m29.p01

Crystal structure prediction of the series of a-amino acids

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Keywords: crystal structure prediction, modelling, density functional theory

Crystal structure prediction (CSP) is becoming an increasingly important tool in the understanding and anticipation of polymorphs of organic crystals. Because CSP is currently only possible for relatively small molecules with limited flexibility, the development of procedures to deal with increasingly more complex molecules, up to those of pharmaceutical importance, is of considerable interest. We are studying the series of a-amino acids starting with alanine. We have investigated the conformation of alanine considering the torsional freedom about the two flexible torsional angles of the molecule; torsion about the amine group and torsion about the carboxyl group. The experimentally observed conformations of alanine in the L and DL-alanine crystal structures were found to be considerably less stable than the optimised structure of alanine obtained by density functional theory (DFT). An analysis of the α-amino acids in the Cambridge Structural Database (CSD) showed that the torsional angle around the amine group shows relatively little variation, with all the conformations being close to staggered (180°) with respect to the hydrogen atom of the α carbon atom. This angle is considerably different from the torsional angle found in the DFT optimised structure (120°) and would be difficult to predict based solely on the energy calculations of the isolated molecule. The effect that the amine torsional angle has on the total energy of the real and computer generated alanine crystal structures has been investigated by systematically varying the angle and monitoring the total (lattice + molecular) energy using both atomic point charges and multipole based models of intermolecular electrostatics. The strategies developed for alanine are extended to some of the larger, more flexible amino acids, and the predictability of the crystal structures of these biologically and pharmaceutically important molecules is discussed.

m29.p02

Importance of molecular shape in the overall stability of hydrogen bond motifs in the crystal structures of various carbamazepine type drugs

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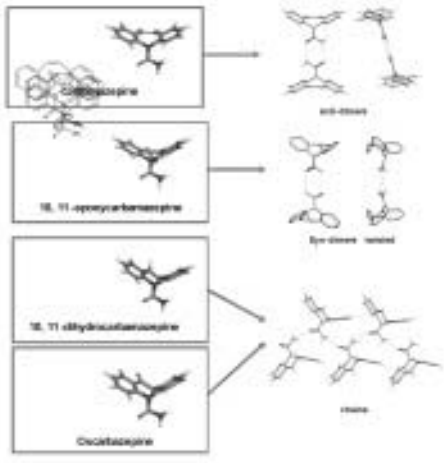
Keywords: crystal structure prediction, hydrogen bonding recognition and computer simulation of structure

A successful crystal structure prediction calculation would find the experimentally observed crystal (or crystals, for polymorphic systems) as the most stable of the thousands of hypothetical crystal structures generated computationally. Both experimental and hypothetical crystal structures constitute a unique source of information. Carbamazepine, a first generation anticonvulsant, is known to crystallize in four polymorphic forms and cocrystallize with various solvents. Except in the case of cocrystallizations with acids, all polymorphs and solvates exhibit the same type of hydrogen bonding: anti-carboxamide dimers (Figure). On the other hand, two derivatives of the drug (oxcarbazepine and 10,11-dihydrocarbamazepine) adopt chain motifs in their crystal structures and the epoxy derivative (10,11-epoxycarbamazepine) shows a third mode of hydrogen bonding: syn-dimers.



In order to rationalize the differences in hydrogen bonding caused by these small changes in molecular structure, predictions of the low energy crystal structures of these drugs were performed and hydrogen bond patterns in both the hypothetical and experimental structures were analyzed. In addition, interactions energies between pairs of molecules were also calculated using the SCDS-Pixel approach [1,2]. We also address the importance of overall molecular shape and its influence on the packing and the hydrogen bond arrangements in these structures.

[1] Gavezzotti, A. *Crystengcomm* 2003, *5, 429-438.*
[2] Gavezzotti, A. *Crystengcomm* 2003, *5, 439-446.*