Introduction to the Scientific Community – Inorganic Chemistry

Synthesis and Encapsulation Studies of Supramolecular Coordination Complexes as Drug Delivery Systems

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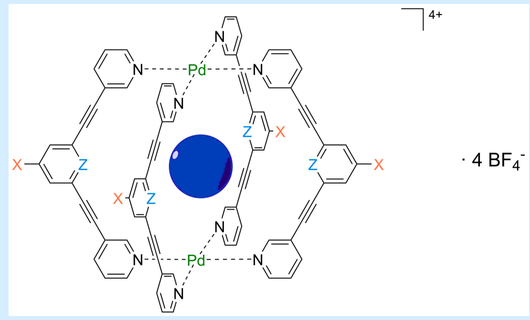
Introduction

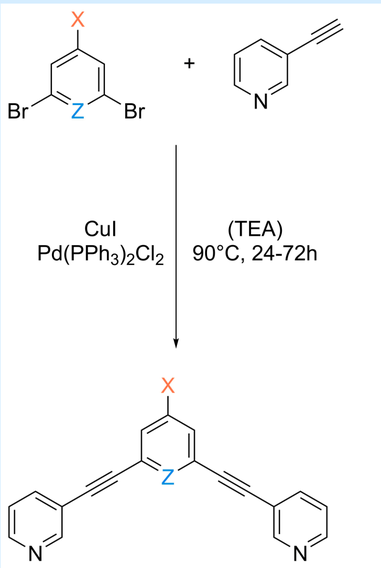
According to the *Institute for Health Metrics and Evaluation*, cancer is the world's second most common cause of death, which makes precise diagnostic and therapy all the more important.[1] Recently, supramolecular coordination complexes for biomedical applications are on the rise due to their variously adjustable properties. By the interplay of metal ions, counter ions, ligands and their *exo*- and *endo*-functionalities as well as the conjugated biomolecules the cages can be adapted to an unlimited number of desired applications. In this work, the synthesis and the encapsulation properties of $[Pd_2L_4](BF_4)_4$ (L = *endo*-/*exo*-functionalized bispyridinyl ligand) cages was investigated by ^{1}H-NMR spectroscopy for the application as drug delivery systems and the results are presented in this poster. Here, the anticancer agent cisplatin and perrhenate, the cold analogue of the radiotracer $^{99m}TcO_4^-$, were chosen as the model guest molecules. While the targeted delivery of cisplatin is of great interest due to its systemic toxicity and the development of cisplatin-resistant tumors, the directed transport of imaging agents will reduce background signals and even enable passage of the blood-brain barrier to improve cerebral imaging.[2,3]



General structure of a $[Pd_2L_4](BF_4)_4$ complex with an encapsulated guest (blue). *Exo* (X)- and *endo* (Z)-groups are depicted in orange and blue.

Synthesis of the Ligands

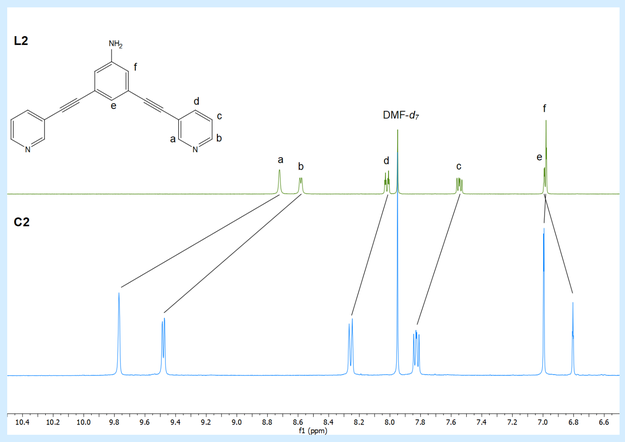
Sonogashira cross-coupling was performed to obtain the bispyridinyl ligands. **L4** could only be isolated as the monosubstituted product.



L1a: X = COOH, Z = CH (96%)
L1b: X = COOBn, Z = CH (98%)
L2: X = NH_2, Z = CH (provided)
L3a: X = COOH, Z = N (94%)
L3b: X = COOBn, Z = N (63%)
L4: X = NH_2, Z = N
L5: X = CH_2COOH, Z = CH (provided)

Synthesis of the Cages

The Pd-metallacages were accessed *via* coordination-driven self-assembly within 1h.

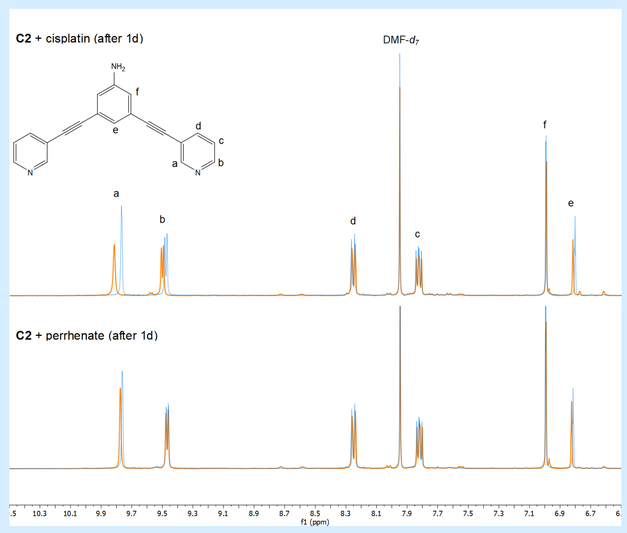


^{1}H-NMR spectrum of ligand **L2** (top) and the respective cage (bottom). Spectra of the other ligands showed similar chemical shifts.

^{1}H-NMR signals of the *α*-pyridinyl protons H_a and H_b are shifted downfield the most ($\Delta\delta$ = 0.83-0.70 ppm) as they experience the electron withdrawing effect of the metal coordination the strongest.[4]

Encapsulation

While perrhenate encapsulation could not be achieved for any of the cages, the encapsulation of cisplatin (2 eq.) could be confirmed for **C2** ($\Delta\delta$ = 0.05-0.02 ppm).[4]



Superimposed ^{1}H-NMR spectra of the encapsulation complexes of **C2** (orange) compared to the empty cage (blue). Cisplatin encapsulation is depicted in the top and reaction with perrhenate in the bottom spectrum.

Conclusion

Although a predictable encapsulation of guest molecules could not be certainly proven in this work, the $[M_2L_4]^{4+}$ cages have great potential. While the Sonogashira cross-coupling is a very useful approach for constructing the bidentate ligands as it offers a huge pool of structures by combining various *exo*- and *endo*-functionalized building blocks, the coordination-driven self-assembly is a universal method of low synthetic effort to generate the metallacages. To conclude, their simple motif, the ease of access as well as the unlimited possibilities of composition and functionalization make the $[M_2L_4]^{4+}$ cages a promising approach for biomedical purposes and might open the way to theranostics.[5]

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[1] M. Roser, H. Ritchie, "Burden of Disease," can be found under https://ourworldindata.org/burden-of-disease, **2016**.
[2] N. J. Wheate, S. Walker, G. E. Craig, R. Oun, Dalt. Trans. **2010**, 39, 8113.
[3] B. Woods, R. D. M. Silva, C. Schmidt, D. Wragg, M. Cavaco, V. Neves, V. F. C. Ferreira, L. Gano, T. S. Morais, F. Mendes, et al., Bioconjug. Chem. **2021**, DOI 10.1021/acs.bioconjchem.0c00659.
[4] B. Woods, M. N. Wenzel, T. Williams, S. R. Thomas, R. L. Jenkins, A. Casini, Front. Chem. **2019**, 7, 68.
[5] A. Pöthig, A. Casini, Theranostics **2019**, 9, 3150.