Development of MRI Contrast Agents Based On Iron Complexes

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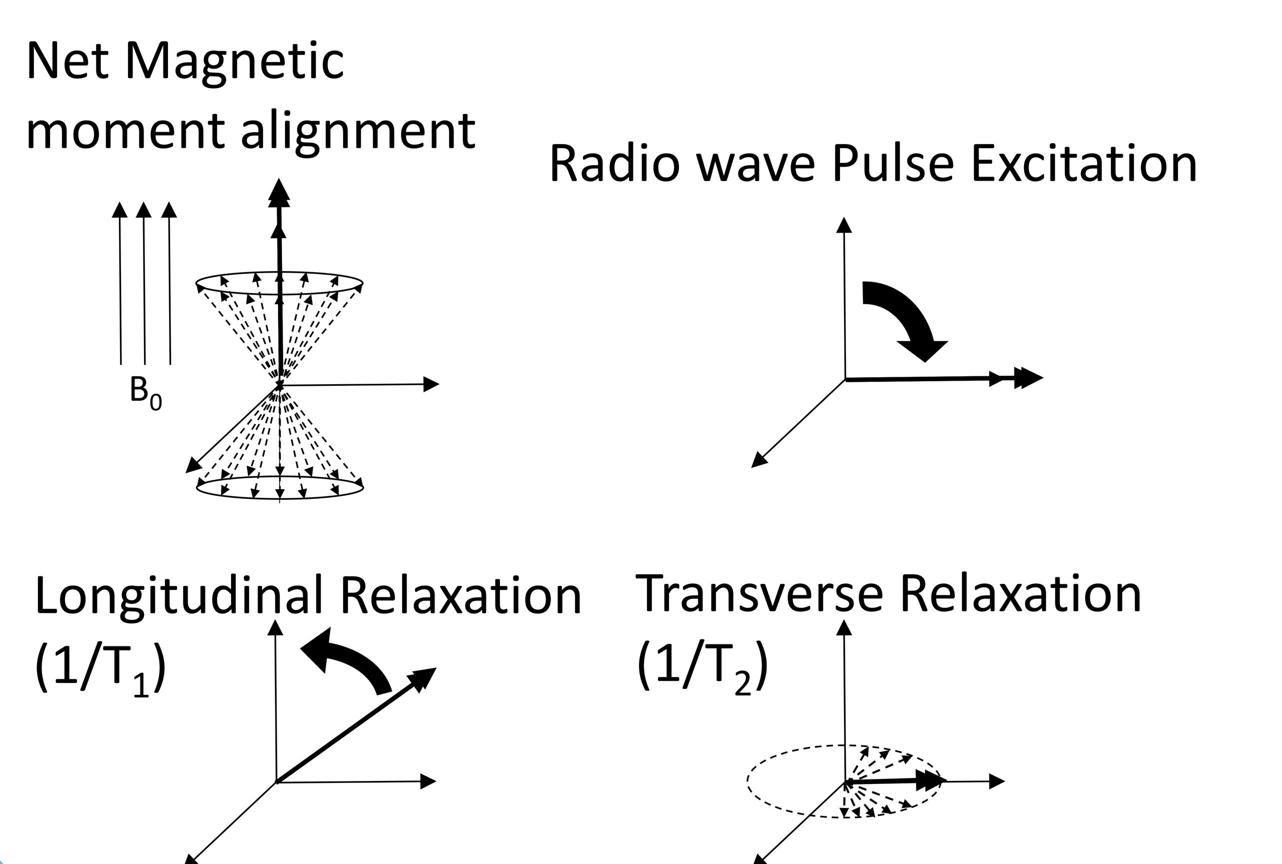
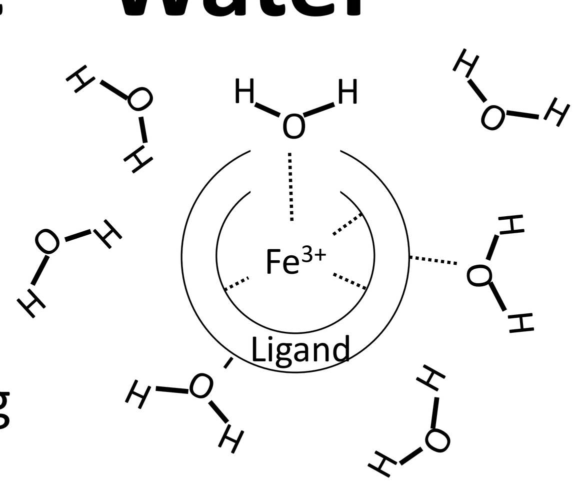
MRI & Contrast Agents Overview:

- MRI – Magnetic Resonance Imaging
- Magnetic field + radio frequency pulses
- Water hydrogen nuclei magnetic moment interacts with magnetic field
- Absorption and emission of energy through relaxation processes
- Contrast agent perturbs water's proton relaxivity through chemical interactions
- Results in different relaxation rates and subsequent image contrast on an MRI
- Contrast helps physicians diagnosis disease and better visualize abnormalities

MRI Relaxation Processes:



Contrast Agent – Water Interactions:



- Inner Sphere (Coordination Bonding)
- Outer Sphere (H-bonding and proximity effects)

Methods – Data Acquisition:

- 4.7 T MRI scanner and 9.4 T NMR Spectrometer
- Water enriched with ^{17}O
- Gather variable temperature measurements
- Collect frequency shift data ($\Delta v_{observed}$ & $\Delta v_{solvent}$)
- Convert to reduced relaxivity data ($1/T_{2r}$)
- Fit data to equations to obtain information on water exchange rate constants

Modeling Contrast Agent Interactions:

- Swift – Connick Equations:

(1a)
$$\frac{1}{T_{2r}} = \frac{\pi}{P_m} * (\Delta v_{observed} - \Delta v_{solvent}) = \frac{1}{\tau_m} * \frac{(T_{2m}^{-1} + T_{2m}^{-1} * \tau_m^{-1} + \Delta\omega_m^2)}{(T_{2m}^{-1} + \tau_m^{-1})^2 + \Delta\omega_m^2} + \frac{1}{T_{2os}}$$

(1b)
$$\frac{1}{T_{2r}} = \frac{\pi}{P_m} * (\Delta v_{observed} - \Delta v_{solvent}) = \frac{1}{\tau_m} * \frac{\Delta\omega_m^2}{\tau_m^{-2} + \Delta\omega_m^2}$$

- Eyring Equations:

(2a)
$$\frac{1}{\tau_m} = k_{ex} = \frac{k_b * T}{h} * \exp\left(\frac{\Delta S^{\ddagger}}{R} - \frac{\Delta H^{\ddagger}}{R * T}\right)$$

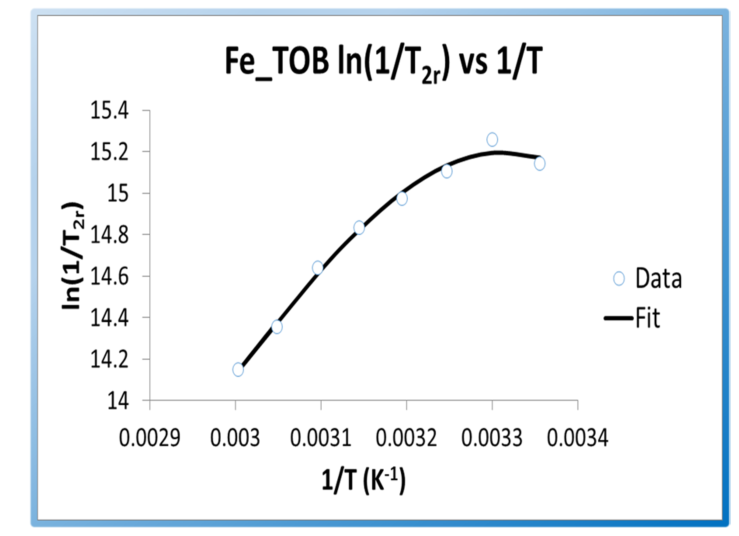
(2b)
$$\frac{1}{\tau_m} = kex = \frac{kex^{298}}{298.15} * T * \exp\left(\frac{\Delta H^{\ddagger}}{R} * \left(\frac{1}{298.15} - \frac{1}{T}\right)\right)$$

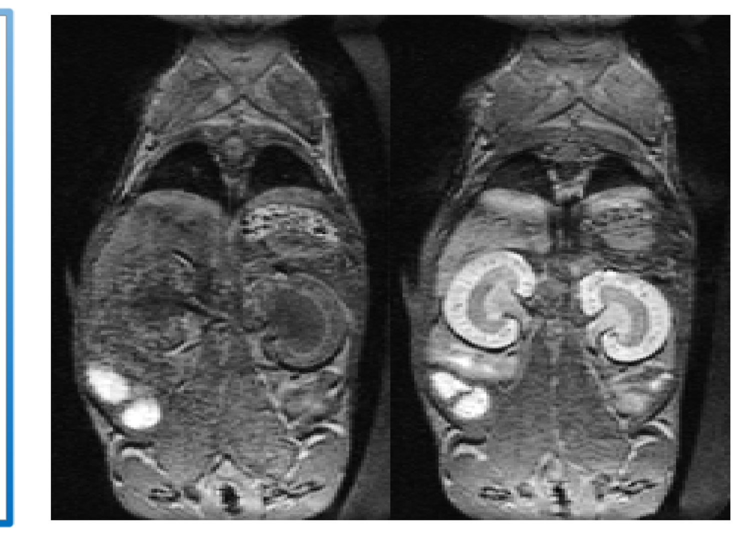
- Bloembergen Equations:

(3a)
$$\Delta\omega_m = \frac{g_L \mu_b S(S+1)B}{T}\left(\frac{A}{\hbar}\right)$$

(3b)
$$\Delta\omega_m = \frac{C}{T}$$

Results and Discussion:





- Fitting (left) of variable temperature ^{17}O NMR shifts show an excellent fit of data points to equations 1b, 2b, and 3b
- *in vivo* MRI images before (center right) and after (right) contrast agent administration show a clear generation of contrast in the kidneys after 30 minutes

Conclusions:

- Iron agents generated kidney contrast, which was a desired result
- Fitting method was proven to be effective and reliable for modelling and activation parameter determination with the compounds tested
- k_{ex} was determined to be 15(±2)*10^5 s^{-1}
- Further studies and modeling of additional Fe(III) contrast agents are underway.
- Toxicology and pharmacology studies are warranted

References:

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