Analysis of the Reduction of 1,2-Dimethyl-5-nitroimidazole Using Cyclic Voltammetry

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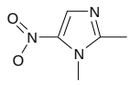
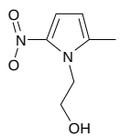
Nitroimidazoles are known to be medicinally active against protozoan diseases such as giardiasis that are most common in countries with poor sanitation. Giardiasis is an infection of the small intestine, which leads to such symptoms as dehydration and the body's inability to absorb adequate nutrients from the intestines. The full mechanistic action of nitroimidazoles is not yet known, but it is known that the compounds are activated by reduction. The goal of this study is to develop a better understanding of the reactivity of reduced nitroimidazoles by studying the electrochemistry of simple nitroimidazoles in the presence of different acids. The acids change the reduction pathway of the compounds. It is believed that the intermediates in the reduction pathway of the compound lead to bacterial cell death. In particular, the compound investigated in this study is 1,2-dimethyl-5-nitroimidazole, which has a very similar structure to the widely used drug metronidazole.

Chart 1. Structures of 1,2-dimethyl-5-nitroimidazole, metronidazole



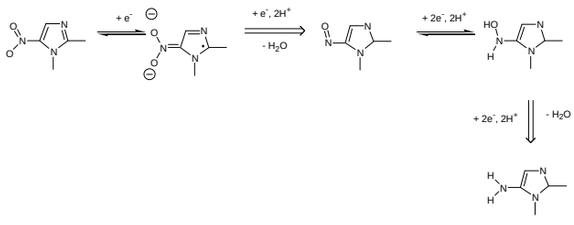
1,2-Dimethyl-5-Nitroimidazole



Metronidazole

1,2-dimethyl-5-nitroimidazole, a commercially made compound commonly used in veterinary medicine, has different substituents than that of metronidazole (Chart 1), but has an identical nitro group. Having a nitro group in common with metronidazole is important, since the reaction pathway proceeds with changes to the nitro group

Scheme 1. Reduction Pathway of 1,2-dimethyl-5-nitroimidazole



Scheme 1 shows the expected reduction pathway of 1,2-dimethyl-5-nitroimidazole. The first 1 electron reduction produces the radical anion intermediate. A second 2 electron, 2 proton reduction produces the nitroso compound with the loss of water. After the third 2 electron, 2 proton reduction the hydroxylamine is produced. The hydroxylamine can be further reduced into the amine compound.

There are several theories regarding the mechanism by which the nitroimidazoles induce cell death in protozoans. The first theory is that the radical anion causes DNA damage. A second theory is that the further reduced intermediates, either the nitroso (NO) or hydroxylamine (NHOH) compounds, react with thiols in the cell. This reactivity with thiols could cause a decrease in intracellular thiols and disrupt the cellular redox balance. A third theory is that the nitroimidazoles could react with cysteines on proteins, which would lead to the deactivation of proteins.

This study of 1,2-dimethyl-5-nitroimidazole shows that the reduction pathway differs from that of metronidazole, though both are similar in structure except for one substituent. In the CV's of the 1,2-dimethyl-5-nitroimidazole, there is a major product peak at potential of -0.75 V vs Fc. From previous studies, the nitroso compound has been ruled out as the source of this peak. Other hypotheses that the peak is due to nitrite or hydroxide can be ruled out since additions of nitrite and hydroxide indicate different behavior. Based on these findings, our current hypothesis is that the source of this peak may be the deprotonated hydroxylamine.

Two cycle scans and varied scan rate CV's of the 1,2-dimethyl-5-nitroimidazole produced no observable nitroso peaks, indicating that the 1,2-dimethyl-5-nitroimidazole undergoes additional reactions not outlined in Chart 1.

Acid addition has shown that cysteine reacts more with the 1,2-dimethyl-5-nitroimidazole than naphthol. Since both acids have the same pKa, it can be assumed that cysteine undergoes additional reactions consistent with the proposed reaction of thiols with further reduced intermediates. Comparing the results of the additions of cysteine to the 1,2-dimethyl-5-nitroimidazole versus cysteine additions to nitrobenzene in a related study, the 1,2-dimethyl-5-nitroimidazole seems to react faster with cysteine. Despite the similar redox potential of nitrobenzene to the 1,2-dimethyl-5-nitroimidazole and the fact that nitrobenzene undergoes similar reactions as the 1,2-dimethyl-5-nitroimidazole, nitrobenzene has no activity as a drug, and thus is not expected to exhibit significant reactivity with cellular thiols. If the action of the drug is through reaction with thiols as has been proposed, this may explain why 1,2-dimethyl-5-nitroimidazole is active as a drug while nitrobenzene is not.

Results so far with 1,2-dimethyl-5-nitroimidazole have increased our understanding of the compound's biological behavior. A greater understanding of this behavior will aid in the development of new types of drugs against parasitic and bacterial diseases.