Self-Disproportion of Enantiomers (SDE)

Jesse Panger
Denmark Lab Group Meeting
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“...‘Application of routine achiral column chromatography for the work up and isolation of product sulfoxides can result in a flawed description of stereochemical outcome’...This warning was further conveyed by Kagan et al. in several subsequent publications but was generally neither heard nor acknowledged by the wider research community.”
What will not be discussed

• Kinetic Resolution (DKR)

\[
\text{Me} \xrightarrow{(S,S) \text{-cat} \text{TMSN}_3} \text{Me} \xrightarrow{1. \text{CSA, MeOH}} \text{TMSO} \xrightarrow{2. \text{Pd/C, H}_2, \text{MeOH}} \text{HO} \xrightarrow{} \text{N}_3
\]

• Formation of diastereomers* (indirect separation)

• Other exogenous chiral sources (i.e. chiral HPLC)

*by other exogenous chiral compounds

Nature of Racemates

1. Racemate consists of a 1:1 mechanical mixture or conglomerate of crystals of the two enantiomers (homochiral molecules).

2. Racemate consists of crystals in which the two enantiomers coexist in the same unit cell termed a racemic compound.

3. Racemate consists of solid solution of two enantiomers in an unordered crystal lattice termed a pseudoracematel.

4. Racemate of two distinct, isosteric compounds of opposite handedness in a crystalline phase is a quasiracematel.

Origins of the SDE Phenomenon

• 1895: samples of (+)-coniine and (-)-coniine heated upon mixing\(^1\)

\[ \text{coniine} \]

• 1969: NMR spectra of optically pure, racemic, and non-racemic samples of dihydroquinine had peak areas proportional to the relative amounts of enantiomers\(^2\)

\[ \text{dihydroquinine} \]

• 1969 – Horeau: observed that the energy differences between racemic mixtures and optically pure samples ‘are too small to be used to change the optical composition of a mixture upon distillation.’\(^3\)

• 1983: Racemic \(^{14}\)C-labelled nicotine co-injected with (-)-(S)-nicotine divided into 2 peaks on HPLC\(^4\)

Principle of Enantiomeric Separations

- Inseparable racemic mixture
  - Reaction 1: \(R \, S + S \, S\)
  - Reaction 2: \(R \, S + S \, S\)
  - Reaction 3: \(R \, R \, R \, R\) + \(S \, S \, S \, S\)

- Homochiral
  - Reaction 4: \(S \, S \, S \, S\)

- Separable non-racemic mixture
  - Reaction 5: \(R \, S + S \, S\)
  - Reaction 6: \(R \, R \, R \, R\) + \(S \, S\)

References:
SDE-Phoric Groups

1. \( \text{Chiral amides}^{1} \)
2. \( \alpha \) and \( \beta \)-amino acid esters\(^{2} \)
3. \(-\text{CF}_{3} \text{ adjacent to stereocenter}^{3} \)
4. \( \text{Sulfoxides}^{4} \)

# Terminologies

<table>
<thead>
<tr>
<th>Term</th>
<th>Basis</th>
<th>Ref.</th>
</tr>
</thead>
</table>
IR Studies of 2-butanol

a = (S) or (R)-2-butanol
b = Racemic 2-butanol

For all concentrations (CCl₄) of pure enantiomers, the spectra are identical. Racemic mixtures, however, have far less intense bands around the dimer and oligomer region.
NMR Studies

Portion of 100-MHz NMR spectrum of (-)-dihydroquinine in 0.36 M CDCl₃

Portion of 100-MHz NMR spectrum of racemic dihydroquinine in 0.35 M CDCl₃

“Concentration studies revealed that the NMR spectra of the pure enantiomers, the racemate, and various mixtures thereof on high dilution tend to become identical.”

Portion of 100-MHz NMR spectrum of artificial 1:1 mixture of racemic and natural (-)-dihydroquinine in 0.27 M CDCl₃

### NMR Studies Cont.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>δ</th>
<th>Relative content of L enantiomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>6.127</td>
<td>1.0</td>
</tr>
<tr>
<td>0</td>
<td>6.389</td>
<td>0.9</td>
</tr>
<tr>
<td>-20</td>
<td>6.729</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5</td>
</tr>
</tbody>
</table>

Self-induced chemical shift nonequivalence (Δδ) of the amide –NH proton in 0.1 M CCl₄

N-acetylvaline tert-butyl ester

Homochiral L-L dimer

NMR Studies Cont.

Relative content of L enantiomer

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>1.0</th>
<th>0.9</th>
<th>0.7</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>δ</td>
<td>Δδ_\text{L}</td>
<td>Δδ_\text{D}</td>
<td>ΔΔδ</td>
</tr>
<tr>
<td></td>
<td>δ</td>
<td>6.127</td>
<td>0.011</td>
<td>0.097</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>6.389</td>
<td>0.010</td>
<td>0.143</td>
</tr>
<tr>
<td></td>
<td>-20</td>
<td>6.729</td>
<td>0.004</td>
<td>0.163</td>
</tr>
</tbody>
</table>

Self-induced chemical shift nonequivalence (Δδ) of the amide –NH proton in 0.1 M CCl₄

N-acetylvaline tert-butyl ester

9:1 mixture of L and D (NH proton)

Homochiral L-L dimer

Intermolecular Interactions

- Electrostatic interactions
- H-bonding
- Dipole-dipole
- $\pi-\pi$ stacking
- van der Waals
Chromatography: Stereogenic Carbon

Naturally occurring as (S)-(−)-Nicotine

Racemic $^{14}\text{C}$-nicotine-(+)-bitartrate
+ unlabeled (−)-nicotine

OR

Racemic $^{14}\text{C}$-nicotine free base
+ unlabeled (−)-nicotine

Partisil PXS SCX
cation-exchange

2 peaks

Racemic $^{14}\text{C}$-nicotine-(+)-bitartrate

OR

Racemic $^{14}\text{C}$-nicotine free base

1 peak

* performed on two different HPLC systems

Chromatography: $^{14}\text{C}$-labeled Nicotine

Racemic $^{14}\text{C}$-nicotine-$(+)$-bitartrate

Racemic $^{14}\text{C}$-nicotine-$(+)$-bitartrate & $(+)$-nicotine

Racemic nicotine

Role of Tartrate?

Racemic $^{14}\text{C}$-nicotine-$(+)$-bitartrate & $(-)$-nicotine

Chromatography: Removing Variables

Rules out the tartrate counterion and the position of the radiolabel itself as potential contributors to the splitting of peaks

New Question: What about protonation on nitrogen?

With all diastereo- and enantiotopic factors considered, there must be some intrinsic property that gives rise to split peaks.\(^a\)

\(^a\)All measurements repeated on rPHPLC
“Self-Amplification of Optical Activity”

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Enantiomeric Depletion</th>
<th>Enantiomeric Enrichment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First fraction</td>
<td>74%</td>
<td>97%</td>
</tr>
<tr>
<td>Last fraction</td>
<td>74%</td>
<td>46%</td>
</tr>
</tbody>
</table>

Chromatography on kieselguhr deactivated with 6% water, 40 g/g sample

(S)-1 R^1 = i-Pr, R^2 = H, R^3 = Me; 70.7% ee
(S,S)-2 R^1 = c-Hex, R^2 = R^3 = i-Pr; 57% ee

5% EtOAc:Hex to 7.5%

(S)-1 90:10 Hex:EtOAc
(S,S)-2 95:5 Hex:EtOAc

Chromatography: Sulfoxides

Sulfoxides: Control Studies

1. Ruled out pollution by contaminants by mixing two enantiomerically pure sulfoxides (80% ee) and re-subjecting to flash chromatography

   → Similar distribution of ee’s

2. Ruled out racemization by performing chromatography on enantiopure sulfoxide

   → Obtained each fraction as >99.5% ee

3. Increased the silica loading by 3-fold

   → No improvement in efficiency

4. Decreased the silica loading by 2-fold

   → No improvement in efficiency

5. Switched to alumina as the stationary phase

   → Similar distribution of ee’s and less pronounced overall

Final curiosity: 65% ee of (R)-Fc-S(O)-Ph eluted 79% ee of (S) in the first fraction and 94% (R) in the final fraction

**Sulfoxides: Standard for Reporting Effect of SDE**

\[
\text{Me}^+\text{S}^+\text{O}^-\text{Cl}^- + (-)-menthol \xrightarrow{\text{pyridine, Et}_2\text{O}} \begin{array}{c}
\text{Me}^+\text{S}^+\text{O}^- \text{O}^- \text{O}^- \\
\text{(S) minor}
\end{array}
\]

\[
\begin{array}{c}
\text{Me}^+\text{S}^+\text{O}^- \text{O}^- \text{O}^- \\
\text{(R) major}
\end{array} \xrightarrow{n-C_6H_{11}\cdot \text{MgBr}, \text{benzene}} \begin{array}{c}
\text{Me}^+\text{S}^+\text{O}^- \\
\text{n-C}_6\text{H}_{11}
\end{array}
\]

34.6% ee

<table>
<thead>
<tr>
<th>Eluent (10mL per 3-6 min.)</th>
<th>Mass (mg)</th>
<th>Early (10 mL)</th>
<th>Middle (50 mL)</th>
<th>Final (250 mL)</th>
<th>Total</th>
<th>1st fraction %ee</th>
<th>Last fraction %ee</th>
<th>Δee</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM:EtOAc (5:1)</td>
<td>112</td>
<td>10</td>
<td>12</td>
<td>1</td>
<td>950</td>
<td>74.3</td>
<td>28.6</td>
<td>45.7</td>
</tr>
<tr>
<td>EtOAc</td>
<td>108</td>
<td>20</td>
<td>10</td>
<td>1</td>
<td>950</td>
<td>97.4</td>
<td>3.9</td>
<td>93.5</td>
</tr>
<tr>
<td>EtOAc:c-Hex (5:1)</td>
<td>109</td>
<td>20</td>
<td>10</td>
<td>1</td>
<td>950</td>
<td>&gt;99.9</td>
<td>13.0</td>
<td>87.0</td>
</tr>
<tr>
<td>EtOAc:c-Hex (1:1)^a</td>
<td>79</td>
<td>5</td>
<td>3</td>
<td>7 (10 mL)</td>
<td>270</td>
<td>34.2</td>
<td>41.8</td>
<td>-7.6</td>
</tr>
</tbody>
</table>

^a Neutral alumina and 35.2% ee of starting sulfoxide

Sulfoxides: Standard for Reporting Effect of SDE

\[
\begin{align*}
\text{MeSO}^+\text{Cl}^- + (-)-\text{menthol} & \xrightarrow{\text{pyridine} \ \text{Et}_2\text{O}} \text{MeSO}^+\text{Omenthyl}^- \quad \text{(S) minor} \\
\text{MeSO}^+\text{Omenthyl}^- & \xrightarrow{n-C_5\text{H}_{11}\text{MgBr} \ \text{benzene}} \text{MeSO}^+\left(\text{R},\text{C}_5\text{H}_{11}\right) \quad \text{(R) major} \\
\end{align*}
\]

34.6% ee

Chromatographic run of EtOAc:c-Hex (5:1)

## Prazoles

![Chemical structures of Prazoles](Prazoles.png)

Omeprazole  | Lansoprazole  | Pantoprazole  | Raberprazole

### 1 g Esomeprazol

<table>
<thead>
<tr>
<th>Eluent</th>
<th>Starting ee</th>
<th>First fraction % ee</th>
<th>Last fraction % ee</th>
<th>Δee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>76.2</td>
<td>83.4</td>
<td>69.8</td>
<td>13.6</td>
</tr>
<tr>
<td>DCM/MeOH (25:1)</td>
<td>76.2</td>
<td>77.2</td>
<td>75.2</td>
<td>2.0</td>
</tr>
<tr>
<td>EtOAc/PE (3:1)</td>
<td>76.2</td>
<td>96.6</td>
<td>74.0</td>
<td>22.6</td>
</tr>
<tr>
<td>EtOAc/DCM (2:1)</td>
<td>76.2</td>
<td>99.8</td>
<td>61.2</td>
<td>38.6</td>
</tr>
<tr>
<td>MTBE</td>
<td>88.2</td>
<td>&gt;99.9</td>
<td>80.0</td>
<td>20.0</td>
</tr>
<tr>
<td>MTBE</td>
<td>&gt;99.5</td>
<td>&gt;99.5</td>
<td>&gt;99.5</td>
<td>0</td>
</tr>
<tr>
<td>MTBE (racemic)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Prazoles

Racemic omeprazole

\[ K_{\text{hetero}} = 25.2 \pm 4.0 \, \text{M}^{-1} \]
\[ K_{\text{homo}} = 14.0 \pm 3.5 \, \text{M}^{-1} \]

Space group \( \text{P} \bar{1}; (C_i) \)


The Magic Trifluoromethyl Effect

\[ Rf = CF_3, R = CH_2COOalk \]

\[ Rf = CF_3, C_2F_5, C_3F_7 \]

<table>
<thead>
<tr>
<th>Fraction</th>
<th>ee (mass %)</th>
<th>Fraction</th>
<th>ee (mass %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.1 (3.3)</td>
<td>11</td>
<td>94.3 (91.9)</td>
</tr>
<tr>
<td>2</td>
<td>15.7 (7.9)</td>
<td>12</td>
<td>95.9 (93.5)</td>
</tr>
<tr>
<td>3</td>
<td>32.2 (12.1)</td>
<td>13</td>
<td>96.9 (95.2)</td>
</tr>
<tr>
<td>4</td>
<td>43.9 (25.3)</td>
<td>14</td>
<td>97.3 (96.3)</td>
</tr>
<tr>
<td>5</td>
<td>56.5 (39.2)</td>
<td>15</td>
<td>96.9 (97.9)</td>
</tr>
<tr>
<td>6</td>
<td><strong>66.3 (52.6)</strong></td>
<td>16</td>
<td>98.6 (97.9)</td>
</tr>
<tr>
<td>7</td>
<td>76.1 (64.5)</td>
<td>17</td>
<td>99.5 (98.5)</td>
</tr>
<tr>
<td>8</td>
<td>82.2 (74.0)</td>
<td>18</td>
<td>&gt;99.9 (99.1)</td>
</tr>
<tr>
<td>9</td>
<td>86.2 (81.6)</td>
<td>19</td>
<td>&gt;99.9 (99.6)</td>
</tr>
<tr>
<td>10</td>
<td>91.0 (87.6)</td>
<td>20</td>
<td>&gt;99.9 (&gt;99.9)</td>
</tr>
</tbody>
</table>

\[ % \text{ ee determined by chiral stationary phase HPLC} \]

The Magic Trifluoromethyl Effect

Effect of Solvent


Hex:EtOAc 5:1
95% ee

Hex:EtOAc 5:1
31.1% ee

Hex:Et₂O 1:1
66.6% ee

CHCl₃
66.6% ee

*Result replicated three times to rule out experimental error

Perfluoroalkyls: A Rationale

Models of heterochiral and homochiral interactions of trifluoromethyl-containing compounds

- 40% of pharmaceuticals as of 2011 contain at least 1 fluorine atom

Why Fluorine?

1. Strong electron-withdrawing effect of F, especially perfluoroalkyls, results in polarization of σ and π bonds, increasing the extent of H-bonding and thereby leading to a preference for high-order aggregates.

2. Electronegativity of F favors dipole-dipole electrostatic interactions.

3. Physicochemical properties of fluorinated compounds differ from the non-fluorinated alkyls in areas such as solubility, boiling/melting points, volatility, lower viscosity, increased density, low surface tension, and refractive index all generally lead to higher self-segregation of enantiomeric associates.

4. Strong stereo-controlling effects that can direct the spatial arrangements in the formation of crystallographic lattices in general preferring homo-enantiomeric associates.

With all this in mind, the exact role played by a CF$_3$ group is, shortly, very complicated.

Chromatography: Further Examples

Chiral shift reagent  Protected amino ester  Chlormezanone

BINOL eluted on aminopropylsilica gel

Camazepam

Matusch, R.; Coors, C. Angew. Chem., Int. Ed. 1989, 28, 626
Chromatography: Helical chirality

<table>
<thead>
<tr>
<th>Helicenediol</th>
<th>% ee of sample</th>
<th>% ee of 1st fraction</th>
<th>ee (%) of last fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>66</td>
<td>55</td>
<td>77</td>
</tr>
<tr>
<td>M</td>
<td>82</td>
<td>69</td>
<td>89</td>
</tr>
<tr>
<td>P</td>
<td>92</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>P</td>
<td>67</td>
<td>64</td>
<td>72</td>
</tr>
<tr>
<td>P</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>P</td>
<td>42</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>P</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Elute with Hex:EtOH

No change in ee

Recrystallization of P with EtOH showed ethanol inclusion

Recrystallization of P (69% ee) with Hex:EtOAc (3:1)

Racemic crystals + mother liquor of 97% ee

Chromatography: $C_2$ Symmetric Possessing Two Stereogenic Carbons

<table>
<thead>
<tr>
<th>Substrate</th>
<th>ee (%)</th>
<th>Fraction</th>
<th>ee (%)</th>
<th>Wt (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>1</td>
<td>99</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>86</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>1</td>
<td>84</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>77</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>73</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>1</td>
<td>70</td>
<td>38</td>
</tr>
<tr>
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<td></td>
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<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>42</td>
<td>33</td>
</tr>
</tbody>
</table>

Chirality in Molecules Lacking Strong IMFs

<table>
<thead>
<tr>
<th>10 mL Fraction</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
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<td>4</td>
<td>67</td>
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<td>5</td>
<td>64</td>
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<td>62</td>
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<td>7</td>
<td>60</td>
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<td>8</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>51</td>
</tr>
</tbody>
</table>

- No H-bond donor-acceptor like the amides
- Moderate dipole-dipole of carbonyls

(R)-Spirobrassinin - Natural Product Record-Holder

Earlier fractions >98% ee
Later fractions ~6% ee

Earlier fractions 90% ee
Later fractions 22% ee


Preliminary Conclusions

• SDE can be a **blessing** as a means to obtain enantiopure samples from scalemates

• SDE can be a **curse**:  
  • Errors in reported results  
  • Miscomprehension of reaction pathway  
  • Disrupting mechanistic interpretation  
  • Misevaluation of the practicality of (un)reported methodologies
Prebiotic Homochirality

Why are amino acids and other molecules chiral? Moreover, why is there a preponderance of one handedness over another?

Proposed answers other than SDE

- Autocatalysis (Blackmond, Soai)
- Equilibrating reactions (Mauksch)

- Requires highly tuned, externally controlled systems
  - Does not account for the predominance of α-methyl-α-amino acids in meteorites and interstellar ices found as the S enantiomer
- Chirogenesis is a process of decreasing entropy

Proposed answers by SDE

- Entropically neutral
- Spontaneous – as we will soon see.

Group Discussion

• What might be a better nomenclature for the phenomenon herein described as the self-disproportionation of enantiomers?

• What might the SDE effect bear on prebiotic homochirality?
Other Manifestations of SDE

- Sublimation
- Distillation?
- Recrystallization
- Ultracentrifugation
  - Suspension
  - Precipitation
- Chromatography
Sublimation + Tag

Covalent Bond Formation → Sublimation

Achiral sublimation enabling tag
Enantiomerically pure compound
Enantiomerically enriched compound
Racemic compound

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{CH}_n\text{F}_{3-n} \\
\text{H}_2\text{N} \cdot \text{Ph} & \quad \text{MeSO}_2\text{Cl} \cdot \text{MelM}
\end{align*}
\]

DCM, rt. overnight

\[
\begin{align*}
\text{F}_3\text{C} \quad \text{CH}_n\text{F}_{3-n} \\
\text{CF}_3 & \quad \text{CH}_n\text{F}_{3-n} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

78-87% yield for each of the racemates and (R)-enriched α-(phenyl)ethylamines

\( \text{a} \ (n=0), \ \text{b} \ (n=1), \ \text{c} \ (n=3) \)

Sublimation 2: Tag-Free and Curious


Wallach’s rule: racemic crystals tend to be denser than their chiral counterparts

However, melting points are molecule-dependent

“The modification with the lowest melting point should...sublime preferentially.”

“It is important to note that it is not always the lowest melting form that sublimes preferentially”

38% yield 62% yield
Properties of Racemates and their Enantiomeric Components

M = enantiomeric purity greater than that of eutectic
N = enantiomeric purity less than that of eutectic
Te = lowest sublimation temperature of racemate

Case 1: Partially resolved conglomerates – subliming fraction is racemic and thus enantiomeric purity of non-sublimed solid is increased.

Case 2: Racemic compound with enantiomeric purity less than that of the eutectic – subliming fraction has greater enantiomeric purity, residue is enriched in racemate.

Case 3: Racemic compound with enantiomeric purity greater than that of the eutectic – subliming fraction has diminished enantiomeric purity, residue is enriched in enantiomer
Size Exclusion Chromatography

- Opposed to other column chromatography relying on adsorption/desorption properties, SEC separates molecules based on size.

\[
\text{F}_3\text{C}-\text{O} \rightarrow \text{SEC (CHC}_3\text{)} \rightarrow \text{O}
\]

\[75.0\% \text{ ee}\]

- \(F_1 = 99.9\% \text{ ee}; F_2 = 98.5\% \text{ ee}; F_3 = 27.1\% \text{ ee}; F_4 = 0.0\% \text{ ee}\)

- Problem: crystallization yields conglomerates

- Accidental solution: Sublimation of conglomerates yielded truly racemic crystals.

- Homochiral (P2\text{\textsubscript{1}}2\text{\textsubscript{1}}2\text{\textsubscript{1}})
  - Density = 1.456 g/mL
  - M.P. = 79 °C

- Heterochiral (P2\text{\textsubscript{1}}/n)
  - Density = 1.522 g/mL
  - M.P. = 57 °C

Recrystallization vs. SDE via Chromatography

Case 1: Partially resolved conglomerates comprising 5-10% of minor enantiomer.
- Little or no advantage vs. chromatography in theory. In practice, nearly all of the excess enantiomer can be isolated from the scalemate by recrystallization in higher yields.

Case 2: Solid solutions (e.g. pseudoracemates)
- No gain in enantiopurification can be effected by recrystallization and so SDE via chromatography holds an advantage (although this is only in rare cases).

Case 3: Scalemic compounds
- Method of enantiopurification depends on many factors including starting purity and the eutectic point.

Generally: For recrystallization to be effective, the sample must be crystalline.

Recrystallization: Energetics

- Methods of enantiomer separation by recrystallization
  - Crystal picking (Triage)
  - Preferential crystallization: inoculation of saturated solution of scalemate with seed crystals of one of the enantiomers.
  - Conglomerates: each enantiomer must crystallize as one handedness, often aided by and large excess of that enantiomer in solution and by successive recrystallizations.

Binary phase diagram for melting point

**Kinetic Recrystallization**: Seeding with an enantiopure crystal leads to an unequal rate of crystallization of the two enantiomers. Rotation of the mother liquor drops to zero then changes sign.

---

Recrystallization: Ternary Phase Diagram

$P_1 =$ Starting material with $ee < ee_{eu}$

$A =$ composition of solution saturated with pure $S$ enantiomer

$E/E' =$ eutectic points (3 phases in equilibrium)

$r =$ racemate

$L =$ achiral solvent

At $P_1$, the desired $S$ enantiomer can be enriched in the liquid phase and ee of product will be the same as the ee of eutectic if the system remains in region of $rES$.

$$\text{yield}_{max} = \frac{ee_0(1 + ee_{eu})}{ee_{eu}(1 + ee_0)}$$

Defines the intersection of lines $LP_1$ and $rE$ as point $M$ which is the maximum theoretical yield.

Distillation?

\[ \rho_M = \rho_A x_D + \rho_A x_L = \rho_A \]

\( \rho_M = \) vapor pressure of a mixture \\
\( \rho_A = \) vapor pressure of pure enantiomer

“Contrary to crystallization or sublimation, distillation of a partially resolved mixture is an operation that cannot lead to a modification of the enantiomeric purity.”


Distillation: CF$_3$-Induced Curiosity

Role of –CF$_3$ is to (1) increase volatility and (2) increases the hydrogen-bond donor capabilities of, in the top case, the trifluoroacetamide moiety towards the carbonyl

Ultracentrifugation/Suspension Precipitation

- Previously used to separate biopolymers from mixtures or even ssDNA from dsDNA but never for the separation of chiral small molecules.
- Solid racemic compounds and the enantiopure counterparts can vary by as much as 5% in their densities.¹

![Chemical structure of Nycodenz®](image)

Density (g/mL) = 1.393 1.395 1.400

“Our future work will explore the general applicability of our approach...Therefore, the separation by the well-established density gradient ultracentrifugation has a great feasibility.”²

Gravity-Driven Dispersion

\[
\begin{align*}
\text{H}_2\text{N} & \text{CO}_2\text{H} \\
\text{Ph} & \text{PhCl/PhBr} \\
\rho = 1.35 & (\text{S}) - 90\% \text{ ee} \\
& 440 \text{ mg} \\
\rho = 1.106 \text{ g/mL PhCl solution} & \rho = 1.35 \text{ g/mL PhCl/PhBr solution} \\
\text{Slowly add PhBr} & \rho = 1.495 \text{ g/mL} \\
50\% \text{ ee} & 13\% \text{ ee} \\
\text{Powdered mixture of racemic and enantiopure crystals} & 90\% \text{ ee} \\
\Delta \text{ee} = 77\% & \Delta \text{ee} = 39\% \\
\text{H}_2\text{N} & \text{NH}_2 \\
& \text{NH}_3^+ \\
& \text{NO}_2 \\
& \text{O} \\
& \text{C} \\
& \text{O} \\
\Delta \text{ee} = 18\%
\end{align*}
\]

Gas Chromatography: A Novelty

General Problems with SDE by GC
- High concentrations required to observe SDE can overload column
- Hypersensitive to any change in variables

In a survey of 12,000 cases, there were several abnormal dichotomies.

SDE in Total Synthesis

\[
\text{TsNH} \xrightarrow{\text{n-BuLi, -78 °C, Cyclobutanone}} \text{TsNH} \xrightarrow{(S)\text{-cat.}, 5 \text{ Å MS}} \text{NTsI} \xrightarrow{\text{LiHMDS, PhNTf}_2} \text{OTf}
\]

99% yield, 80% ee


<table>
<thead>
<tr>
<th>Fraction (9.0 mg)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Σ Weight(%)∗ee(%) = 89%</th>
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</thead>
<tbody>
<tr>
<td>Weight (%)</td>
<td>35.5</td>
<td>27.2</td>
<td>16.8</td>
<td>4.7</td>
<td>15.8</td>
<td></td>
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<tr>
<td>ee (%)</td>
<td>&gt;99</td>
<td>96</td>
<td>82</td>
<td>76</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>
Words for the practicing chemist

• From the literature it is often unclear at what stage the ee was measured and the physical processes performed on the sample.

• Practice caution when reporting the stereochemical outcome of a reaction (over- or underestimating the ee).

• Take care to safeguard against unintended manipulations in the processing of the sample.

• SDE is likely always taking place during chromatography of scalemic samples but its magnitude is the only question.
Conclusion & Outlook

• Experimentally convenient way to obtain optically pure material

• No additional chiral components necessary

• Develop a method to establish the presence of homo- and hetero-associates

• Predicting the magnitude of SDE

• Gain recognition among the wider research community