Organic crystal polymorphism: A benchmark for dispersion corrected mean field electronic structure methods

Gerit Brandenburg <g.brandenburg@ucl.ac.uk> | 2016-08-29

ECM30 - Crystal energy landscapes: computation and uses - Basel, CHE

Department of Chemistry
University College London

General goals

(1) Accuracy of computed crystal properties

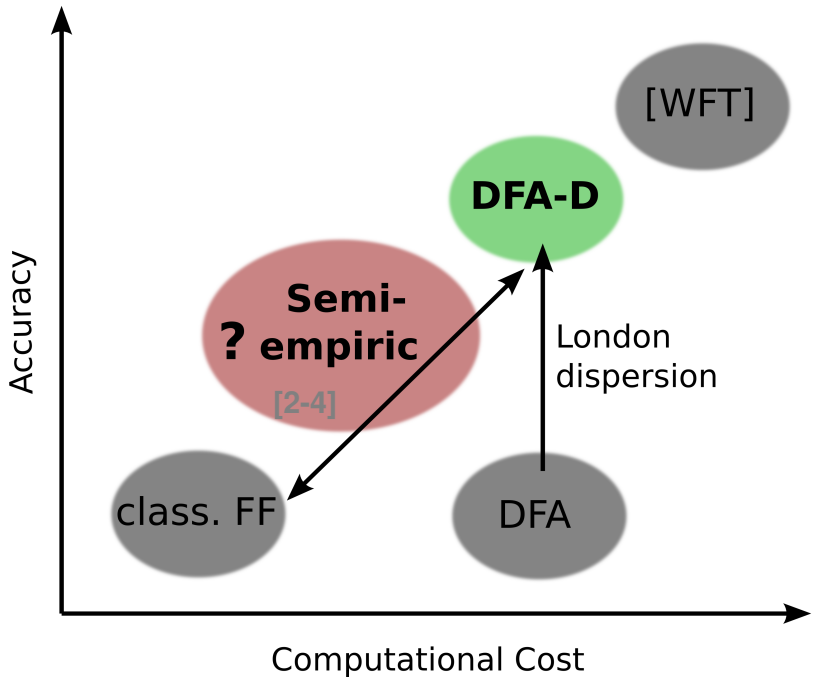
- Error compensation for relative crystal stabilities?
- Is the chemical accuracy of ~ 4 kJ/mol enough?

(2) Beyond lattice energy for real application

- Do we need free energies?
- How wrong is the harmonic approximation?

Intermolecular interactions have to include the van-der-Waals force

Formally exact expression vs. pratical approaches[1]



D3 compared to **MBD@scsTS**

- no full multi-body sum, no SCS
  $\rightarrow$ smaller numerical complexity
- less coarse grained
- better disp. coefficients for small to medium sized molecules
  $\rightarrow$ residual long-range error $< 5\%$

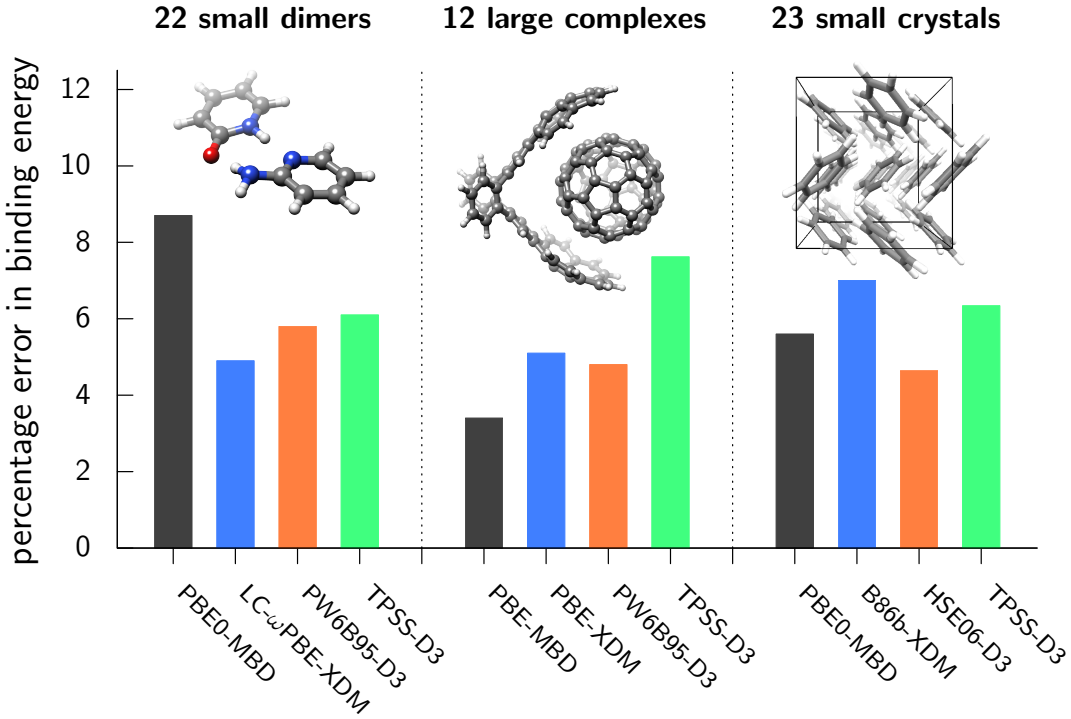
[1] S. Grimme, A. Hansen, JGB, C. Bannwarth, *Chem. Rev.* **116**, 5105 (2016)

[2] M. Cutini, B. Civalleri, M. Corno, R. Orlando, JGB, L. Maschio, P. Ugliengoa *J. Chem. Theory Comput.* **12**, 3340 (2016)

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

[4] JGB, E. Caldeweyher, S. Grimme, *Phys. Chem. Chem. Phys.* **18**, 15519 (2016)

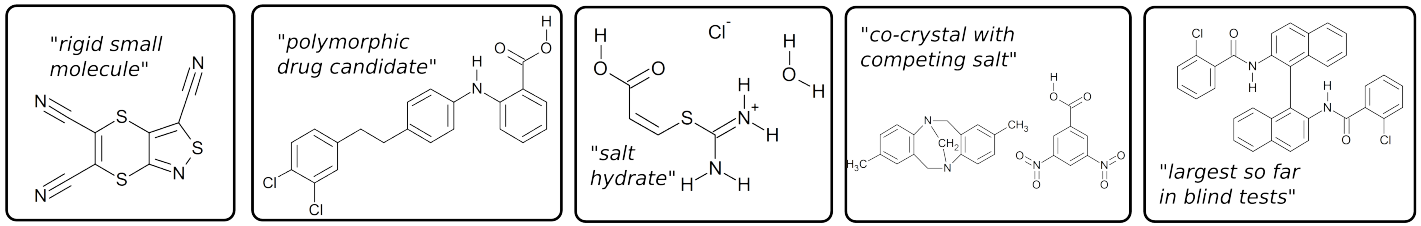
Absolute binding energies are close to the chemical accuracy



- small molecule and benzene crystal thoroughly converged
  $\rightarrow$ reference error < 1 kJ/mol[5]
- back-corrected sublimation enthalpies used
  $\rightarrow$ reference error ~ 5 kJ/mol

[5] J. Yang, W. Hu, D. Usvyat, D. Matthews, M. Schütz, G. K.-L. Chan, *Science*, **345**, 640 (2014)

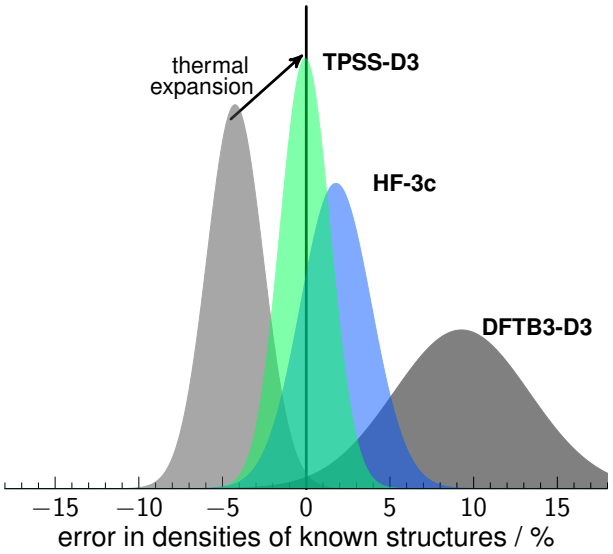
Is relative crystal stability easier?



- extract polymorph candidates from 6th CSP blind challenge[6,7]
- 9 known polymorphs + 10 diverse low energy hypothetical structures

Assumptions

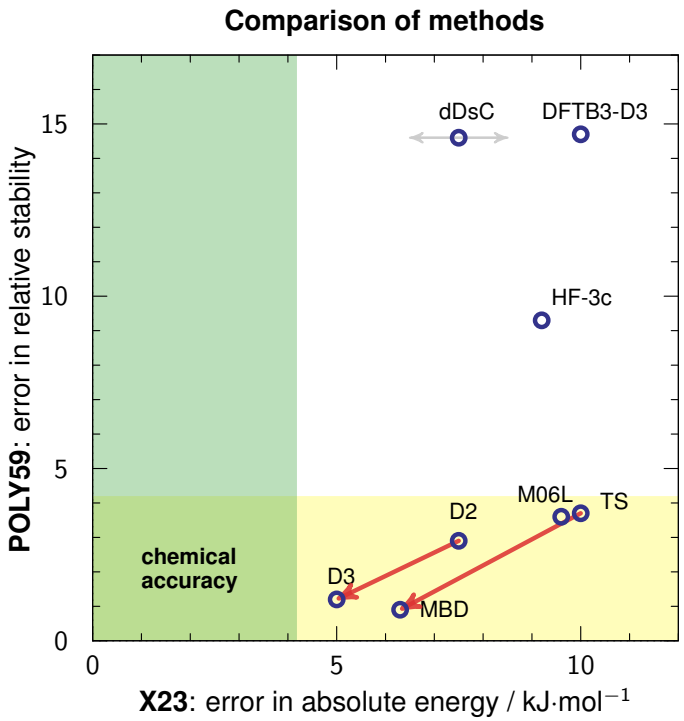
- thermodynamic minimum is measured
- $E_{\mathrm{latt}}(0\,\mathrm{K})$ enough for relative stability
- modeling of thermal expansion improves agreement between computed and measured crystal structures



[6] A. M. Reilly, R. I. Cooper, C. S. Adjiman, S. Bhattacharya, et al. *Acta Cryst. B* **72**, 439 (2016)

[7] JGB, S. Grimme, *Acta Cryst. B* **72**, 502 (2016)

Error compensation less than hoped



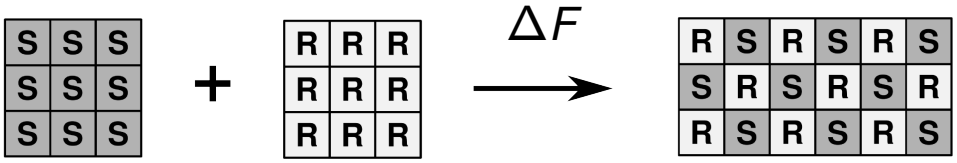
- clear improvement with modern methods D2→D3 and TS→MBD
- gain factor 2-4 for relative stabilities reaching chemical accuracy
- several structures within 1 kJ/mol energy window

Remaining problems

- ∼50 % of reported polymorphs are within 2 kJ/mol[8] → hard to distinguish
- neglected free energy contributions and kinetic effects ∼1-4 kJ/mol

[8] A. J. Cruz-Cabeza, S. M. Reutzel-Edens, J. Bernstein *Chem. Soc. Rev.* **44**, 8619 (2015)

Relative energies of chiral crystals depend on thermodynamic conditions



Free energy difference depends on phonon modes[9,10]

$$\Delta F(T) = \overbrace{\Delta E_{\text{latt}} + \Delta E_{\text{ZPVE}}}^{\text{crystal at 0K}} + \int_0^T \mathrm{d}T\ \Delta C_P(T)$$

$$C_P(T) = C_V(T) + \alpha^2\, \mathcal{K}\, V\, T \qquad \alpha: \text{ thermal expansion}$$

Approximations to model enantiomeric excess:

(A) Can the phonon modes be neglected?

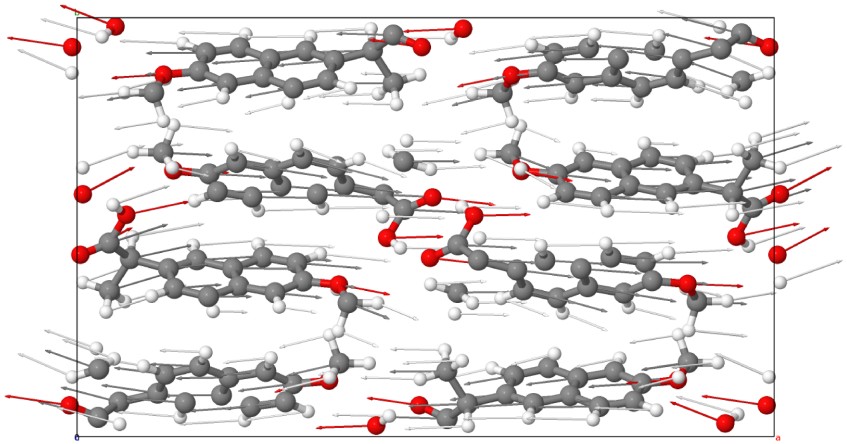
(B) Are anharmonic expansion effects important?

[9] D. E. Braun, M. Ardid-Candel, E. D'Oria, P. G. Karamertzanis, J.-B. Arlin, A. J. Florence, A. G. Jones, S. L. Price *Cryst. Growth Des.* **11**, 5695 (2011)

[10] A. Otero-de-la-Roza, B. H. Cao, I. K. Price, J. E. Hein, E. R. Johnson, *Angew. Chem. Int. Ed.* **53**, 7879 (2014)

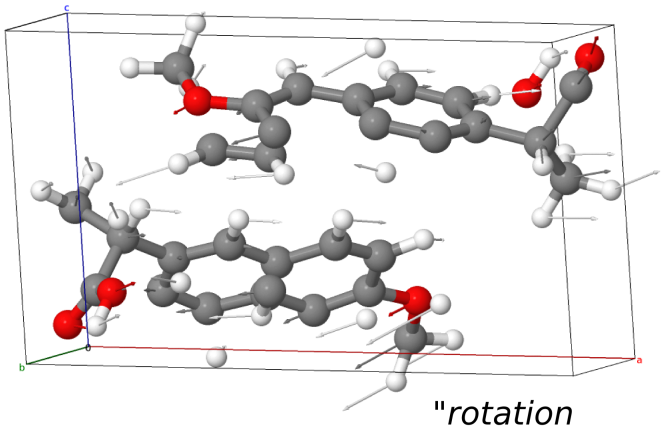
Low and high frequency modes of naproxen depend on the crystal packing

racemic Pbca, Z'=1 ρ=1.29 g/cm^3



"double layer sliding"

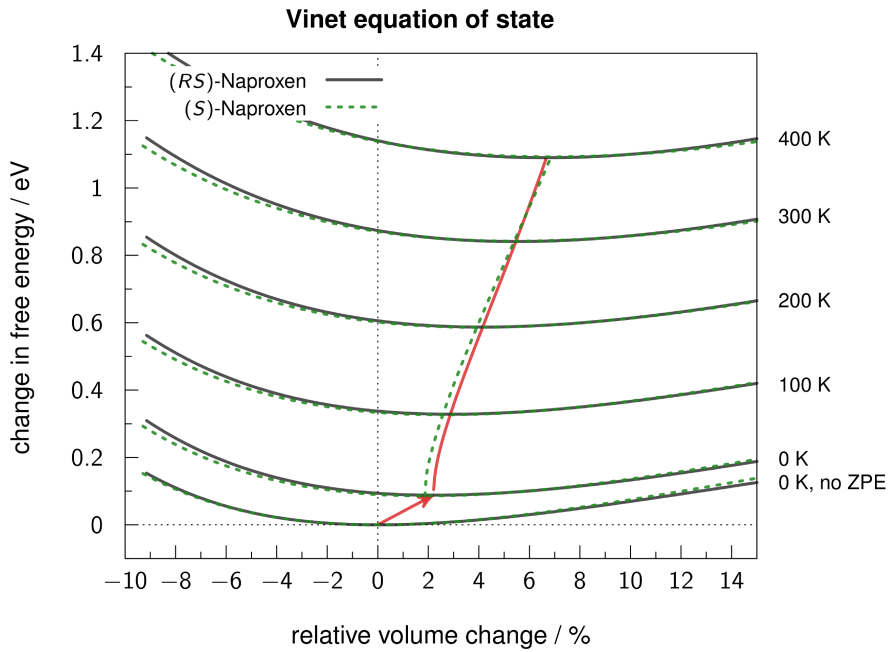
enantiopure: P2$_1$, Z'=1, ρ=1.27g/cm^3

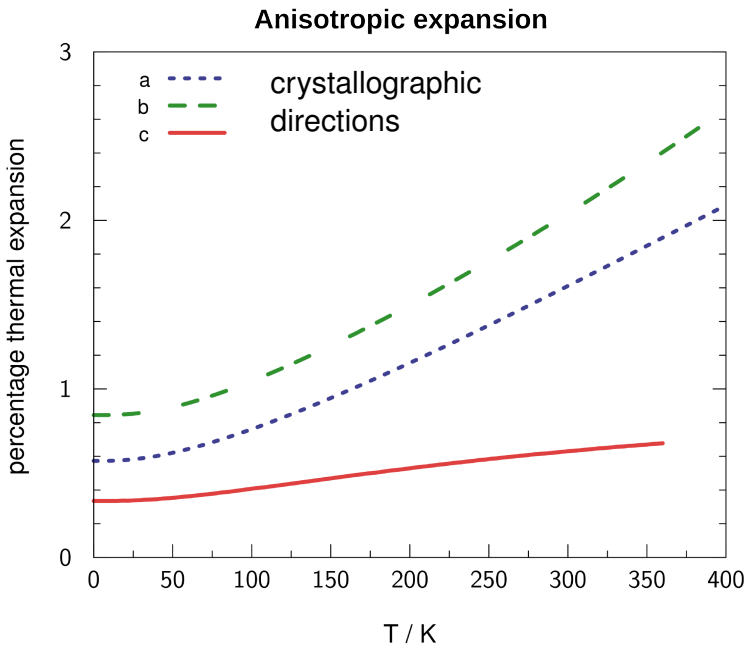


"rotation around CMA"

- different low energy modes $\longrightarrow$ variation in ΔC_P
- modified H-bonding network $\longrightarrow$ variation in ΔE_{ZPVE}
- verified by Raman/IR spectra and C_p measurements

Quasi-harmonic approximation reveals anisotropic thermal expansion

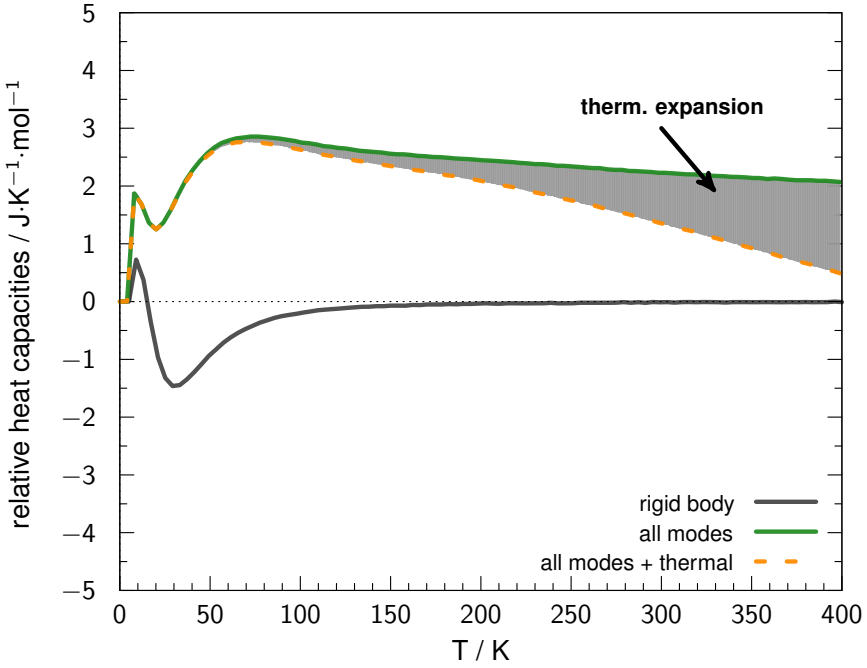




- substantial zero-point effect
- expansion highly anisotropic

[*] Quasi-harmonic treatment at DFTB3-D3 level: constraint V optimization with EOS fit

Variations in heat capacities will affect the relative crystal stability



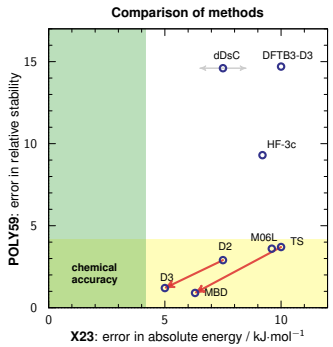
- rigid-body treatment cannot capture high modes
- thermal expansion significantly influences relative heat capacities
- has to be checked against experimental measurements

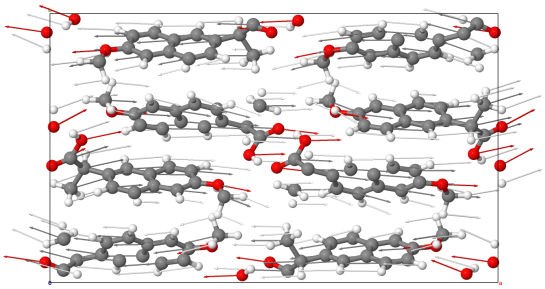
[11] H. Buchholz, M, Stein, H. Lorenz, A. Seidel-Morgenstern, R. Hylton, JGB, S. L. Price, *in preparation*

Summary

Conclusions

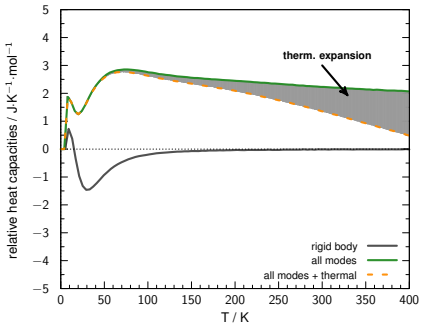
- relative energy can be computed within chemical accuracy
- higher accuracy needed for most polymorphs
- for realistic applications anharmonic effects have to be modeled





Outlook and possible improvements

- higher methods for CSP ranking E_{latt}
- free energy contributions ΔF validated against experiment



Acknowledgements

Collaborators

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- Sally Price (London)
- Angelos Michaelides (London)
- Andreas Seidel-Morgenstern (Magdeburg)
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Thanks