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Dynamic Nuclear Polarization

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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.

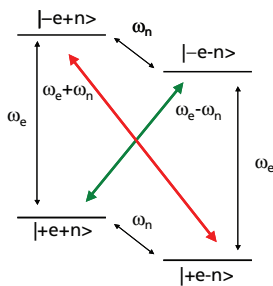


Figure 1. Energy level diagram for a coupled electron-nuclear spin system. The normally forbidden transitions (colored arrows) can be excited by microwave irradiation, resulting in dramatically increased nuclear polarizations.

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

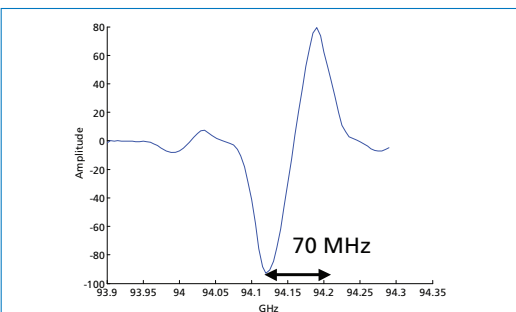


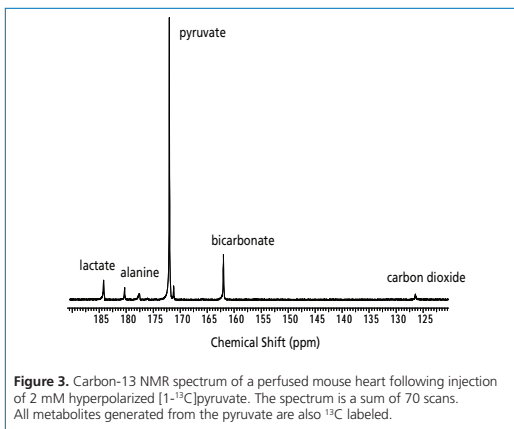
Figure 2. DNP enhancement curve as a function of frequency for $[1-^{13}\text{C}]\text{pyruvate}$ mixed with the trityl radical. Each data point was collected after irradiation for 300 seconds, which is not long enough to reach the equilibrium polarization. The 70 MHz splitting observed would lead one 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

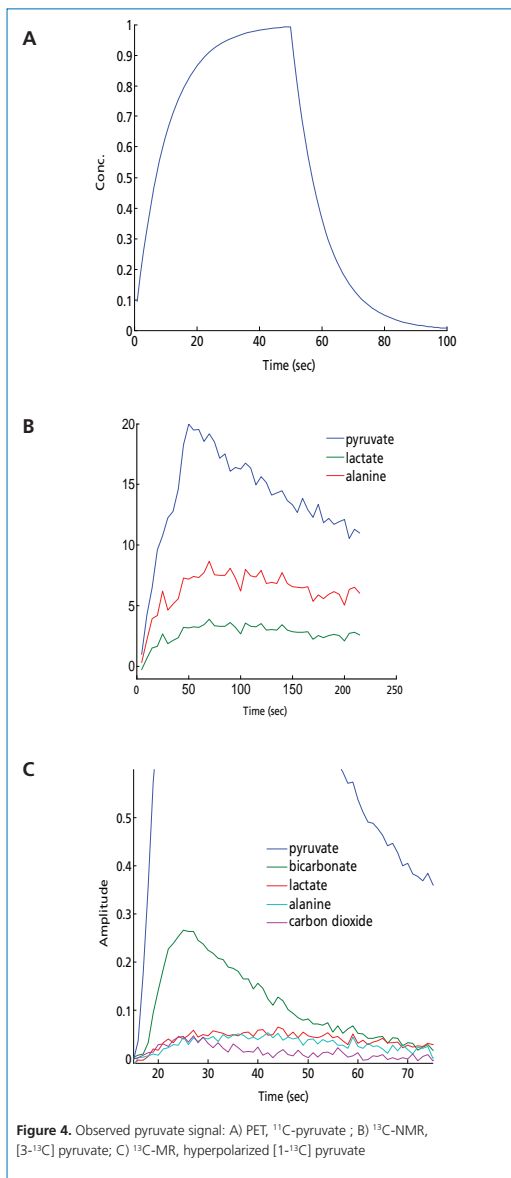
The DNP method developed by Golman and co-workers has several essential elements that allow the spectacular signal enhancements seen to date.¹¹ First, the experiment is carried out at 1.2 to 1.4 K. At room temperature, the enhancement from DNP goes as the ratio of the gyromagnetic ratios of the dipolar coupled spins. At these very low temperatures, the Boltzmann distribution begins to display exponential behavior; at 1.4 K the electrons are ~92% polarized as opposed to less than 1% for ¹H and ¹³C. 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 T₁ 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 ~190 °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 T₁ 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



The central feature that makes imaging or spectroscopy using hyperpolarized ¹³C 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 [1-¹³C]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 ¹¹C labeled pyruvate, [3-¹³C]pyruvate, and hyperpolarized [1-¹³C]pyruvate, for injection into a commonly used model of metabolism, the perfused rat heart. Observation of the ¹¹C 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 [3-¹³C]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 ¹³C label is possible, flux into CO₂ 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 H¹³CO₃⁻ has been used as a means of assessing pH



by monitoring the equilibrium between CO₂ and bicarbonate.¹⁹ This method of pH measurement has the unique advantage of injecting a completely benign compound as the sensor. Hyperpolarized [1-¹³C]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}

Conclusion

In summary, hyperpolarization of ¹³C 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 polarize 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

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Compounds of Interest

Cat. No.	Description	Isotopic Purity
279285	Acetic Acid-1- ¹³ C	99 atom % ¹³ C
279307	Acetic Acid-2- ¹³ C	99 atom % ¹³ C
282022	Acetic Acid- ¹³ C ₂	99 atom % ¹³ C
299189	Acetone-1,3- ¹³ C ₂	99 atom % ¹³ C
299197	Acetone-2- ¹³ C	99 atom % ¹³ C
491667	Acetone- ¹³ C ₃	99 atom % ¹³ C
658650	Acetyl -1,2- ¹³ C ₂ Coenzyme A, lithium salt	99 atom % ¹³ C
665223	Acetylene Dicarboxylic Acid-1- ¹³ C, disodium salt	99 atom % ¹³ C
489867	L-Alanine-1- ¹³ C	99 atom % ¹³ C
486779	L-Alanine-2- ¹³ C	99 atom % ¹³ C
489948	L-Alanine-3- ¹³ C	99 atom % ¹³ C
604682	L-Alanine-2,3- ¹³ C ₂	99 atom % ¹³ C
489875	L-Alanine- ¹³ C ₃	99 atom % ¹³ C
588741	4-Amino-TEMPO-Piperidinyl-d ₁₇	98 atom % D
363006	Ammonium- ¹⁵ N Acetate	98 atom % ¹⁵ N
579866	L-Asparagine-4- ¹³ C monohydrate	99 atom % ¹³ C
489972	L-Aspartic Acid-1- ¹³ C	99 atom % ¹³ C
679860	tert-Butan-2- ¹³ C, d ₃ -ol	99 atom % ¹³ C, 98 atom % D
488372	Butyric Acid-1- ¹³ C	99 atom % ¹³ C
588547	Butyric Acid-2- ¹³ C	99 atom % ¹³ C
615706	Butyric-Acid-4,4,4-d ₃	98 atom % D
707996 NEW	Choline-2- ¹³ C, 1,1,2,2-d ₄ Chloride	99 atom % ¹³ C, 98 atom % D
609269	Choline- ¹⁵ N Chloride	98 atom % ¹⁵ N
655708	Diethyl Glutarate- ¹³ C ₅	99 atom % ¹³ C
324523	Ethanol-1- ¹³ C	99 atom % ¹³ C

Cat. No.	Description	Isotopic Purity
427047	Ethanol-2- ¹³ C	99 atom % ¹³ C
427039	Ethanol- ¹³ C ₂	99 atom % ¹³ C
682586	Ethanol- ¹³ C ₂ ,d ₃	99 atom % ¹³ C, 98 atom % D
606316	Ethanolamine-2- ¹³ C	99 atom % ¹³ C
606294	Ethanolamine- ¹³ C ₂	99 atom % ¹³ C
606308	Ethanolamine- ¹³ C ₂ -HCl	99 atom % ¹³ C
485640	Ethyl Acetoacetate-1,3- ¹³ C ₂	99 atom % ¹³ C
485659	Ethyl Acetoacetate-2,4- ¹³ C ₂	99 atom % ¹³ C
489263	Ethyl Acetoacetate-1,2,3,4- ¹³ C ₄	99 atom % ¹³ C
676594	Ethyl Pyruvate-3- ¹³ C	99 atom % ¹³ C
415553	D-Fructose-1- ¹³ C	99 atom % ¹³ C
587621	D-Fructose- ¹³ C ₆	99 atom % ¹³ C
606073	Fumaric Acid-2,3- ¹³ C ₂	99 atom % ¹³ C
606014	Fumaric Acid- ¹³ C ₄	99 atom % ¹³ C
415545	D-Galactose-1- ¹³ C	99 atom % ¹³ C
661406	D-Galactose-1- ¹³ C, S&P tested	99 atom % ¹³ C
454621	D-Galactose-2- ¹³ C	99 atom % ¹³ C
605379	D-Galactose- ¹³ C ₆	99 atom % ¹³ C
297046	D-Glucose-1- ¹³ C	99 atom % ¹³ C
660655	D-Glucose-1- ¹³ C, S&P tested	99 atom % ¹³ C
310794	D-Glucose-2- ¹³ C	99 atom % ¹³ C
661457	D-Glucose-2- ¹³ C, S&P tested	99 atom % ¹³ C
310808	D-Glucose-6- ¹³ C	99 atom % ¹³ C
661430	D-Glucose-6- ¹³ C, S&P tested	99 atom % ¹³ C
453188	D-Glucose-1,2- ¹³ C ₂	99 atom % ¹³ C
661422	D-Glucose-1,2-, S&P tested	99 atom % ¹³ C
453196	D-Glucose-1,6- ¹³ C ₂	99 atom % ¹³ C

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Cat. No.	Description	Isotopic Purity
661449	D-Glucose-1,6- ¹³ C ₂ , S&P tested	99 atom % ¹³ C
605506	D-Glucose-2,5- ¹³ C ₂	99 atom % ¹³ C
389374	D-Glucose- ¹³ C ₆	99 atom % ¹³ C
660663	D-Glucose- ¹³ C ₆ , S&P tested	99 atom % ¹³ C
282650	D-Glucose-6,6-d ₂	98 atom % D
661414	D-Glucose-6,6-d ₂ , S&P tested	98 atom % D
552003	D-Glucose-C-d ₇	98 atom % D
604968	L-Glutamic Acid-1- ¹³ C	99 atom % ¹³ C
605123	L-Glutamic Acid-2- ¹³ C	99 atom % ¹³ C
490016	L-Glutamic Acid-3- ¹³ C	99 atom % ¹³ C
587672	L-Glutamic Acid-4- ¹³ C	99 atom % ¹³ C
492922	L-Glutamic Acid-5- ¹³ C	99 atom % ¹³ C
604860	L-Glutamic Acid- ¹³ C ₅	99 atom % ¹³ C
691682 NEW	L-Glutamic Acid-3,4- ¹³ C	99 atom % ¹³ C
605018	L-Glutamine-1- ¹³ C	99 atom % ¹³ C
605085	L-Glutamine-2- ¹³ C	99 atom % ¹³ C
604941	L-Glutamine-3- ¹³ C	99 atom % ¹³ C
604690	L-Glutamine-5- ¹³ C (amide- ¹³ C)	99 atom % ¹³ C
605220	L-Glutamine-1,2- ¹³ C ₂	99 atom % ¹³ C
660809	L-Glutamine-1,2- ¹³ C ₂ , S&P tested	99 atom % ¹³ C
605166	L-Glutamine- ¹³ C ₅	99 atom % ¹³ C
608122	L-Glutamine-2- ¹³ C, ¹⁵ N, (amine- ¹⁵ N)	99 atom % ¹³ C, 98 atom % ¹⁵ N
489484	Glycerol-2- ¹³ C	99 atom % ¹³ C
661465	Glycerol-2- ¹³ C, S&P tested	99 atom % ¹³ C
492639	Glycerol-1,3- ¹³ C ₂	99 atom % ¹³ C
489476	Glycerol- ¹³ C ₃	99 atom % ¹³ C
660701	Glycerol- ¹³ C ₃ , S&P tested	99 atom % ¹³ C
454524	Glycerol-1,1,2,3,3-d ₅	98 atom % D
487686	4-Hydroxy-TEMPO-d ₁₇	98 atom % D
705748 NEW	4-Hydroxy-TEMPO- ¹⁵ N	98 atom % ¹⁵ N
604771	L-Isoleucine-1- ¹³ C	99 atom % ¹³ C
292168	Lauric Acid-1- ¹³ C	99 atom % ¹³ C
660671	Lauric Acid-1- ¹³ C, S&P tested	99 atom % ¹³ C
490059	L-Leucine-1- ¹³ C	99 atom % ¹³ C
604909	L-Leucine-1,2- ¹³ C ₂ , S&P tested	99 atom % ¹³ C
490067	L-Leucine-1- ¹³ C, ¹⁵ N	99 atom % ¹³ C, 98 atom % ¹⁵ N
607657	L-Leucine-2- ¹³ C, ¹⁵ N	99 atom % ¹³ C, 98 atom % ¹⁵ N
486825	L-Leucine-5,5,5-d ₃	98 atom % D
661554	L-Leucine-5,5,5-d ₃ , S&P tested	98 atom % D
340960	L-Leucine- ¹⁵ N	98 atom % ¹⁵ N
605735	Linoleic Acid- ¹³ C ₁₈	99 atom % ¹³ C
660833	L-Lysine-1- ¹³ C-HCl, S&P tested	99 atom % ¹³ C
454613	D-Mannitol-1- ¹³ C	99 atom % ¹³ C
605492	D-Mannitol- ¹³ C ₆	99 atom % ¹³ C
415537	D-Mannose-1- ¹³ C	99 atom % ¹³ C
657579	Malonyl - ¹³ C ₃ Coenzyme A, lithium salt	99 atom % ¹³ C
490873	Myristic Acid -1- ¹³ C	99 atom % ¹³ C

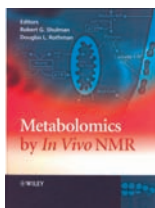
Cat. No.	Description	Isotopic Purity
661155	Myristic Acid -1- ¹³ C, S&P tested	99 atom % ¹³ C
605689	Myristic Acid - ¹³ C ₁₄	99 atom % ¹³ C
296457	Octanoic Acid-1- ¹³ C	99 atom % ¹³ C
591076	Octanoic Acid-2- ¹³ C	99 atom % ¹³ C
493163	Octanoic Acid-1,2,3,4- ¹³ C ₄	99 atom % ¹³ C
703885 NEW	Octanoyl-2,4,6,8- ¹³ C ₄ Coenzyme A, lithium salt	99 atom % ¹³ C
490423	Oleic Acid-1- ¹³ C	99 atom % ¹³ C
661589	Oleic Acid-1- ¹³ C, S&P tested	99 atom % ¹³ C
646458	Oleic Acid-1,2,3,7,8,9,10- ¹³ C ₇	99 atom % ¹³ C
490431	Oleic Acid- ¹³ C ₁₈	99 atom % ¹³ C
597120	Oleoyl-1- ¹³ C-L-Carnitine-HCl	99 atom % ¹³ C
644404	Oleoyl- ¹³ C ₁₈ -L-Carnitine-HCl	99 atom % ¹³ C
675768	Oleoyl- ¹³ C ₁₈ Coenzyme A, lithium salt	99 atom % ¹³ C
485268	4-Oxo-TEMPO-d ₁₆	98 atom % D
696471	4-Oxo-TEMPO-1- ¹⁵ N	98 atom % ¹⁵ N
487740	4-Oxo-TEMPO-d ₁₆ , ¹⁵ N	98 atom % ¹⁵ N 98 atom % D
591173	4-Oxo- TEMPO -d ₁₇ ,1- ¹⁵ N	98 atom % ¹⁵ N, 98 atom % D
292125	Palmitic Acid-1- ¹³ C	99 atom % ¹³ C
661597	Palmitic Acid-1- ¹³ C, S&P tested	99 atom % ¹³ C
492752	Palmitic Acid-2- ¹³ C	99 atom % ¹³ C
605646	Palmitic Acid -16- ¹³ C	99 atom % ¹³ C
485802	Palmitic Acid -1,2- ¹³ C ₂	99 atom % ¹³ C
489611	Palmitic Acid- 1,2,3,4- ¹³ C ₄	99 atom % ¹³ C
605786	Palmitic Acid-2,4,6,8,10,12,14,16- ¹³ C ₈	99 atom % ¹³ C
605573	Palmitic Acid- ¹³ C ₁₆	99 atom % ¹³ C
679372	Palmitic Acid- ¹³ C ₁₆ , S&P tested	99 atom % ¹³ C
662127	Palmitoyl-1,2,3,4- ¹³ C ₄ -L-Carnitine-HCl	99 atom % ¹³ C
658200	Palmitoyl-1- ¹³ C Coenzyme A, lithium salt	99 atom % ¹³ C
655716	Palmitoyl- ¹³ C ₁₆ Coenzyme A, lithium salt	99 atom % ¹³ C
605042	L-Phenyl-1- ¹³ C-alanine	99 atom % ¹³ C
490091	L-Phenylalanine-1- ¹³ C	99 atom % ¹³ C
490113	L-Phenylalanine-2- ¹³ C	99 atom % ¹³ C
608017	L-Phenylalanine- ¹³ C ₉ , ¹⁵ N	99 atom % ¹³ C, 98 atom % ¹⁵ N
605816	Potassium Linoleate ¹³ C ₁₈	99 atom % ¹³ C
489646	Potassium Palmitate -1- ¹³ C	99 atom % ¹³ C
661481	Potassium Palmitate -1- ¹³ C, S&P tested	99 atom % ¹³ C
605808	Potassium Palmitate -1,2,3,4- ¹³ C ₄ , S&P tested	99 atom % ¹³ C
676454	Potassium Palmitate-1,3,5,7,9- ¹³ C ₅	99 atom % ¹³ C
605751	Potassium Palmitate - ¹³ C ₁₆	99 atom % ¹³ C
282448	Propionic Acid-1- ¹³ C	99 atom % ¹³ C
589497	L-Proline-1- ¹³ C	99 atom % ¹³ C
661627	L-Proline-1- ¹³ C, S&P tested	99 atom % ¹³ C
677175	Pyruvic-1- ¹³ C Acid (free acid)	99 atom % ¹³ C
692670 NEW	Pyruvic-2- ¹³ C Acid (free acid)	99 atom % ¹³ C



Cat. No.	Description	Isotopic Purity
490156	L-Serine-1- ¹³ C	99 atom % ¹³ C
485985	L-Serine-2- ¹³ C, ¹⁵ N	99 atom % ¹³ C, 98 atom % ¹⁵ N
279293	Sodium Acetate-1- ¹³ C	99 atom % ¹³ C
668656	Sodium Acetate-1- ¹³ C, S&P tested	99 atom % ¹³ C
279315	Sodium Acetate-2- ¹³ C	99 atom % ¹³ C
660310	Sodium Acetate-2- ¹³ C, S&P tested	99 atom % ¹³ C
282014	Sodium Acetate- ¹³ C ₂	99 atom % ¹³ C
663859	Sodium Acetate- ¹³ C ₂ , S&P tested	99 atom % ¹³ C
292656	Sodium Butyrate-1- ¹³ C	99 atom % ¹³ C
485357	Sodium Butyrate-2- ¹³ C	99 atom % ¹³ C
588563	Sodium Butyrate-3- ¹³ C	99 atom % ¹³ C
603929	Sodium Butyrate-1,2- ¹³ C ₂	99 atom % ¹³ C
492000	Sodium Butyrate-2,4- ¹³ C ₂	99 atom % ¹³ C
488380	Sodium Butyrate- ¹³ C ₄	99 atom % ¹³ C
707198 NEW	Sodium Dichloroacetate- ¹³ C ₂	99 atom % ¹³ C
660302	Sodium D-3-Hydroxybutyrate-1,2- ¹³ C ₂ , S&P tested	99 atom % ¹³ C
606111	Sodium D-3-Hydroxybutyrate-1,3- ¹³ C ₂	99 atom % ¹³ C
674117	Sodium D-3-Hydroxybutyrate-2,4- ¹³ C ₂	99 atom % ¹³ C
696323	Sodium DL-3-Hydroxybutyrate-1- ¹³ C	99 atom % ¹³ C
492302	Sodium DL-3-Hydroxybutyrate-4- ¹³ C	99 atom % ¹³ C
488895	Sodium DL-3-Hydroxybutyrate-1,3- ¹³ C ₂	99 atom % ¹³ C
492299	Sodium DL-3-Hydroxybutyrate-2,4- ¹³ C ₂	99 atom % ¹³ C
606030	Sodium DL-3-Hydroxybutyrate- ¹³ C ₄	99 atom % ¹³ C
676144	Sodium D-Lactate-3- ¹³ C solution	99 atom % ¹³ C
606022	Sodium L-Lactate-1- ¹³ C solution	99 atom % ¹³ C
589209	Sodium L-Lactate-2- ¹³ C solution	99 atom % ¹³ C
490040	Sodium L-Lactate-3- ¹³ C solution	99 atom % ¹³ C

Cat. No.	Description	Isotopic Purity
606006	Sodium L-Lactate-2,3- ¹³ C ₂ solution	99 atom % ¹³ C
485926	Sodium L-Lactate- ¹³ C ₃ solution	99 atom % ¹³ C
589217	Sodium L-Lactate-2-d ₁ solution	99 atom % ¹³ C
657204	Sodium Octanoate-2,4,6,8- ¹³ C ₄	99 atom % ¹³ C
279455	Sodium Propionate-1- ¹³ C	99 atom % ¹³ C
490660	Sodium Propionate-2- ¹³ C	99 atom % ¹³ C
490679	Sodium Propionate-3- ¹³ C	99 atom % ¹³ C
493325	Sodium Propionate-1,2- ¹³ C ₂	99 atom % ¹³ C
493333	Sodium Propionate-2,3- ¹³ C ₂	99 atom % ¹³ C
490636	Sodium Propionate- ¹³ C ₃	99 atom % ¹³ C
660949	Sodium Propionate- ¹³ C ₃ , S&P tested	99 atom % ¹³ C
490709	Sodium Pyruvate-1- ¹³ C	99 atom % ¹³ C
490725	Sodium Pyruvate-2- ¹³ C	99 atom % ¹³ C
490733	Sodium Pyruvate-3- ¹³ C	99 atom % ¹³ C
493392	Sodium Pyruvate-1,2- ¹³ C ₂	99 atom % ¹³ C
486191	Sodium Pyruvate-2,3- ¹³ C ₂	99 atom % ¹³ C
490717	Sodium Pyruvate- ¹³ C ₃	99 atom % ¹³ C
660957	Sodium Pyruvate- ¹³ C ₃ , S&P tested	99 atom % ¹³ C,
702242 NEW	Sodium Pyruvate-2- ¹³ C, 3,3,3-d ₃	99 atom % ¹³ C, 97 atom % D
299162	Stearic Acid-1- ¹³ C	99 atom % ¹³ C
591491	Stearic Acid-2- ¹³ C	99 atom % ¹³ C
605581	Stearic Acid- ¹³ C ₁₈	99 atom % ¹³ C
675776	Stearoyl- ¹³ C ₁₈ Coenzyme A, lithium salt	99 atom % ¹³ C
485349	Succinic Acid-1,4- ¹³ C ₂	99 atom % ¹³ C
605417	Sucrose- ¹³ C ₁₂	99 atom % ¹³ C
331104	D-Xylose-1- ¹³ C	99 atom % ¹³ C
666378	D-Xylose- ¹³ C ₅	98 atom % ¹³ C

Books of Interest



Z703737

Metabolomics by
In Vivo NMR
by Robert G. Shulman and
Douglas L. Rothman



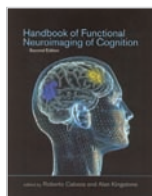
Z651990

Imaging in Neuroscience and
Development: A Laboratory Manual
by R. Yuste and A. Konnerth



Z731498

PET Chemistry
by P. Schubinger



Z731471

Handbook of Functional Neuroimaging
of Cognition, 2nd edition
by R. Cabeza and A. Kingstone

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

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

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

Literature of Interest

- 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.
- Taylor, 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 H₂¹⁷O using an efficient $^{17}\text{O}_2$ delivery system.
- 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.
- 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.

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



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more than 3,000 people
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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 (Helium-3) or ^{129}Xe (Xenon-129) 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

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

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

Literature of Interest

1. Fain, S. B.; Korosec, F. R.; Holmes, J. H.; O'Halloran, R.; Sorkness, R. L.; Grist, T.; *M. J Magn Reson Imaging* **2007**, *May*; 25(5), 910-23. Review. Functional lung imaging using hyperpolarized gas MRI.
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 ¹⁸FDG (Fluoro-deoxyglucose). ¹⁸FDG 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. (18F)-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.
- Alexánderon, 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

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

Additional Products for PET Imaging

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

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 tests results for each batch are displayed on the Certificate of Analysis, accessible at sigma-aldrich.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	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

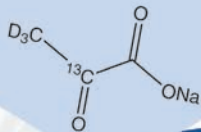
Molecular Weight: 20.02

CAS No. 143 14-42-2

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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