# Towards a New Paradigm in Molecular Crystal Polymorph Prediction

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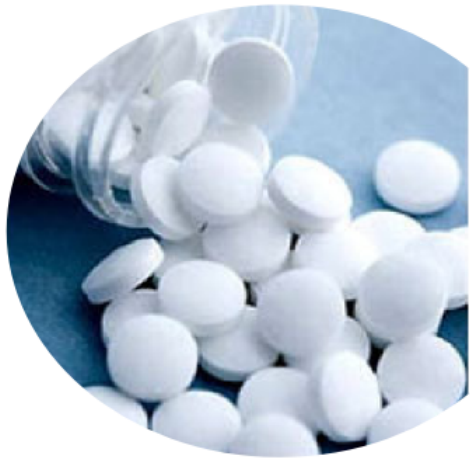
# Outline of talk

# Understanding phenomena in nature



## How can a Gecko stick to a glass wall?

- cannot be explained by classical mechanics
- quantum mechanical description needed for London dispersion

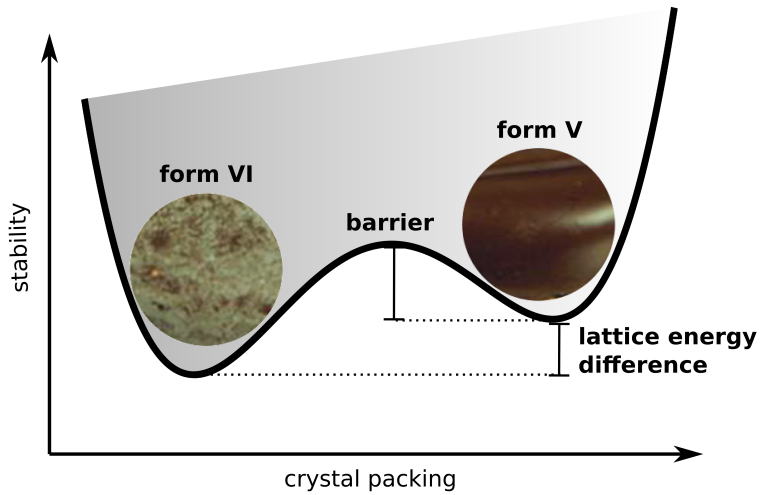
## Why does a tablet change its properties?

- van der Waals interaction stabilizes tablet dependent on its form
- relevant for production process and dosage

# Many properties depend on the polymorphic form of a crystal

## Polymorphism

- ability of a molecule to crystallize in more than one structure
- properties change with crystal packing, e.g. solubility, color, etc.[1]



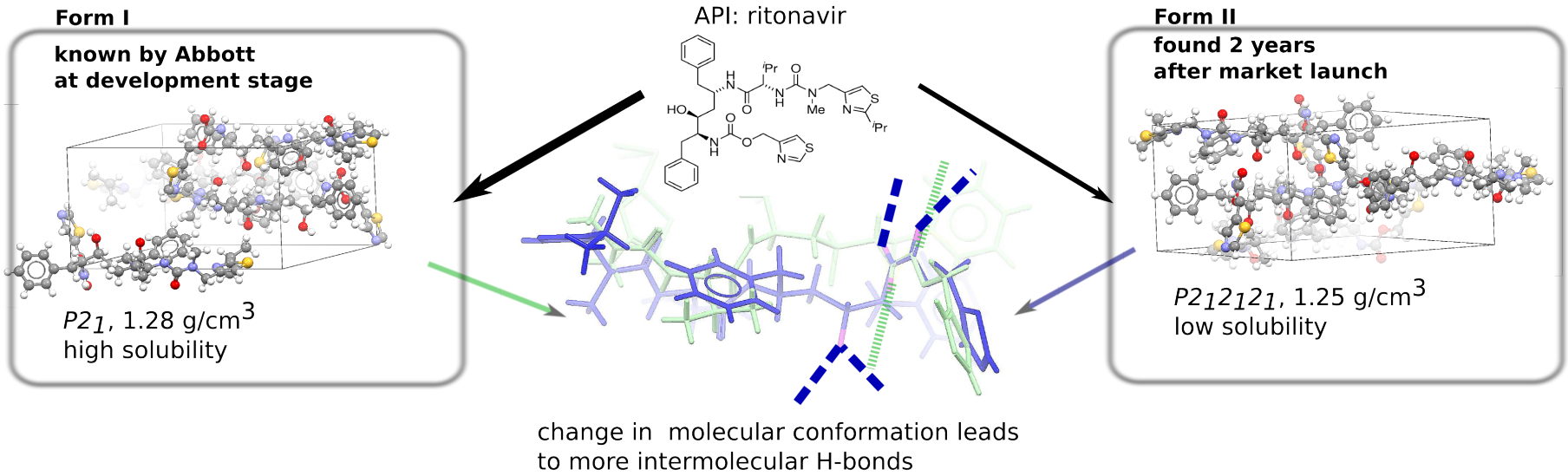

- cocoa butter (form VI) has a dull surface, soft texture, higher melting point
- metastable form V has glossy surface, crisp hardness, melts at 300 K[2]


[1] A. J. Cruz-Cabeza, S. M. Reutzel-Edens, J. Bernstein, *Chem. Soc. Rev.* **44**, 8619-8635 (2015).

[2] S. T. Beckett, *Science of Chocolate*; RSC Paperbacks (2000).

[3] S. L. Price, JGB, *Molecular Crystal Structure Prediction; Non-covalent interactions in Quantum Chemistry and Physics*, G. DiLabio, A. Otero-de-la-Roza, Eds., Elsevier Australia, Melbourne, in press (2017).

# Late appearing polymorph disrupted supply of antiviral drug ritonavir




- ritonavir was industrially produced in form I for 2 years
- more stable form II suddenly crystallized
- much lower solubility made reformulation necessary[4]

  → Tools to predict possible polymorphs would be valuable

[4] J. Bauer, et al., *J. Pharm. Res.* **18**, 859-866 (2001)

# Outline of talk

# Predict most stable crystal polymorphs based on the molecular diagram

The inability to predict something as simple as how a molecule would crystallize is one of the continuing scandals in the physical sciences.[5,6]

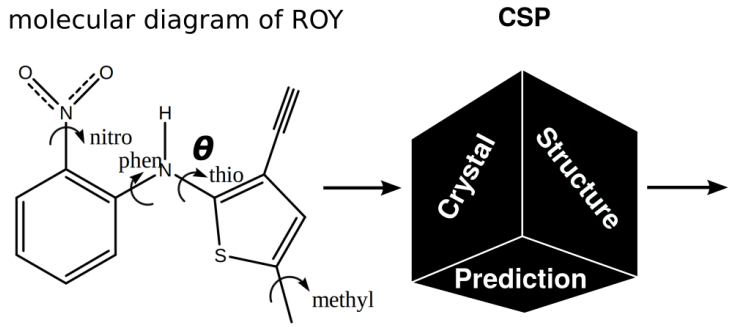
**Task**

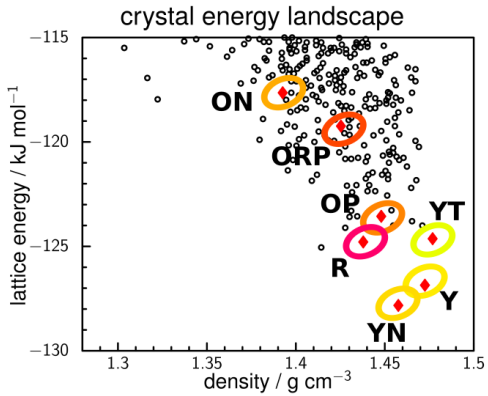
- molecule is chosen due to its chemical/physical/biological properties.
- based on the molecular diagram only, the most stable crystal structures should be predicted.
- predict properties of interest for the most promising candidates.

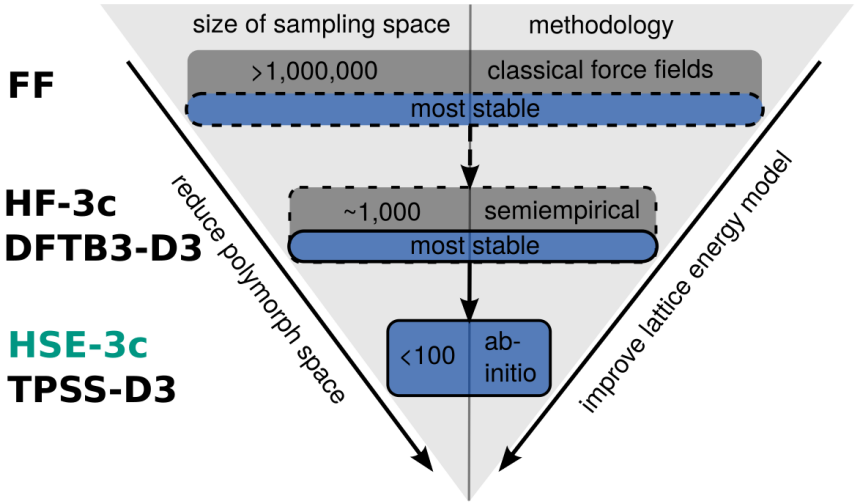
[5] A. Gavezzotti, *Acc. Chem. Res.* **27**, 309-314 (1994).

[6] J. Maddox, *Nature* **335**, 201-201 (1988).

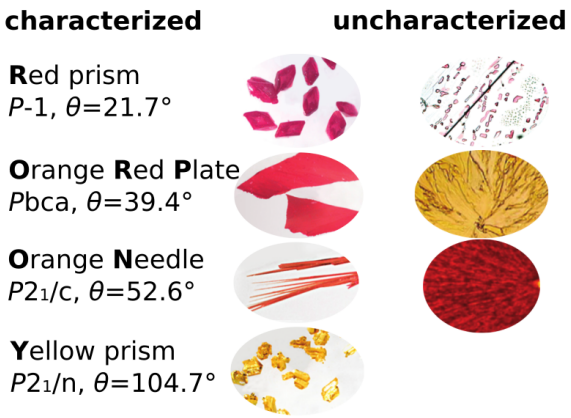
# Sampling and energetic ranking for crystal structure prediction




**Properties**
of ROY polymorphs



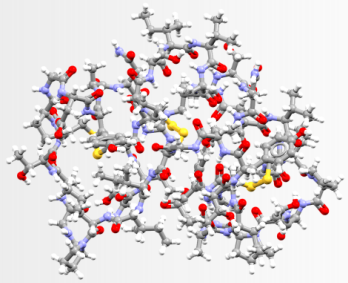


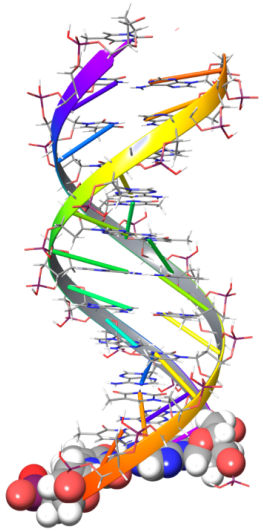
[7] S. Price, *Chem. Soc. Rev.* **43**, 2098 (2014)

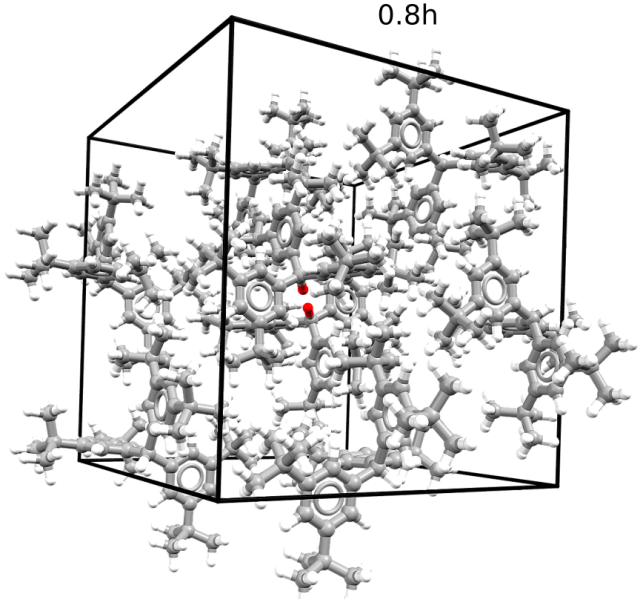
[8] M. Vasileiadis, A. V. Kazantsev, P. G. Karamertzanis, C. S. Adjiman, C. C. Pantelides, *Acta Cryst. B* **68**, 677 (2012)

# Fast electronic structure with ab-initio accuracy

| | gas phase protein | DNA helix | molecular crystal |
|---|---|---|---|
| **dim:** | 0D | 1D | 3D |
| **#atoms/unit:** | 647 (647) | 726 (66) | 856 (37) |
| **wall time:** (**HSE-3c** on 16 cores) | 5h | 0.5h | 0.8h |







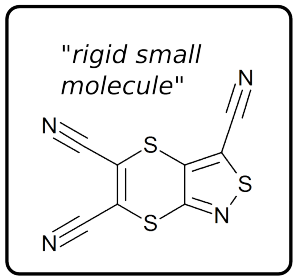
- fast computer code CRYSTAL17[9] with cost-efficient methods[10]
- enabling routine electronic structure calculation of large systems

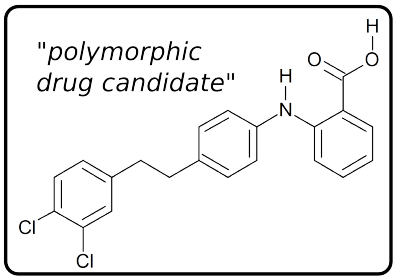

[9] R. Dovesi, et al., *Int. J. Quantum Chem.*, **114**, 1287-1317 (2014)

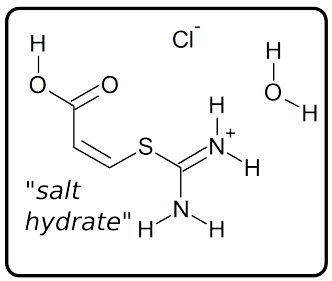
[10] JGB, E. Caldeweyher, S. Grimme, *Phys. Chem. Chem. Phys.*, **18**, 15519 (2016)

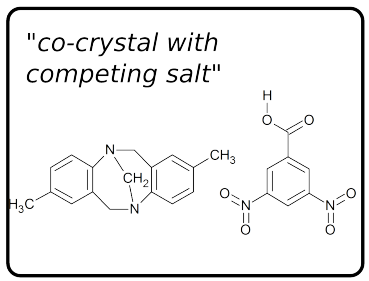
# Outline of talk

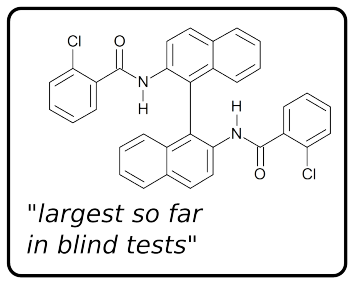
# Promising results in the 6$^{th}$ blind test




| | 22 | 23 | 24 | 25 | 26 |
|---|---|---|---|---|---|
| PBE | 2 | 1-9 | 6 | 3 | 1 |
| PBE-D3 | **1** | **1-9** | **1** | **1** | **1** |
| PBE-MBD | 1 | 1-7 | 1 | 2 | 1 |
| vdW-DF2 | 1 | 4-8 | 1 | 3 | 2 |
| M06L | 1 | 4-13 | 1 | 1 | 7 |

lattice energy on fixed TPSS-D3 structures

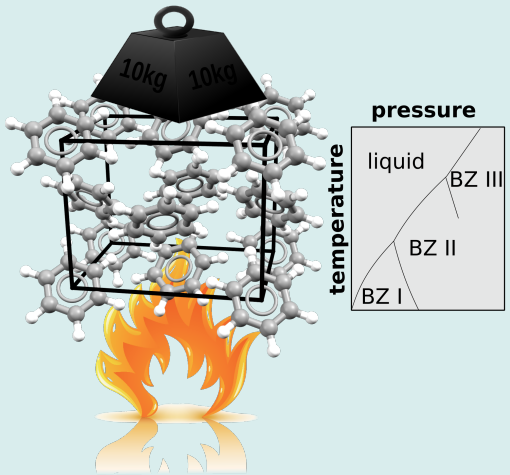
- good lattice energy based ranking of PBE-D3[11—13]
- some structures lost in FF $\longrightarrow$ DFT transition


[11] A. Reilly, et al. *Acta Cryst. B*, **72**, 439 (2016) [12] JGB, S. Grimme *Acta Cryst. B*, **72**, 502 (2016)

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

# Further improvement needed for reliable crystal structure prediction

## 1. Influence of thermodynamic




- *P*-*T*-dependent phase diagramm
- polymorph can change with thermodynamic conditions[14]

## 2. Accurate lattice energy

- improve DFT methods[15]
- many-body methods, like RPA and DMC are promising.[16]

## 3. Treatment of flexibility

- QM derived intramolecular FF
- machine learning potentials with DFT training set

[14] QHA based work in progress [15] triple-$\zeta$ based composite method B97-3c under development

[16] A. Zen, JGB, J. Klimes, D. Alfè, A. Michaelides, *Phys. Rev. Lett.*, to be submitted (2017)

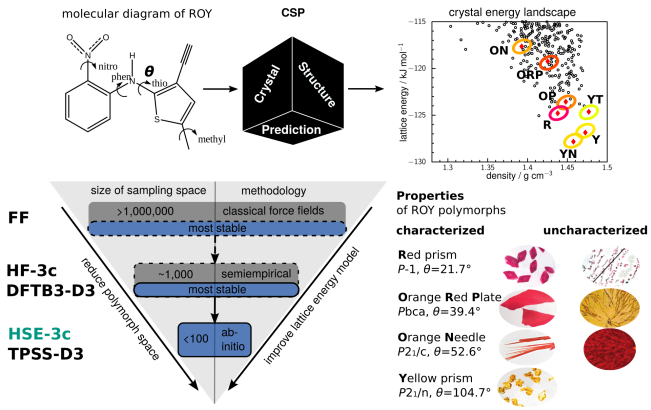
# Summary

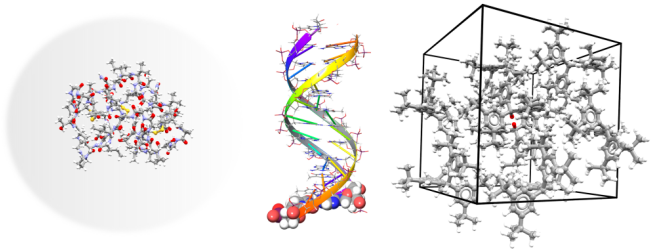
## Conclusions

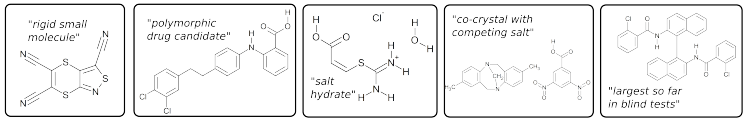
- organic CSP is formidable challenge
- cost-efficient QM methods (HSE-3c) useful for fast electronic structures
- promising results of crystal energy rankings in CSP blind test

## **Outlook** and possible improvements

- exploring the merit of DFT-D methods in context of CSP further
- analysis of free energies contributions





# Acknowledgements


## Collaborators

- Stefan Grimme (Bonn)
- Sally Price (London)
- Angelos Michaelides (London)
- Felix Fernandez-Alonso (Harwell Oxford)
- John Perdew (Philadelphia)
- Bartolomeo Civalleri (Torino)
- Roberto Orlando† (Torino)
- Anthony Reilly (Cambridge)

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# Thanks

# Key references

- Dispersion corrections and DFT development:

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

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

- DFA-DISP for crystal structure prediction:

  JGB, S. Grimme, *Top. Curr. Chem*, **345**, 1 (2014)

  A. Reilly, , R. I. Cooper, C. S. Adjiman, S. Bhattacharya, D. A. Boese, JGB, et al. *Acta Cryst. B*, **72**, 439 (2016)

  S. L. Price, JGB, *Molecular Crystal Structure Prediction*, Elsevier, Melbourne, Australia, in press (2017).

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