Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 96 (2012) 468–479

Contents lists available at SciVerse ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

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

Multiple heating rate kinetic parameters, thermal, X-ray diffraction studies of newly synthesized octahedral copper complexes based on bromo-coumarins along with their antioxidant, anti-tubercular and antimicrobial activity evaluation

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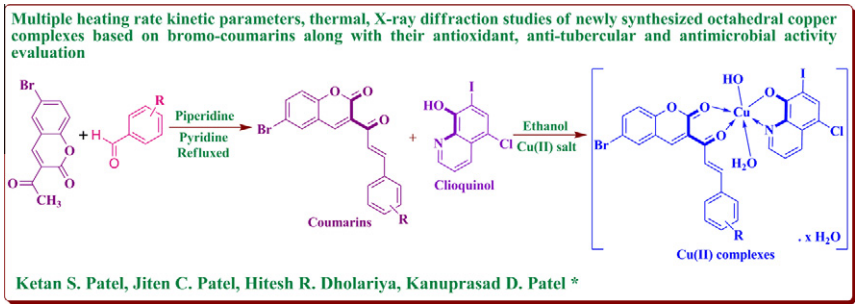
HIGHLIGHTS

- Mixed-ligand Cu(II) complexes based on bromo-coumarins with Clioquinol.
- Octahedral geometry was confirmed using electronic spectra and magnetic measurement.
- X-ray diffraction studies and multi-heating-rate kinetic parameters measurements of Cu(II) complexes.
- Antioxidant, anti-tubercular and antimicrobial studies of complexes.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 31 March 2012
Received in revised form 17 May 2012
Accepted 26 May 2012
Available online 4 June 2012

Keywords:
Clioquinol
Isoconversional method
Antioxidant
Anti-tubercular
Powder XRD

ABSTRACT

Series of new Cu(II) complexes were synthesized by classical thermal technique. The biologically potent ligands (L) were prepared by refluxing 6-brom 3-acetyl coumarin with aldehydes in the presence of piperidine in ethanol. The Cu(II) complexes have been synthesized by mixing an aqueous solution of $Cu(NO_3)_2$ in 1:1 molar ratios with ethanolic bidentate ligands and Clioquinol. The structures of the ligands and their copper complexes were investigated and confirmed by the elemental analysis, FT-IR, ^1H NMR, ^{13}C NMR, mass spectral and powder X-ray diffraction studies respectively. Thermal behaviour of newly synthesized mixed ligand Cu(II) complexes were investigated by means of thermogravimetry, differential thermogravimetry, differential scanning calorimetry, electronic spectra and magnetic measurements. Dynamic scan of DSC experiments for Cu(II) complexes were taken at different heating rates (2.5–20 °C min^{-1}). Kinetic parameters for second step degradation of all complexes obtained by Kissinger's and Ozawa's methods were in good agreement. On the basis of these studies it is clear that ligands coordinated to metal atom in a monobasic bidentate mode, by O—O and O—N donor system. Thus, suitable octahedral geometry for hexa-coordinated state has been suggested for the metal complexes. Both the ligands as well as its complexes have been screened for their *in vitro* antioxidant, anti-tubercular and antimicrobial activities. All were found to be significant potent compared to parent ligands employed for complexation.

1. Introduction

Interest in coumarin chemistry has flourished for many years; basically from a result of the wide spread use of coumarin derivatives. Coumarin was basic molecule found in family of many derivatives, like a simplest naturally occurring phenolic substance possessing fused benzene and α-pyrone rings. Naturally occurring as well as synthetic derivatives of coumarin compound have importance in wide range of fields such as medicinal chemistry, biochemistry, plant science and pharmacology [1]. A large number of structurally novel coumarin derivatives have been ultimately reported to show substantial cytotoxic and anti-HIV activity in vitro and in vivo [2]. The coumarin exists in a variety of forms, due to the various substitutions possible in their basic structure, which

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http://dx.doi.org/10.1016/j.saa.2012.05.057

modulate their biological activity [3,4]. The coumarin derivatives are known to have diverse applications as anti-HIV [5–8], antibacterial [9,10], anthelminthic [11], anti-inflammatory [12–14] and antioxidant activities [15–14], anticoagulants, spasmolytics, anticancer drugs or as plant growth regulating agents [18–20]. Their complexation ability in respect to different metal ions has been studied and discussed widely in a considerable number of investigations [21–24]. It has been found that the binding of a metal to coumarin moiety retains or even enhances its biological activity [25–27]. In recent years the metal ions such as copper(II), iron(II), iron(III) or platinum(II) exert wide biological activity, for example against tumor cells. Also chromones, flavonoids and coumarins have been known for similar properties. From above facts those complexes of metals and ligands would be more active than the basic compounds. The biological activity of these complexes recently described in the literature is similar to widely used carboplatin [28–33]. Apart from the medicinal, biological and pharmacological applications coumarins are also used as sweeteners, fixatives of perfumes, additives in food, odour stabilizers in tobacco and an odour masker in paints and rubber [33].

Clioquinol (5-chloro-7-iodo-8-hydoxyquinoline) belongs to the quinoline class of compounds was first prepared in Germany by Ciba–Geigy during the last century. Clioquinol was used as antibiotics for the period of 1950s to 1970s [34,35]. Moreover, Clioquinol (CQ) is an antibiotic with metal-binding properties which has been shown to have anticancer activity in a number of experimental model systems [36,37]. Although Clioquinol has a long history of use in humans, it was observed that 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 extensively used and have criticized the epidemiological data that led to its banning [38,39]. Because of optimistic data in animal studies, Clioquinol has been administered in clinical trials for Alzheimer's disease without reappearance of SMON [40,41], prompting careful re-evaluation of its use as a therapeutic agent. Clioquinol was widely used as an antibiotic for the treatment of amoebic dysentery and skin infection [42]. Regardless of it being a controversial compound, CQ can still serve as a model compound from which analogues could be developed that exploit its copper binding potential but avoid its negative associations. CQ is a lipophilic compound that is capable of forming stable complexes with Cu(II) ions [43]. Furthermore, the complexes of CQ with copper and zinc metal ions recognized for their biological effects which are significantly allied with protein aggregation and degeneration process in the brain [43], also these complexes have been used as an antimicrobial agent since many years [44]. Coumarin and CQ used as capable applicant for biological aspects [45]. Many reports were available on its credited [46].

Here the continuation of our earlier work [47,48], in present communication we describe synthesis, characteristic, spectroscopic properties, powder X-ray diffraction study and thermal aspects of newly coumarin based mixed ligand Cu(II) complexes as well as antioxidant, anti-tubercular and antimicrobial screening of newly synthesized compounds. Kissinger [49,50] and Flynn–Wall–Ozawa (FWO) [51,52] kinetic methods were employed to evaluate the kinetic parameters i.e. activation energies and the pre-exponential factor.

2. Experimental

2.1. Materials

All reagents were of analytical reagent (AR) grade purchased from Spectro Chem. Ltd., Mumbai-India and used without further purification. Solvents employed were distilled, purified and dried by standard procedures prior to use [53]. Clioquinol was purchased from Agro Chemical Division, Atul Ltd., Valsad-India. The metal nitrates were used in hydrated form.

2.2. Physical measurements

All reactions were monitored by thin-layer chromatography (TLC on alluminium plates coated with silica gel 60 F_{254}, 0.25 mm thickness, E. Merck, Mumbai-India) and detection of the components were measured under UV light or explore in Iodine chamber. Carbon, hydrogen and nitrogen were estimated by elemental analyzer Perkin–Elmer, USA 2400-II CHN analyzer. Metal ion analyses was carry out by the dissolution of solid complex in hot concentrated nitric acid, further diluting with distilled water and filtered to remove the precipitated organic ligands. Remaining solution was neutralized with ammonia solution and the metal ions were titrated against EDTA. ^{1}H and ^{13}C NMR measurements were carried out on Advance-II 400 Bruker NMR spectrometer, SAIF, Chandigarh. The chemical shifts were measured with respect to TMS which used as internal standard and DMSO-d_6 used as solvent. Infrared spectra of solids were recorded in the region 4000–400 cm^{-1} on a Nicolet Impact 400D Fourier-Transform Infrared Spectrophotometer using KBr pellets. The FAB mass spectrum of the complex was recorded at SAIF, CDRI, Lucknow with JEOL SX-102/DA-6000 mass spectrometer. Melting point of the ligands and metal complexes were measured by open capillary tube method. Solid state magnetic susceptibility measurements were carried out at room temperature using a Gouy's magnetic susceptibility balance with mercury tetrathiocyanato cobaltate(II) being used as a reference standard ($g = 16.44 \times 10^{-6}$ c.g.s. units). Molar susceptibility was corrected using Pascal's constant [54]. Thermal decomposition (TG/DTG) analysis was obtained by a model Diamond TG/DTA, Perkin–Elmer, USA. The experiments were performed in N_2 atmosphere at a heating rate of 20 °C min^{-1} in the temperature range 30–840 °C. DSC analyses were carried out using Perkin–Elmer USA, Differncial Scanning Calorimetry (DSC-PYRIS-1). DSC analyses of complexes were also evaluated from dynamic scanning experiments at multiple heating rates of 2.5, 5, 10, 15 and 20 °C min^{-1}, respectively, with the best resolution and comparative results achieved at a scanning rate of 10 °C min^{-1}. The samples sizes were ranged in mass from 3 to 8 mg were heated in Al_2O_3 crucible. The electronic spectra were collected using LAMBDA 19 UV/Vis/NIR spectrophotometer in the region 200–1200 nm.

2.3. Crystallographic analysis

X-ray diffraction intensities were carried out with ±0.0025 accuracy using XRD Diffractometer (powder), Xpert MPD, Philips, Holland equipped with 2 kW power and Cu target X-ray tube used as a source of wavelength 1.542 Å, while the data were accumulate using JCPDF database. The detector used in the system was Xe-filled counterate and 2° θ measurement range of the instrument is 3° to 136°. The system contains goniometer was operated on vertical and horizontal mode with θ–θ and θ–2θ position respectively with radius 130–230 mm.

2.4. Synthesis of 3-acetyl coumarin

3-Acetyl coumarin was prepared according to the reported method [55]. A mixture of 6-Bromo salicylaldehyde (0.1 mol, 12.2 g), ethyl acetoacetate (0.1 mol, 13.0 g) and 3–4 drop piperidine were stirred for 10 min at room temperature in a 100 mL round bottom flask. After 10 min it was heated for 30 min in water bath. A yellow solid obtained was taken out and washed with cold