A Compact, Portable 4.7 T Driven NMR System for Reaction Monitoring.

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ABSTRACT

We have been using a newly developed 4.7 T (200 MHz ^{1}H operating frequency) cryogen-free NMR system which utilizes a high-temperature (~14 K) superconducting magnet cooled by a standard helium compressor, driven by a high stability power supply, and utilizing a new state-of-the-art single board spectrometer. The system is designed to be portable, allowing for rapid cooling and ramping of the magnet to field without the need for expensive cryogens or a trained engineer. We have been using this system, coupled with a microcoil flow probe to investigate a multitude of samples, ranging from traditional organic compounds to complex reaction mixtures. To date, primarily 1D ^{1}H NMR data on these samples has been acquired. We are working toward utilizing more sophisticated multi-dimensional gradient-based experiments on this system to provide additional information on reaction mixtures in both a “stop-flow” and flow-through mode. This system works well for reaction monitoring, as it provides intermediate resolution between lower resolution 60 MHz spectrometers and traditional higher-field superconducting spectrometers at 400 MHz and above. This poster will provide an overview of this new technology and demonstrate the data we are able to achieve.

INTRODUCTION

The heart of this new spectrometer is a 4.7 T (200 MHz ^{1}H frequency) high temperature (Tc ~ 110 K) superconducting (HTS) wire used to create the magnet. With the use of this HTS magnet, it is not necessary to use liquid cryogens to cool the magnet as is done in traditional NMR spectrometer designs. Rather, cooling for the magnet is achieved through the use of a standard helium compressor (as would be used in a cryoplatform) to deliver gaseous helium to a coldhead on the magnet which refrigerates to near the temperature of liquid helium. The typical operating temperature of the magnet is approximately 18 K, and this is maintained solely with the cryocooler. A second unique feature of this magnet is the ability of the instrument operator to quickly and easily ramp it to field without the need for additional engineering staff or maintenance equipment. Once the command is given for the magnet to be ramped to field, it is quickly (~5 min) brought to its operating magnet field and held at field by an external power supply. Should the need arise, the magnet can be quickly de-energized by the user.

The Compact NMRD Analyzer uses a standard (Bruker) sixteen-channel shim stack which fits into the 51mm room temperature bore of the 200 MHz HTS magnet. A new sixteen-channel RS2D shim power supply (2U rack-mount) works with the RS2D SpinIt software to provide computer-programmed shim currents (with optional current monitoring). Up to 500mA of current are available, as needed, for each shim channel. A standard Protasis CapNMR ICG probe is used for detection. This microcoil probe uses a fixed flowcell and typically does not require reshimming between samples (in the same solvent). Enhanced locking and drift correction were designed to stabilize the HTS magnet, which does not drift continuously downward like a traditional superconducting magnet, but rather oscillates with fluctuations in the power supply.

The NMR spectrometer is a modular design (RS^{2}D, Bischwiller, France), making use of a control PC running Spin-It software as well as NMRCube hardware, a compact field programmable gate array spectrometer. Currently, 100 W (proton) and 140 W (carbon) RF amplifiers (Tomco, Stepney, South Australia) are used in the spectrometer, although the output of these amplifiers is excessive and could be scaled back considerably. Several one and two-dimensional homonuclear experiments have been run on the system to date (proton, ^{1}H-^{1}H COSY). We anticipate running heteronuclear experiments (^{1}H-^{13}C HSQC, HMBC) in the very near future, as well as implementing gradients for gradient-based experiments.

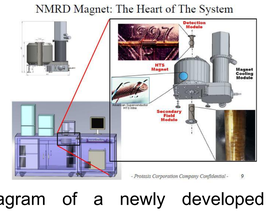


Figure 1. Diagram of a newly developed cryogen-free NMR spectrometer.

Figure 2 shows a picture of the 200 MHz cryogen-free NMR system in our lab. The probe (black) protrudes from the top of the magnet (red) on the right side of the system. The spectrometer control PC and boards, amplifiers, and magnet driver amp are contained within the body of the stainless steel spectrometer console.

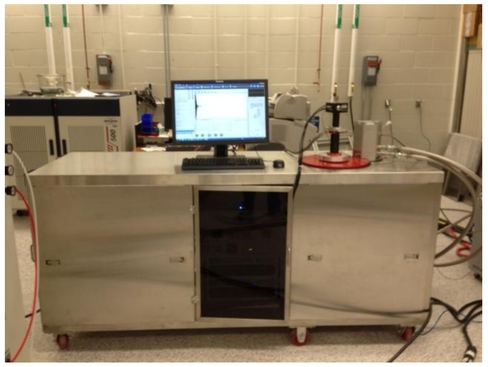


Figure 2. Photo of the new 200 MHz cryogen free NMR system installed and operational in our lab.

RESULTS

The NMR system was installed in our laboratory and shown to meet the key design specifications. These included a proton lineshape specification on chloroform in acetone of less than 1.5 Hz at half height (Figure 3) as well as an observed splitting of the anomeric proton in sucrose of greater than 20% with LB = 0.7 (Figure 4).

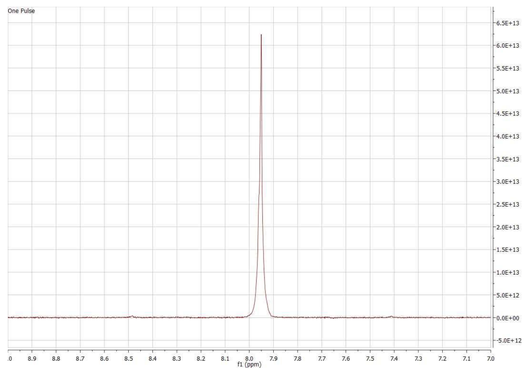


Figure 3. Lineshape spectrum (chloroform in acetone-d_6) acquired on the new 200 MHz cryogen free NMR system.

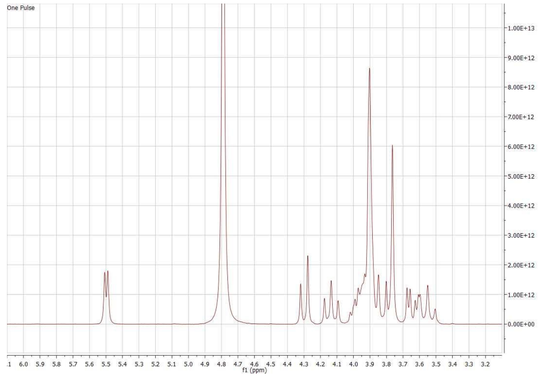


Figure 4. Sucrose sample in D_2O acquired on the new 200 MHz cryogen free NMR system.

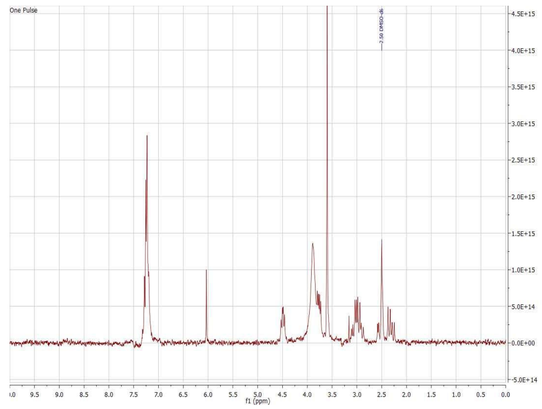


Figure 5. ^{1}H NMR spectrum of aspartame in DMSO-d_6 acquired at 200 MHz.

Figure 6 shows the ^{1}H-^{1}H COSY spectrum of aspartame acquired at 200 MHz on the new spectrometer. Gradients are not yet functional on the system, so this spectrum was acquired with phase cycling for cancellation.

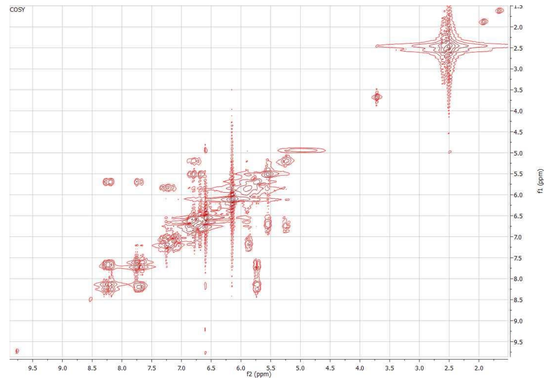
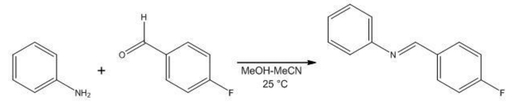


Figure 6. ^{1}H-^{1}H COSY spectrum of aspartame in DMSO-d_6.

One of the key attributes of the current setup is that it has been designed to be portable so that it can be moved to a variety of different labs for reaction monitoring work. The goal of this system is to be able to move from small-scale lab chemistry to larger scale reactors to be able to follow chemistry as it progresses through the drug development process

In order to test the ability to monitor ^{1}H spectra during a reaction, the reaction of p-fluorobenzaldehyde with aniline to the corresponding imine product (Scheme 1) was monitored.



Scheme 1. Reaction of p-fluorobenzaldehyde with aniline to form the corresponding imine product

Figure 7 shows the ^{1}H NMR data acquired at one time-point midway through the reaction of p-fluorobenzaldehyde with aniline to form the corresponding imine product. The aldehyde proton from the p-fluorobenzaldehyde is the furthest downfield peak at 9.9 ppm. This reactant is being consumed and the imine product resonance (8.5 ppm) is observed to increase in intensity.

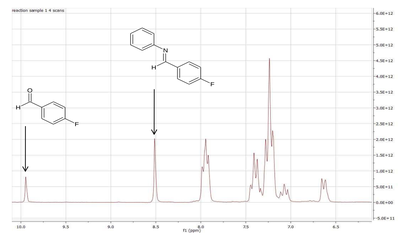


Figure 7. ^{1}H NMR spectrum of a single time-point during the reaction of p-fluorobenzaldehyde with aniline to form the corresponding imine product.

EXPERIMENTAL

NMR data was acquired on a 200 MHz (4.7 T) NMR spectrometer utilizing a cryogen-free magnet (HTS-110, Lower Hutt, New Zealand) making use of a high T_c superconducting wire (AMSC, Devens, MA) and driven by a high-stability (3 ppm), programmable, 200 A power supply (Danfysik System 8500, Jylinge, Denmark).

Cooling of the magnet to 14 K was achieved through the use of a Cryomech PT805 Pulse Tube cryorefrigerator (Syracuse, NY) supported by a CP2800 helium compressor. The helium compressor and high stability power supply were cooled with recirculating house chilled water.

NMR data was acquired using Java-based SpinIt software on NMRCube, a compact FPGA (field-programmable gate array) spectrometer (RS2D, Bischwiller, France). The networked software allows remote operation. Enhanced locking and drift correction were designed to stabilize the HTS magnet. Spectra were typically referenced to the solvent signal.

^{1}H NMR spectra were typically acquired into 32768 data points with a spectral width of 10,000 Hz. A 1 to 5 second relaxation delay was used for the acquisition of all spectra.

There is no sign of vibration-induced artifacts in the spectra from cold-head reciprocation and any environmental noise, such that the magnet does not use or require vibration isolation. Additionally, there is no evidence of any 60 Hz noise from the power source in any of the data generated so far.

CONCLUSIONS and FUTURE DIRECTIONS

The work presented in this poster demonstrates that the 200 MHz cryogen-free NMR system in our laboratory is fully operational and produces high-quality NMR data. The system has been ramped to and from field several times and continues to operate with no difficulties. Additionally, the magnet has been at field for several months continuously and has continued to perform flawlessly. In the event of the loss of cooling water or the failure of the cryo-cooler, the system has shut itself down without quenching as would be observed in the failure of a traditional NMR magnet.

We have begun the integration of this NMR system into our workflow, and see it filling a unique niche. It opens up many new avenues of research that have not been possible using traditional superconducting magnets. It is now possible to “take the NMR to the chemistry” as opposed to having to having to bring all NMR reaction monitoring work to the NMR laboratory. This could have applications for working with highly potent reagents which may require handling in a special processing suite, relocating the “open access NMR lab” based upon projects needs, among other applications. We continue to explore new applications for this system, from the application to traditional experiments to new applications in NMR reaction monitoring that have been opened up by the portability of the system.

Additionally, as cryogen costs continue to climb, the ability to operate a cryogen-free system eliminates the cost of both the cryogens and the time spent filling the magnet, allowing both to be used for more suitable purposes.