Oxygen Intermediates in Non-Heme Iron Systems: Spectropscopic and Quantum Chemical Studies of Activated Bleomycin Reactivity

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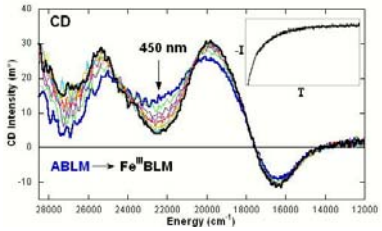
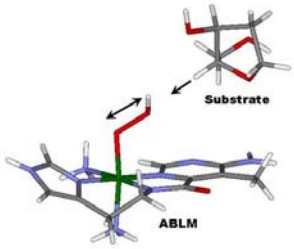
A wide variety of chemical and biological reactions that require dioxygen binding and activation are catalyzed by mononuclear non-heme iron enzymes. The first well-characterized reactive oxygen intermediate in a non-heme iron system is activated bleomycin (ABLM), the kinetically competent form of the anticancer drug Bleomycin (BLM). ABLM, a low-spin, end-on Fe^{III} hydroperoxo complex, is the last intermediate detected prior to DNA strand scission, which occurs via H-atom abstraction from the C4' position of the DNA ribose sugar. Very little is known about the mechanistic steps or catalytic species of the ABLM reaction.

We have investigated the thermodynamics and kinetics of ABLM reactivity using spectroscopic and quantum chemical methods. Using CD spectroscopy, we can directly monitor the kinetics of ABLM decay. Substrate and deuterium isotope studies show that the rate of ABLM decay is dependent on H-atom donation. We have studied the possibilities of homolytic and heterolytic O-O bond cleavage by the Fe^{III}-OOH complex,[1,2] and evaluated the 2-dimensional reaction coordinate for the direct H-atom abstraction of the deoxyribose 4'-H by ABLM.

These studies provide a deeper understanding of the reactivity of ABLM and related oxygen intermediates in non-heme iron systems.





References:

(1) Neese, F.; Zaleski, J. M.; Loeb Zaleski, K.; Solomon, E. I. *J. Am. Chem. Soc.* **2000**, *122*, 11703-11724.

(2) Solomon, E. I.; Decker, A.; Lehnert, N. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3589-3594.

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