Distinguishing weak hydrogen bonding with NMR

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Results published: M. Kibalchenko, D. Lee, L. Shao, M. C. Payne, J. J. Titman, J. R. Yates, (2010). Distinguishing hydrogen bonding networks in alpha-D-galactose using NMR experiments and first principles calculations. Chem. Phys. Lett. In press doi:10.1016/j.cplett.2010.08.077

Aim: distinguishing hydrogen bonds

- hydrogen bonding is the most important of all directional intermolecular interactions

- determines:

  - molecular conformations

  - molecular aggregations

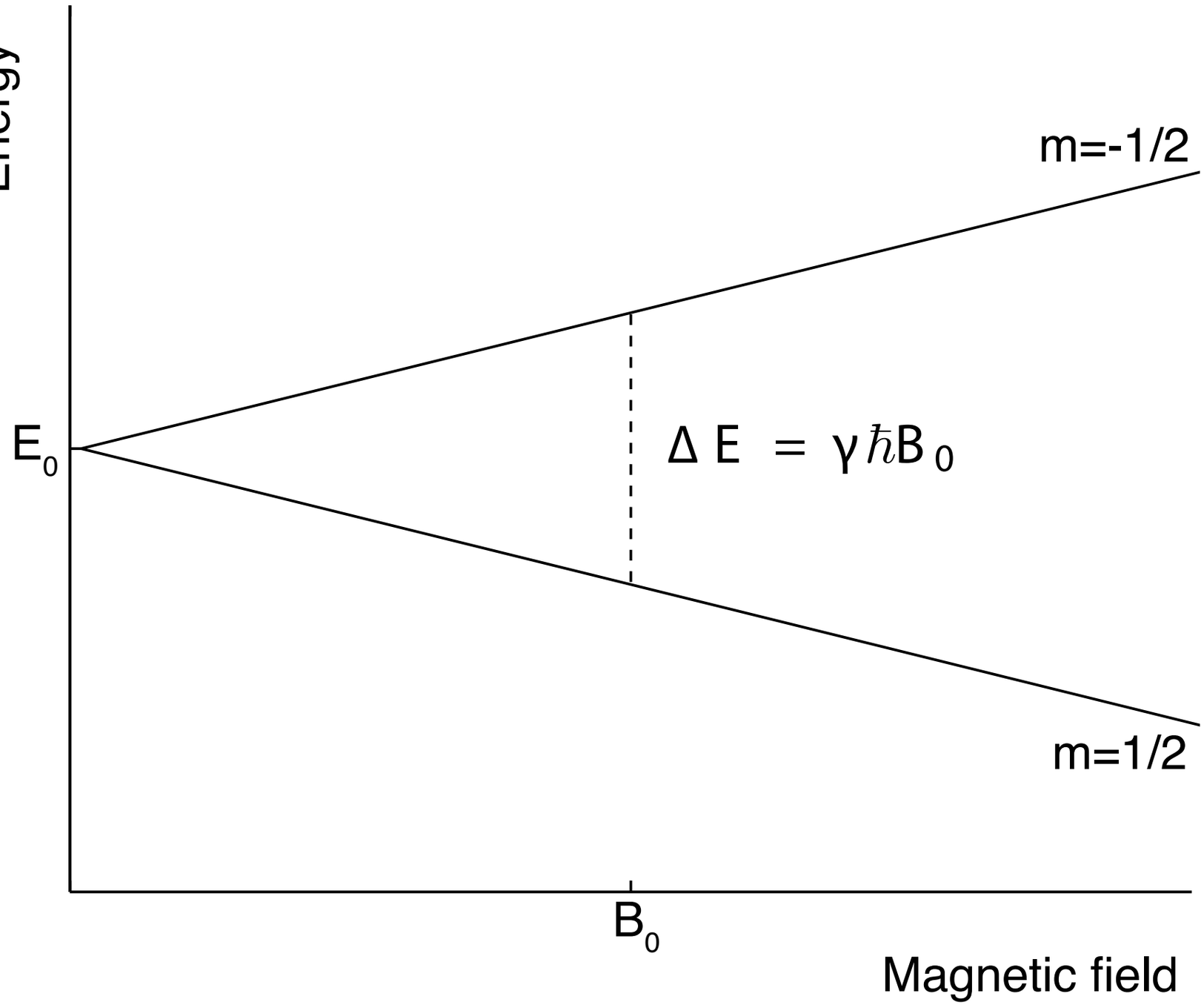
  - function of many chemical systems from inorganic to biological

[1] Steiner, T. Angew. Chem., Int. Ed. 2002, 41, 48-76

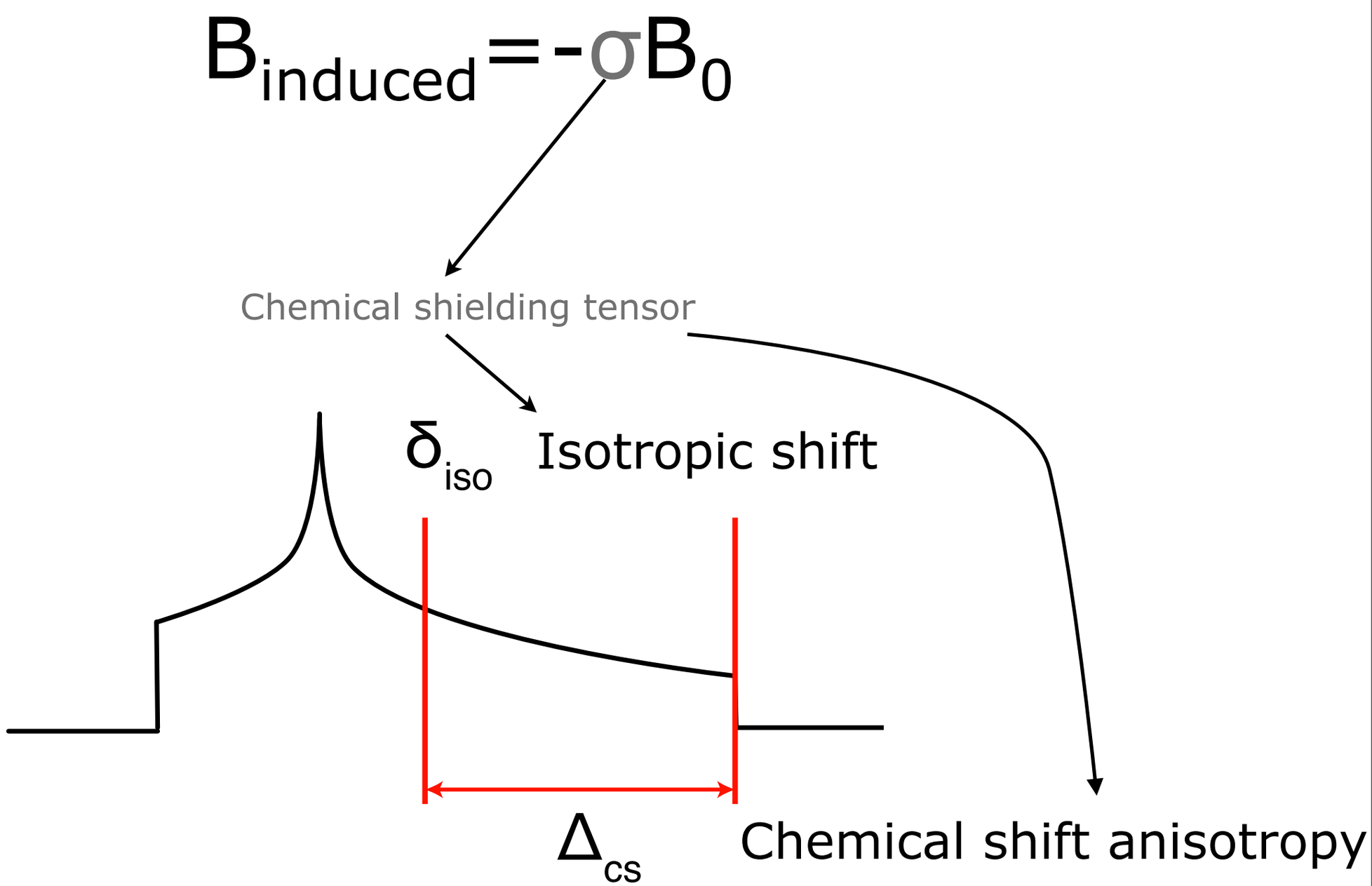
Aim: distinguishing hydrogen bonds

- Can I use NMR to distinguish hydrogen bonding networks?
- How to do it? - which nuclei do we need to measure?

Introduction: nuclear magnetic resonance



Introduction: nuclear magnetic resonance



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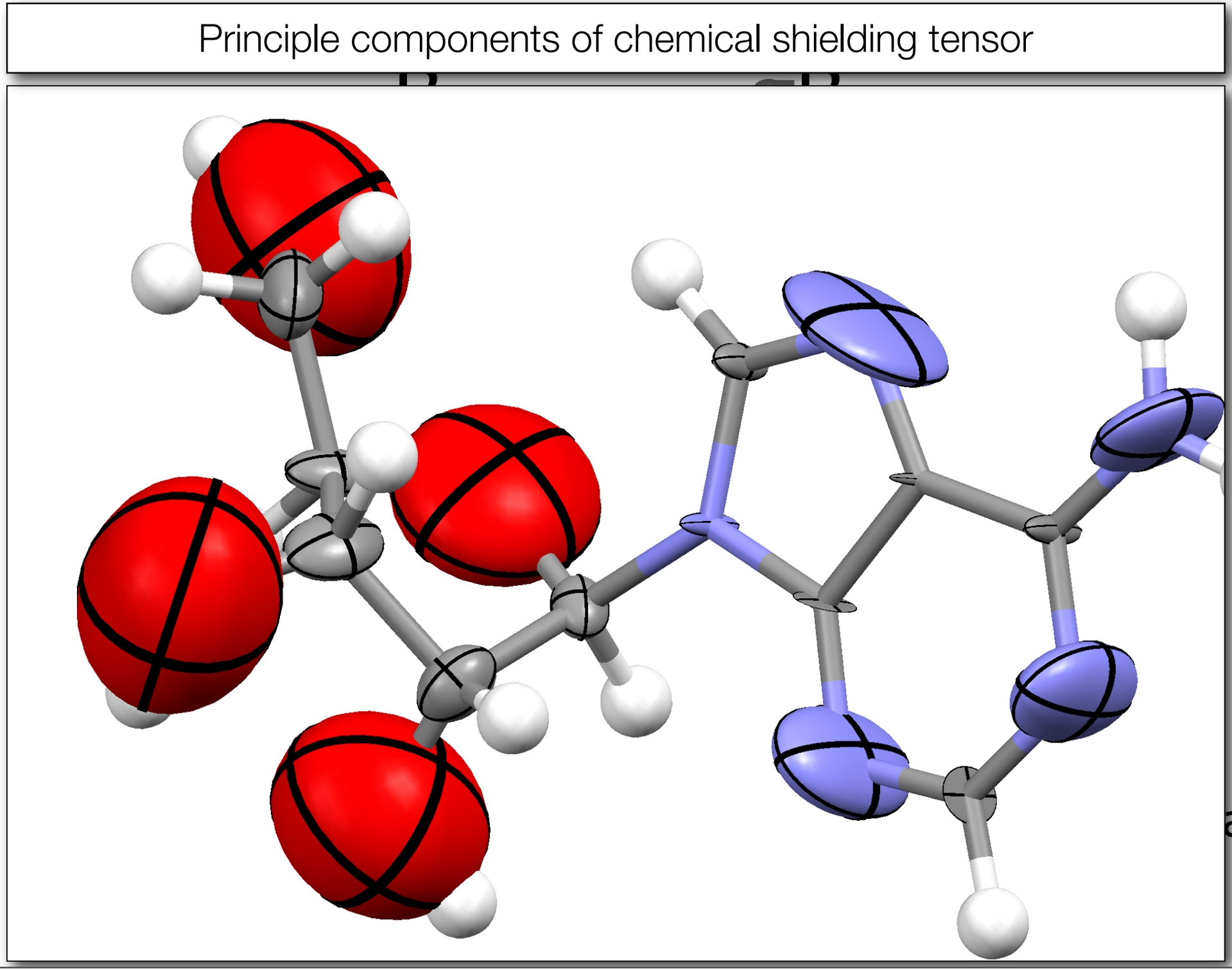
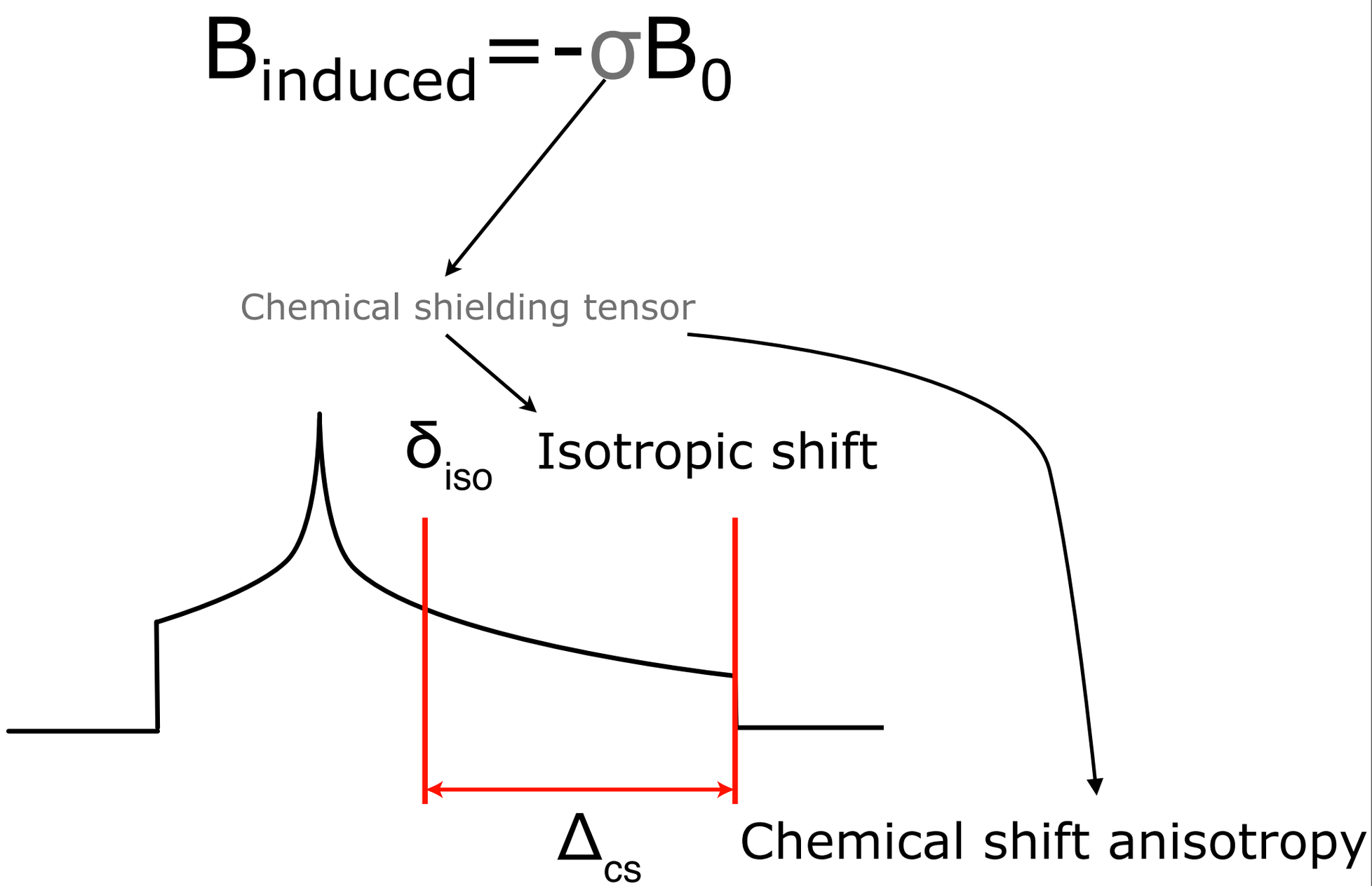


anisotropy

Introduction: nuclear magnetic resonance

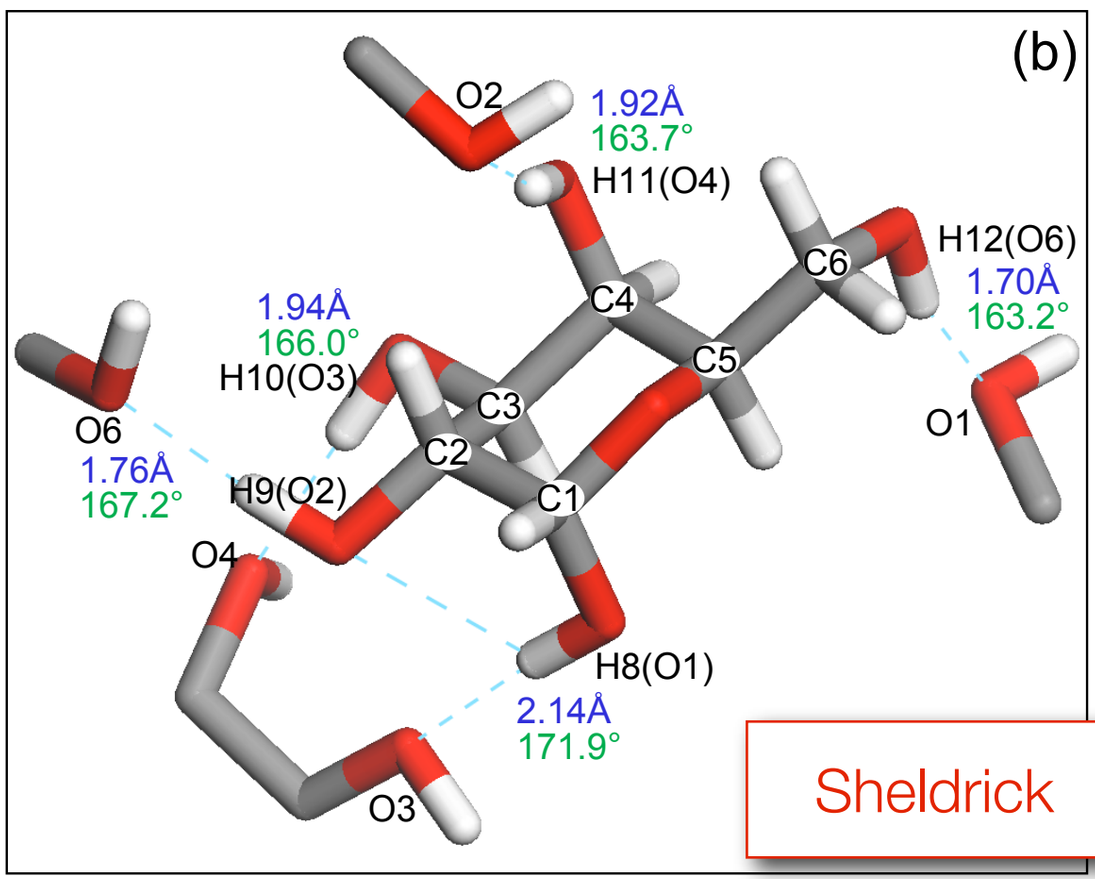


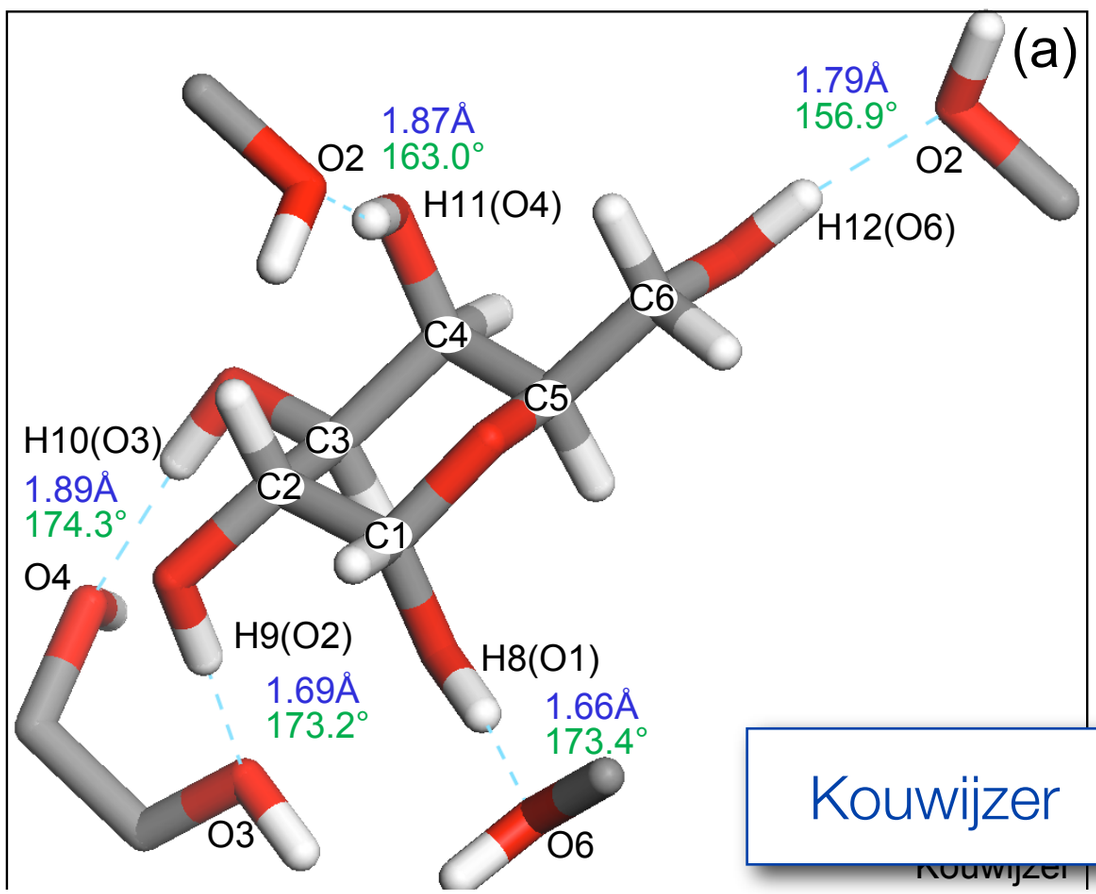
System of interest: alpha-D-galactose

- three X-ray derived molecular crystal structures presenting three differing hydrogen bonding networks

after hydrogen atom geometry optimisation:

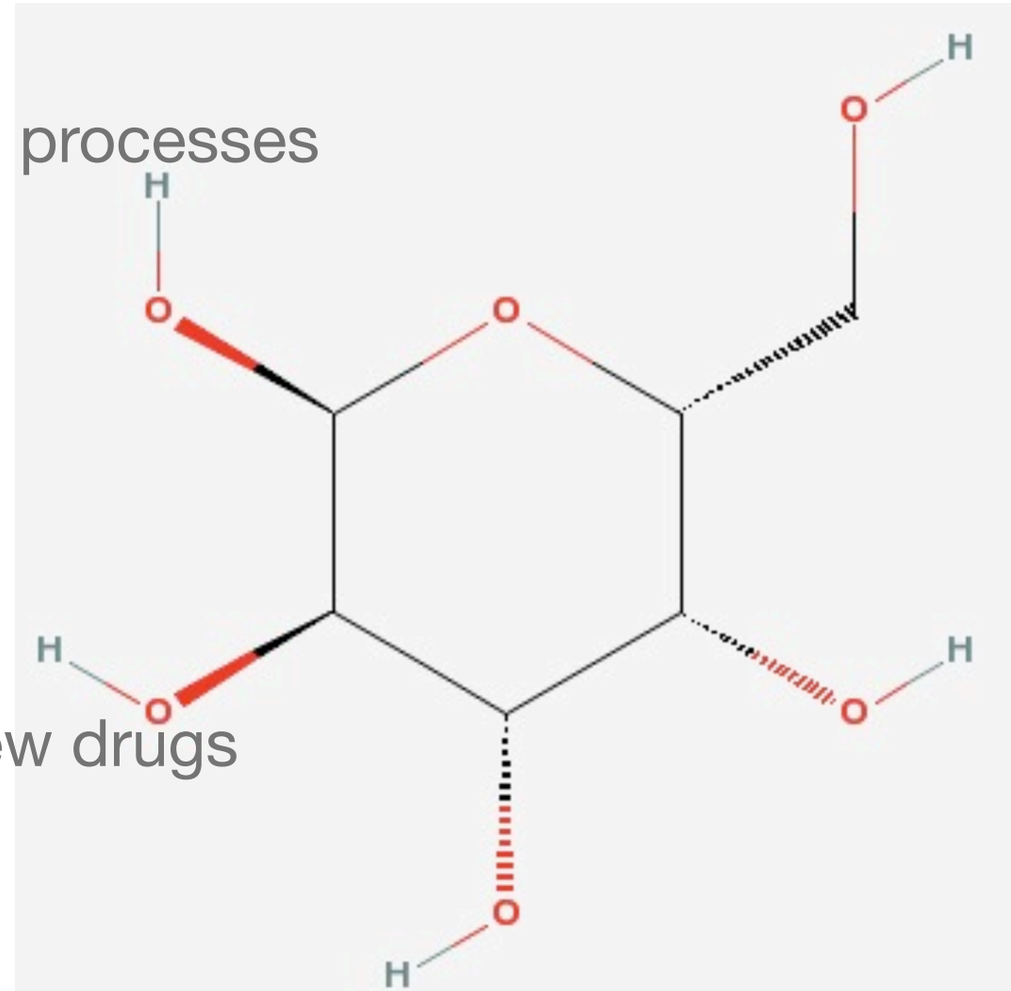
- two differing hydrogen bonding networks - which is the true one?





System of interest: alpha-D-galactose

- monosaccharide, usually bound to a non-carbohydrate molecule
- acts as an intermediate in numerous biological processes
- occurs naturally in foods
- popular food additive
- used in pharmaceutical R&D as the core for new drugs



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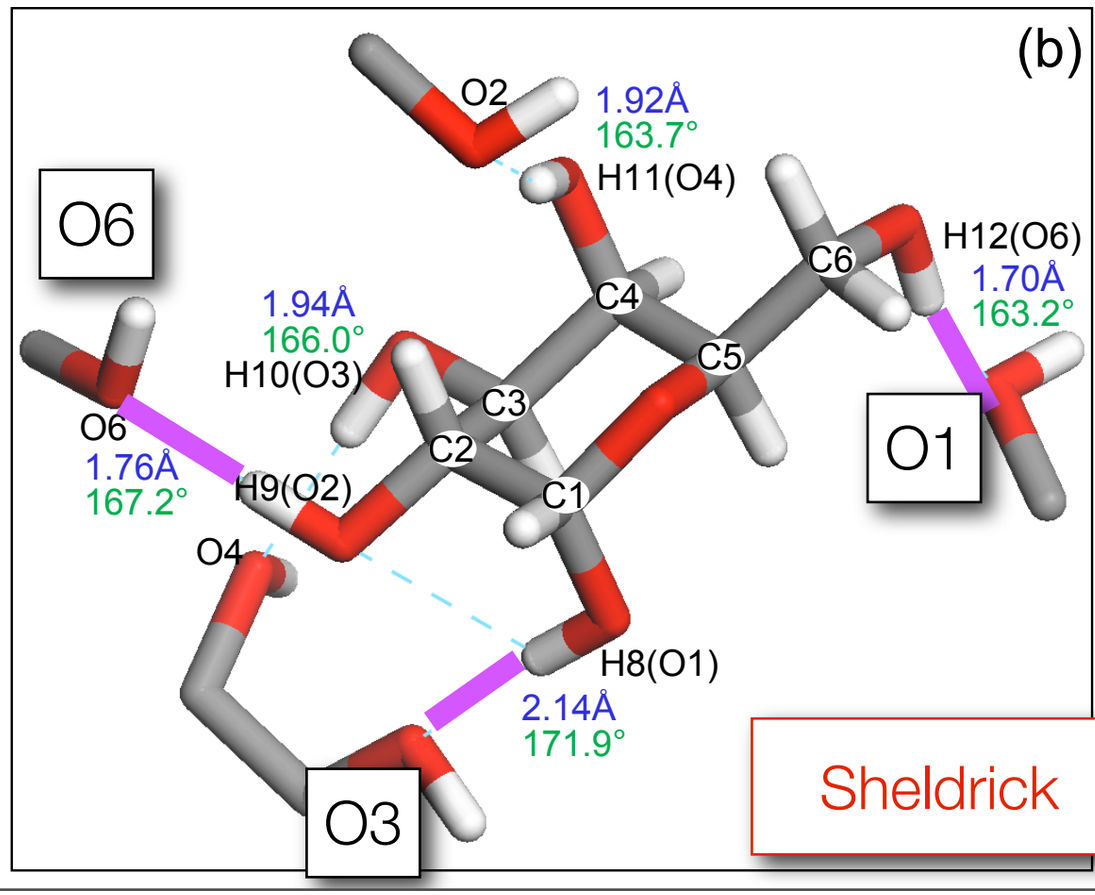
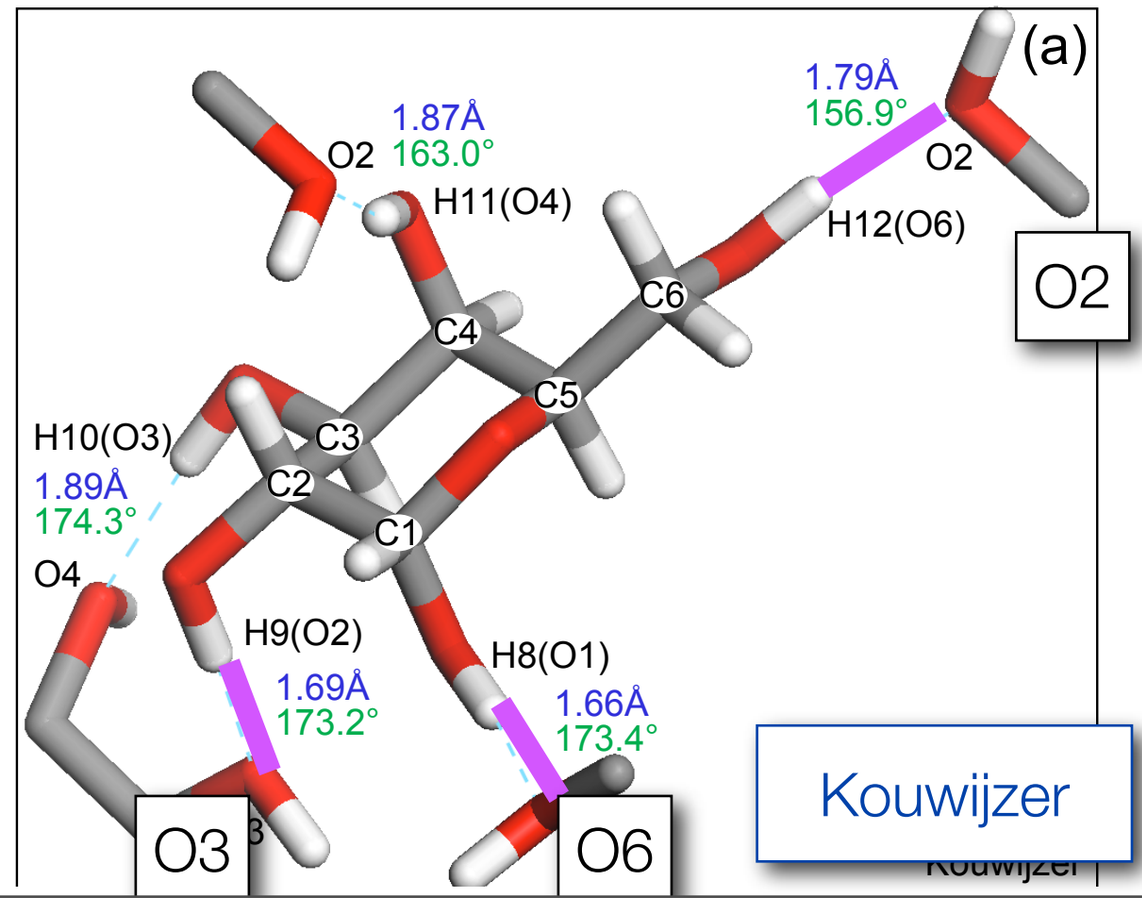




Available experimental data - Carbon atom NMR

	Kouwijzer		Sheldrick	
	δ_{iso}	Δ_{cs}	δ_{iso}	Δ_{cs}
Mean Absolute Error (ppm)	0.9	1.1	1.4	1.5
Max Absolute Error (ppm)	2.5	2.5	4.1	2.1

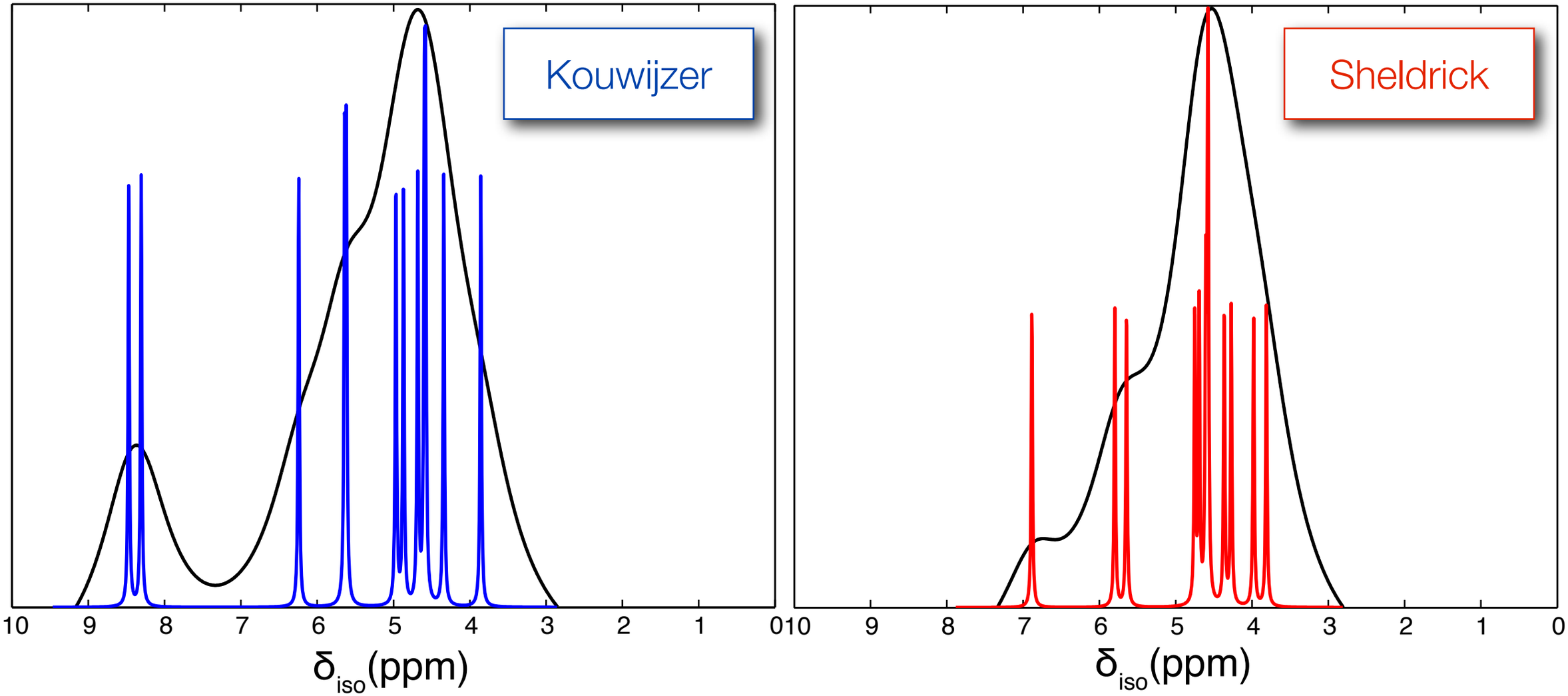
alpha-D-galactose $C_6H_{12}O_6$

	Kanters	
	δ_{iso}	Δ_{cs}
Mean Absolute Error (ppm)	0.9	0.8
Max Absolute Error (ppm)	2.7	1.3

beta-D-fructose $C_6H_{12}O_6$

What about Hydrogens and Oxygens?

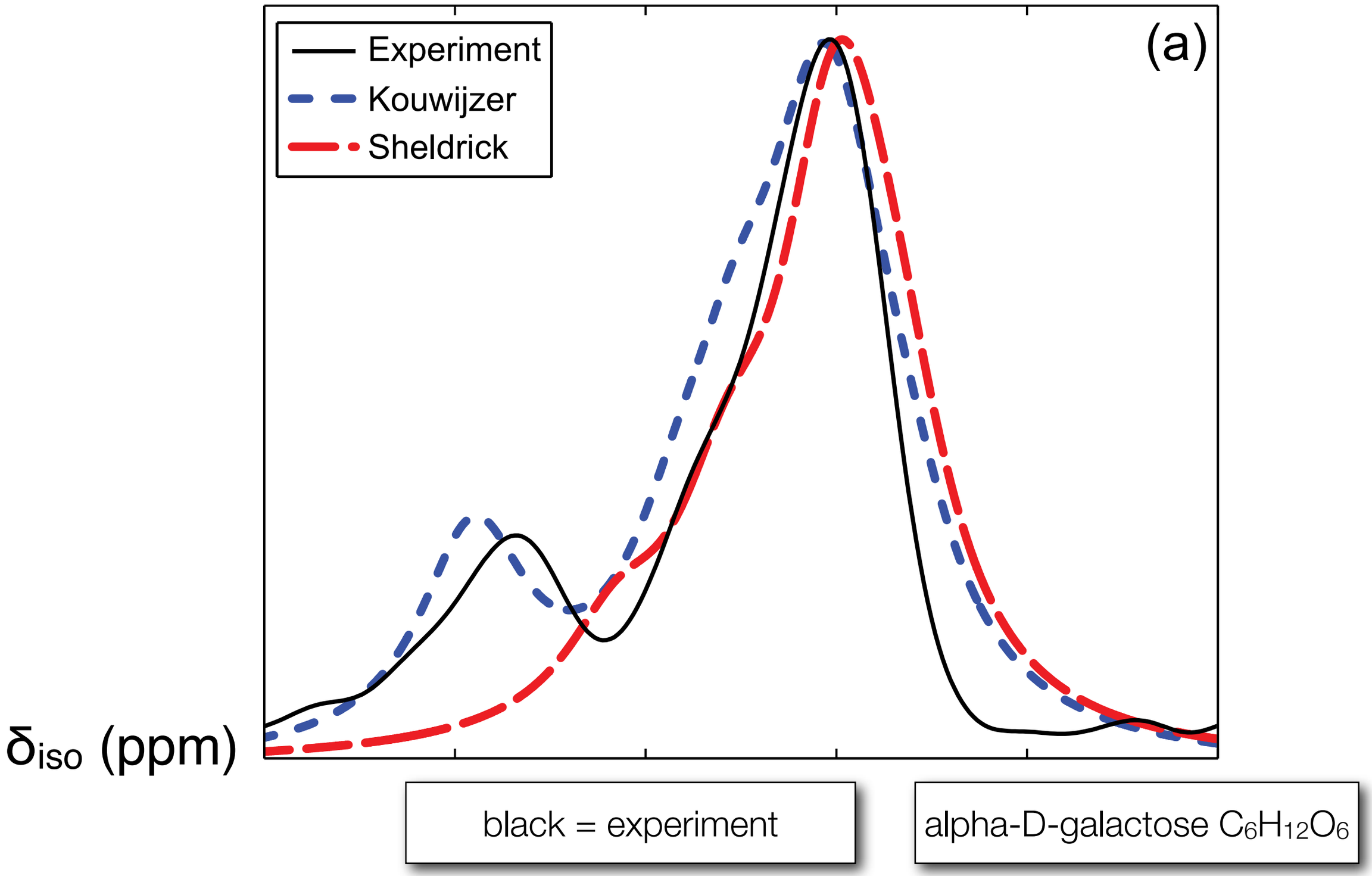
- identified hydrogens could show a difference even for low resolution NMR experiment. Prediction:



What about Hydrogens and Oxygens?

- for oxygen, isotropic shifts differ by 12.8 ppm maximum between equivalent atomic sites
- however, oxygen isotropic shifts are known to span hundreds of ppm
- therefore, unclear how accurately experiment could differentiate 12.8 ppm

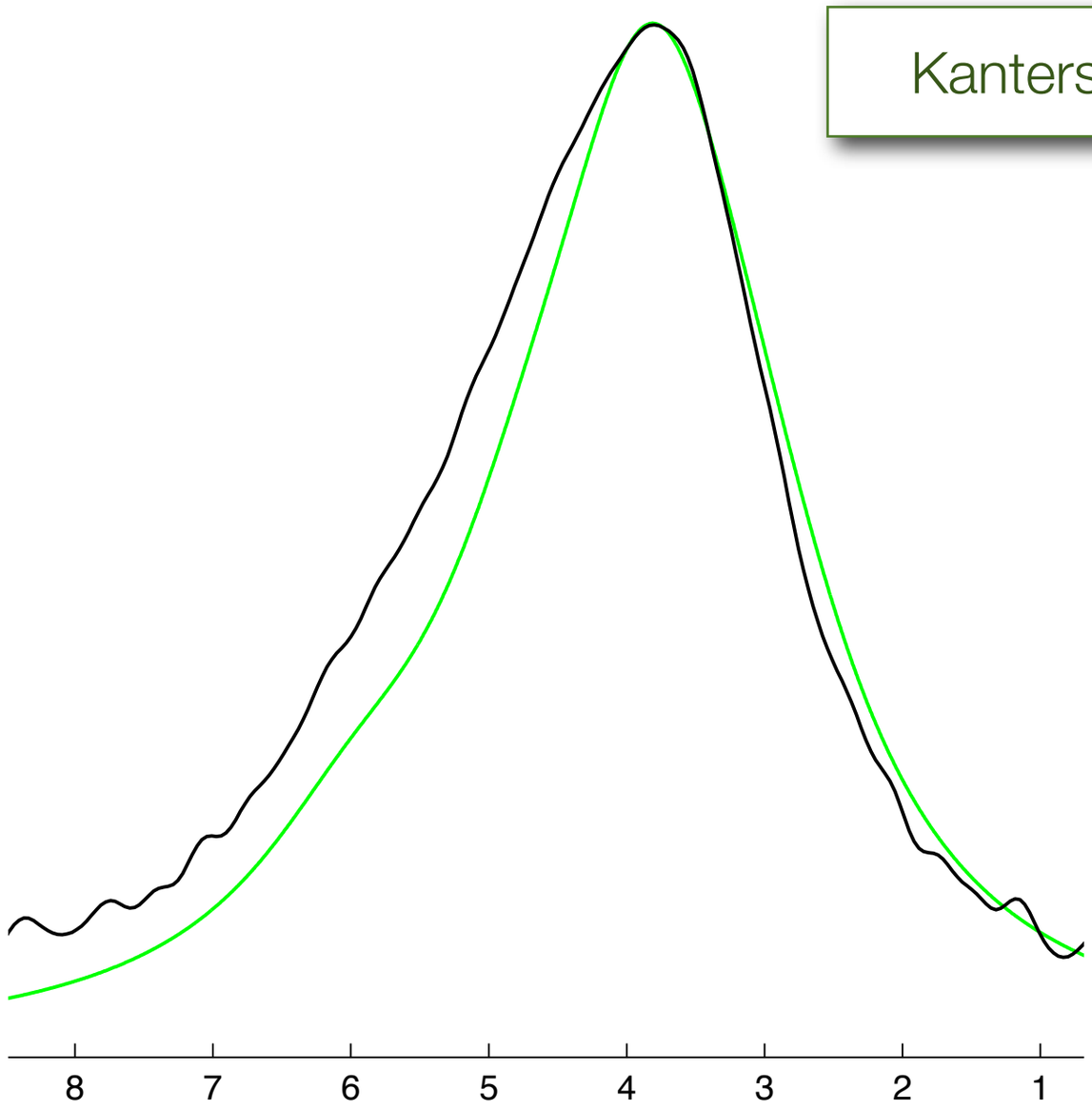
Recent hydrogen nmr results:



black = experiment

alpha-D-galactose $C_6H_{12}O_6$

Recent hydrogen nmr results:



δ_{iso} (ppm)

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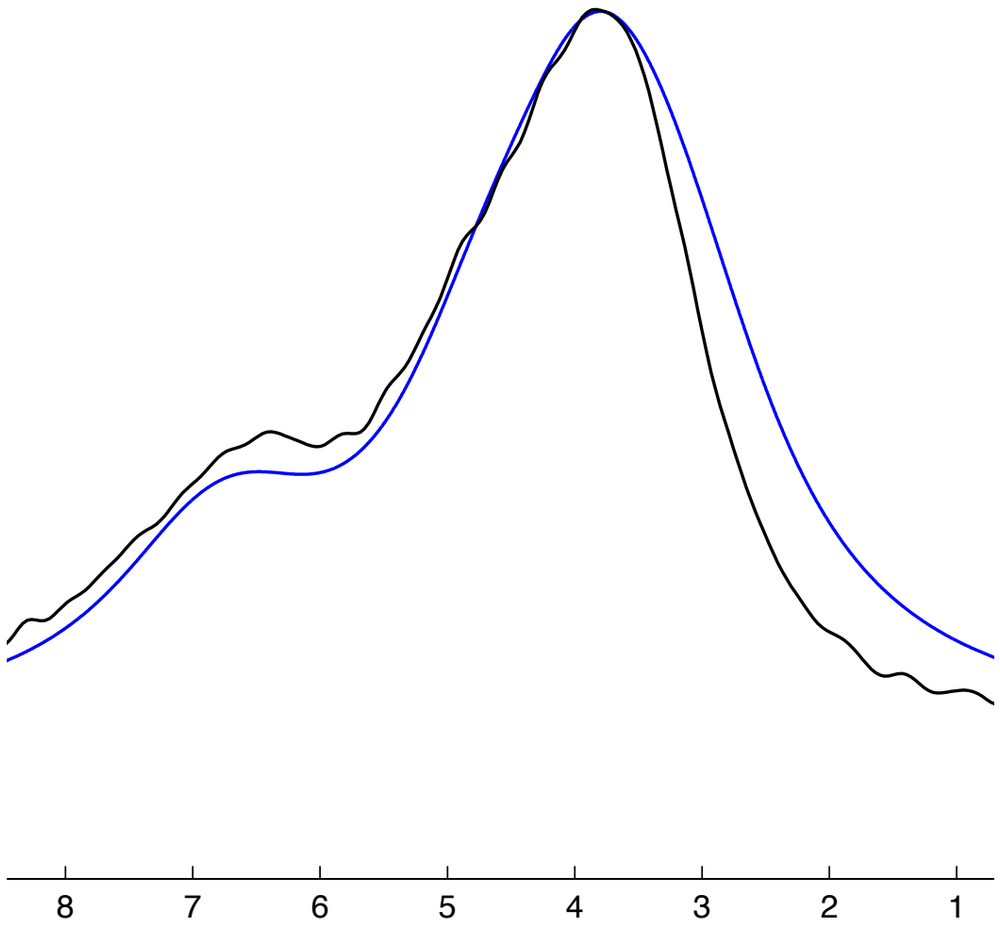
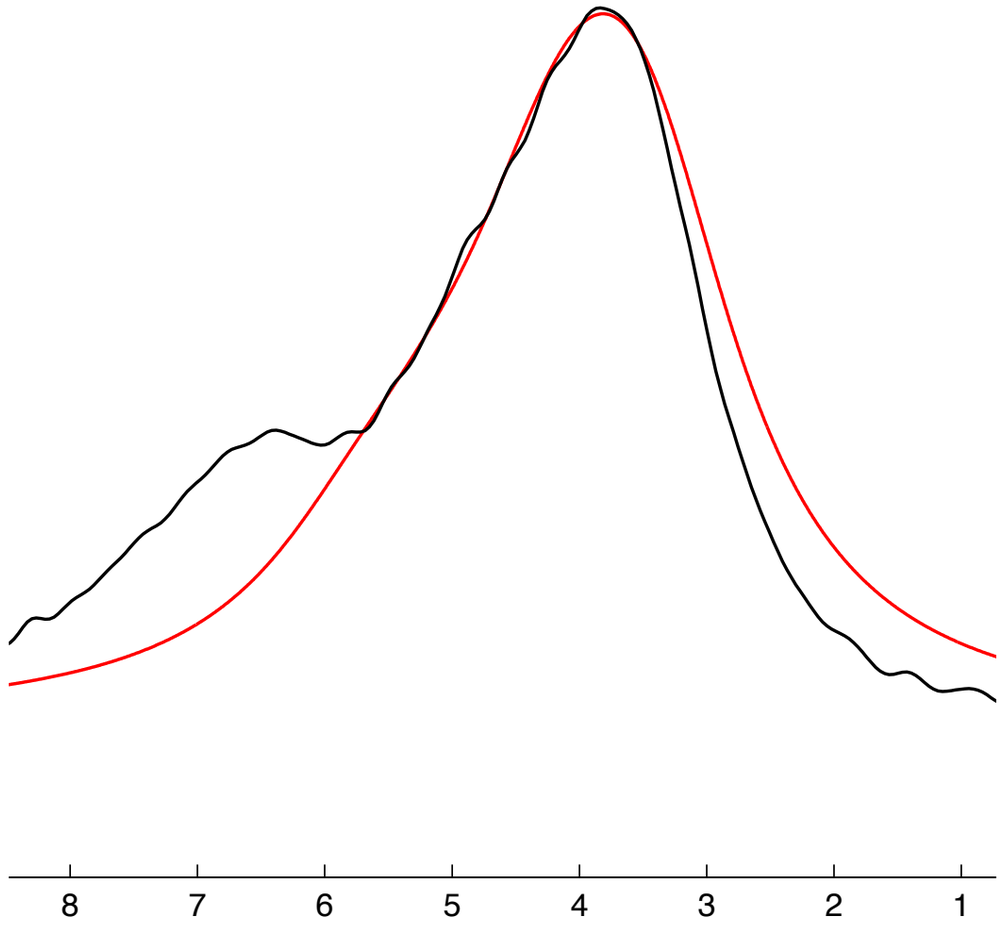
beta-D-fructose $C_6H_{12}O_6$

Recent hydrogen nmr results:

Kouwijzer



Sheldrick



δ_{iso} (ppm)

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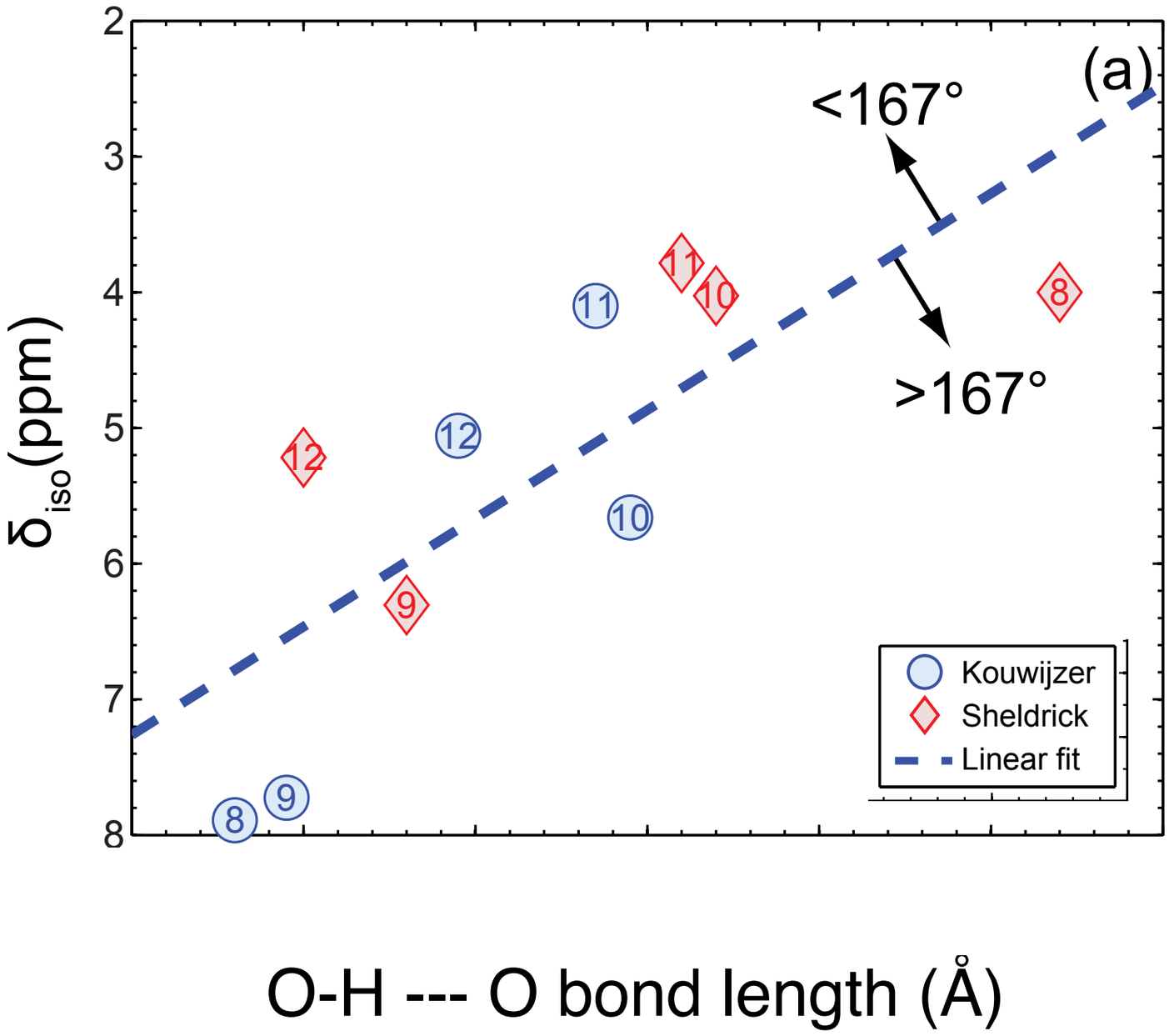
alpha-D-galactose $C_6H_{12}O_6$

some correlations



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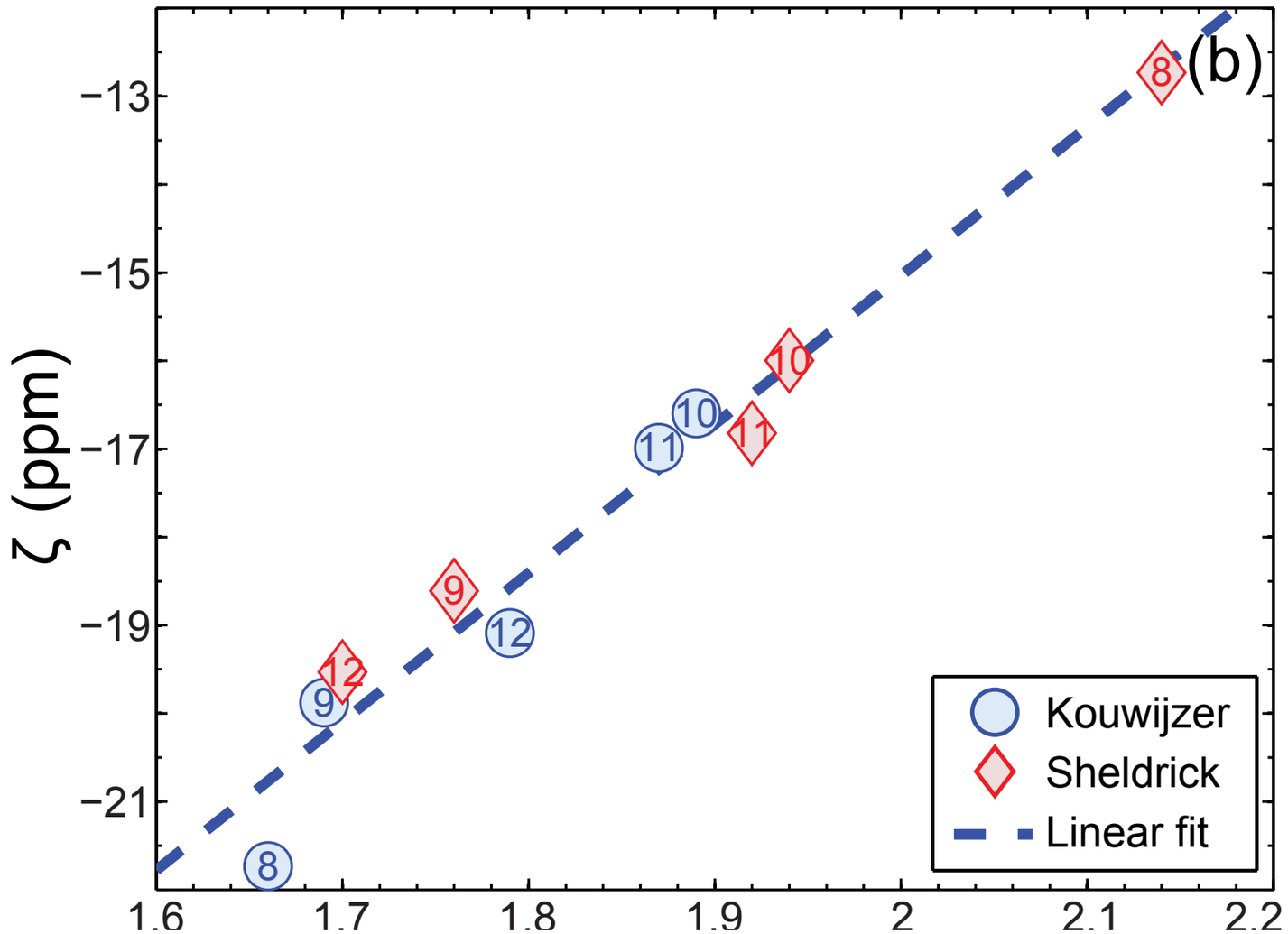

Conclusion

- hydrogen bonding network in alpha-D-galactose is established
- showed that combination of NMR experiment and calculations from first principles is extremely powerful for structure determination - even weak interactions such as hydrogen bonds
- hydrogens are obviously good candidates for studying hydrogen bonding, but even carbon NMR shows a small preference
- usefulness of oxygen NMR is unclear, but could potentially be more useful than carbons since oxygen atoms are quadrupolar and experiment could measure electric field gradient interactions
- results provide justification for the study of larger biological systems

Acknowledgements

- Jonathan Yates, Mike Payne
- Jeremy Titman, Daniel Lee, Limin Shao, Nottingham University, UK

TCM

EPSRC

Thank you for listening

back up slides