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A cationic aqua complex of an orthoplatinated primary amine – A versatile intermediate for derivatization

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ABSTRACT

In the presence of silver salts of weakly or non-coordinating anions, the iodo ligand in a cycloplatinated complex of phenylethylamine may be replaced by a coordinated water molecule. The resulting cationic aqua complex may either be isolated in the form of its tetrafluoroborate or perchlorate salt or prepared *in situ*. In subsequent derivatization reactions, the aqua ligand may be substituted under mild conditions. Two classes of cycloplatinated primary amines, interesting in view of their potential cytostatic properties, are accessible via this useful intermediate: Its aqua ligand may be displaced either by (pseudo)halides or by neutral donor ligands. With the anionic (pseudo)halides, neutral water-insoluble coordination compounds are obtained: The corresponding isocyanato complex has been structurally characterized, and we have converted the original iodo complex into a radiolabeled derivative. With neutral Lewis bases, cationic complexes of moderate solubility are formed; we report the crystal structure of the 3,5-lutidine derivative.

Introduction

Cope and Friedrich initiated the orthometallation of activated benzyl amines with palladium and platinum in the late 1960ies [1]. Since these first reports concerning exclusively tertiary amines, cyclopalladation has developed into a rather general reaction for a wide range of substrates. A major breakthrough was the use of palladium acetate as the metalating agent for primary [2] and even electron deficient amines [3]. Excellent reviews covering the advances in cyclopalladation [4] and the more general subject of cyclometallation [5] are available. In contrast to these advances in the field of cyclopalladation, only little progress had been made for the cycloplatination of primary amines until 2007 [6]. In 2008, our group reported the first convenient synthesis which allowed the cycloplatination of primary amines with good yields [7]. This reaction proceeds via a mixed-valence platinum iodide precursor and an intermediate *trans* complex; it results in an orthoplatinated amine which chelates a Pt(II) cation, with the remaining coordination sites in the square planar complex occupied by an anionic iodo and a neutral donor ligand. In this direct product of the cycloplatination **1** (Scheme 1), the donor ligand corresponds to a second (neutral, non-deprotonated) equivalent of the same amine which is metalated under C–H activation. We have shown earlier [7] that the σ-donor amine may be substituted by alternative nucleophiles such as pyridine derivatives or phosphanes. In this contribution, we report that **1** may be converted at ambient temperature into the stable cationic aqua complex **2** which represents a suitable intermediate for new cationic and neutral complexes, including a radiolabeled species. Scheme 1 summarizes our results.

We do not only add more examples to a rarely studied class of compounds: Our interest in cycloplatinated primary amines also stems from the fact that they represent candidates for cytostatic drugs. In square-planar Pt(II) complexes, two leaving groups in *cis* geometry are required. The non-leaving groups should be as inert as possible; amines have proven most successful, and they should possess at least one N–H hydrogen bond donor function [8]. Cycloplatinated amines, N,C-chelating the Pt cation in *cis* configuration, might well represent a suitable organometallic scaffold for a drug. However, the second structural requirement above could obviously not be fulfilled by tertiary amines, the original substrates of cycloplatination: rather, cycloplatination of primary or secondary amines is mandatory for this purpose. We note that the vast majority of Pt-based candidates for cytostatic drugs are coordination compounds whereas organoplatinum derivatives have only rarely been considered [9].

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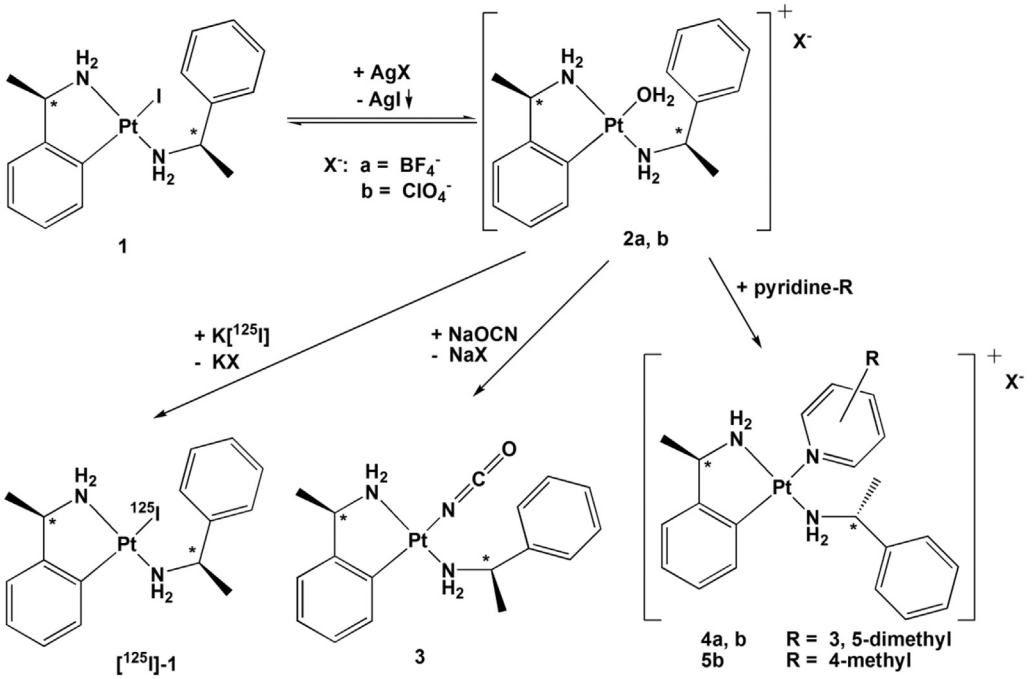


Scheme 1. Summary of compounds characterized in this work.

Nuclear molecular imaging enables the detection of physiological functions by non-toxic trace amounts (in the nmol range) of the probe. The most commonly used iodine isotopes are ^{123}I, ^{124}I, ^{125}I, and ^{131}I [10]. The selection of a suitable radionuclide for an individual case should especially consider the half-life which has to fit to the expected biokinetic of the probe and the medical application in therapy or diagnosis by PET(positron emission tomography) and SPECT(single-photon emission computed tomography). The easily accessible^{123}I with a medium half-life of 13.2 h is most favorable for SPECT, whereas ^{124}I (half-life of 4.2 d) allows studies of slow processes over days by the highly resolutive and sensitive PET-technology [11]. However, its use so far is limited to research purposes, because of its low availability and the fact that only 26% of the decays result in positron emission. ^{131}I is the main isotope in therapy being capable to monitor the therapy by SPECT. ^{125}I in contrast, with a half-life of 60 d and a short range of its electron radiation, is preferred in *in vitro* investigations as well as in chemical evaluations.

The often described *in vivo* de-iodination of [*I]radiotracer is enhanced in directly labeled, unmodified tyrosine or tyrosine containing peptides/proteins, and is always an impact when investigating new compounds [12].

Experimental section

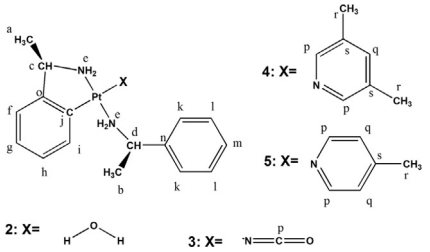
Instrumentation

NMR spectra were recorded on a Bruker Avance II Ultrashield™ plus 400 (^{1}H NMR: 400 MHz; ^{13}C NMR: 100.6 MHz; ^{195}Pt NMR: 86 MHz); ^{1}H and ^{13}C resonances are referenced to TMS, and ^{195}Pt to H_2PtCl_6. Powder diffraction experiments were performed at room temperature on flat samples with a Stoe & Cie STADI P diffractometer equipped with an imageplate detector with constant ω-angle of 55° using germanium-monochromated Cu-Kα1 radiation (λ = 1.54051 Å). CHN microanalyses were obtained from the Institute of Organic Chemistry, RWTH Aachen University, using a HERAEUS CHNO-Rapid. Infrared spectra were recorded on KBr pellets with an Avatar 360 FTIR spectrometer from Nicolet.

General comment

For easier comparison, all NMR spectra were registered in CD_3OD.

Diagram for spectroscopic assignments of **2**–**5**:



CAUTION! Although no hazards were encountered in the context of this study, perchlorate salts of metal complexes are potentially explosive; only small quantities should be handled.

*Synthesis of the aqua complex **2a***

In a 50 mL round bottom flask, 56 mg (0.1 mmol) of **1**, which was prepared as described by Calmuschi-Cula and Englert [7], were suspended in 7 mL of methanol. An equimolar amount of $AgBF_4$ (19 mg, 0.1 mmol) was dissolved in 1 mL of methanol. This solution was slowly added to the above suspension, and the resulting mixture was vigorously stirred for 30 min. The phases were separated by centrifugation; the amount of AgI recovered from the precipitate indicates quantitative conversion. **2a**·$5H_2O$ may be isolated by evaporation of its solution; the yield in isolated microcrystalline solid is 54 mg (almost quantitative). (Alternatively, the clear solution of **2a** may be stored in methanol or water at 4 °C for further derivatization.)