



Iron-Organic Contrast Agent for Xenon Biosensing

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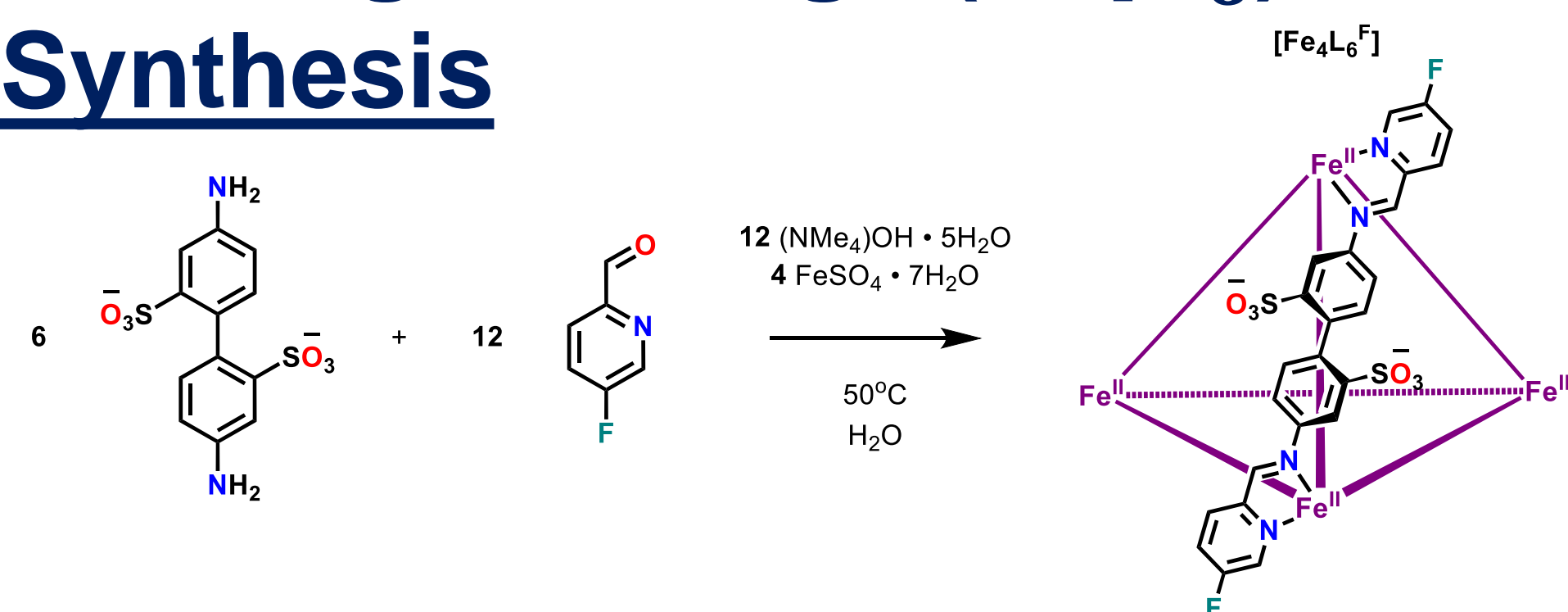


Background

- ^{129}Xe , an inert anesthetic, has promising applications in magnetic resonance imaging (MRI) and spectroscopy (MRS) due to its $\frac{1}{2}$ nuclear spin and large chemical shift window.^{1,2}
- Self-assembled metal-organic cages are easily synthesized compared to cryptophanes and other capsules.^{1,2}
- By functionalizing these metal-organic cages, new Xe contrast agents can be used to increase the precision of current MRI technologies.

Iron-Organic Cage ($\text{Fe}_4\text{L}_6^{\text{F}}$)

Synthesis



Scheme 1: Synthesis of self-assembled iron-organic cage ($\text{Fe}_4\text{L}_6^{\text{F}}$); only one of the edges of the tetrahedron is shown with the rest of the edges being identical

Hyperpolarized ^{129}Xe Chemical Exchange Saturation Transfer (CEST)

The change in polarization of the hyperpolarized (hp) xenon can be quantified and gives a good indication of how well the cage would act as a contrast agent for MRI.

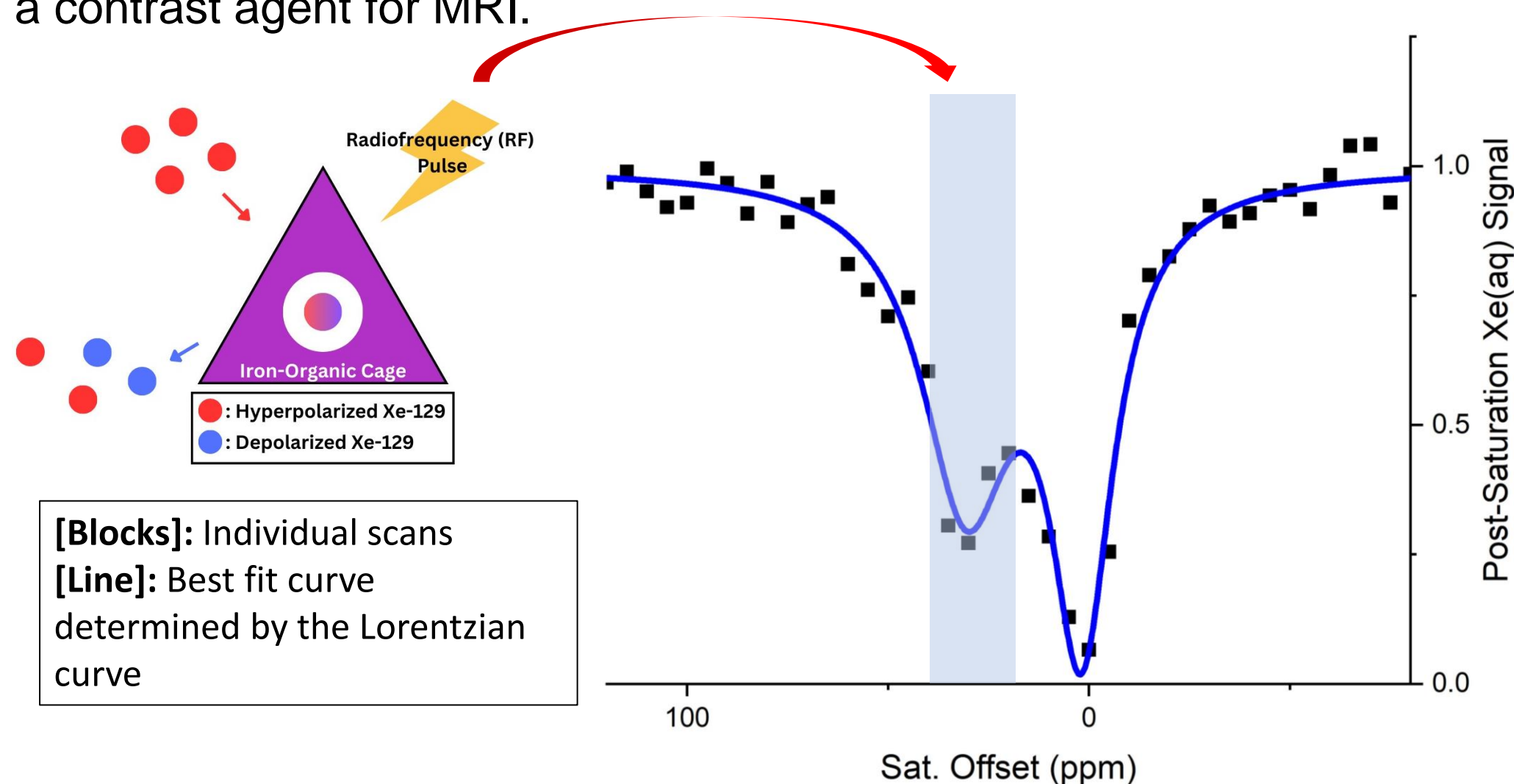


Figure 1: Hyper-CEST data for $50\ \mu\text{M}\ \text{Fe}_4\text{L}_6^{\text{F}}$ where saturation offset is referenced to xenon in water. The lightly shaded region indicates the depolarization of aqueous hp Xe-129 by the fluorinated cage.

Crystallization of $\text{Fe}_4\text{L}_6^{\text{F}}$

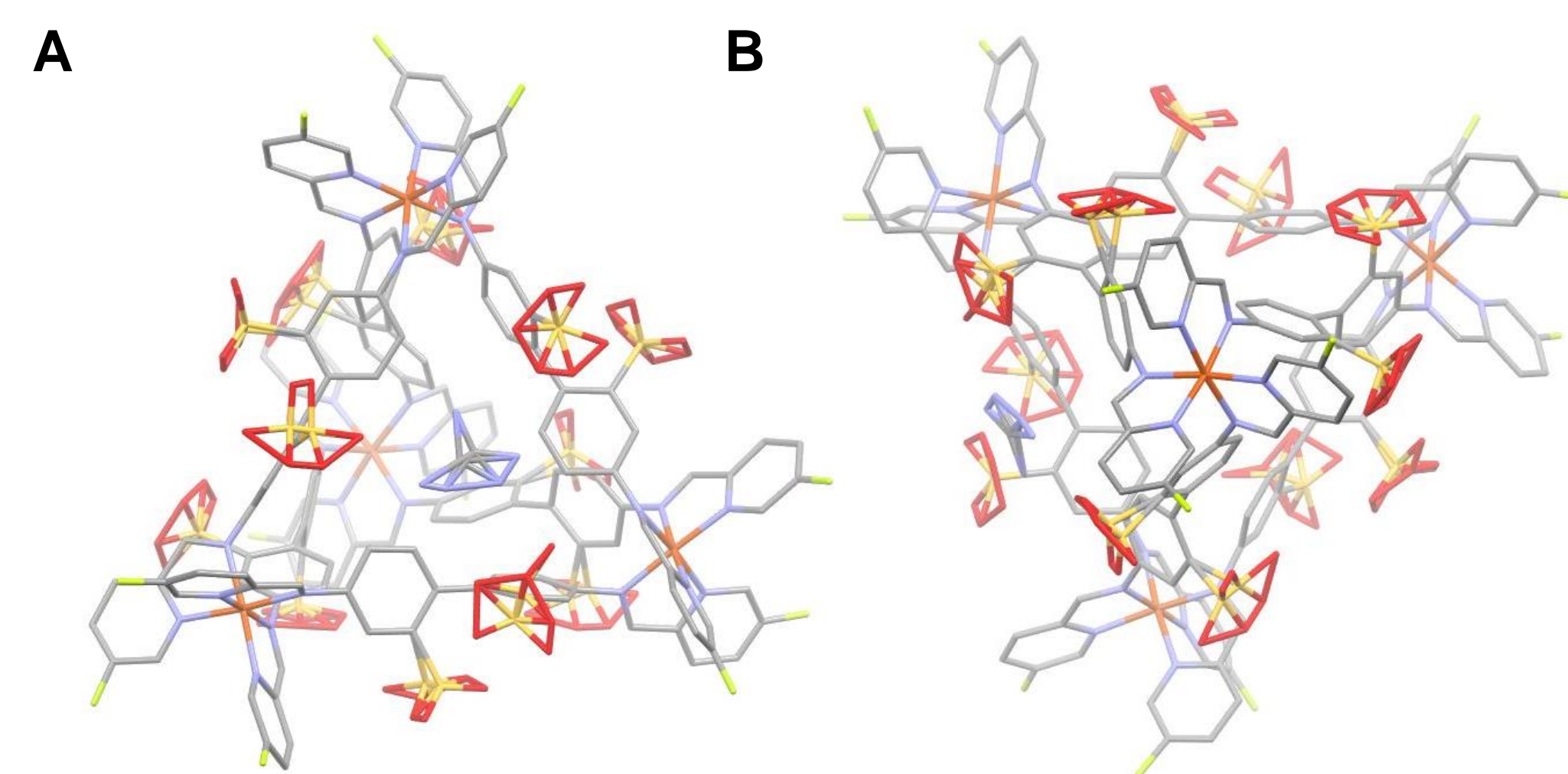


Figure 2: Crystal structure of $\text{Fe}_4\text{L}_6^{\text{F}}$. Crystals were grown under nitrogen using guanidinium to help with the crystallization process; guanidinium is exhibited on each face of the tetrahedral structure. Red = oxygen, yellow = sulfur, gray = carbon, blue = nitrogen, and green = fluorine; hydrogens are not depicted (A) Guanidinium angle; (B) Iron angle

Iron Cage	Fe – Fe (distance)	Fe – N _{diamine} (distance)	Fe – N _{aldehyde} (distance)	Hyper-CEST	Guanidinium on faces
$\text{Fe}_4\text{L}_6^{\text{F}}$	12.892Å	1.979Å	1.977Å	Yes	4
$\text{Fe}_4\text{L}_6^{\text{H}}$	12.874Å	1.983Å	1.971Å	Negligible	1

Table 1: Comparison of crystal structure properties and hyper-CEST activity of the $\text{Fe}_4\text{L}_6^{\text{H}}$ (fluorine cage, but all fluorine are replaced with hydrogen) and $\text{Fe}_4\text{L}_6^{\text{F}}$ cages. Despite similar shape and size, the two cages display different properties. Crystal structure data for $\text{Fe}_4\text{L}_6^{\text{F}}$ is from the literature³.

Ligand Exchange of $\text{Fe}_4\text{L}_6^{\text{X}}$

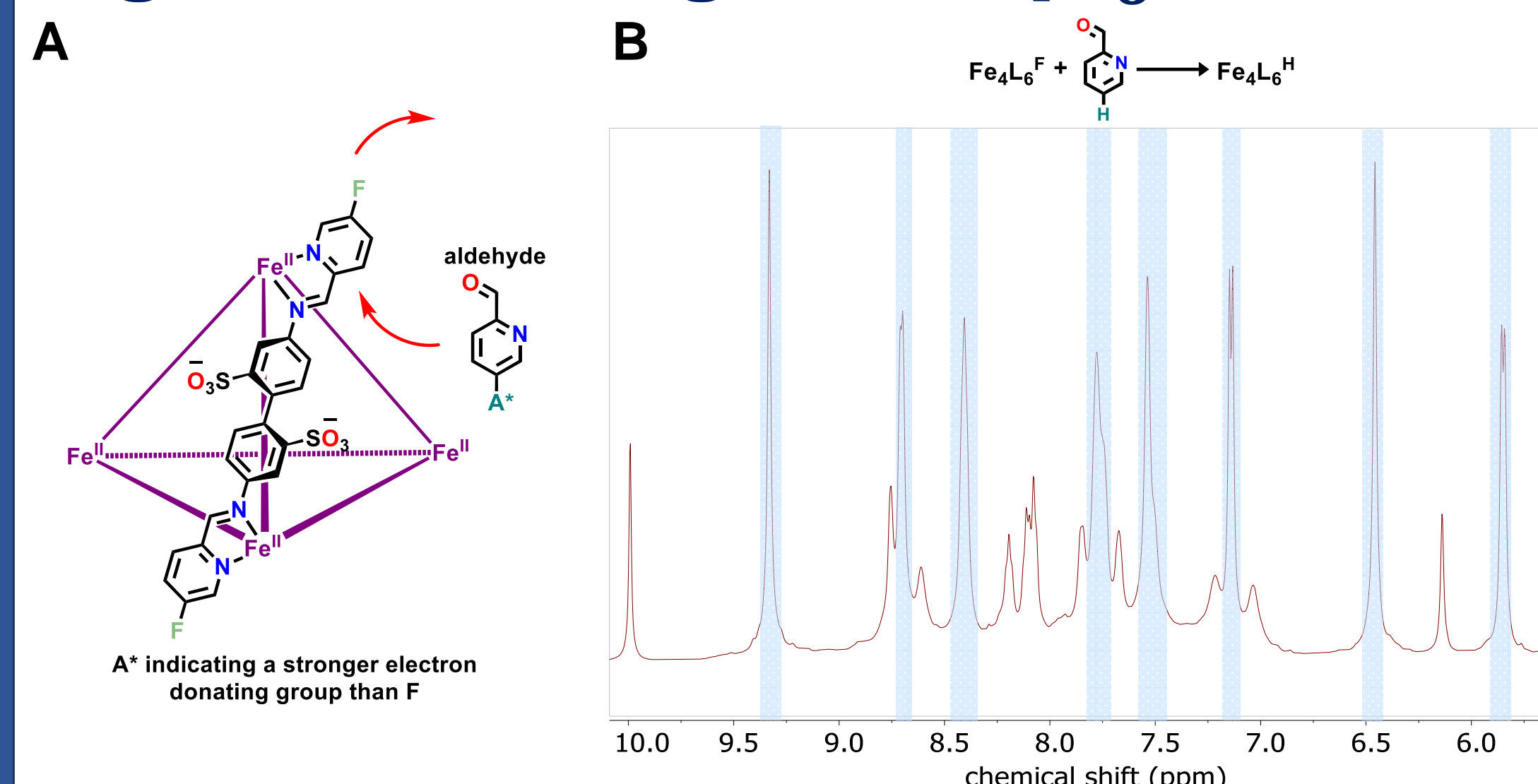


Figure 3: (A) Because the electron-withdrawing fluorine weakens the imine bond of the cage, reacting assembled $\text{Fe}_4\text{L}_6^{\text{F}}$ at $50\ ^\circ\text{C}$ with a stronger electron-donating aldehyde results in the replacement of the fluoroaldehydes with the more electron-donating aldehyde, forming a new cage. (B) ^1H NMR of the reaction mixture of $\text{Fe}_4\text{L}_6^{\text{F}}$ and picolinaldehyde at $50\ ^\circ\text{C}$. The peaks in the blue shaded regions match the reported resonances of the hydrogen cage ($\text{Fe}_4\text{L}_6^{\text{H}}$).³

General Trend of $\text{Fe}_4\text{L}_6^{\text{X}}$

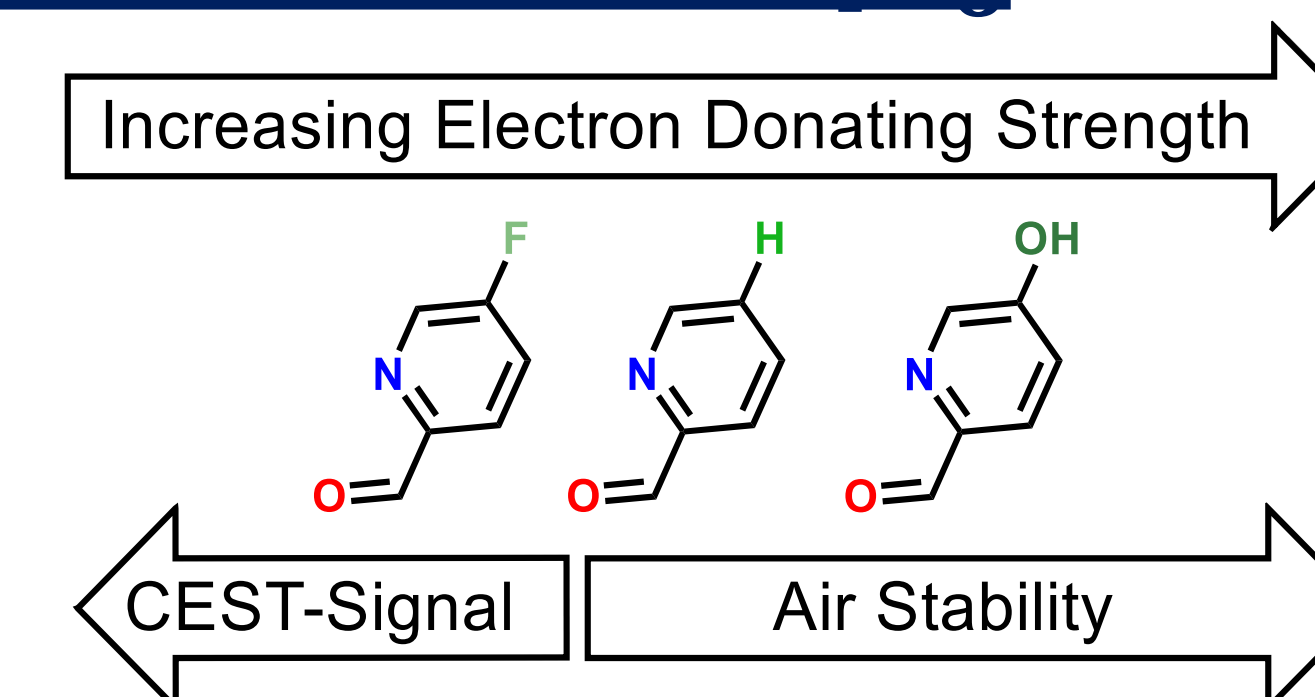


Figure 4: As the aldehydes on the cage contain a stronger electron donating group, the resulting cage becomes more air stable but exhibits less CEST signal perhaps due to strong bond strength.

Synthesized Cages Allow for Future Biological Applications

- The unique properties of the fluorine cage set the stage for potential ligand exchange that can lead to an o-propargyl heteroleptic cage.
- Additional routes to functionalize the iron-organic cage are to add a targeting group through nucleophilic aromatic substitution of $\text{Fe}_4\text{L}_6^{\text{F}}$ or through cross coupling of $\text{Fe}_4\text{L}_6^{\text{Br}}$.

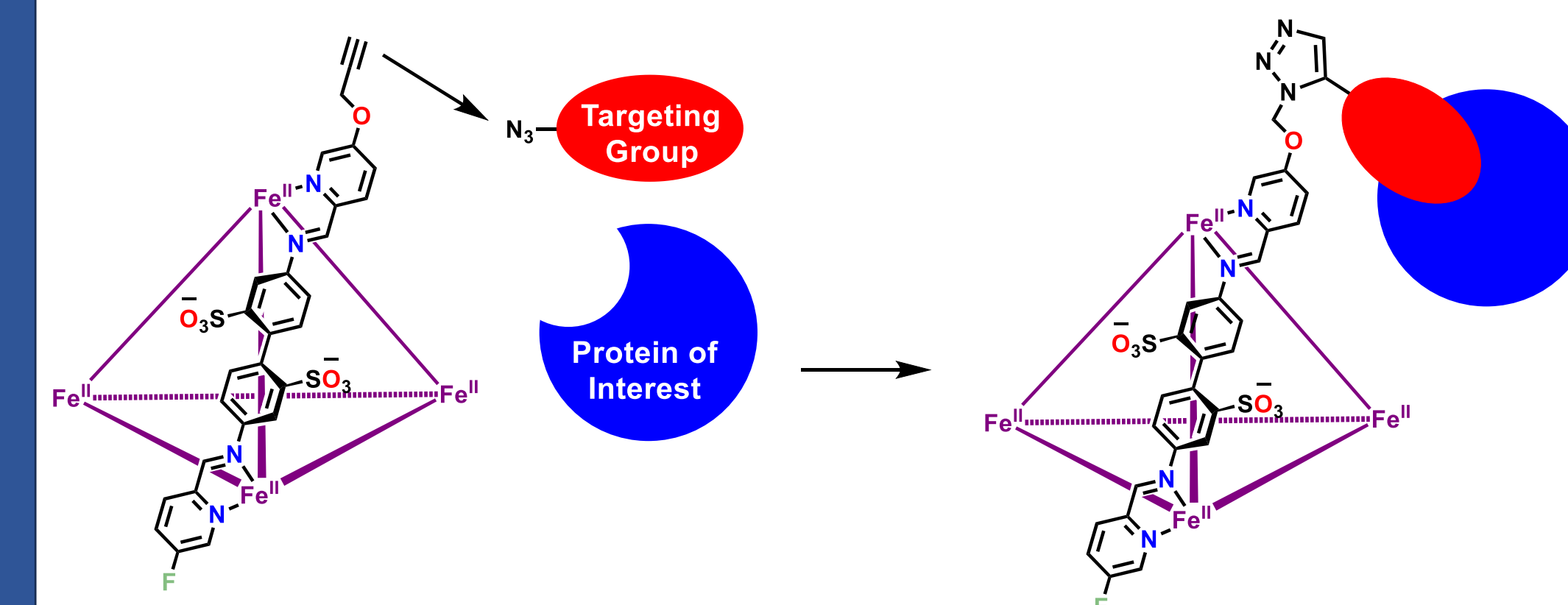


Figure 5: Knowing that the o-propargyl (OP) is a donating group, we can substitute one of the 5-fluoropicolinaldehydes on the fluorine cage with OP-picolinaldehyde. This would still allow the cage to exhibit good CEST-signaling while also enabling click chemistry to generate new targeted biosensors.

References

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