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Synthesis, characterization, crystal structure and antimicrobial activities of new *trans N*,*N*-substituted macrocyclic dioxocyclam and their copper(II) and nickel(II) complexes

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ABSTRACT

New *trans*-disubstituted macrocyclic ligands, 1,8-[*N*,*N*-bis(3-formyl-12-hydroxy-5-methyl)benzyl]-5,12-dioxo-1,4,8,11-tetraazacyclotetradecane (L^1), 1,8-[*N*,*N*-bis(3-formyl-12-hydroxy-5-bromo)benzyl]-5,12-dioxo-1,4,8,11-tetraazacyclotetradecane (L^2), *N*,*N*-bis[1,8-dibenzoyl]-5,12-dioxo-1,4,8,11-tetraazacyclotetradecane (L^3), *N*,*N*-bis[1,8-(2-nitrobenzoyl)]-5,12-dioxo-1,4,8,11-tetraazacyclotetradecane (L^4), and *N*,*N*-bis[1,8-(4-nitrobenzoyl)]-5,12-dioxo-1,4,8,11-tetraazacyclotetradecane (L^5) were synthesized. The ligands were characterized by elemental analysis, FT IR, ^{1}H NMR and mass spectrometry studies. The crystal structure of L^1 is also reported. The copper(II) and nickel(II) complexes of these ligands were prepared and characterized by elemental analysis, FT IR, UV–Vis and mass spectral studies. The cyclic voltammogram of the complexes of ligand L^{1-3} show one-electron quasi-reversible reduction wave in the region −0.65 to −1.13 V, whereas that of L^4 and L^5 show two quasi-reversible reduction peaks. Nickel(II) complexes show one electron quasi-reversible oxidation wave at a positive potential in the range +0.95 to +1.06 V. The ESR spectra of the mononuclear copper(II) complexes show four lines, characteristic of square-planar geometry with nuclear hyperfine spin 3/2. All copper(II) complexes show a normal room temperature magnetic moment value μ_{eff} 1.70–1.73 BM which is close to the spin only value of 1.73 BM. Kinetic studies on the oxidation of pyrocatechol to *o*-quinone using the copper(II) complexes as catalysts and hydrolysis of 4-nitrophenylphosphate using the copper(II) and nickel(II) complexes as catalysts were carried out. The ligands and their complexes were also screened for antimicrobial activity against Gram-positive, Gram-negative bacteria and human pathogenic fungi.

1. Introduction

Fourteen-membered cyclam (1,4,8,11-tetraazacyclotetradecane) is one of the most versatile tetraamine ligands owing to their coordination properties and their wide range of applications [1,2]. Among potential applications of the metal complexes of these ligands are the selective removal of toxic metals from waste streams radiotherapy and contrast agents for magnetic resonance imaging [3–5]. Dioxocyclams belong to a subgroup which is claimed to be a structural intermediate between oligopeptides and saturated polyamines and which has also been extensively investigated [6]. Typically, the 14-membered dioxocyclams, like porphyrins and corrin, incorporate metal ions into their cavities and form stable square planar complexes with several configurations [7,8]. Oxopolyamines have been extensively studied due to their important biological functions and some unusual properties [9,10].

It is possible to carry out the modification of tetraaza macrocyclic ligands to control and tune the redox properties of coordinated metal centres [11]. Variations can be introduced by altering the macrocyclic ring size or by placing substituents on the nitrogen donors and/or ring framework. Of these approaches, N-functionalization with four identical pendant arms is straightforward [12]. So far, great effort has been devoted to the incorporation of functionalized pendant groups into a saturated macrocyclic tetraamine structure to modify its conformational properties and the redox properties of its metal complexes [13–15].

The cyclam derivatives are also used as spacers (i.e., the bridge between the coordinating units) because of their exceptional coordination properties and the abundant available literature describing efficient and straightforward N- or C-substitution strategies [16]. The nature and redox state of the metal ions located in the

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macrocyclic spacer units drastically influences their properties [17]. Gasnier et al. [18] have reported supramolecular coordination materials based on a bis-terpyridine-functionalized dioxocyclam ligand.

The chemistry of N-functionalized cyclam based compartmental ligands and their copper(II) and nickel(II) complexes remain an important field of research. Macrocyclic dioxotetraamines bearing functionalized pendant groups are powerful chelating agents, and can coordinate with many transition metal ions to form complexes which are effective oxidants and biomimetic redox catalysts [19]. However, up to now, only a few examples of such functionalized macrocyclic dioxotetraamines have been reported [20,21]. Herein, we report the synthesis and characterization of five new macrocyclic dioxocyclam ligands and their complexation properties with Cu(II) and Ni(II) as well as the crystal structure of the ligand L^1.

2. Experimental

2.1. Analytical and physical measurements

Elemental analysis of the complexes was obtained using a Haereus CHN rapid analyzer. FT IR spectra were recorded on a Shimadzu FT IR 8300 series spectrophotometer in the range 4000–400 cm^{-1} using spectral grade KBr. ^1H NMR spectra were recorded using a JEOL GSX 400 MHz NMR spectrometer. Atomic absorption spectral data were recorded using a Varian spectra AA-200 model atomic absorption spectrophotometer. FAB^+ mass spectrum was obtained on a JEOL SX102/DA-6000 Mass Spectrometer using m-nitro benzyl alcohol (NBA) as the matrix. The accelerating voltage was 10 kV and the spectrum was recorded at room temperature. Electronic spectral studies were carried out on a Hitachi 320 spectrophotometer in the range 200–1100 nm. Molar conductivity was measured by using an Elico digital conductivity bridge model CM-88 using freshly prepared solution of the complex in dimethylformamide. Cyclic voltammograms were obtained on a CHI-600A electrochemical analyzer. The measurements were carried out under oxygen-free conditions using a three-electrode cell in which a glassy carbon electrode was the working electrode, a saturated Ag/AgCl electrode was the reference electrode and platinum wire was used as the auxiliary electrode. A ferrocene/ferrocenium (1+) couple was used as an internal standard and $E_{1/2}$ of the ferrocene/ferrocenium (Fc/Fc^+) couple under the experimental condition was 470 mV. Tetra(*n*-butyl)ammonium perchlorate (TBAP) was used as the supporting electrolyte. Room temperature magnetic moments were measured on a PAR vibrating sample magnetometer Model-155. X-band EPR spectra were recorded at 25 °C on a Varian EPR-E 112 spectrometer using diphenylpicrylhydrazine (DPPH) as the reference. Catalytic oxidation of catechol to *o*-quinone by the copper complexes and hydrolysis of 4-nitrophenylphosphate by the copper and nickel complexes were studied in 10^{-3} M dimethylformamide solutions. The oxidation reactions were followed spectrophotometrically with the strongest absorption band of *o*-quinone at 390 nm and monitoring the increase in absorbance; the hydrolysis of 4-nitrophenylphosphate was monitored by following the UV absorbance change at 420 nm (assigned to the 4-nitrophenolate anion) as a function of time. A plot of log $(A_\infty/A_\infty - A_t)$ versus time was made for each complex and the rate constants for the catalytic oxidations and hydrolysis of 4-nitrophenylphosphate were calculated.

The ligand L^1 was crystallized from chloroform solution in the space group $P2_1/n$ with two half-molecules of the macrocycle and one molecule of chloroform solvent in the asymmetric unit. Light yellow crystal of the ligand L^1, 0.30 × 0.25 × 0.20 mm, was used for indexing and intensity data collection was carried out using Bruker SMART APEX-CCD diffractometer equipped with a fine focus, 3 kW sealed tube X-ray source and graphite monochromated Mo Kα radiation at 293(2) K. The data covered over a hemisphere of reciprocal space by a combination of three sets of exposures; each set had a different ø angle (0°, 88° and 180°) for the crystal and each exposure of 10 s covered 0.3° in ω. The detector was at a distance of 4 cm from the crystal and the swing angle of the detector was −35°. Cell refinement and data reduction were performed by the SMART and SAINT programs [22]. The final unit cell was obtained from xyz centroids of reflections after integration. Intensity data were corrected for Lorentz and polarization effects, scale variation, for decay and absorption: a multi scan absorption correction was applied, based on the intensities of symmetry related reflections measured at different angular settings (SADABS) and reduced to F_o^2.

The structure was solved by direct methods using the program SHELXS-97 [23], a package for crystal structure solution using direct methods. All non-hydrogen atoms were refined anisotropically [23] by full-matrix least-square procedures with the weight $w = 1/[\sigma^2(F_o^2) + (0.2000P)^2]$, where $P = (F_o^2 + 2F_o^2)/3$. Some of the hydrogen atoms were geometrically fixed and allowed to ride on the parent carbon atom and other hydrogen atoms were located from the different Fourier map and refined isotropically. The CCDC reference number is 723256. The crystallographic data and structure refinement for the ligand L^1 are given in Table S1. The selected bond lengths and angles are listed in Table S2.

2.2. Chemicals and reagents

Synthesis of the parent ligand, 1,4,8,11,-tetraazacyclotetradecane 5,12-dione, as well as 5-methyl salicylaldehyde, 3-chloromethyl-5-methyl salicylaldehyde and 3-chloromethyl-5-bromo salicylaldehyde were carried out according to literature methods [24,25]. Benzoyl chloride and nitrobenzoyl chlorides were purchased from Sigma–Aldrich and used as such. Analytical grade methanol, acetonitrile and dimethylformamide were purchased from Qualigens and used as such. TBAP was used as supporting electrolyte in electrochemical measurement was purchased from Fluka and recrystallised from hot methanol. (**Caution!** TBAP is potentially explosive; hence care should be taken in handling the compound). All other chemicals and solvents were of analytical grade and were used as received without any further purification.

2.3. Synthesis of the ligands

2.3.1. Synthesis of 1,8-[N,N-bis(3-formyl-12-hydroxy-5-methyl)-benzyl]-5,12-dioxo-1,4,8,11-tetraazacyclotetradecane (L^1)

Two equivalent of 3-chloromethyl-5-methyl salicylaldehyde (1.47 g, 0.008 mol) in 50 mL of acetonitrile was rapidly added to 5,12-dioxo-1,4,8,11-tetraazacyclotetradecane (1 g, 0.004 mol) dissolved in 50 mL of hot acetonitrile and stirred for 24 h. The yellow precipitate obtained was filtered, washed with small quantity of acetonitrile and dried under vacuum. This was recrystallized from water to afford L^1 as a yellowish white solid.

Yield: 1.72 g (75 %) M.p: 300 °C. *Anal.* Calc. for $[C_{28}H_{34}O_6N_4]$: C, 64.33; H, 6.56; N, 10.70. Found: C, 64.23; H, 6.47; N, 10.60%; Selected IR (KBr) (ν/cm^{-1}): 3398 ν(OH), 3289 ν(NH), 1670, 1648 ν(C=O). 1H NMR (δ ppm in $CDCl_3$): 1.17 (s, 6H, CH_3), 1.9–2.26 (m, 12H, α-CH_2), 3.35–3.43 (m, 4H, CH_2–CH_2–C=O), 4.4–4.6 (m, 4H, benzylic CH_2), 7.26 (m, 4H, Ar–H), 9.77 (s, 2H, Ar–CHO), 9.86 (s, 2H, CH_2–NH). λ_{max}, nm (ε, M^{-1} cm^{-1}) in DMF: 276 (22 450).

2.3.2. Synthesis of 1,8-[N,N-bis(3-formyl-12-hydroxy-5-bromo)-benzyl]-5,12-dioxo-1,4,8,11-tetraazacyclotetradecane (L^2)

Ligand L^2 was prepared by a method similar to that described for L^1 by using 3-chloromethyl-5-bromo salicylaldehyde (1.82 g,