Dynamic Nuclear Polarization – from Polarized Targets to Metabolic Imaging

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Abstract. Until recently the main application of dynamic nuclear polarization techniques has been in nuclear and particle physics, where they are used to polarize nuclei in bulk matter to be employed as polarized solid targets for particle beams probing the spin dependence of nuclear interactions. These techniques have now become most promising for applications in biomedical magnetic resonance and the knowledge gained in forty years of target development becomes of immediate interest.

1 Introduction

Since the first experiments performed in the early sixties, polarized solid targets are a key experimental tool in the investigation of spin effects in nuclear and particle physics interactions. The constant development in cryogenics and magnet technology, a better understanding of the solid-state mechanisms of the dynamic nuclear polarization (DNP) process and its consequent exploitation for devising new methods and searching for better target materials have led to maturity of the conventional type of polarized solid targets. A historical overview of the first thirty years of development with an exhaustive list of references is found in ref. 1. In general, the maximum achievable nuclear polarization in the target sample is the crucial parameter deciding on the feasibility of a scattering experiment. The experiment-specific constraints complicate and often contradict the task. A detailed knowledge of the mechanisms of DNP in various materials at different magnetic fields and temperatures is therefore essential. The large body of knowledge so accumulated is relevant for other applications of DNP, e.g., in neutron scattering [2], but has only recently become of immediate interest for nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) applications through an experiment of Ardenkjær-Larsen et al. [3].

This short note discusses a few aspects concerning the development of polarizable samples which might be of importance for new applications and

collects some references which give access to the original polarized target work.

2 Technical Aspects of the DNP Apparatus

Experimental constraints in particle physics experiments, e.g., small interaction cross section, low magnetic fields, no cryogenic environment, no additional material on the beam path, heavy ionizing particles, have often required the development of dedicated solutions: large frozen spin targets [4], scintillating polarized targets [5], very thin polarized probes for radioactive ion beams [6] or a frozen spin target for a cold neutron beam, to mention the most recent. As compared with these efforts, a hyperpolarization system might at first sight seem to be considerably less demanding. However, a proper design is most important to reach the lowest possible temperature during the DNP process. On one side, this requires a well-performing cryogenic system, as well as a sample holder and cavity geometry that makes an efficient use of the irradiated microwave power. The design of the latter is constrained by fitting the sample dissolution unit. An example of a very versatile and efficient system is described in ref. 7.

3 Polarizable Substances

Of course, for all applications a high density of polarizable nuclei in the sample is important. A breakthrough was achieved when in the late 1960s high proton polarizations could be obtained in glassy frozen beads of butanol and water doped with porphyrine [8], which replaced the originally employed lanthanum magnesium nitrate targets. Since then, the class of frozen solutions of alcohols and water doped with free radicals has been of main importance in target physics and forty years of development have yielded a large library of polarizable substances [9].

For such samples the increase of the nuclear polarization induced by DNP, relative to the thermal equilibrium polarization which is given by Boltzmann statistics, is typically two orders of magnitude and proton polarizations close to unity have been achieved. Already in an early phase of research the DNP behavior of nuclei heavier than hydrogen has been investigated, and ^{13}C nuclei have been polarized to more than 20% in isotopically enriched 1-butanol [10].

The properties of the electron spin system, be it a paramagnetic ion, a stable radical or a radiation-induced center, are crucial for achieving the nuclear polarization. Hyperfine interactions and g -value anisotropy leave their signature in the electron spin resonance (ESR) line shape and determine, depending on the magnetic field, the polarization mechanism and its efficiency.

Chemical doping is a most common and well-established method. Generally the radical ESR lines are quite broad, leading to a less efficient or no DNP process at higher fields (ca. 5 T) [11, 12]. An exception are the radicals of the trityl class, which are, due to an almost absent hyperfine interaction and g -value anisotropy, best suited to polarize nuclei with small magnetic moments (deuterons, ^{13}C)

Table 1. Deuteron polarizations P_D obtained in glassy samples.^a

Radical	$\Delta g/g$ ($\times 10^{-3}$)	D (mT)	Solvent	B (T)	T (K)	P_D (%)	T_s (mK)	Reference
EDBA-Cr ^V	6	12.3	d-butanol	2.5	0.2	49	0.96	11
				3.5	0.2	18	2.8	11
				5	0.2	0		11
TEMPO	3.6	5.25	d-butanol	2.5	0.2	39	1.3	12
				5	0.2	10	10	12
				5	1	25	4.1	16
Bi-TEMPO	3.6		d-polystyrene	3.5	1.1	65 ^b	4.6	17
Hydroxyalkyl	1.25	3.1	d-butanol	2.5	1	12	4.3	13
				5	1	50	1.9	16
				6.55	1	62	1.9	16
Trityl	0.27	0.87	d-propanediol	2.5	0.2	81	0.44	13
				2.5	1	14	3.7	13

^a D is the ESR line width measured at 2.5 T [22], B and T give the magnetic field and the bath temperature, and T_s is the spin temperature corresponding to the nuclear polarization.

^b Only the polarization of the residual protons has been measured.

[13]. Problems due to solubility of this radical in certain matrices have to be solved. Radiation doping has seen a revival during the last years. Its application has been recently extended from ammonia [14] and lithium compounds [15] to alcohols [13]. Good results have been obtained for deuterated alcohols [16] where the created hydroxyalkyl has a quite narrow ESR line.

Table 1 presents a selection of literature data on DNP in deuterated glassy samples using the most common paramagnetic dopants performed at different temperature and field values.

4 Remarks on Thermal Mixing – Borghini Model

In most glassy substances which are doped with one of the above-mentioned electron spin systems, thermal mixing [17] is the main DNP mechanism present in the temperature range around 1 K and at moderate fields. It is important to realize that thermal mixing is a two-step process and thus distinct physical quantities determine its overall efficiency. For an optimum dynamic cooling of the electronic dipole–dipole reservoir, its heat capacity, i.e., energy width D , should be small. Identifying D as the ESR line shape including all inhomogeneous broadenings and assuming a fast cross-relaxation between different packets of electron spins, a maximum value for the inverse spin temperature $\beta_s = 1/kT_s$, corresponding to the maximum enhancement achievable by DNP, can be given as [18, 19]

$$\beta_{\max} = \beta_L \frac{\omega_0}{2D} \left(\frac{T_{1Z}}{T_{1D}} \right)^{1/2}. \quad (1)$$

Here $\beta_L = 1/kT_L$ is the inverse lattice temperature, ω_0 is the electron Larmor frequency, T_{1Z} and T_{1D} are the electronic Zeeman and dipolar relaxation times, respectively. Ideally all nuclei in the sample would acquire the temperature T_S of the electronic dipole–dipole system and the corresponding polarization P of a spin system with spin I and magnetic moment μ in a magnetic field B is given by the Brillouin function

$$P = \frac{\langle I_z \rangle}{I} = B_1 \left(\frac{\mu B}{kT} \right)^{I=1/2} = \tanh \left(\frac{\mu B}{2kT} \right)$$

with the temperature $T = T_S$.

The theoretical treatment leading to Eq. (1) is strictly valid only at high temperature. This drawback was overcome by using a simplified model for electronic spin systems with hyperfine interactions and g -anisotropies [18, 19]. The model is able to predict remarkably well the maximum nuclear polarization obtained in frozen alcohols at moderate fields and temperatures but shows discrepancies under more extreme conditions ($T \sim 0.2$ K and $B \sim 5$ T) [20], where in certain cases the model assumptions can be violated. Further it only makes a prediction for the minimum temperature of the electronic dipole–dipole system which has still to be transmitted to the nuclear spin system.

Equation (1) therefore gives just an upper limit for the maximum bulk polarization that can be achieved and actually often only much lower values are obtained, which hints to the importance of the second step, the proper thermal mixing that occurs without irradiation. It consists essentially of a flip-flop of two electron spins together with a flip of a nuclear spin, thus, its efficiency depends on the microscopic structure of the material [21]. Further, being a relaxation process, thermal mixing gets hindered at very low temperatures ($T \sim 0.2$ K), a point that has so far not yet been appropriately considered. The restriction a wide ESR line imposes on the efficiency of the overall DNP process at low temperatures [22] turns out to be much less stringent at temperatures of practical relevance for hyperpolarization applications. Whereas with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) free radicals at a magnetic field of 5 T only 12% deuteron polarization has been obtained in *d*-butanol at 0.2 K [13], 24% could be achieved at 1 K [16], which better corresponds to the predictions of the Borghini model. A similar behavior has been observed in propanediol-D6 doped with Cr^V complexes [20].

The DNP data given in Table 1 illustrate well the above statements.

5 DNP of Molecules in Solution

Assuming an ideal thermal mixing as the DNP mechanism, the nuclei of a molecule homogeneously dissolved in a solvent can be considered as belonging to the total nuclear reservoir and will acquire, like the solvent nuclei, a polarization corresponding to the minimum spin temperature that can be achieved in

the electron–electron dipolar system. Of course, slight differences in the DNP behavior between the solute and the solvent can be expected, as distances between the nuclear and the electron spins determine the efficiency of the second step of the thermal mixing process. This can be especially prominent if the solute density gets too low to assure an efficient transport of the polarization via spin diffusion. Besides these reservations it seems to be straightforward to apply the knowledge from the preparation of polarized target samples with some adaptation to the requirements of MRI and MR spectroscopy. The main challenge is to find biologically compatible solutions containing a small concentration of an efficient paramagnetic center well suited for DNP in which components of biological interest, e.g., labelled metabolic precursors, can be easily dissolved.

Recently, substances have been studied in an extensive series of measurements which could be well regarded as model systems for hyperpolarization applications [23]. Instead of using a proprietary triarylmethyl radical we chose the readily available TEMPO free radical as a paramagnetic center. TEMPO, which, at the concentrations of interest, has very low toxicity, dissolves well in water-alcohol mixtures and its DNP characteristics have been studied in various polarized target applications. Now for glassy samples, the choice of solvent systems is not always straightforward, as shown by the maximum of proton polarization of ethanol-water mixtures [8]. We chose water-ethanol and water-glycerol, in which ^{13}C -labeled sodium acetate and glycine, respectively, have been dissolved to a typical concentration of a few moles per liter. Up to 12% ^{13}C polarization and close to 50% proton polarization were achieved at about 1.2 K in a magnetic field of about 3.5 T under irradiation with about 97 GHz microwaves, which corresponds to an enhancement of more than 15000 with respect to the thermal equilibrium polarization in a 9.4 T magnet at room temperature. The maximum polarizations obtained for the different nuclear species present in a particular sample always corresponded to a single spin temperature, as can be expected from the thermal mixing mechanism. We further found that the DNP properties of the solute compounds are mainly determined by the solvent matrix which suggests that the approach is quite generally applicable to polarize molecules of a metabolic interest. Optimum substances are now routinely used in MRI experiments employing a DNP prepolarizer coupled to a rodent MRI scanner [7].

6 Prospects and Conclusion

Alcohol-water mixtures, standard substances used in polarized targets, are well suited as solvents for molecules of a biological interest. Being homogeneously dissolved, the nuclei of the dissolved molecule will acquire the same spin temperature as the solvent, as demonstrated in a series of experiments. Around the operating conditions of today's hyperpolarizer systems ($T = 1\text{ K}$, $B = 3.35\text{ T}$), according to the Borghini model the maximum achievable nuclear polarization depends linearly on the field and temperature (for discussions see ref. 7). Experi-

mental hints are such that this behavior is expected to be valid up to higher fields, which leads to the conclusion that higher polarizations could be achieved by performing the DNP at higher field, irrespective of the radical used, provided that its ESR line width still overlaps the nuclear Larmor frequency and the electron spin cross-relaxation remains efficient.

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