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Supporting information

Simple Analytical Model for Signal Amplification by Reversible Exchange (SABRE) process

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1. Dissociative substrate and associative hydrogen exchange

Substrate exchange is a dissociative process (see Figure 1a of the main text), and the rate of its exchange (W_S) depends only on the catalyst concentration:

$$W_\mathrm{S} = k_\mathrm{S}^\mathrm{d}[\mathbf{C}]$$

Hydrogen exchange is an associative process (see Figure 1b of the main text), and the rate of its exchange may be found as follows:

$$W_{\mathrm{H}_2} = k_{\mathrm{H}_2}^\mathrm{d}[\mathbf{C}]^\ddagger$$

where dihydride-dihydrogen intermediate $[\mathbf{C}]^\ddagger$ is a short-lived intermediate for which quasi-stationary conditions can apply:

$$[\mathbf{C}]^\ddagger = \frac{k_{\mathrm{H}_2}^\mathrm{a}}{2k_{\mathrm{H}_2}^\mathrm{d}}[\mathbf{H_2}][\mathbf{C_1}]$$

The substrate and the complex are in a chemical equilibrium, hence

$$[\mathbf{C_1}] = \frac{k_\mathrm{S}^\mathrm{d}[\mathbf{C}]}{k_\mathrm{S}^\mathrm{a}[\mathbf{S}]} = \mathbf{K}_\mathrm{S}\frac{[\mathbf{C}]}{[\mathbf{S}]}$$

Therefore,

$$W_{\mathrm{H}_2} = k_{\mathrm{H}_2}^\mathrm{d}\frac{k_{\mathrm{H}_2}^\mathrm{a}}{2k_{\mathrm{H}_2}^\mathrm{d}}[\mathbf{H_2}]\mathbf{K}_\mathrm{S}\frac{[\mathbf{C}]}{[\mathbf{S}]} = \left(\frac{k_{\mathrm{H}_2}^\mathrm{a}k_\mathrm{S}^\mathrm{d}}{2k_\mathrm{S}^\mathrm{a}[\mathbf{S}]}[\mathbf{H_2}]\right)[\mathbf{C}]$$

Usually, the effective kinetic constant $k_{\mathrm{H}_2}^\mathrm{eff}$, measured by EXSY, is the quantity enclosed in brackets in the above equation. The expression explains its linear dependence on the hydrogen concentration and a reciprocal dependence on the substrate concentration. However, it is more convenient to express the hydrogen exchange constant as $k_{\mathrm{H}_2} = k_{\mathrm{H}_2}^\mathrm{a}k_\mathrm{S}^\mathrm{d}/2k_\mathrm{S}^\mathrm{a}$ since it has the dimension of $[\mathrm{s}^{-1}]$ (see eq. 1 of the main text), so that $k_{\mathrm{H}_2}^\mathrm{eff} = k_{\mathrm{H}_2}[\mathbf{H_2}]/[\mathbf{S}]$ and the second order kinetic constant used for writing kinetic equations is $k_{\mathrm{H}_2}^{'} = k_{\mathrm{H}_2}/[\mathbf{S}] = k_{\mathrm{H}_2}^\mathrm{eff}/[\mathbf{H_2}]$.

2. Introduction of "hyperpolarized species" C* and S*

Let us denote the fractions of parahydrogen and orthohydrogen in the hydrogen gas as x_p and x_o, respectively ($x_p + x_o = 1$). It is convenient to inroduce the imbalance of hydrogen isomer concentrations, $[\mathrm{H}_2^*]$, or hydrogen singlet-triplet imbalance (STI):

$$[\mathrm{H}_2^*] = [\mathrm{H}_2(|S\rangle)] - \frac{1}{3}\sum_{i=1,0,-1}[\mathrm{H}_2(|T_i\rangle)] = \left(x_p - \frac{x_o}{3}\right)[\mathrm{H}_2] = \frac{4x_p - 1}{3}[\mathrm{H}_2]$$

It is obvious that after one event of hydrogen exchange with the catalyst, the hydrogen STI is converted directly to the STI of iridium hydride protons:

$$[\mathrm{C}^*] = \left[\mathrm{C}_{|S\rangle}\right] - \frac{1}{3}\sum_{i=1,0,-1}\left[\mathrm{C}_{|T_i\rangle}\right]$$

Let us show that one event of polarization transfer in the complex C* produces the imbalance of substrate states (S*):

$$[\mathrm{S}^*] = \left[S_{|\beta\rangle}\right] - \left[S_{|\alpha\rangle}\right]$$

In the initial thermally equilibrated solution, the amounts of substrate molecules with "spin up" and "spin down" are almost the same. When SABRE complex is formed and placed in the magnetic field corresponding to a LAC between $|S\alpha\rangle$ and $|T_+\beta\rangle$, the coherent polarization transfer starts to occur between these states while other states remain unaffected (Figure 1Sb).

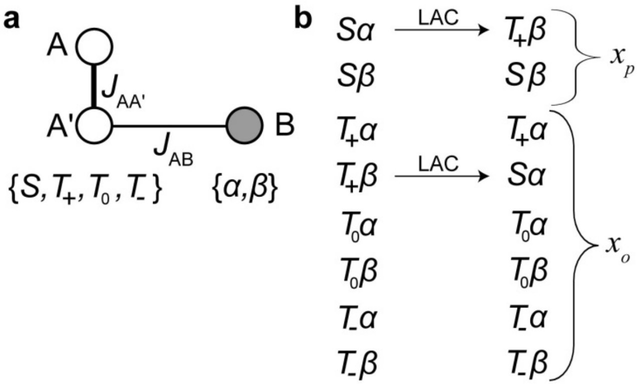

Figure 1S. a) Schematic representation of an AA'B spin system. Spins A and A' are strongly coupled at any field, thus, their states are represented using the singlet-triplet basis. The state of spin B are represented using the Zeeman states for spin 1/2. b) Schematic representation of the SABRE process. In the LAC region, the states $|S\alpha\rangle$ and $|T_+\beta\rangle$ interconvert while other states remain unaffected.

An imbalance of substrate states is the difference between concentrations of substrate spins "down" and spins "up"; assuming complete conversion of spin order at the LAC, we can write

$$[\mathrm{S}^*] = \left[S_{|\beta\rangle}\right] - \left[S_{|\alpha\rangle}\right] = \left(x_p + \frac{x_o}{3} - \frac{2x_o}{3}\right)[\mathrm{S}] = \frac{4x_p - 1}{3}[\mathrm{S}]$$

Thereby, one mole of H_2^* may be in principle converted to one mole of C* and subsequently to S^*. This means that H_2^*, C* and S^* indeed may be seen as chemical species formed during the SABRE build-up process and thus, kinetic analysis can be applied to their concentrations. The ratio of $[S^*]$ and $[S]$ is simply the polarization of S:

$$|P| = \frac{[\mathrm{S}^*]}{[\mathrm{S}]}$$

3. Incoherent polarization accumulation in SABRE experiments

Coherent polarization transfer starts to occur after parahydrogen association with Ir-complex. However, because of the incoherent nature of association and dissociation steps between hydrogen and the complex, all coherences are averaged out very quickly after the start of parahydrogen bubbling, and thus, the resulting process can be treated as an incoherent accumulation of population for some of the spin levels. We may treat this as a kinetic step. Let us assume the following kinetic steps:

I) $\mathbf{C}$ + $\mathbf{H_2^*} \xrightarrow{k'_{\mathrm{H}_2}}$ $\mathbf{C}^*$ + H_2 with the rate W_{H_2}

II) $\mathbf{C}^* \xrightarrow{R_\mathrm{C}}$ 0, relaxation in complex with the rate $R_\mathrm{C} = 1/T_1^\mathrm{C}$

III) $\mathbf{C}^* \xrightarrow{\lambda k_\mathrm{S}^\mathrm{d}}$ $\mathbf{C_1}$ + $\mathbf{S}^*$, hyperpolarized substrate dissociation from the complex

IV) $\mathbf{C_1}$ + $\mathbf{S}^* \xrightarrow{\lambda' k_\mathrm{S}^\mathrm{a}}$ $\mathbf{C}^*$, substrate association with the complex

V) $\mathbf{S}^* \xrightarrow{R_\mathrm{S}}$ 0, relaxation of substrate with the rate $R_\mathrm{S} = 1/T_1^\mathrm{S}$

where $\mathbf{C}$ is the catalyst, $\mathbf{S}$ is the substrate, $\mathbf{H_2}$ is dihydrogen, $\mathbf{C}^*$ is the hyperpolarized catalyst (an imbalance between catalyst states), $\mathbf{S}^*$ is the hyperpolarized substrate (an imbalance between substrate states), $\mathbf{H_2^*}$ is the hydrogen isomer imbalance concentration; λ and λ' are polarization transfer efficiency factors, which stand for the efficiency of the interconversion between $\mathbf{C}^*$ and $\mathbf{S}^*$ (see section 6). It is important that hyperpolarized species $\mathbf{C}^*$ and $\mathbf{S}^*$ simply vanish in stages (II) and (V) when their thermal polarization is neglected.

Since the rate of parahydrogen supply is usually high: $W_{in} \approx 100 - 10000$ [mM/s] (calculated from the typical range of *p*-H_2 inflow pressures and flow rates),[1] one may consider very fast enforcement of stationary conditions for $[\mathbf{H_2^*}]$ in solution, and thus, stationary hydrogen STI concentration is given by the maximum possible equilibrium hydrogen concentration $[\mathbf{H_2^*}] \approx \frac{4x_p - 1}{3}[\mathbf{H_2}]_{\max}$.

Kinetic equations for hyperpolarized species $\mathbf{C}^*$ and $\mathbf{S}^*$:

$$\frac{d[\mathbf{C}^*]}{dt} = k'_{\mathrm{H}_2}[\mathbf{H}_2^*][\mathbf{C}] - \left(R_\mathrm{C} + \lambda k_\mathrm{S}^\mathrm{d}\right)[\mathbf{C}^*] + \lambda' k_\mathrm{S}^\mathrm{a}[\mathbf{C_1}][\mathbf{S}^*]$$

$$\frac{d[\mathbf{S}^*]}{dt} = \lambda k_\mathrm{S}^\mathrm{d}[\mathbf{C}^*] - \left(R_\mathrm{S} + \lambda' k_\mathrm{S}^\mathrm{a}[\mathbf{C_1}]\right)[\mathbf{S}^*]$$

After some time of parahydrogen bubbling, the system comes to a steady-state:

$$\frac{d[\mathbf{C}^*]}{dt} = 0; \ \frac{d[\mathbf{S}^*]}{dt} = 0$$

One may find that

$$[\mathbf{C}^*] = k'_{\mathrm{H}_2}[\mathbf{H}_2^*][\mathbf{C}]\frac{R_\mathrm{S} + \lambda' k_\mathrm{S}^\mathrm{a}[\mathbf{C_1}]}{R_\mathrm{C}R_\mathrm{S} + R_\mathrm{C}\lambda' k_\mathrm{S}^\mathrm{a}[\mathbf{C_1}] + \lambda k_\mathrm{S}^\mathrm{d} R_\mathrm{S}} = \frac{k'_{\mathrm{H}_2}[\mathbf{H}_2^*][\mathbf{C}]\left(R_\mathrm{S} + \lambda' k_\mathrm{S}^\mathrm{d}\frac{[\mathbf{C}]}{[\mathbf{S}]}\right)}{R_\mathrm{S}\left(R_\mathrm{C} + \lambda k_\mathrm{S}^\mathrm{d}\right) + R_\mathrm{C}\lambda' k_\mathrm{S}^\mathrm{d}\frac{[\mathbf{C}]}{[\mathbf{S}]}}$$

$$[\mathbf{S}^*] = k'_{\mathrm{H}_2}[\mathbf{H}_2^*][\mathbf{C}]\frac{\lambda k_\mathrm{S}^\mathrm{d}}{R_\mathrm{C}R_\mathrm{S} + R_\mathrm{C}\lambda' k_\mathrm{S}^\mathrm{a}[\mathbf{C_1}] + \lambda k_\mathrm{S}^\mathrm{d} R_\mathrm{S}} = k'_{\mathrm{H}_2}[\mathbf{H}_2^*][\mathbf{C}]\frac{\lambda k_\mathrm{S}^\mathrm{d}}{R_\mathrm{S}\left(R_\mathrm{C} + \lambda k_\mathrm{S}^\mathrm{d}\right) + R_\mathrm{C}\lambda' k_\mathrm{S}^\mathrm{d}\frac{[\mathbf{C}]}{[\mathbf{S}]}}$$

The actual NMR signal enhancement factor is the ratio of "hyperpolarized substrate concentration" and the actual substrate concentration, that is why, after expressing $k'_{\mathrm{H}_2} = k_{\mathrm{H}_2}/[\mathbf{S}]$, one can get:

$$|\varepsilon| = \eta|P| = \eta\frac{[\mathbf{S}^*]}{[\mathbf{S}]} = \eta\left(\frac{4x_p - 1}{3}\right)\frac{[\mathbf{H_2}][\mathbf{C}]}{[\mathbf{S}]^2}\frac{\lambda k_\mathrm{S}^\mathrm{d} k_{\mathrm{H}_2}}{R_\mathrm{S}\left(R_\mathrm{C} + \lambda k_\mathrm{S}^\mathrm{d}\right) + R_\mathrm{C}\lambda' k_\mathrm{S}^\mathrm{d}\frac{[\mathbf{C}]}{[\mathbf{S}]}}$$

where η is the theoretical maximum enhancement factor which can be obtained in SABRE experiments. For the coherent mechanism the maximum is 50% (see section 6):

$$\eta = \frac{0.5}{P_\mathrm{th}} = \frac{kT}{\gamma\hbar B_0}$$

Factors λ and λ' describe the efficiency of spin order transfer from $|S\alpha\rangle$ to $|T_+\beta\rangle$ and vice versa. For coherent polarization transfer (e. g. conventional low-field SABRE) it is natural to consider them to be equal ($\lambda = \lambda' = \lambda_\mathrm{coh}$). However, they are not considered to be equal for incoherent polarization transfer mechanism (e. g. high-field SABRE) and thus, should be distinguished. However, since the majority of SABRE experiments is dealing with coherent polarization transfer mechanism, in formula (3) of the main text we omit the difference between λ and λ'.

We now consider a different situation when a strongly bound co-substrate ($\mathbf{I}$) and only low (micromolar) concentrations of the substrate are used. In this case, the main exchange will be the exchange with the co-substrate:

$$\mathbf{C_I} \rightleftarrows \mathbf{C_1} + \mathbf{I}, \text{ with equilibrium constant } \mathbf{K}_\mathrm{I}$$

and exchange with the substrate of interest:

$$\mathbf{C} \rightleftarrows \mathbf{C_1} + \mathbf{S}, \text{ with equilibrium constant } \mathbf{K}_\mathrm{S}$$

The amount of intermediate species $[\mathbf{C_1}]$ will depend predominantly on the co-substrate concentration:

$$[\mathbf{C_1}] = \mathbf{K}_\mathrm{I}\frac{[\mathbf{C_I}]}{[\mathbf{I}]} = \mathbf{K}_\mathrm{S}\frac{[\mathbf{C}]}{[\mathbf{S}]}$$

$$k_{\mathrm{H_2}}^{'} = \frac{k_{\mathrm{H_2}}}{[\mathbf{I}]}$$

For low substrate concentrations the kinetic scheme has to be slightly modified in order to distinguish between complex $\mathbf{C_I}$ containing only strongly bound co-substrate and $\mathbf{C}$ — complex containing both the co-substrate and the substrate of interest:

I) $\mathbf{C_I} + \mathbf{H_2^*} \xrightarrow{k_{\mathrm{H_2}}^{'}} \mathbf{C_I^*} + \mathrm{H_2}$ with the rate $W_{\mathrm{H_2}}$

II) $\mathbf{C_I^*} \xrightarrow{R_{\mathrm{C_I}}} 0$, relaxation of complex with the co-substrate with the rate $R_{\mathrm{C_I}} = 1/T_1^{\mathrm{C_I}}$

III) $\mathbf{C_I^*} \overset{\mathbf{K}_\mathrm{I}}{\leftrightarrow} \mathbf{C_1^*} + \mathbf{I}$, exchange of the strongly bound substrate **I**

IV) $\mathbf{C_1^*} + \mathbf{S} \xrightarrow{k_\mathrm{S}^\mathrm{a}} \mathbf{C^*}$, association of the substrate with the complex

V) $\mathbf{C^*} \xrightarrow{R_\mathrm{C}} 0$, relaxation in complex with rate $R_\mathrm{C} = 1/T_1^\mathrm{C}$

VI) $\mathbf{C^*} \xrightarrow{k_\mathrm{S}^\mathrm{d}} \mathbf{C_1} + \mathbf{S^*}$, dissociation of the substrate from the complex

VII) $\mathbf{S^*} \xrightarrow{R_\mathrm{S}} 0$, relaxation of substrate with rate $R_\mathrm{S} = 1/T_1^\mathrm{S}$

Here we will consider $\lambda = \lambda^{'} = 1$ for simplicity.

Now we have

$$\frac{d[\mathbf{C^*}]}{dt} = k_\mathrm{S}^\mathrm{a}[\mathbf{C_1^*}][\mathbf{S}] - \left(R_\mathrm{C} + k_\mathrm{S}^\mathrm{d}\right)[\mathbf{C^*}] = 0$$

$$\frac{d[\mathbf{S^*}]}{dt} = k_\mathrm{S}^\mathrm{d}[\mathbf{C^*}] - R_\mathrm{S}[\mathbf{S^*}] = 0$$

By taking into account chemical equilibrium between $\mathrm{C_1}$ and $\mathrm{C_I}$ one can find that:

$$[\mathbf{C_1^*}] = \frac{\mathbf{K}_\mathrm{I}[\mathbf{C_I^*}]}{[\mathbf{I}]} = \frac{\mathbf{K}_\mathrm{I}}{[\mathbf{I}]}\left(\frac{k_{\mathrm{H_2}}[\mathbf{C}]_\mathbf{0}[\mathbf{H_2^*}]}{[\mathbf{I}]R_{\mathrm{C_I}}}\right)$$

and

$$[\mathbf{C}^*] = \frac{k_{\mathrm{S}}^{\mathrm{a}}[\mathbf{S}]}{R_{\mathrm{C}} + k_{\mathrm{S}}^{\mathrm{d}}}\left(\frac{k_{\mathrm{H_2}}\mathbf{K}_{\mathrm{I}}}{R_{\mathrm{C_I}}}\frac{[\mathbf{H}_2^*][\mathbf{C}]_{\mathbf{0}}}{[\mathbf{I}]^2}\right)$$

and

$$[\mathbf{S}^*] = \left(\frac{k_{\mathrm{S}}^{\mathrm{d}}}{R_{\mathrm{S}}}\right)[\mathbf{C}^*] = \left(\frac{k_{\mathrm{S}}^{\mathrm{d}}}{R_{\mathrm{S}}}\right)\frac{k_{\mathrm{S}}^{\mathrm{a}}}{R_{\mathrm{C}} + k_{\mathrm{S}}^{\mathrm{d}}}\left(\frac{k_{\mathrm{H_2}}\mathbf{K}_{\mathrm{I}}}{R_{\mathrm{C_I}}}\frac{[\mathbf{H}_2^*][\mathbf{C}]_{\mathbf{0}}}{[\mathbf{I}]^2}\right)[\mathbf{S}]$$

with polarized substrate concentration being linearly proportional to the substrate concentration.

4. Substrate relaxation time in the presence of the catalyst

Let us consider the following kinetic scheme:

$$[\mathbf{S}] \overset{R_{\mathrm{S}}}{\leftarrow} [\mathbf{S}^*] \overset{\mathrm{K}_{\mathbf{S}}}{\leftrightarrow} [\mathbf{C}^*] \overset{R_{\mathrm{C}}}{\rightarrow} [\mathbf{C}]$$

Where the asterisk denotes the substrates in a non-equilibrium state. The corresponding kinetic equations are the following:

$$\frac{d[\mathbf{C}^*]}{dt} = -R_{\mathrm{C}}[\mathbf{C}^*] - k_{\mathrm{S}}^{\mathrm{d}}[\mathbf{C}^*] + k_{\mathrm{S}}^{\mathrm{a}}[\mathbf{S}^*][\mathbf{C}_{\mathbf{1}}]$$

$$\frac{d[\mathbf{S}^*]}{dt} = -R_{\mathrm{S}}[\mathbf{S}^*] + k_{\mathrm{S}}^{\mathrm{d}}[\mathbf{C}^*] - k_{\mathrm{S}}^{\mathrm{a}}[\mathbf{S}^*][\mathbf{C}_{\mathbf{1}}]$$

where R_S is the relaxation rate of free substrate and R_C is the relaxation rate of the substrate in the complex.

The substrate and the complex are in a fast exchange even comparable to the complex relaxation time. That is why one may assume a quasi-equilibrium, $[\mathbf{C}^*]/[\mathbf{S}^*] = [\mathbf{C}_{\mathbf{1}}]/\mathrm{K}_{\mathbf{S}} = [\mathbf{C}]/[\mathbf{S}]$:

$$\frac{d[\mathbf{C}^*]}{dt} + \frac{d[\mathbf{S}^*]}{dt} = \left(1 + \frac{[\mathbf{C}]}{[\mathbf{S}]}\right)\frac{d[\mathbf{S}^*]}{dt} = -\left(R_{\mathrm{S}} + R_{\mathrm{C}}\frac{[\mathbf{C}]}{[\mathbf{S}]}\right)[\mathbf{S}^*]$$

$$\frac{d[\mathbf{S}^*]}{dt} = -\left(R_{\mathrm{S}} + R_{\mathrm{C}}\frac{[\mathbf{C}]}{[\mathbf{S}]}\right)/\left(1 + \frac{[\mathbf{C}]}{[\mathbf{S}]}\right)[\mathbf{S}^*]$$

It is seen that parameter R_{eff} describes the effective relaxation rate of the free substrate in the presence of the catalyst:

$$R_{\mathrm{eff}} = \frac{R_{\mathrm{S}} + R_{\mathrm{C}}\frac{[\mathbf{C}]}{[\mathbf{S}]}}{1 + \frac{[\mathbf{C}]}{[\mathbf{S}]}}$$

Free substrate relaxation rate (R_{S}) of small molecules (e. g. pyridine) only slightly depends on the magnetic field. However, the relaxation rate for the complex can depend on the external magnetic field due to two factors: (i) the change of the motional regime (spectral density dependence on the magnetic field) and (ii) the change of the eigenstates of the coupled spin system (the Hamiltonian dependence on the magnetic field).[2] The T_1 relaxation dispersion for individual spins in the AA'B system is shown in Figure 2S (the calculation is described in [2]). In the model we used the following experimental data: T_1 of AA'-protons is 0.9 s at 16.4 Tesla (Ir-HH protons in $[\mathrm{Ir(IMes)(Py)_3H_2}]^+$), T_1 of B-proton is 3.6 s (ortho-Py in $[\mathrm{Ir(IMes)(Py)_3H_2}]^+$); the correlation time was estimated by analyzing the T_1 relaxation field dependence of [Ir(IMes)(COD)Cl] as 1.2 ns. The rate R_C is the "*average*" relaxation rate of Ir-HH and the substrate in the complex. From the calculations it is seen that at the LAC the R_C should be close to 1 s^{-1} (Figure 2S).

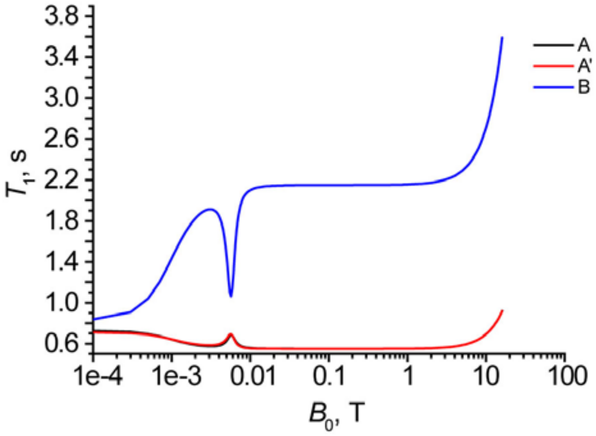

Figure 2S. Estimated T_1 relaxation times for protons of the AA'B spin system. The substantial reduction of B-proton T_1 at LAC field (~6 mT) is due to the strong coupling with AA'-protons. The NMR parameters are: $\delta_B - \delta_A = 30$ ppm, $J_{\mathrm{AA}'} = -7$ Hz, $J_{\mathrm{A'B}} = 0$ and $J_{\mathrm{AB}} = 1$ Hz. The correlation time $\tau_\mathrm{C} = 1.2$ ns is estimated by the analysis of T_1 relaxation dispersion of protons in [Ir(IMes)(COD)Cl].

5. Analysis of energy levels

Coherent polarization transfer in SABRE is known to be the main mechanism that creates hyperpolarization at low magnetic fields.[3,4] To explain coherent mechanism in SABRE it is easy to use the simplest spin system, that is, an AA'B-type three spin system. Here AA'-protons represent Ir-HH (hydride protons of SABRE complexes) protons and B is a single proton of a substrate. The Hamiltonian of the nuclei spin system is

$$\hat{H} = -v_A(I_{Az} + I_{A'z}) - v_B I_{Bz} + J_A(\boldsymbol{I}_A, \boldsymbol{I}_{A'}) + J_{AB}(\boldsymbol{I}_A, \boldsymbol{I}_B) + J_{A'B}(\boldsymbol{I}_{A'}, \boldsymbol{I}_B)$$

where $v_i = (1+\delta_i)\gamma B/2\pi$, B is the magnetic field, γ is the gyromagnetic ratio, δ is the chemical shift.

It is known that coherent polarization transfer is most efficient at a Level Anti-Crossing (LAC).[5] In Figure 3S we present the magnetic field dependences of energy level differences (frequencies) between states that correlate with $|S\alpha\rangle$ and $|T_+\beta\rangle$-states at high magnetic fields. The minimum in frequency corresponds to the LAC between $|S\alpha\rangle$ and $|T_+\beta\rangle$ spin states.

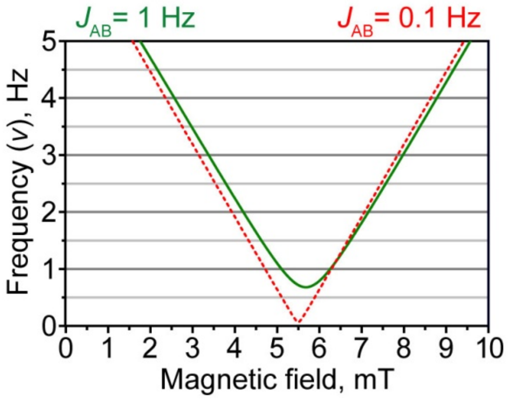

Figure 3S. Calculated energy levels differences (frequencies) for pairs of crossing levels $|S\alpha\rangle$ and $|T_+\beta\rangle$ as a function of magnetic field for the three-spin system AA'B. Here AA'-protons represent Ir-HH protons and B is a single proton of a substrate. NMR parameters are: $\delta_B - \delta_A = 30$ ppm, $J_{\mathrm{AA}'} = -7$ Hz, $J_{\mathrm{A}'\mathrm{B}} = 0$ and $J_{\mathrm{AB}} = 1$ Hz (green solid line) or $J_{\mathrm{AB}} = 0.1$ Hz (red dashed line).

To determine the magnetic field of the LAC (B_{LAC}) and the gap between the two energy levels at LAC, v_{LAC}, let us separate $\hat{H}$ into the main part:

$$\hat{H}_0 = -v_A(I_{Az} + I_{A'z}) - v_B I_{Bz} + J_A(\boldsymbol{I}_A, \boldsymbol{I}_{A'}) + \Sigma(I_{Az} + I_{A'z}, I_{Bz}),$$

and the perturbation:

$$\hat{V} = \Delta(I_{Az} - I_{A'z}, I_{Bz}) + J_{AB}\left[(I_{Ax}, I_{Bx}) + \left(I_{Ay}, I_{By}\right)\right] + J_{A'B}\left[(I_{A'x}, I_{Bx}) + \left(I_{A'y}, I_{By}\right)\right]$$

where $\Sigma = (J_{AB} + J_{A'B})/2$ and $\Delta = (J_{AB} - J_{A'B})/2$.

Then $|K\varphi\rangle$ states are the eigenstates of $\hat{H}_0$ where $|K\rangle$ is $|T_+\rangle$, $|T_0\rangle$, $|T_-\rangle$ or $|S\rangle$ state of AA'-protons and $|\varphi\rangle$ is $|\alpha\rangle$ or $|\beta\rangle$ state of B-proton. The main part of the Hamiltonian, $\hat{H}_0$, determines the energy levels of the spin system, and $\hat{V}$ plays a role only when two energy levels cross. The eigenvalues of $\hat{H}_0$ are the following:

$$\hat{H}_0 \begin{pmatrix} |T_+\alpha\rangle \\ |T_+\beta\rangle \\ |S\alpha\rangle \\ |T_0\alpha\rangle \\ |T_-\alpha\rangle \\ |\ S\beta\rangle \\ |T_0\beta\rangle \\ |T_-\beta\rangle \end{pmatrix} = \begin{pmatrix} -v_A - v_B/2 + J_A/4 + \Sigma/2 \\ -v_A + v_B/2 + J_A/4 - \Sigma/2 \\ -v_B/2 - 3/4J_A \\ -v_B/2 + J_A/4 \\ +v_A - v_B/2 + J_A/4 - \Sigma/2 \\ +v_B/2 - 3/4J_A \\ -v_B/2 + J_A/4 \\ +v_A + v_B/2 + J_A/4 + \Sigma/2 \end{pmatrix} \begin{pmatrix} |T_+\alpha\rangle \\ |T_+\beta\rangle \\ |S\alpha\rangle \\ |T_0\alpha\rangle \\ |T_-\alpha\rangle \\ |\ S\beta\rangle \\ |T_0\beta\rangle \\ |T_-\beta\rangle \end{pmatrix}$$

The energy levels of $|S\alpha\rangle$ and $|T_+\beta\rangle$ cross each other when:

$$v_B - v_A = -J_A + \Sigma/2 \cong -J_A \qquad \text{(S1)}$$

When the two energy levels degenerate, one has to use the perturbation theory. The corresponding matrix elements of $\hat{V}$ are:

$$\langle S\alpha|\hat{V}|S\alpha\rangle = 0$$

$$\langle T_+\beta|\hat{V}|T_+\beta\rangle = 0$$

$$\langle T_+\beta|\hat{V}|S\alpha\rangle = -\frac{\Delta}{\sqrt{2}}$$

Perturbation, $\hat{V}$, leads to the splitting of the energy levels that, in turn, leads to the following gap between the energy levels:

$$v_{\mathrm{LAC}} = \frac{\omega_{\mathrm{LAC}}}{2\pi} = 2 \cdot \frac{\Delta}{\sqrt{2}} = \frac{J_{AB} - J_{A'B}}{\sqrt{2}} \qquad \text{(S2)}$$

This value determines the oscillation frequency for the $|S\alpha\rangle \rightarrow |T_+\beta\rangle$ transition. The analytical equations for v_{LAC} (S1) and B_{LAC} (S2) give the same results as the numerical calculation shown in Figure 3S. It is important to emphasize the conditions when perturbation theory can be applied. The equations (S1) and (S2) are precise only when $|J_{AB} - J_{A'B}| \ll |J_{AA'}|$. Therefore, it is not correct to use similar approach to describe the LAC when $|J_{AB} - J_{A'B}| \geq |J_{AA'}|$ which is the case of SABRE complex with, e. g., ^{15}N-pyridine.[1] In Ir(IMes) complex[6] with ^{15}N-pyridine $|J_{AB} - J_{A'B}| \sim 20\ Hz$ and $|J_{AA'}| \sim 7\ Hz$, therefore one has to use a numerical calculation.

6. Coherent vs. incoherent polarization transfer in SABRE

a) Coherent polarization transfer in SABRE at LAC

Polarization transfer in SABRE is most efficient at low magnetic fields because the coherent mechanism is operative at a LAC. In the present model we assume that "hyperpolarized SABRE complexes", C*, are formed simultaneously at -0 time instant and then spin order starts to evolve. After a short period of free evolution time (“Evolution time” in Figure 4S) C* dissociates and one can determine polarization of the free substrate, S*. Figure 4S shows two kinetics of substrate polarization for different values of J_{AB}. It is important to emphasize that polarization (P) of the free substrate for AA'B spin system of protons (see Figure 1S) oscillates around -50% of polarization with the frequency v_{LAC}:

$$P = (\cos 2\pi v_{\mathrm{LAC}}\,\tau - 1) \cdot 50\% \qquad \text{(S3)}$$

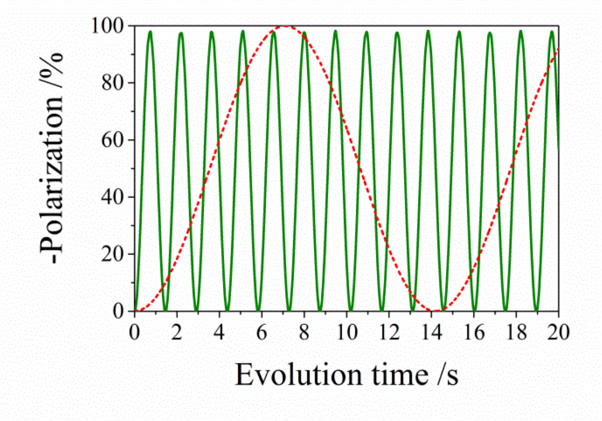

Figure 4S. Polarization dependence of the free substrate subensemble on the time period "Evolution time" at LAC field (~6 mT). The SABRE complex was generated instantaneously at time $t = -0$ and freely evolved during the time period "Evolution time". Then the complex dissociates and the free substrate is released. NMR parameters are the same as in Figure 1S. The dependence can be fitted with the following function: $(\cos 2\pi v_{LAC} t - 1) \cdot 50\%$, where v_{LAC} is the frequency of LAC.

When the magnetic field is different from B_{LAC}, the frequency of oscillation becomes higher because at LAC one has $v \to \min(v) = v_{\mathrm{LAC}}$, but the amplitude of oscillations is reduced because of less entanglement between the spin states.

Because dissociation of complexes is distributed in time, one has to take into account various lifetimes of the SABRE complexes. To achieve that, one has to convolute the oscillatory kinetics with a function that describes complex dissociation. Using the chemical scheme presented in the main text, it is easy to show that dissociation function is proportional to $\exp(-k_{\mathrm{S}}^{\mathrm{d}} \cdot t)$. Indeed, in the associative mechanism of hydrogen exchange, even for hydrogen to be exchanged the complex has to release one of the substrate molecules, which is governed by $k_{\mathrm{S}}^{\mathrm{d}}$.

The result of polarization convolution (S3) with the dissociation function is the following:

$$P = \frac{\int_0^{+\infty} e^{-k_{\mathrm{S}}^{\mathrm{d}} t} (\cos 2\pi v_{\mathrm{LAC}}\, t - 1) \cdot 50\%\, dt}{\int_0^{+\infty} e^{-k_{\mathrm{S}}^{\mathrm{d}} t}\, dt} = -\frac{50\%}{\left(k_{\mathrm{S}}^{\mathrm{d}}/\omega_{\mathrm{LAC}}\right)^2 + 1} = -50\% \cdot \lambda_{\mathrm{coh}}$$

where $\omega_{\mathrm{LAC}} = 2\pi v_{\mathrm{LAC}}$ is the angular LAC frequency, λ_{coh} — polarization transfer efficiency factor for coherent SABRE mechanism. The latter quantity, $\lambda_{\mathrm{coh}} \leq 1$ and equals to 1 when $k_S^d = 0$.

Polarization dependences on $k_{\mathrm{S}}^{\mathrm{d}}$ are shown in Figure 5S. It is seen that the larger $J_{\mathrm{AB}} - J_{\mathrm{A'B}}$ value is, the easier it is to transfer polarization from Ir-HH to the substrate because polarization transfer is faster and the sufficient lifetime of the substrate in complex $(1/k_{\mathrm{S}}^{\mathrm{d}})$ can be shorter. This model gives the maximum SABRE polarization of -50%.

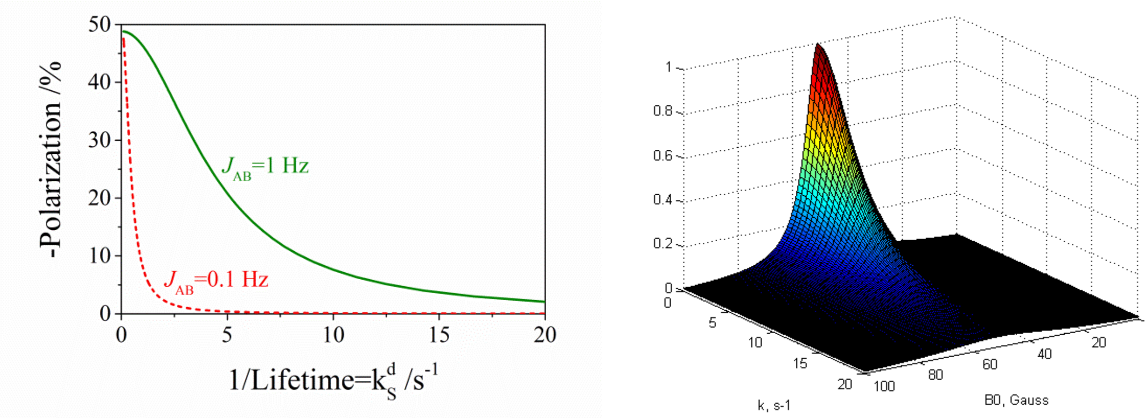

Figure 5S. Left — the dependence of the polarization of free substrate on the SABRE complex dissociation constant $k_{\mathrm{S}}^{\mathrm{d}}$. It is assumed that the kinetics of complex dissociation can be described by $\exp(-k_{\mathrm{S}}^{\mathrm{d}} \cdot t)$. Then $P\left(\omega_{\mathrm{LAC}}, k_{\mathrm{S}}^{\mathrm{d}}\right) = -\frac{50\%}{\left(k_{\mathrm{S}}^{\mathrm{d}}/\omega_{LAC}\right)^2+1}$. Here $\omega_{\mathrm{LAC}} = 2\pi J_{\mathrm{AB}}/\sqrt{2}$. The NMR parameters are: $\delta_B - \delta_A = 30$ ppm, $J_{\mathrm{AA'}} = -7$ Hz, $J_{\mathrm{A'B}} = 0$ and $J_{\mathrm{AB}} = 1$ Hz (green solid line) or $J_{\mathrm{AB}} = 0.1$ Hz (red dashed line). Right — the dependence of λ_{coh} on $k_{\mathrm{S}}^{\mathrm{d}}$ and the magnetic field.

Taking into account the polarization reduction due to the different complex lifetimes obtained earlier, the theoretical signal enhancement factor for substrate (η) may be calculated as:

$$\eta = \frac{0.5}{P_{th}} = \frac{kT}{\gamma\hbar B_0}$$

Here $P_{\mathrm{th}} = \frac{\gamma\hbar B_0}{2kT}$ is thermal polarization.

b) Coherent polarization transfer in SABRE at arbitrary magnetic field

Now let us derive an expression for SABRE polarization P at arbitrary magnetic field. Initially the system starts with the pure singlet state of two Ir-HH protons (AA'-protons) in the three-spin system of AA’B type. We have to divide the system in two equal subensembles with the following wave functions:

$$|\phi(-0)\rangle = |S\beta\rangle$$
$$|\psi(-0)\rangle = |S\alpha\rangle$$

Coherent dynamics can occur only between $|S\alpha\rangle$ and $|T_+\beta\rangle$ states, therefore $|\phi\rangle$ is time independent and we need to find only the time evolution of $|\psi\rangle$. At the LAC, the states $|S\alpha\rangle$ and $|T_+\beta\rangle$ are not eigen states of the Hamiltonian. The modified states are:

$$\begin{cases} |1\rangle = \cos\theta\,|S\alpha\rangle + \sin\theta\,|T_+\beta\rangle \\ |2\rangle = -\sin\theta\,|S\alpha\rangle + \cos\theta\,|T_+\beta\rangle \end{cases}$$

where $E_{|S\alpha\rangle} = \langle S\alpha|\hat{H}|S\alpha\rangle$, $E_{|T_+\beta\rangle} = \langle T_+\beta|\hat{H}|T_+\beta\rangle$, $V = |\langle T_+\beta|\hat{H}|S\alpha\rangle|$ and $\tan 2\theta = 2V/|E_{|S\alpha\rangle} - E_{|T_+\beta\rangle}|$. The $|S\alpha\rangle$ state can be represented by eigenfunction in the following way: $|S\alpha\rangle = \cos\theta\,|1\rangle - \sin\theta\,|2\rangle$. Then the time dependence of the system wave function is

$$|\psi(t)\rangle = \cos\theta\,|1\rangle e^{-iE_1 t} - \sin\theta\,|2\rangle e^{-iE_2 t} =$$
$$= \left(|S\alpha\rangle\left(\cos^2\theta\, e^{-i\omega t/2} + \sin^2\theta\, e^{+i\omega t/2}\right) - i|T_+\beta\rangle \sin 2\theta \sin(\omega\tau/2)\right) e^{-i(E_1+E_2)t/2}$$

where we introduce an angular frequency $\omega = E_1 - E_2$ (here energy *E* has dimension rad/s). Using the time dependence of this wavefunction it is easy to find the populations of all spin states (note that there are two equally populated subensembles):

$$\begin{cases} 2P_{|S\alpha\rangle} = 1 - \sin^2 2\theta \sin^2(\omega\tau/2) \\ 2P_{|T_+\beta\rangle} = \sin^2 2\theta \sin^2(\omega\tau/2) \\ 2P_{|S\beta\rangle} = 1 \end{cases}$$

Using these populations one can immediately determine the polarization of B-proton:

$$P(B) = P_{|\alpha\rangle} - P_{|\beta\rangle} = P_{|S\alpha\rangle} - P_{|T_+\beta\rangle} - P_{|S\beta\rangle} = -\sin^2 2\theta \sin^2\left(\frac{\omega\tau}{2}\right) = \sin^2 2\theta \frac{\cos\omega\,t - 1}{2}$$

Therefore near LAC $\eta = \frac{0.5}{P_{th}} \sin^2 2\theta$, where $\sin^2 2\theta \to 1$ when $\omega \to \omega_{\mathrm{LAC}}$ and $\sin^2 2\theta \to 0$ otherwise.

c) Incoherent polarization transfer in SABRE

It is interesting to compare the result for coherent polarization transfer (which is usually operative at low magnetic fields) with incoherent transfer by cross-relaxation (which is likely to operate at high fields). Equations for cross-relaxation are the following:

$$\begin{cases} \dfrac{dS}{dt} = -R_{\mathrm{A}}S \\ \dfrac{dI_{\mathrm{z}}}{dt} = -R_{\mathrm{B}}I_{\mathrm{z}} + \sigma S \end{cases}$$

where S is the singlet spin order for AA' protons; I_z is the integral polarization for substrate (B) proton; R_{A} is the relaxation rate for AA' protons; R_{B} is the relaxation rate ($1/T_1$) for B proton; σ is the rate of cross-relaxation. Cross-relaxation is written only for I_{z}, it is neglected in the first equation due to very high population of singlet spin order. For initial conditions $S = 1$ and $I_{\mathrm{z}} = 0$ the solution of the system is

$$I_z(t) = \frac{\sigma}{R_{\mathrm{A}} - R_{\mathrm{B}}}\left(e^{-R_{\mathrm{B}}t} - e^{-R_{\mathrm{A}}t}\right) \tag{S4}$$

Polarization convolution (eq. S4) with dissociation function gives the following result:

$$P = \frac{\int_0^\infty I_{\mathrm{z}}(t)e^{-k_{\mathrm{S}}^{\mathrm{d}}t}dt}{\int_0^\infty e^{-k_{\mathrm{S}}^{\mathrm{d}}t}dt} = \frac{\sigma k_{\mathrm{S}}^{\mathrm{d}}}{R_{\mathrm{A}} - R_{\mathrm{B}}}\left(\frac{1}{k_{\mathrm{S}}^{\mathrm{d}} + R_{\mathrm{B}}} - \frac{1}{k_{\mathrm{S}}^{\mathrm{d}} + R_{\mathrm{A}}}\right) = \frac{\sigma}{\left(\sqrt{R_{\mathrm{A}}} + \sqrt{R_1}\right)^2} \cdot \frac{k_{\mathrm{S}}^{\mathrm{d}}\left(\sqrt{R_{\mathrm{A}}} + \sqrt{R_{\mathrm{B}}}\right)^2}{\left(k_{\mathrm{S}}^{\mathrm{d}} + R_{\mathrm{A}}\right)\left(k_{\mathrm{S}}^{\mathrm{d}} + R_{\mathrm{B}}\right)}$$

$$= P_{\mathrm{max}} \cdot \lambda_{\mathrm{incoh}}$$

here the term $\lambda_{\mathrm{incoh}} = \frac{k_{\mathrm{S}}^{\mathrm{d}}\left(\sqrt{R_{\mathrm{A}}} + \sqrt{R_{\mathrm{B}}}\right)^2}{\left(k_{\mathrm{S}}^{\mathrm{d}} + R_{\mathrm{A}}\right)\left(k_{\mathrm{S}}^{\mathrm{d}} + R_{\mathrm{B}}\right)}$ was isolated (by analogy with λ_{coh}) because it is changing between 0 and 1 and $\lambda_{\mathrm{incoh}} = 1$ when $k_{\mathrm{S}}^{\mathrm{d}} = \sqrt{R_{\mathrm{A}}R_{\mathrm{B}}}$. The quantity $P_{\mathrm{max}} = \frac{\sigma}{\left(\sqrt{R_{\mathrm{A}}} + \sqrt{R_{\mathrm{B}}}\right)^2}$ describes the effective spin order of substrate (spin B).

d) Dependence of enhancement factor on $k_{\mathrm{S}}^{\mathrm{d}}$

After substitution of λ_{coh} and λ_{incoh} (assuming $\lambda_{\mathrm{coh}} = \lambda_{\mathrm{coh}}^{'}$ and $\lambda_{\mathrm{incoh}}^{'} = 0$) to eq. (3) of the main text for both coherent and incoherent polarization transfer mechanisms, one can find the dependence of the enhancement factor on the substrate dissociation rate constant:

$$|\varepsilon|_{\mathrm{coh}} \propto A_1 \frac{k_{\mathrm{S}}^{\mathrm{d}}}{B_1\left(\left(k_{\mathrm{S}}^{\mathrm{d}}/\omega_{\mathrm{LAC}}\right)^2 + 1\right) + C_1 k_{\mathrm{S}}^{\mathrm{d}}} \tag{S5}$$

$$|\varepsilon|_{\mathrm{incoh}} \propto A_2 \frac{\left(k_{\mathrm{S}}^{\mathrm{d}}\right)^2}{B_2\left(k_{\mathrm{S}}^{\mathrm{d}} + R_{\mathrm{A}}\right)\left(k_{\mathrm{S}}^{\mathrm{d}} + R_{\mathrm{B}}\right) + C_2\left(k_{\mathrm{S}}^{\mathrm{d}}\right)^2} \tag{S6}$$

here A_1, B_1, C_1 and A_2, B_2, and C_2 are parameters for low-field and high-field SABRE.

It is seen that for $k_{\mathrm{S}}^{\mathrm{d}} \to \infty$, in the case of coherent polarization transfer $|\varepsilon| \propto 1/k_{\mathrm{S}}^{\mathrm{d}}$, while for the incoherent mechanism $|\varepsilon| \to \mathrm{const}$. This is a «mathematical» explanation of «quantum Zeno» effect for SABRE. For a high dissociation rate, polarization transfer efficiency is reduced in both cases, but the rate of decrease is higher for coherent processes. If one keeps the equilibrium constant for substrate exchange fixed and increases the rate constants of both associative and dissociative exchange, the enhancement will go to a plateau for high-field SABRE (incoherent polarization transfer) but will decrease for low-field SABRE (coherent polarization transfer).

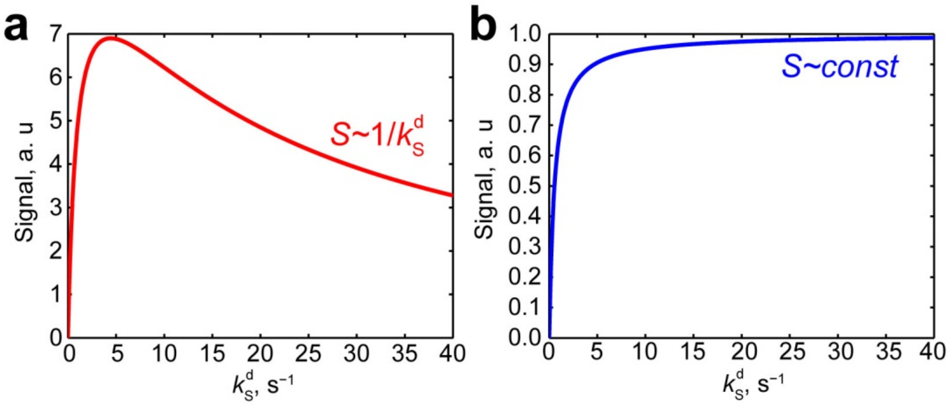

Figure 6S. Anticipated dependence of SABRE signal on the dissociation constant $k_{\mathrm{S}}^{\mathrm{d}}$ for (a) low-field SABRE (eq. S5), (b) high-field SABRE (eq. S6).

It is seen that there is an optimal $k_{\mathrm{S}}^{\mathrm{d}}$ value for the low-field SABRE process for which polarization and the available signal are largest, while for high-field SABRE higher dissociation rates are preferable.

The value of the optimal dissociation constant $k_{\mathrm{S}}^{\mathrm{d}}$ (for simplicity here referred to as k) for low-field SABRE can be found by taking a derivative of eq. (S5):

$$\frac{\partial \varepsilon_{coh}}{\partial k} = \left(\mathrm{A}\frac{f}{\mathrm{B}+\mathrm{C}f} \right)'_{k} = 0$$

where $f = k/(1 + k^2/\omega_{\mathrm{LAC}}^2)$, A, B and C are numerical factors.

$$\frac{\partial \varepsilon_{coh}}{\partial k} = \frac{\partial \varepsilon_{coh}}{\partial f}\frac{\partial f}{\partial k} = \mathrm{A}\frac{\mathrm{B}}{(\mathrm{B}+\mathrm{C}f)^2}\frac{\omega_{\mathrm{LAC}}^2\,(\omega_{\mathrm{LAC}}^2 - k^2)}{(k^2 + \omega_{\mathrm{LAC}}^2)^2} = 0$$

and it is seen that $\frac{\partial \varepsilon_{coh}}{\partial k} = 0$ when $k_{\mathrm{S}}^{\mathrm{d}} = \omega_{\mathrm{LAC}}$.

7. Analysis of literature data

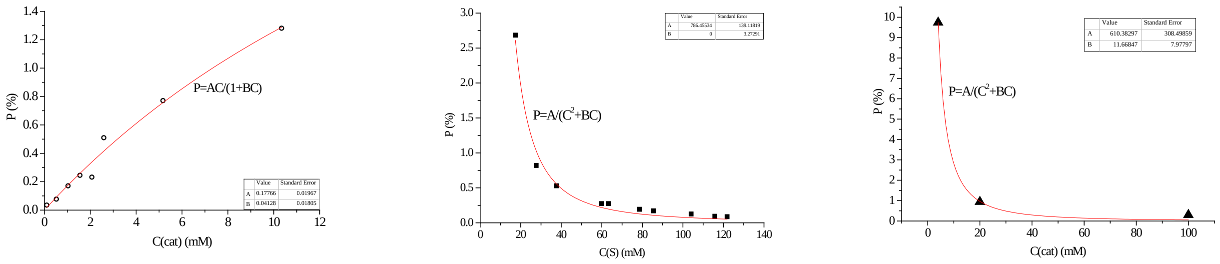

Figure 7S. Polarization dependences on the catalyst and substrate loading (the same as Figure 4 of the main text) and their fit with eq. (2) of the main text. The data are from supplementary materials of corresponding articles (see Table 1S).

Table 1S. Data for polarization as a function of catalyst or substrate loading. Other system parameters were kept constant in all data series. The data are from supplementary materials of corresponding articles.

Cowley et al.[6]		Appleby et al.[7]		Truong et al.[1]	
P, %	[C], mM	*P*, %	[S], mM	*P*, %	[S], mM
0.04	0.1	2.68*	17.3	9.74	4
0.08	0.52	0.82*	27.6	0.94	20
0.17	1.03	0.27*	63.3	0.3	100
0.25	1.55	0.17*	85.5		
0.23	2.07	0.09*	115.7		
0.51	2.59	0.53**	37.6		
0.77	5.17	0.27**	59.8		
1.28	10.34	0.19**	78.6		
		0.13**	104.1		
		0.09**	121.8		

* — data for pyridazine

** — data for phthalazine

References

(1) Truong, M. L.; Theis, T.; Coffey, A. M.; Shchepin, R. V.; Waddell, K. W.; Shi, F.; Goodson, B. M.; Warren, W. S.; Chekmenev, E. Y. *The Journal of Physical Chemistry C* **2015**, *119*, 8786.

(2) Pravdivtsev, A. N.; Yurkovskaya, A. V.; Vieth, H.-M.; Ivanov, K. L. *The Journal of chemical physics* **2014**, *141*, 155101.

(3) Adams, R. W.; Duckett, S. B.; Green, R. A.; Williamson, D. C.; Green, G. G. R. *J. Chem. Phys.* **2009**, *131*, 194505.

(4) Pravdivtsev, A. N.; Yurkovskaya, A. V.; Vieth, H.-M.; Ivanov, K. L.; Kaptein, R. *ChemPhysChem* **2013**, *14*, 3327.

(5) Ivanov, K. L.; Pravdivtsev, A. N.; Yurkovskaya, A. V.; Vieth, H.-M.; Kaptein, R. *Prog. Nucl. Magn. Reson. Spectrosc.* **2014**, *81*, 1.

(6) Cowley, M. J.; Adams, R. W.; Atkinson, K. D.; Cockett, M. C. R.; Duckett, S. B.; Green, G. G. R.; Lohman, J. A. B.; Kerssebaum, R.; Kilgour, D.; Mewis, R. E. *J. Am. Chem. Soc.* **2011**, *133*, 6134.

(7) Appleby, K. M.; Mewis, R. E.; Olaru, A. M.; Green, G. G.; Fairlamb, I. J.; Duckett, S. B. *Chemical Science* **2015**.