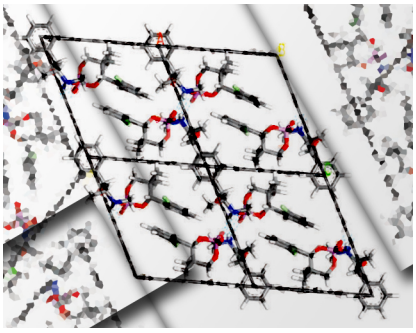
CASE STUDY

CRYSTAL STRUCTURE PREDICTION OF DIASTEREOMERIC SALTS: A STEP TOWARDS THE RATIONALIZATION OF RACEMATE RESOLUTION



The Accelrys Polymorph predictor empowers the innovation in solidstate poreprties; for example in racemate resolution a key step in the purification of synthesised materials and chemical substances.

Key Product

- Polymorph Predictor™

Industry sector

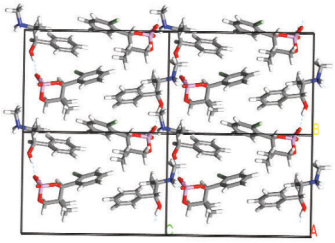
- Pharmaceutical

Researchers at Accelrys have used Polymorph Predictor™ to examine the solid state packing alternatives of diastereomeric salts. The simulations potentially lead to a predictive model for racemate resolution by preferential crystallization of diastereomeric salts.

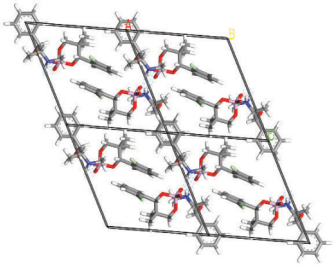
As the two enantiomers of a compound often have profoundly different properties, chirality is very important in science. For example, a chemical can be either a ß-blocker or a contraceptive depending on its chirality, or one can taste either bitter or sweet.

When a chiral compound can not be obtained in an optically pure form either by synthesis or isolation from natural products, the racemate can be separated into its enantiomers by co-crystallization with a resolving agent, an optically pure acid or base, resulting in two diastereomeric salts with different structures and important physical properties, e.g. solubility.

Finding what would be an ideal resolving agent requires a predictive model of the crystal packing alternatives for both diastereomers. Using a thermodynamic model,[1] the resolution efficiency of a



Predicted crystal structure of the global minimum of the n-sal



Predicted crystal structure of the global minimum of the p-salt

candidate resolving agent is indicated by the energy difference between the global energy minima found for the two diastereomeric salts. With the increase in computing power, validated crystal structure prediction methods from the knowledge of just the contents of the asymmetric unit cell are now available.[2]

Using Polymorph Predictor, crystal structure prediction simulations were carried out to explore the solid state packing alternatives of a pair of diastereomeric salts of a chlorine-substituted cyclic phosphoric acid (the resolving agent, also called cyclophos) and the two enantiomers of ephedrine. Judging by the lattice energies for the predicted global minima, the n-salt is more stable than the p-salt, agreeing with the experimental observation. Note that the naming convention of the diastereomeric salts is based on the optical activity of the co-crystallizing acid and base molecules, so that the (++) or (- -) salt is denoted the p-salt and the (+ -) or (- +) salt is denoted the n-salt.

The resolution efficiency for ephedrine by cyclophos was predicted to be 0.61 according to the energy difference between the two global minima. Although this value is less than half the experimental value of 1.37, the result is encouraging considering the complexity of these calculations.

Three experimentally observed diasteromeric salts (two polymorphic forms for n-salt and one p-salt) were correctly predicted with an error in calculated lattice energy of less than 3 kcal/mol.[1] This represents a significant achievement in crystal structure prediction due to the complexity of the mathematical search problem at hand (two distinct molecules in the asymmetric unit, one of which is flexible) and due to the complex energetics of these organic salts.

The study indicates that the simulations could help reduce a list of potential resolving agents to the most promising candidates. Such computational approach potentially lead to a predictive model for racemate resolution by preferential crystallization of diastereomeric salts.

To learn more about Materials Studio by Accelrys, go to **accelrys.com/materials-studio**

REFERENCES

1. F. J. J. Leusen, J. Cryst. Growth & Design, 2003, , 189-192.
2. 'Computational Approaches to Crystal Structure and Polymorph Prediction,' F.J.J. Leusen, S. Wilke, P. Verwer, and G.E. Engel, in Implications of Molecular and Materials Structure for New Technologies, NATO Science Series E, J.A.K. Howard, F.H. Allen, and G.P. Shields, Eds., Kluwer Academic:Dordrecht, The Netherlands, 1999, volume 360, 303-314