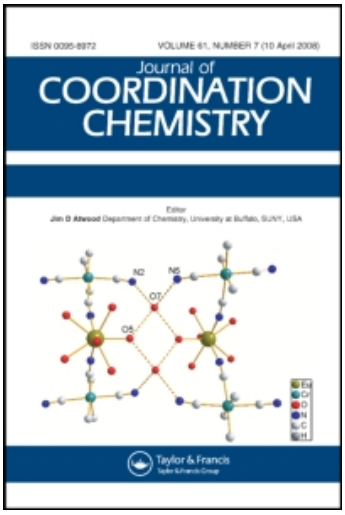

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CHIRAL PHOSPHINE LIGANDS DERIVED FROM SUGARS. 8. SYNTHESES OF GOLD(I) COMPLEXES CONTAINING CHIRAL SUGAR PHOSPHINES AND PYRIDINE-1-OXIDE-2-THIOLATE

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Gold(I) compounds [Au(n-MBPA)(2-mpoS)] (2-mpoS = pyridine-1-oxide-2-thiolate; **1**, n = 2; **2**, n = 3) with a chiral phosphine derived from glucose (n-MBPA = methyl 4,6-*O*-benzylidene-n-deoxy-n-(diphenylphosphino)-α-D-altropyranoside, n = 2, 3) have been prepared and characterized by ^{1}H, ^{13}C and ^{31}P NMR and molecular vibration spectroscopy. The spectroscopic data suggest a monodentate mode of coordination for 2-mpoS ligand through the S donor.

Keywords: gold(I); chiral phosphine; pyridine-1-oxide-2-thiolate; spectroscopy

INTRODUCTION

Gold(I) thiolate complexes have been used for the treatment of rheumatoid arthritis for over 60 years. Recently, it has been demonstrated that the phosphinegold(I) hioglucose derivative 'auranofin' [(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-*S*)(triethylphosphine)]gold(I) is efficacious and well tolerated, and exhibits therapeutic properties superior to traditional chrysotherapeutic agents for the treatment of rheumatoid arthritis;[1–3] it has also been found to be highly cytotoxic towards tumour cells[4] and active against interperitoneal P388 leukaemia.[5] The associated toxicity of this class of compounds, however, has

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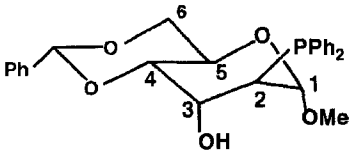
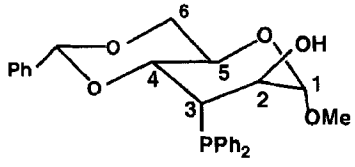
precluded some of them from further development as practical drugs.[6] Consequently, the chemistry of gold(I) has attracted renewed attention generated by the necessity to prepare less toxic derivatives while retaining efficacy,[7–14] and partly because of the photochemistry of d^{10} gold(I) complexes.[15–19] The phosphine ligands in most of the complexes reported with the P-Au-S chromophore are common organophosphines such as triphenylphosphine and triethylphosphine. It is of interest to use phosphine-containing sugar derivatived to prepare new gold(I) derivatives.[20] In addition, complexes of pyridine-1-oxide-2-thiolate exhibit also certain biological activity.[21] This contribution reports the synthesis and characterization of the gold(I) compounds [Au(n-MBPA)(2-mpoS)] (2-mpoS = pyridine-1-oxide-2-thiolate; **1**, n = 2; **2**, n = 3) with chiral phosphines (n-MBPA = methyl 4,6-*O*-benzylidene-n-deoxy-n-(diphenylphosphino)-α-D-altropyranoside) derived from glucose.[22–23]



2 MBPA



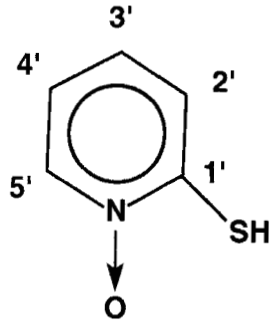
3 MBPA

EXPERIMENTAL

Materials and Instrumentation

The ligand pyridine-1-oxide-2-thiolate (sodium salt; 2-mpoSNa) was used as supplied. Analytical grade solvents were used without further purification. The chiral phosphines n-MBPA (n = 2, 3)[22–23] and the complexes [Au(n-MBPA)Cl] (n = 2, 3)[20] were prepared by published methods.

Elemental analyses were performed by the Chemical Analysis Division of this Institute. Infrared spectra (IR) were measured on a Nicolet Magna 750 FT spectrophotometer (CsI discs, 4000–100 cm^{-1}). Resonance Raman spectra (RR) were recorded on a Nicolet 910 FT Raman spectrometer using a Raman 1064 nm source at a resolution of 2 cm^{-1} with 300 scans. NMR spectra were measured in DMSO-d_6 on a Varian Unity 500 spectrometer operating at 499.98 MHz for ^1H, 125.71 MHz for ^{13}C, and 202.36 MHz for ^{31}P. Chemical shifts are expressed in parts per million (ppm) down-field from internal TMS (^1H and ^{13}C) or external 85% H_3PO_4 (^{31}P) standards as positive values.



Preparations

General Procedure

A CH_2Cl_2 solution (5 cm^3) of [Au(n-MBPA)Cl] (n = 2, or 3) (23 mg, 0.033 mmol) was mixed with a MeOH solution (5 cm^3) of 2-mpoSNa (5.2 mg, 0.035 mmol). The mixture was stirred for 2 h at room temperature and left to stand overnight. The solution was filtered and the filtrate was left to evaporate slowly to obtain the desired products.

[Au(2-MBPA)(2-mpoS)] **1**: colourless, yield 85%. *Anal.* Calc. for $C_{31}H_{31}AuNO_6PS$(%): C, 48.1; H, 4.0; N, 1.8 Found: C, 48.2; H, 4.0; N, 1.5. ^1H NMR (δ): 8.4-7.0 [m, 19H, aryl-H], 5.62 [s, 1H, PhC<u>H</u>], 5.32 [d, 1H, O<u>H</u>, $^3J_{HH}$ = 3.0 Hz], 5.03 [m, 1H, H(5)], 4.42 [d, 1H, H(1), $^2J_{PH}$ = 10.5 Hz], 4.24 [m, 1H, H(*6e*)], 4.21 [m, 1H, H(3)], 4.89 [m, 1H, H(4)], 3.86 [s(br), 1H, H(2)], 3.70 [t, 1H, H(*6a*), $^3J_{HH}$ = $^3J_{HH}$ = 9.0 Hz], 3.15 [s, 3H, C<u>H</u>$_3$] ppm. ^{13}C NMR (δ): 155–117 [aryl-C], 155.0 [C(1′)], 130.4 [C(2′)], 125.3 [C(3′)], 119.4 [C(4′)], 140.1 [C(5′)], 101.2 [Ph<u>C</u>H], 97.2 [C(1), $^2J_{PC}$ = 16.5 Hz], 76.48 [C(5)], 68.5 [C(6)], 64.0 [C(4)], 57.8 [C(3)], 55.1 [<u>C</u>H$_3$], 44.8 [C(2), $^1J_{PH}$ = 30.2 Hz] ppm. ^{31}P NMR (δ): 36.4 ppm. IR(CsI, disc.): ν(aryl-H), 2931 (w), 2831 (w); ν(C=C), 1668(s), 1437 (s); ν(N—O), 1261(m); ν(Au—P), 393 (w); ν(Au—S), 307 (w) cm^{-1}. RR (KBr): ν(Au—P), 401 (w); ν(Au—S), 320 (w) cm^{-1}.

[Au(3-MBPA)(2-mpoS)] **2**: colourless, yield 81%. *Anal.* Calc. for $C_{31}H_{31}AuNO_6PS$(%): C, 48.1; H, 4.0; N, 1.8. Found: C, 48.0; H, 4.1; N, 1.7. ^1H NMR (δ): 8.3–6.7 [m, 19H, aryl-H], 5.71 [d, 1H, O<u>H</u>, $^3J_{HH}$ = 4.0 Hz], 5.57 [s, 1H, PhC<u>H</u>], 5.20 [m, 1H, H(5)], 4.68 [m, 1H, H(4)], 4.47 [s, 1H, H(1)], 4.17 [dd, 1H, H(*6e*), $^2J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 5.0 Hz], 4.12 [dd, 1H, H(3), $^2J_{PH}$ = 15.5 Hz, $^3J_{HH}$ = 6.5 Hz], 3.75 [t, 1H, H(*6a*), $^2J_{HH}$ = $^3J_{HH}$ = 10.0 Hz], 3.52 [s(br), 1H, H(2)] ppm. ^{13}C NMR (δ): 155-119 [aryl-C], 155.3 [C(1′)], 130.3 [C(2′)], 124.1 [C(3′)], 119.3 [C(4′)], 140.0 [C(5′)], 101.1 [Ph<u>C</u>H)], 99.9 [C(1)], 75.2 [C(4)], 69.0 [C(6)], 68.2 [C(2)], 60.4 [C(5)], 53.5 [<u>C</u>H$_3$], 40 [C(3)] ppm. ^{31}P NMR (δ): 33.2 ppm.

IR(CsI. disc.): ν(aryl-H), 2969 (w), 2931 (w), 2889 (w); ν (C=C), 1457 (s); ν(N—O), 1263(m); ν(Au—P), 403 (w); ν(Au—S), 310 (w) cm^{-1}. RR (KBr): ν(Au—P), 408 (w); ν(Au—S), 306 (w) cm^{-1}.

RESULTS AND DISCUSSION

Molecular Vibration Spectra

The compounds [Au(n-MBPA)Cl] (n = 2, 3)[20] react readily with pyridine-1-oxide-2-thiolate at room temperature to form the complexes [Au(n-MBPA)(2-mpoS)] (2-mpoS = pyridine-1-oxide-2-thiolate; **1**, n = 2; 2, n = 3) in high yields. The C-S stretching frequency can not be assigned owing to overlapping in the region 1100–1000 cm^{-1}, but ν(N—O) at *ca* 1260 cm^{-1} for **1** and **2** are nearly identical to that of 2-mpoSNa, implying that mpoS coordinates to gold(I) through the S and not the O donor. In addition, ν(Au—S) in region 320–306 cm^{-1} for **1**–**2** observed and comparable to those of [{Au(3-MBPA)}$_3$S]Cl (314 cm^{-1})[24] and [Au(PR_3(SCN)] (303–291 cm^{-1}).[25] These facts are consistent with gold(I) having greater affinity for S than for O donors. The ν(Au—P) stretching mode in the range 408–393 cm^{-1} is assignable and comparable to those reported for the compounds [Au(n-MBPA)X] (395–368, n =2, 3),[20] [{Au(3-MBPA)}$_3$S]Cl [384(IR), 390(RR) cm^{-1}],[24] and [Au(PR_3X] (381-361 cm^{-1}, X = Cl, Br, SCN).[25]

NMR Spectroscopy

Integrations for ^{1}H NMR spectra are consistent with formulation of the complexes as [Au(n-MBPA)(2-mpoS)] (**1**, n = 2; **2**, n = 3). Even at 500 MHz, the ^{1}H NMR spectra can not be analyzed easily, mainly owing to long-range virtual coupling.[26] Therefore the ^{1}H-^{1}H COSY (Figure 1 for **2**) and ^{1}H-^{13}C HMQC (Figure 2 for **2**) techniques were applied to overcome this difficulty. For **2**, the signals at 4.24 and 3.71 ppm correlating to 69.0 ppm in ^{1}H-^{13}C HMQC spectrum (Figure 2), indicating a CH_2 group, were assigned to H(*6a*) and H(*6e*), respectively. In the ^{1}H-^{1}H COSY spectrum (Figure 1), H(5) was assigned to the signal at 5.20 ppm [C(5) at 60.4 ppm], which is correlated to both H(*6a*) and H(*6e*) and H(4) at 4.68 ppm (C(4) at 75.2 ppm). The signal at 4.12 ppm correlated to H(4) was then assigned as H(3) (the signal for C(3) was immersed in that of DMSO). Correlations of H(3)-H(2) and H(2)-H(1) were not observed, implying that the torsion angles of H(3)-C(3)-C(2)-H(2) and H(2)-C(2)-C(1)-H(1) are close to 90° in DMSO solution. In comparison with the spectra of the free ligand 3-MBPA and the complex [Au(3-MBPA)Cl],[20] the signal at 4.47 ppm was assigned to H(1) and that at 3.52 ppm to H(2) (C(1) and C(2) at 99.9 and 68.2 ppm, respectively). The ^{1}H and ^{13}C NMR of **1** was assigned similarly.

On replacing Cl^- by pyridine-1-oxide-2-thiolate (2-mpoS), the protons on the carbon atoms of the altropyranose rings bound directly to the phosphorus atom shift downfield; the resonance of H(2) shifts from 3.60 ppm in [Au(2-MBPA)Cl] to 3.86 ppm in [Au(2-MBPA)(2-mpoS)], and that of H(3) from 3.77 ppm in [Au (3-MBPA)Cl] to 4.12 ppm in [Au(3-MBPA)(2-boS)]. The positions of the signals of the other protons of altropyranose rings change little.[20] These results are consistent with the fact that the gold(I) locally perturbs the electron distribution of the alkyl protons.[26] Similar shifting is also observed in the $^{31}P\{^1H\}$ NMR spectra, in which the single peak at 34.0 ppm for **1** and at 33.2 ppm for **2** shifts downfield by 3.7 and 4.9 ppm, respectively, in comparison to the starting material [Au(n-MBPA)Cl] (30.3 and 28.3 ppm, respectively).[20] Consistent with these phenomena, the C(1′) resonances of 2-mpoS ligands (155.0 and 155.3 ppm for **1** and **2**, respectively) are shifted upfield compared with 2-mpoSNa (163.9 ppm) in DMSO-d_6. The changes in C(5′) (140.1 and 140.0 ppm for **1** and **2**, respectively, and 139.1 ppm for 2-mpoSNa) are very small. The effects on C(1′) and C(5′) also demonstrate that the mpoS ligand coordinates to gold(I) through S, as suggested by IR spectroscopy.

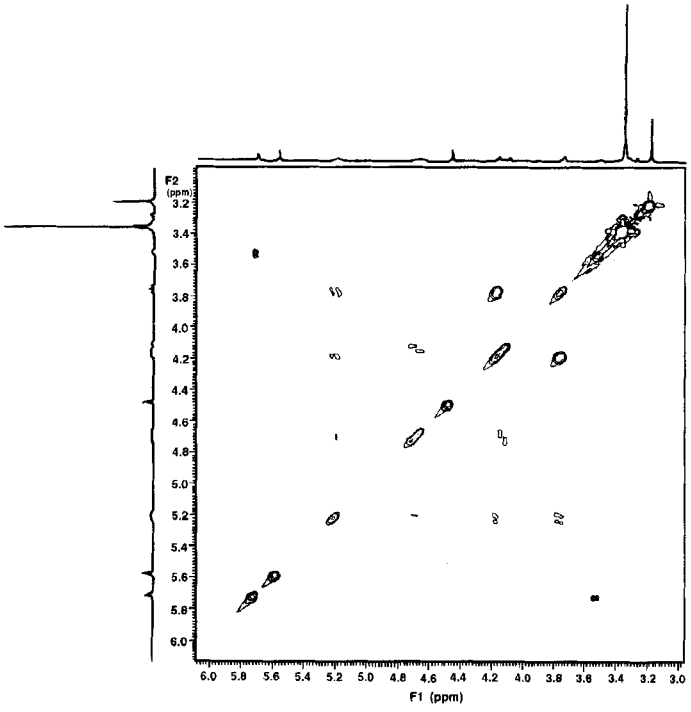


FIGURE 1 Partial ^1H-^1H COSY spectrum of [Au(3-MBPA)(2-mpoS)] (2).

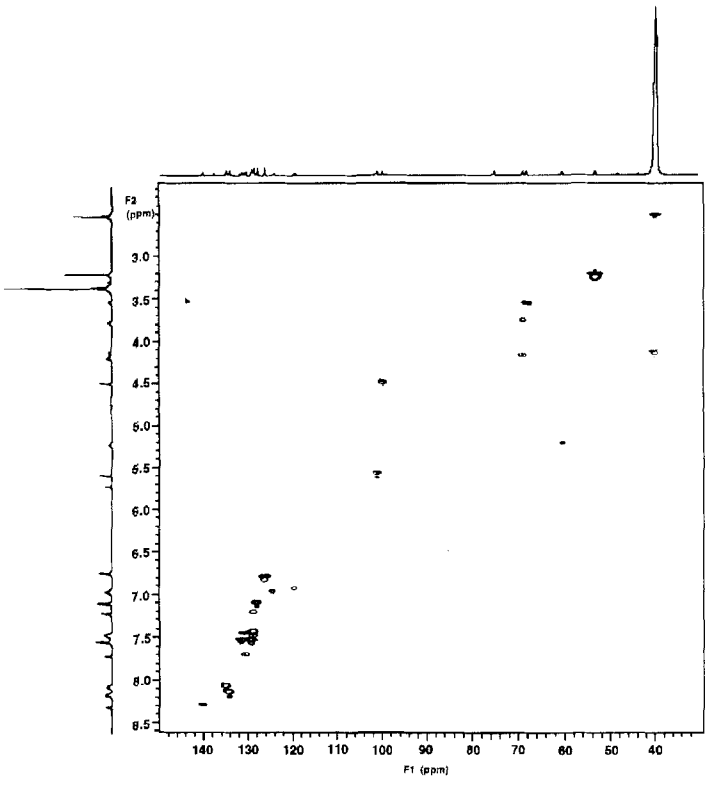


FIGURE 2 Partial ^{1}H-^{13}C HMQC spectrum of [Au(3-MBPA)(2-mpoS)] (2).

Acknowledgments

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