Modeling and Prediction of the Crystal Structure of Pharmaceutical Cocrystals

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Outline

● Introduction
  ● the use of cocrystals in pharmaceutical industry
  ● the role of computational chemistry in understanding organic solid state

● Computational methodology
  ● molecular model, model for the intermolecular forces
  ● multi-stage crystal structure prediction

● Applications and experimental validation

● Conclusions
Introduction

Solid-phase properties & cocrystallisation

- Solid-phase physical properties depend on crystal structure
  - density, colour, solubility, dissolution rate, elastic constants

- Cocrystallisation with pharmaceutically acceptable (GRAS) compounds\(^1-3\)
  - does not affect pharmacological activity of API
  - can improve physical properties, e.g. solubility, hygroscopicity, compaction behaviour

\(^2\) P. Vishweshwar, J.A. McMahon, J.A. Bis, M.J. Zaworotko, *J. Pharm. Sci.*, **2006**, 95, 499-516
Experimental & computational screening of cocrystals

- Experimental screening for cocrystal formers is not trivial
  - solution crystallisation requires “symmetric” phase diagram
  - dry or solvent-assisted grinding techniques,1 hot-stage microscopy2
  - difficult to automate, labour intensive

- Prediction of crystal energy landscape can play a role in
  - understanding polymorphism
  - linking molecular structure to physical properties
  - screening cocrystal formers,3,4 counterions and predicting solvate formation

  - cocrystal is favoured if more stable than crystal structures of component molecules

4 P.G. Karamertzanis, A.V. Kazantsev et al., J.Comp.Th.Comp., 2008, accepted
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Methodology
Prediction of crystal structures

Degrees of freedom:

- three lattice lengths \(a, b\) and \(c\)
- three lattice angles \(\alpha, \beta\) and \(\gamma\)
- crystallographic positions of all atoms \(\hat{r}_{ji}, \quad i = 1, \ldots, N, \quad j = 1, \ldots, Z\)

Crystal structure prediction:

Determine all low-energy structures that can correspond to stable/metastable polymorphs
Methodology

Modelling of thermodynamic stability

- Prediction of thermodynamic stability requires the minimisation of Gibbs free energy:
  $$G(T, P) = U + PV - TS$$

- Most computational approaches minimise the lattice energy at 0 Pa and 0 K
  - includes intramolecular energy penalty to deform gas-phase molecular conformation
  - PV contribution only becomes significant at very high pressures
  - entropy differences are small but important when energy differences are small
  - our model at present only includes rigid-body, $k=0$ vibrational contributions

- Assume infinite crystals with no defects

- Assume thermodynamic control
  - effect of solvent, supersaturation conditions and impurities ignored
Methodology

Intramolecular and intermolecular energy

- Rigid-body approximation not applicable to majority of systems
- Successful prediction depends on correct modelling of balance of inter- and intramolecular forces

Intramolecular Energy, $\Delta E^{\text{intra}}$ (kJ mol$^{-1}$)

Intermolecular Energy, $U^{\text{inter}}$ (kJ mol$^{-1}$)

Lattice energy, $U^{\text{inter}} + \Delta E^{\text{intra}}$ (kJ mol$^{-1}$)

QM derived
Methodology

Intermolecular forces

- Realistic accuracy requires moments up to at least quadrupole
  - distributed multipole analysis
  - fitted to electrostatic potentials

- Electrostatic contribution to lattice energy ~ accuracy $\Psi$
  - model lone pairs, $\pi$-$\pi$ interactions…
  - reproduce hydrogen bond geometries and energies$^{1,2}$

- Typically repulsion-dispersion forces are modelled with empirical, isotropic models
  - certain functional groups require anisotropic repulsion (Cl, Br)
  - progressing towards fully non-empirical repulsion-dispersion and polarisation models$^{3,4}$

Model for intermolecular forces is conformationally dependent

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1 D.J. Willock et al., *J.Comp.Chem.*, 1995, 16, 628-647
Methodology

Search for low-energy crystal structures

- Complex, multidimensional optimisation problem
  - all statistically significant space groups
  - two crystallographically independent entities in the asymmetric unit
    - cocrystals, salts and also solvates, hydrates
  - large number of intramolecular degrees of freedom

- Modelling challenge
  - hypothetical structures often differ by only a few kJ/mol
  - requires highly accurate models based on QM calculations

- Search needs to be both extensive and accurate
  - mutually conflicting requirements…
  - need to adopt a multi-stage approach
    - eliminate clearly unstable minima using efficient models
    - perform CPU-intensive calculations for a limited number of structures only
Methodology

Modelling of molecular flexibility

- Molecular deformation energy comparable to the stabilisation due to improved packing
  - compute molecular model and intramolecular energy from first principles

- Intermolecular forces weak compared with forces between covalently bonded atoms

- Intramolecular degrees of freedom partitioned
  - “flexible” d.o.f.
    - usually subset of torsion angles
    - optimised simultaneously with lattice variables
  - “rigid” d.o.f.
    - bond lengths, most bond angles, aromatic rings…
    - fixed at gas phase values or
    - QM optimised for isolated molecule with “flexible” d.o.f. fixed

\[
\Delta E^{\text{intra}} \left( \theta^f \right) = \min_{\theta'} E^{\text{intra}} \left( \theta^r; \theta^f \right) - \min_{\theta} E^{\text{intra}}
\]

\[
\theta(\theta^f) = \arg \min_{\theta'} E^{\text{intra}} \left( \theta^r; \theta^f \right)
\]

QM intramolecular energy = f (flexible d.o.f.)

rigid d.o.f. = f (flexible d.o.f.)
Methodology

Multistage search algorithm

- **Stage I**
  - Flexible d.o.f.: Optimised
  - Rigid d.o.f.: Fixed
  - Intramolecular energy: Hermite polynomial on grid determined via QM
  - Intermolecular electrostatic: Conformationally-invariant multipole moments
  - Intermolecular dispersion/repulsion: Isotropic exp-6
  - Accuracy: 1-2 days
  - Computational cost: Sec - Min

- **Stage II**
  - Flexible d.o.f.: Optimised
  - Rigid d.o.f.: Fixed
  - Intramolecular energy: Hermite polynomial on grid determined via QM
  - Intermolecular electrostatic: Conformationally-invariant multipole moments
  - Intermolecular dispersion/repulsion: Isotropic exp-6
  - Accuracy: 30 min – 2 hours
  - Computational cost: 2

- **Stage III**
  - Flexible d.o.f.: Optimised
  - Rigid d.o.f.: Fixed
  - Intramolecular energy: “On-the-fly” QM during lattice minimisation
  - Intermolecular electrostatic: Conformationally-dependent multipole moments “On-the-fly” QM
  - Intermolecular dispersion/repulsion: Isotropic exp-6
  - Accuracy: 1-2 days
  - Computational cost: 2

References:

Methodology

Quality of QM charge density representation

- Atomic charge representation is inaccurate; large errors in the vicinity of amine group
- Charge density around hydrogen bond acceptors and donors sensitive to basis set quality

\[ \text{MP2(fc)/6-31G(d,p)} \]
- Atomic charges (CHELPG)
  - range \([-0.638, 0.674]\)

\[ \text{MP2(fc)/aug-cc-pVTZ} \]
- Atomic multipoles (up to rank 4)
  - range \([-0.608, 0.713]\)
- Atomic multipoles (up to rank 4)
  - range \([-0.636, 0.734]\)

Stage 1
- stage 1

Stage 2 & 3
Methodology

Conformational transferability of multipoles (stage 2)

QM electrostatic potential (eV)
• multipole moments up to rank 4
• PB36-31G(d,p) charge density

ESP error (eV)
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Experimental information and computational details

Single component crystals

4-aminobenzoic acid
β polymorph, $Z' = 1$, $P2_1/n$, hydrogen bonded dimers
α polymorph, $Z' = 2$, $P2_1/n$, COOH⋯NH2 HB

4-nitrophénylacétique acid
$Z' = 1$, $P\overline{b}ca$

Cocrystals

4-aminobenzoic acid: 2,2'-bipyridine
$Z' = 3/2$, $P2_1/n$

4-aminobenzoic acid: 4-nitrophénylacétique acid
$Z' = 2$, $P2_1/a$

Computational model

- **Intramolecular energy** computed at HF/6-31G(d,p)
- **Distributed multipoles** for intermolecular electrostatic interactions computed from MP2/6-31G(d,p) wavefunction
- **Intermolecular repulsion-dispersion** computed with Williams parameterisation\(^1\)
  - modified pyridine nitrogen-carboxylic proton term

\(^1\) D.E. Williams, *J. Comp. Chem.*, 2001, 22, 1154
Applications
4-nitrophenylacetic acid

- **Stage I**
  - ~50,000 local minimisations

- **Stage II**
  - ~1400 lowest energy, distinct stage I minima
    - atomic charges are not sufficient
  - rigid-body reminimisation with exact multipoles and $\Delta E^{\text{intra}}$
    - intermolecular force-field is conformationally dependent

- **Stage III**
  - ~20 lowest, distinct stage II minima
Applications

4-nitrophenylacetic acid – final results

Density (g cm\(^{-3}\))

Stage 3 lattice energy (kJ mol\(^{-1}\))

experimental crystal
Applications

Overall results for pure components

For all three molecules:
- significant re-ranking from stage to stage
  - less pronounced for 2,2'-bipyridine
  - no strong, directional intermolecular interactions
- known crystal structures are predicted at the global minima at stage 3
Applications

4-aminobenzoic acid:2,2'-bipyridine (2:1, P1, P2_1)

Density (g cm$^{-3}$)

Stage 3 relative lattice energy (kJ mol$^{-1}$)

Cocrystal favoured (ABA form $\alpha$)

Cocrystal favoured (ABA form $\beta$)

Experimental crystal
Cocrystal structure prediction

Overall results

- Experimentally determined structures always found in the search
- 4-aminobenzoic:2,2'-bipyridine experimental crystal close to the global minimum
  - cocrystallisation favourable
- 4-aminobenzoic:4-nitrophenylacetic acid
  - experimental crystal \( \sim 10 \text{ kJ mol}^{-1} \) less stable that the global minimum
  - cocrystallisation not favoured
Applications

Some putative cocrystal structures

- Several low-energy structures contain $R_2^2(8)$
  4-aminobenzoic acid homodimers
  - 4-nitrophenylacetic acid carboxylic group hydrogen bonded to amine nitrogen
- No 4-nitrophenylacetic acid homodimers
- The majority of motifs can be found in the CSD

**experimental**

- Experimental, $P2_1/a$, -217.6 kJ mol$^{-1}$, 1.458 g cm$^{-3}$

**predicted**

- Global minimum, $P2_1/c$, -228.1 kJ mol$^{-1}$, 1.456 g cm$^{-3}$
- 6th lowest minimum, $P2_1/c$, -224.7 kJ mol$^{-1}$, 1.486 g cm$^{-3}$
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Conclusions

- Significant theoretical advances
  - intermolecular forces and lattice calculations
  - prediction of crystal structure of multi-component systems: salts, cocrystals, solvates

- Lattice calculations assume thermodynamic control
  - crystallisation outcome also depends on conditions other than T,P
    - solvent, impurities, seeding, nucleation inhibitors or promoters, interfaces
  - concomitant polymorphs\(^1\) and disappearing polymorphs\(^2\)
  - kinetic effects possibly more pronounced when intermolecular forces are strong

- Cannot yet reliably predict which polymorphs will be observed
  - global minimisation generates too many equi-energetic structures

- But... predicted polymorphic landscape can provide insights in
  - providing reassurance... or targets for crystallisation screens\(^3\)
  - deciphering factors that influence crystallisation
  - explaining and anticipating disorder\(^4\)
  - assisting solution from PXRD measurements...
  - revealing if any other potential polymorph could have favourable properties...

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