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Diastereomeric salt resolution of Praziquanamine rationalized and optimized via phase diagrams

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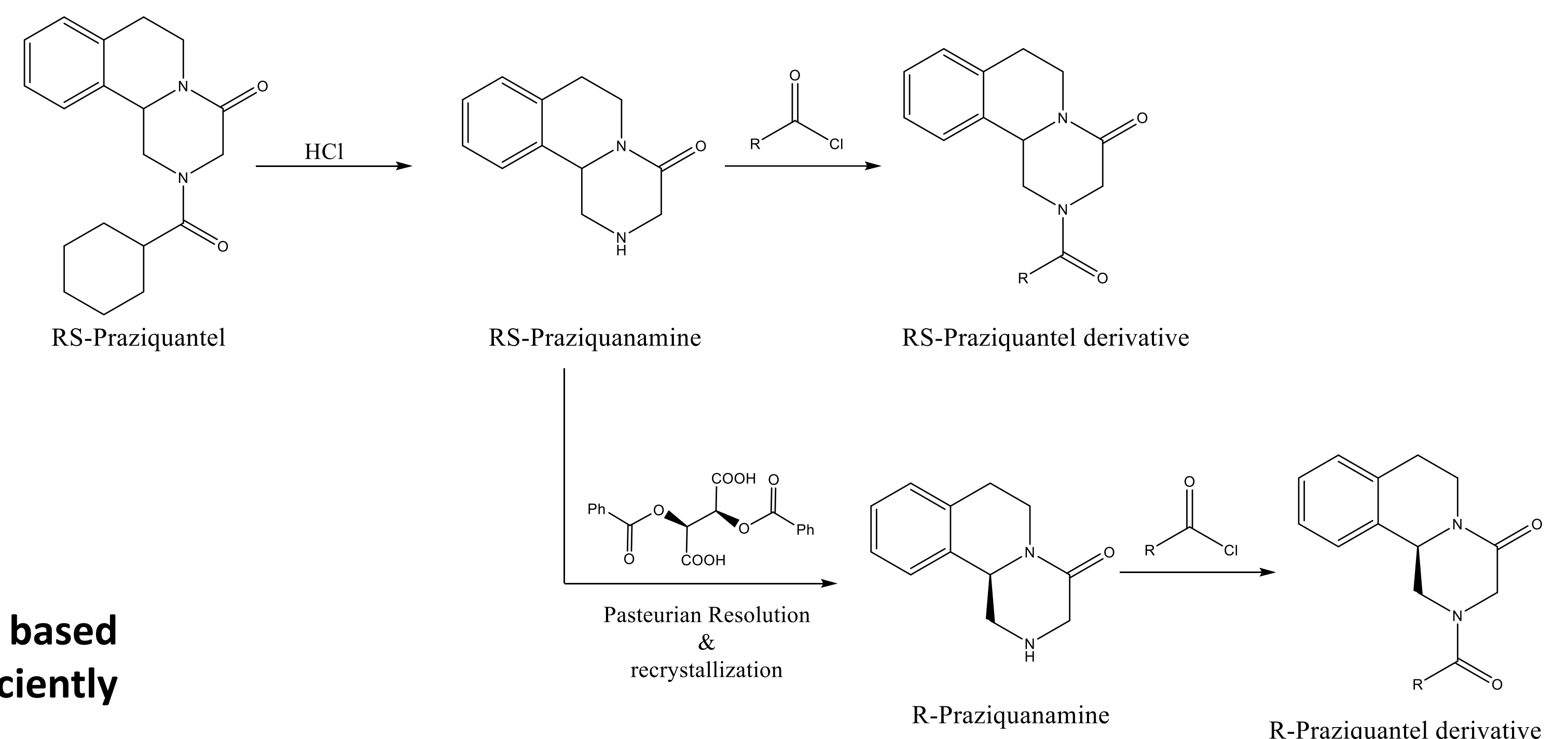
Introduction

Praziquantel is a medicine against the parasitic worm infection schistosomiasis marketed as a racemic mixture while only the R-enantiomer is active. Praziquantel is crystallizing as a racemic compound and therefore crystallization-enhanced resolution methods cannot be applied directly. We need access to enantiopure derivatives of praziquantel to study their conglomerate formation, crystal structure and crystallization behavior.^[1]

Woelfle *et al.* reported a two steps Pasteurian resolution of Praziquanamine : ^[2]

Step	IPA / H ₂ O Solvent ratio	Crystallization temperature (°C)	Yield (%)	ee (%)
1	Resolution in 4:1	20	88	79
2	Recrystallization in 3:2	5	66	97

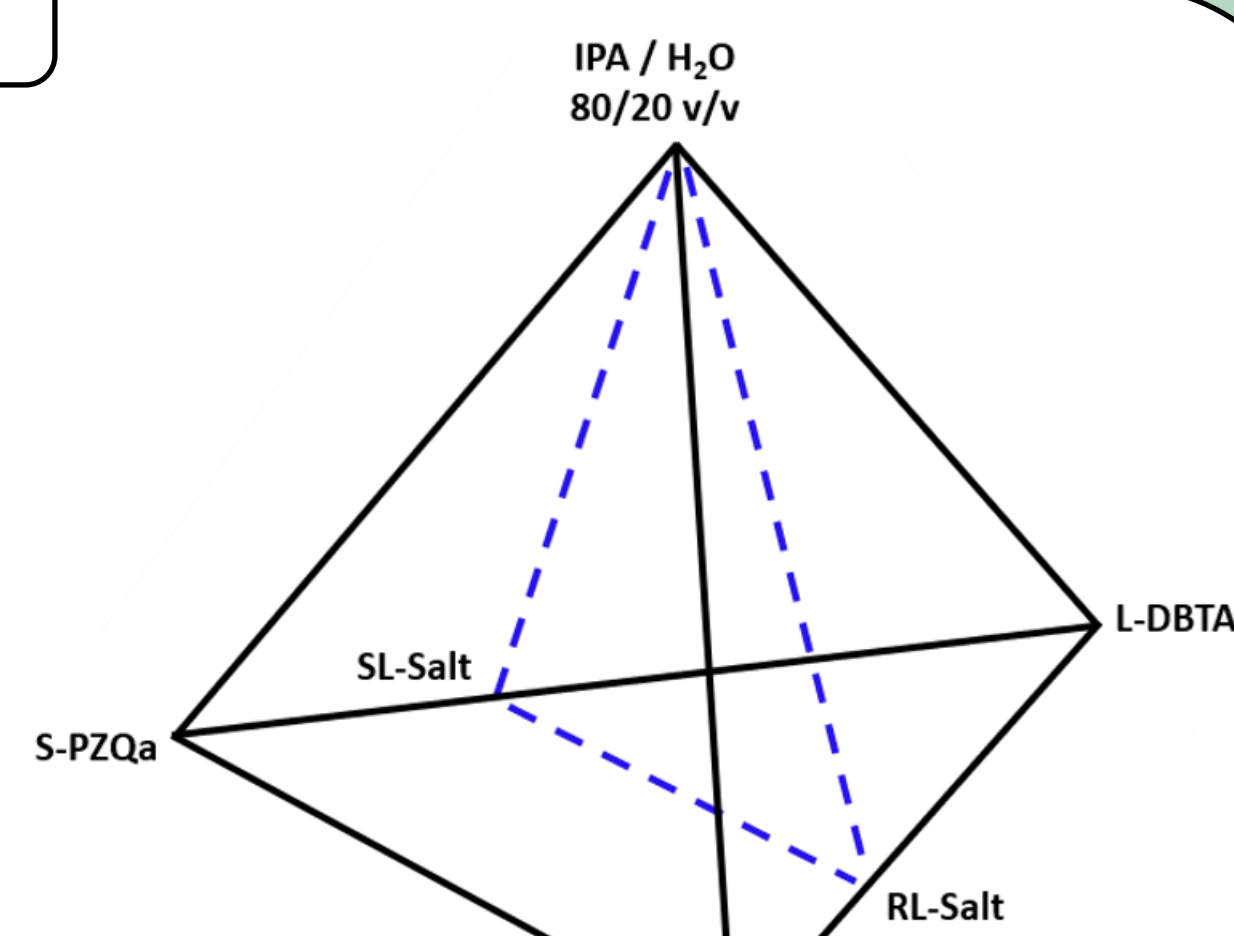
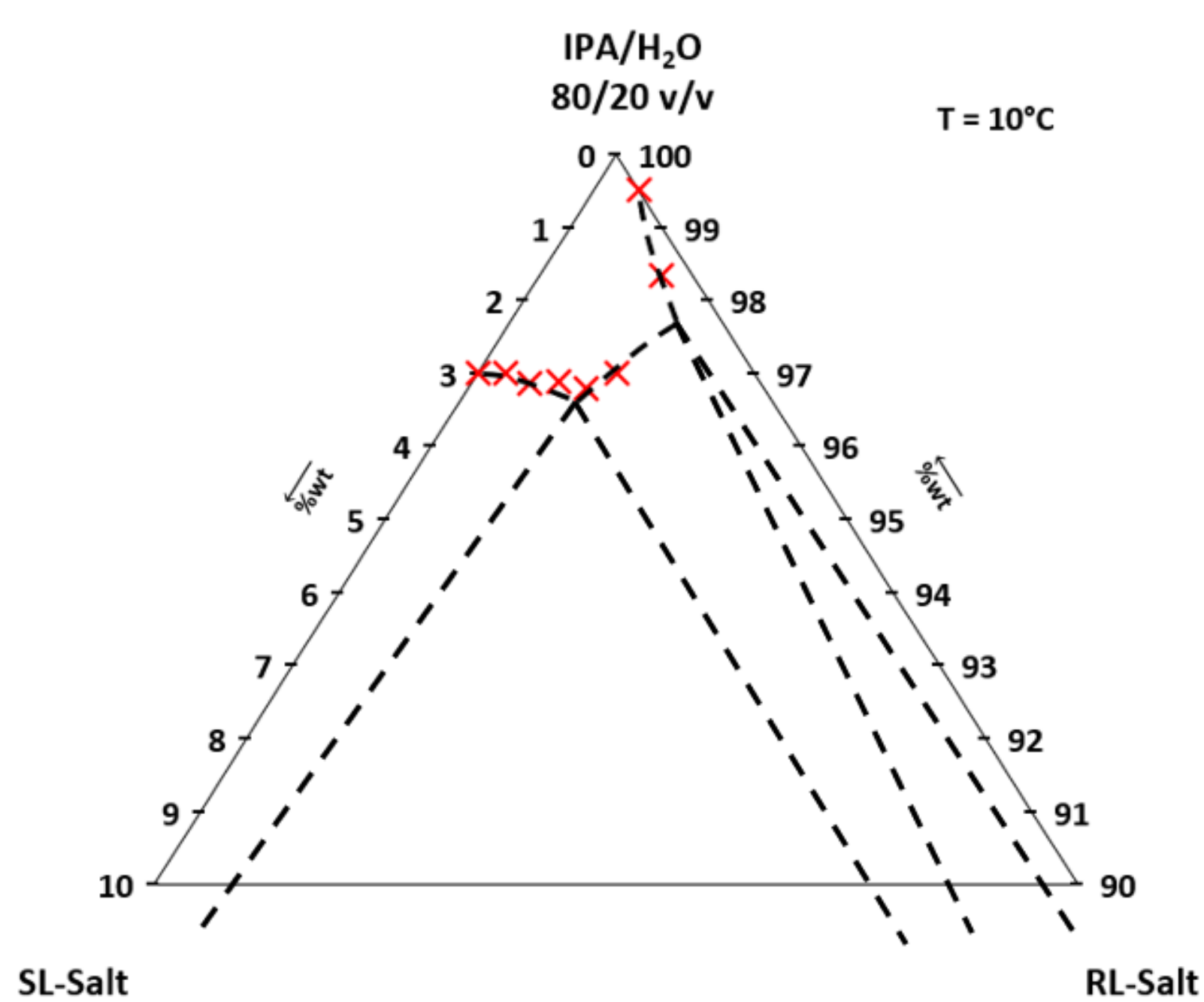
In this context, we aim to optimize the resolution of praziquanamine based on the knowledge of the quaternary phase diagram in order to efficiently obtain enantiopure praziquanamine in high yield and purity.



Solubility

Quaternary system :

- R-PZQa / S-PZQa / L-DBTA / IPA-H₂O (80/20 v/v)

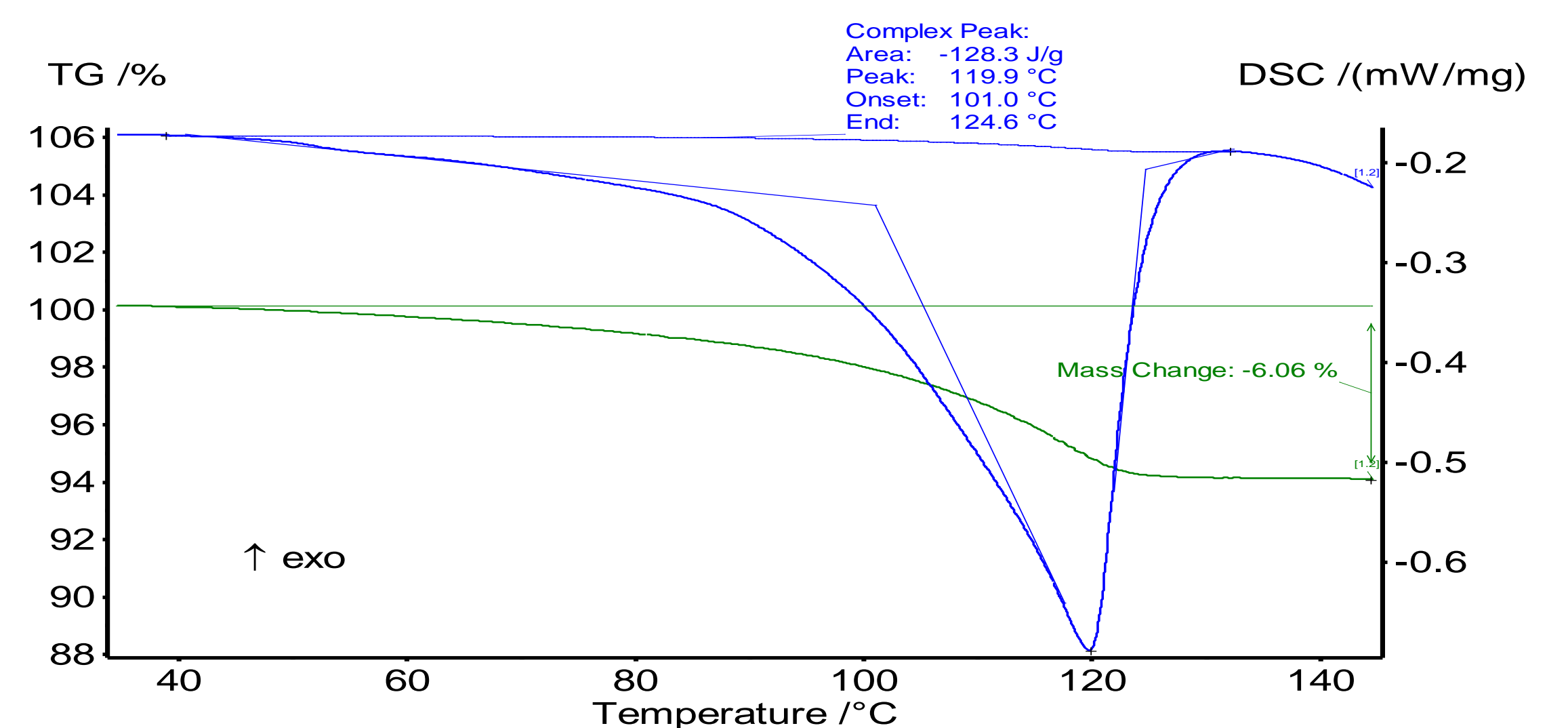


The solubility curves are consistent for 3 different solid phases.

What are the solid phases in equilibrium in this system?

Solid state behavior

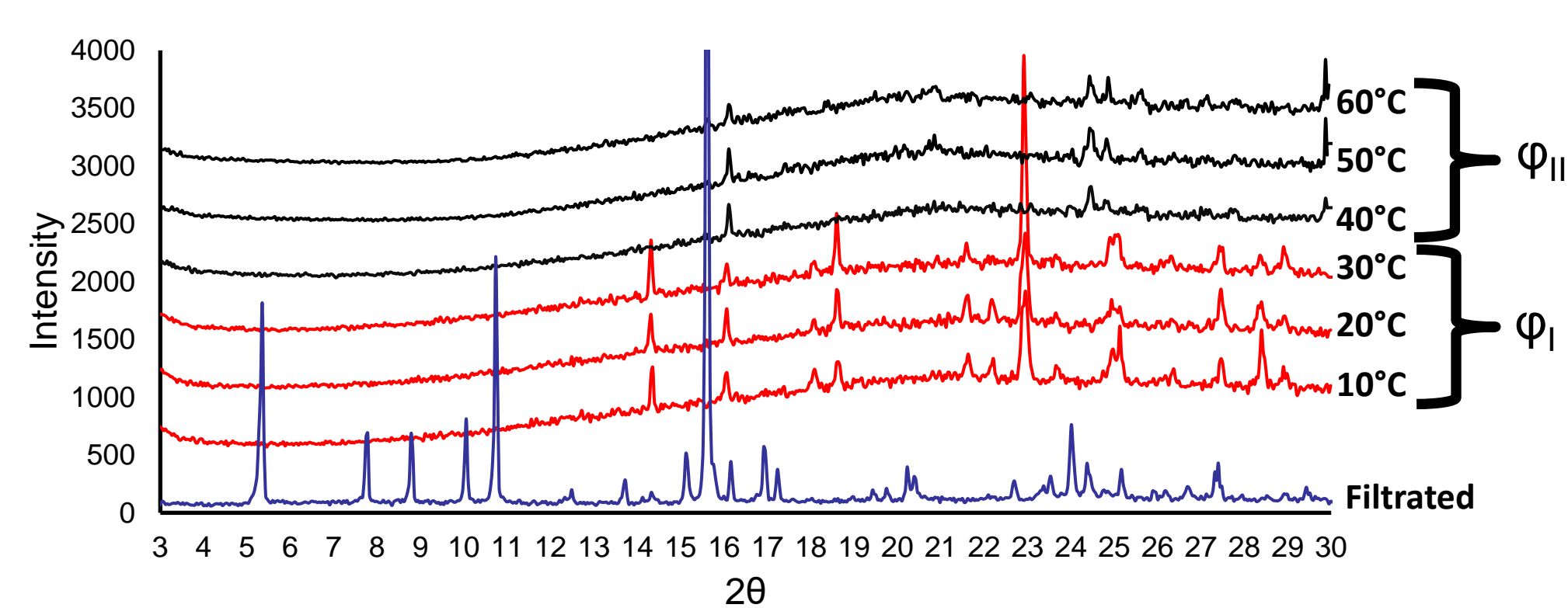
TGA-DSC on recrystallized RL-Salt (>99%ee) obtained by Pasteurian resolution :



Mass loss corresponding to a dihydrate salt : R-PZQa_L-DBTA•2H₂O

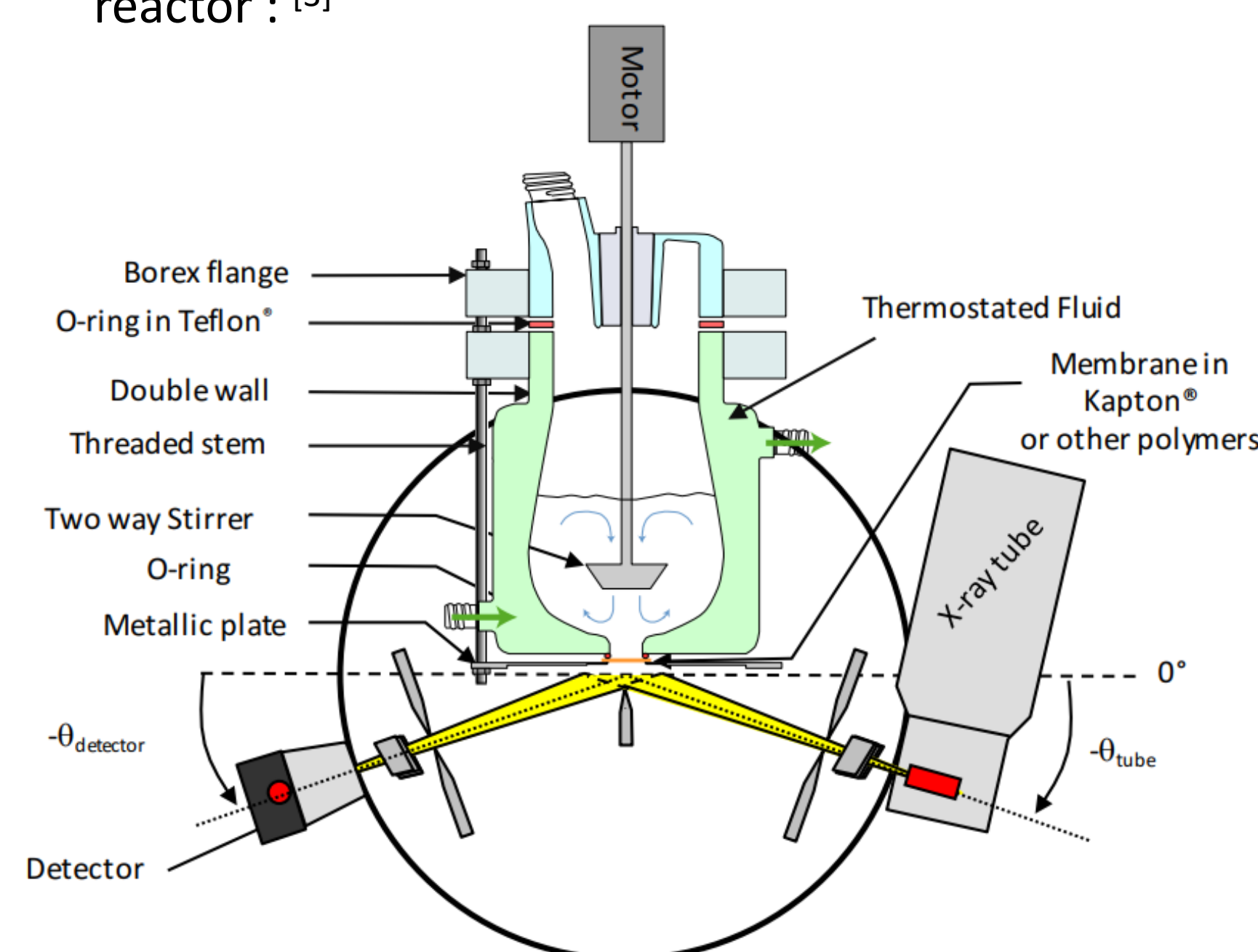
Suspension behavior

InSitu XRPD of 1:1 PZQa_L-DBTA in IPA/H₂O solvent at different temperature :

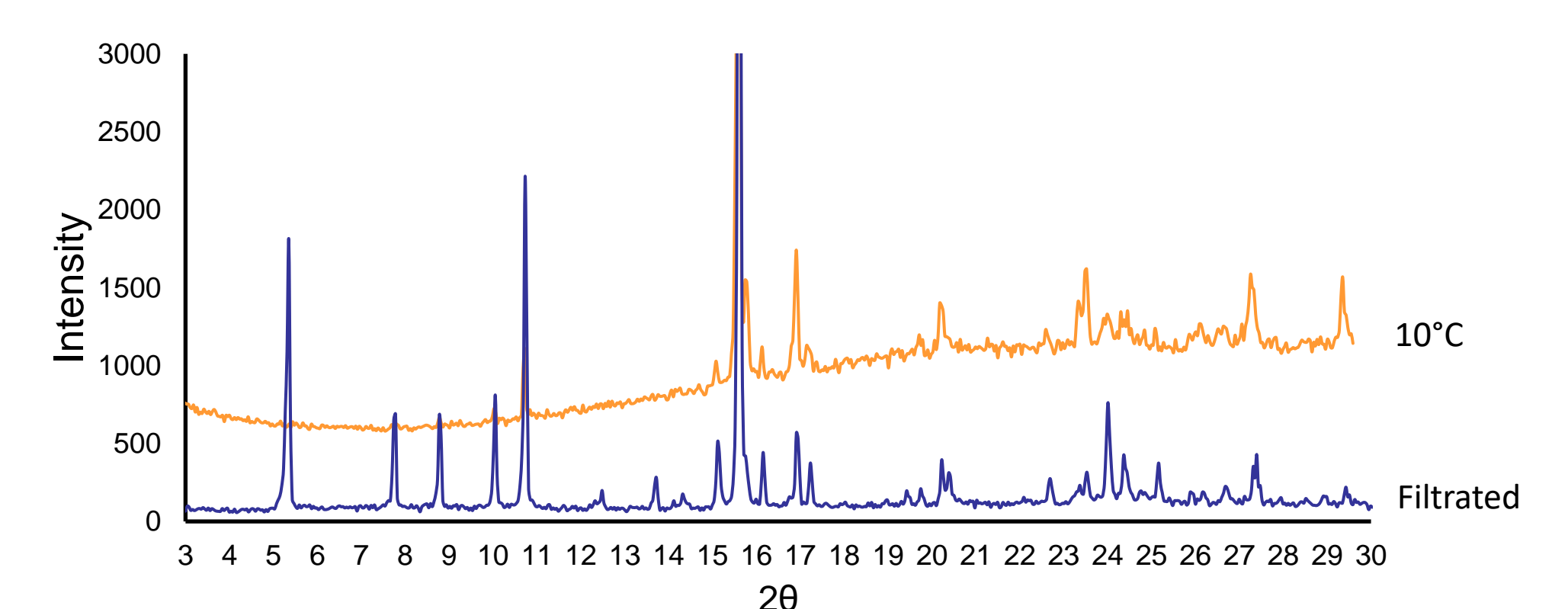


- Different solid phases in suspension at an equimolar ratio PZQa_L-DBTA
- Transition $\phi_I \rightarrow \phi_{II}$ above 30°C
- Solid phase transformation after filtration $\phi_I \rightarrow$ R-PZQa_L-DBTA•2H₂O

Schematic view of InSituX[®] diffractometer and reactor : ^[3]



InSitu XRPD of recrystallized salt (>99%ee) obtained by Pasteurian resolution in IPA/H₂O solvent :



R-PZQa_L-DBTA•2H₂O stable in suspension at an equimolar ratio R-PZQa_L-DBTA

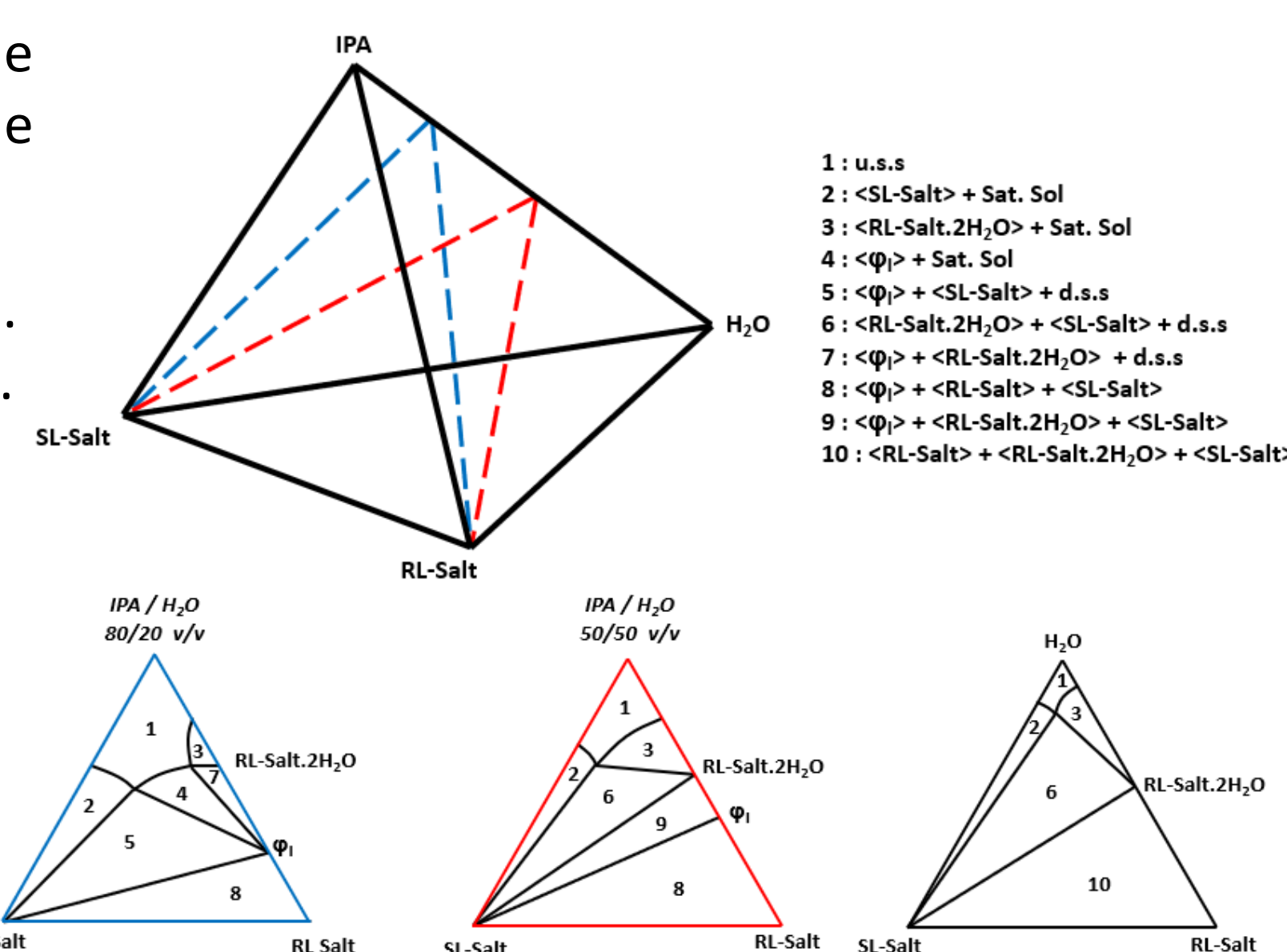
Optimization

Hypothesis : increasing the amount of water will promote the phase domain of the dihydrate salt improving the enantiomeric excess of the first step.

- 1:1 IPA / H₂O : Higher enantiomeric excess but lower yield.
- 0:1 IPA / H₂O : Lower enantiomeric excess and lower yield.

IPA / H ₂ O Solvent ratio	temperature (°C)	Yield (%)	ee (%) ¹
4:1	10	40	90
1:1	20	44	96
0:1	20	42	< 10

¹Determined by polarimetry; $[\alpha]_D^{20} = -306$ ^[2]



Conclusion

Solid phases ϕ_I and ϕ_{II} are stable in solution but transform to a dihydrate salt upon filtration.

The optimization of the Pasteurian resolution using different solvent mixtures showed that

- Increasing the amount of water up to 50%vol gives a higher ee but a lower yield in the first step than the previously reported resolution. ^[2]
- The low ee obtained at increased water fractions can be explained by the low solubility of both salt in this solvent.
- A recrystallization step is still needed to obtain enantiopure praziquanamine.

[1] Valenti, G., Tinnemans, P., Baglai, I., Noorduyn, W.L., Kaptein, B., Leeman, M., ter Horst, J.H., Kellogg, R.M., (2021), *Angew. Chem. Int. Ed.*, 60: 5279-5282.

[2] Woelfle, M., Seerden, J.-P., De Gooijer, J., Pouwer, K., Olliaro, P. and Todd M.H. (2011), *PLoS Negl Trop Dis*, 5(9): e1260.

[3] Coquerel, G., Sanselme, M. and Lafontaine A. (2016), WO2012/136921 A1.