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Investigation of the Binary System of Proxyphylline Enantiomers: Phase Diagram Determination

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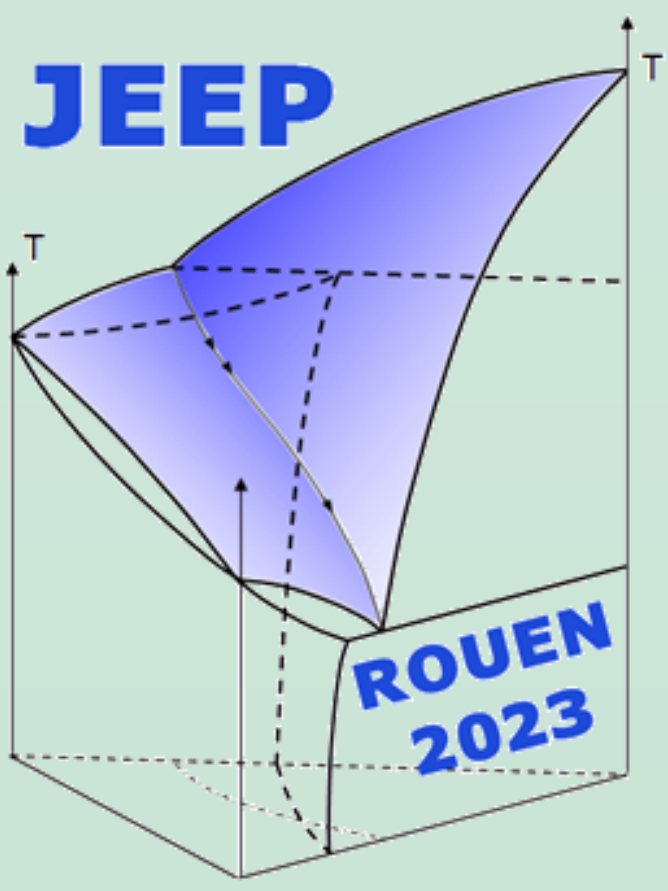
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Introduction

Proxiphylline :

- Xanthine-based chiral API derived from Theophylline
- Vasodilator, cardiac stimulant and bronchodilator

Three different "modifications" of the racemic composition highlighted by Griesser *et al.*^[1]

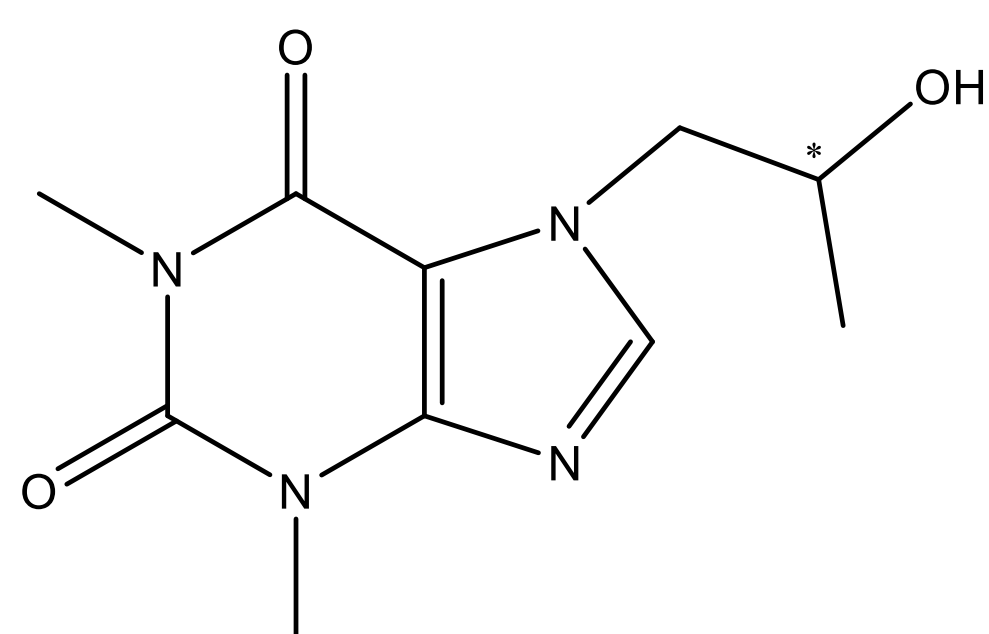
- Mod. I (melting at 133.5°C),
- Mod. II (melting at 113.5°C)
- Mod. III (melting at ca. 82-85°C)

Solid-state classifications?

Crystallization-enhanced chiral resolution by Harfouche *et al.*^[2] :

- Preferential crystallization on a metastable conglomerate of Proxiphylline

Identification and Investigations of the different phases involved in this heterogeneous system



Molecular structure of Proxiphylline

Racemic composition

Stable racemic form :

=> RI [$T_{fus}^{RI} = 134.0^{\circ}C$; $\Delta H_{fus}^{RI} = 22.4 \text{ kJ.mol}^{-1}$]

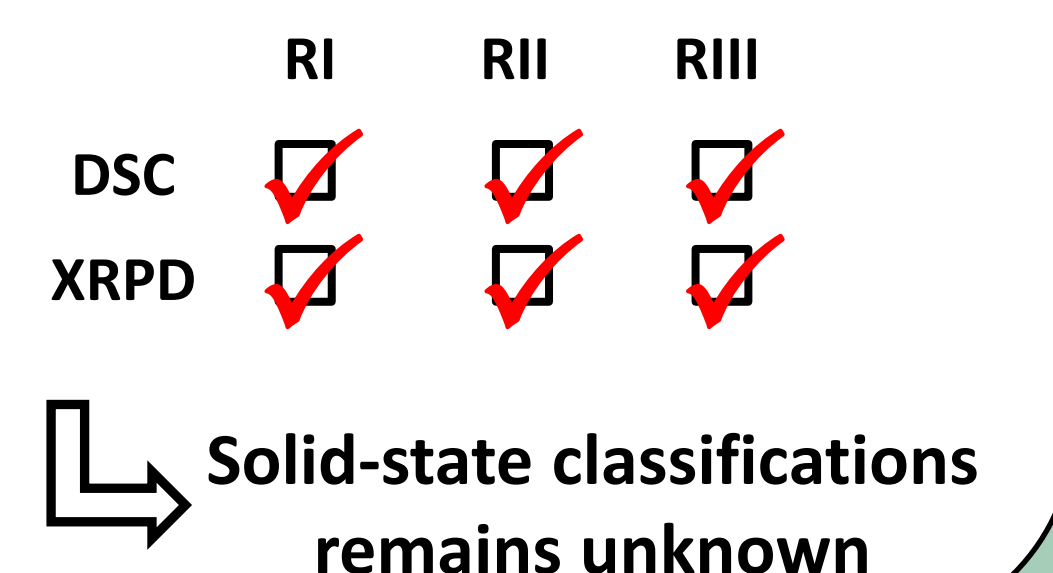
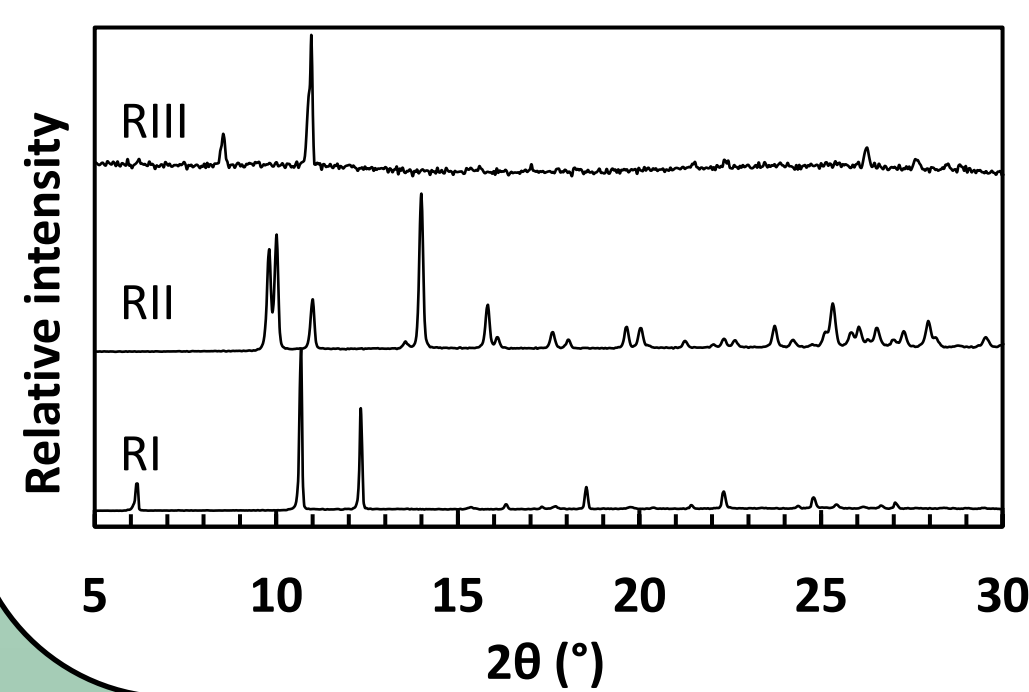
Annealing the SuperCooled Melt (SCM) :

- at 80°C for 30 minutes

=> RII ($T_{fus}^{RII} = 111.5^{\circ}C$; $\Delta H_{fus}^{RII} = 15.2 \text{ kJ.mol}^{-1}$)

- At 80°C for 10 minutes

=> RIII ($T_{fus}^{RIII} = 84.5^{\circ}C$; $\Delta H_{fus}^{RIII} = ?$)

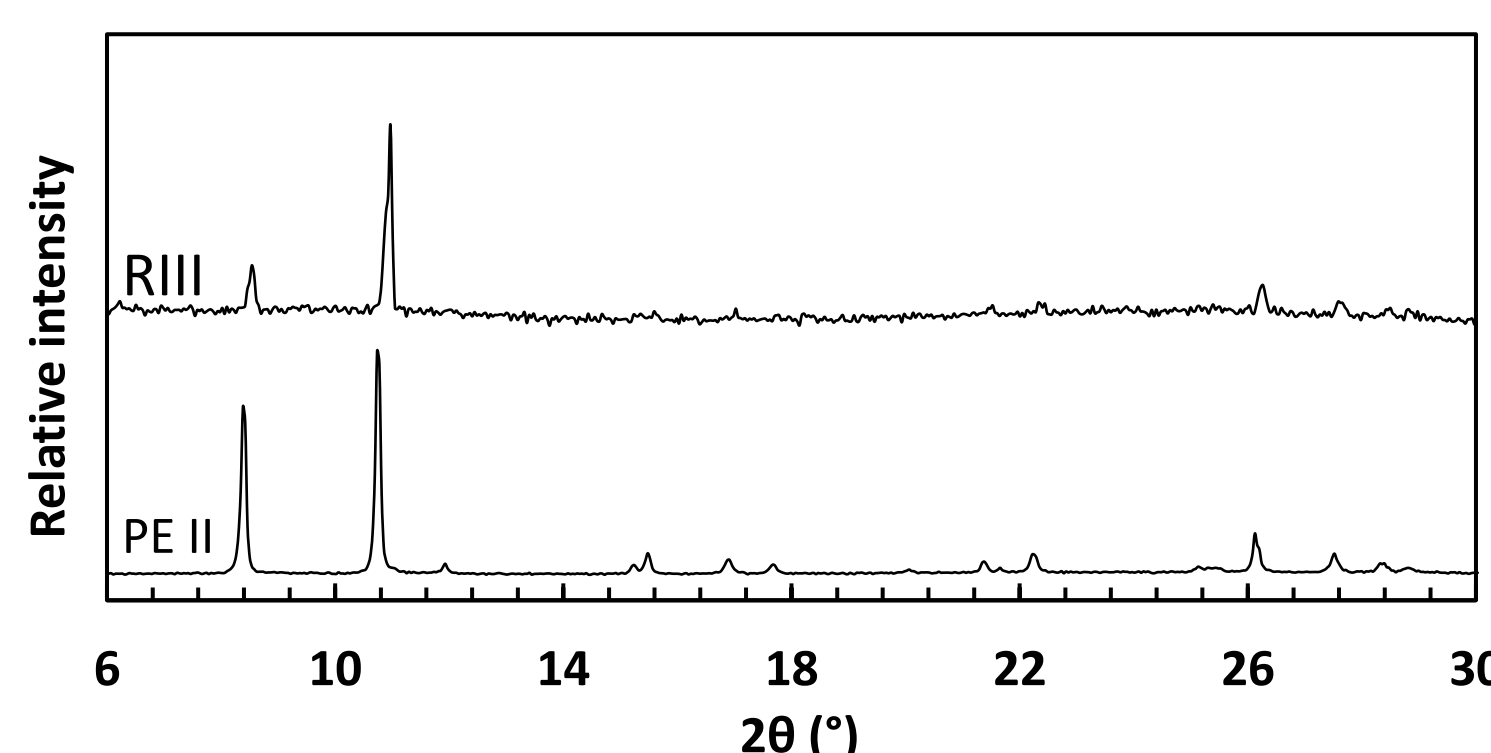


Solid-state classifications remains unknown

RIII

PE II

XRPD comparaison



Superimposable XRPD patterns
Racemic conglomerate **cPE II** [■]

Enantiopure composition

Stable enantiopure form :

=> PEI [$T_{fus}^{PEI} = 148.3^{\circ}C$; $\Delta H_{fus}^{PEI} = 25.6 \text{ kJ.mol}^{-1}$]

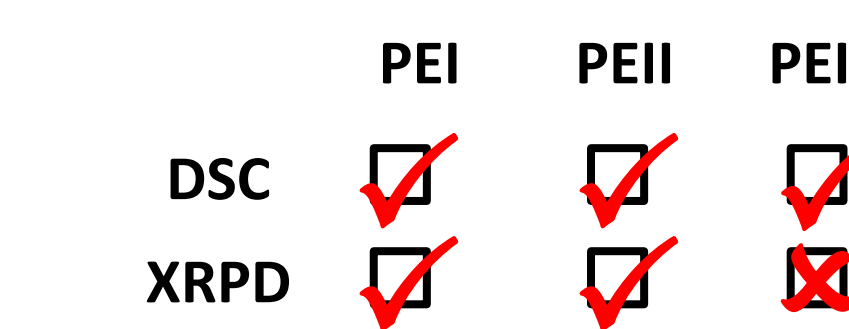
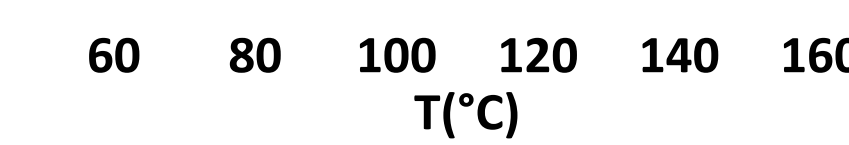
Recrystallization from the SuperCooled Melt :

- Annealing at 80°C for 30min

=> PEII ($T_{fus}^{PEII} = 116.1^{\circ}C$; $\Delta H_{fus}^{PEII} = ?$)

- Heating the SCM from 25 to 160°C at 10K.min⁻¹

=> PEIII ($T_{fus}^{PEIII} = 98.4^{\circ}C$; $\Delta H_{fus}^{PEIII} = ?$)



High metastability of PEIII

Stable equilibria

RI / PEI

DSC measurements of Physical mixtures of RI and PEI at compositions $0.5 < X_{(R)} < 1$

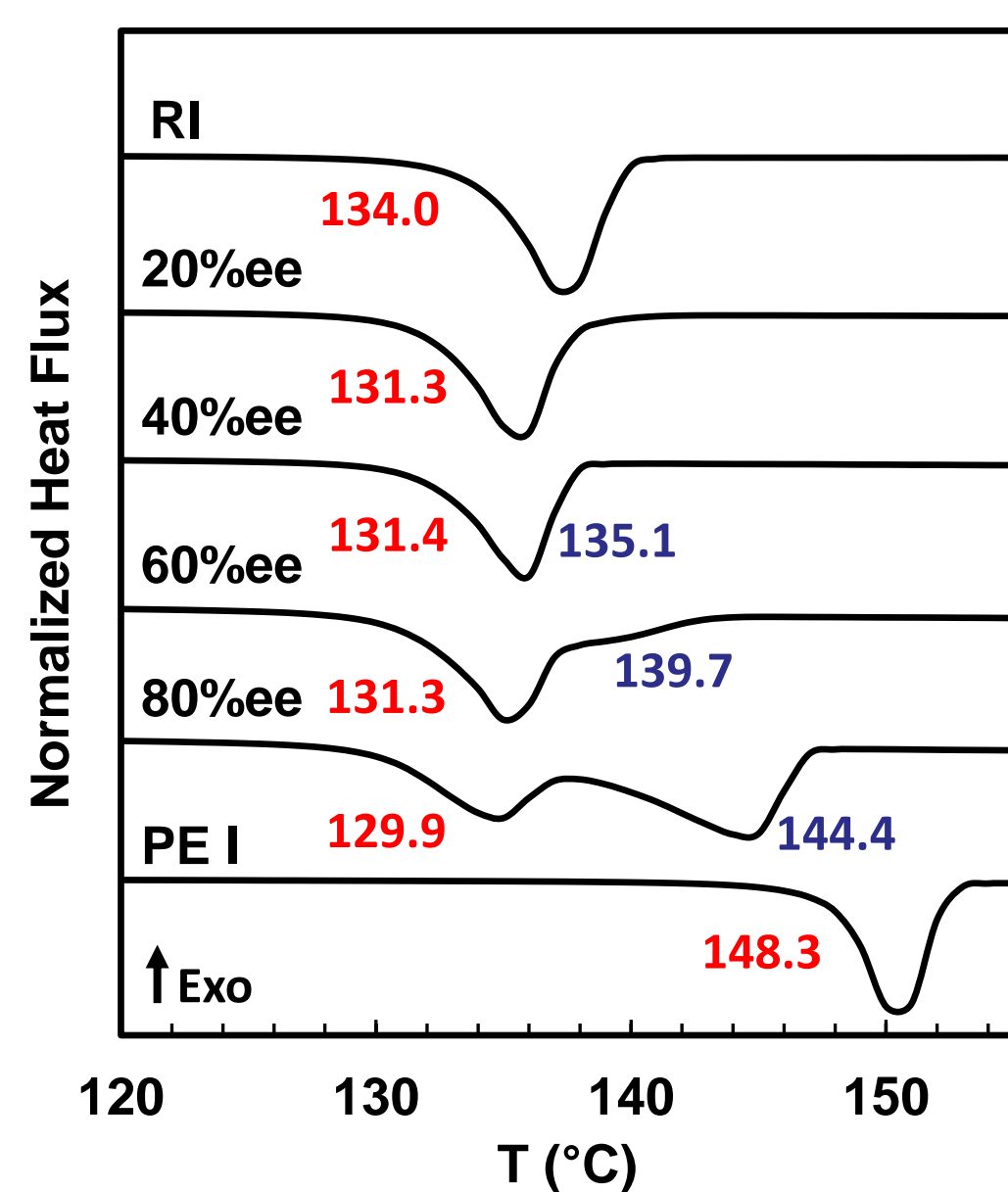
- (i) An endothermic invariant at ca. 131°C

=> Eutectic Invariant

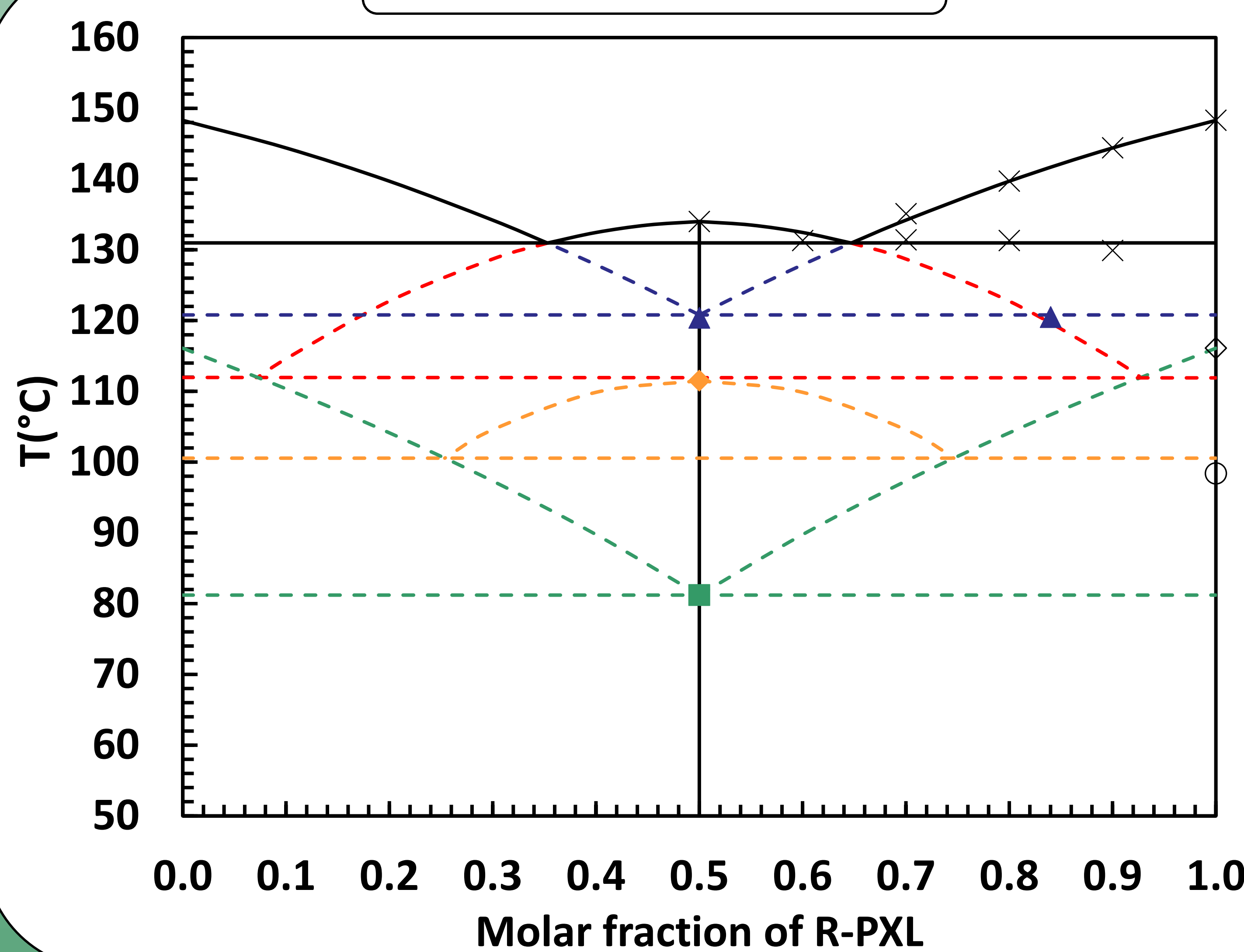
- (ii) An endothermic signal varying between the melting points of pure RI and PEI

=> Liquid

Corresponding experimental points for eutectic invariant and liquidus: (X)



Binary phase diagram



Predicted invariants

Theoretical calculation

Schröder van-Laar and Prigogine-Defay^[3] simplified equation :

$$\ln x = \frac{\Delta H_{fus}}{R} \left(\frac{1}{T_{fus}} - \frac{1}{T_x} \right)$$

$$\ln[4x(1-x)] = \frac{2\Delta H_{fus}}{R} \left(\frac{1}{T_{fus}} - \frac{1}{T_x} \right)$$

- Predict the invariant of **cPE I** & **RI/PE I**

- Estimate the value of $\Delta H_{fus}^{PE II}$ based on experimental determination of $T_{fus}^{cPE II}$

Prediction of two metastable invariants :
RI/PEII and **RII/PEII**

Red and orange dashed lines : Predicted

Equilibrium	Invariant Temperature (°C)		
	Predicted	Measured by DSC	Recalculated
RI / PEI	128.6	131.0	n/a
RI / PEII	n/a	n/a	111.9
RII / PEII	n/a	n/a	100.6
cPEI	111.2	120.4	n/a
(cPEII)	n/a	81.2	n/a

Conclusion

The binary phase diagram between PXL enantiomers presents :

- Three polymorphs of the pure enantiomer (i.e., PE I, PE II, PE III)
- Two polymorphs of the racemic compound (i.e., RI and RII)

Monotropic relationship

Predicted and recalculated invariants via SVL & PD simplified equations

Metastable conglomerates **cPEI** & **cPEII** experimentally characterized

Poor agreement between predicted ($T=111.2^{\circ}C$) and measured ($T=120.4^{\circ}C$) invariant temperatures of **cPEI**

Non-ideal thermodynamic behavior

Hot Stage Microscopy video of SCM experiment on PEII available here !



Enjoy !