NMR data for **2**: experimental ($CDCl_3$, 294–297 K): $\delta(^{11}B)$ ($\delta(^1H)$; $^1J_{B,H}$): BH(1) −30.5 (+1.20; 164 Hz), BH(2) +0.4 (+3.17; 171 Hz), BH(3) −29.6 (+1.74; 165 Hz), BH(4) +4.5 (+2.75; 156 Hz), BH(7) +3.8 (+3.53; 170 Hz), BH(9) −22.8 (+2.28; 121 Hz); CH signals at $\delta(^1H) = +7.12$, +6.82, +2.92 (2H, accidental coincidence), +2.75, +2.49, and +2.13; calculated (II/IGLO//MP2/6-31G*):[4, 5] $\delta(^{11}B)$ ($\Delta\delta$): B(1) −29.8 (−0.7), B(2) +2.4 (+2.0), B(3) −31.6 (+2.0), B(4) +8.5 (−4.0), B(7) +5.7 (−1.9), and B(9) −24.1 (+1.3); IR (KBr): $\tilde{\nu} = 3059$, 2987 cm^{-1} (CH=CH ?); MS (70 eV): m/z (%): 150 (25) [M^+], 148 (100) [$M^+ - H_2$].

NMR data for **3**: experimental ($CDCl_3$, 294–297 K): $\delta(^{11}B)$ ($\delta(^1H)$; $^1J_{B,H}$): BH(1) −39.7 (+0.52; 148 Hz, BH(2) +32.4 (+5.04; 170 Hz), BH(3) −31.1 (+0.61; 160 Hz), BH(4) +0.4 (+3.53; 170 Hz), BH(5) −5.5 (+2.70; *J* not measurable due to overlap), BH(6) −7.9 (+1.81; 157 Hz), BCH_3(10) −5.2 (CH_3 at +0.28); CH signals at $\delta(^1H) = +3.05$, +2.90, +2.67, +1.87, +1.39 and +1.25; calculated (II/IGLO//MP2/6-31G*):[4, 5] $\delta(^{11}B)$ ($\Delta\delta$): B(1) −42.1 (−2.4), B(2) +33.9 (+1.5), B(3) −31.5 (−0.4), B(4) −2.5 (+2.1), B(5) −5.3 (−0.2), B(6) −4.4 (−3.5), B(10) −7.8 (−2.6); MS (70 eV): m/z (%): 164 (38) [M^+], 162 (100) [$M^+ - H_2$].

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DNA-Based Assembly of Gold Nanocrystals**

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The ability to generate assemblies of metallic, magnetic, or semiconducting nanocrystals, in which the relative spatial arrangement of two or more distinct nanocrystals is controlled, would allow for a systematic investigation of the physical properties of these novel structures.[1] A number of reports have described methods for organizing nanocrystals into arrays using small molecules,[2] nano-patterned templates,[3] and crystallization.[4] Recently, methods that use biopolymers to assemble nanocrystals have appeared in the literature.[5] For example, Au nanocrystals derivatized with complementary single-stranded DNAs (ssDNAs) can be hybridized to each other to form periodic arrays.[6] In a preliminary report, we showed that nanocrystals modified with ssDNA could be arranged into homodimeric and homotrimeric assemblies.[7] We now report the synthesis of heterodimeric and heterotrimeric "nanocrystal molecules" in which Watson–Crick base-pairing interactions are used to control the relative spatial arrangement of Au nanocrystals that are 5 and 10 nm in diameter. A preliminary characterization of the optical properties of these assemblies is also reported.

DNA is an ideal template for the formation of nanocrystal molecules due to its ability to form well-defined secondary and tertiary structures and its similarity in size to nanocrystals. To use DNA in this capacity, nanocrystals must first be complexed with ligands that stabilize them in aqueous buffers. Secondly, ssDNA must be site-specifically modified with moieties that covalently bind to the complexed nanocrystals such that the resulting conjugates effectively hybridize to complementary ssDNA. In addition, methods for purifying the nanocrystal molecules from their synthetic precursors or undesired larger assemblies are likely to be needed.

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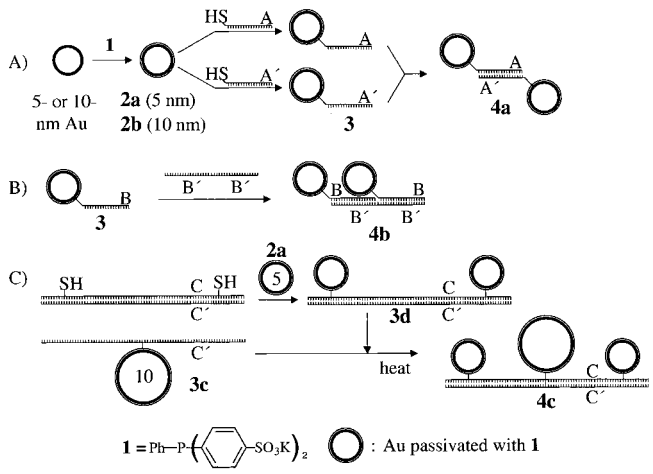
Gold nanocrystals were stabilized by complexation with dipotassium bis(*p*-sulfonatophenyl)phenylphosphane dihydrate (**1**).[8] Gold nanocrystals with a diameter of 5 or 10 nm that were complexed with **1** (→**2a** and **2b**, respectively) did not aggregate in aqueous buffers and could be subjected to repeated cycles of NaCl precipitation. The sensitivity of **2a** and **2b** to salt concentration was size-dependent: the 5-nm nanocrystals could be manipulated in 0.3 M NaCl and 1 mM $MgCl_2$, but the 10-nm nanocrystals precipitated above 0.15 M NaCl and aggregated irreversibly in 1 mM $MgCl_2$. Both **2a** and **2b** were stable in solutions ranging in pH value from 3–9; they were also stable to heating (95 °C) for short times in aqueous buffers. Since **2a** and **2b** migrated through agarose gels and were stable to repeated cycles of separation and recovery, electrophoresis was used as the primary analytical and preparative method in these studies.

It was found that thiol groups, incorporated into ssDNA at either the 5′ terminus or the C5 position of 2′-deoxyuridine nucleotides, penetrated the ligand "shells" of **2a** and **2b** and reacted directly with the surfaces of the Au nanocrystals.[9] In a typical modification reaction, 0.9 equivalents of ssDNA were added to a 1–10 μM solution of nanocrystal **2a** or **2b**.[10] Although 5- and 10-nm Au nanocrystals derivatized with less than one equivalent of short ssDNA had similar mobilities to **2a** and **2b**, nanocrystals modified with longer ssDNA (>60 nucleotides) or double-stranded DNA (dsDNA) (>40 base pairs) migrated distinctly slower than **2a** and **2b** through 3% agarose gels.[11]

Three strategies were examined for the generation of heterodimeric and heterotrimeric nanocrystal molecules (Scheme 1). The first involved the use of two complementary



Scheme 1. Synthesis strategies A–C for nanocrystal assembly (see the text for details). The labels A′, B′, and C′ denote oligonucleotide sequences complementary to sequences A, B, and C, respectively.

5′-ssDNA/nanocrystal conjugates to form double-stranded nanocrystal molecules (Scheme 1A). Dimers and trimers synthesized by this method had zero and one single-stranded breaks (or "nicks"), respectively. In the second approach, the 5′-ssDNA/nanocrystal conjugates were assembled onto an unmodified template strand (Scheme 1B), resulting in dimers and trimers with one and two nicks, respectively. The third approach was used to synthesize trimers with no nicks. Two complementary oligonucleotides were synthesized with either one or two thiols extending from the C-5 position of deoxyuridine nucleotides. These oligonucleotides position three nanocrystals in a collinear arrangement along one face of the double helix, with at least ten base pairs of dsDNA on each side of the modified nucleotides (Scheme 1C). For a typical assembly reaction involving either of the first two methods, conjugate **3** was directly treated with the complementary ssDNA, which was either attached to other nanocrystals (Scheme 1A) or added as a template free in solution (Scheme 1B). These mixtures were incubated from one to four days at room temperature. For the assembly synthesized according to Scheme 1C, the ssDNA with two thiols was hybridized to non-thiolated complementary ssDNA prior to the addition of Au nanocrystals to avoid the formation of a 1:1 chelate between the flexible, thiolated ssDNA and a single Au nanocrystal. Product **3d** was purified by electrophoresis and then incubated with **3c** to yield trimer **4c**. All of the desired products were purified from the crude reaction mixtures by preparative electrophoresis on 3–4% agarose gels. The Au nanocrystals were visible to the naked eye on agarose gels as red bands. The products were isolated by electrophoresis of the desired bands into glassfiber microfilters backed with dialysis membranes.

Dimer and trimer nanocrystal molecules generated by all three assembly strategies were characterized by transmission electron microscopy (TEM). A TEM image of a twice-purified 5-nm homodimer (Scheme 1B) shows that more than 90% of the Au nanocrystals present in the image are found in dimeric structures (Figure 1). To examine the level of control

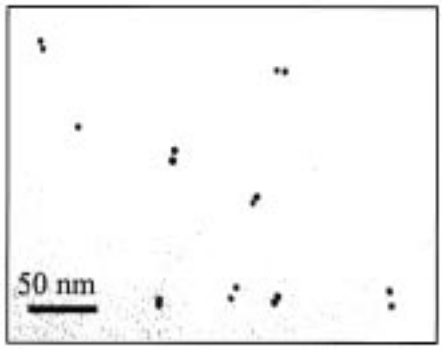


Figure 1. A typical TEM image of a 5-nm homodimer formed by the strategy in Scheme 1B; more than 90% of the Au in this image is found in dimeric structures.

over the spacing between nanocrystals in dimeric assemblies, TEM images of three sets of 10-nm homodimers (Scheme 1A) constructed with dsDNA sequences ranging from 18–38 base pairs were evaluated statistically. One hundred examples of each dimer were measured; the distances between the nanocrystal edges averaged 1.2 nm (with distances of 0–6 nm observed), 1.5 nm (with distances of 0–6 nm observed), and 5.8 nm (with distances of 0–15 nm observed) for the sequences with 18, 28, and 38 base pairs, respectively. The lengths of the dsDNAs between the nanocrystals for the sequences with 18, 28, and 38 base pairs were calculated to be 6.1, 9.5, and 12.9 nm, respectively. The high

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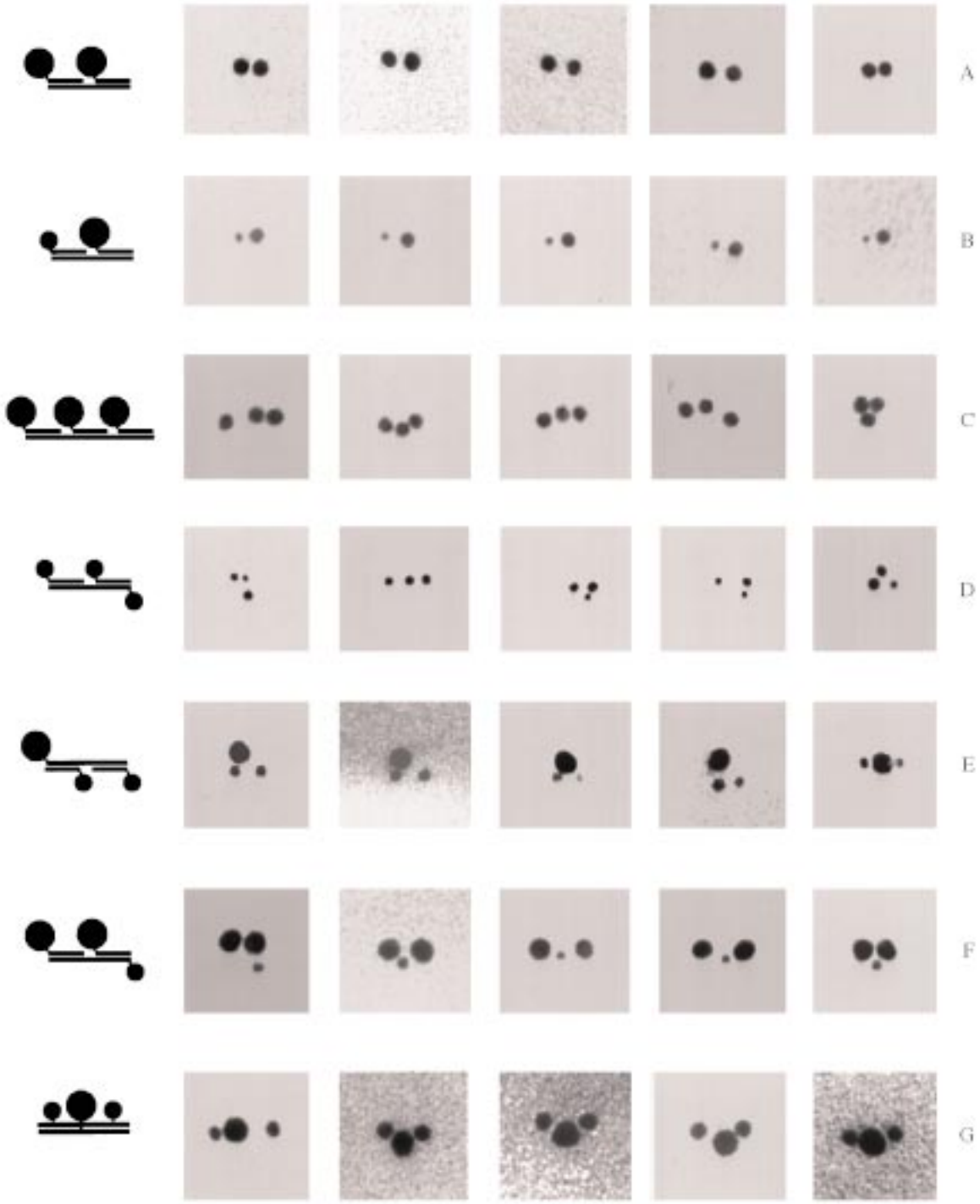

Figure 2. Schematic illustrations and representative TEM images for specific nanocrystal molecules. See Scheme 1 for the synthesis strategies. A) 10-nm homodimer, synthesis strategy B; B) 10-/5-nm heterodimer, strategy B; C) 10-nm homotrimer, strategy B; D) 5-nm homotrimer, strategy A; E) 10-/5-/5-nm heterotrimer, strategy A; F) 5-/10-/10-nm heterotrimer, strategy A; G) 5-/10-/5-nm heterotrimer, strategy C.

variability of the experimental values for the nanocrystal spacings is primarily due to the flexibility of the 1-nm-long 5′ linker arms. Bending of the dsDNA, the affinity of one Au nanocrystal for another,[12] and the process of depositing the nanocrystal molecules onto grids for TEM imaging may also affect the spacings.

Representative images of homodimers, heterodimers, homotrimers, and heterotrimers synthesized according to Schemes 1 A and 1 B, which produce nicked structures, are shown in Figures 2 A – F. The TEM images of the trimers show spatial arrangements of the particles ranging from collinear to triangular (Figures 2 C – F), again indicating flexibility. The set of images of a heterotrimer synthesized by Scheme 1 C (Figure 2 G) shows a much more consistent arrangement of particles than do the images in Figures 2 C – F. This supports the hypothesis that nicks contribute significantly to the flexibility of DNA – nanocrystal assemblies prepared according to Schemes 1 A or 1 B.

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The optical properties of Au nanocrystals and their assemblies depend on the size, shape, and/or spacings of the nanocrystals. When DNA is used to prepare extended aggregates of Au nanocrystals, pronounced changes in the optical spectra are observed that result from the collective electronic interactions of the nanocrystals.[6] Generalized Mie theory for a Au – nanocrystal pair predicts that the plasmon band should red shift slightly, decrease in intensity, and broaden as the distance between two nanocrystals becomes smaller than the sum of their radii. The electronic interactions between Au nanocrystals separated by distances greater than the sum of their radii, however, are only expected to produce a slight broadening of the spectrum and no noticeable red shift.[13] After normalization of the UV/Vis spectrum of the 10-nm monomeric DNA-modified gold species **3** and the spectrum of 10-nm homodimer **4a**,[14] a decrease in the absorbance at 520 nm and some broadening of the absorption to longer wavelengths for the dimer was observed (Figure 3).

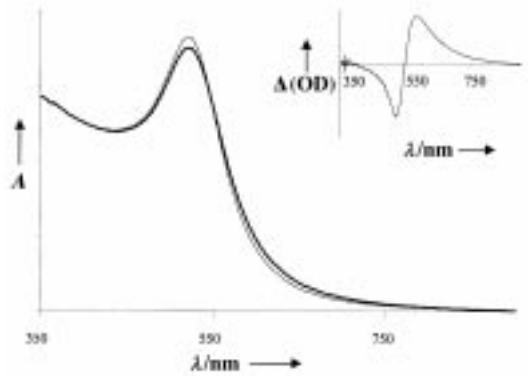

Figure 3. UV/vis spectra for 10-nm Au – ssDNA conjugate **3** (thin line) and 10-nm homodimer **4a** (bold line) assembled using 18-base-pair dsDNA. Inset: subtraction of the monomer spectrum from the dimer spectrum after normalization of the two spectra at 450 and 900 nm.

Subtraction of the spectra showed a maximum increase in absorbance at 582 nm for the dimer (inset of Figure 3). Since the effect of assembly observed in the optical spectrum of homodimer **4a** is small, the nanocrystal pairs are potentially spaced more than 5 nm apart in solution.

In this report, DNA was used to prepare specific, designed, nonperiodic arrangements of nanocrystals. The resulting assemblies are not structurally rigid, even in the case where the DNA has no nicks in it. Thus, we conclude that the present combination of linker molecules and duplex DNA is not sufficiently rigid to dictate a precise spatial arrangement of nanocrystals. In some cases, the ability to code sequences of nanocrystals without structural rigidity may be desirable. For instance, catalytic and photoactive systems may require simple colocalization of a number of nanocrystals. However, many more applications will require precise control of spatial separation, and it is quite likely that this can be achieved using oligonucleotide templates constructed from antiparallel double-crossover components.[15]

Experimental Section

General procedures: Gold nanocrystals with a diameter of 5 and 10 nm were purchased from Ted Pella (Redding, CA). Salt **1** was purchased from Strem Chemicals (Newburyport, MA). Agarose was purchased from Gibco (Gaithersburg, MD). All biological buffers were from Sigma Chemical (St. Louis, MO); water was purified using a Millipore system. Microconcentrators were purchased from Amicon (Beverly, MA). Desalting by Fast Protein Liquid Chromatography (FPLC) was performed on a Superdex 75 HR 10/30 column (3 mM 2,2-bis(hydroxymethyl-2,2′,2″-nitrilotris(ethanol) (Bis-Tris), 1 mM ethylenediaminetetraacetic acid (EDTA), pH 6.5).

Gold complexation: For a typical reaction, an aqueous solution (100 mL) of 5-nm or 10-nm Au nanocrystals was stirred with a large excess of **1** (10 – 20 mg) at room temperature for more than 10 h. The nanocrystals were precipitated by adding solid NaCl to the reaction mixture until the color changed from burgundy red to blue. The sample was centrifuged ($500 \times g$) to pellet the nanocrystals, and the supernatant was removed. The nanocrystals were redissolved in an aqueous solution of **1** (25 mg in 100 mL of water). Methanol was added to this solution until the color again changed from red to blue. Centrifugation and decanting were repeated, followed by dissolution of the nanocrystals in the aqueous solution of **1**.

Oligonucleotide Synthesis: The DNA was synthesized on an Applied Biosystems 391A PCRmate. All reagents used in automated synthesis were purchased from Glen Research (Sterling, VA), including the 5′-thiol modifier C6 used in the synthesis of the 5′-thiolated DNA (Scheme 1 A, B) and the amino modifier C6 dT used to synthesize the trimeric system with internal thiols (Scheme 1 C). The DNA was synthesized with the 5′-trityl protecting group (trityl = CPh_3) intact and purified by HPLC using a reverse-phase C18 column (218TP54, Vydac Technologies) and a 1 % per minute gradient of acetonitrile in 50 mM triethylammonium acetate (TEAA, pH 7.0) over 30 min. Once purified, the non-thiolated DNA was detritylated by treatment with 80 % AcOH in water (v/v) for 30 min. The 5′-thiolated DNA was detritylated by mixing 20 nmol of oligonucleotide in 100 mM TEAA (pH 6.5) with 1M $AgNO_3$ (4 μL) for 30 min at room temperature. Then 1M 1,4-dithiothreitol (DTT, 8 μL) was added, which led to the formation of a yellow precipitate. The reaction mixture was centrifuged, the supernatant loaded onto a NAP-5 column, and the DNA eluted with 3 mM Bis-Tris and 1 mM EDTA (pH 6.5). Finally, the thiol-modified oligonucleotides were desalted by FPLC prior to use. The thiol concentration of a desalted solution was determined by titration with 5,5′-dithiobis(2-nitrobenzoic acid).

DNA Sequences: Figure 1: 5′-XCAGTCAGGCAGTCAGTCA-3′, 5′-TGACTGACTGCCTGACTGTTGACTGACTGCCTGACTG-3′;[7] Figures 2 A, B: 5′-XATGGCAACTATACGCGCTAGAGTCGTTT-3′ (oligo 1), 5′-XCTAATCCGCACAGCCTATCGACCATGCT-3′, 5′-AGCATGGTCGATAGGAAACGACTCTAGCGC-3′;[16] Figure 2 C: (oligo 1), 5′-AAACGACTCTAGCGCAAACGACTCTAGCGCAAACGACTCTAGCGC-3′; Figures 2 D – F: 5′-XGCGCTAGAGTCGTTT-3′, 5′-XAAACGACTCTAGCGCTAAACGACTCTAGCGC, where X = 5′-thiol; Figure 2 G: 5′-GGCATGGTCYACGTCACGCTAGTCAGTCATCTTGCACTAAGTCCTTGAGAACGTCACGCTAGTCAGTCAYACTCTAGCGC-3′, 5′-GCGCTAGAGTATCACTGACTAGCGTGACGTTCTCAAGGACYTAGTGCAAGATGACTGACTAGCGTGACGTAGACCATGCC-3′, where Y = amino modifier dT. Complementary dimers: 5′-XTGACTGACTGCCTGACTG-3′, 5′-XCAGTCAGGCAGTCAGTCA-3′; 5′-XAGCATGGTCGATAGGCTGTGCGGATTAG-3′, 5′-XCTAATCCGCACAGCCTATCGGACCATGCT-3′; 5′-XACGTCACGCTAGTCAGTCATCTTGCACTATGTCCTTGA-3′, 5′-XTCAAGGACATAGTGCAAGATGACTGACTAGCGTGACGT-3′, where X = 5′-thiol.

Nanocrystal molecule assembly (Schemes 1 A, B): Thiolated ssDNA (0.9 equiv) was added to a 100 mM aqueous NaCl solution of 1 – 10 μM **2a** or **2b** and incubated at room temperature for more than one hour to yield the oligonucleotide – nanocrystal conjugate **3**. Conjugate **3** was mixed with an equimolar amount of a complementary oligonucleotide strand, which was either attached to nanocrystals or unmodified. This mixture was incubated at room temperature for one to four days.

Nanocrystal molecule assembly (Scheme 1 C): Two complementary 80-mer strands were synthesized as shown in Scheme 1 C. Oligonucleotide C has two amino modifier dTs, whereas C′ has one. An oligonucleotide identical in sequence to C′ but containing no modified bases was also synthesized.

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The purified amine-containing oligonucleotides (500 nmol) were suspended in aqueous 100 mM NaH_2PO_4 (250 μL, pH 7.5). A 20 mM solution (50 μL) of 3-(2-pyridylthio)propionic acid *N*-hydroxysuccinimide ester (Aldrich) in DMSO was added, and the reaction mixture was incubated at room temperature for 4 h.[17] The reaction mixture was desalted by FPLC, purified by reverse-phase HPLC using a 0.5% per minute gradient of acetonitrile in 50 mM TEAA (pH 7) over 30 min, lyophilized, and resuspended in 100 mM NaH_2PO_4 (pH 7.5). The modified oligonucleotides were deprotected by the addition of 1M DTT (20 μL) for 30 minutes, after which they were desalted by FPLC. Deprotected oligonucleotide C′ was mixed directly with 1–10 μM 10-nm Au in 0.1M aqueous NaCl solution, whereas oligonucleotide C was first hybridized to unmodified C′ for 30 min followed by addition of 5-nm Au (10 equiv) in 0.1M aqueous NaCl solution. The conjugates of strand C′ with a single 10-nm Au nanocrystal and of the duplexed strand C with two 5-nm Au particles were purified on 3% agarose gels and collected. Microcon 100s were used to exchange the purified conjugates into aqueous 0.1M TEAA (pH 6.5, 0.05M NaCl). Equimolar amounts of the two conjugates were mixed, heated to 95 °C for 5 min, and allowed to cool slowly to room temperature. The trimer products, which were obtained in yields of approximately 30% based on **3c**, were purified on 4% agarose gels.

Nanocrystal molecule purification: Agarose gels (3–4%) were used to analyze and isolate the desired structures. Tris-borate EDTA (1X, TBE) was used as the running buffer. Glycerol loading buffer (6X) was used to load the samples onto the gels.[18] After electrophoresis, samples were isolated by slicing the gel in front of the desired band and inserting glassfiber microfilters (Whatman GF/C) that were backed with dialysis membranes (Spectra/Por, MWCO: 10000). The bands were incorporated into the paper by electrophoresis. The filter/membrane pieces were then placed with the filter facing down into 0.5-mL Eppendorf tubes which had been pierced at the bottom with 26-gauge needles. These Eppendorf tubes were fitted into 1.5-mL Eppendorf tubes and centrifuged for one minute ($14000 \times g$) to isolate the desired products. Syringe tip filters (Millipore, 0.45 μm) were used to remove residual glass fibers from the resulting solutions. Typically, isolated yields were 30–40% (dimers) and 20–30% (trimers) based on the nanocrystal starting materials.

TEM procedures: A Jeol-100CX instrument was used to image the samples at 80 kV. Copper grids (400 mesh) coated with a layer of Formvar were subjected to an argon plasma (30 s at 50 mTorr), after which solutions of the nanocrystal molecules (0.1–0.01 μM) were deposited for one minute. Excess solution was removed by wicking, and the grids were dried in air. The diameters of the 5-nm nanocrystals shown in Figure 2D–G are not uniform due to contrast differences that result from variation in the thickness of the Formvar used in imaging the samples.

UV/Vis studies: UV/Vis spectra were measured on an HP8453 UV-Vis spectrophotometer using 40- or 100-μL masked quartz cuvettes. The monomer and dimer bands were collected from the same gel lanes in 1X TBE buffer. The dimer bands were typically purified a second time. Spectra were taken of monomer and dimer samples that had been diluted with 1X until the absorbances at 520 nm for the two samples were similar but not necessarily identical. The spectra for the dimer and monomer were normalized at 450 and 900 nm before comparison or subtraction.

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[9] When **2a** and **2b** were mixed with a large excess of thiolated ssDNA, they exhibited the properties of the DNA-modified Au nanocrystals previously described.[6]

[10] At least 0.1M NaCl was required in the buffer for the DNA modification to proceed in high yield, presumably to minimize the electrostatic interactions between the phosphate backbone of DNA and the nanocrystal ligand shell. Gold nanocrystals modified with less than 0.9 equivalents of ssDNA gave low yields of the molecules, whereas gold nanocrystals modified with more than 0.9 equivalents cross-linked to form aggregates that were larger than the desired molecules.

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