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Denaturation of Protein by Chlorine Dioxide: Oxidative Modification of Tryptophan and Tyrosine Residues†

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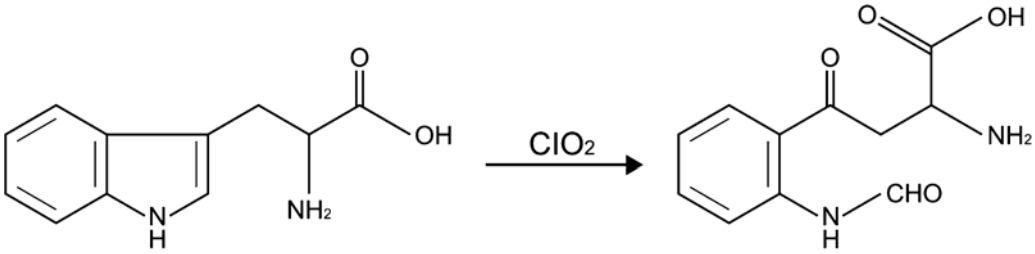
Abstract



Tryptophan *N*-Formylkynurenine

Oxychlorine compounds, such as hypochlorous acid (HOCl) and chlorine dioxide (ClO_2), have potent antimicrobial activity. Although the biochemical mechanism of the antimicrobial activity of HOCl has been extensively investigated, little is known about that of ClO_2. Using bovine serum albumin and glucose-6-phosphate dehydrogenase of *Saccharomyces cerevisiae* as model proteins, here I demonstrate that the antimicrobial activity of ClO_2 is attributable primarily to its protein-denaturing activity. By solubility analysis, circular dichroism spectroscopy, differential scanning calorimetry, and measurement of enzymatic activity, I demonstrate that protein is rapidly denatured by ClO_2 with a concomitant decrease in the concentration of ClO_2 in the reaction mixture. Circular dichroism spectra of the ClO_2-treated proteins show a change in ellipticity at 220 nm, indicating a decrease in α-helical content. Differential scanning calorimetry shows that transition temperature and endothermic transition enthalpy of heat-induced unfolding decrease in the ClO_2-treated protein. The enzymatic activity of glucose-6-phosphate dehydrogenase decreases to 10% within 15 s of treatment with 10 μM ClO_2. Elemental analyses show that oxygen, but not chlorine, atoms are incorporated in the ClO_2-treated protein, providing direct evidence that protein is oxidized by ClO_2. Furthermore, mass spectrometry and nuclear magnetic resonance spectroscopy show that tryptophan residues become *N*-formylkynurenine and tyrosine residues become 3,4-dihydroxyphenylalanine (DOPA) or 2,4,5-trihydroxyphenylalanine (TOPA) in the ClO_2-treated proteins. Taking these results together, I conclude that microbes are inactivated by ClO_2 owing to denaturation of constituent proteins critical to their integrity and/or function, and that this denaturation is caused primarily by covalent oxidative modification of their tryptophan and tyrosine residues.

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