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Spin polarization transfer mechanisms of SABRE: A magnetic field dependent study

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ABSTRACT

We have investigated the magnetic field dependence of Signal Amplification By Reversible Exchange (SABRE) arising from binding of *para*-hydrogen (p-H_2) and a substrate to a suitable transition metal complex. The magnetic field dependence of the amplification of the ^1H Nuclear Magnetic Resonance (NMR) signals of the released substrates and dihydrogen, and the transient transition metal dihydride species shows characteristic patterns, which is explained using the theory presented here. The generation of SABRE is most efficient at low magnetic fields due to coherent spin mixing at nuclear spin Level Anti-Crossings (LACs) in the SABRE complexes. We studied two Ir-complexes and have shown that the presence of a ^{31}P atom in the SABRE complex doubles the number of LACs and, consequently, the number of peaks in the SABRE field dependence. Interestingly, the polarization of SABRE substrates is always accompanied by the *para*-to-*ortho* conversion in dihydride species that results in enhancement of the NMR signal of free (H_2) and catalyst-bound H_2 (Ir-HH). The field dependences of hyperpolarized H_2 and Ir-HH by means of SABRE are studied here, for the first time, in detail. The field dependences depend on the chemical shifts and coupling constants of Ir-HH, in which the polarization transfer takes place. A negative coupling constant of −7 Hz between the two chemically equivalent but magnetically inequivalent hydride nuclei is determined, which indicates that Ir-HH is a dihydride with an HH distance larger than 2 Å. Finally, the field dependence of SABRE at high fields as found earlier has been investigated and attributed to polarization transfer to the substrate by cross-relaxation. The present study provides further evidence for the key role of LACs in the formation of SABRE-derived polarization. Understanding the spin dynamics behind the SABRE method opens the way to optimizing its performance and overcoming the main limitation of NMR, its notoriously low sensitivity.

1. Introduction

Signal Amplification by Reversible Exchange (SABRE) is a variant of *Para*-Hydrogen Induced Polarization (PHIP) and a method to generate strong non-thermal nuclear spin polarization (called spin hyperpolarization) to enhance the Nuclear Magnetic Resonance (NMR) signal intensities of a substrate. The reactions that lead to SABRE are shown in Scheme 1 as described in Ref. [1]. In SABRE, a suitable transition metal catalyst dissolved in an organic solvent is used, which forms a complex with H_2 and a substrate [2] (although SABRE experiments in water are also feasible [3]). In the "reversible exchange stage" non-polarized H_2 is replaced by polarized *para*-H_2 (p-H_2, the H_2 molecule in its singlet nuclear spin state), which transfers its polarization to the liganded substrate. The mechanism of polarization formation in this process is also depicted in Scheme 1. Eventually the polarized substrate leaves the metal and joins a pool of free polarized substrate in solution. As long as p-H_2 is available this process can be repeated leading

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Abbreviations: LAC, Level Anti-Crossing; MRI, Magnetic Resonance Imaging; NMR, Nuclear Magnetic Resonance; NSPD, Nuclear Spin Polarization Dispersion; o-H_2, *ortho*-H_2; p-H_2, *para*-H_2; PHIP, Para-Hydrogen Induced Polarization; Py, pyridine (aPy, axial Py; ePy, equatorial Py; fPy, free Py); SABRE, Signal Amplification By Reversible Exchange.

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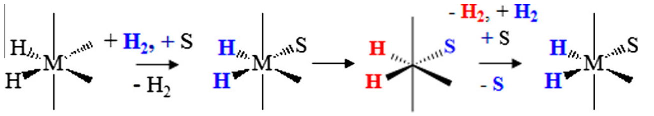


Scheme 1. Catalyzed SABRE polarization transfer from p-H_2 (H_2) to a substrate S according to Ref. [1] results in the formation of polarization of S and H_2. Here p-H_2 and o-H_2 are shown in bold face in blue and red, respectively; the hyperpolarized substrate molecule is shown in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

to a substantial substrate polarization, which will survive until it decays by relaxation. Based on new experiments and computations discussed later, we clearly demonstrate that not only the substrate is polarized but the leaving dihydrogen exhibits an opposite polarization due to enrichment of *ortho*-H_2 (o-H_2, the triplet spin isomer). The SABRE process avoids hydrogenation of double or triple bonds by p-H_2 used in other versions of PHIP leading to consumption of the substrate. SABRE gets around the chemical conversion and can provide NMR signal enhancements up to four orders of magnitude. This technique has been used in mobile low-field Magnetic Resonance Imaging (MRI) [4], for NMR detection at nanomolar concentration [5,6] and for biomedical applications [7].

The key question in SABRE is the mechanism of spin transfer from p-H_2 to the substrate, see Scheme 1. An important related question is at what magnetic fields the SABRE-derived signal enhancements are the highest. With the aim to determine the SABRE field dependence (which we will call Nuclear Spin Polarization Dispersion, NSPD, by analogy with well-established relaxation studies) we have combined a p-H_2 bubbling device [8] with a field-cycling spectrometer, where the whole NMR probe can be shuttled between low and high fields [9]. Using this setup and exploiting the quantum–mechanical density matrix formalism, the SABRE polarization dispersion of Crabtree's catalyst (the description of SABRE catalysts is given below) was recently explored from an experimental and theoretical standpoint [10]. It was shown that the main parameters, which determine the polarization transfer at low magnetic fields, are the chemical shifts and scalar couplings of the active SABRE complex. The transfer occurs when spin functions of the same total spin mix at fields that correspond to so-called "Level Anti-Crossings (LACs)".

Despite the initial success in analyzing the SABRE field dependence by using the notion of LACs it is not clear whether this concept provides the general description of polarization transfer in field-dependent SABRE experiments. To confirm our expectations that polarization is transferred predominantly at LACs there is a need to collect the missing pieces of the puzzle in order to establish the complete description of the NSPDs. More specifically, the LAC-based description predicts strong effects of hetero-nuclei on the SABRE field dependence: the presence of a spin-1/2 heteronucleus is expected to double the number of relevant LACs and, consequently, the number of features in the SABRE field dependence. So far, SABRE field dependences have not been analyzed for ^{31}P-containing and phosphorus-free SABRE complexes under the same experimental conditions. In addition, the LAC-based coherent polarization transfer mechanism implies that polarization on the substrate is accompanied by a transition of H_2 from the NMR-silent *para*-state to an *ortho*-state giving observable magnetization of H_2. Indeed, Barskiy et al. [11] observed in the case of the Imes catalyst also hyperpolarized o-H_2. Polarized NMR signals coming from o-H_2 have also been found by Fekete et al. [12] but their origin was not discussed. Up to now, the H_2 polarization has not been analyzed systematically, most likely, because of experimental difficulties, namely, the short relaxation times of H_2 (~1 s). This inspired us to look closer at the H_2 polarization both experimentally and theoretically. Specifically, we study the polarization of the H_2-molecule and of the catalyst-bound dihydride, Ir-HH (cf. complexes **2** and **6** in Scheme 2), which is expected to have the same field dependence as the substrate, but is opposite in sign when the LAC-based mechanism is operative. Finally, with the aim to find out whether there are sizeable polarization transfer effects in other complexes we study the complete magnetic field dependence of SABRE.

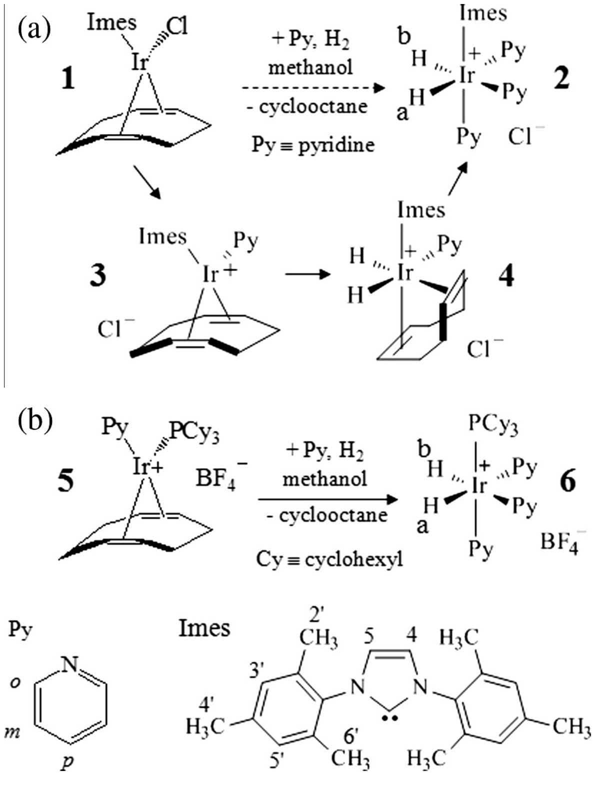
Hence, to fill the missing gaps in the description of the SABRE effect and to obtain complete understanding of the underlying spin dynamics we perform here SABRE experiments at variable magnetic fields from 0.1 mT to 16.4 T for SABRE complexes, with and without the phosphorus atom. We also analyze the full NSPD of o-H_2; our setup enables measurements of the full NSPD curve even despite fast spin relaxation of H_2. The ultimate goal of our investigation is to show that LACs give the dominant contribution to SABRE and drastically simplify the analysis of NSPDs.

In general, analysis of the NSPD based on LACs not only provides a simple way to look at the complex spin dynamics in SABRE complexes but also enables (i) identifying active SABRE complexes and (ii) obtaining their NMR parameters, which are difficult to access by NMR experiments with thermally polarized spins. Notably, the values and signs of the scalar coupling between the hydride nuclei can be obtained, which, in turn, provide information on proton–proton distances [13] and can vary over a wide range [14–17]. Applications of LACs, for instance, for designing high-field SABRE experiments are also discussed in the paper.

2. Methods

2.1. Sample preparation

Presently, two SABRE catalysts are commonly used. One is [IrCl(COD)(Imes)] (**1**, Imes ≡ 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, COD ≡ cycloocta-1,5-diene), which forms the corresponding



Scheme 2. (a) Formation of the Iridium dihydride **2** from the Iridium complex **1** with Imes ≡ 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene as ligand *via* the intermediate complexes **3** and **4**. (b) Formation of the Iridium dihydride **6** from Crabtree's complex **5**. In both cases the cycloocta-1,5-diene ligand is released as hydrogenated species. Structures of pyridine (Py) and Imes are also shown. Ir-HH protons are indicated as Ha and Hb.