

Conversion of a proton para order into ^{13}C polarization by rf irradiation, for use in MRI

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Résumé

Conversion de l'ordre para d'une paire de protons en polarisation de ^{13}C par irradiation rf, pour utilisation en IRM. Nous décrivons la théorie de la production de carbone 13 hyper polarisé dans des petites molécules organiques marquées, pour utilisation comme agents de contraste moléculaires en IRM, par un processus en deux grandes étapes. La première est une hydrogénation catalytique avec de l'hydrogène para dans un petit champ magnétique statique sous irradiation de radiofréquence, dont l'effet est de produire une paire de protons moléculaires dans un pur état para. La seconde étape convertit cet ordre para en hyperpolarisation globale d'un carbone 13 voisin par une séquence d'impulsions de radiofréquence aux fréquences de résonance des deux espèces de spins. La polarisation théorique finale est proche de l'unité. Le processus, mis en œuvre avec succès, ne dure que quelques secondes. *Pour citer cet article : M. Goldman, H. Jóhannesson, C. R. Physique 6 (2005).*

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Abstract

We describe the theory of production of hyperpolarized ^{13}C in small organic molecules, for use as molecular contrast agents in MRI, by a two-step process. The first is a catalyzed hydrogenation with para-hydrogen in a small dc magnetic field under rf irradiation, resulting in a molecular proton pair in the pure para state. The second step converts this para order into net hyperpolarization of a nearby carbon 13 through a sequence of rf pulses at the resonance frequencies of both spin species. The final theoretical polarization is close to unity. The whole process, which was successfully implemented, takes a few seconds. *To cite this article: M. Goldman, H. Jóhannesson, C. R. Physique 6 (2005).*

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Version française abrégée

L'hydrogénation d'une molécule organique par de l'hydrogène para conduit à un état initial de spin para des deux protons, hautement ordonné, qui évolue ensuite. Ce phénomène appelé PHIP [1–3], a donné lieu à de nombreuses études [4]. Le laboratoire de Malmö a initié son utilisation pour convertir cet ordre en hyperpolarisation d'un ^{13}C voisin de la paire de protons, par une méthode de champ cyclé [5–9]. Le présent article concerne la base théorique d'une autre méthode, plus efficace, utilisant des irradiations de radiofréquences aux fréquences de résonance des deux espèces de spins, en continu ou en impulsions [10,11]. Le matériau de départ, obtenu par synthèse, consiste en molécules totalement marquées en deutérium ainsi qu'en carbone 13 en un site proche d'une double ou triple liaison. La première étape est la réaction d'hydrogénation catalytique effectuée dans champ magnétique faible en présence d'une irradiation continue à la fréquence de résonance des protons, ce qui a pour effet de découpler l'état singulet (para) des protons de l'état triplet (ortho). Il en résulte qu'en fin d'hydrogénation toutes les molécules sont dans l'état singulet, ce qui évite la perte d'ordre que provoquerait l'évolution du système dans un champ statique seul. Après arrêt de l'irradiation, dans la seconde étape la manipulation des spins s'effectue en deux temps, chacun comportant plusieurs phases, et maintient le système dans le sous-espace d'aimantation totale nulle pour les protons. Sa théorie est énormément simplifiée par l'utilisation d'une image géométrique introduisant, pour décrire le système des spins des protons, des spins 1/2 fictifs couplés à des champs magnétiques fictifs. L'étude préalable du second temps permet de déterminer la forme optimum que doit avoir la matrice densité à son début. Ce second temps comporte si nécessaire plusieurs phases, chacune conduisant à la formation d'une composante transversale de polarisation du ^{13}C qu'une impulsion combine avec la composante longitudinale résultant de la phase précédente pour rendre la polarisation totale longitudinale. C'est pour le premier temps que l'image géométrique est irremplaçable pour rendre intuitive la marche à suivre pour passer de l'état singulet suivant l'hydrogénation à la matrice densité optimum avant le second temps, par une combinaison de périodes d'évolution libre et d'impulsions de 180° sur l'une ou l'autre espèce de spins. La polarisation théorique finale peut en principe être rendue aussi proche de l'unité que l'on veut, en fonction du nombre de phases de polarisation dans le second temps. La manipulation des spins dure une fraction de seconde, tandis que le processus total, hydrogénation et manipulation des spins, mis en œuvre avec succès, ne dure en tout que quelques secondes.

1. Introduction

Following the hydrogenation of an organic molecule with para-hydrogen, the two protons are initially in the highly ordered para spin state. This shows up by the observation of large anti-phase NMR signals. This phenomenon, now usually called PHIP, for Para-Hydrogen-Induced-Polarization, was discovered both theoretically and experimentally by Bowers and Weitekamp [1–3], who used two different implementations dubbed PASADENA and ALTADENA. Numerous studies followed, in particular on the transfer of order to hetero nuclei. Many of them are described in a review article by Bowers [4]. The use of PHIP for MRI was initiated in the Malmö laboratory [5–9] in the form of a field-cycling method for turning the molecular proton para order into a large polarization of a nearby ^{13}C spin, and using the polarized compound as a molecular contrast agent.

Another method, more effective than the preceding one, was developed and successfully implemented in the same laboratory [10,11]. The present Note does not dwell on the various steps of the experimental design and its implementation, but is devoted to outlining the theoretical basis of the method. It uses a constant low magnetic field and radiofrequency irradiation, continuous during the hydrogenation and in the form of pulses for the order conversion. We begin by recalling the properties of para-hydrogen.

1.1. The para-hydrogen molecule

The two nuclear spins 1/2 of a hydrogen molecule are coupled to form a triplet of total spin 1, called ortho-hydrogen, and a singlet of spin 0, called para-hydrogen. Their spin functions are symmetric and antisymmetric, respectively. They have the following well-known forms:

$$|1\rangle = |++\rangle, \quad |0\rangle = \frac{1}{\sqrt{2}}(|+-\rangle + |-+\rangle), \quad |-1\rangle = |--\rangle, \quad |s\rangle = \frac{1}{\sqrt{2}}(|+-\rangle - |-+\rangle) \quad (1)$$

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

The molecule also possesses rotational states of quantum number J and energy (in Kelvin):

$$E(J) = \Theta_r J(J+1), \quad \Theta_r = 85.3 \text{ K}. \quad (2)$$

The Pauli principle imposes that in the singlet and triplet states the rotational quantum number be even and odd, respectively. The ground state is the singlet state with $J = 0$, and the nearest state is the triplet state with $J = 1$, of energy 170.6 K above.

Therefore, below, say, 20 K the thermal equilibrium corresponds to nearly pure para-hydrogen with $J = 0$. In pure hydrogen the conversion rate is extremely low. It can become large in the presence of a commercially available catalyst, and thermal equilibrium can be reached quickly.

Brought back to room temperature, the gas remains in the para state because of the low conversion rate.

2. The para-hydrogenated molecule

We consider synthetic molecules where all hydrogen present before hydrogenation are labeled with deuterons, and with a carbon atom labeled with ^{13}C near a double or triple bond where the hydrogenation is to take place. In the liquid state and in a field low enough for the difference in proton resonance frequencies due to their chemical shifts to be negligible, the system composed of the two protons and of the carbon 13 is of the form $\text{AA}'\text{X}$.

2.1. The initial density matrix and the spin Hamiltonian

Let \mathbf{I}_1 and \mathbf{I}_2 be the spin operators of the protons and \mathbf{S} that of the carbon. From the property:

$$\mathbf{I}_1 \cdot \mathbf{I}_2 = \begin{cases} 1/4 & \text{for the triplet,} \\ -3/4 & \text{for the singlet,} \end{cases} \quad (3)$$

it follows that the singlet state produced by the hydrogenation corresponds to an initial density matrix of the form:

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

As for the effective Hamiltonian, in a doubly rotating frame it reduces to the indirect scalar interactions, truncated for the proton-carbon pairs, because the difference of Larmor frequencies is much larger than the $I-S$ interactions:

$$H = J_{12}\mathbf{I}_1 \cdot \mathbf{I}_2 + J_{1S}I_{1z}S_z + J_{2S}I_{2z}S_z. \quad (5)$$

The method with rf irradiation to be described is a variant for which all evolutions are limited to the subspace with $I_{1z} + I_{2z} = 0$, a basis of which 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 . The useful part of the Hamiltonian is its projection in this subspace, still called H :

$$H = J_{12}(I_{1x}I_{2x} + I_{1y}I_{2y}) + \frac{1}{2}(J_{1S} - J_{2S})(I_{1z} - I_{2z})S_z + J_{12}I_{1z}I_{2z}. \quad (6)$$

The last term is a constant in the subspace and it can be forgotten.

2.2. Geometrical picture

When considering the proton spins only in the subspace, the latter splits into two 2D spaces, for $S_z = \pm\frac{1}{2}$, in which the quantum evolutions are isomorphic to 3D rotations. It is then possible to use a fictitious spin $1/2$, called K , as follows:

$$I_{1x}I_{2x} + I_{1y}I_{2y} \rightarrow K_x, \quad \frac{1}{2}(I_{1z} - I_{2z}) \rightarrow K_z, \quad I_{1y}I_{2x} - I_{1x}I_{2y} \rightarrow K_y = i[K_x, K_z]. \quad (7)$$

Using the further notations:

$$\frac{1}{2}(J_{1S} - J_{2S}) = a, \quad J_{12} = b, \quad (8)$$

the expressions of the Hamiltonian and initial density matrix become:

$$H = a2S_zK_z + bK_x, \quad \sigma_{\text{ini}} = \frac{1}{8}(1 - 4I_{1z}I_{2z} - 4K_x). \quad (9)$$

The Hamiltonian has the form of the Zeeman interaction of the fictitious spin K with a fictitious magnetic field. We write it separately for the two values of S_z :

$$H_+ = aK_z + bK_x = \Omega K_Z, \quad H_- = -aK_z + bK_x = \Omega K_{Z'}. \quad (10)$$

The geometric picture is shown for H_+ in Fig. 1, together with extra features for future use.

The angle θ is defined through: $\arctan\theta = b/a$. In the $S_z = -1/2$ sub-subspace, the fictitious field is along an axis OZ' symmetrical to OZ with respect to the axis Ox . For later use we also introduce $\alpha = 90^\circ - \theta$, the axis Ox orthogonal to OZ ,

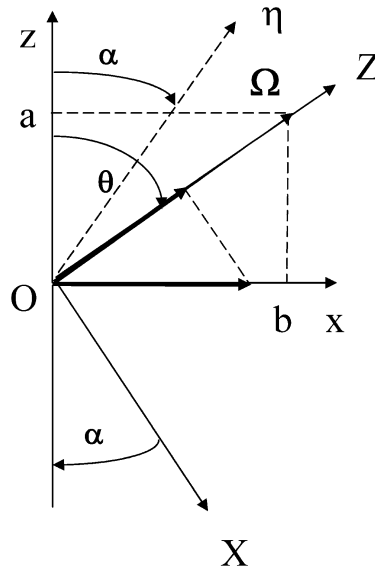


Fig. 1. Fictitious field (in frequency units) and its components for $S_z = 1/2$. Unit vector along K_x and its projection on OZ .

Fig. 1. Champ fictif (en unités de fréquence) et ses composantes pour $S_z = 1/2$. Vecteur unité le long de K_x et sa projection sur OZ .

that is at an angle $\theta + 90 = 180 - \alpha$ from Oz , and the axis $O\eta$, symmetric of OX with respect to Ox , that is at an angle α from Oz and $\theta - \alpha$ from OZ .

The initial density matrix in the subspace can then be written:

$$\sigma_{\text{ini}} = \frac{1}{8}(1 - 4I_{1z}I_{2z} - 4K_x) = \frac{1}{4} - \frac{1}{2}K_x. \quad (11)$$

The only significant term is K_x . For the rest of the evolution, we write:

$$\sigma(t) = \frac{1}{4} - \frac{1}{2}\rho(t) \quad (12)$$

and we follow the evolution of ρ . For a free evolution in the two sub-subspaces associated with the two values of $S_z = \pm \frac{1}{2}$, the geometric picture of ρ is that of two fictitious vector spins: $\rho = \rho_+ + \rho_-$. Their evolution is simply a precession with frequency Ω : around OZ for ρ_+ and OZ' for ρ_- .

3. The hydrogenation reaction

If the hydrogenation reaction simply took place in a field large enough to allow truncating the I - S indirect interactions, the precessions of the vectors ρ_{\pm} of the individual molecules, hydrogenated at different times, would result in an isotropic distribution of precession angles and their final average would reduce to the projection of K_x on the axes OZ and OZ' in the two sub-subspaces, which amounts to a loss of order equal to $\sin\theta$. In order to avoid this loss, the whole hydrogenation reaction vessel is subjected both to a constant dc field and to an rf irradiation at the proton Larmor frequency during the whole duration of the reaction. The result of this irradiation is to add to the Hamiltonian (6) a term $\omega_1(I_{1x} + I_{2x})$, which *decouples* the singlet state from the triplet state. Since the new term commutes with $\mathbf{I}_1 \cdot \mathbf{I}_2$, the spin density matrix of each newly hydrogenated molecule does not evolve with time, and all molecules remain in the singlet state until the end of the hydrogenation process.

4. The order conversion

We neglect throughout spin-lattice relaxation. The conversion is performed in two successive steps, each of which may consist of several phases. The first step uses only free evolution periods under the Hamiltonian of Eq. (9), and 180° pulses on either spins I or S , and therefore it leaves the system density matrix within the subspace. The final operator ρ can only contain components K_x , $2S_zK_z$ and $2S_zK_y$. This first step is aimed at creating a form of ρ optimized for the second step. It is therefore necessary to analyse the second step first.

4.1. The second step

At the end of the first step, we perform a 90° pulse around Oy on the spin S (the carbon spin) thereby turning the operator S_z into S_x . This move is a necessary one (to within the pulse phase): it is the only way to introduce density matrix elements between the two sub-subspaces whose partial Hamiltonians have different dependences on the quantum value of S_z . This point was already noted by Natterer et al. [12]. The time evolution of the possible components of the density matrix is as follows (we use $\sin \theta = s$, $\cos \theta = c$):

$$\begin{aligned} K_x &\rightarrow (s^2 + c^2 \cos \Omega t) K_x + c \sin \Omega t (2K_y S_z) + sc(1 - \cos \Omega t) (2K_z S_z), \\ 2K_z S_x &\rightarrow c \sin \Omega t S_y - s \sin \Omega t (2K_y S_x) + \cos \Omega t (2K_z S_x), \\ 2K_y S_x &\rightarrow sc(1 - \cos \Omega t) S_y + (c^2 + s^2 \cos \Omega t) (2K_y S_x) + s \sin \Omega t (2K_z S_x). \end{aligned} \quad (13)$$

By examination of this formula it is found that, provided $|s| > \frac{1}{2}$, which we will suppose true, the most effective way is to start from the component $2K_y S_x$ at the end of the first step, and to wait for half a period ($\cos \Omega t = -1$), which yields:

$$\rho_1 = \sin(2\theta) S_y + \cos(2\theta) (2K_y S_x). \quad (14)$$

Next, one performs a 90° pulse on S around Ox to transform S_y into the longitudinal operator S_z without affecting the remaining term. The resulting S polarization is equal to $\sin(2\theta)$. This is the end of the process if $\sin(2\theta)$ is close to unity.

4.1.1. Successive 'pumping' phases

If $\sin(2\theta)$ is not very close to unity, one can continue the process, that is, let the evolution proceed for another half period. The longitudinal component of the spin S does not change: it remains unaffected by the Hamiltonian and its relaxation time is long. We obtain:

$$\rho_2 = \sin(2\theta) (S_z + \cos(2\theta) S_y) + \cos^2(2\theta) (2K_y S_x). \quad (15)$$

We now have two components of the spin S in quadrature. What is then needed is a pulse on S around Ox , of angle $\beta = \arctan(\cos(2\theta))$, to obtain a longitudinal polarization of S equal to:

$$P_S(2) = \sin(2\theta) \cdot \sqrt{1 + \cos^2(2\theta)}. \quad (16)$$

We can repeat the process. By induction, the square of the S polarization after n pumping phases is equal to:

$$P_S^2(n) = 1 - \cos^{2n}(2\theta) \quad (17)$$

whereas the pulse angle β_n to be applied after the n th phase is deduced from:

$$\tan^2 \beta_n = \frac{\sin^2(2\theta) \cos^{2(n-1)}(2\theta)}{1 - \cos^{2(n-1)}(2\theta)}. \quad (18)$$

It decreases when n increases. As for the signs of the pulse angles, they depend on the sign of $\cos(2\theta)$: their successive signs remain the same if this cosine is positive, and alternate if it is negative.

4.2. The first step

To produce the optimum form of ρ at the end of the first step, namely $2K_y S_x$, one begins by creating $\rho = 2K_y S_z$ and then applies a 90° pulse on S around Oy . This will be analysed for $S_z = +\frac{1}{2}$, for which the initial $\rho_+ = K_x$ has to be transformed into K_y . The evolution of ρ_- will be symmetrical. The way of achieving this is as follows, with reference to Fig. 1. After the steady rf irradiation is cut off, one first manages, through a procedure outlined below, to bring the vector ρ_+ in an orientation such that its projection on the plane Ozx is parallel to the axis $O\eta$. Then one performs a 180° pulse on either the spins I or the spin S . According to Eqs. (7), the effect of such a pulse is:

$$K_x \rightarrow K_x, \quad 2K_z S_x \rightarrow -2K_z S_x, \quad 2K_y S_x \rightarrow -2K_y S_x. \quad (19)$$

Therefore, after the pulse the projection of ρ_+ is parallel to OX , that is, its component along OZ vanishes. One then waits for the precession to bring this vector parallel to OY , that is, $\rho_+ = K_y$. It is easily seen that under the same procedure one has $\rho_- = -K_y$, so that one obtains finally the required form $\rho = 2K_y S_z$, before the 90° pulse on S . In practice, after the irradiation cutoff, the motion of ρ_+ is a precession around the axis OZ at constant angle α . Starting from K_x , the minimum possible angle between $O\eta$ and ρ_+ , $\theta - 2\alpha = 90^\circ - 3\alpha$, is reached after half a period, for a precession angle of 180° , with ρ_+ in the

plane Ozx . If this angle is negative, that is if $\alpha \geq 30^\circ$, or $\theta \leq 60^\circ$, this corresponds to an overshoot. Therefore, it is possible to reach a position of ρ_+ such that its projection on the plane Ozx is parallel to the axis $O\eta$ with a precession angle smaller than 180° .

If the angle $\theta > 60^\circ$, one has to use a longer sequence. After the rf irradiation is cut off, one waits for half a period to bring the vector ρ_+ in the plane Ozx , then performs a 180° pulse and repeat the process if necessary until the angle γ between Ox and ρ_+ (an even multiple of α) is such that a 180° precession around OZ would result in an angle with $O\eta$, $\theta - 2\alpha - \gamma = 90^\circ - 3\alpha - \gamma \leq 0$, that is $\gamma \geq 90 - 3\alpha$. The last precession, with an angle smaller than 180° is now able to bring ρ_+ to the desired position where its projection on the plane Ozx is parallel to $O\eta$. A 180° pulse followed by a final precession brings it parallel to OY . It is therefore always possible to produce the optimum form of $\rho = 2K_y S_z$ before the 90° pulse on S and the beginning of the second step.

5. The echo pulses

As in standard NMR, frequency differences affect adversely the effectiveness of the method by producing spurious phase differences. The inhomogeneity of the external dc field affects only the transverse components of the spin S during the second step of the ordering process. In addition, the two protons may have different resonance frequencies, because of the neglected effect of their chemical shift difference and of possible different indirect interactions with the deuterons. In terms of the fictitious spin K , the latter add to the effective fictitious field an extra term parallel to Oz and independent of the spin S , that is neither parallel to the orientations OZ nor OZ' of the effective fields. The standard cure for such defects is to apply 180° echo pulses. In the present case, they have two special features. Firstly, these pulses must not affect the effective static Hamiltonian (6), which necessitates the use of two simultaneous 180° pulses on both spins I and S . Secondly, the extra fictitious Zeeman term δK_z does not commute with the Hamiltonian of the upper Eq. (9). As a consequence, echo pulses in the middle of each interval between useful pulses do not exactly cancel the effect of this extra term. A way which proves effective for not-too-large values of δ , both from simulations and experiment, consists in applying, during each interval between free evolutions, *two* double echo pulses at 1/4th and 3/4th of the time interval.

6. Illustrations

We give figures for two compounds, hydroxyethylpropionate and succinic acid.

6.1. Hydroxyethylpropionate

The relevant parameters, as determined from NMR spectra, are:

$$\begin{aligned} J_{12} &= 7.57 \text{ Hz}, & J_{1S} &= 7.24 \text{ Hz}, & J_{2S} &= -5.62 \text{ Hz}, \\ a &= 6.43 \text{ Hz}, & b &= 7.57 \text{ Hz}, & \theta &= 49.66^\circ, & \sin(2\theta) &= 0.9868. \end{aligned} \quad (20)$$

The first step requires only two evolution periods, of durations 28.28 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 per cent. The complete pulse sequence is shown in Fig. 2.

Remark 1. Within the description given in this article, the first 180° pulse, on the spins I in Fig. 2, could as well have been performed on the spins S . The reason why a pulse on I is preferable to a pulse on S will be discussed in detail in a future article.

6.2. Succinic acid

The relevant parameters, not known with accuracy, are provisionally:

$$\begin{aligned} J_{12} &= 7 \text{ Hz}, & J_{1S} &= 7 \text{ Hz}, & J_{2S} &= 0, \\ a &= 3.5 \text{ Hz}, & b &= 7 \text{ Hz}, & \theta &= 63.435^\circ, & \sin(2\theta) &= 0.800. \end{aligned} \quad (21)$$

The consequence of the large value of θ is that the first step requires two evolution phases, each one followed by a 180° pulse, for obtaining a vector ρ_+ normal to OZ and one more to bring it parallel to OY . 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 couplings are not known accurately.

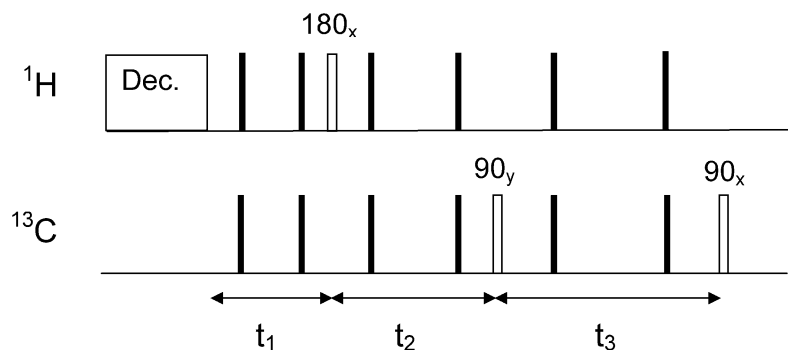


Fig. 2. Pulse sequence for hydroxyethylpropionate. Following the rf decoupling, there are only three ‘useful’ pulses (in white). The others (black bars) are the echo pulses, at 1/4th and 3/4th of each free evolution period.

Fig. 2. Séquence d’impulsions pour l’hydroxyethylpropionate. Après le découplage rf, il n’y a que trois impulsions « utiles » (en blanc). Les autres (barres noires) sont des impulsions d’écho, à 1/4 et 3/4 de chaque période d’évolution libre.

7. Conclusion

We have developed an efficient pulse method for producing hydrogenated molecules with a proton pair in a pure para state, and then converting its order into a ^{13}C polarization close to unity. The use of a geometric picture of fictitious spins coupled to a fictitious magnetic field was a decisive help in the first step of the method for determining the best procedure to determine and create the optimum density matrix at the beginning of the second step, the one in which the order conversion to net carbon polarization takes place. The description of a variant method using pulses, theoretically as efficient as the present one, is postponed to a later publication.

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References

- [1] C.R. Bowers, D.P. Weitekamp, *Phys. Rev. Lett.* 57 (1986) 2645–2648.
- [2] C.R. Bowers, D.P. Weitekamp, *J. Am. Chem. Soc.* 109 (1987) 5541–5542.
- [3] M.G. Pravica, D.P. Weitekamp, *Chem. Phys. Lett.* 145 (4) (1998) 255–258.
- [4] C.R. Bowers, in: D.M. Grant, R.K. Harris (Eds.), *Encyclopedia of Nuclear Magnetic Resonance*, vol. 9, John Wiley and Sons, Chichester, 2002, pp. 750–769.
- [5] Patent WO 00/71166.
- [6] K. Golman, O. Axelsson, H. Jóhannesson, S. Månsson, C. Olofsson, J.S. Petersson, *Magn. Reson. Med.* 46 (2001) 1–5.
- [7] H. Jóhannesson, O. Axelsson, M. Karlsson, *C. R. Physique* 5 (2004) 315–324.
- [8] K. Golman, L.E. Olsson, O. Axelsson, S. Månsson, M. Karlsson, J.S. Petersson, *The Brit. J. Radiol.* 76 (2003) S118–S127.
- [9] M. Goldman, H. Jóhannesson, O. Axelsson, M. Karlsson, *Magn. Reson. Imag.* (2005), in press.
- [10] Patent WO 2004/019995.
- [11] M. Goldman, H. Jóhannesson, O. Axelsson, M. Karlsson, C. R. Chimie, in press.
- [12] J. Natterer, O. Schedletzky, J. Barkemeyer, J. Bargon, S.J. Glaser, *J. Magn. Reson.* 133 (1998) 92–97.