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Molecular recognition between adenine or 2,6-diaminopurine and copper(II) chelates with N,O_2,S-tripodal tetradentate chelators having thioether or disulfide donor groups

Josefa María González-Pérez [a,*], Duane Choquesillo-Lazarte [b], Alicia Domínguez-Martín [a,1], Hanan El Bakkali [a], María Eugenia García-Rubiño [c], Inmaculada Pérez-Toro [a], Ester Vílchez-Rodríguez [a], Alfonso Castiñeiras [d], Valeria Marina Nurchi [e], Juan Niclós-Gutiérrez [a]

[a] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain
[b] Laboratorio de Estudios Cristalográficos, IACT, CSIC—University of Granada, Avenida de las Palmeras 4, Armilla 18100 Granada, Spain
[c] Department of Organic and Pharmaceutical Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain
[d] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain
[e] Dipartimento di Scienze Chimiche e Geologiche, Università di Cagliari, Cittadela Universitaria, 09042 Monserrato, CA, Italy

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ABSTRACT

Five novel ternary copper(II) complexes with the N,O_2,S-tripodal tetradentate chelators N,N-bis(carboxymethyl)-S-benzylcysteaminate(2-) ion (BCBC) or N,N,N′,N′-tetrakis(carboxymethyl)cystaminate(4-) ion (TCC) and adenine (Hade), 2,6-diaminopurine (Hdap), 2,2′-bipyridine (bpy) or 1,10-phenanthroline (phen) as co-ligand were synthesized and characterized by X-ray diffraction and other physical methods: $[Cu_2(BCBC)_2(\mu_2\text{-}N3,N7\text{-}H(N9)ade)(H_2O)_2]\cdot H_2O$ (**1**), $[Cu_2(BCBC)_2(\mu_2\text{-}N7,N9\text{-}H(N3)dap)(H_2O)_2]\cdot 4H_2O$ (**2**), $[Cu_2(\mu_2\text{-}TCC)(H(N9)ade)_2(H_2O)_2]\cdot 10H_2O$ (**3**), $[Cu_2(\mu_2\text{-}TCC)(bpy)_2]\cdot 15H_2O$ (**4**) and $[Cu_2(\mu_2\text{-}TCC)(phen)_2]\cdot 14H_2O$ (**5**). The crystal structure of $H_4TCC\cdot 3H_2O$ was also determined. All ternary Cu(II) complexes have molecular structures. The N-(2-mercaptoethyl)-iminodiacetate moieties of BCBC or TCC ligands play a NO_2 + S-tripodal tetradentate role, with the S-(thioether or disulfide) atom as the apical/distal donor of the copper(II) center. In **1**–**3**, the iminodiacetate moiety exhibits a mer-NO_2 conformation (two nearly coplanar chelate rings) while in **4** and **5** (with bpy or phen as coligand) it displays a fac-NO + O (apical/distal) conformation. We conclude that the formation of the Cu–S(thioether or disulfide) bonds is strongly favored by the N-branched topology of the S-ligands in the reported compounds.

1. Introduction

Metal complexes with bio-ligands or synthetic pharmaceuticals containing soft sulfur donor atoms have been the focused of great interest over the past decades. It is currently understood that the remarkably soft, negatively charged, thiolate atom (i.e. that in the side-chain of cysteinate residues) is a good sigma-donor albeit poor pi-acceptor atom. Thiolate plays important roles in biological systems [1] such as (a) approaching the relative stabilities of copper oxidation states, matching the Cu(I)/Cu(II) couple in blue copper proteins, as well as the blue copper centers of other metallo-proteins, (b) metal binding of Zn(II), Cu(I) and Cd(II) ions in metallothioneins, (c) building the stable Fe–S cluster centers in iron–sulfur proteins or (d) scavenging soft metal ions from biological systems. In contrast, neutral S-thioether (also involved in red-ox metal sites of blue copper proteins, i.e. that in methionine side-chain) is considered a poorer sigma-donor than pi-acceptor atom. A similar behavior could be expected for the S-atoms of disulfide groups. It is assumed that the metal binding affinity follows the general order S-thiolate > S-thioether > S-disulfide. Consequently, the thiolate and to a lesser extent the S-thioether atoms play relevant metal binding roles in biological and bio-inspired model systems [2,3].

The overlap of red-ox and coordination processes related to the interaction of Cu(II) ions and thiols, that can yield soft copper(I) atoms and the corresponding oxidized disulfide forms, is well documented [4]. Indeed mixed-valence copper cores have been structurally characterized for the systems Cu(I,II)-D-penicillamine-Cl [5] and Cu(I,II)-β,β-dimethylcysteaminate [6], although their significance within the D-penicillamine treatment of Wilson disease is still uncertain. In contrast, there is a rather limited evidence of metal ion interactions with disulfide groups present in bio-ligands. Coordinating reactions between disulfide groups (as oxidized forms of thiols) and Cu(II) ions are not altered by red-ox chemistry and can yield complexes with more or less strong

* Corresponding author.
E-mail addresses: jmgp@ugr.es (J.M. González-Pérez), alicia.dominguez@chem.uzh.ch (A. Domínguez-Martín).
[1] Present address: Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland.

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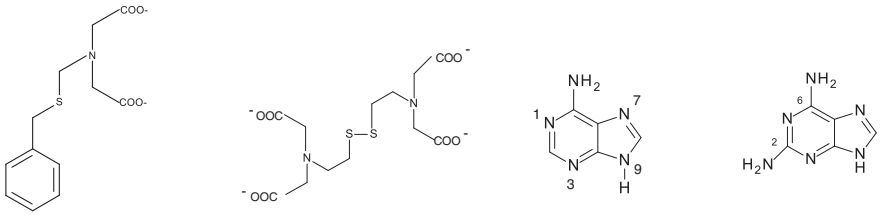

N,N-bis(carboxymethyl)-S-benzylcysteaminate(2-) (BCBC)

N,N,N',N'-tetrakis(carboxymethyl)cystaminate(4-) (TCC)

Adenine (Hade)

2,6-Diaminopurine (Hdap)

Fig. 1. Formulas of the two NO_2S-tripodal tetradentate chelators and purine-like ligands used in this work.

Cu^{II}–S(disulfide) bonds. In this sense, the structures of Cu(II) complexes with D-penicillamine disulfide (D-pds) [7] or oxidized glutathione (GSSG) [8] revealed that the disulfide group can act as monodentate as well as bridging-bidentate for copper(II) centers, respectively.

This work aims to deepen the knowledge of ternary copper(II) complexes having a chelator with S-thioether or S-disulfide group and a purine-like ligand. To this purpose, the N,N-bis(carboxymethyl)-S-benzylcysteaminate(2-) (BCBC) and N,N,N′,N′-tetrakis(carboxymethyl) cystaminate(4-) (TCC) ions and adenine (Hade) or 2,6-diaminopurine (Hdap) have been selected as chelators and N-coligands, respectively (Fig. 1). In the Cambridge Structural Database (CSD, version 5.34, updated May 2014) there are no structural evidences for the free H_2BCBC acid or BCBC-metal complexes. The molecular and/or crystal structure of the binary Cu(II)-TCC chelate (a polymer with formula $\{[Cu_2(\mu_2\text{-TCC})(H_2O)_2]\cdot 4H_2O\}_n$ [9]), and two mixed-ligand complexes $[Cu_2(\mu_2\text{-TCC})(Him)_2(H_2O)_2]\cdot 2H_2O$ [10] and $[Cu_2(\mu_2\text{-TCC})(H5Meim)_2]\cdot 2H_2O$ [11] (Him = imidazole, H5Meim = the 'remote' tautomer 5-methylimidazole of H(4/5)Meim) have been previously reported by our research group. In all these compounds, the disulfide group of TCC acts as binding-bidentate group between two Cu(II) centers where each half of TCC plays a NO_2S-tripodal tetradentate chelating role. The crystallographic study of the novel compounds represents our major goal. This high resolution technique proves the mixed-ligand nature of the novel compounds and also allows describing in detail the metal-binding pattern of the chelators to the N-coligands. In this context, Sóvágó et al. concluded from solution data that glycyl-L-cysteine disulfide, $(HGly\text{-}Cys)_2$, was able to bind Ni(II), Cu(II) and Zn(II) giving complexes without metal-S(disulfide) bonds, which was supported by the crystal structure determination of the $\{[Ni(Gly\text{-}Cys)_2]\cdot H_2O\}_n$ complex [12]. A recent study by Chakravarty et al. [13] on ternary Cu(II) complexes derived from S-methyl-L-cysteinate(1-) ligand (SMC) and N,N′-bidentate α,α′-aromatic diimines (phenanthroline and closely related aromatic diimines) also revealed that the Cu–S(thioether) bond is missing in complexes with general formula [Cu(SMC)(phen or related N-coligand)(H_2O)].

2. Materials and methods

2.1. Reagents

All used reagents (except for the $H_2BCBC\cdot 0.5H_2O$ and $H_4TCC\cdot 3H_2O$ acids) and solvents are commercially available in Sigma-Aldrich, Acros or other suppliers, and were used as received.

2.2. Synthesis of S-containing chelating ligands and metal complexes

Syntheses for the S-containing ligands used in the present study have already been reported by Chiotellis et al. [2] and others. The here reported procedures are optimized methods that yield defined hydrated samples of high purity. Indeed, they have been successfully used for the synthesis of ternary metal complexes. In addition, suitable X-ray single-crystals of one of the ligands have also been obtained first time (see Sections 2.2.2 and 3.1).

2.2.1. N,N-bis(carboxymethyl)-S-benzylcysteamine acid hemihydrate ($H_2BCBC\cdot 0.5H_2O$)

A cooled aqueous solution of KOH (30.9 g, 0.55 mol in 200 ml of water) was drop-wise added under N_2 flow to an aqueous solution of chloroacetic acid (18.9 g, 0.20 mol in 100 ml) placed in a three-neck round-bottom flask, maintaining the reaction mixture under 0 °C with the aid of an ice-salt bath. To the resulting alkaline solution of potassium chloroacetate, an aqueous solution of S-benzylcysteamine hydrochloride (20.4 g, 0.10 mol in 100 ml) was slowly added. The solution was then heated to 80 °C and stirred under N_2 flow for 5 h. After cooling at room temperature, the reaction mixture was acidified to pH ~6 with 6 M HCl and then concentrated at reduced pressure to half of its initial volume. Afterwards, the solution was placed in an ice-NaCl bath to force the precipitation of a white product. This solid was identified as KCl (the main by-product) and removed by filtration. The partially desalinized mother liquors were diluted into 100 ml of water and again acidified (pH ~2.5) with 6 M HCl. The solution was then placed once more in an ice-salt bath to accomplish the precipitation of a crude white powder (~20 g). This powder was dissolved in water (200 ml) with the aid of stirring and the addition of small amounts of $NaHCO_3$ (from a weighted sample in excess). The further addition of HCl 6 M (equivalent to the required amount of $NaHCO_3$) produced the precipitation of the final product, a white sample of $H_2BCBC\cdot 0.5H_2O$ acid. The acid was collected by filtration, washed with cool water, ethanol and diethyl ether and then air dried. Yield: 14.25 g (48.7%). Elemental analysis, calculated for $C_{13}H_{18}NO_{4.5}S$: C 53.41, H 6.21, N 4.79, S 10.97. Experimental: C 53.78, H 6.25, N 4.82, S 10.77. ^{1}H NMR (300 MHz, DMSO-d6, SD2.1.b) δ 7.52 (d, J = 4.0 Hz, 4H), 7.46 (m, 1H), 3.94 (s, 2H), 3.63 (s, 4H), 3.03 (m, 2H), 2.70 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d6, SD2.1.b) δ 172.44, 138.84, 128.81, 128.32, 126.73, 54.53, 53.66, 35.01, 28.79. FT-IR (cm^{-1}, KBr disk, SD2.2.b): $\nu_{as}(H_2O) + \nu$(O–H) of –COOH 3425, $\nu_s(H_2O)$ ~3250, $\nu(C\text{–}H)_{arom}$ 3027, $\nu_{as}(CH_2)$ 2971 and 2924, $\nu_s(CH_2)$ 2862. A broad (due to H-bonding interactions) and intense band at 1692 overlaps the contribution of the modes $\nu(C{=}O)$ of –COOH, $\delta(H_2O)$, $\nu_{as}(COO)$ of $-COO^-$ and $\delta(N^+\text{–}H)$, $\nu(C\text{–}O) + \delta(O\text{–}H)$ of –COOH 1401. $\nu_s(COO)$ 1359, $\delta(O\text{–}H)$ 1281 and $\pi(O\text{–}H)$ 876 of –COOH, $\pi(C\text{–}H)_{arom}$ 776 and 709 (five adjacent aromatic C–H bonds usually show these bands at 770–730 and 710–690), $\nu(C\text{–}S)$ 615.

2.2.2. N,N,N′,N″-tetrakis(carboxymethyl)cystamine acid three-hydrate ($H_4TCC\cdot 3H_2O$)

This synthesis was performed in a similar way as described in the previous section. A solution of chloroacetic acid (23.6 g, 0.25 mol in 100 ml of water) was cooled (<0 °C) in a water-salt bath and then