Pure shift NMR: Applications

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Outline

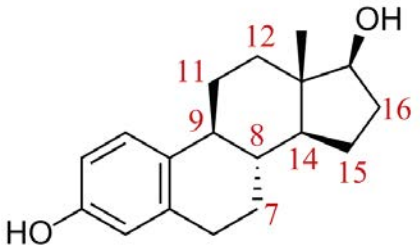
The problem: spectral overlap in complex spectra

Pure shift NMR: achieving ultra-high resolution

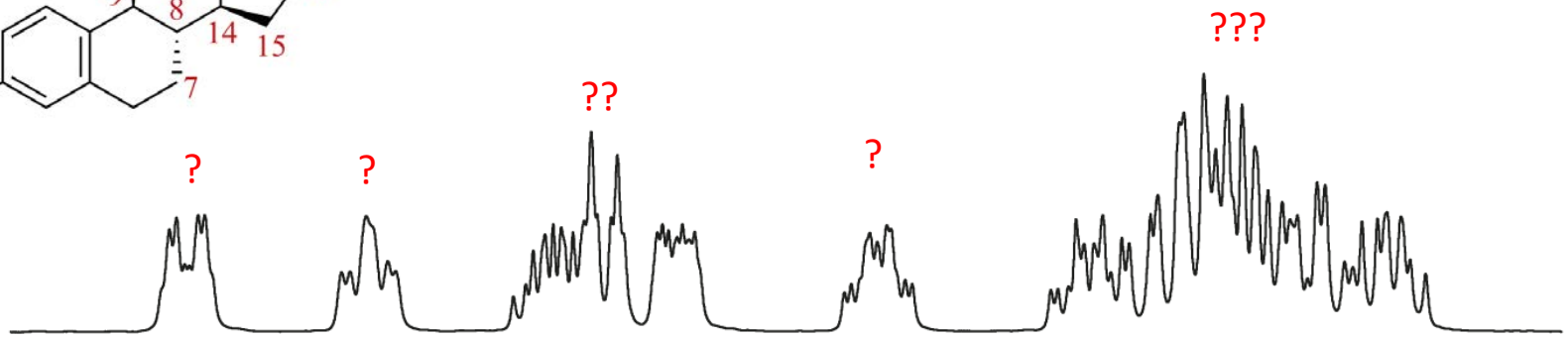
Recovering coupling information when needed

Applications and assignment

Pure shift NMR



Estradiol: 500 MHz ^{1}H spectrum



Chemical shifts (δ_H)

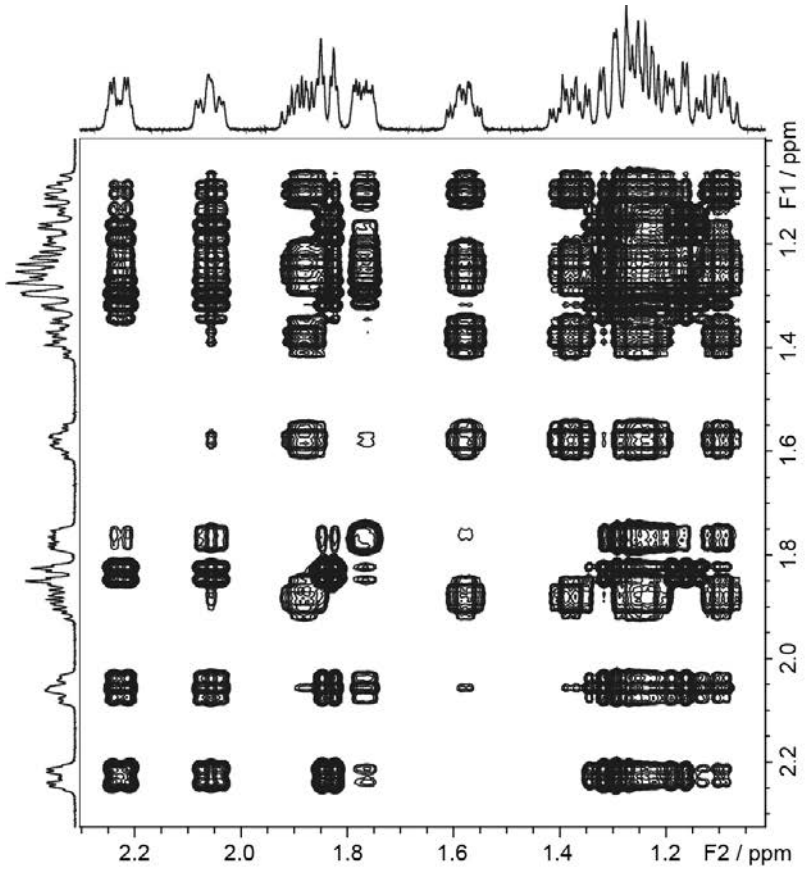
Homonuclear couplings (J_{HH})

Overlap reduced by an order of magnitude

Angew. Chem. Int. Ed. **2014**, 53, 6990

2D Pure shift NMR

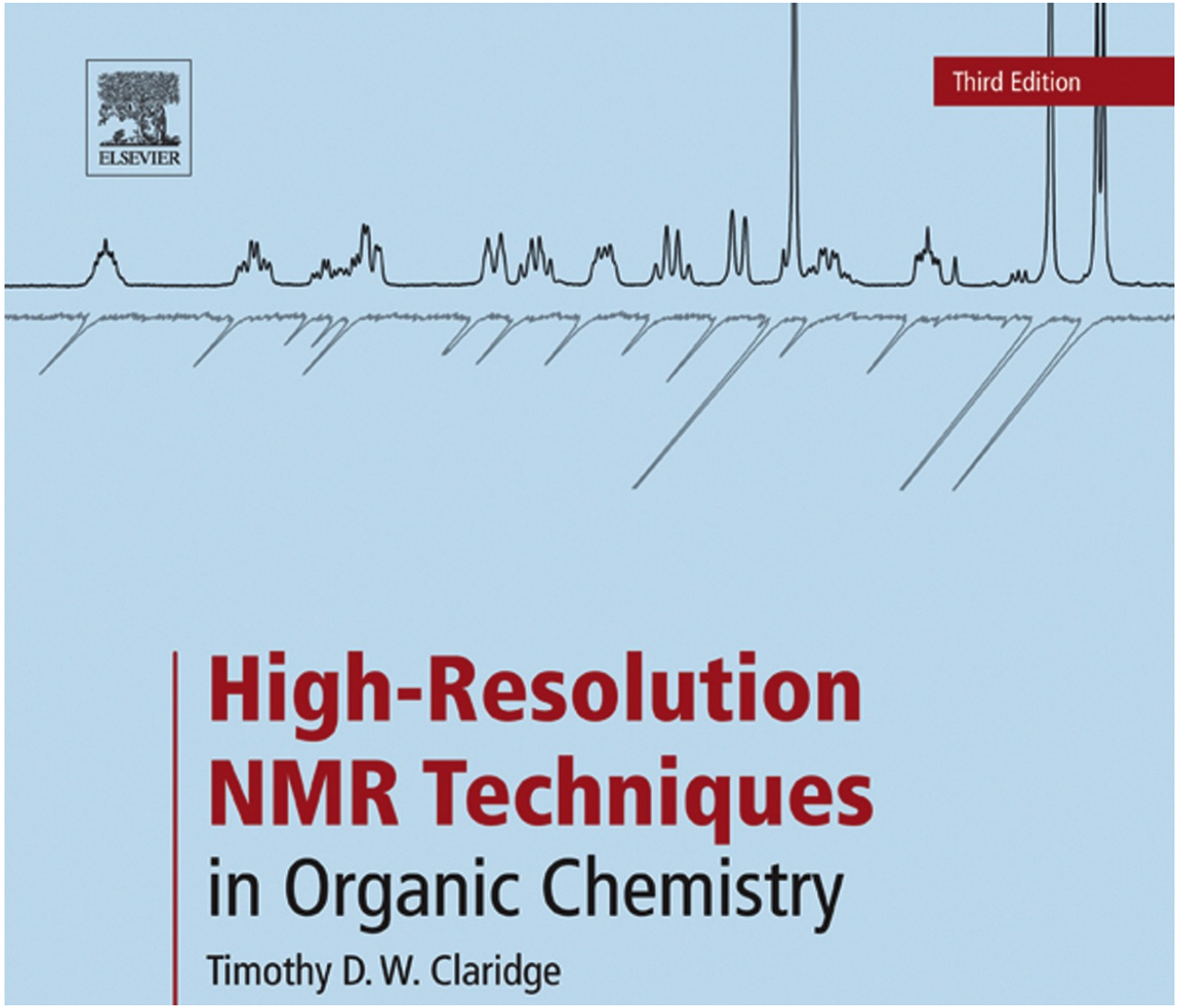
Estradiol: 500 MHz TOCSY



Coupling information at pure shift resolution

J. Am. Chem. Soc. **2014**, 136, 11867

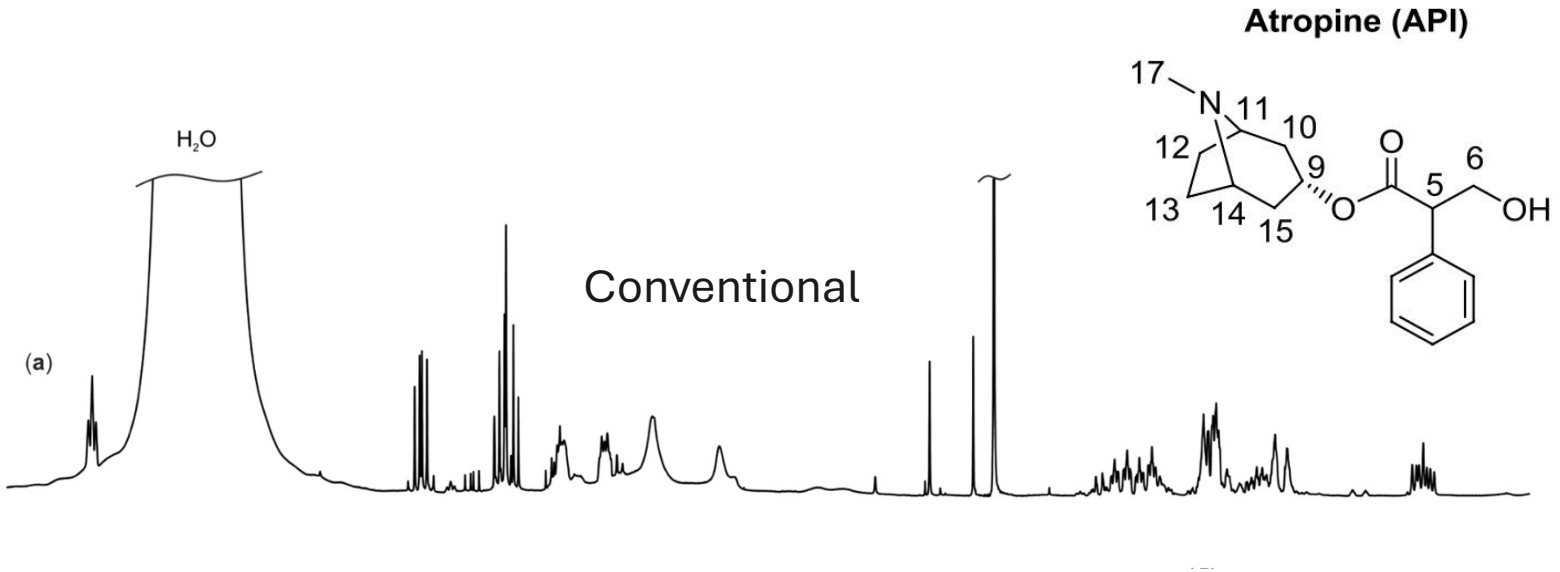
Pure shift NMR



Pure shift NMR suppresses multiplet structure to give a substantial improvement in resolution, comparable of going from a standard 500 MHz spectrometer to a hypothetical 5 GHz one

Adams, R. W. *EMagRes* 2007, 3 (4), 295–309.
Zangger, K. *Prog. Nucl. Magn. Reson. Spectrosc*. 2015, 86–87, 1–20.
Castañar, L. *Magn. Reson. Chem*. 2017, 55 (1), 47–53
M. Foroozandeh, G. A. Morris and M. Nilsson, *Chemistry-a European Journal*, 2018, **24**, 13988-14000.
J. A. Aguilar, S. Faulkner, M. Nilsson and G. A. Morris, *Angew. Chem. Int. Ed.*, 2010, **49**, 3901-3903.

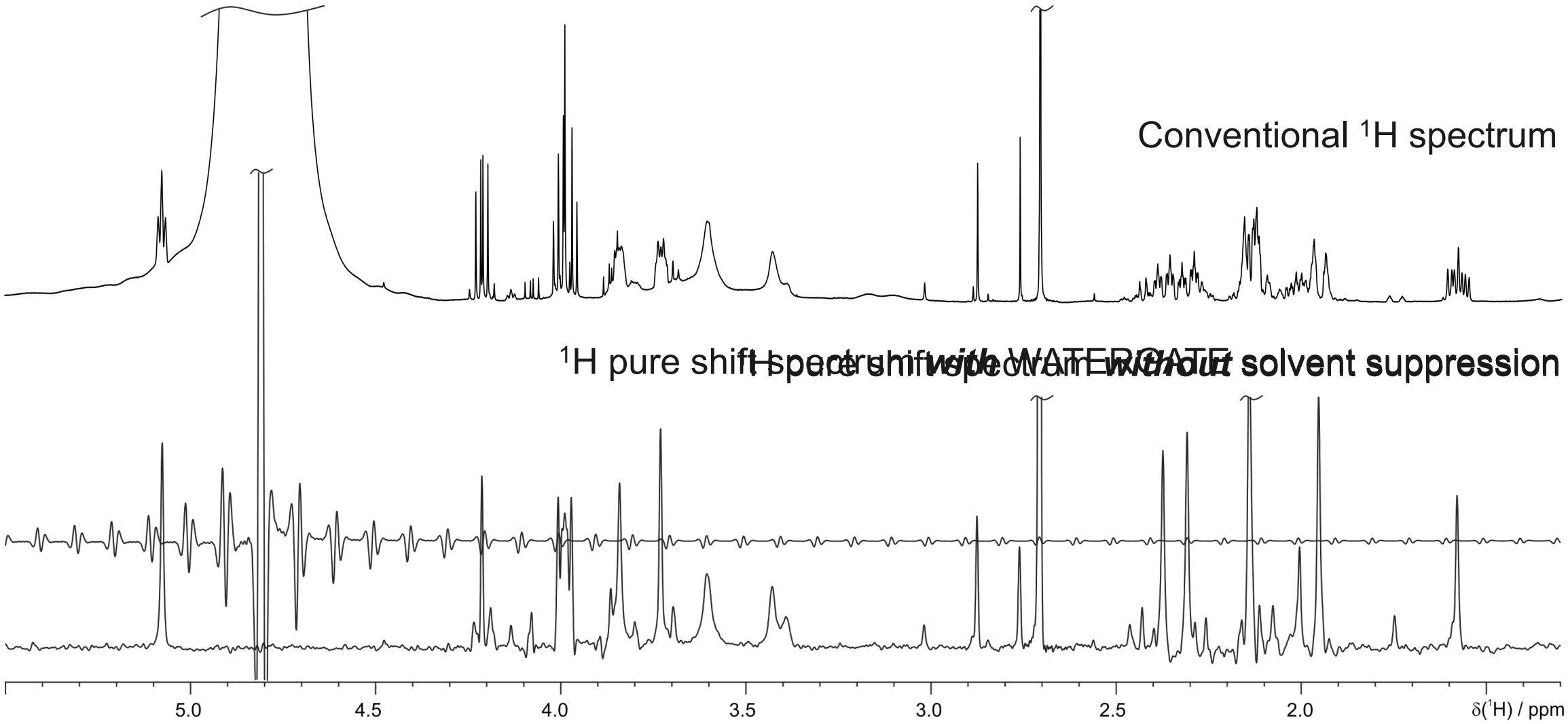
^{1}H NMR of eye-drop formulation



Pure shift reveals minor components

Anal. Chem., **2024**, 96, 3879

Pure shift with strong solvent signal

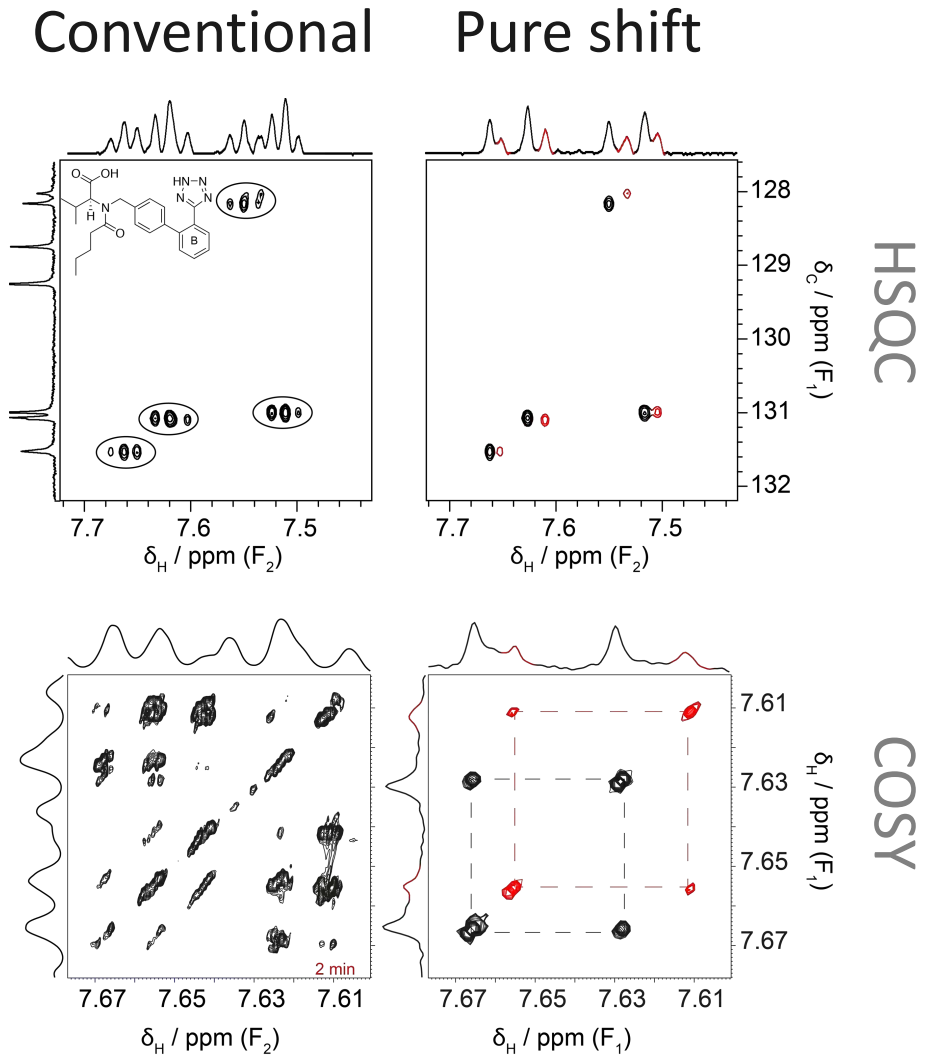


Anal. Chem., **2024**, 96, 3879

Pure shift: revealing hidden peaks

- **Impurity in valsartan formulation**
- **Conventional HSQC/COSY**: impurity not evident (overlap/ similar spin systems
- **Pure shift HSQC/COSY**: impurity becomes obvious.

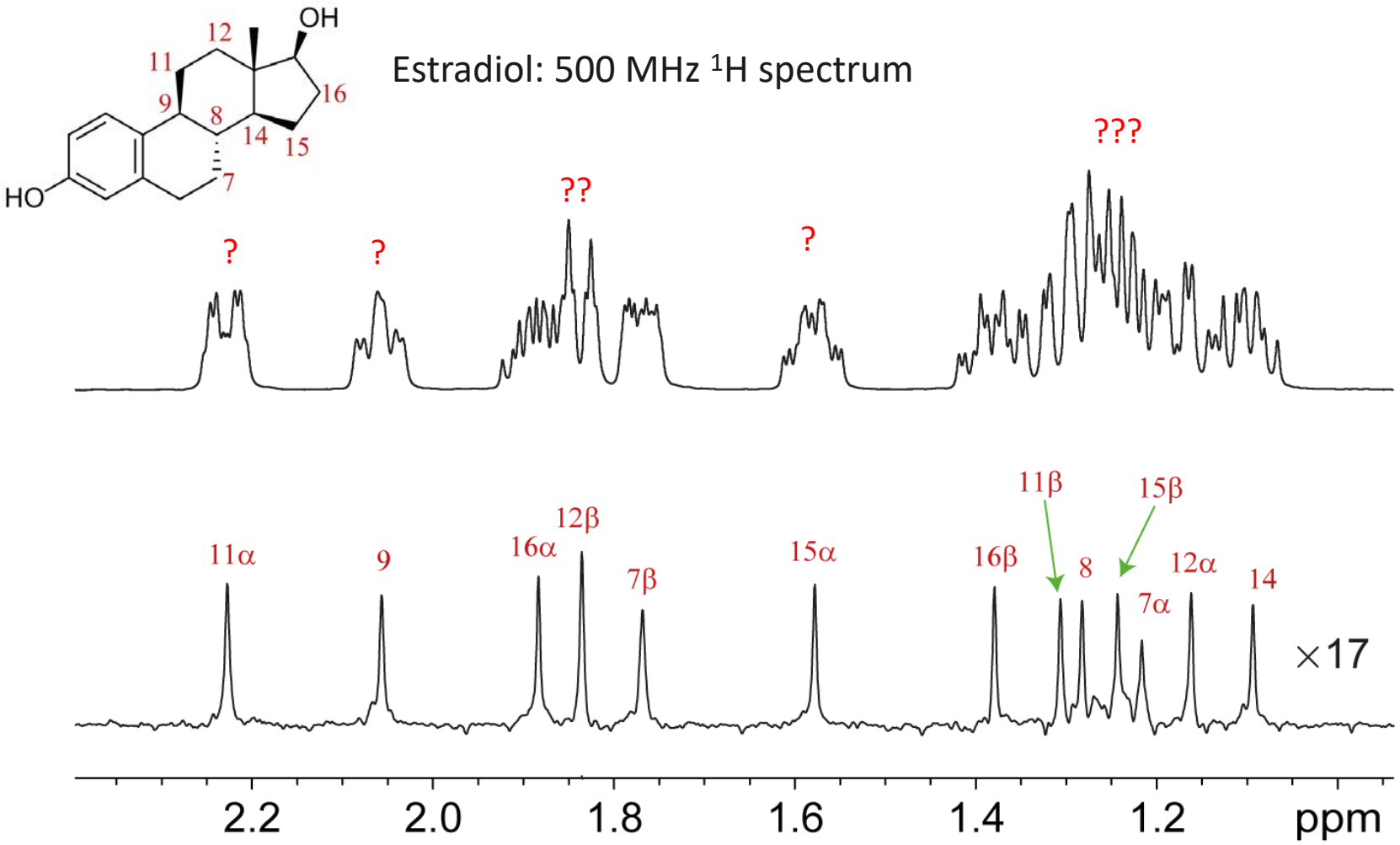
Same acquisition time: COSY 2 min; HSQC 14 min



Pure shift reveals impurity correlations hidden by overlap

RSC Advs. **2015**, 5, 52902

Pure shift NMR – resolution vs coupling



✓ **Resolution gained**

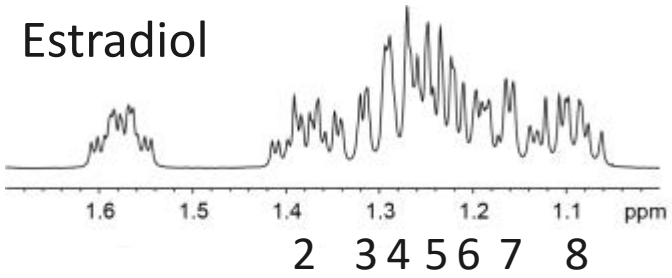
× **Coupling lost**

Can we recover coupling information?

Angew. Chem. Int. Ed. **2014**, 53, 6990

Pure Shift NMR – 2DJ recovering lost coupling structure

Estradiol



5

2

6

3

7

4

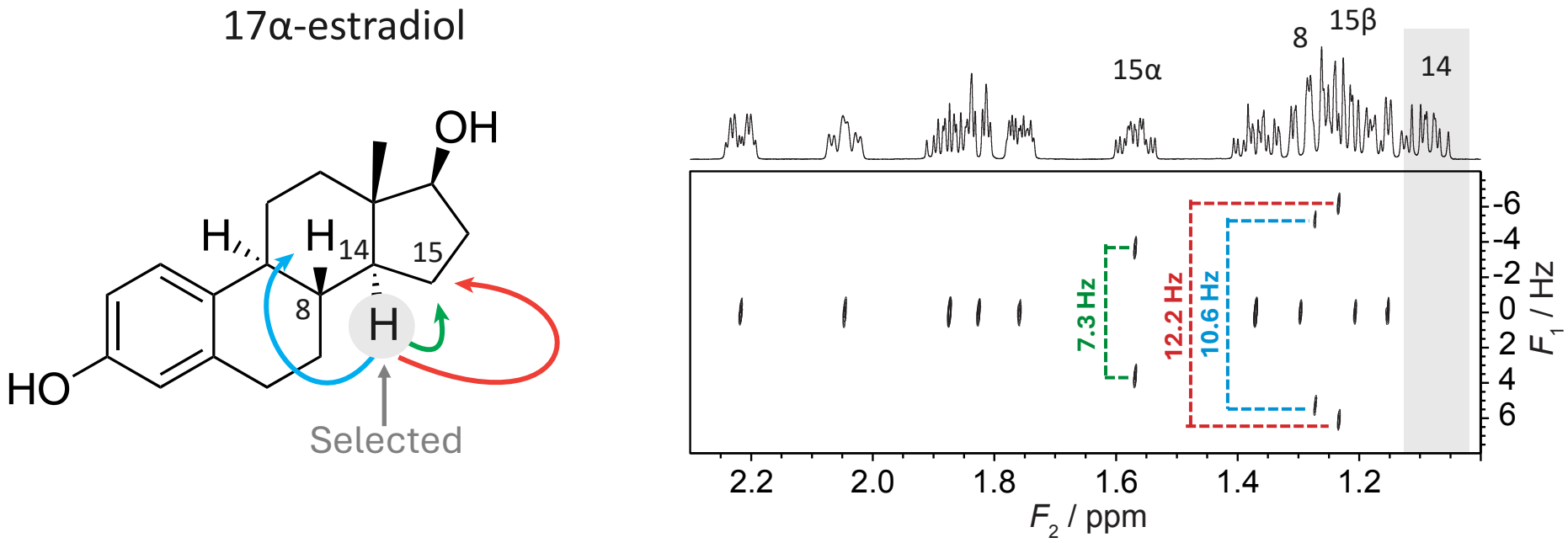
8

Phase sensitive 2DJ

- Full multiplets
- Moderate cost in sensitivity (√2)

Chem. Commun. **2015**, 51, 15410

PSYCHEDELIC: individual J couplings

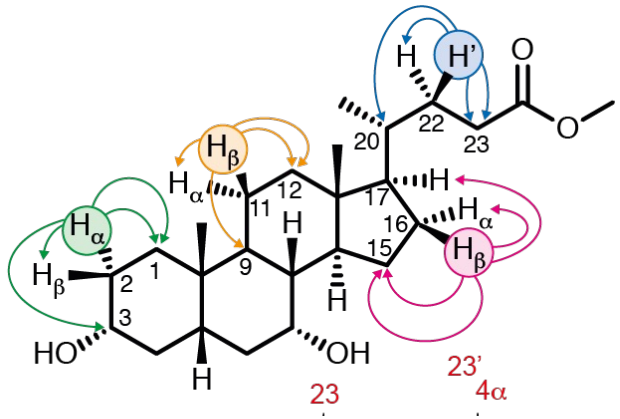


Selected-spin homonuclear J couplings – with pure shift resolution

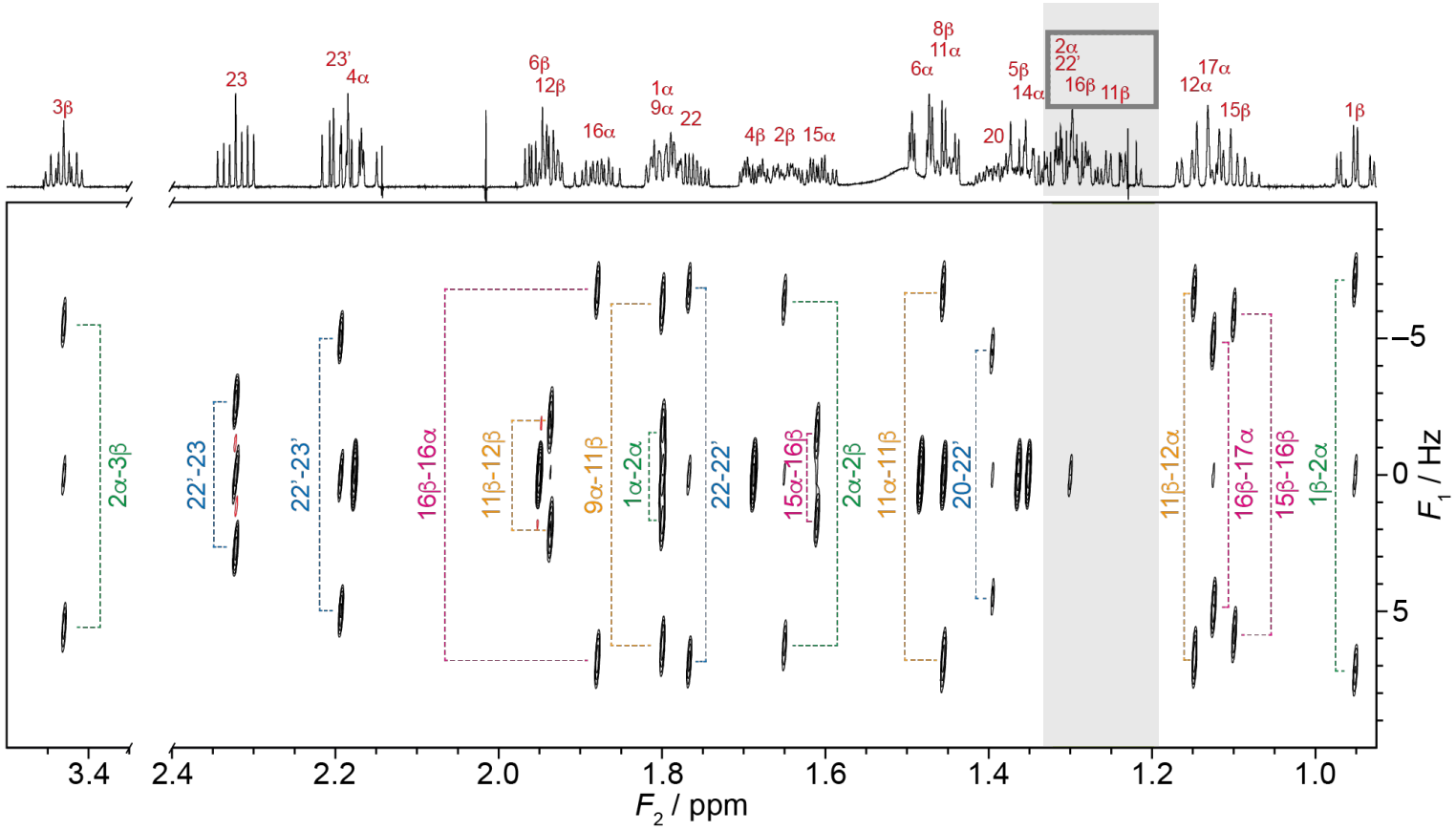
Angew. Chem. Int. Ed. **2016**, 55, 1090

PSYCHEDELIC: multiple spins in one experiment

chenodeoxycholic acid

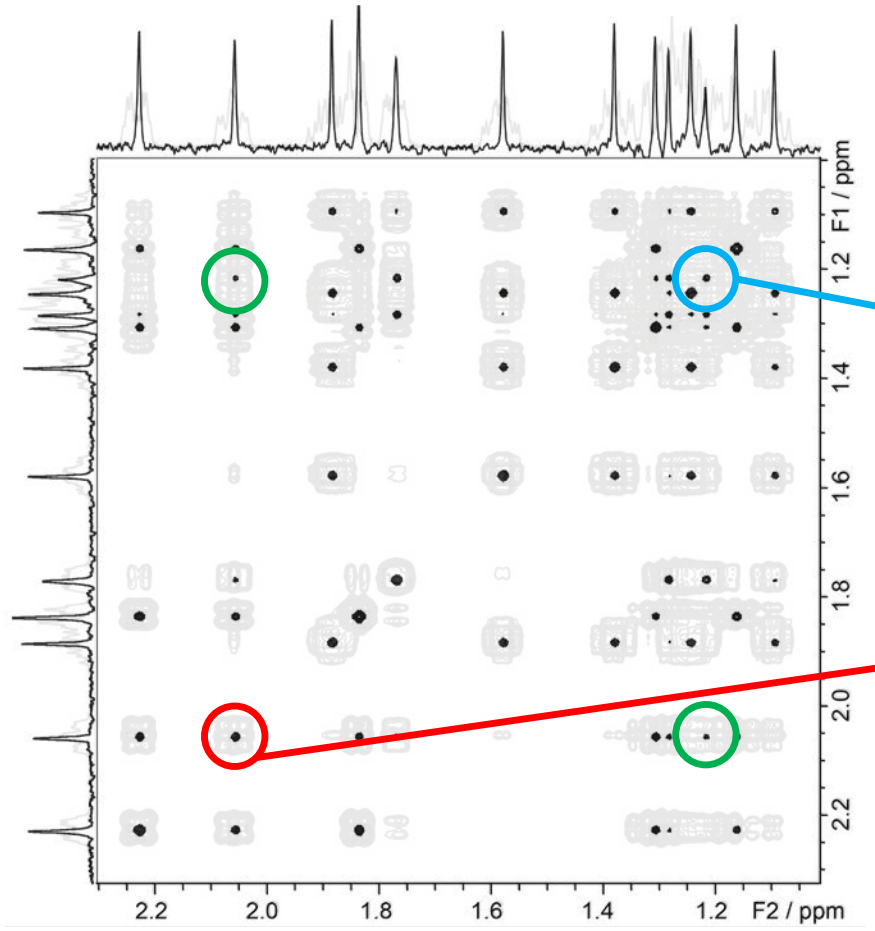


Colours = different selected spins



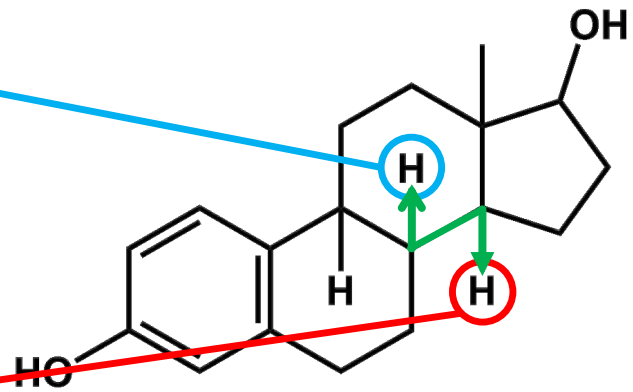
Multiple selected spins (not mutually coupled) in one experiment

Pure shift TOCSY



TOCSY

green line: *J* coupling pathway



Estradiol

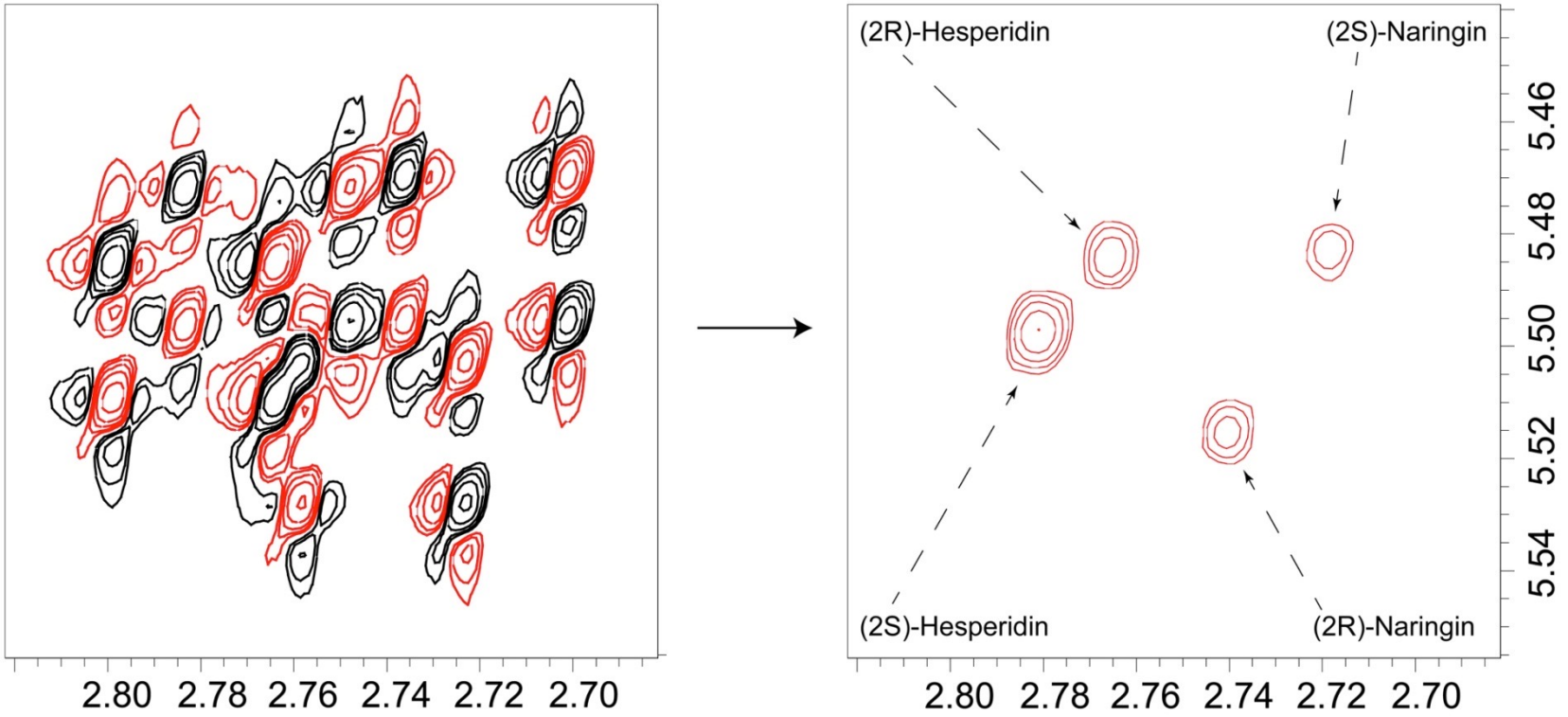
2D correlations with pure shift resolution

J. Am. Chem. Soc., **2014**,136, 11867

Pure shift MQF-COSY

Conventional

Pure shift

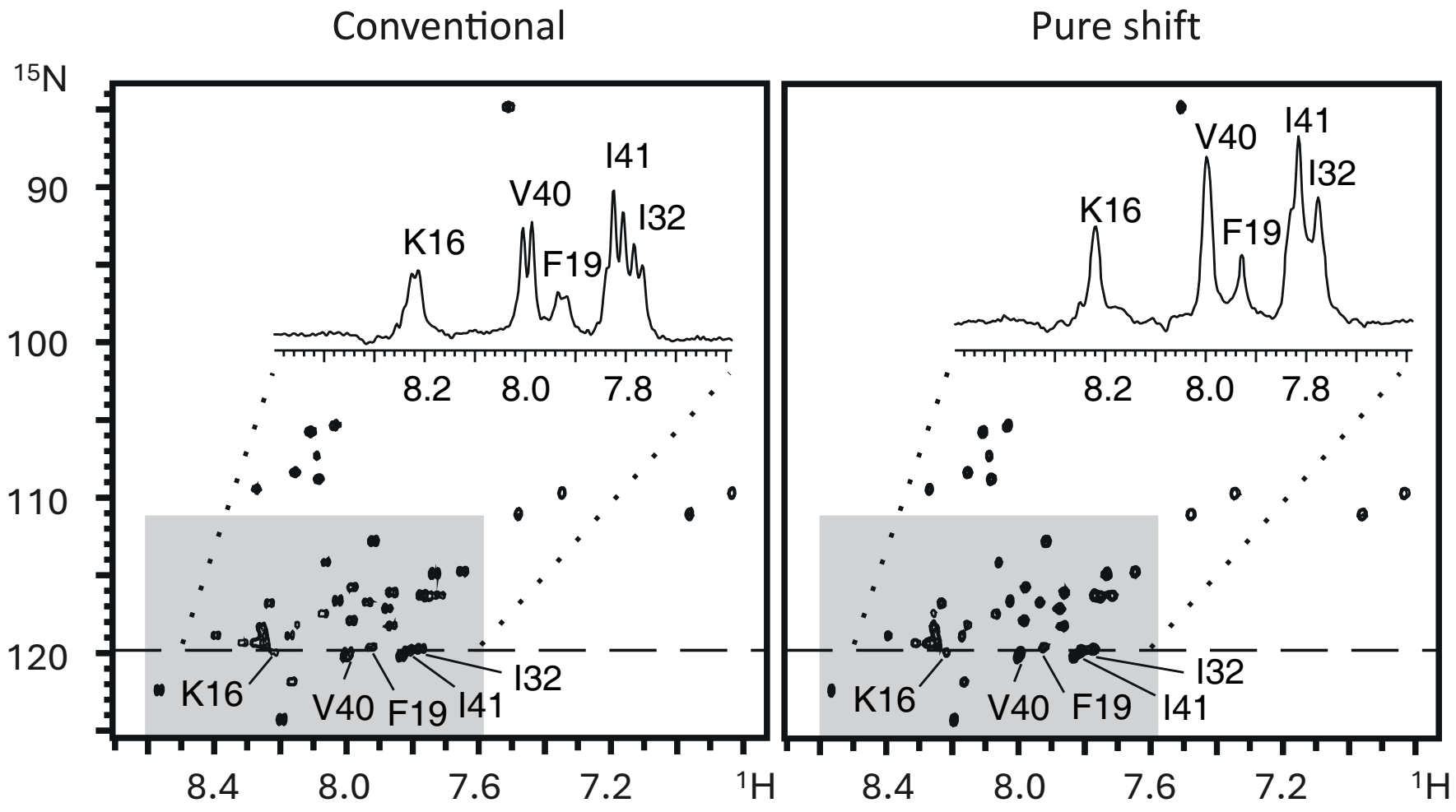


Mixture of 2R/2S isomers:
hesperidin + naringin

2D pure shift enables isomer discrimination

Angew. Chem. Int. Ed. **2012**, 51, 6460

Pure shift real-time HSQC

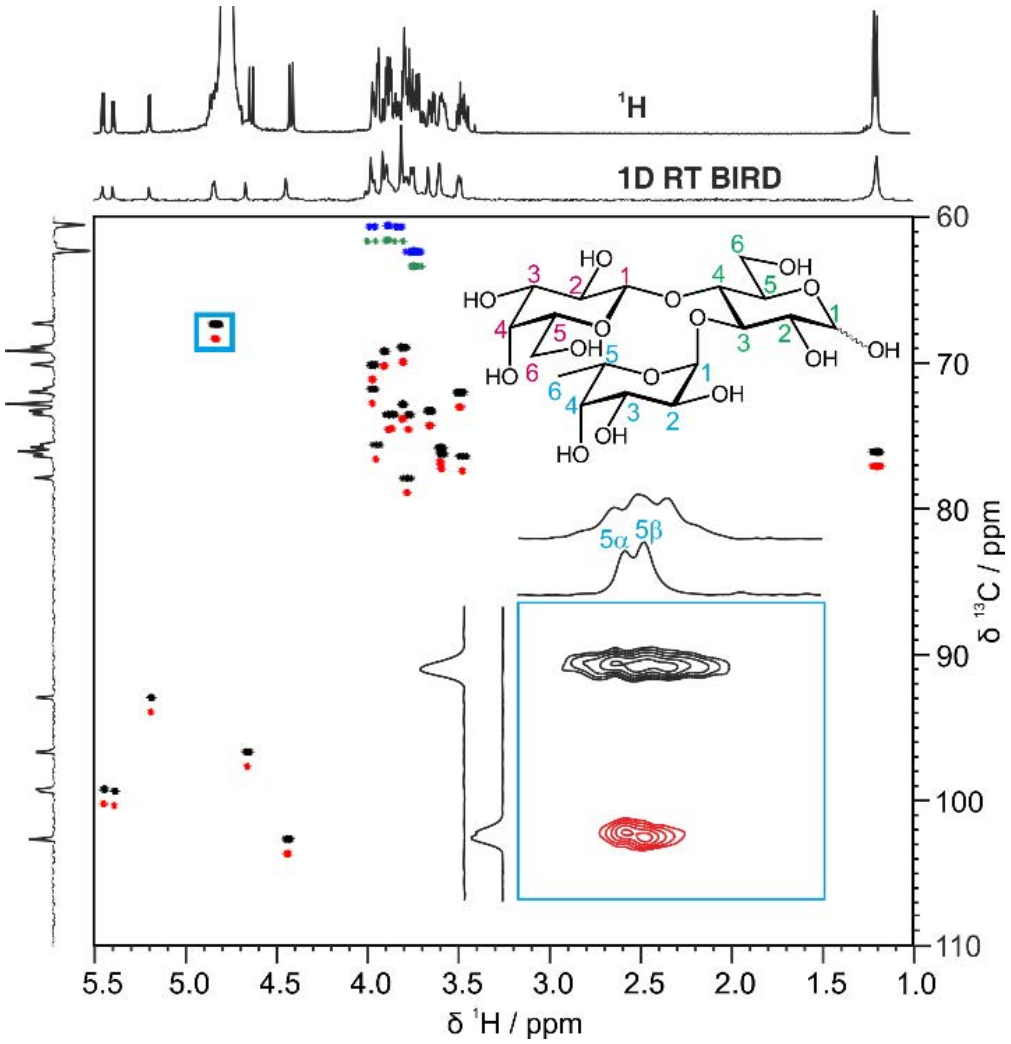


^{15}N-labeled Alzheimer's β-peptide

Pure shift improves both resolution and sensitivity

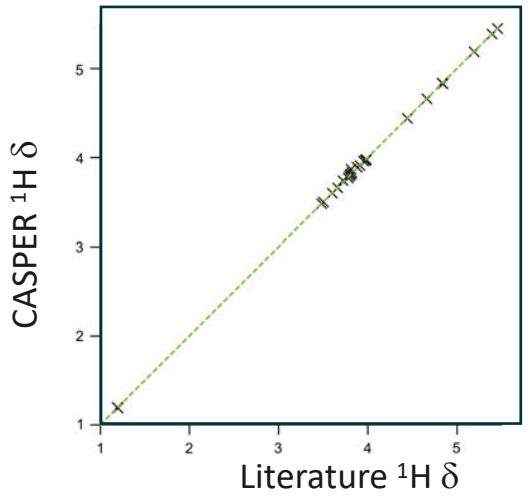
Angew. Chem. Int. Ed. **2013**, 52, 11616

Pure shift HSQC in computer-assisted assignment

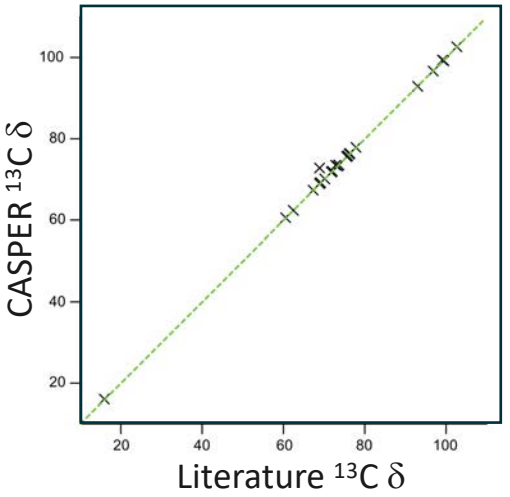


- 3-fucosyllactose (human milk oligosaccharide): **conventional** vs **pure shift** HSQC
- Automatic $^{1}H/^{13}C$ assignment (CASPER): agrees with literature

^{1}H assignment



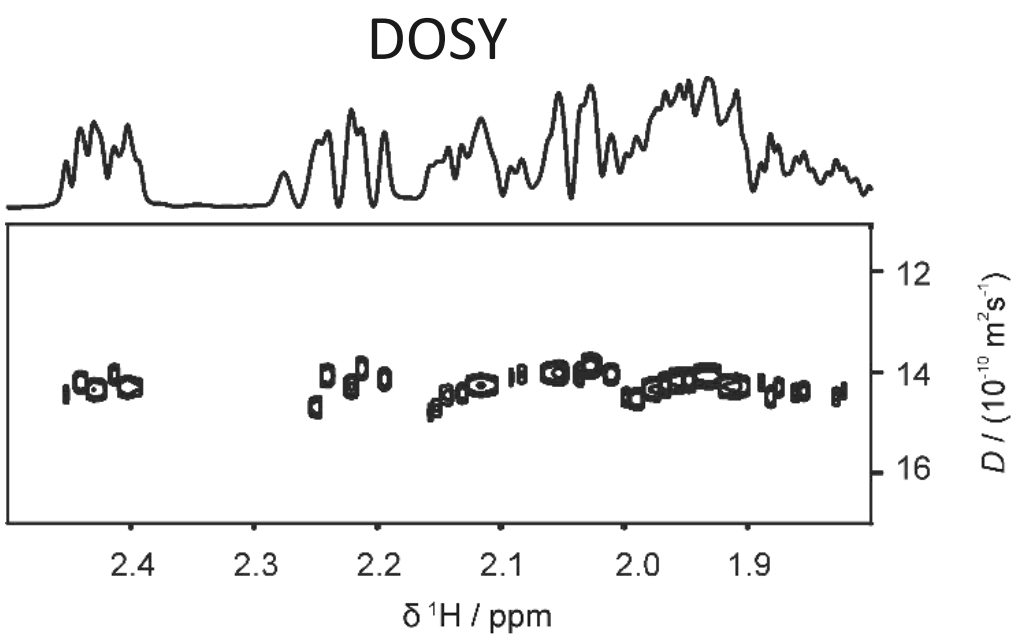
^{13}C assignment

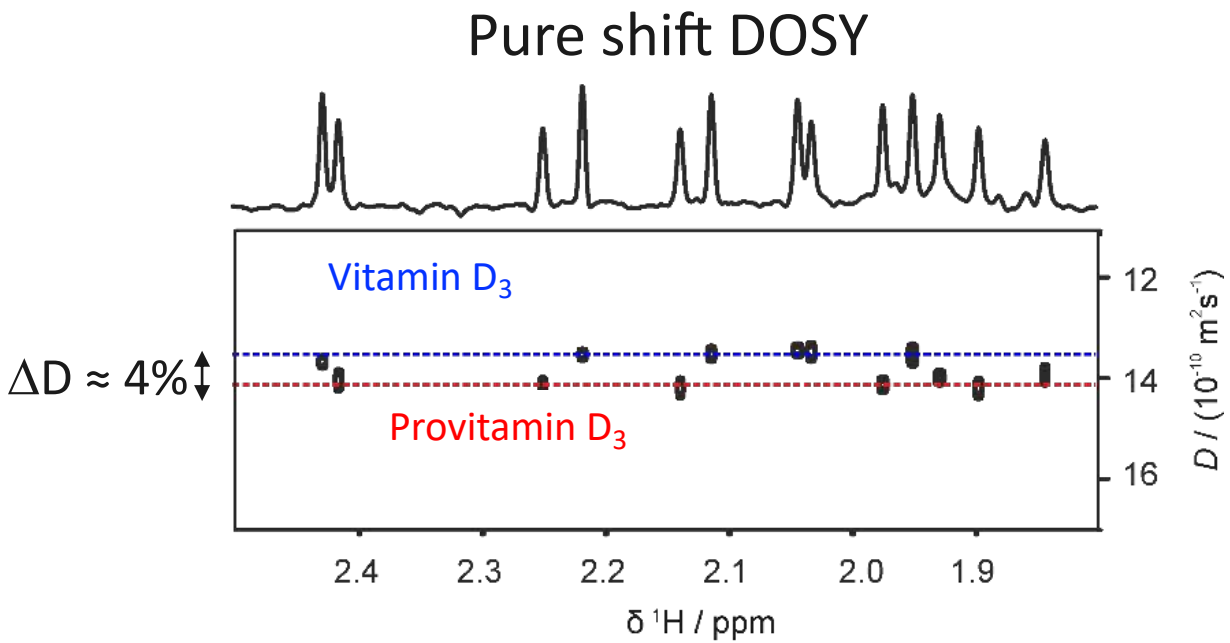


One peak per CH_n correlation enables automated peak-picking

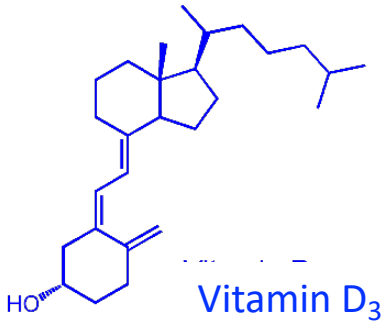
Org. Biomol. Chem. **2023**, 21, 2984
Angew. Chem. Int. Ed. **2013**, 52, 11616

Pure shift DOSY

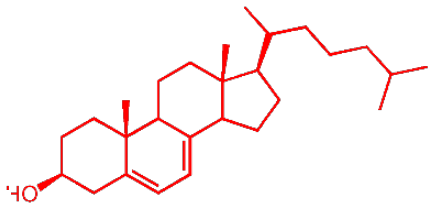




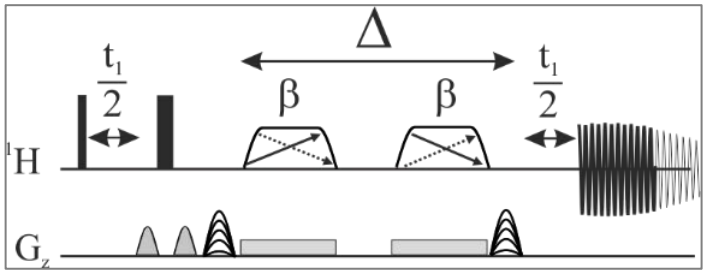
ΔD ≈ 4%



Vitamin D_3



Provitamin D_3



PSYCHEiDOSY

Reduced overlap improves diffusion discrimination

Angew. Chem. Int. Ed. **2016**, 55, 15579.

Analysis of complex mixtures

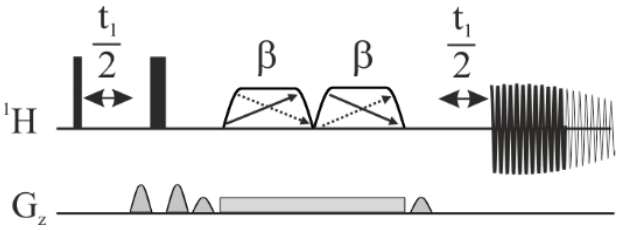
^{1}H NMR

^{1}H Pure shift

2.2 1.8 1.4 1.0 δ(^{1}H) / ppm

Sample + sequence

Peppermint oil

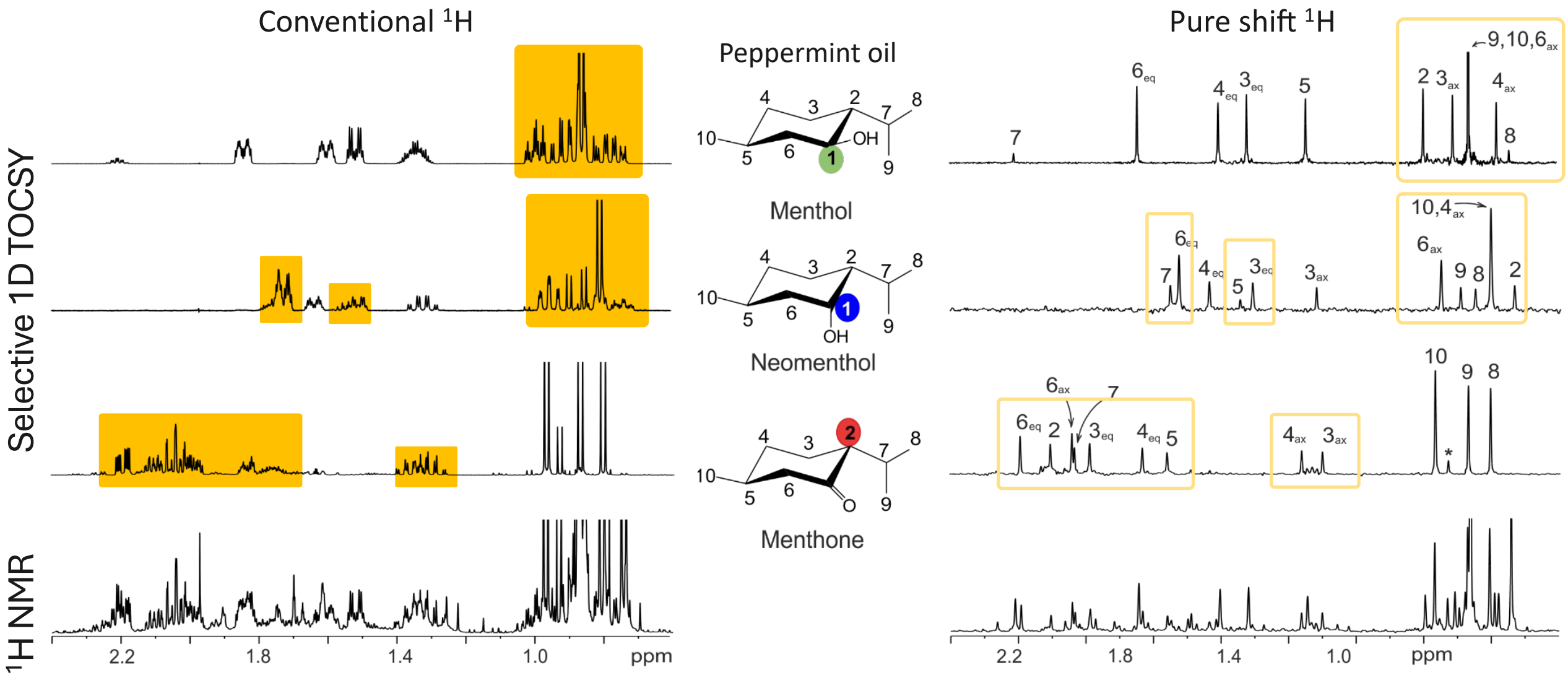


PSYCHE sequence

Pure shift provides ultra-high resolution ^{1}H NMR spectra

RSC Adv. **2016**, 6, 100063

Selective 1D TOCSY



1D TOCSY resolution improved by pure shift

RSC Adv. **2016**, 6, 100063

Pure shift FESTA: resolving fluorinated spin systems by ^{19}F editing

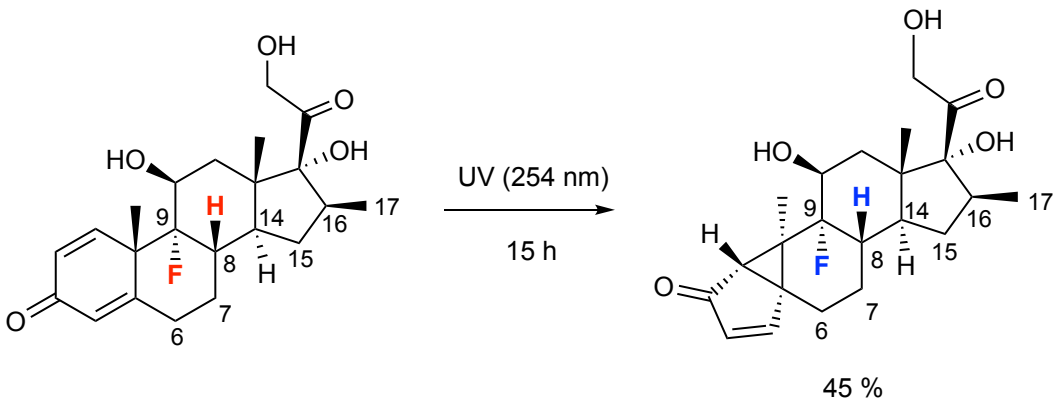
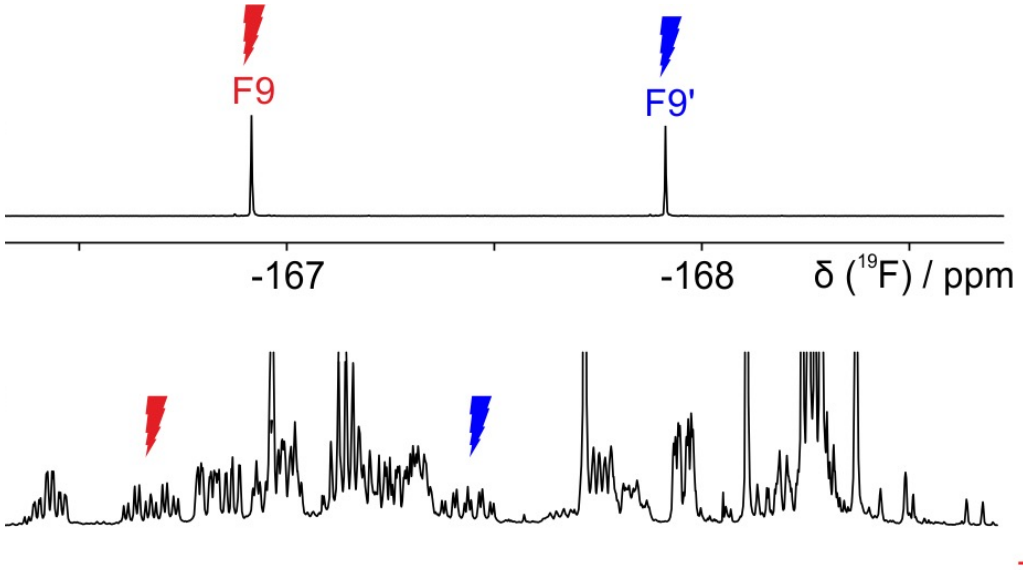


Photo-degradation of betamethasone



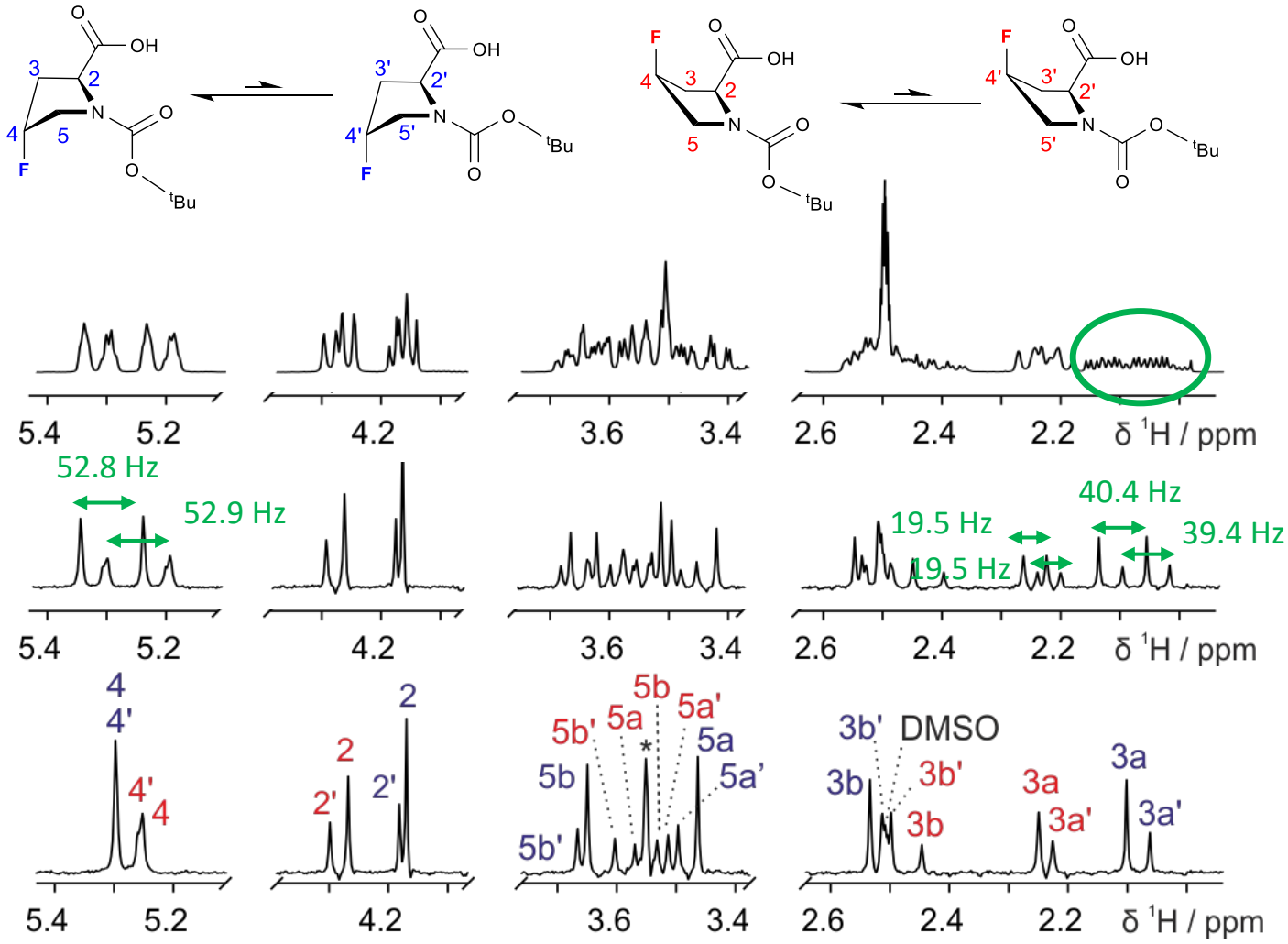
FESTA selects the spin system; pure shift resolves every signal within it

Magn.Reson.Chem. **2023**, 61, 606

Decoupled pure shift NMR

(4*S*)-N-Boc-L-fluoroproline

(4*R*)-N-Boc-L-fluoroproline



J_{HH} =|0 - 25| Hz

J_{HF} =|0 - 60| Hz

^{1}H NMR

Pure shift

Removes ^{1}H-^{1}H couplings

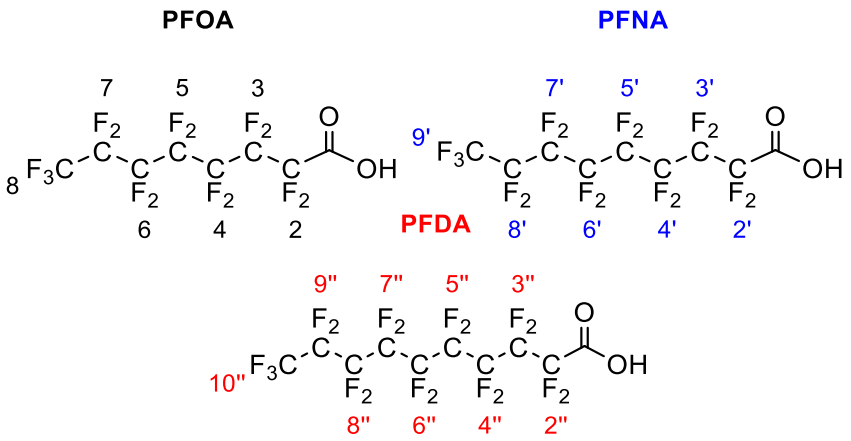
Fully decoupled

Removes ^{1}H-^{1}H couplings and ^{1}H-X couplings

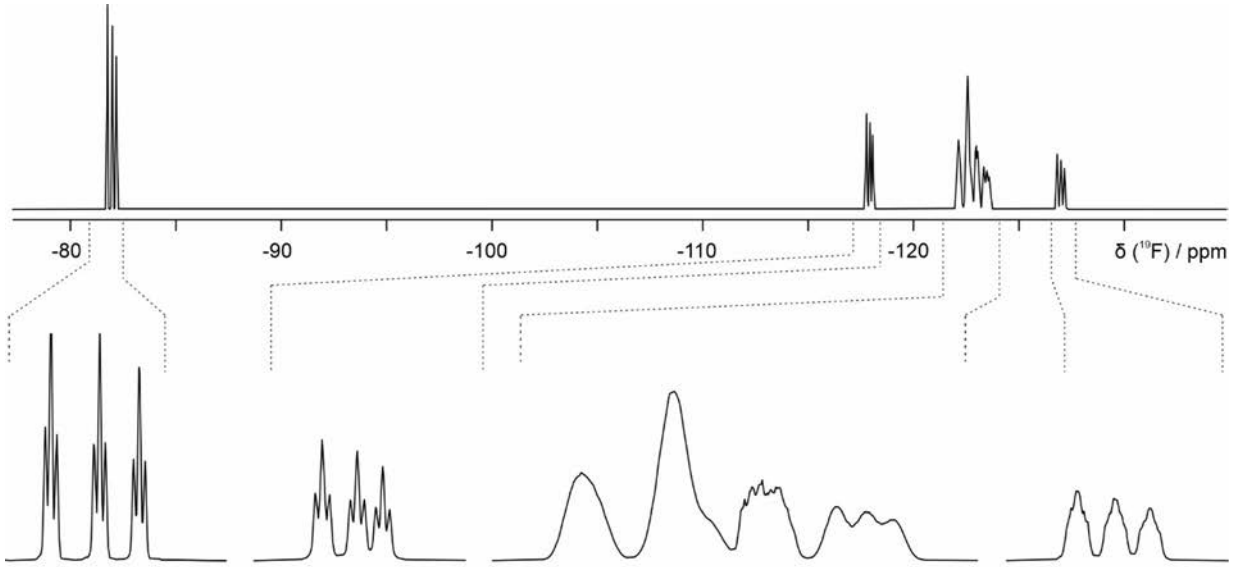
Removing ^{1}H–X couplings reveals true pure shift resolution

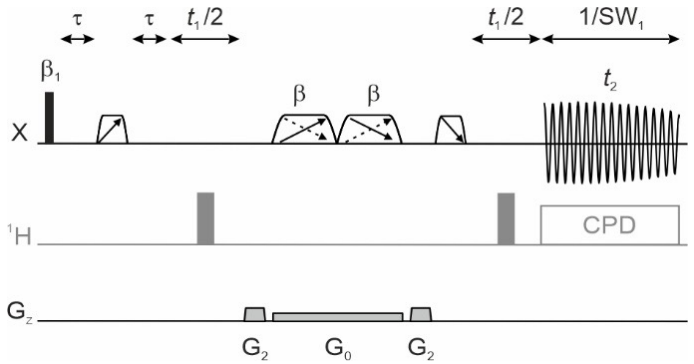
ChemPhysChem. **2022**, 23, e2022004

Broadband ^{19}F pure shift NMR



Mixture of toxic environmental fluorinated contaminants

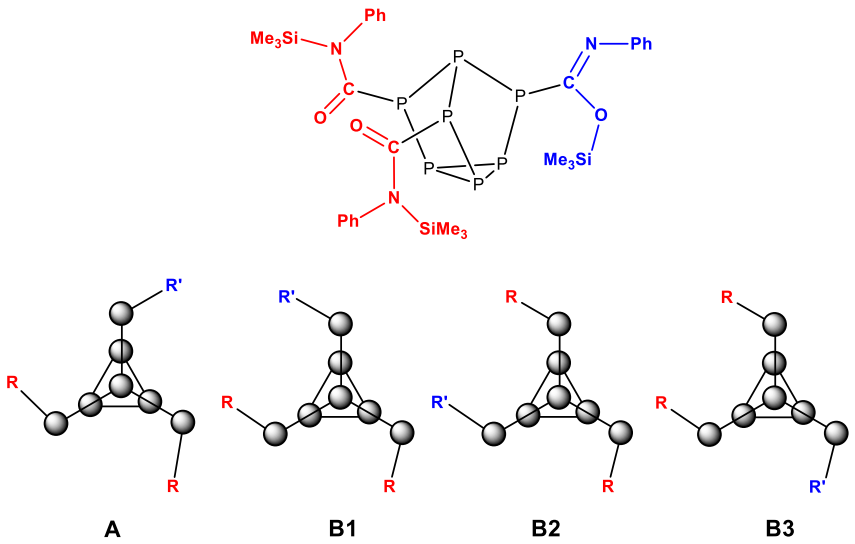




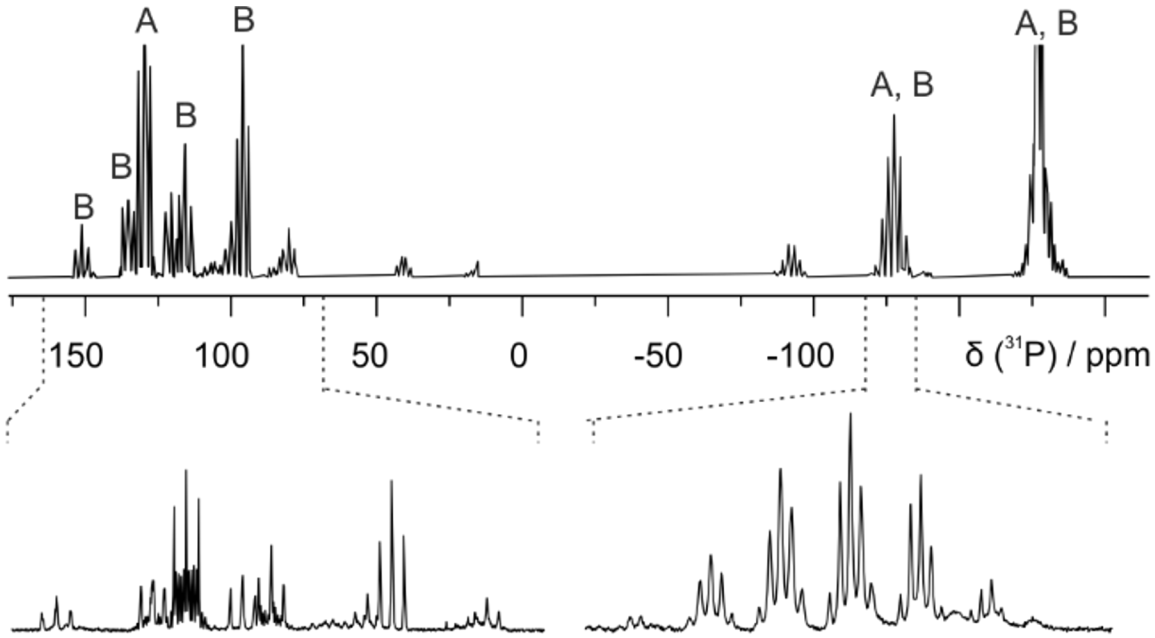
Pure shift resolves chain-length defining CF_2 groups in PFAS

Commun. Chem. **2026** In press

Broadband ^{31}P pure shift NMR



Isomers of $(PhNCO\text{-}SiMe_3)_3P_7$



Phosphorous pure shift resolves isomers

Commun. Chem. **2026** In press

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Manchester Group

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Alexandra Shread (Bruker)

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… and other collaborators (with thanks)

MANCHESTER 1824 The University of Manchester

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

UKRI Engineering and Physical Sciences Research Council

THE ROYAL SOCIETY

UKRI Biotechnology and Biological Sciences Research Council

FAPESP

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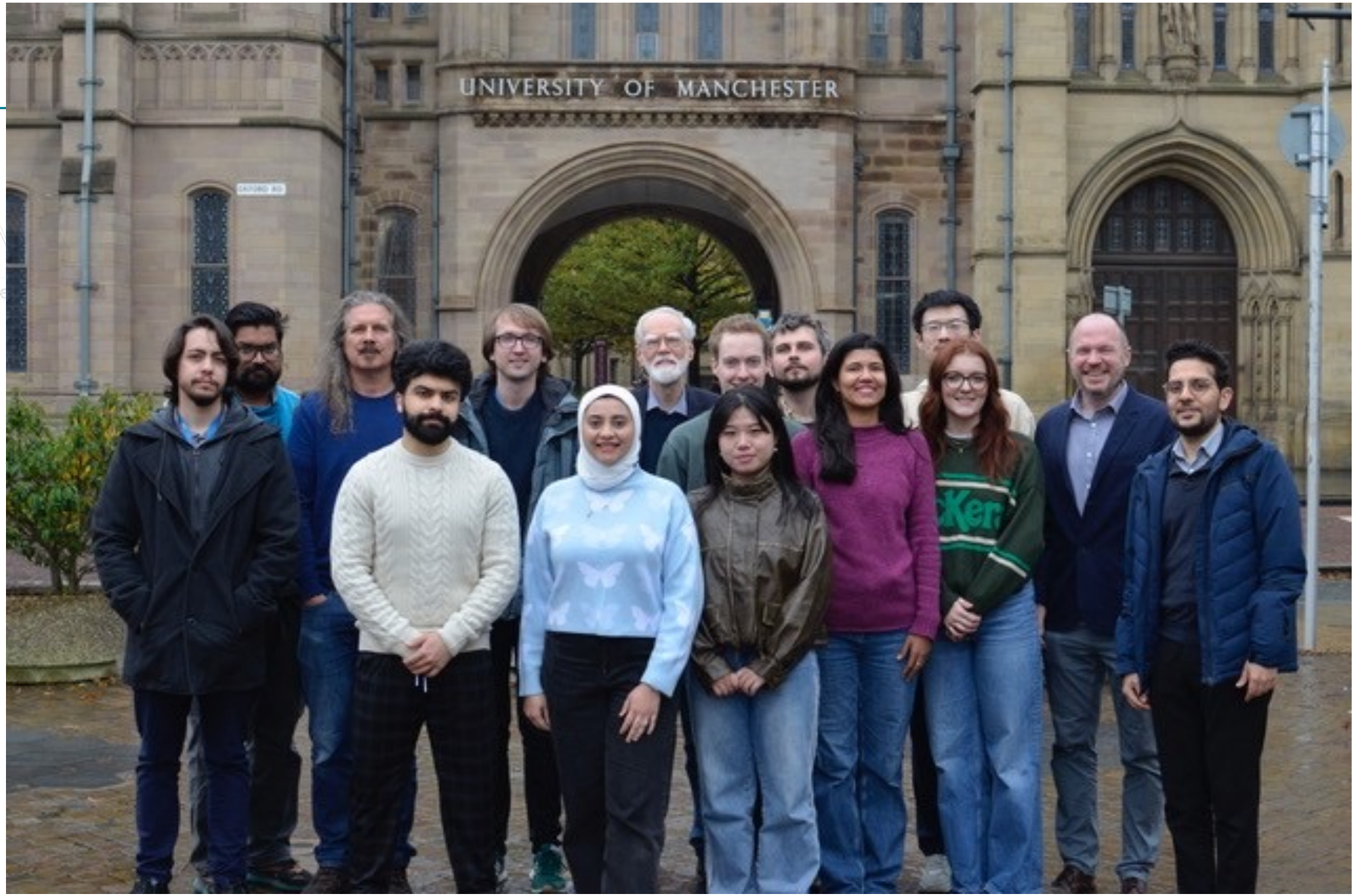
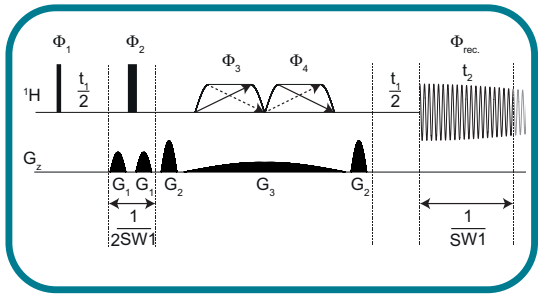


Resources from the Manchester NMR Methodology Group



Pulse sequences

GNAT

Software tools

Workshops & talks

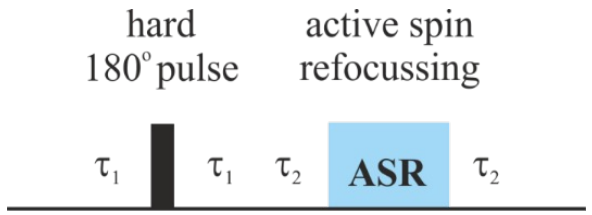
Scan for resources

nmr.chemistry.manchester.ac.uk

Pure shift methodology

Pure shift key ideas

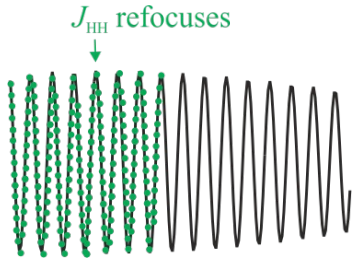
J-refocussing element



J_{HH} is refocused while $\mathbf{d}_H$ evolves

(for active spin only)

Chunking data acquisition

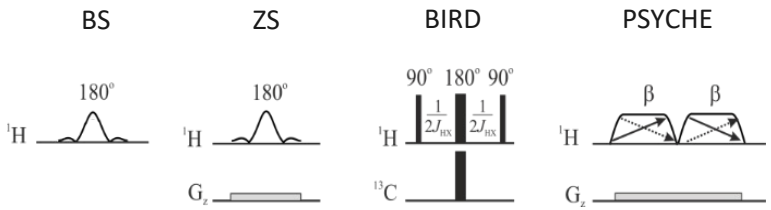


Chunk duration (t_c) << $1/J_{HH}$

J_{HH} refocused in the middle

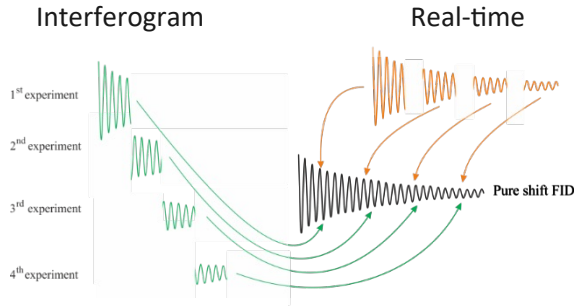
Pure shift methods

Active spin refocussing

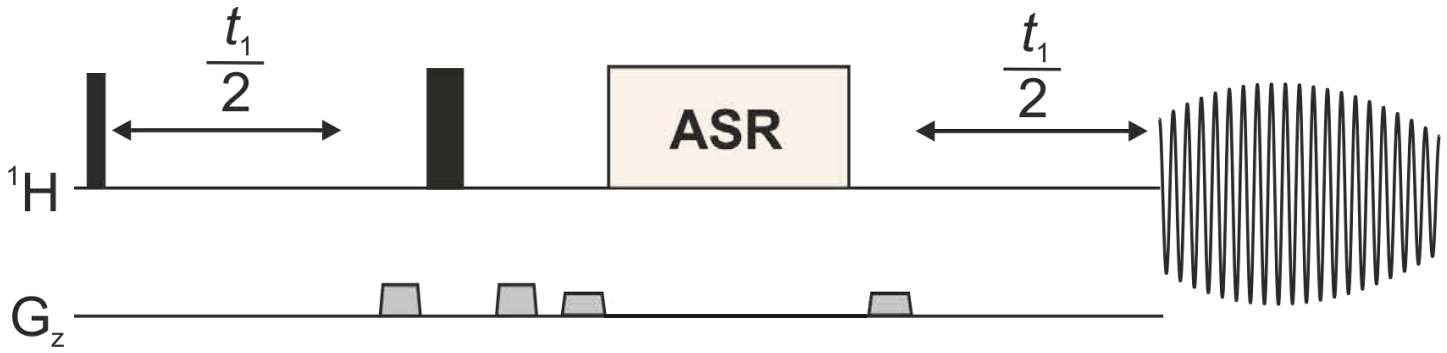


Divides the spins into *active* (observed) and *passive* spins (non observed)

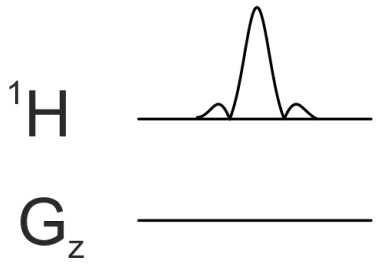
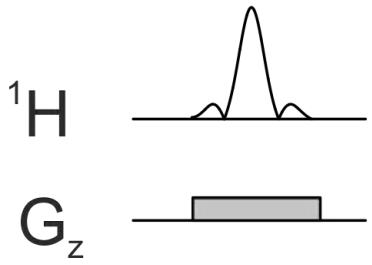
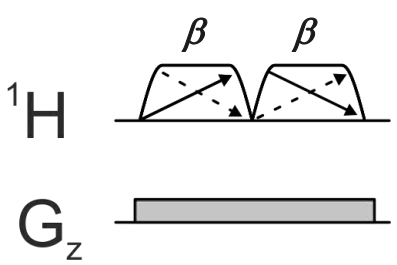
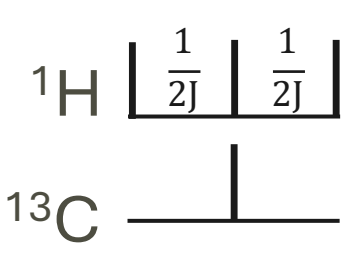
Acquisition methods



Basic pure shift sequence



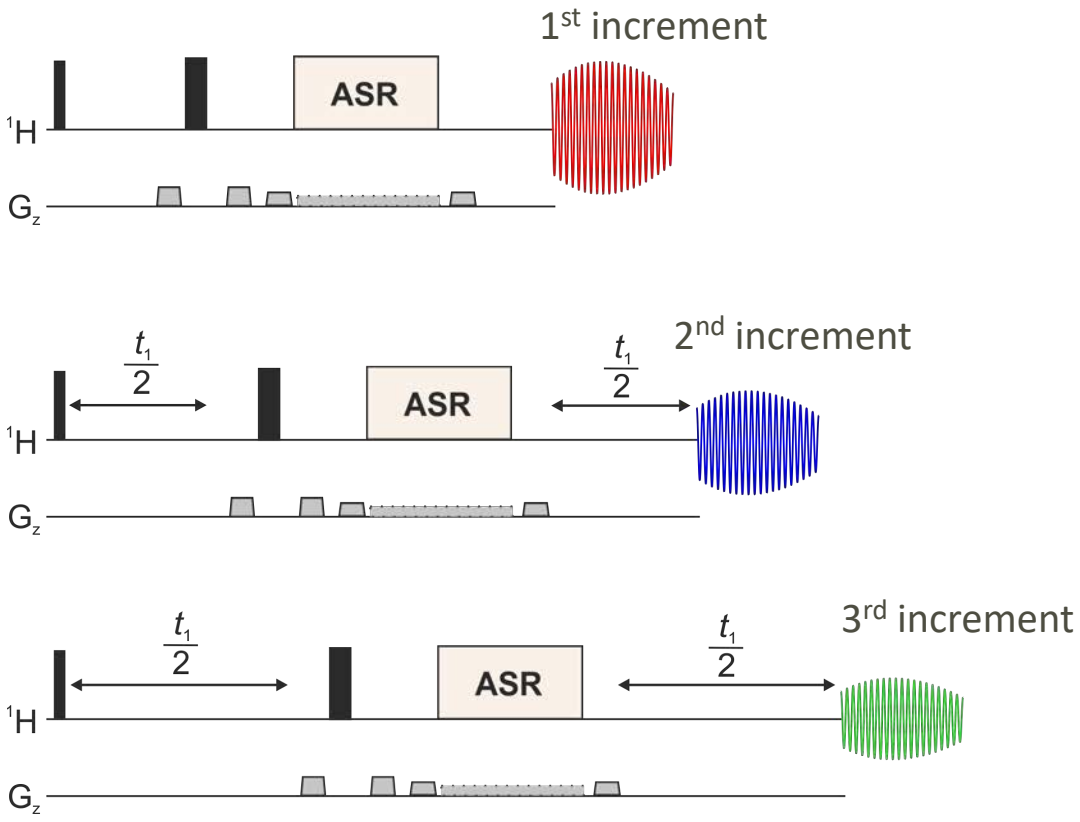
Active **S**pin **R**efocussing

	Band selective	Zangger-Sterk	PSYCHE	BIRD
				
Sensitivity:	≥ 100%	0.5 – 10%	3 – 20%	≈1%
Broadband:	✗	✓	✓	✓

ASR enables pure shift; implementation determines sensitivity, bandwidth, and artefacts.

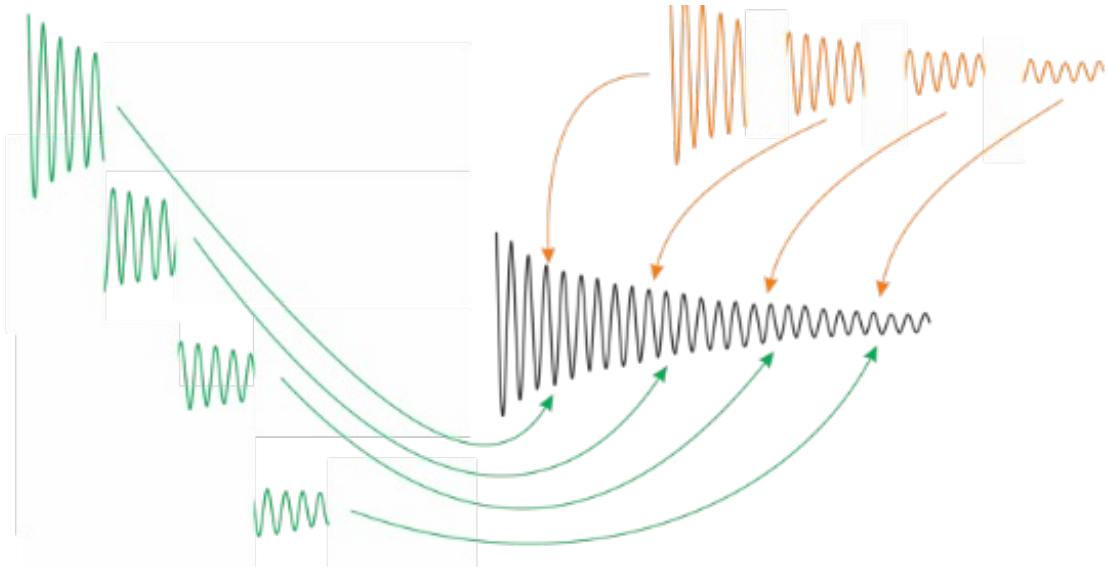
Acquisition of pure shift – interferogram method

Acquire ‘chunked’ FID in increments



Interferogram

Real-time



Short chunks suppress J-evolution while preserving chemical shift evolution