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Synthesis of α-Amino Acids from Glucosamine-HCl and its Derivatives by Aerobic Oxidation in Water Catalyzed by Au Nanoparticles on Basic Supports

Youtaro Ohmi, Shun Nishimura, and Kohki Ebitani*[a]

In recent years, the number of investigations on utilization of glucosaminic acid (GlcNA, 2-amino-2-deoxy-D-gluconic acid; Figure 1a) has increased because of its advanced application for the industrial, agricultural, medical, and food fields.[1]

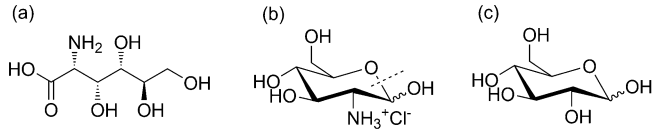


Figure 1. Structures of (a) glucosaminic acid (GlcNA), (b) glucosamine-HCl (GlcN-HCl), and (c) glucose.

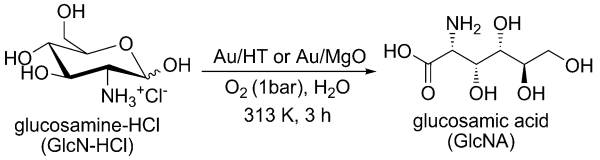
GlcNA is a member of the "chiral pool" and thus has been used as a starting chemical for the asymmetric synthesis of various amino acids[2] and glycosidase inhibitors such as (+)-castanospermine, (+)-6-epicastanospermine, (+)-2-epideoxy-mannojirimycine, and polyhydroxypyrrolidine.[3] GlcNA is also used as a biocompatible, non-toxic ligand chelate with many metals for potential medical applications.[4–6] For example, water-dispersible magnetic iron oxide nanoparticles, with a uniform spherical shape (10–13 nm), were synthesized with GlcNA and their anticancer behavior was explored.[6] GlcNA has also been identified as a promising sweetener and condiment.[1]

Synthesis of GlcNA from glucosamine-HCl (GlcN-HCl, Figure 1b) is preferable because GlcN-HCl is commercially produced by the hydrolysis of chitosan derived from chitin by using hydrochloric acid.[7,8] This transformation will open up route for the utilization of marine biomass sources such as crustacean shells for the synthesis of value-added chemicals. In addition to the enzymatic synthesis of GlcNA from GlcN-HCl,[9] inorganic catalysts have been used for this transformation.[10,11] Gu and Xia reported an aerobic oxidation of GlcN-HCl in water by a Pd–Bi catalyst supported on cylindrical active charcoal (Pd-Bi/C) at 303 K.[10] A high isolated yield of GlcNA was achieved (70%); however, this catalytic system needs NaOH and $KHCO_3$ as external bases. Electrocatalytic oxidation of glucosamine using carbon felt electrodes modified with 2 nm-sized Au nanoparticles in alkali solutions has been also reported.[10] Since GlcN-HCl dissolves little in organic solvents and exhibits low thermal stability, transformation reactions have to be performed in water as the solvent at low temperatures. For example, treatment at high temperatures in the presence of acid in water afforded levulinic acid and 5-hydroxymethylfurfural (HMF).[12]

Oxidation of GlcN-HCl into GlcNA involves carbon–oxygen bond cleavage (see dashed line in Figure 1b). Based on the analogue structure of GlcN-HCl and glucose (Figure 1c), we surveyed the literature on the aerobic oxidation of glucose into gluconic acid by heterogeneous catalysts in water.[13–17] It has been shown that the carbon-supported metal nanoparticles acted as catalytic sites for the aqueous oxidation of glucose in the presence of NaOH.[13,14] Especially Au nanoparticles with a 2–6 nm diameter exhibited high catalytic activity for glucose oxidation[15,17] as well as for other oxidation reactions using molecular oxygen as an oxidant in organic solvents.[18,19]

Recently, we found that the aerobic and aqueous oxidative dehydrogenation of alcohols such as glycerol and HMF into the corresponding carbonyl compounds efficiently proceeded under base-free conditions when using hydrotalcite (HT)-supported Au nanoparticles with 3–5 nm diameter as heterogeneous catalyst in water.[20] HT has been known as a unique solid base catalyst that is able to operate in water[21] and has been frequently used as support for metal species such as Au,[19] Ru,[22] Ag,[23] Pt,[24] and AuPd bimetallic particles.[25]

Based on the proposal that the metal-catalyzed oxidation of GlcN-HCl to GlcNA is essentially an oxidative dehydrogenation reaction of alcohols,[1,10] Au/HT is expected to promote oxidation of GlcN-HCl into GlcNA under base-free conditions. Herein, we report a highly efficient synthesis of GlcNA from GlcN-HCl under aqueous and base-free conditions by using the heterogeneous Au/HT catalyst in the presence of molecular oxygen at 1 bar (Scheme 1). In addition to HT, we also used MgO as basic support[26] for Au nanoparticles to improve the reusability of the catalyst. Furthermore, the Au nanoparticles on basic supports are found to be effective for the synthesis of α-amino



Scheme 1. Aerobic and aqueous oxidation of glucosamine-HCl (GlcN-HCl) into glucosaminic acid (GlcNA) catalyzed by Au nanoparticles dispersed on basic supports.

[a] Y. Ohmi, Dr. S. Nishimura, Prof. Dr. K. Ebitani
School of Materials Science
Japan Advanced Institute of Science and Technology
1-1 Asahidai, Nomi, 923-1292 (Japan)
E-mail: ebitani@jaist.ac.jp

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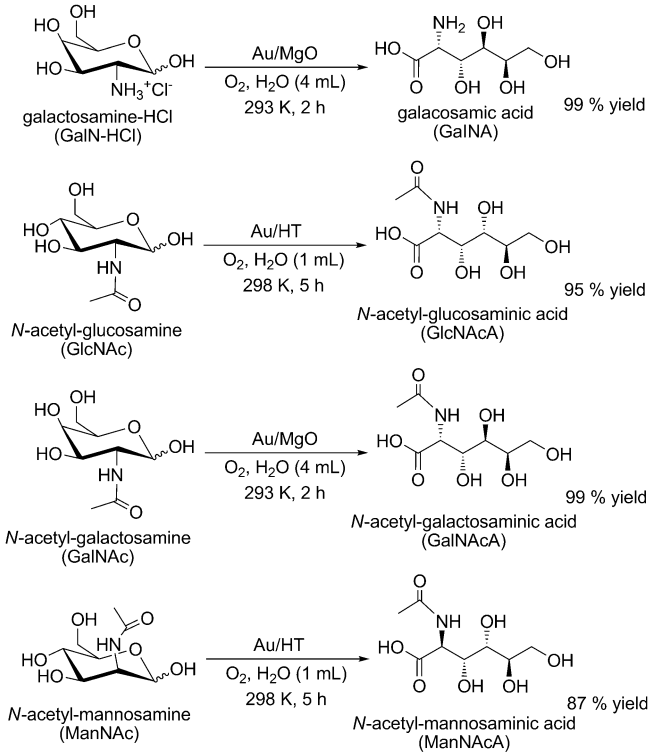
acids, such as galactosaminic acid (GalNA), *N*-acetyl-glucosaminic acid (GlcNAcA), *N*-acetyl-galactosaminic acid (GalNAcA), and *N*-acetyl-mannosaminic acid (ManNAcA), from glucosamine derivatives (Scheme 2).



Scheme 2. Aerobic oxidation of glucosamine derivatives (amino sugars) to the corresponding α-amino acids using Au nanoparticles immobilized on basic supports in water. Reaction conditions: substrate (0.1 mmol), catalyst (20 mg), O_2 flow (30 mL min^{-1}), 500 rpm.

Table 1 lists the results of aerobic oxidation of GlcN-HCl into GlcNA in water by various supported Au catalysts at 313 K together with mean size of supported Au particle. The Au nanoparticles on basic supports such as HT and MgO efficiently catalyzed the selective oxidation of GlcN-HCl into GlcNA under mild reaction conditions. The turnover numbers (TONs) normalized to total Au for 2.0 wt% Au/HT and 0.9 wt% Au/MgO were >75 and >164, respectively.[27] The Au particles on hydroxyapatite (HAP)[28] and Al_2O_3 could catalyze the GlcN-HCl oxidation; however, the yields of GlcNA were low. Interestingly, the Au species on TiO_2 and SiO_2 with slightly larger particle sizes did not show any catalytic activity under the present conditions. As the parent HT did not catalyze the reaction, the Au nanoparticles are catalytically active sites for the oxidation.

Table 1. Aerobic Oxidation of Glucosamine-HCl (GlcN-HCl) in Water by Various Supported Au Catalysts.[a]

Entry	Catalyst	Loading[b] [wt%]	Yield of GlcNA[c] [%]	Mean particle size[d] [nm]
1	Au/HT	2.0	89	3.1
2	Au/MgO	0.9	93	2.9
3	Au/CaO	1.1	81	2.9
4	Au/HAP	0.8	37	2.9
5	Au/Al_2O_3	1.8	22	2.7
6	Au/TiO_2	0.7	0	4.6
7	Au/SiO_2	0.5	0	6.6
8	HT	–	0	–

[a] Reaction conditions: GlcN-HCl (4 mmol), catalyst (0.50 g), H_2O (20 mL), 313 K, 3 h, O_2 flow (50 mL min^{-1}), 500 rpm. [b] Au loads were determined by ICP. [c] Determined by HPLC. [d] Estimated by 300 particles in TEM images.

Reusability of the supported Au catalysts was examined in the oxidation of GlcN-HCl (Figure 2). For the Au/HT catalyst, the activity gradually decreased during the recycling experiment. The yield of GlcNA was 70% in the 2nd reuse.[29] Use of the more basic MgO as support improved the reusability of the Au nanoparticles; a high catalytic activity was retained even in the 2nd reuse experiment. According to the Au L_3-edge X-ray absorption near edge structure (XANES) spectra, the Au nanoparticles kept their metallic states before and after the reaction in both catalysts (Figure S1 a). However, the Au/HT showed a slight growth of the Au nanoparticles after the reaction as expected by |Fourier transform| (|FT|) of EXAFS (Figure S1 b). It is known that the basicity of MgO is stronger than that of HT.[26] The base sites on the surface of MgO may strongly interact with Au nanoparticles to prevent Au particle growth.

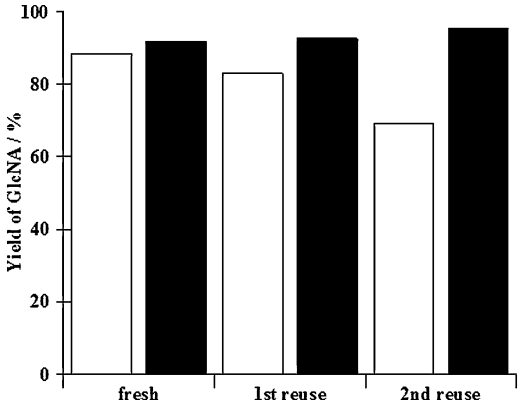


Figure 2. Recycle experiments of Au/HT (white bars) and Au/MgO (black bars). Reaction conditions: GlcN-HCl (4 mmol), catalyst (0.5 g), H_2O (20 mL), 313 K, 3 h, O_2 flow (50 mL min^{-1}), 500 rpm.

Encouraged by the above results, we further applied the heterogeneous catalytic system to the aerobic oxidation of glucosamine derivatives (amino sugars) such as galactosamine-HCl (GalN-HCl), *N*-acetyl-glucosamine (GlcNAc), *N*-acetyl-galactosamine (GalNAc), and *N*-acetyl-mannosamine (ManNAc) into α-amino acids by using Au/MgO and Au/HT in water. Generally, α-amino acids are synthesized by the Strecker reaction using carbonyl compounds, amines, and HCN, and are starting materials for drug synthesis.[30] GlcNAc has been also obtained from the chitin derivative.[8] The results are summarized in Scheme 2. Various *N*-acetylated compounds could be converted into the corresponding α-amino acids in high yields under mild reaction conditions.[31] The structures of these α-amino

acids were confirmed by NMR and mass spectroscopy measurements (see the Supporting Information, SI).

In summary, we have demonstrated the versatility of Au nanoparticles supported on basic materials as a reusable heterogeneous catalyst for aerobic oxidation of glucosamine derivatives into the corresponding α-amino acids in water under mild reaction conditions. Further application of the presented catalytic system for the selective transformation of biomass-derived compounds into value-added chemicals is currently under investigation.[32]

Experimental Section

Materials: $HAuCl_4 \cdot 4H_2O$, ammonium solution (25%, aqueous), galactosamine hydrochloride (GalN-HCl), and *N*-acetyl-galactosamine (GalNAc) were purchased from Wako Pure Chemicals. D-(+)-glucosamine hydrochloride (GlcN-HCl, 98% purity), *N*-acetyl-glucosamine (GlcNAc), and *N*-acetyl-mannosamine (ManNAc) were purchased from TCI. D-glucosaminic acid (GlcNA) was purchased from Tronto Research Chemical Inc. Hydrotalcite (HT, Mg/Al = 5, AD-550 PF) was supplied by Tomita Pharmaceuticals Co., Ltd. MgO was obtained from the Catalysis Society of Japan as JRC-MGO-4 (particle size; 1000 Å). MeOH and acetone were purchased from Kanto Chemicals.

Preparation of supported Au nanoparticle catalysts: HT (2 g) was added to an aqueous solution of $HAuCl_4 \cdot 4H_2O$ (0.2 mmol, 80 mL), and the mixture was stirred at room temperature. After 10 min stirring, an aqueous NH_3 solution (25%, 0.8 mL) was added, and the mixture was stirred for 6 h at room temperature (pH = 10–11), followed by refluxing for 30 min. The resultant solid (pale yellow) was filtered and washed with water (1.0 L) and dried at room temperature. The obtained solid was calcined at 473 K for 4 h, affording Au^0/HT catalyst (pale purplish red). The Au^0 nanoparticles on various supports were also prepared by performing the same procedure. The real loading amounts of Au for each sample were estimated by means an inductively coupled plasma (ICP) analysis and are listed in Table 1.

Characterization: Inductively coupled plasma atomic emission spectroscopy (ICP-AES) was performed by using a Shimadzu ICPS-7000 ver.2 to estimate the weight% of Au in the catalysts. Transmission electron microscopy (TEM; Hitachi H-7100) was performed at 100 kV accelerating voltage. X-ray absorption fine structure (XAFS) measurements was performed at the BL01B1 station in SPring-8 synchrotron radiation facility, Japan. Au L_3-edge XAFS spectra was recorded at room temperature by the transmission method. NMR spectra were measured using AVANCE III (Bruker BopSin Inc.) at 400 MHz for ^1H, 101 MHz for ^{13}C, ^1H–^1H correlation spectroscopy (COSY), hetero-nuclear multiple quantum coherence (HMQC), and hetero-nuclery multiple-bond connectivity (HMBC modes). Analysis of the product by oxidation of GlcN-HCl was performed on ESI mass spectroscopy (LCQ DECA XP, Thermoelectron Co. Ltd.). Fourier transform ion cyclotron resonance (FT-ICR) mass spectroscopy was measured by using a Solarix-JA (Bruker Daltonics Co. Ltd.) to determine the precise mass of GalNA, GlcNAcA, GalNAcA, and ManNAcA.

General Oxidation Procedure: Oxidation of GlcN-HCl was performed in a Schlenk flask equipped with a reflux condenser. The reaction was typically carried out using GlcN-HCl (442 mg, 4 mmol), Au/HT (0.5 g), and distilled water (20 mL) at 313 K for 3 h under an O_2 flow (50 mL min^{-1}). The reaction mixture was magnetically stirred (500 rpm). After the reaction, the mixture was centrifuged for 20 min (4000 rpm) to separate the catalyst. After filtration of the collected supernatant solution by a filter (Millex-LG 0.20 μm), a part of the solution was analyzed by HPLC analysis.

Product analysis by HPLC: Yield of GlcNA was determined by using a HPLC (WATERS 515 pump) equipped with Shodex Asahipak NH22P-50 3E column and using a refractive index detector (WATERS 2414). The conditions were set as follows: eluent 40% aqueous EtOH; column temperature 323 K; flow rate 0.5 mL min^{-1}. For HPLC analysis of GalNA, GlcNAcA, GalNAcA, and ManNAcA, pure water was used as an eluent with 1 mL min^{-1} flow rate.

Isolation of products: After the reaction, the heterogeneous mixture was centrifuged for 20 min (4000 rpm) to separate the catalyst. The collected supernatant was condensed under a vacuum at room temperature. In the case of the oxidation of GlcN-HCl, the condensed liquid was mixed with MeOH. After centrifuging the mixture for 20 min (4000 rpm), the precipitate was recovered and dried under a vacuum, yielding a white powder. The powder was subjected to ^1H-, ^{13}C-, HMQC NMR, and ESI-MS spectroscopy. Comparison with authentic samples confirmed that the isolated compound was GlcNA (see SI in the Supporting Information). In the case of the oxidation of GalN-HCl into GalNA, the condensed liquid was mixed with MeOH and acetone (acetone/condensed liquid = 1:6 in volume). After centrifuging the mixture for 20 min (4000 rpm), a precipitate was recovered and dried under a vacuum, yielding a white powders. The powders were subjected to ^1H-, ^{13}C-, ^1H-^1H COSY, HSQC NMR, and FT-ICR MS spectroscopy. For the products of GlcNAcA, GalNAcA, and ManNAcA, the condensed liquid was simply evaporated, and the obtained precipitate was dried under a vacuum, yieldin a white powders. All data are consistent with the structures of GlcNAcA, GalNAcA, and ManNAcA (see SI in the Supporting Information).

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[31] The reactivity of amino sugars is as follows; GalN-HCl $>$ GlcN-HCl $>$ GalNAc $>$ GlcNAc $>$ ManNAc. The low reactivity of ManNAc can be explained by steric hindrance between the acetyl groups of ManNAc and the catalytically active Au sites.
[32] After removal of the Au/MgO catalyst from the reaction mixture, the oxidation of GalNAc did not proceed (Figure S2 in the Supporting Information). This indicates that the aerobic oxidation of GlcN-HCl and its derivatives to α-amino acids occurred on the surface of the Au/MgO catalyst.

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