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Sample formulations for dissolution dynamic nuclear polarization

Théo El Daraï[a†] and Sami Jannin[a]

[a] Centre de Résonance Magnétique Nucléaire à Très Hauts Champs - FRE 2034 Université de Lyon / CNRS / Université Claude Bernard Lyon 1 / ENS de Lyon, 5 Rue de la Doua, 69100 Villeurbanne, France
[†] theo.el-darai@univ-lyon1.fr

Abstract

Hyperpolarization by dissolution dynamic nuclear polarization (dDNP) can boost magnetic resonance sensitivity by several orders of magnitude. The method relies on the transfer of electron spin polarization to the surrounding nuclear spins in the solid-state at low temperatures and moderate magnetic fields. One critical aspect for the success of a dDNP experiment is the sample formulation. Sample formulations have continually evolved, from frozen glassy solutions to complex hybrid polarizing solids, enabling faster and more repeatable DNP, as well as new applications to molecular systems that could not have be addressed before. In this review, we present some of the most important scientific advances related to sample formulations with a historical perspective, from the invention of DNP until today.

Keywords: Hyperpolarization, Dissolution Dynamic Nuclear Polarization, Sample Formulation, Free Radicals

1. Introduction

Nuclear magnetic resonance (NMR) was discovered in the 1930s by I. Rabi and co-workers,[1] and has kept evolving ever since as an increasingly powerful analytical tool, in particular with the advance of very high magnetic fields. Very few analytical methods can address so many applications, such as: eluding molecular structures, determining and quantifying components in mixtures or characterizing reactivity.[2] However, other methods, such as mass spectrometry, have strong advantages in comparison with NMR, such as higher sensitivity (inductively coupled plasma mass spectrometry ICPMS can detect at the ppb concentration) and selectivity.

This lack of sensitivity in magnetic resonance experiments often turns out to be a critical limitation. To alleviate this Achilles' heel, researchers have started proposing suitable solutions since the early 1950s, and a full branch of science, known as hyperpolarization, has since flourished.[3]

The hyperpolarization method discussed in this review is based on a technique called dynamic nuclear polarization (DNP)[4,5] hypothesized by A. Overhauser in 1953. DNP has the potential to strongly enhance the sensitivity in magnetic resonance experiments by transferring the polarization of electron spins to the surrounding nuclear spins via microwave irradiation. If the concept remains the same today, then sample formulation and DNP conditions have greatly evolved during the second half of the previous century and several approaches have emerged which complement historical Overhauser DNP, such as triplet: DNP,[6,7] DNP under magic angle spinning conditions (MAS DNP)[8] and more recently dissolution DNP (dDNP).[9]

dDNP consists of polarizing the nuclear spins of a frozen sample in a moderate magnetic field (<12 T) and at very low temperatures (<10 K) and subsequently dissolving it quickly with a hot stream of water, and then transferring and injecting the resulting hyperpolarized liquid sample inside an NMR or MRI machine. This method has enabled numerous applications such as metabolic imaging in living human patients.[10]

The DNP methods used in dDNP experiments have significantly evolved over the years in a quest for more efficiency (higher polarizations and faster build-ups), increased biocompatibility, etc. In particular, sample formulations have greatly evolved with, for example: the advance of stable and soluble free radicals used as polarizing agents; and the use of increasingly bio-compatible sample formulations ranging from homogeneously vitrified solvent mixtures to material based polarizing matrices. In this review, we describe how sample formulations used in dDNP have evolved in parallel to DNP methods. This is in complement to another recent review also partially covering the subject of sample formulations in dDNP.[11]

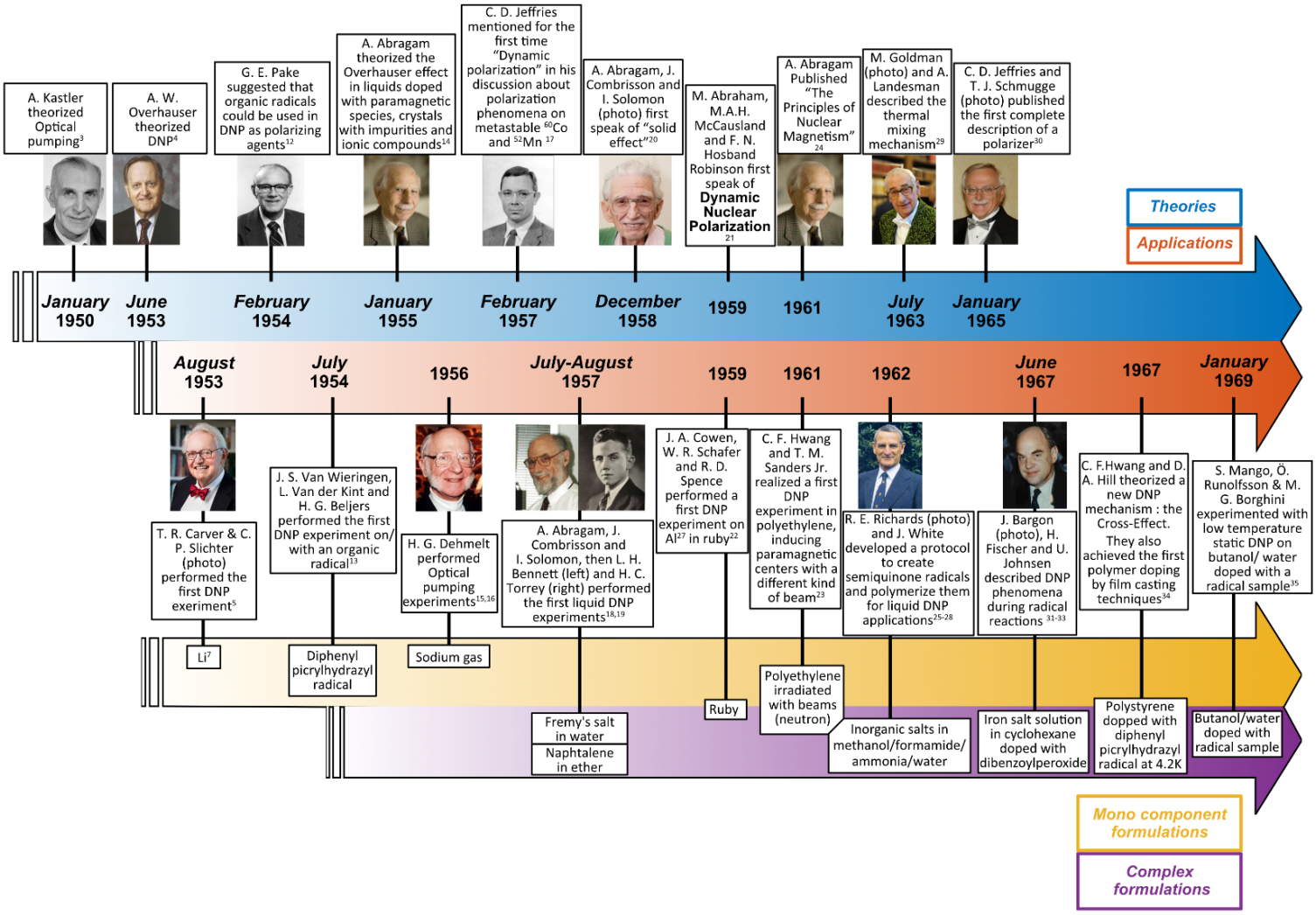


Figure 1: DNP birth and growing from 1950 to 1970.

2. Origins of dissolution DNP – from the 1950s until 2003

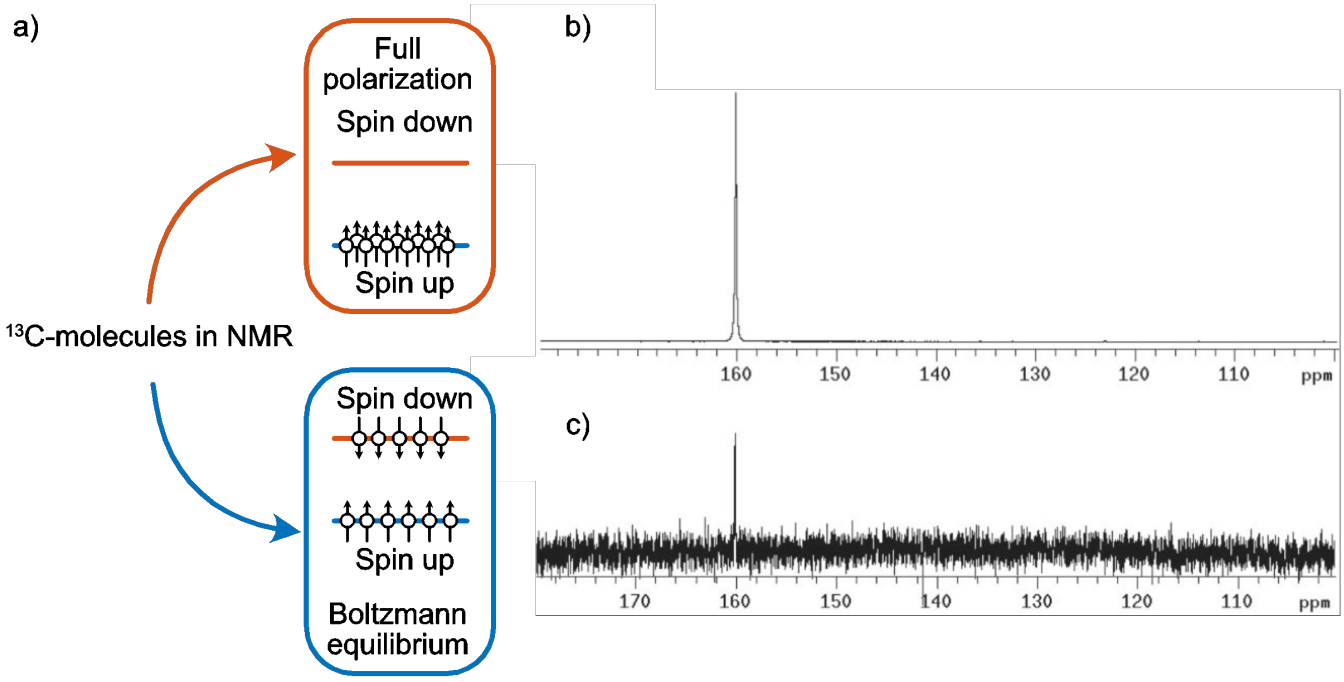


Figure 2: DNP effect on magnetic resonance signal. a) Theoretical spin distribution in traditional experiment compared with DNP. b) 13C spectrum of urea (natural abundance 13C) hyperpolarized by the DNP-NMR method. The concentration of urea was 59.6mM, and the polarization was 20%. c) Thermal equilibrium spectrum of the same sample at 9.4 T and room temperature. This spectrum is acquired under Ernst-angle conditions (pulse angle of 13.5° and repetition time of 1 s based on a T1 of 60 s) with full 1H decoupling. The signal is averaged during 65 h (232,128 transients). Figure adapted from works of Ardenkjær-Larsen & *al.* [9] Copyright 2003 Proceedings of the National Academy of Sciences.

Magnetic resonance signals arise from excitation and observation of coherences involving two or more nuclear spin states. In a nuclear spin-½ system (^{1}H or ^{13}C spins, for example), the signal observed proportionally originates from the difference in population between spin states. At thermal equilibrium, nuclear spins populations simply follow the Boltzmann distribution (see Figure 2.a). In typical magnetic resonance conditions (such as room temperature and high magnetic fields <30 T),[36] nuclear spin populations remain extremely close to being evenly distributed. The population difference, normalized by the total number of spins, called nuclear spin polarization, hardly exceeds 10 ppm for proton spins at 298 K and 3 T, which explains why magnetic resonance often displays a relatively low sensitivity.

In the 1950s the idea emerged that it would be possible to modify the Boltzmann distribution to increase nuclear spin polarization by several means: A. Kastler theorized in 1950 a method known as optical pumping,[3] and A. Overhauser first described in 1953 the concept of DNP.[3] A proof of concept DNP experiment appeared a few months later in the same year by T. Carver & C. Schlichter on a metallic ^{7}Li sample.[5] In the DNP approach, unpaired electron spins more polarized than nuclear spins are involved. Organic radicals were quickly anticipated to be good candidates for DNP as mentioned in 1954 by G. Pack,[12] after a first proof of concept experiment was performed on neat diphenyl picrylhydrazyl Radical (DPPH) in July of the same year by H. G. Beljers & *al.*.[13]

Few months later, in 1955, A. Abragam demonstrated the so called "Overhauser effect" in several kinds of non-metallic samples such as liquids doped with paramagnetic species.[14] The DNP research field became extremely active during this period.

C. Jeffries introduced the terms of "dynamic polarization" in 1957 during his studies of transition metals by DNP enhanced NMR.[17] Later on, the first DNP experiment on a liquid sample was performed by A. Abragam, J. C. Combrisson & I. Solomon,[18] and then by L. Bennett & H. Torrey.[19] I. Solomon & *al.* described in 1958 a DNP mechanism observed at low temperature in silicon called the "solid-effect".[20] This DNP effect was used the year after by C. Hwang & T. Sanders Jr. with a first experiment on a polymer doped with paramagnetic species induced by gamma ray, neutron, proton and electron beam irradiation.[23] The same year, M. Abraham, M. McCausland & F. Robinson pinned the final name to the method, namely "dynamic nuclear polarization".[21] In 1962, R. E. Richards & J. W. White described in a series of articles an impressive study including DNP of solutions using metals and semiquinone (organic radicals) produced by a protocol they developed specifically for this application.[25–28] This somehow was the foundation of DNP sample formulations used today with a ternary composition: solvent mixture that forms a glass upon freezing, free radicals as polarizing agents and analytes of

interest. It was also the first time that polymers were doped with radicals (DPPH) and analyzed by DNP enhanced NMR by using a film casting method.

During the 1980s, several important DNP breakthroughs occurred such as DNP with photo-excited triplet states as polarizing agents in 1982.[6,7] This method, which can be coupled with dissolution, has its own formulation history with a lot of recent developments that are well described in other papers.[37]

Only few months after this, magic angle spinning DNP (MAS DNP) was developed by G. M. C. de Vette & *al*..[8] before that C. Russell Bowers & D. P. Weitekamp predicted and discovered the method called "parahydrogen and synthesis allow dramatically enhanced nuclear alignment" (PASADENA) in 1986.[38,39]

Finally, in 2003, J. H. Ardenkjær-Larsen & *al.* invented the dissolution DNP (dDNP) experiment[9] (see Figure 2.b & c) in which a sample polarized by DNP at very low temperatures is rapidly dissolved and melted to the liquid-state while retaining part of the polarization in view of liquid-state magnetic resonance experiments in which the sample was composed of urea (as the analyte, 29%wt), glycerol/water as glass forming solvent and trityl radical as polarizing agent. A first proof of concept of in-vivo MRI application was soon published in 2003, showing the enormous potential of the method in a medical context (see Figure 2),[40] especially for cancer detection.[41]

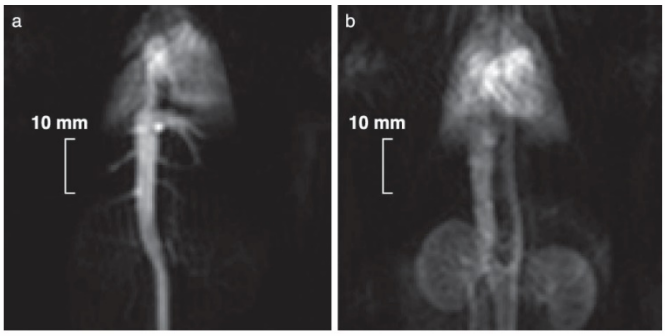


Figure 3. 13C coronal projection images of a rat. **a)** The image acquisitions were started immediately and **b)** 2 s after completing the injection of the contrast agent. The scan time of each image was 0.24 s. For other pulse-sequence parameters see Imaging Experiments section of the original paper. Figure adapted from works of Leunbah & *al.* [40] Copyright 2003 Proceedings of the National Academy of Sciences.

3. Sample formulations in dDNP

Since the invention of dDNP, several key contributions with regard to sample formulations have been made, which contributed to an increase in the variety of molecules studied, their concentration and polarization. In this section, we describe theses sample formulation developments in detail, covering four main categories.

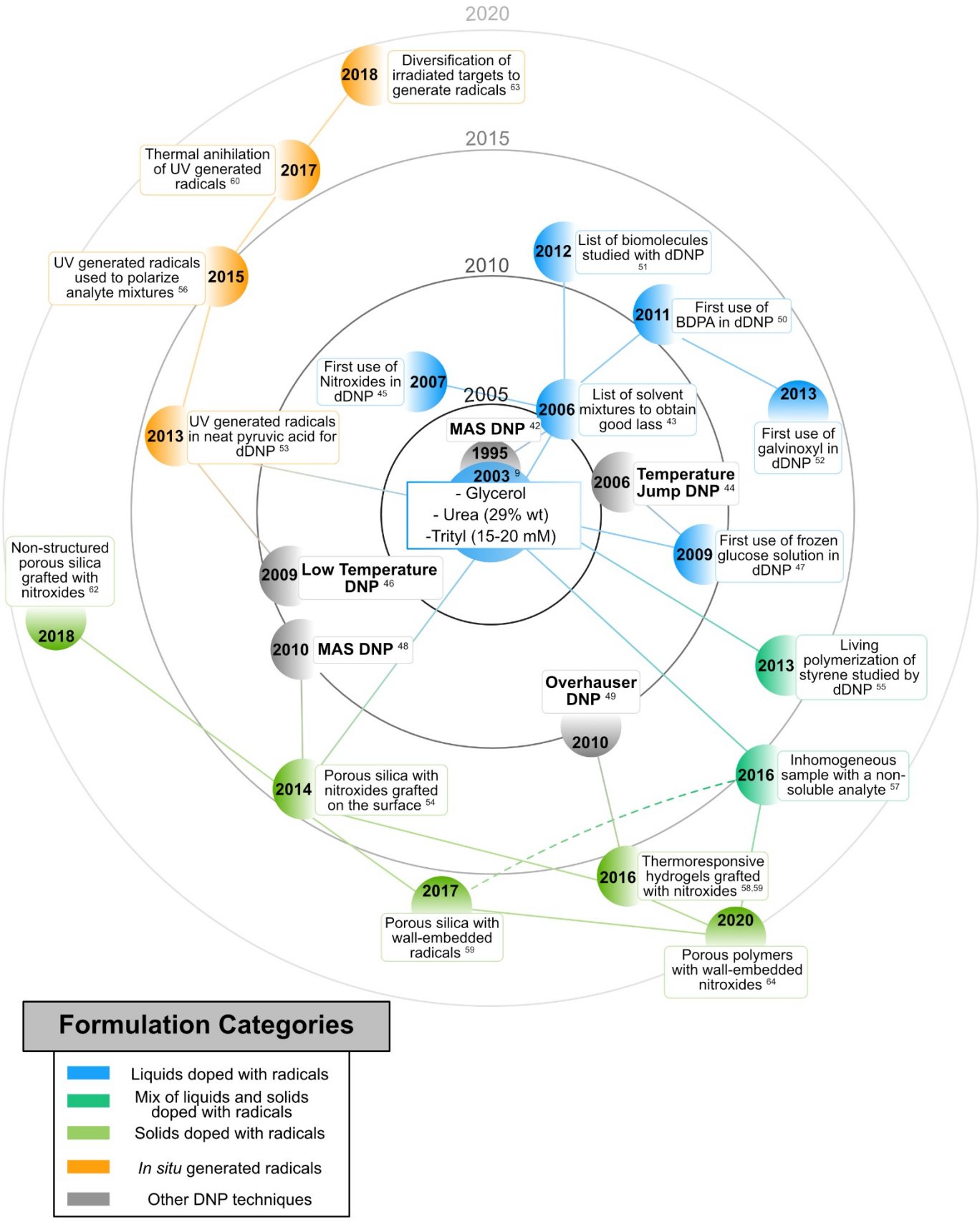


Figure 4. Main evolution of dDNP sample formulations over time.

3.1. Polarizing agents for dDNP

One of the simplest strategies to dope DNP samples with required paramagnetic centers consists of adding persistent organic free radicals (or as recently demonstrated, metal complexes),[65] however, this has never been done for dissolution DNP experiments so far. The three most important requirements for the electron spins are i) a linewidth on the order (slightly larger) than the NMR transition of the target nuclear spin, ii) a moderate relaxation with typical times ranging from 0.1 to 1 second at liquid helium temperatures so as to enable efficient microwave saturation with limited power, and iii) their presence at relatively low concentrations typically ranging from 10 to 50 mM so as to engender electron-electron dipolar couplings in a range suitable for DNP mechanisms such as cross-effect or thermal mixing to take place. A long list of free radical molecules have been developed and tuned for MAS DNP,[66] however, in dDNP it is only mainly two categories of free radicals that are regularly used:

Nitroxide radicals: Especially 2,2,6,6 Tetramethylpiperidin-1-yl-oxyl (TEMPO) derivatives. Nitroxides present a broad EPR line due to the g-anisotropy and hyperfine coupling to nitrogen (see Figure 5), making it suitable for thermal mixing or corss-effect DNP mechanism for both protons and carbons. Indeed, proton transition energy under dDNP conditions lies within the EPR width. However direct carbon polarization remains less efficient than for narrower line radicals. This class of radicals was used the first time in DNP in 1962 (Fremy's salt) by R. E. Richards & J. W. White[26] and then in 1970 (cyclic nitroxide) by E. H. Poindexter & *al.* [67,68] together with other kinds of radicals such as phenoxyl radicals.[67–70] EPR properties of nitroxides, studied in 1965 by H. M. McConnell[71], turned out to be particularly suitable to polarize proton spins in dDNP conditions (~7 T and ~1.0 K<T<4.2 K). This family of radicals is also intensively used to design biradicals such as AMUPOL and TOTAPOL for MAS DNP.[72] However, the dDNP performances of such biradicals still remains below the performances of nitroxides radicals which are also more affordable in general.[73] With all these advantages, TEMPO and derivatives were used for example in early dDNP studies by A. Comment *et al.*.[45] Furthermore, nitroxides have the advantage to be quite stable without the common risk of dimerization.[74–76] The use of di-radicals has been shown to improve performances under MAS-DNP conditions,[66] but never under dDNP conditions, despite several attempts never published in peer-reviewed journals (see for example the PhD thesis of B. Vuichoud [73]).

Triphenylmethyl radicals: Trityl and α,γ-bisdiphenylene-β-phenylallyl (BDPA). Aromatic-carbon based radicals present very limited hyperfine couplings and very low g-anisotropy, making them very efficient for direct ^{13}C polarization, while leaving ^{1}H spins unpolarized. BDPA was first used for DNP between 1965 and 1966 by W. Müller-Warmuth & *al.*[77,78], before E. H. Poindexter & *al.* a few years after.[67,69,70] E. H. Poindexter & G. R. Neil also first used perchlorotriphenylmethyl (a trityl derivative) in DNP for the first time in 1970.[79] The narrower EPR lines of those radicals allows them to directly polarize ^{13}C spins to higher values in comparison with nitroxides.[73] Both BDPA and trityl are relatively stable in solution but with nevertheless a tendency to form dimers.[76,80] It has been also demonstrated that gadolinium salts can have a positive impact on the polarization of ^{13}C spins using trityl as a polarizing source in dDNP experimental conditions.[81]

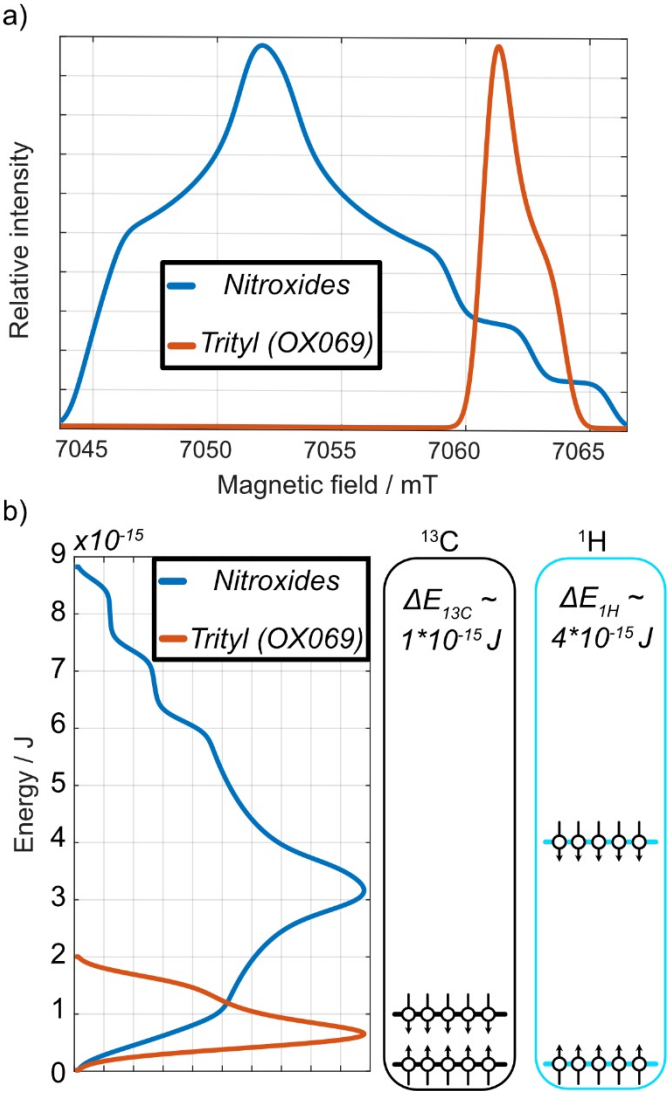


Figure 5. a) Simulated spectra of nitroxides (g_{xyz}=[2.008 2.006 2.003], A_{xyz}=[20 20 90] MHz) and trityl OX069 (g_{xyz}=[2.00358 2.0034 2.00262][82]) at 1.2K & 7.05T (198 GHz). b) EPR energy linewidth of nitroxides and trityl at 1.2K & 7.05T (198 GHz) compared with ^{1}H and ^{13}C transition in same conditions.

We can conclude that in dDNP experiments, three radicals (nitroxides, trityl and BDPA) are predominantly used in modern-day experiments. However, some unpublished work suggests that radical design could be improved further enabling better dDNP results.[73] There are indeed plenty of stable radicals which have not yet been tested in dDNP conditions (B_0<12 T and ~1.0 K<T<4.2 K).[76] Radical design and optimization is an active field in MAS DNP,[66] but this is not yet the case for dDNP.

3.2. Matrices doped with stable radicals

Frozen solutions are the simplest variety of sample formulations in dDNP. Such sample formulations were mainly developed between 1982 and 2003 for MAS DNP or low temperature DNP with a typical composition of:

1) one solvent (or more);
2) a glassing agent (such as glycerol);
3) a free radical (usually organic free radicals);
4) and the analyte (or mixture) of interest.

These sample formulation constituents are very close to what was used long ago by R. E. Richards & J. W. White in 1962[25–28], and became increasingly widespread in DNP at the end of the last century. With such samples, that are prepared as liquids and subsequently frozen, it is crucial upon freezing to prevent any crystallization or more generally phase separation[83] which could lead to a highly non-statistical distribution of the polarizing agent generally implying low DNP performances. Crystallization is mainly due to the inverse Leidenfrost phenomenon which slows down the cooling efficiency of the liquid nitrogen bath and so generates an inhomogeneous sample.[84] Based on this finding a solution to obtain glassy samples without frozen agents was developed by cooling down isopentane with liquid nitrogen and using a spray to generate small droplets that fall into the isopentane and are frozen fast enough as to be vitrified.[85]

Even if such an approach is extremely promising, glassing agents are still widely used in dDNP. On this subject, the group of R. G. Griffin, with K. N. Hu & others, tested a non-exhaustive list of solvent mixtures with various glassing agents in order to find good sample compositions which inevitably form glasses when frozen at liquid nitrogen temperatures and below.[43] From all the possible frozen agents we would like to highlight two of them:

i) Glycerol was historically the first glassing agent used in dDNP. Furthermore, in our laboratory we often use as standard glassing solution made of water/glycerol in a volumetric proportion of 40/60 doped with 50 mM of TEMPOL. Such sample composition was first described in 1995 by R. G. Griffin & *al.* in both MAS and static DNP experiments [42,86], and is designated as "*DNP Juice"*.
ii) Glucose and other sugars (such as fructose, trehalose plus some isomers) are also interesting glassing agents. These are metabolites that can be directly used in biological applications or can alternatively be used as replacements for glycerol since they exhibit increased biocompatible. For example, this was used in temperature jump DNP experiments in 2006 by R. G. Griffin & *al.* (Glucose)[44] before being used in dDNP in 2009 by J. Kurhanewicz & *al.* (Fructose)[47] and in 2013 by T. Harris, H. Degani & L. Frydman (Glucose).[41] However, glucose has the disadvantage of requiring a larger volume fraction than glycerol in order to be efficient.

Glycerol and sugars are preferred glassing agents due to their biocompatibility, non-toxicity, and the ability to correctly solubilize salts when combined with water. All those advantages are essential for biological applications of dDNP. Other glassing agents may also be used (DMSO, ethylene glycol, ethanol, or pyruvic acid) and can be further enhanced by adding more complex molecules such as polymers designed to avoid the nucleation process[87] (not used yet in dDNP today). Such sample formulations (G are simple, and have been used to polarize many metabolites[51] and remains today the most common way to prepare a dDNP sample. Target molecules are therefore (most of the time) dissolved in a solvent mixture to avoid distribution inhomogeneity in order to achieve fast and optimal polarization. However, it is also possible to disperse non-soluble molecules into a non-solvent in order to obtain a two phases sample with additional interesting properties (in particular long ^{13}C nuclear spin-lattice relaxation times), however, potentially with lower dDNP performances.[88] Heterogeneous samples are often used in MAS DNP to study polymers, dispersed particles or interfaces.[89]

Deuteration of the DNP solution is an important parameter to adjust, and may have a benefit or negative effect on DNP performances depending on the polarizing agent used (Figure 6).[90] Indeed deuteration is beneficial for radials with large EPR lines, increasing both polarization and build-up rates, unlike narrow linewidth radicals which are negatively impacted. Two phenomena are mainly impacted by deuteration: the ^{1}H spin diffusion and the lower Zeeman heat load.

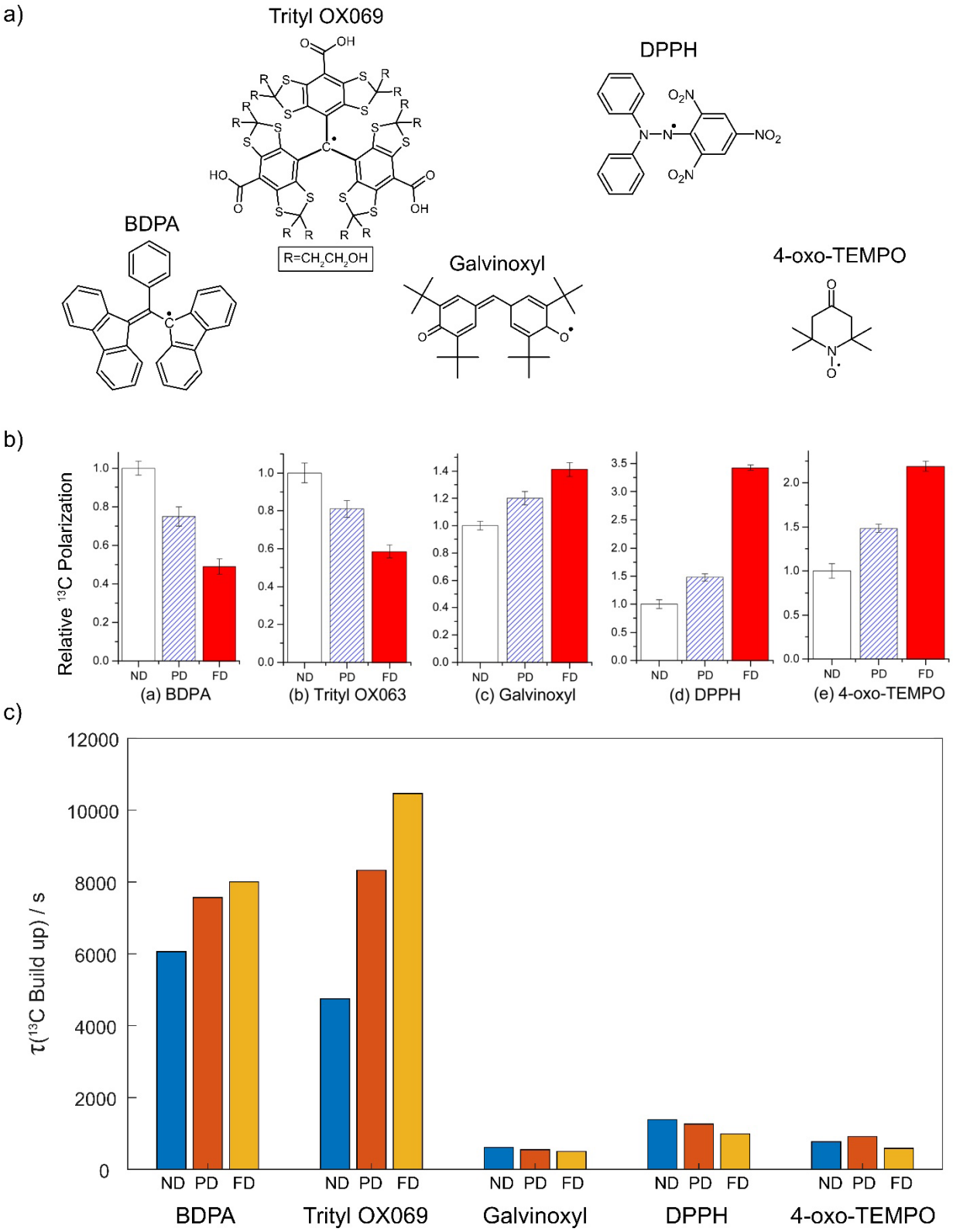


Figure 6. a) Radicals used for DNP at 3.35 T and 1.1 K, sorted from the thinnest to the largest EPR linewidth at 100K under W-band conditions. b) Relative ^{13}C polarization of each radicals depending if the solvent is not deuterated (ND), partially deuterated (ND) or fully deuterated (FD). c) Exponential constant time of build-up obtained for each radicals depending if the solvent is not deuterated (ND), partially deuterated (ND) or fully deuterated (FD). Figure adapted from works of Lumata & al. [90] Copyright 2013 Phys. Chem. Chem. Phys.

It is also important to control quite precisely the concentration of polarizing agents in the DNP solution to obtain optimal polarizations. Indeed, the dDNP performances usually increase and reach a plateau as the radical concentration is increased (see Figure 11.b or ref 73). However, for a concentration greater than the optimal concentration, performances can be significantly impacted.[91,92] Furthermore, for indirect approaches such dDNP with CP, or when using heterogeneous polarizing matrices: ^{1}H spin diffusion can play a crucial role, and therefore ^{1}H spin concentration also may

further be optimized.[93,94] Finally, it is also possible to dope solids such as polymers with free radicals by a film casting method[34,95] or by including "spectator" radicals directly during polymerization.[96] This approach produces non-porous polymers sometimes used in MAS DNP.[97]

3.3 Paramagnetic centers created in-situ

Another way to dope samples with radicals in either frozen solution or solids consists of inducing them directly using light, particle beams or electrical discharges[98]. This strategy, although more complex to put in place that using stable radicals, displays a number of advantages:

i) the sample formulation does not require glassing agents;
ii) there is no need to eliminate radicals after dissolution in the case of biomedical applications (by filtration or reduction);
iii) and such approaches are potentially compatible with recent concepts for the transport of hyperpolarization in the case where the paramagnetic centers can be annihilated at low temperatures[60].

However, this method also has some limitations:

i) the method has to be adapted for different sample formulations;
ii) and the attainable concentration of paramagnetic centers induced can be a limiting factor for DNP, depending on the sample formulation.

Since the first DNP experiment with neutron beams,[23] this method has been developed further, in particular in 1979 when T. O. Niinikoski & J. M. Rieubland used the CERN Synchro-cyclotron to apply a 580 MeV proton beam on frozen ammonia.[99] Their experiment showed an impressive proton polarization of higher than 90% and opened a wide field of research.[100] In 2010, S. Koizumi & *al.*, used a UV beam to induce radicals in a frozen solution of butanol doped with phenol[46] (See fig. 4). The authors mentioned back then clearly the possibility to use such method in dDNP experiments.

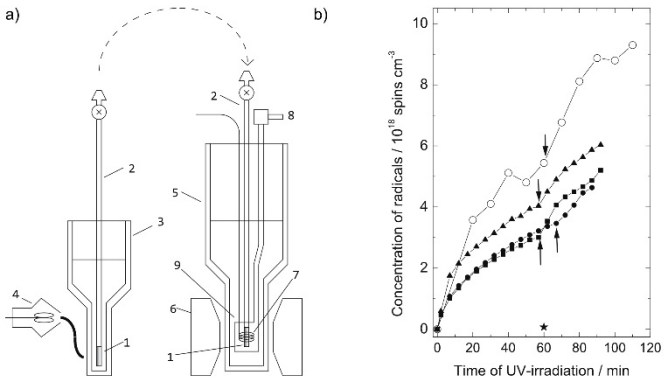


Figure 7. a) UV-Irradiation and DNP systems. **b)** Concentration of free radicals as a function of UV-irradiation time. Figure adapted from works of Koizumi & *al.* [46] Copyright 2009 Elsevier Inc. All rights reserved.

In 2013, A. Comment & *al.* realized a first dDNP experiment using UV induced radicals in neat pyruvic acid[53] and coupled the approach with *in vivo* MRI (see fig. 5).

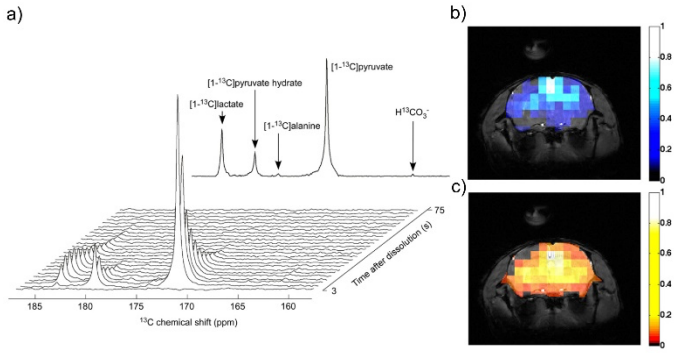


Figure 8. *In vivo* real-time pyruvate metabolism. **a)** *In vivo* ^{13}C MR data recorded following the injection of 300 µL of 80 ± 5 mM [1-^{13}C]pyruvate solution hyperpolarized by dDNP using polarizing agents created by UV irradiation. The 5-mm^3 resolution balanced steady state free precession sequence ^{13}C images recorded using interleaved selective excitations of [1-^{13}C]pyruvate **b)** and [1-^{13}C]lactate **c)** superimposed to ^{1}H anatomical images of a mouse head. Figure adapted from works of Comment & al. [53] Copyright 2013 Proceedings of the National Academy of Sciences.

One great advantage of this approach in dDNP is the possibility to thermally annihilate these radicals by simply increasing the sample temperature, which may be coupled with hyperpolarized sample transport[57] in the near future (see fig. 6).[60]

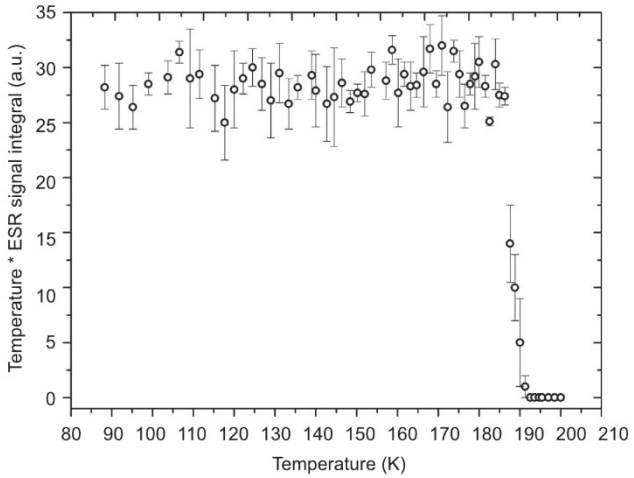


Figure 9. Annihilation of photo-induced radicals. ESR signal integral multiplied by temperature as a function of temperature. Figure adapted from works of Comment & *al.* [60] Copyright 2017.

3.4. Polarizing Matrices

The last sample formulation category described here consists of porous materials with free radicals located on the surface of the pores or in the bulk of the matrix. Such formulations have several advantages in dDNP:

i) no glassing agent is required;

ii) matrices can be removed more easily from the hyperpolarized solution after/during the dissolution process (thus, reducing paramagnetic relaxation);
iii) the free radicals may be protected from any molecules of interest that would usually scavenge them under conventional sample formulations[101];
iv) and a well-controlled sample heterogeneity can be taken advantage of to develop further hyperpolarization sample transport[57] strategies.

However, it can also bring some additional difficulties to overcome:

i) filtration needs to be designed in an optimal way;
ii) performances of the DNP process may depend strongly on the material properties (pore size, distribution of radical, etc.);
iii) and some free radicals may not survive the synthesis process.

We can find examples of such matrices in the 1980s for flow NMR analysis by J. Van Delden & *al.* who developed different matrices made of polymers or silica, both grafted with nitroxides[102] (following the synthesis described in Figure 10).

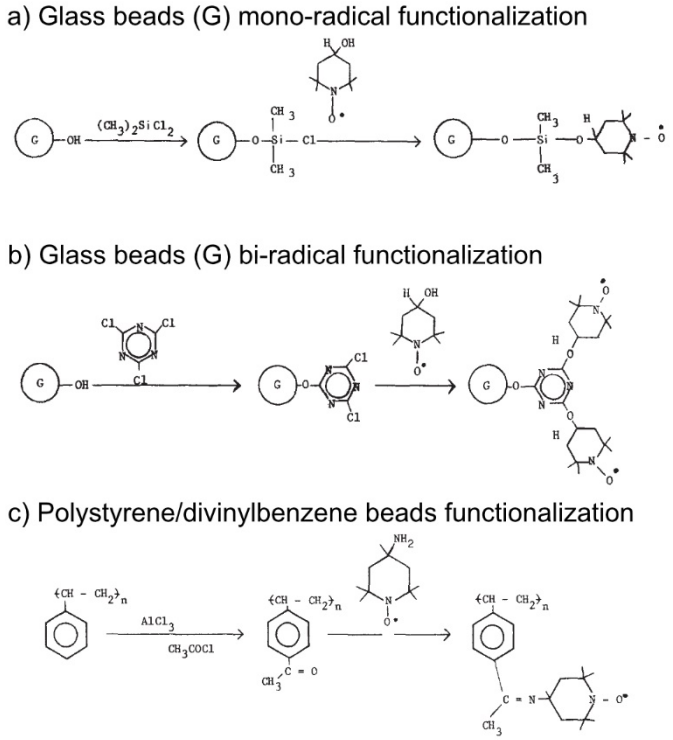


Figure 10. Chemical grafting of nitroxides on **a)**,**b)** mesoporous glass beads and **c)** on cross-linked polystyrene beads. Figure adapted from works of Van Delden & *al.* [102] Copyright 1980 Journal of magnetic resonance.

These materials have been used for continuous flow DNP by Harry C. Dorn & *al.* in 1988 at room temperature.[103] The global concept of using porous silica beads doped with radicals was used later in 2010 for MAS-DNP,[48] just before being used for dDNP in 2013. This class of matrices (called HYPSO) were used for dDNP by D. Gajan & *al.*[104]. In this study, first materials were template with tube shape pores between 8 and 10.6 nm and specific surface around 650-850 m²/g. First HYPSOs was grafted with both nitroxides or trityl derivatives and reached ^{13}C polarizations around 25% with optimal radical concentration around 75 µmol/g. Main changes in next generations of dDNP silica materials came from their pore structures: silica was templated to have spherical interconnected holes instead of hexagonal tubes, increasing polarization ultimately reached. More recently, morphology stopped being templated resulting in non-structured materials with even highest polarization ($P(^1H) > 90\%$ and $P(^{13}C) \sim 50\%$, see Figure 11). Average pore diameter of this last generation of HYPSO was a little bit smaller (4.2 nm), as well as specific surface area (450 m²/g). [62]

Such kinds of silica-based matrices are today still used in multiple fields (MAS, d-DNP, EPR…) and further improvement/changes occurs in this domain (radicals located in the silica walls rather than the surface for instance).[105,106]

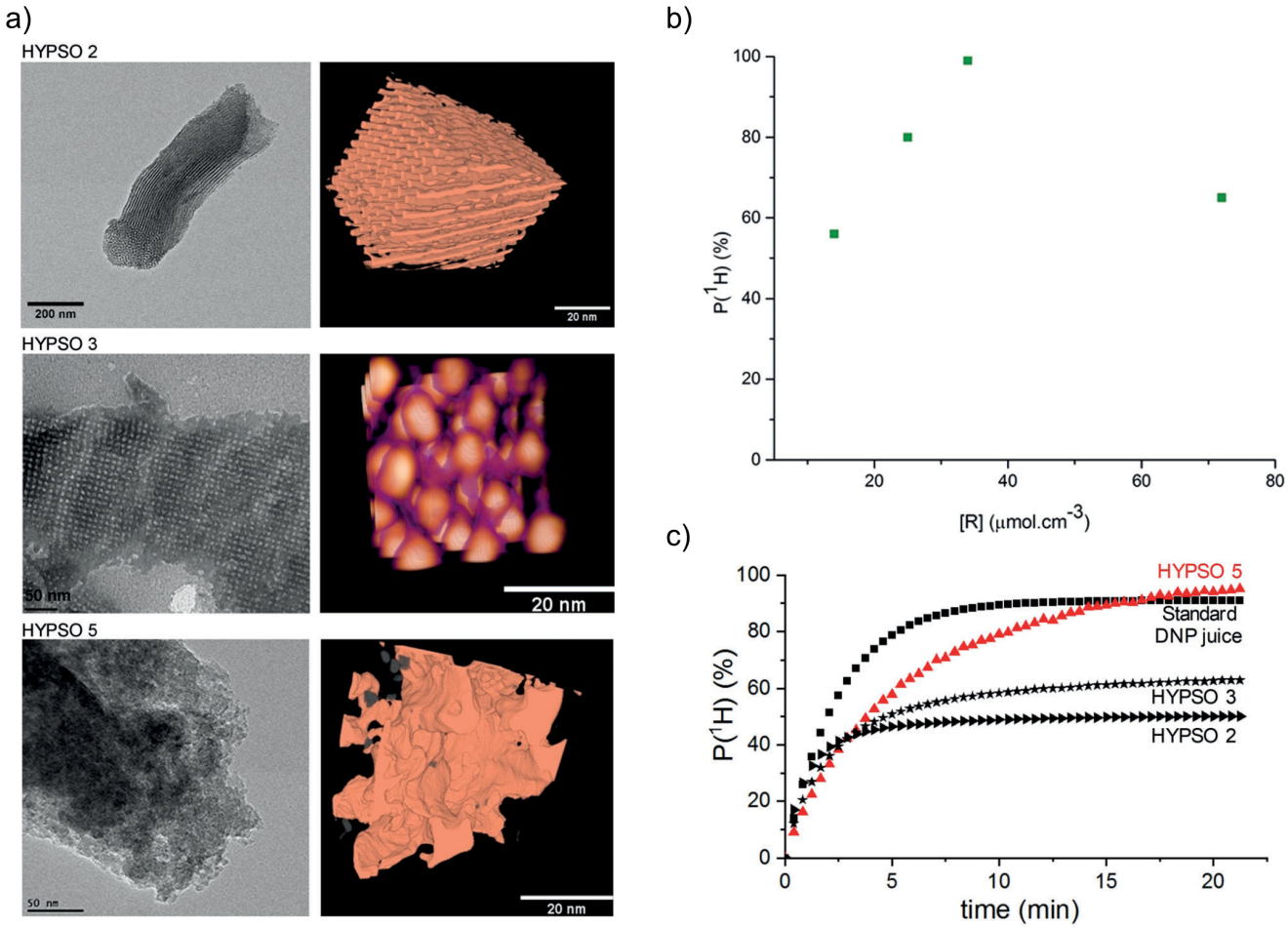


Figure 11. a) TEM (left) and ET (right) images of HYPSO 2, 3, and 5. b) Proton polarization values at 1.2 K against the radical concentration for HYPSO 5 impregnated with a mixture of H2O/D2O (2:8 v/v). The proton polarization values are given with an error of 5%. c) ^{1}H DNP buildup curves for samples displaying three different structures: optimal HYPSO 2 with [PA]=79 umol.cm^{-3} (black triangles), HYPSO 3 with [PA]=67 umol.cm^{-3} (black stars), 1/19-HYPSO 5 with [PA]=34 umol.cm^{-3} (red triangles), and a conventional homogeneous DNP formulation (black squares). Figure adapted from works of Thieuleux & *al.* [62] Copyright 2018 Angewandte.

Polymer matrices with free radicals have been only recently used as polarizing agents, first for Overhauser DNP in 2006 by Songi Han's & *al.*,[107,108] and then in 2010 by Kerstin Münnemann & *al.*.[109] In these studies, nitroxides were covalently attached to sepharose beads in the first case and on a thermoresponsive gel in the second case. It is worth noticing the fact that such gel is probably the first porous polarizing agent designed and used in DNP.

Polymers were used as polarizing agents for dDNP in 2016 by T. Cheng & *al.*[58] (the porous thermoresponsive hydrogel developed by Kerstin Münnemann's) & B. Vuichoud & *al.*[59] (a thermoresponsive thermoplastic which can be dispersed as a powder in the sample and precipitate during the dissolution). Based on this, we recently developed a new category of porous thermoset containing nitroxides covalently attached and dispersed in the walls (HYPOP).

In comparison with silica beads, polymers present lower polarization efficiency (P(^{1}H) ~0.6 and P(^{13}C) ~0.25) and bigger pore size (~1 µm). Such large pore size gives longer build-up times, but allow for slower relaxation due to the non-vicinity of the electrons with the target molecules (few hours) at 4K and a few Tesla. Such matrices could be used in a context of storage and possibly transport of hyperpolarization to remote locations.[64]

4. Conclusion and outlook

As we described the different sample formulations which has been used in dDNP, two observations can be made:

i) formulation diversity in dDNP is still relatively underdeveloped in comparison with the breadth of sample formulations that are reported in MAS DNP,[89] triplet DNP [37] and Overhauser DNP;[110]

ii) and most of the sample formulations used today in dDNP have originally been developed for other kind of DNP and later on borrowed in this field (*DNP juice*™ from MAS DNP, thermoresponsive hydrogels from Overhauser DNP, UV induced radicals from low temperature DNP etc).

This can be explained by the fact that dDNP is rather new and is not as widespread in terms of instrument access or commercial infrastructure as compared with other methods. Moreover, most of the active dDNP groups are focusing their

efforts on biomedical applications rather than methodological development. There are still a number of innovative and smart sample formulations which could, in suitable cases, be adapted to dDNP, such as covalent organic frameworks[111] or electrical-discharge induced radicals.[112]

One of the main scientific challenge that remains to be tackled concerns the broad accessibility of hyperpolarization in laboratories, MRI canters or hospitals that do not (and cannot) have the instrumentation and trained personnel available on site. To overcome this issue, the generation of transportable hyperpolarization and remote delivery appears as a solution that could radically democratize the use of hyperpolarization. Such advances appear to be possible in the near future with the production of non-persistent radicals by UV irradiation or by the generation of long-lived hyperpolarization in soaked porous hyperpolarizing matrices.

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed.

Photo references

Anatole Abragam:
https://alpine-conference.org/wp-content/uploads/2018/12/Goldman-200x300.jpg

Joachim Bargon:
http://www.thch.uni-bonn.de/pctc/bargon/bio.html

Lawrence H. Bennett:
https://www2.seas.gwu.edu/~lbennett/bennett.gif

Hans Georg Dehmelt:
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Maurice Goldman:
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