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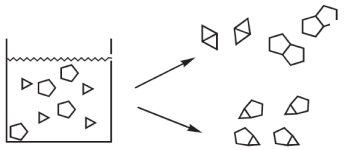

Theoretical characterization of co-crystalization

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Kiu Shahrokh, Adam VanWart,
and Jill Zwickl

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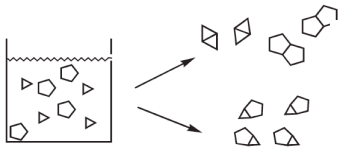
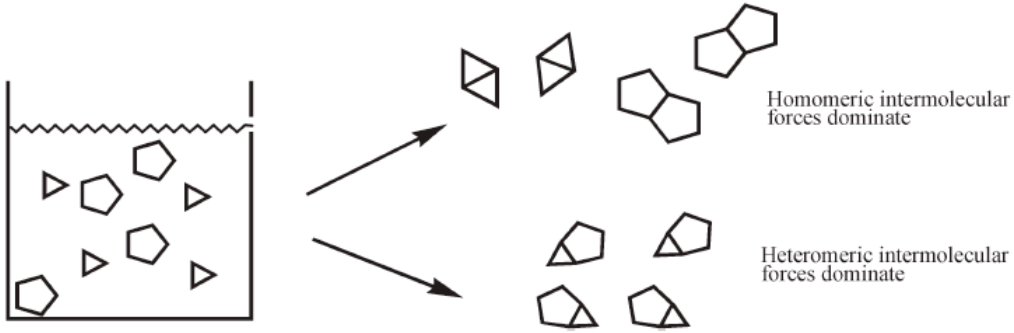
Introduction



- Formation of co-crystals



Scheme 1 Recrystallization (homomeric) or co-crystallization (heteromeric)?

CrystEngComm, 2005, 7(72), 439–448

- Library of supramolecular reagants for use in pharmaceuticals, etc.
- Hydrogen-bond directed co-crystal formation
  - Previous work: H-bond strength determined by pK_a values

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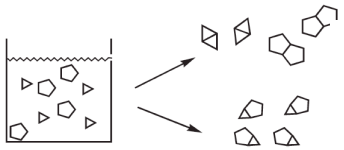
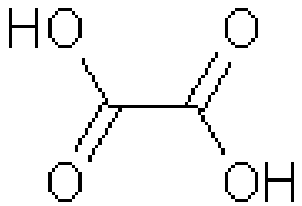
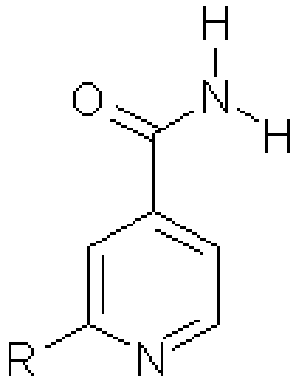


Research Questions

- Can we predict the products of a co-crystallization reaction using noncovalent interaction energies between reagents?



A



B

Compare values of ΔE_{AA}, ΔE_{BB}, and ΔE_{AB}

- Given two binding partners, can we identify the co-crystal structure?
  - Basin hopping Monte Carlo

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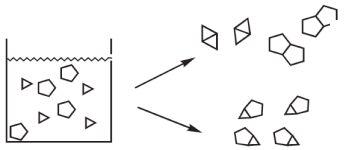


Identifying synthetic targets

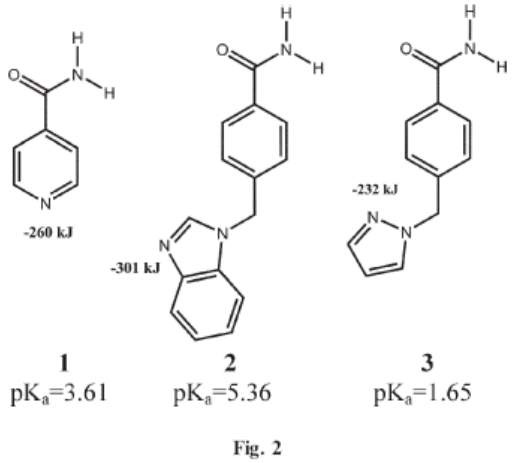
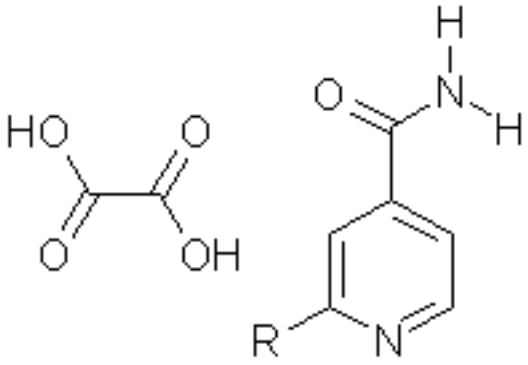
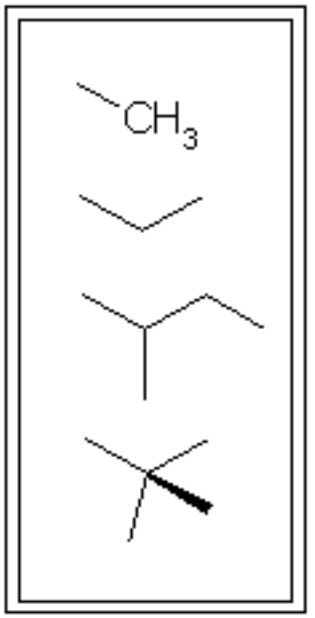


Fig. 2



A B

R =



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- Add substituents that can alter propensity for crystallization via steric interactions. These will be added at several positions.
- Synthesis targets will be identified from calculated A-B interaction energies.

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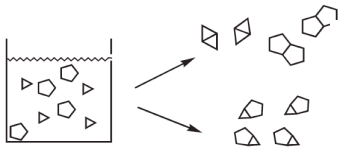
Quantum mechanical computation of binding energies



- Benchmark studies
  - CCSD(T)
  - aug-cc-pVTZ
  - counterpoise correction
  - Compare to DFT(+D) results for B3LYP, PBE, M05-2X, M06-2X, and BOP
- Interaction energy computations
  - DFT (with an empricial correction for dispersion)
  - aug-cc-pVTZ

$$\Delta E(AB) = E^{AB}_{dimer\ basis} - [E^{A}_{dimer\ basis} + E^{B}_{dimer\ basis}]$$

$$\Delta\Delta E = \Delta E(AB) - \Delta E(BB)$$

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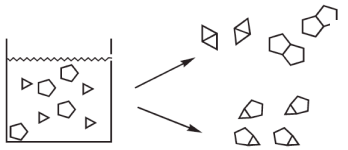

Synthesis and Crystalization

- Synthesize the base analogs
- Confirm structure with mass spec and NMR
- X-ray crystallography studies will be used to identify co-crystals

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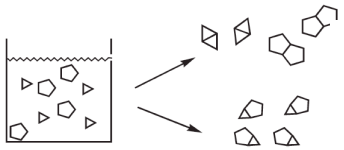
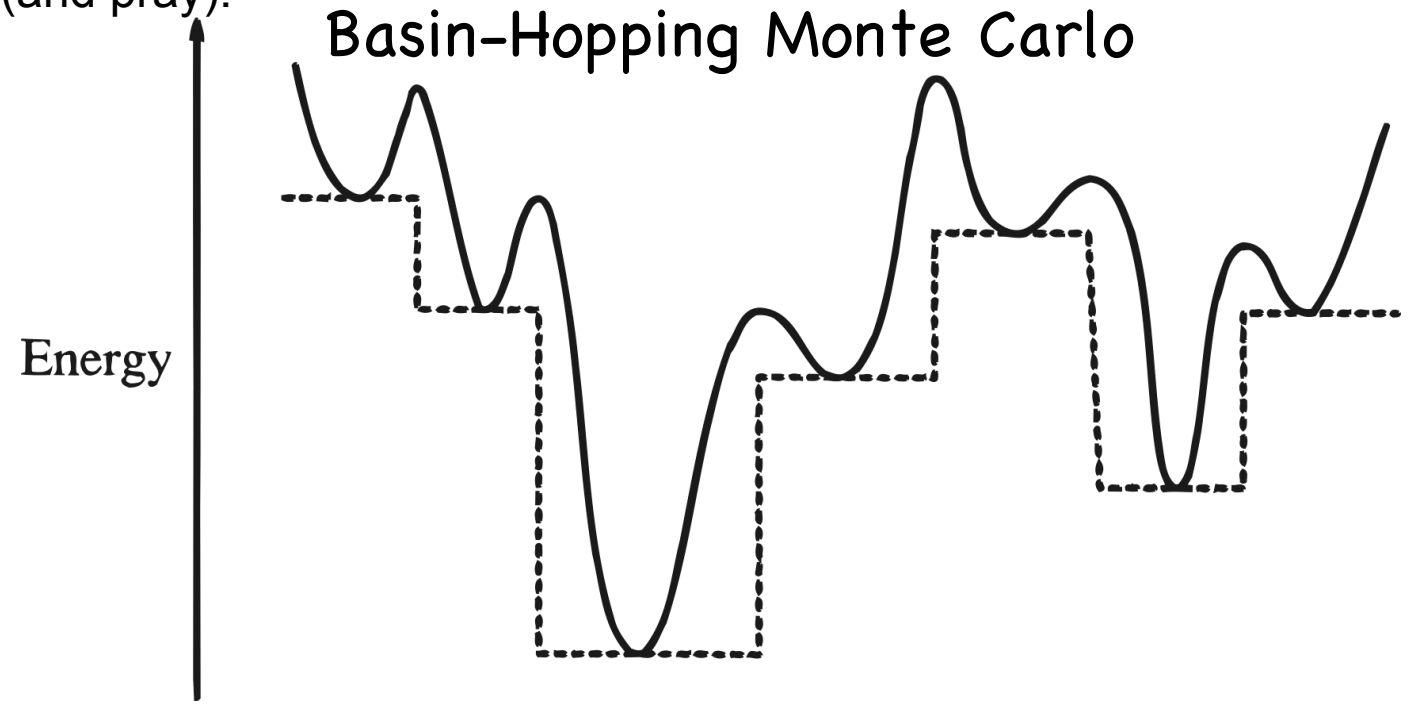


Correlating cluster interactions to crystal structure

- If ab initio calculations predict a particular low energy dimer, does that dimer appear in the most stable in a condensed-phase system?
- Use basin hopping Monte Carlo to attempt to find the global minimum (and pray).



J. Phys. Chem. A **1997** 101, 5111-5116

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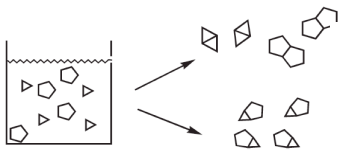

Outline of crystal structure protocol

stuff molecules into a box

Basin-Hopping Monte Carlo

find lowest ~1000 structures with 'cheap' potential

optimize with 'fancy' ff to ~100 geometries

optimize with DFT for lowest 20 geometries

analyze structures for similarity and unit cell structure

- Constant pressure BHMC
- Coordinate system for minimizing energy
- Plane wave DFT has periodic replication. However, are dispersion corrected functionals available in the plane wave variety?

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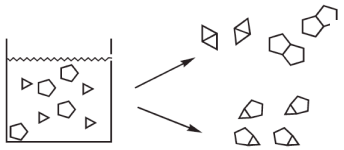

Anticipated Results

- Identify a acid-base analog pair which will not form a co-crystal to serve as a negative control.
- Identify a predictive model based on the $\Delta\Delta E$ between the AB and AA or BB dimers.
- Examine the relationship between the low energy dimers identified by quantum mechanics and the dimers that appear in the crystal structure.

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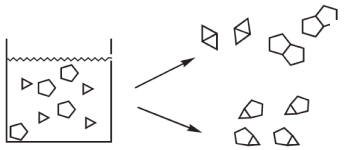

Potential Challenges

- The crystals may not be of high enough resolution to correctly identify the structure of the dimer pairs.
- Co-crystals may be formed in unpredicted conformations.

- There is no guarantee that we will find the global minimum, or that that structure will be the correct crystal structure. Can additional calculations be used to identify the global free energy minimum out of a small subset determined from BHMC?