Understanding the Origin of Suicide Inactivation in the Extradiol Dioxygenases

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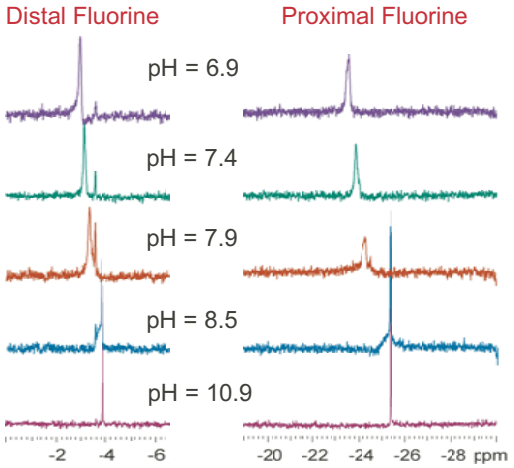
Our aim is to understand why most chlorinated substrates lead to suicide inactivation of non-heme Fe(II)-containing ring-cleaving dioxygenases, such as the well-characterized extradiol catechol dioxygenases. We are using a multi-faceted approach:

1. Paramagnetic NMR studies of enzyme-bound substrate, in order to characterize its pK_a and electronic structure.

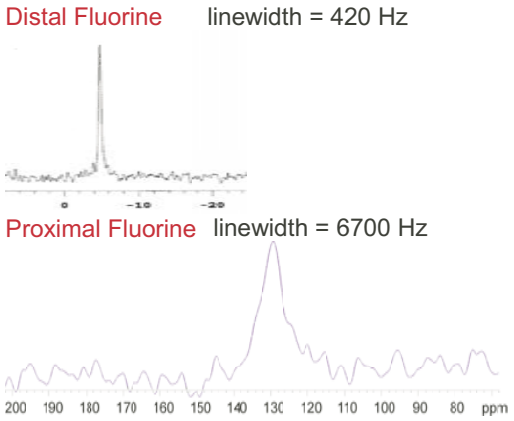
2. Characterization of model complexes with ligands similar to those found in the enzyme active site (facial-capping triad of N, N, O).

3. Biochemical studies of unusual Fe(II)-containing ring-cleaving dioxygenases that can cleave chlorinated substrates.

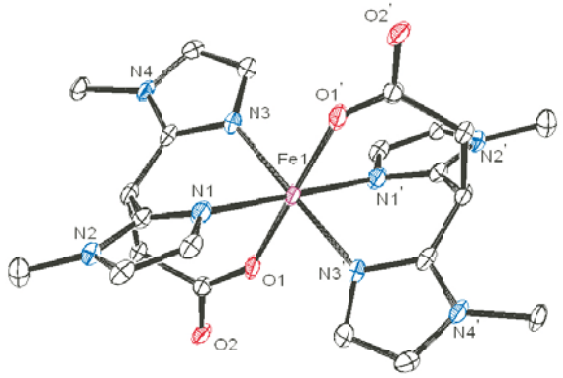
Aqueous substrate (4,4'-difluoro-2,3-dihydroxybiphenyl):



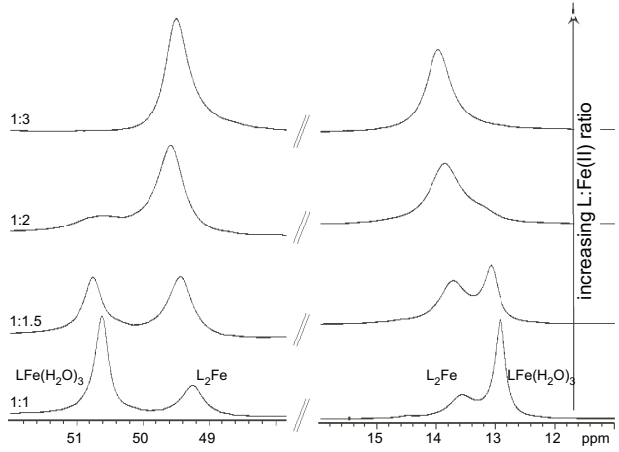
Enzyme-bound substrate:



Structure of L_2Fe complex:



NMR evidence for $L_2Fe/L_2Fe(H_2O)_3$ equilibrium:



Homology-based structural model of 2,6-dichloro-*p*-hydroquinone dioxygenase: