1D GEMSTONE NOESY

Literature Seminar
2021/12/25

Yuuki Watanabe

1. Background of NMR

2. Single-scan selective excitation (GEMSTONE-NOESY)

NMR Spectroscopy Hot Paper

Single-Scan Selective Excitation of Individual NMR Signals in Overlapping Multiplets

Peter Kiraly, Nicolas Kern, Mateusz P. Plesniak, Mathias Nilsson, David J. Procter, Gareth A. Morris, and Ralph W. Adams**

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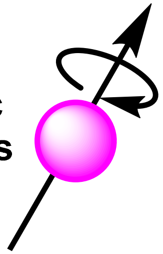
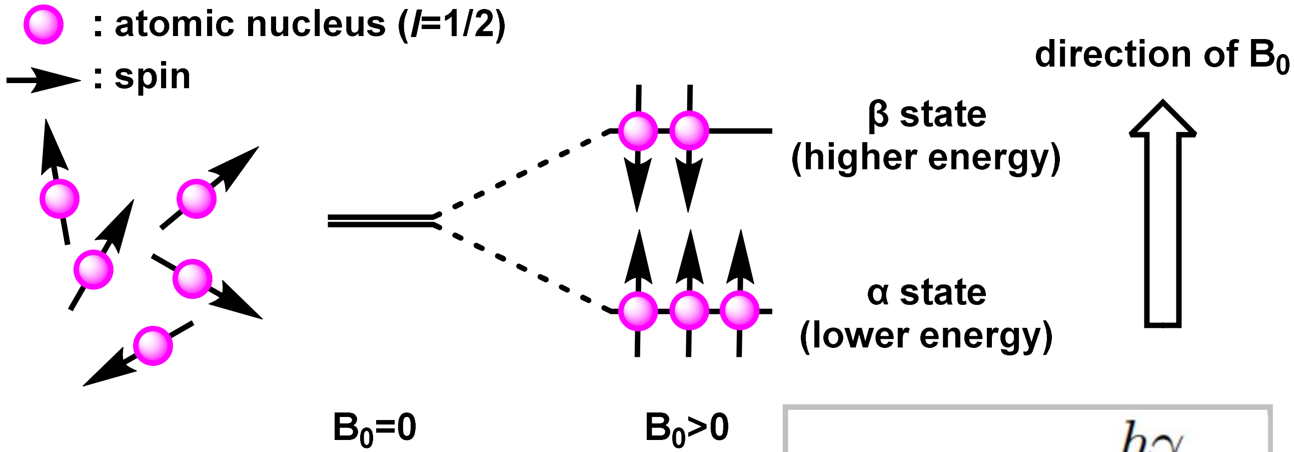
NMR (Nuclear Magnetic Resonance)



- All atomic nuclei have spin quantum number "*I*".
- Certain atomic nuclei (*I*≠0) have a property called spin.
- Each nucleus can have 2*I*+1 linearly independent spin states
  In absence of B_0: degenerated
  In presence of B_0: splitted

I	nucleus
0	^{12}C, ^{16}O, ^{28}Si...
1/2	^{1}H, ^{13}C, ^{15}N...
1	^{2}H, ^{14}N...



nucleus	γ
^{1}H	26.8
^{13}C	6.73
^{19}F	25.2

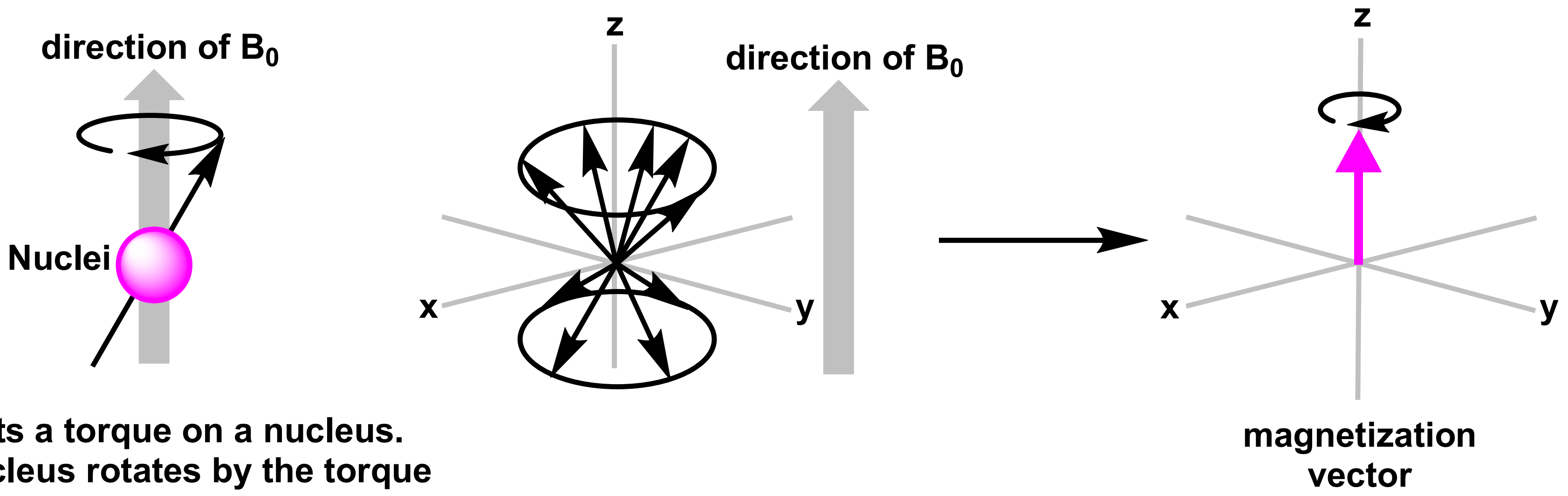
$$\Delta E = h\nu = \frac{h\gamma}{2\pi} B_0$$

(B_0 = 9.39 T
⇒ν(^{1}H) = 400 MHz)

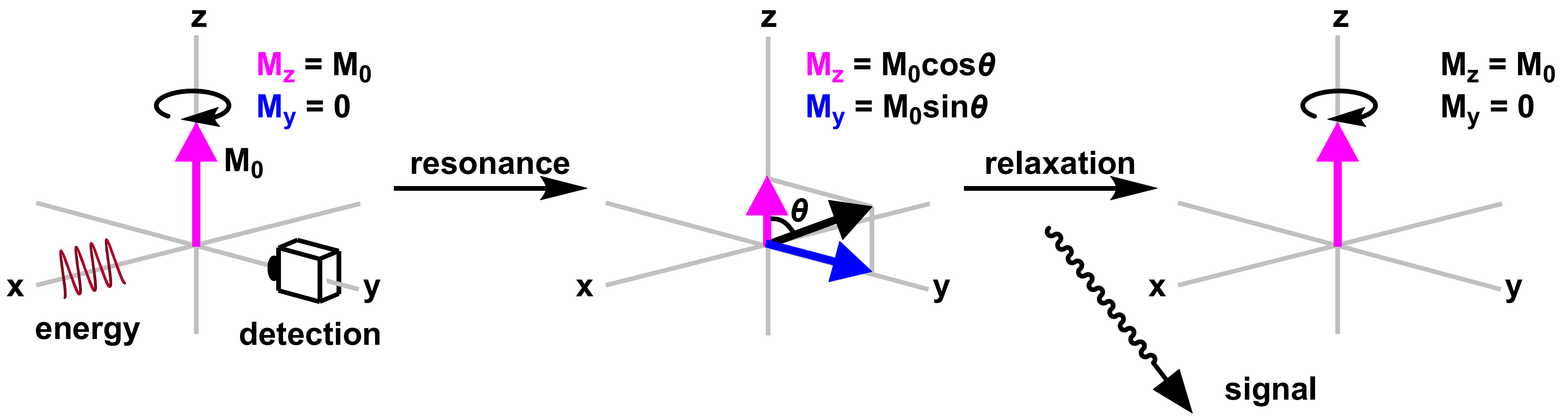
When the electromagnetic wave which has the exactly same energy as ΔE, the nucleus absorbs the energy and get excited (resonance).

有機化学のための高分解能NMRテクニック; Claridge, T. D.W.　著, 竹内敬人、西川実希　訳

Magnetization Vector



B_0 exerts a torque on a nucleus.
The nucleus rotates by the torque
and the motion is called Larmor precession.



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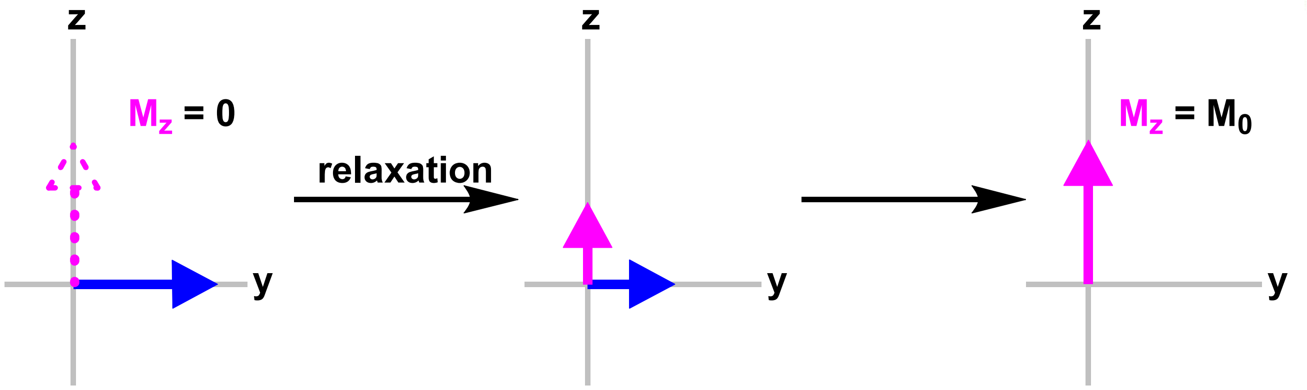
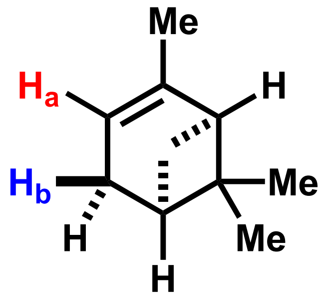
Relaxation

(i) longitudinal relaxation (T_1 relaxation)

$$M_z = M_0(1 - e^{-\frac{t}{T_1}})$$



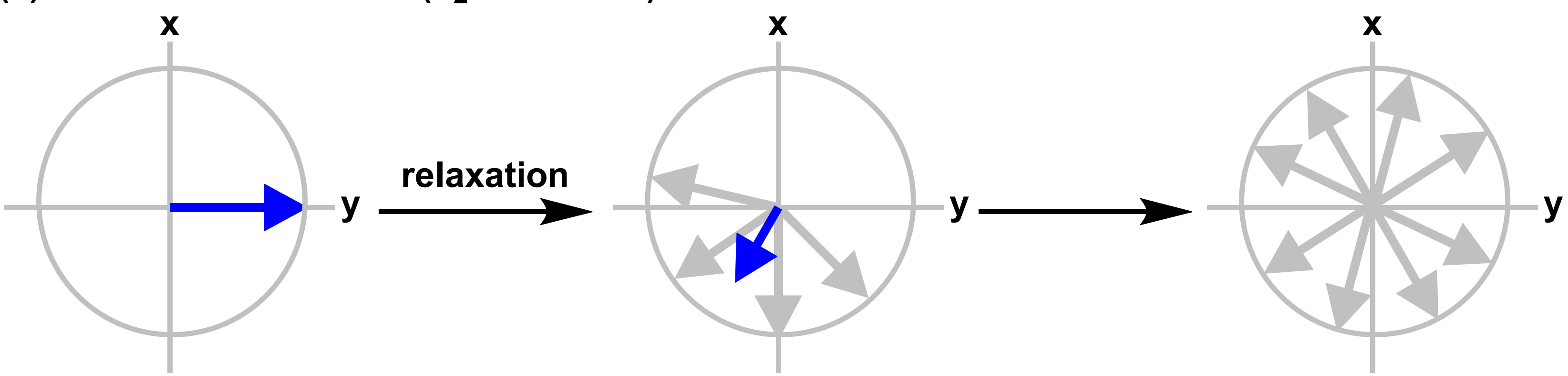
immediately after 90° pulse | **equilibrium state**



α-pinene

H_a: T_1 = 5.3 s
H_b: T_1 = 3.3 s

(ii) transverse relaxation (T_2 relaxation)



immediately after 90° pulse

The transverse relaxation is observed as a free induction decay (FID). NMR machine measures this FID.

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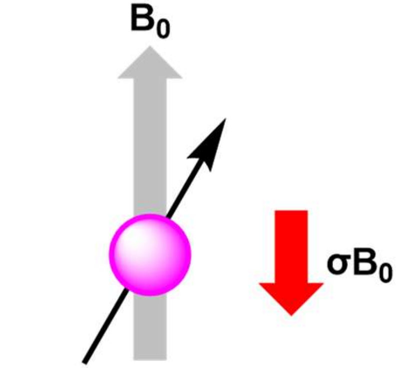
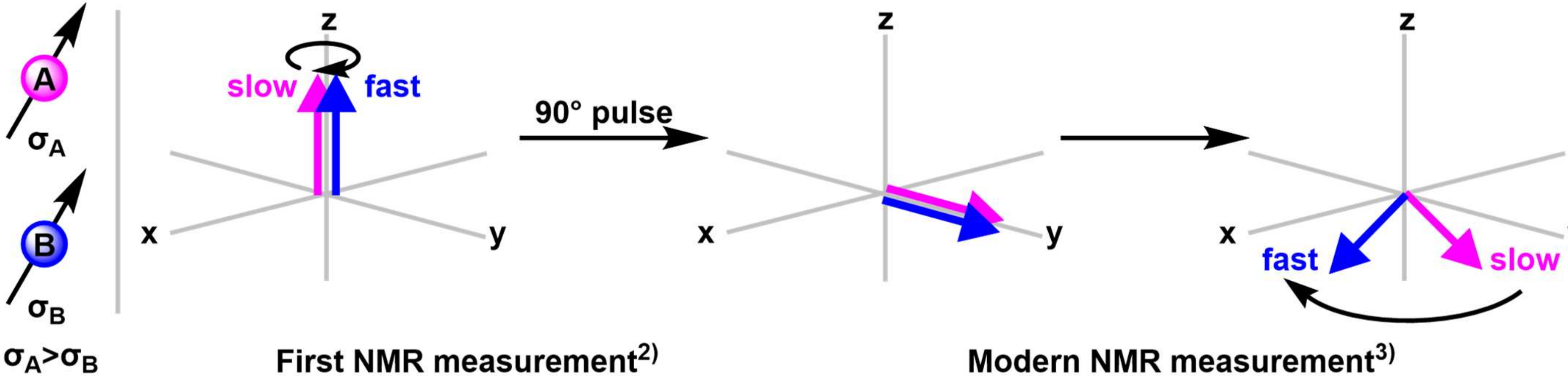
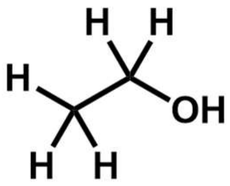
Chemical Shift



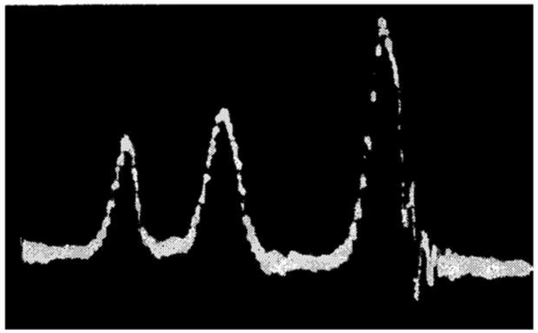
The nuclei is affected by its electronic state.
The electronic effect is proportional to B_0 and it's calculated as σB_0.
(σ:shield constant)
Therefore, the exact frequency is calculated as $\gamma B_0(1-\sigma)$.



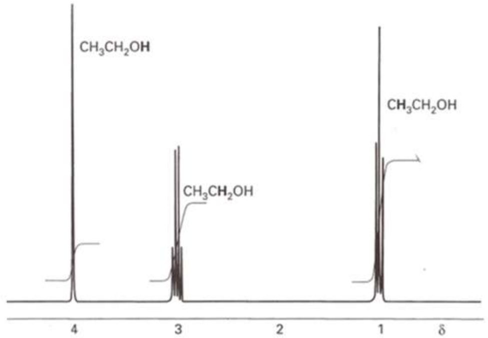


ethanol

First NMR measurement[2)]



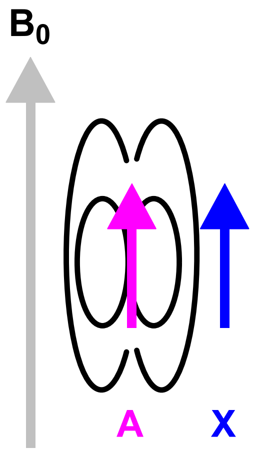
Modern NMR measurement[3)]



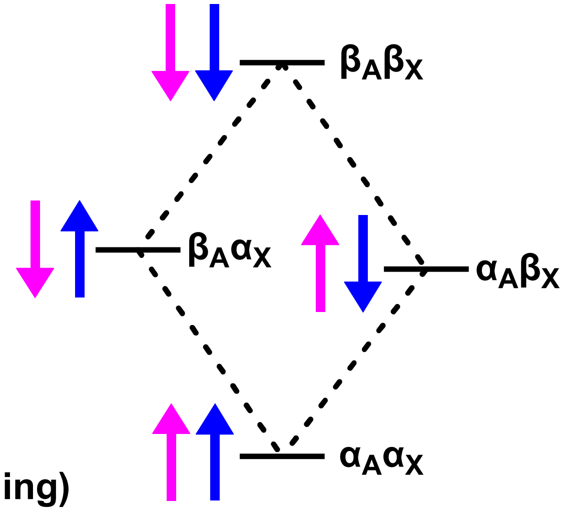
1)有機化学のためのための高分解能NMRテクニック; Claridge, T. D.W. 著, 竹内敬人、西川実希 訳
2) Arnoid, J. T.; Dharmatti, S. S.; Packard, M. E. *J. Chem. Phys.* **1951**, *19*, 507.
3) Gerothanassis, I. P.; Troganis, A.; Exarchou, V.; Barbarossou, K. *Chem. Educ. Res. Pract*. **2002**, *3*, 229.

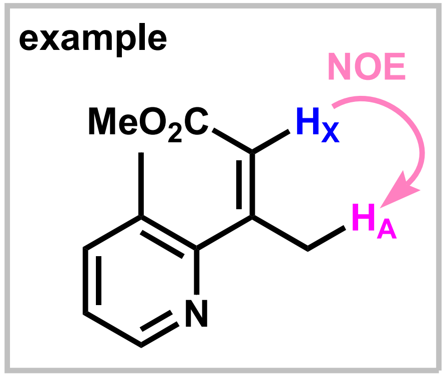
NOE

NOE (Nuclear Overhauser Effect):
the transfer of nuclear spin polarization from one to another via cross-relaxation

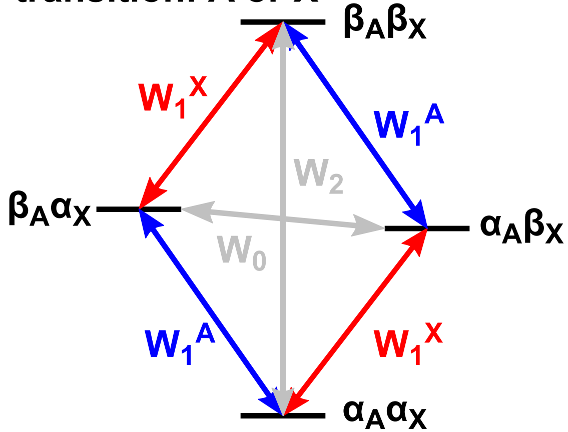


A,X: ^{1}H (no *J* coupling)

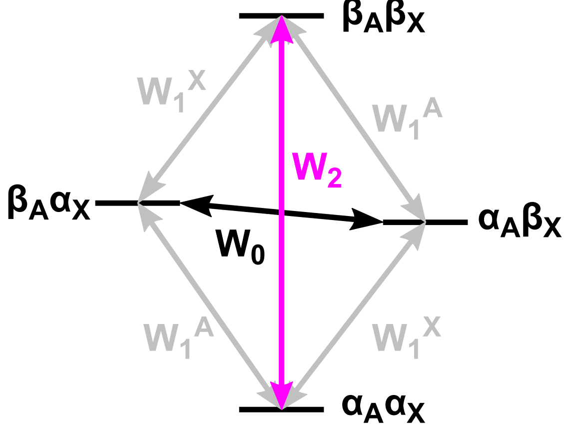




<transition: A or X>



<transition: A and X>



W_1^A,W_1^X: observed on ^{1}H NMR

W_0,W_2: observed on NOE spectrum

有機化学のための高分解能NMRテクニック; Claridge, T. D.W.　著, 竹内敬人、西川実希　訳
Wang, Y.; Nagai, T.; Watanabe, I.; Hagiwara, K.; Inoue, M. *J. Am. Chem. Soc.* **2021**, *143*, 21037.

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Prof. Gareth A. Morris

Prof. Gareth A. Morris

1972~1981: B.D., Ph.D., and research fellow
@Magdalen College Oxford
(by Prof. Ray Freeman)
1982~: Research fellow @Manchester
2014~: Fellow of Royal Society

Award:
RSC Corday-Morgan prize and medal in 1988
Leverhulme Fellowship in 1996
Russell Varian Prize for NMR in 2011

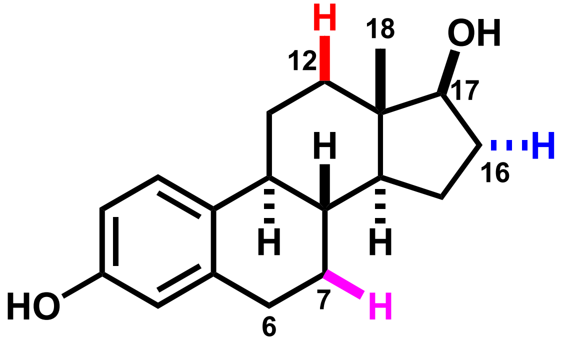
Reserach Topic: NMR Methodology
·INEPT (Insensitive Nuclei Enhanced by Polarisation Transfer)

·DANTE (Delays Alternating with Nutation for Tailored Excitation)

Musaev, D. G.; Kaledin, A.; Shi, B. -F.; Yu, J. -Q. *J. Am. Chem. Soc.* **2012**, *134*, 1690.

NOE Measurement in Complex Natural Product

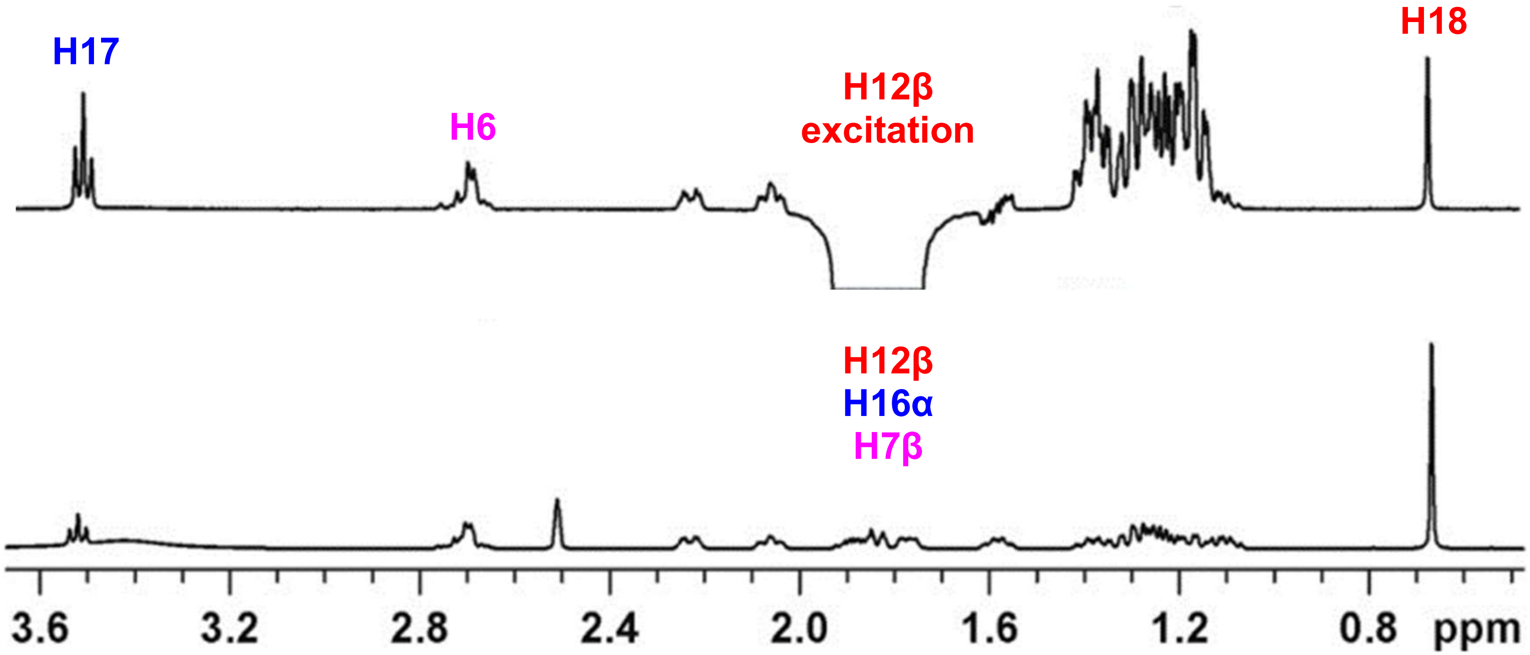
In many cases, 1D-NOE experiment has a big problem of over-lapping



17β-estradiol

1.9-1.7 ppm: 3 protons (H12β, H16α, H7β) are overlapped.

NOE experiments (H12β): H16α and H7β are also excited.
→Many signals are observed.



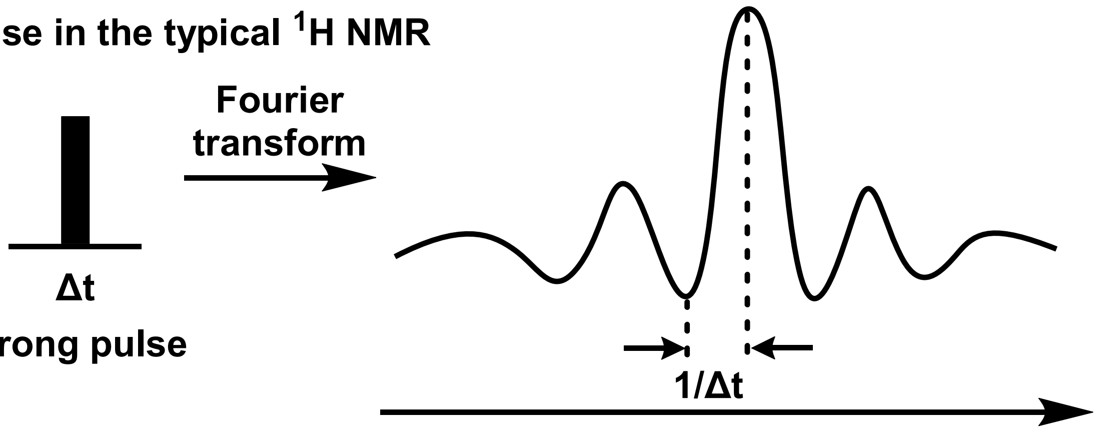
→Development of NMR method for the selective excitation of "one" peak is essential for structure determination

Kiraly, P.; Kern, N.; Plesniak, M. P.; Nilsson, M.; Procter, D.; Morris, G. A.; Adams, R. W. *Angew. Chem. Int. Ed.* **2021**, *60*, 666.

Selective Excitation Pulse

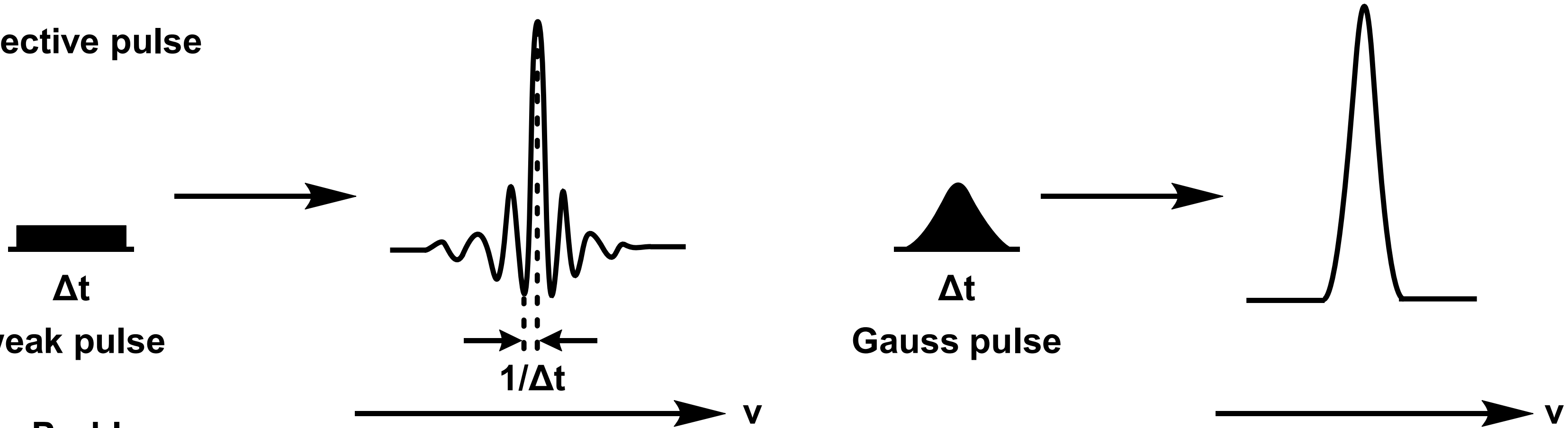
Based on Heisenberg's uncertainty principle, the frequency of pulse spreads (1/Δt)

·Pulse in the typical [1]H NMR



= wide range of frequency

·Selective pulse



Problem:
· the range of selective pulse is 70 Hz (insufficient)
· single use of this pulse is limited (the advantage of pulse field gradient (PFG))

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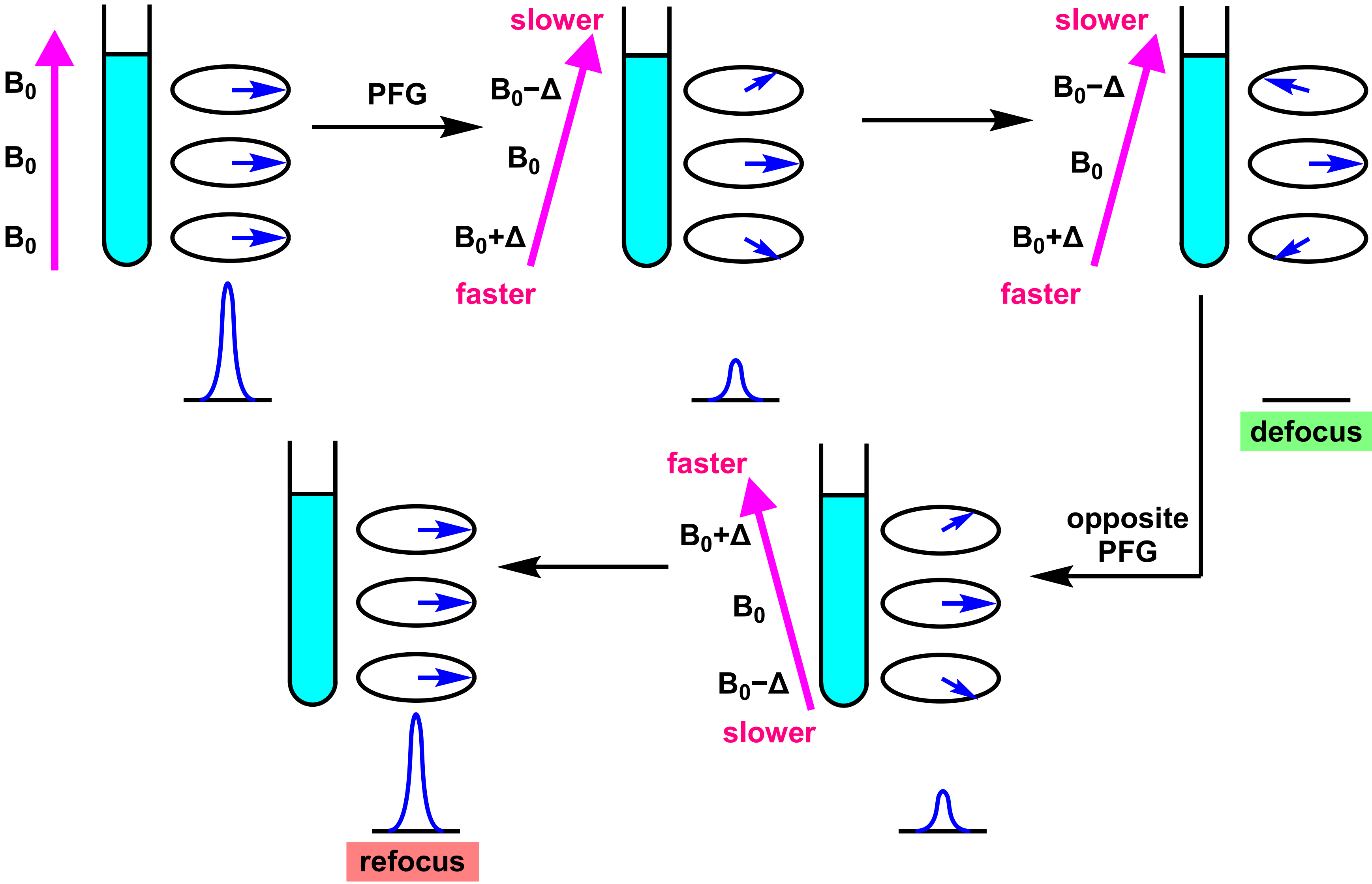
有機化学のための高分解能NMRテクニック; Claridge, T. D.W.　著, 竹内敬人、西川実希　訳

Pulse Field Gradient (PFG)

Pulse Field Gradient (PFG): changing B_0 around a sample with gradient



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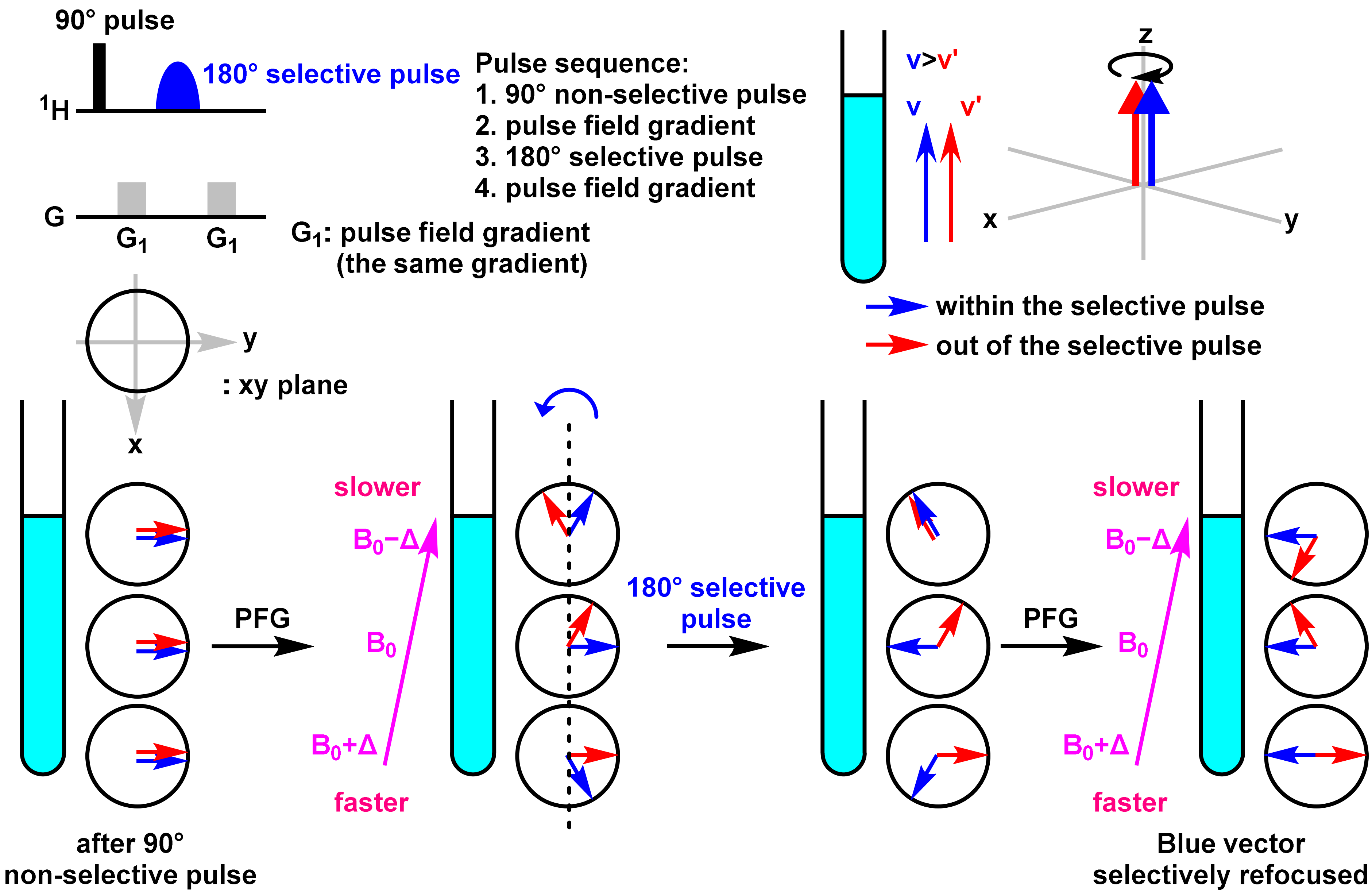
Kiraly, P.; Kern, N.; Plesniak, M. P.; Nilsson, M.; Procter, D.; Morris, G. A.; Adams, R. W. *Angew. Chem. Int. Ed.* **2021**, *60*, 666.

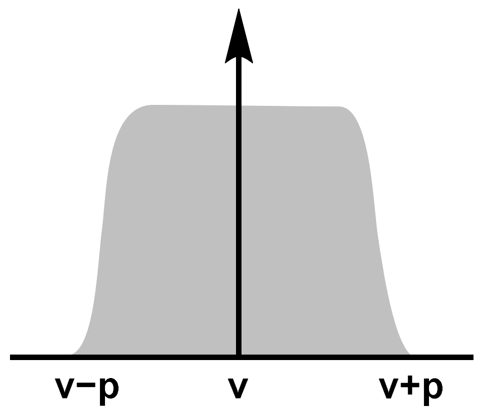
Combination of Selective Excitation and PFG

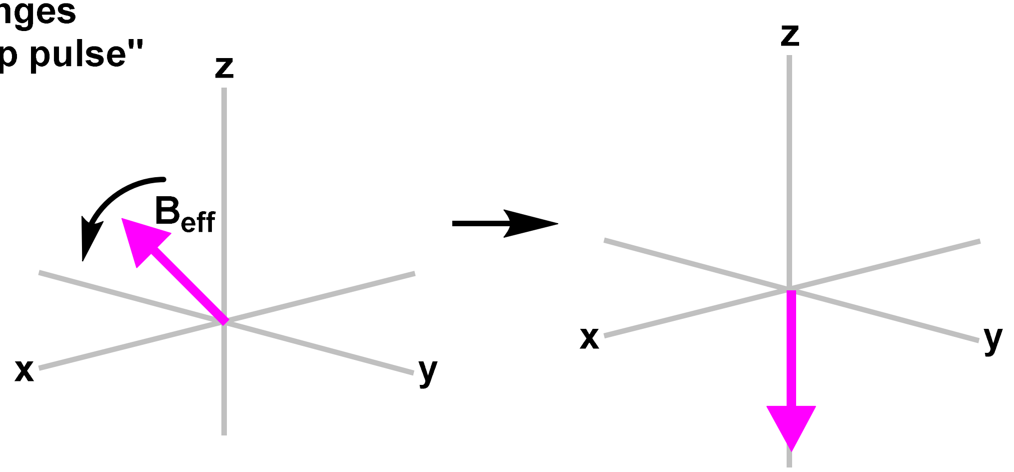


有機化学のための高分解能NMRテクニック; Claridge, T. D.W.　著, 竹内敬人、西川実希　訳

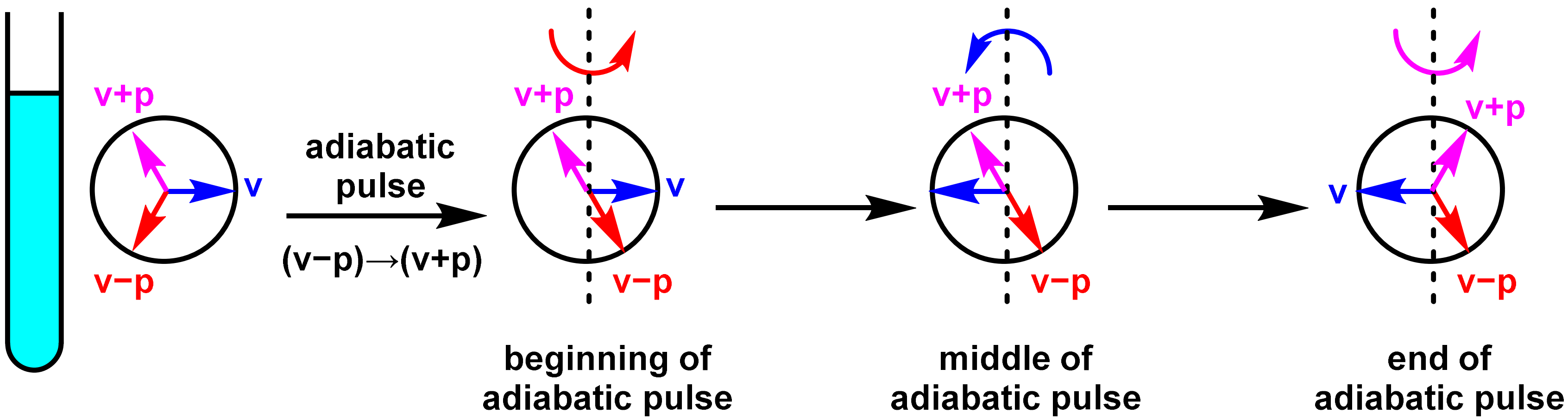
Adiabatic Pulse

Adiabatic pulse
- Relatively weak 180° pulse
- The frequency of pulse gradually changes
- This pulse can be thought as a "sweap pulse"



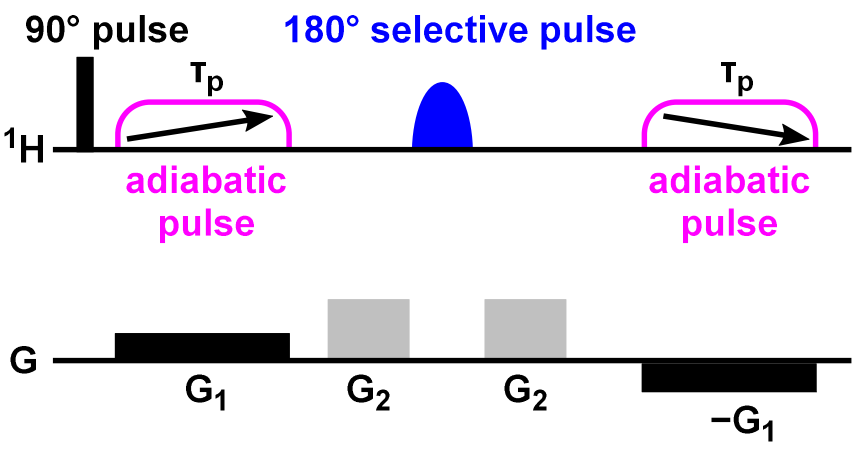


This pulse can be represented by 180° pulses that occur when the frequency matches.



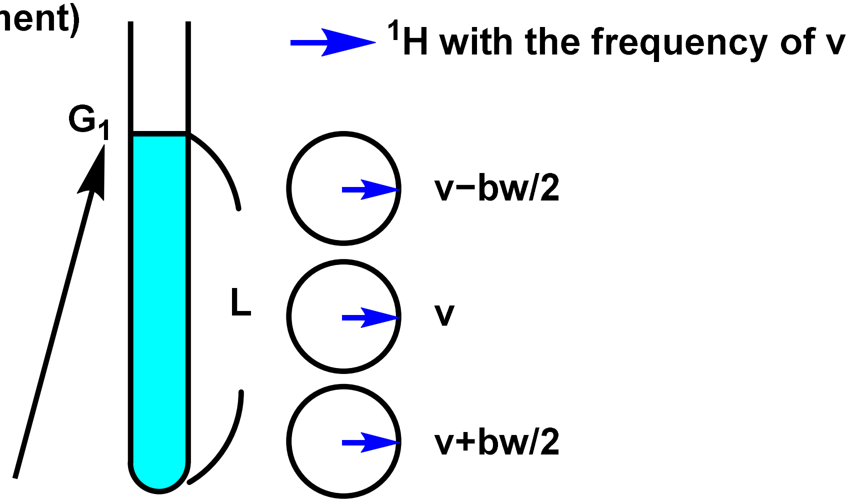
有機化学のための高分解能NMRテクニック; Claridge, T. D.W.　著, 竹内敬人、西川実希　訳
Pelupessy, P. *J. Am. Chem. Soc*. **2003**, *125*, 12345.

GEMSTONE



Pulse sequence:
1. 90° non-selective pulse
2. adiabatic pulse in the presence of PFG (G_1)
3. another PFG ($G_1 \neq G_2$)
4. 180° selective pulse
5. PFG (G_2)
6. adiabatic pulse in the presence of PFG ($-G_1$)

τ_p: constant time (defined before NMR measurement)
G_1, G_2: pulse field gradient



<key point>
G_1 and the range of adiabatic pulse is matched.

range of adiabatic pulse: $\left(\nu - \frac{bw}{2}\right) \sim \left(\nu + \frac{bw}{2}\right)$

$$bw = \frac{\gamma G_1 L}{2\pi}$$

v = frequency of the signal of interest (Hz)
L = sample length (cm)
G_1 = field gradient (G/cm)

→Desired ^1H can be excited all area in the sample, while other ^1H isn't excited at all or partially excited.

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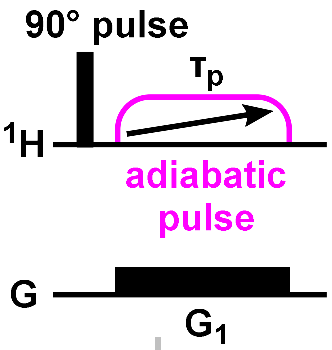
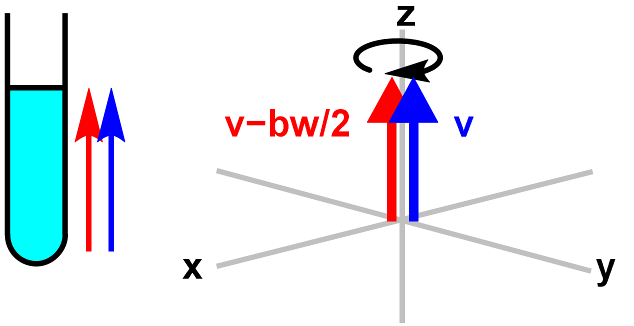
Spin Defocus



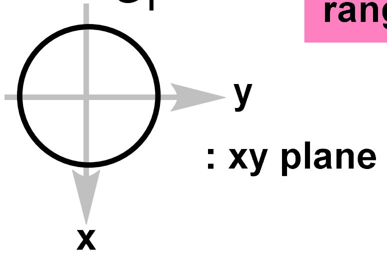
τ_p: constant time
(defined before NMR measurement)

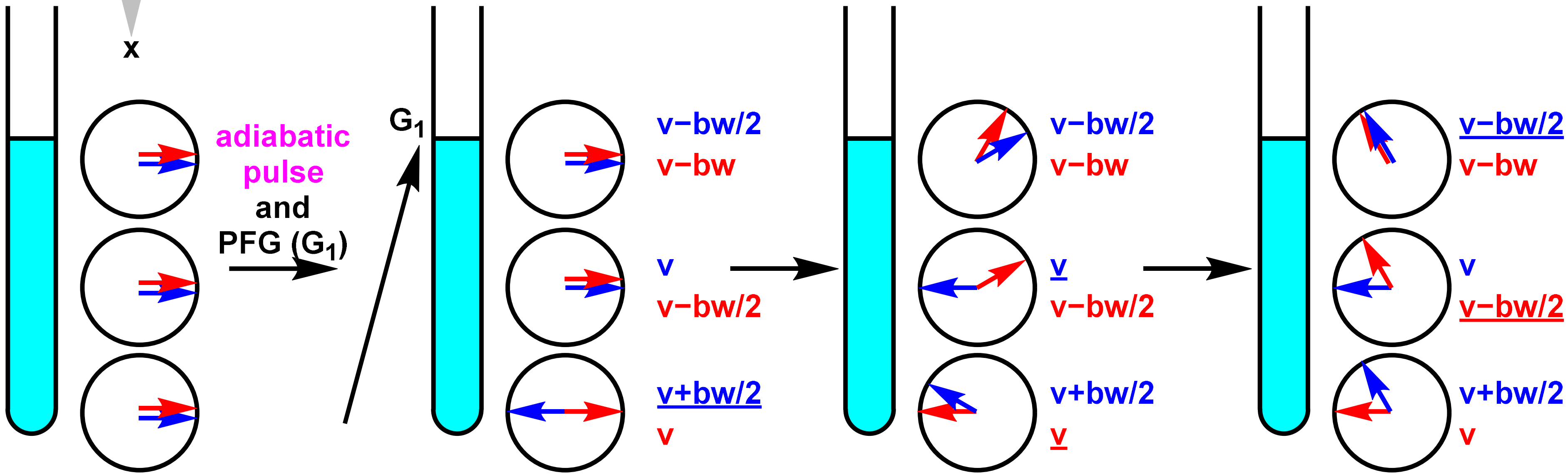
Pulse sequence:
1. 90° non-selective pulse
2. adiabatic pulse in the presence of PFG

range and vector: (v+bw/2)→(v−bw/2)



interest ^{1}H
not interested ^{1}H
(closed chemical shift to interested ^{1}H)





after 90° non-selective pulse

beginning of pulse
adiabatic pulse started from v+bw/2

middle of pulse
adiabatic pulse excited the frequency of v

end of pulse
adiabatic pulse excited the frequency of v−bw/2

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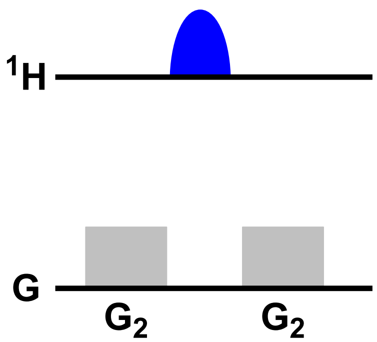
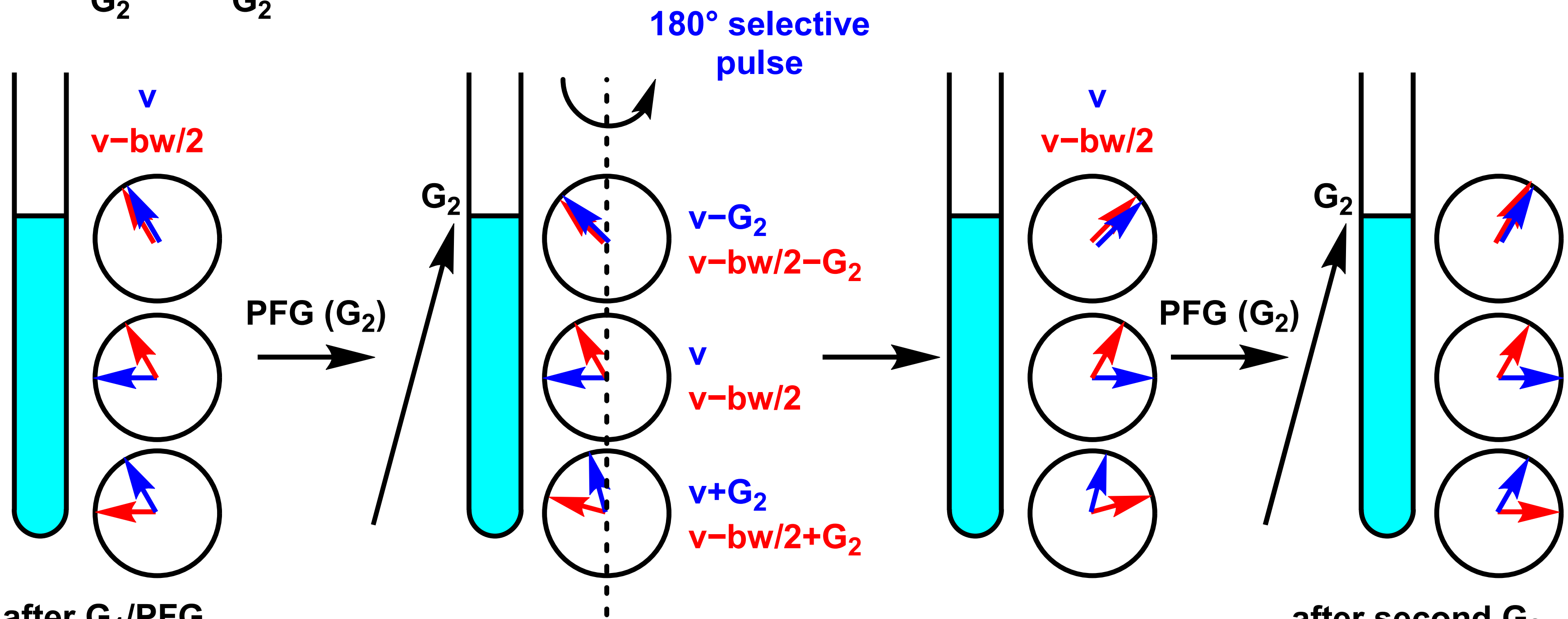
Selective 180° Retention

180° selective pulse



Pulse sequence:
3. another PFG ($G_1 \neq G_2$)
4. 180° selective pulse
5. PFG (G_2)

- **180° selective pulse: excites both blue [1]H and red [1]H (their chemical shift are very similar)**
- **G_2-180-G_2 pulses don't affect on the relative phase of peaks within the selective pulse.**



after G_1/PFG
frequency of each [1]H turns back to v and v−bw/2, respectively

after second G_2

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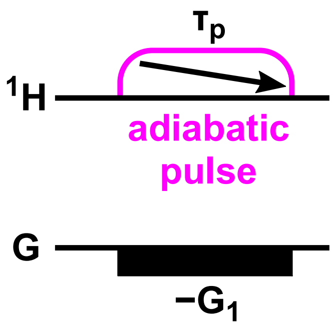
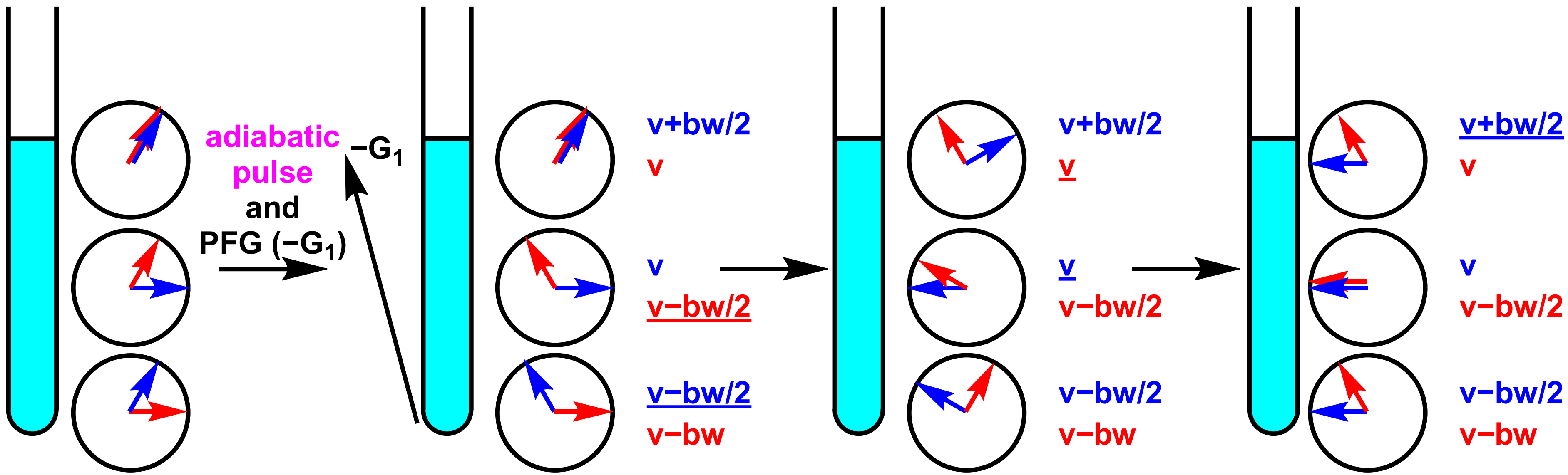
Refocus of Desired Peak



τ_p: constant time
(defined before NMR measurement)

Pulse sequence:
1. 90° non-selective pulse
2. adiabatic pulse in the presence of PFG



beginning of pulse
adiabatic pulse started from v−bw/2

half of pulse
adiabatic pulse excited the frequency of v

end of pulse
adiabatic pulse excited the frequency of v+bw/2

Blue ^{1}H refocused

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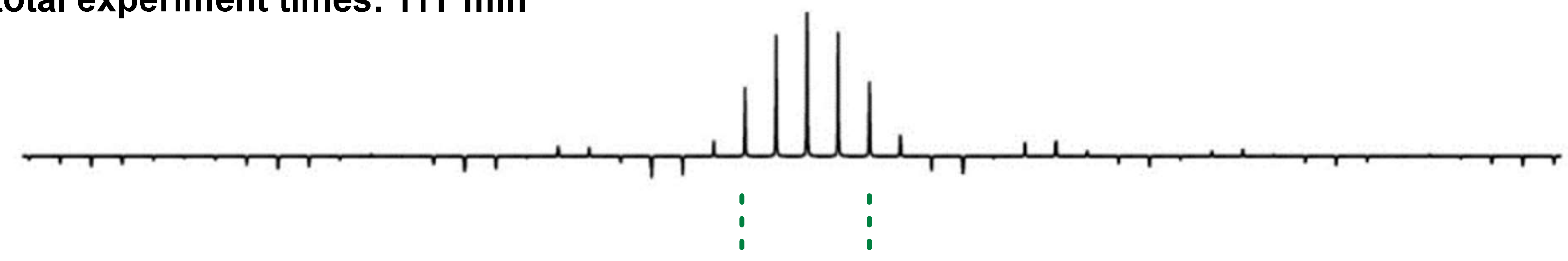
Comparison of VT-CSSF and GEMSTONE

Excitation profiles: the range of frequency which the pulse can excite

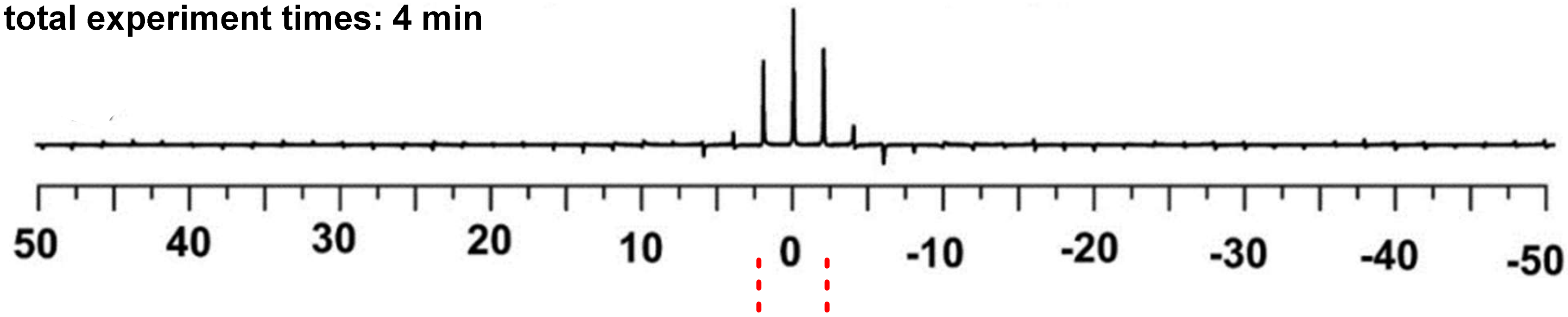
(a)VT-CSSF (previous chemical shift selection method)[1)]

total experiment times: 111 min



(b)GEMSTONE[2)]

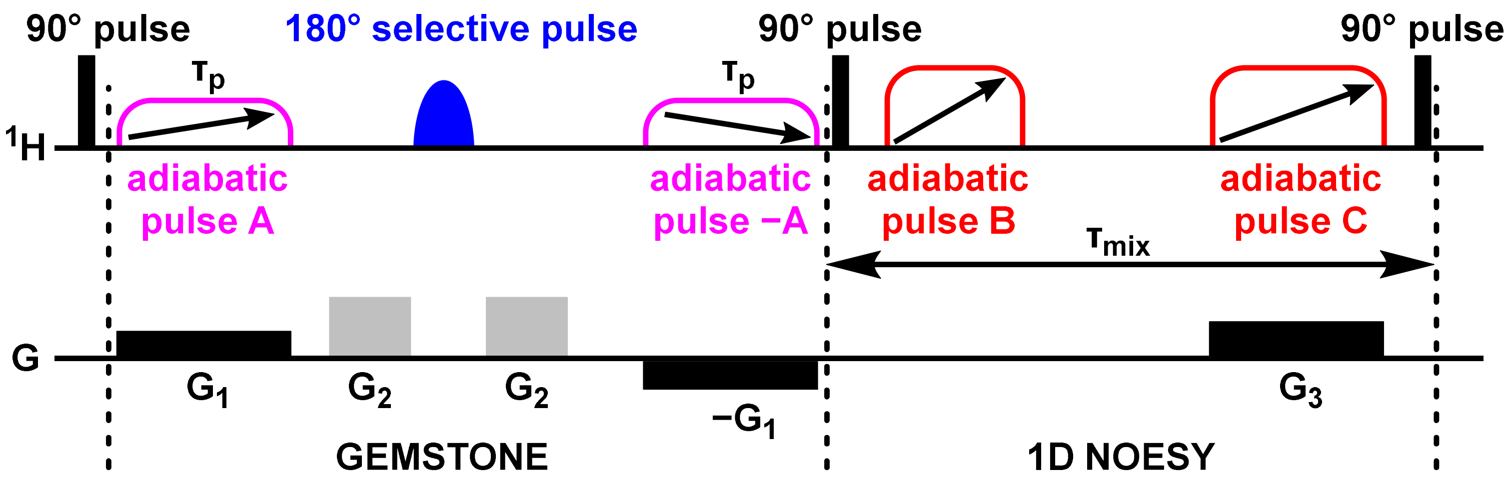
total experiment times: 4 min



GEMSTONE can be the new critical method for chemical shift filter.

1) Robinson, P. T.; Pham, T. N.; Uhrin, D. *J. Magn. Reason*. **2004**, *170*, 97.
2) Kiraly, P.; Kern, N.; Plesniak, M. P.; Nilsson, M.; Procter, D.; Morris, G. A.; Adams, R. W. *Angew. Chem. Int. Ed.* **2021**, *60*, 666.

1D GEMSTONE-NOESY (1)

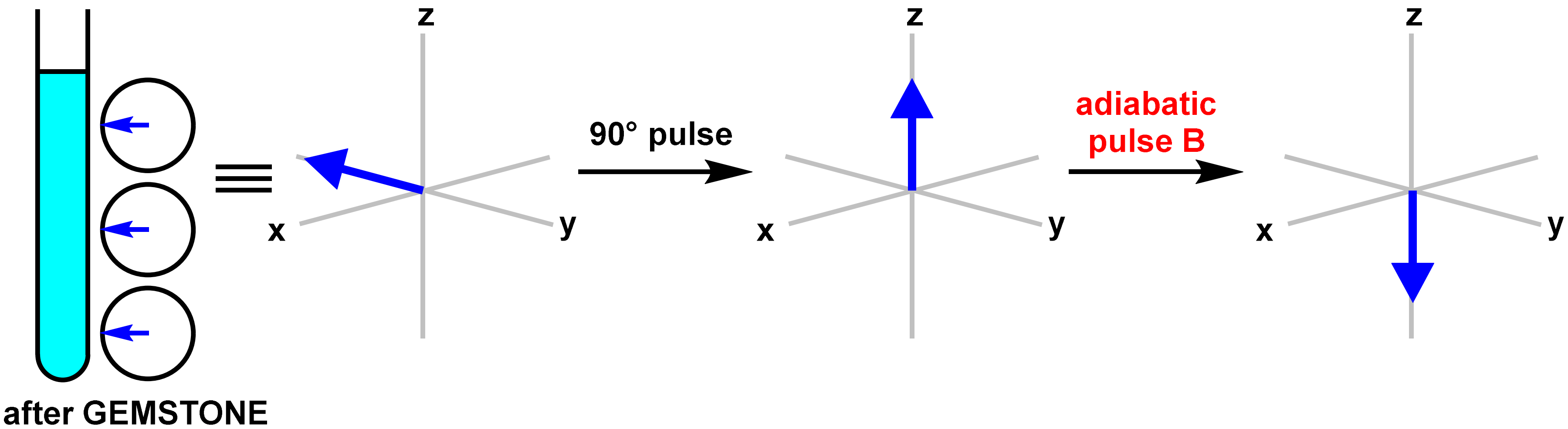


pulse A: narrow range (bw), pulse B,C: wide range (all ^1H)

<strategy>

For 1D NOESY, selection of excited ^1H is necessary.

In this experiment, the selection step is conducted by GEMSTONE.



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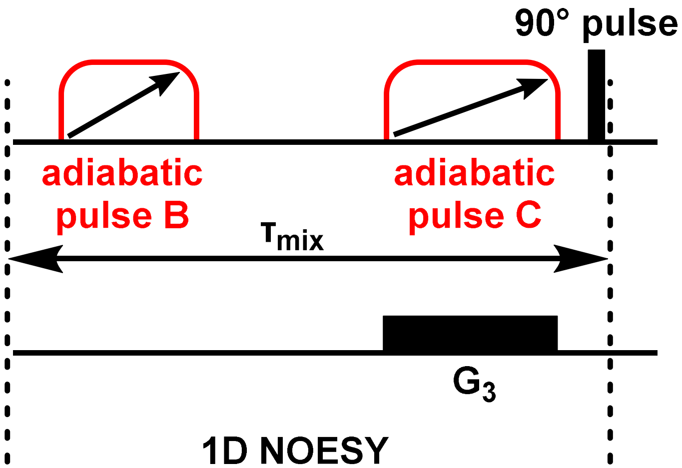
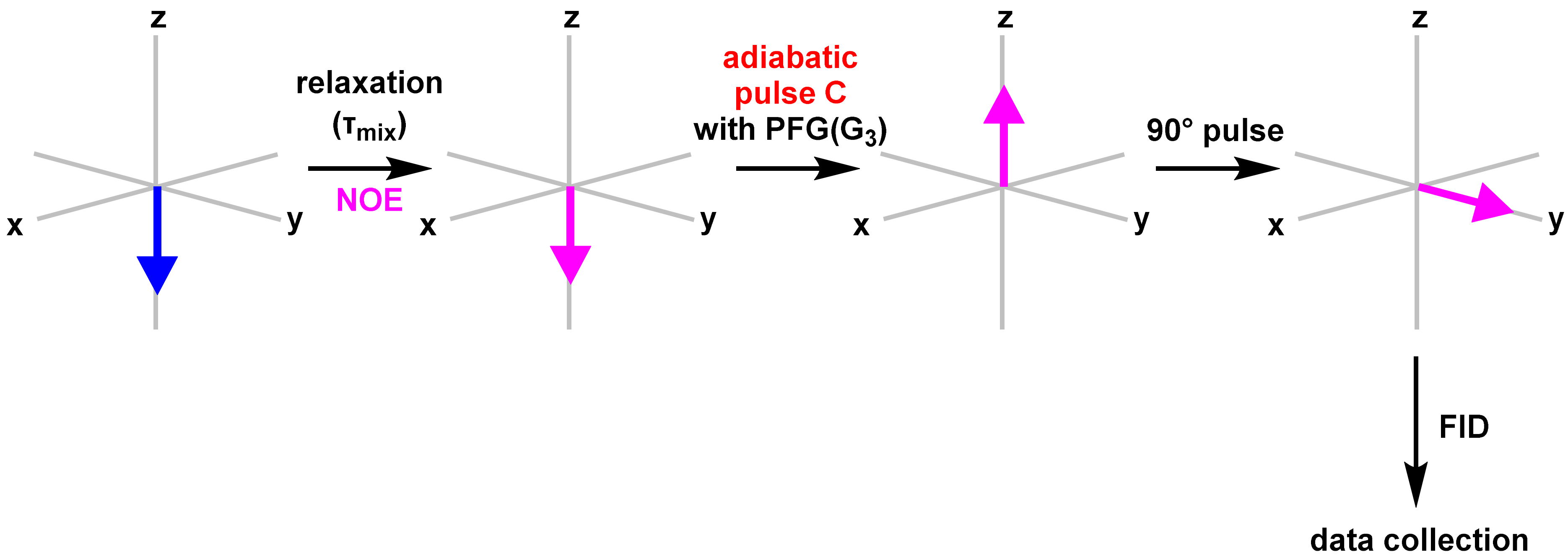
1D GEMSTONE-NOESY (2)



·During the mixing time (τ_{mix}), blue vector got relaxation.
→NOE is observed (transitional NOE)
→Magnetization vector with NOE (magenta) is generated.

·Adiabatic pulse C with PFG disappears some noise, while desired vector isn't affected by the pulse.



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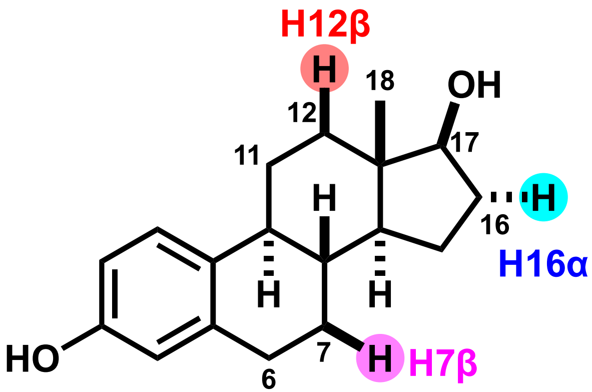
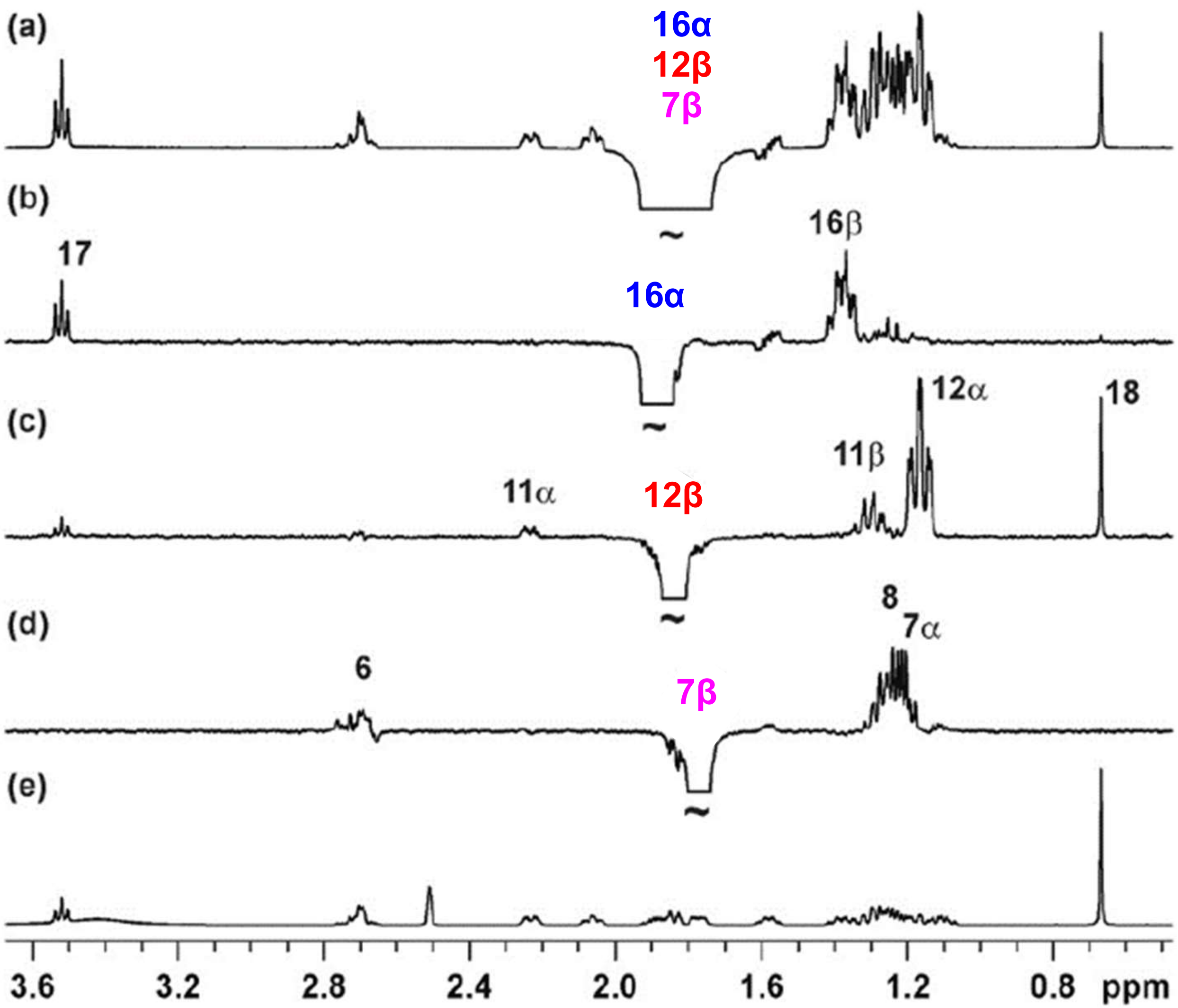
Example of 1D GEMSTONE-NOESY



17β-estradiol



a) normal 1D NOESY
b)-d) 1D GEMSTONE-NOESY
 b) 16α selective
 c) 12β selective
 d) 7β selective
e) ^{1}H NMR spectra

sample: 62 mM in DMSO-d_6
experiment times: 12 minutes

Selective excitation is achieved and clean NOESY charts are obtained

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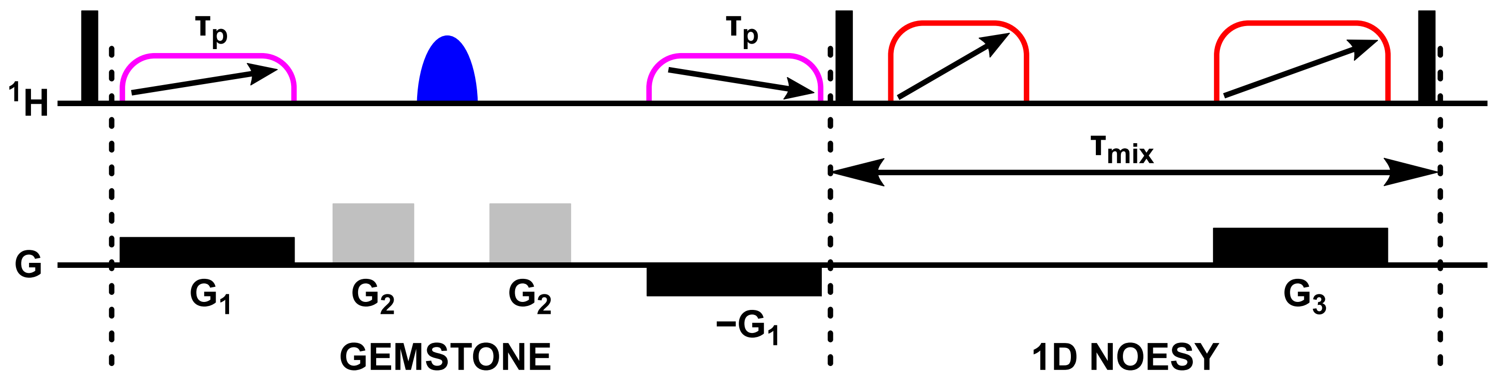
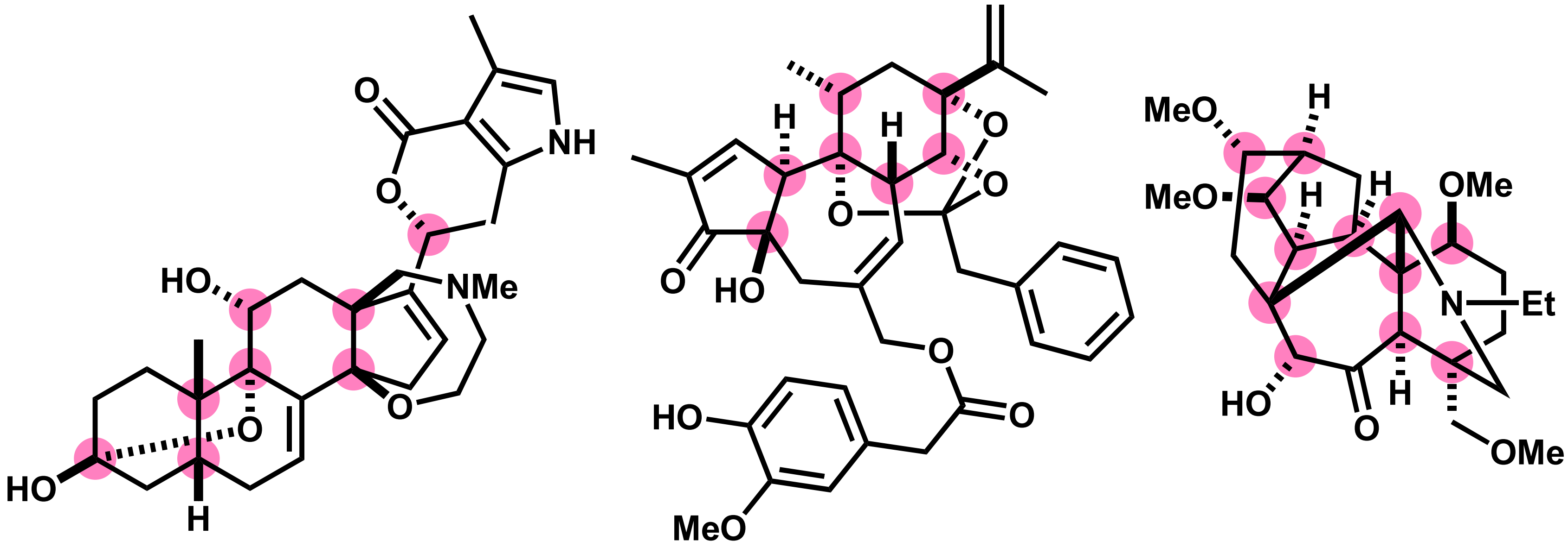
Summary

GEMSTONE: new NMR method for chemical shift selective filter

GEMSTONE-NOESY: new NMR for determining the stereochemistry of organic compound



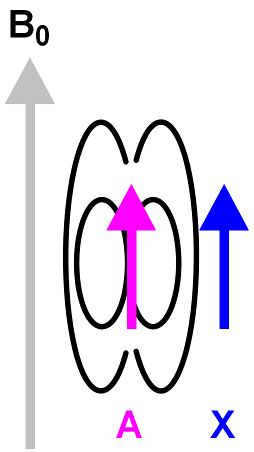


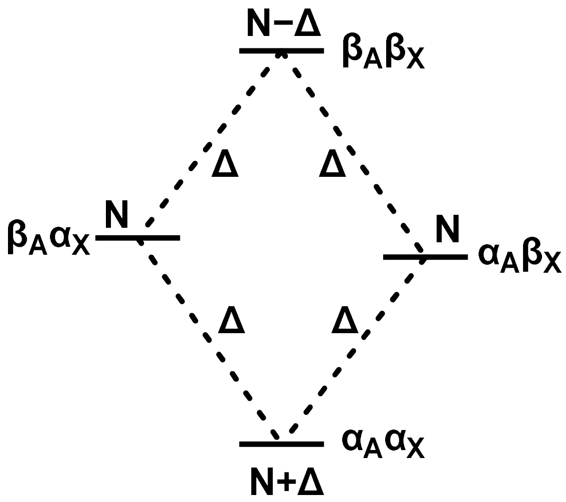
batrachotoxin **resiniferatoxin** **puberuline C**

Appendix

NOE (1)

NOE (Nuclear Overhauser Effect):
the transfer of nuclear spin polarization from one to another via cross-relaxation

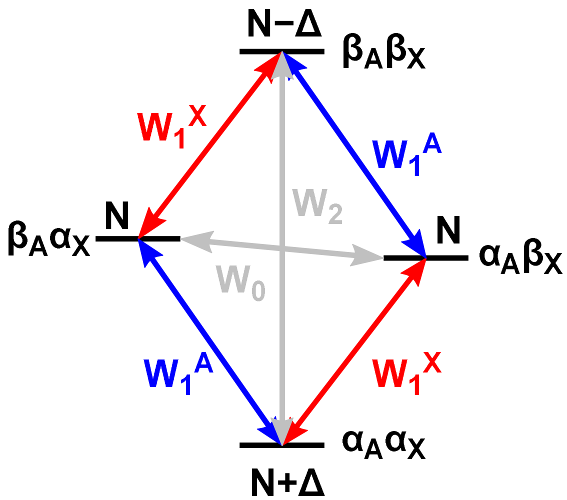




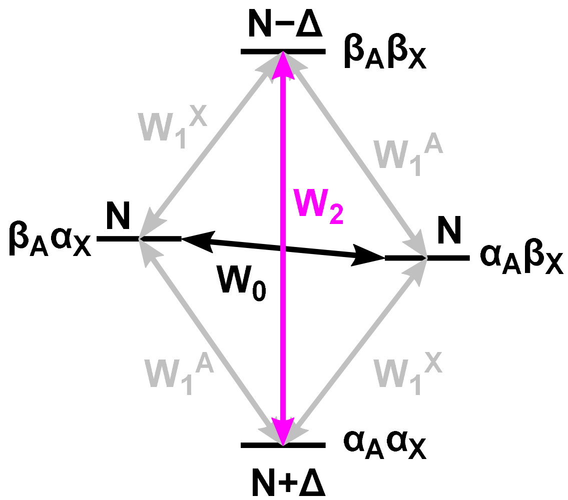
A,X: ^{1}H (no J coupling)
Total number of molecule: 4N

The energy of $β_Aα_X$ and $β_Aα_X$: almost the same
⇒the number of possession at $β_Aα_X$ and $α_Aβ_X$: N

The excitation energy (α→β): almost the same
⇒difference of the numebr at each state is same: Δ



W_1^A,W_1^X: observed on ^{1}H NMR



W_0,W_2: observed on NOE spectrum

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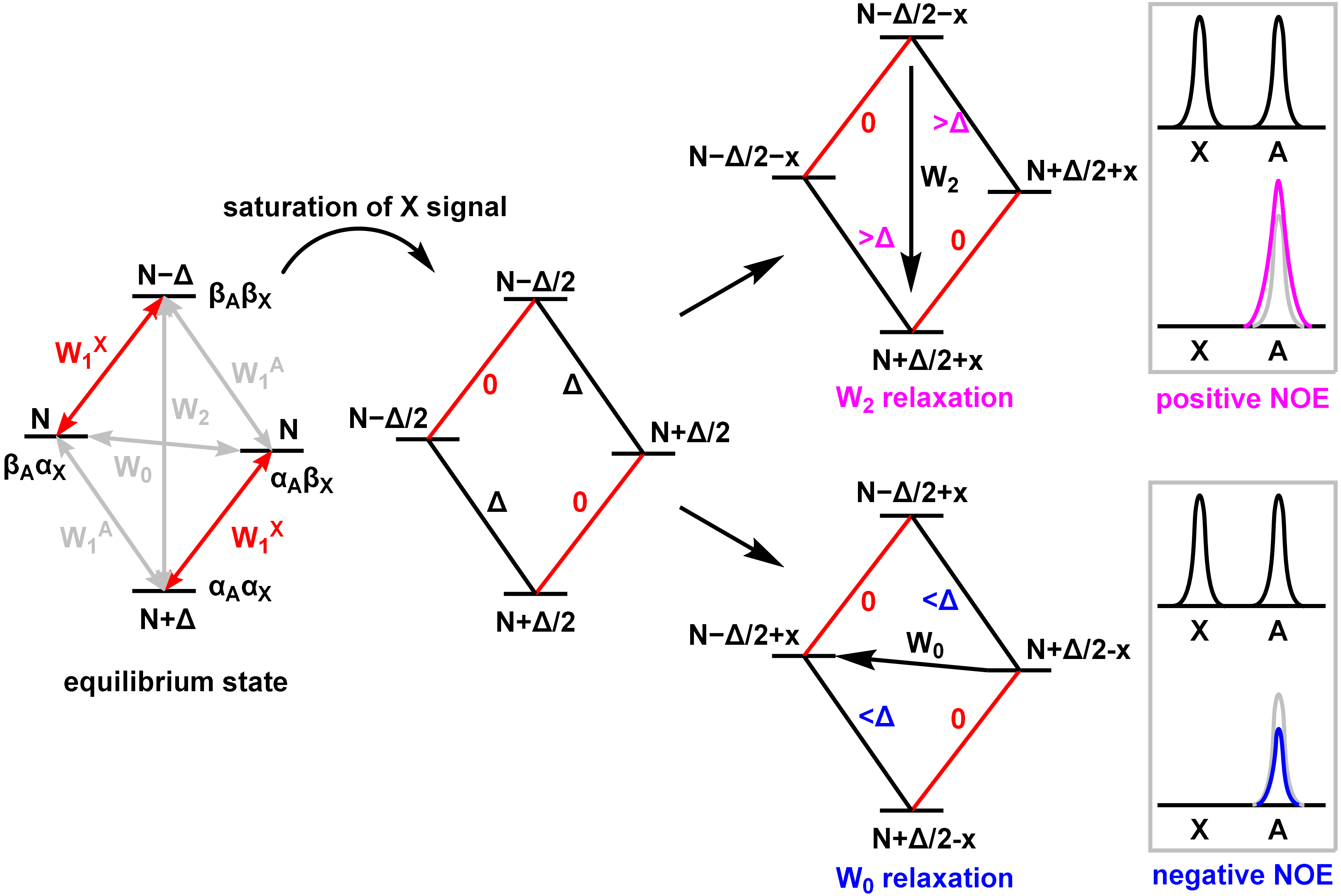
NOE (2)



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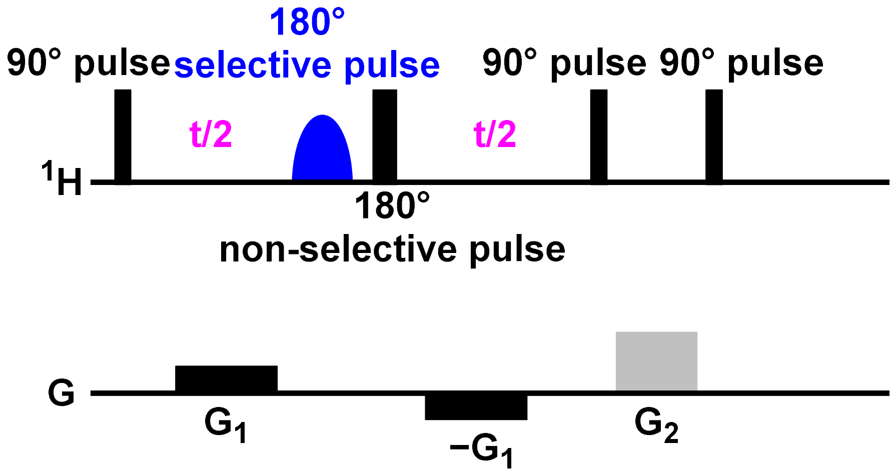
VT-CSSF

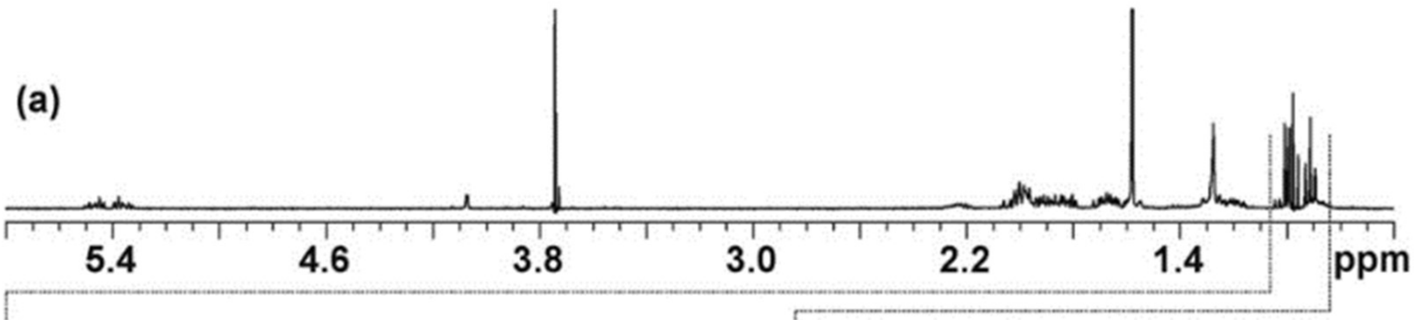


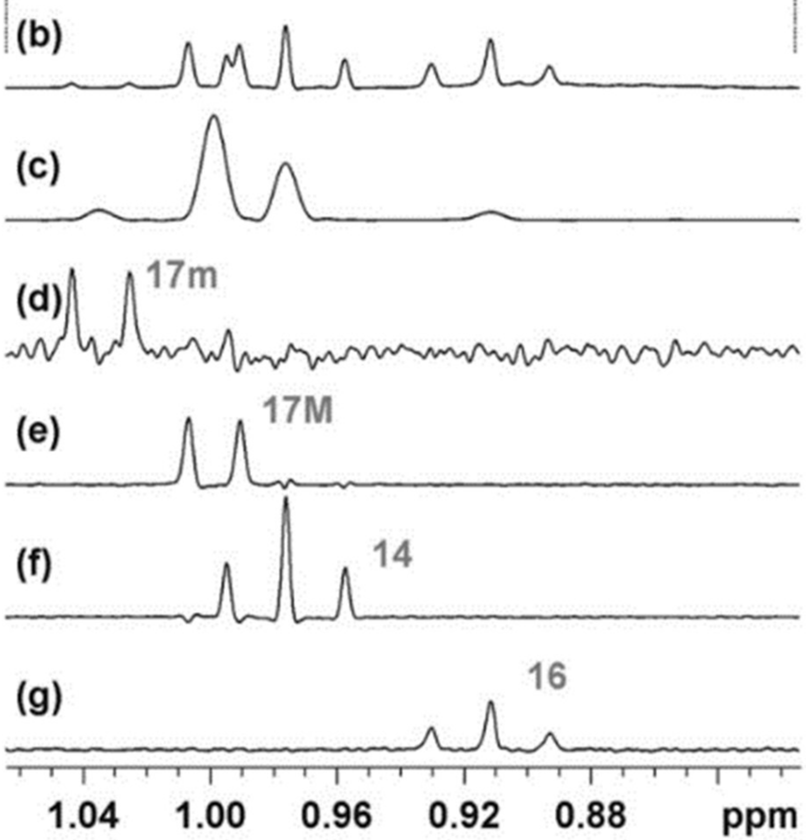
Pulse sequence:
1. 90° non-selective pulse
2. PFG (G_1)
3. 180° selective pulse
4. 180° non-selective pulse
5. PFG ($-G_1$)
6. 90° non-selective pulse
7. PFG (G_2)
8. 90° non-selective pulse

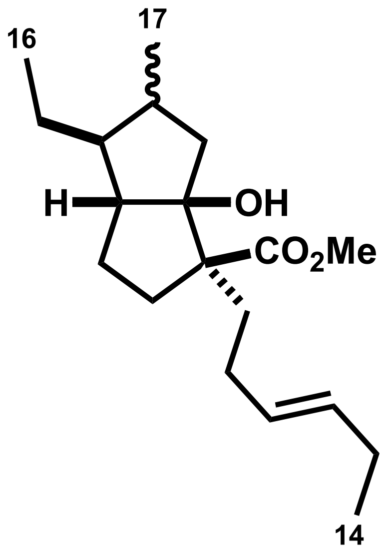
t: increment of VT-CSSF
NMR experiments repeat several time changing t.
→Overall experiment time is relatively long.

1) Robinson, P. T.; Pham, T. N.; Uhrin, D. *J. Magn. Reason*. **2004**, *170*, 97.
2) Kiraly, P.; Kern, N.; Plesniak, M. P.; Nilsson, M.; Procter, D.; Morris, G. A.; Adams, R. W. *Angew. Chem. Int. Ed.* **2021**, *60*, 666.

Example of GEMSTONE-NOESY







a) ^{1}H NMR of 1 and 17-*epi* 1
b) conventional ^{1}H NMR
c) pure-shift NMR
d-g) GEMSTONE experiment

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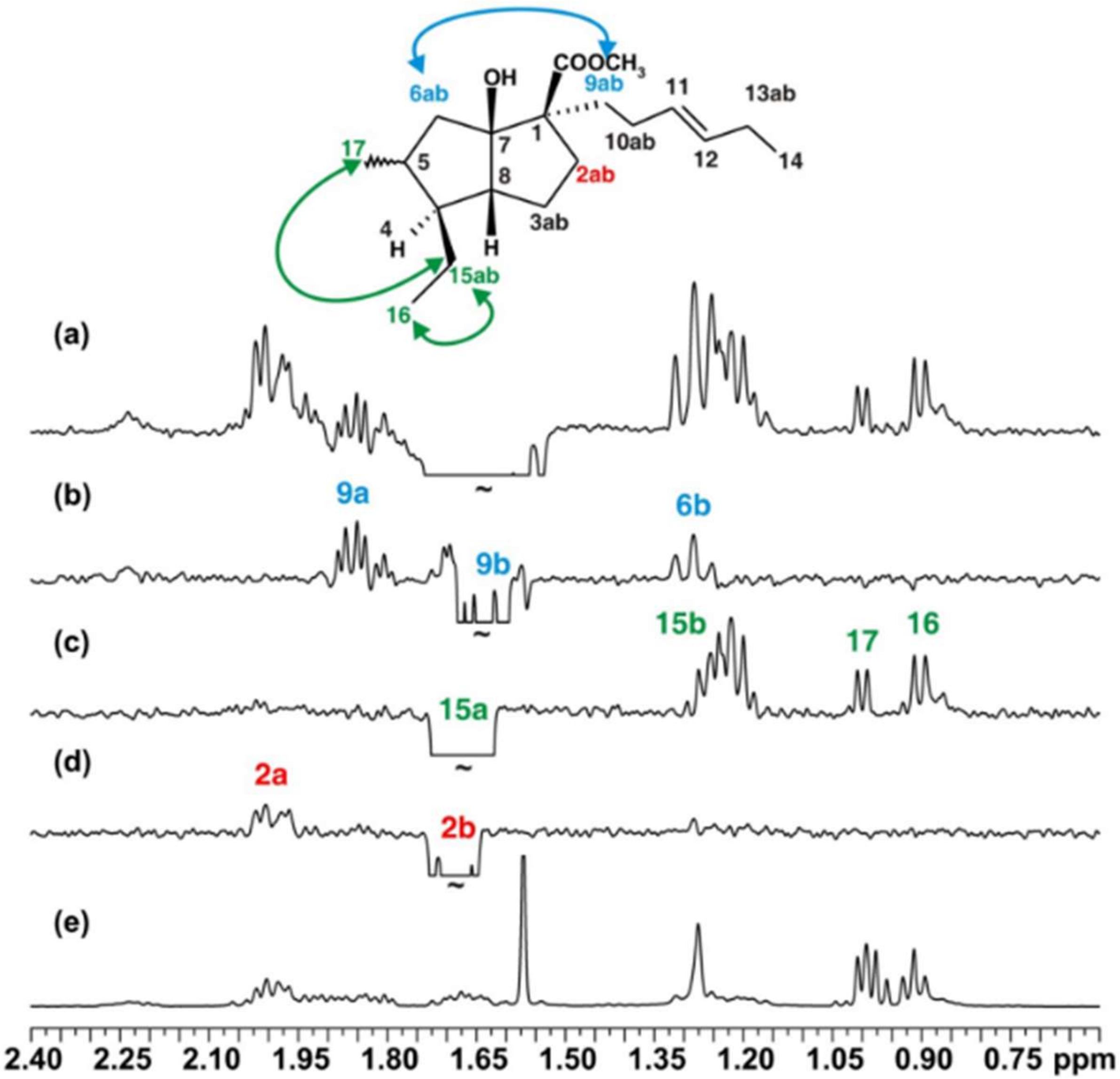
Example of GEMSTONE-NOESY



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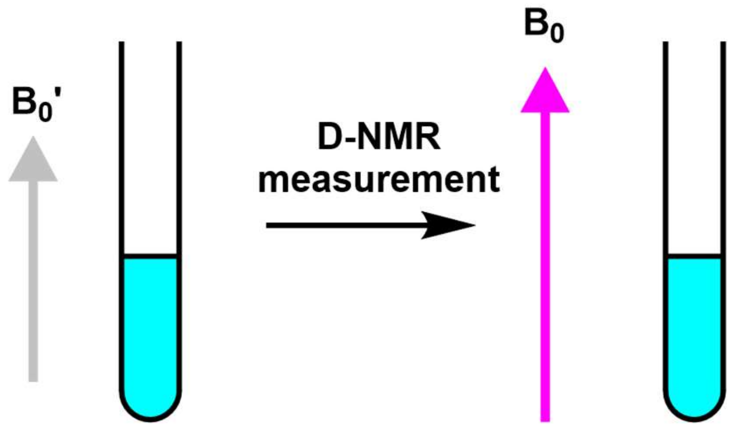
Auto Lock

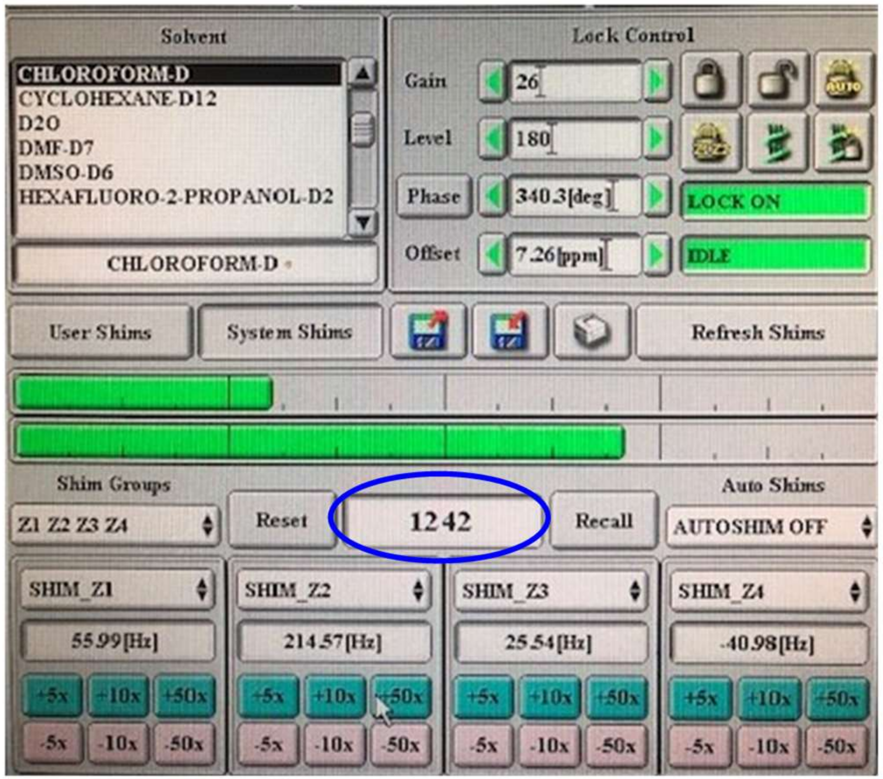
Magnetic field (B_0) is generated by superconductive magnet.
However, B_0 easily changes due to some effect (called drift).
→Measuring B_0 and correcting the distortion: Auto lock

nucleus	*I*	*γ*
^{1}H	1/2	26.8
^{2}H(D)	1	4.13

·^{2}H(D) is also detectable on NMR.
·Its frequency is very different from ^{1}H.
→The signal of D in the solvent is used for Auto lock.

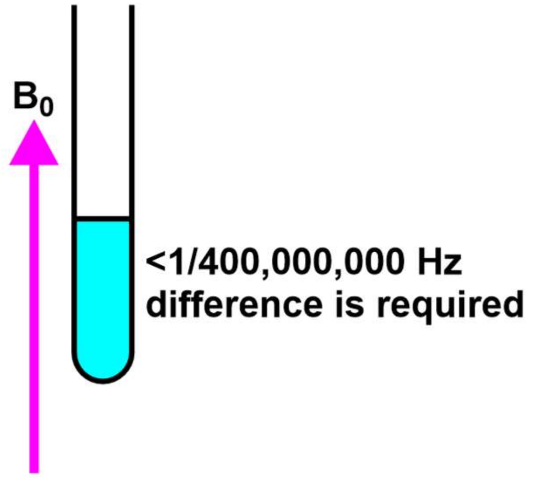


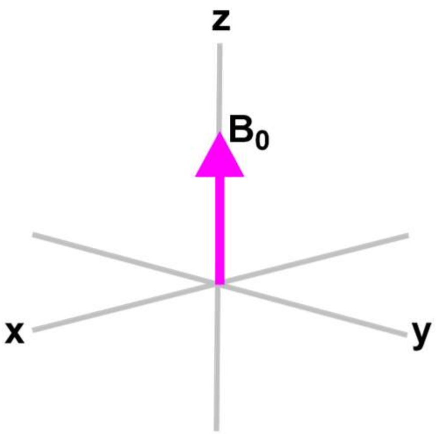
sample in *d*-solvent



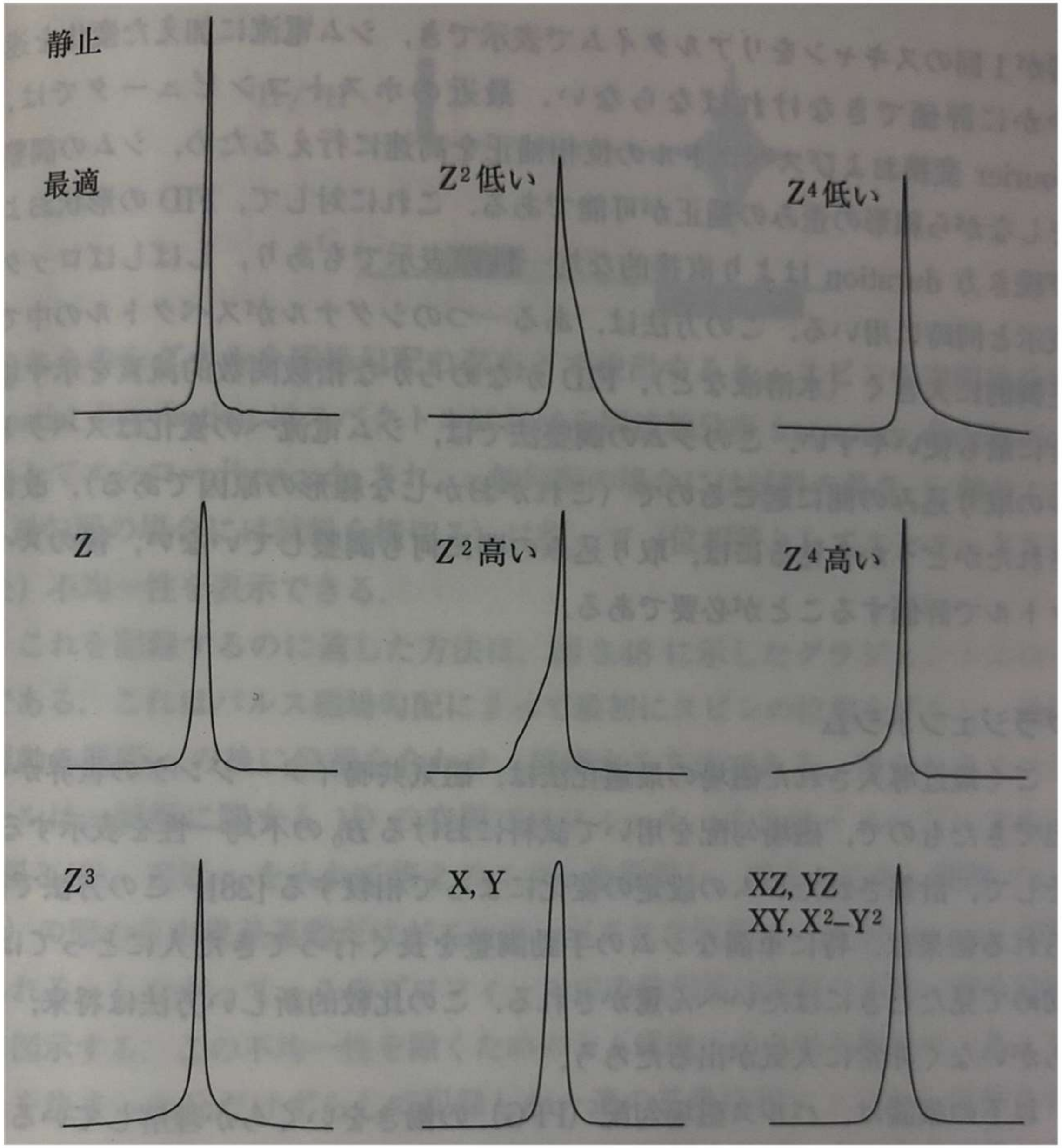
Shimming

Shimming: correction of B_0



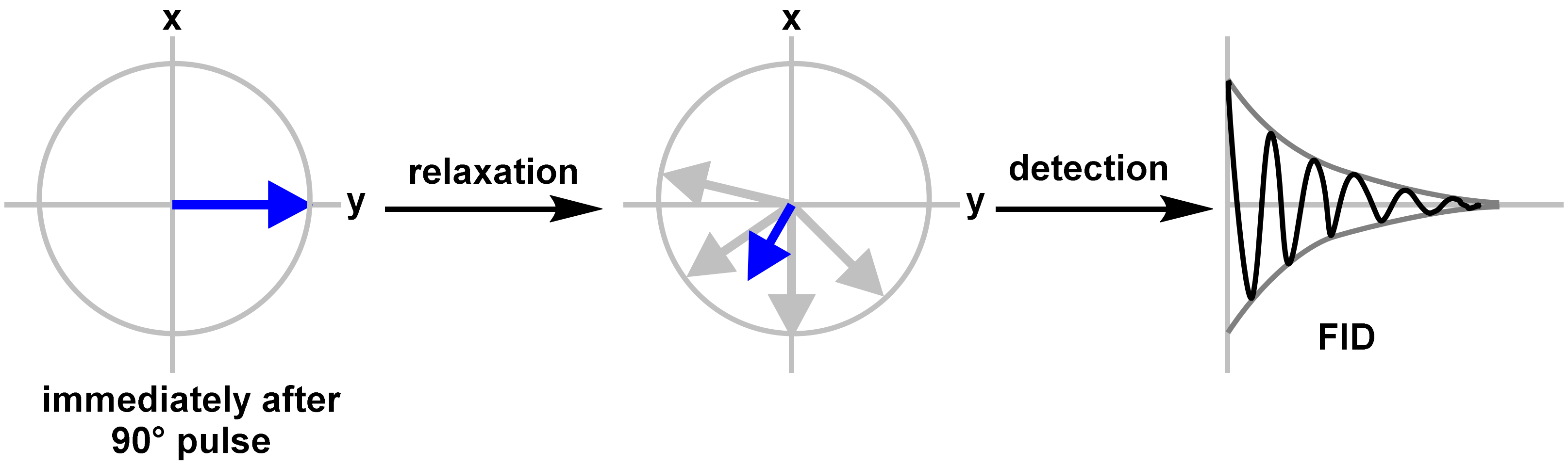


z axis: Z1, Z2, Z3...
XY plane: XY, X^2-Y^2...



有機化学のための高分解能NMRテクニック; 竹内敬人、西川実希　訳

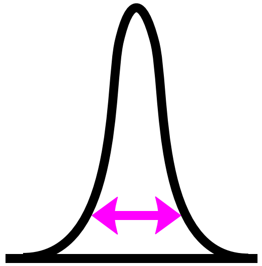
Data Processing and Broadening Factor (BF)



$$FID : I(t) = I_0(\cos 2\pi\nu_0 t)e^{-\frac{t}{T_2}} \cdot e^{-(BF)t}$$

BF: broadening factor

$$F(x) = \int_{-\infty}^{\infty} I e^{-2\pi i t x} dt$$



$$\Delta\nu = \frac{1 + T_2 \cdot BF}{\pi T_2}$$

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Understanding for ”Tesla”

refrigerator magnet
5 mT

Neodymium magnet
1.25 T

Water has a property of diamagnetism.
(In presence of strong magnetic field, water repels to the field.)

→Animals (they have much water in their body) can defy the gravity.

16 T

Ig Nover Prize (2000)

Berry, M. V.; Geim, A. K. *Eur. J. Phys.* **1997**, *18*, 307.