Polimorphism of R-encenicline hydrochloride:

Access to the highest number of structurally characterized polymorphs using desolvation of varius solvates

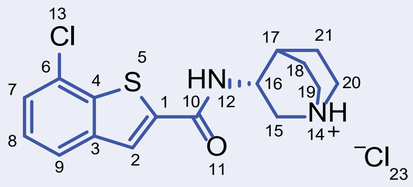
Artis Kons[a], Agris Bērziņš[a] and Toms Rekis[b]

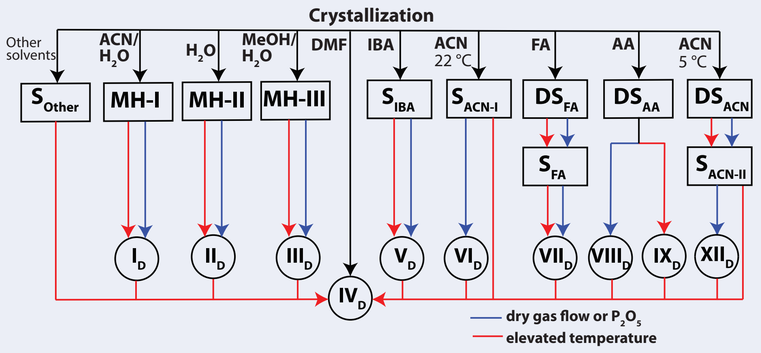
a - Faculty of Chemistry, University of Latvia, Riga, Latvia
b - Laboratory of Crystallography, University of Bayreuth, Bayreuth, Germany

UNIVERSITY OF LATVIA ANNO 1919
FLPP FUNDAMENTAL AND APPLIED RESEARCH PROJECTS
LATVIJAS UNIVERSITĀTES FONDS

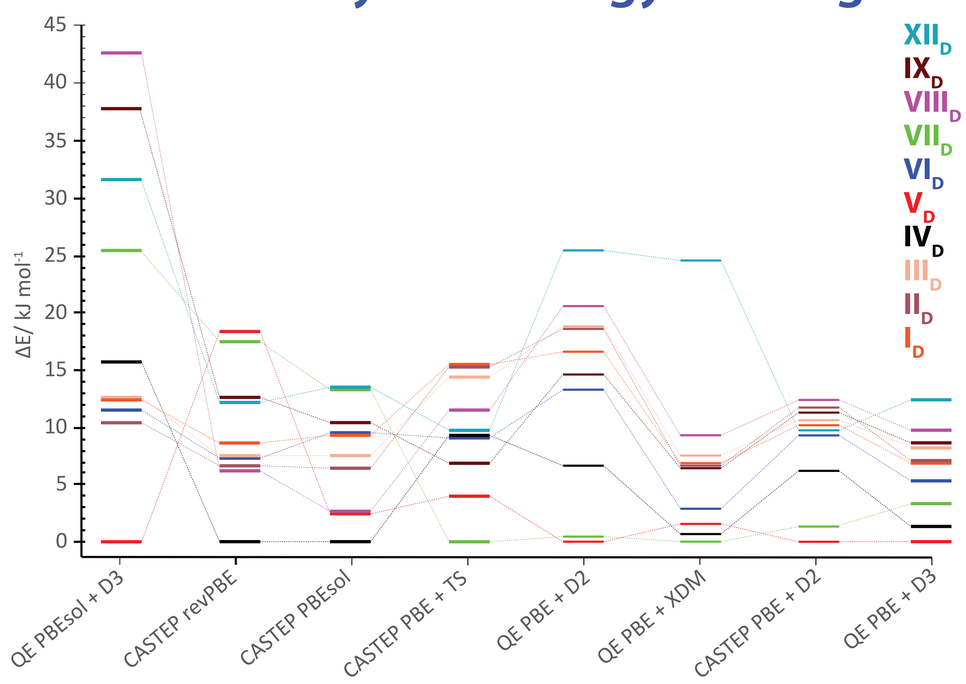
Introduction

In a study of the solid form landscape of R- encenicline hydrochloride, it was found that this compound forms at least 30 solvates and 12 neat polymorphs and presents the first published example of polymorphism with a record breaking 10 solved crystal structures. All thermodynamically metastable polymorphscan be accessed only through desolvation of various hydrates/solvates.





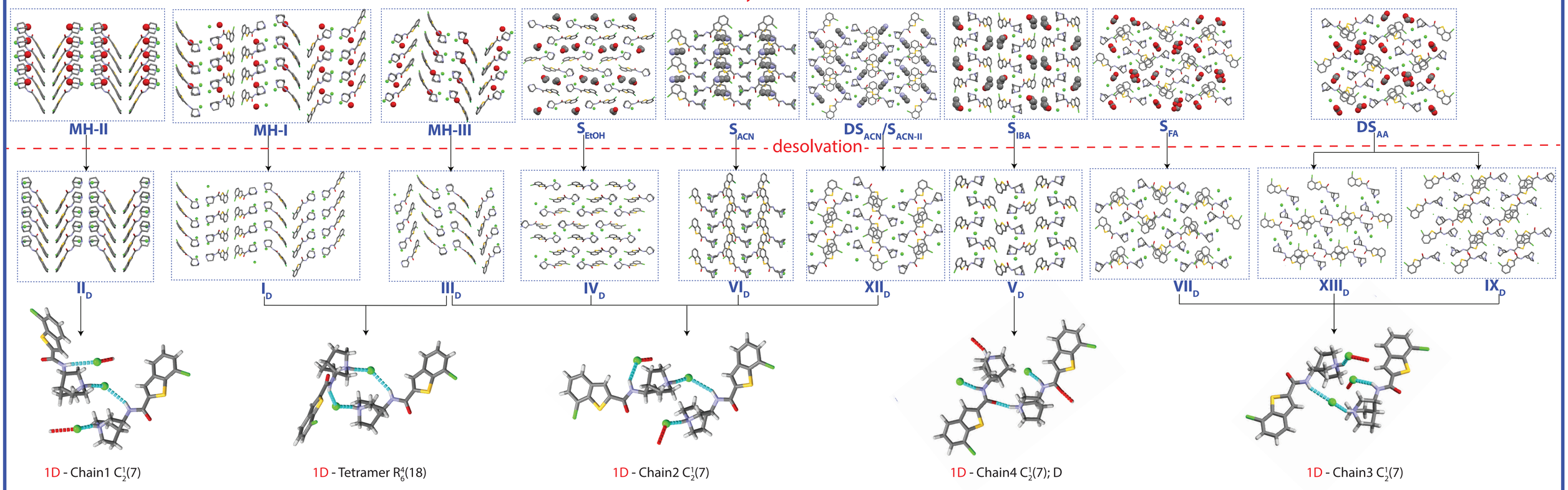
Stability and energy ranking

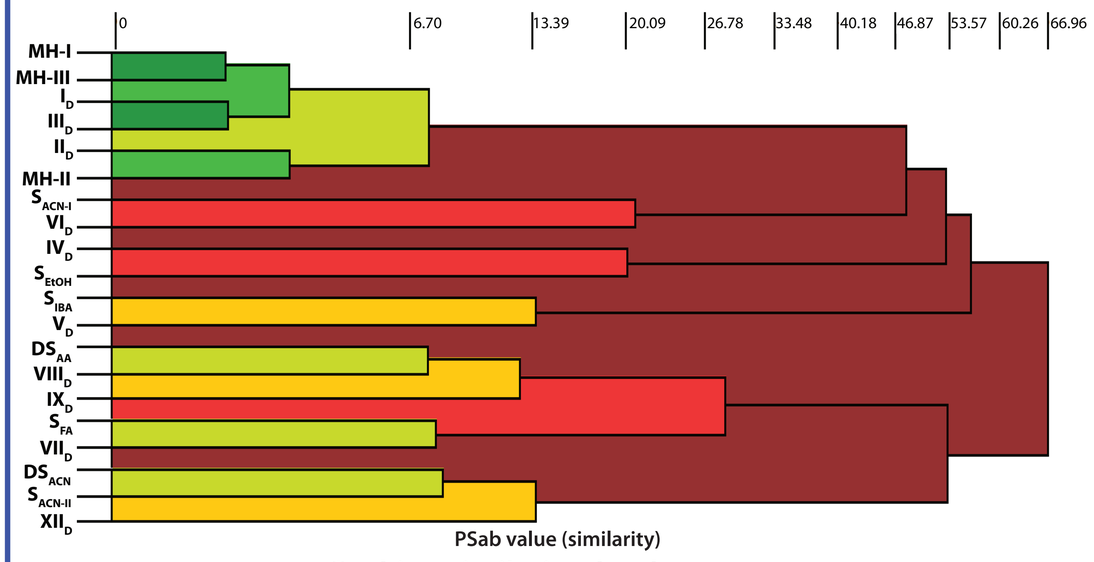


Energy rankings for fully optimized structures using different pseudopotentials and/ or dispersion corrections

- In slurry bridging experiments under ambient conditions in n-heptane, all polymorphs converted to form $\mathbf{IV}_D$
- According to the heat of transition rule $\mathbf{V}_D$ and $\mathbf{IV}_D$ have an enantiotropic thermodynamic relationship
- Polymorph $\mathbf{IV}_D$ exhibits the highest melting point (286 ± 1 °C) and heat of fusion 21 ± 2 kJ mol^{-1} , while all the other polymorphs convert to form $\mathbf{IV}_D$ during the heating
- Overall, the PBE +D3 computational approach yields the most reliable energy ranking and all ten polymorphs are located within the range of 12.2 kJ mol^{-1}

Crystal packing similarity





Packing similarity dendrogram

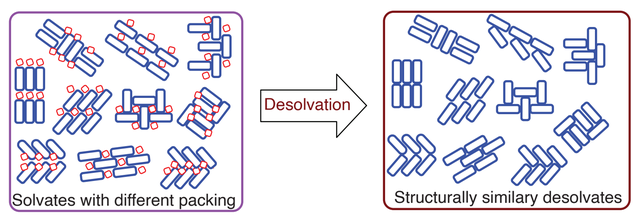
- The space groups of the polymorphs are the same as those of the corresponding precursor solvates, and even the lattice parameters in most of the solvate–desolvate pairs are similar.
- The driving force for the formation of the analyzed solvates mainly seems to be the incorporation of solvent molecules to reduce the void space
- In the desolvatiom process the characteristic hydrogen bond network and packing present in the solvates are always maintained
- In monohydrates water compensates for the unsatisfied hydrogen bond acceptors present in the dehydrates and forms more complex hydrogen bonding networks
- From the packing similarity dendrogram, it can be identified that in all cases the closest packing characteristics are between precursor solvates and their respective desolvated phases

Acknowledgement

This research has been funded by the Latvian Council of Science, project “Crystal Engineering of Pharmaceutical Multicomponent Phases for More Efficient Crystalline Phase Design,” project No. lzp-2018/1-0312 and University of Latvia Foundation troughAS “Mikrotikls” supported project “Development of Integrated Experimental and Computer Modeling Research Methodology for Prediction of the Properties and Diversity of Phases of Active Pharmaceutical Solids.”

For more information see article:

10.1021/acs.cgd.9b00648



Presented @ 32nd European Crystallographic Meeting, Vienna (Austria) 2019