Structure-Function Correlations in the α-Keto Acid Dioxygenases HPPD and HmaS: Insight into O_2 Activation and Reactivity

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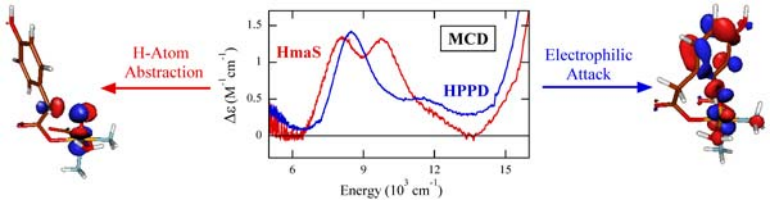
The α-ketoglutarate (α-KG)-dependent dioxygenases comprise a large class of mononuclear non-heme iron enzymes that require Fe^{II}, α-KG and O_2 for catalysis. A sub-class of these enzymes exist which are unique, incorporating both atoms of dioxygen into a single substrate as the α-keto acid moiety is covalently attached to the substrate, paralleling the extradiol dioxygenases where the catecholate substrate also supplies the extra electrons required for O_2 activation. One member of this sub-class, (4-hydroxyphenyl)pyruvate dioxygenase (HPPD), catalyzes the conversion of (4-hydroxyphenyl)pyruvate (HPP) to homogentisate as part of tyrosine catabolism while another member, 4-hydroxymandelate synthase (HmaS), uses the same substrate (HPP) as HPPD but forms a different product, 4-hydroxymandelate. These enzymes exhibit different iron-oxygen intermediate reactivities, electrophilic attack (HPPD) vs. H-atom abstraction (HmaS). We have employed a ferrous methodology combining circular dichroism and variable-temperature variable-field magnetic circular dichroism to elucidate the geometric and electronic structures of the active sites of these enzymes (1, 2). These studies provide molecular level insight into O_2 activation in these enzymes and the active site features that affect their different reactivities towards a conserved substrate.



1. Neidig, M. L.; Kavana, M.; Moran, G. R.; Solomon, E. I. *J. Am. Chem. Soc.* **2004**, *126*, 4486.
2. Neidig, M. L.; Choroba, O. W.; Spencer, J. B.; Solomon, E. I., submitted.

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