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Characterization, photocleavage, molecular modeling, and DNA- and BSA-binding studies of Cu(II) and Ni(II) complexes with the non-steroidal anti-inflammatory drug meloxicam

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ABSTRACT

Two complexes of Cu(II) and Ni(II) with the non-steroidal anti-inflammatory drug meloxicam (H_2mel, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxammide-1,1-dioxide), *trans*-[Cu(Hmel)$_2$(THF)$_2$] (**1**) and *trans*-[Ni(Hmel)$_2$(DMF)$_2$] (**2**), were synthesized and characterized. The interaction of the complexes with DNA and bovine serum albumin (BSA) was investigated. Molecular docking and molecular dynamic simulation methods were also used for modeling the binding of the complexes to DNA and BSA and good agreements were found between the experimental and theoretical results. All the results suggest that the interaction mode between the complexes and DNA was major groove binding. The quenching mechanism of the BSA fluorescence by the complexes is a static quenching. Gel electrophoresis assay demonstrates the ability of the complexes to cleave the supercoiled plasmid DNA (pUC57 plasmid DNA).

1. Introduction

In recent years, the interaction between drugs and transition metal complexes is active research area in bioinorganic chemistry and has played a very important role in medicine, pharmacy and diagnostics [1–3].

Non-steroidal anti-inflammatory drugs (NSAIDs) are large group of drugs which suppress inflammation in a manner similar to steroids, but with fewer side effects. There are seven chemical classes for NSAIDs, *viz.* phenylalkanoic acids, anthranilic acids, oxicams, salicylate derivatives, sulfonamides, propanamide, and furanones [4]. Most NSAIDs act as nonselective inhibitors of the cyclooxygenase enzyme, inhibiting both the COX-1 (constitutive form) and COX-2 (inducible form) isoenzymes. The "oxicam" family is a well-known class of drugs, that they are widely used as analgesic, anti-inflammatory and antipyretic agents [5]. Meloxicam (H_2mel) (Scheme 1) is a subclass of the oxicam [6]. It has been recognized as a selective COX-2 inhibitor with fewer adverse side effects [7,8]. Meloxicam can be classified as Class II based on the biopharmaceutical classification system (BCS), which means low aqueous solubility and rapid absorption (high permeability) through the gastrointestinal tract [9].

Coordination of oxicam ligand to metal ion can provide an enhanced activity of the drug because of the synergism between the ligand and metal properties [10]. The importance of complexes with NSAIDs as ligands has been mentioned in several articles and reviews [11–25]. The meloxicam as coordinating ligand has at least three different coordination modes to metal ions: (i) a mono-dentate ligand *via* the pyridyl or thiazolyl nitrogen towards Pt(II) and Pd(II) [26,27], (ii) a singly deprotonated chelating ligand *via* the pyridyl or thiazolyl nitrogen and the amide oxygen towards Cu(II) and Cd(II) [28], and (iii) a di-anionic tri-dentate ligand *via* the amide oxygen and nitrogen, and the pyridyl nitrogen towards Sn(II) [29].

In the deprotonated form of meloxicam, the enolic oxygen is not involved in coordination but instead is linked to the N–H function *via* a strong intramolecular hydrogen bond made possible by the *ZZZ*–Hmel$^-$ and *ZZE*–Hmel$^-$ conformations and deprotonated meloxicam is coordinated to the metal ion through the amide

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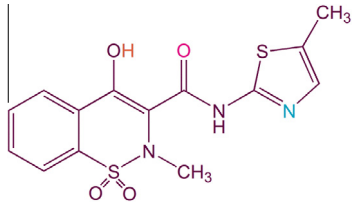


Scheme 1. Molecular structure of meloxicam (H_2mel).

oxygen and the nitrogen atom from the thiazolyl ring [30]. The coordination mode of the meloxicam ligand *via* the amide oxygen and the nitrogen atom of the thiazolyl ring is shown in Scheme 2.

Ni(II) and Cu(II) complexes have been receiving much attention due to biological applicability, such as antiepileptic, antibacterial, antifungal, antimicrobial, anticancer, and antiproliferative activities [31–38].The Cu(II)–NSAID complexes enhance the anti-inflammatory activity of NSAID and reduce the gastro intestinal (GI) toxicity compared to the bare drugs [39,40]. Additionally, the Cu(II)–NSAID complexes have remarkable anticancer effects [4]. For instance, Sarkar et al. have studied the DNA interaction of some Cu(II) complexes with piroxicam and meloxicam which exhibited anticancer activity. They showed that the complexes bind strongly to DNA-backbone possibly with an intercalation mode [5]. Also, spectroscopic studies of the binding of Cu(II) complexes of oxicam [41] and mechanism of interaction of the NSAIDs meloxicam with serum albumin have been reported [42].

Therefore, it is essential to explore the interactions of the complexes with DNA and protein in order to design effective chemotherapeutic agents and better anticancer drugs with improved potential [43].

This paper is in continuation of our previous studies on oxicam family [10,44,45]. Here, we report the synthesis and structural characterization of two neutral mononuclear complexes with the meloxicam ligand, *trans*-[Cu(Hmel)$_2$(THF)$_2$] (**1**) and *trans*-[Ni(Hmel)$_2$(DMF)$_2$] (**2**).

The investigation of the biological properties of the complexes with DNA and BSA performed with UV–Vis and fluorescence spectroscopy. In addition, the DNA photocleavage activity of the complexes with the pUC57 plasmid DNA has also been carried out. Finally, the interactions of the complexes to BSA and DNA were modeled by molecular docking and molecular dynamic simulation methods.

2. Experimental

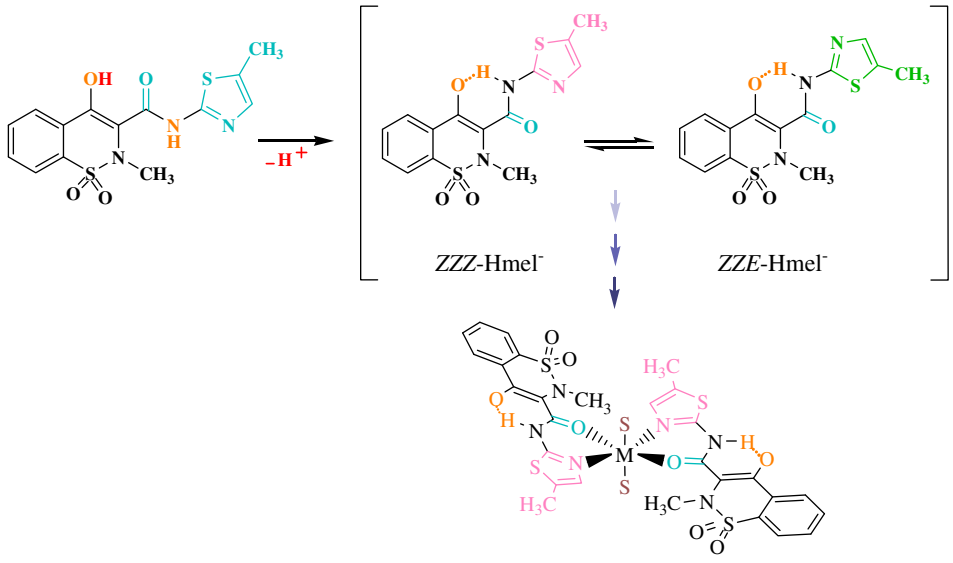
2.1. General considerations

All reagents and solvents were of analytical grade and used without further purification. Meloxicam was a gift from the Farabi Pharmaceutical Company. Analytical grade Cu(CH$_3$COO)$_2$·H$_2$O, Ni(CH$_3$COO)$_2$·4H$_2$O, Tris (hydroxymethyl)-aminomethane (Tris) buffer, and ethidium bromide (3,8-diamino-5-ethyl-6-phenylphenanthridinium bromide, EB) were purchased from Merck. Double-stranded fish sperm deoxyribonucleic acid (ds-FS-DNA), bovine serum albumin (BSA) and agarose (molecular biology grade) were obtained from Sigma–Aldrich. Doubly distilled water was used for preparation of all solutions. Elemental analysis was performed using a Heraeus CHN-O-Rapid elemental analyzer. FT-IR spectra were recorded in the solid state (KBr disk) on a FT-IR JASCO 680-PLUS spectrophotometer in the spectral range 4000–400 cm^{-1}. UV–Vis absorption spectra were recorded on a JASCO 7580 spectrophotometer using a 1 cm path length cell. Fluorescence survey was performed on a Perkin–Elmer LS55 fluorescence spectrofluorometer. The molecular docking study was carried out by using *Autodock vina* program [46]. All molecular images and animations were produced using Molegro Virtual Docker (MVD) [47] and UCSF Chimera [48] packages. The schematic two-dimensional representations of the docking results were performed using LIGPLOT+ [49].

2.2. Synthesis

2.2.1. Synthesis of *trans*-[Cu(Hmel)$_2$(THF)$_2$] (**1**)

Meloxicam (0.4 mmol, 140 mg) and Cu(CH$_3$COO)$_2$·H$_2$O (0.2 mmol, 40 mg) were dissolved separately in hot ethanol (20 and 10 mL, respectively). The two solutions were mixed and the reaction mixture was stirred for ca. 90 min at 40 °C. The green solid that precipitated was filtered off, washed twice with hot ethanol and then dried in the air at room temperature. The microcrystalline product was recrystallized from THF. Yield: 80%. *Anal.* Calc. for $C_{36}H_{40}CuN_6O_{10}S_4$ (MW = 908.54 g/mol): C, 47.59; H, 4.44; N, 9.25. Found: C, 47.72; H, 4.48; N, 9.21%. IR (KBr disk, cm^{-1}): 1599 (m), 1340 (s), 1172 (s). UV–Vis (3% DMSO–5 mM Tris–HCl/10 mM NaCl buffer, λ_{max}/nm (ε/M^{-1} cm^{-1})): 363 (36,608), 269 (20,885), and 237 (20,044).



Scheme 2. *ZZZ* and *ZZE* conformations of Hmel$^-$.