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Cu(I) complexes of bis(methyl)(thia/selena) salen ligands: Synthesis, characterization, redox behavior and DNA binding studies

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ABSTRACT

Mononuclear cuprous complexes **1** and **2**, $[\{CH_3E(o\text{-}C_6H_4)CH=NCH_2\}_2Cu]ClO_4$; E = S/Se, have been synthesized by the reaction of bis(methyl)(thia/selena) salen ligands and $[Cu(CH_3CN)_4]ClO_4$. Both the products were characterized by elemental analysis, ESI-MS, FT-IR, $^1H/^{13}C/^{77}Se$ NMR, and cyclic voltammetry. The complexes possess tetrahedral geometry around metal center with the N_2S_2/N_2Se_2 coordination core. Cyclic voltammograms of complexes **1** and **2** displayed reversible anodic waves at $E_{1/2} = +0.08$ V and +0.10 V, respectively, corresponding to the Cu(I)/Cu(II) redox couple. DNA binding studies of both the complexes were performed applying absorbance, fluorescence and molecular docking techniques. Competitive binding experiment of complexes with ct-DNA against ethidium bromide is performed to predict the mode of binding. The results indicate the groove binding mode of complexes **1** and **2** to DNA. The binding constants revealed the strong binding affinity of complexes towards ct-DNA.

1. Introduction

Salen/salphen ligand systems (derived from the Schiff-base coupling of salicylidehyde and ethylendiamine/*o*-phenylenediamine) are one of the most popular ligand systems in inorganic chemistry. It offers the potential tetradentate (N_2O_2) chelating system and hence, wide variety of metal ions have been engaged with such system. Salen based metal complexes have been explored extensively due to their versatile applications such as in catalysis [1], luminescence [2], magnetism [3], biological studies [4] and material science [5]. Metal salen systems have recently been used for the development of metal-organic frameworks for heterogeneous catalysis, gas storage and molecular trapping [6]. Although, salen systems are widely studied ligands, their sulphur and selenium analogues (thia-salen and selena-salen) are not much explored so far, mainly due to the synthetic complications including instability of thiol and selenol groups compared to the hydroxy group of salen.

On the other hand, with the establishment of structure of double stranded DNA and mechanism of its interaction with *cis*-platin, the study of DNA-metal complex interaction has been a target of chemists in the search of anticancer drugs [7]. DNA-metal interaction studies have recently been explored as different ways *viz* DNA–metal base pairs, template-directed modified DNA-metal complex and non-covalent interaction of DNA-metal complex [8]. The non-covalent interaction of DNA with metal complex can lead to groove binding, intercalation or DNA cleavage. Covalently modified metallosalen-DNA which provide site-specific binding have been explored recently for higher order nanostructures [9].

Template-directed assembly of metallosalen-DNA conjugates has attracted great attention in past few years [10]. Carell and coworkers strategically synthesized metallosalen-DNA hairpin conjugate, using three components (salicylaldehyde, diamine and metal ion), inside a DNA duplex which resulted in tremendous stabilization of the duplex structure [11]. Brissos et al. reported the luminescent zinc salphen complexes as potential DNA-intercalator agents and demonstrated their utility as bio-markers for cell imaging [12]. Xie et al. also reported the library of Zn-Salen/Salphen complexes as fluorescent probes for live cell imaging [13]. Recently, Su et al. reported the interstrand crosslinking of metal ion coordinating pyrazole and salen ligandosides resulting in stable multi-copper ion complexing DNA double helix structures [14]. DNA binding property of substituted Zn-salphen complexes was recently studied by Giannicchi et al. [15]. They found that the presence of strong electron-withdrawing nitro substituent increased the electrophilic character of the metal center and thus responsible for the strongest interaction with plasmid DNA.

Thus, the DNA binding study of alkylated (thia/selena)salen-Cu(I) complexes (as electrophilic complex cations) could be worth. Moreover, many metallo-proteins/metallo-enzymes such as hemocyanin, cupredoxins, tyrosinase and nitritereductase, playing crucial role in biochemistry, have Cu(I) center as their active site [16]. $N_2S_2Cu(I)$ coordination core, derived from (*S*)-cysteine, (*S*)-methionine and two (N)-histidine, is of particular importance as active site in blue copper protein (type-I) [17]. We have been interested in developing the metallo-salen/

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salphen derivatives and exploring their properties [18]. Here, we are reporting the Cu(I) complexes of ligands $\mathbf{L^a}$ and $\mathbf{L^b}$ (Scheme 1), their electrochemistry and DNA binding studies are investigated and reported. Cu(I) ion, being the soft acid, has strong affinity towards heavier chalcogen atoms.

2. Experimental

2.1. Synthesis

Ligand $\mathbf{L^a}$ and $\mathbf{L^b}$ were prepared according to the literature [19]. Synthesis of complexes is mentioned below:

1: 99.5 mg of $[Cu(CH_3CN)_4]ClO_4$ (0.304 mmol) and 100 mg of ligand $\mathbf{L^a}$ (0.304 mmol) were refluxed in 5 mL of dry methanol for 3 h under inert atmosphere. Yellow precipitate appeared immediately during the reaction. The precipitate was filtered, washed thoroughly with methanol and dried in vacuum.

Caution: Perchlorate salts are potentially explosive and care should be taken in handling them.

Yield: 130 mg (87%). M. p.: 206 °C. Anal. calc. for $C_{18}H_{20}N_2S_2CuClO_4$: C, 43.99; H, 4.10; N, 5.70. Found: C, 43.64; H, 4.26; N, 5.51%. ESI-MS: Calc. for $C_{18}H_{20}N_2S_2Cu$: *m/z* 391.0364. Found 391.2753. IR (cm^{-1}, KBr): 1630(s), 1586(m), 1462(w), 1432(m), 1287(w), 1086(s), 1020(m), 971(m), 776(s), 765(s), 623(s), 468(w). ^1H NMR (δ, ppm, DMSO-d_6): 8.77 (s, 2H); 7.74 (d, J = 7.00 Hz, 2H); 7.50 (m, 4H); 7.32 (d, J = 6.50 Hz, 2H); 3.89 (s, 4H), 2.52 (s, 6H). ^{13}C NMR (δ, ppm, DMSO-d_6): 162.48, 136.94, 132.42, 131.90, 129.54, 128.02, 125.82, 60.79, 17.21.

2: Complex **2** was prepared in similar way to complex **1**, using 128 mg (0.304 mmol) of Ligand $\mathbf{L^b}$

Yield: 105 mg (76%). M. p.: 190 °C (dec.). Anal. calc. for $C_{18}H_{20}N_2Se_2CuClO_4$: C, 36.94; H, 3.44; N, 4.79. Found: C, 36.39; H, 3.61; N, 4.57%. ESI-MS: Calc. for $C_{18}H_{20}N_2Se_2Cu$: *m/z* 486.9253. Found 487.0814. IR (cm^{-1}, KBr): 1654(m), 1626(m), 1583(w), 1461(w), 1421(m), 1386(w), 1336(w), 1286(w), 1271(w), 1216(w), 1083(s), 1030(m), 964(m), 929(w), 9119(w), 765(s), 622(m), 463(w). ^1H NMR (δ, ppm, DMSO-d_6): 8.69 (s, 2H); 7.70 (d, J = 7.50 Hz, 2H); 7.60 (d, J = 7.50 Hz, 2H); 7.45 (t, J = 7.50 Hz, 2H); 7.39 (t, J = 7.50 Hz, 2H); 3.99 (s, 4H), 2.32 (s, 6H). ^{13}C NMR (δ, ppm, DMSO-d_6): 164.04, 133.95, 132.34, 132.03, 131.77, 129.37, 127.60, 61.28, 11.27. ^{77}Se NMR (δ, ppm, DMSO-d_6): 257.

2.2. Materials and physical measurements

All chemicals and solvents were received from Aldrich/Merck of reagent grade and used as such. NMR spectra were recorded on a Bruker AVANCE 500 FT-NMR spectrometer using DMSO-d_6 as solvent and chemical shift values are reported in ppm (δ scale) relative to Me_4Si either as internal standard or with respect to solvent residual peak. Infrared spectra were measured on KBr disk with a Perkin-Elmer spectrophotometer. The mass spectra were recorded on a WATERS micromass Q-Tof micro™ instrument. Elemental analyses were carried out on a Carlo-Erba model 1106 elemental analyzer. Cyclic voltammetry was performed with a computer-controlled Princeton Applied Research 263 A electrochemical workstation using platinum (Pt) disk as a working electrode, Pt-wire as the counter electrode and $Ag/AgNO_3$ (10 mM in acetonitrile) as the reference electrode. Tetrabutylammonium perchlorate (0.1 M in acetonitrile) was used as supporting electrolyte.

2.3. Computational details

Density functional theory (DFT) calculations were performed using the Gaussian 09 [20] program at the B3LYP/6-31G(d) level [21]. Counter anion is eliminated and the mono positive complex cations are used for the calculations.

2.4. DNA binding study

2.4.1. Absorption method

The absorbance spectra were scanned by keeping the concentration of the complex constant (10^{-4} M) and varying the concentration of DNA (8.11×10^{-6} to 4.86×10^{-5} M), after each successive addition of ct-DNA, followed by 10 min of incubation, in Tris buffer. The intrinsic binding constant, K_b of complex with ct-DNA is determined according to the Eq. (1) [22],

$$[\mathbf{DNA}]/(\boldsymbol{\varepsilon_a}-\boldsymbol{\varepsilon_f}) = [\mathbf{DNA}]/(\boldsymbol{\varepsilon_b}-\boldsymbol{\varepsilon_f}) + 1/K_b(\boldsymbol{\varepsilon_b}-\boldsymbol{\varepsilon_f}) \quad (1)$$

Where, [DNA] is the concentration of ct-DNA, ε_f, ε_a and ε_b correspond to the extinction coefficients, for the DNA free metal complex, apparent metal complex (for each addition of ct-DNA to the complex) and fully bound metal complex, respectively. In plots of [DNA] / ($\varepsilon_a - \varepsilon_f$) versus [DNA], K_b is given by the ratio of the slope to intercept. % hyperchromicity is calculated using the formula, % hyperchromicity = ($A_{free} - A_{bound}$) / A_{free}, where A denotes absorbance.

2.4.2. Fluorescence method

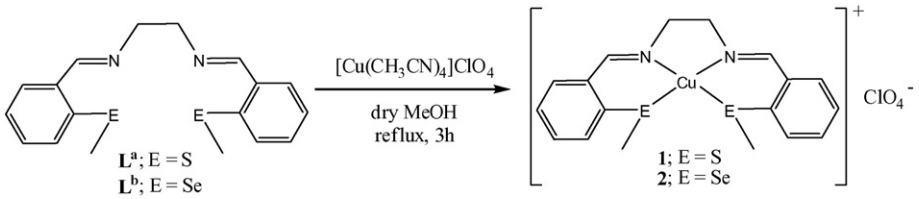
Fluorescence emission study is carried out by keeping concentration of metal complex constant and varying the concentration of ct-DNA. Fluorescence intensities were recorded after every successive addition of DNA solution, followed by 10 min of incubation. The values obtained were calculated following the Eq. (2),

$$\log(|F_0 - F|/F) = \log K_f + n\log[DNA] \quad (2)$$

Where, F_0 and F are the fluorescence intensities of the fluorophore in the absence and presence of different concentrations of ct-DNA and n is the number of binding sites. The linear relationship is obtained for log(F − F_0) / F versus log [DNA]. The values of K_f clearly underscore the affinity of complexes for DNA [23].

In fluorescence competitive binding studies, DNA was pre-treated with EB for 30 min. Fluorescence experiments were conducted by adding the complex solution to the samples containing 10 μM EB and 100 μM ct-DNA and the effect on the emission intensity was measured. The results were analyzed through Stern-Volmer Eq. (3) [24].

$$\mathbf{F_0}/\mathbf{F} = \mathbf{F} + K_{sv}[\mathbf{Q}] \quad (3)$$



Scheme 1. Synthesis of complexes **1** and **2**.