

The Reaction of Nickel(II) Peptide Complexes with Molecular Oxygen

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Summary Tetra- and penta-peptide complexes of Ni^{II} consume O₂ in neutral solutions as the metal ion catalyses the oxidation of the peptide to give a number of products including amides of amino-acids and of peptides, oxo-acids, and CO₂.

TETRAGLYCINE (H₂NCH₂·CONH·CH₂·CONH·CH₂·CONH·CH₂·CO₂H) will form a square-planar complex with nickel(II) having an amine and three peptide nitrogens co-ordinated to nickel (the three peptide hydrogens are ionized).^{1,2} Titrations of nickel(II) and tetraglycine mixtures are slow to reach I-H equilibria.^{1,3} Subsequent absorption spectral

changes have been reported^{3,4} and were attributed to peptide hydrolysis.³ We also find that there are slow reactions associated with the acid-base equilibria. However, the additional reactions are due to the uptake of oxygen and the oxidation of the ligand.

Emphasis in past studies of O₂ reactions with metal complexes has been on metal ions such as Co^{II}, Cu^I, Fe^{II}, Cr^{II}, and Ir^I, which are able to form stable higher oxidation states.⁵ A number of cobalt(II) complexes, including those of some amino-acids and peptides, can interact reversibly with molecular oxygen.⁵

The significance of the present report is that nickel(II),

normally not easily oxidized,[†] is activated by peptide co-ordination so that it reacts with molecular oxygen and catalyses the oxidation of the ligand. We find similar reactions with Cu^{II}-peptide complexes.⁶ Pentaglycine and tetra-L-alanine also are oxidized, but triglycine is much slower to react. The maximum rate of O₂ consumption occurs at pH 7–8. The oxidations are much slower at pH 10–12 and do not occur below pH 6. The uptake of O₂ from solution can be fairly rapid. A 0.0125 M-nickel-tetraglycine solution at 37°, pH 8, will completely deplete the dissolved oxygen in about 3 min.

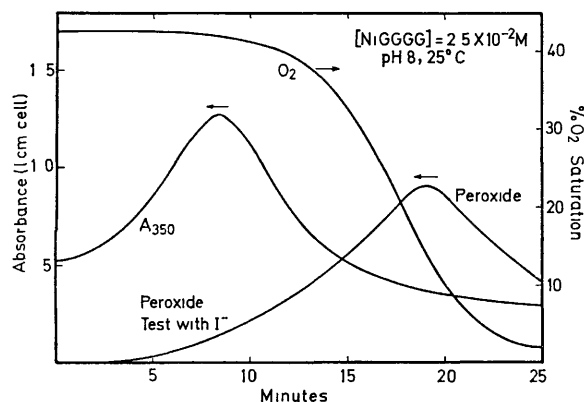


FIGURE Molecular oxygen reaction with nickel(II)-tetraglycine at pH 8. The % O₂ saturation is measured with an O₂ electrode. The absorbance is for the solution itself at 350 nm and the peroxide curve is for 1 ml portions in 10 ml of acidic potassium iodide.

The consumption of O₂ by nickel-tetraglycine, as shown in the Figure, has an induction period followed by an autocatalytic reaction. During the induction period a large absorbance increase occurs in the near-u v region. This absorption, which is also observed in the Cu^{II} reactions, is similar to the charge-transfer band found with the Co^{II}-O₂ complexes, but relatively little O₂ has been consumed when the absorbance (at 350 nm) reaches its maximum. It appears that the intermediate formed initiates other reactions of O₂. At the end of the reaction there is no absorption due to this species. Samples of the reaction mixture which were withdrawn and tested with iodide ion gave positive tests for peroxide. The peroxide concentration reaches a maximum during the period of most rapid O₂ consumption. The final products with either an excess of nickel-tetraglycine or with an excess of O₂ have no peroxide present.

In the pH range of maximum reactivity NiH₂L⁻ is the major tetraglycine (HL) species and NiH₁L is a minor species. The NiL⁺ complex appears to be unreactive and the NiH₃L²⁻ complex is much less reactive than the other complexes.

We postulate a reaction mechanism which begins with the formation of small amounts of a Ni^{II}-H₂L-O₂ complex. This initiates H atom or electron transfer to the co-ordinated oxygen and starts an autocatalytic reaction due to the formation of a peptide free-radical. Oxygen is consumed in a series of propagation steps similar to those postulated in the radiation-induced oxidation of amides.⁷ The peptide radical which initiates the reaction need not be the same as that formed in the propagation steps. There are a number of products (see the Table) indicating more than one point

TABLE

Products from nickel-tetraglycine reaction with O₂^a

Product	Moles % ^b
Triglycine amide ^c	38
Glycine amide ^c	21
Ammonia ^c	12
Diglycine amide ^c	5
Di- and tri-glycine (total) ^c	5
Glycine ^c	2
Carbon dioxide ^d	84
Glyoxylic acid ^e	26

^a 20 h O₂ bubbling in 0.1 M reactant at pH 8, 25°

^b Relative to tetraglycine destroyed (72%)

^c Determined with an amino acid analyser

^d Detected by glc, determined by absorption in Ascarite

^e After acid hydrolysis, detected by tlc and determined colorimetrically (N. S. T. Lui and O. A. Roels, *Analyt. Biochem.*, 1970, **38**, 202)

of oxidation. These products are similar to those formed in radiation studies of oxygenated peptide solutions.⁸ Some reaction product appears to inhibit the oxidation because 20–25% of the tetraglycine is always left.

The spontaneity, speed, and mild conditions of these metal peptide reactions with O₂ make them particularly interesting in relation to biological oxidations.

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[†] However, a Ni^{III} deprotonated amide complex has been recently reported (J. J. Bour, P. J. M. W. L. Birker, and J. J. Steggerda, *Inorg. Chem.*, 1971, **10**, 1202)

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³ M. K. Kim and A. E. Martell, *J. Amer. Chem. Soc.*, 1967, **89**, 5138

⁴ P. I. Chamberlin, Ph. D. Thesis, State University of New York at Buffalo, 1968

⁵ For a recent review see R. G. Wilkins, "Biomorganic Chemistry", *Adv. in Chem. Series*, Vol. 100, Amer. Chem. Soc., Washington, D. C., 1971, p. 111

⁶ G. L. Burce, E. B. Paniago, and D. W. Margerum, unpublished data

⁷ (a) I. Rosenthal, "The Chemistry of Amides", ed. J. Zabicky, Interscience, New York, 1970, p. 298, (b) O. H. Wheeler, *ibid.*, p. 320

⁸ W. Garrison, M. Kland-English, H. S. Sokol, and M. E. Jayko, *J. Phys. Chem.*, 1970, **74**, 4506