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Superoxo radical scavenging action by common analgesic drug paracetamol: A model kinetic study

Bula Singh [a,*], Ranendu Sekhar Das [b], Rupendranath Banerjee [b], Subrata Mukhopadhyay [b]

[a] Department of Chemistry, Visva-Bharati, Santiniketan 731 235, India
[b] Department of Chemistry, Jadavpur University, Kolkata 700 032, India

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ABSTRACT

In acid perchlorate media ($[H^+]$ = 1.0–3.0 M), each mole of paracetamol, $HOC_6H_4NHCOCH_3$ (APAP), at ambient temperature quantitatively reduces two mole of the metallo-superoxo complex, μ-superoxo-bis[pentaamminecobalt(III)]$^{5+}$, $[(NH_3)_5Co(III)(\mu\text{-}O_2)Co(III)(NH_3)_5]^{5+}$ (**1**). Here, complex **1** is reduced to $[(NH_3)_5Co(OH_2)]^{3+}$, Co^{2+}, O_2 and NH_4^+ and APAP itself is oxidised to quinone oxime and acetic acid. With a large excess of APAP over **1**, the reduction follows first-order kinetics. The observed first-order rate constant (k_o) increases linearly with increasing $[H^+]$ as well as with T_{APAP} (T_{APAP} being the analytical concentration of APAP). The protonated form of APAP, *viz*. $APAPH^+$ seems to be the kinetically reactive reductant species. The enrichment of aqueous reaction media with D_2O retards the reaction and thus it appears that the reaction proceeds through an electroprotic mechanism. A relatively small $\Delta H^{\neq}$ (57 ± 2 kJ M^{-1}) and moderately negative $\Delta S^{\neq}$ (−68 ± 8 JK^{-1} M^{-1}) supports a compact transition state.

1. Introduction

Oxygen, as it is the terminal oxidant in respiration cycle in aerobic organisms, is one of the key factors to sustain higher forms of life. The singlet oxygen ($^3O_2$), present in air is less reactive than its different reduced derivatives [1] like superoxide (O_2^-), peroxide (O_2^{2-}) and hydroxyl radical (·OH). These radicals having independent existence with one or more unpaired electrons form a part of reactive oxygen species (ROS) [2]. The limited production of ROS in normal physiological and metabolic processes plays crucial roles in respiratory chain, immune systems and signalling pathways [3–7]. In biological systems ROS are also deliberately generated through oxidative burst by phagocyte NADPH oxidase to defend against harmful microbial pathogens. But several exogenous and endogenous reasons may cause overproduction of ROS to tip off the balance between the former and the natural antioxidant defence systems [8] fostering severe damages to all the essential bio-macromolecules, like, carbohydrates, proteins, lipids and nucleic acids [9–16] resulting in metabolic and cellular disorders. This alarming situation, called 'oxidative stress' may even lead to critical diseases like cancer, heart problems, Alzheimer's or Parkinson's disease [17–26]. In present day life the deleterious effect of ROS and other xenobiotics on almost every living system in all biospheres resulting from the mounting level of pollutions due to different anthropogenic activities have been a major concern for all [27–31].

In this work we have chosen a metal bound superoxo species $[(NH_3)_5Co(III)(\mu\text{-}O_2)Co(III)(NH_3)_5]^{5+}$ (**1**) as a suitable model for ROS and studied the kinetics of reduction of **1** by acetaminophen (abbreviated as APAP which is N-acetyl-4-aminophenol) [32,33]. APAP is one of the most common water soluble analgesic drugs which has been reported to inhibit the formation of ROS rather than eliminating it [34–36]. However, we have observed that APAP can effectively reduce and mineralize the superoxo complex **1**. The motivation of the study comes from the fact that it may help to open up the possibility of administering the common drugs of the same genre as APAP in efficiently reducing the ROS toxicity.

2. Experimental

2.1. Materials

Cobalt(II) chloride hexahydrate (BIOSOL), ammonia (Merck), ammonium peroxodisulfate (Merck), orthophosphoric acid (Merck), perchloric acid (Merck), acetaminophen (Aldrich), sodium perchlorate (Aldrich), and deuterium oxide, D_2O (Aldrich, 99%) were used as received. Doubly distilled water was used throughout the experiments. Perchloric acid was standardized against standard sodium hydroxide solution in the usual way [37].

* Corresponding author. Tel.: +91 94331 63075; fax: +91 33 2414 6223.
E-mail addresses: singhbula@rediffmail.com (B. Singh), ju_subrata@yahoo.co.in, smukhopadhyay@chemistry.jdvu.ac.in (S. Mukhopadhyay).

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2.2. Preparation and characterization of complex **1**

The metallo-superoxide complex (**1**) was synthesized following a literature process [38] with necessary modifications [39]. First, a μ-peroxo-cobalt(III) complex is prepared from $CoCl_2$, $6H_2O$ and then it is oxidized to superoxo complex by ammonium peroxodisulfate. The pentachloride salt of **1** was converted to perchlorate salt by the following procedure: pentachloride salt was dissolved in 40% orthophosphoric acid and filtered; $HClO_4$ (70%) was added drop wise to the filtrate to precipitate the perchlorate salt. Pure perchlorate salt of **1** was obtained by recrystallization from 10% $HClO_4$.

Complex **1** was characterized by UV–Vis absorption and FTIR study. Complex **1** shows characteristic UV–Vis absorption peak at 481 nm and 670 nm and the purity of **1** was ascertained from the molar extinction coefficient (ε) value at 670 nm (ε in $M^{-1}\,cm^{-1}$, found 860; reported 890 [38]). FT-IR spectrum for complex **1** (Fig. 1) shows the main absorption bands at 1626 (s), 1336 (s) and 1321 cm^{-1} (s) for d_{as} (NH_3) and 835 cm^{-1} (s) for r_r (NH_3) which are in close agreement with the literature values for similar di-bridged metallo superoxide complex (d_{as}, asymmetric deformation vibration; r_r rocking vibration) [40]. The presence of the peak at 1086 cm^{-1} (s) confirms the presence of the bridging superoxo group [41].

2.3. Instrumentation

Absorbance and UV–Vis spectra were recorded using a Shimadzu spectrophotometer (UV-1700) with 1.00 cm quartz cuvettes equipped with electrically controlled thermostat. Fourier Transform Infrared (FTIR) data were collected using a Shimadzu FT-IR 8400S. Mass spectrometry (ESI positive mode) was done by micro mass Q-TOF micro (LCMS) spectrometer. ^{13}C NMR spectra were recorded at 400 MHz Bruker spectrometer using tetramethylsilane as an internal standard.

2.4. Kinetics

Both complex **1** and APAP are stable in aqueous acid media at room temperature and APAP is not hydrolysed under the kinetic conditions employed [42–44]. But the addition of APAP to **1** in acid perchlorate media (1.0–3.0 M) gradually decreased the absorbance of **1**. A representative UV–Vis spectral change of **1** with time is shown in Fig. 2. The kinetics were studied in acid media at 25.0 ± 0.1 °C and at a fixed ionic strength, I = 3.0 M, maintained with $NaClO_4$, unless mentioned otherwise. A large excess of APAP over **1** were maintained in all the kinetic runs to ensure pseudo first-order conditions. The reacting solutions were prepared by the addition of measured amount of acidic solution of **1** and sodium perchlorate followed by the addition of freshly prepared aqueous solution of APAP. The reaction was followed by the decrease in absorbance at 670 nm (Fig. 3), the characteristic visible absorption peak of **1**, where all other species in the reaction mixture are transparent. The observed first-order rate constants (k_o) were derived using non-linear standard least-squares fit to the first-order equation of such decay with time.

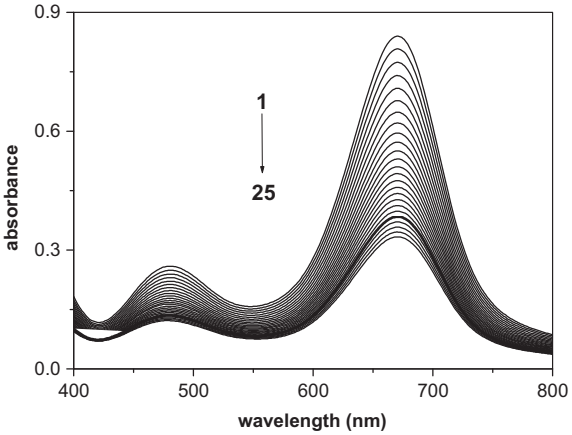

Fig. 2. Observed spectral changes when **1** was reduced with APAP. Spectra were recorded at an interval of 2 min. Condition: [**1**] = 1.0 mM; T_{APAP} = 10.0 mM; [H^+] = 1.5 M; I = 3.0 M; T = 25.0 ± 0.1 °C. Spectrum 1 represents the pure complex **1**.

2.5. Stoichiometry

Estimation of unreacted APAP using conventional analytical techniques [42–44] as an aftermath of the reaction when APAP was used in sufficient excess over **1** was not convincing because the results were random and inconsistent probably due to interference from reaction products. Thus, stoichiometric determinations were carried out by titrating the metallosuperoxide **1** with different amount of APAP. For this purpose, several sets of **1** with varying concentrations were reacted with deficit amounts of APAP and when the reactions reached equilibrium, absorbance of the reaction mixtures at 670 nm (A_e) were noted whence unreacted [1] was determined from the difference between the absorbance of the pure **1** (A_0) and A_e (Table S1, see Supplementary information).

The reduction products from **1** were identified and quantified from the absorbance of the final spectrum of the reaction mixture

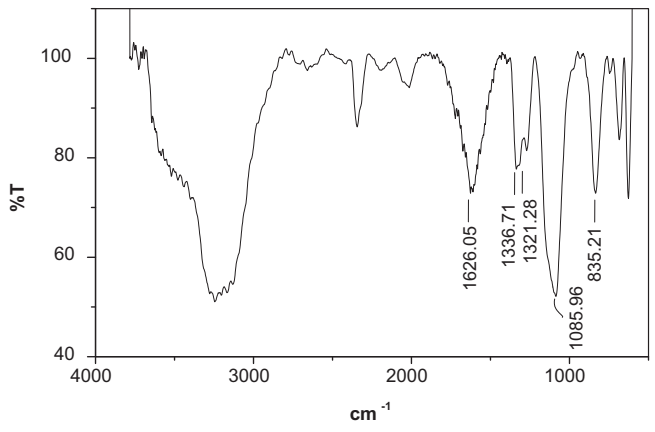

Fig. 1. FT-IR spectrum of metallo-superoxo complex **1**.

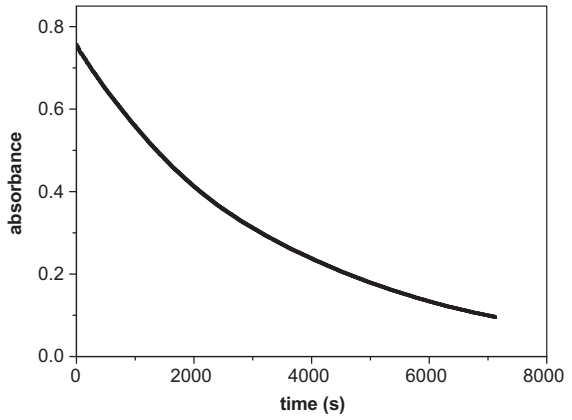

Fig. 3. Reduction of **1** by APAP follows first-order kinetics. Condition: [**1**] = 1.0 mM; T_{APAP} = 10.0 mM; [H^+] = 1.5 M; I = 3.0 M; T = 25.0 ± 0.1 °C.