Simulating the active sites of copper-trafficking proteins. Density functional structural and spectroscopy studies on copper(I) complexes with thiols, carboxylato, amide and phenol ligands

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ABSTRACT

A series of mononuclear binary and ternary Cu(I) complexes with formato, formamide, methylphenol, and methanethiolato ligands were optimized at DFT-B3LYP/6-31G** (BS1) and DFT-B3LYP/6-311++G** (BS2) levels of theory. The solvent effect was taken into account via PCM method (BS1W and BS2W, respectively). The coordination arrangement for [Cu'(SCH3/S(H)CH3)(OOCH)]−/0 and [Cu'(SCH3/S(H)CH3)(O(H)(C6H4)CH3)]0/+ was pseudo-linear and for [Cu'(SCH3/S(H)CH3)(OOCH)(OC(H)NH2)]−/0 was pseudo-trigonal. The [Cu'(S-S(H)CH3/CuI(S-SCH3)]+/0 link even to amide carbonyl and to general O(H)R residues (R=C6H5CH3). [Cu'(SCH3)2(O(H)(C6H4)CH3)]− went towards dissociation of the O(H)(C6H4)CH3 ligand, whereas [Cu'(S(H)CH3)2(O(H)(C6H5)CH3)]+ converged nicely, maintaining the hydroxy function linked to the metal. The trends of total electronic energies seemed to be significant, suggesting that linear CuS2 coordination is more suitable than CuS, CuS3 and CuS4 arrangements. The formation energies of [Cu'(S(H)CH3/ S(CH3))2(OCOCH3)]0/− were higher than those of [Cu'(S(H)CH3/SCH3)]+/− on starting from [Cu'(S(H)CH3/Cu'S(SCH3)]+/0 by ca. 11−9 kcal mol−1 (BS2W). The structural arrangements, bond distances, and angles as well as computed spectroscopic parameters resulted in good agreement with experimental data for corresponding synthetic complexes and with metal site regions of several copper(I)-proteins. These data help in interpreting structural data of complex biological systems and in constructing reliable force fields for molecular mechanics computations.

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1. Introduction

Several proteins are believed to be actively involved in copper trafficking and storage, and even small biomolecules such as glutathione (GSH) play an important role in binding copper in vivo [1, 2]. Sometimes copper proteins are involved in serious human diseases like Parkinson and Menkes pathologies and the structural studies at metal sites might help in understanding the molecular mechanism of such health disorders [3–5]. The solution structures of the human metallochaperone HAH1, apo-HAH1 monomer, and of the copper(I)-bound form, have been studied via NMR spectroscopy [6]. Metals play an important role in folding and stability of proteins in vitro and in vivo and at the same time the protein conformational changes help in metal storage and trafficking, particularly in copper(I) [7]. The experimental structures for proteins in general and copper(I)-proteins also are often affected by large errors regarding the coordination sphere owing to complexity of the systems. In the present work, we report on selected structures optimized via density functional (DFT) methods of some models of copper(I) binary and ternary complexes, with low-molecular weight ligands, on the relevant selected computed structural parameters, spectroscopic data, and energy aspects.

2. Computational method

Methanoic acid (formic acid) HOOCH, 1, formato OOCH\(^{-}\), 2, formamide OC(H)NH\(_2\), 3, 4-methylphenol (p-cresol) O(H)(C\(_6\)H\(_4\))CH\(_2\), 4, [Cu(OOCH)], 5, [Cu(SCH\(_3\))(OOCH)]\(^{-}\), 6, [Cu(S(H)CH\(_2\))(OOCH)], 7, [Cu(S(H)CH\(_2\))(OC(H)NH\(_2\))], 8, [Cu(S(H)CH\(_2\))(OOCH)(OC(H)NH\(_2\))], 9, [Cu(SCH\(_3\))(O(H)(C\(_6\)H\(_4\))CH\(_3\))], 10, [Cu(S(H)CH\(_2\))(O(H)(C\(_6\)H\(_4\))CH\(_3\))], 11, [Cu(SCH\(_3\))(O(H)(C\(_6\)H\(_4\))CH\(_3\))], 12, [Cu(S(H)CH\(_2\))(O(H)(C\(_6\)H\(_4\))CH\(_3\))], 13 (gas phase), were optimized at the DFT-B3LYP/6-31G** (BS1) and at DFT-B3LYP/6-311++G** (BS2) levels. The solvent effect (water, via PCM method) was taken into account (BS1W and BS2W, respectively).

Density functional computations were performed using the Gaussian03/Rev.D.02 [8] and Gaussian09/Rev.D.01 [9] packages implemented on IBM SP5 and SP6, and high efficiency EURORA machines at CINECA (Inter-University Computing Center, Casalecchio di Reno, Bologna, Italy). All the structures were fully optimized at the gas phase using the B3LYP method [10] and the 6-31G** (BS1) and B3LYP/6-311++G** (BS2) basis sets for all the atoms [10]. The solvent (water) effect was also taken into account using PCM method [10, 11] and in these cases the levels of theory were named BS1W and BS2W, respectively, depending on the basis sets.

All Cu(I)-complex structures were computed at spin multiplicity 1. The optimizations were carried out to reach the convergence criteria implemented on the Gaussian03/09 packages (maximum force, 0.000450 Hartrees/Bohr; RMS Force 0.000300 Hartrees/Bohr; maximum displacement 0.001800 Å; RMS Displacement 0.001200 Å). The Hessian analysis was also performed and the structures were accepted as “fully optimized” at no imaginary frequencies. Computations of nuclear magnetic shielding tensors were computed for selected molecules through the NMR Gage-Independent Atomic Orbitals (GIAO) option [10] implemented in Gaussian09. Molecular drawings were obtained using GaussView03 software [12] implemented on a PC Intel® Core™ i7-4650U CPU @ 1.70 GHz 2.30GHx machine.

3. Results and discussion

Free ligands and copper(I)-complex optimized molecules and relative total electronic energies (Eel, Hartrees) are listed in Table 1. Selected computed structures and selected bond distances and angles are shown in the figures and reported in tables within each respective section (see below).

3.1. Structures

After having analyzed the Cu(I)-complexes that contained the selected S-donor ligands as reported in a previous report [13], in order to study the effect of expanding the coordination arrangement and the
type of donors, some O-donor molecules were selected and fully optimized, i.e. HCOOH, HCOO$^-$ and OC(H)NH$_2$, and O(H)(C$_6$H$_4$)CH$_3$.

For HOOCH, 1, OOCH$^-$, 2, OC(H)NH$_2$, 3, and O(H)(C$_6$H$_4$)CH$_3$, 4, owing to the absence of any major difference between the computed parameters at different basis sets BS1 and BS2, and the fact that even the solvent effects were marginal and maximum deviation with respect to BS2 was below 0.6%, the BS1/BS1W levels of theory (Figure 1a, Table 2) could be considered adequate for structure simulations that contain CHO atoms, at least regarding the molecules examined in the present work.

Regarding formate anion OOCH$^-$, 2 (Figure 1b and Table 2), the computations showed that upon deprotonation one of the C–O bond distances increased by 0.049 Å and the other decreased by 0.092 Å. The H–C bond distance increased by 0.053 Å. The O–C–O bond angle increased by 5.9°. In the case of formamide OC(H)NH$_2$, 3 (Figure 1c), the C–O, C–N, H–C and H–N bond distances changed from 1.216,
therefore the changes were within 1.5% of the absolute value. The computed structure for 1,4-(hydroxyl) (methyl)benzene (p-methylphenol), HO(C₆H₄)CH₃, had C–O, O–H and C–O–H bond parameters of 1.372, 0.963 Å, and 109.6° computed at BS2 and 1.374, 0.965 Å, and 109.9° at BS2W. Regarding Table 2. Selected computed bond distances (Å) and angles (°) for free ligand molecules: HCOOH, 1, HCOO⁻, 2, OC(H)NH₂, 3, and O(H) (C₆H₅)CH₂, 4, as fully optimized at BS1, (BS2), [BS1W], and [BS2W] levels of theory (see text for method details).

![Diagram](image_url)
Table 3. Selected computed bond distances (Å) and angles (°) for optimized structures [Cu'(OOCH)], 5, [Cu'(SCH₃)(OOCH)]⁺, 6, [Cu'(S(H)CH₃)(OOCH)], 7, as calculated at BS1, (BS2), [BS1W], and [BS2W] levels of theory (see text for method details).

| Vector | 5   | 6   | 7   | Vector | 5   | 6   | 7   |
|--------|-----|-----|-----|--------|-----|-----|-----|
| S–H    | 1.354 |     |     | S–C    | 1.847 |     |     |
|        | (1.353) |     |     |        | (1.851) |     |     |
|        | [1.351] |     |     |        | [1.851] |     |     |
| Cu–S   | 2.114 | 2.069 |     | Cu–O2  | 1.965 | 1.819 | 2.012 |
|        | (2.181) | (2.211) |     |        | (2.101) | (1.904) | (1.897) |
|        | [2.105] | [2.081] |     |        | [1.850] | [1.820] | [2.039] |
|        | (2.172) | (2.211) |     |        | (1.910) | (1.906) | (1.891) |
| O1–C1  | 1.269 | 1.230 | 1.267 | O2–C1  | 1.269 | 1.292 | 1.266 |
|        | (1.262) | (1.229) | (1.233) |        | (1.262) | (1.284) | (1.291) |
|        | [1.248] | [1.234] | [1.265] |        | [1.285] | [1.293] | [1.266] |
|        | (1.232) | (1.235) | (1.232) |        | (1.288) | (1.283) | (1.288) |
| Cu–O1/Cu…O1 | 1.965 | 3.071 | 2.014 |        |        |        |     |
|        | (2.101) | (3.253) | (2.651) |        |        |        |     |
|        | [2.245] | [2.960] | [2.040] |        |        |        |     |
|        | (2.901) | (3.153) | (3.069) |        |        |        |     |
| Cu–S–H | 112.1 |     |     | Cu–S–C | 104.6 | 115.2 |     |
|        | (98.8) |     |     |        | (104.4) | (110.9) |     |
|        | [110.6] |     |     |        | [107.6] | [114.5] |     |
|        | (99.8) |     |     |        | (105.2) | [107.1] |     |
| Cu–O2–C2 | 83.8 | 120.9 | 86.0 | S–Cu–O2 | 174.9 | 146.1 |     |
|        | (86.4) | (126.8) | (86.4) |        | (175.2) | (175.2) |     |
|        | [93.6] | [117.3] | [86.4] |        | [173.6] | [145.8] |     |
|        | (114.0) | (123.7) | (120.8) |        | (177.8) | (175.1) |     |
| O2–C2–O1 | 123.1 | 129.6 | 121.4 | H–S–C2 | 95.0 |     |     |
|        | (123.4) | (129.2) | (125.6) |        | (97.5) |     |     |
|        | [123.7] | [128.1] | [121.5] |        | [95.7] |     |     |
|        | (126.7) | (127.6) | (127.2) |        | (98.1) |     |     |
| S–Cu…O1 | 137.5 | 146.6 |     |        |        |        |     |
|        | (141.8) | (119.1) |     |        |        |        |     |
|        | [135.1] | [147.5] |     |        |        |        |     |
|        | (137.0) | (137.5) |     |        |        |        |     |

Figure 3. Computed structure for [Cu'(SCH₃)(OOCH)]⁺, 6, at (a) BS2, (b) BS1W, and (c) BS2W levels of theory.

Figure 4. Computed structures for [Cu'(S(H)CH₃)(OOCH)], 7, at (a) BS1, (b) BS2, (c) BS1W, and (d) BS2W levels of theory.
the SCH$_3^-$ ligand (Figure 1e, f), selected computed bond parameters were 1.844 Å (C–S), 1.103 Å (C–H), and 112.6° (H–C–S) (BS1). It is evident that neither significant basis set effects nor major solvent (water) effects could be found within the BS1, BS2, BS1W, and BS2W levels of theory. Thus, the choice must be dictated by computational and time costs of resources.

For [Cu(SCH$_3$)(OOCH)], 5, [Cu(SCH$_3$)(OOCH)$^-$], 6, and [Cu(S(H)CH$_3$)(OOCH)], 7, the influences of basis set types and addition of a formato ligand on the structural parameters of Cu(I)-thiol/thiolato complexes were analyzed. Selected optimized structures for [Cu(OOCH)], 5, are represented in Figure 2 and Table 3. The coordination mode was from pure O,O-bidentate (BS1 and BS2) to an almost O-monodentate one (BS2W), thus showing that the effect of solvent as well as the type of basis set is significant for such Cu(I)-carboxylato interaction. The Cu–O bond distances and Cu…O contact distances are 2.101 × 2 Å (BS2), 1.850 and 2.245 Å (BS1W), and 1.910 and 2.901 Å (BS2W). The C=O bond distances were 1.262 × 2 Å (BS2), 1.285 Å (O–Cu) and 1.248 Å (O…Cu) (BS1W), 1.288 Å (O–Cu) and 1.232 Å (O…Cu) (BS2W). Regarding the O–C–O bond angle, the values were 123.4° (BS2), 123.7° (BS1W) and 126.7° (BS2W), respectively. On adding a formato HCOO$^-$ ligand to [Cu(SCH$_3$)], the Cu(I) center had a quasi-linear arrangement (Figure 3) both at BS1 and BS2 levels (S–Cu–O, 174.9 and 175.2°, respectively). The structure computed at BS1 level had the same shape as that reported in Figure 3a even though some parameters were significantly different. In fact, the computed Cu–S and Cu–O2 bond distances were 2.114 and 1.819 Å (BS1), and 2.181 and 1.904 Å (BS2). The O1 from carboxylato was not linked to Cu(I), Cu…O1 being 3.071 Å (BS1) and 3.253 Å (BS2) (van der Waals radii: Cu, 1.4 Å and O, 1.52 Å [14]). When the PCM solvent treatment (water) was considered, the structures were successfully optimized, both at BS1W and BS2W levels, but the respective arrangements differed significantly (Figure 3b, c). Cu–S and Cu–O2 bond distances were 2.172 and 1.906 Å (BS2 W), respectively, whereas the Cu…O1 contact distance was 3.153 Å (BS2W). Therefore, upon addition of the formato ligand, the computed Cu–S bond distance lengthened from...
2.024 Å [13] to 2.114 Å (BS1), whereas the S–C bond distance did not change appreciably. On the contrary, the O2–C bond distance at formato lengthened significantly upon formation of a coordination bond to Cu–SCH3 (from 1.254, up to 1.292 Å). The non-metal-bound C=O bond underwent a shortening from 1.254 to 1.230 Å. Thus, upon metal ligation, the effects on CO bond lengths paralleled those caused by protonation but the magnitude were lower by metal than by proton. From a search on the CSD [15] data base, it was possible to download the structures of several metal(II)-formato complexes.

Table 4. Selected computed bond distances (Å) and angles (°) for the optimized structures [Cu\{SCH3\}2{OC(O)NH2}]+, 8, and [Cu\{S(H)CH3\}2{OC(O)NH2}]+, 9, as calculated at BS1, (BS2), [BS1W], and [BS2W] levels of theory (see text for method details; dnc, did not converge).

| Vector  | Syn | Anti |
|---------|-----|------|
| S–H     |     |      |
|         | 1.351 |      |
|         | (1.349) |      |
|         | [1.349] |      |
|         | [1.349] |      |
| Cu–S    |     |      |
|         | 2.198 |      |
|         | (2.178) |      |
|         | [2.202] |      |
| O1–C2   |     |      |
|         | 1.243 |      |
|         | (1.282) |      |
|         | [1.280] |      |
| Cu…O1   |     |      |
|         | 2.852 |      |
|         | (3.127) |      |
|         | [2.721] |      |
| Cu–C3   |     |      |
|         | 1.954 |      |
|         | (1.972) |      |
|         | [1.972] |      |
| C3–N    |     |      |
|         | 1.403 |      |
|         | (1.391) |      |
|         | [1.391] |      |
| Cu–S–H  |     |      |
|         | 104.4 |      |
|         | (112.1) |      |
|         | [111.5] |      |
|         | [102.5] |      |
| Cu–O2–C2|     |      |
|         | 109.1 |      |
|         | (121.8) |      |
|         | [105.9] |      |
| O2–C2–O1|     |      |
|         | 128.9 |      |
|         | (126.7) |      |
|         | (127.3) |      |
| S–Cu…O1|     |      |
|         | 120.2 |      |
|         | (131.3) |      |
|         | [109.5] |      |
| O2–Cu–O3|     |      |
|         | 106.6 |      |
|         | (103.6) |      |
|         | [105.6] |      |
| O3–C3–N3|     |      |
|         | 119.5 |      |
|         | (127.1) |      |
|         | [119.8] |      |
| N3…O   |     |      |
|         | 3.075 |      |
|         | (3.031) |      |
|         | [2.834] |      |
|         | (2.856) |      |
The carboxylato/carboxyl ligand often bridged the metal centers and in those cases the two C–O bonds showed almost the same length (see e.g. [16], where the two O–C bonds had lengths of 1.230–1.270 Å). On the contrary, from a similar search on CSD database, structures that contain Cu(I) and formato are few. One of those structures was reported for a molecule of formic acid (O-monodentate) linked to a tricoordinate Cu(I) center [17], whereas a formate anion is co-crystallized. The $\text{S(H)CH}_3$ metal derivative $[\text{CuI(S(H)CH}_3](\text{OOCH})]$, 7, was also fully optimized, both at BS1 and BS2 levels of theory, and showed different final arrangements with respect to the carboxylato group (Figure 4) even though the starting structure was similar to that optimized for $[\text{CuI(SCH}_3](\text{OOCH})]^{-}$, 6 (i.e. with CH$_3$ and HCO groupings anti to each other with respect to the S–Cu–O line, Figure 3a). Using a quasi-linear input structure for O–Cu–S (175°), the optimization at BS1 brought about an O,O–Cu chelate (Figure 4a), characterized by Cu–O bond distances that averaged 2.013 Å and by a Cu–S bond distance that measured 2.069 Å. At BS2 level, the optimized structure had a quasi-linear arrangement around copper (S–Cu–O, 175.2°). The refined model presented the methyl group syn to the carbonyl oxygens, also (weakly) bound to the metal center (Figure 3b). The coordination bond distances were 2.211, 1.897, and 2.651 Å for Cu–S, Cu–O$_2$(trans to S), and Cu…O$_1$(syn to CH$_3$), respectively. When the treatment of solvent effects was performed at a BS1W level, the structure converged to an arrangement very similar to that reported for BS1 at gas phase (Figure 4c), where the carboxylato chelated the metal. Computed Cu–S and Cu–O$_2$/O$_1$ bond distances were 2.081 and 2.039 Å (av). When the computations were carried out at the BS2W level, the refined structure showed significant differences in coordinate mode from carboxylato and orientation of methyl group (Figure 4d). The Cu–S, Cu–O$_2$, and Cu…O$_1$ bond and interatomic distances were 2.211, 1.891, and 3.069 Å, respectively.

Therefore, it is evident that both $\text{SCH}_3$ and $\text{S(H)CH}_3$ linked to Cu(I) may allow monodentate or bidentate coordination mode for formato, and in the case of monodentate a second (weaker) Cu…O linking interaction was also operative. The linkage of Cu(I) to carboxylato seemed to be rare from searches on databases of experimental data and never reported for biological macromolecular systems.
Regarding \([\text{Cu}^{+}(\text{SCH}_3)(\text{OOCH})(\text{OC(H)NH}_2)]^+\), 8, and \([\text{Cu}^{+}(\text{SHCH}_3)(\text{OOCH})(\text{OC(H)NH}_2)]\), 9, the influence of addition of an amide ligand to \([\text{Cu}^{+}(\text{SCH}_3)(\text{OOCH})]^+\), 6, coordinated to Cu(1) via oxygen, produced

\begin{table}[h]
\centering
\begin{tabular}{lcccc}
\hline
 & 10 & 11 & 12 & 13 \\
\hline
S–H & 1.350 & 1.841 & 2.075 & 1.406 \\
 & (1.352) & (1.351) & (2.092) & (1.439) \\
 & [1.348] & [1.348] & [2.107] & [1.403] \\
 & (1.351) & (1.350) & (2.210) & (1.402) \\
S–C & 1.846 & 1.841 & 2.110 & 1.422 \\
 & (1.851) & (1.848) & (2.010) & (1.439) \\
 & [1.850] & [1.837] & [1.859] & [1.397] \\
 & (1.855) & (1.843) & [1.853] & [1.390] \\
Cu–S & 2.075 & 2.110 & 2.132 & 1.406 \\
 & (2.139) & (2.209) & (2.203) & (1.439) \\
 & [2.092] & [2.107] & [2.094] & [1.403] \\
 & (2.159) & (2.210) & [2.209] & [1.402] \\
Cu–O & 1.887 & 1.857 & 1.841 & 1.442 \\
 & (1.993) & (1.927) & (1.954) & (1.439) \\
 & [1.873] & [1.866] & [2.236] & [1.397] \\
 & (1.973) & [2.962] & [2.228] & [1.397] \\
O–H & 0.966 & 0.960 & 0.960 & 0.960 \\
 & (0.964) & (0.965) & (0.974) & (0.965) \\
 & [0.968] & [0.968] & [1.002] & [0.968] \\
 & (0.966) & (0.966) & [0.967] & [0.966] \\
O–C & 1.406 & 1.422 & 1.343 & 1.442 \\
 & (1.400) & (1.439) & (1.353) & (1.439) \\
 & [1.400] & [1.403] & [1.360] & [1.397] \\
 & (1.398) & [1.402] & [1.370] & [1.389] \\
C–C(o) & 1.386/1.391 & 1.384/1.387 & 1.404/1.405 & 1.388/1.390 \\
 & (1.387/1.389) & (1.384/1.386) & (1.405/1.410) & (1.388/1.389) \\
 & [1.387/1.392] & [1.386/1.390] & [1.400/1.401] & [1.391/1.391] \\
 & (1.389 × 2) & (1.387/1.389) & (1.396/1.398) & (1.391/1.391) \\
C(o)–C(m) & 1.398/1.389 & 1.397/1.391 & 1.395/1.390 & 1.396/1.395 \\
 & (1.395/1.391) & (1.394/1.393) & (1.395/1.391) & (1.394/1.394) \\
 & [1.399/1.390] & [1.399/1.390] & [1.397/1.392] & [1.396/1.394] \\
 & (1.395/1.393) & (1.3947/1.394) & (1.394/1.394) & (1.395/1.393) \\
C(m)–C(p) & 1.399/1.404 & 1.402/1.403 & 1.399/1.402 & 1.401/1.403 \\
 & (1.396/1.401) & (1.400/1.401) & (1.403/1.411) & (1.401/1.401) \\
 & [1.400/1.405] & [1.400/1.404] & [1.402/1.404] & [1.401/1.402] \\
 & (1.399/1.400) & (1.399/1.400) & (1.400/1.400) & (1.399/1.401) \\
C(p)–C(Me) & 1.510 & 1.509 & 1.513 & 1.509 \\
 & (1.510) & (1.508) & (1.513) & (1.508) \\
 & [1.511] & [1.510] & [1.511] & [1.511] \\
 & (1.510) & (1.510) & [1.511] & [1.510] \\
S–Cu–S & 180.0 & 180.0 & 180.0 & 126.0 \\
 & (176.6) & (176.4) & (172.7) & (122.5) \\
 & [172.7] & [172.7] & [172.7] & [122.5] \\
 & (180.0) & (180.0) & (180.0) & (144.0) \\
S–Cu–O & 169.6 & 173.5 & 79.9/100.1 & 114.5/119.5 \\
 & (176.6) & (176.4) & (55.6/124.4) & (104.6/106.5) \\
 & [172.7] & [171.9] & [86.5/99.2] & [116.6/120.3] \\
 & (177.5) & [177.8] & [77.2/102.8] & [104.5/111.5] \\
Cu–S–C & 108.0 & 112.7 & 110.1/112.3 & 113.1/113.8 \\
 & (105.1) & (108.4) & (107.2/109.1) & (109.1/109.8) \\
 & [107.9] & [110.8] & [105.7/108.2] & [111.1/114.2] \\
 & (105.0) & [106.8] & [108.1/109.3] & [106.9/107.6] \\
Cu–O–C & 164.9 & 151.5 & 168.9 & 124.8 \\
 & (130.6) & (124.7) & (118.2) & (122.5) \\
 & [118.5] & [118.3] & [108.5] & [127.3] \\
 & (131.3) & (131.1) & [153.5] & [129.6] \\
\hline
\end{tabular}
\caption{Selected bond distances (Å) and angles (°) for optimized structures: \([\text{Cu}(\text{SCH}_3)(\text{OOCH})(\text{OC(H)NH}_2)]^+\), 10, \([\text{Cu}(\text{SHCH}_3)(\text{OOCH})(\text{OC(H)NH}_2)]\), 11, \([\text{Cu}(\text{SCH}_3)(\text{OOCH})(\text{OC(H)NH}_2)][\text{Cu}(\text{SCH}_3)(\text{OOCH})]^-\), 12, and \([\text{Cu}(\text{SHCH}_3)(\text{OOCH})(\text{OC(H)NH}_2)][\text{Cu}(\text{SCH}_3)(\text{OOCH})]^2+\), 13, as calculated via DFT method at BS1, (BS2), [BS1W], and [BS2W] levels of theory (see text for method details).}
\end{table}

\*The structures did not fully converged at BS1, BS2 and BS1W levels of theory (see text for details).
Figure 8. Diagrams show the structures relevant to \([\text{Cu}(\text{SCH}_3)(\text{O}(\text{H})(\text{C}_6\text{H}_4\text{CH}_3))\text{]}^+\), 11: (a) input structure used for the optimizations; (b) and (c) structures as optimized at the BS1 and BS2 levels of theory, respectively.

Figure 9. (a) Input structure for optimization of the model \([\text{Cu}(\text{SCH}_3)(\text{O}(\text{H})(\text{C}_6\text{H}_4\text{CH}_3))\text{]}^-\), 12, at BS1, BS2, BS1W, BS2W levels. The structure was submitted to 30 cycles of refinement at the BS1 level (b); to 58 cycles of refinement at the BS1W level (c); to 20 cycles of refinement at the BS2 level (d) and to 27 cycles of refinement at BS2W level (e).

Figure 10. Diagrams show the structures for \([\text{Cu}(\text{SCH}_3)(\text{O}(\text{H})(\text{C}_6\text{H}_4\text{CH}_3))\text{]}^+\), 13, as computed at (a) BS1 and (b) BS2 levels of theory.
optimized structures that were strictly dependent on the input model orientation. Two input structures (Figure 5a, b), having an almost planar trigonal arrangement around Cu(I) for the three donors (SO(c,carboxylato),O(a,amide)), successfully converged at BS1 level to an almost $\eta^2$-coordination arrangement between the Cu atom and the O=C(a) ligand moiety (Figure 5c, d and Table 4).

The optimized Cu–O(a) and Cu–O(c) bond distances were 1.978 and 1.969, and 1.947 and 1.978 Å for the two models (8syn and 8anti, Figure 5c, d), respectively. The carboxylato ligand showed a weak chelating behavior just in one of the structures: the two Cu–O bond distances were 1.969, 3.001, and 1.978 Å for the two structures, respectively. The N(a)–H…O(c) interaction had N…O and Ĥ values by 2.955 Å and 160.2°, and 3.075 Å and 153.7°. Once the orientation of the SCH$_3^-$ residue was syn with respect to the carboxylato, the structure was the more stable one (by just 1.26 kcal mol$^{-1}$). It is interesting to note that when the same input structure (Figure 5a) was taken into account at the BS2 level, a [Cu(SCH$_3$)(OOCH)]⁻…OC(H)NH$_2$ adduct was optimized. The system was stabilized by two hydrogen bonds (Figure 5e). The Cu–S and Cu–O(c) bond distances were 2.178 and 1.905 Å, whereas the Cu…O contact distance was relatively long (3.127 Å). It has to be noted that the amide molecule is almost coplanar with the set of atoms S–Cu–O–C–O of the coordination molecule. The latter had almost collinear S–Cu and Cu–O vectors (S–Cu–O, 176.9°).

Once the solvent effect was taken into account (BS1W), [Cu(SCH$_3$)(OOCH)(OC(H)NH$_2$)]⁻ (8syn) was optimized and the coordination bond distances were 2.202, 1.982, 1.902, and 1.972 Å for Cu–S, Cu–O(c), Cu–O(a), and Cu–C(a), respectively. Finally, the Cu…O bond distance was 2.721 Å, showing the presence of a weak chelating interaction and a (4 + 1) coordination mode.

The S(H)CH$_3$ complex [Cu(S(H)CH$_3$)(OOCH)(OC(H)NH$_2$)], 9, showed an analogous behavior regarding the flexibility of the optimized structures with respect to the input arrangements. At the BS1 level, the more stable structure (by ca. 6 kcal mol$^{-1}$) had the CH$_3$ group anti (Figure 6a, b and Table 4) with respect to carboxylato residue (contrary to the result obtained for the SCH$_3^-$ derivative). The most stable structure was favored by a strong N–H…O hydrogen bond (N…O, 2.726 Å; Ĥ, 175.7°). On the contrary, the structure with the CH$_3$ group syn with respect to carboxylato ligand showed a weaker N–H…O hydrogen bond. From a coordination stand point, the two structures were very different showing a three-coordination through S, O(c), O(a) for the more stable one (9anti), with respect to a four-coordination through S, two O(c), and an O(a), for the other (9syn). The optimization at the BS2 level for 9 was carried out by starting from the more stable molecule previously optimized at BS1 and brought about a refined structure that is presented in Figure 6c. On introducing the treatment of solvent (water, BS1W), the optimized structure (Figure 6d) did not change much with respect to those obtained for the gas phase both at BS1 and BS2. Therefore, the addition of an amide ligand into the coordination arrangement of the ternary Cu(I)–thiolato–formato complexes might introduce a variety of stabilizing intramolecular hydrogen bond and hydrogen bond type interactions, and showed that the amide might behave as $\eta^1$–O donor or $\eta^2$–O,C donor.

For [Cu(S(CH$_3$))(O(H)(C$_6$H$_4$)CH$_3$)], 10 (Figure 7 and Table 5), one can quickly see that for both the basis sets (BS1 and BS2) the orientation of the benzene ring with respect to the coordination O–Cu and Cu–S vectors is almost the same, differently to what computed for the corresponding methanethiol derivative 11 (see below). For the hydroxylmethylbenzene–methanethiolato complex, the coordination vectors were almost coplanar with the benzene system and an ortho C–H function pointing towards the Cu center, H…Cu contact being 2.283 Å (BS1) and 2.850 Å (BS2). The Cu–S and Cu–O bond distances were 2.075 and 1.887 Å (BS1), and 2.139 and 1.993 Å (BS2), respectively.

About [Cu(S(H)CH$_3$)(O(H)(C$_6$H$_4$)CH$_3$)]$^+$, 11 (Figure 8 and Table 5), the computed Cu–S bond distance was 2.110 Å (BS1) and 2.209 Å (BS2), whereas the Cu–O bond length was 1.857 Å (BS1) and 1.927 Å (BS2); the lengthening caused by the extension of basis set being ca 5% for Cu–S and 4% for Cu–O. The coordination angle was close to idealized values for two-coordination (180°) for both structures: 173.5° (BS1) and 176.4° (BS2). Noteworthy, the orientation of the benzene ring with respect to the coordination vectors was much dependent on the type of basis set; the C–C–O–Cu torsion angles being ca. 0° (BS1) and ca. 90° (BS2). Once the solvent effect was considered at BS2 (BS2W), the Cu–S, Cu–O and O–Cu–S
optimized parameters were 2.210, 1.954 Å, and 177.8°. The (ortho)H…Cu contact distance was 2.875 Å, the agnostic-type interaction that could be at BS1, was not confirmed.

On passing to [Cu(SCH₃)₂(O(H)(C₆H₄)CH₃)]⁻, 12, several structure optimization attempts using BS1, BS2, BS1W, and BS2W levels of theory and starting from the model reported in Figure 9a did not reach acceptable convergence (see above computational methods). In fact, the O(H)(C₆H₄)CH₃ entity moved out from the metal coordination and the Cu(SCH₃)₂ residue reached an almost linear arrangement (Figure 9b, c). The structure optimizations were halted when the total electronic energy reached an almost plateau, and in general when the last step structures had not an acceptable chemical meaning in terms of coordination of the hydroxyl function through the oxygen donor. An interesting finding was that the O(H)(1,4-C₆H₄CH₃) ligand moved towards complete dissociation from metal and the bis(methanethiolato)copper(I) residue reached linearity [13]. On adding a second S(H)CH₃ ligand to copper(I) in the 11 model to bring about [Cu′(S(H)CH₃)₂(O(H)(C₆H₄)CH₃)]⁺, 13, the structure had a pseudo-trigonal arrangement at metal (BS2, Figure 10 and Table 5). The S–Cu–S bond angle was larger at BS2 (148.9°) than at BS1 (126.0°), showing a significant effect by the basis set type. The computed Cu–S bond distances averaged 2.280 Å (BS2). The lengthening effect on the Cu–O bond distance by the basis set expansion was even larger: Cu–O 1.960 Å (BS1) and 2.208 Å (BS2).

The experimental structures for small coordination molecules that contained Cu(I) were not many (CSD, [15]). The structure coded FOSTIR [18] was relevant to a molecule in which a Cu(I) was linked to (CS⁻ and (CO)O⁻ donors; the Cu–S and Cu–O bond distances were 2.35 and 2.25 Å, respectively. A second molecule, coded JAQROI [19], showed a Cu(I) linked to CS⁻ where Cu–S distances averaged 2.42 Å, and a Cu(I) was linked to COO⁻ (Cu–O lengths averaged 2.19 Å). Therefore, the estimated (DFT-computed) bond distances from the present work can be considered in agreement with those from experiments and also in agreement with values from a previous work from this laboratory [13] and citations therein.

As a partial conclusion for structural aspects, we wish to say that the effect of adding a carboxylato ligand (in this work, formato ligand was considered a model of glutamyl or aspartyl carboxylate group) to a Cu–SCH₃⁻/–S(H)CH₃ fragment (here considered as a Cu–S(cysteinyl group)) was small. In fact, lengthening on the Cu–S bond was just 0.034 Å (1.6%) when compared to the addition of a second methyl sulfide anion 0.058 Å (2.7%), even though formato should demand more space. In other words, the addition of formato to a Cu–SCH₃⁻ coordination group weakened the existing Cu–S bond less than the addition of a second SCH₃⁻/S(H)CH₃ ligand. Second, amide groups were able to form adducts with the [CuI(S(H)CH₃)₂(O(H)(C₆H₄)CH₃)]⁻ complexes, via Cu–O(a) and even Cu–C(a)/O(a) (η²-coordination arrangement).

Furthermore, a search on the coordination modes at Cu(I) in some metal–protein systems via PDB [20] revealed several consistencies with the computed models; on the contrary, for other aspects the proposed structures from solid-state XRD studies and from NMR solution studies are unusual when compared to present theory models.

The first selected example is that coded 4BTE [3]. That structure had a Cu(I) ion almost linearly coordinated (S–Cu–S, 154°) by two mercapto-cysteinyl functions at the homodimer interface (Figure 1S) of the DJ-1 protein. The Cu–S bond distance as obtained from the experimental structure was unacceptably short 1.93 Å (van der Waals radii being Cu, 1.40 Å and S, 1.80 Å [14]). On the basis of the computations reported in the present work, [13] and on the values of van der Waals radii [14], one can say that the coordination arrangement is chemically reasonable and the values of bond lengths are acceptable only if probable high standard deviations are taken into account. Furthermore, the structure coded 4BTE [3] had an almost linear S–Cu–S arrangement and that situation was nicely reached even upon refining the system [CuI(SCH₃)₂(O(H)(C₆H₄)CH₃)]; these latter partially refined structures had Cu–S bond distances of ca. 2.207 Å (BS2 and BS2W) that well compare with those from fully optimized structure of [CuI(SCH₃)₂]⁻ (ca. 2.200 Å from BS2 and BS2W [13]).

Another interesting example is that reported in the series of structures coded 1KVJ [5] that showed a Cu(I) center linked by two cysteinyl groups (Cu–S, 2.16 Å; S–Cu–S, 145°) and by a serine OH group (Cu–O, 1.97 Å) from the ATP7A protein associated with the Menkes disease (Figure 2S). The structure is in excellent agreement with the optimized one for the model [Cu′(S(H)CH₃)₂(O(H)(C₆H₄)CH₃)]⁺, 13 (Figure 10b), that at BS2 has a S–Cu–S bond angle of 148.9° and Cu–S bond distances by 2.280 Å (av),
Table 6. Energy of formation (ΔE_form, kcal mol⁻¹) as optimized at BS1, (BS2), [BS1W], and [BS2W] levels of theory. Computed values are not corrected for the basis set superposition error (BSSE) if not explicitly reported.

| Reaction                                      | ΔE_form  |
|------------------------------------------------|----------|
|                                                 | BS1      | (BS2)   | [BS1W]  | [BS2W]  |
| Cu⁺ + S(SCH₃)⁻ → [Cu(S(SCH₃))⁺]            | -231.08  | (-197.40) | [-87.04] | (-54.89) |
| Cu⁺ + 2 S(SCH₃)⁻ → [Cu₂(S(SCH₃))₃⁺]        | -313.48  | (-265.09) | [-141.36] | (-98.09) |
| [Cu(S(SCH₃))⁺ + S(SCH₃)⁻ → [Cu(S(SCH₃))₂⁺] | -82.42   | (-67.68)  | [-54.31]  | (-43.20)  |
| Cu⁺ + S(H(CH₃)CH₃)⁺ → [Cu(S(H(CH₃)CH₃))⁺] | -80.02   | (-53.93)  | [-58.91]  | (-28.95)  |
| Cu⁺ + 2 S(H(CH₃)CH₃)⁺ → [Cu₂(S(H(CH₃)CH₃))₃⁺] | -134.16 | (-98.22)  | [-95.61]  | (-57.67)  |
| [Cu₂(S(H(CH₃)CH₃))₃⁺ + S(SCH₃)⁻ → [Cu₂(S(S(H(CH₃)CH₃))₂⁺] | -54.14   | (-44.28)  | [-36.70]  | (-28.73)  |
| [Cu(S(SCH₃))⁺ + S(H(CH₃)CH₃)⁺ → [Cu(S(SCH₃))(S(H(CH₃)CH₃))⁺] | -38.08   | (-26.03)  | [-32.03]  | (-25.36)  |
| Cu⁺ + OOC(CH₃) → 5                           | -220.80  | (-178.96) | [-89.82]  | (-39.30)  |
|                                                 | (-180.65) |         |          |          |
| Cu⁺ + S(h)CH₃⁻ + HCOO⁻ → 6                   | -283.18  | (-254.91) | [-148.33] | (-88.57)  |
| [Cu(S(SCH₃))⁺ + HCOO⁻ → 6                   | -86.11   | (-57.51)  | [-61.29]  | (-33.68)  |
| [Cu(OOCH)⁺ + SCH⁻ → 6                      | -86.38   | (-75.95)  | [-58.51]  | (-49.27)  |
| [Cu⁺ + S(H(CH₃)CH₃)⁺ + HCOO⁻ → 7           | -275.19  | (-209.76) | [-129.29] | (-69.13)  |
| [Cu(S(SCH₃))⁺ + S(H(CH₃)CH₃)⁺ → 7          | -195.17  | (-155.83) | [-70.38]  | (-40.19)  |
| [Cu(OOCH)⁺ + S(H(CH₃)CH₃)⁺ → 7             | -44.39   | (-30.80)  | [-39.46]  | (-29.83)  |
| Cu⁺ + S(SCH₃)⁺ + HCOO⁻ + OC(H)NH₂ → 8syn    | -304.96  | (-271.40) | [-164.61] | (-88.74)  |
| [Cu(S(SCH₃))⁺ + OC(H)NH₂ → 8syn             | -21.78   | (-16.49)  | [-16.28]  | (-0.16)   |
| Cu⁺ + S(H)CH₃⁺ + HCOO⁻ + OC(H)NH₂ → 9anti   | -300.11  | (-225.80) | [-149.60] | (-74.94)  |
| [Cu(S(SCH₃))⁺ + OC(H)NH₂ → 9anti            | -24.92   | (-16.04)  | [-20.31]  | (-5.80)   |
| Cu⁺ + S(SCH₃)⁺ + O(H)(H)CH₃CH₃ → 10         | -269.98  | (-217.07) | [-123.26] | (-72.78)  |
| [Cu(S(SCH₃))⁺ + O(H)(H)CH₃CH₃ → 10          | -38.92   | (-19.67)  | [-36.22]  | (-17.88)  |
| [Cu(S(SCH₃))⁺ + S(SCH₃)⁺ → [Cu₂(S(SCH₃))₃⁺] | -82.42   | (-67.68)  | [-54.31]  | (-43.20)  |
| [Cu(S(SCH₃))⁺ + S(H(CH₃)CH₃)⁺ → [Cu₂(S(S(CH₃)CH₃))₃⁺] | -38.08   | (-26.03)  | [-34.71]  | (-25.36)  |
| Cu⁺ + 2 S(SCH₃)⁺ + O(H)(H)CH₃CH₃ → 12        | -329.58  | (-270.93) | [-153.94] | (-97.39)  |
| [Cu(S(SCH₃))⁺ + O(H)(H)CH₃CH₃ → 12          | -16.10   | (-5.85)   | [-12.59]  | (0.70)    |
| [Cu(S(SCH₃))⁺ + S(SCH₃)⁺ → [Cu₂(S(SCH₃))₃⁺] | -52.73   | (57.18)   | [-9.86]   | (-2.60)   |
| Cu⁺ + 2 S(H)CH₃⁺ + O(H)(H)CH₃CH₃ → 13        | -161.12  | (-110.69) | [-112.12] | (-59.73)  |
| [Cu(S(SCH₃))⁺ + O(H)(H)CH₃CH₃ → 13          | (110.05) |          |          |          |
| [Cu(S(SCH₃))⁺ + S(H)CH₃⁺ → [Cu₂(S(SCH₃))₂⁺] | -26.96   | (-12.47)  | [-16.51]  | (-2.06)   |
| [Cu(S(SCH₃))⁺ + S(H)CH₃⁺ → [Cu₂(S(SCH₃))₂⁺] | -25.56   | (-15.05)  | [-18.13]  | (-8.74)   |

Data from [13].
Values after BSSE correction.
Model not fully optimized.

and Cu–O by 2.208 Å (BS2). One has to take into account the high standard deviations about structural parameters for large biomolecules as determined via solution studies. Noticeably, the metal center for structures coded 1KVJ was linked also to a carbonyl oxygen at Cu–O distance by 2.134 Å.

A third noticeable example was the PDB structure coded 1TL4 that reported on solution structures of the apo and Cu(I)-loaded human metallochaperone HAH1 [6] (Figure 3S). A biscysteinato Cu(I) was linked weakly by an amide oxygen Cu–O 2.692 Å; the Cu–S bond distances averaged 2.16 Â and S–Cu–S bond angle was ca. 153°. Therefore, the computations showed structural parameters that were similar to some experimental findings. The theory allowed better evaluation of certain bond distances from experiment that were grossly determined because of the complexity of large biomolecules, and disorder and thermal motion. In fact, the short bond distance Cu–S 1.925 Å claimed for structure 4BTE is barely acceptable when compared to the sum of covalent radii (Cu, 1.38 and S, 1.02 Å) [14], and to computed Cu–S bond distances by 2.205 and 2.243 Å at BS2 level for [Cu(S(SCH₃))₂⁺]⁺ or [Cu(S(H)CH₃)₂⁺]⁺ [13]. The experimental methods from XRD at solid state and from NMR in solution could then find benefit from the computed values at the stage of interpreting density Fourier maps and magnetic tensor values.

### 3.2. Energy

The values of total electronic energies (see Table 1) for selected computed models allowed the evaluation of selected formation energies (Table 6). The total electronic energies were computed at the DFT-BS1, -BS2, -BS1W, and -BS2W levels of theory, respectively. Attempts to compute more reliable
absolute energy and thermal parameters were preliminarily done at higher levels but it was found that just \textit{ab initio} CCSD(T)/-6-311++G** could bring about reliable values. Unfortunately, those computations require computational times and costs that could not be reached in the present project. Therefore, qualitative inferences were only performed using a comparative analysis of electronic energies.

The formation energy for [Cu(I)(OOC\textsubscript{H})], \textbf{5}, was −39.30 kcal mol\(^{-1}\) when computed at BS2W; instead the corresponding value for [Cu(SCH\textsubscript{3})] was −54.89 kcal mol\(^{-1}\), showing a gap by ca. 15.6 kcal mol\(^{-1}\) in favor of bond formation at thiolato. Therefore, the formation energy computations gave strong rationale to Cu–S linkage in copper-trafficking protein, at least when computed at the more expanded basis set, and the effect of solvent was taken into account (BS2W). Similar trends were observed for models computed at BS2 (different by 18.4 kcal mol\(^{-1}\)) between Cu–S and Cu–O formation. The complex formation energy for [Cu(I)(OOC\textsubscript{H})], \textbf{5}, when computed at BS2 level was even corrected for the basis set superposition error (BSSE): the uncorrected and corrected values differ by 1.7 kcal mol\(^{-1}\) (i.e. by less than 1\%). The same observation is valid for the BSSE correction for larger complex molecules. The overall electronic formation energies (Δ\textit{E}\textsubscript{el}) for [Cu(SCH\textsubscript{3})(OOC\textsubscript{H})]\textsuperscript{+}, \textbf{6}, and [Cu(S(H)CH\textsubscript{3})(OOC\textsubscript{H})], \textbf{7}, computed at BS2W were −88.57 and −69.13 kcal mol\(^{-1}\), respectively. Therefore, the protonation at sulfur for [Cu(SCH\textsubscript{3})(OOC\textsubscript{H})] required +19.44 kcal mol\(^{-1}\) (BS2W) that was comparable to that for [Cu(SCH\textsubscript{3})] (+25.94 kcal mol\(^{-1}\), BS2W). Furthermore, the overall formation energies for [Cu(SCH\textsubscript{3})(OOC\textsubscript{H})](OC(H)NH\textsubscript{3})\textsuperscript{+}, \textbf{8}, and [Cu(S(H)CH\textsubscript{3})(OOC\textsubscript{H})](OC(H)NH\textsubscript{3})], \textbf{9}, were −88.74 and −74.94 kcal mol\(^{-1}\) (BS2W), respectively, and the protonation at methanethiolato ligand required +13.80 kcal mol\(^{-1}\) (BS2W).

Hence, the protonation at sulfur for Cu(I)-complexes that contain a sulfide ligand were in the range (+14) – (+26) kcal mol\(^{-1}\). These values were comparable to the magnitude of the formation energy of a couple of standard hydrogen bonds of the type O–H…O, O–H…N, N–H…O that form or dissociate frequently in any enzyme and protein conformational rearrangements. In other words, protonation/deprotonation at thiolato/thiol of CuI(SR)/CuI(S(H)R) functions, that is the key process for storage/release of Cu(I) in copper-trafficking proteins, is easily regulated by subtle pH changes and protein conformational alterations.

The computed formation energy for [Cu(SCH\textsubscript{3})(OOC\textsubscript{H})]\textsuperscript{+}, \textbf{6}, from [Cu(SCH\textsubscript{3})] and OOC\textsubscript{H} was −33.68 kcal mol\(^{-1}\) (BS2W) and its magnitude was lower by ca. 9.5 kcal mol\(^{-1}\) than the computed formation of [Cu(SCH\textsubscript{3})]\textsuperscript{+} from [Cu(SCH\textsubscript{3})] and CH\textsubscript{3}S\textsuperscript{−} (−43.20 kcal mol\(^{-1}\), BS2W).

Therefore, the formation of further coordinate bonds to carboxylate groups other than Cu(I)–thiolato linkages reinforced the stability of Cu(I) complexes less than the formation of another bond to thiolato itself. One can speculate that {CuI(S\textsubscript{2})} entities are more suited for copper(I) storage and transport than {CuO/S} type complexes.

Addition of an amidic function, simulated by OC(H)NH\textsubscript{3}, to [Cu(SCH\textsubscript{3})(OOC\textsubscript{H})]\textsuperscript{+} (obtaining the 8\textsubscript{syn} model) was slightly stabilizing by −16.28 kcal mol\(^{-1}\) (BS1W) and −0.16 kcal mol\(^{-1}\) (BS2W). That finding could be a rationale to the paucity of (Cu(S)(OCamide)) groupings found in structures of copper(I) proteins revealed both in solid state and solution [20] even if the molar ratio amidic group/Cu(I) is high for each protein.

The electronic formation energy for [Cu(SCH\textsubscript{3})\textsubscript{2}(O(H)(C\textsubscript{6}H\textsubscript{4})CH\textsubscript{3})], \textbf{12}, was −270.93 (BS2) and −97.39 (BS2W) kcal mol\(^{-1}\), which can be compared to the respective values for [Cu(SCH\textsubscript{3})\textsubscript{3}\textsuperscript{2−}] being −207.90 and −100.70 kcal mol\(^{-1}\) (BS2 and BS2W, respectively [13]). In case that the equilibrium for the addition of a third methanethiolato ligand to [Cu(SCH\textsubscript{3})\textsubscript{2}\textsuperscript{2−}] was considered, the reaction electronic energy was −2.60 kcal mol\(^{-1}\) (BS2W). The addition of a third thiolato to a mononuclear bis(thiolato)Cu(I) compares well with the formation of a {Cu\textsubscript{2}S\textsubscript{2}(O(H)R)} tricoordinate entity.

Regarding [Cu(S(H)CH\textsubscript{3})(O(H)(C\textsubscript{6}H\textsubscript{4})CH\textsubscript{3})], \textbf{13}, the formation energies were expectedly lower than those for the thiolato derivative, but still exoenergetic by −161.12, −110.69, −112.12, and −59.73 kcal mol\(^{-1}\) at BS1, BS2, BS1W, and BS2W levels of theory, respectively (noteworthy, the correction for BSSE at BS2 through “counterpoise” option of Gaussian09 gave −110.05 kcal mol\(^{-1}\), that meant a very small variation). The reaction energy for addition of an O(H)(C\textsubscript{6}H\textsubscript{4})CH\textsubscript{3} ligand to the bis(methanethiol)Cu(I) complex cation was −12.47 and −2.06 kcal mol\(^{-1}\) when computed at BS2 and BS2W levels, respectively. Addition of a methanethiol ligand to bis(methanethiol)Cu(I) cation gave computed reaction
energy values by $-15.05$ and $-8.74$ kcal mol$^{-1}$ at BS2 and BS2W levels, showing that the formation of a tricoordinate Cu(I) complex with three methanethiol or with two methanethiol and a O(H)R function is almost equivalent from an energy standpoint, and more favorable than the corresponding reactions relevant to the thiolato derivatives.

The computed formation and partial reaction energies gave rationale at least to a couple of experimental findings of complex structural types at solid state and solution phase. First, the mononuclear tris(methanethiolato)Cu(I) anion is energetically unfavored and had no experimentally relevant structure (or at least they are very rare). Even the bis(methanethiolato)(O(H)R)copper(I) species did not have a significant stabilizing contribution. Thus, just the structures of the type [Cu(SR)$_2$] were found through computations (and possibly through experiments). This does not mean that [Cu(SR)$_2$] or [Cu(SR)$_2$(O(H)R)] structures do not exist or that they will not be found in the future, but based on the data the absence/paucity of structures of the type [Cu(SR)$_2$] or [Cu(SR)$_2$(O(H)R)] has a rationale on electronic formation energy values. Second, the mononuclear tris(methanethiolato)Cu(I) and bis(methanethiolato)(O(H)R)Cu(I) species had overall formation energy and partial reaction energy contributions more exoenergetic than the corresponding thiolato derivative and the formation of tricoordinate [Cu(SI(R)R)O(H)R]$^+$ species is possible. This was experimentally certified in solution and solid state for some biologically significant species. Third, the addition of a methanethiol ligand to (methanethiolato)copper(I) to bring about [Cu(SCH$_3$)S(H)CH$_3$] had lower thermal effects (i.e. $-25.36$ kcal mol$^{-1}$, BS2W) than the addition of a second methanethiolate ligand to (methanethiolato)copper(I) to produce [Cu(SCH$_3$)$_2$] (i.e. $-43.20$ kcal mol$^{-1}$, BS2W).

### 3.3. Vibrations

Analysis of infrared data for [Cu(OOCH)], 5, [Cu(SCH$_3$)(OOCH)]$^-$, 6, [Cu(SI(H)CH$_3$)(OOCH)], 7, [Cu(SCH$_3$)(OOCH)(OC(H)NH$_2$)]$^-$, 8, and [Cu(SI(H)CH$_3$)(OOCH)(OC(H)NH$_2$)], 9, revealed that computed frequencies and respective intensity depend significantly on basis set types and on inclusion of solvent effects (on the contrary the computed force constants were in general not much influenced by the basis set type and solvation). The data discussed in this paragraph will be mostly those from computations at BS2 and BS2W.

Selected computed infrared effects at BS2 and BS2W levels of theory are reported in Table 7 (and Table 1S) and Figure 4S. Notes for the selected model molecules are: (i) on passing from the ternary methanethiolato derivative (6) to the methanethiolate one (7), the frequency for the intense absorption attributable to the ν(C=H)formato vibration increased by ca. 20 cm$^{-1}$ (BS2W); (ii) the computed ν(C=O)$_{formato}$ stretching frequency was 1615 cm$^{-1}$ for 6, while for 7 the same C=O movement had a small blue shift to 1622 cm$^{-1}$. The magnitudes for infrared intensities (high for several vibrations) were 191.14 km mol$^{-1}$ (7, ν(C=O)$_{formato}$), and 1007.50 km mol$^{-1}$ (7, ν(C=O)$_{formato}$), as computed at BS2W; (iii) analysis for the S–H stretches were predicted to cause low intensity infrared effects centered at 2657 cm$^{-1}$ (4.32 km mol$^{-1}$) for 7 and 2664 cm$^{-1}$ (1.09 km mol$^{-1}$) for 9 as computed at BS2W; (iv) the computed stretching frequencies for the combined km mol$^{-1}$ O$_{formato}$–Cu and S–Cu symmetric and asymmetric movements for 7 were 449 cm$^{-1}$ (23.10 km mol$^{-1}$) and 285 cm$^{-1}$ (2.27 km mol$^{-1}$), respectively.

As the reported experimental infrared bands corresponding to S–H stretching mode were 2525–2600 cm$^{-1}$ [21–23], a scale factor by 0.96 was estimated and the latter is in agreement with data previously reported [24]. The scaled frequencies are also reported in Table 7 (and Table 1S).

The spectra for [Cu(SI(H)CH$_3$)(O(H)(C$_6$H$_4$)CH$_3$)], 10, [Cu(SI(H)CH$_3$)(O(H)(C$_6$H$_4$)CH$_3$)]$^+$, 11, and [Cu(SI(H)CH$_3$)(O(H)(C$_6$H$_4$)CH$_3$)]$^-$, 13 (computed at BS2 and BS2W), are reported in Figure 5S and listed in Table 8, whereas the structure for [Cu(SI(H)CH$_3$)(O(H)(C$_6$H$_4$)CH$_3$)]$^-$, 12, did not converge up to all the criteria implemented in Gaussian09 (for all the levels of theory used in this work) and hence the analysis of frequencies was not performed. The band relevant to the (R)O-H stretch was always intense and of high energy: 3812 cm$^{-1}$ and 110.55 km mol$^{-1}$ (BS1), 3812 cm$^{-1}$ and 244.25 km mol$^{-1}$ (BS1W), 3828 cm$^{-1}$ 108.47 km mol$^{-1}$ (BS2) and 3801 cm$^{-1}$ and 239.54 km mol$^{-1}$ (BS2W) for the thiolato derivative 10, the effect of solvent being higher at the more expanded basis set. On introducing the proton on sulfur
Table 7. Selected computed infrared data as computed at (Bs2) and (Bs2W) levels of theory [uncorrected frequency (cm\(^{-1}\)) / corrected frequency (cm\(^{-1}\), scale factor 0.96) / intensity (km mol\(^{-1}\)) / force constant (mDyne/Å) for the ternary and quaternary Cu(i) complex molecules with formato, methanethiolato, methanethiol, formato, formamide ([Cu\((\text{OOCH})\)], 5, [Cu\((\text{SCH}_3)\)(\text{OOCH})\]^\(-\), 6, [Cu\((\text{S}(\text{CH}_3})\)(\text{OOCH})\)(\text{OC}(\text{HN})\)_2]), 7, [Cu\((\text{S}(\text{CH}_3})\)(\text{OOCH})(\text{OC}(\text{HN})\)_2] \(^+\), 8, and [Cu\((\text{S}(\text{CH}_3})\)(\text{OOCH})(\text{OC}(\text{HN})\)_2]) \(^-\), 9. Symbols for movements are: stretching \(\nu\), bending \(\delta\), symmetric sym, asymmetric asym, single bond –, double bond =, intermediate between single and double bond ÷.

| Vibrations                        | Molecules |
|----------------------------------|-----------|
| \(\nu(\text{trans to CO})\text{N–H}\) | 5         | 6         | 7         | 8\(^a\) | 9         |
| \(\nu(\text{trans to CO})\text{N–H+}\nu\) (cis to CO)N-H asym | (3074/2951/27.44/6.1575) | (3163/3036/1.53/6.220) | (3090/2966/20.33/6.2239) | (3168/3041/0.91/6.5381) | (3650/3504/71.47/8.4860) |
| \(\nu(\text{CH}_3)\text{C–H}\) | (3114/2989/20.85/6.3256) | (3068/2945/30.25/6.103) | (3076/2953/12.80/5.7289) | (3165/3038/2.90/6.5375) | (3648/3502/147.44/8.5146) |
| \(\nu(\text{formato})\text{C–H}\) | (3022/2901/42.58/5.8433) | (2958/2840/137.87/5.5746) |  |  |  |
| \(\nu(\text{amide})\text{C–H}\) |  |  |  |  |  |
| \(\nu(\text{formato})\text{C–H}\) |  |  |  |  |  |
| \(\nu(\text{amide})\text{C–O}\) |  |  |  |  |  |
| \(\delta(\text{amide})\text{O=C–H}\) |  |  |  |  |  |
| \(\delta\text{Cu–S–H}\) |  |  |  |  |  |

(continued)
$\nu$(formato)Cu–O$^+$Cu–S(sym)

$\nu$(amide)O–Cu

$\delta$Cu–O(formato), oop

$\delta$S–Cu–O

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| Vibrations                  | 5            | 6            | 7            | 8*           | 9            |
|-----------------------------|--------------|--------------|--------------|--------------|--------------|
| $\nu$(formato)Cu–O$^+$Cu–S(sym) | (439/421/39.39/1.5476) | (456/438/14.81/1.6712) | (446/428/33.81/1.5921) | (399/383/21.71/0.9890) | (357/343/23.15/0.8648) |
| $\nu$Cu–O                  | (329/316/26.86/1.0990) | (441/423/49.15/1.5832) | (449/431/23.10/1.4946) | (357/343/23.15/0.8648) | 
| $\nu$(amide)O–Cu            | (313/300/3.14/0.7854) | (319/306/3.72/0.8188) | (228/219/3.52/0.2840) | (233/224/21.18/0.1718) | 
| $\nu$Cu–O$^+$Cu–S(sym)      | (316/303/5.82/0.8057) | (279/268/6.62/0.3466) | (285/274/2.27/0.5761) | (196/188/5.93/0.2497) | 
| $\nu$Cu–O$^+$Cu–S(asym)     | (279/268/6.62/0.3466) | (285/274/2.27/0.5761) | (196/188/5.93/0.2497) | (191/183/42.80/0.1006) | 
| $\nu$Cu–O$^+$Cu–S(asym)     | (279/268/6.62/0.3466) | (285/274/2.27/0.5761) | (196/188/5.93/0.2497) | (191/183/42.80/0.1006) | 

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*a* The structure for 8, when computed at the BS2W level, did not strictly reach full convergence criteria in terms of forces and movements. The hessian analysis was not carried out at BS2W.
thiol derivative, 11) the frequency did not change significantly, 3804 cm\(^{-1}\) and 172.97 km mol\(^{-1}\) (BS2), and 3801 cm\(^{-1}\) and 228.84 km mol\(^{-1}\) (BS2W).

The effect relevant to the S–H stretching motion had computed infrared weak bands at 2646 cm\(^{-1}\)

| Vibrations | Molecules |
|------------|-----------|
| \(\nu\)O–H | (3828/3675/108.47/9.2076) | (3804/3652/172.97/9.0982) | (3809/3657/96.11/9.1175) |
| \(\nu\)S–H | (3801/3649/239.34/9.0826) | (3801/3649/228.84/9.0781) | (3801/3649/170.60/9.0767) |
| \(\delta\)C–H + \(\delta\)C–C–C | (1644/1578/20.12/9.4891) | (1631/1566/4.39/10.1619) | (1645/1579/6.13/9.3797) |
| \(\delta\)C–C–C | (1541/1479/136.57/3.5375) | (1532/1471/84.56/3.3949) | (1538/1476/103.14/3.4876) |
| \(\delta\)C–O–H+ \(\delta\)C–H | (837/804/25.24/0.5750) | (832/799/31.77/0.5516) | (833/799/35.13/0.5680) |
| \(\delta\)C–O–H | (837/804/25.24/0.5750) | (832/799/31.77/0.5516) | (833/799/35.13/0.5680) |
| \(\nu\)Cu–O+ | (514/493/35.14/0.3752) | (523/502/13.13/0.4474) | (529/508/2.61/0.6311) |
| \(\delta\)Cu–O+ | (514/493/35.14/0.3752) | (523/502/13.13/0.4474) | (529/508/2.61/0.6311) |
| \(\delta\)O–H,oop Cu/O/C | (247/237/84.33/0.0420) | (250/240/166.44/0.0418) | |

Table 8. Selected computed infrared data as computed at (BS2) and (BS2W) levels of theory [uncorrected frequencies (cm\(^{-1}\)) / corrected frequency (cm\(^{-1}\), scale factor 0.96) / intensity (km mol\(^{-1}\)) for the ternary Cu(II) complex molecules with methanethiolato, methanethiol, 4-methylphenol ([Cu(i)(SCH\(_3\))(O)(C\(_6\)H\(_4\)(CH\(_3\)))]), 10, [Cu(S(H)CH\(_3\))(O)(C\(_6\)H\(_4\)(CH\(_3\)))]\(^+\), 11, [Cu(S)(H)\(_2\)(C\(_6\)H\(_4\)(CH\(_3\)))\(^+\)]\(^-\), 13. Symbols for movements are: stretching \(\nu\), bending \(\delta\), symmetric sym, asymmetric asym, single bond –, double bond =, intermediate single/double bond ÷.
were recorded for the bis(thiol)(O(H)R) derivative 13: 2647 cm$^{-1}$ (2.64 km mol$^{-1}$) and 2652 cm$^{-1}$ (11.67 km mol$^{-1}$) (BS2), and 2664 cm$^{-1}$ (1.87 km mol$^{-1}$) and 2656 cm$^{-1}$ (1.68 km mol$^{-1}$) (BS2W). Upon scaling the frequency values for the scale factor discussed above, bands at 2544 and 2554 cm$^{-1}$ (at BS2 and BS2W levels, respectively) were computed for $\nu$(S–H) and 2649 cm$^{-1}$ for $\nu$(O–H), the latter being in good agreement with literature values [21, 24].

### 3.4. 1H-NMR chemical shifts

Computed 1H-NMR chemical shifts (from TMS) for selected model molecules as computed at BS2W level of theory are reported in Figure 6S and in Table 9. The signals for CH$_3$S$^-$ and CH$_3$SH methyl protons as computed on the optimized structures occur at 2.35 ± 0.22 ppm [Cu(I(S(H)CH$_3$))]$^+$, 1.85 ± 0.28 ppm [Cu(I(SCH$_3$)(O(H)(C$_6$H$_4$)CH$_3$))], 2.35 ± 0.24 ppm [Cu(I(S(H)CH$_3$)(O(H)(C$_6$H$_4$)CH$_3$))]$^+$ and 2.28 ± 0.26 ppm [Cu(I(S(H)CH$_3$)$_2$(O(H)(C$_6$H$_4$)CH$_3$))]$^+$ from TMS. These values are in agreement with those of the signals for methylene protons recorded by others for the Cu(I)/cysteine system in aqueous media (pH 7.0) at increasing metal concentrations (3.0–3.2 ppm) [25].

The computed chemical shifts (TMS) for H(S) signals occur at 3.76 ppm ([Cu(I(S(H)CH$_3$))]$^+$), 3.66 ppm ([Cu(I(SCH$_3$)(O(H)(C$_6$H$_4$)CH$_3$))]$^+$) and 3.25 ± 0.14 ppm ([Cu(I(S(H)CH$_3$)$_2$(O(H)(C$_6$H$_4$)CH$_3$))]$^+$).

Noteworthy, NMR-GIAO computations at BS2W level were quite reliable for estimating 1H chemical shifts for organic molecules [26] and metal complexes [25]. Therefore, it can be reasonably assumed that even for the complex molecules studied in the present work, the chemical shift values are significant. The H(S) proton underwent a shielding effect corresponding to ca. 0.50–0.40 ppm upon coordination of a further methanethiol to cationic species like [Cu(S(H)CH$_3$)]$^+$ and [Cu(S(H)CH$_3$)(O(H)(C$_6$H$_4$)CH$_3$)]$^+$ to bring about [Cu(S(H)CH$_3$)$_2$(O(H)(C$_6$H$_4$)CH$_3$)]$^+$. Instead, the shielding effects for cysteine-type (S)CH protons for Cu(I) complexes are much more limited and barely detectable. The H(O) protons of phenols linked to Cu(I) complexes underwent significant shielding (ca. 0.50 ppm) on passing from a mono-methanethiol derivative to a bis(methanethiol) one.

### 4. Conclusion

The work provided rationale for several structural features of selected copper protein systems involved in copper trafficking found experimentally at the solid state and in the solution phase via X-ray diffraction and NMR techniques, especially those that involve mononuclear coordination. Most remarkably, the investigation of estimated qualitative energy of formation of the computed models explained that the linear CuS$_2$ coordination mode was the most favorable both for thiolato S(–)R and thiol S(H)R type ligands when compared to CuS, CuS$_3$, and CuS$_4$ modes. Then, the grafting on the CuS$_2$ skeleton by certain hard donor groups like alcohol/phenol(O(H)R) and carboxylate and amide functions are suitable for further stabilizing the overall coordination scaffolding.

Moreover, the structural findings in the present work represent an aid for better interpreting the experimental data from XRD and NMR techniques. At that regard, the work provided a comparative analysis among four levels of theory: the computed results from BS2 level of theory should be selected...
when linking interactions between Cu(I) and sulfur are involved. The treatment of solvation effects via PCM methods (solvent, water, and BS2W) did not have dramatic influence on structural parameters and on reaction energies, even though it should always be adopted (unless it is not advisable for the high computational costs).

5. Supporting material

Diagrams showing portions of experimental Cu(I) proteins are reported in the literature: DJ-1 Parkinsonism-associated protein (Figure 1S); ATP7A protein associated with the Menkes disease (Figure 2S), human metallochaperone HAH1 (Figure 3S). Selected computed infrared data as computed at (BS2) and (BS2W) levels of theory for the ternary and quaternary Cu(I) complex molecules with formato, methanethiolato, methanethiol, formato, formamide ([Cu\((\text{OOCH})\)], 5, [Cu\((\text{SCH}_3)(\text{OOCH})]\), 6, [Cu\((\text{S}(\text{H})\text{CH}_3)(\text{OOCH})]\), 7, [Cu\((\text{SCH}_3)(\text{OC}(\text{H})\text{NH}_2)(\text{OOCH})]\), 8, and [Cu\((\text{S}(\text{H})\text{CH}_3)(\text{OC}(\text{H})\text{NH}_2)(\text{OC}(\text{H})\text{NH}_2))\]) 9, and relevant spectra are reported in Table 1S, Figures 4S and 5S. Diagrams showing \(^1^H\)-NMR spectra for selected complex molecules with thiolato and methanethiolato ligands (reference, TMS at BS2W level of theory) are also reported in Figure 6S. Cartesian coordinates for fully optimized structures (and a few interesting not converging ones, partially optimized) are reported in Tables SI-SLXXVI.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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