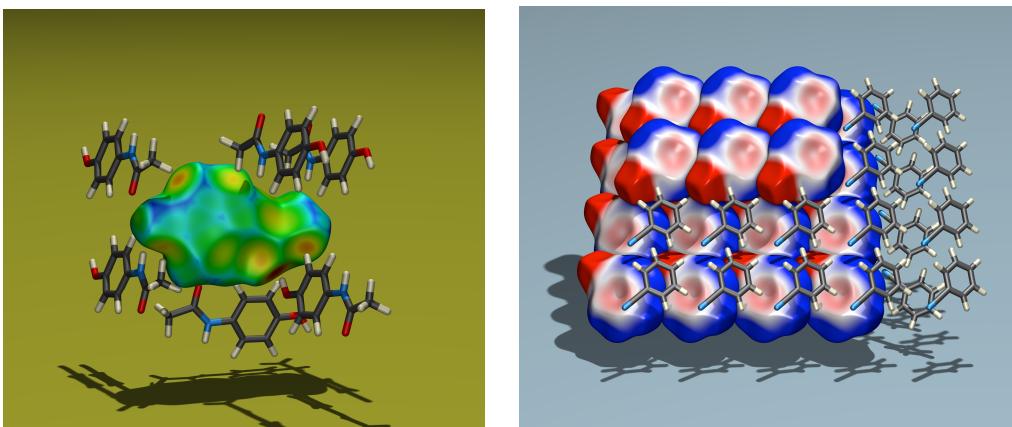


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## **Computational contributions to crystal engineering**

Guest edited by Angelo Gavezzotti  
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# Computational contributions to crystal engineering

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“Crystal engineering” is a broad concept that includes all endeavours to prepare a chemical compound aiming at the properties of the aggregate of molecules rather than at the properties of the molecule itself.

Chemically speaking, the obvious way of making a compound is by working at the bench, where the advantage is that one can watch and size up the real substance in one’s own hands. Chemical connectivity and even the fine stereochemistry of natural compounds can be controlled by the astonishing capabilities of modern synthetic methods. On the other hand, for organic molecules very little can be done in terms of control of the properties of the resulting aggregates. One may end up with anything between a fluid of variable rheological properties, and a proper crystal. For the latter, the three-dimensional structure is *a priori* difficult to predict and almost impossible to control.

Molecular simulation by computer, only twenty years ago at an early stage of development, has nowadays evolved into a robust companion, if not even a precursor, of the synthetic effort. Databases of hundreds of thousands of crystal structures are nowadays available on laptop computers. The evolution of computer hardware allows faster

computation and also faster development of new algorithms and testing of new theories. Even on standard personal computers, without recourse to massive parallelization or clustering, a reliable calculation of the lattice energy and lattice vibrations of an organic compound has passed from a matter of hours to a matter of seconds. The use of periodic-lattice molecular-orbital calculations including to some extent electron correlation apply to sizeable organic crystals or, for an evaluation of intermolecular energies, to dimers of substantial (30-atom) molecules.

Crystal structure prediction by computer, or polymorph prediction, has evolved to the point where a narrow range of possible crystalline structures can be foreseen from molecular connectivity alone, at least for some classes of organic compounds. There are broad connections with the currently very hot field of recognition, prediction and control of polymorphism in the manufacturing of pharmaceutical products.

Even more important than thermodynamics and relative enthalpies or free energies is the dynamic study of the early stages of molecular aggregation by evolutionary simulation. Molecular dynamics, Monte Carlo, and the variants thereof, offer at least a preliminary view of the stages of molecular recognition for

a better understanding or for a prediction of the final outcome of a crystallization process and of the dynamics of phase changes.

There remain three great challenges in computational contributions to crystal engineering. The first is a completion of our understanding and rationalization of the intermolecular potential, together with the development of a suitable computational scheme that should join a sound adherence to the physics of the interaction with easy reproducibility and fast implementation. The second is a reliable assessment of the capability of various quantum mechanical methods in the reproduction of correlation energies, which are essential to the calculation of crystal energies. The third is bridging the time gap in the simulation of nucleation, a phenomenon which in reality occurs on a timescale of seconds, while simulations are limited to times three orders of magnitude shorter. It is perhaps in the direction of a better knowledge of kinetic paths, rather than of relative stabilities, that computational efforts should be directed in the near future.

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