REACTIONS OF HYDROXYALKYL RADICALS WITH NICKEL(II) AND COPPER(II) COMPLEXES OF 2-METHYL-5-NITRO-1H-IMIDAZOLE-1-ETHANOL: A STEADY-STATE GAMMA-RADIOLYSIS AND FLASH PHOTOLYSIS STUDY

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The yields for the loss of chromophore of Ni(II) and Cu(II) complexes of metronidazole, G(−Ni(II)M) and G(−Cu(II)M), reached almost zero when their aqueous solutions were γ-irradiated in the presence of 0.4 mol·dm⁻³ of MeOH, EtOH, i-PrOH and t-BuOH in aerated medium. However, under N₂O saturated conditions, these yields attained limiting values which suggests that the hydroxyalkyl radicals, derived from the alcohols by reaction with OH, react with the complexes in deaerated medium. But in aerated medium they react preferentially with O₂. The rate constants for the reactions of the different hydroxyalkyl radicals with the complexes have been determined by the flash photolysis technique and the plausible mechanisms for the reactions have been suggested.

Among the nitroheterocyclic compounds, metronidazole has received considerable attention both for its ability to act as a radiosensitizer¹⁻⁴ and its selective toxicity towards hypoxic cells.⁵,⁶ Metallation of the drug can increase its overall sensitizing effect by increasing its DNA binding ability and electron affinity.⁷⁻¹⁰ The transition metal ion complexes of Ni(II) and Cu(II) are known to bind to DNA¹¹⁻¹³ and some of them have been found to be good sensitizers of hypoxic cells.¹⁴⁻¹⁶ The radiosensitization by the complexes involves some kind of interaction between the complexes and the radicals generated in the target due to the action of radiation. Hence, it is important to study the interactions of different radical species which are likely to be generated in irradiated aqueous solutions with the complexes. The reactions induced by OH and e⁻aq with the Ni(II) and Cu(II) complexes of metronidazole have been studied previously.¹⁷,¹⁸

The radiosensitizing effect of the nitro heterocyclic drugs has been found to be related to the ability to capture an electron by the nitro group.¹⁹⁻²¹ Since the reactions of e⁻aq are usually studied in the presence of OH scavengers such as alcohols. It is important to study whether the hydroxyalkyl radicals generated by the reaction of OH
with an alcohol do have any interaction with the drug. In this paper we present evidence for the occurrence of reactions of the different hydroxyalkyl radicals with Ni(II)M and Cu(II)M. To elucidate the mechanism of such reactions, the reactions have been studied using both flash photolysis and steady state γ-radiolysis and the results obtained with the two complexes have been compared.

**Experimental**

*MATERIALS*: Metronidazole (obtained from Sigma) and all other reagents were of A.R. grade. The Ni(II) complex of metronidazole was prepared as its sulphate salt (molecular formula C₆H₉N₃NiO₇S), while the copper complex was prepared as the acetate salt (molecular formula CuC₁₀H₁₅N₃O₇). The methods of preparation of the Ni(II) and Cu(II) complexes of metronidazole, Ni(II)M and Cu(II)M, have been described earlier.¹⁷,¹⁸

*Gamma-irradiation*: Aqueous solutions of Ni(II)M and Cu(II)M (1 × 10⁻⁴ mol·dm⁻³) saturated with N₂O in the presence of different alcohols were exposed to a ⁶⁰Co γ-source. The dose rate 10 Gy/min was measured with the help of a Fricke dosimeter, taking \( G(Fe^{+3}) = 15.6 \).

*Analysis*: The loss of chromophore of Ni(II)M and Cu(II)M after irradiation in the presence of alcohols were determined spectrophotometrically at 320 nm and 315 nm, respectively, at different absorbed doses. The respective \( G \) values were determined from the linear slopes of the yield vs. dose plots. The formation of nitrite was tested with sulphanilic acid and 1-naphthylamine.²² Cu(I) was determined spectrophotometrically with neo cuproin by measuring the absorbance of its neo cuproin complex at 457 nm.²³

*Generation of hydroxyalkyl radicals flash photolytically*: The OH radicals were generated by flash photolysis of an aqueous solution of \( H₂O₂ \),²⁴ where the following reactions occur

\[
H₂O₂ + hv \rightarrow 2OH
\]

\[
OH + H₂O₂ \rightarrow HO₂ + H₂O
\]

\[
HO₂ + HO₂ \rightarrow H₂O₂ + O₂
\]

In the presence of alcohols, the generated OH radicals react with them resulting in the formation of the respective hydroxyalkyl radicals:

\[
RH + OH \rightarrow R + H₂O
\]