PRO AGRO LECTORIUM

Coordination Chemistry: Green Synthesis and Applications

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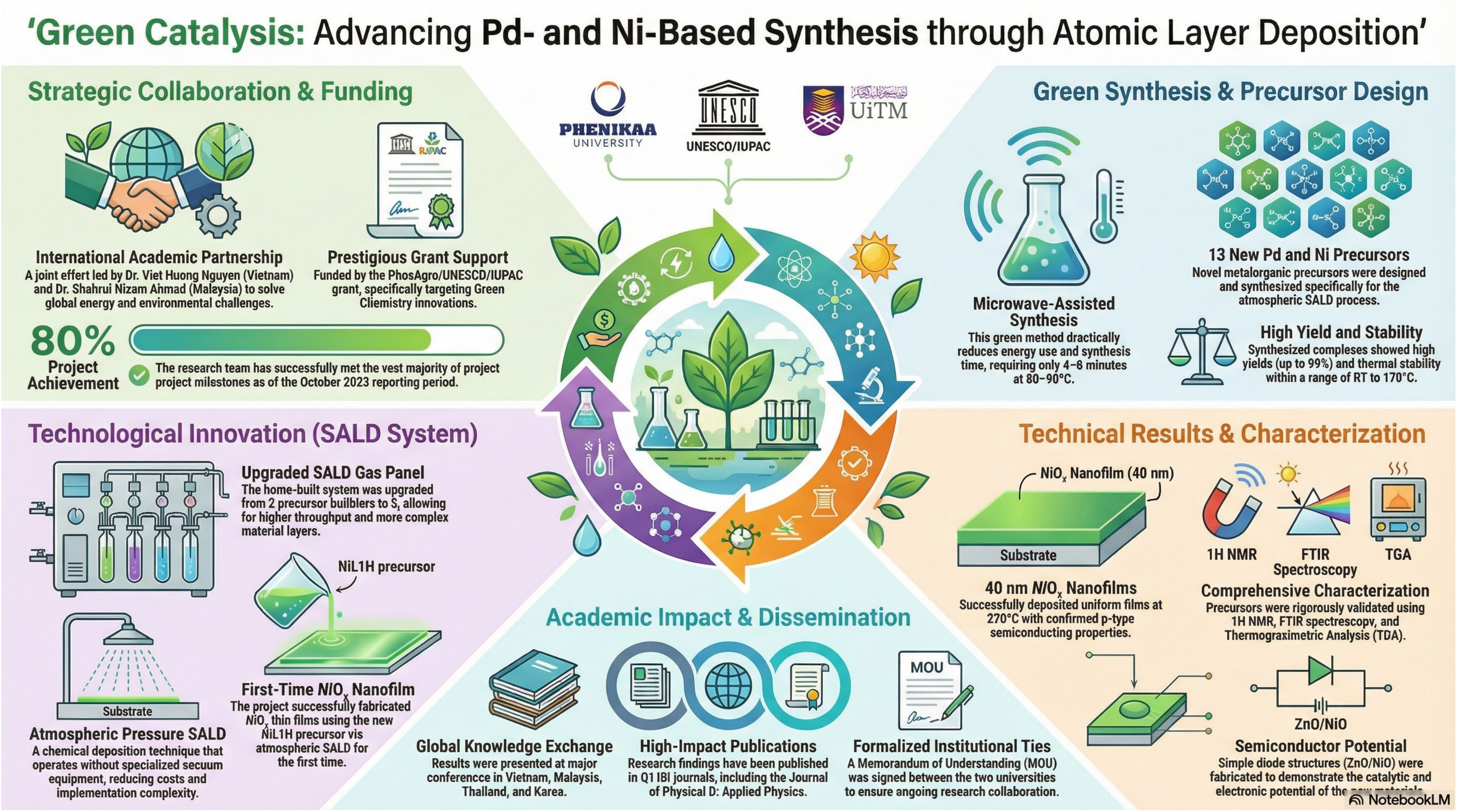
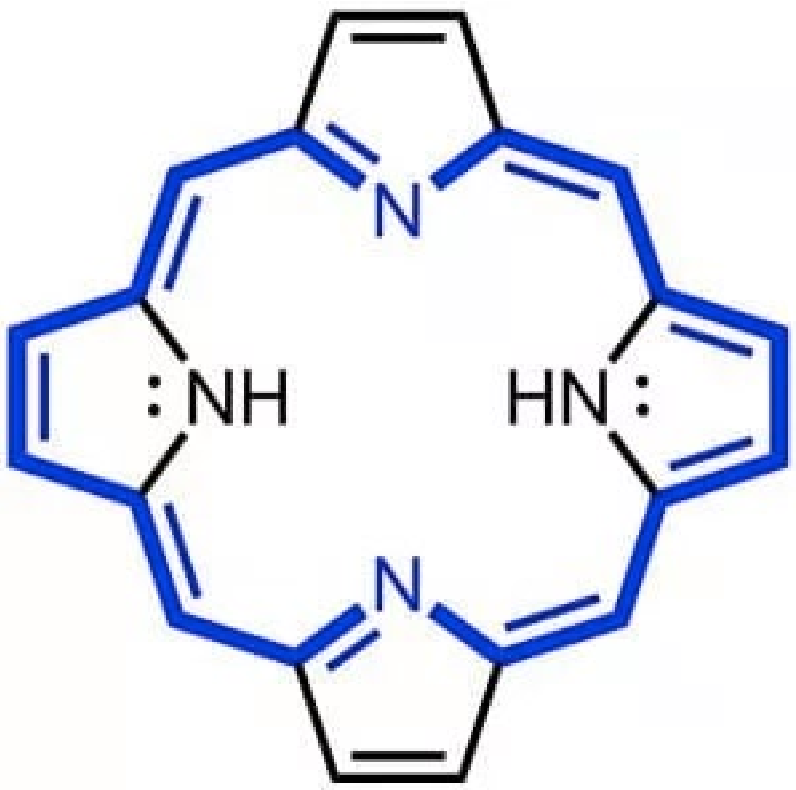
Overview of IUPAC/UNESCO/PhosAgro Green Chemistry Grant



Metal Complexes

- Metal complexes- a combination between organic ligands and metal salts
- Example
  - Porphyrin ligand- the ring-shaped porphyrin molecules bind an array of metal ions, with each combination associated with different biological functions



Porphyrin

- Chlorophylls bind **magnesium** to play a pivotal role in photosynthesis.
- Heme binds **iron** to coordinate molecular oxygen and carbon-dioxide transport, supports the electron-transport chains necessary for cellular respiration and contributes to the catalytic activities of many enzymes

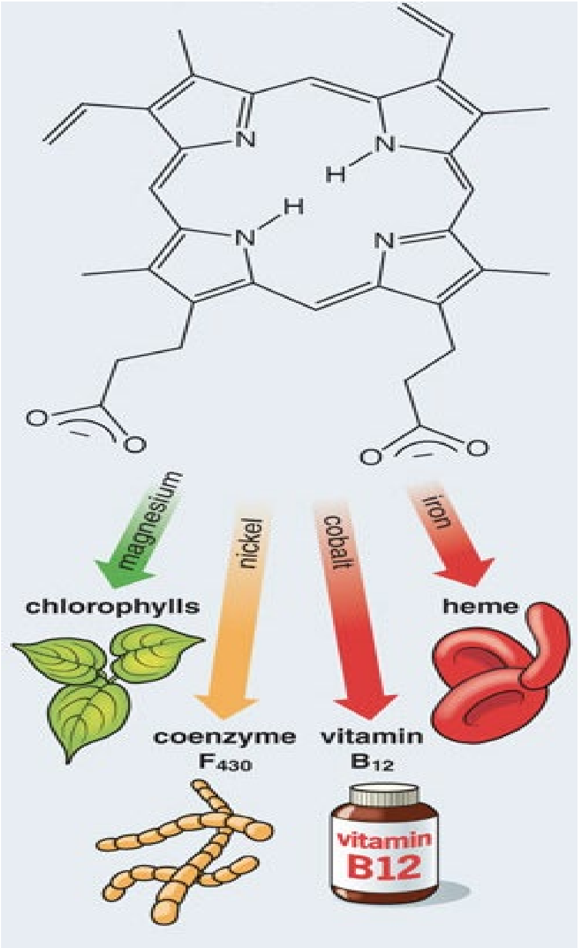
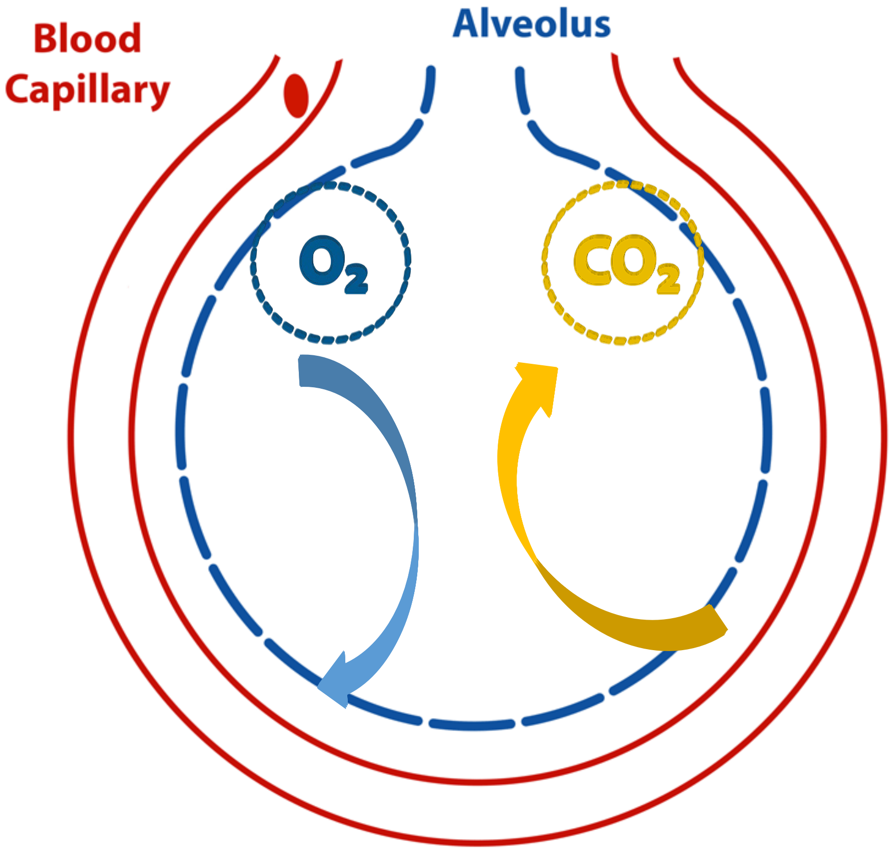


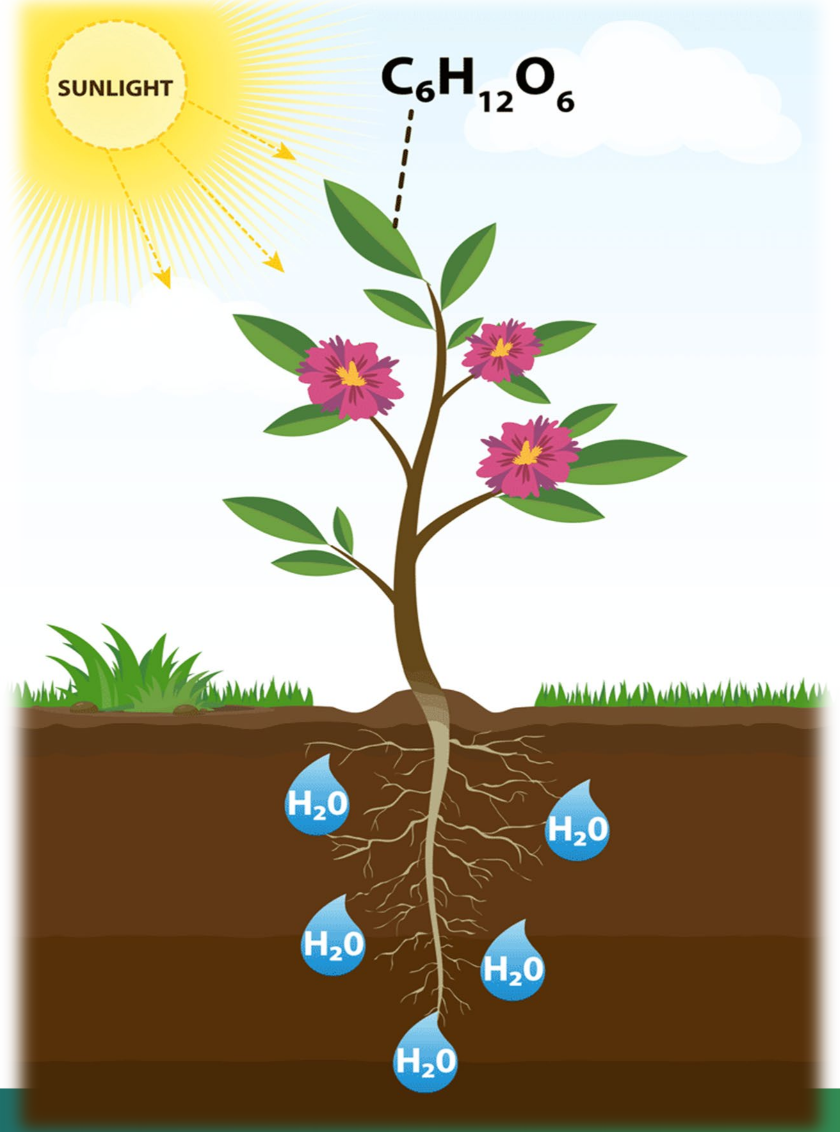
Image courtesy from: American Scientist

Respiration and Photosynthesis



Hemoglobin

Exchange of O_2 and CO_2 gases in almost all vertebrates



Chlorophyll

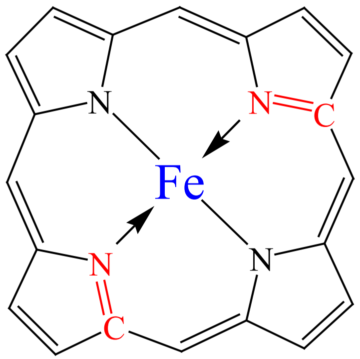
Making $C_6H_{12}O_6$ (glucose) and O_2

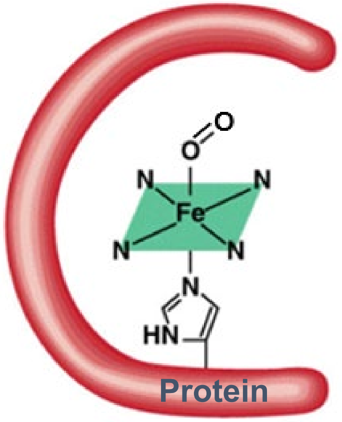
from CO_2 and H_2O

in the presence of sunlight

Respiration and Photosynthesis

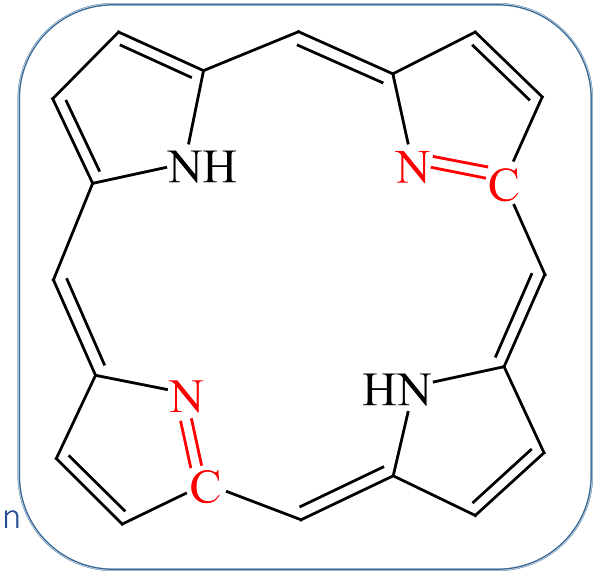
Hemoglobin





Oxyhemoglobin

- Formed when the C=N groups and N of the pyrrole in porhyrin bond with an Fe metal centre
- The fifth coordination position binds with histidine to anchor the heme onto protein
- The sixth coordination position on Fe centre is used to bind O2 – oxyhemoglobin (red)
- CO_2 is bound to the protein chains of the structure – carbaminohemoglobin (bluish red)
- Thus hemoglobin acts as a gas transportation in almost all vertebrates



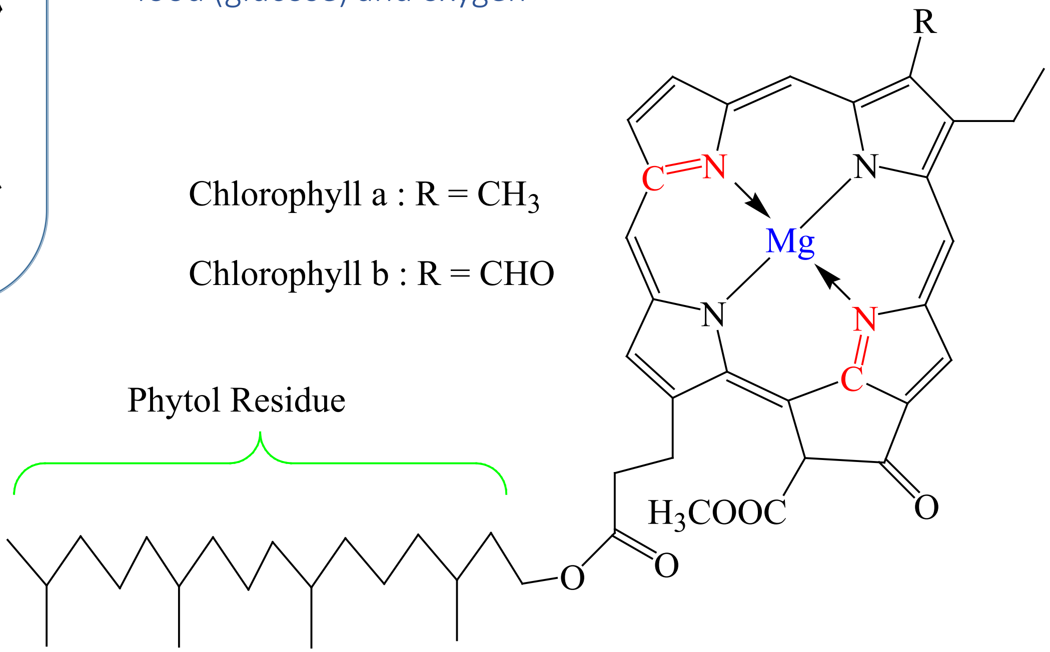
Porphyrin

A Naturally Occurring Imine

Macrocyclic

Chlorophyll

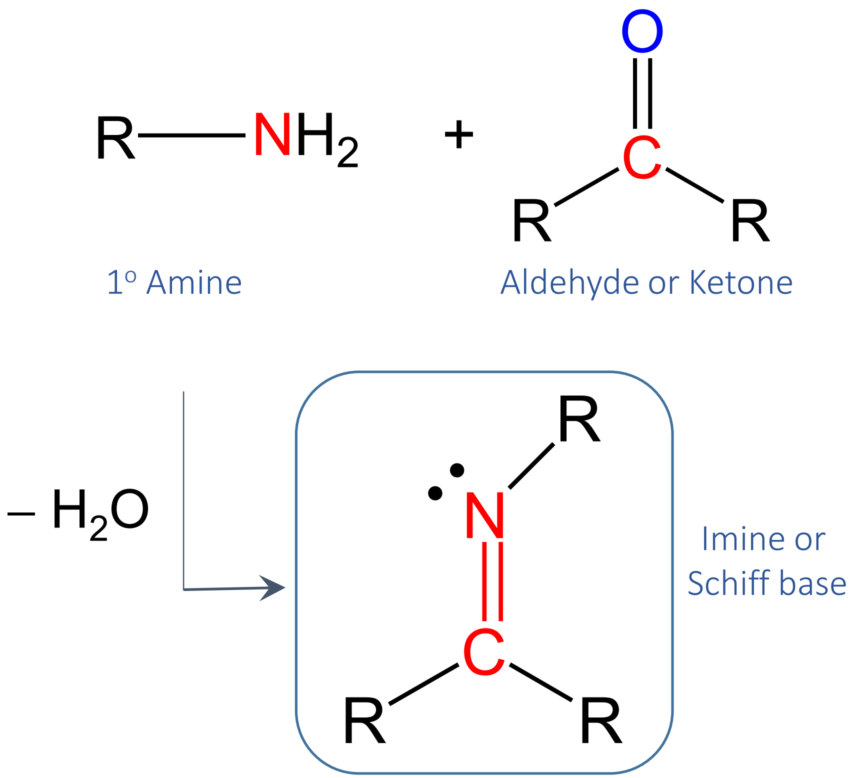
- Formed when the C=N groups and N of the pyrrole in porhyrin bond with a Mg metal centre
- The long phytol residue traps light energy
- Chlorophyl is capable of channeling light energy into chemical energy to convert carbon dioxide and water into food (glucose) and oxygen



Metal Complexes

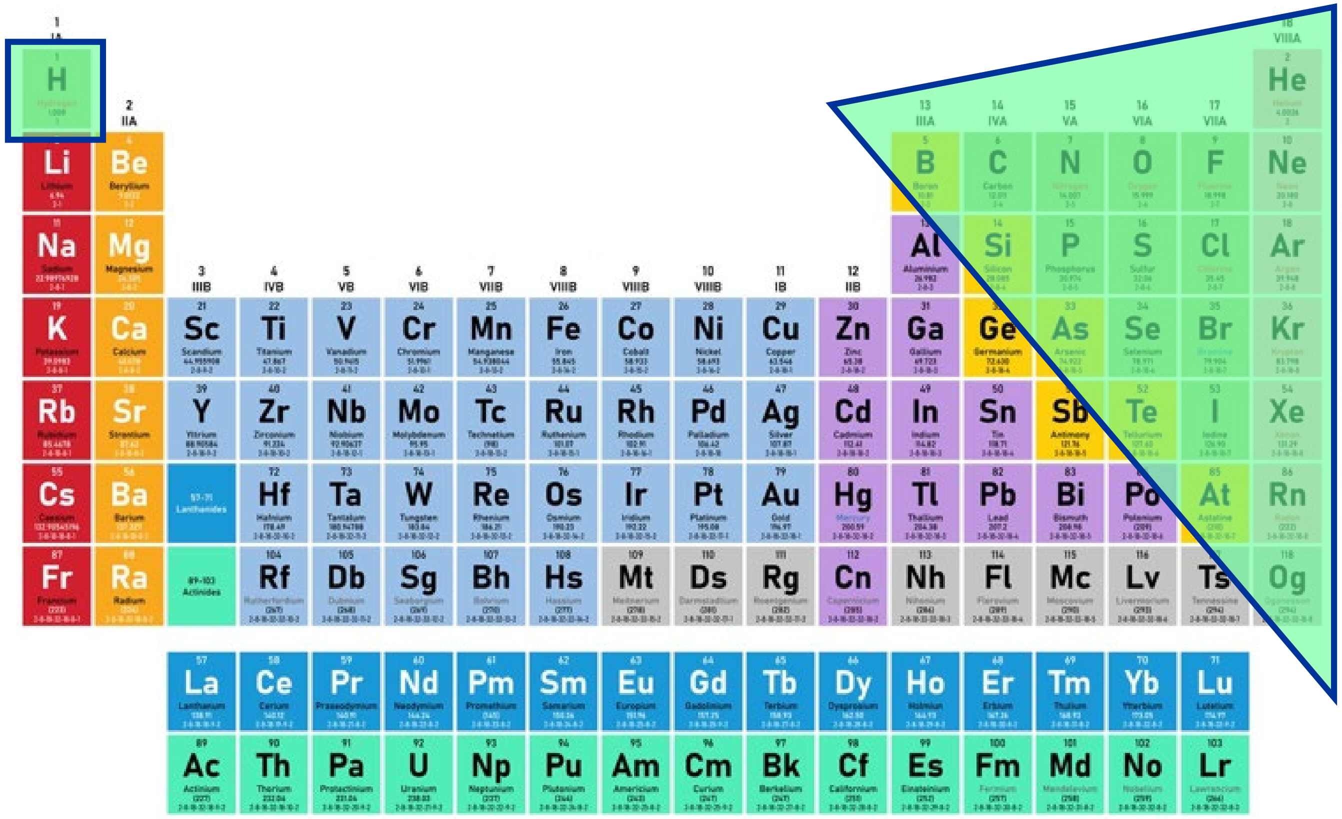
Schiff Bases/Imine

Compounds containing C=N functional group(s), produced when primary amines (-NH_2) undergo condensation with active carbonyls (-C=O)

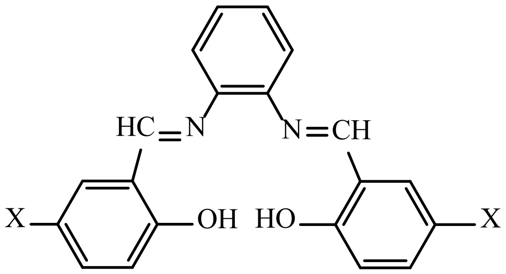


Metals

All elements in the Periodic Table except H and those located on the top right, above the purple coloured boxes

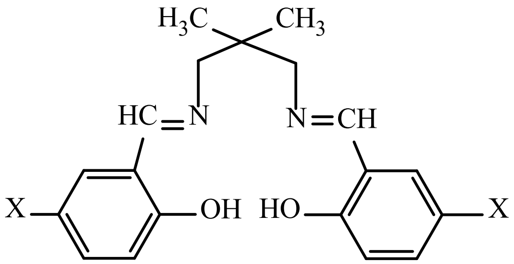


Schiff Bases



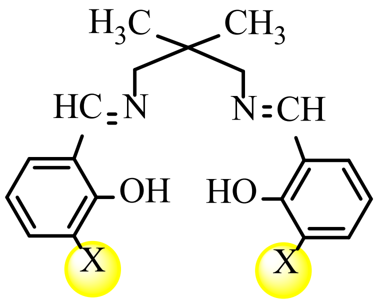
X=H, F, Cl, CH_3, OCH_3, NO_2

L1 Series



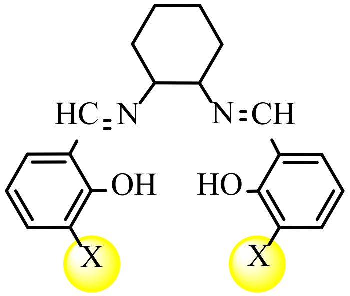
X=H, F, Cl, CH_3, OCH_3, NO_2

L2 Series



X= H, F, Cl, CH_3, OCH_3

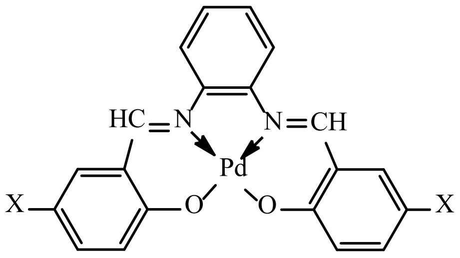
AD1 Series



X = H, F, Cl, CH_3, OCH_3

AD2 Series

Schiff Base Metal Complexes



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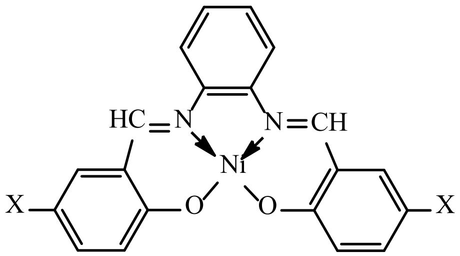

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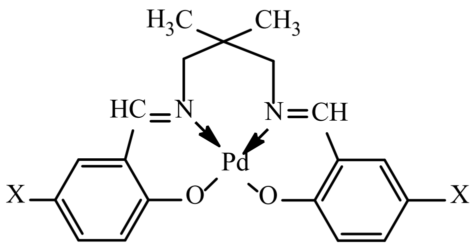
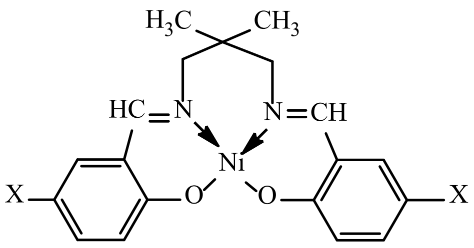
L1 Metal Complexes

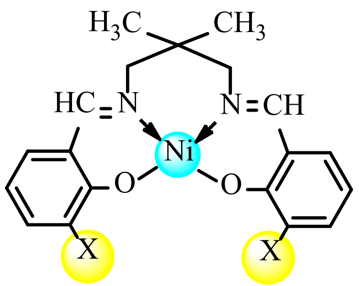


X=H, F, Cl, CH_3, OCH_3, NO_2

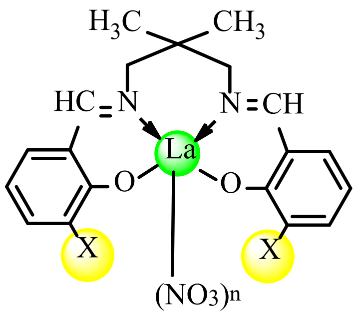


X= NO_2

L2 Metal Complexes

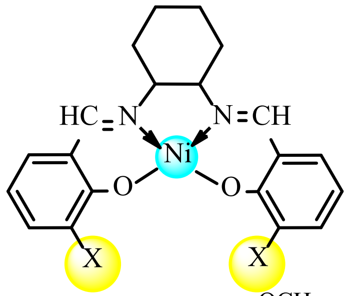


X= H, F, Cl, CH_3, OCH_3

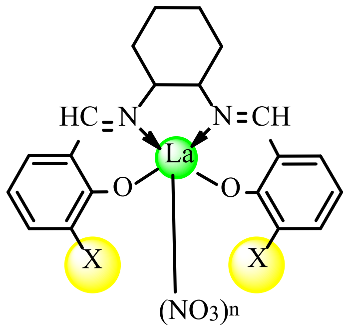


X= H, F, CH_3, OCH_3

AD1 Metal Complexes



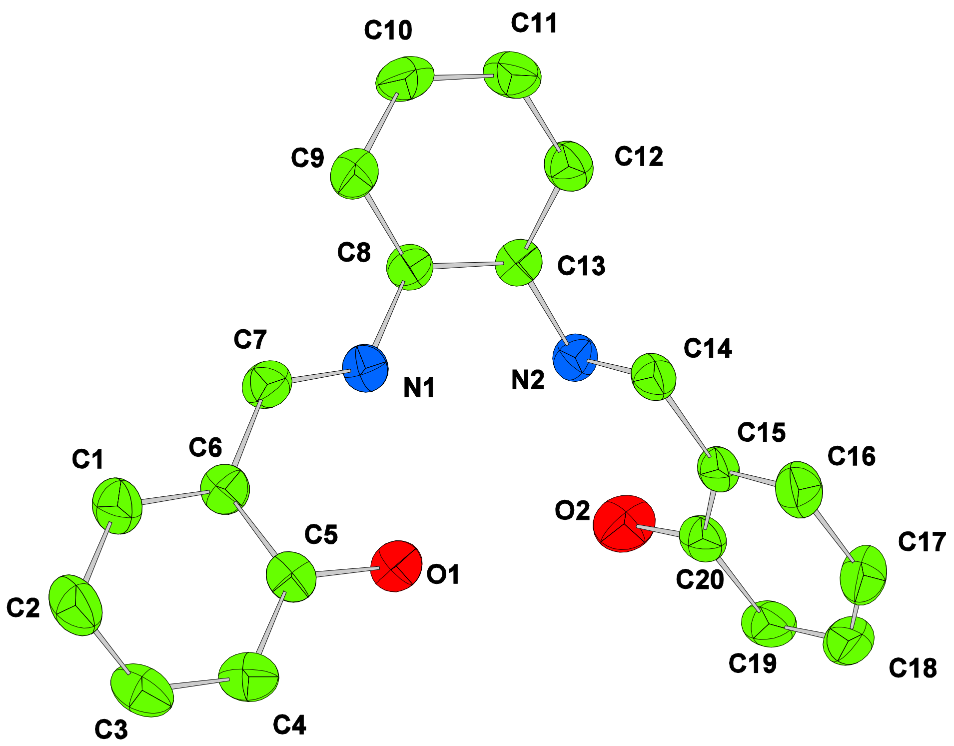
X = H, F, Cl, CH_3, OCH_3

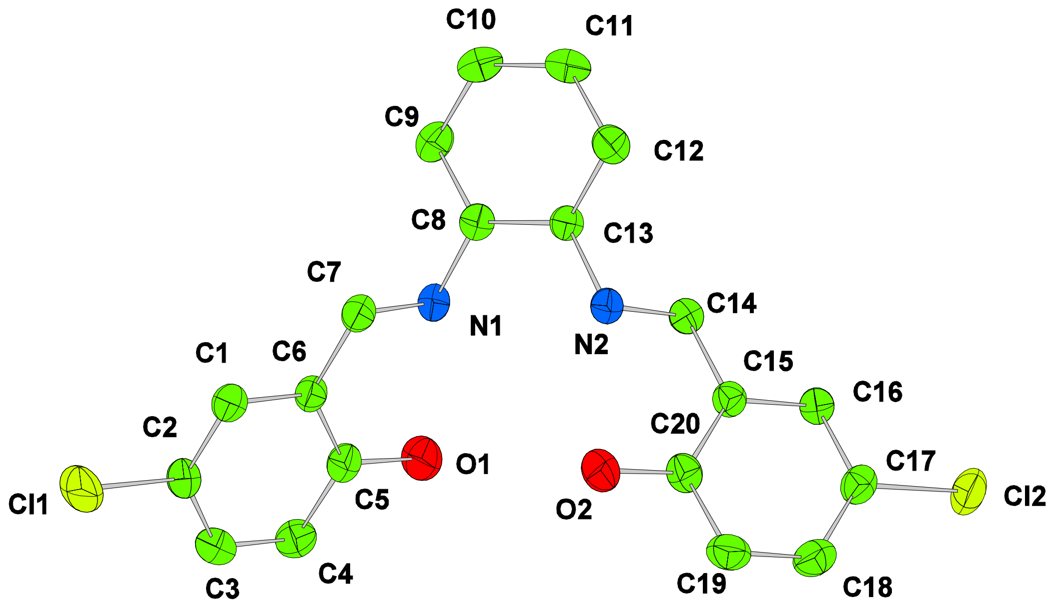


X = H, F, Cl, OCH_3

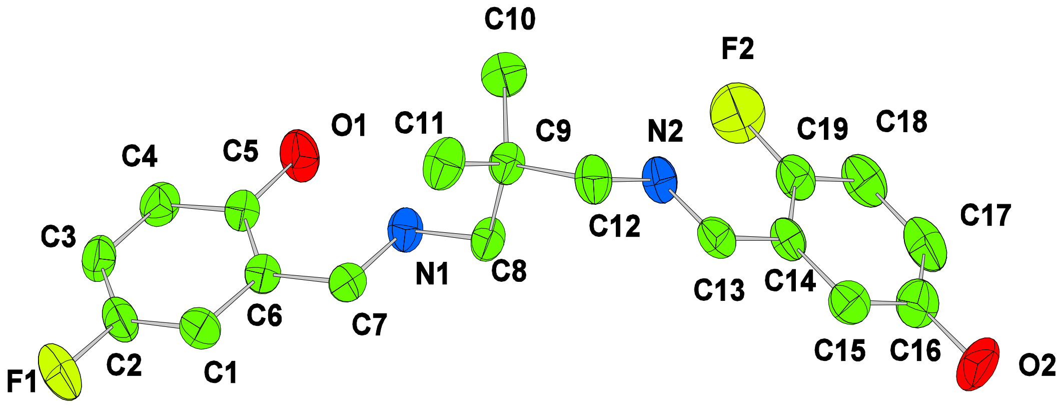
AD2 Metal Complexes

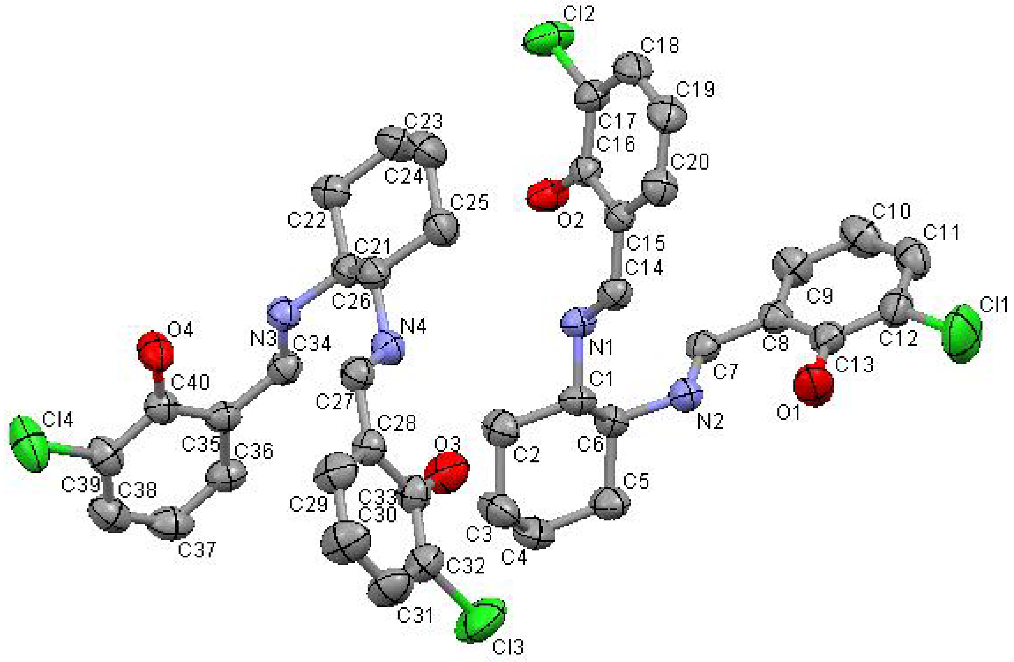
Crystal Structures of Schiff Base Ligands



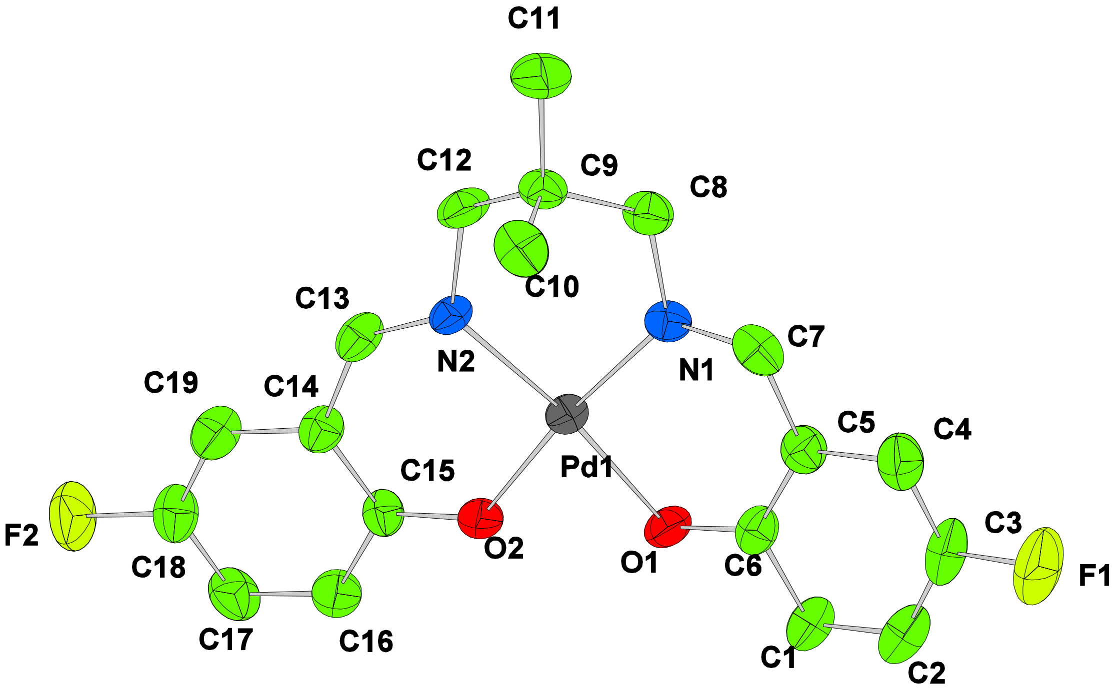


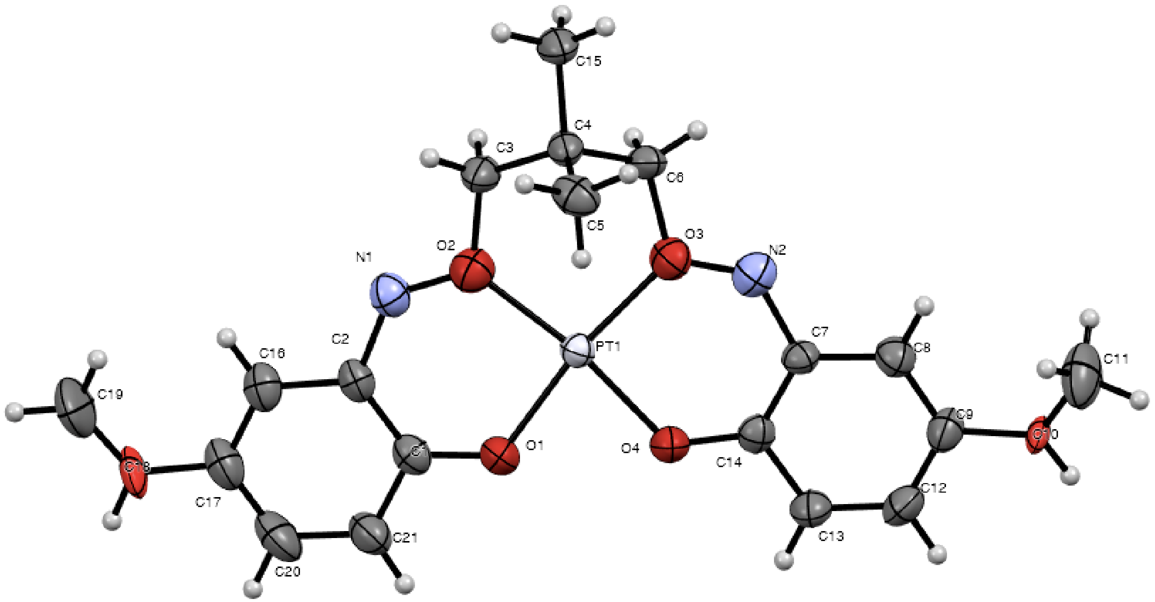
Crystal Structures of Schiff Base Ligands



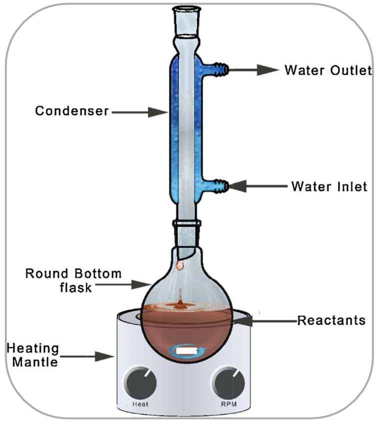


Crystal Structures of Schiff Base Complexes





Conventional vs Microwave-Assisted Synthesis



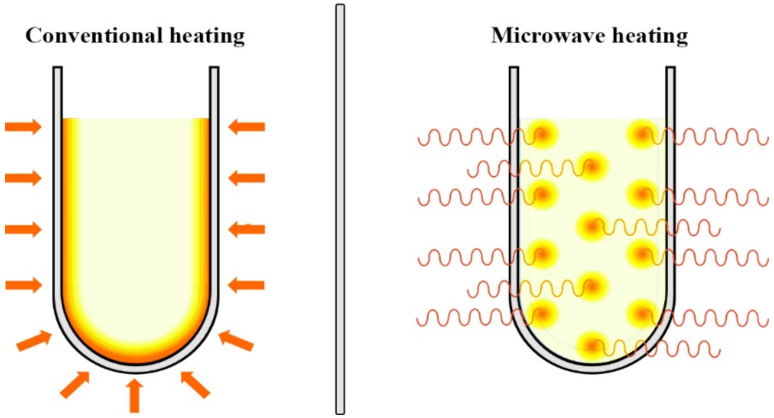


Illustration of heat introduction into reaction mixture in conventional heating and microwave heating (wiki.anton-paar.com)

	Conventional Method (CM)	Microwave-assisted Method (MM)
Reaction time (min)	1440 minutes (24 hours)	10 minutes (0.7 % of CM)
Solvent used (mL)	30 mL	10 mL (30 % of CM)
Product yield (%)	34.7 %	64.5 % (1.85 times greater than CM)
Electricity usage	43200 kJ	212.4kJ (0.49 % of CM)
Water usage	Running water for chilling of reflux condenser for 24 hours	No water used

Comparative analysis conventional reflux and microwave-assisted syntheses for Zn4(L1)2 tetranuclear complex (Khaidir et al., 2020)

Green chemistry and ecofriendly conditions

Simple operational procedure

Short reaction time

High percentage yield

Green Synthesis

Green Chemistry

- The design, development and implementation of chemical products and processes that reduce or eliminate the use and generation of hazardous substances

Atom Economy

- Synthetic methods should be designed to maximize incorporation of all materials used in the process into the final product.
- % Atom Economy = (FW of atoms desired/FW of all reactants) X 100
- Some atoms used , some atoms wasted!
- 2nd Principle of Green Chemistry

Characterization

Physicochemical Properties

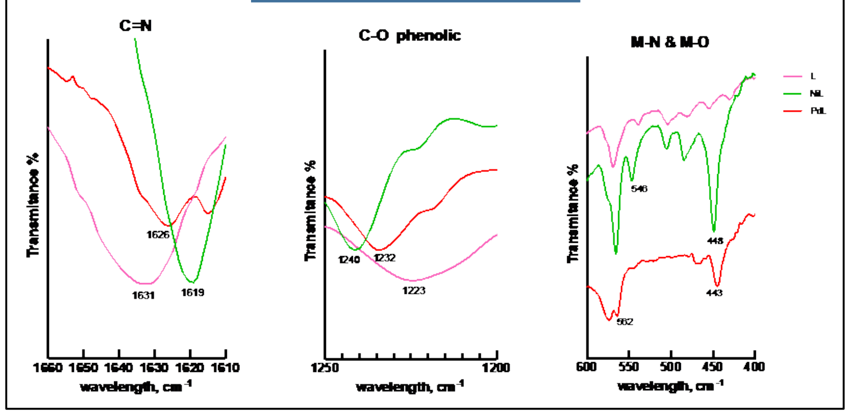
Ligand

Molecular formula: $C_{17}H_{18}N_2O_4$
Molecular weight: 314.34
Yield (%): 99.10
Melting Point (°C): 165-169
Elemental Percentages **Found** (Calculated):
64.28(64.96), 5.83(5.77) , 7.64(8.91)

Pd(II) mononuclear complexes

Molecular formula: $C_{17}H_{18}N_2NiO_4(H_2O)$
Molecular weight: 495.80
Yield (%): 88.74
Melting Point (°C): 355-357
Elemental Percentages **Found** (Calculated):
46.83(46.75) , 3.86(4.15) , 4.79(6.45)

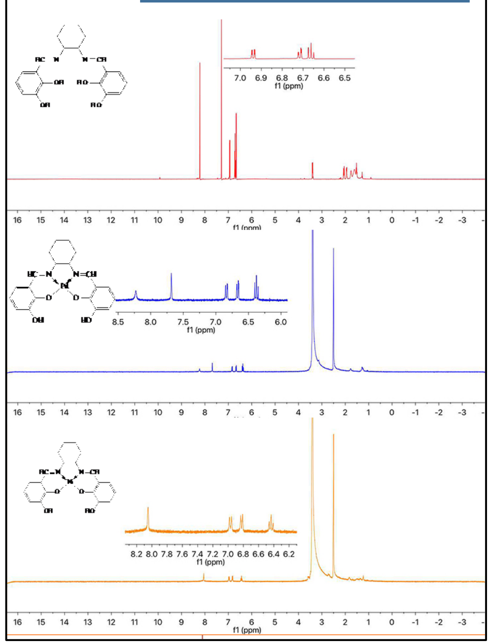
IR Spectroscopy



Observation:

- Shifting of C=N, C-O phenolic, C-O methoxy peak to lower frequencies
- Appearance of new M-N and M-O peak
  - Indicating that the metal centres coordinated to the ligands through azomethine N, and phenolic O.
  - Lowering of bond order of the C=N and C-O bonds due to sharing of lone pair of electrons of N and O donor atoms with metal centre
  - Supported by appearance of M-N and M-O new peaks in complexes

^1H NMR Spectroscopy

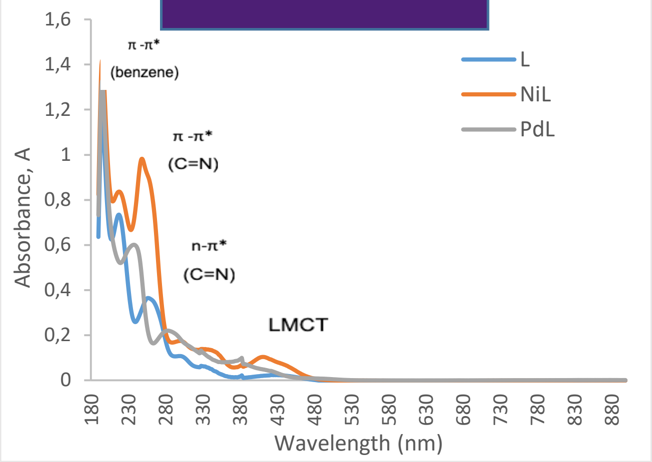


Upon complexation:

- The phenolic proton signal disappeared, indicating that the phenolic O bonded to metal center upon deprotonation of –OH
- The azomethine proton peak shifted to upfield region, inferring shielding by the metal centre bonded to the azomethine N

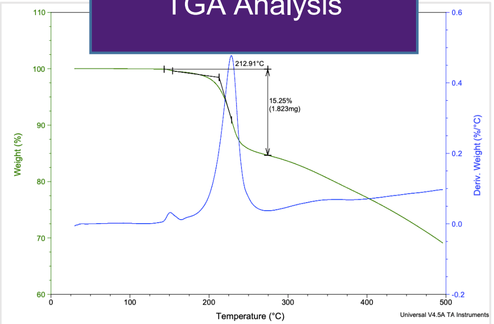
Characterization

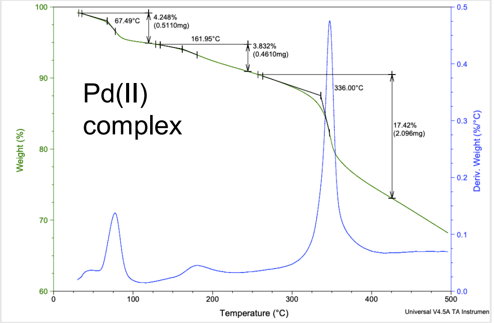
UV-Vis Spectroscopy



- Upon complexation:
  - The complexes showed a bathrochromic shifting (red shift to higher wavelength) for both the π–π* transition bands
  - Inductive effect of the donation of lone pair of electrons on the imine N caused lowering of electron density on the C=N bond, making it weaker
- The LMCT peaks arise due to the charge transfer from the HOMO of the ligand to the *d*-orbitals of metals

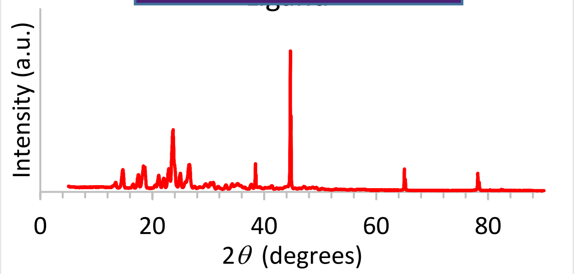
TGA Analysis

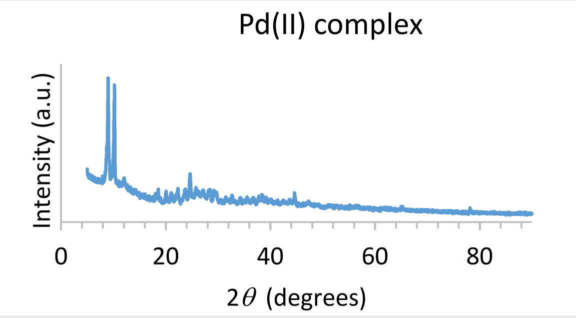




- The thermograph of the ligands reveals that there is no decomposition observed at temperatures below 200 ºC. This suggests that the absence of water molecules is evident in the structure
- The data analysis reveals that the metal complexes underwent a multi-stage decomposition process.
- The initial phase of gradual weight loss can be ascribed to the decomposition of lattice water molecules.

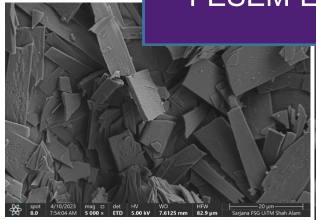
Powder XRD

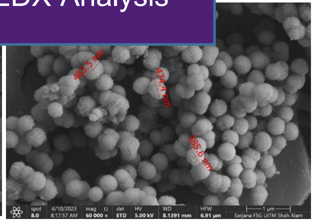


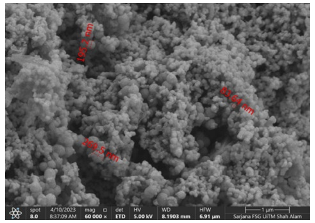


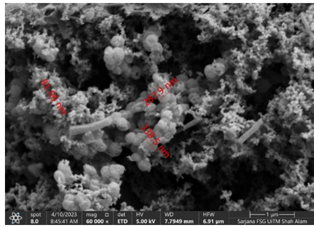
- The diffractograms of the ligand display a sharp and strong crystalline peaks, indicating their crystalline properties
- The complexes shows a low peak intensity
- The observed emergence and disappearance of peaks in the complexes suggest the coordination of ligand-metal ion upon complexation.

FESEM-EDX Analysis


Ligand


Mononuclear Pd(II) complex


Dinuclear Pd(II) complex


Tetranuclear Pd(II) complex

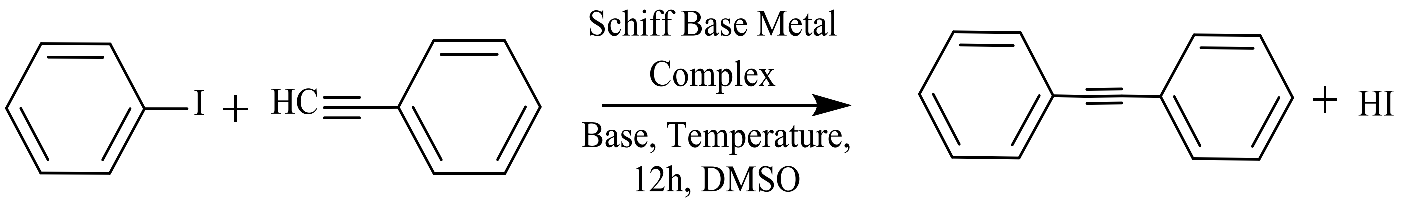
Element	Atom[%]			
	Ligand	Mono Pd(II)	Di (Pd(II)	Tetra Pd(II)
Carbon	72.36	72.36	44.89	16.93
Oxygen	18.94	18.94	27.19	10.55
Nitrogen	8.70	7.38	6.94	2.70
Palladium	-	17.85	20.97	69.82
	100.00	100.00	100.00	100.00

Ligand
Shape: blocked irregular shape
Average particle size: <20 µm

Pd(II) complexes
Size: spherical morphology with a smooth surface
Average particle size: 81.06 – 483.5 nm

Catalytic Activities of Schiff Base Complexes in Sonogashira Reaction

- Screening
- Optimization reaction condition
- Catalytic studies at optimum condition
- Isolation of coupling product



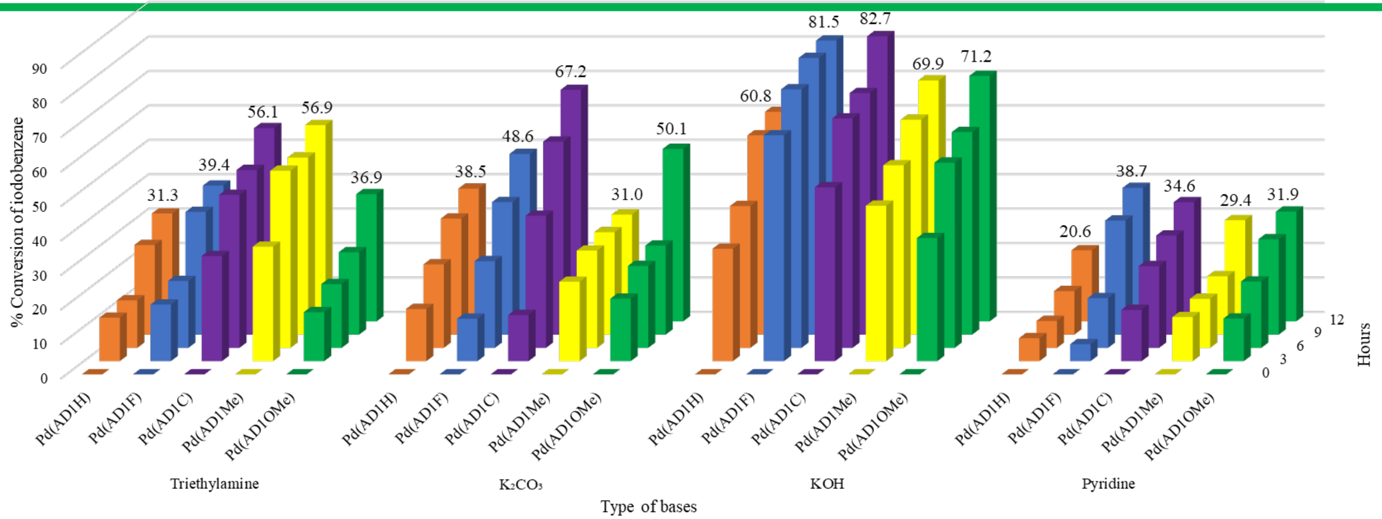
1.0 mmol iodobenzene

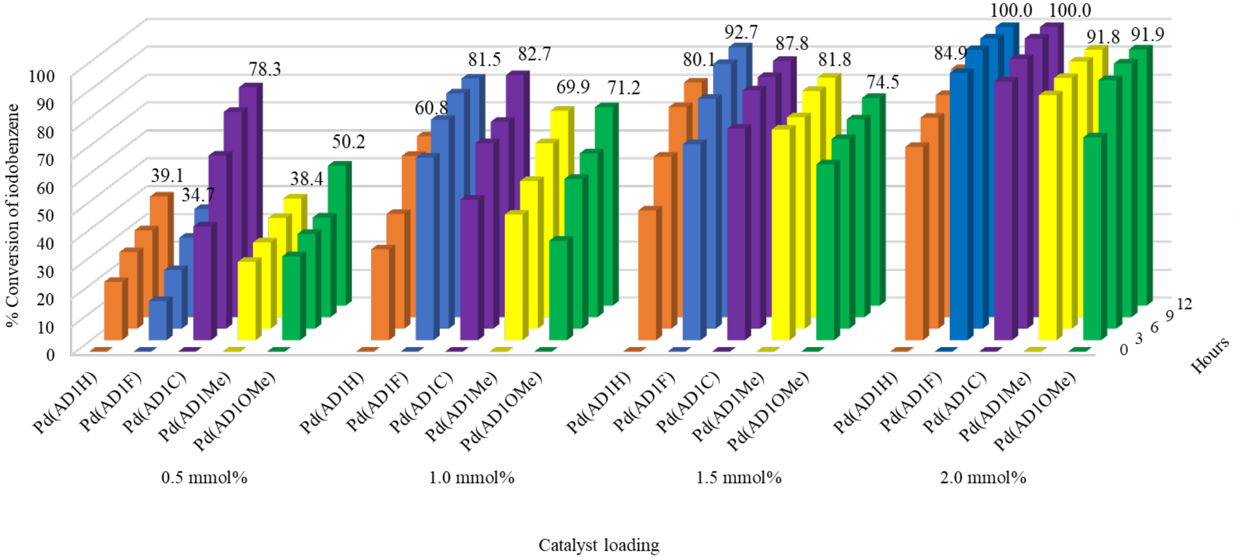
1.5 mmol phenylacetylene

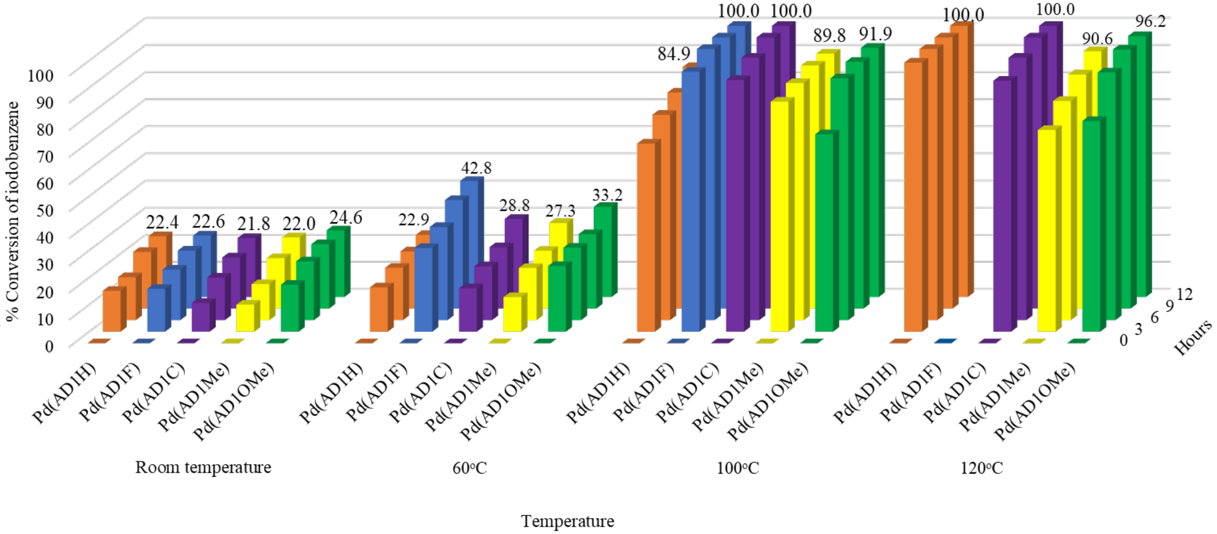
Diphenylacetylene

Catalytic Activities of Schiff Base Complexes in Sonogashira Reaction

- Type of bases
- Catalyst loading
- Temperature

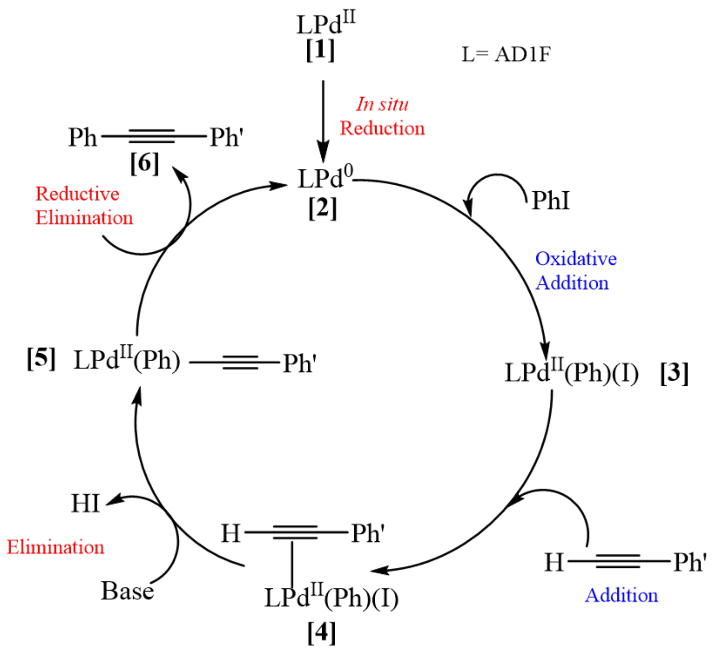


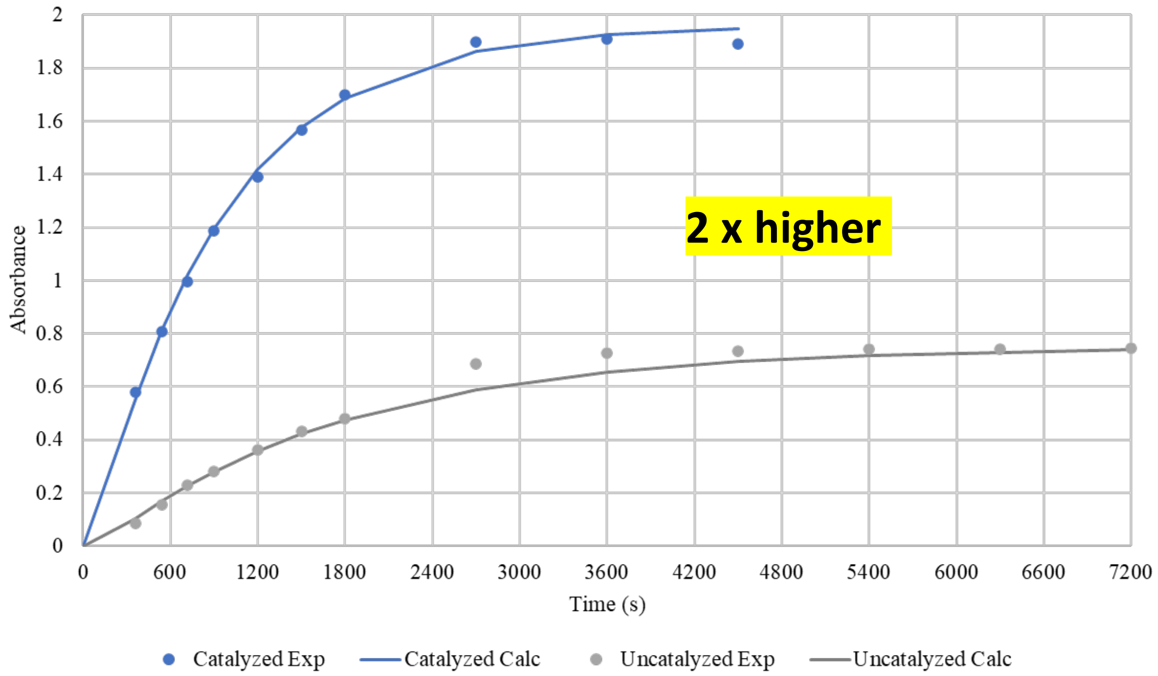




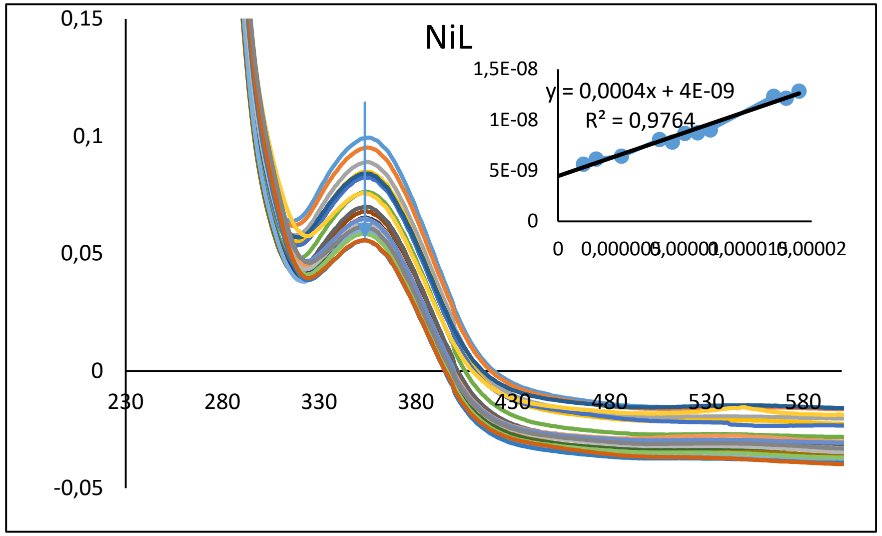
Kinetic properties of Sonogashira reaction

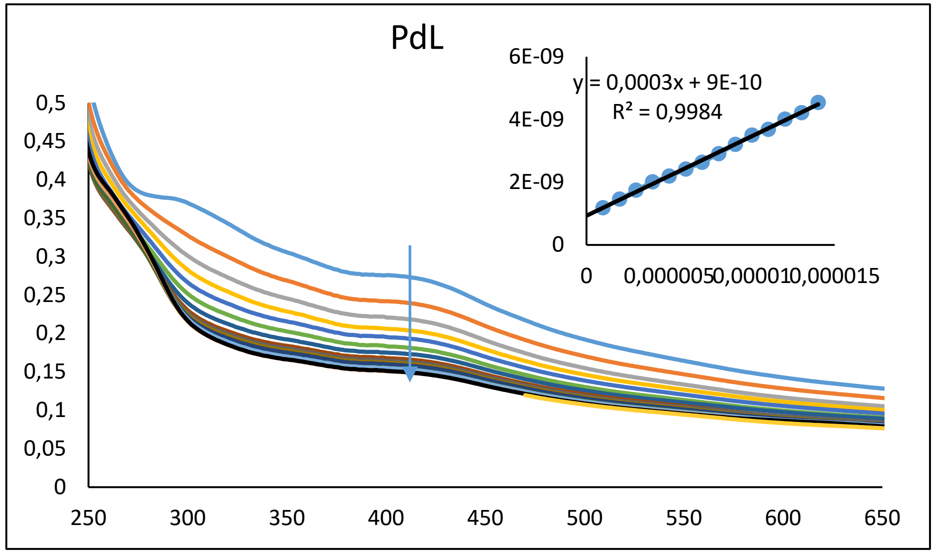
Proposed mechanism of catalyzed copper-free Sonogashira reaction

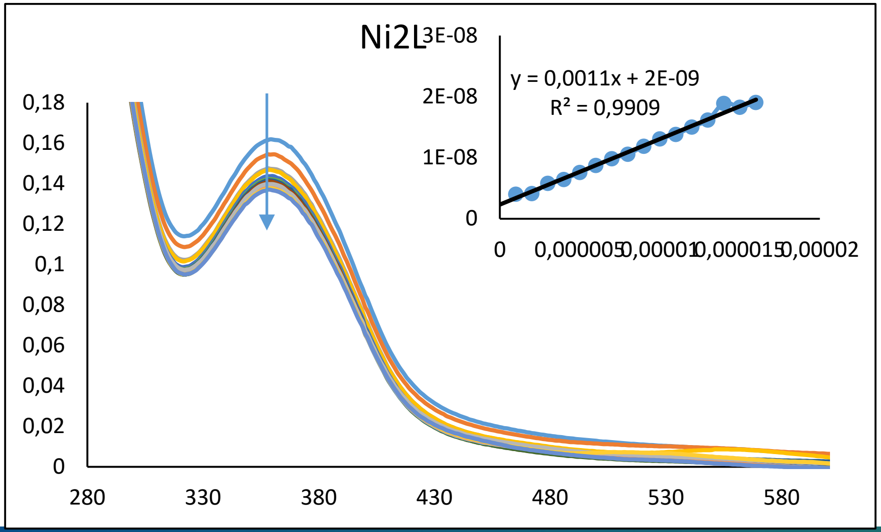


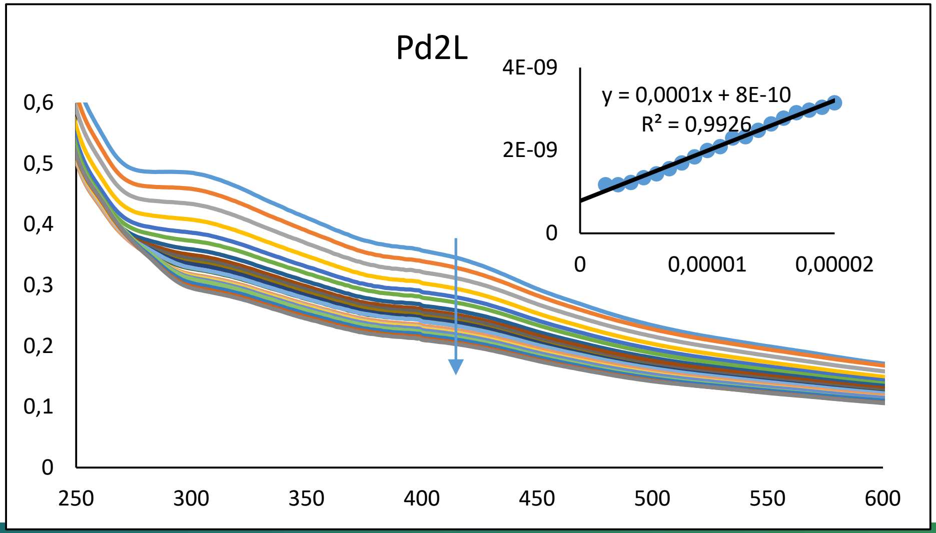


DNA Binding Studies Using Schiff Base Ligands and Complexes



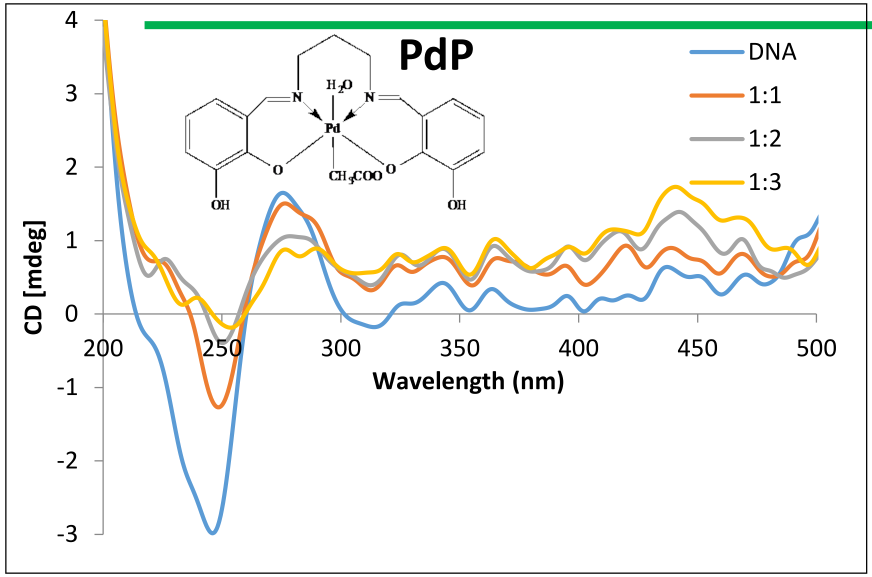


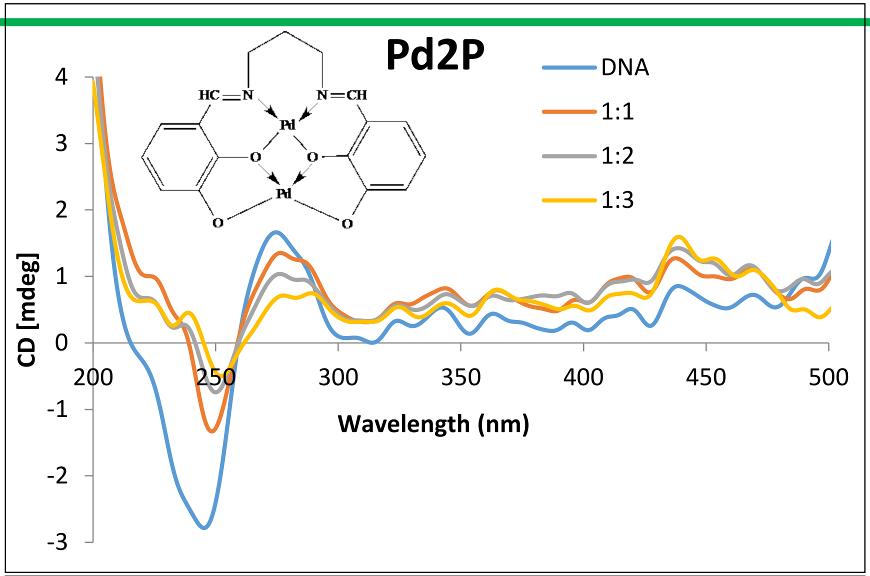


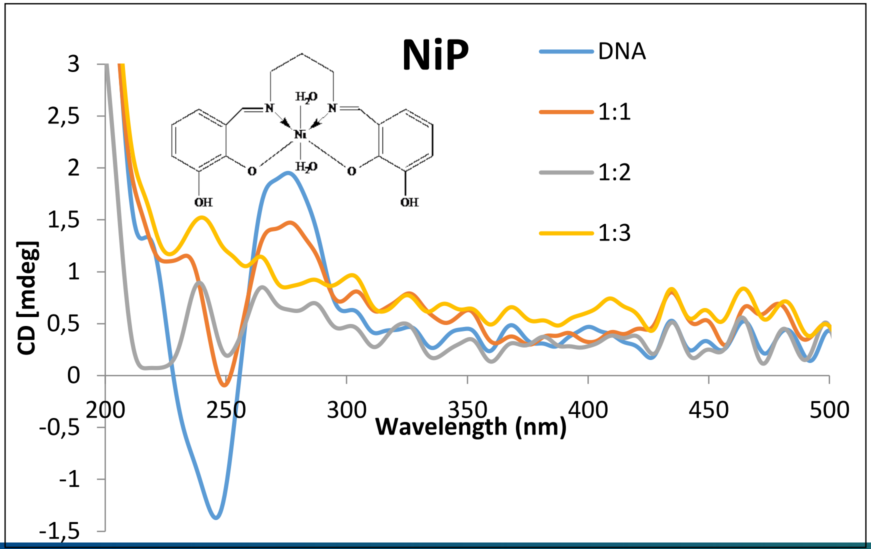


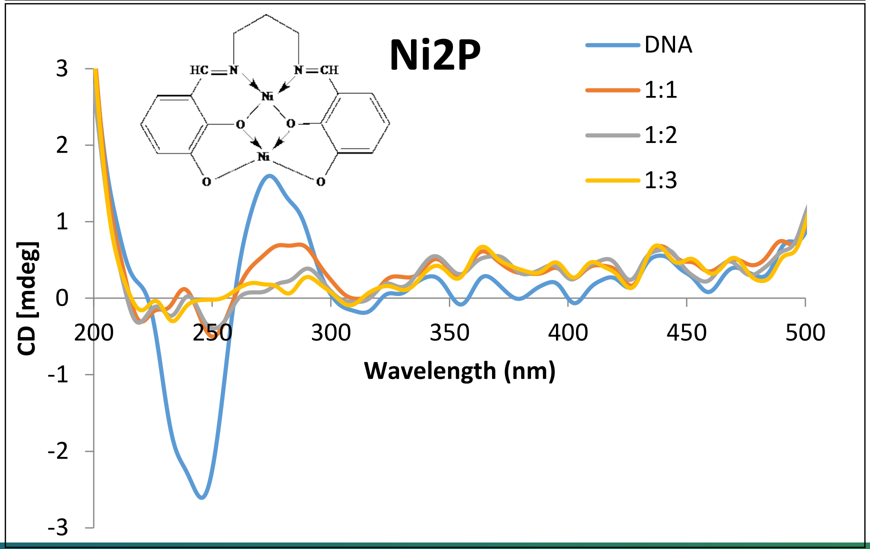
- Hypochromism observed at 361 and 417nm likely due to the compound bind to the DNA helix via intercalation.
- The DNA binding study with ct-DNA revealed that the nickel(II) dinuclear complexes shows the highest binding constant of 1.57×10^6

DNA Binding Studies (Circular Dichroism)









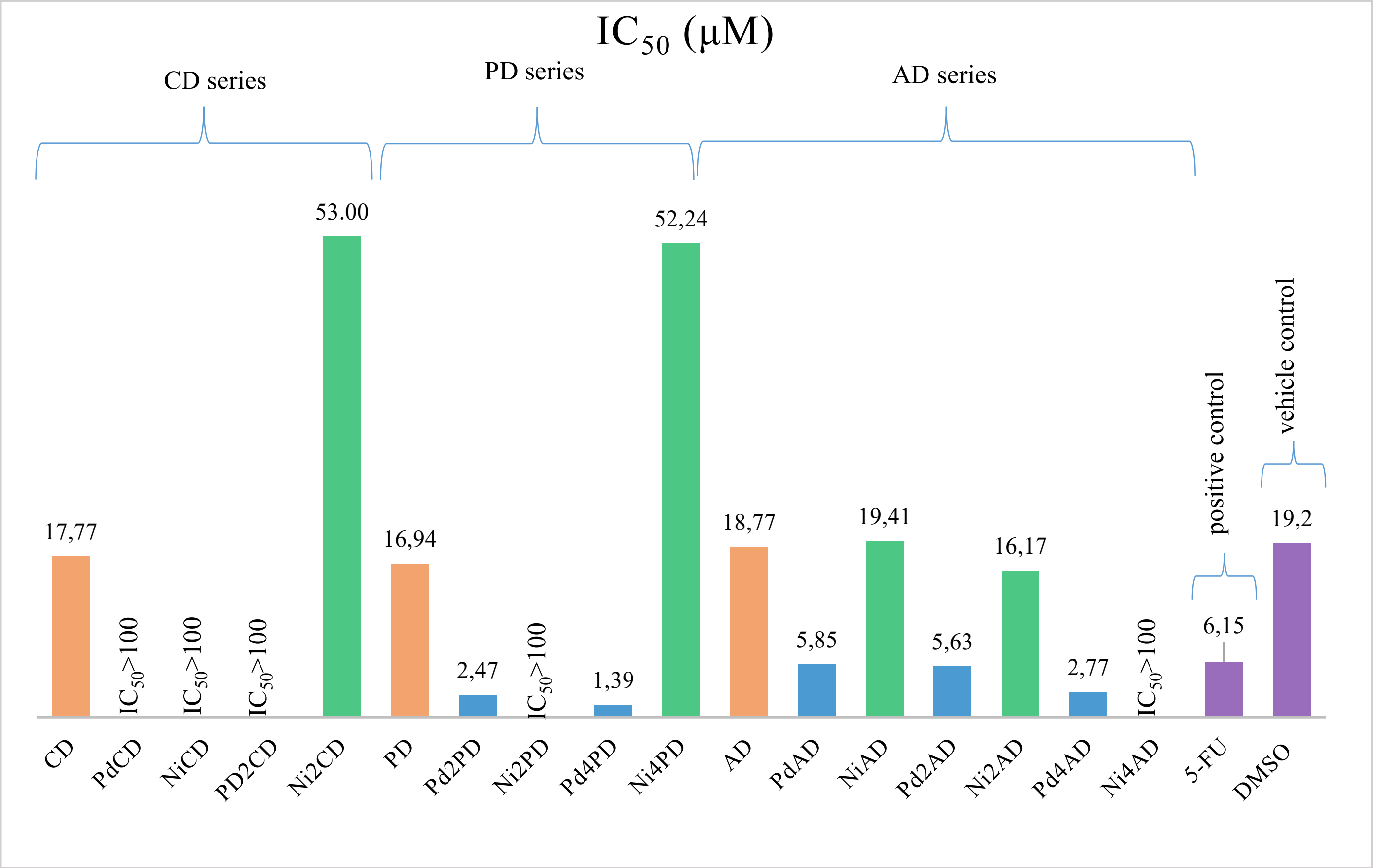
- CtDNA spectrum consist of:

a) Positive band near 276nm due to p-p base stacking.

b) Negative band near 245nm due to helicity of DNA. This band is sensitive to the binding of small molecule.

c) Simple groove binder and electrostatic interaction show less or no perturbation on the base stacking and helicity, while intercalation decrease or increase the intensities of positive and negative bands.

Cytotoxicity Studies



a) 5 complexes (Pd_2PD = 2.47µM, Pd_4PD= 1.39 µM, PdAD = 5.85µM, Pd_2AD = 5.63µM and Pd_4AD = 2.77 µM) were discovered to possess a potency higher than standard drug 5-fluorouracil (5-FU) with a concentration of 6.15µM.

b) The ligands itself has some ability to interact with the DNA and retarding its growth.

c) PD (phenyl- ligand) series shows a better anticancer properties compared to CD (cyclic- ligand) and AD (aliphatic-ligand) series as it contains more aromatic groups that could intercalate between stacked base pairs leading to an alteration of DNA winding, which lengthens and stiffens the DNA duplex that lead to cell death.

d) The Pd(II) complexes exhibits superior anticancer properties compared to Ni(II) complexes.

e) Tetranuclear complexes reveal highest anticancer activity, followed by dinuclear and mononuclear complexes. The anticancer properties of complexes is increased when the number of nuclearity increased (more metals)

Coordination Chemistry Group (CCG)

Coordination Chemistry: Green Synthesis and Applications

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Thank you!