Au(C^N)Cl_2 vs. Au(N^N)Cl_2 coordination motifs: reactivity with the HIV-1 nucleocapsid zinc finger protein and GSH

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Au(III)-based electrophiles undergo two competitive processes when facing a target sulfur-containing biomolecule: redox mechanism and ligand replacement. This competition, of wide interest in coordination chemistry, can also be explored when targeting biomolecules. As a target, we selected the HIV-1 nucleocapsid protein NCp7 zinc finger 2, which contains two $Cys_2HisCys$ zinc finger (ZnF) motifs and is essential during many steps of the viral cycle.[1,2] As a benchmark for biologically relevant redox processes, GSH was also selected.

For the Au(N^N)Cl_2 coordination motif, ligand replacement happens really fast and reduction of Au(III) is also a possibility based on the interaction of $[Au(2,2'\text{-bipy})Cl_2]^+$, $[Au(4,4'\text{-dimethyl-}2,2'\text{-bipy})Cl_2]^+$ and $[Au(phen)Cl_2]^+$ with both NCp7 and GSH. Here no AuL-protein adduct was observed and AuF was the main gold-containing species obtained (in multiple charge states, 4+ at 605.49, 3+ at 806.98 m/z). Some species assigned to the oxidized apo-peptide were also identified, reinforcing the hypothesis of Au(III) reduction. On the other hand for the motif Au(C^N)Cl_2 a high redox stability was achieved. When interacting with NCp7 (F2), Au(bzpy)Cl_2 (bzpy = *benzylpyridine*) formed multiple [Au(III)(bzpy)]-F adducts, indicating Cl^- replacement by Cys residues from NCp7 (F2). Cys attack was further confirmed by the presence of (bzpy)-oxiapo species at multiple charge states (5+ at 478.81, 4+ at 598.26 m/z), indicating the formation of C-S bonds between the ligand bzpy and Cys residues catalyzed by Au(III). Multiple [Au(III)(bzpy)] units were also incorporated into the protein, with the most abundant gold-containing signal corresponding to 3[Au(III)(bzpy)]-F in multiple charge states (4+ at 829.27, 3+ at 1105.36 m/z), matching the number of Cys residues available in the structure of NCp7 (F2). A bimetallic species corresponding to [Au(III)(bzpy)]-ZnF^{3+} at 884.31 m/z was also identified. When interacting with GSH, only chloride replacement was observed for [Au(bzpy)Cl_2], as exemplified by the species at 671.12 m/z, assigned to $[Au(bzpy)\text{-}GSH]^+$. It is also worth mentioning the remarkable selectivity observed for [Au(bzpy)Cl_2] towards Cys (S) and not His (N), based on the experimental data discussed so far. The interaction with GSH was further monitored by ^{1}H NMR and, up to 24 hours, the ligand bzpy remained coordinated in a bidentate way (C^N), as evidenced by the coupling splitting of the bridging CH_2 on the ligand.

In this work we demonstrated the unique behavior of Au(bzpy)Cl_2 when targeting sulfur-containing biomolecule. The high redox stability when compared Au(N^N)Cl_2 allows the compound to form stable Au(III)(bzpy)-F adducts and also to remain structurally stable in presence of GSH. This behavior is unique among metal-based zinc ejectors, resembling the reactivity of organic covalent zinc ejectors.[3]

References

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