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Research paper

Cobalt (II), zirconium(IV), calcium(II) complexes with dipicolinic acid and imidazole derivatives: X-ray studies, thermal analyses, evaluation as *in vitro* antibacterial and cytotoxic agents

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ABSTRACT

Four coordination complexes, $[2\text{-mimH}]_2[Co(pydc)_2][ClO_4].H_2O$ (**1**), $[2\text{-mimH}]_2[Zr(pydc)_3]$ (**2**), $[imiH]_2[Zr(pydc)_3].4H_2O$ (**3**) and $[Ca(pydcH_2)_2(H_2O)]_2[Co(pydc)_2]_2{\cdot}6H_2O$ (**4**) have been prepared from the reaction between proton-transfer compounds containing pyridine-2,6-dicarboxylic acid ($pydcH_2$) with 2-methylimidazole (2-mim) and imidazole (imi) in 1:2 M ratio and metal salts. These compounds have been characterized by spectroscopic methods and single crystal X-ray diffraction technique was used to determine their structures. Also, thermal analyses (TGA/DTA) were carried out on all the synthetic compounds. Then the agar dilution and diffusion methods were used to determine the antibacterial activity of the ligands and their complexes on the growth profile of two pathogenic Gram-positive bacteria namely *Staphylococcus aureus* and *Bacillus cereus* and also two Gram- negative bacteria namely *Escherichia* coli and *Klebsiella oxytoca*. The highest antibacterial activity was exhibited by ($pydcH_2$) and complex (**2**) at MIC values between 75 and 175 μg/mL. These two compounds exhibited stronger effects than gentamicin as a standard drug toward *Klebsiella oxytoca*. The anti-proliferative activity of compounds was evaluated *in vitro* using oxaliplatin as a positive control against MCF7 (a human breast cancer), HL60 (a human lymphocyte) and HT29 (a human colon adenocarcinoma) cell lines. Selective and significant cytotoxic effect of complex (**4**) was observed on MCF7 cells (IC_{50} = 10 μM, Cell viability 62.12%).

1. Introduction

Metal complexes of N- [1] and O-donor heterocyclic ligands are important due to their applications in biology and pharmacology [2–3]. From the point of chemistry, such ligands have been attracting considerable attention due to their structural characteristics to bind to metal ions and to build novel coordination architectures by both strong (e.g. O—H···O) and weak (e.g. C—H···O and C—H···N) hydrogen bonds and also, aromatic π-π stacking interactions [4]. Investigations have shown that pyridine-2,6-dicarboxylic acid, due its ability to give stable chelates with different versatile flexible coordination modes with metal ions, the great affinity to form strong hydrogen bonds and its biological activities has a key role in coordination chemistry and biochemistry. One of the most important reactions of this compound is proton transfer in acid/base systems [5]. Polycarboxylic acids were used as building blocks for formation of metal coordination complexes by the proton-transfer processes [6–9]. The construction of a proton-transfer complex results in a high dipole moment (10–12 D) characteristic of ion pairs, generally [10].

Heretofore, several studies have been done to establish the proton-transfer of carboxylic acids to amines and also, to synthesis of metal complexes from these compounds [11,12]. Proton-transfer in molecular associations between carboxylic acids and lewis bases provides significant stability upon the structure making process. Such stability is seen in more hydrogen bonding associations particularly in the systems involving the protonated amine functional groups [13]. As is clear, proton-transfer is one of the fundamental concepts in physics, chemistry and biochemistry, as it is the main process in reactions such as auto ionization in water, the anomalously high proton mobility in water, acid-base neutralization reactions, proton pumping through membrane protein channels, and enzyme catalysis [14]. The researches show that ligands

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have critical roles in determining the nature of interactions involved in the recognition of biological target sites, such as DNA, enzymes and protein receptors. Such variables provide enormous potential diversity for the design of metallodrugs [15]. It should also be mentioned that pyridine derivatives have biological and pharmacological applications as anticoagulants, antihistamines, antiseptics, antiarrhythmics, and antirheumatics [16] or N-substituted derivatives of imidazole and 2-methylimidazole exhibit variety of pharmacological properties, such as antiparasitic, antifungal, and antimicrobial activities. According to this, these compounds were investigated for antibacterial activity against *Escherichia Coli*, *Staphylococcus aureus* and *Pseudomanas aureginosa* by S. Khabnadideh and co-workers [17]. But in most of the cases, the metal complexes indicate higher bioactivities than the free ligands [18], and some side effects and drug-resistance may reduce upon complexation [19,20]. In 1981, C. E. Morris and coworkers exhibited that solutions of zirconium(IV) complexes can be used to bind organic antimicrobial agents to cotton fabric. The fabrics were tested for activity against the bacteria *Staphylococcus aureus* and *Staphylococcus epidermidi* and also the fungus *Trichophyton mentagrophytes,* and excellent results was obtained [21]. In recent decades, complexes of cobalt and calcium have been used in medicine [22]. Researches proved that cobalt complexes possess capability in antibacterial, antimicrobial, antitumor and many other biological activities [23]. Also, they could be promising anticancer agents. The diverse physiochemical properties of cobalt have enabled the preparation of several complexes with different cytotoxic modes of action. The favorite redox properties of cobalt under physiological conditions have enabled the delivery of bioactive ligands and fluorophores to hypoxic and/or acidic cancer cells. Finally, it has facilitated detection of hypoxic cells in three-dimensional cell culture models. Unprecedented strategies to treat and detect hypoxic tumors in hard to reach regions within the body might be obtained by further modifications and optimizations of these compounds [24]. In the cytotoxicity effects discussion, metallocene-diacido complexes containing transition metals, such as titanium, vanadium, niobium, zirconium, and molybdenum, exhibit variable antitumor activity for a wide spectrum of murine and human tumors with reduced toxicity as compared to cisplatin [25].

Following these studies, our research group have focused on forming ion pairs between pyridine-2,6-dicarboxylic acid and imidazole derivatives. 2-Methylimidazole is one of the simple nitrogen-containing heterocyclic compounds that is widely used as chemical intermediate in the manufacture of pharmaceuticals [17]. The improvements in its biological properties can be further obtained by slight modifications in the substituents on the basic imidazole nucleus. Some imidazole drugs, at high concentrations, could exert direct inhibitory effects on membranes, without interference with sterols and sterol esters [26,27]. Imidazole incarnation as the functional group of the histidine residue is commonly associated with protein subunits that operate to transport protons from place to place. It can pick up a proton on one of its N atoms to form a cation and deliver another hydrogen from the other N to a second site due to its specific structural features. This sort of shuttling action might be as part of the catalytic mechanism of a number of enzymes [28]. Generally, the interaction of metal ions with ligands has been recognized as an important area for research.

Metals due to their variable oxidation states, number and types of coordinated ligands, and coordinative geometry after complexation can exhibit a variety of properties. In turn, numerous clinical trials have been carried out to assess the efficacy of metal based drugs as treatment for human diseases, including malaria, upper respiratory tract infections, urinary tract infections, sinus infections, vaginal yeast infections, ENT infections, cuts and fungal skin infections and even for sexually transmitted diseases like gonorrhea. Favourable effects have been observed in the aforementioned fields [15].Therefore, it is noteworthy emphasizing point to synthesize metal complexes and investigate their biological activity.

In this regard, the present paper reports synthesis, spectroscopic, elemental, and thermal analyses, crystal structures, antibacterial and anticancer properties of ($pydcH_2$) complexes with imidazole derivatives including $[2\text{-mimH}]_2[Co(pydc)_2][ClO_4]\cdot H_2O$ (**1**), $[2\text{-mimH}]_2[Zr\ (pydc)_3]$ (**2**), $[imiH]_2[Zr(pydc)_3]\cdot 4H_2O$ (**3**) and $[Ca(pydcH_2)_2(H_2O)]_2[Co(pydc)_2]_2\cdot 6H_2O$ (**4**). The compounds (**1**)–(**3**) consist of anionic metal complexes with protonated imidazole derivatives as counter cations. Surprisingly, (**4**) is a co-crystal compound since two Co(II) and Ca(II) complexes with different coordination geometries are crystallized simultaneously. In the next section of the research, the bioactivity studies are done on compounds (**1**)–(**4**) and their ligands, comparatively.

2. Experimental section

2.1. Material and apparatus

Pyridine-2,6-dicarboxylic acid, 2-methylimidazol, imidazole, zirconium(IV) chloride, cobalt(II) nitrate hexahydrate, calcium(II) nitrate tetrahydrate were purchased from the commercial sources and used as received. The solvents were distilled for all synthetic works. The infra-red spectra were recorded on a Bruker Vector 22 FT-IR spectrometer using KBr pellets. Electronic spectra were recorded on Specord 210, Analytic Jena spectrophotometer in the range of 200–900 nm at room temperature. Microanalyses (C, H, N) were measured with a Perkin-Elmer 2004(II) elemental analyzer. The ^1H NMR and ^{13}C NMR spectra (250 MHz) were obtained from Bruker Ultrashield 250 spectrometer. Melting points were obtained on an Electrothermal IA-9100 apparatus. Thermal analyses (TG–DTG) including the thermogravimetry (TG) and derivative thermogravimetry (DTG) were carried out using a PL-1500 TGA apparatus with heating rate of 10 °C min^{-1} in O_2 atmosphere.

2.2. Syntheses

2.2.1. Synthesis of $[2\text{-mimH}]_2[Co(pydc)_2][ClO_4]\cdot H_2O$

The proton-transfer compound was prepared according to reported method in our previous work [29]. 1 equiv. of pyridine-2,6-dicarboxylic acid reacted with 2 equiv. of 2-methylimidazole in tetrahydrofouran. Yield (93%). M.p: 169 °C.

Then, this compound (0.165 g, 0.5 mmol) and $Co(NO_3)_2\cdot 6H_2O$ (0.073 g, 0.25 mmol) were dissolved in distilled water (10 mL) and stirred for 30 min at room temperature. Two drops of hydrochloric acid was added until a clear solution was obtained (pH = 6). The mother liquid was kept at room temperature. Brown transparent crystals were collected after 60 days. Yield (72%). M.p 208 °C. Anal. Calcd for $C_{22}H_{28}N_6O_{16}ClCo$: C, 36.32; H, 3.85; N, 11.56%. Found: C, 36.39; H, 3.82; N, 11.49%. IR bands (KBr disk, υ (cm^{-1})): 3419br, 3119w, 2921w, 2706w, 1640 s, 1608 s, 1419 s, 1374 s, 1343 s, 1320 s, 1274 s, 1173 s, 912 s, 762 s, 725 s. ^1H NMR (D_2O): H 2.01 ppm (s, 3H, CH_3), H 6.78 ppm (s, 2H, $(2\text{-mimH})^+$), H 8.36–8.38 (d, 4H, $pydc^{2-}$), H 8.56–8.60 (t, 2H, $pydc^{2-}$). ^{13}C NMR (D_2O): C 9.88 ppm (CH_3, 2-mimH^+), C 117.56 ppm (C_{meta}, $pydc^{2-}$), C 126.21 ppm (C_{para}, $pydc^{2-}$), C 143.63 ppm (C_{ortho}, $pydc^{2-}$), C 145.07 ppm (*C*2, 2-mimH^+), C 146.01 ppm (C1, 2-mimH^+), 164.69 ppm (CO, $pydc^{2-}$). UV–Vis (λ, nm): 270, 291.

2.2.2. Synthesis of $[2\text{-mimH}]_2[Zr(pydc)_3]$

The experimental procedure for preparation of complex (**2**) was similar to complex (**1**) with a replacement of $Co(NO_3)_2\cdot 6H_2O$ by $ZrCl_4$ (0.25 mmol, 0.058 g). The colorless crystals were collected after 22 days. Yield (81%). M.p 394 °C decomp. Anal. Calcd for