Figure 1. The structure of Abl (SH3-SH2-Kinase) in complex with an ATP site inhibitor (top) and a myristate site inhibitor (bottom), and showing the location of the T315I mutation (sphere in ATP binding site).

Keywords: kinase, allosteric, inhibitor, drug discovery

KN-6 Organic crystal structure prediction – from fundamental research to industrial application

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Crystal structure prediction is the task of deriving the observable three-dimensional crystal structures of organic molecules from their chemical structure alone. Prediction methods face the mathematical challenge of sampling a search space that grows exponentially with the number of degrees of freedom and the physical challenge of calculating lattice free energy differences with an accuracy that should be better than the order of magnitude of typical lattice energy differences between polymorphs.

The state-of-the-art was assessed by a series of blind tests in 1999, 2001, 2004, 2007, 2010 and 2015. In the last three blind tests, the highest success rate was scored with an approach implemented in the computer program GRACE. Dispersion-corrected density functional theory (DFT-D) calculations [1] are used to first generate reference data to which a tailor-made force field is fitted from scratch [2] for every chemical compound under consideration. The tailor-made force field is then used in conjunction with a Monte Carlo parallel tempering algorithm to generate crystal structures that are further optimized at DFT-D level. Statistical control mechanisms ensure that all crystal structures in a user-defined target energy window are found with a user-defined level of confidence.

The 2015 blind test [3] has demonstrated the ability of GRACE to perform crystal structure predictions using fully automated workflows, to handle two flexible molecules per asymmetric unit and to predict the crystal structure of the hydrate of a chloride salt.

Looking back on a dozen case studies published on drug-like molecules by various authors and an equal number of confidential studies with GRACE, a picture emerges how crystal structure prediction in an industrial working environment helps to rationalize crystallization behaviour, to understand solid-state forms, to solve crystal structures and to flag missing more stable forms. The emerging ability to find new crystal forms by rational crystallization experiment design based on the knowledge of the computed crystal energy landscape is illustrated by the example of Dalcetrapib [4].

[1] Neumann, M. A. and Perrin, M.-A. J. Phys. Chem. B 109: 15531-15541 (2005)
[2] Neumann, M. A. J. Phys. Chem. B 112: 9810-9829 (2008)
[3] Reilly, A. M. et al. Acta Cryst. B, submitted for publication (2016)
[4] Neumann, M. A. et al. Nature Communications 6, art7793 (2015)

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