HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2022 July 25.

Published in final edited form as:

Angew Chem Int Ed Engl. 2017 September 25; 56(40): 12112–12116. doi:10.1002/anie.201704970.

Diazirines as Potential Molecular Imaging Tags: Probing the Requirements for Efficient and Long-Lived SABRE-Induced Hyperpolarization

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201704970.

Conflict of interest
The authors declare no conflict of interest.

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Abstract

Diazirines are an attractive class of potential molecular tags for magnetic resonance imaging owing to their biocompatibility and ease of incorporation into a large variety of molecules. As recently reported, $^{15}N_2$-diazirine can be hyperpolarized by the SABRE-SHEATH method, sustaining both singlet and magnetization states, thus offering a path to long-lived polarization storage. Herein, we show the generality of this approach by illustrating that the diazirine tag alone is sufficient for achieving excellent signal enhancements with long-lasting polarization. Our investigations reveal the critical role of Lewis basic additives, including water, on achieving SABRE-promoted hyperpolarization. The application of this strategy to a $^{15}N_2$-diazirine-containing choline derivative demonstrates the potential of $^{15}N_2$-diazirines as molecular imaging tags for biomedical applications.

Keywords

diazirine; hyperpolarization; imaging agents; iridium; structure–activity relationships

*M*agnetic resonance imaging (MRI) is a powerful, non-invasive approach, based on nuclear magnetic resonance (NMR) spectroscopy, to visualize structure and function with high spatial and temporal resolution. Yet one of the most critical challenges of magnetic resonance (NMR and MRI),[1] is poor nuclear polarization at thermal equilibrium associated with low sensitivity, especially for nuclei of low natural abundance such as ^{13}C and ^{15}N. Hyperpolarization induces non-equilibrium polarization, increasing fractional magnetization of target nuclei, and therefore raises detectable signal by several orders of magnitude.[2] Hyperpolarized heteronuclei (e.g., ^{13}C and ^{15}N) often allow signal detection for extended time periods, due to their large relaxation time (T_1) compared to ^{1}H.[3] Among different hyperpolarization techniques,[4] Signal amplification by reversible exchange (SABRE) has been established as an experimentally simple and cost-effective method,[5] which uses para-hydrogen[6] as hyperpolarization source and iridium N-heterocyclic carbene complexes as catalysts.[7] More recently, it has been shown to hyperpolarize ^{15}N nuclei efficiently in a process termed SABRE in shield enables alignment transfer to (SABRE-SHEATH).[8]

In the context of developing novel NMR and MRI strategies using hyperpolarized markers, we envisioned that $^{15}N_2$-diazirine motifs could serve as unique hyperpolarizable tags. First, the structure of the double ^{15}N-labeled diazirines gives access to observable ^{15}N singlets, which support long-lived states. Furthermore, $^{15}N_2$-diazirines have several attractive features, making them excellent candidates for imaging tags. For example, diazirines have been successfully incorporated into a large number of biologically relevant small molecules, metabolites, and biomolecules. They are small in size, therefore imparting minimal alteration to the original molecule's properties,[9] and are known to be biocompatible and stable under either acidic or basic conditions. Indeed, diazirines have been extensively applied as photoaffinity labelling tags for biochemical investigations.[10] To explore the

feasibility of a $^{15}N_2$-diazirine as a potential imaging tag, we have investigated the hyperpolarization of $^{15}N_2$-labeled diazirine **1** by SABRE-SHEATH (Figure 1).[11] These studies established that $^{15}N_2$-diazirine **1** is capable of being hyperpolarized, achieving a 15000-fold signal enhancement ($\mathcal{E}$) over thermal signal at the diazirine nitrogen atoms. Additionally, we found relaxation time constants of both $^{15}N_2$ magnetization (T_1) and singlet spin order (T_s) to be orders of magnitude larger than typical polarization decay time constants.[11]

Herein, we report our investigations on the potential of diazirines to serve as molecular tags, which would provide enhanced signals with long lifetimes via SABRE-SHEATH. Several aspects had to first be assessed regarding diazirine hyperpolarization—a prerequisite for their ability to serve as general molecular tags. As the coordination of **1** to the iridium catalyst is essential for hyperpolarization by SABRE-SHEATH, we needed to clarify if either the nitrile or carboxylic acid group within **1** (Figure 1) were necessary for binding to iridium, thereby bringing the diazirine into the metalQs coordination sphere, or if the diazirine alone were sufficient. Additionally, we chose deuterated structure **1** in our previous studies with the hypothesis, based on related ^{13}C-based hyperpolarization,[12] that deuteration proximal to the diazirine functionality in **1** would help to extend the T_1 lifetime by reducing polarization loss. Yet the effects of deuteration within the molecule on the magnitude of hyperpolarization and its lifetime remained unclear. Finally, it would be desirable to establish the applicability of diazirines as molecular tags in biologically important molecules while retaining long-lasting hyperpolarization with large signal enhancements.

Our studies began with examining the structural features necessary for a diazirine-containing molecule to undergo SABRE-SHEATH hyperpolarization. To compare with the original structure of diazirine **1**, a series of structural analogues **2–4** was prepared (Scheme 1). The absence of the Lewis basic carboxylic acid or nitrile group in **2–4** allowed us to probe the contribution of each functional group in successful diazirine hyperpolarization systematically. This would indicate whether the functional group might be involved in direct coordination to the catalyst (mode **I**) or if chelation were unnecessary, that is, the diazirine alone were sufficient to bind to Ir (mode **II**). Note that the hindered silyl ether of diazirine **4** was chosen to discourage, sterically and electronically, its coordination to the metal center. When subjected to standard SABRE-SHEATH conditions with pyridyl Ir precatalyst **A** (Scheme 1), cyanodiazirine **2**, carboxylic acid-containing **3**, and TBS-protected ether **4** are all efficiently hyperpolarized ($\mathcal{E}$=7100, 3500, and 6400 at 8.45 T, respectively). Additionally, each substrate displays a T_1 of 3–4 minutes at 1 T. The relatively small differences in signal enhancement and T_1 among compounds **2–4** implies that while chelation might be possible in some cases (mode **I**), it is not required to achieve hyperpolarization. Therefore, coordination mode **II** is likely operative for diazirine hyperpolarization with complex **A**.[13]

During the SABRE-SHEATH hyperpolarization of diazirines **2–4**, no hyperpolarization was observed for any substrate when the neutral Ir-chloride precatalyst **B** was employed under identical conditions to those with complex **A** (Table 1, entries 1, 5, and 9). Interestingly, the addition of exogenous Lewis bases restored effective hyperpolarization with complex **B**. For example, in the presence of pyridine, diazirines **2–4** were hyperpolarized with T_1

values of 2–4 min (entries 2, 6, and 10). Acetonitrile as an additive also enabled signal enhancements to be observed (entries 3, 7, and 11), although the volatility of this additive proved problematic in some instances (e.g., low signal enhancement and large T_1 error with silyl ether-containing diazirine **4**, entry 11). It is noteworthy that diazirine **2**, bearing a cyano group, is insufficient on its own to allow for SABRE hyperpolarization but exogenous nitrile, even though in lower concentration, is able to reverse this deficiency. The addition of D_2O as a Lewis base is also sufficient to bring about diazirine hyperpolarization (entries 4, 8, and 12); these conditions are similar to those originally reported for **1**. Presumably the smaller steric presence of D_2O compared to [D_4]MeOH, the solvent, is the prime factor in facilitating SABRE-SHEATH in these instances even though the D_2O concentration is significantly lower. Signal enhancements and T_1 times are similar to those with pyridine or acetonitrile additives.

The fact that no signal enhancement was observed for any of the diazirines **2–4** with precatalyst **B** in the absence of a Lewis basic additive suggests that the diazirine moiety is either incapable of substituting the chloro ligand of **B** in the catalyst initiation step and/or of forming an active catalyst with three *facially*-coordinated diazirine ligands due to steric congestion (Figure 2, complex **III**). Attempts to substitute the chloride in complex **B** for a diazirine stoichiometrically, which would then lead to **III** upon para-hydrogen addition, failed to generate any observable reaction. We cannot rule out that **III** might be formed in small quantities in the presence of one of the Lewis basic additives; however, it is most likely that polarization transfer occurs from either complex **IV** or **V**.

We prepared a series of isotopomers of diazirine **2** to determine the effect of deuteration at the α-positions of the diazirine motif on hyperpolarization and T_1 relaxation times (Figure 3). We used Ir complex **B** in the presence of pyridine additive for a comparative study. Diazirines ***d*$_0$-2, 2**, and ***d*$_5$-2** all provide comparable T_1 values of approximately three minutes at 1 T (Figure 3A), showing that deuterium incorporation does not strongly affect T_1 relaxation. The negligible effect of deuterium is consistent with small differences of T_1 between ***d*$_0$-2** and ***d*$_5$-2**(Figure 3B).[14]

The study of the field dependence of T_1 relaxation rates is of special interest (Figure 3B) because for body-noise dominated hyperpolarized MRI, the signal-to-noise is roughly field independent whereas signal decay time constants are not.[15] Thus, it is important for future applications and choice of optimal MRI field strength to understand at what magnetic field we observe longest hyperpolarization lifetimes. Mechanistically, SABRE-SHEATH involves coherent polarization transfer from p-H_2 to ^{15}N at the region of Level Anti Crossings,[16] which is most efficient at about 0.6 μT for the characteristic J_{HH} and J_{NH} couplings in iridium-diazirine complexes. Commercial MRI operates between 1 T and 4 T. It is therefore noteworthy that T_1 did not vary significantly over a large magnetic field range, falling significantly only at very high field strength (Figure 3B). The data indicate that magnetic fields of about 1 T and slightly below may be most advantageous for future applications, which is intriguing given the ongoing progress in low-field NMR[17] and low-field MRI.[18]

We have established the independence of the $^{15}N_2$-diazirine motif for SABRE-SHEATH hyperpolarization and its ability to deliver long-lasting polarization. To demonstrate the

applicability of $^{15}N_2$-diazirines as molecular tags for biologically important molecules, we prepared $^{15}N_2$-diazirine-tagged choline derivative **5** (Figure 4). It has been shown that choline analogues, in which a methyl group is replaced with an alkyl chain of up to five carbon atoms in length, incorporate efficiently into phospholipids.[19] Subjecting **5** to SABRE-SHEATH hyperpolarization with Ir precatalyst **B** in the presence of pyridine or D_2O as the Lewis base leads to greater than 2000-fold signal enhancement with T_1 of approximately three minutes. Compared to ^{15}N-choline hyperpolarized by dynamic nuclear polarization (DNP),[20] the effectiveness observed on hyperpolarized **5** by SABRE-SHEATH is comparable yet SABRE-SHEATH is operationally a simpler and more economical protocol. Particularly encouraging is the effective enhancement and long-lasting polarization observed in the presence of D_2O, presenting an important first step toward biomedical in vivo applications with this tag.

In summary, we have established the independence of the $^{15}N_{2-}$ diazirine group from other functional groups for SABRE-SHEATH hyperpolarization and its ability to support long-lasting hyperpolarization for signal enhancement, marking its potential as a molecular tag for NMR and MRI. Furthermore, the studies on different SABRE-SHEATH hyperpolarization conditions reveal a critical contribution of Lewis basic additives for generating active Ir catalysts for polarization transfer. These studies also provide some structural information regarding the likely coordination sphere at Ir in SABRE-SHEATH with diazirines. Finally, successful hyperpolarization of a $^{15}N_2$-diazirine-containing choline derivative demonstrates the applicability of $^{15}N_2$-diazirine tags within biologically relevant molecules. Future studies are directed towards incorporating $^{15}N_2$-diazirines into other biologically active molecules and their studies in molecular imaging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We gratefully acknowledge the NSF (CHE-1363008 to W.S.W.), Camille and Henry Dreyfus Foundation (Teacher-Scholar Award to Q.W.), and Duke University for financial support of this work.

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See more details in the Supporting Information. T1 as a function of magnetic field is estimated by the signal intensity of the sample after a time delay of 60 s upon subjection to the SABRE-SHEATH procedure.

b) A noticable difference was observed for enhancement levels of d0–2, 2, and d5–2, which might be contributed by the coupling between 15N and deuterium. Due to the relatively large error range in the current experimental data, it remains to be confirmed in further studies.

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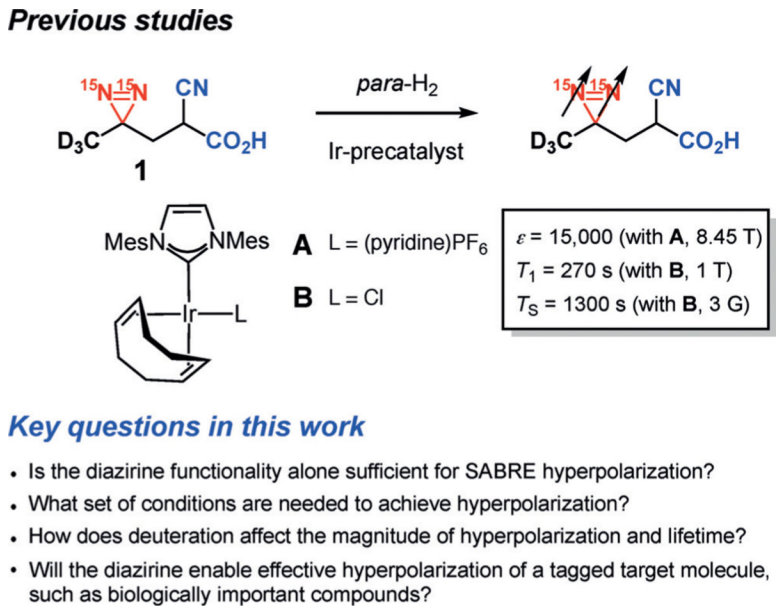
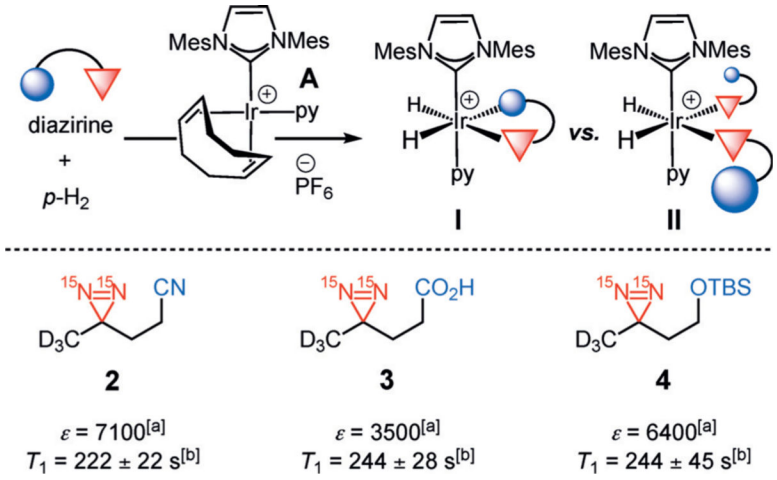


Figure 1.

$^{15}N_2$-diazirines as potential molecular tags for MRI by SABRE-SHEATH hyperpolarization.



Scheme 1.

Hyperpolarization of $^{15}N_2$-diazirines **2–4**. Standard conditions: diazirines **2–4** (12.5 mm) and Ir precatalyst **A** (125 μm) in [D_4]MeOH. [a] Signal enhancement measured at 8.45 T and calculated by comparison to a reference of neat ^{15}N-acetonitrile. [b] T_1 measured at 1 T. Mes=2,4,6-trimethylphenyl; py=pyridyl; TBS=*tert*-butyldimethylsilyl.

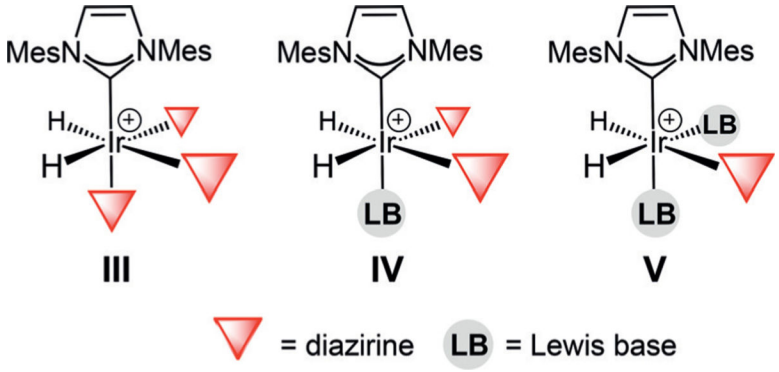


Figure 2.
Possible coordination modes for SABRE-promoted hyperpolarization of diazirines.

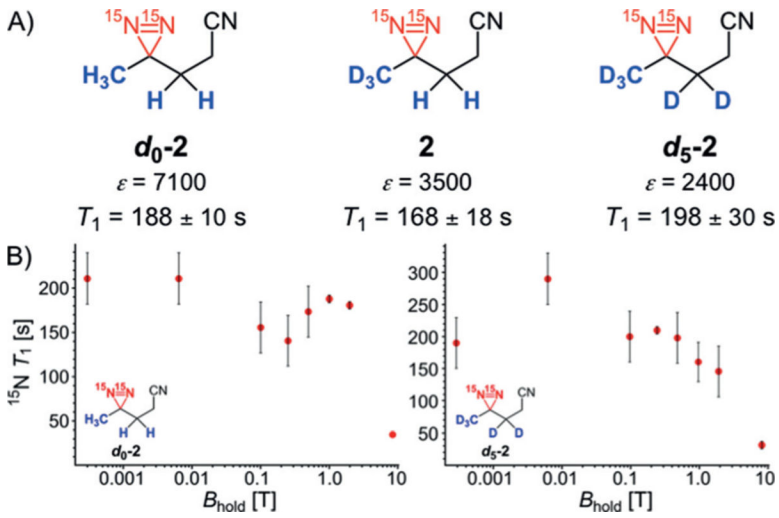
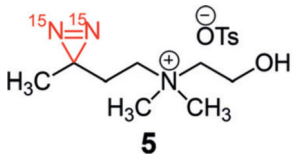


Figure 3.

Effect of deuteration on T_1-relaxation rates and enhancements $\mathcal{E}$ of $^{15}N_2$-diazirine **2**. A) Negligible effect of deuteration of diazirines **2** on T_1-relaxation rates at 1 T (within the experimental error). B) T_1-relaxation rate for ^{15}N polarization of $\boldsymbol{d_0}$**−2** and $\boldsymbol{d_5}$**-2** as a function of the magnetic field. SABRE-SHEATH conditions: diazirine $\boldsymbol{d_0}$**-2, 2**, or $\boldsymbol{d_5}$**-2** (12.5 mm) in [D_4]MeOH, Ir precatalyst **B** (125 μm), and pyridine (1.00 mm).



5

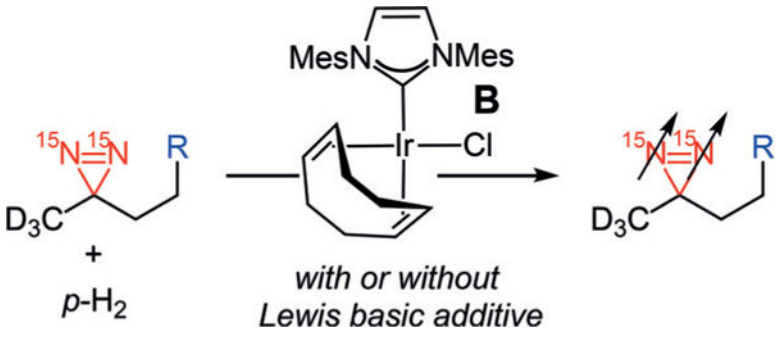
	with ***pyridine***	***D₂O***
ε (8.45 T)	= 6800	2000
T_1 (1 T)	= 222 ± 8 s	179 ± 19 s

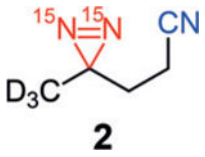
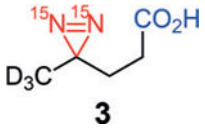
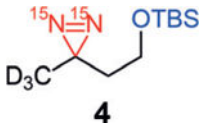
Figure 4.

Hyperpolarization of $^{15}N_2$-diazirine-tagged choline derivative **5**. SABRE-SHEATH conditions: **5** (12.5 mm) and Ir precatalyst **B** (125 μm) in [D_4]MeOH with either pyridine (1.00 mm) or D_2O (925 mm). Signal enhancement measured at 8.45 T and calculated by comparison to a reference of neat ^{15}N-acetonitrile. T_1 measured at 1 T. See the Supporting Information for more measurements at other fields. Ts=*p*-toluenesulfonyl.

Table 1:

Hyperpolarization of diazirines **2–4** with Ir-chloride precatalyst **B** via the SABRE-SHEATH method.[a]



Entry	Diazirine	Additive	ε[e]	T_1 [s] [f]
1	 2	none	–[g]	n/a
2[b]		pyridine	3500	168 ± 18
3[c]		MeCN	3400	179 ± 16
4[d]		D_2O	11200	176 ± 3
5	 3	none	–[g]	n/a
6[b]		pyridine	6000	215 ± 22
7[c]		MeCN	3200	172 ± 17
8[d]		D_2O	1900	234 ± 28
9	 4	none	–[g]	n/a
10[b]		pyridine	16 000	141 ± 4
11[c]		MeCN	1000	263 ± 83[h]
12[d]		D_2O	2500	164 ± 25

[a] Conditions for all experiments: diazirines **2**–**4** (12.5 mm) and Ir precatalyst **B** (125 μm) in [D_4]MeOH. See the Supporting Information for more details on the hyperpolarization method.

[b] Pyridine (1.00 mm, 8 equiv with respect to **B**).

[c] Acetonitrile (1.00 mm).

[d] D_2O (925 mm).

[e] Signal enhancement measured at 8.45 T and calculated by comparison to a reference of neat ^{15}N-acetonitrile.

[f] T_1 measured at 1 T. See the Supporting Information for measurements at other fields.

[g] No hyperpolarized signal observed.

[h] The low signal enhancement and volatility of acetonitrile contribute to the larger T_1 error. n/a=not applicable.