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Chiral purity limitation: discovery of a partial solid solution

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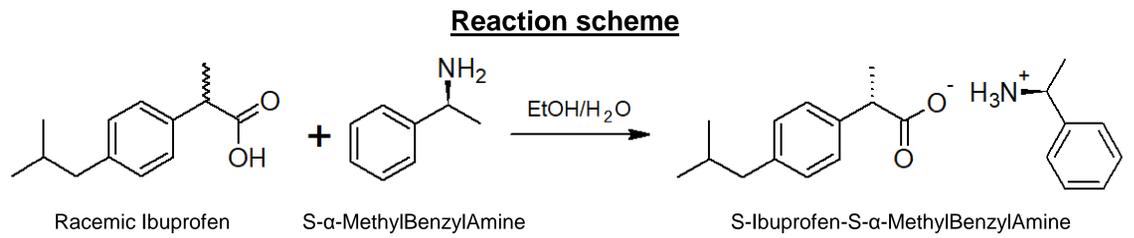
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Context

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

↳ Chiral resolution by crystallization using S- α -MethylBenzylAmine (S- α MBA)

↳ Formation of S-Ibuprofen-S- α -MethylBenzylAmine (S-Ibu-S- α MBA)

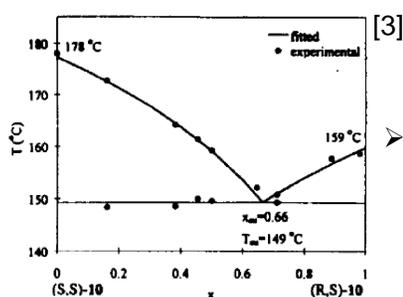


⇒ Observed limit of the chiral purity reachable (87% of S-Ibu-S- α MBA)

⇒ Detection of peak shifts in XRPD analysis

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

Investigation [2]

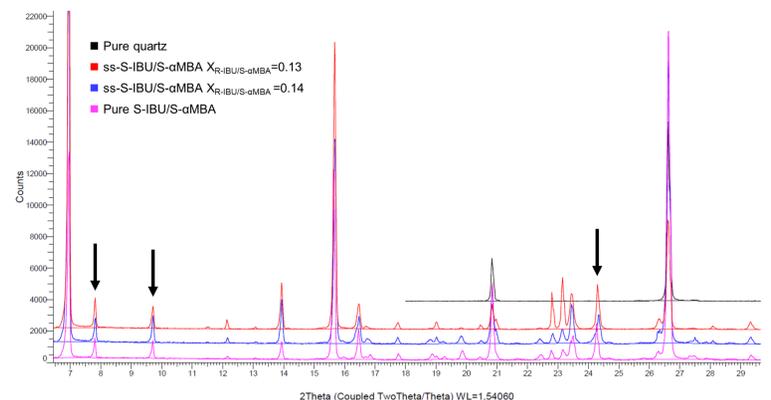


↳ Phase diagram exhibiting a simple eutectic at 150°C according to Ebberts *et al.* [3]

• DSC measurements at different compositions between $X_{R\text{-Ibu-S-}\alpha\text{MBA}}=0$ and 0.5

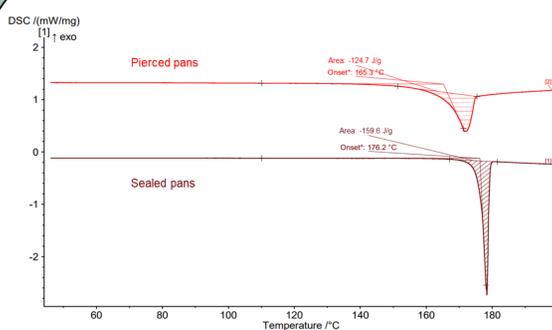
↳ Melting temperatures and eutectic invariant temperature → Phase diagram

↳ Eutectic enthalpies → Tammann graph



• XRPD analysis: small peak shifts when composition S-Ibu-S- α MBA/R-Ibu-S- α MBA changes

DSC measurements



DSC analysis operating conditions impact the results

Measurements with pierced pans

No

Sublimation

Measurements with sealed pans

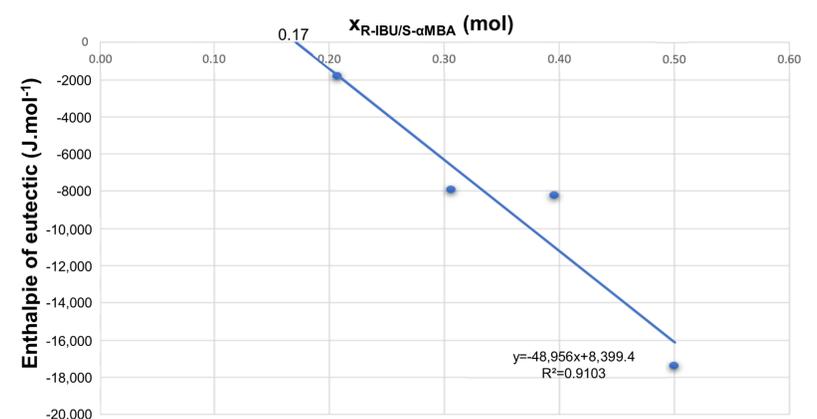
Yes

-

Eutectic temperature consistency with literature

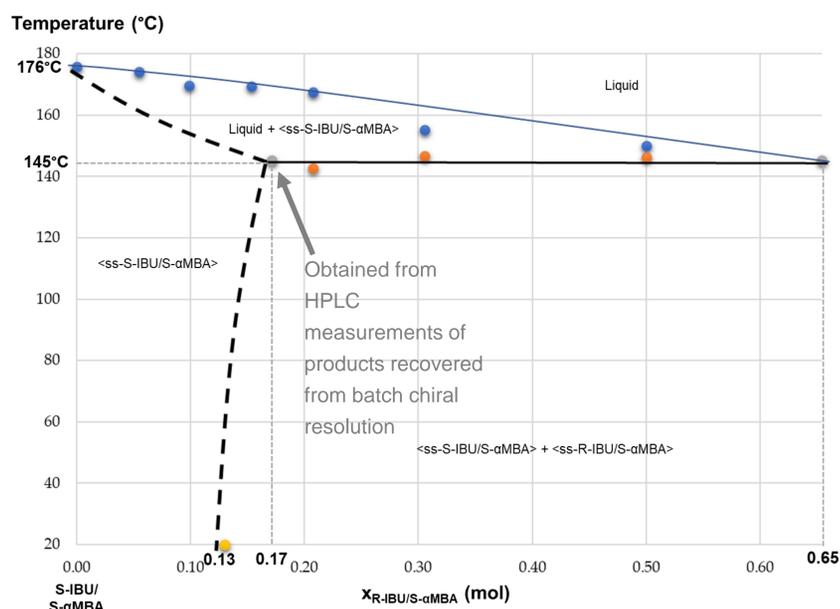
Observed phenomenon

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- α MBA/R-Ibu-S- α MBA 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.