Synthesis and structural characterization of a new silver(I) complex with miconazole

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Abstract: Fungal infections have a considerable impact on global public health, and their prevalence has increased substantially over recent decades. Presently, five major classes of antifungal agents, polyenes, azoles, allylamines, caspofungins, and pyrimidine analogues, are used in the treatment of invasive fungal infections. Of these, azoles are the most commonly utilized for the treatment of these infections. In this study, we synthesized and structurally characterized a new silver(I) complex with antifungal agent miconazole (mcz), $[Ag(mcz)_2]PF_6$. The complex was synthesized by reacting $AgPF_6$ with mcz in 1 : 2 molar ratio in ethanol at room temperature for 3–4 h. The synthesized silver(I) complex was characterized by spectroscopic (NMR, IR, UV-Vis) methods, while its crystal structure was determined by single-crystal X-ray diffraction analysis. In this complex, two mcz molecules are monodentately coordinated to the silver(I) ion *via* the imidazole nitrogen atom, forming an $[Ag(mcz)_2]^+$ cation which is neutralized by the PF_6^- counterion. The solution stability of the synthesized complex was evaluated by UV-Vis spectroscopy, as well as measuring its molar conductivity.

Keywords: silver(I) complex, miconazole, crystal structure

1. Introduction

Miconazole (mcz), an imidazole derivative, has been extensively utilized for more than five decades in the effective treatment of superficial and cutaneous infections [1]. However, the emergence of resistance to this antifungal agent has escalated significantly, mainly as a result of its widespread and often inappropriate use [1]. Given the narrow antifungal spectrum of miconazole, along with the increasing resistance and other associated limitations, there is an urgent need for the identification of novel compounds that can address these challenges. It is known that coordination of biologically active compounds with metal ions can significantly modulate and improve their activities [2]. Therefore, combining biologically active organic compounds with metal ions, which have shown antimicrobial properties, is used as a strategy to overcome antifungal resistance. Consequently, in this study, we used miconazole as a ligand for the synthesis of a new silver(I) complex, $[Ag(mcz)_2]PF_6$, which was characterized using spectroscopic and crystallographic methods.

2. Methodology

2.1. Materials and measurements

Silver(I) hexafluorophosphate, ethanol, acetonitrile, dimethyl sulfoxide (DMSO) and deuterated dimethyl sulfoxide (DMSO-d_6) were purchased from Sigma-Aldrich. All chemicals were of analytical reagent grade and used without further purification.

A Perkin-Elmer Spectrum Two spectrometer was used for recording IR spectra as KBr pellets over the range of 4000-450 cm^{-1}. The ^{1}H NMR spectra were recorded at room temperature on a Varian Gemini 2000 spectrometer at 200 MHz at room temperature. 5.0 mg of the compound was dissolved in 0.6 mL of DMSO-d_6 and transferred into a 5 mm NMR tube. Chemical shifts, δ, are reported in ppm and scalar couplings (J) are reported in Hertz (*Hz*). The UV-Vis spectra were recorded over the wavelength range of 1100-200 nm on a Shimadzu UV-1800 spectrophotometer. The concentration of the solution of the complex was 8.0×10^{-4} M. The molar conductivity of the complex was measured on a digital conductivity-meter Crison Multimeter MM 41 after its dissolution in DMSO. The concentration of the solution of the complex was 1.0×10^{-3} M.

2.2. Synthesis of the $[Ag(mcz)_2]PF_6$ complex

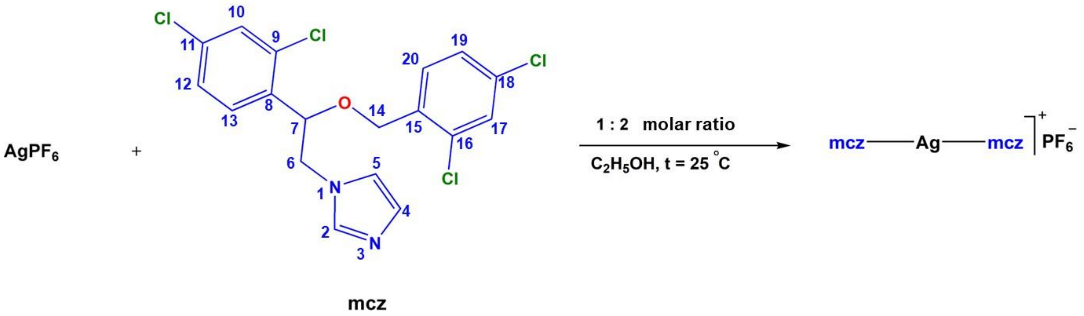
The solution of 0.5 mmol of $AgPF_6$ (126.4 mg) in 5.0 mL of ethanol was added slowly under stirring to the solution of 1.0 mmol of miconazole (416.1 mg) in 10.0 mL of ethanol. The obtained solution was stirred in the dark, at room temperature, for 3–4 h. The collorless crystals of the complex were obtained after the white solid product, precipitated from the reaction mixture, was dissolved in 10.0 mL of acetonitrile. Yield (calculated on the basis of miconazole): 363.5 mg (67%).

IR (KBr, ν, cm^{-1}): 3176w, 3135w, 3092w, 3029w (ν(C_{ar}–H)), 2921w (ν(C–H)), 1591m, 1562m, 1529m, 1470m (ν(C_{ar}=C_{ar}) and ν(C_{ar}=N)), 1095s (ν(C_{ar}–Cl)), 829vs (ν(PF_6)), 792m (γ(Car–H)). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.81 (*s*, 1H, C2H), 7.70 (*d*, J = 2.0 Hz, 1H, C17H), 7.59 (*d*, J = 1.7 Hz, 1H, C4H), 7.49 (*dd*, J = 8.4, 2.0 Hz, 1H, C5H), 7.45 – 7.34 (*m*, 3H, C10H, C19H, C20H), 7.24 (*s*, 1H, C12H), 7.01 (*s*, 1H, C13H), 5.11 (*t*, J = 5.5 Hz, 1H, C7H), 4.42 (*d*, J = 7.1 Hz, 2H, C14H), 4.39 (*d*, J = 5.8 Hz, 2H, C6H). UV-Vis (DMSO, λ_{max}, nm): 272 ($\varepsilon = 1.0 \times 10^3$ M^{-1}cm^{-1}). Λ_M (DMSO): 29.4 Ω^{-1} cm^2 mol^{-1}.

3. Results and Discussion

3.1. Synthesis of the [Ag(mcz)$_2$]PF$_6$ complex

The synthesis of the silver(I) complex, [Ag(mcz)$_2$]PF$_6$ (Scheme 1), was carried out according to the procedure described in the Methodology section. The reactants, AgPF$_6$ and mcz, were mixed in a 1 : 2 molar ratio in ethanol, at room temperature and in the absence of light. ^{1}H NMR, IR and UV-Vis spectroscopy were used for the characterization of this complex, while its molecular structure was determined by single-crystal X-ray diffraction analysis.



Scheme 1. Reaction scheme for the synthesis of the silver(I) complex. Numeration of atoms of the mcz ligand was used for ^{1}H NMR characterization.

3.2. Description of the single crystal structure

In the silver(I) complex, two mcz ligands are monodentately coordinated to the silver(I) ion *via* the nitrogen atom N3 of the imidazole ring, forming the cationic [Ag(mcz)$_2$]$^+$ species, which is neutralized by the PF$_6^-$ counterion (Figure 1). The two nitrogen atoms of the two mcz ligands are equidistant from the silver(I) ion (d(Ag1–N3) = 2.079(3) Å) and form a slightly distorted linear geometry around the metal center (N3–Ag1–N3′ = 176(1)°).

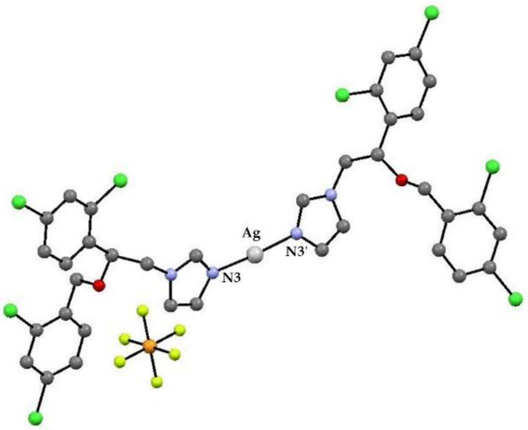


Figure 1. Crystal structure of [Ag(mcz)$_2$]PF$_6$ complex. Thermal ellipsoids are drawn at the 50% probability level.

3.3. Spectroscopic characterization

The IR spectrum contains bands that can be attributed to the characteristic vibrations of mcz coordinated to the silver(I) ion, as well as those arising from the PF$_6^-$ counterion.

Therefore, a very strong band is present at 829 cm^{-1}, which is consistent with the absence of coordination of PF_6^- with the silver(I) ion.

In the ^{1}H NMR spectrum of the complex, all proton signals are shifted upfield in respect to those of the uncordinated miconazole.

3.4. Solution stability

The UV-Vis measurements were repeated after standing of the solution of $[Ag(mcz)_2]PF_6$ complex at room temperature in the absence of light for 48 h to study its solution stability. No significant changes were seen between the initial UV-Vis spectrum and the one recorded after 48 h, which in accordance with the fact that the mcz ligand remains coordinated to the silver(I) ion in solution. The molar conductivity value of the complex is consistent with its 1:1 electrolytic nature.

4. Conclusions

In this study, a novel silver(I) complex with the antifungal agent miconazole (mcz) as ligand, $[Ag(mcz)_2]PF_6$, was synthesized and structurally characterized. Crystallographic results revealed that this complex adopts a distorted linear geometry, with two mcz ligands coordinated to the silver(I) ion, while PF_6^- acts as the counterion. In DMSO solution, the mcz ligands remain coordinated to the silver(I) ion for at least 48 h.

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