Dublin City University
School of Chemical Sciences

From Benzamides to Macrocyclic Imides *and beyond*…

Dr. John F. Gallagher
Dr. Seán Ó Gallchóir

Experiences at the interface of crystallography and molecular modelling

HEA
Higher Education Authority
An tÚdarás um Ard-Oideachas

AN ROINN OIDEACHAIS AGUS EOLAIOCHTA | DEPARTMENT OF EDUCATION AND SCIENCE

NDP
NATIONAL DEVELOPMENT PLAN

Ireland's EU Structural Funds Programmes 2007 - 2013
Co-funded by the Irish Government and the European Union

EUROPEAN REGIONAL DEVELOPMENT FUND

Research seminar

Structural systematics:

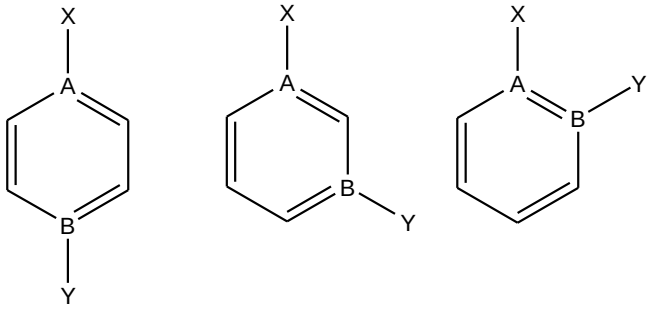
1	**Benzamides** **Carboxamides**	**Isomer grids (*n* × *m*)**
2	**Imides**	**Macrocycles and building blocks**

Websites:

http://scripts.iucr.org/cgi-bin/iucrid_details?id=3300
http://www.youtube.com/channel/UC9FOUhx_uqnj9uyObrcnmUQ/videos
http://doras.dcu.ie/view/people/Gallagher,_John_F=2E.html

Introduction

Structural systematics:

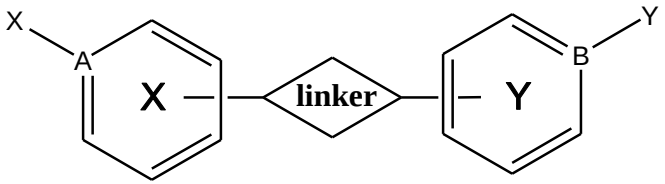


Isomer grids:

- Sets of isomers where two or more identical (or different) moieties occupy different positions.

- Moiety (A, B, X, Y) is usually attached to or in the ring:
  - substituent (functional group, X, Me, OMe)
  - heteroatom (N, O, S).

- 1-, 2-, 3- or *n*-dimensional



Devise and use a variety of scaffolds

Introduction

2D - 3 × 3 Isomer grids

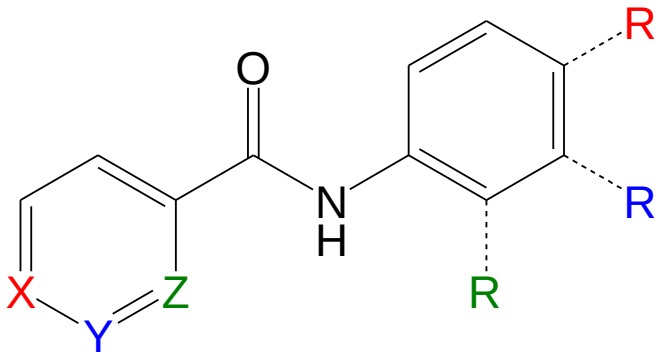
Benzamides (Ph-C[O]NH-Pyr) Rxx

Pyridinecarboxamides (Pyr-C[O]NH-Ph) NxxR

Carbamates (Pyr-NHC[O]O-Ph) CxxR

***R* = M (CH_3), F, Cl, Br, OMe (OCH_3)**

	para	*meta*	*ortho*
para	pp	pm	po
meta	mp	mm	mo
ortho	op	om	oo



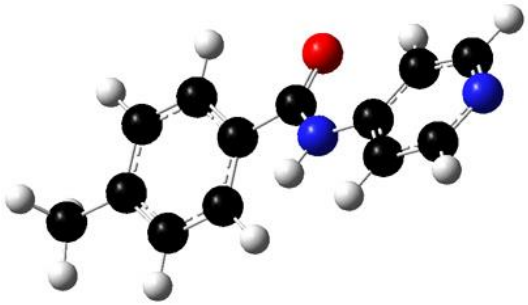
X, Y, Z = N

Methods

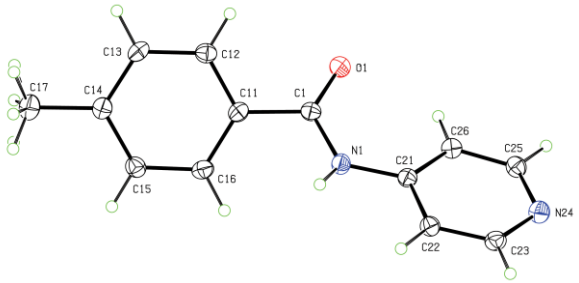
Bridging *in silico* modelling methods and solid-state crystallography

Two approaches in structural science

Molecular modelling (*gas phase*/solvent) *In silico*



X-ray crystallography (solid-state)

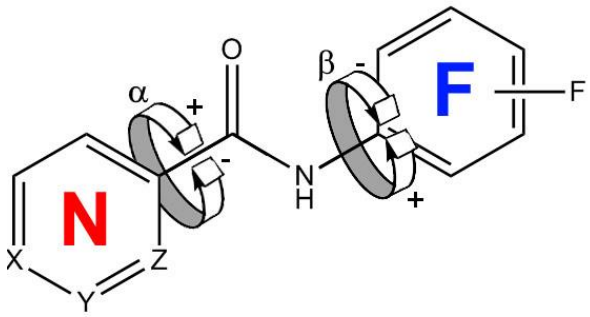


Direct Comparisons

Experimental Approaches

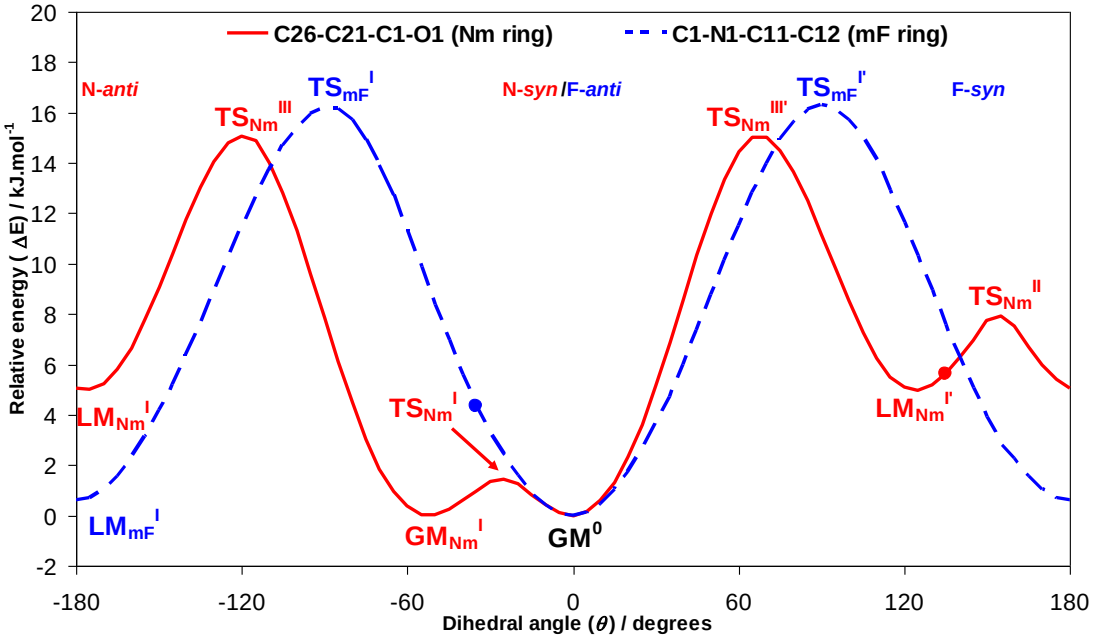
Conformational analysis

Potential **E**nergy **S**urface diagrams (profiles)

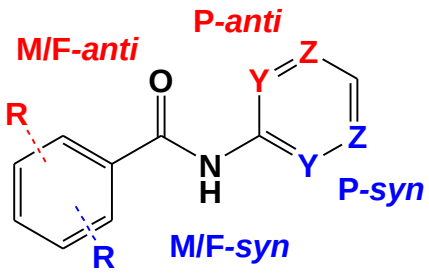


X, Y, Z = N/C-H

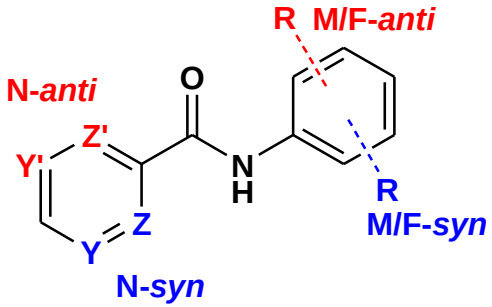
NmmF



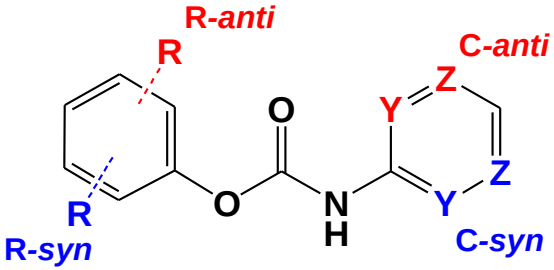
Asymmetric isomers



Mxx, Fxx

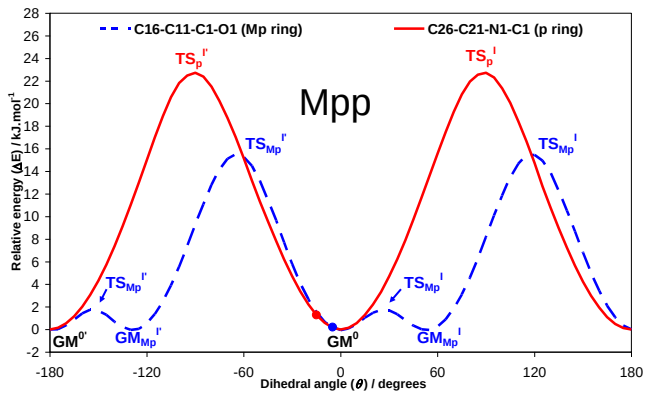


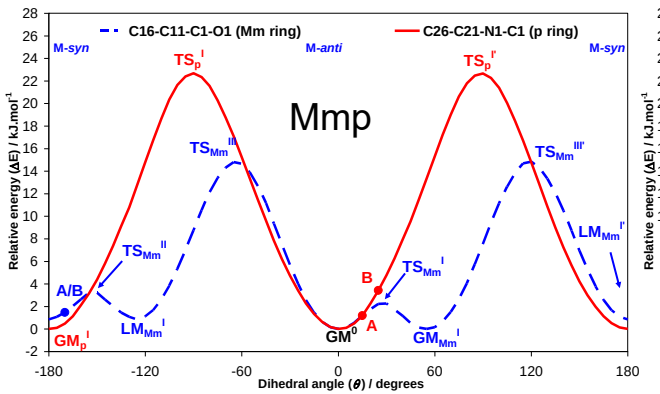
NxxF, NxxM

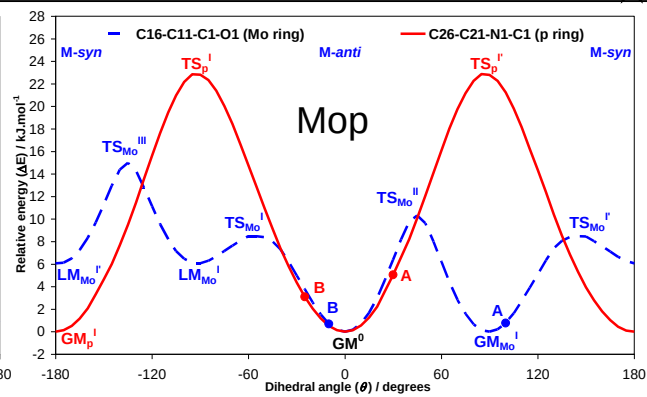


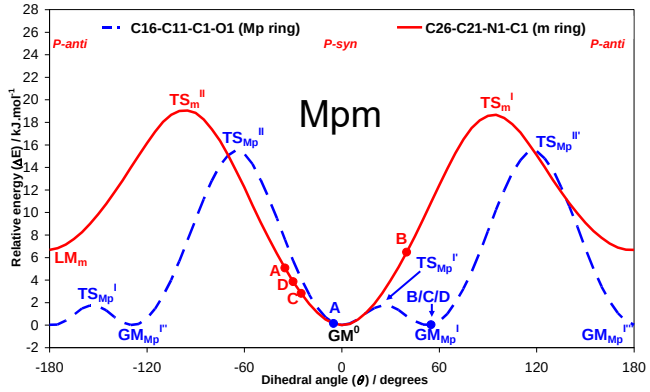
CxxR, R=F, Cl, Br, OMe, M

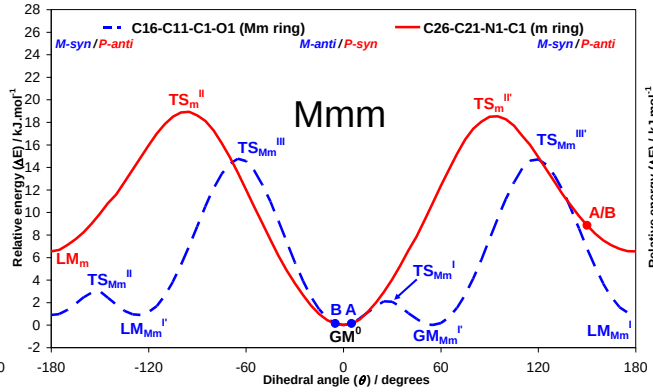
Mxx PES diagrams

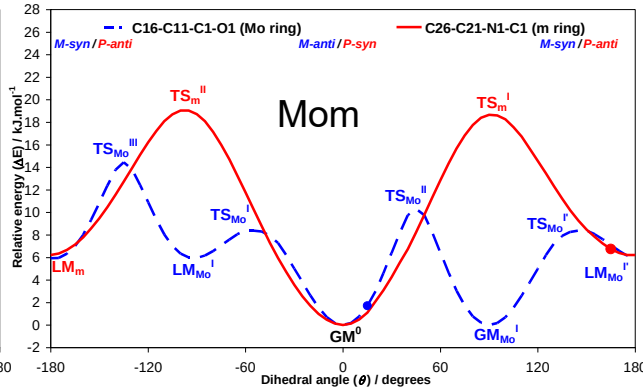


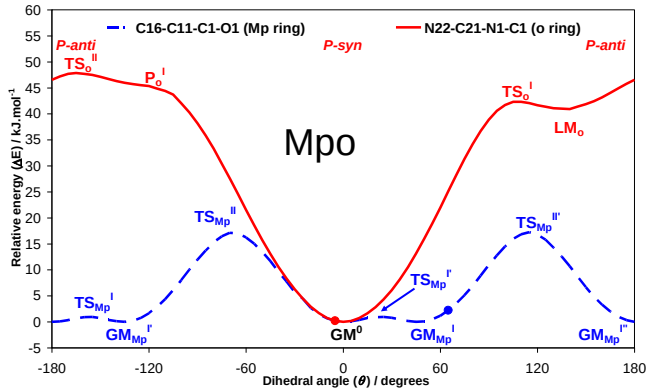


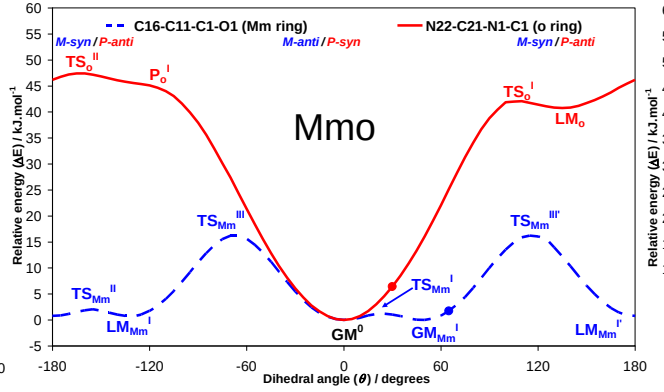


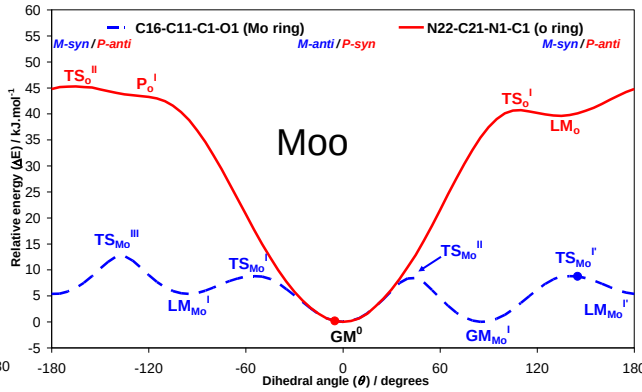






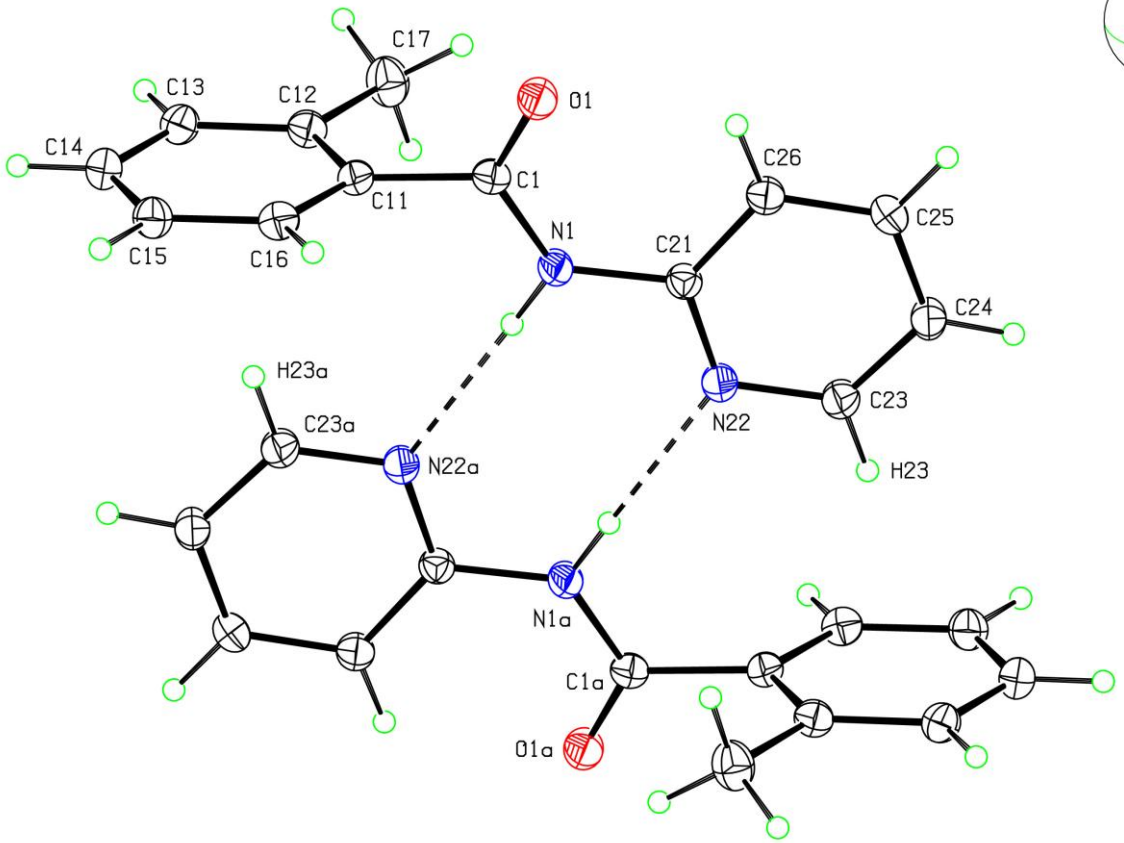


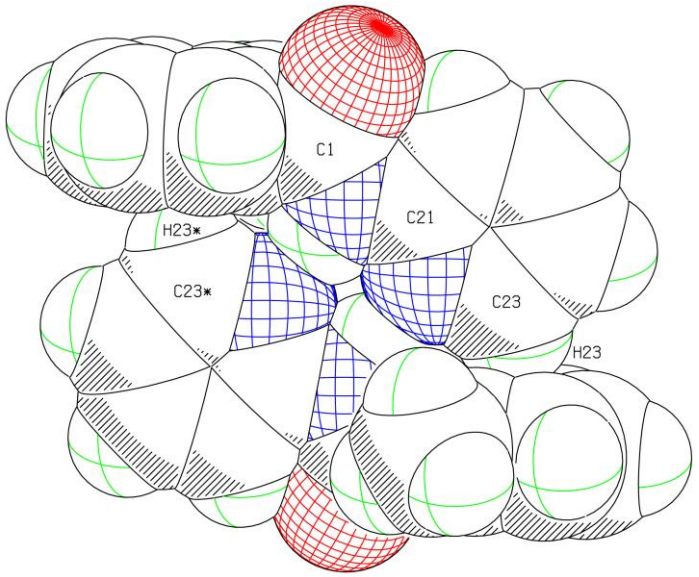




Moo structural highlight

Moo





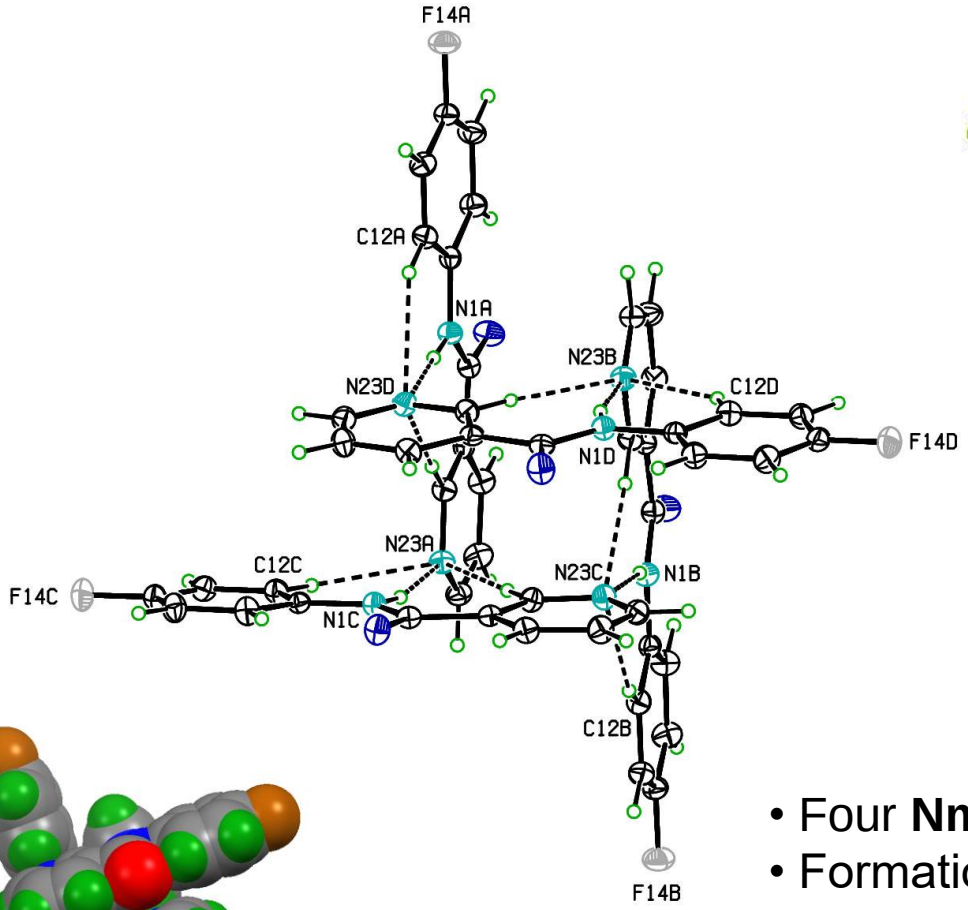
Hydrogen bonded dimer *via* a $R^2_2(8)$ ring system.

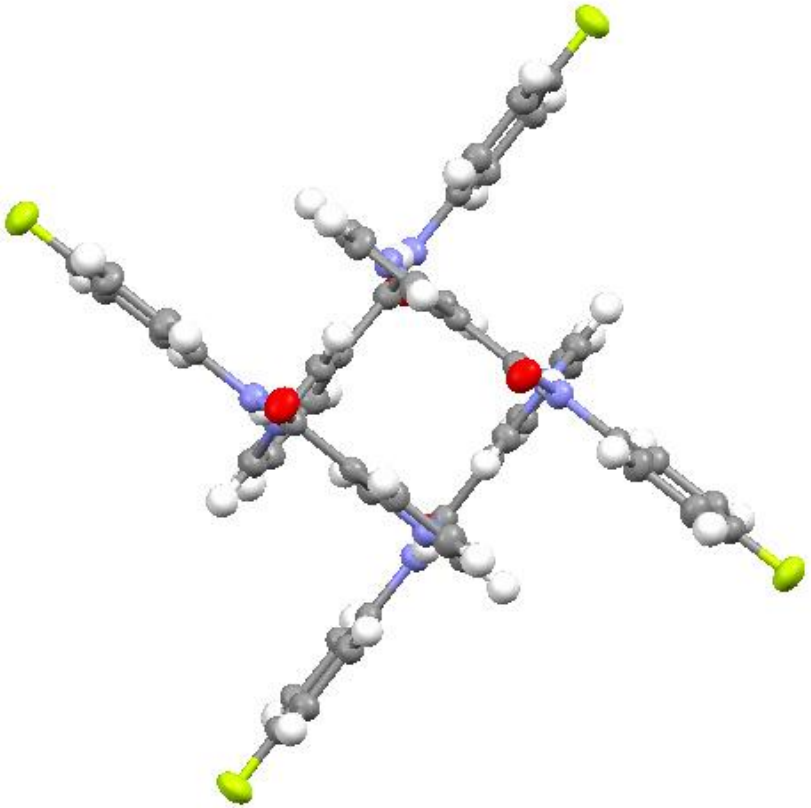
Moo - **short** C–H…*π*(arene) - (2.33 Å)

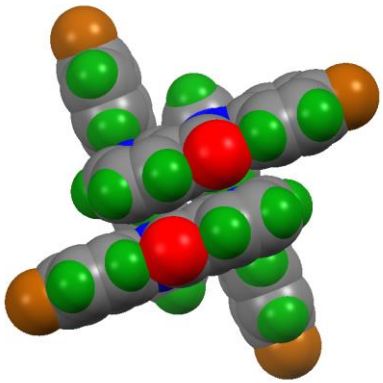
http://youtu.be/_5cZIz-cCGQ

NmpF structural highlight

Hydrogen bonded tetramer





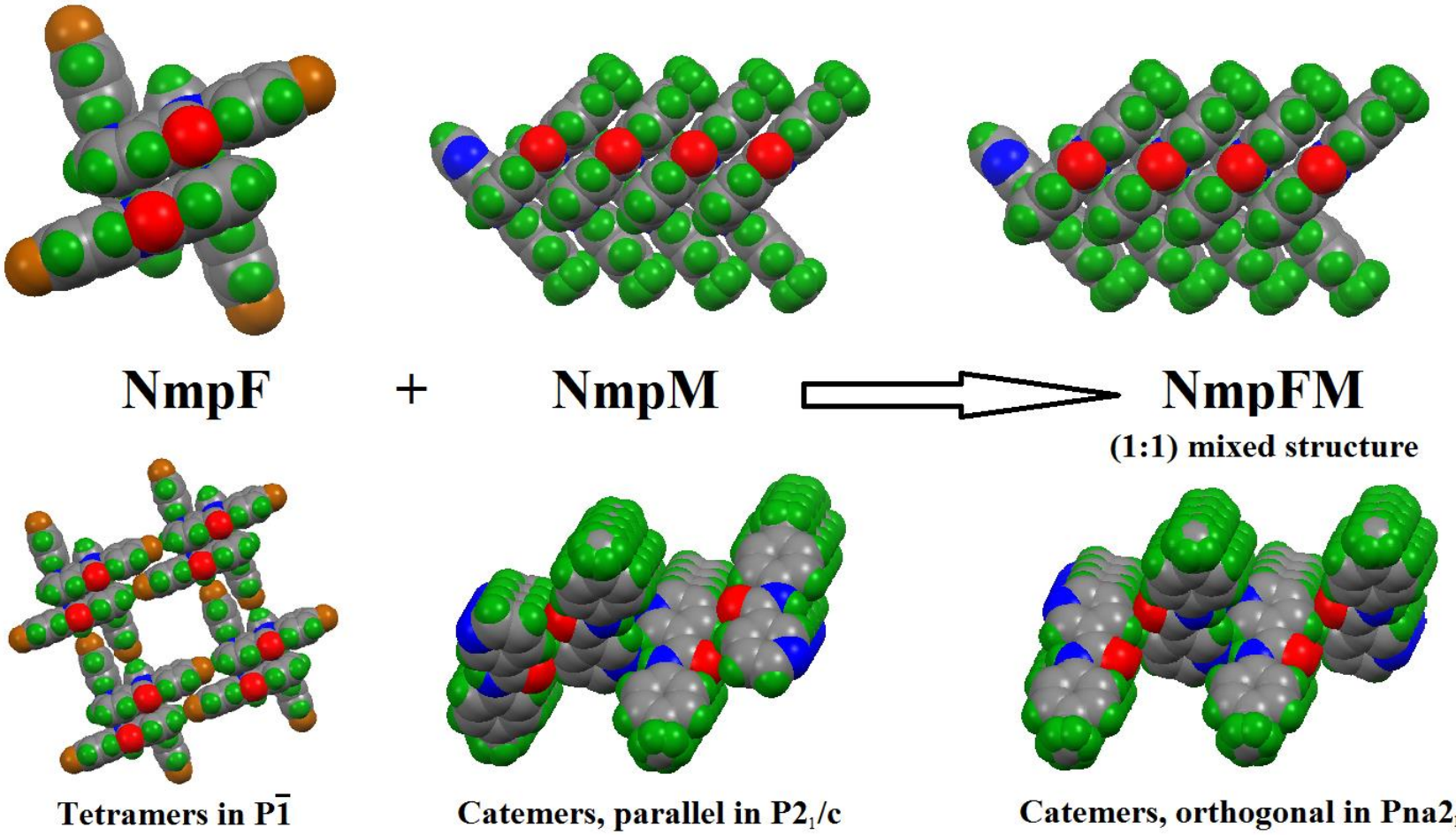


NmpF

- Four **NmpF** form a cyclic tetramer
- Formation of a '***St. Brigid's***' cross

http://youtu.be/gmD7Tr5l_uw

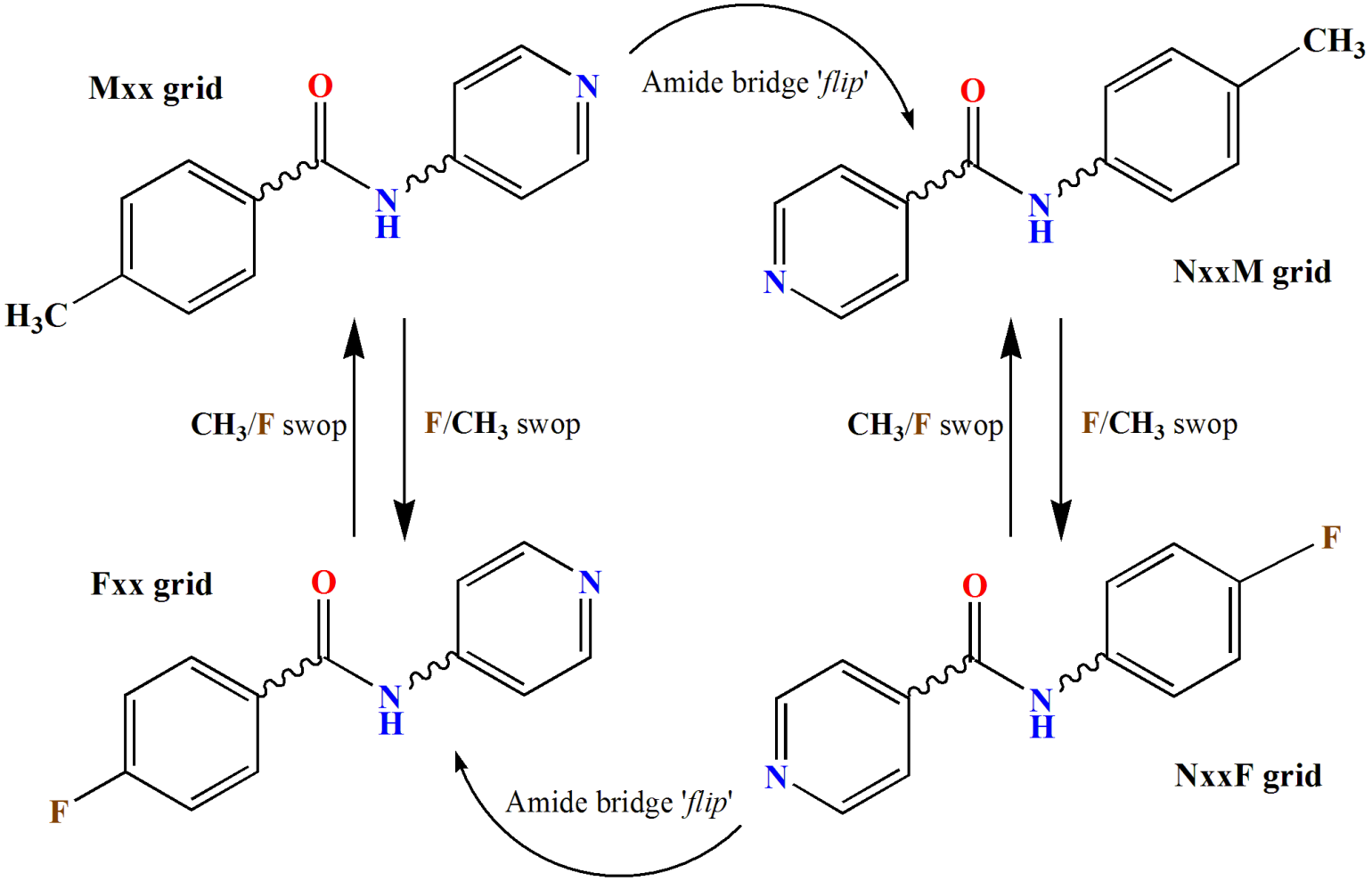
Solid-state solutions



NmpM formam cadeias catemer - se misturado (1:1) com **NmpF** obtém-se um tipo diferente de cadeia catemeric em **NmpFM**

Isomer grids

Relationships between the series of isomer grids



Melting Point Analysis

Correlation of the melting points – Carnelley's rule

		benzamides			pyridinecarboxamides			
	Mxx	Mp	Mm	Mo	No	Nm	Np	NxxM
M	p	181♦	106	129	105	148	162♦	pM
M	m	128	91	108	50*	115	142	mM
M	o	105	79*	116	65	107	125	oM
F	o	120	77*	85	107	117	140♦	oF
F	m	150, 148	151	89	78*	122	132	mF
F	p	187♦	186	135	94	133	135	pF
	Fxx[b]	Fp	Fm	Fo	No	Nm	Np	NxxF

Average melting point range for all 37 compounds with highest denoted by ♦ and lowest by *

- **Green** labels highlight the **N-H...N** interaction
- **Orange** labels the **N-H...O=C** hydrogen bonds
- Melting points for compounds in non-centrosymmetric space groups are underlined.

Substituent position is more important than the nature of the (CH_3/F) substituent.

Four isomer grid summary

Four main hydrogen bonding types:

1. N–H…$N_{pyridine}$ chains – except **NmpF** (tetramers) and **NmpM** (catemers).
2. N–H…O=C_{amide} chains.
3. N–H…$N_{pyridine}$ (intramolecular) in **NoxM**, **NoxF.**
4. N–H…$N_{pyridine}$ dimers in **Fxo**, **Mxo.**

Conformational analyses (PES scans) *gas phase* and comparisons of optimised geometries with solid state molecular structures:

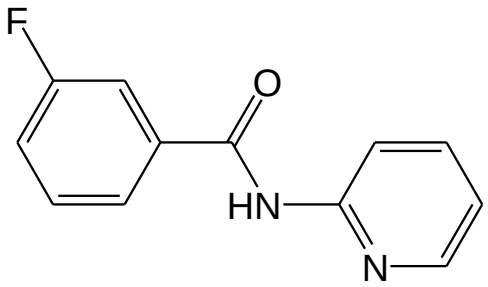
- highlight unusual solid state conformations,
- explain relationships with aggregation processes;

Benzamide/pyridinecarboxamide isomer grids reveal a high degree of similarity in their solid state aggregation and physicochemical properties

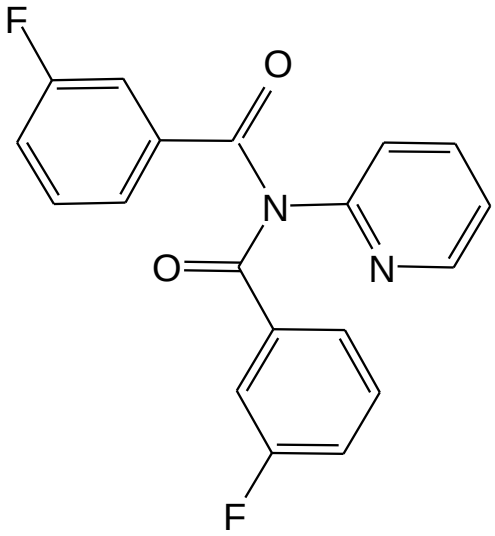
Imides - exploiting a side-reaction

Imide chemistry – a reaction that gives two products!

Reactions with 2-aminopyridine provide two products

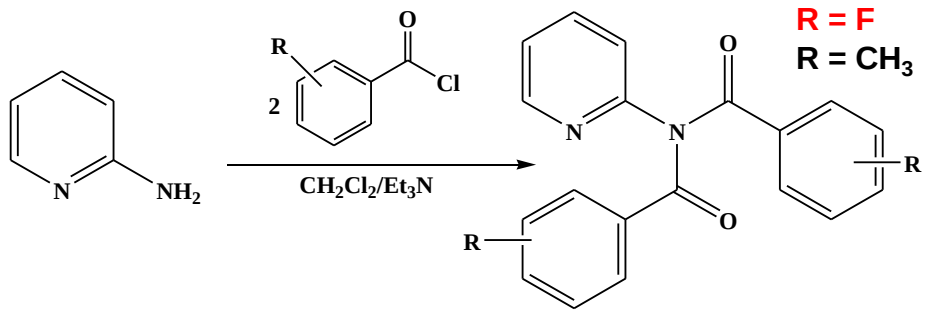


1:1 Benzamide (above) and **2:1** Imide (below)

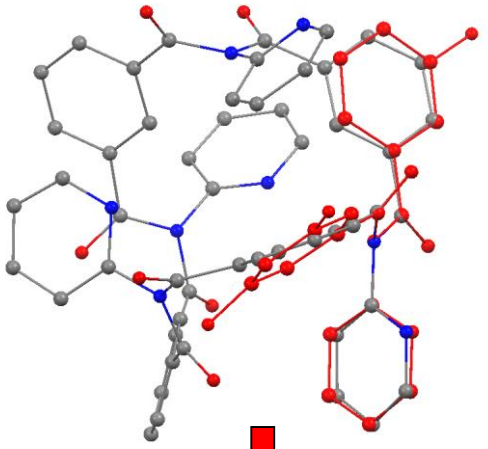


Imides in Macrocycles

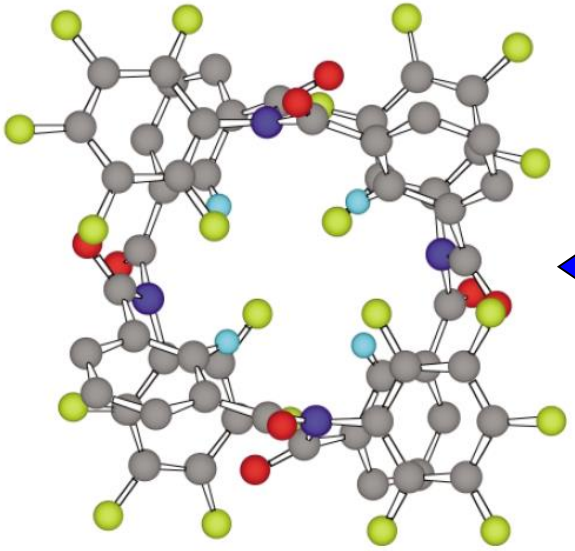
Historical perspective – from amide derivatives; Evans & Gale 2004

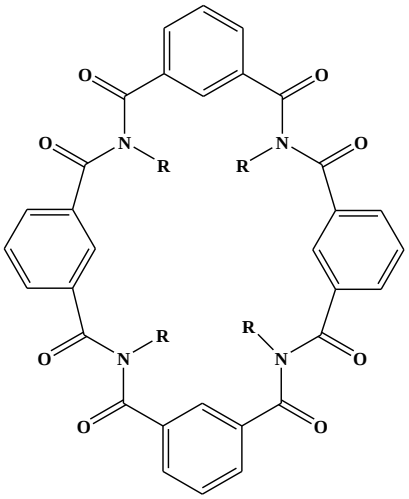


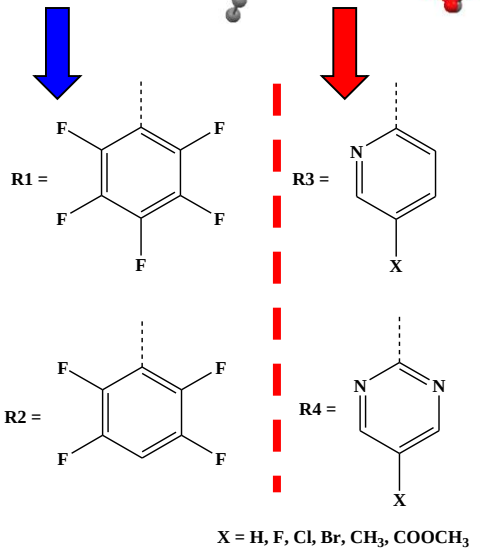
Fxo → Fxod
Mxo → Mxod



J. F. Gallagher, K. Donnelly and A. J. Lough, *Acta Cryst.* **2009**, **E65**, O102-O103.





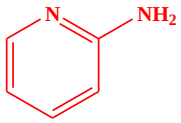


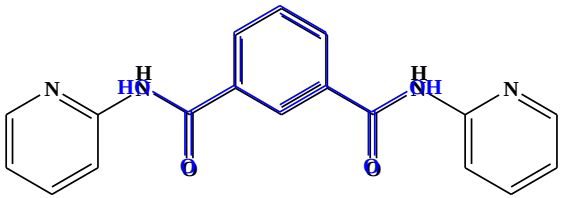
L. S. Evans and P. A. Gale, *Chem. Commun.*, **2004**, 1286-1287. **R1**/**R2** only

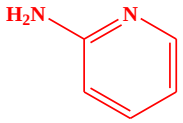
Reaction of isophthaloyl dichloride with tetra-/pentafluoranilines

Tennimides and trezimides

- **Synthesis**
- Method 1: ‘2+2’ (synthesise **H-DIP** from isophthalic acid and 2-aminopyridine)



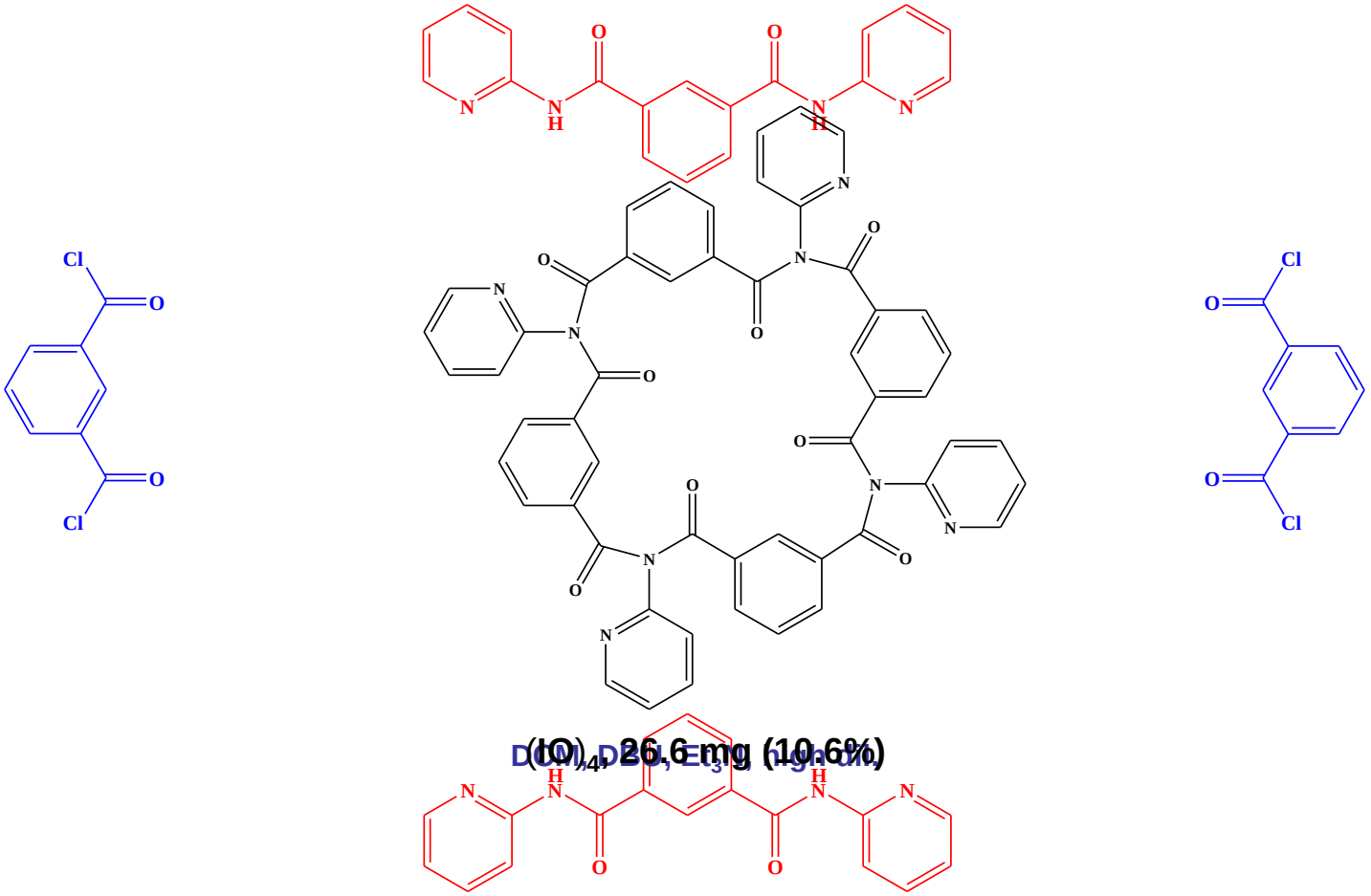




***N*^{1},*N*^{3}-di(pyridin-2-yl)isophthalamide (H-DIP)**

Tennimides and trezimides

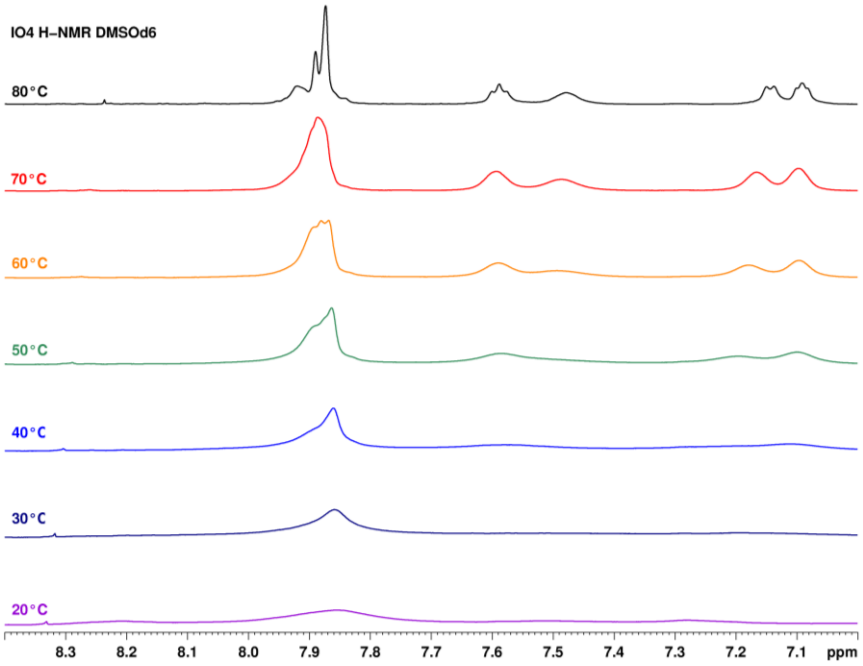
- **Synthesis of the tetramer (tennimide)**
- Method 1: 2+2 (condense **H-DIP** with isophthaloyl chloride, high dilution method)



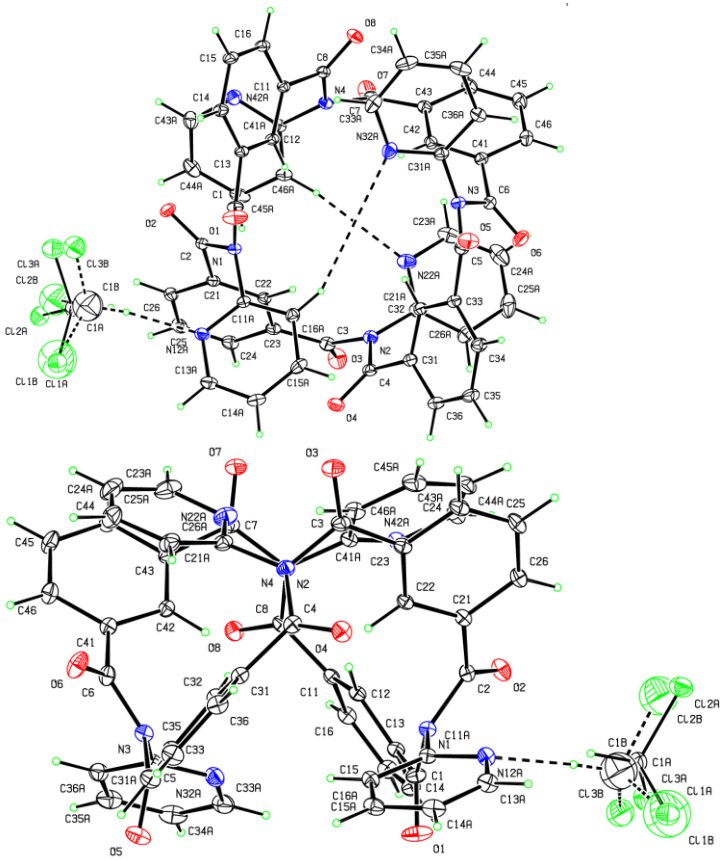
(IO)$_4$, 26.6 mg (10.6%)

Tennimides and trezimides

- **Synthesis of the tetramer (tennimide)**
- Method 1: '2+2' (condense **H-DIP** with isophthaloyl chloride, high dilution method)



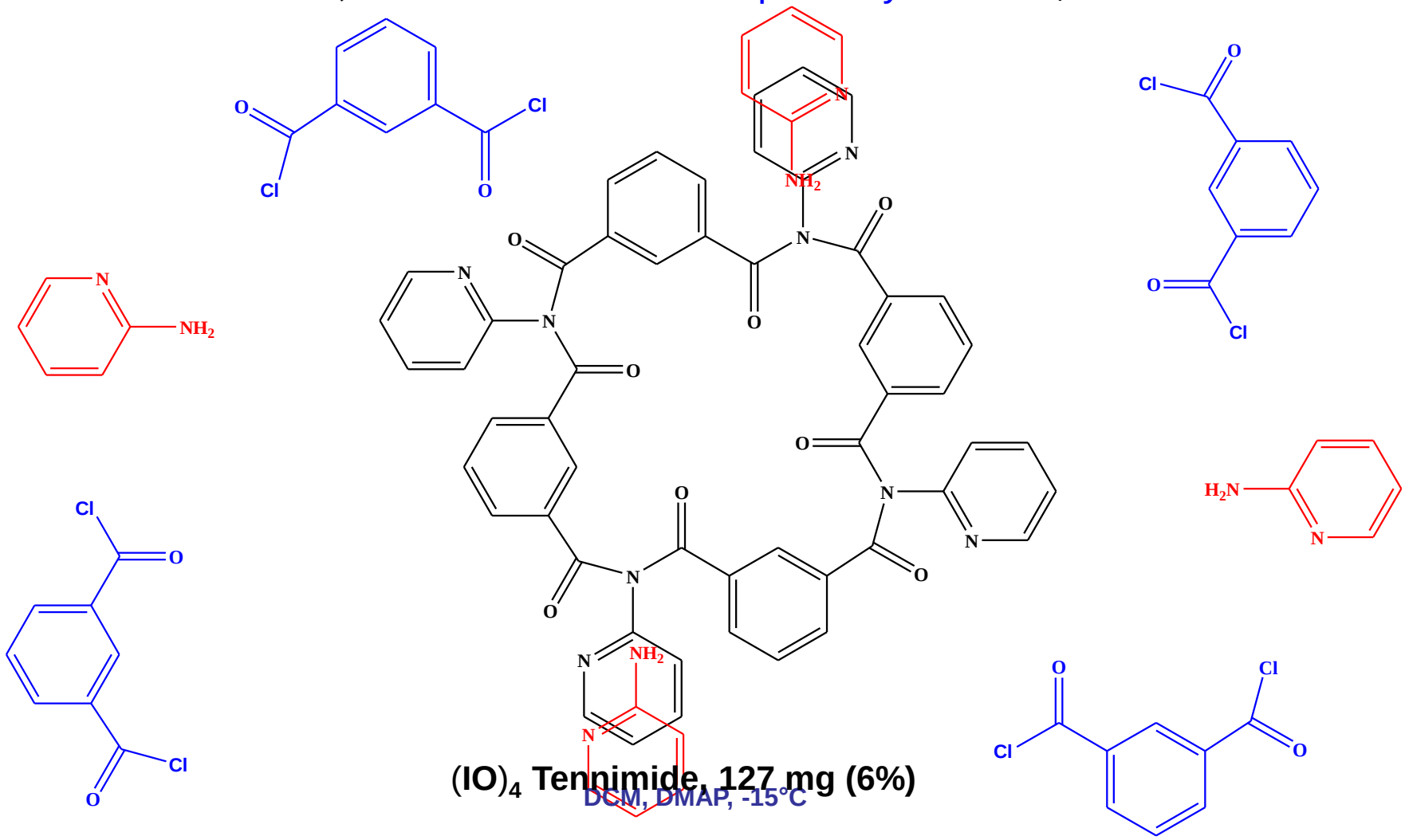
- Good yield, clean product, only $(\mathbf{IO})_4$
- **NOT easily REPRODUCIBLE!**



Triclinic $\bar{P}1$

Tennimides and trezimides

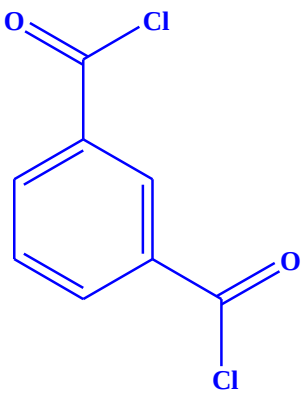
- **Synthesis of the tetramer (tennimide)**
- Method 2: ‘4+4’, condense 2-AP with isophthaloyl chloride, low dilution.

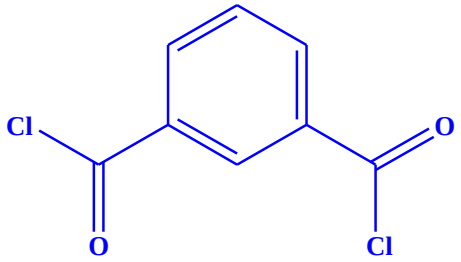


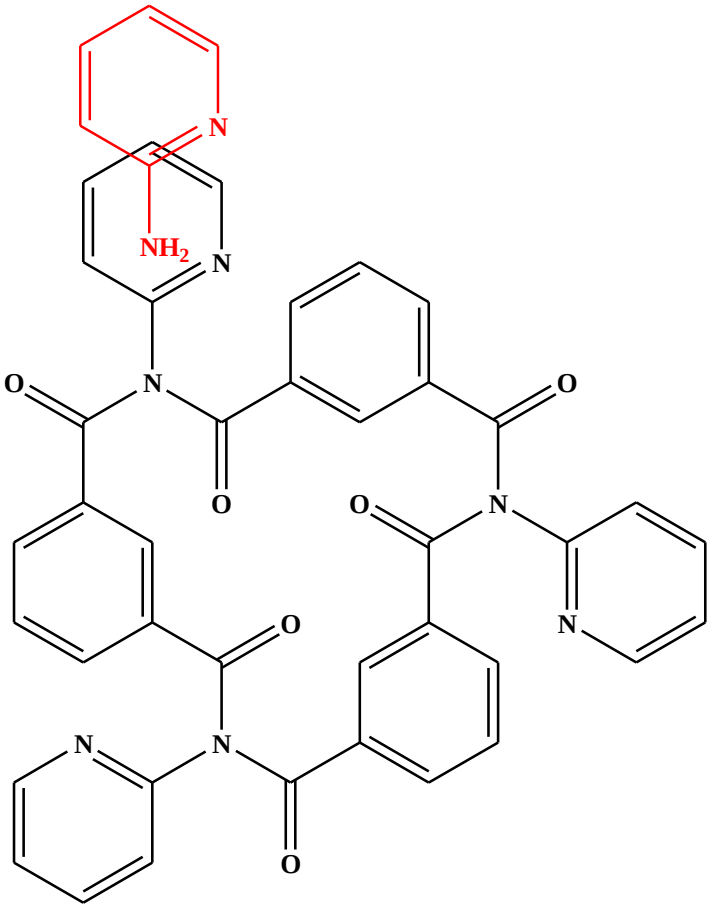
$(IO)_4$ Tennimide, 127 mg (6%)

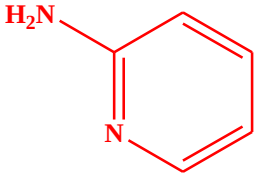
Tennimides and trezimides

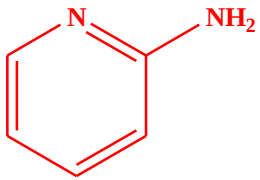
Concomitant cyclisation, '3+3' trezimide

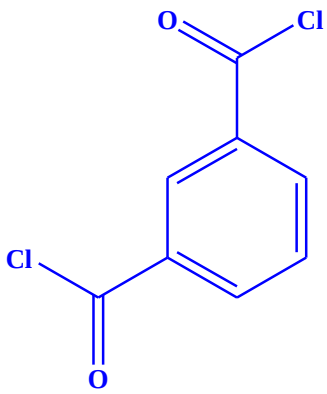








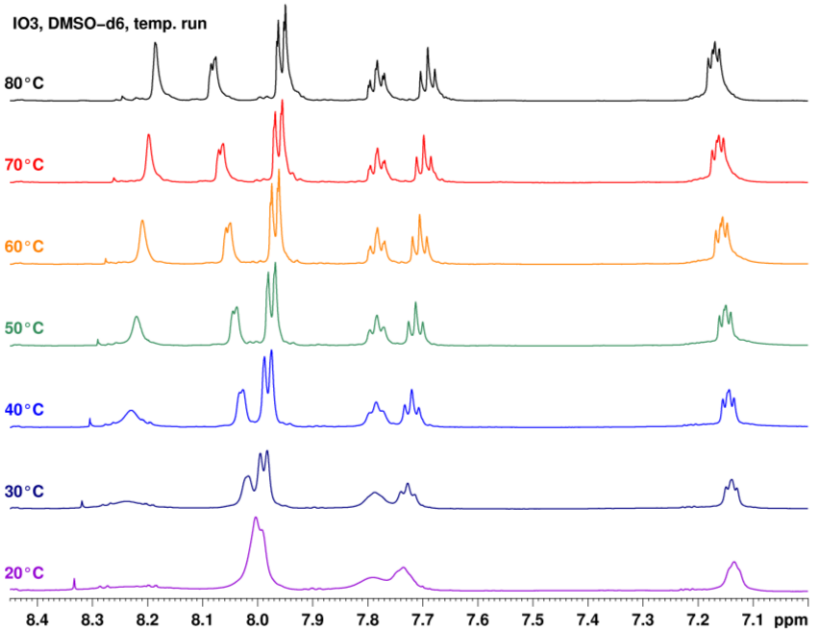


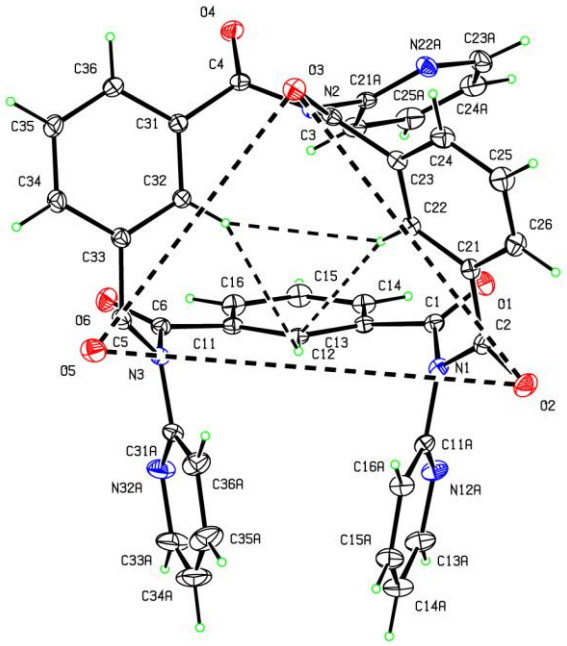


$(\mathbf{IO})_3$ trezimide, 149 mg (7%)

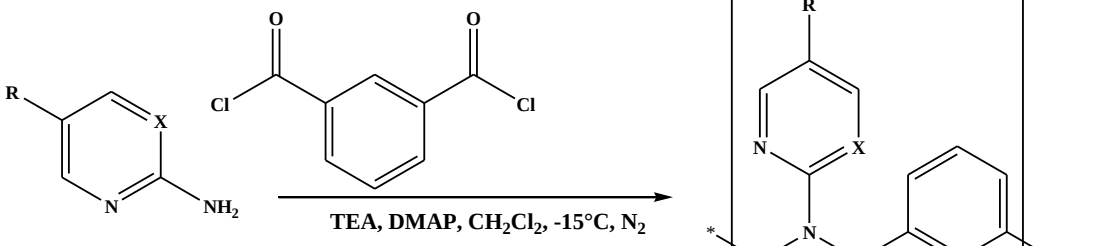
Tennimides and trezimides

- **$(IO)_3$ Trezimide**



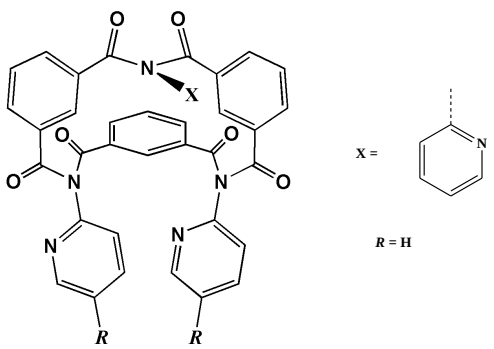


$(IO)_3$, $P2_1/n$, ***P*** conformation



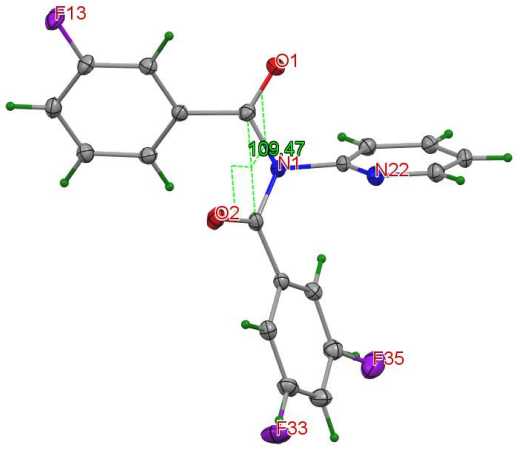
X = C-H or **N**

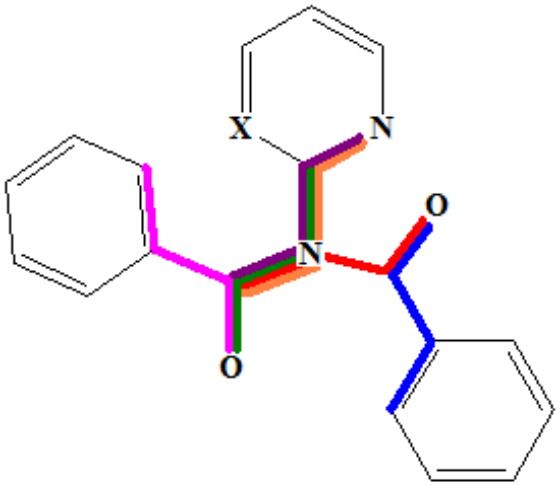
R = **H**, **F**, **Cl**, **Br**, **CH_3**, **$COOCH_3$**

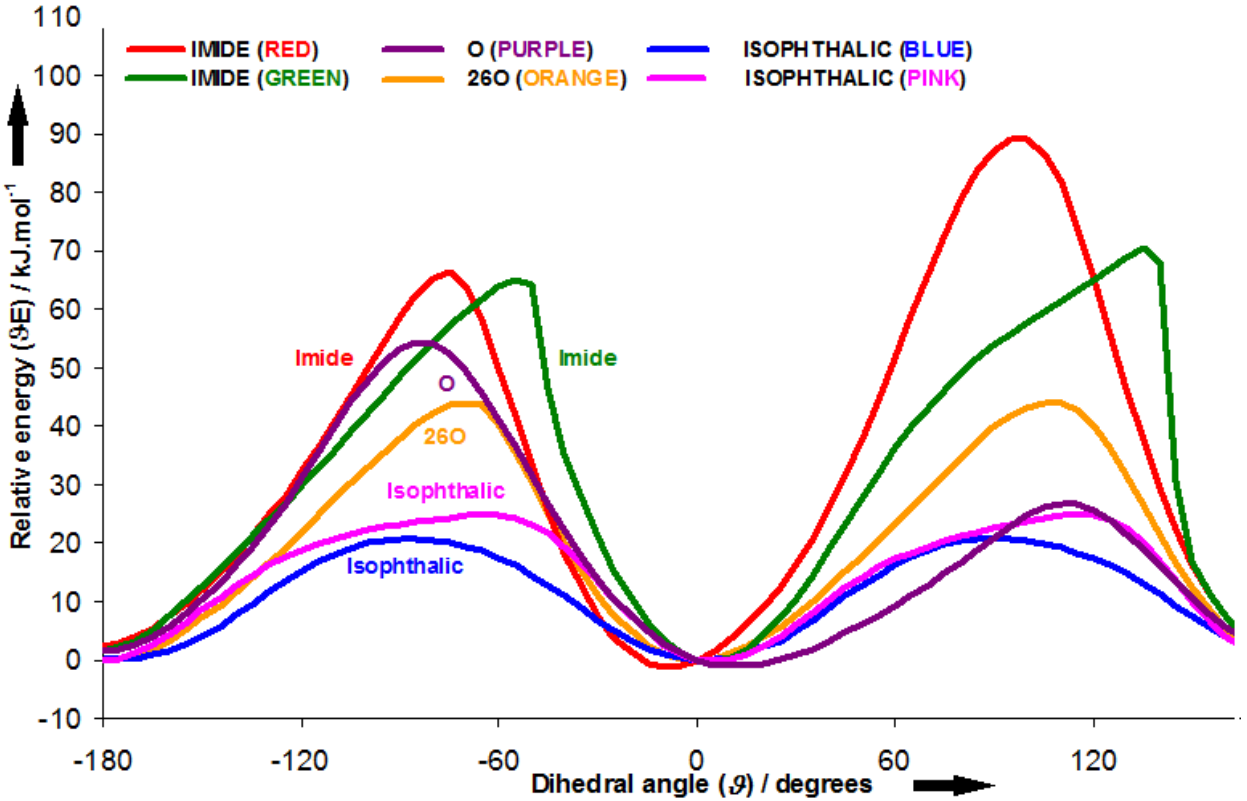


Tennimides and trezimides

Modelling the imide *hinge* – Potential Energy Surface scans

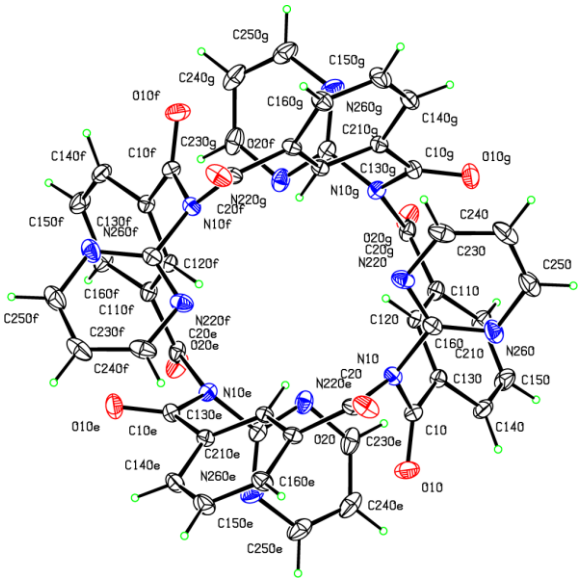


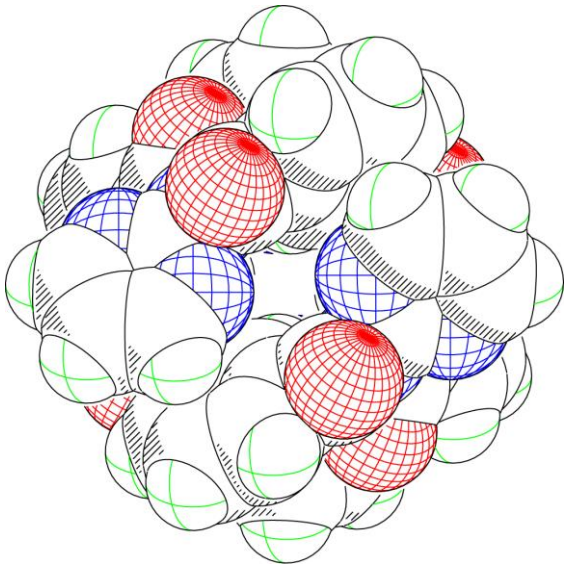




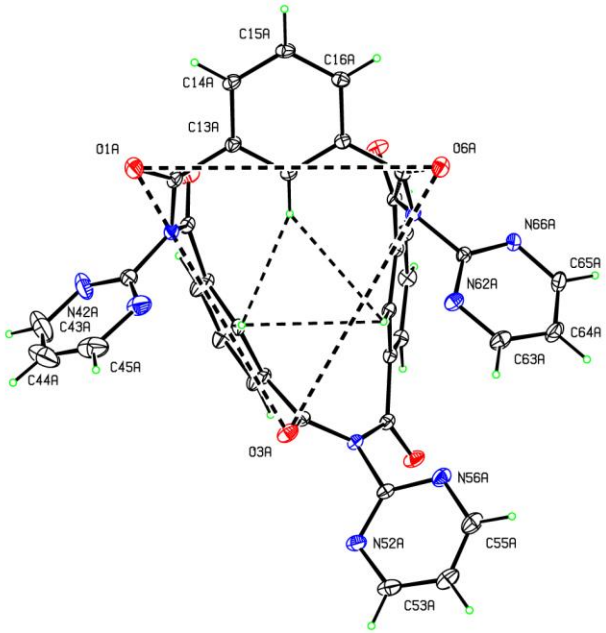
Tennimides and trezimides

- $(\mathbf{26IO})_3$ and $(\mathbf{26IO})_4$ **–** from **2-aminopyrimidine**
- $(\mathbf{26IO})_4$**:** ***closed-closed***, ***closed-open***, ***open-open*** **conformations**
- $(\mathbf{26IO})_3$**:** has the ***R* conformation** **(different to the *P* conformation!)**





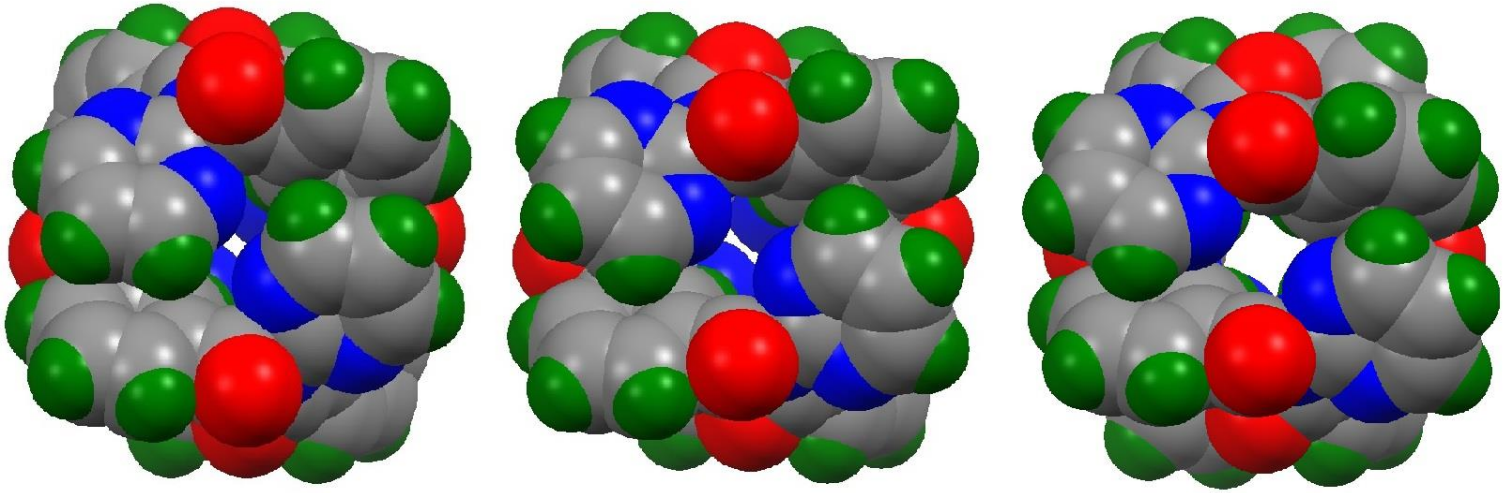
ORTEP and CPK view of $(\mathbf{26IO})_4$ as molecule O), in $P\bar{4}2_1c$



An ORTEP diagram of $(\mathbf{26IO})_3$ (as molecule A), $\bar{P}1$

Tennimides and trezimides

- **(26IO)$_3$** and **(26IO)$_4$ –** from **2-aminopyrimidine**
- **(26IO)$_4$: *closed-closed*, *closed-open*, *open-open* conformations**
- **A useful example of conformational distortion in the solid-state.**

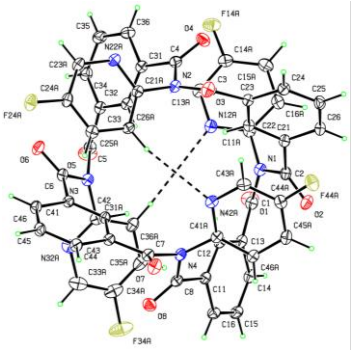


closed-closed *open-closed* *open-open*

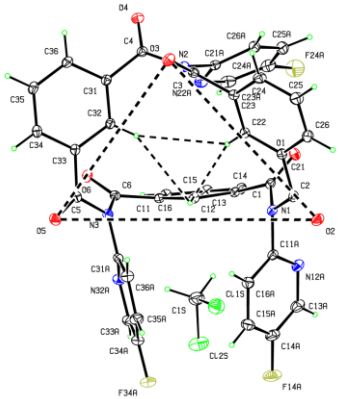
Three **(26IO)$_4$** solid-state conformations in an **unusual** crystal structure

Tennimides and trezimides

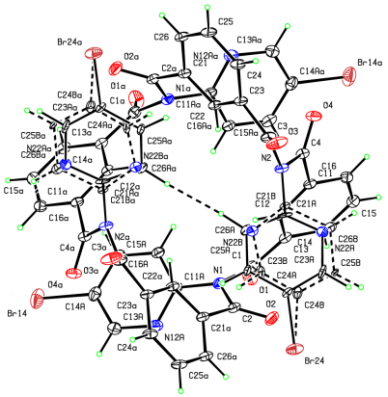
Halo-derivatives – 4-X-2-aminopyridine/pyrimidine $(XIO)_{3/4}$- $(26XIO)_{3/4}$



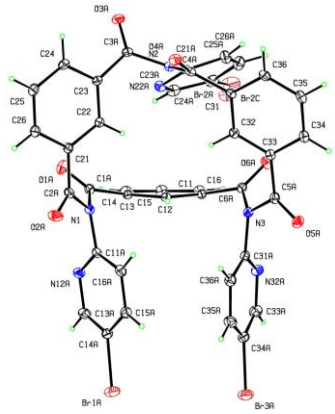
$(FIO)_4$, $\bar{P}1$



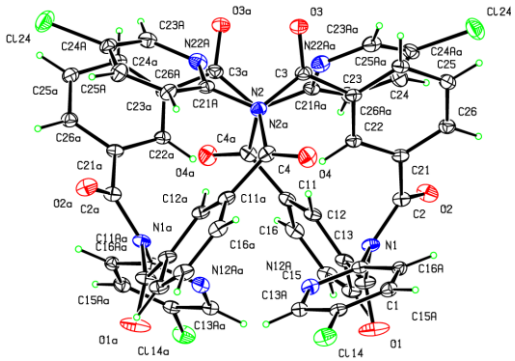
$(FIO)_3$, $P2_1/c$



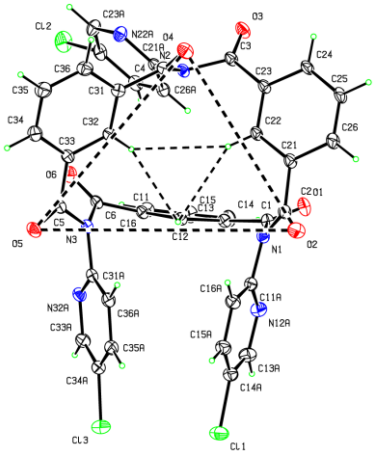
$(BrIO)_4$, *Pccn*



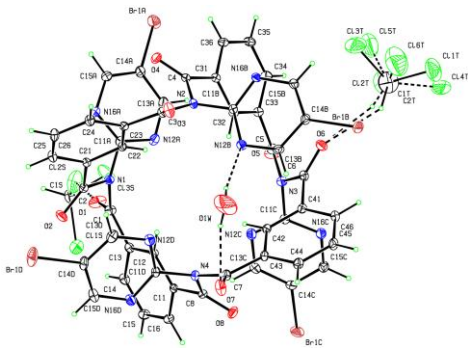
$(BrIO)_3$, $P2_1/n$



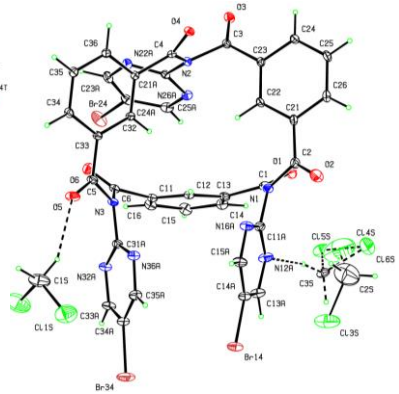
$(ClIO)_4$, *Pccn*



$(ClIO)_3$, *Fdd2*



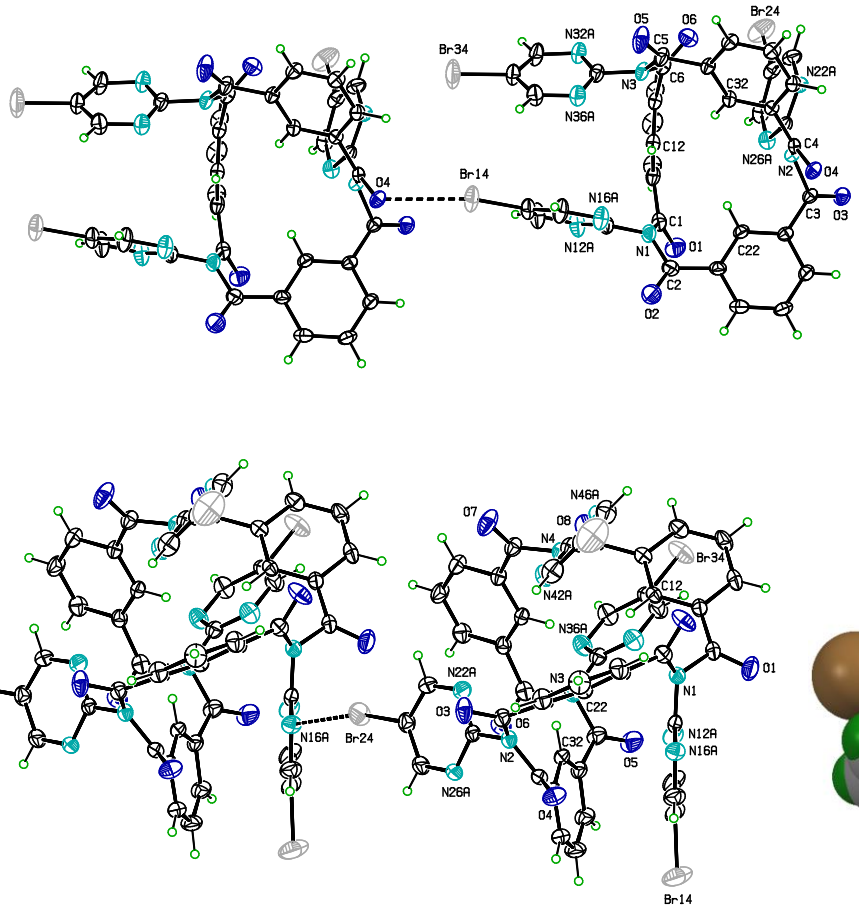
$(26BrIO)_4$, $P2_1/n$

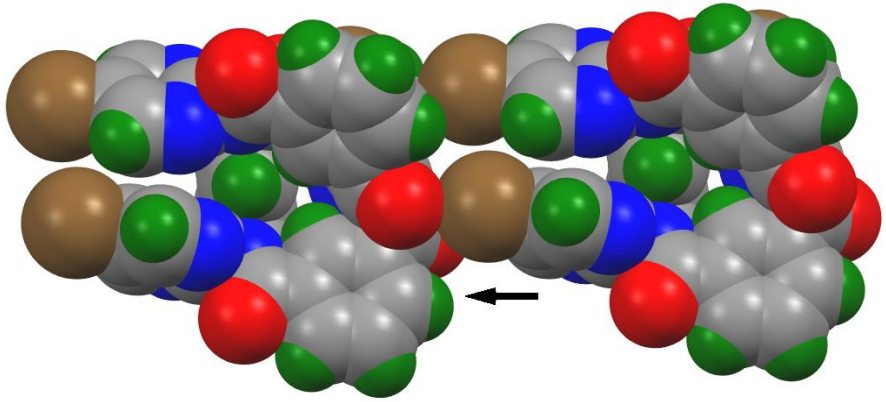


$(26BrIO)_3$, $P\bar{1}$

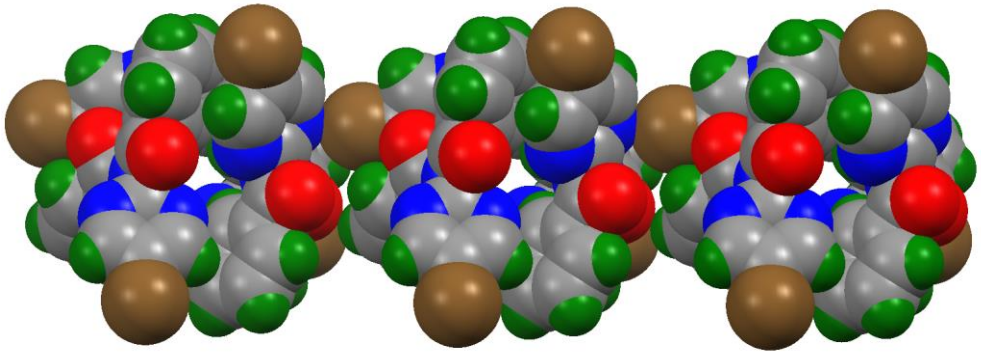
Tennimides and trezimides

Halogen bonding in the $(26BrIO)_{3/4}$ macrocycles





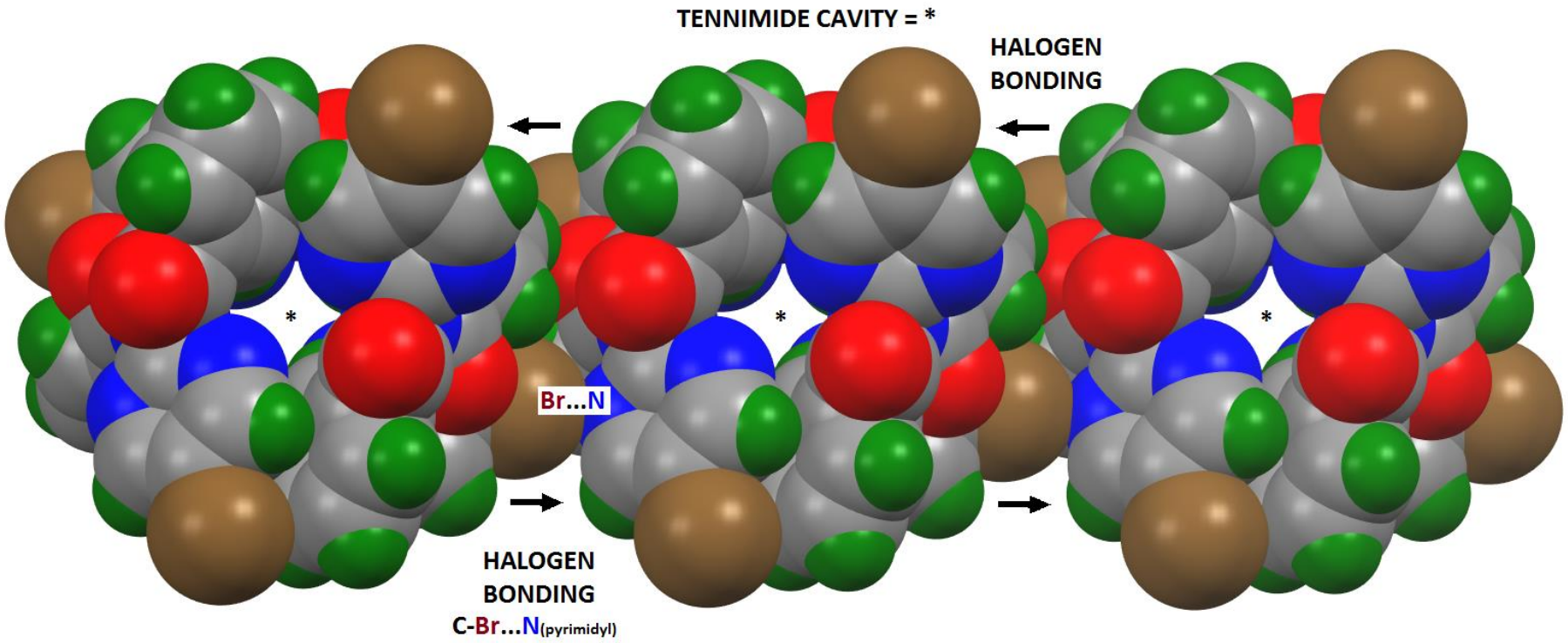
$(26BrIO)_3$, $P\bar{1}$



$(26BrIO)_4$ in $P2_1/n$ (with $N_c = 0.89$)

Tennimides and trezimides

Halogen bonding in the $(26BrIO)_{3/4}$ macrocycles



$(26BrIO)_4$ in $P2_1/n$ (with $N_c = 0.89$)

Trezimides and Tennimides

- **View these trezimide and tennimide macrocycles on YouTube**
- http://www.youtube.com/tennimidandtrezimid

- Synthesis: simple, one step, simple separation/purification, modest yields.

- A crystal structure for every macrocycle synthesised.

- **Tennimides** are stable and relatively rigid, **trezimides** are less stable, more flexible; **trezimide** conformations - ***P*** in $(\mathbf{IO})_3$ and ***R*** in $(\mathbf{26IO})_3$.

- **Trezimides** and **tennimides** formed utilizing the preferred conformation
- of the imide linker moiety (±90±15°) for cyclisation.

- **Halogen bonding** involving Br…N/O=C/π(arene) (with $\boldsymbol{N_c} \geq \mathbf{0.89}$)

- http://www.youtube.com/channel/UC9FOUhx_uqnj9uyObrcnmUQ/videos

Overall Summary

- A study of small molecule solid-state and computational models.
- Benzamide/pyridinecarboxamides (25%) have different solid-state conformations compared to *ab initio* calculations.
- Conformational analyses - useful in rationalising structural results and where there is difficulty in obtaining quality crystals.
- **Moo, Foo, NmpF, NmpM – <u>unusual structures</u>**.
- Importance of substituent position rather than substituent nature.
- **Trezimides** and **Tennimides**
- **ClxxandNxxCl finalised with Brxx/NxxBr under study…**
- **Imide expansion for unsymmetrical imides and new macrocycles…**

Recent publications

Structural systematics and conformational analyses of a 3 × 3 isomer grid of fluoro-N-(pyridyl)-benzamides: physicochemical correlations, polymorphism and isomorphous relationships. Pavle Mocilac, Katie Donnelly & John F. Gallagher, *Acta Crystallographica Section B – Structural Science,* **2012**, **68**, 189 – 203. DOI: 10.1107/S0108768112006799.

Entry point into new trimeric and tetrameric imide-based macrocyclic esters derived from isophthaloyl dichloride and methyl 6-aminonicotinate. Pavle Mocilac and John F. Gallagher, *Acta Crystallographica B – Structural Science*, **2013**, **69**, 62–69. DOI: 10.1107/S0108768112047416.

Trezimides and Tennimides: New Imide-Based Macrocycles. Pavle Mocilac and John F. Gallagher, *The Journal of Organic Chemistry*, **2013**, **78(6),** 2355–2361. DOI: 10.1021/jo302448h.

Short C-H…F interactions involving the 2,5-difluorobenzene group: Understanding the role of fluorine in aggregation and complex C-F/C-H disorder in a 2 × 6 isomer grid. Pavle Mocilac, I.A. Osman and John F. Gallagher, *CrystEngComm*, **2016**, **18,** 5764–5776**.** DOI: 10.1039/c6ce00795c and https://youtu.be/v753ZMTVYRs

Halogenated tennimides and trezimides: Impact of halogen bonding and solvent role on porous network formation and inclusion. Pavle Mocilac and John F. Gallagher, *CrystEngComm,* **2016**, **18,** 2375–2384. DOI: 10.1039/c5ce02052b and https://www.youtube.com/watch?v=SvPoVCTLweY

Structural Systematics and Conformational Analyses of an isomer grid of nine Tolyl-*N*-pyridinyl-carbamates. Pavle Mocilac and John F. Gallagher, *Structural Chemistry*, **2017**, **28,** 697–708. DOI: 10.1007/s11224-016-0851-5.

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Visiting Undergraduates: (**from ENSIACET, Toulouse, France**)
Ms. Chloe Violin, Ms. Marie Bélières, Ms. Marion Lefevre & Ms. Audrey Arrighi.

Crystal structures (**Fxx** and **Mxx** series)
Dr. Alan J. Lough, University of Toronto, Toronto, Canada.

Irish Centre for High-End Computing:
Dr. Alin M. Elena and Dr. Jean-Christophe Desplat

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An tÚdarás um Ard-Oideachas

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