

HIGHLANDS IN CHEMISTRY SEMINAR SERIES



JIM TANKO

VIRGINIA TECH

“What do Designer Drugs, Parkinson’s Disease, and the Persistent Radical Effect have in Common?”

JANUARY 28, 2022

2:30PM ET

HAHN HALL NORTH 140

FACULTY HOST:
WEBSTER SANTOS

Monoamine oxidase-A and -B (MAO-A and MAO-B) are important enzymes that are expressed in the majority of mammalian tissues. Their roles in the oxidative metabolism of the biogenic amines dopamine, norepinephrine, epinephrine and serotonin are well documented. Efforts to develop selective inhibitors of MAO-A and MAO-B for the treatment of depression and neurodegenerative disorders, respectively, have been ongoing for more than three decades. The catalytic pathway involves the net 2-electron oxidation of the substrate in a reaction that is coupled to the 2-electron reduction of the oxidized flavin (FAD) cofactor. Three mechanisms (and variants thereof) have been proposed to account for the initial steps of the catalytic mechanism, i.e., the MAO catalyzed oxidation of the amine to an imine. The key elements of these are illustrated below with benzyl amine as a substrate: a) Polar, nucleophilic, b) hydride transfer, and c) single electron transfer (SET). Of these, it is probably fair to say that the SET pathway has fallen out of favor and is no longer considered viable.

Generally, the only reported tertiary amines that are MAO-A or -B substrates are members of the 1,4-disubstituted-1,2,3,6-tetrahydropyridinyl system. This seminar will describe the results of studies on the mechanism of the reaction between 1-methyl-4-(1-methyl-1H-pyrrol-2-yl)-1,2,3,6-tetrahydropyridine (MMTP) and a chemical model for MAO: 5-ethyl-3-methylflavinium perchlorate (Fl⁺). The results demonstrate that SET is back on the menu as a likely mechanism for the MAO catalyzed oxidation of tertiary amines such as MMTP and derivatives. It is suggested that the ability to form a highly stabilized radical, unique to cyclic, allylic tertiary amines such as MMTP and derivatives, drives the SET process.