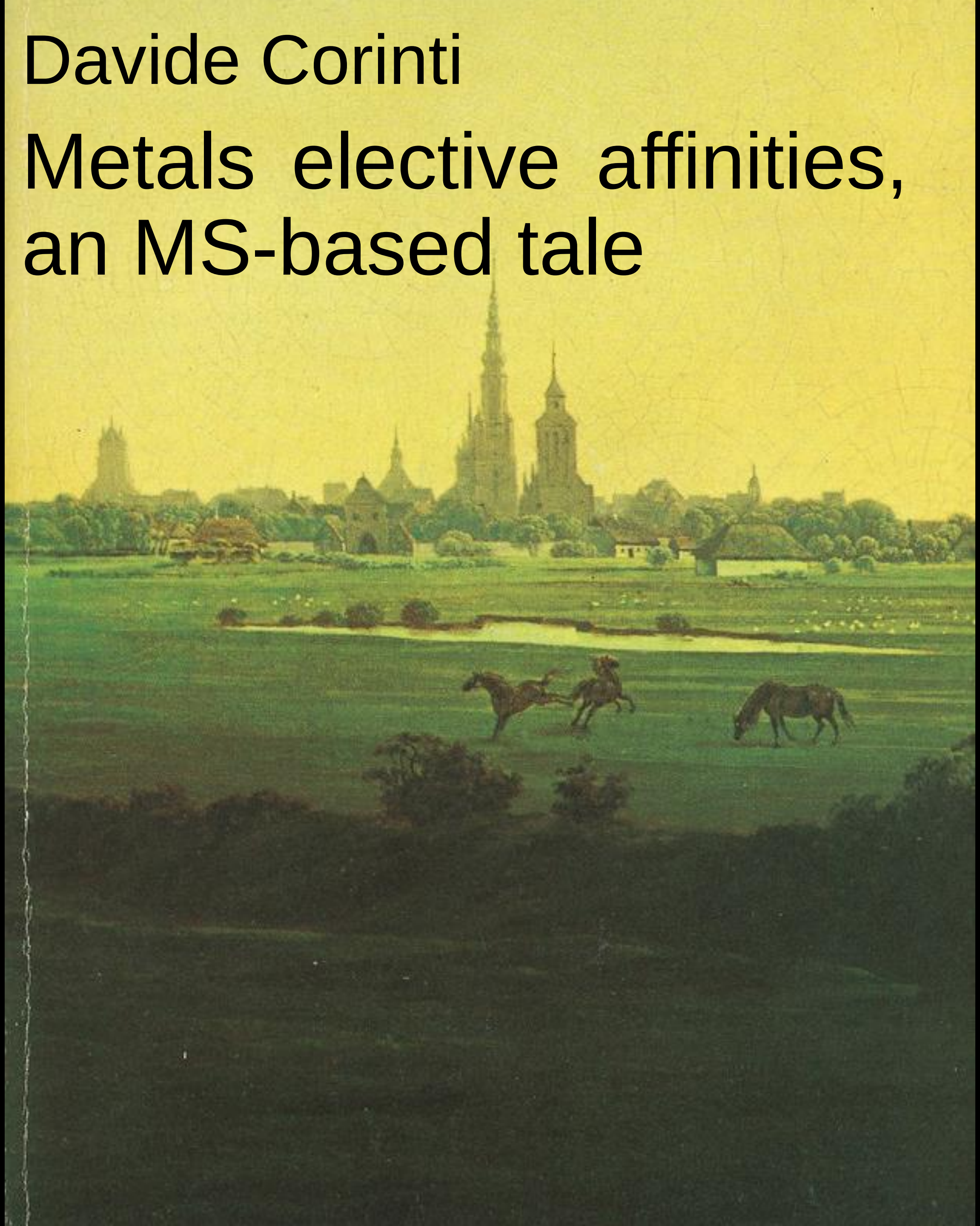

Davide Corinti

Metals elective affinities, an MS-based tale

SAPIENZA
UNIVERSITÀ DI ROMA

From ion-molecule reactions to the activation of non-covalent encounter complexes: mass spectrometry-based methods to explore the reactivity of metal complexes

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M. Elisa Crestoni

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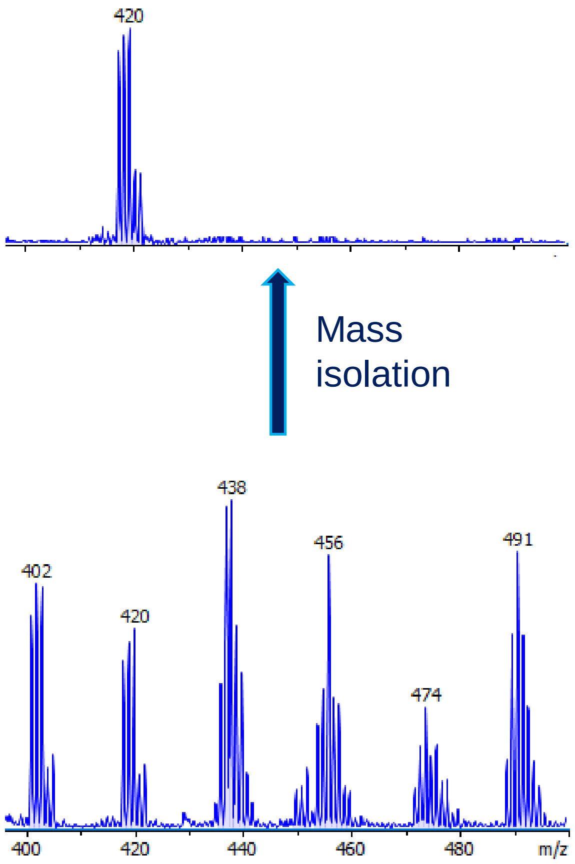
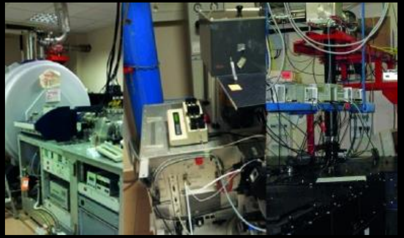
davide.corinti@uniroma1.it



Mass spectrometry characterization and isolation

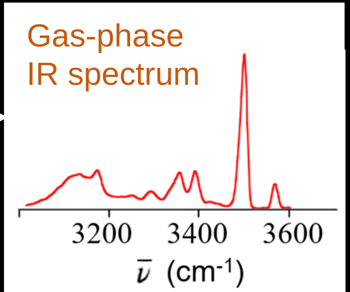
Structural characterization

Free electron laser ($900-2000\ cm^{-1}$)

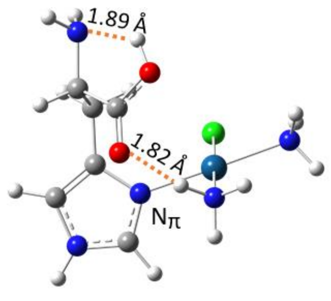


Laser OPO/OPA ($2800-3700\ cm^{-1}$)

IR multiple photon dissociation (IRMPD) spectroscopy

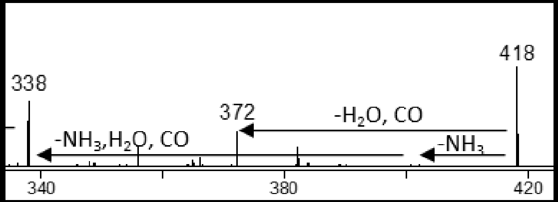

Gas-phase IR spectrum

Quantum mechanics calculations



Vibrational mode assignment

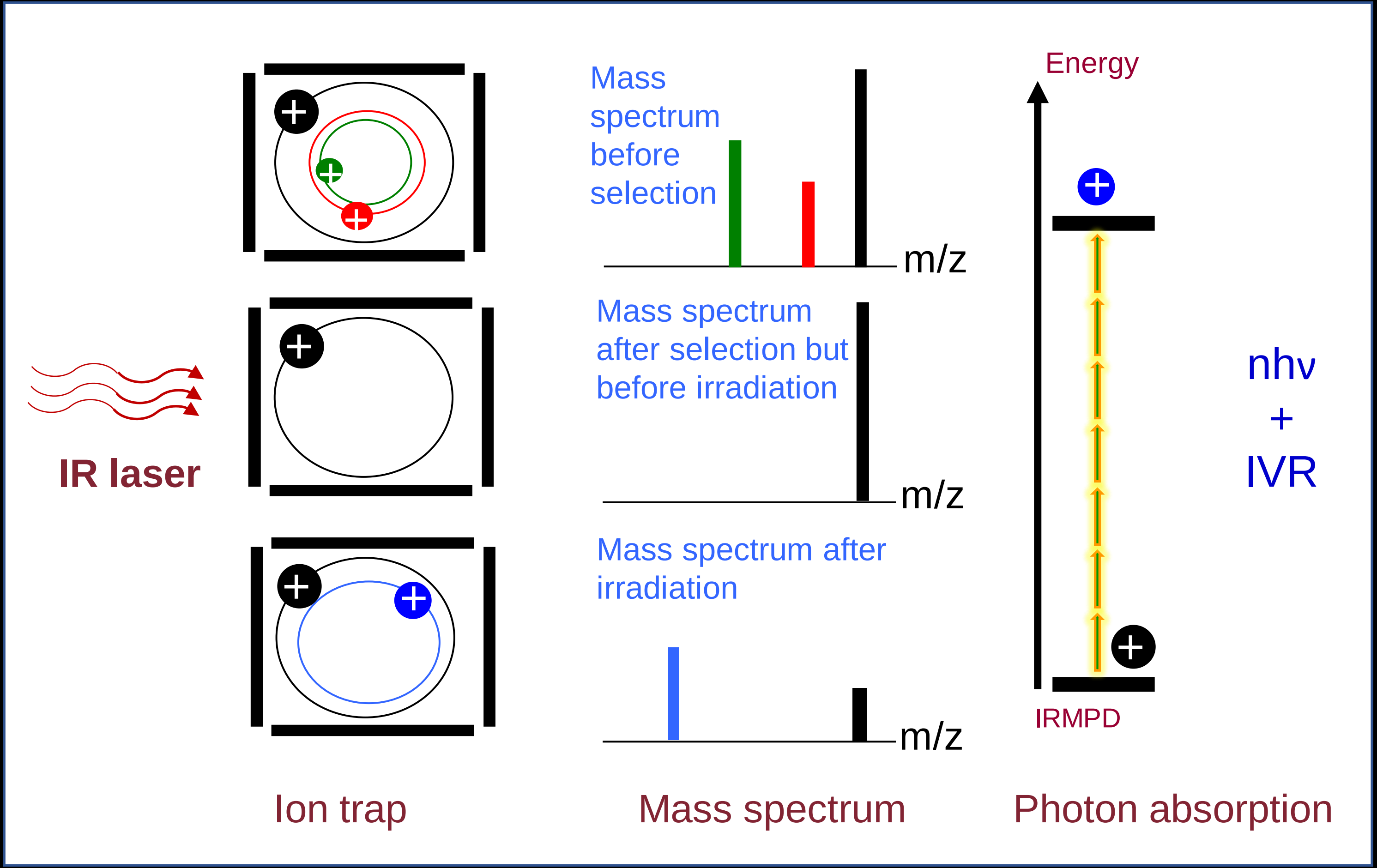
Collision Induced Dissociation (CID)



Gas-phase reactivity

EU FT-ICR MS

IRMPD spectroscopy



IR laser

Mass spectrum before selection

m/z

Mass spectrum after selection but before irradiation

m/z

Mass spectrum after irradiation

m/z

Energy

IRMPD

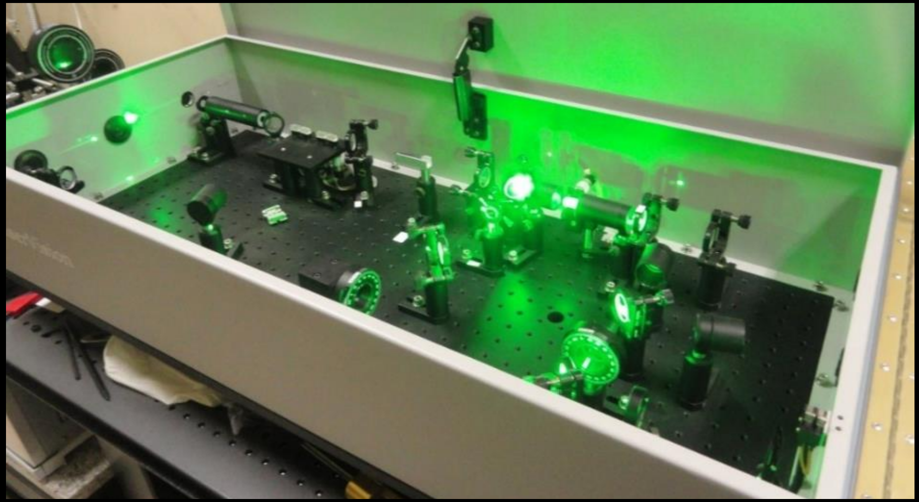
nhν + IVR

Ion trap

Mass spectrum

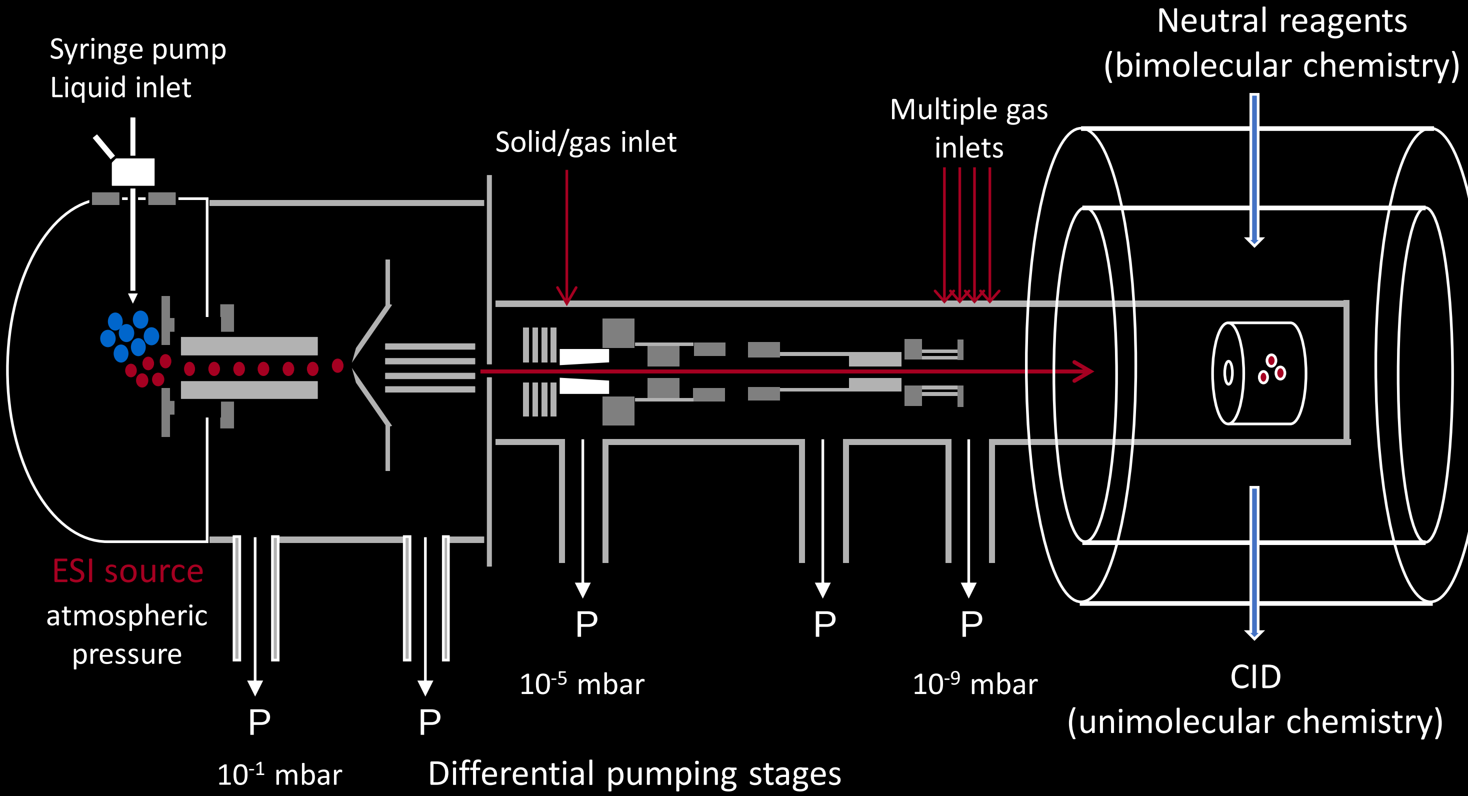
Photon absorption

Free electron laser (900-2000 cm^{-1})

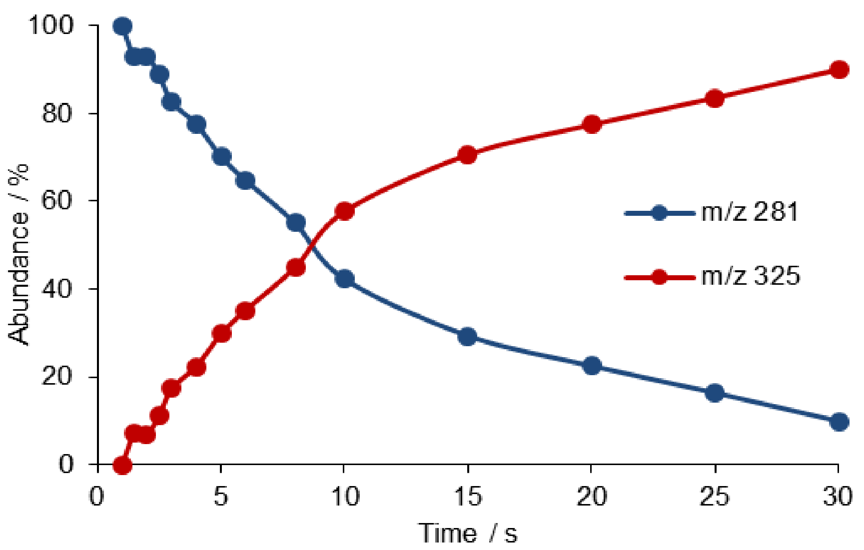


Laser OPO/OPA (2800-3700 cm^{-1})

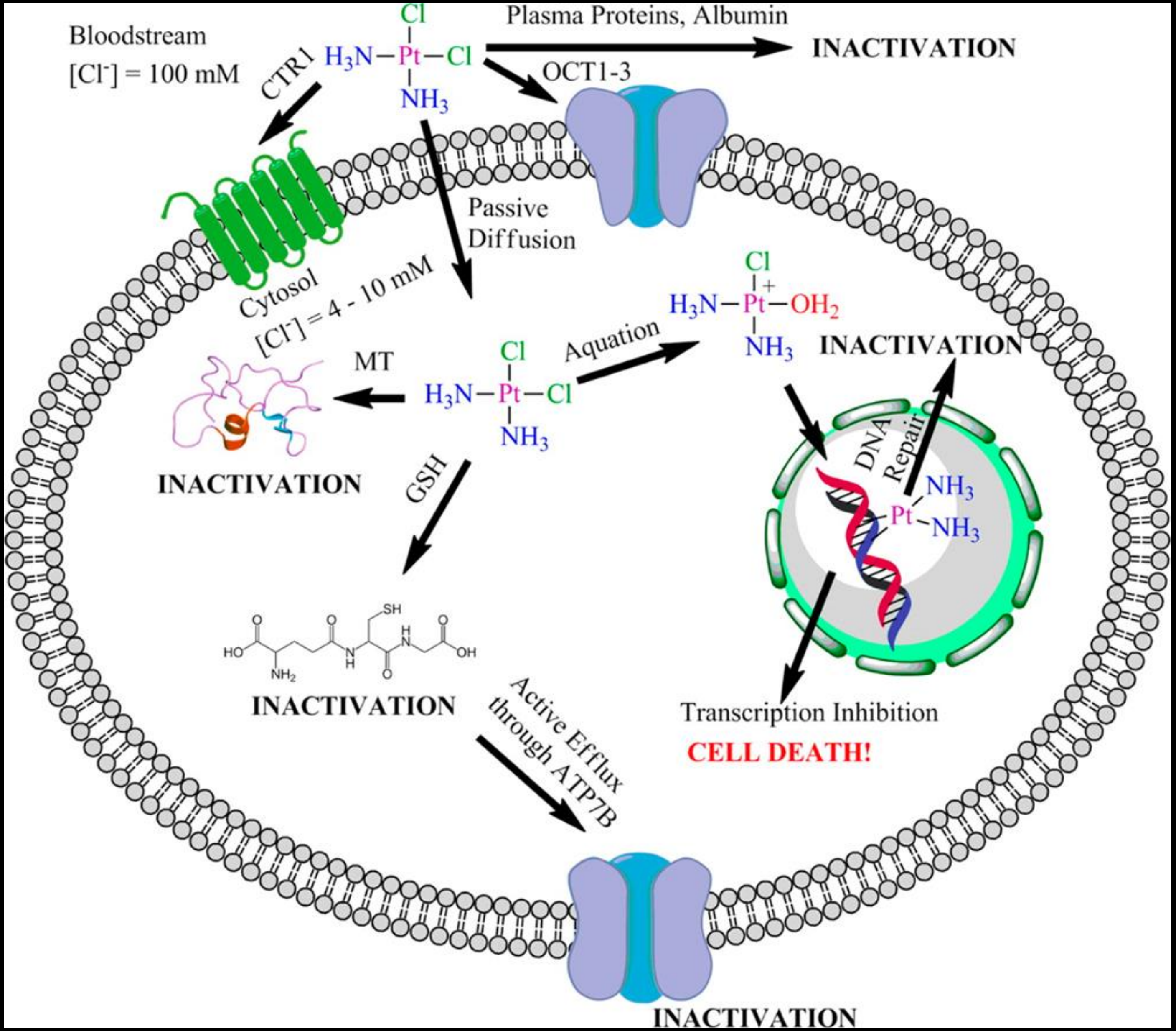
Mass spectrometry for bimolecular reactivity

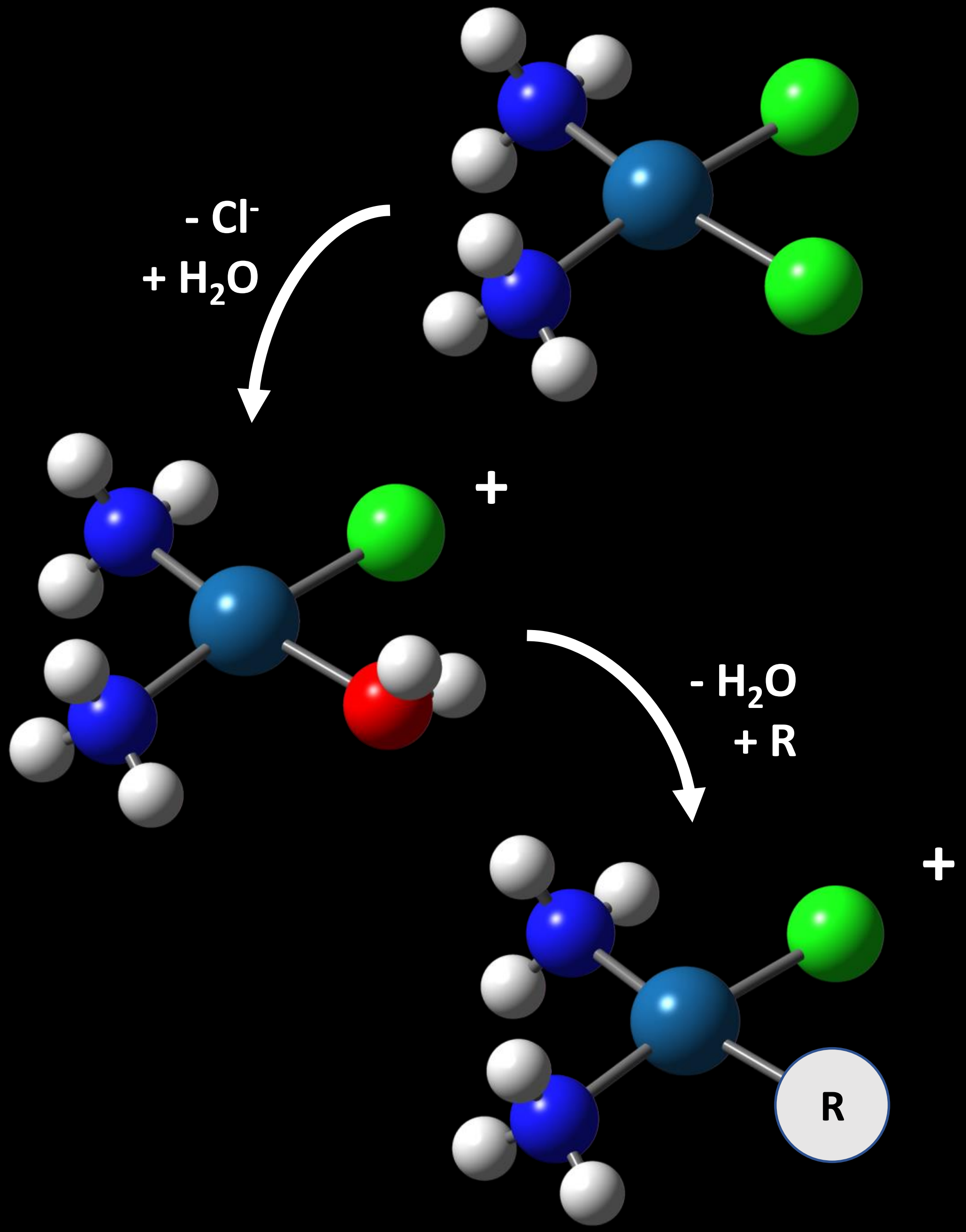


Time dependence of ion abundancies for the reaction of *cis*-$[PtCl(NH_3)_2(H_2O)]^+$ (m/z 281) with DMS forming $[PtCl(NH_3)_2(DMS)]^+$ at m/z 325 in the FT-ICR cell at the DMS pressure of 1.5×10^{-7} mbar.



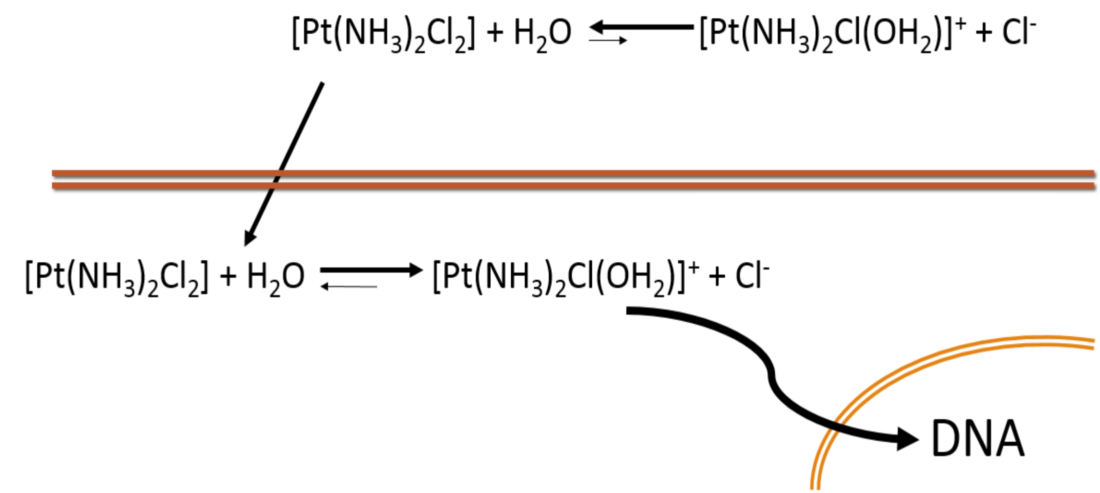
CISPLATIN LIGAND SUBSTITUTION BY AMINOACIDS AND MODEL LIGANDS: STRUCTURE AND REACTIVITY OF ISOLATED ENCOUNTER COMPLEXES





Johnstone, Suntharalingam, Lippard *Chem. Rev.* **2016**, *116*, 3436-3486.

Cisplatin hydrolysis equilibria



$[Pt(NH_3)_2Cl_2] + H_2O \leftrightharpoons [Pt(NH_3)_2Cl(OH_2)]^+ + Cl^-$

$[Pt(NH_3)_2Cl_2] + H_2O \rightleftharpoons [Pt(NH_3)_2Cl(OH_2)]^+ + Cl^-$

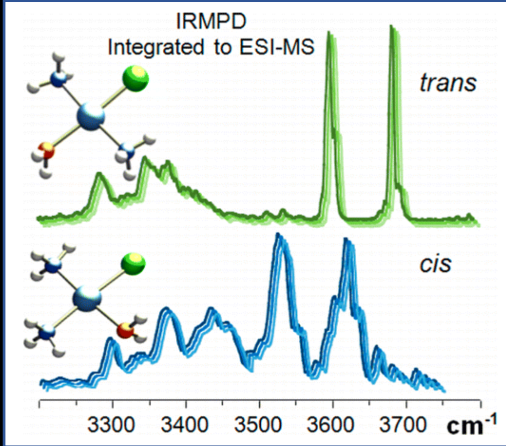
DNA

$\boxed{[PtCl(NH_3)_2(H_2O)]^+} \rightleftharpoons [PtCl(NH_3)_2(OH)] + H^+$

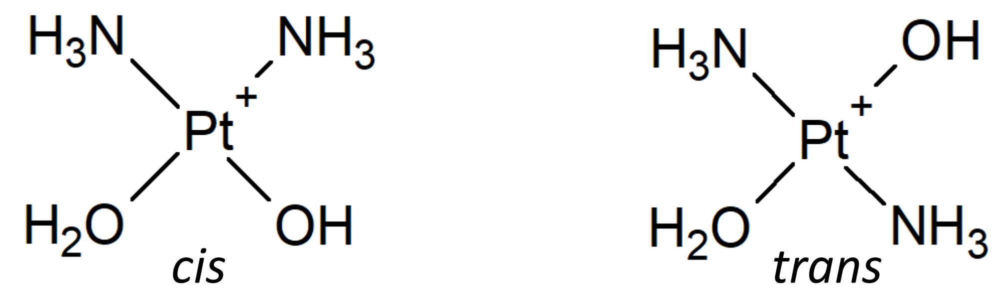
$[PtCl(NH_3)_2(H_2O)]^+ + H_2O \rightleftharpoons [Pt(NH_3)_2(H_2O)_2]^{2+} + Cl^-$

$[Pt(NH_3)_2(H_2O)_2]^{2+} \rightleftharpoons [Pt(OH)(NH_3)_2(H_2O)]^+ + H^+$

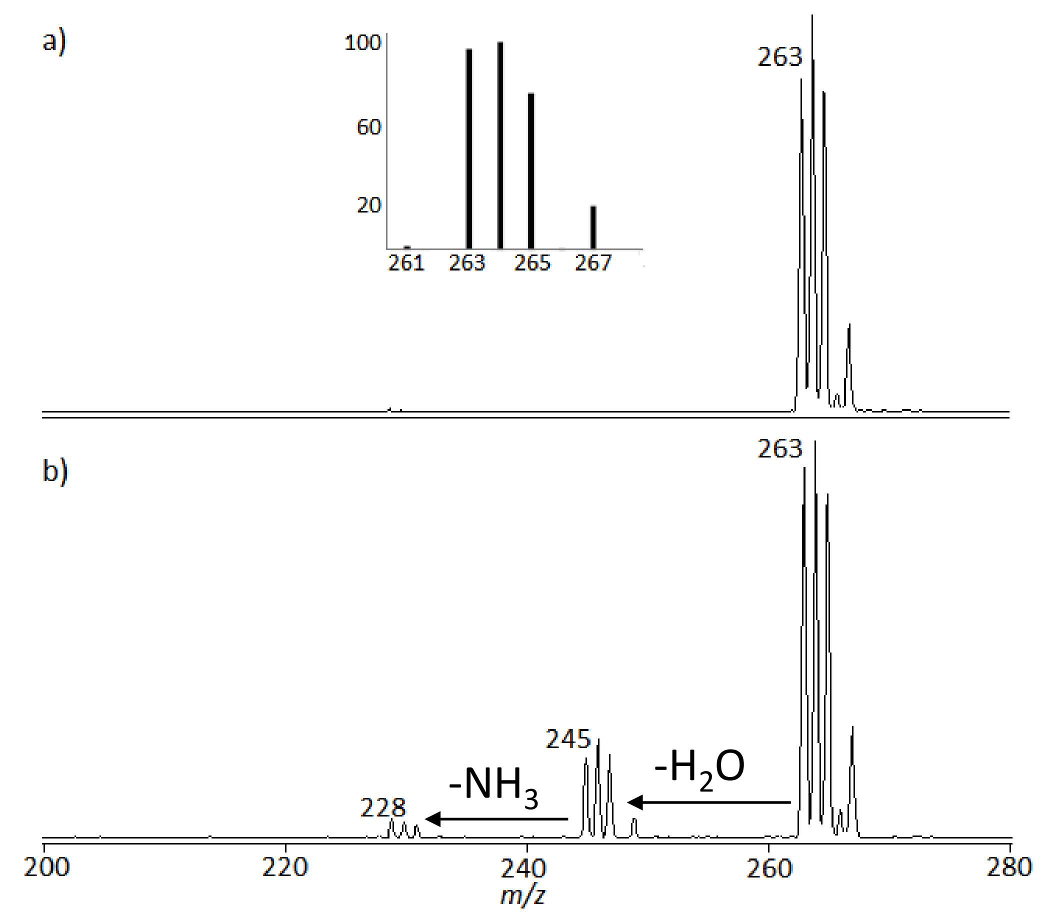
$\boxed{[Pt(OH)(NH_3)_2(H_2O)]^+} \rightleftharpoons [Pt(OH)_2(NH_3)_2] + H^+$



J. Phys. Chem. Lett. **2013**, 4, 3631-3635



$[Pt(OH)(NH_3)_2(H_2O)]^+$ isolation and characterization

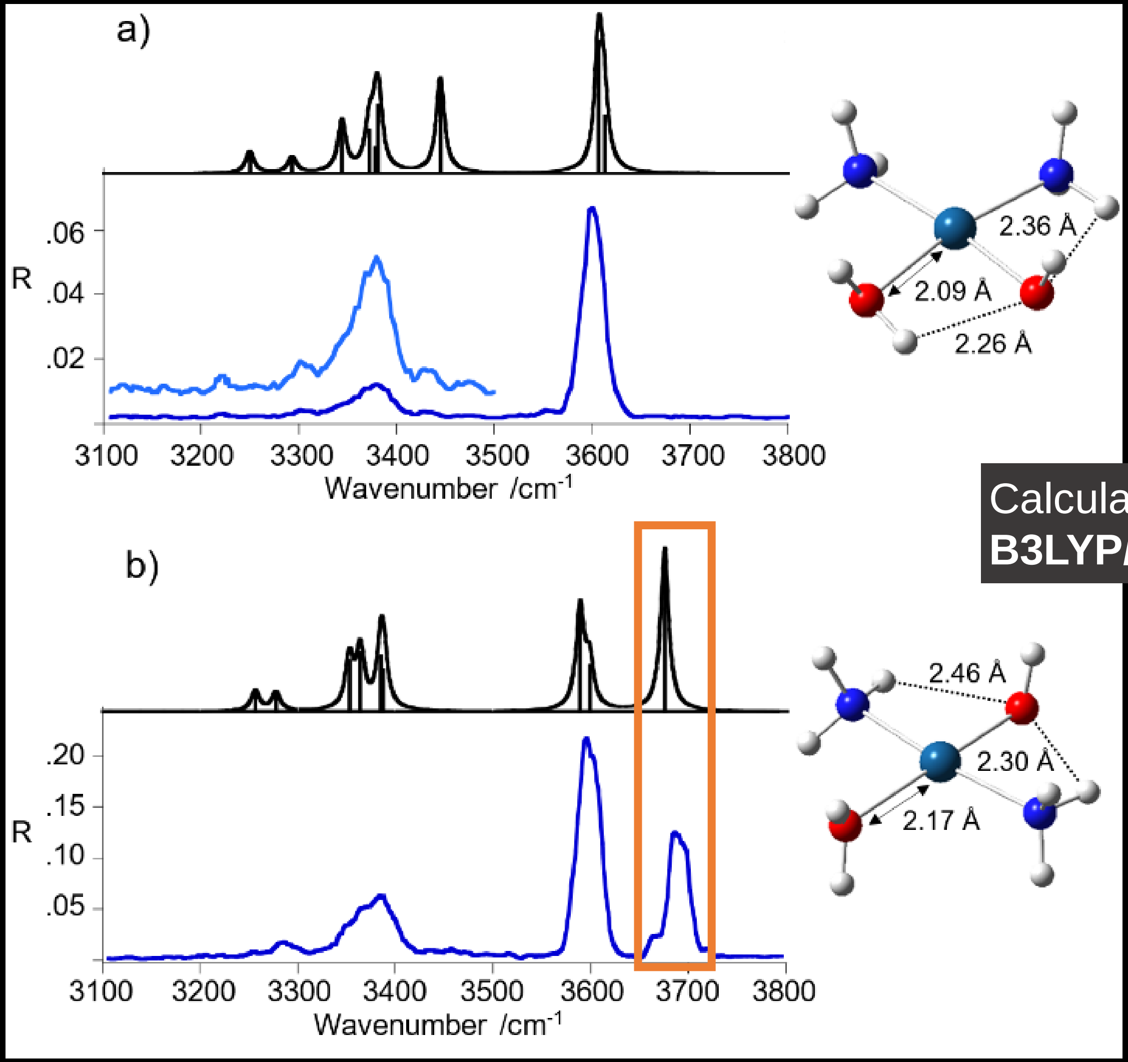


The mass spectra show the isolated *trans*-$[Pt(OH)(NH_3)_2(H_2O)]^+$ ions (*m/z* 263) prior to (a) and after (b) being irradiated by IR photons at 3600 cm^{-1} (Esquire 6000). The calculated pattern shown in the inset confirms the elemental composition of the isolated ion.

Both cisplatin and transplatin aqueous solutions were incubated for two days in order to increase the abundance of $[Pt(OH)(NH_3)_2(H_2O)]^+$ ions, at the expense of $[PtCl(NH_3)_2(H_2O)]^+$**.**

IRMPD spectroscopy of $[Pt(OH)(NH_3)_2(H_2O)]^+$

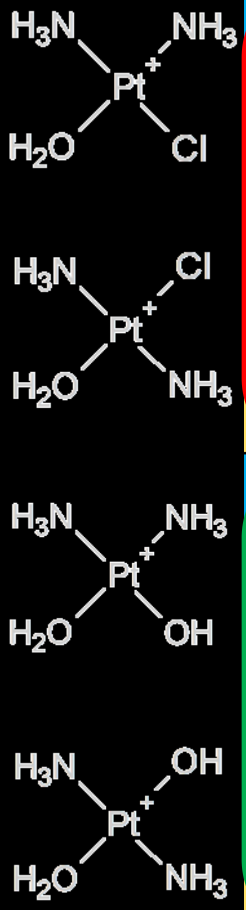
The figure shows the IRMPD spectra of *cis*-$[Pt(OH)(NH_3)_2(H_2O)]^+$ (a) and *trans*-$[Pt(OH)(NH_3)_2(H_2O)]^+$ (b) (blue profiles) compared with the calculated linear IR spectra (black profiles) of the optimized geometries reported on the left.



Calculations made at the **B3LYP/aug-cc-pVTZ** level

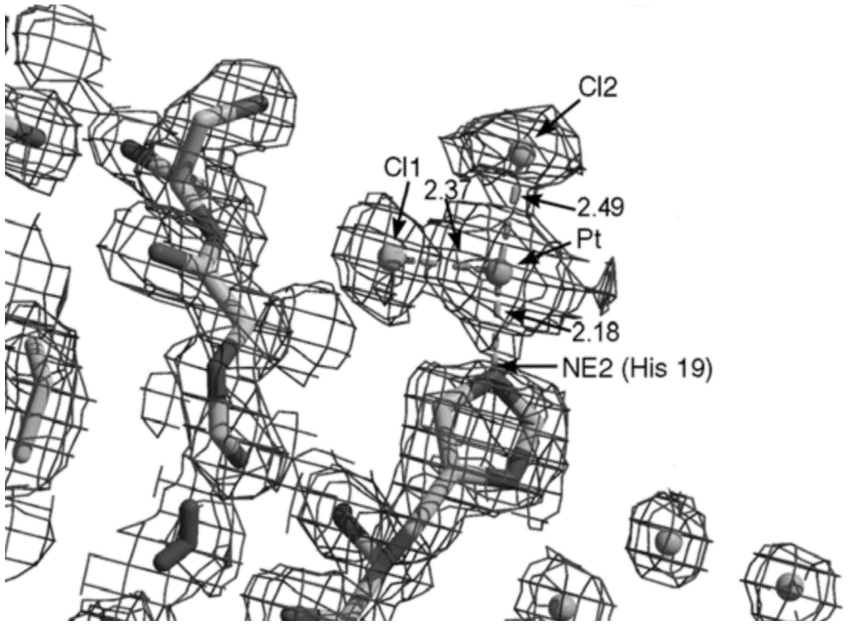
Corinti, Coletti, Re, Piccirillo, Giampà, Crestoni and Fornarini *RSC Adv.* **2017**, *7*, 15877

Cisplatin activity



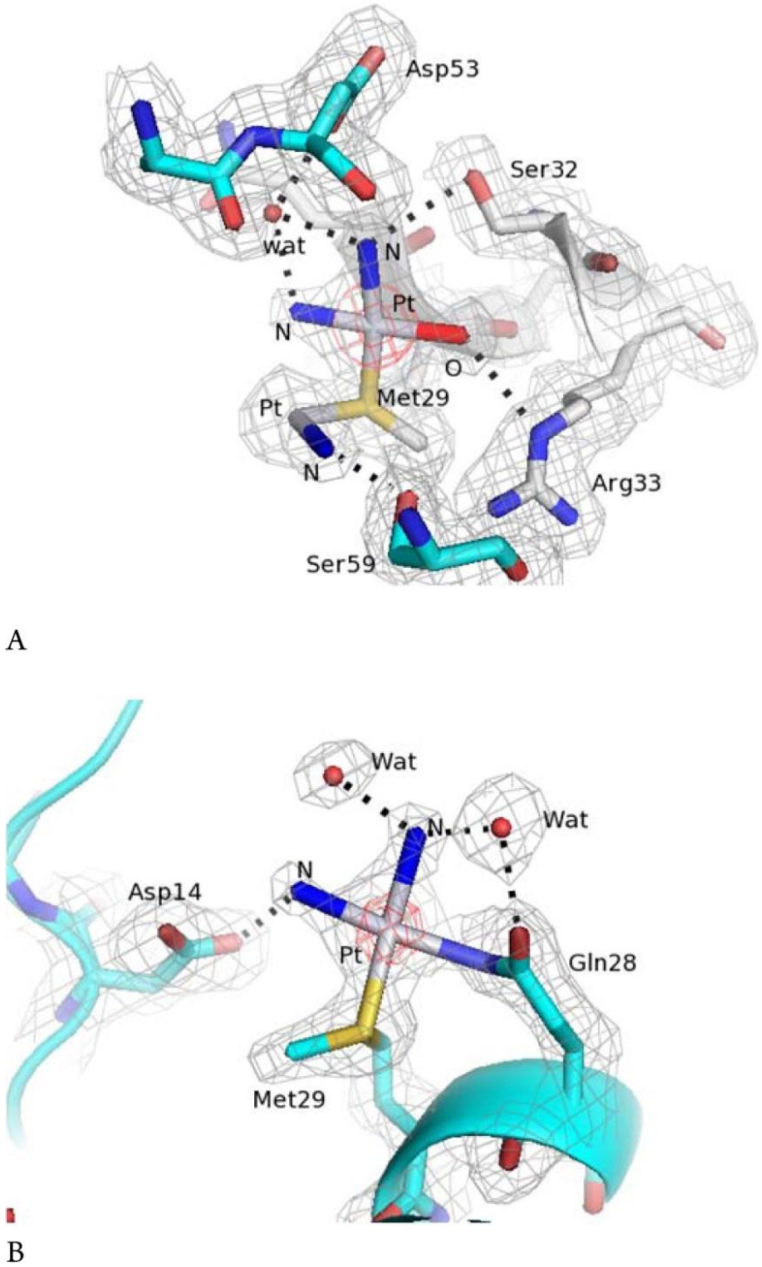
Reagent Ion	Neutral	k_{exp}[a]	Eff (%)
cis-$[PtCl(NH_3)_2(H_2O)]^+$	TMP	3.7	2.5
	pyridine	0.6	0.41[b]
	thioanisole	1.4	1.1
	dimethylsulfide	0.034	0.026
trans-$[PtCl(NH_3)_2(H_2O)]^+$	TMP	3.3	2.3
	pyridine	1.4	0.93[c]
	thioanisole	7.7	6.3
	dimethylsulfide	2.4	1.7
cis-$[Pt(OH)(NH_3)_2(H_2O)]^+$	TMP	0.96	0.66
	pyridine	0.46	0.31[d]
	thioanisole	0.1	0.08
	dimethylsulfide	n.r.[e]	
trans-$[Pt(OH)(NH_3)_2(H_2O)]^+$	TMP	1.1	0.78
	pyridine	0.05	0.03[f]
	thioanisole	0.46	0.37
	dimethylsulfide	n. r.[e]	

- All the reactions show low efficiences as expected with Pt^{II} complexes.
- Chloride-containing complexes have higher efficiencies than their hydroxo counterparts;
- TMP is the most reactive compound in the gas-phase among the studied ligands;
- The trans-effect seems to be an important factor in the kinetic of the substitution reactions, in particular regarding TA and DMS.



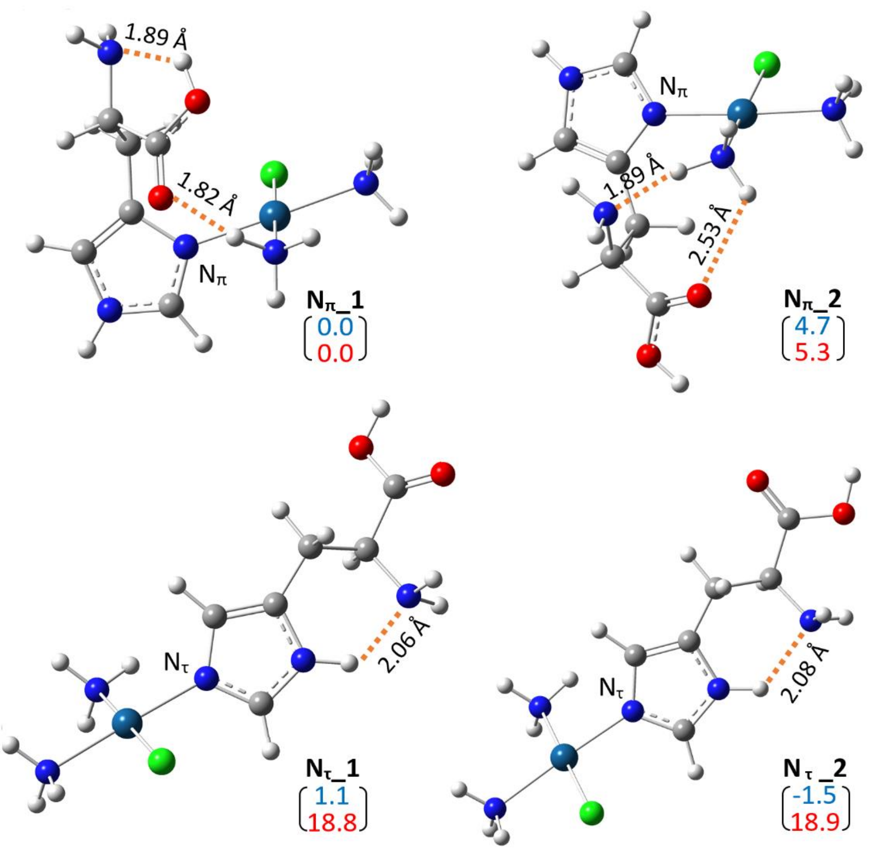
Angew. Chem. Int. **2006** 45, 1267 –1269

L. Messori et al. *Inorg Chem* **2014** *53*, 3929.

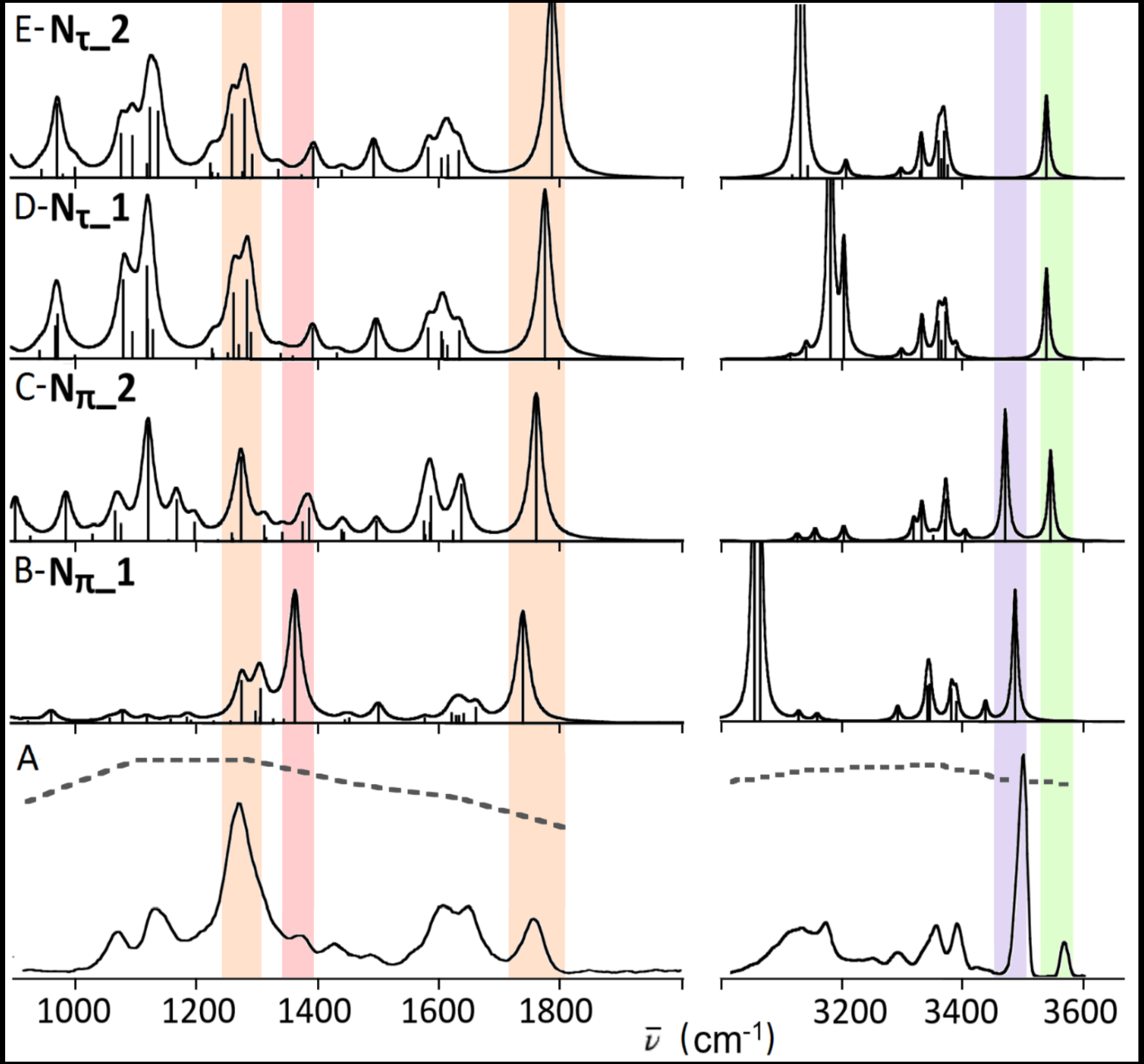


Characterization of *cis*-$[PtCl(NH_3)_2(His)]^+$

Anharmonic frequencies calculated at the **B3LYP/6-311+G**** level are reported unscaled.

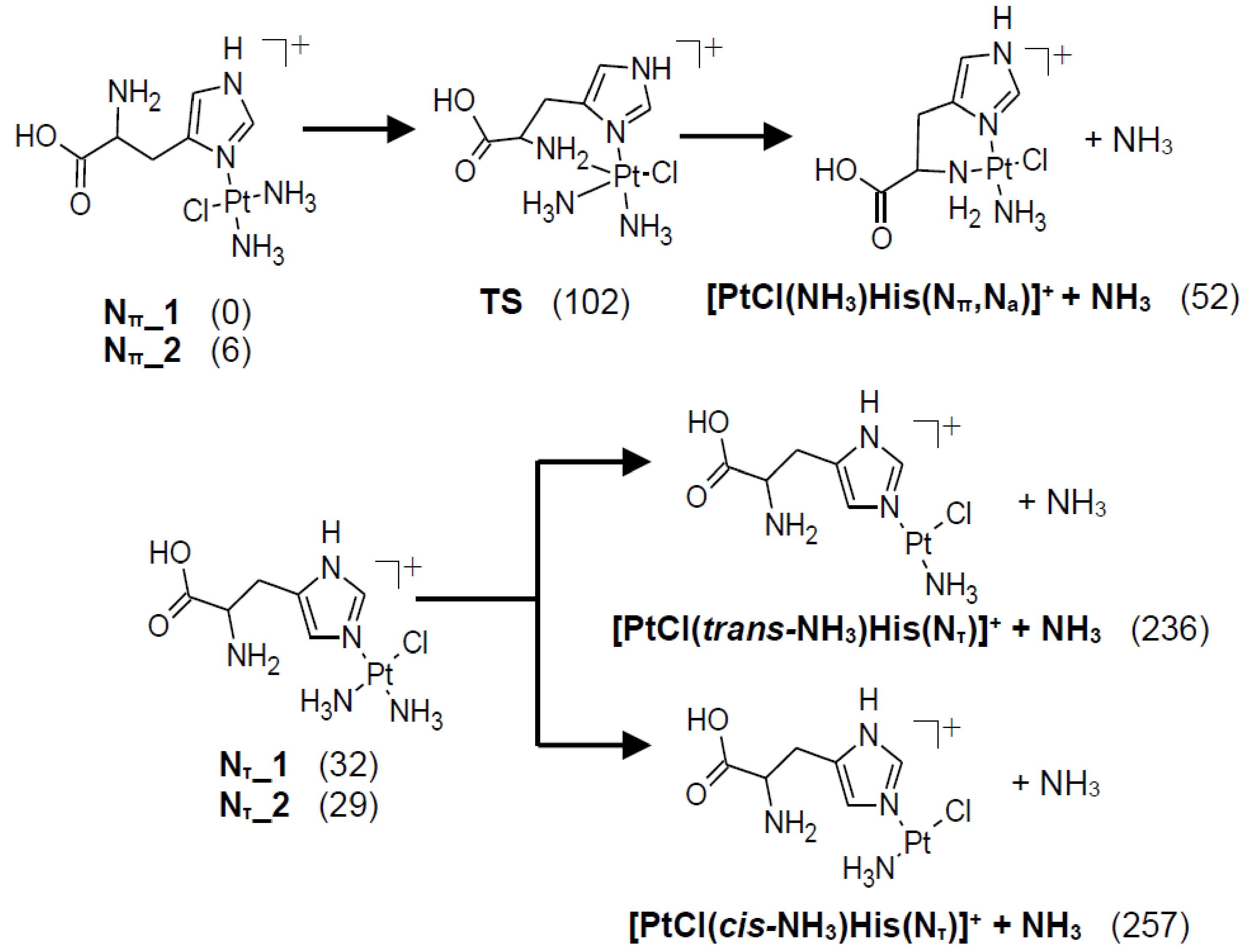


Geometries optimized at the **B3LYP/6-311+G** (Pt = LanL2TZ)** level, relative free energies at 298 K are reported in **blue** for the **B3LYP/6-311+G**** and in **red** for the **ωB97-XD/6-311+G**** levels



D. Corinti, A. De Petris, C. Coletti, N. Re, B. Chiavarino, M.E. Crestoni, S. Fornarini,, ChemPhysChem. 18 (2017) 318–325.

Fragmentation paths for **N_π** and **N_τ** isomers. Relative enthalpies at 298 K in kJ mol^{-1} calculated at ωB97X-D/6-311+G** level are in parentheses.



N_π_1 (0)
N_π_2 (6)

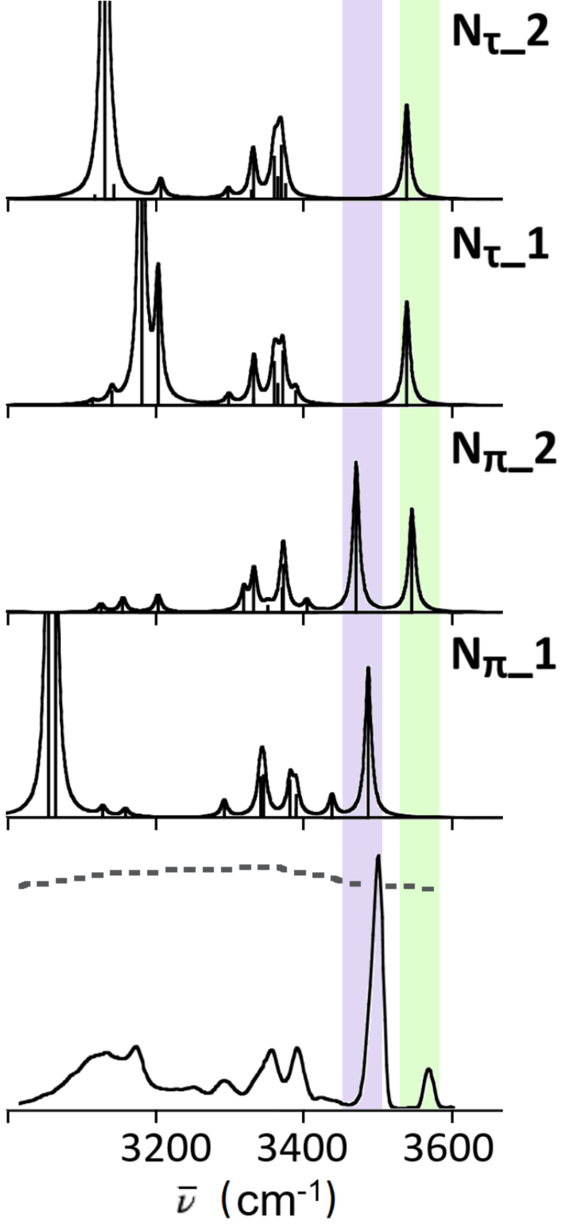
TS (102)

$[PtCl(NH_3)His(N_\pi,N_a)]^+ + NH_3$ (52)

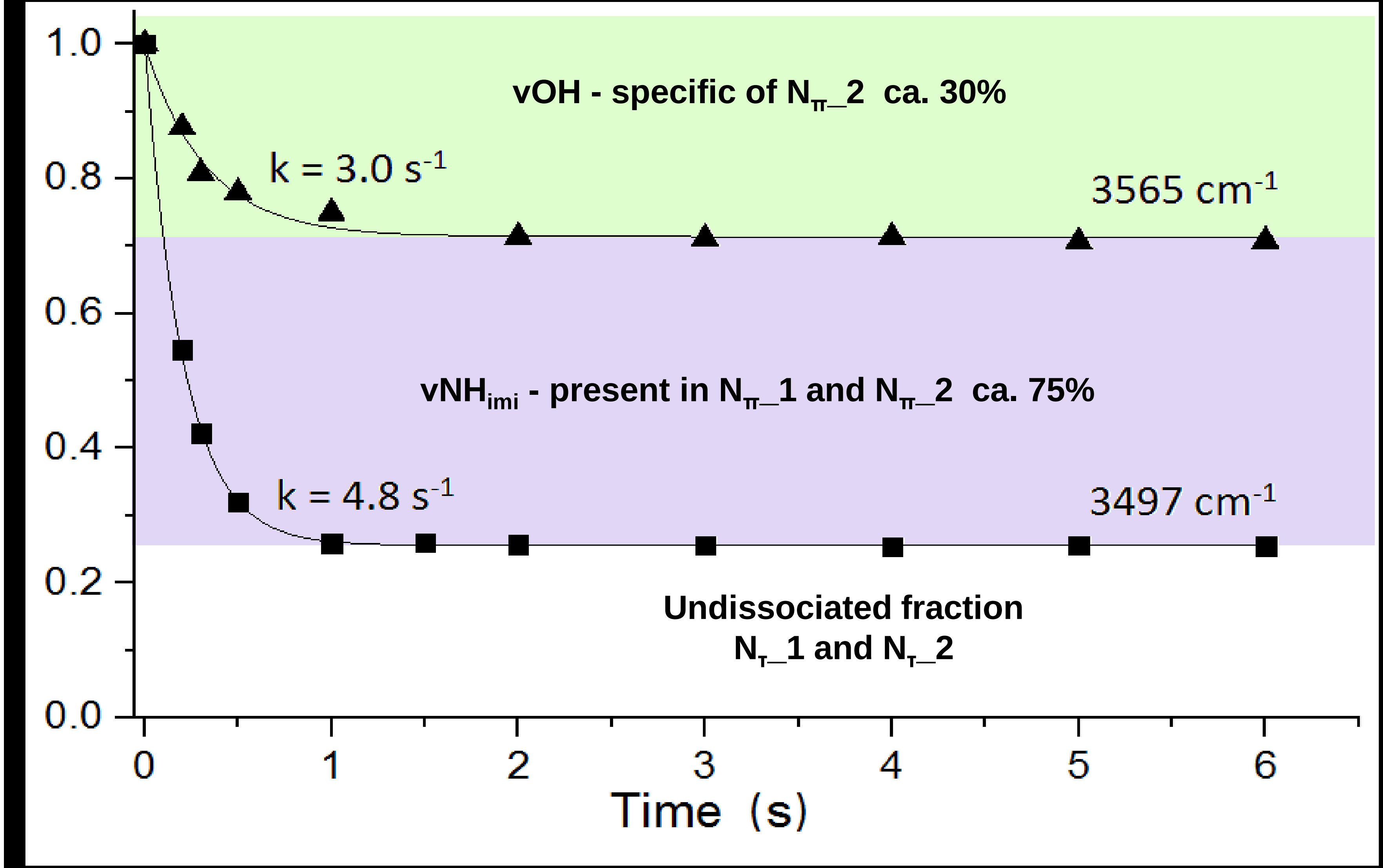
N_τ_1 (32)
N_τ_2 (29)

$[PtCl(\textit{trans}\text{-}NH_3)His(N_\tau)]^+ + NH_3$ (236)

$[PtCl(\textit{cis}\text{-}NH_3)His(N_\tau)]^+ + NH_3$ (257)



Photofragmentation kinetics

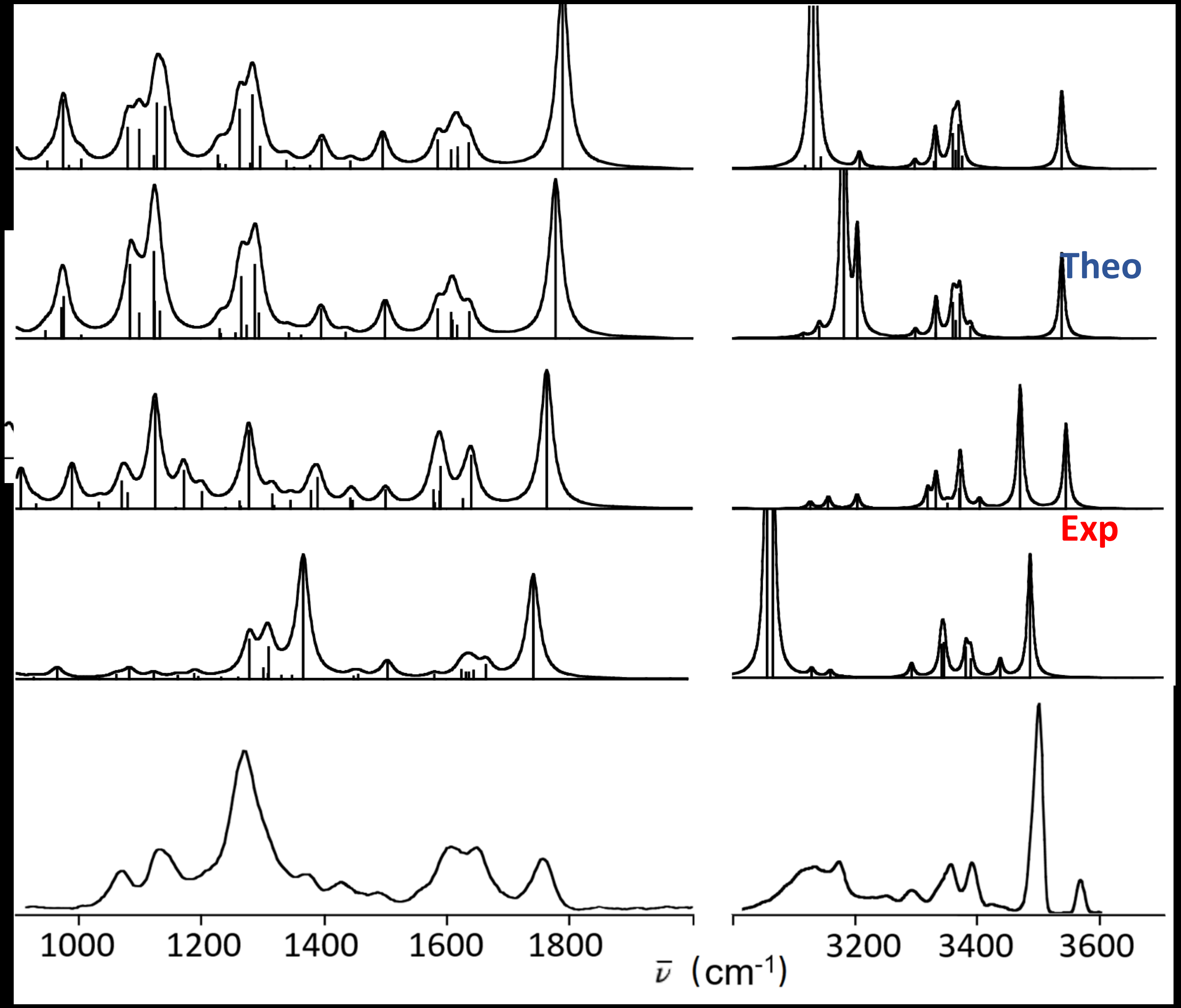


IRMPD kinetics for isomers quantification

Averaged theoretical spectrum from experimental obtained conformer percentages:

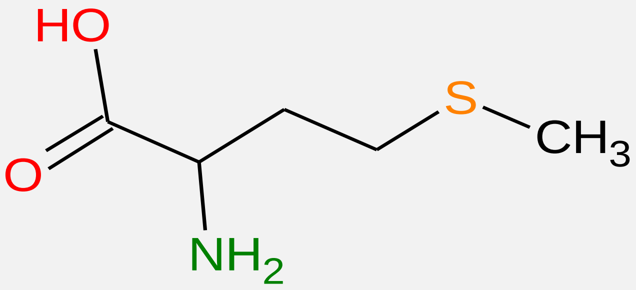
- 45% **N_{π}_1**
- 30% **N_{π}_2**
- 20% **N_{τ}_1** and **N_{τ}_2**

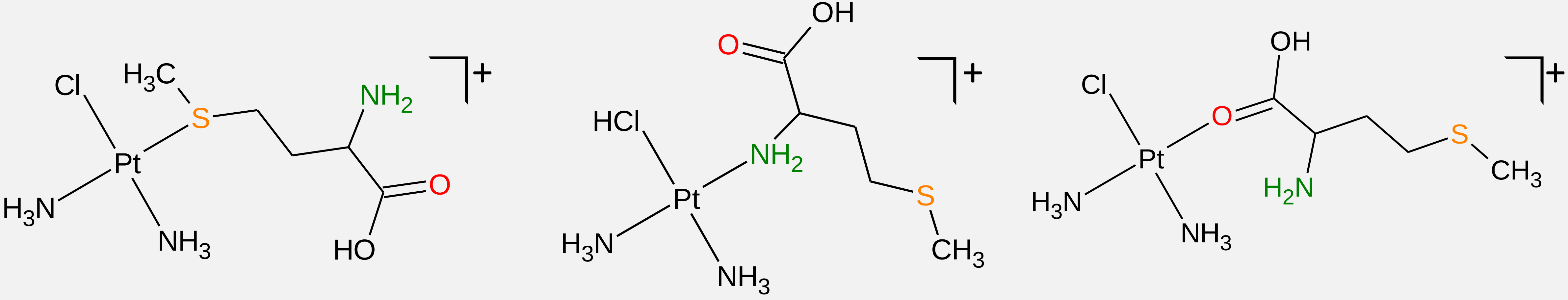
IRMPD spectrum



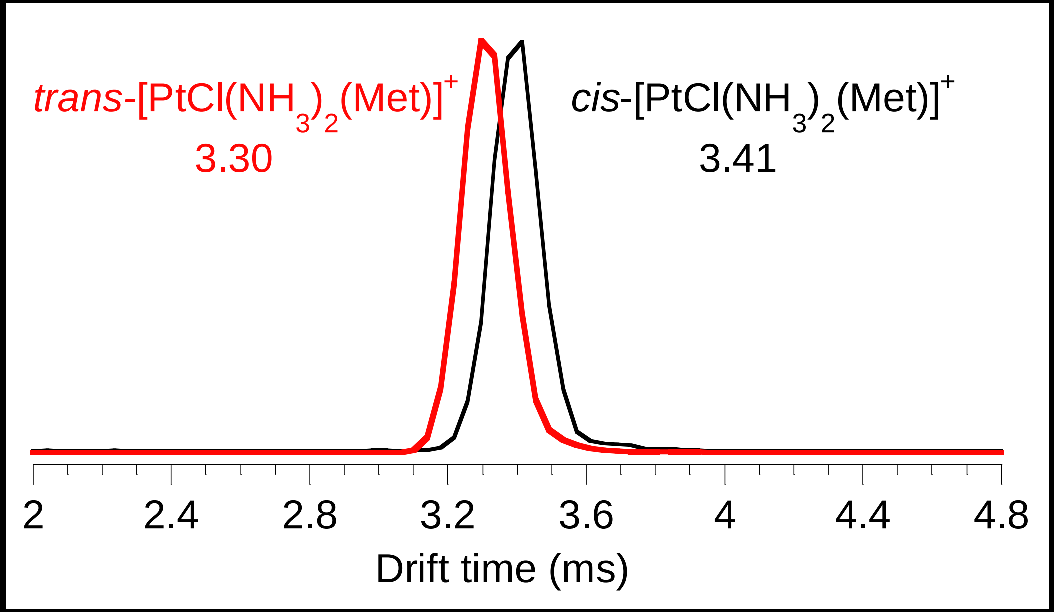
Characterization of *cis*- and trans-$[PtCl(NH_3)_2(Met)]^+$

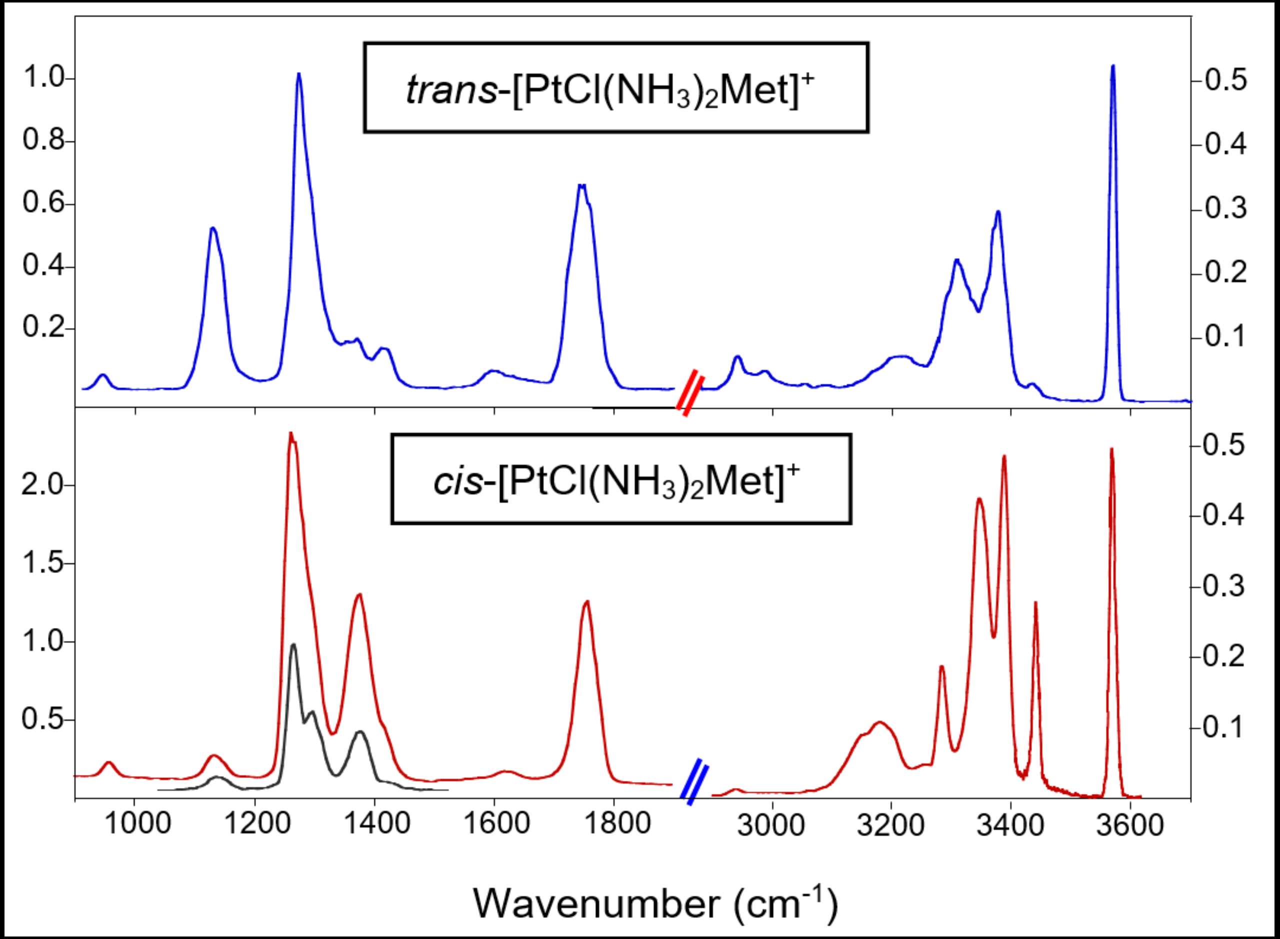
Methionine





IM and IRMPD experiments

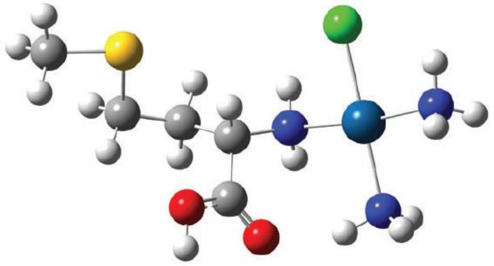




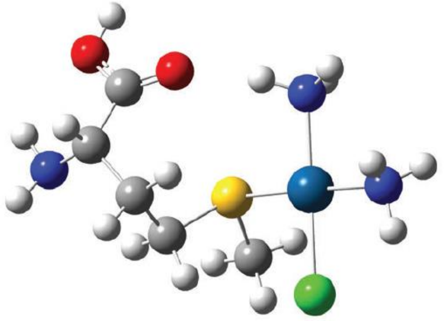
Paciotti, Corinti, De Petris, Ciavardini, Piccirillo,Coletti, Re, Maitre, Bellina, Barran, Chiavarino, Crestoni, Fornarini *PCCP* **2017**, *19*, 26697-26707.

Characterization of *cis*-[PtCl$(NH_3)_2$(Met)]$^+$

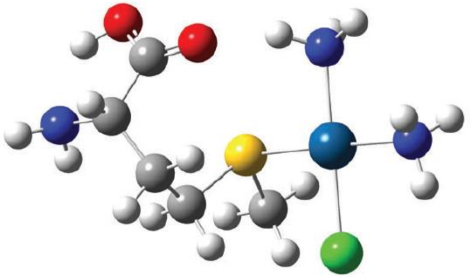
Geometries optimized at the **B3LYP/6-311++G(2df,pd) (Pt = LanL2TZ-f)** level, relative free energies and relative free enthalpies (*italics*) at 298 K are reported.



cN1(17.7, *24.8*)

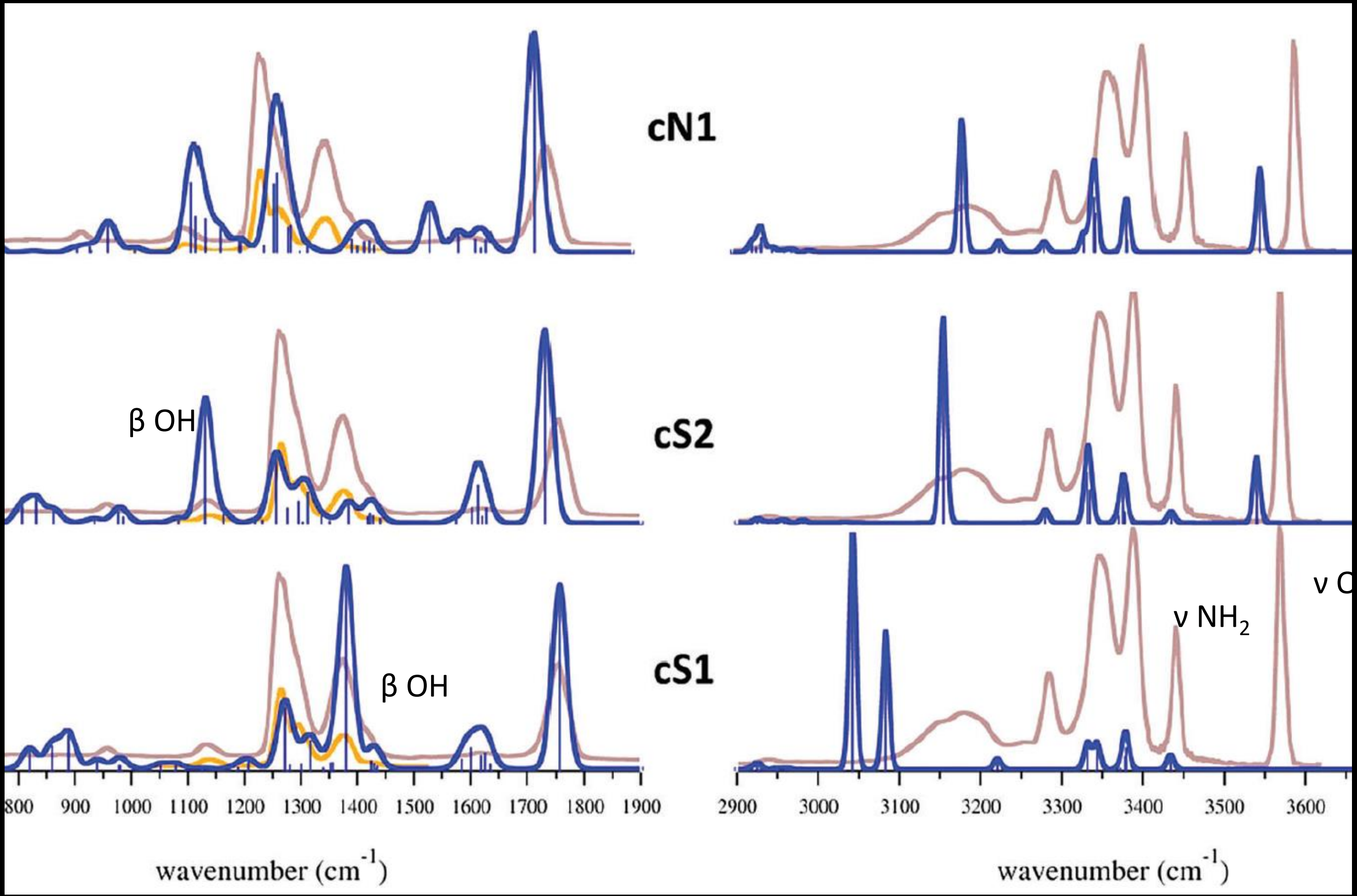


cS2(3.8,*5.9*)

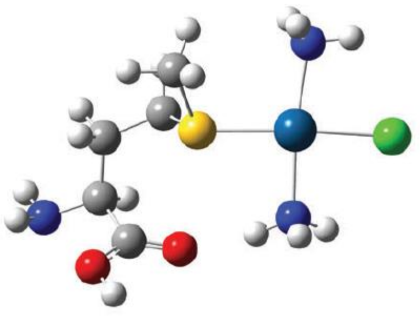


cS1 (0.0, *0.0*)

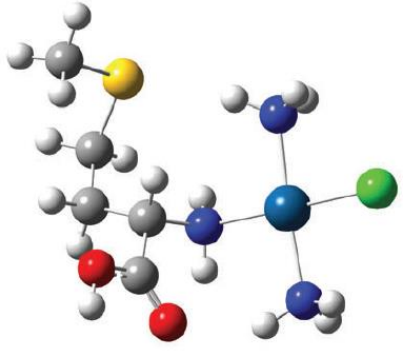
Anharmonic linear IR spectra



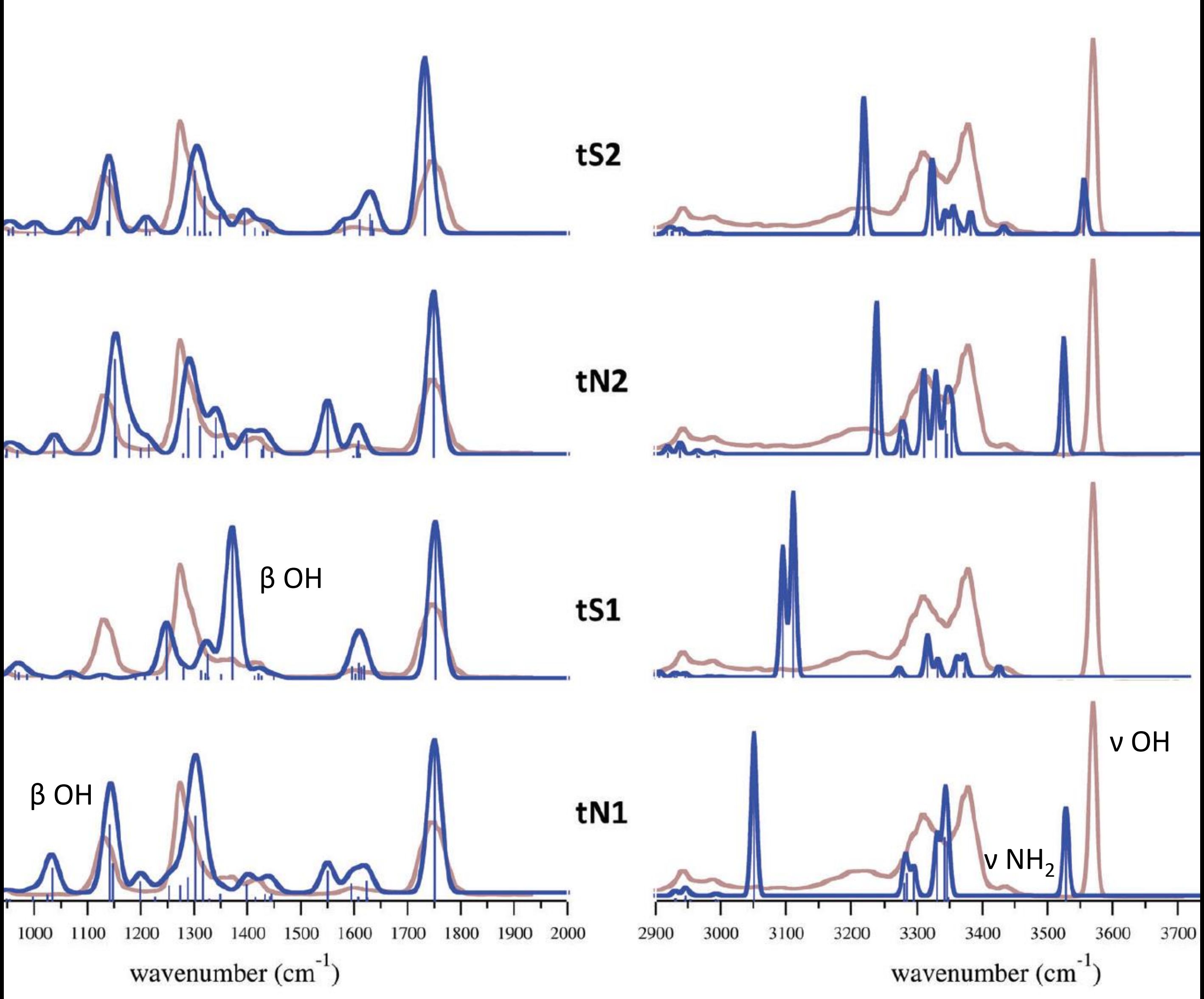
Characterization of *trans*-$[PtCl(NH_3)_2(Met)]^+$

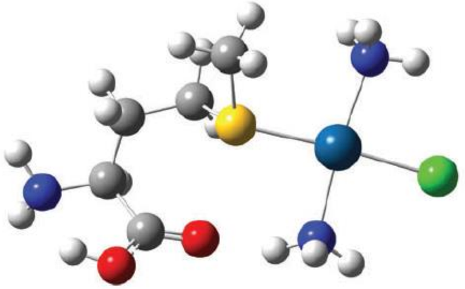


tS2 (13.5, *19.5*)

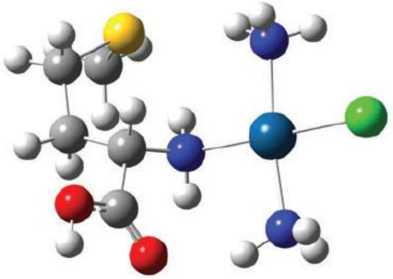


tN2 (5.9, *6.3*)



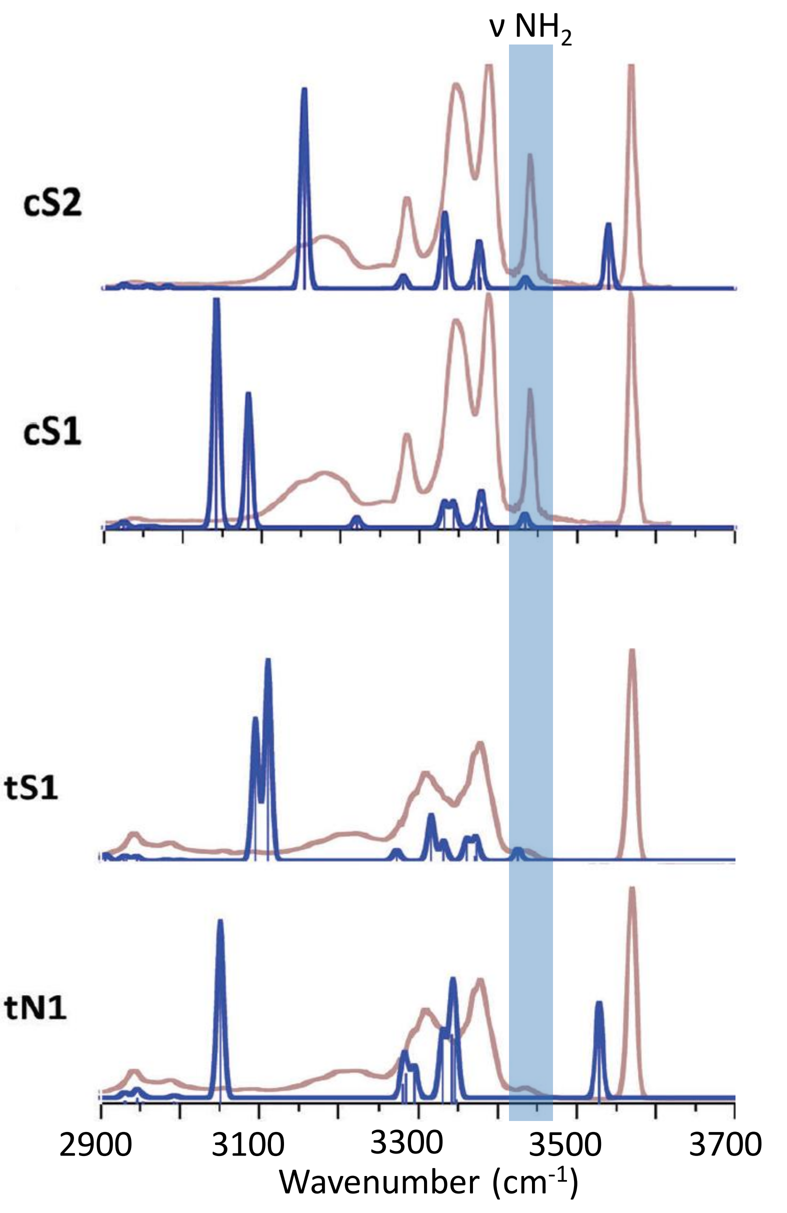


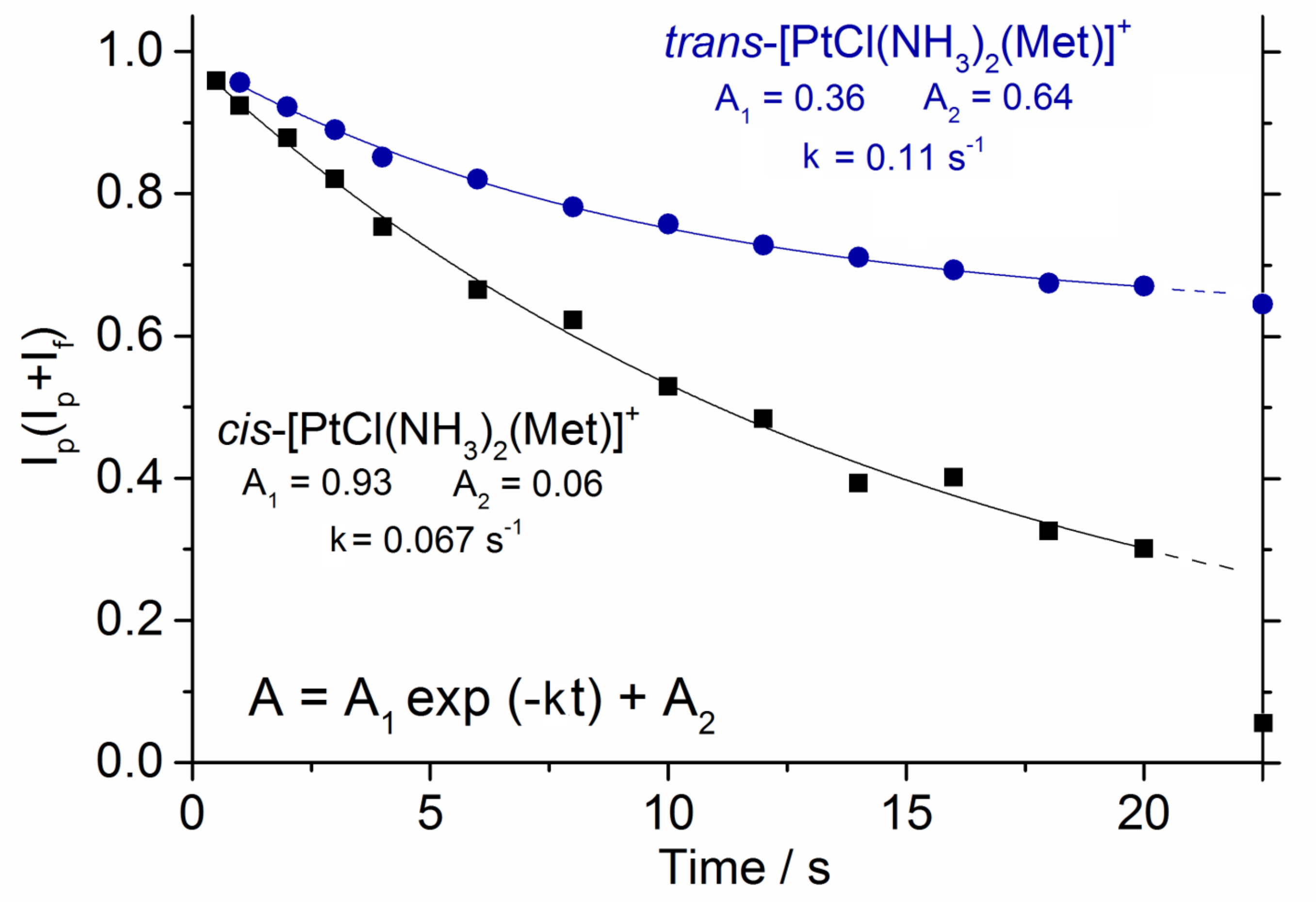
tS1 (1.2, *0.0*)



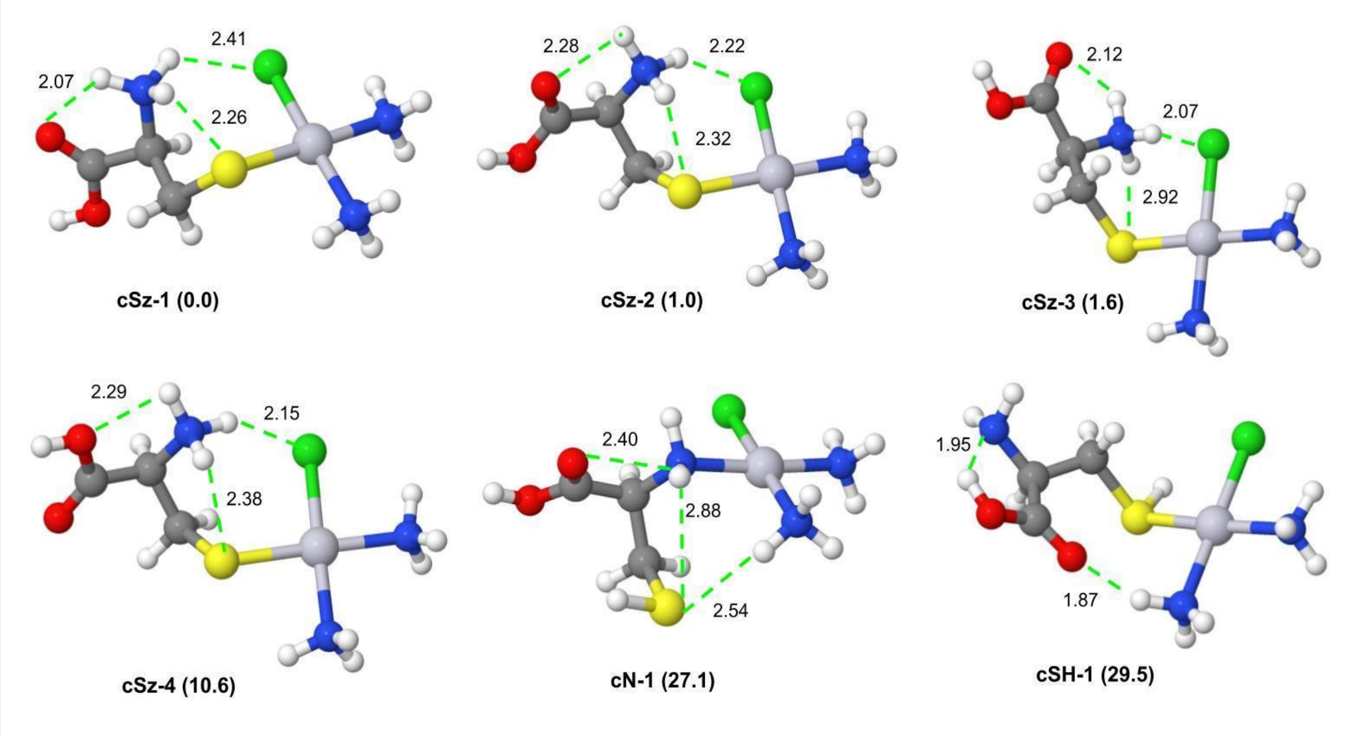
tN1 (0.0, *2.2*)

Photofragmentation kinetics





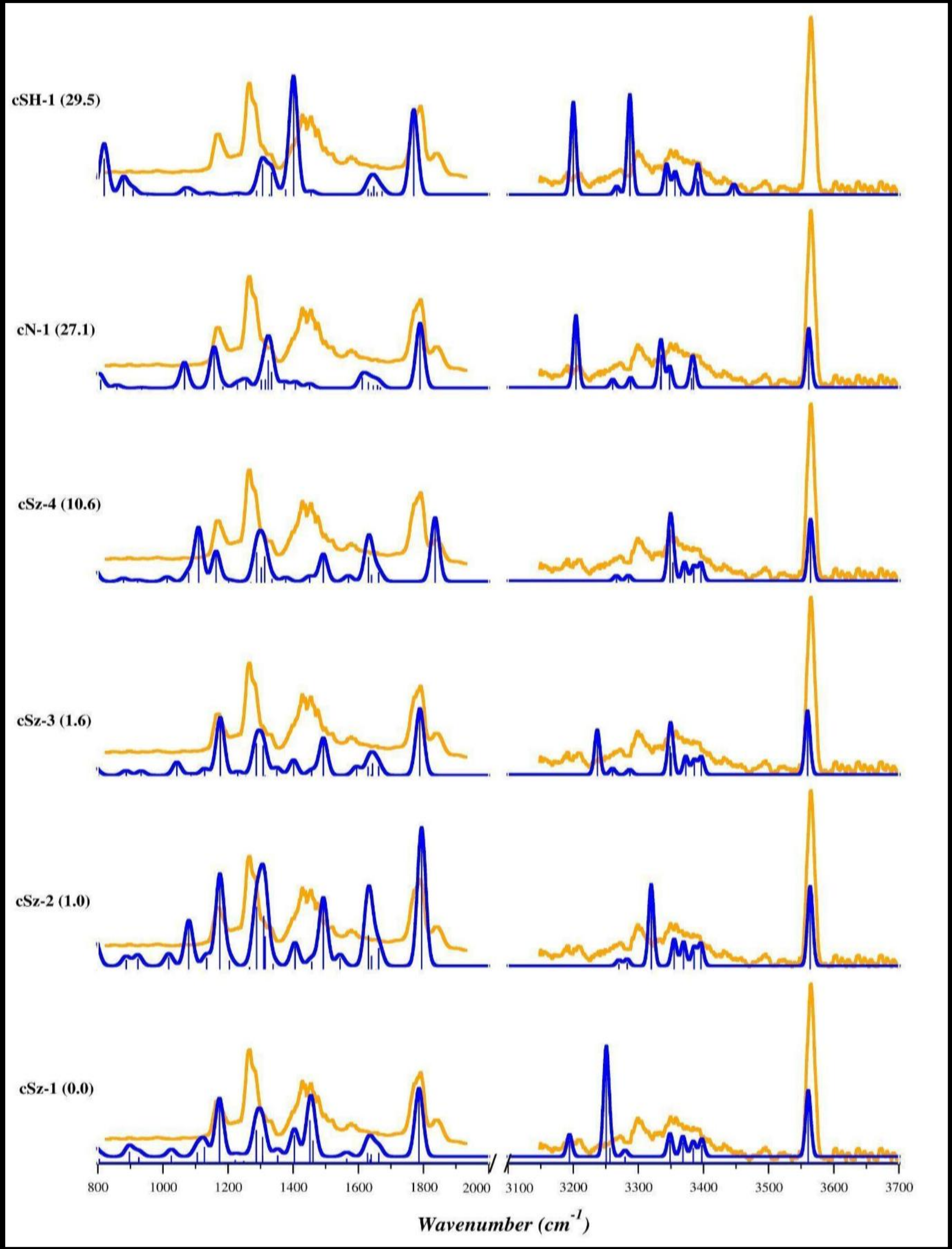
Characterization of *cis*-$[PtCl(NH_3)_2(Cys)]^+$



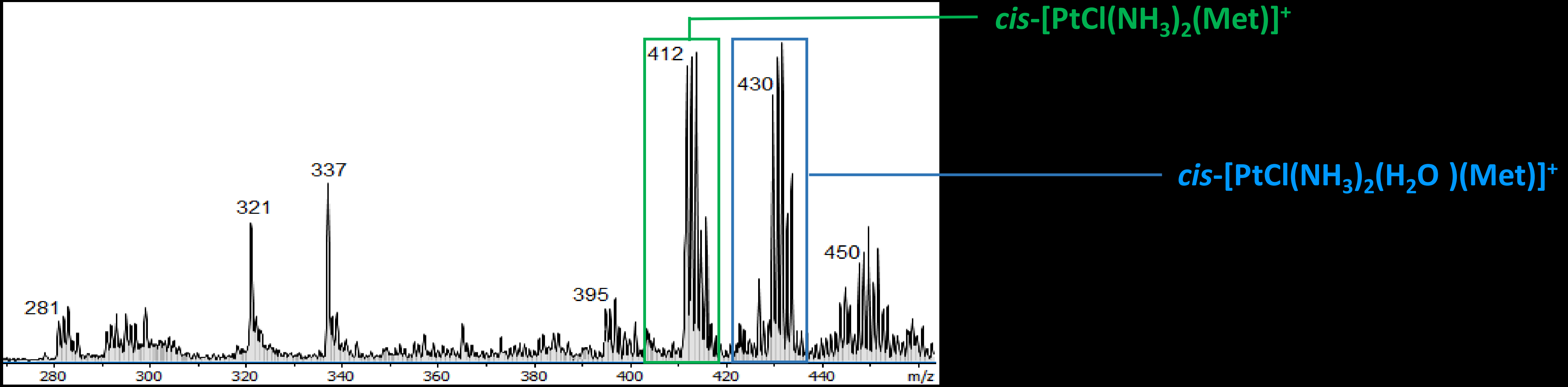
Geometries optimized at the **B3LYP/6-311++G(2df,pd) (Pt = LanL2TZ-f)** level, relative free energies and relative free enthalpies (*italics*) at 298 K are reported.

D. Corinti, R. Paciotti, C. Coletti, N. Re, B. Chiavarino, M.E. Crestoni, S. Fornarini, J. Inorg. Biochem. 237 (2022) 112017.

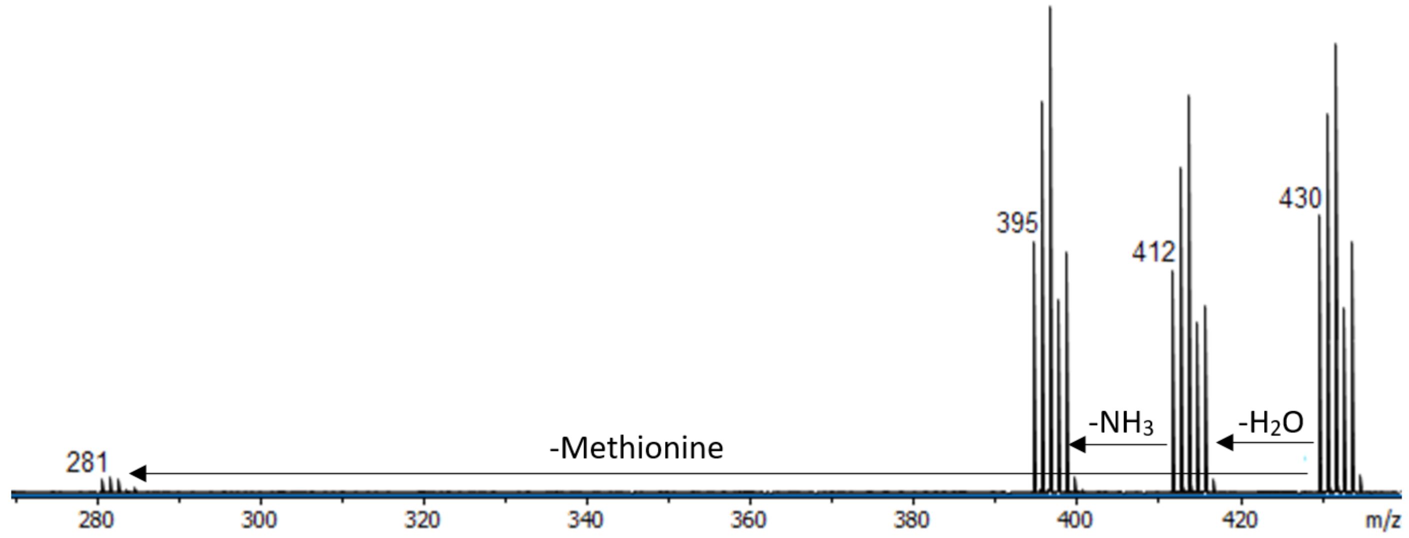
Harmonic IR spectra



Characterization of *cis*-[PtCl$(NH_3)_2(H_2O)$(Met)]$^+$

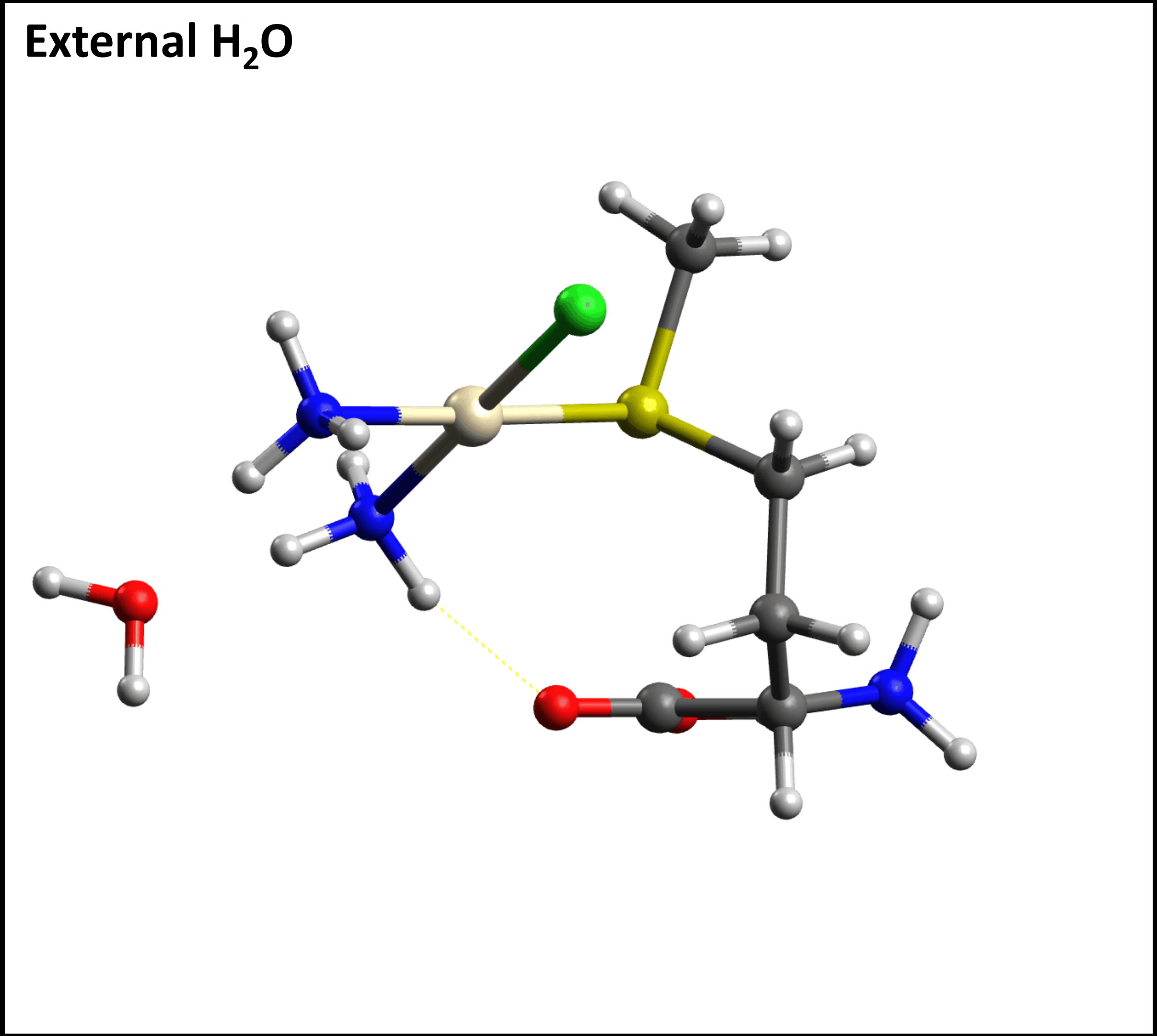


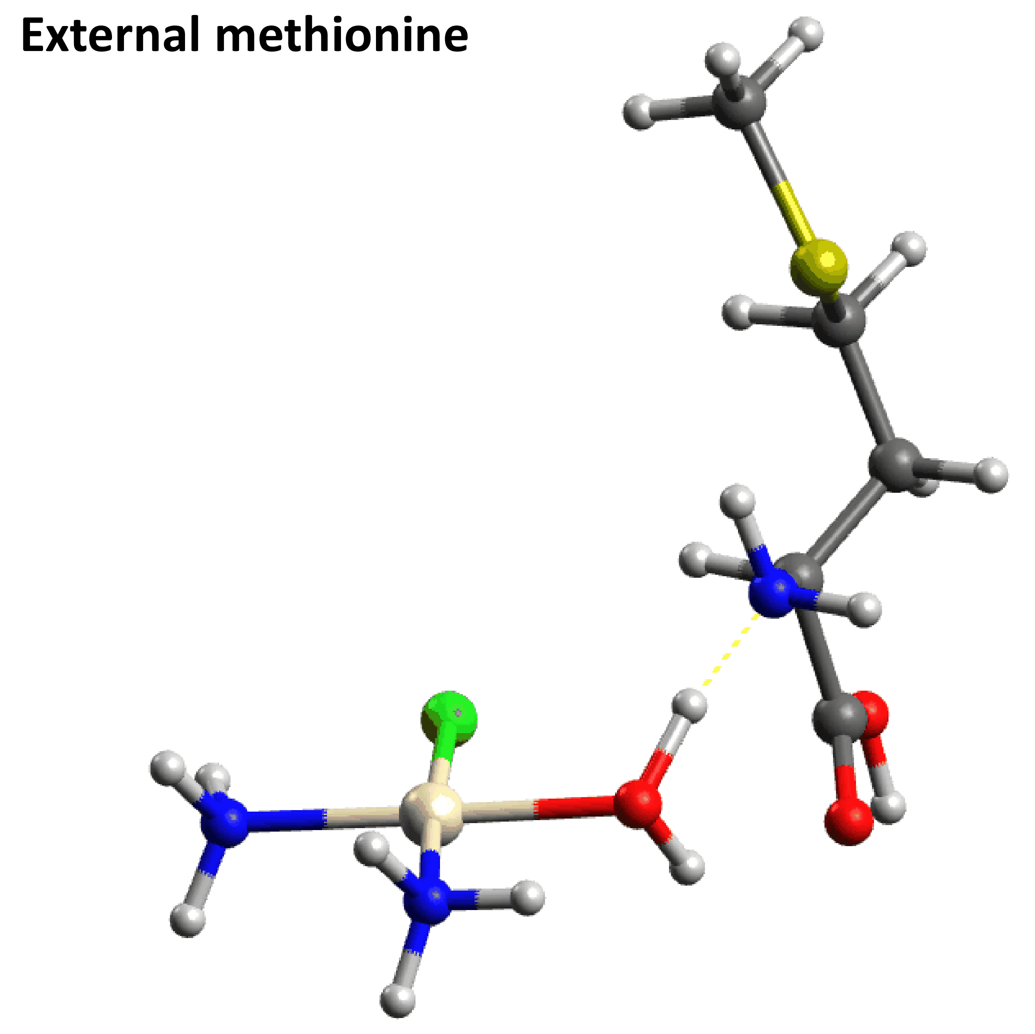
Mass spectrum recorded upon selection and irradiation at 1273 cm^{-1} of **cis-[PtCl$(NH_3)_2(H_2O)$(Met)]$^+$** ions at *m/z* 430



R. Paciotti, D. Corinti, P. Maitre, C. Coletti, N. Re, B. Chiavarino, M.E. Crestoni, S. Fornarini, J. Am. Soc. Mass Spectrom. 32 (2021) 2206–2217.

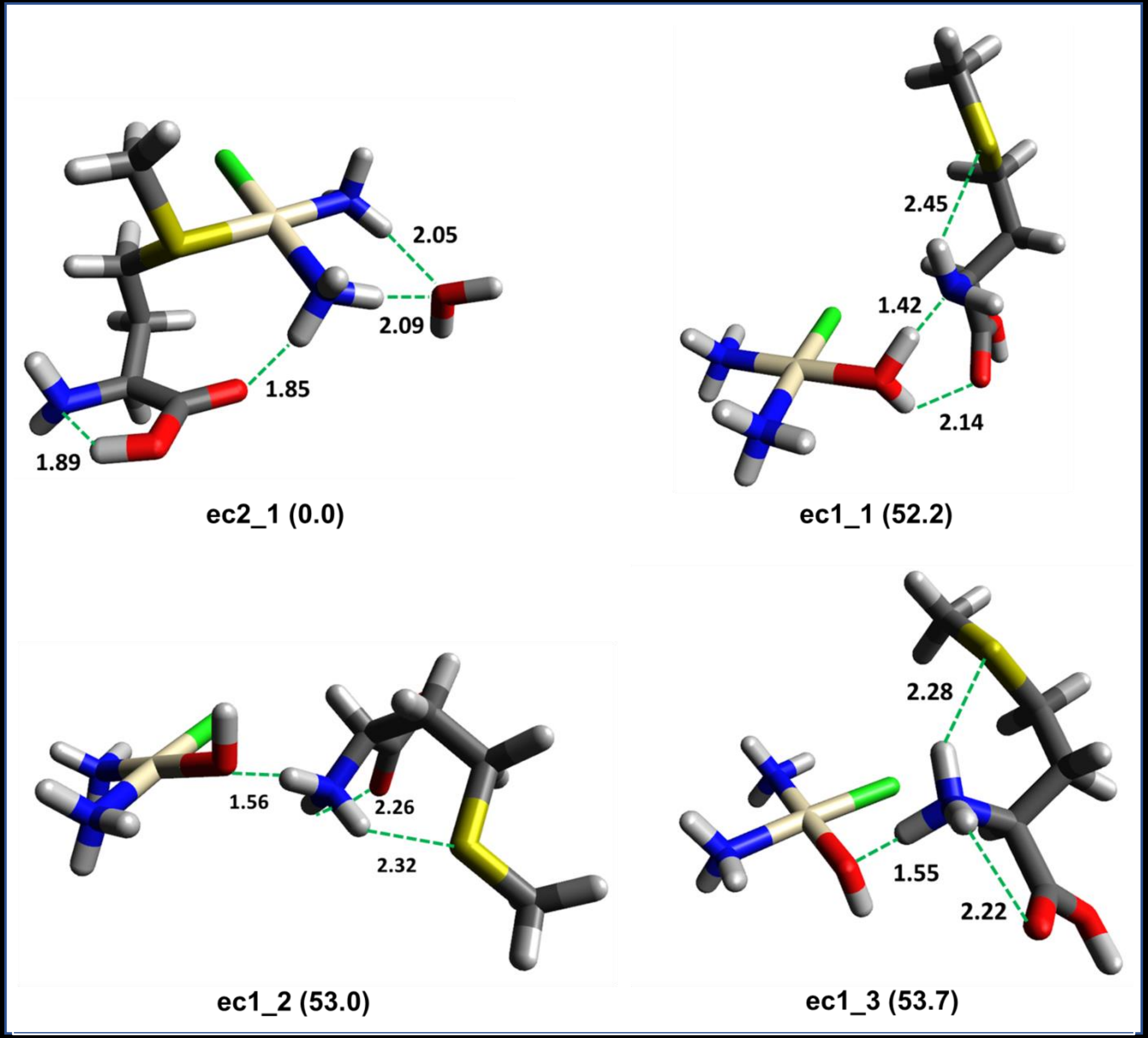
cis-$[PtCl(NH_3)_2(H_2O)(Met)]^+$

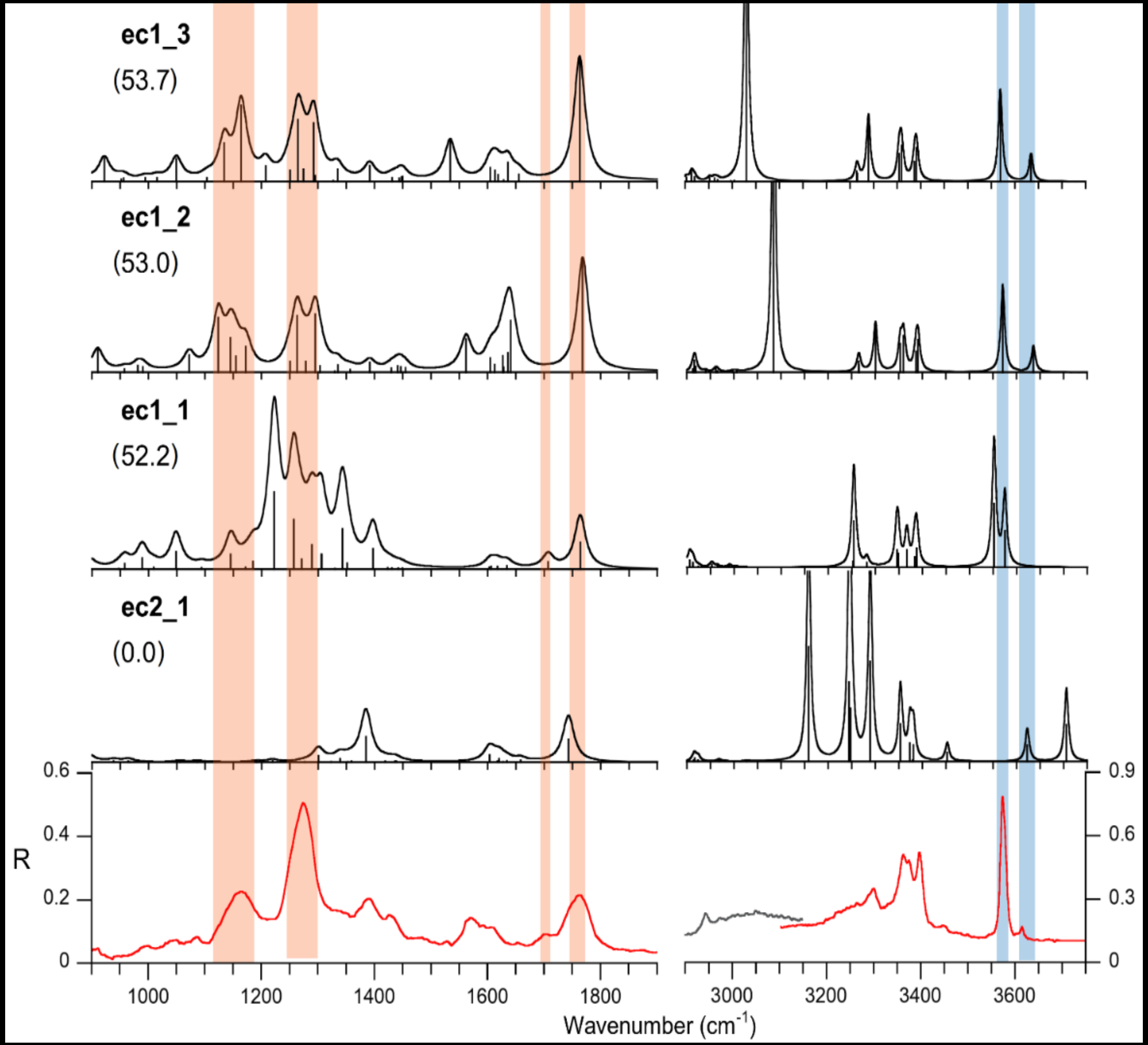




Optimized geometries at 6-311+G(2df,pd) level (S = 6-311+G(3df), Pt = LANL2TZ-f)

Relative free energy values (kJ mol^{-1}) are reported in parenthesis. Hydrogen bond distances (Å) are indicated by green dashed lines.

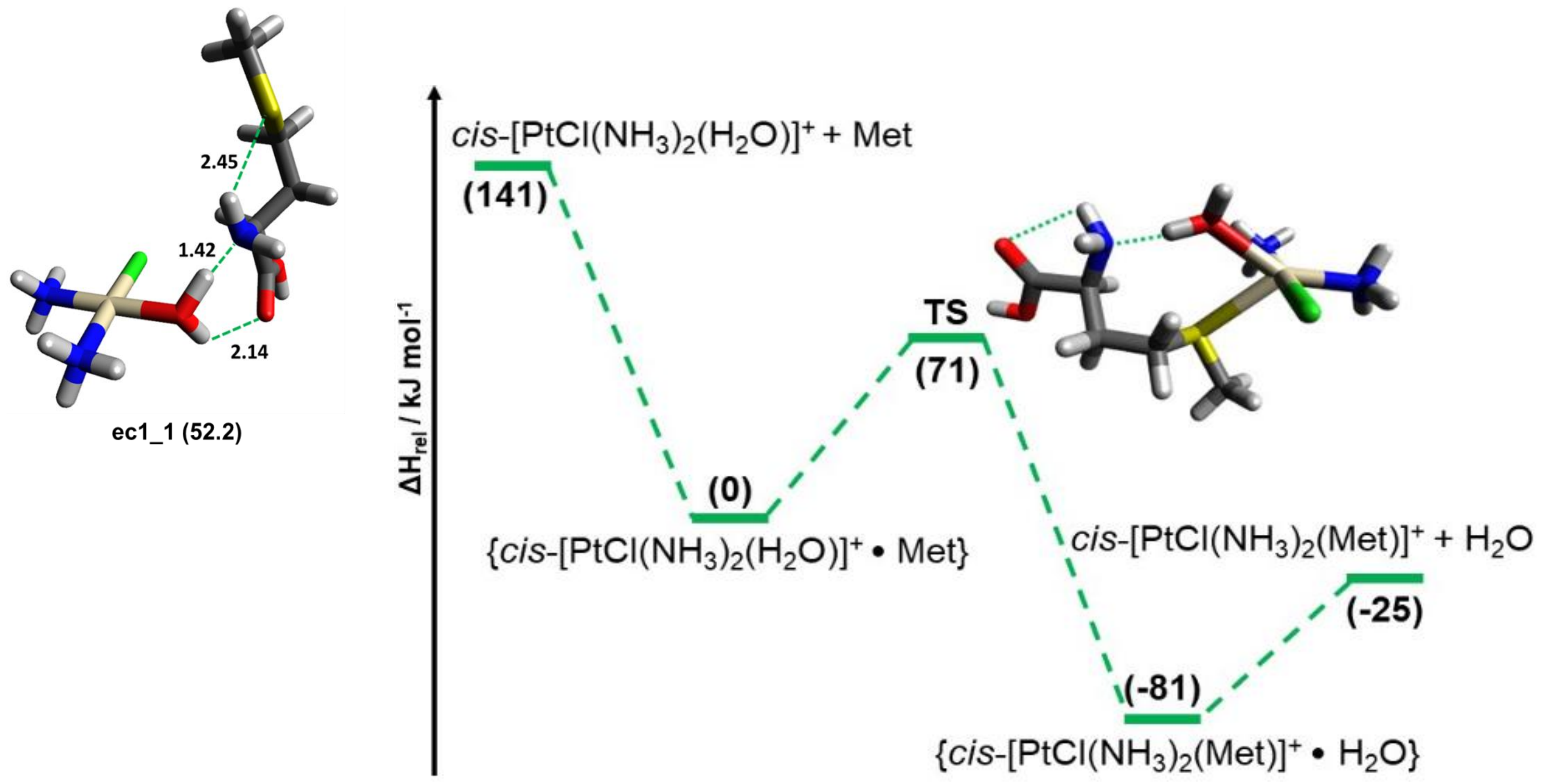




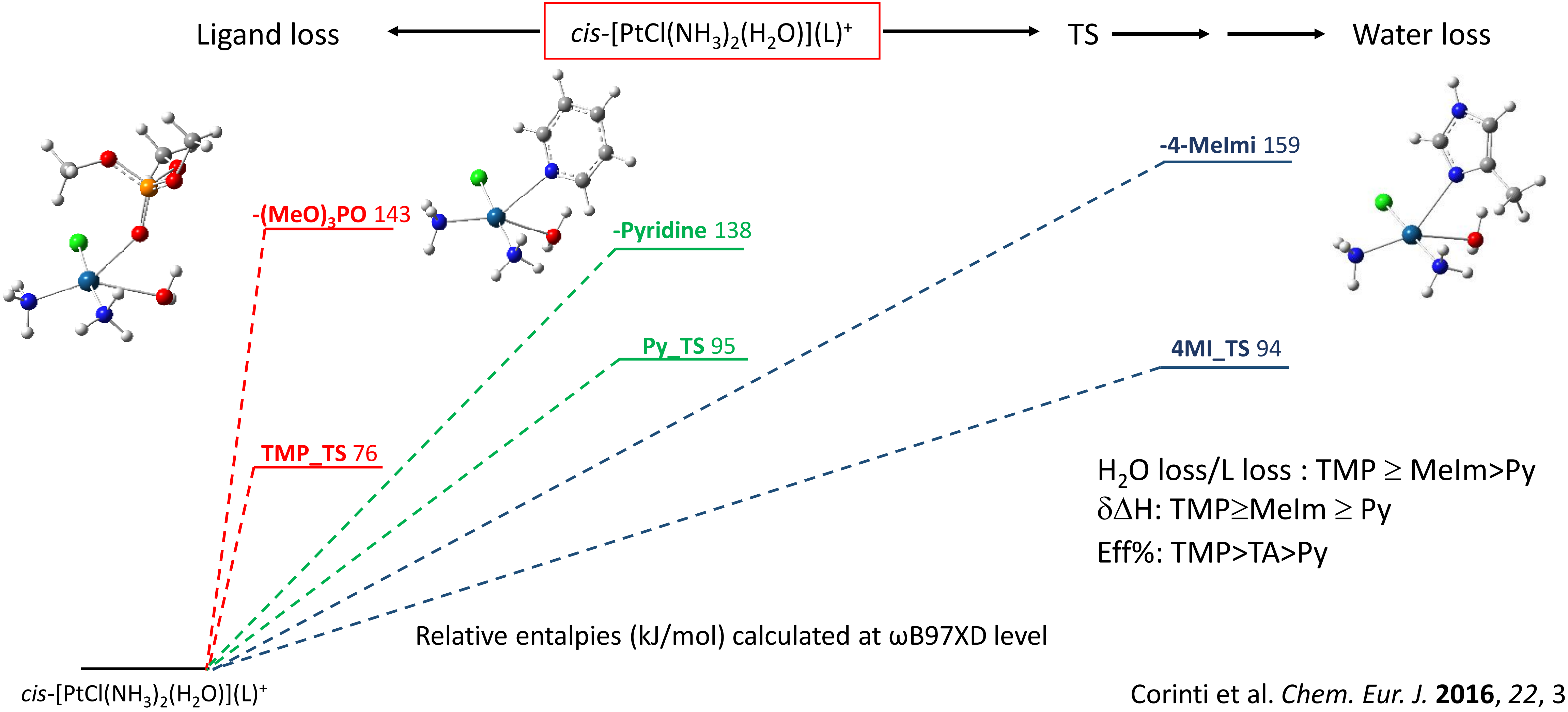
Theoretical frequencies have been scaled by 0.974 and 0.957 in the 900-1900 cm^{-1} and the 3100-3700 cm^{-1} ranges, respectively.

Potential Energy Surface for the reaction of cis-$[PtCl(NH_3)_2(H_2O)]^+$ with Met

Relative enthalpies (kJ/mol) calculated at ωB97XD level



Potential Energy Surface for the reaction of cis-$[PtCl(NH_3)_2(H_2O)]^+$ with L (L= Py, 4-MeIm, TMP)



Ligand loss ← *cis*-$[PtCl(NH_3)_2(H_2O)](L)^+$ → TS → → Water loss

-$(MeO)_3$PO 143

TMP_TS 76

-Pyridine 138

Py_TS 95

-4-MeImi 159

4MI_TS 94

cis-$[PtCl(NH_3)_2(H_2O)](L)^+$

Relative entalpies (kJ/mol) calculated at ωB97XD level

H_2O loss/L loss : TMP ≥ MeIm>Py

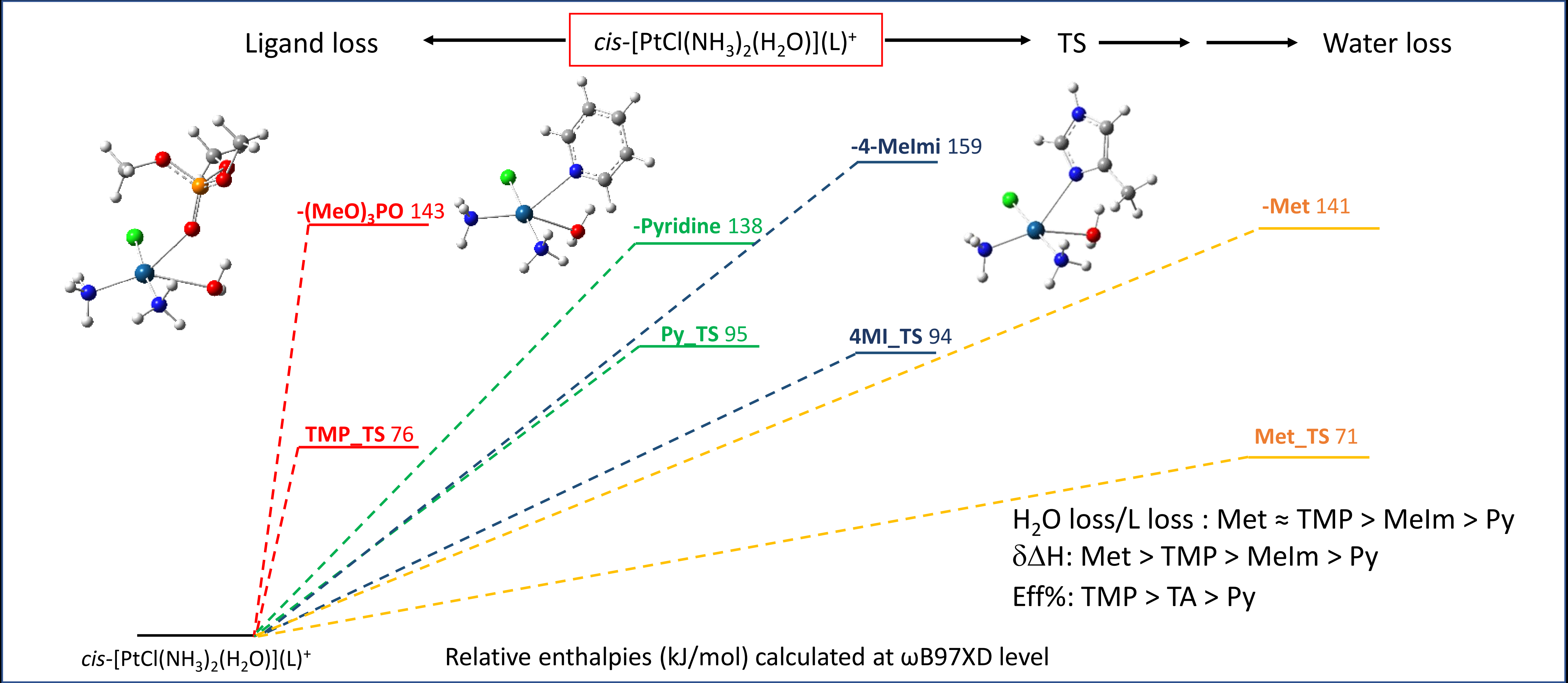
δΔH: TMP≥MeIm ≥ Py

Eff%: TMP>TA>Py

Corinti et al. *Chem. Eur. J.* **2016**, *22*, 3794

Corinti et al. *Int. J. Mass Spectrom.* **2019**, *435*, 7-17

Potential Energy Surface for the reaction of $cis\text{-}[PtCl(NH_3)_2(H_2O)]^+$ with L (L= Py, 4-MeIm, TMP, Met)



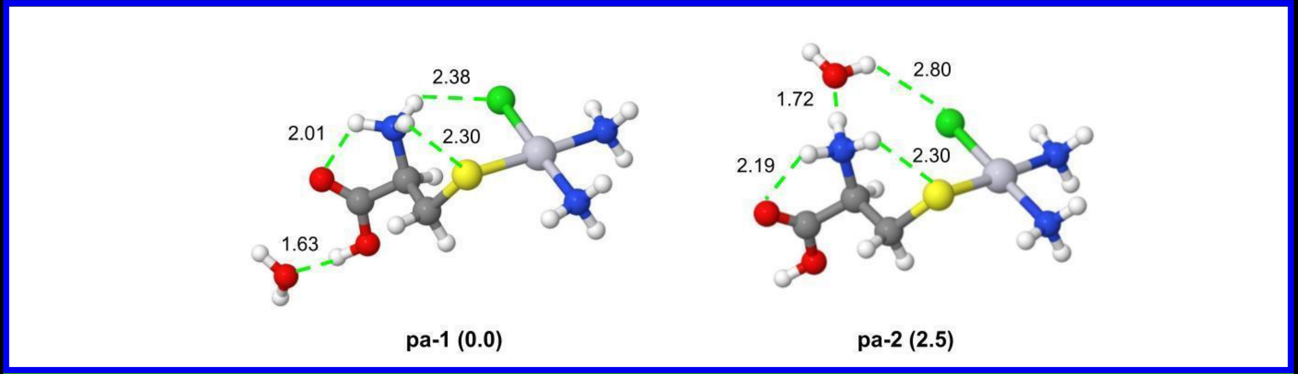
H_2O loss/L loss : Met ≈ TMP > MeIm > Py
$\delta\Delta H$: Met > TMP > MeIm > Py
Eff%: TMP > TA > Py

Relative enthalpies (kJ/mol) calculated at ωB97XD level

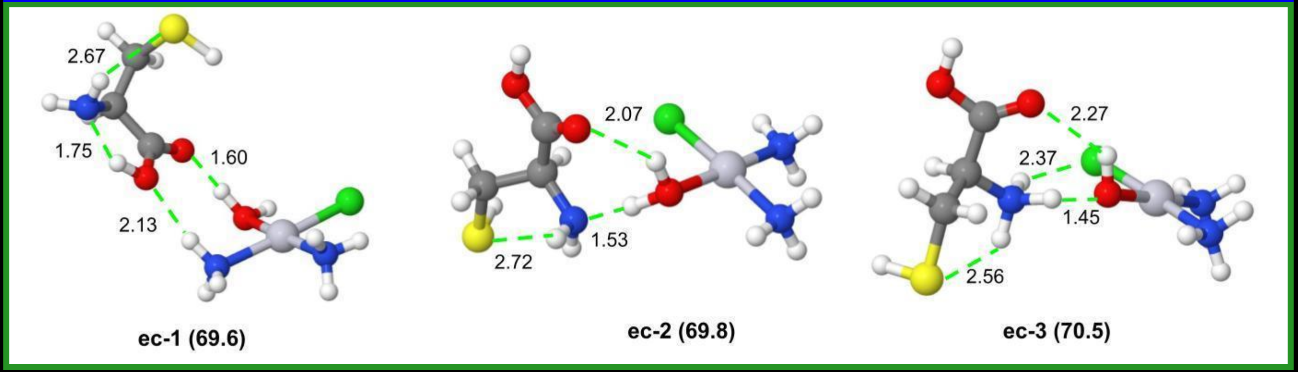
R. Paciotti, D. Corinti, P. Maitre, C. Coletti, N. Re, B. Chiavarino, M.E. Crestoni, S. Fornarini, J. Am. Soc. Mass Spectrom. 32 (2021) 2206–2217.

Characterization of *cis*-$[PtCl(NH_3)_2(H_2O)(Cys)]^+$

Optimized geometries at 6-311+G(2df,pd) level (S = 6-311+G(3df), Pt = LANL2TZ-f)

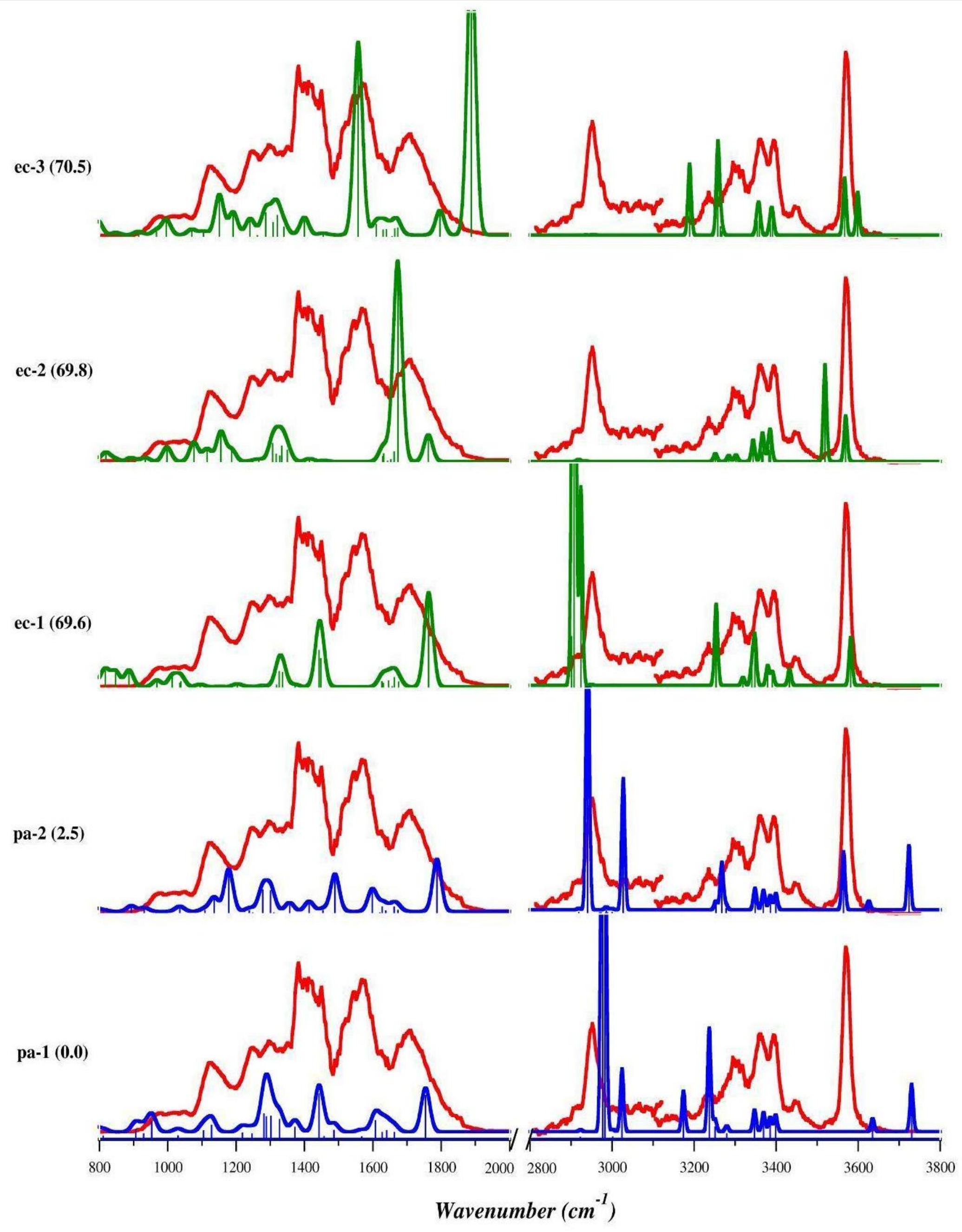


pa-1 (0.0) **pa-2 (2.5)**



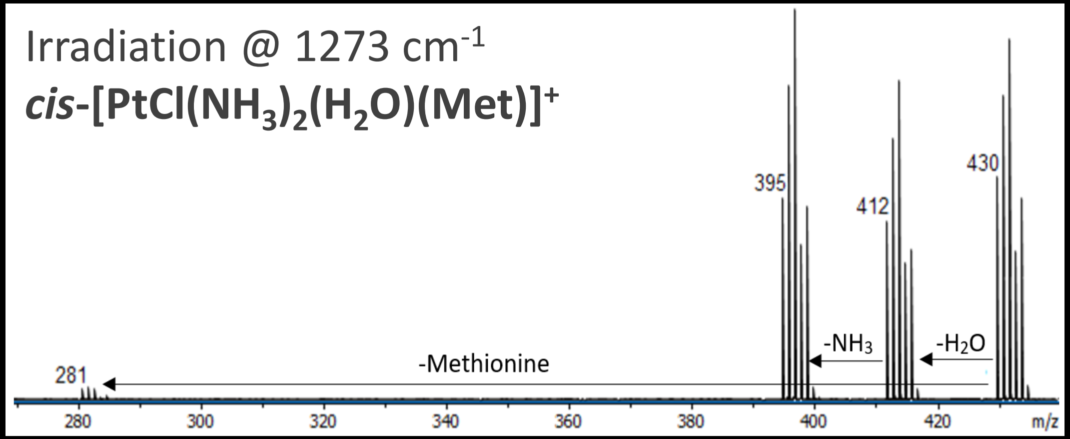
ec-1 (69.6) **ec-2 (69.8)** **ec-3 (70.5)**

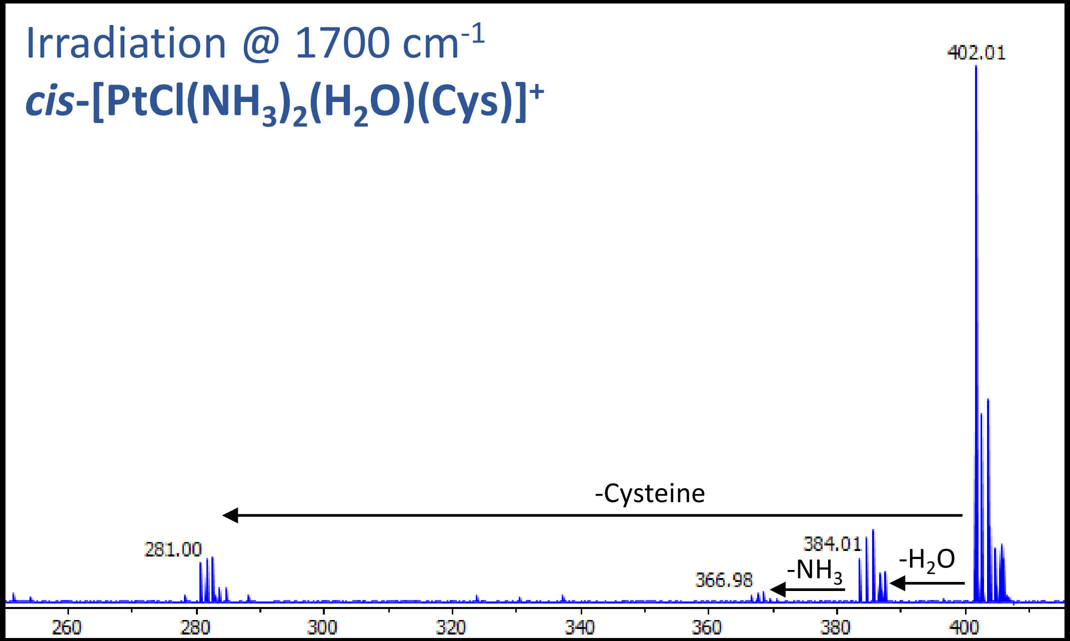
Theoretical frequencies have been scaled by 0.99 and 0.96 in the 800-2000 cm^{-1} and the 2800-3800 cm^{-1} ranges, respectively.

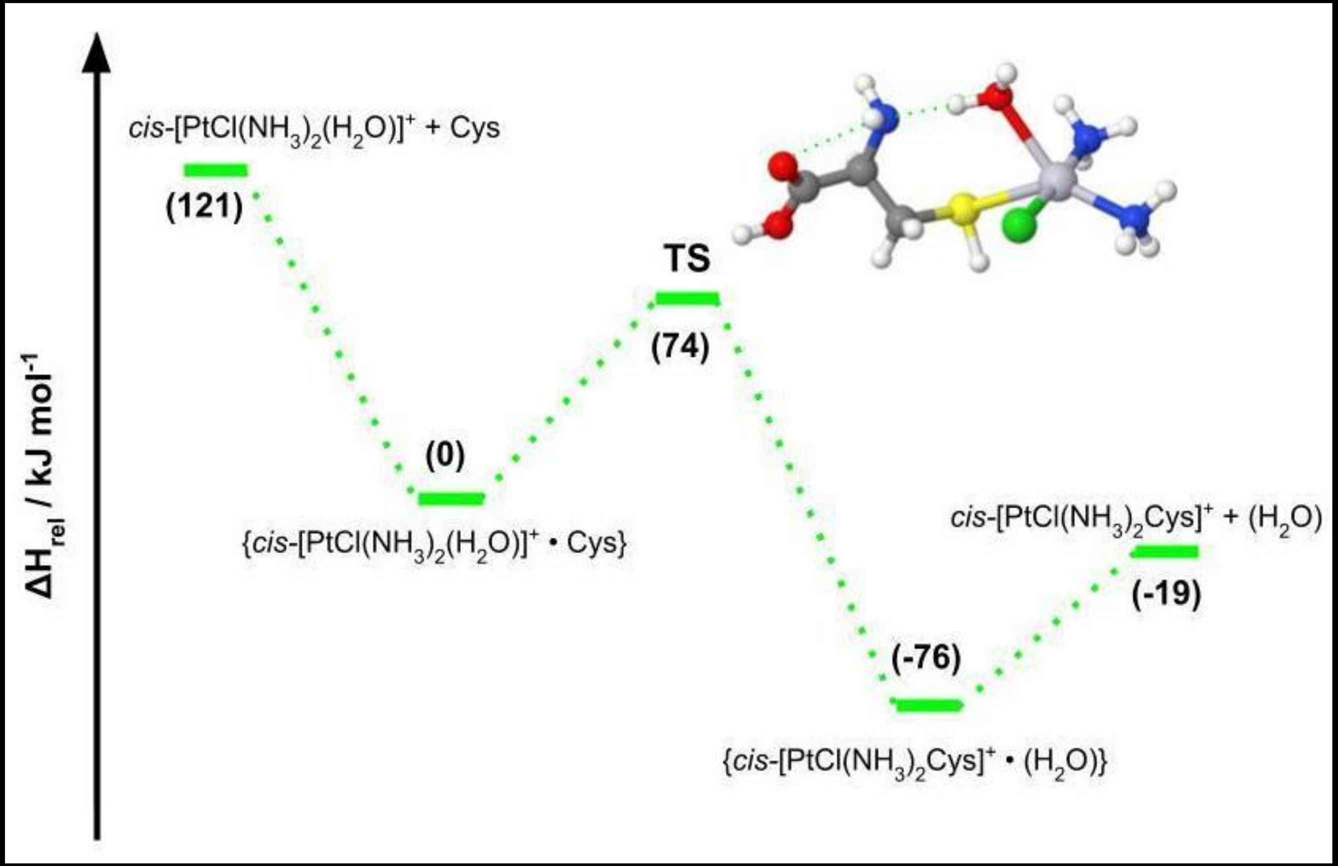


D. Corinti et al. J. Inorg. Biochem. 237 (2022) 112017.

Potential Energy Surface for the reaction of cis-$[PtCl(NH_3)_2(H_2O)]^+$ with Cys







Water loss/ligand loss ratio obtained upon activation of $\{cis\text{-}[PtCl(NH_3)_2(H_2O)]^{+}\cdot(L)\}$ compared with calculated energies and gas-phase efficiencies for the substitution reaction.

Ligand (L)	**H_2O loss/L loss (%)**	**ΔH[a]**	**Efficiency (%)[b]**
Pyridine[e]	5	43	0.41
Cysteine	75	47	- [d]
Thioanisole[e]	- [c]	48	1.1
4(5)-methylimidazole[e]	82	65	- [d]
Trimethylphosphate[e]	91	67	2.5
Acetamide[f]	94	61	- [d]
Dimethylacetamide[f]	94	65	- [d]
Urea[f]	94	59	- [d]
Methionine[g]	97	70	- [d]
Thiourea[f]	- [c]	74	- [d]

[a] Difference in enthalpy between the threshold energy for the back dissociation of L for the ec and the pentacoordinated TS in kJ mol^{-1}. [b] Efficiencies from gas-phase ion-molecule reactions in the cell of an FT-ICR. [c] Encounter complex not found in the cisplatin/L mixed solution. [d] Vapor pressure of the neutral ligand too low for the experiment.

Mass spectrometry allowed us to isolate and characterize the very early reactive intermediates generated from the **primary interaction** of **cisplatin** with methionine and cysteine.

IRMPD kinetics on isomer-specific vibrational modes permitted to quantify the percentages of isomers and conformers forming the gas-phase population of *cis*-$[PtCl(NH_3)_2(His)]^+$.

Encounter complex involved in the substitution reaction of hydrolized cisplatin with an aminoacid has been isolated and fully characterized.

Relative information about the **substitution reaction kinetics** were obtained from the analysis of (photo)fragmentation channels.

Assaying the selective interaction of a cytotoxic dinuclear copper(II) complex with phosphate ligands

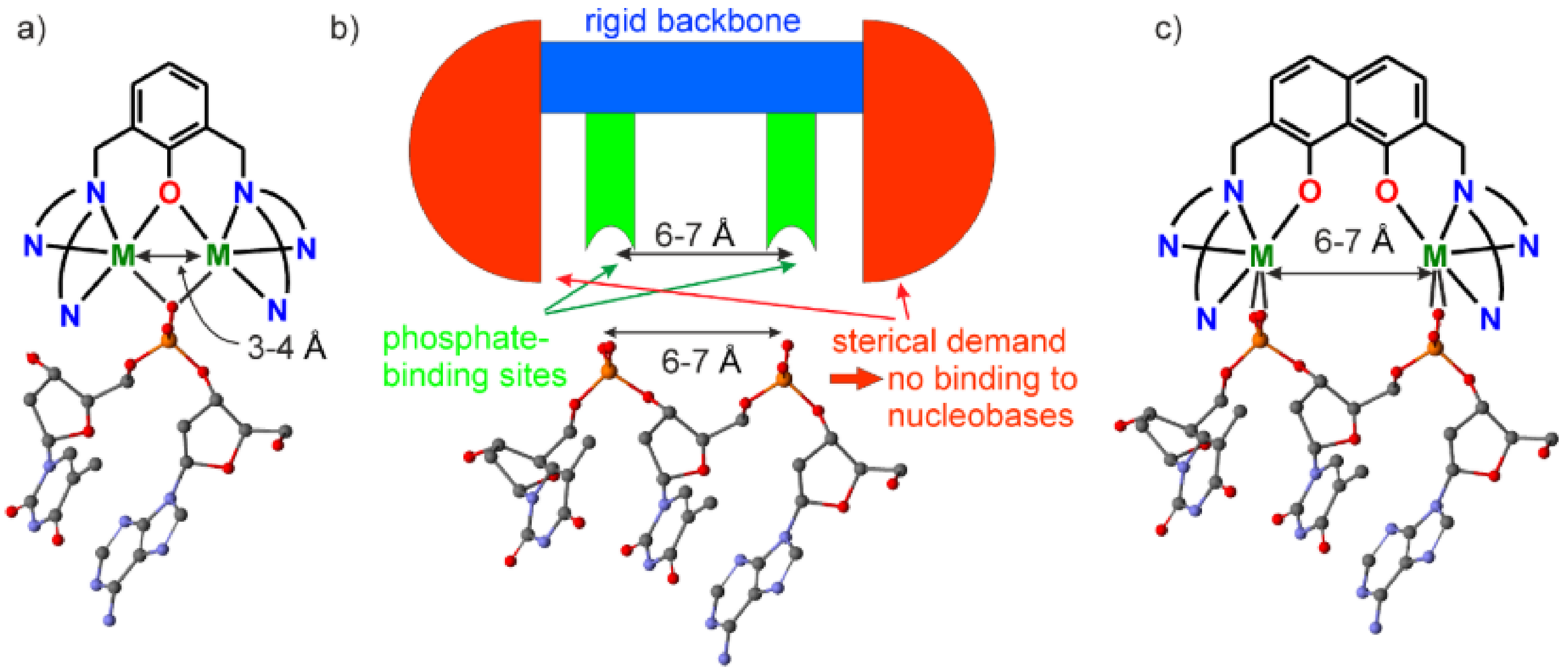
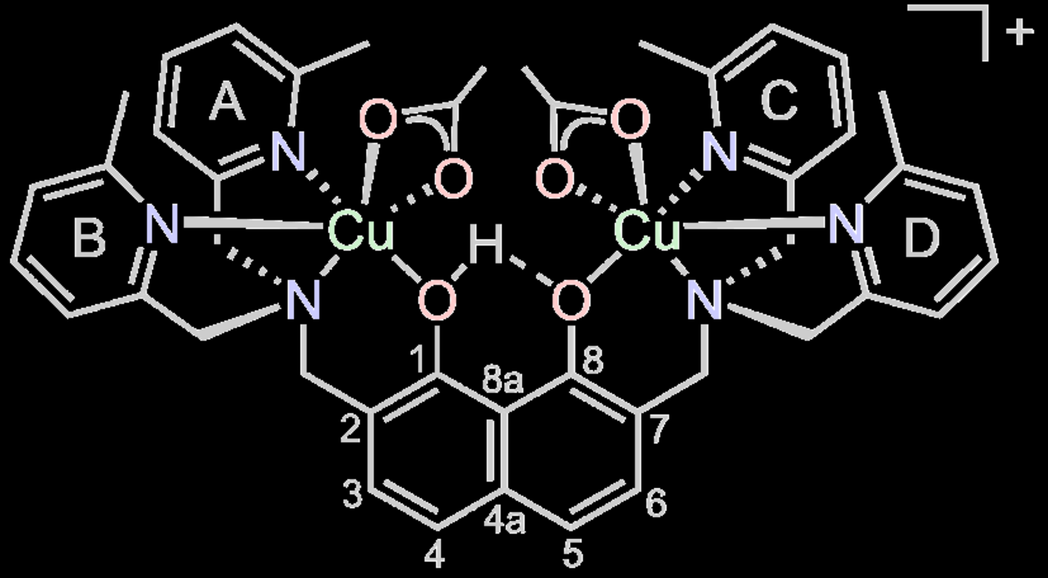
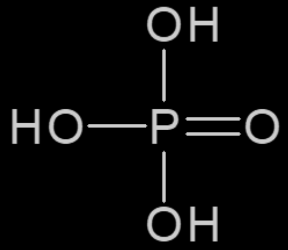


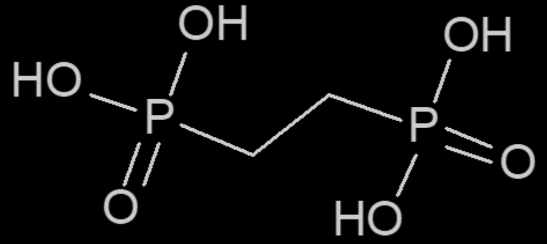
Figure 1. (a) Family of dinuclear complexes with hydrolytic reactivity based on dinucleating Robson ligands with a central phenolate. Two metal ions coordinate to one DNA phosphate. (b) Design concept for a dinuclear complex binding to two neighboring phosphates of the DNA backbone. (c) Molecular realization by a family of dinuclear complexes based on 2,7-disubstituted 1,8-naphthalenediol ligands. Please note that the two metal ions cannot coordinate to one DNA phosphate but are preorganized to coordinate to two neighboring DNA phosphates.

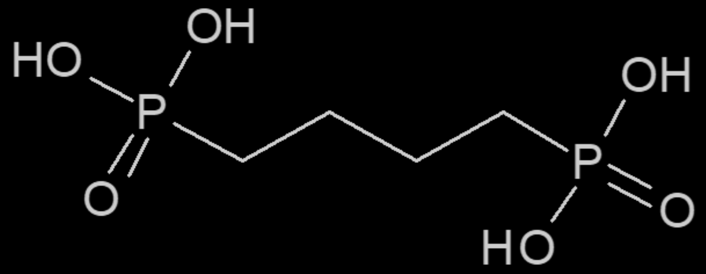
T. Glaser et al. Rational Design of a Cytotoxic Dinuclear Cu_2 Complex That Binds by Molecular Recognition at Two Neighboring Phosphates of the DNA Backbone, Inorg. Chem. 54 (2015) 2679–2690. doi:10.1021/ic5028465.

$[1(OAc)_2]^+$





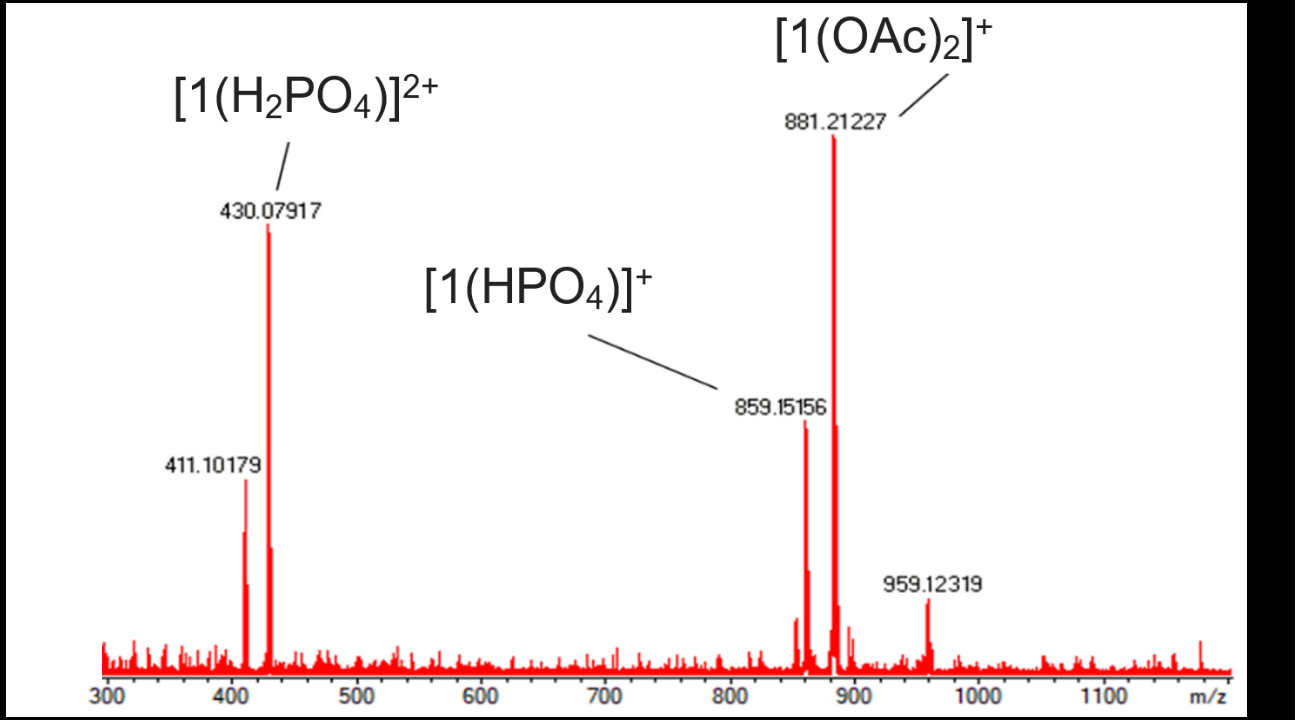


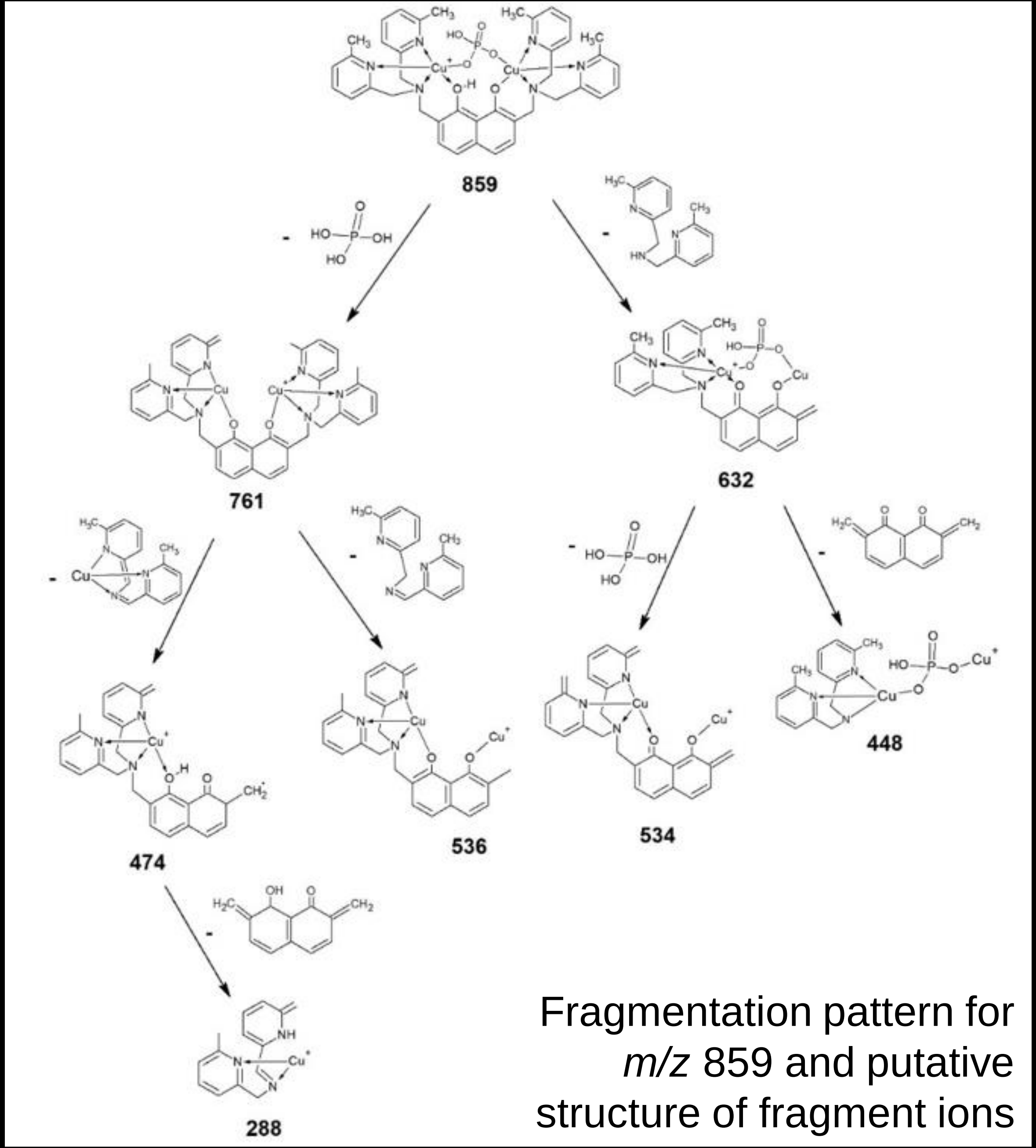


dAMP

dGMP

Corinti, Maccelli, Giampà, Fornarini, Berden, Oomens,
Schwarzbich, Glaser, Crestoni, *Submitted*, 2022

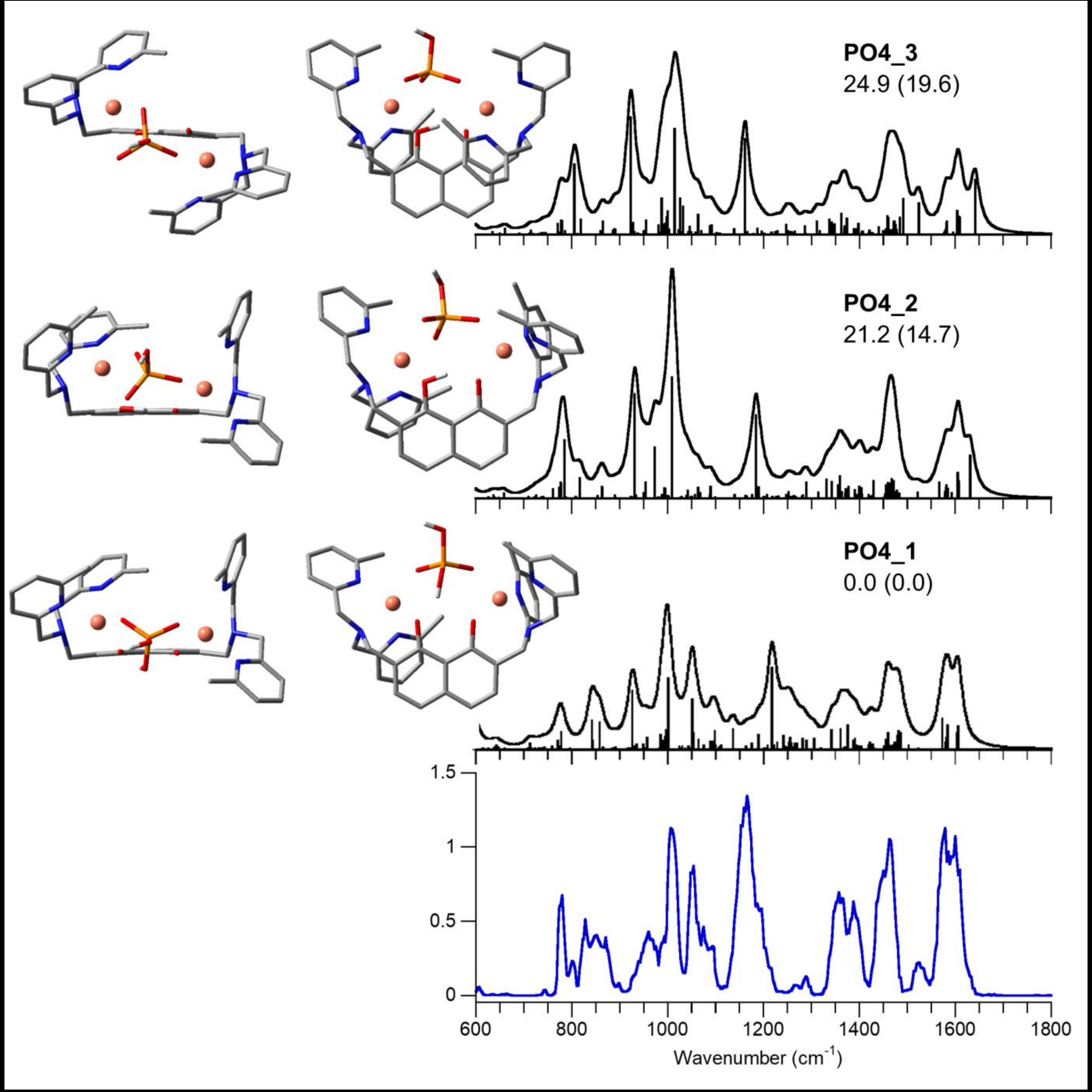




Fragmentation pattern for *m/z* 859 and putative structure of fragment ions

IRMPD spectrum of [**1(HPO4)**]$^+$ (bottom panel) compared with calculated IR spectra of selected conformers.

Relative free energies (enthalpies in parentheses) at 298 K in kJ mol^{-1}.

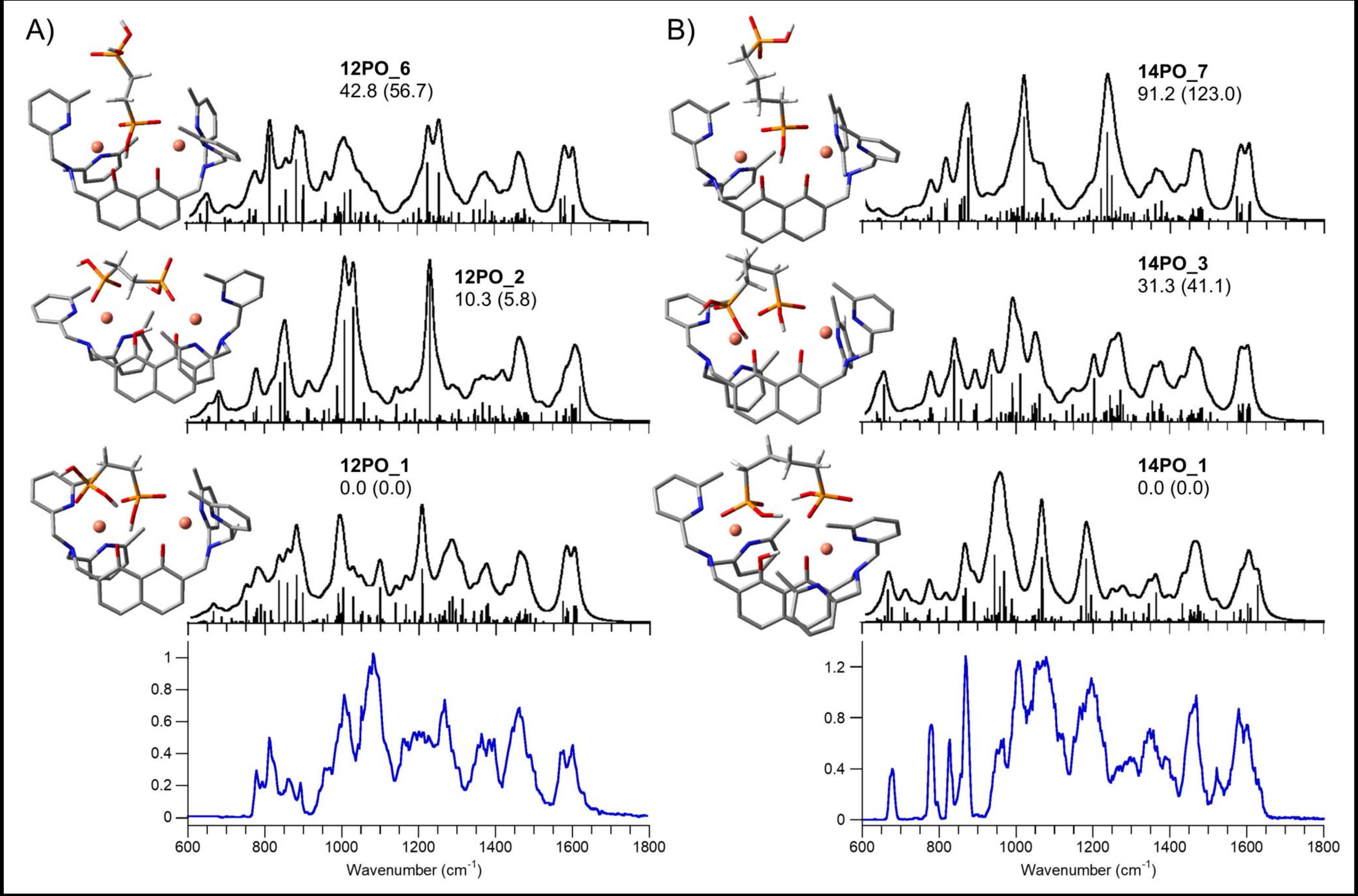


Geometry optimization and frequency analysis at B3LYP/6-31+G*

Energies at B3LYP//M06-2X/def2TZVP level

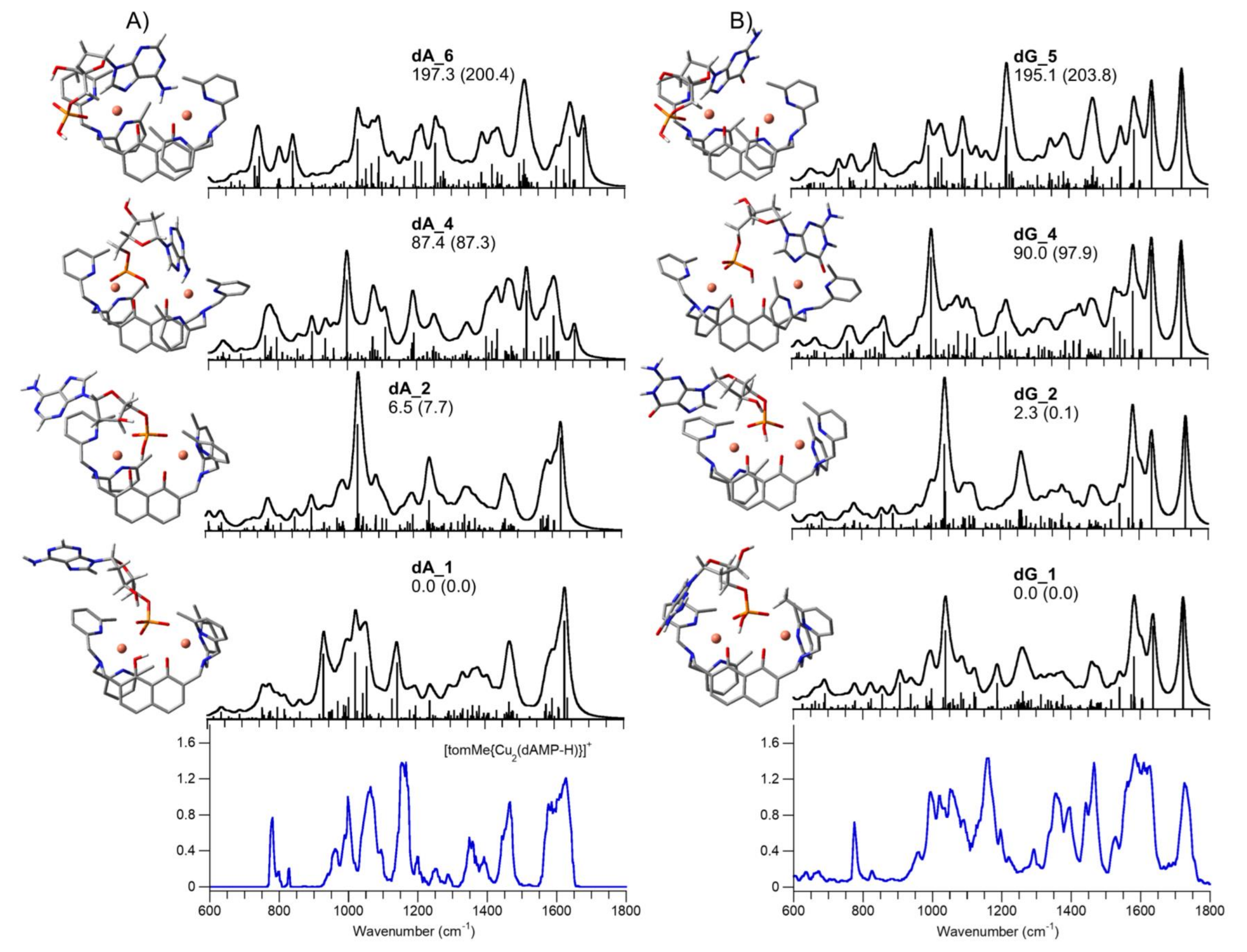
IRMPD spectra of [**1(1,2PO)**]$^+$ (panel A, bottom) and [**1(1,4PO)**]$^+$ (panel B, bottom) compared with calculated IR spectra of selected conformers.

Relative free energies (enthalpies in parentheses) at 298 K are in kJ mol^{-1}.



IRMPD spectra of [**1(dAMP-H)**]$^+$ (panel A, bottom) and [**1(dGMP-H)**]$^+$ (panel B, bottom) compared with calculated IR spectra of selected conformers.

Relative free energies (enthalpies in parentheses) at 298 K are in kJ mol^{-1}.



A detailed description of the **binding motifs of the dinuclear Cu^{II}** complex obtained by **ligand exchange** of $[(HtomMe)\{Cu(OAc)\}_2]^+$ with representative **phosphate-containing ligands**, L, ranging from inorganic phosphate up to mononucleotides, i.e. dAMP and dGMP, has been gathered.

Evidence for **direct Cu-phosphate contacts has been obtained** by a combination of tandem mass spectrometry, IRMPD spectroscopy in the fingerprint region and quantum-chemical calculations.

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Prof. Thorsten Glaser

Prof. Perdita Barran
Dr. Bruno Bellina

Dr. Marco Giampà

Thank you for your attention