

CRYSTALS STRUCTURES OF MODERATLY COMPLEX ORGANIC MOLECULES ARE PREDICTABLE

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A comprehensive computational strategy for the prediction of crystal structures is presented that has scored an unprecedented 4 in 4 success rate at the 2007 CCDC blind test on crystal structure prediction.

Key components of the new approach, implemented in the GRACE (Generation, Ranking And Characterization Engine) software package, are a hybrid method [1] for the accurate calculation of lattice energies, a robust procedure for the parameterization of tailor-made force fields and a novel approach for crystal structure generation. The hybrid method combines DFT calculations by means of the VASP program [2-4] with an empirical van der Waals correction. It is used for the final lattice energy ranking and acts as a reference standard for force field parameterization. A tailor-made force field is derived for each molecule for which the crystal structure is to be predicted. The force field and the fitting procedure have been designed to allow for a maximum amount of customizability while avoiding redundancy, such that hundreds of force field parameters can be refined simultaneously. The tailor-made force field is used for crystal structure generation and for the preparation of Hessian matrices for the final lattice energy optimization with the hybrid method. Based on the known statistical deviation between the tailor-made force field and the hybrid method, a shortlist of crystal structures from a small energy window is selected for the final optimization and lattice energy ranking with the hybrid method.

In addition to the blind test results, validation studies for 15 organic molecules are presented, including ethane, ethylene, acetylene, methanol, urea, acetic acid, cyclohexane-1,4-dione, paracetamol, CCDC blind test molecules I to VI and a pharmaceutical compound for which crystal structures have been predicted in a blind test fashion. 17 out of the 18 experimentally observed crystal forms of these molecules are found among the first two most stable predicted crystal structures.

The current range of applicability and the potential of the new approach are discussed with a focus on pharmaceutical molecules.

[1] Neumann, M. A., Perrin, M.-A., *J. Phys. Chem B*, 2005, 109, 15531-15541. [2] Kresse, G., Hafner, J., *Phys. Rev B*, 1993, 47, 558. [3] Kresse, G., Furthmüller, J., *Phys. Rev. B*, 1996, 54, 11169. [4] Kresse, G., Joubert, D., *Phys. Rev. B*, 1999, 59, 1758