Harnessing polarisation transfer to indazole and imidazole through signal amplification by reversible exchange to improve their NMR detectability

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The signal amplification by reversible exchange (SABRE) approach has been used to hyperpolarise the substrates indazole and imidazole in the presence of the co-ligand acetonitrile through the action of the precatalysts [IrCl(COD)(IMes)] and [IrCl(COD)(SIMes)]. $^1$H-labelled forms of these catalysts were also examined. Our comparison of the two precatalysts [IrCl(COD)(IMes)] and [IrCl(COD)(SIMes)], coupled with $^1$H labelling of the N-heterocyclic carbene and associated relaxation and polarisation field variation studies, demonstrates the critical and collective role these parameters play in controlling the efficiency of signal amplification by reversible exchange. Ultimately, with imidazole, a 700-fold $^1$H signal gain per proton is produced at 400 MHz, whilst for indazole, a 90-fold increase per proton is achieved. The co-ligand acetonitrile proved to optimally exhibit a 190-fold signal gain per proton in these measurements, with the associated studies revealing the importance the substrate plays in controlling this value. Copyright © 2017 The Authors. Magnetic Resonance in Chemistry published by John Wiley & Sons Ltd.

Keywords: SABRE; indazole; imidazole; iridium catalyst

Introduction

Hyperpolarisation methods are being used widely to improve the sensitivity of nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) to substrate detection.\(^{[1,2]}\) Signal amplification by reversible exchange (SABRE) is one such method where the nuclear spin order from parahydrogen (p-H$_2$) is used to sensitise substrate detection.\(^{[3-5]}\) The process of SABRE relies on breaking the magnetic symmetry of two protons that were originally located within a p-H$_2$ molecule, whilst retaining a spin–spin coupling between them in addition to introducing new couplings between them and the substrate to be hyperpolarised.\(^{[5,6]}\) This is achieved by creating a SABRE catalyst that acts as a scaffold to bind both p-H$_2$ and the substrate such that it allows polarisation transfer through the resulting scalar coupling network. The process of SABRE is also affected by the magnetic field that is experienced by the catalyst during this process that is often called the polarisation transfer field (PTF).\(^{[6]}\) An active SABRE catalyst can break the symmetry of these two protons in one of two ways detailed in Scheme 1 for indazole, where the co-ligand is acetonitrile and the precatalyst is [IrCl(COD)(IMes)] \(1a\).\(^{[7]}\) As the original substrate molecule is reformed after ligand dissociation, there is no change in its chemical identity during this process, but it has now become a hyperpolarised (HP) species. SABRE catalysts based on N-heterocyclic carbene (NHC) iridium complexes that contain 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) or 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene (SIMes) ligands are used in this study.\(^{[8,9]}\) Although studies on other templates and a range of substrates have been described in the literature.\(^{[6,9,10]}\) A number of theoretical approaches have been used to model the SABRE effect, of which the level-anti-crossing approach provides a readily understandable solution.\(^{[11]}\) Recently, the role of relaxation within the SABRE catalyst has also become recognised, and models are being developed that take this into account.\(^{[7,12]}\) These studies have collectively confirmed that the time the substrate spends on the catalyst plays an important role in establishing the level of hyperpolarisation it gains. As a consequence, the ligating power of the substrate, which is linked to the pKa of the binding site, is important, as too strong an interaction can lead to low success by reducing overall exposure to p-H$_2$.

One of the drivers for the development of hyperpolarisation methods is the potential to collect in vivo data on a hyperpolarised agent that may ultimately prove to be diagnostic of health.\(^{[10b]}\) Another is the use of high-sensitivity methods in analytical chemistry.\(^{[10a,13]}\) Other routes to hyperpolarisation include dynamic nuclear polarisation,\(^{[2]}\) parahydrogen-induced polarisation\(^{[6b,14]}\) with substrate functionalisation and spin-exchange optical pumping.\(^{[10c,15]}\)
We have selected indazole (ind) and imidazole (im), for this study because this family of nitrogen-containing heterocycles plays a role in a wide variety of biological processes. Additionally, the imidazole motif is also present in the amino acid histidine and the hormone histamine. Furthermore, antifungal agents such as flutrimazole and antibiotics such as metronidazole also contain this structural element. Indazole derivatives therefore take an important place in healthcare as their biological activities include anti-inflammatory, antimicrobial, anti-HIV and anticancer roles.

Early reports on SABRE with indazole by Dücker et al. using the first generation of phosphine-based SABRE catalysts were observed to produce a 2-fold NMR signal enhancement. A study on imidazole by Moreno et al. using the second generation of carbene-based SABRE catalysts produced an improved response. Chekmenev et al. has also reported on the hyperpolarisation of imidazole, with the supplementary information suggesting that a 100-fold signal enhancement is produced in H-2 and 50-fold gain in H-4 and H-5. Here, we describe a series of high-field studies on polarisation transfer to both of these substrates where we detect their H-4 and 13C NMR signals. We seek to improve on the degree of SABRE response by exploring the effect of catalyst structure and the use of a co-ligand, in addition to varying the pH of the methanol solutions that are employed. It has recently been established that pH effects during SABRE can be substantial.

The role for a co-ligand during SABRE has been highlighted several times. In one manifestation, the use of a 2H-labelled substrate allows the SABRE effect to be successfully focussed into the protons of a second substrate. Specifically, we show here that complex 2a of Scheme 1 readily forms through the binding of two indazole ligands and one acetonitrile ligand. In SABRE catalysts of this type, the hydride ligands are therefore made chemically and magnetically inequivalent. The second form of catalyst, 3a, contains three indazole ligands, and now, polarisation transfer is facilitated by magnetic inequivalence effects. The mechanisms of ligand exchange in these types of complex have been examined previously when the substrate is pyridine and underpin the SABRE effect. These studies have enabled the hyperpolarisation of acetonitrile and reveal that it is possible to improve the pyridine response when CD3CN is used. More recently, the hyperpolarisation of acetonitrile by SABRE has been considered. Here, we show that, for type 2 complexes, the acetonitrile ligand is more labile than indazole and imidazole. The level of signal enhancement resulting from SABRE relates to the ligand exchange rate constants because polarisation transfer proceeds via the small J-coupling that exists between the hydride ligand and polarisation acceptor. Understanding these effects is critical to optimisation of SABRE. It has also been suggested that because transfer is slow, relaxation by the SABRE catalyst can limit performance, and a simple and readily understandable model to assess this has been reported by Koptyug. We therefore also report on the effects of catalyst deuteration on the level of SABRE by reference to appropriate isotopologues of IMes and SIMes, and by combining these approaches, we achieve high-field signal gains in excess of 700-fold. Our co-ligand strategy also enables significant CH3CN hyperpolarisation to the achieved.
Results and Discussion

IrCl(NHC)(COD)-derived signal amplification by reversible exchange of indazole: formation of [Ir(H$_2$(ind)$_2$(NCCH$_3$)(NHC)]Cl (2) and [Ir(H)$_2$(ind)$_3$(NHC)]Cl (3)

[IrCl(COD)(IMes)] (1a) and [IrCl(COD)(SIMes)] (1b) were found to react with indazole (4–10-fold excess, relative to iridium) and acetonitrile (3-fold excess) to form equilibrium mixtures of [Ir(H)$_2$(ind)$_2$(NCCH$_3$)(IMes)]Cl (2) and [Ir(H)$_2$(ind)$_3$(IMes)]Cl (3). These four complexes have been characterised by multinuclear NMR spectroscopy, the details of which can be found in the Supporting Information. In the case of 1a, when the initial ligand ratio of indazole–acetonitrile is 10:3, products 2a and 3a exist in a 1:34 ratio, and hence, 3a dominates. These complexes are diagnostically identified by the chemical shifts of their hydride ligands, which appear at $\delta_H$ = 20.91 and 21.32 in 2a and at $\delta_H$ = 21.26 in 3a respectively in MeOD at 298 K. The associated product ratio indicates a weaker Ir–NCMe bond, when compared with Ir–N$_{\text{indazole}}$, and thus, 3a is thermodynamically more stable than 2a. In contrast, the analogous reaction with 1b yields 2b and 3b in the ratio 1:50 under the same initial conditions. This indicates that the relative bond energies of the Ir–NC and Ir–N$_{\text{indazole}}$ lie further apart when SIMes is the ancillary ligand as there is an even higher preference for 3b. The corresponding hydride chemical shifts for 2b are $\delta_H$ = −20.95 and −21.28, whilst that for 3b is $\delta_H$ = −21.23. The hydride chemical shifts in the related complexes 2a and 3a, and 2b and 3b, are therefore very similar to one another and hence not strongly dependent on the identity of the NHC. Figure 1, panels (a), (b) and (c), shows the aromatic and hydride regions of a series of $^1$H-NMR spectra in methanol-d$_4$ that were obtained with indazole. The NMR trace in panel (a) corresponds to one that was obtained before the addition of H$_2$, and signals for H-3 through H-8 of indazole are indicated. The addition of H$_2$ changes this response as 2a and 3a form with the new resonances for the coordinated indazole ligands being indicated with the * and ● labels (equatorial and axial ligands respectively, panel (b)). The hydride region of this NMR spectrum (right) reveals that 3a dominates.

Figure 1. Plots (a), (b) and (c) show the aromatic and hydride regions of a series of $^1$H-NMR spectra that were obtained in methanol-d$_4$ solution with 1a and indazole.
When this reaction is completed with \( p-H_2 \) and observed by \(^1\)H-NMR spectroscopy, the hydride ligand signals of \([\text{Ir}(H)_2(\text{ind})_2(\text{NCH}_3)(\text{NHC})]Cl (2)\) exhibit antiphase character due to the parahydrogen-induced polarisation effect in the corresponding \(^1\)H-NMR spectra (Fig. 1c, right). The average relative signal intensity gain for the polarised hydride resonances of 2a is eight times larger than those of 2b in comparable experiments (refer to Fig. 1c for a typical result). In addition, the equivalent hydride ligand signals of \([\text{Ir}(H)_2(\text{ind})_3(\text{NHC})]Cl (3)\) both exhibit a weak in-phase signal gain when they are first observed when sample transfer from low field, but this gain lies just 1.6-fold in favour of 3a over 2a. The difference in 2a/2b signal enhancement level is consistent with the fact that the observed rate of \( H_2 \) loss at 298 K, as determined by exchange spectroscopy methods, from 2a is 0.65 s\(^{-1}\), and just 0.08 s\(^{-1}\) for 3a. Hence, there is more rapid \( p-H_2 \) introduction into 2a and a larger signal gain results. These enhancement data therefore indicate that the presence of the acetonitrile facilitates more rapid IrH/H\(_2\) exchange in agreement with observations reported previously for the related products that form with pyridine.\(^{17}\)

Using an automated polariser

A solution containing such a mixture of 2a and 3a, and free indazole, was subsequently probed for SABRE. These measurements were made in an automated flow apparatus that has been described previously.\(^{10a}\) This device, the Polariser, is represented in Fig. 2. It was designed to enable a solution that contains the catalyst and the hyperpolarisation target to be polarised using \( p-H_2 \) within a mixing chamber (MC) that is located in low field. The MC is surrounded by coil that can be used to generate a precise local magnetic field in the range \(-140\) to \(+140\) G and is located within a \( \mu \)-metal shield to screen the effect of the earth’s field. For the flow measurements conducted in this study, a 3 ml mixture of methanol-\( d_4 \) solution is typically employed that contains the iridium catalyst at a concentration of between 5 and 7 mM. It also contains 2–3 molar equivalents of the co-ligand acetonitrile and 10 molar equivalents of the target substrate. Once a substrate is hyperpolarised, after bubbling \( p-H_2 \) through the solution for a predefined period, bubbling is stopped, and a 3-s \( N_2 \) purge activated. The solution then flows under nitrogen pressure into the NMR probe head for measurement in a process that takes 0.6 s, although a further delay of 0.1 s is added to allow the solution to settle before the NMR measurement is started. NMR measurement then proceeds in the usual way, although a receiver gain of 1 is typically employed to deal with the strongly enhanced signals we expect to detect. It takes therefore a total of 4.8 s to make a measurement after the SABRE step has been completed. During this time, the sample moves from low to high field and therefore experiences a range of magnetic environments and hence relaxation effects. These effects will act to reduce the level of detected SABRE and must play a larger role in shrinking the measured response of any rapidly relaxing signals. By employing this flow approach, the solution can ultimately be returned to the MC in order for it to be repolarised and the process started again. In this way, signal averaging, signal reproducibility and variable PTF plots can be constructed by repeated analysis of the same sample.

By using this equipment, we are able to precisely vary a number of parameters that control the SABRE effect in order to optimise them. When the initial concentration of 1a in methanol-\( d_4 \) was 6.5 mM, and 49.4 mM of indazole and 17.0 mM of acetonitrile were introduced, strong SABRE enhancements were visible in the NMR signals of both these reagents. The maximum proton signal enhancement for the five non-exchangeable protons of indazole proved to total 115-fold that equates to a signal gain of \( \sim 20 \) per proton and resulted when the sample had been exposed to a 70 G magnetic field in conjunction with 20 s of exposure to \( p-H_2 \) (Supporting Information, Fig. S1). The corresponding acetonitrile proton signal was observed to achieve a maximum enhancement of 145-fold after transfer at 80 G that equates to an \( \sim 50 \) fold gain per proton (Supporting Information, Fig. S2). Previously, such a high level of polarisation transfer into acetonitrile has only been seen when a deuterated ligand scaffold is employed in conjunction with the co-ligand pyridine.\(^{17}\) This study therefore reveals the importance of the co-ligand in controlling the level of polarisation transfer into a weakly bound ligand, in this case acetonitrile. We note that Tessari et al. further developed the co-ligand approach to enable analyte quantification at low loadings.\(^{28}\) Additionally, the efficiency of the SABRE effect is PTF dependant as a consequence of the matching conditions that must be met between the chemical shift and coupling values within the catalyst.\(^{12,29}\) It is therefore usual to quote optimal PTF values when
reporting data in a similar way to quoting absorption maxima in UV spectroscopy.

When a 6.6 mM solution of 1b was examined in the presence of similar 10 and 3-fold ligand excesses respectively, SABRE was again observed. Now, however, the total indazole proton signal enhancement within the five sites increased to 234-fold (~47 per proton) after transfer at a PTF of 70 G and a 20-s $p$-$H_2$ exposure time. The corresponding acetonitrile signal gain was 266-fold at 80 G. Hence, the catalyst derived from 1b exhibits superior performance to that derived from 1a. This observation is in agreement with the fact that the effective rate of build-up of indazole in solution, via dissociation from dominant 3a and 3b, at 298 K is 0.26 and 0.64 s$^{-1}$ respectively. Scheme 2 illustrates the SABRE process in a conceptual form. The effective rate of build-up of free substrate in solution used here is defined as the observed rate of magnetisation transfer from the H-3 resonance of 3 into the corresponding signal for free indazole and has units of per second (refer to Supporting Information).

We also undertook a series of control measurements under analogous conditions without acetonitrile. The corresponding H-3 signal of indazole was observed to yield a 330-fold signal again under these conditions where 3a is the catalyst after transfer at 60 G.

**Signal amplification by reversible exchange hyperpolarisation of residual CHD$_2$OD and CD$_3$OH**

Mechanistically, the loss of indazole from 3 and acetonitrile from 2 will lead to a common 16-electron intermediate, $[\text{Ir(H)}_2(\text{ind})_2(\text{NHC})]\text{Cl}$, alongside hyperpolarised indazole and acetonitrile respectively (Scheme 1). Both $H_2$, indazole or methanol can then coordinate to this intermediate, with $p$-$H_2$ binding providing the route by which the cycling of $p$-hydrogen is achieved that underpins SABRE. As methanol is present in far larger excess than either indazole or acetonitrile, its binding is assured, and single-spin hyperpolarisation is consequently observed in these experiments in the residual CHD$_2$OD and CD$_3$OH solvent signals as detailed in Fig. 3. For systems derived from 1a, transfer into the solvent is most readily evident after transfer at 70 G, with both of the residual solvent signals showing a phase change, from absorption to emission, on moving between transfer fields of 50 and 60 G. The maximum signal enhancement seen for these signals, relative to those seen under thermal conditions, was 2.6-fold for the CHD$_2$OD peak and 3.0-fold for the CD$_3$OH peak. This small level of signal gain results from the low proportion of $^1$H-labelled species in CD$_3$OD, which means that most of the methanol binding to the associated 16-electron intermediate $[\text{Ir(H)}_2(\text{ind})_2(\text{NHC})]\text{Cl}$ forms $[\text{Ir(H)}_2(\text{ind})_2(\text{CD}_3\text{OD})(\text{NHC})]\text{Cl}$ that will be unproductive for methanol-SABRE. Furthermore, the concentration of $[\text{Ir(H)}_2(\text{ind})_2(\text{methanol})(\text{NHC})]\text{Cl}$ must also be low as this species is not detected in these NMR spectra.

Under SABRE, the level of signal enhancement builds as the exposure time to $p$-$H_2$ increases prior to reaching a relaxation-controlled maximum.$^{[22]}$ This is commonly referred to as the bubbling time when using the automated system described earlier, and it might be expected that a signal builds up in intensity before reaching a plateau.$^{[10a]}$ The low efficiency of the methanol CHD$_2$ enhancement allows this effect to be visualised, as detailed in Fig. 4.
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Figure 4. Plot of the p-H₂ bubbling time versus the level of CHD₂OD signal gain. The change in signal phase results from the combination of a positive thermal signal and a negative hyperpolarised signal for the CHD₂OD resonance.

that shows a change in signal phase as the bubbling time is increased; the SABRE effect creates a negative signal that eventually outweighs the thermally polarised state that produces the positive background peak. Bubbling times between 5 and 70 s were examined that contrast with the 20 s needed to see SABRE with acetonitrile or indazole.

We have also probed the effect of adding CD₂OH and H₂O to these CD₂OD solutions in order to increase the proportion of CD₂OH in solution. These results are detailed in the Supporting Information and reveal complex behaviour. When H₂O is added, the indazole, acetonitrile, methanol and HOD signal gains all first increase in size before falling as the level of doping is increased. The origin of this fall with added H₂O is likely to result from the reduced solubility of H₂ in water and the associated decrease in ¹H relaxation times. A related series of solutions were then examined in the presence of HCl and NaOH. No significant changes in the level of proton indazole or solvent signal enhancement were evident. This contrasts with the results of Moreno et al. who saw an increased level of polarisation transfer into the solvent molecules in acid solution at low field. We note though that it takes 4.8 s to move the sample from the external MC into the high-field magnet where our measurements are made, and hence, relaxation could account for this difference.

Effect of changing the ligand scaffold to d₂₂-IMes or d₂₂-SIMes on the level of signal amplification by reversible exchange shown by indazole

Upon replacing the protio form of these NHC ligands with their deuterated variants d₂₂-IMes and d₂₂-SIMes, the levels of indazole and acetonitrile proton signal enhancements under SABRE changed as detailed in Table 1. For d₂₂-IMes, the maximum indazole proton signal enhancement was now obtained at 90 G rather than 70 G, and after 35 s of contact with p-H₂, rather than the 20 s used earlier. Its final value is, however, reduced from 115-fold to just 82-fold, and hence, it can be concluded that in this case, ³H-labelling of the catalyst has a negative effect on the level of indazole polarisation that is achieved when compared with the IMes system. In contrast, the acetonitrile proton signal enhancement level increased very dramatically from the original 145-fold value to 572-fold, with transfer now taking place at 90 G rather than the original 80 G field value (190-fold per proton). Hence, polarisation transfer into acetonitrile has become more facile, and as a consequence, it now receives the largest SABRE benefit.

The corresponding change to d₂₂-SIMes, however, resulted in an indazole signal gain that averaged to ~91-fold per proton, and a 372-fold CH₃CN signal gain at the same transfer field values as used earlier, which remained optimal. Deuterating the carbene ligand of 1a therefore leads to a 41% fall in indazole polarisation, but for 1b, it leads to a 60% increase. We note that increases in temperature result in further increases in these signal gains as the ligand exchange rates are slow relative to what might be expected to be their optimum values. In contrast, deuterating the IMes ligand associated with 2a leads to a 300% gain in acetonitrile polarisation, whilst for 2b, it leads to a 17% fall. This difference will be rationalised later.

Effect of polarisation transfer field on the level of signal amplification by reversible exchange shown by indazole

Figure 5 illustrates how the PTF affects the indazole proton enhancement level as a function of ligand scaffold deuteration. In the case of 3, there is one unique hydride coupling into the bound indazole ligand that will lead to transfer to proton H-3 of Scheme 1; the hydride couplings across the bridge into the second phenyl ring are expected to be too small to receive direct polarisation transfer via the hydride ligand. Protons H-8, H-5, H-7 and H-6 will therefore achieve their hyperpolarised states via relayed transfer through H-3. This behaviour accounts for the fact that when the SABRE efficiency of 3 is examined, as a function of PTF, a signal maximum is evident for all of these protons (Fig. 5). The breadth of the peak seen in the PTF profile changes, narrowing with deuteration of the NHC, and hence, we conclude that the matching transfer condition narrows when the deuterated ligands are employed. These changes mean that there is a greater need to place the sample in an appropriate PTF when undertaking studies with deuterated ligands.

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**Table 1. Overall proton signal enhancement values (fold) returned for indazole and CH₃CN as a function of catalyst at 9.4 T using the polarisation transfer field detailed in brackets**

| Catalyst | Indazole | Acetonitrile |
|----------|----------|--------------|
| IMes     | 116 (70 G) | 146 (80 G)  |
| d₂₂-IMes | 82 (90 G)  | 572 (90 G)  |
| SIMes    | 294 (70 G) | 437 (80 G)  |
| d₂₂-SIMes| 457 (70 G) | 372 (80 G)  |

The associated reagent concentrations were 6.5 mM (iridium), 65 mM (indazole) and 19.5 mM (acetonitrile).
Effect of relaxation within the signal amplification by reversible exchange catalyst on the level of indazole signal enhancement

An effect that needs to be considered when rationalising these results is that of relaxation within the catalyst, which is predicted to be reduced by deuteration. The importance of this stems from the fact that the bound and free forms of the ligands are in dynamic exchange, and hence, any increase in relaxation time of the associated protons in the catalyst should be seen directly in the response of the free substrate. For example, if the lifetime of the catalyst is too long, the associated signals will suffer from greater relaxation during the polarisation transfer step, and hence, increasing the catalyst's intrinsic proton relaxation times should be beneficial. In contrast, if ligand exchange is rapid, then the relaxation times of the free substrate will reflect more closely those of the bound form and that will act to limit the period over which hyperpolarised signals for the free substrate can be seen.

The relaxation times of the five protons of indazole and acetonitrile in a methanol-d₄ solution under 3 bar H₂ without the catalyst at 298 K were therefore determined. They are 22.2 s for proton H-3, 12.8 s for H-8, 12.5 s for H-5, 8.5 s for H-7 and 9.3 s for H-6 with the acetonitrile value being 14.4 s at 9.4 T. Upon adding the catalyst and H₂ to this solution, and repeating the associated measurements at 298 K, the apparent relaxation time for proton H-3 of free indazole, and that of the free acetonitrile resonance, was found to decrease to 12.3 and 8.7 s respectively, whilst those for the remaining four indazole sites fell by a smaller amount (Table 2). We confirm therefore that the presence of the catalyst reduces the measured relaxation times of the free substrate in solution and therefore acts to limit the period over which it can be viewed with a high-sensitivity response.

Cooling the sample to reduce the associated ligand exchange rates would be expected to suppress this relaxation-based behaviour. We therefore undertook a control measurement on indazole at 263 K in methanol-d₄ at the same 50 mM concentration. The corresponding T₁ values were now 17.4, 7.2, 7.2, 4.0 and 4.5 s respectively. Hence, as expected, lowering of the temperature reduces the T₁ values of indazole. The corresponding T₁ values were then determined for the protons of bound and free indazole in a mixture with 3 at 263 K. Now, as predicted, the corresponding bound proton values proved to be dramatically smaller than those of the free substrate, which, in turn, were remarkably similar to those determined without 3. The size of the relaxation effects seen for 3b proved to be even larger at 298 K in accordance with the higher ligand exchange rates exhibited by this complex, and we therefore conclude that relaxation of the hyperpolarisation prior to ligand dissociation is limiting. The corresponding relaxation data for the catalysts containing d₂₅-SIMes or d₂₅-IMes ligands were also determined and found to differ from those of their protio counterparts as shown in Table 2. We note that even though these parameters have been determined at high field, and the transfer process occurs at low field where the relaxation times will be different, a substantial effect has been seen. Given that the ligand exchange rates would not be predicted to change with remote 2H labelling, and the hydride-proton couplings should also remain constant, this behaviour suggests that the ancillary ligands of the catalyst play a role through relaxation during the SABRE process.

Polarisation transfer into the ¹³C response of indazole, acetonitrile and methanol

SABRE is also evident in the ¹³C resonances of indazole, acetonitrile and methanol as detailed in Fig. 6 for a 35-s contact time with p-H₂ and the 1a-derived catalyst system. Polarisation transfer into the quaternary ¹³C signal for C₆ of indazole reaches a maximum at
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Table 2. Experimental $T_1$ values determined at 9.4 T in methanol-$d_4$ solution for the indicated proton nuclei of free and bound indazole at 263 and 298 K respectively

| Site 263 K | IMes $T_1$ (s) | $d_{22}$-IMes $T_1$ (s) | SIMes $T_1$ (s) | $d_{22}$-SIMes $T_1$ (s) |
|------------|----------------|------------------------|----------------|---------------------|
|            | Free Coord    | Free Coord             | Free Coord     | Free Coord          |
| H-3 15 ± 4 $^a$ | 0.9           | 4.8                    | 0.8            | 16.1                |
| H-8 7.0    | b             | 3.5                    | 1.4            | 8.4                 |
| H-5 7.0    | 1.9           | 3.3                    | 1.6            | 7.3                 |
| H-7 4.1    | 2.2           | 2.6                    | —              | 4.6                 |
| H-6 8.2    | 1.7           | 2.7                    | 0.9            | 4.8                 |
| NCMe       | 8.2           | 4.8                    | —              | 11.5                |
| H-3 13.6   | 2.1           | 9.8                    | 1.9            | 11.8                |
| H-8 10.3   | 5.8           | 7.4                    | 3.7            | 10.8                |
| H-5 10.5   | 2.7           | 7.5                    | —              | 10.9                |
| H-7 6.7    | 4.0           | 5.5                    | 2.3            | 7.0                 |
| H-6 7.2    | —             | 5.6                    | —              | 7.6                 |
| NCMe       | 8.7           | 8.9                    | —              | 12.4                |

The associated reagent concentrations were 6.5 mM (iridium), 65 mM (indazole) and 19.5 mM (acetonitrile), and the labelling follows that in Scheme 1.

$^a$Peak behaviour anomalous due to $^2$H label incorporation.

Figure 6. Polarisation transfer field effects seen on the intensity of the $^{13}$C NMR signals of indazole and NCCH₃ that result from signal amplification by reversible exchange.

40 G (132-fold) with transfer into quaternary C₆ being observed between 50 (58-fold) and 60 G, and 80 and 90 G, although there is a minimum at 70 G. The effect of the PTF on $^{13}$C transfer is therefore complex and reflects the number of different coupling pathways in operation. The size of the SABRE effect is PTF dependant with the $^{13}$C quaternary signal of free acetonitrile readily appearing at 116 ppm after transfer a ~0G in a μ-metal shield (a $^{15}$N signal can also be seen, refer to Supporting Information). Upon increasing the transfer field beyond this value, the acetonitrile signal gain reduces, but at points beyond 100 G, it is again observed through an enhanced signal. We note that we do not observe polarisation transfer into the $^{13}$CH₃ group of acetonitrile nor into...
the $^{13}\text{C}$ atoms of methanol-$d_4$ under these conditions. This is consistent with earlier reports that detail how optimal $^{13}\text{C}$ transfer proceeds via small $^{1}J_{\text{CH}}$ couplings rather than the larger $^{2}J_{\text{CH}}$ couplings.$^{[22]}$

The levels of $^{13}\text{C}$ signal gain achieved with 1b proved smaller than those with 1a as detailed in the Supporting Information, and the replacement of the SIMes or IMes ligands with $d_{22}$-SIMes and $d_{22}$-IMes respectively also led to worse SABRE performance with the maximum $^{13}\text{C}$ signal enhancement seen for site A (Scheme 1) being 63-fold in the latter case; adding acid into this system did not improved these signal enhancement levels.

**Reaction of IrCl(NHC)(COD) with imidazole, H$_2$ and acetonitrile and the observation of signal amplification by reversible exchange**

[IrCl(COD)(IMes)] (1a) and [IrCl(COD)(SIMes)] (1b) were then used to hyperpolarise imidazole (im). Similar 5 mM methanol-$d_4$ solutions of 1 or 2 were employed, with a 10-fold excess of imidazole and a 3-fold excess of acetonitrile. For 1a, 97% of the products were now in the form [Ir(H)$_2$(im)$_3$(IMes)]Cl (5a) with the remaining 3% corresponding to [Ir(H)$_2$(NMe)$_2$(IMes)]Cl (4a) as detailed in Scheme 2. In the case of 1b, the reaction proceeded cleanly to form 5b as the sole product. Characterisation data for these products are detailed in the Supporting Information. When the SABRE effect was explored for imidazole, $p$-H$_2$ contact times of 60 s were used, rather than the 25–30 s time for indazole, as this resulted in the detection of larger signal enhancements.

**Effect of polarisation transfer field on signal amplification by reversible exchange with imidazole**

Figure 7 illustrates how the PTF affects the imidazole proton signal enhancement level as a function of catalyst. In 5, there are three unique spin–spin couplings between the hydride ligand (trans) and the imidazole protons in the SABRE transfer catalysts of.
Scheme 3 and six routes to relayed transfer between the three protons. These three protons exhibit chemical shifts of $\delta_{H_4}$ 6.82, 6.86 (H-4 and H-5) and 6.9 (H-2) in 5a and will all receive polarisation under SABRE with different efficiencies according to the PTF and couplings they experience at the point of transfer. Consequently, upon the dissociation of hyperpolarised imidazole from 5, all three of its proton signals should appear enhanced, but only two signals are actually seen, at $\delta_{H_4}$ 7.70 and 7.07, due to the fact the resonances for H-4 and H-5 have effectively identical chemical shifts. As expected, the SABRE results, with imidazole, therefore show a strong PTF dependence as detailed in Fig. 7. For H-2, a signal peak is seen that reaches a maximum at a PTF value of 70 G, whilst the strong PTF dependence as detailed in Fig. 7. For H-2, a signal peak is seen that reaches a maximum at a PTF value of 70 G, whilst the combination signal for H-4 and H-5 now shows a bimodal result with maxima at 50 and 90 G.

Level of signal amplification by reversible exchange found for imidazole

In methanol-$d_6$, the 1a-derived catalyst system proved to deliver signal enhancements of 606-fold and 830-fold for these two signals respectively per proton, which equates to a total signal enhancement value of 2042-fold within im. It would therefore appear that the NCHN motif, rather than the CHCH arrangement, receives the highest level of SABRE transfer. The overall signal gain clearly exceeds the level seen for indazole where the corresponding value was just 115-fold, as detailed in Table 4. Furthermore, upon moving to 1b, the overall signal enhancement falls to 1028-fold that contrasts with the indazole return of 146-fold, and the CHCH arrangement receives the most benefit. We can therefore conclude that imidazole is better suited to SABRE than indazole.

We also undertook a series of control measurements under analogous conditions without acetonitrile. The corresponding H-2 signal of imidazole was now observed to yield a 551-fold signal gain under these conditions after transfer at 60 G, whilst the signals for H-4/5 yielded a 410-fold gain after transfer at 70 G per proton. Hence, imidazole polarises better in the presence of acetonitrile.

These results also proved to be pH sensitive, with the overall proton signal enhancement seen for imidazole dropping to 1475-fold (H-2, 571-fold) with 1a in the presence of HCl$_{aq}$ as summarised in Table 3. Additionally, the acetonitrile signal gains, relative to those seen with indazole, proved to be much lower in accordance with the reduced concentrations of the associated catalyst 4. The level of SABRE exhibited by the solvent CHD$_2$OD is also worse than that seen with indazole in accordance with 4 that plays a role in this process, but can be improved 20-fold by $^2$H labelling the IMes ligand.

Imidazole ligand exchange rates in the active signal amplification by reversible exchange catalyst

The free imidazole build-up rate in solution of 5a, without HCl, proved to be 3.39 s$^{-1}$ and its H$_2$ loss rate 3.68 s$^{-1}$. However, in the presence of 0.8 equivalent HCl, the imidazole build-up rate in solution fell to 2.52 s$^{-1}$, whilst the apparent H$_2$ loss rate became 4.75 s$^{-1}$. For 5b, without HCl, the ligand build-up rate was 1.04 s$^{-1}$ and the H$_2$ loss rate 1.75 s$^{-1}$, but with HCl (0.8 equivalents), they became 1.11 and 1.85 s$^{-1}$ respectively. These ligand build-up rates are therefore faster than those seen for indazole and that must account for the improved SABRE performance seen with imidazole. However, it is interesting to see that the IMes system now exchanges more rapidly than the SIMes form which suggests the reduced volume$^{[9,33]}$ term associated with the NHC plays a greater role here in promoting ligand loss. Promotion of H$_2$ loss in acidic solution suggests that the complex is susceptible to protonation that would be detrimental to SABRE.$^{[10d]}

Effect of changing the ligand scaffold to d$_{22}$IMes or d$_{22}$SIMes on the level of signal amplification by reversible exchange shown by imidazole

When the catalysts d$_{22}$IMes-1a and d$_{22}$SIMes-1b are deployed with imidazole, the signal intensities seen under SABRE in indazole and acetonitrile fall dramatically.

Table 3. Indicated proton signal enhancement levels achieved at 298 K, with a PTF of 80 G, when measured at 9.4 T, by the action of the precatalysts 1a and 1b on imidazole, with and without HCl, where the concentrations are 6.5 mM iridium, 65 mM indazole and 19.5 mM acetonitrile

| Resonance (without HCl) | IMes $d_{22}$IMes SIMes | d$_{22}$SIMes |
|-------------------------|--------------------------|---------------|
| H-2                     | −830                     | −198          | −517  | −280          |
| H-4 and H-5             | −606                     | −300          | −197  | −206          |
| CD$_2$OD                | 1.5                      | 10            | 1.4   | 1.2           |
| CHD$_2$OD               | 2.5                      | 45            | 7.5   | 0.5           |
| NCMe                    | −35                      | −30           | −4    | 0             |

| Resonance (with 5 mM HCl) | IMes $d_{22}$IMes SIMes | d$_{22}$SIMes |
|---------------------------|--------------------------|---------------|
| H-2                       | −571                     | −210          | −647  | −225          |
| H-4 and H-5               | −456                     | −153          | −562  | −251          |
| CD$_2$OD                  | −22                      | −13           | −7    | −31           |
| CHD$_2$OD                 | 2                        | 0.2           | 1.5   | 0.5           |
| NCMe                      | −16                      | −168          | −12   | 11            |
Effect of relaxation within the signal amplification by reversible exchange catalyst on the level of imidazole signal enhancement

The relaxation times of the protons in imidazole were also studied in a similar way to those of indazole and are presented in Tables 4 and 5. The corresponding values for the free substrates in degassed methanol-d₄ solution are 51.1 s for H-2 and 26.6 s for the H-4 and H-5 response of imidazole, whilst the value for CH₃CN was 16.3 s at 298 K (the corresponding values at 263 K are 33.3, 13.5 and 11.4 s respectively). It is notable that the relaxation times for free imidazole are larger than those of indazole, with the N-isolated proton H-2 having a value of 51 s. At 298 K, this value falls by 67% to 16.9 s in the presence of 5a, whilst the corresponding fall in indazole H-2 T₁ value was 39% under analogous conditions and is consistent with the higher ligand exchange rates for imidazole.

For IMes, at 263 K, the relaxation times within 5a of the three magnetisation receptors are 3.1 s (H-2), 1.6 and 1.0 s (H-4 and H-5), whilst for 5b, they are 3.5, 1.8 and 1.9 s respectively, and hence, all are larger than the 0.9-s value determined for H-3 in 3a. This behaviour is therefore consistent with the improvement in SABRE efficiency that is seen on moving to imidazole. In the 2H-labelled form of 5a, the corresponding T₁ values increase to 4.3, 2.4 and 1.2 s respectively, whilst in 5b, they become 3.7, 1.4 and 1.9 s. Both of these sets of values at 9.4 T are therefore larger than those resulting from the corresponding 1H-labelled catalysts. It is therefore clear that these high-field values are not a good indicator of the role relaxation plays during SABRE transfer in low field.

Polarisation transfer to ¹³C in imidazole

A series of hyperpolarised imidazole ¹³C-NMR spectra were also recorded using a methanol-d₄ solution that initially contained a 7-fold imidazole and 3-fold acetonitrile excess relative to 1a, with and without HCl. These NMR spectra are detailed in Fig. 8. The ¹³C signals of free imidazole also proved to exhibit far greater signal gains than those found for indazole. For the signal due to CA, a strong response was seen, whilst the averaged signal, observed for the two remaining CH sites, was weaker. The intensities exhibited by these signals are again field dependent with both showing maxima after transfer at ca. 40 and 90 G. In contrast, upon adding acid, the signals for CB appear strongly (Fig. 8 right), presumably due to a sharpening of the response due to the increased rate of NH site interchange, although no effect is seen in the PTF plot. When 1b is employed, the corresponding signal gains on CB were around 10 times better than those seen with 1a in neutral solution. When acid was added, the level of ¹³C response resulting from 1b increased by a further 12-fold. We can therefore conclude that whilst IMes is the better motif for ¹H-SABRE, ¹³C-SABRE benefits from deploying SIMes. When the corresponding

Table 4. Experimental T₁ values, determined at 9.4 T in methanol-d₄ solution for the indicated proton nuclei of free and bound imidazole (5b) at 263 and 298 K respectively

| Catalyst       | Proton/T₁ (s) | 263 K | 298 K | 298 K (with HCl) |
|----------------|---------------|-------|-------|------------------|
|                | IMes          | d₂₂-IMes | IMes | d₂₂-IMes | IMes | d₂₂-IMes |
| Free substrates| H-2           | 33.7   | 25.5  | 16.9  | 22.9  | 15.8  | 21.8  |
|                | H-4 and H-5   | 14.1   | 12.0  | 12.2  | 15.1  | 11.9  | 14.8  |
|                | NCMe          | 8.2    | 9.6   | 8.3   | 9.5   | 7.9   | 10.3  |
| Bound imidazole| H-2 eq        | 3.1    | 4.3   | 13.7  | 14.1  | 8.7   | 13.4  |
|                | H-4 eq        | 1.6    | 2.4   | 13.6  | 17.4  | 11.2  | 17.8  |
|                | H-5 eq        | 1.0    | 1.2   | 9.3   | 9.4   | 3.2   | 6.6   |
|                | H-2 ax        | 4.1    | 3.1   | 4.0   | 3.0   | 4.4   | 7.6   |
|                | H-4 ax        | 2.7    | 3.6   | 7.9   | 3.5   | 9.5   | 7.1   |
|                | H-5 ax        | 2.8    | 4.1   | 4.6   | 2.5   | 5.5   | 4.9   |

Table 5. ¹³C-NMR signal enhancement levels seen for the indicated carbon signals of imidazole as a function of catalyst (optimum polarisation transfer field in brackets) at 9.4 T, with and without 5 mM HCl

| Catalyst | ¹³C signal | Cₐ | C₈ | ¹³C signal | Cₐ | C₈ |
|----------|------------|----|----|------------|----|----|
|          | Without HCl| With HCl | Without HCl | With HCl |
| IMes     | 61 (90 G)  | 9 (120 G) | 59 (90 G)  | 40 (30 G) |
| d₂₂-IMes | 243 (90 G) | — | 144 (80 G) | 149 (40 G) |
| SIMes    | 446 (100 G)| 89 (100 G) | 365 (90 G) | 489 (110 G) |
| d₂₂-SIMes| 274 (110 G)| — | 221 (30 G) | 322 (30 G) |

The associated reagent concentrations were 6.5 mM (iridium), 65 mM (imidazole) and 19.5 mM (acetonitrile).
$d_{22}$-IMes and $d_{22}$-SIMes forms are examined, no real benefits are seen in neutral solution, but in slightly acidic solution, $d_{22}$-SIMes did yield a further doubling in $^{13}$C polarisation level. It is therefore clear that the optimal catalyst for SABRE depends on the NMR active nucleus that is targeted. We note that $^{15}$N signals can also be seen after transfer in the $\mu$-metal shield as described in the Supporting Information.

**Conclusions**

In conclusion, we have described a series of studies on the SABRE hyperpolarisation of the substrates indazole and imidazole, in the presence and absence of the co-ligand acetonitrile, using the precatalysts [IrCl(COD)(IMes)] and [IrCl(COD)(SIMes)]. These studies reveal that SABRE delivers a 830-fold signal enhancement for the H-3 resonance of imidazole and a 178-fold improvement for the H-2 resonance of indazole at 9.4 T in the presence of acetonitrile. These results have been rationalised by studies on the catalyst, [Ir(H)$_2$(IMes)(pyridine)$_3$]Cl, which is 22 s$^{-1}$ for IMes and 5a for SIMes, whilst for imidazole, they were 3.68 and 4.08 s$^{-1}$. Hence, the higher substrate loss rate matches with the observation of better SABRE performance in the hyperpolarisation of imidazole through 5a. However, all three of these free ligand build-up rates are substantially smaller than that exhibited for pyridine by [Ir(H)$_2$(IMes)(pyridine)$_3$]Cl, which is 22 s$^{-1}$. The hyperpolarisation of indazole and imidazole reported here is therefore less efficient than that achieved for pyridine.\[92a\]

One further impact of these ligand exchange values is reflected in the optimum $p$-H$_2$ contact time, which is referred to here as the bubbling time when the automated polariser is used. Whilst polarisation transfer proceeds under J-coupling, the catalyst gains its polarisation for transfer through the addition of fresh $p$-H$_2$. Hence, if the complex lifetime is short, $p$-H$_2$ addition and transfer must proceed on a relatively rapid timescale, and a short bubbling time can be employed. If the catalyst lifetime is longer, $p$-H$_2$ addition and transfer will proceed on a slower timescale, and a longer bubbling time can be employed to reach the point where relaxation acts to limit the ultimate level of polarisation that is exhibited by the free substrate. The recent paper by Barskiy et al. develops these points.\[11d\] It is for this reason that we used a 20-s bubbling time when detecting a $^1$H response for indazole, extending to 35 s when looking at the corresponding $^{13}$C signals, and 60 s for imidazole. Furthermore, upon changing the NHC to SIMes, the corresponding indazole build-up rates increase to 0.64 s$^{-1}$ for 3b but fall to 1.04 s$^{-1}$ for 5b. This suggests that for indazole, SIMes works better due to higher exchange, but for imidazole, the reverse is found experimentally, and hence, the $H_2$ exchange rate must be more critical.

We also utilised a series of $^2$H-labelled forms of these catalysts with a view to improve on the level of SABRE by harnessing...
potentially catalyse the reduction of small molecules, such as 
the 
the 

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Harnessing polarisation transfer to indazole and imidazole

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.