Modeling Dioxygen Activation and Substrate Hydroxylation at Monocopper Enzyme Sites

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The activation of molecular oxygen at monocopper centers plays an important role in biology, and in particular with regard to the biosynthesis of neurohormones by the Cu-containing enzymes dopamine β-monooxygenase (DβM) and the peptidylglycine α-hydroxylating monooxygenase (PHM) component of the bifunctional peptidylglycine α-amidating monooxygenase (PAM). In order to gain an understanding of the first stage of the catalysis (i.e. dioxygen activation at the monocopper active sites), 1:1 Cu/O_2 adducts coordinated to the biomimetic β-diketiminate and anilido-imine ligands of Tolman and co-workers[1,2] have been studied using a combination of DFT and CASPT2 methods, a protocol which stems from earlier work on closely related systems.[3,4] Following this, the 1:1 Cu/O_2 adducts were thoroughly characterized; reduction potentials were calculated and pK_a values of the Cu-hydroperoxo forms were determined. Formation of a Cu(III)-oxo species is also considered. Finally, the hydrogen-atom abstraction reaction with substrates possessing a range of C–H bond strengths is studied using the 1:1 Cu/O_2 adducts, Cu-hydroperoxo, Cu(III)-oxo, and Cu(III)-hydroxide species as potential catalysts. The relative reactivity of the different species are contrasted and related back to their individual properties. The results provide insight as to the nature of the species which hydroxylates substrate in DβM and PHM and the catalytic mechanisms of these enzymes.

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