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Synthesis, characterization, and cytotoxicity of trimethylplatinum(IV) complexes with 2-thiocytosine and 1-methyl-2-thiocytosine ligands

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ABSTRACT

The reaction of $[PtMe_3(MeOH)(bpy)][BF_4]$ (**1**) with the thionucleobases 2-thiocytosine (SCy, **2**) and 1-methyl-2-thiocytosine (1-MeSCy, **3**) resulted in the formation of the complexes $[PtMe_3(bpy)(SCy\text{-}\kappa S)][BF_4]$ (**4**) and $[PtMe_3(bpy)(1\text{-}MeSCy\text{-}\kappa S)][BF_4]$ (**5**), respectively. The complexes were characterized by ^1H and ^{13}C NMR spectroscopy as well as by single-crystal X-ray analyses of **4** · MeOH and **5**. In **4** · MeOH two strong hydrogen bonds (N4–H···N3′: N4···N3′ 2.976(7) Å) between the thiocytosine ligands give rise to base pairing thus forming dinuclear cations $[\{PtMe_3(bpy)(SCy\text{-}\kappa S)\}_2]^{2+}$. In both complexes the platinum atom is octahedrally coordinated $[PtC_3N_2S]$ by three methyl ligands, the 2,2′-bipyridine ligand and the κS coordinated nucleobase (configuration index: *OC*-6-33). The structural investigations gave evidence that the sulfur atoms of the nucleobase ligands in **4** · MeOH and **5** have to be regarded as sp^3 and sp^2 hybridized, respectively. Thus, the ligand in **4** · MeOH has to be considered as the deprotonated thiol-amino form of thiocytosine being reprotonated at N1. In complex **5** the 1-MeSCy is coordinated in its thione-amino form. DFT-calculations of the base-paired dinuclear cation in **4** as well as of **4** itself gave proof of the strength of the hydrogen bond (8.5 kcal/mol) and exhibited that cation–anion interactions influence the conformation of the complex. *In vitro* cytotoxicity studies of **4** and **5** using nine different human tumor cell lines revealed moderate cytotoxic activity.

1. Introduction

Since Carbon discovered in 1965 the presence of 2-thiouracil in tRNA of *Escherichia coli* [1] the role of thiopyrimidine nucleobases and their biological activity was investigated intensified, although they have not been studied as frequently as their oxygen analogues. It was found that also 4-thiouracil [2] and 2-thiocytosine [3–5] are present in tRNA of several sources. These thionucleobases and their derivatives show biological activity. Whereas the thionucleobases possess antiviral properties [6,7], derivatives of their nucleosides are potential antitumor agents [7,8]. Platinum complexes and their applications as cancerostatica were established with the discovery of cisplatin in 1965 by Rosenberg et al. [9]. Since then numerous platinum complexes have been synthesized, especially with platinum in the oxidation state II, among them also complexes with pyrimidine-2-thione ligands, which showed cytotoxic activities sometimes higher than cisplatin and even against cisplatin resistant cell lines [10–12]. Also platinum(IV) complexes proved to be highly promising as anticancer agents. They may have some advantages over platinum(II) complexes due to their greater kinetic inertness that may result in a reduced toxicity and allow oral application [13–15]. We are interested in the syntheses of platinum(IV) complexes with bioactive nitrogen and sulfur containing ligands, like thio derivatives of pyrimidine nucleobases because of several reasons. The combination of two potentially cancerostatic building blocks in one compound could lead to compounds with increased antitumor activities. From the coordination chemistry point of view these nucleobases exhibit manifold donor sites (*N*, *S*) and they can coordinate in a mono or bidentate fashion and also act as bridging ligands. To get control of their binding modes to metal centers is a challenge. In platinum(II) complexes *N*-bound 2-thiocytosine ligands were found [16]. In continuation of our work on the coordination of sulfur-substituted heterocycles to platinum(IV) [17], we report here the synthesis and characterization of trimethylplatinum(IV) complexes with 2-thiocytosine and 1-methyl-2-thiocytosine ligands.

2. Results and discussion

2.1. Synthesis and characterization of $[PtMe_3(bpy)(L)][BF_4]$ (L = SCy **4**; 1-MeSCy, **5**)

The reaction of $[PtMe_3I(bpy)]$ with silver tetrafluoroborate in methanol resulted in the formation of $[PtMe_3(bpy)(MeOH)][BF_4]$

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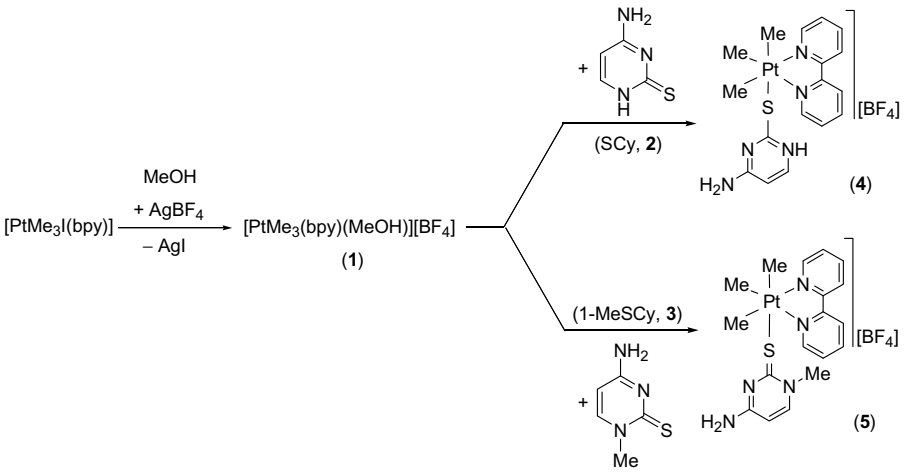


Scheme 1.

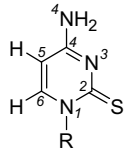
(**1**) (Scheme 1). This complex was prepared in situ and the subsequent reaction with an equimolar amount of the corresponding nucleobase (2-thiocytosine, SCy, **2**; 1-methyl-2-thiocytosine, 1-MeSCy, **3**) yielded the ionic complexes $[PtMe_3(bpy)(L)][BF_4]$ (L = SCy-κS, **4**; 1-MeSCy-κS, **5**)

The air-stable yellow complexes were isolated in 62% (**4**) and 41% yield (**5**) and identified by ^{1}H and ^{13}C NMR spectroscopy as well as by X-ray diffraction measurements. Selected ^{1}H and ^{13}C NMR data are given in Table 1. In accordance with the formula given in Scheme 1, two chemically inequivalent methyl H and C atoms were found, namely one of the methyl ligands in *trans* position to the 2,2′-bipyridine ligand and one for the methyl ligand *trans* to the coordinated thionucleobase. In complexes **4** and **5** the coupling constants ($^2J_{Pt,H}$, $^1J_{Pt,C}$) *trans* to the thionucleobase are very similar, showing that 2-thiocytosine (**2**) and its methylated derivative **3** exert virtually the same *trans* influence. In DMSO-d_6 the NH protons give rise to three (12.4, N*H*; 8.0/7.4 ppm, NH_2) and two (7.9/7.3 ppm, NH_2) broad signals for complex **4** and **5**, respectively. Due to fast H/D exchange, no *NH*-resonances were found in methanol-d_4.

Table 1
Selected ^{1}H and ^{13}C NMR spectroscopical data (δ in ppm, J in Hz) for $[PtMe_3(bpy)(L)][BF_4]$ (L = SCy, **4**; 1-MeSCy, **5**) in CD_3OD

	4 (L = SCy)		**5** (L = 1-MeSCy)	
	$\delta_H(^2J_{Pt,H})$	$\delta_C(^1J_{Pt,C})$	δ_H ($^2J_{Pt,H}$)	δ_C ($^1J_{Pt,C}$)
Me (*trans* to S)	0.45 (69.72)	2.6 (642.06)	0.47 (69.31)	2.7 (649.50)
Me (*trans* to N)	1.22 (69.30)	−4.9 (669.91)	1.25 (69.10)	−4.7 (669.26)
H5/C5[a]	5.97	99.6	6.00	100.3
H6/C6	7.28	143.4	7.58	148.6
N1–Me			3.46	44.3

[a] Numbering scheme:



(**I**, R = H, Me)

2.2. Structures of $[PtMe_3(bpy)(L)][BF_4]$ (L = SCy, **4**; 1-MeSCy, **5**)

Suitable crystals of **4** and **5** for X-ray diffraction analyses were obtained from methanol/diethyl ether/*n*-pentane solutions at 4 °C. Complex **4** · MeOH crystallizes in the centrosymmetric space group $P2_1/n$. The crystal consists of base-paired dinuclear $[\{PtMe_3(bpy)(SCy\text{-}\kappa S)\}_2]^{2+}$ cations, tetrafluoroborate anions and a solvent molecule. The structure of the cation is shown in Fig. 1. Selected bond lengths and angles are given in Table 2.

Two hydrogen bonds (N4–H···N3′: N4···N3′ 2.976(7) Å) between the thiocytosine ligands give rise to base pairing thus forming dinuclear cations that exhibit crystallographically imposed inversion symmetry. In contrast, 2-thiocytosine (**2**) crystallizes in dimers being held together by one N1–H···N3′ (N1···N3′ 3.022 Å) and one N4′–H′···S (N4′···S 3.345 Å) hydrogen bond [18]. The platinum atom is octahedrally coordinated by three methyl ligands in facial configuration, the 2,2′-bipyridine and the *S* bound 2-thiocytosine ligand. The pyrimidine ring of the thiocytosine ligand is nearly planar, while the nitrogen atom of the amino group and the sulfur atom are deviated by 0.044 Å and 0.136 Å from this plane, respectively. Coordination of 2-thiocytosine (**2**) in complex **4** · MeOH gives rise to a remarkably lengthening of the C2–S bond (1.745(7) Å versus 1.702 Å [18]). The Pt–S bond (2.524(2) Å) is even longer than those in thioether platinum(IV) complexes (median: 2.405 Å, lower/upper quartile: 2.336/2.452 Å; n = 67; n – number of observations) [19]. This long C2–S bond together with the C2–S–Pt angle (103.0(2)°) and an angle of 78.2° between the Pt–S vector and the thiocytosine plane (distance of Pt from the mean ligand plane: 2.52 Å; see Fig. 1b) indicates that the sulfur atom of the thiocytosine ligand has to be described as sp^3 hybridized. In rough approximation the planes between the thiocytosine and the bipyridine ligand are parallel (interplanar angle: 12.0(2)°). Considering the distance between these two planes of about 3.2 Å, a stabilization by π–π stacking has to be taken into consideration.

The cations $[\{PtMe_3(bpy)(SCy\text{-}\kappa S)\}_2]^{2+}$ form hydrogen bonds to the tetrafluoroborate anions (N1–H···F4: N1···F4 2.748(9) Å) and to the solvate MeOH molecules (N4–H···O: N4···O 2.935(8) Å). Furthermore, as shown in Fig. 2, the cations are packed like a "staircase" in infinite columns. Neighbored molecules are related by an inversion symmetry. The interplanar distance between the two bpy ligands of 3.5 Å and the displacement[1] of the N10, C11–C15 rings of 26° indicate that there is a stabilization through π–π and σ–π (C–H···π) interactions as thoroughly discussed in Ref. [20].

$[PtMe_3(bpy)(1\text{-}MeSCy\text{-}\kappa S)][BF_4]$ (**5**) crystallizes in the space group $C2/c$. The crystal consists of $[PtMe_3(bpy)(1\text{-}MeSCy\text{-}\kappa S)]^+$ cations and disordered tetrafluoroborate anions. The structure of the cation of **5** is shown in Fig. 3. Selected bond lengths and angles

[1] The displacement, measured by the angle between the ring normal and the centroid–centroid vector, is a measure for the ring–ring overlap [20].