Investigation of Non-covalent Complexation Between Biomolecules and Polynuclear Platinum Drugs: A Study By ESI Ion-Trap Mass Spectrometry

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Electrospray ionization mass spectrometry (ESI-MS) has been used to investigate the noncovalent complexation between a unique class of positively charged di and trinuclear platinum anticancer drugs that bind only through electrostatic interaction with biomolecules such as DNA and proteins. The "soft ionization" of electrospray allows for the electrostatic bonding between these platinum drugs and the biomolecules to be maintained in the gas phase. These polynuclear platinum complexes depart from the general paradigm of binding to biomolecules in comparison to current clinically used platinum drugs, cisplatin, oxaliplatin, and even the recently developed BBR3464. We have designed an assay that allows us to determine how binding stochiometry is affected with variation in the overall charge of the platinum complex and to what effect linker groups play in the association of these polynuclear complexes to biomolecules. Two of the platinum drug complexes, $[\{Pt(NH_3)_3\}_2\text{-}NH_2\text{-}(CH_2)_6\text{-}NH_2]^{4+}$ and $[\{Pt(dien)\}_2\text{-}NH_2\text{-}(CH_2)_3\text{-}NH_2\text{-}(CH_2)_4\text{ -}NH_2]^{5+}$ were allowed to associate with an 18mer oligonucletide 5′- TCT CCC AGC GTG CGC CAT-3′ specific for the BCL-2 gene sequence. Mass spectrometry indicates that the presence of the dien ligands on the platinum results in much lower binding ratios compared to complexes of similar charge, but with amine ligands. This suggests that for these electrostatic polynuclear complexes, the ability to form hydrogen bonds with the DNA may be more important in controlling the binding affinity than the overall charge of the complex.

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