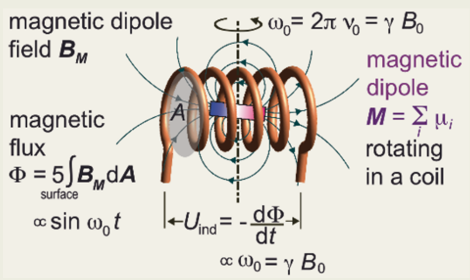
6. Hyperpolarization

Polarization and spin order
Electron spin resonance
Polarization transfer from electrons: DNP
    Overhauser DNP
    DNP assisted by temperature
    DNP assisted by light: Diamonds and gases
Transfer of spin order: Para-hydrogen

B. Blümich, *Essential NMR*,
https://doi.org/10.1007/978-3-030-10704-8_6

The NMR Experiment

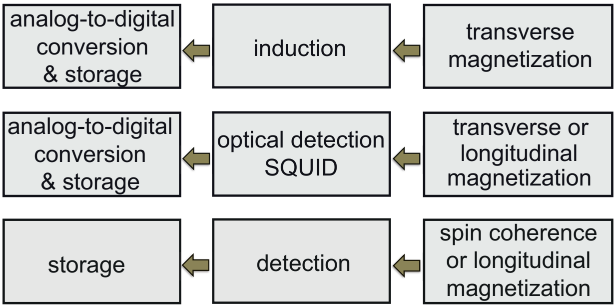


Faraday's law of induction: The voltage U_{ind} induced in N closed loops equals the rate of change of the magnetic flux Φ enclosed by the loops

The flux is the magnetic field $\boldsymbol{B}_M$ times the areas $\boldsymbol{A}$ of the loops through which it passes

The magnetic field is generated by the sum $\boldsymbol{M}$ of all magnetic dipoles μ

$\boldsymbol{M}$ is proportional to the magnetic polarization



Conventional scheme
for low to high frequencies

analog-to-digital conversion & storage ⇦ induction ⇦ transverse magnetization

Alternative schemes
for very low frequencies

analog-to-digital conversion & storage ⇦ optical detection SQUID ⇦ transverse or longitudinal magnetization

General scheme

storage ⇦ detection ⇦ spin coherence or longitudinal magnetization

Nuclear Polarization and Sensitivity

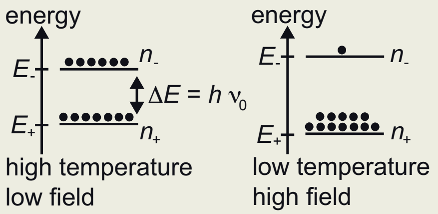
- The *nuclear polarization* is the dipolar *longitudinal magnetization*
- It is given by the sum of population differences of energy levels between which transitions can be stimulated by radio-frequency photons
- Since a photon has spin 1, these energy levels differ in magnetic quantum number m by $|\Delta m| = 1$
- The polarization defines the signal amplitude M_0 after an excitation pulse provided all off-diagonal elements in the density matrix are zero before
- In *thermodynamic equilibrium* it is given by the *Boltzmann distribution*. For N spins, $M_0 = N\gamma\hbar \dfrac{\sum_{m=-I}^{m=I} m \exp\{m\hbar\,\omega_0/k_B T\}}{\sum_{m=-I}^{m=I} \exp\{m\hbar\,\omega_0/k_B T\}}$, and at high temperature, $M_0 \propto B_0$
- The *sensitivity of NMR* is specified by the *signal-to-noise ratio S/N*
- With *inductive detection* it is given by the electromotive force (voltage) induced in the detection coil relative to the standard deviation of the noise
- The induced voltage is proportional to the polarization and the time-derivative of the magnetic flux resulting from the sum of nuclear magnetic moments, which oscillates with the *Larmor frequency* $\omega_0 = \gamma\,B_0$ in the detection field B_0
- Therefore, the sensitivity is proportional to the product of the nuclear polarization and the strength B_0 of the detection field: $S/N \propto M_0\,B_0$

Improving the Sensitivity of NMR

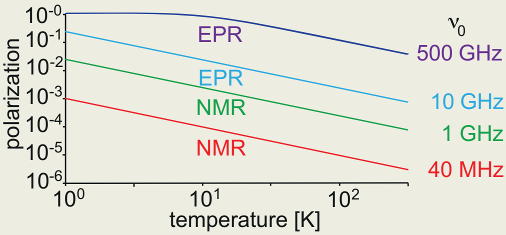
Separate the polarization and detection processes

Thermal spin-½ polarization

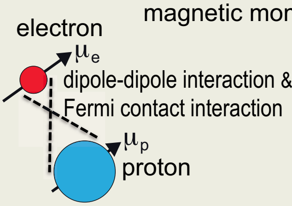
$$\frac{n_+ - n_-}{n_+ + n_-} = \frac{1 - \exp\{-h\,\nu_0/(k_B T)\}}{1 + \exp\{-h\,\nu_0/(k_B T)\}} \xrightarrow[\text{high } T]{} \frac{h\,\nu_0}{2\,k_B T}$$



Electron versus proton polarization



Polarization transfer from electrons



magnetic moment $\mu = \frac{q}{2\,m_{p,e}\hbar}$

$\frac{m_p}{m_e} = 1836$

$E_m = -m_{S,I}\, g\, \mu\, B_0$

$\Delta E = g\, \mu\, B_0$

$g_e \approx 2$

$g_{proton} \approx 5.6$

$\rightarrow \nu_e \approx 658\ \nu_{1H}$

$m_S = \pm½ = m_I$

Transfer of spin order

Perfect order	Description
↑↑↑↑↑↑↑↑	uncoupled spins polarization $\frac{n_+ - n_-}{n_+ + n_-}$
⇅ ⇅ ⇅ ⇅	coupled spin pairs singlet state $\boldsymbol{I} = \boldsymbol{I}_1 + \boldsymbol{I}_2 = \mathbf{0}$ singlet order $\frac{n_{singlets}}{n_{singlets} + n_{triplets}}$

Boosting the Sensitivity

- In ordinary NMR experiments single-quantum spin coherence, i.e. transverse magnetization is detected
- The conventional form of detection is *nuclear induction*
- If the spins are thermally polarized in the detection field, the *sensitivity* of induction NMR is roughly proportional to the square of the NMR frequency
- Alternative schemes separate the polarization and detection steps to optimize each individually
- At low frequencies the *longitudinal magnetization* (*polarization*) and the *transverse magnetization* can be detected with high sensitivity optically as well as with superconducting quantum interference devices (*SQUIDS*)
- The amplitude of the detected magnetization can be increased beyond the thermodynamic equilibrium value of the longitudinal magnetization by transferring spin order from sources with higher spin order
- For example, the Larmor frequency of electrons is 658 times higher than for ^{1}H
- At low temperature the *electron polarization* can approach 100 %
- It can be transferred to nuclei with *dynamic nuclear polarization* (*DNP*)
- For that unpaired electrons need to be available at sufficiently high density
- Another source of spin order is *para-hydrogen*. There, the two proton spins are aligned in antiparallel manner, producing a singlet state with zero total spin
- When breaking the symmetry of *p*-H_2, this spin order can be transferred to nuclear target spins by chemical reaction or through *spin-spin coupling*

EPR Equipment

EPR frequencies

Microwave band	Frequency	Wavelength	Magnetic field
S	3.0 GHz	100.0 mm	0.107 T
X	9.5 GHz	3.15 mm	0.339 T
K	23 GHz	13.0 mm	0.82 T
Q	35 GHz	8.6 mm	1.25 T
W	95 GHz	3.15 mm	3.3 T
D	140 GHz	2.1 mm	4.9 T
-	360 GHz	0.83 mm	12.8 T

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Yevgeny Konstantinovich Zavoisky - Евгений Константинович Завойский, 1907 – 1976

Pulsed X to Q band EPR spectrometer

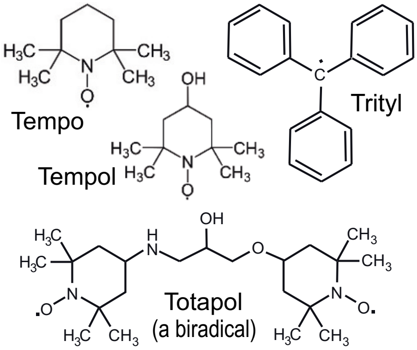
Courtesy of Rüdiger Eichel, FZ Jülich

X-band CW EPR spectrometer

Benchtop EPR spectrometer

(Courtesy of Magnettech GmbH, Berlin)

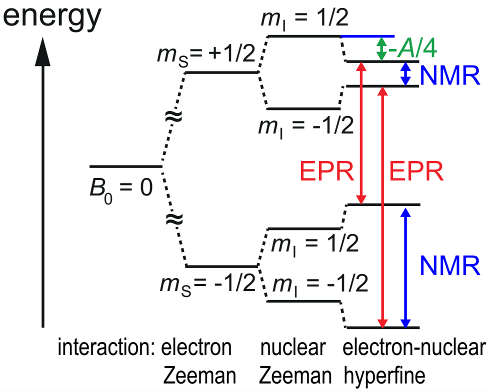
Some stable radicals for EPR



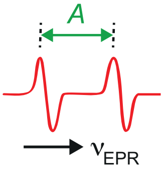
Electron Paramagnetic Resonance: EPR

- *EPR* for *electron paramagnetic resonance* and *ESR* for *electron spin resonance* are used synonymously
- EPR was discovered in 1944 by Yevgeny Konstantinovich Zavoisky in Kazan
- Independently the method was developed by Brebis Bleaney in Great Britain
- EPR is a magnetic resonance technique similar to NMR. It relies on the presence of *unpaired electrons*
- Stable unpaired electrons are rare in nature, so that stable free radicals are introduced into the sample as spin probes to report sample properties by EPR
- Whereas typical NMR frequencies employed for chemical analysis are in the radio-frequency regime between 40 and 1000 MHz, typical EPR frequencies are in the microwave regime between 3 - 500 GHz
- The higher resonance frequencies make EPR more sensitive than NMR
- EPR relaxation times are in the microsecond range and thus much shorter than NMR relaxation times, so that EPR lines are broad compared to NMR lines
- EPR spectra can cover bandwidths of several hundred Megahertz so that *pulsed excitation* is *frequency selective*
- Many EPR spectra are still measured today with the *continuous wave* technique by sweeping the magnetic field in such a way, that absorption spectra are obtained in derivative mode

One Electron Interacting with One Spin-½ Nucleus



$\mathbf{H} = - g_e \mu_e \boldsymbol{B}_0 \mathbf{S}_z - g_n \mu_n \boldsymbol{B}_0 \mathbf{I}_z - h\, \mathbf{S}\, \mathbf{A}\, \mathbf{I}$
with
$E(m_S,m_I) = - m_S\, g_e\, \mu_e\, B_0 - m_I\, g_n\, \mu_n\, B_0 - h\, m_S\, A\, m_I$



CW EPR-spectra, usually show the resonance absorption lines in derivative mode

First-order selection rule

$\Delta m_S = \pm 1$ and $\Delta m_I = 0$

In solid-state EPR, the first-order selection rule can be violated when the nuclear Zeeman and the hyperfine interactions are of similar magnitude. Then transitions with simultaneous *I* and *S* spin flips ($\Delta m_S = \pm 1$ and $\Delta m_I = \pm 1$) become weakly allowed, and the EPR signal is affected by the nuclear Zeeman and quadrupole interactions. As this effect occurs mainly in solids it is called the “solid effect”

Basic Theory

- The *Hamiltonian* of one electron spin interacting with nuclear spins *k* is given by

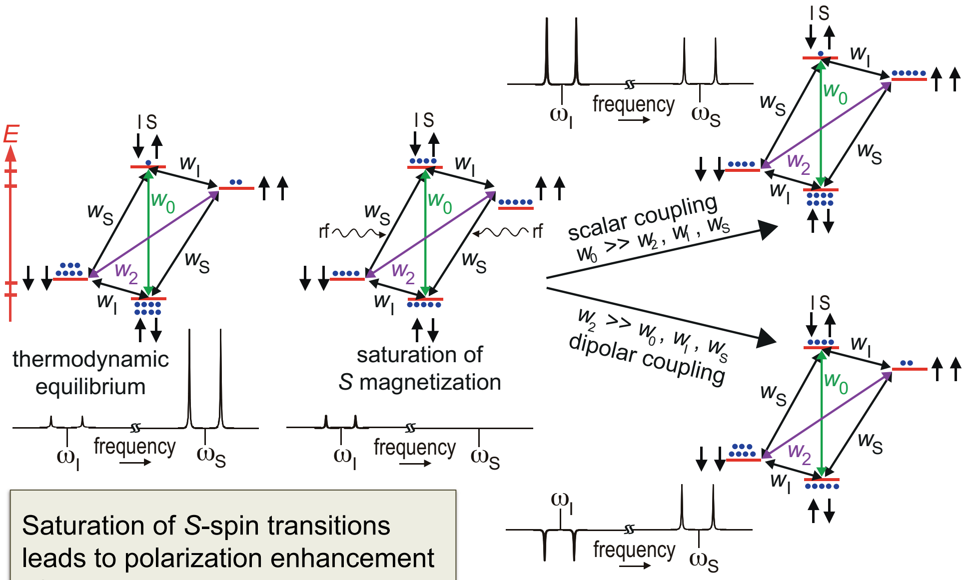
$$\mathbf{H}_{\text{spin}} = \underbrace{- g_e\, \mu_e\, \boldsymbol{B}_0\, \mathbf{S}}_{\substack{\text{Zeeman int.,}\\ \text{electron spin}}} \underbrace{- \Sigma\, g_{n,k}\, \mu_n\, \boldsymbol{B}_0\, \mathbf{I}_k}_{\substack{\text{Zeeman int.,}\\ \text{nuclear spin}}} \underbrace{- h\, \Sigma\, \mathbf{S}\, \mathbf{A}_k\, \mathbf{I}_k}_{\substack{\text{hyperfine}\\ \text{interaction}}} - \underbrace{h\, \Sigma\, \mathbf{I}_k\, \mathbf{Q}_k\, \mathbf{I}_k}_{\substack{\text{quadrupole}\\ \text{interaction}}},$$

  where μ_n is the nuclear magnetic moment, $\mathbf{I}_k$ the nuclear spin vector operator, $\mathbf{A}_k$ the electron nuclear hyperfine tensor in Hz, and $\mathbf{Q}_k$ the nuclear quadrupole coupling tensor in Hz
- Considering just one electron interacting with one spin ½ nucleus one obtains in the NMR notation

$$\mathbf{H}_{\text{spin}} = -\gamma_S\, \hbar\, \mathbf{S}\, \boldsymbol{B}_0 - \gamma_I\, \hbar\, \mathbf{I}\, \boldsymbol{B}_0$$
$$- \gamma_S\, \gamma_I\, \hbar^2\, (8\pi/3)\, |\Psi(0)|^2\, (\mathbf{I}\, \mathbf{S}) - \gamma_S\, \gamma_I\, \hbar^2\, [3\, (\mathbf{I}\, \boldsymbol{r})\, (\mathbf{S}\, \boldsymbol{r})\, /r^5 - \mathbf{I}\, \mathbf{S}\, /r^3].$$

  Terms 1 and 2 are the *Zeeman interactions* of the electron and the nucleus. Term 3 is the scalar *Fermi contact interaction* which corresponds to the *J-coupling* between nuclear spins in NMR. Here $\Psi(0)$ is the electron‘s wave function at the nucleus. Term 4 is the time- and distance-dependent direct *dipole-dipole interaction* between electron and nucleus
- The first-order selection rules for EPR transitions allow changes in *magnetic quantum numbers* $\Delta m_S = \pm 1$ and $\Delta m_I = 0$, so that the electron spin orientation changes but not the nuclear spin orientation
- The associated energy difference defines the hyperfine constant *A* in MHz

Overhauser DNP in a Two-Spin System



Saturation of *S*-spin transitions leads to polarization enhancement of *I* spins by cross-relaxation

Dynamic Nuclear Polarization: DNP

- *DNP* denotes the transfer of electron spin polarization to atomic nuclei by means of a coupling between electrons and nuclei
- In a system of two types of spins *I* and *S* interacting in a static magnetic field the populations of the energy levels depend on the spin polarizations, e.g. the polarization of the *I* spins depends on the polarization of the *S* spins
- When saturating the *S*-spin transitions by irradiation with frequency ν_S the differences in *S*-spin populations vanish
- If either the zero-quantum cross-relaxation rate w_0 or the double-quantum cross-relaxation rate w_2 is larger than the single-quantum relaxation rate w_1, the *I*-spin population differences increase
- This was predicted by A. Overhauser and is known as the *Overhauser effect*
- When the *S* spins are electrons and the *I* spins nuclei, the effect is termed *dynamic nuclear polarization,* in short: *DNP*
- In liquids, only *Overhauser DNP* by *cross-relaxation* is observed for electron und nuclear spins coupled indirectly by the the *Fermi contact interaction*
- In solids the direct dipole-dipole interaction enables further DNP mechanisms. These are the *solid effect*, the *cross effect*, and *thermal mixing*
- All of them may arise simultaneously and enhance the nuclear polarization
- DNP enables studies within hours that otherwise would take months to conduct and introduces contrast between species that otherwise appear alike

Making Use of Overhauser DNP

Theory: The *Overhauser-DNP enhancement* $E = M_{zI} / M_{0I} = 1 - \rho f s \, |\gamma_S| / \gamma_I$ is calculated from the relaxation rates w_i, where

M_{zI}: current nuclear polarization (hyperpolarization)
M_{0I}: nuclear thermodynamic equilibrium polarization
$\rho = (w_2 - w_0) / (w_0 + 2w_1 + w_2)$ is the coupling factor
$f = (w_0 + 2w_1 + w_2) / (w_0 + 2w_1 + w_2 + w^0)$ is the leakage factor
$s = (M_{0S} - M_{zS}) / M_{0S}$ is the saturation factor
with
M_{zS}: partially saturated electron polarization
M_{0S}: thermodynamic equilibrium electronic polarization
$w^0 = 1/T_1^0$ is the longitudinal nuclear relaxation rate without free radicals

The maximum enhancement is $E = 658$ for protons

The use of Overhauser-DNP

The *saturation factor s* approaches 1 for optimum EPR saturation

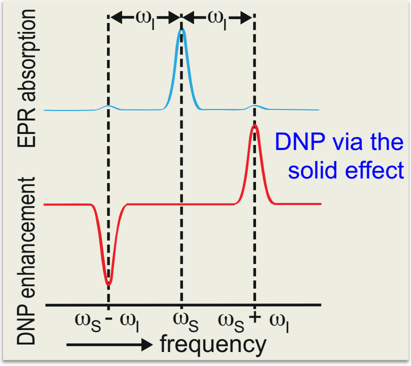
The *leakage factor* can be estimated from the NMR relaxation times T_1 and T_1^0 with and without free electron spins present, respectively, as $f = 1 - T_1/T_1^0$

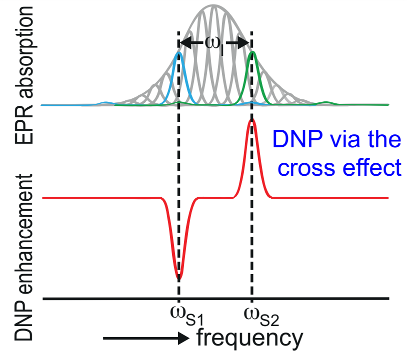
Overhauser DNP experiments aim at determining the *coupling factor* ρ. It critically depends on the strength and fluctuation of the electron-nuclear interaction. From models based on spectral densities of motion, molecular translational diffusion coefficients can be determined in the vicinity of spin probes marking particular environments such as the surface water in proteins

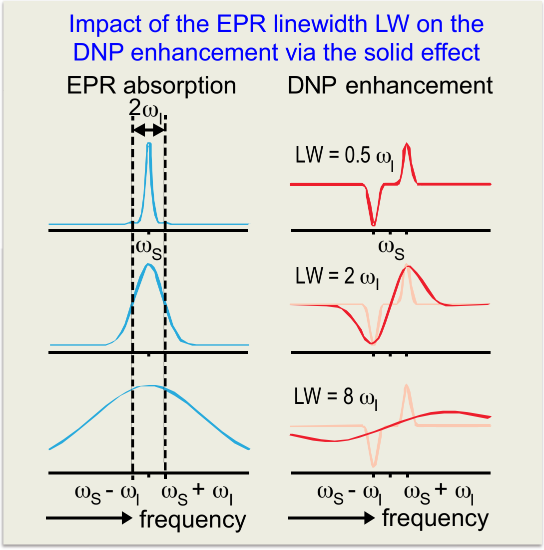
Overhauser DNP

- The energy level diagram of an electron spin interacting with a nuclear spin ½ accounts for a difference in sign of the gyromagnetic ratios of particles with masses *m* and opposite charges *q*, $\hbar \gamma = g \mu = g q/(2m)$
- Saturating the electron transitions enhances the NMR signal if w_0 or $w_2 > w_1$
- In the limit of pure *dipole-dipole coupling* $w_2 = 6 w_0$, and the NMR signal is enhanced negatively
- In the limit of pure *scalar coupling*, *cross-relaxation* proceeds only through w_0, and the NMR signal is enhanced positively
- The cross-relaxation rates w_0 and w_2 are large if energy between spins and lattice can be exchanged
- This is the case if the scalar or the dipolar electron-nuclear couplings are modulated through *translational* or *rotational motion* with an inverse *correlation time* τ (100 ps) similar to the electron resonance frequency (10 GHz at 0.35 T)
- Translational collisions of small molecules in liquids, e.g. have correlation times of about 100 ps, while the rotational motion of a complex of two small molecules can have correlation times on the order of 10 ps
- Therefore, the DNP enhancement of the liquid-state NMR signal at 10 GHz EPR frequency essentially reports *diffusion* of small molecules

The Solid Effect and the Cross Effect







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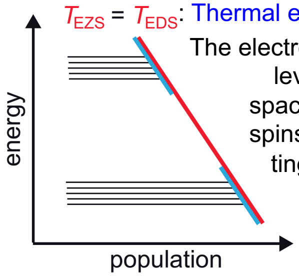
The Solid Effect

- Polarization is transferred, when coupled spins cross-relax or flip
- While the *Overhauser effect* relies on time-dependent interactions between electron and nuclear spins, other mechanisms rely on time-independent couplings and predominantly the direct coupling in solids
- The *solid effect* arises when the electrons are irradiated at frequency $\nu_{rf} = \nu_S \pm \nu_I$ with an offset of the nuclear resonance frequency ν_I above or below their resonance frequency ν_S to excite zero- or double-quantum transitions directly
- Depending on the offset, the nuclei are hyperpolarized with different signs
- These transitions are forbidden in first-order perturbation theory, but are weakly allowed in second order at high B_1 field and low B_0 field
- The transition probability and the *enhancement* scale with ν_I^{-2}. This dependence limits the use of the solid effect to low field
- Moreover, the electron-spin resonance-line width should be smaller than the NMR resonance frequency, so that only one of the two transitions $\nu_S \pm \nu_I$ is stimulated at a time to avoid cancellation of NMR signal amplitudes
- For an inhomogeneously broadened, wide EPR line, *hyperpolarization* is generated at both frequencies and signals interfere destructively
- Therefore, *stable radicals* like trityl are utilized which give rise to narrow lines
- Once nuclear polarization has been created locally it spreads across the sample volume by *spin diffusion*

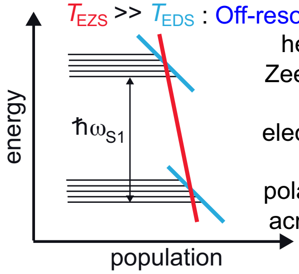
Thermal Mixing

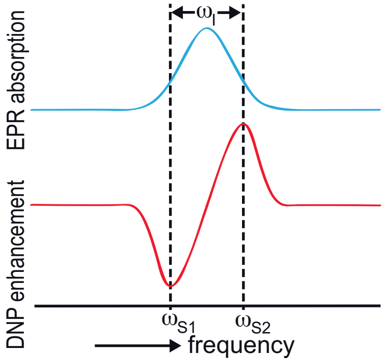
$T_{EZS} = T_{EDS}$: Thermal equilibrium



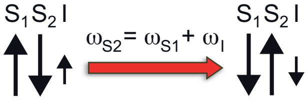
The electron-spin energy levels are closely spaced when many spins couple, resulting in a homogeneously broadened line

$T_{EZS} >> T_{EDS}$: Off-resonance irradiation heats the electron-Zeeman bath on the expense of the electron dipolar bath and generates a polarization gradient across the EPR line





The nuclear Zeeman bath is cooled by the electron dipolar bath via energy conserving three-spin transitions

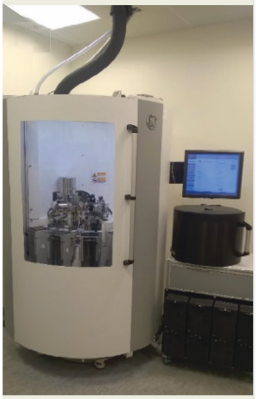


The Cross Effect and Thermal Mixing

- The cross effect and thermal mixing are three-spin processes of two electron spins and one nuclear spin satisfying the matching condition $\omega_{S2} - \omega_{S1} = \omega_I$
- Other than the *solid effect*, both effects arise from irradiating allowed transitions
- The *cross effect* requires an EPR resonance inhomogeneously broadened by *g* anisotropy with homogeneous linewidths smaller than ω_I
- The difference in electron Larmor frequencies provides the energy for the nuclear spin flip; biradicals improve the DNP efficiency
- With MAS the cross effect is currently the most efficient DNP mechanism
- Under MAS the energy levels shift periodically, and the polarization is transferred by reoccurring *level anti-crossings*
- *Thermal mixing* requires an EPR resonance with a linewidth on the order of the NMR frequency, homogeneously broadened from many interacting electrons
- The electron-electron coupling provides the energy for the nuclear spin flip
- Thermal mixing is explained in terms of spin temperature equilibrating between three interacting baths, the electron Zeeman system EZS, the electron dipolar system EDS, and the nuclear Zeeman system NZS
- Weak off-resonance irradiation produces a polarization gradient across the EPR line, equivalent to cooling the EDS
- Being in contact with the EDS bath, the NZS bath is then cooled by energy conserving three-spin processes leading to DNP enhancement
- Although the enhancements by the cross effect and thermal mixing scale with B_0^{-1}, both are successfully used at high field

Practice of Dissolution DNP

GE Spinlab DNP hyperpolarizer for imaging of metabolic activity



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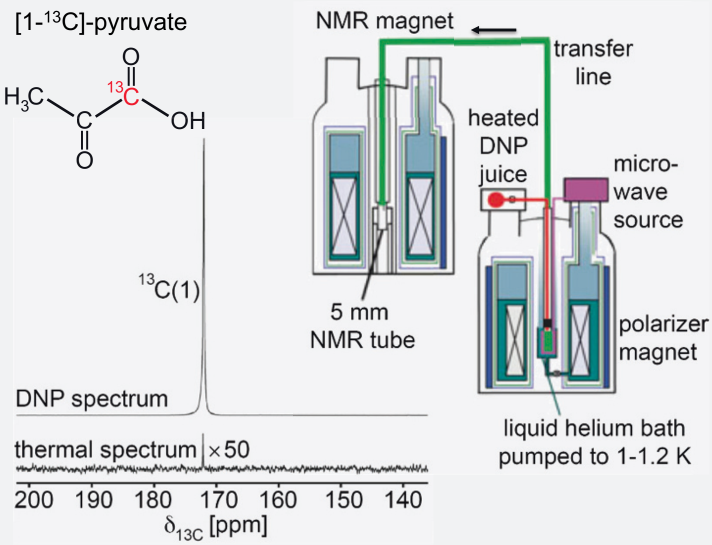
Dissolution DNP ^{13}C spectroscopy



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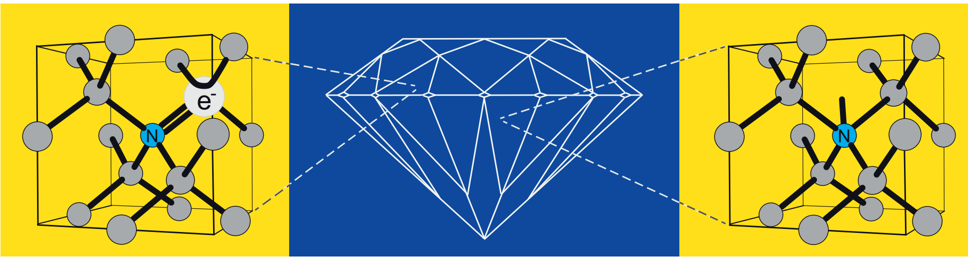
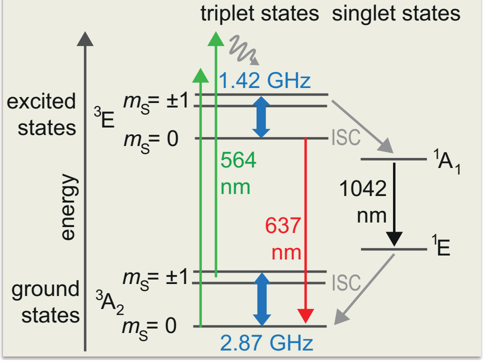
The Use of DNP

- The largest *DNP enhancement* is achieved at high field and low temperature
- Depending on type of nucleus and field strength, three to five orders of magnitude in polarization can be gained by freezing liquid samples with the free radicals into a glass
- *DNP juice*, a mixture of 60/30/10 (vol%) d_8-glycerol/D_2O/H_2O is a popular solvent for the stable radicals and the target molecules. It forms a glass upon cooling and avoids *crystallization* damage in particular to biological materials
- The polarization step takes minutes to tens of minutes
- Often protons are hyperpolarized first and then polarization is transferred to other nuclei
- Low sample concentrations can be analyzed in single scans by MAS that otherwise would require weeks and months of signal averaging
- With *dissolution DNP*, on the other hand, the hyperpolarized, glassy sample is rapidly melted for analysis by liquid-state NMR spectroscopy or MRI
- This temperature-jump method yields polarization levels in the two-digit percent range
- DNP hyperpolarized *pyruvate* injected into living organisms accumulates in regions of high metabolic activity such as cancerous tissue and lightens up in MRI
- Tumor cells convert pyruvate into lactate, while healthy cells produce bicarbonate
- Spectroscopic ^{13}C MRI detection of selectively ^{13}C enriched and hyperpolarized pyruvate reveals details of the pyruvate digestion into metabolites
- Commercial instruments such as General Electric’s *Spinlab* or Oxford Instruments’ *Hypersense* produce biocompatible solutions of DNP hyperpolarized tracer molecules for molecular imaging in minutes with a 10.000 fold gain in sensitivity

Defects in Diamond




Zero-field NV$^-$ energy-level diagram

Transfer of optically induced electron polarization to nuclei

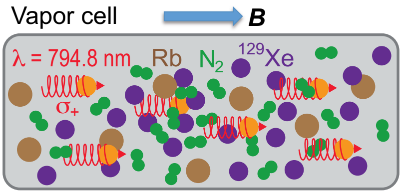
- 90% electron spin polarization can be gained in less than 1 μs
- It is transferred to ^{13}C nuclei by Overhauser DNP, the solid effect, and through level anti-crossings at low field
- ^{13}C polarization spreads across the diamond lattice by spin diffusion
- Hyperpolarized nano-diamond powders are envisioned as biocompatible ^{13}C markers in MRI and as polarization sources for nuclei in liquid molecules

DNP from Nitrogen Vacancy Centers in Diamond

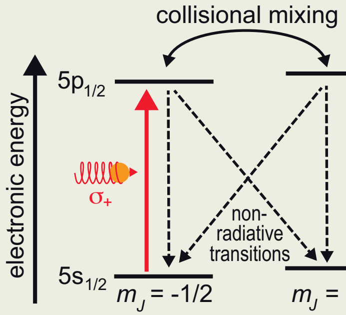
- High thermal electron polarization results from high field and low temperature
- High electron polarization can also be created at low field and high temperature by *optical pumping* of crystal defects such as NV$^-$ and P1 defects in *diamond*
- Uncharged *nitrogen vacancy* (NV) defects in diamond occupy two neighboring lattice sites, one being occupied by a nitrogen atom and the other being vacant
- The vacant site has three unpaired electrons in rapid exchange. Two form a quasi covalent bond via the lone pair of the nitrogen, and one electron can pair with a negative charge resulting in an *NV$^-$ defect* with electron spin $S = 1$
- In a diamond *P1 defect* an N Atom substitutes a C atom, leaving one $S = ½$ unsaturated electron spin
- The optical energies of the NV$^-$ center are split by the electron spin states
- When excited with a green *laser* at higher than the transition energy, phonons are generated, which enhance the non-radiative depopulation of the $m_S = \pm 1$ excited states, whereas the $m_S = 0$ state depopulates mainly radiatively
- The populations of the $m_S = \pm 1$ excited states preferably relax by inter-system crossing (ISC) to the $m_S = 0$ ground state so that it's population is increased preferentially, and the electron-spin states can be detected optically
- In a magnetic field, the *Zeeman interaction* shifts the energy levels. They are further split by the electron-nuclear hyperfine interaction
- Whereas the $\Delta m_S = 1$ transitions depend on the diamond orientation, the $\Delta m_S = 2$ transition does not, so that it lends itself for DNP in *diamond powder*

Hyperpolarization of Xenon Gas

Resonant irradiation with circularly polarized light

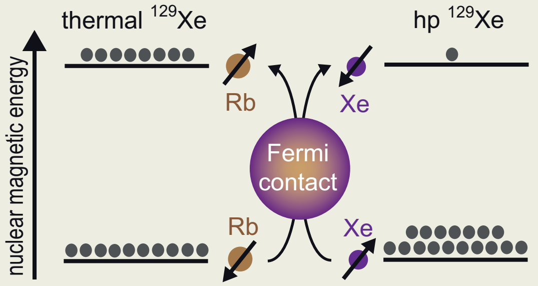


Optical hyperpolarization of Rb electron spins



m_J is the magnetic spin-orbit angular momentum quantum number

Hyperpolarization of ^{129}Xe nuclear spins by Fermi contact with optically polarized Rb electron spins in collision complexes



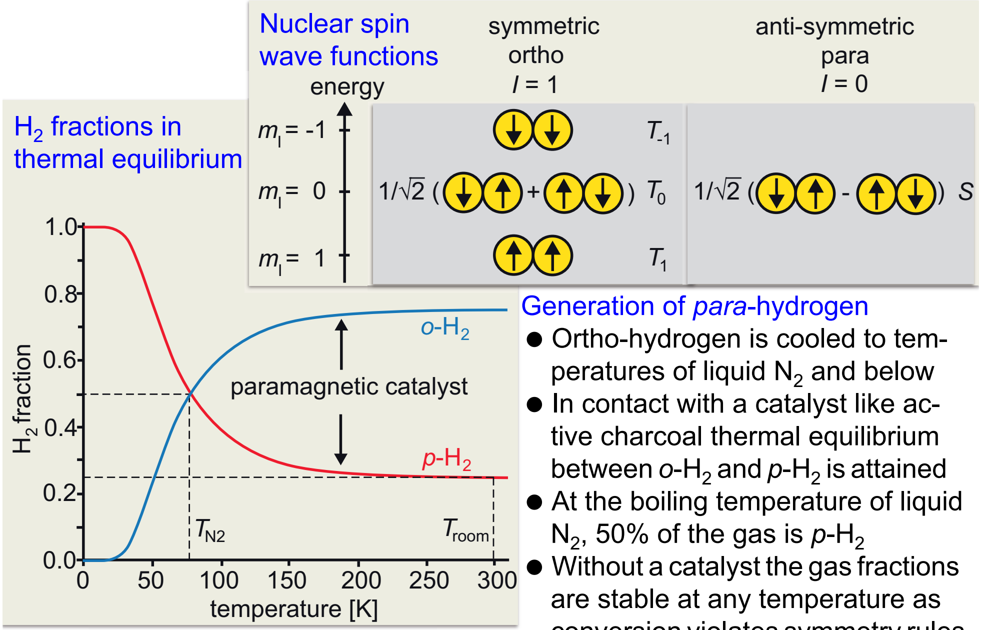
Hyperpolarization of noble gases

- Electron spins in alkali metal vapor are polarized by spin-state selective light excitation competing with nonselective relaxation
- Alkali-metal electron-spin polarization is transferred to noble gas nuclei by the electron-nuclear hyperfine interaction during gas-phase collisions between both atoms

Hyperpolarization of Noble Gases

- The nuclear spins of *noble gas atoms* like ^{129}Xe, ^{83}Kr and ^{3}He can be hyperpolarized by *Spin-Exchange Optical Pumping* (*SEOP*)
- They serve to image void spaces like the lung, and trapped in cages chemically linked to marker molecules report the host chemistry by their chemical shift
- Most commonly ^{129}*Xe* (I = 1/2) is hyperpolarized. It's natural abundance is 26%
- In 1949 Alfred Kastler (1966 Nobel Prize in Physics) showed that the electron spins in alkali metal vapors can be polarized with circularly polarized *laser* light
- Subsequently Happer showed that the electron-spin order can be transferred to the nuclear spins of ^{3}He and ^{126}Xe gas mixed with the alkali vapor
- Today large quantities of *noble gases* can be hyperpolarized up to nearly 100%
- By irradiating *rubidium vapor* resonantly with σ^+ polarized light, conservation of angular momentum selectively depletes the ground-state m_J = -1/2 population
- Rb collisions with gas atoms or molecules equalize both excited-state m_J = ±1/2 populations and repopulate both m_J = ±1/2 ground-states at similar rates
- Collisions with N_2 buffer gas quench stimulated Rb emissions
- Continual light exposure then builds up Rb electron-spin polarization
- The polarization is kept by a weak magnetic field in direction of the laser light
- It is transferred from Rb electrons to ^{129}Xe nuclei via the *hyperfine interaction* in collisions assisted by N_2 forming long-lived van-der-Waals complexes
- The exceptionally wide Xe *chemical shift* range of 8000 ppm helps to identify different chemical and physical environments

Generation of p-H_2



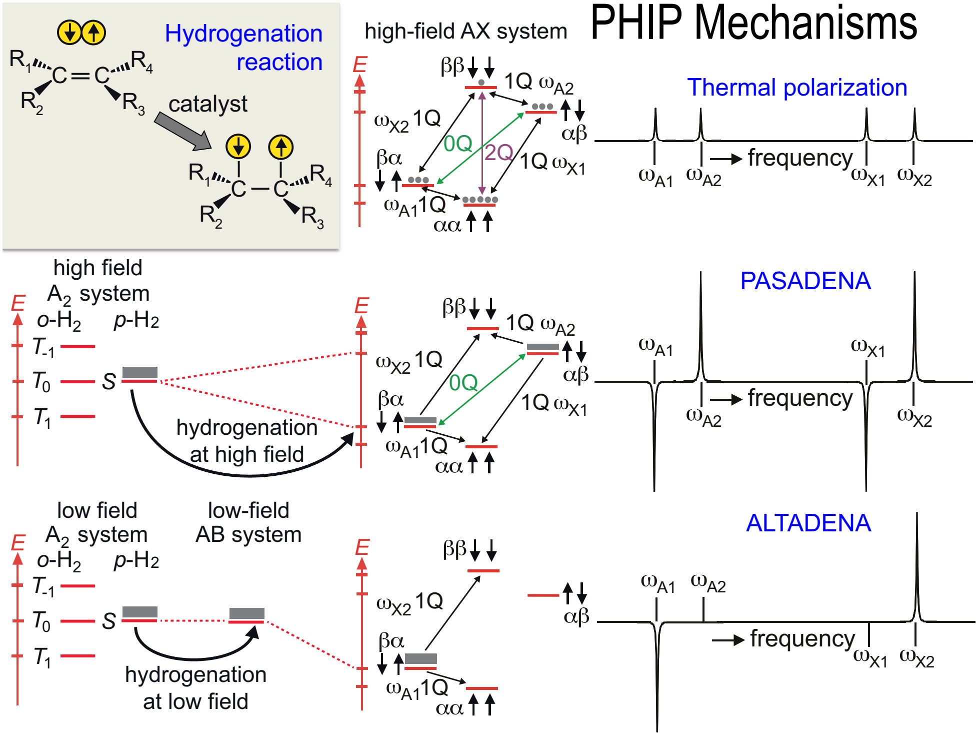
Generation of *para*-hydrogen

- Ortho-hydrogen is cooled to temperatures of liquid N_2 and below
- In contact with a catalyst like active charcoal thermal equilibrium between o-H_2 and p-H_2 is attained
- At the boiling temperature of liquid N_2, 50% of the gas is p-H_2
- Without a catalyst the gas fractions are stable at any temperature as conversion violates symmetry rules

Para-Hydrogen

- *Para-hydrogen* provides nuclear *spin order* that can be transferred to molecules by chemical reaction and by physical contact
- The chemical pathway is known as *PHIP* (*Para-Hydrogen Induced Polarization*) and the physical pathway as *SABRE* (*Signal Amplification By Reversible Exchange*)
- The two proton spins of the hydrogen atom can be paired in four ways and grouped according to symmetry under exchange of spins
- In *ortho*-hydrogen both spins are parallel with total nuclear spin I = 1, and the nuclear spin wave function is symmetric. In p-H_2 the nuclear magnetic moment is zero, so I = 0, and the wave function is anti-symmetric
- At room temperature the four states of hydrogen are about equally probable
- Due to symmetry of the H_2 wave function including nuclear spin states and molecular rotation, p-H_2 is more abundant in thermal equilibrium at low temperature
- Because transitions between different spin symmetries are forbidden, o- and p-H_2 fractions equilibrate only with assistance of a symmetry breaking *catalyst*
- *Para*-H_2 is generated from o-H_2 by passing it over a catalyst at low temperature
- Free from *catalyst* it can be stored at room temperature for long time
- Since the nuclear spin of p-H_2 is zero, it does not produce any NMR signal
- PHIP and SABRE break the symmetry of p-H_2 and generate NMR signal

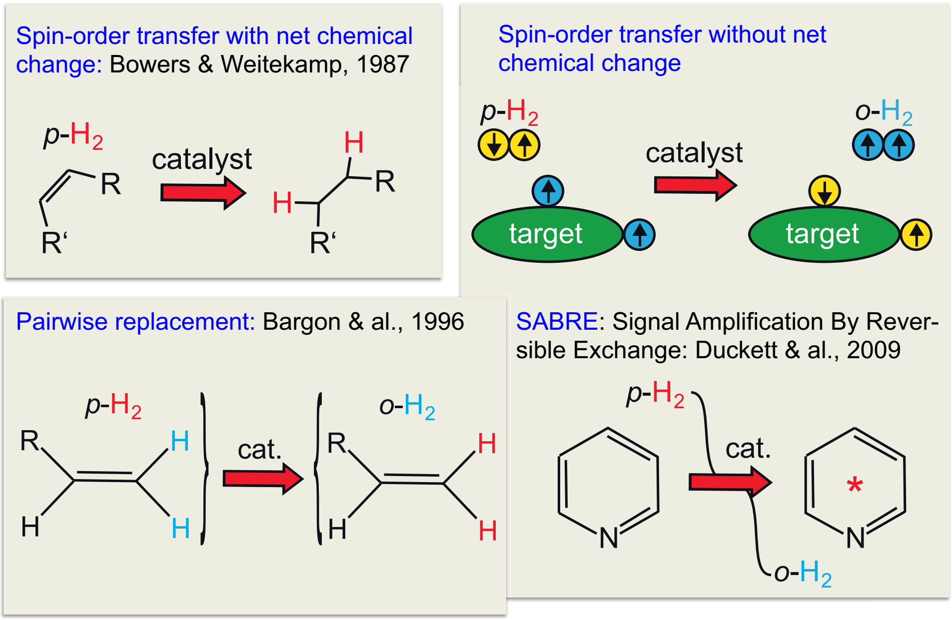
PHIP Mechanisms



Para-Hydrogen Induced Polarization: PHIP

- *PHIP* denotes a hydrogenation reaction with *p*-H_2 where the *spin order* is preserved in the product but the magnetic equivalence is lifted
- Depending on whether the reaction proceeds at low or high magnetic field, different energy levels are populated
- The reaction at high field in the weak coupling limit is known as *PASADENA* (Para-Hydrogen and Synthesis Allow Dramatic Nuclear Alignment)
- Here the A_2 spin system of the two equivalent proton spins from *p*-H_2 is transformed into an AX system, whereby only $m = 0$ states are populated but the magnetic degeneracy is lifted, resulting in two anti-phase doublets
- The reaction at low field in the strong coupling limit is known as *ALTADENA* (Adiabatic Longitudinal Transport After Dissociation Engenders Net Alignment)
- At low field the *J*-coupling is large compared to the chemical shift difference, so that the spin system is classified as an AB system
- A 45° excitation pulse generates a single line with maximum intensity
- Following transfer of the sample to high field, the AB system becomes an AX system, and only two of the four single-quantum transitions are observed
- PHIP is used to study hydrogenation reactions and to produce hyperpolarized gases like propane from propyne for MRI of voids
- PHIP and SABRE rely on chemical expertise for *hyperpolarization* in identifying *catalysts* suitable for the reaction and the complex formation, respectively, while DNP requires extensive equipment resources

Spin-Order Transfer from p-H_2



Spin-order transfer with net chemical change: Bowers & Weitekamp, 1987

Spin-order transfer without net chemical change

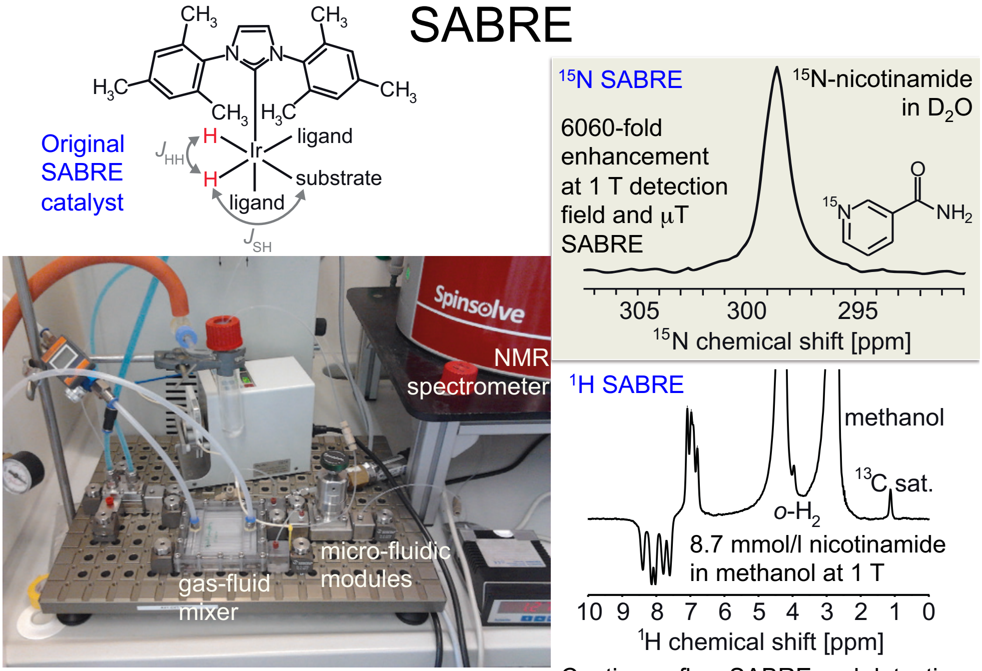
Pairwise replacement: Bargon & al., 1996

SABRE: Signal Amplification By Reversible Exchange: Duckett & al., 2009

More Ways of Tapping the p-H_2 Spin Order

- The hydrogenation PHIP involves a reaction with p-H_2 as one educt, producing a product in which the two hydrogen atoms appear at different chemical shifts so that their former magnetic equivalence in the H_2 molecule is lifted
- Other ways of transferring spin order from p-H_2 do not change the net chemistry of the molecule targeted for hyperpolarization
- One way is the pairwise *chemical replacement* of two hydrogens in the target molecule by the two singlet p-H_2 atoms
- Another way is the *physical transfer of spin order* from a p-H_2 molecule to a target molecule during the lifetime of a temporary complex between both molecules by means of *spin-spin coupling* between both molecules
- This non-hydrogenative polarization transfer is termed *SABRE*
- To extend the lifetime of collision complexes in solution, *polarization transfer catalysts* are employed, which are inefficient in the chemical sense of lowering the energy of the transition state for a chemical transformation
- The key to polarizing a large class of molecules by SABRE is competence in chemical catalysis
- The challenge to master is to maintain the *spin order* during transfer within the lifetime of the complex, in particular in protic solvents like life-sustaining water, where protons exchange rapidly

SABRE



From S. Lehmkuhl, M. Wiese, L. Schubert, M. Held, M. Küppers, M. Wessling, B. Blümich, **J. Magn. Reson. 291** (2018) 8, Fig. 2 with permission

Continous-flow SABRE and detection with a compact NMR spectrometer

Polarization Transfer by SABRE

- Typical *SABRE polarization transfer catalysts* are Ir^{III} complexes bearing bulky electron-donating ligands that contain *cis*-hydrides and three coordinated ligands
- The ligands are solvent molecules or substrate molecules like nitriles, diazirines, pyridine, and other molecules containing aromatic nitrogen atoms
- The equatorial *cis*-hydrides and ligands exchange rapidly between p-H_2 and o-H_2 as well as between polarized and unpolarized substrate molecules
- *Spin-order* from p-H_2 to unpolarized substrate is transferred coherently through the *J-coupling* network acting during the lifetime of the complex
- *Transfer paths* are enabled by matching transition energies of hydride and substrate nuclei
- For ^1H target nuclei optimum matching fields are around 6.5 mT; for heteronuclei like ^{15}N they are in the μT regime below the earth magnetic field of 50 μT
- A wide range of analytes can be hyperpolarized by relaying the p-H_2 spin order through exchangeable protons of hyperpolarized intermediates
- Even water can be hyperpolarized although it’s hydrogen solubility is low
- As with DNP, substrates for use as biomarkers need to be free of *catalyst*
- Flow *hyperpolarization* with continual replacement of o-H_2 by p-H_2 enables signal averaging and considerable degrees of experimental freedom for detecting trace concentrations from analytes