystallization.^{1–4} These techniques highly depend on reaction conditions such as slight changes in temperature, pressure, etc. Hence, each reaction parameter needs careful optimisation.

Supercritical carbon dioxide (scCO₂) might be used as a solvent in chiral resolutions^{5,6} as well as an antisolvent in precipitation processes.⁷ Gas antisolvent (GAS) precipitation is fast and less solvent-intensive than traditional crystallizations. Using carbon dioxide as a solvent or antisolvent has some benefits, especially due to its non-flammable, non-explosive nature while being readily available and non-toxic in trace amounts. Supercritical fluid extraction (SFE) with carbon dioxide (CO₂) has

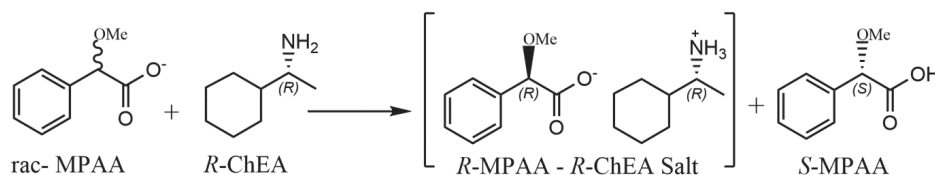
been successfully used in resolutions of various compounds.^{8–11} In some cases, diastereomeric salt formation using a modified version of the Pope-Peachy method showed high dependence on changes in pressure and temperature, thus affecting the enantiomeric excess (*ee*) of the products.^{12–14}

α -Methoxyphenylacetic acid (MPAA) is widely used as a resolving agent and building block in various organic syntheses.¹⁵ Phenylacetic acids and their derivatives are very versatile platform molecules. Several derivatives show a broad range of biological activity, i.e. antibacterial, herbicide, plant growth regulator, etc. The syntheses of MPAA and its derivatives were briefly summarized by Edward *et al.*¹⁶

Diastereomeric salt formation of racemic α -methoxyphenylacetic acid (MPAA) using (*R*)-(-)-1-cyclohexylethylamine (CHEA) as an enantiopure resolving agent is presented (Scheme 1) via GAS method for the first time in this study.

Resolution of racemic α -methoxyphenylacetic acid (MPAA) with (*R*)-(-)-1-cyclohexylethylamine (CHEA) was carried out using a 2:1 molar ratio, at 40 °C, being stirred for 1 h under 12 MPa CO₂ pressure.

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Scheme 1 – Scheme of resolution

Materials and methods

Materials

Racemic α -methoxyphenylacetic acid (purity >98 %, HPLC) was purchased from TCI Ltd., Belgium. Enantiopure (*R*)- α -methoxyphenylacetic acid (purity \geq 99 %, HPLC) and both enantiopure forms of 1-cyclohexylethylamine ((*R*)-CHEA, purity >98 %, GC-MS and (*S*)-CHEA, purity >98 %) were purchased from Sigma–Aldrich Hungary Ltd., (Budapest, Hungary). CO₂ (99.5 %) was purchased from Linde Gas Hungary Co. (Budapest, Hungary). Methanol, acetonitrile, toluene, 2-propanol and ethanol (>99 %, GC) were purchased from Merck Ltd., (Darmstadt, Germany).

Experimental methods

View cell experiments

The variable-volume view cell (New Ways of Analytics, Germany) used in this study is schematically depicted in Figure 1. It is equipped with a transparent zirconium oxide window and a stainless steel piston. The maximum volume of the cell is 70 mL.

Limits for pressure and temperature are 75 MPa and 150 °C, respectively. A known amount of solid sample was placed in the view cell, and in case of using a cosolvent, a known amount of cosolvent was also injected. Then the cell was sealed and pressurized with CO₂ by an ISCO 260D syringe pump (1). The injected mass of CO₂ was calculated from the volume change in the pump and with the CO₂ density obtained from NIST Chemistry Webbook¹⁷ calculated with measured pressure and temperature conditions at (1). Pressure was increased by decreasing the cell volume at constant temperature until a homogeneous solution was observed. After minimum 20 minutes of equilibration, the pressure was slowly decreased by increasing the volume of the cell at constant temperature and molar composition. Cloud points were observed visually.

Gas antisolvent experiments

GAS precipitation experiments were carried out in a high-pressure autoclave shown in Figure 2.

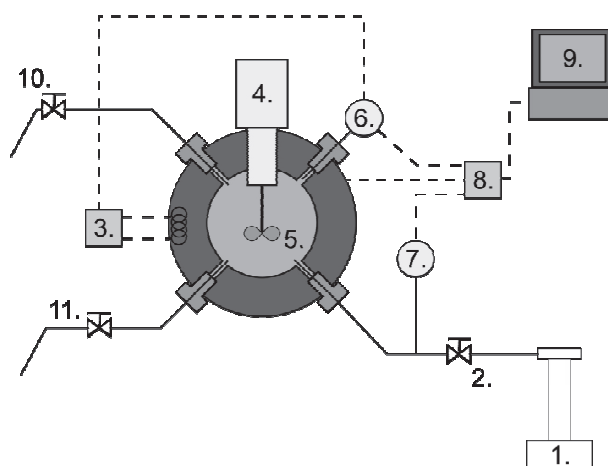


Fig. 1 – Variable volume high pressure view cell: 1. ISCO 260D syringe pump; 2. regulating valve; 3. temperature regulator and heating rods; 4. magnetically coupled stirrer; 5. piston; 6. thermocouple and temperature transducer; 7. pressure transducer; 8. analog-digital converter; 9. data logger PC; 10. connection and depressurizing valve for sampling the upper phase; 11. lower phase sampling port and depressurizing valve

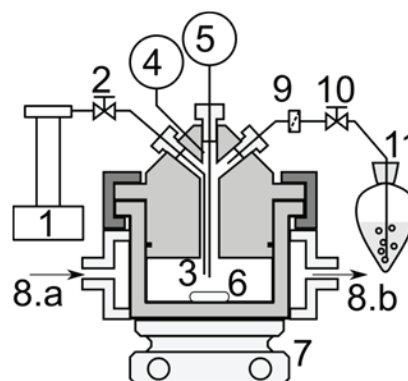


Fig. 2 – Schematic representation of the high pressure autoclave (not proportional): 1. ISCO 260D syringe pump; 2. inlet valve; 3. CO₂ inlet pipe; 4. pressure transducer; 5. thermocouple; 6. stir bar; 7. magnetic stirrer; 8.a and b. tempered water; 9. 0.5 μ m filter; 10. outlet valve; 11. liquid trap

The reactants (100 ± 0.5 mg (0.60 ± 0.003 mmol) of racemic MPAA and a calculated amount of (*R*)-CHEA (typically 38 ± 0.5 mg equivalent to 0.30 ± 0.03 mmol) were dissolved separately in 1.5 ± 0.006 mL of solvent. After complete dissolution, the solutions were charged into the tempered autoclave. The autoclave was sealed and filled with CO₂ to the

desired pressure followed by stirring for 1 hour for complete precipitation. Before depressurization, the reactor was washed with three-fold volume (90 mL) of scCO_2 at the pressure and temperature of the reactor in order to extract the CO_2 -soluble components. This extract was trapped in methanol. The solid, crystalline sample recovered from the reactor after depressurization is referred to as the raffinate. The main component of the extract was unreacted MPAA whereas raffinate consists of diastereomeric salts.

Atmospheric reference experiments

The starting reactants were dissolved separately in a minimal amount of solvent. After complete dissolution at 40 °C, both stocks were mixed with excess solvent and kept under magnetic stirring for 1 hour at 50 °C in water bath followed by 1 hour of natural cooling. The solid crystals were filtered using a G-4 Glass filter and air-dried.

Analytical methods

Capillary electrophoresis (CE)

The enantiomeric excess of the sample was determined on a Hewlett Packard $^{3\text{D}}$ CE system (Hewlett Packard, Waldbronn, Germany) equipped with a diode array UV detector. Uncoated fused-silica capillaries of 58.5 cm effective and 50.0 cm total length (FSOT, Composite Metal Services Ltd., Worcestershire, UK) were applied throughout the study. Samples and capillaries were tempered at 25 °C; the analytes were detected at 200 nm. The capillary was flushed with 0.1 M NaOH, and purified water for 30 seconds each subsequently, and finally with the running buffer for 60 seconds before every analysis. Samples were injected using 50 mbar pressure for 5 seconds, the applied voltage was +20 kV. Peaks were evaluated using Chemstation (Hewlett Packard) software.

Britton-Robinson buffer (BRB, containing 50 mM boric, acetic and phosphoric acid) was used as a background electrolyte. The desired pH was set to 9.0 by adjusting with 0.2 M NaOH. The final running buffers were filtered through a 0.22 mm Millex-GV syringe filters (Millipore, Bedford, USA). Diastereomeric salt mixture samples were dissolved in methanol to obtain 1 mg mL^{-1} stock solutions (related to dry material) and diluted further with ethanol:water 50 % v/v 100-fold to achieve optimal peak areas. As a chiral selector, 10 mM of 6-monodeoxy-6-amino- β -cyclodextrin was applied in all experiments.

Powder X-ray diffraction (XRD)

XRD measurements were done on a PANalytical X'Pert Pro MPD diffractometer (PANalytical,

Almelo, The Netherlands), equipped with an X'celerator detector in θ - θ arrangement to the beam source, at the Cu $K\alpha$ wavelength (1.5408 Å) applying 40 kV tension and 30 mA current. Diffractograms were recorded in the 1°–42° range.

Scanning electron microscopy (SEM)

SEM images were recorded by a JEOL JSM 5500-LV scanning electron microscope using 20 kV voltage and a secondary electron detector. For SEM studies, samples were covered with a 5–10 nm Au layer to make them conductive.

Calculation methods

The appropriate molar ratio (mr) plays a key role in any resolution system. Molar ratio was calculated as $mr = n_{res}/n_{rac}$, where n denotes the molar quantity and the indices *res* and *rac* refer to the resolving agent and racemic compound, respectively. Enantiomeric excess values (Equation 1) were calculated from the peak areas obtained by capillary electrophoresis.

$$ee = \left| \frac{A_R - A_S}{A_R + A_S} \right| \quad (1)$$

In the above equation, A_R and A_S refer to the areas of respective MPAA enantiomers of capillary electropherograms.

Yields for extracts and raffinates are the ratio of the recovered mass and theoretical mass of the certain fraction estimating full conversion and complete separation. The selectivity (S) of a given fraction was calculated by multiplying the enantiomeric excess and the yield. Indices *extr* and *raff* denote extract and raffinate, respectively.

$$S_{extr} = Y_{extr} \cdot ee_{extr} \text{ and } S_{raff} = Y_{raff} \cdot ee_{raff}$$

Results and discussion

Determination of solubility

For the development of a novel antisolvent based resolution, it is necessary to have preliminary information on the solubility of the components involved. Since there is no literature data available on the solubilities of MPAA, CHEA, or their diastereomeric salts in high pressure CO_2 , the necessary data was measured by cloud point determination.

The solubility of *rac*-MPAA in CO_2 increases with increasing pressure at a given temperature, e.g. at 37 °C and 8.7 MPa the solubility is 6.3 mg g^{-1} (mass fraction), while at 11.2 MPa 10 mg g^{-1} can be dissolved. The cloud point pressure of the same solution increases with temperature, e.g. the 6.3 mg g^{-1}

mass fraction solution is homogeneous above 8.7, 11.2 and 12.7 MPa at 37.1, 44.8 and 51.0 °C, respectively.

While a fair solubility of the *rac*-MPAA in scCO₂ is required for an efficient extraction of the unreacted enantiomers, an organic solvent is also required to dissolve all components including the diastereomeric salts. Components *rac*-MPAA and (*R*)-CHEA are highly soluble in polar solvents and also show reasonable solubility in non-polar solvents (Table 1). The higher solubility in polar solvents is attributed to the presence of carboxylic and amine functional groups in their chemical structure. Those solvents were selected for the further experiments in which both MPAA and CHEA have high (>1 g mL⁻¹) solubility.

As (*R*)-CHEA is a primary amine, it readily reacts with carbon dioxide and forms a carbamate. Its carbamate is white, solid and crystalline. The carbamate formed by the carbon dioxide content of air and that formed in scCO₂ are similar.¹⁷ If stirring is not applied, the formed solid saves the remaining liquid (*R*)-CHEA from being consumed by CO₂. Neither (*R*)-CHEA nor its carbamate has any reasonable solubility in pure carbon dioxide.

Selection of solvents for GAS

The solvents, which have good dissolving power for all components involved (Table 1), were also tested for their applicability in gas antisolvent precipitation. These preliminary results are summarized in Table 2.

Although alcohols seemed to be promising in solvent screening (Table 1 and 2), at resolution experiments, ester by-product formation was observed. Experiments with a mixture of ether–acetonitrile (1:1) also showed good results but were excluded due to safety concerns. Mixture of equal amounts of toluene–acetonitrile showed the best results for solubility of *rac*-MPAA, (*R*)-CHEA and precipitation of its diastereomeric salt during screening, thus this solvent mixture was selected for optimisation of process conditions.

Characterisation of diastereomeric salts

Powder XRD

The resolving agent reacts with both enantiomers of MPAA and forms the corresponding (*R,R*)- and (*S,R*)- salts. Since (*S*)-MPAA is commercially available, while (*R*)-MPAA is not, (*S,S*)-diastereomeric salt patterns were used as references of the (*R,R*)-salt, while (*S,R*)-salt as the (*R,S*)-salt's reference, according to the Marckwald principle.¹⁸ The XRD patterns of the formed solid product was compared against the reference diastereomeric salts

Table 1 – Solubility of MPAA, CHEA in organic solvents at ambient temperatures and pressures (solvents are listed in decreasing polarity)

Solvent	Solubility of <i>rac</i> -MPAA (g mL ⁻¹) at 26 °C	Solubility of CHEA (g mL ⁻¹) at 26 °C
Acetonitrile	2.29	2.70
Methanol	2.97	3.86
Ethanol	2.94	3.95
2-Propanol	2.80	3.83
EtOH:2-PrOH (1:1)	2.85	3.83
Ethyl acetate	0.05	Insoluble
Ethanol:Ethyl acetate	1.30	0.70
Toluene	1.80	1.20
Toluene:Acetonitrile (1:1)	1.30	1.87
Methyl isobutyl ketone	0.80	Insoluble
Ether	2.10	0.35
Ether: Acetonitrile (1:1)	2.50	1.35
Hexane	0.20	Insoluble

Table 2 – Effect of solvent on salt formation at 12 MPa, 40 °C, 8.8 g CO₂/g solvent and 0.026 g mL⁻¹ MPAA and 0.013 g mL⁻¹ CHEA in the reactor and at atmospheric conditions

Solvent	Atmospheric reference, observation, results	GAS precipitation		
		Precipitation observed	<i>ee_R</i> (%)	<i>Y_R</i> (%)
Methanol	No	Yes	56	23
Ethanol	No	Yes	70	21
Toluene	No	Yes	50	52
Acetonitrile	No	Yes	34	60
Toluene:Acetonitrile (1:1)	Yes, <i>ee</i> = 42 %, <i>Y</i> = 78 %	Yes	55	80
Ethanol:2-Propanol (1:1)	No	Yes	56	71

(Figure 3). XRD patterns of the (*S,S*)-salt and (*S,R*)-salt are different which proves that the two salts are crystallized in different crystalline structures. Comparing the XRD patterns of the same salts prepared with GAS or atmospheric crystallization methods, one may conclude that the peak positions and ratios are the same, suggesting similar crystal structures, but the GAS method results in an increased crystallinity.

Scanning Electron Microscopy (SEM) confirmed the formation of fibrous, elongated needle-like crystals under GAS conditions. Higher crystallinity was observed under scCO₂ conditions

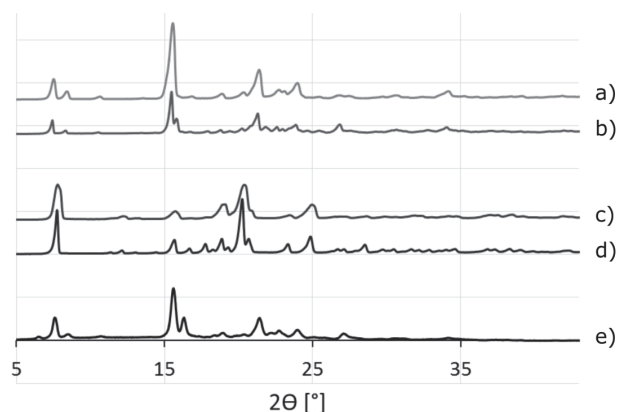


Fig. 3 – XRD patterns of diastereomeric salts a) (S,R) salt, atmospheric, b) (S,R)-salt GAS, c) (S,S)-salt, atmospheric, d) (S,R)-salt, GAS, e) rac-MPAA- (R)-CHEA salt (0.5 molar ratio)

than under atmospheric conditions via 4–6 hours crystallization time. Crystallization at atmospheric conditions using Tol-AcN mixed solvent shows different crystal habits (Figure 4); however, the crystal structures were similar for salts prepared with atmospheric and gas antisolvent technique.

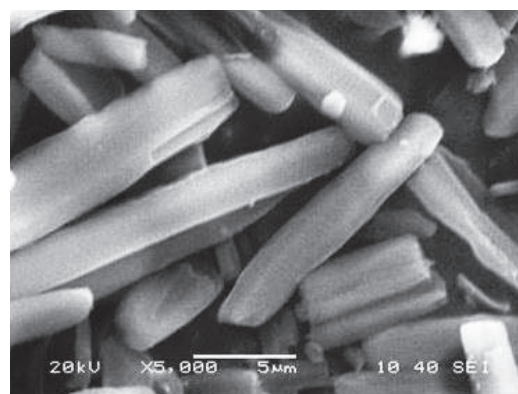
Optimization of the gas antisolvent precipitation

After successful screening experiments, detailed optimization of the process was performed regarding the molar ratio of the resolving agent to the racemic acid, pressure and temperature of GAS precipitation.

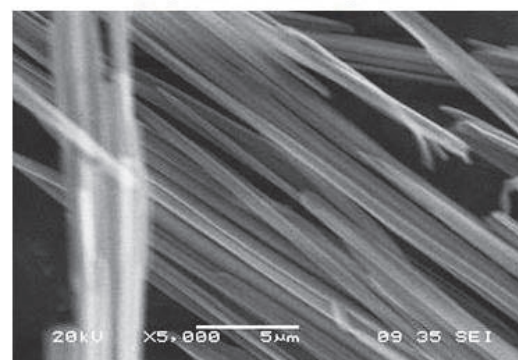
Regarding the molar ratio of reactants, the best selectivity was achieved using a 0.5 ratio of racemate: resolving agent (Table 3). The half equivalent method or commonly known as the modified Pope-Peachy method is the best suitable for the resolution, as typical in the supercritical resolution techniques.¹⁹ The equivalent method, i.e. Pasteur's method, gives a diastereomeric salt with worse optical purity and selectivity. However, it is worthwhile mentioning that the resolution produces solid, crystalline diastereomeric salt with 1:1 molar ratio (*mr*) as well. Furthermore, since the yield is the mass of recovered crystalline salt versus the theoretical mass of the salt, from the same amount of

Table 3 – Effect of molar ratio on diastereomeric salt formation. Reaction condition: 40 °C at 12 MPa pressure, 21 g CO₂/g solvent, 1 h.

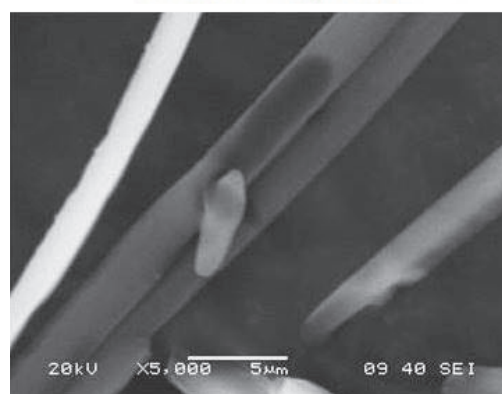
Molar ratio rac-MPAA: R-CHEA	<i>ee_R</i> (%)	<i>Y_R</i> (%)	<i>S_R</i> (%)
1	28	77	0.22
0.5	55	80	0.44
0.25	47	65	0.31



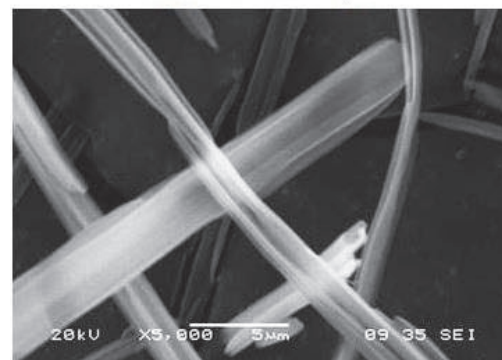
(1) S-S atmospheric



(2) S-R atmospheric



(3) S-S GAS



(4) S-R GAS

Fig. 4 – SEM pattern: (1 and 2) (S,S)- and (S,R)-salt, atmospheric condition (40 °C, 1 h, without CO₂ pressure, (3 and 4) (S,S)- and (S,R)-salt, GAS condition (40 °C, 1 h at 12 MPa CO₂ pressure, 8.8 g CO₂/g solvent)

racemic acid, approx. two times as much salt was prepared at $mr = 1$ than at $mr = 0.5$. Total recoveries of material at each molar ratio were above 80 %.

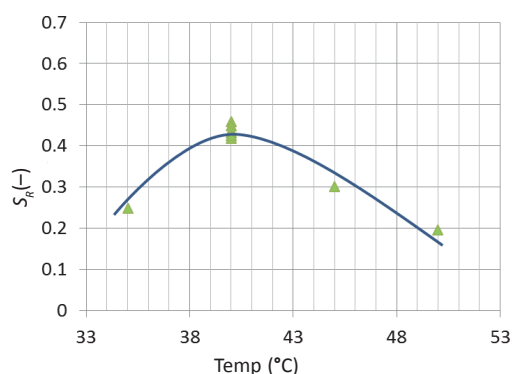


Fig. 5 – Effect of temperature on diastereomeric salt formation. Reaction conditions: 0.5 molar ratio at 12 MPa for 1 h.

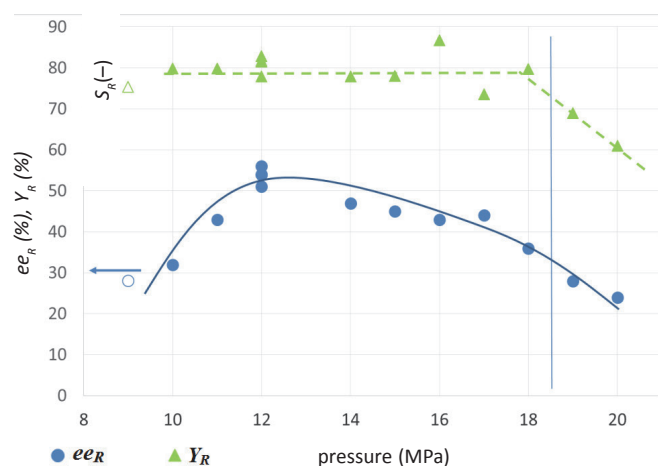


Fig. 6 – Effect of pressure on diastereomeric salt formation. Reaction conditions: 0.5 molar ratio at 40 °C for 1 h. Empty symbols indicate wet raffinates. The lines are to guide the eye.

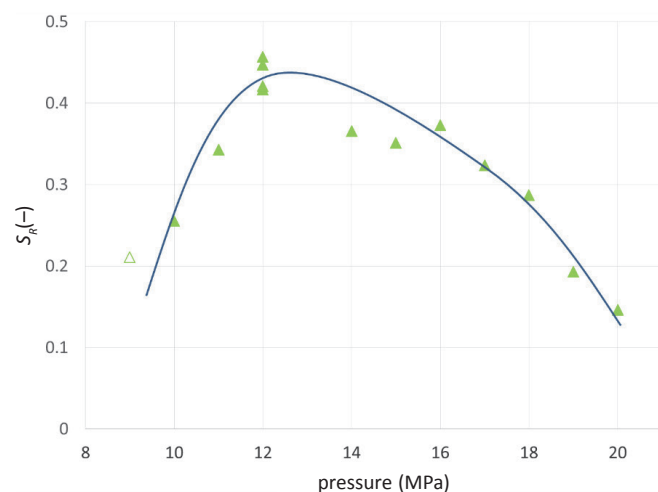


Fig. 7 – Effect of pressure on selectivity of diastereomeric salt formation. Reaction conditions: 0.5 molar ratio at 40 °C for 1 h. Empty symbols indicate wet raffinates. The line is to guide the eye.

Temperature effects at 12 MPa and 0.5 molar ratio are shown in Figure 5. There is a clear optimum of the selectivity at approx. 40 °C, which is mainly due to the variation of the ee values.

The effect of pressure on the resolution system was studied at 40 °C, CO_2 pressure ranged between 9 and 21 MPa (Figure 6 and 7). Below 10 MPa pressure, a wet raffinate was recovered with poor enantiomeric excess and slightly lower yield. The raffinates with the highest ee -s (50–55 %) were prepared at 12 MPa. Above 16 MPa, further increase in pressure causes significant decrease in the yield. The dependence of selectivity on pressure is plotted in Figure 7. The increase in CO_2 pressure increases the density of CO_2 . However, as the concentration of the organic solvent was kept constant, the increase in pressure also means an increase in the CO_2 :organic solvent ratio, as at constant temperature by increasing pressure the density of CO_2 increases. Solubilities of the compounds involved increase by increasing pressure but decrease with increasing CO_2 :solvent ratio. The observation that there is an optimum density (dissolving power) is in accordance with our previous results. Please note that in the referred previous work the diastereomeric salts of *cis*-permetric acid and phenylethyl amine were crystallized from CO_2 only, using carbon dioxide as the reaction medium.²⁰

Conclusions

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 obtained diastereomeric salts show similar diastereomeric excess values as optimized atmospheric resolutions, but show higher crystallinity and yields while requiring significantly lower processing time. The results obtained by GAS antisolvent method show a good perspective for development of a semi-continuous process.

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Nomenclature

Symbols

- A* – area, –
ee – enantiomeric excess, –
mr – molar ratio, –
n – molar quantity, mol
S – selectivity, –
Y – yield, –

Subscripts

- rac – racemic material
 res – resolving agent
 ext – extract
 raff – raffinate

Abbreviations

- scCO₂ – supercritical carbon dioxide
 GAS – gas antisolvent
 SEM – scanning electron microscopy
 XRD – X-ray powder diffraction
 CE – capillary electrophoresis

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