



UNIVERSITAT DE BARCELONA



Scientific-Technical Services UB

Plataforma de Polimorfisme i Calorimetria

Crystal Engineering Strategies: Design of new Synthons and Enhancement of API's Solubility

Dr. Rafel Prohens

Solubility Enhancement of an API

- Physical modification: particle size reduction
- Drug dispersion in carriers: solid dispersions
- Additives/Complexation: cyclodextrins
- Surfactants: microemulsions
- Co-solvents (GRAS approved)
- Solid-state modification: salt formation, solid-state stabilisation of the amorphous state, etc...

Solid State Methods For Improving Solubility And Dissolution Rates

- Habit modification
- Crystal Polymorphism
- Solvates and hydrates
- Salts
- Cocrystals

Crystal Engineering Strategies For Improving Solubility And Dissolution Rates

- Habit modification
- Crystal Polymorphism
- Solvates and hydrates
- Salts
- Cocrystals

OVERVIEW

Crystal Engineering Strategies

- Enhancement of solubility and other properties
 - Salts
 - Hydrates
 - Cocrystals
- Study of Supramolecular Synthons
 - Squaramides

A Supramolecular Synthone is...

“... a structural unit within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions”

A Supramolecular Synthons is...

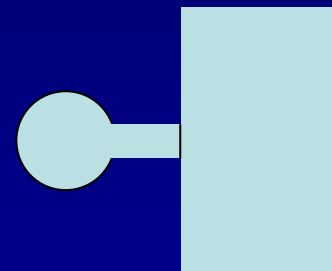
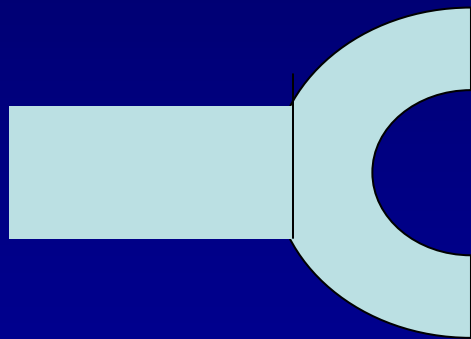
Component A

Component B

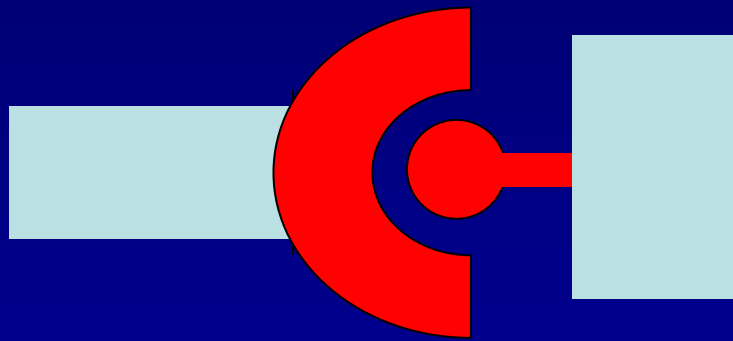


Complementary
Functional Groups

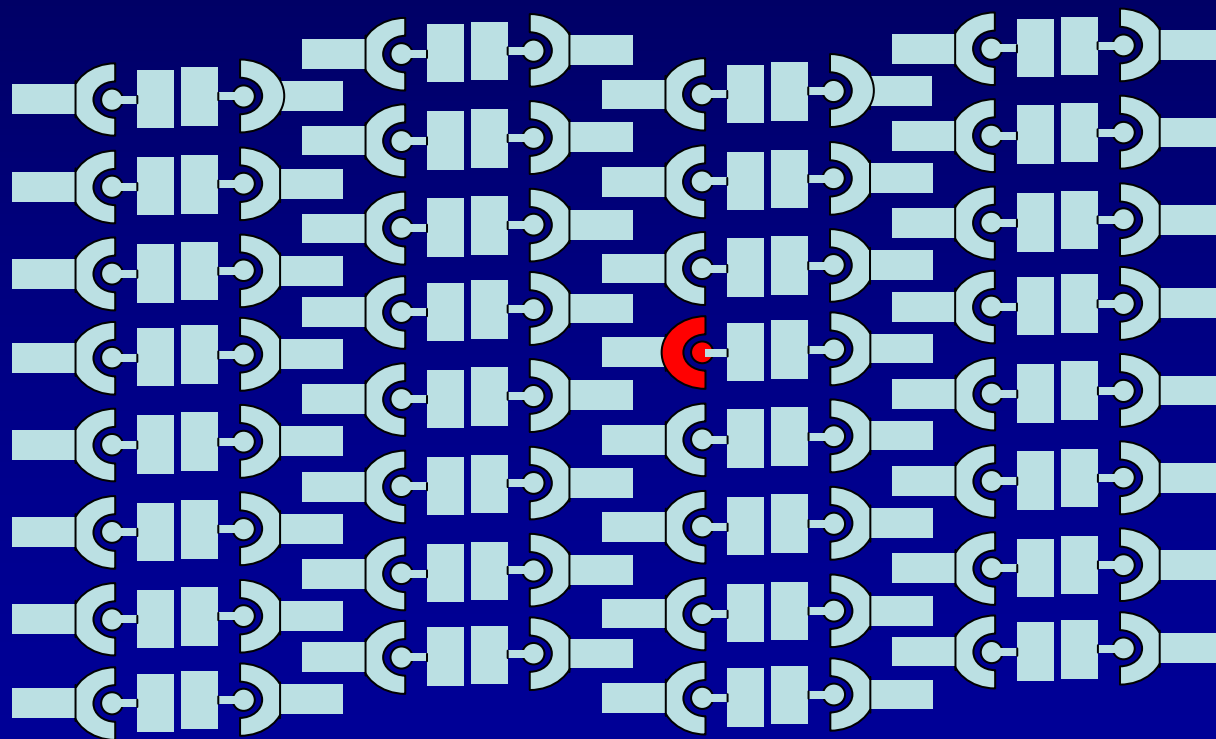
A Supramolecular Synthone is...



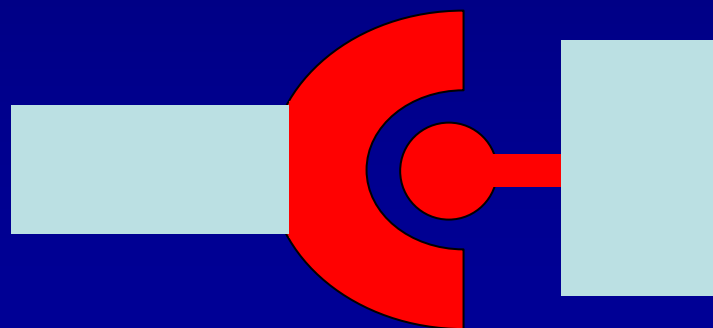
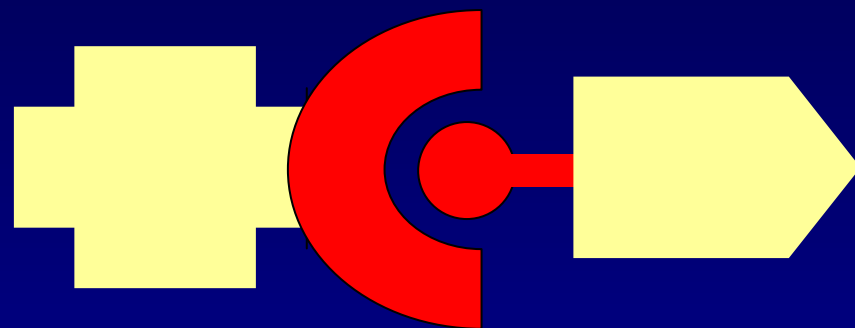
A Supramolecular Synthone is...



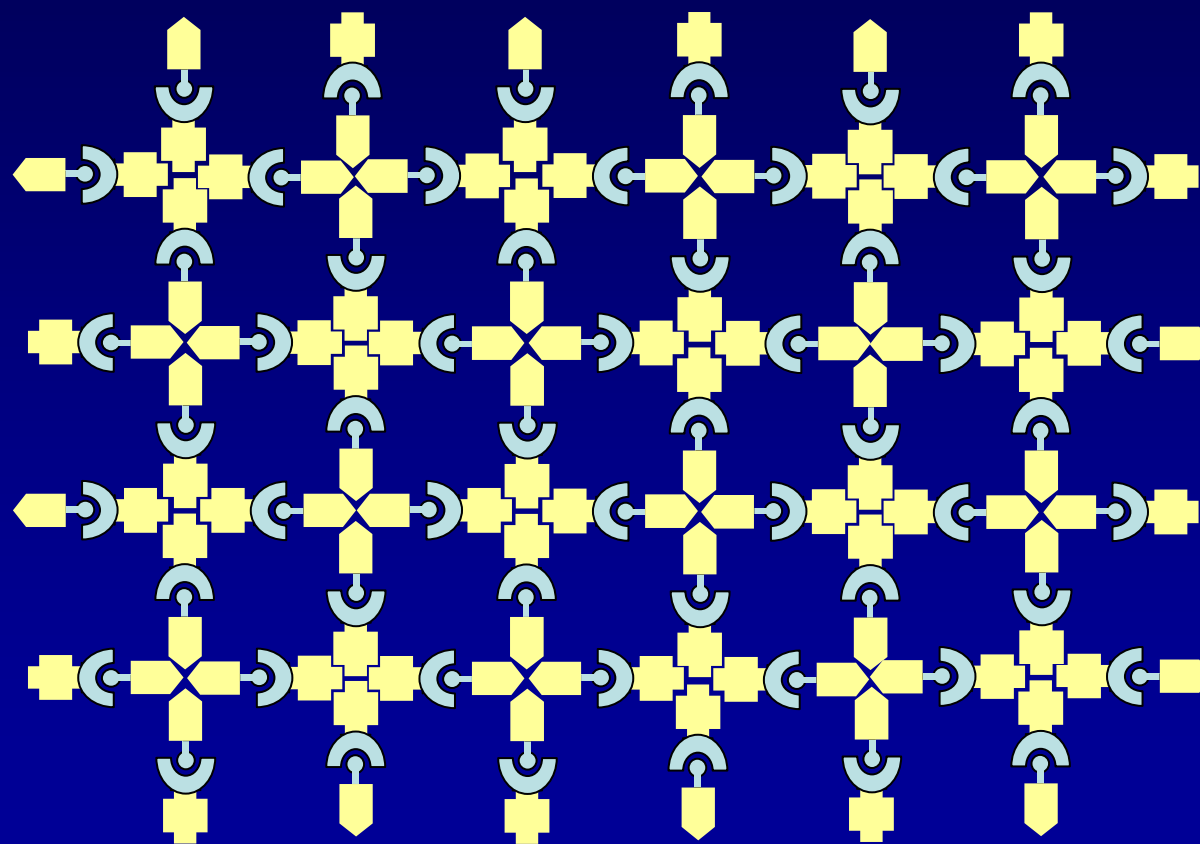
A Supramolecular Synthons is...



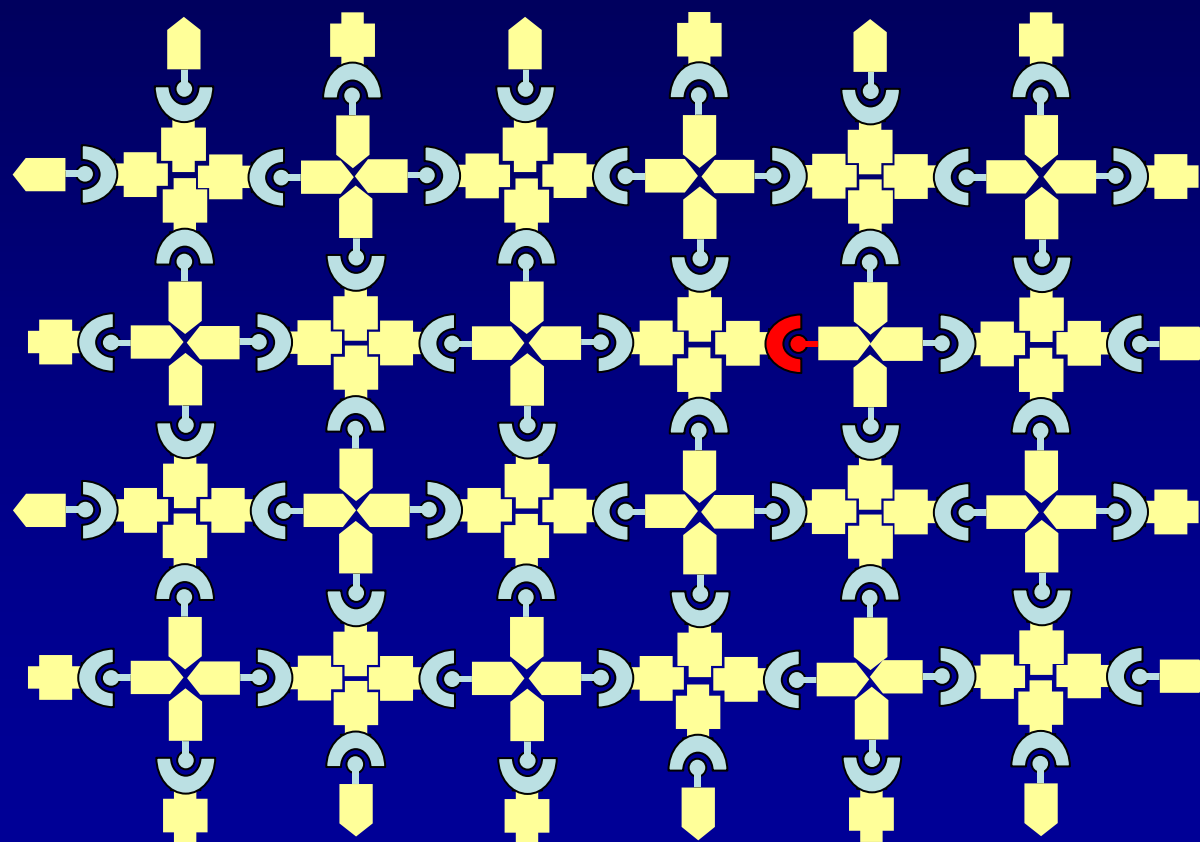
A Supramolecular Synthons is...



A Supramolecular Synthons is...

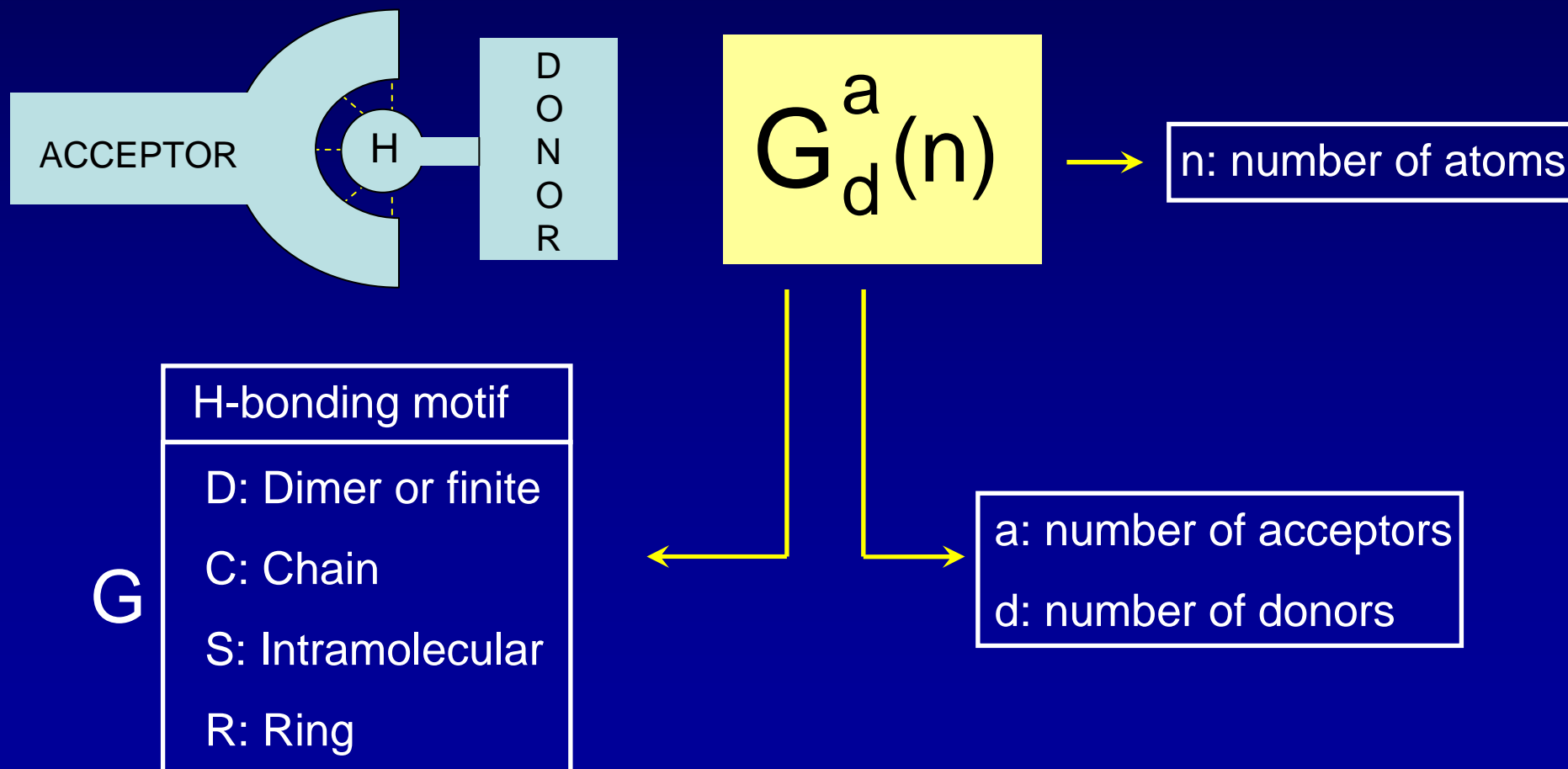


A Supramolecular Synthons is...

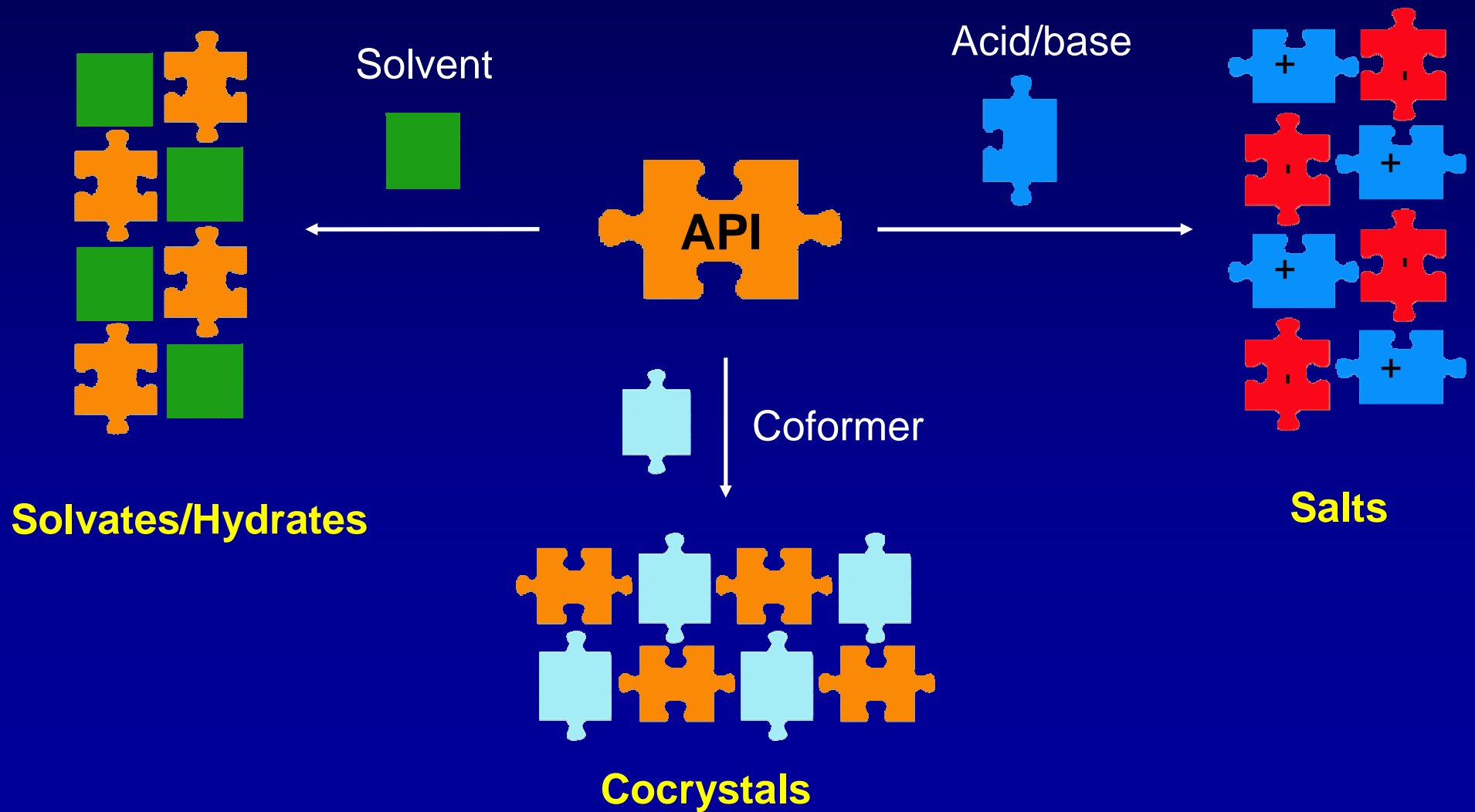


Using Graph Sets in Hydrogen-bond arrays

To define the morphology of hydrogen bonding patterns in crystal structures



Three case-studies



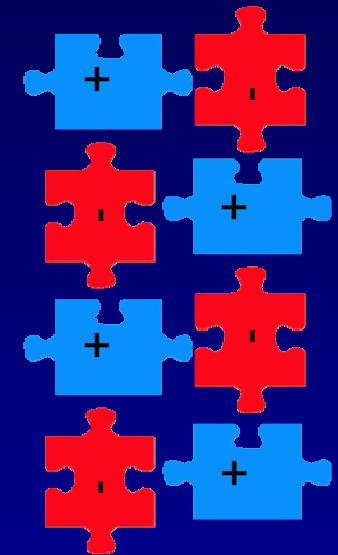
Three case-studies



Ziprasidone



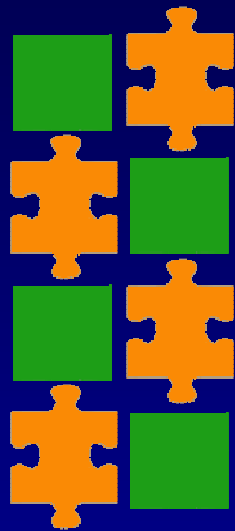
Acid/base



Salts



Three case-studies



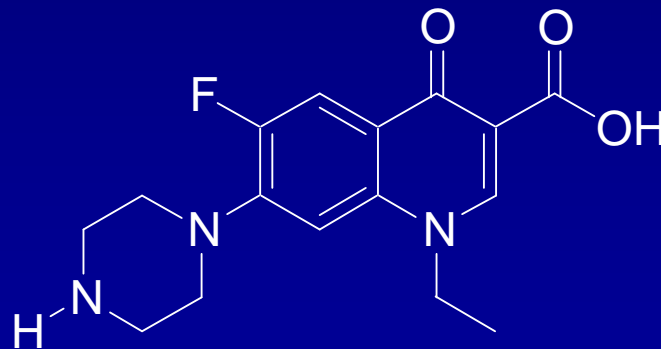
Solvent



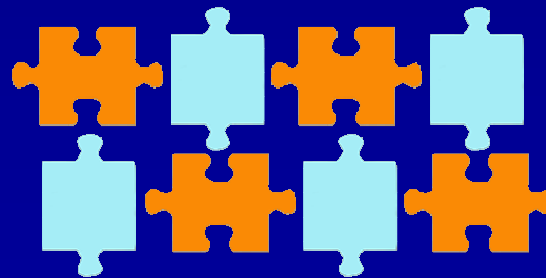
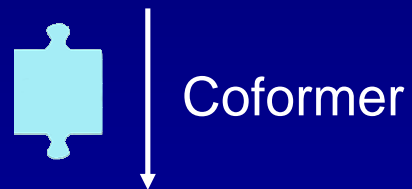
Norfloxacin



Solvates/Hydrates

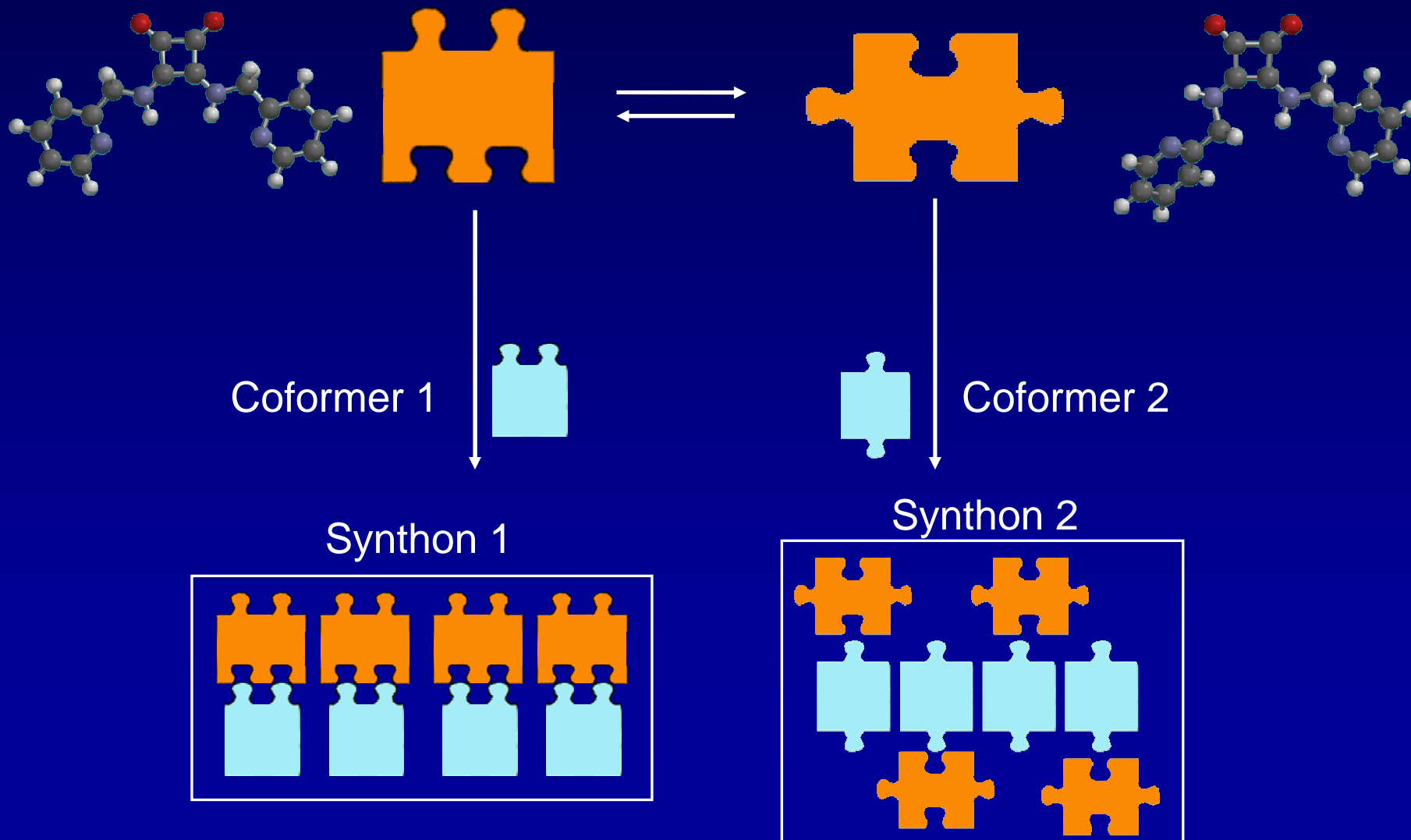


Three case-studies



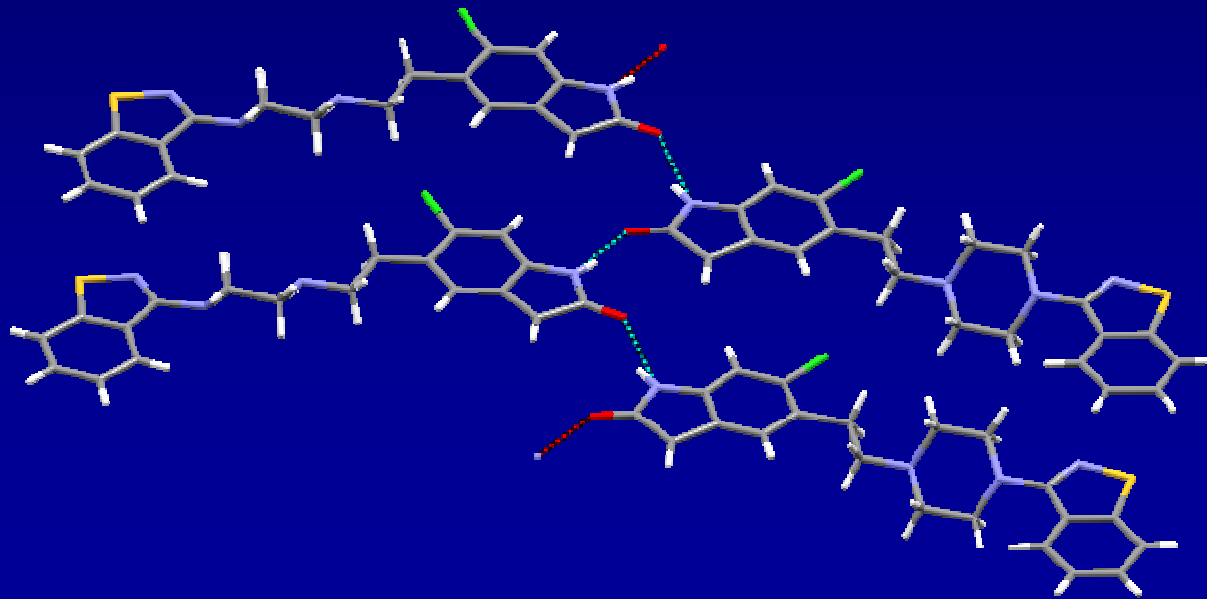
Cocrystals

Design and study of new synthons



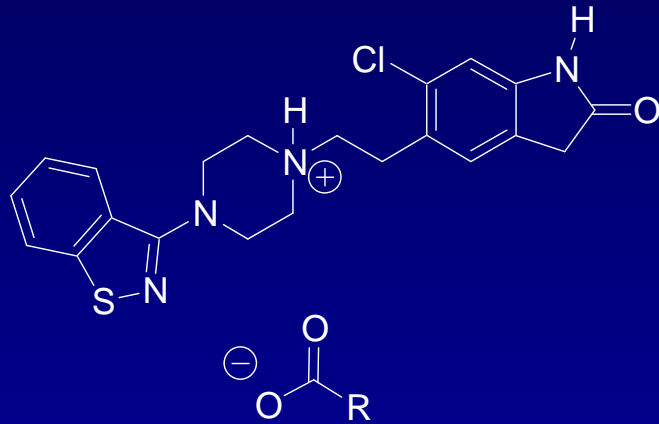
Ziprasidone

- Low Solubility in water $\sim 0.3 \mu\text{g/mL}$
- Two ionisable groups in the molecule with pK_a values 8.4 and 13.3



Salt or Cocystal?

$$\Delta pK_a = pK_a (\text{base}) - pK_a (\text{acid})$$



Salt

$$\Delta pK_a > 3$$



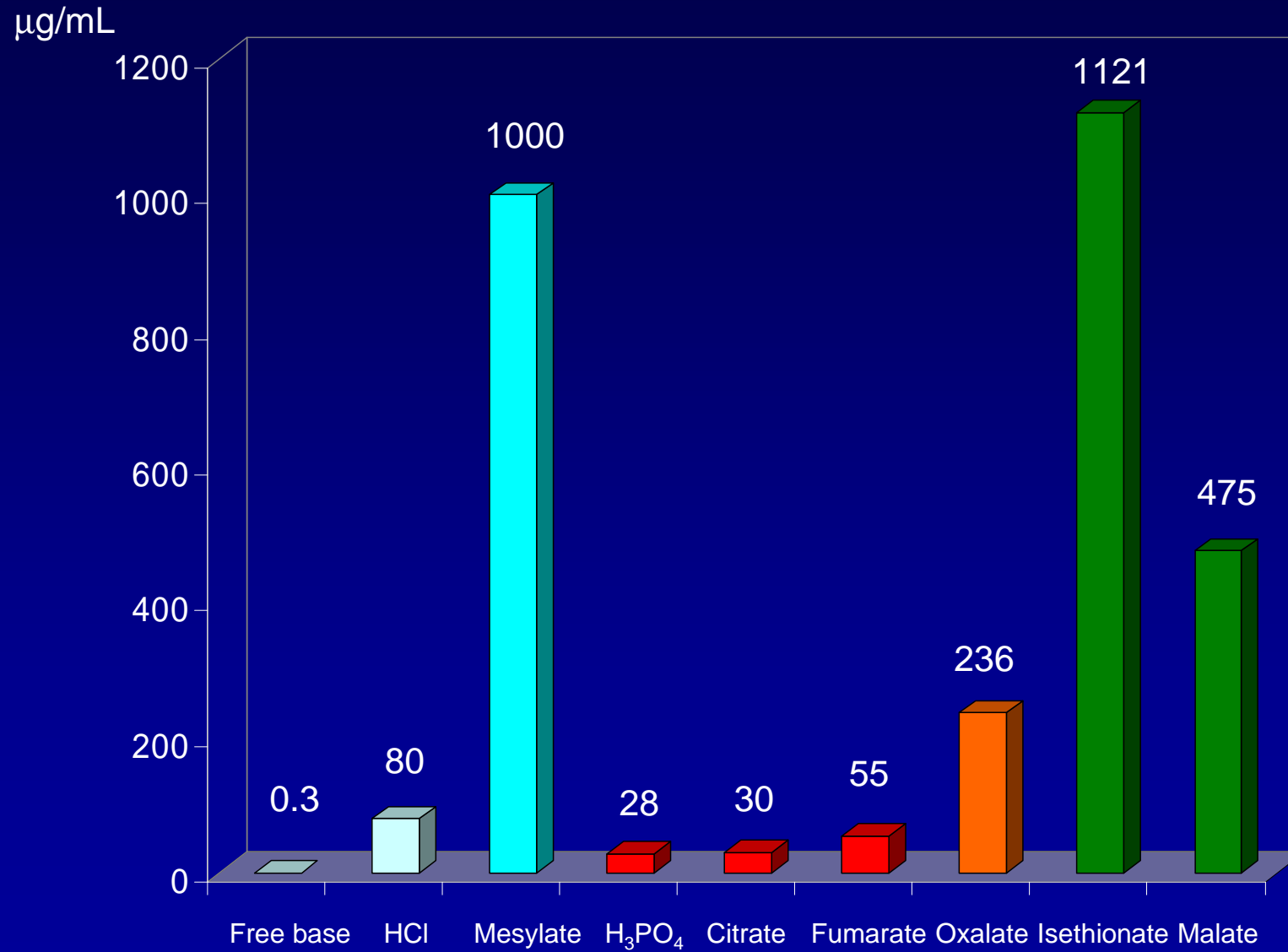
Cocrystal

$$\Delta pK_a < 3$$

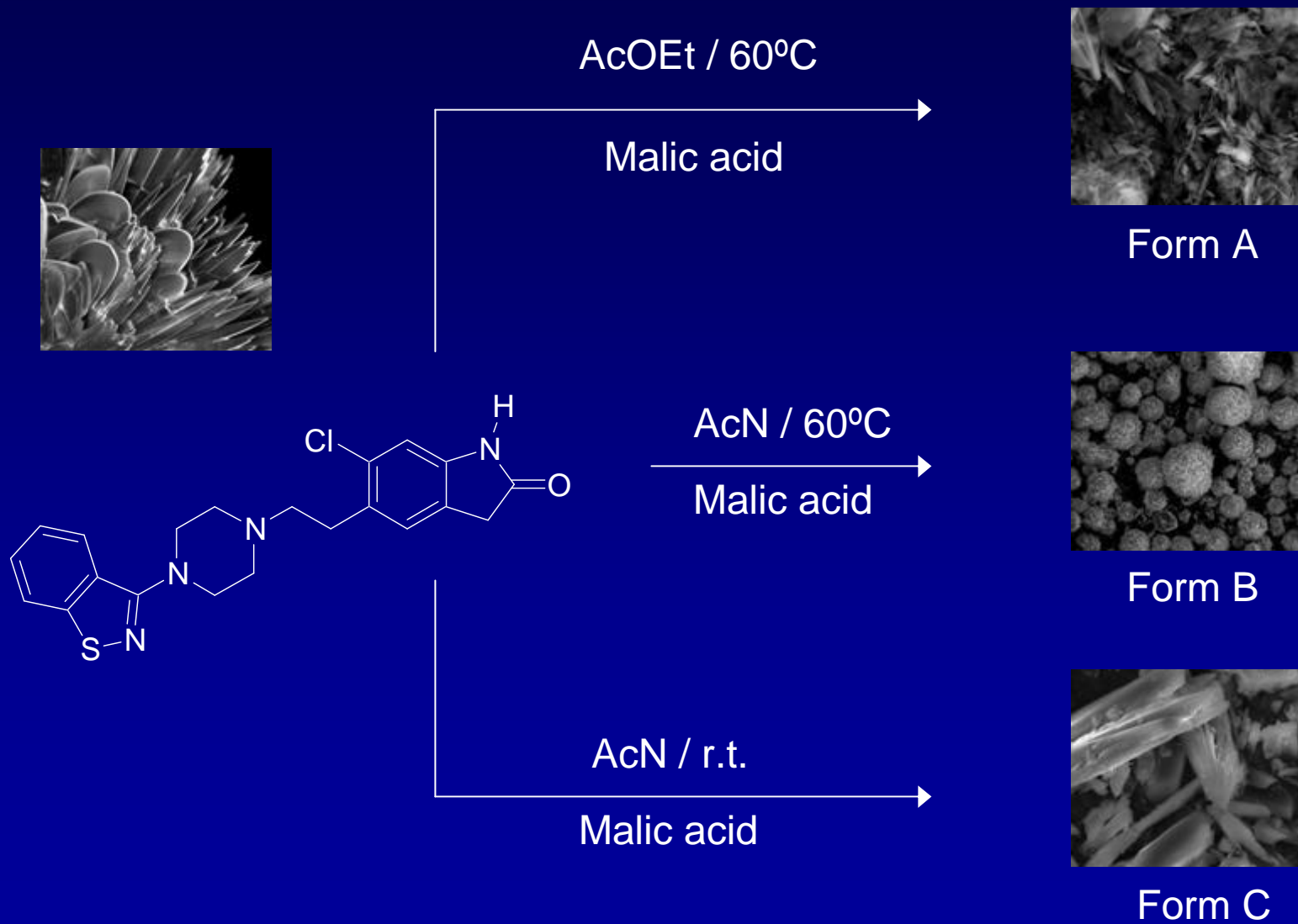
Microscale salt screening

Acid	pK _a	Salt	Acid	pK _a	Salt
<chem>H3PO4</chem> Phosphoric	1.96	✓	<chem>OC(=O)/C=C/C(=O)O</chem> Fumaric	3.03	✓
<chem>OC(=O)C(O)(C(=O)O)C(O)C(=O)O</chem> Citric	3.13	✓	<chem>OC(=O)C(=O)C(=O)O</chem> Oxalic	1.27	✓
<chem>OC(=O)C(O)C(=O)O</chem> Malic	3.46	✓	<chem>OC(=O)CC(S(=O)(=O)O)O</chem> Isethionic	1.66	✓
<chem>CC(O)C(=O)O</chem> Lactic	3.85	X	<chem>OC(=O)CCCCC(=O)O</chem> Glutaric	4.34	X
<chem>OC(O)C(O)C(O)C(O)C(=O)O</chem> Gluconic	3.86	X	<chem>OC(=O)CC(N)C(=O)O</chem> Glutamic	4.25	X
<chem>OC(=O)C=CC(=O)O</chem> Maleic	1.97	X	<chem>OS(=O)(=O)c1ccc2c(c1)ccc(S(=O)(=O)O)c2</chem> Armstrong's	-3.37	X

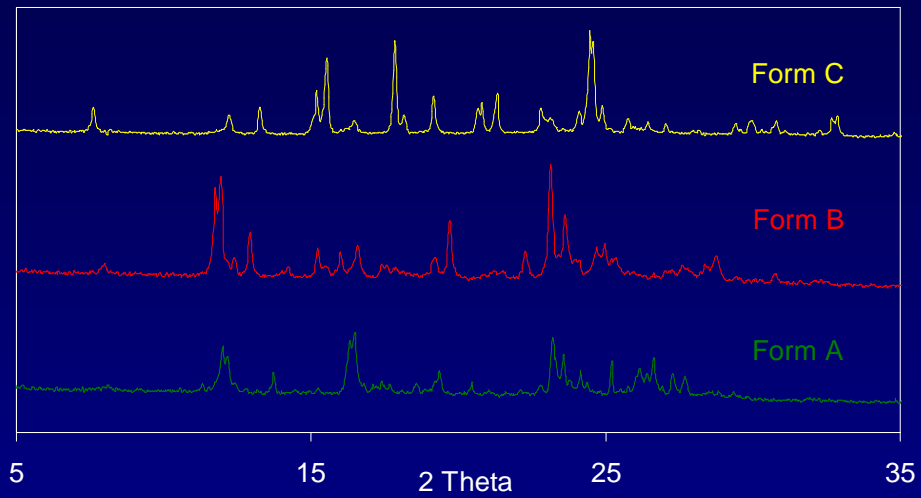
Aqueous solubilities of Ziprasidone salts



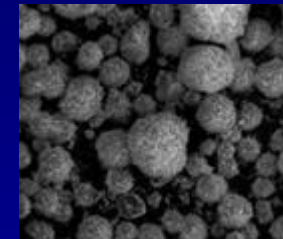
Polymorphic Salt Screening



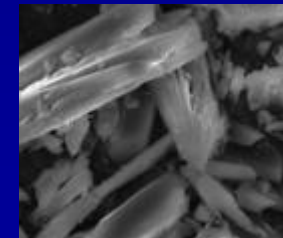
Polymorphism of Ziprasidone Malate



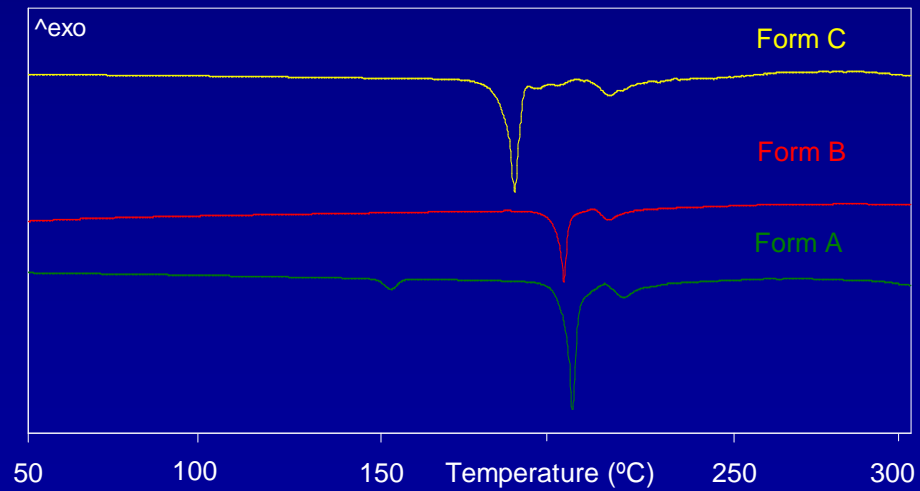
Form A



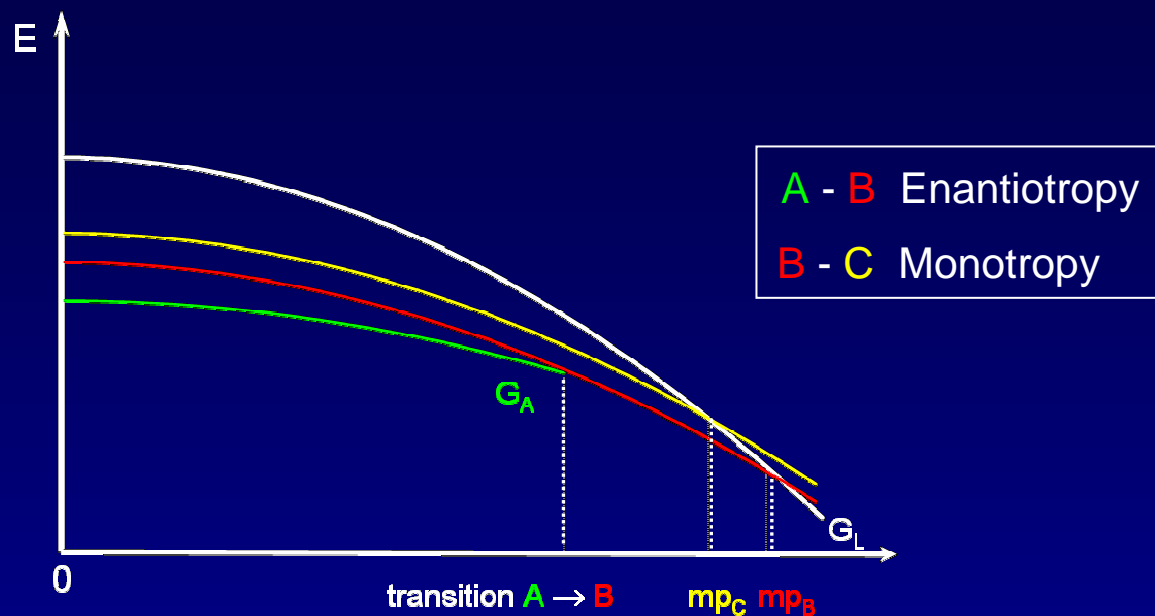
Form B



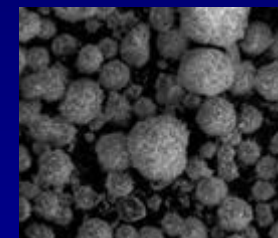
Form C



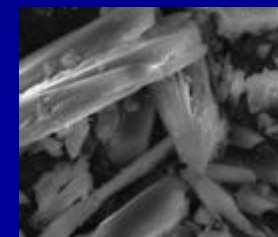
Polymorphism of Ziprasidone Malate



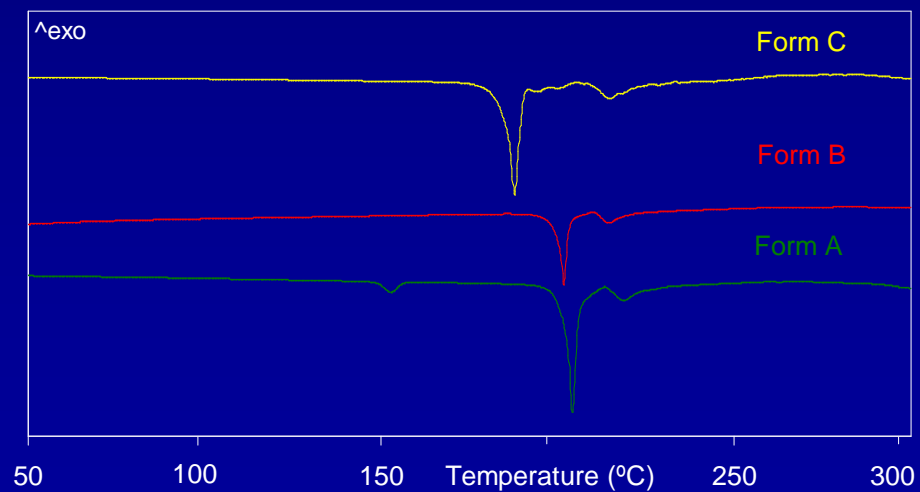
Form A



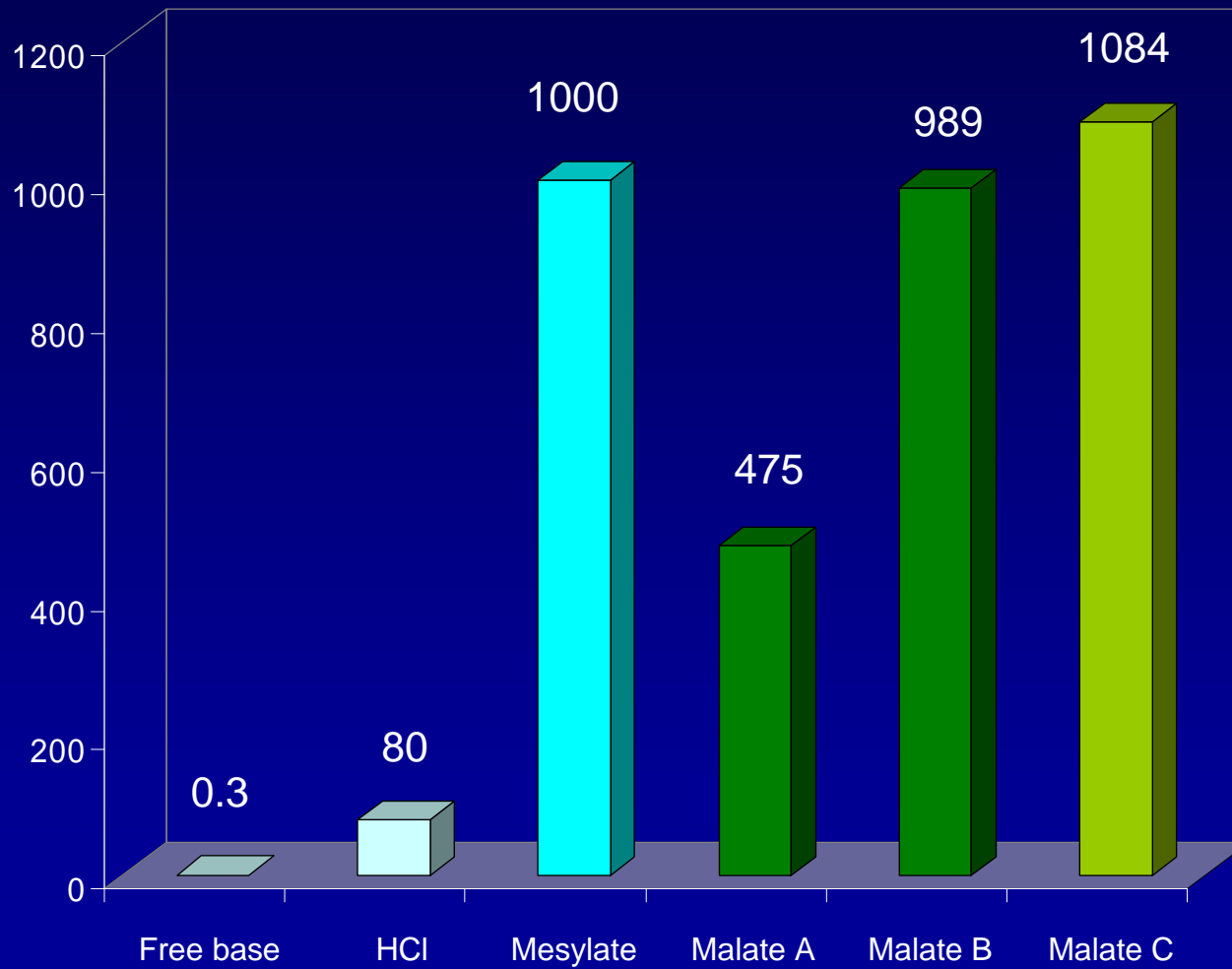
Form B



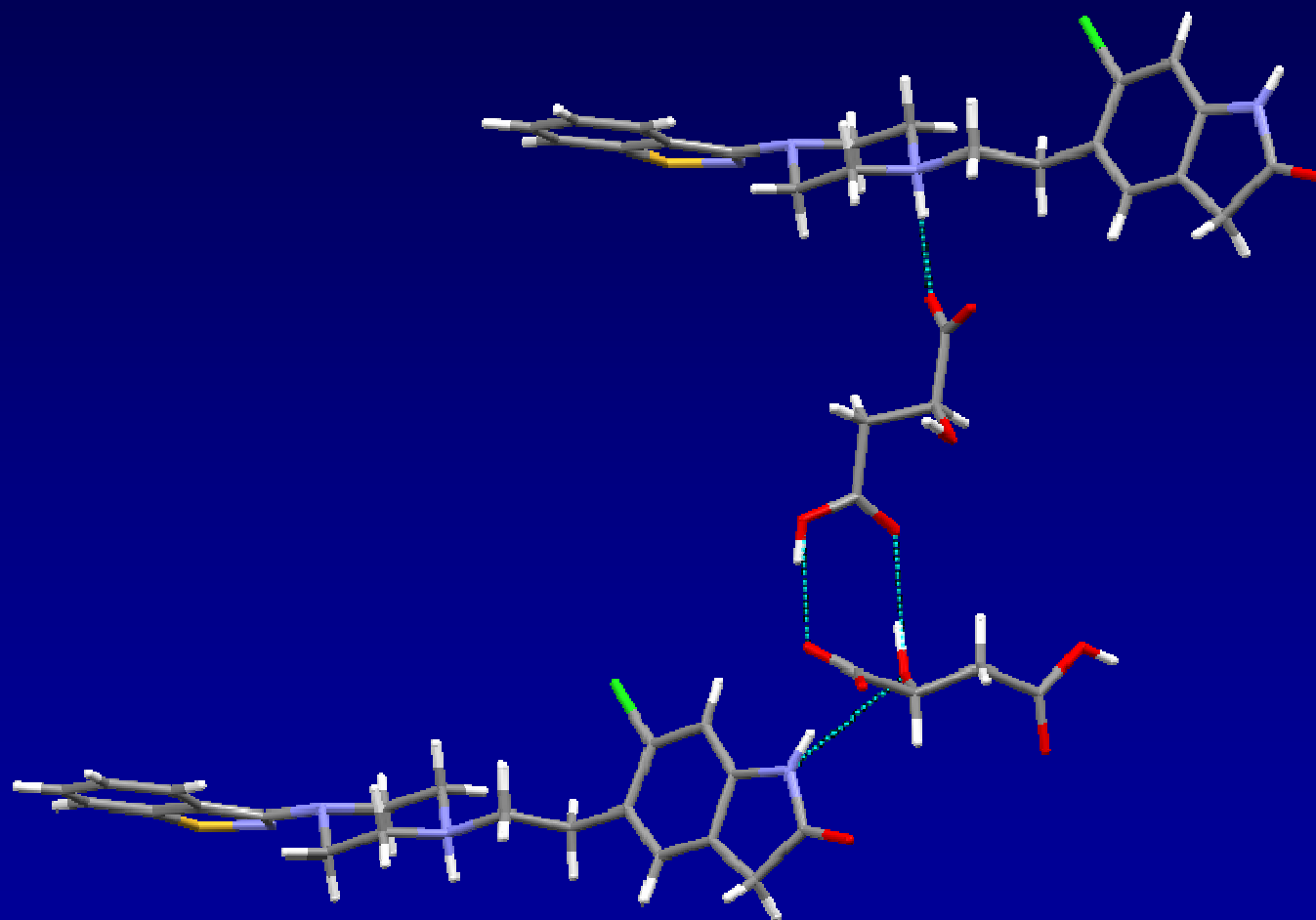
Form C



Aqueous solubilities of Ziprasidone malates



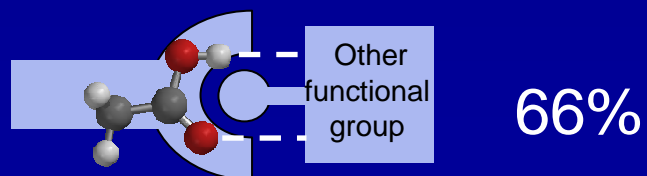
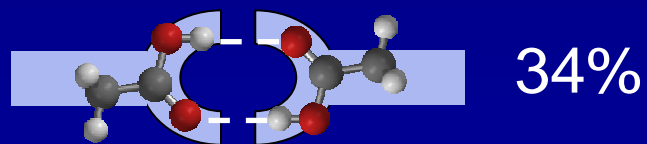
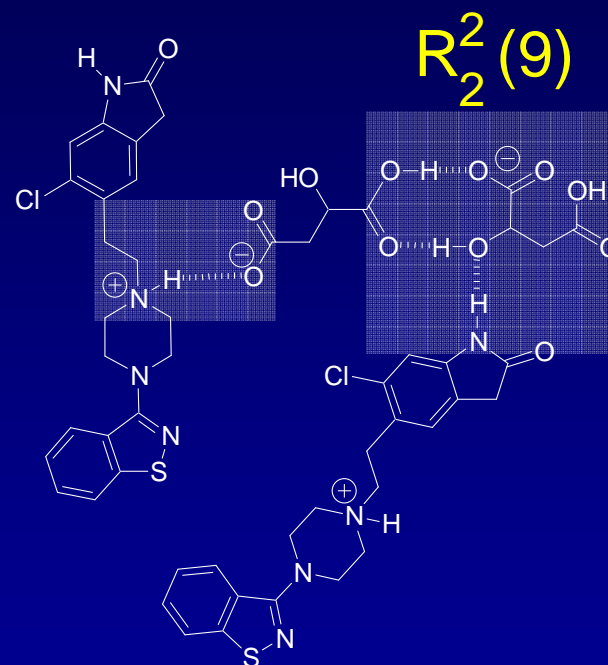
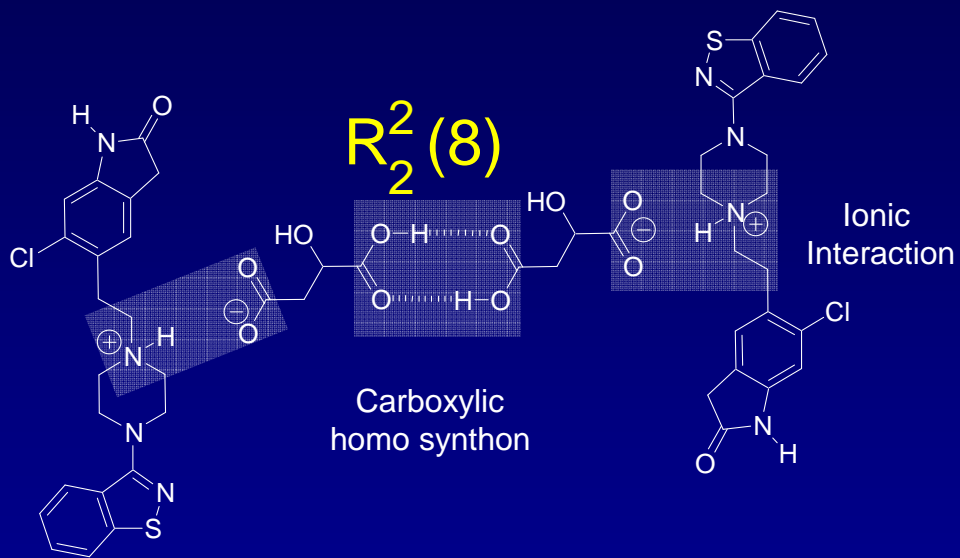
Ziprasidone Malate Form C



Ziprasidone Malate Form C

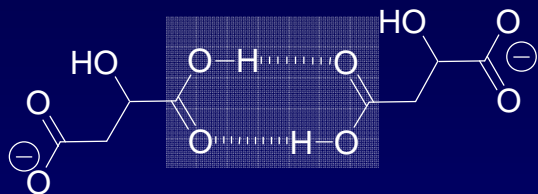
Possible Synthons

Observed Synthons

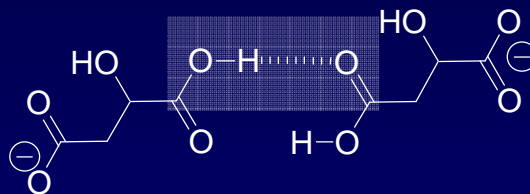


Hierarchy of Synthons: 32 malate structures in the CCDC

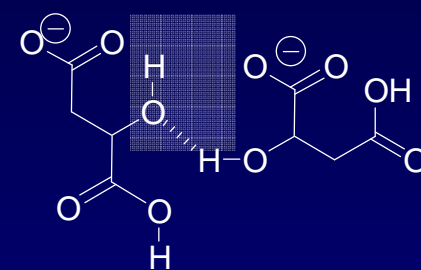
1 hit



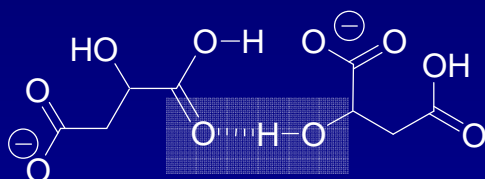
2 hits



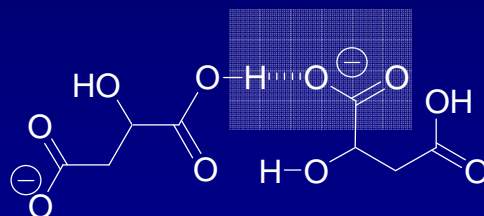
3 hits



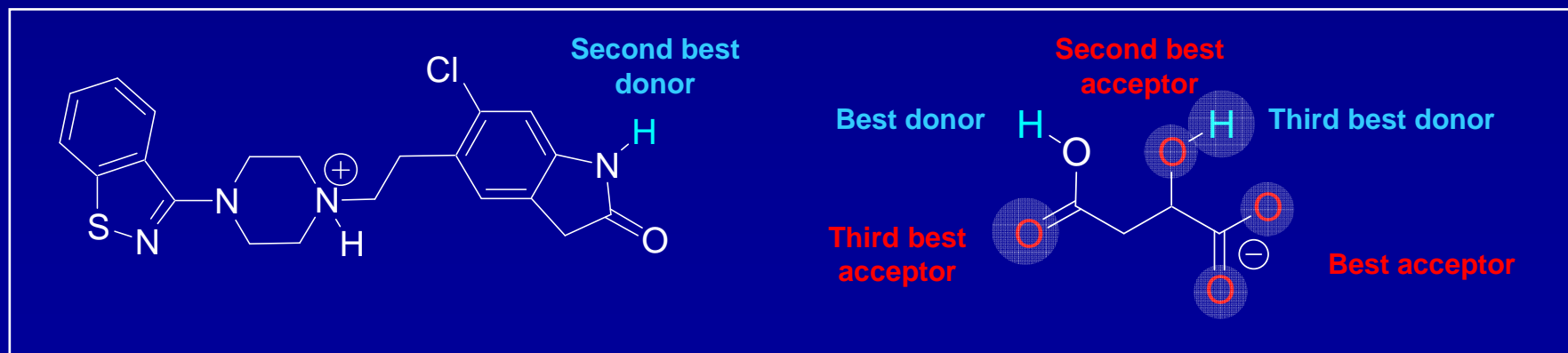
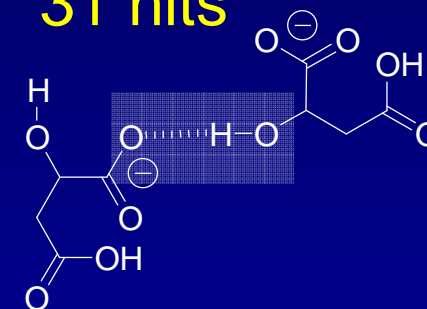
17 hits



30 hits



31 hits



Norfloxacin

3 polymorphic anhydrous forms

Methanolate

Several Hydrates

Salts

Cocrystals

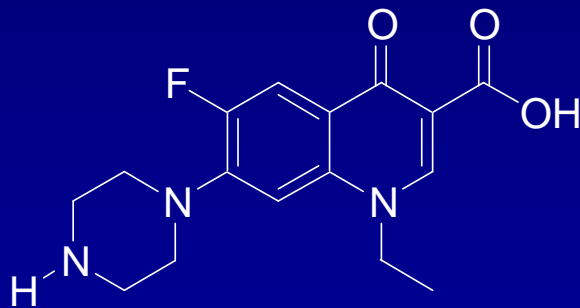


Norfloxacin Bioavailability

“It is a rule that a solvate is always the most stable and therefore the least soluble form in its own solvent”

Rolf Hilfiker. *Polymorphism in the Pharmaceutical Industry*. 2006

Neutral Anhydrous forms



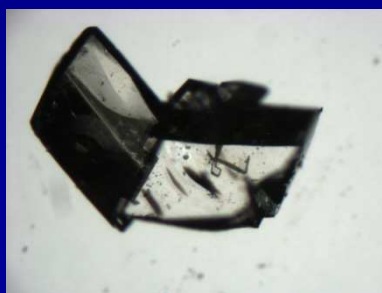
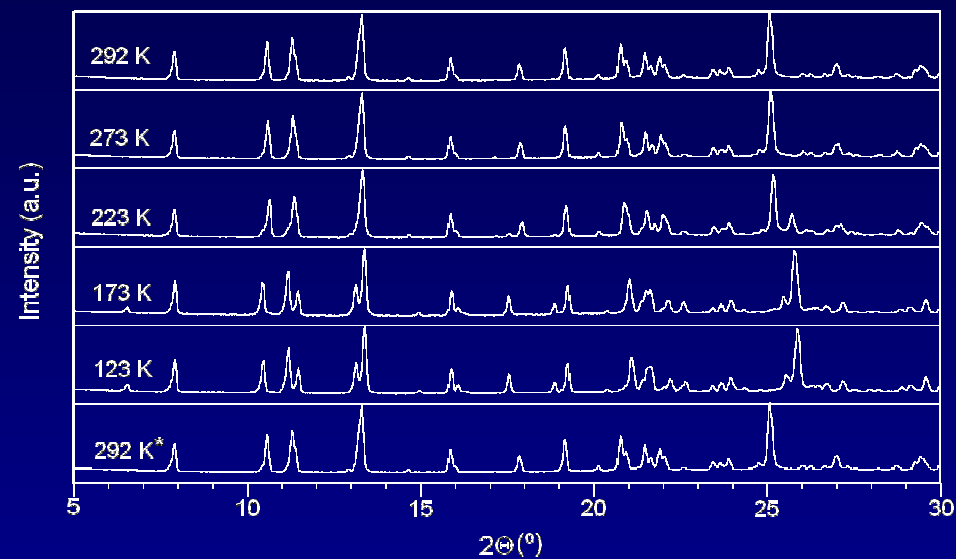
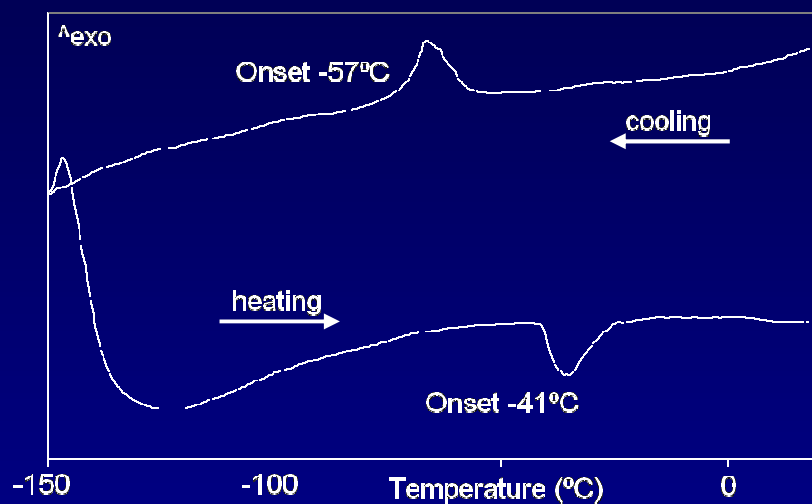
Zwitterionic hydrates



Lower ← Solubility → Higher

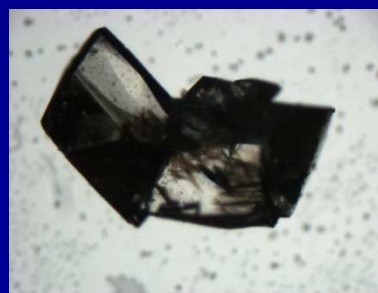
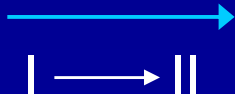
Piperazinyl protonated ring in hydrates explains greater solubility

A new polymorphic sesquihydrate



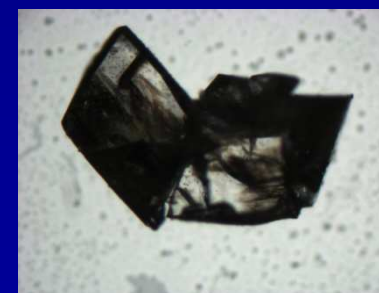
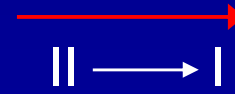
22 °C

Cooling



-69°C

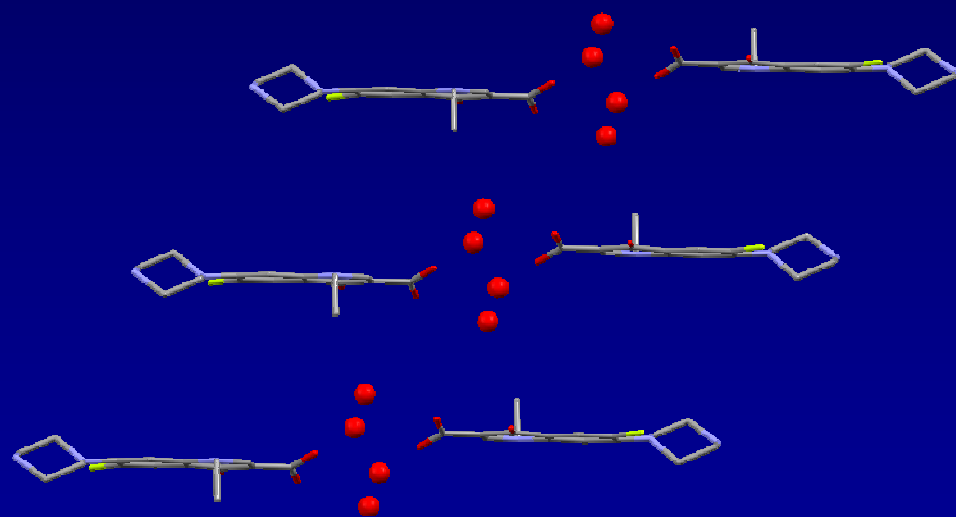
Heating



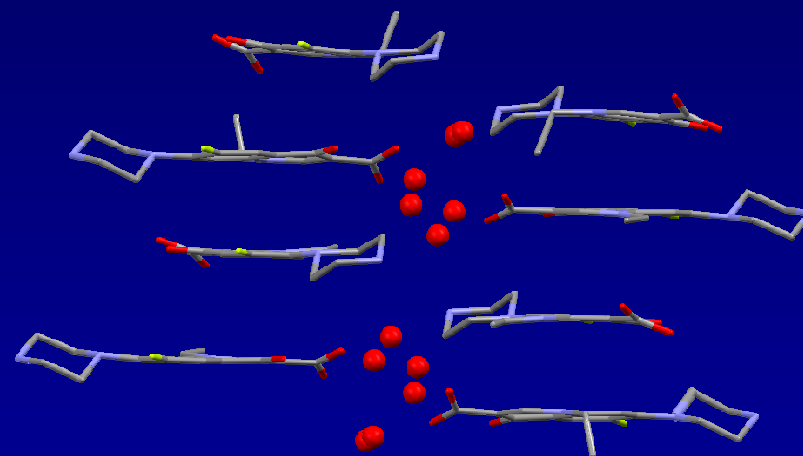
-35°C

A new polymorphic sesquihydrate

Form I

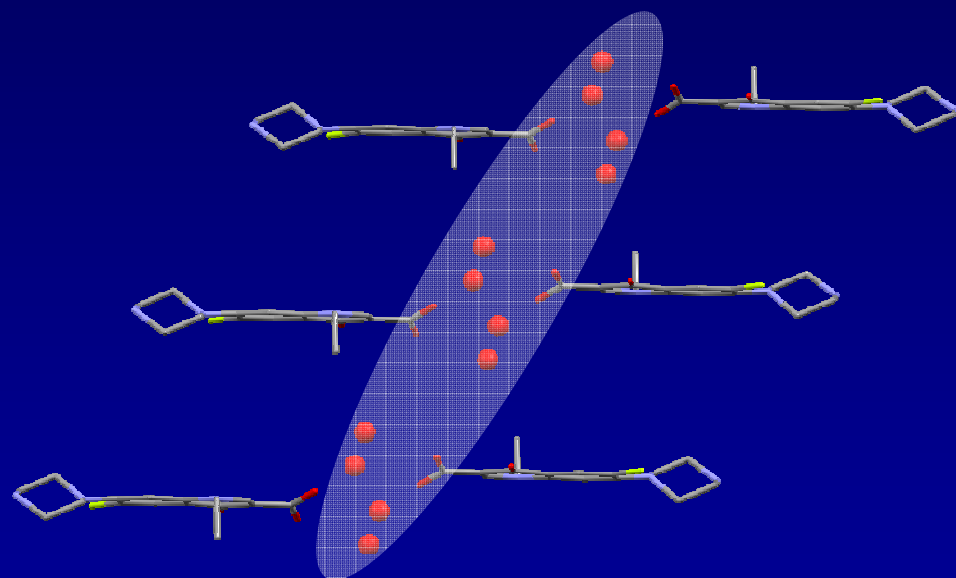


Form II

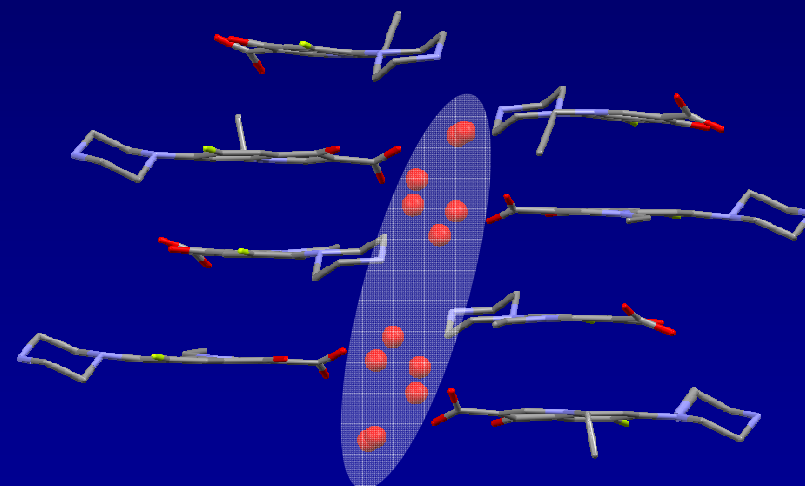


A new polymorphic sesquihydrate

Form I



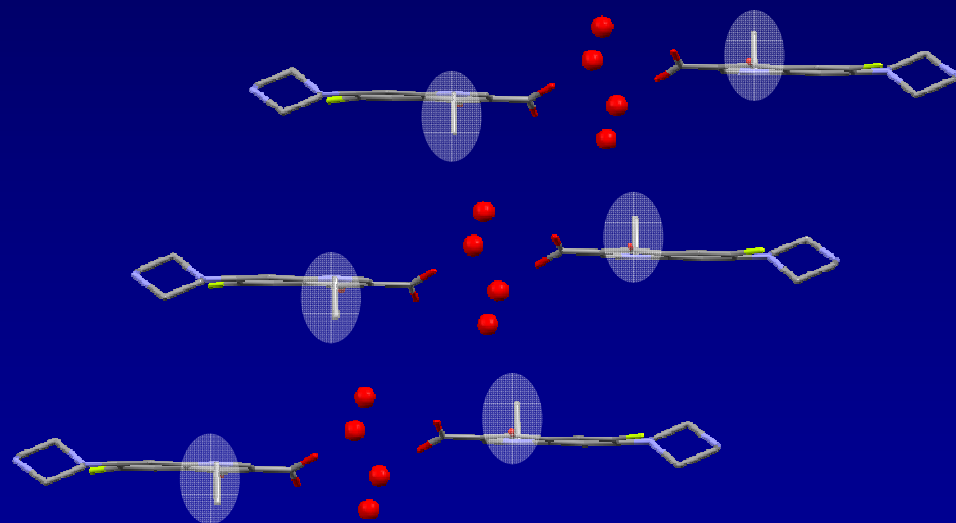
Form II



Water Channels

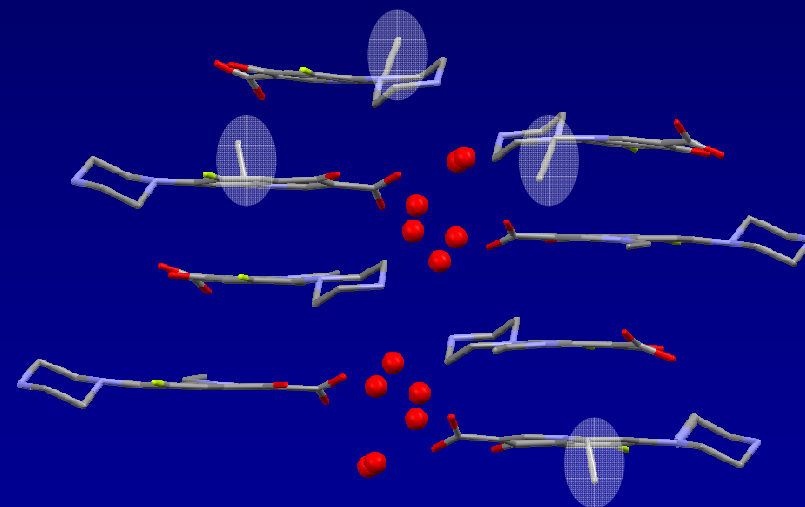
A new polymorphic sesquihydrate

Form I



One conformation

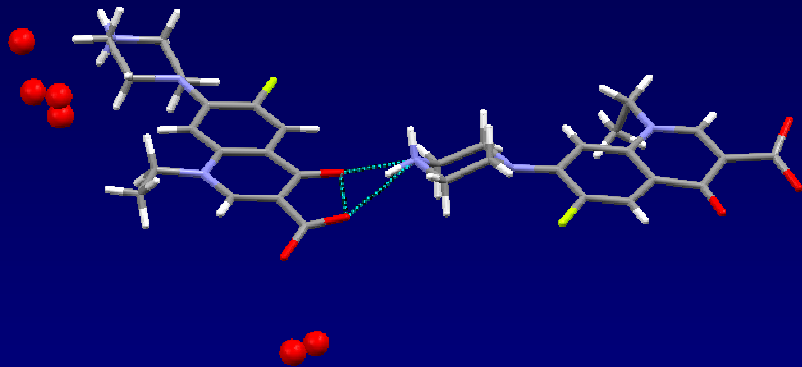
Form II



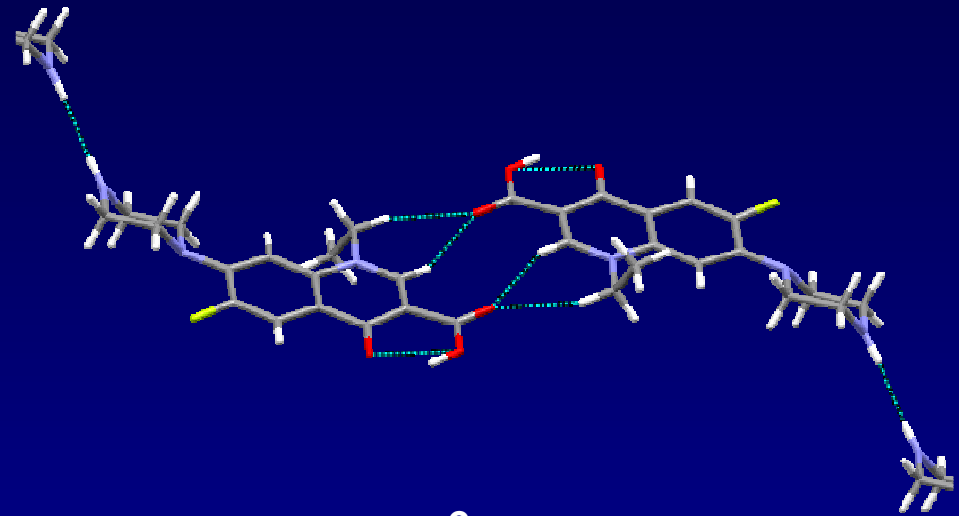
Two conformations

Different Ethyl Conformation

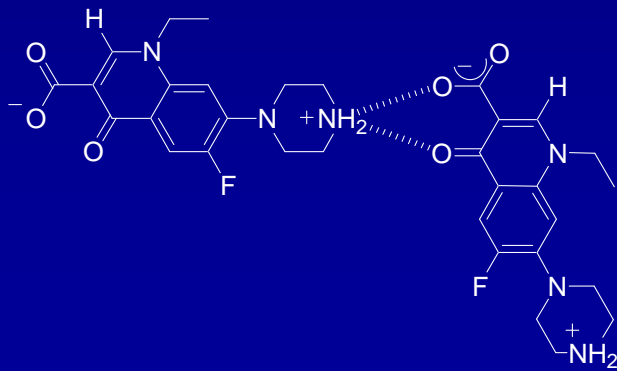
Hydrates vs Anhydrous



$R_2^2(8)$



$R_2^2(10)$



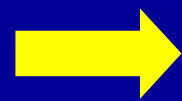
API: non-disclosure agreement



The most stable polymorph (**Form A**) is protected by patent

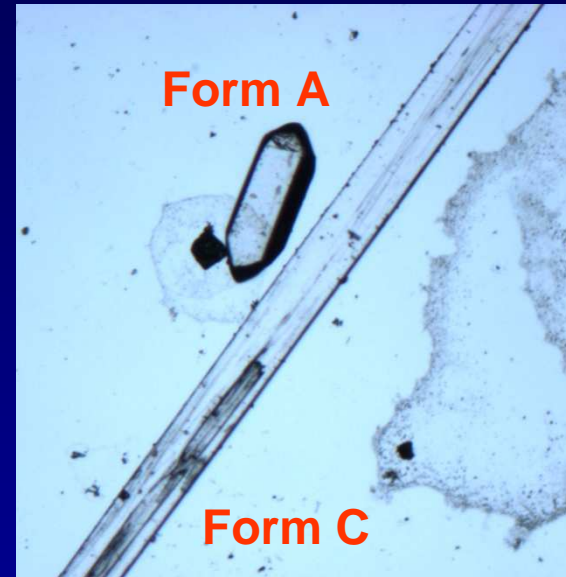
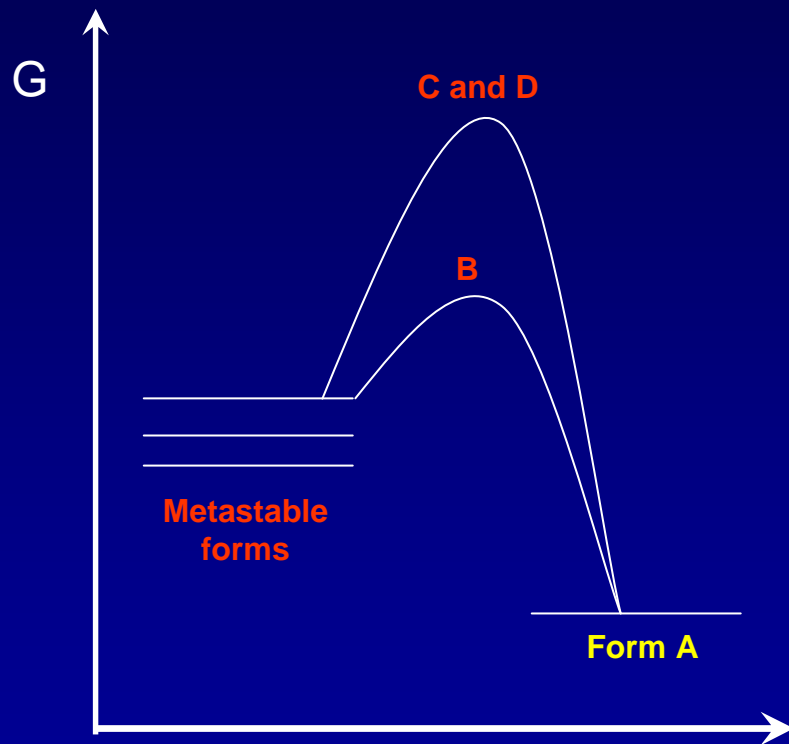


Polymorph Screening



3 new metastable polymorphs obtained
always with traces of **Form A**

Polymorphism Screening

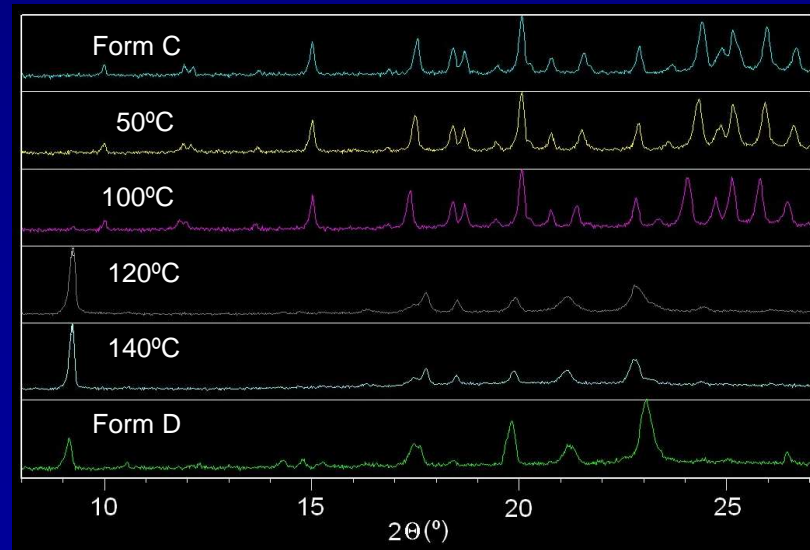
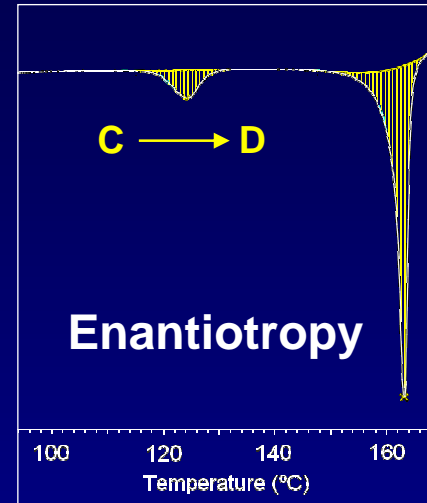
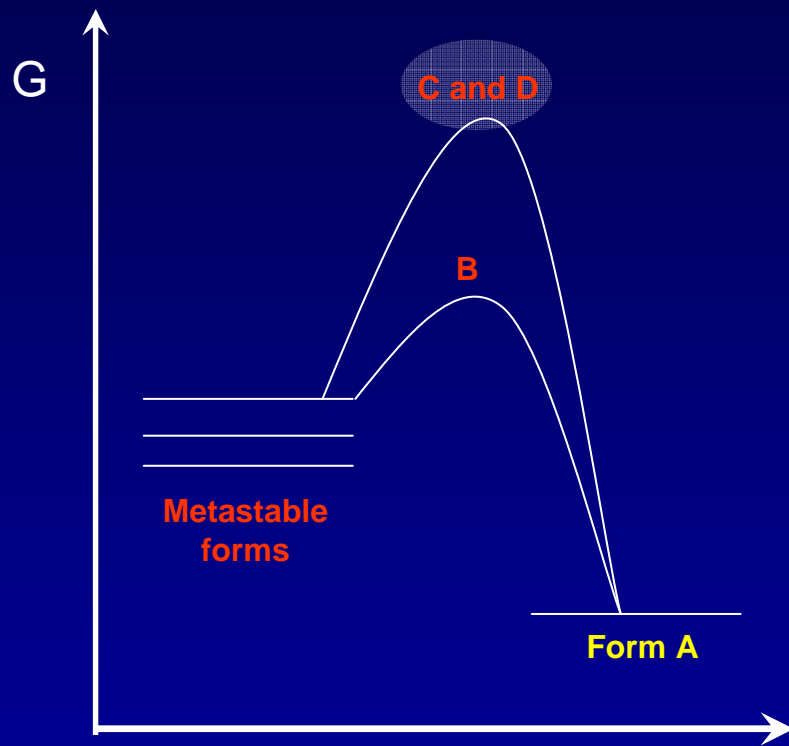


Concomitant Polymorphs

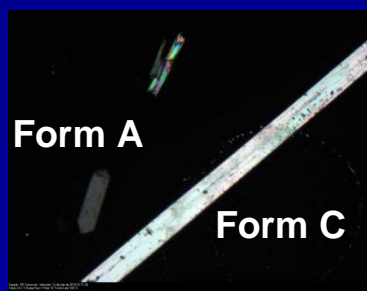
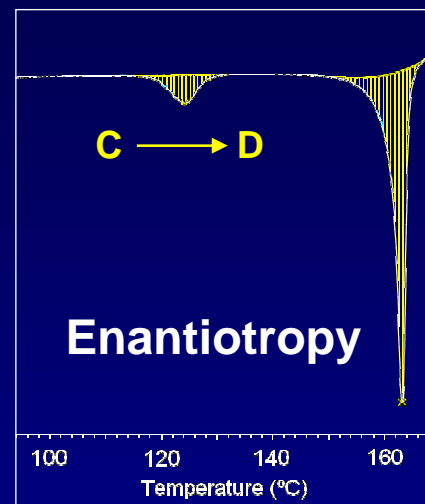
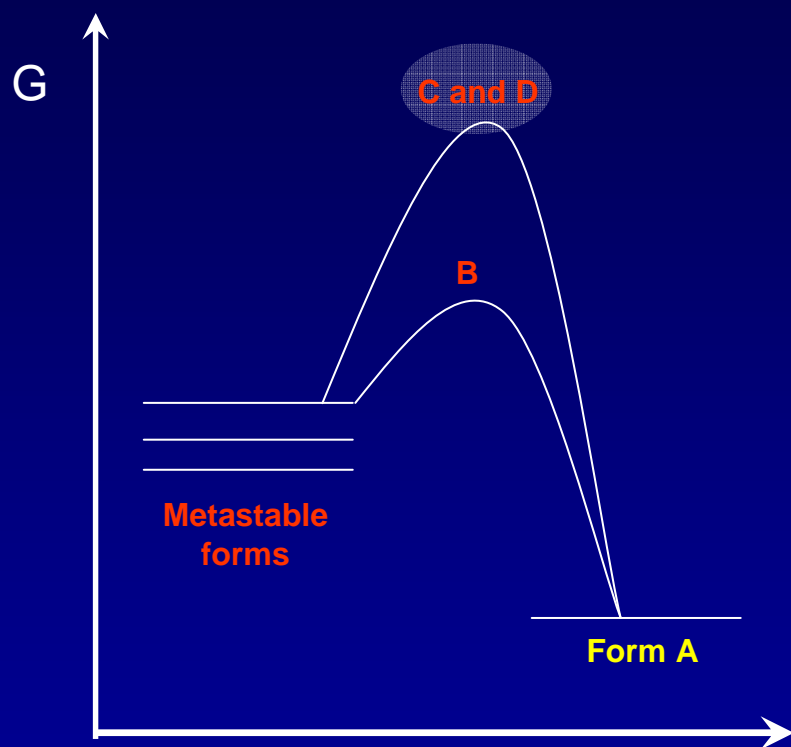


Significantly different synthons

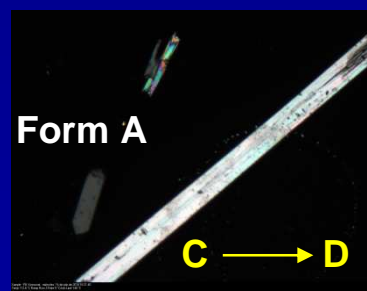
Polymorphism Screening



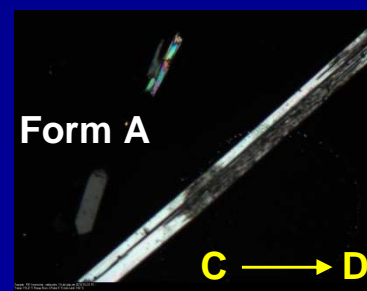
Polymorphism Screening



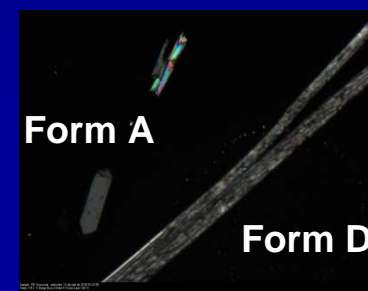
23 °C



113 °C

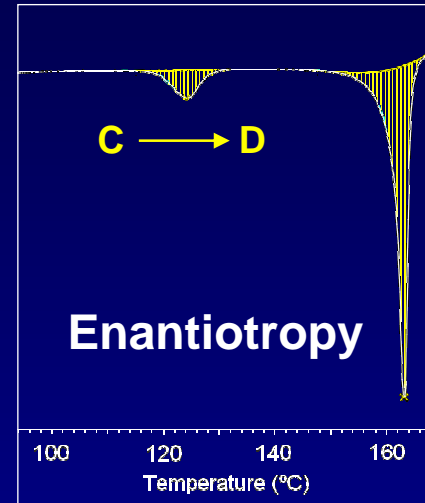
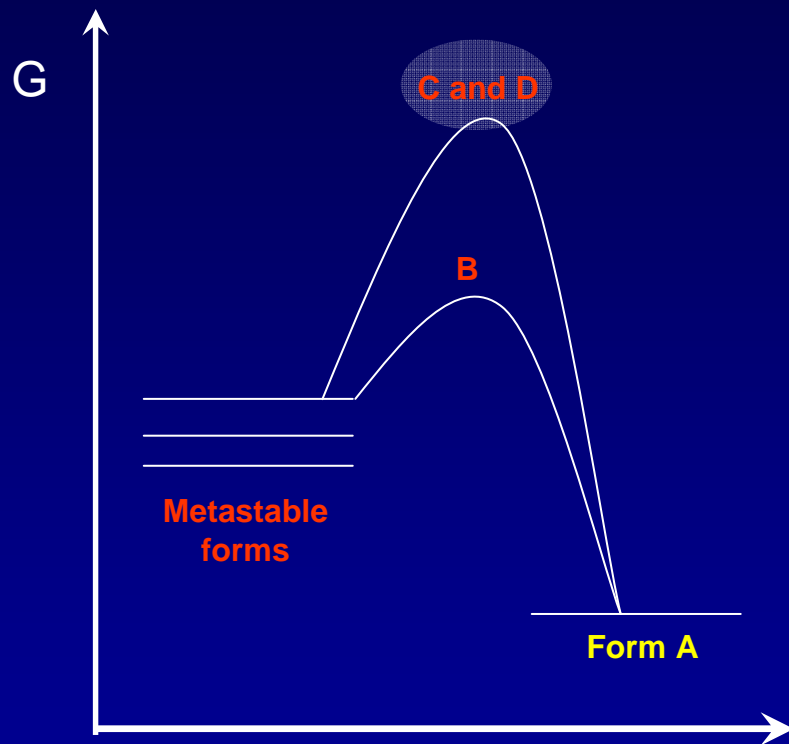


116 °C



119 °C

Polymorphism Screening

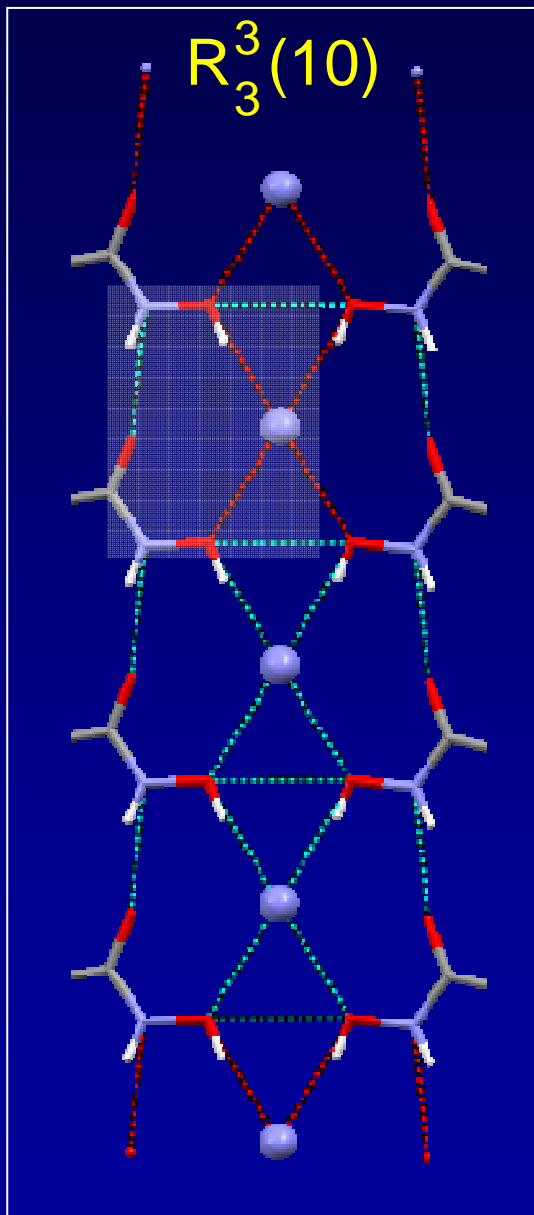


C and D forms cannot be obtained totally free of the patented form A

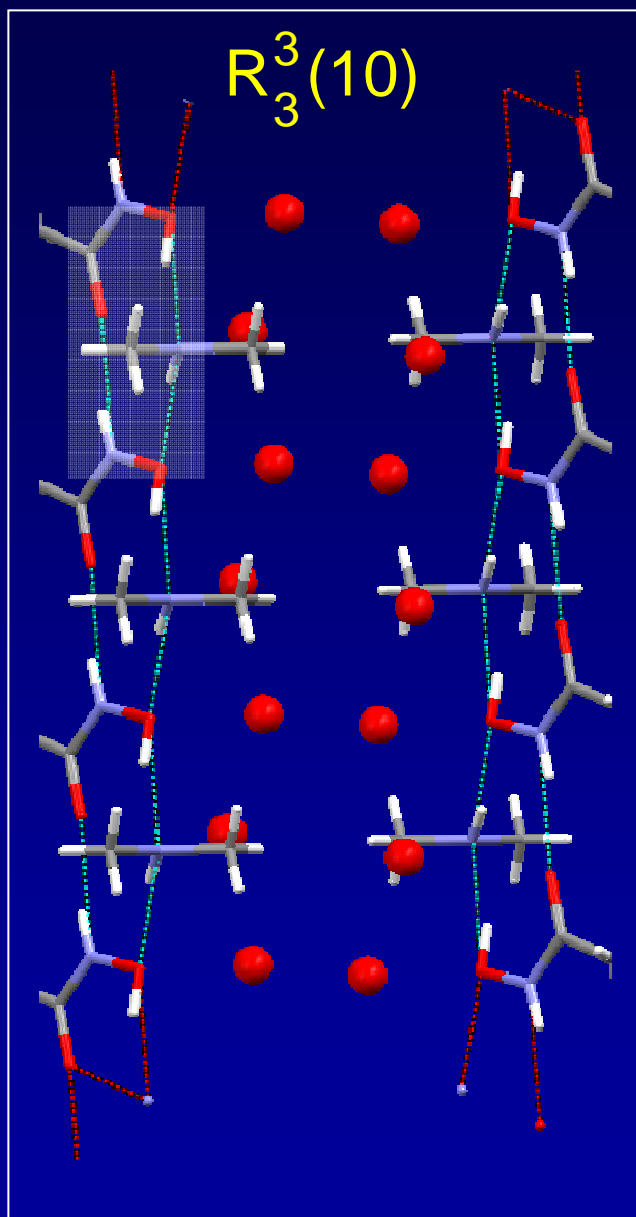


Cocrystal Screening

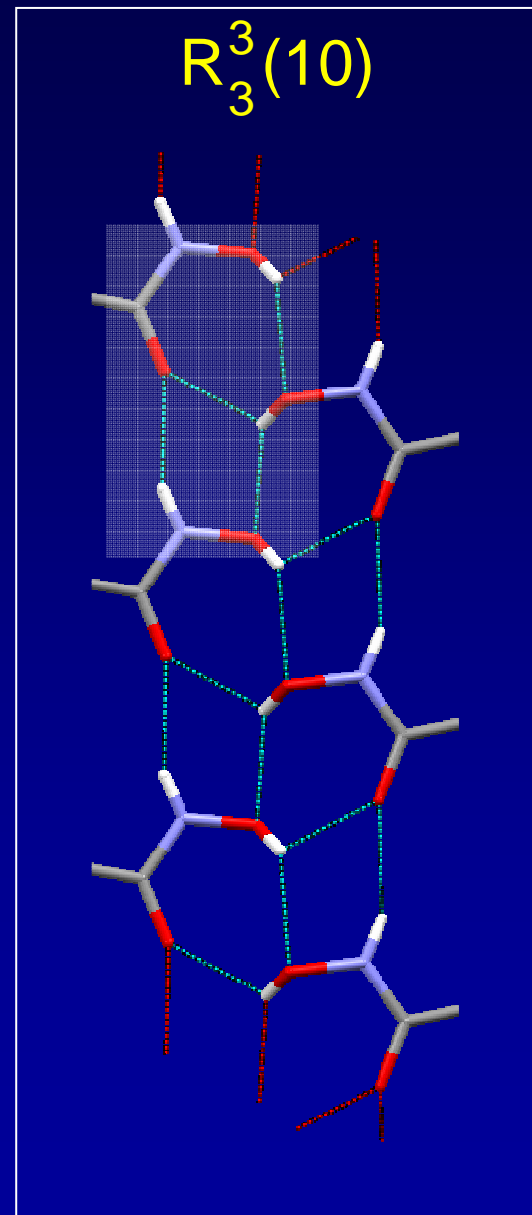
API-NH₃ - Cocrystal



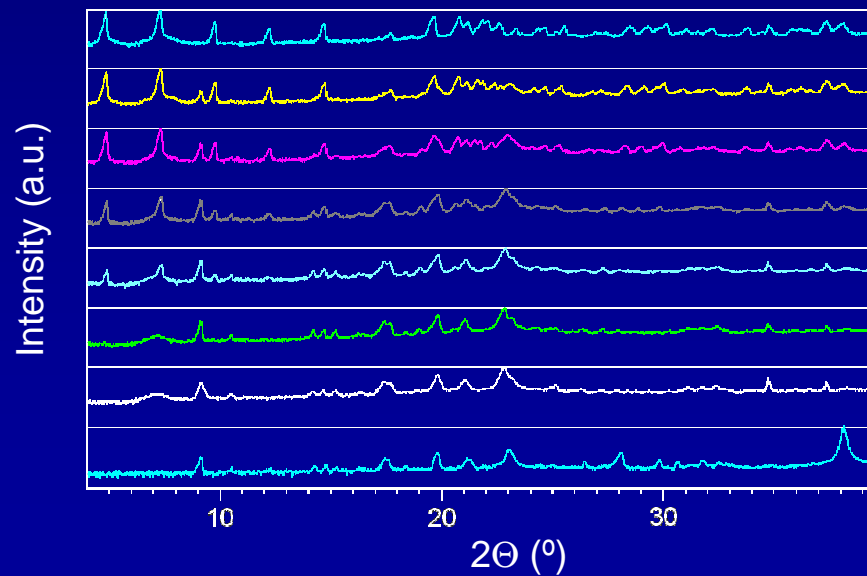
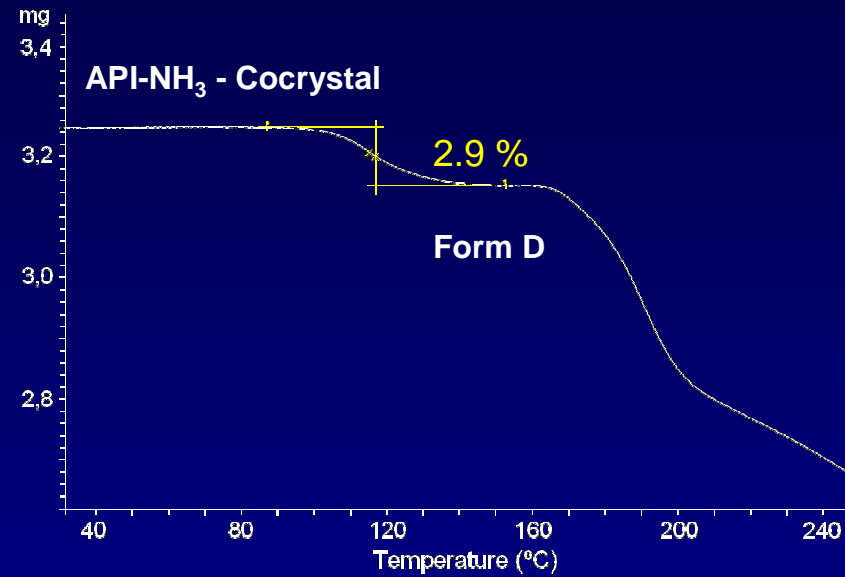
API-H₂O-NHMe₂ - Cocrystal



Form C



Ammonia Cocystal



API-NH₃ - Cocystal

50 °C

70 °C

90 °C

100 °C

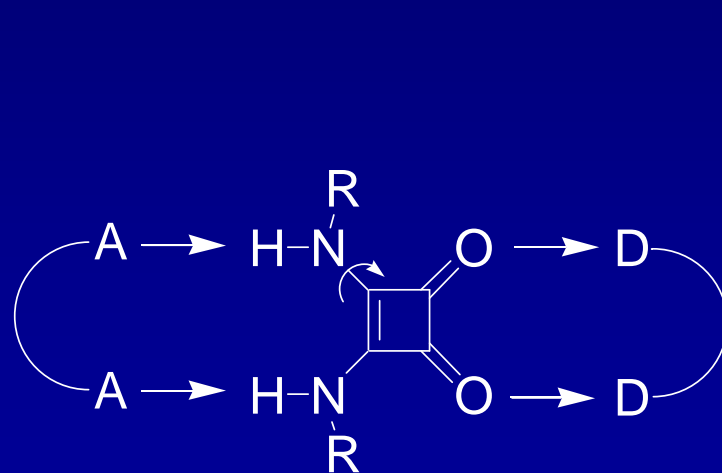
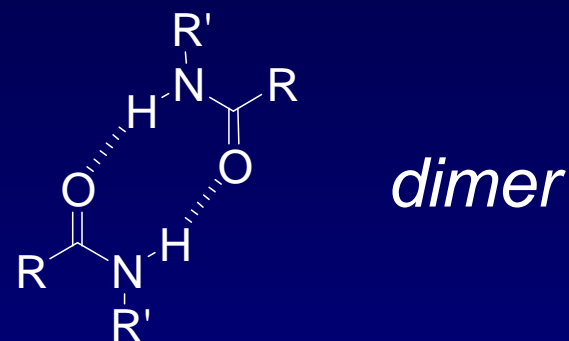
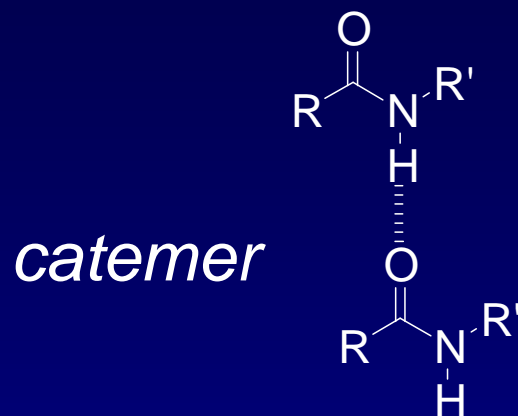
110 °C

120 °C

Form D

Squaramides in
Supramolecular Synthons:
a case study

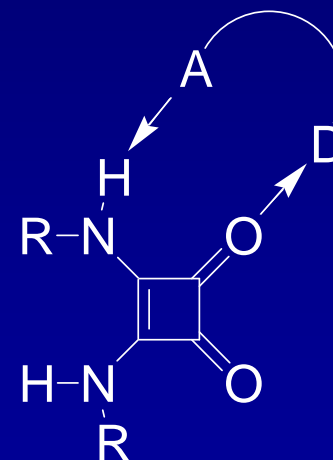
Double Donor-Acceptor H-bonding Supramolecular Synthons



anti / anti

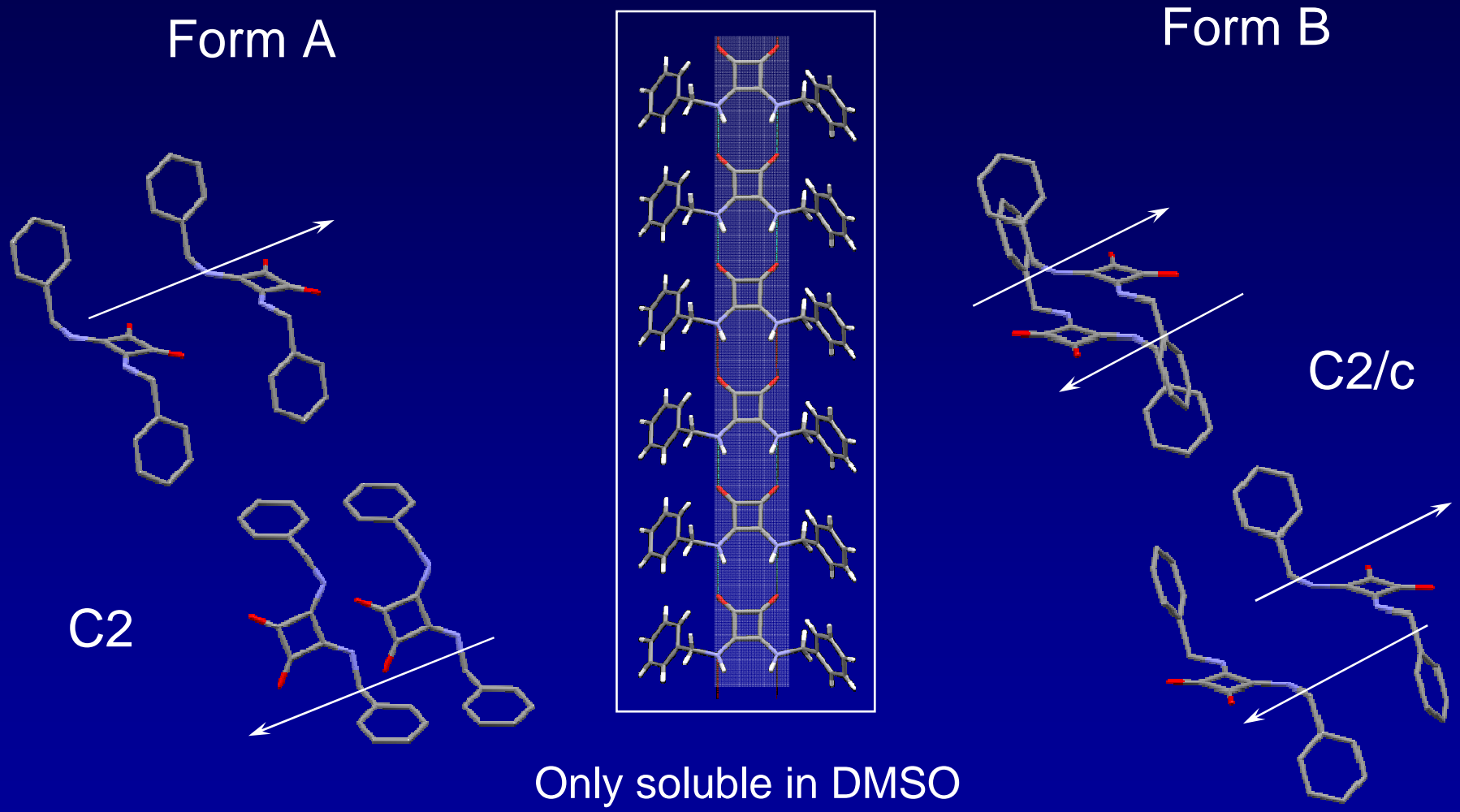


$R_2^2(n)$

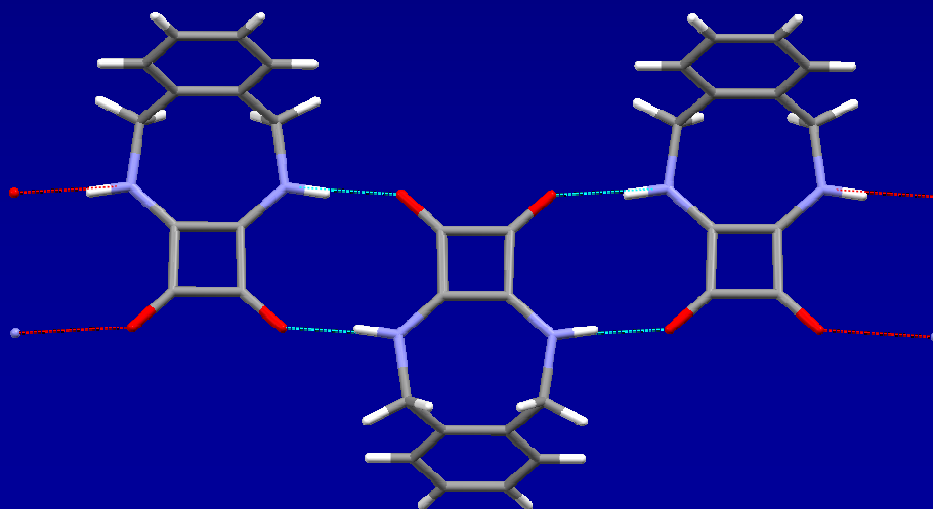
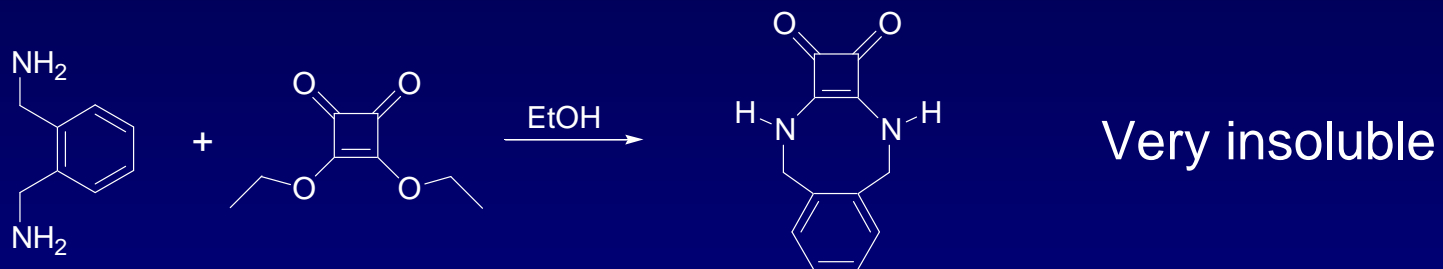


anti / syn

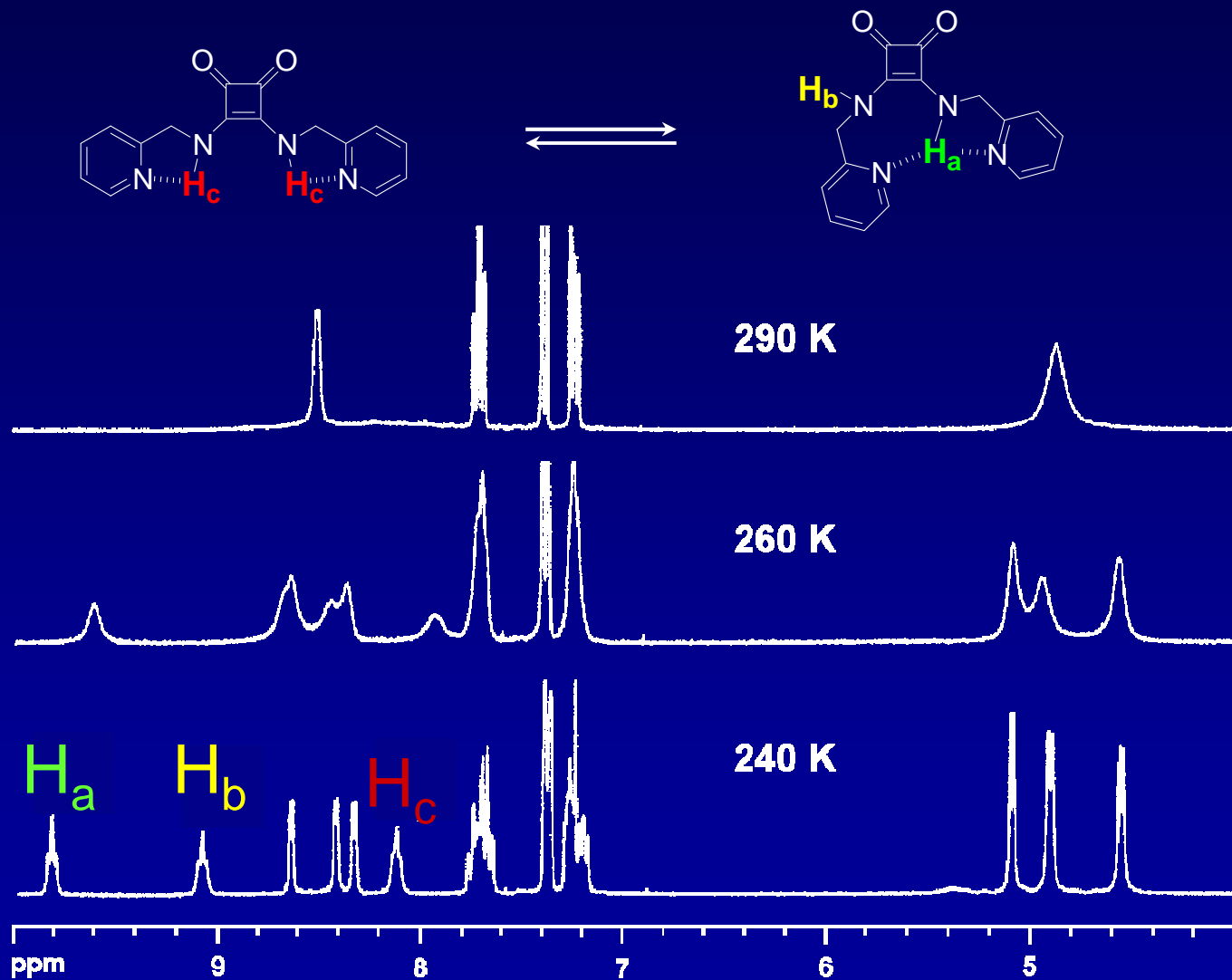
Head-to-tail H-bonding motif



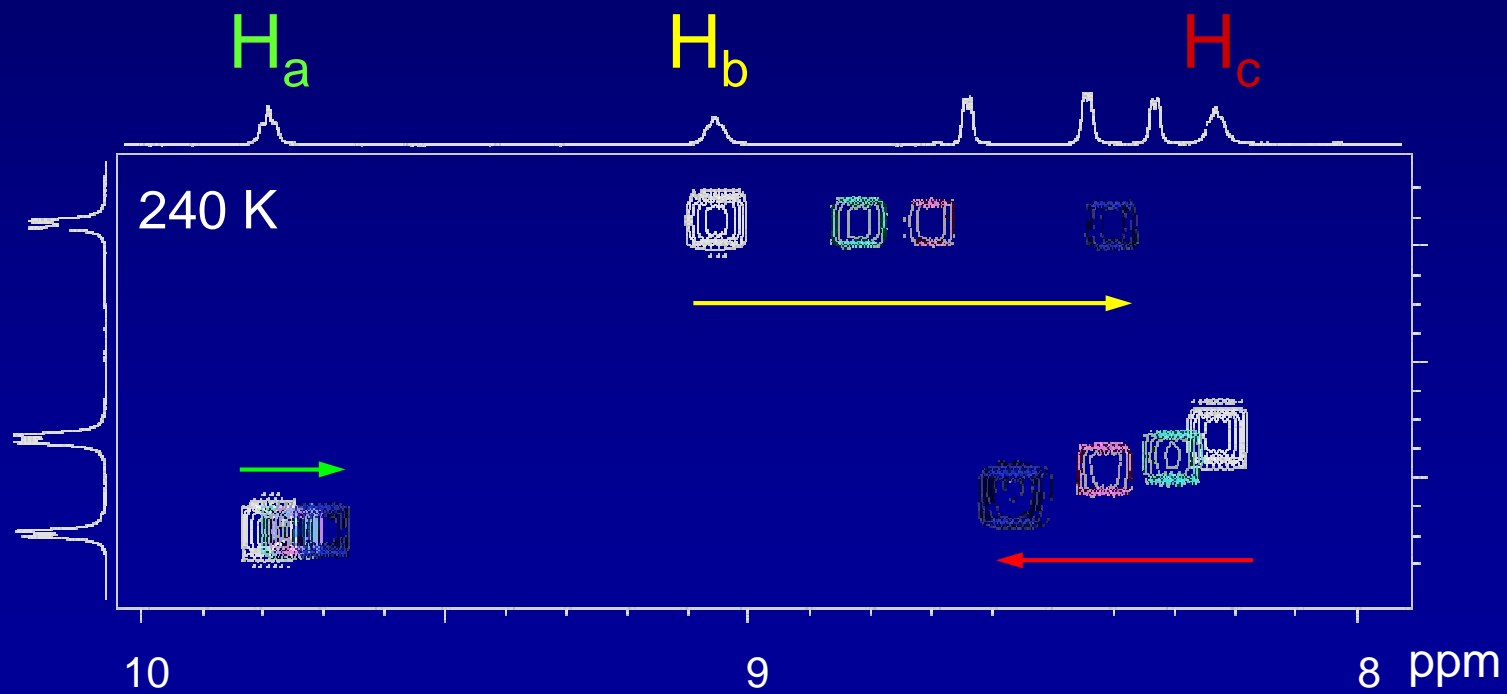
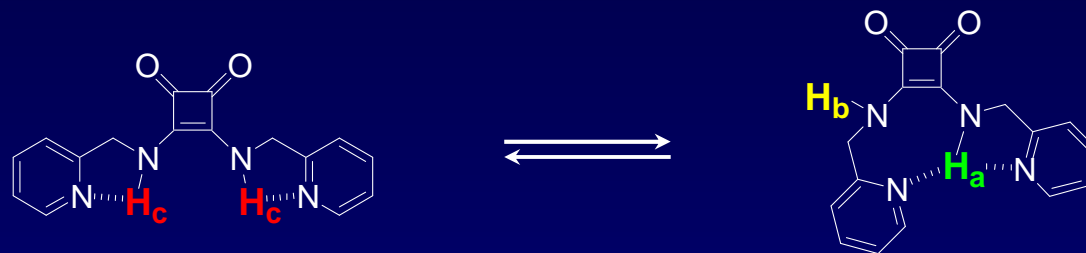
The anti/syn synthon is also geometrically favorable



Conformational Equilibrium in Solution (CDCl₃)



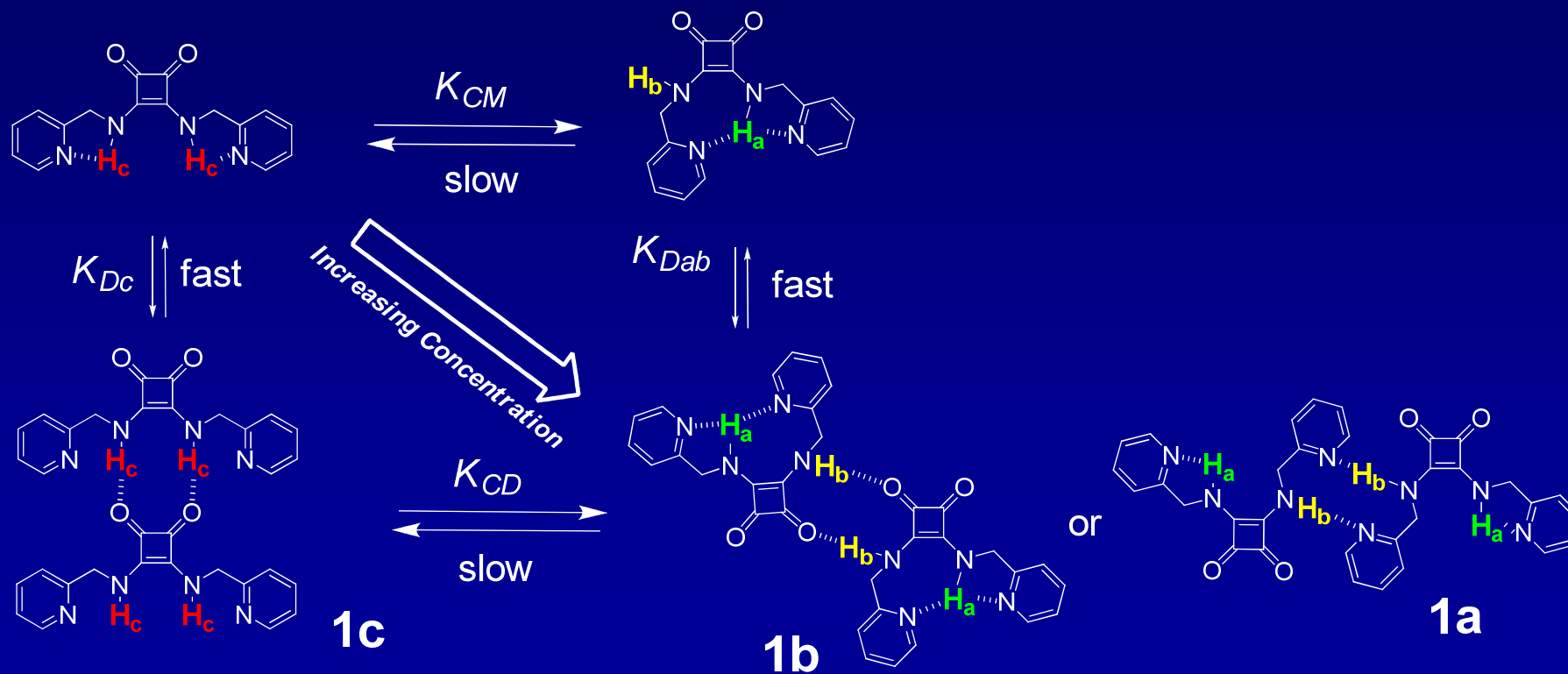
2D-NMR Dilution Experiment



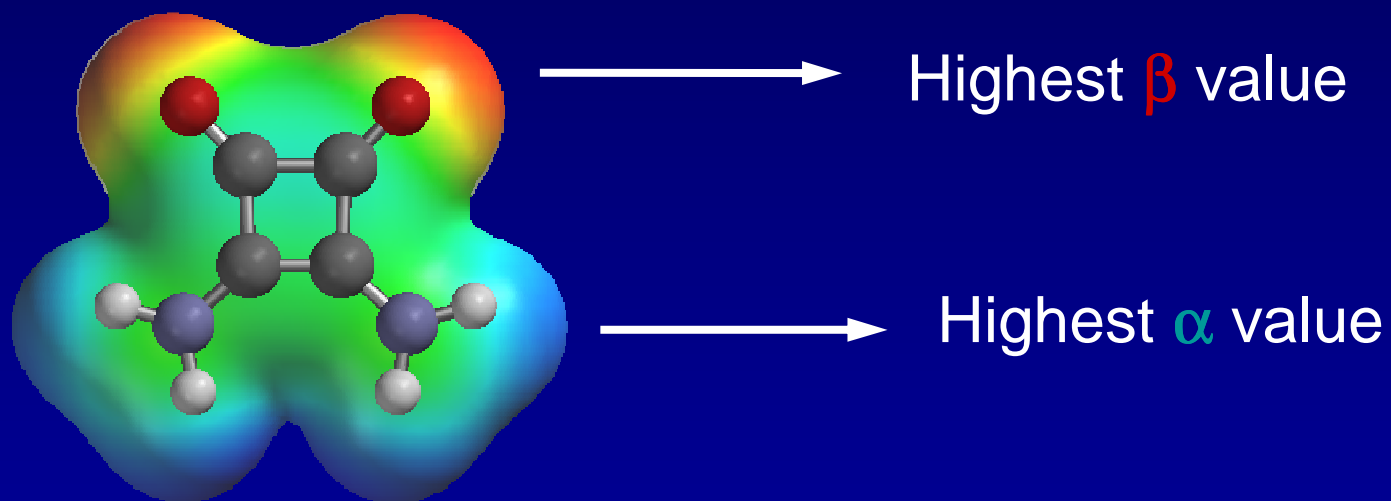
Thermodynamic Equilibrium in Solution

Approximate Values of the Equilibrium Constants

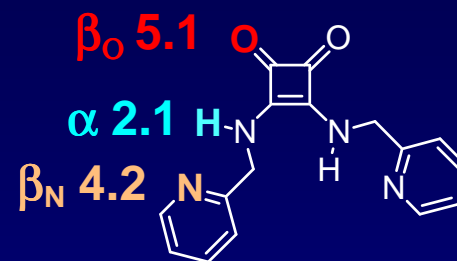
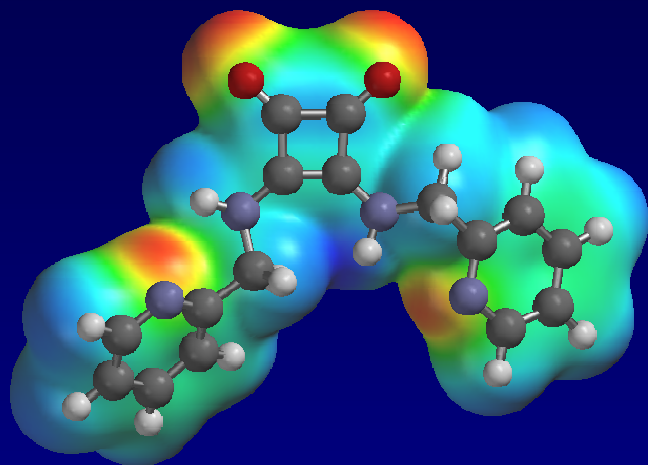
K_{CM}	K_{CD}	K_{Dab}	K_{Dc}
2.5	0.56	8600	790



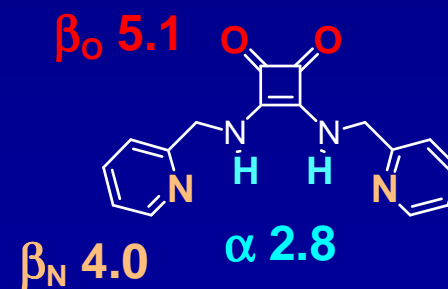
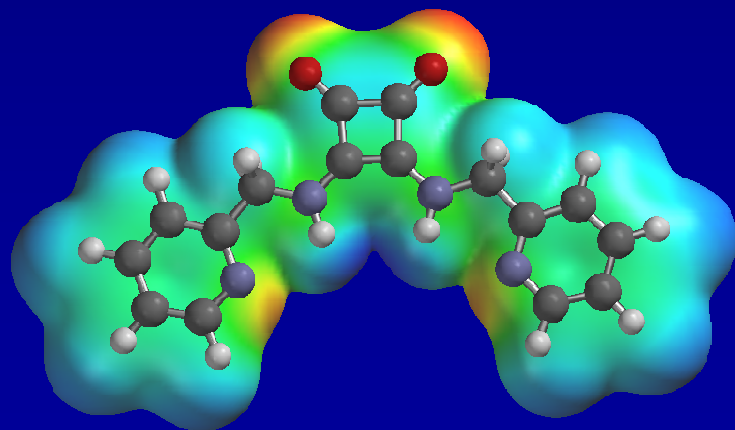
Molecular Electrostatic Potential Surface



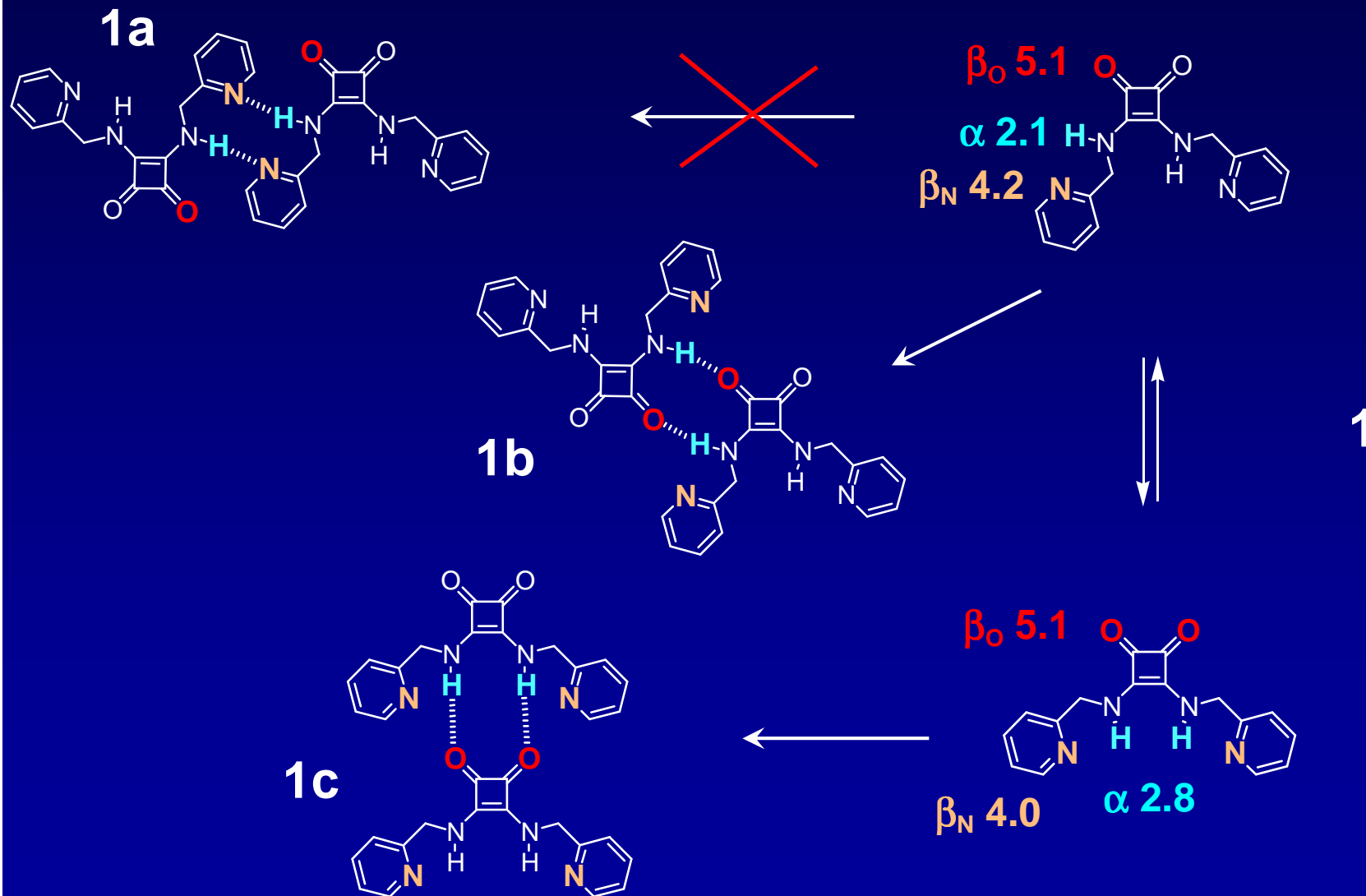
Solution vs Solid State



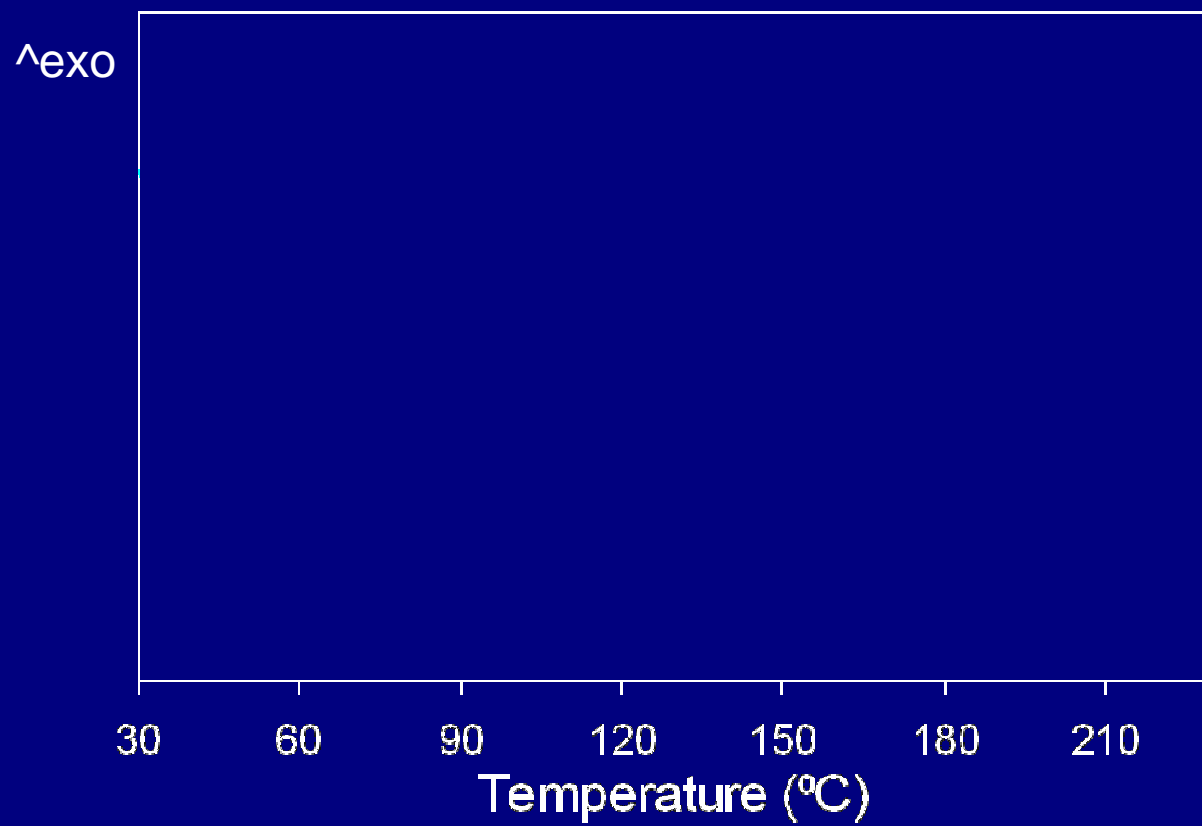
1



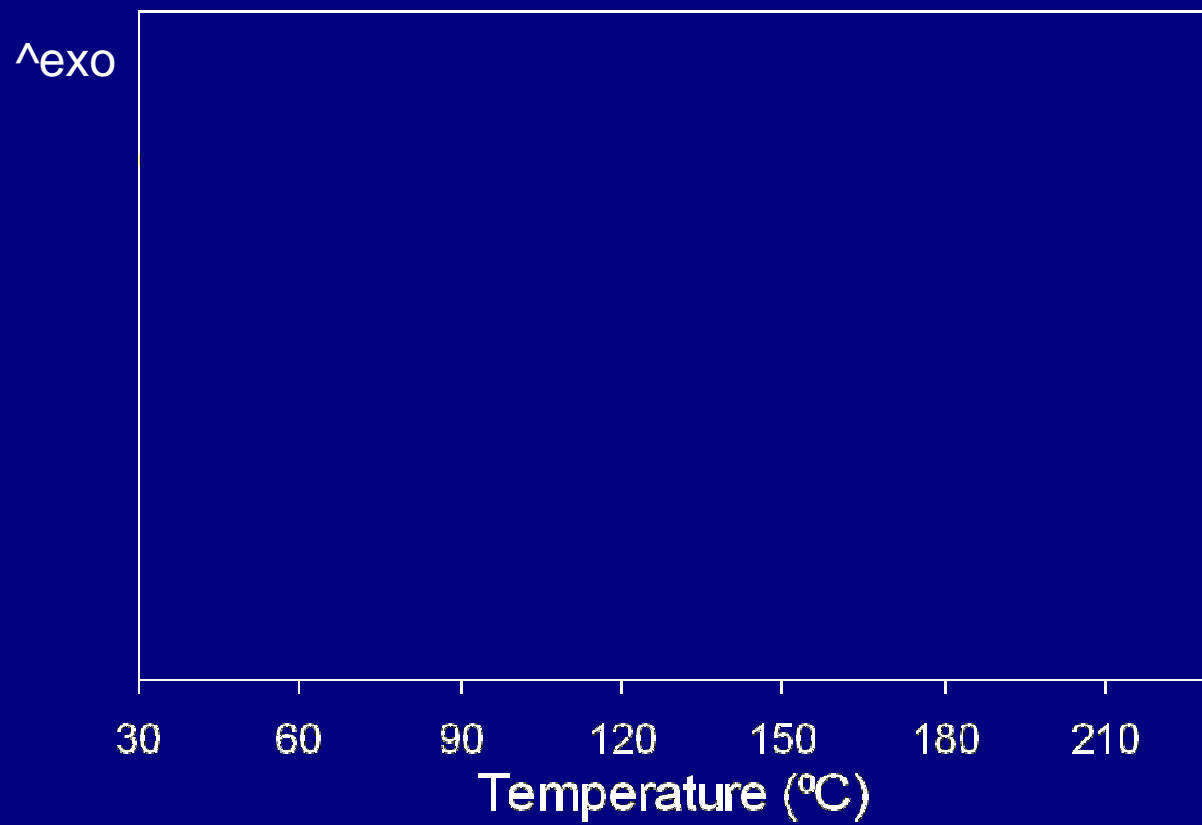
Solution vs Solid State



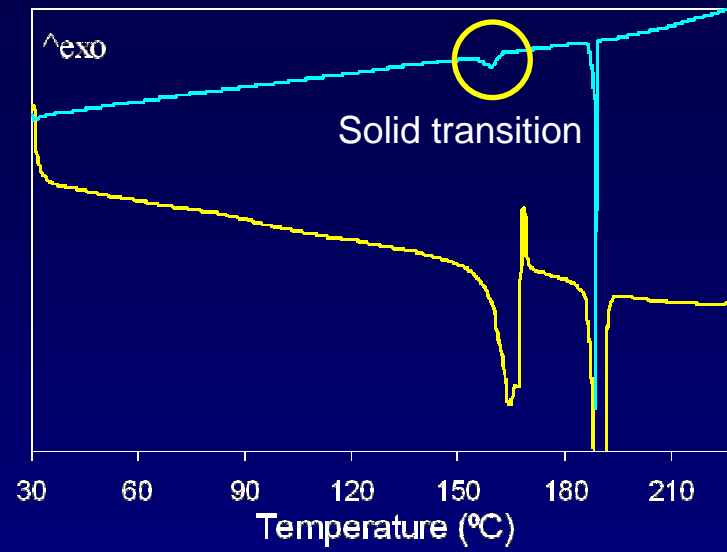
Two Polymorphs



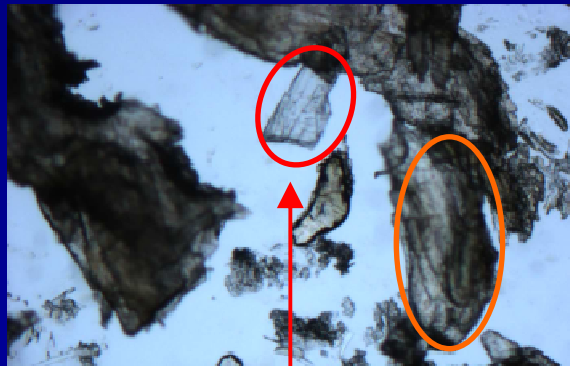
Two Polymorphs



Two Polymorphs



120 °C



Melting

130 °C



Solid transition

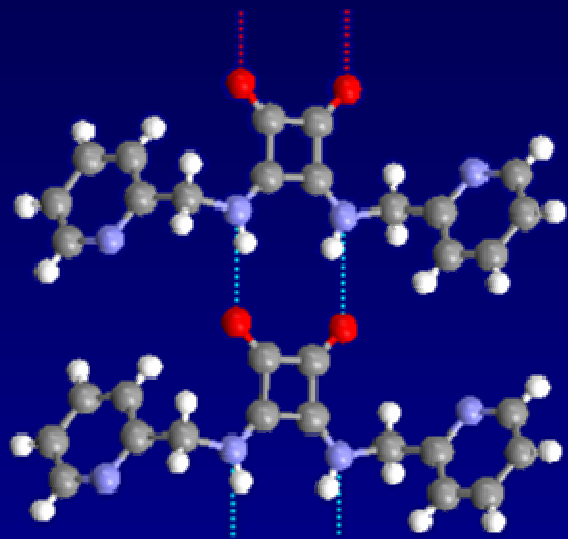
150 °C



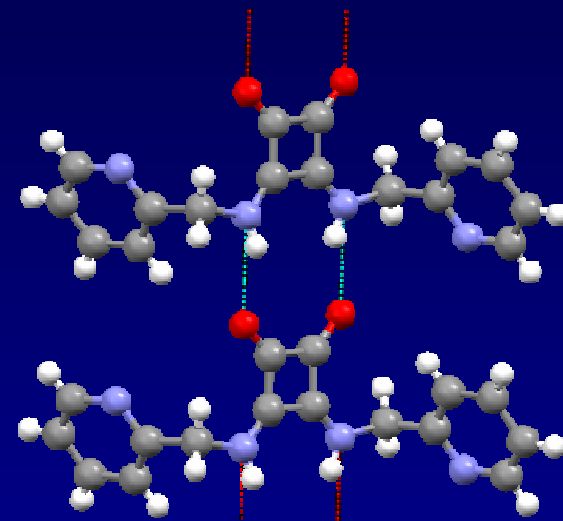
Crystallization from the melt

Two Polymorphs

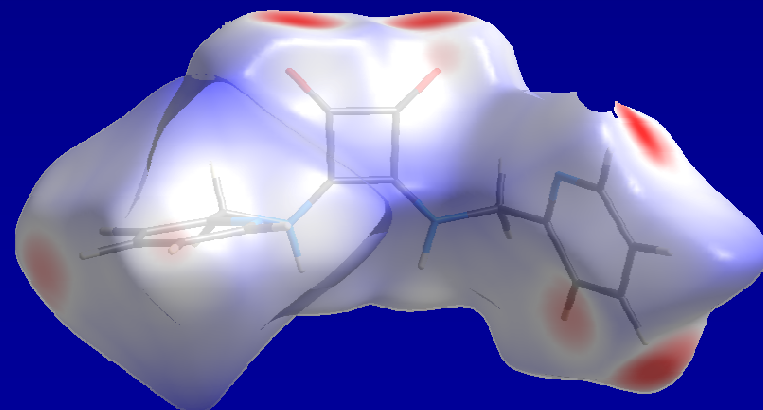
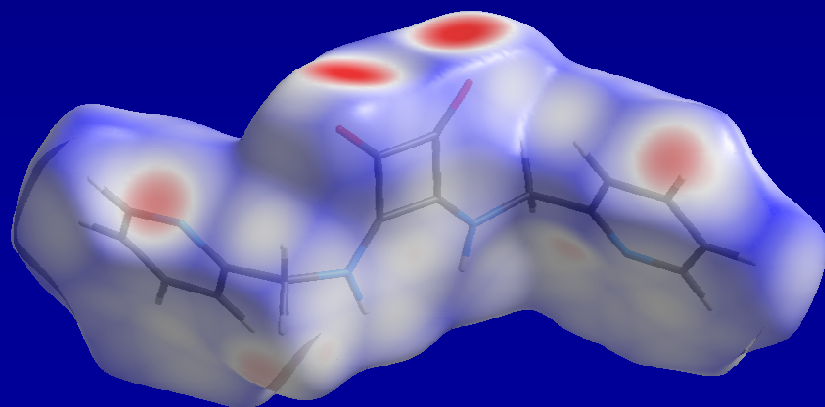
Form I



Form II



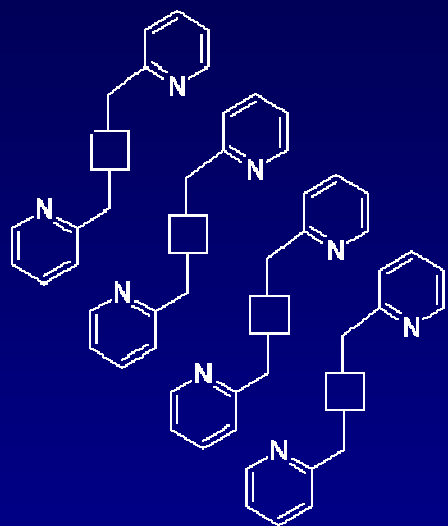
$R_2^2(10)$



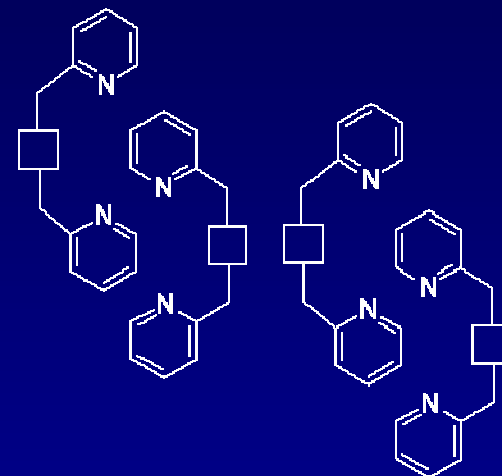
Hirshfeld's Surfaces

Two Polymorphs

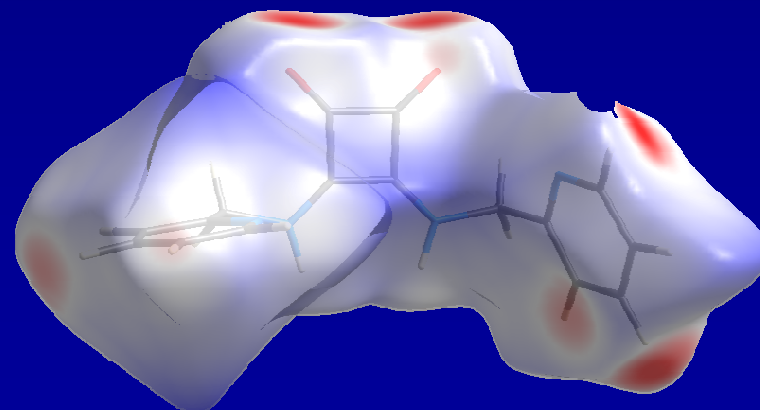
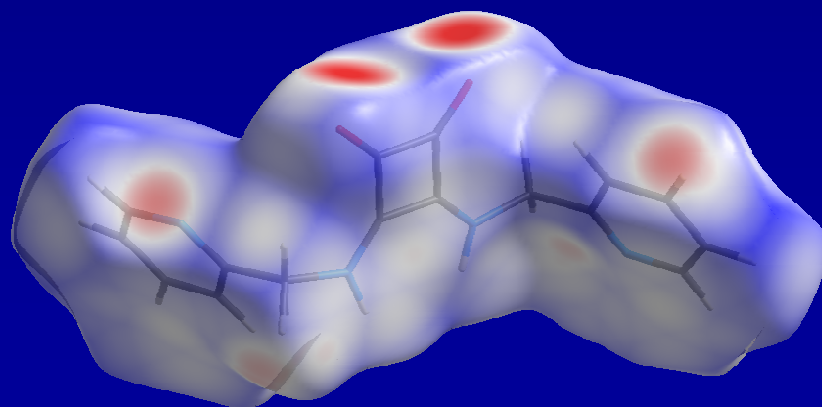
Form I



Form II

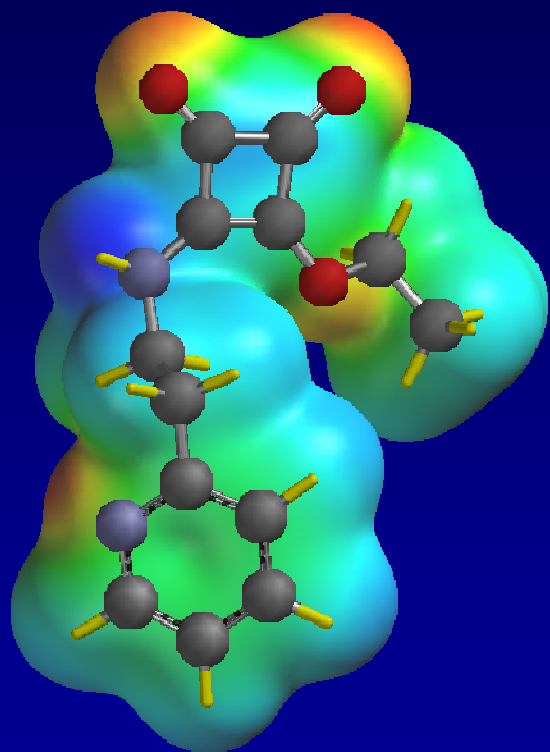


$R_2^2(10)$

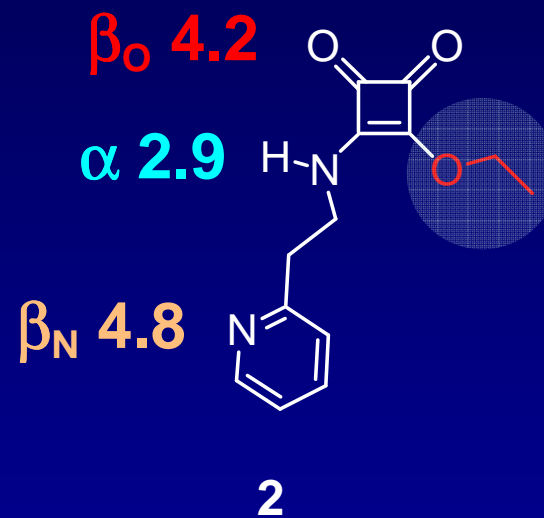


Hirshfeld's Surfaces

Breaking the head-to-tail motif

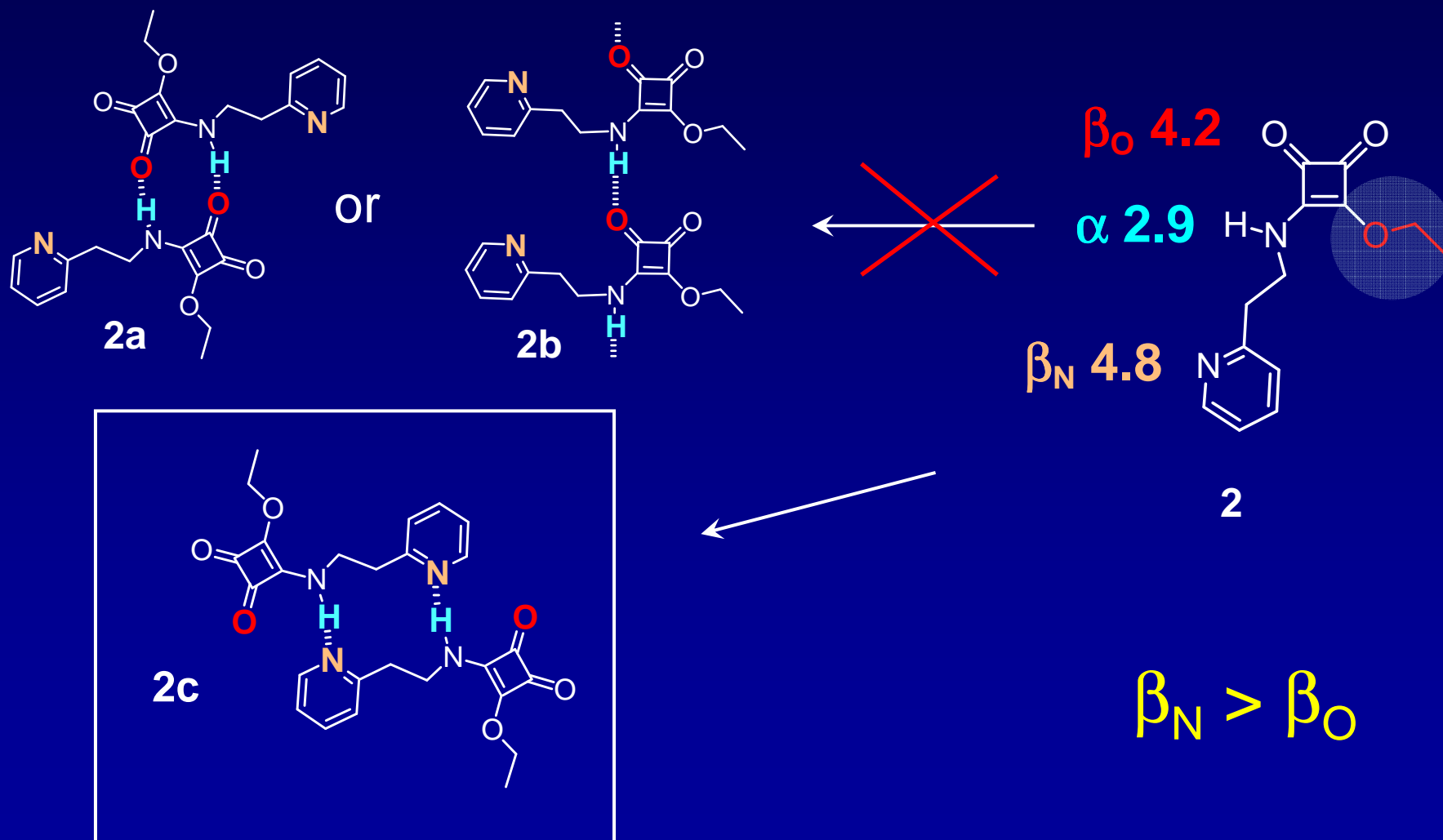


MEP Surface

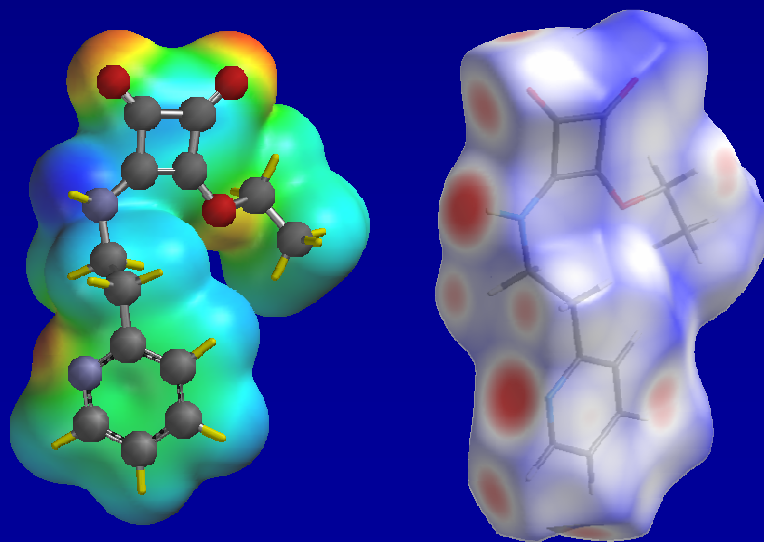
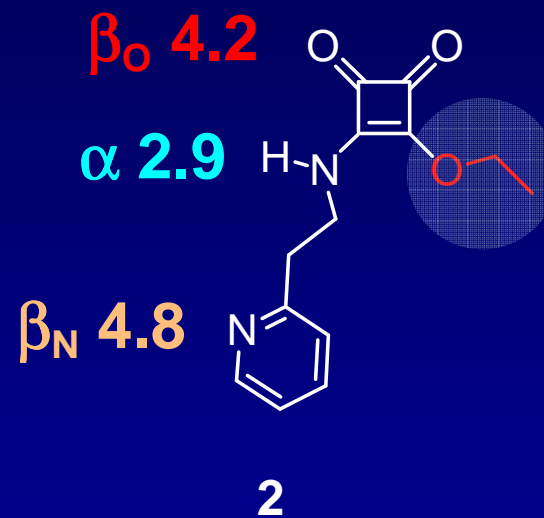
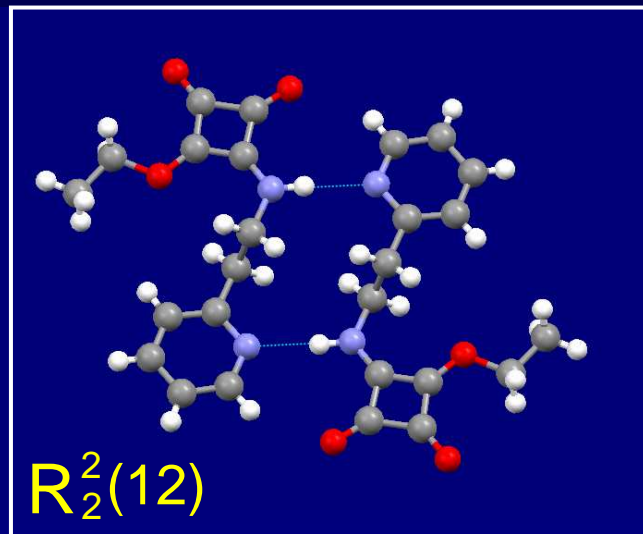


$$\beta_{\text{N}} > \beta_{\text{O}}$$

Breaking the head-to-tail motif

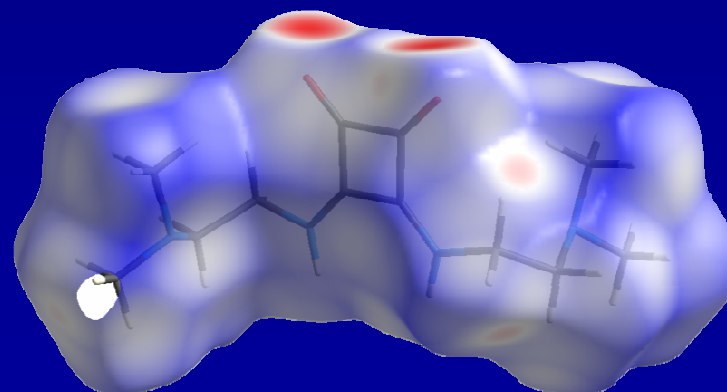
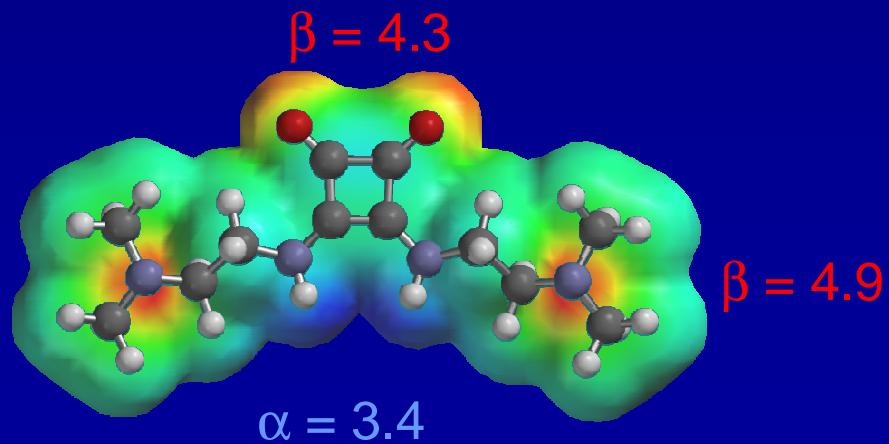
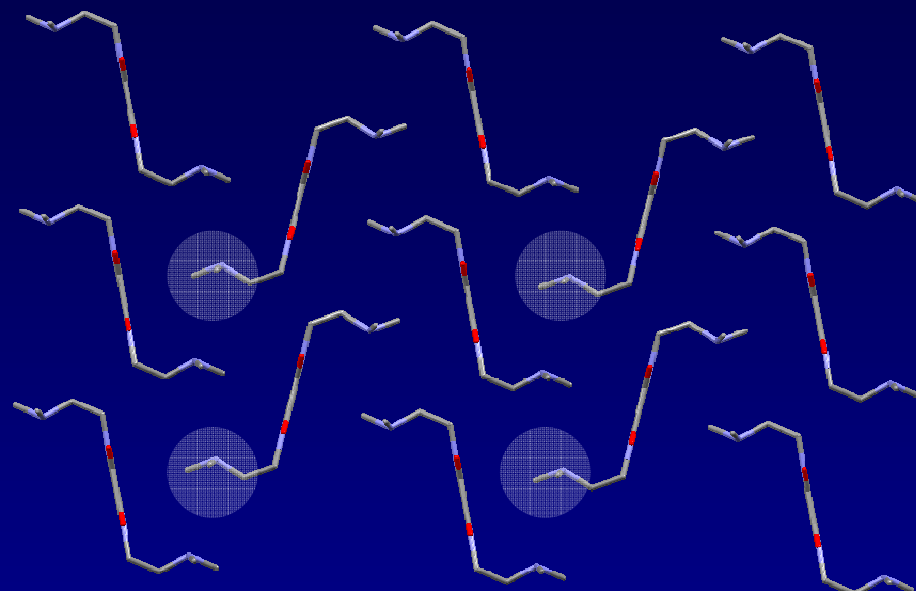
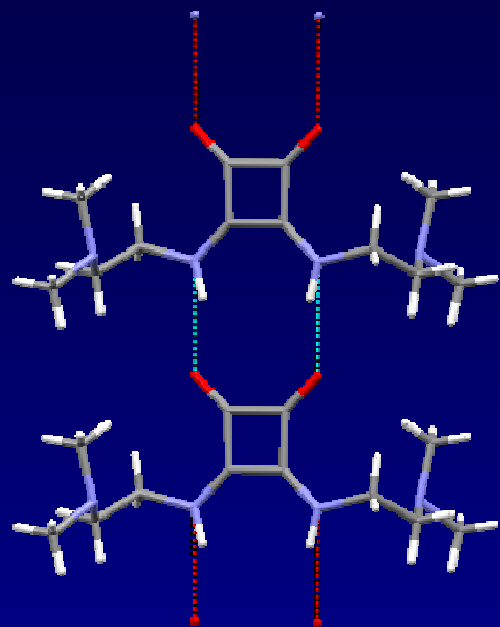


Breaking the head-to-tail synthon

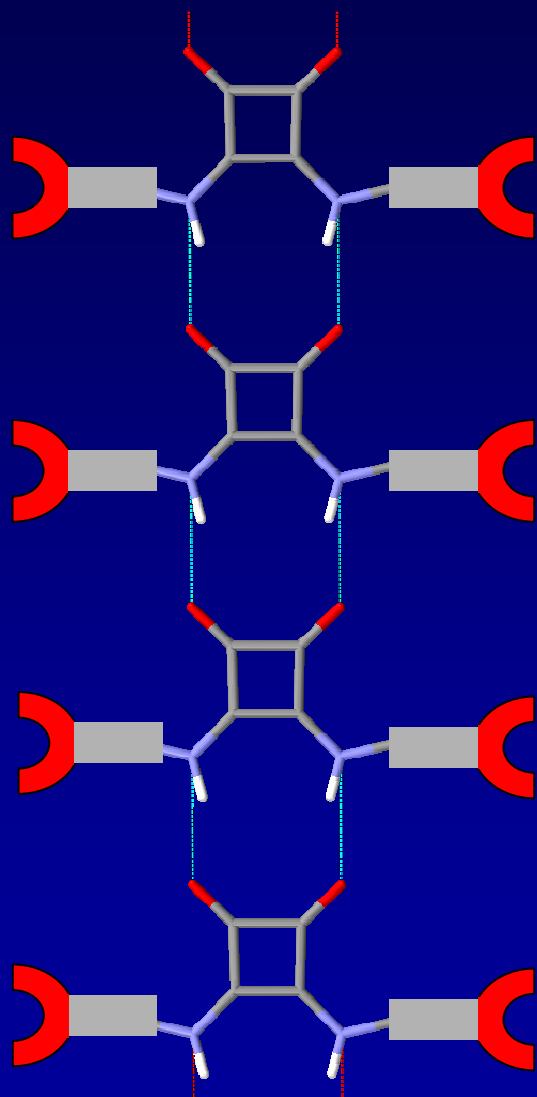


$$\beta_N > \beta_O$$

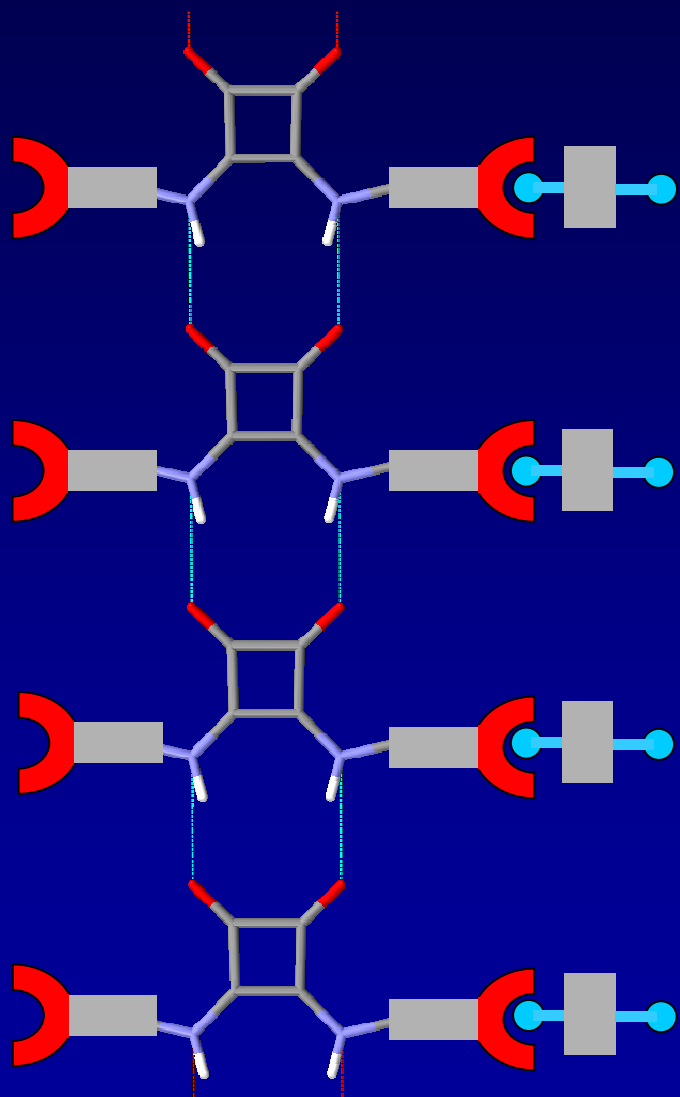
Stronger competitors cannot inhibit the head-to-tail synthon



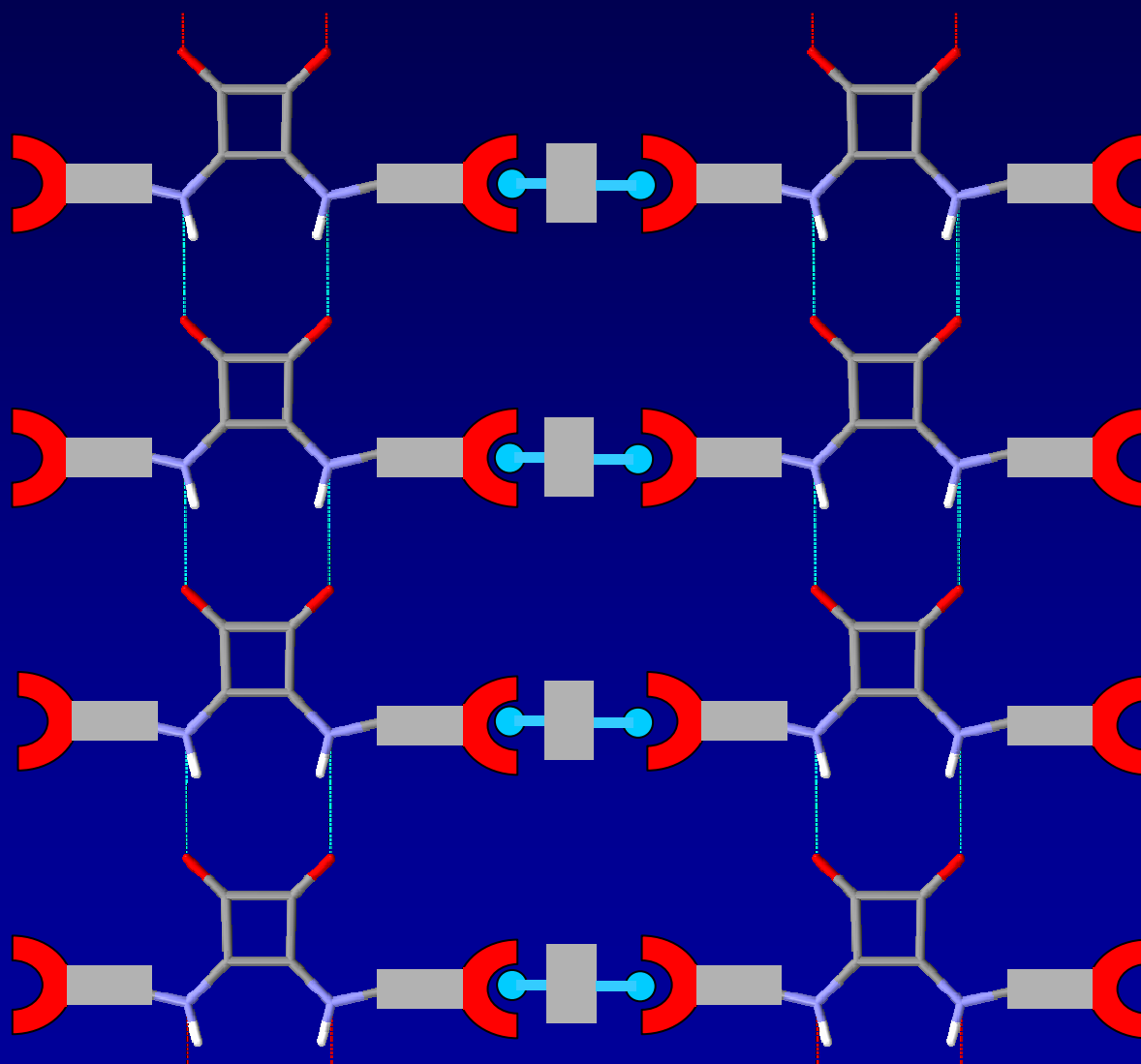
SQ head-to-tail as a scaffold for new cocrystal structures



SQ head-to-tail as a scaffold for new cocrystal structures

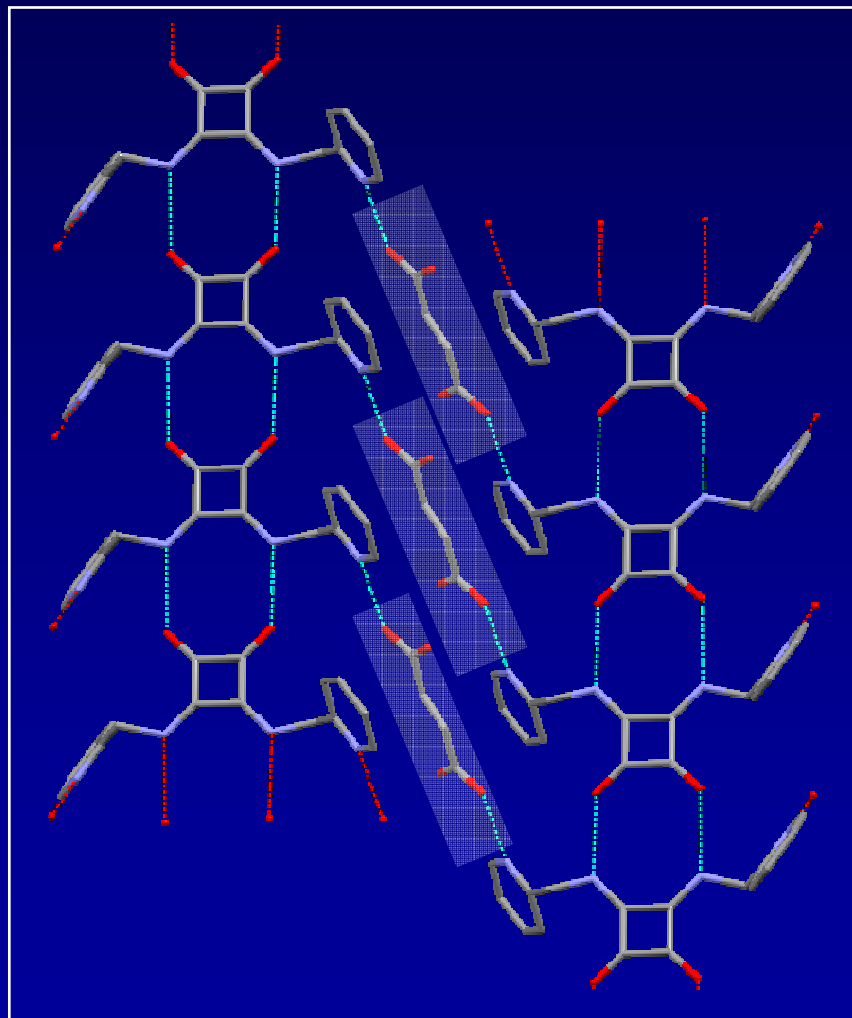


SQ head-to-tail as a scaffold for new cocrystal structures

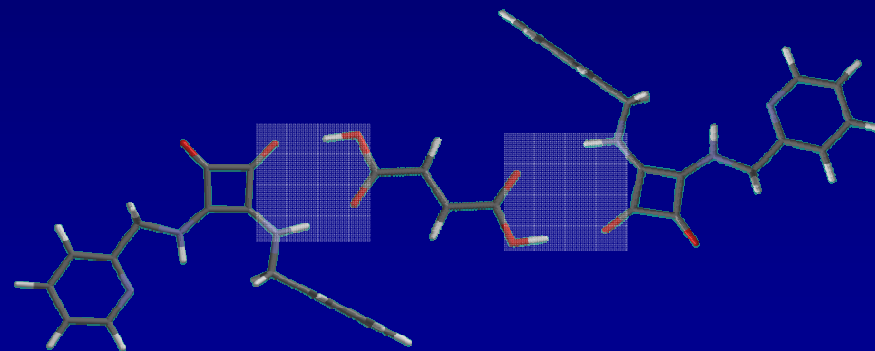


Cocrystal Screening

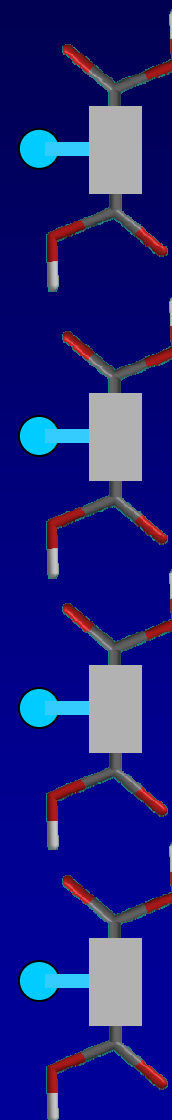
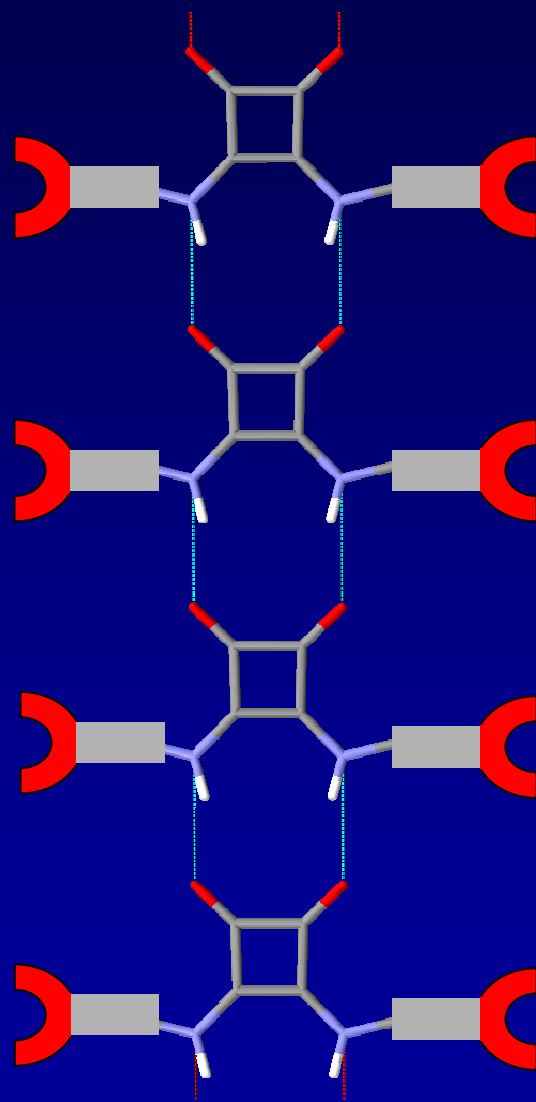
Fumaric acid – squaramide cocrystal



Synthons not found

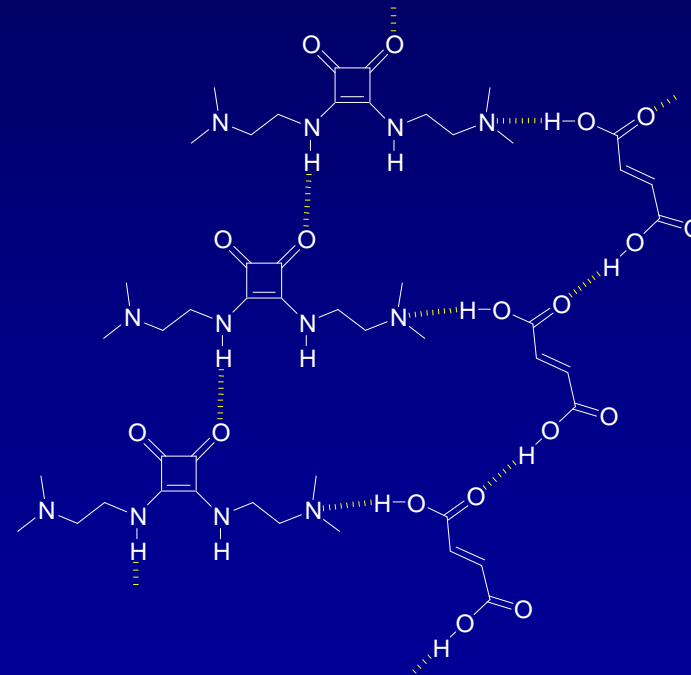
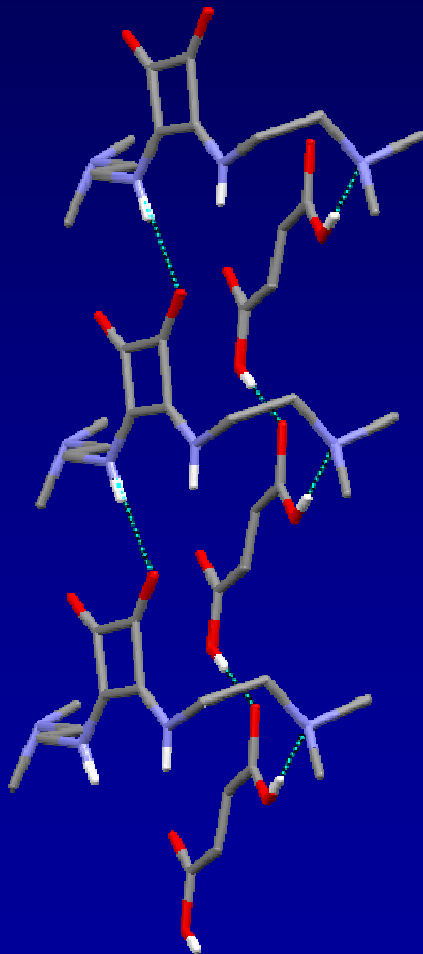


SQ head-to-tail as a scaffold for new cocrystal structures

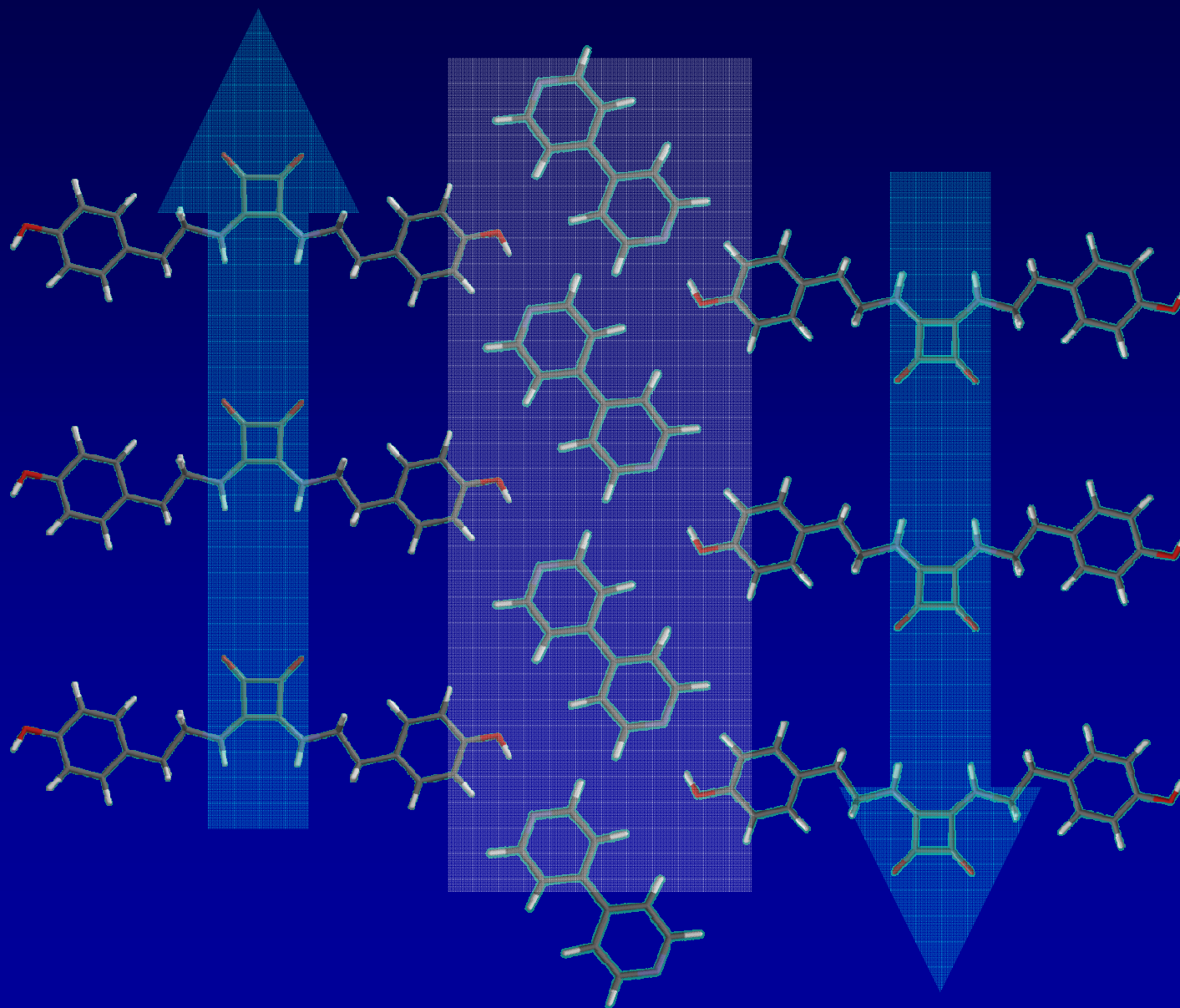


Cocrystal Screening

Fumaric acid – squaramide cocrystal



SQ head-to-tail as a scaffold for new cocrystal structures





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