For fairly rigid,
non-ionic and ionic
molecules

Can provide vital
input for com-
pound patenting
and registration

MS Modeling Datasheet

Polymorph Predictor

Polymorph Predictor™ allows you to predict potential polymorphs of a given compound directly from the molecular structure. Polymorphism is the ability for a compound to crystallize in more than one chemically identical but crystallographically distinct form. Crystalline materials are prevalent in many industries, including pharmaceuticals, agrochemicals, pigments, dyes, explosives, and specialty chemicals. Polymorphs may differ in key properties such as shelf-life, bioavailability, solubility, morphology, vapor pressure, density, color, and shock sensitivity. It is therefore important to know how many polymorphs are possible as well as how their properties might differ when working in the solid state.

The challenges faced

Once a particular solid form of a material is chosen for its desired properties, researchers need to control the crystallization and formulation conditions so that unwanted polymorphs do not appear. In order to do so, they need to fully understand the structural aspects of each polymorph. This knowledge is also important for patenting and registration purposes.

The most common method for determining a crystal structure is to grow quality crystals for single crystal X-ray diffraction. Growing single crystals of appropriate size, however, is often difficult or even impossible. Furthermore, one can not be certain that all possible polymorphs have been discovered experimentally. Thus, methods that help predict potential stable and metastable crystal packing arrangements from the knowledge of just the contents of the asymmetric unit, would be extremely valuable.

What does Polymorph Predictor do?

Polymorph Predictor has been developed for polymorph prediction of fairly rigid, non-ionic or ionic molecules composed mostly of carbon, nitrogen, oxygen, and hydrogen (1, 2, 3). The approach is based on the generation of possible packing arrangements in all reasonable space groups to search for the low-lying minima in lattice energy.

Polymorph Predictor employs the following procedure:

- A fast and reliable Monte Carlo simulated annealing process (MC-SA) searches the lattice energy hypersurface for probable crystal packing alternatives, typically generating thousands of possible structures.
- Optionally, these potential structures are clustered into unique groups based on packing similarity.
- The geometry of each unique structure is optimized with respect to all degrees of freedom.
- The optimized structures are clustered again to remove duplicates.
- The final structures are ranked according to lattice energy.

The resulting low-energy crystal structures are potential polymorphs. Powder patterns simulated for these structures can be compared to experimental powder data for verification using MS Modeling's Reflex. Additionally, Rietveld refinement can be performed to optimize the agreement with the experimental powder data.

The Materials Studio advantage

Polymorph Predictor is operated within MS Modeling, Materials Studio®'s modeling and simulation suite. MS Modeling's integrated model building and editing tools enable you to construct, visualize, and manipulate molecular structures in an asymmetric unit or structures of crystalline solids (e.g. drugs, pigments, metal oxides, and zeolites).

Potential crystalline structures suggested by the Polymorph Predictor can be analyzed using MS Modeling's new spreadsheet-like table (called a study table) environment. The study table combines an easy association of structures and crystalline properties (e.g. space group, cell parameters, density, and energy

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for each structure) with powerful sorting and plotting functionality. It also provides a flexible and convenient way to evaluate additional structural properties for developing quantitative structure-property relationship models.

The potential crystalline structures can further be optimized using molecular mechanics tools (Discover, Forcite, and COMPASS), or quantum mechanics tools (VAMP, DMol^3, or CASTEP). Results can easily be shared with colleagues and copied to standard word processors, spreadsheets, and presentation packages.

How does Polymorph Predictor work?

The goal of Polymorph Predictor is to search for low-lying minima of a high-dimensional potential energy surfaces representing all possible packing arrangements of molecules in a crystalline environment as a function of space groups, lattice parameters, and contents of an asymmetric unit.
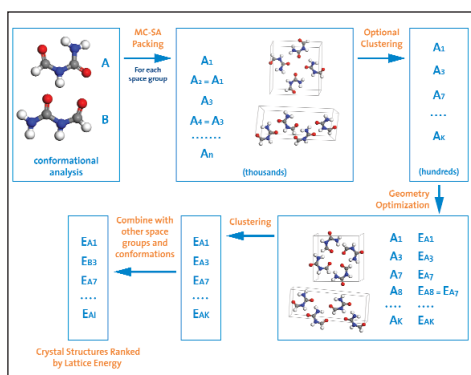
▲ *Polymorph Predictor workflow*

How does Polymorph Predictor benefit you?

Polymorphism has been recognized as a phenomenon that many industries are increasingly trying to control and exploit. The appearance of an undesirable polymorph late in product development can lead to costly delays. In order to control polymorphism, researchers need to understand how the crystal structures of each polymorph differ. Knowledge of polymorphic forms is also important for patenting and registration purposes. Polymorph Predictor searches for all possible packing arrangements of crystalline materials from their molecular structures. Once the different crystal structures are known, additional analyses can be performed to help explain other characteristics unique to each polymorph, including analysis of surface chemistry for different facets.

Researchers can define parameters for each step with an easy-to-use graphical user interface. The required input is the molecular structures of the contents of an asymmetric unit. The starting conformations of these molecules can be imported from an existing crystal structure or created using 3D Sketcher tools in Materials Visualizer and conformational analysis through dynamics simulations (Discover).

Polymorph Predictor can be utilized in two ways:
1. When experimental powder data is available, it may be used to aid the identification of the correct crystal structure from the list of generated trial structures using the Powder Comparison feature and to refine the structural parameters using the Rietveld method in Reflex.
2. Ab initio prediction of polymorphs when experimental powder data is not available.

Polymorph Predictor can be used alone or as the first step in a sophisticated structural analysis with other modules in MS Modeling. Materials Visualizer can be used to examine the packing arrangement and hydrogen bonding for each structure. In order to control crystal shape and growth, the surface chemistry can also be analyzed. Furthermore, if medium- to high-quality experimental powder data is available, Reflex Plus, better suited to analyze salts, solvates, and more flexible compounds, can be used to determine the structure directly from the powder data.

Polymorph Predictor, combined with other crystallization tools in MS Modeling, focuses the power of computational chemistry and molecular modeling on a problem with incredible commercial implications. The technology is well validated and robust compared to other existing algorithms (4, 5).

Features
Set Up
• The initial molecular structure can easily be imported from other sources or created using the 3D Sketcher within Materials Visualizer.
• Dynamics simulations allow for identification of low-energy conformations to be used as starting struc-structures in the simulation.

- A variety of force fields, as well as quantum mechanics techniques, are available for calculating atomic charges and molecular geometries providing flexibility in the energy calculations.
- Crystals with more than one molecule in the asymmetric unit can be considered.
- Multiple default settings allow for simple operations, or advanced users can adjust individual simulation parameters as necessary.
- The default settings include the 10 most popular space groups which account for over 85% of all published organic crystal structures, while all possible space groups can be examined.

Running Jobs
- All Polymorph Predictor jobs are run in the background freeing up the MS Modeling client for other research.
- All Polymorph Predictor jobs can be submitted to remote computer servers.

Results
- Simulation results for each space group are stored in trajectory files for further analysis.

Analysis
- Analysis is carried out with the help of spreadsheet-like tables, called study tables.
- Multiple trajectories files (e.g. corresponding to different space groups) can be imported into a study table to be analyzed simultaneously.
- When each trajectory file is loaded, various properties such as space group, energy and cell parameters, are automatically entered into the study table as well.
- Each crystal structure is embedded in the study table, which can be viewed independently and displayed along with various properties.
- The Powder Comparison analysis feature allows for the automated quantitative comparison of experimental powder data to simulated powder patterns for each generated structure.
- The Crystal Similarity Measure analysis feature allows for the automated quantitative comparison of experimentally determined crystal structure to each generated structure.
- A variety of property calculations, including Powder Comparison and Crystal Similarity measures, can be carried out on all or a subset of the crystal structures in a study table.
- Crystal structures in a study table can be sorted according to one or more properties, e.g. total energy, or density.
- A user specified subset can be filtered out from a study table into a new table.
- All or part of a study table can be copied and pasted into Microsoft Excel® and Microsoft Word®.
- Flexible graph plotting enables plotting property distribution for each property and two properties against each other, and plotting to a selected subset.
- Chart and study table documents are interactive.

References

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System Details

Operated through the MS Modeling user interface on Windows® 2000 and XP. CPU intensive Polymorph calculations can be executed on Windows ® 2000, 2003, XP, SGI IRIX, Red Hat Linux IA32.