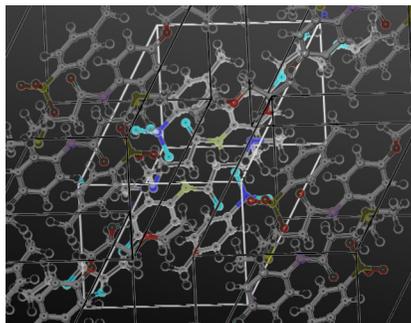


CRYSTAL STRUCTURE SOLUTION OF A METASTABLE POLYMORPH FROM POWDER X-RAY DIFFRACTION DATA



“Reflex Plus part of materials studio was key in identifying a minor and unstable phase in our solid state system”

Dr. Rui Tamura
Kyoto University

Key Product

- MS Modeling Reflex Plus

Industry sector

- Pharmaceutical

Organizations

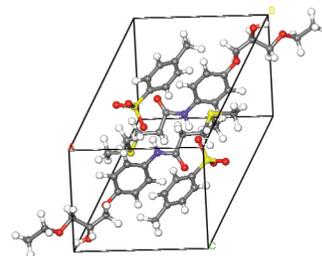
- Taiho Pharmaceutical Co. Ltd
- Japan Kyoto University, Japan

Researchers at the Taiho Pharmaceutical Co. Ltd, Japan, and Kyoto University, Japan, have used MS Modeling’s Reflex Plus to determine the crystal structure of a metastable polymorph of a racemic sulfonium *p*-toluenesulfonate.

The study successfully showed that the crystal structure of a metastable polymorph could be determined successfully by using its powder X-ray diffraction data measured with laboratory X-ray sources.

This finding will aid the crystal engineering of organic materials, in particular in the pharmaceutical industry.

The control of polymorphism is an important subject, especially in the pharmaceutical industry. This is because polymorph properties, such as electric and thermal conductivity, color, magnetism, thermal stability, solubility, and dissociation rate vary widely. It is vital that researchers involved in the formulation of crystalline products be able to select the polymorph with correct properties and anticipate problems such as unwanted crystallization of other polymorphs. Also, the control of



Crystal structure of the δ -form of (+/-)-1

polymorphism will lead to the knowledge of the mechanism of multistage polymorphic transitions - the process of nucleation or crystal growth at the beginning of crystallization from solvents.

With this in mind, researchers at the Taiho Pharmaceutical Co. Ltd, Japan and Kyoto University, Japan, used modeling to study one of the metastable polymorphs of (+/-)-[2-[4-(3-ethoxy-2-hydroxypropoxy) phenylcarbamoyl]- ethyl]dimethylsulfonium

p-toluenesulfonate (**1**).¹ The scientists chose compound **1** as it shows an unusual enantiomeric resolution caused by polymorphic transition during the crystallization of racemic mixed crystals - a process known as preferential enrichment.

The desired δ -form crystals of (+/-)-**1** were first obtained by selective crystallization. A supersaturated solution of **1** was pseudoseeded with the δ -form seed crystals of an analogous compound. δ -form crystals of (+/-)-**1** were obtained as a monophasic powder sample.

Powder X-ray diffraction patterns for the obtained δ -form crystals were recorded and then used for crystal structure determination by using MS Modeling's Reflex Plus.

The study confirmed the existence of the metastable δ -polymorphic form of (+/-)-**1**. The metastability of the δ -form crystal has been rationalized on the basis of its crystal structure. As the methodology used is applicable to other systems in which the occurrence of polymorphic transition from metastable to stable occurs during crystallization, the techniques used can be applied in crystal engineering.

Using the same technique, the researchers reported² a new mode of the solvent-assisted solid-to-solid transformation of the first-formed and least stable Y-polymorphic form into the most stable ϵ -polymorphic form occurring during crystallization from the supersaturated EtOH solution of (+/-)-[2-[4-(3-ethoxy-2-hydroxypropoxy)phenylcarbamoyl]ethyl]trimethylammonium benzenesulfonate [(+/-)-**2**], also showing the unusual enantiomeric resolution phenomenon called preferential enrichment. The crystal structure of the new ϵ -form was determined once again with Reflex Plus. The mechanism of the polymorphic transition was elucidated by comparing the crystal structure of the Y-form with that of the ϵ -form.

Dr. Rui Tamura, Kyoto University, said, "It is now possible to easily solve the crystal structures of the metastable polymorphs or the stable polymorphs formed after exhaustive polymorphic transitions, which are usually obtained as the powder samples."

"Reflex Plus was invaluable in this work because it enabled us to study the mechanism of preferential enrichment, caused by polymorphic transition during crystallization of a certain kind of racemic mixed crystals (pseudoracemates or solid solutions) of the two enantiomers. This could not be done without the software."

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

REFERENCES

1. H. Miura, T. Ushio, K. Nagai, D. Fujimoto, Z. Lepp, H. Takahashi, and R. Tamura, *J. Cryst. Growth & Design*, 2003, **3(6)**, 959-965.
2. H. Miura, T. Ushio, K. Nagai, D. Fujimoto, Z. Lepp, H. Takahashi, and R. Tamura, *J. Cryst. Growth & Design*, 2003, **3(6)**, 973-979.