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Synthesis and Structure of the First Ruthenated Benzodiazepines

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Summary: [{RuCl(cym)}$_2$(μ-Cl)$_2$] (cym = η^6-p-methylisopropylbenzene) serves as precursor to synthesize the two first ruthenated benzodiazepines in which deprotonated diazepam is coordinated to a {RuCl(cym)} fragment. In complex ***1****, obtained by treatment with diazepam in the presence of NaBPh$_4$ and NEt$_3$, the coordination is through the imine nitrogen and an ortho carbon of the phenyl substituent. In* ***2****, obtained by reaction of deprotonated diazepam with the metal dimer, the coordination is through the imine nitrogen and the adjacent sp^3 carbon of the benzodiazepine.*

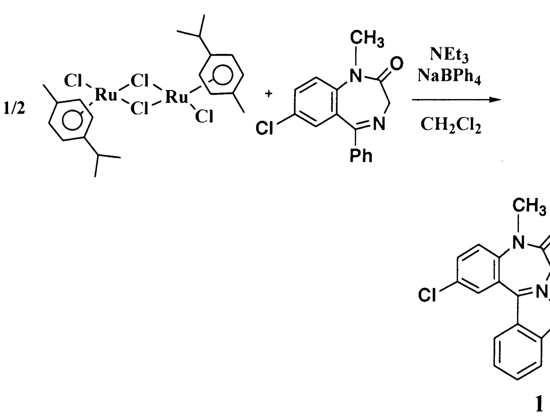
Introduction

In addition to the well-known psychotherapeutic properties of 1,4-benzodiazepines, benzodiazepine derivatives were found to display anticancer activity.[1] Given the recent reports of the anticancer activity of areneruthenium(II) complexes,[2] benzodiazepine complexes of areneruthenium(II) fragments, previously unknown, are interesting synthetic targets. We have chosen as starting material the benzodiazepine 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (diazepam, commercially known as Valium). Given the antitumor activity of metal complexes containing cyclometalated ligands,[3] we first aimed for the orthometalation of diazepam. Whereas cyclometalation reactions have been extensively studied with other metal fragments, including ruthenium examples, only recently has an effective route to cyclometalated areneruthenium complexes been reported.[4]

Results and Discussion

The reaction of [{RuCl(cym)}$_2$(μ-Cl)$_2$][5] (cym = η^6-*p*-methylisopropylbenzene) with diazepam in the presence of the base NEt$_3$ and NaBPh$_4$ afforded the orthometalated complex **1** (Scheme 1).

Scheme 1



In our case, the employment of a noncoordinating solvent and room temperature avoided arene-displacement reactions.[4] Is also noteworthy that the dimeric precursor, commercially available or easily prepared in one step from RuCl$_3$·H$_2$O, does not need to be activated by a previous bridge cleavage/chloride abstraction step.[5]

The structure of **1**, determined by X-ray diffraction (Figure 1), consisted of a {RuCl(cym)} fragment coordinated to the imine nitrogen, N(4), and to one of the ortho carbons of the phenyl substituents of diazepam, C(13), defining the five-membered ring Ru−N(4)−C(5)−C(12)−C(13). The Ru−N and Ru−C distances (2.055(4) and 2.038(5) Å, respectively) are similar to those found in the five-membered rings of known areneruthenium complexes with orthometalated amines.[6]

Cyclometalated derivatives of benzodiazepines with palladium and platinum were previously known;[7] however, **1** is the first ruthenium complex of a benzodiazepine.

As a second approach toward the synthesis of areneruthenium derivatives of diazepam, we reacted the

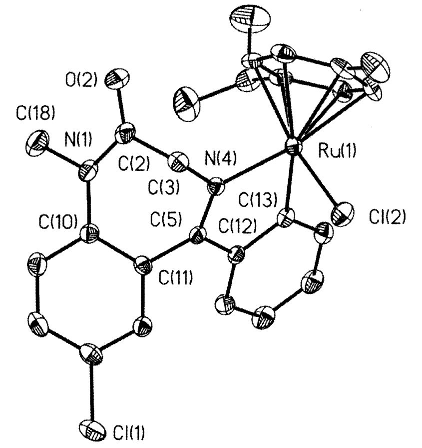


Figure 1. Thermal ellipsoid (30%) plot of complex **1**.

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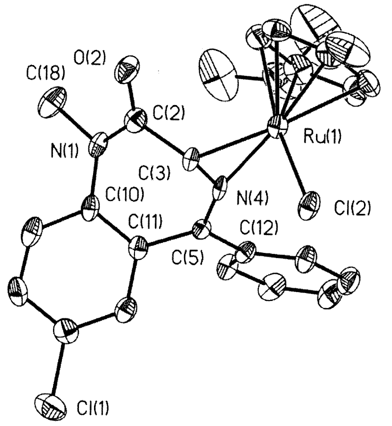
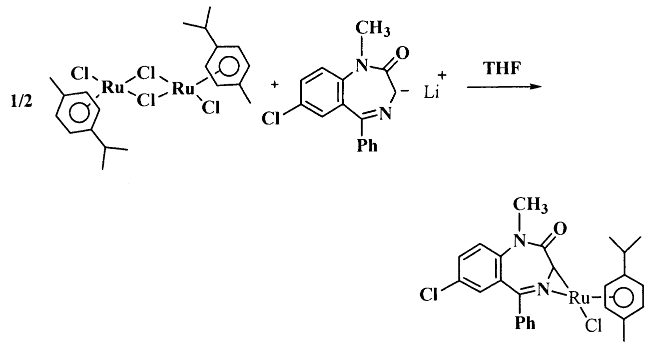


Figure 2. Thermal ellipsoid (30%) plot of complex **2**.

Scheme 2



2

carbanion resulting from the C(3) lithiation of diazepam[8] with [{RuCl(cym)}$_2$(μ-Cl)$_2$], as depicted in Scheme 2. C(3)-metalated diazepam has been employed for the synthesis of a gold complex, resulting in coordination of the benzodiazepine ligand through only that carbon atom.[9] In contrast, **2** (for which the crystal structure has been determined by X-ray diffraction; see Figure 2) features a ligand resulting from deprotonation of diazepam coordinated to a {RuCl(cym)} fragment through C(3) and the imine nitrogen N(4). Therefore, **1** and **2** are isomers.

Due to the vicinal position of the C(3) and N(4) atoms, a three-membered ring (metallaaziridine or metallaazacyclopropane) is present in the structure of complex **2**. Three-membered rings of this kind are known with early transition metals;[10] however, this is the first example within a ruthenium complex.[11] Furthermore, this is a unprecedented coordination mode for a metalated benzodiazepine derivative.

Experimental Section

General conditions were given elsewhere.[12]

Synthesis of 1. Under dinitrogen, diazepam (0.20 g, 0.70 mmol) was added to a solution of [{RuCl(cym)}$_2$(μ-Cl)$_2$] (0.21 g, 0.35 mmol), NaBPh$_4$ (0.24 g, 0.70 mmol), and NEt$_3$ (0.24 mL, 1.72 mmol) in CH$_2$Cl$_2$ (20 mL). After 3.5 days stirring, solvent evaporation in vacuo, extraction of the residue (CH$_2$Cl$_2$, 10 mL), filtration (silica gel), in vacuo concentration (to 5 mL), and layering with hexane (20 mL) afforded, after 2 days at −20 °C, red crystals. Yield: 0.39 g, 81%. Anal. Calcd for C$_{26}$H$_{26}$Cl$_2$N$_2$ORu: C, 56.32; H, 4.72; N, 5.05. Found: C, 56.50; H, 4.57; N, 5.38. ^{1}H NMR (CDCl$_3$): δ 8.24−7.10(m, 7H, Ph); 5.72(t(7), 2H, C$_6$H$_4$); 5.53(d(5), 1H, C$_6$H$_4$); 5.24(d(12), 1H, CH$_2$ diazepam); 4.91(d(5), 1H, C$_6$H$_4$); 4.60(d(12), 1H, CH$_2$ diazepam); 5.70(qAB, 4H, C$_6$H$_4$); 3.39(s, 3H, CH$_3$ diazepam); 2.34(m, 1H, CH(^{i}Pr)); 2.12(s, 3H, CH$_3$ C$_6$H$_4$); 0.97(d(7), CH$_3$(^{i}Pr)); 0.66(d(7), CH$_3$(^{i}Pr)). ^{13}C{^{1}H} NMR (CDCl$_3$): 189.1(s, Cortho); 175.8(s, C=N); 169.5(s, CO); 143.8, 141.4, 139.8, 136.1, 131.4, 130.3, 130.1, 129.8, 129.5, 129.40(s, Ph diazepam); 107.1(s, C(C$_6$H$_4$)), 100.8(s, C(C$_6$H$_4$)); 93.2, 92.9, 80.6, 77.5(s, CH(C$_6$H$_4$)); 65.9(s, CH$_2$ diazepam); 38.4(s, CH$_3$ diazepam); 31.0(s, CH$_3$(^{i}Pr)); 23.2(s, CH$_3$(^{i}Pr)); 20.6(s, CH(^{i}Pr)); 19.0(s, CH$_3$ (C$_6$H$_4$)). X-ray quality crystals of the ethanol hemisolvate were obtained by crystallization of this material from toluene/ethanol.

Synthesis of 2. To a solution of the carbanion resulting from the C(3) metalation of diazepam (0.20 g, 0.70 mmol) in THF (10 mL) was added a solution of [{RuCl(cym)}$_2$(μ-Cl)$_2$] (0.21 g, 0.35 mmol) at −78 °C. After stirring (1.5 days), solvent evaporation in vacuo, extraction of the residue (CH$_2$Cl$_2$, 10 mL), filtration (silica gel), in vacuo concentration (to 5 mL), and layering with hexane (20 mL) afforded, after 2 days at −20 °C, red crystals. Yield: 0.30 g, 77%. Anal. Calcd for C$_{26}$H$_{26}$Cl$_2$N$_2$ORu: C, 56.32; H, 4.72; N, 5.05. Found: C, 56.09; H, 4.90; N, 5.22. ^{1}H NMR (CDCl$_3$): δ 8.1−7.3(m, 8H, Ph); 5.55(t(6), 2H, C$_6$H$_4$); 5.11(d(6), 1H, C$_6$H$_4$); 4.88(d(5), 1H, C$_6$H$_4$); 3.78(s, 1H, CH diazepam); 3.31(s, 3H, CH$_3$ diazepam); 2.22(m, 1H, CH(^{i}Pr)); 1.82(s, 3H, CH$_3$(C$_6$H$_4$); 1.08(d(7), CH$_3$(^{i}Pr)); 1.02(d(7), CH$_3$(^{i}Pr)). ^{13}C{^{1}H} NMR (CDCl$_3$): 177.1(s, C=N); 165.3(s, CO); 143.1, 134.9, 132.2, 131.7, 129.8, 128.9, 128.6, 123.6(s, Ph diazepam); 101.6(s, C(C$_6$H$_4$)); 94.5(s, C(C$_6$H$_4$)); 84.5, 83.8, 83.2, 82.1(s, CH(C$_6$H$_4$)); 39.8(s, CH diazepam); 37.5(s, CH$_3$ diazepam); 29.8(s, CH$_3$ (^{i}Pr)); 22.3(s, CH$_3$ (^{i}Pr)); 22.1(s, CH(^{i}Pr)); 19.6(s, CH$_3$ (C$_6$H$_4$)).

Crystal data for 1: C$_{27}$H$_{29}$Cl$_2$N$_2$O$_{1.5}$Ru, $M = 577.49$, monoclinic, space group $P2_1/n$, $a = 18.3046(16)$ Å, $b = 14.0908(12)$ Å, $c = 19.5929(6)$ Å, $\beta = 96.667(2)°$, $Z = 8$, $V = 5019.4(8)$ Å^3, $\rho = 1.528$ g/cm^{-3}; $T = 299(2)$ K; $\lambda = 0.71073$, 32284 reflections measured, 7256 unique ($R_{\mathrm{int}} = 0.0689$), R1 = 0.0434 and wR2 = 0.1004.

Crystal data for 2: C$_{26}$H$_{26}$Cl$_2$N$_2$ORu, $M = 554.46$, orthorhombic, space group $Pbca$, $a = 13.541(4)$ Å, $b = 18.168(6)$ Å, $c = 24.862(8)$ Å, $Z = 8$, $V = 6116(3)$ Å^3, $\rho = 1.204$ g/cm^{-3}; $T = 295(2)$ K; $\lambda = 0.71073$, 37625 reflections measured, 4408 unique ($R_{\mathrm{int}} = 0.0938$), R1 = 0.0767 and wR2 = 0.2126.

Supporting Information Available: Tables giving positional and thermal parameters and bond distances and bond angles for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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