Introduction to the Scientific Community – Inorganic Chemistry

Metal-based Supramolecular Drug Delivery Systems for Metallodrugs

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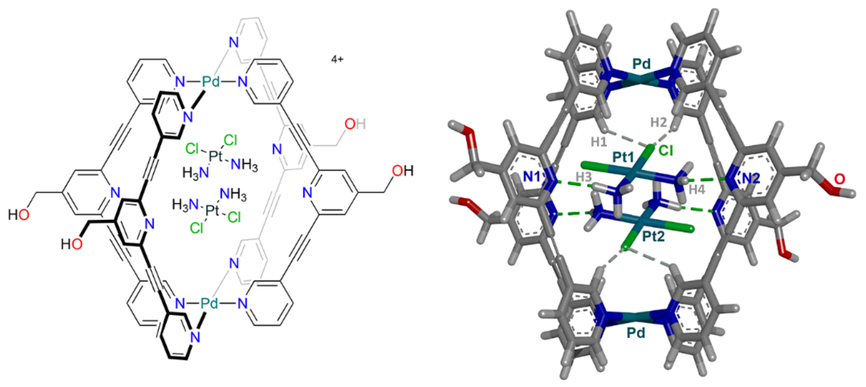
Introduction

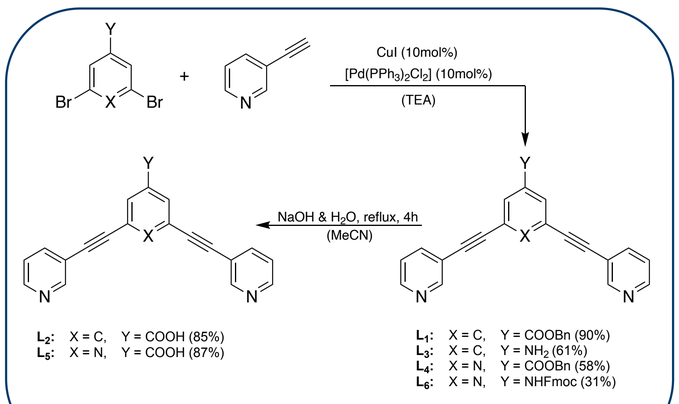
Besides cardiovascular and respiratory diseases, cancer is one of the most serious health problems in the world and it is ranked as one of the leading causes of death globally.[1] During the last few years, supramolecular coordination complexes (SCCs) have attracted much interest in medicinal chemistry due to their utility in host-guest chemistry as delivery systems for different drugs, like the anti-cancer compound Cisplatin. The scope of this work was to synthesize and characterize six different organic ligands and further, nine platinum(II)- and three palladium(II)-based metallacages of the general structure $[M_2L_4]^{4+}$ for their future application as drug delivery systems. The functionalization in endo- and exo-position of the ligands was varied for this study. The metallacages were synthesized via self-assembly of the ligands and a palladium- or an *in situ* generated platinum salt. The characterization of the obtained metallacages *via* ^{1}H nuclear magnetic resonance (NMR) spectroscopy indicated the presence of SCCs of lower ligand coordination (macrocycles) as main products and the cages in low quantities, but no crystal structures *via* single-crystal X-ray diffraction (SC-XRD) were obtained to determine the actual structure.



Scheme (left) and crystal structure (right) of a $[Pd_2L_4]^{4+}$ metallacage encapsulating two molecules of Cisplatin, reported by Casini *et al.*[2] Reprinted from [3].

Organic Linkers

Synthesis of the organic linkers *via* the Sonogashira cross-coupling reaction:



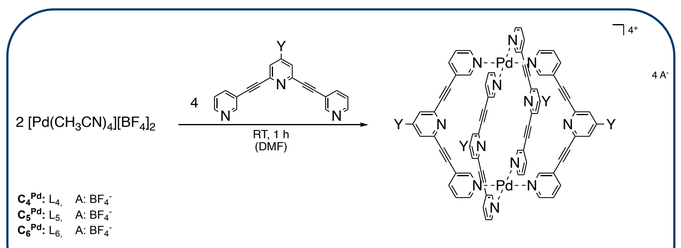
L_2: X = C, Y = COOH (85%)
L_5: X = N, Y = COOH (87%)

L_1: X = C, Y = COOBn (90%)
L_3: X = C, Y = NH_2 (61%)
L_4: X = N, Y = COOBn (58%)
L_6: X = N, Y = NHFmoc (31%)

Synthetic route to the organic linkers.

Protection of the functional groups prior to cross coupling using protection groups to prevent the coordination of the funtional groups to the palladium center of the catalyst, resulting in a termination of the catalytic cycle.

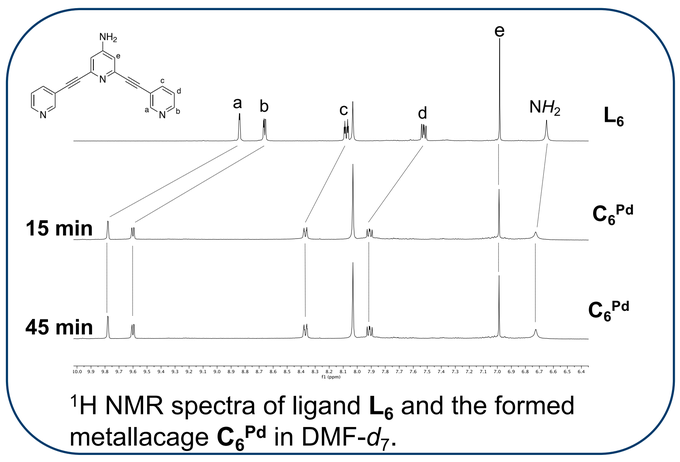
Pd(II)-based Metallacages



C_4^{Pd}: L_4, A: BF_4^-
C_5^{Pd}: L_5, A: BF_4^-
C_6^{Pd}: L_6, A: BF_4^-

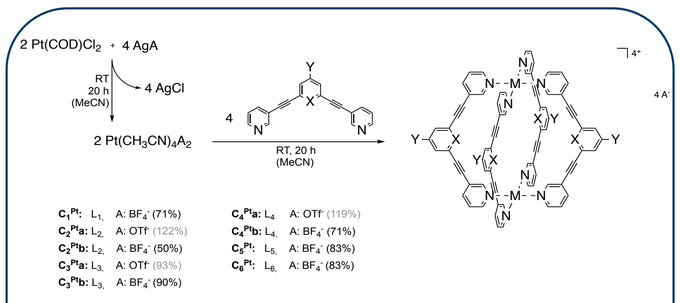
Synthetic route to the Pd(II) metallacages.

Formation of the cages indicated by downfield shift of the signals of the ligands in the ^{1}H NMR spectrum due to electron withdrawing properties of the metal center:



^{1}H NMR spectra of ligand **L_6** and the formed metallacage **C_6^{Pd}** in DMF-d_7.

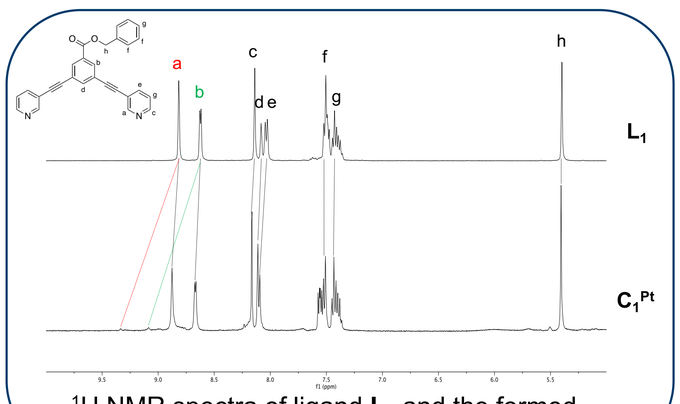
Pt(II)-based Metallacages



C_1^{Pt}: L_1, A: BF_4^- (71%)
C_2^{Pt}a: L_2, A: OTf^- (122%)
C_2^{Pt}b: L_2, A: BF_4^- (50%)
C_3^{Pt}a: L_3, A: OTf^- (93%)
C_3^{Pt}b: L_3, A: BF_4^- (90%)

C_4^{Pt}a: L_4 A: OTf^- (119%)
C_4^{Pt}b: L_4, A: BF_4^- (71%)
C_5^{Pt}: L_5, A: BF_4^- (83%)
C_6^{Pt}: L_6, A: BF_4^- (83%)

Synthetic route to the Pt(II) metallacages.



^{1}H NMR spectra of ligand **L_1** and the formed metallacage **C_1^{Pt}** in DMSO-d_6.

Small shifts in the ^{1}H NMR spectrum, assuming the formation of SCCs with less coordinated ligands as a main product.

Conclusion

The synthesis of various metallacages was performed for their future use in medicinal chemistry. Six different ligands were synthesized. For **L_6**, a modified synthetic procedure was applied with a new protection group and changed reaction conditions. The ligands were used for the synthesis of nine Pt(II)-based metallacages, using an i*n situ* generated Pt(II) salt. An insufficient formation of the Pt(II) salt and the presence of other ligands were suggested to intervene with the formation of the Pt(II) cages. The investigation of three Pd(II)-based metallacages did not lead to measurable crystals and only characterization *via* ^{1}H NMR was performed. The results of this study indicated the formation of the desired $[Pd_2L_4]^{4+}$ metallacage. For the future, the potential of the metallacages as drug delivery systems is to be researched after successful synthesis and characterization *via* SC-XRD.

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[1] H. Sung, J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, *CA: Cancer J. Clin.* **2020**, *71*, 209-249.
[2] A. Schmidt, V. Molano, M. Hollering, A. Pöthig, A. Casini, F. E. Kühn, *Chem. Eur. J.* **2016**, *22*, 2253-2256.
[3] A. Casini, B. Woods, M. Wenzel, *Inorg. Chem.* **2017**, *56*, 14715-14729.