Metallization of DNA Hydrogel – Application of Soft Matter Host for Preparation and Nesting of Catalytic Nanoparticles

Anatoly Zinchenko, Yuxin Che, Shota Taniguchi, Larisa I. Lopatina, Vladimir G. Sergeyev, Shizuaki Murata*

Graduate School of Environmental Studies, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464-8601, Japan, Department of Chemistry, Moscow State University, Moscow, 119899, Russia

E-mail: zinchenko@urban.env.nagoya-u.ac.jp

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Abstract Nanoparticles (NPs) of Au, Ag, Pt, Pd, Cu, and Ni of 2-3 nm average size and narrow size distributions were synthesized in DNA cross-linked hydrogels by reducing corresponding metal precursors by sodium borohydride. DNA hydrogel plays a role of a universal reactor in which the reduction of metal precursor results in a formation of 2-3 nm ultrafine metal NPs regardless of metal used. Hydrogels metallized with various metals showed catalytic activity in the reduction of nitroaromatic compounds and the catalytic activity of metallized hydrogels changed as follows: Pd > Ag ≈ Au ≈ Cu > Ni > Pt. DNA hydrogel-based "soft catalysts" elaborated in this study are promising for green organic synthesis in aqueous media as well as for biomedical *in vivo* applications.

1. Introduction

Catalysis by noble metal nanoparticles (NP) and clusters has gained tremendous attention during past decades. (Cuenya 2010; Daniel and Astruc 2004; Haruta 2005; Stratakis and Garcia 2012) It is generally performed by either utilizing catalytic NP deposited on a suitable solid

substrate such as TiO_2 particles (heterogeneous catalysis) or in solutions of dispersed NP (homogeneous catalysis). Besides these well-established types of catalysts, NPs embedded into polymeric matrices such as hydrogels or dendrimers compose a relatively new class of promising catalytic systems (Lu et al. 2009; Lu et al. 2007; Miwa et al. 2014; Ramtenki et al. 2012; Welsch et al. 2010; Zinchenko et al. 2014) that possess features of both homo- and heterogeneous catalysts. Furthermore, utilization of polymer-based soft material as a support for NP opens up numerous opportunities to control catalytic performance of catalyst by changing a state of hydrogel matrix to enable easy recovery and reuse of the nanocatalysts embedded into hydrogel.

Recently, we reported the preparation of DNA-hydrogel-based hybrid material containing catalytic gold NPs (Zinchenko et al. 2014) and showed some of its interesting properties (Che et al. 2015). In comparison to hybrid hydrogels made of other synthetic polymers (Bahram et al. 2014; Hortiguela et al. 2011; Kim and Lee 2007; Lu et al. 2006; Lu et al. 2009; Lu et al. 2007; Mitra and Das 2008; Ozay et al. 2011; Ramtenki et al. 2012; Sahiner et al. 2010; Sahiner et al. 2011; Wang et al. 2004; Welsch et al. 2010; Yoon et al. 2009; Zhu et al. 2012), utilization of DNA is promising both from a viewpoint of facile preparation of catalytic NPs by two-step absorption/reduction of a noble metal precursor and size control of generated gold NP (Zinchenko et al. 2014). Therefore, DNA hydrogel is promising to be further developed toward hydrogels with NP of transition metals other than gold such as Pd, Pt, etc. that are also widely used in catalysis. Importantly, the interaction mechanisms of DNA with various metal ions substantially differ (Anastassopoulou 2003; Sissoeff et al. 1976), and the understanding of the factors affecting interaction of a metal precursor with DNA, metal NP growth, stability of NP, and their catalytic activity are still to be addressed. Herein, we describe DNA metallization with transition metals commonly used in catalytic applications and discuss the influence of the nature of metal on structural and catalytic properties of DNA-based “soft catalysts”.

2. Results and Discussion

2.1 Preparation of DNA hybrid hydrogels

DNA extracted from salmon milt (7000 bp average length, ca. 85% double-stranded DNA) was cross-linked by ethylene glycol diethyl ether (EGDE) at elevated temperatures as reported previously.(Amiya and Tanaka 1987; Zinchenko et al. 2014) According to gravimetric analysis, DNA hydrogels contained *ca.* 1-5% (w/w) of DNA depending on conditions of hydrogel preparation. DNA hydrogel exhibited typical for polyelectrolyte gels behavior such as swelling-shrinking transition under varying ionic strength and pH. During the cross-linking, DNA denaturated significantly and only *ca.* 5% of double-stranded DNA remained in hydrogel according to PicoGreen assay described in details elsewhere.(Fernandez-Solis et al. 2015)

Metallization of DNA hydrogel was performed by a two-step procedure illustrated in **Figure 1A**: absorption of a metal precursor by DNA hydrogel and reduction of metal precursor by $NaBH_4$. Corresponding photographic images of DNA hydrogels after absorption of metal precursors and reduction are shown in **Figure 1B**. Chemical formulas of metal precursors used for hydrogel metallization are summarized in **Table 1**. Experimentally, approximately 50 mg DNA hydrogel film (*ca.* $1.2 \times 1.2 \times 0.3$ cm^3) was soaked in a solution of a metal precursor for several hours to establish equilibrium. Times necessary for saturation of DNA hydrogel with metal precursor and the absorbed amount of each metal per DNA nucleotide are summarized in **Table 1**. (Supporting information available) Equilibrium was reached within 1-5 hours and uptake rates of the metal precursors by DNA hydrogel was in a range 0.5-0.7 moles of metal ions per mole of DNA nucleotides. The difference in the uptake times and rates depended on the mechanism of DNA interaction with a particular metal precursor. Efficient intercalation of Ag^+ into DNA double-helix or strong coordination of $\{Pt(NH_3)_2\}^{2+}$ with DNA bases, respectively (Jensen and Davidson 1966; Takahara et al. 1995), results in faster absorption of these precursors. On the other hand, DNA binding with $AuCl_4^-$ and $PdCl_4^{2-}$ is a two-step

kinetically slow process,(Mandal and Nandi 1979) which involves substitution of Cl^- ligands of transition metal ion by nitrogen-containing DNA bases; therefore, the uptake times are longer.

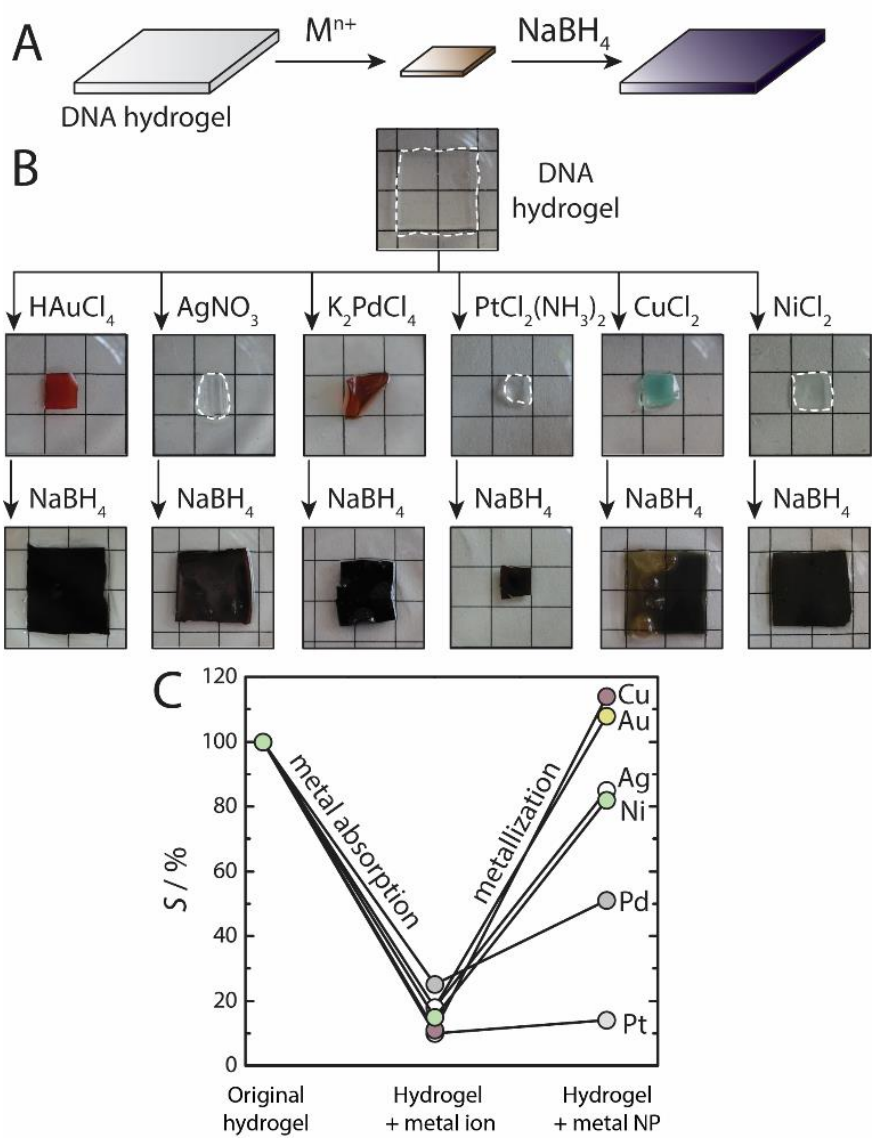

Figure 1. A. Schematics of two-step metallization of DNA hydrogel. Washing steps after metal absorption and reduction are omitted. **B.** Corresponding photographic images of DNA hydrogel films before and after absorption of metal precursor and metallization. Grid size is 6 mm. **C.** Relative change of a surface area (*S*) of DNA hydrogel film after absorption of various metal precursors and their reduction.

Absorption of any type of metal precursors by DNA hydrogel caused hydrogel shrinking due to neutralization of DNA charge by positively charged metal ions and suppression of the repulsive interactions between DNA negatively-charged segments. **Figure 1C** shows the

change of DNA hydrogel film surface area after saturation with metal precursor and its reduction. The degree of DNA hydrogel shrinking during metal precursor uptake was comparable for each precursor and varied within 70-90% (**Figure 1C**) indicating strong binding character of all studied metal ions to DNA. After absorbance of metal precursors, they were reduced by placing hydrogel into 20 mM solution of $NaBH_4$ (**Figure 1A,B)**. Reduction of metal precursor was accompanied by drastic colour change of hydrogels and swelling to a different extent (**Figure 1C**).

Table 1. Chemical structures of metal precursors, uptake efficiencies of metal precursor by DNA hydrogel shown as mole percentages of metal atoms per DNA nucleotides, uptake times, and resistance of metallized hydrogels to DNase digestion.

Metal	**Precursor**	**Uptake efficiency[a] / %**	**Absorption time / h**	**Digestion by DNase[c]**
Au	$HAuCl_4$	70 ± 10	3 h	Yes
Ag	$AgNO_3$	55 ± 5	< 1 h	Yes
Pd	K_2PdCl_4	65 ± 5	5 h	No
Pt	H_2PtCl_4	65 ± 10	< 1 h	No
	$PtCl_2(NH_3)_2$	50 ± 5	< 1 h	n/a[c]
Cu	$CuCl_2$	-		Yes (slow)
Ni	$NiCl_2$	-		Yes (slow)[b]

[a]Data were obtained by atomic absorption spectroscopy; [b]NPs dissolved during digestion; [c]No NPs are formed during reduction

Degree of hydrogel volume recovery strongly depended on the nature of metal used. In particular, the size of hydrogels metallized with Au, Cu, Ag, and Ni recovered completely, while there was almost no swelling of DNA hydrogels containing platinum. Moderate swelling was observed for the hydrogel metallized with palladium. Different swelling behaviour of hybrid hydrogel after metallization can be explained by different interaction of metal NP with DNA. The effect of strong adhesion of some classes of nanoparticles to hydrogels has been

previously demonstrated;(Rose et al. 2014) therefore, strong nonspecific interaction between DNA and Pt NP(Yang et al. 2006) may result in cross-linking of DNA by NP that prevents hydrogel from swelling.

For further analysis, metallized hydrogels were decomposed either enzymatically or by ultrasonic sonication and the obtained stable colloidal suspensions were characterized by UV-vis spectroscopy and transmission electron microscopy (TEM). Absorption of each type of metal precursor resulted in the complete inhibition of DNase activity towards DNA digestion in hydrogel. In contrast, after reduction of the absorbed metal precursors, the activity of DNase toward DNA degradation revived for most of metals except Pd and Pt (**Table 1**). It is assumed that binding of transitions metals to DNA induces structural changes that prevent DNase binding to DNA and its functioning. Contrastingly, after reduction of metal ions, most of the hydrogels (except those metallized with Pd and Pt) were readily digested by DNase. Correlation of incomplete swelling of Pt- and Pd-metallized hydrogels with their resistance to DNase digestion suggests that strong interaction of NP with DNA prevents DNase form sliding along DNA and performing DNA hydrolysis.

NPs formed after DNA metallization were directly observed by transmission electron microscopy (TEM). **Figure 2** shows TEM images of NPs obtained after hydrogels decomposition together with NP size distributions. Regardless of metal used, reduction of metal ion inside DNA hydrogel yields very small metal NP of average size 2-3 nm. Formation of small NP inside DNA hydrogel can be explained by a facile nucleation of NP on DNA that results in an explosive formation of many nucleation centres growing to small NP. Templating of small size NP is an important property of DNA hydrogel as a matrix because, according to earlier studies, metal particles synthesised in hydrogels made of other than DNA synthetic polymers are much larger, usually, on the order of 10 nm and above.(Hortiguela et al. 2011; Kim and Lee 2007; Ramtenki et al. 2012; Zhu et al. 2012)

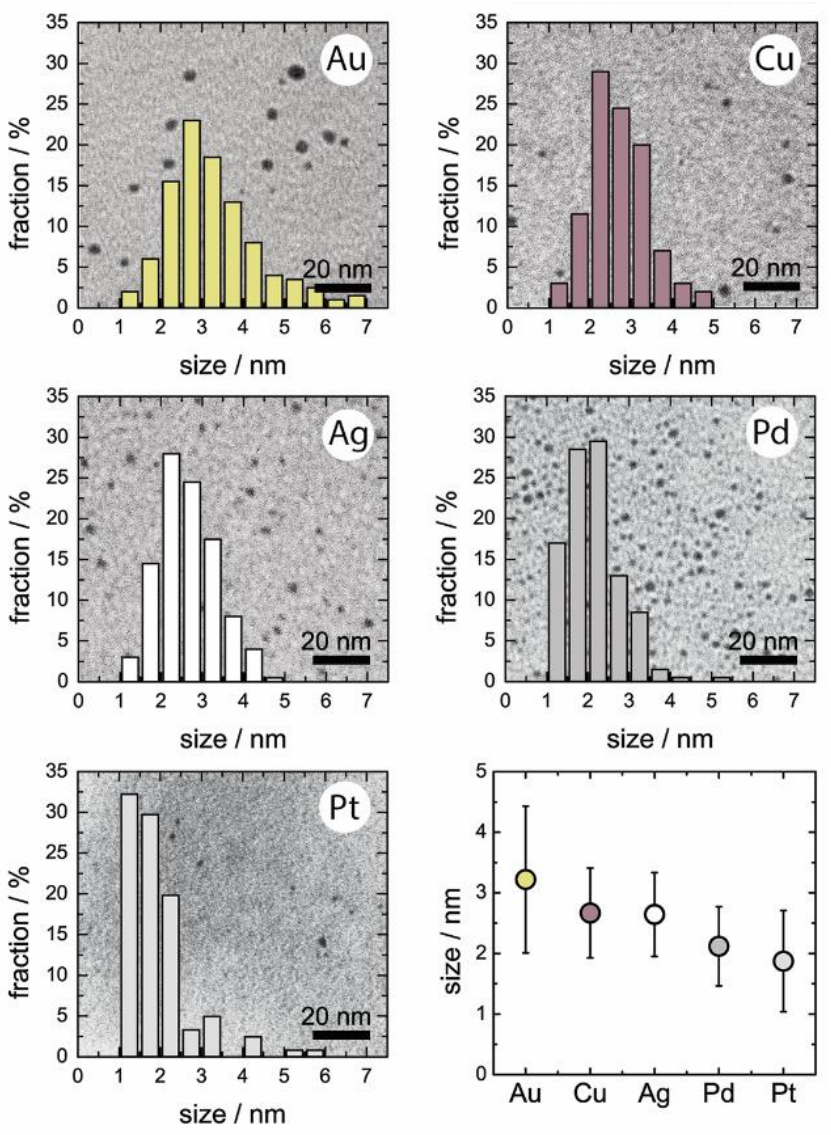

Figure 2. Typical TEM images and size distributions of metal NPs synthesized in DNA hydrogel dispersed by enzymatic digestion or sonication of corresponding hybrid hydrogels. Size distributions were obtained by measuring *ca.* 500 NP in each sample. The bottom right graph shows average sizes of NP together with standard deviations. Ni NP were not observed as a result of their dissolution during TEM sample preparation.

2.2 Catalysis by metallized DNA hydrogels

Catalytic activities of hybrid hydrogels were compared using a model catalytic system: reduction of *p*-nitrophenol to *p*-aminophenol by $NaBH_4$. The catalysts were prepared based on the same amount of DNA hydrogel. Due to difference in the absorbed amount of metal

precursor by DNA hydrogel and difference in size of NP, total available surface of NP in every case is different.

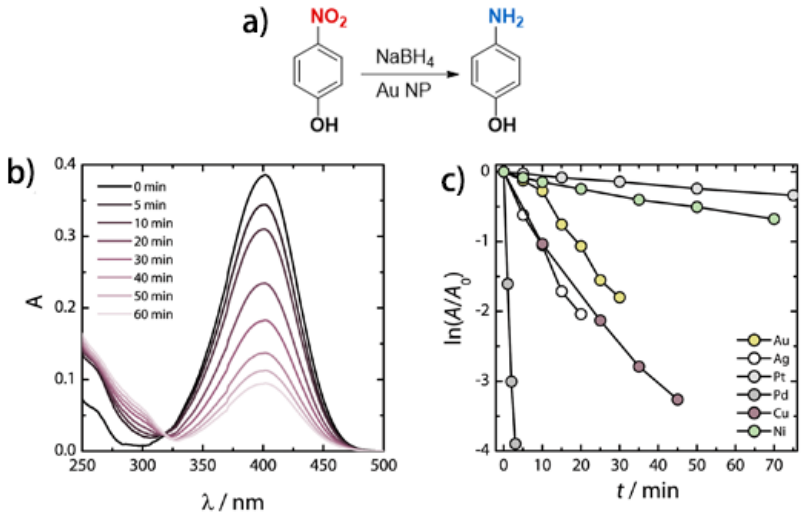

Figure 3. (a) Reaction of *p*-nitrophenol reduction by $NaBH_4$ using hybrid hydrogels. (b) Time-dependent changes in UV-vis absorbance spectra of a solution containing 0.02 mM *p*-nitrophenol, 10 mM $NaBH_4$, and hybrid hydrogel metallized by silver. (c) Kinetic curves of *p*-nitrophenol reduction catalysed by hybrid hydrogels containing NP of various metals built in coordinates of the first-order kinetics. The slope of the kinetic curve obtained for reaction without catalyst was zero.

Conversion of *p*-nitrophenol to *p*-aminophenol was monitored spectroscopically as a decrease in UV-Vis absorbance intensity of *p*-nitrophenol at 400 nm (**Figure 3A**). The obtained time dependences of 400 nm absorbance decrease were then built in the coordinates of the first-order reaction (**Figure 3B**), i.e. $\ln(A/A_0)$ over reaction time, where A and A_0 are current and initial absorbances of *p*-nitrophenol, respectively. **Figure 3** shows that all the hybrid hydrogels are catalytically active. Linear dependences were obtained for all the samples of metallized hydrogels indicating the first-order kinetic reaction in a good agreement with past studies.(Gu et al. 2014; Wunder et al. 2010) Apparent rate constants (k_{app}) were calculated from the slopes of the linear dependences (**Figure 3C**). Catalytic activities of metallized hydrogels largely varied depending on metal used for DNA hydrogel metallization (**Figure 2**). Due to the

difference of DNA coordination properties of studied ions as well as the difference of NP sizes and their densities in hydrogels the calculation of catalytic activities per NP or per NP surface area and the accurate comparison of the catalytic activities of hybrid hydrogels is difficult. Despite of this interplay of various parameters, a number of general conclusions can be made. There is no correlation between the catalytic activity of hybrid hydrogel (**Figure 3C**) and the size of embedded NPs (**Figure 2, bottom-right**). On the other hand, the obtained series of catalytic activities of metallized hydrogels (**Figure 3C**) is in a good agreement with earlier reports on *p*-nitrophenol catalytic reduction over metal nanoparticles (**Table 2**), where high catalytic activity of Pd NP was found. Metallized hydrogels containing Au, Ag, or Cu NP are moderately active and Ag NP are more active than Au NP as we observed in our study. In contrast, the catalytic activity of hydrogels metallized with Pt was at least 100 times lower than that of hydrogel containing Pd NP. Very low catalytic activity of platinated DNA hydrogel can be attributed to the catalysis of $NaBH_4$ degradation by Pt NP rather than *p*-nitrophenol reduction. Indeed, it was shown that hydrolysis of $NaBH_4$ is virtually absent in systems with Au, Ag, and Pd NP, while it is efficiently catalysed by Pt NP.(Garron et al. 2010) Very low catalytic activity of Pt NP in hollow silica shells was found by Tan et al. (Tan et al. 2016) yet there are studies reported a moderate catalytic activity of Pt NP. This inconsistency might be a result of different correlation between rates of *p*-nitrophenol reduction and $NaBH_4$ degradation that depends on an experimental system. Finally, low catalytic activity of Ni NP is caused by their gradual dissolution due to high ionization tendency and instability of Ni NP as it was discussed above.

Table 2. Comparison of catalytic activity of noble metal NP in *p*-nitrophenol reduction reaction.

Type of NP	Relative activity of NP	References
Dendrimer-encapsulated NP	Pd > Au ≈ Pt > Cu	(Pozun et al. 2013)
NP on graphene oxide	Pd > Ag > Au	(Yang et al. 2013)
NP in mesoporous silica	Pd > Pt > Au	(El-Sheikh et al. 2013)

NP in hollow silica shells	Pd > Ag > Au >> Pt	(Tan et al. 2016)
This study	Pd > Ag ≈ Au ≈ Cu > Ni > Pt	

3. Conclusions

DNA hydrogel is a robust matrix for concentrating of transition metal ions and preparation of NP that can be used for catalytic applications. Metallization of DNA hydrogels by Au, Ag, Pt, Pd, Cu, and Ni results in a formation of hybrid hydrogel with well dispersed NP of several nm size which are stabilized in the matrix of DNA hydrogel and are catalytically active. These "soft" hybrid materials are also promising as benign environmental as well as *in vivo* catalysts.

4. Experimental Section

Materials: DNA sodium salt (ca. 7 kbp, ca. 90% purity) extracted from salmon milt was a gift from Maruha Nichiro Holdings, Inc. (Japan). Tetramethylethylenediamine (TMEDA) from Sigma (USA), ethylene glycol diglycidyl ether (EGDE) from TCI (Japan), sodium borohydride ($NaBH_4$) from Aldrich (USA), p-nitrophenol, sodium hydroxide (NaOH), and sodium chloride (NaCl) from Wako Pure Chemical Industries, Ltd. (Japan) were used as received. Deoxyribonuclease I from Bovine Pancreas was purchased from Wako Pure Chemical Industries, Ltd. (Japan). Milli-Q water purified by Simplicity UV apparatus (Millipore, Japan) was used in all experiments.

Hydrogen tetrachloroaurate ($HAuCl_4$) (30 wt.% solution in dilute hydrochloric acid, 99.99%), sodium hexachloroplatinate (Na_2PtCl_4) of 99.99% purity, silver nitrate ($AgNO_3$) of 99.9999% purity from Sigma-Aldrich, cis-diammineplatinum (II) dichloride (cis-$[PtCl_2(NH_3)_2]$) from TCI (Japan), potassium tetrachloropalladate (II) (K_2PdCl_4) of 99.99% purity from Sigma-Aldrich, copper (II) chloride dihydrate ($CuCl_2 \cdot 2H_2O$), nickel (II) chloride hexahydrate ($NiCl_2 \cdot 6H_2O$) were used as metal precursors.

UV–Vis spectroscopy: Spectra of DNA, NP, and p-nitrophenol in solution were recorded on a Jasco V-630 spectrophotometer (Japan) in 1 mL quartz cells at room temperature.

Atomic absorption spectroscopy. Quantitative analysis of the concentration of metal ions in solution was performed on a Hitachi Z-5710 atomic absorption spectrometer (Japan). Standard 1000 ppm solutions of analysed metals were purchased from Wako Pure Chemical Industries, Ltd. (Japan) and used for standard curve measurements.

Transmission electron microscopy (TEM): TEM observations were performed at room temperature on a Hitachi H-800 microscope (Japan) at 200 kV acceleration voltage. Hybrid hydrogels were homogenized by sonication with Tairec VP-5S, ultrasonic homogenizer (Japan) at 20 kHz and power below 50W for 5 min. Gold and silver hybrid hydrogels were dissolved in solution of DNase. Twenty μL of analysing sample solution was placed onto a 3 mm copper grid covered with a collodion film. After 3 min the solution was removed from the surface of a grid with a filter paper, and the samples were dried under ambient conditions overnight prior to observations.

Preparation of hydrogel films from DNA: Two percent (2%) solution of DNA in Milli-Q water was prepared by stirring of DNA in water at room temperature during 1 day. To 3 mL 2% solution of DNA were added 30 μL of 0.5 M NaOH, solution 9.6 μL of EGDE, and 3 μL of TMEDA. The components were stirred in a 30 mm diameter Petri dish at 35°C for 60 min, and the resulted viscous mixture was then heated at 90 °C for 20 min and at 50 °C for 2 h covered with upper glass, and for 2 h in the open air. The resulted DNA hydrogel film was repeatedly washed by large volumes of 1 mM NaCl solution to remove non-cross-linked DNA and other unreacted chemicals and stored in the same saline solution.

Synthesis of metal NPs inside hydrogel: DNA hydrogel films (ca. 50 mg) were placed into 4 mL solution of 2.5 mM $HAuCl_4$, $AgNO_3$, cis-$[PtCl_2(NH_3)_2]$, K_2PdCl_4, or 2 mL solution of 0.1 mM $CuCl_2 \cdot 2H_2O$ or $NiCl_2 \cdot 6H_2O$, respectively, and incubated overnight at room temperature.

The resulted hydrogel films were washed by 5 mL of Milli-Q water for 0.5 h and then 5 mL of freshly prepared solution of 20 mM $NaBH_4$ was added to reduce metal ions.

Enzymatic decomposition of metallized DNA hydrogel: Stock solution of deoxyribonuclease I (DNase) was prepare by dissolving 10 mg of DNase in 0.5 M solution of NaCl (300 μL) and Milli-Q water (700 μL). Twenty μg of a metallized DNA hydrogel was placed in solution prepared by mixing 4700 μL of MilliQ water, 50 μL of 1 M $MgCl_2$, 250 μL of 1 M Tris buffer, 25 μL of DNase stock solution, and the solution incubated at 37 °C for 2 hours.

Catalytic reduction of p-nitrophenol: Two mL of reaction solution containing 0.02 mM p-nitrophenol and 10 mM $NaBH_4$ were added to a hybrid hydrogel and time-resolved UV-vis spectra of supernatant above hydrogel were recorded.

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