# CSP of flexible pharmaceutical-like molecules: DFTB as an intermediate optimization method and for free energy estimation

**Gerit Brandenburg** <g.brandenburg@ucl.ac.uk> | 12th of July 2018

FARADAY DISCUSSION: METHODS AND APPLICATIONS OF CRYSTAL STRUCTURE PREDICTION, CAMBRIDGE, UK

## Team

**Luca Iuzzolino (UCL)**

**Patrick McCabe (CCDC)**

**Sarah L. Price (UCL)**

**Gerit Brandenburg (Göttingen)**

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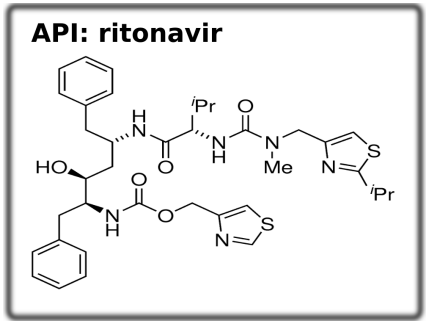
cposs

Department of Chemistry – University College London
Institut für Physikalische Chemie – Universität Göttingen

gerit-brandenburg.de

# Challenge of treating the flexibility of large pharmaceutical-like molecules




- ritonavir is API with typical flexibility
- need of fast electronic structure method that can treat flexibility

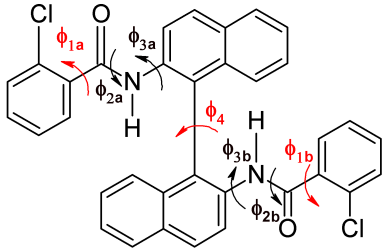
**D**ensity **F**unctional **T**ight **B**inding (DFTB3-D3):
*3rd order, self consistent charges, 3OB atom-pair parameter, D3 dispersion*

- huge speed-up compared to DFT ($\sim$4 orders of magnitudes)
- full treatment of all degrees of freedom
- good experience for proteins & energies of small molecular crystals

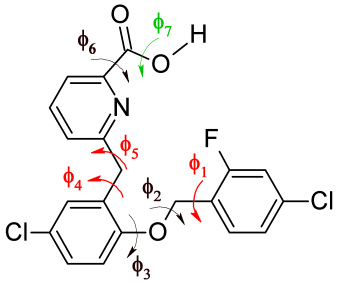
[1] A. S. Christensen, T. Kubař, Q. Cui, M. Elstner, *Chem. Rev.* **116**, 5301 (2016).

[2] JGB, S. Grimme, *J. Phys. Chem. Lett.* **5**, 1785 (2014).

# Focus on flexible molecules with previous CSP studies



Molecule XXVI



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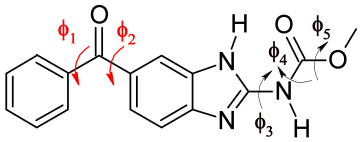
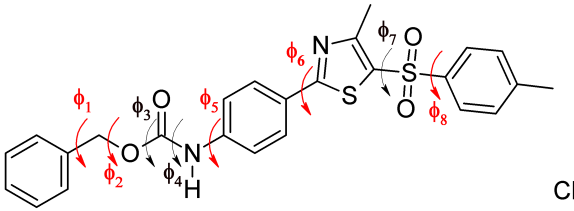
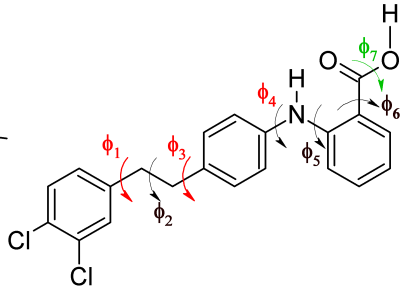


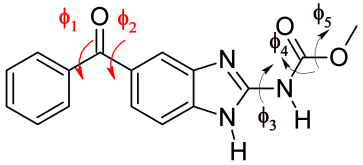
A-Mebendazole



Molecule XX



Molecule XXIII



C-Mebendazole

Possible advantages of DFTB3-D3 as an (intermediate) CSP step

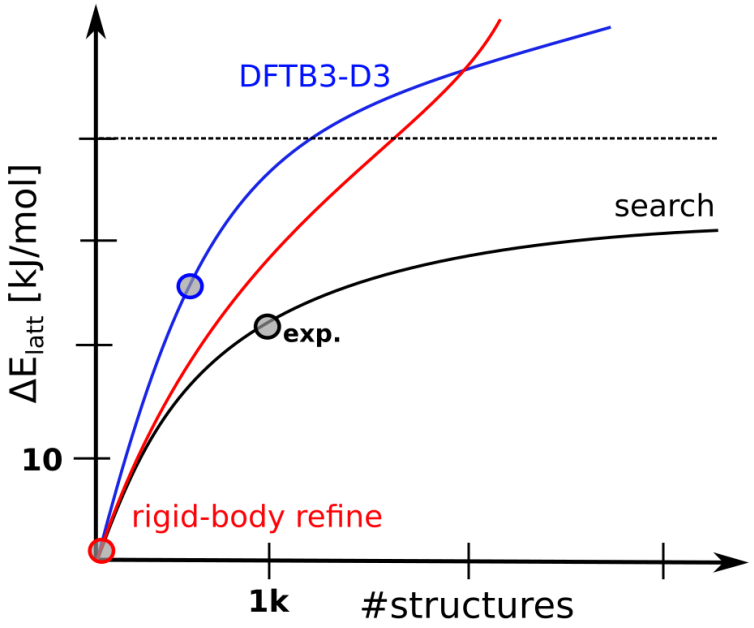
(1) improving geometries

(2) improving energy ranking

(3) reducing # minima

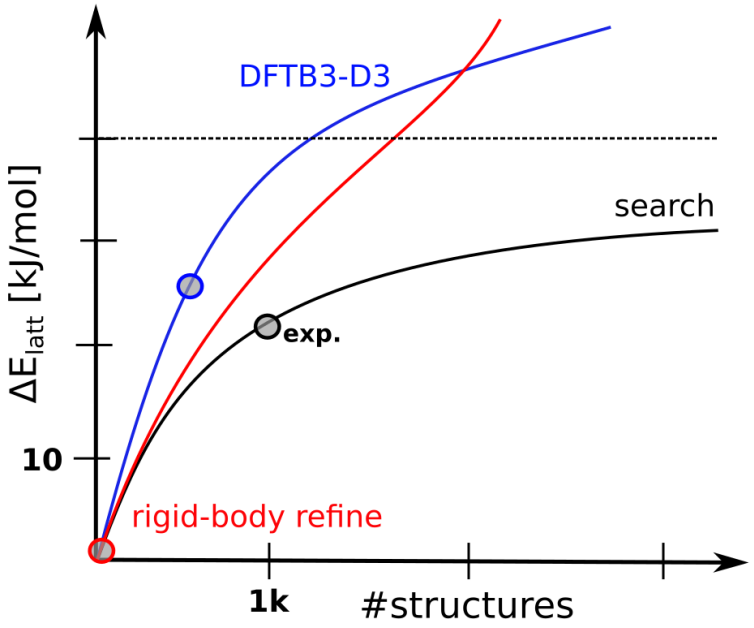
(4) free energy contributions

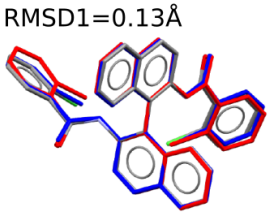
# Though poor energetic ranking geometries improved




- 2.2 Mio structures generated for XXVI, 9 000 processed to reranking
- experimental polymorph is rather high in energy by DFTB3-D3
- successful reranking using rigid DFTB3-D3 structure

# Though poor energetic ranking geometries improved

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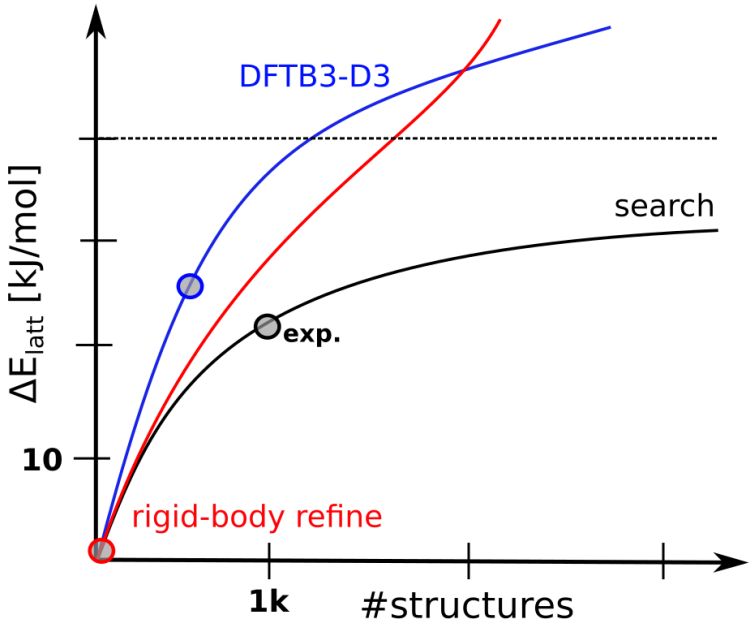
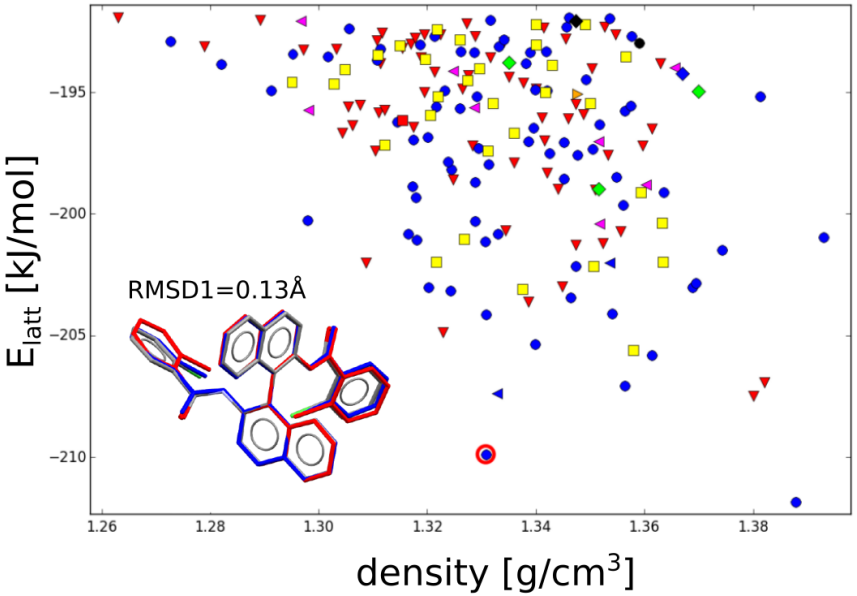
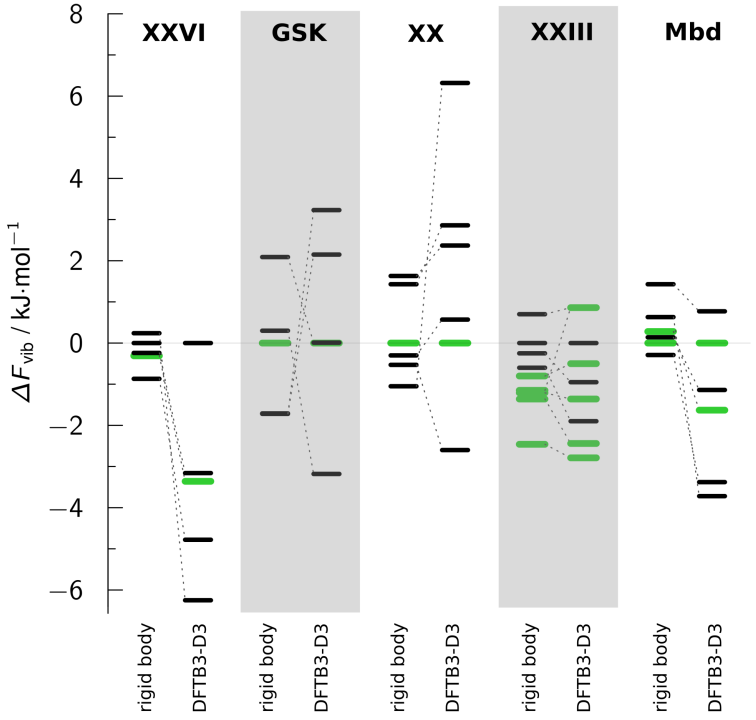



- 2.2 Mio structures generated for XXVI, 9 000 processed to reranking
- experimental polymorph is rather high in energy by DFTB3-D3
- successful reranking using rigid DFTB3-D3 structure
- final energy landscape: no important structure is lost

# Impact of harmonic free energy contributions to relative stability

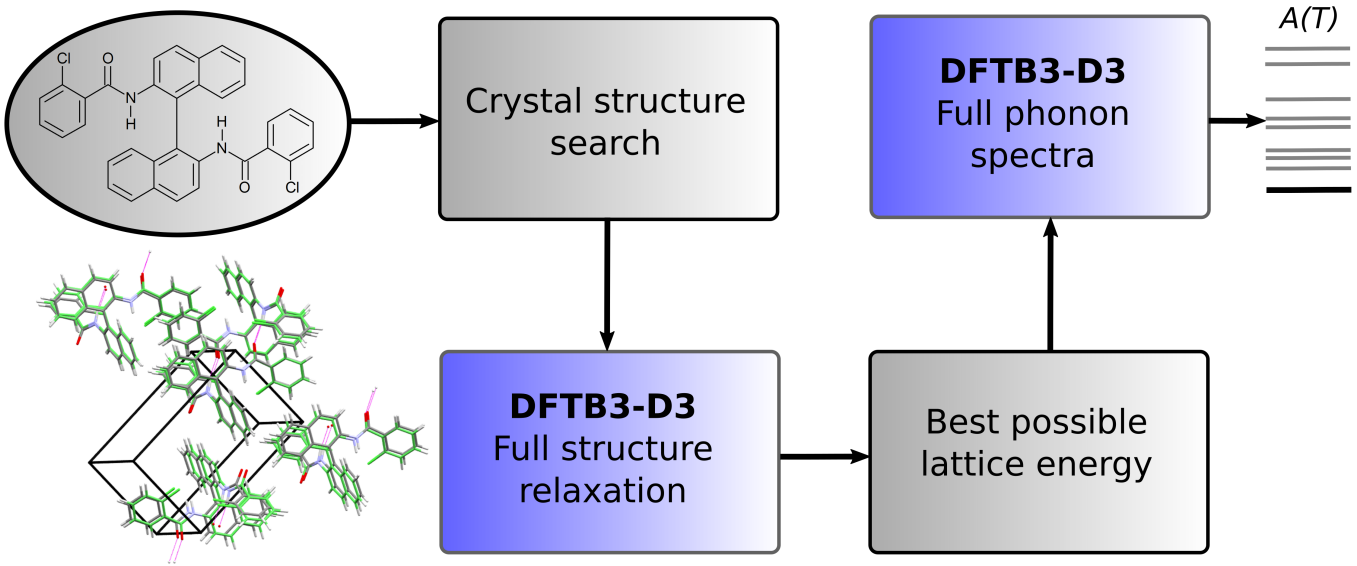



- significant impact of ZPE and thermal contribution on relative stability
- modified ranking of several putative polymorphs
- treating molecules as rigid underestimates the free energy
- rigid-body estimate: 9% of polymorph change stability upon including thermal contributions


[3] A.J. Cruz-Cabeza, J. Bernstein, *Chem. Rev.* **114** 2170 (2014).

[4] J. Nyman, G. M. Day, *CrystEngComm* **17**, 5154 (2015).

# DFTB3-D3 intermediate optimization would be scaleable for larger molecules




Possible merits of DFTB3-D3

(1) improving geometries **yes**

(2) improving energy ranking **no**

(3) reducing # minima **partially**

(4) free energy contributions **yes**

[5] L. Iuzzolino, P. McCabe, S. L. Price, JGB, *Faraday Discuss.*, DOI: 10.1039/C8FD00010G (2018).

# Key references

- Crystal structure prediction:

  L. Iuzzolino, P. McCabeb, S. L. Price, JGB,
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  M. Mortazavi, JGB, R. J. Maurer, A. Tkatchenko *J. Phys. Chem. Lett.*, **9**, 399 (2018).

  S. L. Price, JGB, *Molecular Crystal Structure Prediction*, G. DiLabio, A. Otero-de-la-Roza, Eds., Elsevier Australia, *ISBN: 9780128098356* (2017).

- Beyond-harmonic free energy:

  JGB, J. Potticary, H. A. Sparkes, S. L. Price, S. R. Hall, *J. Phys. Chem. Lett.*, **8**, 4319 (2017).

  H. Buchholz, R. K. Hylton, JGB, A. Seidel-Morgenstern, H. Lorenz, M. Stein, S. L. Price, *Cryst. Growth. Des.*, **17**, 4676 (2017).

- Chemically accurate lattice energy:

  A. Zen, JGB, J. Klimeš, A. Tkatchenko, D. Alfè, A. Michaelides, *PNAS*, **115**, 1724 (2018).