Control and Prediction of the Organic Solid State
A Basic Technology project of the Research Councils UK

Intermolecular Interactions in Solids
- organic, (model) pharmaceuticals, energetics

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Accounts of Chemical Research 2009, 42, 117
Int. Reviews Phys. Chem. 2008, 27, 541

Prof Anthony J Stone & Dr Alston Misquitta, Cambridge
Int. Reviews Phys. Chem. 2007, 26, 193
Outline

- Polymorphism - the challenge of the organic solid state
- Progress in organic crystal structure prediction by searching for global minimum in lattice energy
- Contrasting periodic electronic structure methods & model intermolecular potential methods (isolated molecule $\rho(r)$)
- Distributed Multipole electrostatic models + empirical repulsion-dispersion

- Fully non-empirical model intermolecular potentials
  - Blind prediction of crystal structure of rigid non-polar molecule
- Inclusion of induction
- Inclusion of molecular flexibility
- Limitations of thermodynamics
Organic crystals – strong covalent bonds & weak intermolecular forces

- Millions of man-made organic molecules
- Some can be solved by single crystal diffraction
- Some only form microcrystalline powders
- Some crystallize in different ways i.e. have polymorphs

Crystals parabanic acid ~ 3-5mm are relatively large

Cambridge Structural Database >250,000 entries
<1% polymorphic pairs
But commercial screening gives ~50% polymorphs, 90% multiple solids
Polymorphism - a common phenomenon?

Polymorphism - the ability of a substance to adopt more than one crystal structure

- since different physical properties, a major cause for concern when products transform from one polymorph to another.
  - Pigments - change colour.
  - Chocolate - need polymorph of cocoa butter that melts at 37 °C.
  - Explosives - change of detonation properties
  - Pharmaceuticals change dissolution rate

Difficulty in establishing that all polymorphs are known

- Regulatory requirement for pharmaceuticals that all reasonable experiments are performed in order to identify the maximum number of crystalline forms
- McCrone (1965) “the number of forms of a compound is proportional to the time and energy spent in research on that compound”
Polymorphism – a (decreasingly) mysterious phenomenon

Because of problems in establishing that all polymorphs are known
- Some appear after decades of crystallization work on compound
- Some “disappear” after a more stable polymorph is discovered.

Used to justify “morphic fields” in *A New Science of Life* by Sheldrake
“best candidate for burning there has been for many years”
Maddox, Editor Nature 1981

= serious problems in reproducing conditions to obtain metastable form (seeding, impurities, etc)
Which drugs may have undiscovered polymorphs?

- 1998 Abbott Laboratories anti-HIV drug Ritonavir produced new polymorph during manufacture after 2.5 years.
- Problem affected plants in different countries.
- “Unfortunately, there is nothing we can do today to prevent a hurricane from striking any community or polymorphism from striking any drug” Sun, Abbott Laboratories, press conference.

Can we predict whether the drug may have a polymorph that is more thermodynamically stable than the known forms?
The original challenge

Develop a computational method to predict the crystal structure of a molecule without experimental input

From chemical diagram derive cell parameters, space group, fractional coordinates to define molecular and crystal structure
## Results of CCDC Blind Tests – Limited Success?

<table>
<thead>
<tr>
<th>Year</th>
<th>Guesses</th>
<th>Correct</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>~11 x 3</td>
<td></td>
<td>Rigid Polymorphic Stable 0 Metastable 4</td>
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<tr>
<td>2001</td>
<td>~15 x 3</td>
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<td>Rigid 2 correct Later polymorphs</td>
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<tr>
<td>2004</td>
<td>~16 x 3</td>
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<td>Rigid Unfortunately not blind 4 correct</td>
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</table>


![Chemical Structures]
But significant progress in 2007
GM Day + 15 groups, Acta Cryst B in press

Correct 4/14  4/14  3/12  2/12 in top 3

Advanced models for energies can predict these crystal structures as global minimum in lattice energy
(i.e. only with state-of-art expensive computational chemistry, but with both electronic and atomistic approaches)

Implies target structures are the most stable polymorph both at experimental temperature and 0K.
Advanced models for lattice energies of organic solids

• Dispersion-corrected electronic structure method GRACE DFT (VASP standard, PW91 functional) + an atom-atom $C_6/R^6$ correction, smoothly damped by a functional form fitted to a wide range of C,H,O,N,Cl,S organic crystal structures

• or anisotropic atom-atom models for intermolecular forces + ab initio calcs on isolated molecules for conformational change within crystal

  Lattice energy $E_{\text{latt}} = U_{\text{inter}} + \Delta E_{\text{intra}}$

  Intermolecular energy between rigid molecules in crystal geometry
  Change in internal energy of molecules between crystal and gas
Testing case of inter- intra- split


- α o-acetamidobenzamide has an **intra**molecular H-bond
- β has an extra **inter**
- \( \Delta E_{\text{intra}} \) is large & depends on \( \Psi \)!
- \( U_{\text{inter}} \) is greater for β but not enough!
Problem: Induction modelled better in intramolecular energy, than inter


Adding differential induction energy of ~ 14 kJ mol$^{-1}$ produces more reasonable relative energies

How far can we go with perturbation approach? Zwitterions, such as glycine?

Electrostatic potentials (kJ mol$^{-1}$) on 2 x van der Waals surface
What about electronic structure methods?

- Dispersion-corrected DFT gives reasonable minima and less absurd relative energies
- Others expand cell in non-H-bond directions
- \( \alpha \rightarrow \beta \) T>150 °C exothermic ~2 kJ mol\(^{-1}\)
- Extrapolation to 0K problematic
How accurate do you need?

Compromise between cost & accuracy
Crystal structure prediction searches compare
3000 (dense structures in common packing MOLPAK)
to $10^5$ (systematic complete search CRYSTAL PREDICTOR)
crystal structures for a rigid molecule
Model intermolecular potential + Monomer $\Delta E_{\text{intra}}$
approach can be systematically improved.
Highest accuracy calculations may only be needed
for 20 – 100 crystal structures in ~ 5 -10 kJ/mol of
global minimum
Model intermolecular potentials for rigid organic molecules must include:

- **Repulsion** ~ determines contact distances
- **Dispersion** ~ significant stabilizing energy, providing close packing. May dominate in some directions e.g. stacking of hydrogen-bonded sheets
- **Electrostatic** – dominates hydrogen-bonding directionality, $\pi-\pi$ stacking & very orientation dependent
  - Ignore induction (~ absorb in empirically fitted repulsion-dispersion)
Electrostatic model from $\rho(r)$

- Analyze to give sets of atomic multipoles to represent charge distribution

- Represents lone-pairs, $\pi$-electrons etc

- Electrostatic contribution to lattice energy $\sim$ accuracy $\Psi$, excluding penetration $\text{Cl}_2 \rho - \rho$ spherical atoms
Distributed Multipole Analysis
Stone AJ & Alderton M Molec. Phys. 1985, 56 1047

There are many ways to divide $\rho(r)$ into atoms….

Want to optimize convergence at van der Waals contacts

Use properties of Gaussian Basis sets

Terms $\phi_i \phi_j$ give rise to multipoles $Q_{0,0}$ to $Q_{l_1+l_2,k}$

Multipoles not on nuclei, “moved” to nearest, giving infinite series

Hence $\pi$ orbital density produces significant quadrupoles $Q_{2,k}$

Molecules with $\Psi$ from $s,p$ basis need multipole series up to $R^{-5}$

Modern large basis sets – method adapted to use integration of diffuse contributions

Program GDMA to derive DMA from GAUSSIAN density file
DMA + empirical exp-6 potential

- All other terms in atom-atom potential

\[ U = \sum_{i \in 1, k \in 2} U_{ik} = \sum_{i \in 1, k \in 2} \left( A_{it}A_{kk} \right)^{1/2} \exp\left(-\left( B_{it} + B_{kk} \right)R_{ik} / 2 \right) - \left( C_{tt}C_{kk} \right)^{1/2} / R_{ik}^6 \]


\[ \text{Interaction site ~ X-ray site} \]
Relative energies depend on electrostatic model

atomic charge model

<table>
<thead>
<tr>
<th>density (g/cm$^3$)</th>
<th>relative energy (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.52</td>
<td>0</td>
</tr>
<tr>
<td>1.62</td>
<td>1.52</td>
</tr>
</tbody>
</table>

$\Delta E = +4.2 \text{ kJ/mol}$

observed crystal: dimers

DMA gives better results

atomic multipoles

density (g/cm$^3$)

relative energy (kJ/mol)

chains

dimers

global minimum

dimers
A more general test

50 small organics
→ 62 known crystal structures

- small & fairly rigid
- range of molecular shapes and sizes
- many common functional groups
Hydrogen bonded crystals show greater improvement with DMA model.

No observed crystal structures farther than 5.1 kJ/mol from the global minimum.

Crystal Energy Landscape and polymorph screening complementarity

- Carbemazepine, a very heavily studied anti-epileptic has many forms, but all involve $R_2^2(8)$ hydrogen bonding
- Suitably rigid for computational search
- Suitably diverse solid state for validation of novel automated solvent crystallization screening system - and perhaps finding new forms
Crystal energy landscape shows mixture of dimers and chain structures.
Prediction gave target to automated polymorph screen

- Robot dissolved CBZ in 66 solvents, filtered and crystallized in five protocols
  - Saturation condition and temperature
  - Cooling rate
  - Agitation
- PXRD analysis
  eg High $T_{\text{sat}}$, 5 °C /min, 850rpm
  - I ♦ II ★ III • mix ▲ solvate
  - □ no crystals

PCA solvent diagram
What did we learn?

- No chain based form found – why not? Challenge to theory
- 6 known + 3 new solvates (+ 3 later) found
- Form IV not found in solvent crystallizations - crystallized in presence of polymer or by sublimation, from melt etc.
- Otherwise polymorphic form more dependent on crystallization protocol than solvent
Refine relative energies by using DMA of bigger basis set $\Psi$.

Allowing limited flexibility + better basis set for electrostatic energies stabilizes thermodynamic form.

The thermodynamically stable polymorph III is probably the most thermodynamically stable...
Or might a chain polymorph yet be found?

- Discovery of carbemazepine in catemer in 1:1 solid solution with dihydrocarbemazepine
- Crystal isomeric with a predicted CBZ catemer structure
Model Intermolecular Potentials

Desiderata

• Atom-atom potentials
• Accurate & include many-body effects
• Hierarchy of potentials of increasing detail
• Can allow for molecular flexibility
• Can establish transferability
• Easy to create!

Getting there over the decades

Many-body expansion

\[ V_{ABC...} = \sum_{X < Y} V_{XY} + \sum_{X < Y < Z} \Delta V_{XYZ} + \cdots \]

Polarizable model
(distributed multipoles & polarizabilities)

Crystals of organic molecules:
Large contribution from long range summations
Dense = various van der Waals contacts

Molecular properties
(distributed multipoles, polarizabilities & \( C_n \))

SAPT(DFT)
Analytic atom-atom potential

\[ V_{\text{int}} = \sum_{ab} V_{ab} \]

\[ V_{ab} = e^{-\alpha_{ab}(R_{ab} - \rho(\Omega_{ab}))} \]
\[ + \left\{ Q_{lm}^{a/b}; \alpha_{lm,l'm'}^{a/b} \right\} \]
\[ - \frac{C_{6}^{ab}}{R_{ab}^{6}} - \frac{C_{7}^{ab}}{R_{ab}^{7}} \]

Exchange, penetration
Electrostatics, polarization
many-body effects
Dispersion
Need to partition $\rho(r)$ into atoms

Density fitting

Replace $\rho(r)$ product of orbitals by linear expansion in new basis set

$\rho(r) = \sum_p c_p \chi_p(r)$

Use orbitals centred on atom to define its charge density

$\rho^a(r) = \sum_{p \in a} c_p \chi_p(r)$

Variant depending on contribution
Anisotropic atom-atom repulsion - effect of lone pairs


- Polar-flattening, need anistropic short range model as range of orientations sampled
Non-empirical repulsion models based on overlap of $\rho(r)$

- Assume: repulsion $\propto$ overlap of charge distributions
  \[ U_{\text{rep}} = KS_\rho = K \int \rho^A(r) \rho^B(r) \, dr \]

- $\rho(r)$ divided into atoms $\Rightarrow S_\rho$ in atom-atom form.
  
  Fit anisotropic $S_\rho$ model
  - Minimizing parameters, avoiding correlation
  - Testing transferability

- Fit $K$ to Intermolecular Perturbation Theory dimer calculations of short range terms
  
  • improve with method IMPT$\Rightarrow$ SAPT(DFT),
  • include exchange-repulsion + penetration+....??
  • assess accuracy in fit $\ ?K^{ab}$
Develop anisotropic Cl repulsion model

Atom-atom form

\[ A \exp(-\alpha (R - \rho(\Omega))) \]

where

\[ \rho(\Omega) = \rho_0 + \rho_1 (z_1 \cdot R + z_2 \cdot R) + \rho_2 (3z_1 r^2 + 3z_2 R^2 - 2)/2 \]

Anisotropy consistent “lone pair” density

Towards nonempirical \( \Psi \) based potentials for organics
- only choice atomic \( C_6 \) dispersion from experiment

1990 Cl\(_2\) crystal reproduced by overlap repulsion model
RJ Wheatley & SLP, Mol.Phys 71, 1381

2003 Extended to series of 12 chlorobenzene crystals & properties  GM Day & SLP, JACS, 125, 16434
Model proved predictive for low temperature $\beta$ polymorph of


Closely related structures but 1$^{st}$ order phase transition

$\beta \rightarrow \alpha$ 186 K $\Delta H = 0.095$ kJ mol$^{-1}$

Symmetry change so polymorphs

Differences reproduced by model potential

Search found $\beta \sim$ same energy $\alpha$ and $\sim 3$ kJ mol$^{-1}$ more stable than unknown structures
Dispersion needs polarizability models


• Calculate frequency-dependent density susceptibility by SAPT(DFT)
  – Change in electron density at \( r \) from \( \delta \) perturbation in potential at \( r' \) at frequency \( \omega \)

• Use *modified* density fitting to define region of atoms \( a \) and \( a' \)

\[
\alpha(r, r'; \omega) = \sum_{pq} \tilde{C}_{pq}(\omega) \chi_p(r) \chi_q(r')
\]

• Calculate atom-atom polarizabilities

\[
\alpha_{aa}^{aa} = \sum_{p \in a} \sum_{q \in a'} \tilde{C}_{pq} \int d^3r \hat{Q}_t(r-r_a) \chi_p(r) \int d^3r' \hat{Q}_a(r'-r_a) \chi_q(r')
\]

• External field at \( a \) induces changes in \( Q_a' \) through local \( \alpha_{aa}^{aa} \), which in turn lead to induced moments at other atoms described by non-local \( \alpha_{aa'}^{aa} \)

Charge-flow polarizabilities!
Practical atomic polarizabilities $\alpha_{tu}^a(\omega)$


**Localize** to remove non-local terms


Lillestolen, TC; Wheatley, RJ J.Phys.Chem.A 2007, 111, 11141

**Refine** atomic $\alpha_{tu}^a(\omega)$ up to given rank by fitting to reproduce grid of point-to-point polarizabilities

Response of electrostatic potential at Q to unit charge oscillating at P


\[ \hat{\mathcal{O}}^P(r) = \frac{qP}{4\pi\varepsilon_0|P-r|} \]

\[ \alpha_{PQ}(\omega) = \iint \alpha(r, r'|\omega)\hat{\mathcal{O}}^P(r)\hat{\mathcal{O}}^Q(r')drdr' \]

William-Stone-Misquitta (WSM) method avoids unphysical “buried” polarizabilities & allows evaluation of errors as truncate series
Difference maps of the induction energy (kJ mol\(^{-1}\)) arising from a charge \(q\) atomic units on the vdW \(x^2\) surface of formamide taken against SAPT(DFT) second-order induction energies.


Errors in induction energy of formamide

Non-local polarizabilities

Localized

Refined
Dispersion models

\[ E_{\text{disp}}^{\text{asymp}} = -\frac{\hbar}{\pi} \sum_{a \in A, b \in B} T_{tu}^{ab} T_{t'u'}^{ab} \int_0^\infty \alpha_{tt'}(i\nu)\alpha_{uu'}(i\nu) d\nu \]

\[ = - \sum_{a \in A, b \in B} \left( \frac{C_6^{ab}(\Omega)}{R_{ab}^6} + \frac{C_7^{ab}(\Omega)}{R_{ab}^7} + \frac{C_8^{ab}(\Omega)}{R_{ab}^8} + \cdots \right) \]

- Rank 3 polarizabilities and dispersion coefficients to \( C_{12} \) for every pair of sites.

- Anisotropic.

- Tang-Toennies damping function with

\[ \beta = \sqrt{2I_A} + \sqrt{2I_B} \]
Fully non-empirical potential for 2007 blind test

\[ U \approx E_{exch}^1(KS) + E_{elst}^1(KS) + E_{ind,d-class}^2 + E_{disp,d}(C_8) \]

\[ \approx \sum_{a \in A, b \in B} G \exp[-\alpha_{ab}(R_{ab} - \rho(\Omega_{ab}))] + E_{elst}(DMA, L4) - C_6 / R_{ab}^6 \]

- DMA & dispersion coefficients (via \( \alpha_{\mu \nu}^\omega(\omega) \)) & overlap model asymptotically corrected PBE0, Sadlej pVTZ basis
- Use 1400 SAPT(DFT) dimer energies to fix \( E_{sr} = \sum K_{ab} S_{\rho}^{ab} \)
- Fully ab initio based anisotropic atom-atom intermolecular potential
Lattice energy landscape

5000 Crystal Predictor → 1200 DMA+FIT in 12 kJ mol\(^{-1}\) → 211 specific potential

Global minimum is correct structure
Significant success?

• Model derived from theory, monomer & dimer $\Psi$ predicts solid state packing
  – Challenging in size of molecule and number of electrons
  – But also done by other methods

• Approach general for specific potentials
  – For RIGID molecules, with negligible induction
Is induction important in organic crystals?


Use >15Å radius crystal cluster to estimate induced moments by two contrasting methods

Central polarizable molecule in field

Distributed multipoles & WSM polarizabilities from asym. corr PBE0 Sadlej

ORIENT

\[ Q_{lm} + \Delta Q_{lm} \]

Self-Consistent Electronic Response to Point Charge Field (SCERP)

Field from CHELPG atomic charges polarizing molecule PBE0 aug-cc-pVTZ

GAUSSIAN
All models take ~6 cycles to converge induced moments $\Delta Q_{lk}$.

Figure 3 Convergence of $E_{\text{ind},d\text{-class}}$ showing the error $E^{(2-n+1)} - E^{(2-\infty)}$ in the induction for different truncations of the infinite sum.
Electrostatic field difference Norm ($E_{\text{DMA}}-E_{\text{Q}}$) for $\alpha$ oxalyl dihydrazide on 1.8x van der Waals surface. Maximum is 0.226 V/Å.


Induced electrostatic potential for naphthalene, for the 1.1 x van der Waals surface.
Can quantify contribution to lattice energy from $\Delta Q_{lk}$

Without induction $E_{latt}$ for $\beta$–$\varepsilon$
-130-138 kJ mol$^{-1}$

$E_{latt}$ for $\alpha$
-110 kJ mol$^{-1}$

$\varepsilon$ has too short N–H
Apply to relative stability carbamazepine structures

Induction favours dimers over catemers in carbamazepine

Need to be able to minimize $E_{\text{latt}}$ with induction in DMACRYS
Cannot add induction to empirical exp-6 potentials

- Polarizable molecule
- Weak fields
- Exptal $E_{\text{ind}} = -8.2 \text{ kJ mol}^{-1}$

- For some competitive structures
- $E_{\text{ind}} = -1.2$ to $-3.8 \text{ kJ mol}^{-1}$
- problems in damping with constant coeff $\beta$
- induction small but will stabilize known structure.

Induction energy probed using a damped unit point charge on the 1.8x vdW surface. Range is $-12.6$ to $-70.0 \text{ kJ mol}^{-1}$
Extension to more complex systems – flexible molecules

- Molecule may distort its conformation from “gas phase” optimum conformer, with penalty $\Delta E_{\text{intra}}$, to give improved intermolecular interactions and lower $U_{\text{inter}}$
- Need $E_{\text{latt}} = U_{\text{inter}} + \Delta E_{\text{intra}}$ crystal landscape
- Balance very demanding of accuracy – calculate $\Delta E_{\text{intra}}$ \textit{ab initio} by best affordable method
- Beware intramolecular Basis Set Superposition Error!
- Also increases search problem
Progesterone


Form 2 only stable when recrystallized in presence related steroid C3O3H

?? Original polymorphism from synthetic impurities

<table>
<thead>
<tr>
<th>conformation (torsion $\phi_1$, deg)</th>
<th>HF/6-31G(d,p) (kJ mol$^{-1}$)</th>
<th>MP2/6-31G(d,p) (kJ mol$^{-1}$)</th>
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</thead>
<tbody>
<tr>
<td>-65.0</td>
<td>2.84</td>
<td>2.91</td>
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<tr>
<td>-80</td>
<td>1.53</td>
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<tr>
<td>-93.3 (<em>in vacuo</em>)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>-110</td>
<td>1.87</td>
<td>2.29</td>
</tr>
<tr>
<td>-190</td>
<td>1.82</td>
<td>3.90</td>
</tr>
</tbody>
</table>
Known orthorhombic polymorphs correspond to the two most stable structures in chiral space groups.

If inversion centres are allowed significantly more stable packing arrangements are obtained, as get “ideal” $>\text{C}=\text{O}$⋯$\text{O}=\text{C}<\text{ interaction}$ Allen et al. 1998, Acta Cryst B54, 320.
Prediction verified!

Lancaster, RW; Karamertzanis, PG; Hulme, AT; Tocher, DA; Covey, DF; Price, SL, *Chem. Commun.*, 2006, 47, 4921

Overlay of global minimum and experimental racemic structure

This experimental crystallization required half of the world’s available quantity of the synthetic enantiomer (2.5 mg)!

Many Thanks to Doug Covey, Washington University School of Medicine for providing this sample in exchange for the predictions, as a blind test.
Refine conformational modelling

DMAflex to simultaneously refine torsion angles within crystal structures

\[ \text{i.e. simplex optimize } U_{\text{inter}} + \Delta E_{\text{intra}}(\text{MP2, 631G**}) \text{ by coupling} \]

DMACRYST, GAUSSIAN, GDMA, recalculating DMA each point

Now developing DMAflex-Quick – use precalc \( \Delta E_{\text{intra}} \) surface + analytically rotated multipoles

Chain still energetically favoured, but smaller \( \Delta E \), better basis set DMA + induction, favours known form.
Other issues to consider for calculating crystal energy landscapes

Compromise accuracy of $E_{\text{latt}}$ model with
- Extent of search
- Including effect Temperature & pressure
  - Thermodynamic control depends on free energy (at crystallization temperature)
  - Harmonic rigid-body modes?
  - Full Molecular Dynamics simulations?
  - Crystallization under thermodynamic control?

Which low energy structures may be observed polymorphs??
Some low energy structures will not be found

Blindtest predicted dimers ~ chains
invited search for dimer polymorph
Screen found plastic phase + chain polymorph & solvates
Imide can readily rearrange hydrogen bonds to most stable form
chain within computational error

Electrostatic potential on the water-accessible surface
Scale ±60 kJ/mol
Crystal energy landscape is very specific to molecule

- Accuracy in relative crystal energies versus energy gaps in crystal landscape
- We can improve accuracy in relative energies, but the molecule determines the energy differences
- Consider a simple rigid molecule search
  - ab initio optimized rigid molecular structure
  - Distributed Multipole electrostatics + empirical exp-6 intermolecular potential
  - Compare lattice energy minima generated by MOLPAK search Z’=1, common space groups
- For all available isomers C₆H₃Cl₂NO₂
Isomers have different landscapes

The ease of prediction depends on the specific molecule available.
Aspirin – an ongoing headache?
conformation in crystal ~ local minimum in gas phase
Ouvrard, C, Price, SL, Crys Growth Des 2004, 6, 344

Do searches with ab initio optimized structures (+ planar transition states)

ΔE_{intra}=0

H-bonds kinetically disfavoured?

Too susceptible to shear

Dimers from solution?

ΔE_{intra}= 3.5 kJ/mol
New metastable polymorph aspirin

Form II of Aspirin – Confirming Calculated Structure

<table>
<thead>
<tr>
<th>Reduced Cell Parameters</th>
<th>Form I (ACSAL01)</th>
<th>Form II (expt.)</th>
<th>Predicted Form [AK22]</th>
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<tr>
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<tr>
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<tr>
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<tr>
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<tr>
<td>mp = 144 °C</td>
<td>mp = 135 °C</td>
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<td></td>
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</tbody>
</table>


Metastability consistent with predicted shear susceptibility – same layers

Also consistent with stacking faults, “polymorphic domains” Bond et al. 2007 Angew Chem Int Ed 46, 618

? interchangeable motifs “predict” disorder/ modulated structures/growth variability
CPOSS database of computed crystal structures and properties

- currently >100 molecules
- to complement experimental studies
- to improve with better computational models
Grateful Thanks to

- **Intermolecular forces**
- **Alston Misquitta, Gareth Welch, Emeritus Prof Anthony Stone**
- **CPOSS**
- Panos Karamertzanis, Sarah Barnett, Derek Tocher, Bob Lancaster
- Alastair Florence et al. (Strathclyde), many others + Louise Price

**Programs**
- DMACRYS/REL Maurice Leslie (STFC, retd) et al. [www.cposs.org.uk](http://www.cposs.org.uk)
- CAMCASP AJ Stone Alston Misquitta (Cambridge) [www.stone.ch.cam.ac.uk](http://www.stone.ch.cam.ac.uk)
- MOLPAK, H Ammon (Maryland)

**Blind Tests**
- CCDC & CSP community for blind tests

**Funding**
- EPSRC including e-Science
- Basic Technology Program of RC UK for funding Control and Prediction of the Organic Solid State [www.cposs.org.uk](http://www.cposs.org.uk) and now providing Translation Funding