# Dense room temperature polarised nuclear targets using SABRE chemical hyperpolarisation – R&D status

Joint APP, HEPP and NP Conference - April 2024

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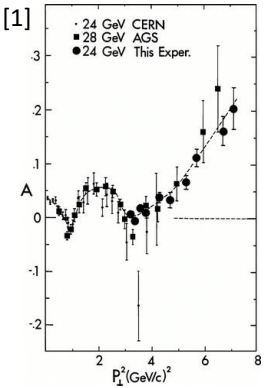
# Polarised nuclear targets

- Help to answer questions such as:

  *"How do quarks and gluons carry the spin of protons?"*

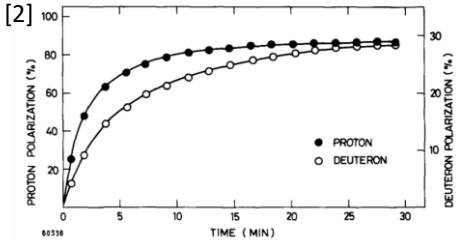
- Current targets use frozen ammonia/butanol polarized by DNP.
- Cannot keep up with increasing beam intensities.
  - Strong depolarisation effects from heat deposition.
  - Long polarisation build-up times.
- We hope SABRE can resolve these issues.

[1]




*Proton analysing power*

[2]




*DNP polarisation build-up*

[3]

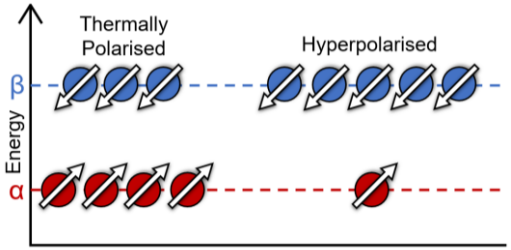
*MAMI Frozen spin target*


[1] G. Crabb and W. Meyer, Annual Review of Nuclear and Particle Science, vol. 47, no. 1, pp. 67–109, Dec. 1997.
[2] de Boer W. CERN Yellow Report 74-11 (1974); J. of Low-Temp. Phys. 22:185 (1976).
[3] Thomas, A. et. al, Phys. Part. Nuclei 44, 964–967 (2013).

# Hyperpolarisation and *para*hydrogen

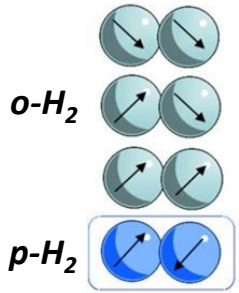
Hyperpolarisation → greater than equilibrium spin polarisation, given by: $P = \frac{p_\alpha - p_\beta}{p_\alpha + p_\beta}$

Thermal equilibrium polarisation: $P_{eq} = \tanh\left(\frac{\hbar\gamma B_0}{2k_B T}\right) \ll 1$

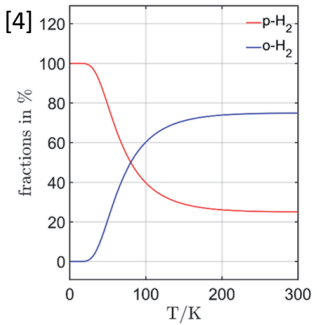



Parahydrogen (*p*-$H_2$) → Singlet nuclear spin isomer of molecular hydrogen ($H_2$).

Readily produced by passing $H_2$ over a ferromagnetic catalyst at low temperatures.




Spin configurations of $H_2$.



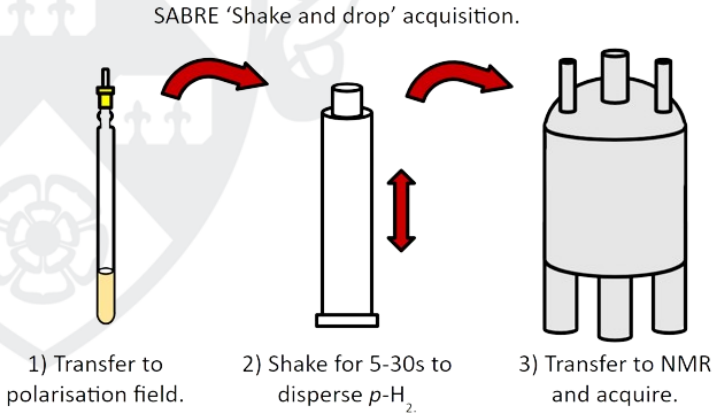

*p*-$H_2$ % by temperature.

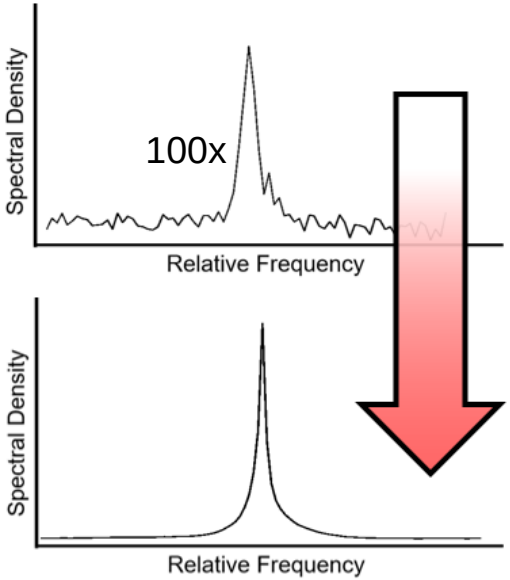
*p*-$H_2$ generator at CHyM.

[4] G. Buntkowsky et. Al, RSC Adv, vol. 12, no. 20, pp. 12477–12506, Apr. 2022.

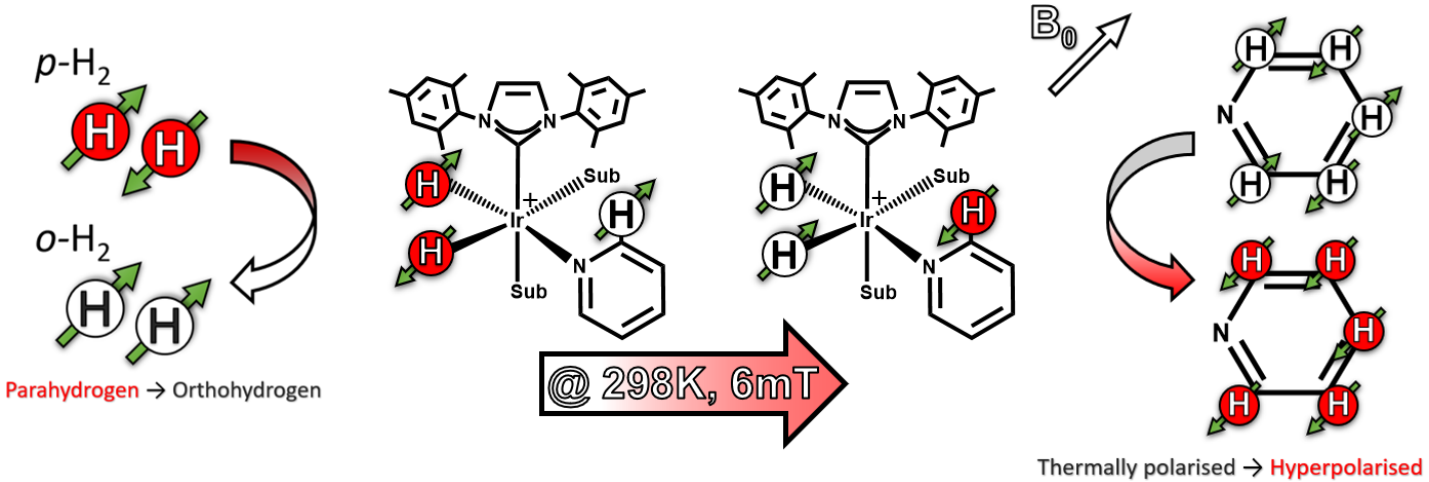
# SABRE

- Chemically-catalysed nuclear hyperpolarisation technique.
- Uses *p*-$H_2$ feedstock of spin order.
- Works at **room temperature** in **weak magnetic fields** (µT-mT).
- Polarisation can be **generated continuously**.
- **$^{1}$H, $^{13}$C, $^{15}$N** (+ more).

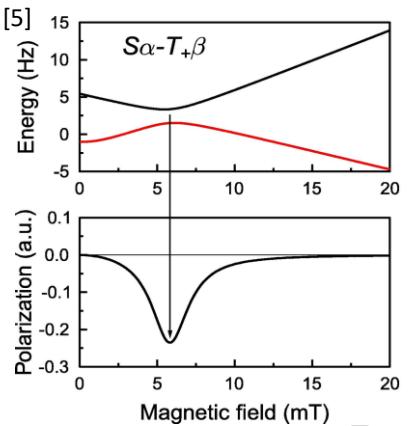


# SABRE spin order transfer




- SABRE substrates and *p*-$H_2$ brought together by SABRE catalyst.
- Spin exchange occurs through $J_{HH}$ couplings.
- LACs for an allow the transition Sα → $T_+$β at specific magnetic fields.
- Polarisation reaches a maximum within seconds.

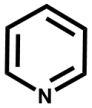
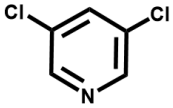
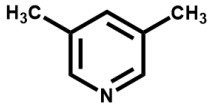
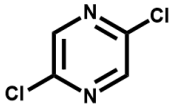



*LACs for SABRE*

[5] Barskiy et. al, S. Knecht, Prog Nucl Magn Reson Spectrosc, vol. 114–115, pp. 33–70, Oct. 2019.

# Substrate comparison

Data from selected substrates under equivalent conditions.

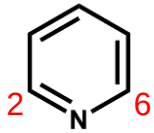
| Pyridine | 3,5-Dichloropyridine | 3,5-Dimethylpyridine | 2,5-Dichloropyrazine |
|---|---|---|---|
| $C_5H_5N$ | $C_5H_3Cl_2N$ | $C_7H_9N$ | $C_4H_2Cl_2N_2$ |
| Polarisable proportion of protons (%) | | | |
| 11.9 | 4.1 | 15.5 | 2.6 |
| Polarisation yield (%) | | | |
| 1.4 | 2.9 | 0.15 | Low (N/A) |
| Avg $T_1$ (s) | | | |
| 40.0 | 83.8 | 12.2 | 128.5 |
|  |  |  |  |

Trends seen:

+ Methyl group: Polarisable protons ↑, Polarisation lifetime ↓.
+ Halogen: Polarisable protons ↓, Polarisation lifetime ↑.

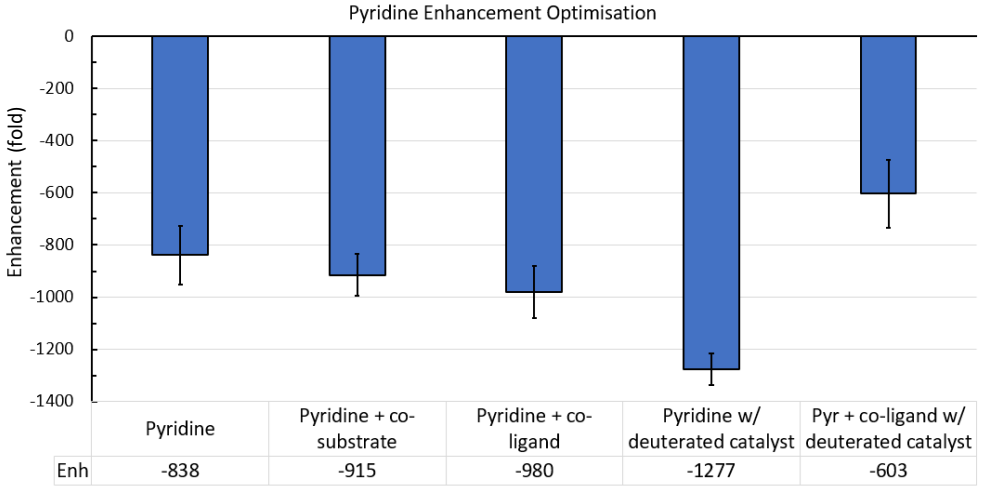
→ Addition of low-$\gamma$ nuclei can reduce relaxation in hyperpolarised material.

→ Addition of halide/methyl groups can reduce binding efficiency, especially in positions 2 & 6.

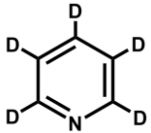


# Pyridine Enhancement Optimisation

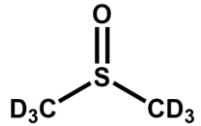
Substrate of interest due to high polarizable proton fraction and high yields.



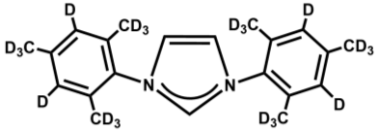

| | Pyridine | Pyridine + co-substrate | Pyridine + co-ligand | Pyridine w/ deuterated catalyst | Pyr + co-ligand w/ deuterated catalyst |
|---|---|---|---|---|---|
| Enh | -838 | -915 | -980 | -1277 | -603 |




Pyridine-$d_5$ co-substrate




DMSO-$d_6$ co-ligand



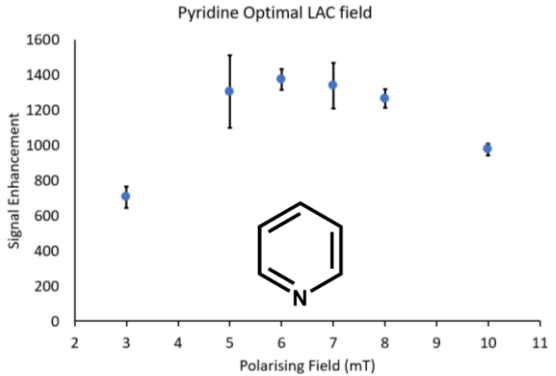

IMes-$d_{22}$ deuterated catalyst NHC

\+ Co-substrate: Enh ↑

\+ Co-ligand: Enh ↑↑

\+ Deuterated catalyst: Enh ↑↑↑

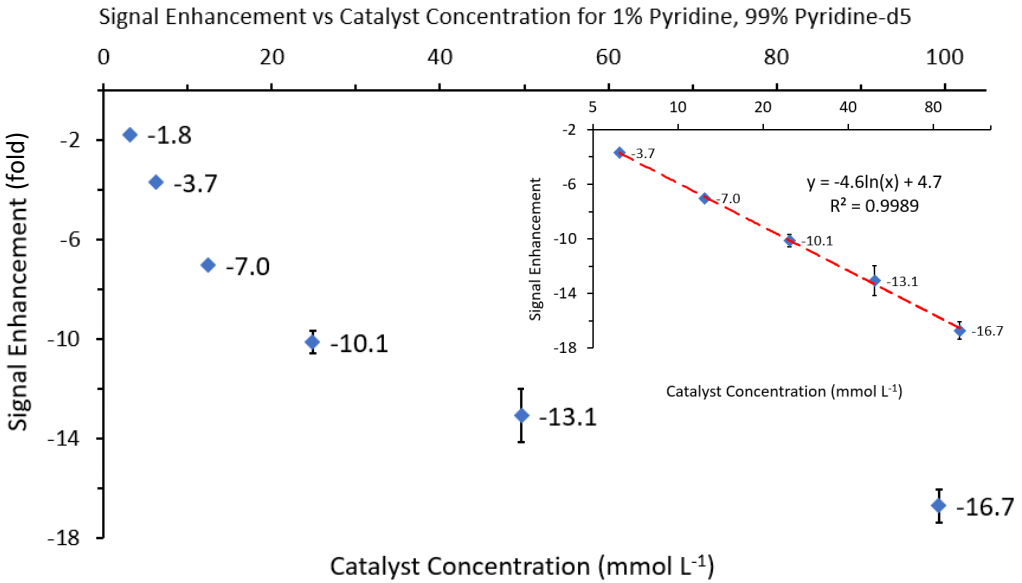
\+ Co-ligand and deuterated catalyst: Enh ↓




→ Optimum field for LAC found to be 6 mT for $^1$H.

# Limitations of *p*-$H_2$ solubility

SABRE typically performed in solution using MeOD-$d_4$/DCM-$d_2$ as a solvent.
What happens if SABRE is performed on a neat solution of substrate?



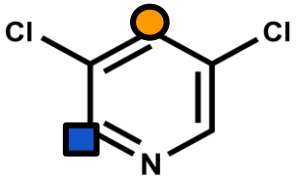

- Signal enhancement (Enh) seen is $10^2$-$10^3$ fold lower than for optimal conditions.
- Enh doesn't scale linearly with catalyst concentration - dependence is logarithmic.
- Solubility of *p*-$H_2$ in solution is the limiting factor.

→ Polarization of neat liquids via SABRE is not feasible without extreme pressures.

# Relaxation studies on model substrate

Relaxation decay constant, $T_1$, is a key metric in hyperpolarisation:

- Determines the maximum polarisation levels that can be reached.
- Long $T_1$ reduces the need for high $p$-$H_2$ pressures and catalyst concentrations.




Model substrate - 3,5-dichloropyridine

Conclusions:

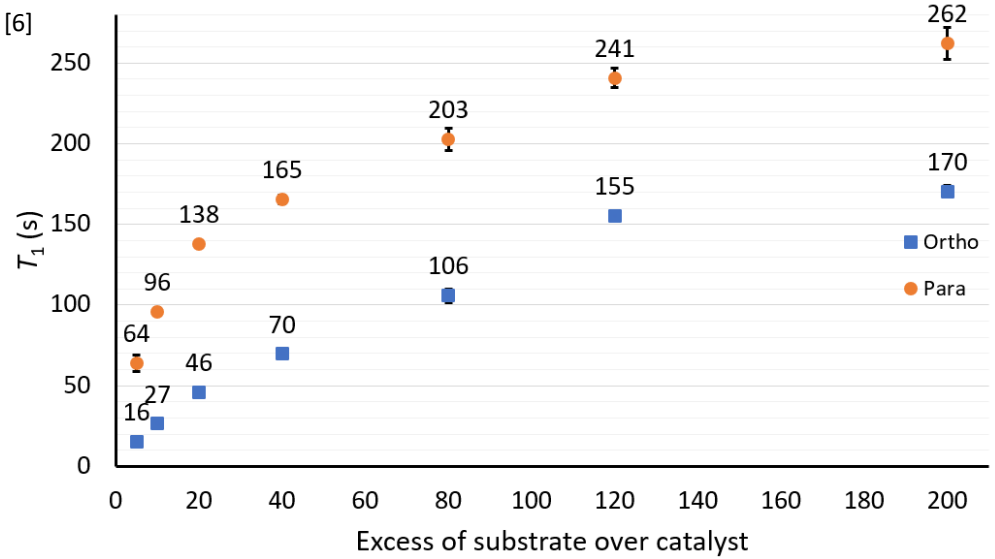
a) Relative catalyst concentration in solution is the primary driver of relaxation.

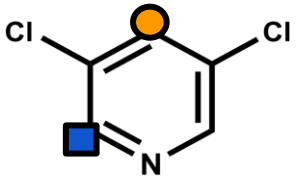
b) Dependence of relaxation on holding field is small in the range 1.4-11.7T.

c) Relaxation $T_1$ peaks at 30°C.

# Relaxation studies on model substrate

a) Variation of $T_1$ with substrate excess

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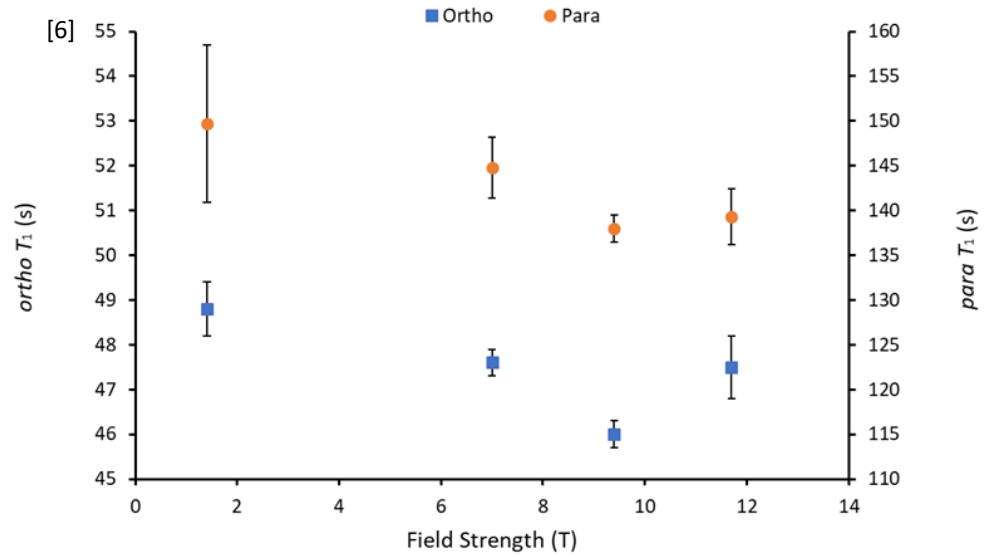
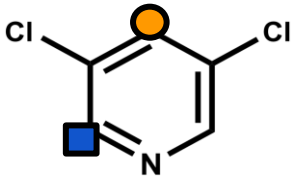
[6] B. J. Tickner et al., ACS Catal, vol. 14, no. 2, pp. 994–1004, Jan. 2024.

# Relaxation studies on model substrate

## b) Variation of $T_1$ with holding field

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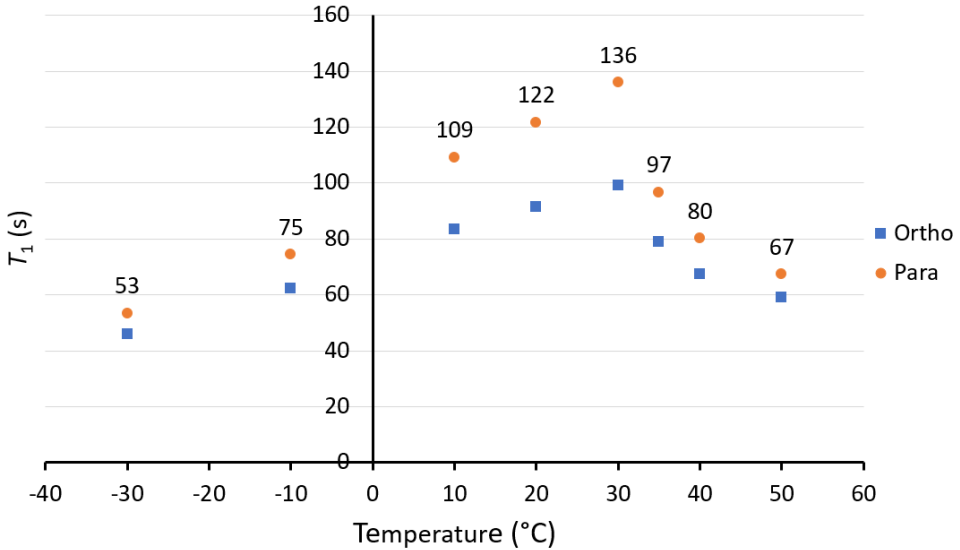
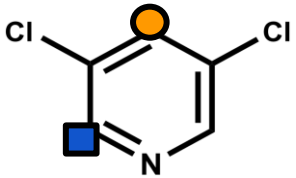
[6] B. J. Tickner et al., ACS Catal, vol. 14, no. 2, pp. 994–1004, Jan. 2024.

# Relaxation studies on model substrate

c) Variation of $T_1$ with temperature

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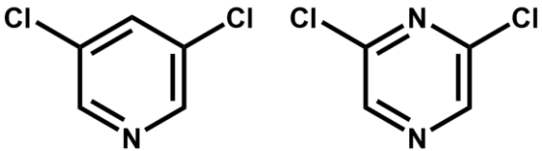
# Polarization resilience test @ MAMI

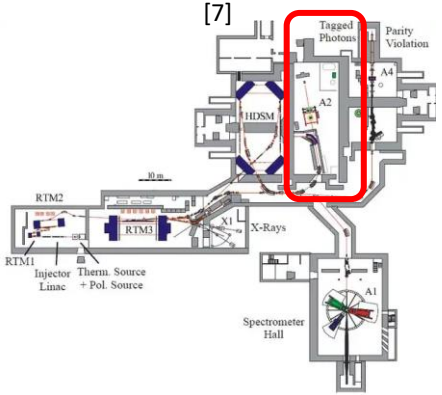
Aim → Test resilience of SABRE hyperpolarization to an incident photon beam by monitoring rate of polarization decay.

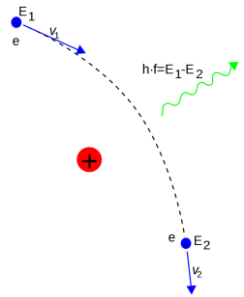
- Facility produces energy-tagged Bremsstrahlung photons from a high energy electron beam. E = 40 MeV → 1.6 GeV.
- 2 halogenated pyridine/pyrazines chosen for long polarisation lifetimes.
- Additional sample left in high dose area (electron beam dump) to investigate effects of radiation damage.
- Measurements made using commercially available, low cost benchtop MRI.

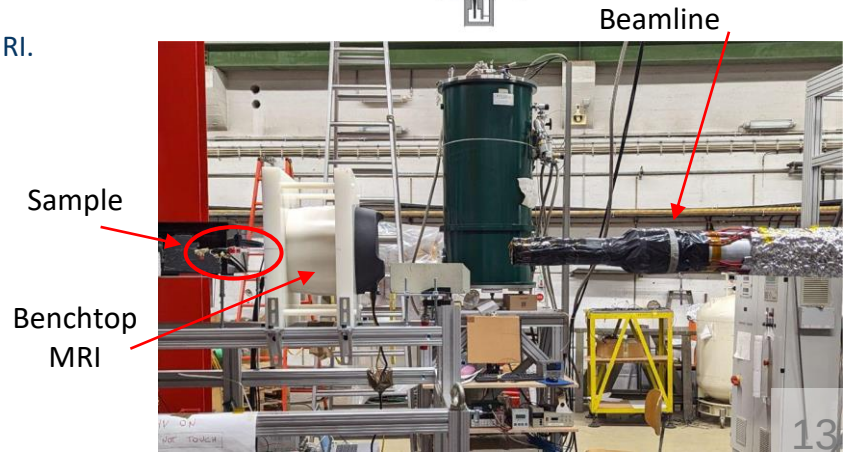



Test substrates - 3,5-dichloropyridine (left), 3,5-dichloropyrazine (right).

[7]



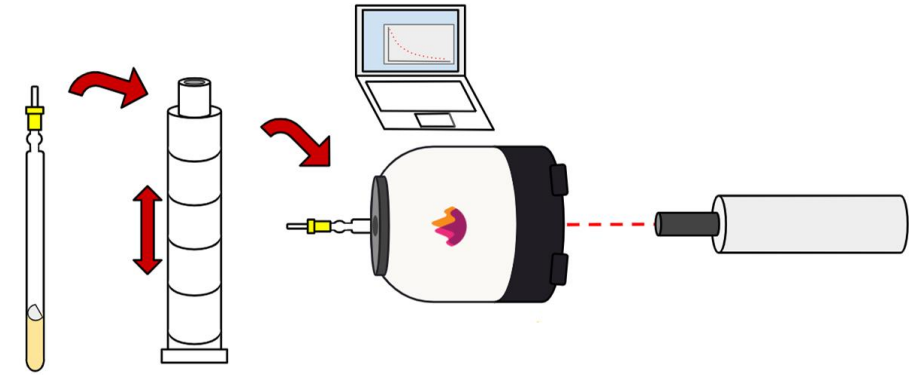




[7] Floorplan of the MAMI facility, by Ostrickm, licensed under CC-BY-SA-3.0.

# Experimental procedure and pulse sequence

## Experimental procedure:



1) Prepare sample and pressurise to 5 bar.

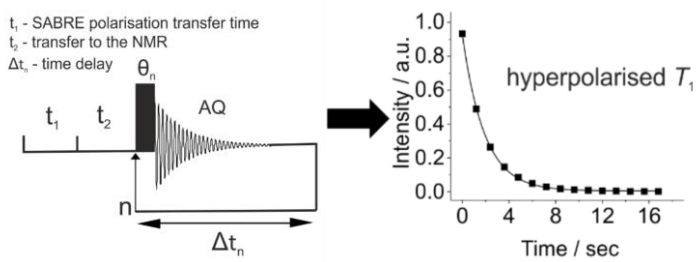
2) Transfer to Halbach array & shake for 45s.

3) Transfer to MRI & start acquisition.

4) Vacate hall and turn on photon beam.

## Pulse sequence:

[8]

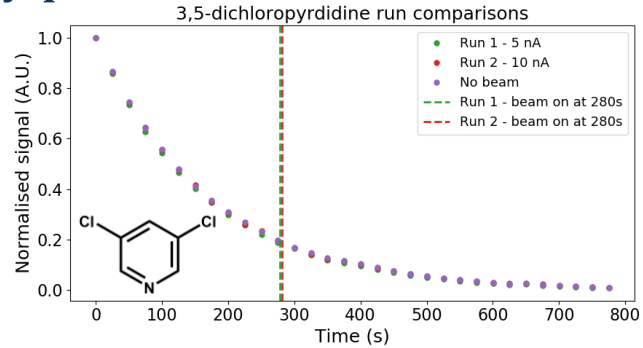


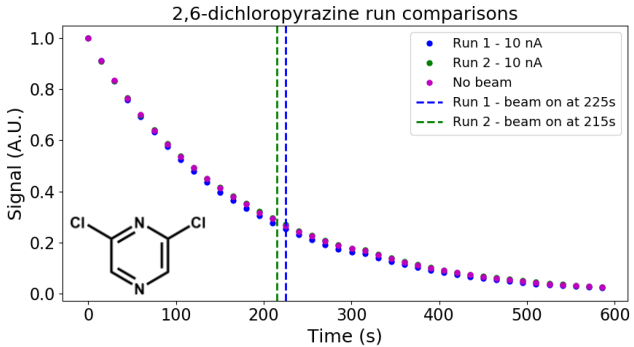

Variable flip angle pulse sequence uses many small flip angle RF pulses to sample the magnetisation.

[8] O. Semenova et. al, Anal Chem, vol. 91, no. 10, pp. 6695–6701, 2019.

# Results from MAMI

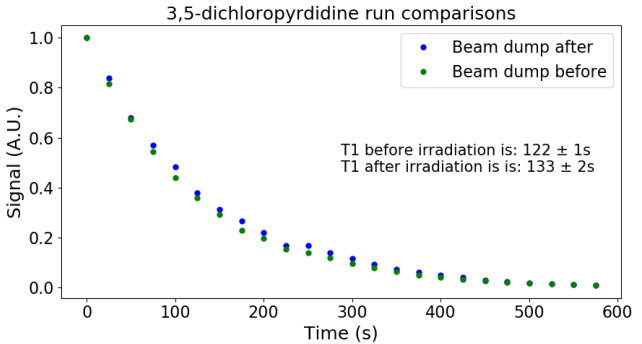
## Decay plots




→ No visible change in relaxation rate for runs with/without beam.

## High dose sample

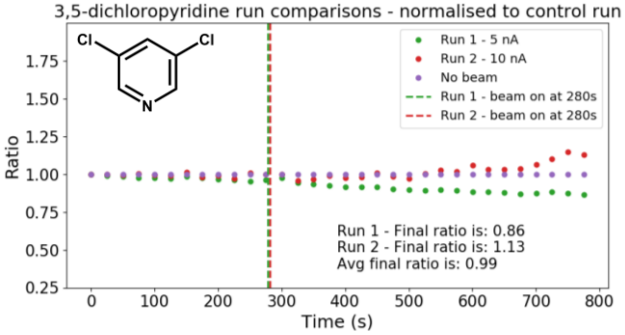


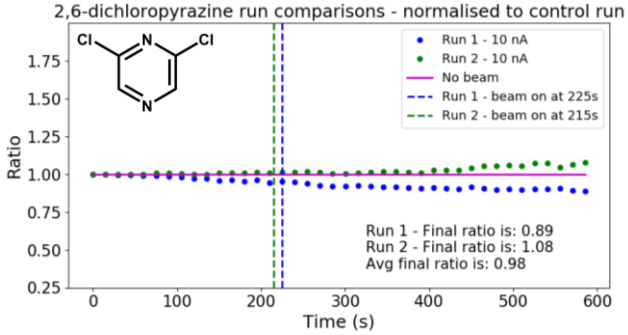

Irradiated in highest dose area of the facility - electron beam dump.

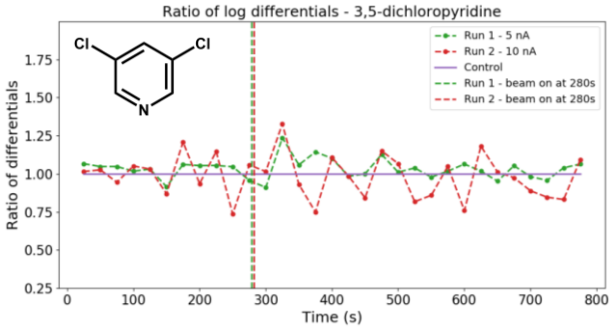
- $T_1$ increased by 9%.
- Polarisation yield decreased by 13%.
- No colour change.

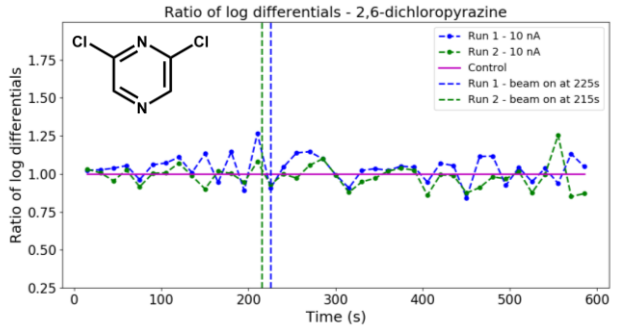
→ Polarisation catalyst not significantly affected.

# MAMI results continued




| Run | Mean ratio before beam | Mean ratio after beam |
|---|---|---|
| Run 1 | 1.02±0.05 | 1.04±0.07 |
| Run 2 | 1.00±0.02 | 0.97±0.15 |
| Avg | 1.01±0.07 | 1.01±0.10 |

| Run | Mean ratio before beam | Mean ratio after beam |
|---|---|---|
| Run 1 | 1.04±0.06 | 1.03±0.09 |
| Run 2 | 0.99±0.05 | 0.98±0.09 |
| Avg | 1.02±0.04 | 1.0±0.07 |

Ratio of polarized signal in beam-on and control measurements.

- Avg. ratio to control is close to 1.

Ratio of log. gradients of the beam-on runs to the control run.

Ratio of 1 shows same rate of decay - ratio of 0.5/2 shows half/double rate of decay.

→ No evidence for significant levels of beam-induced decay.

# Summary

SABRE is a **cost-effective** and easy to implement nuclear polarization technique which operates at **room temperature** in **weak fields** and may be able to overcome some of the issues facing DNP polarized targets.

→ Comprehensive substrate scope performed with **key substrates of interest identified.**

→ Optimisation of polarization yields undertaken with **>10% $^{1}$H polarization achieved.**

→ Relaxation studies performed to identify optimum running conditions.

→ First measurements on the **resilience of SABRE polarization** to an incident photon beam & effects of high accumulated dose.

→ Showed that polarization monitoring can be performed accurately on a **commercially available, low-cost** benchtop MRI.

# Acknowledgements

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CHyM Dec ‘23

Nuclear Physics Dec ‘23

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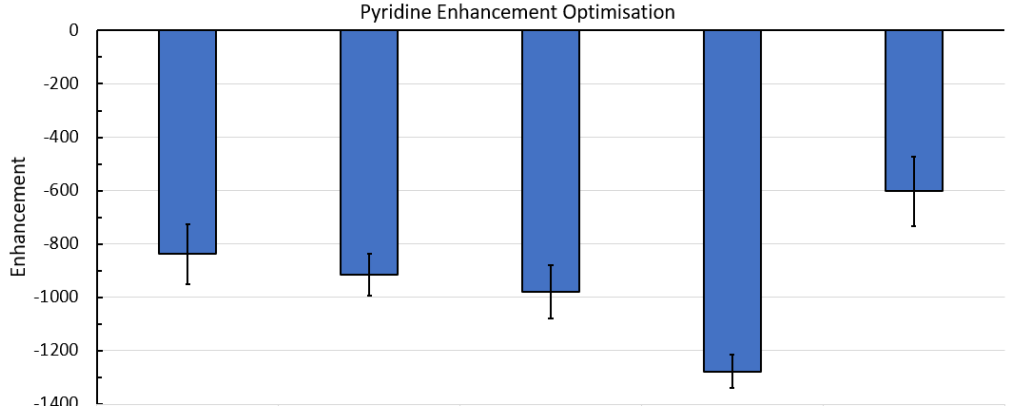
# Supplementary Slides

Joint APP, HEPP and NP Conference - April 2024

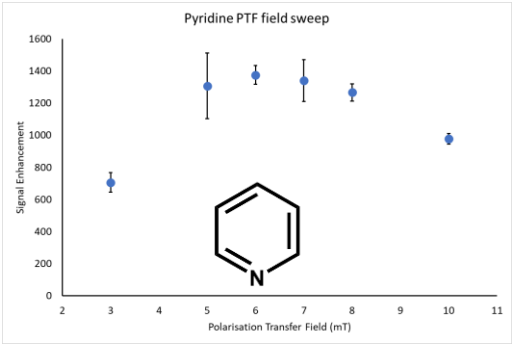
# Pyridine Enhancement Optimisation

Substrate of interest due to high polarizable proton fraction and high yields.

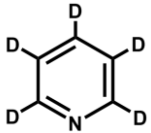



| | 5 equiv. Pyridine | 5/3 equiv. Pyr + 10/3 equiv. co-substrate | 5 equiv. Pyr w/ co-ligand | 5 equiv. Pyr w/ deuterated catalyst | 5 equiv. Pyr w/ co-ligand and deuterated catalyst |
|---|---|---|---|---|---|
| Enh | -838 | -915 | -980 | -1277 | -603 |

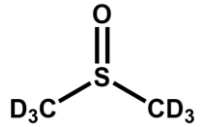
+ Deuterated co-substrate: Enh ↑
+ Co-ligand: Enh ↑↑
+ Deuterated catalyst: Enh ↑↑↑
+ Co-ligand and deuterated catalyst: Enh ↓



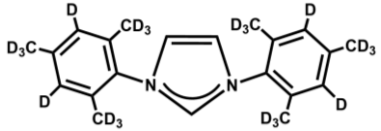

→ Optimum PTF found to be 6 mT for $^{1}$H.




Pyridine-$d_5$ co-substrate



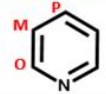
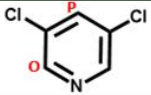

DMSO-$d_6$ co-ligand

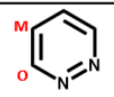
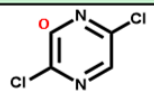
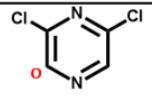



IMes-$d_{22}$ deuterated catalyst NHC

# Substrate comparison

Data from selected substrates under equal conditions (40 equiv. substrate, 5 equiv. DMSO-d6 co-ligand in DCM-d2).

| Pyridine | 3,5-Dichloropyridine | Pyrazine | Pyrimidine |
|---|---|---|---|
| $C_5H_5N$ | $C_5H_3Cl_2N$ | $C_4H_4N_2$ | $C_4H_4N_2$ |
| Polarisable proportion of protons (%) | | | |
| 11.9 | 4.1 | 9.5 | 9.5 |
| Average polarisation yield (%) [Total] | | | |
| 1.37±0.08 | 2.87 ± 0.02 | 1.82 ± 0.05 | 0.54 ± 0.09 |
| T1 relaxation const. (s) | | | |
| O/M/P = 41.2/39.5/37.0 | O/P = 69.4 / 112.6 | O = 42.0 | 1/2/3 = 69.5/49.8/37.8 |
|  |  |  |  |

| Pyridazine | 2,5-Dichloropyrazine | 2,6-Dichloropyrazine | 3,5-Dimethylpyridine |
|---|---|---|---|
| $C_4H_4N_2$ | $C_4H_2Cl_2N_2$ | $C_4H_2Cl_2N_2$ | $C_7H_9N$ |
| Polarisable proportion of protons (%) | | | |
| 9.5 | 2.7 | 2.7 | 15.5 |
| Average polarisation yield (%) | | | |
| 0.49±0.06 | N/A (Low) | 0.86+-0.03 | ~0.15 |
| T1 relaxation const. (s) | | | |
| O/M = 37.7/41.2 | O = 128.5 | O = 61.8 | O/M/P = 16.9/8.1/27.0 |
|  |  |  |  |

Trends seen:

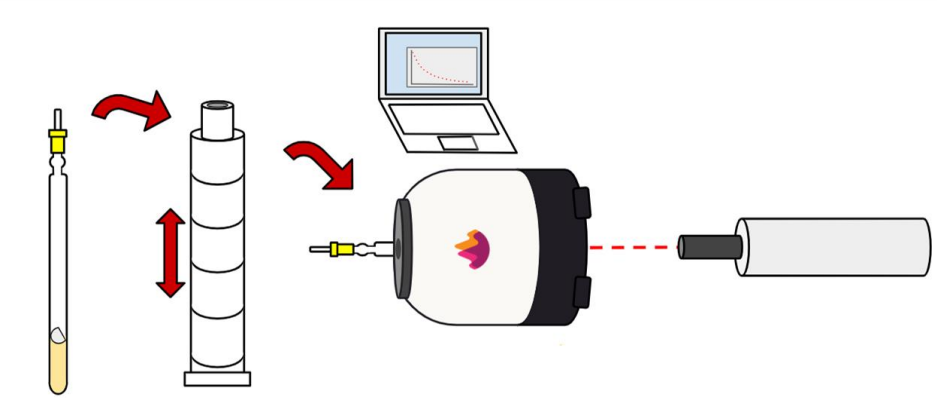
+ Methyl group: Polarizable protons ↑, Polarization lifetime ↓
+ Halogen: Polarizable protons ↓, Polarization lifetime ↑

→ Addition of low-$\gamma$ nuclei can reduce relaxation in hyperpolarized material.

→ Addition of halide/methyl groups can cause steric hindrance, especially in positions 2 & 6.

# Experimental procedure and pulse sequence:

## Experimental procedure:



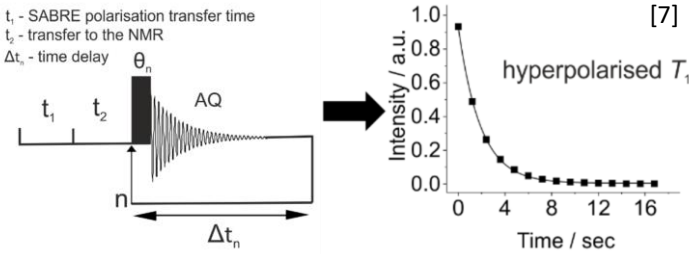
1) Prepare sample and pressurise to 5 bar.

2) Transfer to Halbach array & shake for 45s.

3) Transfer to MRI & start acquisition.

4) Vacate hall and turn on photon beam.

## Pulse sequence:




[7]

Variable flip angle pulse sequence uses small tip angle RF pulses to sample the magnetisation:

$$M_{z,n} = M_{z,n-1} \exp\left(\frac{-\Delta t_{n-1}}{T_1}\right) \cos\theta_n$$

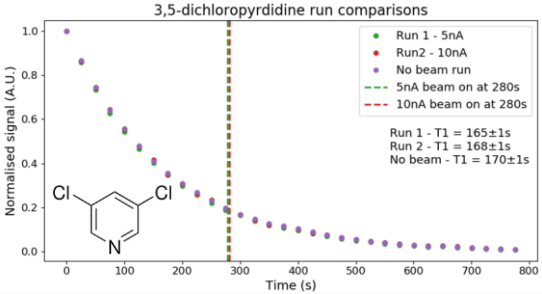
$$M_{xy,n} = M_{z,n} \sin\theta_n$$

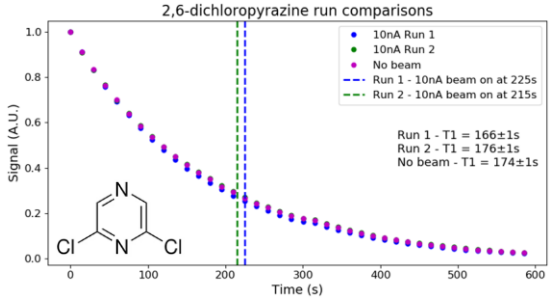
$M_{z,n}$ and $M_{xy,n}$ are the longitudinal and transverse magnetisation, $\Delta t_n$ is the delay following, and $\theta_n$ is the tip angle used for the $n^{th}$ scan.

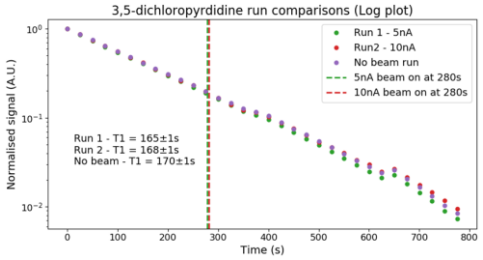
[7] O. Semenova, P. M. Richardson, A. J. Parrott, A. Nordon, M. E. Halse, and S. B. Duckett, "Reaction Monitoring Using SABRE-Hyperpolarized Benchtop (1 T) NMR Spectroscopy," Anal Chem, vol. 91, no. 10, pp. 6695–6701, 2019, doi: 10.1021/acs.analchem.9b00729.

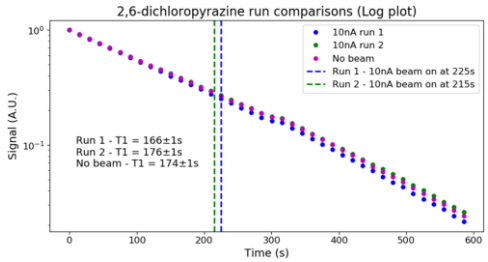
# Results

## Decay plots



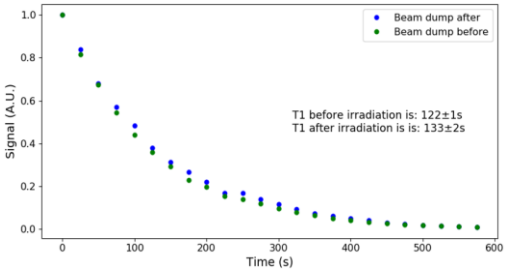




→ No visible change in relaxation rate for runs with/without beam.

## High dose sample




Irradiated in highest dose area of the facility - electron beam dump.

- T1 increased by 9%.
- Polarisation yield decreased by 13%
- No colour change.

→ Polarisation catalyst not significantly affected.