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Preliminary Communication

Five- and six-membered indole-fused platinacycles

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Abstract

Gramine ($C_8H_5NHCH_2NMe_2$) **4** undergoes regioselective metallation at C-2 by $[Pt(DMSO)_2Cl_2]$ to form the first structurally characterised indole-fused platinacycle σ-$[Pt(C_8H_4NHCH_2NMe_2)(DMSO)Cl]$ **1**; tryptamine ($C_8H_5NHCH_2CH_2NH_2$) **5** and (S)-tryptophan methyl ester $C_8H_5NHCH_2CH(NH_2)CO_2Me$ **6** give respectively σ-$[Pt(C_8H_4NHCH_2CH_2NH_2)(DMSO)Cl]$ **2** and σ-$[Pt\{(S)\text{-}C_8H_4NHCH_2CH(NH_2)\}\text{-}CO_2Me\}(DMSO)Cl]$ **3**.

Keywords: Platinum; *Ortho*-metallation; X-ray structure; Indole platinacycles

The heteroatom-directed cyclometallation reaction has been a topic of interest over the last decades owing mainly to its potential utility in organic and organometallic synthesis [1]. Although considerable attention has been devoted to the reactivity of several benzenoid and heteroaromatic systems in cyclometallation, much less interest has been shown in the chemistry of indole derivatives [2]. In this preliminary communication we describe the synthesis and structure of hitherto unknown 5- and 6-membered indole-fused *ortho*-platinacycles **1**, **2** and **3**, involving gramine **4**, tryptamine **5** and (S)-tryptophan methyl ester **6** respectively as C,*N*-bidentate ligands.

Reaction of 4–6 with various Pt(II) salts and complexes under standard conditions always led to undefined mixtures containing metallic Pt and starting material. Cyclometallation could only be achieved when *cis*-$[Pt(DMSO)_2Cl_2]$ [3] reacted with the donor (i.e. **4**) in refluxing EtOH (30 min) in the presence of NaOAc as a proton acceptor. Monomeric σ-$[Pt(C_8H_4NHCH_2NMe_2)(DMSO)Cl]$ **1** was obtained as pale yellow needles in nearly quantitative yield from this reaction. The ^1H, ^{13}C and ^{195}Pt NMR spectra indicated that a single isomer was formed. The loss of a broad singlet (at 7.12 ppm; H-2) and the presence of a quaternary carbon resonance at 133.5 ppm instead of a methine carbon resonance (at 123.4 ppm; C-2) in **4** are consistent with *ortho*- [C-2 as σ-donor] rather than *peri*-cyclometallation [C-4 as a σ-donor]. Furthermore, the NMe resonances after metallation and the values of coupling constants ($^3J_{Pt-H}$) are both indicative of a good donor *trans* to the NMe and reflect the strong σ Pt–C interaction [4]. The observation of a single SMe resonance at 3.57 ppm with ^{195}Pt satellites ($^3J_{Pt-H}$ 26 Hz) as well as the $\nu_{(S-O)}$ at 1124 cm^{-1} in the IR spectrum indicate an *S*-bonded DMSO configuration [5]. The crystal structure of complex **1** (as CH_2Cl_2 solvate) [1]

[1] Crystal Data for **1**: $C_{13}H_{19}ClN_2OPtS.CH_2Cl_2$, M = 566.85, monoclinic, space group $P2_1/c$ (no. 14), $a = 6.179(1)$, $b = 9.307(1)$, $c = 31.218(4)$ Å, $\beta = 92.17(1)°$, $U = 1793.9(5)$ Å^3, $F(000)$ 1088, $Z = 4$, $D_c = 2.099$ g cm^{-3}, Mo Kα radiation ($\lambda = 0.71073$ Å), μ(Mo Kα) = 84.7 cm^{-1}. Reflections with $2° < \theta < 25°$ measured on a CAD4 diffractometer at room temperature.

Data corrected for Lorentz-polarization, decay, absorption and secondary extinction effects. 2474 independent reflections having $I > 3\sigma(I)$ were used in the structure refinement with anisotropical displacement parameters assigned to all the non-hydrogen atoms. Final R value 0.037 ($R_w = 0.050$).

Atomic coordinates, displacement parameters, interatomic distances and angles have been deposited at the Cambridge Crystallographic Data Centre.

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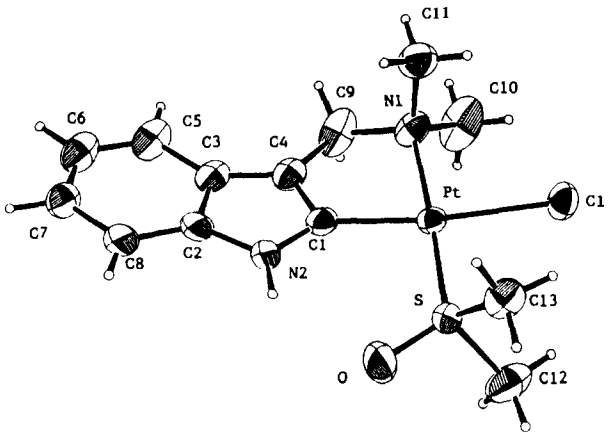
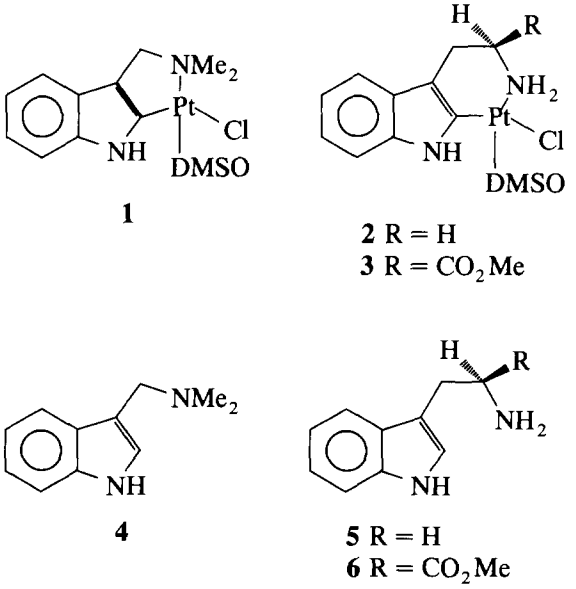


Fig. 1. ORTEP drawing of complex **1**. Thermal ellipsoids are drawn at 30% probability. Relevant bond distances (Å) are: Pt–Cl 2.394 (2), Pt–S 2.180 (2), Pt–N(1) 2.124(5), Pt–C(1) 1.973 (7), N(2)–C(1) 1.364 (9), N(2)–C(2) 1.386 (8), C(1)–C(4) 1.352 (9), C(2)–C(3) 1.385 (10), C(3)–C(4) 1.400 (9), C(4)–C(9) 1.521 (11), N(1)–C(9) 1.521 (9), S–O 1.455 (7), S–C(12) 1.780 (9), S–C(13) 1.760 (8).

conclusively showed that NMe_2 moiety directs metallation to the 2-position, producing a five-membered ring system with an (*SP-4-4*)-stereochemistry [6] with the halogen ligand *trans* to the carbon σ-donor, consistent with $\nu_{(Pt-Cl)}$ at 280 cm^{-1} (see Fig. 1) [7].

In view of the biological importance of 3-substituted indoles such as tryptamine **5** and (*S*)-tryptophan (as its methyl ester, **6**), we have prepared similarly the corresponding 6-membered platinacycles **2** (85% yield) and **3** (78% yield). The observed regioselectivity [*ortho*- vs. *peri*-cyclometallation] can be rationalized in terms of the more effective delocalization of the positive charge in the σ-complex (Wheland intermediate) formed on attack of the electrophilic metal centre at C(2) rather than C(4) of the 3-substituted indole ring [8]. Both complexes **2** and **3** crystallised as very thin plates which were unsuitable for X-ray crystallography but their stereochemistry was inferred from spectroscopic data and solid-state structure of the congener **1**. [2]. The indole NH chemical shift of **1** was shifted further upfield than the analogous proton of the 6-membered platinacycles **2** and **3**. This can be attributed to different extents of metal-to-ligand back-bonding between the filled t_{2g} orbitals of Pt and the vacant π^* orbitals of the indole ring [9].

Finally, it is well known that certain *ortho*-metallated complexes of Pt have been shown to bind covalently to DNA [10] and so our platinacycles may give rise to a new series of Pt-based drugs with cytotoxic activity.



Scheme 1.

[2] Satisfactory elemental analyses were obtained for derivatives **1–3**. σ-[Pt($C_8H_4NHCH_2NMe_2$)(DMSO)Cl]**1**: m.p. 215°C(dec.)(CH_2Cl_2/hexane); IR(nujol, ν/cm^{-1}): 3389, 3373, 3362, 1651, 1377, 1124, 1018, 852, 769, 280, 254; ^{1}H NMR[300 MHz, $CDCl_3$; δ(ppm)/J(Hz)] **3**.10(6H, s, NMe_2), 3.57 (6H, s, $^3J_{Pt-H}$ 26.1, SMe_2), 4.07 (2H, s, $^3J_{Pt-H}$ 25, CH_2N), 6.99 (2H, m, H-5 and H-6), 7.30 (1H, dd, J_{H-H} 8.7, 2.9; H-7), 7.33(1H, dd, J_{H-H} 8.8, 3.1; H-4), 9.40(1H, s, N*H*); ^{13}C NMR[75.0 Hz, $CDCl_3$, δ(ppm)/J(Hz)] 46.3(CH_3–S, $^2J_{Pt-C}$ 63), 53.3(CH_3–N, $^2J_{Pt-C}$ 53.3), 68.2(CH_2–N, $^2J_{Pt-C}$ 34), 111.0(C-7), 116.7(C-4), 118.5(C-5), 119.1(C-3), 119.6(C-6), 125.2(C-3a), 133.5(C-Pt), 138.0(C-7a); ^{195}Pt NMR (64.4 MHz, K_2PtCl_6, $CDCl_3$) δ −3709; EI-MS 482[M^+·(^{195}Pt)], 404, 368, 366, 323, 173, 130.

[Pt($C_6H_4NHCH_2CH_2NH_2$)(DMSO)Cl] **2**: m.p. 155°C(dec.) (EtOH); IR(nujol, ν/cm^{-1}): 3411, 3234, 1652, 1557, 1126, 1026, 275, 253; ^{1}H NMR ($CDCl_3$) 2.91 (2H, M, $^3J_{Pt-H}$ 60; N-CH_2), 3.04 (2H, t, J_{H-H} 6), 3.44 (6H, s, $^3J_{Pt-H}$ 22; S*Me*$_2$), 4.09 (2H, br s, $^2J_{Pt-H}$ 66, NH_2), 7.00(2H, m, H-5 and H-6), 7.29 (1H, dd, J_{H-H} 8.6, 3.0; H-7), 7.36(1H, dd, J_{H-H} 8.7, 3.1; H-4), 10.30(1H, br s, $^3J_{Pt-H_2}$25; NH); ^{13}C NMR ($CDCl_3$) 24.8(CH_2, $^3J_{Pt-C}$ 20), 42.3(N–CH_2, $^2J_{Pt-C}$ 60), 46.4(S–CH_2, $^3J_{Pt-C}$ 22), 108.9(C-3), 110.4(C-7), 115.2(C-Pt), 116.2(C-4), 118.3(C-5), 120.3(C-6), 128.4(C-3a), 136.7(C-7a); ^{195}Pt NMR-3711; EI-MS 468($M^{+\cdot}$), 390, 351, 323, 173, 130.

σ-[Pt{(S)$C_8H_4NHCH_2CH(NH_2)CO_2Me$}(DMSO)Cl] **3**: m.p. 225°C(dec.) (EtOH); IR(ν/cm^{-1}): 3334, 3225, 3218, 3127, 1731, 1465, 1273, 1225, 1128, 273, 256; ^{1}H NMR ($CDCl_3$) 3.15(2H, AB part of ABX system, $^2J_{H-H}$ 15.6; $\Delta\nu$ 191 Hz; CH_2CH), 3.46(3H, s, $^3J_{Pt-H}$ 23; S*Me*), 3.53(3H, s, $^3J_{Pt-H}$ 23; S*Me*), 3.74(3H, s, O*Me*), 3.78 (1H, X part of ABX system, $^3J_{H-H}$ 11, 376; C*H*N), 4.26(1H, dd, $^3J_{H-H}$ 11, 11; $^2J_{Pt-H}$ 50; N*H*), 4.72(1H, dd, $^3J_{H-H}$ 11, 2.5; $^2J_{Pt-H}$ 70; N*H*), 7.01(2H, m, H-5 and H-6), 7.35 (2H, m, H-4 and H-7), 10.20(1H, s, $^3J_{Pt-H}$ 26; N*H*); ^{13}C NMR($CDCl_3$) 27.4(CH_2C, $^3J_{Pt-C}$ 26), 46.3(S-*Me*, $^2J_{Pt-C}$ 53), 46.9 (S-*Me*, $^2J_{Pt-C}$ 53), 53.1(O*Me*), 54.4(*C*HN), 108.6(C-3), 110.5(C-7), 116.2(C-4), 116.7(C-Pt), 118.5(C-5), 120.3(C-6), 128.3(C-3a), 136.5(C-7a), 171.0(C=O); ^{195}Pt NMR ($CDCl_3$) δ −3712; $[\alpha]_D$ −32.4°(*c* 2.46; $CHCl_3$); UV[MeCN, λ_{max}(nm)] 240 and 312; CD[MeCN, $\lambda(\Delta\varepsilon)$] 235(+5.33), 245(0), 260(−2.5), 292(−0.33), 317(−2.16), 367(0); EI-MS 526($M^{+\cdot}$), 448, 411, 351, 323, 218, 130, 117. The atoms in the indole ring have been numbered according to IUPAC rules.

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