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Direct and Indirect Hyperpolarisation of Amines using Parahydrogen

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Nuclear Magnetic Resonance (NMR) and Magnetic Resonance Imaging (MRI) are two widely used techniques for the study of molecules and materials. Hyperpolarisation methods, such as Signal Amplification by Reversible Exchange (SABRE), turn typically weak magnetic resonance responses into strong signals. In this article we detail how it is possible to hyper polarise the $^{1}H$, $^{13}C$ and $^{15}N$ nuclei of a range of amines. This involved showing how primary amines form a stable but labile complex of the type [Ir(H)$_2$(IMes)(amid)$_2$Cl] that allow parahydrogen to relay its latent polarization into the amine. By opt imising the temperature and parahydrogen pressure a 1000-fold per proton NMR signal gain for diaziridinediazonium is achieved at 9.4 T. Additionally, we show that sterically hindered and electron poor amines that bind poorly to iridium can be hyperpolarised by either employing a co-ligand for complex stabilization, or harnessing the fact that it is possible to exchange hyperpolarised protons between amines in a mixture, through the recently reported SABRE-RELAY method.

The successful refinements have significant potential to extend the classes of agent that can be hyperpolarised by readily accessible parahydrogen.

Introduction

Hyperpolarisation methods are used to overcome the inherent insensitivity of nuclear magnetic resonance (NMR) spectroscopy and magnetic resonance imaging (MRI) where their use may lead to dramatic time and cost savings. One such hyperpolarisation method, Parahydrogen-induced Polarisation (PHIP), produces the required non-Boltzmann nuclear spin distribution by the incorporation of parahydrogen ($p$-H$_2$), an example of a nuclear singlet, into a suitable substrate molecule. This effect was shown to yield an enhanced NMR signal in 1987 and has been the subject of intense investigation, 1. 2 A drawback of PHIP though, is the requirement for chemical change, caused by $p$-H$_2$ addition to an unsaturated centre such as an alkene. However, recently a $p$-H$_2$ technique that does not change the chemical identity of the sensitised molecule, called Signal Amplification By Reversible Exchange (SABRE), was reported. 3. 4 In this process, $p$-H$_2$ is not directly incorporated into the substrate. Instead, polarisation is transferred via the $J$-coupling network that exists within a metal complex that co-locates $p$-H$_2$ derived hydride ligands and a weakly bound substrate (ligand). 5 6 Ligand exchange with excess unbound substrate and $p$-H$_2$ enables the build-up of a pool of polarised substrate molecules in solution in a catalytic fashion as shown in Scheme 1. 7

The SABRE polari sation of $^{1}H$ nuclei typically utilises a $^{15}N$ coupling between the catalysts hydride and substrate ligand protons. Tessari et al. have quantified the small spin-spin couplings to be $\approx 1.2$ Hz. 8 Alternatively, stronger $^{15}N$ couplings have now been used to achieve $^{15}N$ polarisation transfer at micro-Tesla fields in a variant known as SABRE-SHEATH (SABRE-in-shield) which enables alignment transfer to heteronuclei. 9, 10 Intramolecular spin-spin coupling networks within the substrate subsequently enables transfer to remote spins which do not exhibit direct coupling to the hydride ligands. 11

One of the most effective precatalysts for this process is [IrCl(COD)(IMes)] (1) (where IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, COD = cis,cis-1,5-cyclooctadiene) which, after reaction with $p$-H$_2$ and an excess of substrate, typically forms [Ir(H)$_2$(IMes)(substrate)]Cl in protic solvents such as methanol. 12 Neutral active catalysts of the type [Ir(H)$_2$(Cl)(IMes)(substrate)]Cl have also been reported to achieve similar results. 13 These metal based polarisation transfer catalysts have been shown to act on a range of substrates that contain multiple bonds to nitrogen, such as nictinamidobenzimidazoles, 14 pyrrole, 15 imines, 16 diazirines 17 and nitrites. 18 These enable the polarisation of $^{15}N$, $^{1}H$, $^{13}C$ and $^{15}P$ nuclei that yield substantially enhanced NMR responses in just a few seconds. 19 20 In fact, $^{15}N$ polarisations of 50% have been reported, while for $^{1}H$, values of over 20% have been achieved. 21

While SABRE-induced polarisation can also be achieved using in-field rf transfer methods, 22, 23 whose efficiency varies with pulse sequence, spontaneous polarisation transfer occurs readily at low-field and it is this method we employ here. Moreover, as predicted 24 it has also been established that SABRE can be used to produce hyperpolarised singlet states 25 with long lifetimes through transfer in ultra-low field,

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or after the implementation of rf. transfer. Hence the diversity of applications found for this approach is growing and it clearly reflects not only a successful medium to test hyperpolarisation concepts but a potential route to transform the analytical potential of NMR.

In this article, we introduce a new class of substrate into the SABRE repertoire, the amine. This is achieved by the formation of iridium-amine complexes of type \([\text{Ir(H)}_{\text{III}}(\text{IMes})(\text{RNH})_{\text{II}}]\)Cl (2, Scheme 1), whose kinetic behaviour is determined. Whilst the synthesis and use of iridium-amine complexes has been reported for catalytic transformations such as hydrogenation,\(^{11,12}\) we use them here for polarisation transfer catalysis. We have recently shown a limited number of amines are amenable to SABRE. Here, we start by detailing the hyperpolarisation of ammonia and benzylamine (BnNH\(_2\)) and its associated optimisation to achieve large NMR signal enhancements. We then show how hyperpolarisation can be achieved in a range of primary amines. Upon changing to sterically bulky primary amines, secondary amines or aromatic amines, we show that an active SABRE catalyst does not form upon reaction with 1. However, we exemplify co-ligand and relayed polarisation transfer protocols to overcome this limitation and hence expand further the range of amines amenable to polarisation by \(\text{rf} \cdot \text{H}^+\).

Results and Discussion

Direct \(^1\text{H}\) Hyperpolarisation of Ammonia and BnNH\(_2\) by SABRE

Our objective was to investigate the efficiency of the SABRE polarisation of amines and ammonia and to determine their ligand exchange dynamics. A 5 mM solution of 1 in dry dichloromethane-\(d_2\) containing an excess of NH\(_3\) relative to 1 at 298 K was therefore prepared. The aprotic solvent ensures that we maintain the necessary J-coupling network in \([\text{Ir(H)}_{\text{III}}(\text{IMes})(\text{NH})_{\text{II}}]\)Cl (2-NH\(_3\)) during the study, as rapid \(^2\text{H}\) exchange results to form ND\(_3\) in deuterated protic solvents. This complex yields a hydride signal at \(\delta = -23.8\), alongside a broad response at \(\delta = 0.47\) for free NH\(_3\). The corresponding equatorial and axial NH\(_3\) ligand \(^1\text{H}\) NMR signals of 2-NH\(_3\) appear at \(\delta = 2.19\) and 2.88 respectively. \(^2\text{D}^\text{H}^\text{15N}\) HMQC measurements were subsequently used to locate the corresponding \(^{15}\text{N}\) signal for these ligands at \(\delta_{\text{axial}} = 47.8\) and \(\delta_{\text{equatorial}} = 35.5\). Full characterisation data for 2-NH\(_3\) is available in the ESL.\(^{13}\) EXSY methods were then used to probe NH\(_3\) and H\(_2\) loss in 2-NH\(_3\). At 298 K, the associated rate constant for NH\(_3\) loss proved to be 1.64 s\(^{-1}\) while that of H\(_2\) loss is 0.32 s\(^{-1}\). For comparison, the dissociation rate for pyridine in \([\text{Ir(H)}_{\text{III}}(\text{IMes})(\text{py})]\)Cl is 13.2 s\(^{-1}\) and suggests a higher stability for 2-NH\(_3\), which agrees with the greater basicity of NH\(_3\) relative to pyridine.\(^{14}\)

As 2-NH\(_3\) undergoes both NH\(_3\) and H\(_2\) loss in solution, we sought to prove that it underwent SABRE catalysis. Thus, a bar pressure of p-H\(_2\) was introduced at 298 K and polarisation transfer was conducted at 60 G. A \(^1\text{H}\) NMR spectrum at 9.4 T was then recorded which showed a 154-fold signal enhancement per proton for the free NH\(_3\) response while the corresponding equatorial ligand signal, at \(\delta_{\text{eq}} = 2.19\), showed a 77-fold enhanced response (Figure 1). Hence 2-NH\(_3\) acts as a SABRE catalyst as it produces a hyperpolarised free ammonia response. In the presence of water, the observed signal enhancement off he protons in free NH\(_3\) decreased to 40-fold per proton, matching that now observed for the equatorially bound NH\(_3\) ligand. This drop is reflected in the signal at \(\delta = 1.88\), for what is a H\(_2\) response, exhibiting a 75-fold signal gain per proton due to concomitant proton exchange; the ratio of 2-NH\(_3\) : H\(_2\) : O\(_2\) : NH\(_3\) in this sample was 1 : 5 : 17.5. Under these conditions, the \(T_1\) value for free NH\(_3\) in the presence of the active SABRE catalyst was measured by inversion recovery to be 5.5 s.

Figure 1: (a) The hyperpolarised \(^1\text{H}\) NMR spectra of 1 at 30 s with slow re-establishment (400 MHz, 298 K). (b) 2D EXSY measurements of 1 show a characteristic SABRE polarisation of 9.4 T NMR spectra (fast s.

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The SABRE-induced hyperpolarisation of benzylamine (BnNH₂) was also investigated. A sample containing 5 (5 mM) and BnNH₂ (10 eq.) in dichloromethane-d₆ solution was exposed to 3 bar of H₂. The immediate formation of [Ir(H)(IMes)(BnNH₂)Cl] (2-BnNH₂) was observed. It gives a characteristic resonance in the ¹H NMR spectrum at δ = 23.97. Full characterisation data for this product is available in the ESI. Interestingly, the ¹H NMR spectrum of 2-BnNH₂ showed that the BnNH ligand that lies ₀trans烝edequivalents for its NH protons at δ = 2.92 and 2.30, and CH₂ protons at δ = 3.60 and 3.18. This is due to hindered rotation around the Ir-N bond which results in an up/down distinction for the resonances of the equatorial ligand. In contrast, the axial ligand yields single responses which are equivalent at δ = 4.24 (NH₂) and δ = 3.83 (CH₂) due to free rotation about the NMR timescale of the Ir-N bond. The corresponding EXSY derivative constant for equatorial BnNH ligand formed from 2-BnNH₂ was 3.33 s⁻¹ while the rate of H₂ loss was 2.83 s⁻¹ at 298 K. Hence, the rate of BnNH loss is higher than that of NH₂ loss in 2-BnNH₂. This difference is due to NH₂ forming a stronger Ir-N bond as reflected in the relative pKₐ values and suggests that it might perform better under SABRE that NH₂.

This was examined by p-H₃-based polarisation transfer at 60 G which resulted in hyperpolarised free BnNH₂ in solution. The signal enhancements were quantified to be 72 (NH₂), 56 (CH₂) and 194-fold (Ph) per proton as shown in Figure 2a. However, by using d₁-BnNH₂ instead, we were able to focus the SABRE polarisation into the two amino protons at one and this led to an improved signal enhancement of 916-fold per proton (Figure 2b).

Effect of Catalyst to Substrate Ratio on SABRE Polarisation
Previous studies have shown that the SABRE effect is dependent upon the catalyst to substrate ratio as a consequence of kinetic and relaxation effects. Therefore, we studied the effect of changing the ratio of BnNH₂ to Ir(10 eq.) in dichloromethane-d₆ solution containing 3 bar of H₂, which resulted in hyperpolarised free BnNH₂. It was found that similar total polarisation levels result within experimental error during these experiments (see ESI). Hence, we conclude that the observed signal enhancements under these conditions are essentially independent of ligand excess which suggests that slow exchange and fast relaxation within the catalyst restrict the maximum polarisation level.

Effect of p-H₂ Pressure on SABRE Polarisation of BnNH₂
As SABRE derives its polarisation from p-H₂, it could be the limiting reagent in this catalytic process and therefore affect the observed substrate polarisation level. Up until this point, we have been utilising 3 bar pressure of p-H₂, which reflects an α₀ 6-fold excess when compared to the 50 mM substrate present in a 5 mM NMR tube. A sample containing 5 (5 mM) BnNH₂ (50 mM, 10 eq.) in dichloromethane-d₂ solution was therefore prepared and exposed to between 2 and 4 bar of p-H₂. The resulting signal gains, after polarisation transfer at 60 G, are shown in Figure S14 (see ESI) and a strong dependence on p-H₂ pressure is seen. This is consistent with the fact that H₂ exchange takes place after ligand dissociation and the remaining equatorial bound BnNH ligand will experience a higher level of ligand H₂ polarisation (see Scheme 1). When d₁-BnNH₂ is examined with 4 bar of p-H₂, the NH signal gain increases to 1079-fold per proton from the 916-fold signal gain achieved with 3 bar.

Effect of Temperature on SABRE Polarisation of BnNH₂
The temperature at which SABRE is conducted is also known to affect the efficiency of the polarisation transfer due to changes in the lifetime of the SABRE-active catalyst. We found here that cooling a dichloromethane-d₂ solution containing 5 (5 mM) BnNH₂ and 3 bar p-H₂ to 288 K results in a reduction in the signal gain at 60 G (Figure S15, ESI). Conversely, 308 K gave an improved response with the overall polarisation level increasing by ~40%. This fits with the observed rate constant for BnNH₂ dissociation increasing to 9.85 s⁻¹ from the 3.33 s⁻¹ value at 298 K. We...
therefore con clude the retained polarisation level in BnNH₂ is improved by the faster rate of substrate dissociation and shorter catalyst lifetime. For NH₂, a 251-fold ¹H signal gain per NH proton is observed at 308 K when compared to the 154-fold value at 298 K. This is consistent with the NH₂ dissociation rate constant to 10.42 s⁻¹ at 308 K when compared to 1.64 s⁻¹ at 298 K.

**SABRE Transfer to ¹C and ¹⁵N**

SABRE-induced hyperpolarisation of ¹C was also observed for BnNH₂. Whilst polarisation transfer into the ortho phenyl carbon was readily observed using a standard ¹C acquisition sequence after polarisation transfer 60 G under 4 bar of H₂, the other ¹C resonances had poor signal-to-noise ratios. We overcame this by using a ²H-²H-coupled INEPT experiment that gave rise to a spectrum showing all 5 carbon environments after polarisation transfer at 60 G. We utilised long-range 7-¹H couplings to transfer the polarisation. ¹C signal gains of up to 65-fold were achieved using this method (Figure 3a). We further note that there is a very strong polarisation transfer field dependence on the BnNH₂ signal intensities, which is consistent with earlier reports on pyridine.¹²

When BnNH₂ is used instead of BnNH, the detection of a hyperpolarised ¹⁵N response is readily evident as shown in Figure 3b. The ¹⁵N signal gain for the free material in solution proved to be ~880-fold after polarisation transfer at 60 G and 308 K. The equatorially bound ¹⁵N resonance at 8.59, is 4 times larger than the free amine signal. As the ratio of free amine to equatorially bound BnNH₂ in solution is actually 7:2, the rate of BnNH₂ loss must be relatively slow, even at 308 K. Under this 60 G condition, polarisation transfer is likely to occur via the \[ J_{\text{NH}} \] coupling between the BnNH₂ and the hydride ligands. To investigate the effect of using a \[ J_{\text{NH}} \] coupling we repeated this measurement after polarization transfer with a µ-metal shield (ca. 350-fold shielding). Under these SABRE-SHEATH type conditions, an ~800-fold ¹⁵N signal gain was observed and further optimisation may therefore be needed to maximise this response. The corresponding ¹H signal gains with its ¹⁵N labelled material after transfer at 60 G were now 39: (NH₂), 34: (CH₂) and 52-fold (O). These compare to the analogous values of 72-, 56- and 192-fold respectively with BnNH₂. Interestingly, the ¹H polarisation levels therefore decrease with ¹⁵N addition and we propose that this is an example of spin dilution.

**Expand the Substrate Range**

In order to test the generality of amine polarisation via SABRE, we prepared a series of samples containing 1.5 (mM) and 10 eq. of the substrates shown in Figure 4 in dichloromethane-d₆ solution. These substrates include a number of primary amines and each is successfully hyperpolarised after transfer at 60 G upon reaction with [Ir(H)Cl(IMes)]₂ (amine). In fact, SABRE-polarisation of phenethylamine (PEA) and phenylpropylamine (PPA) results in strong signal enhancements and transfer is found to proceed across the corresponding C₁ and C₂ carbon chains into their phenyl rings. For PEA we found that the NH₂ ¹H signal gain is actually increased to 108-fold per proton compared to the 72-fold BnNH₂ value, and that the OCH₂ bridge gave 50-fold (NCH₂) and 45-fold (OH) enhancement per proton. The C₂ proton containing phenyl group gave a 92-fold gain per proton. Spin-isolation of the phenyl group, by substituting on other linkages, as in phenoxethylamine (ROEA) resulted in signal enhancements of 99- (NH₂), 47- (NCH₂), 147- (CH₂) and as expected, just 8-fold (Ph) per proton for our test sample.

Therefore, we conclude that polarisation transfer across the amine linker is inefficient at 60 G and a stronger aliphatic proton resonance results. The amines phenethylamine, phenoxethylamine and propylamine were also studied as shown in Figure 4. In all cases, the formation of [Ir(H)(Nitrile amine)]₂ was indicated (see ESI) and polarisation transfer resulted.

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When secondary amines, such as dibenzylamine, were examined, no evidence for the formation of an active SABRE catalyst was observed. A similar result was observed for sterically hindered primary amines, such as isopropylamine and aromatic amines, such as aniline. Sterically demanding substrates, such as 2,6-lutidine, have been previously shown to be unable to be polarised using SABRE. A full list of the amines probed in this study is available in the ESI. We therefore postulate that sterically demanding or electron deficient amines fail to activate and form the necessary [Ir(H)](ammine)Cl SABRE catalyst.

This problem could be overcome for anil ne by the addition of the co-ligand 1-methyl-1,2,3-triazole (mtz) or CH$_2$CN. For the corresponding sample containing 1 (5 mM), aniline (10 eq.) and mtz (3 eq.) in dichloromethane-$_d_2$, we achieved signal enhancements of 51-fold for the NH group and 17-fold for the phenyl group, per proton. These signal gains are summarised in Figure 5. When CH$_2$CN (8 eq.) is used instead of mtz, the polari sati on levels increase to 806- (NH$_1$) and 193-fold (Ph) per proton. The active complex in this SABRE process was characterised as [Ir(H)](IMes)(aniline)CH$_2$CN]Cl and yields a distinct hydrid e resonance at $\delta$ = 24.78 ppm. Utilisation of such a co-substrate strategy was however unsuccessful for the secondary amines as detailed in the ESI.

For isopropylamine (PrNH$_2$), the SABRE-RELAY polarised NH$_2$ signal showed a 220-fold signal gain while 27- and 150-fold enhancements were seen for the CH and CH$_2$ resonances respectively. This reflects a breakthrough as PrNH$_2$ was unable to be directly polarised by SABRE due to the steric bulk preventing adequate binding. Dibenzylamine (BnNH$_2$) was also successfully polarised using this method, and yields $^1$H signal gains of 274- (NH), 200- (CH$_3$) and 395-fold (Ph) per proton. Additionally, a $^1$H spectrum can be acquired in a single scan on these materials after polarisation transfer at 60 G such that a 475-fold signal gain for the CH$_3$ resonance is observed. Full NMR spectra are available in the ESI. Furthermore, the aromatic can be anil ine, now exhibits a 150-fold NH proton signal enhancement and a 9-fold signal gain for the phenyl ring under analogous conditions. We note that these signal gains are lower than those seen when CH$_2$CN is used as a co-ligand to achieve direct SABRE transfer as detailed in Figure 5.

We suggest that this difference in behaviour arises because a 60 G polarisation transfer field is no-longer optimal for intra-molecular polarisation transfer after proton exchange. This is clearly not the case for transfer via directly bound aniline and the complexes scalar coupling network which is in fact commonly maximised for $^1$H transfer at 60 G.

From these results we can conclude that the SABRE-RELAY effect is able to polarise sterically hindered primary amines,

Figure 5: $^1$H NMR signal gains on a propy rotonosubstrate for mediated SABRE-NMR resonance when hydri de protons are polarised by SABRE using pre-catalyst 1 in dichloromethane-$_d_2$ solution. Per proton signal gains are given for the indicated $^1$H sites (* average across two sites due to peak overlap) observed at $\delta$ = 24.78 ppm. Corresponding $^1$H NMR spectra for thermally polarised and SABRE polarised experiments are given in the ESI.

Indirect Hyperpolarisation of Amines by SABRE-RELAY

As expected, substrate binding to the metal centre is needed for polarisation transfer to occur. We hypothesised that these amines might also be hyperpolarised indirectly. In this scenario, hyperpolarisation of a primary amine or ammonia is achieved and subsequent proton exchange, which may be mediated by residual water, allows for a polarised proton to be shuttled into the non-SABRE-active amine. Subsequent intra-substrate polarisation transfer then relays the signal gain more widely in this agent.

In order to test this hypothesis, a series of samples containing 1 (5 mM), target amine (10 eq.) and NH$_2$ (5-5 eq.) were prepared in dichloromethane-$_d_2$ solution. 2-NH$_2$ for med in all cases as confirmed by the presence of a hydrid e resonance in the corresponding $^1$H NMR spectra at $\delta$ = 23.8 ppm. Polarisation transfer was then conducted at 60 G, and the resulting signal gains that were observed at 9.4 T are presented in Figure 6.
secondary amines and aromatic amines that are not themselves accessible to SABRE. Thus, the scope of amine polarisation is vastly increased.

![Figure 6: 1H NMR signals observed per proton for indicated amine resonances when hyperpolarised by SABRE-RELAY using 2-NH$_2$ at 9.4 T.](image)

**Conclusions**

In summary, we have shown here how SABRE can be used to hyperpolarise a series of primary amines. This substrate extension opens up the SABRE approach to operate with a much wider range of analytes than was previously thought possible, as we extend beyond the original aromatic N-heterocycles, imines and nitrides. Activity is achieved by the formation of a series of complexes of the form [Ir(H)(IMes)(amine)]Cl. Relaxation studies, in conjunction with ligand dissociation rate measurements were used to demonstrate that the high relative stability of these complexes acts to limit the degree of SABRE signal gain. This hypothesis is consistent with the fact that increasing the p$_H_2$ pressure or reaction temperature leads to improved signal gains. Therefore, significant catalytic optimisation will be important if very high levels of hyperpolarisation are to be achieved by this route in the future.

Nonetheless, in the case of BnNH$_2$, 1H NMR signal enhancement values of ~100-fold per NH proton were achieved for benzylamine using [IrCl(COD)(IMes)]. Consequently, when d$_5$-benzylamine was used, the resulting focusing of the hyperpolarisation into the NH$_2$ resonance resulted in a 900-fold signal enhancement per proton at 9.4 T with a p$_H_2$ pressure of 3 bar. This value reduced to 33-fold for BnN$_2$H$_2$ after transfer at 60 G. Hence, we predict that further improvements can be made through a more detailed study of the effect of isotopic labelling. We have also demonstrated transfer to $^{13}$C and $^{15}$N with diagnostic NMR spectra being collected at a 35 mM concentration in a single scan. We predict that application of high-field SABRE transfer techniques, such as the LIGHT-SABRE approach, might subsequently enable this process to work inside the magnet, but note that a rigorous study of the effect the polarisation transfer field plays on the resulting signal enhancement levels is justified.

In the course of these studies we found that sterically hindered primary amines, secondary amines and aromatic amines were unable to form an active SABRE catalyst of the type [Ir(H$_2$(IMes)(amine))Cl]. This meant that direct polari sati on of such a complex was not possible. We found for aniline that the addition of a co-ligand such as CH$_2$CN overcame this problem via the formation of [Ir(H$_2$(IMes)(aniline))[CH$_3$CN]Cl] such that signal enhancements of up to 306-fold per NH proton could be achieved.

An indirect route was described to overcome this limitation more generally, such that hindered primary amines, secondary amines and aromatic amines can be hyperpolarised by SABRE-RELAY. Now, a SABRE-hyperpolarised intermediate, such as ammonia, is able to readily transfer polarisation into agents such as isopropylamine, benzylamine and aniline via either direct proton exchange or mediated by residual water present in the sample. This approach expands the range of amines that can be hyperpolarised without changing their chemical identity through interactions with p$_H_2$.

Given the increase in signal intensity that is observed for the amines in this study, we are now working towards their use as agents for mechanistic study in transfer hydrogenation, hydroamination, and vitally important N$_2$ fixation reactions. We have also shown that the SABRE-RELAY method has recently been shown to offer a route to hyperpolarise an even larger range of hydrogen transfer acceptors using OH functional groups. Optimisation of the intermediaries NH polarisation level reflects a key part to optimisation of this technique and hence these results will be of interest to any potential developer.

**Conflicts of interest**

The authors declare no conflicts of interest.

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