

Role of Protons in and around Strongly Coupled Nitroxide Biradicals for Cross-Effect Dynamic Nuclear Polarization

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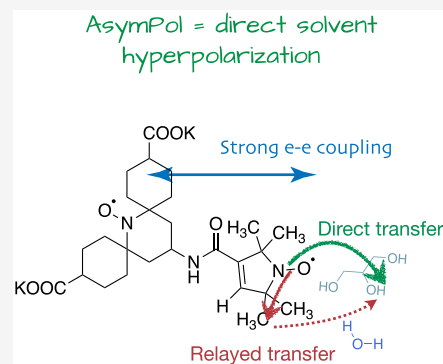


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Supporting Information

ABSTRACT: In magic angle spinning dynamic nuclear polarization (DNP), biradicals such as bis-nitroxides are used to hyperpolarize protons under microwave irradiation through the cross-effect mechanism. This mechanism relies on electron–electron spin interactions (dipolar coupling and exchange interaction) and electron–nuclear spin interactions (hyperfine coupling) to hyperpolarize the protons surrounding the biradical. This hyperpolarization is then transferred to the bulk sample via nuclear spin diffusion. However, the involvement of the protons in the biradical in the cross-effect DNP process has been under debate. In this work, we address this question by exploring the hyperpolarization pathways in and around bis-nitroxides. We demonstrate that for biradicals with strong electron–electron interactions, as in the case of the AsymPols, the protons on the biradical may not be necessary to quickly generate hyperpolarization. Instead, such biradicals can efficiently, and directly, polarize the surrounding protons of the solvent. The findings should impact the design of the next generation of biradicals.



Solid-state nuclear magnetic resonance (NMR) is one of the most potent ways to access atomic-scale information about solids.¹ However, the inherent low sensitivity of solid-state NMR limits its application in investigating low concentrations of NMR active species. This limited sensitivity primarily arises from the low polarization level of the nuclear spins at thermal equilibrium. In contrast, electron spins have greater spin polarization, due to their higher gyromagnetic ratio ($|\gamma_e/\gamma_H| \sim 658$). Using the coupling between electron and nearby nuclear spins and using microwave (μ w) irradiation at an appropriate frequency, one can increase the nuclear spin polarization through a process called dynamic nuclear polarization (DNP).²

In the past two decades, DNP has been combined with magic angle spinning (MAS) at high magnetic fields using high-power μ w sources, which has enabled the acquisition of MAS NMR spectra with high resolution and sensitivity.^{3–10} DNP has revolutionized the field of solid-state NMR and enabled numerous applications for both biological and material samples,^{11–23} in particular at natural isotopic abundance.^{24–27}

As of today, MAS-DNP is best carried out using biradicals as polarizing agents,^{28,29} which generate high nuclear spin hyperpolarization via a mechanism called the cross-effect (CE).^{30–33} Biradicals are paramagnetic molecules, with two unpaired electron spins, that are dissolved in glass-forming matrices such as glycerol/water mixtures and typically used to polarize the protons present in these matrices. The hyperpolarization can be subsequently transferred to the nuclear spins of interest via cross-polarization.³⁴

The cross-effect DNP mechanism relies on optimal relative g-tensor orientations in the biradical,^{32,35–38} strong interelec-

tron spin couplings,^{39–44} and sufficiently long electron spin relaxation times. Nuclear hyperpolarization has been improved by preparing bulky molecules^{45–49} and by designing pathways for polarization transfer.⁵⁰ Importantly, the cross-effect DNP mechanism relies on the existence of a coupling between the radical centers through space (dipolar coupling, $D_{a,b}$) and through overlap of orbitals (exchange interaction, $J_{a,b}$); cumulatively, these interactions are termed e–e couplings, hereafter. In addition, the electron paramagnetic resonance (EPR) spectral width ($\Delta\omega$) of the biradicals must be greater than the Larmor frequency of the protons.

A detailed analysis of the cross-effect under MAS has been the subject of several previous reports.^{30–33,36,51,52} Briefly, μ w irradiation generates a polarization difference between the two electron spins in the biradical that is transferred to nearby protons. These events occur periodically due to the spinning of the sample and the large breadth of the EPR spectrum and have been dubbed “rotor events”.³² The transfer of the electron spin polarization difference to the proton spins occurs during the cross-effect rotor events. The rate of electron to nucleus polarization transfer involves e–e couplings, pseudosecular hyperfine couplings between electron and proton spins ($A_{a,n}^{\pm}$

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and $A_{b,n}^{\pm}$), and the inverse of the Larmor frequency of the nucleus (ω_n).^{31,32,53}

Using the Landau–Zener approximation under MAS, the initial rate of polarization transfer between the biradical and the nuclear spin can be expressed as follows (see the Supporting Information for details):

$$R_{CE} \propto \frac{\pi}{2(\Delta\omega_a + \Delta\omega_b)} \left| \frac{\langle (D_{a,b} + 2J_{a,b})^2 \rangle \langle (A_{a,n}^{\pm} - A_{b,n}^{\pm})^2 \rangle}{\omega_n^2} \right| \quad (1)$$

As such, the cross-effect can polarize protons that are close to the electron spins, and the resulting nuclear hyperpolarization is then transferred to protons further away via nuclear spin diffusion.⁵⁴ Thus, protons that are close are essential for receiving the hyperpolarization and transmitting the hyperpolarization away from the biradical.

Under standard DNP experimental conditions, proton homonuclear spin diffusion is rapid.^{55,56} Indeed, protons far from the biradical (hereafter termed bulk protons) have very similar Larmor frequencies and strong dipolar couplings, resulting in an efficient homonuclear spin diffusion. However, the spin diffusion between the protons in the vicinity of the biradical and those further away is hindered by the presence of the hyperfine couplings that change their effective Larmor frequency, resulting in a slow transmission of polarization to the bulk protons. The region to which these nearby protons with sizable hyperfine couplings belong is often termed the spin diffusion barrier, and its role in the DNP process has been the subject of a long-standing debate.^{50,57–60}

In recent years, the role of these nearby protons has been under scrutiny. The advent of numerical models that can account for a large number of nuclear spins has highlighted the importance of protons near the biradical.^{53,61–63} It has been shown that these nearby protons can periodically exchange their polarization when their Larmor frequency is equal via nuclear dipolar rotor events and thus are essential to the DNP process under MAS.^{32,53,63,64}

Recently, the protons on the biradicals have been the center of an extensive study, for example, in the case of the bTBK biradical family,³⁵ that possess modest $D_{a,b}$ values of ~ 30 MHz.^{61,65} In this comprehensive work, the authors selectively deuterated TEKPol⁶⁶ and showed that removing the protons on the molecule lead to a slower hyperpolarization process, i.e., a longer nuclear hyperpolarization time T_B . These observations highlight the importance of strong electron–nuclear hyperfine couplings in the cross-effect rate, in agreement with eq 1.

However, eq 1 also shows that the initial polarization transfer rate can be modulated by changing the e–e couplings. This rationale was the basis of the design of the AsymPol family of biradicals (Figure 3).^{40,41} The AsymPols were designed using a conjugated amide linker that enables the proximity between the two moieties leading to large couplings with a $D_{a,b}$ of 56 MHz and a $J_{a,b}$ of ~ 95 and ~ 120 MHz (for each of the two conformers).⁴¹ These strong e–e couplings result in increased cross-effect rates, and therefore, AsymPol biradicals can generate hyperpolarization very quickly.^{40,41} This raises a simple question: are protons on the biradical as critical in the case of the AsymPols?

In this Letter, we demonstrate experimentally that, unlike in previous studies,^{50,67,68} the protons on the AsymPols are not required for hyperpolarization. We first show that the experimental build-up times are not affected by selective

deuteration of AsymPol-COOK, a new derivative of the AsymPols (Figure 1). We then analyze theoretically the

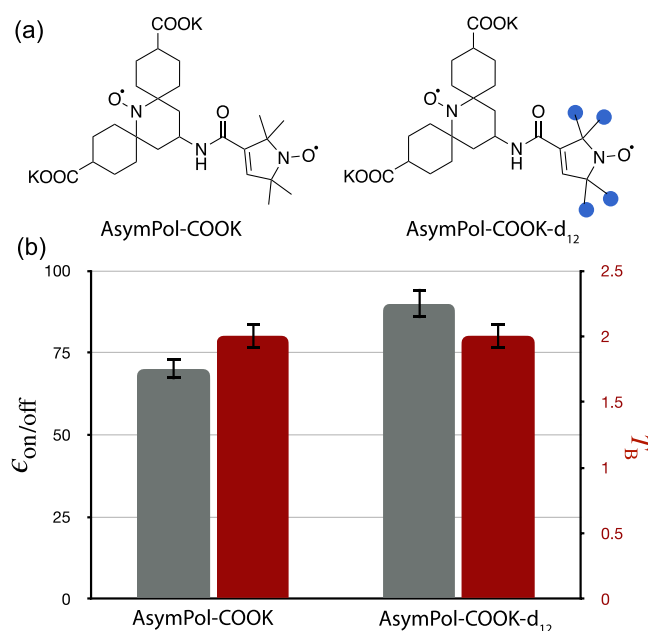


Figure 1. (a) Structures of AsymPol-COOK tested under MAS-DNP at 14.1 T. Deuterated sites are colored blue. (b) Experimental results: enhancement $\epsilon_{on/off}$ (gray bars, left axis) and build-up time T_B (red bars, right axis) for 10 \pm 1 mM AsymPol-COOK and AsymPol-COOK-d₁₂ in a glycerol-*d*₈/D₂O/H₂O mixture (6/3/1 volume ratio).

process using advanced numerical MAS-DNP simulations. After demonstrating the ability of the numerical methods to predict the build-up times for several complex cases, we then predict the role of the protons on AMUPol⁶⁹ and on a AsymPol derivative. We finally discuss how the hyperpolarization is transferred in both cases using a new analytical model and its experimental consequences on the design of new biradicals.

As described above, AsymPols have strong e–e couplings in comparison to TEKPol or AMUPol. This difference is reflected in the initial polarization transfer, which can be indirectly measured by the characteristic time taken to generate bulk hyperpolarization in a radical solution called the build-up time, T_B . It has been demonstrated that the measured build-up time reflects the combined effects of the initial CE polarization rate and the spin diffusion rate (inside and outside of the so-called spin diffusion barrier).^{53,57}

We explored the impact of selective deuteration of AsymPol-COOK and its impact on T_B and the DNP enhancements ($\epsilon_{on/off}$). We carried out the synthesis of AsymPol-COOK as well as AsymPol-COOK-d₁₂ (Figure 1a and Scheme S1). AsymPol-COOK is a new water-soluble derivative of AsymPol that is easier to synthesize than AsymPol-POK.⁴⁰

The MAS-DNP experiments used a 10 \pm 1 mM solution of AsymPol-COOK and AsymPol-COOK-d₁₂ in a glycerol-*d*₈/D₂O/H₂O glass-forming matrix (6/3/1 volume ratio) (see the Supporting Information for EPR data). The build-up time and enhancement $\epsilon_{on/off}$ of the two biradicals were measured at 8 kHz and 14.1 T, respectively (Figure 1b; see the Supporting Information for details). The enhancement for the partially deuterated biradical ($\epsilon_{on/off} = 88 \pm 2$) is higher than for the fully protonated one ($\epsilon_{on/off} = 68 \pm 2$). This observation is in

Table 1. Evolution of the Polarization Build-up Time (T_B) as a Function of the Main Magnetic Field Strength for 5 or 10 mM AMUPol in a Glycerol- d_8 /D₂O/H₂O Mixture (6/3/1 volume ratio) at $[^1\text{H}] = 11\text{ M}$

B_0 , MAS frequency	T_B (s)			
	experimental (10 mM)	simulation (10 mM)	experimental (5 mM)	simulation (5 mM)
9.4 T, 8 kHz	3.5 ⁶⁹	3.6	7 ⁷⁰	7.3
9.4 T, 40 kHz	3.8 ⁷¹	4.1	7.1 ⁷¹	7.7
14.1 T, 8 kHz	4.8 ^{63,69}	4.5	—	8.7
18.8 T, 8 kHz	5 ⁷²	5	15 ⁷¹	10.2
18.8 T, 40 kHz ⁷²	6.6	6.1	18 ⁷¹	11.3

line with previous works in which deuterating the methyl groups at the α position of the nitroxide group yielded larger enhancements^{47,67,68} unlike deuteration of TEKPol.⁵⁰ Removal of the protons on the fast relaxing methyl groups has been shown to increase the electron spin relaxation times, which likely affects the microwave saturation factor and observed enhancements.^{47,67,68} These effects are not completely understood and will be the subject of future work.

Most importantly, the build-up times are identical for both biradicals [$T_B \sim 2 \pm 0.1\text{ s}$ (see the Supporting Information for details)]. This is in stark contrast with any previously reported results in which T_B increased under deuteration.^{47,50,67,68} This observation reveals a fundamentally different DNP process for the AsymPols in which the protons on the molecules appear to play a minor role.

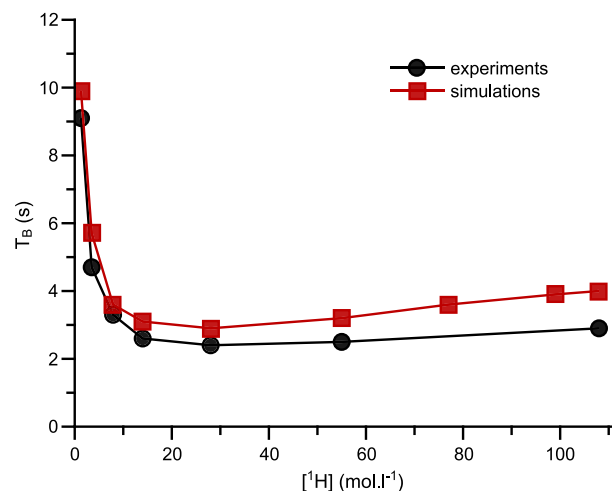
To understand the underlying mechanism, we used a previously introduced numerical simulation of the MAS-DNP process. We first benchmarked our reported model^{41,63} to prove it robustly predicts the build-up time under different conditions for both AMUPol and the AsymPols. This simulation program is used here to simulate the MAS-DNP process with the biradical placed at the center of a box made of the matrix in which it is dissolved. This model is suitable to represent how the polarization is transferred from the biradical to the bulk nuclei and thus predict T_B .

The calculations use structures obtained from molecular dynamics (MD) simulations as input and describe the MAS-DNP process and the spin diffusion around the biradical, under certain approximations.^{41,63} It makes extensive use of the Landau–Zener approximation applied in the Liouville space⁵³ to ensure a linear scaling of the problem with the number of spins. In addition, the model takes as input the biradical geometry, e–e coupling, and electron–proton interactions. All of these parameters can be reasonably obtained from density functional theory (DFT).^{41,61,63} We note that both isotropic (Fermi contact) and anisotropic (dipolar) hyperfine couplings are calculated using DFT simulations and are essential for accurately predicting the build-up times, as has also been noted previously (see the Supporting Information for the hyperfine couplings used).^{41,50,63} This model was developed to simulate the cases of AMUPol or AsymPol-POK at a concentration of 10 mM for moderate MAS frequency, and proton concentration $[^1\text{H}] = 11\text{ M}$.^{41,63} Here we also demonstrate its ability to simulate cases beyond its initial focus.

First, the model was tested on the well-characterized AMUPol biradical (Figure 3a). AMUPol is a water-soluble bis-nitroxide introduced by Sauvee *et al.*,⁶⁹ and it possesses relatively strong e–e couplings with a $D_{a,b}$ of 35 MHz and a $J_{a,b}$ of -15 MHz .^{61,73} Under MAS, $D_{a,b} + 2J_{a,b}$ ranges from -100 to 20 MHz , which enables relatively short build-up times on the order of a few seconds. As such, AMUPol is an excellent polarizing agent. Table 1 reports T_B as a function of the main

magnetic field intensity for AMUPol when $[^1\text{H}] = 11\text{ M}$ and different MAS frequencies (8 or 40 kHz). The corresponding simulations show good agreement with the experiments. The magnetic field and MAS frequency trends are clearly reproduced for both biradical concentrations (Table 1). Note that the enhancements were also calculated (Supporting Information), but the multi-nucleus model alone cannot accurately calculate the enhancements, as previously noted.^{61,74}

To further test the robustness of the model, T_B was simulated for different proton concentrations and compared with the results recently published by Prisco *et al.* (Figure 2).⁵⁷

**Figure 2.** Plot showing T_B as a function of $[^1\text{H}]$ for 12 mM AMUPol dissolved in a glycerol/H₂O mixture (6/4 volume ratio) and a glycerol- d_8 /D₂O mixture (6/4 volume ratio). Black circles represent experimental data extracted from ref 57; red squares represent data from simulations in this work.

The excellent agreement between experiments and simulations demonstrates the validity of this multi-nucleus model used in the simulations to predict AMUPol and in particular its ability to capture the impact of local $[^1\text{H}]$ variations.

Finally, it should be noted that in previous publications,⁴¹ the model was expanded to enable simulation of the case of strongly coupled biradicals. As such, we have previously demonstrated that the model can accurately predict the build-up times of AsymPol-POK and c-AsymPol-POK at 9.4, 14.1, and 18.8 T at various spinning frequencies.⁴¹ In summary, the numerical model consistently delivers reliable simulations across various scenarios and for various structures.

We subsequently investigated the impact of the degree of deuteration of the radicals (Figure 3a) on the DNP build-up times at two different magnetic fields, 9.4 and 14.1 T (Figure 3b).

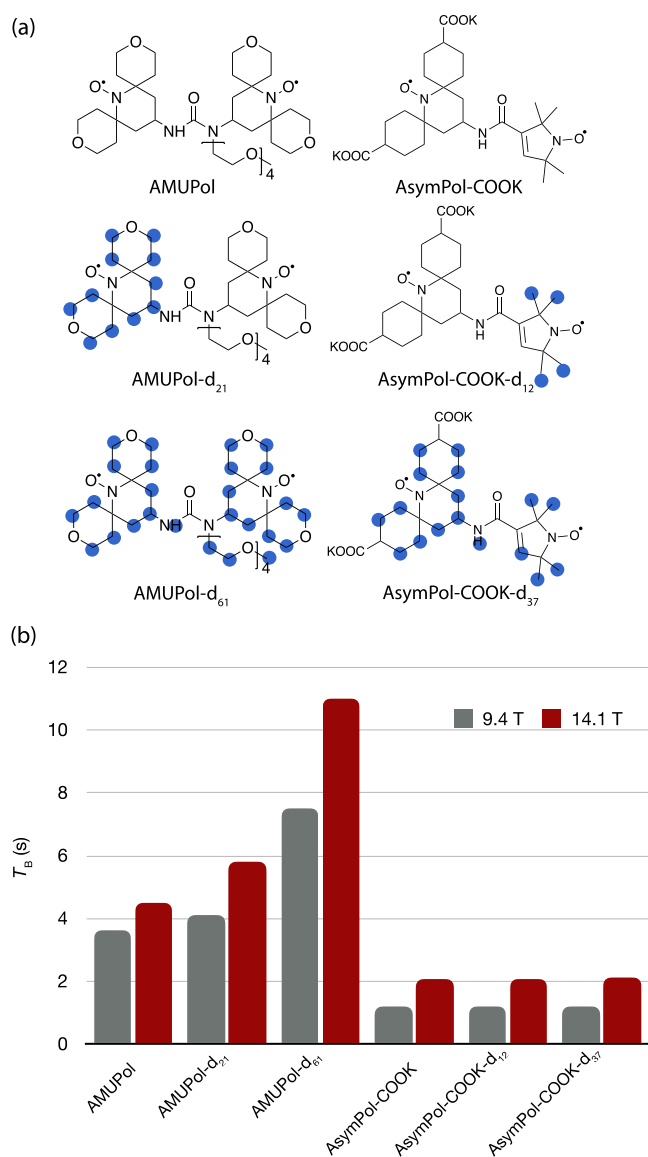


Figure 3. (a) Biradical structures tested for MAS-DNP. Deuterated sites are colored blue. (b) Calculated build-up times for 10 mM AMUPol or 10 mM AsymPol-COOK dissolved in a glycerol-*d*₈/D₂O/H₂O mixture. Three different deuteration levels of the biradicals have been simulated: no deuteration, one radical moiety deuterated, and fully deuterated.

First, the nondeuterated biradicals were tested *in silico* (Figure 3b); AsymPol-COOK yields build-up times shorter than those of AMUPol. At both 9.4 and 14.1 T, AsymPol-COOK is predicted to have build-up times 3-fold shorter than those of AMUPol [1.2 s vs 3.6 s and 2.0 s vs 4.5 s, respectively (Figure 3b)]. The simulations were then carried out for the biradicals in which only one moiety was deuterated. In that case, the build-up time of AMUPol increases to 4.1 and 5.8 s at 9.4 and 14.1 T, respectively (Figure 3b). On the contrary, the build-up times of AsymPol-COOK are unaffected by deuteration. When the biradicals are fully deuterated, similar trends are observed. The build-up time of AMUPol becomes significantly longer (7.5 and 11.0 s at 9.4 and 14.1 T, respectively), while the build-up time of AsymPol-COOK increases only negligibly and remains very close to 1.2 and 2.1 s at 9.4 and 14.1 T, respectively.

These simulations show differing trends. For AMUPol, the protons on the biradicals are essential for generating quick nuclear hyperpolarization, while there is no apparent role for these protons in the propagation of hyperpolarization for AsymPol-COOK. It is important to note that the behavior of the AsymPols does not depend on the site that is deuterated. Indeed, the same trend is observed for simulations with AsymPol-COOK-*d*₂₄, where only the six-membered nitroxide ring and the spirocycles were deuterated and for the fully deuterated version of c-AsymPol-COOK (see the Supporting Information) in which the local proton concentration is similar to that of AMUPol or the recently introduced HydrOPol.⁷⁵

The hyperpolarization via cross-effect MAS-DNP involves generation of an electron spin polarization difference that is transferred to the surrounding nuclei. This process involves the hyperfine couplings and the couplings between the two electron spins in biradicals. In strict terms, the efficiency of the polarization transfer depends on the efficiency of the cross-effect rotor events (obtained via the Landau–Zener approximation) and the number of such events per rotor period. These two factors depend on not only the crystallite orientation but also the relative orientations of the g-tensors.^{31,32,36} Because the evolution of the proton polarization is slow compared to the MAS rate,^{31,53,62,63} we will ignore the discontinuities induced by the rotor events.

The transfer of polarization from the radicals to the bulk nuclei can take two different pathways: (1) polarization of the protons on the molecule followed by spin diffusion to the bulk protons and (2) direct polarization of solvent protons followed by spin diffusion to the bulk protons.

These two pathways can coexist, but their relative contribution may depend on the rate of polarization transfer from the biradicals to each proton (i.e., the cross-effect efficiency) and the rate of the spin diffusion between protons that are strongly coupled to the electron in the region of the spin diffusion barrier (which depends on the density of protons⁵⁰). The two pathways do not possess the same weight when comparing AMUPol and the AsymPols.

The polarization of the protons in and around the biradical can be approximately described as a set of equations connecting the two pools of protons, i.e., those protons that are on the biradical (N_{birad}) and those that are in the solvent (N_{solv}):

$$\begin{aligned} \frac{dP_{\text{birad}}}{dt} &= -R_{\text{CE}}^{\text{birad}}(P_{\text{birad}} - \Delta P_e) - R_{1,n}^{\text{birad}}(P_{\text{birad}} - P_B) \\ &\quad - R_{\text{SD}}^{\text{b} \rightarrow \text{s}}(P_{\text{birad}} - P_{\text{solv}}) \\ \frac{dP_{\text{solv}}}{dt} &= -R_{\text{CE}}^{\text{solv}}(P_{\text{solv}} - \Delta P_e) - R_{1,n}^{\text{solv}}(P_{\text{solv}} - P_B) \\ &\quad - R_{\text{SD}}^{\text{b} \rightarrow \text{s}}N_{\text{birad}}/N_{\text{solv}}(P_{\text{solv}} - P_{\text{birad}}) \end{aligned} \quad (2)$$

where $R_{\text{CE}}^{\text{birad}}$ and $R_{\text{CE}}^{\text{solv}}$ are the average R_{CE} values for the protons on the biradicals and in the solvent, respectively, $R_{1,n}^{\text{birad}}$ and $R_{1,n}^{\text{solv}}$ are the nuclear relaxation rates for the protons on the biradicals and in the solvent, respectively, $R_{\text{SD}}^{\text{b} \rightarrow \text{s}}$ is the spin diffusion or exchange rate between the two pools of protons, P_B is the thermal equilibrium polarization, P_{birad} and P_{solv} are polarization levels of the protons on the biradical molecule and solvent matrix, respectively, and ΔP_e is the absolute value of the polarization difference between the electron spins at steady state.^{32,36}

If we assume that the proton distribution around both biradicals is similar, which results in a similar magnitude of hyperfine couplings, then R_{SD} and A^\pm are identical. Furthermore, we assume that the EPR line widths are also similar for both biradicals ($\Delta\omega_{Asym} \approx \Delta\omega_{AMU}$), and this implies that the ratio

$$\frac{R_{CE}^{birad}(AsymPol)}{R_{CE}^{birad}(AMUPol)} = \frac{R_{CE}^{solv}(AsymPol)}{R_{CE}^{solv}(AMUPol)} = \frac{|D_{Asym} + 2J_{Asym}|^2}{|D_{AMU} + 2J_{AMU}|^2} \quad (3)$$

mainly depends on ratio of the strength of the e–e couplings of both biradicals. For AMUPol, $|D_{AMU} + 2J_{AMU}|$ spans the range of 20–100 MHz, while in the case of AsymPols, $|D_{Asym} + 2J_{Asym}|$ spans a range of 120–300 MHz. Therefore, taking the angular average, the AsymPols can hyperpolarize protons faster due to larger R_{CE} values by a factor $(|D_{Asym}| + 2J_{Asym})/(|D_{AMU}| + 2J_{AMU})^2 \sim 25$ as compared to AMUPol.

As a consequence of this much stronger R_{CE} , AsymPol can achieve the same polarization rate as AMUPol on protons that have hyperfine couplings that are 5 times smaller, i.e., located $\approx 5^{1/3}$ (≈ 2) times further away assuming all other parameters are constant. Therefore, AsymPol can more easily hyperpolarize protons in the solvent and does not require the protons on the biradical as predicted by simulations.

Because the polarization build-up time of AsymPol is unchanged ($T_B \approx 2$ s), this means that the transfer rate $R_{SD}^{b \rightarrow s} \frac{N_{birad}}{N_{solv}}$ between the protons of biradical and those of the solvent can be neglected compared to $R_{CE}^{solv}(AsymPol)$. Therefore, the equations become decoupled:

$$\begin{aligned} \frac{dP_{Asym}}{dt} &= -R_{CE}^{Asym}(P_{Asym} - \Delta P_e^{Asym}) - R_{1,n}^{Asym}(P_{Asym} - P_B) \\ \frac{dP_{solv}}{dt} &= -R_{CE}^{solv}(P_{solv} - \Delta P_e^{Asym}) - R_{1,n}^{solv}(P_{solv} - P_B) \end{aligned} \quad (4)$$

In contrast, the large change for T_B in AMUPol versus AMUPol- d_{21} , from 4.5 to 5.8 s, means that $R_{CE}^{solv}(AMUPol) < R_{SD}$. For AMUPol, the equation then becomes

$$\begin{aligned} \frac{dP_{AMU}}{dt} &= -R_{CE}^{AMU}(P_{AMU} - \Delta P_e^{AMU}) - R_{1,n}^{AMU} \\ &\quad (P_{AMU} - P_B) - R_{SD}^{b \rightarrow s}(P_{AMU} - P_{solv}) \\ \frac{dP_{solv}}{dt} &= -R_{1,n}^{solv}(P_{solv} - P_B) - \frac{R_{SD}^{b \rightarrow s} N_{birad}}{N_{solv}}(P_{solv} - P_{AMU}) \end{aligned} \quad (5)$$

Using the appropriate order of magnitude for those quantities in the equation, this simple model can reproduce the simulated trends (details in the Supporting Information). At 14.1 T, $R_{CE}^{birad} = 11$ s^{−1} and $R_{CE}^{solv} = 0.6$ s^{−1} for AMUPol while $R_{CE}^{birad} = 319$ s^{−1} and $R_{CE}^{solv} = 15.8$ s^{−1} for AsymPol-COOK. To obtain a good agreement between the experimental build-up times and those predicted by the rate equations, the model required that $R_{SD}^{b \rightarrow s}$ be ~ 4 s^{−1}. This value agrees with the simplifications made to eqs 4 and 5. This simple rate equation model provides semi-quantitative results as it predicts the correct order of magnitude and provides insight into the physical process. The importance of the protons in the biradical largely depends on the relative size of R_{CE}^{solv} and $R_{SD}^{b \rightarrow s}$. However, the simple rate equations model cannot substitute

the more accurate multi-nucleus model used to perform calculations described above.

The preferred polarization pathways for AMUPol and AsymPol at 14.1 T are shown schematically in Figure 4. As

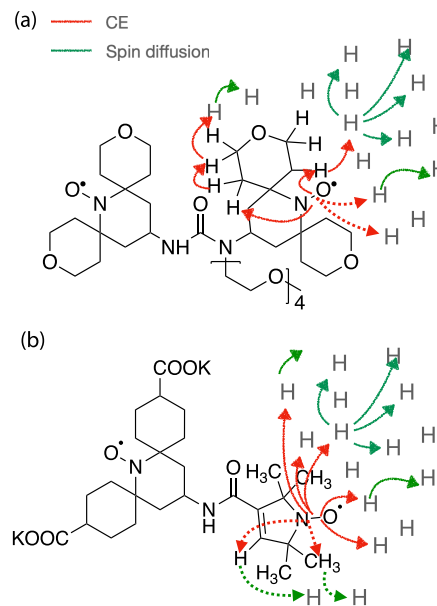


Figure 4. Hyperpolarization pathways for (a) AMUPol and (b) AsymPol-COOK. Red arrows indicate direct polarization transfer via CE, and green arrows indicate proton homonuclear spin diffusion. The solid line corresponds to the preferred pathway, while dotted lines correspond to the less favorable ones.

R_{CE} decreases with field due to the combined effect of $\Delta\omega_a + \Delta\omega_b$ and ω_n^2 in eq 1, the build-up times tend to be longer at high fields.⁷¹ Under very high field conditions, the protons on the biradicals may once again be important for the AsymPols, as the spin diffusion constant $R_{SD}^{b \rightarrow s}$ is likely field independent. However, using the rate equation model $R_{CE}^{solv}(AsymPol) \approx R_{SD}^{b \rightarrow s}$, this should occur for a B_0 of ≈ 22 T, i.e., 950 MHz NMR frequency. In addition, MAS-DNP simulations for a higher solvent proton concentration (66 M) show that in that case the protons in the solvent can play a more prominent role. The effect of biradical deuteration remains important, but due to the higher ¹H concentration, the protons around the biradical play a more active part in the hyperpolarization process (see the Supporting Information).

We note that in the previous work on the series of deuterated TEKPol,⁵⁰ the cross-effect rate is likely limited by relatively weak e–e couplings in comparison to those of the AsymPols. Consequently, the dominant pathway is the hyperpolarization of the closest spins on the biradical molecule. Analogous arguments are also valid for the observations made by Oschkinat and co-workers in the case of TOTAPOL.⁶⁷ A corollary of our analysis is that biradical deuteration would not impact the build-up times at lower fields and that it may be beneficial to deuterate those biradicals to enhance the MAS-DNP performance. For AMUPol, this should occur for a magnetic field of ~ 7.4 T.

Finally, an increase in R_{CE} is desirable, but increasing the level of e–e coupling may not be the only solution. Indeed, a large e–e coupling can favor electron–electron cross-relaxation that prevents the generation of a large ΔP_e ,³² and

if it is larger than $|\omega_n|$, the CE rotor events disappear.^{42,44} It is possible that the presence of electron–electron cross-relaxation limits the performance of the AsymPols and other biradicals with large e–e couplings.^{42,44}

Instead, an increase in R_{CE} can equivalently be achieved by using biradicals with correct relative orientations (which increases the number of CE rotor events)³⁶ or by using heterobiradicals,^{42,76,77} i.e., molecules made of two different radical types with different EPR line widths. The latter impacts $\Delta\omega_a + \Delta\omega_b$ in eq 1.

In this work, we have studied the hyperpolarization pathways around AsymPol-COOK, a new water-soluble derivative of the AsymPol family. The experiments showed that the build-up time is unaffected by selective deuteration, unlike previous studies.^{50,67,68} To understand the underlying mechanism, numerical simulations were performed on two commonly used families of biradicals for MAS-DNP experiments, AMUPol and the AsymPols. After demonstrating that the MAS-DNP simulations can reproduce the experimental build-up times of AMUPol under numerous conditions, we predicted the effect of biradical deuteration using AMUPol and AsymPol-COOK as models. The simulations revealed that T_B values for AsymPols do not change under any of the deuteration levels tested. This contrasts with previous reports, notably those on the bTbK family,^{35,50} and indicates a different pathway for the hyperpolarization around the AsymPol confirming the experiments.

These results show that protons near the radical centers of biradicals with moderate e–e coupling play a significant role in the hyperpolarization pathways. Another highlight of this work is that the so-called diffusion barrier is rather permissible in the case of MAS-DNP; in this region, the hyperpolarization transfer is slowed but not quenched as the term “barrier” might imply.

Taken together, our results not only reveal the intricacies of the hyperpolarization mechanism but also demonstrate that when the e–e couplings are large, protons on the biradical are not necessary. The next generation of biradicals should thus focus on increasing the level of the e–e interaction but also improve the relative g-tensor orientation or build on the potential of heterobiradicals. This will favor an efficient polarization transfer even in difficult media, i.e., fully protonated media,^{41,57} but also cases in which the targeted nuclear spin is at a low concentration or is not present on the biradical, e.g., ¹⁹F. We note that a similar conclusion has been reached in a recent preprint.⁷⁸

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jpclett.3c03472>.

Simulation parameters and experimental conditions (PDF)

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Notes

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