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# Water-Soluble Narrow Line Radicals for Dynamic Nuclear Polarization

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*Dynamic Nuclear Polarization, Persistent Radicals, Water-soluble*

Supporting Information Placeholder

**ABSTRACT:** The synthesis of air-stable highly water-soluble organic radicals containing a 1,3-bisdiphenylene-2-phenylallyl (BDPA) core is reported. A sulfonated derivative, SA-BDPA, retains the narrow EPR linewidth (<30 MHz at 5 T) of the parent BDPA in highly concentrated glycerol/water solutions (40 mM), which enables its use as polarizing agent for solid effect dynamic nuclear polarization (SE DNP). Sensitivity enhancement of 110 was obtained in high field magic-angle-spinning nuclear magnetic resonance (MAS NMR) experiments. The ease of synthesis and high maximum enhancements obtained with the BDPA-based radicals constitute a major advance over the trityl-type narrow line polarization agents.

Dynamic nuclear polarization (DNP) is used to significantly enhance the limited sensitivity of nuclear magnetic resonance (NMR) studies of small molecules and complex biological systems.<sup>1</sup> The increased sensitivity and decreased measurement time afforded by DNP allow observation of transient (e.g., photochemical intermediates) and metabolic processes. DNP coupled with multidimensional magic angle spinning NMR (MAS NMR) is useful in structural studies of proteins that cannot be crystallized, for example, membrane and amyloid proteins.<sup>2</sup>

DNP relies on the transfer of polarization from relatively highly polarized unpaired electron spins to nuclear spins (e.g., <sup>1</sup>H or <sup>13</sup>C) via microwave irradiation of the electron paramagnetic resonance (EPR) spectrum. Unpaired electrons are supplied by the polarizing agents, which in most cases are persistent radical species added to a glass forming solvent. The solid effect<sup>3</sup> (SE) DNP is a two-spin process, which relies on the polarization transfer between a single electron spin and a nuclear spin. This method requires a polarization agent with both the homogeneous EPR linewidth ( $\delta$ ) and the inhomogeneous spectral breadth ( $\Delta$ ) smaller than the nuclear Larmor frequency ( $\delta, \Delta < \omega_0$ ). Trityl-type<sup>4</sup> and BDPA-based<sup>5</sup> radicals satisfy these requirements at high magnetic fields.

Trityl-type radicals CT-03 and OX063<sup>6</sup> (Figure 1) exhibit narrow EPR linewidths ( $\Delta = 50$  MHz at 140 GHz) and have been used successfully in DNP NMR experiments, and in vivo EPR imaging of tissue oxygenation and pH.<sup>7</sup> However, a lengthy synthesis<sup>8</sup> contributes to the high cost of these radicals and limits their use as routine polarizing agents.

BDPA is an air stable persistent radical that shows no dimerization in solid or in solution and has a narrow EPR linewidth<sup>9</sup> ( $\Delta \sim 25$  MHz at 140 GHz). The ability of BDPA to transfer polarization was investigated via SE DNP in a poly-

styrene matrix,<sup>10</sup> and, recently, via dissolution DNP in sulfolane.<sup>11</sup> While BDPA was proven to be an excellent polarization agent, its utility in biological applications is limited by its lack of solubility in aqueous media. Only one water-soluble BDPA derivative has been described.<sup>12</sup> But again, its water solubility is limited, and DNP experiments with this compound were not pursued. We report an efficient synthesis of highly water-soluble BDPA derivatives that preserve the desirable DNP properties of BDPA and expand its application to aqueous systems.

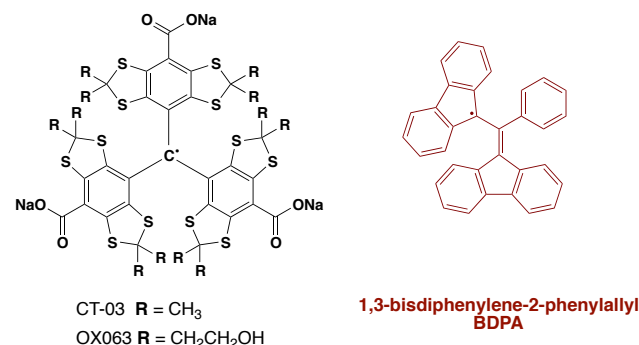
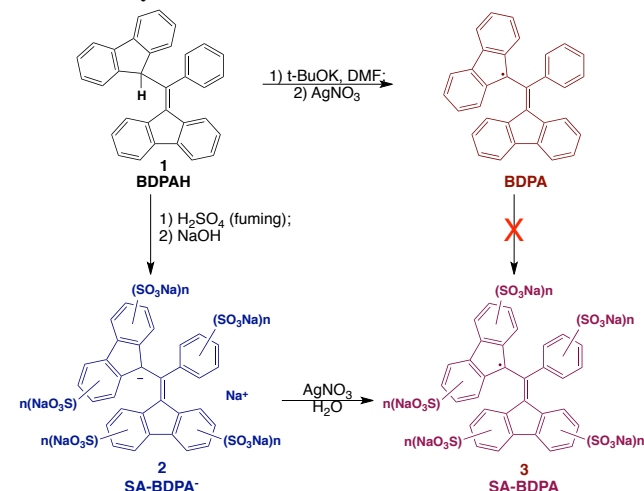


Figure 1. Trityl-type radicals and BDPA.

BDPA precursor, BDPAH<sup>13</sup> (1) can be prepared in 4 steps from fluorene and benzaldehyde. Whereas BDPA radical decomposes in strong acid, treatment of BDPAH (1) with fuming sulfuric acid followed by oxidation with silver nitrate yielded an extremely water-soluble mixture of sulfonated radicals SA-BDPA 3. (Scheme 1)

Scheme 1. Synthesis of the water-soluble SA-BDPA radical



The shape of the UV-Vis spectrum, the redox behavior, and the EPR spectrum of **3** closely resemble those of BDPA. The sulfonate groups red shift the absorption maxima of the carbanion **2** and the SA-BDPA radical **3** by ca. 20 nm relative to those of BDPA anion and BDPA. As shown in Figure 2, SA-BDPA in water has a strong absorption in the visible region ( $\lambda_{\text{max}} = 508 \text{ nm } D_0 \rightarrow D_2$ ) and a weak absorption in the near-infrared region ( $\lambda_{\text{max}} = 881 \text{ nm } D_0 \rightarrow D_1$ ). BDPA in dichloromethane has similar absorption maxima, which are 485 and 859 nm, respectively.<sup>12,14</sup> Similar to BDPA, SA-BDPA is reduced under basic conditions (e.g., aqueous NaOH in the presence of catalytic amounts of acetone, THF, DMSO, or ascorbate). The resulting SA-BDPA<sup>-</sup> anion (**2**) can be re-oxidized to **3** chemically (e.g., by  $\text{AgNO}_3$ ) or electrochemically.

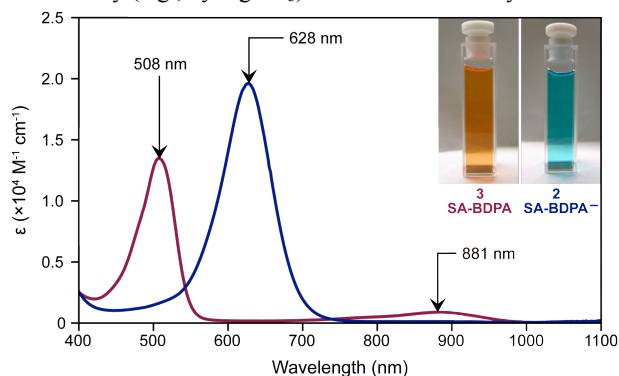


Figure 2. SA-BDPA (**3**) and its anion **2** in water.

Also, SA-BDPA is air stable both in solution and as a solid. Unlike BDPA, however, SA-BDPA does not partition into organic solvents, and is soluble in water in all proportions. The EPR spectrum of SA-BDPA (Figure 3) shows no evidence of aggregate formation or radical dimerization in liquid or frozen solution. The solution EPR spectrum features a hyperfine pattern typical of BDPA-type radicals with nine lines as a result of coupling to eight protons with similar coupling constants of about 5.1 MHz (Figure 3, A). In frozen solution, the linewidth ( $\Delta = 26 \text{ MHz}$  at 9 GHz, full width at half maximum (FWHM)) is dominated by unresolved hyperfine couplings to protons and perfectly matches the envelope of the solution spectrum (Figure 3, B). At 140 GHz the line broadens insignificantly to  $\Delta = 28 \text{ MHz}$ , as a result of very small  $g$ -anisotropy (Figure 3, C). This small  $g$ -anisotropy qualifies SA-BDPA as an interesting new polarizing agent for SE DNP at even higher fields (e.g., 9.4 T). Trityl's linewidth, on the other hand, increases linearly with the external field, because  $g$ -anisotropy is the dominant broadening mechanism in that case.<sup>15</sup>

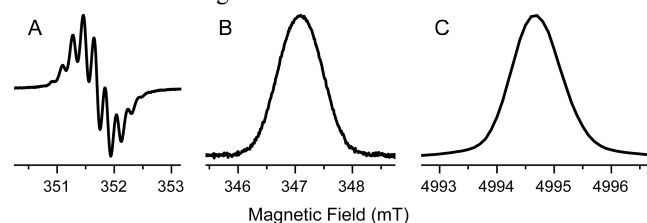


Figure 3. SA-BDPA (**3**) EPR spectra. A: 1 mM solution in water; (9.856 GHz, RT, cw EPR). B: 1 mM frozen solution in 60/40 (v/v) glycerol- $d_8$ /D $_2$ O (9.745 GHz, 80 K, echo detected). C: 1 mM frozen solution in 60/40 (v/v) glycerol- $d_8$ /D $_2$ O (140.0 GHz, 80 K, echo detected).

Encouraged by SA-BDPA's desirable properties, we proceeded to test SA-BDPA as a polarization agent for SE DNP. In Figure 4 we show the field dependent DNP enhancement at 5 T (140 GHz microwave frequency) obtained with a 40 mM frozen solution of SA-BDPA in glycerol- $d_8$ /D $_2$ O/H $_2$ O (60/30/10 v/v) in comparison with the commonly used trityl polarizing agent OX063. The glass-forming glycerol/water mixture is crucial, because it prevents phase separation of solutes and allows for efficient nuclear spin-diffusion. Furthermore, it acts as a cryo-protectant to prevent potential cold-denaturation of proteins.  $^1\text{H}$  signal enhancement by DNP was directly observed via a Bloch decay as function of the external magnetic field. Both radicals give a frequency profile typical of the well-resolved solid effect with a positive and a negative peak separated by twice the Larmor frequency of the nucleus polarized, and centered around the EPR resonance. As expected, the smaller linewidth of SA-BDPA is retained in the DNP field profile. The enhancement factors were determined with a Hartmann-Hahn cross-polarization step to  $^{13}\text{C}$  at the respective field of maximum enhancement (1 M  $^{13}\text{C}$ -urea was added to provide sufficient  $^{13}\text{C}$  for detection of thermal equilibrium polarization). SA-BDPA yields an NMR signal enhancement of  $\varepsilon = 61$  by comparison of on- and off-signal after  $1.3 \times T_B$  (where  $T_B$  is the time constant of polarization build-up) at 6 W microwave power, which is  $\sim 30\%$  higher than the enhancement obtained with OX063 under the same conditions.<sup>16</sup>

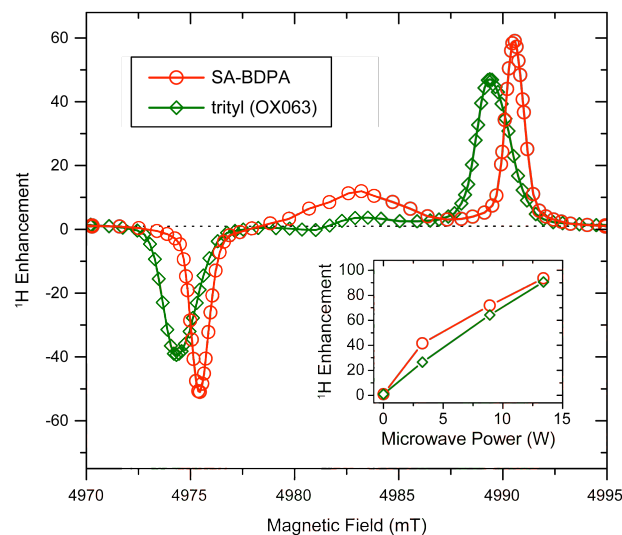


Figure 4. Field-dependent  $^1\text{H}$  DNP enhancement of 40 mM SA-BDPA (red) in glycerol- $d_8$ /D $_2$ O/H $_2$ O (60/30/10 v/v) in comparison with trityl OX063 (green) recorded using  $\sim 6 \text{ W}$  of microwave power. Inset: power dependence of  $^1\text{H}$  enhancement measured at respective field maximum by  $^1\text{H}$ - $^{13}\text{C}$  CP. Trityl OX063 comparison data taken from reference<sup>16</sup> (recorded under similar conditions).

In addition to the signals attributed to the SE, another feature centered at the EPR resonance field of 4983 mT is observed for SA-BDPA. Experiments have shown a  $^1\text{H}$  enhancement of  $\sim 8$  independent of the applied microwave power in the range between 2.4 and 10 W. This flat power dependence together with the symmetric shape and increased width of this feature lead us to conclude that the underlying mechanism is solely based on direct saturation of the EPR resonance and nuclear polarization is induced via cross-relaxation, similar to the Overhauser effect. Cross effect or thermal mixing is un-

likely to be causing this peak, because both mechanisms require a much larger EPR linewidth and typically yield a DNP field profile with regions of positive and negative enhancements and an overall width comparable to the EPR linewidth. For direct comparison, an overlay of the DNP field profile and the EPR spectrum of SA-BDPA is shown in Figure S3. In fact, we attributed the feature in the center of the trityl profile to CE/TM.<sup>16</sup> However, the SA-BDPA profile does not show any sign of CE/TM, which is in accordance with the significantly reduced linewidth of SA-BDPA compared to trityl (28 MHz vs. 50 MHz).

Previous studies of the solid effect have shown that the polarization enhancement is accompanied by a decrease in the time constant at which nuclear longitudinal polarization builds up.<sup>16,17</sup> Therefore, a careful analysis of the build-up dynamics and extrapolation of the signal intensity at infinite polarization time is crucial in order to prevent misinterpretation of data (Figure 5). We report enhancement values extrapolated to infinite polarization time.

Buildup time constants  $T_B$  show values between 43 s and 31 s depending on the incident microwave power and obtained enhancements (Figure 5). The reduction of  $T_B$  by SE DNP compared to  $T_1$  leads to a further increase of sensitivity due to a more rapid recycling of NMR experiments.<sup>17</sup> At the highest microwave power the enhancement factor is  $\epsilon = 94$ , while the gain in sensitivity is  $\epsilon\sqrt{T_1/T_B} = 110$ . However, the overall build-up time constant values (including  $T_1$ ) are  $\sim 50\%$  larger in comparison with trityl OX063 under similar conditions,<sup>16</sup> which is attributed to less efficient longitudinal relaxation enhancement of protons by the paramagnetic species.

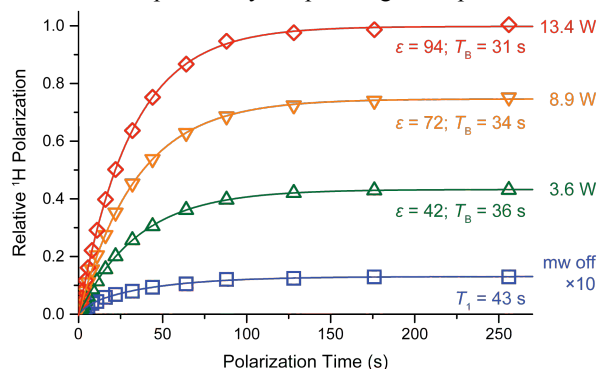


Figure 5. Polarization buildup curves obtained with 40 mM SA-BDPA in glycerol-*d*<sub>8</sub>/D<sub>2</sub>O/H<sub>2</sub>O (60/30/10 v/v) at different microwave power levels and without mw irradiation (multiplied by a factor 10 to enhance visibility).

This explanation is further supported by significantly slower spin-lattice relaxation of the respective electron spin ( $T_1 = 56$  ms in SA-BDPA vs. 1.3 ms in trityl, Figure S2). This longer spin-lattice relaxation time constant might also lead to a “saturation effect” observed in microwave power dependent measurements of the <sup>1</sup>H DNP enhancement. While trityl shows a near linear power dependence, the enhancements obtained with SA-BDPA are more than 50 % larger at lowest applied power, but approach those obtained with trityl at the highest gyrotron output power available (Figure 4, inset).

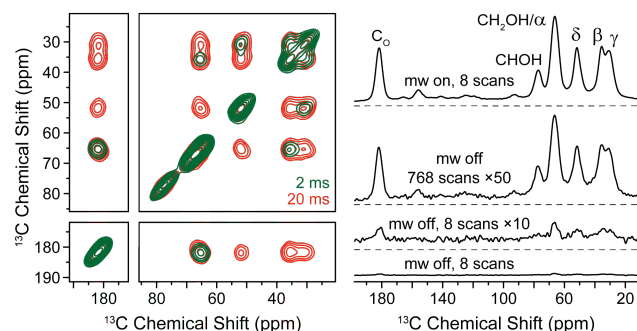


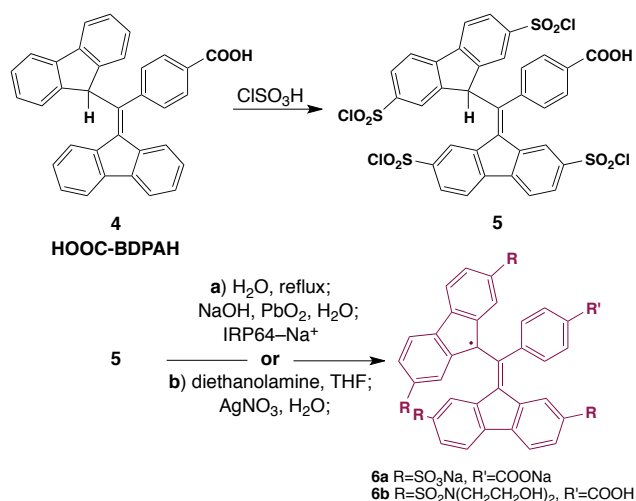
Figure 6. DNP enhanced 2D <sup>13</sup>C-<sup>13</sup>C correlation spectrum (spin-diffusion) using 2 ms (green) and 20 ms (red) mixing time (left), and <sup>13</sup>C CPMAS spectra (right) of 0.1 M <sup>13</sup>C<sub>5</sub>-proline polarized by 40 mM SA-BDPA in glycerol-*d*<sub>8</sub>/D<sub>2</sub>O/H<sub>2</sub>O (60/30/10 v/v) under 8.9 W microwave irradiation.

In Figure 6 we demonstrate the application of SA-BDPA in 1D DNP enhanced CPMAS and 2D <sup>13</sup>C-<sup>13</sup>C correlation spectra of a 0.1 M solution of uniformly <sup>13</sup>C labeled proline. <sup>13</sup>C-<sup>13</sup>C mixing was achieved using spin-diffusion assisted by a DARR field applied to <sup>1</sup>H.<sup>18</sup> Mixing was limited either to a one-bond distance (Figure 6, green), or allowed to occur between all nuclei in the small molecule (Figure 6, red) by allowing spin-diffusion for a mixing period of 2 ms or 20 ms, respectively. In both cases all expected cross-peaks are present and clearly resolved. <sup>1</sup>H signal enhancement was determined as  $\epsilon = 50$  by comparison of 1D signal amplitudes with and without microwave irradiation (Figure 6, right). Slightly lower DNP enhancements as compared to the experiments using urea could be caused by less efficient irradiation of the entire sample volume (a fully packed NMR rotor was used for proline while urea experiments were conducted in a center packed rotor). Additionally, different <sup>1</sup>H relaxation properties induced by alicyclic side chain dynamics could lead to lower equilibrium polarization.

SA-BDPA is an effective narrow line DNP agent with outstanding water solubility. However, access to a family of peripherally substituted BDPA derivatives is advantageous because experience indicates that a single polarization agent may not suffice for all analytes.<sup>19</sup> For example, DNP NMR experiments may be compromised if the polarizing agent binds the analyte, causing significant paramagnetic broadening of the NMR signals of interest. Therefore, we set out to develop a modular route to access differentially functionalized water-soluble BDPA derivatives. Reaction of HOOC-BDPAH (4)<sup>20</sup> with chlorosulfonic acid produces chlorosulfonate 5 that can be hydrolyzed or reacted with nucleophiles prior to oxidation to give both ionic and neutral polarization agents.<sup>21</sup> For example, treatment of 5 with sodium hydroxide in water followed by AgNO<sub>3</sub> oxidation and cation exchange gave 6a – a highly water-soluble ionic radical similar to SA-BDPA (Scheme 2). Replacing NaOH with diethanolamine gave a neutral radical 6b.

#### Scheme 2. Modular approach to the water-soluble BDPA-based radicals





Unfortunately **6b** formed aggregates in glycerol-water mixture as apparent by its EPR spectrum at 80 K (Figure S1). However, it may be used to polarize pyruvate via dissolution DNP in metabolic imaging.<sup>22</sup>

In summary, we have developed water-soluble BDPA-based persistent radicals as effective SE DNP agents. Trityl-type EPR probes have been used to measure tissue oxygenation and pH<sup>23</sup>, and we are currently investigating whether water-soluble BDPA derivatives can find application in this field. We anticipate that biradicals and multiradicals incorporating the water-soluble BDPA cores will be useful for cross effect (CE) DNP.

## ASSOCIATED CONTENT

**Supporting Information.** Detailed experimental procedures and characterization of **3**, **6a** and **6b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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TOC Graphic

