Manipulating the Hamiltonian: decoupling and recoupling

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Decoupling

This means the use of some pulse sequence to average a dipolar coupling.

Decoupling is used to:

* ⋆ improve resolution in NMR spectra of dilute spins (often carbon-13) by removing dipolar couplings to a heteronucleus (often proton)

* ⋆ improve resolution in proton or fluorine-19 NMR spectra by removing homonuclear couplings

Recoupling

This means the use of some pulse sequence which is synchronized with the MAS rotor to reintroduce an averaged dipolar coupling.

Recoupling is used to:

* ⋆ measure interatomic distances and dihedral angles.

* ⋆ establish dipolar correlations in a two-dimensional NMR experiment.

$$H_D \propto 3I_{1z}I_{2z} - \mathbf{I}_1 \cdot \mathbf{I}_2 = 2I_{1z}I_{2z} - \frac{1}{2}\left(I_1^+ I_2^- + I_1^- I_2^+ \right)$$

There are two parts to the homonuclear dipolar Hamiltonian:

* ★ an inhomogeneous part which shifts the energies of the Zeeman eigenstates

* ★ a homogeneous part which mixes degenerate Zeeman states and causes line broadening
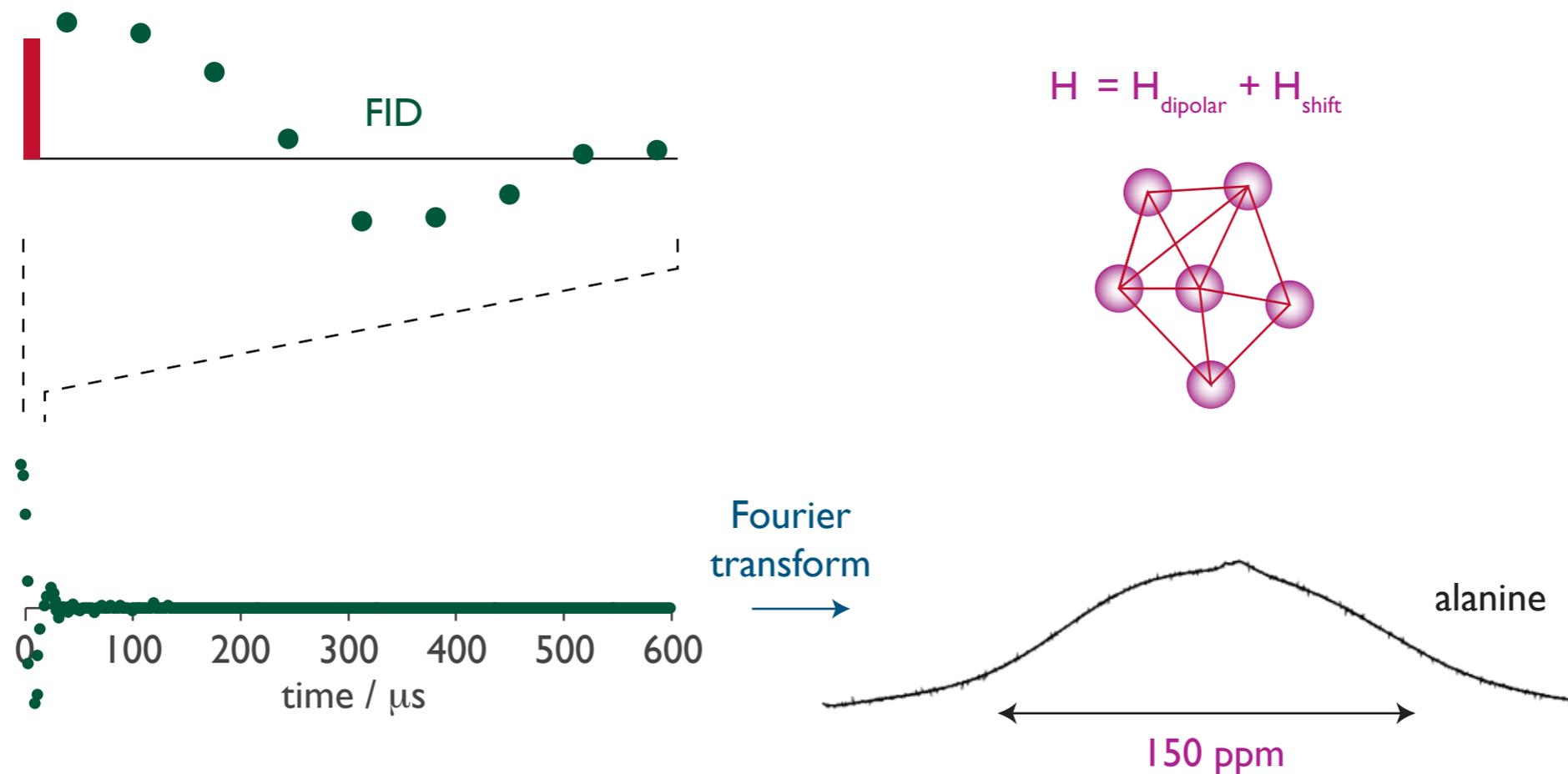
The homogeneous term also causes energy conserving "flip-flop" transitions between degenerate states at a rate which depends on the dipolar coupling. The flip-flop transitions mean that the state of the spin system fluctuates and when ν_R/d is small this interferes with the MAS averaging.

Proton NMR of glycine

inhomogeneous part

homogeneous part

ν_R / kHz

0

5

10

15

500 ppm
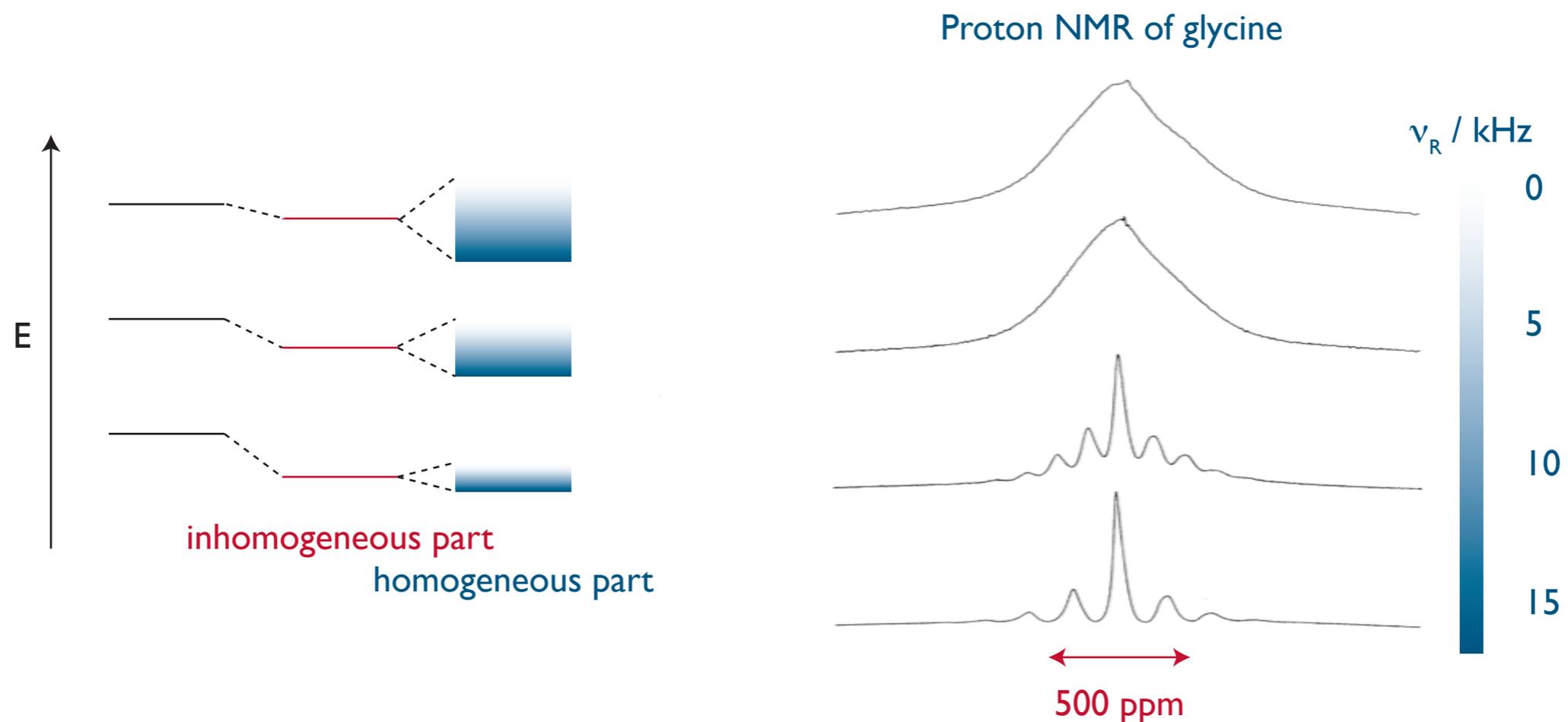
Homogeneous dipolar interactions are more effectively averaged in spin space.

Under the influence of the homonuclear dipolar Hamiltonian the proton FID decays rapidly, leading to a very broad line with no resolution of chemical sites.

FID

$H = H_{dipolar} + H_{shift}$

0   100   200   300   400   500   600
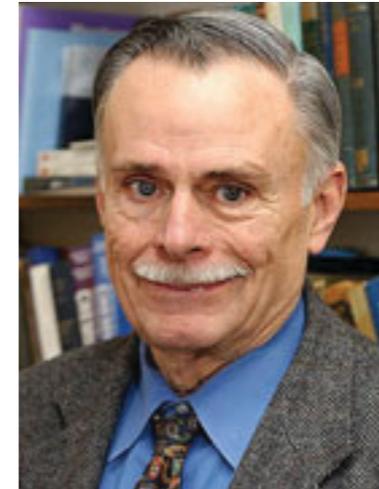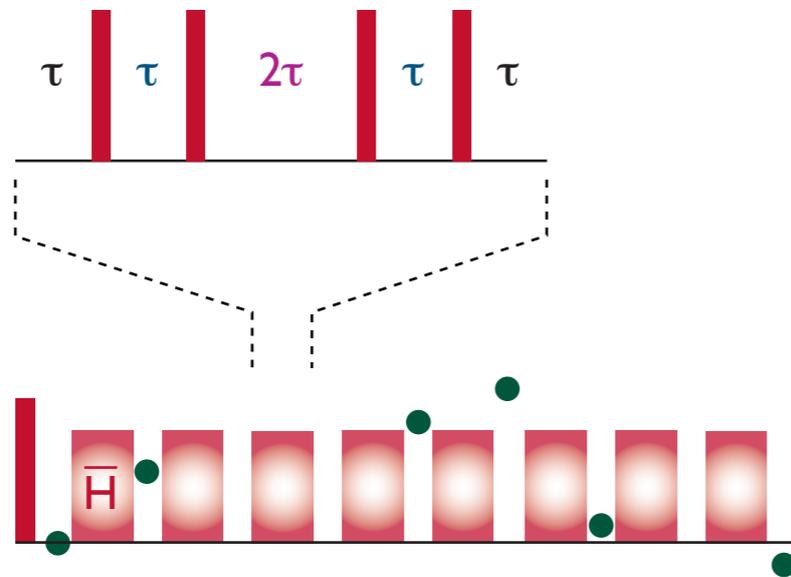
time / μs

Fourier transform

alanine

150 ppm

Homonuclear decoupling involves:

- ★ sampling the FID stroboscopically, between bursts of a multi-pulse sequence
- ★ with the multi-pulse sequence the spins appear to evolve under an effective Hamiltonian
- ★ when the dipolar part of the effective Hamiltonian is zero, the FID decays more slowly and chemical sites are resolved.
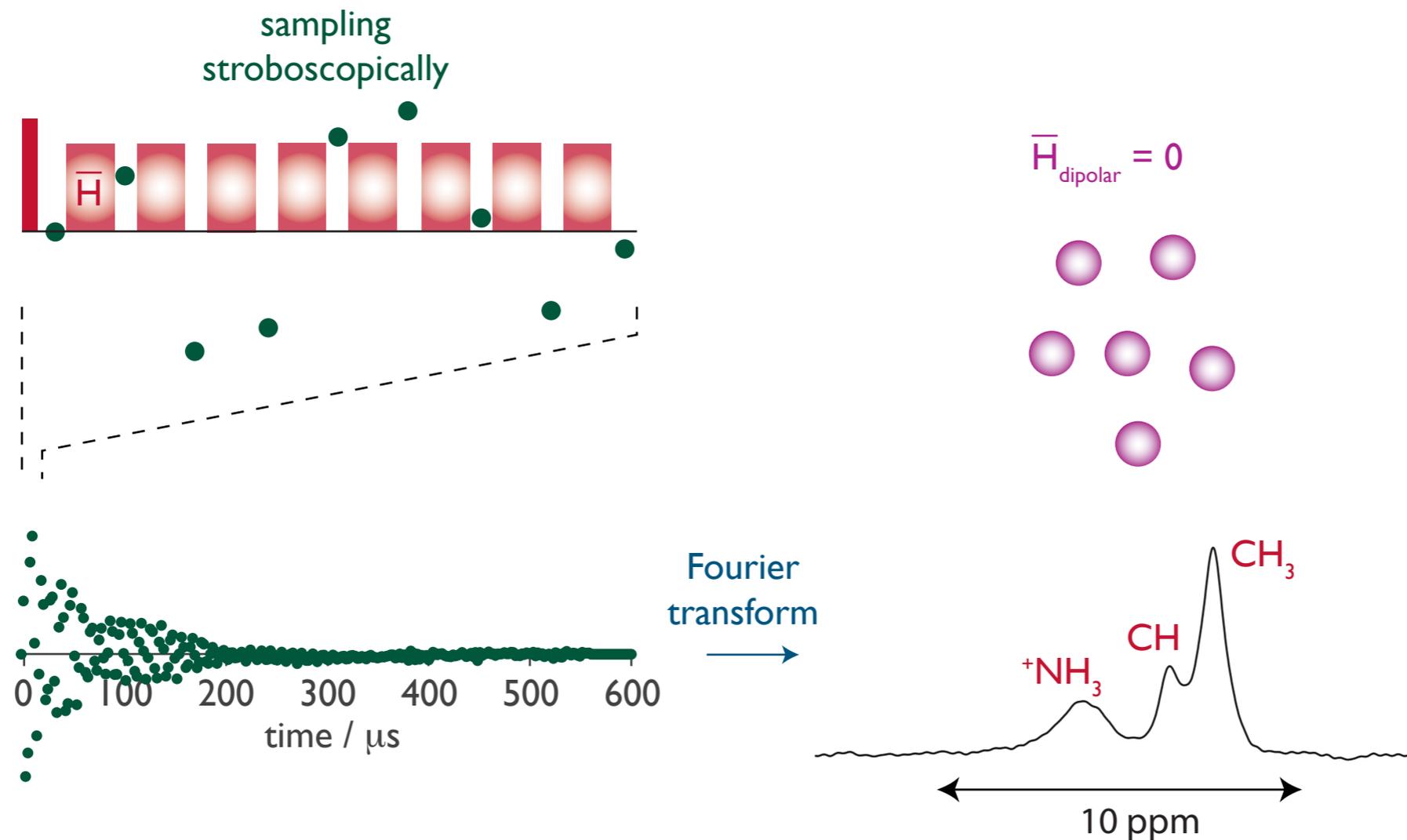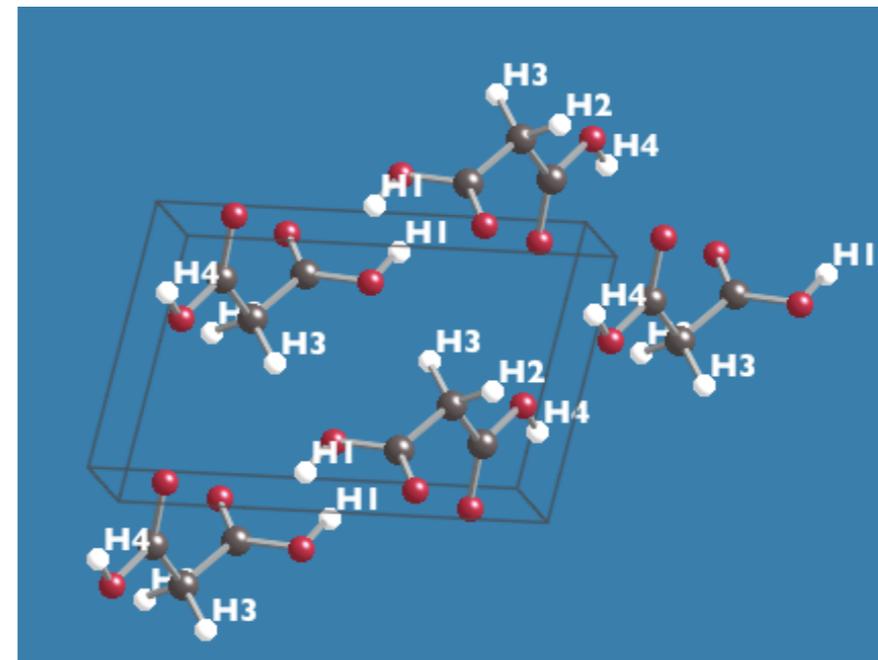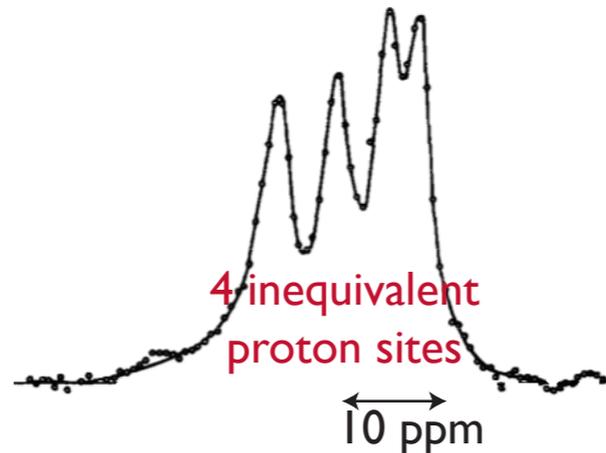
WAHUHA

The simplest multi-pulse sequence for homonuclear decoupling is the WAHUHA sequence which consists of 4 $\pi/2$ pulses separated by short delays with a cycle time $\tau_c \sim 20\ \mu s$.

John Waugh

malonic acid single crystal

4 inequivalent proton sites

10 ppm

U. Haeberlen, U. Kohlschütter, J. Kempf, H.W. Spiess and H. Zimmerman, *Chem. Phys.,* **3**, 248 (1974).

Assuming:

* a periodic Hamiltonian H(t) which is piecewise-constant in each of j intervals of length τ_j so that:

$$H(t) = H_j$$

$$\tau_c = \sum_j \tau_j$$

* stroboscopic observation synchronized with the period of the Hamiltonian

then it is possible to express the entire multi-pulse sequence as a single transformation under an effective Hamiltonian given by the Baker-Campbell-Hausdorff expansion:

$$\bar{H} = \bar{H}^{(0)} + \bar{H}^{(1)} + \dots$$

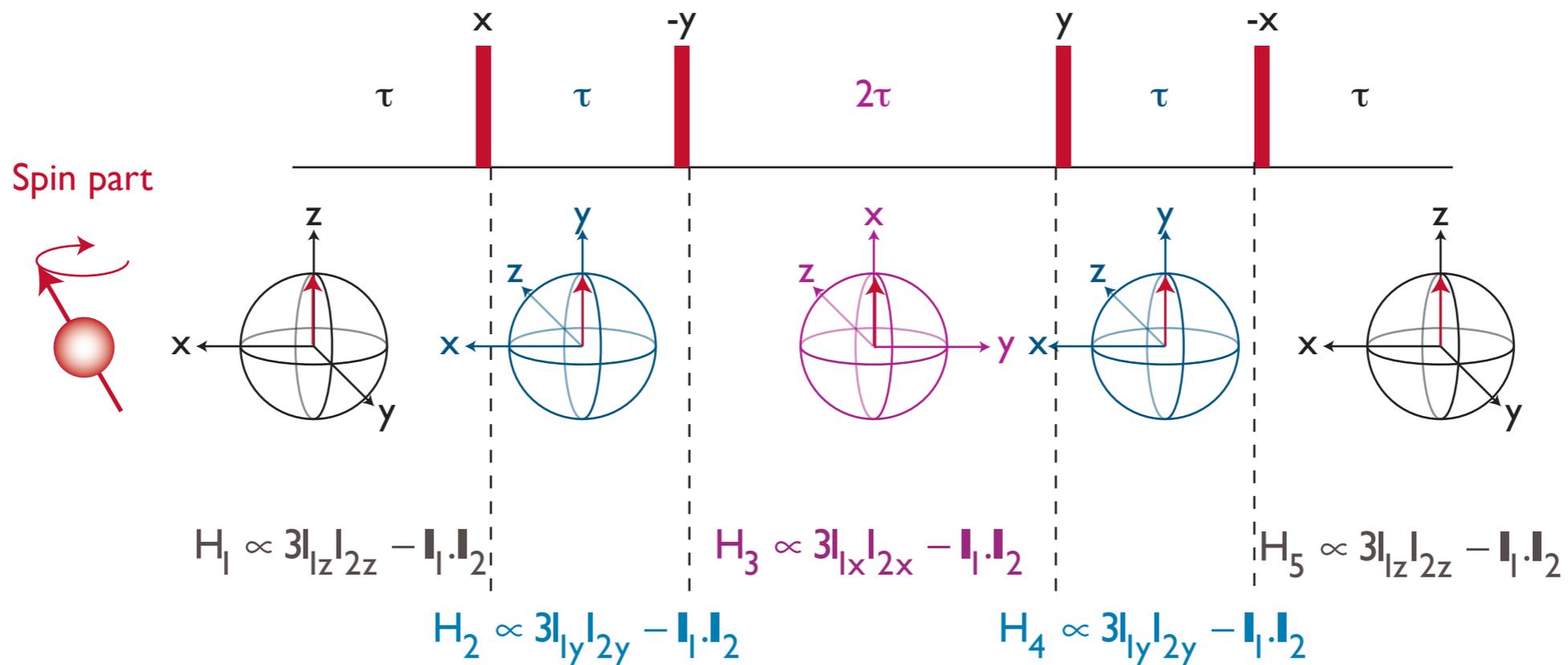$$\bar{H}^{(0)} = \frac{1}{\tau_c}\left\{H_1\tau_1 + H_2\tau_2 + \dots + H_j\tau_j\right\}$$

$$\bar{H}^{(1)} = -\frac{i}{2\tau_c}\left\{\left[H_2\tau_2, H_1\tau_1\right] + \left[H_3\tau_3, H_2\tau_2\right] + \left[H_3\tau_3, H_1\tau_1\right] + \dots\right\}$$

where the lowest order term is the average Hamiltonian. For the Baker-Campbell-Hausdorff expansion to converge (i.e. for the multi-pulse sequence to work) $1/\tau_c > |H|$.

Note: if $\tau_c \sim 20\ \mu s$ lines up to 50 kHz in width can be narrowed.

For a multi-pulse sequence the internal Hamiltonian is piecewise constant in the interaction representation or toggling frame which is defined by the successive frame transformations induced by the pulses.

Spin part

$H_1 \propto 3I_{1z}I_{2z} - \mathbf{I}_1 \cdot \mathbf{I}_2$

$H_2 \propto 3I_{1y}I_{2y} - \mathbf{I}_1 \cdot \mathbf{I}_2$

$H_3 \propto 3I_{1x}I_{2x} - \mathbf{I}_1 \cdot \mathbf{I}_2$

$H_4 \propto 3I_{1y}I_{2y} - \mathbf{I}_1 \cdot \mathbf{I}_2$

$H_5 \propto 3I_{1z}I_{2z} - \mathbf{I}_1 \cdot \mathbf{I}_2$

$$\bar{H}^{(0)} = \frac{1}{\tau_c}\left\{H_1\tau_1 + H_2\tau_2 + \ldots + H_j\tau_j\right\} \propto \frac{1}{6\tau}\left\{6\tau\left(I_{1z}I_{2z} + I_{1y}I_{2y} + I_{1x}I_{2x}\right) - 6\tau\,\mathbf{I}_1 \cdot \mathbf{I}_2\right\} = 0$$

Much effort has been expended modifying the basic sequence so that:

* ★ higher order terms are removed from the effective Hamiltonian
* ★ terms arising from rf field inhomogeneity, pulse imperfections and resonance offset are compensated
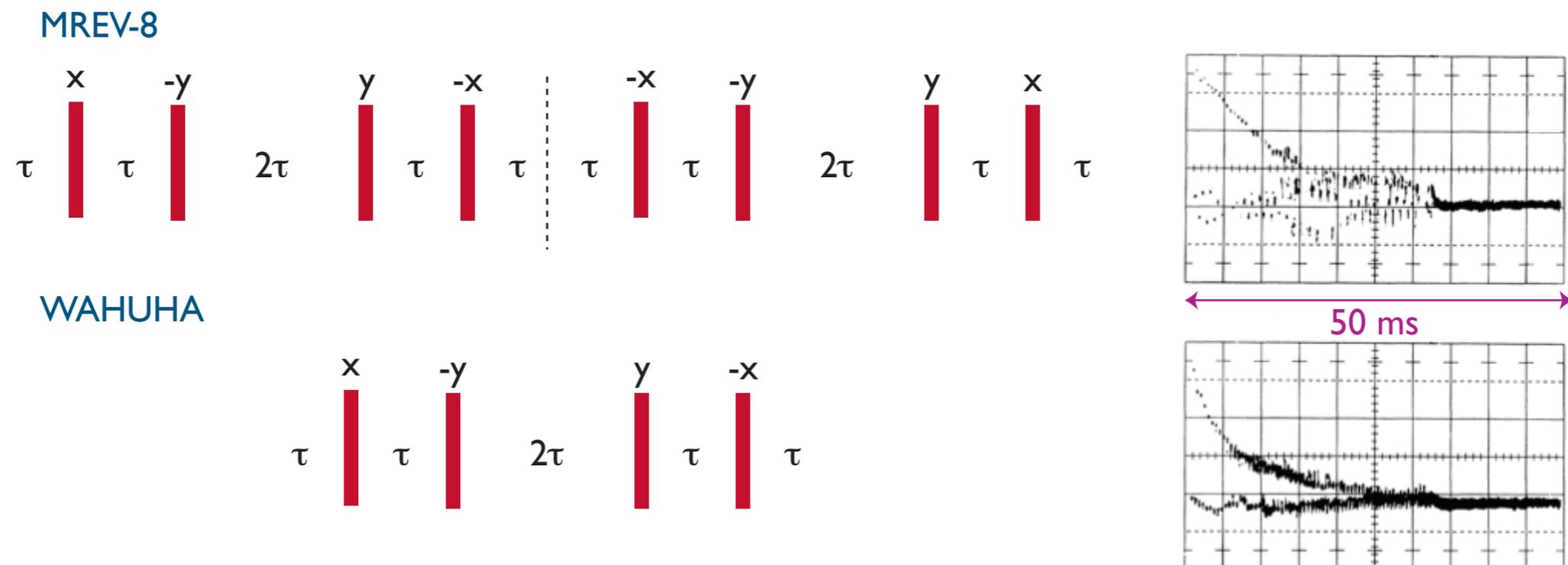
Symmetric cycles

When

$$H(t) = H(\tau_c - t)$$

the cycle is symmetric and all odd-order terms cancel.

Supercycles

For example, MREV-8 repeats the basic WAHUHA cycle twice with the x pulses reversed in phase. This removes the effects of rf inhomogeneity, since toggling frame terms in I_z are inverted during the second half.
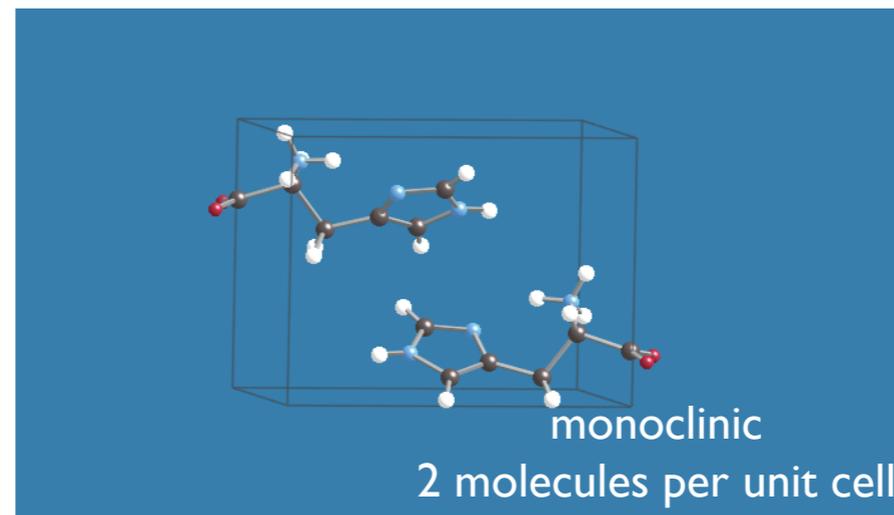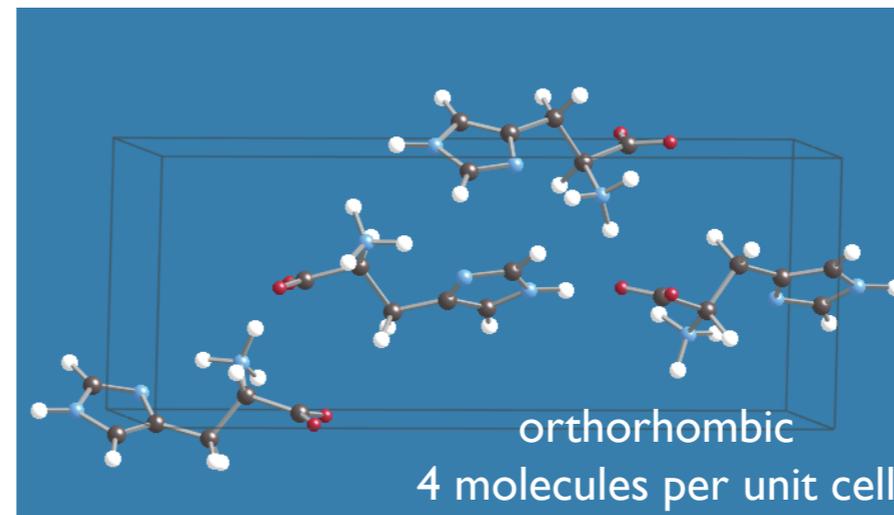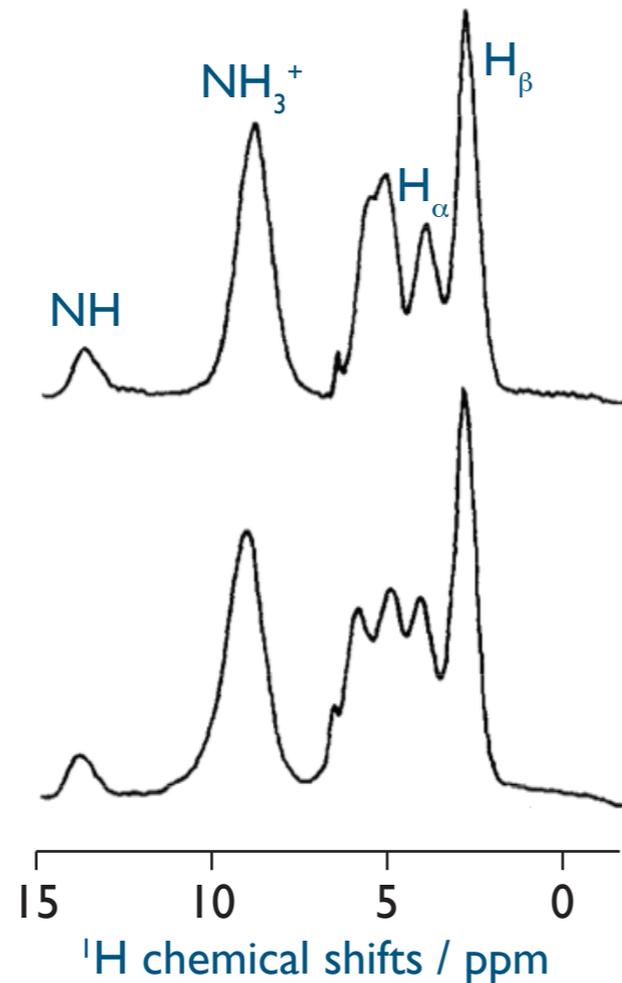
MREV-8

WAHUHA

50 ms

P. Mansfield, M. J. Orchard, D. C. Stalker and K. H. B. Richards, *Phys. Rev. B*, **7**, 90 (1973).

CRAMPS

★ combines the spin-space averaging of a multi-pulse sequence with the sample-space averaging of magic angle spinning.

★ assumes that the sample is static for the duration of the multi-pulse sequence (i.e. $\tau_c \ll \tau_R$) to avoid interference between the two averaging processes.
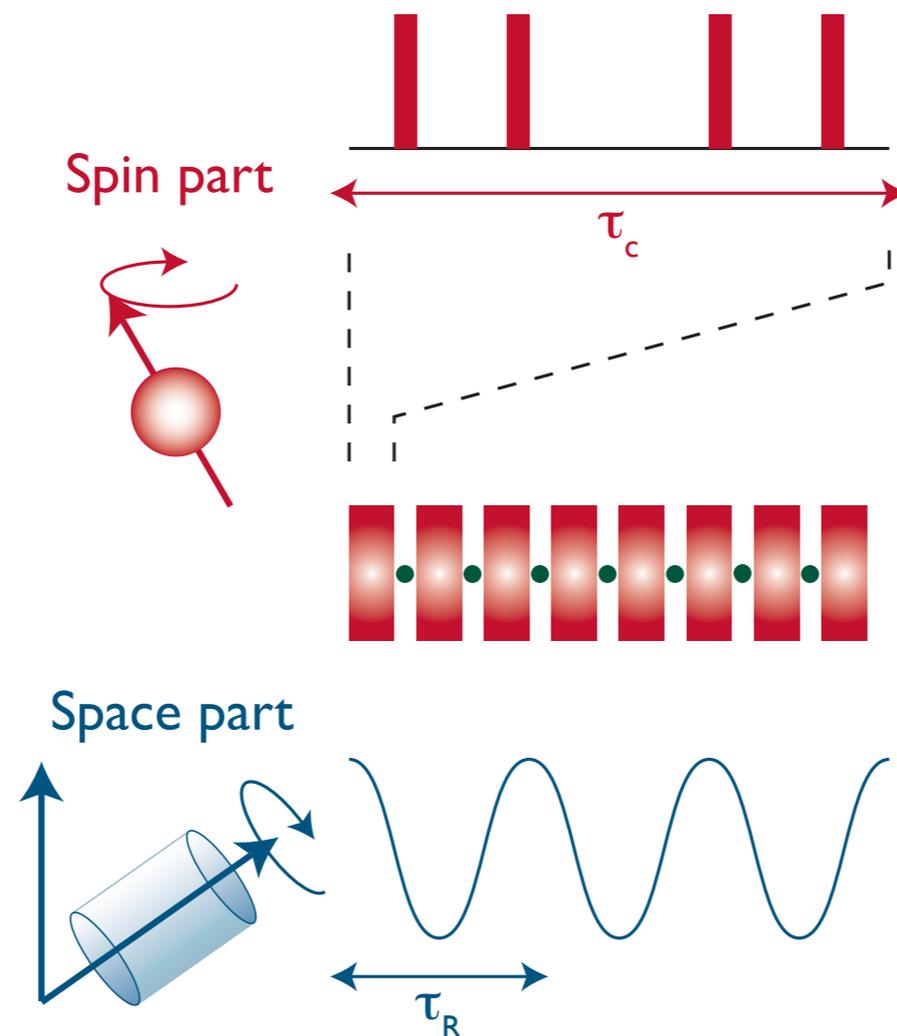
Distinguishing polymorphs in amino acids by CRAMPS

The two polymorphs of histidine have different crystal structures with different numbers of molecules in the unit cell and can be clearly differentiated by CRAMPS (MREV-8 with MAS at 5 kHz).

orthorhombic
4 molecules per unit cell

monoclinic
2 molecules per unit cell

H. Kimuraa, K. Nakamuraa, A. Eguchia, H. Sugisawab, K. Deguchib, K. Ebisawa, E. Suzuki, and A. Shojia, *J. Mol. Struct.*, **447**, 247 (1998).
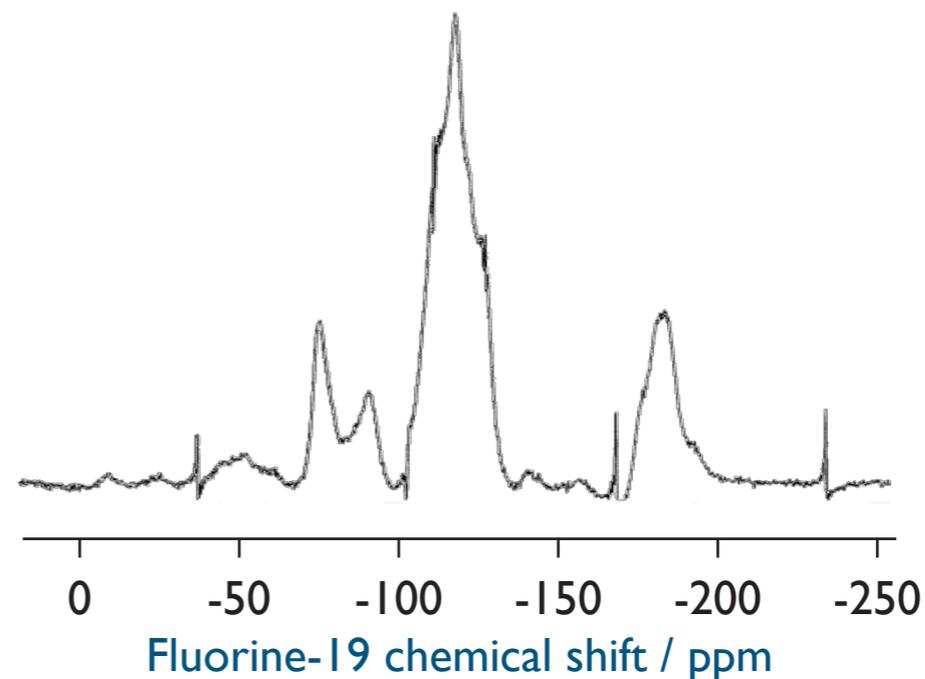
Structures of fluorinated polymers by CRAMPS

Fluorine-19 is the only nucleus other than proton which is 100 % abundant and has a high magnetogyric ratio.
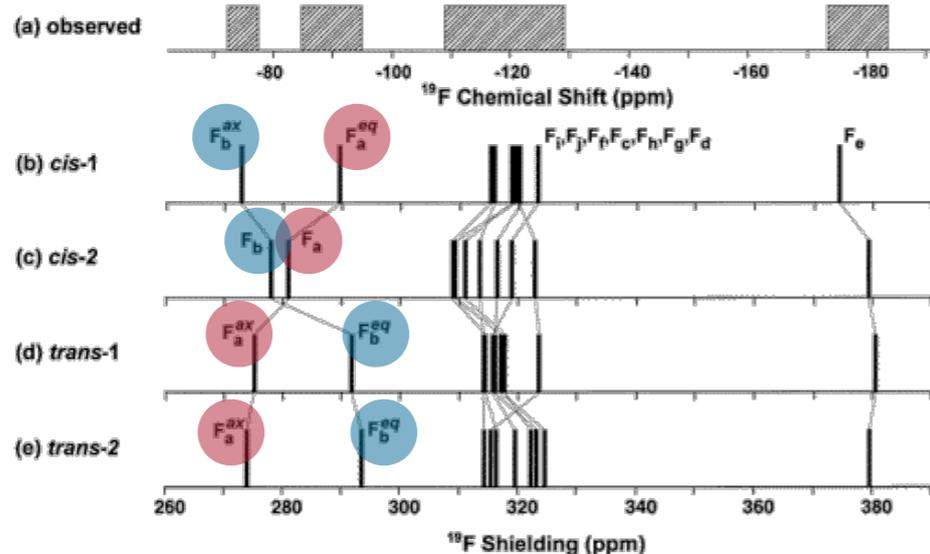
4 stereoisomers of an amorphous cyclized perfluoropolymer
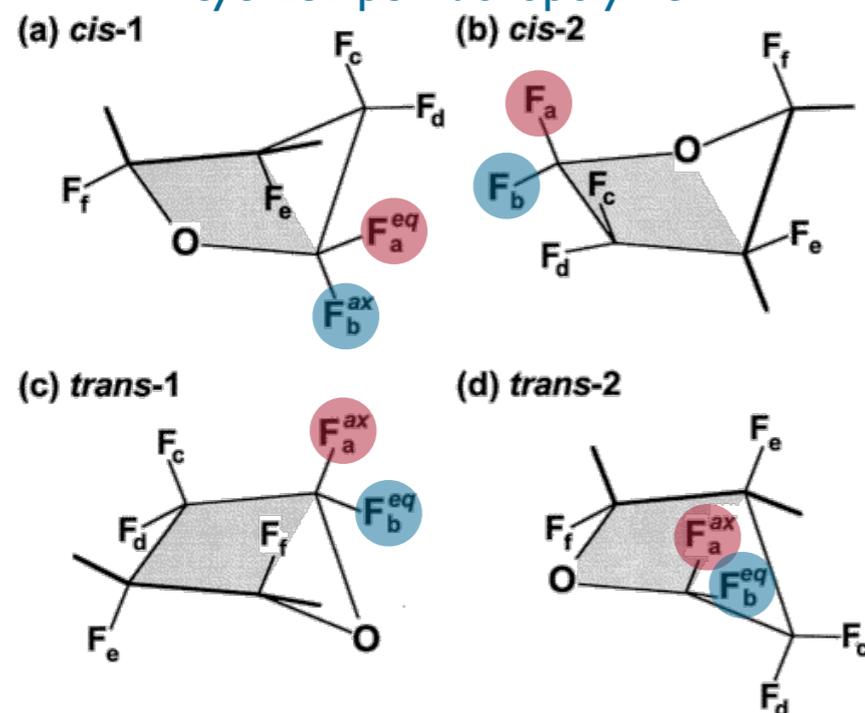
DFT fluorine-19 shift calculations

MREV-8 with τ_c = 39 μs and MAS at 6 kHz

Fluorine-19 chemical shift / ppm

Each line is a superposition of contributions from different stereoisomers.

S. Ando, R.K. Harris, J. Hirschinger, S.A. Reinsberg, and U. Scheler *Macromolecules*, **34**, 66 (2001).
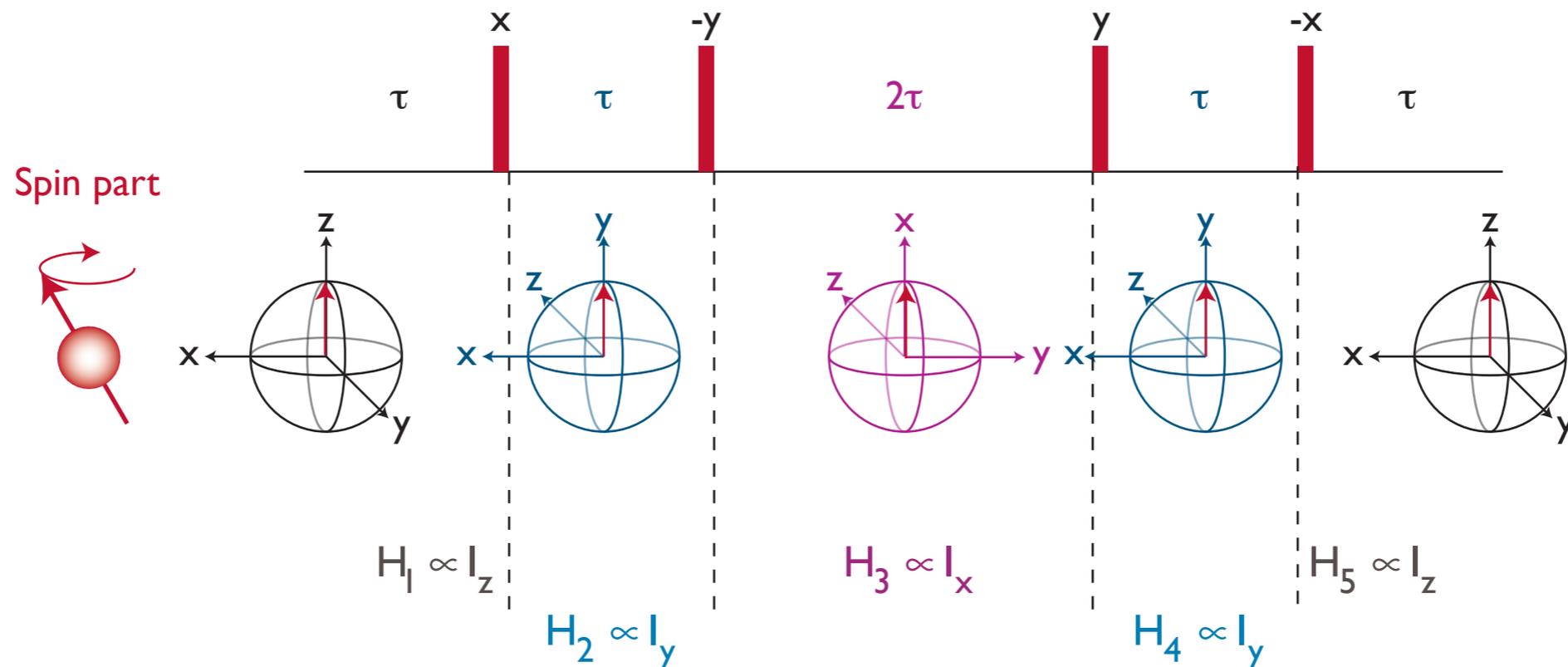
"Don't try this at home."

Sampling must take place in the windows between the multi-pulse cycles and sufficient time must be left to allow probe ringdown, otherwise the receiver can be damaged.

Second averaging. Homonuclear decoupling is most efficient when the multi-pulse sequence is applied off-resonance, because of second averaging effects.

Phase transients. The main pulse imperfection which cannot be easily compensated by a supercycle. The effects of phase transients can be minimized by detuning the probe/amplifier slightly.

Chemical shift scaling. Chemical shift evolution is around an effective field, so observed shifts are scaled. The scaling factor can be calculated, but is usually found empirically.


$$\bar{H}^{(0)} = \frac{1}{\tau_c}\left\{H_1\tau_1 + H_2\tau_2 + \ldots + H_j\tau_j\right\} \propto \frac{1}{6\tau}\left\{2\left(I_z + I_y + I_x\right)\tau\right\} = \frac{1}{3}\left(I_z + I_y + I_x\right)$$

* This method consists of a period of evolution about an effective field (the resultant of the resonance offset and the radiofrequency field B_1) oriented at the magic angle and can be considered as a spin-space variant of magic angle spinning.

* Supercycles can be constructed by alternating periods of positive and negative offset frequency coupled with alternating B_1 phase.

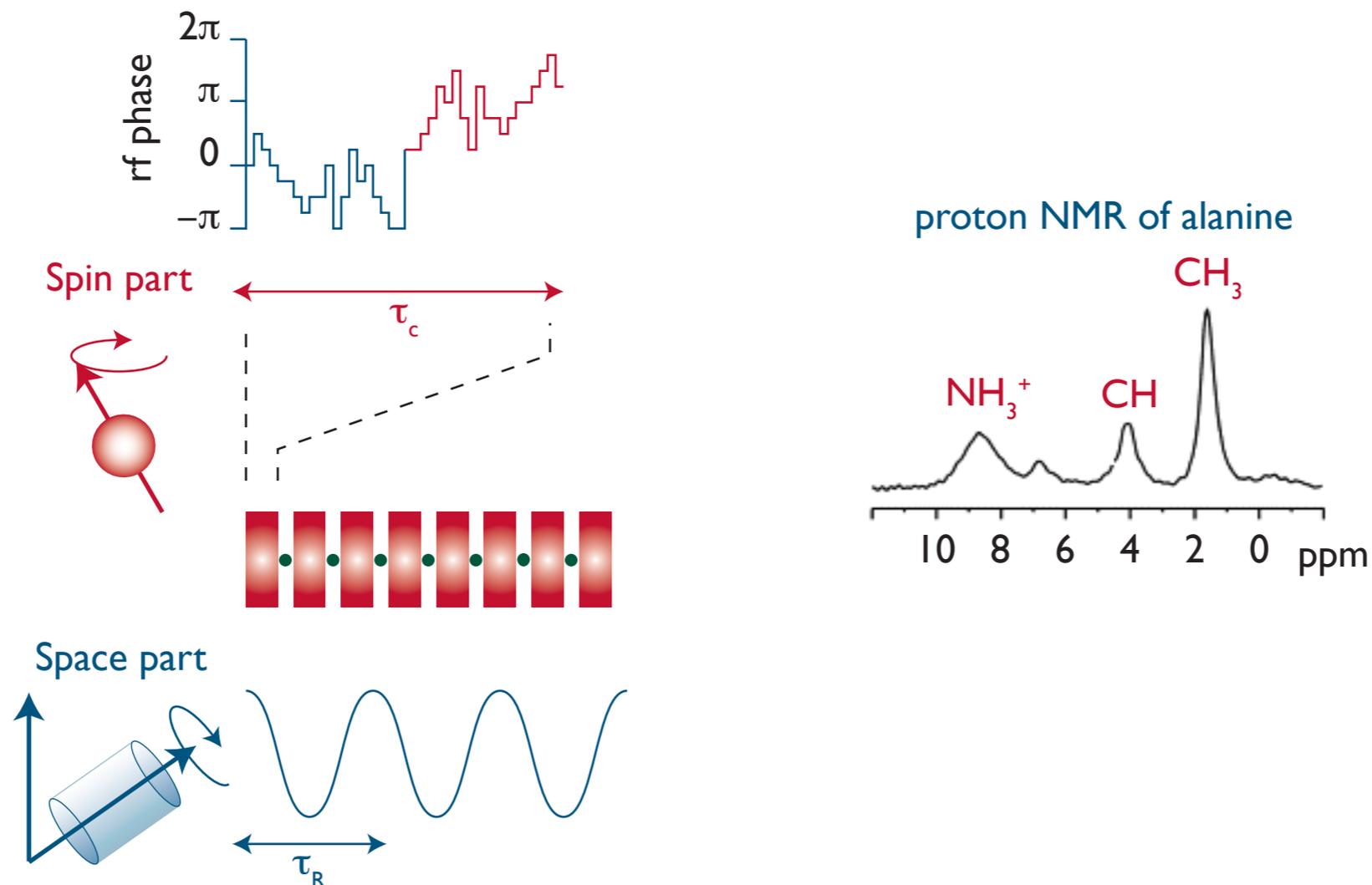sample-space magic angle rotation   spin-space magic angle rotation

A. Bielecki, A. C. Kolbert and M. H. Levitt, *Chem. Phys. Lett.,* **155**, 341 (1989).
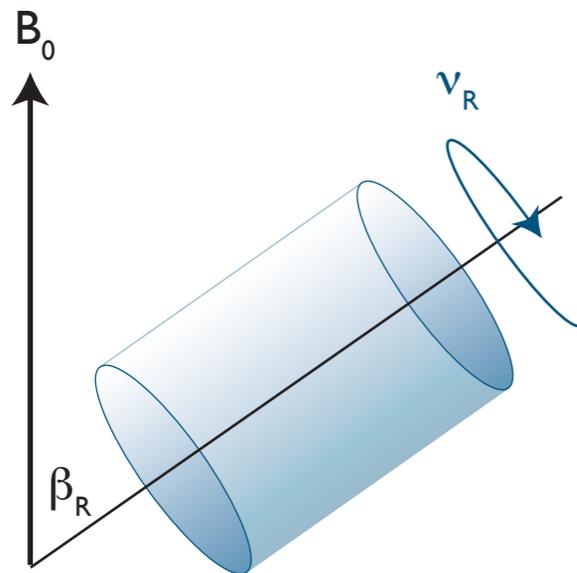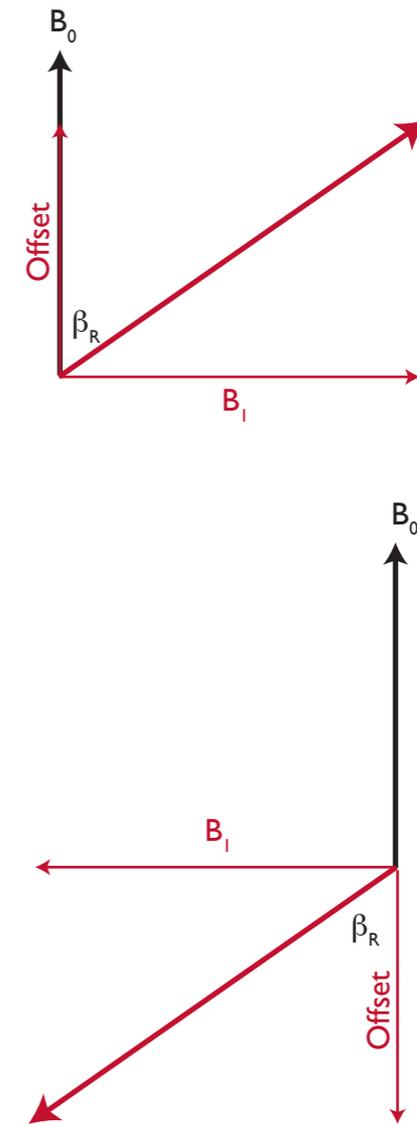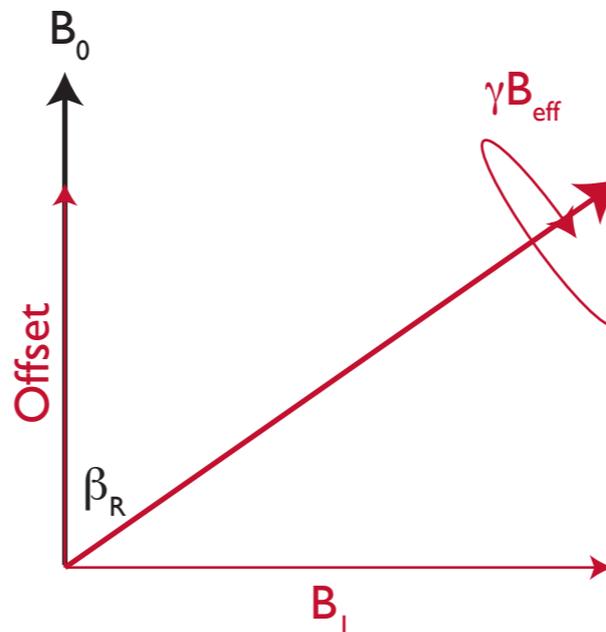
DUMBO

This method replaces the multi-pulse sequence with a continuously phase modulated radiofrequency pulse.

Note:

* the phase shifts are obtained by optimizing the linewidth of a simulated proton spectrum.

* theoretically the experiment only works in the CRAMPS regime ($\tau_c \ll \tau_R$), but practically it operates well with $\tau_c = 30$ μs and $\nu_R = 25$ kHz.

proton NMR of alanine

A. Lesage, D. Sakellariou, S. Hediger, B. Elena, P. Charmont, S. Seuernagel and L. Emsley, *J. Magn. Reson.,* **163**, 105 (2003).

NMR Crystallography

The build-up of cross peak intensity in high-resolution proton-proton spin diffusion spectra with increasing mixing time can be simulated in terms of a sum over the behavior for a set of individual proton-proton contacts which in turn depend on the unit cell parameters etc.
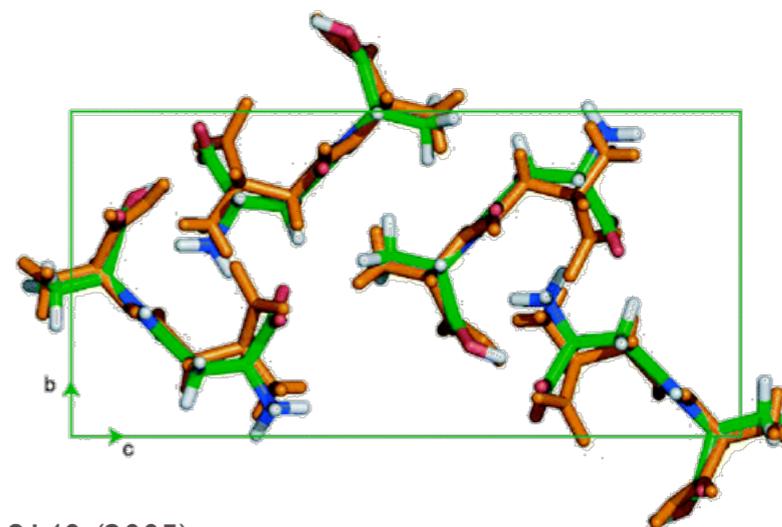
Two-dimensional proton-proton
spin diffusion correlation
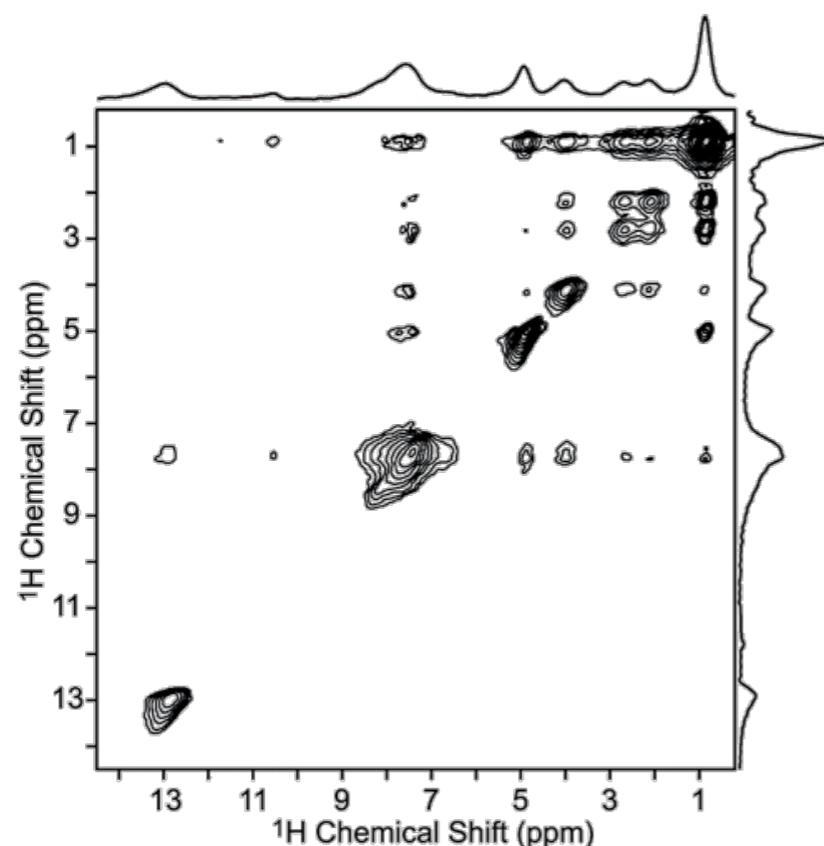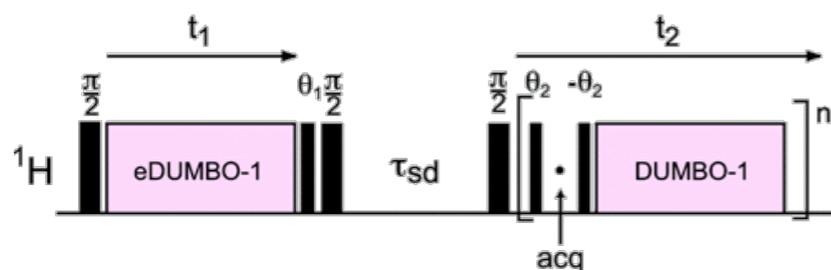
Analysis of cross peak intensities
in terms of proton-proton distances
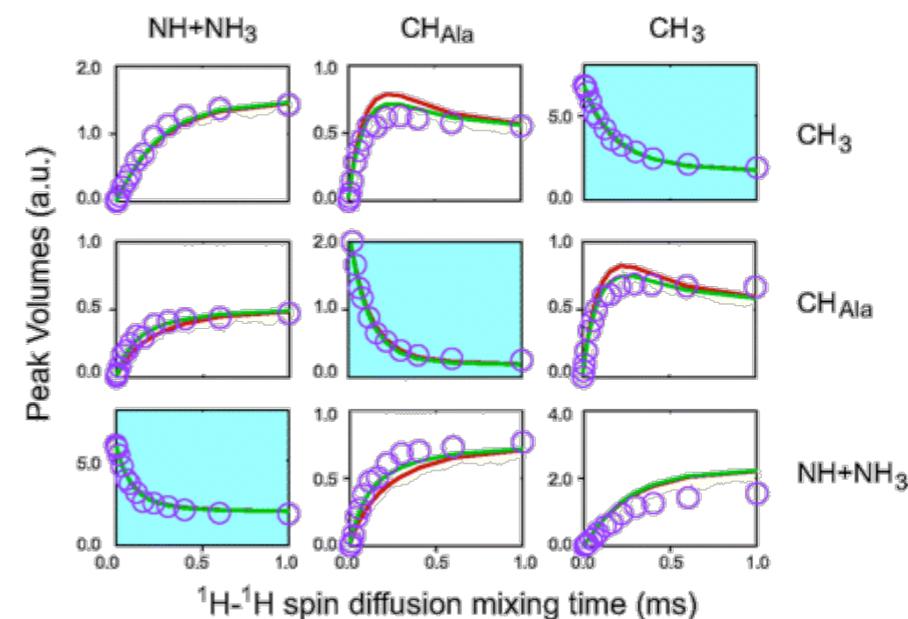
Comparison with X-ray structure

B. Elena and L. Emsley, *J. Am Chem. Soc.*, **127**, 9140 (2005).

Decoupling

This means the use of some pulse sequence to average a dipolar coupling.

Decoupling is used to:

- ⋆ improve resolution in NMR spectra of dilute spins (often carbon-13) by removing dipolar couplings to a heteronucleus (often proton)
- ⋆ improve resolution in proton or fluorine-19 NMR spectra by removing homonuclear couplings

Recoupling

This means the use of some pulse sequence which is synchronized with the MAS rotor to reintroduce an averaged dipolar coupling.

Recoupling is used to:

- ⋆ measure interatomic distances and dihedral angles.
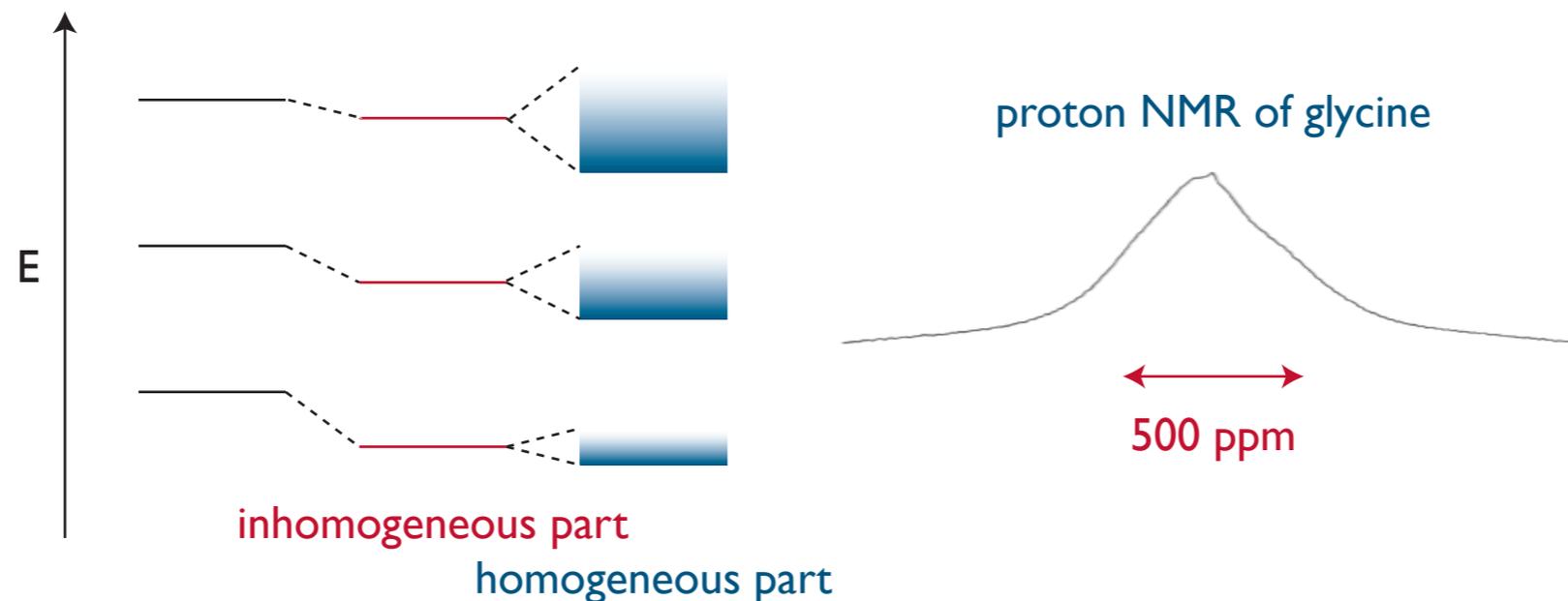- ⋆ establish dipolar correlations in a two-dimensional NMR experiment.

$$H_D \propto 3I_{1z}I_{2z} - \mathbf{I_1}.\mathbf{I_2} = 2I_{1z}I_{2z} - \frac{1}{2}\left(I_1^+I_2^- + I_1^-I_2^+\right)$$

There are two parts to the homonuclear dipolar Hamiltonian:

★   an inhomogeneous part which shifts the energies of the Zeeman eigenstates

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The homogeneous term also causes energy conserving "flip-flop" transitions between degenerate states at a rate which depends on the dipolar coupling.
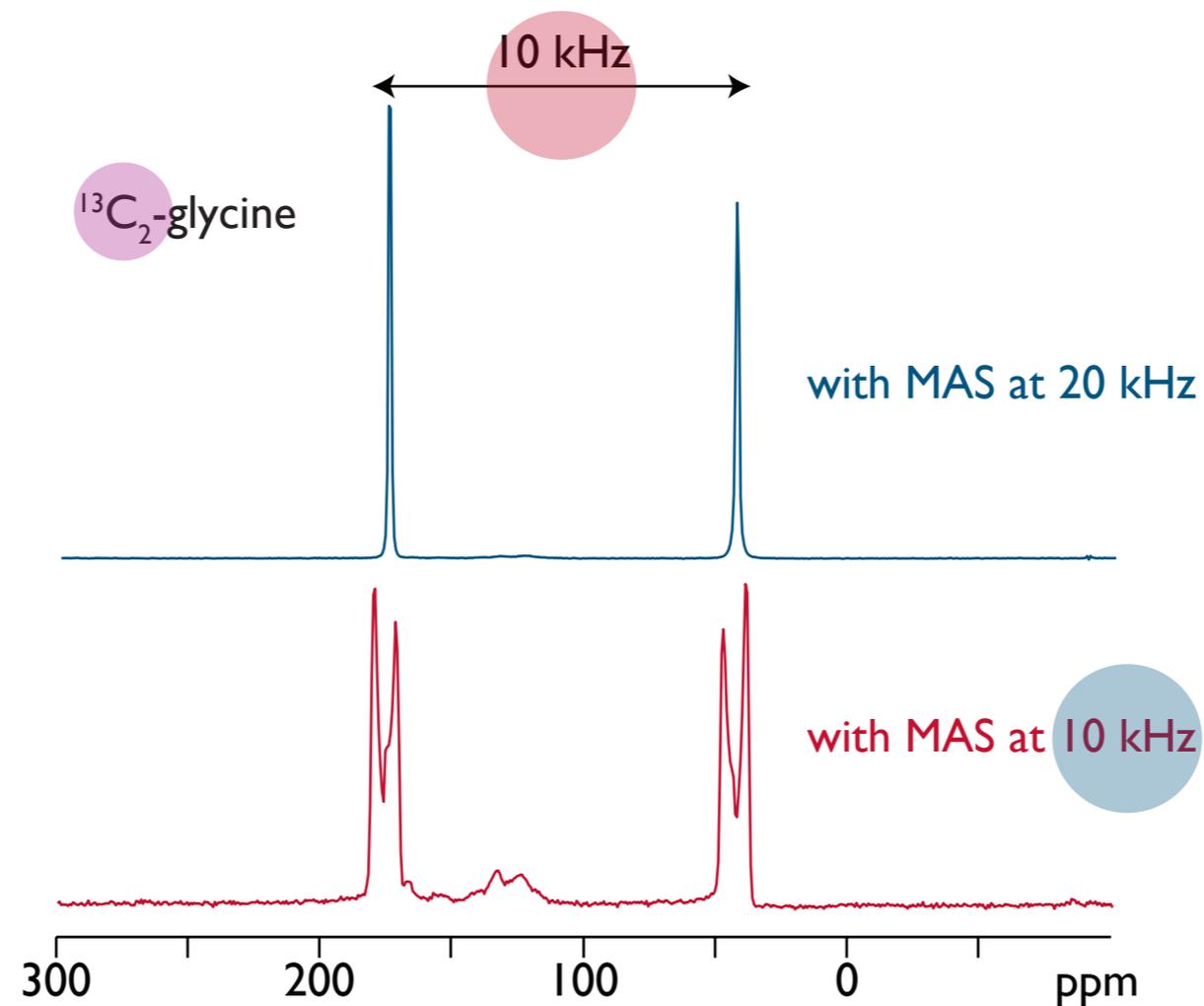
E

proton NMR of glycine

500 ppm

inhomogeneous part

homogeneous part

The flip-flop transitions cause a dynamic process called spin diffusion which acts to return any non-equilibrium proton polarization to equilibrium.

Rotational Resonance

In a sample containing isolated pairs of dipolar-coupled spins, broadenings and splittings occur when the rotational resonance condition is satisfied:

$$\Delta\delta_{iso} = n\nu_R$$

where n is a small integer.

$^{13}C_2$-glycine

10 kHz

with MAS at 20 kHz

with MAS at 10 kHz

300   200   100   0   ppm

M. H. Levitt, D. P. Raleigh, F. Creuzet and R. G. Griffin, *J. Chem. Phys.*, **92**, 6347 (1992).

* In a dipolar-coupled spin pair there are four nuclear spin eigenvalues.

* Under MAS their energies are modulated by the spinning at $\pm\nu_R$ and $\pm2\nu_R$.

* The zero-quantum splitting depends on the isotropic shift difference.

$|\beta\beta>$

$|\alpha\beta>$

$|\beta\alpha>$

$|\alpha\alpha>$
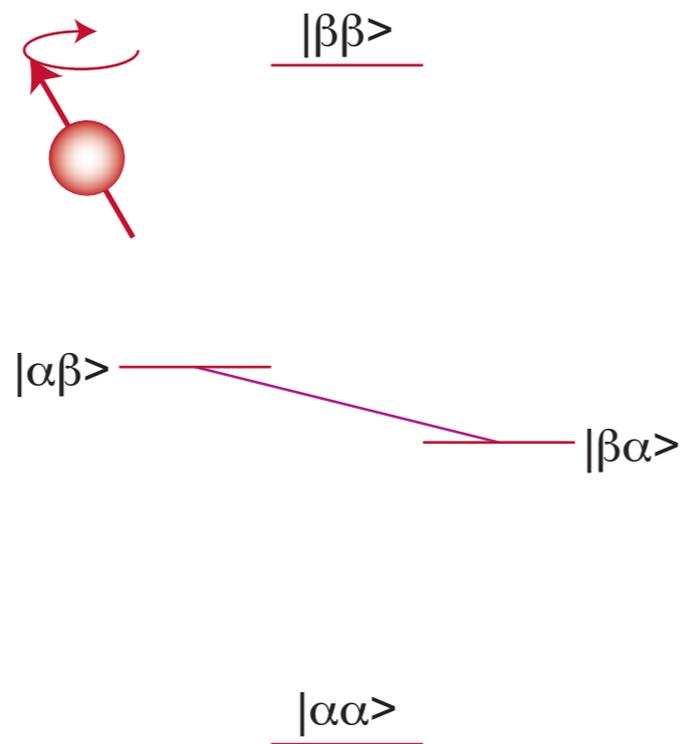
* Under MAS the flip-flop part of the dipolar coupling is modulated by the spinning at $\pm v_R$ and $\pm 2v_R$.

* Think of these as providing quanta of MAS rotor energy which interact with the eigenstates.
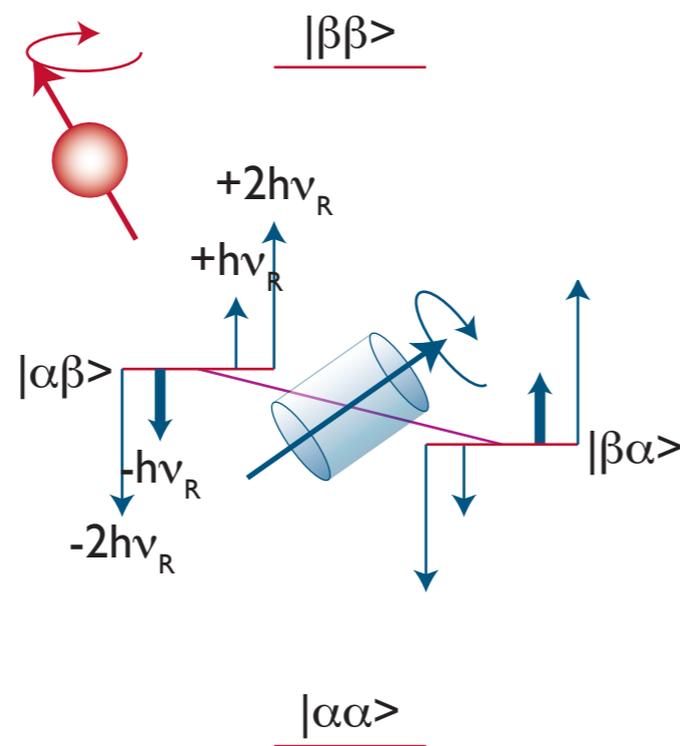
- ★ MAS quanta which are not close to the zero-quantum splitting cause broadenings of the eigenstates.
- ★ MAS quanta which are **resonant** with the zero-quantum splitting have a dramatic effect on the spectrum and split the eigenstates into two time-independent virtual states separated by an energy which depends on d and on orientation.
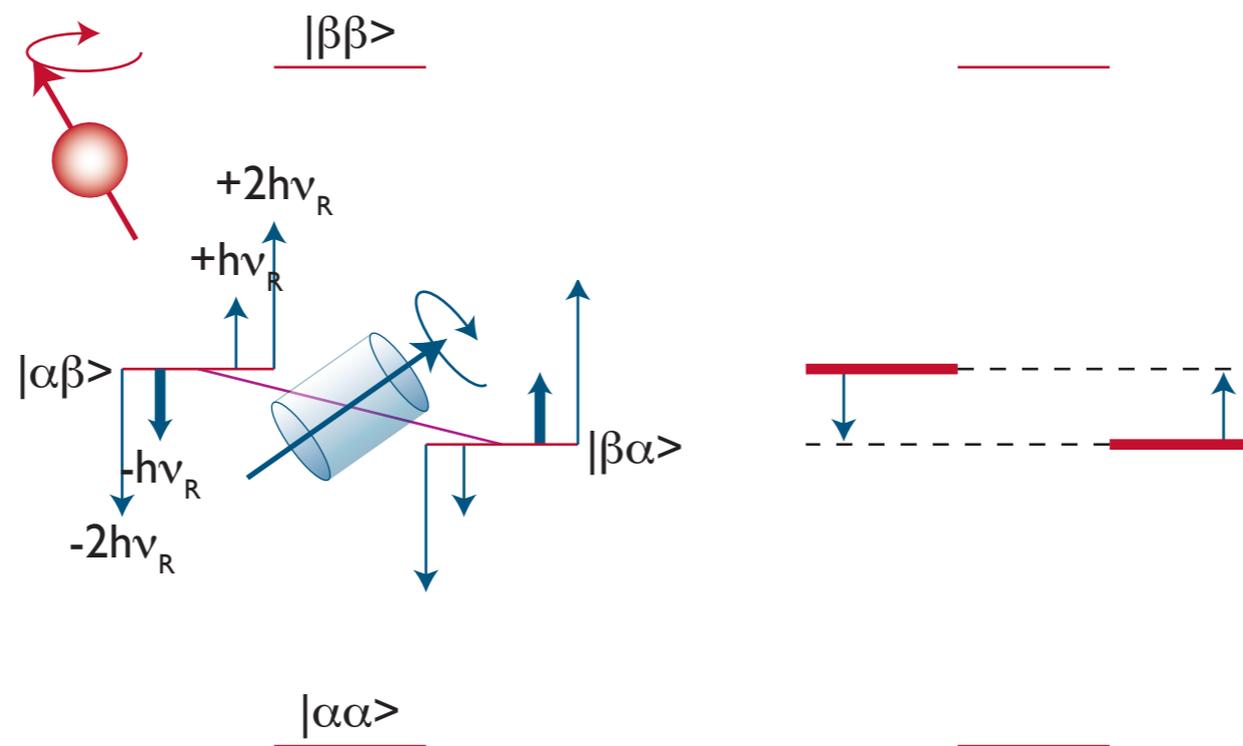
* This splitting results in **8** observable transitions which are all powder broadened.
* Although the good resolution of a MAS spectrum is retained, the lineshapes depend on the dipolar coupling.
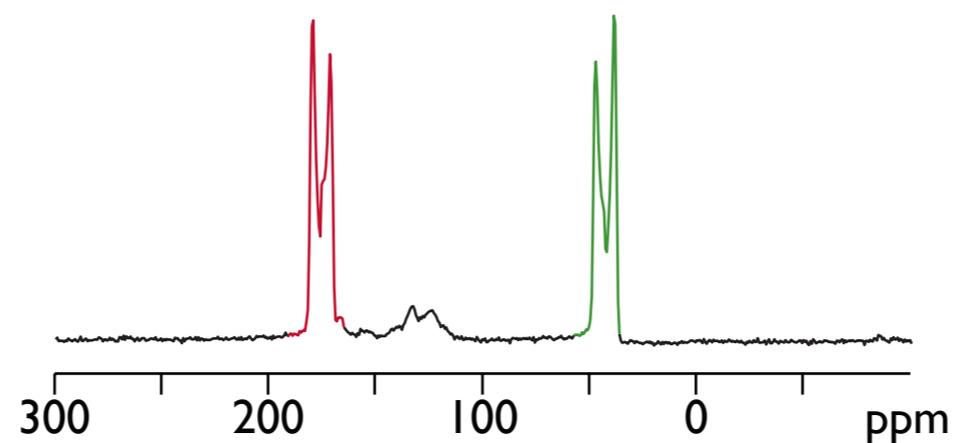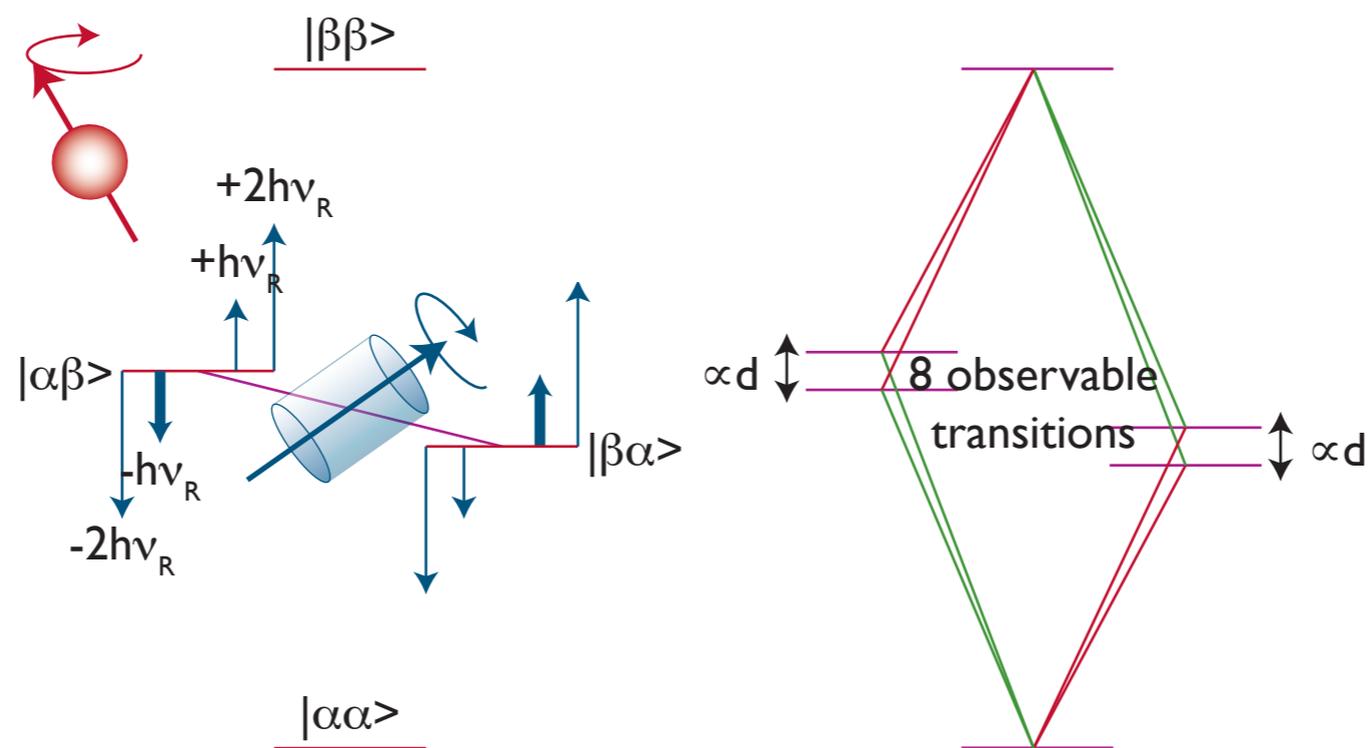
Magnetization exchange

* Rotational "resonance" is so-called because the small flip-flop term has a large effect on the spin dynamics when an MAS modulated flip-flop component is resonant with the shift difference.
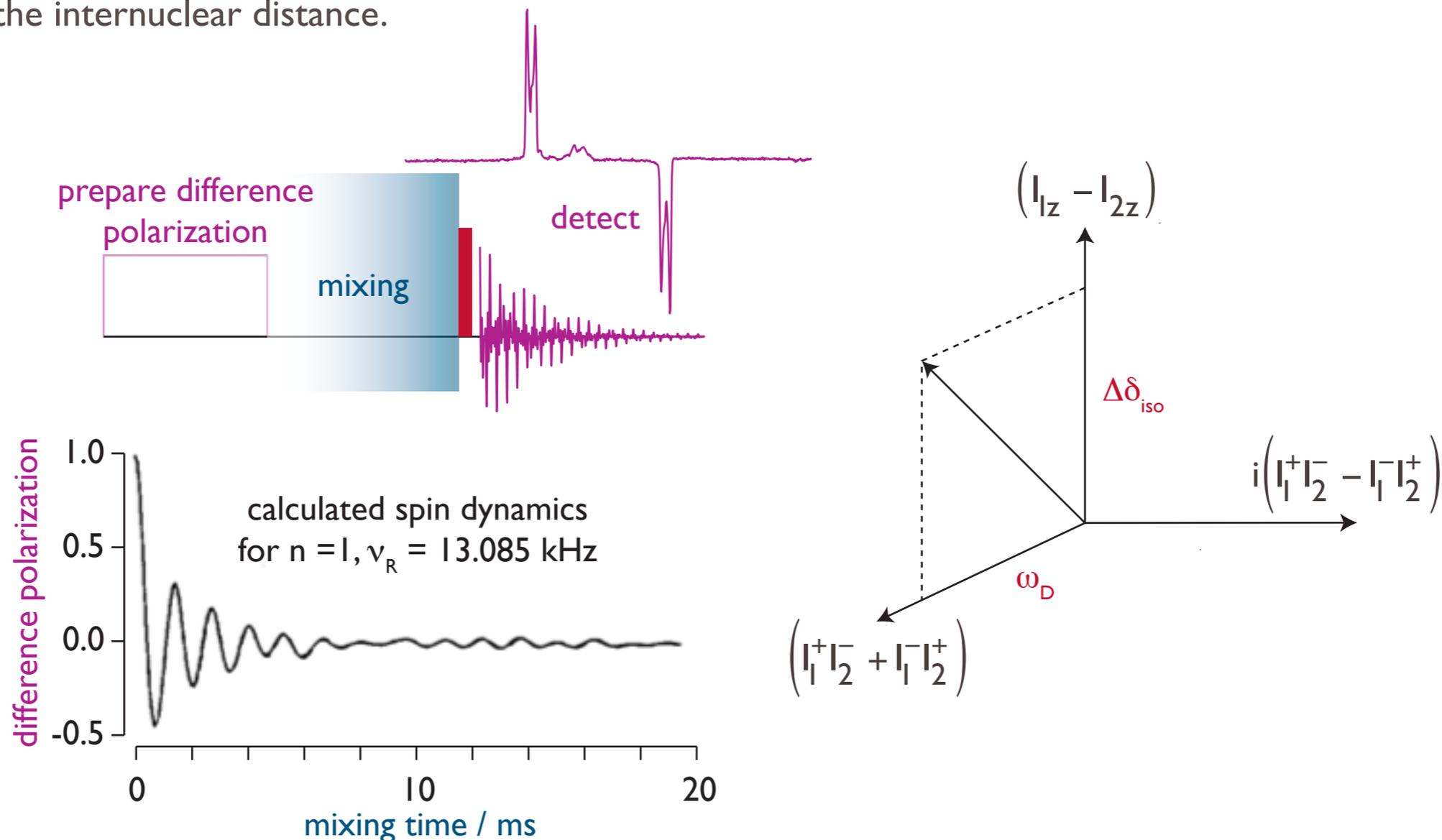
* This results in a rotor-driven spin diffusion process which causes the difference polarization to evolve.

* The oscillations observed for the difference polarization depend on the dipolar coupling and hence on the internuclear distance.

prepare difference
polarization

mixing

detect

calculated spin dynamics
for $n = 1$, ν_R = 13.085 kHz

difference polarization

mixing time / ms

$\left(I_{1z} - I_{2z}\right)$

$\Delta\delta_{iso}$

$i\left(I_1^+I_2^- - I_1^-I_2^+\right)$

ω_D

$\left(I_1^+I_2^- + I_1^-I_2^+\right)$

$$I_{1z} - I_{2z} \xrightarrow{\frac{\omega_D}{2}\left(I_1^+I_2^- + I_1^-I_2^+\right)\tau} \left(I_{1z} - I_{2z}\right)\cos\omega_D\tau + i\left(I_1^+I_2^- - I_1^-I_2^+\right)\sin\omega_D\tau$$
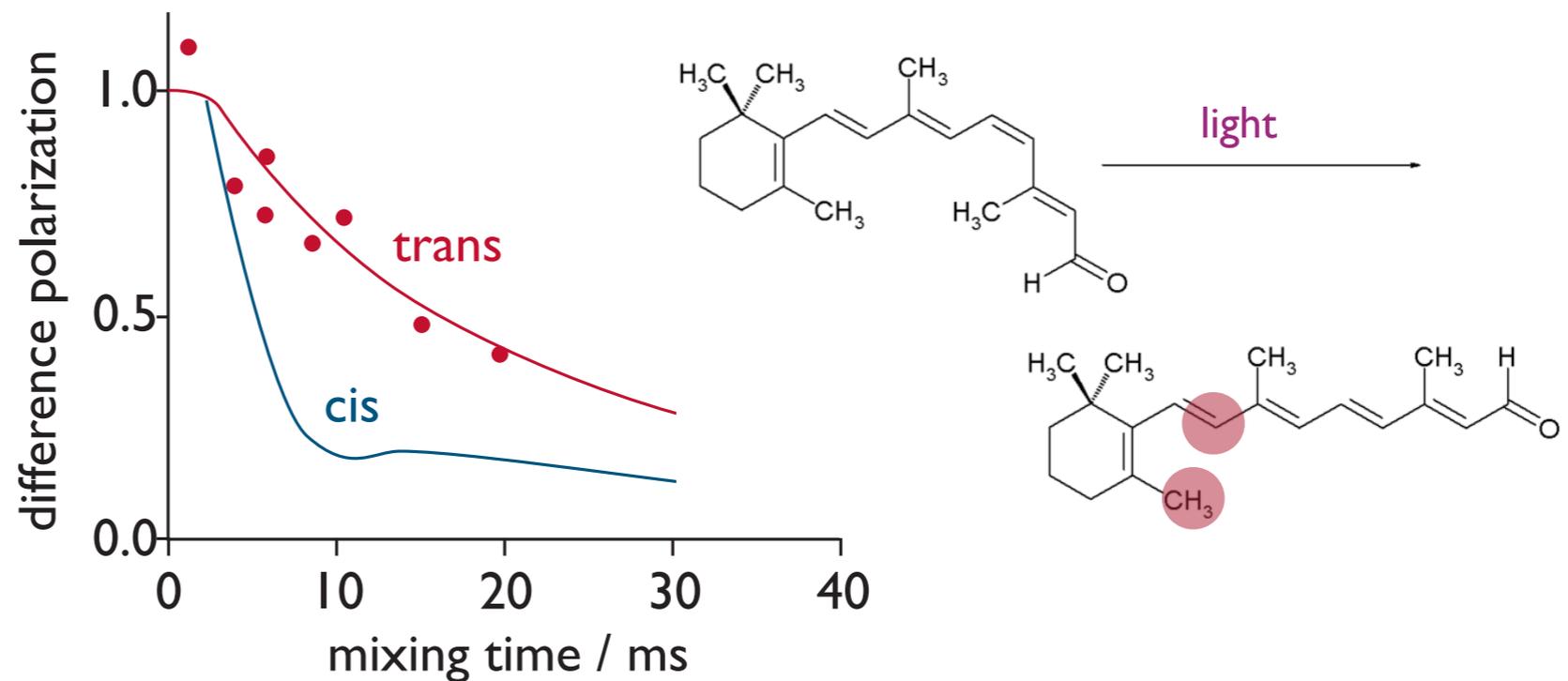
Conformation of retinal bound to bacteriorhodopsin

★ Rhodopsin is a pigment of the retina which is responsible for the first events in the perception of light.

★ It consists of a protein opsin, comprising 7 transmembrane helices, surrounding a covalently bound cofactor 11-cis retinal.

★ A series of isomerization steps triggered by light convert 11-cis-retinal into all-trans-retinal and in turn this induces a conformational change in the opsin which activates an associated G protein and triggers a messenger cascade.
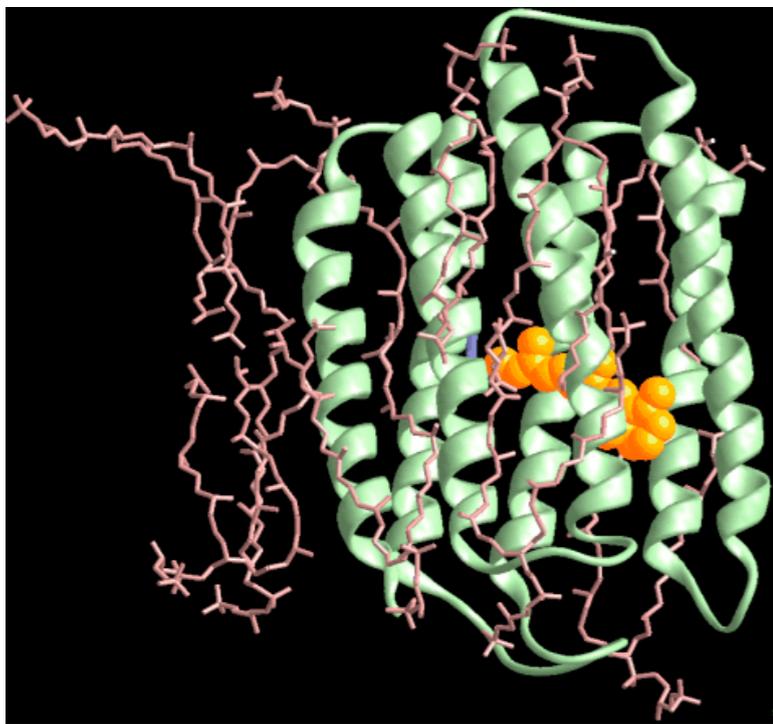
Retinal bound to bacteriorhodopsin

Rotational resonance magnetization transfer for [8,18 $^{13}C_2$]-retinal

difference polarization

trans

cis

mixing time / ms

light

A. E. McDermott, F. Creuzet, R. Gebhard, K. van der Hoef, M. H. Levitt, J. Herzfeld, J. Lugtenburg and R. G. Griffin, *Biochemistry,* **33**, 6129 (1994).

Heteronuclear Dipolar Recoupling

- ★ Without the ^{15}N π pulses the ^{13}C-^{15}N heteronuclear dipolar coupling is refocused after τ_R by the MAS.

- ★ When the ^{15}N π pulses are applied they interfere with the refocusing and cause loss of ^{13}C signal.

- ★ The dephasing of the ^{13}C signal depends in a quantitative way on the heteronuclear dipolar coupling and hence the ^{13}C-^{15}N distance.
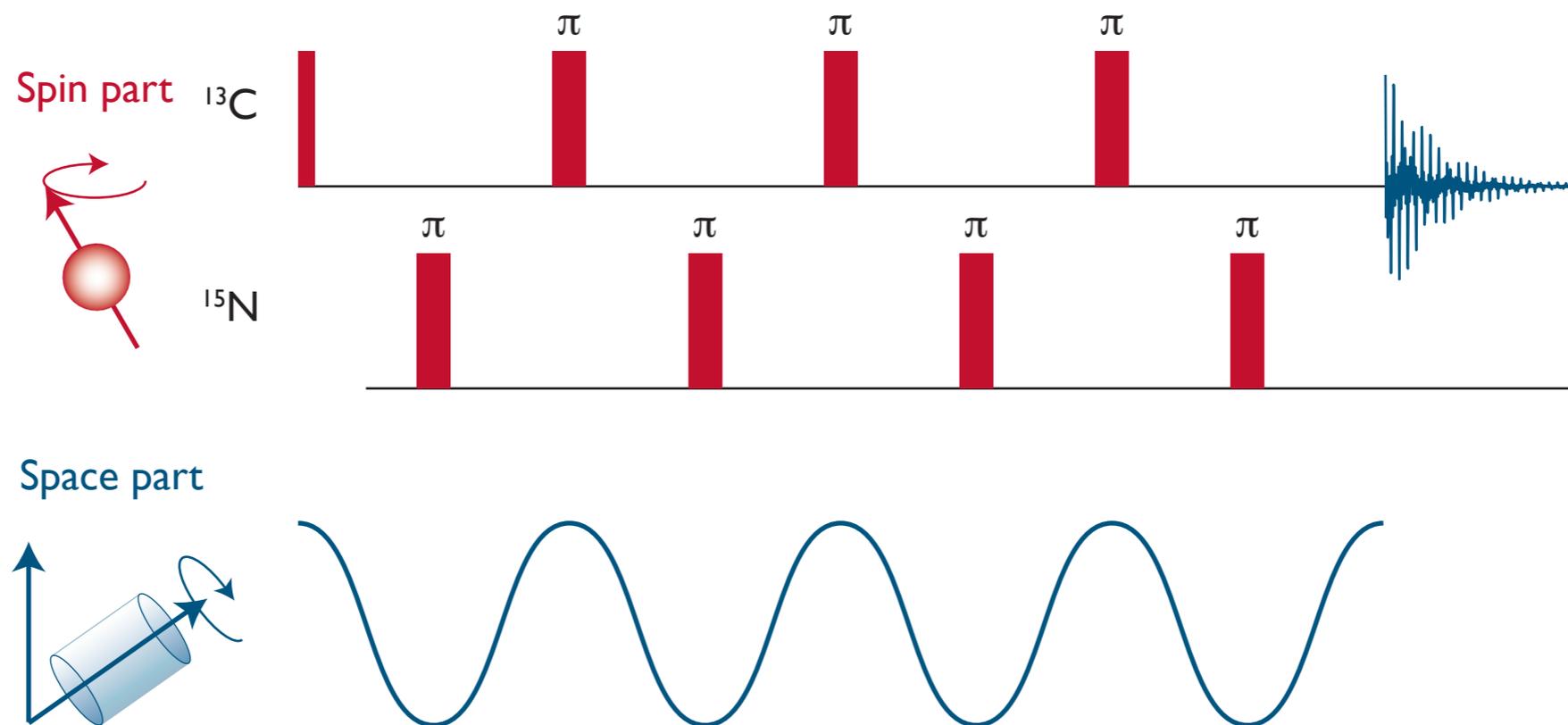
For ^{13}C-methyl-β-^{15}N-aminoglucoside REDOR dephasing curves indicate a bimodal distribution of conformations in a 68:32 ratio, with ^{13}C-^{15}N distances of 4.31 and 3.55 Å, respectively.

^{13}C-methyl-β-^{15}N-aminoglucoside
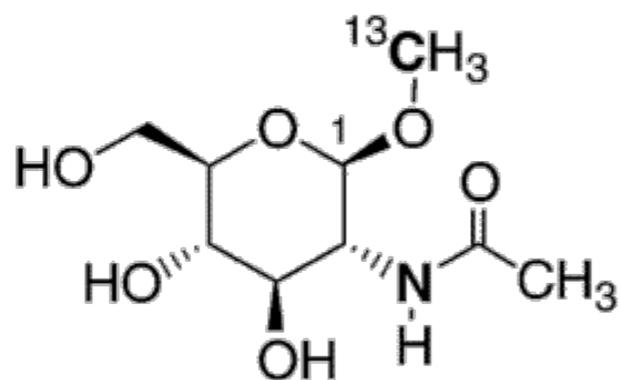
Calculated conformational energy as a function of glycosidic dihedral angle
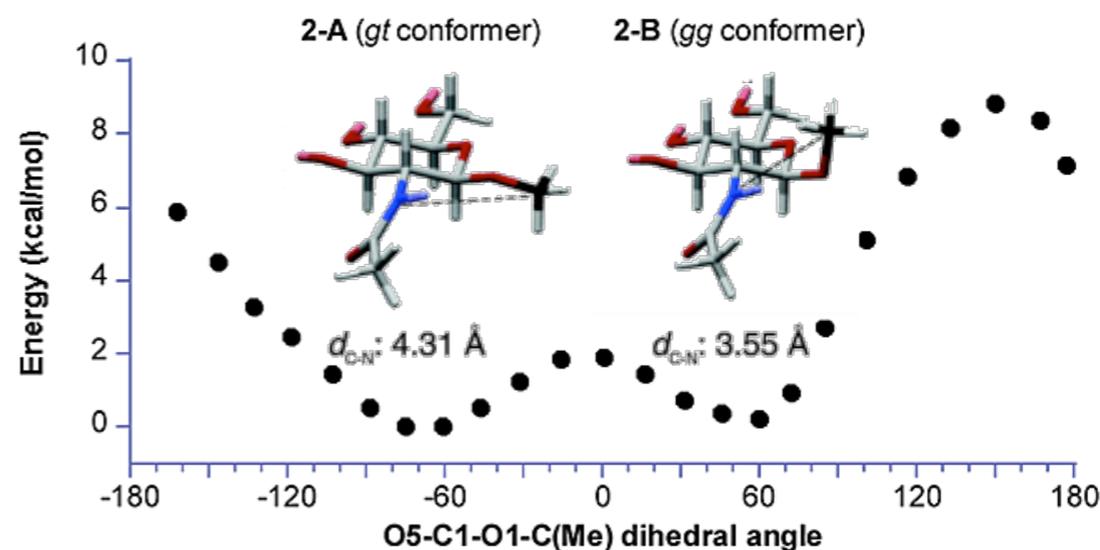
REDOR dephasing curve with fits to one and two internuclear distances

L. J. Smith, F. P. Boulineau, D. Raftery, and A. Wei, *J. Am. Chem. Soc.*, **125**, 14958 (2003).
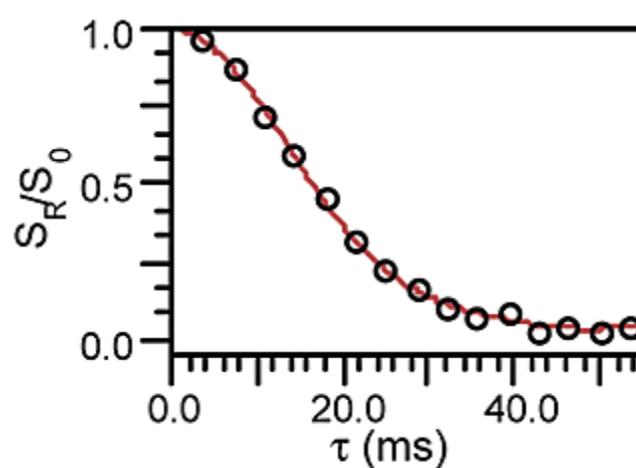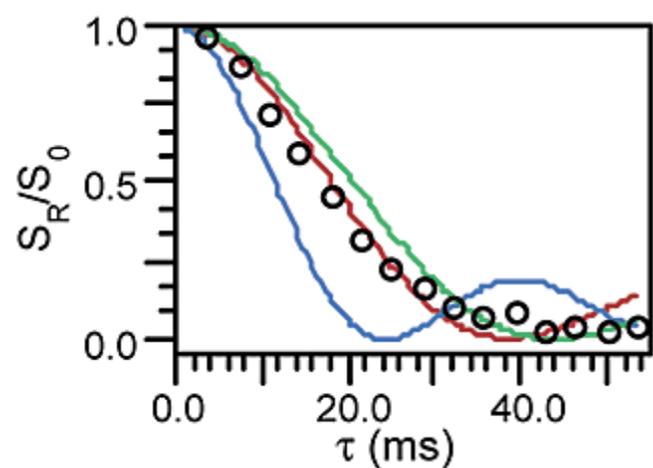
All nuclear spin Hamiltonians can be written as products of space and spin tensor operators:
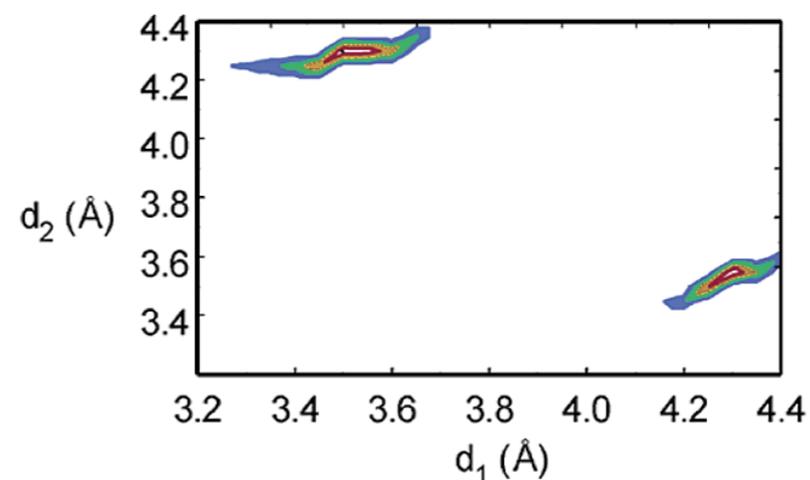
$$H = \sum_{L=0}^{2} \sum_{m=-L}^{L} (-1)^m A_m^L T_{-m}^L$$

spin part

space part

The rank of the tensors and therefore the way they transform under rotations or pulses varies according to the interaction.

Interaction	Space	Spin
Isotropic shift	0	1
Shift Anisotropy	2	1
Scalar coupling	0	0
Homonuclear dipolar coupling	2	2
Heteronuclear dipolar coupling	2	1 for each spin

C and R recoupling symmetries

This provides the basis of general methods for recoupling one interaction without interference from the others because the combinations of spin and space tensor components which are retained in the average Hamiltonian depend on the symmetry of the recoupling pulse sequence.

Cycles

π Rotations

P   0 1 2 3   n

0 1 2 3 4 5 6 7   n

Spin part

rf phase
$2\pi p\nu/n$

rf phase
$\pm 2\pi\nu/n$

Space part

Rotor phase
N periods

Rotor phase
N periods

Cn_N^ν symmetry

Rn_N^ν symmetry

$$\bar{H}^{(0)} \propto A_m^L T_\mu^\Lambda \quad \text{if} \quad \left(Nm - \nu\mu = nk\right)$$

$$\bar{H}^{(0)} \propto A_m^L T_\mu^\Lambda \quad \text{if} \quad \left(Nm - \nu\mu = nk_\Lambda\right)$$

where k_Λ is odd if Λ is odd

M. Carravetta, M. Edén, X. Zhao, A. Brinkmann and M. H. Levitt, *Chem. Phys. Lett.*, **321**, 205 (2000).

The spin-space selection diagram illustrates which combinations of spin and space components are retained in the average Hamiltonian for the recoupling sequence.

The spin-space selection diagram shows that with n = 7 and N = 2 only space-spin components $(m, \mu) = (+1, -2)$ or $(-1, +2)$ are retained in the average Hamiltonian. Hence, the $C7_2{}^1$ sequence results in a pure double-quantum dipolar Hamiltonian, although only certain orientations are efficiently recoupled.

$$\bar{H}^{(0)} = \frac{1}{2}\omega_{C7}I_1^+I_2^+ + \frac{1}{2}\omega_{C7}^*I_1^-I_2^-$$

$$\omega_{C7} = \frac{-343\left(i + e^{(i\pi/14)}\right)}{520\pi\sqrt{2}}d\sin 2\beta e^{-i\gamma}$$

Many other symmetries have been proposed to

* recouple other interactions
* reduce the effects of B1 field inhomogeneity, resonance offset or pulse imperfections

Nm - νμ = nk

Space (m)   Spin (μ)

+2   -2
            -1
            0
+1   +1
N = 2   +2
0
            ν = 1
-1

-2

n = 7
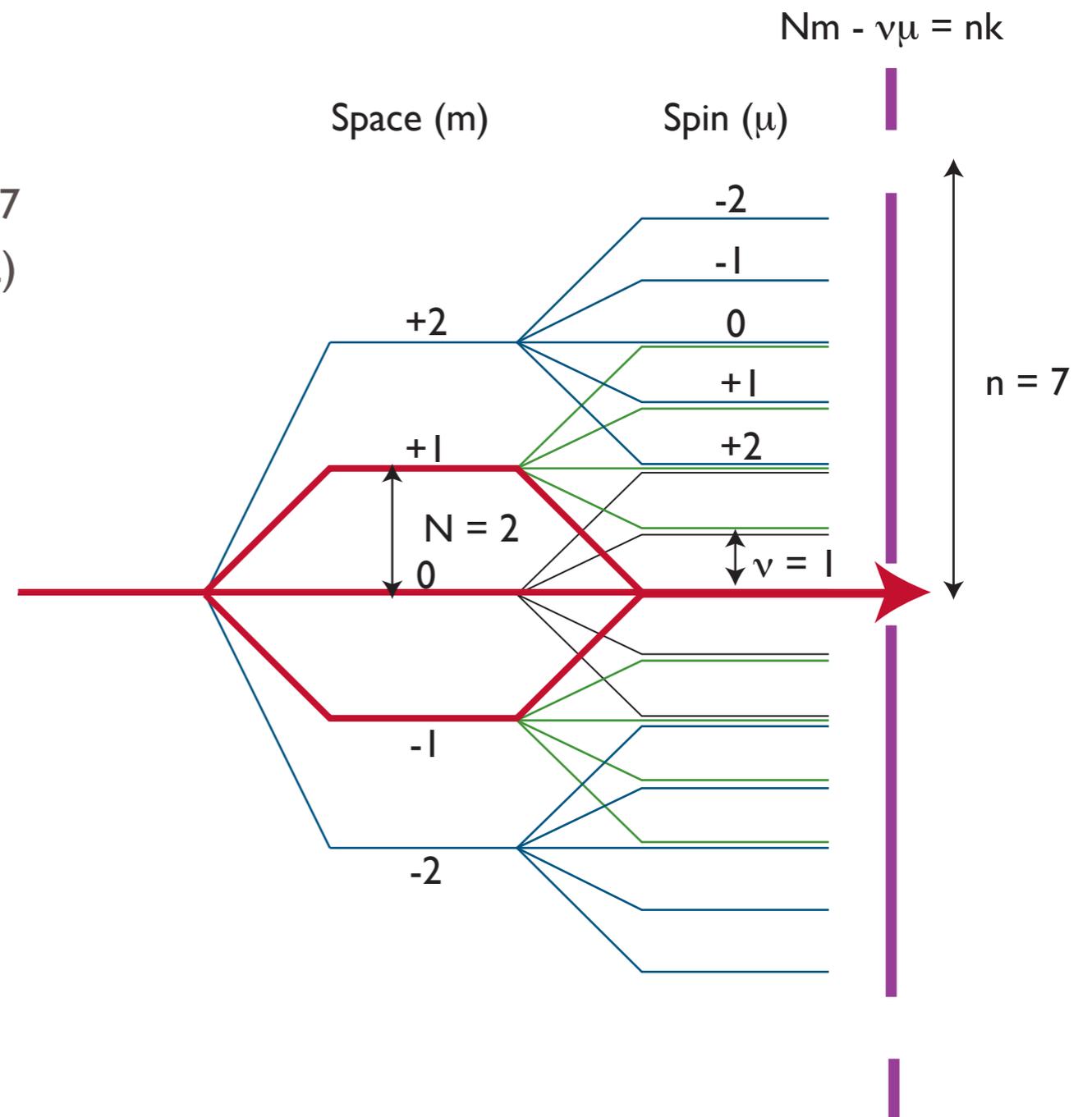
Measuring interatomic distances by DQ excitation

The double-quantum dipolar Hamiltonian causes the sum polarization to evolve into coherence associated with a forbidden double-quantum transition at a rate which depends on the dipolar coupling between the two spins involved,
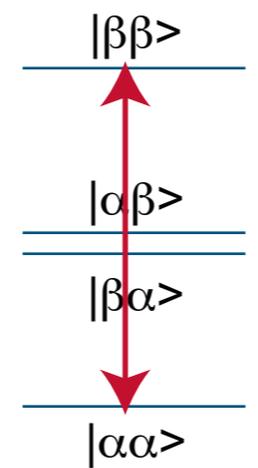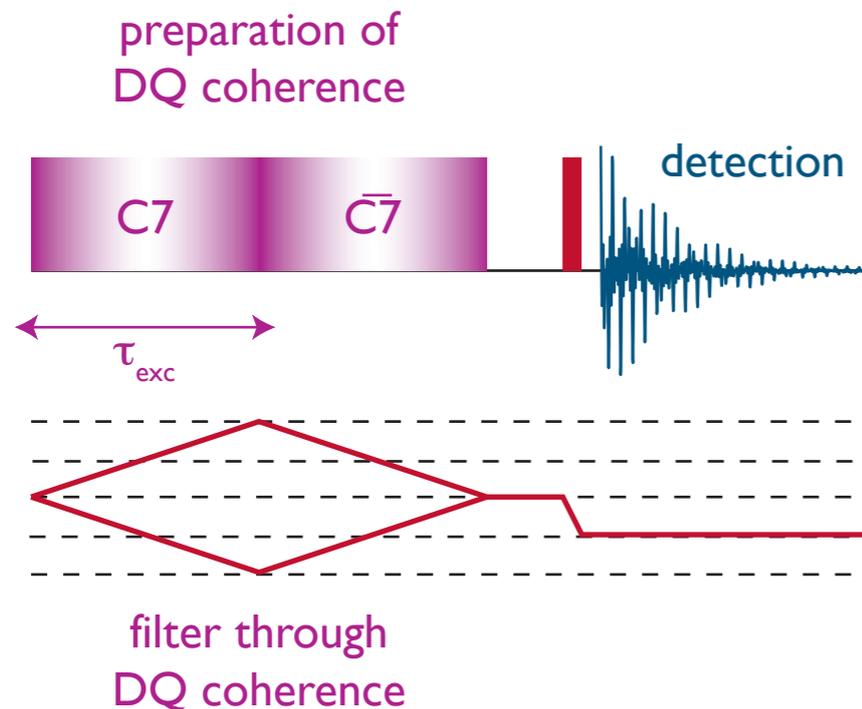
Monitoring the oscillations of a signal which has been filtered through double quantum allows the dipolar coupling and hence the interatomic distance to be measured.

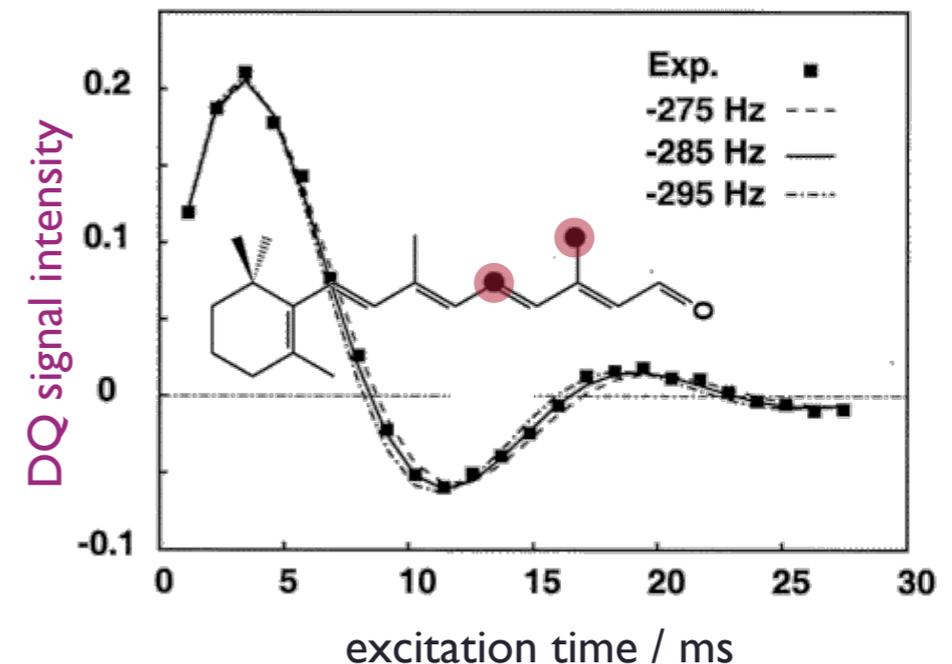This can be achieved with a precision of ±2 pm for distances up to 300 pm.

Sum polarization   DQ coherence

$$I_{1z} + I_{2z} \xrightarrow{\frac{\omega_D}{2}\left(I_1^+I_2^+ + I_1^-I_2^-\right)\tau} \left(I_{1z} + I_{2z}\right)\cos\omega_D\tau + i\left(I_1^+I_2^+ - I_1^-I_2^-\right)\sin\omega_D\tau$$

preparation of
DQ coherence

detection

$|\beta\beta\rangle$

$|\alpha\beta\rangle$

$|\beta\alpha\rangle$

$|\alpha\alpha\rangle$

τ_{exc}

filter through
DQ coherence

DQ transition

DQ signal intensity

	Exp.	■
	-275 Hz	- - -
	-285 Hz	——
	-295 Hz	-·-·-

excitation time / ms

Summary

Average Hamiltonian theory allows multi-pulse sequences to be designed which manipulate the nuclear spin Hamiltonian.

Common examples include:

  * ⋆ **Decoupling** to improve resolution in proton and fluorine-19 spectra by removing dipolar couplings.

  * ⋆ **Recoupling** to reintroduce an averaged dipolar coupling to measure interatomic distances

Many sophisticated methods (supercycles, symmetry etc.) allow the design of sequences which

  * ⋆ approximate the desired Hamiltonian to high order

  * ⋆ are robust to common sources of error