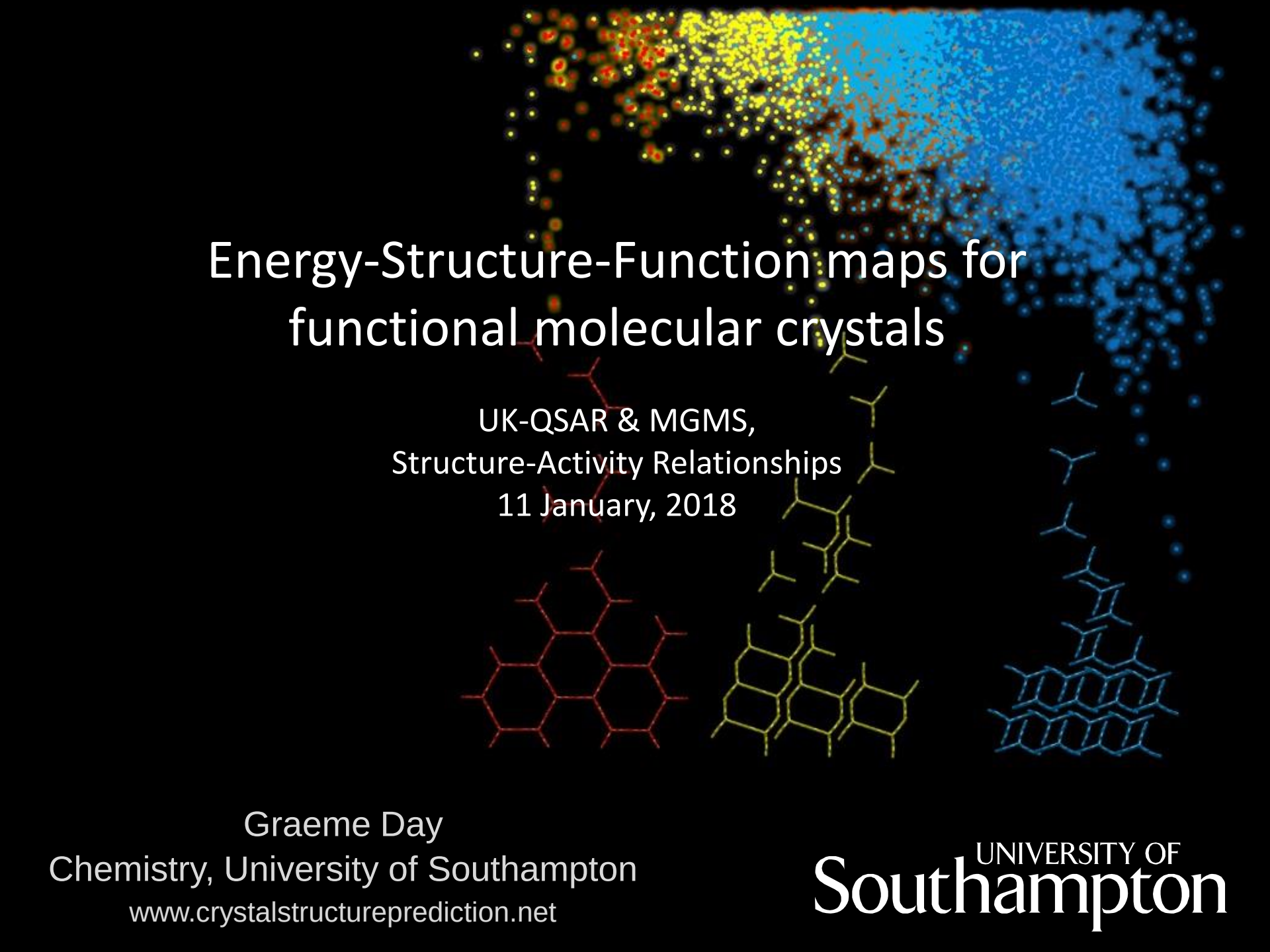


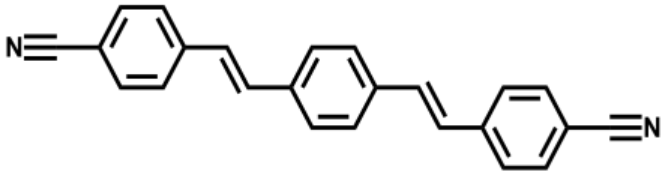
Energy-Structure-Function maps for functional molecular crystals

UK-QSAR & MGMS,
Structure-Activity Relationships
11 January, 2018

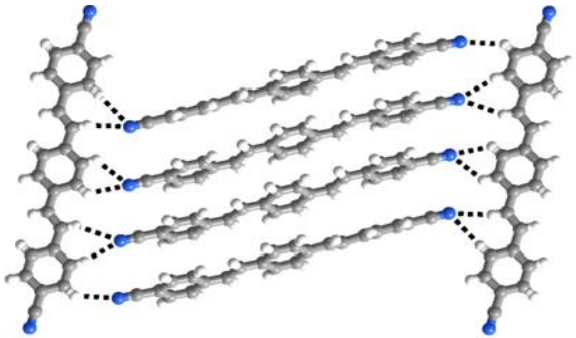
Graeme Day
Chemistry, University of Southampton
www.crystalstructureprediction.net

UNIVERSITY OF Southampton

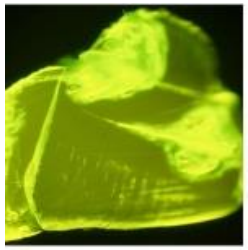
Crystal engineering



molecule
(1,4-bis-*p*-cyano-styrylbenzene)



crystal structure



property: Fluorescence
Single crystal under UV (365 nm)

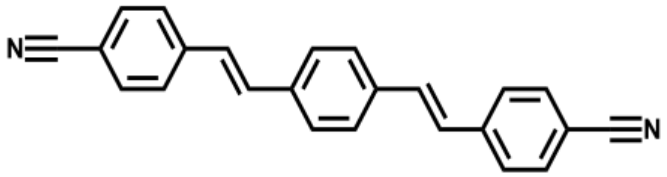
Understanding relationship between molecular structure and crystal packing

and

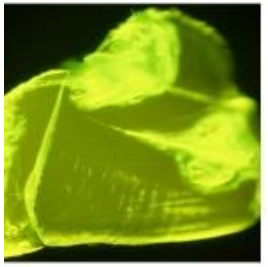
Structure-property relationships

"design" of materials with targeted properties

The challenge of design in molecular crystals



target property
(*e.g.* luminescence)

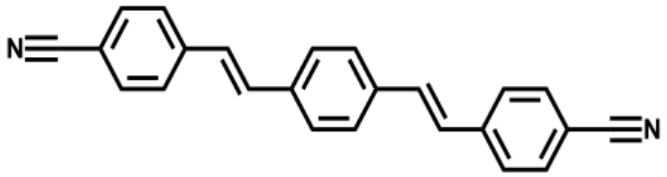


$\lambda_{emission}^{max}$ 532 nm

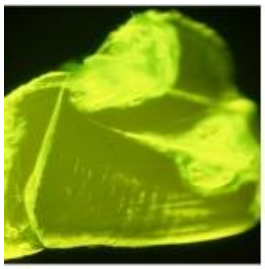
generally a function of
intrinsic molecular properties

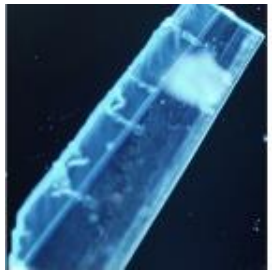
Angew. Chem. Int. Ed, *50*, 12483 (2011)

The challenge of design in molecular crystals



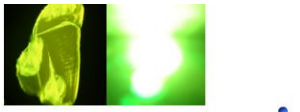
target property
(*e.g.* luminescence)

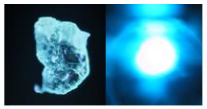


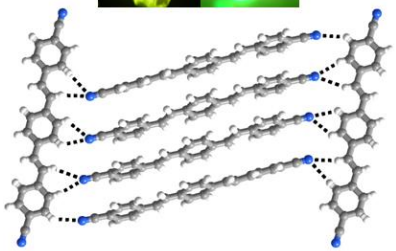


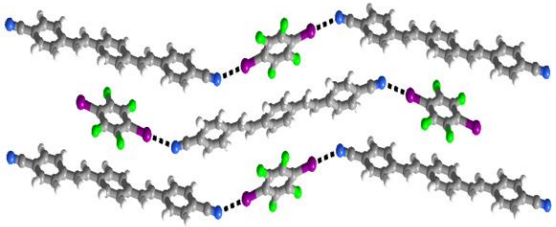
$\lambda_{emission}^{max}$ 532 nm 462 nm

Angew. Chem. Int. Ed, *50*, 12483 (2011)







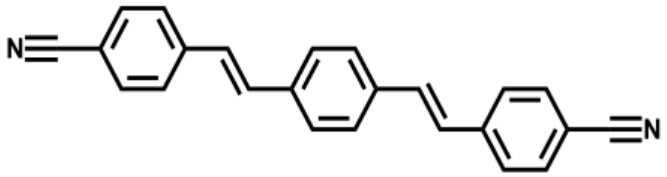


generally a function of
intrinsic molecular properties

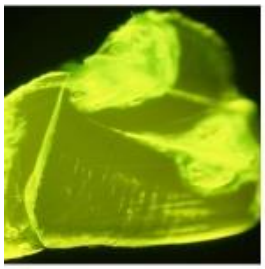
and

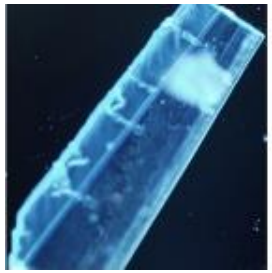
solid state arrangement

The challenge of design in molecular crystals



target property
(*e.g.* luminescence)





$\lambda_{emission}^{max}$ 532 nm 462 nm

Angew. Chem. Int. Ed, *50*, 12483 (2011)

Our challenge

molecular synthesis is well developed
relatively reliable and transferable routes to creating chemical functionality
But what should we synthesise?

unpredictability of crystallisation - self-assembly process
What will be the solid state structure of molecule X?

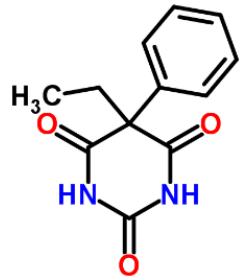
structure-function relationship can be complex
What packing arrangement do we want?

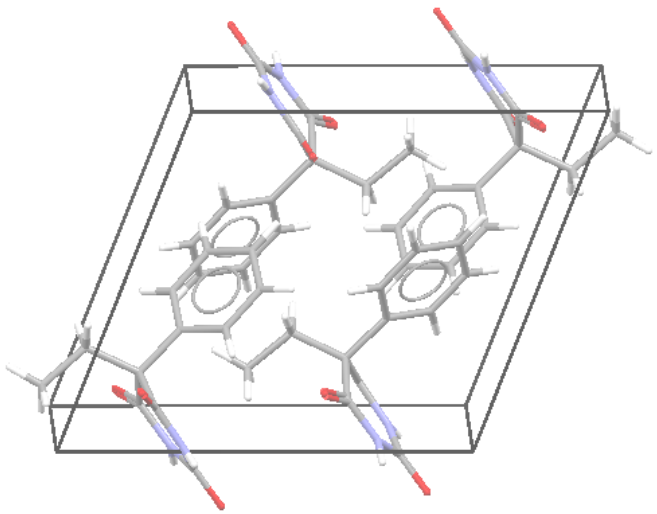
generally a function of
intrinsic molecular properties

and

solid state arrangement

Crystal structure prediction (CSP)





What we hope to get out of CSP

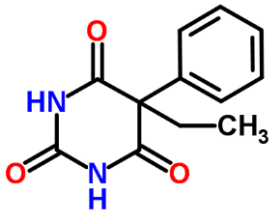
- A complete (as possible) set of the possible crystalline structures for a given molecule (or mixture of molecules).

- Their relative stabilities.
  - lattice energies
  - recent progress: quasi-harmonic free energies: P, T-dependence of structures and relative stabilities

  Nyman and Day, *Phys.Chem.Chem.Phys.*, *18*, 31132 (2016)

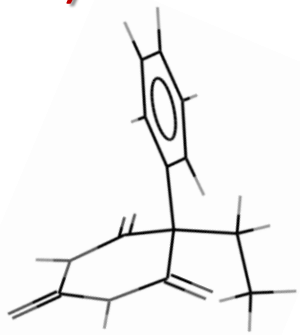
- Structures that are “accurate enough”
  - as models for structure determination
  - for property prediction

Crystal structure prediction (CSP)



conformer searching

QM methods

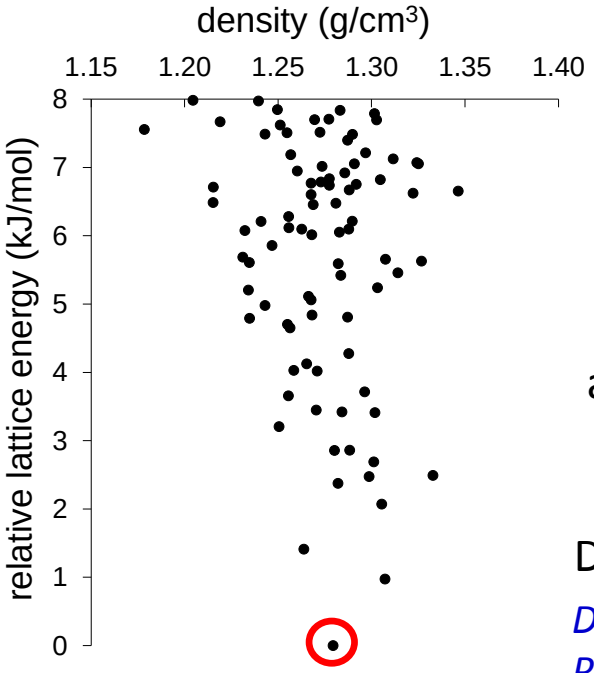


Generate crystal structures with *all* low energy conformers

- sample: molecular positions & orientations, unit cell dimensions
- allow different space group symmetries

Low-discrepancy sampling

Global Lattice Energy Explorer
J. Chem. Theory Comput., *12*, 910 (2016)



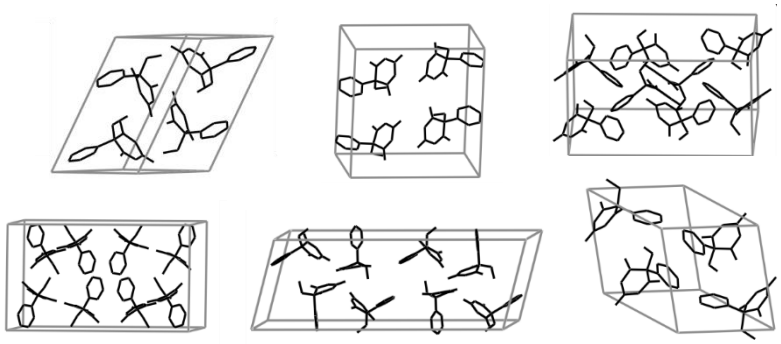
Lattice energy minimisation

intermolecular: anisotropic atom-atom force fields

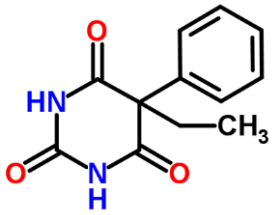
+

DFT intramolecular

DMACRYS
PCCP, *12*, 8478 (2010)



Crystal structure prediction (CSP)

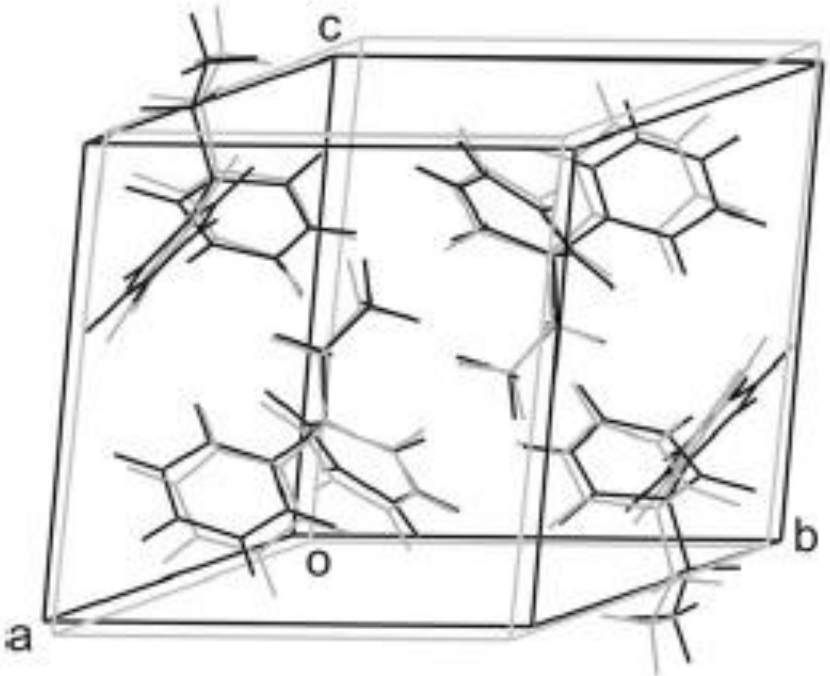


conformer searching

QM methods

Grey = X-ray diffraction determined structure of thermodynamically stable form

Black = global minimum from CSP



Phys.Chem.Chem.Phys., 9, 1693 (2007)

al structures
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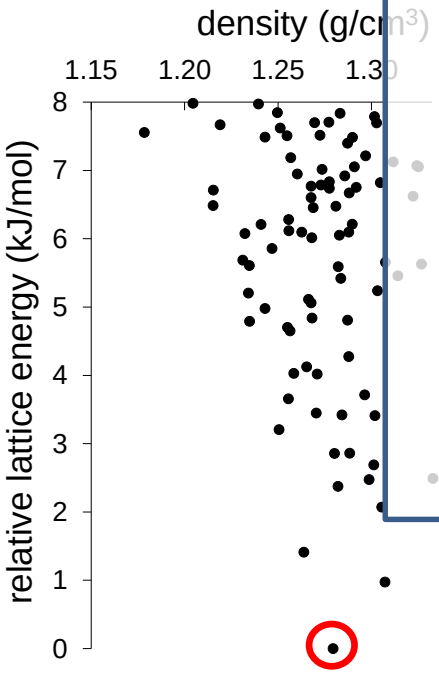
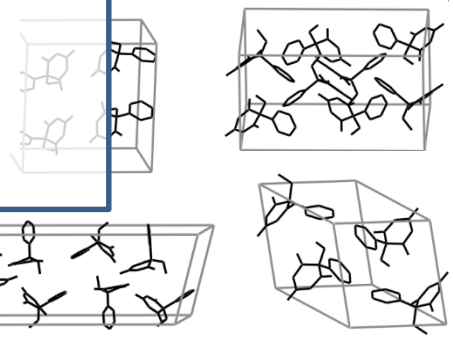


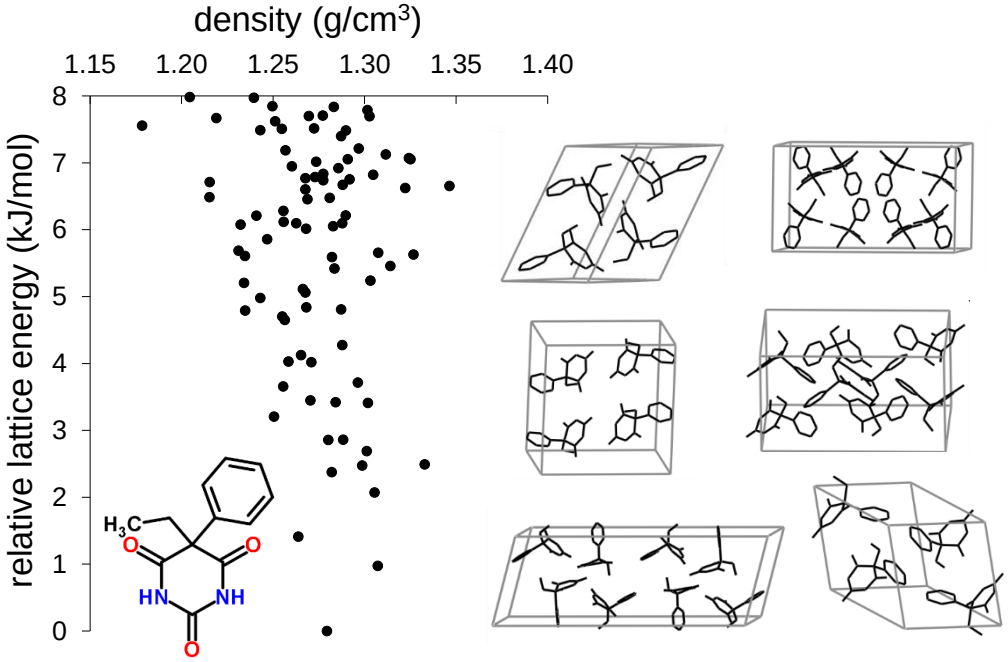


DFT intramolecular

DMACRYS

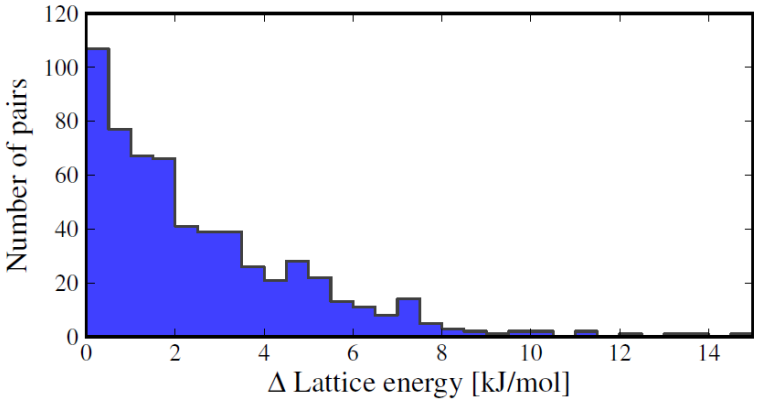
PCCP, *12*, 8478 (2010)

Distributions of energy minima

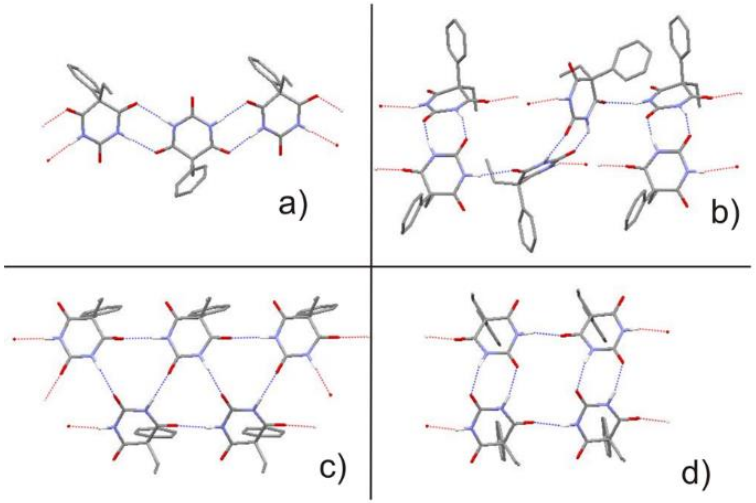


Day et al, PCCP (2007), 9, 1693

Calculations on over 500 pairs of known polymorphs:

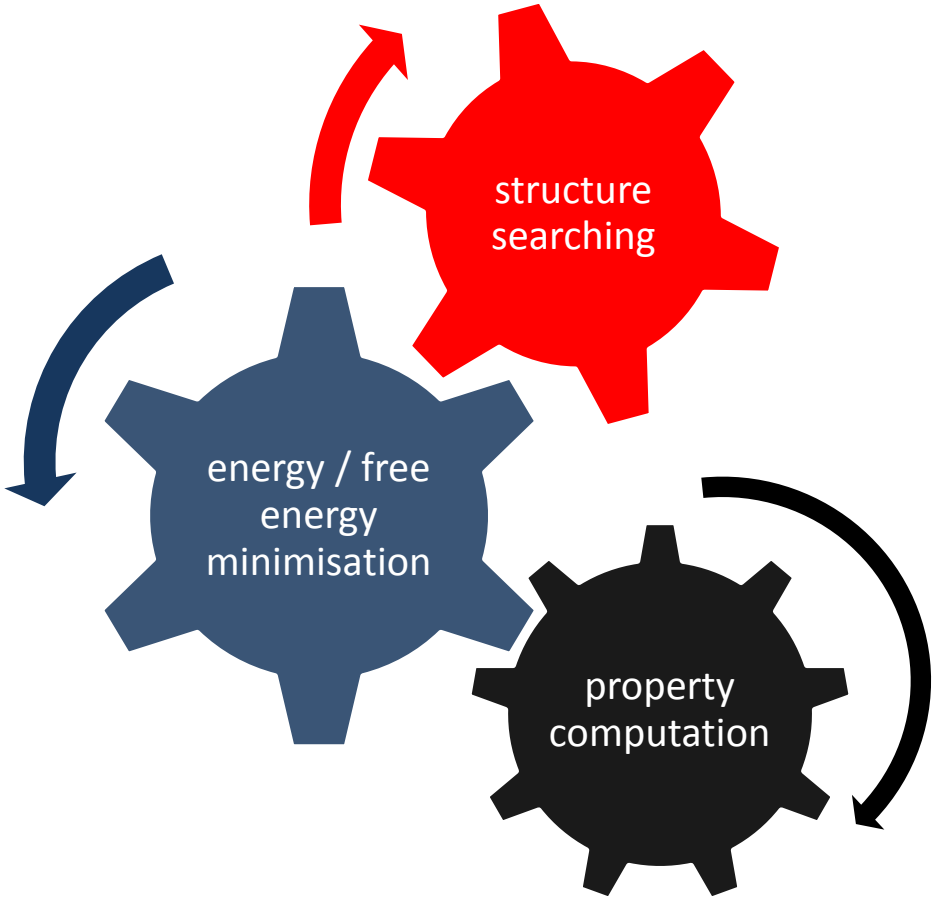


Nyman & Day, *CrystEngComm* (2015), 17, 5154



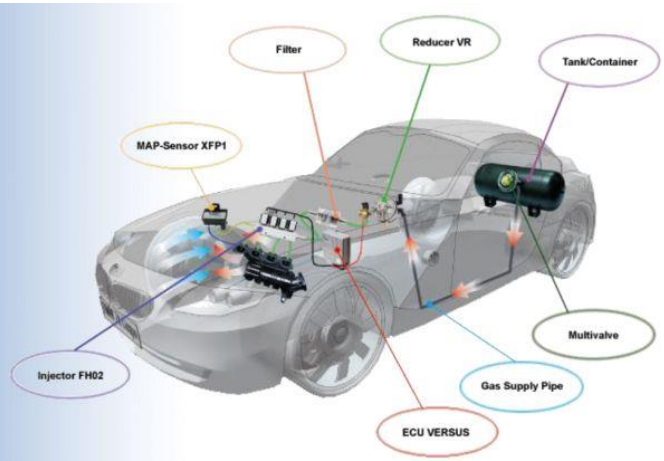
crystal packing is susceptible to small chemical changes

CSP in materials exploration



Case study: computer-guided discovery of a porous molecular crystal

Target property: Methane storage

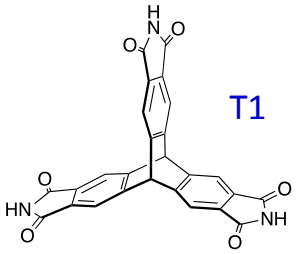


- volumetric deliverable capacity is most relevant metric
- deliverable capacity = storage capacity – residual capacity
  - Records: 180–190 v STP/v
  - **> 150 v STP/v is 'good'**

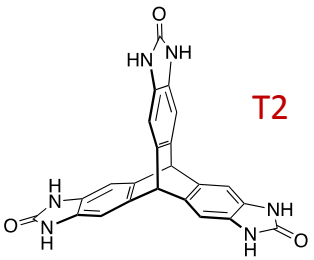
Methane deliverable capacities for the best reported materials
(all are metal organic frameworks)

	Uptake at 65 bar (v STP/v)	Deliverable capacity (v STP/v)[a]	Ref.
HKUST-1	262	181	b
MOF-5	215	185	b
PCN-14	240	160	b
Mg-MOF-74	230	143	b
Ni-MOF-74	259	141	b
Co-MOF-74	249	136	b
NU-125	232	183	c
NU-111	206	179	c
UTSA-20	230	170	c
UTSA-80a	233	174	d
Co(bdp)	203	197	e

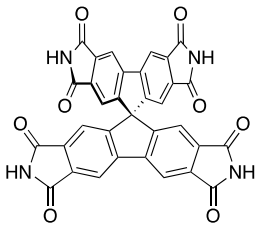
[a] The difference in uptake between 65 bar and 5.8 bar [for **T2**, HKUST-1, MOF-5, & Co(bdp)] or 5 bar (for the rest). [b] Mason *et al.*, *Chem. Sci.*, **2014**, *5*, 32–51. [c] Peng *et al.*, *J. Am. Chem. Soc.*, **2013**, *135 (32)*, 11887–11894. [d] Wen *et al.*, *J. Mater. Chem. A*, **2014**, *2*, 11516–11522. [e] Mason *et al.*, *Nature*, **2015**, *527*, 357–361.



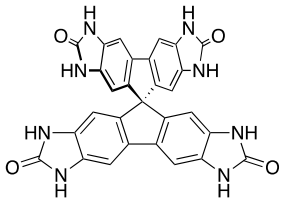
T1



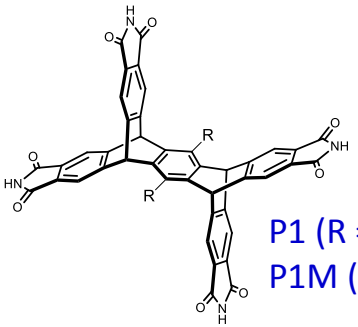
T2



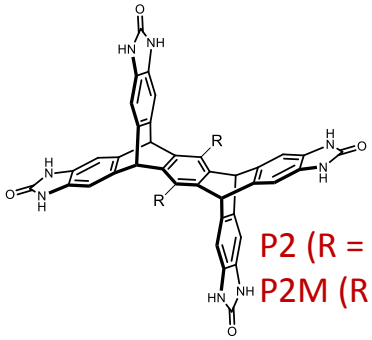
S1



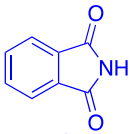
S2



P1 (R = H)
P1M (R = CH_3)



P2 (R = H)
P2M (R = CH_3)



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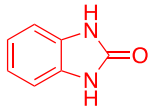


benzimidazolones

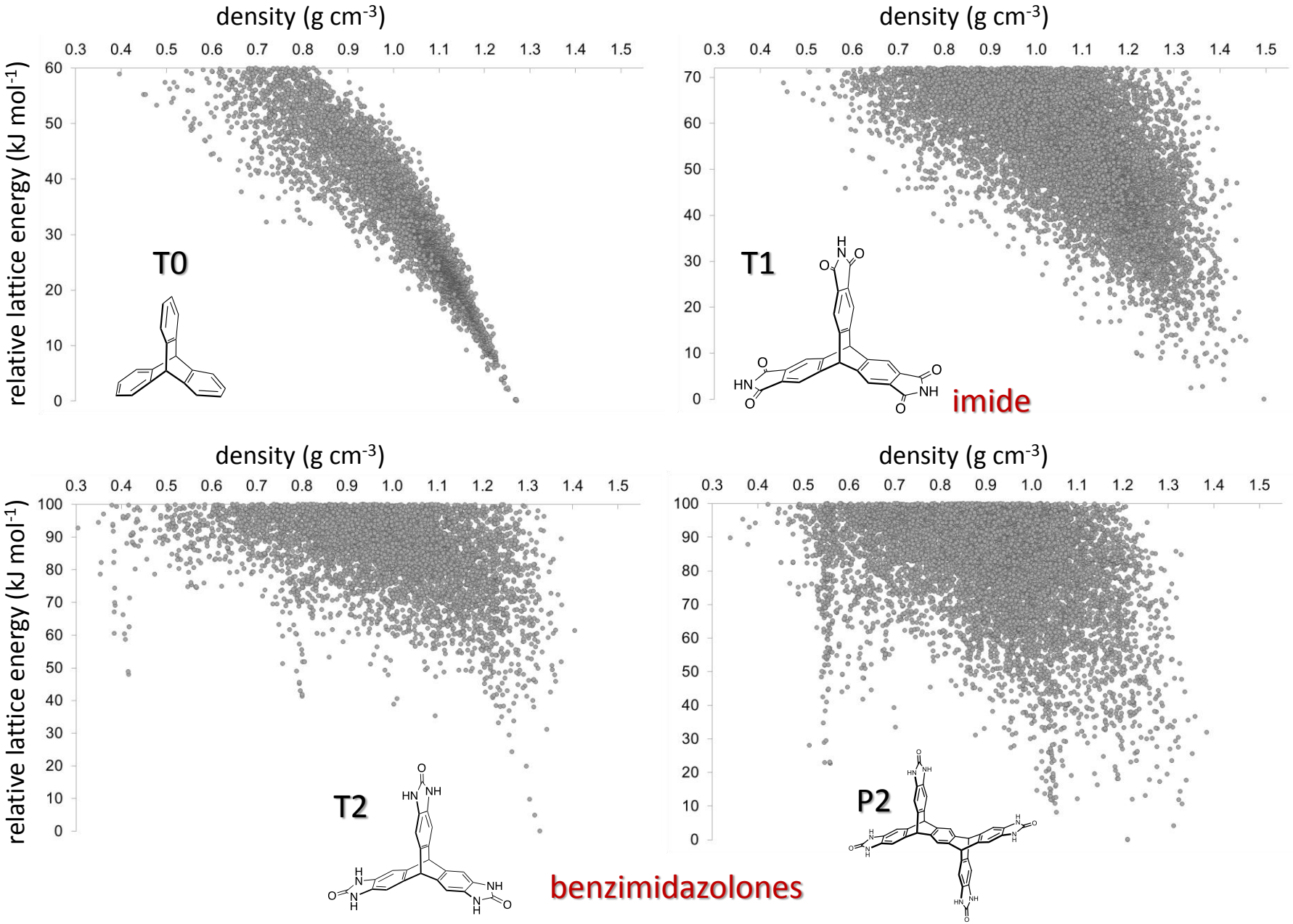
Design Hypothesis – rigid molecular core + strong, directional interactions to form porous networks

Question – which of a set of candidate molecules is most likely to give properties we require for a given application?

Nature (2017), *543*, 657-664

Porous crystal discovery: energy – density distributions

GLEE: J. Chem. Theory Comput., 12, 910 (2016)



Porous crystal discovery: energy – density distributions

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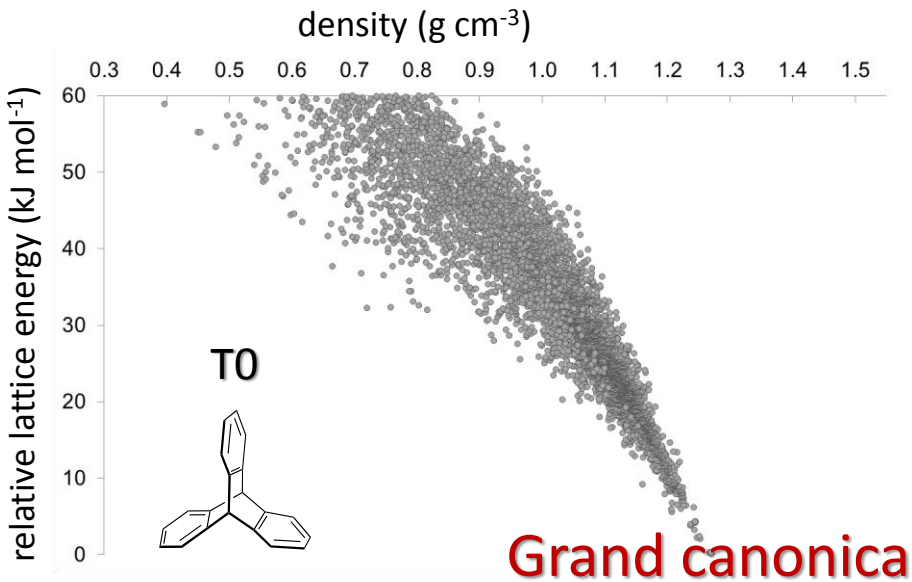
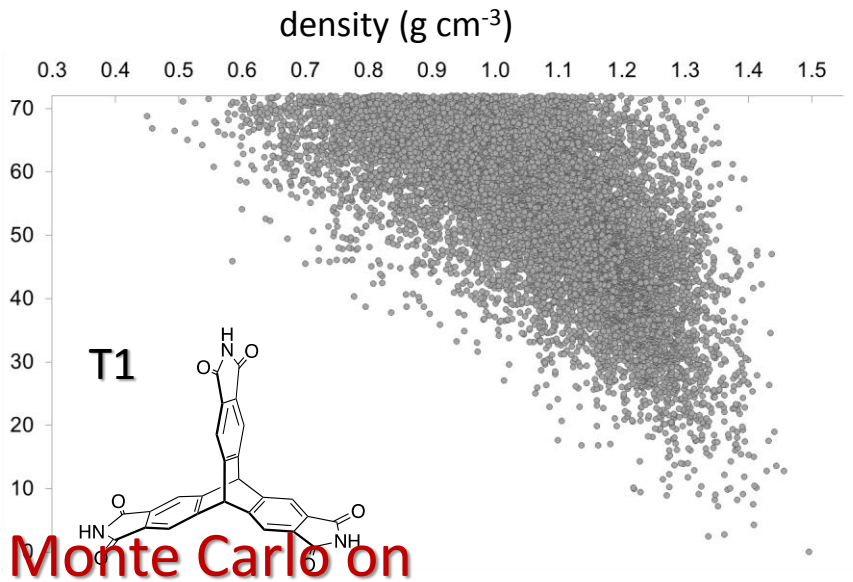
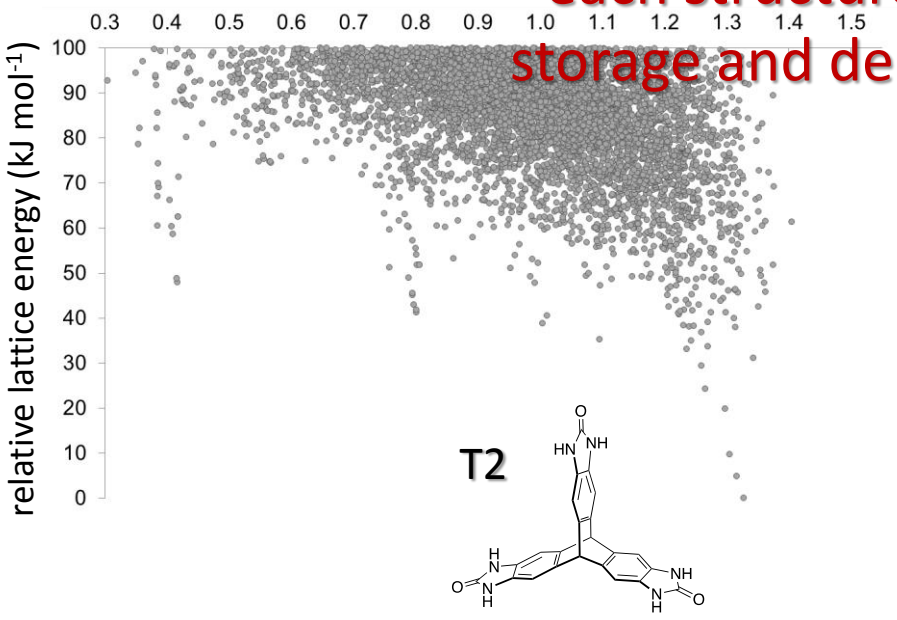
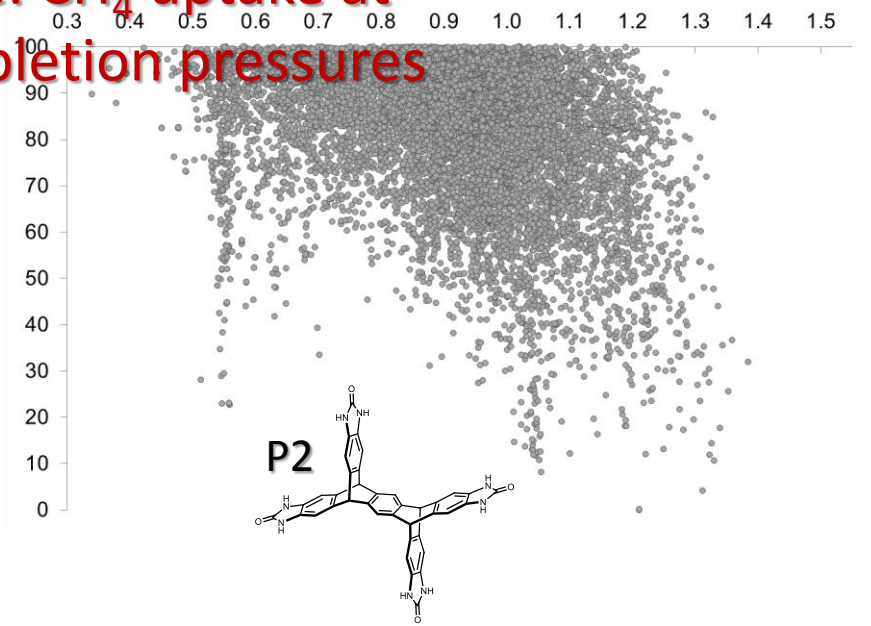


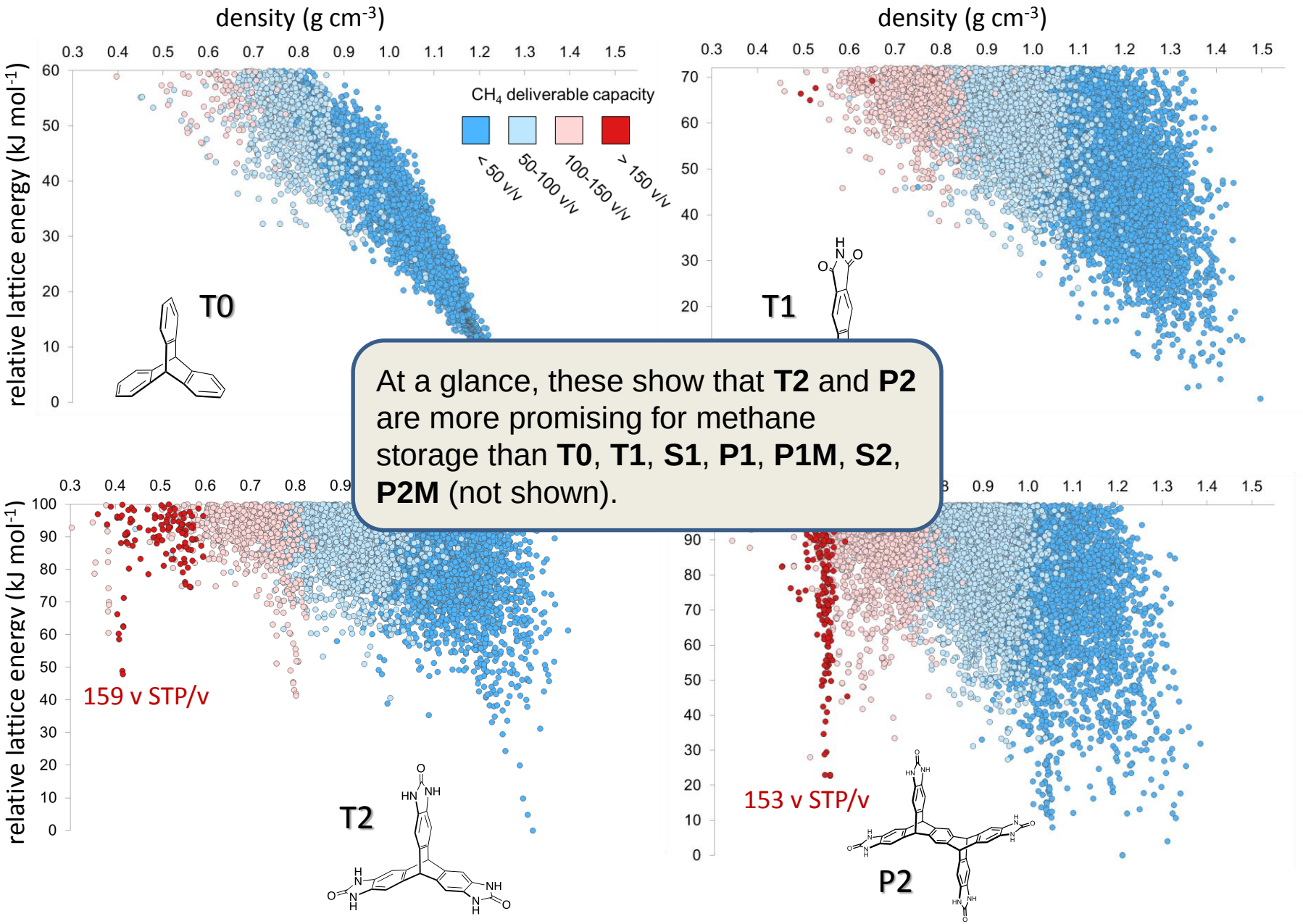


Grand canonical Monte Carlo on each structure: CH_4 uptake at storage and depletion pressures



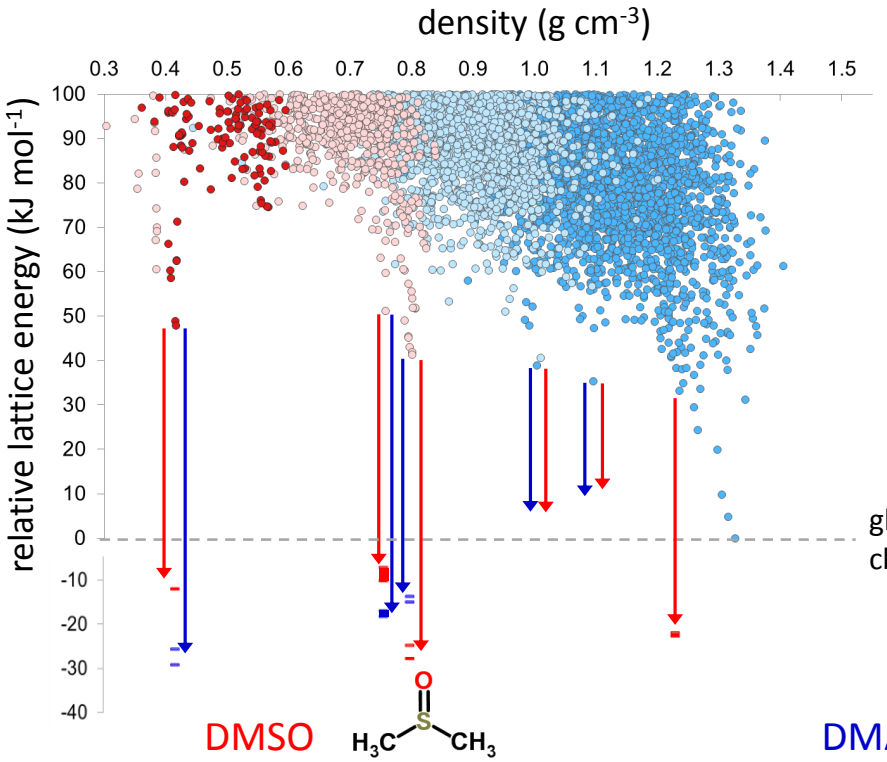


Energy-structure-function maps: methane deliverable capacity



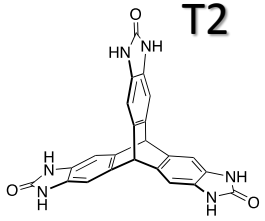
At a glance, these show that **T2** and **P2** are more promising for methane storage than **T0**, **T1**, **S1**, **P1**, **P1M**, **S2**, **P2M** (not shown).

Porous crystal discovery: T2 solvent stabilisation

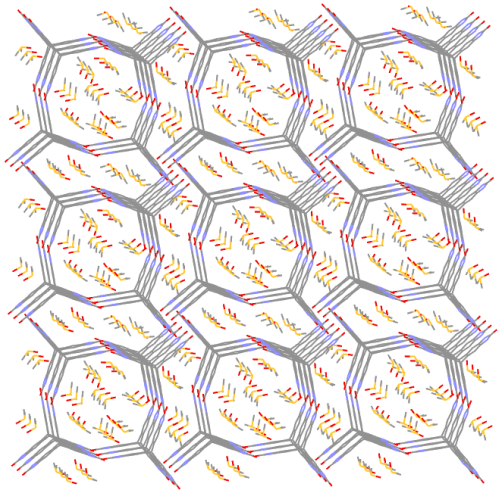


global minimum,
close packed, non-porous

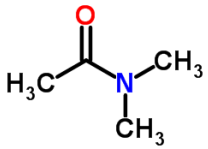
T2

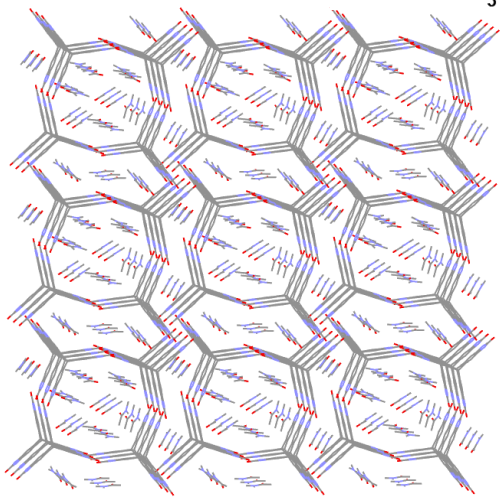


DMSO



DMAc





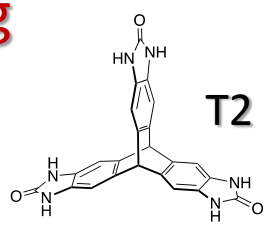
Structures filled with solvent by Monte Carlo simulation with variable solvent loading.

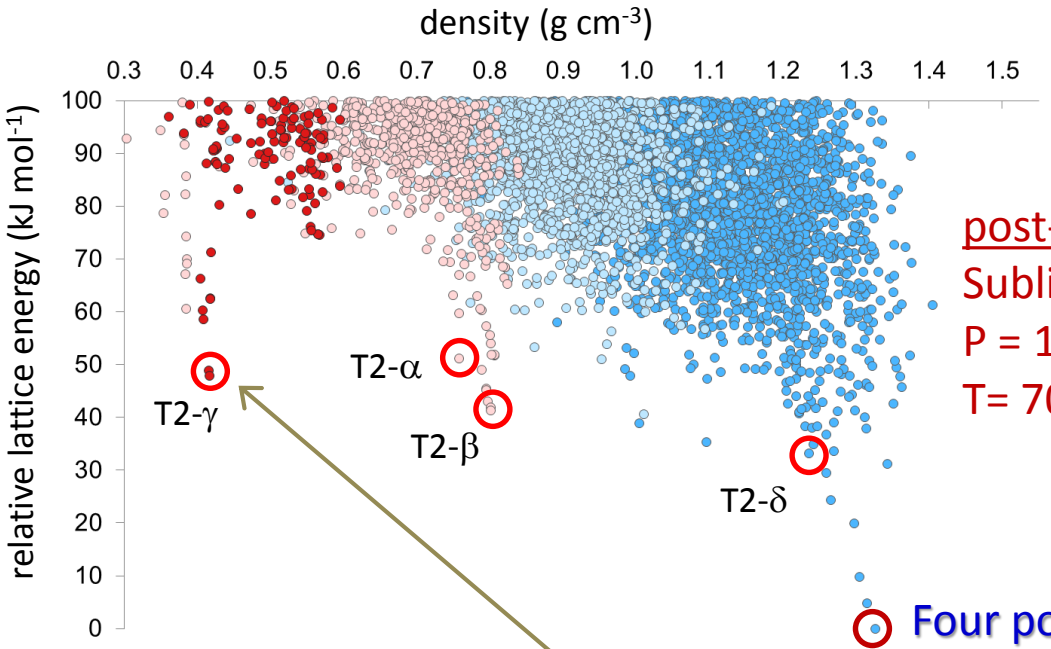
Final energies corrected by simulation on bulk solvent and corrected for difference in dynamical energies between liquid and crystal.

Some, *but not all*, porous structures can be stabilised with respect to the global minimum.

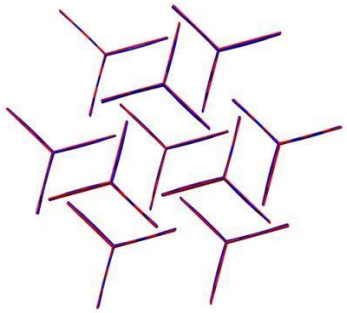
Stabilising influence of different solvents varies between porous structures → possible solvent selectivity.

T2 synthesis and crystallisation screening





post-publication
Sublimation at
P = 1 x 10^{-3} hPa (10^{-6} bar)
T= 700 °C

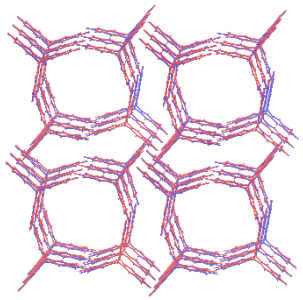


$RMSD_{30}$ = 0.135 Å

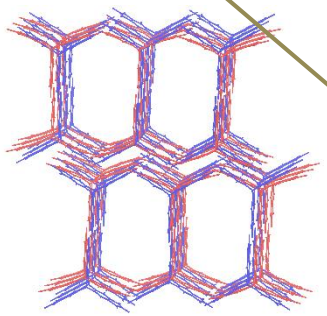
Four porous phases.
All can be desolvated, if done carefully.

Structures found during crystallisation screening:

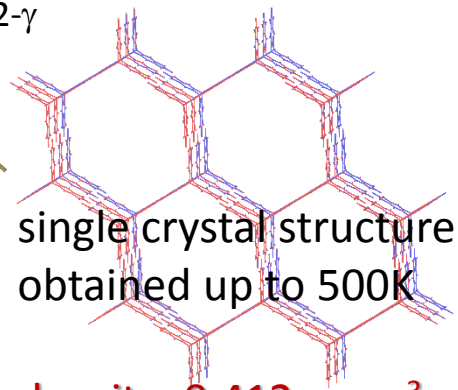
T2-α



T2-β



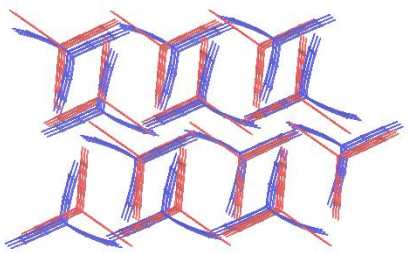
T2-γ



single crystal structure obtained up to 500K

density: 0.412 g cm^{-3}
pore size: 1.99 nm

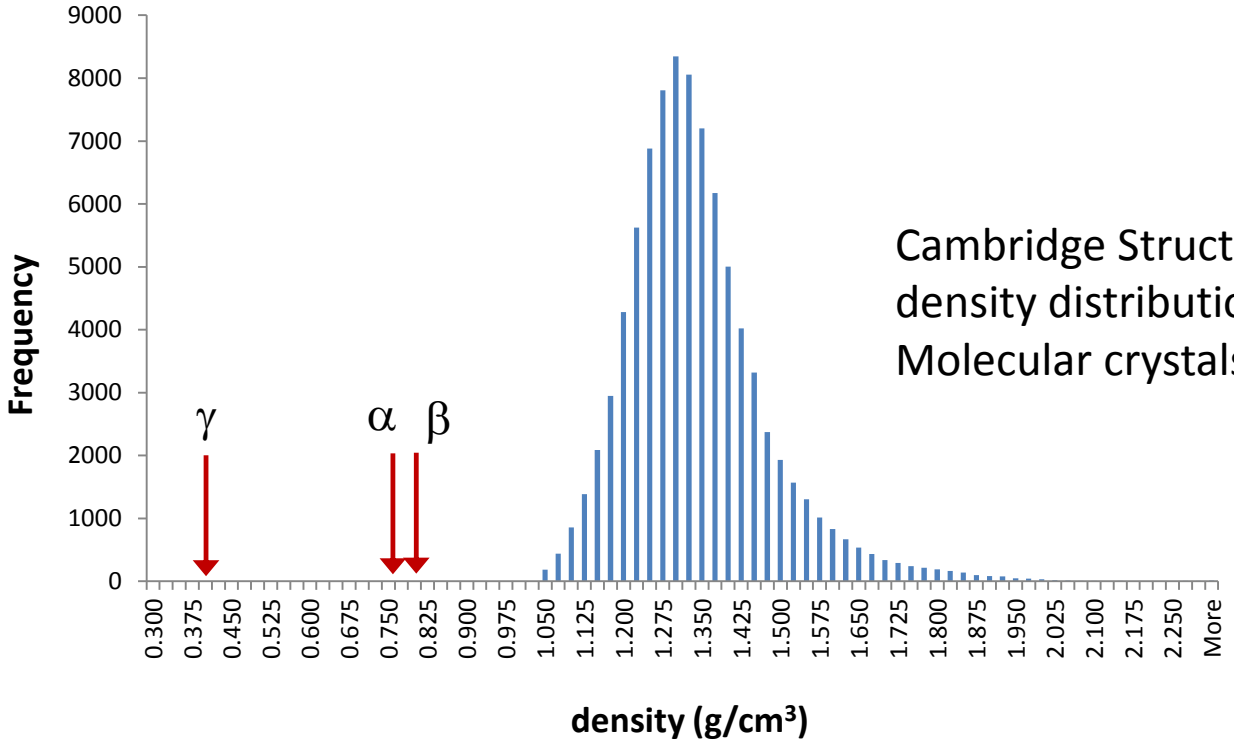
T2-δ



predicted (red) vs X-ray structure (blue)

Nature (2017), *543*, 657-664

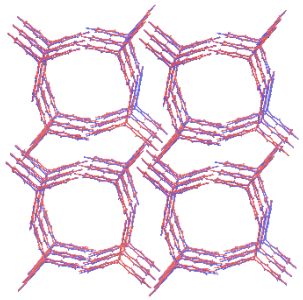
T2 synthesis and crystallisation screening



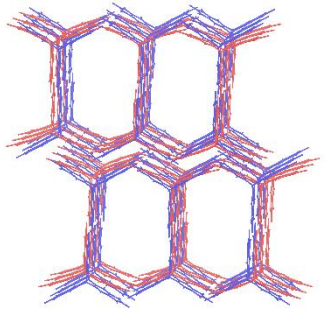
Cambridge Structural Database
density distribution
Molecular crystals, C, N, O, H

Structures found during crystallisation screening:

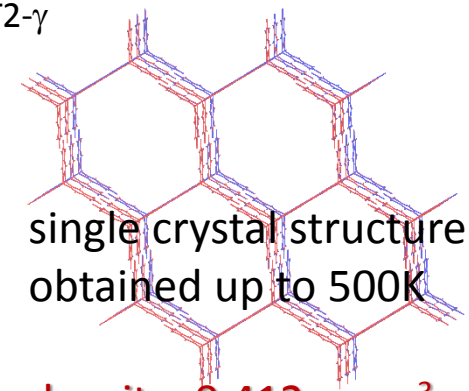
T2-α



T2-β



T2-γ



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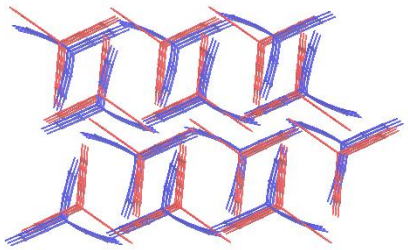
T2-δ

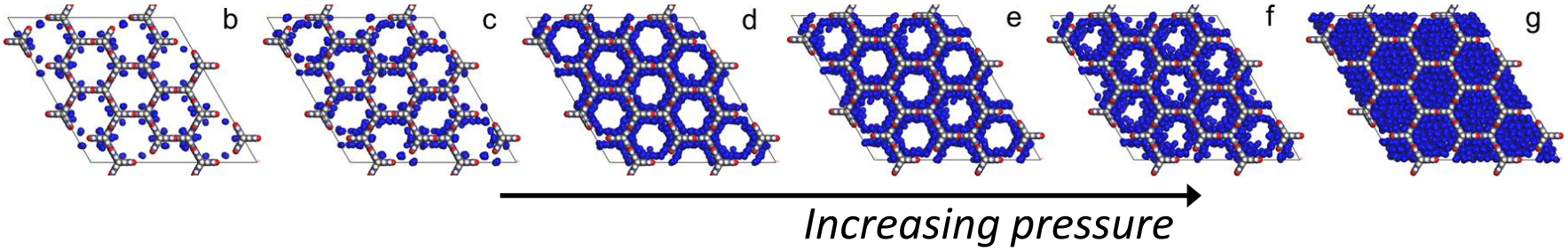


predicted (red) vs X-ray structure (blue)

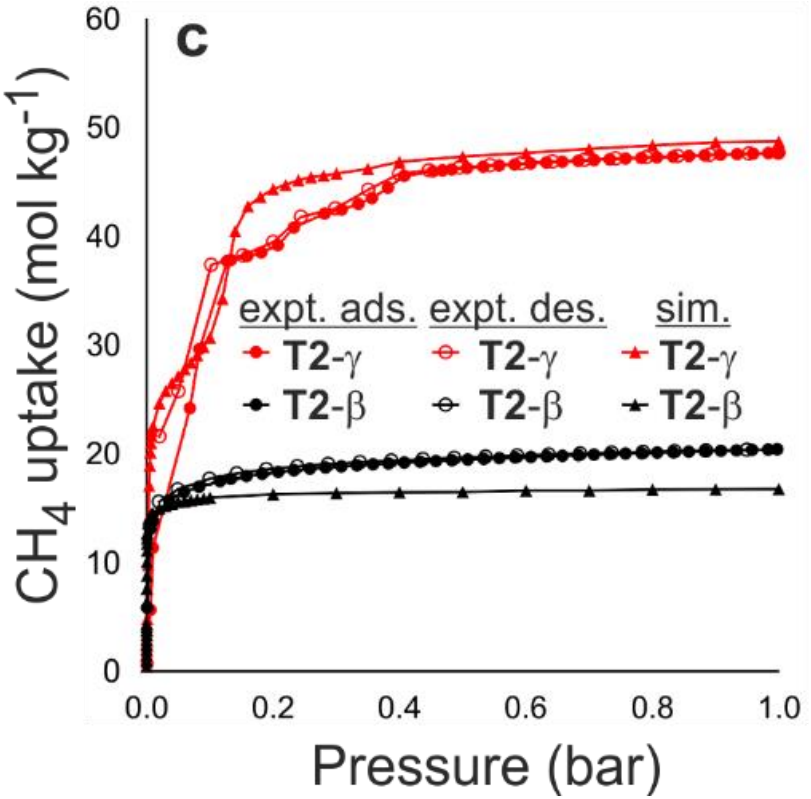
Nature (2017), *543*, 657-664

T2 experimental vs predicted properties

Sorption isotherms can be predicted *a priori*.



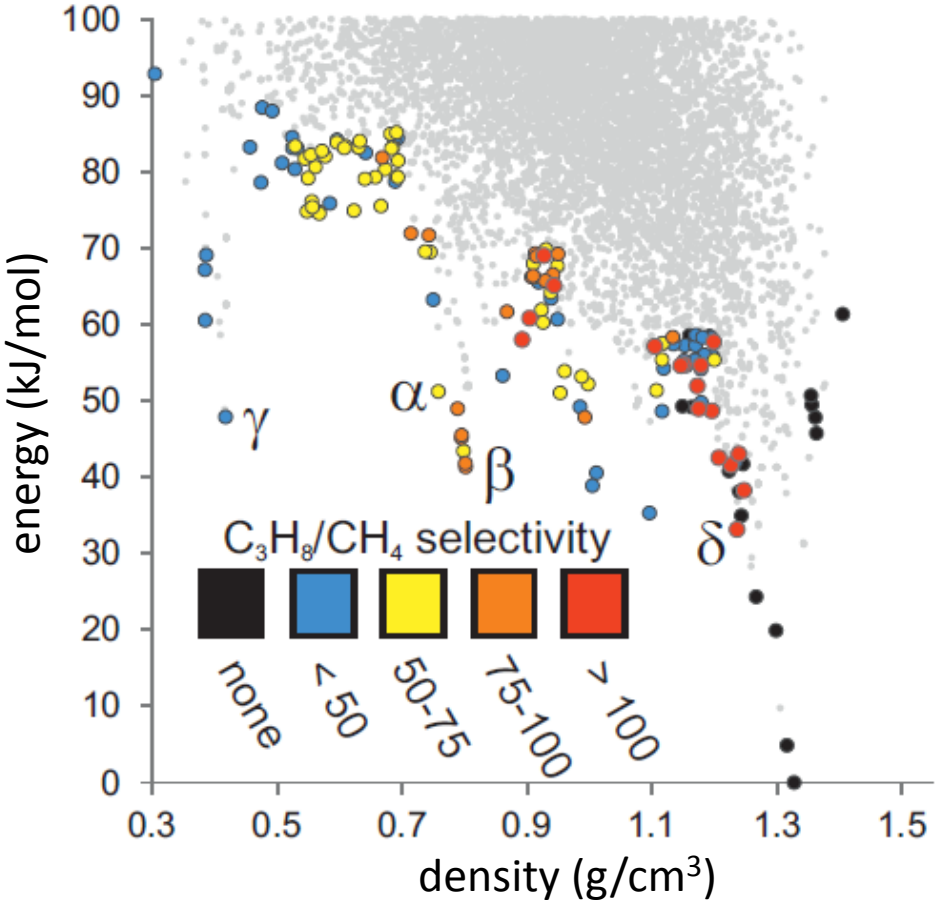
expt vs grand canonical Monte Carlo

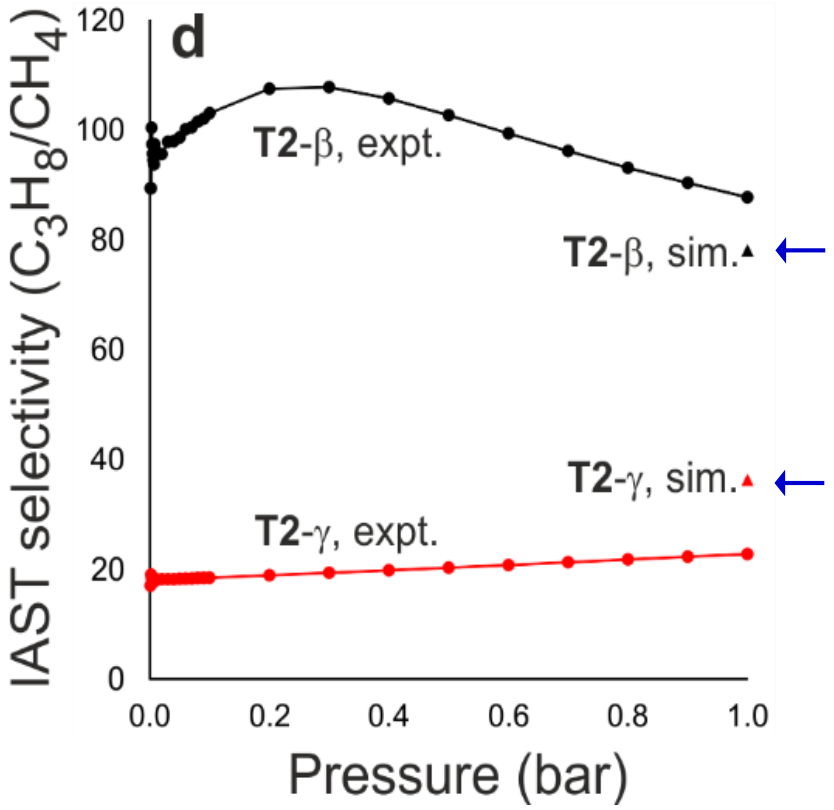


ESF maps for gas selectivity

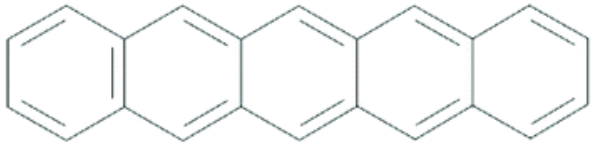
Energy-Structure-Function maps can be produced for *any target property that is calculable from crystal structure.*

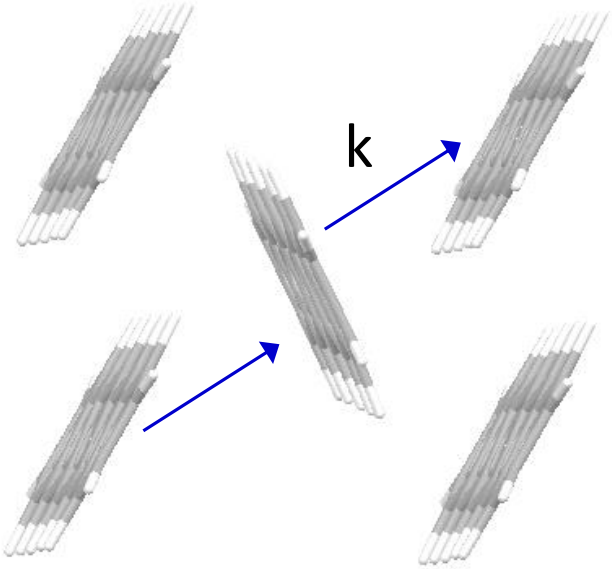
C_3H_8 / CH_4 selectivity prediction





Electron or hole transport in molecular crystals
high mobility organic semiconductors





High mobilities often seen in polyaromatic hydrocarbons, *eg.* pentacene.

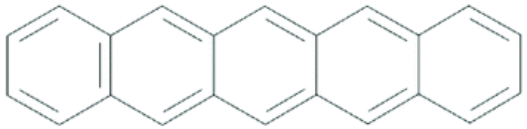
<u>hoping rate</u>

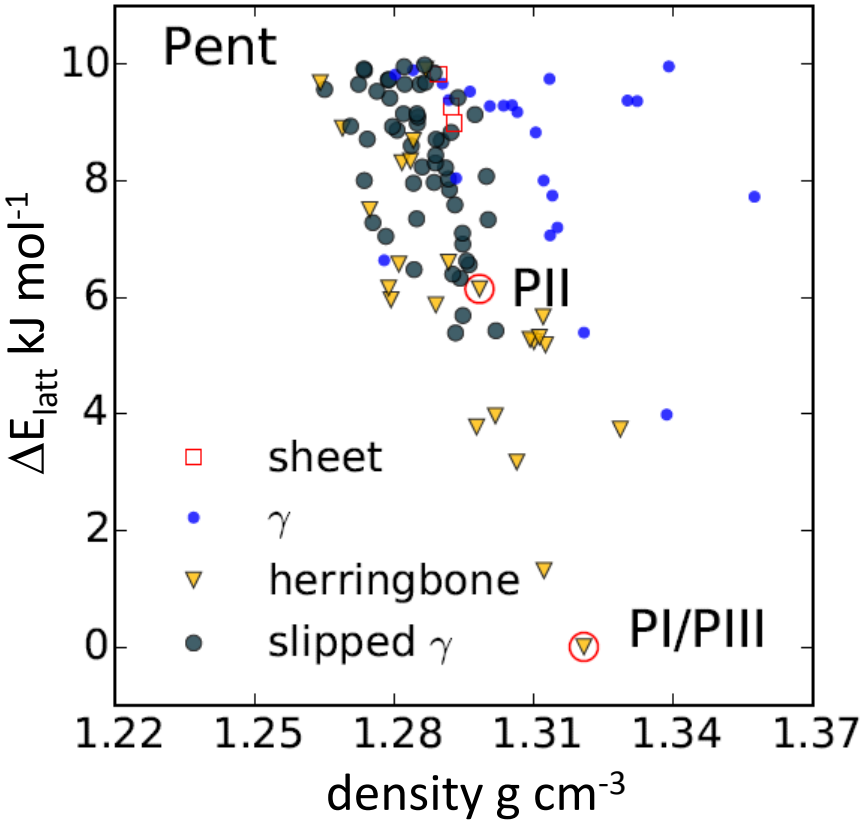
$$k = (t^2/\hbar)(\pi/\lambda kT)^{\frac{1}{2}} e^{(-\lambda/4kT)} \rightarrow \text{mobility}$$

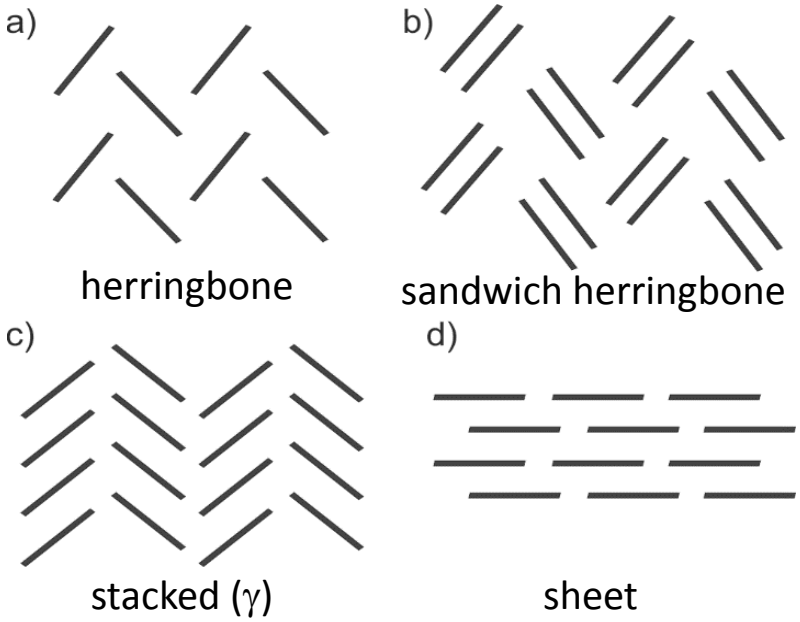
λ = molecular reorganisation energy: molecular property

t = electronic coupling (transfer integral): depends on packing

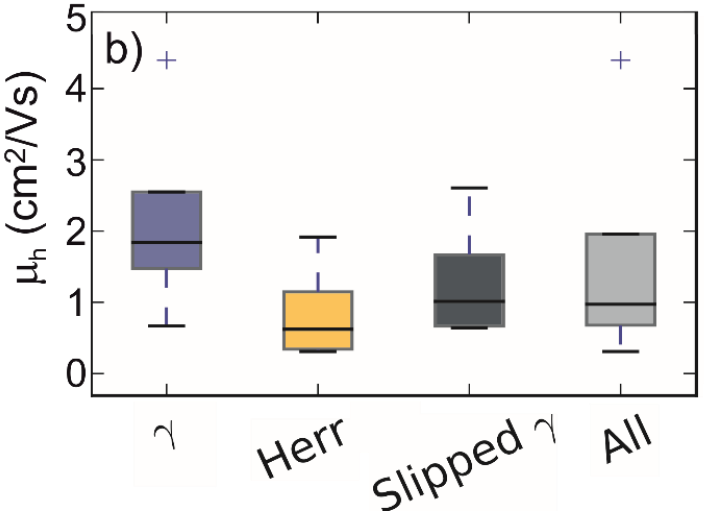
Pentacene hole mobility landscape





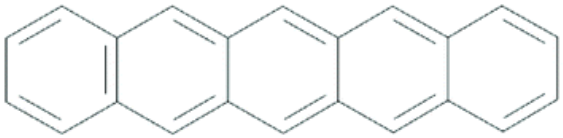


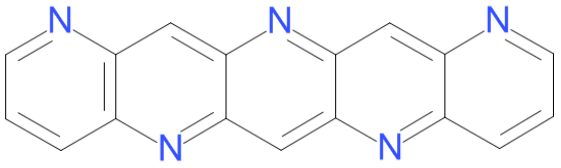
Extracting structure-property relationships

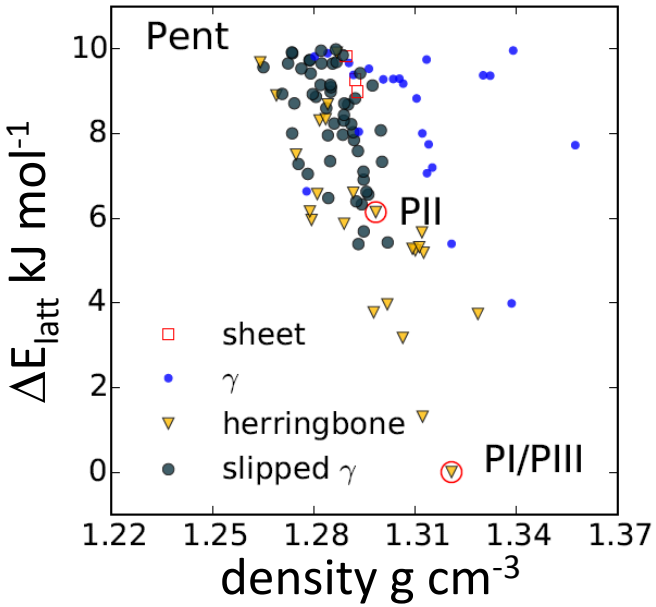


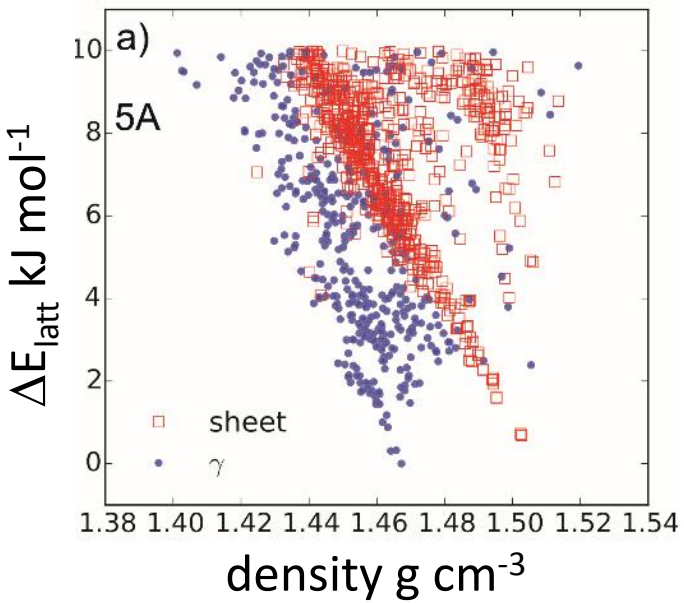
Campbell, Yang, Day, *J. Mat. Chem. C* (2017), 5, 757.

Effects of substitution on the packing landscape

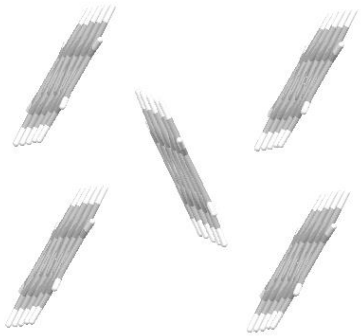


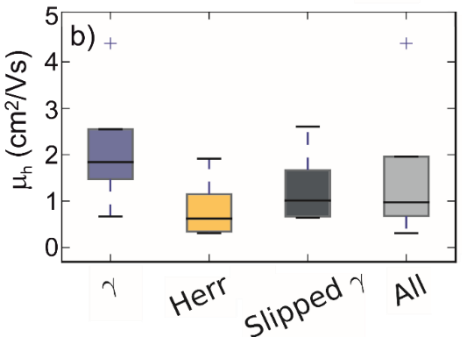


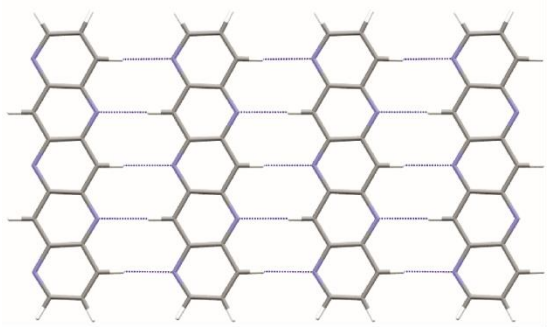




Recall pentacene mobility results:

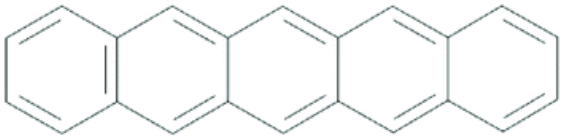


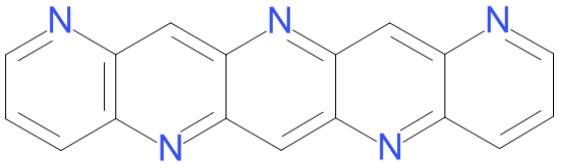


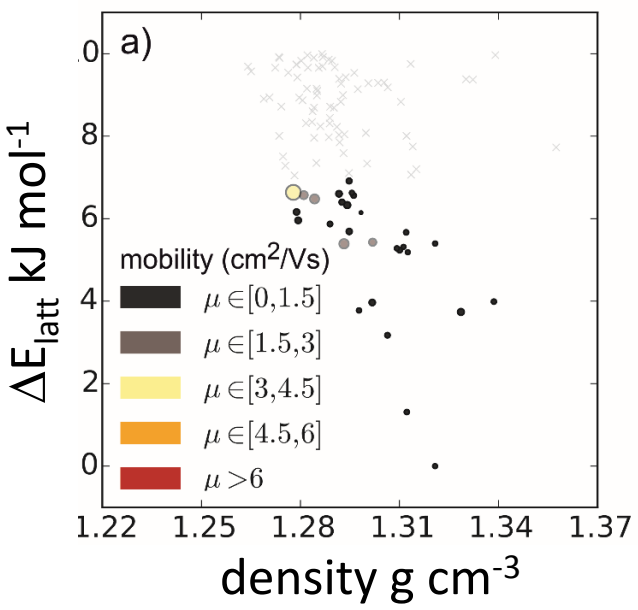


Campbell, Yang, Day, *J. Mat. Chem. C* (2017), 5, 757.

Effects of substitution on the packing landscape

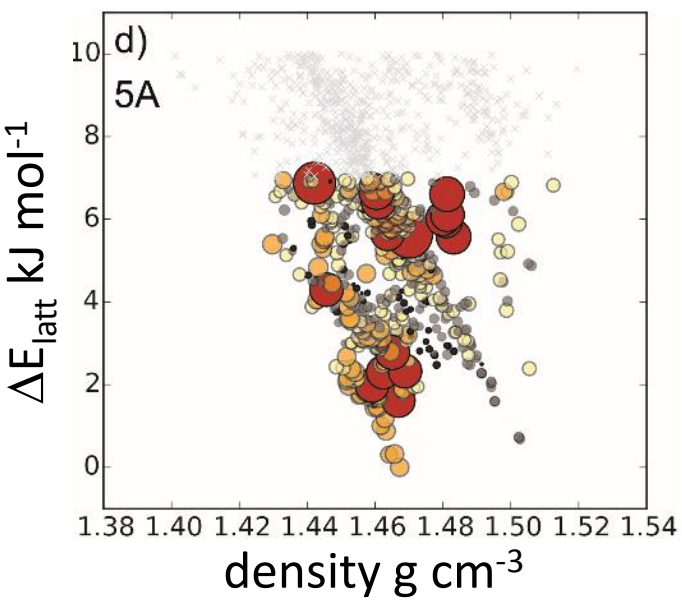


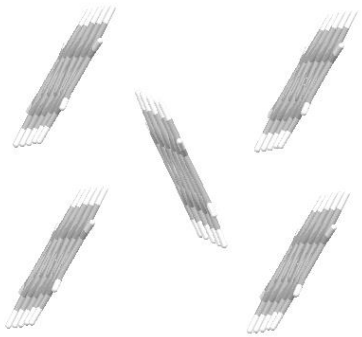


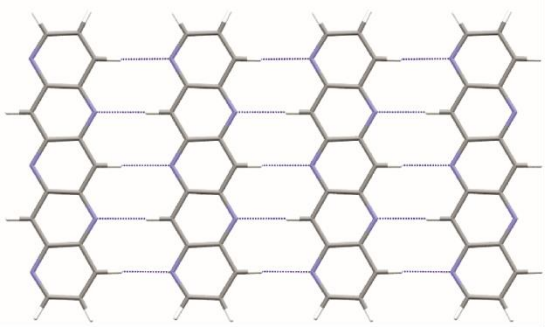


hole or electron mobility landscapes

$\mu \in [0,1.5]$
$\mu \in [1.5,3]$
$\mu \in [3,4.5]$
$\mu \in [4.5,6]$
$\mu > 6$ cm²/Vs

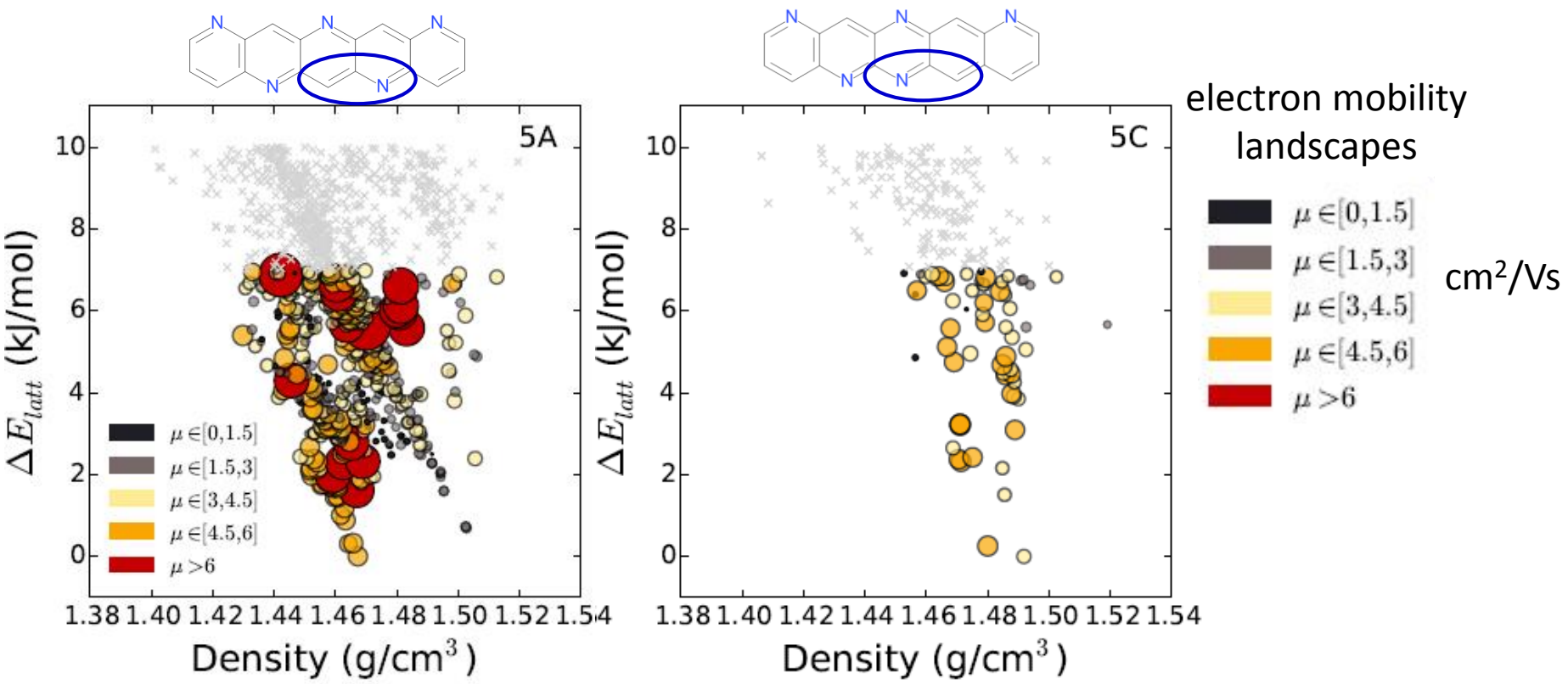






Campbell, Yang, Day, *J. Mat. Chem. C* (2017), 5, 757.

substitution pattern effects

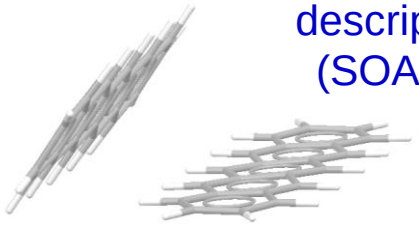


The mobility landscape is very sensitive to molecular and crystal structure.

Campbell, Yang, Day, *J. Mat. Chem. C* (2017), 5, 757.

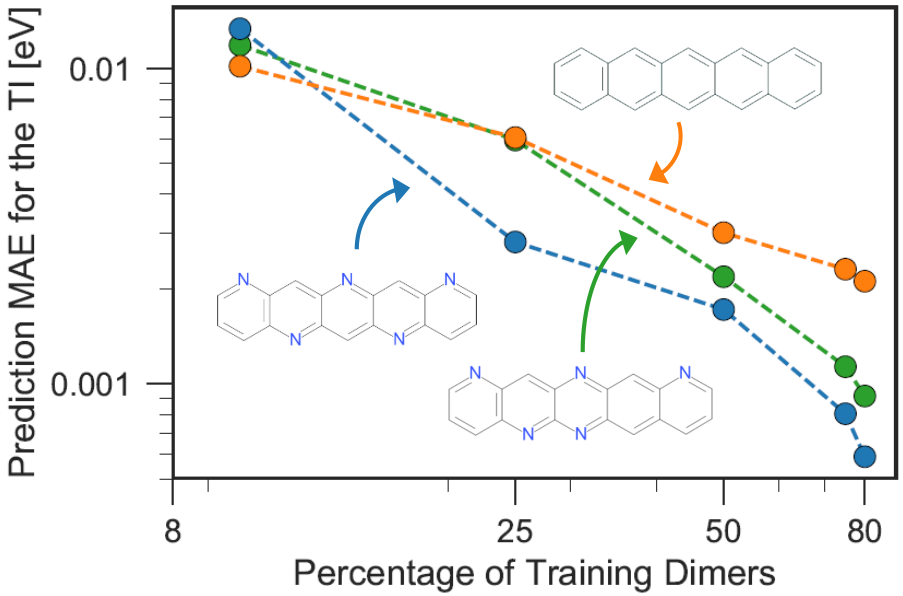
Towards higher-throughput ESF map generation

- CSP calculations on rigid, pentacene-sized molecules now < 1 day (using ~200 CPUs)
- Property predictions become the limiting step
- Machine learning looks promising for accelerating property predictions.



geometric descriptor (SOAP) → Gaussian process regression

$$k = (t^2/\hbar)(\pi/\lambda kT)^{\frac{1}{2}} e^{(-\lambda/4kT)}$$



Chem. Sci. (2018) 9, 1289-1300

SOAP descriptor and structural similarity

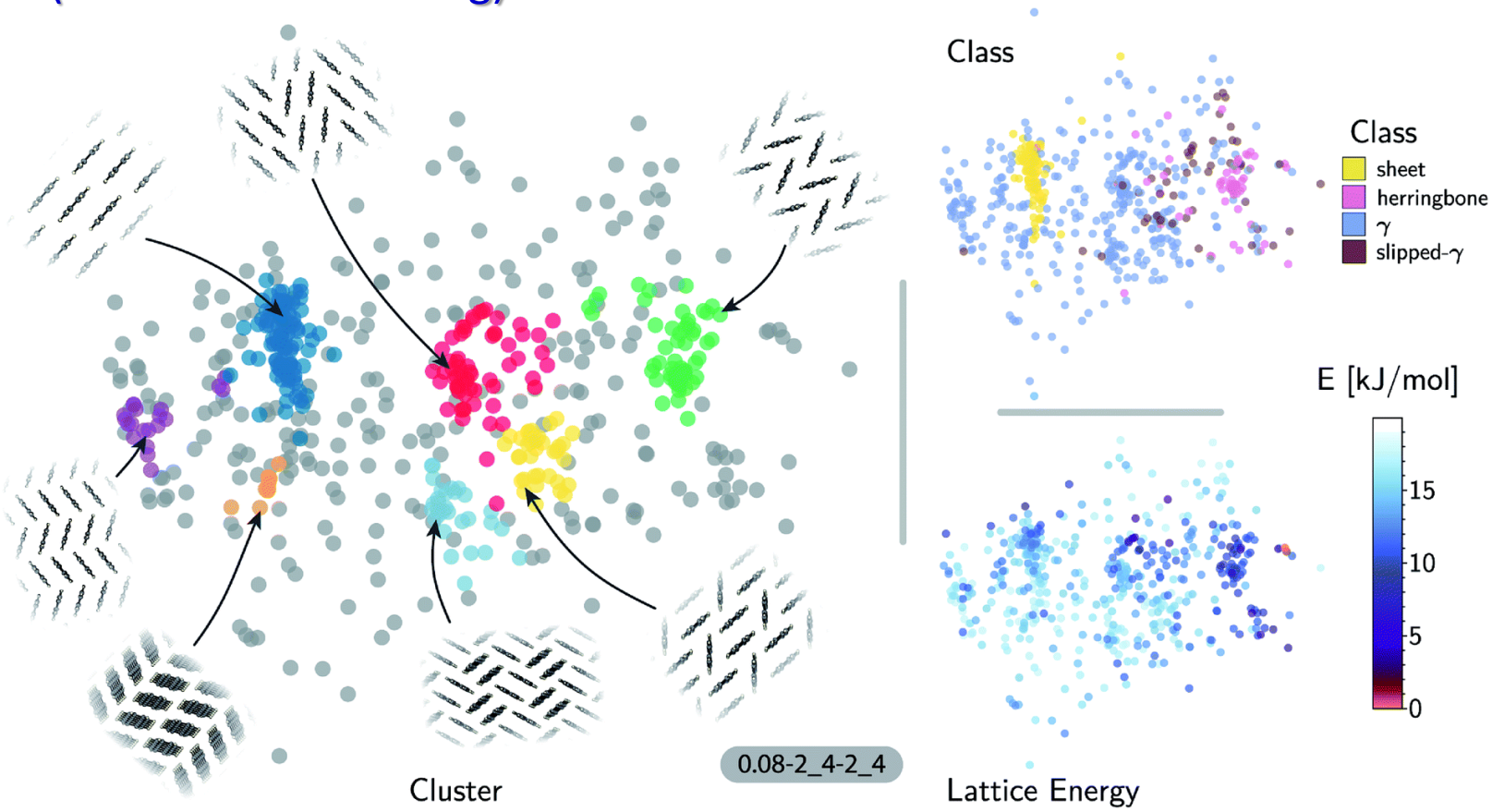
$$\rho_{\mathcal{X}_i^{\mathrm{A}}}{}^{\alpha}(\boldsymbol{r}) = \sum_{k \in A^{\alpha}} \exp\left[-\left(\boldsymbol{r}-\boldsymbol{r}_k\right)^2 / 2\varsigma^2\right] f_{r_c}\left(|\boldsymbol{r}_{ik}|\right).$$

$$k\left(\mathcal{X}_i^{\mathrm{A}}, \mathcal{X}_j^{\mathrm{B}}\right) = \int_{\mathrm{SO}(3)} \left| \sum_{\alpha} \int_{\mathbb{R}^3} \rho_{\mathcal{X}_i^{\mathrm{A}}}{}^{\alpha}(\boldsymbol{r}) \rho_{\mathcal{X}_j^{\mathrm{B}}}{}^{\alpha}(\boldsymbol{r}) \mathrm{d}\boldsymbol{r} \right|^2 \mathrm{d}\hat{R},$$

$$C_{ij}(\mathrm{A},\mathrm{B}) = k\left(\mathcal{X}_i^{\mathrm{A}}, \mathcal{X}_j^{\mathrm{B}}\right) \Big/ \sqrt{k\left(\mathcal{X}_i^{\mathrm{A}}, \mathcal{X}_i^{\mathrm{A}}\right) k\left(\mathcal{X}_j^{\mathrm{B}}, \mathcal{X}_j^{\mathrm{B}}\right)},$$

De, Bartok, Csanyi, Ceriotti, Phys. Chem. Chem. Phys (2016) 18, 13754-13769

Dimensional reduction (sketch-map) and structure classification (HDBSCAN* clustering)



Summary

- Crystal structure prediction methods are finding an increasing role in materials discovery, particularly where combined with property prediction calculations.

- Energy-structure-function maps:
  at-a-glance assessment of possible properties for a molecule

- Based on predictive calculations (CSP + property simulations).
  - Can study hypothetical molecules $\rightarrow$ helps prioritise synthesis

- Could be used for any *calculable* property
  - Use for pharmaceutical materials: property variability across the polymorphic landscape (mechanical properties, crystal habit)
  - Crystal structure landscapes are rich with structure-property relationship information: many crystal structures of the *same* molecule.
  - Structure classification methods (SOAP, HDBSCAN*) will help develop solid-state structure-property relationships.

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Peter Spackman

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ARCHER – EPSRC HEC Materials Chemistry Consortium, EP/L000202

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