Study of electronic effects in organometallic complexes using mass spectrometry and their application in medicinal chemistry

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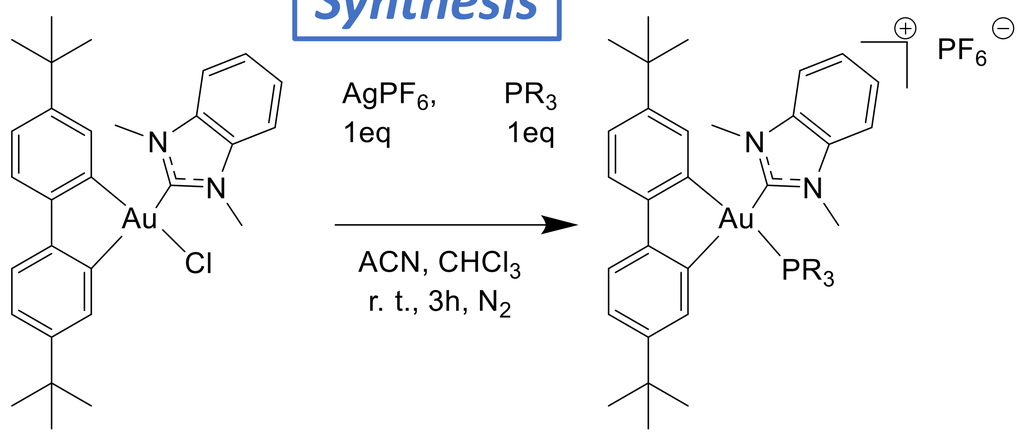
Introduction

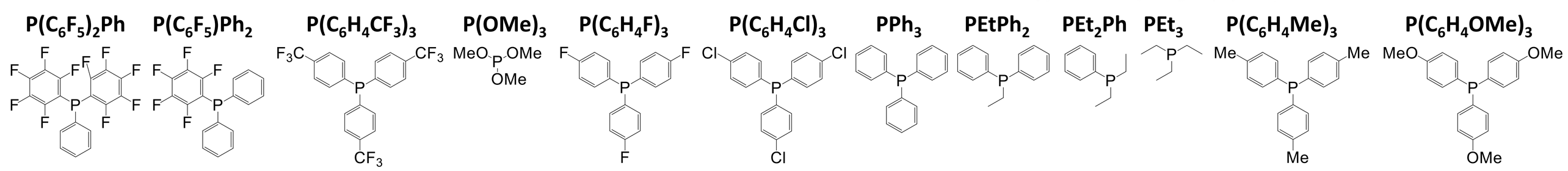
- Phosphino-Gold based complexes are of interest as potential anticancer agents [1,2].
- The understanding of the molecular mechanism of mode of action of the complexes is limited [3].
- To improve the efficacy of these complexes and understand their mechanism of action, we need to understand the effects of ligands.
- A large family of phosphine ligands with various electronic effects have been investigated.
- The electronic effects of the ligands were assessed by measuring the bond dissociation energy of the Metal ligand bond using mass spectrometry [4].

Synthesis

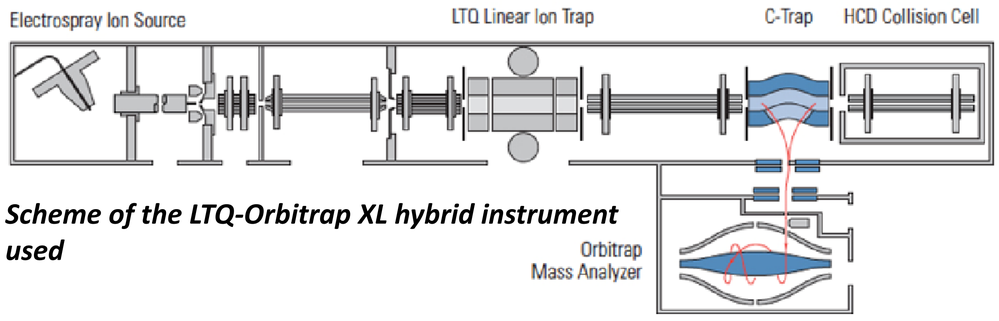


Reaction of formation of the gold(III) complexes

$P(C_6F_5)_2Ph$ $P(C_6F_5)Ph_2$ $P(C_6H_4CF_3)_3$ $P(OMe)_3$ $P(C_6H_4F)_3$ $P(C_6H_4Cl)_3$ PPh_3 $PEtPh_2$ PEt_2Ph PEt_3 $P(C_6H_4Me)_3$ $P(C_6H_4OMe)_3$



Structures of the various subsituents studied



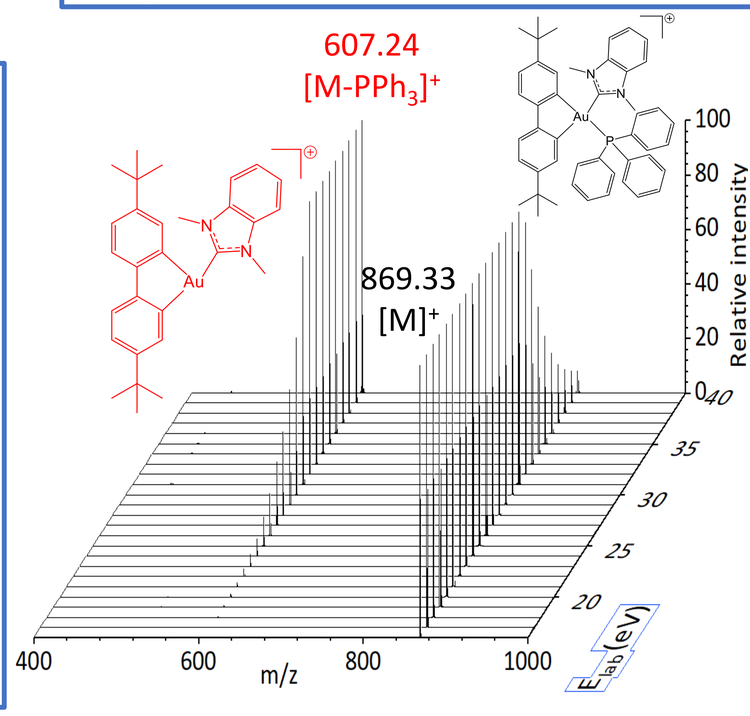
Scheme of the LTQ-Orbitrap XL hybrid instrument used

Experimental setup

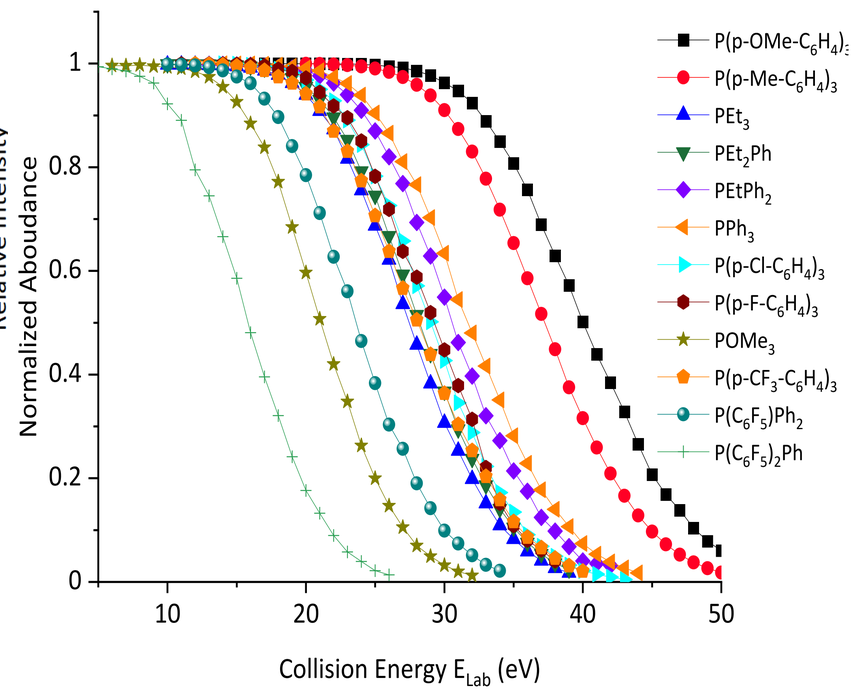
- Ions are formed by an electrospray source and analyzed in a LTQ-Orbitrap XL hybrid instrument (ThermoFisher Corporation, San Jose, USA).
- Precursor ions are isolated in the Linear Ion Trap and accelerated into a collision cell containing N_2 leading to the formation of fragments.

Kinetic modelling and theoretical calculations

- Determination of the Survival Yield (SY) of the precursor ion: $SY=\frac{I_{(P^+)}}{I_{(P^+)}+\sum I_{(F^+)}}$, $I_{(P^+)}$ the abundance of the precursor ion, $\sum I_{(F^+)}$ the sum of abundances of fragment ions.
- Kinetic treatment based on the RRKM theory [5] with the *MassKinetics* software [6] to obtain the difference between the dissociation barrier and that of the precursor ion (E_0).
- Theoretical values of Bond Dissociation Energys (BDEs) obtained using the Density Functional Theory M06/def2-TZVP with the GAUSSIAN 16 software) [7].

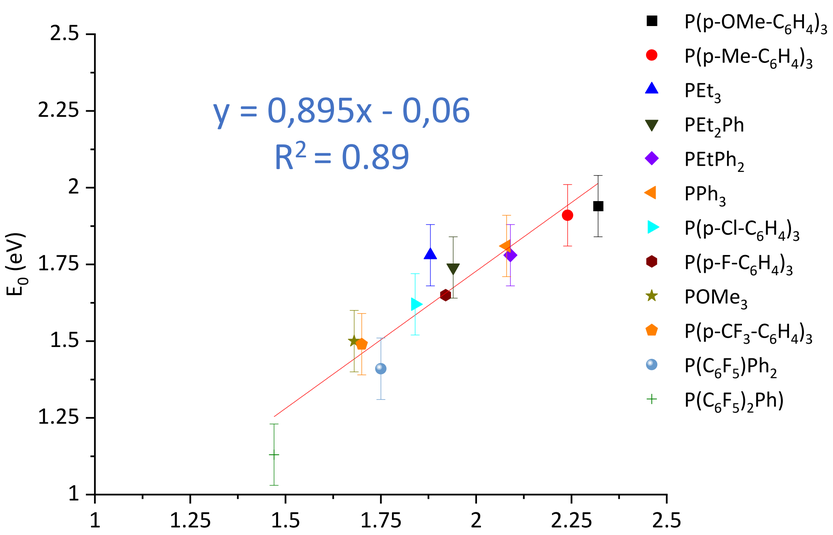


HCD fragmentation spectrum of [(C^ C)Au (NHC)(PPH$_3$)]$^+$



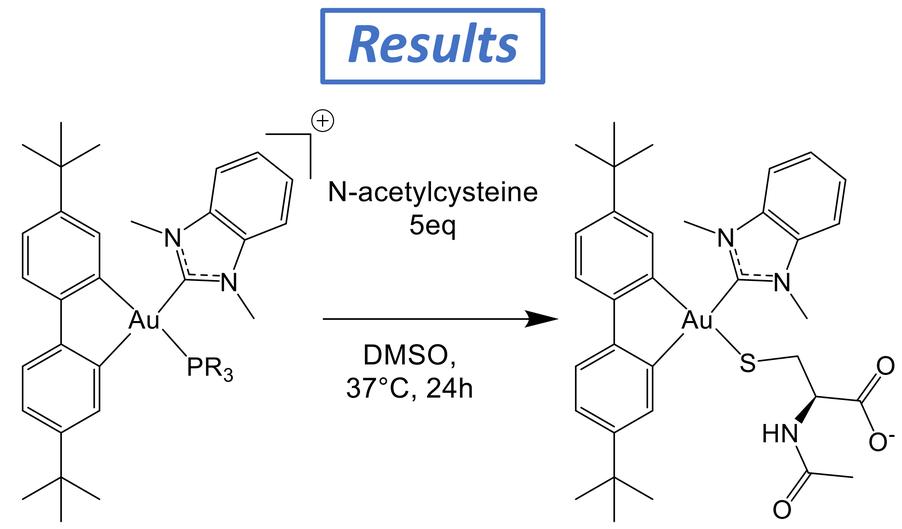
Survival yield of the complexes as a function of the collision energy

Results

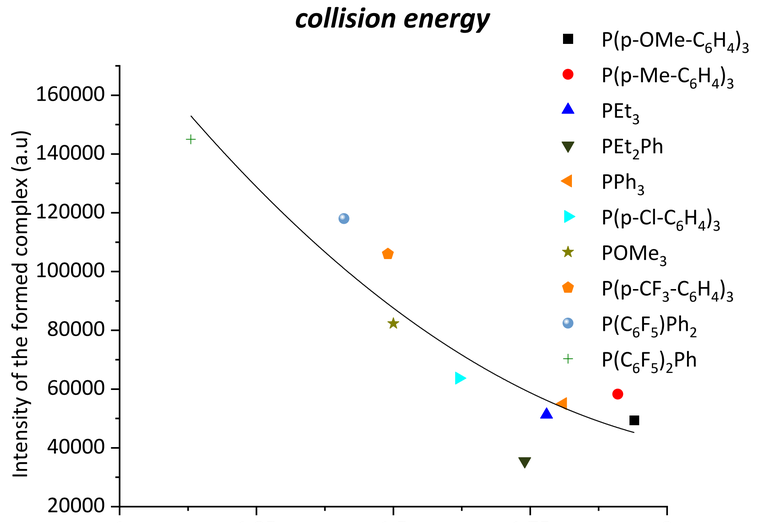


BDE (eV)

Experimental measurements E_0 (eV) versus calculated BDEs (eV)

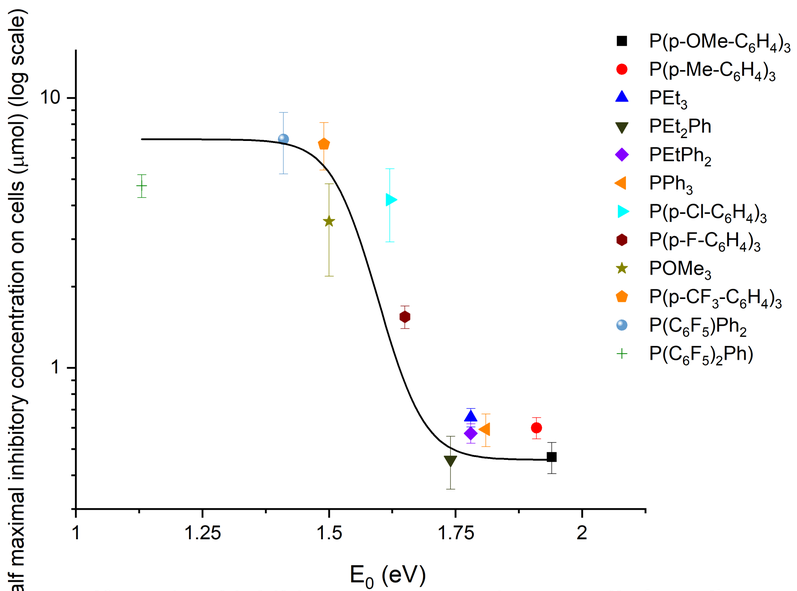


Incubation protocol to test the reactivity of the complex toward N-acetylcysteine



E$_0$ (eV)

Intensity of the complex formed with N-acetylcysteine versus Experimental measurements E_0 (eV)



Half maximal inhibitory concentration on cells (μmol) versus Experimental measurements E_0 (eV)

Conclusion and Perspectives

- A series of 12 $[(C^C)Au(NHC)(PR_3)]^+$ complexes were synthetised, isolated and characterized.
- Experimental and theoretical values of bond dissociation energies of the M-L bond were obtained and correlated well. They confirm the expected trends of the ligand donating effects : the richest phosphines are able to donate more to the metal and thus render the Au-L bond stronger.
- There is a correlation between complex stability and median inhibitory concentration.
- The Reactivity of a complex is not necessarily linked to its toxicity.
- Develop a quantitative method for measuring reactivity by mass spectrometry.
- Measure lipophilicity and cellular uptake of complexes.

References: ***1***-Kim, J. H.; Reeder, E.; Parkin, S.; Awuah, S. G., *Sci. Rep,* **2019**. *9* (1)**,2-** Srinivasa Reddy, T.; Privér, S. H.; Rao, V. V.; Mirzadeh, N.; Bhargava, S. K., *Dalton Trans.,* **2018**, *47* (43), 15312–15323, **3-**Yeo, C.; Ooi, K.; Tiekink, E., *Molecules,* **2018**, *23* (6), 1410.**, 4-**Bourehil, L., et al., *Inorg. Chem.,* **2023.** *62* (33), 13304-13314**, 5-**Marcus, R.A., *J. Chem. Phys.*, **1952**. 20(3): p. 359-364, **6**-*Drahos,L. and K. Vékey R.A. ,JMS.,* **2001**. *36(3): p. 237-263,* **7-** Frisch, M.J., et al., *Gaussian 16 Rev. C.01*, **2016.**