A deeper understanding of nature's catalysts

Start Time: Thursday, March 21, 2024

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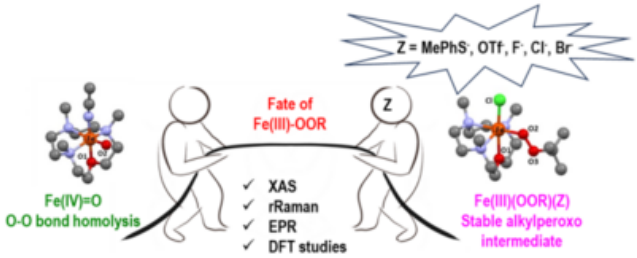

Catalytic reactions are essential for a wide variety of chemical processes in nature. Enzymes act as catalysts here, accelerating chemical reactions precisely and specifically. Interestingly, there are enzymes with structurally very similar active sites, but which trigger completely different chemical reactions. Why nature designed its catalysts in such a way is not yet understood.

One example are the two enzymes superoxide reductase (SOR) and cytochrome P450, which occur in many forms of life. While these two enzymes have very similar active sites containing iron ions they have different functions: SOR catalyzes the conversion of highly reactive and toxic superoxide ($O_2^{-\bullet}$) into less toxic hydrogen peroxide (H_2O_2). Enzymes of the cytochrome P450 family catalyze different hydrogen and oxygen atom transfer reactions. In their catalytic cycles, iron(III)peroxy intermediates (Fe^{III}–OOR(H) intermediates) have been identified as key components.

In an effort to understand nature's rationale for using similar active sites for apparently opposite functions in these enzymes, a team of researchers from the UniSysCat groups of Holger Dau, Peter Hildebrandt and Kallol Ray synthesized and studied S = 5/2 $[Fe^{III}(12\text{-TMCO})(OOR)L']^{+}$ with different ligands L and S = 1 $[Fe^{IV}(12\text{-TMCO})(O)(CH_3CN)]^{2+}$ complexes. Using a combination of sophisticated spectroscopic techniques (X-ray absorption spectroscopy (XAS), resonance Raman and electron paramagnetic resonance (EPR) spectroscopy) and density functional theory (DFT) they shed light on the mechanism of the active site of the enzyme SOR.

It is known, which chemical reactions take place at the active sites of the two enzymes: In SOR, the $[Fe^{III}(His)_4(Cys)OOH]$ intermediate undergoes a proton-mediated Fe–O bond cleavage to release H_2O_2. In contrast, the $[Fe^{III}$(protoporphyrin-IX)(Cys)OOR(H)] intermediate in cytochrome

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P450 undergoes O–O bond cleavage to initiate the hydrogen and oxygen atom transfer reactions. However, attempts to explain the different fates of the Fe^{III}–OOR(H) intermediates on the basis of their different spin states have not yet provided a conclusive picture.

The current study provides a basis to discuss the function of the high-spin active site of SOR: it demonstrates the importance of *cis*-anionic ligand donations for the stabilization of high-spin iron(III)–peroxo complexes. Thus, it emphasizes the importance of subtle electronic changes and secondary interactions for the stability of biologically relevant metal-oxygen intermediates. Finally,it provides some rationale for the dramatically different outcomes of the chemistry of iron(III)peroxy intermediates formed in the catalytic cycles of SOR (Fe–O cleavage) and cytochrome P450 (O–O bond lysis) in similar N_4S coordination environments.

This study has been published in *Chemical Sciences:* T. Devi, K. Dutta, J. Deutscher et *al.* A high-spin alkylperoxo–iron(iii) complex with cis-anionic ligands: implications for the superoxide reductase mechanism. Chem. Sci., 2024,**15**, 528-533. https://doi.org/10.1039/D3SC05603A

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