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Hyperpolarization of ^{13}C through order transfer from parahydrogen: A new contrast agent for MRI

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Abstract

The order within proton pairs in organic molecules, resulting from hydrogenation with parahydrogen, can be transferred in great part to nearby carbon 13 spins through adequate field manipulations. The molecules with hyperpolarized ^{13}C thus obtained can be used as new contrast agents of high efficiency in MRI.

After a brief presentation of the hydrogenation process and apparatus, in relatively low magnetic field, we describe the procedure of order transfer to the ^{13}C spins through a sudden drop from the initial field to zero field followed by an adiabatic remagnetization. The expected final polarizations in the absence of relaxation are given for several compounds. Finally, we show an example of MR images observed in vivo on animals as an illustration of the contrast capacity of this new method.

Keywords: Parahydrogen-induced polarization; Adiabatic; Field cycling; MRI; Contrast agents

1. Introduction

It was in the late 1980s that Bowers and Weitekamp [1,2] discovered, both theoretically and experimentally, that the hydrogenation of small organic molecules with parahydrogen led to a highly ordered spin state conspicuously showing up by the observation of very large NMR signals for the corresponding protons. The names of PASADENA [2] and ALTADENA [3], initially introduced by Weitekamp, are now superseded in practice by the name *PHIP*, for parahydrogen-induced polarization. Extensive studies have been made on the transfer of spin order to heteronuclei [4–9]. A review article on PHIP has been written by Bowers [10].

The use of PHIP for MRI has been initiated in the Malmö lab [11] in the form of a field-cycling method for turning the proton spin order into a substantial polarization of a nearby carbon 13 and using the latter as a contrast agent. (See also Refs. [12,13] and references therein.) The present paper, which is essentially devoted to giving a simple description of this method, is organized as follows. In Section 2, we recall briefly the nature and properties of parahydrogen. In Section 3, we discuss the AA'X system (a two protons–one ^{13}C spin system) resulting from the hydrogenation of the molecules, its interactions and the proton spin order produced by the use of parahydrogenation as well as the intuitive evidence that a field-cycling method might produce a polarization of the carbon spin. In Section 4, we describe the field-cycling method, the principle of its implementation and the method of prediction of the final carbon polarization. In Section 5, we give a simplified account of the experimental implementation of the method. In Section 6, we give an example of its results through an in vivo series of MR images of a guinea pig head. Section 7 gives a brief conclusion of the study.

2. Properties of parahydrogen

The two nuclear spins ½ of a hydrogen molecule are coupled to form a triplet of total spin 1, called orthohydrogen, and a singlet of spin 0, called parahydrogen. Their spin functions are symmetric and antisymmetric, respectively. If + and − stand for the positive or negative values

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of the two protons' spin values along a given axis, the various spin functions are of the well-known form:

$$\begin{array}{rl} & |1\rangle \;= |++\rangle, \\ \text{Triplet}: & |0\rangle \;= \frac{1}{\sqrt{2}}(|+-\rangle + |-+\rangle), \\ & |-1\rangle \;= |--\rangle, \\ \text{Singlet}: & |s\rangle \;= \frac{1}{\sqrt{2}}(|+-\rangle - |-+\rangle) \end{array} \tag{1}$$

The molecules being also characterized by a rotational quantum number, it results from the quantum-mechanical requirement that the total wave function be totally antisymmetric with respect to the two protons that the singlet and triplet spin states are only allowed rotational states with even (symmetric) and odd (antisymmetric) rotational quantum numbers, respectively. The energy of a rotational state of quantum numbers J is equal to:

$$\begin{array}{l} E(J) = \Theta_r J(J+1), \\ \Theta_r;\ 85.3\ \text{K} \end{array} \tag{2}$$

and its rotational degeneracy is equal to $2J+1$, to which one must add the spin degeneracy.

The energy separation between the ground states of parahydrogen ($J=0$) and orthohydrogen ($J=1$) being about 171 K, the thermal-equilibrium fraction of parahydrogen decreases when the temperature is increased, from 1 at low temperature (practically liquid hydrogen) to ¼ at high temperature, when all four states of para and ortho are equally populated (practically room temperature). In this last case, the rotational states are populated up to about $J=5$. This variation is shown in Fig. 1. However, the conversion rate is extremely slow in the absence of an efficient catalyst.

Let $\mathbf{I}_1$ and $\mathbf{I}_2$ be the spin operators of the two protons. From the easily proven property:

$$\mathbf{I_1}\cdot\mathbf{I_2} = 1/4 \ \text{ for the triplet}, \ = -3/4 \ \text{ for the singlet}, \tag{3}$$

it results that the spin density matrices of orthohydrogen and parahydrogen are respectively equal to:

$$\sigma_{\text{ortho}} = \frac{1}{4}(1+4/3\mathbf{I}_1\cdot\mathbf{I}_2) \tag{4}$$

$$\sigma_{\text{para}} = \frac{1}{4}(1-4\mathbf{I}_1\cdot\mathbf{I}_2) \tag{5}$$

The former corresponds to probabilities 1/3 for each state of the ortho triplet and the latter to probability 1 for the para singlet.

In the following, we always assume that the hydrogen is in the pure para state. The extension to the case when the hydrogen is only partly para is trivial.

3. The parahydrogenated molecule

3.1. The density matrix of the hydrogenated molecule

We consider molecules where all hydrogen atoms present before the parahydrogenation are deuterons and which contain a ^{13}C atom near the double bond where the hydrogenation is to take place. Immediately following the hydrogenation of a molecule, the spin state of the two protons is the same as that of the initial para molecule (i.e., a singlet of spin wave function equal to that of the singlet state). This is independent of the value of the ^{13}C spin component S_z: both states $|s,+\rangle$ and $|s,-\rangle$ have probability ½; that is, the density matrix, in the new 8×8 Hilbert space, is:

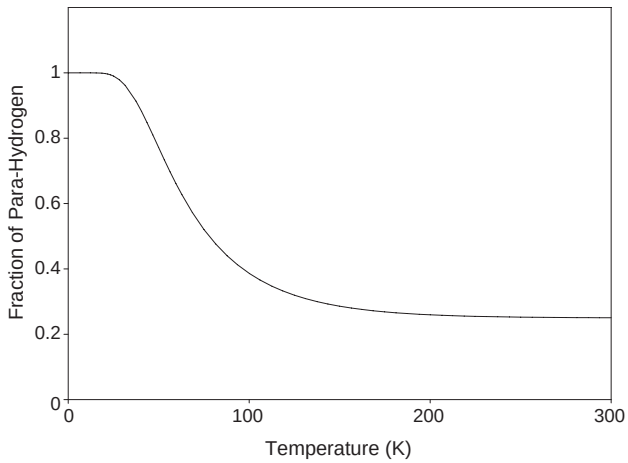

Fig. 1. Variation of the parahydrogen fraction at thermal equilibrium as a function of temperature.

$$\sigma_{\text{ini}} = \frac{1}{8}(1-4\mathbf{I}_1\cdot\mathbf{I}_2) \tag{6}$$

However, this density matrix is not diagonal with respect to the spin Hamiltonian of the molecule. As a result, the diagonal elements remain constant, whereas the off-diagonal elements oscillate. The hydrogenation taking place at different, randomly distributed times for the different molecules, the steady-state density matrix at the end of the hydrogenation is simply the projection of the matrix Eq. 6 on the Hamiltonian eigenstates.

3.2. The Hamiltonian in high and zero fields

We neglect the chemical shift difference of the two proton spins and we have, for the AA'X system, the following Hamiltonian:

$$\begin{array}{l} \mathrm{H} = \omega_I(I_{1z}+I_{2z}) + \omega_S S_z \\ \quad + J_{12}\mathbf{I}_1\cdot\mathbf{I}_2 + J_{1S}\mathbf{I}_1\cdot\mathbf{S} + J_{2S}\mathbf{I}_2\cdot\mathbf{S} \end{array} \tag{7}$$

In such a high field that $|\omega_{\mathrm{I}} - \omega_{\mathrm{S}}| \gg |J_{1\mathrm{S}}|,|J_{2\mathrm{S}}|$, we can truncate the I–S interactions:

$$\mathbf{I}_i\cdot\mathbf{S} \rightarrow I_{iz}S_z \tag{8}$$

The J_{iS} being a few Hz, the earth field is already "high."

The truncation is not permitted in zero field. Therefore, the eigenstates of the Hamiltonian, involving the spin S, are different from those in high field, hence the idea that a cycling of the field between high and zero might result in the building up of a polarization of the spin S.

4. The field-cycling method

This method involves two consecutive steps. Starting from the steady-state density matrix in high field, the field is suddenly dropped to zero, where the density matrix evolves so as to reduce to the projection of its initial form on the zero-field Hamiltonian eigenstates. The second step consists of an adiabatic increase of the field, during which the populations follow the time-dependent eigenstates. It is therefore necessary to know to which values of S_z the high-field transforms of the zero-field eigenstates will correspond.

In high field, thanks to the truncation (8), the populated eigenstates are combinations of the states $|s, \varepsilon\rangle$ and $|0, \varepsilon\rangle$, where s and 0 correspond to the proton singlet and the 0 triplet state and ε to the value +½ or −½ of S_z, or $|+-, \varepsilon\rangle$ and $|-+, \varepsilon\rangle$. This is due to the fact that if $J_{1S} \neq J_{2S}$, the Hamiltonian (7), truncated according to (8), has matrix elements between the states $|+-, \varepsilon\rangle$ and $|-+, \varepsilon\rangle$. In low field, when the truncation (8) is not valid, one has to include matrix elements between the states $|+-, \varepsilon\rangle, |-+, \varepsilon\rangle$ and the states $|\pm 1, -\varepsilon\rangle$. The relevant part of the Hamiltonian then spans two 3-dimensional subspaces of respective bases:

$$|- \ -, +\rangle, |+ \ -, -\rangle, |- \ +, -\rangle \tag{9}$$

$$|+ \ +, -\rangle, |+ \ -, +\rangle, |- \ +, +\rangle \tag{10}$$

We have computed the variation of the eigenvalues in these two triads as a function of the Larmor frequency of the spin I, larger than that of the spin S. Its magnetic moment being positive, the Zeeman energy of the state I_z=+1 decreases when the field increases. It is the opposite for the state I_z=−1. The results are plotted in Figs. 2 and 3 for the triads of states (9) and (10), respectively. It can be seen that when increasing the field, the eigenlevels do not cross. Therefore, in the triad (9), the zero-field state of highest energy corresponds to I_z=−1, S_z=+½ after remagnetization and the other two correspond to S_z=−½. In the triad (10),

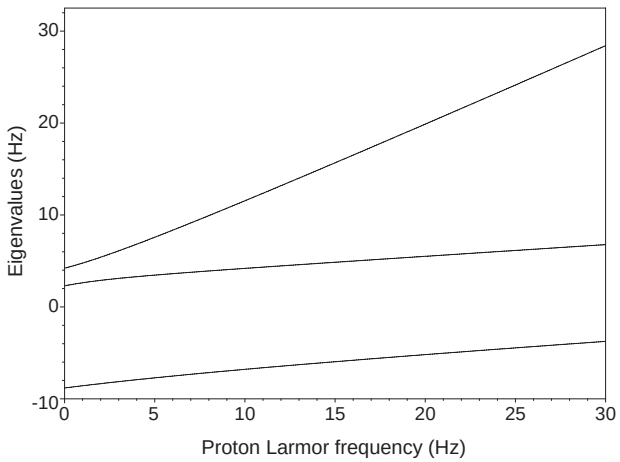

Fig. 2. Hydroxyethylpropionate. Eigenvalues of the spin system as a function of proton Larmor frequency in the partial basis $|- \ -,+\rangle, |+ \ -, -\rangle, |- \ +, -\rangle$.

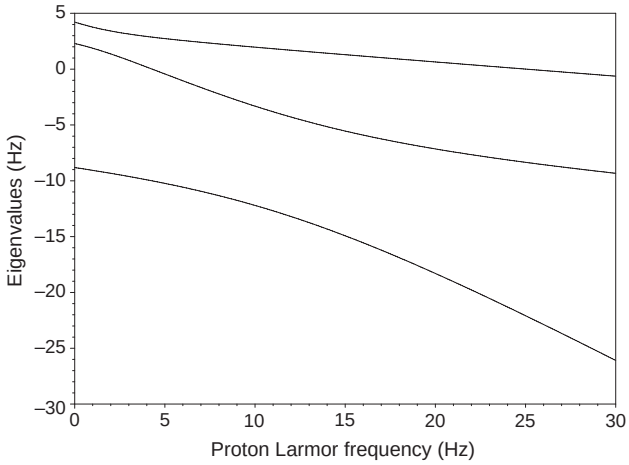

Fig. 3. Hydroxyethylpropionate. Eigenvalues of the spin system as a function of proton Larmor frequency in the partial basis $|+ \ +,-\rangle, |+ \ -, +\rangle, |- \ +, +\rangle$.

the zero-field state of lowest energy corresponds to S_z=−½ after remagnetization and the other two correspond to S_z=+½.

Knowing the density matrix in zero field (i.e., the populations of the various eigenstates on one hand and the values of S_z they will yield upon adiabatic remagnetization on the other), we are in a position to compute the corresponding theoretically expected S polarization. The results for a selection of molecules are given below.

Succinic acid: −71.7%.
O-acetyl lactate: −74.3%.
Maleic acid: −54.5%.
Hydroxyethylpropionate: −61.7%.

These figures are to be compared with the thermal equilibrium polarization of ^{13}C under usual imaging conditions — body temperature and magnetic field of 1.5 T — that is:

$$P_{eq}(310 \text{ K}, 1.5 \text{ T}) = 1.2 \times 10^{-6} \tag{11}$$

The actual adiabatic efficiency for a given field increase profile and timing can be ascertained only through a computer simulation of the spin system evolution under the time-dependent Hamiltonian.

5. Schematic description of the experimental implementation

Parahydrogen was produced by passing hydrogen gas through the commercial catalyst C*CHEM (P.O. Box 640, Lafayette, CO 80026,USA) at a temperature of 14 K, producing a nearly pure parahydrogen. A reactor chamber, kept at a temperature of 333 K, is filled with parahydrogen to a pressure of 10 bar. A narrow jet of a mixture of the substrate and the catalyst is sprayed into the reactor. After 3 s, the liquid is transferred into the low-field chamber, where it stays for 0.5 s in a field of 100 μT, then decreased

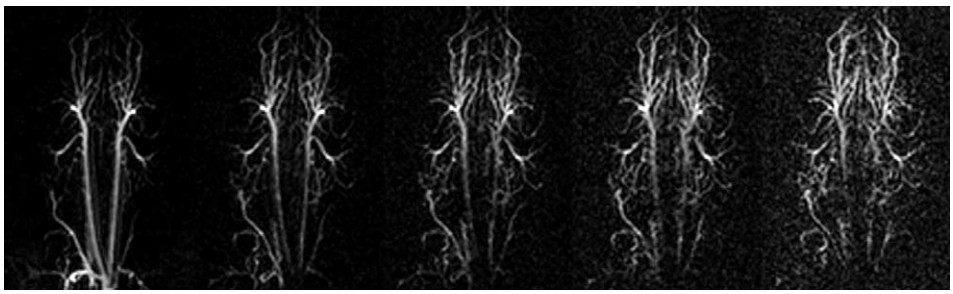

Fig. 4. Angiography of a guinea pig head with hyperpolarized hydroxyethylpropionate. Successive ^{13}C images at 480-ms intervals following the injection of the contrast agent. (Courtesy of S. Månsson, Department of Experimental Research, Malmö University Hospital, Malmö, Sweden).

to about 30 nT in 1 ms. The field is subsequently increased exponentially back to 100 μT in a time of the order of 1 s, the solution is filtered so as to remove the catalyst, a fraction is used for polarization calibration by NMR and the rest is transferred into a syringe for imaging purposes. The whole process is under computer control. The experiments are usually run on 5 ml of aqueous solution of the organic compound, at a concentration around 0.5 to 1 M.

One of the most largely used compounds was hydroxyethylpropionate, produced by parahydrogenation of hydroxyethylacrylate in the presence of a rhodium catalyst. The optimum adiabatic remagnetization duration was 1.2 s. The maximum ^{13}C polarization achieved was about 21–25%, about 2×10^5 times the thermal equilibrium value. The carbon relaxation times T_1 and T_2 in vivo at body temperature were about 60 and 5 s, respectively.

6. Experimental illustration of imaging

The only example given is that of head and neck angiography of guinea pigs from injection of water solutions of hydroxyethylpropionate, with a ^{13}C polarization of 25%. The concentration of the compound was 0.5 M. The injection of 3 ml of solution in 2 s was made in the arcus aortae through an arterial catheter, after which ^{13}C images of the head were produced by the trueFISP method [14], in a 1.5 T whole body scanner (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany). The imaging volume consisted of coronal slices of thickness larger than the animal. The in-plane resolution varied from about 1×1 to 0.6×0.6 mm^2 in different experiments. Fig. 4 shows a series of five successive images, each of scanning duration 480 ms and in-plane resolution of 0.625×0.625 mm^2. The acquisition of the first image was started immediately after the injection. One can follow the dynamics of progression of the solution through the intricate network of blood vessels.

7. Conclusion

Hyperpolarized ^{13}C is a completely new contrast agent for MRI, with unique characteristics of great promise. To list but a few, it is produced in a very short time (a few seconds), it requires an equipment extremely modest both in size and cost compared with the imager, the polarization produced is so much larger than that of the ^{13}C spins of the molecules in the organism at thermal equilibrium that, in practice, only the injected compound contributes to the observed images, which provides an unparalleled contrast for dynamic studies, etc. Although still in a preliminary state in need of improvement and development, hyperpolarization already proves to be effective and promises to be of remarkable usefulness in medical MRI and could eventually find useful applications in other domains. One of the purposes of this study was to show that the method of hyperpolarization through PHIP does work, even if not perfectly yet, and that it can already be put to practical use. Work continues on this type of contrast agents and progress is under way.

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