

Converting para-hydrogen spin order into net ^{13}C magnetization

An interesting application of PHIP NMR spectroscopy

The low natural abundance in addition to low gyromagnetic ratio of ^{13}C delivers a low Signal to Noise Ratio (SNR) in ^{13}C NMR spectroscopy, forcing to use concentrated samples and signal averaging.

Hyperpolarization methods can be used to enhance signal strength. Para-Hydrogen Induced Polarization (PHIP) is a very efficient and versatile technique to increase polarization by means of a hydrogenation reaction using para- H_2 (parahydrogenation reactions).

ParaHyperpol™ conjugates an improved para-hydrogenation reactor with a highly reliable pulse programmer for polarization transfer at low magnetic field.

PHIP applications

- ▲ rapid characterization of low-yield products and intermediates to elucidate the reaction mechanisms of hydrogenation reactions
- ▲ study of the enantio- and stereoselectivity of hydrogenation reactions
- ▲ enhanced detection of heteronuclear resonances (such as ^{13}C and ^{15}N) and indirect observation of transient reaction intermediate



System highlights

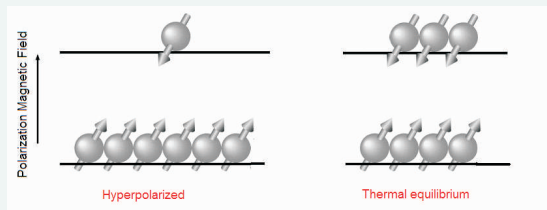
- Table-top system
- 50 mT permanent magnet
- $^1\text{H}/^{13}\text{C}$ double resonance probe
- High pressure, high efficiency 15 ml reaction chamber
- Multichannel RF NMR digital console
- Injection-Collection system

References

- J. Natterer, J. Bargon, *Progr. Nucl. Magn. Reson. Spectr.*, 31, 293 (1997)
- M. Goldman, H. Johannesson, O. Axelsson, M. Karlsson, *C. R. Chim.*, 9, 357 (2006)
- H. Johannesson, O. Axelsson, M. Karlsson, *C. R. Phys.*, 5, 315 (2004)

What is Hyperpolarization ?

Hyperpolarization refers to a molecule that can be polarized in a magnetic field by artificially creating a non-equilibrium distribution of the nuclei compared to the thermal equilibrium.



What is PHIP?

ParaHydrogen Induced Polarization (PHIP) is a versatile technique to obtain hyperpolarized molecules exhibiting strong NMR signals in solution.

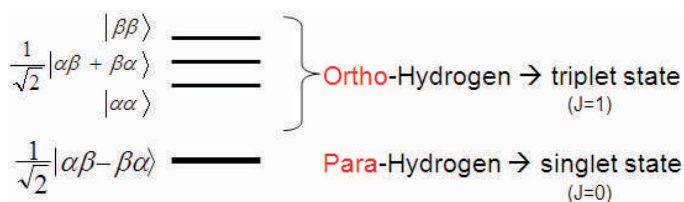
The polarization is increased via a chemical reaction involving **para-hydrogen** (a state where the hydrogen nuclei have antiparallel nuclear spins).

The non-equilibrium spin order of the para-hydrogen molecule can be converted to polarization of other nearby nuclei of the substrate.

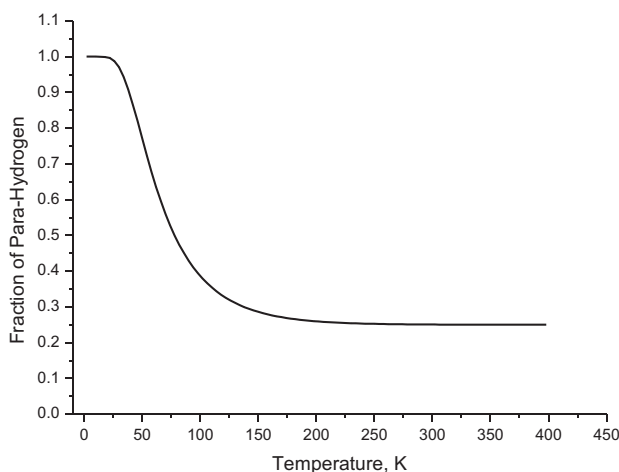
Consequently, the population of the energy levels of their spin states deviates from the Boltzmann distribution characteristic for systems in thermal equilibrium. This leads to absorption and emission signals in the NMR spectra if recorded in situ and a *theoretical signal increase of up to 10^5 -fold*, which is in practice limited, however, by the relaxation processes, occurring at the intermediate stages and in the products.

Ortho- and para-hydrogen

Ortho- and para-hydrogen are the two spin isomers of the hydrogen molecule. Para- H_2 is a singlet state ($J=0$), while ortho- H_2 is a triplet state ($J=1$).



Statistical thermodynamics allows us to calculate ortho- and para-hydrogen percentages as a function of temperature.

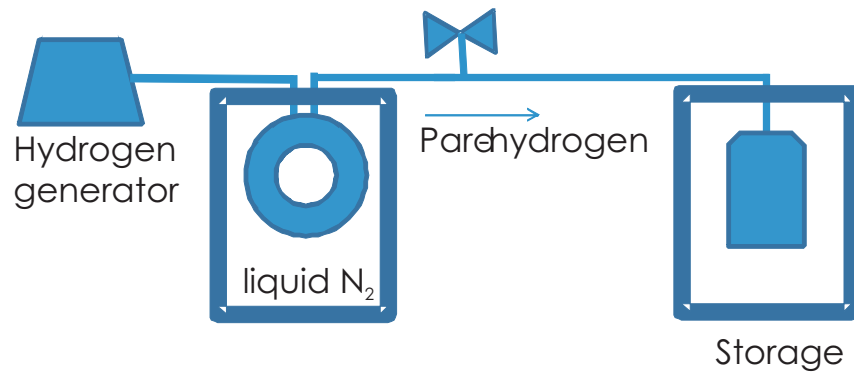


Normal hydrogen molecule H_2 consists of 75% ortho- and 25% para-hydrogen.

In absence of a catalyst the conversion of ortho to para-hydrogen (or viceversa) is extremely slow because, in principle, it is forbidden by symmetry rules.

With a catalyst and low temperatures it is possible to obtain a mixture of hydrogen enriched in the para nuclear spin isomer. Commonly para-H₂ is produced inside a glass bulbe, loaded with Fe₂O₃ and charcoal, at 77 K (para-H₂ 52%).

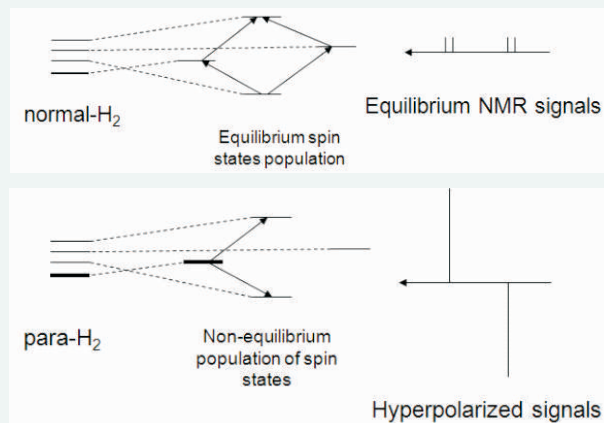
Invento is developing a cryogenic system in order to increase the para-H₂ enrichment degree



Higher level of para-H₂ can be attained by using a cryo-system, operating at temperature lower than 77 K.

Para-Hydrogenation Reaction

When hydrogen is enriched in the para-isomer, the non-equilibrium condition can be converted to hyperpolarization in parahydrogenation products.



In order to transform the antiphase polarization into an in-phase signal, an appropriate pulse sequence can be applied into a very low field NMR spectrometer.

The correct application of the pulse sequence requires the accurate calibration of ¹H and ¹³C pulses. In particular the ¹³C pulse calibration was obtained using an on-purpose Field Cycling method.

INVENTO Srl

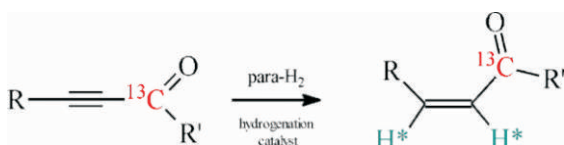
c/o MBC, Torino University, 213T Incubator
Via Nizza, 52 - 10126 Torino
Tel. +39 011 6706496 - Fax +39 011 6706487
www.invento-lab.com info@invento-lab.com

STELAR Srl

via E. Fermi, 4 - 27035 Mede PV Italy
Tel. +39 0384 820096 - Fax +39 0384 805056
www.stelar.it info@stelar.it

From para-hydrogen to net ^{13}C magnetization using a tailored $^1\text{H}/^{13}\text{C}$ pulse sequence on ParaHyperpol™

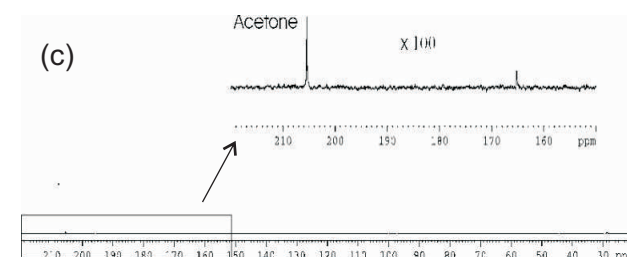
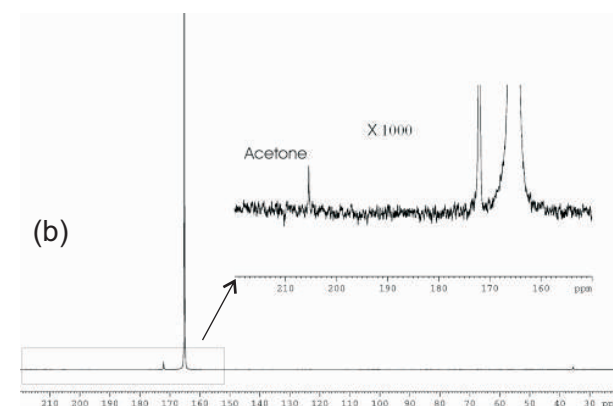
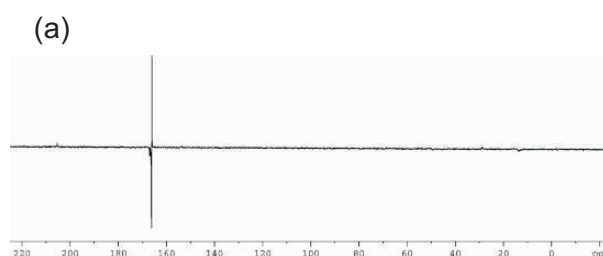
- ✧ A special reactor chamber is filled with parahydrogen to a pressure of 4 bars.
- ✧ A mixture of substrate and catalyst is sprayed into the reactor by means of a properly designed device.
- ✧ The parahydrogenation reaction is carried out inside a wide-bore low-field magnet (0.05 T) and a double resonance probe.
- ✧ Heteronuclei hyperpolarization achieved by means of spontaneous magnetization transfer inside the hydrogenated molecule results in antiphase signals.



- ✧ By the application of a tailored pulse sequence, it is possible to obtain an in-phase signal

- ✧ Figure (c) shows the spectrum acquired at thermal equilibrium (after longitudinal relaxation).

- ✧ Compared with fig.(b), the **enhancement factor of the hyperpolarized ^{13}C signal is about 40000.**



- ✓ The application of new pulse sequences allows the set-up of novel NMR experiments
- ✓ The system is controlled by a multichannel NMR console