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## Chiral purity limitation: discovery of a partial solid solution

Laureline Marc, Chrystal Lopes, Jean-Marie Schneider, Morgane Sanselme,  
G rard Coquerel

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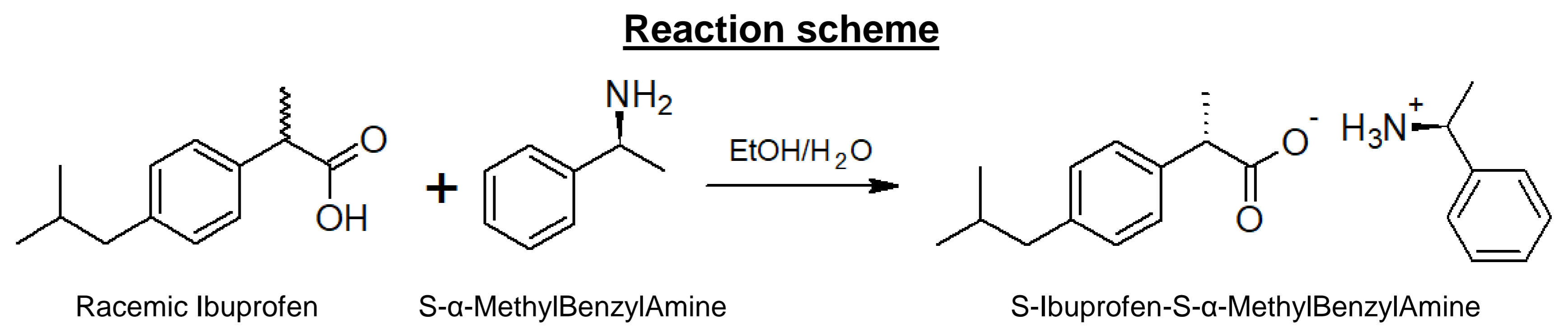
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## Context

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

↳ Chiral resolution by crystallization using S- $\alpha$ -MethylBenzylAmine (S- $\alpha$ MBA)

↳ Formation of S-Ibuprofen-S- $\alpha$ -MethylBenzylAmine (S-Ibu-S- $\alpha$ MBA)

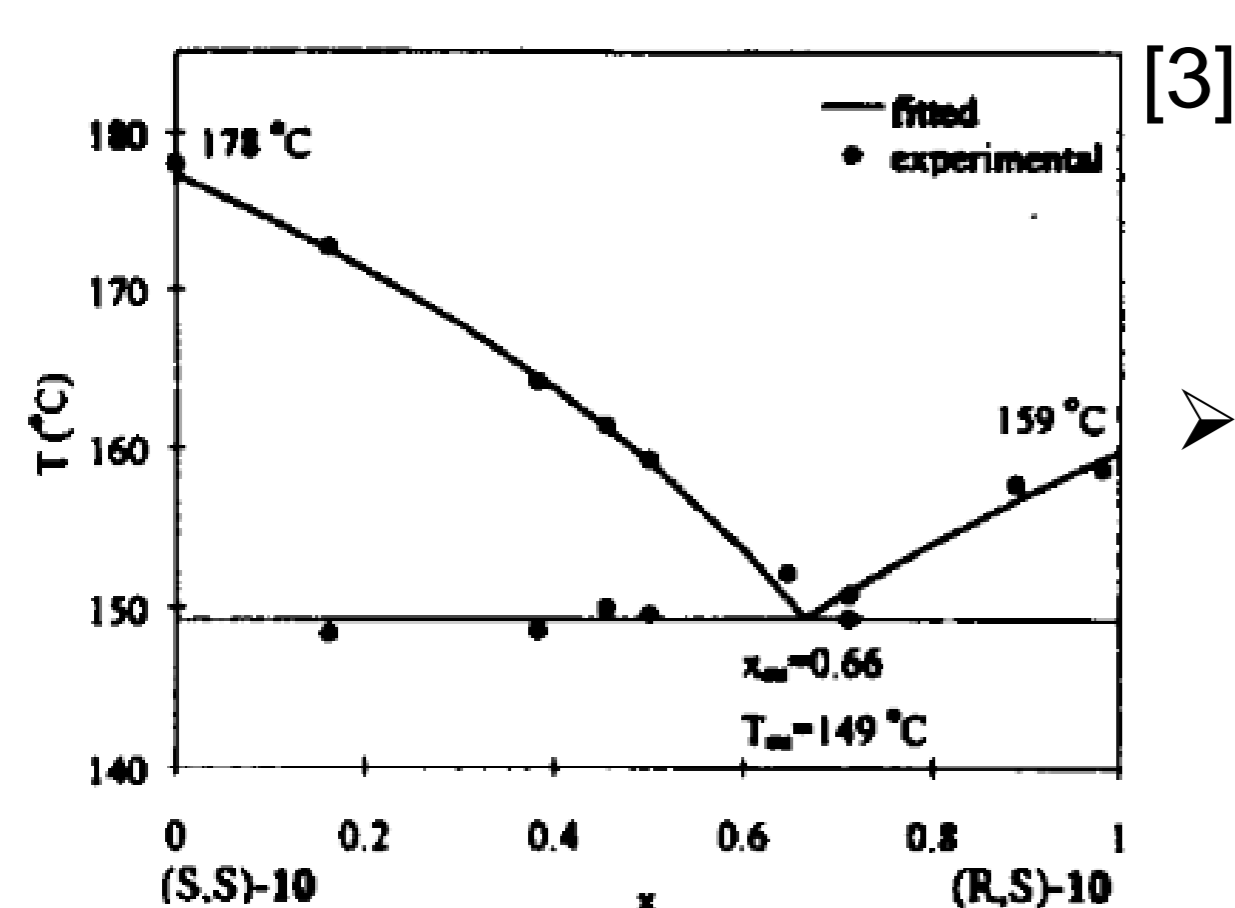


⇒ Observed limit of the chiral purity reachable (87% of S-Ibu-S- $\alpha$ MBA)

⇒ Detection of peak shifts in XRPD analysis

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

## Investigation [2]

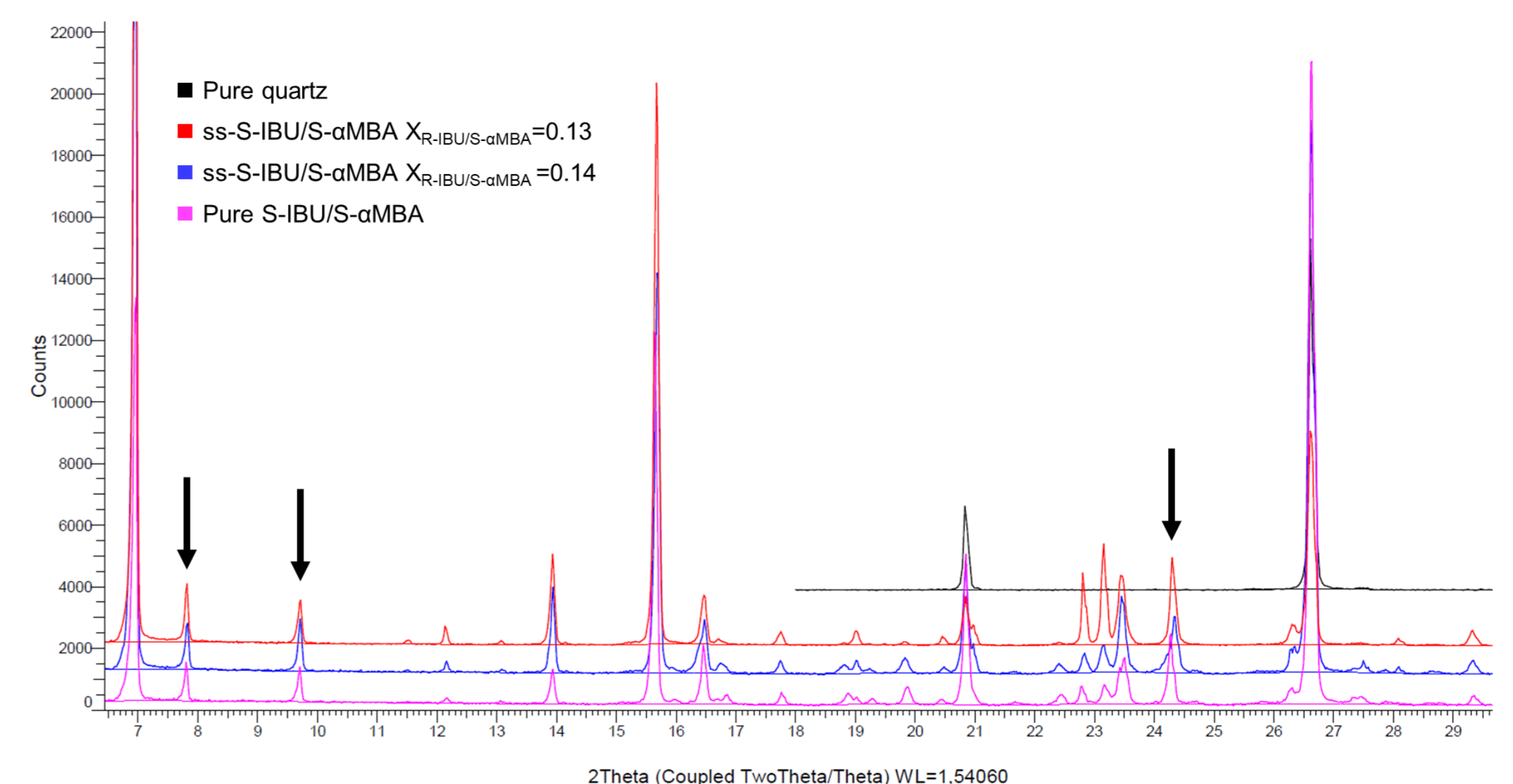


↳ Phase diagram exhibiting a simple eutectic at 150°C according to Ebberts *et al.* [3]

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

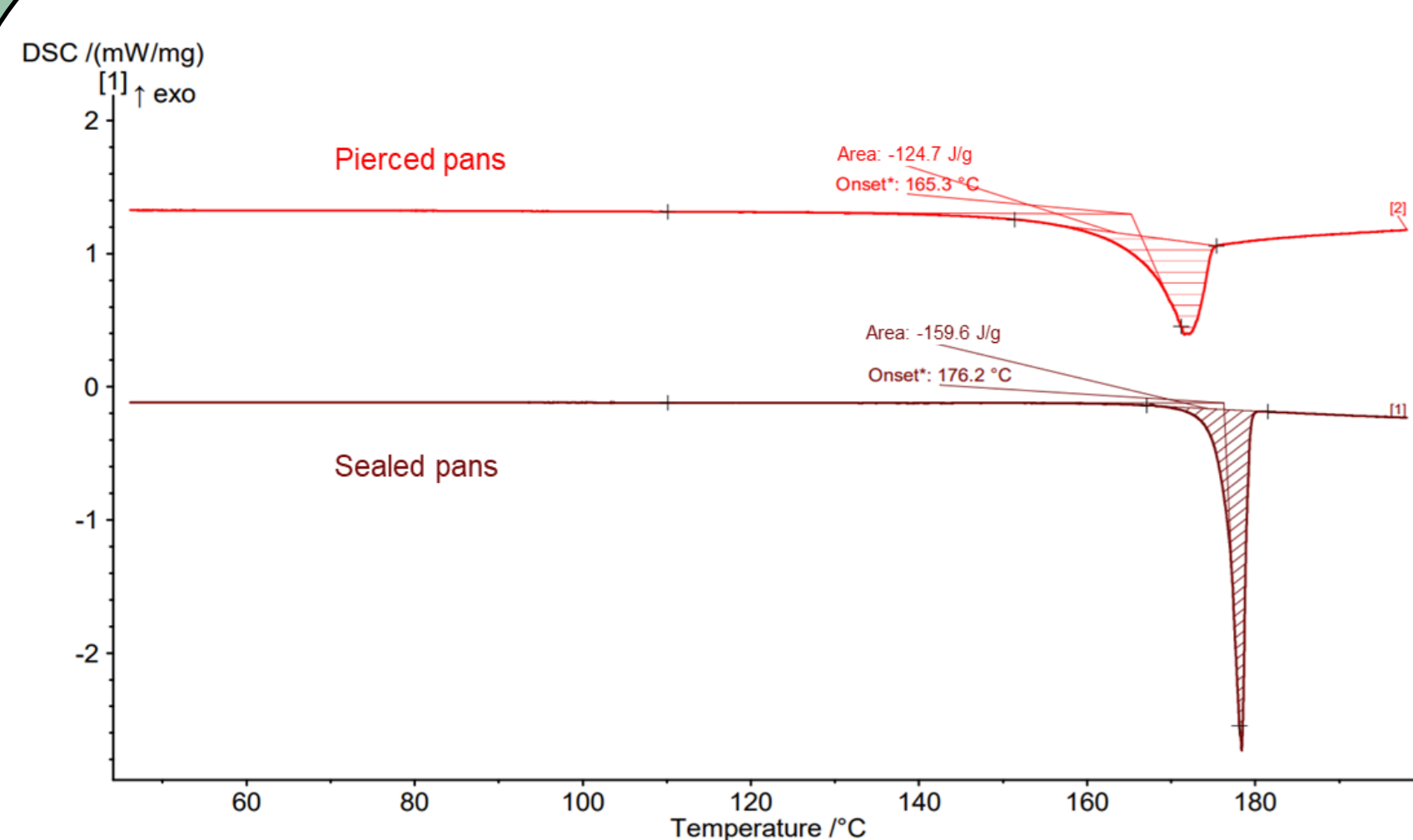
↳ Melting temperatures and eutectic invariant temperature → Phase diagram

↳ Eutectic enthalpies → Tammann graph



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

## DSC measurements



DSC analysis operating conditions impact the results

Measurements with pierced pans

Measurements with sealed pans

Eutectic temperature consistency with literature

No

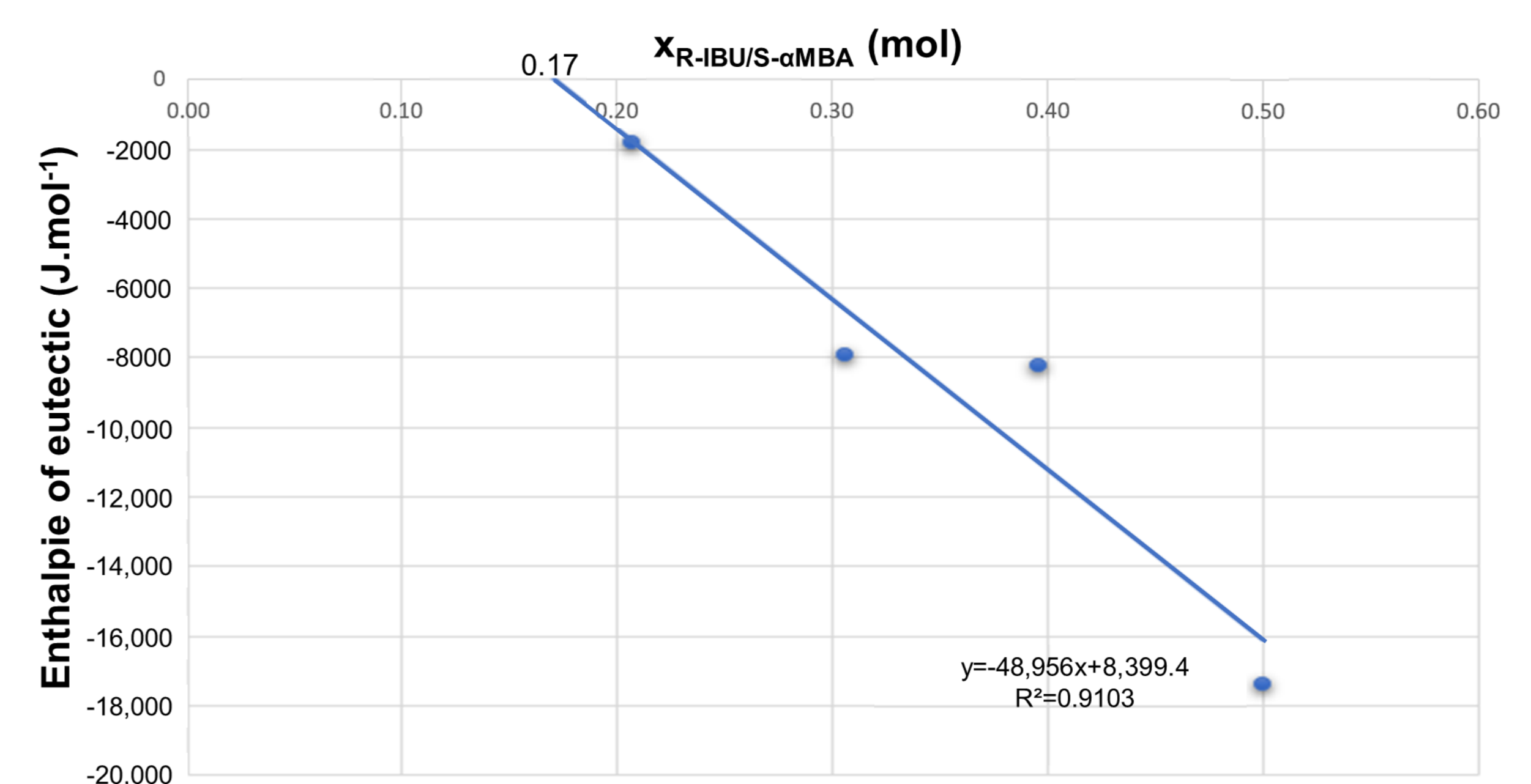
Yes

Observed phenomenon

Sublimation

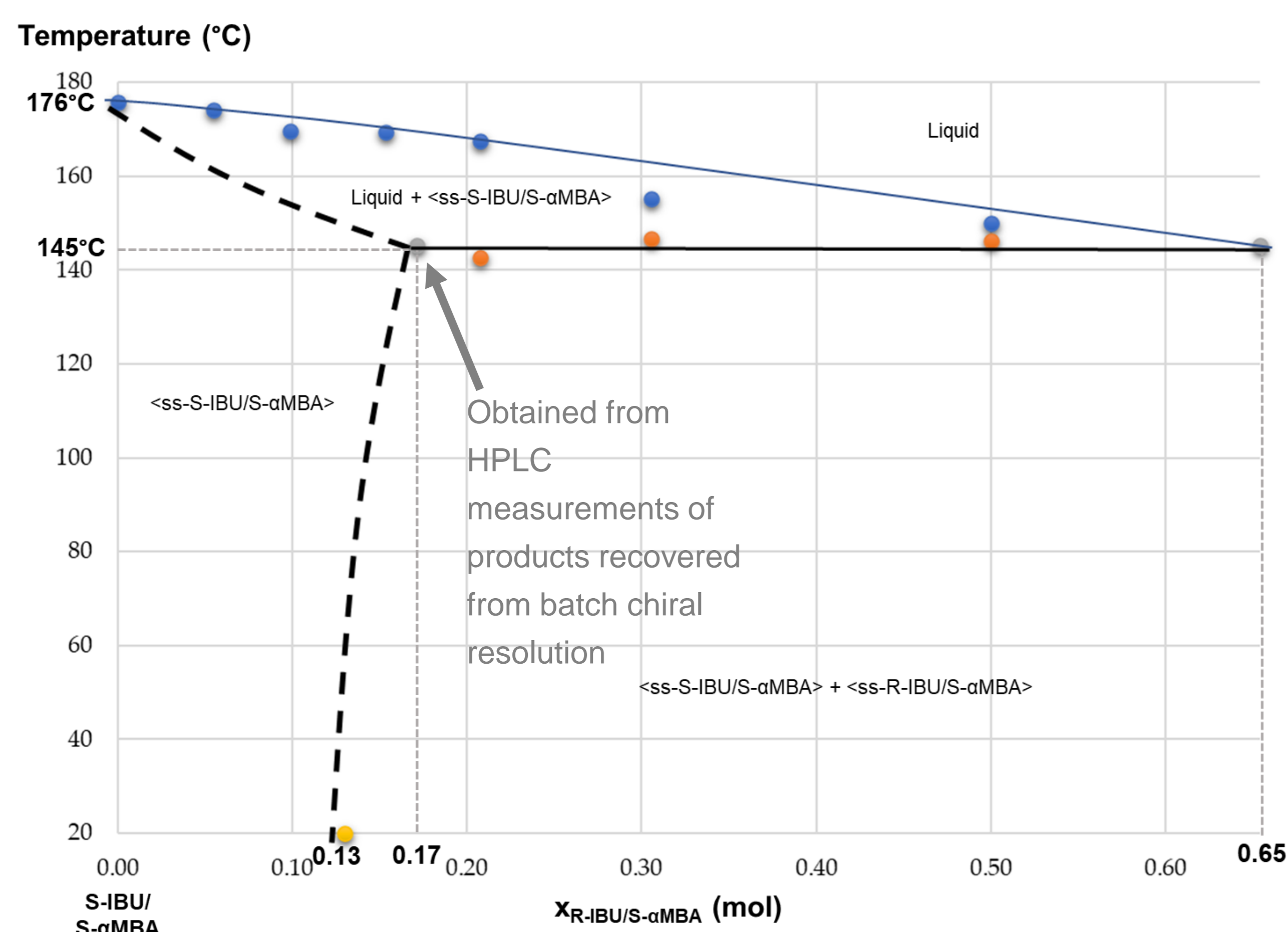
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## Tammann graph



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- $\alpha$ MBA/R-Ibu-S- $\alpha$ 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.