“Archetype structures” link disorder, polymorphism, and solid solutions via energy

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Keywords: Disorder, Quantum Crystallography, Polymorphism, Solid Solutions

The concept of “archetype structure” links disorder to polymorphism and solid solutions [1], since non-disordered archetypes obtained experimentally in pure form, i.e., without disorder, would be considered polymorphs, or different components of a solid solution. Archetype structures also provide a rationale why disorder occurs based on energy [2] (together with other relevant criteria [3]). Further concept applicability is to crystal structures with solvent disorder on special positions. These systems crystallize as an overlay of archetypes, usually through adding translation symmetry when the solvent itself has higher molecular symmetry. A lower-symmetry subgroup of an experimentally found average structure of higher symmetry (an aristotype [4]) is then observed for the archetype. Several examples from the drug subset [5] of the CSD were evaluated and will be presented.

The concept directly leads to a new practice of modelling disorder in experimental least-squares (LSQ) refinement, where a structural archetype is contributing to an average structure composed of non-disordered components. In this practice, archetypes are initially extracted from a disordered crystal structure – as if each component was not disordered – to provide input for separate quantum mechanical (QM) optimization. When subsequently recombining optimized atomic coordinates of an archetype into a structural model, overlapping atoms would not permit LSQ refinement of their atomic position and displacement parameters due to parameter correlation (depending on experimental resolution and extent of pseudo-symmetry). Therefore, we incorporate structure-specific restraints from QM geometry optimization in refinement, and an entire archetype, rather than only disordered atoms, is assigned a disorder PART. To generate 1,2 (bond distance DFIX) and 1,3 (bond angle DANG) restraints for avoiding hard EXYZ constraints for proximate atoms, we rely on results from molecule-in-cluster (MIC) optimization [6]; proximate atoms however share their atomic displacement parameters (ADPs) via EADP constraints. We convert computational output to SHELXL input with the program BAERLAUCH [7].

Starting from experimental input (single-crystal X-ray, electron, or powder diffraction) subdivided into archetypes, MIC optimisation of the asymmetric unit content in a cluster of molecules then does not only provide restraints but permits cross-validation of structural model and quantum chemical results. It was found that the energy of the asymmetric unit of archetypes forming a disordered average structure is within very tight bounds, usually within RT, with T being the temperature and R the ideal gas constant [2]. Another aspect of MIC optimization is that it makes series of structures comparable when different experimental resolution and data quality are encountered. Overall “archetype structures” are useful from a quantum crystallographic point of view, since archetypes link structure and energy, the essence of quantum crystallography. To accurately quantify energy differences or to support that energetic equality (or similarity) underlies symmetry, we use density functional theory with dispersion correction (DFT-D). Such DFT-D energies of molecules in crystal structures can e.g. be obtained from ONIOM [8] energy partitioning.

Ultimately energy-based analysis using archetypes can be useful in real life application. It can for example guide practical applications in the pharmaceutical industry, as illustrated for predicting cocystal formation for guiding experimental screening [9].


We would like to acknowledge T. Wager and H. Moebitz for support and P. Müller for discussions.