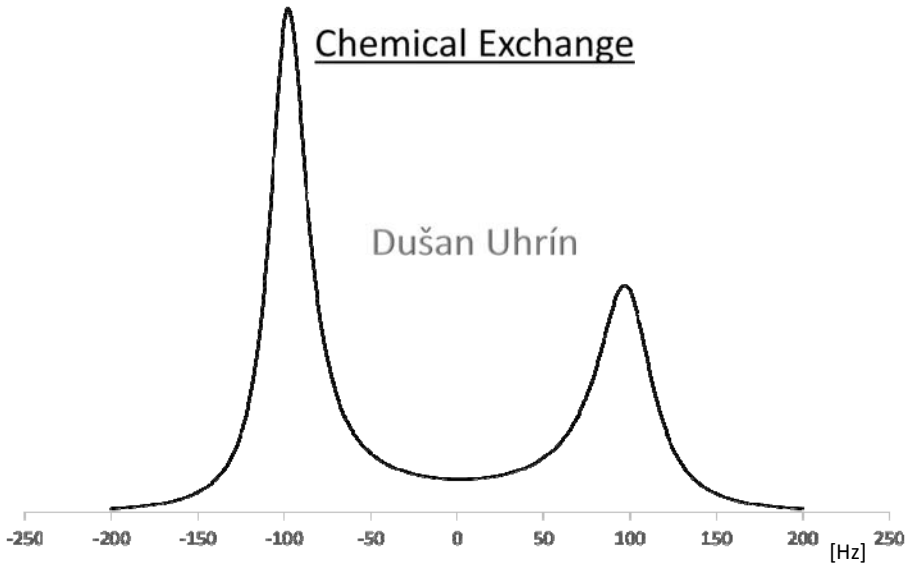
Chemical Exchange



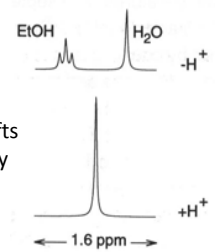
2017 Postgraduate Course in Liquid State NMR Spectroscopy
School of Chemistry, University of Edinburgh, December 5-6, 2017

What come first to mind when hearing "chemical exchange" ?

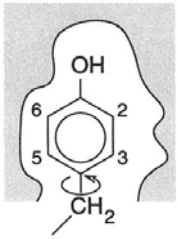
Example I
Intermolecular exchange
Exchange of labile protons

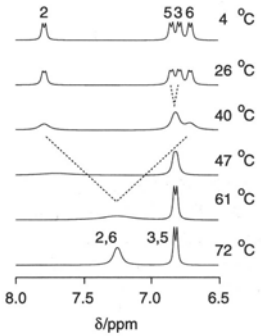
OH in ethanol/water without a catalyst (H^+)

With a catalyst (H^+)
- averaging of chemical shifts
- quenching of *J* coupling by chemical exchange



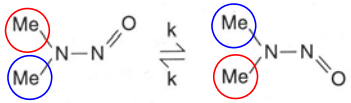
Example II. Hindered rotation of a tyrosine side chain in the core of a protein.



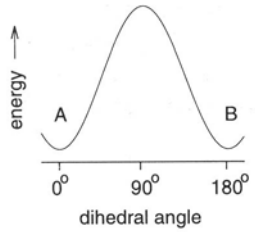


Chemical exchange:
Change of the environment while NMR signal is measured

Dynamic equilibrium between two conformations with equal energy, or a **symmetrical two-site exchange**:



Dimethylnitrosamine



$$A \underset{k_{BA}}{\overset{k_{AB}}{\leftrightarrow}} B$$

Temperature affects the rate constant of the exchange

$k_{ex} = k_{AB} + k_{BA}$ [s^{-1}] (in many equations describing exchange)

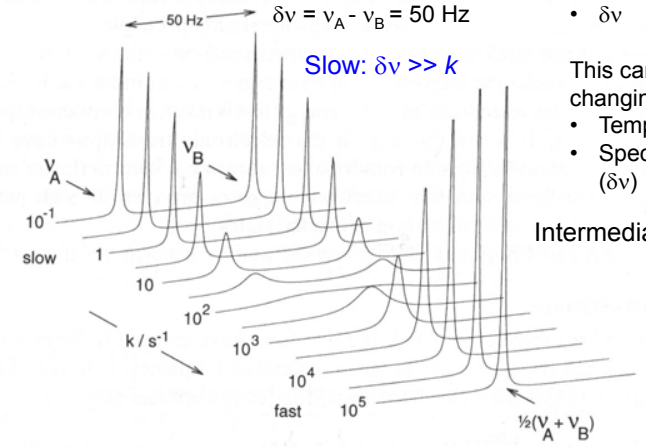
Average lifetime: $\tau_A = 1/k_{AB}$ [s]
$\tau_B = 1/k_{BA}$ [s]

Effects of the N=O group is different on the two Me groups – in a rigid structure they have different chemical shifts

Rotation around the N-N bond is slowed down because of the conjugation of the free electron pairs of N and N=O electrons

Exchange between two sites with equal population

^{1}H spectrum of dimethylnitrosamine



Exchange regime can be affected by changing
- *k*
- $\delta\nu$

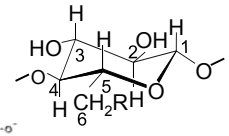
This can be achieved by changing
- Temperature (*k*)
- Spectrometer frequency ($\delta\nu$)

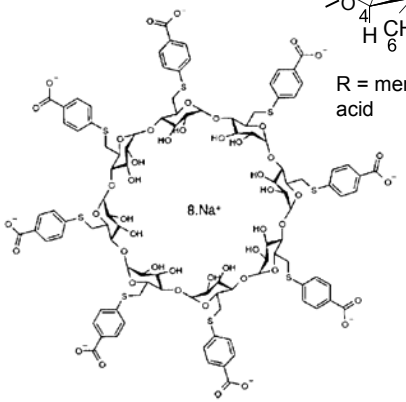
Intermediate: $\delta\nu \sim k$

The process is slow (two signals), intermediate (broad signals) or fast (one signal) on the NMR time scale depending on the relation between $\delta\nu$ and *k*.

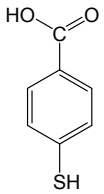
Example I: Derivative of γ cyclodextrin, **I**

β-D-glucose





R = mercaptobenzoic acid

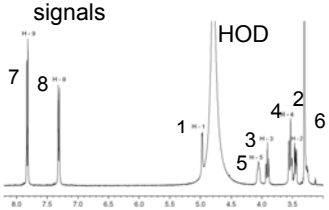


Inclusion of mercaptobenzoic acid at any time into the cyclodextrin cavity breaks the symmetry.

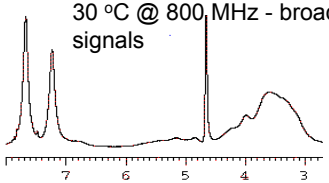
Instead of one set of signals, eight sets per each of the proton type are observed.

^{1}H spectrum of **I**

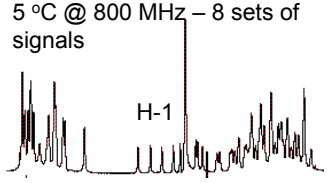
30 °C @ 400 MHz - one set of signals



30 °C @ 800 MHz - broad signals



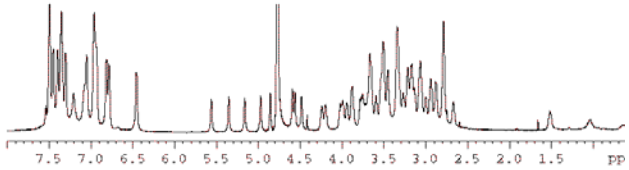
5 °C @ 800 MHz – 8 sets of signals

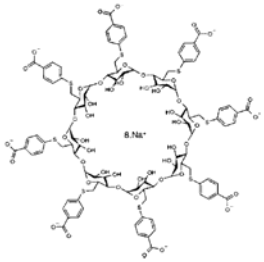


EXSY (Chemical **EX**change **S**pectroscop**Y**) – NOESY pulse sequence

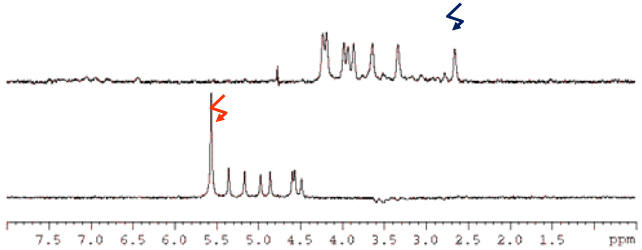
Correlates spins that exchange between different chemical environments.

1D ^{1}H NMR spectrum





1D EXSY spectra of **I** at 800 MHz and 5 °C

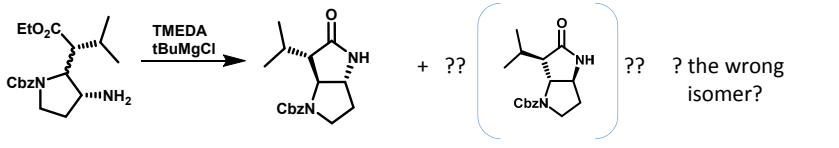


Eight H-4 protons

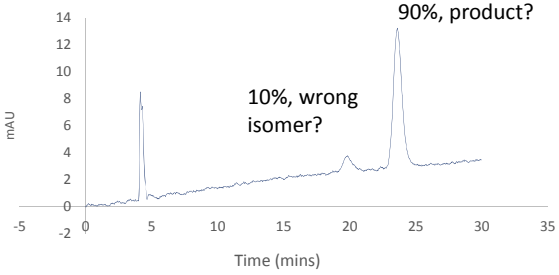
Eight H-1 protons

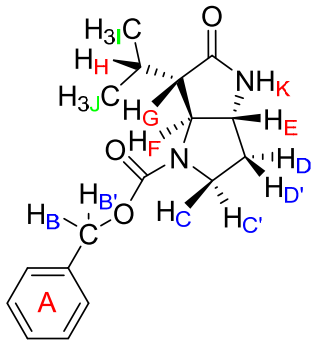
Cameron, K.S., Fielding, L., Palin, V., Uhrín, D, *Magn. Reson. Chem.* **43,** 647-653 (2005)

Troubles with cyclisation



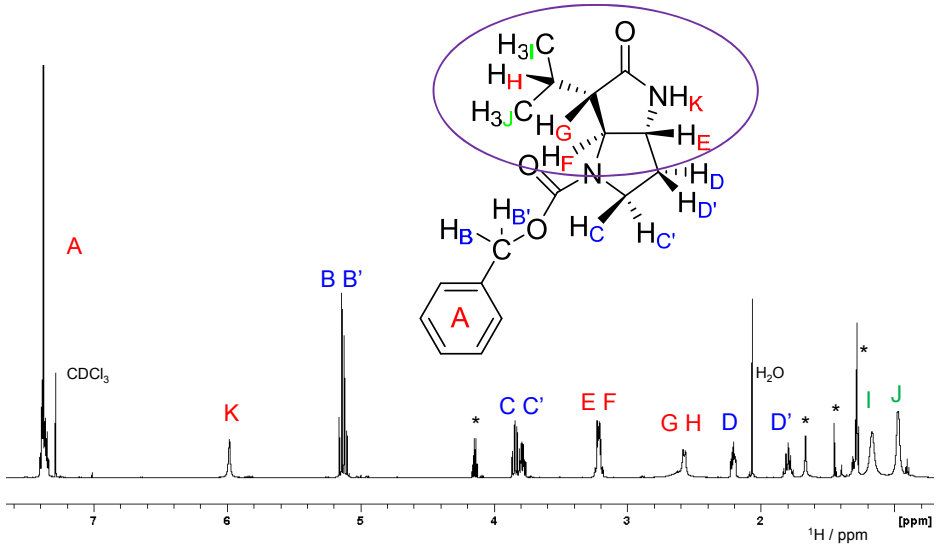
Chiral HPLC of VE228





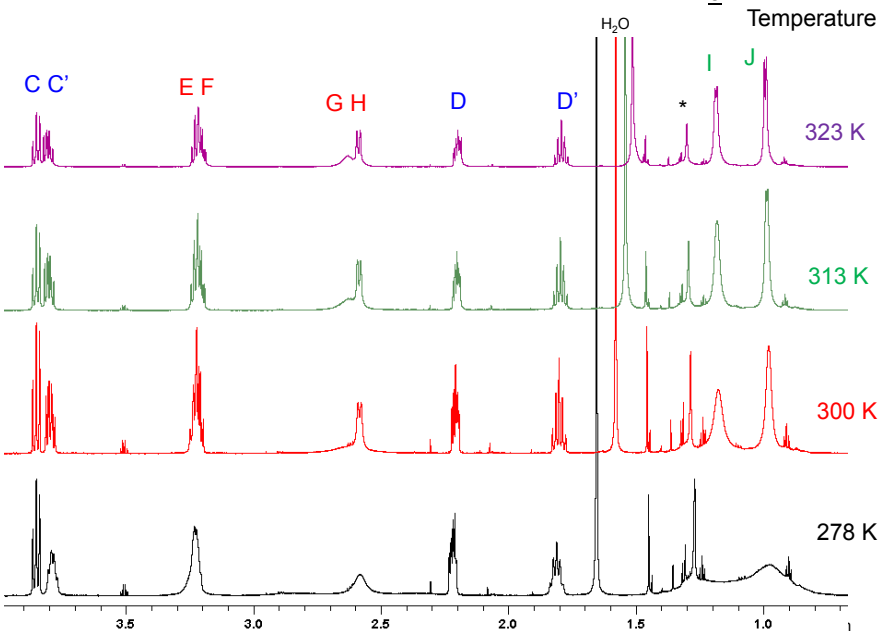
Courtesy of Vikki Evans

600 MHz ^{1}H NMR spectrum at 300 K in $CDCl_3$

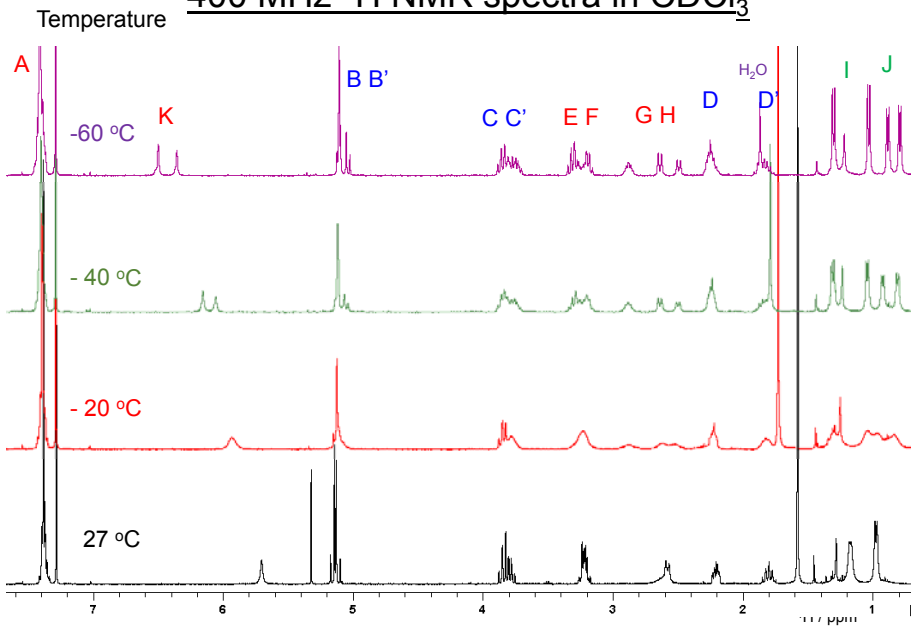


* impurities

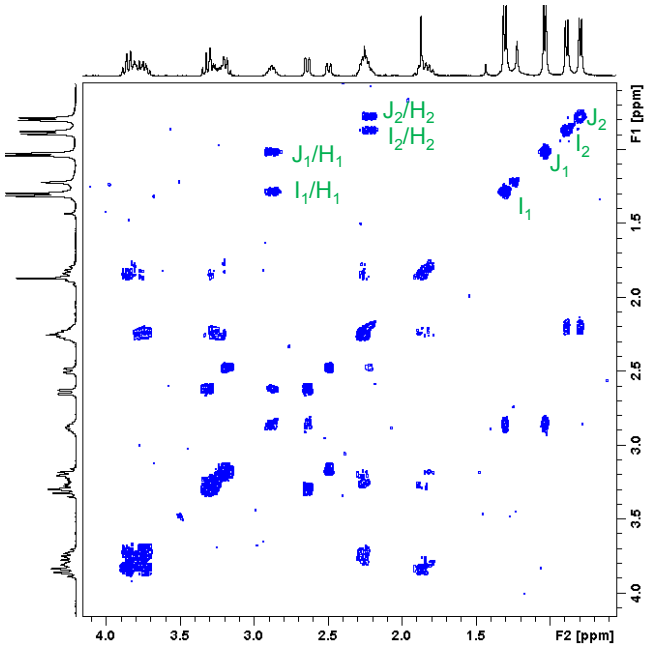
800 MHz ^{1}H NMR spectra in $CDCl_3$

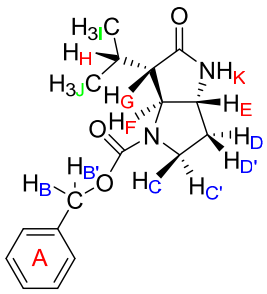


400 MHz ^{1}H NMR spectra in $CDCl_3$



400 MHz COSY spectrum at -60 °C in $CDCl_3$



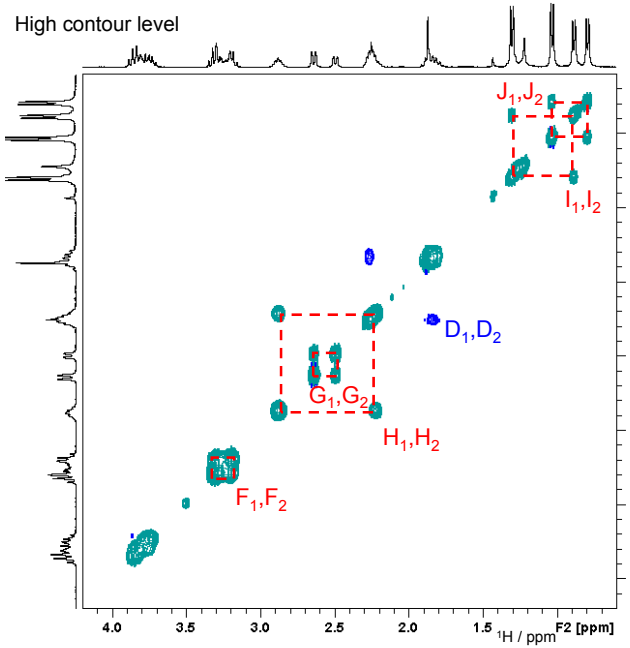


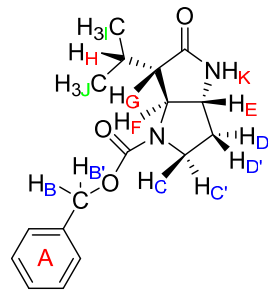
No J_1,J_2 or J_1,H_2 cross peaks

No COSY cross peaks between different rotamers!

400 MHz NOESY spectrum at -60 °C in $CDCl_3$

High contour level



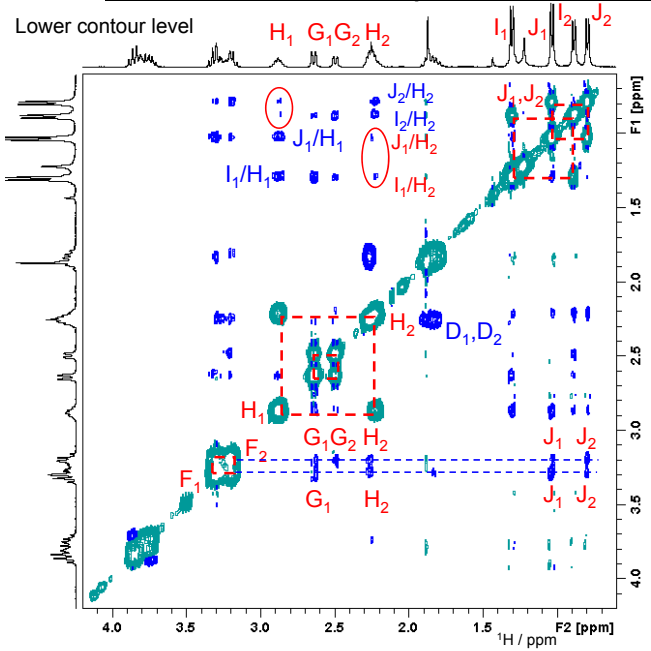


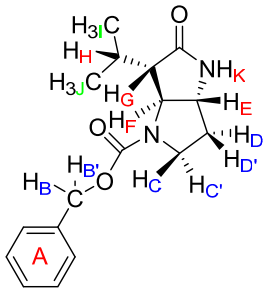
Intense chemical exchange negative cross peaks – green, e.g. I_1, I_2.

Positive through space cross peaks – blue

EXSYcross peaks between different rotamers!

400 MHz NOESY spectrum at -60 °C in $CDCl_3$



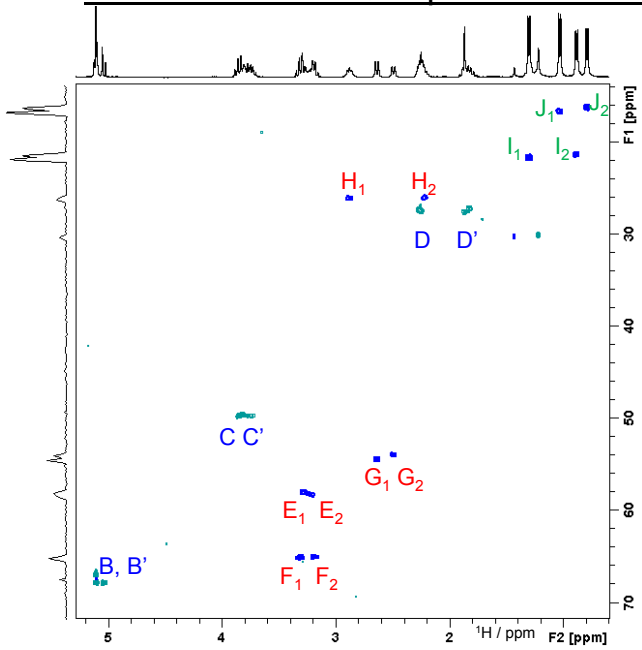


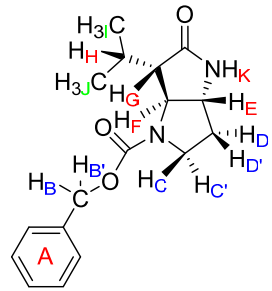
Negative (chemical exchange) cross peaks - green

(Positive) through space cross peaks – blue

(Positive) cross peaks also appear between different rotamers!

400 MHz 2D HSQC spectrum at -60 °C in $CDCl_3$

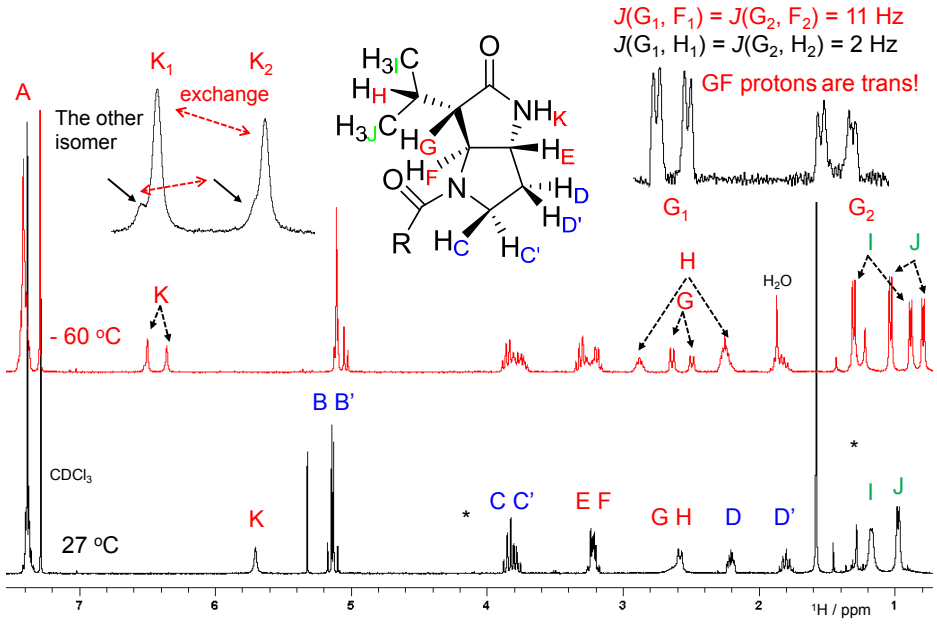




No HSQC cross peaks between different rotamers!

^{13}C chemical shift also differ between different rotamers (typically less)

400 MHz ^1H NMR spectra in $CDCl_3$



Literature and Acknowledgements

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Dynamic Nuclear Magnetic Resonance spectroscopy, Edited by : Lloyd Jackman ISBN: 978-0-12-378850-4, Academic Press 1975
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http://chemnmr.colorado.edu/manuals/DNMR_Calculations.pdf

Juraj Bella

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