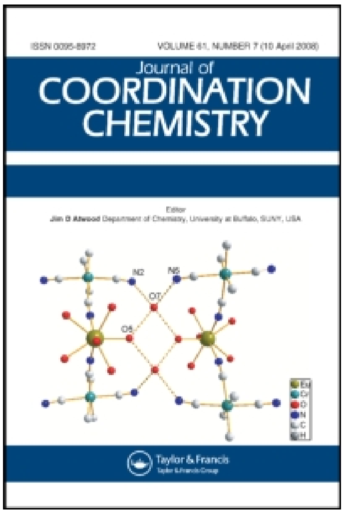

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EFFECT OF ZINC ON THE INTERACTION OF COPPER AND A SIMPLE PEPTIDE MOLECULE WITH HYDROGEN PEROXIDE

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Reaction of copper and of copper in presence of zinc with glycylglycine H_2Gg, $H_2NCH_2CONHCH_2COOH$ (in ratios 1:2 and 1:1:2, respectively), and an excess of hydrogen peroxide results in the formation of a novel peroxy complex $[Cu(O_2^{2-})\ (H_2Gg)_2].2H_2O$ and a mixed metal peroxo carbonate complex $[Cu,\ Zn(O_2^{2-})(CO_3)(H_2O)_4]$, respectively. A notable feature of the reaction is the facile decomposition of the peptide bond at room temperature on addition of zinc to the system.

KEYWORDS: Glycylglycine, hydrogen peroxide, copper, zinc

INTRODUCTION

The inherently stable peptide bond has a significant role to play in many important biological reactions and extensive work has been reported on enzyme-catalysed reactions involving large peptide molecules.[1] Considerable work has also been reported on the interaction of simple protein molecules with reactive oxygen species such as the superoxide ion and the hydroxyl radical (which are easily generated by Fenton-type reactions involving metals and hydrogen peroxide) with a view to understand the mechanism of degradation of cells and tissues.[2] Although synthesis and characterization of transition metal complexes containing biologically active ligands and peroxo groups have been reported extensively[3] little is known of the influence of an additional metal centre on the abovementioned peroxo complexes. The present work includes a study of the mutual influence of different metal ions on the abovementioned interactions, as it would be expected to be of interest not only due to multifaced coordination phenomena and redox behaviour of peroxo groups, but also to the relevance of these systems to many important metallo enzyme reactions.[3] We have reported earlier the effect of zinc on the interaction of some Cu(II) amino acid complexes with H_2O_2 and in this communication we report the effect of zinc on Cu(II)-glycylglycine (H_2Gg) interactions with H_2O_2.

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EXPERIMENTAL

All chemicals and reagents used were of AR grade; 30% aqueous H_2O_2 solution was used for reactions. The reactions were carried out in aqueous media under ambient conditions.

IR spectra were recorded with a FTIR Cygnus 100 spectrometer using CsI discs with both nujol and flurolube mulls. Diffuse reflectance spectra of solid complexes were measured on a Shimadzu 210-A spectrophotometer using $BaSO_4$ as reference standard in the region 200-800 nm. ESR spectra of powdered samples were recorded both at room and liquid nitrogen temperatures at X-band frequencies on a Bruker ESP300 spectrometer using DPPH as internal field marker. Thermogravimetric (TG) measurements were carried out in air on a Shimadzu DT-30 micro TG instrument, with the sample weight in the 10 mg range. Cyclic voltammograms of aqueous solutions of the compounds containing potassium nitratge (KNO_3)(*ca* 0.1 mol dm^{-3}) as background electrolyte were recorded using a PAR 174 polaragraphic analyser. All measurements were carried out under nitrogen atmosphere at room temperature, with a dropping mercury working electrode, platinum wire auxilliary electrode and saturated Hg/Hg^{2+} reference electrode.

Copper and zinc were determined by the atomic absorption method, C, H and N were determined by microanalysis. Peroxo oxygen atoms (O_2^{2-}) were determined by the ceric sulphate method.[4]

$[Cu(O_2^{2-})(H_2Gg)_2]2H_2O$, *1*

To an aqueous suspension of copper metal powder (1 mmol), an aqueous solution of glycylglycine (2 mmol) was added along with about 3 cm^3 of 30% H_2O_2 and the mixture stirred at room temperature. Most of the copper dissolved within 30 min., giving a blue solution, which slowly turned blueish green. However, complete dissolution of copper powder was effected by stirring the solution for about three hours. The clear, bluish green solution, after filtration, was dried over P_2O_5 *in vacuo* when a dark green compound was isolated. The compound decomposed with melting at 165–170°C. Analysis, calculated for $CuC_8N_4H_{20}O_{10}$: Cu, 16.06; C, 24.27; N, 14.15; H, 5.05; O_2^{2-}, 8.09%. Found: Cu, 16.77; C, 24.5; N, 14.60; H, 4.7; O_2^{2-}, 7.95%. IR absorption bands: 3410 (br, s), 3252 (br,m), 1665 (br, s), 1591 (br,s), 1482 (w), 1445 (w), 1379 (br), 613 (br, m), 470 (br,m).

$[Cu,Zn(O_2^{2-})(CO_3)(H_2O)_4]$, *2*

To the reaction mixture containing an aqueous suspension of copper and zinc (1 mmol each) and glycylglycine (2 mmol), about 5 cm^3 of 30% hydrogen peroxide solution was added with stirring at room temperature. The reaction started exothermically and therefore warranted cooling. For complete dissolution of both copper and zinc powders, continuous stirring of the mixture was carried out for about 72 h. It was observed that all copper powder dissolved first, giving a dark blue supernatant, while zinc dissolved slowly giving simultaneously a green precipitate and decreasing the intensity of the blue supernatant. While at the beginning of the reaction no ammonia gas evolution was observed, after a lapse of about 24 h, slow evolution of ammonia gas (with increased intensity later) was observed. Ammonia gas was qualitatively identified by its smell and by testing with pH paper placed at the mouth of the vessel. The precipitate was filtered, washed with water, acetone and dried *in vacuo*. The compound on heating decomposed at 180°C without melting. Analysis, calculated for $CuZnCH_3O_9$: Cu, 21.69; Zn, 22.32; C, 4.09; H, 2.73; O_2^{2-}, 10.92%. Found: Cu, 21,75; Zn, 22.70; C, 3.90; H, 2.3; O_2^{2-}, 11.10%. IR absorption bands : 3300 (br,vs), 1635 (br,s), 1471 (br,vs), 1415 (br,vs), 920 (w), 892 (m), 845 (m), 769 (w), 613 (s), 477 (s), 466 (s), 322 (w).

RESULTS AND DISCUSSION

While **2** is stable in air at room temperature, compound **1** is hygroscopic. Both are insoluble in common organic solvents and very sparingly soluble in water. They decompose on heating beyond 180°C. The homogeneity of **2** was ascertained by comparing its properties with that of corresponding individual carbonates (as no XRD data could be used due to the amorphous nature of **2**). Compound **1** could be easily differentiated by its hygroscopic nature and colour (green) from that of the corresponding non-peroxo Cu(II)[5,6] glycylglycine complex: a stable and water soluble, dark blue compound.

ESR spectra of powdered **1** and **2** were measured both at room temperature (298 K) and liquid nitrogen temperature (77 K). Compound **1** exhibits an isotropic broad resonance signal at both the temperatures with a g_{iso} value of 2.138. An axial spectrum was reported for the corresponding non-peroxo compound[7–9] which also has different physical appearance, properties and g value, thus suggesting a different coordination environment and geometry around Cu(II) in **1**. The negligible variation of ESR spectrum at 77 K compared to that at 298 K, probably indicates a static stereochemistry of Cu(II) in **1**. Compound **2** was found to be diamagnetic and no ESR signal was observed.

The diffuse reflectance spectrum of **1** shows a broad absorption band centred around 680 nm, which, on the basis of its intensity and position, can be attributed to Cu(II) d-d transition, and a very high intensity charge transfer band at 350 nm in the region reported for $O_2^{2-} \rightarrow Cu(II)$.[10,11] Compound **2** exhibits a broad absorption peak at 730 nm due to a d-d transition along with a CT band at 350 nm due to either $O_2^{2-} \rightarrow Cu(II)$ or $CO_3^{2-} \rightarrow Cu(II)$. [12] The considerable decrease in d-d transition energy in **2** as compared to **1** is in accord with the replacement of coordinating N atoms of Gg by O_2^{2-} and CO_3^{2-} groups.[13] The positions of the d-d absorption bands in **2** are similar to the bands observed in synthetic mixtures of Cu and Zn carbonates.

The IR spectrum of **1** exhibits only two strong bands in the 1700-1500 cm^{-1} region, in contrast to the structurally characterized simple Cu(II) glyclyglycine[14] complex in which terdentate coordination of Gg is established (5 strong bands in that region). Bands at 1665 cm^{-1} and 1591 cm^{-1} for **1** are attributable to deformation modes of (NH_3^+) and assymetric stretching modes of (COO^-) of glycylglycine in the zwitterionic form[15,16] and the broad bands at 3410 cm^{-1} and 3252 cm^{-1} are assigned to lattice water stretching vibration and $\nu(NH_3^+)$ modes in accordance with reported data.[17] The IR spectrum of **1** clearly indicates the presence of a coordinated peroxo (O_2^{2-}) group due to the $\nu(O_2^{2-})$ band at 765 cm^{-1} which is absent in the corresponding non-peroxo compound and is in the region reported for the intra-peroxo stretch in many similar types of peroxo complexes.[3] The absence of IR bands attributable to superoxide or monodentate bridging peroxo stretching vibrations in the expected regions[19] suggests a side-on bidentate coordination, which is also corroborated from the red shift of the d-d transition band (λ_{max}) of **1** compared to the corresponding non-peroxo compound.[18] If (O_2^{2-}) is acting as a terminal bidentate ligand (C_{2v}),then two more stretching vibrations, *viz*, ν_{assym} ($\mathrm{Cu}{<}^{O}_{O}$) and ν_{sym} ($\mathrm{Cu}{<}^{O}_{O}$) are expected. Accordingly, medium broad bands at 613 cm^{-1} and 470 cm^{-1} are tentatively assigned to those modes due to their absence in the corresponding non-peroxo compound[18] and free ligand. These are in accord with data for other Cu peroxo complexes.[19,20]

Compound **2** shows IR stretching bands attributable to a coordinated carbonate group[21–23] at 1471 cm^{-1}, 1415 cm^{-1} (ν_3), 892, 845 cm^{-1} (ν_2), 787, 769 cm^{-1} (ν_4). The coordination of a water molecule is identified by the $\nu(H_2O)$ band at 3320 cm^{-1}, δ (H_2O) at 1635 cm^{-1} and $T(H_2O)$ at 613 cm^{-1} [17] (TGA results also suggests coordinated water molecules, *vide infra*). The absence of any strong absorption bands in the 1550-1600 cm^{-1} and 1250-1300 cm^{-1} regions (ν_3 mode of CO_3^{2-}) suggests that the CO_3^{2-} group functions as a non-bridging bidentate.[23] However, unambiguous assignments of $\nu(O_2^{2-})$ could not be made due to overlap of CO_3^{2-} bands in the 700–900 cm^{-1} region.

Thermogravimetric analysis of **1** in air shows a gradual weight loss from 50°C to 800°C, beyond which the weight remains constant to 1000°C. The black residue was identified as cupric oxide by XRD. Total loss upto 750°C is 76.7% (expected 79.8%). Compound **2** shows a total weight loss of 29.5% to 500°C. No weight loss was observed before 150°C and beyond 500°C. The residue was identified as a mixture of Cu and Zn oxides and carbonate by XRD (expected total loss 30.04%). The TGA results corroborate the stoichiometric formulae. Initial weight loss corresponding to 4 water molecules at greater than 150°C for **2** in contrast to an initial weight loss corresponding to two water molecules in the 50-100°C range for **1** supports the coordination of water molecules and presence of lattice water molecules (inferred from the IR) in **2** and **1**, respectively.

Cyclic voltammograms were recorded at DME in the + 0.2 to − 2.0 V range (0-2 μA) with reference to an Hg/Hg^{2+} electrode at a scan speed of 50 mV/sec, while the differential pulse polorograms were recorded at a slower scan rate of 5 mV s^{-1}. Compound **1** exhibits one cathodic peak at − 0.38 V with no anodic peak in the reverse scan. Compound **2** shows two cathodic peaks at − 0.2 V and -1.02 V and one anodic peak at − 0.98 V in the reverse scan. Cyclic voltammograms of blank solutions containing 30% aqueous H_2O_2 were also taken along with the compounds for comparison of data. The single cathodic peak at **1** could be attributed to reduction of Cu(II)-Gg ion in accordance with the reported electrochemical behaviour of the corresponding non-peroxo compound[24–26] and also suggests that it is an irreversible phenomenon. In case of **2** the cathodic peaks could be attributed to reduction of Cu(II) and Zn(II) ions (identified by the change in intensity of the reduced peak on adding corresponding individual Cu(II) and Zn(II) solutions). The considerable increase in cathodic behaviour of Cu(II) in **1** compared to **2** is in accordance with the change in the ligand environment and coordination geometry around Cu(II) and suggests that the glycylglycine molecule exerts stabilizing effect on reduction of Cu(II) to Cu(I) state. The anodic oxidation peak observed in the reverse scan for **2** indicates the oxidation of Zn.

To summarise the preceding discussion of **1**, IR data suggests the presence of a coordinated peroxide group in a side-on, bidentate fashion (its presence is also confirmed by analytical determination) and the absence of coordinated water molecules. It is likely that glycylglycine functions as a bidentate ligand through coordination of carboxyl and imide groups. ESR and electronic spectral data is suggestive of an octahedral coordination around Cu(II). Thus, **1** may be formulated as $[Cu(O_2^{2-})(H_2Gg)_2]2H_2O$.

For the mixed metal peroxo carbonate **2**, λ_{max} at 730 nm is in the range reported for a distorted octahedral CuO_6 chromophore.[27] The diamagnetic nature of **2** suggests considerable antiferromagnetic interactions between adjacent Cu(II) centres. IR data supports bidentate (non bridging) coordination of carbonate and peroxo groups. Thus **2** may be represented by structural formula as $[Cu, Zn(O_2^{2-})(CO_3)(H_2O)_4]$.

Since our earlier studies[3] indicated that small amino acid molecules like glycine and aspartic acid could be converted to carbonate by deamination on addition of Zn to the Cu - amino acid - H_2O_2 system at room temperature, the work discussed in this paper was undertaken with a view to ascertain whether same effect could be observed in the case of simple peptide molecules like glycylglycine. Although the peptide bond is relatively stable and difficult to break under ordinary conditions, this study clearly shows the novel effect of Zn on the abovementioned interactions. This novel phenomenon may be due to metal ion cleavage of the OH-OH bond of H_2O_2, liberating powerful oxidative species (Fenton type), which react immediately with the substrate, or be due to metal ion polarisation of the $C=O$ bond of the peptide group with consequent increase of its electrophilic character[28] (or both effects). It was reported that in presence of dioxygen, amino acids are converted to keto acids *via* oxidative deamination.[29,30] Hence it is of interest to note that in presence of Cu, Zn and H_2O_2 the simple amino acids/peptide undergoes conversion to carbonate *via* deamination.

This study demonstrates interesting and perhaps significant results which may be of relevance to some important biochemical reactions; the small peptide molecule glycylglycine converts to carbonate in the presence of Zn, Cu and H_2O_2 by deamination. In the absence of zinc, a novel Cu peroxy glycylglycine complex is formed. This signifies the effect of Zn in the interaction of Cu-peptides with H_2O_2.

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