Radiation-detected Zero to UltraLow-Field Nuclear Magnetic Resonance (β-ZULF-NMR) and studies of NMR polarization techniques

Kadri Muuga

Supervisors: Prof. Magdalena Kowalska, Dr. Amy Sparks

August 23, 2023

Abstract

During my 8-week stay at CERN, I had the privilege to be involved in the VITO (Versatile Ion Polarization Technique Online) group that is part of ISOLDE to work on a project on radiation-detected NMR. The group's goal was to build a low-field β-NMR setup, that would make it possible to use NMR on radioactive isotopes with lower cost, portable equipment and significantly higher sensitivity than is possible with conventional NMR. I was involved in the experiments at CERN, Geneva hospital and the University of Geneva, looked into scientific literature to write overviews about how polarization techniques can be used for the group's future activities and helped with the construction of beamline at the ISOLDE experimental hall before the beamtime.

ISOLDE

ISOLDE is CERN's longest-running research facility that was connected to the cyclosynchotron (CS) in 1967. The main activity of ISOLDE is studying nuclear physics through experiments on unstable nuclei **[1]**. ISOLDE is connected to the Proton Synchrotron Booster, which provides a proton beam to create unstable isotopes for nuclear physics research. **[2]**

The VITO beamline uses optical polarization to polarize unstable nuclei and measure their asymmetric emission of β-radiation. Its applications are in studying the metal ion interactions with DNA and in very sensitive radiation-detected NMR studies. **[2]**

Nuclear Magnetic Resonance (NMR)

NMR is a very common nuclear probing technique used in Chemistry, Physics, Biology and Materials Science. NMR is based on the different energy levels of spin states in a magnetic field, as seen on Figure 1. Without any external magnetic field, all spin orientations are equivalent. However, if an external magnetic field is applied, the states split, and the energy difference between them is measured in an NMR experiment.

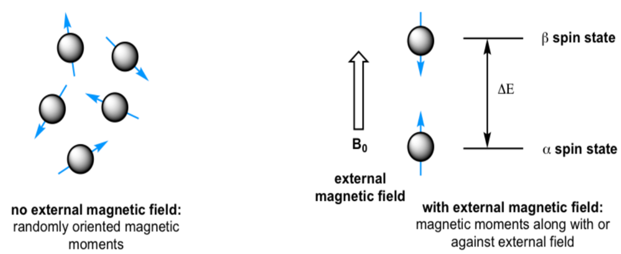

Figure 1. Energy state splitting of a nucleus with spin ½ **[3]**

The sensitivity of NMR techniques is closely connected to spin polarization levels. Polarization refers to the proportion of spins that occupy one energy state with respect to the other. For instance, all spins of the sample being in a "spin down" state would correspond to absolute polarization.

In a conventional NMR experiment, radiofrequency pulses are used to flip the spin states of the nuclei. Since this process raises the system to a higher energy state, the spins will relax back to achieve their equilibrium. As the spins flip, energy is released in the form of radiofrequency pulses, which are detected by a superconducting coil. If the sample is more polarized, more spins will be involved in relaxation and the signal is enhanced.

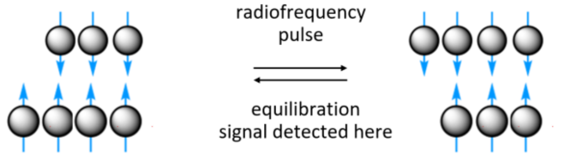

Figure 2. The NMR experiment

The main limit of NMR applications is its inherent low sensitivity. The energy difference between the spin states is typically small and gives nearly equal populations of spin states even at low temperatures and high magnetic fields. The populations are governed by the Boltzmann equation:

$$P(E) = \frac{N_\alpha}{N_\beta} = e^{-\frac{\Delta E}{kT}} \quad \textbf{(1)}$$

For example, the population difference of ^1H spin states is compared for magnetic field strengths 7.07 T and 11.75 T at 298K:

$$\frac{P\,(7.07\ T)}{P\,(11.75\ T)} = e^{-\frac{\Delta v \cdot h}{kT}} = e^{-\frac{(300-500)\cdot 10^6 Hz \cdot h}{k \cdot 298\ K}} = 0.9999678 \quad \textbf{(2)}$$

where $\Delta\nu$ the Larmor frequency difference, h is Planck's constant, k is Boltzmann's constant and T is temperature. This is also demonstrated schematically in Figure 3.

Increasing the magnetic field is one way to improve NMR sensitivity and raise polarization "by brute force", but there are other more effective techniques like optical pumping (used at the VITO beamline) **[4]**, signal-amplification by reversible exchange (SABRE) **[5]**, dynamic nuclear polarization (DNP) **[6]** and others. Aligning the spins in one direction can increase the sensitivity of NMR up to 10^5 times **[7]**.

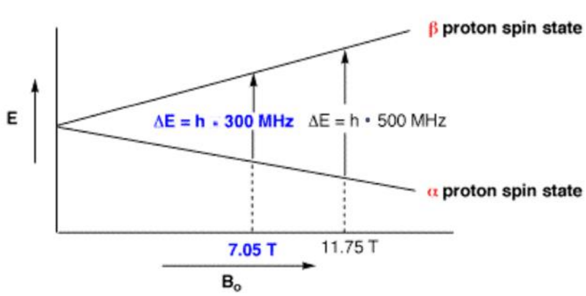

Figure 3. Energy splitting as a function of the magnetic field. The frequency corresponding to the transition between the spin states is proportional to field strength and magnetic moment **[8]**

β-NMR

β-NMR is a development of NMR that is used on radioactive nuclei. The detection is not done via an induced magnetization in an RF coil, but rather by asymmetric beta-decay of the particles due to the weak interaction which does not conserve parity (Fig 6,7). Beta-particles can be detected very efficiently (10^4 times enhancement compared to conventional NMR), and with optical polarization, the technique is up to a billion times more sensitive than conventional NMR. **[9]**

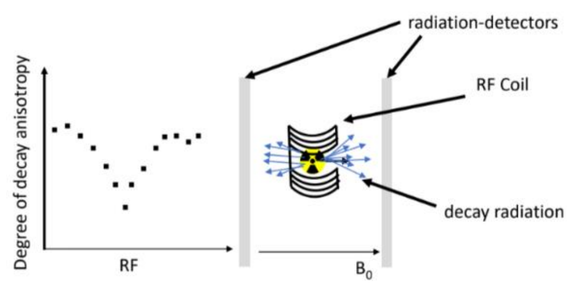

Figure 4. Detection of beta-decay asymmetry. Courtesy of J. Croese

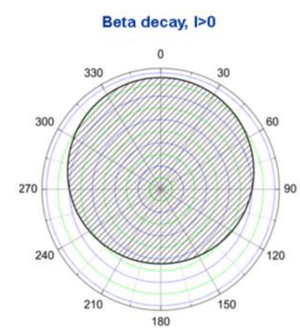

Figure 5. Angular distribution of β-emission of the polarized β-active nuclei. Courtesy of M. Kowalska

ZULF-NMR

Zero to UltraLow Field (ZULF) NMR is an NMR technique that operates in the microtesla regime.

High-magnetic field NMR magnets are widely used in science, but cost of the order of $1 million, often require low temperatures and high magnetic field homogeneity and are immobile. ZULF-NMR allows NMR equipment to be significantly cheaper and smaller by not using very strong magnets. However, low-field NMR requires the use of alternative polarization techniques and detection mechanisms, for instance, magnetic field sensors, to achieve sufficient sensitivity. **[7]**

β-ZULF-NMR

My group at CERN was focused on building a β-ZULF-NMR setup. The setup takes advantage of radioactive nuclei to combine the sensitivity of β-detection with SABRE-assisted ZULF-NMR. The potential is to extend NMR applications and make the technique cheaper and more portable.

Signal Amplification by Reversible Exchange (SABRE)

SABRE is a polarization technique that involves using the spin order of para-hydrogen to hyperpolarize the molecules in the sample. Para-H_2 is a form of hydrogen with the nuclear spins aligned in opposite directions. Para- and ortho-H_2 cannot interconvert without breaking the chemical bond between them and almost pure para-H_2 can be synthesized at low temperatures.

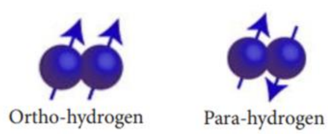

Figure 6. Ortho- and para-hydrogen **[5]**

SABRE needs a transition metal catalyst that facilitates the spin transfers without modifying the substrates chemically. In the experiment, para-H_2 is bubbled through the solution containing the substrate. The hydrogen molecules bind to an iridium catalyst and a spin flip of one of the H molecules occurs simultaneously with the spin flip of the substrate. Over time, the substrate molecules with flipped spin accumulate and the sample becomes hyperpolarized, as illustrated on Figure 7.

Part of my project involved looking into literature and writing an overview of the (bio-) molecules containing the isotopes ^{19}F, ^{15}N and ^{13}C that have been hyperpolarized with the SABRE technique. Being able to apply SABRE to biomolecules is the first step in being able to use them for β-ZULF-NMR.

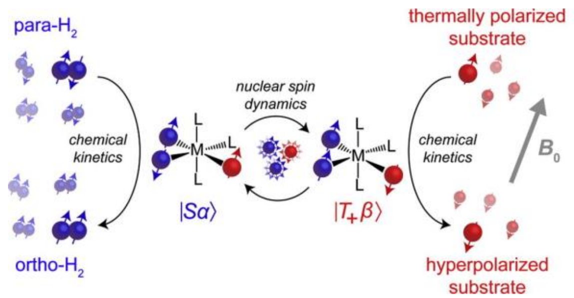

Figure 7. Illustration of the SABRE working principle **[5]**

Dynamic Nuclear Polarization (DNP) in Liquids

Dynamic nuclear polarization uses radical molecules and low temperatures to hyperpolarize the electrons in the sample and microwaves to transfer this polarization to the nuclear spin ensemble. It is a widely used method in solid-state NMR studies. Using liquids is desirable as the molecular motions average out the line broadening effects and most biological systems or molecules are in their natural state in solutions. However, the methods have their limitations. Liquid DNP can be done as a rapid melting process where the sample is hyperpolarized at a temperature of around 1-2 K, moved to a higher-field setup and rapidly melted before measuring the NMR spectrum. DNP can also be done directly on liquid samples, but the drawback is that the sample heats up and the sample size of only a few microliters is achievable. [**6**]

My role was to research how DNP had been applied in liquids for compounds containing ^{19}F and ^{15}N nuclei. ^{15}N was more commonly used, but there had been studies done on ^{19}F isotopes.

Experiments

I was involved in experiments at CERN, Geneva hospital and the University of Geneva. The goal of the experiments at the hospital was to test the β-NMR and SABRE setup with $^{13}NH_3$ molecules. $^{13}NH_3$ was produced at the hospital as a $^{13}NH_3OH$ solution in picomolar concentrations, which is commonly used for PET imaging. The experiments need to be done near the isotope production site as the half-time of $^{13}NH_3$ is 10 minutes. The β-decay asymmetry was monitored over time.

The goal of the experiments at CERN and the University of Geneva was to obtain reference measurements of stable isotopes with conventional NMR. At CERN, I was involved in setting up a high-field (~1.2T) NMR electromagnet. The goal was to be able to benchmark SABRE on stable isotopes with chemical shift resolution and measure their polarization before the transition to measurements under ZULF conditions.

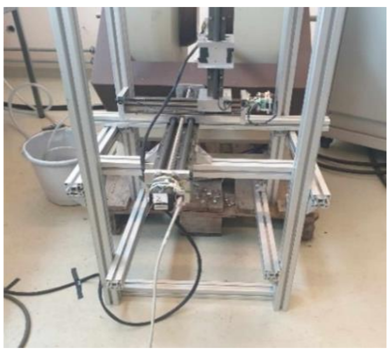

Figure 8. An illustration of being a summer student at CERN: I built a stand for the magnetometer.

The instrument on the stand (Fig. 12) is measuring magnetic field homogeneity over time. The measurements were needed to create a feedback loop with a variable resistor which alters the current to stabilize the field over time. I was using Python to clean and plot the field value data.

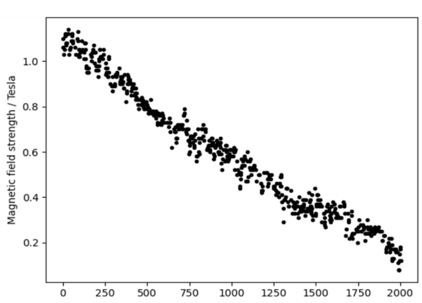

Figure 9. The magnetic field change with respect to time

In addition to being involved in the β-NMR project, I was working at the ISOLDE experimental hall with the setup of experiments before the beamtime. It was a valuable experience to work with the whole VITO team and see the amount of thought and planning needed to conduct the experiments on the beamline.

Figure 10. The experimental hall at ISOLDE

Conclusion

While being at CERN as a summer student, I have had the opportunity to work on both practical experiments and the theoretical side of polarization techniques. I appreciate having been able to contribute to the project on β-ZULF-NMR, participate in the group's discussions and be involved in constructing the experimental setup before the beamtime.

Acknowledgement

I would like to thank the members of the VITO group for creating a fun and supportive atmosphere, which has made for a memorable stay. More specifically, I would like to thank my supervisors Prof. Magdalena Kowalska and Dr. Amy Sparks for their support.

References

[1] Borge, M. J. G. and Blaum, K. *J. Phys. G: Nucl. Part. Phys.* 45 010301 (2018)

[2] Kowalska, M. "The many faces of ISOLDE", *epnews* 2021

[3] Lin, X. Organic Chemistry I *KPU Pressbooks* 2021

[4] Goodson, B. M. Nuclear Magnetic Resonance of Laser-Polarized Noble Gases in Molecules, Materials, and Organisms. *Journal of Magnetic Resonance* 2002; 155(2). https://doi.org/10.1006/jmre.2001.2341

[5] Barskiy DA, Knecht S, Yurkovskaya A V., Ivanov KL. SABRE: Chemical kinetics and spin dynamics of the formation of hyperpolarization. *Prog Nucl Magn Reson Spectrosc*. 2019;114-115. doi:10.1016/j.pnmrs.2019.05.005

[6] Plainchont, B., Berruyer, P., Dumez, J. N., Jannin, S., & Giraudeau, P. Dynamic Nuclear Polarization Opens New Perspectives for NMR Spectroscopy in Analytical Chemistry. *Analytical Chemistry*, 2018 90(6). https://doi.org/10.1021/acs.analchem.7b05236

[7] Jiang M, Bian J, Li Q, et al. Zero- to ultralow-field nuclear magnetic resonance and its applications. *Fundamental Research*. 2021;1(1). doi:10.1016/j.fmre.2020.12.007

[8] "Spin states, magnetic fields, and electromagnetic radiation", *orgchemboulder* 2011

[9] Kowalska, M. NMR on unstable nuclei. 2023 [Manuscript submitted for publication]