

Producing Safe Spin-Polarized Metabolites for Magnetic Resonance Imaging

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Abstract

There is significant interest in improved sensitivity and decreased measurement times for nuclear magnetic resonance and magnetic resonance imaging of small molecules, especially those with ^{13}C and ^{15}N spin labels. A source of spin polarizations of order unity is spin-exchange optical pumping, which produces ^{129}Xe with fractional polarization of order unity, about 10^5 higher than is achieved at equilibrium in high field. The research presented, is the development and testing of components of an apparatus intended to bring target molecules, such as acetic acid, into the close (near 1 nm) contact with hyperpolarized ^{129}Xe atoms as needed to effect rapid equalization of their spin temperatures through dipolar couplings. Specifically, an apparatus has been designed and is being built with the intention of rapidly depositing a gaseous mixture of xenon and the target molecule as a homogeneous solid under a strong magnetic field, then dropping the field strength to allow spin equalization through dipolar couplings followed by rapid production of a liquid sample of the target molecule at room temperature.

1 Background and Literature

1.1 Hyperpolarization Background

Nuclear magnetic resonance (NMR) is a widely used spectroscopic method in chemistry due to its chemical specificity and nondestructive character. These advantages are of even greater importance for in vivo applications, where they can be combined with magnetic resonance imaging (MRI) to localize specific molecules and chemical reactions within living organisms.

The principal barriers to extending these methods to diverse problems in biology and medicine are the limited sensitivity and long measurement times of NMR. The usual methods rely on equilibrium spin polarization of a few parts per million, which typically develops in 1-100 s for molecules in solution within the high magnetic field of the spectrometer. The resulting signals from abundant metabolites at millimolar concentrations are measurable in this way in seconds to minutes using naturally occurring protons. However, the complex mixture of

species present and the large background signal from water are impediments to the use of in vivo proton NMR. Labeling molecules of biological interest with ^{13}C greatly improves the chemical specificity, since this isotope has a large range of chemical shifts and a low natural abundance background. The metabolic fate of injected spin-labeled molecules can be followed over minutes to hours. This is the basis of a few diagnostic procedures[1], but these remain expensive due to the high cost of the labeled compounds and the lengthy examination time within the spectrometer.

A new approach to overcome the limited sensitivity and long measurement times is to align the nuclear spins of the molecules of interest to values of order unity just prior to their injection and NMR or MRI observation[2, 3, 4]. This provides a transient signal with an enhancement of up to about 10,000 fold, allowing 2D images to be obtained in less than 1 s and series of tens of images or spectra to be obtained in about a minute, the time scale of the spin-lattice relaxation time T_1 for favorable spin $\frac{1}{2}$ sites. To date, such hyperpolarization has been achieved using dynamic nuclear polarization (DNP), which requires microwave irradiation of the sample at about 1 K for several hours, and PASADENA (Parahydrogen And Synthesis Allow Dramatically Enhanced Nuclear Alignment) which works at liquid-state temperatures in seconds, but only for molecules that can be prepared by molecular addition of dihydrogen. Thus, there is a need for a method which is more general than PASADENA, but faster and more convenient than DNP.

One possible alternative to both PASADENA and DNP is transferring spin polarization from ^{129}Xe to ^{13}C nuclei in the molecule of interest. ^{129}Xe can be polarized by spin-exchange optical pumping[5] via polarization transfer from the electron spin of Rb to the nuclear spin of xenon. Polarizations achieved by these techniques (up to 70%) exceed room temperature thermal polarization of xenon in high field by the factor of around 10^5 . Different techniques have been developed to transfer polarization in solution from xenon to other nuclei[6] to improve the sensitivity. However, the efficiency of these techniques is intrinsically low and does not exceed a few percent. The work presented here seeks an efficient method to bring about polarization transfer in the solid state using direct dipolar couplings which exist between the spins of the target molecule and the nuclear spin of xenon. The end goal is to construct an apparatus that can be fed an input stream of hyperpolarized ^{129}Xe mixed with the target molecule in the gas phase and produce an aqueous solution of the target molecule in an NMR tube at room temperature.

1.2 Related Literature

Of interest to this project is previous work on freezing hyperpolarized xenon without losing polarization, as well as previous attempts to transfer polarization from ^{129}Xe to other nuclei by dipole-dipole couplings.

Both the gas and solid states of xenon have well-known and reasonably long T_1 values; however there is evidence that intermediate "slushy" phases may have much shorter T_1 values. This suggests that it is important that

the gas be given a very cold surface on which to condense so that it freezes immediately, minimizing time in intermediate phases. The conservation of spin polarization during freezing and thawing of hyperpolarized xenon was improved in Ruset's work with Hersman at the University of New Hampshire[7]. This group developed protocols for freezing hyperpolarized xenon gas for transport with minimal polarization loss. Although the freezing point of xenon is more than 80 K than that of liquid nitrogen, attempts to deposit xenon from the gas phase produce a porous material with unknown, but presumably reduced heat conductivity. Ruset solved this problem by using a large coiled condenser which he slowly immersed in liquid nitrogen so that new cold surface was constantly exposed. He found that that if he exposed $\sim 30 \text{ cm}^2/\text{minute}$ of fresh surface area at 77 K with a gas flow of 50 sccm, he could freeze and then boil off the xenon without measurable loss of hyperpolarization. However, if he increased the rate of gas flow, he began to lose polarization.

In 1993, Gatzke et al.[8] first demonstrated polarization transfer from hyperpolarized xenon by dipole couplings at low field. Using a mixture of xenon isotopes, polarization was transferred from ^{129}Xe to ^{131}Xe in the solid state under a mixing field of 100 G, achieving a 5% polarization of ^{131}Xe ; one-third of the initial polarization of the ^{129}Xe . They also measured the T_1 of bulk ^{129}Xe at 77 K as a function of field strength. They found that at fields as low as 200 G, the T_1 remained around 80 minutes, but once the field dropped below that value the T_1 fell rapidly, reaching around 8 minutes at 50 G.

Pines' group at the University of California at Berkeley attempted to extend this result to cross polarization from ^{129}Xe to ^{13}C nuclei in small molecules with limited success[9, 10]. Their ^{13}C polarization was only a few percent of predicted values in carbon dioxide and no measurable transfer was observed to carbon monoxide, acetylene, or trichloroethylene. They attributed this to incomplete mixing of the xenon and carbon dioxide used in their experiments and difficulty in getting this gas mixture to freeze uniformly, as well as unexpectedly short carbon T_1 values. While their experiments were largely unsuccessful, they are of some use in guiding thoughts on the matter of mixing and rapidly freezing xenon-organic gas mixtures.

Also of interest is work done in Jansch's group at Philipps University, Marburg on apparatus design for and results from a project to measure the T_1 of thin films of ^{129}Xe deposited on metal surfaces. Gerhard, et al.[11] measured T_1 of thin xenon films, observing a T_1 of approximately 15 min for a $1 \mu\text{m}$ film of xenon at 60 K and 2 T. Gerhard also provides some advice on the construction of tubing to transport hyperpolarized xenon. Specifically, tests were run to determine what hyperpolarization loss was incurred for streaming hyperpolarized xenon gas across several different surfaces. As expected, ferromagnetic materials led to significant polarization losses (90% for iron and two of three stainless steel samples), and metals with some ferromagnetic content (brass and the third stainless steel sample) led to lower but still measurable polarization losses. Copper, silver, gold, aluminum, molybdenum, tungsten, and solder (several alloys) were found to produce no measurable polarization loss. Multiple layers of Teflon tape over an iron sample only reduced the polarization loss to

60%. As a final note, the inhomogeneous field of a small, strong permanent magnet in direct contact with glass tubing reduced the polarization by 50%. No estimate for either B or its gradient is given, but this work raises the issues of avoiding transport through gradients at low field.

Jänsch's group also reports findings on the best ways to cool and deliver xenon samples. Gerhard, et al.[11] reports that xenon was stored as a solid in a liquid nitrogen reservoir and that bursts of xenon gas were released by temporarily removing the xenon to the presumably warmer vapor phase nearby. Stahl, et al.[12] discusses the necessary temperatures for depositing xenon and how to obtain them. Stahl found that liquid nitrogen cooling under reduced pressure proved insufficient for getting below 70 K and that it was necessary to resort to liquid helium cooling to get down to the 60 K temperatures needed to adsorb xenon on a surface at ultra-high vacuum. Dr. Natalia Lisitza and Dr. Eduard Chekmenev in the Weitekamp lab recently showed that it is possible to condense xenon "snow" on a surface by cooling that surface to 77 K and exposing it to room temperature xenon[13]. However, their set-up did not allow them to measure the pressures involved. Stahl suggests that a minimum pressure of at least 1 mbar is required to condense xenon on a surface cooled by liquid nitrogen at 77 K. This is consistent with the partial pressure of xenon, which is 1 Torr (1.3 mbar) at 100 K.

2 Spin Temperature Theory

In order to calculate the sort of efficiency one might expect for xenon-to-carbon polarization transfer, we need to consider the concept of spin temperature. The following explanation and calculations are based on a 1958 paper by Abragam and Proctor of the Centre d'Etudes Nucléaires de Saclay, Gif-sur-Yvette[14].

2.1 Theory for a System of Two Spin-1/2 Ensembles

The basic definition of spin temperature is based on the Boltzmann exponential law. At the macroscopic level, so long as the system is in a constant or near-constant DC field B_0 the population of spins P_i in energy level E_i is given by a Boltzmann distribution:

$$P_i = \exp[-E_i/k_B T] / \sum_i \exp[-E_i/k_B T] \quad (1)$$

or, in operator notation:

$$\rho = \exp[-\mathcal{H}/k_B T] / \text{Tr}[\exp[-\mathcal{H}/k_B T]] \quad (2)$$

where T is the temperature of the lattice and \mathcal{H} is the Hamiltonian of the spin system. One additional condition is that T_1 is sufficiently long that experiments of $\tau \ll T_1$ can be performed. This assumption is reasonable for both ^{129}Xe and ^{13}C . Additionally, while Abragam and Proctor consider both $I=1/2$ and $I>1/2$

systems, for brevity I will limit this summary to $I=1/2$ systems such as ^{129}Xe and ^{13}C .

Let us break up the Hamiltonian as $\mathcal{H} = \mathcal{H}^0 + \mathcal{H}^1$ where $\mathcal{H}^0 = \sum_i \mathcal{H}_i^0$ is the sum of the energies of the spins under B_0 and $\mathcal{H}^1 = \sum_{i < k} \mathcal{H}_{ik}^1$ is the sum of the energies from spin-spin interactions. The simplest case to consider, then, is the high-field case where spin-spin interactions can be ignored. In this case, since $\mathcal{H}^0 \gg \mathcal{H}^1$, the spin temperature is trivial:

$$P_+/P_- = \exp[-\gamma\hbar B_0/k_B T] \quad (3)$$

and it is clear that, when B_0 is varied slowly enough to be adiabatic in the quantum sense (i.e. P_+/P_- is constant), T must be directly proportional to B_0 . This essentially tells us that at high field there will not be any polarization exchange between xenon and carbon, which we could have predicted, since polarization does not conserve energy if the gyromagnetic ratios of two spins differ. This is also consistent with the high-temperature limit of Curie's Law ($P_+/P_- = CB/T$ where C is constant). More interesting is the question of what will happen when we lower the field to a value where the differences in Larmor frequencies is comparable to spin-spin couplings or lower. One might expect that lowering B_0 to zero would remove the need to conserve spin energy from B_0 and cause spins to randomize. If that were the case, then lowering the DC field to zero would be an irreversible process and destroy polarization. However, when B_0 goes to zero, the \mathcal{H}^1 term of the Hamiltonian becomes important and spin-spin interactions can prevent complete randomization. Experiment shows that in fact an adiabatic passage through $B_0 = 0$ does not change the observed polarization when one returns to high field.

Under low-field conditions in this many-body problem, the energy levels are quasi-continuous and no experiment is likely to involve passage slow enough to be adiabatic. Certainly, in this experiment we need to transition between high and low field fairly quickly and do not have time to even attempt an adiabatic passage. Furthermore, while in high field we can treat the carbon and xenon nuclei as separate and independent systems, each with its own spin temperature, this assumption breaks down in low field, where the spins will couple. Thus, the question that we need to consider for this experiment is: what will happen to the spin temperatures of the two systems initially at high field B_0 when they are brought into contact by a passage to low mixing field B^* ? Let us treat this generally for ensembles of two spin-1/2 nuclei with initial spin temperatures T'_i and T''_i . When the system arrives at B^* , the systems will have temperatures $T' = T'_i B^*/B_0$ and $T'' = T''_i B^*/B_0$. However, since at the mixing field the systems are coupled, it is the total energy rather than separate system energies, that is conserved. Thus we must calculate the new spin temperature from the total energy. Where N' and N'' are the number of atoms of each nucleus, we have:

$$\frac{1}{T} = \frac{(N'/T')\gamma'^2 + (N''/T'')\gamma''^2}{N'\gamma'^2 + N''\gamma''^2} \quad (4)$$

Letting $\mu = N''\gamma''^2/N'\gamma'^2$ we have:

$$\frac{1}{T} = \frac{(1/T') + (\mu/T'')}{1 + \mu} = \frac{B_0 (1/T'_i) + (\mu/T''_i)}{B^* (1 + \mu)} \quad (5)$$

so that if we return to B_0 we have spin temperature $T_f = B_0 T / B^*$. Then, if the initial magnetic moments were M'_i and M''_i , then we have final magnetic moments of:

$$M'_f = (M'_i + M''_i)/(1 + \mu) \quad (6)$$

$$M''_f = \mu(M'_i + M''_i)/(1 + \mu) \quad (7)$$

Notice that the exact value of the mixing field does not appear in these formulae; they are generally valid for any mixing field that is significantly greater than the local field produced by the nuclear spins themselves, but low enough that a common Zeeman spin temperature is reached at a rate fast compared to spin-lattice relaxation. Thus the details of the dynamics as a function of field are not critical to the predictions.

2.2 Calculations for a System of ^{129}Xe and ^{13}C Spins

Using these equations, the expected final polarization of the carbon nuclei can be found. Since xenon gas enriched in ^{129}Xe and depleted of ^{131}Xe will be used, it is reasonable to assume a $^{129}\text{Xe}:$ ^{13}C ratio of 2:1 with no competing spins present. Then, assuming that the storage field (~ 200 G) is high enough that spin relaxation is negligible over a few minutes and that the mixing field (~ 10 G) is low enough that complete mixing occurs during the 10 ms that the sample is in the mixing field, it should be possible to use the above model to calculate a theoretical value for the obtainable ^{13}C polarization. Initial carbon polarization is zero, and it is reasonable to assume an initial xenon polarization of 0.50 as this is obtainable with commercially available polarizers from Xemed. A xenon-to-carbon ratio of up to 10:1 is practical, but a ratio of 2:1 is used for illustrative calculations.

With these assumptions, the initial inverse spin temperatures β for the xenon and carbon are 16.1 J^{-1} and 0 J^{-1} respectively. This gives a final spin temperature for the system after mixing of 11.4 J^{-1} . Once the system returns to the storage field, the spin polarizations of the xenon and carbon are 0.35 and -0.32 (negative because the magnetic moments of xenon and carbon have different signs). The final carbon polarization of -0.32, 64% of the initial ^{129}Xe polarization is significantly higher than past experimental results for xenon-to-carbon spin transfer[9, 10, 13]. It should be noted, however, that Gatzke's ^{129}Xe to ^{131}Xe achieved $\sim 30\%$ of the initial polarization[8].

2.3 Calculation for a System of ^{129}Xe and ^{13}C Spins with ^{131}Xe and ^1H Added

The previous calculation assumed that ^{129}Xe and ^{13}C were the only NMR-active nuclei present. However, since the intended target molecules include small

organic molecules, protons will typically be present. In the specific case of acetic acid, there are four protons for every two carbon atoms. Furthermore, natural xenon is not pure ^{129}Xe . While ^{129}Xe is the only $I = 1/2$ nucleus, there is also a high-abundance $I = 3/2$ nucleus, ^{131}Xe . Hyperpolarization experiments with xenon are usually done with samples enriched in ^{129}Xe and depleted in ^{131}Xe , since quadrupole relaxation of ^{131}Xe causes it to lose polarization relatively rapidly. However, these samples are not completely free of ^{131}Xe ; for example Bowers used xenon with a $^{129}\text{Xe}:$ ^{131}Xe ratio of 67:1 while Gatzke worked with a ratio of 27:1[10, 8].

Unfortunately, it is not entirely clear what the ^{131}Xe - ^{129}Xe mixing field was. Gatzke’s study of ^{129}Xe relaxation and ^{129}Xe -to- ^{131}Xe spin transfer suggests that, at 77 K, transfer may begin as high as 150 G, though complete mixing probably requires a lower field[8]. In comparison, Bowers’s study of ^{129}Xe -to- ^{13}C transfer after deposition from the gas phase used mixing fields as high as 35 G without decrease in spin transfer[10].

In order to calculate the effects of mixing with protons and ^{131}Xe , additional calculations were done by extending equation 4 to three- and four-nucleus cases. The acetic acid C:H ratio of 1:2 was assumed and ^{131}Xe relaxation due to quadrupole interactions was assumed to be negligible during the short mixing period. This last assumption seems reasonable based on a measurement of $T_1 = 1$ s for ^{131}Xe in solid state at 77 K[15]. However, initial ^{131}Xe polarization was set at zero since the sample would be expected to have relaxed by quadrupole interactions before mixing. Since it is not known what $^{129}\text{Xe}:$ ^{131}Xe ratio we will be able to obtain from suppliers, Gatzke’s ratio of 27:1 was used. With the addition of protons, the final carbon polarization was significantly reduced. Using a Xe:C ratio of 4:1, the final polarization is -0.06 (12% of initial ^{129}Xe polarization); using a less-likely but still plausible ratio of 8:1, the final polarization is -0.10 (20% of initial ^{129}Xe polarization). These numbers are not significantly altered by the inclusion of ^{131}Xe .

3 Overview of the Apparatus

The basic goal of this project is to produce an apparatus that can accept as input a gas-phase mixture of a small metabolite and hyperpolarized xenon, freeze the mixture homogeneously at high field, drop the field to allow spin temperature equilibration, and then warm the sample to room temperature, boiling off the xenon and delivering the sample as a biologically-ready aqueous solution at room temperature. The major unsolved problem in achieving this is finding a way to deposit the xenon-metabolite mixture that both is rapid enough to prevent significant xenon relaxation and results in a sufficiently homogeneous mixture for efficient spin temperature equilibration to occur. The chosen approach to solving this problem is to deposit the mixture on a liquid-nitrogen cooled condenser, the surface of which will be scraped off at a frequency of around 1 Hz. Based on Ruset’s work on freezing xenon, it seems likely that the “snow” produced when xenon is deposited from the gas phase on a 77 K surface is a poor heat conductor

and that as the layer of snow grows, the surface temperature soon rises far above 77 K, resulting in slower freezing and significant loss of spin through relaxation. Regularly scraping the snow off the surface of the condenser should maintain a surface temperature sufficiently close to 77 K for xenon to deposit promptly to a solid with negligible spin relaxation during the process.

The general design for the apparatus was drawn up with these goals in mind. In order to rapidly deposit the xenon-acetic acid mixture as a solid inside a magnetic field, a cold finger using a cryogenic coolant is needed. It is necessary that the condensation step take place under vacuum to avoid condensation of air along with the xenon-acetic acid mixture. The need for vacuum is one of the two primary constraints on the apparatus, the other being the need to maintain a >200 G B-field over any part of the apparatus which will contain solid xenon in order to maintain long T_1 values in the sample. This field needs to be able to be shut off for the spin-temperature mixing step, but it also needs to be maintained for tens of minutes during deposition. To avoid the difficulties of operating a 200 G electromagnet in a vacuum for an extended period, it was decided to use a Halbach array permanent magnet to produce the high field needed during condensation, and then to drop the sample into a lower-field Helmholtz coil outside of the vacuum to obtain the lower field needed for dipole-dipole coupling to occur. Since the magnet will not need to operate in vacuum or fit into the vacuum bell jar, it has proved possible to adapt a Helmholtz coil already present in the Weitekamp lab for this purpose.

In order to maintain a vacuum over the entire setup, the apparatus will be built on an aluminum plate underneath a bell jar. To isolate the liquid nitrogen from the vacuum and the target molecules; it will be introduced—and gas will be removed—through copper tubing going through the base plate. The xenon-acetic acid mixture will be introduced by another tube through the base plate. It will be freely released into the bell jar through a nozzle surrounding the cold finger, but the total amount (< 10 mmol) will be small enough to avoid producing a positive pressure in the bell jar.

The condenser for the xenon-acetic acid mixture will consist of a tungsten condenser, connected to a reservoir of liquid N_2 . As the sample is condensing, a copper scraper will rotate around the condenser, scraping the condensed sample into an NMR tube. This will serve to keep the the layer of condensed gas thin, allowing for good conductivity so that it will rapidly reach 77K and neither have time to diffuse and segregate nor to relax rapidly in an intermediate slushy state. Both the condenser and the NMR tube will be within a Halbach array to maintain the xenon at high field until all of the sample has condensed. At this point, the NMR tube will be dropped into the Helmholtz coil, which will provide a field of 200 G. The field will be dropped to ~ 10 G for ~ 10 ms, then returned to 200 G. Warm water will be added through the NMR tube cap to warm the sample to room temperature and dissolve it in aqueous solution. The scraper will be turned by an electric motor inside the bell jar but well away from the Halbach magnet.

Using a 3-D computer-aided design program called Minos, a three-dimensional line drawing of the apparatus (Figure 1) has been created. This step was par-

Table 1: feedthrough Coordinates

feedthrough	Center	Height Above	Radius Above	Height Below	Radius Below
liquid nitrogen	x = 0 y = -290	352	88	532	56
xenon	x = 0 y = +290	352	88	532	56
power	x = -288 y = -40	352	88	24	128
thermocouple	x = -290 y = +110	288	56	192	56
vacuum pump	x = -290 y = +185	96	8	499	8
vacuum gauge	x = -290 y = -185	96	8	499	8

(All distances given in 1/64"; heights are above and below the bottom of the base plate.)

ticularly important because fitting all of the necessary feedthroughs into the limited space available in the bell jar was a delicate task, especially since it was necessary to make room for the Helmholtz coil 3 cm below the base plate (as explained in Section 4.3)

4 Magnet Set-Up

While using a single magnet for the entire experiment would be mechanically simpler, there are two significant benefits from the decision to use a two-magnet system. First of all, a two-magnet system means that the Helmholtz coil does not have to operate in vacuum. Since the sample deposition process will likely take around ten minutes (Section 5.2) and the magnet needs to operate at >200 G during the process, keeping a Helmholtz coil—even a water-cooled Helmholtz coil—from overheating in vacuum would be a significant challenge. Secondly, using a permanent magnet during the deposition phase means that a much stronger field—possibly as great as 1 T—can be maintained during deposition. While it is not clear that a stronger field will have much influence on the xenon T_1 [8], using a 1 T field will make it possible to do in-situ NMR of the condenser and the sample collection tube during deposition. It is anticipated that this will be useful for trouble-shooting, and to confirm that the xenon is not unduly relaxing during the deposition process.

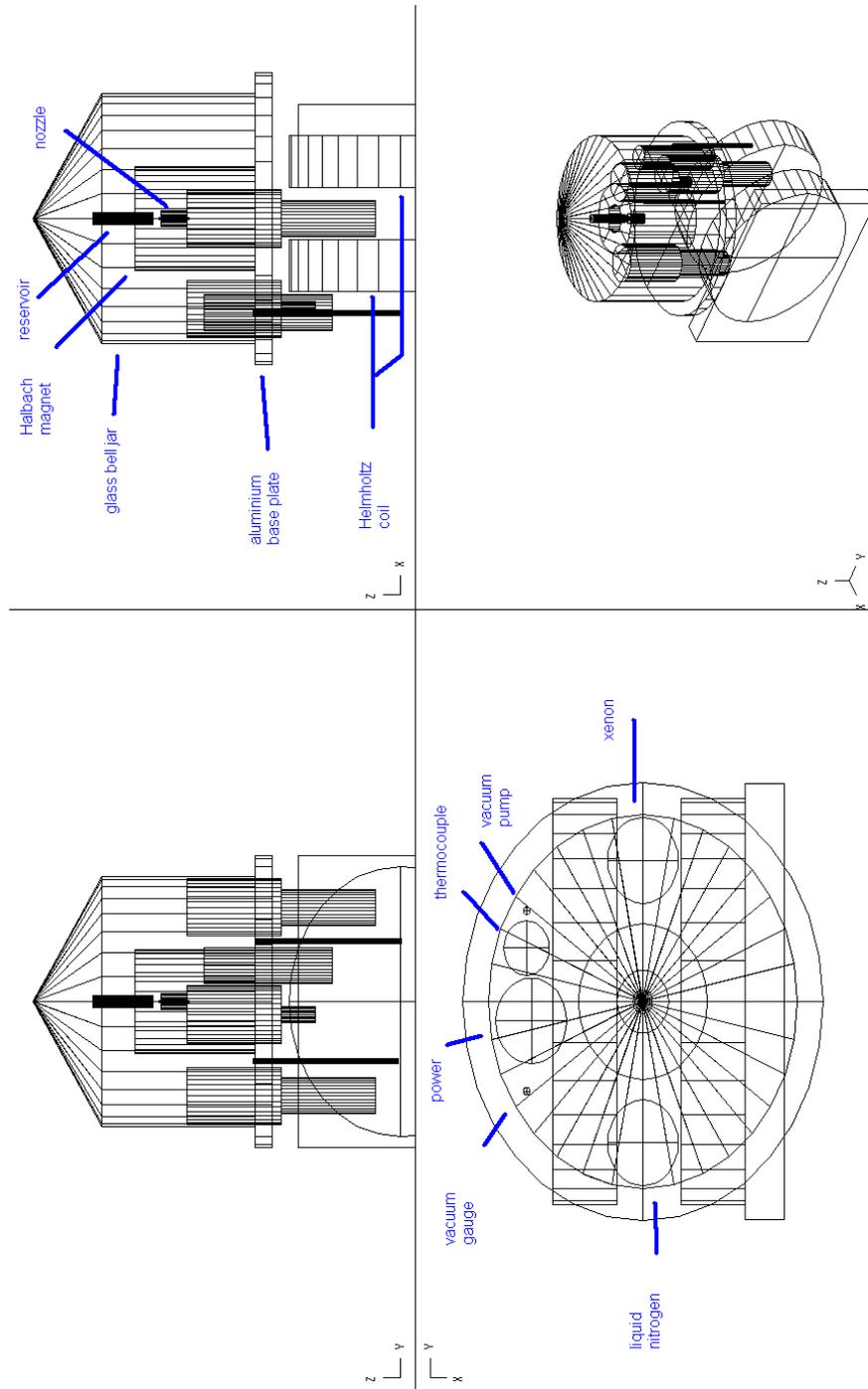


Figure 1: 3-D CAD Drawing of Apparatus

4.1 Helmholtz Coil

To provide the variable magnetic field needed for spin-temperature mixing between ^{129}Xe and ^{13}C , a Helmholtz coil will be used. The coil in question was constructed for an unrelated past project, but is sufficiently large and capable of providing the needed field strength over a sufficiently large area. The two coils are separated by 6.5 cm and each coil is 6.5 cm thick. The inner diameter is 20 cm and the outer diameter is 33 cm. The total resistance of the coil was measured at 11.2 Ω , with the two coils separately measured at 5.8 Ω and 5.9 Ω . The magnet is water-cooled and was designed to produce fields up to 700 G with a current of 10 A for extended periods. The maximum field as a function of current was measured at ~ 70 G/A using a hand-held gaussmeter. At the radius of the coil, down the central plane of the magnet, the field was around 40% of the maximum field. The maximum negative field was achieved on the central plane at a radius of 19 cm.

A study done at Princeton[8] on the T_1 of hyperpolarized solid ^{129}Xe at 77 K and different field strengths suggests that T_1 of xenon under these conditions does not start to drop off significantly until the field drops below 200 G and that the T_1 is ~ 80 minutes at that field.

The central region of the magnet, where the field is at least 80% of maximum, appears to be large enough to contain the sample. Based on this, it is hypothesized that a field of 250 G in the Helmholtz coil should be sufficient to maintain polarization. If this is the case, a maximum field of 320 G should suffice, requiring a current of 4.6 A and implying a maximum negative field of -32 G. Even if the entire interior of the coil is needed, which seems unlikely, a maximum field of 625 G (within the design specs of the magnet) should be sufficient, requiring a current of 9 A and producing a maximum negative field of -63 G.

Because the Helmholtz coil has had some problems in the past with short-circuits and insulation burn-throughs at high current, it has been decided that, to avoid risk of damage to the coil, it should not be operated at more than about 420 G (6 A) unless it becomes clear that doing so is necessary. However, it appears that this upper bound should be sufficient to produce the necessary field. An HP 6675A programmable power supply was found which seems capable of providing the necessary voltage and current to operate it. This is the power supply that was used in testing the field-to-current ratio and characterizing the shape of the field.

4.2 Halbach Magnet

The most significant component of the apparatus which has not yet been purchased is the Halbach magnet for the condenser. There are a number of conflicting requirements for this magnet. An inner diameter of at least 5 cm is desired to allow room for the condenser, nozzle, and possibly for an NMR coil to allow in-situ hyperpolarization measurements. To allow room for feedthroughs and other attachments on the plate outside of the magnet, the magnet's outer diam-

eter needs to be not much more than 13 cm or so. Finally, the magnet's height is limited to around 18 cm by the need to fit components on top of it within the bell jar. Besides physical constraints there are requirements for the magnetic field. It must fall off slowly enough that it can cancel the negative field outside the Helmholtz coil: since the maximum for this field is about 50 G at 2.5 cm below the bottom of the Halbach magnet, the Halbach magnet's field strength at this point should be around 100 G or so. At the same time, though, it needs to drop off fast enough that turning off the Helmholtz coil will drop the field to as little as 10 G in the central area of the coil to allow for spin temperature mixing. Also, in order to allow NMR to be conducted in the Halbach magnet, a field of nearly 1 T with a homogeneity of 100 ppm or better in a volume with a diameter of 5 mm and a height of 25 mm is desired. Discussions are currently underway with several magnet manufacturers regarding the manufacture of such a magnet.

4.3 Transferring the Sample

The need to transfer the sample between the Halbach magnet and the Helmholtz coil is an aspect of using a two-magnet system. It is necessary to arrange the locations and field characteristics of the two magnets so that the Halbach magnet will make a negligible component to the field at the core of the Helmholtz coil (so that shutting off the coil for mixing effectively shuts off the field there) while at the same time ensuring that the field on the path the sample traverses between the two magnets never falls too low or passes through zero.

Initially, the magnetic modeling program Radia[17] was used to model the fields of various types of Helmholtz coils and Halbach magnets. Once it was determined that the two-magnet design was practical, a Helmholtz coil already present in the Weitekamp lab was tested and found to be acceptable for the purpose. The measured field characteristics of that magnet are discussed in Section 4.1. As a result of the decision to use the preexisting Helmholtz coil, one of the criteria in selecting a Halbach magnet is field properties that allow us to use it with the Helmholtz coil to produce a field with the properties discussed in the previous paragraph.

While a supplier and a design for the Halbach magnet have not been settled on, some discussions with manufacturers have taken place. Specifically, preliminary plans for a Halbach magnet were developed in discussion with Aster Enterprises, Inc. of Acton, MA. For a Halbach magnet 15 cm in height, 13 cm in outer diameter, and with a clear inner bore of 5 cm, they supplied the field strength plot in Figure 2. The field properties of the Helmholtz coil have been measured with a gaussmeter and it was determined that the maximum negative field produced by the coil was 10% of the maximum positive field, and was produced in a ring with a radius approximately 2.5 cm greater than that of the coil. Thus, if the maximum field for the coil is set at 500 G—an upper limit on what is safe for the magnet; no more than 320 G should be needed—the maximum negative field will be 50 G at a point 2.5 cm above the top of the coil. To prevent the sample from falling through a field of less than +100 G,

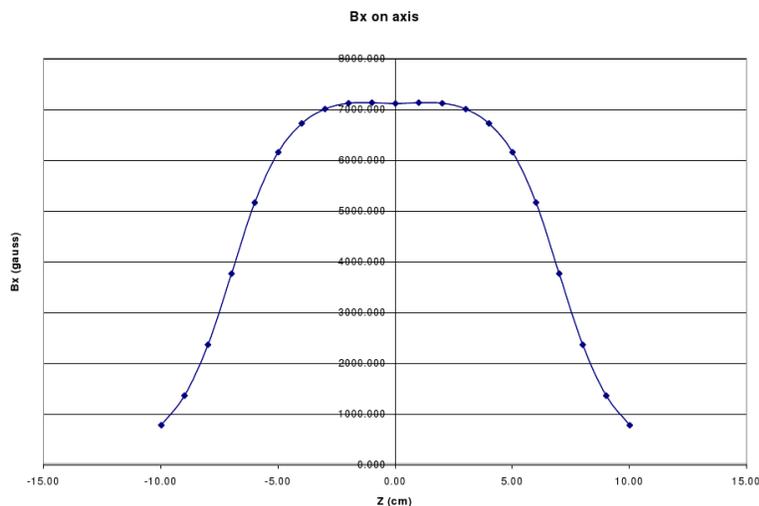


Figure 2: Halbach Magnet Field Strength Plot

the Halbach magnet needs to have a field strength of at least 150 G at a point 2.5 cm above the top of the coil. Based on the plot in Figure 2, it appears that 500 G occurs at a distance from the center of about 11 cm and 200 G occurs at around 12 cm. Of this distance, 7.5 cm are taken up by the bottom half of the Halbach magnet, and another 2.5 cm are taken up by the aluminum base plate. This suggests that having the Helmholtz coil 2 cm or so below the base plate should meet these criteria for B along the sample's path. As such, the plan outlined in Figure 1, with a distance of 1" (2.54 cm) between the top of the Helmholtz coil and the bottom of the plate, is reasonable, especially since it leaves about 1.5 cm of room to bring the coil closer if so desired.

5 Sample Handling Set-Up

While magnet issues have been important, the sample handling system has probably been the most difficult part of this project to design, due to the fact that it is the part where the literature provides the least guidance. The basic goals have been to design a system that maintains xenon polarization, that keeps the mixture of xenon and target molecule homogeneous, and that can process the sample rapidly (especially for those parts of the handling that occur after polarization is transferred to the target molecule).

5.1 Liquid Nitrogen Reservoir and Condenser

The condenser set-up consists of a glass liquid nitrogen reservoir and a tungsten rod, the upper half of which is inside the reservoir. This allows the exposed

rod to act as a condenser thin enough that xenon scraped off of it will fall into the mouth of a standard 5 mm NMR tube while still cooling the condenser by direct contact to liquid nitrogen.

The design of the liquid nitrogen reservoir is fairly tightly constrained, given that it must be short enough to fit between the Halbach magnet and the top of the bell jar and, at the same time, narrow enough that a bevel gear to turn the scraper can use it as an axle, all while holding enough liquid nitrogen to keep the condenser at a constant 77 K. The reservoir was designed with a 10 cm height constraint, based on an estimated height of 15-20 cm for the Halbach magnet. Leaving 4 cm for the nitrogen in and nitrogen out connections and the space between them, this gives a maximum reasonable height for the reservoir of 6 cm. The o.d. of the reservoir was set at 1.5 cm as this seemed to be the widest reasonable i.d. for the bevel gears. Finally, since the liquid nitrogen feedthrough requires the nitrogen in and nitrogen out tubes pass through the base plate as one unit, it is much preferable to have them attach to the nitrogen reservoir on the same side.

Using a height of 6 cm but an i.d. of 1.0 cm (from an o.d. of 1.5 cm) gives a volume of 4.7 mL. Using basic thermodynamics, it is possible to calculate the cooling power of a certain amount of liquid nitrogen. Liquid nitrogen has a density of 0.807 g/mL and a specific heat of vaporization of 199 J/g. Thus, vaporizing all of the liquid nitrogen in a 4 mL reservoir would require 640 J. The xenon sample releases 150 J by condensing from a solid at liquid nitrogen temperatures to a gas at room temperature (see Section 5.3.2). This calculation is conservative: while removal of 150 J would be needed to freeze the xenon, it is not desirable to boil off all of the liquid nitrogen, and, if necessary, liquid nitrogen can be added continually to keep the level in the reservoir constant. Tungsten has a heat capacity of 2.6 J/mL-K, and a tungsten rod condenser 3 mm in diameter and around 10 cm tall has a volume of 0.5 mL of tungsten. This means that without heat flow from the nitrogen, the tungsten would have to increase in temperature by about 115 K to provide the 150 J needed to cool and freeze the xenon, which is clearly unacceptable. From these calculations, it is clear that pre-cooling the condenser is insufficient—nitrogen boil off in the reservoir is needed to keep the condenser cold—but that a 4 mL reservoir is reasonable and that an even smaller reservoir would probably be acceptable.

Since copper wire seems to be the best choice for the scraper—it is stiff, easily obtainable, and non-ferromagnetic—a different metal is needed for the condenser to avoid pitting as the scraper rubs against the condenser[18]. Tungsten welding electrodes, easily obtainable in the desired size, are non-ferromagnetic and non-radioactive, and so were selected for the purpose. Pure tungsten welding electrodes, catalog no. 8000A84 (1/8" (0.3 cm) diameter, 6 1/2" (16.5 cm) long), were purchased from McMaster-Carr Supply Company of Elmhurst, IL. W

A photo of the condenser/reservoir set-up can be seen in Figure 3.

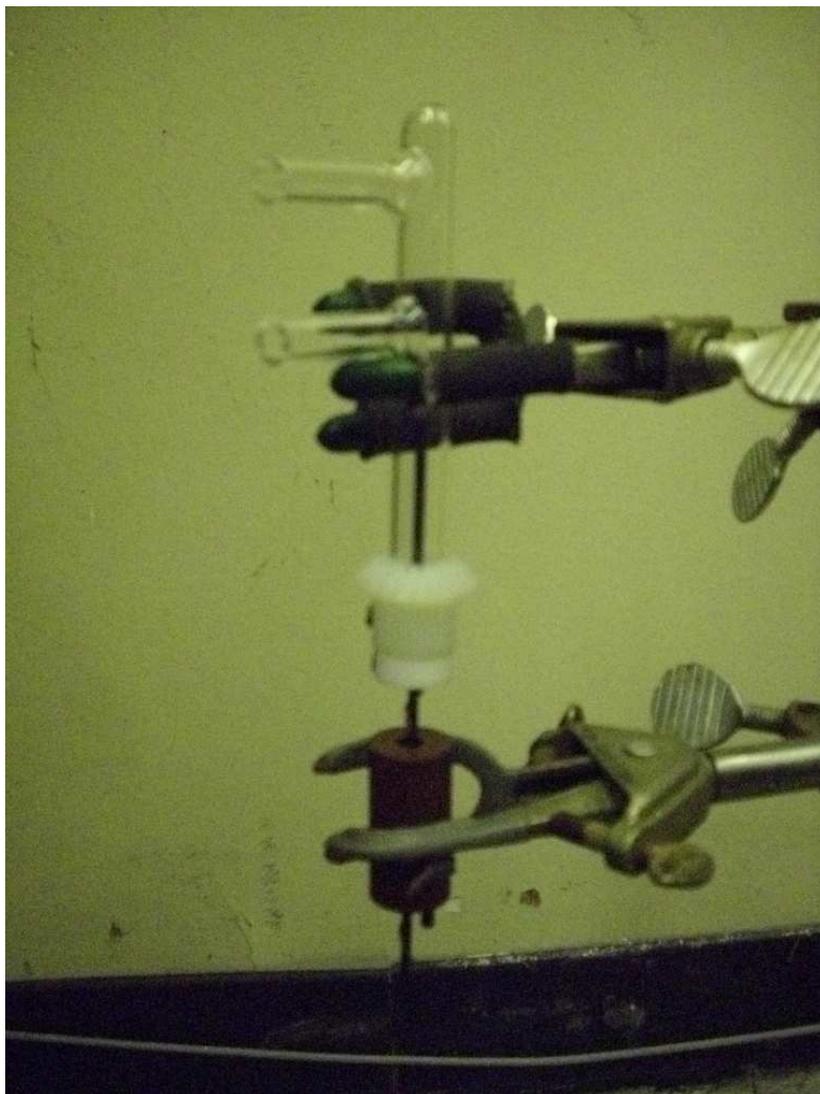


Figure 3: Photo of Condenser/Reservoir Set-Up

5.2 Nozzle

One of the primary interesting challenges in this project is developing a mechanism for creating a homogeneous solid mixture of xenon and the target molecule. While the proposed scraper system should allow rapid freezing and prevent the xenon and target molecule from segregating by diffusion, it is still necessary that they be sprayed evenly over the surface of the cold finger at the proper rate for the scraper to keep the ice from becoming too thick. In order to allow this, calculations have been done to determine an optimal flow rate and a special nozzle has been manufactured by the Chemistry Department machine shop.

The first issue to consider is how quickly the gas mixture should be deposited on the cold finger. If the condenser is 3 mm in diameter and 3 cm long, it has about 2.5 cm² of surface area. Assuming a scraper speed of 5 Hz, this is 12.5 cm² of surface area every second. Since the xenon atoms will significantly outnumber the target molecules, the following calculations are based on using pure xenon. A single xenon atom should take up about $1 \times 10^{-19} \text{ m}^2$, and about 8 mmol (5×10^{21} atoms) of xenon will be used. This means that 500 m² of xenon monolayer will be deposited. If the deposition process takes ten minutes (a conservative upper bound, given the need to minimize relaxation during deposition), then the total available surface area will be around 0.6 m², so each layer will have to be ~ 700 atoms thick, that is about 0.25 μm thick before being scraped again. Much slower scraping would reduce the need for such a tight mechanical tolerance and is expected to be satisfactory since in Ruset's experiment with pure xenon, snow accumulated to >1 mm thickness while spin relaxation remained negligible on a ten minute time scale. However, in light of minimal information about the heat conductivity of the xenon snow and the practical issues of operating the scraper, it is expected that some experimentation with flow rate and scraper speed will be needed.

If 0.00125 m² of surface are to be covered to a thickness of 700 atoms every second, a flow rate of 9×10^{18} atoms per second (14 $\mu\text{mol/s}$) is needed. At this point, relative pressures and the initial temperature of the gas become very important, and the issue of how thick a tube is needed for the xenon flow becomes a fluid dynamics problem that can only be solved if one knows the initial pressure and temperature of the xenon. However, calculations done using an on line pipe flow fluid dynamics calculator[19] suggest that the real limiting factor is the inner diameter of the tube used. Thus, the nozzle was designed assuming an in flow tube with an inner diameter of 3/32 inch (2.4 mm). The basic factors considered in designing the nozzle were a wish to keep the number of holes drilled to a reasonable number (to keep machine shop costs reasonable) and at the same time to minimize the diameters of the holes to prevent those nearest to the input hose from picking up the entire gas flow. As a result, the nozzle design uses 48 holes with a diameter of 1/128 inch (0.20 mm).

The nozzle itself consists of donut-style annulus made of a sealed outer ring with a 1/16 inch (1.6 mm) o.d. connection to allow 3/32 inch (2.4 mm) i.d. xenon inlet tube to be attached to it. The nozzle has a height of 1-1/4 in (3.2 cm), an inner diameter of 7/32 inch (0.56 cm), and an outer diameter of 3/4

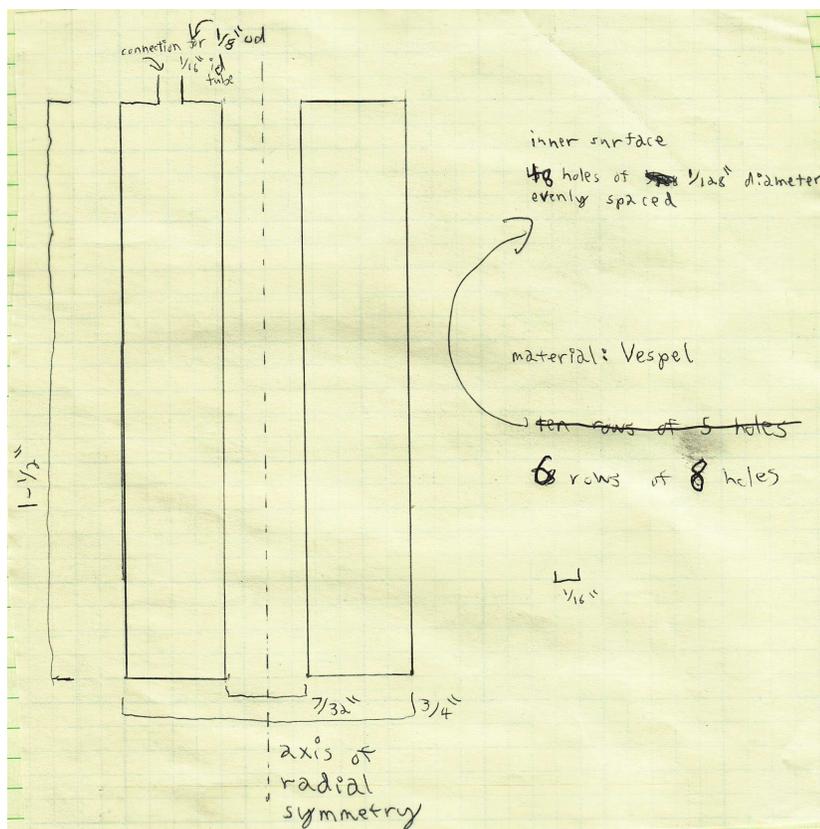


Figure 4: Design Plan for Nozzle

inch (1.9 cm). The inner surface of the ring is perforated with 48 holes of $1/128"$ (0.2 mm) diameter, evenly spaced in six columns of eight holes each. The whole nozzle is made of Vespel, a plastic with particularly good cold and vacuum tolerance (it can be lowered to liquid nitrogen temperatures and be exposed to ultra-high vacuum without issue if necessary). Figure 4 shows the design plan from which the machine shop made the nozzle.

5.3 Other Components

5.3.1 Gas Mixture Input

It was originally intended that the gas mixture would be prepared in a gas sampling bag at atmospheric pressure and released into the apparatus by using the pressure differential between atmospheric pressure and the vacuum inside the bell jar. Three 1.5 L Tedlar gas sampling bags (Jensen Inert catalog number GST0015-0610) have been purchased for storing and transporting the gas-phase mixture of target molecule and hyperpolarized xenon. They were selected based

on past experience by workers in the Weitekamp group regarding materials unlikely to induce relaxation in hyperpolarized xenon gas[13].

Another issue related to gas mixture input is that it is important not to relax the xenon gas by putting it through a significant magnetic field gradient, as pointed out by Gerhard[11]. Because of constrained space in the bell jar, and the general design of the apparatus, it will be necessary to pass the xenon-in line fairly close to the Halbach magnet. It may be possible to do this in a way that minimizes field gradients once the Halbach magnet is obtained and its gradients can be measured; however it will likely be necessary to protect the xenon in line with mu-metal, a high magnetic susceptibility alloy used to insulate against magnetic fields.

5.3.2 Sample Delivery

Approximately 1 mL of warm (340 K) water will be added through the NMR tube cap to boil off the xenon and dissolve the acetic acid at room temperature. This number was determined by calculating the amount of heat needed to warm the sample to room temperature and vaporize the xenon. Since the sample will have a large excess of xenon, calculations were done based on a pure xenon sample. To heat solid xenon from 77 K to 161 K, 2.7 kJ/mol is required. The heat of fusion for xenon is around 65 J/mol and the heat of vaporization is 12.6 kJ/mol. Heating xenon gas from 161 K to 300 K at constant pressure requires 2.8 kJ/mol. This sums to about 18 kJ/mol. Since the sample is about 0.008 mol, we should need about 150 J to boil off the xenon. Water has a heat capacity of 4.18 J/mL-K near room temperature, so 1 mL of water at 340 K will be cooled to 300 K by releasing enough heat to warm the sample to 300 K and boil off the xenon.

5.3.3 Vacuum Equipment

The Halbach magnet and xenon delivery / deposition set up are contained in a vacuum bell jar with an implosion shield. The bell jar is cylindrical with a rounded top. The diameter is 12", the center height is 13", and the height of the cylindrical portion alone is 9". A 1 in \times 18 in \times 18 in aluminum plate, McMaster-Carr catalog number 9040K65, was purchased to serve as the base plate. A number of vacuum feedthroughs were purchased from ISP Insulator Seal to bring power and fluids through the baseplate. For thermocouples to determine the temperature of the condenser, a six pin type-E thermocouple feedthrough (no. 9312011) was selected. Liquid nitrogen will enter and boil-off nitrogen gas will exit through a two-tube Swagelok liquid N2 feedthrough (no. 9812105). Xenon will enter the bell jar through one tube of a two-tube Swagelok liquid feedthrough (no. 9812005); the other tube will be sealed. To power the motor, a four-pin medium power electrical feedthrough (no. 9422028) will be used. A vacuum gauge set-up and vacuum pump already present in the Weitekamp lab will also be installed.

5.3.4 Motor and Controller

The scraper will be turned by a chain of two nylon bevel gears and a 7.5 cm aluminum drive shaft leading to an electric motor well off-center from the Halbach magnet. It is hoped that distance will be sufficient to keep the magnet from interfering with it; if this proves impossible it may need to be shielded with mu-metal. Two gearhead motors were purchased from Jameco Electronics for this purpose (catalog number 253455, operating frequency of 200 RPM (3.3 Hz), and catalog number 253446, operating frequency 600 RPM (10 Hz)). Using a kit-built Velleman K8004 DC to Pulse Width Modulator the operating speeds of the motors can be lowered without decreasing torque by converting a constant DC current into a series of pulses. By varying the pulse rate, one can reduce the speed of the motor while maintaining the rated operating voltage of the motor during the pulses, so that the motor operates in pulses at full torque rather than continuously but with diminished torque due to underpowering. Using this controller, it will be possible to experiment with varying the scraper speed without concerns about decreased torque.

6 Initial Construction and Experiments

The nozzle-condenser-motor set-up has been constructed and is ready for testing. The updated liquid nitrogen reservoir has been constructed with the tungsten rod condenser embedded in it as described above. Based on the experience of a graduate student in Professor Zewail's lab with nylon in vacuum, we decided that nylon was the best choice for the gears, since it is completely nonmagnetic and should not have outgassing problems at 0.1 torr. The department machine shop attached a nylon bevel gear to the reservoir as described above. Attached to the bottom of the gear is a copper wire, which is wrapped around the condenser as a scraper. This set-up, along with the xenon nozzle and the scraper motor, has been set up using clamp stands for testing.

The next logical step is to test the nozzle scraper. The initial tests will consist of pressurized carbon dioxide being run through the nozzle while the condenser is cooled with liquid nitrogen. This will be done at room pressure to make it easier to access and adjust parts without having to repeatedly pump down a bell jar, and to allow experiments to be performed before the vacuum apparatus is constructed. Assuming the nozzle works as expected, further tests will be done using the scraper set up, using the electric motors at a variety of frequencies.

These experiments should allow us to confirm that the nozzle design evenly distributes snow over the condenser, that the scraper removes it effectively, and that the accumulation and scraping rates can be controlled to produce thin surfaces and the new surface area to flow rate ratios that we think are necessary based on Ruset's work. After these tests, construction of the apparatus can continue and experiments can be done under vacuum and with xenon. Eventually, once a Halbach magnet is obtained, experiments with hyperpolarized xenon and

small biomolecules can commence.

7 Conclusions

Unfortunately, time constraints have not allowed the apparatus detailed herein to be completed or fully tested. However, the overall design appears to be workable, and all necessary parts have been obtained with the exception of the Halbach magnet (the design of which has been discussed with potential suppliers). Work on constructing and testing the apparatus will be continued by others in the Weitekamp lab, however, and if it is successful, will lead to a new method of preparing hyperpolarized samples of metabolites for *en vivo* studies.

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A Mathematica Code for Spin Temperature Calculations

Initial Conditions

```
(*sets initial conditions for experiment*)
polInitialXe129 = 0.50; (* initial polarization of the (deltaN/N) xenon-129
in the storage field *)
polInitialXe131 = 0; (* initial polarization of the (deltaN/N) xenon-131,
assumed zero due to relaxation in the storage field *)
polInitialC13 = 0; (* initial polarization of the carbon (deltaN/N) in the
storage field *)
polInitialH1 = 0; (* initial polarization of the protons (deltaN/N) in the
storage field *)
bMixing = .001; (* mixing field in Tesla (though this cancels out so units
unimportant) *)
bStorage = .04; (* storage field in Tesla (though this cancels out so units
\unimportant) *)
ratio = 8; (* ratio of number of xenon-129 / carbon-13 nuclei *)
ratioCXe = 1/8; (* ratio of number of carbon-13 / xenon-129 nuclei *)
```

ratioHXe = 1/4; (* ratio of number of hydrogen-1 / xenon-129 nuclei, calculated for acetic acid \ (CH3COOH) *)
 ratioXeXe = 1; (*unity by definition, used to make later formulae more \ symmetric*)
 ratio131129 = 1/27; (*ratio of number of xenon-131 / xenon-129 nuclei*, based on Gatzke, et al.*)

Fundamental Constants

(*values for physical constants*)

gammaXe129 = -11.777*2*Pi; (* magnetogyric ratio of xenon-129 *)
 gammaXe131 = 3.5159*2*Pi; (* magnetogyric ratio of xenon-131 *)
 gammaC13 = 10.705 *2*Pi ; (* magnetogyric ratio of carbon-13 *)
 gammaH1 = 42.5775*2*Pi; (* magnetogyric ratio of protons *)
 momentXe129 = -0.77686; (* magnetic moment of xenon-129 *)
 momentXe131 = 0.69066; (* magnetic moment of xenon-131 *)
 momentC13 = 0.702381; (* magnetic moment of carbon-13 *)
 momentH1 = 2.79277; (* magnetic moment of protons *)
 spinXe129 = 1/2; (* spin of xenon-129 *)
 spinC13 = 1/2; (* spin of carbon-13 *)

Functions for Xe-129 and C-13 Only

(*calculations including two nuclei*)

betaXe129 = polInitialXe129 / (momentXe129 * bStorage) (* initial inverse spin temperature of the xenon *)
 betaC13 = polInitialC13 / (momentC13 * bStorage) (* initial inverse spin \ temperature of the carbon *)
 alpha = (gammaXe129^2 * ratio * spinXe129 * (1 + spinXe129)) / (gammaC13 ^2 * spinC13 * (1 + spinC13)) (* internal calculation for finding beta_final from the Gaede thesis *)
 betaFinal = (betaC13 + alpha*betaXe129) / (1 + alpha) (* function from the Gaede thesis *)
 polFinalXe129 = momentXe129 * bStorage * betaFinal (* final polarization of the xenon *) (* derived from eq 18 in Abragam and Proctor paper *)
 polFinalC13 = momentC13 * bStorage * betaFinal (* final polarization of the \ carbon *) (* derived from eq 18 in Abragam and Proctor paper *)

Functions for Xe-129 and C-13 and H-1

(*calculatoinis including three nuclei*)

betaXe129 = polInitialXe129 / (momentXe129 * bStorage) (* initial inverse spin temperature of the xenon *)
 betaC13 = polInitialC13 / (momentC13 * bStorage) (* initial inverse spin \ temperature of the carbon *)

```

    betaH1 = polInitialH1/(momentH1 * bStorage) (* initial inverse spin tem-
perature of the carbon *)
    betaPrimeXe129 = betaXe129 * bStorage / bMixing
    betaPrimeC13 = betaC13 * bStorage / bMixing
    betaPrimeH1 = betaH1 * bStorage / bMixing
    betaDoublePrime =
    (ratioXeXe*betaPrimeXe129*gammaXe129*gammaXe129 + ratioCXe*betaPrimeC13*gammaC13*gamma
+ ratioHXe*betaPrimeH1*gammaH1*gammaH1)
    / (ratioXeXe*gammaXe129*gammaXe129 + ratioCXe*gammaC13*gammaC13
+ ratioHXe* gammaH1*gammaH1)
    (* derived from eq 16 in Abragam and Proctor paper \ *)
    betaFinal=betaDoublePrime*bMixing/bStorage (* derived from eq 18 in
Abragam and Proctor paper *)
    polFinalXe129 = momentXe129 * bStorage * betaFinal (* final polarization
of the xenon *) (* derived from eq 18 in Abragam and Proctor paper *)
    polFinalC13 = momentC13 * bStorage * betaFinal (* final polarization of
the \ carbon *) (* derived from eq 18 in Abragam and Proctor paper *)
    polFinalH1 = momentH1 * bStorage * betaFinal (* final polarization of the
carbon *) (* derived from eq 18 in Abragam and Proctor paper *)

```

Functions for Xe-129, C-13, H-1, and Xe-131

```

(*calculations including four nuclei*)
    betaXe129= polInitialXe129/(momentXe129 * bStorage) (* initial inverse
spin temperature of the xenon *)
    betaXe131= polInitialXe131/(momentXe131 * bStorage) (* initial inverse
spin temperature of the xenon *)
    betaC13 = polInitialC13/(momentC13 * bStorage) (* initial inverse spin \
temperature of the carbon *)
    betaH1 = polInitialH1/(momentH1 * bStorage) (* initial inverse spin tem-
perature of the carbon *)
    betaPrimeXe129 = betaXe129 * bStorage / bMixing
    betaPrimeXe131 = betaXe131 * bStorage / bMixing
    betaPrimeC13 = betaC13 * bStorage / bMixing
    betaPrimeH1 = betaH1 * bStorage / bMixing
    betaDoublePrime =
    (ratioXeXe*betaPrimeXe129*gammaXe129*gammaXe129 + 5*ratio131129*betaPrimeXe131*gammaXe131
+ ratioCXe*betaPrimeC13*gammaC13*gammaC13 + ratioHXe*betaPrimeH1*gammaH1*gammaH1)
    / (ratioXeXe*gammaXe129*gammaXe129 +5* ratio131129*gammaXe131*
gammaXe131
    + ratioCXe*gammaC13*gammaC13 + ratioHXe*gammaH1*gammaH1 \ )
    (* derived from eq 16 in Abragam and Proctor paper *)
    betaFinal=betaDoublePrime*bMixing/bStorage (* derived from eq 18 in
Abragam and Proctor paper *)
    polFinalXe129 = momentXe129 * bStorage * betaFinal (* final polarization
of the xenon *) (* derived from eq 18 in Abragam and Proctor paper *)

```

$\text{polFinalXe131} = \text{momentXe131} * \text{bStorage} * \text{betaFinal}$ (* final polarization of \ the xenon *) (* derived from eq 18 in Abragam and Proctor paper *)
 $\text{polFinalC13} = \text{momentC13} * \text{bStorage} * \text{betaFinal}$ (* final polarization of the \ carbon *) (* derived from eq 18 in Abragam and Proctor paper *)
 $\text{polFinalH1} = \text{momentH1} * \text{bStorage} * \text{betaFinal}$ (* final polarization of the carbon *) (* derived from eq 18 in Abragam and Proctor paper *)

Comments on Assumptions

(* xenon - 131 assumed to be negligible; storage field assumed to be high enough that no mixing occurs; mixing field assumed to be low enough that mixing occurs; transition assumed to take no time*)