Vibrational Spectroscopy of Platinum(II) Complexes Relevant in Antitumor Activity

Alberto De Petris, Alessandra Ciavardini, Barbara Chiavarino, Simonetta Fornarini, Debora Scuderi, Philippe Maitre, Jean-Yves Salpin, Maria-Elisa Crestoni

Vibrational Spectroscopy of Platinum(II) Complexes Relevant in Antitumor Activity

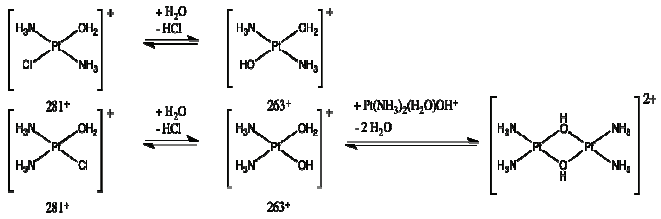
A. De Petris[1], A. Ciavardini[1], B. Chiavarino[1], S. Fornarini[1], D. Scuderi[2], P. Maitre[2], J.-Y. Salpin[3], M.E. Crestoni[1]

1 Dipartimento di Chimica e Tencologie del Farmaco, La Sapienza Università di Roma, P.le Aldo Moro 5, 00185, Roma, Italy
2 Laboratoire de Chimie Physique, UMR8000 CNRS Faculté des Sciences, Université Paris Sud, Bâtiment 350. 91405 Orsay Cedx, France
3 Université d'Evry Val d'Essonne, Laboratoire Analyse et Modélisation pour la Biologie er l'Environment, Boulevard Francois Mitterand, 91025 Evry, France

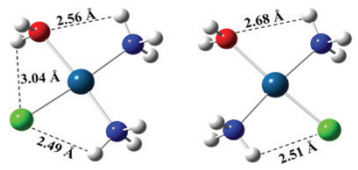
Cisplatin (*cis*-diamminedichloroplatinum(II) is the first platinum-based antitumor agent, and it is still widely used in chemotherapy. In the cytoplasm, the administered drug undergoes spontaneous hydrolysis by nucleophilic substitution of chloride with water. The cationic chloro-monoaqua form, *cis*-$[PtCl(NH_3)_2(H_2O)]^+$, characterized by a pKa value of 6.5, is the relevant intermediate at physiological pH, that can ultimately give rise to DNA and protein adducts through easy substitution of water by nitrogen/sulfur donor ligands.

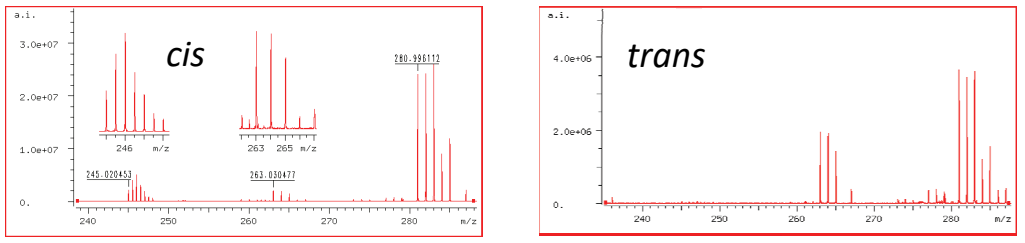
Electrospray ionization has allowed *cis*- and *trans*-$[PtCl(NH_3)_2(H_2O)]^+$ species to be obtained as free ions in the gas phase where they were sampled by infrared multiple photon dissociation (IRMPD) spectroscopy in the NH/OH stretching frequency range (3200−3800 cm^{-1}), using a tabletop optical parametric oscillator/amplifier (OPO/OPA) laser system coupled to a quadrupole ion trap mass spectrometer @Università Sapienza, Roma (ITALY).

Hydrolysis of cisplatin and transplatin

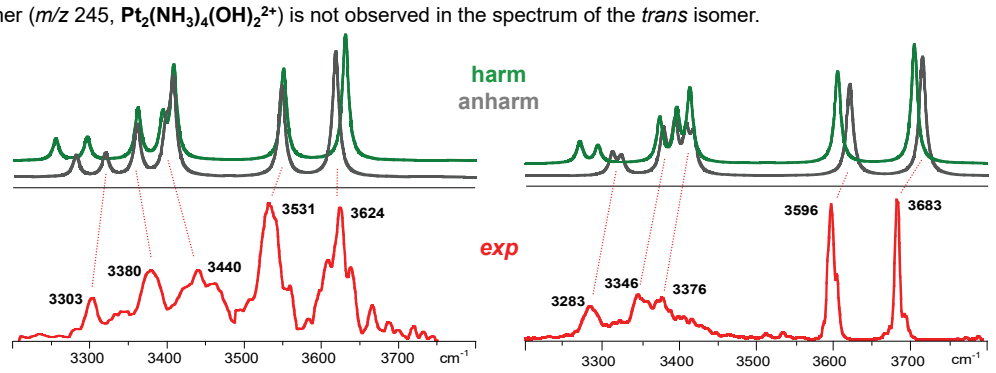


Optimized Geometries computed at the MP2/6-311G(d,p) level of theory.





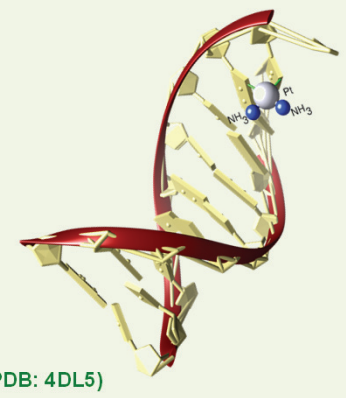
ESI-FTICR mass spectra of the two sampled ions obtained in the mass range of *m/z* 240-290. The platinum dimer (*m/z* 245, $Pt_2(NH_3)_4(OH)_2^{2+}$) is not observed in the spectrum of the *trans* isomer.



Experimental IRMPD spectrum of *cis*- and *trans*-$[PtCl(NH_3)_2(H_2O)]^+$ compared to calculated IR spectra according to MP2 anharmonic and harmonic frequency computations [De Petris A., Ciavardini A., Coletti C., Re N., Chiavarino B., Crestoni M. E. and Fornarini S., *J. Phys. Chem. Lett.* **2013**, 4, *3631-3635*].

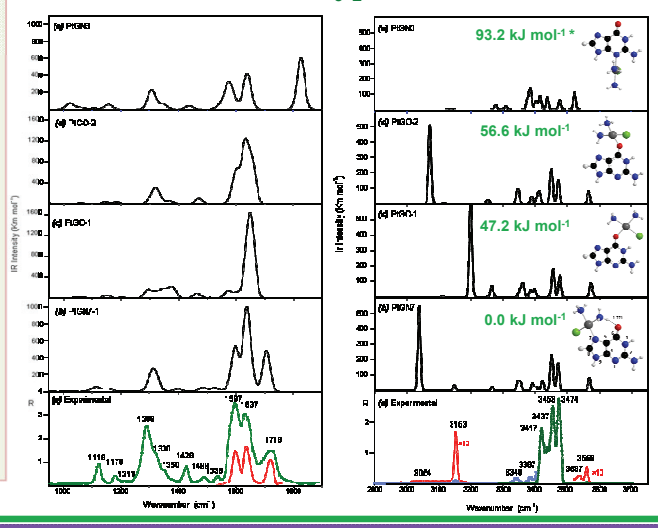
Moreover, an accurate characterization of *cis*-$[Pt(NH_3)_2$(**Guanine**$)Cl]^+$ and *cis*-$[Pt(NH_3)_2$(**Adenine**$)Cl]^+$, models of the monofunctional adducts between cisplatin and the nucleobases of DNA, has been gathered using IR spectroscopy in two spectral regions, 950−1900 and 2900−3700 cm^{-1}, using two different IR radiation sources, the free electron laser (FEL) at the Centre Laser Infrarouge d'Orsay (CLIO) facility and an optical parametric oscillator/amplifier (OPO/OPA) laser system @Università Sapienza, Roma (ITALY) respectively.

Crystal structures of DNA complexed with intrastrand cisplatin-1,2-cross-linked



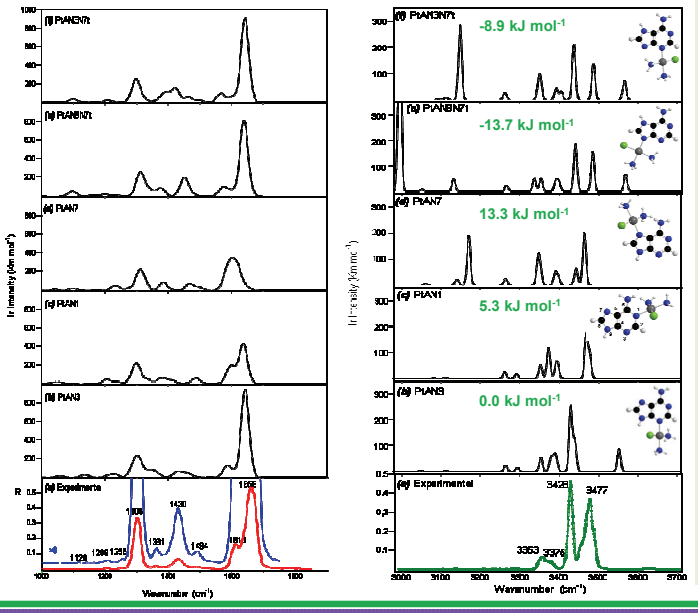
(PDB: 4DL5)

cis-$[Pt(NH_3)_2(G)Cl]^+$



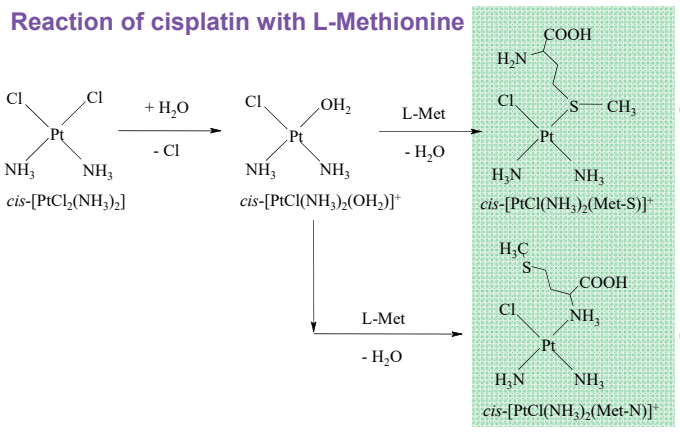
The cisplatin residue is attached to the N7, N3, or carbonyl oxygen atom, (O6), of guanine and to the N7, N3, or N1 position of adenine, respectively. The IRMPD spectra of *cis*-$[Pt(NH_3)_2(A)Cl]^+$ are consistent with the presence of two major isomers, PtAN3 and PtAN1, where Pt is bound to the N3 and N1 positions of native adenine, respectively.

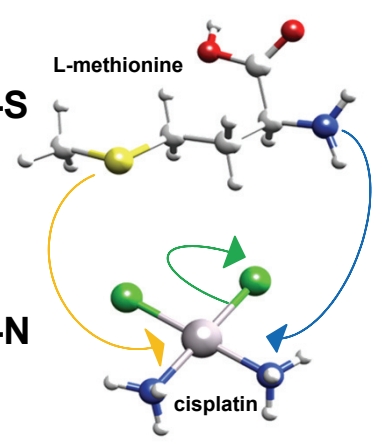
cis-$[Pt(NH_3)_2(A)Cl]^+$



The preferred platinum coordination site on adenine seems to be N3, which is not observed in the cell because such a site is located in the internal groove and not easily accessible at an intrastrand cross-linking. In agreement with computational results, computed at the B3LYP/LACV3P/6-311G level of theory, the IR characterization of *cis*-$[Pt(NH_3)_2(G)Cl]^+$ points to a covalent structure where Pt is bound to the N7 atom of guanine, with a hydrogen-bonding interaction between a hydrogen atom of one NH3 ligand and the carbonyl oxygen of guanine** [Chiavarino B., Crestoni M. E., Fornarini S., Scuderi D. and Salpin J. Y., *J. Am. Chem. Soc.* **2013**, 135, *1445-1455*].

Reaction of cisplatin with L-Methionine





Work is currently underway to characterize the cisplatin derived complexes with the sulfur-containing molecules, which serve as a drug reservoir available for platination of DNA in the nucleus of tumor cells. The interaction of cisplatin with biological thiols, including L-methionine, glutathione and cysteine/thiotheneine, has been associated to resistance, and drug detoxification.

L-methionine and cisplatin may form various monodentate adducts, depending on the site of Pt(II) coordination, either at **N** or **S** atom. An extensive conformational search for low-energy candidate structures has been performed, followed by ab initio calculations at the B3LYP/6-311+G(d,p) level of theory.