

Four-Stranded Coordination Helices Containing Silver–Adenine (Purine) Metallaquartets

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This Communication describes structures of a family of silver–adenine (purine) metallaquartets that occur in a four-stranded coordination motif, bearing a close resemblance to nucleic acid quadruplexes. Using modified purine frameworks, it is further demonstrated that subtle variations in nucleobase heterocycle are tolerable and a metallaquartet is obtained irrespective of the substitution, thus suggesting a high-propensity silver–adenine interaction to achieve quartet structures. All of the solid-state structures studied were orthorhombic, belonging to the *Fdd2* space group.

Metal ion–nucleic acid interactions govern fundamental aspects of structural stabilization and biological functions ascribed to these macromolecules.¹ The presence of cations in the environment not only is necessary for charge neutralization of the nucleic acid polyanion but also holds considerable importance for the emergence and stability of DNA and RNA tertiary folds.² Nucleobase frameworks, with or without metal ion interactions, are crucial for the identification of quadruplexes in telomeric DNA and nuclease-hypersensitive promoter regions, RNA, and group I intron tertiary structures, such as the adenosine platforms.³

Guanosine-quartet formation, one of the possible interaction schemes in nucleic acids, is an interesting base-pairing phenomenon with significant structural ramifications and biological consequences.^{3a,4} In addition to this well-studied base-tetrad scheme, crystal structures of other RNA quadruplexes suggest that the adenine skeleton also favors base-

tetrad formation.⁵ Consequently, adenine-mediated tetraplexes have been studied in designed oligonucleotide segments with the help of crystal structure, solution NMR, and molecular dynamics simulations.^{5,6}

Forays into the expanded base-pair regimen allow crafting of artificial situations to stabilize higher order nucleic acid–nucleobase constructs with the hope of generating interesting design paradigms for novel architectures.⁷ In this context, the hydrogen-bonded structure and the stability of adenine tetrads with the help of theoretical calculations have been described in the literature, where the conformations supportive of A tetrads were projected to adopt a bowl-like structure.⁸ Quartets with a mixed-nucleobase regimen and involvement of two metal ions with a single nucleobase have been reported.⁹ Continuing with our efforts in developing metalated adenine polymers,¹⁰ we have described silver–adenine interaction at neutral and basic pH,¹¹ where only the former condition afforded the formation of metallaquartets.

9-substituted adenine offers three main coordination sites, N1, N3, and N7, of which N1 and N7 are predominantly used for metal ion complexation.¹² While most of the literature reports center around mono- and bidentate coordination modes in substituted adenine moieties,^{3a,13} the 3*N*

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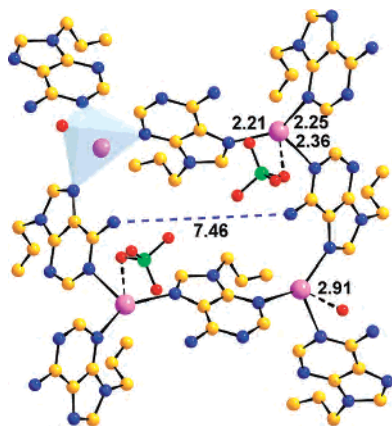


Figure 1. Solid-state structure of silver–adenine metallaquartet **1**, with perchlorate counteranions, and selected bond lengths and interatomic distances. Hydrogen atoms are omitted for clarity. Color code: pink, silver; orange, carbon; blue, nitrogen; green, chlorine; red, oxygen.

(μ -N1,N3,N7) coordination mode for 9-substituted adenine is rare, and so far two such examples, one with a heterometallic complex with the involvement of Pt/2Ag, have been reported, where N1 and N3 are coordinated to silver and N7 is coordinated to platinum,¹⁴ with the other being a homometallic silver complex.^{11b} Some reports also describe an unusual μ -N3,N7,N9 coordination mode with an adeninate ion.¹⁵ An exocyclic amino group is found to coordinate under mild basic conditions¹⁶ and to some ruthenium complexes.¹⁷

In a continuation of our previous work,¹¹ we introduced three key modifications in the adenine skeleton (Scheme S1 in the Supporting Information) involving an *n*-propyl group at N9, use of three silver counteranions, viz., NO_3^- , ClO_4^- , and BF_4^- , and the replacement of the N6 exocyclic amino group with a Cl6 chloro substituent. Namely, five complexes, 9-allyladenine–silver perchlorate (**1**; *Caution! perchlorate salts are potentially hazardous and should be handled with care*), 9-allyladenine–silver tetrafluoroborate (**2**), 9-allyl-6-chloropurine–silver nitrate (**3**), 9-propyladenine–silver nitrate (**4**), and 9-propyl-6-chloropurine–silver nitrate (**5**), were prepared. Solid-state structural analysis of these complexes suggests that metallaquartet formation occurs irrespective of the counteranions and subtle structural changes in the purine ring framework.

Crystals suitable for X-ray diffraction for complexes **1** and **3–5** (Figures 1 and 2) were grown either by a layering technique or from their saturated solution, followed by slow evaporation. Crystal growth occurred over a period of 1 week and, notably, all five metallaquartet crystals obtained be-

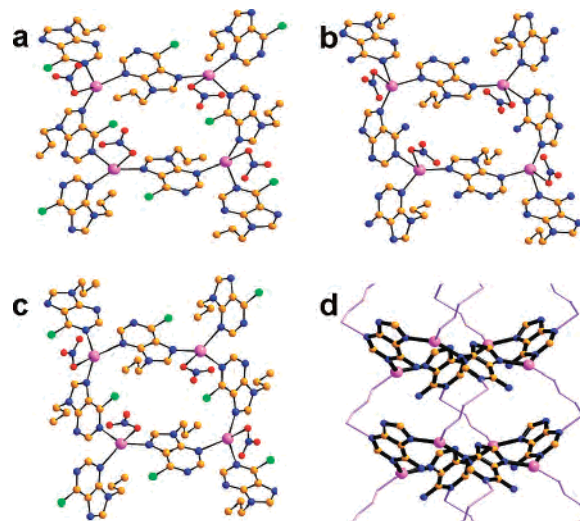


Figure 2. Solid-state structures of (a) **3**, (b) **4**, and (c) **5** showing silver–adenine-mediated metallaquartets. (d) Four-stranded helical wire-frame coordination motif, as viewed along the *c* axis. Two adjacent bowl-shaped quartets, with one adenine being contributed from a strand, are stacked one over the other. Hydrogen atoms are omitted for clarity. Color code: pink, silver; orange, carbon; blue, nitrogen; green, chlorine; red, oxygen.

longed to the same orthorhombic space group *Fdd2* (No. 43) (Table S1 in the Supporting Information).

The asymmetric units were composed of a silver ion, corresponding anion, and one ligand, where silver ions coordinated to three different nitrogen atoms of three ligand molecules. In other words, each molecule of 9-modified adenine coordinated to three silver ions, affording two different types of coordination polymeric motifs (Figure 1): one with the participation of N3 and N7 and the other involving N1 and N3 coordination, giving rise to helical architectures. This coordination environment leads to the formation of silver–adenine (purine) quartets with four silver atoms positioned at the corners of a distorted rectangle. The structures of **3–5** are nearly identical upon cursory inspection, but a careful analysis reveals differences in their bond angles and lengths.

The angles of N1–Ag–N7 and N3–Ag–N7 range from 106.52 to 117.92° and from 133.01 to 145.38°, respectively, for the five complexes, and the distances between silver atoms of the two sides of the distorted rectangle are in the ranges of 8.60–9.46 and 10.17–11.37 Å. The distances between silver and nitrogen atoms are also noticeably in the same range, varying from 2.33 to 2.43 Å for Ag–N1, from 2.23 to 2.30 Å for Ag–N3, and from 2.18 to 2.23 Å for Ag–N7 (Table S2 in the Supporting Information). The central part of the quartet comprises two inwardly projected N9 substituents and two inwardly projected exocyclic N6 substituents.

The void size of these metallaquartets varies from 4.8 to 8.2% of the total cell volume, as calculated by *PLATON*, ignoring the presence of solvent molecules (Figure 3 and Table S3 in the Supporting Information). However, void size variation is not predictable in this small set of crystal structures. For example, the void size where ClO_4^- is present as a counteranion is 6.4% of the total cell volume, but a comparatively smaller BF_4^- counteranion results in a void

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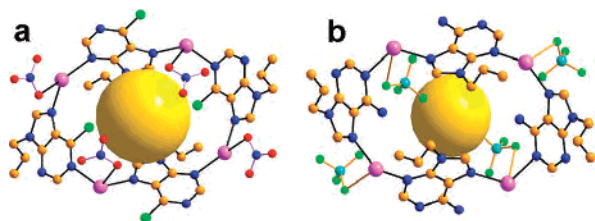


Figure 3. Maximum and minimum void sizes observed in five different metallaquartets: (a) **5** (8.2% of the total cell volume 4792.8 Å³) and (b) **2** (4.8% of the total cell volume 4932.8 Å³), respectively. Color code: pink, silver; orange, carbon; red, oxygen; blue, nitrogen; green, chlorine; aqua, fluorine.

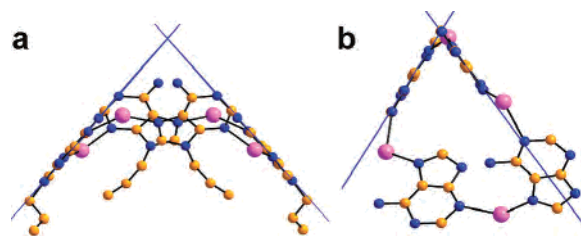


Figure 4. Representation of the two dihedral angles in **2**: (a) for the opposite adenine residues; (b) for the adjacent adenine residues.

size of 4.8%. The void spaces in complexes **1–3** are filled with water or methanol solvent molecules. However, no solvent molecule was detected in the void spaces of complexes **4** and **5**.

Analogous to the natural systems, four adenines (purines) are contributed by four coordination helices, which, in turn, are tethered with the help of intervening silver ions (Figure 2d). The quartets are separated by 7.5–8.0 Å along the crystallographic *c* axis, depending on the complex studied. For complexes **1**, **2**, and **4**, the exocyclic amino group N6 is flanked by two anions within hydrogen-bond-forming distances, while in complexes lacking an exocyclic amino group, the chlorine substituent appears to form a weak hydrogen bond (C–H···Cl) with the methylene hydrogen of the allyl group within a C···Cl distance of 3.9 Å.¹⁸

A bowl-shaped spatial disposition of the four bases is evident in metallaquartets and coordination helices (Figures 2d and 4a,b). A closer inspection reveals that the angle between the planes of opposite nucleobases passing through N1, N3, N7, and N9 is 80–89°, while that of the adjacent

bases is ~54–66° (Table S4 in the Supporting Information). Such bowl-shaped curvature resulting from the coordination environment of silver is similar to unmetalated homoadenine tetrads in natural nucleic acid quadruplexes, which are formed via intermolecular hydrogen-bonding interactions.⁸

Bioinspiration from nucleic acids has emerged as an expedient approach for the construction of complex architectures.¹⁹ In this vein, modifications in nucleic acid quadruplexes have been invoked for the innovative design of RNA-based uncharged tetraplexes,²⁰ metal-sensing four-stranded hybrids,²¹ and DNA nanomachines based on duplex–quadruplex exchange,²² to name a few. The current study extends quadruplex mimicry into the realm of reproducible nucleobase metallaquartet coordination motifs, which are formed via silver–adenine (purine) interactions. Notably, subtle changes in the purine heterocycle substitution and counteranion did not affect metallaquartet formation in the examples studied and reported. These results may also help in the understanding of the role of the silver ion binding to nucleic acids, leading to conformational transitions.²³

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Supporting Information Available: Synthetic procedures, characterization, X-ray crystallographic file in CIF format, and ORTEP diagrams. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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