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Design and implementation of ^{13}C hyper polarization from para-hydrogen, for new MRI contrast agents

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Abstract

The order within proton pairs in organic molecules, resulting from hydrogenation with para-hydrogen, 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, and a summary of the order transfer to the ^{13}C spins through field-cycling, we describe the use of radio-frequency irradiation, by CW and by pulses, to produce such an order transfer. We consider in turn the various steps involved, their rationale and their optimization. The final polarizations expected from both methods in the absence of relaxation are compared. Finally, some MRI pictures observed in vivo on animals are shown as an illustration of the contrast capacity of these methods. ***To cite this article: M. Goldman et al., C. R. Chimie 9 (2006)***.

Résumé

L'ordre dans les paires de protons de molécules organiques, résultant de l'hydrogénation par de l'hydrogène para, peut être transféré en grande partie à des atomes de ^{13}C voisins par des manipulations de champ appropriées. Les molécules contenant du ^{13}C ainsi obtenues peuvent être utilisées comme de nouveaux agents de contraste en IRM. Après une brève présentation du processus et de l'appareillage d'hydrogénation et un résumé du transfert d'ordre aux spins de ^{13}C par cyclage de champ, nous décrivons l'utilisation d'irradiations de radiofréquence, en continu et en impulsions, pour produire un tel transfert d'ordre. Nous considérons tour à tour les différentes étapes, leur logique et leur optimisation. Nous prédisons les polarisations finales prédites pour les deux méthodes en l'absence de relaxation. Finalement, quelques images IRM observées in vivo sur des animaux sont présentées comme illustration de la capacité de contraste de ces méthodes. ***Pour citer cet article : M. Goldman et al., C. R. Chimie 9 (2006)***.

Keywords: Para-hydrogen induced polarization; Pulses; MRI; Contrast agents

Mots clés : Polarisation induite par le para hydrogène ; Impulsions ; IRM ; Agents de contraste

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1. Introduction

When para-hydrogen is used for the hydrogenation of small organic molecules, the spin state of the two protons is initially conserved in the new proton pair. This shows up, after proper procedures, as an observation of very large anti-phase NMR signals from the corresponding proton pair. This phenomenon was discovered both theoretically and experimentally by Bowers and Weitekamp [1,2]. Two main procedures, using either a high or low field during hydrogenation, were given the names of PASADENA [2] and ALTADENA [3]. It is now usual to call the phenomenon PHIP, for Para-Hydrogen-Induced-Polarization. Numerous studies have been made, in particular on the transfer of spin order to heteronuclei. Many are described, together with a variety of other applications, in a review article by Bowers [4].

The use of PHIP for MRI was initiated in the Malmö laboratory for small ^{13}C-labelled organic molecules, in the form of a method of field-cycling between high and zero magnetic fields for turning the para spin order of the proton pair into a net polarization of a nearby carbon 13, which was used in turn as a contrast agent [5–9]. This method will be but shortly described. The main purpose of the present article is to describe a new PHIP method developed in Malmö for MRI, a pulse method of order transfer from para-hydrogen to ^{13}C, in a constant low dc field. A word is needed to specify the meaning of order transfer. The fact that after para-hydrogenation the two proton spins are in the singlet state, one out of four possible spin states, corresponds to low entropy for the proton pair, referred to as order. The order transfer consists in turning it, through adequate evolutions and rf pulses, into a low Zeeman entropy of the carbon spin in the magnetic field, showing up by an increased polarization.

1.1. The para-hydrogen molecule

The hydrogen molecule exists in two different spin states: a triplet symmetric state of total spin 1, called ortho-hydrogen, and an antisymmetric state of spin 0 called para-hydrogen. Their spin wave functions are:

$$\begin{aligned} &|1\rangle = |{+}{+}\rangle,\ |0\rangle = \frac{1}{\sqrt{2}}\left(|{+}\ {-}\rangle + |{-}\ {+}\rangle\right),\\ &|{-}1\rangle = |{-}\ {-}\rangle,\\ &|s\rangle = \frac{1}{\sqrt{2}}\left(|{+}\ {-}\rangle - |{-}\ {+}\rangle\right) \end{aligned} \tag{1}$$

where + and – refer to the values $\pm\frac{1}{2}$ of I_{1z} and I_{2z}, respectively.

A well-known and important property of these states, used later is:

$$\begin{aligned} &\langle T|\mathbf{I}_1\cdot\mathbf{I}_2|T\rangle = \frac{1}{4} \text{ for any ket in the triplet subspace,}\\ &\langle s|\mathbf{I}_1\cdot\mathbf{I}_2|s\rangle = -\frac{3}{4} \text{ in the singlet subspace} \end{aligned} \tag{2}$$

The molecules also possess rotational states with quantum numbers J and energies (in temperature units, convenient in the present case):

$$E(J) = \Theta_r J(J+1), \quad \Theta_r = 85.3\ \text{K} \tag{3}$$

In order to comply with the Pauli principle, the para molecules have even J values, and the ortho molecules odd J values. The energy separation between the para state $J = 0$ and the ortho state $J = 1$ being 170.6 K, thermal equilibrium at low temperature, say below 20 K, corresponds to practically pure para-H_2. It can be reached in a short time in the presence of a commercially available catalyst. At room temperature and without a catalyst, the rate of conversion of para-hydrogen to ortho is exceeding slow, and it would remain in the highly ordered singlet para state for days or weeks, much longer than the duration of an experiment, typically a few seconds.

1.2. The para-hydrogenated molecule

The para-hydrogen is used for the hydrogenation of small organic molecules, with a double, or possibly triple bond and with a nearby ^{13}C. The other nuclear spins present in the molecules depend on the method used for the order transfer, for reasons analyzed later.

We call $\mathbf{I}_i$ the spin operators of the various protons (there may be more than those added by the hydrogenation with para-hydrogen) and $\mathbf{S}$ that of the carbon. The spin Hamiltonian of the system consists of Zeeman and indirect interaction terms:

$$\mathrm{H} = \omega_I \sum_i I_{iz} + \omega_S S_z + \sum_{i,j} J_{ij}\mathbf{I}_i\cdot\mathbf{I}_j + \sum_i J_{iS}\mathbf{I}_i\cdot\mathbf{S} \tag{4}$$

In a 'high' field, such that $|\omega_I - \omega_S| \gg |J_{1S}|, |J_{2S}|$ (the earth field is already high), and when using a doubly rotating frame where the effect of the Zeeman terms does not show up, the only effective part of the I–S

terms is the secular one, time-independent in this frame. Then the corresponding effective Hamiltonian is:

$$H_{eff} = \sum_{i,j} J_{ij} \mathbf{I}_i \cdot \mathbf{I}_j + \sum_i J_{iS} I_{iz} S_z \quad (5)$$

If the field is reduced to zero, the Zeeman term no longer exists and the full indirect scalar products must be retained. The Hamiltonian is then:

$$H(0) = \sum_{i,j} J_{ij}\ \mathbf{I}_i \cdot \mathbf{I}_j + \sum_i J_{iS} \mathbf{I}_i \cdot \mathbf{S} \quad (6)$$

As for the spin density matrix, just after hydrogenation, the proton pair added to the molecule remains in the singlet state and, according to the properties (Eq. (2)), the initial density matrix is equal to:

$$\sigma_{ini} = \frac{1}{n} (1 - 4\, \mathbf{I}_1 \cdot \mathbf{I}_2) \quad (7)$$

where $\mathbf{I}_1$ and $\mathbf{I}_2$ are the added protons and n is the dimension of the spin Hilbert space of a molecule. Its further evolution depends on the order conversion method used. In all of them, the duration of an experiment is much shorter than all nuclear relaxation times.

2. The field-cycling method

This method was described in previous articles [6–9] and its present description is just a brief summary of it. We consider the case when in the initial compound all hydrogen nuclei are protons and the molecule is only labeled in ^{13}C at the appropriate carbon site. We neglect throughout the nuclear relaxation times, much longer that the duration of an experiment.

The hydrogenation is performed in a static magnetic field high enough to warrant the truncation of all scalar interaction between different nuclear species and the effective Hamiltonian is of the form (Eq. (5)). The initial density matrix (Eq. (7)) is not diagonal and its off-diagonal elements oscillate as a function of time. Since the various molecules are hydrogenated at different times, the phases of their respective off-diagonal elements acquire a large spread and their average quickly vanishes. Then the steady-state density matrix at the end of the hydrogenation reduces to the projection of the initial density matrix on the eigenstates of the Hamiltonian (Eq. (5)). This is followed in two steps.

Firstly the field is suddenly dropped to zero, where the Hamiltonian is of the form (Eq. (6)). It differs from the effective Hamiltonian (Eq. (5)) in high-field by the addition of flip-flop terms between heteronuclear spin pairs. The density matrix evolution from its high-field steady-state form is such that its diagonal elements on the zero-field Hamiltonian, which are simply the probabilities of presence in its eigenstates, proportional to the populations of these states, remain constant whereas the off-diagonal elements oscillate as a function of time.

Then, the field is raised adiabatically, in about 1 s, and the density matrix follows by continuity the changing Hamiltonian eigenstates in the following sense: the diagonal elements remain unaltered, and the off-diagonal elements oscillate with an instantaneous frequency equal to the frequency difference between eigenstates plus a small topological phase (Berry phase) of no relevance to the present problem. Back in the initial high-field, the result turns out to be a net polarization of the ^{13}C spins S, depending only on the diagonal elements.

The value of this polarization can only be predicted by computer simulation, if one knows all indirect interaction constants. We give below the figure obtained for hydroxyethylpropionate:

$$P_S\,(\text{final}) = -28\%. \quad (8)$$

Simulations show that, when prior to the hydrogenation the molecule is deuterated rather than protonated, the final S polarization is lower, whence the use of a fully protonated compound.

3. The pulse method

The order transfer method is performed in a constant dc field. The initial molecules are in principle fully deuterated, in addition to the ^{13}C spin labeling. The reason is that the deuterium indirect interactions with the other spins is small, due to its low gyromagnetic ratio, so that the presence of deuterium may be neglected in first approximation (see, however, the experimental section). After a catalytic hydrogenation, the molecule contains two protons spins $\mathbf{I}_1$ and $\mathbf{I}_2$, and one ^{13}C spin $\mathbf{S}$, besides the neglected deuterons. In sufficiently low field, one can forget the proton resonance frequency differences, and one has in practice an AA'X system. According to Eq. (5) and (7), the effective Hamiltonian and initial density matrices are:

$$H_{eff} = J_{12}\, \mathbf{I}_1 \cdot \mathbf{I}_2 + J_{1S}\, I_{1z}\, S_z + J_{2S}\, I_{2z}\, S_z \quad (9)$$

$$\sigma_{ini} = \frac{1}{8} (1 - 4\, \mathbf{I}_1 \cdot \mathbf{I}_2) \quad (10)$$

We have designed several pulse methods, but we describe only one of them [10,11], which has been experimentally implemented. In this method, the proton pulses are always 180° pulses around an axis normal to Oz, so that the density matrix, initially in the subspace with zero proton polarization (Eq. (10)), always remains in it. A basis of this subspace consists of the four kets $|+-,\pm\rangle$ and $|-+,\pm\rangle$, where the last sign refers to the value $\pm\frac{1}{2}$ of S_z. (An alternative basis could have consisted of the kets $|s,\pm\rangle$ and $|0,\pm\rangle$, using the singlet and 0 triplet states of the protons). The useful part of the effective Hamiltonian (Eq. (9)), simply called H, is its projection in this subspace:

$$\begin{aligned} \mathrm{H} &= J_{12}\ (I_{1x} I_{2x} + I_{1y} I_{2y}) \\ &+ \frac{1}{2}\ (J_{1S} - J_{2S})\ (I_{1z} - I_{2z})\ S_z + J_{12} I_{1z} I_{2z} \end{aligned} \tag{11}$$

The last term on the right-hand side is a constant in the subspace and it can be forgotten.

3.1. Geometrical picture

It enormously simplifies the design of an appropriate pulse sequence to use a fictitious spin 1/2 called K for describing the various proton spin operators in the subspace, as follows:

$$\begin{aligned} I_{1x} I_{2x} + I_{1y} I_{2y} \quad &\rightarrow\ K_x \\ \frac{1}{2}\ (I_{1z} - I_{2z}) \quad &\rightarrow\ K_z \\ I_{1y} I_{2x} - I_{1x} I_{2y} \quad &\rightarrow\ K_y = i[K_x, K_z] \end{aligned} \tag{12}$$

Using $\frac{1}{2}\ (J_{1S} - J_{2S}) = a, J_{12} = b$, the Hamiltonian (11) and initial density matrix (Eq. (10)) read:

$$\mathrm{H} = a\ 2\ S_z\ K_z + b\ K_x \tag{13}$$

$$\sigma_{\mathrm{ini}} = \frac{1}{8}\ (1 - 4\ I_{1z} I_{2z} - 4\ K_x) \tag{14}$$

The Hamiltonian has the form of a Zeeman interaction of the fictitious spin K with a fictitious magnetic field, of different orientations for the two values $\pm\frac{1}{2}$ of S_z. This picture is shown in Fig. 1 for the sub-subspace with $S_z = +\frac{1}{2}$.

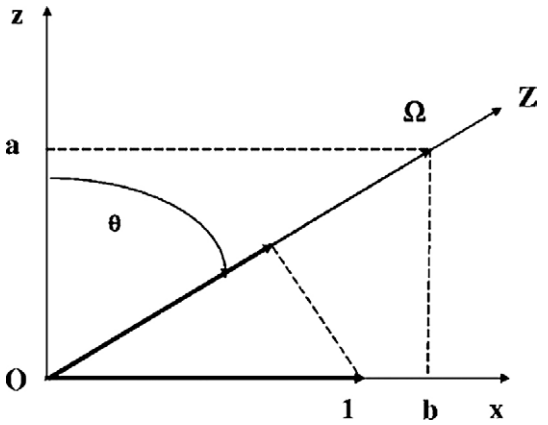

Fig. 1. Fictitious field (in frequency units) and its components for $S_z = 1/2$.
Unit vector along K_x and its projection on OZ.

The angle θ is defined through:

$$\tan(\theta) = b/a = 2J_{12}/(J_{1S} - J_{2S}) \tag{15}$$

For $S_z = -\frac{1}{2}$, the effective field is along an axis OZ' symmetrical to OZ with respect to Ox.

In the following, we write the density matrix in the form:

$$\sigma(t) = \frac{1}{4} - \frac{1}{2}\rho(t), \qquad \rho(0) = K_x \tag{16}$$

and we follow the evolution of $\rho(t)$, which in the two sub-subspaces $S_z = \pm\frac{1}{2}$, reduces to two vector operators, called ρ_+ and ρ_-.

3.2. The hydrogenation procedure

If the hydrogenation simply took place in a static magnetic field, as for the cycling method, the projection of the initial density matrix on the eigenstates of the Hamiltonian would correspond, by reference to Fig. 1, to the projection of the initial unit vector K_x on the axes OZ and OZ', with magnitude sin θ. This corresponds to a reduction of the initial para order by the same factor. In order to avoid this loss, the hydrogenation in the magnetic field is performed under a strong rf irradiation at the proton Larmor frequency. With respect to the extra interaction term $\omega_1(I_{1x} + I_{2x})$, the operator $K_z = \frac{1}{2}(I_{1z} - I_{2z})$ in the Hamiltonian is

non-secular, that is ineffective, and it must be discarded. The consequence of this truncation is that the singlet state becomes isolated from the triplet state. As long as the irradiation lasts, the hydrogenated molecules, created in the singlet state, do not evolve and remain in that state. At the end of the irradiation, all molecules are in the singlet state, without loss of order, and it is at this stage that their common evolution starts, for the conversion into carbon polarization, through a combination of free evolutions and of rf pulses. This process involves two successive steps.

3.3. Order transfer. First step

The purpose of this step is to prepare the density matrix in a form appropriate for the second step to yield the largest ^{13}C polarization. We state the corresponding form for ρ, whose derivation is given in ref. [11]:

$$\rho_{opt} = 2\, K_y\, S_x \tag{17}$$

It is achieved by first producing a density matrix:

$$\rho = 2\, K_y\, S_z \ ; \text{or } \rho_{\pm} = \pm\, K_y, \tag{18}$$

and then applying a 90° around Oy on the spin S.

In the geometric picture, the free evolution in each sub-subspace is a precession of the vector $\rho_{\pm}$ around either axis OZ or OZ′. As for the pulses, it can be checked from (Eq. (12)) that a 180° pulse on I around any axis normal to O*z* is equivalent to a 180° pulse on the fictitious spin K around an axis parallel to O*x*: it leaves the component K_x unaltered and reverses the signs of the components K_z and K_y. A combination of free evolution periods and of 180° pulses on either I or S, described in some detail in ref. [11], yields the desired result. It is the greatest advantage of the geometric picture to make these evolutions so transparent that the design of the best way for achieving this goal becomes intuitive.

3.4. Order transfer. Second step

Starting from any combination of the operators $2\, K_y\, S_x$, $2\, K_z\, S_x$, K_x for ρ, their further evolution, as determined by the Hamiltonian (Eq. (13)), depends on a system of four differential equations involving these three operators plus S_y. Its solution is analytic and simple. For the optimum form (Eq. (17)) for ρ, one obtains after 180° precession, i.e. after duration of half a period:

$$\rho = \sin(2\theta)\ S_y + \cos(2\theta)(2K_y S_x) \tag{19}$$

which is a 90° rotation around O*x* transforms into:

$$\rho_1 = \sin(2\theta)\ S_z + \cos(2\theta)(2K_y\, S_x) \tag{20}$$

The net result is the production of a longitudinal S polarization, which does not evolve under the effect of the Hamiltonian and whose relaxation time is long, plus an operator component of form identical to the initial one. One may then wait for another half period so as to obtain:

$$\rho_2 = \sin(2\theta)\ S_z + \sin(2\theta)\cos(2\theta)\ S_y + \cos(2\theta)^2(2K_y S_x) \tag{21}$$

We have now two components of S polarization, which can be transformed into pure longitudinal polarization by a pulse on S, of angle $\beta = \arctan(\cos(2\theta))$. The corresponding polarization is:

$$P_S(2) = \sin(2\theta) \cdot \sqrt{1 + \cos^{\ 2}(2\theta)} \tag{22}$$

We may continue and add further 'pumping' phases until the final polarization is sufficiently close to unity.

As numerical illustrations, we consider only two compounds, hydroxyethylpropionate and succinic acid. In hydroxyethylpropionate, the parameters have been determined by NMR in the laboratory, and the sequence was designed accordingly. The first step requires only two evolution periods, of durations 28.28 ms and 36.20 ms. The theoretical polarization after one pumping phase in the second step, of duration 50.34 ms, is equal to 98.68%. The complete pulse sequence is shown in Fig. 2. It can be checked that the first pulse of 180° around O*x* on the carbon spin could as well have been applied to the proton spins. The choice is a matter of convenience. The echo pulses are shortly commented in the next section.

In succinic acid, only provisional, ill known parameters were available. From them, the first step requires two evolution phases followed by a 180° pulse, plus a third one followed by a 90° pulse. In the second step, successive pumping phases yield the following polarizations: 0.800, 0.933, 0.976, 0.992, etc. These are approximate figures since the coupling are not known accurately. The total duration of the order transfer is a few tenths of a second.

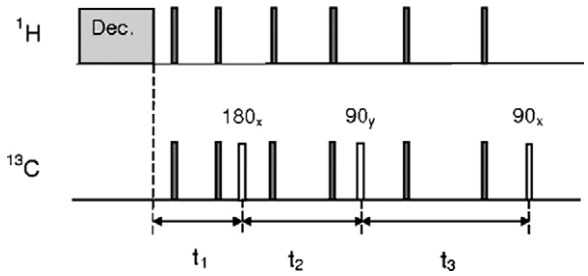

Fig. 2. Pulse sequence for hydroxyethylpropionate.
Following the rf decoupling, there are only three 'useful' pulses (in white).
The others (in gray) are 180°echo pulses, at 1/4th and 3/4th of each free evolution period.
Durations: t_1 = 28.28 ms, t_2 = 36.20 ms, t_3 = 50.34 ms.

4. Implementation of the methods

Para-hydrogen is produced by passing hydrogen gas through the commercial catalyst C*CHEM (P.O. Box 640, Lafayette, Colorado 80026, USA) at a temperature of 14 K, producing nearly pure para-hydrogen. A reactor chamber, kept at the temperature of 333 K, is filled with para-hydrogen to a pressure of 10 bars. A narrow jet of a mixture of the substrate and the catalyst is sprayed into the reactor. The total duration of the hydrogenation is 1–1.5 s, after which some time is left for the liquid to quiet down. After conversion of the para order into ^{13}C polarization, the solution is filtered 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 a 5 ml of aqueous solution of the organic compound, at a concentration around 0.5–1 M.

In the field-cycling method, 3 s after the beginning of the reaction the liquid is transferred into the low field chamber, where it stays for 0.5 s in a field of 100 μT, then decreased 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, which is the end of conversion process.

In the pulse method, the dc field being equal to 1.76 mT, the continuous rf irradiation at the proton Larmor frequency of 75 kHz is applied for a duration of 3–4 s before the beginning of the order conversion by the pulse sequence. The longitudinal Zeeman relaxation time of the protons is in the 10 s range, whereas the carbon longitudinal Zeeman relaxation time and that of the proton singlet state are both of the order of 1 min. Therefore, relaxation loss during an experiment remains limited. Echo pulses are needed to compensate for the effect of field inhomogeneities on the evolution of the transverse components of S, and for indirect interactions with the deuterium spins. The perturbing term for the spins I, of the form $\delta(I_{1z} - I_{2z}) = \delta K_z$, does not commute with the Hamiltonian (Eq. (13)), and is but partly compensated for by an echo pulse at the middle of a free evolution period. The use of two echo pulses, at 1/4th and 3/4th of each free evolution period yields a much better compensation, as shown by calculation and computer simulations. Simultaneous echo pulses on both spins I and S are necessary in order to leave the Hamiltonian (Eq. (13)) unaffected.

The most successful compound, and the only one used so far in practice, was hydroxyethylpropionate, produced by para-hydrogenation of hydroxyethylacrylate in the presence of a rhodium catalyst. In the field-cycling method using a fully protonated molecule, the maximum ^{13}C polarization achieved was about 21–25%, to be compared with the theoretical prediction of 28%. The difference can reasonably be ascribed to spin-lattice relaxation of both carbon 13 and protons during the adiabatic remagnetization, so that the yield of purely para-hydrogenated molecules production during the catalytic hydrogenation actually seems close to unity.

For the pulse method, the compound used differed from the one considered in the theory, for economical reasons in preliminary experiments. Only the acrylate part of the initial molecule was deuterated, and the hydroxyethyl part remained protonated. The theoretical polarization predicted by simulations in this case is 83.7%, whereas the observed maximum polarization was about 49–50%. The difference is likely to arise mainly from the departure of the rf pulses from ideal conditions. The latter were designed by a combination of theoretical considerations and computer simulations, taking into account the finite field homogeneity and possible drift, as well as the Bloch–Siegert effect, particularly noticeable because of the proximity of the proton and carbon Larmor frequencies in the low dc field used experimentally. These ideal pulse conditions could not be implemented with the existing rf equipment. Hopefully, things might improve in the future.

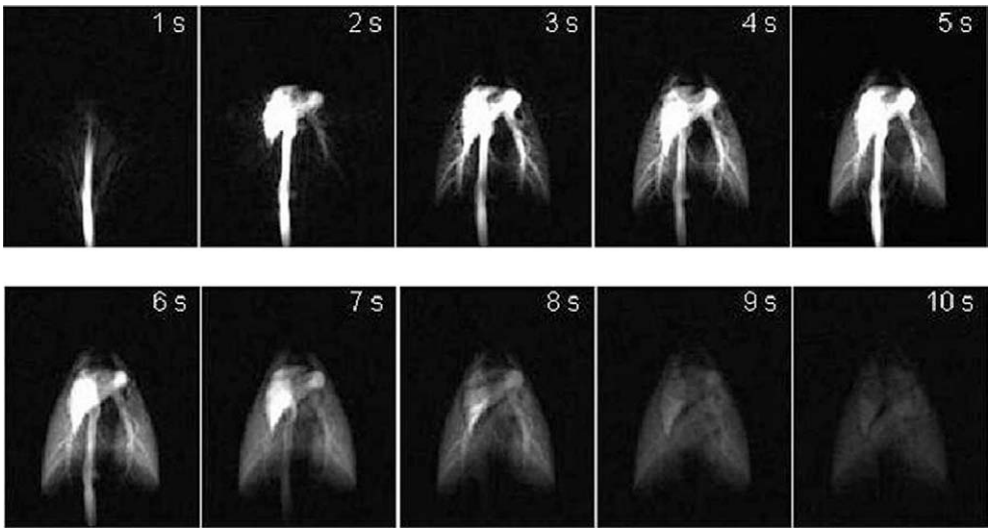

Fig. 3. Series of 10 successive angiographic images of a pig chest, taken at 1 s intervals following the injection of hyperpolarized hydroxyethylpropionate.
(After ref. [8], with permission of *The British Journal of Radiology*).

5. Experimental illustration of imaging

The only illustration given, in Fig. 3, is that of a pig chest angiography using hyperpolarized hydroxyethylpropionate [8]. Successive ^{13}C images by the TrueFISP method, following the intravenous injection into the leg of 5 ml of a 0.5 M solution of the compound, were taken at 1 s intervals. The slice thickness was larger than the pig. The scan time for each image was 470 ms, using a matrix of 104×128 and a pixel size of 2.5×2.5 mm^2. One can clearly follow the dynamics of progression of blood through the various vessels of the lungs.

6. Conclusion

The use of small organic molecules with hyperpolarized carbon-13, as contrast agents in MRI, has definitely come of age. The maximum polarization obtained, already quite noticeable, could be increased by nearly a factor two in the future in the pulse method. The main feature of this new type of contrast agents is that it can be produced in a very short time, a few seconds, with modest equipment as compared with a MRI machine, both in size and price. Its unique quality is that, because the carbon polarization is so much larger than the thermal equilibrium value of the organic molecules in the organism (about 1.2×10^{-6} in a 1.5 T imager), only the injected compound does practically contribute to the observed images, with no interference from other spins and a remarkably large signal-to-noise ratio. This is true even with the limited polarizations obtained in the field-cycling method. This new approach to MRI opens the way to dynamic studies in vivo of great potential usefulness, whose value would complement that of normal proton imaging.

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