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Review

Ru^{III}(EDTA) mediated activation of redox signalling molecules

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ABSTRACT

The different Ru^{III}(EDTA) complexes ($EDTA^{4-}$ = ethylenediaminetetraacetate) formed in aqueous solution are prospective in many ways and have unique features that make them significant for biochemical applications. The advancement of Ru^{III}(EDTA) mediated bioinorganic reactions in terms of unravelling their mechanistic information has not been systematically reviewed to date. Hence, the subject of this review comprises the most recent advances in Ru^{III}(EDTA) chemistry with regard to bioinorganic reaction mechanisms involving Ru^{III}(EDTA) complexes. This review mainly covers the application of Ru^{III}(EDTA) complexes as catalysts or mediators in homogeneous reaction systems for the activation of redox signalling molecules, viz. H_2O_2, thiols (RSH), NO and H_2S, highlighting the authors' own recent studies on such catalytic systems. Details of the reaction mechanisms have been revealed for peroxide activation, thiol oxidation, S-nitrosylation of thiols, and dioxygen activation involving Ru^{III}(EDTA) complexes. This review also covers progress in unravelling the mechanism of Ru^{III}(EDTA) mediated oxidation of thiols using $KHSO_5$ as a precursor oxidant.

Contents

1. Introduction

Redox signalling is a process of utmost importance for the detection of damaged cells, as well as repair, and replacement of damaged cells inside tissue. The redox signalling molecules can be classified into two categories: (i) reactive oxygen species (ROS) and (ii) reductive species (RS). It is now widely accepted that low-molecular weight molecules like hydrogen peroxide (H_2O_2),

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cellular thiols (RSH), nitric oxide (NO) and hydrogen sulphide (H_2S) are known to act as the key molecules in various intracellular signalling processes and metabolic regulation [1–3]. The present review elaborates on the application of Ru^{III}(EDTA) complexes in the activation of the aforementioned signalling molecules, and demonstrates the catalytic role of the ruthenium complexes as functional models in redox reactions of such molecules. Since kinetic information of such redox processes appears to be of great significance to rationalize the need of preferential reaction pathway(s) that meets the signalling criteria, the discussion in this review will focus on the kinetics and mechanism of the Ru^{III}(EDTA) mediated activation and catalytic transformation of the aforementioned signalling molecules, with representative achievements from our most recent studies.

2. Background chemistry

Although, examples of EDTA complexes of other metals, M (M = Mn [4], Cu [5], Ni [6], Co [7], Cr [8], V [9], Ti [9] and Ir [10]) are available in the literature, they were not exhaustively studied to explore their prospective in different applications, unlike their ruthenium analogue. However, the picture is somewhat different as regards the Fe(EDTA) complex. Reports on the use of the Fe (EDTA) complex to model the reactivity of catalytic species involved in biological systems, are available in the literature [11,12]. The Ru(III) complex containing the EDTA chelate is of continued interest [13–15] in its own right and in the context of its catalytic ability to mimic enzymatic reactions. The kinetic lability of the Ru^{III}(EDTA) complex towards water displacement reactions, and a range of accessible and stable oxidation states, make Ru (EDTA) complexes attractive candidates for catalytic applications. In the recent past, the significance of Ru^{III}(EDTA) complexes towards contributing to the mechanistic understanding of biologically important reactions, has been further explored. The aim of this contribution is to bring into focus such activities of Ru^{III}(EDTA) that are of particular relevance for biological systems, and have not been reviewed hitherto.

The donor character of the 'EDTA' ligand is quite comparable to many biological enzymes, which make use of carboxylate and amine donors from amino acids to bind to the metal centre. The 'EDTA' ligand forms a very stable 1:1 metal complex with ruthenium. The $K[Ru^{III}(HEDTA)Cl]$ complex was isolated as a pale yellow solid. It rapidly converts into the $[Ru^{III}(HEDTA)(H_2O)]$ species when dissolved in water [16,17]. It was shown earlier [16,17], and later established by crystallographic studies [18], that the 'EDTA' ligand functions as a penta-dentate ligand towards Ru(III) with a protonated pendant acetate arm. The sixth coordination site of the ruthenium centre in the Ru^{III}(EDTA) complex is occupied by a water molecule at low pH or by an hydroxide ion at high pH (see Scheme 1). The pK_a values related to the acid-dissociation equilibria of the pendant carboxylic acid arm and the coordinated water molecule are 2.4 and 7.6, respectively, at 25 °C [16,17]. Electrochemical studies of the Ru^{III}(EDTA) complex have shown that the electron transfer process is rapid and reversible for the Ru^{III}/Ru^{II} couple ($E_{1/2}$ = −0.04 V vs. NHE) [16].

The spectrum of the Ru^{III}(EDTA) complex in aqueous solution is featureless in the visible region, however, a sharp peak at 283 nm ($\varepsilon_{max} = 2800 \pm 50\ M^{-1}\ cm^{-1}$) and a shoulder at 350 nm ($\varepsilon_{max} = 680 \pm 10\ M^{-1}\ cm^{-1}$) are observed in the UV region [16,17]. The $[Ru^{III}(HEDTA)H_2O]$ complex is remarkably labile towards substitution in the pH range 4–6, since it then exists in its most labile form, $[Ru(EDTA)(H_2O)]^-$ [16,17]. An associative interchange (I_a) pathway involving the pendant carboxylate group, was proposed to be responsible for its remarkable lability towards substitution reactions [19]. It is noteworthy that though Ru(III) is the predominant oxidation state under physiological conditions, Ru(II), Ru(IV) and Ru(V) oxidation states are readily accessible in the presence of biological reductants (e.g., ascorbate or thiols) [14] or oxidants (e.g. O_2 or H_2O_2), respectively [14].

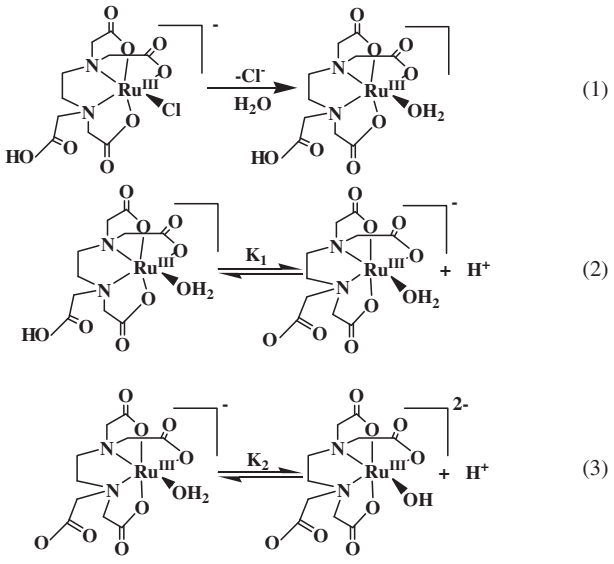
3. Ru^{III}(EDTA) mediated activation of H_2O_2

Hydrogen peroxide (H_2O_2) is an important relatively stable non-radical reactive oxygen species (ROS) [20]. At low concentrations, H_2O_2 acts as a signalling molecule involved in the regulation of specific biological/physiological processes [21]. The activation of hydrogen peroxide is highly intriguing where enzymes with exceptional performance have challenged chemists for many decades to match or improve them.

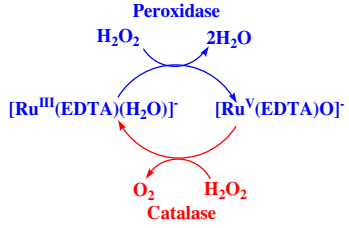
There are two major classes of peroxide-activating enzymes, the peroxidases and the catalases, both of which are primarily haeme-based. Peroxidases transfer two oxidation equivalents from H_2O_2 to reducing substrates [22,23], whereas catalases promote the disproportionation of H_2O_2 into dioxygen and water [24,25]. The two reactivity channels are often in competition in the chemistry of a single enzyme. Thus, the catalase–peroxidase enzymes perform both functions [26–28]. The Ru^{III}(EDTA) complex can mimic such H_2O_2-metabolizing enzymes as demonstrated in Scheme 2.

3.1. Peroxidase activity of the Ru^{III}(EDTA) complex

The reaction of $[Ru^{III}(EDTA)(H_2O)]^-$ with H_2O_2 results in the rapid formation of the hydroperoxo species, $[Ru^{III}(EDTA)(OOH)]^{2-}$ typically showing a band at 425 nm (Fig. 1a) [29]. The kinetic trace at 425 nm (Fig. 1b) clearly demonstrates the intermediate nature of the species formed at this wavelength.



Scheme 1. Acid-dissociation equilibria of $[Ru^{III}(HEDTA)(H_2O)]$.



Scheme 2. Peroxidase and catalase activities of $[Ru^{III}(EDTA)(H_2O)]^-$.