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Synthesis, antimicrobial activity, structural and spectral characterization and DFT calculations of Co(II), Ni(II), Cu(II) and Pd(II) complexes of 4-amino-5-pyrimidinecarbonitrile

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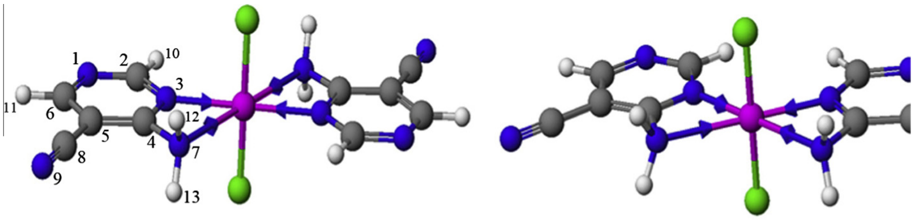
HIGHLIGHTS

- Synthesis of Co^{2+}, Ni^{2+}, Cu^{2+} and Pd^{2+} 4-amino-5-pyrimidinecarbonitrile complexes (APC).
- Molar conductance and spectroscopic studies favors non-electrolytic $[M(APC)_2Cl_2]$ complexes.
- Bidentate APC was observed for all complexes except Pd(II) where APC act as a monodentate ligand.
- DFT geometry optimization at 6-31G(d) basis set except for Pd where LanL2DZ were chosen.

GRAPHICAL ABSTRACT



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Dedicated to the pure spirit of Professor M.S. Afifi who passed away during the preparation of the manuscript.

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ABSTRACT

Co(II), Ni(II), Cu(II) and Pd(II) complexes of 4-amino-5-pyrimidinecarbonitrile (APC) have been synthesized and characterized using elemental analysis, magnetic susceptibility, mass spectrometry, infrared (4000–200 cm^{-1}), UV–Visible (200–1100 nm), ^{1}H NMR and ESR spectroscopy as well as TGA analysis. The molar conductance measurements in DMSO imply non-electrolytic complexes, formulated as $[M(APC)_2Cl_2]$ where M = Co(II), Ni(II), Cu(II) and Pd(II). The infrared spectra of Co(II), Ni(II) and Cu(II) complexes indicate a bidentate type of bonding for APC through the *exocyclic* amino and adjacent pyrimidine nitrogen as donors whereas APC coordinated to Pd(II) ion as a monodentated ligand via a pyrimidine nitrogen donor. The magnetic measurements and the electronic absorption spectra support distorted octahedral geometries for Co(II), Ni(II) and Cu(II) complexes however a square planar complex was favored for the Pd(II) complex (C_{2h} skeleton symmetry). In addition, we carried out B3LYP and ω-B97XD geometry optimization at 6-31G(d) basis set except for Pd(II) where we implemented LanL2DZ/6-31G(d) combined basis set. The computational results favor *all trans* geometrical isomers where amino N, pyrimidine N and Cl are *trans* to each other (structure **1**). Finally, APC and its divalent metal ion complexes were screened for their antibacterial activity, and the synthesized complexes were found to be more potent antimicrobial agents than APC against one or more microbial species.

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Introduction

Synthesis and structural investigations on transition metal complexes of pyrimidine derived ligands have attracted significant interests because of their relevant biological properties [1,2] electrochemical properties [3] and widespread pharmaceutical applications [4,5]. Moreover, their coordination diversity [6–8] enables the formation of metal ion complexes of notable *antitumor* [9,10] and *antimicrobial* [11] bioactivity. 2-Aminopyrimidine (2AP) and 4-aminopyrimidine (4AP) could act as mono-dentate ligands through the endocyclic ring nitrogen donors [12,13] or through the exocyclic *amino* nitrogen [14,15] otherwise act as bidentate ligands via *amino* and adjacent pyrimidine nitrogen atoms [16,17]. Therefore, 4-amino-5-pyrimidinecarbonitrile (APC) was our target ligand to investigate its coordination behavior toward selected transition elements as well as the biological activities of resulting complexes.

APC has considerable binding versatility as it may include monodentate binding through *exo* (N_7 or N_9) or *endo* (N_3 or N_1) nitrogen atoms or bidentate chelation via the N_7 and N_9 or N_7 and N_3 atoms. Synthesis of Co(II), Ni(II), Cu(II) and Pd(II) APC complexes was performed and structural and spectral characterization of the resulting complexes were investigated using elemental analysis, magnetic susceptibility measurements and thermal studies along with a variety of spectroscopic techniques (infrared, UV–Vis, mass, ^{1}H NMR and ESR). A theoretical emphasis on the geometrical isomers of APC metal complexes was carried out using DFT–B3LYP [18,19] and ω-B97XD [20] with 6-31G(d) basis set except for the Pd(II) complex where effective core potential (ECP) LanL2DZ basis set was used [21], employing the Gaussian 09 program [22]. Finally, the biological activities of APC and its complexes were examined by screening their ability to inhibit the growth of some bacterial and fungal strains.

Experimental

Materials

All chemicals were purchased from Sigma–Aldrich and Merck and used without further purification. 4-Amino-5-pyrimidinecarbonitrile, $CoCl_2{\cdot}6H_2O$, $NiCl_2{\cdot}6H_2O$, $CuCl_2{\cdot}2H_2O$, $PdCl_2$ and KCl had a purity grade from 98% to 99%. CsI and organic solvents were of spectroscopic and analytical grade (99%), respectively and were used without further purification.

Synthesis of APC–metal complexes ($\mathbf{I_{a-d}}$)

The $K_2[PdCl_4]$ complex which served as the starting material to prepare the APC palladium complex was synthesized using $PdCl_2$ and KCl as previously described [23]. Co(II), Ni(II), Cu(II) and Pd(II) APC complexes ($\mathbf{I_{a-d}}$) were prepared by the gradual addition of 1.0 mmol of $CoCl_2$, $NiCl_2$, $CuCl_2$ and $K_2[PdCl_4]$ in ethanol (30 mL), respectively to a hot solution of 1.0 mmol of 4-amino-5-pyrimidinecarbonitrile dissolved in 30 mL of absolute ethanol with continuous stirring. The reaction mixture was refluxed for 3 h, the resulting precipitates were filtered by suction, washed with absolute ethanol followed by diethyl ether and air dried. The melting points of all four complexes were found to be above 300 °C. The newly synthesized APC complexes ($\mathbf{I_{a-d}}$) are air-stable, insoluble in H_2O, ethanol and methanol but completely soluble in dimethylsulfoxide (DMSO).

Instrumentation and spectroscopic measurement

Elemental analyses (carbon, hydrogen and nitrogen percentages) for the prepared complexes ($\mathbf{I_{a-d}}$) were determined. Metal contents were determined (using an AAS6 Vario flame atomic absorption spectrophotometer) in a solution prepared by decomposing each prepared complex using hot concentrated HNO_3. The reported elemental analysis of complexes ($\mathbf{I_{a-d}}$) include the experimentally found percentages of C, H, N and metal (Co^{2+}, Ni^{2+} and Cu^{2+}) in addition to the calculated percentage on the basis of the suggested formulas are given in Table 1.

The infrared spectra of solid APC and its complexes ($\mathbf{I_{b-d}}$) were recorded from 4000 to 200 cm^{-1} on a Perkin Elmer Spectrum 100 FT-IR spectrophotometer using the CsI disk technique at Sultan Qaboos University, Muscat, Sultanate of Oman. To improve the S/N ratio, forty scans were collected utilizing 1.0 cm^{-1} resolution. The solid FT-IR spectrum (4000–400 cm^{-1}) of APC cobalt complex ($\mathbf{I_a}$) was recorded using a KBr disk using Nicolet 6700 FT-IR spectrophotometer at Ain Shams university, Cairo, Egypt. The infrared spectra of APC and its complexes ($\mathbf{I_{a-d}}$) are displayed in Fig. 1 and the observed bands are listed in Table 2.The UV–Vis electronic absorption spectra of complexes $\mathbf{I_{a-d}}$ were recorded in the spectral range (1100–200 nm) with the samples dissolved in DMSO (Supplement Fig. S1) using Perkin-Elmer Lambda 35 UV/Vis Spectrophotometer fitted with a quartz cell of 1.0 cm path length. The mass spectra of solid samples were measured with the aid of a Shimadzu QP-2010 Plus using electron ionization mode (Supplement Fig. S2). The ^{1}H NMR spectra of APC and its palladium complex ($\mathbf{I_d}$) dissolved DMSO-d_6 were recorded on a Varian Mercury VX-300 NMR spectrometer at 300 MHz and using tetramethylsilane (TMS) as an internal reference (Supplement Fig. S3).

The molar conductivities for 1×10^{-3} mol L^{-1} DMSO solutions of APC metal complexes were measured using Jenway 4010 conductivity meter (Table 1). Magnetic susceptibilities of ($\mathbf{I_{a-d}}$) complexes were measured employing the Gouy method using a magnetic susceptibility balance at room temperature (Sherwood Scientific England). The results are in favor of paramagnetic complexes for ($\mathbf{I_{a-c}}$) whereas the Pd complex ($\mathbf{I_d}$) is found to be diamagnetic (Table 1). Thermal gravimetric analyses (TGA) of the samples were carried out under an inert nitrogen atmosphere using a Shimadzu TGA-50H (Supplement Fig. S4). A heating rate of 10 °C/min was used in the temperature range of 25–1000 °C. Electron spin resonance (ESR) measurement of crystalline Cu–APC complex (Fig. 2) was recorded at room temperature on a Bruker BioSpin GmbH spectrometer at 9.71 GHz using 2,2-diphenylpyridylhydrazone (DPPH) as standard, $g = 2.0037$). The above measurements were performed at the Micro-analytical Center, Cairo University, Giza, Egypt.

Pharmacology

The *in vitro* evaluation of antimicrobial activity was carried out at the microbiology lab, Al-Azhar University, Nasr City, Egypt to determine antibacterial and antifungal activities of APC and its complexes ($\mathbf{I_{a-d}}$). The *in vitro* antimicrobial activities were tested against Gram-positive bacteria (*Staphylococcus aureus*; NCTC 7447 and *Bacillus subtilis*; NCTC 10400), Gram-negative bacteria (*Escherichia coli*; NCTC 10416, *Pseudomonas aeruginosa*; ATCC 10145), Unicellular Fungi (*Candida albicans*; IMRU 3669) and Filamentous Fungi (*Aspergillus niger*, AT CC 16404).

Cultures of bacteria or yeasts were inoculated in the form of a loopful of each test organism into about 20 mL of Muller Hinton agar medium for bacteria and malt extract agar medium for yeast at 45 °C, tilled and poured into sterile plates and left to solidify. In case of fungi, the spore suspension technique (Dox agar medium) was employed. Plugs were cut out of these cultures with a Cork-borer, 100 μg/mL of APC and its complexes were dissolved in DMSO (used as control) and then 0.10 mL of the solution (active ingredient) was transferred into each hole in the test plate. The petri dishes were kept in a refrigerator for diffusion just before