

## FLAVIN-N5OOH: A MOST POWERFUL NUCLEOPHILE AND BASE IN NATURE

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Flavoenzymes can mediate a large variety of oxidation reactions via the activation of oxygen. As such, the chemistry of flavoenzymes is an important field that has not yet attained its full scope/recognition. Normally, the  $O_2$  activation occurs at the C4a site of the flavin cofactor, yielding the flavin C4a-(hydro)hydroperoxyl species in monooxygenases or oxidases. Using extensive MD simulations, QM/MM calculations and QM calculations, our studies reveal the formation of the common nucleophilic species, flavin-N5OOH, in two distinct flavoenzymes (RutA and EncM). Our studies show that flavin-N5OOH acts as a powerful nucleophile that promotes C–N cleavage of uracil in RutA, and a powerful base in the deprotonation of substrates in EncM. We reason that flavin-N5OOH can be a common reactive species in the superfamily of flavoenzymes, which accomplishes the generally selective general base catalysis, and the C–X (X= N, S, Cl, O) cleavage reactions that are otherwise challenging by solvated hydroxide ion base. These results expand our understanding of the chemistry and catalysis of flavoenzymes.

