PANACEA/NIH Maglab workshop

Practical aspects of Dynamic Nuclear Polarization

Frédéric Mentink-Vigier

NATIONAL HIGH MAGNETIC FIELD LABORATORY

NIH NSF PANACEA

Today's aim

What are the instrumentation limitations?

What are the samples' constraints?

Where is DNP useful, where is it not?

What pulse sequences are useful?

What do you you need to pay attention to?

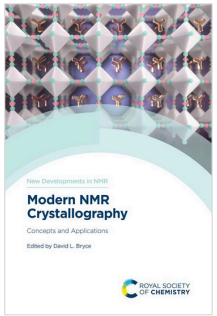
FYI

ROYAL SOCIETY OF CHEMISTRY

Search...

Books

Browse books | Series | Collections | For authors



NEW DEVELOPMENTS IN NMR

Modern NMR Crystallography: Concepts and Applications

Edited by David L. Bryce

Volume 36

DOI: https://doi.org/10.1039/9781837673179

Hardback ISBN: 978-1-83767-066-6

PDF ISBN: 978-1-83767-317-9

EPUB ISBN: 978-1-83767-318-6

Special Collection: 2025 eBook Collection

Series: New Developments in NMR

No. of Pages: 800

BOOK CHAPTER

Chapter 10: Dynamic Nuclear Polarization for Solid-state NMR Spectroscopy

By Daniel Lee ; Frederic Mentink-Vigier

DOI: https://doi.org/10.1039/9781837673179-00256

Published: 31 Mar 2025

Special Collection: 2025 eBook Collection

Series: New Developments in NMR

Page range: 256 - 308

Get permissions | Cite | Share

Dynamic nuclear polarization (DNP) is a transformative technique in the field of solid-state nuclear magnetic resonance (NMR) spectroscopy that improves the detection sensitivity of nuclear spin signals by orders of magnitude. By capitalizing on the large electron spin polarization, DNP has opened new avenues for the NMR detection of species with low concentration, nuclei with low isotopic abundance, and traditionally challenging isotopes. This has pushed the boundaries of NMR crystallography by facilitating studies of complex biological systems, catalytic systems, and a wide range of materials. Herein, both the theory and methodology behind the current application of DNP for solid-state NMR spectroscopy are detailed.

Aim at providing an accessible introduction to DNP and its applications

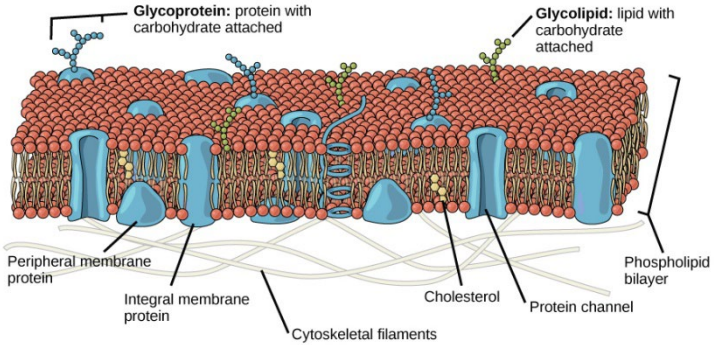
Where is DNP useful

- When sensitivity is low if:
  - Very long recycling delays
  - When isotope of interest is in low concentration
  - When NMR line is very broad

- Isotopically labelled compounds
  - Proteins in biologically relevant media/concentrations
  - Protein in-cell
  - Amyloids (hard to produce in large quantities)

- Samples that cannot be labelled
  - Natural compounds because of $$$$ or time
    - insect wings, bones, wood, soil
  - Complex to apply
    - Low yield synthesis, or metabolomic pathway

- Inherently low concentration
  - Catalyst surface
  - Minor defects in sample (e.g. cross-linking in polymers)



https://courses.lumenlearning.com/suny-wmopen-biology1/chapter/structure-of-the-membrane/

- Most DNP applications are on $^{1}H \rightarrow X$ (Cross-Polarization)
- Direct DNP to low gamma nuclei is still very challenging (a handful of applications)

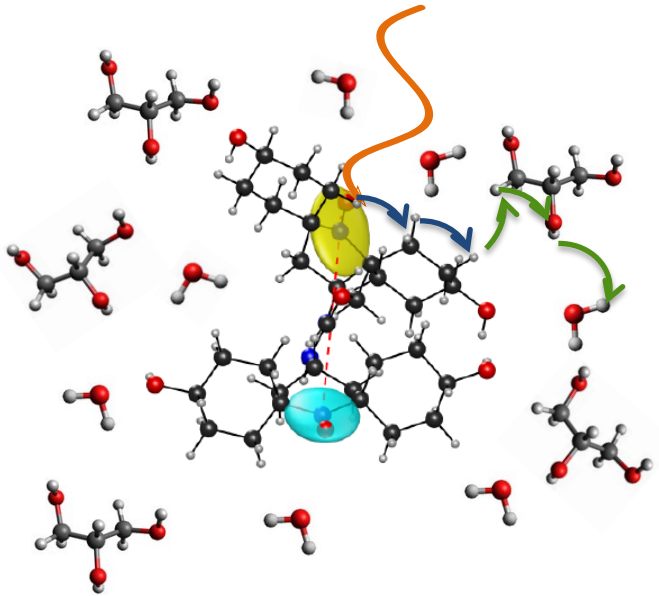
How does DNP “works*”

- * I will only focus on [^{1}H]

Microwave perturbs the radical polarization → Source of hyperpolarization

Nuclear hyperpolarization is generated on local [^{1}H] and transferred to the surroundings → Transfer at a certain rate, R_{DNP}

Then transferred to the surroundings → Equilibration via Fick’s law



$$\frac{dP_n(\vec{r},t)}{dt} = -R_{1,n}(\vec{r})(P_n(t,\vec{r}) - P_n^B) - R_{\mathrm{DNP}}(\vec{r})(P_n(t,\vec{r}) - P_{\mathrm{DNP}}) + D(\vec{r})\nabla^2 P_n(t,r)$$

A simple model

- Diffusion equation of nuclear polarization P_n (like Fick equation)

$$\frac{dP_n(\vec{r},t)}{dt} = -R_{1,n}(\vec{r})(P_n(t,\vec{r}) - P_n^B) - R_{\mathrm{DNP}}(\vec{r})(P_n(t,\vec{r}) - P_{\mathrm{DNP}}) + D(\vec{r})\nabla^2 P_n(t,\vec{r})$$

Thermal equilibrium → goes back to P_n^B

Hyperpolarization → source is P_{DNP}

Diffusion in between nuclei

- Spin diffusion is fast (case of ^{1}H) → take average over $\vec{r}$

$$\frac{d\langle P_n(t)\rangle}{dt} = -\langle R_{1,n}\rangle(\langle P_n(t)\rangle - P_n^B) - \langle R_{\mathrm{DNP}}\rangle(\langle P_n(t)\rangle - P_{\mathrm{DNP}})$$

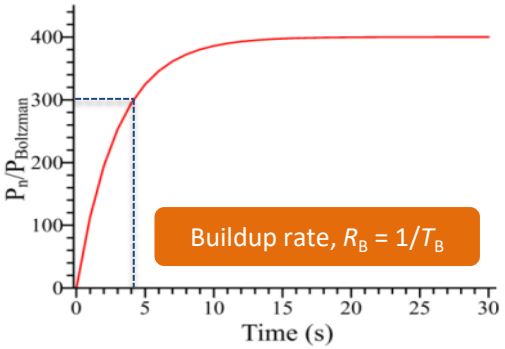
$\langle R_{\mathrm{DNP}}\rangle \propto \frac{N_{\mathrm{DNP}}}{N_{Total}}$, N_{DNP} number of protons undergoing DNP

- Solving (no brackets for simplicity)

$$P_n(t) = \frac{R_{\mathrm{DNP}}P_{\mathrm{DNP}} + R_{1,n}P_n^B}{R_{\mathrm{DNP}} + R_{1,n}}\left(1 - \mathrm{e}^{-(R_{\mathrm{DNP}}+R_{1,n})t}\right)$$

hyperpolarization

Buildup rate, $R_B = 1/T_B$



$$\frac{R_{\mathrm{DNP}}P_{\mathrm{DNP}} + R_{1,n}P_n^B}{R_{\mathrm{CE}} + R_{1,n}}$$

hyperpolarization

A simple model (analysis)

$$P_n(t) = \frac{R_{\mathrm{DNP}}P_{\mathrm{DNP}} + R_{1,n}P_n^B}{R_{\mathrm{DNP}} + R_{1,n}}\left(1 - \mathrm{e}^{-(R_{\mathrm{DNP}}+R_{1,n})t}\right)$$

Hyperpolarization

Buildup rate

Case #1

If $R_{\mathrm{DNP}} \ll R_{1,\mathrm{n}}$
(fast 1H relaxation/slow DNP)

$$\frac{1}{T_B} = R_B = R_{\mathrm{DNP}} + R_{1,n} \approx R_{1,n} = \frac{1}{T_{1,n}}$$

T_B dominated by [^{1}H] relaxation

$$P_n(\infty) = \frac{R_{\mathrm{DNP}}P_{\mathrm{DNP}} + R_{1,n}P_n^B}{R_{\mathrm{DNP}} + R_{1,n}} \approx P_n^B + \frac{R_{\mathrm{DNP}}}{R_{1,n}}P_{\mathrm{DNP}}$$

No or weak DNP

Case #2

If $R_{\mathrm{DNP}} \gg R_{1,\mathrm{n}}$
(slow 1H relaxation/fast DNP)

$$\frac{1}{T_B} = R_{\mathrm{DNP}} + R_{1,n} \approx R_{\mathrm{DNP}}$$

T_B dominated by DNP

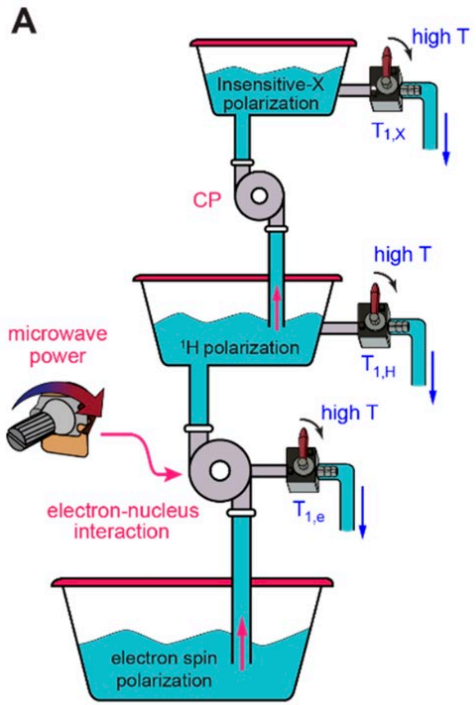
$$P_n(\infty) = \frac{R_{\mathrm{DNP}}P_{\mathrm{DNP}} + R_{1,n}P_n^B}{R_{\mathrm{DNP}} + R_{1,n}} \approx P_{\mathrm{DNP}}$$

Hyperpolarization limited by P_{DNP}
(electron spin dynamics)

First take-home message

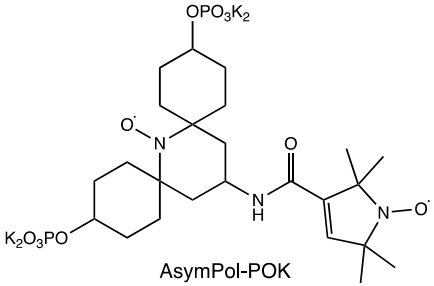
- **DNP mechanism must be efficient with respect to the nuclear relaxation**
- If $T_{1,n} = \frac{1}{R_{1,n}} \ll \frac{1}{R_{DNP}}$ → no DNP
- Samples with fast relaxation means no DNP
  - Samples with fast relaxing groups
    - solvent with –Me groups must be deuterated, e.g. D6-DMSO
    - Small drugs with Phenyl/-Me groups
    - Proteins with many -Me
    - Membrane with aliphatic groups
  - Sample with O_2 dissolved (e.g. organic solvents)
  - At 100 K, samples with paramagnetic species (e.g. “coal like” structures)
  - Sample that do not form a glass (i.e. radical do not have long enough relaxation)

- Some solution:
  - Use deuterated solvents
  - Remove oxygen. (glove box/freeze pump/thaw)
  - Use biradicals with fast R_{DNP} (e.g. AsymPol-POK/AsymPol-TEK)
  - Some biradicals have fast R_{DNP} → no need to deuterate samples

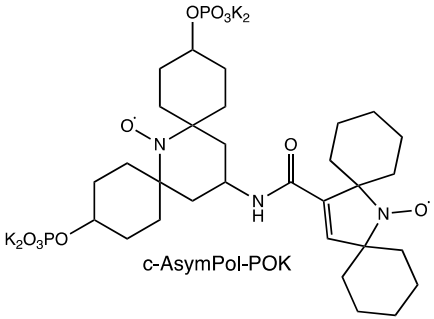


N. Ghassemi, A. Poulhazan, F. Deligey, F. Mentink-Vigier, I. Marcotte and T. Wang, Chem. Rev., 2022

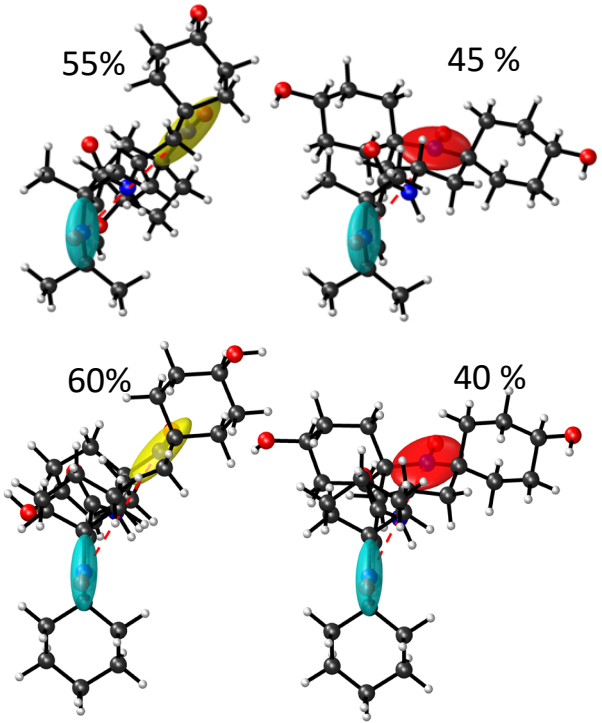
Quantitative simulations: AsymPols

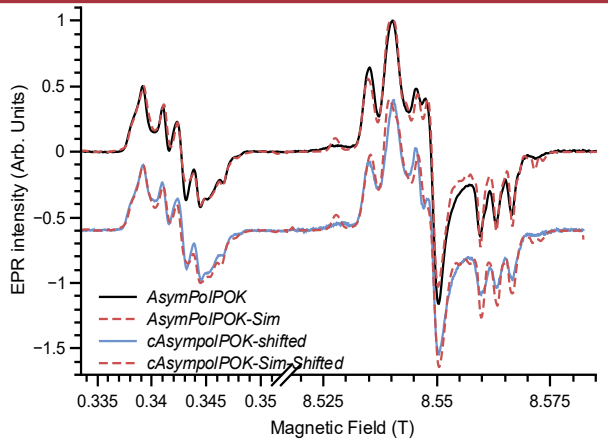


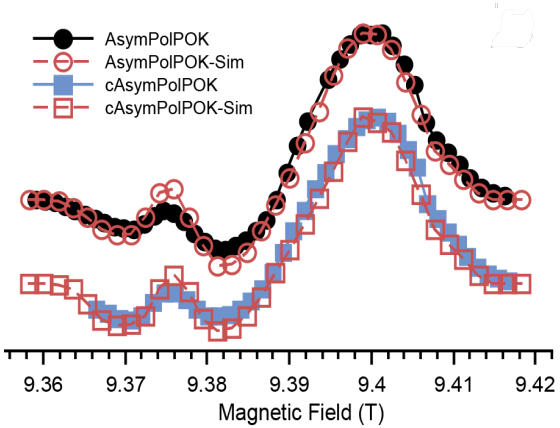
AsymPol-POK



c-AsymPol-POK







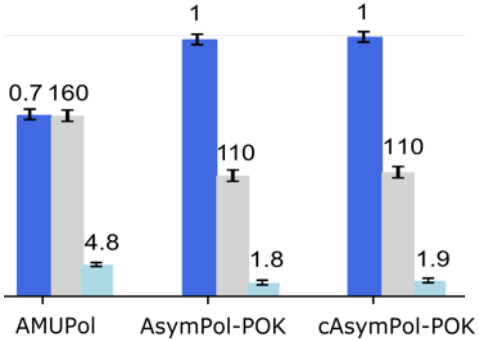
- Large *D* = 56 MHz and *J* = *100 MHz*
- *Perform admirably in protonated media*[1,2]

1. R. Harrabi et al. Angew Chem Int Ed, 2022, 61, e202114103.
2. R. Wei, et al., Angew Chem Int Ed, 2025, e202505944.

AsymPols in protonated medium

- Impact of [^{1}H] in matrix

d_8-glycerol/D_2O/H_2O (6:3:1 v/v)

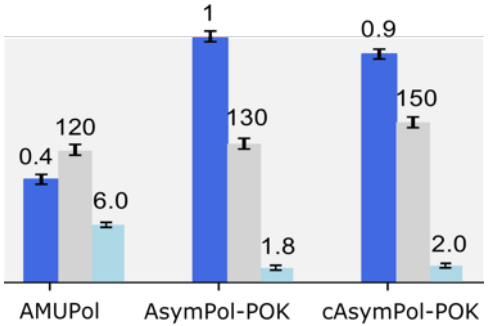


$\epsilon_B/\sqrt{T_B}$

T_B

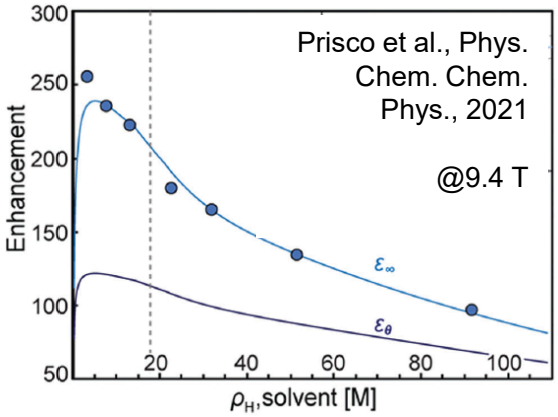
$\epsilon_{on/off}$

glycerol/H_2O (6:4 v/v)



At 14.1 T / 600 MHz

- AMUPol worse performance at high [^{1}H]
- AsymPol better performance at high [^{1}H]



Exp / Sim	ϵ_B	ϵ_{Depo}	T_B (s)	$\epsilon_B/\sqrt{T_B}$
AsymPol-POK	97 / **120**	0.75 / **0.74**	2 / **2**	70 / **85**
c-AsymPol-POK	112 / **127**	0.75 / **0.78**	2 / **2.05**	80 / **90**

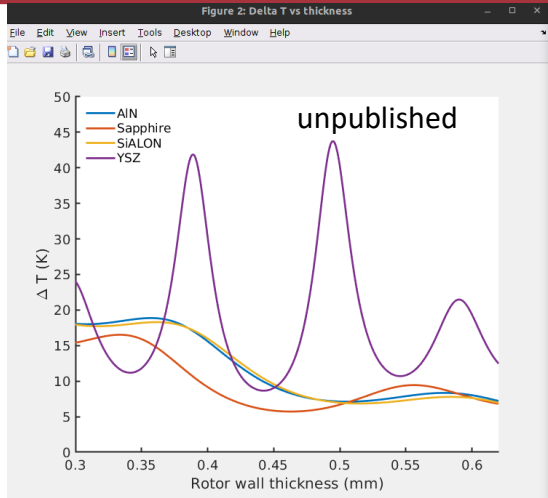
- T_B does not change!
- Deuteration not mandatory for biradicals
- What happens with “spin diffusion” barrier when D/J are large?

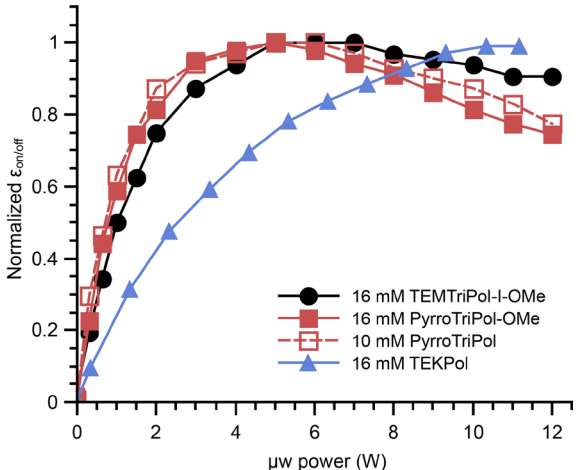
1. R. Harrabi et al. Angew Chem Int Ed, 2022, 61, e202114103.
2. R. Wei, et al., Angew Chem Int Ed, 2025, e202505944.

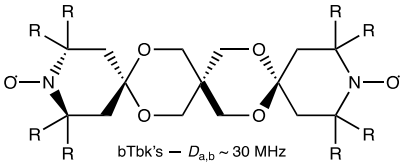
Second take-home message

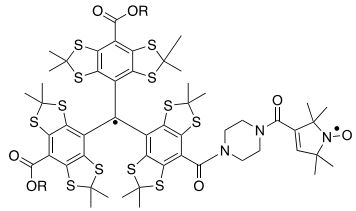
- Sample with large microwave absorption
  - Impossible to create P_{DNP}
  - Example:
    - Some conductive samples
    - Ionic liquids
    - Some membrane proteins (can “melt” under irradiation)

- Solution
  - Use lower μw power and find the right balance between Temperature and Enhancement
  - Use a biradical with lower μ w request power[1]
  - Add powder sapphire powder to you sample → helps improve B1 field[2] and dissipate the heat[3]





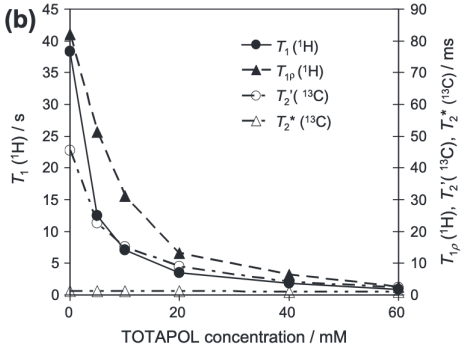


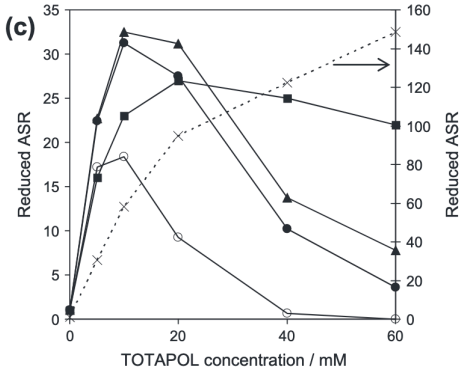


1. T. Halbritter, R. Harrabi, S. Paul, J. Van Tol, D. Lee, S. Hediger, S. Th. Sigurdsson, F. Mentink-Vigier and G. De Paëpe, Chem. Sci., 2023
2. D. J. Kubicki, A. J. Rossini, A. Purea, A. Zagdoun, O. Ouari, P. Tordo, F. Engelke, A. Lesage and L. Emsley, J. Am. Chem. Soc., 2014
3. F. J. Scott, S. Eddy, T. Gullion and F. Mentink-Vigier, Sorbitol-Based Glass Matrices Enable Dynamic Nuclear Polarization beyond 200 K, J. Phys. Chem. Lett., 2024

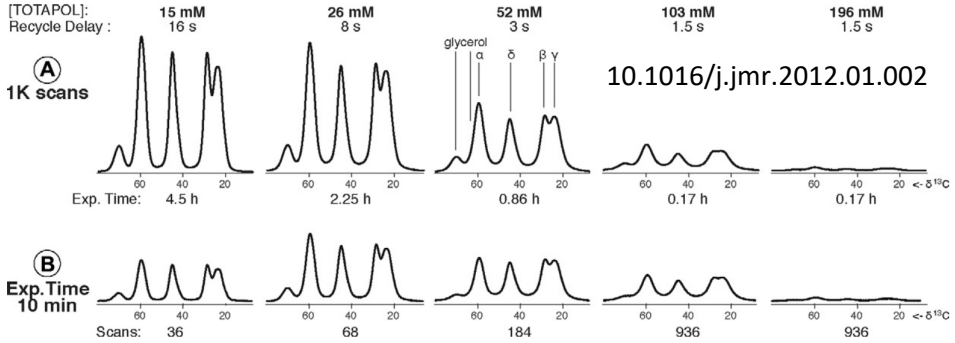
Biradicals concentration?

- What is the optimal biradical concentrations?
  - Depends on the aim:
    - If multiple coherence transfer, then low concentration





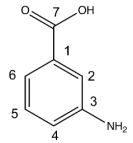
10.1016/j.jmr.2013.12.005



10.1016/j.jmr.2012.01.002

Low concentration = slower T_B ($\langle R_{DNP} \rangle \propto \frac{N_{DNP}}{N_{Total}}$)

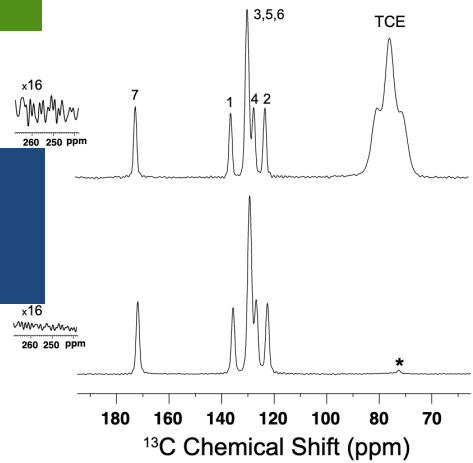
→Use biradicals with the fastest build-up time



Should I always use low [birad]?

May be not: → erase signals from solvent

10.1016/j.ssnmr.2019.02.002



Instrument limitations

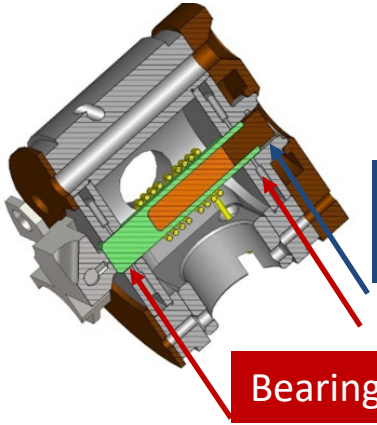
- Low temperature required for DNP
  - Favors long relaxation times
  - Maintains sample temperature under microwave

- N_2 is the cheapest solution
  - N2 liquid at 77 K and 1 bar
  - N2 liquid at 85 K and 2 bars

- Limit of spinning frequency: speed of sound in N_2
  - If gas speed > speed of sound → chaotic flow
  - At 300 K and 1 bar → 360 m/s
  - At 100 K and 1 bar → 200 m/s

Expectation : $\nu_{r,MAX}(100\ K) \approx \nu_{r,MAX}(300\ K) \times \frac{200}{360}$

  - For 3.2 mm, 300 K → 24 kHz, 100 K → 14 kHz
  - For 1.3 mm, 300 K → 65 kHz, 100 K → 35 kHz
  - For 0.7 mm, 300 K → 110 kHz, 100 K → 60 kHz



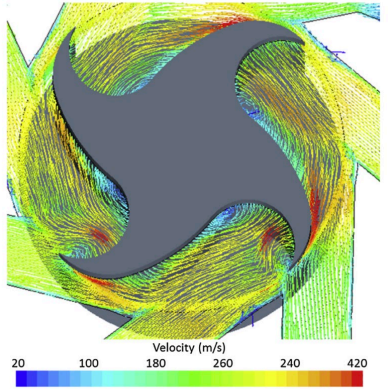


Fig. 6. Velocity vectors of the drive gas in the turbine region at 67 kHz.

Not all pulse sequences possible
Adapt to the sample

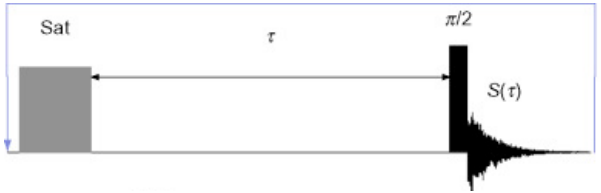
What should I do for DNP?

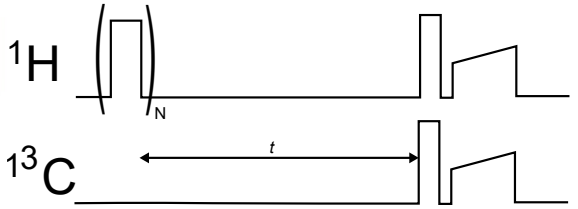
- Can I do DNP with any paramagnetic center?
  - Short answer: No

- Long answer:
  - P_{DNP}
    - EPR spectrum should be close to organic radical because NMR magnets/mw source cannot change field/frequency more than 1%
    - Electron relaxation time long enough? mw power large enough?
  - R_{DNP}
    - Is there enough paramagnetic center vs nuclei?
    - EPR spectrum may be narrow, only solid effect will work → best at low field

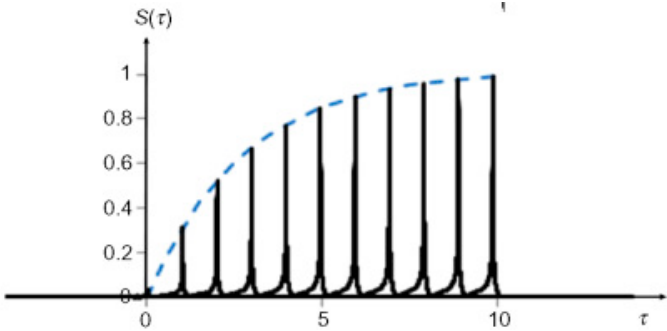
Useful pulse sequences

- Simplest ones always
  - Simple saturation followed by proton FID
    - Do it with or without microwave irradiation
  - $^{1}H \rightarrow X$ (X = ^{13}C) Cross-polarization

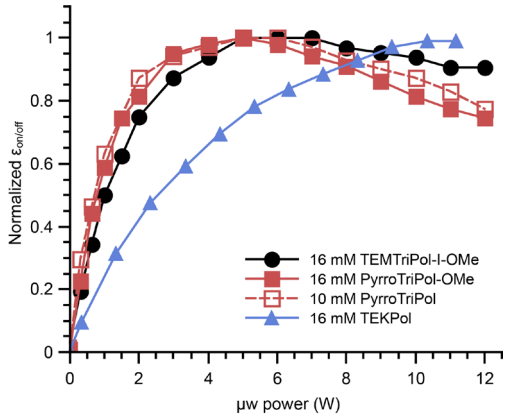




  - Saturation recovery → measures the build-up time T_B



- Why?
  - Proton FID
    - Observe if there is enhancement
    - Optimize the microwave power (avoid sample's melting)
  - Saturation recovery
    - Determine optimal recycling delay (how often to pulse)
    - Debugging tool
      - If T_B is long then radical is too low concentration (likely a low enhancement is observed)
      - If T_B is very short + no DNP → $T_{1,n}$ is too short, DNP will be hard
      - If T_B is very short and lots of DNP → may be too much radical



Useful pulse sequences, for enriched samples:

- Homonuclear coupling same as regular NMR
  - Rely on homonuclear coupling: DARR, PDSD

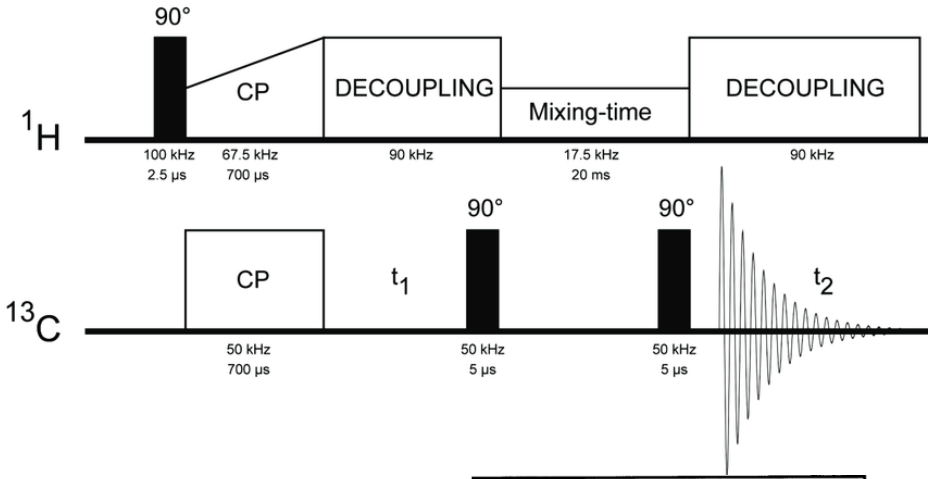
  Probes X-X proximities, e.g. ^{13}C-^{13}C

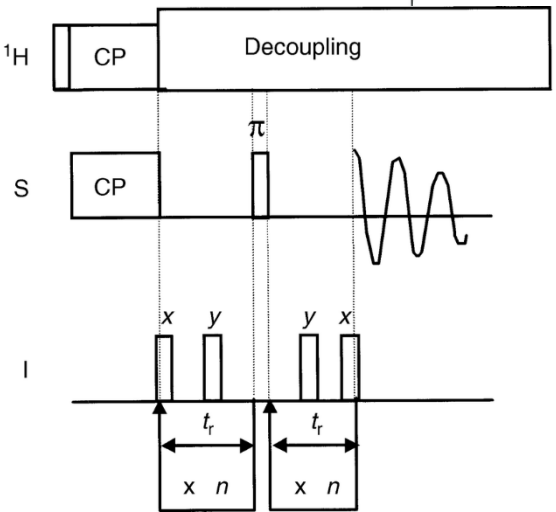
- Hetero-nuclear coupling same as regular NMR
  - Double CP, probe X-Y bonding network

  e.g.
  - J-based inadequate
  - REDOR → measure X-Y distances

- Experiment works because:
  - DARR, PDSD → there are ^{13}C-^{13}C couplings → diagonal not dominant
  - REDOR, there is dephasing → contrast

- Note: at natural isotopic abundance
  - Diagonal peak of SQ/SQ homonuclear experiment → large, tiny cross-peaks
  - REDOR, no significant dephasing, and/or no selectivity (see all the neighboring ^{13}C)





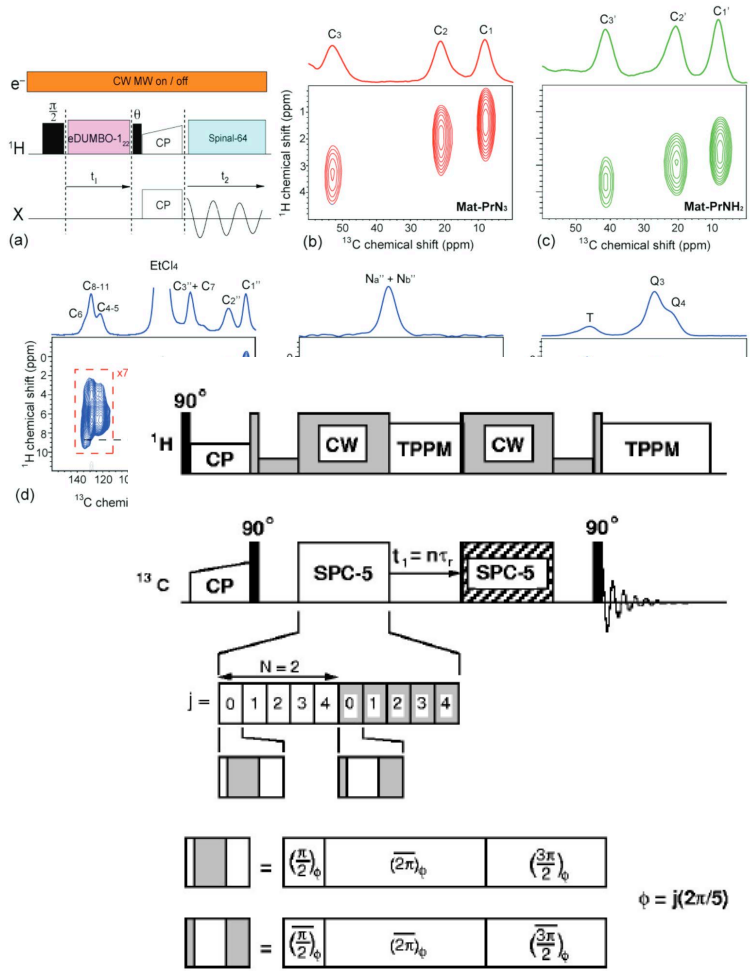
Useful pulse sequences, sample at Natural isotopic abundance

- Heteronuclear
  - ^{1}H-X HETCOR, (e.g FLSG, PMLG, DUMBO… e.g. 10.1021/ja4092038)
  - ^{1}H-CP-Y-X double CP HETCOR (e.g. 10.1021/jacs.5b09964)
  - TEDOR (e.g. 10.1021/jacs.8b09002)

- Homonuclear
  - X-X spin diffusion is very slow e.g. ^{13}C-^{13}C,
  - ^{13}C = 1 % of all carbon → probability of ^{13}C-^{13}C contact → 0.01%
  - DARR/RFDR → mostly a diagonal peak, cross peak very weak

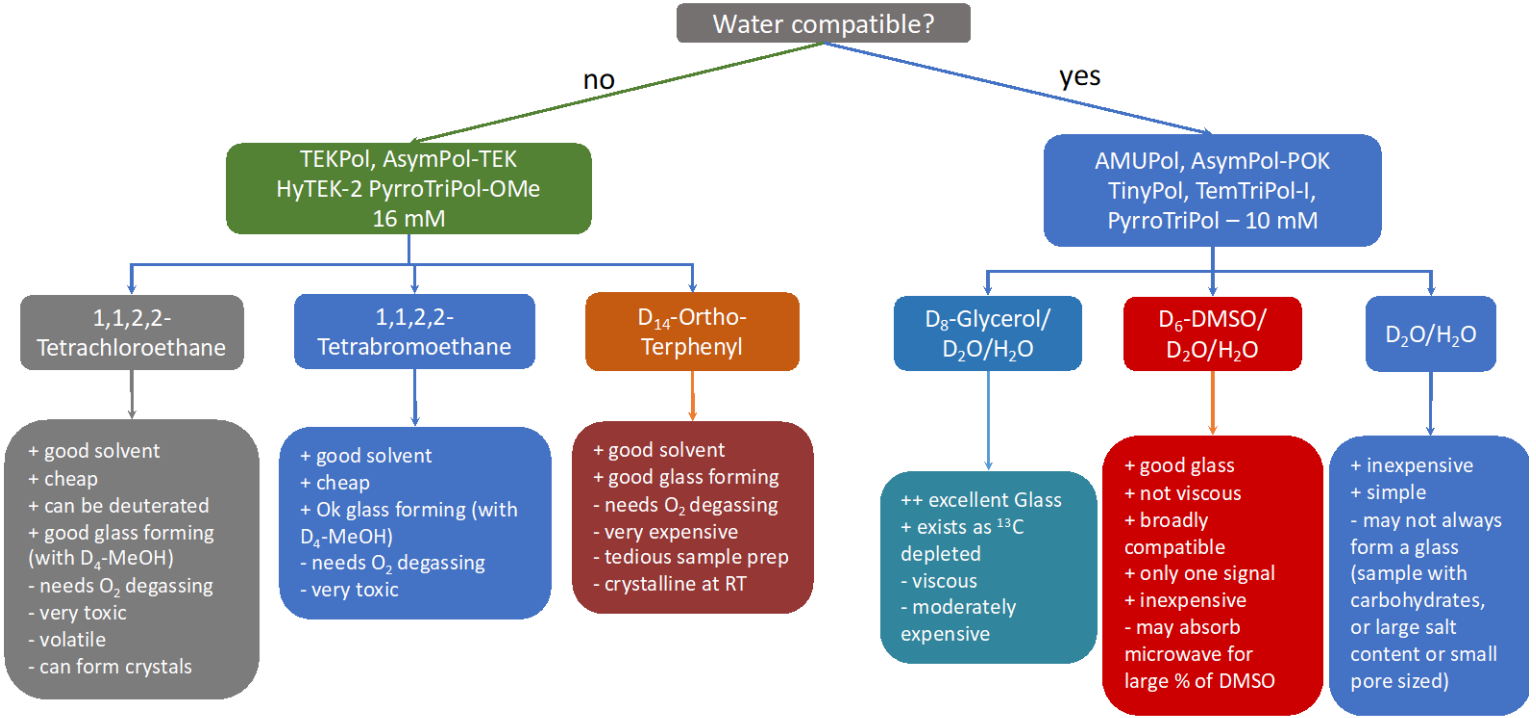
  - Instead use double quantum
    - SQ/DQ pulse sequences e
      - Inadequate (10.1021/ja308135r)
      - POST-C7 / SPC-5 (10.1002/anie.201206102)
    - CH-HC (10.1021/acs.jpcc.7b08841, low efficiency)
    - DQ-filtered DARR (10.1016/j.jmr.2022.107144)

Examples, not a full list…



Sample preparation workflow

- Suggestion (from 10.1039/9781837673179-00256):



Funding

- This workshop has received funding from:
  - The European Union's Horizon 2020 research and innovation programme under Grant Agreement No 101008500
  - The National Resource for Advanced NMR Technology, which is funded by NIH RM1-GM148766.
  - The National High Magnetic Field Laboratory (NHMFL), which is funded by the National Science Foundation Cooperative Agreement (DMR-2128556) and by the State of Florida.
  - Bruker Biospin