



From crystals to amorphous materials: Pair distribution function, modelling and solid state NMR

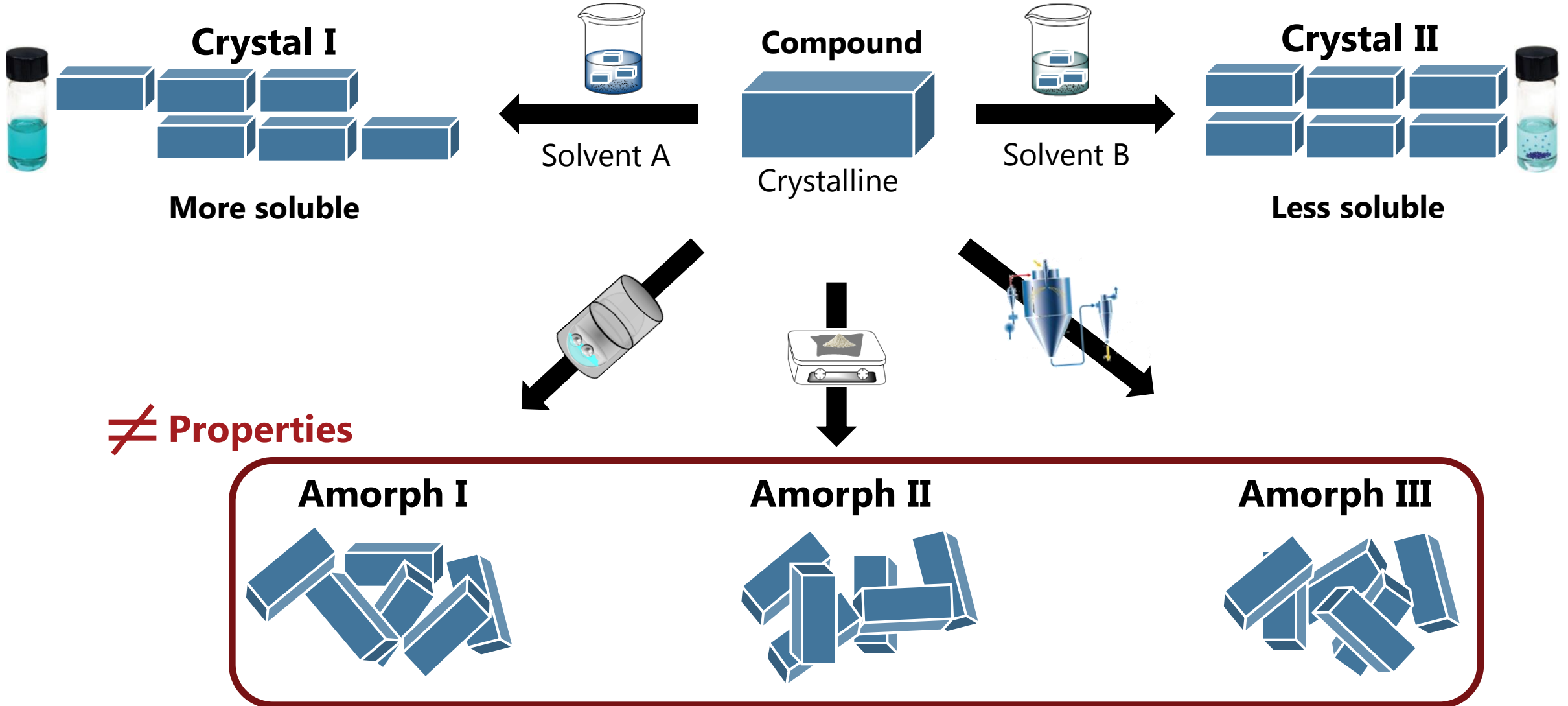
Inês C. B. Martins, Department of Pharmacy,
14/06/2022

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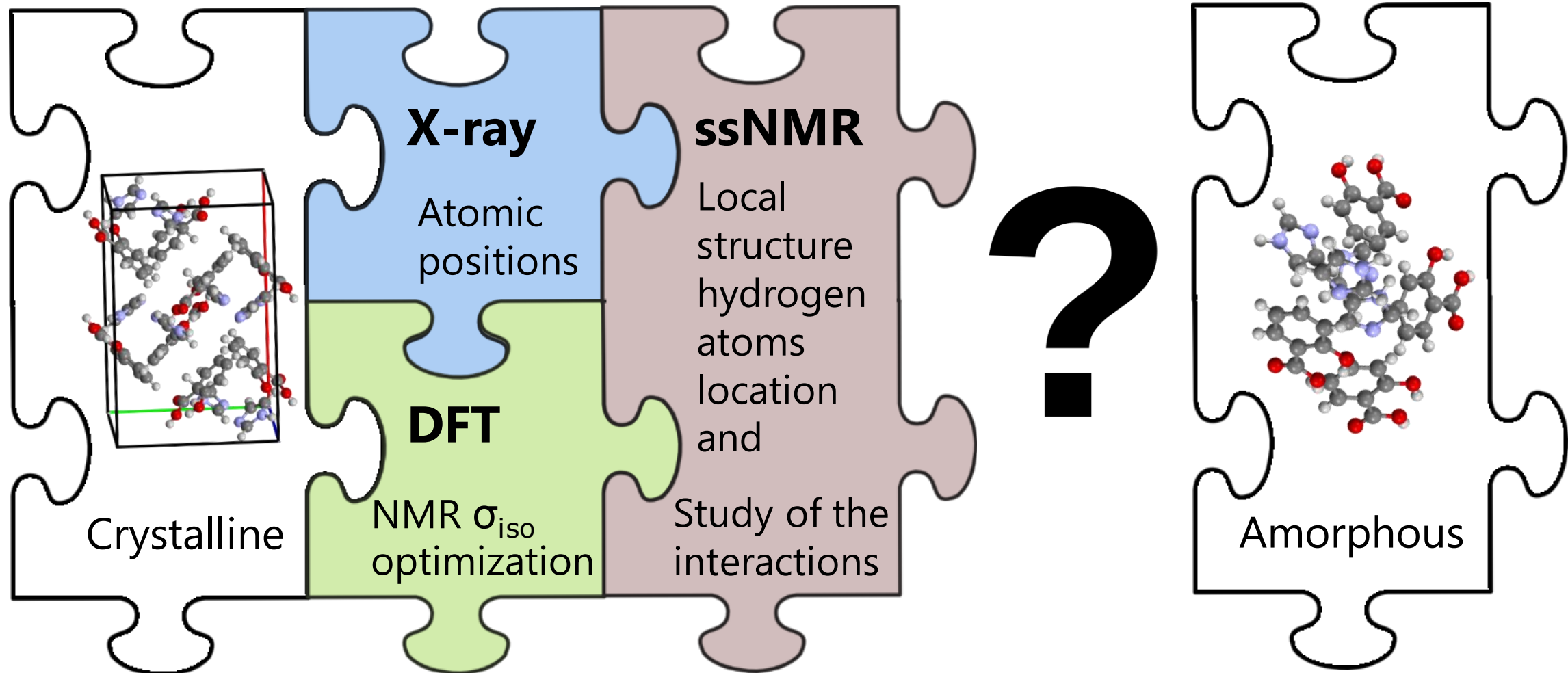
UNIVERSITY OF COPENHAGEN



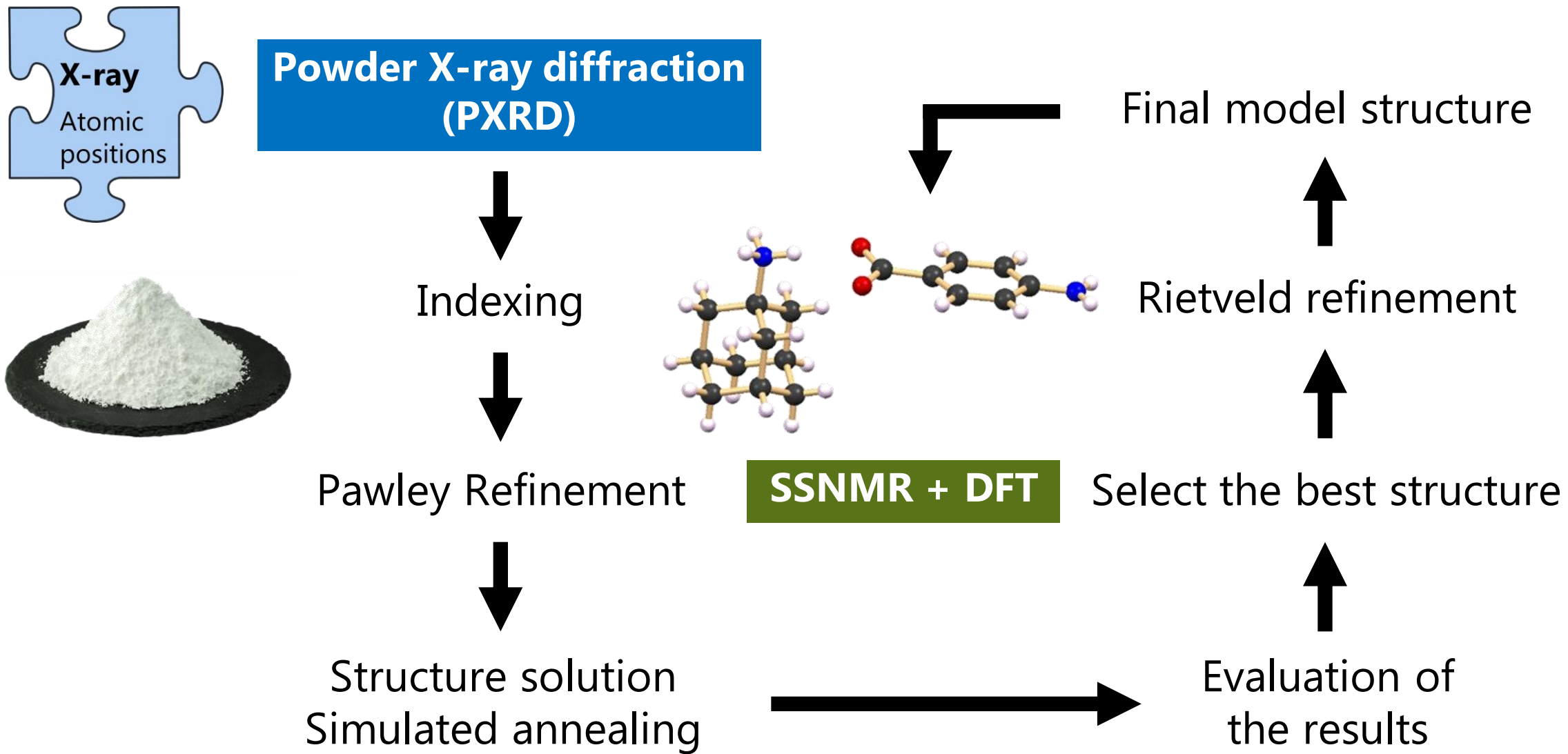
Crystalline or amorphous materials? Understanding their importance



Structure solution: the jigsaw puzzle



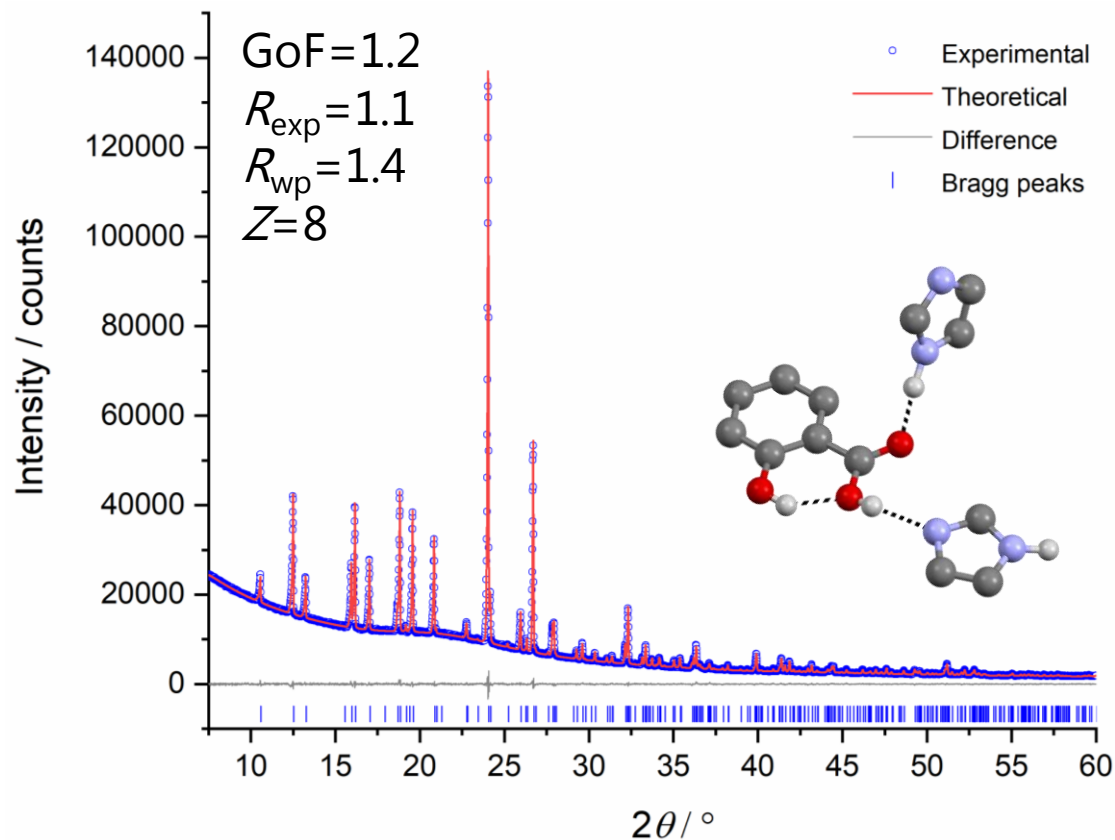
Powder X-ray diffraction (PXRD)



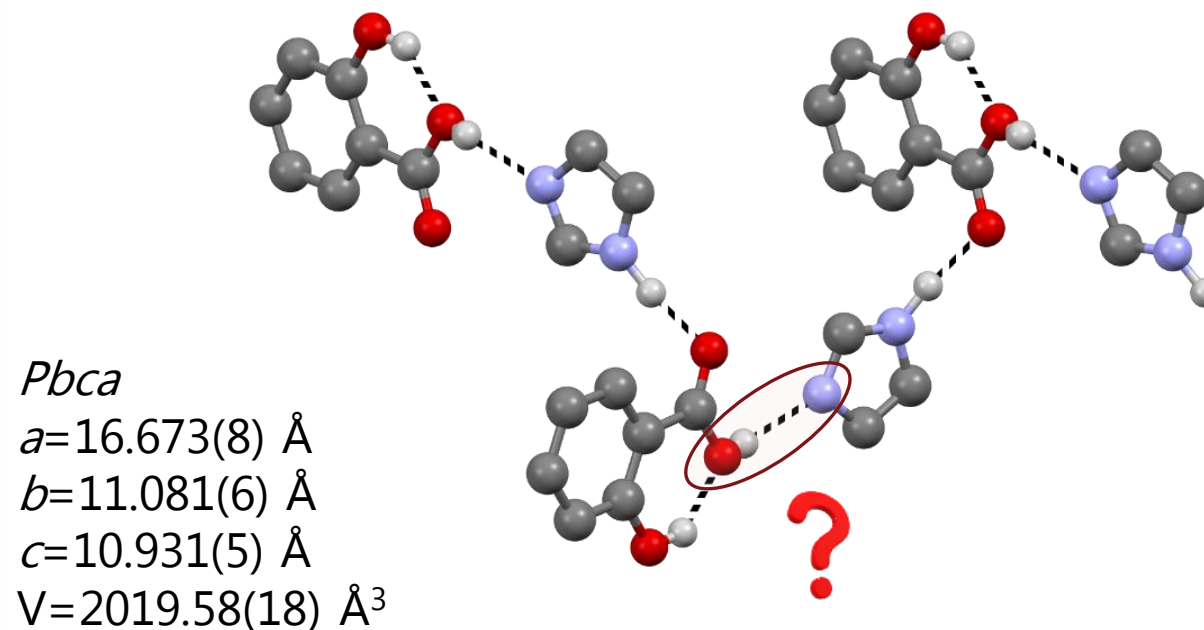
Structure solution by PXRD

Salicylic acid with imidazolium

Rietveld refinement



Crystal structure

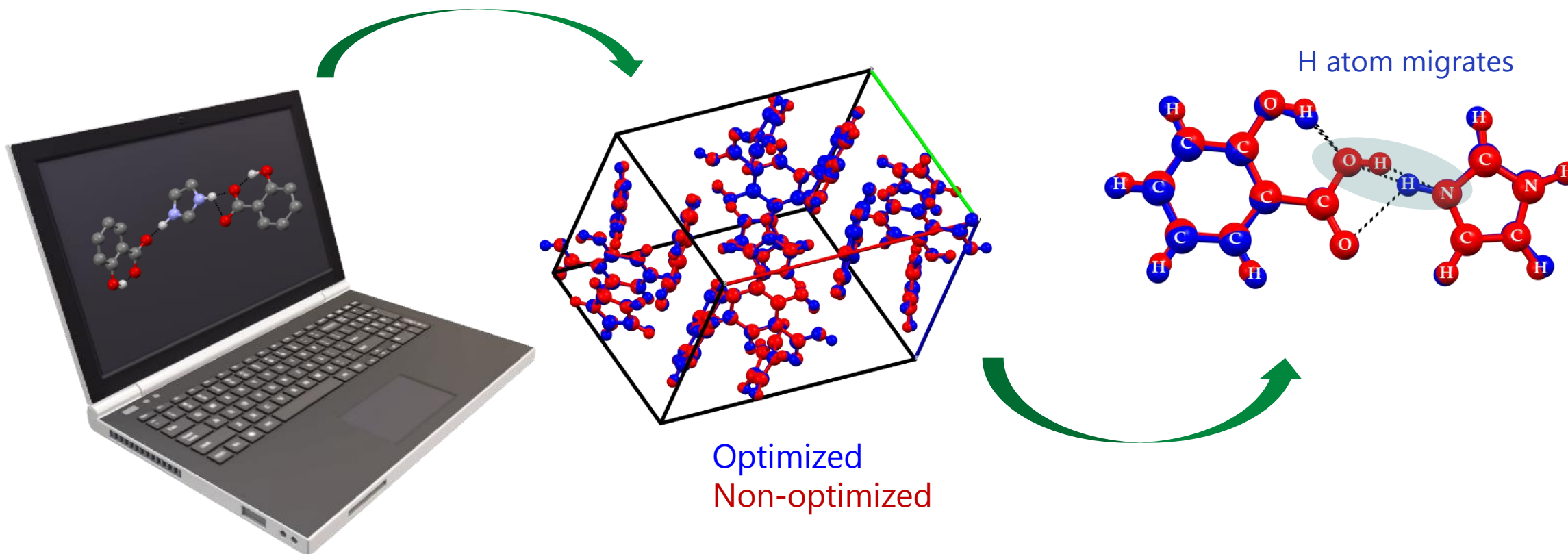
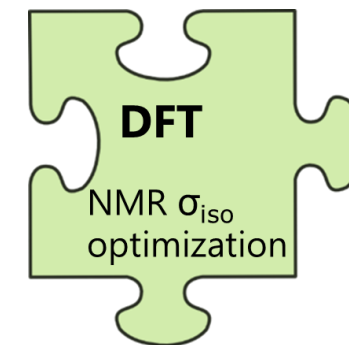


Co-crystal or salt?

Density functional theory (DFT) calculations

Salicylic acid with imidazolium

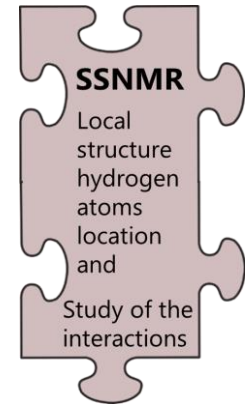
Quantum Espresso



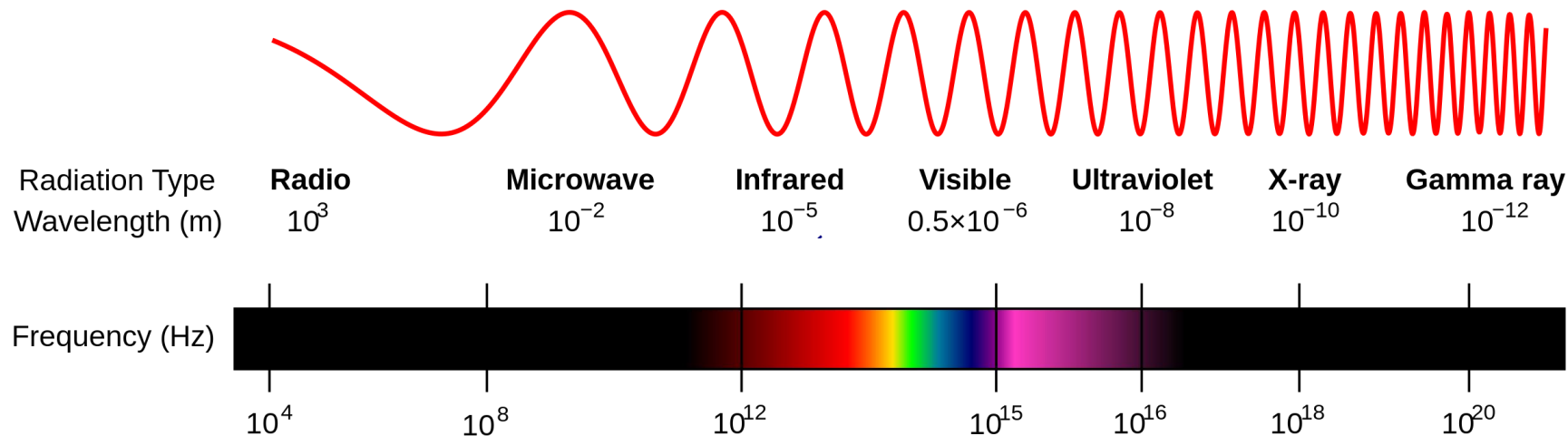
Nuclear magnetic resonance (NMR)

Principle of the NMR

The **nucleus** of an atom placed in a magnetic field and exposed to **electromagnetic radiation** resonates at a **specific frequency of that radiation**



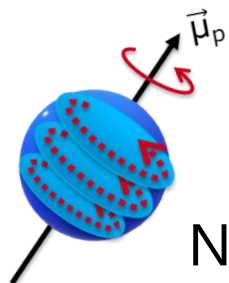
The electromagnetic spectrum



← NMR uses **Radio frequency (RF)** radiation

Nuclear magnetic resonance (NMR)

Nuclei properties



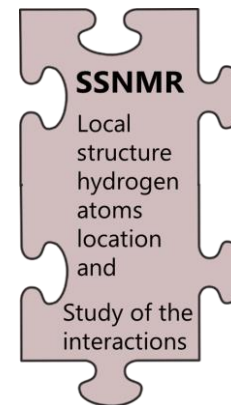
Nuclei with...

an **ODD** number of **protons**

AND/OR

an **ODD** number of **neutrons**

Have a property called **spin**



^1H

1 proton
0 neutrons
Spin



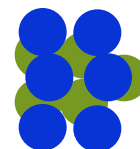
^2H (D)

1 proton
1 neutron
Spin



^4He

2 protons
2 neutrons
No spin



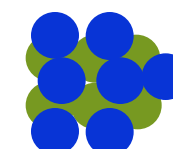
^{11}B

5 protons
6 neutrons
Spin



^{12}C

6 protons
6 neutrons
No spin



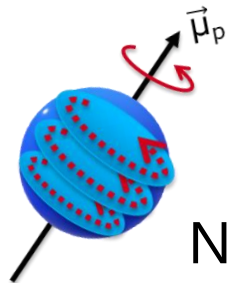
^{13}C

6 protons
7 neutrons
Spin

Nuclear magnetic resonance (NMR)

Nuclei properties

Spin has a **value** (I), which can either be an **integer** or a **half-integer**



Nuclei with...

an **ODD** number of **protons**

AND

an **ODD** number of **neutrons**

Have **integer** spins

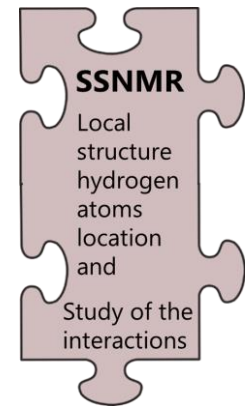
There are **only a handful** of **integer-spin** nuclei:

$${}^2\text{H} = 1$$

$${}^6\text{Li} = 1$$

$${}^{10}\text{B} = 3$$

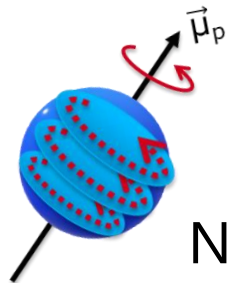
$${}^{14}\text{N} = 1$$



Nuclear magnetic resonance (NMR)

Nuclei properties

Spin has a **value** (I), which can either be an integer or a half-integer



Nuclei with...

an **ODD** number of **protons**

OR

an **ODD** number of **neutrons**

Have **half-integer** spins

There are **many half-integer-spin** nuclei, some examples:

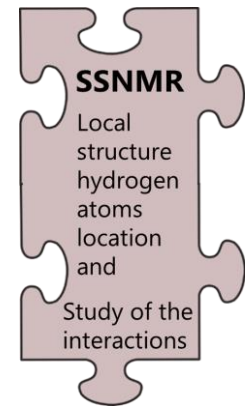
$${}^1\text{H} = 1/2$$

$${}^{13}\text{C} = 1/2$$

$${}^{15}\text{N} = 1/2$$

$${}^{19}\text{F} = 1/2$$

$${}^{31}\text{P} = 1/2$$

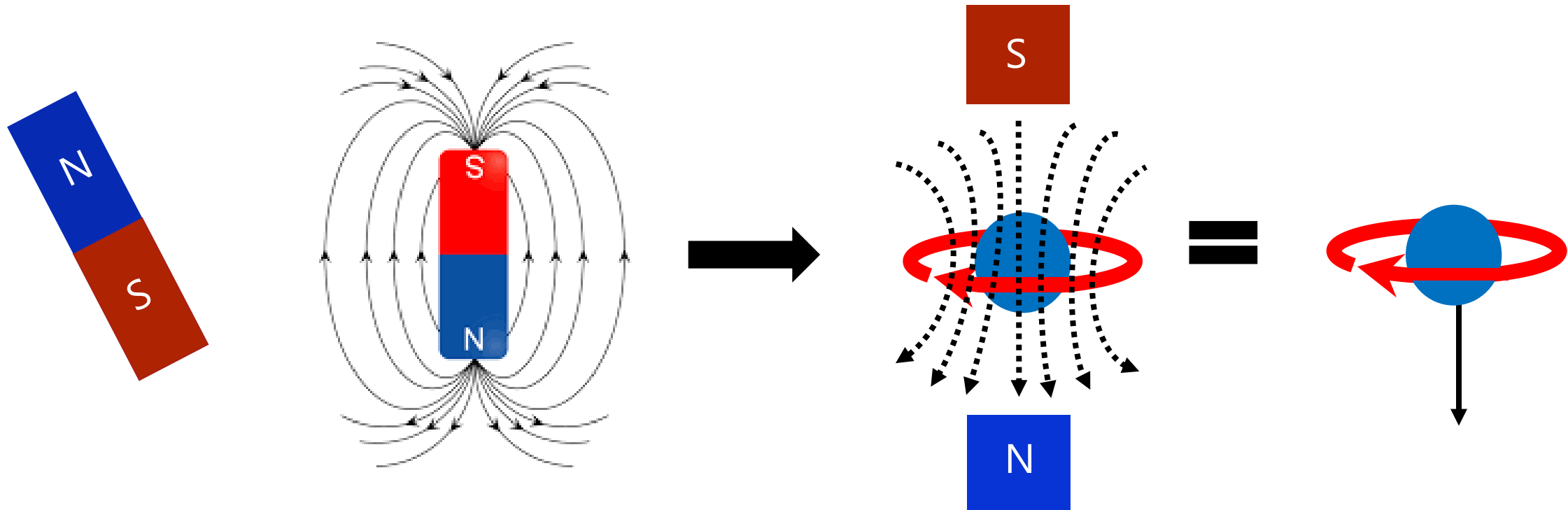
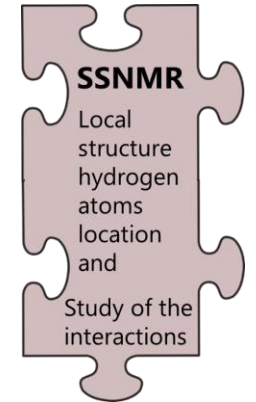


Nuclear magnetic resonance (NMR)

Nuclei properties

Nuclei are **charged particles** (**protons** are **positively charged**)

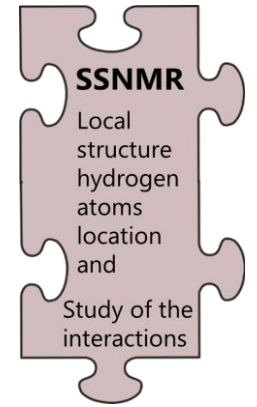
Electric charges in movement generate a **magnetic field**



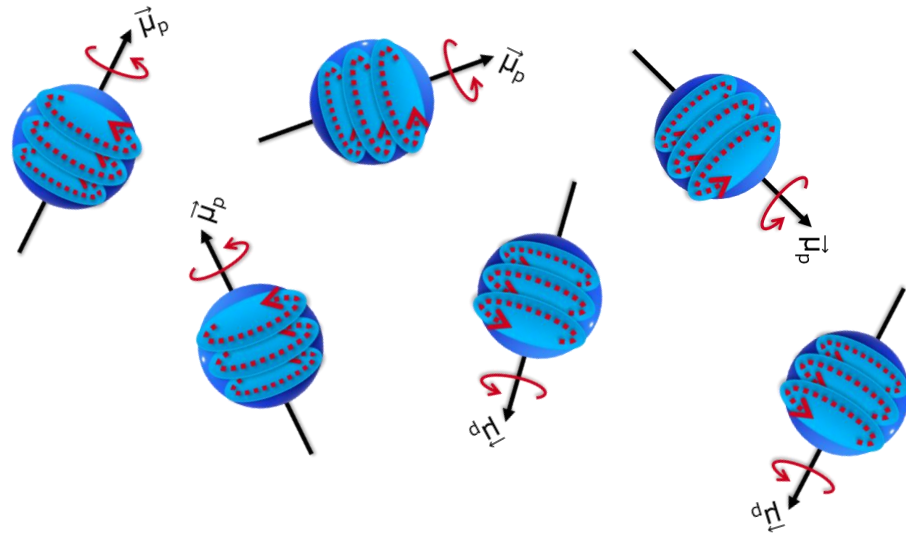
Nuclear magnetic resonance (NMR)

Nuclei properties

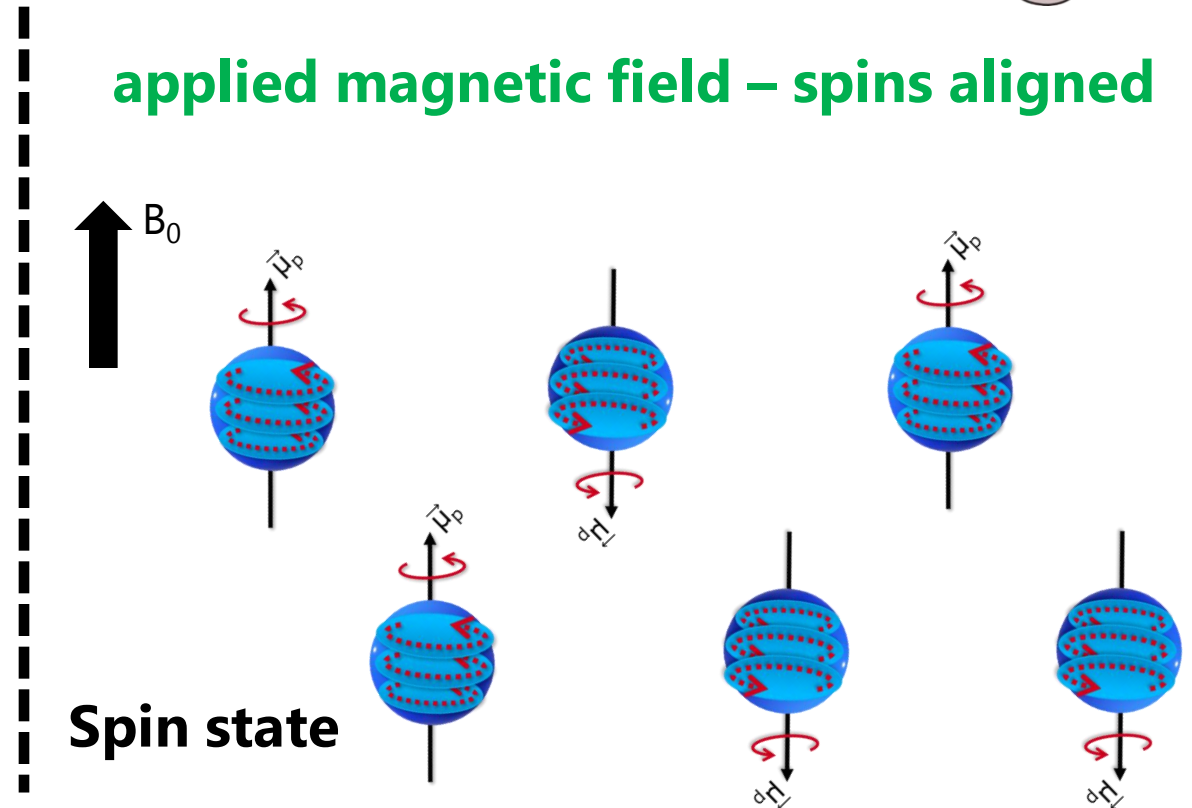
Under normal conditions, nuclei orient their spin **randomly**



No magnetic field – disordered spins



applied magnetic field – spins aligned



Nuclear magnetic resonance (NMR)

Spin states

The total number of spin states after applying a magnetic field:

Number of spin states = $2I + 1$ (I is the spin value)

$${}^1\mathbf{H} (I = 1/2) = \mathbf{2}$$

$${}^{10}\mathbf{B} (I = 3) = \mathbf{7}$$

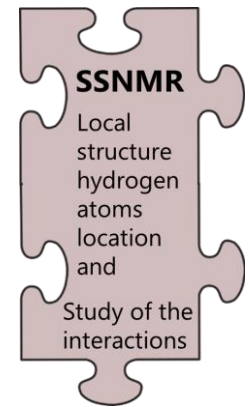
$${}^2\mathbf{H} (I = 1) = \mathbf{3}$$

$${}^{11}\mathbf{B} (I = 3/2) = \mathbf{4}$$

$${}^{13}\mathbf{C} (I = 1/2) = \mathbf{2}$$

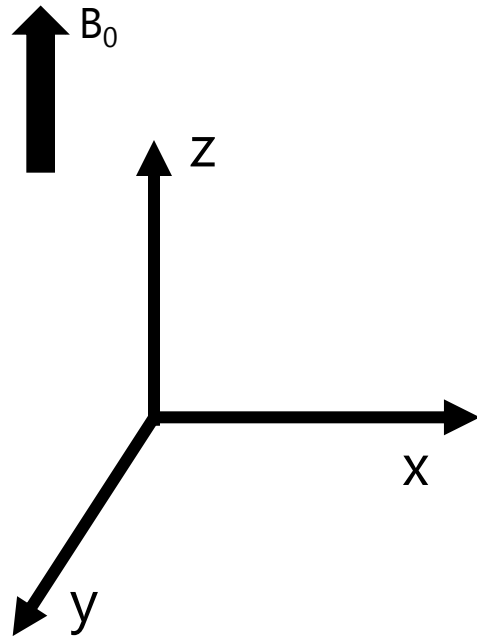
$${}^{209}\mathbf{Bi} (I = 9/2) = \mathbf{10}$$

The vast majority of the time we work with 1/2 spin nuclei (${}^1\mathbf{H}$ and ${}^{13}\mathbf{C}$)

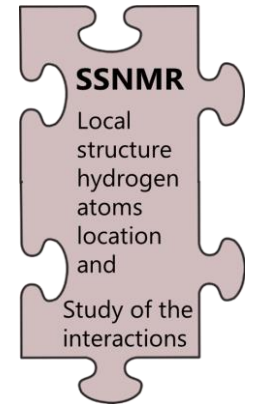
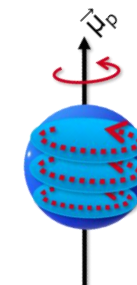
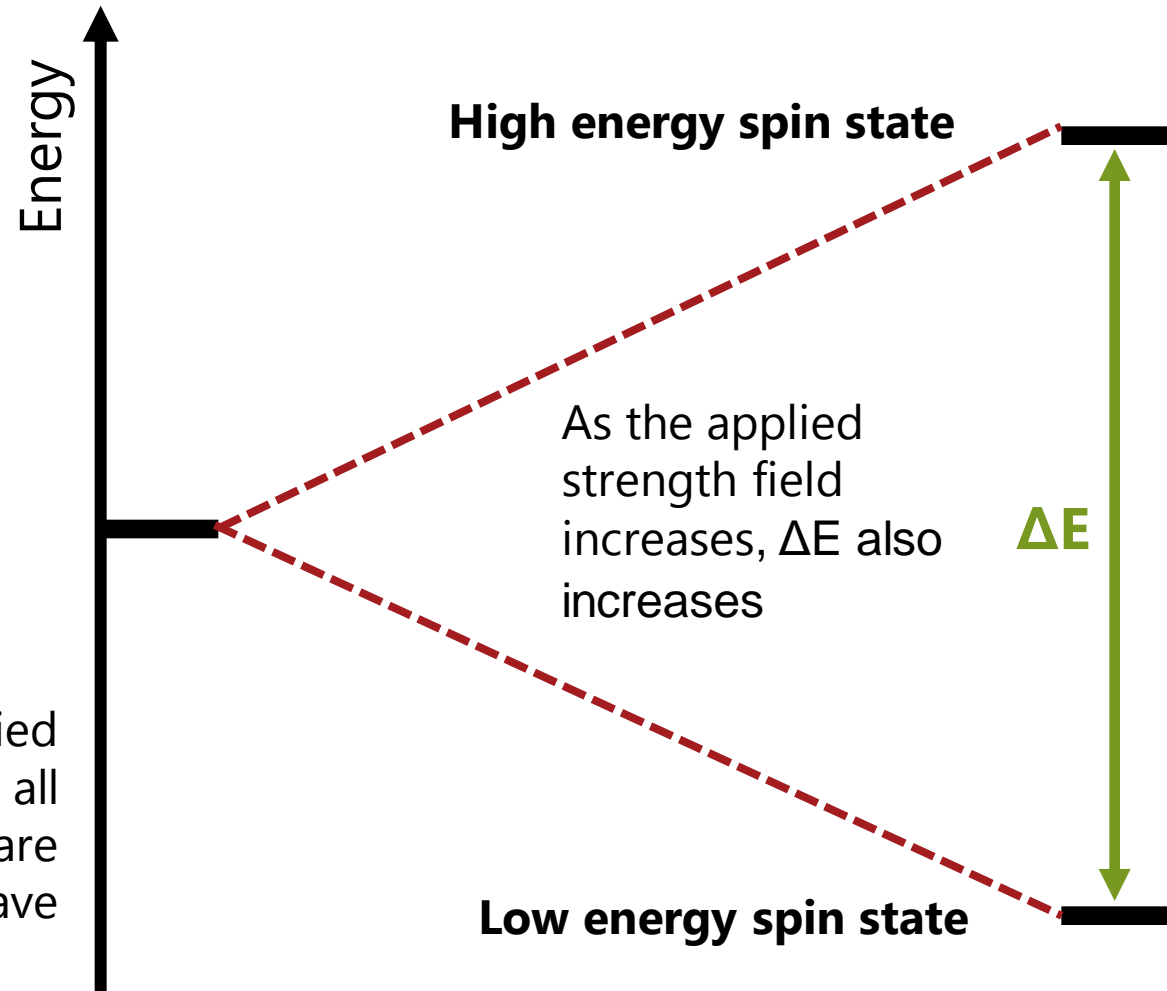


Nuclear magnetic resonance (NMR)

Spin states



With no applied magnetic field, all spins state are degenerated (have the same energy)

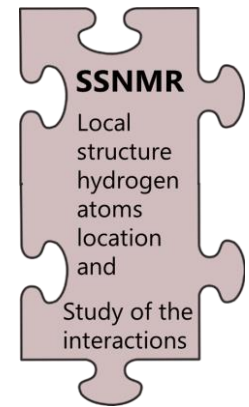


For nucleus **1/2 spin**, **2 states** are observed

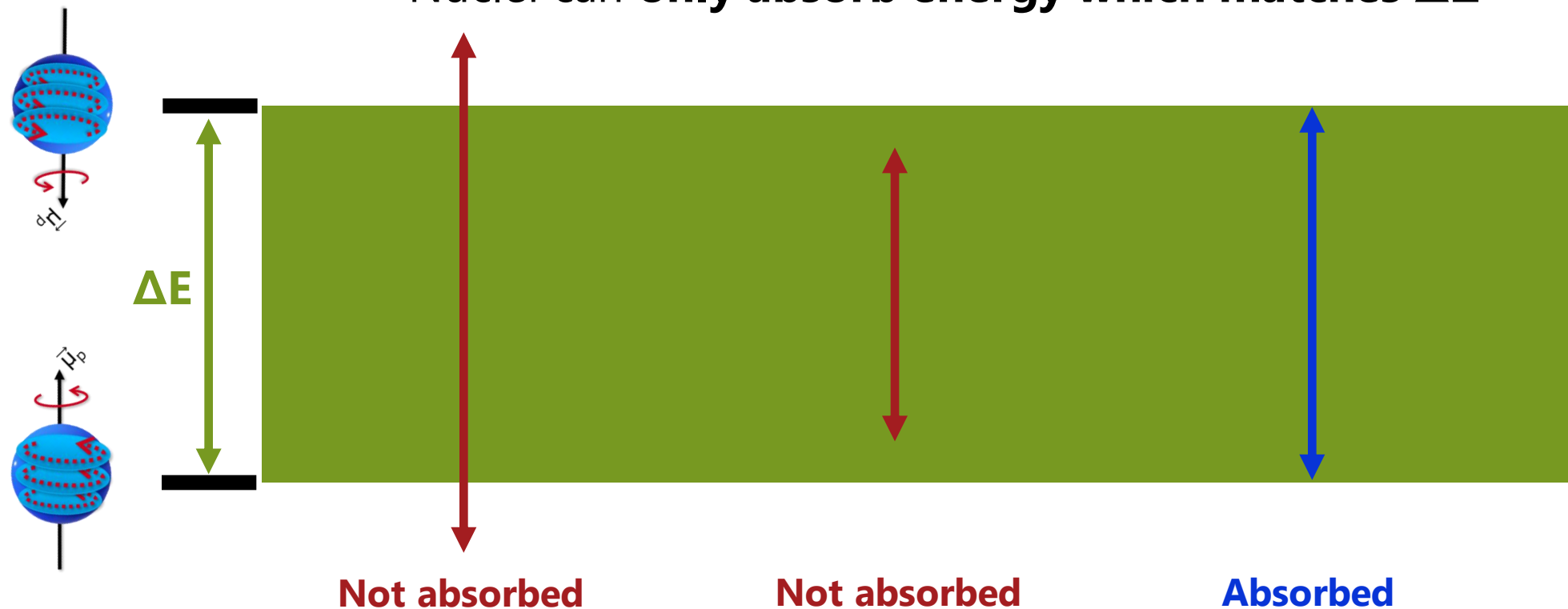
Nuclear magnetic resonance (NMR)

How can we obtain the spectra?

NMR spectrum is obtained from applying energy to the system in the form of varying frequencies of **RF frequency**



Nuclei can **only absorb energy which matches ΔE**

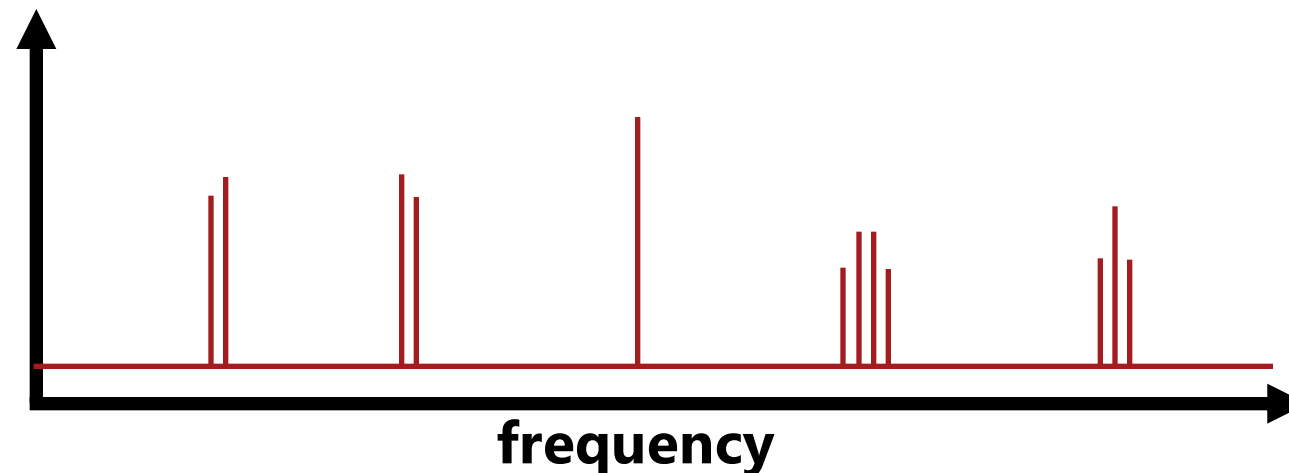
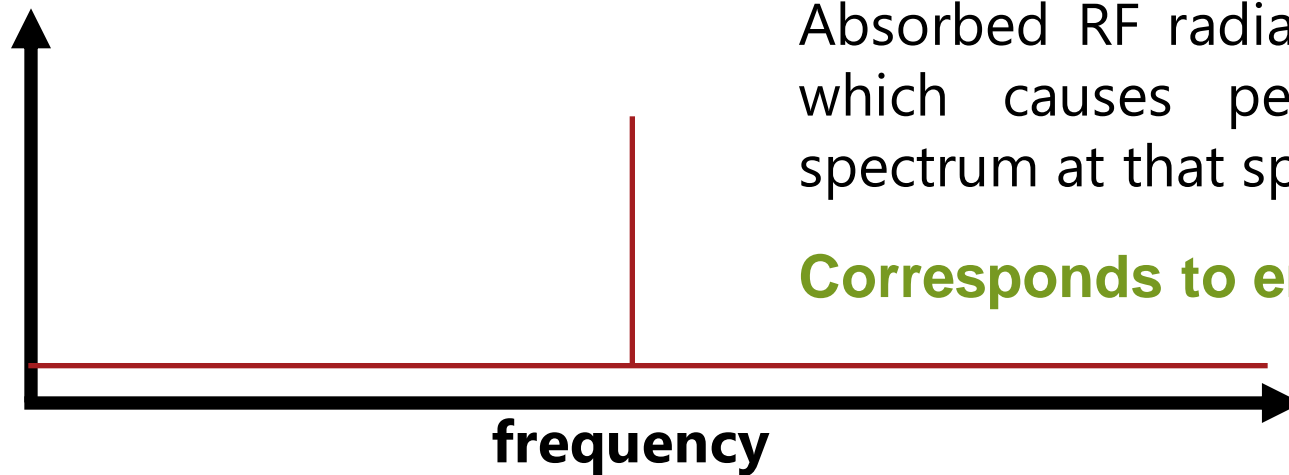


Nuclear magnetic resonance (NMR)

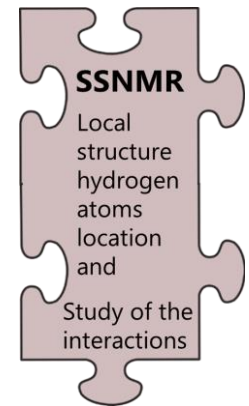
How can we obtain the spectra?

Absorbed RF radiation induces resonance, which causes peak to appear in the spectrum at that specific frequency

Corresponds to energy of ΔE



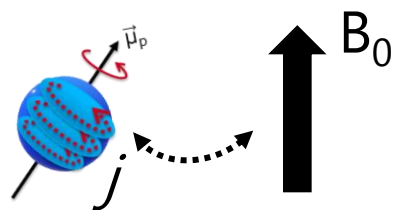
Multiple nuclei with different $\Delta E \rightarrow$ multiple signals at different frequencies



Nuclear magnetic resonance (NMR)

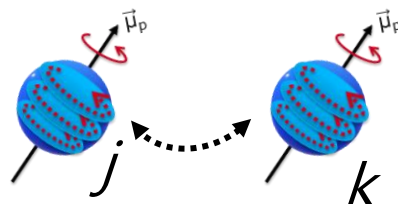
Types of interactions

- Zeeman interaction



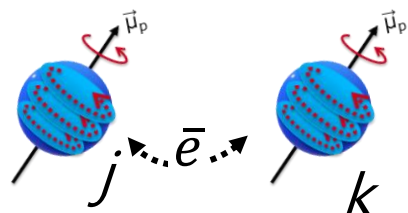
$$\hat{H}_Z = -\gamma \times \vec{I}_j \times \vec{B}_0$$

- Direct dipolar interaction



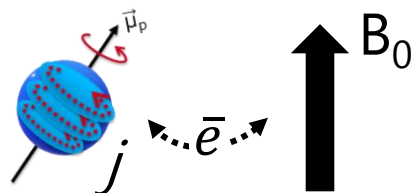
$$\hat{H}_{jk}^{DD} = \vec{I}_j \times \vec{D}_{jk} \times \vec{I}_k$$

- J coupling

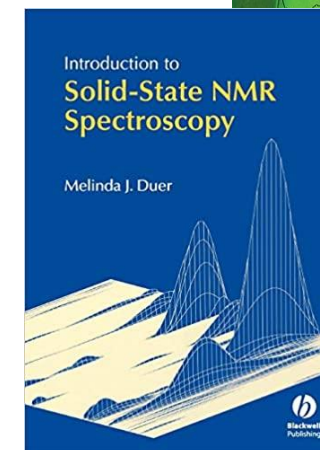
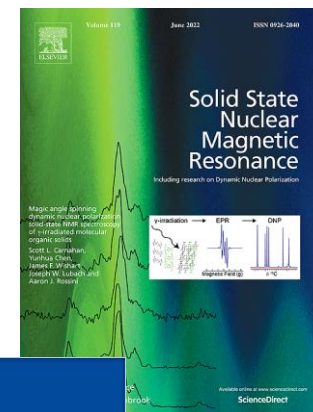
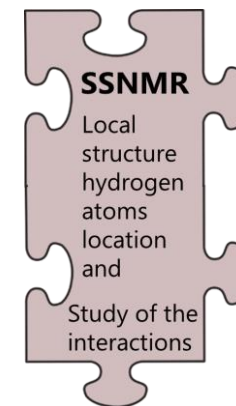


$$\hat{H}_{jk}^J = \vec{I}_j \times \vec{J}_{jk} \times \vec{I}_k$$

- Chemical shift



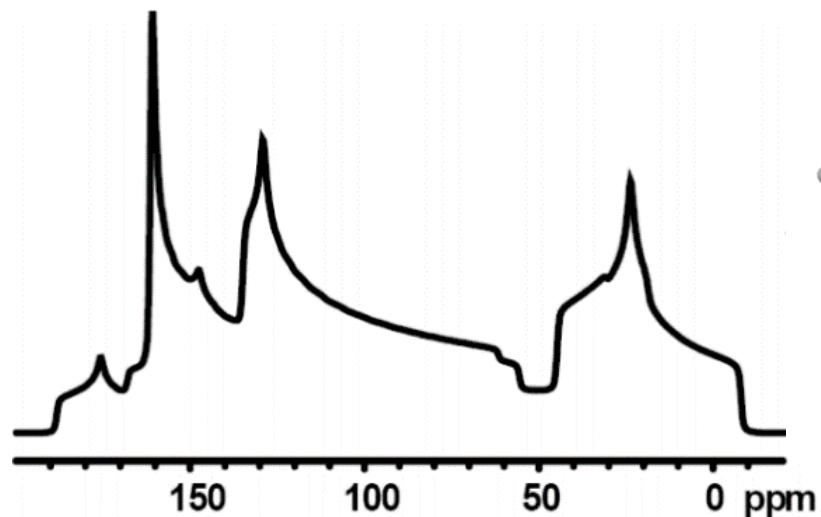
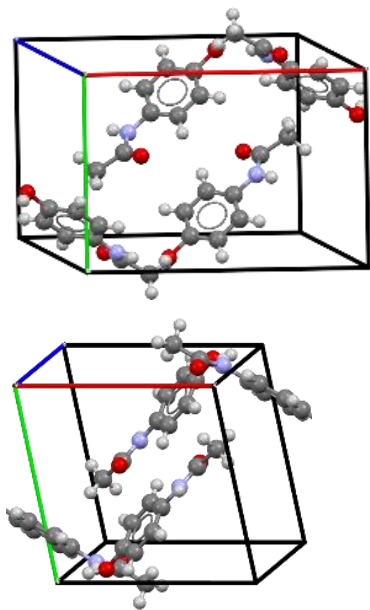
$$\hat{H}_j^{CS} = \nu_j \times \vec{I}_j \times \vec{\sigma}_j \times \vec{B}_0$$



Solid-state NMR (ssNMR)

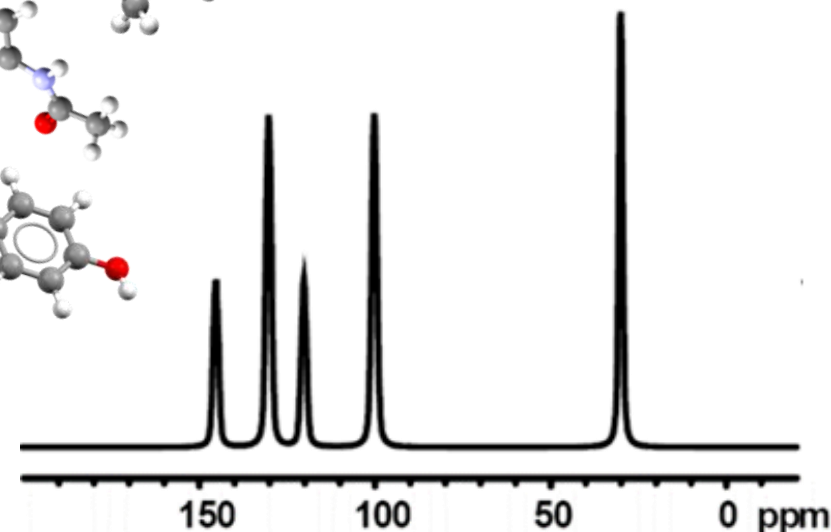
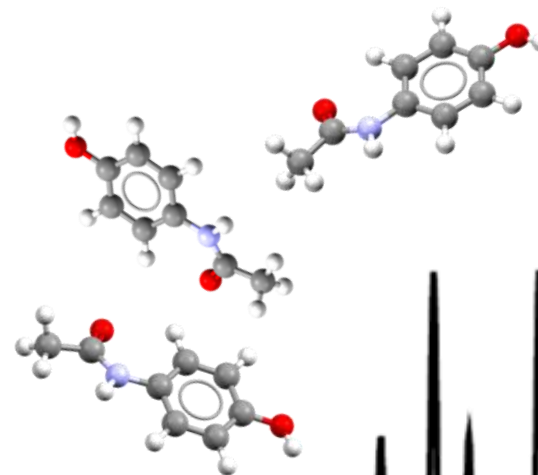
Solids vs liquids

Solids

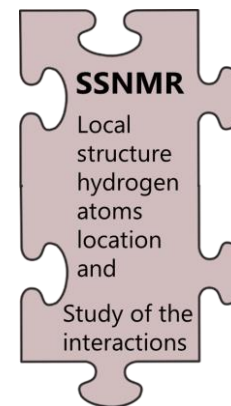


Interactions depend on the molecule orientation – **anisotropy**

Liquids



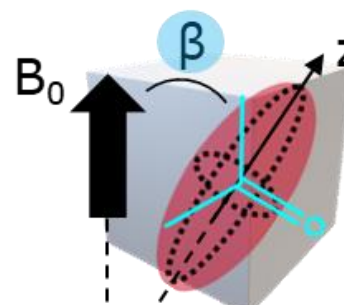
Rapid random tumbling averages anisotropic chemical shifts and couplings



Solid-state NMR (ssNMR)

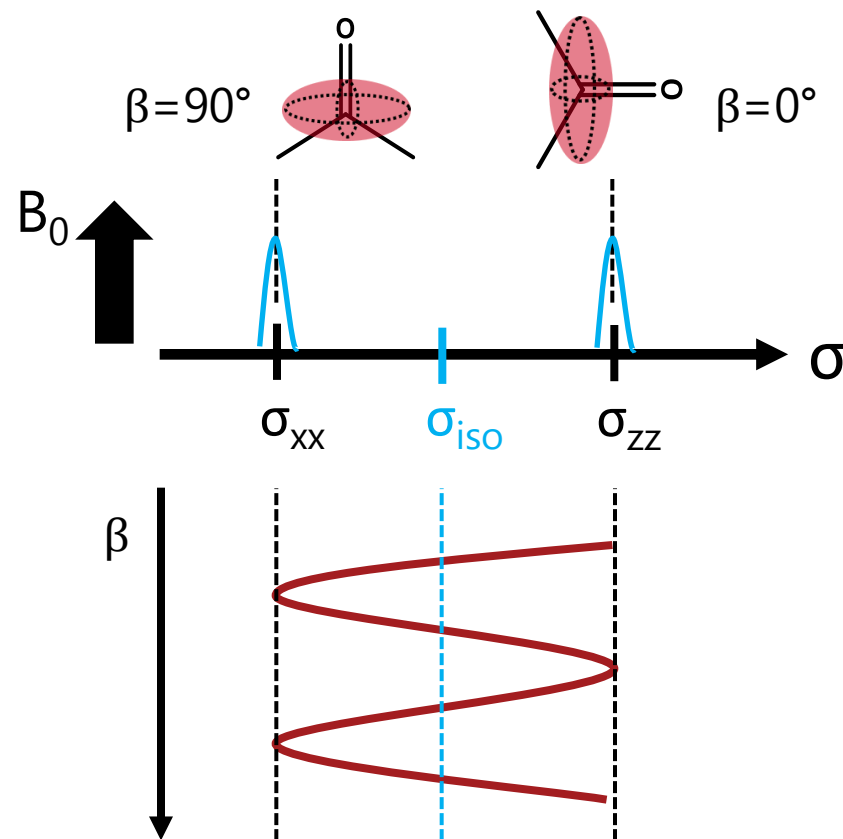
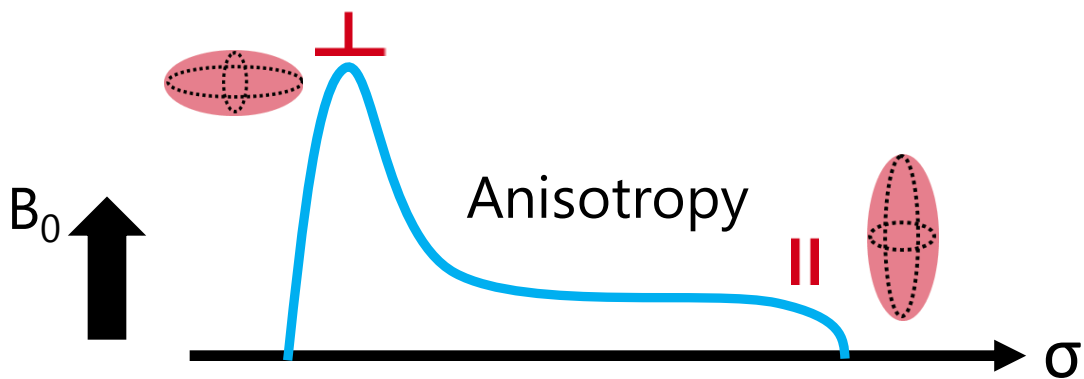
How chemical shift varies?

For one single orientation



$$\hat{H}_{CS} = \gamma \vec{B}_0 I_z (\underbrace{\sigma_{xx} \sin^2\beta + \sigma_{zz} \cos^2\beta}_{\sigma(\beta)})$$

 Static conditions

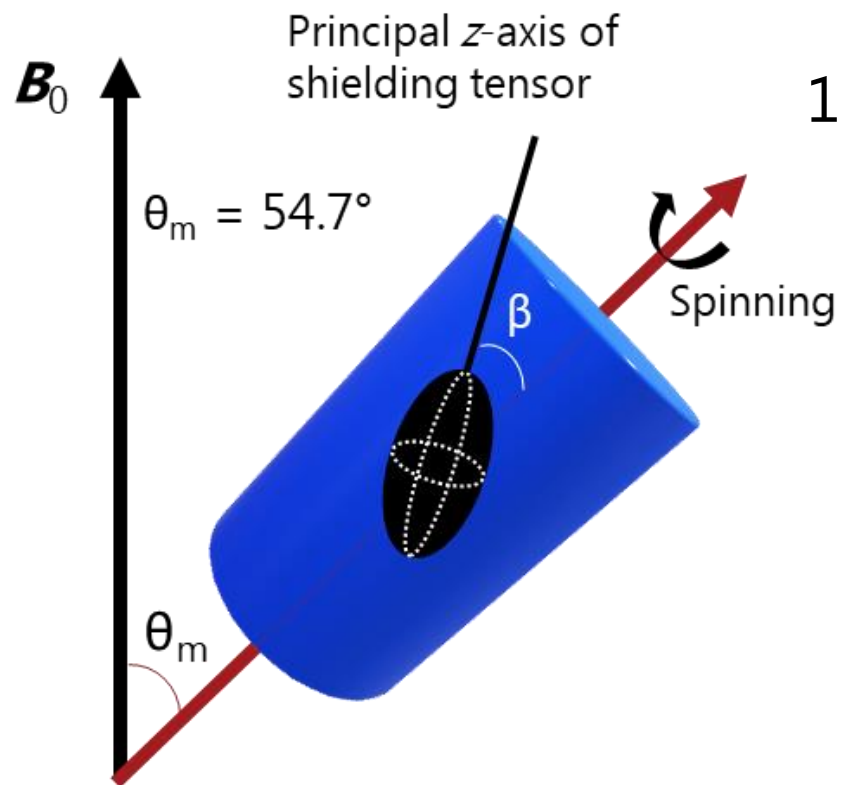


SSNMR
Local structure
hydrogen
atoms
location
and
Study of the
interactions

Solid-state NMR (ssNMR)

Magic angle spinning

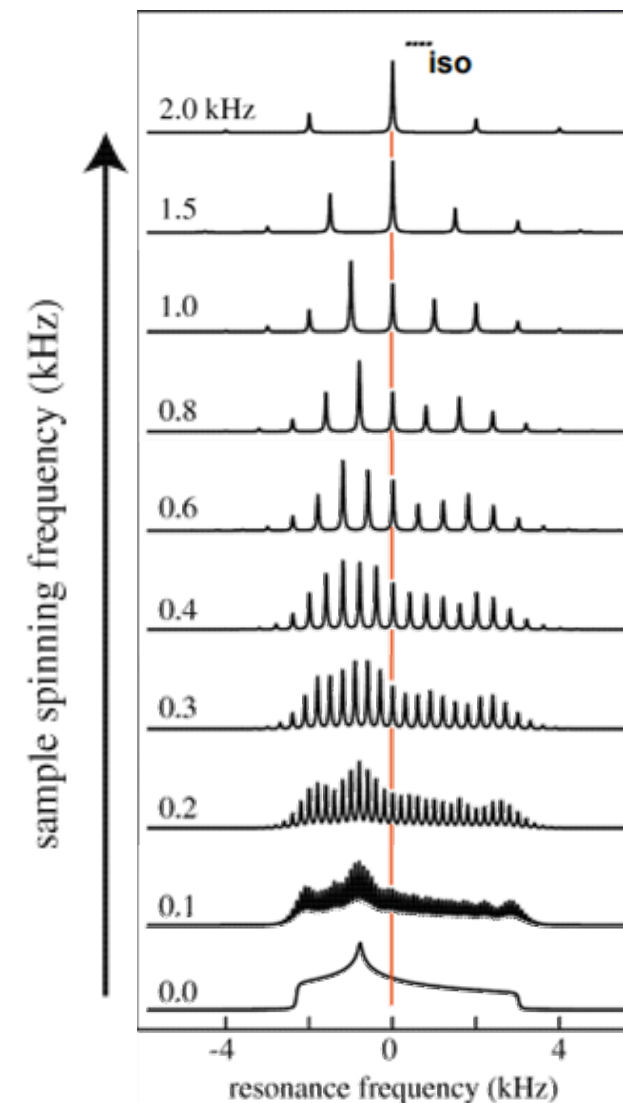
Anisotropic interactions can be suppressed using MAS – artificial molecular movement



$$1 - 3\cos^2\theta_m = 0$$

Line width – dipole-dipole interaction and chemical shift anisotropy $1 - 3\cos^2\theta_m$

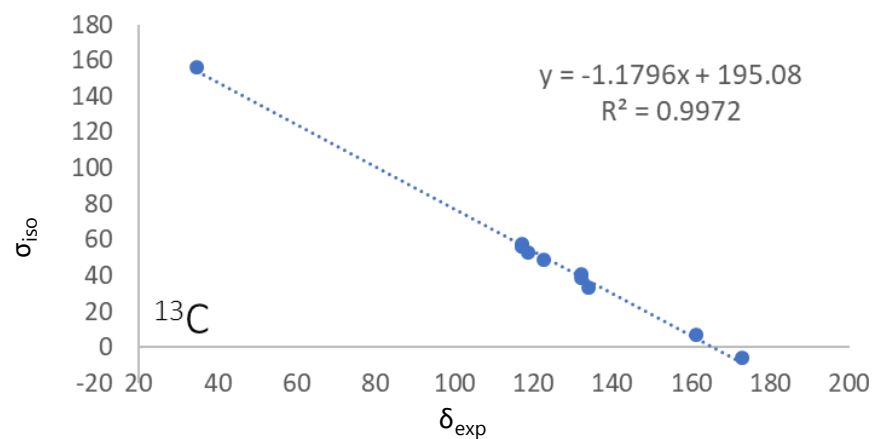
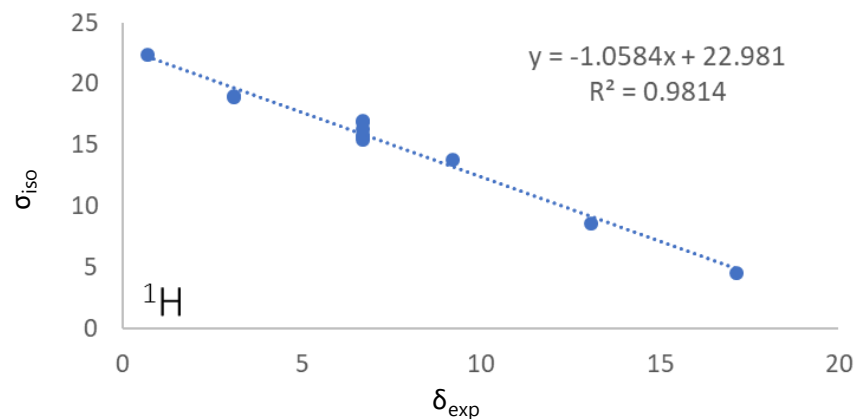
Frequency of spinning large as the spectrum width



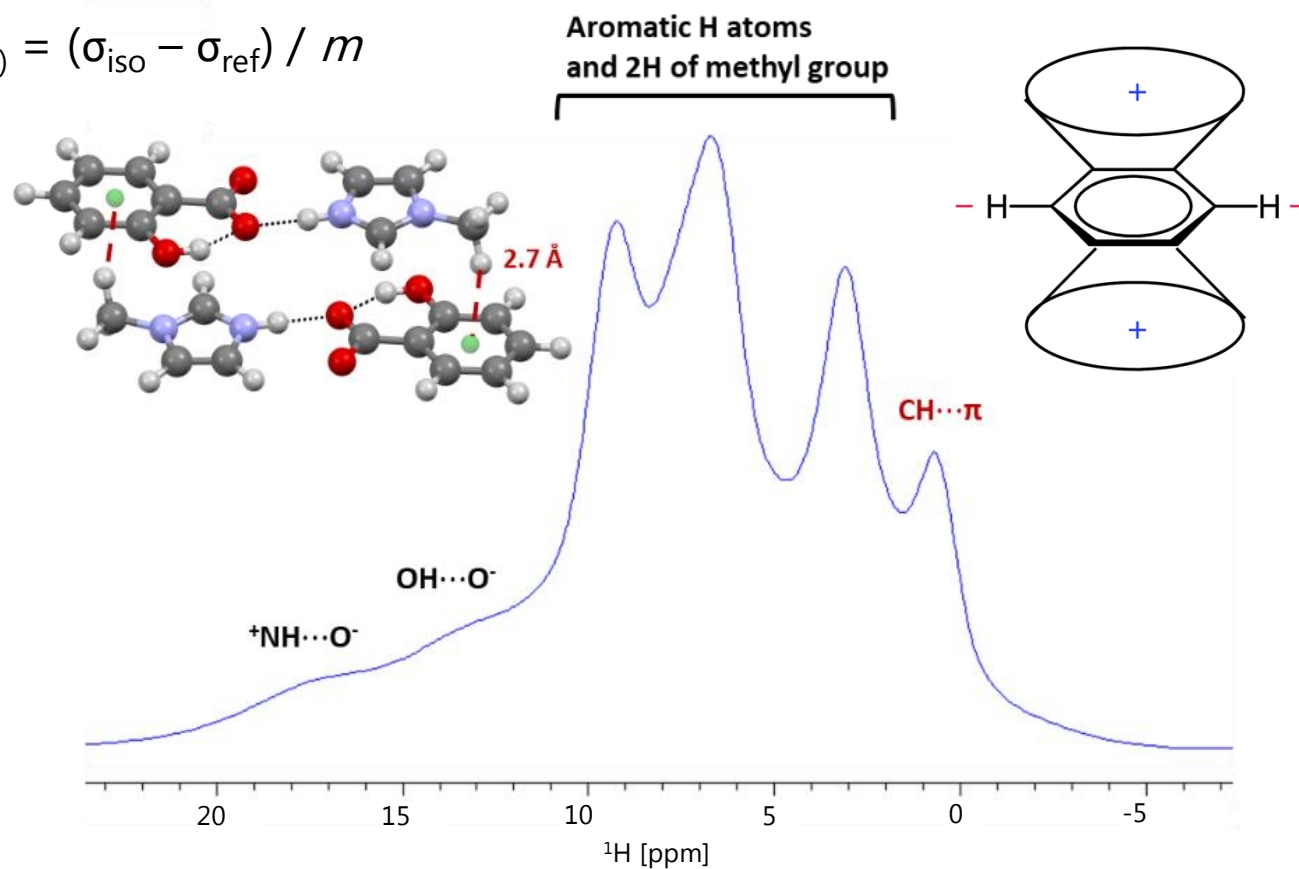
Solid-state NMR (ssNMR)

Salicylic acid with imidazolium

Periodic DFT calculations – Quantum Espresso



$$\delta_{\text{iso(DFT)}} = (\sigma_{\text{iso}} - \sigma_{\text{ref}}) / m$$



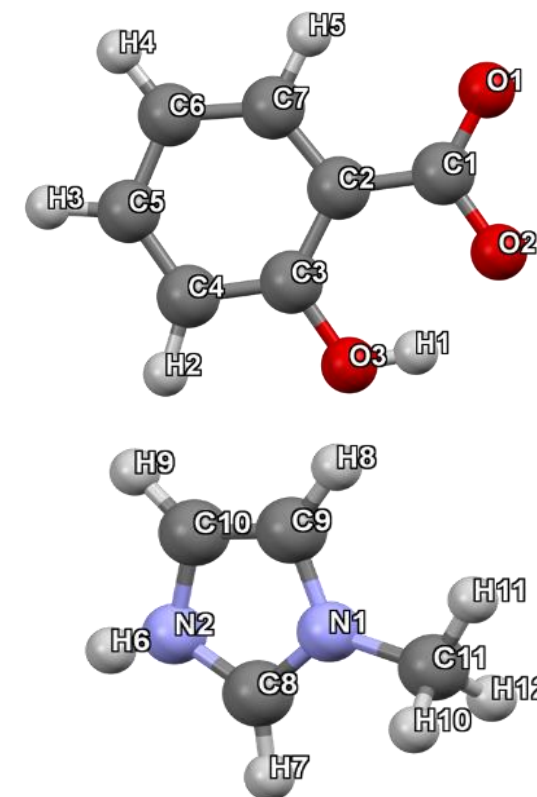
Solid-state NMR (ssNMR)

Salicylic acid with imidazolium

ssNMR calculation parameters

$$\delta_{\text{iso(DFT)}} = (\sigma_{\text{iso}} - \sigma_{\text{ref}}) / m$$

Atom label	$\delta_{\text{iso(exp)}}$ /ppm	$\delta_{\text{iso(DFT)}}$ /ppm	$\delta_{\text{iso(exp)}} - \delta_{\text{iso(DFT)}}$	$(\delta_{\text{iso(exp)}} - \delta_{\text{iso(DFT)}})^2$	RMSD
H1	13.1	13.6	-0.5	0.25	0.339
H2	6.7	6.8	-0.07	0.005	
H3	6.7	6.3	0.4	0.16	
H4	6.7	5.7	1.03	1.06	
H5	6.7	5.7	1.03	1.06	
H6	17.1	17.4	-0.3	0.09	
H7	6.7	6.9	-0.2	0.04	
H8	9.2	8.7	0.5	0.25	
H9	6.7	7.1	-0.4	0.16	
H10	3.1	3.8	-0.7	0.49	
H11	3.1	3.8	-0.7	0.49	
H12	0.7	0.6	0.1	0.01	



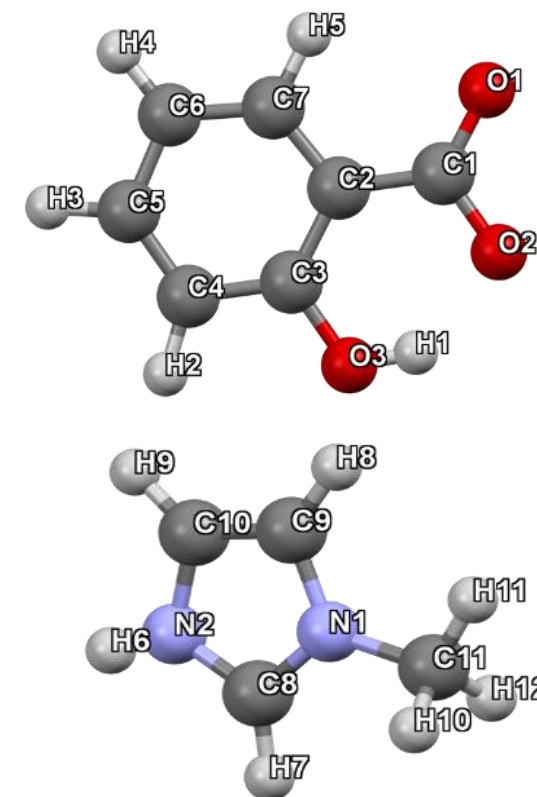
Solid-state NMR (ssNMR)

Salicylic acid with imidazolium

ssNMR calculation parameters

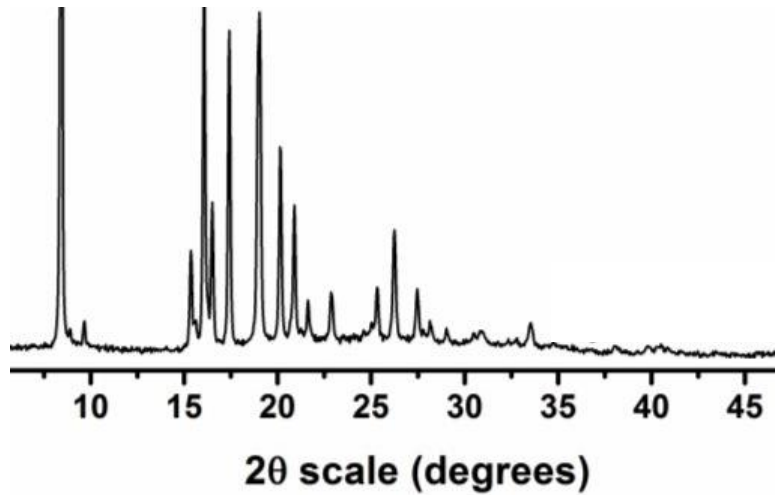
$$\delta_{\text{iso(DFT)}} = (\sigma_{\text{iso}} - \sigma_{\text{ref}}) / m$$

Atom label	$\delta_{\text{iso(exp)}}$ /ppm	$\delta_{\text{iso(DFT)}}$ /ppm	$\delta_{\text{iso(exp)}} - \delta_{\text{iso(DFT)}}$	$(\delta_{\text{iso(exp)}} - \delta_{\text{iso(DFT)}})^2$	RMSD
C1	172.9	171.2	1.7	2.89	1.085
C2	117.0	117.8	-0.8	0.64	
C3	161.1	159.9	1.2	1.44	
C4	117.0	117.4	-0.4	0.16	
C5	132.2	132.7	-0.5	0.25	
C6	117.0	116.8	0.2	0.04	
C7	132.2	131.7	0.5	0.25	
C8	133.9	135.0	-1.1	1.21	
C9	122.5	123.4	-0.9	0.81	
C10	118.8	120.1	-1.3	1.69	
C11	34.8	33.2	1.6	2.56	

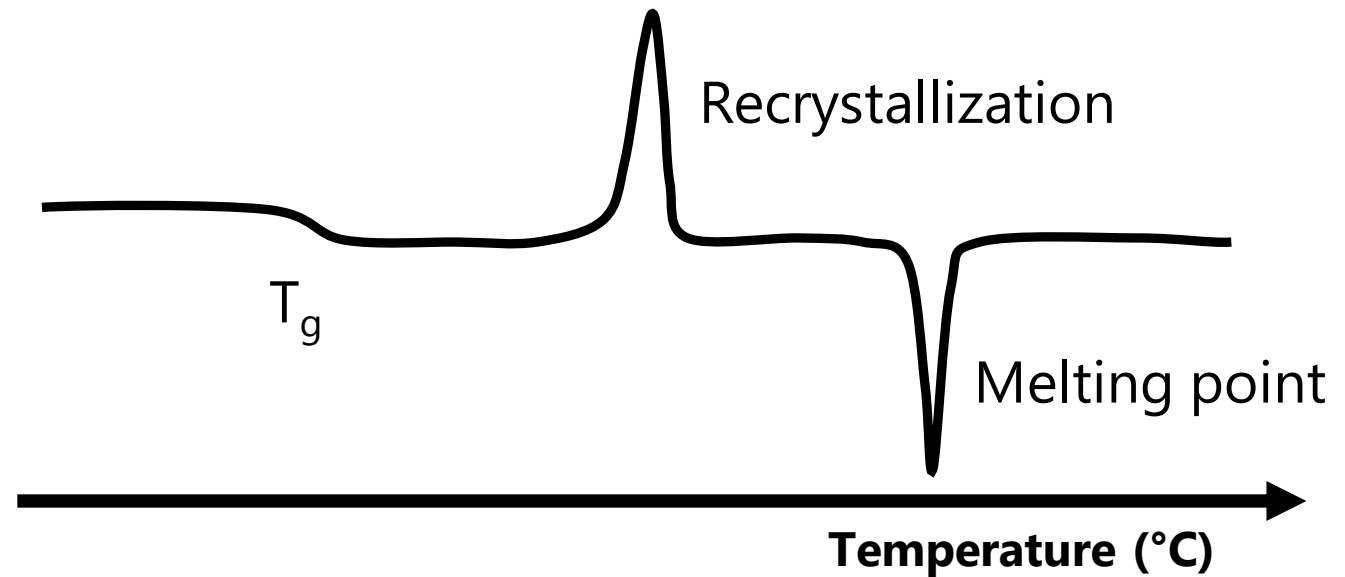
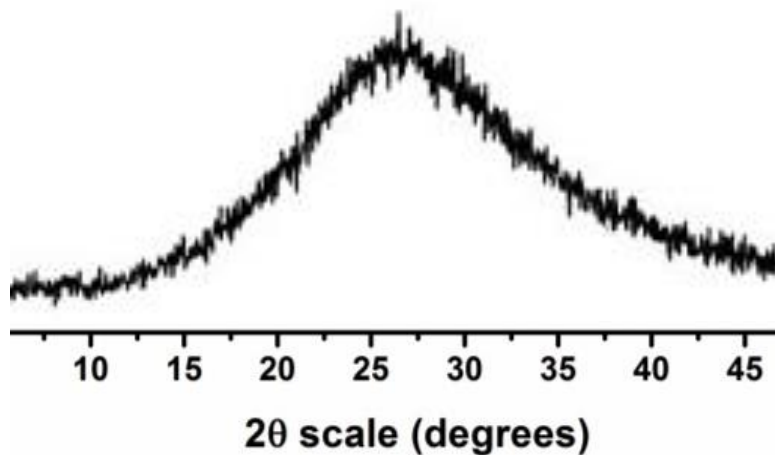
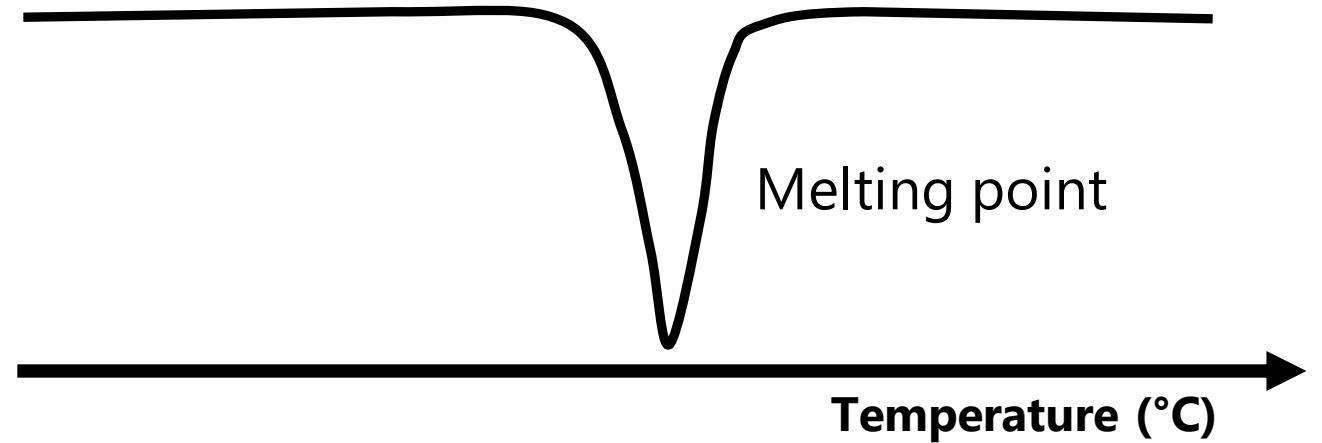


Crystalline vs amorphous

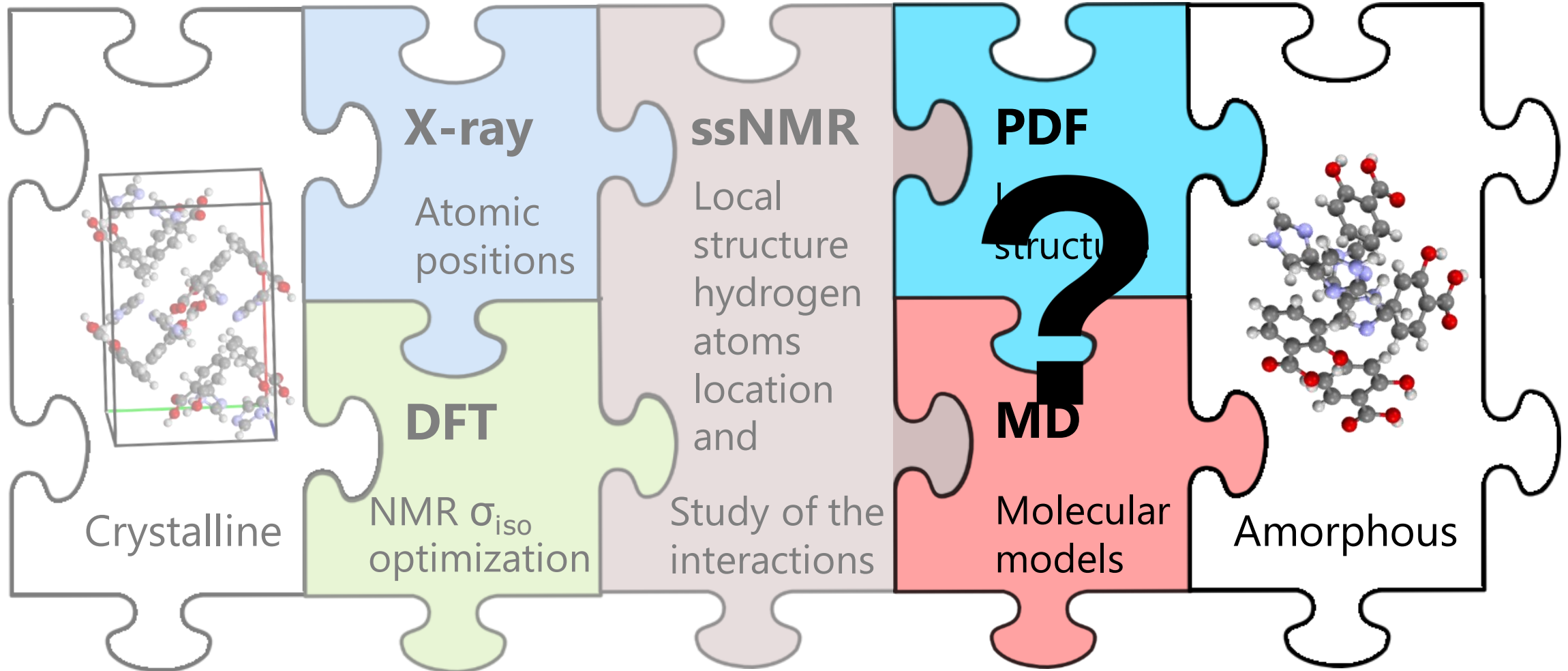
PXRD



DSC

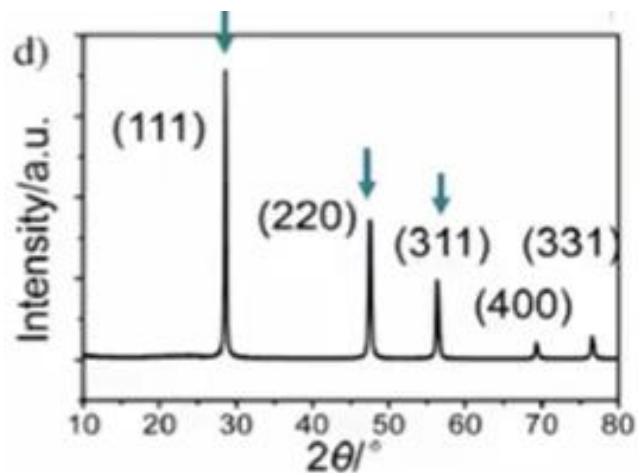


Structure solution: the jigsaw puzzle



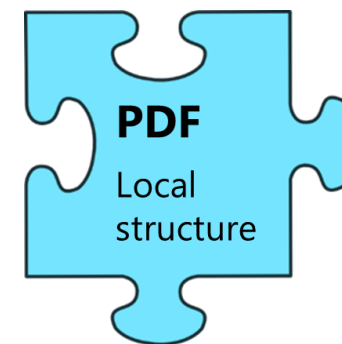
Pair distribution function (PDF) analysis

X-ray diffraction – Bragg's law



$$n\lambda = 2d \sin \theta$$

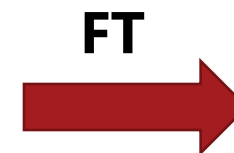
A **single peak** represents a **periodic occurrence** of an **atomic plane** in a crystal



Pair distribution function

Total scattering (Braggs + diffuse scattering) collected at reciprocal space

$$Q = \frac{4\pi \sin \theta}{\lambda}$$



Real space information

Pair distribution function (PDF) analysis

Use XRD data, convert to Q-space, calculate F (Q)

$$Q = \frac{4\pi \sin \theta}{\lambda}$$

$$F(Q) = Q[S(Q) - 1]$$

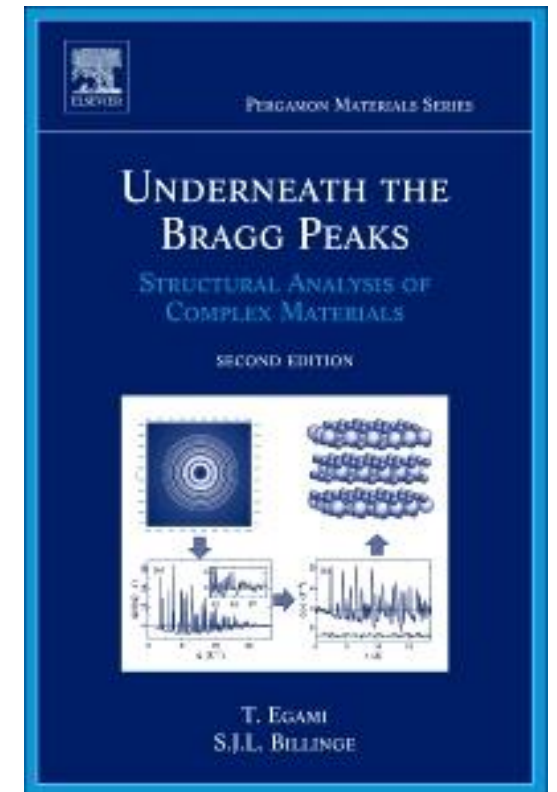
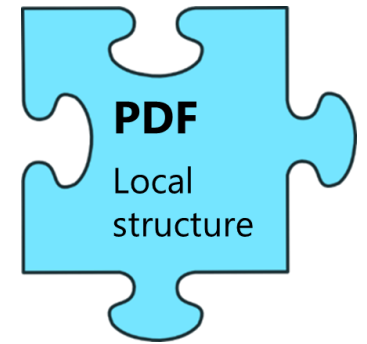
S (Q) = total scattering

Fourier transform

$$G(r) = \frac{2}{\pi} \int_{Q=0}^{Q_{max}} F(Q) \sin(Qr) dq = 4\pi r \rho_0 (g(r) - 1)$$

Real space relation

$$\rho(r) = \rho_0 g(r) = \frac{1}{4\pi N r^2} \sum_v \sum_{\mu} \delta(rv - r_{\mu})$$

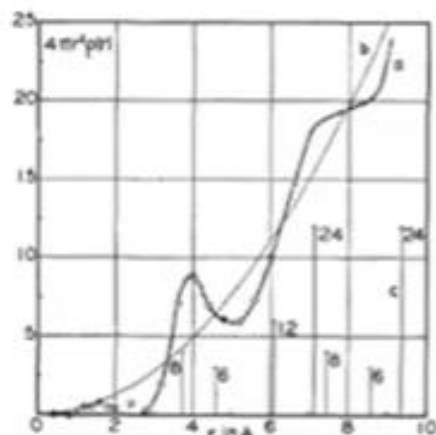
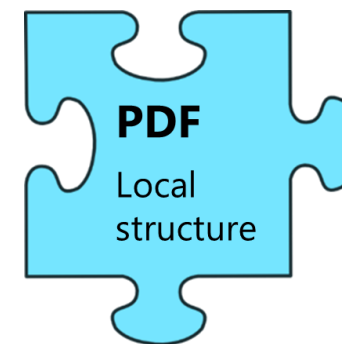


History of PDF – Not a new technique

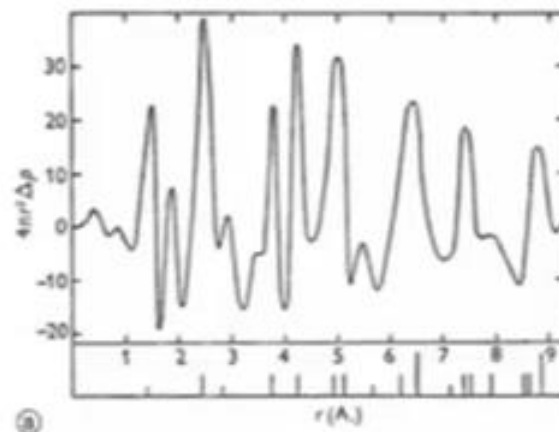
1915: Peter Debye, Debye formula

1927: Prins and Zernik, Fourier relationship to PDF

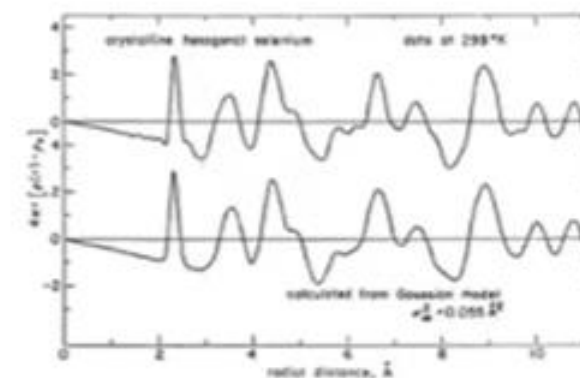
1930: Debye and Menke, First PDF: Liquid Hg



1936, Tarasov and Warren, liquid sodium

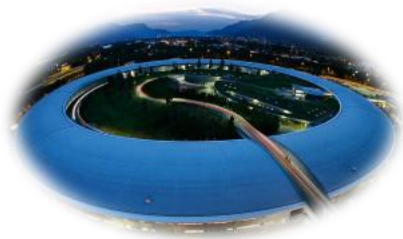
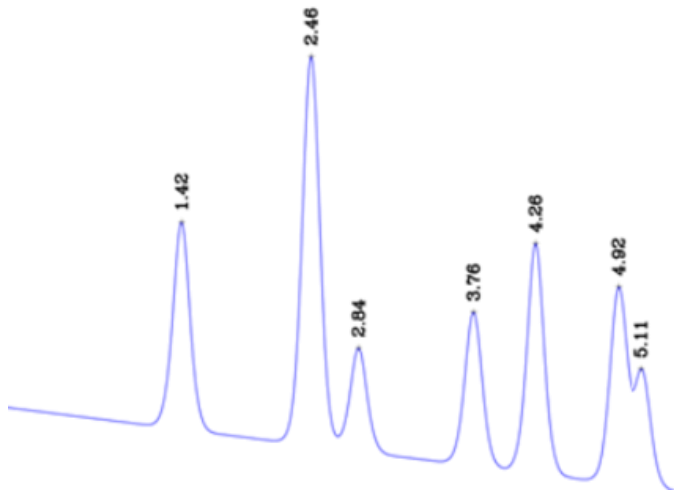
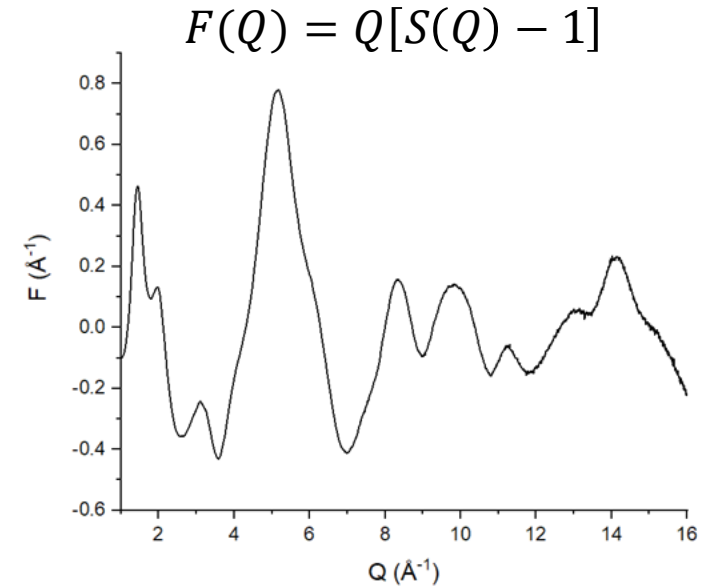
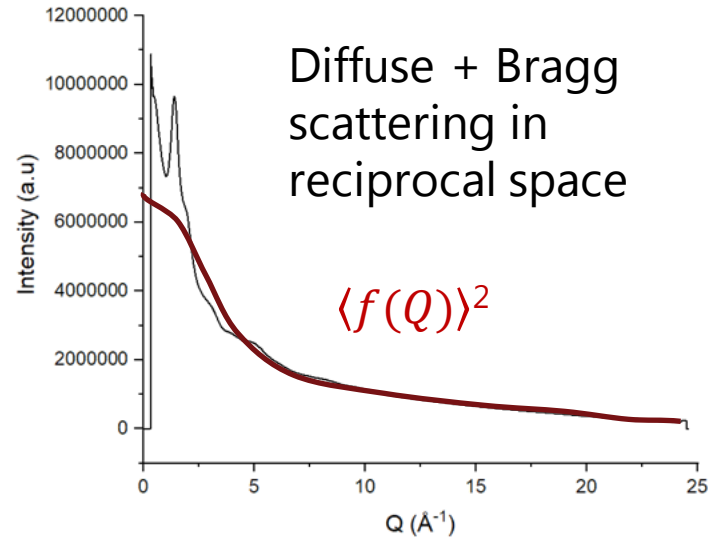
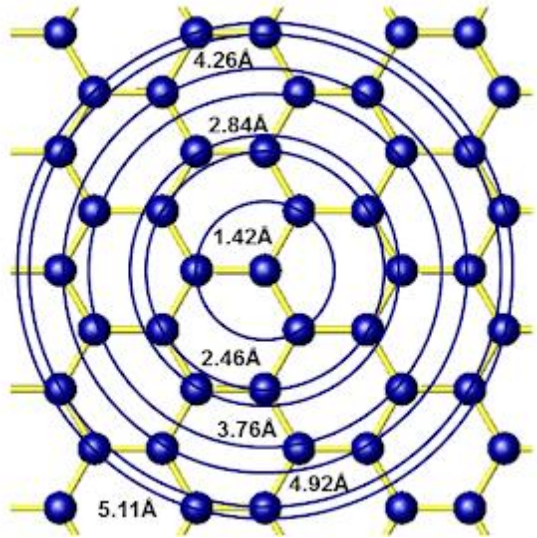


1950: Rosalind Franklin, disordered carbon

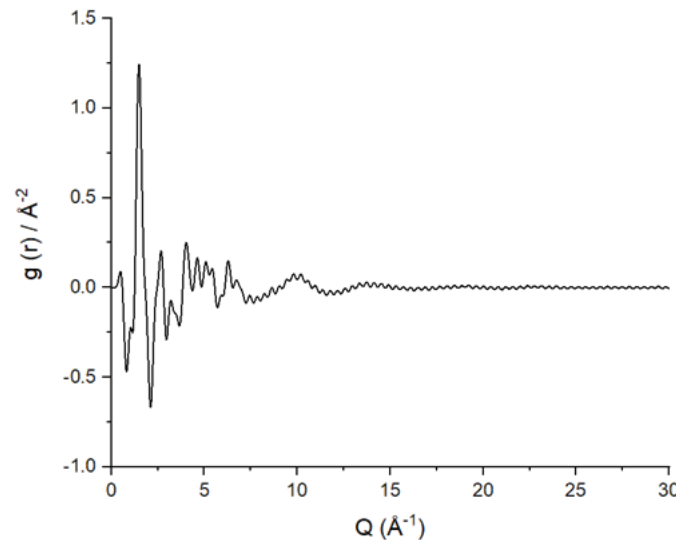


1968: Kaplow and Averbach, amorphous Se

Pair distribution function (PDF) analysis

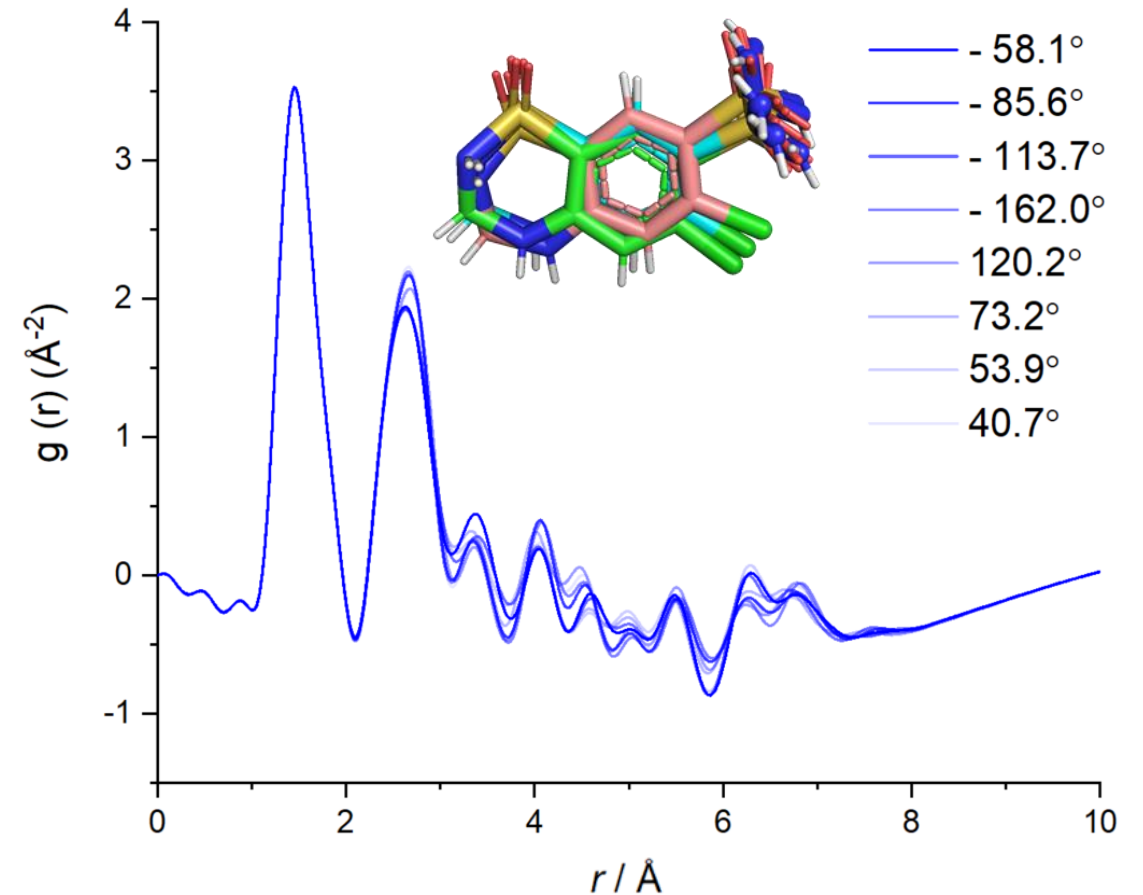
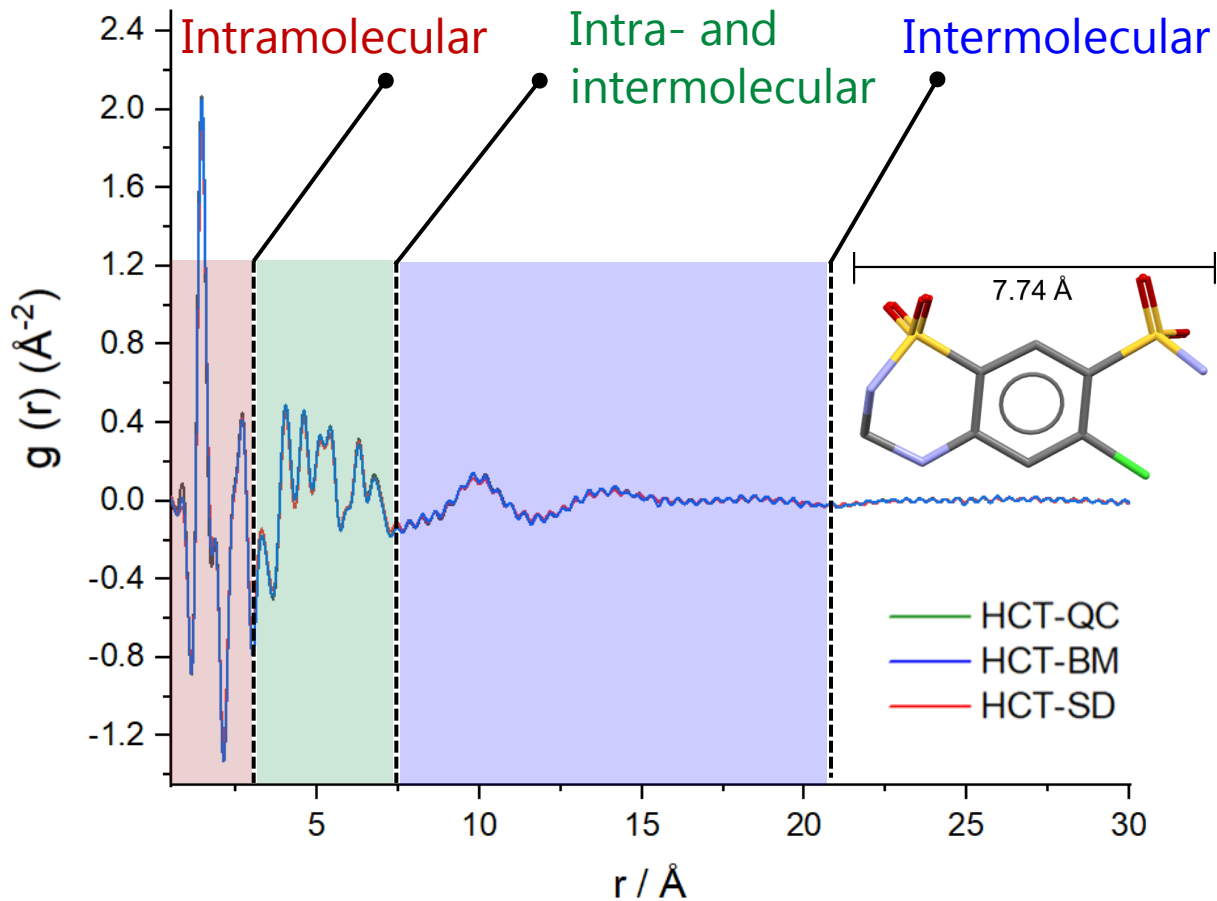


High energy X-rays, extremely short wavelengths



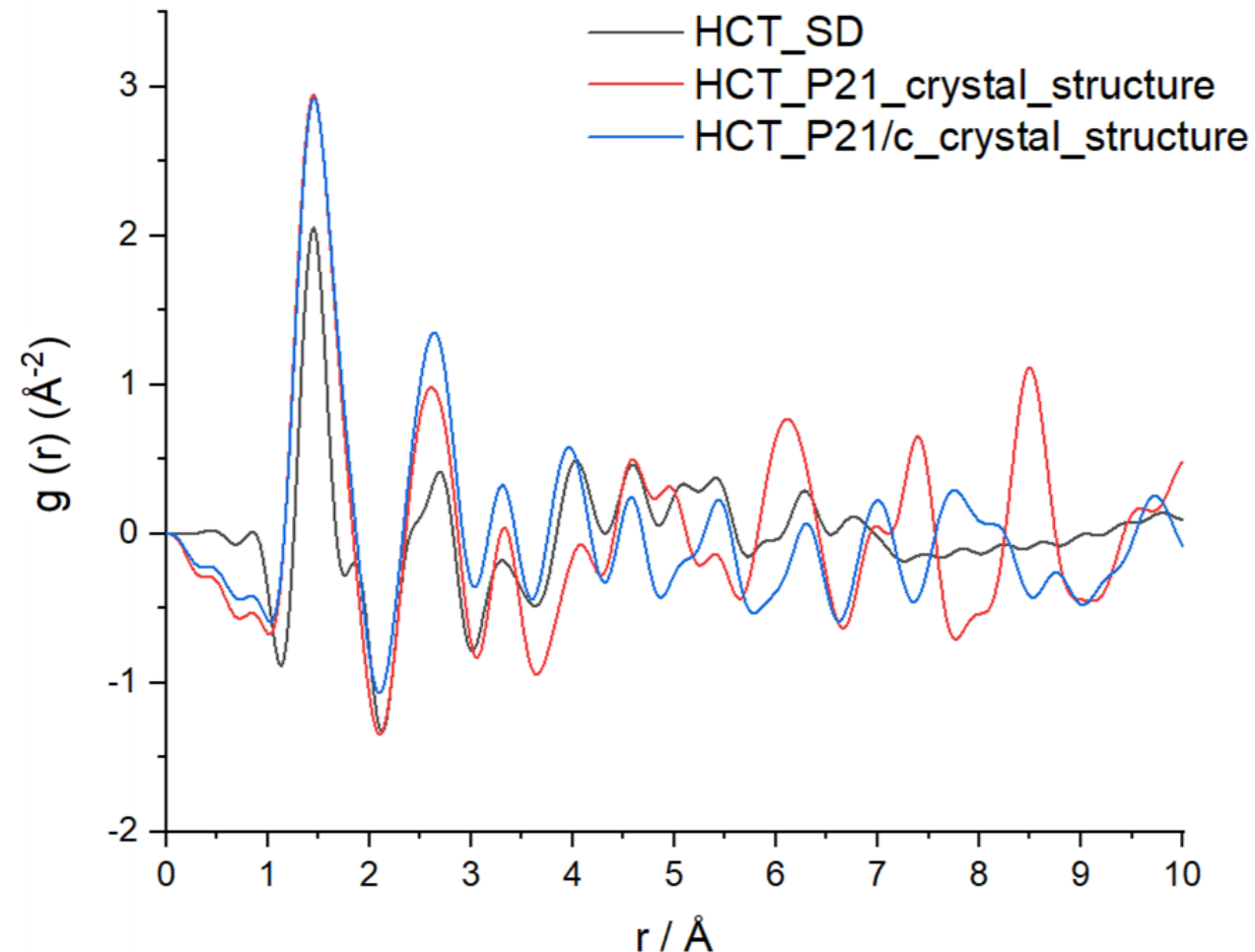
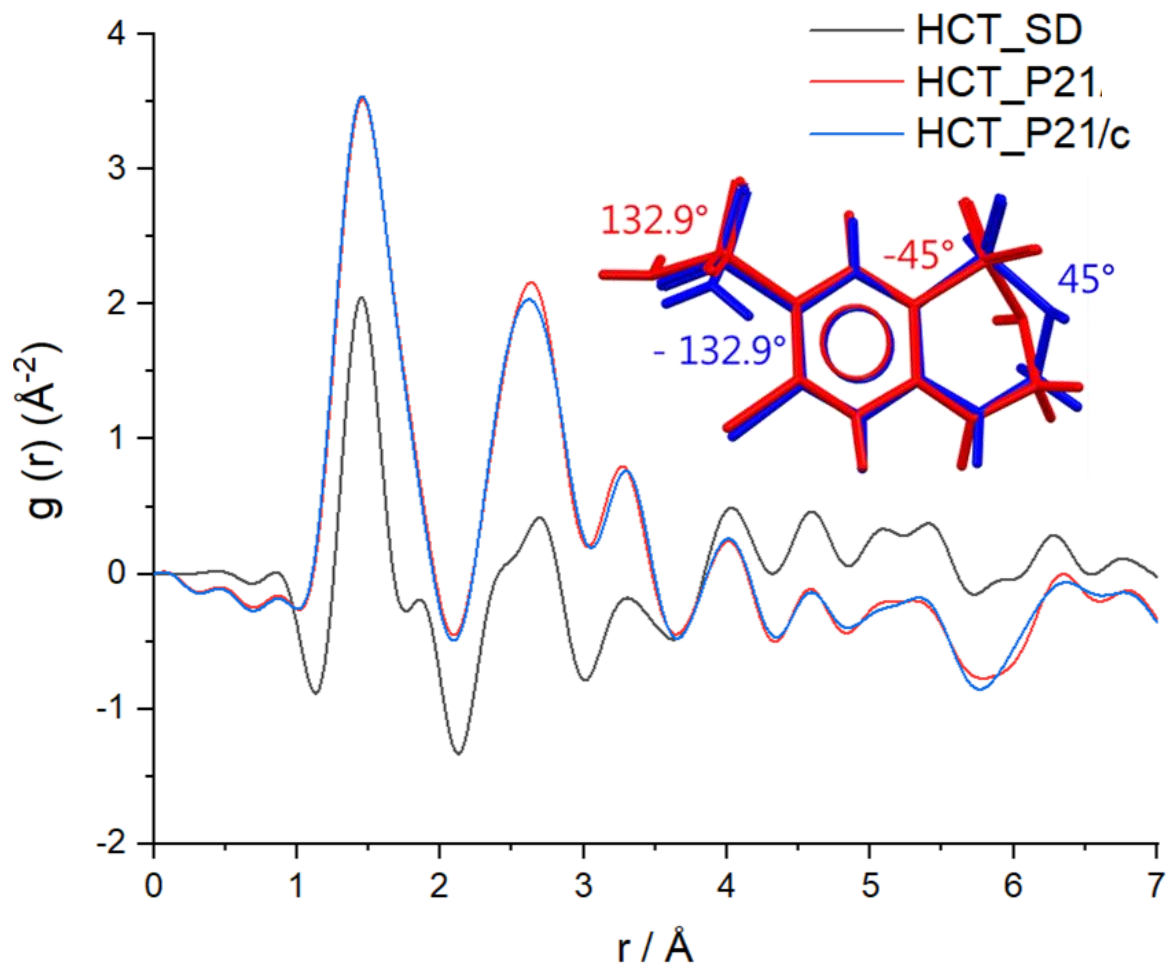
PDF analysis – the case study of HCT

What information can be extracted?



Molecular organization of amorphous HCT

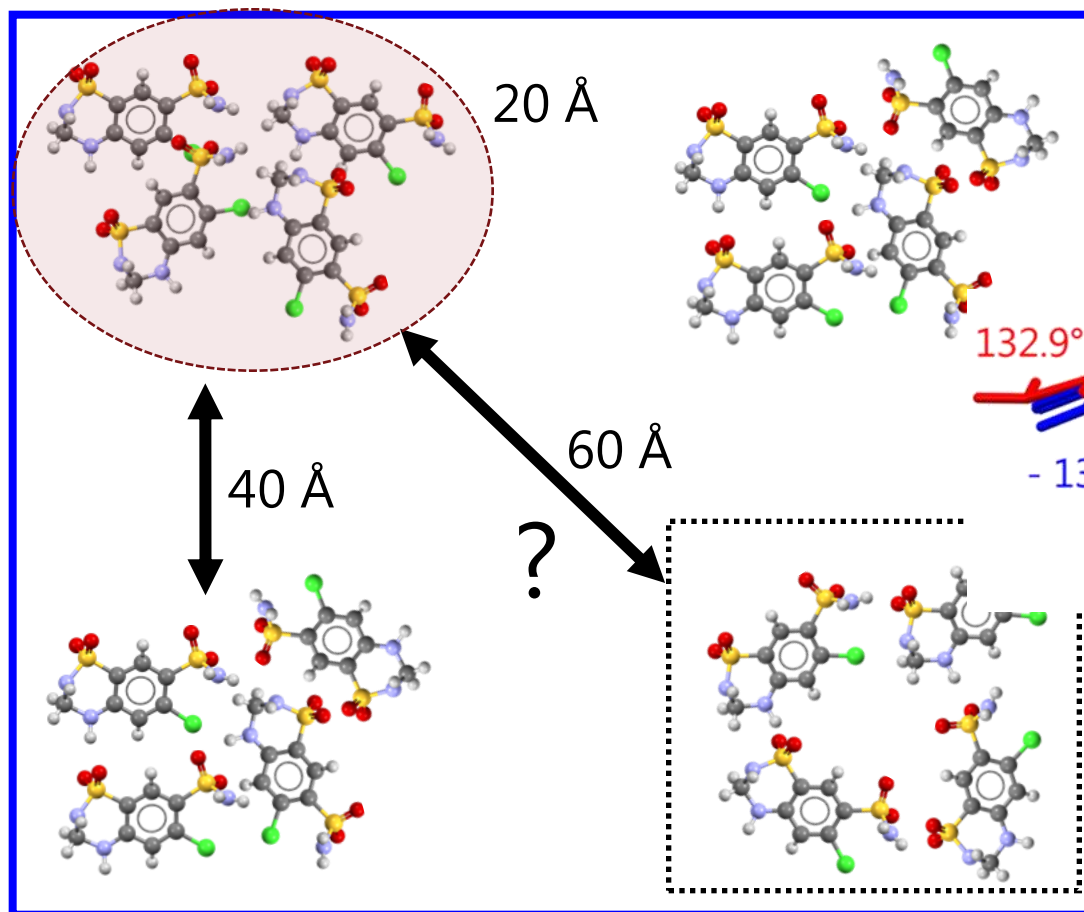
Comparison of HCT in amorphous and crystalline states



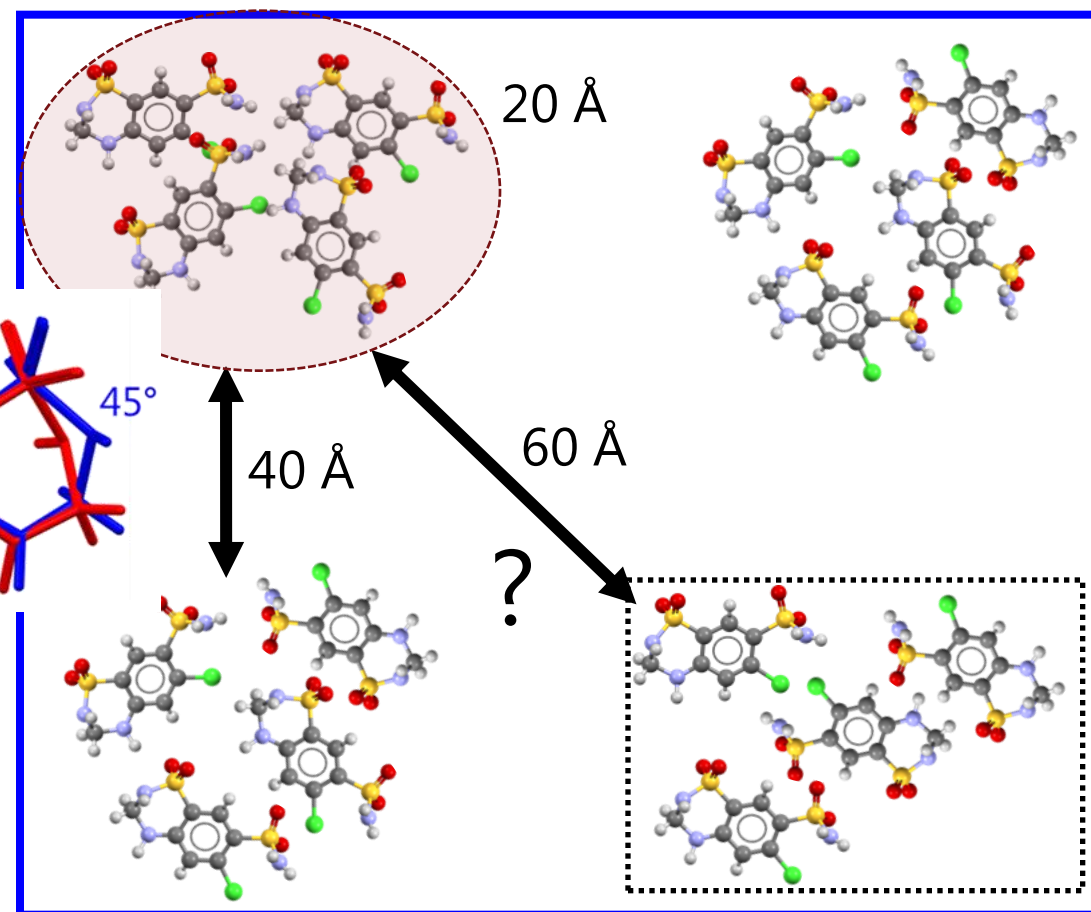
Molecular organization of amorphous HCT

What may happen at longer range distances?

HCT from SD

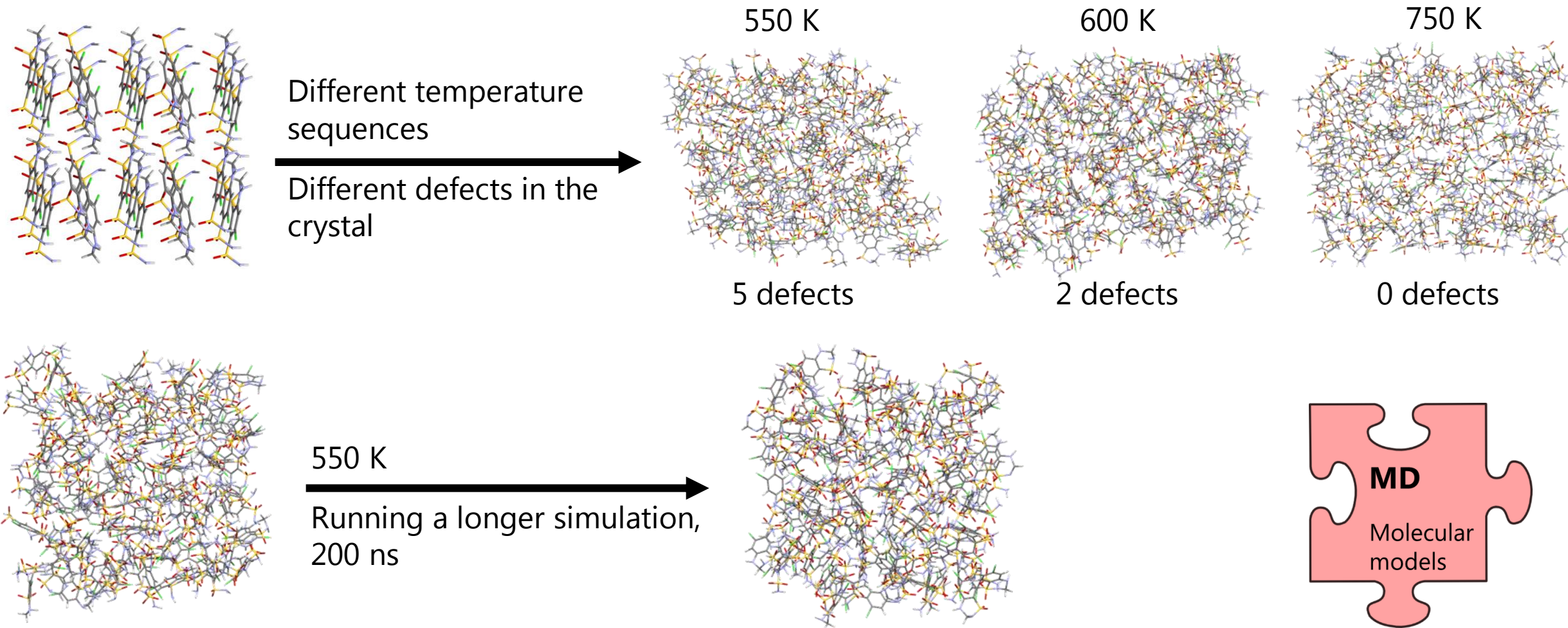


HCT from QC or BM



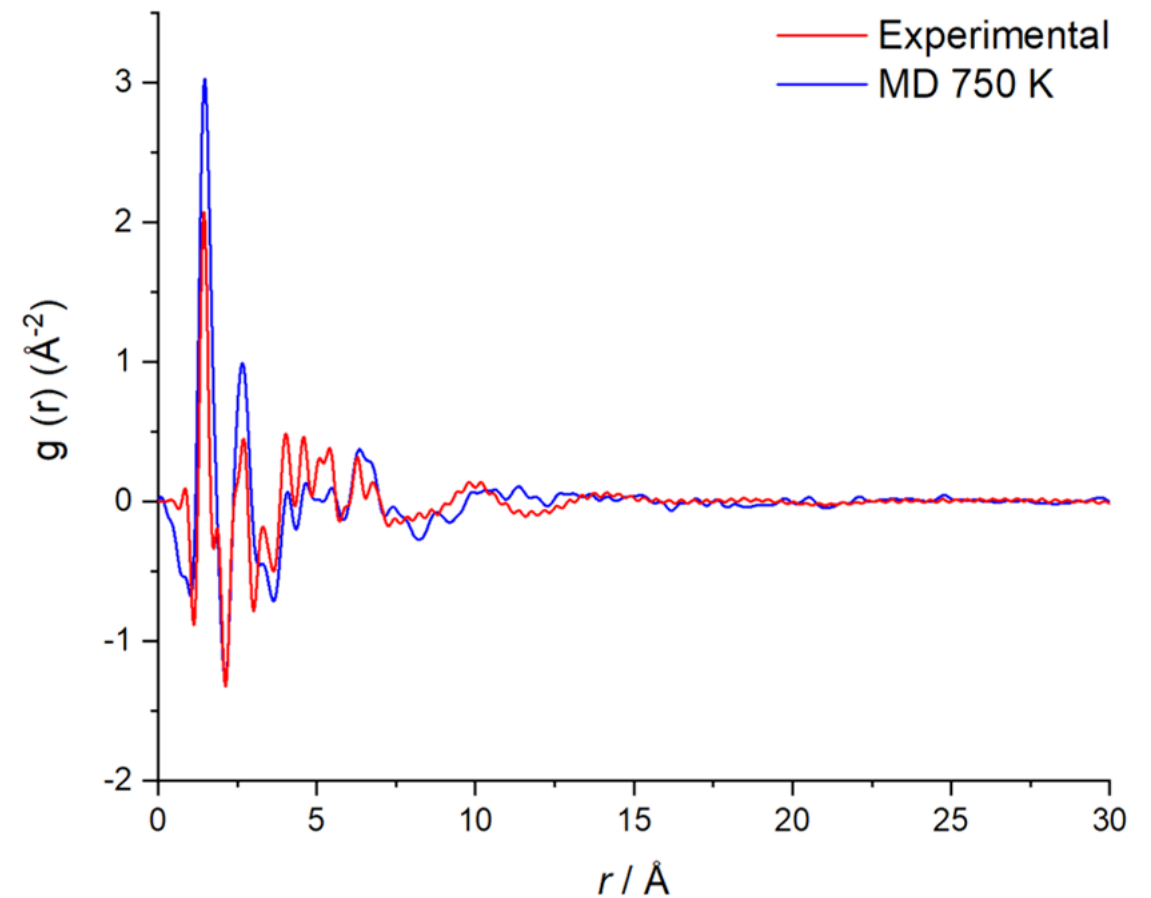
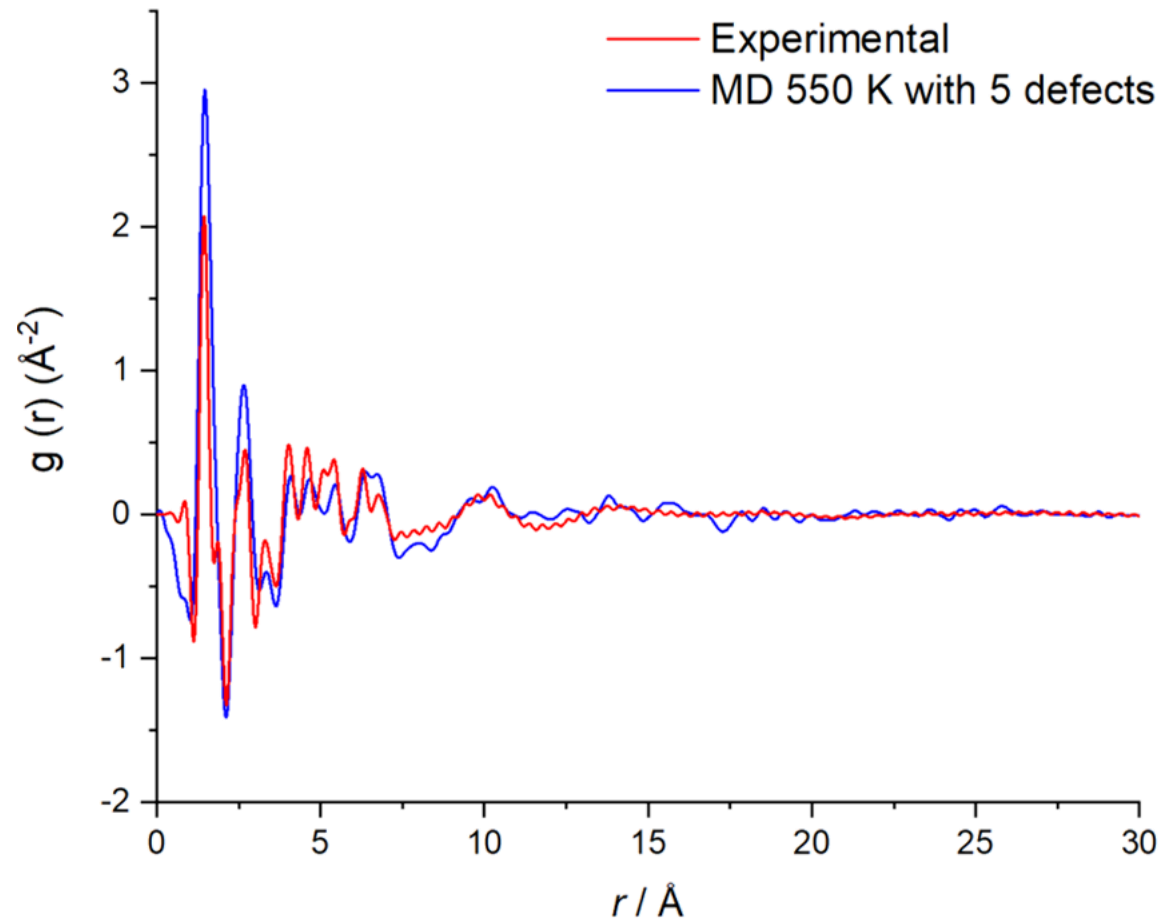
Understanding the molecular organization of amorphous HCT

Molecular Dynamic simulations of QC



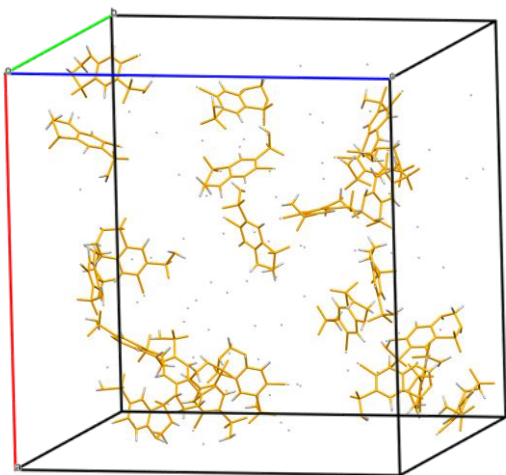
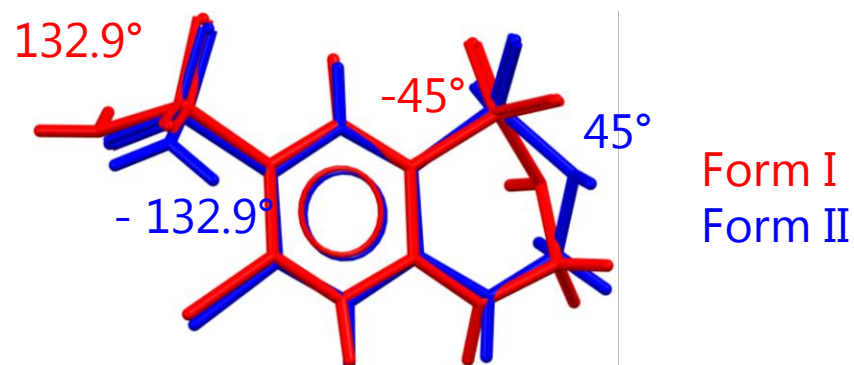
Understanding the molecular organization of amorphous HCT

Comparison between experimental and simulated PDF data of QC method

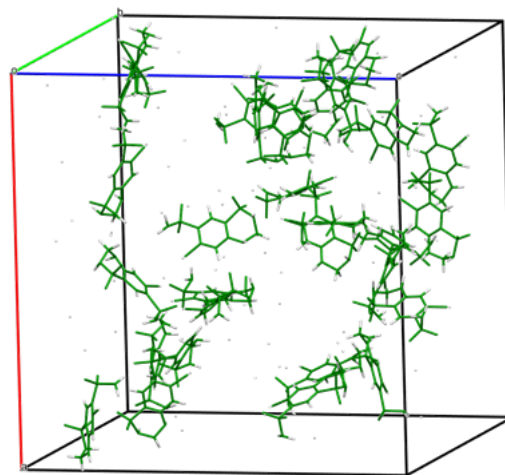


Understanding the molecular organization of amorphous HCT

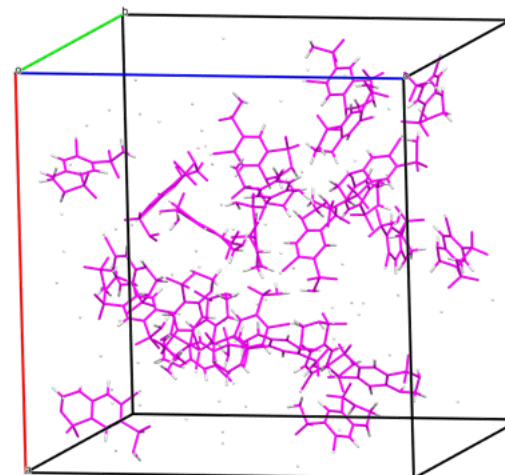
Dihedral angle distribution of QC method



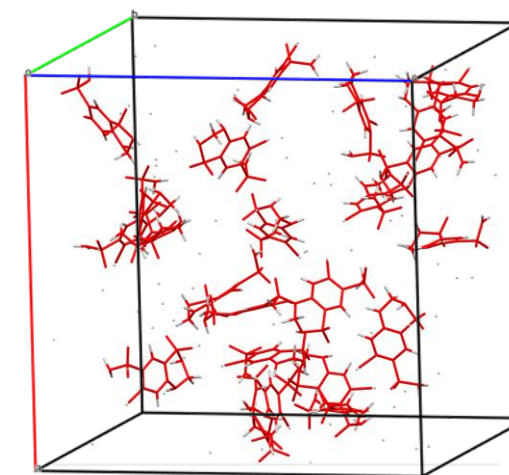
25% similar to
form II



29% with +132°
and +45°



24% similar
to form I



22% with -132°
and -45°

Understanding the molecular organization of amorphous HCT

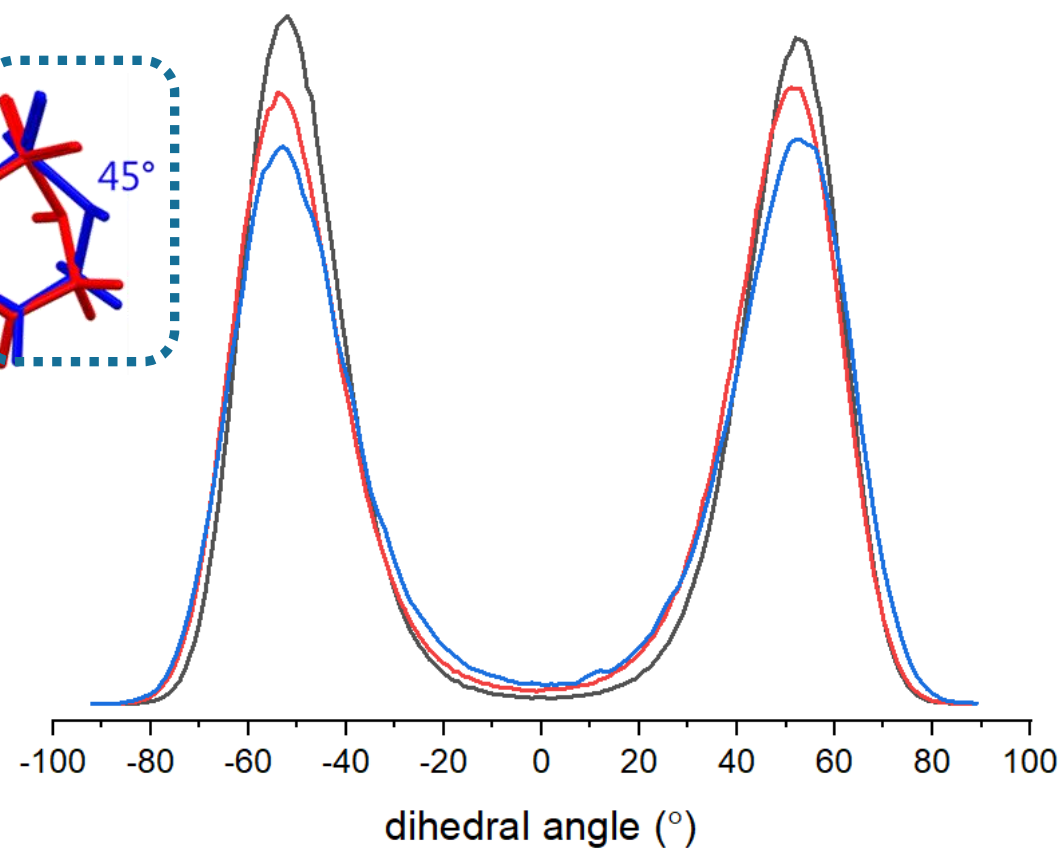
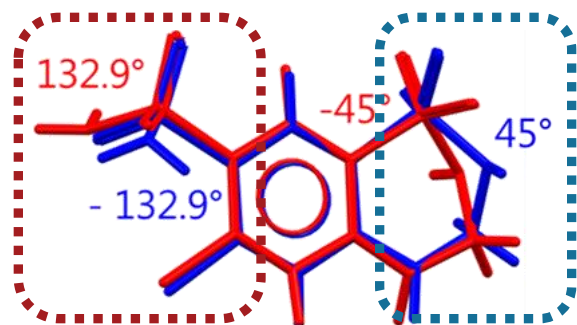
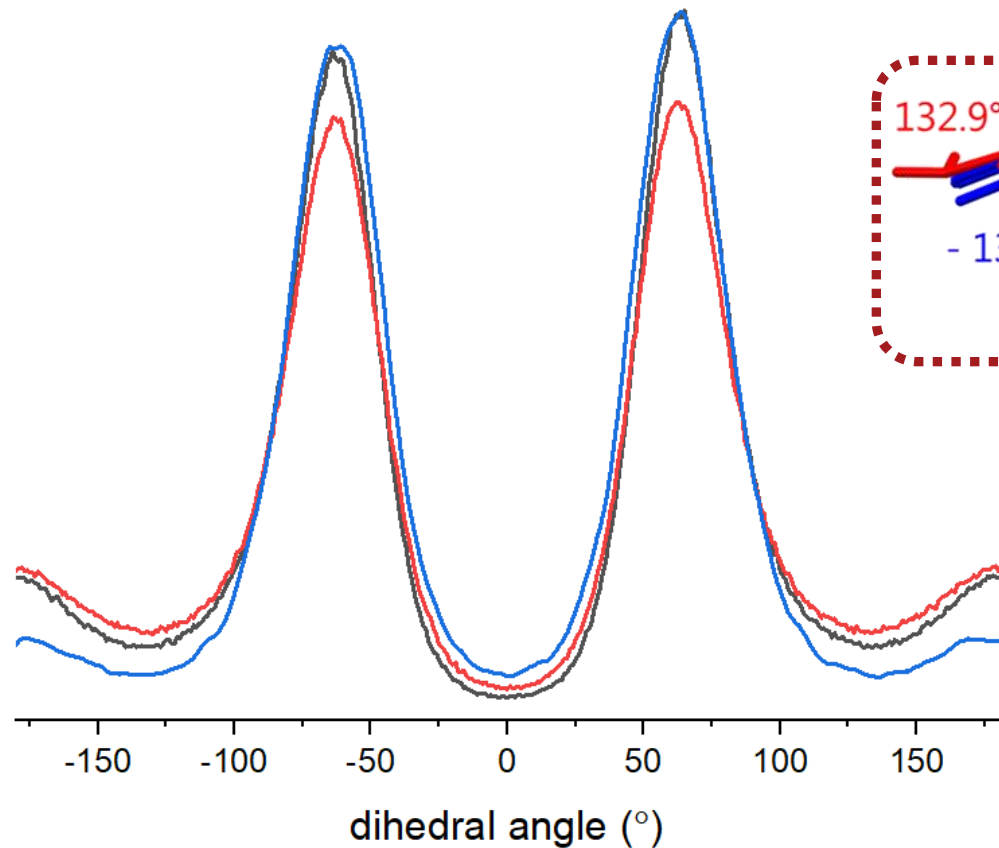
Dihedral angle distribution of QC method

C4-C5-S1-N3

— 550 K_random box
 — 550 K_5 defects
 — 600 K_2 defects

C1-N1-C2-N2

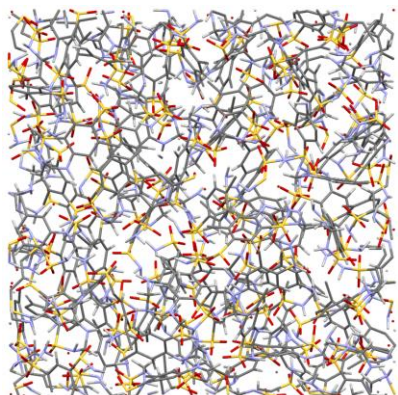
— 550 K_random box
 — 550 K_5 defects
 — 600 K_2 defects



Understanding the molecular organization of amorphous HCT

Molecular Dynamic simulations of SD

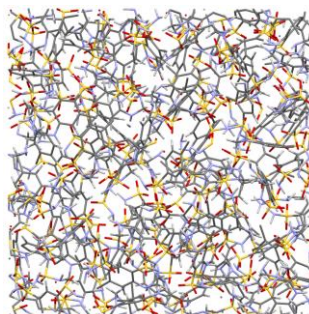
100 HCT + 1000 EtOH



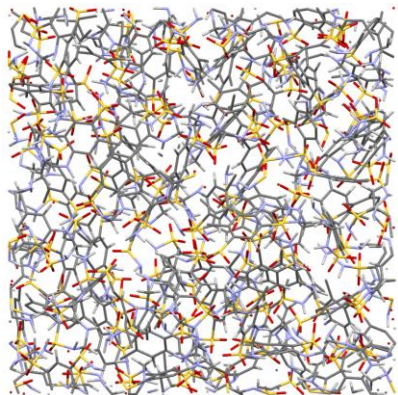
100 ps

- i) -5 EtOH mol
- ii) -10 EtOH mol

353 K



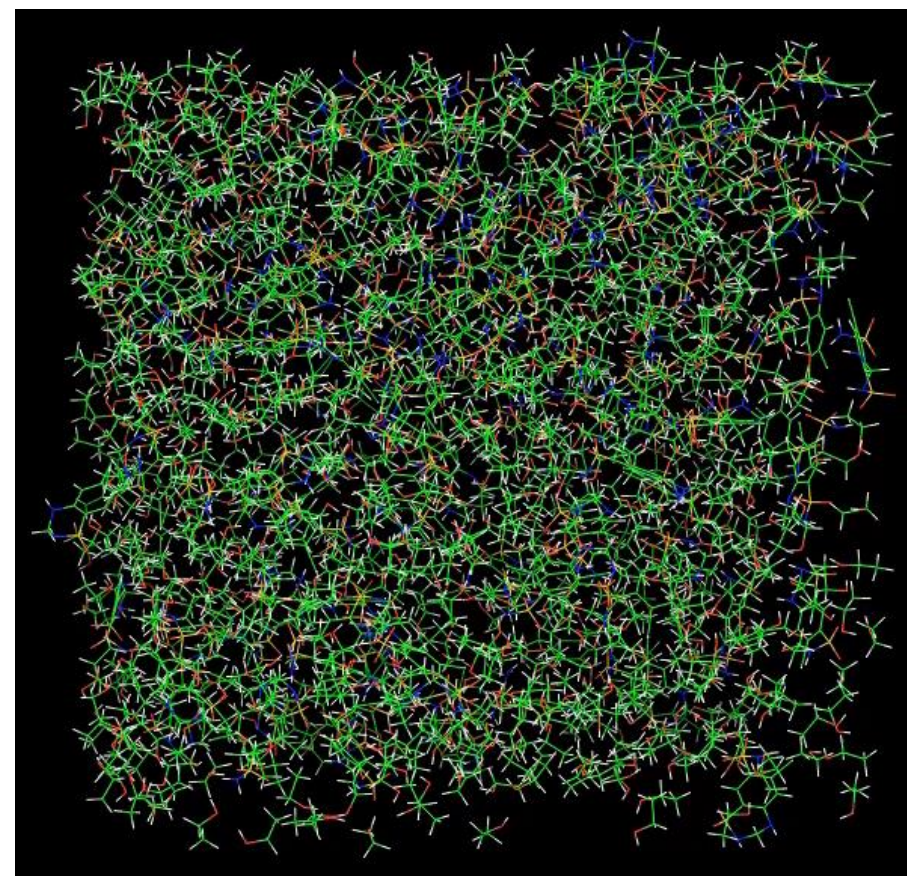
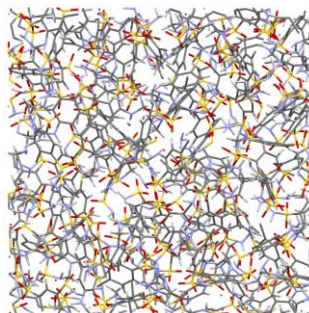
100 HCT + 1000 EtOH



10 ps

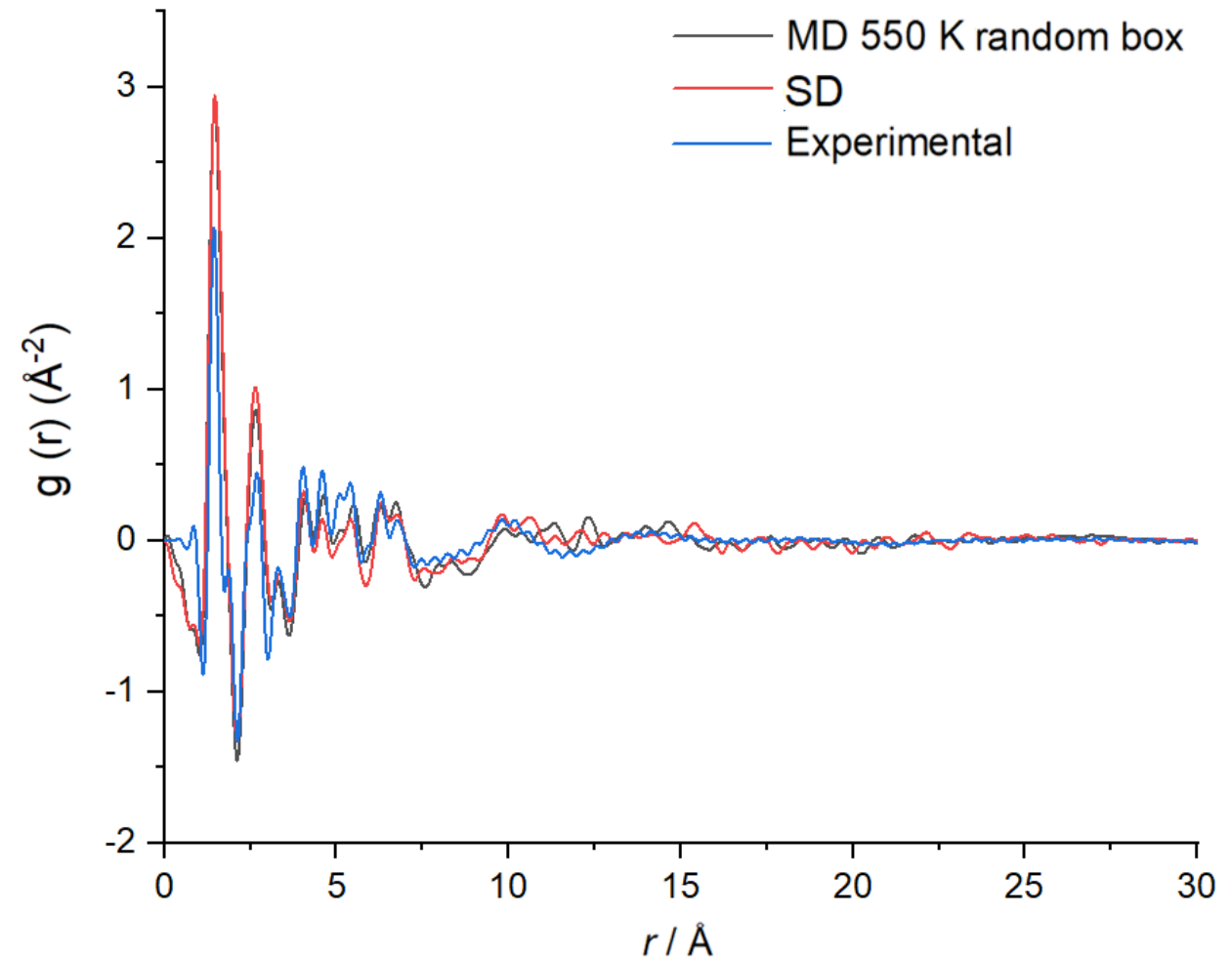
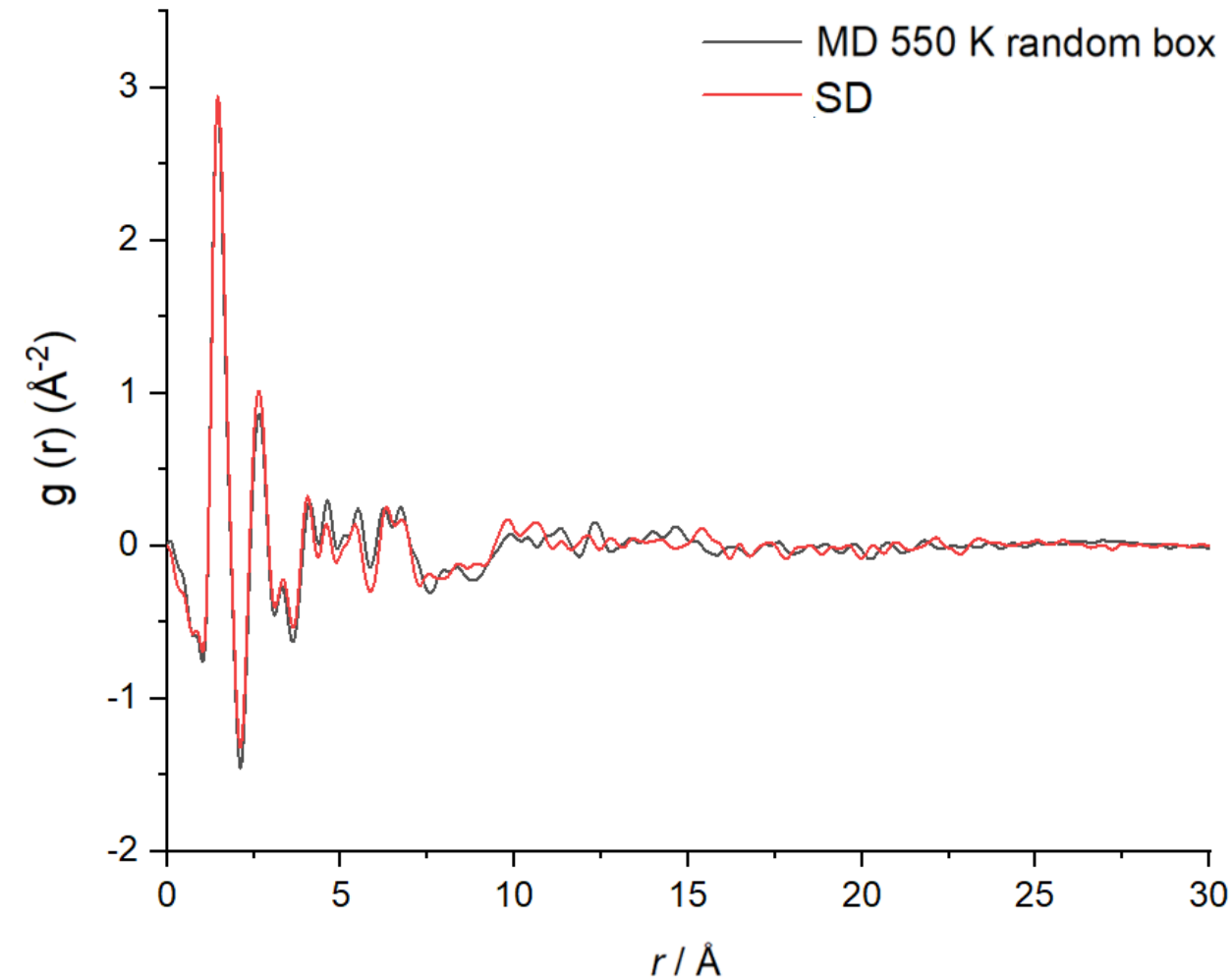
- i) -5 EtOH mol
- ii) -10 EtOH mol

353 K



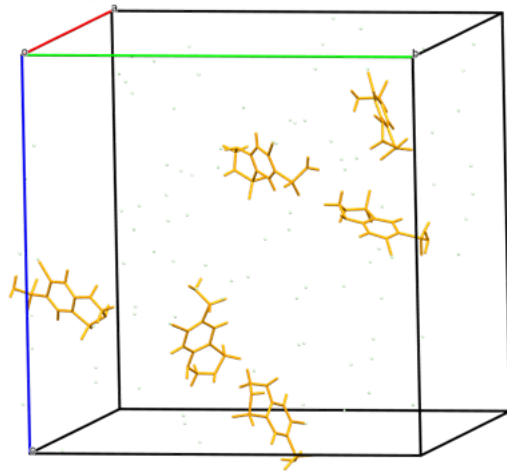
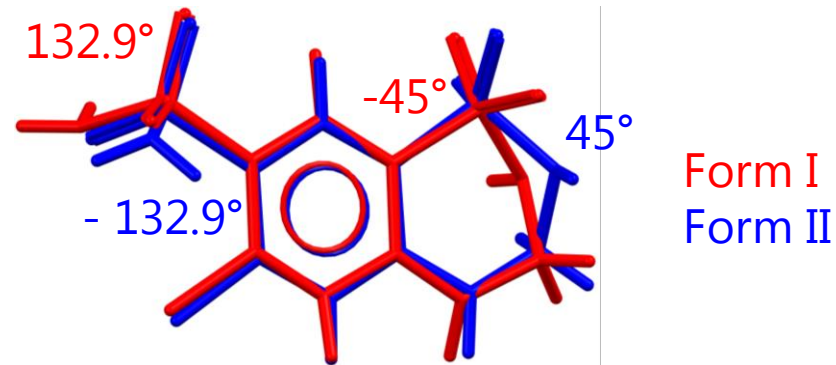
Understanding the molecular organization of amorphous HCT

Comparison between simulated and experimental PDF data of SD method

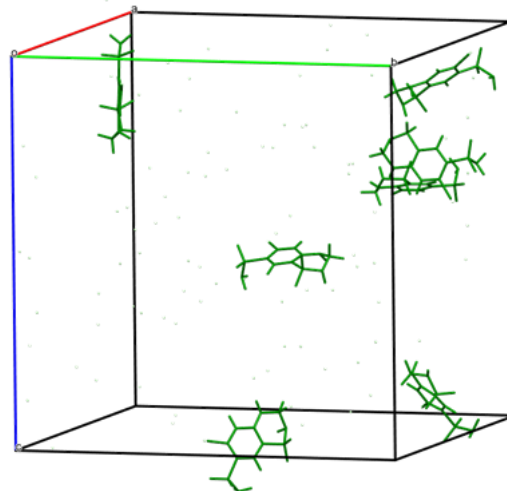


Understanding the molecular organization of amorphous HCT

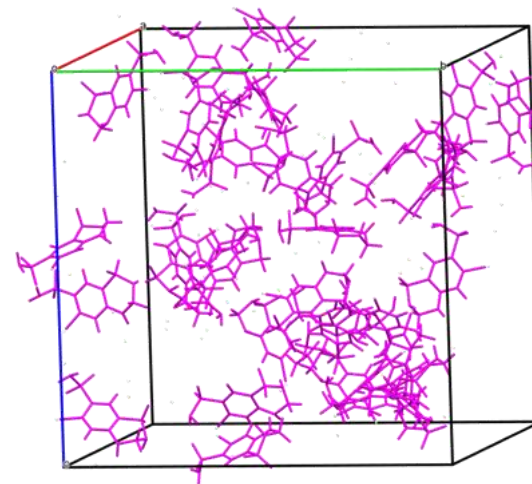
Dihedral angle distribution of SD method



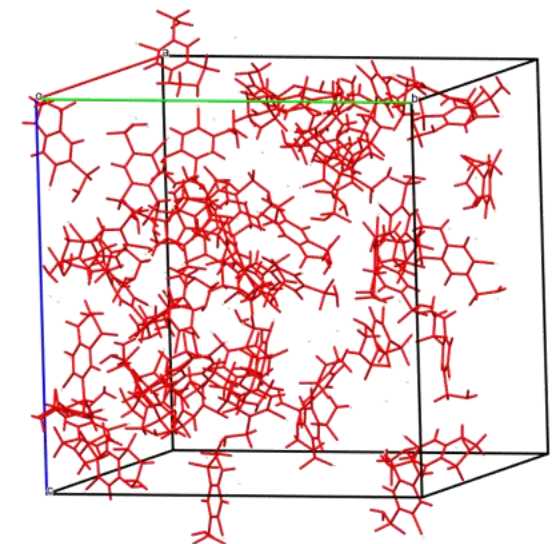
6% similar to form II



7% with +132° and +45°



36% similar to form I



51% with -132° and -45°

Understanding the molecular organization of amorphous HCT

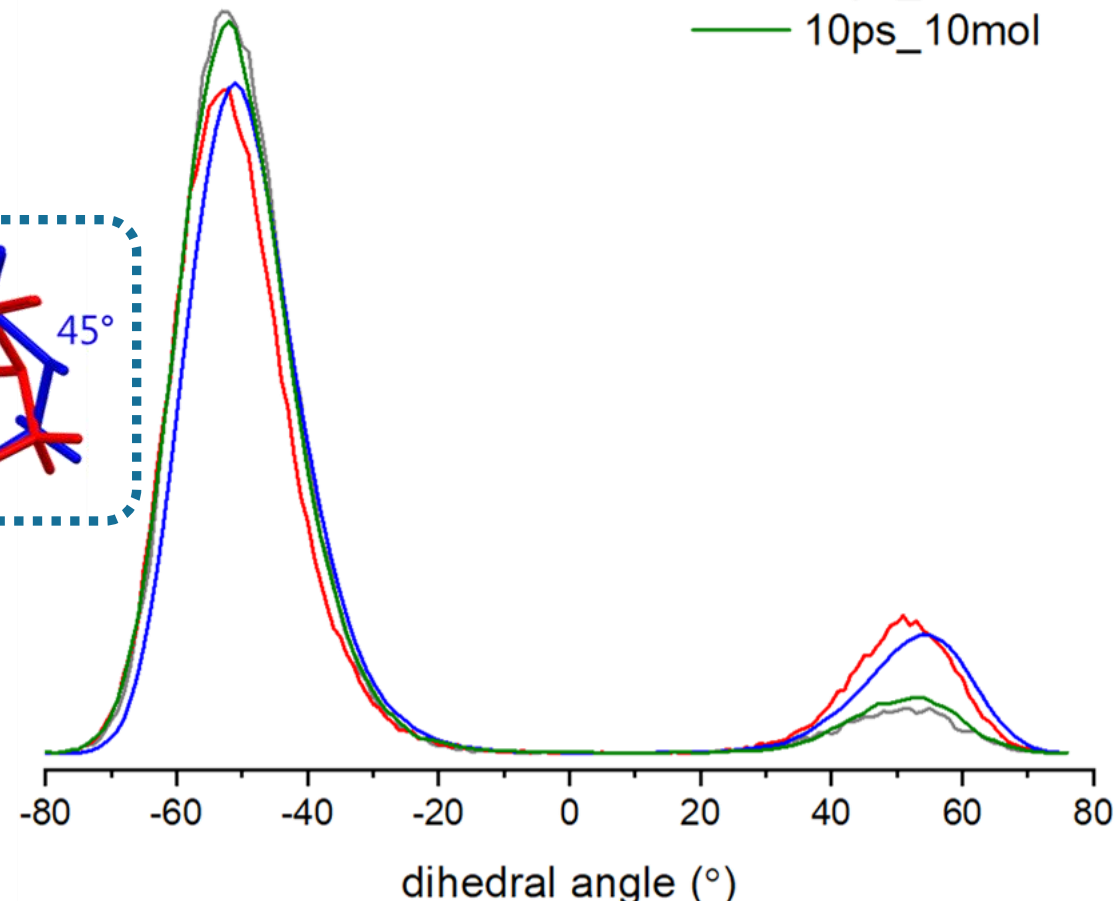
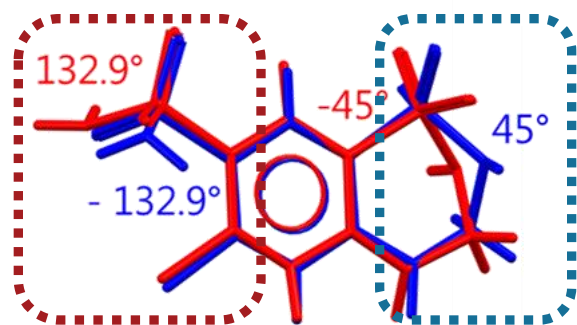
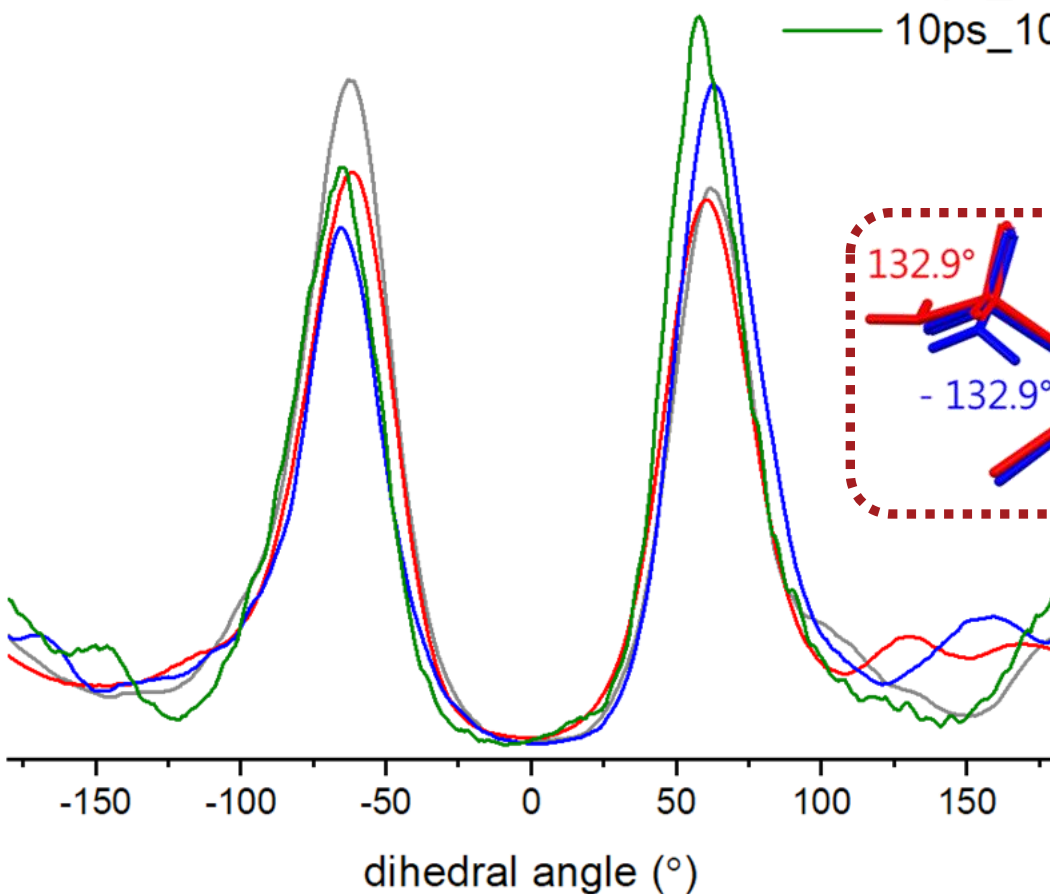
Dihedral angle distribution of SD method

C4-C5-S1-N3

- 100ps_5mol
- 100ps_10mol
- 10ps_5mol
- 10ps_10mol

C1-N1-C2-N2

- 100ps_5mol
- 100ps_10mol
- 10ps_5mol
- 10ps_10mol



Take home message

Determining the structure of both crystalline and amorphous materials is like solving a jigsaw puzzle – it can be more or less complex, but several pieces (structural methods) are needed to accurately determine the structural models we do need.



Acknowledgments

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Assoc. Prof. Kirsten Ø. Jensen

Dr. Anders Larsen



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