Ligand Exchange

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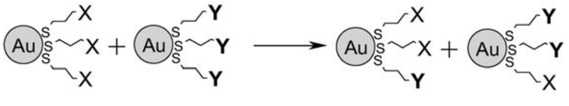
Hopping of Thiolate Ligands between Au Nanoparticles Revealed by EPR Spectroscopy**

*Mouna Zachary and Victor Chechik**

Herein, we exploit the sensitivity of electron paramagnetic resonance (EPR) spectroscopy to spin–spin interactions in order to monitor the exchange of ligands between Au nanoparticles. The ligand exchange in Au nanoparticles is a very efficient tool for particle functionalization and has hence attracted much attention.[1] A number of mechanisms have been suggested for this reaction, including associative (S_N2 type), dissociative (S_N1 type), and diffusion-limited Langmuir kinetics.[2] It appears that the nature of the incoming ligand (e.g., thiol or disulfide) plays an important role in controlling the reaction mechanism.

A related reaction is that of the exchange of ligands between nanoparticles (e.g., ligands X and Y between nanoparticles **1** and **2**, respectively; Scheme 1). This is also a very important process as it bears upon the stability of heterogeneously functionalized nanoparticles and the stability of nanoparticle mixtures.



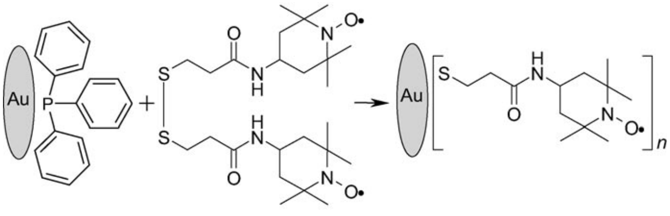
1 **2** **3** **4**

Scheme 1. Schematic illustration of an interparticle ligand-exchange reaction.

Very little, however, is known about this reaction primarily because it is very difficult to study. Indeed, many properties of the starting materials **1** and **2** and the products **3** and **4** (Scheme 1) are indistinguishable, and special markers must be used to monitor this reaction. For instance, Mayya and Sastry used different core material (e.g., Au and Ag) to differentiate between the nanoparticles and show that interparticle exchange takes place.[3] Murray and co-workers made nanoparticles **1** and **2** (Scheme 1) soluble in immiscible solvents (water and toluene) and thus were able to observe the transfer of ligands from one phase to another.[4] These authors also showed that there is transfer of the metal between the nanoparticles.

An inspection of Scheme 1, however, shows a critical difference between starting material **1** and product **4**. In the starting material, the ligands X are surrounded by the same ligands, whereas in the product, they are incorporated into a layer of different ligands. Hence, the interparticle exchange can be monitored by a technique that is sensitive to the interactions between adjacent ligands X (Scheme 1). An example of such an analytical technique is EPR spectroscopy. It is sensitive to the interactions between adjacent paramagnetic species and hence can differentiate between the starting material and the products of the interparticle ligand-exchange reaction.

With these considerations in mind, we have explored the reaction between Au nanoparticles functionalized with a nitroxide spin label **1** and a series of unlabeled nanoparticles **2**. Spin-labeled nanoparticles **1** were prepared by a ligand-exchange reaction between the bis-nitroxide disulfide **5** and triphenylphosphine-protected Au nanoparticles **6** (Scheme 2).



6 **5** **1**

Scheme 2. Synthesis of spin-labeled nanoparticles.

The exchange reaction between ligand **5** and particles **6** was carried out overnight at room temperature with a ratio of bis-nitroxide disulfide/Au nanoparticles of 80:1. Under these conditions, most triphenylphosphine ligands are replaced by the disulfide ligand to give nitroxide-coated nanoparticles **1**.[5] The solution EPR spectrum of nanoparticles **1** showed a single broad line owing to strong spin-exchange interactions between adjacent nitroxides, which is consistent with the high density of nitroxide-derivatized ligands on the Au nanoparticles surface.

Nanoparticles **1** had diameter of approximately 1.7 nm as determined by TEM microscopy (Figure 1 a). The UV spectra showed a very weak plasmon peak (shoulder at around 520 nm, Figure 1 b), which is consistent with the small particle size.

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[*] Dr. M. Zachary, Dr. V. Chechik
Department of Chemistry
University of York
Heslington, York YO10 5DD (UK)
Fax: (+44) 1904-432-516
E-mail: vc4@york.ac.uk

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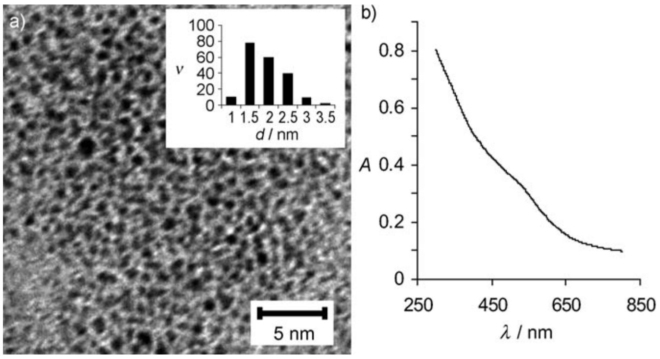


Figure 1. TEM and UV data for nanoparticles **1**.

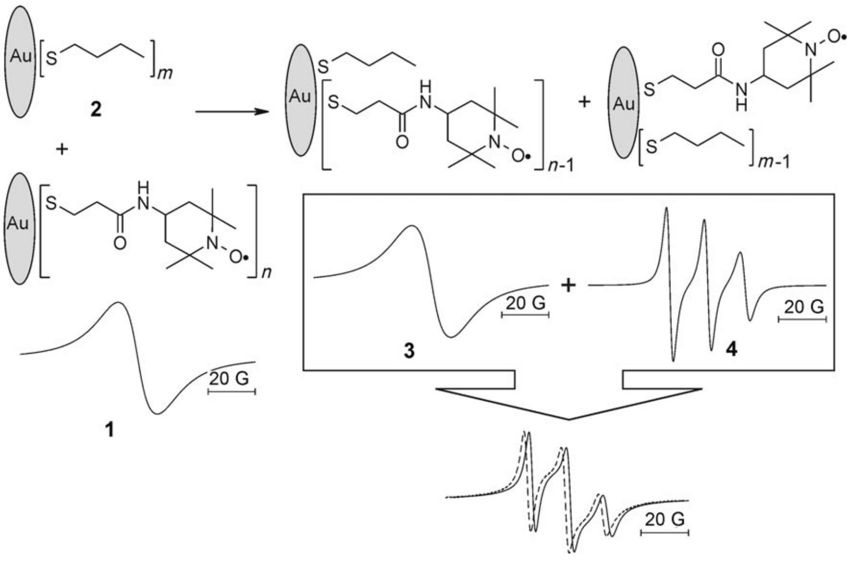
Alkanethiol-protected nanoparticles **2** were prepared by following a standard Brust protocol.[6] Octane, butane, and octadecanethiol were used as stabilizing ligands. These nanoparticles were approximately 2.5 nm in diameter. It was essential to ensure the absence of free-thiol impurities in the nanoparticles **2** as thiols can react with the spin-labeled nanoparticles, leading to loss of the EPR signal. Special care was therefore taken to further purify nanoparticles **2** by gel-permeation chromatography (GPC). ^{1}H NMR spectra of the purified nanoparticles showed absence of small-molecule contamination (as evidenced by the absence of sharp peaks attributable to the alkanethiol and/or tetraalkylammonium phase-transfer agent).

Following an overnight reaction between spin-labeled particles **1** and octanethiol-protected nanoparticles **2**, the spectrum line shape changed dramatically to reflect the presence of monoradical species, which were well-separated from other spin labels (dotted line in Scheme 3). The double integral intensity of the spectra did not change; hence there was no spin-label decomposition during the reaction. We believe that these spectral changes are due to the hopping of spin labels from the labeled particles onto unlabeled ones. Our earlier results suggest that the EPR spectra of nanoparticles with more than five nitroxide groups per particle are dominated by a broad line.[5] On the other hand, particles coated with one or two nitroxide ligands give predominantly a triplet spectrum. Thus, hopping of the ligands between the nanoparticles should lead to the increased contribution of the triplet component in the EPR spectra. The complex spectral-line shape of reaction mixtures can be readily deconvoluted into the contributions of the broad line (high-coverage spin-labeled particles) and a triplet (isolated spin labels).

To obtain information about the mechanism of interparticle exchange, we explored the kinetics of this reaction. The reaction was too slow at room temperature to be monitored conveniently. The triplet contribution to the EPR spectrum remained quite small (< 10 %) and significant changes to the line shape were still observed after 24 h of reaction. Therefore, we carried out kinetic runs at 70 °C in chlorobenzene (inert common solvent for nanoparticles **1** and **2** and with a high boiling point). At this temperature, changes in the EPR line shape were observed within minutes and reactions reached completion in only a few hours.

To test the stability of the spin-labeled nanoparticles **1** under reaction conditions, we heated their solution without the addition of nanoparticles **2** and monitored the mixture by EPR spectroscopy. Any desorption of the ligand from the surface of nanoparticles **1** would result in the appearance of a sharp triplet signal in the spectrum owing to formation of rapidly tumbling small mononitroxide species. Even after prolonged heating (6 h), we observed only minimal formation of the triplet (below 1–2 % of the total EPR intensity). This control experiment proved the absence of appreciable ligand loss from the nanoparticle surface under these reaction conditions. Nonetheless, these experiments do not exclude the possibility of forming a low steady-state concentration of the desorbed ligand and a small number of vacant sites on the nanoparticles.

The kinetic analysis of the interparticle-exchange reaction between nanoparticles **1** and **2** was carried out as follows. The reaction was only monitored at low conversion levels (below approximately 20–25 %), and nanoparticles **2** were used in a 7–20-fold excess (to ensure pseudo-first-order conditions). At this low conversion level, the organic shell in nanoparticles **3** still retains more than 50 % of the spin labels and hence gives a broad line signal, the same as for nanoparticles **1** (Scheme 3). With particles **2** in excess (particularly at low conversion levels), most of the nanoparticles **4** will only have one spin label and hence give a triplet spectrum (Scheme 3). The constant double integral intensity throughout the reactions confirmed the absence of spin-label decomposition. Under these reaction conditions, the deconvolution of experimental spectra into the contribu-



Scheme 3. The interparticle ligand-exchange reaction and the corresponding simulated EPR spectra. The spectra at the bottom show the experimental (dotted line, offset for clarity) and simulated (solid line) spectra for the exchange reaction mixture.

tions of broad lines and triplets thus gives direct information about the relative amount of species **4** in the mixture. The obvious disadvantage of our approach is that it is limited to reactions that use nanoparticle **2** in excess and can only be applied to monitor reactions at low conversion levels. Nonetheless, this method provides important kinetic data on the interparticle exchange that are extremely difficult to obtain by using other techniques.

All experimental spectra were fitted with three Lorentzian lines with constant double integral intensity (to account for the triplet component) and a Gaussian line to account for the broad-line component. The relative ratios of triplet component in the overall spectra showed good fits with the first-order rate equation (Figure 2). Although more-complex kinetic laws can be envisaged owing to the heterogeneity of binding sites on the nanoparticle surface, a simple first-order equation can be used as a convenient benchmark to compare the reactivity in different kinetic runs.

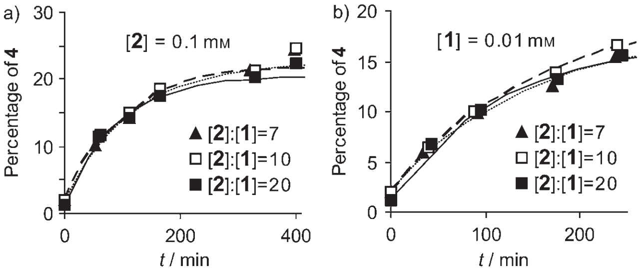


Figure 2. Typical kinetic traces for the interparticle ligand-exchange of spin-labeled nanoparticles **1** and octanethiol-protected nanoparticles **2**. a) and b) show a series of runs with a constant concentration of particles **2** and **1**, respectively. The lines show the best fit with pseudo-first-order kinetics for the ratio of reagents [**2**]:[**1**] = 7 (dotted line), 10 (dashed line), and 20 (solid line), respectively.

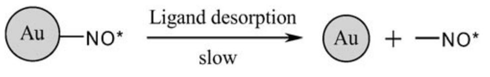
We carried out two series of experiments. In one series (Figure 2a), the concentration of alkanethiol-protected nanoparticles was kept constant while the concentration of spin-labeled particles was varied; in another series (Figure 2b), the concentration of alkanethiol-protected nanoparticles was varied while the concentration of spin-labeled nanoparticles was kept constant (Figure 2). The range of concentrations used was limited by the solubility of the nanoparticles and the sensitivity of the EPR spectroscopy. Rate constants and the maximum extent of the reaction are shown in Table 1. Owing to significant errors of EPR deconvolution and integration of broad spectra, we estimate that the accuracy of the kinetic data is approximately 20%. Table 1, entries 2 and 5 illustrate the typical reproducibility of the kinetic runs. The data in Table 1 were obtained in air; a control experiment showed that the rate constants do not change if the reaction is carried out in an inert atmosphere.

Table 1: First-order rate constants and maximum conversion for the interparticle-exchange reaction of spin-labeled nanoparticles **1** and octanethiol-protected nanoparticles **2**.

[**1**] [mM]	[**2**] [mM]	Rate constant [s^{-1}]	Maximum extent of reaction [%]
0.01	0.07	1.1×10^{-4}	18.4
0.01	0.1	1.1×10^{-4}	20.2
0.01	0.2	1.4×10^{-4}	17.2
0.014	0.1	1.2×10^{-4}	24.7
0.01	0.1	1.4×10^{-4}	24.2
0.005	0.1	1.6×10^{-4}	21.8

Interestingly, the reactions never reached completion. Despite the excess of nanoparticles **2**, only approximately 20% of the spin labels from nanoparticles **1** can migrate. Importantly, the maximum extent of reaction (Table 1) is independent of the initial concentrations within experimental error. Therefore, the reaction cannot be described as a thermodynamic equilibrium. The maximum conversion is thus linked to the number of exchangeable sites on the surface of nanoparticles **1** (nanoparticles **2** were always in significant excess). The rather small number of exchangeable sites (about 20%) can be tentatively explained by the interparticle exchange occurring preferentially at the vertex or defect sites on the Au surface.[1]

The kinetic data provide further insight in the reaction mechanism. All data showed good fit with the first-order rate equation. The first-order rate constant is virtually independent of the concentration of reagents. This can also be visually observed in Figure 2 as the kinetic data for different concentrations are indistinguishable within experimental error. This implies that the reaction is zeroth order with respect to the octanethiol-coated particles **2** (the reaction rate is not affected by changing the concentration of these nanoparticles). We believe, therefore, that the reaction follows a dissociative mechanism. In the rate-determining step, the spin-labeled ligand desorbs from the nanoparticle **1**, thus creating a vacancy on the nanoparticle surface. The consequent reactions are faster and do not influence the overall rate of the interparticle exchange (Scheme 4). The exact fate of the reaction intermediate is unclear, although it seems logical to suggest that the further reactions include dissociation of alkanethiol ligand from nanoparticles **2** followed by adsorption of the ligands on the vacant sites on the nanoparticle surface. The nature of the desorbing species is also not clear; it could be a thiolate ion, a disulfide group, or an Au–thiolate complex.[7]



Scheme 4. Rate-determining step of the interparticle ligand-exchange reaction.

The proposed mechanism fits very well with the data for the exchange of nanoparticles **1** with nanoparticles protected by butane- and octadecanethiol. In all cases, the rate constants and the maximum extent of reaction were independent of the reagent concentration within experimental error and equal to those for octanethiol-coated particles. This lack of dependence of the kinetic parameters on the chain length of the ligand in alkanethiol-coated particles further supports the dissociative reaction mechanism (the alkanethiol-coated nanoparticles do not participate in the rate-determining step of this mechanism).

These mechanistic findings echo our earlier study of ligand-exchange reactions of thiol-protected nanoparticles with disulfide groups.[8] Both reactions involve ligand desorption in the rate-determining step and the extent of both reactions is limited to a few of the most reactive sites on the nanoparticle surface. It is likely that these mechanistic details are quite general and applicable to many processes involving exchange with weak ligands. Exchange with strong ligands (e.g., thiol groups) follows different mechanistic pathways.[2]

In conclusion, we have demonstrated that EPR spectroscopy can be readily applied to monitor interparticle exchange by using spin-labeled Au nanoparticles. The interparticle exchange is a slow reaction affecting only approximately 20 % of the binding sites on the nanoparticle surface. The kinetic analysis shows that this reaction follows a dissociative mechanism with ligand desorption from the nanoparticle surface in the rate-determining step.

Experimental Section

GPC was carried out by using Biobeads SX-1 gel. EPR spectra were recorded on a JEOL JES RE-1X spectrometer operating at the X-band by using 100 kHz modulation frequency.

Spin-labeled ligand **5** was synthesized as described previously.[9] Nanoparticles **2** were synthesized according to a literature protocol[7] by using a 1:1 Au/thiol ratio and additionally purified by GPC by using toluene as the eluent. The nanoparticles travel through the GPC column as a colored narrow band, which facilitates collection of the fractions. We found this purification method to be very efficient. Nanoparticles **6** were prepared by using a literature procedure[10] and were purified by GPC with dichloromethane as the eluent. Nanoparticles **1**[7] were prepared by mixing the appropriate amount of nanoparticle **6** solution in dichloromethane (0.5 mм) with ligand **5**. The reaction mixture was left overnight and separated by GPC with dichloromethane as the eluent. The complete absence of sharp peaks of the free ligand **5** (used in excess) in the EPR spectra of the purified nanoparticles confirms the efficiency of GPC purification and the absence of small-molecule impurities in the nanoparticle preparations. Interparticle-exchange reactions were carried out by mixing the appropriate amounts of stock solutions of nanoparticles **1** and **2** in chlorobenzene at 70 °C.

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