Inhibition of DNA Transcription Using Cationic Mixed Monolayer Protected Gold Clusters

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Abstract: Efficient recognition of DNA is a prerequisite for the development of biological effectors, including transcription and translation regulators, transfection vectors, and DNA sensors. To provide an effective scaffold for multivalent interactions with DNA, we have fabricated mixed monolayer protected gold clusters (MMPCs) functionalized with tetraalkylammonium ligands that can interact with the DNA backbone via charge complementarity. Binding studies indicate that the MMPCs and DNA form a charge-neutralized, nonaggregated assembly. The interactions controlling these assemblies are highly efficient, completely inhibiting transcription by T7 RNA polymerase in vitro.

Creation of synthetic systems possessing DNA binding affinities comparable to repressor proteins is a long-standing goal in both bioorganic and medicinal chemistry.[1] The successful development of such systems would allow direct control of cellular processes through regulation of transcription, with concomitant modulation of protein production. Additionally, this efficient binding, combined with charge compensation, is a prerequisite for the creation of efficient transfection vectors for gene therapy.[2]

Gene regulation by synthetic systems requires a DNA binding affinity similar to those found in repressor protein−DNA interactions. A key requirement in the design of synthetic systems with sufficient affinity to affect DNA expression is the creation of efficient multivalent host−DNA interactions. Recent studies have shown that small molecules,[3] nanoparticles,[4] dendrimers,[5] and polymers[6] are capable of efficient DNA recognition, and in some cases, inhibition of transcription machinery. In these systems, however, the creation of suitably preorganized scaffolding for the controlled display of recognition elements presents a significant design challenge. For small molecules, this challenge arises from the detailed synthesis required for a rigid scaffold containing several functional groups. For polymer systems, precise placement of substituents along the backbone as well as polymer macroconformation in solution can be difficult to control.

One alternative scaffold for the creation of DNA-binding systems is Mixed Monolayer Protected Gold Clusters (MMPCs).[7] The self-assembled monolayer covering of these nanoparticles presents a highly organized surface for the recognition of biomacromolecules that is of a similar size scale (6−10 nm)[8] to that of DNA-binding proteins.[9] The central metal core rigidifies the particle, limiting the organic components to a much smaller subset of structures than a similarly sized polymer counterpart. In addition to providing a suitably sized scaffold for biomacromolecular recognition, the gold core allows the

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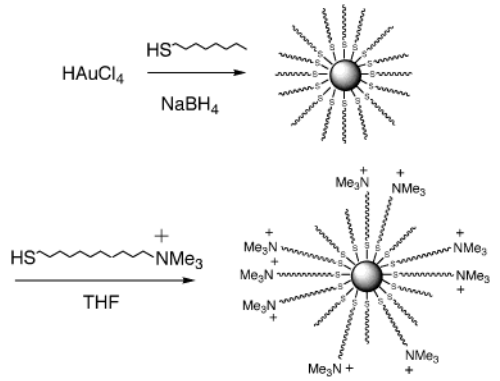
Scheme 1. MMPC **1** Fabrication via the Brust and Murray Reactions



presentation of recognition elements on the nanoparticle surface to be controlled in subsequent templation steps due to the mobility of the thiols on the metal surface.[10]

To explore the application of gold nanoparticles to the recognition of double-stranded DNA,[11] we synthesized MMPC **1** via Murray place displacement[12] of 2 nm octanethiol-functionalized Au nanoparticles with 11-trimethylammonium-undecanethiol units (Scheme 1). The mixed monolayer of this MMPC system is designed to interact with DNA based on the electrostatic attraction of the positively charged quaternary ammonium salt and the negatively charged DNA phosphate groups (Figure 1).[13] We anticipated that the charge complementarity of the nanoparticles and DNA would bind with a high affinity,[14] as many proteins involved in gene regulation dedicate the majority of DNA-bound amino acid side chains to neutralization of the phosphate backbone.[15]

Methods and Materials

MMPC Preparation. Fabrication of the C_8-functionalized nanoparticle and synthesis of the cationic thiol, *N*,*N*,*N*-trimethyl(11-mercaptoundecyl)ammonium chloride, were completed via previously reported procedures.[16] In a typical preparation of the cation-functionalized clusters, *N*,*N*,*N*-trimethyl(11-mercaptoundecyl)ammonium chloride (50 mg, 0.18 mmol) was added to 50 mg of C_8-functionalized nanoparticles in 10 mL of THF and degassed for approximately 30 min. After the mixture was stirred under argon for 2 days at room temperature, the black precipitate of trimethylammonium-functionalized MMPC **1** was purified by removal of solvent in vacuo, and repeated washing with dichloromethane. The MMPC core size before and after introduction of the trimethylammonium thiol was determined by TEM

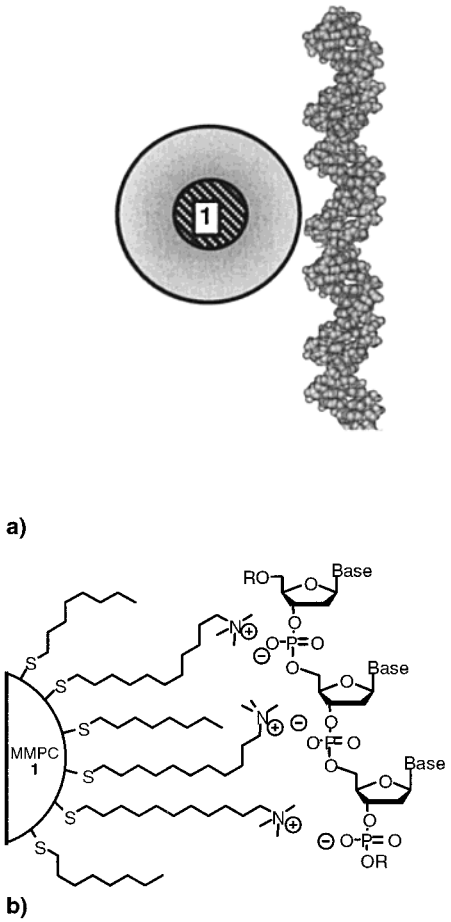


Figure 1. (a) MMPC **1** and 37-mer DNA counterpart (to scale). (b) Specific interactions formed between the cationic trimethylammonium side chains of MMPC **1** and the anionic DNA.

to be 2 nm.[17] NMR end-group analysis indicated that the ammonium side chain functionality was 71% of the thiol monolayer, or ~68 thiols per particle.[18] The MMPCs were stable at room temperature as a particulate compound or in aqueous solution.

DNA Synthesis. Oligonucleotides were synthesized (1.0 μmol scale) on a Perseptive Biosystems Expedite 8909 Nucleic Acids Synthesis System using standard procedures. Cleavage from the support and base deprotection was accomplished by treatment with concentrated NH_4-OH (16 h, 37 °C). Strands were purified via elution with 20% acetonitrile from an Amberchrom CG-161C Synthetic Adsorbant/Chromatographic Resin column (Toso-Haas). The oligomers were then concentrated to dryness and redissolved in TE buffer (pH 8.0). Complementary strands were annealed by combining equivalent molar amounts of the individual sequences (100 mM final concentration), heating to 90 °C, and slowly cooling to room temperature. DNA was stored at −20 °C.

Dynamic Light Scattering. MMPC **1** and an MMPC **1**:DNA solution (0.9:1 molar ratio) were examined with an argon laser tuned to 514 nm using ALV-5000 software. The MMPC **1** samples were prepared in distilled, deionized water. Data were collected for 30 s, and scans repeated until scattering due to transient dust was eliminated.[19]

UV−Vis Analysis. The UV−vis spectra of the DNA alone (2 μM DNA in TE buffer), nanoparticles alone (2.16 μM MMPC **1** in TE buffer), and the combined particles (0.5 μM DNA, 0.45 μM MMPC **1** in TE buffer) were recorded. Absorption at 260 nm was adjusted for

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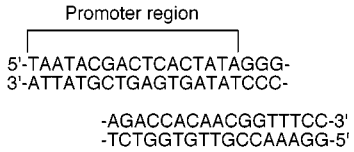
(19) Parameters obtained in DLS scans, including a complete list of radii obtained, are available in the Supporting Information.

Scheme 2. DNA 37-Mer Sequence Used



concentration differences and compared. To prepare the combined sample, 1.5 μL of 180 mM MMPC **1** was added to the DNA solution.[20]

Binding Ratio Analysis. The MMPC **1**:DNA interaction was examined using a UV/vis centrifugation assay.[5,21] In a typical experiment, DNA was diluted in TE buffer to a final DNA concentration between 0.3 and 0.5 μM (UV absorption between 0.3 and 0.5). The nanoparticles were added incrementally from a stock solution, and the UV signal recorded at 260 and 520 nm; 260 nm represents the maximum absorption for DNA, while the value at 520 nm was recorded to determine the contribution of the gold nanoparticles to the overall UV spectrum. By examination of the nanoparticles in the absence of DNA, it was thus possible to subtract the contribution of the nanoparticles to the signal at 260 nm. After each scan, the tube was centrifuged at 4570 × g for 5 or 10 min, and then another scan was taken. Control samples were prepared with the same concentration of DNA, and observed through time with and without centrifugation. An additional control assay was performed using a carboxylic acid-functionalized MMPC.[22] These samples showed no indication of aggregation.

T7 RNA Polymerase Assay. This assay was performed as previously described.[23] Briefly, the DNA template is incubated with the nanoparticles to facilitate binding. The nucleotide triphosphates, present in excess, include ^{32}P-labeled GTP for isotopic detection. The DNA−nanoparticle solution is mixed with the nucleotide triphosphates (>1 min, 37 °C), followed by addition of the enzyme to a final 1:1 enzyme:DNA ratio (0.2 μM). The enzymatic reaction proceeds for 10 min before being quenched with 15 mmol of EDTA in 95% formamide. The RNA transcripts are quantified using a Storm 840 phosphorimager to determine the extent of reaction, with the transcription level attained in the absence of MMPC **1** set to 100% transcription. The experiments reported here were performed with a range of 1.8−7.2 equiv of MMPC per DNA strand.

Results and Discussion

Studies of the interaction of MMPC **1** with a DNA host were performed using a double stranded 37-mer: the sequence of the 37-mer includes a 5′−17-base promoter region recognized by T7-RNA polymerase, with the remaining 20 nucleotides used as a template for the RNA products (Scheme 2). Characterization of the DNA−nanoparticle ensembles in solution was carried out using UV−vis analysis and dynamic light scattering (DLS). These experiments indicate that at low colloid equivalents small assemblies are formed. The absence of extended aggregates is evidenced by a minimal 6% change in UV−vis absorbance of DNA upon addition of MMPC **1**.[24] DLS confirms that there are no large aggregates: the addition of DNA to a solution of MMPC **1** indicates aggregates with an r_g of 9.9 ± 3.6 nm.[25] This wide range suggests a dynamic process is occurring which we attribute to either the reversible binding of MMPC particles to the DNA strand or the DNA strand itself changing conformation in solution.[26]

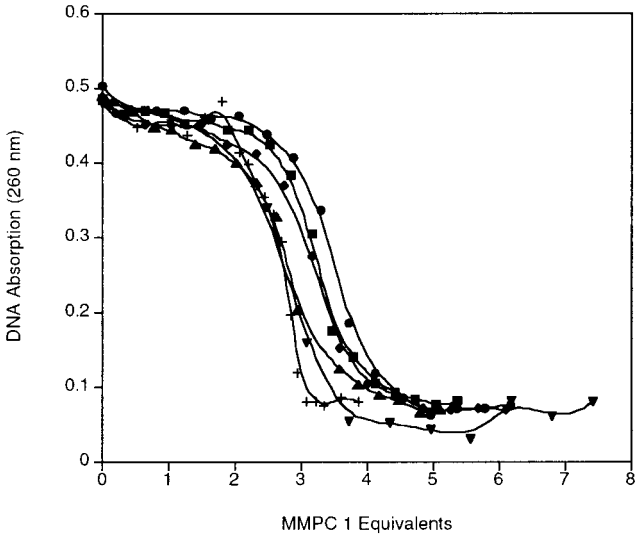


Figure 2. DNA absorption observed in the UV/vis centrifugation assay. The critical mass of nanoparticles necessary for binding all DNA causes the precipitation of the DNA strands from solution, resulting in a loss of signal at 260 nm.

The stoichiometry of the DNA−nanoparticle complexation process was established via a UV/vis centrifugation assay.[5,21] In this assay, the addition of an agent that binds DNA converts the coiled strands into condensed strands, which precipitate out with centrifugation. Determination of the critical mass of the condensing agent indicates the binding ratio of the two molecules. From this, it was established that the MMPC **1**-DNA 37-mer particle ratio is 3.3:1 (Figure 2). This nanoparticle:DNA ratio is logical based on the relative length scales of the two molecules: the DNA strand is approximately 12.5 nm in length, while each MMPC (including the thiol monolayer) is ∼6 nm. This suggests that four nanoparticles could bind to each strand, two on each "side" of the DNA strand. This assembly agrees well with the particle sizes observed using DLS.[27]

Effective demonstration of functional recognition was established by exploring the effects of MMPC **1**−DNA interaction on T7 RNA polymerase transcription. The K_d of T7 RNA polymerase is approximately 5 nM; to successfully compete for the DNA substrate, the affinity of the nanoparticle must be of similar magnitude.[28] Use of a previously described in vitro assay indicates that the binding affinity is great enough that MMPC **1** is able to inhibit T7 RNA polymerase from producing RNA oligomers.[23] As shown in Figure 3a, MMPC **1** completely inhibits transcription when present above a 4:1 ratio. Transcrip-

(20) This small volume may cause slight concentration differences, introducing possible error in signal determination.

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(23) Weston, B. F.; Kuzmine, I.; Martin, C. T. *J. Mol. Biol.* **1997**, *272*, 21−30.

(24) This change is within experimental error; at later time points (3−18 h) that are not relevant to these studies, however, decreases in absorbance indicative of aggregation were observed. For examples of the use of UV−vis absorbance to explore nanoparticle aggregation, see: Liu, J.; Mendoza, S.; Roman, E.; Lynn, M. J.; Xu, R.; Kaifer, A. E. *J. Am. Chem. Soc.* **1999**, *121*, 4304−4305. Weisbecker, C. S.; Merritt, M. V.; Whitesides, G. M. *Langmuir* **1996**, *12*, 3763−3772.

(25) The r_g observed is somewhat larger than that expected for the MMPC **1**-DNA aggregate, consistent with the presence of a hydration sphere: Freifelder, D. M. *Physical Biochemistry*; W. H. Freeman and Company: New York, NY, 1982; pp 1−37.

(26) This is in contrast to behavior in vacuo, as studied by TEM. Although the aggregates formed in TEM experiments conform to previous studies of nanoparticle/polymer interactions, evaporation of the solvent for electron microscopy is expected to induce aggregation processes not representative of the interaction of the components in solution. With TEM, we see extended assemblies formed only in the presence of both DNA strands and MMPCs. For a recent discussion of a related process, see: Kumar, A.; Pattarkine, M.; Bhadbhade, M.; Mandale, A. B.; Ganesh, K. N.; Datar, S. S.; Dharmadhikari, C. V.; Sastry, M. *Adv. Mater.* **2001**, *13*, 341−344.

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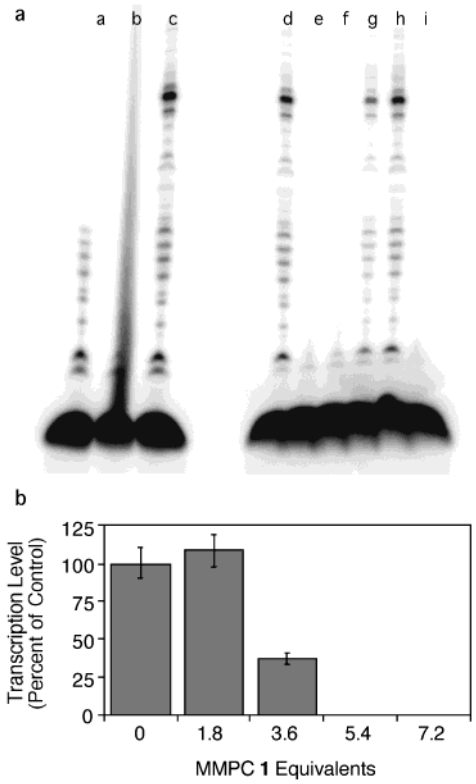

Figure 3. (a) Representative acrylamide gel electrophoresis of RNA products produced in the T7 RNA polymerase transcription assay. The enzyme assay contained 0.2 μM DNA substrate and 0.2 μM polymerase. Lanes a−c: Control assays with either (a) 166 μM (830 equiv), (b) 830 μM (4150 equiv), or (c) 0 μM nanoparticles added to previously transcribed RNA. Lanes d−h: Assays completed in the presence of diminishing amounts of MMPC (d) no nanoparticles and (e) 1.44, (f) 1.08, (g) 0.72, and (h) 0.36 μM nanoparticles. Lane i: The assay performed with only DNA strands and RNA nucleotides. The large spots at the bottom of the gels are unreacted ^{32}P-GTP. (b) The amount of RNA detected relative to levels produced in the absence of MMPCs (100% transcription). Slightly higher levels of transcription observed for low concentrations of nanoparticles (1.8 equiv or less) are indistinguishable from the control (0 equiv) within experimental error.

tion levels increase to 40% with a MMPC **1**−DNA molar ratio of 3.6:1, while still lower concentrations of **1** have little effect on enzyme activity. The inhibition observed is highly concentration dependent, evidenced by the sharp transition between successful inhibition and successful transcription. The mechanism of this inhibition can be explained by the size ratio of the two molecules. Above a 4:1 MMPC **1**:DNA ratio, the 12 nm DNA would be fully bound by the 6 nm nanoparticles, preventing the polymerase from any interaction that would promote transcription. Below the 4:1 ratio, the DNA will not be completely blocked by the MMPCs; those strands whose promoter bases are not bound to nanoparticles will be accessible to the enzyme, resulting in limited transcription. As the ratio drops further below 4:1, increasing quantities of DNA are available for transcription. The presence of a nanoparticle concentration that gives intermediate levels of transcription indicates that the inhibition of the transcription process does not occur through a highly aggregated, cooperative all-or-none process in aqueous solution, consistent with the above UV−vis and light scattering experiments.

To demonstrate that MMPCs are truly inhibiting enzymatic activity, and not just preventing the correct analysis of RNA products, controls were performed in which nanoparticles were added to a completed reaction in which RNA transcripts (in the absence of any particles) had been successfully produced. In the presence of up to 4150 equiv of MMPC **1**, RNA products were still observed to some extent, either as discrete bands or as an elongated smear (Figure 3a, lanes a−c). Based on the ability of the RNA to come off the baseline into the gel under these very high nanoparticle concentrations, the lack of RNA products observed in the lower concentrations (Figure 3a, lanes e−g) must arise from the ability of MMPC **1** to stop transcription. To determine the origin of the dimer produced in reaction conditions under which all other transcripts were depleted (lanes e and f), an additional control was performed (lane i) with no nanoparticles *and no polymerase* present. The appearance of a similar spot in this lane successfully indicates that the dimer and trimer are not artifacts due to the presence of MMPC **1**, but instead may be due to low levels of impurities in the ^{32}P-GTP. The lack of RNA transcripts produced at appropriate MMPC **1** concentrations, in combination with controls indicating that the RNA transcripts are not disturbed in other ways during the course of the analysis, confirms that it is the specific interaction of the nanoparticles with the DNA that disrupts this enzymatic process.

Conclusions. The development of systems capable of efficiently recognizing DNA sequences for biomedical or analytical purposes remains an important goal in bioorganic chemistry. Gold nanoparticles represent a versatile scaffold for biologically relevant molecules. We have demonstrated that MMPC **1** displays not only the DNA-binding ability common of multiply charged systems studied, such as polymers, dendrimers, or small molecules, but also is capable of inhibiting a transcription enzyme, T7 RNA polymerase, from producing RNA products. Nanoparticle **1** binds DNA in a stoichiometric, nonaggregated fashion with sufficient affinity to disrupt recognition and transcription by a well-evolved enzyme, demonstrating the viability of these particles for further application to biological applications, including transfection vectors. We are also exploring the incorporation of additional functional groups into the MMPC monolayer to provide sequence-specific recognition of DNA, with the ultimate goal being the creation of efficient gene regulation systems.

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Supporting Information Available: NMR of MMPC **1**, DLS hydrodynamic radii, TEM sample preparation, and pictures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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