Silver Clusters

International Edition: DOI: 10.1002/anie.201502917
German Edition: DOI: 10.1002/ange.201502917

Ag_2 and Ag_3 Clusters: Synthesis, Characterization, and Interaction with DNA**

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Abstract: *Subnanometric samples, containing exclusively Ag_2 and Ag_3 clusters, were synthesized for the first time by kinetic control using an electrochemical technique without the use of surfactants or capping agents. By combination of thermodynamic and kinetic measurements and theoretical calculations, we show herein that Ag_3 clusters interact with DNA through intercalation, inducing significant structural distortion to the DNA. The lifetime of Ag_3 clusters in the intercalated position is two to three orders of magnitude longer than for classical organic intercalators, such as ethidium bromide or proflavine.*

The interaction of Ag clusters with DNA has been used as a template method to prepare luminescent Ag clusters (see, for example, Refs. [1–6]), which have in turn been further developed as highly sensitive fluorescent sensors (see Ref. [7] for an example). In spite of the large number of studies carried out in this area, the nature of the interactions between Ag clusters and DNA remains largely unknown. Additionally, it has been recognized that the chemistry of clusters very much depends on the cluster size. For example, narrow cluster size windows have been reported for clusters with catalytic properties (see, for examples, Refs. [8–10]), showing that the cluster size is a very important parameter which has a major influence on their physicochemical properties. Therefore, to shed light on the interaction of DNA with clusters, one should use stable cluster samples with the narrowest possible size distribution. At the same time, because the capping agent can also have a large influence on such an interaction, one should use clusters without surfactants or other types of strong binding ligands. These requirements render the synthesis of such cluster samples a major challenge. We will show herein that this objective can be achieved using kinetic control techniques,[11,12] allowing us to synthesize for the first time the smallest reported naked Ag clusters (Ag_2 and Ag_3). Using UV/Vis absorption, fluorescence, and circular dichroism spectroscopies, viscosity and kinetic (stopped flow) measurements, and quantum mechanics/molecular mechanics (QM/MM) calculations, we studied the interaction of these clusters with DNA. Results show that Ag_3 clusters (unlike Ag_2) interact with DNA through intercalation, inducing significant structural distortion to the DNA.

The synthesis of atomic quantum clusters (denoted Ag-AQCs) without any surfactant was carried out by modification of a previously reported electrochemical method (see the Experimental Section in the Supporting Information).[13] It has been shown that the nanoparticle size can be controlled with electrochemical techniques by changing the current density.[14] However, this method needs some modifications in order to prepare stable clusters. Key to the production of small Ag clusters is the use of very slow kinetics with a very low concentration of Ag ions in solution, as previously reported.[12] To achieve the formation of stable, small Ag clusters, it is required that: a) the current densities should be much lower than those normally achieved using supporting electrolytes, requiring the use of miliQ water with no added electrolytes for the synthesis; b) the concentration of Ag ions must be kept at very low levels, ensuring that the clusters will grow very slowly.[11] After the electrochemical synthesis, it is also very important to remove any excess of Ag ions which have not been reduced because the presence of such ions causes the Ag cluster solution to become unstable, and further growth of clusters takes place until all Ag ions have been taken up. With this in mind, excess Ag ions in the solution are eliminated by precipitation with NaCl immediately after the

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[**] This work was supported by Obra Social "la Caixa" (OSLC-2012-007), the European Commission through the FEDER and FP7 programs (0681_InveNNta_1_E; FutureNanoNeeds, FP7-Grant 604602), the MCI Spain (MAT2010-20442 and MAT2011-28673-C02-01), MINECO Spain (MAT2012-36754-C02-01, CTQ2014-58812-C2-2-R), Xunta de Galicia Spain (GRC2013-044, FEDER Funds). D.B. is grateful for the postdoctoral grant from Xunta de Galicia Spain (POS-A/2013/018). F.G.R. and L.J.G. thank the CONICET for grant 01035 and the SXS Beamline (LNLS, Campinas, Brazil) for partial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201502917.

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synthesis. In this way very stable cluster solutions can be obtained as can be concluded by the fact that their physicochemical properties remain unchanged for years (see also below). It has also been observed that this purification process does not change the properties of clusters. For example, the luminescence of the clusters do not change after elimination of excess Ag ions. Furthermore, these clusters are uncharged species, as can be deduced from the fact that they do not migrate in electrophoresis gel experiments (results not shown).

AFM images show that the cluster sizes are approximately 300 pm in height (Figure 1 A and B), which implies that they are 2D clusters with less than 10 atoms.[15] Ag-AQCs do not show the characteristic Ag surface plasmon band, indicating

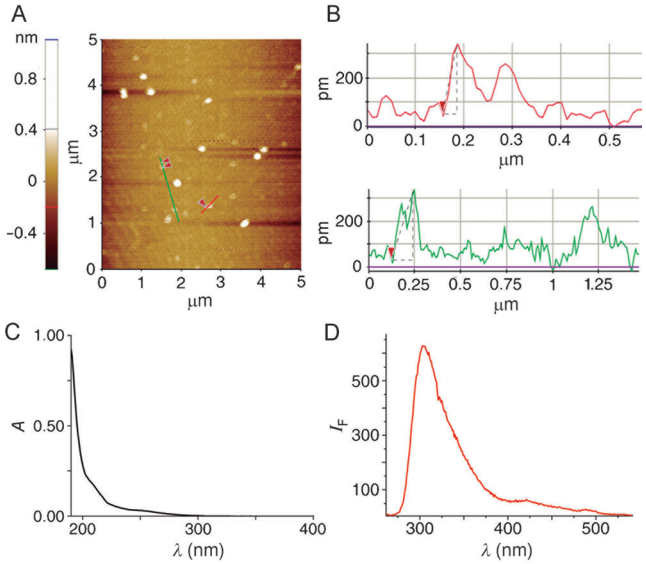

Figure 1. A) AFM picture of Ag-AQCs deposited on mica (mean square roughness ≈150 pm) and B) AFM height profiles measured through the red and green lines depicted in (A), plotting distance (x axis) against height (y axis). C) UV/Vis absorption spectrum of Ag-AQCs dispersions in water. D) Fluorescence emission spectra (λ_{exc} = 230 nm) of the Ag-AQCs cluster dispersions. I_F = fluorescence intensity.

that, contrary to nanoparticles, they do not have free electrons (Figure 1 C). As a result of the quantum size confinement, there is a splitting of the energy levels at the Fermi level, which impinges on clusters with luminescent properties.[16] Figure 1 D shows that the synthesized Ag clusters also display luminescent properties with a maximum emission band centered at $\lambda \approx 305$ nm obtained upon excitation at $\lambda =$ 230 nm. A good correlation between the emission wavelength and the cluster size has been found,[16,17] so that emission bands with higher energy are observed as the cluster size decreases. The emission energy of the synthesized clusters, being larger than the one previously reported for Ag_5 or Ag_6 clusters, points to a smaller cluster size.[18] Assuming the spherical jellium model, which seems to be a fairly close approximation for small clusters (see, for example, Ref. [16]), the number of atoms, N, within the clusters can be calculated by the simple expression, $N = (E_F/E_g)^3$, where E_F and E_g represent the Fermi level (5.4 eV for bulk Ag) and the HOMO–LUMO energy bandgap, respectively (HOMO = highest occupied molecular orbital, LUMO = lowest unoccupied molecular orbital). The bandgap can be approximated by the emission peak (4.0 eV), from which it follows $N = 2.4$, that is, clusters should contain between 2 and 3 atoms.

A more precise characterization of the cluster samples was carried out by ESI-TOF mass spectrometry, a soft ionization technique employed to avoid fragmentation.[18,19] Figure S1 in the Supporting Information shows the presence of only Ag_2 and Ag_3 clusters in the Ag-AQCs samples, which is in good agreement with the values calculated based on the luminescence measurements.

Further characterization of the cluster samples was carried out by X-ray absorption spectroscopy using synchrotron radiation. Figure S2 shows the XANES (X-ray absorption near-edge structure) cluster profile at the L_3 absorption edge. This profile is different from typical Ag ionic compounds, such as AgCl and Ag_2O, as it shows no oxidation of Ag atoms, and has the same structure, albeit more smooth, than metallic Ag.

As a result of the large HOMO–LUMO bandgap these Ag-AQCs are very stable, that is, they have a very low tendency to undergo oxidation or reduction. This stability can be inferred from the XANES results and the cyclic voltammogram of Ag-AQCs deposited on glassy carbon. Figure S3 shows that clusters cannot be oxidized or reduced over the entire electrode potential window (−0.7 V to +1.7 V versus RHE, where RHE is the reversible hydrogen electrode). Therefore, the high stability of these very small cluster samples, in contrast to large clusters, is associated with their very large bandgap, which makes them very difficult to reduce or oxidize at room temperature. Cluster aggregation and fusion (in the sense of breaking bonds and forming new ones) to form nanoparticles takes place only at temperatures above approximately 120 °C. The formation of nanoparticles can be observed by the disappearance of the luminescence and the appearance of the typical plasmon band of the formed Ag nanoparticles, as will be reported elsewhere.

Ag-AQCs have been observed to interact with DNA. Figure 2 shows the change in the UV/Vis absorption (Figure 2 A) and fluorescence (Figure 2 B) spectra of the cluster solution with increasing concentrations of DNA. The binding isotherms derived from these experiments have allowed us to evaluate the binding constant for the reaction Ag-AQCs + DNA⇄Ag-AQCs/DNA. The binding isotherms deduced at 25 °C, pH 7, and an ionic strength of 0.1 M were always monophasic (Figure 2A, B, C, insets), indicating that only one type of complex is present. The apparent binding constants, K_{app}, obtained using the Hildebrand–Benesi equation (see Section III in the Supporting Information and Figure S4) were $(5.0 \pm 1.3) \times 10^4\,M^{-1}$ and $(4.1 \pm 0.7) \times 10^4\,M^{-1}$ for the UV/Vis absorption and fluorescence experiments, respectively, indicating good correlation between these two estimates. Circular dichroism (CD) experiments were also carried out to investigate the structural changes caused in DNA by their interaction with Ag-AQC. Previously, we have verified that these clusters are achiral in nature; the interaction at different $c_{Ag\text{-}AQC}/c_{DNA}$ ratios is shown in Figure 2 C. The red and blue shifts ($\Delta\lambda = 3$ and 4 nm) in ellipticity at $\lambda = 275$ nm and

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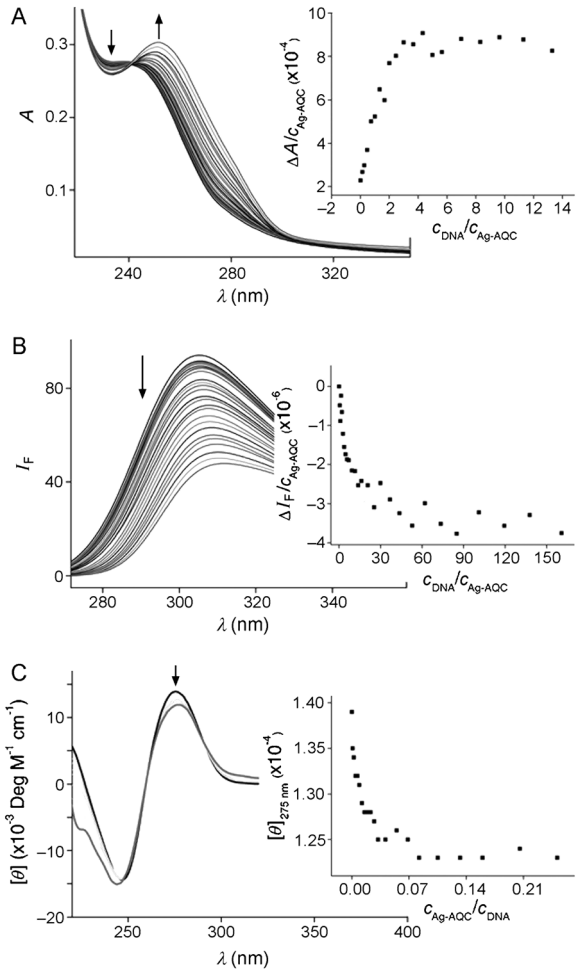

Figure 2. A) UV/Vis absorption spectra. $c^0_{\text{Ag-AQC}} = 0.6\ \mu\text{M}$. B) Fluorescence spectra. $c^0_{\text{Ag-AQC}} = 3.1\ \mu\text{M}$, $\lambda_{\text{exc}} = 230$ nm. I_F = fluorescence intensity. C) Circular dichroism spectra. $c^0_{\text{DNA}} = 98\ \mu\text{M}$. ionic strength = 0.1 M, pH 7.0, 25 °C. Insets: binding isotherms measured at $\lambda_A = 260$ nm (A), $\lambda_{\text{em}} = 305$ nm (B), and molar ellipticity at $\lambda = 275$ nm (C). Arrows in (A) and (B) indicate spectral changes with increasing c_{DNA}, arrow in (C) indicates increasing $c_{\text{Ag-AGC}}$.

247 nm, respectively, and the observed isodichroic point at $\lambda = 290$ nm indicate a significant change in the structural properties of the system as a result of interactions between Ag-AQCs and DNA. A plot of the changes in molar ellipticity observed at $\lambda = 275$ nm (Figure 2C, inset) shows a plateau from $C_{\text{Ag-AQC}}/C_{\text{DNA}} = 0.08$, that is, the molar ellipticity of DNA is affected only at very small cluster concentrations.

To gain a deeper insight into the cluster/DNA interaction, viscometry experiments were also carried out. Viscosity is an efficient tool to determine the ability of small molecules to affect the DNA contour length. Intercalation of a dye between the DNA base pairs causes local unwinding of the strand with elongation of the double helix.[20] The viscosity of the dye/polynucleotide system is related to the elongation of the polynucleotide according to the equation $L/L_0 = (\eta/\eta_0)^{1/3} = 1 + \beta \times (c_D/c_P)$, where η_0 and L_0 represent the viscosity and contour length, respectively, of the polymer alone, η and L are the same properties related to the dye/polynucleotide system at c_D/c_P ratio and β is the slope parameter.

Figure 3 shows the change of the relative contour length of the double helix of DNA for different $c_{\text{Ag-AQC}}/c_{\text{DNA}}$ ratios. The positive slope of the straight line function, $\beta = 2.0 \pm 0.1$, reveals that Ag-AQCs intercalate into the base pairs of DNA,

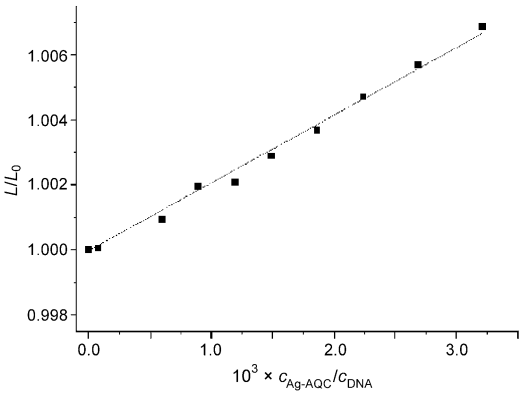

Figure 3. Relative elongation ($L/L_0 = (\eta/\eta_0)^{1/3}$) of the Ag-AQC/DNA system versus the $c_{\text{Ag-AQC}}/c_{\text{DNA}}$ ratio. $c^0_{\text{DNA}} = 2 \times 10^{-4}$ M, pH 7.0, ionic strength = 0.1 M, and $T = 25$ °C.

extending its overall length. It should be recalled here that classical intercalators, such as acridines, ethidium bromide (EB), and doxorrubicine, yielded slopes from 0.7 to 1.0.[21–23] This outcome is reasonable considering that the covalent radii of Ag atoms are longer than those of C atoms (153 pm versus 77 pm), thereby the unwinding and lengthening of the double helix must be higher. The kinetic study and the theoretical calculations will both also confirm intercalation as the mode of binding (see below).

The kinetics of the interactions between Ag-AQCs and DNA was studied using an excess of DNA by means of a stopped-flow technique at an ionic strength of 0.1M, pH 7, and 25 °C. Only one relaxation effect was detected, as indicated by the fact that all the kinetic curves recorded were monoexponential (Figure S5A). The plot of the reciprocal relaxation time, $1/\tau$, versus c_{DNA} gave rise to a straight line plot (Figure S5B). The slope and intercept of this plot yield the kinetic formation and dissociation constants ($k_f = (1.19 \pm 0.08) \times 10^4\ \text{M}^{-1}\text{s}^{-1}$, $k_d = 0.15 \pm 0.06\ \text{s}^{-1}$) of the Ag-AQCs/DNA complex, and the corresponding kinetic equilibrium constant $K = k_f/k_d = (7.9 \pm 0.7) \times 10^4\ \text{M}^{-1}$, is in reasonably good agreement with the K_{app} value (see above or Table S1). It should be noted that the estimation of the apparent binding constant is actually a lower limit because for such an estimation we assumed that all clusters are in the form of Ag_3 (see below). The thermodynamic and kinetic results can only be ascribed to intercalation of clusters into DNA. Moreover, the groove binder features (for example, concave in shape, possibility of forming H-bond formation)[24] are incompatible with the Ag_3 structure (see computational calculations below).

The equilibrium binding constant obtained is comparable to those of well-known intercalating organic species, namely acridines such as proflavine[25] and 9-amino-6-chloro-2-methoxyacridine (ACMA),[26] EB,[27] different cyanines,[28] or 1,10-phenanthrolin-5-amine[29] under the same experimental

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conditions. However, their rate constants are very different to those of the Ag-AQCs/DNA system. For example, for intercalation of proflavine into calf thymus DNA[25] the rate constants are: $k_f = 4.3 \times 10^7\ M^{-1} s^{-1}$ and $k_d = 6.8 \times 10^2\ s^{-1}$, of the same order as with ACMA, cyanines, and phenanthroline, and an order of magnitude higher than for the EB/DNA system ($k_f = 5.4 \times 10^6\ M^{-1} s^{-1}$ and $k_d = 38.5\ s^{-1}$).[27] It can be seen that the formation rate constant for the Ag-AQCs/DNA complex is more than two orders of magnitude lower than for all above mentioned systems. This observation is in agreement with the fact that, contrary to the neutral Ag-AQCs employed herein (pH 7.0), classical intercalators are cationic species, thus favoring their interaction with anionic DNA and their subsequent intercalation. The dissociation rate constant for the Ag-AQCs/DNA complex is three orders of magnitude lower than the one for proflavine/DNA and two orders lower than the one for EB/DNA complexes. Such very long lifetimes of Ag_3 clusters in the intercalated position is a very interesting and unexpected outcome because dissociation constants of intercalating agents are of great diagnostic significance. Slow dissociation rates are regarded as an important criterion as to their efficiency as a cancer therapeutic agent[30] because such drugs remain longer in the intercalated position, thus altering DNA recognition, and therefore, its replication and transcription.

To reinforce the above results on the interaction of Ag-AQCs with DNA and to deduce which clusters are responsible for the observed intercalation, a theoretical study of the interaction of Ag_N ($N = 2,3$) with the two double-helical decanucleotide duplexes d(ATATATATAT)$_2$ and d(GCGCGCGCGC)$_2$, was carried out using two-layer quantum mechanics/molecular mechanics calculations. The structures of the complexes d(ATATATATAT)$_2$/Ag_2, d(GCGCGCGCGC)$_2$/Ag_2, d(ATATATATAT)$_2$/Ag_3, and d(GCGCGCGCGC)$_2$/Ag_3, are shown in Figure 4 (for Ag_3) and Figure S6 (for Ag_2). It can be seen that in the complex d(ATATATATAT)$_2$/Ag_2 there is a covalent bond between Ag_2 and the N3 site of adenine, whereas in d(GCGCGCGCGC)$_2$/Ag_2 there is a covalent bond to the N7 site of guanine. The binding occurs through the major-groove side. Experimentally, slow kinetics ascribable to formation of cluster/DNA covalent bonds were not observed, probably due to the small proportion of Ag_2 present in the solution of AQCs. Attempts to intercalate Ag_2 between the 5th and 6th base pairs in both decanucleotides were unsuccessful, evidently because this intercalation did not correspond to a minimum energy. On the other hand, the geometric optimization of Ag_3 intercalated between the 5th and 6th base pairs of both d(ATATATATAT)$_2$ and d(GCGCGCGCGC)$_2$ corresponds to minimized energy structures, as shown in Figure 4 (see also the Movie in the Supporting Information).

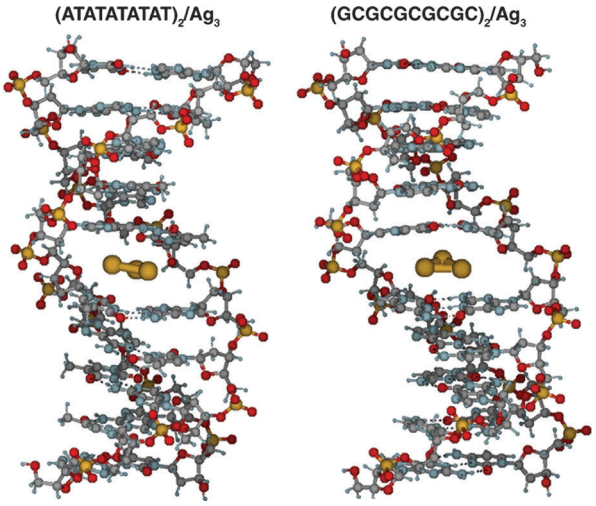

Figure 4. Energy minimized structures of the complexes d(ATATATATAT)$_2$/Ag_3 and d(GCGCGCGCGC)$_2$/Ag_3, obtained by QM/MM calculations, showing the intercalation of an Ag_3 cluster between the 5th and 6th base pairs.

Therefore, these calculations show that only Ag_3 intercalates into DNA, whereas Ag_2 interacts with DNA only by covalent binding. However, only the intercalation of Ag_3 induces heavy structural distortion to the DNA model. Thus, calculations indicate that the Ag_3 cluster is responsible for the changes observed in the UV/Vis absorption, fluorescence, and CD spectra, as well as to the viscosity of DNA solutions (see Figures 2 and 3). We have also calculated the shape of the frontier molecular orbitals of both clusters (plotted in Figure S7). From these calculations, it seems reasonable to hypothesize that the triangular shape of the triatomic molecule permits the existence of delocalized π frontier molecular orbitals, capable of interacting by π–π stacking with adjacent DNA base pairs to the intercalated position.

In conclusion, by using kinetic control Ag samples containing only Ag_2 and Ag_3 clusters were obtained for the first time by an electrochemical method, without the use of surfactants or strongly binding ligands. Thermodynamic, kinetic, and theoretical calculations have allowed us to carry out a detailed analysis of the interaction of DNA with such small Ag clusters, demonstrating the huge influence that the addition of only one atom to the cluster size can have on their interactions with DNA. We further show that the intercalating Ag_3 cluster induces heavy structural distortion in the DNA helix with a lifetime in the intercalated position which is two to three orders of magnitude larger than other well-known intercalating species, thus providing potentially new opportunities for the development of cancer therapeutic drugs.

Keywords: cluster compounds · DNA · electrochemical synthesis · intercalation · silver

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Received: March 30, 2015
Published online: ■■ ■■, ■■■■

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Communications

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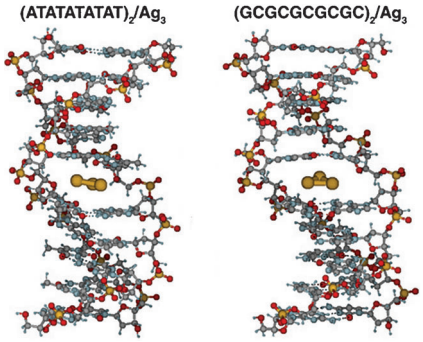
Ag_2 and Ag_3 Clusters: Synthesis, Characterization, and Interaction with DNA



Sandwiching silver in DNA: Subnanometric silver clusters (Ag_2 and Ag_3) were synthesized using a kinetic control procedure. Interaction studies of the clusters with DNA have demonstrated that Ag_2 clusters interact only by covalent binding, whereas Ag_3 clusters intercalate between the base pairs in DNA (see picture) and induce strong conformational changes.

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