



Paramagnetic NMR

- I. Overview of Paramagnetic NMR: Origins
- II. Components of Paramagnetic Shifts
 - Scalar / Contact
 - Dipolar / Pseudocontact
- III. Applications
 - A. Electronic Structure & Spin Distribution
 - B. Stereochem and Structure
 - C. Equilibrium Dynamics & Solvation
 - D. Lanthanide Shift Reagents
 - E. Bioinorganic Applications
 - F. Contrast agents for MRI



Paramagnetic ^1H NMR

Was initially ignored because people thought the signals would be so broad as to be useless.

“They” were wrong, sometimes.

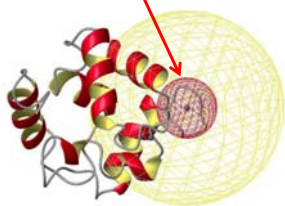
Do see Broader lines. But the range of δ increases hugely. Broadening from fast Spin-Lattice Relaxation (T_{1N}). If lines are too broad, will often give useful EPR. If e- relaxation times are fast enough, T_{1N} is unaffected. Many paramag. cmpds have paramag ^1H NMR & EPR.



Paramagnetic ^1H NMR

The presence of a paramagnetic metal ion causes line broadening of all NMR signals from nuclei close to the metal ion: too close, too broad to be seen!

"Blind Sphere"



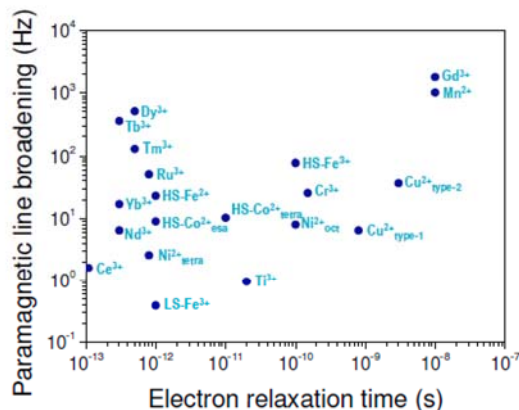
The radius of the "blind" sphere depends on the metal ion.

The size of the blind sphere changes with the nuclear type, being smaller for ^{13}C than for ^1H .

The effect decreases rapidly with increasing distances from metal ion, so that it is negligible outside of an outer "paramagnetic effects" sphere.

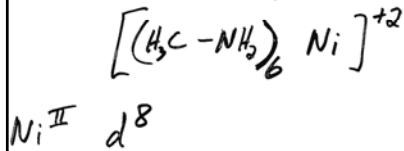
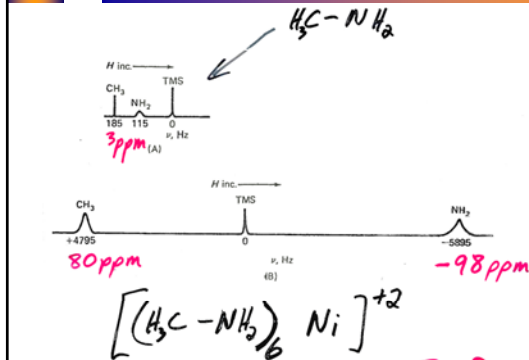


Paramagnetic ^1H NMR



^1H paramagnetic line broadening in the presence of various metal ions shown as a function of the typical values of the electron relaxation time, for a molecule with a reorientation time of 10 ns at 298 K and 900 MHz of proton Larmor frequency, and a metal-nucleus distance of 10 Å

Paramagnetic ^1H NMR



3 Questions

- 1.) Why do we see any NMR at all?
- 2.) Why are shifts so huge?
- 3.) Why CH_3 downfield and NH_2 upfield?

Paramagnetic ^1H NMR: Relaxation Time

If relaxation time of nuclear spins is too fast, No change in observed magnetization is possible.



With unpaired e^- spin, relaxation of e^- spin provides another mechanism for Nuclear spins

$$T_1(\text{nucleus}) \rightarrow 0$$

NMR broadens into baseline

Paramagnetic NMR occurs only if $T_1(\text{electron})$ very fast, so that e^- spin is averaged over NMR lifetime.



When Do We See Paramagnetic NMR?

T_{1e} is very fast compared to NMR
if Ground Spin State is
Multiply Degenerate.



When Do We See Paramagnetic NMR?

i.e. when is e^- spin lifetime very short?

- 1) When Ground State is multiply Degenerate
(T ground state)
- 2) When Zero field Splitting occurs
and permits rapid relaxation

When Do We See Paramagnetic NMR?

Octahedral

d^1
 d^2
 L.S. d^4
 L.S. d^5
 H.S. d^6
 H.S. d^7 (d^8 w ZFS)
 6 Coord Octahedral:
 d^2 V^{III} W^{III}
 d^3 Mo^{III} Re^{IV}
 d^4 L.S. Cr^{II}, L.S. d^5 Mn^{III}, Re^{III}, Os^{IV}
 d^5 L.S. Fe^{III}, Ru^{III}, Os^{III}
 d^6 H.S. Fe^{II}
 d^7 H.S. Co^{II}
 d^8 Co(I), Ni(II)

Tetrahedral

d^1
 other T ground states
 Co^I, Ni^{II}
 Cr^I, Fe^{III}

Paramagnetic NMR Chemical Shifts

e^- spin is small, but its proximity to nucleus is large.

∴ Big Local magnetic field due to unpaired spin density.

∴ Big Shielding/Desielding of nuclei

∴ Big Shifts ($\rightarrow 100$ ppm) possible



Paramagnetic NMR Hamiltonian

$$\hat{H}^e = -g \beta \vec{H} \cdot \hat{S} \quad \text{electron}$$

$$-g_N \beta_N \vec{H}_{\text{eff}} \cdot \hat{I} \quad \text{nuclear}$$

$$+ A \hat{I} \cdot \hat{S} \quad \text{e}^- \text{-nuclear coupling}$$

These determine the energies of the different nuclear (and electronic) spin states (i.e., the Zeeman splitting for the nuclear spin states).

i.e., The Paramagnetic Chemical Shift.



Components of Paramagnetic Shifts

The components of Paramagnetic Shifts are separated into

Scalar or Contact Shift

vs.

Dipolar or Pseudo-Contact Shift

This division is really an artifact of viewing molecules through LCAO-MO:

Both Shifts are due to the same coupling phenomenon of electron mag moment coupling to nuclear mag moment.



Components of Paramagnetic Shifts

Contact Shift – Consider the Electron and Nucleus as simply a coupled doublet,

But with a $J \sim 1 \times 10^6$ Hz !

Not an equal coupling, so intensities are not equal, and the weighted mean position is not at midpoint. Under fast relaxation, doublet collapses into a singlet far away from the original nuclear chemical shift.

Dipolar Shift – through space interaction between electron & nucleus, also called pseudo-contact shift, often small in magnitude.



Scalar or Contact Coupling

Due to direct overlap of unpaired e- spin density **at the nucleus**: “Fermi” contact.

If we assume isotropic unpaired e- density:

$$\hat{H}_{\text{scalar}} = A \vec{I} \cdot \vec{S} \delta(r)$$

isotropic hyperfine coupling constant \uparrow A
 Nuclear Spin moment \uparrow \vec{I}
 electron spin moment \uparrow \vec{S}
 $\delta(r)$

$$\delta(r) = 0 \quad r \neq 0$$

$$\delta(r) = 1 \quad r = 0$$



Scalar or Contact Coupling

For an $S = \frac{1}{2}$ system,

$$A = \left(-\frac{8\pi}{3} g_e \beta\right) (g_N \beta_N) |\psi_{el}(0)|^2 \quad (g = \mu \sqrt{S(S+1)})$$

$$\hat{H}_{\text{scalar}} = A \vec{I} \cdot \vec{S} \delta(r) \rightarrow \text{built into } \psi(0)$$

$$= A \vec{I} \cdot \frac{g_{av} \beta \vec{H} S(S+1)}{3kT} \leftarrow \text{avg. spin polarization}$$

Define an H_{eff} that converts the energy splitting into an effective mag field change:

$$\vec{H}_{\text{eff}} = A g_{av} \frac{\beta S(S+1)}{3kT} \vec{H}$$

= Difference of Diamagnetic
and Scalar Paramagnetic Fields
at Nucleus



Scalar or Contact Coupling

∴ Scalar Contribution to isotropic shift is

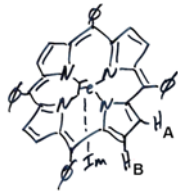
$$\frac{H_{\text{eff}}}{H} = \frac{\Delta \nu}{\nu} = \frac{A g_{av} \beta S(S+1)}{g_N \beta_N 3kT}$$

Scalar Term is "Through bonds" only. Depends on $|\psi(0)|^2 \neq 0$

Note A is Temp Independent but $\Delta \nu$ is not.

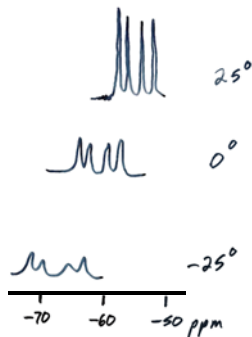


Temperature Dependence of Scalar Coupling



5 coordinate
 $S = 2$

AB System



For comparison,
 H_2TPP has $\delta = 9$ ppm



Through-Bond Propagation of Fermi Contact (i.e., Scalar Coupling) via Spin-Transfer

3 classes:

$L \rightarrow M$ σ spin transfer Spin Polarization \equiv Electron Correlation

$L \rightarrow M$ π spin transfer



$M \rightarrow L$ π back spin transfer

Indirect intra-molecular-orbital spin Polarization



ψ_b not pure d orbital $\therefore L \rightarrow M$ spin transfer

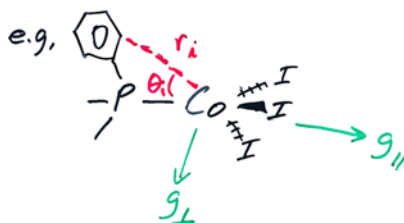


Dipolar or Pseudo-Contact Coupling

If unpaired e- spin density is NOT isotropic, then dipole-dipole interactions "through space" can occur between the e- spin density and the nucleus.

For an axial system, ICBST:

$$\Delta H_{pc} / H = \Delta v_{pc} / v \doteq \frac{B^2 s'(s+1)}{9kT} \left(\frac{1-3\cos^2\theta_i}{r_i^3} \right) \cdot (g_{||}^2 - g_{\perp}^2)$$



Two Contributors to Paramagnetic Shifts

1. Fermi Contact (Scalar)

- Direct Coupling of nuclear & electron spins
- Due to unpaired e⁻ spin density at nucleus

$$-\frac{H_{eff}}{H} = \frac{\Delta v_{fc}}{v} = \frac{A g_N B s(s+1)}{g_N \beta_N 3kT}$$

- "Through Bonds"

2. Pseudocontact, Dipolar Coupling

- Dipole-Dipole Interaction
- Due to Anisotropic Unpaired e⁻ spin Density
- "Through Space"

$$-\frac{\Delta v_{pc}}{\Delta v} \doteq \frac{B^2 s'(s+1)}{9kT} \left(\frac{1-3\cos^2\theta_i}{r_i^3} \right) (g_{||}^2 - g_{\perp}^2)$$

for axial system with localized Paramag.



Where is Paramagnetic NMR Useful?

- Inorganic – any metal that has unpaired e- will cause chemical shift range to be extremely large.
- Proteins – many proteins contain paramagnetic ions (often Fe^{+3}) in their active site. But one can also substitute paramagnetics (e.g., Co^{+2} for Zn^{+2}) into the protein to spread out the chemical shifts near the active site.
- Applications
 - A. Electronic Structure & Spin Distribution
 - B. Stereochem and Structure
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Size of Paramagnetic Chemical Shifts

Metallocene	Paramag Shifts	
	average ^{13}C	average ^1H
$(\text{Cp})_2\text{Ni}$	+1436 ppm	-263
$(\text{Cp})_2\text{Co}$	+577	-56
$(\text{Cp})_2\text{Cr}$	-325	+324
$(\text{Cp})_2\text{V}$	-588	+315

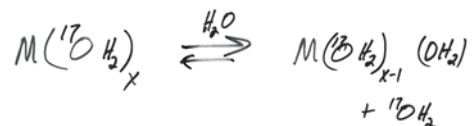
relative to diamag $\text{Fe}(\text{Cp})_2$

some as high as ~ 3000 ppm for ^{13}C
 ~ 450 ppm for ^1H

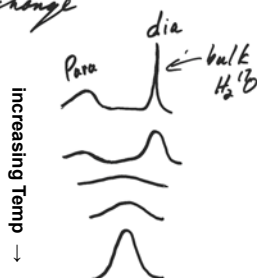


Classic Early Paramagnetic NMR:

Bob Connick, 1960's
Water exchange rates coordinated to metal ions



Line broadening of ^{17}O NMR gives
rates of H_2O exchange



Chemical Shift Range for Paramagnetic NMR

Particularly useful when studying Fe Porphyrins
 $\text{Fe}^{+3} = d^5$, $\text{Fe}^{+2} = d^6$ (may be diamagnetic)

Ex.: Inorg. Chem. 1992, 31, 2248-2255

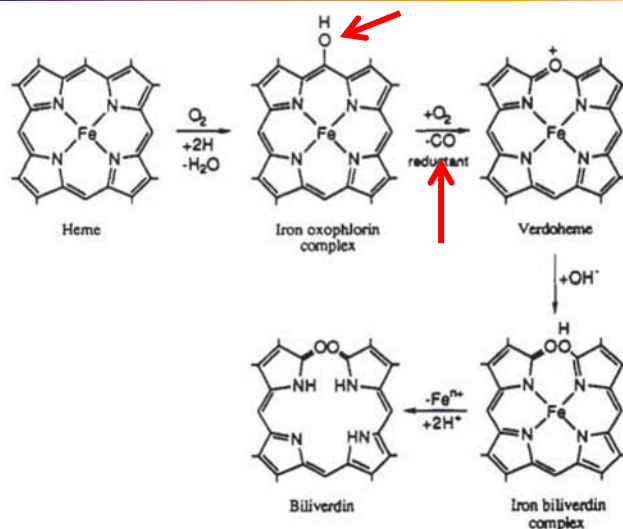
Study undertaken to connect oxidized heme, called an oxophlorin to verdoheme, a known heme breakdown product.

Colors of bruise are due to breakdown of heme to bilirubin (yellow).

Endogenous production of CO!



Heme Degradation



Heme Degradation: Oxophlorin

2250 *Inorganic Chemistry*, Vol. 31, No. 11, 1992

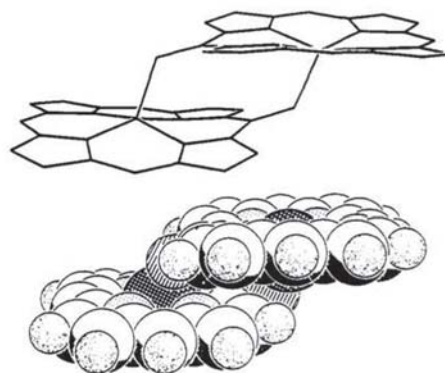
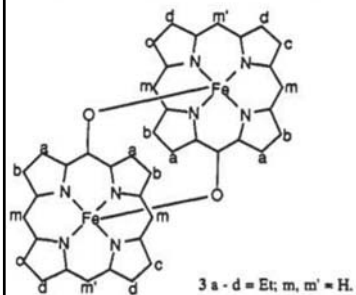
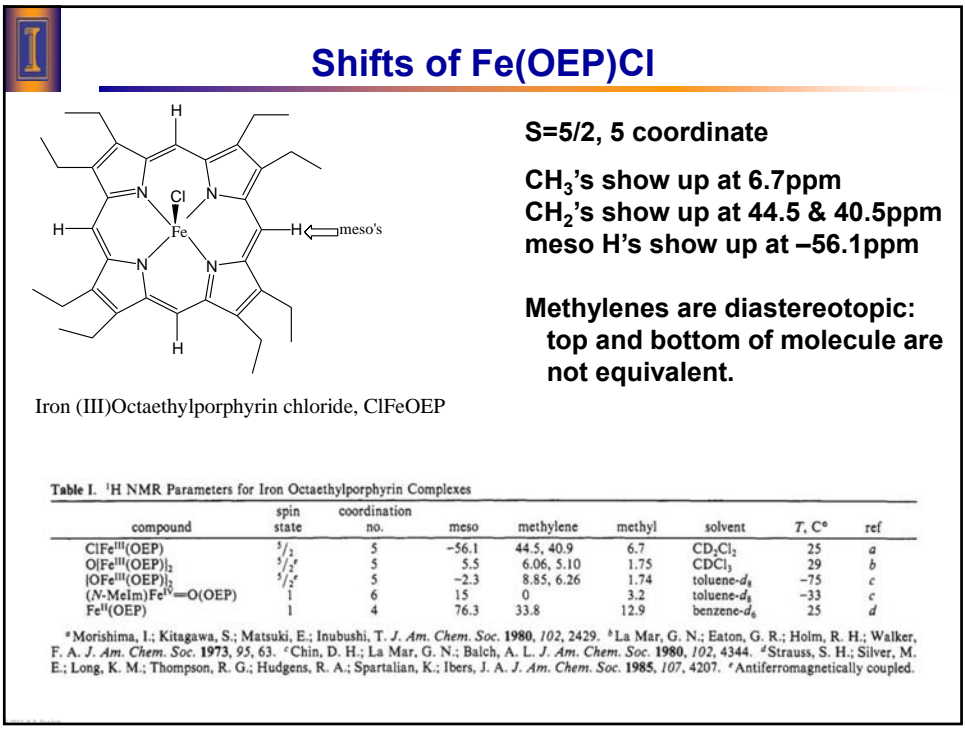
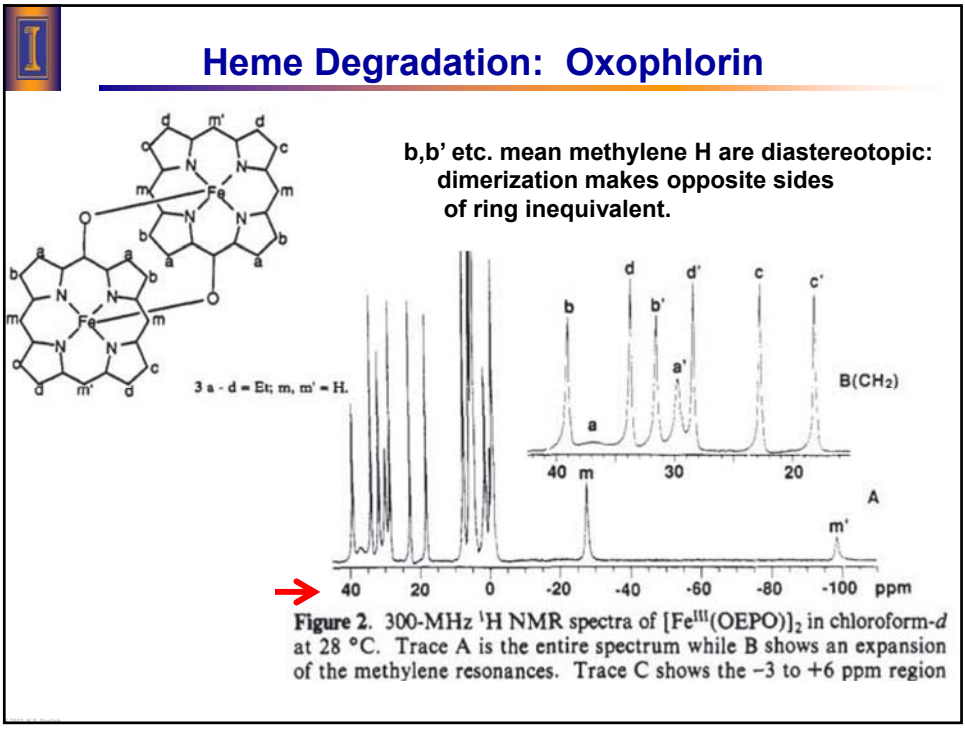
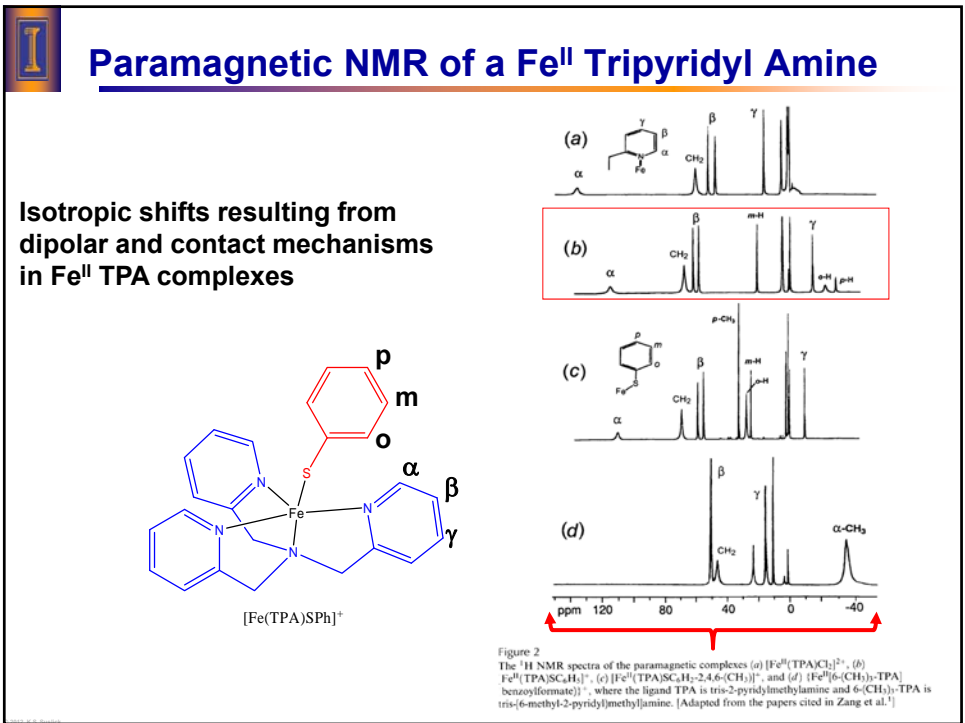
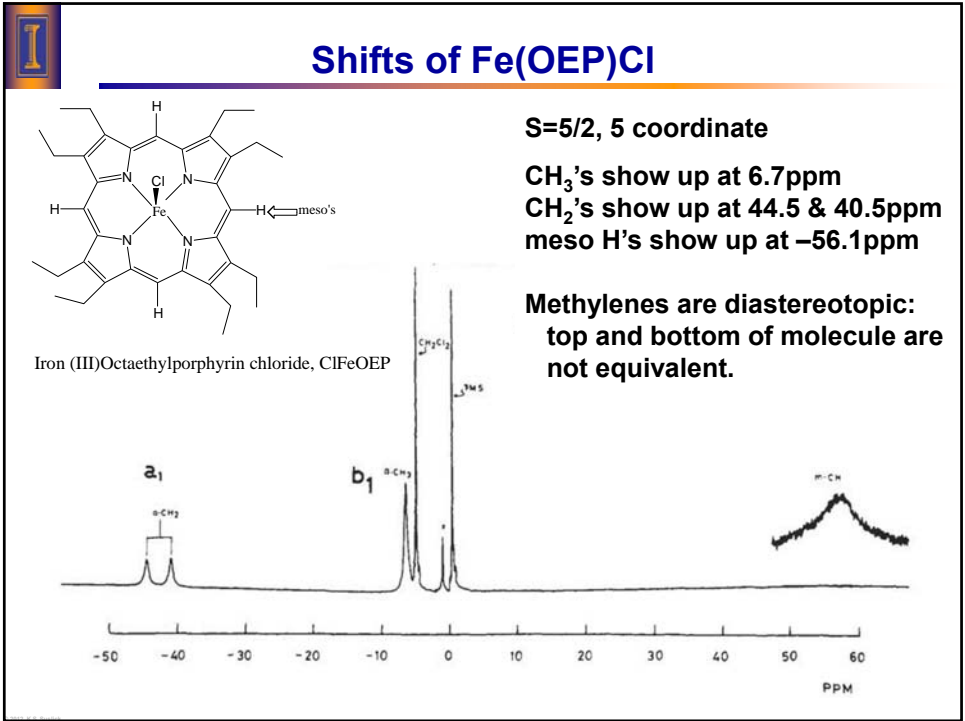


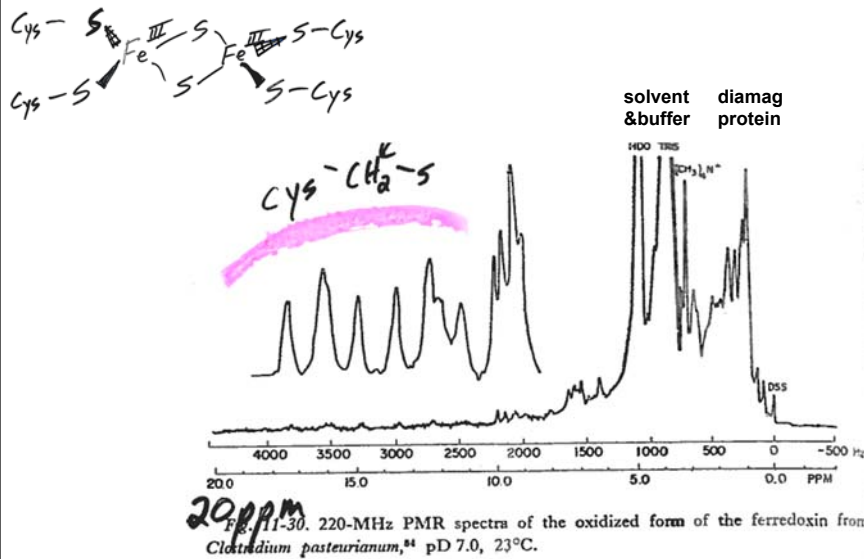
Figure 1. Drawings of the dimer 3 with $a-d = H$ and $m, m' = H$ obtained from molecular mechanics calculations. The top shows a stick diagram with hydrogen atoms omitted while the bottom shows a space filling model that includes the hydrogen atoms.







Paramagnetic NMR of Ferredoxin

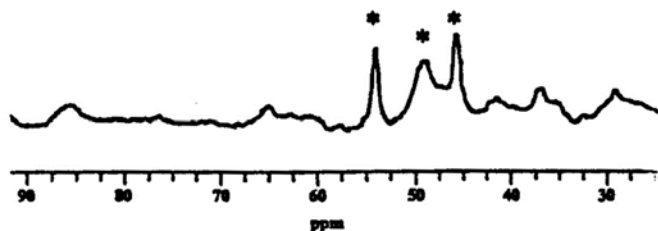


Active Site of β -Lactamase

- β -lactamase enzyme cleaves the lactam ring, preventing the drugs from killing bacteria. It is a protective enzyme in bacteria that imparts antibiotic resistance.
- Active site is ??
- Enzyme is a metalloenzyme but with Zn^{+2} , d^{10} and diamagnetic.
- Replace Zn^{+2} with Co^{+2} (just by ion exchange), and enzyme still retains activity.
- Co^{+2} is paramagnetic. Parts of the protein close to the Co^{+2} will show paramagnetic shifts.



Paramagnetic ^1H NMR of Co(II) substituted β -lactamase

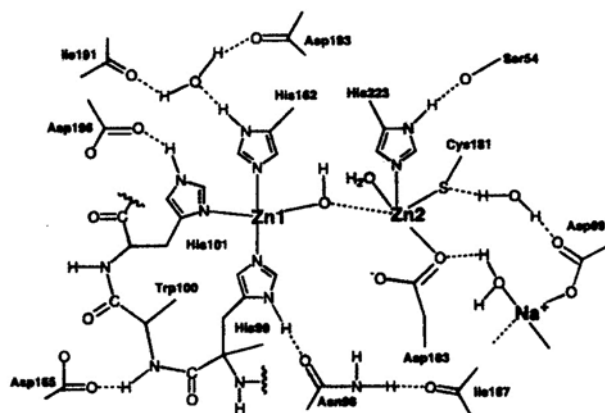


- See three strong signals in 45-55ppm range.
- When D_2O is added these peaks disappear.
- Suggests three different amino acids bind the metal contain exchangeable protons. The imidazole residue of Histidine binds metals, and have exchangeable protons.



Active Site of metallo- β -Lactamase

Scheme 2: Dinuclear Zn(II) Active Site of the *B. fragilis* Metallo- β -lactamase





Structural Uses of Paramagnetic NMR

Paramagnetic NMR Constraints

Nuclear relaxation provides metal-nucleus distances.

Pseudocontact shifts provide the angular coordinates of the metal ion and new structural constraints.

Contact shifts may provide dihedral angle constraints.



Structural Uses of Paramagnetic NMR

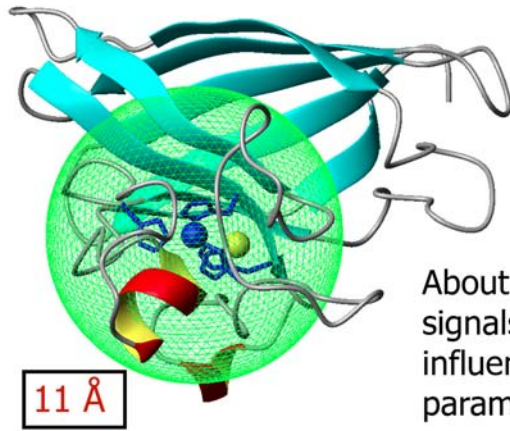
Diamagnetic Reference

Paramagnetic effects are measured as differences in NMR spectra recorded from the target molecule in the paramagnetic and diamagnetic states.

Data measured with a paramagnetic ion must be compared with corresponding data obtained with a chemically similar but diamagnetic metal ion.



Type II Cu²⁺ – Cu,Zn SOD

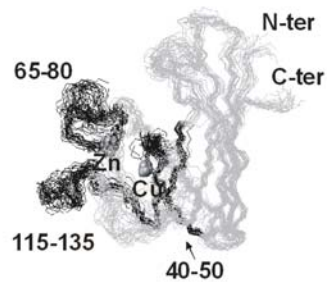


¹H NMR

About 25% of the proton signals are lost due to the influence of the highly paramagnetic copper ion



The final solution structure of monomeric Cu,Zn SOD



1767 NOEs
28 H-bonds
144 Talos
140 + 46 Tailor
31+31 R_1

$RMSD_{bb} = 1.1 \text{ \AA}$

Bertini, Felli, Luchinat, Parigi, Pierattelli, *ChemBioChem*, 2007

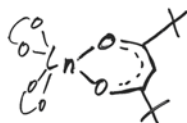


Lanthanide Shift Reagents (S.R.)

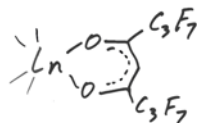
- S.R.s are paramagnetic Lewis Acids that bind to functional groups of organics w/ complex NMR.
- Subsequent paramag shift reduces complexity and increases ease of assignments.
- Amount of shift can be used (under certain conditions) to calculate structures of the organic as bound to the S.R.
- Less useful these days with large field NMRs and multi-dimensional NMR.
- But S.R. became reborn as MRI contrast agents due to increased relaxation rates of interacting waters!



Lanthanide Shift Reagents (S.R.)

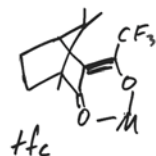


$\text{Ln}(\text{dpm})_3$



$\text{Ln}(\text{fod})_3$
better Lewis acid

Eu & Gd also common



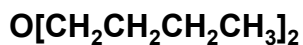
hfc

optically active
camphor derivative
Eu, Pr both from Aldrich



Lanthanide Shift Reagents (S.R.)

NMR of di-n-butyl ether



SR are idiosyncratic:
rely on strength of
Lewis acid-base
interactions.

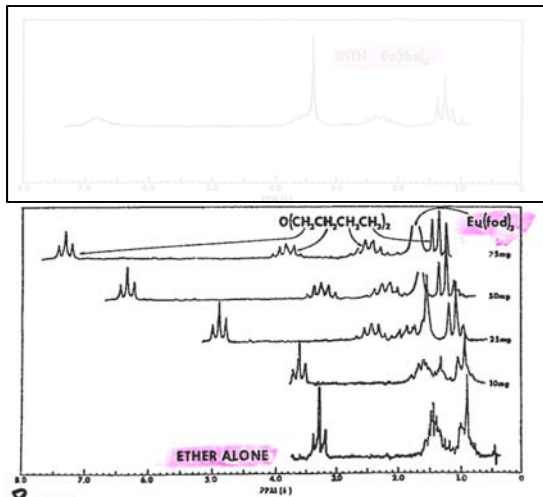


Fig. 12-4. Lower trace: 60-MHz PMR spectra of di-n-butyl ether (13 mg, 1.0×10^{-4} mole) in 0.5 ml CCl_4 containing 0.75 mg (7.5×10^{-4} mole) of $\text{Eu}(\text{fod})_3$; upper trace: CCl_4 solution $1 \times 10^{-4} M$ in ether saturated with $\text{Eu}(\text{dpm})_3$, dpm = thd. Reprinted from Rondeau and Sievers,²⁴ *J. Amer. Chem. Soc.* 93, 1522 (1971). Copyright 1971 by the American Chemical Society. Reprinted by permission of the copyright owner.



MRI Contrast Agents

- Chemical agents influencing the contrast behavior of magnetic resonance images and spectra. Commonly used agents include paramagnetic and superparamagnetic media.
- Contrary to x-ray contrast agents which are directly visible, magnetic resonance imaging contrast agents influence the behavior of the surrounding tissue; thus they are indirect contrast agents



MRI Contrast Agents

Traditional shift and contrast agents are largely based on high relaxivity Gd(III) complexes.

- (1) Fe(III) is substantially less toxic than Gd(III) and therefore holds promise for eventual in vivo applications.**
- (2) The high relaxivity of Gd(III) complexes arises fundamentally from fast ligand exchange rates but comparatively weak f orbital based binding.**