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Five- and Six-Coordinated Silver(I) Complexes Derived from 2,6-(Pyridyl)iminodiadamantanes: Sustained Release of Bioactive Silver toward Bacterial Eradication

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Abstract

Silver(I) complexes of two designed tridentate ligands, namely, 2,6-(pyridyl)-iminoditriazaadamantane (pydTAM) and 2,6-(pyridyl)-iminodiadamantane (pydAm), have been synthesized and structurally characterized. $[\text{Ag}(\text{pydTAM})_2](\text{CF}_3\text{SO}_3)$ (**1**), the hitherto unknown *mer* isomer of a silver(I) octahedral complex, crystallizes in a highly symmetric body-centered cubic $I\bar{4}3m$ space group. Quite in contrast, the Ag^{I} center in the analogous $[\text{Ag}(\text{pydAm})_2](\text{CF}_3\text{SO}_3)$ (**2**) complex resides in a trigonal-bipyramidal geometry and crystallizes in a triclinic $P\bar{1}$ space group with two crystallographically independent molecules in the asymmetric unit. Complex **1** exhibits exceptional solubility in aqueous media and leads to the efficient eradication of several bacterial strains upon sustained release of bioactive silver.

Silver(I) usually adopts linear or tetrahedral geometry in its coordination complexes.^{1, 2} In such complexes, Ag^{I} ions are predominantly two-, three-, and four-coordinated, while five- and six-coordinated silver complexes are very sparse.¹ The paucity of silver(I) complexes with higher coordination number principally arises from the lack of stereochemical preferences associated with a filled-shell d^{10} configuration. A thorough Cambridge Structural Database (CSD) survey revealed only 33 crystal structures of complexes containing six-coordinated Ag^{I} centers with nitrogenous ligands, of which only six structures are truly discrete silver complexes. These six silver complexes are strictly limited by the ligand types, which are either tripodant or macrocyclic in nature. For example, silver(I) complexes of the type $[\text{AgL}]^{2+}$ derived from two different tripodant ligand systems L have been reported (where L = *N, N', N''*-trimethyl-*N, N', N''*-tris(3-pyridyl)-1,3,5-benzenetricarboxamide³ and tris(pyrazol-1-yl)-methane⁴). These silver(I) complexes

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Supporting Information

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Synthetic procedures for the ligands and complexes, details of structure refinement for complexes 1 and 2 (Table S1), intermolecular interactions within the crystal frameworks of 1 and 2 (Figure S1), stability of complex 1 in aqueous media and saline (Figures S2 and S4), UV-vis spectrum of the pydTAM ligand (Figure S3), and bacterial growth curves (Figures S6–S6) (PDF) X-ray crystallographic data in CIF format (CIF)

The authors declare no competing financial interest.

incorporating symmetrically coordinated tripodal ligand systems exhibit *facial* disposition of the donor atoms. The other types of six-coordinated silver(I) complexes, also of the general formula $[\text{AgL}_2]^+$, are derived from polyamine macrocyclic ligands such as 3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane⁵ (also known as sacrophagines) and 1,4,7-triazacyclononane.⁶ In this case, six-coordination of the silver complexes is forced by the ligand structures. However, no six-coordinated silver(I) complex derived from a nonrigid tridentate ligand system with *meridionally* disposed donor atoms has been reported to date. This is undoubtedly an untenable position in terms of chemical synthesis, and we were interested in investigating the possibility of isolating such silver complexes through appropriate ligand design. In such pursuits, we have synthesized two potentially tridentate ligands, namely, 2,6-(pyridyl)iminoditriazaadamantane (pydTAm) and 2,6-(pyridyl)iminodiadamantane (pydAm) (Figure 1). These two structurally similar ligands differ chemically only slightly; in the pydTAm ligand, the bridgehead N atoms (part of the adamantyl moiety) have the capacity to form extensive intermolecular hydrogen bonding unlike the pydAm ligand (Figure 1).

Herein we report a simple one-step reaction of $\text{Ag}(\text{CF}_3\text{SO}_3)$ with 2 equiv of the pydTAm ligand that resulted in a white microcrystalline solid. Further recrystallization of this solid by layering diethyl ether over its acetonitrile solution afforded X-ray-quality crystals. Single-crystal X-ray diffraction on one of those crystals revealed the unusual octahedral coordination around the Ag^{I} center in $[\text{Ag}(\text{pydTAm})_2](\text{CF}_3\text{SO}_3)$ (**1**; Figure 2).

After encountering this unusual solid-state structure of **1**, we were driven by curiosity to isolate and structurally characterize the analogous complex synthesized by a similar method employing the pydAm ligand. Surprisingly, single-crystal X-ray diffraction studies disclosed a very different structure of the resulting complex $[\text{Ag}(\text{pydAm})_2](\text{CF}_3\text{SO}_3)$ (**2**; Figure 2). In this structure, the Ag^{I} center resides in a highly distorted trigonal-bipyramidal coordination sphere and between two potentially tridentate pydAm ligands; one binds the silver in a tridentate fashion and the other in a bidentate fashion.

Complex **1** crystallized in cubic $I\bar{4}3m$ symmetry and the 3-fold axis, which can be visualized along the C–S bond of the triflate counteranion. Quite in contrast, complex **2** comprising a very similar ligand structure crystallized in $P\bar{1}$ symmetry with two crystallographically independent molecules in the asymmetric unit. At the time of the preparation of this report, another space-group-specific CSD survey revealed that to date only 269 crystals of complexes of any metal within the periodic table crystallized in the $I\bar{4}3m$ space group, while 195208 structures with the $P\bar{1}$ space group have emerged. The 269 structures that crystallized with $I\bar{4}3m$ symmetry are mostly dominated by zinc and copper complexes, while only two examples of silver-bearing complexes have been found with the $I\bar{4}3m$ space group.^{7–9} It is worth mentioning that neither of those systems represents a discrete silver complex (such as complex **1**).

The coordination geometry of the Ag^{I} center in complex **1** is distorted octahedral. The two tridentate ligands are orthogonally oriented to each other, resulting in the *mer* isomer. The two five-membered chelate rings and both ligands are coplanar and constitute perfect planes. The dihedral angle between the pyridyl ring and the triazaadamantyl moieties is uniformly 90°. In the case of complex **2**, analysis of one of the molecules within the asymmetric unit

reveals some salient structural features. In **2**, one of the pydAm ligands coordinated the metal center in a tridentate fashion, forming two five-membered chelate rings. These chelate rings are satisfactorily planar with mean deviations of 0.029 and 0.067 Å. The other pydAm ligand binds the metal in a bidentate fashion, resulting in the formation of one five-membered chelate ring (mean deviation, 0.023 Å). In this case, the second imine N atom was disposed in an anti orientation with respect to the pyridyl N atom, thus hindering the possibility of formation of a chelate ring. The dihedral angles between the pyridyl ring and the adamantyl moieties connected with the imine N atoms that are part of the tridentate chelate are rather similar (30.7 and 33.6°). On the other hand, the dihedral angle between the pyridyl ring and the adamantyl moiety connected to the imine N atom that is a part of the bidentate chelate is 17.1°. The adamantyl moiety connected with the imine N atom of this ligand remains noncoordinated with a dihedral angle of 5.4°.

The Ag–N(pyridyl) distance in **1** [2.381(4) Å] is comparable with the average Ag–N(pyridyl) distance of **2** [2.378(4) Å]. However, the Ag–N(imine) distance in **1** [2.677(5) Å] is noticeably longer than the average Ag–N(imine) distance observed in **2** [2.516(5) Å]. The only silver complexes with ligand environments comparable to those of **1** and **2** are [Ag(qyTAM)₂](CF₃SO₃) and [Ag(qAm)₂](CF₃SO₃)¹⁰ where the average Ag–N(quinolyl) distances are 2.339(5) and 2.337(6) Å respectively, slightly shorter than the Ag–N(pyridyl) distances in **1** and **2**. Also, the average Ag–N(imine) distances in [Ag(qyTAM)₂](CF₃SO₃) and [Ag(qAm)₂](CF₃SO₃) complexes [2.569(4) and 2.315(5) Å, respectively] are both significantly shorter than the average Ag–N(imine) distances in **1** and **2**. These differences could be attributed to the considerable strain within the chelate ring upon coordination of the pydTAM and pydAm ligands to the metal centers in **1** and **2**, respectively, which results in a relatively weaker bonding situation.

The crystal packing patterns of the two structures exhibit significant differences in the extended network for the two complexes (Figure 3). Analysis of the crystal packing revealed few nonclassical hydrogen-bonding interactions for both structures. For complex **1**, C–H...N [2.50(4) Å] and, for complex **2**, C–H...O (spanning the range 2.36–2.59 Å) types of intermolecular interactions consolidated the three-dimensional network (see Figure S1). The packing pattern in complex **1** is particularly interesting because of its high crystallographic symmetry (body-centered-cubic). In this pattern, the same molecule exhibits two distinct orientations within the extended framework. In one such orientation, the molecules are aligned in such a way as to form square-shaped cavities, while in the second type of orientation, they are found to be stacked within such cavities (Figure 3, left panel).

Both complexes are stable toward light and dissolve in a variety of organic solvents like dichloromethane, chloroform, acetonitrile, and methanol. Complex **1** is also exceptionally soluble in aqueous media. This has prompted us to examine the efficacy of this complex toward Ag⁺-induced eradication of few selected Gram-positive (*Bacillus subtilis* and *Staphylococcus epidermidis*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacterial strains. All of these pathogens cause serious urinary and gastrointestinal tract infections and complications in burn-wound healing.^{11–13} *P. aeruginosa* can be life-threatening especially in patients with compromised host defense mechanisms and is a frequent cause of nosocomial infections in hospital settings.¹¹

One of the key prerequisites for silver complexes used for the treatment of wound infections is the slow and sustainable release of active Ag^+ to the infected sites. In fact, the major limitation of AgNO_3 (a commonly used silver-based antibacterial agent) toward therapeutic applications is its instantaneous precipitation under physiological settings due to the rapid formation of AgCl . As a consequence, most of the bioactive Ag^+ does not reach the infected sites, resulting in reduced efficacy of the drug and thus often requiring a higher dosage. Silver sulfadiazine (AgSD) is another widely used drug for treating acute burn-wound infections. However, the allergic reaction associated with its sulfadiazine component was proposed to cause a nephrotic syndrome in the patients subject to such treatments.¹⁴ In the present work, complex **1** includes the pharmacologically relevant triazaadamnatyl moiety in its design. This motif not only exerts excellent water solubility but also acts as a lipophilic bullet that facilitates cellular uptake of its complexes. Although silver complexes bearing such moieties are extremely sparse, it has been shown that silver complexes incorporating 1,3,5-triaza-7-phosphaadamantane are effective toward the eradication of bacteria.¹⁵ Solution studies on complex **1** revealed its superior stability in aqueous media, as monitored with the aid of electronic absorption spectroscopy. In such media, complex **1** slowly releases silver over a period of 6 h, as monitored by UV–vis spectroscopy (Figure S2). Furthermore, the stability of **1** was also investigated in the presence of 0.05 mL of 0.15 M NaCl in a 1 mL cuvette containing a solution of **1** (concentration 9×10^{-5} M), and its absorption spectra were monitored over a period of 35 min, as shown in Figure S4. This experiment revealed that complex **1** is considerably stable under physiologically relevant saline media, which makes **1** an excellent Ag donor for slow and sustainable Ag^+ delivery to the wound sites. The minimum inhibitory concentration (MIC) values were determined to assess the antibacterial efficacy of complex **1**, and the results are summarized in Table 1.

From the MIC values, it is evident that, under the same experimental conditions (see the Supporting Information), complex **1** undoubtedly exhibits similar or superior antibacterial activity compared to AgNO_3 and AgSD toward the selected pathogens. A representative example of the bacterial growth curve is shown in Figure 4.

Supplementary Material

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Acknowledgments

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Figure 1.
Tridentate ligands employed in the present work (the donor N atoms are shown in blue).

Figure 2. Molecular structures of 1 (left panel) and 2 (right panel). The boundary thermal ellipsoids are shown at the 50% probability level. H atoms and counteranions are omitted for clarity.

Figure 3.
Extended structures of 1 (left panel) and 2 (right panel).

Figure 4.

Bacterial growth curves for *P. aeruginosa* in the presence of complex 1. The y-axis absorbance is directly proportional to the bacterial population.

Table 1MIC Values (μM) of Complex 1 against Selected Pathogens

compound	<i>E. coli</i>	<i>S. epidermidis</i>	<i>B. subtilis</i>	<i>P. aeruginosa</i>
AgNO ₃	4	2	6	4
AgSD	4	4	10	8
complex 1	2	2	2	4