Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 117 (2014) 662–668

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

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

Effect of substituent of terpyridines on the *in vitro* antioxidant, antitubercular, biocidal and fluorescence studies of copper(II) complexes with clioquinol

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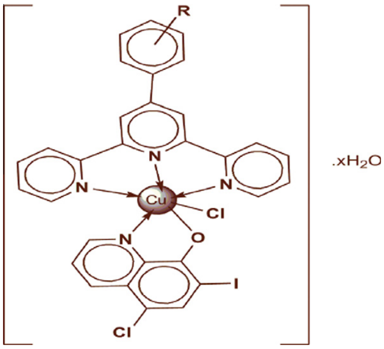
HIGHLIGHTS

- We have synthesized three Cu(II) complexes with various terpyridines.
- Good antioxidant power was shown by complexes as compared to ascorbic acid.
- Compound C_1 excellent activity along with compared to streptomycin.
- MIC for complexes and drug showed good results for all microorganisms.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 24 August 2013
Accepted 7 September 2013
Available online 28 September 2013

Keywords:
Copper(II)
Antioxidant
Antituberculosis
Biocidal activity
Fluorescence

ABSTRACT

An octahedral complexes of copper with clioquinol(CQ) and substituted terpyridine have been synthesized. The Cu(II) complexes have been characterized by elemental analyses, thermogravimetric analyses, magnetic moment measurements, FT-IR, electronic, ^{1}H NMR and FAB mass spectra. Antimycobacterial screening of ligand and its copper compound against *Mycobacterium tuberculosis* shows clear enhancement in the antitubercular activity upon copper complexation. Ferric-reducing anti-oxidant power of all complexes were measured. The fluorescence spectra of complexes show red shift, which may be due to the chelation by the ligands to the metal ion. It enhances ligand ability to accept electrons and decreases the electron transition energy. The antimicrobial efficiency of the complexes were tested on five different microorganisms and showed good biological activity.

Introduction

Many researchers have focused their interests on transition metal complexes because of their extensive applications in wide ranging areas [1]. It is well known that metal ions present in complexes accelerate the drug action and the efficacy of the organic therapeutic agents [2]. The pharmacological efficiencies of metal complexes depends on the nature of the metal ions and the ligands [3]. In co-ordination chemistry, terpyridines are of special interest due to their ability to form stable complexes with many transition metal ions. Such complexes possess interesting photophysical, electrochemical and photochemical properties, allowing constructing extended supramolecular architectures [4]. Clioquinol (5-chloro-7-iodo-8-hydoxyquinoline) is an antibiotic with metal-binding properties which has been shown to have anticancer

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Abbreviations: CQ, clioquinol; L, L^1, L^2, L^3; L^1, 4′-(4-bromophenyl)-2,2′:6′,2″-terpyridine; L^2, 4′-(4-fluorophenyl)-2,2′:6′,2″–terpyridine; L^3, 4′-(4-methoxyphenyl)-2,2′:6′,2″-terpyridine; C_1, $[Cu(L^1)(CQ)Cl]\cdot 3H_2O$; C_2, $[Cu(L^2)(CQ)Cl]\cdot H_2O$; C_3, $[Cu(L^3)(CQ)Cl]\cdot 2H_2O$; B.M., Bohr magneton; TGA, thermogravimetric analysis; LB, Luria Broth.

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http://dx.doi.org/10.1016/j.saa.2013.09.049

activity in several experimental model systems [5–8]. Studies show that clioquinol operates via several different mechanisms of action. We have demonstrated that clioquinol targets zinc to lysosomes [9] and inhibits NF-kappa B activity [6,10]. Clioquinol has also been shown by others to inhibit proteasome activity in various tumor lines [5,8,11]. Although clioquinol has a long history of use in humans, it was judged to be the cause of an epidemic of a rare neurological disease (subacute myeloptic neuropathy (SMON)) in Japan and was banned in many countries. Since that time, others have pointed out that SMON was not seen in other countries where clioquinol was widely used and have criticized the epidemiological data that led to its banning [8,12–14]. Because of promising data in animal studies, clioquinol has been administered in clinical trials for Alzheimer's disease without recurrence of SMON [15,16], prompting careful re-evaluation of its use as a therapeutic agent. Copper has a wide spectrum of effectiveness against a variety of micro-organisms and thus copper-containing compounds such as Bordeaux mixture, and copper sulphate, have been used for the control of plant pathogenic fungi and bacteria on most agricultural crops [17]. Natural chelating agents can reduce copper toxicity by binding part of the available copper, and protect against the toxicity of copper towards bacteria and fungi [18].

At the same time, tuberculosis still remains a major public health problem. The World Health Organisation (WHO) estimates that one third of the population is infected with latent *Mycobacterium tuberculosis* and approximately 3 million people per year decease of illnesses caused by this bacillus [19]. The disease often attacks immunoaltered individuals TB is together with mycoses the most common complication and the cause of death in AIDS patients [20]. A great problem is also migration of inhabitants from the areas with a higher incidence of TB to the regions with a favourable epidemiologic situation. The current TB treatment is not satisfactorily effective in the eradication of latent TB infection [21,22]. This increased risk of developing the infection and the emergence of multi-drug resistant mutants are dictating new approaches in the treatment of mycobacterial disease. Although many studies have investigated the antioxidant properties of resveratrol, there have been only a few reports of antioxidant and antiproliferative effects of hydroxyl-substituted Schiff bases. Towards the development of effective fluorescent molecules the complexes of low energy metal-to-ligand charge transfer (MLCT) excited states are important. Presence of π-acidic coligands in the metal-complex unit has potential efficiency to monitor the MLCT energy. Carbon monoxide is well known π-acidic molecule which may easily regulate energy levels and has been used in many cases for the preparation of luminescent complexes [23,24].

Previously, Kharadi et al., have synthesized a series of fused coumarin derivatives and their transition complexes [25–29]. Present work describes effect of substituent of terpyridines on the *in vitro* antioxidant, antitubercular, biocidal and fluorescence studies of copper(II) complexes with clioquinol.

Experimental

Materials

The solvents were purchased from Merck and used without further purification. Clioquinol was generously supplied by Atul Limited (Valsald, India). Cupric chloride dihydrate was purchased from E. Merck Ltd., Mumbai (India). 2-Acetyl pyridine, p-bromo benzaldehyde, p-fluro benzaldehyde, p-methoxy benzaldehyde were purchased from Loba Chemie PVT. Ltd. (India). Luria Broth (LB) was purchased from Himedia (India).

Instrumentation

Microanalyses (C, H, and N) were done using a 240 Perkin Elmer elemental analyzer. Metal content of the complexes was determined by EDTA titration [30] after decomposing the organic matter with a mixture of $HClO_4$, H_2SO_4, and HNO_3 (1:1.5:2.5). Room temperature magnetic measurement for the complexes was made using Gouy magnetic balance. The Gouy tube was calibrated using mercury(II)tetrathiocyanatocobaltate(II), a calibrant ($Xg = 16.44 \times 10^{-6}$ c.g.s. units at 20 °C). Electronic spectra were recorded on a UV-160A UV–Vis spectrophotometer, Shimadzu (Japan). Infrared spectra were recorded on an FT-IR Shimadzu spectrophotometer as KBr pellets in the range 4000–400 cm^{-1}. The minimum inhibitory concentration (MIC) study was carried out by means of laminar air flow cabinet Toshiba, Delhi (India). The fluorescence behaviors of ligands and their Cu(II) complexes were studied using a Shimadzu RF-1501 fluorescence spectrophotometer with Xe arc lamp as the light source at room temperature. The slit width for excitation and emission was 10 nm, and the scan speed was 1200 nm/min. The FAB mass spectrum of the complex was recorded at SAIF, CDRI, Lucknow with a Jeol SX-102/DA-6000 mass spectrometer. A simultaneous TG/DTG (thermogravimetric/differential thermogravimetric analysis) was obtained using a model 5000/2960 SDT (TA Instruments, USA). The experiments were performed in N_2 atmosphere at a heating rate of 10 °C min^{-1} in the temperature range 50–800 °C, using an Al_2O_3 crucible. The sample sizes ranged in mass from 4.5 to 10 mg. The differential scanning calorimetry (DSC) was recorded using DSC 2920, TA Instruments (USA). The DSC curves were obtained at a heating rate of 10 °C min^{-1} in N_2 atmosphere over the temperature range of 50–400 °C, using an aluminum crucible.

Synthesis of ligands (L^{1-3})

All tridentate ligands were synthesized similarly by following literature procedure [31]. 2-Acetyl pyridine (20.0 mmol) was added to an ethanolic solution of various aldehydes (10.0 mmol in 70 mL EtOH). KOH pellets (26 mmol) and aqueous NH_3 (25%, 0.425 mol) were added to the solution and was stirred at room temperature for 8 h. An off-white solid formed which was collected by filtration, followed by washings with H_2O (3 × 10 mL) and EtOH (2 × 5 mL). Crystallization from $CHCl_3$–MeOH system gives a white crystalline solid. The proposed reaction is shown in Scheme 1.

General procedure for the synthesis of complexes

Ethanolic solution of $CuCl_2{\cdot}2H_2O$ (1.5 mmol) was added to a ethanolic solution of 4′-substituted-2,2′:6′,2″-terpyridine (L^{1-3}) (1.5 mmol), followed by the addition of a previously prepared methanolic solution of clioquinol (1.5 mmol) in presence of CH_3-ONa (1.5 mmol). The pH of the reaction mixture was adjusted to ~6.8. The resulting solution was refluxed for 2 h on a water bath, followed by concentrating to half of its volume. A fine, dark brown amorphous product obtained was washed with ether/hexane and dried in vacuum desiccators in Scheme 2. Physical properties and analytical data of copper(II) complexes with clioquinol and terpyridines in Table 1.

Antioxidant studies

Ferric-reducing anti-oxidant power (FRAP) was measured by a modified method [32]. The antioxidant potentials of compounds were estimated as their power to reduce the TPTZ-Fe(III) complex to TPTZ-Fe(II) complex. This method is simple, fast, and reproducible results can be obtained. Total anti-oxidant capacity of biolog-