COLLEGE OF SCIENCE
CHEMISTRY
VIRGINIA TECH

TANKO RESEARCH GROUP

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

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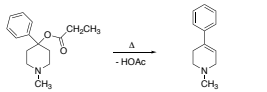
Mechanistic studies with 5-ethyl-3-methyllumiflavinium (Fl^+) perchlorate, a biomimetic model for flavoenzyme monoamine oxidase B (MAO-B) catalysis, and the tertiary, allyl amine 1-methyl-4-(1-methyl-1H-pyrrol-2-yl)-1,2,3,6-tetrahydropyridine (MMTP) reveal that proton coupled electron transfer (PCET) may be an important pathway for MAO catalysis. The first step involves single electron transfer (SET) leading to the free radicals $Fl^{\bullet}$ and $MMTP^{\bullet}$, the latter produced by deprotonation of the initially formed and highly acidic $MMTP^{\bullet+}$. Molecular oxygen (O_2) is found to play a hitherto unrecognized role in the early steps of the oxidation. MMTP and several structurally similar tertiary amines are the only tertiary amines oxidized by MAO, and their structural/electronic properties provide the key to understanding this behavior. A general hypothesis about the role of SET in MAO catalysis, and the recognition that PCET occurs with appropriately substituted substrates is presented.

Parkinson's Disease/Parkinsonism

Clinical syndrome characterized by tremor, bradykinesia, rigidity, and postural instability

- Lewy bodies (abnormal aggregates of protein that develop inside nerve cells)
- Destruction of dopaminergic neurons in the substantia nigra
- Generally a disease that affects the elderly

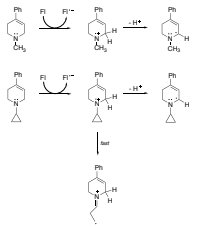
What is a designer drug? A structural or functional analog of a controlled substance that has been designed to mimic the pharmacological effects of the original drug, while avoiding classification as illegal and/or detection in standard drug tests



1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**MPTP**)

- MPTP is lipophilic and can cross blood-brain barrier
- Undergoes oxidation catalyzed by monoamine oxidase B to produce a potent neurotoxin
- Kills primarily dopamine-producing neurons in a part of the brain called the pars compacta of the substantia nigra
- MPTP used to simulate Parkinson's disease to better understand etiology, develop treatment strategies, etc.

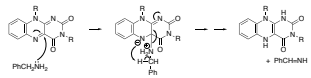
SET Hypothesis for MAO oxidation of amines (Current Status)



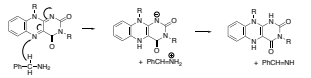
- Paramagnetic intermediates derived from the flavin moiety have never been detected
- Chemical model studies have shown that rearranged products (and flavin-adducts) can arise via a polar, nucleophilic pathway
- Numerous experimental & computational studies strongly support other mechanisms

The two currently accepted mechanisms for MAO-catalyzed oxidations

Polar mechanism:



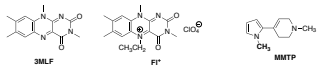
Hydride transfer mechanism:



A glaring omission from recent studies – none have considered the reaction of MAO with tertiary amines

Tertiary amines are not MAO substrates, with the exception of **MPTP** and its structural analogs are the only reported tertiary amines with MAO-B substrate properties

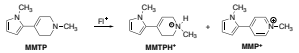
This work: To ascertain the mechanism of reaction of chemical model compounds (biomimetics) with an MPTP derivative



MMTP: 1-methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-1,2,3,6-tetrahydropyridine

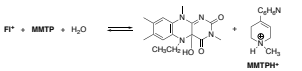
Headline News: It works!

Reaction of **MMTP** with **Fl•** gave rise to two principal products, in nearly quantitative yield: 1) the expected oxidation product **MMP•** and 2) **MMTPH+**, the protonated form of the starting material **MMTP**.

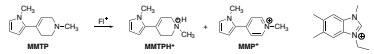


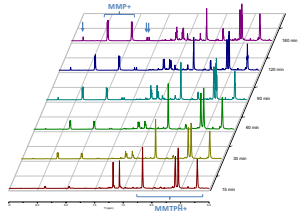
Two small molecules, molecular oxygen (O_2) and water (H_2O) play critical roles in this chemistry

Water (in CH_3CN) introduces a "sideshow" equilibrium. This reaction needs to be studied under rigorously dry conditions and in a glovebox.

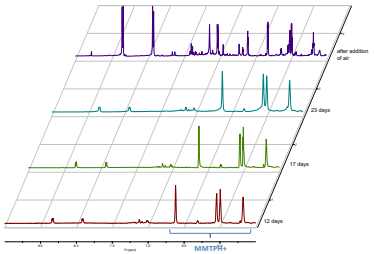


Reaction conducted in the presence of O_2, monitored by ^{1}HNMR (δ 5.5 – 9.0)

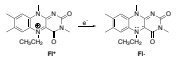


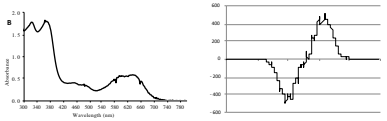


Reaction conducted under anaerobic conditions: "Silent" NMR – only $MMTPH^+$ is detected



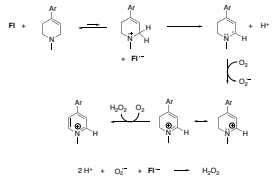
The final two pieces of the puzzle: The UV/Vis spectrum of the reaction of MMTP and Fl^+ (anaerobic conditions) ...and a heartbeat! The EPR spectrum of the reaction of MMTP and Fl^+ (anaerobic conditions)



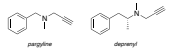


Conclusions and implications

- SET is back on the menu as a viable mechanism for the MAO catalyzed oxidation of tertiary amines such as MPTP. Failure to detect this pathway in previous studies is because other mechanisms operate for primary and secondary amines.
- The ability to form a stabilized radical such as **MMTP•**, which drives the SET process, is unique to allylic tertiary amines such as **MPTP** and derivatives.



- Some mechanism-based MAO-B inhibitors such as the propargylic amines pargyline and selegiline (deprenyl) possess similar functionality, and thus, may also operate via a single electron transfer process.



- While the role of O_2 in completing the catalytic cycle for MAO is known, a possible role of O_2 in the early steps of the mechanism has not been considered. Future studies of MAO catalysis under anaerobic conditions are needed.