

DOCTORAL THESIS

A mechanistic study of the preferential photo-oxidation of the 5-CH₃ substituent of thymine and thymidine mediated by NH₄(VO(O₂)₂(5-NO₂phen))

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**A Mechanistic Study of the Preferential Photo-Oxidation of
the 5-CH₃ Substituent of Thymine and Thymidine
Mediated by NH₄[VO(O₂)₂(5-NO₂phen)]**

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Abstract

The photo-oxidation product profiles of thymine (T) and thymidine (dT) mediated by the $\text{NH}_4[\text{VO}(\text{O}_2)_2(5\text{-NO}_2\text{phen})]$ complex (VPNO₂, where 5-NO₂phen = 5-nitro-1,10-phenanthroline) were characterized and quantified using HPLC, GC-MS, ¹H (and ¹³C) NMR, ESI-HRMS and compared to those obtained using a well-studied photo-oxidant, 2-methyl-1,4-naphthoquinone, also known as menadione (MQ). A preferential oxidation of the 5-CH₃ substituent over the commonly observed oxidation of the electron-rich C5–C6 double bond of thymine was observed in the VPNO₂-mediated reaction, affording, for example, 78% of 5-formyl-2'-deoxyuridine (5-FodU) vs. 12% of thymidine glycol from the photo-oxidation of dT. Thymine/thymidine radical cation, $[\text{T}\bullet]^+$, and thymine/thymidine allyl radical, derived from the 5-CH₃ deprotonation of $[\text{T}\bullet]^+$, were shown to be the key intermediates in this reaction by transient absorption spectroscopy, EPR-spin trapping technique, product profile comparison among thymine and its analogs, namely, 5-ethyluracil and 5-isopropyluracil, together with the substrate kinetic isotope effects (KIE). ¹⁸O₂- and H₂¹⁸O-labeling experiments revealed a scrambling of the formyl oxygen in the 5-formyluracil (5-FoU) and 5-FodU products. This oxygen scrambling was shown to be due to a rapid hydration with the solvent water. The observed strong preference towards

5-CH₃ oxidation was interpreted to be the result of the formation of an association complex between T (and dT) and VPNO₂ (association constant $K_a \sim 10 \text{ M}^{-1}$) based on (1) the upfield shifts observed in the 5-CH₃ and H6 protons of T and dT during NMR titrations with VPNO₂; (2) product quenching in the presence of 5-trifluoromethyluracil (5-CF₃U), an effective competitor for the π -stacking interactions between VPNO₂ and T (and dT); (3) effect of VPNO₂ concentration on product profile; and (4) DFT modeling calculation of the π -stacked adduct of T and VPNO₂, where one of the 5-CH₃ hydrogens of T was positioned within hydrogen bonding distance ($d = 2.563 \text{ \AA}$) to one of the NO₂-oxygens of VPNO₂, which presumably facilitated the 5-CH₃ deprotonation of the thymine/thymidine radical cation generated from a primary one-electron transfer step, leading to the preferential formation of the 5-CHO products observed.

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