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Iridium α-carboxyimine complexes hyperpolarized with *para*hydrogen exist in nuclear singlet states before conversion into iridium carbonates

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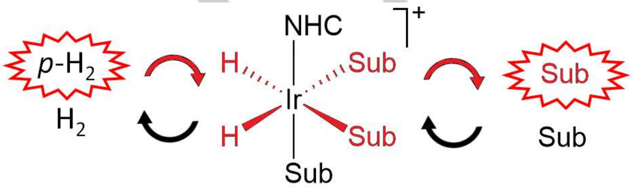
Dedicated to the memory of Robin Virgo

The formation and hyperpolarization of an $[Ir(H)_2(amine)(IMes)(\eta^2\text{-imine})]Cl$ complex that can be created in a hyperpolarized nuclear singlet state is reported. These complexes are formed when an equilibrium mixture of pyruvate, amine (benzylamine or phenylethylamine), and the corresponding imine condensation product, react with preformed $[Ir(H)_2(amine)_3(IMes)]Cl$. These iridium α-carboxyimine complexes exist as two regioisomers differentiated by the position of amine. When examined with *para*-hydrogen the hydride resonances of the isomer with amine trans to hydride become strongly hyperpolarized. The initial hydride singlet states readily transfer to the corresponding $^{13}C_2$ state in the labelled imine and exhibit magnetic state lifetimes of up to 11 seconds. Their ^{13}C signals have been detected with up to 420 fold signal gains at 9.4 T. On a longer timescale, and in the absence of H_2, further reaction leads to the formation of neutral carbonate containing $[Ir(amine)(\eta^2\text{-}CO_3)(IMes)(\eta^2\text{-imine})]$. Complexes are characterized by, IR, MS, NMR and X-ray diffraction.

Nuclear Magnetic Resonance (NMR) is one of the most versatile analytical tools available to physical science. Despite this success, it suffers greatly from low sensitivity due to the weak interaction between nuclear spins and an external magnetic field. As the magnitude of this interaction depends on the nucleus, the effects of insensitivity are more severe for low γ nuclei such as ^{13}C, when compared to ^{1}H, with only 1 in nearly every 800,000 ^{13}C nuclei contributing positively to a signal detected in the 1.5 T field of a routine MRI scanner. Over the last decade hyperpolarization has begun to challenge the insensitivity of magnetic resonance by producing signals many orders of magnitude stronger than those seen under Boltzmann populated conditions.[1] Recently, Dynamic Nuclear Polarization (DNP) has successfully utilized this effect for human disease diagnosis.[2, 3]

A readily accessible hyperpolarization method employs *para*-hydrogen (p-H_2) as the source of its signal gain.[4, 5] This *Para*Hydrogen Induced Polarization (PHIP) approach was pioneered by Weitekamp, Eisenberg, and Bargon in the 1990s and has provided many significant observations in the field of catalysis.[4-7] The related hydrogenation of unsaturated substrates has led to their successful *in vivo* detection.[8-10] A similar approach, called Signal Amplification By Reversible Exchange (SABRE), was first described in 2009.[11, 12] SABRE takes p-H_2, a readily formed spin-zero isomer of H_2, and binds it to a metal complex in a way that allows the rapid transfer of latent hyperpolarization into suitable receptor nuclei without chemical alteration, as shown conceptually in Scheme 1.



Scheme 1. Hyperpolarization is readily created catalytically in a substrate (Sub) *via* p-H_2 derived hydride ligands and a suitable hyperpolarization transfer catalyst (where NHC is an N-heterocyclic carbene).

Suitable ^{1}H receptor nuclei feature in an array of SABRE amenable nitrogen and sulfur containing heterocycles,[13-16] amines[17, 18] and nitriles.[19] The catalyst plays an essential role in this process by controlling the ultimate level of hyperpolarization,[13, 20, 21] with a combination of selective deuteration of both the catalyst and substrate allowing ^{1}H polarization levels of over 50% to be attained.[22] SABRE is truly heteronuclear in scope and very significant improvements in ^{15}N response levels have been realized. These optimally involve low-field SABRE-SHEATH methods, as exemplified for *N*-heterocycles,[23, 24] nitriles,[24] Schiff bases,[25] and diazirines.[26] Others have targeted responses in less well studied nuclei such as ^{13}C,[27, 28] ^{19}F,[29, 30] ^{31}P,[31] ^{119}Sn and ^{31}Si.[32] Furthermore, while the required polarization transfer conditions are readily met at low field, high-field transfer through radio frequency excitation is also feasible.[33] Hence, p-H_2 now reflects a truly versatile hyperpolarization platform and it is not surprising that high sensitivity analytical approaches have been demonstrated.[34, 35] The necessary progress into aqueous media has also been significant and is expected to lead to successful *in vivo* study in the future.[15, 36-38]

In this paper, p-H_2 is used to hyperpolarize a α-carboxyimine complex that is initially created in a singlet state. This achievement stems from the fact that α-carboxyimines are readily formed when pyruvate and an amine combine in a condensation reaction.[39] Here, the imine proves to bind in a bidentate fashion to form an iridium dihydride complex that shows high levels of PHIP. This study starts by exploring the behavior of 0.14 M solutions of sodium pyruvate-1,2-[$^{13}C_2$] in dichloromethane-d_2 that contain 40 μl of H_2O and an equimolar amount of either benzylamine ($BnNH_2$) or phenylethylamine (PEA). Monitoring by ^{13}C NMR spectroscopy (see supporting information) reveals the formation of an equilibrium mixture which includes the corresponding imine products **A** and **B** of Scheme 2 and their hydrated counterparts.[40, 41] In a second stage, samples of [IrCl(COD)(IMes)], **1**, were first reacted with 5 equivalents of $BnNH_2$ or PEA under 3-bar of hydrogen gas to preform $[Ir(H_2)(amine)_3(IMes)]Cl$, **2** or **3**. These known products yield hydride resonances at δ -24.0 (**2**) and δ -23.7 (**3**)

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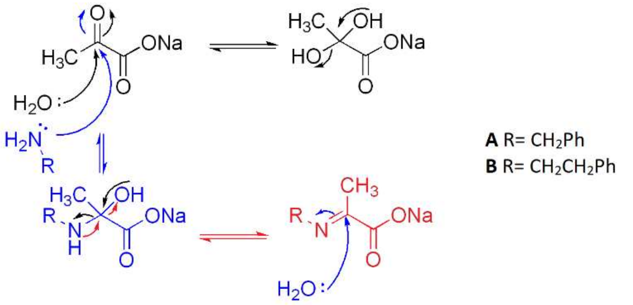
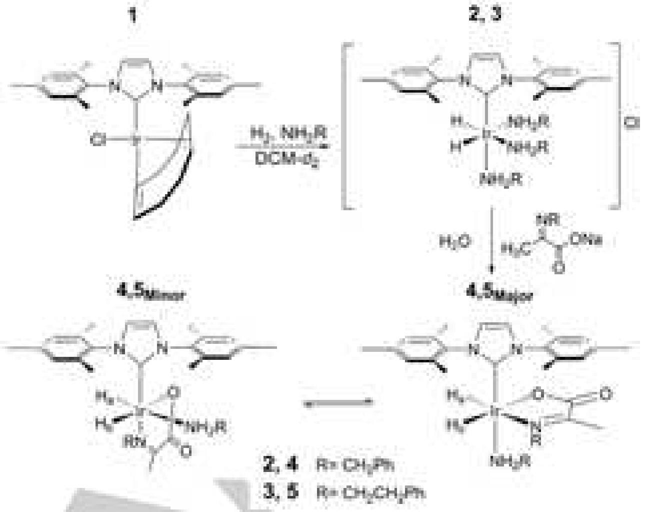
respectively.[18] Furthermore, when these reactions are completed with p-H_2, the free amine's NMR signals become strongly enhanced as a consequence of SABRE.[17, 18]



Scheme 2. Pyruvate and amine react together to form an equilibrium mixture of the imine (**A** or **B**), the hydrated imine, and the starting materials.[42]

When such imine mixtures are added to preformed **2** and **3** and the resulting samples placed under 3-bar of H_2 gas the single hydride resonances of **2** and **3** are replaced in both cases by two pairs of hydrides. When samples of pyruvate are added to **2** or **3** in the presence of p-H_2 a hyperpolarized response for pyruvate is observed, as previously reported, until the conversion to **4** or **5** is complete.[18] For $BnNH_2$, two dominant hydride resonances appear at δ -21.9 and δ -27.6 which share a common splitting of 9.5 Hz that are assigned to complex $\mathbf{4}_{\mathbf{major}}$ of Scheme 3. These hydride resonances sharpen at 245 K where multinuclear NMR measurements using labelled $^{13}C_2$ pyruvate and ^{15}N amine precursors were undertaken. In the corresponding ^{15}N data a connection between the δ -21.9 hydride signal and a ^{15}N signal at δ 276.9 was observed due to a shared *trans* ^1H-^{15}N coupling of 20.7 Hz. A further bound amine ^{15}N signal was seen at δ -2.7 which is located *trans* to the carbene according to nOe measurements. Identification of the ligand *trans* to the hydride yielding the δ -27.6 resonance was secured by the nOe interactions to CH_3 groups of the imine and carbene. Kinetic product $\mathbf{4}_{\mathbf{major}}$ therefore is $[Ir(H_2)(amine)(IMes)(\eta^2\text{-}\mathbf{A})]Cl$ with the ligand arrangement shown in Scheme 3 and logically arises due to the high lability of the amine when located *trans* to hydride.[17, 18] Similar α-ketoimine chelates with late transition metal centers have been reported for ruthenium, cobalt, nickel, copper and zinc.[43-45] The remaining minor product, $\mathbf{4}_{\mathbf{minor}}$ is a regioisomer of $\mathbf{4}_{\mathbf{major}}$, which yields hydride resonances at δ -24.0 and δ -27.4, of which the former is *trans* to $BnNH_2$ as indicated by the 17.5 Hz coupling to a ^{15}N signal at δ -2.47. After imine addition to **2**, $\mathbf{4}_{\mathbf{major}}$ appears to form exclusively, but after 1 hour at 298 K these two species exist in an approximate 1:30 ratio. An equilibrium 1:2 ratio is established after 7 hours with $\mathbf{4}_{\mathbf{major}}$ confirmed as the kinetic and thermodynamic product.

When exchange spectroscopy is used on a slower timescale to probe their dynamic behavior, exchange of the hydride ligands of $\mathbf{4}_{\mathbf{minor}}$ alongside the formation of free H_2 was observed, as illustrated by Figure 1a. The rate of production of free H_2 was estimated to be 15.5 s^{-1} (±0.6) at 283 K. The associated transition state barriers were determined by probing these changes as a function of temperature over the range 253-283 K. The resulting $\Delta H^{\neq}$ value for free H_2 production is 103.7 ± 1.6 kJ mol^{-1} while $\Delta S^{\neq}$ is +145 ± 6 J K^{-1} mol^{-1} as detailed in the supporting information. Increasing amine concentrations suppress the H_2 production pathway in accordance with a process that is preceded by dissociative amine loss. This type of behavior is typical for systems of this type.[46] Furthermore, $\mathbf{4}_{\mathbf{major}}$ appears to be inert on this timescale.



Scheme 3. [IrCl(COD)(IMes)], **1**, reacts with the amines $BnNH_2$ or PEA and H_2 in dichloromethane-d_2 to produce **2** or **3**. Further reaction with an equilibrium mixture of pyruvate and imine yield the Iridium α-carboxyimine complexes **4** and **5**.

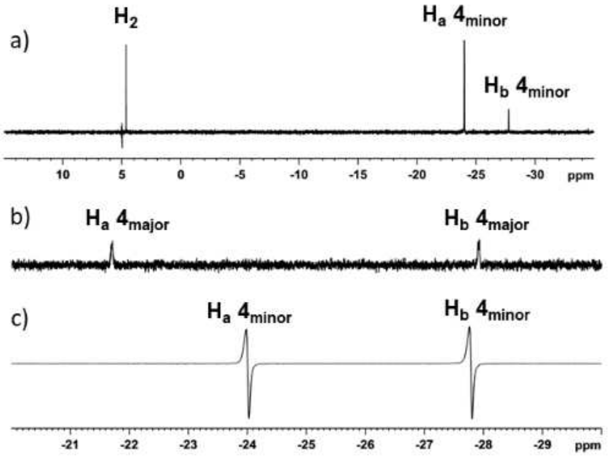


Figure 1. (a) ^1H-EXSY NMR spectrum recorded at 283 K 0.05 s after selective excitation of the H_a resonance δ -24.0 of $\mathbf{4}_{\mathbf{minor}}$ showing exchange peaks with free hydrogen at δ -4.6 and H_b; (b) Reference ^1H NMR spectrum with the corresponding p-H_2-hyperpolarized NMR spectrum (c). The relative vertical expansion of (b):(c) is 32:1.

As a consequence of this visible dihydrogen exchange pathway, we reexamined this process with p-H_2. Now, the hydride resonances of $\mathbf{4}_{\mathbf{minor}}$ become strongly enhanced while those of $\mathbf{4}_{\mathbf{major}}$ remain unaffected (Figure 1c). The PEA system proved to behave in a similar way, forming the corresponding complexes $\mathbf{5}_{\mathbf{minor}}$ and $\mathbf{5}_{\mathbf{major}}$ in a 1:11 ratio at 298 K 1 hour after imine addition to **3**. However, after 7 hours, $\mathbf{5}_{\mathbf{minor}}$ dominates as their ratio becomes 2:1. This suggests that while $\mathbf{5}_{\mathbf{major}}$ is still the kinetic product, $\mathbf{5}_{\mathbf{minor}}$ is now the thermodynamic product. The rate of H_2 appearance from $\mathbf{5}_{\mathbf{minor}}$ proved to be slower than that of $\mathbf{4}_{\mathbf{minor}}$ at 4.11 s^{-1} (±0.06) at 283 K. The corresponding value for $\Delta H^{\neq}$ of H_2 loss is 81.0 ± 2.2 kJ mol^{-1} whilst $\Delta S^{\neq}$ is +53 ± 5 J K^{-1} mol^{-1}. Rates of hydrogen elimination for similar octahedral iridium carbene complexes are slower and range between 0.56 and 5.11 s^{-1} at the higher temperature of 295 K.[32] The hydrogen exchange process for $\mathbf{4}_{\mathbf{minor}}$ and $\mathbf{5}_{\mathbf{minor}}$ is therefore very rapid. Similarly to **4**, $\mathbf{5}_{\mathbf{major}}$ proved to be inert to H_2 loss on this timescale and $\mathbf{5}_{\mathbf{minor}}$ is observed to react reversibly with *p*-H_2 and its hydride resonances exhibit a similar antiphase profile.

When samples of **4** or **5** containing the corresponding 1,2 $^{13}C_2$ labelled imine were shaken with fresh *p*-H_2 at a field of 65 G prior to observation, both of their bound 1,2 $^{13}C_2$ resonances proved to be strongly polarized. However, for a 90° excitation pulse, the two corresponding ^{13}C signals strangely appear in absorption and emission respectively as shown in Figure 2. The average ^{13}C enhancement levels proved to be 420-fold for $\mathbf{4}_{\mathbf{minor}}$ and 280-fold for $\mathbf{5}_{\mathbf{minor}}$. These ^{13}C spins exhibit chemical shift differences of 4.8 and 6.1 ppm for $\mathbf{4}_{\mathbf{minor}}$ and $\mathbf{5}_{\mathbf{minor}}$ respectively at 9.4 T whilst their mutual *J*-coupling constants are equal at 66 Hz. Hence, they are weakly coupled in this observation field but in the fringe field of the magnet (~6 mT) where polarization transfer takes place they are strongly coupled.

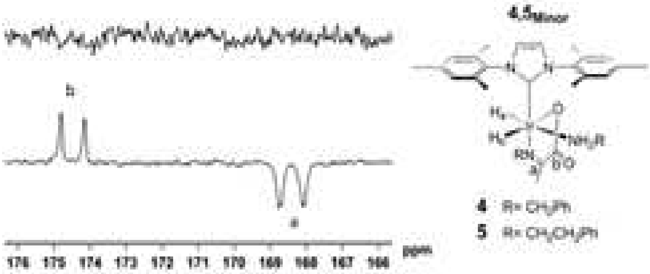


Figure 2. Thermal (top) and hyperpolarized (bottom) ^{13}C spectra of $\mathbf{4}_{\mathbf{minor}}$ after shaking with 3 bar *p*-H_2 for 10 seconds at 65 G. Note that the thermal NMR spectrum has been expanded vertically by a factor of 4 relative to the hyperpolarized response.

In order to account for this strange signal phase behavior the initial singlet state of the dihydride must first evolve on the metal complex under chemical shift and coupling propagators into new singlet order on the bound imine. Adiabatic sample transfer from low to high field then causes the initial $|S_0\rangle$ term to populate just the $|\alpha\beta\rangle$ level, which when probed by a 90° pulse leads to two resonance pairs with opposite phase. This behavior would suggest that a long-lived magnetic state could therefore exist between these ^{13}C spins in the strongly coupled low field regime. We, and others, have previously established routes to create and assess the lifetimes of such states in pairs of coupled spins.[47, 48] When such methods are applied here, the lifetime of the corresponding hyperpolarized magnetic states in low field show a dependence on *p*-H_2 pressure, see supporting information for more detail. It is clear that rapid H_2 exchange continually repolarizes the relaxing sample and therefore these data are reflective of both the *p*-H_2 decay rate and the low-field singlet state lifetime. This was confirmed by repeating the decay profile measurement with interleaved sample shaking to dissolve fresh *p*-H_2. Now, a saw-tooth decay was observed in agreement with competing continuous repolarization. Hence, the signal decay profile is not a mono-exponential process, but instead exhibits bi-exponential behavior with contributions from both the singlet state lifetime and *p*-H_2 repolarizing. These two effects can be deconvoluted by recording measurements at different *p*-H_2 pressures which decay with a variable *p*-H_2 replenishment term, but a fixed low field singlet lifetime. Bi-exponential fitting yields a singlet state lifetime of 10.9 ± 1.1 s and 8.8 ± 1.4 s for $\mathbf{4}_{\mathbf{minor}}$ and $\mathbf{5}_{\mathbf{minor}}$ respectively.

When the hydrogen atmosphere of solutions containing **4** and **5** are replaced by N_2 or air, the slow precipitation of single crystals of products **6** and **7** occurs. Subsequent X-ray diffraction studies reveal that they are the carbonate containing $[Ir(IMes)(\eta^2\text{-}CO_3)(\eta^2\text{-imine})(amine)]$ complexes, for example as shown in Figure 3. While **4** and **5** exist as two regioisomers depending on the geometry of amine, only one isomer of **6** and **7** is observed in the crystalline state. Iridium complexes containing η^2-bound carbonate ligands have been reported.[49] In fact, infrared spectroscopy of the **6** crystals reveal the presence of vibrational bands for ν(OCO) at 1584.18 and 1485.84 cm^{-1} which are characteristic of those of metal carbonates and compare well to those of other iridium and osmium η^2-CO_3 complexes at 1580, 1482 cm^{-1} and 1575 and 1496 cm^{-1} respectively.[50, 51] Solutions of **4** and **5** are stable under H_2 over a time period of many weeks and the addition of $NaHCO_3$ and removal of H_2 failed to speed up the conversion to **6** or **7**. When sodium pyruvate-1-[^{13}C] is used as a starting material for the synthesis of **4**, a $^{13}CO_3$ signal of **6** at δ 172 was observed. This indicates that the η^2-bound carbonate ligands of **6** are derived from pyruvate.

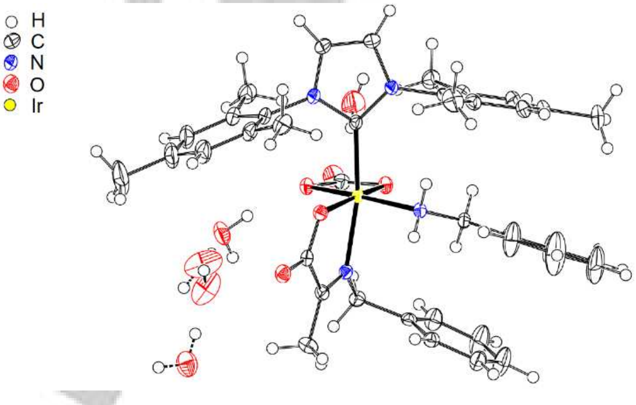


Figure 3. Structure of **6** determined from X-ray crystallography; the anisotropic displacement parameters and waters of crystallization should be noted.

It is known that under physiological conditions pyruvate can be metabolized to carbonates[52] and some metal pyruvate complexes have been reported to thermally degrade at high temperatures to give metal carbonates.[53] Therefore, the conversion of pyruvate into carbonate in a process facilitated by a transition metal complex is not totally unexpected. It is therefore suggested that upon removing the H_2 atmosphere from **4** or **5**, its hydride ligands become replaced by η^1-pyruvate which subsequently rearrange to **6** and **7**. To our knowledge **6** and **7** are the first examples of metal carbonate complexes formed from the metal catalyzed decomposition of pyruvate.

In conclusion, we have shown here that **2** and **3** react rapidly with an *α*-carboxyimine to form **4** and **5** according to Scheme 2. The hydride ligands of the minor isomers of **4** and **5** undergo rapid exchange with *p*-H_2 such that its hydride resonances become very strongly enhanced. Furthermore, we establish that when the imine is 1,2-[^{13}C]$_2$ labelled, polarization flows readily from these hydride sites to dramatically improve the detectability of the imine ^{13}C response. The visible ^{13}C signal intensities at 9.4 T were quantified as exhibiting 420-fold and 280-fold enhancements for $\mathbf{4}_{\mathbf{minor}}$ and $\mathbf{5}_{\mathbf{minor}}$ respectively. Unusually though, the low-field nature of this process creates a long-lived 1,2-[^{13}C]$_2$ state in the first instance, the lifetimes of which approach 11 s. This low field approach[54] has been used previously to access such states in small molecule ^{1}H[55, 56], ^{15}N[57, 58] and ^{13}C[59, 60] spin systems where the longer magnetic state lifetimes are hoped to be useful for the *in vivo* probing of metabolism. Here though we have demonstrated a route to create a continually refreshable heteronuclear singlet state in a metal complex *via* reversible *p*-H_2 addition. Such states may now prove highly beneficial when looking for intermediates in chemical reactions, one of the main early benefits of PHIP. This development will augment continuous hyperpolarization by SABRE approaches[61] that have already seen it used to create the Z-magnetization needed to achieve sub-millihertz resolution[62] and Zero-Field NMR.[63]

Furthermore, upon the removal of the H_2 atmosphere from **4** and **5** a carbonate containing complex is formed which is characterized by IR, NMR, and X-ray diffraction. When pyruvate-$^{13}C_1$ is used, the presence of $^{13}CO_3^{2-}$ in **6** suggests that this product results from decomposition of pyruvate. While both metal carbonates and the transformation of pyruvate into carbonate are known, further work is being directed at elucidating the mechanism of this unusual observation.

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Conflict of interest

The authors declare no conflict of interest

Keywords: *para*hydrogen • singlet states • hyperpolarization • Iridium α-carboxyimine • Iridium carbonates

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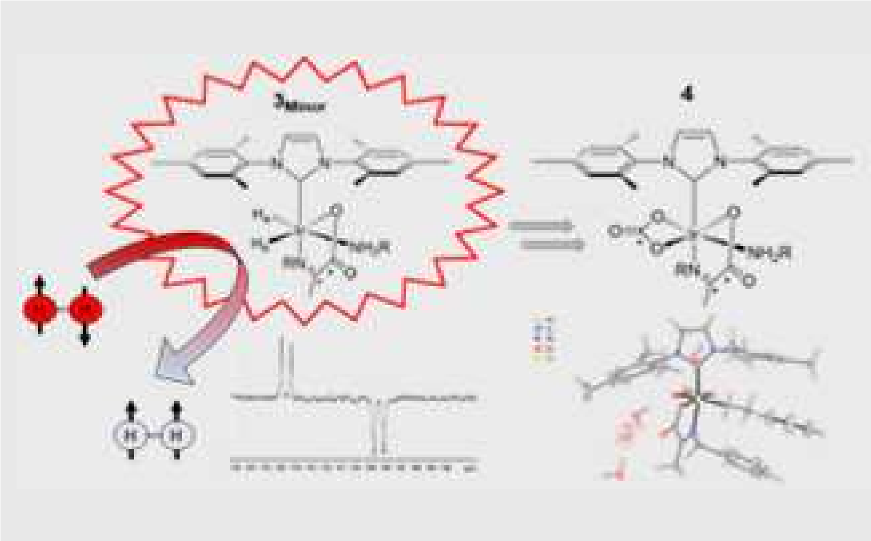

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Iridium α–carboxyimine complexes hyperpolarized with *para*hydrogen exist in nuclear singlet states before conversion into iridium carbonates

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