Ligand effects of NHC–iridium catalysts for signal amplification by reversible exchange (SABRE)†

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SABRE hyperpolarizes substrates by polarization transfer from para-hydrogen in a metal complex. We have measured the signal enhancement of pyridine and its exchange rate in various [Ir(NHC)(Py)2(H)2] complexes to gain insight into their dependence on the N-Heterocyclic Carbene (NHC) ligand’s steric and electronic properties.

Since it was first developed, NMR has become a powerful analytical tool that is now used widely in the fields of chemistry, materials science, medicine. However, because of the small population differences between the nuclear spin states in a magnetic field, NMR is intrinsically insensitive. One way to overcome this insensitivity is to use hyperpolarization techniques to produce non-Boltzmann spin-state distributions. Para-Hydrogen Induced Polarization (PHIP) can be achieved by a fast hydrogenation reaction with the para-isomer of molecular hydrogen (\(p-H_2\)). This has the disadvantage that an unaltered moiety needs to be present or incorporated into the molecule of interest.1

Duckett et al.3 have recently reported a new approach, known as Signal Amplification By Reversible Exchange (SABRE), to generate hyperpolarized molecules with \(p-H_2\) without direct hydrogenation, thereby expanding the scope of PHIP significantly. In this approach (Fig. 1) hyperpolarization is achieved by the temporary association of a substrate and \(p-H_2\) in the coordination sphere of a transition metal, whereupon the polarization can be transferred from the \(p-H_2\)-derived hydride ligands to the bound substrate via scalar coupling. The hyperpolarized substrate then dissociates into the bulk solution. Since the development of SABRE, several small molecules have been successfully polarized using this technique,3–5 and even trace detection is possible in low magnetic fields.6–8 The obtained polarization is even large enough for spectroscopy in zero field.9 A theoretical report predicts that the efficiency of polarization transfer from \(p-H_2\) to the substrate depends on both the magnetic field in which the transfer occurs and the ‘lifetime’ of the polarization mediating complex.10 The lifetime of the metal complex in turn depends on the exchange rates of \(p-H_2\) and the substrate in the catalytic complex.

With SABRE, the most commonly used catalyst is Crabtree’s catalyst, \([\text{Ir(COD)}(\text{PCy}_3)(\text{Py})_2][\text{BF}_4]\) (COD = cyclooctadiene; \(\text{Cy} = \text{cyclohexyl}; \text{Py} = \text{pyridine}\)), which forms the active polarization transfer catalyst \(\text{fac,cis-[Ir(H)\_2(\text{PCy}_3)\_2(\text{Py})_2]}[\text{BF}_4]\) upon the addition of \(p-H_2\) and pyridine. A study using various phosphine ligands revealed that electronic and steric effects of the ligands play an important role in the signal enhancement that is achieved. For example, phosphines that are sterically bulky and have strong electron-donating capacity (e.g. \(\text{PCy}_3\)) yielded the highest signal enhancement for pyridine.11

Duckett et al. hypothesized that SABRE could yield even larger signal enhancements by replacing the phosphines with the even stronger electron-donating N-heterocyclic carbene (NHC) ligands.12 They validated this approach for the complex \([\text{Ir(H)}_2(\text{IMes})(\text{py})_2]_2[\text{BF}_4]\) (IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazole-2-ylidine). This IMes ligand yields the best SABRE catalyst for pyridine reported to date, with a 360-fold increase (at 400 MHz) in the ortho proton’s \(^1\text{H-NMR}\) signal strength relative to non-hyperpolarized pyridine.12

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Fig. 1 Formation of active hyperpolarization transfer catalyst 2 from 1 and polarization transfer to pyridine (Py).
We report here on the efficiency of various iridium NHC complexes with aliphatic and aromatic R groups (Fig. 2) as SABRE catalysts. Their steric and electronic properties were quantified by the buried volume (% $V_{bur}$) and an analogue of the Tolman Electronic Parameter (TEP), respectively. To obtain more detailed information regarding the polarization process, we measured the signal enhancement of pyridine and its field dependence for all catalysts. In addition, we determined the lifetime of the complexes by measuring the dissociation rate of pyridine.

In a typical SABRE experiment, a solution of pyridine (100 mM) and 10% catalyst (10 mM) in deuterated methanol was pressurized with 3 bar $p$-$H_2$ (92.5%) in a pre-polarization magnet (+10 to –230 Gauss) and subsequently transferred to a 200 MHz NMR instrument where the spectrum was recorded in a single scan. More detailed information on this process can be found in the ESI. All catalysts were screened, except for catalyst 11, which did not dissolve sufficiently in methanol. The signal enhancements (Fig. 3) were found to be dependent on the pre-polarization field. The maximal signal enhancements are obtained at approx. 80 Gauss and varied slightly among the various catalysts (full details are provided in ESI). Currently, there is no explanation for the exact position of this optimal pre-polarization field.

The highest signal enhancement was obtained with IMes 10, giving enhancements up to 680 at 200 MHz and a pre-polarization field of 70 Gauss, corresponding to a polarization value of 1.11%. This complex was also selected by Dukett et al., who measured an enhancement factor of 360 at 400 MHz, which corresponds to a polarization value of 1.16% and is in reasonable accordance with our result. Of the other complexes (Fig. 3), the aromatic ones also perform well, but the signal enhancement of the next best catalyst, the saturated analogue SIMes 9, is already significantly lower (369 at 90 Gauss). Signal enhancements dropped below 100 when the aromatic R-group of the NHC ligand was replaced with an alkyl group.

The dependence of the enhancement factor on the electron-donating properties of the various NHC ligands is shown in Fig. 3A. Compared to the Tolman Electronic Parameter range covered by phosphine-type ligands (~20 cm$^{-1}$), that of NHC is relatively small (less than 3 cm$^{-1}$). For example the unsaturated ligands IMes 10 and IPr 7 are slightly more donating than their saturated counterparts SIMes 9 and SIPr 6, but there is almost no difference in electronics between the two substituent pairs (mesityl and diisopropylphenyl). Therefore, we conclude that electronic effects in the NHC series are relatively weak, and they do not have a strong influence on the enhancement factor.

Fig. 3B depicts the plot of the signal enhancement versus the steric parameter. We conclude from this plot that the unsaturated ligands (I, 4, 7, 10), that have less steric bulk than their respective saturated analogues (SI, 3, 6, 9), yield higher signal enhancements in all cases. Also, an optimal buried volume emerges which yields the highest signal enhancement. In order to determine the effect of the buried volume on the exchange rate ($k_{\text{cat}}$) of pyridine, selective inversion recovery NMR experiments were performed; with these methodologies slow chemical exchange processes in the range between $10^{-3}$ and $10^{-1}$ s$^{-1}$ can be studied. Fig. 4A reveals that the exchange rate increases with the steric bulk (see ESI for a complete set of values and errors). The only exception is the tert-butyl substituted ligand 5; in this case only a trace amount of active complex is present, because the hydrogenation of cyclooctadiene and dissociation of its product are very slow.

A higher exchange rate of pyridine for the more bulky ligands indicates that the exchange proceeds by a dissociative mechanism, which is in accordance with an earlier thermo-dynamic and DFT study on IMes alone. However, the exchange rate is not directly proportional to the observed signal enhancement, as shown in Fig. 4B. The unsaturated ligands have a slightly slower exchange rate and % $V_{bur}$ than their saturated ligands, but their signal enhancement is higher. The most efficient complex, IMes 10, has an exchange rate of 10.4 s$^{-1}$, which is in reasonable agreement with that reported by Dukett et al. (11.7 s$^{-1}$). On the left side of Fig. 4B (exchange rates below 5.0 s$^{-1}$), the alkyl substituted NHC’s (3, 4, 5, 8) are found, which all have signal enhancements below 100; this means that,
With the exception of the slowly reacting ItBu 5, the pyridine exchange rate increases with %V_{\text{bur}}; this is consistent with a dissociative mechanism for the exchange. The complex with IMes 10 has the optimum value for the exchange rate and %V_{\text{bur}} resulting in the highest enhancement factor. Comparing every unsaturated NHC ligand (I) with its saturated (SI) analogue, the latter is always the bulkier, leading to a higher exchange rate, which nevertheless results in a lower enhancement factor. The property that has the strongest influence on the enhancement factor is the aromatic character of the substituent, which is also reflected in its effect on the pyridine chemical shifts. More research into the exchange rates of H, the exact J-coupling network, and the distances between pyridine and hydride ligands is needed for a full understanding of the polarization transfer.

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Notes and references