One hydrogen bond does not a separation make, or does it?

THE IMPORTANCE OF HIGH RESOLUTION STRUCTURAL DATA

Cape Peninsula University of Technology

Nikoletta B Báthori

Chemistry Department

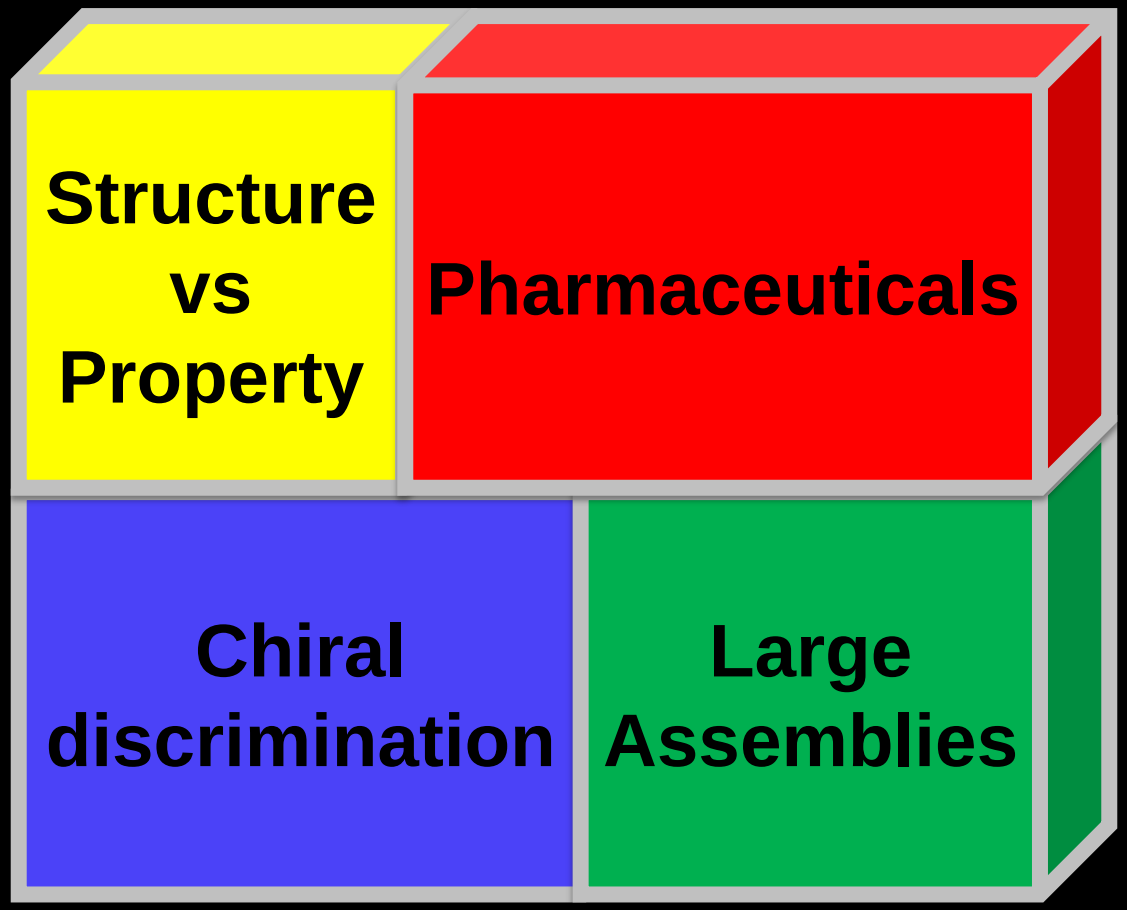
Outline

- The Group
- … and our interest:
- Structure-property relationship
- Pharmaceuticals
- Chiral discrimination
- Acknowledgement

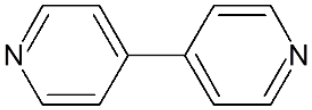
The Group


The South African Chemical Insititute
and the Royal Society of Chemistry
WESTERN CAPE
YOUNG CHEMISTS'
SYMPOSIUM
Thursday 23 October 2014
Chemistry Department, PD Hahn Building,
Upper Campus, UCT
GUEST SPEAKER: PROF. KELLY CHIBALE (UCT)
For more information contact
youngchemists2014@hotmail.com

Interest


Structure vs Property
Pharmaceuticals
Chiral discrimination
Large Assemblies

Structure *vs* Property: multicomponent crystals

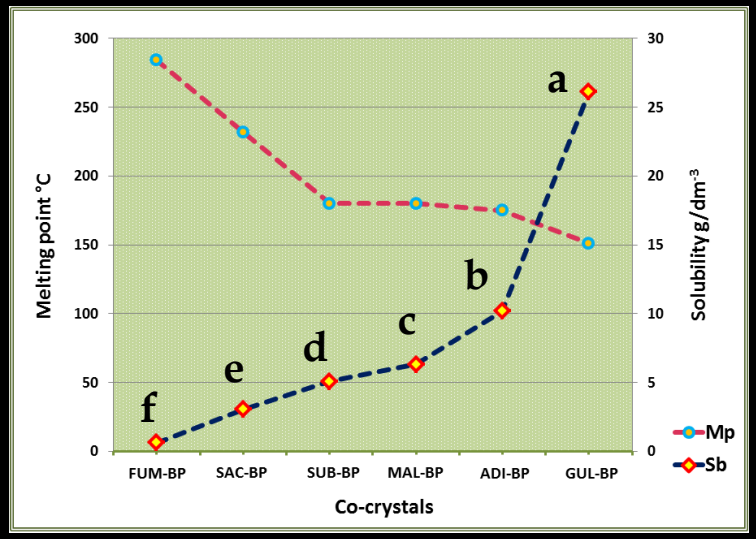


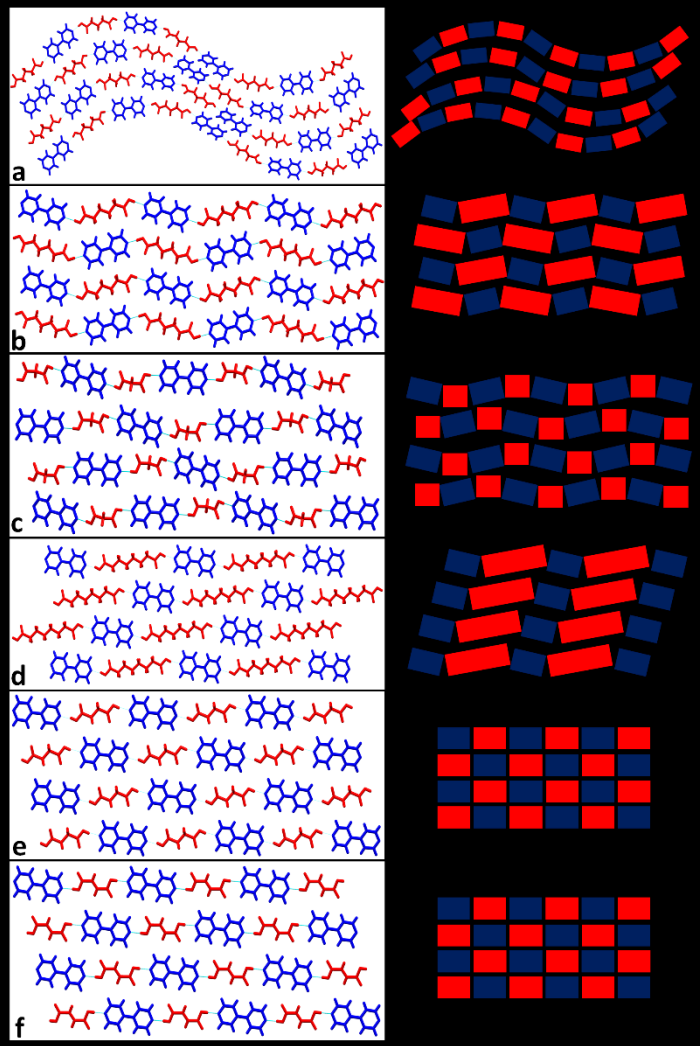
4,4'-bipyridine (BP)

HOOC —(CHx)n —COOH

dicarboxylic acids

acid	x	n	COOH position	symbol
Malonic acid	2	1	cis	MAL
Fumaric acid	1	2	trans	FUM
Succinic acid	2	2	trans	SUC
Glutaric acid	2	3	cis	GLU
Adipic acid	2	4	trans	ADP
Suberic acid	2	6	trans	SUB

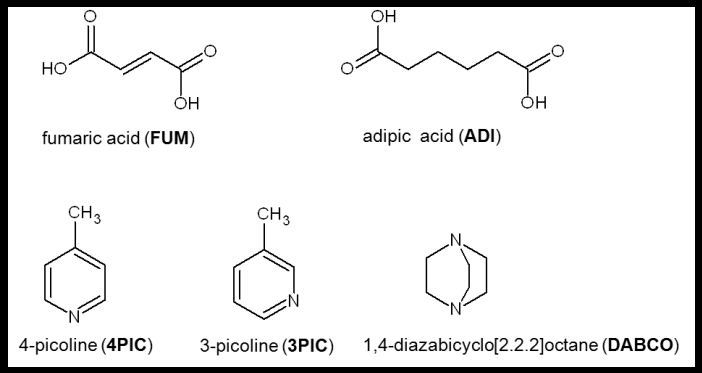


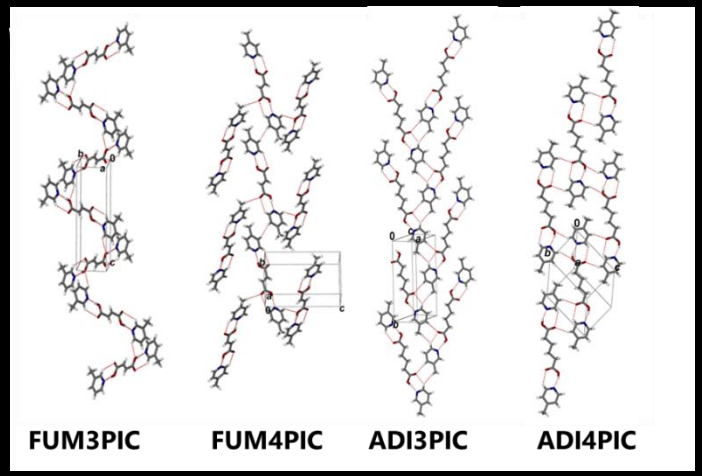


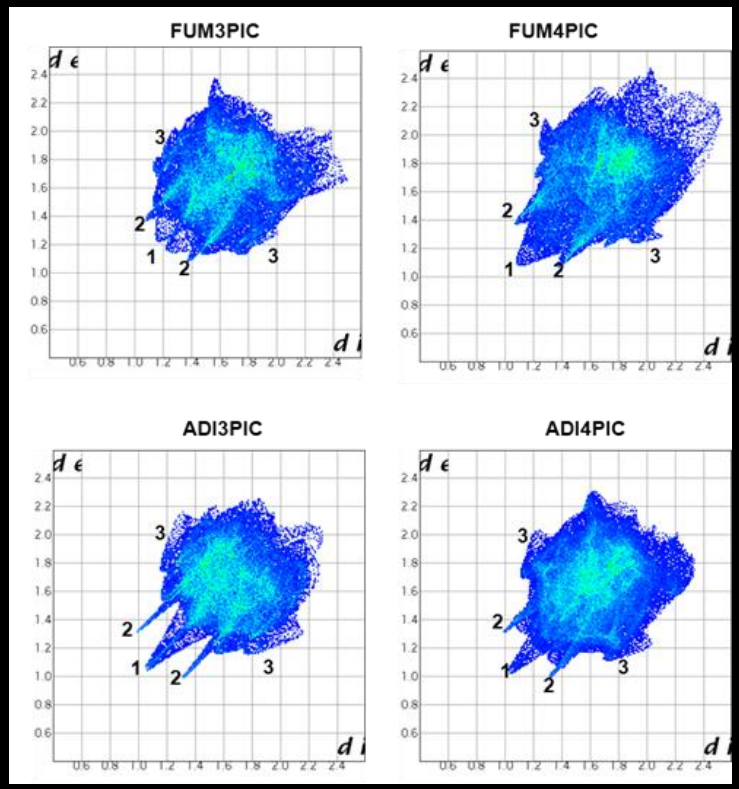
Báthori and Samipillai

'Regularity' of the packing→ property

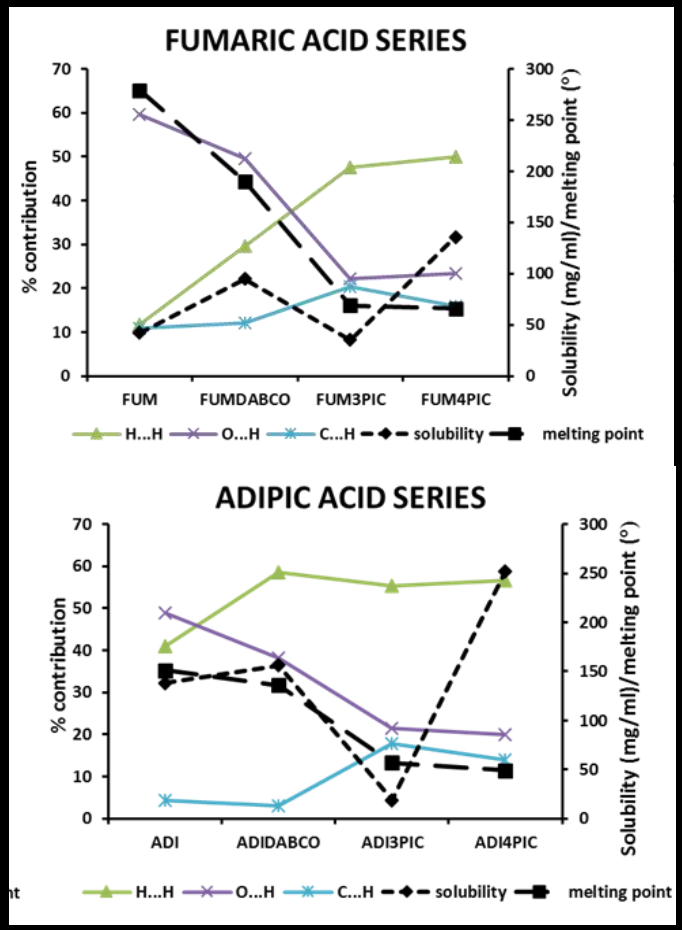
Structure *vs* Property: multicomponent crystals







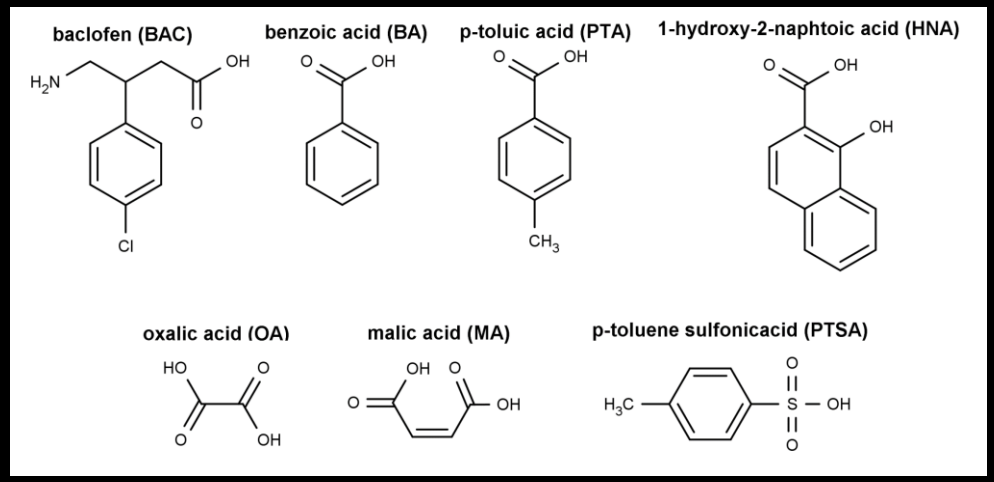
Spikes labelled 1-3 represent the H•••H, O•••H and C•••H interactions.

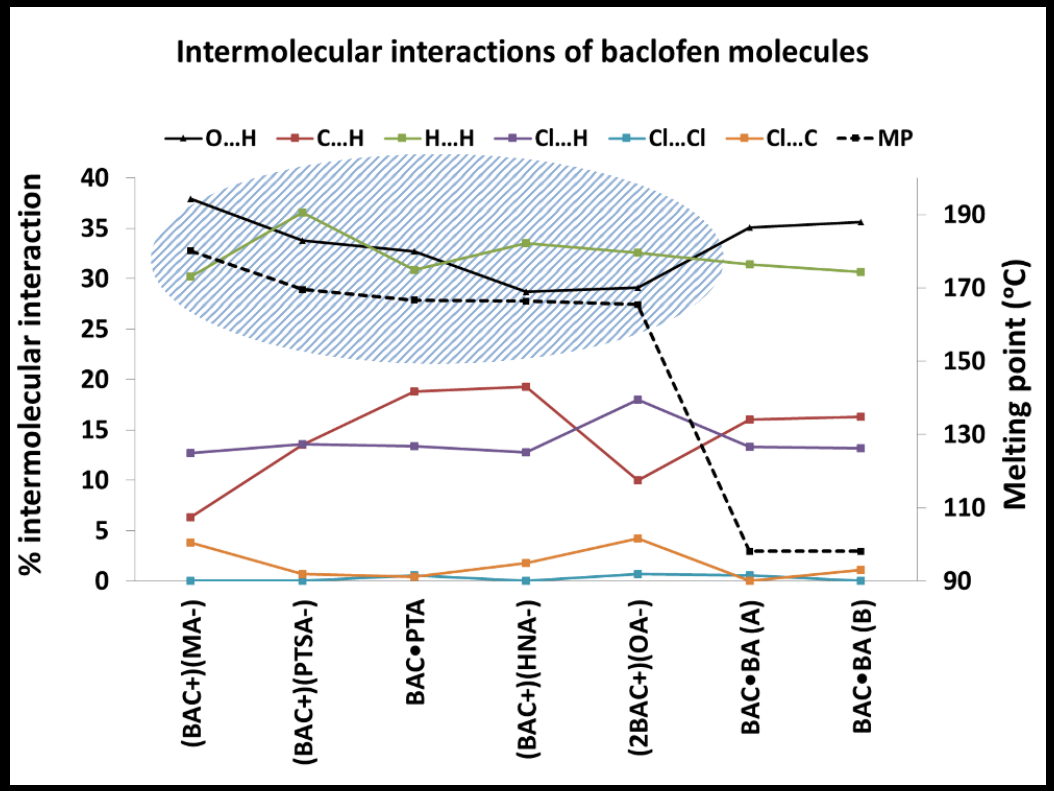


- **a decrease in MP corresponds to a decrease in O···H interactions**
- **the C···H interactions show an inverse relationship to the aqueous solubility**

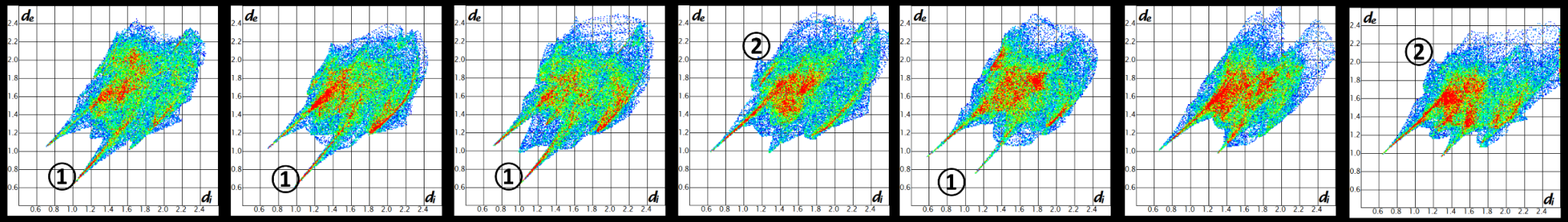
Batisai, Ayamine, Kilinkissa and Báthori, CrystEngComm, 2014, 16, 9992

Pharmaceutical cocrystals/salts



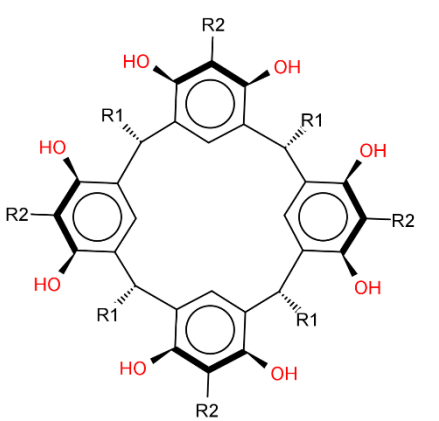


the % of the O⋯H interactions shows a kind of dependence with the melting points of the crystals

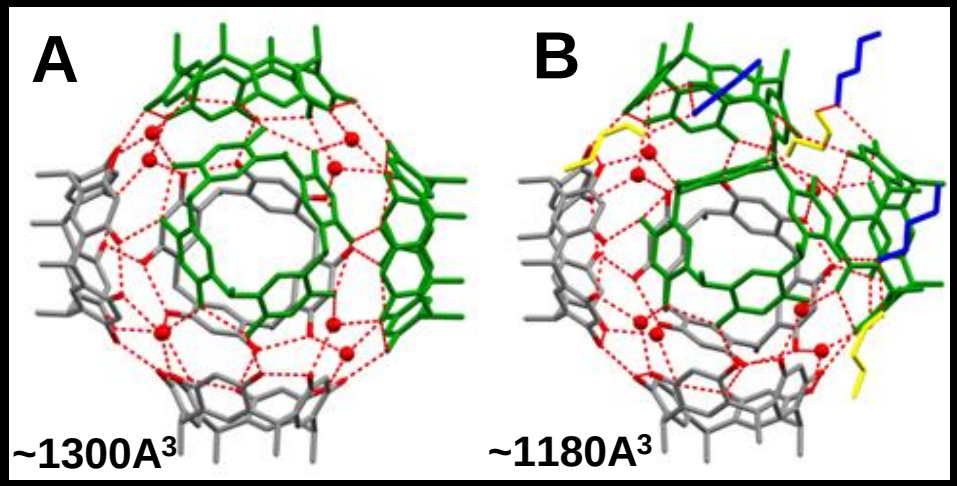


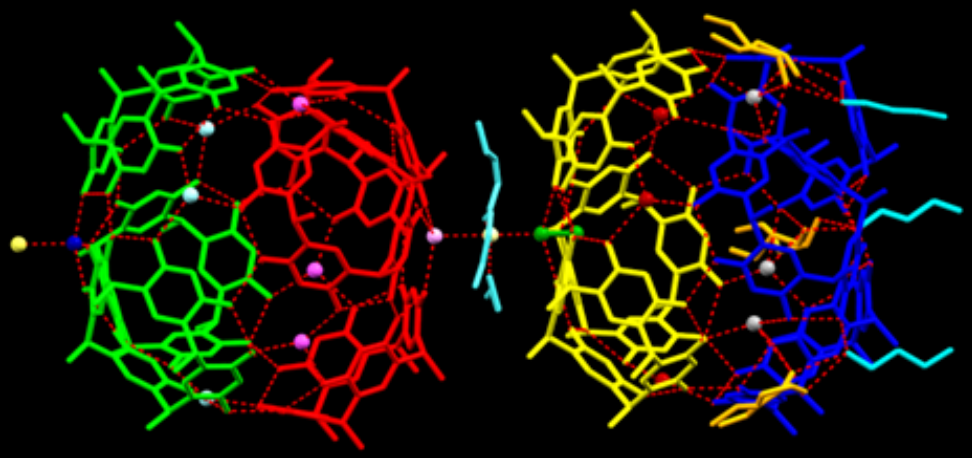
Báthori and Kilinkissa, CrystEngComm, 2015, 17, 8264–8272

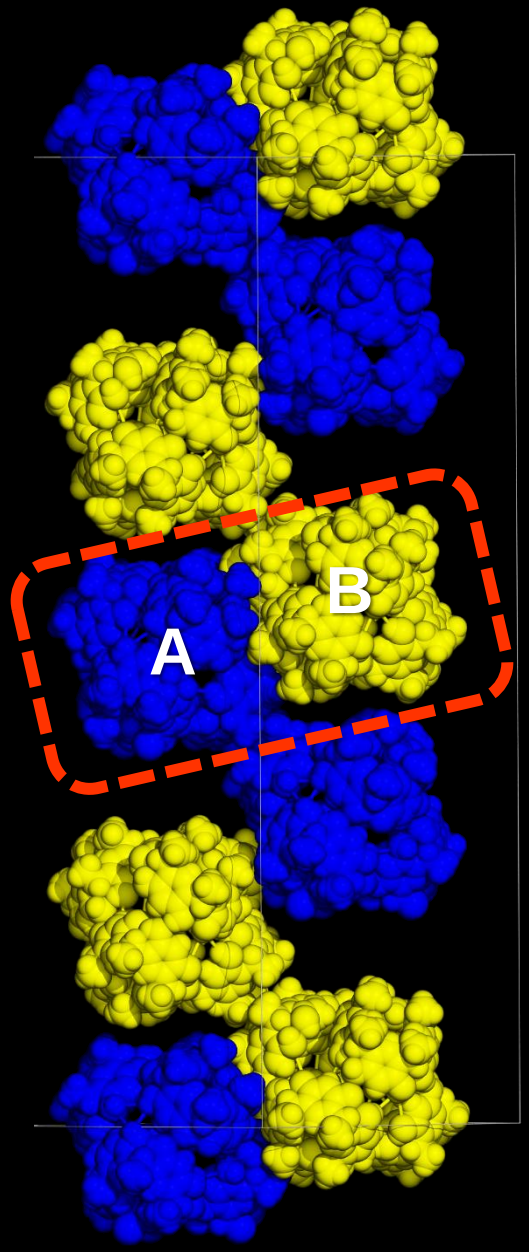
‘Wrapping’ pharmaceuticals into LAS



1a	R1= CH_3	R2= H
1b	R1= $(CH_2)_{10}CH_2$	R2= H
2a	R1= $(CH_2)_2CHCH_2$	R2= OH



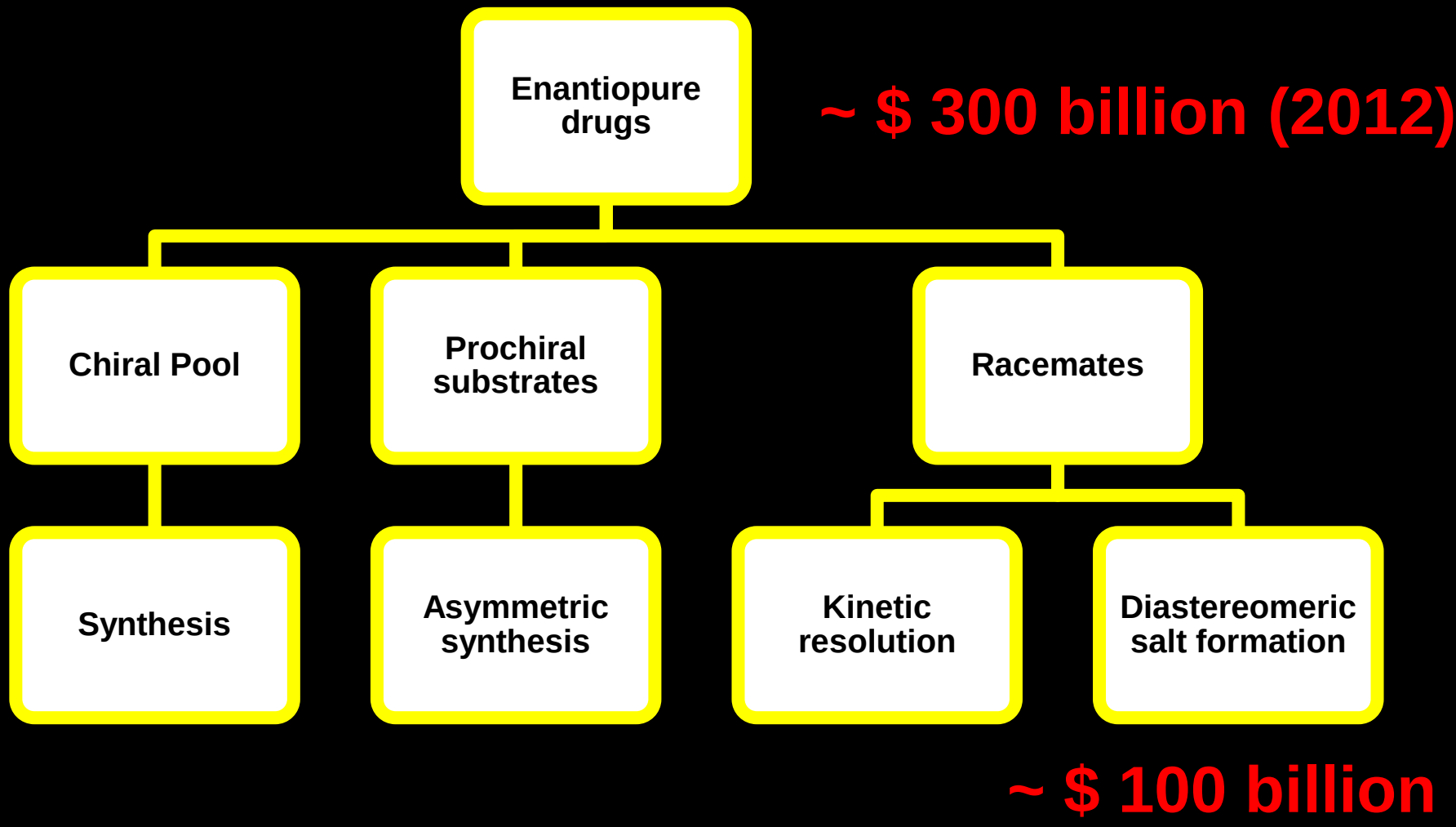




R3c
a= 29.91Å
c= 96.30Å
V= 74614.9Å^3

Oliver, Báthori, Jackson, Kuter and Cruickshank, submitted

Chiral discrimination



Efficient optical resolution

- High level of molecular recognition between the resolving agent (H) and the enantiomers (G) ⇨

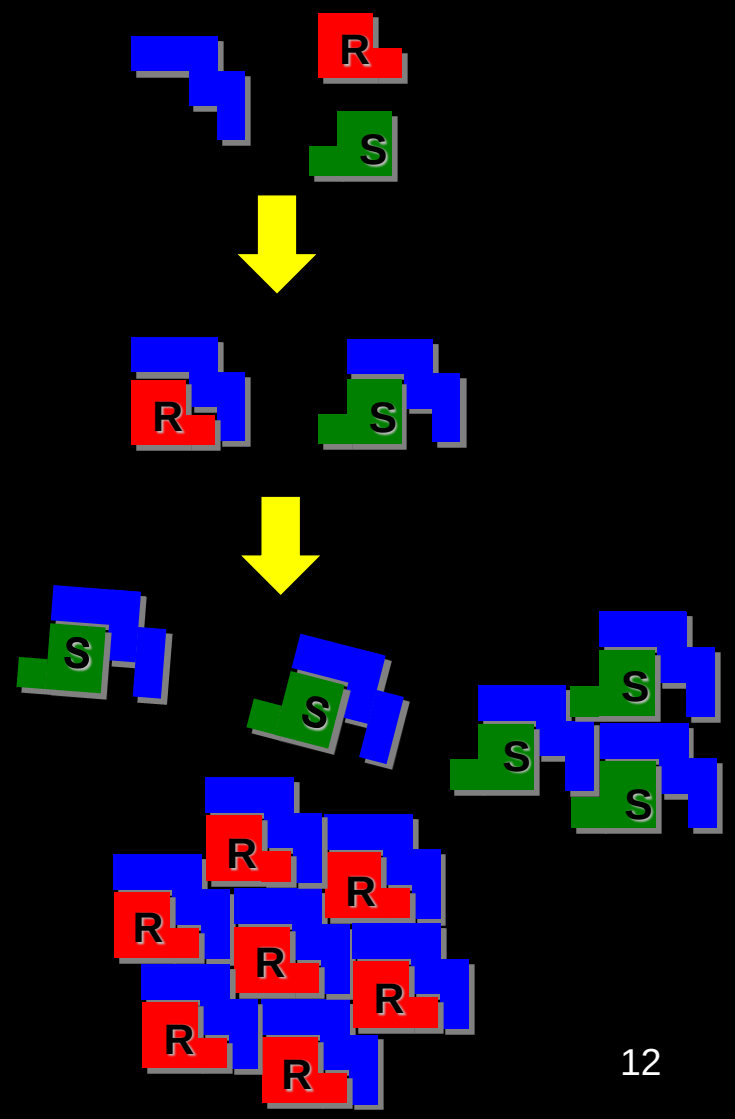
  (1) Complementarity of biding sites

  (2) strengths of the relevant non-bonding interactions

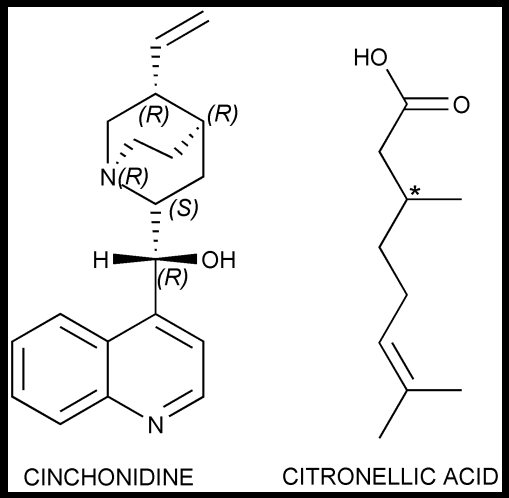
  (3) Conformational adaptability of H

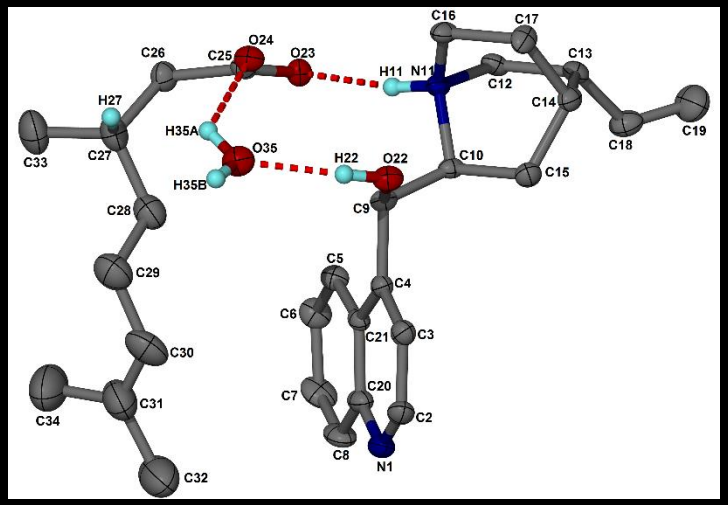
- In solid state ⇨

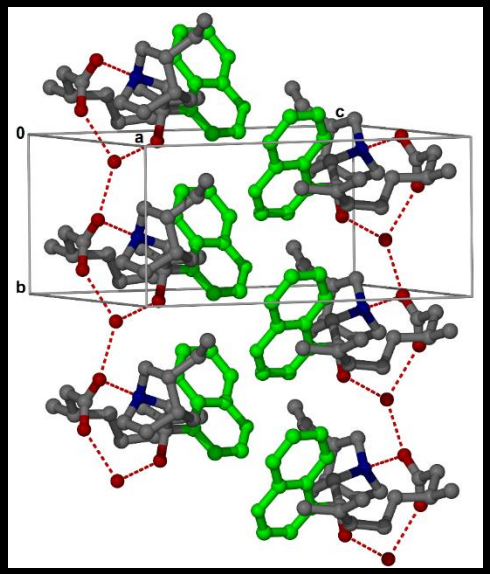
  (4) Good fit of supermolecules



Resolution of citronellic acid

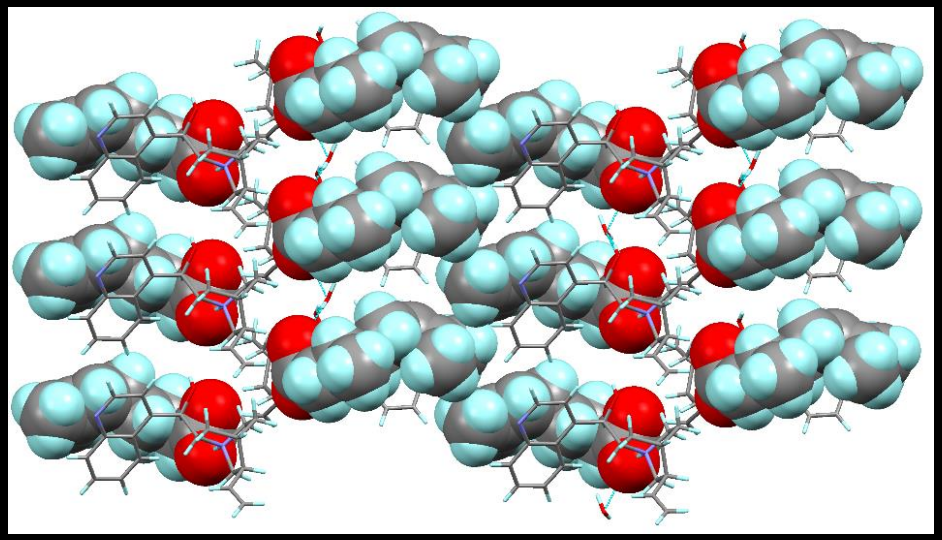






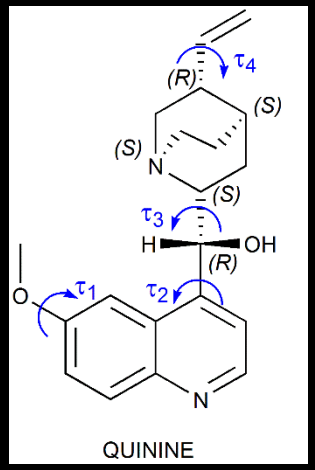
A success…

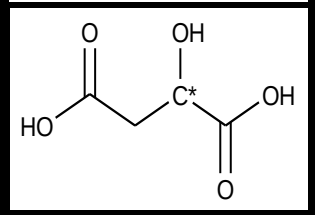
- **strong H bonds- salt formation**
- **Π interactions between CINDs**
- **Aliphatic chains positioned between aromatic rings**



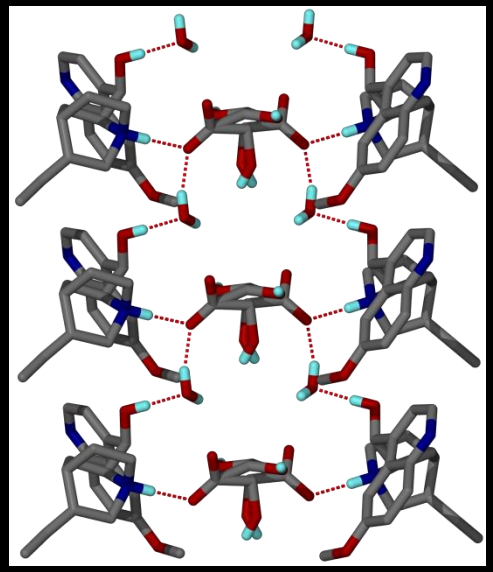
Báthori, Jacobs, Mei and Nassimbeni, J. Chem. Crystallogr. 2013, 43, 373

Resolution of malic acid

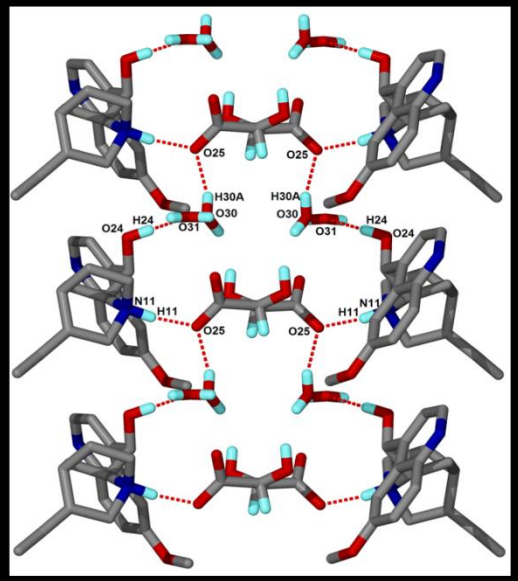




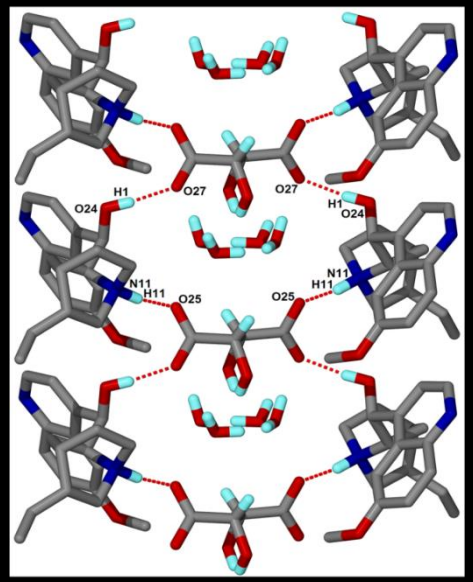
A partial success…



(QUIN$^+$)(0.5(0.75D, 0.25L-malate)).H_2O



(QUIN$^+$)(0.5(D-malate)).H_2O



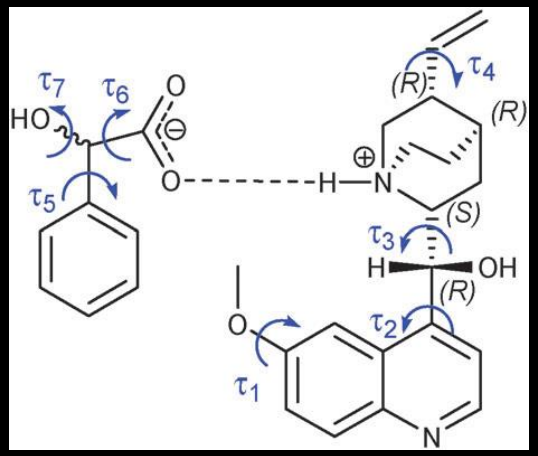
(QUIN$^+$)(0.5(L-malate)).H_2O

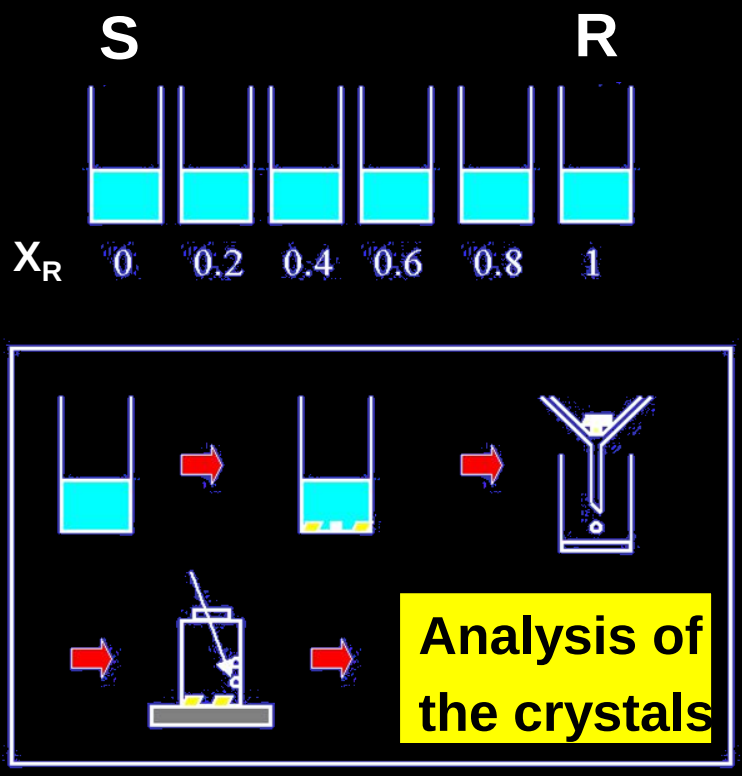
More efficient hydrogen bonds are stabilising the **QUIN-D-Malate** than of **QUIN-L-Malate**

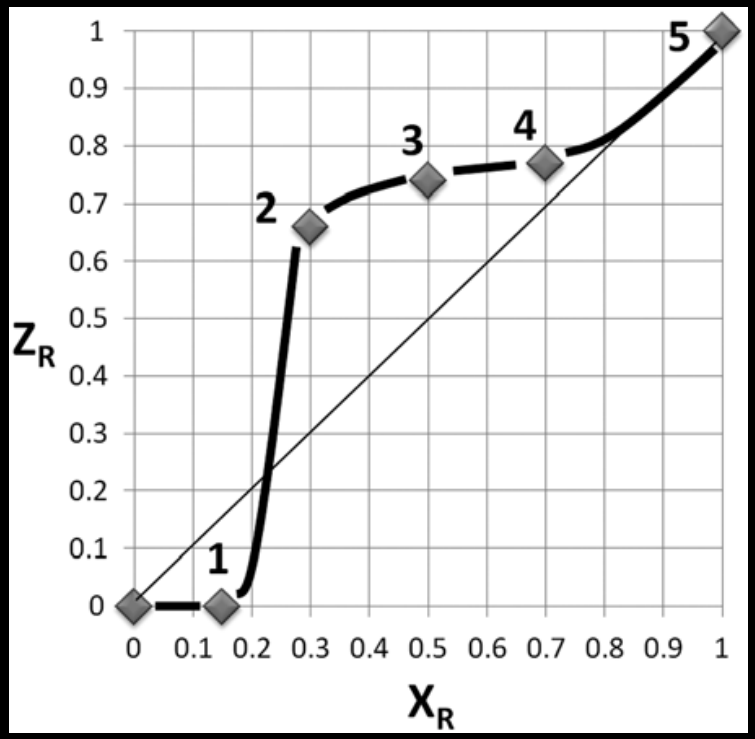
Báthori, Jacobs, Nassimbeni and Sebogisi, S. Afr. J. Chem., 2014, 67, 160

Resolution of mandelic acid

- crystallisation of mandelic acid with quinine from EtOH
- competition experiment

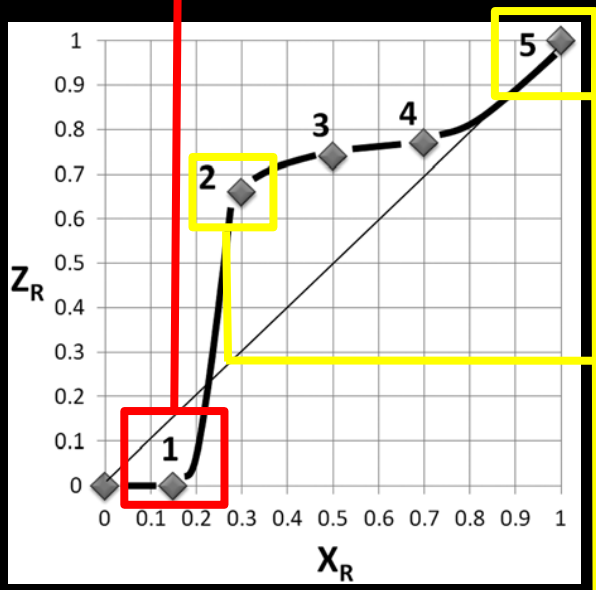


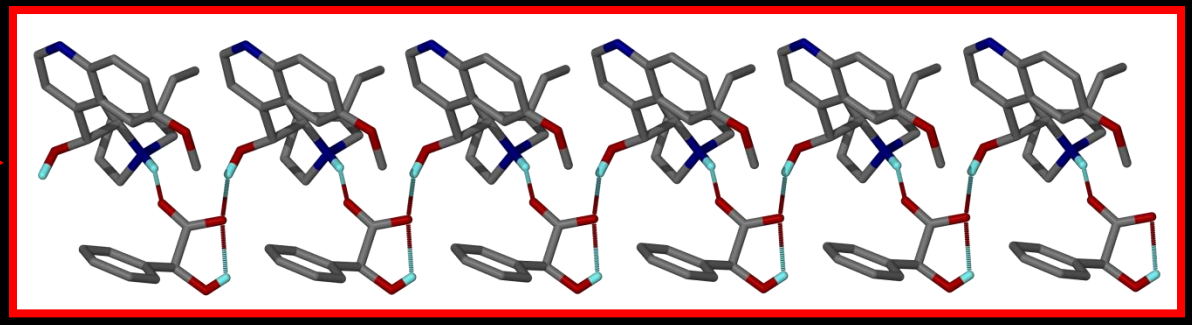




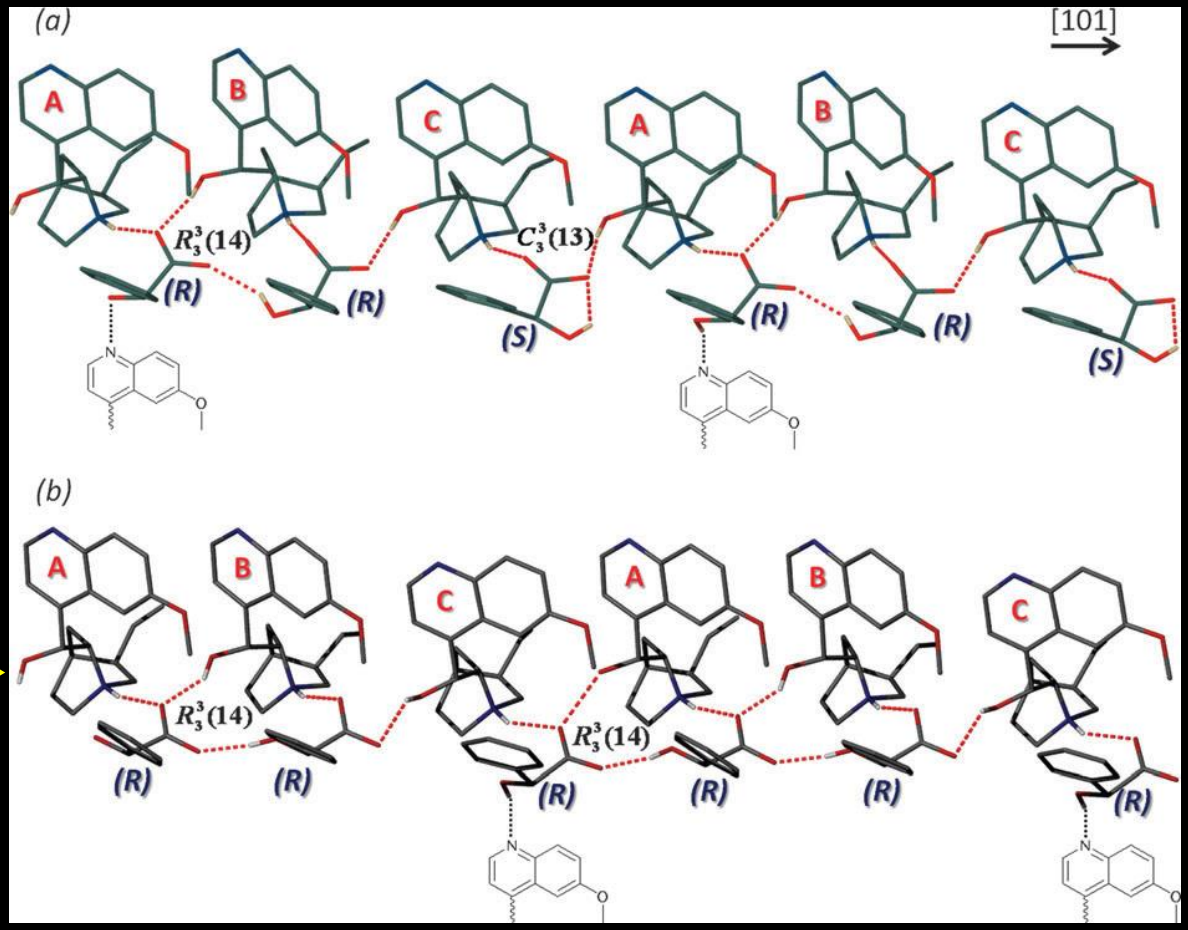
Báthori, Nassimbeni and Oliver, Chem. Commun., 2011, 47, 2670

Crystal packing

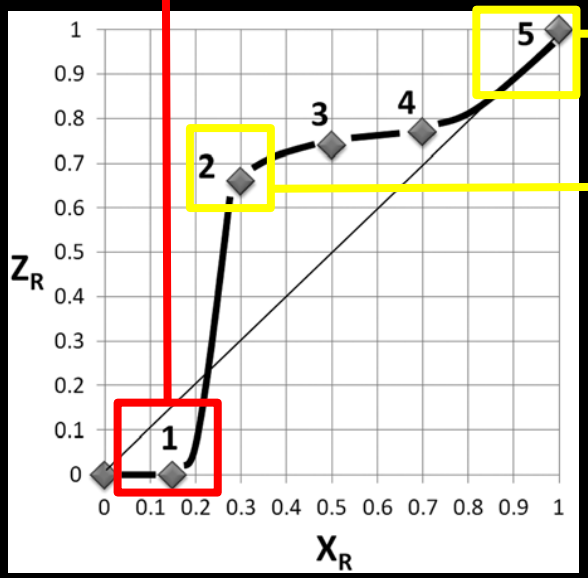


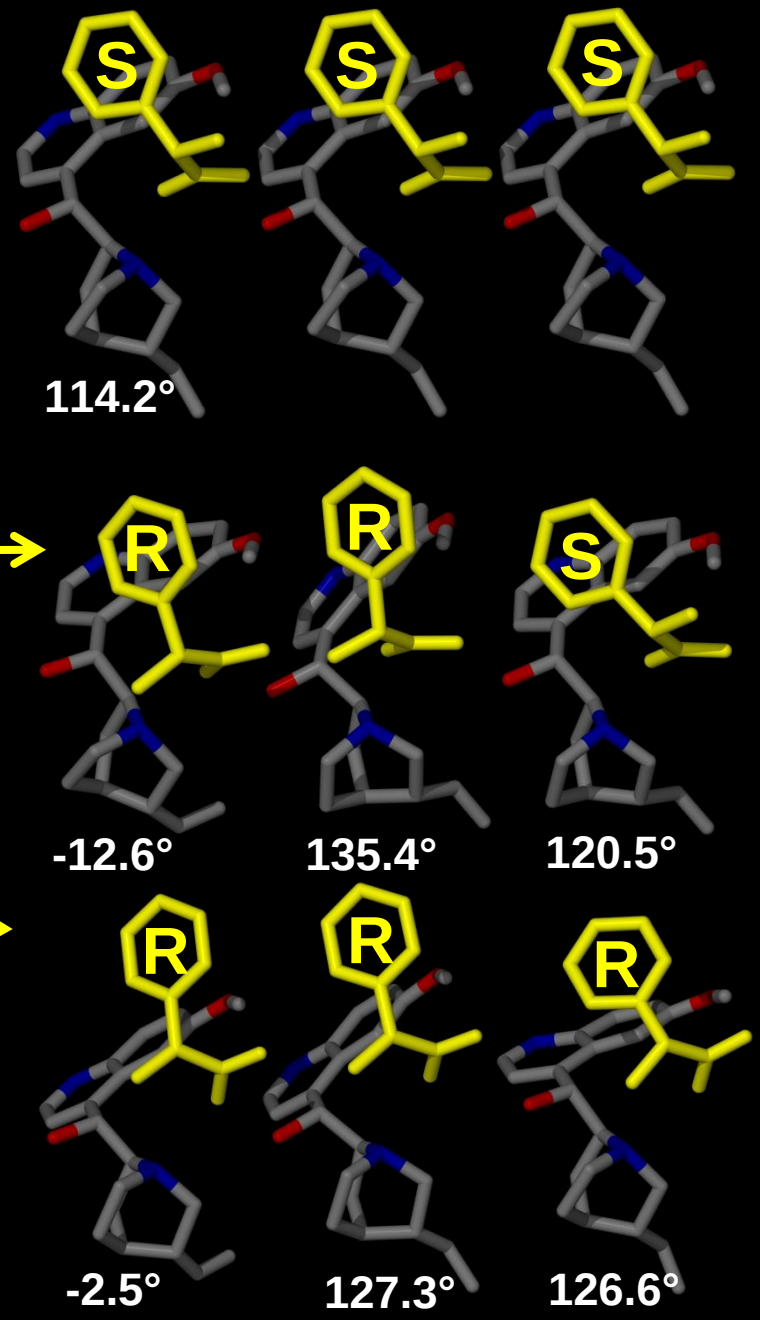


Gjerlov and Larsen, Acta Crystallogr., Sect. C: Cryst. Struct. Commun., 1997, 53, 1505



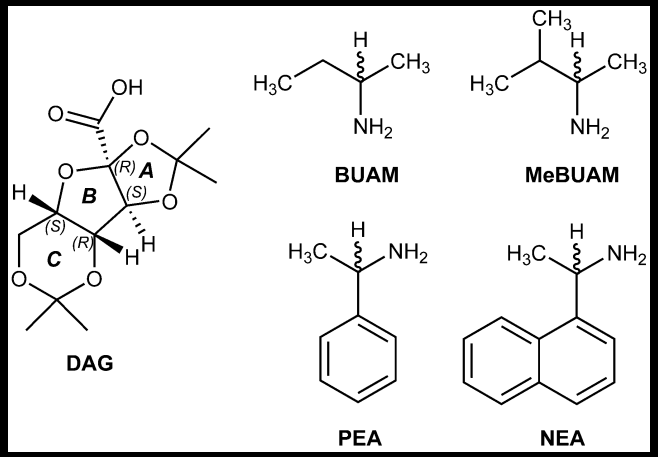
Quinine conformation

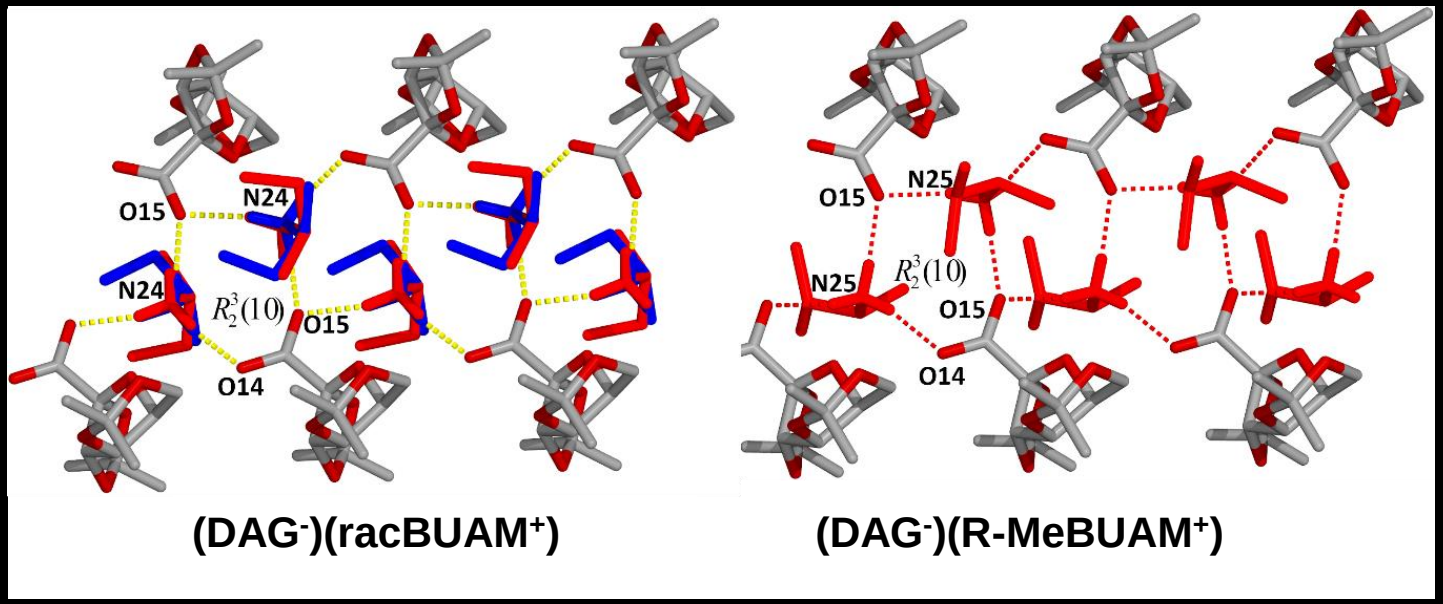




stronger intermolecular forces stabilising **2 (QUIN-R,R,S-Mandelate)** than of **5 (QUIN-R,R,R-Mandelate)**

Resolution of amines

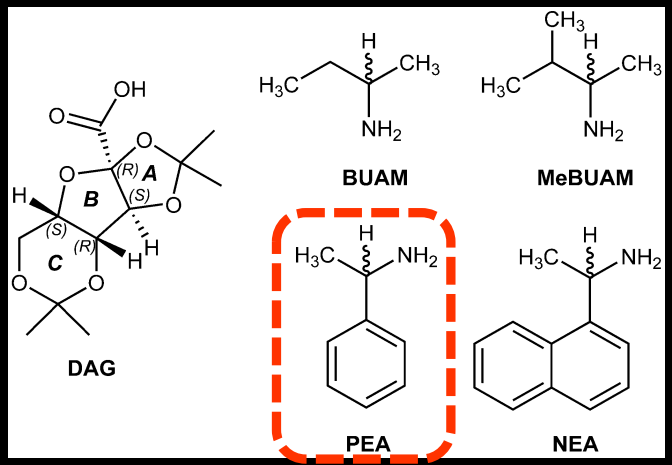


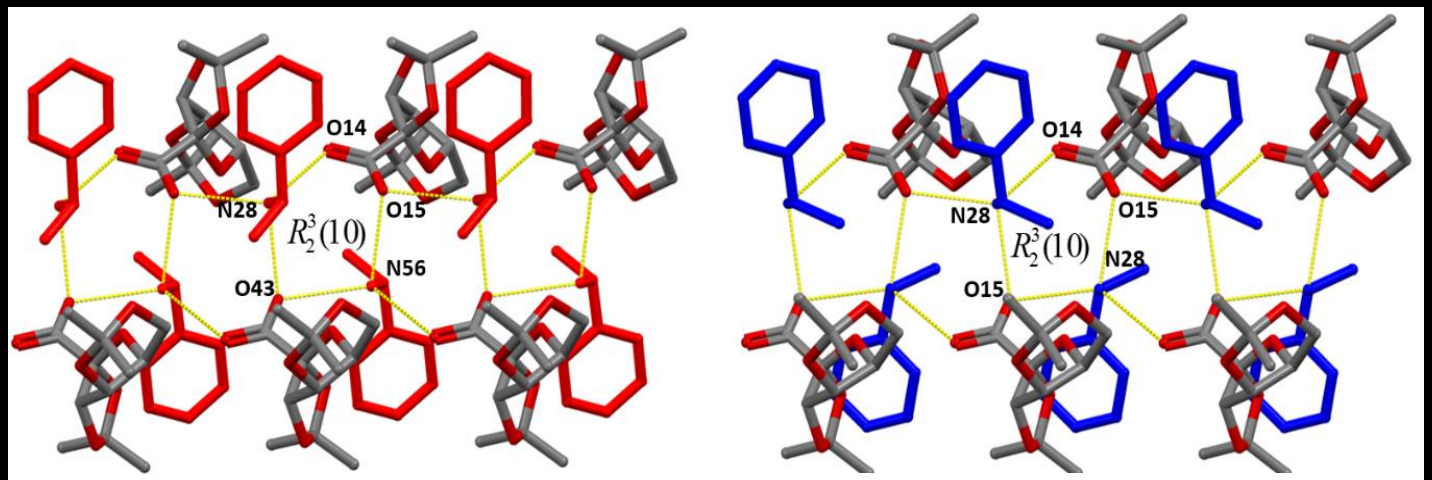


- **BUAM and MeBUAM crystals isostructural**
- **Cannot obtain S-MeBUAM**
- **No selectivity**

Báthori, Nassimbeni and van de Streek. Chem. Commun., 2015, 51, 5664

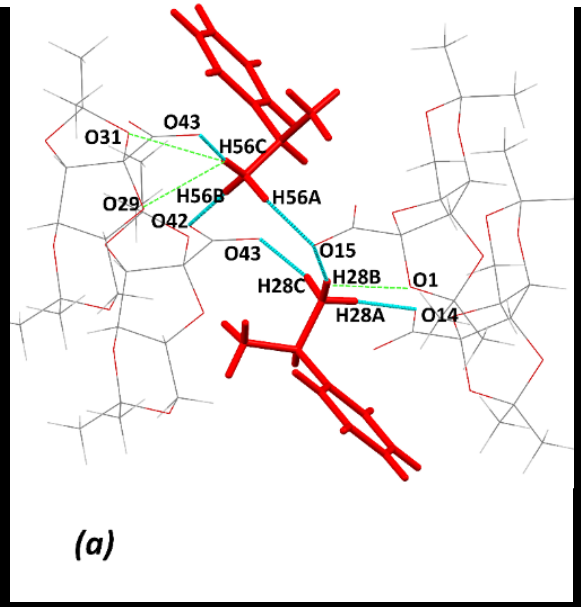
Resolution of amines

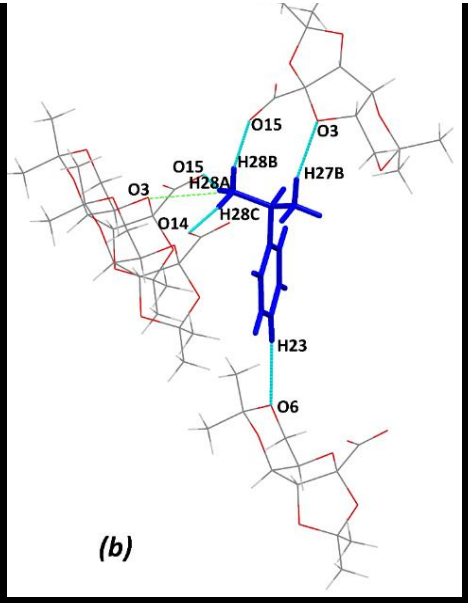




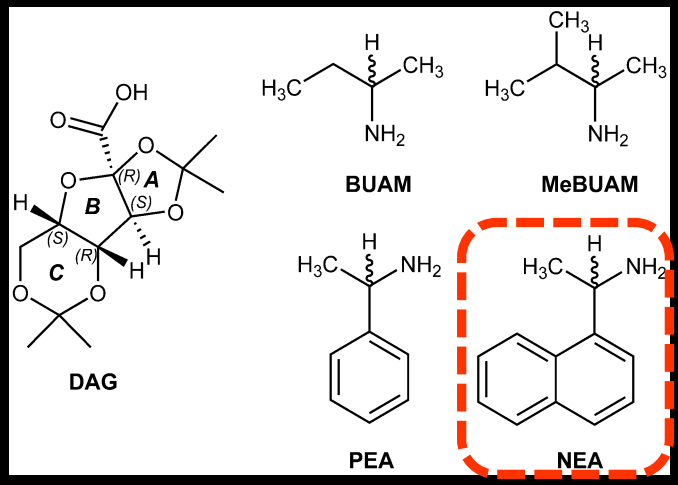
(DAG$^-$)(R-PEA$^+$) (DAG$^-$)(S-PEA$^+$)

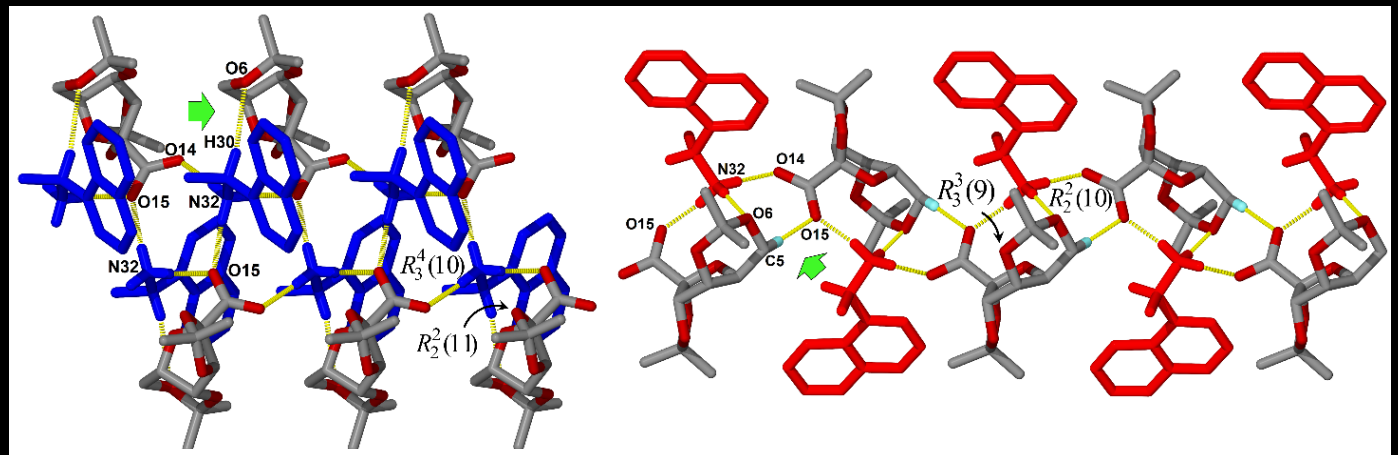
- DAGs are isostrcutural
- Amines in similar positions
- 100% selectivity (R)
- (R) shorter H bonds with better geometry





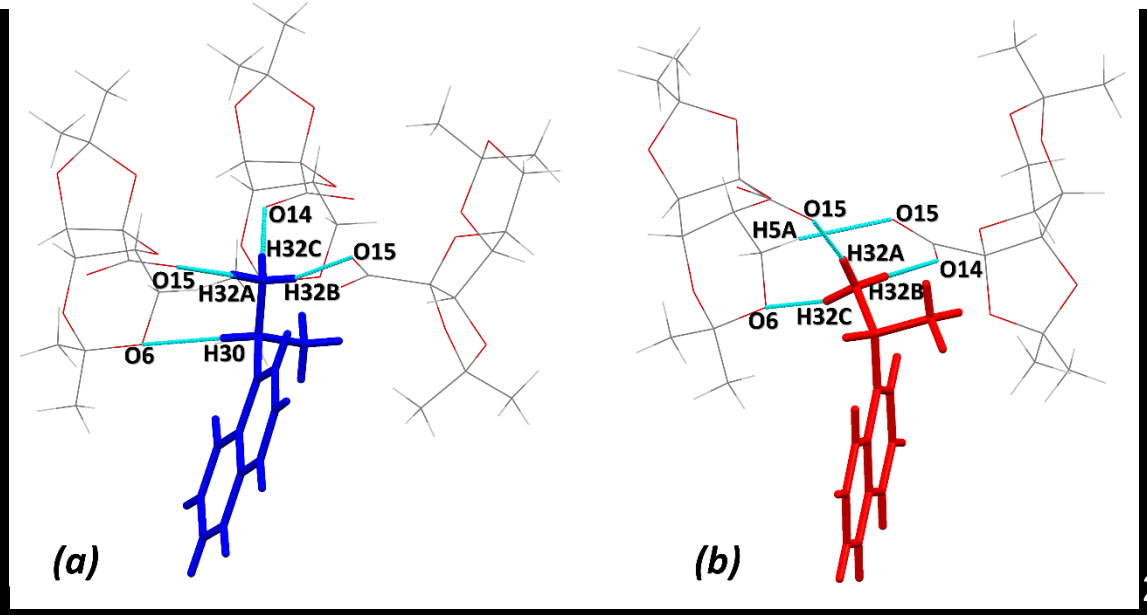
Resolution of amines





(DAG$^-$)(S-NEA$^+$) (DAG$^-$)(R-NEA$^+$)

- Different structures
- Better H bonds in (S)
- (S) formation of additional H bond with ‘chiral’ H



Conclusion:

- accurate structure determination need high resolution data
- may be obtained form laboratory equipment
- occasionally need access to synchrotron radiation

Future?

- crystal structure from powder requires synchrotron radiation
- certain research directions (large assemblies, ‘almost nano structures’, poorly crystallizing compounds, etc.) need better data for accurate structure interpretation

Acknowledgement

- CPUT – URF
- NRF – Pretoria

Past students:
- Dr Eustina Batisai, post doc
- Ms Ornella Kilinkissa, MTech
- Ms Leena Patel, MTech
- Ms Sylvia Kantengwa, MTech
- Ms Karabo Sebogisi, Mtech (Jacobs)
- Dr Marivel Samipillai, post doc

Co-workers/ Collaborators:
- Dr Elise Jane de Vries
- Dr Meredith Hearshaw
- Prof Luigi Nassimbeni (University of Cape Town)
- Dr Clive Oliver (University of Cape Town)
- Dr Gerhard Venter (University of Cape Town)
- Dr Vincent Smith (Stellenbosch University)
- Prof Jacco van de Streek (Copenhagen)