Hydrolysis of equatorial ligands of platinum(IV) complexes

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Pt(II) complexes play an important role in cancer treatment, being administered in about 50% of all chemotherapies. Until today three complexes were approved worldwide, namely cis-, carbo- and oxaliplatin which are used against various forms of cancer. Unfortunately they bring along a range of adverse effects, which are tried to be mitigated by a shifted research focus towards Pt(IV) complexes in the last years. These compounds are kinetically more inert than their Pt(II) counterparts, resulting in slower reactions with biomolecules and consequently less adverse effects. Inside the tumor tissue, these prodrugs are activated by reduction, generating the active Pt(II) complex.

In the here presented work we investigated the stability of a series of biscarboxylato Pt(IV) compounds under physiologically relevant conditions. Surprisingly, several complexes, especially satraplatin and the oxaliplatin derivatives showed significant rates of hydrolysis of the equatorial ligands (also in cell culture medium and serum) which is in strong contrast to the dogma of highly inert Pt(IV) anticancer drugs. After synthesis of the monohydroxido [Pt(DACH)$(OAc)_2$(OH)(oxalate)] and dihydroxido [Pt(DACH)$(OAc)_2(OH)_2$] derivatives, subsequent analysis showed vastly different properties when looking at reduction kinetics, a crucial factor for the activation of Pt(IV) compounds. Consequently, the current understanding of the stability of Pt(IV) complexes needs to be reevaluated and taken into account for future platinum-based drug design. [1]

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[1] Kastner, A., Poetsch, I., Mayr, J., Burda, J.V., Roller, A., Heffeter, P., Keppler, B.K. and Kowol, C.R., *Angew. Chem. Int. Ed.* **2019** A Dogma in Doubt: Hydrolysis of Equatorial Ligands of Pt^{IV} Complexes under Physiological Conditions. https://doi.org/10.1002/anie.201900682