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On the limited stability of BDPA radicals

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Abstract: 1,3-Bis(diphenylene)-2-phenylallyl (BDPA)-based radicals are of interest as polarizing agents for dynamic nuclear polarization (DNP). For this purpose, a BDPA-nitroxide biradical, employing a phosphodiester linkage, was synthesized. Contrary to what is commonly assumed, BDPA-derived radicals were observed to have limited stability. Hence, the effects of various factors on the stability of BDPA radicals were investigated. Solvent polarity was found to play a significant role on degradation; a polar BDPA radical was observed to degrade faster in a non-polar solvent while non-polar radicals were more unstable in polar solvents. The rate of decomposition was found to increase non-linearly with increasing radical concentration; a 2-fold increase in concentration led to a 3-fold increase in the rate of degradation. Collectively, these results indicate that the dimerization is a significant degradation pathway for BDPA radicals and indeed, a dimer of one BDPA radical was detected by mass spectrometry.

Introduction

Nuclear magnetic resonance (NMR) spectroscopy is a versatile technique for elucidating the structures of molecules by utilizing nuclear magnetic moments.^[1] However, a shortcoming of NMR spectroscopy is its inherently low sensitivity due to low nuclear spin polarization, i.e., the small difference between the numbers of nuclear spins that are aligned parallel or anti-parallel to an external magnetic field. This is especially a challenge when trying to measure analytes with natural isotopic abundance or at low concentrations.^[2] In contrast, electrons possess a much larger spin polarization. For example, at 100 K and 9.4 T, proton spin-polarization is about 0.01%, whereas the electron spin-polarization is approximately 10%.^[3] Spin polarization of electrons is transferable to nuclei of interest through a technique called dynamic nuclear polarization (DNP), which subsequently enhances the NMR signal-to-noise ratio.^[2b, 3-4] In theory, 660- and 2600-fold enhancement can be achieved for ¹H and ¹³C, respectively with continuous-wave irradiation.^[3] In DNP experiments, stable organic radicals at mM concentration are generally included in the sample as the source of unpaired electrons and microwave irradiation is used to facilitate polarization transfer from the electrons to the nuclei.^[5]

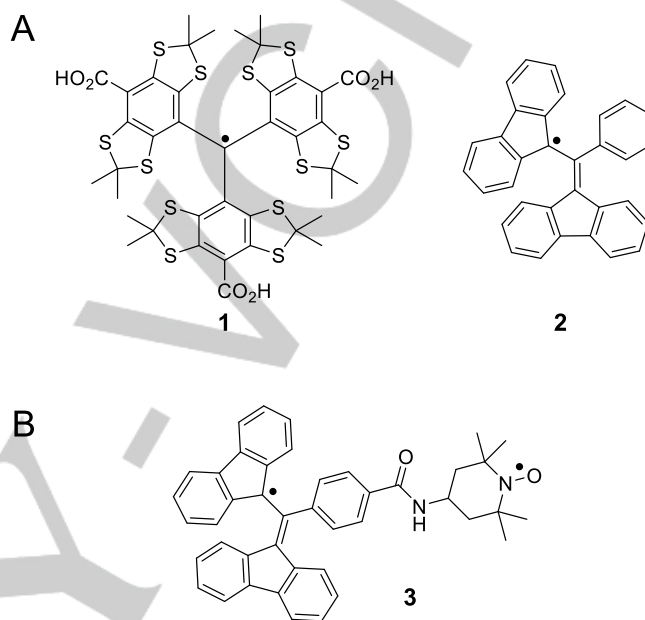


Figure 1. A. Narrow-line carbon-centered radicals, Finland trityl (1)^[13] and 1,3-bis(diphenylene)-2-phenylallyl (BDPA) (2).^[14] B. Previously reported BDPA-TEMPO biradical 3.^[17]

There are three principal mechanisms through which polarization transfer can be accomplished in solid-state NMR using magic angle spinning (MAS), namely the Overhauser Effect (OE),^[6] the Solid Effect (SE),^[7] and the Cross Effect (CE).^[7-8] The CE is the most efficient mechanism for MAS-DNP, especially at higher magnetic fields (>5 T).^[9] The ideal polarizing agent for the CE should have an electron paramagnetic resonance (EPR) spectrum consisting of two sharp lines, separated by the Larmor frequency of the nucleus to be polarized.^[7c, 10] However, there is no radical or radical pair known to possess such an EPR spectrum. Nitroxide biradicals are frequently used as polarizing agents in MAS-DNP as their EPR linewidth is approximately three-fold the proton Larmor frequency, and thus, fulfill the frequency condition for polarizing protons via the CE.^[7b, 7c, 11] The ¹H-polarization can subsequently be transferred to ¹³C or ¹⁵N via cross-polarization.^[12] Carbon-centered radicals, such as the Finland trityl^[13] and 1,3-bis(diphenylene)-2-phenylallyl (BDPA)^[14] (Figure 1A) possess a narrow EPR linewidth.^[15] Since their linewidths are narrower than the proton Larmor frequency, they cannot be used alone to polarize protons. However, when a carbon-centered radical is connected to a nitroxide, the EPR spectrum of such a heterobiradical consists of one sharp line and another much broader line, approximately separated by the proton Larmor frequency.^[9a, 10] Thus, such biradicals are closer to an ideal polarizing agent for MAS-DNP experiments that utilize the CE.

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Another advantage is that lower microwave power can be used for efficient CE, due to presence of the narrow-line, slower relaxing radical.^[9b] Such heterobiradicals also lead to significantly lower depolarization under MAS-DNP conditions, compared to most bis-nitroxides.^[7c, 16] Trityl-nitroxide or BDPA-nitroxide biradicals work especially well at magnetic fields higher than 10 T, where bis-nitroxides give lower enhancements.^[9a, 9c] A trityl-nitroxide biradical^[9a] and a BDPA-nitroxide biradical^[9c] have been shown to yield an enhancement of 65 and 64, respectively at 18.8 T using a 3.2 mm rotor. The enhancement of the latter was tripled using an 1.3 mm MAS-DNP rotor.^[9c] However, this enhancement is still far from the theoretical maximum and thus, there is still need for new polarizing agents with increased efficiency for DNP.

In this paper, we describe synthesis of a new BDPA-nitroxide biradical using a phosphodiester linker. The biradical allowed us to readily quantify the amount of biradical relative to a nitroxide monoradical by EPR spectroscopy, as previously described for the BDPA-TEMPO biradical **3** (Figure 1B).^[17] While preparing and working with BDPA radicals, it became clear that they had limited stability. This was unexpected since BDPA radicals are usually referred to as stable radicals.^[14, 18] However, as stated in the excellent review of Griller and Ingold on persistent carbon-centered radicals: "There is no doubt that the lax use of the word "stable" has introduced a freedom into discussion such that an author almost has the possibility, like Humpty Dumpty, to make "stable" mean just what he chooses."^[19] IUPAC considers the stability of a radical to be a thermodynamic property and for a carbon-centered radical, it can be defined as the energy difference between the C-H bond strength of the radical and a suitable alkane (primary, secondary or tertiary). However, IUPAC recommends the use of "persistence", which refers to a kinetic property, to describe a radical with a half-life greater than several minutes in diluted inert solvents. Keeping in mind that the notion of stable radicals could be ambiguous, Griller and Ingold advised

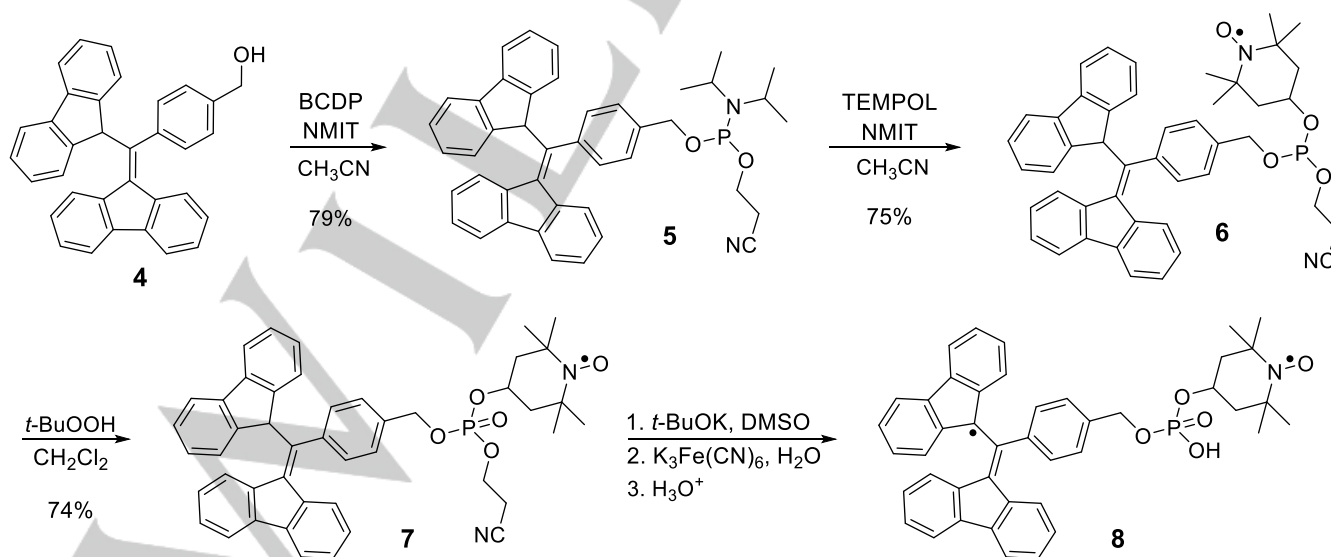
to use the term "stable" only for a radical which is highly unreactive to air, moisture etc., under ambient conditions and can be handled without further precautions similar to most organic compounds.^[19]

Understandably, many papers refer to the original report of the BDPA radical when discussing its persistence, where a footnote states that "A sample kept in air 23 years is unchanged in appearance and shows a high free-radical content."^[14] More recent reports indicate that BDPA may not be as persistent as once thought. For example, in the supporting information of a paper from 2017, it states that "We realized that after being stored in the freezer for 6 months the EPR intensity signal of sample 5 decreases in 15%."^[20] Another paper from 2018 on BDPA-derived biradicals reported that "The radicals are stable for 3 months as powders and stable in TCE solution for 2 weeks, when stored at -18 °C in both cases",^[9c] which also points to instability. Hence, we carried out a systematic investigation of the persistence of BDPA radicals under various conditions. The reaction conditions for generating BDPA radicals were also evaluated as their yields varied greatly with the methods that have been described in the literature.^[9c, 21]

Results and Discussion

Synthesis of the BDPA-nitroxide biradical

The BDPA-nitroxide biradical was prepared utilizing a phosphodiester linker. First, BDPA alcohol **4**^[22] was phosphitylated to give phosphoramidite **5**, which was subsequently reacted with 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPOL), followed by an oxidation to give phosphodiester **7** (Scheme 1). The corresponding BDPA-nitroxide biradical (**8**) was generated by treating **7** sequentially with *t*-BuOK and K₃Fe(CN)₆.



Scheme 1. Synthesis of BDPA-TEMPO biradical **8** containing a phosphodiester linker. BCDP: Bis(2-cyanoethyl)-*N,N*-diisopropylphosphoramidite. NMIT: *N*-Methylimidazolium triflate.

Figure 2 shows EPR spectra of three different radicals. A single peak (**Figure 2**, top) was observed for the carbon-centered BDPA monoradical **2**, whereas nitroxide monoradical **7** shows the characteristic three peaks of nitroxides (**Figure 2**, middle). The spectrum of **8** (**Figure 2**, bottom) shows the presence of two components.^[17, 20] Biradical **8** has three peaks in its spectrum, but the width of the spectrum is narrower than that of nitroxide **7**, due to strong J-coupling (~100 MHz) between the TEMPO and the BDPA radical.^[17, 20] The other component is a nitroxide monoradical derived from **8**, where one of its three peaks is well separated from the spectrum of **8** (**Figure 2**, bottom, asterisk). The ratio of these two spectral components representing the biradical and the nitroxide monoradical, can be quantified by double integration of the EPR spectrum (Supporting Information).^[17] The amount of biradical **8**, relative to the nitroxide monoradical, was determined to be 80-85%. This was slightly lower than the reported amount (92%) for BDPA-TEMPO biradical **3** (**Figure 1B**).^[17] Hence, we decided to evaluate the different methods that have been reported for preparation of BDPA radicals.

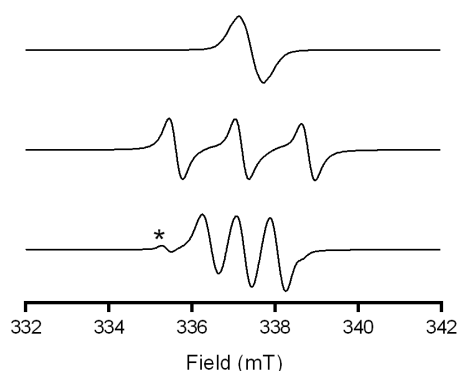


Figure 2. EPR spectra of BDPA radical **2** (top), nitroxide radical **7** (middle) and BDPA-nitroxide biradical **8** (bottom). The peak marked by asterisk in the biradical spectrum originated from a nitroxide monoradical that is present in the sample of the biradical. Experimental parameters: 9.43 GHz, microwave power 1 mW, sweep width 12 mT, modulation 0.2 mT, 23 °C.

Optimization of the conditions used to prepare BDPA radicals

To find the optimal conditions for the synthesis of BDPA radicals, precursor **7** was reacted with various bases in different solvents to give a carbanion, which was treated with an oxidizing agent to yield biradical **8**. A subsequent extraction of the biradical from the reaction mixture was carried out without any further purification and an EPR spectrum was immediately recorded. The spectrum was doubly integrated, as described above, to obtain the amount of the biradical relative to the nitroxide monoradical. **Figure 3** shows the results obtained for DMSO:*t*-BuOH (9:1), DMSO, DMF and CH₂Cl₂ as a function of the base used (*t*-BuOK, DBU and aq. NaOH). Both AgNO₃^[17, 21a, 23] and K₃Fe(CN)₆^[18, 21b, 21c] the oxidizing agents commonly used for the oxidation of the carbanion to the radical, yielded similar results (**Figure 3** and **Figure S4**).

Reaction in DMSO:*t*-BuOH (9:1) with *t*-BuOK followed by oxidation with AgNO₃, the conditions reported for the generation of biradical **3**,^[17] led to ca. 85% of biradical **8**. Reactions in the polar aprotic solvents, DMF^[21b, 21c] and DMSO^[17, 23] gave ca. 90% of biradical (**Figure 3**). However, the amount of the biradical dropped drastically to ca. 30%, when the reaction was carried out in a non-polar solvent (CH₂Cl₂), which required using DBU as a base,^[9c, 20, 22] since *t*-BuOK and aq. NaOH are not soluble in CH₂Cl₂. Use of DBU^[9c, 20, 22] and aq. NaOH^[21b] as the base instead of *t*-BuOK in the polar solvents, gave biradical **8** in good yields (75-80%) (**Figure 3**). To conclude, the formation of the biradical was most efficient when the reaction was carried out in a polar aprotic solvent, using a strong base such as *t*-BuOK. This was not unexpected, since a polar solvent should facilitate formation of the intermediate carbanion.

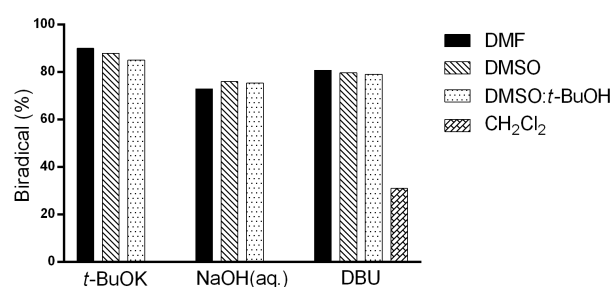


Figure 3. Optimization of the reaction conditions used to generate biradical **8**. Amount of the biradical is shown in different solvents (DMF, DMSO, DMSO:*t*-BuOH 9:1, CH₂Cl₂) and for different bases (*t*-BuOK, aq. NaOH, DBU), using AgNO₃ as the oxidizing agent.

Persistence of BDPA radicals

The rapid decomposition of BDPA radicals that we unexpectedly observed prompted us to investigate the effect of various factors, such as solvents, temperature and oxygen, on the persistence of the BDPA radicals. As demonstrated above, EPR spectroscopy can be readily used to quantify the amount of biradical **8** relative to the nitroxide monoradical present in the sample. Hence, EPR was used to determine the rate of degradation of **8** under different conditions; this method was corroborated by UV-vis spectroscopy, following the absorption signal of the BDPA radical around 490 nm (**Figure S7**). Chromatographic purification of biradical **8** was carried out prior to these studies. However, the “purified” samples contained only about 70% of the biradical, relative to the nitroxide monoradical, due to decomposition of the BDPA moiety during the purification process. Therefore, a pure sample of the biradical could not be obtained.

First, the solvent-dependent persistence of biradical **8** at 23 °C was investigated (**Figure 4A**). Solutions of **8** were prepared in 1,2-dichloroethane (DCE), MeOH and DMSO (5 mM) and their EPR spectra were recorded at various time intervals. These solvents were chosen to probe the effect of the solvent polarity. The initial rate of degradation of biradical **8** in different solvents was determined by plotting the amount of the biradical as a function of time (Supporting Information) and found to increase with decreasing polarity of the solvent (**Figure 4A**). The highest rate of

decomposition was observed in DCE, with an initial rate of $(1.79 \pm 0.35) \cdot 10^{-7} \text{ Ms}^{-1}$. The degradation was significantly slower in MeOH and DMSO, $(1.79 \pm 0.03) \cdot 10^{-8} \text{ Ms}^{-1}$ and $(1.50 \pm 0.09) \cdot 10^{-8} \text{ Ms}^{-1}$, respectively.

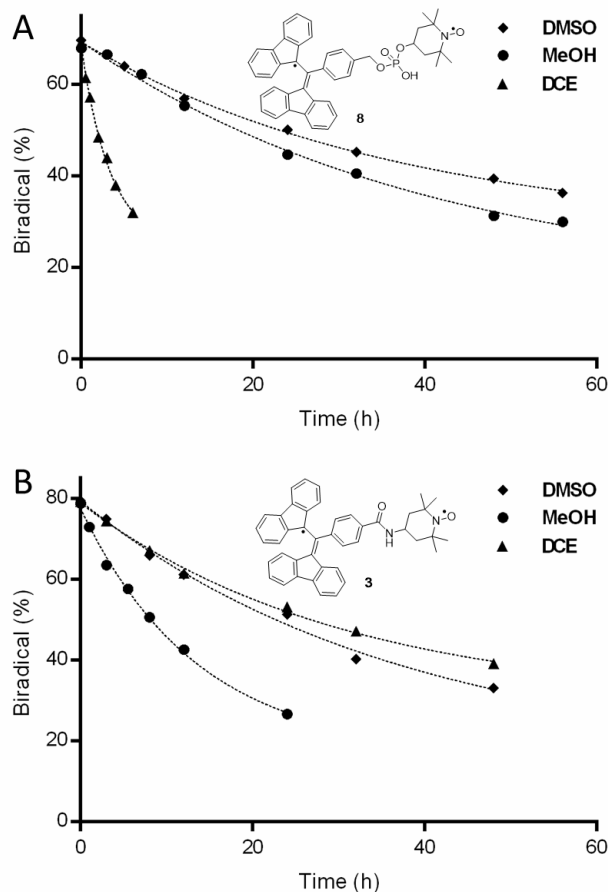


Figure 4. Rate of degradation of two different BDPA-nitroxide biradicals in various solvents (5 mM at 23 °C). The percentage of each biradical relative to a nitroxide monoradical, determined by double integration of its EPR spectrum, was plotted as a function of time and the initial rates of decomposition were calculated accordingly (see Supporting Information). **A.** Biradical **8**; rates (Ms^{-1}): $(1.50 \pm 0.09) \cdot 10^{-8}$ (DMSO), $(1.79 \pm 0.03) \cdot 10^{-8}$ (MeOH), $(1.79 \pm 0.35) \cdot 10^{-7}$ (DCE). **B.** Biradical **3**; rates (Ms^{-1}): $(2.28 \pm 0.15) \cdot 10^{-8}$ (DMSO), $(7.18 \pm 0.64) \cdot 10^{-8}$ (MeOH), $(2.24 \pm 0.23) \cdot 10^{-8}$ (DCE). DCE is 1,2-dichloroethane.

The rate of degradation of biradical **8** in solution was also studied at different concentrations. **Figure 5** shows the initial rates of degradation of **8** in DMSO for a series of solutions with varying concentration at 23 °C. The rate of degradation was found to increase non-linearly with increasing radical concentration. A 2-fold increase in the concentration led to a 3-fold increase in the rate of degradation, which suggests a reaction order of ca. 1.6 with respect to biradical **8**. This result indicates that the well-known reaction with oxygen^[18] may not be the only degradation pathway since the oxidation is presumably a first/pseudo-first

order reaction with respect to the biradical. One plausible explanation is that dimerization of BDPA radicals, which follows a second order kinetics, is also a pathway for degradation. Analysis of the decomposed products of biradical **8** by electrospray ionization (ESI) mass spectrometry indicated formation of multiple products, including the oxygenated products as previously described by Breslin and Fox,^[18] but the dimer of **8** was not found (**Figure S12**). Instead, masses approximately 1.8-fold the monomeric mass of **8** were observed which might be formed from a short-lived dimer. However, we were able to detect a BDPA dimer in the mass spectrum of decomposed products of BDPA radical **S1**, obtained from compound **4** (**Figure S13**). This is, to our knowledge, the first reported indication that dimer formation is a significant pathway for decomposition of BDPA radicals. However, the fact that BDPA radicals dimerize is not surprising, since dimerization of the carbon-centered Gomberg's radical^[24] (triphenylmethyl/trityl) is well-known.^[25] In case of the trityl, introduction of substituents into the aromatic rings has been shown to prevent dimerization, with the Finland trityl being a good example.^[13]

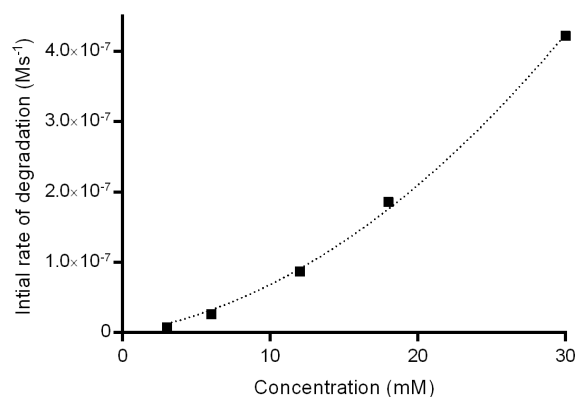


Figure 5. Concentration-dependent initial rates of biradical **8** in DMSO at 23 °C.

To compare the persistence of biradical **8** with other BDPA radicals, the previously reported BDPA-TEMPO biradical **3**^[17] and unsubstituted BDPA radical **2** (**Figure 1**) were synthesized. These radicals are less polar than **8**. **Figure 4B** shows the solvent-dependent rate of degradation of biradical **3** in solution at 23 °C. It was found to be similar to that of **8**, although the solvent-dependence on the rates of decomposition was different. Both **3** and **8** have similar initial rate of degradation in DMSO ($(2.28 \pm 0.15) \cdot 10^{-8} \text{ Ms}^{-1}$) but different rates in DCE and MeOH. In DCE, biradical **3** was considerably more persistent than **8** with an initial rate of degradation $(2.24 \pm 0.23) \cdot 10^{-8} \text{ Ms}^{-1}$, whereas the opposite trend was observed in MeOH ($(7.18 \pm 0.64) \cdot 10^{-8} \text{ Ms}^{-1}$). The unsubstituted BDPA (**2**) showed a similar rate of degradation in solution (**Figure S8**) as the biradicals and the same solvent dependence as **3** ($(3.71 \pm 0.12) \cdot 10^{-8} \text{ Ms}^{-1}$ and $(4.64 \pm 0.18) \cdot 10^{-8} \text{ Ms}^{-1}$ for DCE and DMSO, respectively). In light of the concentration dependence of BDPA decomposition, a possible explanation for this compound-specific solvent effect is aggregation, since the polar biradical **8** degrades faster in a non-

polar solvent and non-polar **2** and **3** are more unstable in a polar solvent. Aggregation would increase the rate of decomposition through dimer formation.

When the temperature was decreased, the degradation of **8** became slower, as expected. The rates decreased by ca. 6-fold for both DCE and MeOH by lowering the temperature from 23 °C to -18 °C (**Figure S9A**). On the other hand, the rate of degradation of **8** in DMSO at -18 °C was unexpectedly observed to be higher ($(3.86 \pm 0.62) \cdot 10^{-8} \text{ Ms}^{-1}$) than at 23 °C ($(1.50 \pm 0.09) \cdot 10^{-8} \text{ Ms}^{-1}$). One plausible explanation is that the radical aggregates due to accumulation of solutes at the crystal boundaries of the frozen DMSO. Quick-freezing in liquid nitrogen followed by incubation at -18 °C, in an attempt to prevent possible aggregation, gave the same result. When the temperature of the DMSO solution was further lowered to -80 °C, a significant increase in the persistence was observed; very little decomposition was observed after a month and after six months ca. 55% biradical remained (**Figure S9B**). Similar decomposition was observed in DCE after six months at -80 °C but ca. 40% biradical remained in MeOH under the same condition. Biradical **8** was found to be stable in the solid state at -80 °C, with no degradation for six months (**Figure S9B**). However, only ca. 38% biradical was intact after a month in the solid state at 23 °C (**Figure S10A**). BDPA radical **2** was also observed to decompose in the solid state under exposure to air (**Figure S10B**), contrary to a previous report.^[14] This degradation was due to oxidation since no decomposition was observed when the solid samples were kept under vacuum for two weeks (**Figure S10B**). Hence, BDPA radicals cannot be termed 'stable', as once considered.^[14] However, the BDPA radicals showed no detectable decomposition when kept at -80 °C in the solid state for longer periods of time (six months).

It is notable that exclusion of light, which has been reported to limit the reaction of BDPA radicals with oxygen,^[18] had no noticeable effects on the rate of decomposition. Formation of the same products was observed in presence and absence of light, both by ESI mass spectrometry and high-performance liquid chromatography (HPLC) (**Figure S11B**). Removal of oxygen by saturation with Ar and keeping the solution under a positive pressure of Ar, decreased the rate of degradation only by 1.5-2-fold (**Figure S11A**).

Conclusions

In conclusion, we have shed some light on the instability of BDPA radicals, both in solution and the solid state, which provides guidelines of how to handle BDPA radicals that are prepared for MAS-DNP NMR experiments. The strong electronic coupling between the BDPA and nitroxide radicals of biradical **8** enabled quantification of its rate of decomposition by EPR spectroscopy. The BDPA radicals reported here were found to be stable as solids at -80 °C with no noticeable decomposition for six months, but under all other conditions we observed degradation in this time-frame. The radical concentration was found to significantly affect the rate of decomposition non-linearly; a 2-fold increase in

the concentration resulted in a 3-fold increase in the rate of decomposition. A dimer of BDPA radical **S1** was detected by mass spectrometry, indicating that dimerization of BDPA radicals is one pathway of decomposition. The polarity of the solvent affected the rate of BDPA decomposition: a polar radical degraded faster in a non-polar solvent whereas a non-polar radical was less persistent in a polar solvent. In light of the concentration-dependent persistence of BDPA radicals, the solvent-dependent increase in the rate of decomposition is likely due to aggregation of the radicals, which would facilitate decomposition through dimer formation. When synthesizing new BDPA radicals that are more persistent as polarizing agents for DNP, it might be advisable to focus on structures that prevent dimer formation. Synthesis of more stable BDPA radicals, keeping this design principle in mind, is under way in our laboratory and will be reported in due course.

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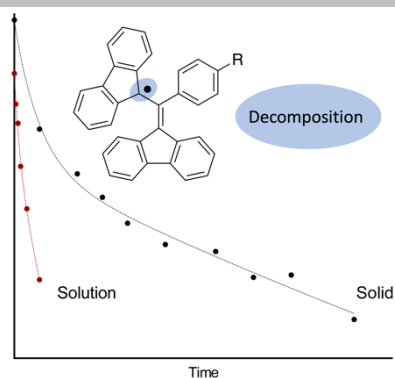
Keywords: BDPA, dynamic nuclear polarization, EPR spectroscopy, radical stability, radicals

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FULL PAPER

Instability of BDPA radicals: BDPA radicals have limited persistence both in solution and the solid state. Decomposition in the solid state was found to be due to oxidation while dimer formation is a significant pathway of decomposition in solution.



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