Working with Barnett Rosenberg: A Personal Appreciation of my Postdoctoral Time at MSU and on an Exciting Project, the "Platinum Pyrimidine Blues"

Bernhard Lippert, Fakultät Chemie und Chemische Biologie (CCB), Technische Universität Dortmund, 44221 Dortmund, Germany (bernhard.lippert@tu-dortmund.de)

The "Platinum Pyrimidine Blues", first reported by Rosenberg and coworkers in 1975, [1] and prepared by reacting the diaqua species of Cisplatin (*cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$) with pyrimidine (pym) nucleobases, derivatives of these, or other related ligands (e.g. linear or cyclic amides, …) in a 1:1-ratio, were considered potential second generation Pt drugs then. Although it soon became clear that the "blues" were complicated mixtures of (conventional) colorless or yellowish diamagnetic Pt^{II} species and deeply colored (green, blue, purple) paramagnetic mixed-valence Pt compounds of varying average oxidation states (for a summary see [2]), reasons for their antitumor activity remained, and in fact still are, obscure. At present, 40 years later, only a single representative of Rosenberg's original "Pt pym blues", with the model nucleobase 1-methyluracil, is fully characterized, isolated according to a modified version of the original Rosenberg protocol. [3] There are numerous other examples of compounds with related ligands now available, which display similar structural principles, namely the stacking of dinuclear Pt entities permitting short Pt-Pt contacts and partial metal oxidation. [4] However, there can be no doubt that alternative principles, leading to Pt-Pt interactions, do exist, e.g. following a partial release of NH_3 ligands or as a consequence of rotational isomerism of the pym bases. A crucial and as yet not fully answered question surrounding the "blues", is as to which component/s is/are responsible for their biological effects.

A postdoc with Rosenberg for over two years (1974-1976), and right in a period when the excitement on the "Pt pyrimidine blues" was truly high, the mystery of their composition has remained an intellectual challenge to the author and his own research group for the time to come.

The lecture will provide an overview of the systematic studies carried out when back in Germany in trying to elucidate in particular the nature of possible di- and oligomeric diamagnetic components of the complex mixtures of the “Pt pyrimidine blues” and their potential relationship to deeply colored Pt oxidation products. This work has been extended also to Cytosine nucleobase compounds, species not elaborated on by Rosenberg in his early study.

[1] J.P. Davidson, P.J. Faber, R.G. Fischer, Jr., S. Mansy, H.J. Peresie, B. Rosenberg, L. VanCamp, *Cancer Chemother. Rep. Part 1,* **1975**, *59*, 287.

[2] B. Lippert in *Cisplatin – Chemistry and Biochemistry of a Leading Anticancer Drug* (Ed. B. Lippert), HVCA/Wiley-VCH, Zurich/Weinheim, **1999**, pp. 379-403.

[3] P.K. Mascharak, I.D. Williams, S.J. Lippard, *J. Am. Chem. Soc.,* **1984**, *106*, 6428; T.V. O’Halloran, P.K. Mascharak, I.D. Williams, M.M. Roberts, S.J. Lippard, *Inorg. Chem.,***1987**, *26*, 1261.

[4] K. Matsumoto, *Bull. Chem. Soc. Jpn.,* **1985**, *58,* 651; K. Matsumoto, K. Sakai, *Adv. Inorg. Chem.* **2000**, *49*, 375.