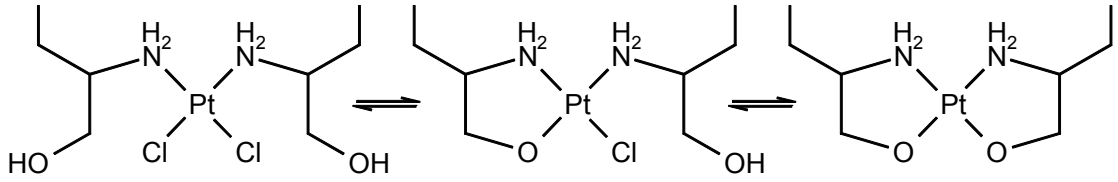
LOW PH IN SOLID TUMORS - SELECTIVE ACTIVATION OF ANTICANCER PLATINUM COMPLEXES

Kristof Meelich[a], Markus Galanski[a], Vladimir B. Arion[a], Michael A. Jakupec[a], Petra Schluga[a], Christian G. Hartinger[a], Nikolai Graf v. Keyserlingk[b], and Bernhard K. Keppler[a]

[a]Institute of Inorganic Chemistry – Bioinorganic-, Environmental-, and Radiochemistry, University of Vienna, A-1090 Vienna, Austria
[b]Faustus Forschungs Compagnie Translational Cancer Research GmbH, D-04109 Leipzig, Germany

Since the successful introduction of cisplatin, a wide spectrum of platinum compounds has been synthesized and tested [1]. Nevertheless, only a limited number made their way into clinical trials, just three of them have been approved for a worldwide use. The low selectivity of most anticancer agents still appears to be a major problem; severe side effects or ineffective treatment are the results. The search for a more selective and tumor targeted therapy was the stimulus for the design of pH sensitive platinum complexes. It is known that most solid tumors display increased hypoxia, which results in a decrease of pH (5.5 - 7.4). The acidic environment, which is usually a problem for weak base organic drugs, could advantageously be used for the introduction of pH sensitive agents, such as aminoalcoholato platinum(II) complexes.



These substances show a pH-driven reversible intramolecular ligand exchange reaction in aqueous solution. At pH (7.4) ring-closed species are formed, which display a significantly low reactivity. Also a low cytotoxicity of the mentioned ring-closed forms could be found. On the other hand, the ring-opened complexes, which are formed at lower pH, as found in tissues of solid tumors, are far more reactive. Respectively a much stronger cytotoxic effect was observed at pH 6. Two aminoalcoholato complexes have been studied in detail: Synthesis, characterization, chemical behavior, and cytotoxicity are described. In both cases, the ring closed species appear to be remarkably stable substances, also in aqueous solution under physiological pH and chloride ion concentration [2].
These interesting results provide evidence that the concept of administration of rather unreactive drugs and activation under acidic pH conditions, can be realized.

Acknowledgement: The support of the FWF and COST is gratefully acknowledged.

[1] M. A. Jakupec, M. Galanski, B. K. Keppler, Rev. Physiol. Biochem. Pharmacol. (2003), 146 1-53.
[2] M. Galanski, C. Baumgartner, K. Meelich, V. B. Arion, M. Fremuth, M. A. Jakupec, P. Schluga, C. G. Hartinger, N. Graf v. Keyserlingk, B. K. Keppler, Inorg. Chim. Acta (2004), 357(11), 3237-3244.