

Chiral purity limitation: discovery of a partial solid solution

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Chiral purity limitation: discovery of a partial solid solution

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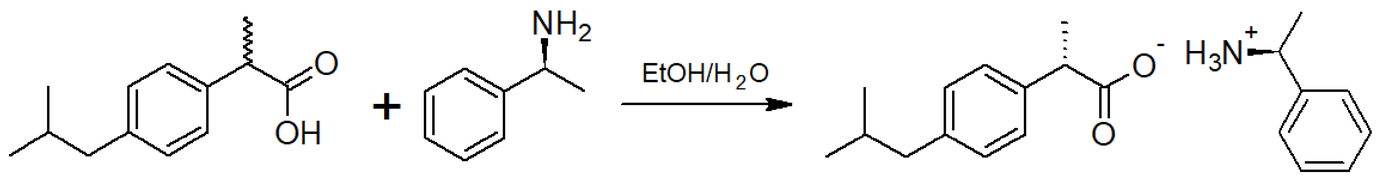
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Context

Greater therapeutic effect for **S-Ibuprofen** (S-Ibu) [1]

- **Chiral resolution** by **crystallization** using S-α-MethylBenzylAmine (**S-αMBA**)
  - Formation of **S-Ibuprofen-S-α-MethylBenzylAmine** (S-Ibu-S-αMBA)

Reaction scheme



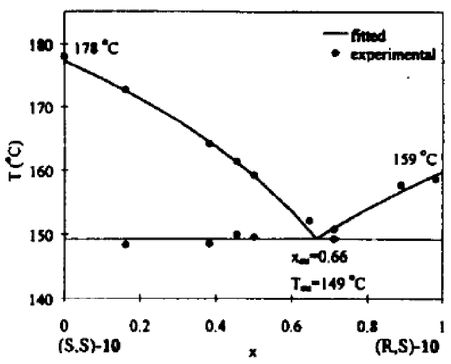
Racemic Ibuprofen — S-α-MethylBenzylAmine — S-Ibuprofen-S-α-MethylBenzylAmine

⇒ Observed **limit** of the **chiral purity** reachable (87% of S-Ibu-S-αMBA)

⇒ Detection of **peak shifts** in **XRPD** analysis

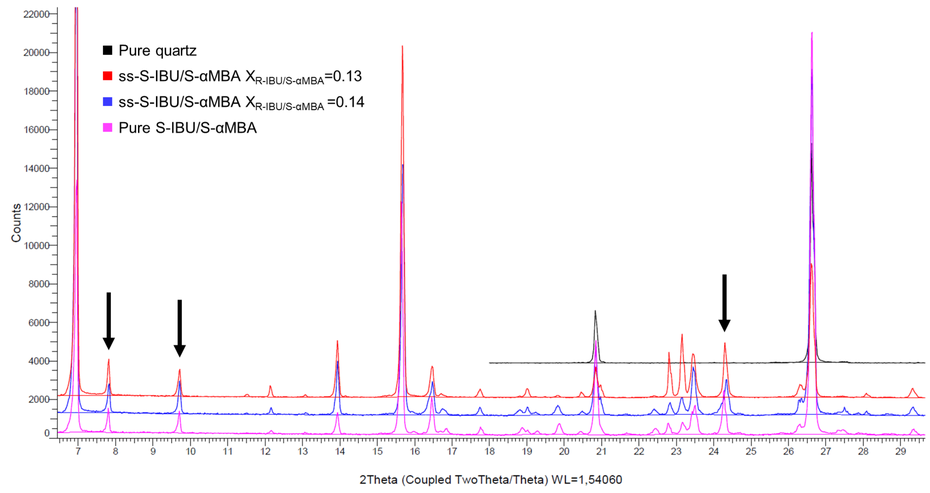
Existence of a partial solid solution restraining the maximum chiral purity accessible?

Investigation [2]



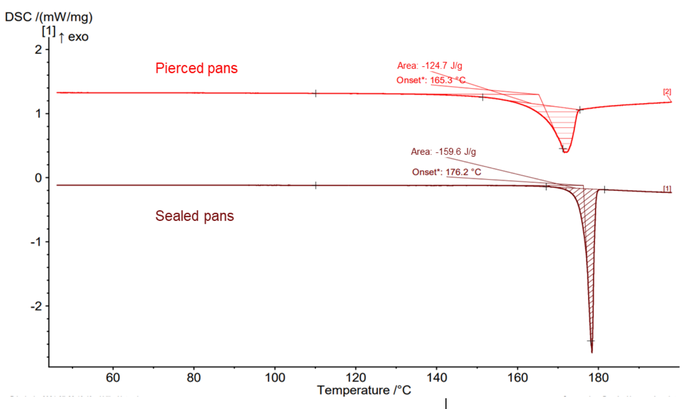
[3]

- Phase diagram exhibiting a **simple eutectic** at 150°C according to **Ebbers *et al.*** [3]



- **DSC measurements** at **different compositions** between $X_{R\text{-Ibu-S-}\alpha MBA}$=0 and 0.5
  - **Melting temperatures** and **eutectic invariant temperature** → **Phase diagram**
  - **Eutectic enthalpies** → **Tammann graph**
- **XRPD** analysis: small **peak shifts** when composition S-Ibu-S-αMBA/R-Ibu-S-αMBA changes

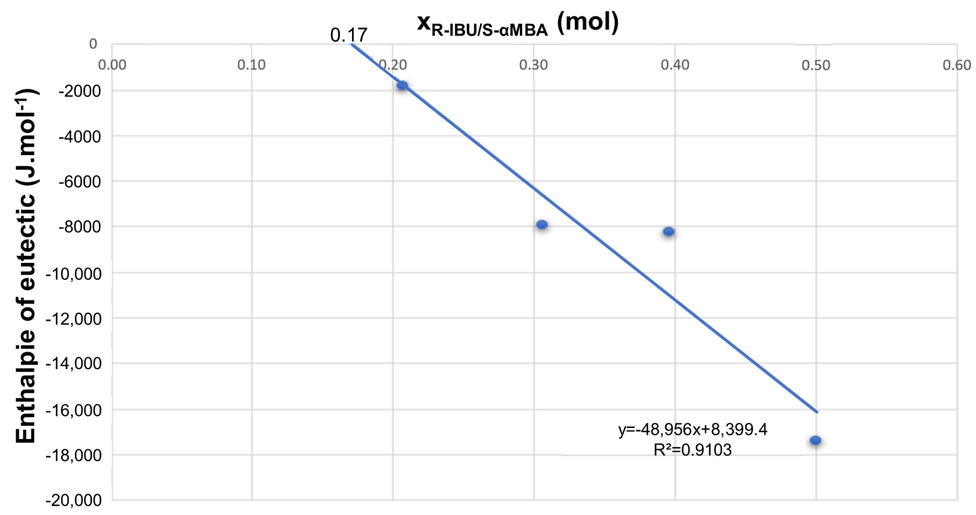
DSC measurements



DSC analysis **operating conditions** **impact** the results

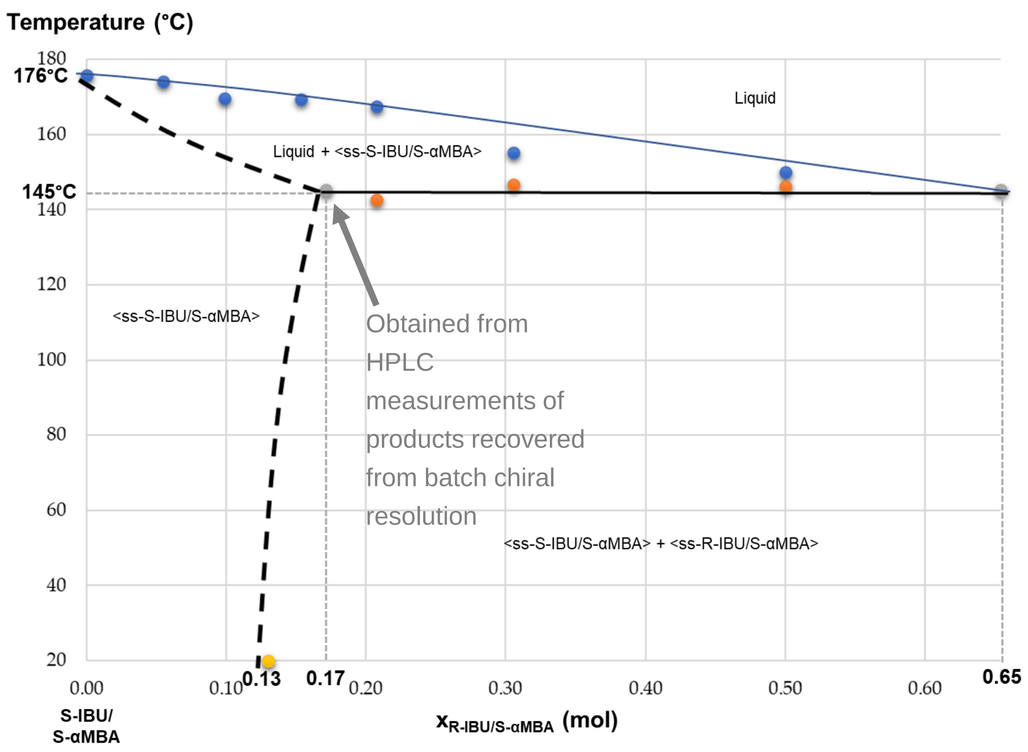
	Measurements with pierced pans	**Measurements with sealed pans**
Eutectic temperature *consistency with literature*	No	Yes
Observed phenomenon	Sublimation	-

Tammann graph



The **intersection** with **abscissa** axis gives the **eutectic composition.**

Revised phase diagram



Conclusions

- The **Schröder van Laar** equation has been used to confirm the eutectic composition and temperature. Calculated results are **consistent** with the experimental ones.
- Contrary to published data [3], the **binary system between S-Ibu-S-αMBA/R-Ibu-S-αMBA** does not only exhibit a simple eutectic:
  - A **partial solid solution** has been evidenced for the less soluble salt [2].
- This partial solid solution is the **cause** of the **limitations in chiral purity**.
- In order to prevent sublimation, **DSC** measurements were performed in **sealed pans**. In sealed pans, **pressure increases with temperature**, which induces a **measurement bias:**
  - ***The 'real' phase diagram cannot be determined with usual DSC apparatus.***

[References]. [1] A. M. Evans, Clinical Rheumatology, vol20, n°1, p. 9-14 (2001). [2] L. Marc *et al.*, Crystals, **vol. 11**, n°10, p. 1188 (2021). [3] E. J. Ebbers *et al.*, Tetrahedron: Asymmetry, **vol. 8**, n°24, p. 4047-4057. (1997).