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

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Reaction of 2,6-diacetylpyridine bis(N-o-tolylthiosemicarbazone), H₂L₁, with K₂PtCl₄ and further recrystallization in DMSO/MeOH of the [PtL₁] complex obtained, led to the isolation of the novel platinum complex, [PtL₂], 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 resulting asymmetrical ligand acts as a dia ion tetradentate donor, coordinating to the platinum(II) center in a square planar geometry through the Npyridinic atom and the Nimidinic and S atoms from one thiosemicarbazone arm, the fourth coordination position is occupied by the Nimidinic atom of the other arm.

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Reaction of methanolic suspension (20 mL) of H₂L¹ ligand (1.0 mmol) with K₂PtCl₄ (1.0 mmol) in water for 5 h at room temperature yielded a brown precipitate which was filtered, washed with MeOH and Et₂O, purified by crystallization from DMSO and dried in vacuo. Analytical and spectroscopic characterization [20] was consistent with the formation of the expected neutral [PtL¹] complex (Scheme 1).

Further recrystallization of [PtL¹] 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, [PtL²], in which the 2,6-diaceetylpyridine 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 reagent. 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(PPh₃)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 catalytic systems 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 [PtL¹] 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-diaceetyl-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 [PtL²] 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 [PtL²] shows at 100 μM concentration, a very low cellular growth inhibition (~50%) and therefore did not have evaluable cytotoxicity (IC₅₀>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 [PtL²], which crystallized with one DMSO molecule in the monoclinic P2₁ 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 Npyridinic atom and the Niminic and the S atoms from one thiosemicarbazone arm. The fourth coordination position is occupied by the Nhydrazinic atom of the other arm generating two typical five membered (PtSCN and PtNCCN) and one six membered (PtNCCN) chelate rings. Coordination by the Nhydrazinic atom, although uncommon, has been found in the bibliography for some palladium and nickel bis(thiosemicarbazone) complexes.[149–150]

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.[151–153]

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-Nhydrazinic thiosemicarbazone arm also presents thiol-C – S bond [1.81(3) Å] as well as an unexpected S – H bond.[154–155]

It is well known that compounds containing thiosemicarbazone functional groups exhibit thiol–thione tautomorism, but unsubstituted and monosubstituted ones, >C=S – NH – C(S) – NH, are capable of stabilizing a third thiol form (Scheme 2). This is consistent with the C(15) – N(5) = 1.64 Å and C(17) – N(7) bond lengths [1.309(17) and 1.295(17) Å respectively] which correspond formally to double bonds whereas 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 [PtL²].](image-url)
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 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 40; e-mail: deposit@ccdc.cam.ac.uk. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jico.2012.10.022.

References
$\nu = 1523$ (s, CN-thioamide I), $\nu = 849$ (w, CS-thioamide IV). $^{1}H$ NMR (300 MHz, d$_6$-DMSO, ppm), $\delta = 10.77, 9.50$ [s, N(1) and N(7), 1H]; $\delta = 8.52$ [d, C(11) and C(13)], 2H); $\delta = 7.98$ [t, C(12), 1H]; $\delta = 7.37 - 7.10$ (m, aromatic-thiosemicarbazide, 8H); $\delta = 2.76$ (s, CH$_3$-thiosemicarbazide, 6H); $\delta = 2.27, 2.21$ (s, CH$_3$-diacetylpyridine, 3H).

[21] Crystal data for complex [PtL$_2$]·DMSO: C$_{27}$H$_{37}$N$_7$O$^+$PtS$_3$, M=766.91, monoclinic, space group $P2_1$, $a=13.7849(6)$ Å, $b=7.0373(3)$ Å, $c=15.8575(6)$ Å, $\alpha = 90^\circ$, $\beta = 113.933(2)^\circ$, $\gamma = 90^\circ$, $V=1406.05(10)$ Å$^3$, $T=296(2)$K, $Z=2$, $D_c=1.811$ Mg/m$^3$, $F(000)=764$, $\mu = 5.249$ mm$^{-1}$, $\lambda = 0.71073$ Å, 16,080 observed reflections, 5150 independent reflections [$R_{int}=0.0495$]. The final agreement factors are $R_1=0.0411$, $wR_2=0.1076$ with $I>2\sigma(I)$ and $R$ indices (all data) $R_1=0.0571$, $wR_2=0.1382$.


