Inorganica Chimica Acta 461 (2017) 221–232

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Research paper

Novel pyridinedicarboxamide derivatives and a polymeric copper(II) complex: Synthesis, structural characterization, electrochemical behavior, catalytic and cytotoxic studies

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ARTICLE INFO

Article history:
Received 10 August 2016
Received in revised form 16 February 2017
Accepted 19 February 2017
Available online 27 February 2017

Keywords:
Amide-based ligands
One-dimensional polymeric complex
Electrochemical behavior
Catalytic activity
Cytotoxicity

ABSTRACT

Two new amide-based ligands, N,N′-bis(2-carboxylphenyl)-2,6-pyridinedicarboxamide (**L1**), N,N′-bis(2-carboxyphenyl ethyl ester)-2,6-pyridinedicarboxamide (**L2**) and a one-dimensional polymeric complex from reaction between (**L1**) and $Cu(NO_3)_2{\cdot}3H_2O$ with the formula of $\{[Cu(CPCP)](DMAP){\cdot}3H_2O\}_n$ [where DMAP is 4-dimethylaminopyridine and CPCP is 6-(2-carboxylatophenylcarbamoyl) picolinate] were synthesized. These compounds have been characterized spectroscopically and their molecular structures were determined by single-crystal X-ray diffraction. Also, thermal analysis (TGA/DTA) was carried out on complex (**3**). Possible mechanisms were proposed for esterification and hydrolysis of (**L1**). Study of electrochemical behavior of compounds using cyclic voltammetry at E of −1.0 to +1.0 V showed two redox couple for complex (**3**) corresponding to Cu(I)/Cu(0) and Cu(II)/Cu(I) at $E^{0'}$ of −0.26 to 0.08 V versus Ag/AgCl. Ligands (**L1**) and (**L2**) did not exhibit any wave in the investigated potential range. Also, complex (**3**) was evaluated for catalytic activity on the oxidation of aromatic and aliphatic alcohols by changing parameters such as the amount of catalyst, oxidant and also reaction temperature. The outstanding catalytic performance of complex (**3**) was confirmed by selective conversion of alcohols to the corresponding aldehydes. The cytotoxic effect of compounds was evaluated using oxaliplatin as a positive control against MCF7 (a human breast cancer), HT29 (a human colon adenocarcinoma) and βTC (a mouse beta pancreatic) cell lines. The cancerous cells exhibited the highest sensitivity to compound (**3**) with IC50 values about 1–10 μM.

1. Introduction

For a long time coordination chemistry of organic amides have been attracted much attention of inorganic chemists as an important part of current chemical problems [1–3]. Molecules containing the amide functionality are a class of compounds with variety of applications in different fields of chemistry and biochemistry. The favorable chemical properties which led to more accurate study of these compounds include variable bonding modes for complexation of metal ions [4], stabilization of metal ions in their different oxidation states [5] and selective extraction of metal ions. From the point of biochemistry, amidic linkages are investigated as the main building units in natural macromolecules such as proteins and polypeptides [6] and synthetic macromolecules such as nylons and Kevlar® [7]. The versatile coordination behavior and potential hemilability of hybrid ligands containing (N, O) made them to be investigated for the synthesis of supramolecular structures [8]. The steric environment and electronic properties of amidic ligands are affected by changing acyl groups or substituents on the nitrogen atom. Many amidic complexes of transition metals and rare-earth metals were studied due to their high activities in catalytic transformations, ring-opening polymerization of lactones, oligomerization and polymerization of ethylene and insertion reactions [9]. Formation of metal complexes with acidic organic ligands, in which the acid group is usually a hydroxide, an amide NH, or a thiol, is facilitated via the deprotonation of the ligand by the addition of a base such as triethylamine, sodium hydride, or use of the corresponding metal acetate [10]. The high donor ability of tertiary amides such as DMA and DMF (which are usually used as solvent) makes it possible for them to coordinate with metal ions in many complexes, directly [11]. On the other hand, metal ions with capability of substituting for amidic hydrogen can coordinate strongly to the amide group [12]. The molecular geometries are affected by the bulky amide groups in these structures [13].

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http://dx.doi.org/10.1016/j.ica.2017.02.023
0020-1693/

Multidentate heterocyclic ligands of pyridylcarboxamides have an important position in biochemistry and coordination chemistry. Several researches have been carried out on bonding and structural motifs involving at this class of ligand; from isolated macrocycles and helicates to dynamic porous frameworks [14]. The regular hydrogen bonding of the amide groups can be used for a special design contributing to the robustness of the frameworks and their thermal stability [15]. A large number of high-valence copper complexes with amide-based ligands were investigated as biomimetic models and catalytic oxidants. The study of coordination structures of $Cu^{2+/3+}$ complexes containing amidic ligands demonstrated that N_{amide} donors are effective in bringing out and stabilizing the high oxidation state of a metal ion [16].

Many transition metal complexes possess capability of enhancing cellular radiation damage both *in vitro* and *in vivo*. Copper(II) ion was studied to modify the radiation response in both mammalian and bacterial cells. The radiosensitizing mechanism in mammalian cells suggested the involvement in reduction of copper(II) to copper(I). Recently, it was recognized that the radiosensitization process may be related to the radiation induced DNA damage, biological damage sensitized by copper ions involve nucleobases and different structure of copper complexes which might bind with double-helical DNA and promote double-strand DNA damage [17]. Although many transition metal complexes have been synthesized and their applications were investigated in various fields [18–20], the biological relevance and rich catalytic activity of copper complexes containing amidic nitrogen donors encouraged us to prepare such compounds. For example copper (II) complexes in addition to their effects on cancer treatment [21–23], can be effective as catalysts for the oxidative organic transformations involving the oxidation of alcohols, alkanes, alkenes and thioethers [24].

These results, along with our interest to design new compounds with catalytic and cytotoxic activity, led us to synthesize and study of new amidic ligands from the reaction of pyridine-2,6-dicarboxylic acid and 2-aminobenzoic acid and also, a Cu(II) complex from (**L1**) [25]. It is noteworthy that despite high stability of amide groups [26], X-ray studies exhibited that one of the amidic bonds was hydrolyzed during the complexation of ligand (**L1**) [27] and an unsymmetrically polymeric Cu(II) complex was synthesized. In this paper, possible mechanisms and some effective factors on the hydrolysis of amides are discussed.

2. Experimental

2.1. Materials and apparatus

Pyridine-2,6-dicarboxylic acid, 2-aminobenzoic acid, 4-dimethylaminopyridine (DMAP), thionyl chloride, hexanol, benzyl alcohol and its derivatives were purchased from the commercial sources and used as received. The solvents were distilled for all synthetic works. Melting points were obtained on an Electrothermal IA-9100 apparatus. The FT-IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer using KBr pellets. Electronic spectra were recorded on Specord 210, Analytik 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 ^{1}H NMR spectra (400 MHz) were obtained from Bruker Ultrashield 400 spectrometer. Thermal behavior was measured with a PL-1500 TGA apparatus with heating rate of 10 °C/min in N_2 atmosphere. The mass spectroscopy (MS) was determined using an Agilent (USA) spectrophotometer. Electrochemical experiments were performed using a μAUTOLAB modular electrochemical system (ECO Chemie, Ultrecht, the Netherlands) equipped with a PGSTAT type III module driven by GPES software in conjunction with a conventional three-electrode system an Ag/AgCl/3 M KCl and platinum wire as reference and counter electrode respectively and a GC as working electrode. The working electrode was polished with aluminum oxide powder on chamois leather and the electrolyte was deoxygenated with nitrogen gas prior to the analysis.

2.2. Synthesis procedures

2.2.1. Synthesis of N,N′-bis(2-carboxylphenyl)-2,6-pyridinedicarboxamide (*L1*)

Synthetic route of compounds are displayed in Scheme 1. At first, anhydrous thionyl chloride (25 mL) was added to pyridine-2,6-dicarboxylic acid (1 mmol, 0.167 g) and refluxed at 80–90 °C under argon atmosphere for 3 h until a clear yellow solution was obtained. The excess thionyl chloride was removed under reduced pressure. The product was dried in vacuum, cooled and obtained white precipitate was dissolved in dichloromethane (15 mL) and then, 2-aminobenzoic acid (2 mmol, 0.274 g) in dry pyridine (20 mL) was added to it. The color of the solution is changed slowly from dark green to brown, with occasional stirring. The solution was stirred overnight at room temperature and during the time period light yellow precipitate was formed. The precipitate was filtered off, washed with water, dried in the air and recrystallized from methanol. Yield (89%). M.p: 279 °C. Found (calc. for $C_{21}H_{15}N_3O_6$): C 62.11 (62.23), H 3.55 (3.70), N 10.49 (10.37)%. Selected IR bands (KBr pellet, cm^{-1}): 3446 m (ν_{NH}), 1693 s, 1660 s (ν_{CO}), UV–Vis: λ_{max} (CH_3OH, nm), 235. EI MS: *m*/*z* 405, M^+.

2.2.2. Synthesis of N,N′-bis(2-carboxyphenyl ethyl ester)-2,6-pyridinedicarboxamide (*L2*) compound (*L1*) (0.5 mmol, 0.203 g) was dissolved in ethanol (30 mL) and sulfuric acid was added to it (100 μL)

The solution was stirred 10 min at room temperature. The cubic yellow single crystals were formed after 15 days. Yield (70%). M.p: 287 °C. Found (calc. for $C_{25}H_{25}N_3O_7$): C 62.81 (62.63), H 5.43 (5.21), N 8.64 (8.76)%. Selected IR bands (KBr pellet, cm^{-1}): 3351 m (ν_{NH}), 1733 s, 1660 s (ν_{CO}), UV–Vis: λ_{max} (CH_3OH, nm), 227. EI MS: *m*/*z* 479, M^+.

2.2.3. Synthesis of {[Cu(CPCP)](DMAP)·3H_2O}$_n$ (*3*)

Under aerobic conditions, aqueous solution of DMAP (0.48 mmol, 0.058 g) was added to a stirring aqueous solution of ligand (**L1**) (0.12 mmol, 0.048 g). The obtained suspension was stirred at 70 °C for 2 h until a light yellow solution was produced. Then aqueous solution of $Cu(NO_3)_2{\cdot}3H_2O$ (0.12 mmol, 0.028 g) was added and the mixture was refluxed at 100 °C for 2 h and evaporated to dryness. The crude product was recrystallized from distillated water as green needle-like crystals. Yield (71%). M.p: 289 °C. Found (calc. for $C_{21}H_{23}N_4O_8Cu$): C 48.15 (48.27), H 4.31 (4.40), N 10.69 (10.72)%. Selected IR bands (KBr pellet, cm^{-1}): 1647 s, 1604 s (*v*CO), UV–Vis: λ_{max} (CH_3OH, nm), 231. EI MS: *m*/*z* 522, M^+.

2.3. X-ray crystallography

The X-ray measurement of single crystal of compounds (**L1**), (**L2**) and (**3**) were carried out using a Bruker SMART APEX II diffractometer equipped with a CCD area detector at 298 K, with graphite-monochromated Mo-Kα radiation, $\lambda = 0.71073$ Å. All refinements were done by the full-matrix least-squares method on F^2 using the SHELX-97 program and absorption corrections were performed using the SADABS program [28a–e]. Software including Bruker APEX II (data collection and cell refinement) and WinGX (publication material) were properly employed [29]. The molecular graphic programs including DIAMOND [30] and MERCURY were used [31]. The crystal and structural refinement data for compounds are given in Table 1.