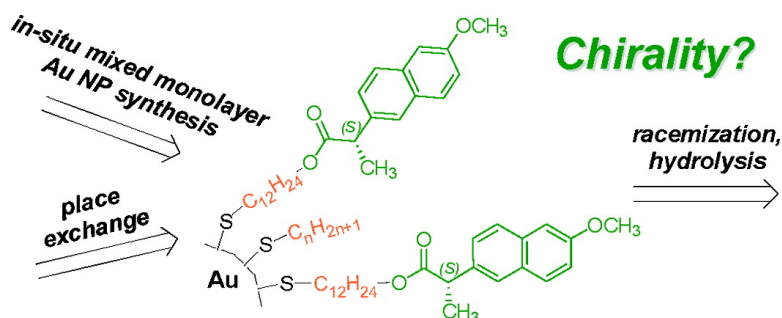Article

Postsynthesis Racemization and Place Exchange Reactions. Another Step To Unravel the Origin of Chirality for Chiral Ligand-Capped Gold Nanoparticles

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Postsynthesis Racemization and Place Exchange Reactions. Another Step To Unravel the Origin of Chirality for Chiral Ligand-Capped Gold Nanoparticles

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Abstract: We examine how postsynthesis nanoparticle ligand shell modifications as a general approach can help in the understanding of currently proposed mechanisms for gold nanoparticle chirality. We compare the CD response of chirally decorated mixed-monolayer-protected gold nanoparticles synthesized in situ with quasi-identical gold nanoparticles either prepared by place exchange reactions or subjected to an aqueous base, resulting in partial hydrolysis and simultaneous partial racemization. We find that the CD response at wavelengths where the free chiral ligand does not absorb strongly depends on the preparation conditions, i.e., in situ synthesis vs place exchange, and that postsynthesis racemization of the chiral ligand produces racemic nanoparticles with no CD response, i.e., no induction of a chiral bias during reductive nanoparticle formation. Considering all experimental results for the described gold nanoparticle system with a $C_{12}H_{24}$ spacer between the nanoparticle surface and chiral center, the so-called "vicinal effect" with the formation of a supramolecular assembly of the chiral moieties seems to be active. Finally, we argue that postsynthesis nanoparticle ligand shell modifications such as racemization and/or place exchange reactions are very powerful tools to unravel contributions of the different gold nanoparticle chirality mechanisms.

Introduction

The origin of chirality in gold nanoparticles (Au NPs) is still an open question, despite extensive theoretical and experimental studies in recent years.[1−12] Three possible mechanisms have been proposed by Whetten et al.[1] in their early paper on glutathione-protected Au NPs: (1) The metal core is chiral, as in the asymmetric structure found in Ni_{39} clusters. (2) The core is achiral, but the thiol groups bound to the Au atoms are in a chiral pattern. (3) The adsorption pattern of the head groups and the core are achiral; only the chiral adsorbate influencing the electronic structure of the metal core contributes to chirality.

The first mechanism can find support from theoretical studies of Garzón et al.,[2] and calculations of Beratan et al.[3] support the second mechanism, i.e., the chiral adsorption pattern. Enlightened by metal surface chirality, a related chiral footprint model was proposed by Bürgi et al.[4] In contrast, Yao et al. prepared penicillamine-capped Au NPs,[5] and more recently penicillamine-capped Ag NPs,[6] and the vicinal effect related to the third mechanism was discussed as the main effect for the origin of chirality of Au NPs (although other possibilities were not ruled out in the discussion and in follow-up studies[8,9]). More recently, the intrinsic chiral properties of Au NPs have been experimentally demonstrated in a landmark paper by Kornberg et al.[13] The authors, using high-resolution X-ray diffraction studies, found that the overall symmetry of the discrete nonchiral *p*-mercaptobenzoic acid-protected Au NPs was chiral (5-fold decahedral symmetry) and that the sulfur atoms bound to the surface Au atoms were chiral centers. Because the capping thiol was achiral (no chiral bias), both enantiomers were found to coexist, making the whole system racemic. This result is similar to the second mechanism proposed by Whetten et al. and related work by other groups.[1,3,4,11] The emerging questions are now the following: (i) Is it possible to favor the formation of one Au NP enantiomer over the other using chiral protecting groups in situ during synthesis? (ii) Is it possible to form a chiral core upon adsorption of a chiral group postsynthesis (either in situ or via place exchange)?

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Scheme 1
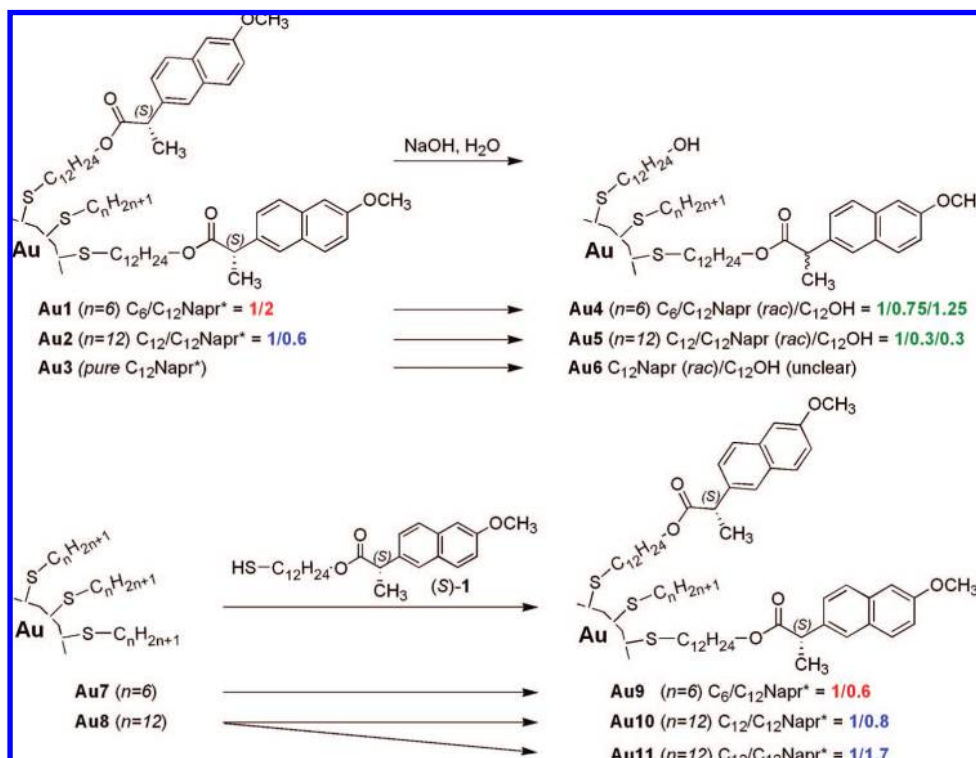
To help answer these questions and disentangle contributions from the three mechanisms, surface ligand reactions could provide some insight. To distinguish between the first and second mechanisms, it is necessary to remove the possible chiral pattern by breaking the Au−S bond without affecting the core (postsynthesis NP modification) and compare the (chir)optical properties before and after. To discern the third mechanism from the other two, the strategy should be to remove the chiral centers without any effect on the surface (Au−S bond) and core. In this way, one should be able to differentiate the three possibilities and clarify major contributions in a given Au NP system. One such strategy has been used by Markovich et al.[7] In their study, Ag NPs synthesized using DNA as the template showed optical activity (CD response at longer wavelengths), but NPs adsorbed postsynthesis onto DNA did not (no CD response). The authors suggested an active chiral core mechanism, although the helical DNA structure, setting this system apart from other chiral thiolate-protected Au NPs, could play a more complex role. Comparable strategies were also described for flat chiral metal surfaces.[14,15]

Initially interested in the transfer of chirality from Au NPs to liquid crystals,[16] we developed chiral dopant-capped Au NPs, i.e., (S)-naproxen-functionalized alkanethiol [(S)-**1**]-capped Au NPs (Au1−Au3),[17] as shown in Scheme 1. In analogy to other studies, Au1−Au3 NPs show a CD response at wavelengths where the free thiol (S)-**1** does not absorb (no related CD).

We here report on post-NP synthesis ligand modifications and place exchange reactions[18] to evaluate contributions of the different gold NP chirality models. First, considering the chemical structure of the (S)-**1** (ester with α-acidic H), hydrolysis reactions to remove chiral moieties and simultaneously racemize the chiral center[19] at the NP would give two possibilities: (i) identical CD response, meaning the Au core is chiral and/or the thiolate binding to the Au atoms is in a chiral pattern, or (ii) no CD response, supporting the third mechanism of Whetten et al.[1] and Yao et al.[5,6] that only the influence of the metal core's electronic structure plays a role. In a second set of experiments we introduced chiral centers to nonchiral (racemic[13]) alkanethiol-capped Au NPs (Au7, Au8) using place exchange reactions and tested the CD response, similar to the experiments by Markovich et al.,[7] but without the likely contributions of a helical arrangement. These methods are schematically summarized in Scheme 1, and the obtained size distributions as determined by TEM are collected in Table 1.

Experimental Section

A description of the synthesis and characterization of Au2 and Au3 can be found in an earlier paper.[17] Au1 was prepared under conditions similar to those of Au2, i.e., in situ synthesis of mixed-monolayer-protected Au NPs.[20] Briefly, for Au1, a mixture of 0.25 g (0.58 mmol) of (S)-**1** thiol, 0.08 mL (0.58 mmol) of hexanethiol, and 0.2 g (0.58 mmol) of HAuCl₄·3H₂O was dissolved in freshly distilled, dry, and, at least initially, peroxide-free THF (70 mL). The resulting solution was stirred for 10 min, after which a freshly prepared solution of 0.22 g (5.8 mmol) of NaBH₄ in DI water (10 mL) was added at once. The mixture was stirred for an additional

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Table 1. Sizes (nm) and Size Distributions[a] of the Investigated Au NPs Au1−Au11[b]

| Au NP	size distribution ± SD (nm)
Au1	1.65 ± 0.39
Au2	1.54 ± 0.38
Au3	3.50 ± 0.81
Au4	1.20 ± 0.23
Au5	1.75 ± 0.40
Au6	−[c]
Au7	1.58 ± 0.44
Au8	1.93 ± 0.47
Au9	1.31 ± 0.29
Au10	1.57 ± 0.43
Au11	1.61 ± 0.42

[a] TEM image analysis of all particles in each image was performed with the following software: Scion Image Beta 4 (Scion Corp.) and/or Image J. [b] Note that there will always be a difference in size as well as size distribution for NPs originating from a reaction of a pre-existing NP sample (e.g., Au4 from Au1) as a different NP population is imaged with (HR)-TEM. [c] Could not be isolated in pure form due to amphiphilicity of the resulting mixed-monolayer-protected Au NPs.

2 h, and then the solvent was evaporated under reduced pressure. The black precipitate was collected and exhaustively washed with ethanol. The purity of the nanoparticles was checked by ^{1}H NMR. Although for both Au1 and Au2 a 1:1 ratio of thiols was used during synthesis, the final NPs show different ratios (1:2 for Au1 vs 1:0.6 for Au2), most probably due to (*S*)-**1** binding more easily to Au and the formation of Au NPs in the presence of the shorter hexanethiol.

The hydrolysis of the ester linkages and simultaneous racemization of the (*S*)-naproxen units (ratio ∼1:1) for Au1−Au3 was achieved by dissolving 10 mg of Au NPs in 40 mL of THF and addition of 20% aqueous NaOH (w/v). The solution was stirred at room temperature under an inert gas atmosphere. The amphipathic Au6 NPs were extremely difficult to purify and unfortunately impossible to isolate, but Au4 and Au5 were isolated and characterized after evaporation of THF, exhaustive washing with water and ethanol, and drying under vacuum. The isolated yield of the NPs after hydrolysis/racemization (Au4−Au6) was about 75% (based on the average molecular weight of the gold nanoparticles assuming a spherical shape). The purity and optical activity were examined by ^{1}H NMR and CD, respectively. Racemization of the (*S*)-naproxen unit under basic conditions was also pursued in control experiments using free (*S*)-**1** under identical conditions.

For the second set of reactions, Au7 and Au8 were first prepared using the same method as that described for Au1−Au3. For the place exchange reaction, 10 mg of Au7 or Au8 and 0.1 g of (*S*)-**1** were dissolved in 40 mL of freshly distilled, dry, and, at least initially, peroxide-free THF, and the resulting solution was stirred at room temperature for 4 days. After evaporation of the solvent, the NPs were purified by repeated washing with CH₃CN. For a second batch of Au8, the exchange reaction was done with twice the amount of chiral (*S*)-**1**. The isolated yield of the NPs after place exchange with (*S*)-**1** (Au9−Au11) was about 79% (based on the average molecular weight of the gold nanoparticles assuming a spherical shape). Purity was checked by ^{1}H NMR before performance of CD measurements.

Using the iodine decomposition method, the ratios between the two or three thiolates (i.e., disulfides after decomposition/oxidation) attached to the surface of all Au NPs before and after hydrolysis/racemization were determined by ^{1}H NMR (ratios of characteristic peaks) as described in detail by Murray et al.[21] and are detailed in
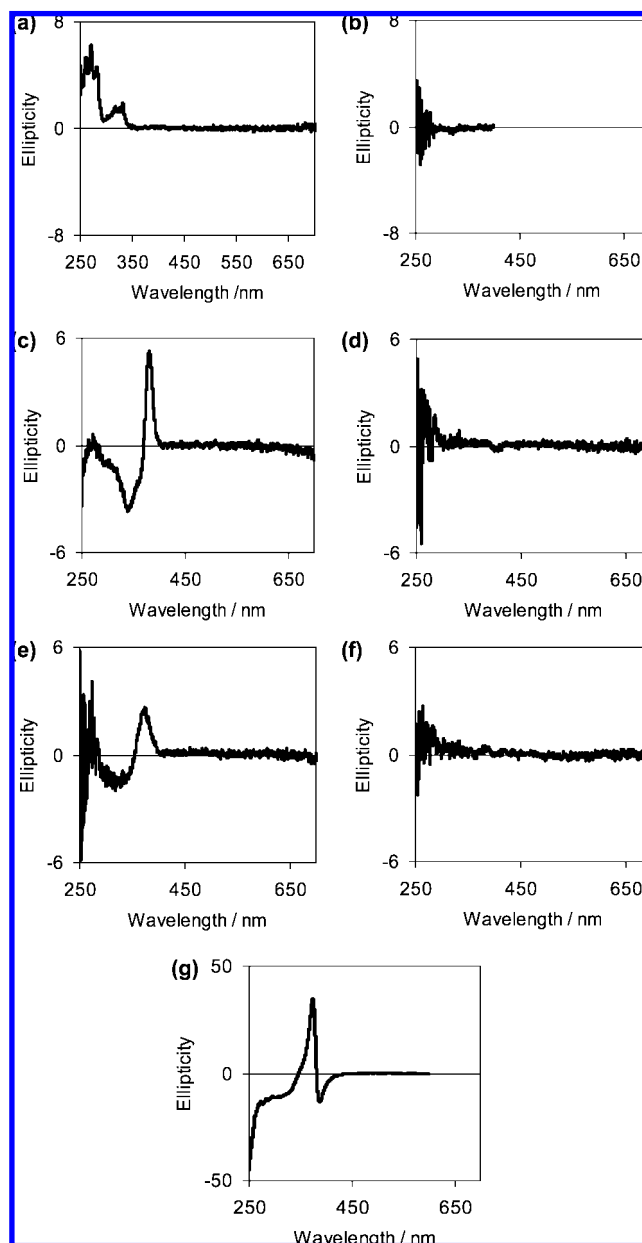
Figure 1. CD spectra of (a) (*S*)-**1**, (b) (±)-**1** (after racemization), (c) Au1, (d) Au4, (e) Au2, (f) Au5, and (g) Au3.

Scheme 1 (for a collection of all ^{1}H NMR and UV−vis absorption spectra see the Supporting Information (SI)).

Results and Discussion

In-Situ-Synthesized Chiral Mixed-Monolayer Au NPs. Similar to other reports on chirally decorated Au NPs, Au1−Au3 show a CD response (i.e., apparent Cotton effects) at wavelengths where the free thiol (*S*)-**1** does not absorb light (Figure 1c for Au1, Figure 1e for Au2, and Figure 1g for Au3). In Yao's paper[7] and in related work by other authors,[3,22] detailed discussions of the Au nanocluster electronic states are presented based on experiments by UV−vis, vis, and near-IR absorption spectroscopy. In a more recent paper by Huang et al.,[23] two absorption maxima (bands) were detected for Au NPs in

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UV−vis experiments at wavelengths of 367 and 383 nm. The authors discussed these bands as originating from metal-centered (Au 5d[10] to 6sp interband transitions) and/or ligand−metal charge-transfer transitions. Similarly for our systems presented here, the absorption peak around 380 nm (e.g., for Au1 and Au2) linked to a chiral response is due to these interband and/ or charge-transfer transitions. An important difference between our system and other chiral Au NPs reported in the literature is the distance of the chiral center from the Au NP surface. Arguments of whether this distance is too far to affect the electronic states of the Au NPs need to be addressed. Initial support comes from the obtained CD spectra. The CD response of Au1−Au3 at wavelengths where the free thiol (*S*)-**1** does not absorb is one point. The second point builds on a recent paper by Rotello et al.[24] describing the use of chiral phenyla-lanine (Phe)-protected Au NPs. In their system, because the chiral center is more remote from the Au NP surface (C24 spacer), the CD response of the Au NPs is rather similar to that of the free thiol at similar wavelengths, despite the possibility of H-bonding and $\pi-\pi$ interaction between the Phe moieties. Hence, the Au NPs in the present study should not be regarded as "simple" chiral ligand-protected Au NPs.

Postsynthesis Racemization. As indicated above, the first step of our strategy was to racemize the chiral centers introduced during in situ mixed-monolayer-protected Au NP synthesis. The ^{1}H NMR spectra of both Au4 and Au5 (see the SI) after treatment with aqueous NaOH still show broad peaks related to the (*S*)-naproxen aromatic ring, indicating only partial removal of the chiral moiety (60% for Au4 and 50% for Au5). In control experiments using free (*S*)-**1**, though much less pronounced, partial survival of the ester linkage of naproxen under these basic conditions was confirmed by NMR and TLC (matching R_f), and almost complete racemization was proven by a close to zero CD response (see Figure 1b) in comparison to pure (*S*)-**1** with a nonzero CD spectrum with several absorption maxima below 340 nm (see Figure 1a). Although a slight difference in reactivity between the Au NPs such as Au1−Au3 and free (*S*)-**1** cannot be entirely excluded,[25] these control experiments confirm the partial racemization/partial removal of the chiral moieties on the Au NP surface.

After hydrolysis/racemization, both Au4 (Figure 1d) and Au5 (Figure 1f) show virtually no CD response in comparison to the clearly observable Cotton effects at longer wavelength for the parent Au1, Au2 (and Au3). These CD results confirm that postsynthesis partial removal and simultaneous racemization of the outer protective layer of the Au NPs synthesized in the presence of a chiral thiol result in macroscopic racemization of these Au NP systems. Hence, for the system presented here based on the results before and after hydrolysis and racemiza-tion, the only explanation for the CD response at longer wavelengths for Au1−Au3 is that the chiral adsorbate influences the electronic structure of the metal core during the reductive NP formation; i.e., the so-called "vicinal effect"[5] is active.

To rule out significant contributions of structural changes of the NP core, HR-TEM images were taken for all NPs (see Figure 2). Considering the NPs' small size (∼1−2 nm), the fact that TEM in this size regime is a generally unsatisfying experiment because uncertainties can be larger than the NP size distribu-
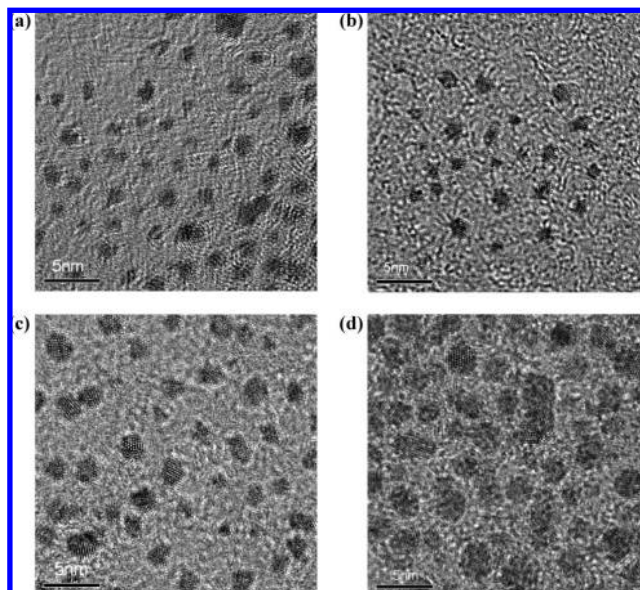

Figure 2. HR-TEM images of (a) Au1, (b) Au4, (c) Au2, and (d) Au5 (scale bars 5 nm). For size distributions see Table 1, and for larger images of Au2 and Au5 see the SI.

tions,[26] the instrument's resolution (∼0.8 nm), and the limited number of NPs we can actually measure from the various images of all investigated TEM grids, no easy detectable difference of the NP shape and surface morphology before and after hydroly-sis indicates that the dramatic change in CD response occurs predominantly as a result of the modification of the outer ligand shell of these Au NPs under mild basic conditions.

As can be seen from the TEM images, the as-synthesized and ligand-shell-modified Au NPs are not discrete or highly monodisperse. The hydrophobic nature of these mixed-monolayer-capped Au NPs and the impossibility to charge these NPs prevent us from using polyacrylamide gel elec-trophoresis (PAGE) to size separate the Au NPs (separation into batches with narrower size distribution) as described for other systems.[1,4−6,8−11]

The obtained CD spectra are the result of mixtures of different sizes of Au NPs, although the size distributions are fairly narrow (around ±0.35 nm). It is well-documented that different sizes of Au NPs show slightly different optical activities,[6] but that chirally decorated metal NPs with related (similar) sizes commonly exhibit similar wavelengths, intensities, and signs of their CD responses. While some reports, analogous to the present investigation, deal with chiral Au NPs without size separation,[7,12] we also noticed that PAGE separation to narrow the size distribution does not necessarily produce discrete NPs[4,6] as used in Kornberg's X-ray diffraction studies.[13] Considering the difference in CD response of Au1 vs Au4 and Au2 vs Au5 and that Whetten's third mechanism is the major contribution to the chirality of Au NPs, the size distribution may not be the major concern, but rather the size itself. All NPs described so far (Au1−Au5) fall into the range of 1−2 nm, as in most other reports, and the effects of a narrower or wider size distribution across different protective ligand systems are likely difficult to assess.

Place Exchange Reaction. To further evaluate the validity of our findings, we also performed place exchange reactions which

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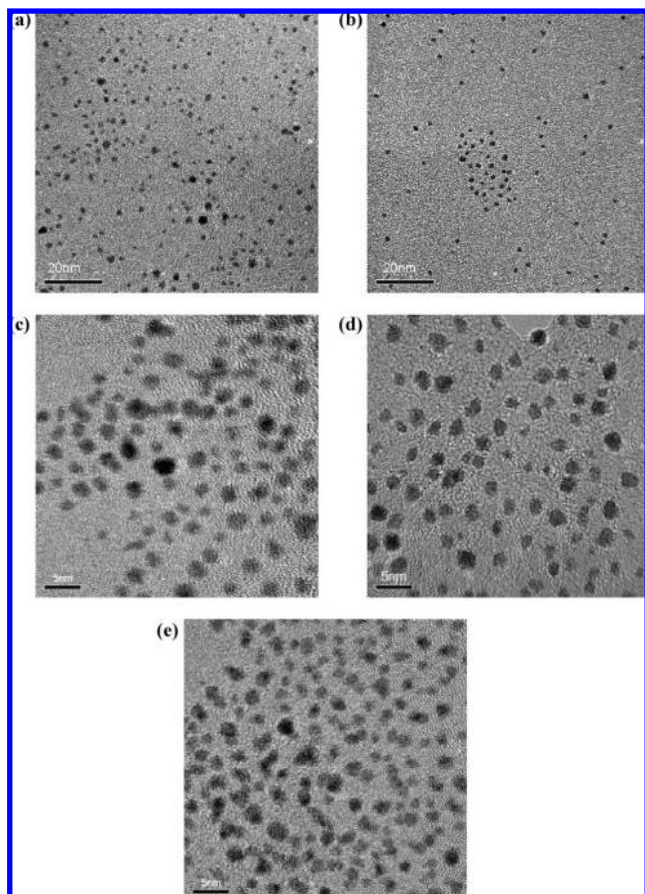
Figure 3. TEM images of (a) Au7 and (b) Au9 (scale bars 20 nm) and HR-TEM images of (c) Au8, (d) Au10, and (e) Au11 (scale bars 5 nm). For size distributions see Table 1.

introduced chiral centers to nonchiral (racemic[13]) 1-hexanethiol- and 1-dodecanethiol-capped Au NPs (Au7, Au8 → Au9−Au11; see Scheme 1). All ^{1}H NMR spectra can be found in the SI, and TEM/HR-TEM images are collected in Figure 3.

After the place exchange reaction, Au9 and Au10 with less or an almost equal amount of chiral thiolate attached to the NP core (in comparison to Au1 and Au2; for ratios see Scheme 1) showed almost no CD response at longer wavelengths. The obtained CD spectra appear similar to the CD spectrum of the free thiol (S)-**1** (CD response below 290 nm in Figure 4a). Note here that Au2 and Au10 have almost identical size and size distribution. This is surprising as, for example, Au10 is characterized by a slightly higher ratio of (S)-**1** attached to the NPs as compared to the in situ synthesized Au2 (C_{12}:C_{12}Napr* = 1:0.8 for Au10 vs 1:0.6 for Au2). This result clearly shows the difference between a chiral bias being present during NP formation in in situ mixed-monolayer-protected Au NP syntheses and introduction of a chiral bias after nanoparticle formation in place exchange reactions. The second batch with a C_{12}:C_{12}-(S)-naproxen thiolate ratio of 1:1.7 (Au11), however, exhibits a CD response similar to that of Au2, which is characterized by an about 2.8-times lower (S)-naproxen content (see Figure 4b). Comparing Au10 and Au11 with Au2, or Au9 with Au1, leads to an important finding, which is that the CD response at longer wavelengths is not related to single chiral adsorbates, but to a supramolecular assembly formed during nanoparticle formation and growth due to $\pi-\pi$ stacking of (S)-naproxen moieties, contributing to the vicinal effect giving the related CD signal. Not clear, however, is the extent of $\pi-\pi$ stacking involved in the supramolecular
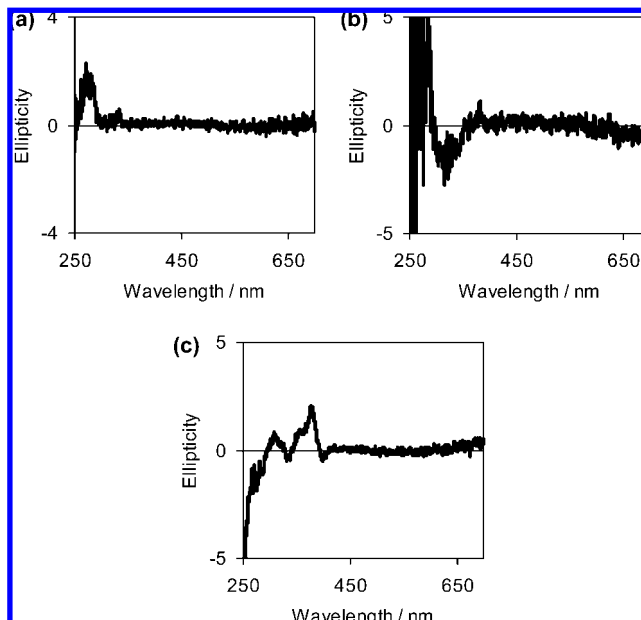

Figure 4. CD spectra of (a) Au9, (b) Au10, and (c) Au11.

assembly that contributes to the CD response especially for Au2. Only about 1/3 of all thiolate protecting groups are (S)-naproxen-functionalized, so a "continuous network" of $\pi-\pi$-stacked naproxen moieties is not expected given the surface curvature of the Au NPs. However, it appears as the most reasonable explanation so far. This is also emphasized by the rather large optical activity of the true monolayer (S)-**1**-capped Au3 NPs (see Figure 1g), for which a complete coverage with $\pi-\pi$-stacked naproxen moieties can be assumed. The space between the Au core and chiral center and the propensity of the ligand group to $\pi-\pi$ stack are also critical. In the system reported by Rotello et al.,[24] a near-quantitative place exchange led to Au NPs exclusively protected with chiral phenylalanine with no Au-related CD signal. This result was observed despite complete coverage with phenylalanine groups that could potentially participate in H-bonding interactions or $\pi-\pi$ stacking, but would participate in the latter much less effectively than the naphthalene-derived (S)-naproxen.

The comparison between the Au2/Au10 and Au2/Au11 couples also reveals that a significantly lower amount of chiral thiol molecules on the NP surface is needed for in-situ-synthesized mixed-monolayer Au NPs to form a supramolecular assembly that gives rise to a clear CD response at longer wavelengths. This appears to lend support to Murray's "edge and vertex" model for place exchange reactions (i.e., if place exchange reactions occur more easily at edges and vertices compared to terraces, formation of these supramolecular assemblies on NP terrace sites would require larger amounts of exchange thiols in place exchange reactions[27]). Related work by Bovet et al. supports the idea of a chiral supramolecular assembly resulting in a two-dimensional chiral Au surface.[28]

Despite numerous attempts to unequivocally elucidate the mechanism for metal NP place exchange reactions, some aspects of this ligand exchange remain uncertain.[29−31] Murray et al. showed that the place exchange reaction is inhibited under a

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protective atmosphere of N$_2$,[29b] but more recently Bürgi et al.,[11] using chiral thiolates, demonstrated that a place exchange reaction did occur in the absence of O$_2$ with the reaction completed within about 5 min—much shorter compared to previous reports.[27,31] Hence, we foresee that chiral Au NPs could potentially serve as probes to study and better understand the mechanism of place exchange reactions.

The result of the present work, comparing the CD response of mixed-monolayer Au NPs along with the ratio of two different thiols, highlights the difference of in situ preparation vs place exchange reaction, yet the mobility of thiolates on the NP surface, as described in several studies,[29,32] could play a key factor too. If the mobility of thiolates is high (fast distribution or segregation of different thiolates across the NP surface in solution), the initial locations of two different thiolates introduced either by in situ synthesis or via place exchange (given the edge and vertex model[27] is active) should give no difference for the chiroptical response of a bulk NP sample if the ratio of the two thiols is similar (as for Au2 and Au10), because a high thiolate mobility would quickly equalize both systems. However, this is not what we observed. Other studies dealt with an inhomogeneous reactivity at different locations of the Au NP surface including the edge and vertex model[27] and other similar models and experiments.[24,33] A possible slow migration of the thiolates (which could also lead to segregation of different thiolates on the NP surface) appears to have little effect on the chiral response we measured for the Au NP. On the basis of our current results, we consider the location (or distribution) of the two thiols on the Au NP surface to be somewhat different for the two synthesis methods. A more even distribution of the chiral thiolates during in situ synthesis appears to allow for an easier formation of a chiral supramolecular assembly that can affect the electronic structure of the Au core. This model would also explain the amplified chiral induction of a chiral nematic liquid crystalline phase with opposite helical sense (compared to that of the free thiol (S)-**1**) using Au2 or Au3 as described in earlier studies.[16,17] In the place exchange reactions, however, the chiral thiolates would dominate at edge and vertex sites and not at terraces (though less significant for smaller NPs), and hence, formation of such a supramolecular assembly seems less likely at lower overall chiral thiolate coverage.

Conclusion

Postsynthesis NP surface ligand reactions (i.e., racemization and hydrolysis) and place exchange reactions were pursued to elucidate the origin of chirality in chiral thiolate-protected Au NPs. In our model, on the basis of a chiral thiolate with a remote chiral center (C$_{12}$H$_{24}$ spacer), the formation of a supramolecular array in the NP ligand corona most strongly contributes to the so-called vicinal effect in Au NPs. For the given system, this appears to be the only effect for the observed chirality. We are currently pursuing studies on related chiral moieties with less or no aromatic content in an attempt to understand contributions from $\pi-\pi$ stacking or other intermolecular attractive interactions such as H-bonding to the chiral response. In addition, studies at elevated temperatures as well as long-term CD experiments, given the Au NPs are stable long enough in solution as well as at higher temperatures without alteration of their size and composition (e.g., via ripening), will provide useful information with respect to thiolate mobility and its impact on the formation of a supramolecular assembly as well as the bulk chiroptic properties of such Au NPs.

Hence, we admit that the present study is not the sole answer to solving the Au NP chirality puzzle, that different mechanisms may be involved for other chiral ligand systems, and that the distance as well as the type of chiral center is critical. Far more important, from our point of view, is the presented methodology of using surface ligand reactions (racemization in particular) and the ligand place exchange reaction to remove or introduce chiral centers from or to the Au NP and at the same time avoiding significant changes to the NP core and/or the Au−S bond. The presented method has proven to be a powerful strategy to discriminate between the proposed mechanisms for Au NP chirality in our system. We therefore believe that this tactic should be a valuable tool for other chiral Au NPs and, in addition, highlights the use of chiral molecules as probes for studying molecular assemblies around Au NPs as well as investigating the edge and vertex model for place exchange reactions.[27]

Supporting Information Available: All ^{1}H NMR spectra (Au1−Au11, (S)-**1**) and additional CD, UV−vis, and TEM data of Au1−Au11. This materials is available free of charge via the Internet at http://pubs.acs.org.

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