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Binuclear copper(II) complex with 2-imidazolylbenzothiazole and bridged chloride ligands

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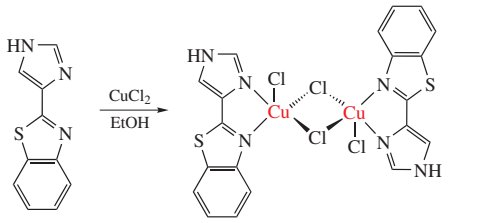
Dimeric chloro-bridged copper(II) complex of $L_2Cu_2Cl_4$ composition [L stands for 2-(1*H*-imidazol-4-yl)-1,3-benzothiazole ligand] was obtained from $CuCl_2 \cdot 2H_2O$ and ligand L in ethanol. According to X-ray diffraction studies, the complex is a dimer with two bridged chloride ligands and two chloride ions coordinated with only copper atom. Cyclic voltammetry demonstrated the stability of dimeric structure of the complex in DMF solution.



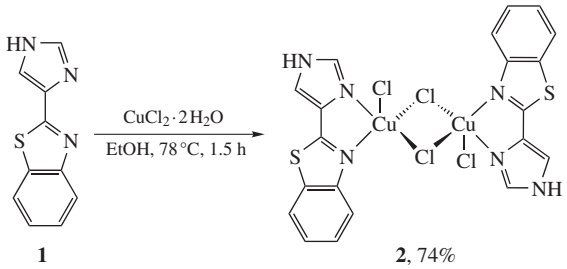
Two Cu^{2+} reduction peaks at 0.25–0.50 V

2-(Het)aryl-substituted benzimidazoles, oxazoles, and thiazoles are important chemotypes of biologically active compounds.[1–7] For example, 2-(4-aminophenyl)benzothiazole possesses an extraordinarily high anticancer activity,[1] while pyridyl-substituted benzothiazoles can serve as helminthicides and nematocides.[8–10] On the other hand, coordination to transition metal ions may increase antiviral and antitumor activity of medicaments.[11]

2-Hetarylazoles can potentially form mononuclear,[12–18] dinuclear[12,19,20] and polymeric[21] complexes with transition metals. While mononuclear copper(II) chloride complexes with 2-hetarylbenzothiazole ligands were described,[12–21] the dimeric complexes of such ligands with bridging chloride anions have remained unknown to date. At the same time, binuclear complexes of transition metals can exhibit magnetic properties[22–26] and can resemble active sites of some biological systems.[25–30] Dinuclear metal complexes containing heterocyclic rings are used as antibiotics, antifungal agents and semiconductor sensors.[31–33]

We have recently obtained and examined a series of mononuclear complexes of $CuCl_2$ with 2-hetarylbenzothiazoles[16–18] and some related ligands,[34] in which copper atoms had a distorted tetrahedral environment and were coordinated by two nitrogen atoms of the organic ligand and two chloride anions. Herein, we found that the similar reaction of $CuCl_2$ with 2-(1*H*-imidazol-4 yl)-1,3-benzothiazole **1** in ethanol on boiling afforded coordination compound **2** having dimeric structure with bridging chloride ligands in 74% yield (Scheme 1).†

The attempted study of complex **2** by ^{1}H NMR was not successful due to the strong broadening of lines, which confirmed the presence of Cu^{II} in its molecule. Dimeric nature of complex **2** was ultimately comfirmed by the X-ray data (Figure 1).‡ Crystal data and selected bond lengths and angles for **2** are given in Online Supplementary Materials. The molecule of **2** has twofold rotation axis symmetry (point group C_2). Two bridge chloride anions and two copper cations form a four-membered ring, a terminal chloride and a bidentate chelating imidazolylbenzothiazole moiety complete five-coordination of copper atoms. The coordination polyhedron appears as a distorted tetragonal pyramid. The bridging Cu_2Cl_2 unit is not planar. Dihedral angle between planes Cl(2)–Cu(1)–Cl(2′) and Cl(2)–Cu(1′)–Cl(2′) is 17.25°. The terminal Cu–Cl(1) distance [Cu(1)–Cl(1) 2.244(2) Å] is slightly shorter than the bridging Cu(1)–Cl(2) and Cu(1)–Cl(2′) distances [2.301(2) Å]. The organic ligand moiety is essentially



1 **2**, 74%

Scheme 1

† *Di-μ-chloro-bis{[2-(1*H*-imidazol-4-yl)-1,3-benzothiazole]chlorocopper(II)}* **2** *(preparation of monocrystals).* A solution of $CuCl_2 \cdot 2H_2O$ (42.5 mg, 0.249 mmol) in EtOH (1 ml) was added to a solution of compound **1** (50 mg, 0.249 mmol) in dioxane (1 ml). In 1 h, the resulting mixture in an open vessel was placed in a sealed larger vessel containing diethyl ether, and this was left for one week. Diffusion of diethyl ether vapor into the reaction mixture caused formation of green crystals which were filtered off and dried in air. Mp > 250 °C. Found (%): C, 60.31; H, 4.03; N, 18.72; S, 14.57. Calc. for $C_{10}H_7Cl_2CuN_3S$ (%): C, 60.36; H, 4.33; N, 19.20; S, 14.65.

‡ *Crystal data for* **2**. Crystals of $C_{10}H_7Cl_2N_3CuS$ (M = 335.69) are monoclinic, space group C_2/c, at 295 K: a = 7.4839(2), b = 15.0351(4) and c = 20.8944(5) Å, β = 94.060(3)°, V = 2345.16(11) Å^3, Z = 8, d_{calc} = = 1.902 g cm^{-3}, μ(CuKα) = 8.304 mm^{-1}, F(000) = 1336. Total of 2267 were measured, 1867 independent reflections (R_{int} = 0.08) were used in a further refinement, which converged to wR_2 = 0.2223 and GOF = 1.086 for all independent reflections [R_1 = 0.0770 was calculated against F for 1867 observed reflections with $I > 2\sigma(I)$]. The measurements were made on a STOE diffractometer.

CCDC 1886202 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

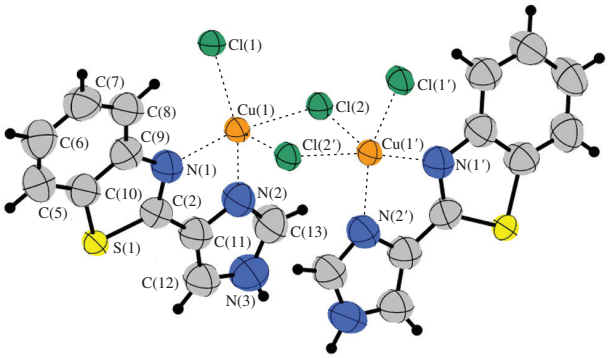


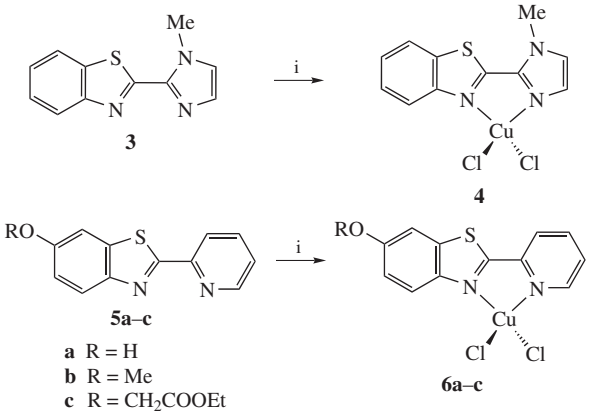
Figure 1 Molecular structure of complex **2**. Displacement ellipsoids are drawn at 50% probability level.

planar; the angle between thiazole and imidazole rings of ligand is about 5°.

As noted above (*cf.* refs. 16–18), the same procedure applied to other related ligands **3** and **5** afforded mononuclear copper complexes **4** and **6** (Scheme 2, for the details see Online Supplementary Materials).

According to the criteria formulated earlier,[35] dinuclear metal complexes can form if (1) the coordination sphere of a metal is incompletely filled with electron donating groups of a polydentate organic ligand and (2) either an organic ligand or an additional inorganic anion contains electron-donating atoms capable of bridging metal centers. Apparently, in the cases of complexation reactions with ligands **3** and **5**, steric hindrances in the ligand moieties do not allow bridging coordination compounds to be obtained, whereas in the case of ligand **1** containing unsubstituted five-membered imidazole cycle, a dimeric complex is formed. Note that ligand **1** in the reaction with copper perchlorate also gave a complex that differed in structural type from the complexes of ligands **3** and **5**.[16]

The possibility of formation of both monomeric and dimeric coordination compounds in the reactions of ligand **1** with $CuCl_2$ raises the question of the exact determination of their structure, since monomeric and dimeric complexes are indistinguishable based on elemental analysis, IR and UV-VIS spectroscopy data. We have found that cyclic voltammetry (CV) could be a convenient method for determining the complexes composition. In fact, CV curves of compound **2** in DMF solution on glassy carbon electrode in the potential region corresponding to the $Cu^{II} \rightarrow Cu^{I}$ reduction (0.28–0.43 V) contain two single-electron peaks corresponding to the sequential reduction of two chloride-bridged copper ions (they should be reduced at different potentials). The subsequent anodic peaks are also doubled, which corresponds to the successive reduction of two ligand fragments of the dimeric



Scheme 2 *Reagents and conditions*: i, $CuCl_2 \cdot 2H_2O$, EtOH, Δ, 1.5 h.

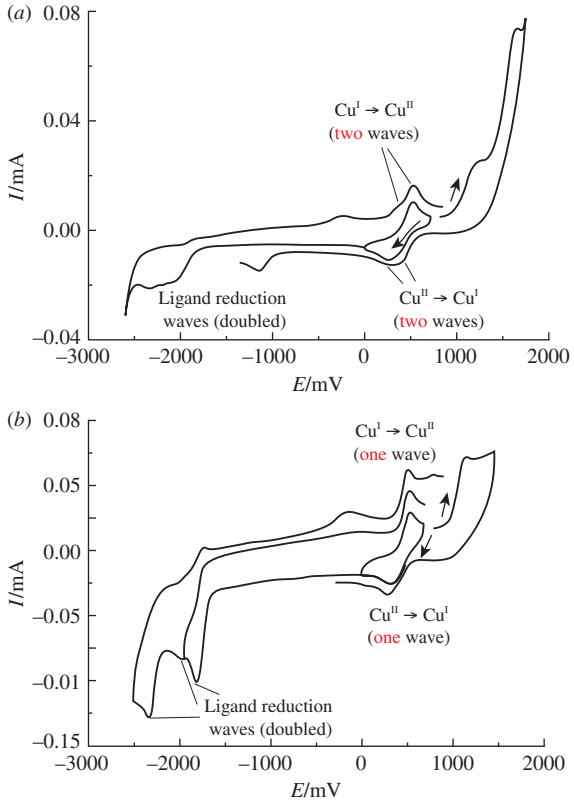


Figure 2 CV curves for complex (*a*) **2** and (*b*) **6c** (DMF, Bu_4NClO_4, GC electrode).

complex at different potential values (Figure 2, Table S3, see Online Supplementary Materials). At the same time, there is only one peak of the $Cu^{II} \rightarrow Cu^{I}$ reduction on CV curves of monomeric complexes **4** and **6** (see Figure 2 and Online Supplementary Materials). Thus, the number of reduction peaks in the 0.25–0.50 V region on CV curve may serve as a criterion for the mono- or dimeric structure of copper(II) chloride complexes with 2-hetarylbenzothiazole ligands.

Ligands **1**, **3**, **5** and copper complexes **2**, **4**, **6** were tested for *in vitro* cytotoxic activity against MCF-7 and A-549 carcinoma cells, and also towards the noncancerous cell line Hek-293 and VA-13. The measurements were carried out using the standard MTT method.[36] The results showed moderate cytotoxicity of all copper complexes against the subjected cancer cell line compared with cisplatin; ligands are significantly less cytotoxic (Table 1).

In summary, dimeric complex of copper(II) chloride with a 2-hetarylbenzothiazole ligand was obtained and characterized using X-ray diffraction data. A convenient electrochemical criterion for the assigning of copper(II) chloride coordination compounds

Table 1 IC_{50} values for ligands **1**, **3** and copper complexes **2**, **4**, **6** (MTT-test).

Compound	IC_{50}/μM			
	A-549	Hek-293t	MCF-7	VA-13
1	154.66±98.8	144.54±98.59	884.1±794.71	67.6±9.74
2	62.06±25.91	52.8±8.56	53.67±9.94	33.84±16.86
3	120.35±68.51	17.88±12.43	62.55±40.11	27.98±16.35
4	24.59±10.3	11.67±7.71	29.66±6.85	21.02±13.8
6a	–[a]	31.98±16.53	37.13±18.91	38.36±11.47
6c	–[a]	58.91±46.5	8.78±4.8	48.19±14.41
DMSO	>	>	>	>
Doxorubicin	27.7±3	0.129±0.037	0.129±0.055	0.51±0.28
Cisplatin	36±4	12.4±4.2	64.13±6.7	14±2.8

[a] Not available.

with 2-hetarylbenzothiazoles to monomeric structure complexes or dimers with bridged chloride anions has been proposed. The reasonable cytotoxicity of coordination compounds of copper(II) chloride with 2-hetarylbenzothiazoles has been established.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.07.030.

References

1 D.-F. Shi, T. D. Bradshaw, S. Wrigley, C. J. McCall, P. Lelieveld, I. Fichtner and M. F. G. Stevens, *J. Med. Chem.*, 1996, **39**, 3375.
2 T. D. Bradshaw, S. Wrigley, D.-F. Shi, R. J. Schultz, K. D. Paull and M. F. G. Stevens, *Br. J. Cancer*, 1998, **77**, 745.
3 M. Lezcano, W. Al-Soufi, M. Novo, E. Rodríguez-Núñez and J. V. Tato, *J. Agric. Food Chem.*, 2002, **50**, 108.
4 Z.-P. Zhuang, M.-P. Kung, A. Wilson, C.-W. Lee, K. Plössl, C. Hou, D. M. Holtzman and H. F. Kung, *J. Med. Chem.*, 2003, **46**, 237.
5 G. Wells, J. M. Berry, T. D. Bradshaw, A. M. Burger, A. Seaton, B. Wang, A. D. Westwell and M. F. G. Stevens, *J. Med. Chem.*, 2003, **46**, 532.
6 D. J. Skalitzky, J. T. Marakovits, K. A. Maegley, A. Ekker, X.-H. Yu, Z. Hostomsky, S. E. Webber, B. W. Eastman, R. Almassy, J. Li, N. J. Curtin, D. R. Newell, A. H. Calvert, R. J. Griffin and B. T. Golding, *J. Med. Chem.*, 2003, **46**, 210.
7 M. I. Kharitonova, I. D. Konstantinova and A. I. Miroshnikov, *Russ. Chem. Rev.*, 2018, **87**, 1111.
8 R. J. Alaimo, S. S. Pelosi, C. J. Hatton and J. E. Gray, *J. Med. Chem.*, 1974, **17**, 775.
9 R. D. Haugwitz, R. G. Angel, G. A. Jacobs, B. V. Maurer, V. L. Narayanan, L. R. Cruthers and J. Szanto, *J. Med. Chem.*, 1982, **25**, 969.
10 R. D. Haugwitz, B. V. Maurer, G. A. Jacobs, V. L. Narayanan, L. R. Cruthers and J. Szanto, *J. Med. Chem.*, 1979, **22**, 1113.
11 J. A. Grim and H. G. Petring, *Cancer Res.*, 1967, **27**, 1278.
12 E. Budzisz, M. Miernicka, I.-P. Lorenz, P. Mayer, E. Balcerczak, U. Krajewska and M. Rozalski, *Eur. J. Med. Chem.*, 2010, **45**, 2613.
13 A. T. Baker, H. A. Goodwin and A. D. Rae, *Inorg. Chem.*, 1987, **26**, 3513.
14 P. U. Maheswari, M. van der Ster, S. Smulders, S. Barends, G. P. van Wezel, C. Massera, S. Roy, H. den Dulk, P. Gamez and J. Reedijk, *Inorg. Chem*., 2008, **47**, 3719.
15 E. K. Beloglazkina, I. V. Yudin, A. G. Majouga, A. A. Moiseeva, A. L. Tursina and N. V. Zyk, *Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 1803 (*Izv. Akad. Nauk, Ser. Khim.*, 2006, 1738).
16 E. K. Beloglazkina, E. S. Barskaya, A. G. Majouga and N. V. Zyk, *Mendeleev Commun.*, 2015, **25**, 148.
17 E. S. Barskaya, V. V. Shorokhov, A. V. Rzheutsky, A. D. Khudyakov, I. V. Yudin, V. A. Tafeenko, N. V. Zyk and E. K. Beloglazkina, *Russ. Chem. Bull., Int. Ed.*, 2019, **68**, 638 (*Izv. Akad. Nauk, Ser. Khim*., 2019, 638).
18 E. S. Barskaya, A. V. Rzheutsky, A. A. Moiseeva, I. V. Yudin, N. V. Zyk and E. K. Beloglazkina, *Russ. Chem. Bull., Int. Ed.*, 2019, **68**, 870 (*Izv. Akad. Nauk, Ser. Khim*., 2019, 870).
19 S. Delgado, A. Gallego, O. Castillo and F. Zamora, *Dalton Trans.*, 2011, **40**, 847.
20 R. Al-Hashemi, N. Safari, A. Abedi, B. Notash, V. Amani and H. R. Khavasi, *J. Coord. Chem.*, 2009, **62**, 2909.
21 N. Wang, X.-Y. Yu, X. Zhang, W.-P. Gao, R. Xin, H. Zhang, Y.-Y. Yang and X.-S. Qu, *J. Coord. Chem.*, 2014, **67**, 837.
22 L. K. Thompson, *Coord. Chem. Rev.*, 2002, **233–234**, 193.
23 P. Chaudhuri, *Coord. Chem. Rev.*, 2003, **243**, 143.
24 G. La Monica and G. A. Ardizzoia, *Prog. Inorg. Chem.*, 1997, **46**, 151.
25 I. N. Shcherbakov and S. I. Levchenkov, *Russ. Chem. Bull., Int. Ed.*, 2018, **67**, 1167 (*Izv. Akad. Nauk, Ser. Khim.*, 2018, 1167).
26 K. A. Myannik, E. K. Beloglazkina, A. A. Moiseeva, T. K. Baryshnikova, V. N. Yarovenko and M. M. Krayushkin, *Mendeleev Commun.*, 2018, **28**, 79.
27 M. Fontecave and J. L. Pierre, *Coord. Chem. Rev.*, 1998, **170**, 125.
28 P. Gamez, P. G. Aubel, W. L. Driessen and J. Reedijk, *Chem. Soc. Rev.*, 2001, **30**, 376.
29 H.-C. Liang, M. Dahan and K. D. Karlin, *Curr. Opin. Chem. Biol.*, 1999, **3**, 168.
30 V. Mahadevan, R. J. M. K. Gebbink and T. D. P. Stack, *Curr. Opin. Chem. Biol.*, 2000, **4**, 228.
31 E. C. Constable, *Coordination Chemistry of Macrocyclic Compounds*, Oxford University Press, Oxford, 1999.
32 D. P. Singh, R. Kumar, V. Malik and P. Tyagi, *Transition Met. Chem.*, 2007, **32**, 1051.
33 P. S. Mane, S. M. Salunke and B. S. More, *Eur. J. Chem.*, 2011, **8**, 245.
34 I. A. Salimova, A. V. Yudina, A. V. Mironov, A. G. Majouga, N. V. Zyk and E. K. Beloglazkina, *Mendeleev Commun.*, 2018, **28**, 524.
35 A. S. Munde, A. N. Jagdale, S. M. Jadhav and T. K. Chondhaker, *J. Korean Chem. Soc.*, 2004, **53**, 407.
36 P. Wang, N. Onozawa-Komatsuzaki, R. Katoh, Y. Himeda, H. Sugihara, H. Arakawa and K. Kasuga, *Chem. Lett.*, 2001, **30**, 940.
37 C. Santini, M. Pellei, V. Gandin, M. Porchia, F. Tisato and C. Marzano, *Chem. Rev.*, 2014, **114**, 815.
38 E. S. Barskaya, E. K. Beloglazkina, A. G. Mazhuga, I. V. Yudin and N. V. Zyk, *Russ. Chem. Bull., Int. Ed.*, 2015, **64**, 1975 (*Izv. Akad. Nauk, Ser. Khim.*, 2015, 1975).

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