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Synthesis, Characterization and Antioxidant Activity of a Novel Organogermanium Sesquioxide with Resveratrol

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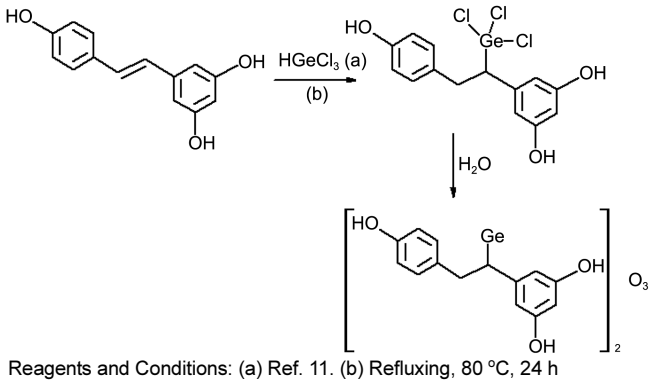
Antioxidants have attracted considerable attention in the field of medicinal chemistry, because the aging and degenerative diseases are related to the oxidation of biological components induced by free radicals.[1] Some serious diseases, such as aging, cancer, and atherosclerosis, have been confirmed to correlate with oxidative stress.[1] An important therapy strategy was supplementations of antioxidants. Polyphenolic compounds are widely distributed in plants and known as strong antioxidants.[2] Metal ions such as copper(II), iron(II) exert wide biological activity. Synergistic effects of polyphenolic compounds with metal ions have recently received great attentions.[3] Numerous studies showed that the additional biological activity can be obtained when polyphenolic compounds complexes with some metal ions.[4]

Germanium (Ge) is a trace element found in several organic substances and its compounds are known to have a broad range of biological activities including antioxidant, anticancer effects.[5] Besides, germanium compounds are low toxicity, especially organogermaniums. So, many researches focus on searching for effective and low-toxic drugs from these compounds. Among the many organogermaniums known, bis-(carboxyethyl germanium) sesquioxide (Ge-132) has been well-studied. Resveratrol (RSV), which is abundant in grape skin, peanuts, and red wine, has been reported to have strong antioxidant activity.[6] Many studies showed synergistic effects between polyphenolic compounds and Ge, such as ascorbic acid,[7,8] caffeic acid[9] and quercetin.[10] These two facts prompted us to check whether there is a synergistic effect between RSV and Ge. Herein, a new organogermanium sesquioxide with RSV has been synthesized without destroying its active groups - phenolic hydroxyl groups (Scheme 1), and characterized by UV-vis, FT-IR, MS, ^{1}H-NMR and elemental analysis.[11,12] The synthesized compound was reddish brown powder and stable at room temperature. It was soluble in methanol, ethanol, acetone, DMF and DMSO, and insoluble in water, dichloromethane and ethyl acetate. The solubility of RSV-Ge in methanol and ethanol was improved compared with RSV. The antioxidant activity of the ligand RSV and RSV-Ge against DPPH radical and hydroxyl radical were investigated.

Polyphenolic compounds are strong hydroxyl-antioxidants and free radical scavengers. The phenolic hydroxyl groups



Reagents and Conditions: (a) Ref. 11. (b) Refluxing, 80 °C, 24 h

Scheme 1. The synthetic routes of RSV-Ge.

play an important role in scavenging radicals, because they can react with free radicals and transfer labile H atoms to radicals.[13] The radical scavenging ability is closely related to the number of hydroxyl groups available. RSV is a strong antioxidant, and its three phenolic hydroxyl groups are available radical scavengers.[14] Germanium, which is known to possess numerous biological activities, was introduced into the molecule structure of RSV without destroying its active groups. It is hopeful to improve antioxidant activity of RSV.

The antioxidant activity of RSV-Ge was tested by hydroxyl radical scavenging assay and DPPH radical scavenging assay, the RSV and Ge-132 served as positive control. The Fenton reaction was selected as the hydroxyl radical source to measure the antioxidant capacity in a manner similar to the *in vivo* generation of the hydroxyl radical.[15] The hydroxyl radical scavenging effects are shown in Figure 1. The average scavenging ratios increase with increasing concentration of RSV and RSV-Ge in the range of 1-20 μg/mL. It is found that RSV-Ge improves the hydroxyl radical scavenging activity. Its EC_{50} (the amount of antioxidant needed to decrease the radical concentration by 50%) is reduced from 3.66 to 2.66 μg/mL. However, Ge-132 shows no hydroxyl radical inhibition, and even accelerates oxidation of hydroxyl radical. The stable radical DPPH is widely used to "evaluate" the antioxidant properties of phenols.[14] The antioxidant activity of RSV, RSV-Ge, and Ge-132 against DPPH radical

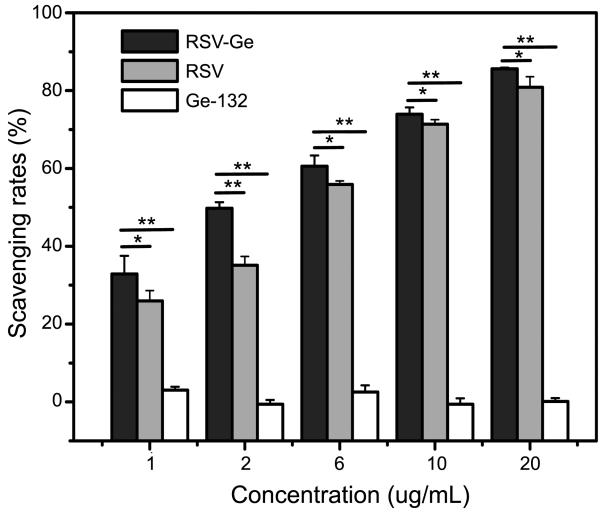


Figure 1. The hydroxyl radical scavenging effects of RSV and RSV-Ge and Ge-132. Data are expressed as means ± standard error obtained from three separate experiments. *P < 0.05, **P < 0.01 as compared to RSV and Ge-132.

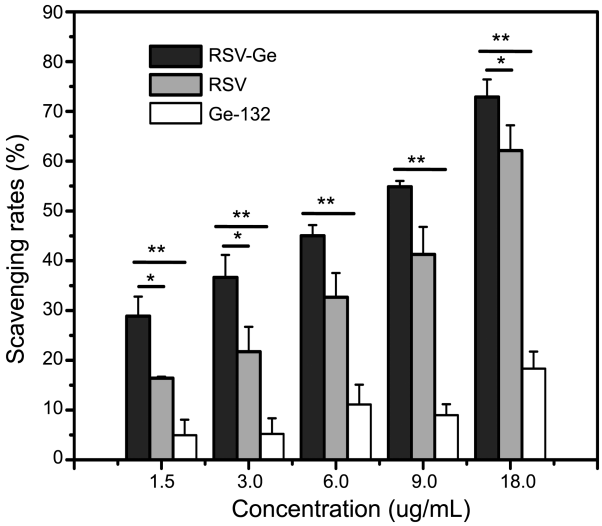
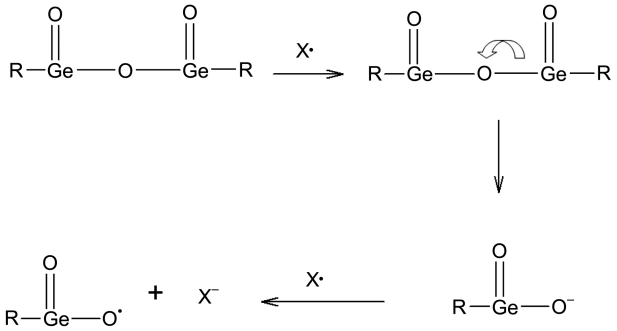


Figure 2. The DPPH radical scavenging effects of RSV, RSV-Ge and Ge-132. Data are expressed as means ± standard error obtained from three separate experiments. *P < 0.05, **P < 0.01 as compared to RSV and Ge-132.

were investigated. It is clear that RSV-Ge has higher DPPH radical scavenging activity than RSV and Ge-132 (Fig. 2). Its EC_{50} is reduced from 11.57 to 6.63 μg/mL. The antioxidant activity studies indicate that RSV-Ge is a more effective radical scavenger than RSV and Ge-132. These results indicate that Ge has a synergistic effect on the antioxidant activity of RSV. Phenol antioxidants react with radicals via hydrogen atom transfer, because hydrogen atom is easy to leave. Considering the –Ge-O– groups are unstable and relatively easy to leave under the effect of free radicals. Proposed antioxidant mechanism of the RSV-Ge compound as below: First, radicals (X·) induced cleavage of Ge-O



Scheme 2. Proposed antioxidant mechanism of the RSV-Ge compound.

networks to give an oxide anion (RGeOO–), then, electron transfer from oxide anion (RGeOO–) to X· (Scheme 2). The antioxidant activity studies indicate that the RSV-Ge may be a potential drug to eliminate the radicals.

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12. 49% Yield. mp > 300 °C. UV-vis: λ_{max} 280 nm. Anal. calcd. for RSV-Ge ($C_{28}H_{26}O_9Ge_2$) (%): C, 51.60; H, 3.99. Found (%): C, 52.09; H, 3.79. IR (KBr) ν (cm^{-1}): 1612, 1511 ν (C=C, ring); 1338, 1148 ν (C-O); 861 ν (Ge-O), 523 ν (Ge-C). ESI-MS: *m/z* 707.6 ([RSV-^{73}Ge·CH_3OH+Na]$^+$). ^{1}H NMR (DMSO-d_6) δ 8.99 (br s, 2H, H3, H5), 8.90 (br s, 1H, H4'), 6.59-6.63 (m, 4H, H2', H3', H5', H6'), 6.00 (s, 1H, H2), 5.98 (s, 1H, H6), 5.95 (s, 1H, H4), 2.90-2.96 (m, 3H, -O_2GeCHCH_2-).
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