Chiral resolution at the solid state

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Introduction

Definition of chirality

The two objects are symmetrical about a mirror plane

The two objects form a pair of enantiomers
Cases of API with one chiral center

Example of Modafinil:

- Modafinil: psychostimulant used in the treatment of narcolepsy
- Enhancement of vigilance cognitive performance
- In 2003 at athletics world championship in France: Kelli White tested positive for Modafinil
- Developed by Cephalon, Inc.: Provigil® (racemate) Nuvegil® (enantiopure)
Synthesis at the industrial scale:

The patented synthesis leads to a racemate containing 50% of each enantiomer.

French Patent 2385693 (1978)

Objective:
To obtain Modafinil as a single enantiomer by crystallization.
Chirality in the case of sulfoxides

S enantiomer

R enantiomer

Mirror plan

Sulphur atom is the stereogenic center

Strategies for chiral resolution

Modafinil is a very weak acid

1. Partial discrimination of S and R enantiomers at the solid state: 
   - **Solid solution**
   - **Mixed crystals**

   For racemic compounds crystal structure only non-centrosymmetric space groups should be allowed.

2. Complete discrimination of S and R enantiomers at the solid state:
   - **Racemic conglomerate**

   For racemic conglomerate crystal structure only non-centrosymmetric space groups should be allowed (chiral crystal structure)

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**Flack, Helvetica Chemica Acta, 86 (2003) 905-921**
Racemic conglomerate

Polymorphism is known for this compound

*Calculated pKa 2.8*

Can be separated by preferential crystallisation (kinetic). The formation of salt with non-chiral base was made to enhance the process efficiency

Strategies for chiral resolution

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reference</th>
</tr>
</thead>
</table>

Calculated pKa 2.8

Can be separated formation of diastereomers (thermodynamic) with α-MBA

*Solid solution*  
*Mixed crystals*

This case is fully described in this talk

Racemic conglomerate

Chiral resolution possible out of equilibrium by seeding.

Solvate formation or cocrystal formation can also be advantageous

Crystal Growth & Design, 7(9) (2007) 1599


*CrystEngComm*, 10, 724 - 733 (2008)

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Characterisation of a partial solid solution

XRPD:

R(-)DMSAM

(±)DMSAM
Single crystal X-ray diffraction

Confirmation of the molecular structure

R(-)DMSAM

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<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Formula</strong></td>
<td>( \text{C}<em>{16}\text{H}</em>{16}\text{SO}_{3} )</td>
</tr>
<tr>
<td><strong>Space group</strong></td>
<td>( \text{P2}_1\text{2}_1\text{2}_1 )</td>
</tr>
<tr>
<td><strong>a / Å</strong></td>
<td>5.693(1)</td>
</tr>
<tr>
<td><strong>b / Å</strong></td>
<td>16.139(2)</td>
</tr>
<tr>
<td><strong>c / Å</strong></td>
<td>16.131(2)</td>
</tr>
<tr>
<td>( \alpha = \beta = \gamma \ / ^\circ )</td>
<td>90.00</td>
</tr>
<tr>
<td><strong>V / Å^3</strong></td>
<td>1482(1)</td>
</tr>
<tr>
<td><strong>Flack parameter</strong></td>
<td>-0.02(6)</td>
</tr>
</tbody>
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Confirmation of the chirality of the molecule
Single crystal X-ray diffraction

Obtained by evaporation of an ethanolic solution of (±)DMSAM

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<td>Space Group</td>
<td>P2_{1}2_{1}2_{1} (P2_{1}2_{1}2_{1})</td>
</tr>
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<td>a / Å</td>
<td>5.711(1) (5.693(1))</td>
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<tr>
<td>α = β = γ /°</td>
<td>90.00 (90.00)</td>
</tr>
<tr>
<td>V / Å³</td>
<td>1470(1) (1482(1))</td>
</tr>
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Flack parameter 0.10(10)

Volume of the unit cell decreases

Presence of R and S enantiomers in the structure
**Characterisation of a partial solid solution**

<table>
<thead>
<tr>
<th>Composition of solutions</th>
<th>ee = 0% (±)DMSAM</th>
<th>ee = 100% R(-)DMSAM</th>
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</tr>
<tr>
<td>Composition of single crystals using structure refinement</td>
<td>ee = 50(±1)%</td>
<td>ee = 100%</td>
</tr>
<tr>
<td>Composition of single crystals using HPLC</td>
<td>ee = 52(±1)%</td>
<td>ee = 98(±1)%</td>
</tr>
</tbody>
</table>

Enantiomeric excess: \( e.e. = \frac{\%R - \%S}{\%R + \%S} \)

(±)DMSAM is made of single particle \%R/%S ≈ 75/25 and 25/75
Preferential crystallization

Application of AS3PC process

AS3PC (Auto Seeded Programmed Polythermic Preferential Crystallization)

Initial conditions

\[
\begin{align*}
(\pm)\text{DMSAM}: & \ 5.33 \ g \\
R(-)\text{DMSAM}: & \ 0.53 \ g \\
\text{Methanol}: & \ 16.08 \ g \\
\text{initial e.e.} & \ = \ 9\%
\end{align*}
\]

\[
\text{Thomo} = 26.5^\circ \text{C}, \text{ complete dissolution of the solute}
\]

\[
\text{TB} = (\text{Thomo} + \text{TL})/2 = 23.5^\circ \text{C}, \text{ starting temperature of the process}
\]

\[
\text{TL} = 20.5^\circ \text{C}, \text{ complete dissolution of } (\pm)\text{DMSAM in the same quantity of solvent}
\]

32 minutes

\[
\text{Tf} = 13^\circ \text{C}, \text{ temperature of filtration at the end of the crystallization}
\]

Crop: 1.198 g of crystals e.e. \(\approx 50\%\) (polarimetry)
Mother liquor weakly enriched in \(<(+)>\) e.e. \(\approx 2\%\) (polarimetry)

Poor efficiency of preferential crystallization

Explanation of the poor efficiency of preferential crystallization

Experimental ternary phase diagram at 20° C

System:
S(+)/R(-)DMSAM/MeOH

Domains of solid solution at 20° C ee [100%-52%]

Solid solution stable at the thermodynamic equilibrium

Study of the enantiomer distribution in mixed crystals

**RAMAN microscopy**

Analyses of single crystals of solid solution (ee 100-50%)

- Partial differentiation between single crystals of solid solution

From a thousand µm³ to 1 µm³ [5]

- At this scale ($2 \times 10^9$ molecules) R and S enantiomers are homogeneously distributed in the crystals
Study of the enantiomer distribution in mixed crystals

X-ray $h0l$ zone image

Plane $h0l$

single crystal ee50%

No segregation of R and S enantiomers has been detected in single crystal of solid solution
Partial and preferential dissolution of mixed crystals

- At 20°C, in a thermostated vial:

Single crystals of solid solution (ee 52%) were immersed in a large excess of saturated solution of R enantiomer in ethanol

After 1 hour, S rich single crystal completely dissolved

After 2 hours, R rich single crystal was partially dissolved

Quasi-ideal behavior which follows Meyerhoffer “double solubility rule” in EtOH
Conclusions

Chiral molecules at the solid state with one (or more) stereogenic centre can crystallise as:

- Racemic compounds (most common case), chiral resolution can not be made at the solid state at the thermodynamic equilibrium.
  - Polymorph/solvate screening, chiral and non-chiral salt screening needs to be performed depending on the pKa of the molecule
- Racemic conglomerates (less common). This case is the most suitable for chiral resolution via preferential crystallisation or salt formation.
- Solid solution (less common). This case may imply a poor efficiency of the chiral resolution. The non-desired enantiomer “pollutes” the crystal of the desired enantiomer even if the form is metastable.
  - A solid solution can be difficult to detect in the following cases:
    - metastable form
    - its stability domain is small
    - the counter-enantiomer does not affect the lattice parameter (no difference can be seen by XRPD)
Acknowledgements

• Cephalon Inc. (West Chester, PA, U.S.A & Mitry-Mory, France) for their collaboration
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