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Palladium(II) and platinum(II) complexes containing dimesyloxy-substituted chiral diamines

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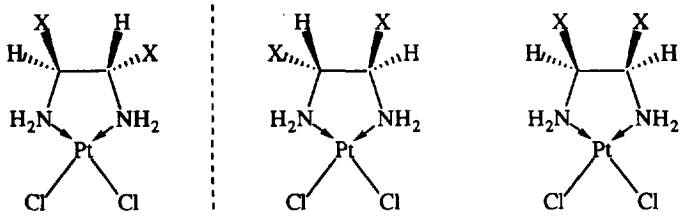
Abstract: The physically stable but chemically reactive square-planar complex (+)-[(dichloro){(S,S)-1,4-dimesyloxy-2,3-butanediamine}palladium(II)] and its platinum(II) analogue have been prepared from the reactions between the dihydrochloride salt of the diamine and K_2MCl_4 (where M=Pd, Pt) in water. The palladium complex has been analysed by X-ray crystallography. In contrast to their metal complexes, the free diamine ligand and its dihydrochloride salt are unstable and cannot be isolated. © 1997 Elsevier Science Ltd

The potential of metal complexation as an adjunct to human medicine is an area of research that has flourished during the past decade.[1] Cisplatin, the first inorganic platinum anti-cancer drug licensed in 1978, represents a drastic departure from other synthetic organic cancer chemotherapeutic agents. To date, this drug, together with its carboplatin analogue, are almost universally used in the treatment of several forms of cancer.[2] Although cisplatin and carboplatin therapy have achieved major improvements in some forms of cancer, unfortunately in some cases remissions are often of limited duration and cisplatin also induces major side effects. Many patients are still not able to tolerate treatment with these inorganic drugs at an effective dose level. We are interested in developing a series of 1,2-difunctionalized ethylene diamine and related bidentates as carrier ligands. By the incorporation of a variety of selected biologically active functional groups into these carrier ligands, it is hoped that the clinical properties of the corresponding inorganic drugs can be modified systemically. In addition, the approach introduces new stereogenic centres at the ethylene carbon linkage. Thus, for any selected functionality, three non-superimposable stable isomers are envisaged for the square-planar platinum(II) drugs. One of our major emphases in this work is on the preparation and evaluation of each drug in its stereoisomeric pure forms. It is well established that, in addition to functionality,[3] stereochemistry plays an important role in medicine and in biology.[4] In this paper, we report the asymmetric synthesis of 1,4-dimesyloxy-2,3-butanediamine and its palladium(II) and platinum(II) complexes. We plan to use these steroisomerically pure complexes directly as the starting materials for our targeted inorganic drugs.



racemic meso

The synthetic difficulties in the asymmetric synthesis and resolution of chiral diamines have been highlighted numerous times, particularly in studies that require all the stereoisomeric forms of the bidentate ligands.[5] We have previously reported an efficient approach to the stereoisomerically pure

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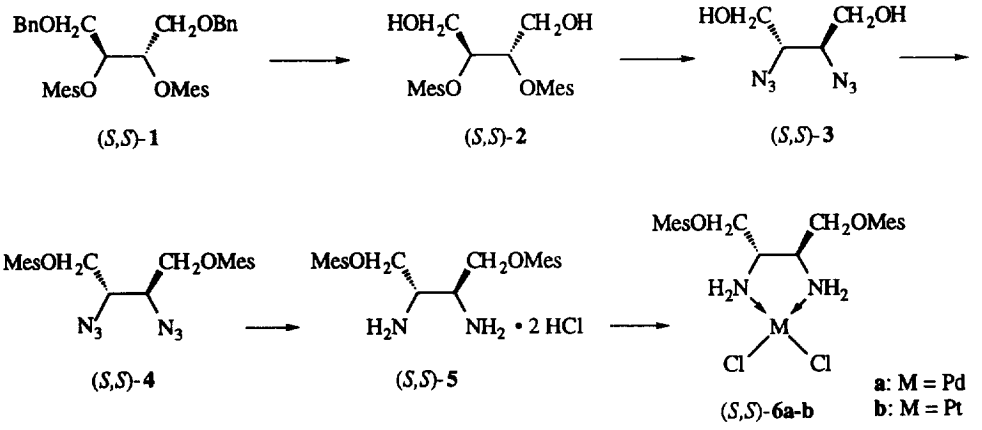
(+), (−) and meso forms of 2,3-diaminobutane using the appropriate forms of tartaric acid as the starting materials.[6] By modifying this approach via a series of protection, deprotection and other organic reactions, in principle, a range of functionalized diamines can be generated in their specific isomeric forms. Instead of designing individual synthetic routes for different functionalities, we chose to use the three forms of tartaric acid to prepare the corresponding 1,4-dimesyloxy-2,3-butanediamine and their palladium(II) and platinum(II) complexes.

Scheme 1 illustrates the synthetic approach to the target dimesyloxy-substituted complexes. Thus, enantiomerically pure (*S,S*)-**1** was obtained from (*R,R*)-tartaric acid using literature methods.[7] Hydrogenolysis of (S,S)-**1** proceeded smoothly in ethanol containing small quantity of concentrated HCl and 10% Pd/C to give the diol (*S,S*)-**2** as a colourless oil in 92% yield with $[\alpha]_D$ −4.76 (*c* 1.2, acetone). Interestingly, the reactive mesylate group remained intact under the hydrogenolysis conditions employed. However, stereospecific displacement of the dimesylate groups can be achieved by treatment of (*S,S*)-**2** with excess sodium azide in dimethylformamide at 70°C to give (*S,S*)-**3** efficiently. After silica chromatography and crystallization from diethyl ether and hexane, the diazido compound was obtained as colourless needles in 70% isolated yield with $[\alpha]_D$ −40.3 (*c* 0.5, diethyl ether). It should be noted that the azide displacement reaction results in the inversion of configurations at the two carbon stereogenic centres. The fact that the prefix (*S,S*) remains unchanged in the conversion of the dimesylate to the diazido species is merely a consequence of the CIP sequence rule.[8] The hydroxy groups in (*S,S*)-**3** reacted smoothly with methanesulfonyl chloride at −25°C in dichloromethane in the presence of triethylamine. Thus, the dimesylate (*S,S*)-**4** was obtained as colourless crystals in 90% yield with $[\alpha]_D$ −10.8 (*c* 1.8, tetrahydrofuran). Hydrogenation of (*S,S*)-**4** by using 10% Pd/C as the catalyst in a concentrated hydrochloric acid–ethanol solvent mixture for 5 h gave the crude diamine (*S,S*)-**5** as its dihydrochloride salt. (*S,S*)-**5** is very unstable in neutral solvent and transforms rapidly into a yet unidentified species upon further purification. The colourless flaky crystals of crude (*S,S*)-**5** was therefore treated directly with K_2PdCl_4 in water. The palladium(II) complex (*S,S*)-**6a** was obtained as bright yellow crystals in 87% isolated yield with $[\alpha]_D$ +71.4 (*c* 0.1, dimethylformamide). In contrast to its diamine precursor, the square-planar palladium(II) complex is stable, both in the solid state and in solution. The X-ray analysis of (*S,S*)-**6a** confirms that the desired chiral palladium complex containing the 1,4-dimesyloxy-2,3-butanediamine has formed (Figure 1) and establishes the *S* absolute configuration at both stereogenic carbon centres.[9,11] It is noteworthy that in (*S,S*)-**6a**, the five-membered chiral chelate ring adopts the predictable λ absolute conformation. Thus the mesyloxy substituents on the ethylenediamine skeleton are occupying the sterically favourable equatorial positions.[10]



Scheme 1.

The platinum(II) complex (*S,S*)-**6b** was prepared similarly. However, the desired product was obtained in only 20% isolated yield as pale yellow microcrystals with $[\alpha]_D$ +58.2 (*c* 0.1, dimethylforma-

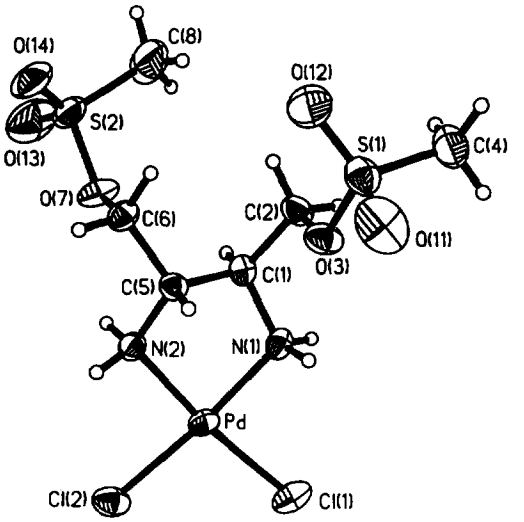


Figure 1. Molecular structure and the absolute stereochemistry of (*S,S*)-**6a**. Selected bond lengths (Å) and angles (deg): Pd–Cl(1), 2.313(1); Pd–Cl(2), 2.322(1); Pd–N(1), 2.025(4); Pd–N(2), 2.036(4); N(1)–C(1), 1.488(6); N(2)–C(5), 1.487(5); S(1)–O(11), 1.418(5); S(1)–O(12), 1.417(5); S(1)–O(3), 1.577(4); S(1)–C(4), 1.752(5); S(2)–O(13), 1.410(6); S(2)-O(14), 1.410(5); S(2)–O(7), 1.571(4); S(2)–C(8), 1.746(8); C(1)–C(2), 1.520(6); C(1)–C(5), 1.526(6); C(2)–O(3), 1.454(6); C(5)-C(6), 1.520(6); C(6)-O(7), 1.445(6); Cl(1)–Pd–Cl(2), 95.1(1); Cl(1)–Pd–N(1), 90.3(1); Cl(2)–Pd–N(1), 174.4(1); Cl(1)–Pd–N(2), 173.5(1); Cl(2)–Pd–N(2), 91.4(1); N(1)–Pd–N(2), 83.2(1); Pd–N(1)–C(1), 109.4(2); Pd–N(2)–C(5), 109.6(2); N(1)–C(1)–C(5), 106.0(3); N(2)–C(5)–C(1), 106.5(3).

mide). Spectroscopic and elemental analyses indicated that the major product generated in this reaction was (dichloro){1-chloro-4-mesyloxy-2,3-butanediamine}platinum(II) which could not be purified by crystallization. This chloro–mesyloxy–diamine chelating ligand could be converted quantitatively into (dichloro){1,4-dichloro-2,3-butanediamine}platinum(II) as fine yellow needles, $[\alpha]_D$ +52.3 (*c* 0.1, dimethylformamide) by treatment with lithium chloride in acetone. Similarly, (dichloro){1,4-dichloro-2,3-butanediamine}palladium(II)was thus obtained from (*S,S*)-**6a** in 75% isolated yield, $[\alpha]_D$ +96.5 (*c* 0.1, dimethylformamide). Interestingly, the displacement of the mesyloxy groups in (*S,S*)-**6a–b** by the chloride ion was found to proceed as least five times faster than the parallel reaction using the non-coordinated (*S,S*)-**4** as the starting material. This striking increase in the rate of displacement is attributed to ligand activation by platinum and palladium ions. Finally, it should be noted that the (*R,R*)- and meso- forms of **6a–b** have been prepared similarily from the commerically available (*S,S*)- and meso forms of tartaric acid, respectively. The conversion of these dimesyloxy-substituted complexes into various selected functionalities will be described in a further paper.

Experimental

General

Reactions involving moisture-sensitive compounds were performed under a positive pressure of purified nitrogen. ^{1}H NMR spectra were recorded at 25°C on a Brucker ACF 300 spectrometer. IR spectra were obtained from a Perkin Elmer 598 spectrometer. Optical rotations were measured on the specified solutions in a 1-dm cell at 25°C with a Perkin Elmer 241 polarimeter. Melting points were determined on an analyser by the Microanalytical Laboratory staff of the Chemistry Department. (*S,S*)-1,4-Dibenzyloxy-2,3-dimesyloxybutane, (*S,S*)-**1**, was obtained to procedures in literature.[7]

(S,S)-2,3-Dimesyloxy-1,4-butanediol, (S,S)-2

(*S,S*)-1,4-Dibenzyloxy-2,3-dimesyloxybutane (15 g, 32.8 mmol) was hydrogenated with 10% palladium on activated carbon (3.5 g) in ethanol (400 mL) in the presence of concentrated hydrochloric

acid (5 mL). After 5 h, the hydrogenation catalyst was filtered off and the crude product was purified by aluminium oxide column chromatography using ethyl acetate as the eluent. Thus (*S,S*)-**2** was obtained as a colourless oil (8.4 g, 92%). Found: C, 26.10; H, 5.14; S, 22.85. $C_6H_{14}O_8S_2$ requires C, 25.90; H, 5.04; S, 23.02. ^{1}H NMR (d_6-acetone) δ 3.20 (s, 6H, 2×SMe), 3.87–3.97 (m, 4H, 2×CH_2O), 4.44 (t, 2H, $^3J_{HH}$=5.65 Hz, 2×OH), 4.89–4.90 (m, 2H, 2×CHO). ^{13}C NMR (d_6-acetone) δ 38.7 (CH_3), 61.4 (CH_2), 81.6 (CH). IR (neat) 3400 (O–H), 1340, 1175 (O=S=O) cm^{-1}.

*(S,S)-2,3-Diazido-1,4-butanediol, (S,S)-**3***

The optically active dimesylate (11.6 g, 41.7 mmol) was treated with sodium azide (5.4 g, 83.5 mmol) in dimethylformamide (500 mL) at 70°C in the presence of concentrated hydrochloric acid (2 mL). After 14 d, the solvent was removed under reduced pressure and the crystalline crude product was extracted into diethyl ether (3×200 mL) and washed with water. After silica column chromatography, the diazido species was crystallized from diethyl ether–hexane as colourless fine needles (4.1 g, 70%). Found: C, 27.96; H, 4.49; N, 48.88. $C_4H_8N_6O_2$ requires C, 27.91; H, 4.65; N, 48.84. ^{1}H NMR (d_6-acetone, D_2O exchange) δ 3.66–3.70 (m, 2H, 2×CHN), 3.76 (dd, 2H, $^2J_{HH}$=11.3 Hz, $^3J_{HH}$=6.8 Hz, 2×C*H*H′O), 3.82 (dd, 2H, $^2J_{HH}$=11.4 Hz, $^3J_{HH}$=4.6 Hz, 2×CH*H*′O). ^{13}C NMR (d_6-acetone) δ 62.8 (CH), 64.2 (CH_2). IR (KBr) 3265 (O–H), 2115 (N_3) cm^{-1}.

Caution! All azides are potentially explosive compounds and must be handled carefully.

*(S,S)-1,4-Dimesyloxy-2,3-diazidobutane, (S,S)-**4***

A solution of methanesulfonyl chloride (1.5 mL, 19.3 mmol) in dichloromethane (10 mL) was added dropwise into a mixture of (*S,S*)-**3** (1.2 g, 7.0 mmol) and triethyl amine (3.5 mL, 23.5 mmol) in dichloromethane (20 mL) at 25°C. After the reaction was stirred for 5 h at the same temperature, water (50 mL) was added. The crude product was extracted into dichloromethane and then recrystallized from ethanol as colourless prisms (2.6 g, 90%). Found: C, 21.98; H, 3.56; N, 25.57; S, 19.47. $C_6H_{12}N_6O_8S_2$ requires C, 21.95; H, 3.66; N, 25.61; S, 19.51. ^{1}H NMR ($CDCl_3$) δ 3.13 (s, 6H, 2×SMe), 3.90–3.96 (m, 2H, 2×CHN), 4.42 (dd, 2H, $^2J_{HH}$=10.9 Hz, $^3J_{HH}$=6.5 Hz, 2×C*H*H′O), 4.46 (dd, 2H, $^2J_{HH}$=10.9 Hz, $^3J_{HH}$=4.9 Hz, 2×CH*H*′O). ^{13}C NMR ($CDCl_3$) δ 37.9 (CH_3), 59.7 (CH), 67.1 (CH_2). IR (neat) 2110 (N_3), 1351, 1175 (O=S=O) cm^{-1}.

*(S,S)-1,4-Dimesyloxy-2,3-butanediamine, (S,S)-**5***

(*S,S*)-1,4-dimesyloxy-2,3-Diazidobutane (0.4 g, 1.2 mmol) was hydrogenated with 10% palladium on activated carbon (80 mg) in ethanol (25 mL) in the presence of concentrated hydrochloric acid (0.8 mL). After 5 h, the hydrogenation catalyst was filtered off. Upon removal of the solvent, the dihydrochloride salt of (*S,S*)-**5** was obtained as unstable colourless flaky crystals. ^{1}H NMR (d_6-DMSO) δ 3.41 (s, 6H, 2×SMe), 4.09–4.14 (m, 2H, 2×CHN), 4.60 (dd, 2H, $^2J_{HH}$=10.6 Hz, $^3J_{HH}$=6.4 Hz, 2×C*H*H′O), 4.75 (dd, 2H, $^2J_{HH}$=10.6 Hz, $^3J_{HH}$=2.2 Hz, 2×CH*H*′O). ^{1}H NMR (D_2O) δ 3.31 (s, 6H, 2×SMe), 4.20–4.21 (m, 2H, 2×CHN), 4.65 (dd, 2H, $^2J_{HH}$=11.3 Hz, $^3J_{HH}$=6.4 Hz, 2×C*H*H′O), 4.70 (dd, 2H, $^2J_{HH}$=11.3 Hz, $^3J_{HH}$=2.6 Hz, 2×CH*H*′O). ^{13}C NMR (D_2O) δ 39.4 (CH_3), 51.8 (CH_2), 67.5 (CH). IR (KBr) 3420, 2995, 1614 (NH), 1347, 1175 (O=S=O) cm^{-1}.

*Dichloro{(S,S)-1,4-dimesyloxy-2,3-butanediamine}palladium(II), (S,S)-**6a***

A solution of (*S,S*)-1,4-dimesyloxy-2,3-butanediamine dihydrochloride (3.1 g, 0.9 mmol) in distilled water (2 mL) was added to a stirring solution of potassium tetrachloropalladate (2.9 g, 0.9 mmol) in water (10 mL). The pale yellow precipitate formed was filtered and washed with cold water (5 mL). Crystallization of the crude product in hot water afforded the dichloro complex as bright yellow crystals (3.5 g, 87%). Found: C, 16.05; H, 3.34; N, 6.12; S, 14.35; Cl, 15.90. $C_6H_{16}Cl_2N_2O_6PdS_2$ requires C, 15.89; H, 3.53; N, 6.18; S, 14.13; Cl, 15.67. ^{1}H NMR (d_7-DMF) δ 3.35 (s, 6H, 2×SMe), 3.45–3.47 (m, 2H, 2×CHN), 4.47 (dd, 2H, $^2J_{HH}$=11.2 Hz, $^3J_{HH}$=4.3 Hz, 2×C*H*H′O), 4.54 (dd, 2H, $^2J_{HH}$=11.2 Hz, $^3J_{HH}$=3.0 Hz, 2×CH*H*′O), 5.13 (bs, 2H, 2×N*H*H′), 5.35 (bs, 2H, 2×NH*H*′). IR (KBr) 3400, 3225, 1560 (NH), 1340, 1175 (O=S=O) cm^{-1}.

*Dichloro{(S,S)-1,4-dimesyloxy-2,3-butanediamine}platinum(II), (S,S)-**6b***

The platinum complex was similarly prepared using (*S,S*)-1,4-dimesyloxy-2,3-butanediamine dihydrochloride (0.4 g, 1.2 mmol) and potassium tetrachloroplatinate (0.5 g, 1.2 mmol): pale yellow crystals (0.1 g, 20%). Found: C, 13.35; H, 2.91; N, 4.97; S, 11.74; Cl, 13.20. $C_6H_{16}Cl_2N_2O_6PtS_2$ requires C, 13.28; H, 2.95; N, 5.17; S, 11.80; Cl, 13.10. ^{1}H NMR (d_7-DMF) δ 3.36 (s, 6H, 2×SMe), 3.40–3.44 (m, 2H, 2×CHN), 4.53–4.62 (m, 4H, 2×CH_2), 5.60 (bs, 2H, 2×N*H*H′), 6.74 (bs, 2H, 2×NH*H*′). ^{1}H NMR (d_6-acetone) δ 3.25 (s, 6H, 2×SMe), 3.66 (bs, 2H, 2×CHN), 4.57 (dd, 2H, $^2J_{HH}$=11.5 Hz, $^3J_{HH}$=4.5 Hz, 2×C*H*H′O), 4.63 (dd, 2H, $^2J_{HH}$=11.5 Hz, $^3J_{HH}$=2.8 Hz, 2×CH*H*′O), 5.05 (bs, 2H, 2×N*H*H′), 5.50 (bs, 2H, 2×NH*H*′). IR (KBr) 3400, 3200, 1560 (NH), 1350, 1175 (O=S=O) cm^{-1}.

Crystal structural analysis

Crystal data for (*S,S*)-**6a**: $C_6H_{16}Cl_2N_2O_6PdS_2$, *M*=453.6, orthorhombic, *a*=6.512(2), *b*=14.068(4), *c*=16.531(5) ,*V*=1514.4(7) ^{3}, space group $P2_12_12_1$, *Z*=4, D_c=1.99 g cm^{-3}, μ(Mo–K_α)=18.73 cm^{-1}, *F*(000)=904. An orange block of dimensions 0.11×0.14×0.30 mm was used. 2035 Independent reflections were measured on a Siemens P3m/V diffractometer with Mo–K_α radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically using full-matrix least-squares using the Shelxtl Plus program to give R_1=0.025, *wR*=0.040 for 1877 independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, $2\theta \leq 55°$] and 173 parameters. The *S* configuration at C(2) and C(5) in the diamine ligand was determined unambiguously *via* i) Flack parameter, x^+=−0.00(4), x^-=+0.85(5) and ii) by an *R*-factor test, wR_2^+=0.073, wR_2^-=0.081 when refinement was run on SHELX 93.

Acknowledgements

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9. Since the conversion of the 1,2-diazido species (*S,S*)-**3** to the palladium complex (*S,S*)-**6a** does not involve any S_N2 reaction at the stereogenic carbon centres, the absolute stereochemistry of (*S,S*)-**3**, with $[\alpha]_D$ −40.3 (*c* 1.0, diethyl ether), is unambiguously established. It is noted that (*S,S*)-**3** has been previously reported by Hanessian *et al.* under the name of *2,3-diazido-2,3-dideoxy-D-threitol*, with $[\alpha]_D$ +41.4 (*c* 0.5, diethyl ether),[11] which is in contrast to our findings. The diazido compound in this earlier report was obtained from the repeated oxidations and reductions of

3,4-diazido-3,4-dideoxy-D-iditol. We believe that the (+)-diazido compound should be named as *2,3-diazido-2,3-dideoxy-L-threitol* in the classic D–L system of stereochemical designations.

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