Electronic Structure Contributions to Reactivity in Xanthine Oxidase and CO Dehydrogenase

Martin L. Kirk[1], Sushilla Knottenbelt[1], Abebe Habtegabre[1], Charles G. Young[2]

[1]*Department of Chemistry, The University of New Mexico, Albuquerque, NM 87131-0001, USA;*
[2]*School of Chemistry, University of Melbourne, Melbourne, VIC 3010, Australia.*

Xanthine oxidase is the prototypical Mo hydroxylase and has been implicated in pro-drug activation and drug metabolism, while XO related aldehyde oxidase catalyzes the reduction of sulfa drugs, and metabolizes famciclovir to the potent antiviral penciclovir, which is effective against herpes simplex (types 1 and 2), varicella zoster, Epstein-Barr, and hepatitis B. We have undertaken detailed spectroscopic and computational studies of XO and relevant small molecule analogues in order to understand the key electronic structure contributions to reactivity at the XO active site. Infrared and Raman spectroscopies have shown that the Mo-$S_{sulfido}$ bond order is two in *cis*-$[MoOS]^{2+}$ units, and is reduced to 1.5 upon one electron reduction to *cis*-$[MoOS]^{1+}$, indicating that the redox active molecular orbital has a profound influence on MoOS bonding and that the redox state of MoOS systems directly affects the relative electro-/nucleophilicity of the terminal sulfido donor. To this end we have completed detailed computational studies to evaluate the nature of the wavefunction during reductive half reaction of XO. The key results here provide new information regarding the formal hydride transfer process that results in substrate oxidation and Mo reduction.

Studies on XO related CO dehydrogenase (CODH), which possess a mixed-metal Mo-$S_{sulfido}$-Cu(I) site, will also be discussed. Detailed spectroscopic studies indicate extensive electron delocalization across the Mo-$S_{sulfido}$-Cu(I) site in relevant small molecule analogues of the CODH site. We have used a valence bond configuration interaction (VBCI) model to assign charge transfer transitions in paramagnetic analogues of CODH, in order to understand CO binding at Cu(I) and superexchange pathways for formal 2 e- transfer from CO to the Mo center.