

pNMR
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Nuclear and electron spin relaxation in paramagnetic systems

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Outline

- What is special about paramagnetic systems?
- Role and mechanisms of electron spin relaxation
- Within and beyond the perturbation regime
- Relaxation mechanisms and theoretical models in pNMR
- Examples/applications

Paramagnetic materials

- Paramagnetic materials have positive magnetic susceptibility, associated with unpaired electrons
- Paramagnetic solutions contain free radicals or transition metal ions/complexes. Oxygen gas (triplet ground state) is also paramagnetic
- Unpaired electron has large magnetic moment, about 650 times that of proton
- This large magnetic moment affects strongly NMR properties, not least relaxation
- Electron spin is strongly coupled to lattice

Electron spin (S) interactions

- Unpaired electrons are usually studied by *electron spin resonance* (ESR, EPR, EMR)
- Spin Hamiltonian for electrons similar but not identical to that of nuclei:

$$\hat{H}_S = \underbrace{-(\mu_B / \hbar) \hat{\mathbf{S}} \cdot \mathbf{g} \cdot \mathbf{B}_0}_{\text{Zeeman}} + \underbrace{\sum_I \hat{\mathbf{S}} \cdot \mathbf{A}_I \cdot \hat{\mathbf{I}}}_{\text{hyperfine}} + \underbrace{\hat{\mathbf{S}} \cdot \mathbf{D} \cdot \hat{\mathbf{S}}}_{\text{ZFS}} \quad (15.1)$$

- *g*-tensor similar to shielding in NMR
- Hyperfine term similar to spin-spin coupling
- Zero-field splitting (ZFS) similar to quadrupolar interaction

Hyperfine interaction

- Electron spin-nuclear spin interaction
- Can be expressed (in non-relativistic limit) as sum of Fermi contact (FC) and dipolar term (DD)
- DD interaction analogous to dipolar interaction between nuclear spin (but stronger, large γ_S)
- FC interaction consequence of the fact that electron spin can have a finite probability to be at the site of nucleus
- FC term proportional to electron spin density at nucleus

$$\mathbf{A}_I = \mathbf{A}_{DD} + \mathbf{A}_{FC} \quad (15.2)$$

traceless, symmetric,
rank-2 tensor

scalar

ZFS interaction

- Occurs only for $S \geq 1$ (triplet states or higher)
- Traceless symmetric ZFS tensor; in molecule-fixed PAS, two components:

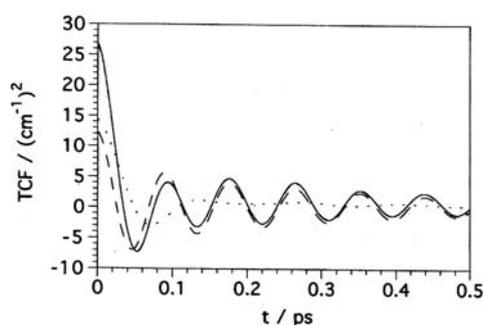
$$D = D_{zz} - \frac{1}{2}(D_{xx} + D_{yy}) \quad \text{ZFS parameter}$$

$$E = \frac{1}{2}(D_{xx} - D_{yy}) \quad \text{ZFS rhombicity} \quad (15.3)$$

- Two physical mechanisms: electron spin-electron spin dipolar interaction, second-order effect of the spin-orbit coupling. The latter dominant in transition metal systems
- ZFS can be very strong (several cm^{-1}), can be stronger than electron Zeeman (about 1 cm^{-1} @ 1 Tesla)
- ZFS time dependent through molecular tumbling

Quantum chemistry & spin relaxation

- Quantum chemistry tools can be used to compute the relevant interaction strengths
- Combining QC and MD can in principle provide also the relevant time correlation functions/ spectral densities



Example: TCF for ZFS in aqueous Ni(II).
From Odellius et al., 1995

$S=1/2$ systems

- Important examples: Cu(II), nitroxide radicals
- Relaxation theory in principle similar to NMR
- Relaxation mechanisms: A-anisotropy, g-anisotropy, spin-rotation
- Interactions much stronger than in NMR, perturbation theory (Redfield theory) not always valid
- Outside of Redfield limit: slow-motion regime
- ESR lineshapes (1D & 2D) for nitroxides studied by Freed & coworkers

S ≥ 1 systems

- Important systems: transition metal & lanthanide ions and complexes
- ESR relaxation often dominated by ZFS
- If the metal ion in low-symmetry complex (lower than O_h or T_d), *static* ZFS, can be modulated by rotation
- Hydrated metal ions: *transient* ZFS modulated by collisions (distortions of the solvation shell)

Bloembergen-Morgan theory

- A Redfield-limit theory, valid for high magnetic field, was formulated in early sixties by Bloembergen & Morgan:

$$\frac{1}{T_{1e}} = \frac{\Delta_t^2}{5} \left(\frac{\tau_v}{1 + \tau_v^2 \omega_S^2} + \frac{4\tau_v}{1 + 4\tau_v^2 \omega_S^2} \right) \quad (15.4)$$

$$\frac{1}{T_{2e}} = \frac{\Delta_t^2}{10} \left(3\tau_v + \frac{5\tau_v}{1 + \tau_v^2 \omega_S^2} + \frac{2\tau_v}{1 + 4\tau_v^2 \omega_S^2} \right)$$

- τ_v : distortional correlation time (pseudorotation);
- Δ_t : magnitude of transient ZFS;

$$\Delta_t^2 = D_{xx}^2 + D_{yy}^2 + D_{zz}^2 = \frac{2}{3} D^2 + 2E^2 \quad (15.5)$$

Generalized BM

- For $S \geq 3/2$, the electron spin relaxation is expected to be multiexponential – can be handled within Redfield limit
- Systems with static and transient ZFS – can be handled within Redfield limit, $\Delta_i^2 \tau_v^2 \ll 1$, $\Delta_s^2 \tau_R^2 \ll 1$

Slow-motion regime for $S \geq 1$

- Consider a system with static ZFS, Δ_s , modulated by tumbling
- Redfield theory requires $\Delta_s^2 \tau_R^2 \ll 1$, which may be difficult to fulfill for systems other than d^5 ($S=5/2$) or f^7 ($S=7/2$)
- If not: slow-motion regime. Include the strongly coupled degrees of freedom (e.g. rotation) in the more carefully studied subsystem, along with spins.
- One way to do it: replace the Redfield equation with the stochastic Liouville equation, SLE

Paramagnetic relaxation enhancement (PRE)

- Macroscopic/microscopic
- Complications by exchange
- P_M : mole fraction bound
- τ_M : exchange lifetime
- Subscript M : in-complex properties
- Subscript P : measured properties
- T_1 most common
- Fast exchange for T_1 : $\tau_M \ll T_{1M}$

$$T_{1P}^{-1} = \frac{P_M}{\tau_M + T_{1M}}$$

$$T_{2P}^{-1} = \frac{P_M}{\tau_M} \left[\frac{T_{2M}^{-2} + (T_{2M}\tau_M)^{-1} + \Delta\omega_M^2}{(T_{2M}^{-1} + \tau_M^{-1})^2 + \Delta\omega_M^2} \right]$$

$$\Delta\omega_P = \frac{P_M \Delta\omega_M}{(\tau_M/T_{2M} + 1)^2 + \tau_M^2 \Delta\omega_M^2}$$

(15.8)

PRE 2.

- Talking about the PRE, one often means the enhancement of spin-lattice relaxation rate
- PRE = inner-sphere + outer-sphere
- PRE usually linear in concentration of paramagnetic agent
- PRE @ 1 mM paramagnetic agent: relaxivity
- PRE (relaxivity) as a function of magnetic field: paramagnetic NMRD, quite common & good test for theories

Modified Solomon-Bloembergen

- Solomon: dipolar relaxation
- Bloembergen: scalar relaxation
- Modified Solomon-Bloembergen (MSB) eqs.

$$\begin{aligned}
 T_{1M}^{-1} &= (T_{1M}^{SC})^{-1} + (T_{1M}^{DD})^{-1} = \frac{2}{3} A_{SC}^2 S(S+1) \frac{\tau_{e2}}{1 + (\omega_S - \omega_I)^2 \tau_{e2}^2} + \\
 &+ \frac{2}{15} S(S+1) b_{IS}^2 \left[\frac{\tau_{c2}}{1 + (\omega_S - \omega_I)^2 \tau_{c2}^2} + \frac{3\tau_{c1}}{1 + \omega_I^2 \tau_{c1}^2} + \frac{6\tau_{e2}}{1 + (\omega_S + \omega_I)^2 \tau_{c2}^2} \right] \approx \\
 &\approx \frac{2}{3} A_{SC}^2 S(S+1) \frac{\tau_{e2}}{1 + (\omega_S - \omega_I)^2 \tau_{e2}^2} + \frac{2}{15} S(S+1) b_{IS}^2 \left[\frac{7\tau_{c2}}{1 + \omega_S^2 \tau_{c2}^2} + \frac{3\tau_{c1}}{1 + \omega_I^2 \tau_{c1}^2} \right] \\
 &\qquad\qquad\qquad (15.9)
 \end{aligned}$$

Correlation times

- Dipolar part usually most important
- Compared to Solomon, correlation times more complicated:

$$\tau_{cj}^{-1} = \tau_R^{-1} + \tau_M^{-1} + T_{je}^{-1}; \quad j = 1, 2$$

$$\tau_{ej}^{-1} = \tau_M^{-1} + T_{je}^{-1}; \quad j = 1, 2$$

- Reorientation, electron spin relaxation & exchange contribute to the modulation of electron spin-nuclear spin DD interaction
- Combine modif. Solomon-Bloembergen eqs with Bloembergen-Morgan theory for electron relaxation: Solomon-Bloembergen-Morgan (SBM) theory

Solomon-type NMRD

- Two dispersions predicted: $\omega_S \tau_{c2} \approx 1$, $\omega_I \tau_{c1} \approx 1$

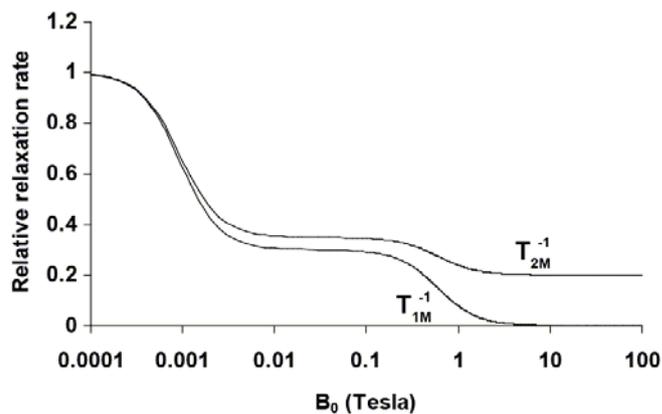


Fig. 15.1

Beyond SBM

- Approximations in SBM
 - Point-dipole: under debate (QC can help!)
 - Isotropic reorientation: probably not critical
 - Decomposition: electron relaxation uncorrelated with rotation. Problematic.
 - Single exponential electron relaxation: can be fixed
 - Redfield for electron relaxation: problematic

Swedish slow-motion theory

- SLE-based, calculations in frequency domain ($J(\omega)$)
- Nuclear spin interacts with a "composite lattice", containing electron spin. The lattice described in terms of electron Zeeman, transient & static ZFS, reorientation & distortion (pseudorotation)
- Calculation of PRE involves setting up and inverting a very large matrix representing the lattice Liouvillean in a complicated basis set. Computationally heavy
- Very general, can be used as benchmark for simpler models
- Equivalent to the Grenoble model (formulated in time domain, $G(t)$)

Slowly-rotating systems

- Consider a complex that rotates fast enough to produce a Lorentzian line ("motional narrowing"), but slowly enough for the rotational motion to be completely inefficient as a source of electron spin relaxation
- Assume that, for every orientation of the complex in the lab frame, electron spin energy levels are determined by static ZFS & Zeeman
- Assume that the electron spin relaxation originates from transient ZFS/distortional correlation time, within Redfield
- Calculate the PRE at every orientation & average over all orientations
- Approach known as "modified Florence method"

Compare Swedish & Italian

- Very good agreement where "modified Florence" valid

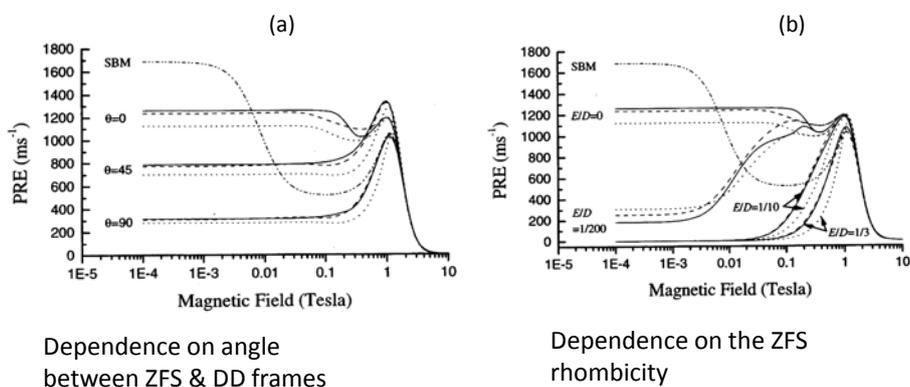


Fig. 15.2

Magnetic susceptibility

- The unequal population (Boltzmann) of electron spin Zeeman levels is the origin of non-vanishing average magnetic moment in paramagnetic compounds

$$\langle S_z \rangle = \frac{\sum \langle S, M_S | S_z | S, M_S \rangle \exp(-g_e \mu_B B_0 M_S / kT)}{\sum \exp(-g_e \mu_B B_0 M_S / kT)} = -\frac{g_e \mu_B S(S+1) B_0}{3kT}$$

$$\hbar \gamma_S = g_e \mu_B$$

Bertini, Luchinat, Parigi

$$\langle \boldsymbol{\mu} \rangle = -\mu_B g_e \langle \hat{S}_z \rangle = \frac{\boldsymbol{\chi} \cdot \mathbf{B}_0}{\mu_0}$$

$\boldsymbol{\chi}$: magnetic susceptibility (tensor), can be anisotropic

Susceptibility anisotropy

- If susceptibility is anisotropic, the magnitude of the electron spin magnetic moment along the field direction orientation-dependent
- The local dipolar field around the average magnetic moment is then *not averaged to zero* by rotation
- The non-zero averaged dipolar field leads to extra shifts of nuclear spin resonances, which depend on position of the nucleus in molecular frame – *pseudocontact shifts*

Curie-spin relaxation

- Also called "magnetic susceptibility relaxation"
- For large complexes (e.g. metalloproteins) with very rapid electron spin relaxation (e.g. lanthanides other than Gd(III)), at high magnetic field:
 - ✓ A sizable equilibrium spin magnetization, "Curie-spin", (isotropic susceptibility):

$$S_C = \langle \hat{S}_z \rangle = g_e \mu_B S(S+1) B_0 / 3k_B T \quad (15.12)$$
 - ✓ The Curie-spin interacts, through DD, with nuclear spins
 - ✓ The interaction is *not* modulated by electron spin relaxation, only by rotation (or exchange)

$$\tau_D^{-1} = \tau_R^{-1} + \tau_M^{-1} \ll \tau_{cl}$$

Curie-spin 2.

- Curie-spin mechanism is more efficient for T_2
- Neglecting the scalar mechanism and the terms containing ω_S :

$$T_{2M}^{-1} = \frac{1}{5} \left(\frac{\mu_0}{4\pi} \right)^2 \gamma_I^2 g_e^2 \mu_B^2 r_{IS}^{-6} \cdot \left\{ S_C^2 \left(4\tau_D + \frac{3\tau_D}{1 + \omega_I^2 \tau_D^2} \right) + \left[\frac{1}{3} S(S+1) - S_C^2 \right] \left(4\tau_{cl} + \frac{3\tau_{cl}}{1 + \omega_I^2 \tau_{cl}^2} \right) \right\}$$

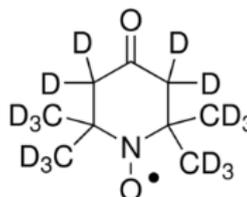
(15.13b)

Outer sphere PRE

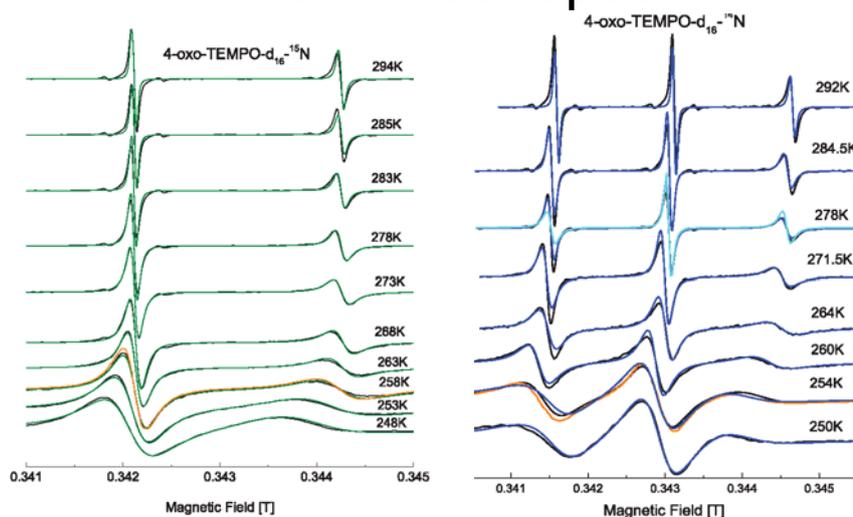
- Nuclear spins can be relaxed by dipolar interaction with electron spin in other molecules
- Recently incorporated into the Swedish slow-motion theory (JCP 130, 174104 (2009)), computationally expensive
- All complications of electron spin relaxation relevant
- In addition: translational diffusion
- Outer sphere PRE important for free radicals in solution, a simpler (Redfield) theory may be useful unless very slow rotation

Nuclear and electronic relaxation in free radicals: an example

- System: propylene glycol + 4-oxo-TEMPO-d₁₆
- Two isotope species: ¹⁴N (*I*=1) & ¹⁵N (*I*=1/2)
- ESR lineshapes and NMRD (10 kHz-20 MHz)
- ESR interpreted using SLE & Redfield
- NMRD interpreted with a recent theory (Kruk *et al.* JCP 2013), Redfield limit



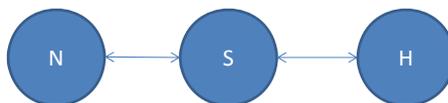
ESR lineshapes



Kruk et al, JCP 2013

Electronic and nuclear spin relaxation

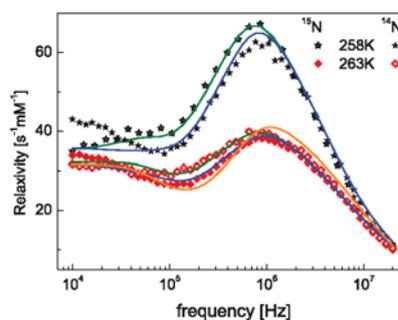
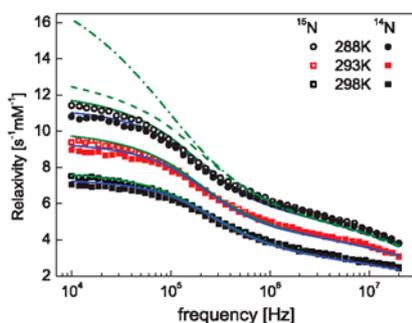
- ESR lines split by isotropic hyperfine interaction
- Electron spin relaxation caused by anisotropic hyperfine (dipolar) with *nitrogen* spin & Δg , modulated by rotation
- Solvent proton relaxation caused by outer-sphere dipolar interaction with electron spin
- Modulation by translational diffusion (dominates at high temp) and electron relaxation (important @ lower temp)



^1H PRE for the solvent

High temp, translational diffusion faster than electron relaxation

Low temp, electron relax \uparrow , diffusion \downarrow



Theoretical models (within Redfield limit) give a consistent description of ESR & NMRD

Application to MRI contrast agents

- MRI contrast agents (CA) function often by enhancing aqueous proton spin-lattice relaxation in certain tissue
- Results of accumulating the CA in that tissue
- CAs often based on Gd(III) chelates, sometimes attached to macromolecules
- CAs should be stable, non-toxic and efficient; efficiency = high relaxivity @ given field
- Good to understand the NMRD profiles

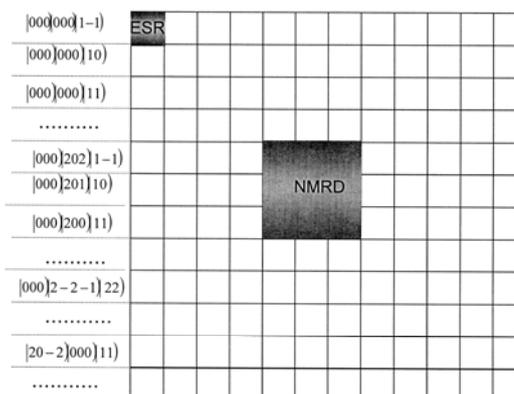
Earlier NMRD & ESR

- Earlier joint treatment of NMRD & ESR successful for small Gd(III) complexes (e.g. $[\text{Gd}(\text{DTPA})\text{H}_2\text{O}]^{2-}$, $[\text{Gd}(\text{DOTA})\text{H}_2\text{O}]^-$) with ESR relaxation within Redfield (Benmelouka, Borel, Holm *et al.*)
- Test case of interest for us: go to larger ligands, make τ_R longer, get outside Redfield

Joint analysis of NMRD & ESR using SLE

- The big matrix

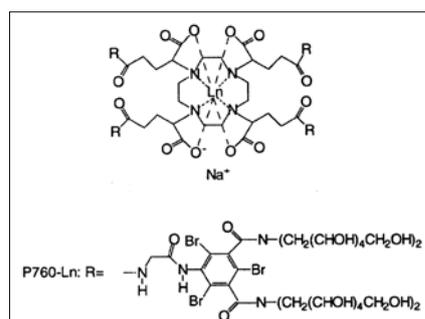
$$\mathbf{M} = i(\mathbf{L} + \omega \mathbf{1})$$
- In principle common for NMRD & ESR
- Evaluated at NMR or ESR frequencies
- Different elements in the inverse



Kruk *et al.*, JCP 2011

Model systems

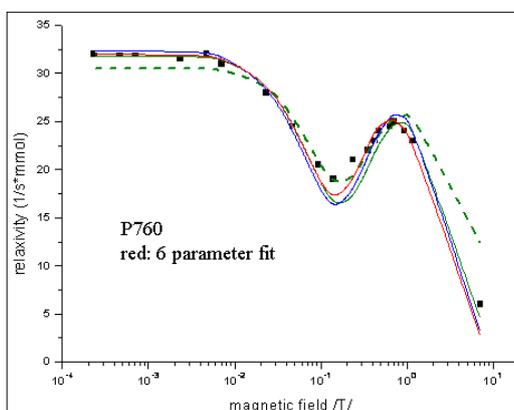
- Two complexes: P760, P792, about 6 kDa
- NMRD measured earlier by Vander Elst *et al.*, also independent estimates of exchange lifetime (τ_M) & τ_R



Vander Elst *et al.*,
Eur. J. Inorg. Chem. 2003

NMRD fitting strategy

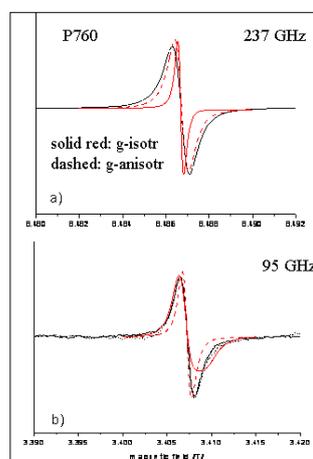
- First attempt: fit NMRD using fixed of τ_M & τ_R
- Final: fit all 6 parameters: (electron-nucleus distance, static & transient ZFS, τ_M , τ_R , τ_D)



Kruk *et al.*, JCP 2011
exp data from Vander Elst

NMRD & ESR: P760

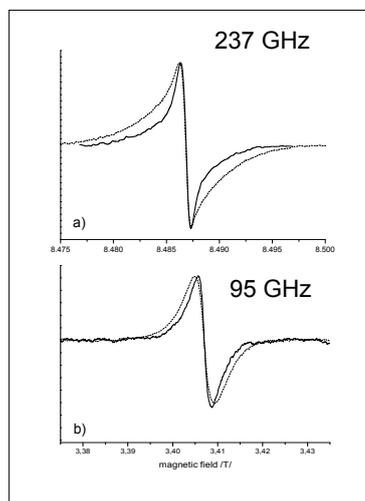
- Use parameters from fitting NMRD & simulate ESR at high fields
- Solid red lines: ESR relaxation only from ZFS
- Dashed red lines: g-anisotropy as additional relaxation mechanism, $\Delta g=0.0018$
- Line-broadening @ 237 GHz, narrowing @ 95 GHz



Kruk *et al.*, JCP 2011

Is g-anisotropy reasonable & necessary?

- The estimates of g-tensor anisotropy appear reasonable (QC could help!)
- However, other explanations may be possible, e.g. concentration effects
- High-field ESR for P792 at two concentrations: 0.285 mM (solid line) & 1 mM (dashed)



NMRD/ESR Gd(III) conclusions

- Predictions of NMRD & ESR lineshapes for Gd(III) using equivalent theoretical tools indicate that the pseudorotation model for ZFS fluctuations captures essential features of electron spin dynamics
- g-tensor anisotropy may play a role at high-field ESR, more work required

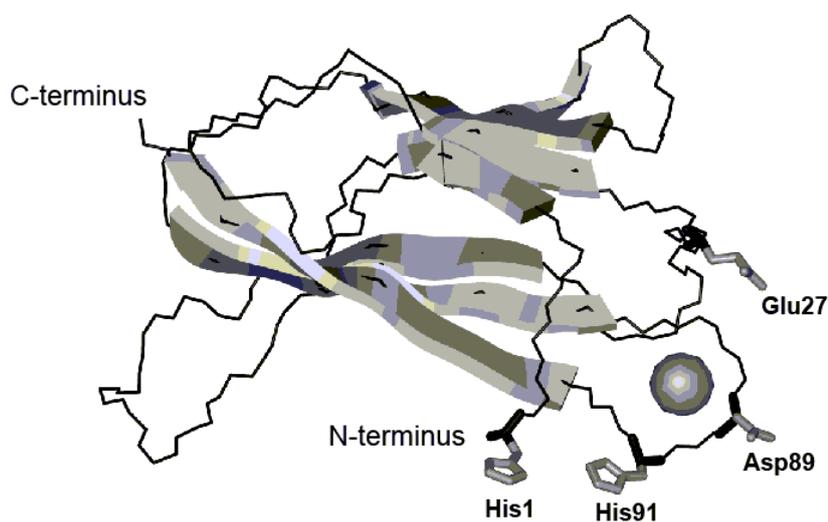
Application to paramagnetic proteins

- Paramagnetic proteins: one measures on protein surrounding the metal center, usually without exchange
- More demanding, very severe broadening of NMR signals in the vicinity of the metal
- T_2^{-1} proportional to γ_I^2 , protons much more broadened than ^{13}C or ^{15}N , "protonless NMR"

Copper-trafficking protein

- ...from *Pseudomonas Syringae*, binds Cu(II)
- Apo-protein and Cu(I) (diamagnetic) analogue, structures known
- Study of electron spin relaxation through NMRD of (exchanging) water protons
- No proton signals closer than about 11 Å from Cu(II)
- ^{13}C PRE, PCSs, along with ^1H NOEs
- Paramagnetic constraints necessary to locate the copper

Copper-trafficking protein 2.



Arnesano *et al.*, JACS 2003

Summary

- Paramagnetic systems, interactions of electron spin, spin Hamiltonian
- Hyperfine interaction, ZFS interaction
- Electron spin relaxation in $S = 1/2$ & $S \geq 1$. Bloembergen-Morgan theory & generalizations
- Slow motion regime, SLE
- PRE, macroscopic/ microscopic, MSB & SBM
- Beyond SBM: slow-motion theory & other methods
- Magnetic susceptibility, pseudocontact shifts, Curie-spin relaxation
- Outer sphere relaxation
- Applications: Viscous liquids, MRI contrast agents & paramagnetic proteins

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- JKs research on paramagnetic relaxation in the last decade:
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 - ✓ Funding: Swedish Research Council