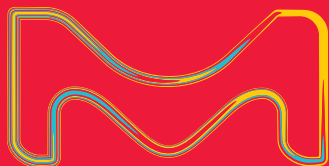


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Dynamic Nuclear Polarization

Dr. Matthew E. Merritt, Assistant Professor,
Advanced Imaging Research Center,
Southwestern Medical Center at Dallas

Dynamic Nuclear Polarization (DNP) is a phenomenon by which high spin polarization, typically derived from a bath of free radical electrons, is transferred to a nuclear spin bath, enhancing the difference between the nuclear energy levels and thereby producing dramatically enhanced NMR signals for detection. The phenomenon was first predicted by Overhauser,¹ but was not observed experimentally until the work of Slichter in metals in 1953.² It was soon understood that the same technique could be used to develop high polarizations of ^1H , ^2H , and ^{13}C in non-conducting solids. This advance became foundational for production of solid targets for high energy physics research.³⁻⁵ High nuclear polarizations in the targets simplified the results of neutron scattering experiments. Subsequently, the DNP method migrated to chemistry, being used to study a variety of structural questions in the solid state.^{6,7} Robert Griffin of MIT has pioneered the use of DNP for signal enhancement in solid state NMR distance measurements for structural biology.⁸ In his method, a water soluble free radical is doped into a matrix containing H_2O /glycerol and the solute molecule/protein to be studied. This method has recently been used to study the K intermediate of bacteriorhodopsin in intact purple membrane.⁹ While DNP is also possible in the liquid state, it is much less efficient due to the diminishment of the intermolecular dipolar couplings by fast molecular tumbling.¹⁰

The production of hyperpolarized molecular imaging agents has sparked great enthusiasm in the MRI community due to its potential application as a clinically viable method for assessing *in vivo* metabolism. Golman and co-workers demonstrated that a hyperpolarized solid may be rapidly melted with a bolus of boiling water and shuttled out of the DNP system using high pressure helium gas.¹¹ The hyperpolarized solute molecule can be used as an imaging agent¹²⁻¹⁴. The most popular molecule to date for hyperpolarization studies has been $[1-^{13}\text{C}]\text{pyruvate}$, though other common metabolites have also been used successfully. This technique now stands as one of the most promising new methods for measuring *in vivo* metabolism.

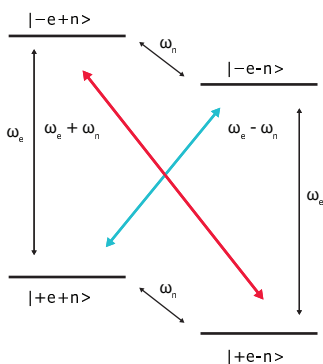


Figure 1. Energy level diagram for a coupled electron-nuclear spin system. The normally forbidden transitions (colored arrows) can be excited by microwave irradiation, resulting in dramatically increased nuclear polarizations.

Dynamic Nuclear Polarization

The DNP phenomenon was first recognized as theoretically possible as an outflow of basic research into the nature of cross relaxation in NMR. Figure 1 shows the energy level diagram for a single electron coupled to a nuclear spin in a strong magnetic field. The gyromagnetic ratio for an electron spin is ~ 2400 times greater than that of a ^{13}C nucleus. Therefore the single quantum transitions associated with the electrons are in the gigahertz regime (94 GHz at 3.35T) while the carbon Larmor frequency is ~ 35 MHz. Normally, zero (Figure 1 red arrow) or double quantum transitions (Figure 1 green arrow) are strictly forbidden. However, the hyperfine coupling between the spins is of sufficient magnitude that the 4 energy levels are not pure states, and consequently these transitions become partially allowed. Under microwave irradiation at the electron resonance frequency \pm the nuclear frequency these transitions are stimulated and the nuclear polarization is enhanced in a positive or negative manner depending on the transition that is irradiated (Figure 2). This is known in the literature as the solid effect. This mechanism is active when the electron resonance has a linewidth of the same order or less than the nuclear Larmor frequency. This is commonly the case when the trityl radical is used for polarizing protons. However, at 3.35T, the FWHM of the electron resonance is ~ 44 MHz.¹⁵ Therefore, when using trityl and ^{13}C , the thermal mixing mechanism is likely the main source of polarization. Thermal mixing is another DNP mechanism that is active when the electron resonance is wider than the nuclear Larmor frequency, as is common when nitroxide radicals such as TEMPO are used or when lower γ nuclei are the targets. An excellent description of the differences between the two mechanisms is outlined in the paper by Comment, et. al.¹⁶ In a somewhat simplified picture, thermal mixing is a three spin effect as opposed to two in the solid effect. It also depends upon strong dipolar couplings between electron spins, in effect, the presence of an electron spin bath that can be described with a single temperature. Irradiation of the bath at a certain frequency causes other coupled electron spins to flip. Since the spins at other resonance frequencies have slightly different energies, the difference can be made up with a coupled nuclear spin. Since a difference in frequencies is still necessary like in the solid effect, thermal mixing again produces characteristic positive and negative enhancements, though the maxima are separated by a number closer to the Larmor frequency of the nucleus (Figure 2). Traditionally, it has been understood that the solid effect required more power than thermal mixing since forbidden transitions are pumped. In thermal mixing, no forbidden transitions are present and therefore it might be expected to be a more efficient mechanism. This likely explains the extremely high polarizations achievable when using trityl and ^{13}C . New bi-radicals seek to increase the available polarization by tethering the free electrons together, resulting in stronger electron dipolar couplings and enhancing thermal mixing for protons.¹⁷

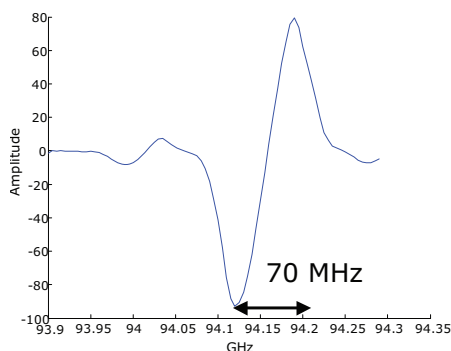


Figure 2. DNP enhancement curve as a function of frequency for $[1-^{13}\text{C}]$ pyruvate mixed with the trityl radical. Each data point was collected after irradiation for 300 seconds, which is not long enough to reach the equilibrium polarization. The 70 MHz splitting observed would lead one to believe that the solid effect is active, but longer irradiation times show a splitting between the maxima of ~ 63 MHz, indicating thermal mixing as the source of enhancement.

Fast Dissolution DNP

The DNP method developed by Golman and co-workers has several essential elements that allow the spectacular signal enhancements seen to date.¹¹ First, the experiment is carried out at 1.2 to 1.4 K. At room temperature, the enhancement from DNP goes as the ratio of the gyromagnetic ratios of the dipolar coupled spins. At these very low temperatures, the Boltzmann distribution begins to display exponential behavior; at 1.4 K the electrons are $\sim 92\%$ polarized as opposed to less than 1% for ^1H and ^{13}C . Consequently, DNP at low temperatures can produce nuclear polarizations in the percent range as well, which is far greater than the enhancement available at room temperature. The second key insight was the realization that the sample could be melted on a time-scale fast enough that large polarizations were left over after the dissolution. The developed polarization decays with the normal T_1 of the nucleus. If the melting is slow, sufficient sensitivity is not retained in the experiment. Typically, melting of a 40 to 200 μL DNP sample is accomplished with 3 mL–6 mL of water at $\sim 190^\circ\text{C}$ and 10 bar of pressure supplied by a compressed helium tank. Due to the constraints imposed by the decay of the magnetization, protonated carbons are typically more difficult to use for DNP. C-1 labeled pyruvate has been a metabolite of choice since the C-3 protons are distal from the observed carbon. Hence, the primary source of relaxation arises from the chemical shift anisotropy. The T_1 of the C-1 carbon of pyruvate is close to 1 minute at 1.5 Tesla and ~ 40 seconds at 14.1 T.

Metabolism using Hyperpolarization Technique

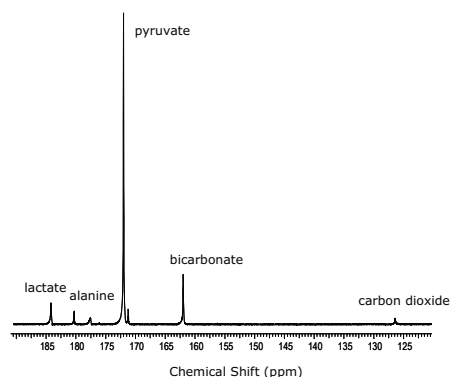


Figure 3. Carbon-13 NMR spectrum of a perfused mouse heart following injection of 2 mM hyperpolarized $[1-^{13}\text{C}]$ pyruvate. The spectrum is a sum of 70 scans. All metabolites generated from the pyruvate are also ^{13}C labeled.

The central feature that makes imaging or spectroscopy using hyperpolarized ^{13}C labeled compounds so appealing is the incredible gains in signal to noise that can be achieved, allowing observation of biochemical reactions *in vivo* and *in vitro* that previously could not be monitored with any technique (Figure 3). The most common example, hyperpolarized $[1-^{13}\text{C}]$ pyruvate illustrates the high information content of MR combined with hyperpolarization in powerful fashion. Figure 4 shows the information available by three different methods for assessing metabolism. Assume that three different samples have been prepared, a ^{13}C labeled pyruvate, $[3-^{13}\text{C}]$ pyruvate, and hyperpolarized $[1-^{13}\text{C}]$ pyruvate, for injection into a commonly used model of metabolism, the perfused rat heart. Observation of the ^{13}C compound by positron emission tomography (PET) will reveal only the uptake of the pyruvate, producing the familiar dose-response curve (Figure 4, A). Observation of the delivery of the $[3-^{13}\text{C}]$ pyruvate by NMR would allow not only the uptake of the pyruvate to be monitored, but also its subsequent metabolism to lactate and alanine. It has been shown that detection of the label using indirect methods such as heteronuclear multiple quantum coherence (HMQC) can allow time points to be taken approximately every 10–20 seconds (Figure 4, B).¹⁸ The bottom panel shows the data that would be obtained following injection of the hyperpolarized substrate (Figure 4, C). Due to the increase in signal to noise, time points can be taken every second, or even faster. Also, since direct detection of the ^{13}C label is possible, flux into CO_2 and bicarbonate is detectable as well. In this lab, the signal to noise gain for the hyperpolarization experiment versus the HMQC method is approximately 50 times, with the bonus of much higher resolution as a function of time following the injection. The power of this technique has already been taken advantage of to study a variety of questions with physiological and pathological significance. Hyperpolarized $\text{H}^{13}\text{CO}_3^-$ has been used as a means of assessing pH by monitoring the equilibrium between CO_2 and bicarbonate.¹⁹ This method of pH measurement has the unique advantage of injecting a completely benign compound as the sensor. Hyperpolarized $[1-^{13}\text{C}]$ pyruvate has been used to measure substrate preference in a perfused heart model, demonstrating the ability to assess flux through a single enzyme catalyzed reaction.²⁰ Workers at Cambridge University and UCSF have already shown that the kinetics of dispersal of hyperpolarized pyruvate is sensitive to cancer *in vivo*.^{21–23} Cardiac dysfunction following myocardial infarction could also potentially be detected with this method.^{24,25}

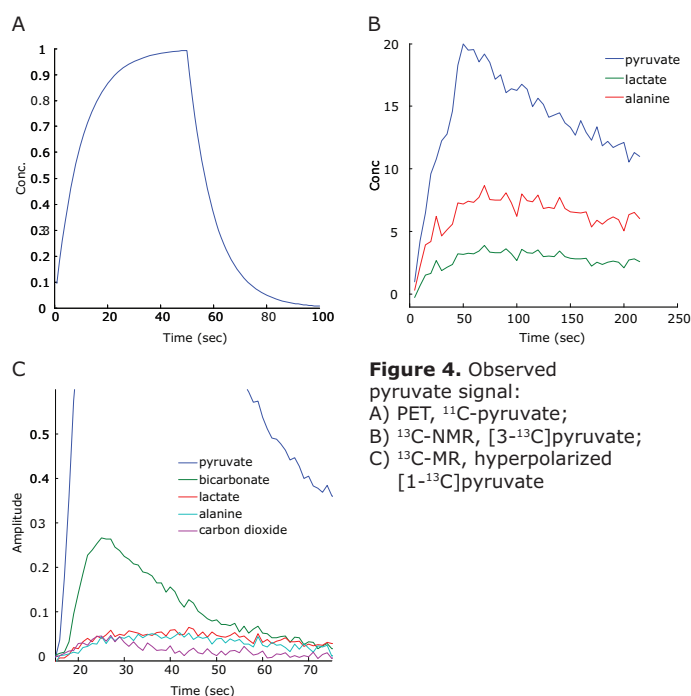


Figure 4. Observed pyruvate signal: A) PET, ^{13}C -pyruvate; B) ^{13}C -NMR, $[3-^{13}\text{C}]$ pyruvate; C) ^{13}C -MR, hyperpolarized $[1-^{13}\text{C}]$ pyruvate

Conclusion

In summary, hyperpolarization of ^{13}C compounds is an extremely promising new avenue for molecular imaging and metabolism studies. Applications to cancer and cardiac metabolism are currently under development. Clinically relevant measures of metabolism with this technique should become available during the next decade.

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Parahydrogen-Induced Polarization

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Parahydrogen-Induced Polarization (PHIP) or Parahydrogen And Synthesis Allow Dramatically Enhanced Nuclear Alignment (PASADENA)¹ is a liquid state chemical technique of hyperpolarization which can be accomplished in seconds at room temperature. Dynamic Nuclear Polarization (DNP) is a solid state method of hyperpolarization where polarizations takes place at low temperature, high magnetic field, and with unpaired electron of selected species (e.g. triaryl radical) to produce strongly polarized nuclear spins in the solid state in hours. The solid sample is subsequently dissolved rapidly in water to create a solution of molecules with hyperpolarized nuclear spins.² DNP polarizer is now commercially available from Oxford Instruments. PHIP is usually accomplished in home-made polarizer systems.^{3,4} PHIP is limited to molecules with unsaturation (double or triple bonds) while DNP is a more general method and may be applied to a wider range of molecules. PHIP is a relatively inexpensive method of hyperpolarization compared to DNP and since the polarization can be accomplished in seconds to minutes in the PHIP polarizer, this technique can be used for several experimental trials within a short period of time. Both DNP and PHIP have been used for *in vivo* applications and real time metabolic and molecular imaging.

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Researchers are using stable isotopes for advanced technologies such as hyperpolarization for *in vivo* MRI imaging^{1,2} to create metabolic profiles to map and study alterations due to diseases. Dynamic Nuclear Polarization (DNP) and Para Hydrogen Induced Polarization (PHIP) are

the two hyperpolarization techniques currently used in MRI. Each technique has its advantages that researchers are exploring for its potential in clinical applications.

Stable isotopes in conjunction with ¹³C-MRS *in vivo* techniques provide a way to explore fluxes through energy related metabolic pathways. Various ¹³C labeled glucose, pyruvate and lactate compounds elucidate tricarboxylic acid (TCA) cycle turnover and glutamate and glutamine metabolism.^{3,4} As such, ¹³C-MRS studies involves understanding metabolism at the molecular level.

Literature of Interest

1. Golman, K.; Zandt, R.; Thaning, M. M. *Proc Natl Acad Sci USA* **2006**, *Jul 25*: 103(30), 270–5. Real-time metabolic imaging.
2. Bhattacharya, P.; Chekmenev, E. Y.; Perman, W. H.; Harris, K. C.; Lin, A. P.; Norton, V. A.; Tan, C. T.; Ross, B. D.; Weitekamp, D. P. *J Magn Reson.* **2007**, *May*: 186(1), 50–5. Towards hyperpolarized ¹³C-succinate imaging of brain cancer.
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Compounds of Interest

Description	Isotopic Purity	Cat. No.
Acetic Acid-1- ¹³ C	99 atom % ¹³ C	279285
Acetic Acid-2- ¹³ C	99 atom % ¹³ C	279307
Acetic Acid- ¹³ C ₂	99 atom % ¹³ C	282022
Acetone-1,3- ¹³ C ₂	99 atom % ¹³ C	299189
Acetone-2- ¹³ C	99 atom % ¹³ C	299197
Acetone- ¹³ C ₃	99 atom % ¹³ C	491667
Acetyl-1,2- ¹³ C ₂ Coenzyme A, lithium salt	99 atom % ¹³ C	658650
Acetylene Dicarboxylic Acid-1- ¹³ C, disodium salt	99 atom % ¹³ C	665223
L-Alanine-1- ¹³ C	99 atom % ¹³ C	489867
L-Alanine-2- ¹³ C	99 atom % ¹³ C	486779
L-Alanine-3- ¹³ C	99 atom % ¹³ C	489948
L-Alanine-2,3- ¹³ C ₂	99 atom % ¹³ C	604682
L-Alanine- ¹³ C ₃	99 atom % ¹³ C	489875
4-Amino-TEMPO-Piperidiny-d ₁₇	98 atom % D	588741
Ammonium- ¹⁵ N Acetate	98 atom % ¹⁵ N	363006
L-Asparagine-4- ¹³ C monohydrate	99 atom % ¹³ C	579866
L-Aspartic Acid-1- ¹³ C	99 atom % ¹³ C	489972
<i>tert</i> -Butan-2- ¹³ C, d ₅ -ol	99 atom % ¹³ C, 98 atom % D	679860
Butyric Acid-1- ¹³ C	99 atom % ¹³ C	488372
Butyric Acid-2- ¹³ C	99 atom % ¹³ C	588547
Butyric-Acid-4,4,4-d ₃	98 atom % D	615706
Choline-2- ¹³ C,1,1,2,2-d ₄ Chloride	99 atom % ¹³ C, 98 atom % D	707996
Choline- ¹⁵ N Chloride	98 atom % ¹⁵ N	609269
Diethyl Glutarate- ¹³ C ₅	99 atom % ¹³ C	655708
Ethanol-1- ¹³ C	99 atom % ¹³ C	324523
Ethanol-2- ¹³ C	99 atom % ¹³ C	427047
Ethanol- ¹³ C ₂	99 atom % ¹³ C	427039
Ethanol- ¹³ C ₂ ,d ₅	99 atom % ¹³ C, 98 atom % D	682586
Ethanolamine-2- ¹³ C	99 atom % ¹³ C	606316
Ethanolamine- ¹³ C ₂	99 atom % ¹³ C	606294
Ethanolamine- ¹³ C ₂ ·HCl	99 atom % ¹³ C	606308
Ethyl Acetoacetate-1,3- ¹³ C ₂	99 atom % ¹³ C	485640
Ethyl Acetoacetate-2,4- ¹³ C ₂	99 atom % ¹³ C	485659
Ethyl Acetoacetate-1,2,3,4- ¹³ C ₄	99 atom % ¹³ C	489263
Ethyl Pyruvate-3- ¹³ C	99 atom % ¹³ C	676594
D-Fructose-1- ¹³ C	99 atom % ¹³ C	415553
D-Fructose- ¹³ C ₆	99 atom % ¹³ C	587621
Fumaric Acid-2,3- ¹³ C ₂	99 atom % ¹³ C	606073
Fumaric Acid- ¹³ C ₄	99 atom % ¹³ C	606014
D-Galactose-1- ¹³ C	99 atom % ¹³ C	415545
D-Galactose-1- ¹³ C, S&P tested	99 atom % ¹³ C	661406
D-Galactose-2- ¹³ C	99 atom % ¹³ C	454621
D-Galactose- ¹³ C ₆	99 atom % ¹³ C	605379
D-Glucose-1- ¹³ C	99 atom % ¹³ C	297046
D-Glucose-1- ¹³ C, S&P tested	99 atom % ¹³ C	660655
D-Glucose-2- ¹³ C	99 atom % ¹³ C	310794
D-Glucose-2- ¹³ C, S&P tested	99 atom % ¹³ C	661457
D-Glucose-6- ¹³ C	99 atom % ¹³ C	310808
D-Glucose-6- ¹³ C, S&P tested	99 atom % ¹³ C	661430
D-Glucose-1,2- ¹³ C ₂	99 atom % ¹³ C	453188
D-Glucose-1,2-, S&P tested	99 atom % ¹³ C	661422
D-Glucose-1,6- ¹³ C ₂	99 atom % ¹³ C	453196
D-Glucose-1,6- ¹³ C ₂ , S&P tested	99 atom % ¹³ C	661449
D-Glucose-2,5- ¹³ C ₂	99 atom % ¹³ C	605506
D-Glucose- ¹³ C ₆	99 atom % ¹³ C	389374
D-Glucose- ¹³ C ₆ , S&P tested	99 atom % ¹³ C	660663
D-Glucose-6,6-d ₂	98 atom % D	282650
D-Glucose-6,6-d ₂ , S&P tested	98 atom % D	661414

Description	Isotopic Purity	Cat. No.
D-Glucose-C-d ₇	98 atom % D	552003
L-Glutamic Acid-1- ¹³ C	99 atom % ¹³ C	604968
L-Glutamic Acid-2- ¹³ C	99 atom % ¹³ C	605123
L-Glutamic Acid-3- ¹³ C	99 atom % ¹³ C	490016
L-Glutamic Acid-4- ¹³ C	99 atom % ¹³ C	587672
L-Glutamic Acid-5- ¹³ C	99 atom % ¹³ C	492922
L-Glutamic Acid- ¹³ C ₅	99 atom % ¹³ C	604860
L-Glutamic Acid-3,4- ¹³ C	99 atom % ¹³ C	691682
L-Glutamine-1- ¹³ C	99 atom % ¹³ C	605018
L-Glutamine-2- ¹³ C	99 atom % ¹³ C	605085
L-Glutamine-3- ¹³ C	99 atom % ¹³ C	604941
L-Glutamine-5- ¹³ C (amide- ¹³ C)	99 atom % ¹³ C	604690
L-Glutamine-1,2- ¹³ C ₂	99 atom % ¹³ C	605220
L-Glutamine-1,2- ¹³ C ₂ , S&P tested	99 atom % ¹³ C	660809
L-Glutamine- ¹³ C ₅	99 atom % ¹³ C	605166
L-Glutamine-2- ¹³ C, ¹⁵ N ₁ (amine- ¹⁵ N)	99 atom % ¹³ C, 98 atom % ¹⁵ N	608122
Glycerol-2- ¹³ C	99 atom % ¹³ C	489484
Glycerol-2- ¹³ C, S&P tested	99 atom % ¹³ C	661465
Glycerol-1,3- ¹³ C ₂	99 atom % ¹³ C	492639
Glycerol- ¹³ C ₃	99 atom % ¹³ C	489476
Glycerol- ¹³ C ₃ , S&P tested	99 atom % ¹³ C	660701
Glycerol-1,1,2,3,3-d ₅	98 atom %D	454524
4-Hydroxy-TEMPO-d ₁₇	98 atom %D	487686
4-Hydroxy-TEMPO- ¹⁵ N	98 atom % ¹⁵ N	705748
L-Isoleucine-1- ¹³ C	99 atom % ¹³ C	604771
Lauric Acid-1- ¹³ C	99 atom % ¹³ C	292168
Lauric Acid-1- ¹³ C, S&P tested	99 atom % ¹³ C	660671
L-Leucine-1- ¹³ C	99 atom % ¹³ C	490059
L-Leucine-1,2- ¹³ C ₂ , S&P tested	99 atom % ¹³ C	604909
L-Leucine-1- ¹³ C, ¹⁵ N	99 atom % ¹³ C, 98 atom % ¹⁵ N	490067
L-Leucine-2- ¹³ C, ¹⁵ N	99 atom % ¹³ C, 98 atom % ¹⁵ N	607657
L-Leucine-5,5,5-d ₃	98 atom % D	486825
L-Leucine-5,5,5-d ₃ , S&P tested	98 atom % D	661554
L-Leucine- ¹⁵ N	98 atom % ¹⁵ N	340960
Linoleic Acid- ¹³ C ₁₈	99 atom % ¹³ C	605735
L-Lysine-1- ¹³ C·HCl, S&P tested	99 atom % ¹³ C	660833
D-Mannitol-1- ¹³ C	99 atom % ¹³ C	454613
D-Mannitol- ¹³ C ₆	99 atom % ¹³ C	605492
D-Mannose-1- ¹³ C	99 atom % ¹³ C	415537
Malonyl- ¹³ C ₃ Coenzyme A, lithium salt	99 atom % ¹³ C	655759
Myristic Acid-1- ¹³ C	99 atom % ¹³ C	490873
Myristic Acid-1- ¹³ C, S&P tested	99 atom % ¹³ C	661155
Myristic Acid- ¹³ C ₁₄	99 atom % ¹³ C	605689
Octanoic Acid-1- ¹³ C	99 atom % ¹³ C	296457
Octanoic Acid-2- ¹³ C	99 atom % ¹³ C	591076
Octanoic Acid-1,2,3,4- ¹³ C ₄	99 atom % ¹³ C	493163
Octanoyl-2,4,6,8- ¹³ C ₄ Coenzyme A, lithium salt	99 atom % ¹³ C	703885
Oleic Acid-1- ¹³ C	99 atom % ¹³ C	490423
Oleic Acid-1- ¹³ C, S&P tested	99 atom % ¹³ C	661589
Oleic Acid-1,2,3,7,8,9,10- ¹³ C ₇	99 atom % ¹³ C	646458
Oleic Acid- ¹³ C ₁₈	99 atom % ¹³ C	490431
Oleoyl-1- ¹³ C-L-Carnitine·HCl	99 atom % ¹³ C	597120
Oleoyl- ¹³ C ₁₈ -L-Carnitine·HCl	99 atom % ¹³ C	644404
Oleoyl- ¹³ C ₁₈ Coenzyme A, lithium salt	99 atom % ¹³ C	675768
4-Oxo-TEMPO-d ₁₆	98 atom % D	485268
4-Oxo-TEMPO-1- ¹⁵ N	98 atom % ¹⁵ N	696471

Description	Isotopic Purity	Cat. No.
4-Oxo-TEMPO-d ₁₆ , ¹⁵ N	98 atom % ¹⁵ N, 98 atom % D	487740
4-Oxo-TEMPO-d ₁₇ , 1- ¹⁵ N	98 atom % ¹⁵ N, 98 atom % D	591173
Palmitic Acid-1- ¹³ C	99 atom % ¹³ C	292125
Palmitic Acid-1- ¹³ C, S&P tested	99 atom % ¹³ C	661597
Palmitic Acid-2- ¹³ C	99 atom % ¹³ C	492752
Palmitic Acid-16- ¹³ C	99 atom % ¹³ C	605646
Palmitic Acid-1,2- ¹³ C ₂	99 atom % ¹³ C	485802
Palmitic Acid-1,2,3,4- ¹³ C ₄	99 atom % ¹³ C	489611
Palmitic Acid-2,4,6,8, 10,12,14, 16- ¹³ C ₈	99 atom % ¹³ C	605786
Palmitic Acid- ¹³ C ₁₆	99 atom % ¹³ C	605573
Palmitic Acid- ¹³ C ₁₆ , S&P tested	99 atom % ¹³ C	679372
Palmitoyl-1,2,3,4- ¹³ C ₄ -L- Carnitine·HCl	99 atom % ¹³ C	662127
Palmitoyl-1- ¹³ C Coenzyme A, lithium salt	99 atom % ¹³ C	658200
Palmitoyl- ¹³ C ₁₆ Coenzyme A, lithium salt	99 atom % ¹³ C	655716
L-Phenyl-1- ¹³ C-alanine	99 atom % ¹³ C	605042
L-Phenylalanine-1- ¹³ C	99 atom % ¹³ C	490091
L-Phenylalanine-2- ¹³ C	99 atom % ¹³ C	490113
L-Phenylalanine- ¹³ C ₉ , ¹⁵ N	99 atom % ¹³ C, 98 atom % ¹⁵ N	608017
Potassium Linoleate ¹³ C ₁₈	99 atom % ¹³ C	605816
Potassium Palmitate-1- ¹³ C	99 atom % ¹³ C	489646
Potassium Palmitate-1- ¹³ C, S&P tested	99 atom % ¹³ C	661481
Potassium Palmitate -1,2,3,4- ¹³ C ₄ , S&P tested	99 atom % ¹³ C	605808
Potassium Palmitate -1,3,5,7,9- ¹³ C ₅	99 atom % ¹³ C	676454
Potassium Palmitate- ¹³ C ₁₆	99 atom % ¹³ C	605751
Propionic Acid-1- ¹³ C	99 atom % ¹³ C	282448
L-Proline-1- ¹³ C	99 atom % ¹³ C	589497
L-Proline-1- ¹³ C, S&P tested	99 atom % ¹³ C	661627
Pyruvic-1- ¹³ C Acid (free acid)	99 atom % ¹³ C	677175
Pyruvic-2- ¹³ C Acid (free acid)	99 atom % ¹³ C	692670
L-Serine-1- ¹³ C	99 atom % ¹³ C	490156
L-Serine-2- ¹³ C, ¹⁵ N	99 atom % ¹³ C, 98 atom % ¹⁵ N	485985
Sodium Acetate-1- ¹³ C	99 atom % ¹³ C	279293
Sodium Acetate-1- ¹³ C, S&P tested	99 atom % ¹³ C	668656
Sodium Acetate-2- ¹³ C	99 atom % ¹³ C	279315
Sodium Acetate-2- ¹³ C, S&P tested	99 atom % ¹³ C	660310
Sodium Acetate- ¹³ C ₂	99 atom % ¹³ C	282014
Sodium Acetate- ¹³ C ₂ , S&P tested	99 atom % ¹³ C	663859
Sodium Butyrate-1- ¹³ C	99 atom % ¹³ C	292656
Sodium Butyrate-2- ¹³ C	99 atom % ¹³ C	485357
Sodium Butyrate-3- ¹³ C	99 atom % ¹³ C	588563

Description	Isotopic Purity	Cat. No.
Sodium Butyrate-1,2- ¹³ C ₂	99 atom % ¹³ C	603929
Sodium Butyrate-2,4- ¹³ C ₂	99 atom % ¹³ C	492000
Sodium Butyrate- ¹³ C ₄	99 atom % ¹³ C	488380
Sodium Dichloroacetate- ¹³ C ₂	99 atom % ¹³ C	707198
Sodium D-3-Hydroxybutyrate- 1,2- ¹³ C ₂ , S&P tested	99 atom % ¹³ C	660302
Sodium D-3-Hydroxybutyrate- 1,3- ¹³ C ₂	99 atom % ¹³ C	606111
Sodium D-3-Hydroxybutyrate- 2,4- ¹³ C ₂	99 atom % ¹³ C	674117
Sodium DL-3-Hydroxybutyrate-1- ¹³ C	99 atom % ¹³ C	696323
Sodium DL-3-Hydroxybutyrate-4- ¹³ C	99 atom % ¹³ C	492302
Sodium DL-3-Hydroxybutyrate- 1,3- ¹³ C ₂	99 atom % ¹³ C	488895
Sodium DL-3-Hydroxybutyrate- 2,4- ¹³ C ₂	99 atom % ¹³ C	492299
Sodium DL-3-Hydroxybutyrate- ¹³ C ₄	99 atom % ¹³ C	606030
Sodium D-Lactate-3- ¹³ C solution	99 atom % ¹³ C	676144
Sodium L-Lactate-1- ¹³ C solution	99 atom % ¹³ C	606022
Sodium L-Lactate-2- ¹³ C solution	99 atom % ¹³ C	589209
Sodium L-Lactate-3- ¹³ C solution	99 atom % ¹³ C	490040
Sodium L-Lactate-2,3- ¹³ C ₂ solution	99 atom % ¹³ C	606006
Sodium L-Lactate- ¹³ C ₃ solution	99 atom % ¹³ C	485926
Sodium L-Lactate-2-d ₁ solution	99 atom % ¹³ C	589217
Sodium Octanoate-2,4,6,8- ¹³ C ₄	99 atom % ¹³ C	657204
Sodium Propionate-1- ¹³ C	99 atom % ¹³ C	279455
Sodium Propionate-2- ¹³ C	99 atom % ¹³ C	490660
Sodium Propionate-3- ¹³ C	99 atom % ¹³ C	490679
Sodium Propionate -1,2- ¹³ C ₂	99 atom % ¹³ C	493325
Sodium Propionate-2,3- ¹³ C ₂	99 atom % ¹³ C	493333
Sodium Propionate- ¹³ C ₃	99 atom % ¹³ C	490636
Sodium Propionate- ¹³ C ₃ , S&P tested	99 atom % ¹³ C	660949
Sodium Pyruvate-1- ¹³ C	99 atom % ¹³ C	490709
Sodium Pyruvate-2- ¹³ C	99 atom % ¹³ C	490725
Sodium Pyruvate-3- ¹³ C	99 atom % ¹³ C	490733
Sodium Pyruvate-1,2- ¹³ C ₂	99 atom % ¹³ C	493392
Sodium Pyruvate-2,3- ¹³ C ₂	99 atom % ¹³ C	486191
Sodium Pyruvate- ¹³ C ₃	99 atom % ¹³ C	490717
Sodium Pyruvate- ¹³ C ₃ , S&P tested	99 atom % ¹³ C, 97 atom % D	660957
Sodium Pyruvate- 2- ¹³ C, 3,3,3-d ₃	99 atom % ¹³ C, 97 atom % D	702242
Stearic Acid-1- ¹³ C	99 atom % ¹³ C	299162
Stearic Acid-2- ¹³ C	99 atom % ¹³ C	591491
Stearic Acid- ¹³ C ₁₈	99 atom % ¹³ C	605581
Stearoyl- ¹³ C ₁₈ Coenzyme A, lithium salt	99 atom % ¹³ C	675776
Succinic Acid-1,4- ¹³ C ₂	99 atom % ¹³ C	485349
Sucrose- ¹³ C ₁₂	99 atom % ¹³ C	605417
D-Xylose-1- ¹³ C	99 atom % ¹³ C	331104
D-Xylose- ¹³ C ₅	98 atom % ¹³ C	666378

Sterility and Pyrogen Tested Material

To prepare these products, our research grade material receives extra processing and testing. Our bulk material receives extra filtering and special handling to control the microbial content of the product. The bulk material is tested for Bacterial Endotoxins and Sterility. The testing is done in bulk form, before subdivision packaging. This bulk test does not guarantee that the subdivision or repackaged aliquot is sterile and pyrogen free when it is received or used by the customer, and does not imply suitability for any particular purpose. If the product must be sterile and pyrogen free for the intended application, we recommend that the product be tested prior to actual use.

Isotopically Labeled Oxygen and Water

Use of ^{17}O or deuterated labeled water in imaging allows researchers to obtain better contrast images and aid in understanding effects of different physiological conditions in an abnormal state. Water- ^{17}O and Oxygen- ^{17}O have been used in MRI to measure cerebral blood flow and to study oxidative metabolism for neurological disorders.¹⁻³ Deuterium oxide (D_2O), a non-visible signal in proton MR has been effectively used with *in vivo* MRI-based techniques to obtain measurement of water fluxes or contrast images.⁴

Labeled Oxygen and Water

Description	Isotopic Purity	Cat. No.
Oxygen- $^{17}\text{O}_2$ (gas)	70 atom % ^{17}O	602779
Oxygen- $^{17}\text{O}_2$ (gas)	60 atom % ^{17}O	602809
Oxygen- $^{17}\text{O}_2$ (gas)	45 atom % ^{17}O	602817
Water- ^{17}O	90 atom % ^{17}O	609862
Water- ^{17}O	80–84.9 atom % ^{17}O	618535
Water- ^{17}O	75–80.9 atom % ^{17}O	603066
Water- ^{17}O	40–44.9 atom % ^{17}O	602965

Description	Isotopic Purity	Cat. No.
Water- ^{17}O	35–39.9 atom % ^{17}O	603007
Water- ^{17}O	25–29.9 atom % ^{17}O	603023
Water- ^{17}O	7–9.9 atom % ^{17}O	645907
Deuterium Oxide	99.9 atom % D	151882
Deuterium Oxide	99.8 atom % D	617385
Deuterium Oxide	99 atom % D	435767
Deuterium Oxide	70 atom % D	613428

Literature of Interest

1. Zhu, X. H.; Zhang, N.; Zhang, Y.; Zhang, X.; Ugurbil, K.; Chen W. *NMR Biomed.* **2005**, Apr;18(2), 83–103 *In vivo* ^{17}O NMR approaches for brain study.
2. Tailor, D. R.; Baumgardner, J. E.; Regatte, R. R.; Leigh, J. S.; Reddy, R. *Neuroimage* **2004**, Jun;22(2), 611–8 Proton MRI of metabolically produced H_2^{17}O using an efficient $^{17}\text{O}_2$ delivery system.
3. Zhang, N.; Zhu, X. H.; Lei, H.; Ugurbil, K.; Chen, W. J. *Cereb Blood Flow Metab.* **2004**, Aug;24(8), 840–8 Simplified methods for calculating cerebral metabolic rate of oxygen based on ^{17}O magnetic resonance spectroscopic imaging measurement during a short $^{17}\text{O}_2$ inhalation.
4. Leung, V. Y. L., et al. *Osteoarthritis and Cartilage*, **2008**, Nov. 16(11), 1312–1318. Age-related degeneration of lumbar intervertebral discs in rabbits revealed by deuterium oxide-assisted MRI.

Nitroxyl Radicals

Nitroxyl radicals are the source for the unpaired electrons needed during the hyperpolarization of a substrate. Labeled radicals can improve the polarization process. Our Stable Isotopes group is committed to design and offer these radicals to enhance your research.

Description	Isotopic Purity	Cat. No.
4-Amino-TEMPO-piperidinyl- d_{17}	98 atom % D	588741
4-Hydroxy-TEMPO- d_{17}	98 atom % D	487686
4-Hydroxy-TEMPO- ^{15}N	98 atom % ^{15}N	705748
4-Oxo-TEMPO- d_{16}	97 atom % D	485268
4-Oxo-TEMPO-1- ^{15}N	98 atom % ^{15}N	696471
4-Oxo-TEMPO- d_{16} , ^{15}N	98 atom % ^{15}N	487740
4-Oxo-TEMPO- d_{17} , 1- ^{15}N	98 atom % ^{15}N	591173



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Antarctica each year?

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Hyperpolarization Using Noble Gases

The challenges of using radioactive gases and obtaining high contrast images of lung for various ventilation disorders, are now answered by images taken after inhalation of hyperpolarized noble gases. ^3He (^3He) or ^{129}Xe (^{129}Xe) can be hyperpolarized by optical pumping of the Rubidium atom via a spin-exchange collision mechanism to obtain higher contrast images for diagnostic lung imaging.^{1,2} There are also studies conducted to obtain "real-time" images by simultaneously using hyperpolarized ^{13}C substrates with ^3He .³ The use of ^{129}Xe also offers the potential for imaging organs other than lungs for circulatory disorders, due to its diffusion properties in blood and tissues.

Hyperpolarization of noble gases such as ^3He and ^{129}Xe offers the following benefits in imaging:

- Provides high contrast images for diagnostic testing in lung imaging
- Allows rapid dynamic imaging using ^3He for various ventilation defects
- Increases the sensitivity of these gases by a factor of 100,000⁴
- ^{129}Xe has the potential to image other organs due to its diffusion properties after inhalation

Noble Gases

Description	Isotopic Purity	Cat. No.
Helium- ^3He (Isotopic Grade)	99.9999 atom %	600253*
Helium- ^3He (Chem Pure Grade)	99.95 atom %	600245*
Xenon- ^{129}Xe	99.95 atom % ^{129}Xe	593923
Xenon- ^{129}Xe	80 atom % ^{129}Xe	602140
Xenon- ^{129}Xe	70 atom % ^{129}Xe	602132

*Due to market fluctuations, please inquire about Helium- ^3He availability

Literature of Interest

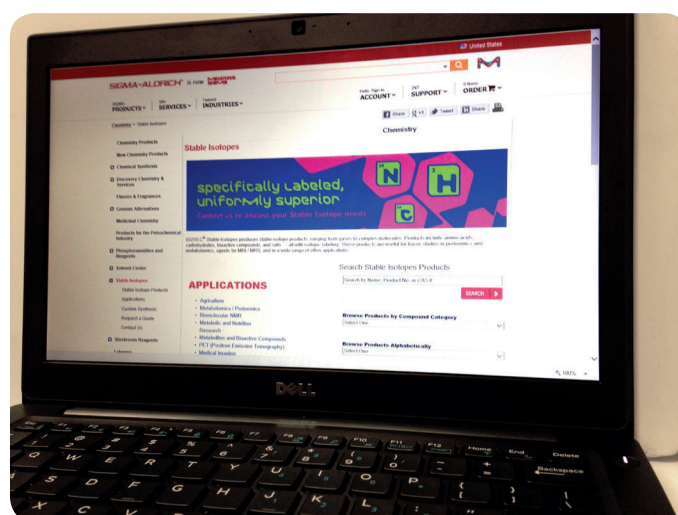
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2. Mugler, J.P. 3rd; Wang, C.; Miller, G. W.; Cates, G. D. Jr.; Mata, J. F.; Brookeman, J. R.; de Lange, E. E.; Altes, T. A. *Acad. Radiol* **2008**, Jun; 15(6), 693–701. Helium-3 diffusion MR imaging of the human lung over multiple time scales.
3. Golman, K.; Olsson, L. E.; Axelsson, O.; Månsson, S.; Karlsson, M.; Petersson, J. S. *Br J Radiol* **2003**, 76 Spec No 2:S, 118–27. Molecular imaging using hyperpolarized ^{13}C .
4. Möller, H. E.; Chen, J. X.; Saam, B.; Hagspiel, K. D.; Johnson, G. A.; Altes, T. A.; de Lange, E. E. *Hans-Ulrich Kauczor Magnetic Resonance in Medicine* **2002**, Jun; 47(6), 1029–51. MRI of the lungs using hyperpolarized noble gases.

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Stable Isotopes in PET

Labeled isotopes used as target materials in imaging have provided insights into understanding various mechanisms of the human physiology and for treatment of diseases. In the PET industry, Water-¹⁸O is widely used for the production of ¹⁸F radionuclides such as ¹⁸F-FDG (Fluoro-deoxyglucose). ¹⁸F-FDG has been used for PET in conjunction with other imaging modalities (CT/SPECT) to diagnose and treat a wide range of diseases from malignancies in the lungs, liver and brain tumors to other neurological disorders such as epilepsy and Alzheimer's.¹⁻³ Water-¹⁶O is a target material for producing ¹³N radionuclides such as ¹³N-Ammonia used for PET myocardial perfusion imaging.^{4,5}

Literature of Interest

- Hoh, C. K. *Nucl Med Biol.* **2007**, Oct;34(7), 737–42. Clinical use of FDG PET.
- Morooka, M.; Kubota, K.; Murata, Y.; Shibuya, H.; Ito, K.; Mochizuki, M.; Akashi, T.; Chiba, T.; Nomura, T.; Ito, H.; Morita, Ann, T. *Nucl Med.* **2008**, Aug;22(7), 635–9. (1 8)F-FDG-PET/CT findings of granulocyte colony stimulating factor (G-CSF)-producing lung tumors.
- Fischman, A. J. *Cancer Treat Res.* **2008**, 143, 67–92. PET Imaging of Brain Tumors.
- Alexánderson, E.; Gómez-León, A.; Vargas, A.; Romero, J. L.; Sierra Fernández, C.; Rodríguez, Valero M.; García-Rojas, L.; Meave, A.; Amigo, M. C. *Rheumatology (Oxford)*. **2008**, Jun; 47 (6), 894–6. Myocardial ischaemia in patients with primary APS: a ¹³N-ammonia PET assessment.
- Mullani, N. A.; Herbst, R. S.; O'Neil, R. G.; Gould, K. L.; Barron, B. J.; Abbruzzese, J. L. *J Nucl Med.* **2008**, Apr;49(4), 517–23. Tumor blood flow measured by PET dynamic imaging of first-pass ¹⁸F-FDG uptake: a comparison with ¹⁵O-labeled water-measured blood flow.

Labeled Target Material

Description	Isotopic Purity	Cat. No.
Water- ¹⁸ O	97 atom % ¹⁸ O	329878
¹⁵ N ₂ /O ₂ (RG) Gas Mix Ratio 39:1	99 atom % ¹⁵ N	600911
¹⁵ N ₂ /O ₂ (RG) Gas Mix Ratio 39:1	95 atom % ¹⁵ N	601020
Oxygen- ¹⁸ O ₂ (gas)	99 atom % ¹⁸ O	602892

Additional Products for PET Imaging

Description	Isotopic Purity	Cat. No.
2-Chloro-2-deoxy-D-glucose		C203
2-Deoxy-2-fluoro-D-glucose		F5006
4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane		291110
Mannose Triflate		M1568
Nitrogen- ¹⁴ N (gas)	99.99 atom % ¹⁴ N	608661
Water- ¹⁶ O	99.99 atom % ¹⁶ O	329886

Water-¹⁸O, 97 atom % for PET Imaging

PET specialists expect consistent, high-quality Water-¹⁸O and our Quality Control department verifies that all of our Water-¹⁸O meet these requirements. QC test results for each batch are displayed on the Certificate of Analysis, accessible at [SigmaAldrich.com](https://www.sigmaaldrich.com)

Test	Methods	Specification
Appearance	Visual	Clear, colorless, free of visible particulate matter
Isotopic Composition (Normalized with respect to Hydrogen isotopes)	MS	Minimum 97 atom% ¹⁸ O Report ¹⁷ O atom% Report ¹⁶ O atom%
Conductivity		≤ 5 μS/cm or μmho/cm
pH		5.5–8.0
Organic Carbon	TOC	≤ 5 ppm
Copper	ICP	≤ 1 ppm
Total Iron/Iron	ICP	≤ 1 ppm
Zinc	ICP	≤ 2 ppm
Calcium	IC	≤ 1 ppm
Potassium	IC	≤ 1 ppm
Magnesium	IC	≤ 1 ppm
Sodium	IC	≤ 2 ppm
Phosphorus/Phosphate	IC	≤ 1 ppm
Sulfur/Sulfate	IC	≤ 1 ppm
Bromide	IC	≤ 1 ppm
Chloride	IC	≤ 1 ppm
Fluoride	IC	≤ 1 ppm
Nitrate	IC	≤ 1 ppm
Ammonium	IC	≤ 1 ppm
Bioburden		≤ 100 CFU/mL
Pyrogen	LAL	≤ 0.25 EU/mL

Catalog No.:
329878

Linear Formula:
H₂¹⁸O

Molecular Weight:
20.02

CAS No.:
14314-42-2

Packaging Specifications:

- Type 1 serum glass vial (or borosilicate)
- Gray butyl rubber, Teflon-coated stopper
- Aluminum crimp seal
- Packaging: 1 g, 0.25 g units

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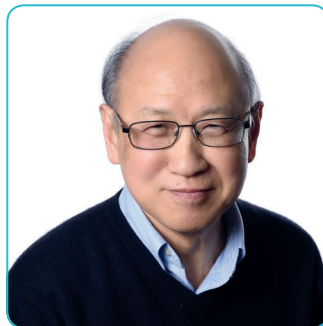
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