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NMR Spectroscopy

Rational Design of Dinitroxide Polarizing Agents for Dynamic Nuclear Polarization to Enhance Overall NMR Sensitivity

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Abstract: We evaluate the overall sensitivity gains provided by a series of eighteen nitroxide biradicals for dynamic nuclear polarization (DNP) solid-state NMR at 9.4 T and 100 K, including eight new biradicals. We find that in the best performing group the factors contributing to the overall sensitivity gains, namely the DNP enhancement, the build-up time, and the contribution factor, often compete with each other leading to very similar overall sensitivity across a range of biradicals. NaphPol and HydroPol are found to provide the best overall sensitivity factors, in organic and aqueous solvents respectively. One of the new biradicals, AMUPolCbm, provides high sensitivity for all three solvent formulations measured here, and can be considered to be a "universal" polarizing agent.

Introduction

Improvements in the sensitivity of nuclear magnetic resonance (NMR) spectroscopy have consistently led to the expansion of its application in chemistry, biology and medicine.[1] To this end, the last 20 years have seen considerable renewed interest in capitalizing on dynamic nuclear polarization (DNP) to enhance sensitivity in both liquid and solid-state NMR experiments. DNP takes advantage of the high gyromagnetic ratio (γ) of electron spins by transferring their larger spin polarization to nearby nuclear spins, resulting in considerable NMR signal enhancement factors.[1–2] In the last decade, DNP enhanced solid-state NMR has grown into a particularly powerful technique.[3] It has been used to address previously inaccessible systems, ranging from nanoparticles[4] and catalysts[5] to battery,[6] photovoltaic,[7] and building materials,[8] nucleic acid arrays,[9] proteins,[10] cells[11] and complex drug formulations.[12]

High resolution solid-state magic angle spinning (MAS) DNP typically involves microwave induced transfer of polarization from electrons to nearby nuclear spins in a frozen solution at $\approx$100 K containing a radical polarizing agent (PA),[3] followed by ^{1}H-^{1}H spin diffusion into the bulk of the sample.[13] At the high magnetic fields typically used in NMR today (e.g. above 9 T), cross effect[14] is usually the most efficient transfer mechanism.[2c] Cross-effect requires two unpaired electron spins and a nuclear spin, and consequently, efficient biradical polarizing agents are at the heart of MAS DNP.

Since the first example of using a nitroxide biradical for MAS DNP, with the introduction of bT2E by Hu et al. in 2004,[15] a large number of biradicals have been developed with the aim of improving DNP performance at fields up to 9.4 T.[11i,16] This has resulted in ^{1}H DNP enhancements (ε_H) at 9.4 T and $\approx$100 K increasing from around a factor of 70 for TOTAPOL[16g] to up to 330 for HydroPol.[16k] This improvement has been achieved by addressing a series of design parameters in the molecular structures that improve the intrinsic DNP properties, including the optimal relative orientation of the electron *g*-tensors,[16b,e,17] increased electron spin saturation factors,[16c,f,h] balanced electron spin couplings,[18] and optimal conformational properties.[16k] For example, recently, we showed that strong electron-nuclear hyperfine couplings and a proton-dense environment provide pathways to rapidly transport hyperpolarization away from the biradical molecule into the bulk of the sample. Using this knowledge, we developed a new biradical NaphPol,[16m] which provided the highest ^{1}H DNP enhancements at 9.4 T in organic solvents (specifically 1,1,2,2-tetrachloroethane (TCE))[19] to date (ε_H=249).

We note that the DNP enhancement (ε) is not the only parameter that needs to be taken into account to determine the overall NMR sensitivity (*S*). Additional factors include

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the build-up time of the polarization (T_B), the quenching due to the presence of the paramagnetic radical, and these have also been discussed in detail.[16h,20] For example, the AsymPol family of biradicals was shown to yield good overall sensitivity due to a short polarization build-up time compensating for a relatively low DNP enhancement factor (as $S \propto \varepsilon/T_B^{-1/2}$).[16j,l]

Given all these factors, it is difficult to assess relative performance of the different biradicals available today. Such an assessment would be useful to guide future directions, and especially in order to break the current glass ceiling in enhancements that appears at around $\varepsilon_H \approx 300$, whereas the theoretical limit is $\varepsilon_H = 658$.

Here, we provide a systematic evaluation of the overall sensitivity gains provided by a series of eighteen nitroxide biradicals (Figure 1) at 9.4 T and 100 K, including eight biradicals that are introduced here for the first time. Surprisingly we find that several of the currently available radicals yield overall sensitivity factors that are very similar. One of the newly introduced radicals, dubbed AMUPolCbm, provides performance equal to or better than this group in both organic and aqueous solvents. Finally, NaphPol and HydroPol provide significantly better (by ≈20 %) overall sensitivity factors than the other radicals tested here, in organic and aqueous solvents respectively.

Results and Discussion

The chemical structures of the eighteen biradicals studied in this work are shown in Figure 1. Depending on their solubility we have evaluated the DNP performance of the biradicals in standard glass-forming matrices used for DNP, including TCE, 6:3:1 (v:v:v) d_8-glycerol:D_2O:H_2O and 6:3:1 (v:v:v) d_6-DMSO:D_2O:H_2O. The latter two formulations are hereafter referred to as glycerol/water and DMSO/water respectively.

In addition to 10 previously introduced state-of-the-art biradicals, here we introduce 8 newly synthesized radicals. The biradicals ABK and ABU are based on the bTbK[16b] and bTurea[21] linkers, respectively, where the TEMPO monoradical moiety is replaced with an ABNO moiety (9-Azabicyclo[3.3.1]nonane *N*-Oxyl). The ABNO moiety is a less hindered radical, and the monoradical yields similar DNP enhancements as compared to TEMPO.[22] C-bcTol is a biradical with a similar framework to bTurea or PyPol,[23] but where the cyclohexyl groups substituting on the TEMPO ring are locked into a closed conformation by the presence of OH groups. bMTbK is a methyl substituted version of bCTbK.[16c] Finally, TEKPolCbo is a biradical with a carbonate linker and AMUPolCbm, PyPolCbm, TEKPolCbm, are biradicals with a carbamate linker to compare with their corresponding namesake counterparts.

In order to obtain clear indications on the effects of structural and magnetic parameters in the multidimensional problem of designing dinitroxides for cross effect DNP, the modification of one parameter, e.g. spin exchange coupling (*J*), without affecting the other parameters such as the relative orientation of the *g*-tensors, the electron relaxation, the dipolar couplings, and the hyperfine couplings, looks appealing when chemically feasible. The analysis of the linker composition on the spin exchange in rigid dinitroxides such as bTurea and bTcarbonate derivatives has shown that spin exchange 'conductivity' of N atoms is lower than that of O atoms, with *J* values of 52 and 85 MHz respectively.[24] The amplitude of spin exchange coupling was proposed to contribute to the cross effect polarizing mechanism, the build-up time and the depolarization process.[25] PyPolCbm and AMUPolCbm have been synthesized to evaluate the effect of increasing *J* values on the DNP properties in the PyPol-type series. The increase of *J* coupling was confirmed by calculating the exchange coupling from the liquid state 9 GHz EPR spectra using ROKI,[26] with *J* values of 56, 55 and 47 MHz for PyPolCbm, AMUPolCbm and AMUPol, respectively.

Samples were studied at 16 mM biradical concentrations, except in the case of AMUPol and AsymPolPOK which were studied at 8–10 mM concentrations to facilitate comparison with previous reports, and HydroPol which is limited by solubility to 10 mM. C-bcTol was studied in 8:1:1 (v:v:v) d_6-DMSO:D_2O:H_2O (referred to as 80 % DMSO/water below) due to its low solubility in the standard (60 %) DMSO/water formulation. Details of the DNP experiments are given in the Experimental section in the SI.

In the following, we measure three key parameters that provide the main contributions to overall sensitivity in DNP enhanced MAS NMR experiments.[16h,20a] Specifically, we measure the ^{1}H DNP enhancement (ε_H), the build-up time of the polarization (T_B), and the degree of signal quenching due to the presence of the paramagnetic radical in the sample, i.e. the contribution factor (θ). The sensitivity in the observed spectra due to these three factors is proportional to the factor:[16h,20a]

$$S = \varepsilon \times \theta \times T_B^{-1/2} \quad (1)$$

We note that the absolute sensitivity is also proportional to other factors, including the sample volume, and linewidths and lineshapes, but these sample dependent factors are not required here in the comparison of radical efficiency.

We immediately note from Eq. (1) that there are three pathways to obtaining higher sensitivity through more efficient radical PAs. The pathway that has been of most focus is to increase ε, where ε is the ratio of the integrated signal intensities in the spectra recorded with and without microwaves. However, recently it has been shown that biradicals developed to have short signal build-up times (T_B) can compensate for lower values of ε.[16j,l] Similarly, another path to increasing sensitivity would be to increase the contribution factor (θ). The contribution factor has been extensively discussed, and in essence for cross effect DNP there are two main contributions, $\theta = \theta_{quench} \times \theta_{depol}$ where θ_{quench} takes account of the loss of signal due to paramagnetic bleaching near the biradical,[20a,27] and θ_{depol} takes account of the loss caused by a reverse DNP effect in the microwave off spectrum.[16j,20b,c]

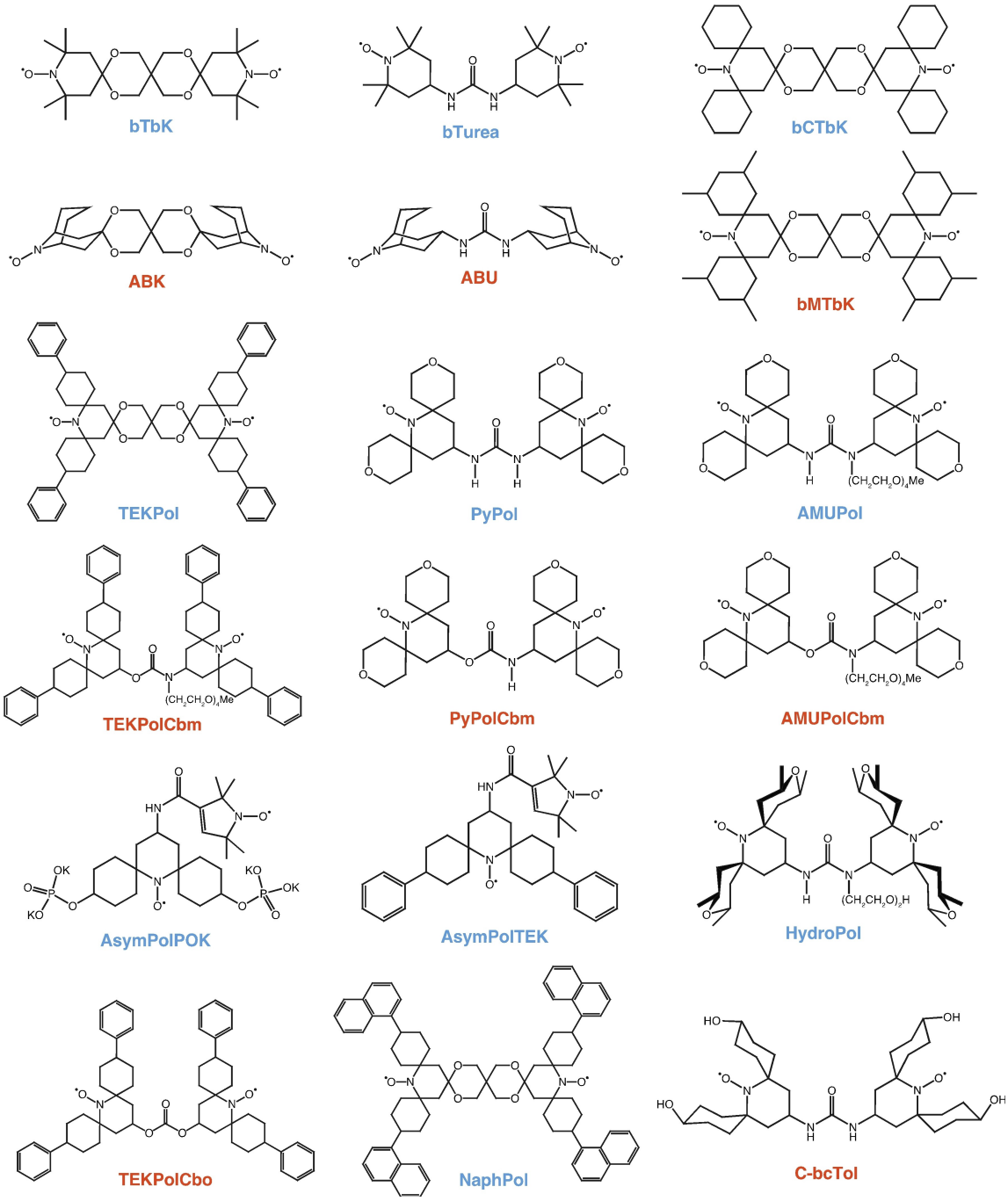

Figure 1. Structures of the biradicals studied in this work. The newly reported biradicals in this work (ABU, ABK, AMUPolCbm, PyPolCbm, bMTbK, TEKPolCbm, TEKPolCbo and C-bcTol), are indicated in orange, while the previously reported or commercially available biradicals (bTbK, bCTbK, bTurea, PyPol, AMUPol, HydroPol, TEKPol, AsymPolPOK, AsymPolTEK and NaphPol) are indicated in blue. Details regarding the syntheses of the new biradicals are provided in the SI.

Generally speaking, the three factors in Eq. (1) are competing. In the examples developed so far, increasing ε usually also decreases θ and increases T_B. Similarly, decreasing T_B usually leads to a decrease in ε. The objective of rational design of polarizing agents is to find new molecules where the advantageous factors outweigh the disadvantageous factors.

In order to evaluate these factors directly, Figure 2 compares the measured ^{1}H DNP enhancements, build-up times and contribution factors of all the biradicals. Figure 3 shows the overall sensitivity factors (S) for all the biradicals.

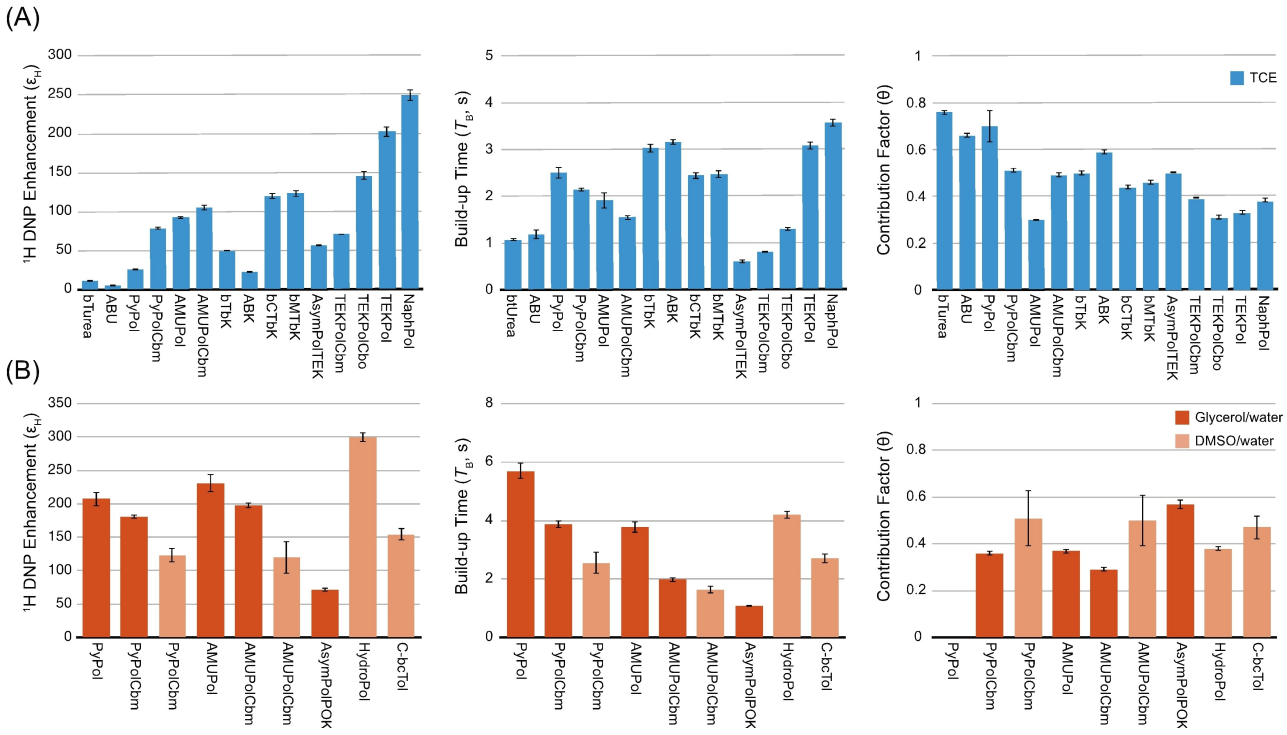

Figure 2. Comparison of the ^{1}H DNP enhancements (ε_H), build up times (T_B), and contribution factors (θ) of the biradicals in (A) TCE, and (B) water-based solvents at ≈100 K and 9.4 T. In (B), performance in 6:3:1 (v:v:v) d_8-glycerol:D_2O:H_2O (dark orange) and 6:3:1 (v:v:v) d_6-DMSO:D_2O:H_2O (light orange) are compared. C-bcTol was studied in 8:1:1 (v:v:v) d_6-DMSO:D_2O:H_2O. θ is calculated as the ratio of the normalized solvent signal intensities in the presence and absence of the biradical. Details of the measurements are given in the experimental section.

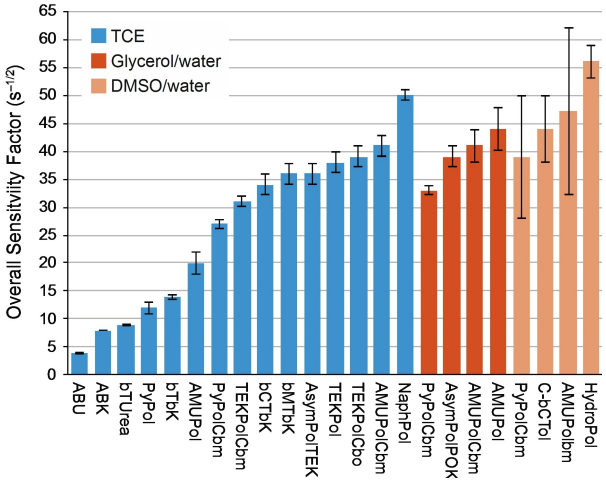

Figure 3. Overall sensitivity factors (*S*) provided by the biradicals in different solvents. *S* takes into account the DNP enhancement (ε), the contribution factor (θ) and the build-up time (T_B) ($S = \varepsilon \times \theta \times T_B^{-1/2}$).

Overall Sensitivity

We immediately see a quite remarkable feature in Figure 3, that despite considerable variations in ε, θ and T_B seen in Figure 2, there is a group of state-of-the-art biradicals that have very similar overall performance. For example, in TCE the overall sensitivity factors of bCTbK,[16c] AsymPolTEK,[28] and TEKPol,[16f] only vary within 12 %. In TCE, the new radicals bMTbK and TEKPolCbo join this group. Notably, the new radical AMUPolCbm performs slightly better (8 %) than TEKPol. We also see that in TCE the recently introduced biradical NaphPol[16m] performs significantly better than the others (32 % better than TEKPol).

A similar feature is seen for the PAs that are soluble in aqueous media. Notably in glycerol/water AsymPolPOK and AMUPol are only different by 13 %. The new biradical AMUPolCbm also joins this group. We note that in DMSO/water HydroPol performs significantly better than the others (20 % better than AMUPolCbm, which is only a few % better than C-bcTol).

We note that AMUPolCbm provides good sensitivity ($S > 40\ s^{-1/2}$) for all three solvent formulations considered here, and can be considered to be a "universal" PA.

In summary, it appears that using the current design strategies for nitroxide biradicals in play today, a large group of PAs can be designed that yield very similar overall DNP performance. Only NaphPol and HydroPol stand out in the collection here, and even then by only 20–30 %. It thus appears that we have reached a glass ceiling in DNP PA performance for cross effect biradicals at 9.4 T and 100 K.

In the following section, we discuss some of the competing factors that lead to the observed equilibration in overall performance.

Factors Contributing to the Overall Sensitivity

Enhancements & Build-Up Times

Perhaps the most interesting feature in the plots of Figure 2 is that radicals that were designed primarily to enhance ε_H, such as TEKPol or AMUPol, also tend to have longer build-up times and lower contribution factors. Conversely, radicals which were designed primarily to have short build-up times, such as AsymPolPOK and AsymPolTEK, also tend to have low enhancements. So far, it appears non-trivial to design a molecule that will simultaneously have both short build-up times *and* high enhancements. The mutual competition between enhancement and build-up time appears to be the main factor that leads to similar overall performance across a range of biradicals.

For example, a hypothetical molecule with a build-up time of 1.0 s (similar to AsymPol family) and an enhancement of 230 (similar to AMUPol), would yield an *S* of 115 (with a contribution factor of 0.5), which is 3 times larger than the best performing biradical so far!

In more detail, Figure 2A shows the results for the biradicals that are soluble in TCE.

The new biradicals ABK and ABU yield $\varepsilon_H = 23$ and 6, respectively, which are both lower than their counterparts bTbK ($\varepsilon_H = 50$) and bTUrea ($\varepsilon_H = 12$). While both pairs of radicals show similar T_B, ABU and bTUrea have much smaller T_B of 1.2 and 1.1 s, respectively, in comparison to bTbK ($T_B = 3.0$ s) and ABK ($T_B = 3.2$ s). We see that the short T_B correlates with a high contribution factor and lower ε_H. However, neither of these new radicals provides overall performance close to the state-of-the-art systems.

A similar observation can be made in case of the bulkier biradicals TEKPol ($T_B = 3.1$ s) and AMUPol ($T_B = 1.9$ s), where the biradical with the urea linker again shows a shorter T_B in comparison to that with a bis-spiroketal linker; this is mostly ascribed to stronger dipolar and exchange couplings between the two unpaired electrons which is expected to accelerate DNP build-up.[16j,29]

For the new carbamate-based radicals AMUPolCbm ($\varepsilon_H = 105$, $T_B = 1.6$ s) and PyPolCbm ($\varepsilon_H = 79$, $T_B = 2.2$ s), we make two observations in comparison to the corresponding AMUPol ($\varepsilon_H = 93$, $T_B = 1.9$ s) and PyPol ($\varepsilon_H = 26$, $T_B = 2.5$ s): (1) the carbamate-based radicals show a slightly shorter T_B which is likely due to the small reduction in linker length in the carbamates; (2) PyPolCbm shows a much higher enhancement than PyPol, which is possibly due to changes in the relative *g*-tensor orientations. AMUPolCbm has an overall performance which puts it among the best performing radicals.

TEKPolCbo introduces another new linker (carbonate), and we see that it yields better performance than TEKPolCbm in TCE (29 %). These results with the carbamate and the carbonate linkers are promising and set the stage for further design of biradicals with these linkers, and for the potential use of these radicals at higher magnetic fields (which will be discussed elsewhere).

The bTbK series of biradicals which has led to the design of bCTbK, TEKPol, and more recently, NaphPol are some of the most efficient biradicals in organic solvents. Consequently, there is interest in further improving their efficiency by improving the DNP enhancements, minimizing depolarization and reducing build-up times. To this end, bMTbK is introduced ($\varepsilon_H = 123$, $T_B = 2.5$ s) which shows nearly identical enhancements and build-up times as bCTbK ($\varepsilon_H = 120$, $T_B = 2.5$ s). This observation is somewhat unexpected given the addition of methyl groups in bMTbK which are known to reduce electron and nuclear spin relaxation times. However, unlike bTbK where the methyl groups are in close proximity to the nitroxide group, the methyl groups in bMTbK are far away and therefore may not significantly influence the electron spin relaxation times (especially the electron T_2), as discussed further below.

Interestingly, the previously reported b-3,5-diMePyTbK has a similar structure to bMTbK, but with a slight difference; in b-3,5-diMePyTbK, the cyclohexyl substituents are replaced by tetrahydropyran groups (in effect, only four methylene groups are replaced by oxygen atoms).[16h] However, b-3,5-diMePyTbK shows a significantly higher $\varepsilon_H \approx 200$ while the build-up times are also longer ($T_B = 3.8$ s). These observations highlight the impact of small structural changes on the observed DNP properties, and the need for more detailed EPR characterization of these systems.

Finally, we studied TEKPolCbm ($\varepsilon_H = 71$, $T_B = 0.8$ s) which showed a much smaller enhancement and a shorter build-up time in comparison to TEKPol ($\varepsilon_H = 202$, $T_B = 3.1$ s), in good agreement with our hypothesis that the carbamate linker provides stronger inter-electron magnetic couplings resulting in faster T_B. This "short build-up" behaviour is reminiscent of the AsymPol series of biradicals[16j,l] and therefore we have also evaluated the performance of AsymPolTEK at 9.4 T.[28] Not surprisingly, as previously shown with AsymPolPOK,[16j,l] AsymPolTEK ($\varepsilon_H = 57$, $T_B = 0.6$ s) shows the shortest T_B of the three. However, the ^{1}H enhancement is also smaller than for TEKPolCbm. TEKPolCbo also has a significantly shorter build-up time ($T_B = 1.3$ s) than TEKPol, but the loss in enhancement ($\varepsilon_H = 146$) is not as significant as for TEKPolCbm, leading to overall performance that is very similar to TEKPol in this case. While the short T_B for these radicals can be explained based on the inter-electron magnetic couplings,[16j,29a] it is harder to provide a rationale for the accompanying reductions in enhancements. One possible explanation is the influence of electron cross relaxation as proposed previously.[30]

Figure 2B compares the factors contributing to overall performance of the water-soluble biradicals in DMSO/water and glycerol/water matrices.

Clearly, HydroPol provides the highest enhancement amongst all the biradicals, whereas AMUPol, PyPol, AMUPolCbm and PyPolCbm all show relatively high enhancements of between 180–240.

On the other hand, as shown previously,[16j] AsymPolPOK displays a much lower ε_H of 71, but in contrast it also shows the shortest T_B of 1.1 s, in the entire series of water-based biradicals. The short T_B is here able to almost completely compensate for the low enhancement, leading to overall sensitivity factor that is nearly the same as AMUPol

or AMUPolCbm, i.e., the enhancement for AsymPolPOK is a factor of 3.2 less than for AMUPol, but the overall sensitivity factor of AsymPolPOK is only 13 % lower than AMUPol. This observation is consistent with that of AsymPolTEK in TCE.

Furthermore, in analogy to the observations made in TCE, AMUPolCbm and PyPolCbm show shorter T_B values of 2.0 and 3.9 s, respectively, in comparison to AMUPol ($T_B = 3.8$ s) and PyPol ($T_B = 5.7$ s) in glycerol/water. All of these observations highlight again the role of stronger inter-electron magnetic couplings to reduce T_B. While strong e-e couplings may influence the cross-effect rate,[29a] strong hyperfine couplings and a proton-dense environment are still necessary to rapidly transport the hyperpolarization which will reduce DNP build-up times.[16m]

Contribution Factors

Finally, we note that paramagnetic signal bleaching and depolarization caused by cross effect biradicals under magic angle spinning are important factors to take into account while quantifying the DNP efficiency.[16h,20,27b] Here, the contribution factor (θ) of all the biradicals were measured as the ratio of the normalized signal intensities in biradical solutions and pure solvents ($\theta = I_r/I_0$). Here we do not disentangle the contributions from bleaching *vs.* depolarization, which has previously been done by other authors.[16j]

The values of θ measured here for bTbK, bCTbK and TEKPol closely match the previous measurements by Kubicki et al.[16h] As expected, and as has been observed previously,[16m] there is a strong correlation between the contribution factor and the enhancement (Figure S1), with high enhancements leading to lower contribution factors.

Electron Spin Relaxation

Previous studies have observed a strong correlation between DNP enhancement factors and the electron spin relaxation parameters of radicals, with longer electron relaxation times typically leading to higher DNP enhancements.[16c,h] In light of this, we measured the Q-band (35 GHz) electron spin relaxation properties of the biradicals in different solvents (Figure 4) for the radicals studied here. Overall, Figure 4A shows a clear correlation between the DNP enhancement factor (ε_H) and the saturation factor ($T_{ir} \times T_m$) for the biradicals studied here. Consistent with previous reports, larger saturation factors afford higher efficiency of the electron saturation, resulting in higher enhancements. We note that this correlation extends to the radicals that have short electron relaxation times, and which yield significantly lower enhancements such as AsymPolPOK, AsymPolTEK and TEKPolCbm.

It is then interesting to see that the DNP build-up times (T_B) are also strongly correlated with the electron spin longitudinal relaxation time (T_{ir}) (Figure 4B). Short electron T_1 relaxation times will result in faster paramagnetic relaxation of nearby nuclear spins, thereby impacting the

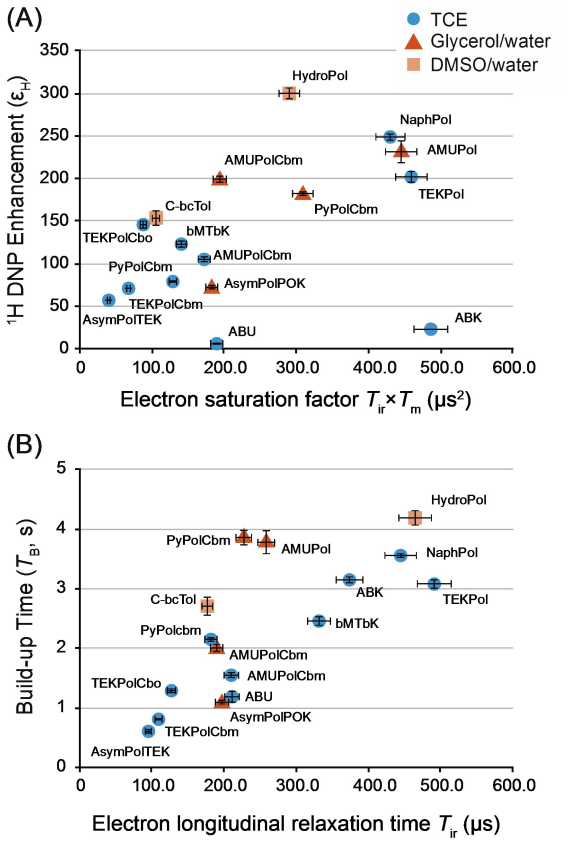

Figure 4. A) DNP enhancements as a function of saturation factor ($T_{ir} \times T_m$), and B) DNP build-up time as a function of electron longitudinal relaxation time (T_{ir}) for selected biradicals in different solvents. EPR measurements were conducted at Q-band, at 105 K.

overall build-up times. This provides another way of looking, this time through the lens of the electron spin relaxation, at the observation established above that when build-up times are short, enhancements are low.

The obvious outliers in Figures 4A are ABK and ABU, which have very low enhancements in comparison to their saturation factors. While the exact cause of the low enhancements is unclear, it is possible this may be due to the lack of optimal relative *g*-tensor orientations. On the other hand, HydroPol shows an anomalously low saturation factor in regard to its enhancement. However, we note that the electron spin T_{ir} for HydroPol is actually as long as expected (Figure S5) and correlates with the other radicals, but that only the T_m is significantly shorter. We ascribe this primarily to the presence of the methyl groups decorating the tetrahydropyran rings. On the other hand, AsymPolPOK, PyPolCbm, AMUPolCbm and AMUPol show similar electron spin T_{ir} values in glycerol/water, but significantly different electron phase memory times (T_m) (Figure S5, Table S4). While the presence of nearby methyl groups in AsymPolPOK may reduce T_m, it is possible that differing electron-electron distances results in different T_B and ε_H values (Figure 4 and Figure S5).

Recent interest to perform in-cell DNP NMR[11g,31] has prompted the design of robust polarizing agents that remain stable under the harsh reducing conditions of cellular environments at room temperature. While biradicals with so-called "closed" or sterically hindered conformations were shown to be stable in reducing environments, they offered lower DNP enhancements and overall sensitivity as compared to their open counterparts.[16k] Here we introduce C-bcTol which is the closed conformer of the previously reported bcTol biradical.[23] Notably, C-bcTol yields a sizeable enhancement ε_H of 154, which is the highest enhancement seen so far in comparison to the series of closed biradical conformers reported previously.[16k] Importantly, the combination of the high enhancement with a build-up time of $T_B = 2.7$ s and the contribution factor yields an overall sensitivity factor of 44 which is only 7 % lower than AMUPolCbm in DMSO/water. While many of the previously reported closed conformers have methyl groups in close proximity to the nitroxide moieties, C-bcTol has hydroxyl groups which may differently influence the solvent accessibility and reduce electron spin relaxation effects. While this rationale is supported by the comparison of monoradicals C-MbPyTol ($\varepsilon_H = 17$, $T_B = 1.5$ s) and C-MPhTO ($\varepsilon_H = 91$ and $T_B = 2.5$ s),[16k] the detailed reasons for the improved efficiency of C-bcTol will be elucidated in a future publication.

Conclusion

We have systematically evaluated the overall DNP NMR sensitivity gains provided by a series of eighteen nitroxide biradicals at 9.4 T and 100 K, including eight biradicals that are introduced here for the first time. We find that although biradicals can significantly differ in the obtained enhancements and build-up times, these factors often compete, and many radicals yield similar overall NMR sensitivity. NaphPol and HydroPol provide the best overall sensitivity factors obtained here, in organic and aqueous solvents respectively. One of the newly introduced radicals, dubbed AMUPolCbm, provides good sensitivity ($S > 40\ s^{-1/2}$) for all three solvent formulations considered here, and can be considered to be a "universal" PA.

The new radicals include new linker motifs based on carbamate and carbonate moieties, which perform well with intermediate build-up times, and open up new design possibilities for the future.

Another new radical, C-bcTol, which has a closed conformation and is more resistant to reducing conditions, yields the highest enhancement seen so far in the closed class of radicals.

As expected, and as has been discussed extensively previously, we find that DNP enhancements and build-up times are both correlated to electron spin relaxation times, and that radicals with higher DNP enhancements also show large depolarization effects, resulting in low contribution factors.

We note that different radicals are used to obtain the best performance at higher fields (e.g. 18–28 T),[32] and that different considerations apply to the signal enhancements in impregnated solids polarized by relay,[3b,13b,33] which will be the subject of separate comparisons, and that lower sample temperatures almost always lead to better DNP performance.[34]

In summary, it appears that using the design strategies in play today, a large group of PAs can be designed that yield very similar overall DNP performance. Only NaphPol and HydroPol stand out in the collection here, and even then by only 20–30 %. It thus appears that we have reached a glass ceiling in DNP PA performance for cross effect dinitroxide biradicals at 9.4 T and 100 K, and new considerations need to be introduced to make further progress in the future. Potential future directions could include a detailed investigation on the biradicals which are exceptions in the trends discussed here (e.g. anomolous high efficiency of C-bcTol), and evaluating the sensitivity of the newly proposed biradicals at high magnetic fields.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available at the following link (https://zenodo.org/doi/10.5281/zenodo.10472538). The data are available under the CC-BY-4.0 (Creative Commons Attribution 4.0 International) license.

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