Involvement of Electron Transfer in the Radical-scavenging Reaction of Resveratrol

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Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) efficiently scavenges an oxygen radical via an electron transfer from resveratrol to the radical in deaerated acetonitrile, which is significantly accelerated by the presence of magnesium ion.

Resveratrol (**1H**, 3,4′,5-trihydroxy-*trans*-stilbene), one of polyphenols found in grapes, has attracted considerable interest because of its antioxidative potential. **1H** has reported to inhibit the oxidation of human low-density lipoprotein (LDL) and reduce the propensity of human plasma and LDL to undergo lipid peroxidation.[1,2] Furthermore, it has been reported that **1H** inhibits its cellular events associated with tumor initiation, promotion, and progression.[3] Besides its beneficial effects, **1H** was also shown to induce genotoxicity through a high frequency of micronucleus and sister chromatid exchange in vitro and DNA-cleaving activity in the presence of Cu^{II}.[4,5] However, very little is known about the detailed mechanism of antioxidative as well as toxic action of **1H**. On the other hand, two mechanisms are known for the antioxidative radical-scavenging reactions of polyphenols: a one-step hydrogen atom transfer from the phenolic OH group; and an electron transfer followed by a proton transfer.[6–8] Metal ions are a powerful tool that can be used to distinguish between these two mechanisms, since electron-transfer reactions are known to be significantly accelerated by their presence.[9] We report herein that the scavenging reaction of galvinoxyl radical ($GO^{\bullet}$), a relatively stable oxygen radical, by **1H** is significantly accelerated by the presence of magnesium ion in deaerated acetonitrile (MeCN). The detailed kinetic data obtained in this study provides valuable information about the antioxidative mechanism of **1H**, leading to the development of novel antioxidants with enhanced antioxidative abilities and reduced toxicity.

Upon addition of **1H** to a deaerated MeCN solution of $GO^{\bullet}$, the absorption band at 428 nm due to $GO^{\bullet}$ disappeared immediately as shown in Figure 1. This spectral change suggests that **1H** can efficiently scavenge $GO^{\bullet}$. The rate of the $GO^{\bullet}$-scavenging reaction by **1H** was measured by monitoring the decrease in absorbance at 428 nm due to $GO^{\bullet}$ using a photodiode array spectrophotometer. The decay of the absorbance at 428 nm due to $GO^{\bullet}$ obeyed pseudo-first-order kinetics when the concentration of **1H** ([**1H**]) was maintained at more than a 10-fold excess of the $GO^{\bullet}$ concentration. The pseudo-first-order rate constants (k_{obs}) increase with increasing [**1H**], exhibiting first-order dependence on [**1H**]. From the slope of the linear plot of k_{obs} vs. [**1H**], the second-order rate constant (k) was determined for the radical-scavenging reaction as $4.1\,dm^3\,mol^{-1}\,s^{-1}$ in deaerated MeCN at 298 K. This k value is significantly smaller than those of representative natural phenolic antioxidants, such as (+)-catechin ($2.6 \times 10\,dm^3\,mol^{-1}\,s^{-1}$)[10] and a vitamin E model ($3.0 \times 10^3\,dm^3\,mol^{-1}\,s^{-1}$).[11]

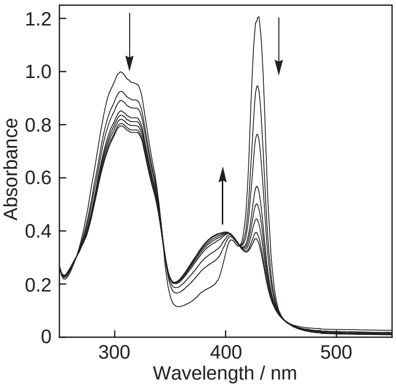


Figure 1. Spectral change observed in the reaction of **1H** ($1.3 \times 10^{-4}\,mol\,dm^{-3}$) with $GO^{\bullet}$ ($8.0 \times 10^{-6}\,mol\,dm^{-3}$) in deaerated MeCN at 298 K (interval: 600 s).

If the radical-scavenging reaction by **1H** involves an electron-transfer process as the rate-determining step, the rates of radical scavenging would be accelerated by the presence of metal ions.[12–14] This was investigated by examining the effect of $Mg(ClO_4)_2$ on the radical-scavenging rate by **1H** in deaerated MeCN. When $Mg(ClO_4)_2$ is added to the **1H**–$GO^{\bullet}$ system in deaerated MeCN, the rate of $GO^{\bullet}$-scavenging reaction by **1H** was significantly accelerated. The k values increase linearly with increasing concentration of $Mg(ClO_4)_2$ as shown in Figure 2. It should be noted that there is no interaction between $GO^{\bullet}$ and Mg^{2+}, since no spectral change was observed in the presence of a large amount of Mg^{2+}. Thus, the radical-scavenging reaction may proceed via an electron transfer from **1H** to $GO^{\bullet}$, which is accelerated by the presence of Mg^{2+}, followed by proton transfer from $\mathbf{1H}^{\bullet+}$ to GO^{-} as shown in Scheme 1. In such a case, the coordination of Mg^{2+} to GO^{-} may stabilize

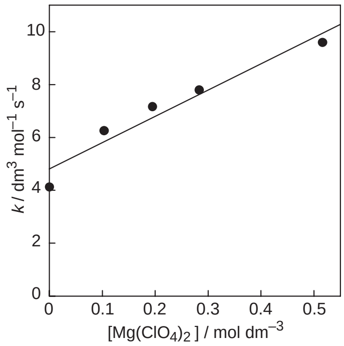
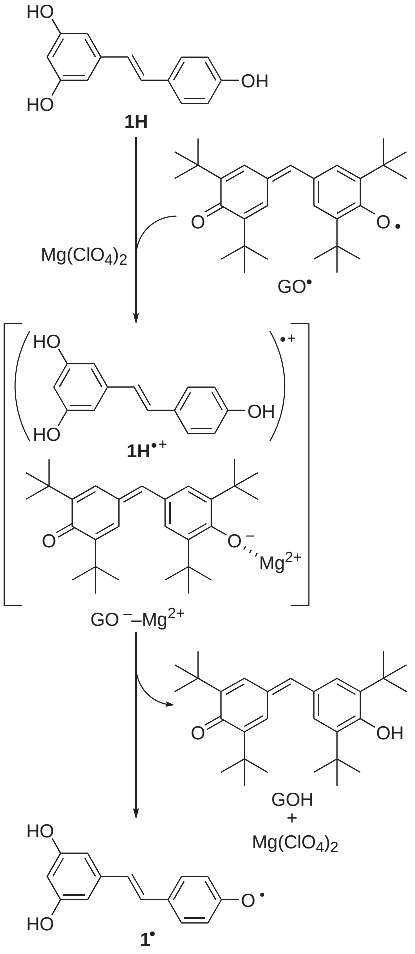


Figure 2. Dependence of k on $[Mg(ClO_4)_2]$ for the reaction of **1H** with $GO^•$ in the presence of $Mg(ClO_4)_2$ in deaerated MeCN at 298 K.



Scheme 1. Mg^{2+}-accelerated $GO^•$-scavenging reaction by **1H** via an electron transfer.[15]

the product, resulting in the acceleration of the electron transfer (Scheme 1).[9,12–14] The one-electron oxidation potential ($E^0_{ox} = 0.84$ V vs. SCE) of **1H** determined by the second-harmonic alternating current voltammetry (SHACV)[16] in deaerated MeCN (0.1 M Bu_4NClO_4) is more positive than the one-electron reduction potential of $GO^•$ ($E^0_{red} = 0.05$ V vs. SCE). This suggests that the reaction may involve a proton-coupled electron-transfer mechanism.[17]

In conclusion, resveratrol (**1H**) scavenges the oxygen radical via electron transfer in deaerated MeCN, which is accelerated by the presence of magnesium ion. The mechanistic information obtained in this study suggests that the introduction of electron-donating groups, such as methyl and methoxy groups, may stabilize the intermediate radical cation $\mathbf{1H}^{•+}$, resulting in the enhancement of the antioxidative abilities of **1H**. The synthesis of novel resveratrol derivatives having one or more methyl groups is currently under way and the results will be published in due time.

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15 Although $\mathbf{1}^•$ could not be detected owing to follow-up radical reactions, density functional theory (DFT) calculations suggest that $\mathbf{1}^•$ may be the most stable among three possible phenoxyl radicals derived from **1H**; See: Ref. 5.

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