

# Oral Contributions

## [MS23-04] Mapping crystalline molecular geometries to the conformational energy landscape

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The most common assumption made in computational methods for crystal structure prediction (CSP) is that the lowest energy crystal structures are the most likely to be observed. For rigid molecules, only the intermolecular contribution to the lattice energy must be considered in evaluating relative energies of candidate structures. A sufficiently accurate intermolecular model therefore enables realistic ranking of such crystal structures. Current methods are generally successful for rigid single component organics, but effective and efficient methods for coping with molecular flexibility are still a challenge [1]. For flexible molecules, improved packing and intermolecular interactions may pay the debt owed by high energy conformations, potentially leading to energetically feasible crystal structures being built from different conformations. This introduces two new challenges to the CSP work flow. First, the molecular geometry must be investigated to identify all conformations which may lead to viable crystal structures. Furthermore, the relative energies of crystal structures of flexible molecules must now include conformational energy as well as intermolecular interactions. The development of methods used for energy ranking of the predicted crystal structures of flexible molecules has progressed well [2] and some approaches for assessing the conformations required for crystal structure prediction have been proposed. [1,3-5] However, the case by case approach leads to very high human analysis times and the brute force conformational searches yield

prohibitively high numbers of conformations. In this work, we have investigated the conformational energy landscape of a large set of organic molecules to answer some questions that will inform the continued development of methods for CSP: By how much do in-crystal conformations vary from gas phase conformations; how much conformational energy cost can be paid by crystal packing; by how much do in-crystal conformations vary between conformational polymorphs and do conformational polymorphs correspond to different gas phase conformations?

## References

- [1] D. a. Bardwell, C. S. Adjiman, Y. a. Arnautova, E. Bartashevich, S. X. M. Boerrigter, D. E. Braun, A. J. Cruz-Cabeza, G. Day, R. G. Della Valle, G. R. Desiraju, B. P. van Eijck, J. C. Facelli, M. B. Ferraro, D. Grillo, M. Habgood, D. W. M. Hofmann, F. Hofmann, K. V. J. Jose, P. G. Karamertzanis, A. V. Kazantsev, J. Kendrick, L. N. Kuleshova, F. J. J. Leusen, V. Maleev, A. J. Misquitta, S. Mohamed, R. J. Needs, M. a. Neumann, D. Nikylov, A. M. Orendt, R. Pal, C. C. Pantelides, C. J. Pickard, L. S. Price, S. L. Price, H. a. Scheraga, J. van de Streek, T. S. Thakur, S. Tiwari, E. Venuti and I. Zhitkov, *Acta crystallographica. Section B, Structural science*, 2011, 67, 535–51.
- [2] A. V. Kazantsev, P. G. Karamertzanis, C. S. Adjiman, C. C. Pantelides, S. L. Price, P. T. A. Galek, G. M. Day and A. J. Cruz-Cabeza, *International journal of pharmaceutics*, 2011, 418, 168–78.
- [3] G. M. Day and T. G. Cooper, *CrystEngComm*, 2010, 12, 2443.
- [4] M. A. Neumann, *J. Phys. Chem. B*, 2008, 112, 9810–29.
- [5] T. G. Cooper, K. E. Hejczyk, W. Jones and G. M. Day, *J. Chem. Theory Comput.*, 2008, 4, 1795–1805

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