Creation and evolution of net proton hyperpolarization arising from para-hydrogenation

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ABSTRACT

When a hydrogenation reaction is carried out with gaseous hydrogen enriched in its para- isomer in the earth magnetic field (prior to adiabatic insertion of the sample in the NMR magnet), enhanced proton longitudinal order (represented by $2I_z^A I_z^B$) is created but also difference of enhanced polarizations ($I_z^A - I_z^B$). In a first part, it is shown theoretically and experimentally that the longitudinal relaxation time of this polarization difference is roughly twice the ones of individual polarizations. The second part is devoted to a pulse sequence designed for transforming this difference into net hyperpolarization. The evolution of this global hyperpolarization is studied experimentally in a third part and it is observed that a fraction of hyperpolarization possesses an effective longitudinal relaxation time similar to the one of the initial polarization difference. Those experimental results are interpreted by numerical calculations based on Solomon-type equations including the longitudinal order and possibly dipolar-csa cross correlation rates.

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1. Introduction

Biomedical applications (especially MRI) of ParaHydrogen (pH$_2$) Induced Polarization (PHIP) [1] make generally use of ^{13}C hyperpolarization. This hyperpolarization originates from the protons of an appropriate molecule which has been subjected to a hydrogenation reaction by gaseous hydrogen enriched in its para isomer. The main reason is that ^{13}C nuclei have generally relaxation times longer than those of protons, thus enabling more time for imaging experiments [2] (which, in addition, will not be perturbed by the strong water proton signal). Moreover protons can be in a complicated spin state, involving at least longitudinal spin orders (see below). Indeed, the problem is to transform the proton spin state into ^{13}C hyperpolarization. A first approach is an INEPT-like pulse sequence [3–6]. Field cycling procedures [2,7] or special pulse sequences [8,9] constitute other ways of achieving ^{13}C hyperpolarization by transfer from enhanced proton spin states. These special pulse sequences have been systematically used in very recent works devoted to biomedical applications of NMR and MRI [10–12]. However, even if the totality of hyperpolarization is transferred, ^{13}C imaging, with respect to ^{1}H imaging, entails a sensitivity loss by a factor of 16 (the square of the gyromagnetic constants ratio). This is a strong incitement for employing directly proton hyperpolarization, provided that the spin states can be really transformed into net hyperpolarization. It is the very problem we

address in this work. Indeed, for a two spin ½ system, in addition to the longitudinal spin order (represented by the operator product $2I_z^A I_z^B$, where A and B are two spins originating from pH$_2$), one may observe a polarization difference (represented by $I_z^A - I_z^B$). As a matter of fact, PASADENA [13] experiments (hydrogenation reaction inside the NMR magnet) yield only longitudinal order while ALTADENA [14] experiments can produce both longitudinal order and polarization difference, [1,14–16]. Longitudinal spin order can be transformed into an observable signal by a radio-frequency (rf) pulse of flip angle smaller than 90° (maximum obtained with a 45° flip angle). The observable signal is however an anti-phase doublet which implies the existence of a J coupling between A and B. This anti-phase doublet is evidently not suitable for most applications since it may not be resolved due to a low value of the J coupling and/or to the static field inhomogeneity. Moreover, it is *not* a polarization. We have therefore to rely on the polarization difference ($I_z^A - I_z^B$). Again it is *neither* a net polarization since A and B may have opposite effects (in imaging experiments, for instance). In a previous publication [17], we determined in which conditions the longitudinal order and the polarization difference were created and the goal of the present work is naturally to devise a procedure for creating a net hyperpolarization. Before describing this procedure (a particular pulse sequence), we shall study the relaxation properties of the polarization difference in order to determine a possible delay between the insertion of the sample in the NMR magnet and the start of the NMR experiment. Finally, the evolution of the net polarization (and of the existing longitudinal order with possible coupling between them), which is of prime

importance in view of many applications (notably as far as imaging experiments are concerned), will be considered experimentally and justified theoretically.

The model we are going to use in this study originates from methyl-d^3 butynoic acid in acetone-d^6 as shown in Fig. 1 [17].

The advantage of this molecule is that it is almost a perfect two-spin system if we neglect possible transfers toward the deuterated
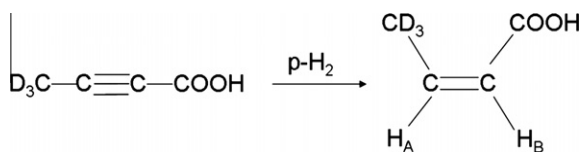

Fig. 1. The model molecule used in this work. It was obtained using an acetone-d^6 solution (0.4 ml) of [Rh(NBD)dppb]$^+$[BF$_4$]$^-$ (20 mM) as catalyst and methyl-d^3 butynoic acid (480 mM). Para-H$_2$ was enriched cooling H$_2$ in liquid nitrogen (77 K) with activated charcoal as ortho-para conversion catalyst. The para-hydrogenation reactions were carried out by shaking the NMR tube (gas tight NMR tubes equipped with Young valve) previously charged with 4 atm of parahydrogen out of the NMR spectrometer (ALTADENA experiment). All the spectra were acquired on a Bruker Avance 600 MHz spectrometer.

methyl directly bound to the double bond. We were able to show both theoretically and experimentally that, with a classical ALTA-DENA experiment (reaction carried out in the earth field), besides the longitudinal order $2I_z^A I_z^B$, even a larger amount of polarization was created but in the form of a *polarization difference* $(I_z^A - I_z^B)$. This is evidenced by the spectra of Fig. 2, owing to the fact that both $2I_z^A I_z^B$ and $(I_z^A - I_z^B)$ are observable by means of a $\pi/4$ pulse while a $\pi/2$ unravels only $(I_z^A - I_z^B)$.

Thus, upon insertion of the sample in the magnet, an enhanced polarization difference (several orders of magnitude larger than the thermal polarization) is available.

2. Relaxation of polarization difference by intramolecular proton relaxation

This is the relaxation behavior between the two hyperpolarized A and B protons. The relevant Solomon equations can be written as

$$\frac{dI_z^A}{dt} = -R_1^A(I_z^A - I^{eq}) - \sigma_{AB}(I_z^B - I^{eq})$$
$$\frac{dI_z^B}{dt} = -R_1^B(I_z^B - I^{eq}) - \sigma_{AB}(I_z^A - I^{eq})$$
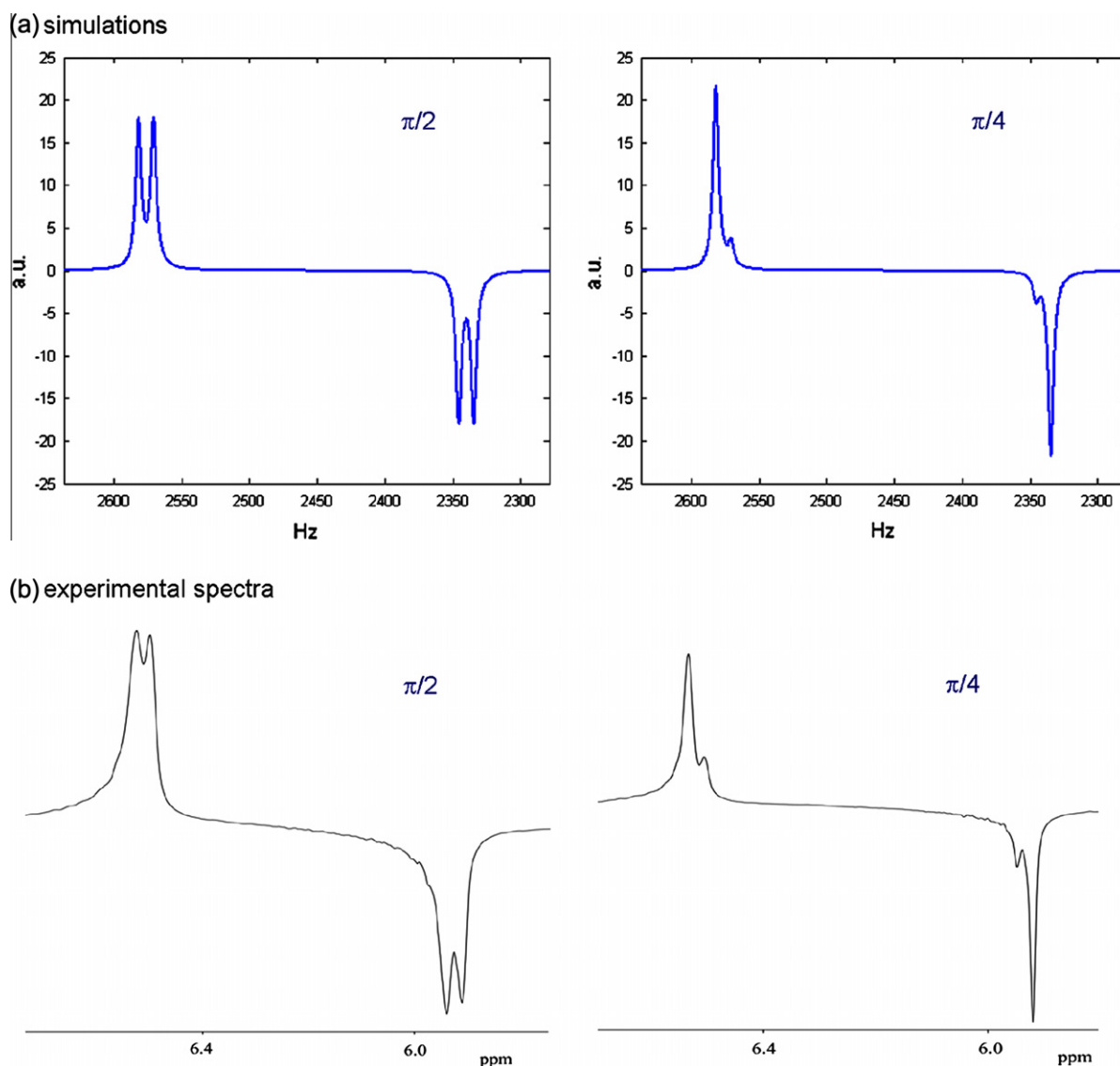
(1)

Fig. 2. Spectra showing the formation of enhanced spin states (ALTADENA experiment): $2I_z^A I_z^B$ and $(I_z^A - I_z^B)$. Left: only $(I_z^A - I_z^B)$. Right: both $2I_z^A I_z^B$ and $(I_z^A - I_z^B)$. From Ref. [17].