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Synthesis of gold nanoparticles with glycosides: synthetic trends based on the structures of glycones and aglycones

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ABSTRACT

A new, room temperature synthetic method for gold nanoparticles from auric acid with glycosides as reducing agents in aqueous NaOH is presented. As a mechanistic study of the oxidation sites on the glycosides, eight sugar-containing reductants (glycoside, glucose, glucuronic acid) have been tested in the synthesis of gold nanoparticles to determine their trends based on the structures of glycones and aglycones. As a result of the comparison among the eight sugar-containing reductants, it was determined that C-6 of glycosides is oxidized to a carboxylic acid during the reduction of auric acid. To detect the oxidized compounds of the glycosides, the reaction mixtures were monitored by ^{13}C NMR. Among the eight sugar-containing reductants, phenyl β-D-glucoside generated the highest synthetic yield of mono-dispersed, round gold nanoparticles (13.15 ± 1.30 nm, 99.7% yield).

Since Faraday first reported colloidal gold nanoparticles (GNPs) in 1857,[1] GNPs have received attention in many fields such as semiconductors,[2,3] cosmetics,[4,5] clinical diagnostics,[6–8] drug carriers,[9–12] and catalysts in organic reactions.[13] Among the numerous synthetic strategies for GNPs, the most common and traditional method, developed by Turkevich et al., is performed by the reduction of aqueous auric acid with citrate in thermal conditions.[14,15] Another well-known method, developed by Brust et al., is a two-phase reaction accomplished using $NaBH_4$ as a reductant in organic solvent and water.[16] Currently, in an effort to avoid toxic materials, synthetic methods for GNPs have been introduced that utilize sugar-containing compounds and extractions of natural plants as reducing agents.[17–19]

Glycosides consist of a glycone and an aglycone group and are categorized into different types of sugars, including glucoside, galctoside, fructoside, and glucuronide. Many glycosides are bioavailable and bioactive compounds that are famous for their skin whitening,[20,21] anti-inflammatory,[22,23] and immune modulator activities.[24–26] Additionally, the conversion of sugars to glucuronide by glucuronidation, which is known as a phase II metabolism, is an essential method for the excretion of toxic chemicals from the human body.[27] Furthermore, glycosides, which are commonly soluble in water, are suitable for the aqueous synthesis of GNPs. To our knowledge, a mechanistic study of glycoside GNP synthesis has not been reported, although many sugar-containing reductants have been used to synthesize GNPs.[17–19]

Herein, a new, facile, room temperature synthetic method for GNPs with glycosides is reported. Also, a mechanism has been suggested considering the reactivity observed in the experiment, where the structure change of reducing sugars **1**–**8** (Fig. 1) showed significant differences in the formation of GNPs. To characterize the GNPs, surface plasmon resonances (SPRs), inductively coupled plasma mass spectrometry (ICP-MS), and high-resolution transmission electron microscopy (HRTEM) data are shown. Additionally, a plausible oxidative product of phenyl β-D-glucoside (**3**) was detected by nuclear magnetic resonance (NMR).

Recently, β-D-glucose (**7**) and hydroquinone (HQ) have been used extensively as reducing agents in organic reactions and to synthesize GNPs in aqueous solution at room temperature.[17,19,28] A cyclic reducing sugar, **7**, is converted to a linear glucose via anomerization and generates aldehyde, which is easily oxidized to carboxylic acid because **7** has a weak hemiacetal bond in aqueous media. The reported oxidation products of **7** were gluconolactone or gluconate by electrocatalytic oxidation.[29] The reducing ability of HQ is attributed to its conversion to benzoquinone via oxidation.[28] Among glycosides, we selected an easily affordable glucoside, arbutin (**1**), which consists of glucose **7** and HQ. Glycoside **1**, which is famous for its various biological activities,[20–22] has been used as a skin whitening agent in cosmetics via the oxidation of C-3′.[21] Our experiment began with an assumption that glycoside **1** has an enough oxidative potential to synthesize GNPs through reduction of auric acid. Probably **1** would prefer a different oxida-

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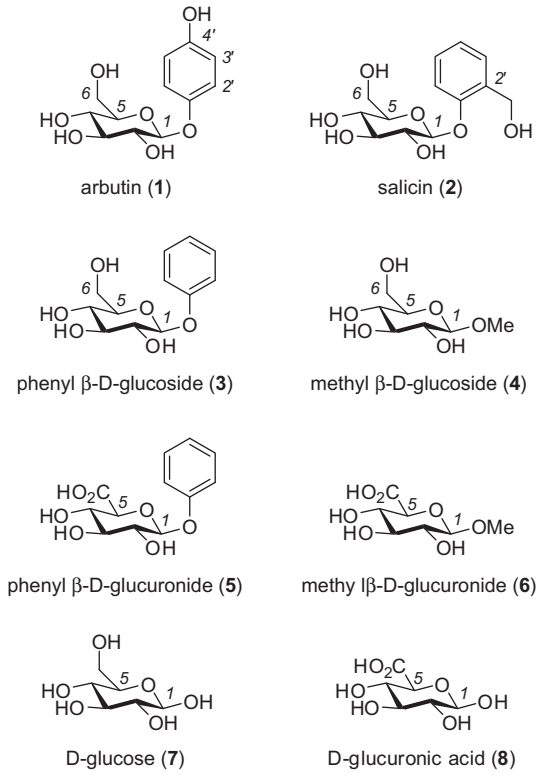

Figure 1. Structures of glycosides (**1**–**6**), glucose (**7**), and glucuronic acid (**8**).

tion pathway rather than conventional hydrolysis-oxidation pathway, since it was known that **1** is difficult to undergo hydrolytic cleavage into **7** and HQ under neutral and basic conditions.

To optimize the reaction condition of glycoside **1** in water, $HAuCl_4$ was selected as a source of gold and surface plasmon resonances (SPRs), and the reaction mixtures were monitored by UV/vis spectroscopy (Table 1). The order of addition for the reagents was as follows: (1) water; (2) aq $HAuCl_4$; (3) aq NaOH for basic conditions; (4) aq reducing agent **1**. Particularly, compound **1** was added last in basic conditions to prevent cleavage of an acetal structure in acidic media. In entry 1, there is a 100-fold higher concentration of **1** than $HAuCl_4$, and no reaction occurred without NaOH solution. The lack of reaction could be due to the pH (2.87) being too low, and this challenge was overcome by controlling the pH. Indeed, adding NaOH enhanced the synthesis of GNPs using the reducing agents citrate,[30] glucose,[19] and HQ.[28] Based on these previous studies, we added aqueous NaOH solution to the reaction procedure. Interestingly, at room temperature, the colorless reaction mixture immediately changed to a purple color, and SPR was detected using UV/vis spectroscopy (entry 3, pH 3.30), while a solution with only $HAuCl_4$ and NaOH without reducing agent **1** did not undergo any color or SPR changes (entry 2). By varying the amount of NaOH, it was determined that 7 mM was the optimal NaOH concentration because it showed the highest absorbance in SPR (entry 4, pH 8.85). GNPs were synthesized at a 40 mM concentration of NaOH (entry 5, pH 10.18), but not at 80 mM (pH 12.07). The pH range for synthesis of GNPs by **1** was estimated to be approximately 3–12 (entries 3–5). To evaluate the influence of reaction temperature, the reaction was performed at 40, 60, and 80 °C, although no significant SPRs were observed at those temperatures (entries 6–8). To determine the maximum concentration of $HAuCl_4$, the concentration was elevated to 1.5 and 2.0 mM. At 1.5 mM, GNPs were synthesized, but no nanoparticles were formed at 2.0 mM (entries 9–10). Based on the variable reaction condition studies in Table 1, it was proved that arbutin (**1**) has sufficient reducing ability to synthesize GNPs. Therefore, the reaction conditions of entry 4 were selected for further investigations into the reactions of glycosides **2**–**6** and their minimum concentrations as reducing agents.

In Table 2, reactions were performed in a two-step sequence. Step 1 was the same as in the reaction condition of entry 4 in Table 1; step 2 involved using or eliminating the centrifuged supernatant, which contained the remaining $HAuCl_4$ and organic reductants. This material was used to obtain both ICP-MS data to calculate the GNP yields and HRTEM images to characterize the shapes and sizes of GNPs. After the two-step procedure, the centrifuged pellet regained a colloidal state via the optional addition of water (0.5 mL). First, the concentration of **1** was changed from 50 mM (entry 4, Table 1) to 5.0 and 0.1 mM (entries 1 and 2). When the concentration of **1** was even 0.1 mM, GNPs were successfully generated (entry 2), but the synthetic yield (62.7%) was decreased compared with that in entry 1 (98.6%). Next, we tested glycosides **2**–**4** and their minimum concentrations in the synthesis of GNPs. The reducing abilities of salicin (**2**), phenyl β-D-glucoside (**3**), and methyl β-D-glucoside (**4**) were investigated during GNP synthesis to compare the effects of different aglycons. Salicin (**2**), whose structure is closely related to that of aspirin, has been used as an analgesic and anti-inflammatory agent in traditional herbal medicines.[31] Phenyl β-D-glucoside (**3**) and methyl β-D-glucoside (**4**) are representative basic structures of aryl and aliphatic alkyl β-D-glucosides, respectively. Using salicin (**2**), GNPs were not synthesized, even at a concentration of 25 mM. At 50 mM of **2** (entry 3), the colorless reaction mixture changed to a dark blue in 15 min after the addition of **2**, but precipitate formed 1 h after the color change. In the case of phenyl β-D-glucoside (**3**) and methyl β-D-glucoside (**4**), GNPs were synthesized at the minimum concentrations of 4 and 5 mM (entries 4 and 5), respectively, in 15 min after the addition of the corresponding reductant. Additionally, 2 mM of NaOH, **3** (pH 7.07) and **4** (pH 8.94) did not make GNPs. The results of entries 1–5 showed that the possible pH range for GNP synthesis using **3** and **4** was narrower than that of **1**. Also, the reducing ability of **3** and **4** was moderate compared to that of **1** while the reducing ability of **2** was too low to synthesize GNPs. Glycoside **4** has no oxidation site on its aglycone part, so the result of entry 5 indicated that the glycone part was essential for reducing $HAuCl_4$.

In the literature, we found a previous report that the primary C-6-hydroxy group was selectively oxidized to carboxylic acid in glycosides.[32] Based on the literature, we hypothesized that (1) the C-6-hydroxy group could be critical to synthesize GNPs and (2) the reducing potential of glycoside may not rely on hydrolysis to glucose, a reducing sugar that generates an aldehyde via anomerization. To prove our hypothesis, in entries 6–9, glucuronides **5** and **6**, glucose **7**, and glucuronic acid **8** were tested under the same conditions used for entries 4 and 5. Glucose **7** synthesized GNPs, as described in a previous report[19] (entry 8). However, glucuronides **5** and **6**, which have a C-5-COOH and did not result in any changes in colors or SPRs, while glucuronic acid **8** synthesized GNPs. Although cyclic glucuronic acid **8** has a C-5-COOH, it could be oxidized at the aldehyde moiety generated via anomerization. Conversely, because glucuronides **5** and **6** have C-5-COOH groups and stronger glycosidic bonds than does glucuronic acid **8**, they may not have the ability to reduce $HAuCl_4$. To prove the presence of oxidized COOH conclusively, a solution of GNPs (**c**) was characterized using ^{13}C NMR. By comparison with the ^{13}C NMR data for glucoside **3** and glucuronide **5**, GNPs (**c**) showed a peak of carbon for a carboxylic acid near 172 ppm, which was detected in **5** but not in **3**.[33] The results of entries 6–9 indicate reactions with glycosides **1**–**4** that have different aglycones. The reaction time with arbutin (**1**) was very fast because **1** may have two oxidation sites at the C-6 and C-3′ positions in both the glycone and aglycone