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Positive Homotropic Allosteric Binding of Silver(I) Cations in a Schiff Base Oligopyrrolic Macrocycle

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Allosteric interactions play a critical role in a number of well-recognized biological processes.[1] In allosteric systems, the binding of a controlling substrate (e.g., ligand, small molecule guest, etc.) to a receptor affects (positively or negatively) the affinity of the system toward subsequent ligands or substrates, thus efficiently modulating the binding of multiple guests in a nonlinear fashion. A desire to reproduce the key features of allosterism in artificial systems has long been a goal within the chemical community[2] since it is appreciated that such efforts can lead to new advances in biomimetic design.

In the case of positive homotropic allosterism, such as is observed in hemoglobin, the binding of a guest causes the receptor to bind a subsequent identical guest with a higher affinity. This effect has proven to be much more difficult to reproduce than either negative or heterotropic allosterism, wherein initial substrate binding either retards subsequent binding or enhances the affinity for other substrates.[3,4]

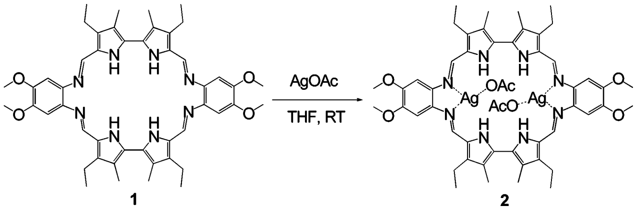
Here we describe the synthesis and characterization of a binuclear silver(I) complex of macrocycle **1** that is formed as the result of a homotropic cooperative ion pair insertion wherein the receptor binds two metal cations and two anions.

The Schiff base oligopyrrolic octaaza macrocycle **1** has been studied in our laboratory as a receptor for neutral substrate complexation[5] and as a binucleating ligand for late first-row transition metal cations (namely, Ni(II), Cu(I), Cu(II), and Zn(II)).[6] Its versatility as a receptor and its ability to stabilize different coordination modes for copper(I) and copper(II) prompted us to investigate its ability to complex second-row transition metal cations. Because of its homology to Cu(I), we elected to commence this work using Ag(I) as the test cation.

The binuclear silver(I) complex **2** was readily prepared in 92% yield by treatment of the free base macrocycle **1** with Ag(I) acetate at room temperature in an argon atmosphere (Scheme 1). The coordination mode depicted in Scheme 1 was then deduced from the ^{1}H NMR spectrum of the isolated product, which included signals for four pyrrolic NH protons (i.e., $\delta = 11.55$ ppm) and six protons ascribed to the acetate counteranions (i.e., $\delta = 1.62$ ppm).

Solid state structural information involving the coordination mode and conformation of complex **2** was obtained from a single-crystal X-ray diffraction analysis. As shown in Figure 1, each Ag(I) ion coordinates to two iminic nitrogen atoms of the macrocycle and to two oxygen atoms of the acetate counterion. Additionally, the two acetate anions participate in hydrogen-bonding interactions with the pyrrolic NH hydrogen atoms (e.g., O1A···HN4 and O2A···HN1 in Figure 1). As a consequence, the two coordination sites on each side of the ligand are tilted such that they are above and below the average plane of the macrocycle, respectively. In the solid state, complex **2** is characterized by another feature, namely, a presumed argentophilic interaction that serves to bring two closed-shell d^{10} Ag(I) cations in two neighboring complexes within a distance (3.1444(5) Å) that is less than twice the van der Waals radius for silver (3.44 Å).

Scheme 1. Synthesis of the Bis-Ag(I) Complex **2**



Since the metal ion coordination produced a red shift of the macrocycle UV absorption band (370 nm, THF, 298 K), the complexation of silver(I) could be followed by monitoring the spectral changes produced as a function of added cation. In particular, when increasing quantities of silver(I) trifluoroacetate or silver(I) *p*-toluenesulfonate[7] were added to solutions of **1** in THF, new bands at 409 or 404 nm, respectively, were seen to grow in at the expense of the original band at 370 nm. Typical binding isotherms obtained from these titrations are shown in Figure 2, while the spectra themselves are included in the Supporting Information.

In the case of the trifluoroacetate salt, the curve showed a linear response to increasing silver(I) concentration and saturated at precisely 2 equiv of Ag(I) ions. Because of this strong response, no quantitative information could be derived; however, a significant binding affinity could be safely inferred.

On the other hand, the binding of silver(I) tosylate appears to be considerably weaker as judged from the fact that more than 2 equiv had to be added to achieve saturation (cf. Figure 2). In this case, the binding isotherm shows the typical sigmoidal behavior characteristic of homotropic allosteric systems. The binding data

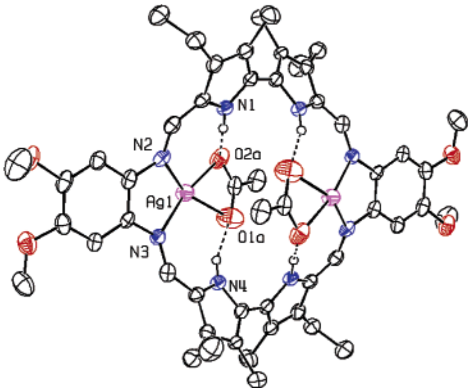


Figure 1. Top view of the bis-Ag(I) complex **2** showing a partial atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Most hydrogen atoms have been removed for clarity. The macrocycle lies around a crystallographic inversion center at 1, 0, 1/2. Selected bond distances (Å): Ag1−N3 2.282(3), Ag1−N2 2.338(3), Ag1−O2A 2.387(3), Ag1−O1A 2.498(4).

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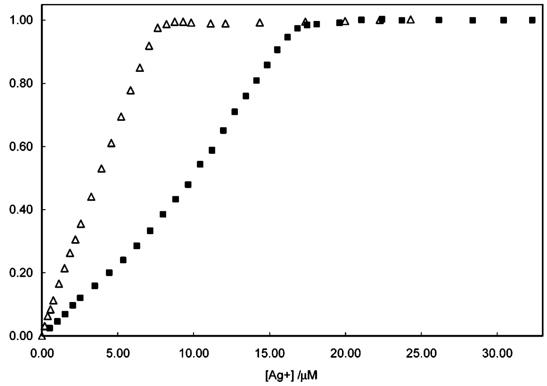

Figure 2. Binding isotherms obtained from the UV−vis titrations of macrocycle **1** with $Ag(O_2CCF_3)$ (△, [**1**] = 4.49 μM) and Ag(*p*-toluenesulfonate) (■, [**1**] = 4.89 μM) in THF at 298 K.

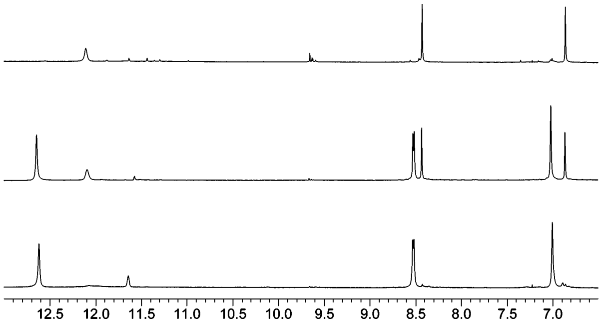

Figure 3. Downfield regions of the ^{1}H NMR spectra (600 MHz, THF-d_8, 193 K) of **1** (top), a mixture of **1** and ~1.3 equiv of $Ag(O_2CCH_3)$ (center) and **2** (bottom). The spectrum of the mixture features two separate sets of resonances for (from left to right) pyrrolic, iminic, and aromatic protons, which were assigned to species **1** and **2**.

were thus analyzed using the Hill equation: $\log(Y/(Y - 1)) = n \log[Ag^+] + \log K$, where Y is the fractional saturation of the host, n is the Hill coefficient, and K is the association constant. From the intercept and slope of the linear plot, we obtained $\log K = 10.2 \pm 0.5$ and $n = 2.0 \pm 0.1$, with a correlation coefficient of 0.99. The Hill coefficient, n, obtained in this way corresponds to the mathematical limit for a positive allosteric system involving two binding sites; it thus serves to confirm the proposal that Ag(I) is bound to macrocycle **1** via a strongly cooperative process.

Further support for the conclusion that the silver(I) binding in **1** is regulated by a positive allosteric effect came from ^{1}H NMR spectroscopic analyses. In particular, the spectrum of a mixture of **1** and ~1.3 equiv of $Ag(O_2CCH_3)$ in THF-d_8 revealed the presence of two species (only) whose broad peaks overlapped. When this sample was cooled to −80 °C, the two sets of peaks were cleanly resolved and could be assigned to the free-base macrocycle **1** and the corresponding bis-silver complex **2** (cf. Figure 3). Thus, even under conditions of intermediate binding site saturation, the coordination of a first Ag(I) cation appears to activate the system toward further coordination. In fact, as expected for a strongly cooperative ditopic receptor, no signals ascribable to a *mono*-Ag(I) complex were observed.

Both in enzymatic and artificial systems, allosterism has been related to a structural modification whereby a first binding event induces a nonlinear response to subsequent guests.[1,2] Generally, this modification involves a conformational change that affects the entropic penalty for ensuing binding events. In the case of synthetic systems, this has been accomplished most successfully via rotation about a symmetry axis of the host.[3,4d,e] In the present case, coordination of a first silver(I) cation, along with concurrent hydrogen-bonding interactions involving the anionic counterion (vide supra), is expected to change the orientation of the pyrrolic units to the up−down conformation seen in the solid state structure of complex **2**. This change in orientation, in turn, allows for the coordination of a second ion pair within a less-hindered and better preorganized coordination site.

The behavior observed with Ag(I) differs from what was seen with the previously reported $M_2^{II}(\mathbf{1})(O_2CCH_3)_4$ complexes (M = Cu(II), Zn(II)),[6] wherein no evidence of cooperative binding was seen. We rationalize this apparent dichotomy in terms of steric effects. In the case of these divalent cations, the first coordinated metal center is expected to retain its two counteranions. As inferred from the structures of the final bis-metal complexes, these counteranions are expected to occupy both sides of the mean macrocycle plane and participate in multiple hydrogen-bonding interactions. Thus, in contrast to what is true for **1** + Ag(I), coordination of a single divalent cation is not likely to produce a preorganized, unhindered site that would favor a subsequent binding event.

Although a complete elucidation of the cooperative behavior of **1** will require further theoretical and experimental analysis, this receptor represents the first example of what could emerge as a new (and potentially large) class of hosts for allosteric binding, namely, multidentate oligopyrrolic macrocycles.

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Supporting Information Available: Synthetic details, X-ray structural data for **2**, UV and NMR spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The hydrogen-bonding acetate ions shown in Figure 1 are clearly noninnocent counterions; so, for the UV−vis titrations, we chose two silver salts that share a sufficient solubility in THF but differ substantially in the bulkiness and geometry of the anion.

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