Reaction of Au(I) complexes with HIV-1 and human zinc finger proteins X-ray absorption spectroscopy

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Current antiretroviral therapies for HIV-1 infection can be considered efficient because they increase life expectancy, but on the other hand, are ineffective to eradicate the infection and resistant strains emerge.[1] To overcome these problems new molecular targets are investigated and new inhibitors are needed to maintain the therapies functional. A recognized molecular target for HIV-1 therapy is the zinc finger (ZnF) protein 7 of the nucleocapsid (NCp7).[2] Gold complexes have been showing inhibition of NCp7 by electrophilic attack of the metal to cysteines leading to the ejection of Zn(II) and formation of so called gold fingers.[3,4] However, structural details of the final products are currently lacking. Early studies on anti-arthritic gold(I)-based drug, auranofin, showed to decrease the viral load of HIV-1 in an infected patient.[1] and recently in studies performed in SIV infected rhesus macaques.[1] Recently our research group studied the interaction of [Ph3PAuL] complexes with NCp7 finding the first formation of Ph_3PAu-apo-peptide as a stable species.[4]

X-ray absorption spectroscopy studies have allowed the development of a model for the coordination environment of gold fingers based on the analysis of gold L3-edge XAS of ZnF+Au systems, and simulations of XANES spectra. The final products of [AuCl(PEt_3)] and auranofin with the C-terminal finger of NCp7 can be definitively categorized as containing S-Au-P coordination spheres, confirming the Lewis acid electrophilic attack on the zinc-bound cysteinates. This conclusion was confirmed by *ab* initio multiple scattering simulations of the XANES spectra of hypothetical compounds with Et_3P-Au-His, Et_3P-Au-Cys, Et_3P-Au-PEt_3 and [AuCl(PEt_3)] itself. XAS could also be used to distinguish between limiting mechanisms involving structurally distinct zinc fingers – the reaction product of [AuCl(PEt_3)] with Sp1 is different from that formed in the reaction of the former with NCp7, containing only gold finger. The XAS spectrum indicating the presence of a more electron rich gold center and a S-Au-S coordination environment for the final product of this reaction was proposed. This result corroborates to the design of more selective compounds.

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