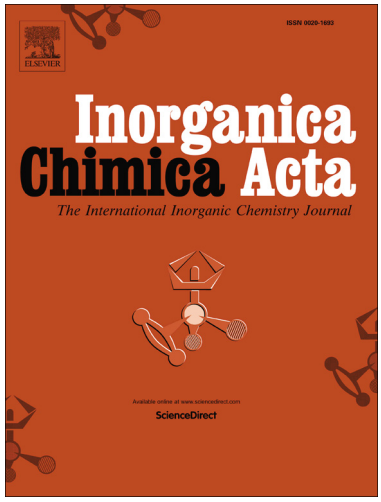

Comparing Pt^{II}- and Pd^{II}-nucleobase coordination chemistry: Why Pd^{II} not always is a good substitute for Pt^{II}

Bernhard Lippert, Pablo J. Sanz Miguel

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Commentary

Comparing Pt^{II}- and Pd^{II}-nucleobase coordination chemistry: Why Pd^{II} not always is a good substitute for Pt^{II}

Bernhard Lippert [a]*, Pablo J. Sanz Miguel [b]*

[a] *Fakultät Chemie und Chemische Biologie, Technische Universität Dortmund, 44221 Dortmund, Germany*

[b] *Departamento de Química Inorgánica, Instituto de Síntesis Química y Catálisis Homogèna (ISQCH), Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain*

Dedicated to Professor Imre Sóvágó, friend and colleague

ABSTRACT

As is well established, numerous similarities exist as far as reactivity patterns and structural features of the d^8 metal ions M = Pd^{2+} and Pt^{2+} are concerned. Here reactions of metal complexes of type *cis*-$[M(a)_2X_2]$ (a = NH_3 or $(a)_2$ = diamine or diimine; X = monodentate or X_2 = bidentate leaving groups) with nucleobases, the constituents of nucleic acids, are discussed and differences regarding intrinsic stability of the starting compounds, kinetics of formation of products, thermodynamics of products, as well as donor site selectivity are pointed out. It is concluded that Pd^{II} complexes representing strict or close analogues of established antitumor Pt^{II} drugs of the Cisplatin-type, if active under *in-vivo* conditions at all, are unlikely to have a similar mode of action as their Pt^{II} congeners. Relationships to supramolecular constructs containing *cis*-$[M(a)_2]^{2+}$ entities are likewise discussed.

Keywords:

Palladium(II); Platinum(II); Binding to Nucleobases and DNA; Kinetics vs. Thermodynamics; Antitumor Activity

**Corresponding authors:*

E-mail addresses: bernhard.lippert@tu-dortmund.de (B. Lippert), pablo.sanz@unizar.es (P.J. Sanz Miguel)

1. Introduction

It is widely accepted among inorganic chemists that the d^8 metal ion Pd^{2+} and its congener Pt^{2+} display similar reaction patterns, in particular if the ligands are identical or closely similar. After all, the two metal ions have practically identical size, usually adopt square-planar coordination geometries, are considered essentially of "soft" nature, but nevertheless have a pronounced affinity for N-donor ligands [1]. Differences in redox chemical behavior of the two metal ions exist, but are probably irrelevant for their biological chemistry. A, or possibly even *the* major difference refers to reactivity: Pd^{II} is estimated to undergo ligand substitution reactions 10^4–10^5 times more rapidly than Pt^{II} [2], a consequence of the lower electron density of Pd^{2+} (44 vs. 76 electrons) and the reduced repulsion in the 5-coordinate transition state. Among simple coordination complexes with a large variety of ligands, e.g. ammonia or amines, halides, or phosphanes, there are indeed numerous isostructural representatives known. It consequently cannot be a surprise that soon after the discovery of the antitumor activity of *cis*-$Pt(NH_3)_2Cl_2$ (Cisplatin) and several related Pt^{II} compounds, the search for active Pd^{II} analogues took off. Although isostructural Pd analogues of clinically applied Pt drugs have been synthesized [3] and tested [4], and despite numerous reports on cytotoxic effects of Pd^{II} complexes in general [5], there is presently no Pd-containing drug clinically approved, in contrast to half a dozen of Pt^{II} compounds as well as several more in clinical trials.

This commentary tries to provide a rationale for this situation by comparing fundamental properties of