

MANUFACTURE, TRANSPORT AND DELIVERY OF MATERIAL CONTAINING HIGHLY POLARIZED NUCLEI

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority of U.S. Provisional Patent Application Serial No. 61/042,398, filed April 4, 2008, U.S. Provisional Patent Application Serial No. 61/111,050, filed November 4, 2008 and U.S. Patent Application Serial No. 12/193,536, filed August 18, 2008. This application is also related to U.S. Provisional Patent Application Serial No. 60/775,196 filed February 21, 2006, U.S. Provisional Patent Application Serial No. 60/802,699 filed May 23, 2006 and U.S. Provisional Patent Application Serial No. 61/042,239 filed April 3, 2008. The disclosure of each of the aforementioned patent applications is incorporated by reference herein in its entirety.

BACKGROUND OF THE DISCLOSURE

Field of the Disclosure

The present disclosure relates to improved materials including hyperpolarized nuclei and techniques for making the same.

Description of Related Art

Recent experiments have demonstrated that hyperpolarization of various nuclei can survive the transition from one molecule to another that takes place during a chemical reaction. For example, it has been shown that hyperpolarized ("HP") ^{13}C nuclei in sodium pyruvate can be metabolized by cancerous tissue and produce HP lactate, alanine and the like.

A further example can be found in the production of HP fumarate, which can be manufactured by first hyperpolarizing nuclei in fumaric acid and then allowing the acid to react with a base solution to form HP fumarate. HP sodium pyruvate (i.e., sodium pyruvate including hyperpolarized nuclei) may be manufactured in a similar fashion. In reactions such as these the amount of polarization lost during the chemical reaction has been shown to be small.

These are examples of chemical reactions in which at least one precursor molecule in the chemical reaction is hyperpolarized so that at least one of the end products of the chemical reaction is in turn hyperpolarized.

In each of the aforementioned examples, Dynamic Nuclear Polarization (DNP) was used to hyperpolarize the precursor molecule. In this process, the molecule to be hyperpolarized is mixed with a polarization agent containing a source of free electrons, typically a trityl radical (TA). In some instances an electron paramagnetic agent (EPA) may be used in conjunction with the TA or by itself.

This method of hyperpolarization is problematic for in vivo applications, as the TA/EPA is strongly contraindicated for in vivo applications. The TA/EPA must then be stringently removed prior to injection of the HP material. However, the level of polarization in the HP material that survives after filtration of the TA/EPA is not presently clear. Moreover, safe levels of exposure to small amounts of TA/EPA have not been established by the FDA. Furthermore, use of this technique is not amenable to the ready transport or storage of hyperpolarized material.

There thus remains a need in the art for improved approaches to manufacture, transport and use of highly polarized materials. The present disclosure provides a solution for these problems.

SUMMARY OF THE DISCLOSURE

Advantages of the present disclosure will be set forth in and become apparent from the description that follows. Additional advantages of the disclosure will be realized and attained by the methods and systems particularly pointed out in the written description and claims hereof, as well as from the appended drawings.

To achieve these and other advantages and in accordance with the purpose of the disclosure, as embodied herein, in one embodiment, the disclosure provides a method of producing a material containing hyperpolarized nuclei. The method includes formatting a first material into a high surface area configuration. Next, in a polarizing cryostat, the first material is exposed to ^3He at a temperature below about 10K and a magnetic field in a manner sufficient to substantially increase the polarization of the first material. The temperature of the first material is then increased without melting or sublimating the first material resulting in nuclei in the first material becoming hyperpolarized. If desired, the first material is then reacted with at least one other material to form a mixture including hyperpolarized nuclei.

In further accordance with the invention, the mixture may be a solution. If desired, the first material may be melted prior to, or as a part of, the reacting step. The first material may be exposed to ^4He after exposing the first material to ^3He . If desired, the first material may be stored in a hyperpolarized condition in a separate cryostat. The first material may be transported in the separate cryostat to a site remote from where it was hyperpolarized prior to reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei. In accordance with a preferred embodiment, the nuclei in the first material includes at least one material selected from the group consisting of ^{13}C , ^{15}N , ^1H , ^{31}P and ^{29}Si .

In further accordance with the disclosure, the method may further include substantially increasing the temperature of the first material without melting or sublimating the material after the initial temperature increase that results in nuclei in the first material becoming hyperpolarized. For example, the temperature may be increased from a first temperature substantially below the temperature at which the T1 of the first material experiences a minimum to a second temperature substantially above the temperature at which the T1 of the first material experiences a minimum. In accordance with one embodiment, the temperature of the first material is increased from a temperature below about 10K to a temperature of about 200K. In accordance with another embodiment, the temperature of the first material may be increased in the presence of a magnetic field at a rate wherein less than about 90 percent of polarization imparted to nuclei in the first material is lost. In accordance with certain preferred embodiments, the temperature of the first material may be increased in the presence of a magnetic field at a rate wherein less than about 80, 70, 60, 50, 40, 30, 20, 10 or 5 percent of polarization imparted to nuclei in the first material is lost. If desired, the first material may be transported to a location within the fringe field of an MR system after the first material has reached the second temperature.

In further accordance with the disclosure, the method may additionally include the step of removing the first material from the polarizing cryostat after the initial temperature increase that results in nuclei in the first material becoming hyperpolarized. By way of further example, the method may further include transferring the first material into a transport cryostat after the initial temperature increase that results in nuclei in the first material becoming hyperpolarized. Accordingly, the transport cryostat may be transported to an end user. The first

material may then be transferred from the transport cryostat into a transfer vessel. The transfer vessel may include a permanent magnet or electromagnet for maintaining the first material in a magnetic field. The method may further include increasing the temperature from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum. The temperature may be raised to the second temperature at substantially the same time the first material is transferred into the transfer vessel. The temperature may be raised to the second temperature in less than about thirty seconds in a magnetic field having a strength between about 0.1 Tesla and about 10 Tesla.

In further accordance with the disclosed embodiments, the method may further include the step of disposing the first material in a mixing device within the fringe field of a MR system. Preferably, at least a portion of the reacting step occurs within the mixing device. If a transfer vessel is used, the magnet of the transfer vessel is preferably turned off or otherwise deactivated or shielded prior to performing an MR system operation.

In further accordance with the disclosure, the first material may include an acid and the at least one other material may include a base. On the other hand, the first material may include a base and the at least one other material may include an acid. Accordingly, the acid may include an acid selected from the group consisting of acetic acid, formic, lactic and pyruvic acid. Preferably, the acid is isotopically enhanced in one or more of its carbon sites with ^{13}C . In accordance with one embodiment, the at least one other material includes sodium, such as in the form of sodium hydroxide and/or sodium bicarbonate. In accordance with still a further aspect, the first material may be a liquid, solid, and/or gas at STP. In accordance with one embodiment, the first material may be frozen in a high surface area configuration such that it has a surface area to volume ratio greater than about $0.1 \text{ m}^2/\text{g}$.

In further accordance with the present disclosure, a method of magnetic resonance (MR) investigation of a subject including a human subject or other organism is provided. The method includes producing a mixture including hyperpolarized nuclei as described herein, administering the mixture to the subject, exposing the subject to radiation of a frequency selected to excite nuclear spin transitions in the hyperpolarized nuclei, and detecting magnetic resonance signals from the subject.

In further accordance with the disclosure, the method may further include generating at least one of an image, dynamic flow data, diffusion data, perfusion data, physiological data or metabolic data from the detected signals. The hyperpolarized nuclei in the mixture preferably have a T1 value of at least 5 seconds at a field strength in the range 0.01-5 T and at a temperature in the range of 20-40°C.

The disclosure further provides a method of producing a material including hyperpolarized nuclei. The method includes increasing the state of polarization of a first material in the absence of a source of free electrons or paramagnetic impurities at a temperature below about 10K in the presence of a magnetic field, increasing the temperature of the first material without melting it resulting in nuclei in the first material becoming hyperpolarized, and reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei. The mixture may include a solution, among other types of mixtures.

In further accordance with the disclosure, the methods described herein may include embodiments wherein the first material includes a methyl group. By way of further example, the methods described herein may include embodiments wherein the resulting mixture includes pairs of bonded nuclei. Preferably, at least a portion of the bonded nuclei are hyperpolarized.

The disclosure further provides a method of producing a material containing hyperpolarized nuclei. The method includes formatting a first material including a methyl group into a high surface area configuration, increasing the nuclear polarization of the first material, and increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material within a time period less than about thirty seconds. The disclosure also provides a method of producing a material containing hyperpolarized nuclei. The method includes formatting a first material including a methyl group into a high surface area configuration, increasing the nuclear polarization of the first material, and increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material within a time period less than about thirty seconds, wherein less than about 90

percent of the polarization is lost when increasing the temperature. In further accordance with the disclosure, the first material may be reacted with at least one other material to form a mixture including hyperpolarized nuclei. In accordance with certain preferred embodiments, less than about 80, 70, 60, 50, 40, 30, 20, 10 or 5 percent of the polarization is lost when increasing the temperature.

The disclosure yet further provides a method of producing a material containing hyperpolarized nuclei. The method includes hyperpolarizing a first material, and increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material.

The disclosure still further provides a method of producing a material containing hyperpolarized nuclei. The method includes formatting a first material into a high surface area configuration and, in a polarizing cryostat, exposing the first material to ^3He at a temperature below about 10K and a magnetic field in a manner sufficient to substantially increase the polarization of the first material. The method also includes reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.

The disclosure also provides a method of producing a mixture including hyperpolarized nuclei including providing a precursor including hyperpolarized nuclei, disposing the precursor in the stray field of an MR system, and reacting the precursor with at least one other material to form a mixture including hyperpolarized nuclei.

In accordance with still a further aspect, the disclosure also provides a hyperpolarized material made according to any of the processes described herein.

In further accordance with the disclosure, an embodiment of a system for producing a material containing hyperpolarized nuclei is provided. The system includes a polarizing cryostat having a vessel for exposing a first material formatted into a high surface area configuration to ^3He at a temperature below about 10K and a magnet adapted and configured to provide a magnetic field in a manner sufficient to substantially increase the polarization of the first material. The system further includes a first heat source for increasing the temperature of the first material without melting or sublimating the first material resulting in nuclei in the first material becoming hyperpolarized. The system still further provides a mixing device for reacting

the first material with at least one other material to form a mixture including hyperpolarized nuclei.

In further accordance with the disclosure, the mixture may be a solution. The system may further include a second heat source for melting the first material to permit the first material to react. The second heat source may include the material with which the first material is mixed in the mixing device. For example, the first material may be melted by dropping it into the material with which the first material is mixed. By way of further example, the first material may melt prior to contacting the material with which the first material is mixed. The system may further include means for exposing the first material to ^4He after exposing the first material to ^3He .

In accordance with a further aspect, the system may further include a transport cryostat in which the first material in a hyperpolarized condition is stored. The transport cryostat is preferably suitable for transporting the first material to a site remote from where the first material was hyperpolarized. In accordance with a preferred embodiment, the nuclei in the first material includes at least one material selected from the group consisting of ^{13}C , ^{15}N , ^1H , ^{31}P and ^{29}Si .

In accordance with another aspect, the system may include means for substantially increasing the temperature of the first material without melting or sublimating the material after the first material becomes hyperpolarized. The system may be adapted and configured to increase the temperature from a first temperature substantially below the temperature at which the T1 of the first material experiences a minimum to a second temperature substantially above the temperature at which the T1 of the first material experiences a minimum. The system is preferably adapted and configured to increase the temperature of the first material from a temperature below about 10K to a temperature of about 200K.

In further accordance with the present disclosure, the system may include a transfer vessel for receiving the first material from the transport cryostat. The transfer vessel preferably includes a magnet for maintaining the first material in a magnetic field. In accordance with a further embodiment, the system includes a mixing device for receiving the first material from the transfer vessel. The mixing device and transfer vessel are preferably adapted and configured to be operated within the fringe field of a MR system. The magnet of the transfer

vessel can be adapted and configured to be turned off prior to performing an MR system operation.

In further accordance with the system, the first material can be a liquid, solid, and/or a gas at STP. The first material is preferably in a high surface area configuration that has a surface area to volume ratio greater than about $0.1 \text{ m}^2/\text{g}$.

The disclosure provides a system of magnetic resonance (MR) investigation of a subject including a human subject or other organism. The MR system includes means for producing a mixture including hyperpolarized nuclei as described herein and an injector for administering the mixture to the subject. The system further includes at least one radio frequency coil for exposing the subject to radiation of a frequency selected to excite nuclear spin transitions in the hyperpolarized nuclei, and a detector for detecting magnetic resonance signals from the subject.

In further accordance with the disclosure, the system may further include means for generating at least one of an image, dynamic flow data, diffusion data, perfusion data, physiological data or metabolic data from signals received from the detector.

The disclosure also provides an exemplary system for producing a material including hyperpolarized nuclei. The system includes means for increasing the state of polarization of a first material in the absence of a source of free electrons or paramagnetic impurities at a temperature below about 10K in the presence of a magnetic field. The system further includes means for increasing the temperature of the first material without melting it resulting in nuclei in the first material becoming hyperpolarized. The system also includes means for reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.

In further accordance with the disclosure, the disclosed systems may utilize a first material that includes a methyl group. If desired, the disclosed systems may be used to make a mixture that includes pairs of bonded nuclei. Preferably, at least a portion of the bonded nuclei are hyperpolarized.

In further accordance with the disclosed embodiments, a system for producing a material containing hyperpolarized nuclei is provided. The system includes means for formatting a first material including a methyl group into a high surface area configuration and means for increasing the nuclear polarization of the first material. The system further includes

means for increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material within a time period less than about thirty seconds.

In further accordance with the disclosure, a system for producing a material containing hyperpolarized nuclei is provided. The system includes means for formatting a first material including a methyl group into a high surface area configuration, and means for increasing the nuclear polarization of the first material. The system further includes means for increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material within a time period less than about thirty seconds, wherein less than about 90 percent of the polarization is lost during the warming step. In accordance with certain preferred embodiments, less than about 80, 70, 60, 50, 40, 30, 20, 10 or 5 percent of the polarization is lost during the warming step.

In further accordance with the disclosure, the system may include means for reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.

In yet further accordance with the disclosure, a system for producing a material containing hyperpolarized nuclei is provided. The system includes means for hyperpolarizing a first material and means for increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material.

In still further accordance with the disclosure, system for producing a material containing hyperpolarized nuclei is provided. The system includes means for formatting a first material into a high surface area configuration, a polarizing cryostat having means for exposing the first material to ^3He at a temperature below about 10K, and a magnet for generating a magnetic field in a manner sufficient to substantially increase the polarization of the first material. The system also includes a mixing device for reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.

In further accordance with the disclosed embodiments, a system for producing a mixture including hyperpolarized nuclei is provided. The system includes means for providing a precursor including hyperpolarized nuclei and means for disposing the precursor in the stray field of an MR system. The system further includes means for reacting the precursor with at least one other material to form a mixture including hyperpolarized nuclei.

It is to be understood that the foregoing general description and the following detailed description are exemplary and are intended to provide further explanation of the disclosed embodiments.

The accompanying drawings, which are incorporated in and constitute part of this specification, are included to illustrate and provide a further understanding of the disclosed methods and systems. Together with the description, the drawings serve to explain principles of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts nuclear polarization decay times (“T1”) vs temperature in differing magnetic fields for several different protonated and deuterated samples of frozen 1-¹³C enriched acetic acid.

Fig. 2 depicts a schematic view of an exemplary method and system in accordance with the disclosed embodiments.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Reference will now be made in detail to the present preferred embodiments of the disclosed embodiments, examples of which are illustrated in the accompanying drawings. The method and corresponding steps of the disclosed embodiments will be described in conjunction with the detailed description of the system.

It is one object of this disclosure to provide exemplary methods whereby nuclei in various molecules may be hyperpolarized without the need for the addition (or use) of toxic catalysts such as a TA/EPA or other catalysts or any polarizing agents (whether or not toxic). In accordance with a preferred embodiment, nuclei in molecules are hyperpolarized which may then be reacted to form ¹³C-bearing molecules of biological interest such as acetates and pyruvates in solution.

In accordance with a particularly preferred embodiment, sodium acetate including hyperpolarized nuclei may be provided. Sodium acetate can play a particularly vital role as a reporter on the metabolic process. Although sodium acetate is typically not a substrate found in significant levels in the blood, it is readily taken up and activated to acetyl-CoA. Acetyl-CoA is oxidized in mitochondria by the TCA cycle to form carbon dioxide (CO_2). In the process of acetyl-CoA oxidation, NADH is generated, which drives oxidative phosphorylation, the reduction of oxygen workload is tightly coupled to O_2 consumption and to the flux of acetyl-CoA through the TCA cycle. Thus, measurement of TCA cycle flux reports the metabolism required for heart function.

In accordance with one exemplary embodiment, a method for making sodium acetate solution including hyperpolarized nuclei may be produced. This may be accomplished, for example, by reacting acetic acid with sodium bicarbonate to produce sodium acetate, water and carbon dioxide gas, wherein nuclei in at least one of the precursors are hyperpolarized. The reaction thus naturally produces a mixture such as a solution that, when optionally combined with buffers, saline or other chemicals, is amenable for in vivo applications as a tracer and/or as a source of metabolic information. Other acids such as lactic, pyruvic and formic acid may additionally or alternatively be used.

Storage and Transfer of Polarized Materials:

Unlike radioactive tracers, the characteristic nuclear polarization decay times (T_1) of materials including hyperpolarized nuclei are a function of their ambient environment. Temperature, magnetic field and the physical state of the material (liquid, solid, gas etc.) all play a role in determining how long the induced nuclear polarization will last before it decays away to thermal equilibrium. Under appropriate conditions T_1 can be made to be quite long. Longer decay times open up the possibility of transporting HP materials (i.e., materials including hyperpolarized nuclei) over large distances. Thus, HP materials can then be supplied as a consumable, removing the need for the user to site a polarizer on its premises and reducing the cost burden.

In addition to temperature and field, the physical state and the chemical composition of the material influences its nuclear polarization decay time. Applicant has measured the T_1 of acetic acid and sodium acetate over a wide range of temperatures and fields. Applicant has discovered that the T_1 of hyperpolarized nuclei in sodium acetate is quite short

over a wide range of temperature (e.g., from 4 K to 300 K). This is too short for hyperpolarized sodium acetate to be transported over any reasonable distance in any kind of reasonable magnetic field without severe loss of polarization. However, the T1 of acetic acid (deuterated) can be very long at $T < 15$ K and in a moderate magnetic field (typically $B \sim 0.1$ T). This discovery permits transporting HP acetic acid (i.e., acetic acid including hyperpolarized nuclei) over large distances and supplying it as a consumable item. Because it is sodium acetate, not acetic acid, which is required for use as an in vivo agent, the acetic acid is converted to sodium acetate just before use.

The DNP method described above does not lend itself well to long term transport or storage of a hyperpolarized material. One reason for this is that the TA/EPA present in the frozen HP material shortens the T1 in the solid state. The TA/EPA cannot be removed without melting the material into its liquid state. However, the T1 of ^{13}C in materials in the liquid state are typically on the order of 10 – 60 seconds. For this reason, long term storage and/or transport of materials hyperpolarized using DNP is not feasible. As a result, DNP polarizers are typically sited very close to the NMR/MRI system that is used to analyze the HP materials they produce.

Placing the polarizer near the NMR/MRI system is problematic for a number of reasons. First, the high cost of these machines imposes a very high cost burden on the end user, both in terms of capital equipment costs and overhead. In addition, the limited payload scalability of a DNP machine means only a small number of scans can be performed per unit time. This in turn limits the diagnostic information that can be obtained using an HP material polarized using DNP techniques. Transport of the final product in its liquid form from the DNP polarizer to the patient also consumes time that is then not available for observation of the desired metabolic process.

It is accordingly another object of this disclosure to describe methods and systems for storing and/or transporting HP materials. In accordance with a preferred embodiment, methods and systems are provided for storing and/or transporting materials that may be used as precursors in a chemical reaction to manufacture a material (e.g., solution) of biological interest including hyperpolarized nuclei. The present disclosure permits transportation over significant distances such that the HP materials may be supplied as a consumable material manufactured at a first location and transported to the end user.

Extraction of HP materials from a Cryostat

Many molecules of biological interest contain a methyl group. Such molecules include sodium acetate, sodium pyruvate, and others. The presence of the methyl group has a profound effect in the handling of HP materials. As can be seen in Fig. 1, the T1 of acetic acid has a minimum well below its melting point. The position of the minimum is somewhat field dependent. The minimum in T1 is a consequence of the rotation of the three ^1H nuclei attached to the methyl carbon. These protons continue to rotate even at low temperatures causing nearby nuclei to relax under field/temperature conditions which would otherwise have very long T1s.

Because of the minimum, low temperature hyperpolarization methods to date have relied on very rapid warming schemes to preserve the polarization of various materials during extraction from the polarizing environment. Typically, this involves exposing the material to superheated water or methanol in the presence of a magnetic field to get the sample to temperatures well above the minimum in a time $\ll T1$.

This approach requires that the amount of material be kept small, so that it may be warmed rapidly. It also means that the polarizer must be very close to the NMR/MRI system that is used for analysis. This is extremely disadvantageous for many user sites where space is at a premium. In addition, when DNP is used to hyperpolarize materials, the DNP device must be kept a certain minimum distance away from the target device (NMR/MRI system).

As noted above, many metabolic substrates contain methyl groups which impose a minimum in T1 at temperatures between the polarizing temperature and the melting temperature. Applicant has discovered that at temperatures much warmer than the minimum, but still much less than the melting or sublimation temperature of the material, T1 is again long enough that short term storage/transport is feasible. This enables the possibility of placing the polarizer (and/or a transport cryostat containing polarized material) well outside the vicinity of the MR magnet. Properly utilizing this discovery requires that the polarized material's temperature be changed from well below the minimum to well above it in a time much less than the relaxation time T1 at any point during this process, without melting or sublimating the material. Once the material is melted its T1 becomes quite short and it must be used immediately.

Applicant has discovered that, by configuring the material to be hyperpolarized into a form that has a high surface area to volume ratio, such as a powder or sinter, the thermal relaxation time of the material can be made very short. This allows its temperature to be

adjusted very quickly. This has the significant advantage of allowing materials to be warmed from the very low temperatures (as an example, $T < 10$ K) required for long term storage/transport to the more moderate temperatures suitable for short term transport (as an example $T \sim 200$ K) without melting and/or undue loss of polarization that may occur as the result of a short T_1 somewhere in the temperature profile of the material in question. In accordance with certain preferred embodiments, the temperature of the hyperpolarized material may be increased in the presence of a magnetic field at a rate wherein less than about 90, 80, 70, 60, 50, 40, 30, 20, 10 or 5 percent of polarization imparted to nuclei in the first material is lost.

The advantage of preparing polarized materials in this manner is that they may then be transported over short distances (for example, from one part of the user site to another) using readily available cryogenic materials (e.g., liquid nitrogen or dry ice) and in relatively low magnetic fields. Another advantage is that the melting time of the material is reduced as the temperature differential between its starting point and melting temperature is decreased.

Configuring materials that are solids at room temperature into high surface area powders is relatively straightforward. For example, well known techniques such as ball milling can be used to reduce the particle size of the solid material to less than a micron if desired. When the material to be powderized is a liquid at room temperature a different approach must be used. Ball milling is not useful for many frozen liquids as the heat of milling melts the particles. Applicant has developed methods to produce high surface area frozen powders of various materials that are liquid under normal standard temperature and pressures and that, either intrinsically or as the result of a chemical reaction, make suitable metabolic substrates for HP MR study purposes. Suitable methods are described, for example, in Applicant's U.S. Patent Application Serial No. 12/193,536, filed August 18, 2008. The aforementioned patent application also discloses various other mixtures that may be achieved in accordance with the present disclosure (e.g., colloids, suspensions, and the like).

Quantum Relaxation Switch "QRS" Process

Heretofore the use of a "brute force" environment to produce high levels of nuclear polarization in materials other than gases has been problematic because the relaxation time of most nuclei under such conditions is very long. Applicant has discovered that, by configuring the material to be polarized as a high surface powder and exposing the surfaces of the powder to ^3He , the magnetic relaxation time can be made much shorter and amenable to

industrial levels of production. Applicant has further discovered that removal of the ^3He from the surface of the material can be accomplished by exposing the material to ^4He . This greatly increases the T1 of the material thus allowing it to be warmed to room temperature without undue loss of polarization. Once the material has been returned to room temperature, nuclei in the material become “hyperpolarized.” As alluded to above, that is to say that the nuclear polarization of some nuclei in the material is well above what it would otherwise be in thermal equilibrium. The material including the “hyperpolarized” nuclei can now be used for a variety of NMR/MRI protocols. Most notably, the material can in and of itself be used as an in vivo MR material or it can be reacted as a precursor with another material to form a third material which is itself useful as an NMR/MRI material.

U.S. Patent No. 6,651,459 (which is incorporated by reference herein in its entirety) describes a technique of producing hyperpolarized gases (i.e., materials that are gaseous at standard conditions). This can be done by way of the following exemplary steps:

- 1) Configuring the gas as a high surface area powder or sinter. As an illustrative non-limiting example, this can be done by freezing the material out on the surface of an aerogel or, more advantageously, as a high surface area “snow”.
- 2) Cooling the gas to “brute force” (very low temperature, very high magnetic field) conditions where the equilibrium nuclear polarization is very high.
- 3) Exposing the frozen gas to overlayers of ^3He . In addition to providing a path for thermal relaxation, the layers of ^3He act to efficiently magnetically relax those nuclei in the topmost layers of the frozen gas to thermal equilibrium which, in “brute force” conditions, is highly polarized. In this sense the unique properties of ^3He are employed as a relaxation agent to hasten the nuclei’s relaxation to a state of high polarization.
- 4) Exposing the frozen gas to overlayers of ^4He . The layers of ^4He act to efficiently remove the ^3He from the surfaces of the frozen gas. This effectively isolates the nuclei and allows them to be warmed back to room temperature without undue loss of polarization.

The above process is known as a “Quantum Relaxation Switch” (QRS) since it describes a technique whereby efficient relaxation of nuclei in a brute force environment can be switched “on” and “off” so as to produce highly polarized nuclei that can be warmed to room temperature to produce HP precursor materials or HP materials for a variety of NMR/MRI

applications. It is important to note that the process does not require the addition of any catalysts and that the brute force environment can be made highly sterile.

Applicant has discovered that the QRS process may be extended to operate on a wide range of materials, rather than only materials that are gases at standard conditions. This requires that the material to be hyperpolarized be configured in a high surface area. Applicant has further discovered that a wide range of liquids may be frozen and powderized so that their surface area to volume ratio is very high. In particular, liquids such as acetic acid that upon chemical reaction make solutions of metabolic substrates suitable for injection and in vivo NMR/MRI protocols are preferred.

The various discoveries described above constitute methods and systems that fully enable the configuration of various materials as high surface area frozen powders, polarizing the material without exposing the materials to catalysts, extracting the polarized materials from the low temperature environment so that they become hyperpolarized (HP), and transporting the hyperpolarized materials to an end user site. It will be recognized that the recitation of “hyperpolarized material” herein is intended to refer to material including hyperpolarized nuclei. If desired, the hyperpolarized materials may be reacted with other materials to form a third HP material that is of use for MRI/NMR applications (e.g., in vivo MRI applications). In accordance with a preferred embodiment, materials are used that contain molecules of interest for biological MRI applications. The following Example is based partially on experience and partially on insight.

Example 1:

Deuterated acetic acid is frozen into high surface area pellets by introducing them into LN₂ in a finely divided form of droplets. The surface area of the pellets is measured by BET to be ~ 5 m²/g. The pellets are placed in the sample chamber of a dilution refrigerator and cooled to T < 100 mK in the presence of a 10 T magnetic field. ³He is added to the sample chamber to hasten magnetic relaxation. Once the sample is polarized (a process which can be monitored using NMR), ⁴He is added to the sample chamber to remove the ³He from the surface of the sample. The sample is warmed to T ~ 5 K and the helium gases are removed. The pellets are removed from the chamber of the polarizing cryostat while being kept in a temperature T < 10 K and in a magnetic field > 0.1 Tesla. The pellets are transferred to a transport cryostat where similar field/temperature conditions are maintained. After transport, the temperature of the

pellets is quickly raised from $T < 10\text{ K}$ to $T \sim 77\text{ K}$, for example, by immersing them in liquid nitrogen. The pellets can then be removed from the transport cryostat and brought into the vicinity of the MR system using a small magnetic field and a suitable cryogenic material to maintain the polarization. The pellets may be rapidly melted by dropping them into heated sodium hydroxide solution in the presence of a magnetic field to create a hyperpolarized mixture, such as in the form of a hyperpolarized sodium acetate solution (i.e., a sodium acetate solution including hyperpolarized nuclei).

If desired, the stray field of the MR system can be used to maintain a magnetic field over the hyperpolarized precursor when the precursor is used to make a hyperpolarized mixture. For example, the hyperpolarized precursor (such as an acid or a base including hyperpolarized nuclei) may be transferred from the polarizing cryostat if nearby (or transport cryostat) into a transfer vessel as depicted in Fig. 2. The temperature of the hyperpolarized precursor may then be elevated from a first temperature below the temperature at which the T_1 of the first material experiences a minimum to a second temperature above the temperature at which the T_1 of the first material experiences a minimum. Preferably, the temperature of the hyperpolarized precursor is elevated from a first temperature substantially below the temperature at which the T_1 of the first material experiences a minimum to a second temperature substantially above the temperature at which the T_1 of the first material experiences a minimum (e.g., from below about 10K to about 200K). This may be achieved, for example, by immersing the precursor in a liquid cryogen, such as liquid argon, nitrogen, xenon or krypton, that has a boiling point well above the temperature at which the T_1 for ^{13}C is at a minimum. Alternatively, the precursor can be heated by passing a gas warmed to about 200K over its surfaces.

As illustrated in Fig. 2, material formatted into a high surface area form is polarized in a cryostat 1. Preferably, the material is polarized at a temperature between about 1mK and 100mK , more preferably between about 10mK and about 40mK . The temperature of the material is then increased, resulting in hyperpolarization (i.e., a state in which the polarization is above that at which it would ordinarily be at thermal equilibrium). The material is then extracted and stored in a transport cryostat 2 that maintains a temperature and magnetic field environment such that decay of the nuclear polarization of the material is slow. This hyperpolarized material may then be transported via the transport cryostat 2 to storage or a terminal location, such as a hospital. The hyperpolarized material is then extracted from the

transport cryostat 2 into an interim cryostat or transfer vessel 3 that maintains the hyperpolarized material at a higher temperature and lower magnetic field suitable for short term transport. Before, during or after the transfer of the hyperpolarized material to transfer vessel 3, its temperature is preferably raised as quickly as possible across the temperature at which the T1 for the material is at a minimum.

For example, the temperature increase is preferably performed in a time period less than 30, 20, 10, or most preferably, 5 seconds long. Preferably, the applied field of the transfer vessel 3 is not in excess of 500 Gauss such that it may be brought safely into proximity of the NMR/MRI system. The hyperpolarized material is then ejected from the transfer vessel 3 into a mixing device 4 where it is converted into a mixture, such as a solution, preferably suitable for in vivo injection. The hyperpolarized solution is injected via a sterile line 5 into a patient 6. An NMR/MRI system 7 is then used to carry out a variety of NMR/MRI protocols.

The transfer vessel 3 includes a compartment 8 for receiving the hyperpolarized precursor material, and includes a magnet 9 such as an electromagnet or permanent magnet for maintaining a magnetic field over the material during the transfer process. Preferably, the mixing device 4 and transfer vessel 3 are disposed within the stray magnetic field 10 of the MR system 7. It will be noted that the depicted field lines are merely intended to be illustrative. Advantageously, this permits the hyperpolarized material to be melted in close proximity to the MR system, thus saving time delivering the resultant solution to the subject during which the polarization of will decay. As further illustrated in Fig. 2, the polarizing cryostat 1 includes a magnet 11 for applying a field thereto, a vessel for containing the material to be hyperpolarized, and a heat source for raising the temperature of the material to facilitate hyperpolarization. Also illustrated is the fact that the polarizing cryostat 1 is in operable communication with a source 14 of ^3He and a source 15 of ^4He . A second heat source 16, that is, a source of material that can be used to heat the hyperpolarized material from a temperature below the temperature at which the hyperpolarized material experiences a minimum T1 to a higher temperature is also illustrated. Fig. 2 also illustrates that system 7 includes a transmit RF coil 17, a detector 18 (such as a receive coil array and supporting hardware), as well as a computer terminal/processor 19 for receiving and processing received data.

In a preferred embodiment, magnet 9 is an electromagnet. This permits the magnetic field of the transfer vessel 3 to be selectively deactivated to prevent the field of the

transfer vessel 3 from interfering with MR system operation. Alternatively, the field can be well-shielded to minimize interference. If desired, the hyperpolarized precursor for making the hyperpolarized mixture may be made on site in relatively close proximity to the MR system.

The methods and systems of the present disclosure, as described above and shown in the drawings, provide for superior hyperpolarized materials and methods for making the same. It will be apparent to those skilled in the art that various modifications and variations can be made in the device and method of the disclosed embodiments without departing from the spirit or scope of the disclosed embodiments. Thus, it is intended that the present disclosure include modifications and variations that are within the scope of the subject disclosure and equivalents.

CLAIMS

What is claimed is:

1. A method of producing a material containing hyperpolarized nuclei, comprising:
 - a) formatting a first material into a high surface area configuration;
 - b) in a polarizing cryostat, exposing the first material to ^3He at a temperature below about 10K and a magnetic field in a manner sufficient to substantially increase the polarization of the first material;
 - c) increasing the temperature of the first material without melting or sublimating the first material resulting in nuclei in the first material becoming hyperpolarized; and
 - d) reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.
2. The method of Claim 1, wherein the mixture is a solution.
3. The method of any of the preceding claims, further comprising melting the first material prior to the reacting step.
4. The method of any of the preceding claims, further comprising melting the first material as part of the reacting step.
5. The method of any of the preceding claims, further comprising exposing the first material to ^4He after exposing the first material to ^3He .
6. The method of any of the preceding claims, further comprising storing the first material in a hyperpolarized condition in a separate cryostat and transporting the first material in the separate cryostat to a site remote from where it was hyperpolarized prior to step (d).
7. The method of any of the preceding claims, wherein the nuclei in the first material includes at least one material selected from the group consisting of ^{13}C , ^{15}N , ^1H , ^{31}P and ^{29}Si .

8. The method of any of the preceding claims, further comprising substantially increasing the temperature of the first material without melting or sublimating the material after step (c).

9. The method of Claim 8, wherein the temperature is increased from a first temperature substantially below the temperature at which the T1 of the first material experiences a minimum to a second temperature substantially above the temperature at which the T1 of the first material experiences a minimum.

10. The method of Claim 9, wherein the temperature of the first material is increased from a temperature below about 10K to a temperature of about 200K.

11. The method of Claim 9, wherein the temperature of the first material is increased in the presence of a magnetic field at a rate wherein less than about 90 percent of polarization imparted to nuclei in the first material is lost.

12. The method of Claim 9, further comprising the step of transporting the first material to a location within the fringe field of an MR system after the first material has reached the second temperature.

13. The method of Claim 2, further including the step of removing the first material from the polarizing cryostat upon completion of step (c).

14. The method of Claim 13, further comprising transferring the first material into a transport cryostat upon completion of step (c).

15. The method of Claim 14, further comprising transporting the transport cryostat to an end user.

16. The method of Claim 15, further comprising transferring the first material from the transport cryostat into a transfer vessel.

17. The method of Claim 16, wherein the transfer vessel includes a magnet for maintaining the first material in a magnetic field.

18. The method of Claim 16, further comprising increasing the temperature from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum.

19. The method of Claim 18, wherein the temperature is raised to the second temperature at substantially the same time the first material is transferred into the transfer vessel.

20. The method of Claim 19, wherein the temperature is raised to the second temperature in less than about thirty seconds in a magnetic field having a strength between about 0.1 Tesla and about 10 Tesla.

21. The method of Claim 18, further comprising the step of disposing the first material in a mixing device within the fringe field of a MR system.

22. The method of Claim 21, wherein at least a portion of the reacting step occurs within the mixing device.

23. The method of Claim 22, wherein the magnet of the transfer vessel is turned off prior to performing an MR system operation.

24. The method of any of the preceding claims, wherein the first material includes an acid and the at least one other material includes a base.

25. The method of any of Claims 1-23, wherein the first material includes a base and the at least one other material includes an acid.

26. The method of any of claims 24-25, wherein the acid includes an acid selected from the group consisting of acetic acid, formic, lactic and pyruvic acid.
27. The method of any of claims 24-25, wherein the acid includes acetic acid.
28. The method of any of claims 24-25, wherein the acid includes formic acid.
29. The method of any of claims 24-25, wherein the acid includes lactic acid.
30. The method of any of claims 24-25, wherein the acid includes pyruvic acid.
31. The method of any of claims 24-30, wherein the acid is isotopically enhanced in one or more of its carbon sites with ^{13}C .
32. The method of any of claims 24-31, wherein the at least one other material includes sodium.
33. The method of Claim 32, wherein the at least one other material includes material selected from the group consisting of sodium hydroxide and sodium bicarbonate.
34. The method of Claim 32, wherein the at least one other material includes sodium bicarbonate.
35. The method of Claim 32, wherein the at least one other material includes sodium hydroxide.
36. The method of any of Claims 1-35, wherein the first material is a liquid at STP.
37. The method of any of Claims 1-35, wherein the first material is a solid at STP.
38. The method of any of Claims 1-35, wherein the first material is a gas at STP.

39. The method of any of the preceding claims, wherein the first material is frozen in step (a) in a manner that it has a surface area to volume ratio greater than about $0.1 \text{ m}^2/\text{g}$.

40. A method of magnetic resonance (MR) investigation of a subject including a human subject or other organism, said method comprising:

- a) producing a mixture including hyperpolarized nuclei in accordance with any of the preceding claims;
- b) administering the mixture to the subject;
- c) exposing the subject to radiation of a frequency selected to excite nuclear spin transitions in the hyperpolarized nuclei; and
- d) detecting magnetic resonance signals from the subject.

41. The method of Claim 40, further comprising generating at least one of an image, dynamic flow data, diffusion data, perfusion data, physiological data or metabolic data from the detected signals.

42. The method of Claim 41 wherein the hyperpolarized nuclei in the mixture have a T1 value of at least 5 seconds at a field strength in the range 0.01-5 T and at a temperature in the range of 20-40°C.

43. A method of producing a material including hyperpolarized nuclei comprising:

- a) increasing the state of polarization of a first material in the absence of a source of free electrons or paramagnetic impurities at a temperature below about 10K in the presence of a magnetic field;
- b) increasing the temperature of the first material without melting it resulting in nuclei in the first material becoming hyperpolarized; and
- c) reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.

44. The method of Claim 43, wherein the mixture is a solution.

45. The method of any of the preceding claims, wherein the first material includes a methyl group.
46. The method of any of the preceding claims, wherein the mixture includes pairs of bonded nuclei.
47. The method of Claim 46, wherein at least a portion of the bonded nuclei are hyperpolarized.
48. A method of producing a material containing hyperpolarized nuclei, comprising:
- a) formatting a first material including a methyl group into a high surface area configuration;
 - b) increasing the nuclear polarization of the first material; and
 - c) increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material within a time period less than about thirty seconds.
49. A method of producing a material containing hyperpolarized nuclei, comprising:
- a) formatting a first material including a methyl group into a high surface area configuration;
 - b) increasing the nuclear polarization of the first material; and
 - c) increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material within a time period less than about thirty seconds, wherein less than about 90 percent of the polarization is lost during the warming step.
50. The method of Claim 49, further comprising reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.

51. A method of producing a material containing hyperpolarized nuclei, comprising:
- hyperpolarizing a first material; and
 - increasing the temperature from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material.
52. A method of producing a material containing hyperpolarized nuclei, comprising:
- formatting a first material into a high surface area configuration;
 - in a polarizing cryostat, exposing the first material to ^3He at a temperature below about 10K and a magnetic field in a manner sufficient to substantially increase the polarization of the first material; and
 - reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.
53. A method of producing a mixture including hyperpolarized nuclei comprising:
- providing a precursor including hyperpolarized nuclei;
 - disposing the precursor in the stray field of an MR system; and
 - reacting the precursor with at least one other material to form a mixture including hyperpolarized nuclei.
54. A hyperpolarized material made according to the process of any of the preceding claims.
55. A system for producing a material containing hyperpolarized nuclei, comprising:
- a polarizing cryostat including a vessel for exposing a first material formatted into a high surface area configuration to ^3He at a temperature below about 10K and a magnet adapted and configured to provide a magnetic field in a manner sufficient to substantially increase the polarization of the first material;

b) a first heat source for increasing the temperature of the first material without melting or sublimating the first material resulting in nuclei in the first material becoming hyperpolarized; and

c) a mixing device for reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.

56. The system of Claim 55, wherein the mixture is a solution.

57. The system of any of the preceding claims, further comprising a second heat source for melting the first material to permit the first material to react.

58. The system of Claim 57, wherein the second heat source includes the material with which the first material is mixed in the mixing device.

59. The system of any of the preceding claims, further comprising means for exposing the first material to ^4He after exposing the first material to ^3He .

60. The system of any of the preceding claims, further comprising a transport cryostat in which the first material in a hyperpolarized condition is stored, the transport cryostat being suitable for transporting the first material to a site remote from where the first material was hyperpolarized.

61. The system of any of the preceding claims, wherein the nuclei in the first material includes at least one material selected from the group consisting of ^{13}C , ^{15}N , ^1H , ^{31}P and ^{29}Si .

62. The system of any of the preceding claims, further comprising means for substantially increasing the temperature of the first material without melting or sublimating the material after the first material becomes hyperpolarized.

63. The system of Claim 62, wherein the system is adapted and configured to increase the temperature from a first temperature substantially below the temperature at which the T1 of the

first material experiences a minimum to a second temperature substantially above the temperature at which the T1 of the first material experiences a minimum.

64. The system of Claim 63, wherein the system is adapted and configured to increase the temperature of the first material from a temperature below about 10K to a temperature of about 200K.

65. The system of Claim 60, further comprising a transfer vessel for receiving the first material from the transport cryostat.

66. The system of Claim 65, wherein the transfer vessel includes a magnet for maintaining the first material in a magnetic field.

67. The system of Claim 65, further comprising a mixing device for receiving the first material from the transfer vessel.

68. The system of Claim 67, wherein the mixing device and transfer vessel are adapted and configured to be operated within the fringe field of a MR system.

69. The system of Claim 68, wherein the magnet of the transfer vessel is adapted and configured to be turned off prior to performing an MR system operation.

70. The system of any of Claims 55-69, wherein the first material is a liquid at STP.

71. The system of any of Claims 55-69, wherein the first material is a solid at STP.

72. The system of any of Claims 55-69, wherein the first material is a gas at STP.

73. The system of any of the preceding claims, wherein the first material is in a high surface area configuration that has a surface area to volume ratio greater than about 0.1 m²/g.

74. A system of magnetic resonance (MR) investigation of a subject including a human subject or other organism, said MR system comprising:

- a) means for producing a mixture including hyperpolarized nuclei in accordance with any of the preceding claims;
- b) an injector for administering the mixture to the subject;
- c) at least one radio frequency coil for exposing the subject to radiation of a frequency selected to excite nuclear spin transitions in the hyperpolarized nuclei; and
- d) a detector for detecting magnetic resonance signals from the subject.

75. The system of Claim 74, further comprising means for generating at least one of an image, dynamic flow data, diffusion data, perfusion data, physiological data or metabolic data from signals received from the detector.

76. A system for producing a material including hyperpolarized nuclei comprising:

- a) means for increasing the state of polarization of a first material in the absence of a source of free electrons or paramagnetic impurities at a temperature below about 10K in the presence of a magnetic field;
- b) means for increasing the temperature of the first material without melting it resulting in nuclei in the first material becoming hyperpolarized; and
- c) means for reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.

77. The system of any of the preceding claims, wherein the first material includes a methyl group.

78. The system of any of the preceding claims, wherein the mixture includes pairs of bonded nuclei.

79. The system of Claim 78, wherein at least a portion of the bonded nuclei are hyperpolarized.

80. A system for producing a material containing hyperpolarized nuclei, comprising:
- a) means for formatting a first material including a methyl group into a high surface area configuration;
 - b) means for increasing the nuclear polarization of the first material; and
 - c) means for increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material within a time period less than about thirty seconds.
81. A system for producing a material containing hyperpolarized nuclei, comprising:
- a) means for formatting a first material including a methyl group into a high surface area configuration;
 - b) means for increasing the nuclear polarization of the first material; and
 - c) means for increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material within a time period less than about thirty seconds, wherein less than about 90 percent of the polarization is lost during the warming step.
82. The system of Claim 81, further comprising means for reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.
83. A system for producing a material containing hyperpolarized nuclei, comprising:
- a) means for hyperpolarizing a first material; and
 - b) means for increasing the temperature of the first material from a first temperature below the temperature at which the T1 of the first material experiences a minimum to a second temperature above the temperature at which the T1 of the first material experiences a minimum without melting or sublimating the first material.
84. A system for producing a material containing hyperpolarized nuclei, comprising:

- a) means for formatting a first material into a high surface area configuration;
- b) a polarizing cryostat including means for exposing the first material to ^3He at a temperature below about 10K and a magnet for generating a magnetic field in a manner sufficient to substantially increase the polarization of the first material; and
- c) a mixing device for reacting the first material with at least one other material to form a mixture including hyperpolarized nuclei.

85. A system for producing a mixture including hyperpolarized nuclei comprising:

- a) means for providing a precursor including hyperpolarized nuclei;
- b) means for disposing the precursor in the stray field of an MR system; and
- c) means for reacting the precursor with at least one other material to form a mixture including hyperpolarized nuclei.