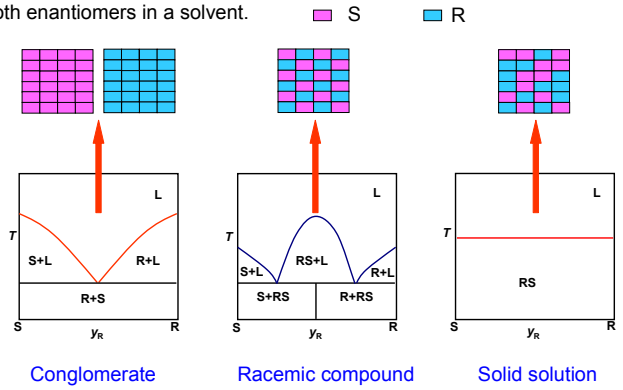
Racemic Compound, Conglomerate, or Solid Solution: Phase Diagram Screening of Chiral Compounds

S. Srisanga, J.H. ter Horst*
Intensified Reaction and Separation Systems, Process & Energy Laboratory,
Delft University of Technology, Leeghwaterstraat 44, 2628CA Delft, The Netherlands

Introduction

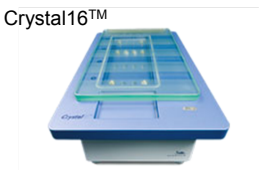
The kind of solid state of a chiral compound has important implications for resolution through crystallization [1]. It is reflected in the *binary phase diagram* [2]. The phase diagram thus gives important information on the possibility of chiral resolution through crystallization. A fast screening method for the ternary phase diagram of a chiral compound would therefore be beneficial. We propose a fast and simple screening method based on saturation temperature measurements of mixed compositions of both enantiomers in a solvent.

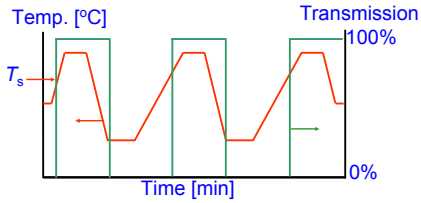


Conglomerate Racemic compound Solid solution

Experimental

- *Equipment*: Crystal16™ of Avantium Technologies
- *Measurement*: saturation temperatures measurement of the mixtures of enantiomers in different solvents
- *Saturation temperature*: temperature at the point the suspension becomes a clear solution upon heating (at 0.5°C per minute)
- *Stirring speed*: 700 rpm





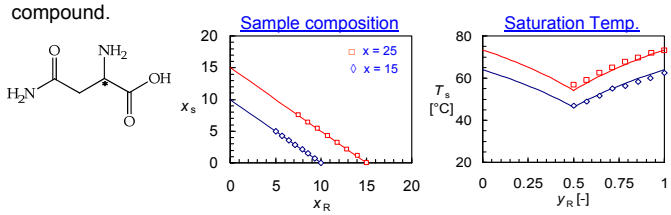
Nomenclature

L = liquid
R = enantiomer R
S = enantiomer S
RS = racemic mixture (50%R+50%S)
T_s = saturation temperature [°C]
x = mole fraction [mmol/mol]
y_R = (solvent free) R-enantiomer fraction

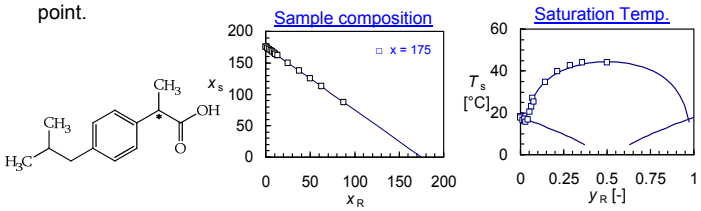
$$y_R = \frac{x_R}{x_R + x_S}$$

Results and discussion

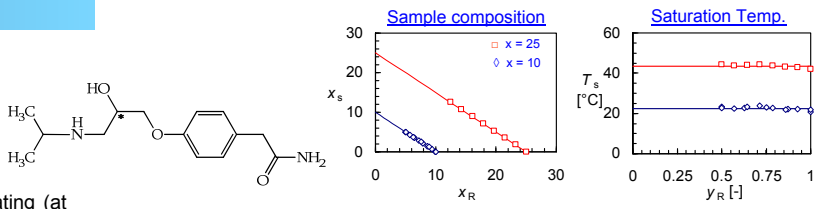
By screening the saturation temperature along y_R at a constant total amount, $x = x_R + x_S$, of enantiomer (left graph of each studied compound) effectively a *pseudo-binary diagram* is determined (right graph). The contour of the measured saturation temperature in the pseudo-binary phase diagram then identify the kind of solid state of the chiral compound.



Asparagine in water behaves as a *conglomerate*, with only one eutectic point.



The phase diagram screening of *ibuprofen in hexane* shows two eutectic points which represent the *racemic compound* behavior.



The near constant saturation temperatures of the series of measurements of *atenolol in ethanol* suggest atenolol to be a *solid solution*.

Conclusion

The phase diagram screening method is a new interesting way to establish the solid state behavior of chiral compounds.

Acknowledgements

The authors thank Somnath Kadam and Herman Kramer for providing RS-ibuprofen materials and solubility data.

References

1. G. Coquerel, *Top Curr Chem* 269 (2007) 1-51
2. J. Jacques, A. Collet, S.H. Wilen. John Wiley & Sons, New York (USA), 1981

Corresponding email: J.H.terHorst@TUDelft.nl