NMR CRYSTALLOGRAPHY:
The new application of combined theoretical and spectroscopic approach for structural description in the solid state

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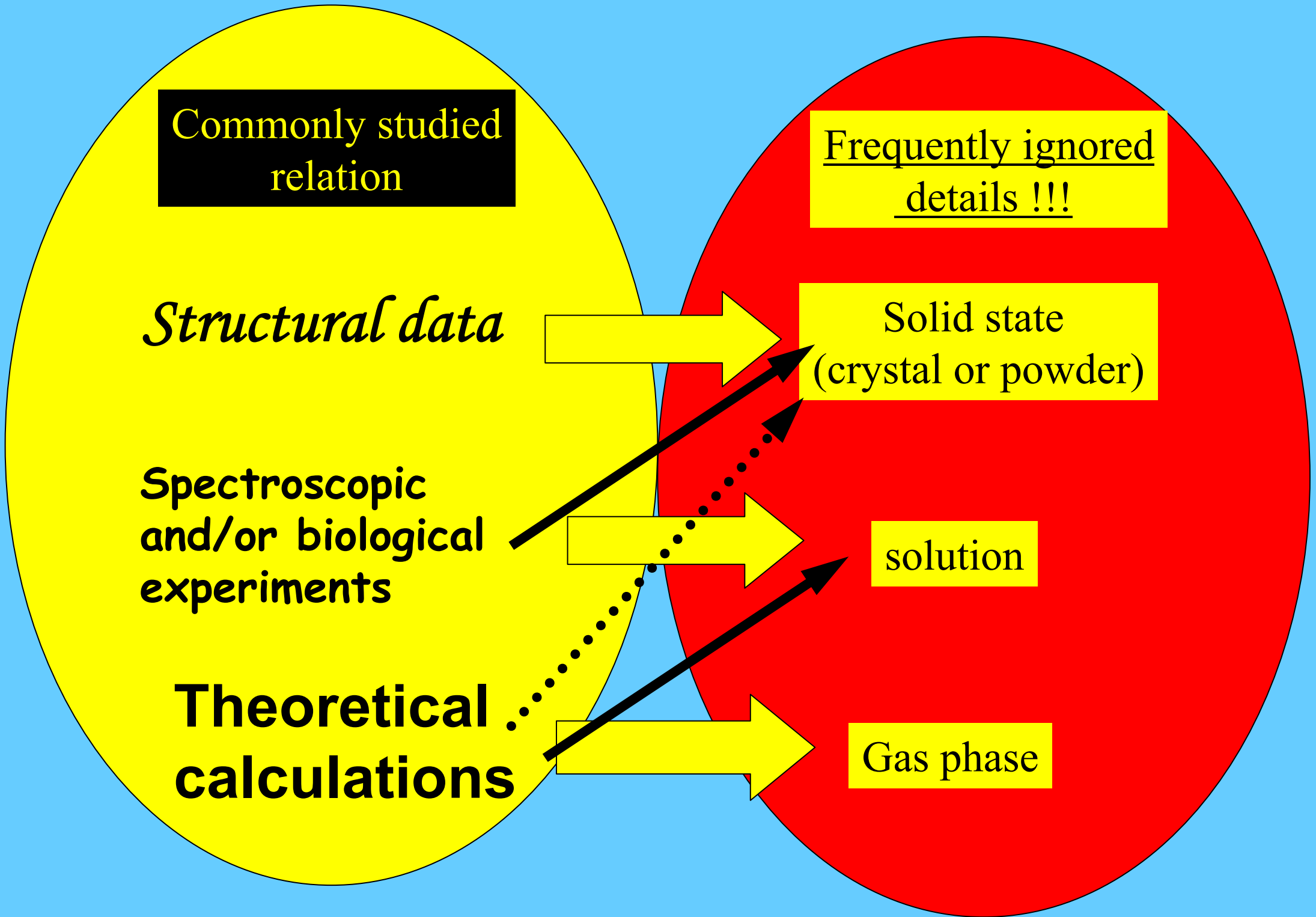
NMR CRYSTALLOGRAPHY

NMR experiments in the solid state ⟷ Single-crystal or powder diffraction

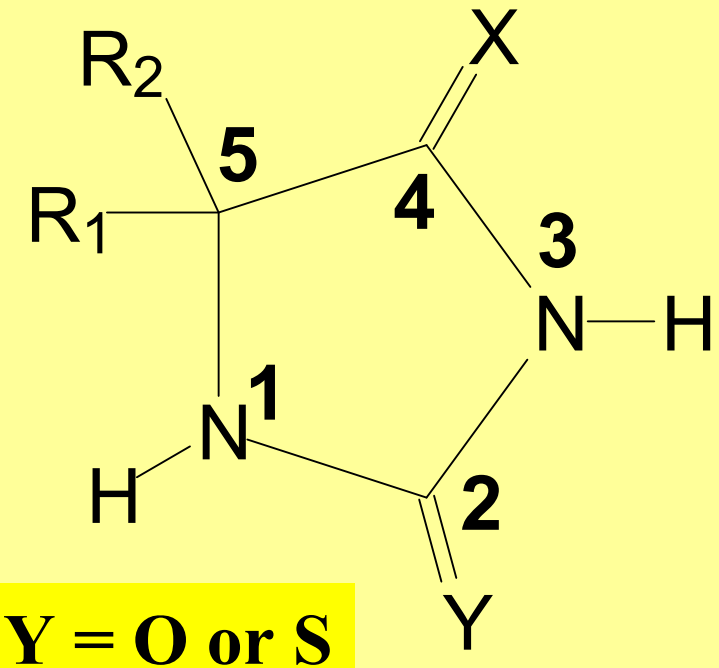
CALCULATIONS

To define a space group, conformational changes or even structural parameters

Application to structural biology, organic and pharmaceutical chemistry, inorganic and materials chemistry


Commonly studied relation
Structural data
Spectroscopic and/or biological experiments
Theoretical calculations
Frequently ignored details !!!
Solid state (crystal or powder)
solution
Gas phase

What are hydantoins
and
Why hydantoins



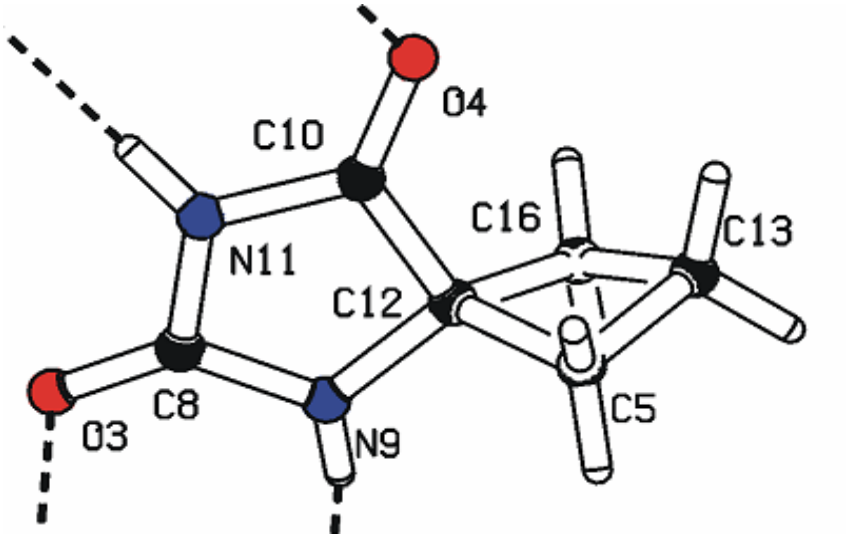
imidazolidine-2,4-dione (by IUPAC)

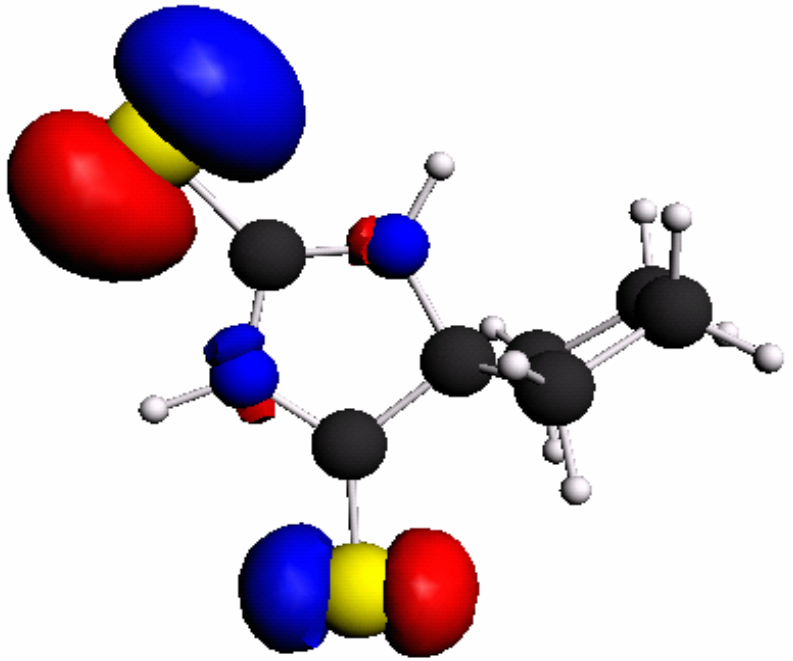
X, Y = O or S

- **Hydantoin derivatives** are well known for their medical applications, e.g. as:
- **antiepileptic drugs** [D. Janz, **Der Nervenarzt** 21 (1950) 113; T. C. Butler, W. J. Waddell, **J. Pharm. Exp. Therapeut.** 110 (1954) 120.] ***Phenytoin, Mephenytoin***
- **Antiproliferative activity** [C. S. A. Kumar, et al., **Inv. New Drugs** 27 (2009) 131; C.V. Kavitha, et al., **Biochem. Pharmacol.** 77 (2009) 348.]
- **inhibition of aldosoreductase** [R. Sarges, R. C. Schnur, J. L. Belletire, M. J. Peterson, **J. Med. Chem.** 31 (1988) 230.]
- **and potential application for treatment of HIV-1 infections** [D. Kim, et al., **Bioorg. Med. Chem. Lett.** 11 (2001) 3099.; D. Kim, et al., **Bioorg. Med. Chem. Lett.** 11 (2001) 3103.].

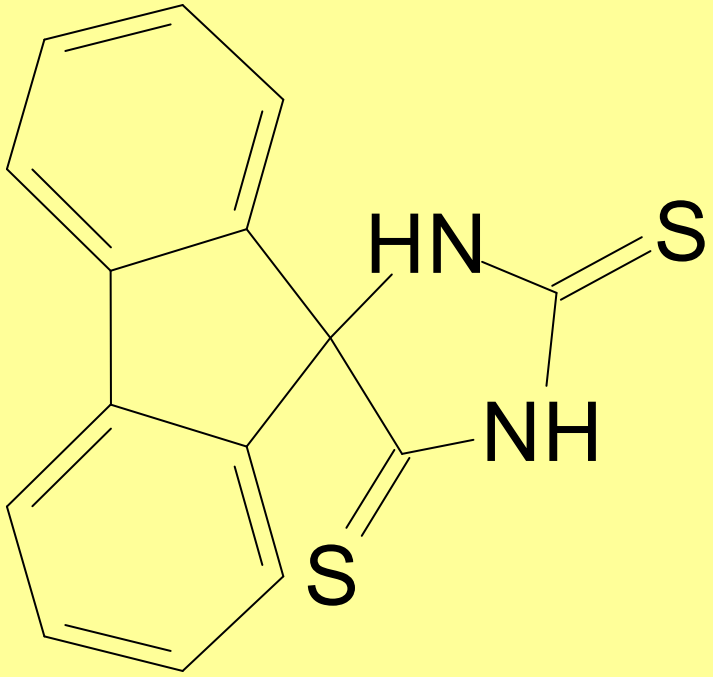
Metal-ion coordination ability,
Biological activity,
BUT
Correct structure – for correct conclusions !!!!

Hydantoins *vs* **thio**-hydantoins

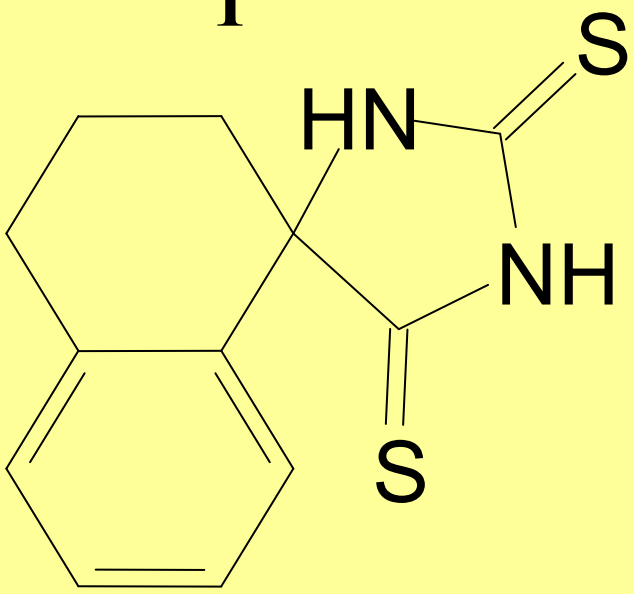




Structure of the studied Spiro-dithio-hydantoins



1



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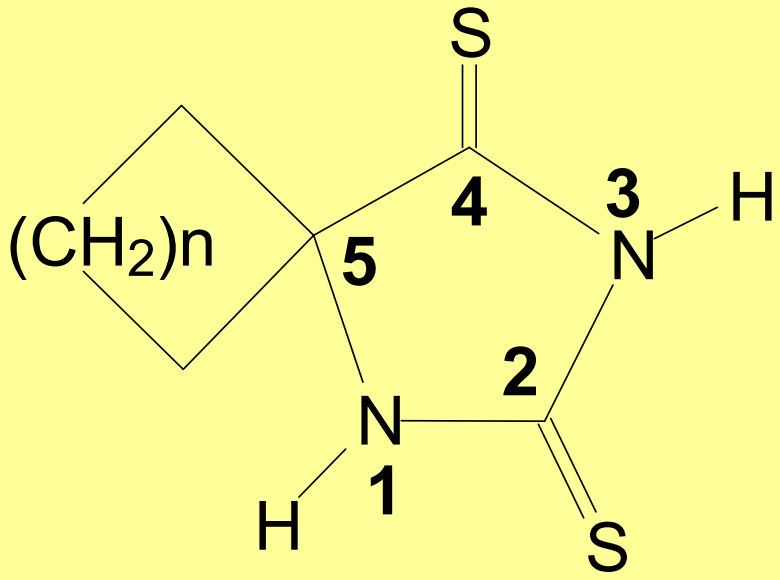

n = 2 - 5; **3 - 6**

The crystal structure of the non-coordinated dithio-hydantoins is available

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Four cycloalkanespiro-4′-imidazolidine-2′,5′-dithiones

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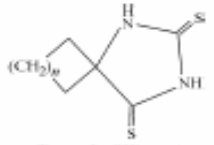
The crystal structures of four cycloalkanespiro-4′-imidazolidine-2′,5′-dithiones, namely cyclopentanespiro-4′-imidazolidine-2′,5′-dithione {systematic name: 1,3-diazaspiro[4.4]nonane-2,4-dithione}, $C_7H_{10}N_2S_2$, cyclohexanespiro-4′-imidazolidine-2′,5′-dithione {systematic name: 1,3-diazaspiro[4.5]decane-2,4-dithione}, $C_8H_{12}N_2S_2$, cycloheptanespiro-4′-imidazolidine-2′,5′-dithione {systematic name: 1,3-diazaspiro[4.6]undecane-2,4-dithione}, $C_9H_{14}N_2S_2$, and cyclooctanespiro-4′-imidazolidine-2′,5′-dithione {systematic name: 1,3-diazaspiro[4.7]dodecane-2,4-dithione}, $C_{10}H_{16}N_2S_2$, have been determined. The three-dimensional packing in all of the structures is based on closely similar chains, in which hydantoin moieties are linked through N—H···S hydrogen bonding. The size of the cycloalkane moiety influences the degree of its deformation. In the cyclooctane compound, the cyclooctane ring assumes both boat–chair and boat–boat conformations.

Comment

The structural characteristics of spirohydantoins are interesting because of their potential biological activities (Somsak *et al.*, 2005). Recently, we began a structural and biological



(I) n=2 (III) n=4
(II) n=3 (IV) n=5

investigation of new hydantoin derivatives and their organometallic complexes (Shivachev *et al.*, 2005). As part of this

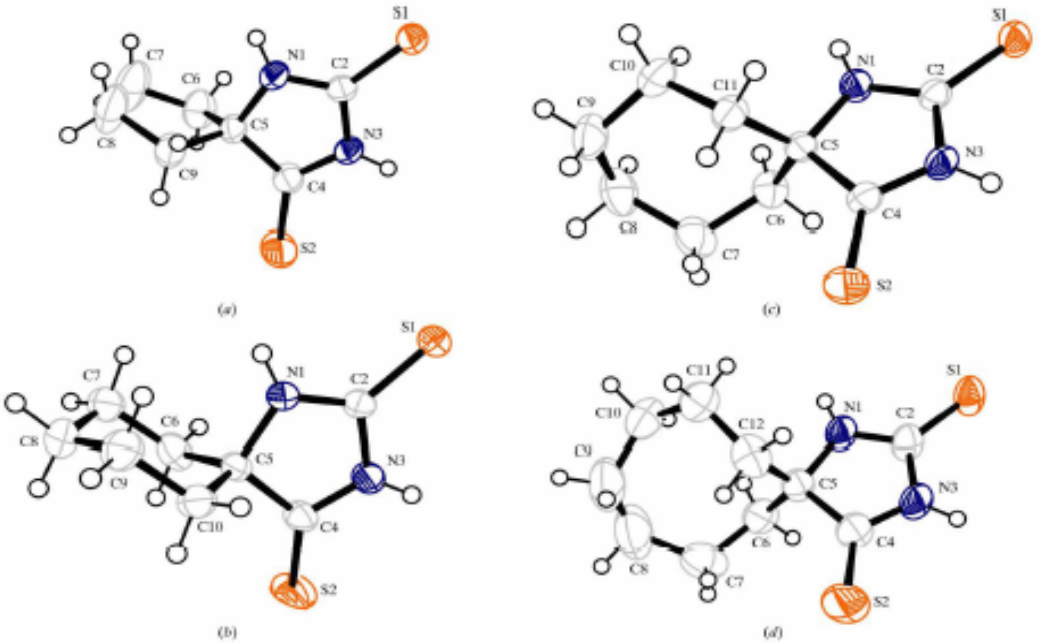


Figure 1
A view of the structure and the atom-numbering scheme of the independent molecule in (*a*) (I), (*b*) (II), (*c*) (III) and (*d*) (IV), showing 50% probability displacement ellipsoids. For compound (IV), only the major (62%) disorder component is represented, the minor (38%) component being omitted for clarity (see *Comment*).

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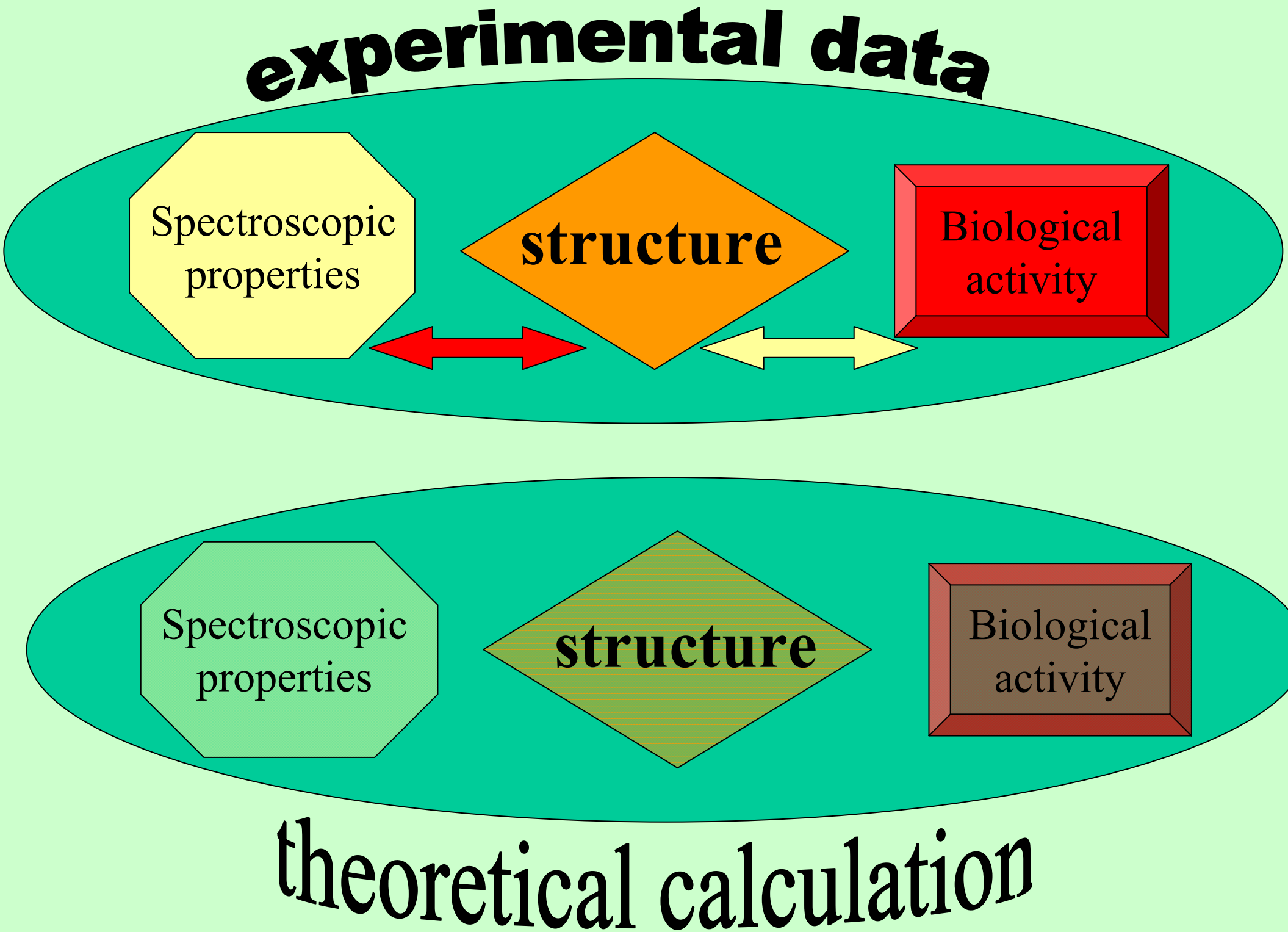
However, none of their metal complexes could be crystallized


experimental data
Spectroscopic properties
structure
Biological activity
Spectroscopic properties
structure
Biological activity
theoretical calculation

Focus on the ^{13}C **NMR shifts** of **C2-**, **C4-** and **C5**-carbon atoms in the hydantoin ring

^{13}C CPMAS NMR spectra

Of the free ligands vs of the complexes

Gas-phase optimized structures (B3LYP/6-31G**)

Of the free ligands *vs* models of the complexes

^{13}C NM shielding constants (GIAO-B3LYP/6-31G**)

Of the free ligands *vs* of the complexes

suggest

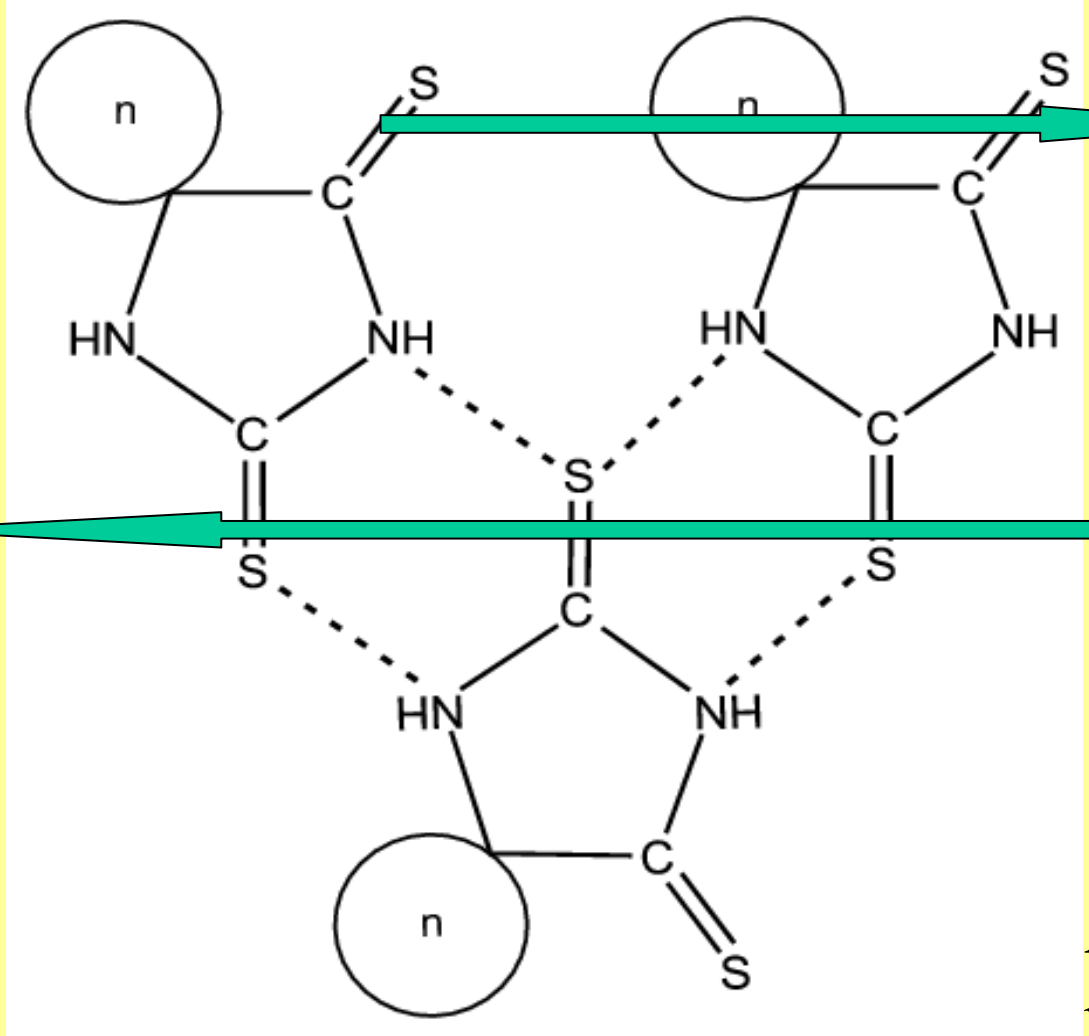
The best model structure of the complexes

1 A. Ahmedova, P. Marinova, K. Paradowska, M. Marinov, I. Wawer, M. Mitewa, ***Polyhedron*** 29 (2010) 1639-1645.
2 A. Ahmedova, P. Marinova, K. Paradowska, N. Stoyanov, I. Wawer, M. Mitewa, ***Inorg. Chim. Acta*** 363 (2010) 3919-3925.

Infinite H-bond network in the crystal structures of compounds **2 – 6**

All C2=S2 groups are involved in 2 inter-molecular H bondings

C4=S4 groups do not form inter-molecular H bonds



All N-H groups participate in inter-molecular H bonds

INTERMOLECULAR INTERACTIONS AND THE CONSEQUENCES

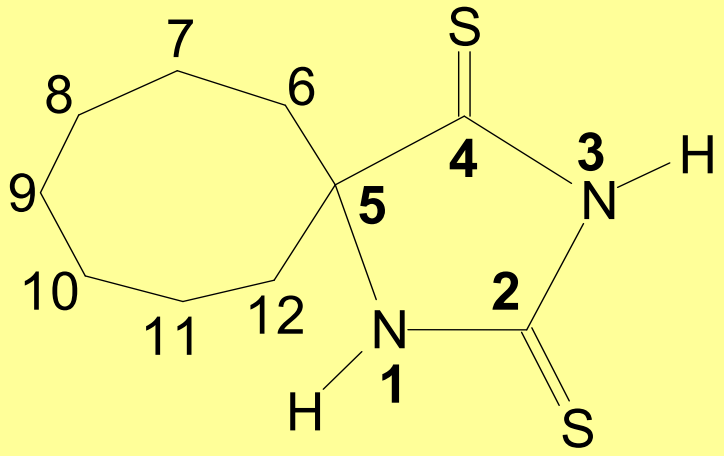
Expected stronger H bonds in the solid state than in solution
and

Elongation of the corresponding bonds
and

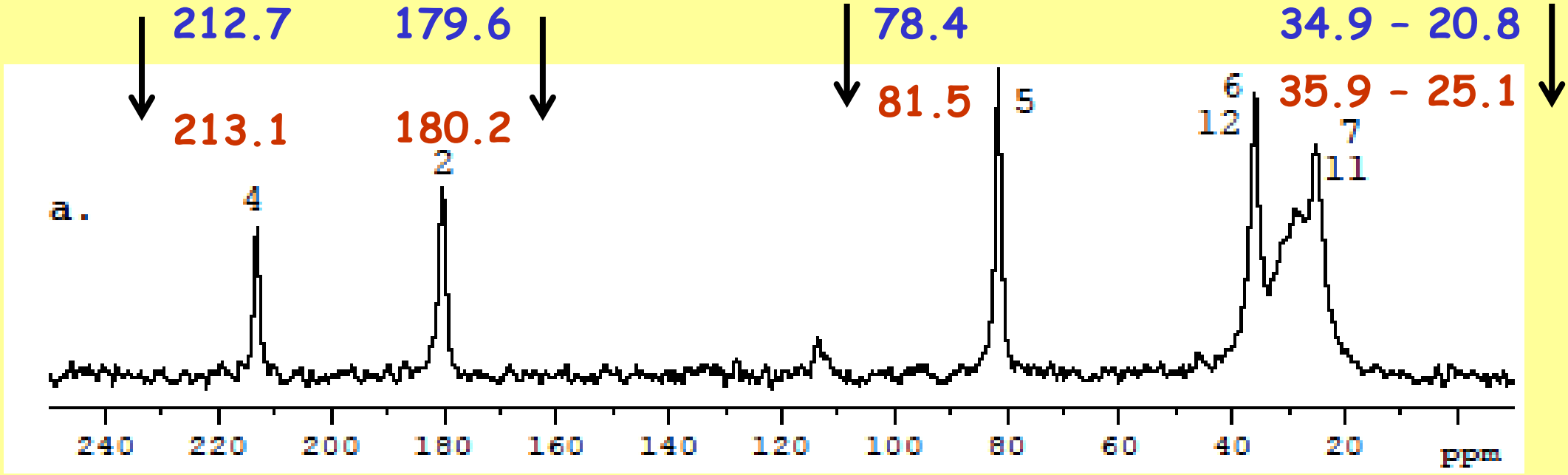
Less shielding of the corresponding C atoms

!!! Pay attention to the non-innocent role of the solvent

^{13}C NMR shifts in ppm in solid state and in DMSO



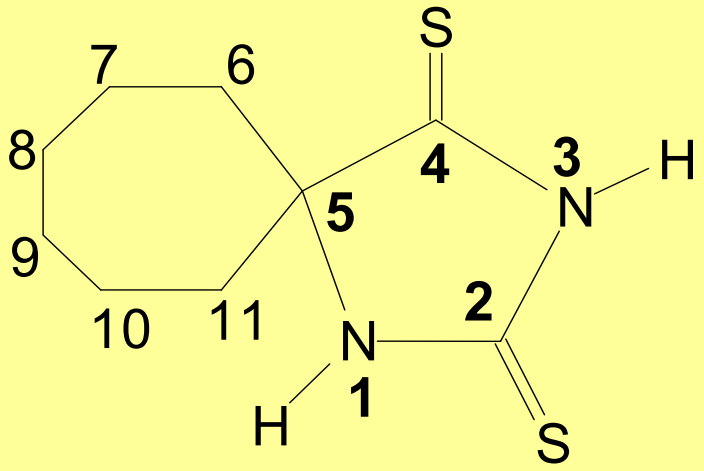
^{13}C NMR shifts in DMSO



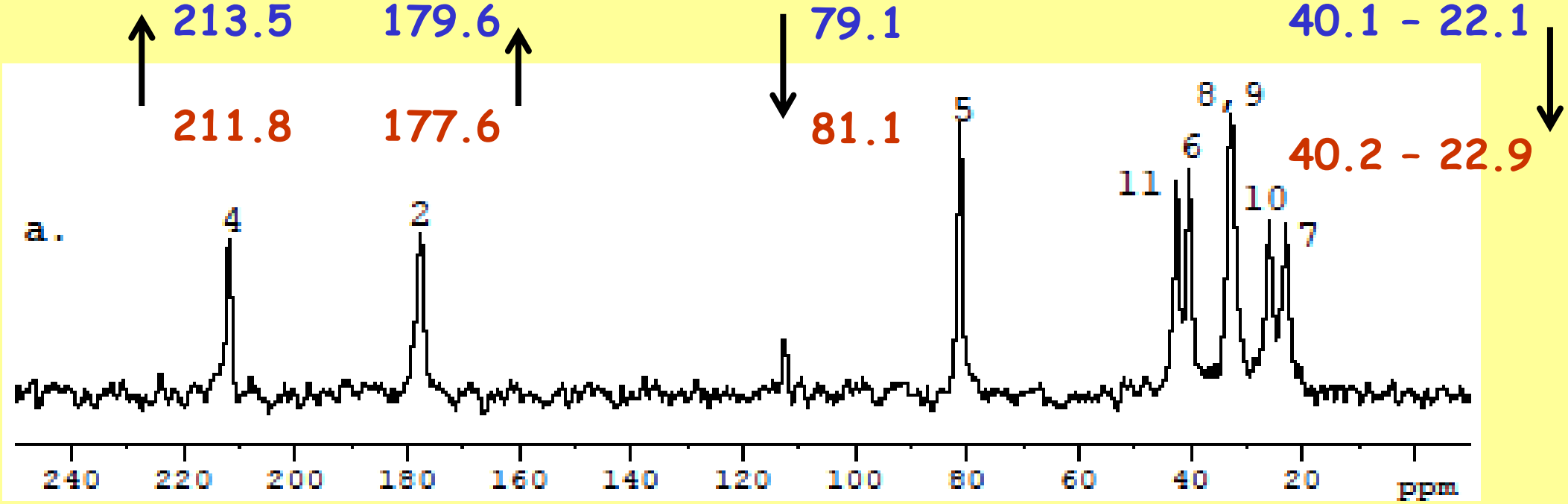
cy8

^{13}C CPMAS NMR spectrum

^{13}C NMR shifts in ppm in solid state and in DMSO



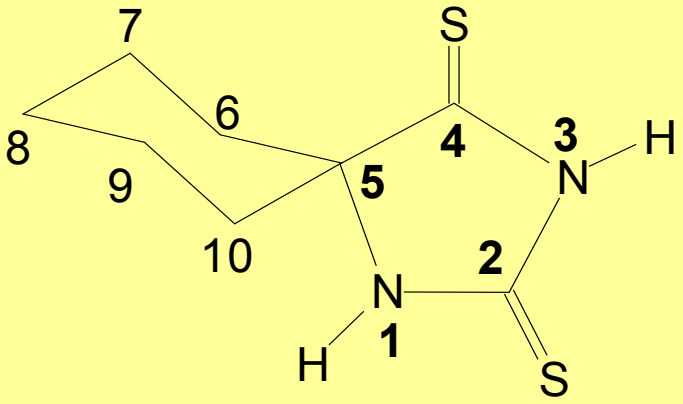
^{13}C NMR shifts in DMSO



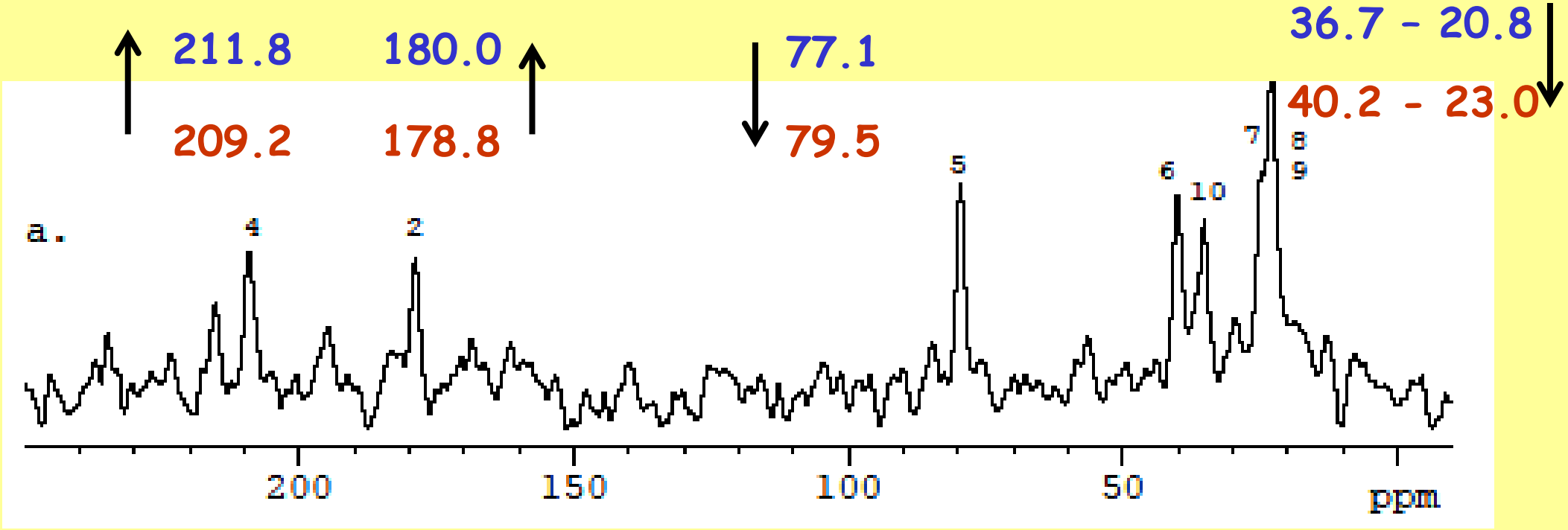
cy7

^{13}C CPMAS NMR spectrum

^{13}C NMR shifts in ppm in solid state and in DMSO



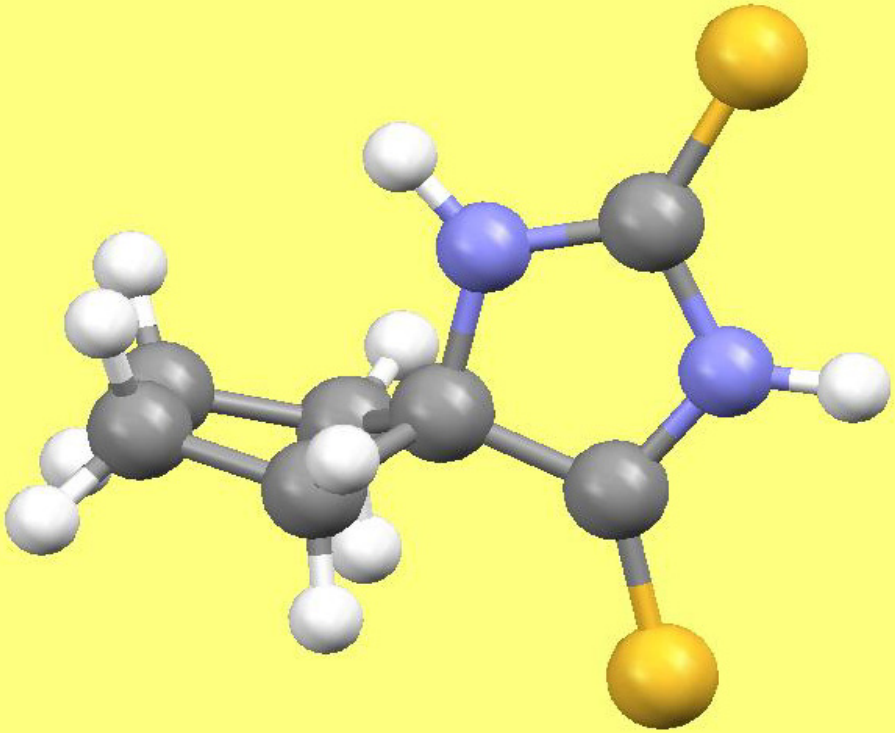
^{13}C NMR shifts in DMSO



cy6

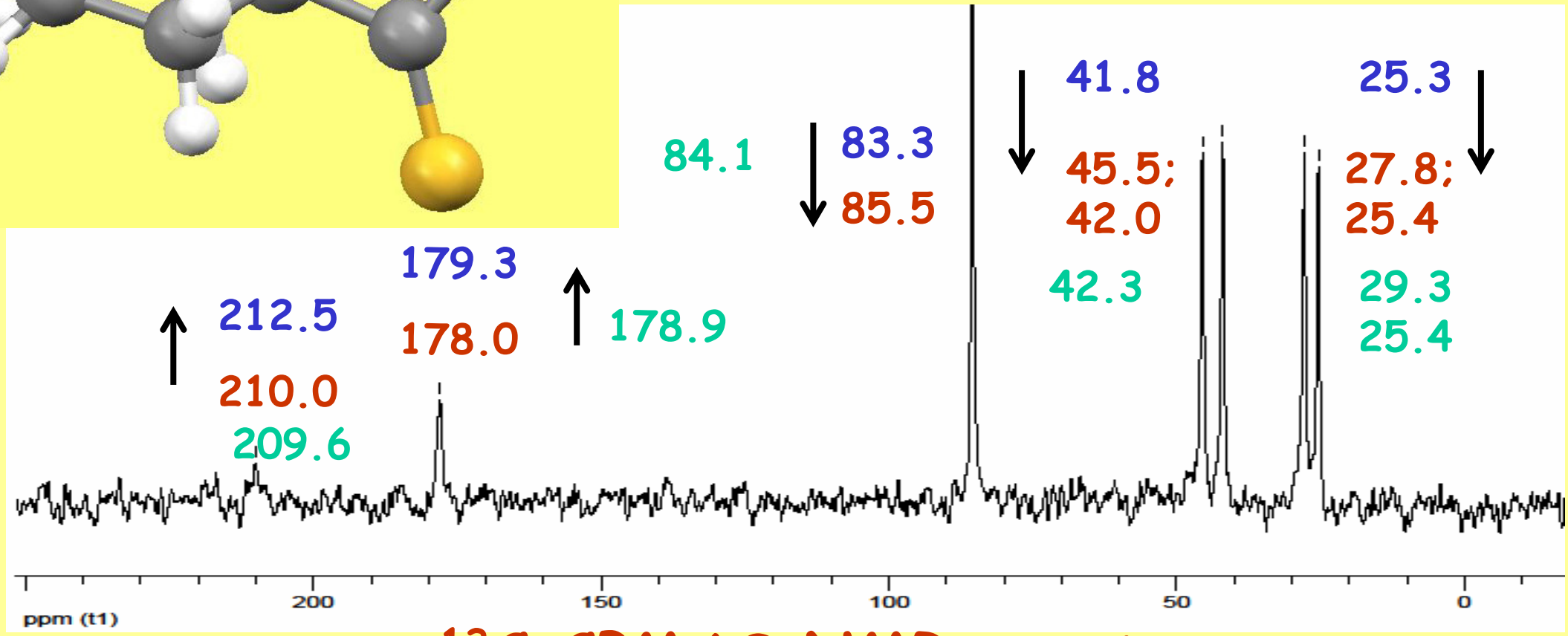
^{13}C CPMAS NMR spectrum

^{13}C NMR shifts in ppm in solid state and in DMSO



in $CDCl_3$

^{13}C NMR shifts in DMSO

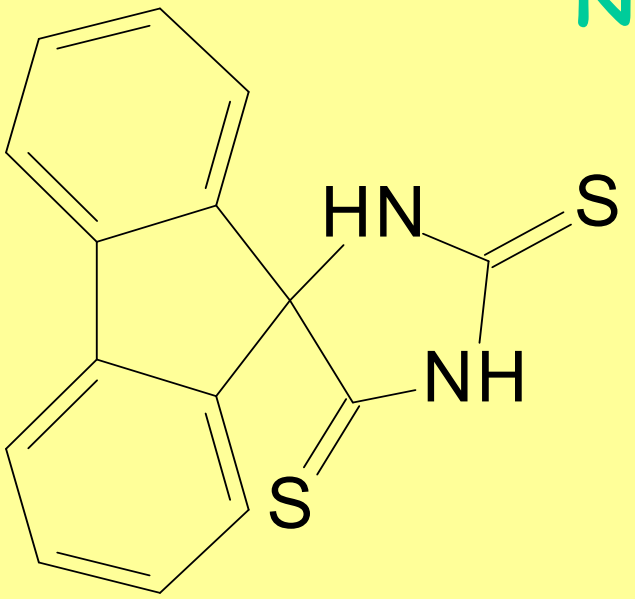


cy5

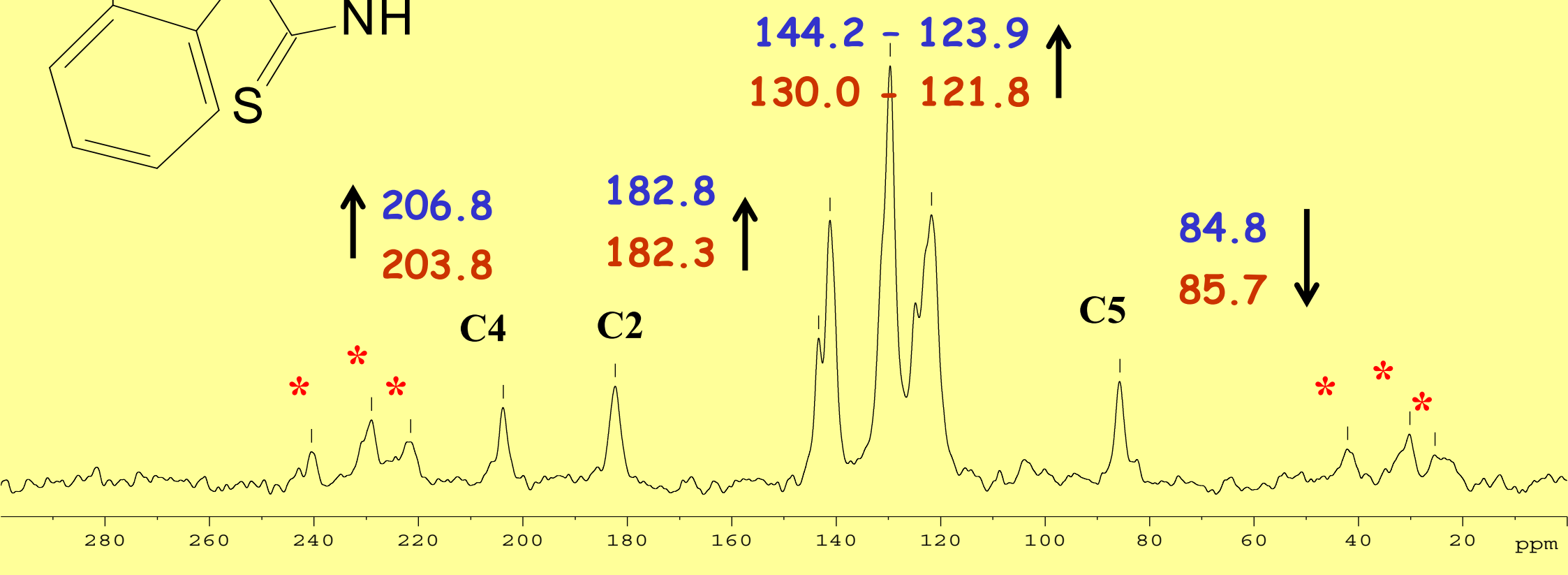
^{13}C CPMAS NMR spectrum

^{13}C NMR shifts in ppm in solid state and in DMSO

NO X-ray structure



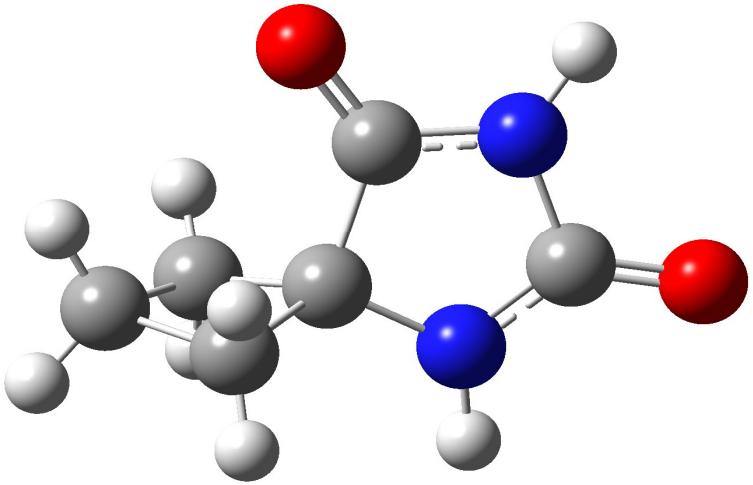
^{13}C NMR shifts in DMSO

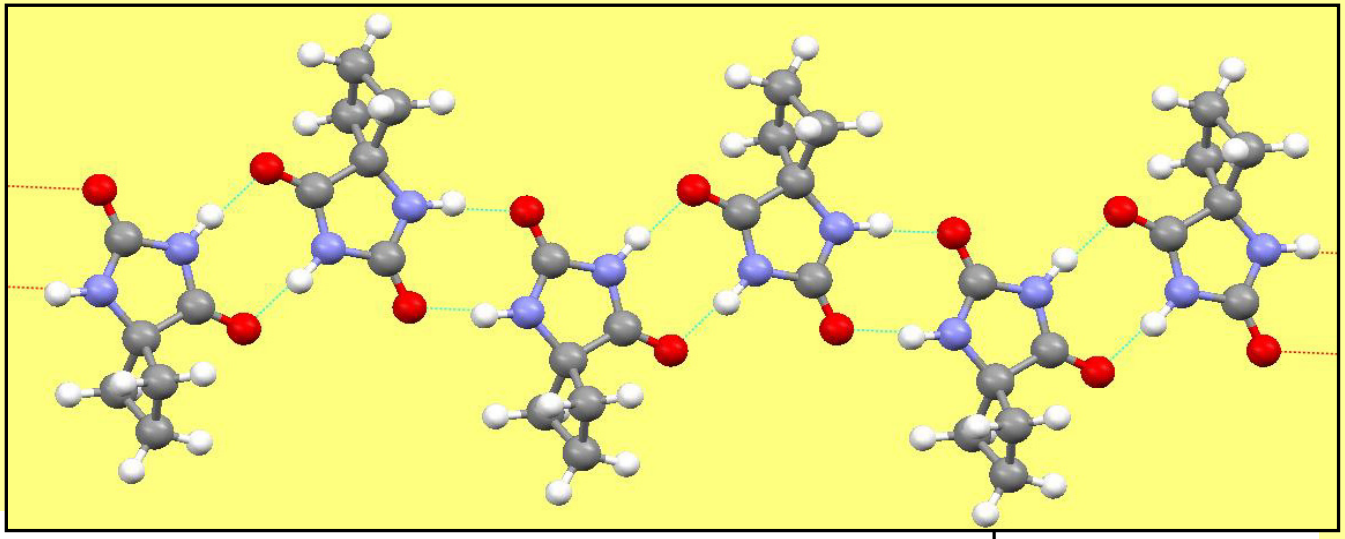


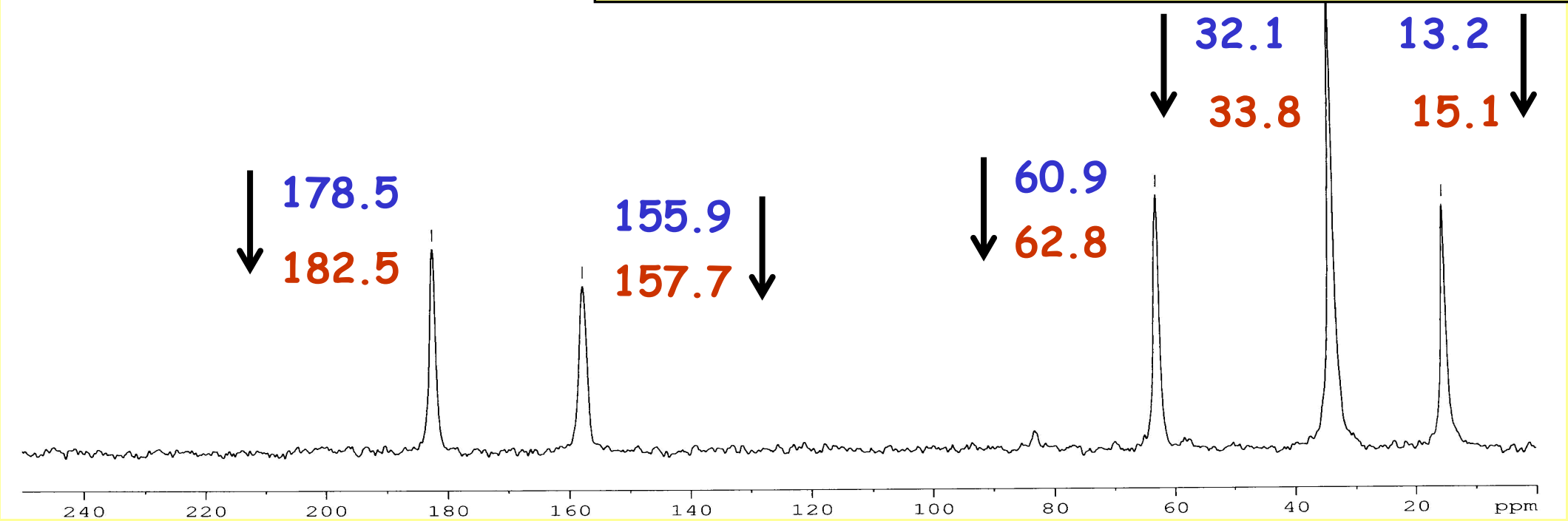
^{13}C CPMAS NMR spectrum

^{13}C NMR shifts in ppm in solid state and in DMSO

Powder diffraction data

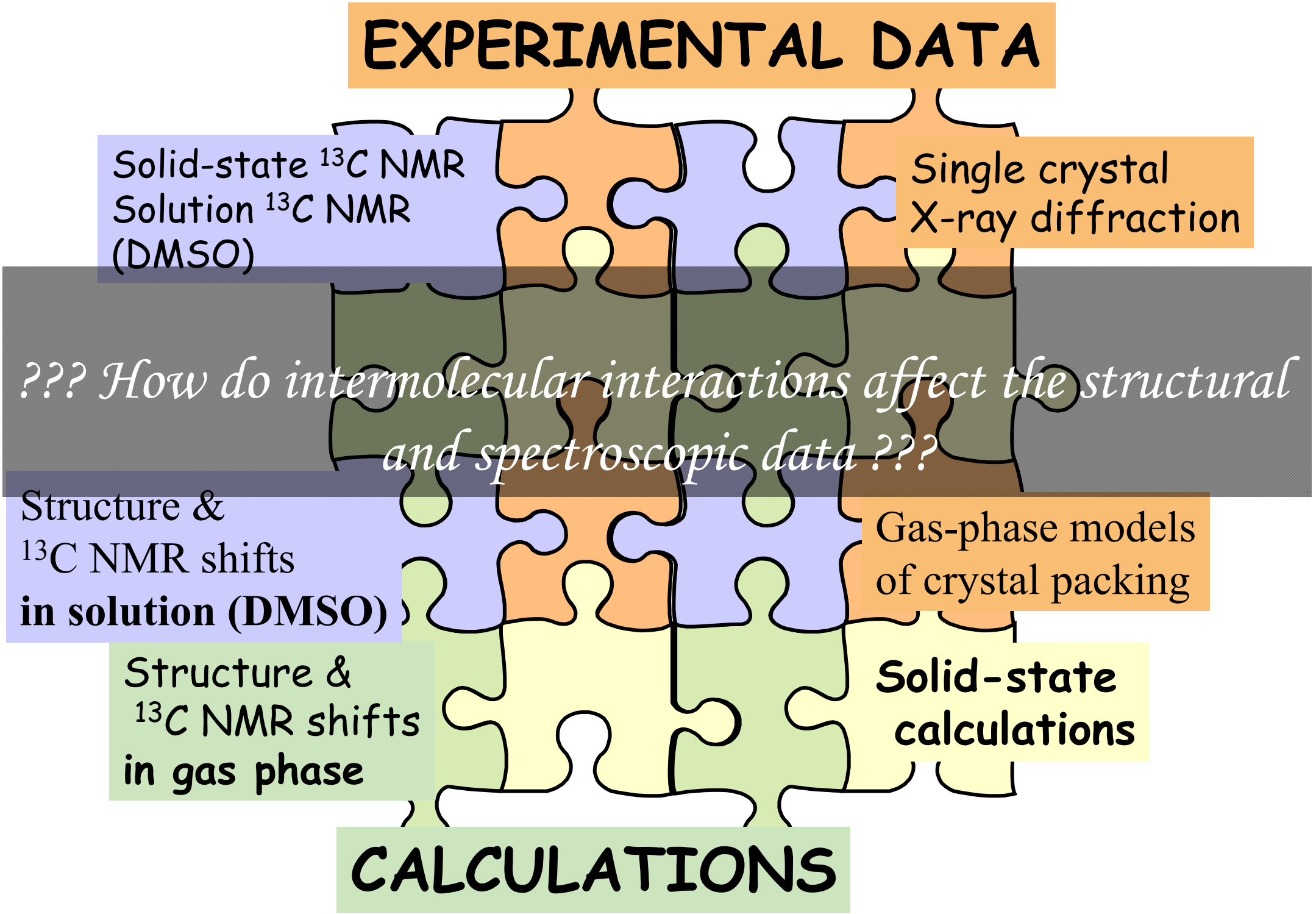






cy4

^{13}C CPMAS NMR spectrum


EXPERIMENTAL DATA
Solid-state ^{13}C NMR
Solution ^{13}C NMR
(DMSO)
Single crystal
X-ray diffraction
??? How do intermolecular interactions affect the structural and spectroscopic data ???
Structure &
^{13}C NMR shifts
in solution (DMSO)
Gas-phase models
of crystal packing
Structure &
^{13}C NMR shifts
in gas phase
Solid-state
calculations
CALCULATIONS

Compare **structural parameters** in the hydantoin ring

^{13}C NMR shifts of C2-, C4- and C5-carbon atoms

X-ray data *vs* **gas-phase optimizations** (B3LYP/6-31G**) of
isolated molecules and
trimers connected *via* intermolecular H bonding

^{13}C NMR in DMSO-d_6 and in solid state (CPMAS) *vs* calculated (GIAO-B3LYP/6-31G**) **shielding constants in gas phase** in DMSO media (IEF-PCM) or of the optimised trimers

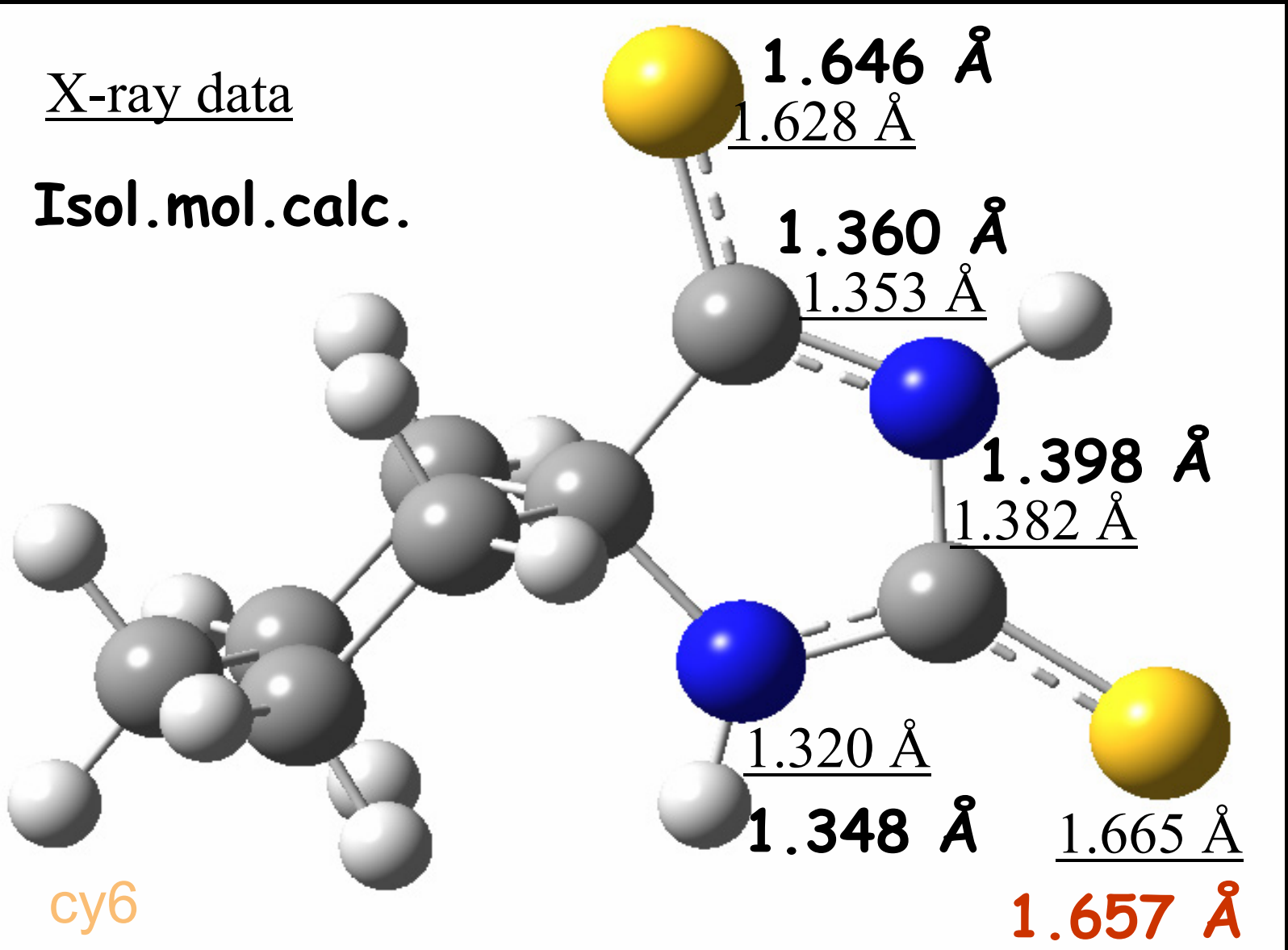
^{13}C NMR shifts

CPMAS: C5 – 79.5 ppm C4 – 209.2 ppm C2 – 178.8 ppm

GIAO-DFT: C5 - 78.1 ppm C4 - 207.0 ppm C2 - 175.0 ppm

X-ray data

Isol.mol.calc.



EXP in DMSO

C5 – 77.1 ppm

C4 – 211.8 ppm

C2 – 180.0 ppm

CALC in DMSO

C5 - 80.8 ppm

C4 - 212.0 ppm

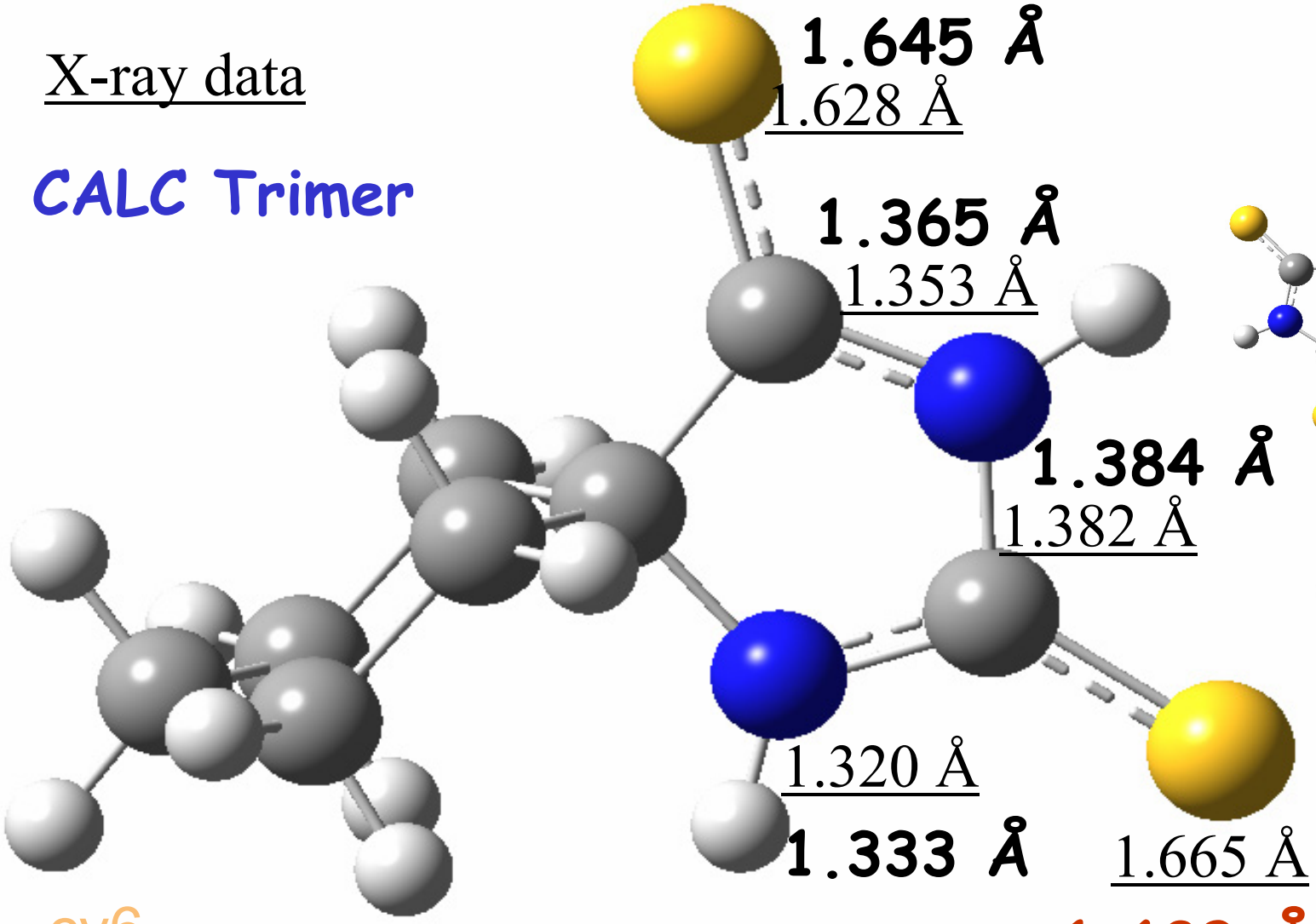
C2 - 176.6 ppm

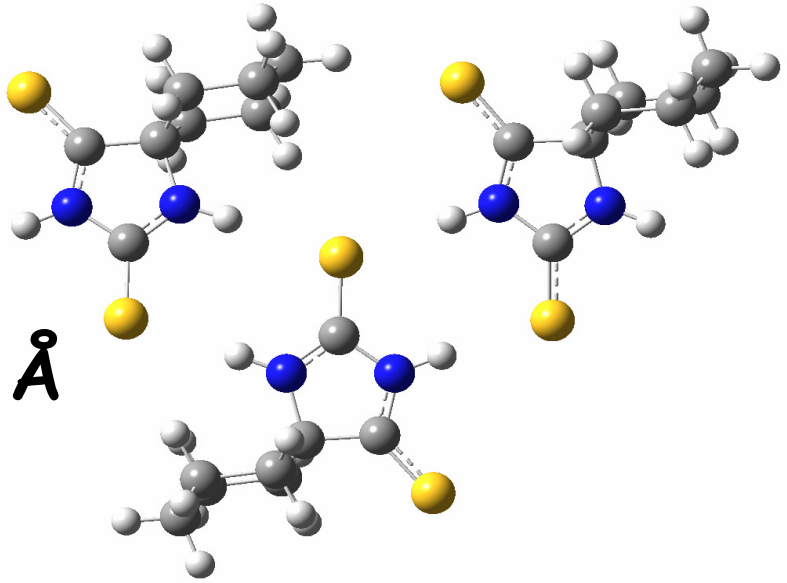
^{13}C NMR shifts

CPMAS:	C5 – 79.5 ppm	C4 – 209.2 ppm	C2 – 178.8 ppm
GIAO-DFT:	C5 - 80.1 ppm	C4 - 209.0 ppm	C2 - 177.2 ppm

X-ray data

CALC Trimer





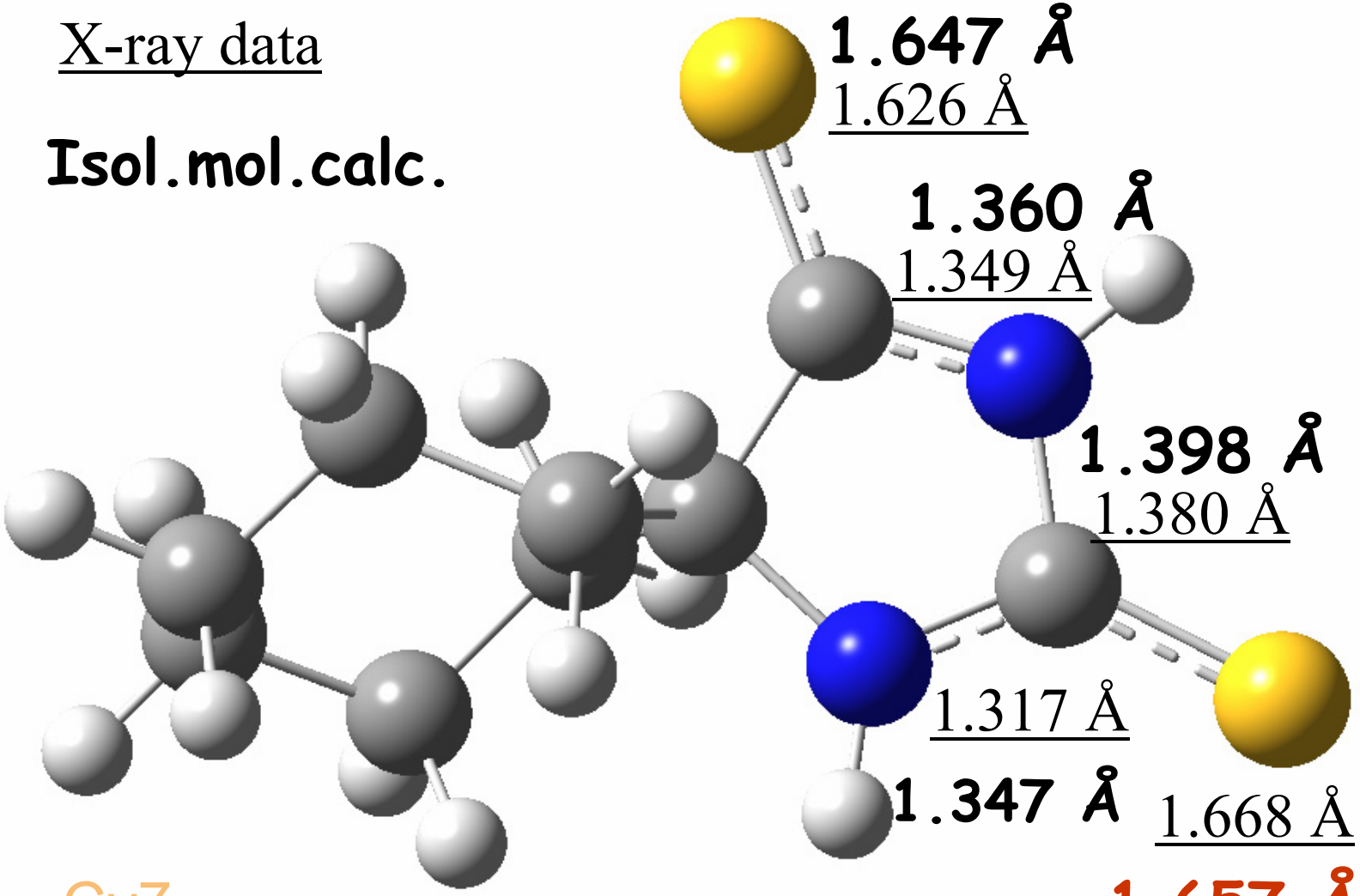
cy6

^{13}C NMR shifts

CPMAS:	C5 – 81.1 ppm	C4 – 211.8 ppm	C2 – 177.6 ppm
GIAO-DFT:	**C5 - 79.8 ppm**	**C4 - 209.2 ppm**	**C2 - 174.2 ppm**

X-ray data

Isol.mol.calc.



Cy7

EXP in DMSO

C5 – 79.1 ppm

C4 – 213.5 ppm

C2 – 179.6 ppm

CALC in DMSO

C5 - 82.6 ppm

C4 - 214.0 ppm

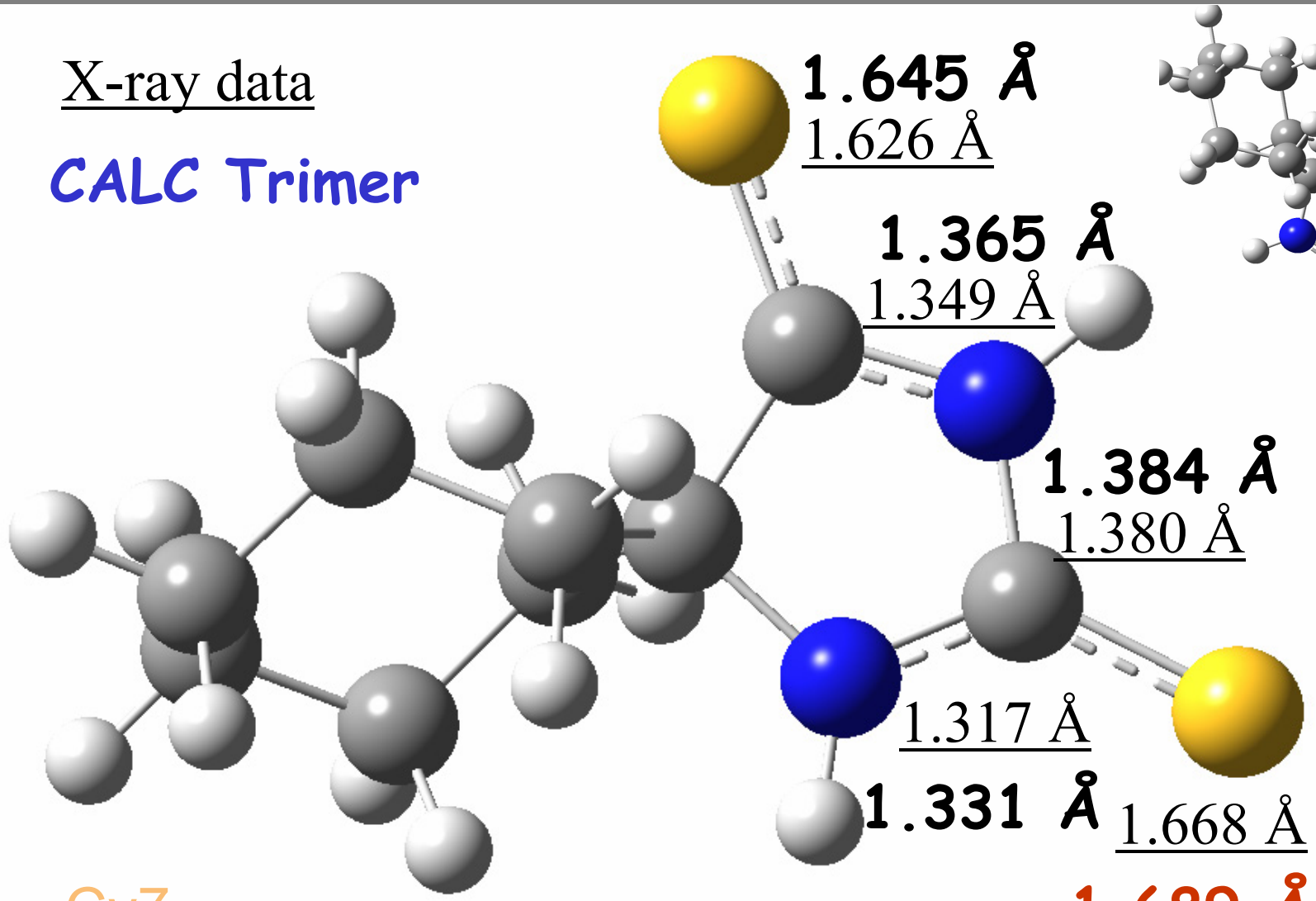
C2 - 175.8 ppm

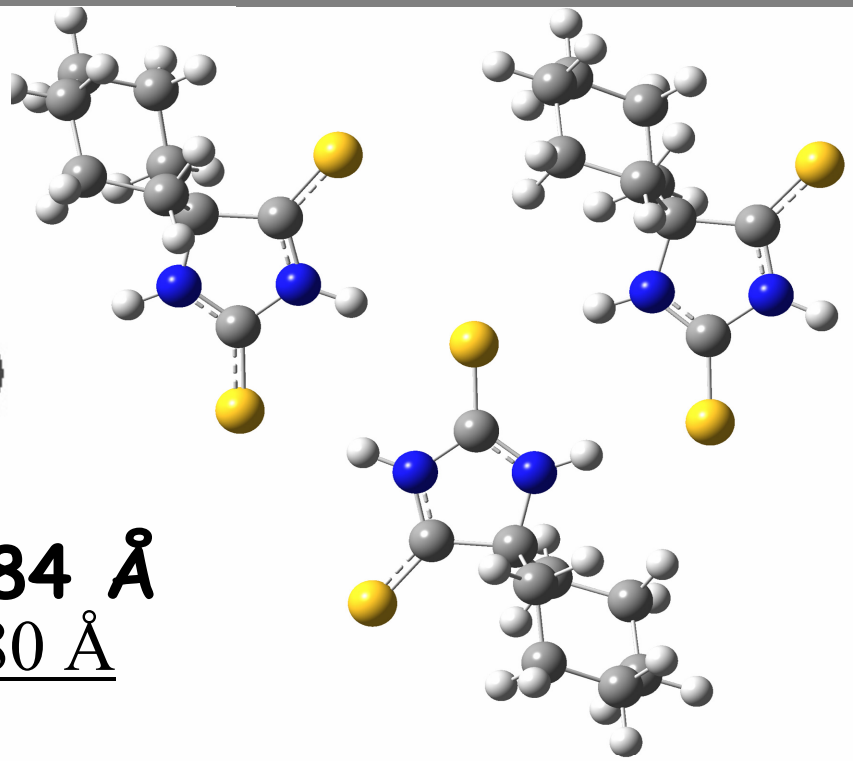
^{13}C NMR shifts

CPMAS:	C5 – 81.1 ppm	C4 – 211.8 ppm	C2 – 177.6 ppm
GIAO-DFT:	C5 - 81.2 ppm	C4 - 211.1 ppm	C2 - 176.0 ppm

X-ray data

CALC Trimer





Cy7

3D Calculations ☺

Calculation of periodic structures with DFT

Use of plane waves and ultrasoft pseudopotentials
(GGA PBE functional)

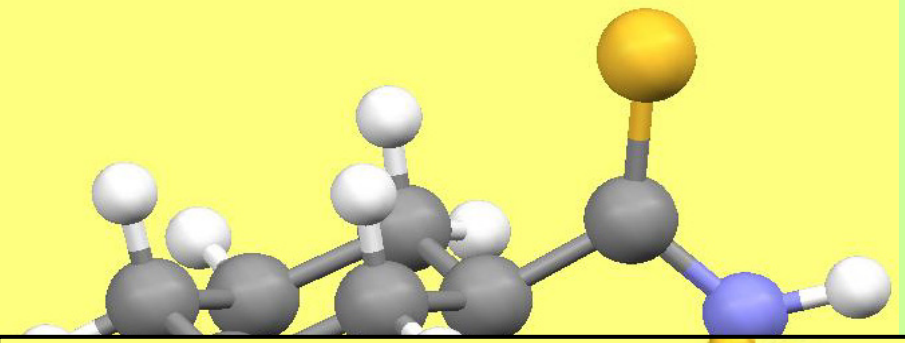
Calculations were performed in the three main groups:

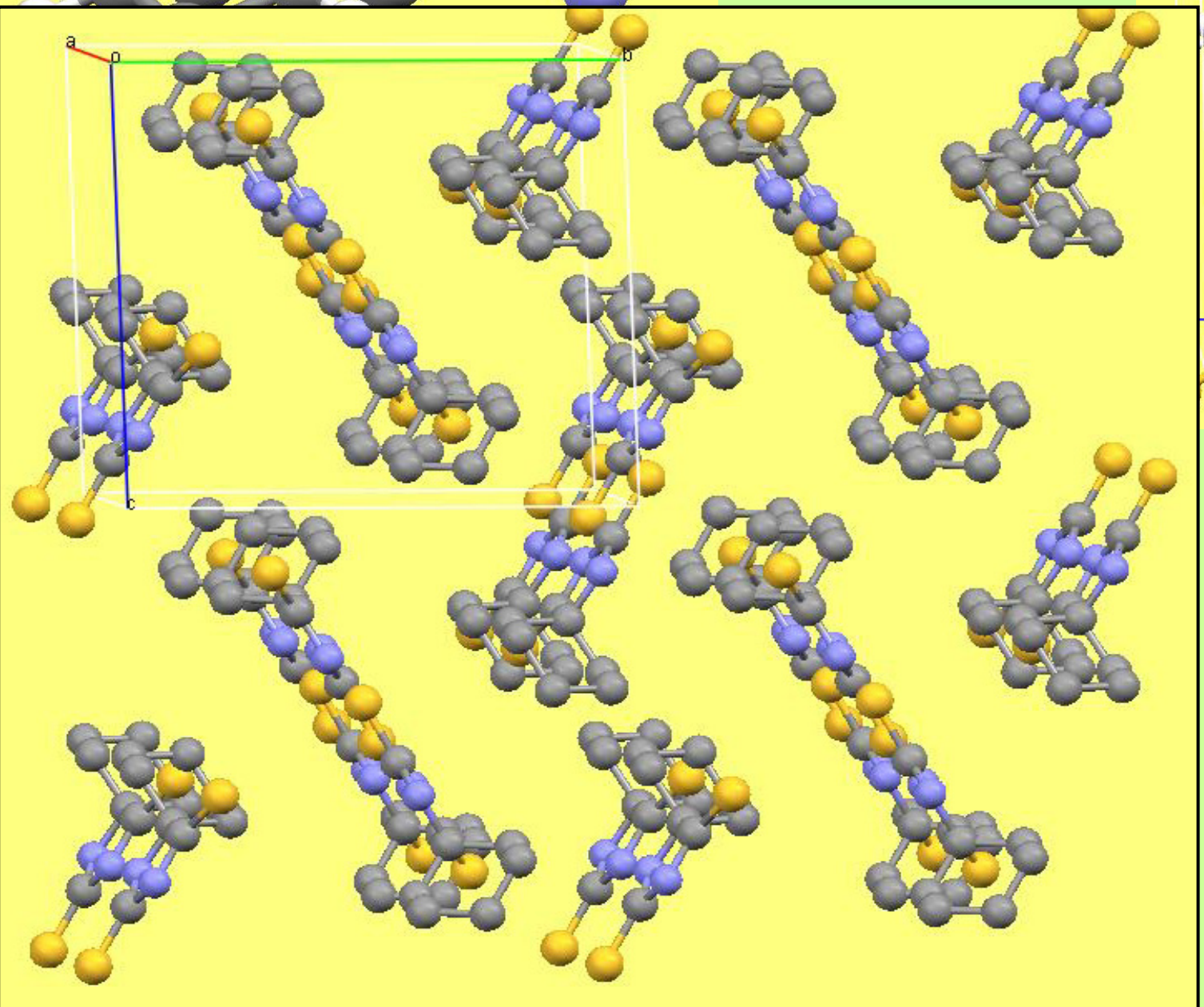
- **for isolated molecules**
- **for layers**
- **for bulk materials**

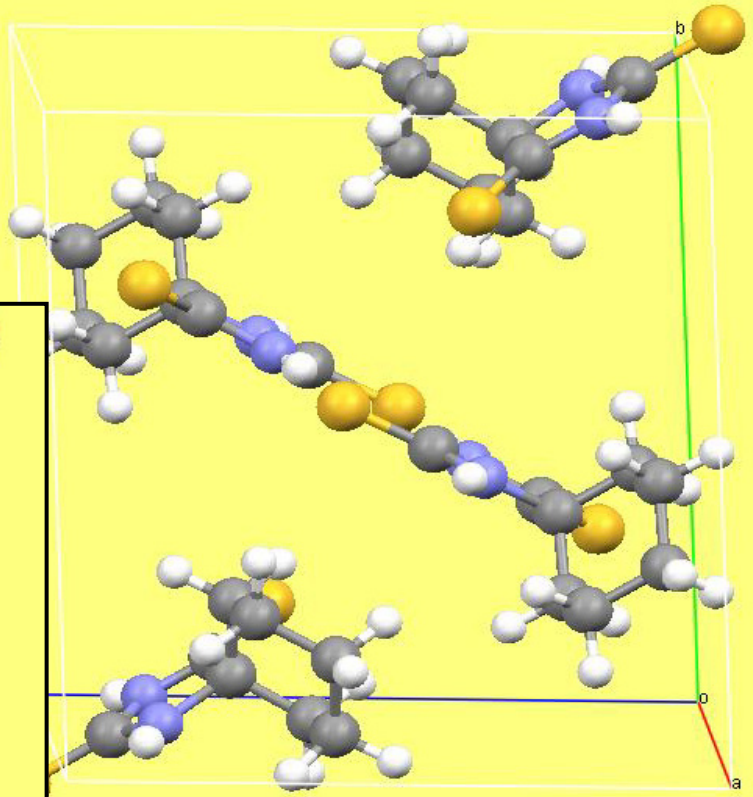
The relaxed structures were used for the calculations of the nuclear magnetic resonance (NMR) chemical shifts of ^{13}C nuclei *via* the GIPAW method (gauge-including projector augmented wave)

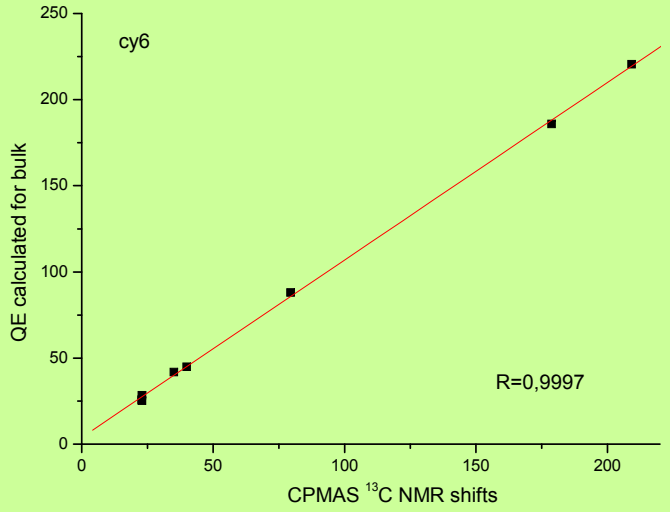
The energies of the interaction between the molecules in the bulk E_{mb} per one molecule were calculated using the following equation:

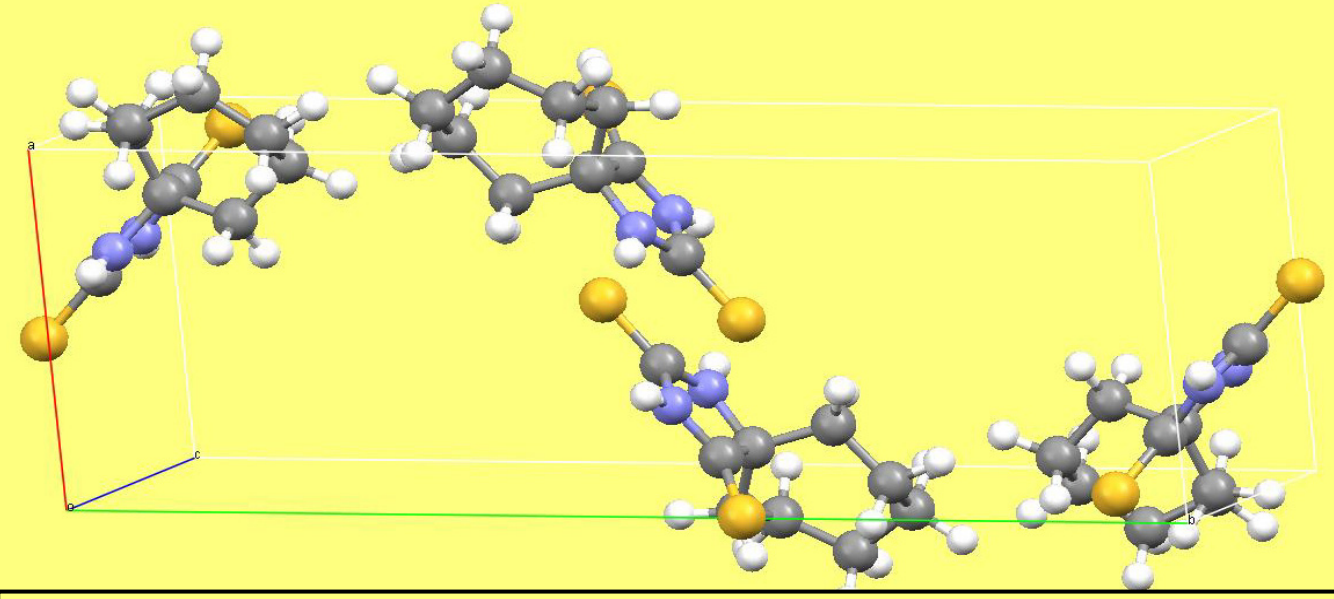
$$E_{mb}=(E_{bulk}-N_b.E_{mol})/N_b$$

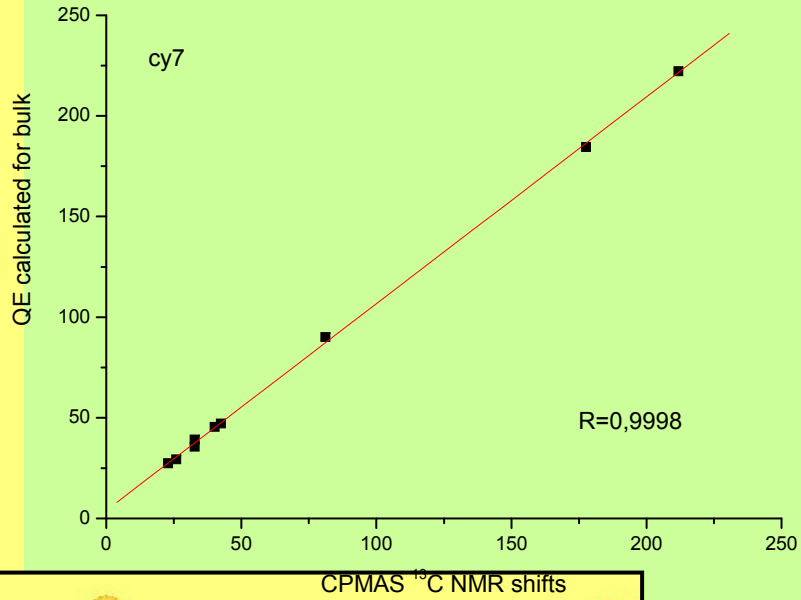


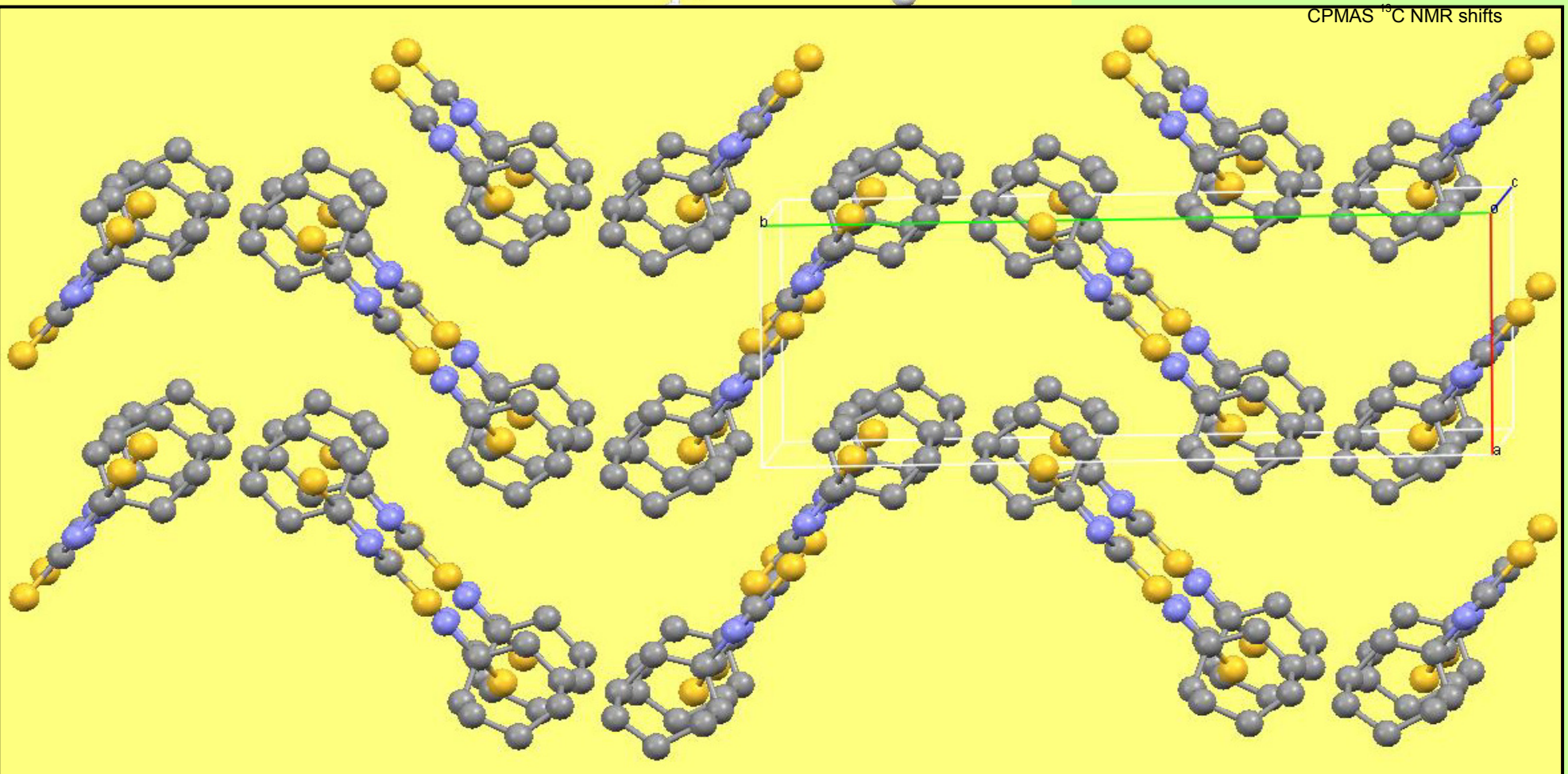

a
o
b
c


b
o
a

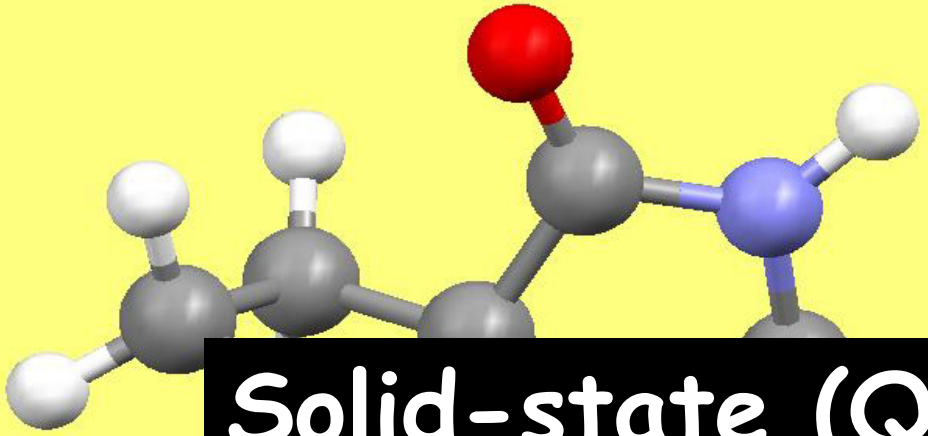

cy6
QE calculated for bulk
CPMAS ^{13}C NMR shifts
R=0,9997
0
50
100
150
200
250

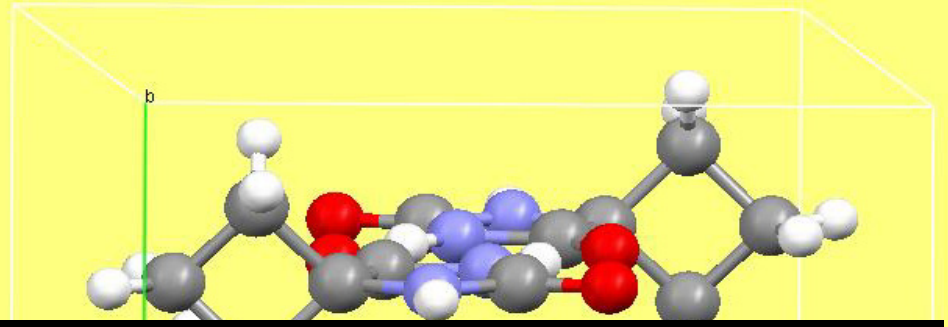

a
c
b


cy7
QE calculated for bulk
CPMAS ^{13}C NMR shifts
R=0,9998
0
50
100
150
200
250

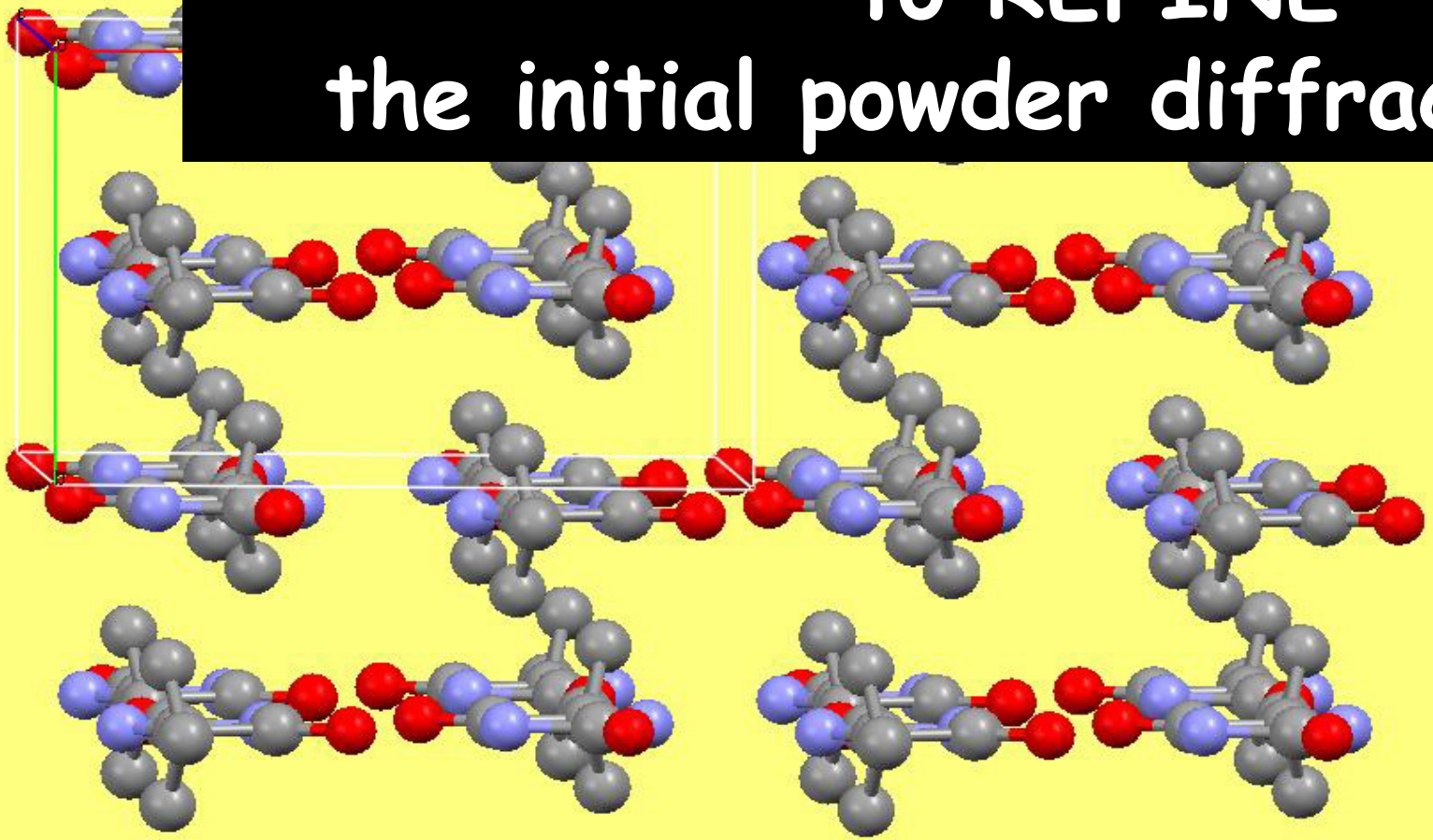

b
c
a

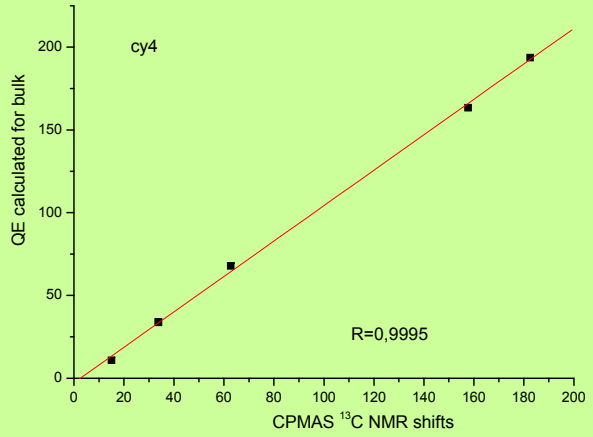
NO single-crystal X-ray structure available

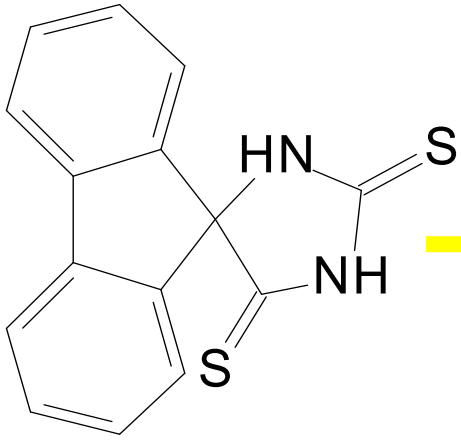




Solid-state (QE) calculations were used to REFINE the initial powder diffraction data

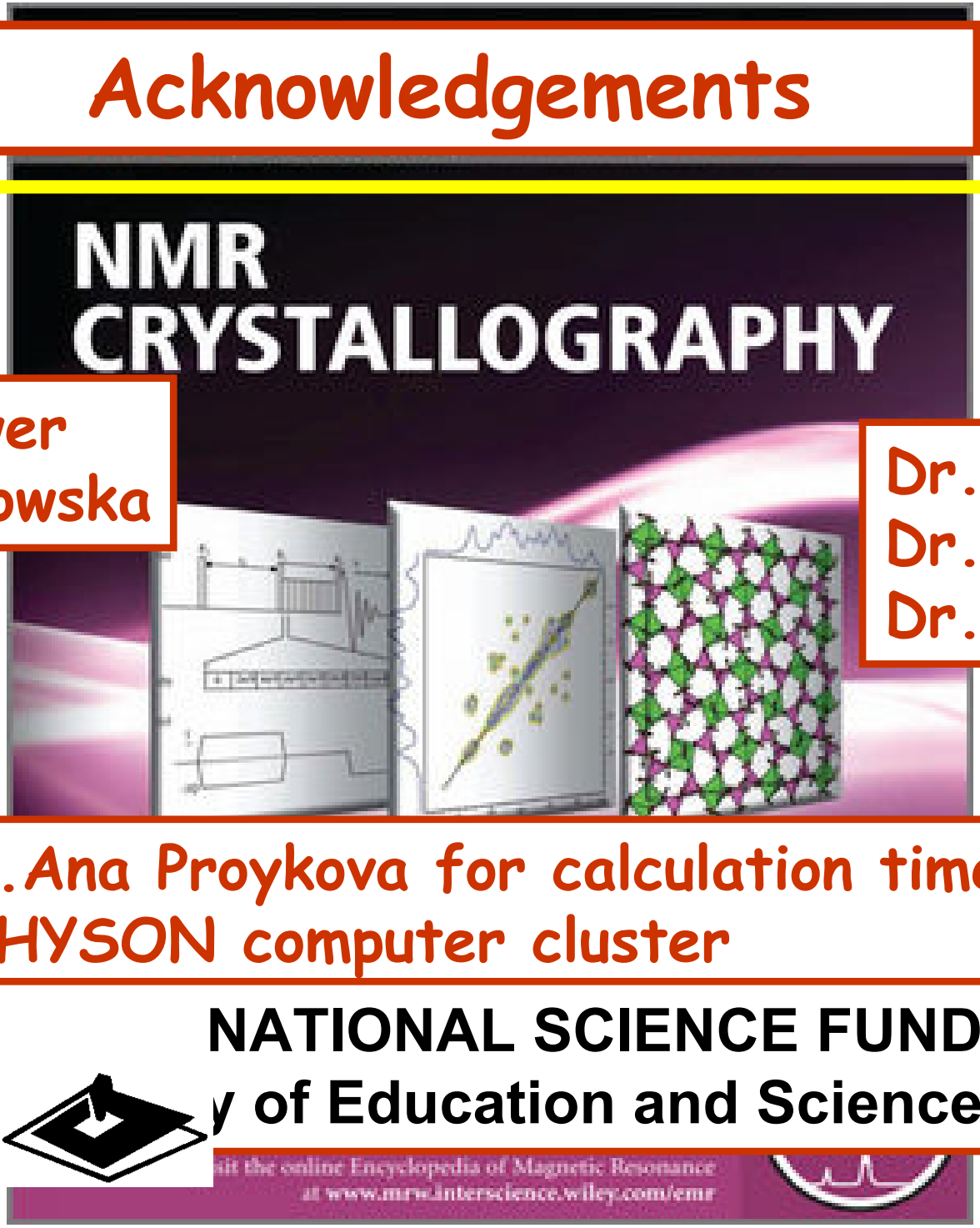






Acknowledgements

Get the solid-state structure



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