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Frédéric A. Perras  
*Ames Laboratory, fperras@ameslab.gov*

Muralikrishna Raju  
*Iowa State University and Ames Laboratory*

Scott L. Carnahan  
*Iowa State University and Ames Laboratory, scottc@iastate.edu*

Dooman Akbarian  
*The Pennsylvania State University*

Adri C. T. van Duin  
*The Pennsylvania State University*

*See next page for additional authors*

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# Full-Scale Ab Initio Simulation of Magic-Angle-Spinning Dynamic Nuclear Polarization

## Abstract

Theoretical models aimed at describing magic-angle-spinning (MAS) dynamic nuclear polarization (DNP) NMR typically face a trade-off between the scientific rigor obtained with a strict quantum mechanical description, and the need for using realistically large spin systems, for instance using phenomenological models. Thus far, neither approach has accurately reproduced experimental results, let alone achieved the generality required to act as a reliable predictive tool. Here, we show that the use of aggressive state-space restrictions and an optimization strategy allows full-scale ab initio MAS-DNP simulations of spin systems containing thousands of nuclei. Our simulations are the first ever to achieve quantitative reproduction of experimental DNP enhancements and their MAS rate dependence for both frozen solutions and solid materials. They also revealed the importance of a previously unrecognized structural feature found in some polarizing agents that helps minimize the sensitivity losses imposed by the spin diffusion barrier.

## Disciplines

Physical Chemistry

## Comments

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## Authors

Frédéric A. Perras, Muralikrishna Raju, Scott L. Carnahan, Dooman Akbarian, Adri C. T. van Duin, Aaron Rossini, and Marek Pruski

# Full-Scale *Ab Initio* Simulation of Magic-Angle-Spinning Dynamic Nuclear Polarization

Frédéric A. Perras,<sup>1\*</sup> Muralikrishna Raju,<sup>1,2</sup> Scott L. Carnahan,<sup>1,2</sup> Dooman Akbarian,<sup>3</sup> Adri C. T. van Duin,<sup>3</sup> Aaron J. Rossini,<sup>1,2</sup> Marek Pruski<sup>1,2</sup>

<sup>1</sup>US DOE, Ames Laboratory, Ames, IA, 50011, USA

<sup>2</sup>Department of Chemistry, Iowa State University, Ames, IA, 50011, USA

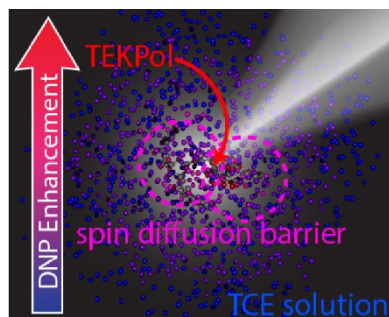
<sup>3</sup>Department of Mechanical Engineering, The Pennsylvania State University, University Park, PA, 16802, USA

\*fperras@ameslab.gov

## Abstract

Theoretical models aimed at describing magic-angle-spinning (MAS) dynamic nuclear polarization (DNP) NMR have great potential in facilitating the *in silico* design of DNP polarizing agents and formulations but must typically face a trade-off between the accuracy of a strict quantum mechanical description, and the need for using realistically large spin systems, for instance using phenomenological models. Here, we show that the use of aggressive state-space restrictions and an optimization strategy allows full-scale *ab initio* MAS-DNP simulations of spin systems containing thousands of nuclei. Our simulations are shown to reproduce experimental DNP enhancements quantitatively, including their MAS rate dependence, for both frozen solutions and solid materials. They also reveal the importance of a previously unrecognized structural feature found in some polarizing agents that helps minimize the sensitivity losses imposed by the spin diffusion barrier.

## Graphical Abstract.



Despite its status as the method of choice for studying the atomic-scale structure of non-periodic materials, solid-state nuclear magnetic resonance (SSNMR) suffers from poor sensitivity, which often limits the ability to characterize materials and molecules with the desired detail. Recently, researchers have begun addressing this limitation with the use of hyperpolarization methods. The most widespread of these is magic-angle-spinning (MAS) dynamic nuclear polarization (DNP),<sup>1,2</sup> which has revolutionized the way surfaces and interfaces are characterized.<sup>3-7</sup>

The sensitivity enhancements that recently became achievable by DNP are remarkably high; however, they are generally far from the theoretical maximum value of  $\gamma_e/\gamma_n$  (658 for  $^1\text{H}$ ). Theoretical simulations have the potential to dramatically accelerate the design of newer polarizing agents and DNP methods;<sup>8-11</sup> however, to date MAS-DNP simulations have been forced to either 1) apply *ab initio* methods to spin systems of limited size<sup>8-17</sup> or 2) use phenomenological models that require parameterization,<sup>18-22</sup> and in some cases have combined the two methods.<sup>8,23</sup>

To overcome this deficit, we recently published a general method for calculating DNP enhancement factors *ab initio* in large systems. This approach uses an optimization strategy predicated on the fact that nuclear polarizations progress towards equilibrium, in a rotor-periodic manner, regardless of initial polarization.<sup>24</sup> By optimizing nuclear polarizations directly to satisfy the condition that they remain constant at the beginning and end of a rotor period it is possible to calculate steady-state DNP enhancements without needing a prohibitively-large propagator. This optimization strategy, however, comes at a cost—since we calculate steady-state polarizations directly, information pertaining to the build-up is lost. A combination of this strategy with the *low-order correlations* in Liouville space (LCL)<sup>25-30</sup> restricted state-space<sup>31-38</sup> method, enabled the calculation of MAS-DNP enhancements in spin systems containing as many as 55 spins; still this

scale proved insufficient to accurately reproduce experimental values. In a subsequent paper,<sup>39</sup> we showed that dramatic computational time savings can be obtained in LCL calculations by restricting the dipolar interactions and basis operators to those between nearest neighbors, similar to the IK-1-type basis set.<sup>40</sup> We have termed this method *locally-restricted* (LR)-LCL. Unlike LCL, the LR-LCL method scales linearly with the system size, allowing for the *ab initio* simulation of systems containing thousands of spins.

In this study, we expand on these two previous works and simulate, for the first time, MAS-DNP in realistically-sized spin systems from first principles. To this aim we have modified our LR-LCL program to introduce (1) cross-effect, (2) electron-electron dipolar, and (3) microwave ( $\mu\text{w}$ ) rotor events using the Landau-Zener formalism described earlier by Thurber et al.<sup>8</sup> and Mentink-Vigier et al,<sup>23</sup> and used in our preceding study (full details are in the supporting information).<sup>24</sup> These events exchange, or deplete in the case of  $\mu\text{w}$  events, polarization between the electrons and nuclei when MAS rotation brings the electrons into resonance with the following conditions: (1)  $|\omega_{e,1} - \omega_{e,2}| = \omega_n$ , (2)  $\omega_{e,1} = \omega_{e,2}$ , and (3)  $\omega_e = \omega_{e,1} - \omega_{\text{MW}}$  ( $\omega_e$ ,  $\omega_n$ ,  $\omega_{\mu\text{w}}$  are the electron Larmor, nuclear Larmor, and  $\mu\text{w}$  frequencies). Note that cross-effect rotor events occur in the absence of  $\mu\text{w}$  irradiation and lead to the reduction of nuclear polarization; an effect known as depolarization.

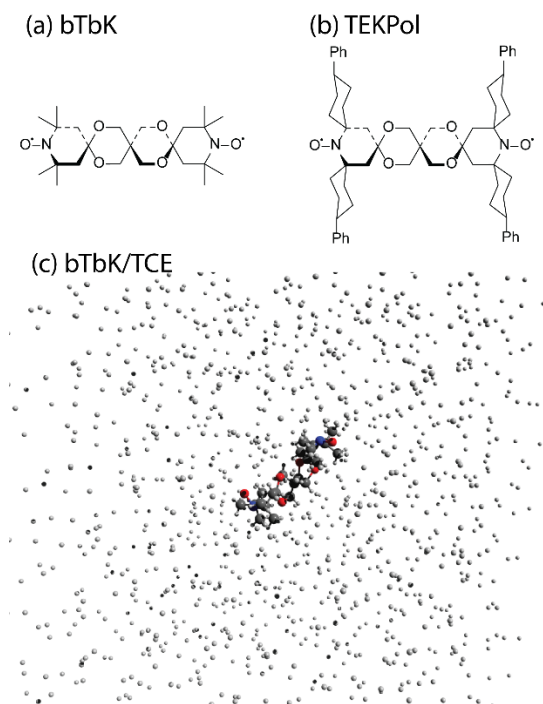
Our theoretical approach is predicated on the following assumptions: 1) product operators involving large numbers of spins minimally impact spin diffusion, 2) dipolar interactions between distant nuclei can be neglected, 3) the electron  $g$  anisotropy is large enough that rotor-induced anticrossing events can be described as fast, and 4) nuclear polarizations are stable at the steady-state. The first two assumptions can be satisfied by performing a basis set convergence test, noting that LR-LCL is exact at its basis set limit. Assumption 3, the Landau-Zener approximation, has

been shown to be reliable in nitroxide systems.<sup>8,23</sup> Lastly, assumption 4 is related to the use of an optimization strategy in lieu of a propagator. Errors due to this assumption may arise if polarizations are altered before larger product operators have a chance to be populated. Our smaller simulations show that this leads to slight (~5%) systematic overestimation of DNP enhancements.

As an initial test of this new simulation framework, we opted for the calculation of DNP enhancement factors in 16 mM 1,1,2,2-tetrachloroethane (TCE) solutions of two common biradical polarizing agents, bTbK<sup>41</sup> and TEKPol, the structures of which are depicted in Figure 1a,b.<sup>42</sup> Conveniently, the LR-LCL approach can be easily altered to perform simulations with periodic boundary conditions and as such can simulate a continuous solution. For this, the unit cell needs only to be large enough that the LR-LCL approach couples just one of the symmetry-generated atoms to a given spin. Note that to include inter-radical interactions in the simulations, a supercell containing multiple biradicals would need to be constructed since symmetry-related radicals have identical g tensor orientations and thus do not generate inter-radical cross-effect events. This is beyond our current computational limitations, but simulations by Mentink-Vigier<sup>23</sup> show that at the concentration studied here (16 mM), with the electron spin-lattice relaxation times ( $T_{1e}$ ) measured for our samples (see supporting information), such effects are negligible. We plan to study this further in a subsequent publication with the use of a hybrid quantum-classical model.

The model solutions were composed of cubic unit cells containing 592 TCE molecules and a single polarizing agent molecule. This corresponds to 1224 and 1256 <sup>1</sup>H spins for the bTbK and TEKPol solutions, respectively, and two electron spins for each agent. ReaxFF-based molecular dynamics simulations<sup>43-48</sup> were run for varying lengths of time and five snapshots from these were extracted for both solutions and geometry-optimized to a unit cell size of 44.62 Å to obtain frozen TCE solution with <sup>1</sup>H densities matching those in pure TCE. Additional information and final spin

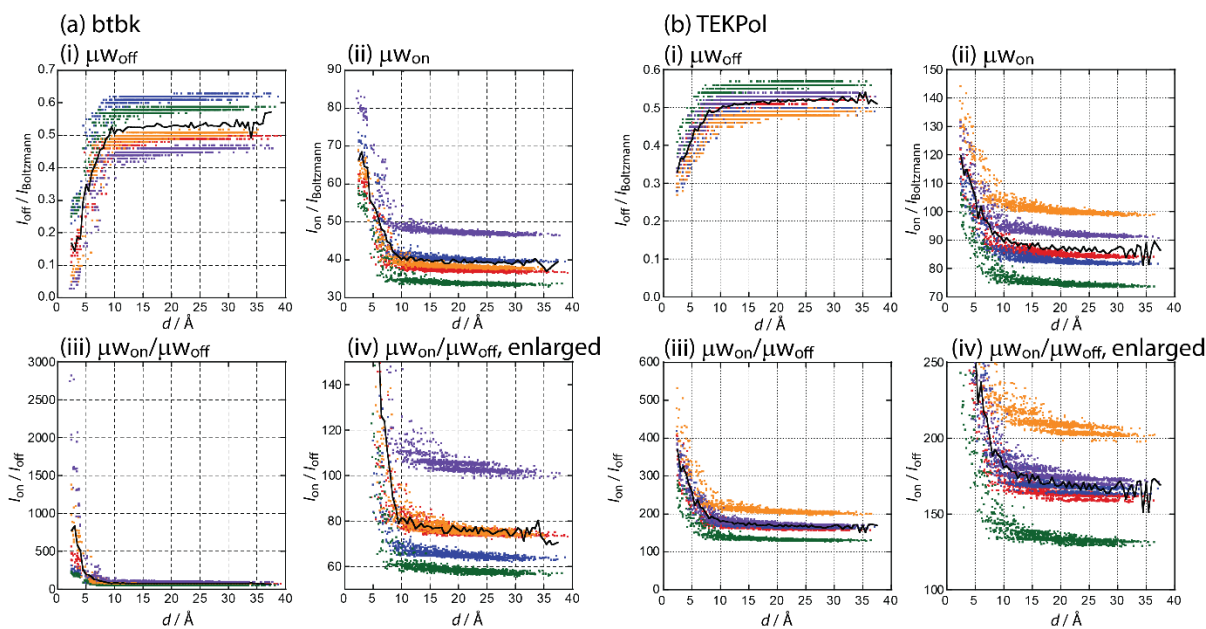
coordinates are given in the supporting information. One such unit cell structure is shown in Figure 1.



**Figure 1.** Structures of the bTbK (a) and TEKPol (b) DNP polarizing agents. (c) Sample unit cell taken from a molecular dynamics simulation of a 16 mM TCE solution of the bTbK polarizing agent. The non-H atoms of the solvent molecules were removed for clarity.

The steady-state polarizations of all nuclei were then calculated for each of these 10 structures with and without  $\mu\text{w}$  irradiation at a MAS rate of 10 kHz. The converged DNP enhancements, on/off enhancements, and cross-effect-induced depolarization factors for bTbK and TEKPol are plotted in Figures 2a and 2b, respectively. Each point represents a single  $^1\text{H}$  spin in the unit cell, and the polarizations are plotted as a function of the distance to the nearest unpaired electron. The five colors correspond to five different snapshots of the solution, with the moving average polarizations shown as the black curve. Differences in polarization between the five

structures are predominantly due to changes in the biradical's conformation. Note that only the molecular structure and  $T_{1e}$  values differed for the calculations performed on the two radicals.



**Figure 2.** Calculated steady-state polarizations of the  $^1\text{H}$  nuclei in TCE solutions of the bTbK (a) and TEKPol (b) radicals with the  $\mu\text{w}$  switched off (i) and on (ii), as a function of the distance between the nucleus and its nearest electron spin. (iii) shows the ratio of the data in (i) and (ii) and corresponds to the expected experimental on/off DNP enhancement factor; the congested portions of both curves are enlarged in (iv). Each color corresponds to a different spin system obtained from snapshots of the MD simulation. Solid black lines correspond to the averages of all spin systems. The MAS frequency was 10 kHz in all cases and the strength of transverse  $\mu\text{w}$  field was 850 kHz.<sup>49</sup>  $T_{1e}$  values were of 9.26 and 41.6  $\mu\text{s}$  for bTbK and TEKPol, respectively and the bulk nuclear  $T_1$  was of 3.5 s, as determined experimentally.

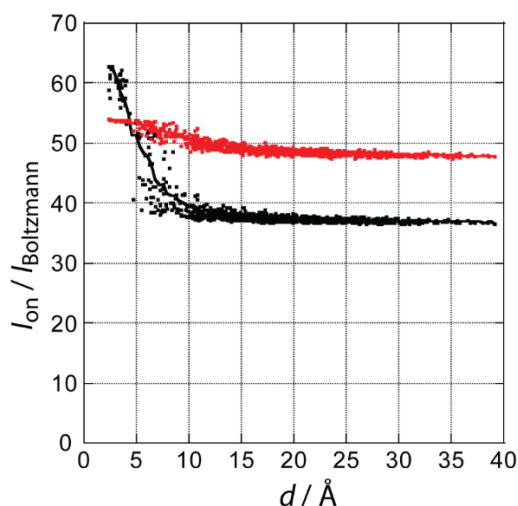
The depolarization factors converge at roughly 0.5 for both samples, as was observed experimentally.<sup>50</sup> Average ‘on/off’ DNP enhancements over five conformations were  $76 \pm 18$  and  $171 \pm 27$  for bTbK and TEKPol, respectively (the error being the standard deviation of the enhancements of the five conformations). Since the  $^1\text{H}$  spins nearest to the radical cannot be observed experimentally due to paramagnetic relaxation, we excluded 100 of such nearest spins from calculations of the average DNP enhancement. These average on/off DNP enhancements are in excellent agreement with the experimental values of 62 and 205;<sup>50</sup> note that this agreement may



improve by considering a greater number of conformations. The accuracy of the simulations suggests that our LCL-LR method could be applied to the *in silico* design of DNP polarizing agents.

In addition, the calculations reveal a key aspect of the DNP behavior of the radicals that, along with  $T_{1e}$ , is responsible for the observed differences in their DNP enhancements. Specifically, for both radicals the polarizations with  $\mu_w$  ( $I_{on}/I_{Boltzmann}$ ) are very large for spins within a few Å of the radicals; however, the polarization and enhancements rapidly drop off and equilibrate at distances greater than 10 Å. Additionally, depolarization decreases  $I_{off}$  to near zero for spins in close proximity to the radicals, which results in unusual  $I_{on}/I_{off}$  ‘enhancements’ exceeding 2500 for the most proximate spins. These features are generally ascribed to the so-called spin diffusion barrier. This barrier arises because spins near the radical are shifted by a strong hyperfine interaction, which reduces the probability of energy-conserving spin flip-flop events (i.e. spin diffusion). We confirmed this by performing a simulation with the hyperfine shift “turned off” which completely removed the initial drop (see Figure 3). Prior to our work, the severity of this drop had not been quantitatively predicted. Notably, the visualizations in Figure 2a(ii) and 2b(ii) show that the drop in polarization is considerably less for TEKPol than for bTbK (30% vs 44%), as is the severity of the depolarization of the nearest  $^1\text{H}$ . Since the nuclear  $T_1$  values were identical for both systems, the observed increased ability of the hyperpolarization to escape TEKPol compared to bTbK must originate from faster spin diffusion away from the core. It thus seems that the phenyl-cyclohexyl substituents in TEKPol play a crucial role in providing uninterrupted spin diffusion paths from the radicals that utilize only stronger intramolecular  $^1\text{H}$ - $^1\text{H}$  dipolar couplings (1.7-2.5 Å), as opposed to the weaker intermolecular couplings in TCE (>3

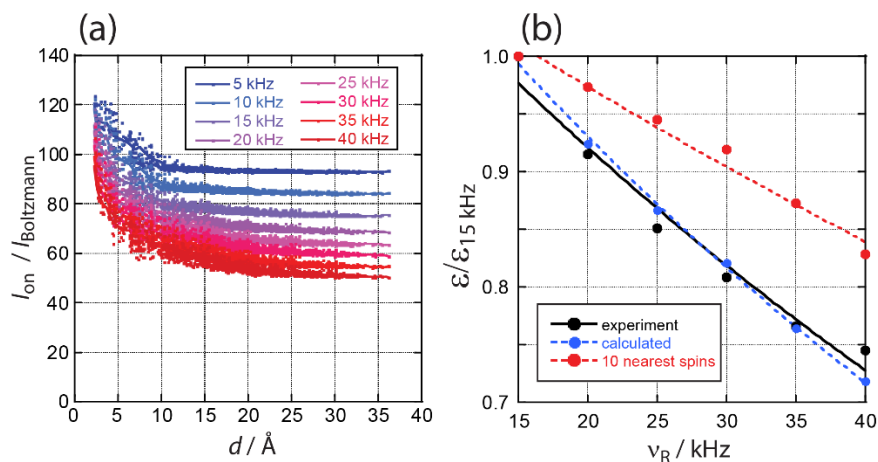
Å ); this in turn accelerates spin diffusion through and away from the barrier. We foresee this to be a feature that should be targeted in the design of next-generation polarizing agents.



**Figure 3.** Comparison of the  $^1\text{H}$  polarizations calculated for one of the bTbK/TCE solutions with hyperfine shifts included (black) or omitted (red) with the  $\mu\text{w}$  turned on. Simulation parameters matched those used in Figure 2.

An additional feature that this level of theory is able to model, that is difficult to reproduce phenomenologically, is the MAS rate dependence of the enhancement factors. This is because there are 3 factors that contribute to this dependence, only the first of which can be easily calculated using lower levels of theory. 1) Electron-electron dipolar rotor events are less efficient at faster MAS, which leads to difficulties in maintaining a polarization difference between the two electrons and lowers enhancements;<sup>12,23</sup> 2) spin diffusion is slowed at faster MAS, leading to less polarization reaching the bulk.<sup>24</sup> and 3) spin diffusion *within* the spin diffusion barrier is accelerated due to the increased frequency-matching of otherwise hyperfine-shifted sites.<sup>24,51</sup> For one of the TEKPol conformations in Figure 2b we have thus repeated the calculation for MAS rates ranging from 5 to 40 kHz (the expected accurate range for LR-LCL); the resulting data are shown in Figure 4. As can be seen, the simulations predict a monotonic drop in DNP efficiency as the spinning frequency is increased (Figure 4a), and this drop agrees quantitatively with our

previous measurements<sup>24</sup> (Figure 4b). Note that if we instead focus on the 10 nearest spins from the radicals (red points in Figure 4b), we observe a much smaller drop in enhancement than was measured experimentally, highlighting the necessity of simulating realistically sized spin systems from first principles.



**Figure 4.** MAS rate dependence of the nuclear polarizations for all  $^1\text{H}$  spins as a function of their distance from their nearest radical (a). Different spinning frequencies are represented in different colors, as indicated in the legend. The experimental (black) and theoretical (blue) relative average DNP enhancements of the  $^1\text{H}$  spins are plotted in (b). The average enhancements of the 10 nearest  $^1\text{H}$  spins in the simulation are shown in red. Simulation parameters matched those used in Figure 2. Experiments were performed with a 1.3-mm rotor filled with a 16 mM TEKPol TCE solution.<sup>24</sup>

As a last case we chose to simulate the DNP-MAS experiment in an inorganic material so as to probe the generality of our approach and whether this type of simulation can be applied to understanding DNP in cases where  $^1\text{H}$  spin diffusion cannot be used to propagate the polarization. We recently reported that large direct  $^{29}\text{Si}$  DNP enhancement of 410 could be obtained in fused quartz that had been irradiated with  $\gamma$ -rays to introduce paramagnetic defects.<sup>52</sup> To represent this structure we used a cristobalite supercell<sup>53</sup> with dimensions of  $\sim 164.1 \text{ \AA}$  to match the 0.3 mM radical concentration, in which the 4882 of the Si positions were randomly assigned to  $^{29}\text{Si}$  (natural abundance of 4.7%). As in the case of  $^1\text{H}$ , this procedure was repeated five times with different

$^{29}\text{Si}$  substitutions. The EPR and NMR parameters were set to the experimentally measured values (see supporting information), and DNP utilized a solid effect (SE) mechanism.

The calculated DNP enhancements for the 4882  $^{29}\text{Si}$  spins in the five fused quartz models are plotted in Figure S4 as a function of the distance from the radical. As can be seen, the gradient in polarization is very steep, with the nearest  $^{29}\text{Si}$  spins having polarizations near the theoretical maximum of  $\sim 3300$  and the more distant nuclei having polarizations that are 1-2 orders of magnitude lower. The spin diffusion barrier is again shown to be a dominant force in determining the bulk enhancements. For instance, one of the model structures featured a  $^{29}\text{Si}$  substitution in the nearest neighbor to the radical site. This  $^{29}\text{Si}$  spin featured an enhancement of nearly 3300, but had the second lowest average DNP enhancement of the series, due to that spin's inability to propagate its polarization to other spins. Averaging the calculated enhancements of the 24,410 spins in the five structures, we obtained an enhancement factor of  $322 \pm 155$  which is in very close agreement with the experimental value of 410, thus demonstrating the generalizability of this form of *ab initio* DNP simulation, and hence its broad applicability to the study of materials.

In summary, we have developed an *ab initio* DNP simulation theory that marries the speed and accuracy of the Landau-Zener DNP and LR-LCL spin diffusion models with our Monte Carlo simulation approach to calculating DNP enhancements in large systems consisting of thousands of nuclear spins. This new framework enables, for the first time, the calculation of DNP enhancements from first principles in realistically sized periodic spin systems. We obtained quantitative agreement, including agreement in MAS-rate dependence, with experimental DNP enhancements in protonated solutions as well as inorganic materials. The simulations additionally revealed that slower electron relaxation is not the sole reason for the superior performance of TEKPol and other polarizing agents with higher molecular weights. These radicals are more

capable of pushing polarization outside of the spin diffusion barrier, which in turn leads to a greater polarization of observable bulk nuclei. We expect that this revelation will be useful in guiding the design of next-generation polarizing agents and will help to further increase the sensitivity of MAS-DNP NMR experiments in the near future.

## Associated Content

**Supporting Information.** Detailed theory for the LR-LCL and DNP simulations, computational (MD and DNP) as well as experimental (NMR and EPR) details, and tables of the spin coordinates, Euler angles, and calculated DNP enhancements from all simulations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## Acknowledgements

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