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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 [1]. Key components of the new approach, implemented in the GRACE software package, are a hybrid method 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 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 to be considered and used for crystal structure generation as well as for the preparation of second derivative 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 lattice energy optimization and ranking. 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.
[1] Neumann, M. A., Leusen, F. J. J., Kendrick, J., Angew. Chem. Int. Ed, 2008, 47, 2427-2430

Keywords: crystal structure prediction, computer modelling solids, polymorphism

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Structure prediction of flexible small molecules - A case study

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Predicting the crystal structures of small molecules from energy calculations is of considerable interest for a number of scientific and industrial purposes. However, in the field of polymorph-forming pharmaceuticals two main problems arise. One is the high degree of internal flexibility of many of the molecules of interest and the consequential large number of possible conformations. The resulting multitude of packing possibilities can overwhelm even fast computers. The other problem is that many of these structures have similar energies. Exact energy modeling is thus necessary to identify the real structures. We checked possible strategies using aripripazole as a test case. For this compound, a number of polymorphs and various solvates are known, as are their respective crystal structures. By comparing the experimental structures with the calculations on all stages, a number of helpful results were established: 1) Quantum-mechanical (QM) energy calculations on the isolated molecule reduce the number of possible conformations drastically. For aripripazole, seven torsional degrees of freedom allow 2916 minimum conformations. Of these, only 296 remain, once correlation of neighboring torsions is considered. Further reduction is possible, if the influence of hydrogen bonds is considered. 2) The molecule has five potential hydrogen bond acceptor sites, but QM calculations reveal that only one of these is realizable. The corresponding hydrogen bonds are realized in all experimental structures. 3) The experimental structures account for all the lowest energies found. Thus, any problem in finding the correct structures is not due to the energy model, but is a matter of the search algorithm and processor time. The treatment of the hydrogen bonds was found to be crucial in this.

Keywords: structural prediction, pharmaceutical organic molecules, energy calculations

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Increasing the effectiveness of evolutionary crystal structure prediction using fingerprint-function

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Evolutionary algorithm approach to crystal structure prediction problems has proven its effectiveness in various applications. Algorithm USPEX (Universal Structure Predictor: Evolutionary Xtallography) allows one to predict the most stable crystal structure for a given compound without requiring any experimental input. This is especially attractive for simulation of materials under extreme conditions. However, the inability to determine the degree of similarity between different structures limits the effectiveness of the algorithm and increases the probability of trapping in a particular basin of the energy surface. To solve this problem we derived a family of specially constructed fingerprint-functions. Fingerprint-function is a function, that is independent of lattice vectors choice and uniquely determines the structure of the crystal. Another important property of these functions is that the degree of correlation between functions calculated for two structures can be used as a good measure for degree of similarity between those structures. We have shown, that after modifying selection and variation operators with the help of fingerprint-functions, the effectiveness of USPEX algorithm was increased. This method also simplifies the search for metastable states by evolutionary algorithms.

Keywords: crystal structure prediction, *ab-initio structure* determination, computer algorithms

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Inverse multislice calculations: A new method for solving complex structures

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The multislice approach has been used for 50 years to find the result of a wave passing through a thick sample. One problem with multislice is that it is difficult to reverse the calculation and find the structure of a sample given measurements of the exit wave. This limits the use of multislice techniques in experimental microscopy, as in general the sample structure is unknown and the aim is to find it. Iterative algorithms for microscopy have been studied since the