



Concerted two-proton-coupled electron transfer from catechols to superoxide via hydrogen bonds



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ABSTRACT

The reaction mechanism between electrogenerated superoxide ($O_2^{\bullet-}$) and catechols as an important functional group of polyphenolic antioxidants was investigated based on electrochemical and electron spin resonance (ESR) spectral measurements and supported by density functional theory (DFT) calculations. The quasi-reversible $O_2/O_2^{\bullet-}$ redox is significantly affected by the presence of a catechol ($CatH_2$), showing the associated reaction, $O_2^{\bullet-} + CatH_2 \rightarrow H_2O_2 + Cat^{\bullet-}$. We proposed that this reaction is governed by one-step one-electron transfer concerted with two phenolic proton movement after initial formation of the hydrogen-bonded complexes between $O_2^{\bullet-}$ and $CatH_2$, which we refer to as concerted two-proton-coupled electron transfer (2PCET) reactions, based on the energetics and kinetics of the reaction obtained by B3P86/6-31+G(d,p) and B3LYP/6-31+G(d,p) calculations, respectively. The concerted 2PCET mechanism for the reaction between $O_2^{\bullet-}$ and $CatH_2$ is demonstrated by the finding that a signal of the $O_2^{\bullet-}$ and HO_2^{\bullet} adducts of 5,5-dimethyl-1-pyrroline-*N*-oxide as a spin trap completely disappears in the ESR spectra of the electrogenerated $O_2^{\bullet-}$ solution containing $CatH_2$. This indicates that the concerted 2PCET reaction is important for the analysis of polyphenolic antioxidants containing an *o*-diphenol ring.

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1. Introduction

It is well recognized that the beneficial properties of polyphenols are primarily related to their antioxidant activities, which are associated with their protective role by interrupting chain reactions, such as lipid peroxidation [1,2]. The catechol ($CatH_2$) moiety is considered an important functional group of polyphenolic antioxidants, such as catechin and quercetin [1–3]. Therefore, numerous studies have investigated the radical-scavenging reaction mechanism with polyphenols containing an *o*-diphenol ring experimentally and theoretically [4–29]. However, whether proton-coupled electron transfer (PCET) mechanisms, i.e., sequential PCET, H-atom transfer (HAT) involving concerted PCET [25–28], and sequential proton loss electron transfer (SPLET) [23,24], are possible remains controversial.

The initial step in many biological free radical reactions is the endogenous production of superoxide ($O_2^{\bullet-}$), an important biological intermediate in living cells [19,20]. Although $O_2^{\bullet-}$ is

not particularly reactive and does not cause significant oxidative damage, it is a very toxic biological agent with some implications. The $O_2^{\bullet-}$ molecule acts as a precursor to other oxidizing agents such as singlet oxygen and peroxynitrite and other highly reactive molecules. The major mechanism for the reaction between $O_2^{\bullet-}$ and phenolic compounds in aprotic solvents such as DMF has been well recognized as a proton-transfer pathway because only one OH is involved [30–34]. Some studies suggest the HAT pathway for the reaction of phenolic compounds against $O_2^{\bullet-}$ generated in an enzymatic system by measurement of IC_{50} values [21,22,29]; however, such studies provide very limited information about the mechanisms involved. Only a few papers describe the $O_2^{\bullet-}$ -scavenging mechanism as a PCET pathway involving HAT, concerted PCET, and SPLET rather than as a proton-transfer pathway [24,26–28]. Studies have reported that the *o*-diphenol ring is involved in the HAT mechanism on the basis of the characteristics of cyclic voltammograms of the $O_2/O_2^{\bullet-}$ redox couple in the presence of phenolic compounds [26–28]. Recent calculations of reaction enthalpies show that there is no mechanism suitable for the $O_2^{\bullet-}$ scavenging reaction by some *o*-diphenol compounds, and the SPLET mechanism for the reaction

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of HO_2^\bullet to protonate $\text{O}_2^{\bullet-}$ with the *o*-diphenols is a more thermodynamically feasible reaction than the HAT mechanism [24]. Apart from the mechanism, the controversy mentioned previously raises concerns that the actual reactant against catechols is $\text{O}_2^{\bullet-}$ or HO_2^\bullet [24,26–28]. However, the SPLET and HAT pathways have the same thermodynamic balance because the reactants and products are the same. Therefore, the competition among the PCET mechanisms is essentially governed by the kinetics of the limiting step of each mechanism favored thermodynamically. The $\text{O}_2^{\bullet-}$ -scavenging mechanism of polyphenolic antioxidants containing a catechol moiety remains unclear. In this study, the electron transfer reaction from some catechols to $\text{O}_2^{\bullet-}$ has been investigated experimentally and theoretically to gain more insight into the mechanism, using electrochemical and kinetic-based competitive spin trap ESR spectral measurements and the DFT calculations of the transition states and the intrinsic reaction coordinate (IRC). We propose a concerted two-proton-coupled electron transfer (concerted 2PCET) mechanism for the $\text{O}_2^{\bullet-}$ -scavenging reaction as a novel PCET pathway.

2. Experimental

2.1. Chemicals

CatH_2 and 4-chlorocatechol (Cl-CatH_2) were purchased from Nacalai Tesque, Inc. and Tokyo Chemical Industry Co., Ltd., respectively. 4,5-Dichlorocatechol ($\text{Cl}_2\text{-CatH}_2$), tetrachlorocatechol ($\text{Cl}_4\text{-CatH}_2$), and 4-methylcatechol ($\text{CH}_3\text{-CatH}_2$) were purchased from Sigma-Aldrich Co. LLC. These were purified by repeated sublimation under decreased pressure. 5,5-Dimethyl-1-pyrroline-*N*-oxide (DMPO) was commercially available from Tokyo Chemical Industry Co., Ltd. and used as received without further purification. Sigma-Aldrich anhydrous DMF was used as a solvent for electrochemical and electron spin resonance (ESR) spectral measurements as received without further purification. Tetrapropylammonium perchlorate (TPAP) was prepared as described previously and used as a supporting electrolyte for DMF [35]. Tetrabutylammonium hydroxide solution (1.0 mol dm^{-3} in methanol) was purchased from Sigma-Aldrich Co. LLC. and used to prepare basic DMF solution for measurements of the $\text{Cl}_4\text{-Cat}^{\bullet-}/\text{Cl}_4\text{-Cat}^{2-}$ redox pair. Ferrocene (Fc) was commercially available from Nacalai Tesque, Inc. and used as a potential reference compound.

2.2. Electrochemical and ESR spectral measurements

Cyclic voltammetry was performed with a three-electrode system consisting of a glassy carbon (GC) working electrode, a coiled platinum counter electrode, and an Ag/AgNO_3 reference electrode (containing CH_3CN solution of 0.1 mol dm^{-3} tetrabutylammonium perchlorate and 0.01 mol dm^{-3} AgNO_3 ; BAS RE-5) at 25°C using a BAS 100B electrochemical workstation coupled to a Dell Optiplex760 PC with BAS electrochemical software to record and analyze the data.

In situ electrochemical ESR spectra were observed using a JEOL JES-FA200 X-band spectrometer. The controlled potential electrolysis of O_2 was performed at room temperature in an electrochemical ESR cell using a 0.5-mm diameter straight Pt wire sealed in a glass capillary as a working electrode [36]. Spin-trap ESR spectra of the DMPO adducts of $\text{O}_2^{\bullet-}$ and HO_2^\bullet were obtained in DMF containing 0.48 mol dm^{-3} DMPO.

Sample solutions were prepared in a glove box completely filled with N_2 gas to prevent contamination by moisture. The DMF solution containing 0.1 mol dm^{-3} TPAP was saturated with O_2 by bubbling for ca. 2–3 min. The gas was passed over the solutions during the electrochemical and ESR spectral measurements to

maintain the concentration of O_2 at a constant level. The equilibrium concentration of O_2 was calculated as $4.8 \times 10^{-3} \text{ mol dm}^{-3}$.

2.3. Theoretical calculations

The geometries of species of CatH_2 , $\text{CH}_3\text{-CatH}_2$, Cl-CatH_2 , $\text{Cl}_2\text{-CatH}_2$, and $\text{Cl}_4\text{-CatH}_2$ involved in $\text{O}_2^{\bullet-}$ scavenging mechanisms were fully optimized by the B3P86 functional method using the 6-31 + G(d,p) basis set. The B3P86 functional provides a particularly accurate evaluation of the thermodynamics of the reaction between phenolic compounds and free radicals [15,37,38]. Zero-point energies and thermal correction, together with the entropies, were used to convert the internal energies to the standard Gibbs energy change (ΔG°) at 298.15 K. To calculate the thermodynamic properties in DMF, the polarized continuum model (PCM) was used with (U)B3P86/6-31 + G(d,p). Calculations of the transition states and the IRC of the $\text{O}_2^{\bullet-}$ -scavenging reaction with CatH_2 , $\text{CH}_3\text{-CatH}_2$, Cl-CatH_2 , $\text{Cl}_2\text{-CatH}_2$, and $\text{Cl}_4\text{-CatH}_2$ were performed at the B3LYP/6-31 + G(d,p) level [39]. Full geometry optimization of the hydrogen-bonded complexes of $\text{O}_2^{\bullet-}$ with the catechols was carried out with no symmetry constraints up to convergence. A subsequent vibrational frequency calculation was undertaken to confirm that the resulting equilibrium geometries were transition states on the potential energy surface. Note that one imaginary frequency was obtained for all the hydrogen-bonded complexes of catechols with $\text{O}_2^{\bullet-}$. The backward and forwarded minimum energy paths from the transition states were evaluated with the IRC algorithm. The natural bond orbital (NBO) technique was used for charge calculations [40]. All calculations were performed on a PC using the Gaussian 09W computational program package [41].

3. Results and Discussion

3.1. Cyclic voltammetry of O_2 in the presence of catechols

In aprotic solvents such as DMF, O_2 shows the quasi-reversible redox wave corresponding to the generation of $\text{O}_2^{\bullet-}$ (black line, Fig. 1). The addition of acidic substrates results in a change from a mono-electronic to a bi-electronic O_2 reduction process, increasing the cathodic current for reduction of O_2 and decreasing the anodic current for reoxidation of $\text{O}_2^{\bullet-}$ [30–34]. Formation of $\text{O}_2^{\bullet-}$ after the primary electron-transfer step associated with proton transfer from the acids leads to the overall irreversible reduction of O_2 to H_2O_2 , driven by the exergonic reduction of the resulting HO_2^\bullet or the disproportionation reaction between $\text{O}_2^{\bullet-}$ and HO_2^\bullet ; however, the presence of catechols results in loss of reversibility in the $\text{O}_2/\text{O}_2^{\bullet-}$ redox couple with a cathodic prepeak and a new anodic peak that appears at a more positive potential than the $\text{O}_2/\text{O}_2^{\bullet-}$ redox pair. Fig. 1a shows the cyclic voltammograms of O_2 in the presence of various concentrations of $\text{Cl}_4\text{-CatH}_2$ as a typical example. The anodic peak that appeared on the reverse scan at -1.2 V can be ascribed to the oxidation of the generated $\text{Cl}_4\text{-Cat}^{2-}$ by comparison with an authentic sample, as shown in Fig. 1a. Depending on the nature of the catechol compounds, the shift in the newly appeared anodic peak potential could be concomitant with a shift of the cathodic prepeak that is visible at a potential more positive than the $\text{O}_2/\text{O}_2^{\bullet-}$ redox, as shown in Fig. 1b. Therefore, the cathodic prepeaks of the $\text{O}_2/\text{O}_2^{\bullet-}$ redox are reasonably attributed to the reduction of $\text{Cl}_4\text{-Cat}^{\bullet-}$ to $\text{Cl}_4\text{-Cat}^{2-}$. The prepeaks include the background current of the O_2 reduction shifted in a positive direction due to the formation of hydrogen bonds with $\text{Cl}_4\text{-CatH}_2$ followed by the PCET reaction. These voltammetric behaviors have been well documented in previous work [27,28], and similar voltammetric behaviors have been

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