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On the reactivity of platinum(IV) complexes: Synthesis and spectroscopic studies of platinum(IV) complexes with hypoxanthine

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Abstract

$Na_2[PtCl_6]$ was found to react with $(HypH)Cl\cdot H_2O$ (**2**) (Hyp = hypoxanthine) in aqueous solution at room temperature yielding $(HypH)_2[PtCl_6]$ (**3**). The same compound was obtained from hexachloroplatinic acid and hypoxanthine. Performing this reaction in methanol at 50 °C complex formation took place yielding the hypoxanthine complex $[PtCl_4(Hyp)_2]$ (**4**). Both compounds were isolated in good yields as faint orange (**3**) and yellow (**4**) precipitates, respectively and characterized by microanalyses, IR and NMR (^1H, ^{13}C, ^{195}Pt) spectroscopies as well as thermal analysis. Based on the data obtained an octahedral molecular structure is proposed for complex **4** with two hypoxanthine ligands coordinated through N7 to platinum(IV).

Keywords: Platinum complexes; Nucleobase ligands; Hypoxanthine; Ligand substitution; NMR; IR

1. Introduction

It is well known that hypoxanthine (**I**) is a naturally occurring purine derivative, and one of the products of the action of xanthine oxidase on xanthine, though more normally in purine degradation, hypoxanthine is oxidized by xanthine oxidase to form xanthine. It is occasionally found as a constituent of nucleic acids where it is present in the anticodon of tRNA in the form of its nucleotide inosine [1]. On the other hand, cisplatin is a well-established antitumor drug and widely used to treat various types of human cancer [2]. Because of the side effects and the need to apply it intravenously decreased the use of cisplatin. Therefore, a large number of other derivatives have been synthesized and tested with respect to their anticancer activity. Reducing the toxicity, a broader spectrum of activity and oral administration are the major goals of both platinum(II) and platinum(IV) drug development [3]. Considerable progress in platinum chemistry was made with the synthesis of kinetically inert platinum(IV) compounds [4]. Such complexes are much more inert than their platinum(II) counter parts and can therefore be administered orally. The ongoing interest in platinum(IV) complexes in chemotherapy [5] led to a revival of interest in the coordination chemistry of platinum(IV), especially involving bioligands. Most of these platinum(IV) complexes were prepared by oxidation of preformed platinum(II) complexes, but this approach may fail due to oxidative degradation of the bioligands. Serious attempts have been made to synthesize Pt(IV) complexes with bioligands via ligand substitution reactions on a Pt(IV) center and succeeded to synthesize those with amino acid ligands [6] and carbohydrate ligands [7]. Due to the limited number of platinum(IV) complexes with cytosine [8], uracil [9] and purine derivatives {theophylline [10], 9-methylxanthine [11] and 9-methyladenine [12]}, we have previously investigated analogous ligand substitution reactions using 9-methyladenine [13], bipyridines, phenanthrolines, and bipyrimidine as heterocyclic *N* donors and other bioligands [14].

To continue our investigation in this area, here we report on preparation and spectroscopic investigations of ligand substitution reactions using hexachloroplatinates ($Na_2[PtCl_6]$ and $H_2[PtCl_6]\cdot 6H_2O$) as starting materials. As nucleobase, we used hypoxanthine (Hyp) to get insight into the course of reactions of this type.

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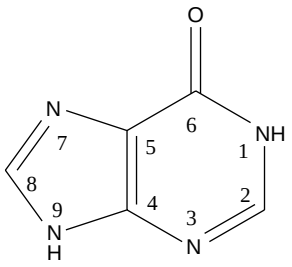

(**I**)

2. Experimental

NMR spectra were recorded on Varian spectrometers Gemini 200, VXR 400 and Unity 500 operating at 200, 400 and 500 MHz for ^{1}H, respectively. Solvent signals (^{1}H, ^{13}C) were used as internal references and $Na_2[PtCl_6]$ (2 M in D_2O, $\delta(^{195}Pt) = 0.0$) as an external reference. Infrared spectra of the reactants and the obtained complexes were recorded from KBr discs (4000–400) using Buck scientific 500-IR spectrophotometer. FT-IR spectra were recorded on a Bruker IFS 66 spectrometer as CsBr pellets. Thermal analysis TG was carried out using a Shimadzu TGA-50 H computerized thermal analysis system. The system includes a program, which process data from the thermal analyzer with the ChromotPac C-R3A. The rate of heating of the samples was kept at 10 °C min^{-1}. Sample masses varied between 2.0 and 4.0 mg were analyzed under N_2 flow at 30 ml min^{-1}. Microanalyses were performed by the Microanalysis Unit of Cairo University, Egypt and the Microanalytical Laboratory of the Chemistry Department at Martin-Luther-Universität Halle-Wittenberg using CHNS-932 (LECO) and vario-EL (elmentar Analysensysteme) elemental analyzers. Chlorine was determined by burning the substance in oxygen with platinum contact and subsequent titration with mercuric nitrate towards diphenylcarbazide.

All of the chemicals used throughout this investigation were extra pure grade. Hexachloroplatinic acid (**1**) (Degussa, Saxonia) and hypoxanthine (Lancaster) were commercially available.

Hypoxanthine (Hyp).

^{1}H NMR (400 MHz, [D$_6$]dmso): δ 7.97 (s, 1H, *H*8), 8.11 (s, 1H, *H*2), 12.71 (br, 2H, N*H*1/N*H*9). ^{13}C NMR (101 MHz, [D$_6$]dmso): δ 119.01 (s, *C*5), 140.119 (s, *C*8), 144.66 (s, *C*2), 153.49 (s, *C*6), 155.38 (s, *C*4).

2.1. Synthesis of (HypH)Cl·H_2O (2)

Reactions of Hyp with equimolar amounts of HCl in water resulted in formation of (HypH)Cl·H_2O.

Anal. found: C, 31.12; H, 3.81; N, 29.19; Cl, 18.41. Anal. calcd for $C_5H_7ClN_4O_2$ (190.59): C, 31.51; H, 3.70; N, 29.40; Cl, 18.60.

^{1}H NMR (400 MHz, [D$_6$]dmso): δ 7.7 (br, ca. 3H, N*H*7/H_2O), 8.24 (s, 1H, *H*2), 9.26 (s, 1H, H8), 13 (br, ca. 2H, N*H*1/N*H*9). ^{13}C NMR (101 MHz, [D$_6$]dmso): δ 115.81 (s, *C*5), 139.03 (s, *C*2), 148.13 (s, *C*8), 148.47 (s, *C*6), 153.35 (s, *C*4).

2.2. Synthesis of (HypH)$_2$[PtCl$_6$] (3)

(a) A solution of (HypH)Cl·H_2O (38.2 mg, 0.20 mmol) in water (3 ml) was added to a solution of $Na_2[PtCl_6]$ (45.7 mg, 0.10 mmol) in water (2 ml). The clear yellow solution was left overnight. Then, the water content was reduced under vacuum without heating to 50%. The faint orange precipitate of complex **3** was filtered off, washed with few drops of methanol and dried in a desiccator in vacuo. Yield: 80.0 mg (58.5%).

(b) To a solution of $H_2[PtCl_6]\cdot 6H_2O$ (104.0 mg, 0.20 mmol) in water (1–2 ml), a solution of hypoxanthine (45.5 mg, 0.40 mmol) in water (6 ml) was added. After about 30 min, complex **3** started to separate as faint orange microcrystals, which were filtered off and washed with few drops of methanol and dried in vacuo. Yield: 96.0 mg (70.2%).

Anal. found: C, 17.69; H, 1.71; N, 16.52; Cl, 31.09. Anal. calcd for $C_{10}H_{10}Cl_6N_8O_2Pt$ (682.05): C, 17.61; H, 1.48; N, 16.43; Cl, 31.19.

^{1}H NMR (400 MHz, [D$_6$]dmso): δ 8.25 (s, 1H, *H*2), 9.11 (s, 1H, *H*8), 12.8 (br, 3H, N*H*1/N*H*7/N*H*9). ^{13}C NMR (126 MHz, [D$_6$]dmso): δ 116.09 (s, *C*5), 139.16 (s, *C*2), 147.77 (s, *C*8), 148.94 (s, *C*6), 153.52 (s, *C*4). ^{195}Pt NMR (107 MHz, [D$_6$]dmso): δ −833 (s).

2.3. Synthesis of [PtCl$_4$(Hyp)$_2$] (4)

A solution of $H_2[PtCl_6]\cdot 6H_2O$ (104.0 mg, 0.20 mmol) in water–methanol (1:9, 10 ml) was added to a suspension of Hyp (45.5 mg, 0.40 mmol) in methanol (20 ml). The clear solution was stirred for about 3 h at 50 °C resulting in precipitation of complex **4** as yellow microcrystals that were filtered off, washed with few drops of water and methanol and dried in a desiccator in vacuo. Yield: 96.0 mg (78.5%).

Anal. found: C, 19.91; H, 1.35; N, 18.28; Cl, 23.12. Anal. calcd for $C_{10}H_8Cl_4N_8O_2Pt$ (609.13): C, 19.72; H, 1.32; N, 18.40; Cl, 23.28.

^{1}H NMR (400 MHz, [D$_6$]dmso): δ 7.69 (s, 1H, *H*2), 8.80 (s + d, $^3J_{Pt,H8} = 14.94$ Hz, 1H, *H*8), 12.7 (br, ca. 2H, N*H*1/N*H*9). ^{13}C NMR (101 MHz, [D$_6$]dmso): δ 114.55 (s, *C*5), 143.0 (s, *C*2), 145.30 (s, *C*8), 149.62 (s, *C*6), 152.69 (s, *C*4). ^{195}Pt NMR (107 MHz, [D$_6$]dmso): δ −358 (s).