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Unprecedented Pt(II) complex of an asymmetric 2,6-diacetylpyridine bis(4N-substituted thiosemicarbazone) ligand

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ABSTRACT

Reaction of 2,6-diacetylpyridine bis(4N-*o*-tolylthiosemicarbazone), $\mathbf{H_2L^1}$, with K_2PtCl_4 and further recrystallization in DMSO/MeOH of the [$\mathbf{PtL^1}$] complex obtained, led to the isolation of the novel platinum complex, [$\mathbf{PtL^2}$], which was structurally characterized by single crystal X-ray diffraction. The molecular structure shows that the ligand has undergone an unexpected chemical transformation viz. reduction of one of the terminal phenyl rings into cyclohexyl. The resulted asymmetrical ligand acts a dianionic tetradentate donor, coordinating to the platinum(II) center in a square planar geometry through the $N_{pyridinic}$ atom and the N_{iminic} and the S atoms from one thiosemicarbazone arm, the fourth coordination position is occupied by the $N_{hydrazinic}$ atom of the other arm.

Thiosemicarbazones ($R_1R_2C{=}N-NH-C(S)-NR_3R_4$) are an important and versatile type of ligands due to the potential donor atoms that they possess, among which sulfur is of paramount importance in the metal–ligand linkage. Moreover the π delocalization and configurational flexibility create the possibility of a variety of coordination modes [1–3].

The coordination capacity of thiosemicarbazones can be further increased, if the parent aldehyde or ketone contains additional functional group in a position suitable for chelation. Particularly, compounds in which the thiosemicarbazone side-chain is attached in the α position to an N-heterocyclic ring, namely α-N-heterocyclic thiosemicarbazones, are strong metal chelating agents and have been reported to be among the most effective ribonucleotide reductase (RR) inhibitors yet identified [4]. Pyridine-2-carbaldehyde thiosemicarbazone was the first member of this class reported to have carcinostatic effects and since then many α-N-heterocyclic thiosemicarbazones and their metal complexes have shown anticancer activity against a wide spectrum of tumor cell lines. Currently, the 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine, Vion Pharmaceuticals, New Haven, CT) is being evaluated in human phase II clinical trials as an antineoplastic therapeutic [5–7].

Although not as intensely studied as the mono(thiosemicarbazones), the α-N-heterocyclic bis(thiosemicarbazones) having the two thiosemicarbazone moieties positioned possess a variety of flexible donor sets and are capable of adopting various coordination modes, leading to enormous structural diversity of their complexes. For example, in the literature a series of dinuclear zinc complexes have been found derived from 2,6-diacetylpyridine bis(thiosemicarbazone) ligands showing [7 + 7], [6 + 6], [6 + 4] and [4 + 4] coordination environments [8–11]. However no structural information about d^8 metal complexes bearing 2,6-diacetylpyridine bis(thiosemicarbazone) ligands has been encountered in the bibliography.

As a part of a program concerning the behavior of α-N-heterocyclic bis(thiosemicarbazones) we have published structural studies of a series of palladium(II) and platinum(II) complexes derived from 3,5-diacetyl-1,2,4-triazol-bis(thiosemicarbazones)[12–18]. In these complexes, the square-planar coordination geometry of the central metal ions is provided by one N atom of the heterocyclic ring, the N_{iminic} and S atoms of one thiosemicarbazone arm and the S of the other thiosemicarbazone arm (dimer complexes) or the P atom of the PPh_3 coligand (mononuclear complexes).

To extend the knowledge in this research field, particularly with respect to the coordination properties of the α-N-heterocyclic bis(thiosemicarbazones) and the stereochemistry and molecular structure of the complexes, we undertook the study of platinum(II) complexes derived from 2,6-diacetylpyridine bis(4N-substituted thiosemicarbazones). Here we report on the synthesis, characterization and crystal structure of a new Pt(II) complex derived from an asymmetric 2,6-diacetylpyridine bis(4N-substituted thiosemicarbazone) ligand.

The novel ligand 2,6-diacetylpyridine bis(4N-*o*-tolylthiosemicarbazone), $\mathbf{H_2L^1}$, was synthesized by refluxing an ethanolic solution (20 mL) of 2,6-diacetylpyridine (1 mmol) with 4N-*o*-tolylthiosemicarbazide (2 mmol), which was prepared as described in reference [18], for 5 h and then was left to stand in ambient temperature. The solution was reduced to half volume and the pale yellow solid formed was filtered, washed with cold EtOH and Et_2O and dried in vacuo. The ligand was characterized by elemental analysis and FAB spectrometry as well as by IR and ^1H NMR spectroscopy [19].

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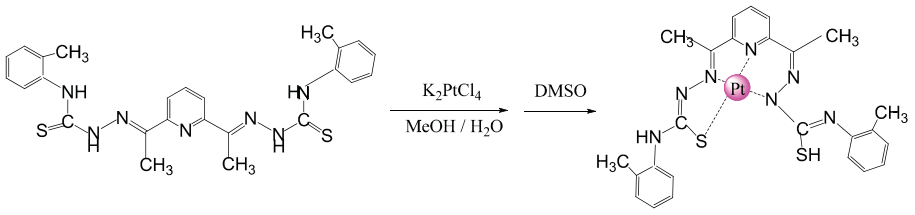


H_2L^1 $[PtL^1]$

Scheme 1.

Reaction of methanolic suspension (20 mL) of H_2L^1 ligand (1.0 mmol) with K_2PtCl_4 (1.0 mmol) in water for 5 h at room temperature yielded a brown precipitate which was filtered, washed with MeOH and Et_2O, purified by crystallization from DMSO and dried in vacuo. Analytical and spectroscopic characterization [20] was consistent with the formation of the expected neutral [PtL^1] complex (Scheme 1).

Further recrystallization of [PtL^1] from DMSO/MeOH led to the isolation of good quality single crystals which were studied by X-ray diffraction techniques [21]. The structural analysis allowed us to identify a new platinum(II) complex, [PtL^2], in which the 2,6-diacetylpyridine bis(^{4}N-*o*-tolylthiosemicarbazone) ligand has undergone an unexpected chemical transformation viz. reduction of one of the terminal phenyl rings into cyclohexyl.

Conventional hydrogenation reactions have implicit use of hydrogen as a reactant. However it is possible that in the presence of a metal complex, a donor ~~hydrogen~~ molecule transfers to a substrate which acts as an acceptor. The donor molecules which undergo dehydrogenation are often the reaction solvents and the catalysts are usually derived from platinum group metals ~~with~~ nitrogen or phosphorus donating ligands with the Wilkinson's catalyst [$RhCl(PPh_3)_3$] being the most prominent [22–24].

By inspection of the literature a few examples of thiosemicarbazone metal complexes exhibiting catalytic activity have been found. The fundamental features of these catalysts are the presence, in the complexes, of stabilizing five membered chelate rings as well as the presence of a labile coordinating bond prone to dissociate to provide an available coordination site [25–27].

In our case, the platinum complex [PtL^1] contains two five membered chelate rings as well as a more rigid and therefore less stable six membered chelate ring. Although further studies are necessary in order to identify the reductant, a possible candidate could be MeOH employed as solvent.

Since we have noticed that platinum(II) complexes derived of 3,5-diacetyl-1,2,4-triazol bis(^{4}N-*o*-tolylthiosemicarbazone) ligand have shown a notable antitumor activity [17] we analyzed the cytotoxic properties of the new complex [PtL^2] by testing its antiproliferative activity in vitro against five human cancer cell lines: NCI-H460 (non-small cell lung cancer), HepG2 (hepatocellular carcinoma), MCF-7 (breast cancer), A2780 and A2780cisR (epithelial ovarian cancer) which are among the lines used in the NCI to identify novel potential anticancer drugs. Surprisingly, the platinum(II) complex [PtL^2] shows at 100 μM concentration, a very low cellular growth inhibition (<50%) and therefore did not have evaluable cytotoxicity (IC_{50} > 100 μM). The substitution of the N-heterocyclic ring (1,2,4-triazol versus pyridine) as well as the hydrogenation on the peripheral tolyl substituent seems to be factors that influence both structure and cytotoxicity.

The molecular structure of the neutral complex [PtL^2], which crystallized with one DMSO molecule in the monoclinic $P2_1$ space group, together with the atom labeling scheme is shown in Fig. 1.

The transformed asymmetrical ligand acts a dianionic tetradentate N,N,N,S-donor, coordinating to the platinum(II) center in a square planar geometry through the $N_{pyridinic}$ atom and the N_{iminic} and the S atoms from one thiosemicarbazone arm. The fourth coordination position is occupied by the $N_{hydrazinic}$ atom of the other arm generating two typical five membered (PtSCNN and PtNCCN) and one six membered (PtNNCCN) chelate rings. Coordination by the $N_{hydrazinic}$ instead of the N_{iminic} atom, although uncommon, has been found in the bibliography for some palladium and nickel bis(thiosemicarbazone) complexes [28–30].

The Pt–N [1.979(7), 2.021(8) and 2.023(8) Å] and Pt–S [2.289(2) Å] bond distances are comparable with those reported for Pt(II) thiosemicarbazone complexes.

Since the two thiosemicarbazone moieties coordinate in a different fashion it would expect that in the bidentate-N^S arm, the C–S distance undergoes significant evolution from the thione to the thiol form [C–S distance of 1.752(9) Å] but it is important to note that the monodentate-$N_{hydrazinic}$ thiosemicarbazone arm also presents thiol C–S bond [1.81(3) Å] as well as an unexpected S–H bond.

It is well known that compounds containing thiosemicarbazone functional groups exhibit thiol–thione tautomerism, but unsubstituted and monosubstituted ones, >C=N–NH–C(S)–NHR, are capable of stabilizing a third thiol form (Scheme 2). This is consistent with the C(15)–N(5) and C(17)–N(7) bond lengths [1.309(17) and 1.295(17) Å respectively] which correspond formally to double bonds while the C(17)–N(6) bond length is longer, 1.408(13) Å.

On the other hand, along the bidentate thiosemicarbazone arm and as consequence of the extensive delocalization of electron density, the

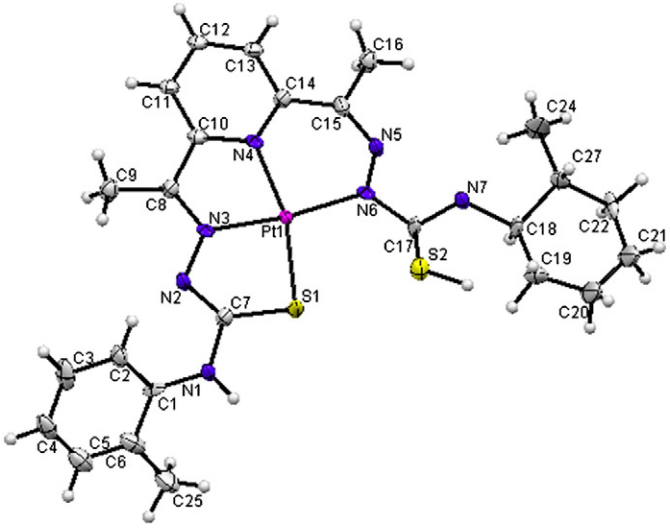
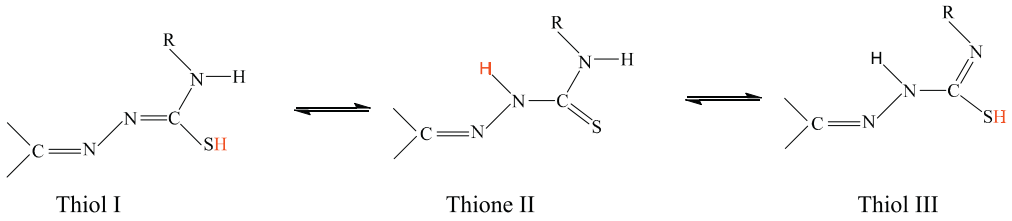


Fig. 1. Molecular structure of platinum(II) complex [PtL^2].



Scheme 2.

C–N and N–N bond distances are intermediate between formal single and double bonds.

Inspection of the angles formed between the platinum(II) ion and the coordinated atoms shows that the metal is contained within a slightly distorted square-planar environment. The distortion is caused by the restricted bite angle of the N(4), N(3), ~~and~~ S(1) donor set as reflected in the S(1)–Pt(1)–N(3) and N(3)–Pt(1)–N(4) angles (less than 90°). The angles N(4)–Pt(1)–N(6) and N(6)–Pt(1)–S(1) are therefore greater than 90°.

The crystal structure is stabilized by intermolecular hydrogen interaction involving the N(1) atom of the bidentate thiosemicarbazone arm and the oxygen atom of the DMSO solvent molecule. Within each molecule, the bis(thiosemicarbazone)-platinum moiety is close to planar, so the supramolecular association also involves π–π stacking interactions between parallel layers of molecules (Fig. 2).

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Appendix A. Supplementary material

Full crystallographic details have been deposited in CIF format with the Cambridge Crystallographic Data Centre. CCDC 890162 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 408; e-mail: deposit@ccdc.cam.ac.uk. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.inoche.2012.10.022.

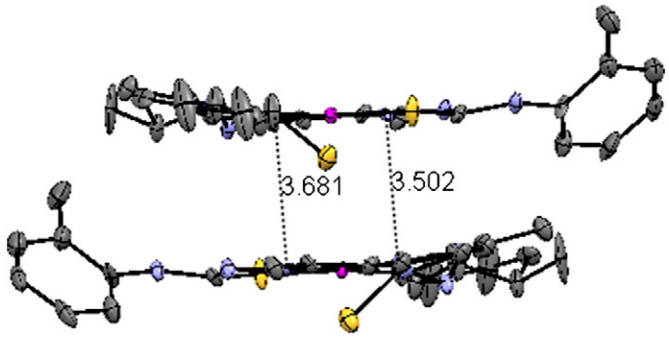

Fig. 2. View of platinum(II) complex [**PtL^2**] showing the parallel disposition of the molecules as a result of π–π stacking interactions.

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[19] Ligand **H$_2$L^1**: Yield (73%). *Anal.* % found: C, 61.00; H, 5.55; N, 19.85; S, 12.90. $C_{25}H_{27}N_7S_2$ requires: C, 61.35; H, 5.50; N, 20.05; S, 13.10. MS(FAB$^+$ with mNBA matrix), m/z = 490 for [**H$_2$L^1**+H]$^+$. IR (KBr, cm^{-1}), υ = 3308, 3238, 3151 (s, NH); υ = 1589 (s, CN), υ = 1520 (s, CN-thioamide I), υ = 878 (m, CS-thioamide IV). ^{1}H NMR (300 MHz, d^6-DMSO, ppm), δ = 10.65 [s, N(2) and N(6), 2H]; 10.10 [s, N(1) and N(7), 2H]; δ = 8.55 [d, C(11) and C(13), 2H]; 7.75 [t, C(12), 1H]; δ = 7.30–7.20 (m, aromatic-thiosemicarbazide, 8H); δ = 2.50 (s, CH_3-thiosemicarbazide, 6H); δ = 2.25 (s, CH_3-diacetylpyridine, 6H).
[20] Complex [**PtL^1**]: Yield (55%). *Anal.* % found: C, 42.35; H, 3.95, N, 13.00; S 12.25; $C_{25}H_{31}N_7PtS_2$·DMSO requires C, 42.45; H, 4.30, N, 12.85; S 12.60%. MS(FAB$^+$ with mNBA matrix), m/z = 683 for [**PtL^1**+H]$^+$. IR (KBr, cm^{-1}), υ = 3353 (s, NH), υ = 1586 (s, CN),

υ = 1523 (s, CN-thioamide I), υ = 849 (w, CS-thioamide IV). ^{1}H NMR (300 MHz, d^6-DMSO, ppm), δ = 10.77, 9.50 [s, N(1) and N(7), 1H]; δ = 8.52 [d, C(11) and C(13), 2H]; 7.98 [t, C(12), 1H]; δ = 7.37–7.10 (m, aromatic-thiosemicarbazide, 8H); δ = 2.76 (s, CH_3-thiosemicarbazide, 6H); δ = 2.27, 2.21 (s, CH_3-diacetylpyridine, 3H).

[21] Crystal data for complex [**PtL^2**]·DMSO: $C_{27}H_{37}N_7OPtS_3$, M = 766.91, monoclinic, space group $P2_1$, a = 13.7849(6) Å, b = 7.0373(3) Å, c = 15.8575(6) Å, α = 90°, β = 113.933(2)°, γ = 90°, V = 1406.05(10) Å^3, T = 296(2) K, Z = 2, D_c = 1.811 Mg/m^3, F(000) = 764, μ = 5.249 mm^{-1}, λ = 0.71073 Å, 16,080 observed reflections, 5150 independent reflections [R(int) = 0.0495]. The final agreement factors are R1 = 0.0411, wR2 = 0.1076 with I > 2σ(I) and R indices (all data) R1 = 0.0571, wR2 = 0.1382.

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