Thiolate Bridging and Metal Exchange in Adducts of a Zinc Finger Model and Pt(II) Complexes: Biomimetic Studies of Protein/Pt/DNA Interactions.

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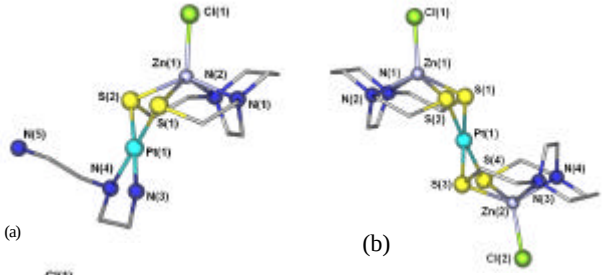
Introduction

HIV-1 nucleocapsid protein (NCp7) is a potential target for antiviral therapy and this protein plays many crucial roles throughout the retrovirus lifecycle as a general nucleic acid binding protein.[1] Retroviral nucleocapsid proteins (NCps) from all strains of known retroviruses contain one or more copies of the conserved CCHC zinc finger or "knuckle" sequence Cys-X_2-Cys-X_4-His-X_4-Cys (X = variable).[2] The concept of ternary Zn(protein), Pt(DNA/RNA) species may have widespread relevance in biology. Recognition of cisplatin-adducted DNA is seen for many proteins, a number of which contain the Zn-finger motif.[3,4] Small molecule study may be predictive of chemical models for the proposed biological structures[5].

Results and Discussion

This work presents the interactions of the complexes [Pt(dien)Cl]Cl or [Pt(terpy)Cl]Cl with Zn monothiolate, $[ZnN_2S_2O_2]$ complex, and the products defined by Electrospray Ionization Mass Spectrometry (ESI-MS) and ^{195}Pt-NMR spectroscopy. A leaving chloride in these Pt(II) complexes facilitates electrophilic substitution involving sulfur-containing zinc finger synthetic models. The reaction between [Pt(dien)Cl]Cl and $[Zn(bme\text{-}dach)]_2$ gave rise to two new major peaks at *m/z* values of 290.9 and 616.3 were assigned to the $[Zn(bme\text{-}dach)(Pt(dien))]^{2+}$ and $[(Zn(bme\text{-}dach)Cl)(Pt(dien))]^{+}$ species, respectively. The ^{195}Pt NMR spectrum of the [Pt(dien)Cl]Cl shows a single peak at -2280.8 ppm, which is typical of Pt^{2+} in an N_3Cl donor environment. Upon reaction of 2 equiv of [Pt(dien)Cl]Cl with 1 equiv of $[Zn(bmedach)]_2$ (i.e. 1Pt:1Zn) over the course of 30 m at 37° C, a new ^{195}Pt NMR peak appeared at -3172.53 ppm (PtN_3S coordination sphere). Furthermore, after one hour, an additional peak was observed at -3267.95 ppm and it is consistent with a $[PtN_2S_2]$ species (Figure A). After two hours, a yellowish precipitate appeared and after isolation the corresponding $[Zn(bme\text{-}dach)Cl]_2Pt$ was observed by x-ray crystallography (Figure B, d(Pt) – 3472.5 ppm).

To examine ligand effects on reactivity, the study was extended to [Pt(terpy)Cl]Cl, a square-planar complex in which the electronic and steric requirements of the rigid tridentate ligand contrasts with those of the diethylenetriamine chelate. The reactions were similarly designed at both 1:1 and 1:2 ratio, and monitored by ESI-MS. The presence of $\{[Zn(terpy)Cl–H^+\}^+$ species was observed, confirming the ejection of the zinc from the dimmer $[ZnN_2S_2O_2]$.



Conclusions

Small molecule models for biologically relevant ternary DNA-Pt-zinc finger protein adducts have been characterized using ^{195}Pt NMR spectroscopy and x-ray crystallography. Specifically for $[Pt(dien)Cl]^+$, opening of the chelate ring is a reflection of the strong *trans* influence of cysteinate, even when modified by an interacting Zn^{2+} ion. In the case of terpy, the observed formation of $[Zn(terpy)Cl]^+$ and [Pt(bme-dach)] moieties demonstrates ligand scrambling, or metal ion exchange. In contrast, no $[Zn(dien)Cl]^+$ species with concomitant zinc ejection is observed in the diethylenetriamine reaction.

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