Electrochemistry of 1-methyl-2-nitroimidazole in the presence of 2-napthol and cysteine

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1-methyl-2-nitroimidazole and its derivatives are highly active biological compounds that can be used for therapeutic purposes. Benznidazole, a 2-nitro derivative, is one of only two drugs currently used for the treatment of Chagas Disease; an infection caused by Trypanosoma cruzi (1). In T-cruzi an enzymatic reduction of the drug takes place, producing the radical intermediates of the 2-nitro compound. It is believed that the radicals react with proteins, and other intracellular components to cause cell damage (2). In cancer treatment, 1-methyl-2-nitroimidazole has been studied as a radiosensitizer of hypoxic cells. However it was discontinued due to complications that arose during phase I clinical trials of the drug. In hypoxic cancers, the unreduced imidazole is what brought about radiosensitization. The enzymatic reduction and the production of the radical intermediates caused peripheral neuropathy and prompted the ending of the trials (3). In both cases, the radical intermediates are believed to play an important role in the drugs' cytotoxicity.

Our aim is to gain a qualitative understanding of the specific redox pathways of 1-methyl-2-nitroimidazole. Cyclic voltammetry experiments with 1-methyl-2-nitroimidazole are being carried out in "dry" DMSO in the presence of 2-napthol and cysteine. The data gathered shows a striking similarity to the more studied system of nitrobenzene (4). With the addition of the weak acids, we believe that 1-methyl-2-nitroimidazole undergoes an initial 2-electron 2-proton reduction to form the hydroxylamine. We detect this on the positive return-scan by the appearance of an oxidation peak at ~ -0.75(Fc/Fc^+)/V. If no more chemistry occurs the, the hydroxylamine can be oxidized into the nitroso.

In the presence of 2-naphthol, the nitroso is detected on the forward scan of the second cycle. This suggests that little to no further reaction takes place with imidazole and 2-naphthol. With cysteine, after the initial 2-electron 2-proton reduction, the cysteine continues to react with the imidazole producing other products thus, the nitroso peak is absent.

To confirm our findings, we are in the process of synthesizing the 1-methylhydroxylaminoimidazole. By testing the synthesized hydroxylamine, we hope to confirm our findings. One of the biggest hurdles in this project is figuring out a viable protocol for making and isolating the hydroxylamine. This is due to the fact that the hydroxylamine is very sensitive to oxygen and degrades quickly in its presence.

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