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Copper(I) halide complexes of 2,2,5,5-tetramethyl-imidazolidine-4-thione: Synthesis, structures, luminescence, thermal stability and interaction with DNA

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Five neutral mononuclear copper(I) halide complexes containing 2,2,5,5-tetramethylimidazolidine-4-thione (tmimdtH) and triphenylphosphane (PPh_3) or tri-*o*-tolylphosphane (totp) have been prepared and structurally characterized by X-ray single-crystal analysis. The complexes containing PPh_3 adopt the usual distorted tetrahedral geometry, while the presence of the bulkier totp forces the formation of three-coordinated trigonal planar species. The interaction of the compounds with calf-thymus DNA was monitored directly via UV-vis spectroscopy, DNA-viscosity measurements and indirectly via its competition with ethidium bromide for DNA studied by fluorescence emission spectroscopy. Intercalation was revealed as the most possible mode of binding. Furthermore, luminescent properties and thermal stabilities of the complexes were investigated.

1. Introduction

Heterocyclic thiones constitute a large family of versatile ligands combining soft and hard coordination sites, thus being capable of selectively binding various metal centers [1,2]. As soft S-donor ligands, they have been widely used during the past three decades in synthesis of complexes of closed-shell d^{10} metal ions, mainly copper(I) and silver(I). While interest in such complexes was initially limited mainly to the study of the factors responsible for the extraordinary variety of molecular structures obtained, attention is recently focused on some of their specific characteristics such as biological and photophysical properties, with the aim to search for respective potential applications.

Copper is an essential trace element participating in a number of cellular processes such as immune function [3], respiration [4], and angiogenesis [5]. Due to its pronounced redox ability, it is found in the active site of various enzymes and proteins, but also in some low molecular weight copper-rich metallothioneins, where the metal is bound to cysteine in stable Cu(I)–thiolate clusters. Understanding of the chemistry behind the physiological thionein function requires precise relevant structural information which could be obtained from the investigation of the coordination behavior of copper in related model complexes of low nuclearity. In this respect, heterocyclic thione ligands are considered as a useful starting point for modelling the cysteine bonding, and their coordination chemistry has been at the focus of interest during the past few decades. Current research trends in biochemistry of copper complexes includes their potential use as antimicrobial [6,7], anti-inflammatory [8,9] and antitumor [10–13] agents. Along this line of research, we recently reported on copper(I) halide and silver(I) complexes of *N*-methylbenzothiazole-2-thione which showed significant antibacterial activity against several Gram-positive and Gram-negative microorganisms [14–17].

Much effort has been also devoted to the investigation of the photophysical properties of coinage metal complexes incorporating heterocyclic thiones in combination with aryl-phosphanes [18–22]. It was found that the emission energy of these complexes, whose emitting state is readily assigned as MLCT or as a distant interligand charge transfer (LLCT) mediated by the copper central metal atom [23], can be tuned through a thione-modification.

The interaction of transition metal ions and complexes with DNA has drawn the research interest since the 1950s [24–26]. During the instrumental progress, novel or improved techniques were employed in order to study the interaction, especially the non-covalent bonding interactions, of inert metal complexes with DNA [27–29]. In regard to the copper(I) compounds, the research could be considered limited when compared to copper(II) compounds; the non-covalent interaction of Cu(I) ion [30] and its complexes with 1,10-phenanthroline and its derivatives as ligands was explored in 1990s [31–33] and since then few reports concerning the interaction of Cu(I) complexes with DNA were found in the literature [34].

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Continuing our investigations on the structural, biological and photophysical properties of heteroleptic thione/phosphane containing coinage metal complexes, we herein report the molecular, spectroscopic and thermal characteristics of some neutral mononuclear copper(I) halide compounds derived from 2,2,5,5-tetramethyl-imidazolidine-4-thione (tmimdtH) and triphenyl- (PPh_3) or tri-*o*-tolylphosphane (totp) (Fig. 1). In accordance with previous observations, it appears that steric requirements on the part of the phosphane ligand used decisively influence the structural characteristics of the complexes been formed. It is worth noting that, compared to most of its counterparts within the quite large class of heterocyclic thioamides, the coordination chemistry of tmimdtH remained so far unexplored, despite of the fact that some imidazolidine-thiones were found to exhibit antimicrobial, antifungal and anti-HIV activity. Further, we present the results of the interaction of the compounds (i.e. tmimdtH and its complexes **1**–**5**) with calf-thymus (CT) DNA, which was studied directly by UV-vis spectroscopy and viscosity measurements and indirectly via the ethidium bromide (EB) displacement ability of the complexes from the EB-DNA conjugate by fluorescence emission spectroscopy, in order to determine the interaction mode and to calculate the DNA-binding constants (K_b) of the complexes.

2. Experimental section

2.1. Materials and instrumentation

Copper(I) halides, triphenylphosphane, tri-*o*-tolylphosphane, 2,2,5,5-tetramethyl-imidazolidine-4-thione, CT DNA, EB, NaCl and trisodium citrate, were purchased from Sigma-Aldrich Co. and all solvents were purchased from Chemlab. All chemicals and solvents were of reagent grade and were used as purchased without any further purification.

DNA stock solution was prepared by dilution of CT DNA to buffer solution (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0) followed by exhaustive stirring for three days, and kept at 4 °C for no longer than a week. The stock solution of CT DNA gave a ratio of UV absorbance at 260 and 280 nm (A_{260}/A_{280}) of ~1.90, indicating that the DNA was sufficiently free of protein contamination [35]. The DNA concentration was determined by the UV absorbance at 260 nm after 1:20 dilution using $\varepsilon = 6600\ M^{-1}\ cm^{-1}$ [36].

Infrared spectra in the region of 4000–200 cm^{-1} were recorded in KBr discs with a Nicolet FT-IR 6700 spectrophotometer. UV–visible (UV–vis) spectra were recorded as nujol mulls and in DMSO solution at concentrations in the range 10^{-5}–10^{-3} M on a Hitachi U-2001 dual beam spectrophotometer. Fluorescence spectra of the solid samples and in solution were recorded on a Hitachi F-7000 fluorescence spectrophotometer. Viscosity experiments were carried out using an ALPHA L Fungilab rotational viscometer equipped with an 18 mL LCP spindle. The simultaneous TG/DTG-DTA curves were obtained on a SETARAM thermal analyzer, model SETSYS-1200. The samples of approximately 6 mg were heated in alumina crucibles in a 50 mL/min flow of nitrogen, at a heating rate 10 °C/min, within the temperature range 20–700 °C.

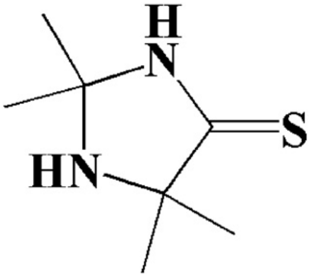

Fig. 1. The heterocyclic thione 2,2,5,5-tetramethyl-imidazolidine-4-thione (tmimdtH) used as ligand.

2.2. Crystal structure determination

Single crystals of $[CuCl(PPh_3)_2(tmimdtH)]$ (**1**), $[CuBr(PPh_3)_2(tmimdtH)]$ (**2**), $[CuI(PPh_3)_2(tmimdtH)]$ (**3**), [CuCl(totp)(tmimdtH)] (**4**) and [CuBr(totp)(tmimdtH)] (**5**), suitable for crystal structure analysis were obtained by slow evaporation of their mother liquids at room temperature. For the structure determination, single crystals of the compounds were mounted on a Bruker Kappa APEX II diffractometer equipped with a triumph monochromator. Data were corrected for absorption effects using the multi-scan method (SADABS) [37]. The collected frames were integrated with the Bruker SAINT software package [38] using a narrow-frame algorithm. The structures were solved using SUPERFLIP package [39] and refined by full-matrix least-squares method on F^2 using the CRYSTALS package version 14.53 [40]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were found and initially refined with soft restraints on the bond lengths and angles to regularize their geometry. In the cases of **3** and **4**, by the end of the refinement, they were positioned using riding constraints. Crystal data as well as some details of data collection and structure refinement are given in Table 1. Illustrations were generated with CAMERON [41].

2.3. General procedure for the synthesis of complexes 1–5

0.25 mmol of solid triarylphosphane (65.5 mg for PPh_3, 76 mg for totp) was added to a solution of 0.125 mmol of copper(I) halide (25 mg for CuCl, 36 mg for CuBr, 47 mg for CuI) in 30 mL of dry acetonitrile. After stirring for 2 h at 50 °C, 0.125 mmol (39.5 mg) of 2,2,5,5-tetramethylimidazolidine-4-thione, dissolved in a small amount (~20 mL) of dry methanol was added and the reaction mixture was stirred for additional 2 h at 50 °C. The resulting solution was filtered for the removal of any residual solids and the filtrate was left to stand in air. Slow evaporation of the solution at ambient gave crystals of the respective compound, which were filtered off and dried under vacuum. In an alternative procedure, compounds **4** and **5** were obtained using half of the above indicated amount of totp.

2.3.1. $[CuCl(PPh_3)_2(tmimdtH)]$, (1)

Colorless crystals, m.p. 188 °C; IR (cm^{-1}): 3281w, 3051w, 2972w, 1585 m, 1541s, 1480s, 1433vs, 1367 m, 1363 m, 1242 m, 1185s, 1092vs, 1056vs, 1027s, 745vs, 694vs, 525vs, 515vs, 505vs, 492 s. UV–vis (λ_{max}, log ε): 210 (5.21), 271 (5.09).

2.3.2. $[CuBr(PPh_3)_2(tmimdtH)]$, (2)

Colorless crystals, m.p. 175 °C; IR (cm^{-1}): 3319w, 3050w, 2977 m, 1585 m, 1525vs, 1480s, 1434vs, 1370s, 1240 m, 1187s, 1092vs, 1052vs, 1027 m, 792 s, 740vs, 693vs, 516vs, 504vs, 490 s. UV–vis (λ_{max}, log ε): 209 (5.05), 266 (4.53).

2.3.3. $[CuI(PPh_3)_2(tmimdtH)]$, (3)

Colorless crystals, m.p. 193 °C; IR (cm^{-1}): 3344w, 3056w, 2974w, 1546 m, 1522s, 1479s, 1432vs, 1363 m, 1363s, 1232 m, 1178 m, 1052 s, 1090vs, 744vs, 694vs, 514vs, 506vs. UV–vis (λ_{max}, log ε): 210 (5.19), 267 (4.52).

2.3.4. [CuCl(totp)(tmimdtH)], (4)

Colorless crystals, m.p. 185 °C; IR (cm^{-1}): 3289 m, 3047w, 2974 m, 1542vs, 1468s, 1448vs, 1385s, 1368s, 1245s, 1187s, 1161s, 1129s, 1047vs, 1008s, 802 s, 757vs, 714vs, 695, 565 s, 462vs. UV–vis (λ_{max}, log ε): 216 (4.79), 270 (4.35).

2.3.5. [CuBr(totp)(tmimdtH)], (5)

Colorless crystals, m.p. 155 °C; IR (cm^{-1}): 3289 s, 3044w, 2979 s, 1587s, 1541vs, 14689vs, 1448vs, 1382s, 1370s, 1245s, 1187vs, 1163vs, 1130s, 1047vs, 1007s, 803 s, 677 m, 759vs, 715vs, 565vs, 486 s, 462vs. UV–vis (λ_{max}, log ε): 214 (4.65), 269 (4.32).