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# MODEL SYSTEMS FOR TYPE I COPPER PROTEINS: STRUCTURES OF COPPER COORDINATION COMPOUNDS WITH THIOETHER AND AZOLE-CONTAINING LIGANDS

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## CONTENTS

## ABBREVIATIONS

| | |
|---|---|
| acac | acetylacetonato |
| EtOH | ethanol |
| MeOH | methanol |
| 4Im01 | 4-(ethylthiomethyl)-5-methylimidazole |
| 4Im02 | 4-(benzylthiomethyl)-5-methylimidazole |
| 4Im03 | 5-methyl-4-(4-methylphenylthiomethyl)imidazole |
| 4Im04 | 4-(propylthiomethyl)imidazole |
| 4Im05 | 4-(*t*-butylthiomethyl)imidazole |
| 4Im06 | 4-(benzylthiomethyl)imidazole |
| 4Im07 | 4-(phenylthiomethyl)imidazole |
| 4Im08 | *N*-cyano-*N*′-methyl-*N*″[2-((5-methyl-4-imidazolyl)methylthio)ethyl]-guanidine (cimetidine) |
| 4Im09 | 1,3-bis(5-methyl-4-imidazolyl)-2-thiapropane |
| 4Im10 | 1,5-bis(4-imidazolyl)-3-thiapentane |

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| | |
|---|---|
| 4Im11 | 4-(2-(aminoethyl)thiomethyl)-5-methylimidazole |
| 4Im12 | 1,6-bis(4-imidazolyl)-2,5-dithiahexane |
| 4Im13 | 1,6-bis(5-methyl-4-imidazolyl)-2,5-dithiahexane |
| 4Im14 | 1,7-bis(5-methyl-4-imidazolyl)-2,6-dithiaheptane |
| 4Im15 | 1,8-bis(4-imidazolyl)-3,6-dithiaoctane |
| 4Im16 | 3-{5-methyl-4-imidazolylmethylthioethyleneiminomethyl}-1-phenylpyridine-2-thione |
| 2Im21 | 1-methyl-2-(2-(methylthio)ethyl)imidazole |
| 2Im22 | 1,3-bis(5-phenyl-2-imidazolyl)-2-thiapropane |
| 2Im23 | 1,3-bis(5-*t*-butyl-2-imidazolyl)-2-thiapropane |
| 2Im24 | 1,6-bis(1-benzyl-2-imidazolyl)-2,5-dithiahexane |
| 2Im25 | *N*-{2-mercapto-2-methyl-1-(1-methyl-2-imidazolyl)propyl}-*N*-methyl-{(1-methyl-2-imidazolyl)methylthio}acetamide |
| 2Bz31 | 2-(ethylthiomethyl)benzimidazole |
| 2Bz32 | 2(*t*-butylthiomethyl)benzimidazole |
| 2Bz33 | 1,3-bis(2-benzimidazolyl)-2-thiapropane |
| 2Bz34 | 1,5-bis(2-benzimidazolyl)-3-thiapentane |
| 2Bz35 | 1,5-bis(1-propyl-2-benzimidazolyl)-3-thiapentane |
| 2Bz36 | 1,5-bis(5,6-dimethyl-2-benzimidazolyl)-3-thiapentane |
| 2Bz37 | 1,7-bis(2-benzimidazolyl)-4-thiaheptane |
| 2Bz38 | 2-mercaptobenzothiazole |
| 2Bz39 | 1,3-bis(2-benzothiazolyl)trisulphan |
| 2Bz40 | 1,6-bis(2-benzimidazolyl)-2,5-dithiahexane |
| 2Bz41 | 1,7-bis(1-methyl-2-benzimidazolyl)-2,6-dithiaheptane |
| 2Bz42 | 1,7-bis(2-benzimidazolyl)-2,6-dithiaheptane |
| 2Bz43 | 1,2-bis(2-benzimidazolylmethylthia)benzene |
| 2Bz44 | 1,8-bis(2-benzimidazolyl)-3,6-dithiaoctane |
| 2Bz45 | 3-{2-benzimidazolylmethylthioethyleneiminomethyl}-1-phenylpyridine-2-thione |
| 1Pz51 | 1-(ethylthiomethyl)-3,5-dimethylpyrazole |
| 1Pz52 | 1-(2-(ethylthio)ethyl)-3,5-dimethylpyrazole |
| 1Pz53 | 1,3-bis(3,5-dimethyl-1-pyrazolyl)-2-thiapropane |
| 1Pz54 | 1,5-bis(3,5-dimethyl-1-pyrazolyl)-3-thiapentane |
| 1Pz55 | 1,6-bis(3,5-dimethyl-1-pyrazolyl)-2,5-dithiahexane |
| 1Pz56 | 1,8-bis(3,5-dimethyl-1-pyrazolyl)-3,6-dithiaoctane |
| 1Pz57 | 1,9-bis(3,5-dimethyl-1-pyrazolyl)-3,7-dithianonane |
| 2Py61 | 2-(methylthiomethyl)pyridine |
| 2Py62 | 2-(ethylthiomethyl)pyridine |
| 2Py63 | 2-(*n*-propylthiomethyl)pyridine |
| 2Py64 | 2-(*t*-butylthiomethyl)pyridine |

| | |
|---|---|
| 2Py65 | 2-(benzylthiomethyl)pyridine |
| 2Py66 | 2-(pentafluorophenylthiomethyl)pyridine |
| 2Py67 | 1,3-bis(2-pyridyl)-2-thiapropane |
| 2Py68 | 1,5-bis(2-pyridyl)-3-thiapentane |
| 2Py69 | 1,6-bis(2-pyridyl)-2,5-dithiahexane |
| 2Py70 | 1,7-bis(2-pyridyl)-2,6-dithiaheptane |
| 2Py71 | 1,8-bis(2-pyridyl)-3,6-dithiaoctane |
| 2Py72 | 1,9-bis(2-pyridyl)-3,7-dithianonane |
| 2Py73 | (2-pyridylmethyl)bis(2-(methylthio)ethyl)amine |
| 2Py74 | (2-pyridylmethyl)bis(2-(ethylthio)ethyl)amine |
| 2Py75 | (2-(2-pyridylethyl))bis(2-(ethylthio)ethyl)amine |
| 2Py76 | 1,4-bis(2-pyridyl)-2-thiabutane |

## A. INTRODUCTION

About a decade ago, the first crystal structures of plastocyanin [1,2] and azurin [3,4] were solved. These structures revealed that in the active sites of the Type I copper proteins the copper ion is coordinated in a distorted tetrahedron or trigonal bipyramid with two histidine nitrogen atoms, a methionine thioether and a cysteine thiolate coordinating to the copper ion. In *alcaligenes denitrificans* azurin [4], an extra carbonyl oxygen was found within bonding distance, completing a trigonal bipyramidal geometry.

Now that crystallography has revealed much about the copper stereochemistry in the Type I copper proteins, systematic investigations of the synthesis of low molecular weight copper complexes have gained importance. Methods for constructing model compounds for Type I copper proteins include the design of ligands with nitrogen and sulphur donor atoms. So far, no complete models have been obtained with the same characteristics as a blue-copper protein. In particular the binding of thiolate groups to copper(II) is hard to accomplish in low molecular weight compounds. The rigid conformation of the protein with only a single cysteine residue near the copper binding site obviously prevents the formation of a disulphide. Therefore the cysteine thiolate function is often mimicked by a thioether function. However, some copper(II)–thiolate complexes are known [5,6]. Recently, a review article has been published on the synthetic model systems containing two thiolate sulphur and two nitrogen donors [7]. The thiolate functions of these ligands are stable against oxidation as a consequence of either steric or electronic constraints. Another recent review deals solely with the cyclic voltammetric behaviour of copper compounds with $N_2S_2$ ligands [8]. In the latter review already an indication is given of the wealth of model compounds for the blue-copper protein.

Chelating ligands containing both sulphur and nitrogen donor atoms of various natures have been designed and synthesized. The imidazole group has often been substituted by other heterocycles such as benzimidazole, pyridine and pyrazole. Two overviews, dealing with azole ligands, describe model systems for copper proteins in general [9,10].

In the last three years, many copper coordination compounds with thioether–imidazole-containing ligands and their structures and properties have been published by our group. Therefore we now undertake an attempt to present an overview of these compounds with special attention to their crystal and molecular structures, to compare them with other published copper structures with thioether–azole or thioether–pyridine ligands. The various ligands and their coordination compounds will be discussed in the following ligand groups:

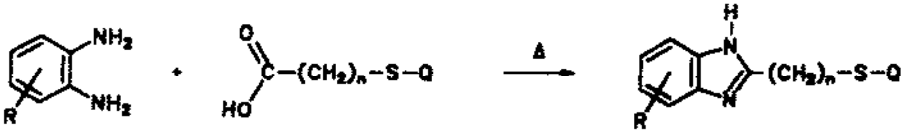
NS donor ligands
$N_2S$ donor ligands
$N_2S_2$ donor ligands
$NN^*SS^-$ donor ligands

To reduce the scope of this review, it is limited to ligands with one of these donor sets. The nitrogen donor atom must originate from 2- or 4-imidazole, 2-benzimidazole, 1-pyrazole or 2-pyridine. Excluded are ligands with other nitrogen donors and larger ligands which can coordinate to more than one copper ion, thus forming binuclear copper compounds, and chelating ligands which do not contain at least one thioether sulphur atom.

The ligands are coded in such a way that the reader can easily recognize which nitrogen donor is present in the ligand.

## B. SYNTHESIS OF THE CHELATING LIGANDS (GENERAL)

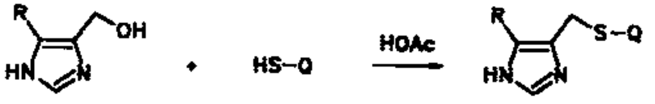
The design and synthesis of ligands for coordination compounds strongly depend on the availability of the desired groups. Benzimidazoles are readily synthesized by the ring-closure reaction of 1,2-diaminobenzene, or a derivative thereof, with a carboxylic acid group, as depicted in reaction (1) [11,12]. (In all reaction schemes in this section, R and Q represent various substituents. For details see Figs. 1, 4, 9 and 14.)



(1)

Several synthetic methods have been reported for this condensation reaction. The wide applicability of this reaction and the abundance of polycarboxylic acids have made it attractive to incorporate the benzimidazole group in chelating ligands [13].

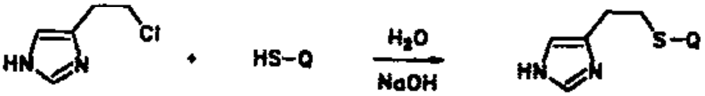
In contrast with benzimidazoles, no general procedure exists for the ring-closure reaction of imidazoles. Many different syntheses of limited scope are known for specific imidazole derivatives in which the substituents are already present in the starting material [11,14]. A very useful compound appears to be 4(5)-hydroxymethylimidazole hydrochloride, which can be prepared from fructose [15]. It has been found that this compound and its 5(4)-methyl derivative, 4(5)-hydroxymethyl-5(4)-methylimidazole, reacts directly with thiols in acetic acid to give the corresponding thioether derivative [16]. This general procedure, which is depicted in reaction (2), has yielded a variety of imidazole–thioether ligands [17]:



(2)

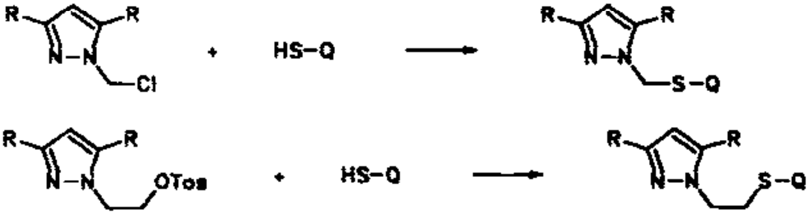
This reaction does not require any intermediate step to activate the methylene group, such as the conversion of the hydroxy group to a chloride [18].

Imidazole–thioether ligands, with 2-imidazole built into the ligand can only be prepared through elaborate multistep syntheses [19–21]. Recently, a route for obtaining a new series of imidazole–thioether ligands, with a larger azole-N to thioether-S separation, was developed [22]. 4-(2-Chloroethyl)imidazole [23] reacts readily with thiolate groups to form the desired imidazole–thioether ligands (reaction (3)):



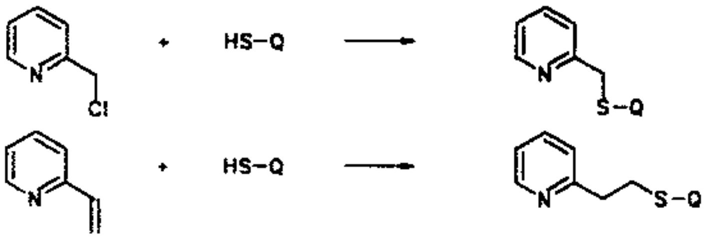
(3)

*N*-Hydroxymethylpyrazoles are readily formed through the condensation of hydrazine with either pentanedione [24], or 1,1,3,3-tetraethoxypropane [25], followed by a reaction with paraformaldehyde [26–28]. *N*-Hydroxyethylpyrazoles are prepared in a one-step synthesis through the condensation of hydroxyethylhydrazine with pentanedione [29] or 1,1,3,3-tetraethoxypropane [30]. These hydroxyalkylpyrazoles are not reactive towards thiol functions, and have to be activated by conversion of the hydroxy group to either a chloride or a tosyl group [29,31] (reactions (4)):



(4)

Pyridine-containing thioether ligands have been known for almost three decades [32]. These ligands are either synthesized from 2-chloromethylpyridine [33–35] or from 2-vinylpyridine with certain thiols [32] (reactions (5)):



(5)

### C. COMPLEXES CONTAINING BIDENTATE NS LIGANDS

To target a tetrahedral environment of the copper ion, resulting in a $CuN_2S_2$ chromophore, two NS ligands are required. Copper(II) complexes with NS ligands, as shown in Fig. 1, in principle experience only minor geometrical constraints because of the limited number of links between the donor atoms.

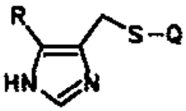
However, with these ligands and copper(II), in almost all cases a distorted octahedral geometry results. In Table 1 the coordination distances of copper complexes with NS ligands are given. Two ligands are usually coordinated in the equatorial plane with the thioether sulphur and the azole nitrogen in mutual trans positions. In the axial positions the two anions or two solvent molecules are coordinated, completing the elongated octahedral geometry.

It is remarkable that in many cases the so-called 'non-coordinating' [36] anions such as tetrafluoroborate and perchlorate are also bound to the copper ion. An example is the structure of $[Cu(4Im01)_2(BF_4)_2]$ [37], a projection of which is shown in Fig. 2, with Cu–F contacts of 2.55 Å. This compound is extremely stable: even a 1:1 chloride–tetrafluoroborate mixture in solution still yields the bis(tetrafluoroborato) complex [37]. Similar complexes were obtained by Aoi et al., namely $[Cu(4Im04)_2(ClO_4)_2]$ [38] and the pyridine-containing compound $[Cu(2Py63)_2(ClO_4)_2]$ [33].

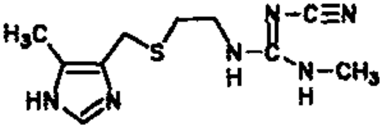
Another striking feature is the presence of the non-coordinating nitrate anion in the compound $[Cu(4Im01)_2(H_2O)_2]$ $(NO_3)_2$ [39], although the nitrate anion is regarded as a better coordinating anion than $BF_4^-$ or $ClO_4^-$. The two water molecules are coordinated in the axial positions, at relatively long distances from the copper ion, the two nitrate anions are very tightly hydrogen bonded to the water molecules and to the imidazole N–H, thereby stabilizing the crystal lattice.

When an even stronger coordinating anion such as the chloride ion in $[Cu(2Bz31)_2Cl_2]$ [40] is used, the equatorial plane is now formed by the two

4-Imidazolyl

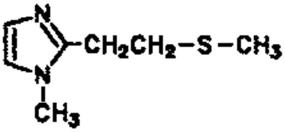


| Code | R | Q | Ref. |
|---|---|---|---|
| 4Im01 | $CH_3$ | $C_2H_5$ | 17, 37, 39, 45, 48 |
| 4Im02 | $CH_3$ | $CH_2C_6H_5$ | 17 |
| 4Im03 | $CH_3$ | $p$-$C_6H_4CH_3$ | 17 |
| 4Im04 | H | $n$-$C_3H_7$ | 33, 38 |
| 4Im05 | H | $t$-$C_4H_9$ | 33, 38 |
| 4Im06 | H | $CH_2C_6H_5$ | 33, 38 |
| 4Im07 | H | $C_6H_5$ | 38 |



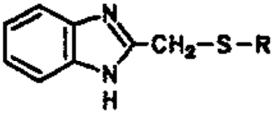
Code 4Im08 [43,44,49,50]

2-Imidazolyl



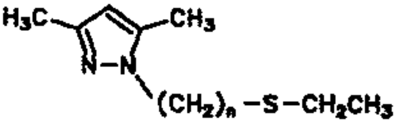
Code 2Im21 [20]

2-Benzimidazolyl



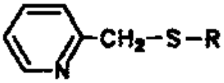
| Code | R | Ref. |
|---|---|---|
| 2Bz31 | $C_2H_5$ | 40 |
| 2Bz32 | $t$-$C_4H_9$ | 52 |

1-Pyrazolyl



| Code | $n$ | Ref. |
|---|---|---|
| 1Pz51 | 1 | 51 |
| 1Pz52 | 2 | 51 |

2-Pyridyl



| Code | R | Ref. |
|---|---|---|
| 2Py61 | $CH_3$ | 33 |
| 2Py62 | $C_2H_5$ | 33, 52 |
| 2Py63 | $n$-$C_3H_7$ | 33 |
| 2Py64 | $t$-$C_4H_9$ | 33, 47, 52 |
| 2Py65 | $CH_2C_6H_5$ | 33 |
| 2Py66 | $C_6F_5$ | 52 |

Fig. 1. Schematic drawing of the bidentate chelating NS ligands.

TABLE 1

Relevant distances (Å) in copper complexes with the NS ligands

| Compound | Ref. | Cu–N | Cu–S | Cu–X | Geometry |
|---|---|---|---|---|---|
| $[Cu(4Im01)(H_2O)_2](NO_3)_2$ | 39 | 1.934(2) | 2.4487(7) | 2.440(2) | Octahedral |
| $[Cu(4Im01)_2(BF_4)_2]$ | 37 | 1.930(6) | 2.413(2) | 2.551(5) | Octahedral |
| $[Cu(4Im04)_2(ClO_4)_2]$ | 38 | 1.940(6) | 2.397(2) | 2.594(6) | Octahedral |
| $[Cu(4Im08)_2](ClO_4)_2$ | 44 | 1.980(6) | 2.790(2) | 2.042(7) | Octahedral |
| $[Cu(4Im08)_2](NO_3)_2$ | 43 | 1.942(2) | 2.419(1) | 2.558(2) | Octahedral |
| $[Cu(2Bz31)_2Cl_2]$ | 40 | 2.000(5) | 3.001(2) | 2.322(2) | Octahedral |
| $[Cu(2Py63)_2(ClO_4)_2]$ | 33 | 2.015(3) | 2.366(1) | 2.501(3) | Octahedral |
| $[Cu_2(4Im01)Br_3]_2$[a] | 46 | 1.964(5) | 2.350(2) | 2.394(1)<br>2.439(1) | Square planar |
| $[Cu(2Py64)Br_2]_2$ | 45 | 2.04(2) | 2.353(5) | 2.412(3)<br>2.356(3)<br>2.965(4) | Square pyramid |
| $[Cu(2Im21)_3](BF_4)_2$ | 20 | 1.960(5)<br>1.966(5)<br>2.030(5) | 2.398(2)<br>2.614(2) | | Square pyramid |
| $[Cu(2Im21)_3](BF_4)_2$ | 20 | 1.985(7)<br>1.997(7)<br>2.119(7) | 2.478(3)<br>2.394(3) | | Trigonal bipyramid |
| $[Cu(2Py64)_2Br]$ | 47 | 2.109(9) | 2.310(3)<br>2.357(3) | 2.424(2) | Tetrahedral[b] |

[a] Mixed-valence compound, distances are only given for the copper(II) coordination sphere.
[b] Copper(I) compound.

azole nitrogen atoms and the chloride ions, and the axial positions are occupied by the thioether sulphur atoms.

The ligand 2Im21 with copper in an M:L ratio of 1:3 yielded two isomers of a compound $[Cu(2Im21)_3](BF_4)_2$ [20]. In both structures, shown in Fig. 3, the copper ion is pentacoordinated by two bidentate coordinating ligands, the fifth position occupied by one monodentate ligand (coordinated with the imidazole nitrogen, the sulphur atom being at a non-bonding distance), resulting in an $N_3S_2$ chromophore. The two isomeric forms are different in their coordination geometry at the copper ion. The isomer shown in Fig. 3(a) has trigonal bipyramidal geometry, with two imidazole nitrogen atoms along the main axis; the trigonal plane is formed by the two sulphur atoms and the third nitrogen donor atom. The isomer in Fig. 3(b) has square pyramidal geometry; the basal plane is formed by the three imidazole nitrogen atoms and one thioether sulphur and the apical position is occupied by the second sulphur atom. Which isomer crystallizes depends on the solvent used [20], while one is easily converted to the other upon standing.

A very special ligand is cimetidine (4Im08), since this has been widely

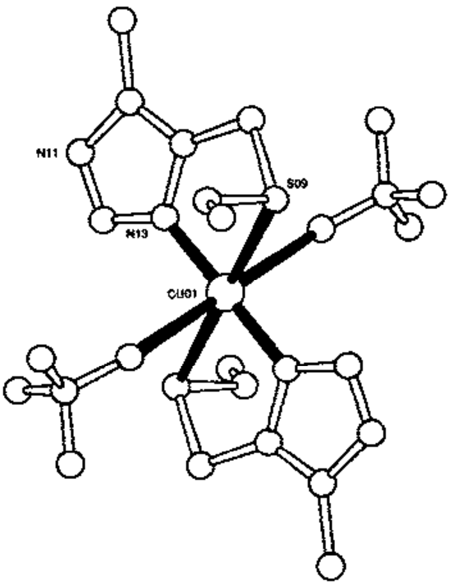


Fig. 2. Pluto projection of [Cu(4Im01)$_2$(BF$_4$)$_2$].

studied as a histamine H$_2$-receptor antagonist [41,42]. The ligand 4Im08 is potentially tridentate, but appears to be a bidentate chelating ligand in the crystal structures described below. Two structures with this ligand have been described, [Cu(4Im08)$_2$] (NO$_3$)$_2$ [43] and [Cu(4Im08)$_2$] (ClO$_4$)$_2$ [44]. Surprisingly, a different coordination geometry was observed although the only difference between these two structures originates in the anions. In both structures the copper ion is coordinated by two ligands in an elongated octahedron. In the nitrate compound the axial positions are occupied by the nitrile-type nitrogen atoms, and the equatorial plane is formed by the imidazole nitrogen atoms and the thioether sulphur atoms. In the perchlorate compound, the equatorial plane is formed by the four nitrogen atoms (two imidazole nitrogen atoms and two nitrile atoms) and the thioether sulphur atoms are at a rather long distance in the axial positions. In both structures the ligand is in bidentate coordination, with the nitrile N atom originating from neighbouring molecules.

With a copper-to-NS ligand ratio of 1:1, a CuNSX$_2$ chromophore would be expected. However, with the ligand 2Py64, a binuclear compound with formula [Cu(2Py64)Br$_2$]$_2$ is formed [45]: two of the four bromide ions are bridging between the two copper ions. The copper ion is coordinated in a square planar geometry with the nitrogen and sulphur donor from the ligand and two bromide ions in the equatorial plane. The third bromide ion is in the apical position at a rather large distance of 2.97 Å.

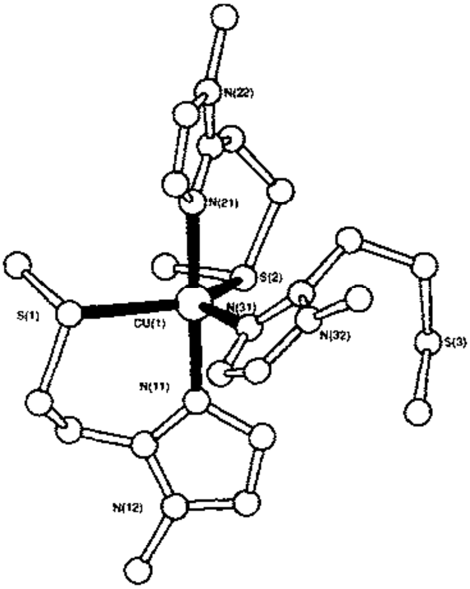


Fig. 3. (a) Pluto projection of the trigonal bipyramidal isomer of $[Cu(2Im21)_3]$ $(BF_4)_2$ based on the atomic coordinates as determined by Glass [20].

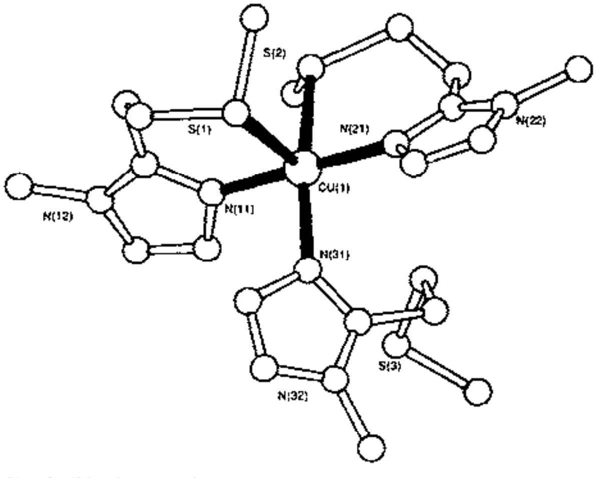


Fig. 3. (b) Pluto projection of the square pyramidal isomer of $[Cu(2Im21)_3]$ $(BF_4)_2$ based on the atomic coordinates as determined by Glass [20].

A unique structure is obtained when the ligand 4Im01 is coordinated to copper bromide: the resulting compound is tetranuclear, of mixed valence with an overall stoichiometry of $[Cu_2(4Im01)Br_3]_2$ [46]. This structure consists of a "dimer of dimers". The bridge within one dimer is formed by two bromide ions between a copper(I) and a copper(II) ion, resulting in [(4Im01)$Cu^{II}Br_2Cu^{I}Br$], while the bridge between the dimers is through the thioether sulphur, again bridging a copper(I) and a copper(II) ion.

Copper(I) compounds with two NS ligands may have a good chance of forming tetrahedral $CuN_2S_2$ compounds, but reports on any such copper(I) compounds have not yet been published. One copper(I) compound with the ligand 2Py64 has been reported, with formula [Cu(2Py64)$_2$Br], but in this compound one of the pyridine nitrogen atoms has been forced away from the coordination sphere by the bromide ion, resulting in a $CuNS_2Br$ chromophore [47].

In summary, bidentate NS ligands yield a variety of copper coordination compounds. Most of these copper compounds have (distorted) octahedral geometry, but some five-coordinated species have also been encountered. In most cases the sulphur atom is coordinated to the copper ion at various distances, although the sulphur atom in these ligands is not forced towards coordination of the copper ion through a chelating effect.

## D. COMPLEXES CONTAINING TRIDENTATE $N_2S$ LIGANDS

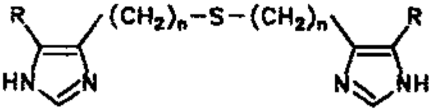
When using one of the tridentate $N_2S$ ligands shown in Fig. 4, one might add a thiol function to complete the desired $N_2SS^-$ chromophore.

Although this is a very interesting point of view, not many reports of such ligands could be found. A few copper compounds with pyridyl $N_2S$ ligands have been reported [53(b),53(c)] but no crystal structures have been described. The lack of copper coordination compounds with the ligand 2Py68 is probably due to synthetic difficulties [53(a)], but the ligand 2Py67 has been prepared in good yield [54,55]. Quite a few different benzimidazole-containing $N_2S$ ligands have been synthesized [56,57], but not much coordination chemistry has been reported. $N_2S$ pyrazole ligands have recently been prepared in our laboratory, but no crystal structures have been published so far [51].

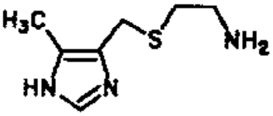
In Table 2 the coordination distances of copper complexes with $N_2S$ ligands are listed.

With the benzimidazole ligand 2Bz35 a copper(I) structure has been reported. The geometry around the copper ion in [Cu(2Bz35)] ($BF_4$) appears to be T-shaped [57]. Three copper(II) structures with such benzimidazole ligands have been described [57,58]. In all structures the copper(II) ion is five coordinate in a square pyramidal coordination geometry, the fourth and fifth positions being occupied by solvent molecules or the anions. In [Cu(2Bz36)($H_2O$)($ClO_4$)]($ClO_4$) [57] and in [Cu(2Bz34)(MeOH)($H_2O$)]($ClO_4$)$_2$ [58] the tridentate ligand is coordinated meridionally with relatively

4-Imidazolyl

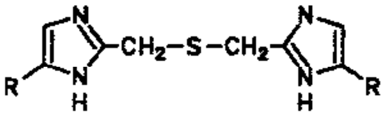


| Code | $n$ | R | Ref. |
|---|---|---|---|
| 4Im09 | 1 | $CH_3$ | 17, 59, 61 |
| 4Im10 | 2 | H | 22 |



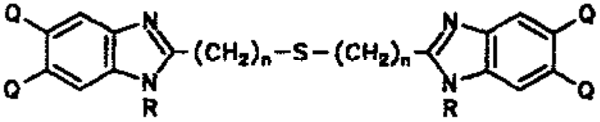
Code 4Im11 [62]

2-Imidazolyl



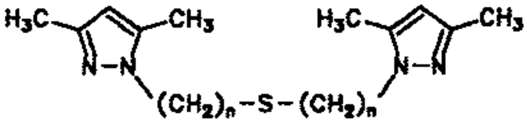
| Code | R | Ref. |
|---|---|---|
| 2Im22 | $C_6H_5$ | 21 |
| 2Im23 | $t$-$C_4H_9$ | 21 |

2-Benzimidazolyl*



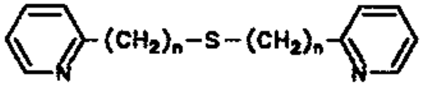
| Code | $n$ | R | Q | Ref. |
|---|---|---|---|---|
| 2Bz33 | 1 | H | H | 57 |
| 2Bz34 | 2 | H | H | 56, 58 |
| 2Bz35 | 2 | $n$-$C_3H_7$ | H | 56, 57 |
| 2Bz36 | 2 | H | $CH_3$ | 56, 57 |
| 2Bz37 | 3 | H | H | 57 |

1-Pyrazolyl



| Code | $n$ | Ref. |
|---|---|---|
| 1Pz53 | 1 | 51 |
| 1Pz54 | 2 | 51 |

2-Pyridyl



| Code | $m$ | $n$ | Ref. |
|---|---|---|---|
| 2Py67 | 1 | 1 | 54, 55, 53(c) |
| 2Py68 | 2 | 2 | 53(a), 53(b) |
| 2Py76 | 1 | 2 | 53(c) |

Fig. 4. Schematic drawing of the tridentate chelating $N_2S$ ligands.

*Note: About 13 other ligands have been described [56,57], with various substituents at the benzimidazole groups. They are not listed here for clarity, as no copper structures have been described for these ligands.

TABLE 2

Relevant distances (Å) in copper complexes with the $N_2S$ ligands

| Compound | Ref. | Cu–N | Cu–S | Cu–X | Geometry |
|---|---|---|---|---|---|
| $[Cu(2Im22)_2](ClO_4)_2$ | 21 | 2.020(9)<br>2.019(7) | 2.824(5) | | Octahedral |
| $[Cu(4Im09)_2](BF_4)_2(EtOH)_2$ | 59 | 2.03(2)<br>1.99(2) | 2.790(8) | | Octahedral |
| $[Cu(4Im09)(NO_3)_2]$ | 59 | 1.939(3)<br>1.943(3) | 2.369(1) | 2.405(2)<br>1.987(2) | Square pyramid |
| $[Cu(4Im10)Cl]_2(ClO_4)_2$ | 22 | 1.950(3)<br>1.948(3) | 2.4162(9) | 2.3132(8)<br>2.861(1) | Square pyramid |
| $[Cu(2Bz34)(MeOH)(H_2O)](ClO_4)_2$ | 58 | 1.984(3)<br>1.978(3) | 2.297(1) | 1.995(2)<br>2.261(3) | Square pyramid |
| $[Cu(2Bz34)(acac)](PF_6)$ | 58 | 2.006(13) | 2.696(5) | 1.918(8) | Square pyramid |
| $[Cu(2Bz36)(H_2O)(ClO_4)](ClO_4)$ | 57 | 1.985(6)<br>1.960(6) | 2.322(2) | 2.045(5)<br>2.346(6) | Square pyramid |
| $[Cu(4Im10)Cl_2]$ | 22 | 1.970(4)<br>1.972(3) | 2.501(1) | 2.321(1)<br>2.477(1) | Trigonal bipyramid |
| $[Cu(4Im10)(NCS)_2]$ | 22 | 1.960(4)<br>1.976(4) | 2.600(2) | 2.004(5)<br>1.994(5) | Trigonal bipyramid |
| $[Cu(2Bz35)](BF_4)$ | 57 | 1.912(5)<br>1.910(5) | 2.469(9) | | T-shaped[a] |
| $[Cu(2Bz38)(2Bz39)](ClO_4)$ | 60 | 2.04(1)<br>2.012(9) | 2.486(4)<br>2.221(4) | | Tetrahedral[a] |

[a] Copper(I) compound.

short Cu–S distances of 2.32 Å and 2.30 Å respectively, because the sulphur atom is forced towards the copper ion by the chelating effect of the ligands. In the first compound the perchlorate anion is coordinated in the apical position at a rather short distance.

In constrast with these structures, the ligand in $[Cu(2Bz34)(acac)](PF_6)$ is coordinated facially (see Fig. 5), again forming a square pyramidal coordination geometry around the copper ion [58]. Now the thioether group is coordinated in the apical position at a rather long bonding distance (Cu–S, 2.70 Å), the basal plane being formed by two benzimidazole nitrogen atoms and two oxygen donor atoms from the pentanedionato anion.

With the 4-imidazole-containing ligands 4Im09 and 4Im10 some five-coordinate complexes were also encountered. $[Cu(4Im09)\ (NO_3)_2]$ appeared to be square pyramidal with both nitrate ions in monodentate coordination, one at a relatively large distance in the apical position [59]. The ligand is coordinated meridionally. The only examples of a trigonal bipyramidal structure within the group of compounds with $N_2S$ ligands are found in the

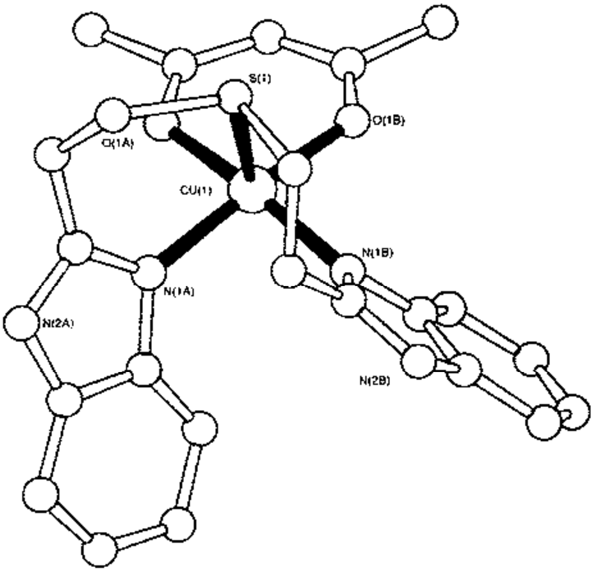


Fig. 5. Pluto projection of $[Cu(2Bz34)(acac)]^+$ based on the atomic coordinates as determined by Addison et al. [58].

compounds $[Cu(4Im10)Cl_2]$ (see Fig. 6) and $[Cu(4Im10)(NCS)_2]$. The copper ion in $[Cu(4Im10)Cl_2]$ is coordinated by the thioether sulphur and the chloride ions in the trigonal plane [22], again with the ligand meridionally coordinated. In the latter compound the geometry is distorted towards square pyramidal.

With the addition of a perchlorate anion to the reaction mixture of $CuCl_2$ and 4Im10, thus forming a mixed-anion compound, one would expect to obtain a four-coordinate copper compound. Instead a binuclear species $[Cu(4Im10)Cl]_2(ClO_4)_2$ with bridging chloride ions results [22]. The copper ion is in a square pyramid, with one of the chloride ions at a very long (semi-coordinating) distance in the apical position.

Another class of compounds can be obtained when the ratio of metal to $N_2S$ ligand is changed to 1:2. $CuN_4S_2$ compounds have been described [21,59] in which the two ligands are coordinated facially, resulting in an elongated octahedral geometry with the four azole nitrogen atoms in the equatorial plane and the two thioether sulphur atoms in the axial positions. In the compound $[Cu(2Im22)_2](ClO_4)_2$ [21] a very long Cu–S distance of 2.82 Å is encountered (see Fig. 7). In $[Cu(4Im09)_2](BF_4)_2(EtOH)_2$ a similar coordination has been observed [59].

Unfortunately, no reports on $N_2SS^*$ compounds have appeared with the ligands described in this section. However, a ligand which itself does not fit in the scope of this review, but which yielded an interesting crystal structure

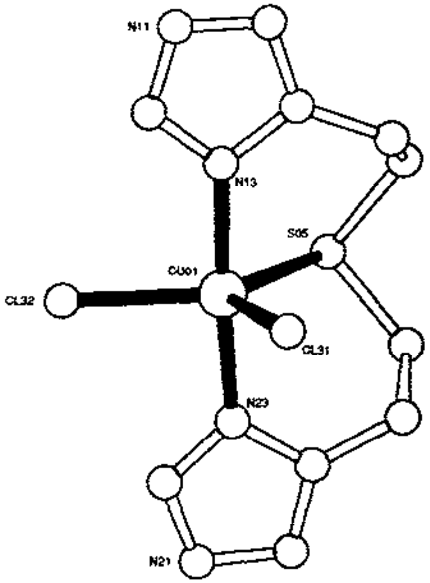


Fig. 6. Pluto projection of [Cu(4Im10)Cl$_2$].

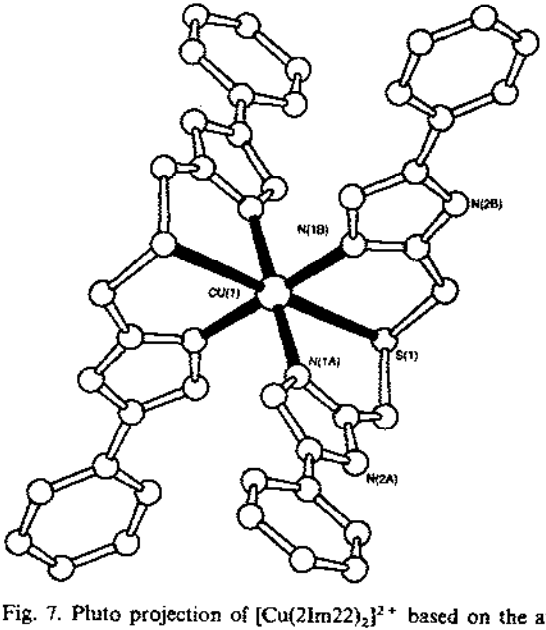


Fig. 7. Pluto projection of [Cu(2Im22)$_2$]$^{2+}$ based on the atomic coordinates as determined by Schugar and coworkers [21].

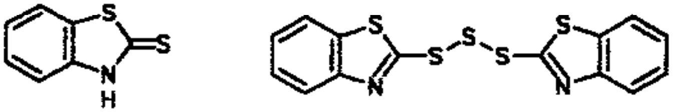


Fig. 8. (a) Schematic drawing of the benzothiazole ligands 2Bz38 and 2Bz39.

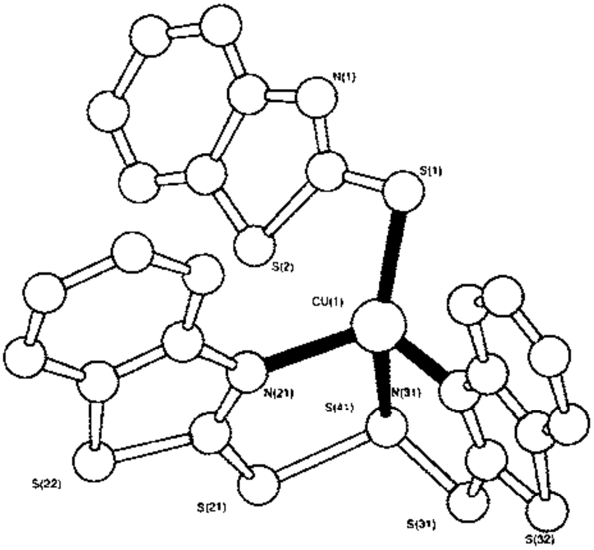
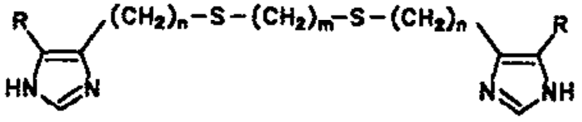


Fig. 8. (b) Pluto projection of $[Cu(2Bz38)(2Bz39)]^+$ based on the atomic coordinates as determined by Jeannin et al. [60].

is mercaptobenzothiazole (2Bz38). When a solution of this ligand reacts with copper(II) perchlorate [60], single crystals of a copper(I) compound are obtained. The crystal structure determination showed that through an unusual sulphur insertion a new tridentate $N_2S$ ligand (2Bz39) had been formed (see Fig. 8(a)). In the resulting compound, the copper ion is coordinated in a distorted tetrahedral geometry with the tridentate ligand coordinating with the two benzothiazole nitrogen atoms and the central (inserted) sulphur atom. The mercaptobenzothiazole group is S-bonded and occupies the fourth position in the thione tautomeric form. The resulting complex with the formula $[Cu(2Bz38)(2Bz39)]^+$ is shown in Fig. 8(b).

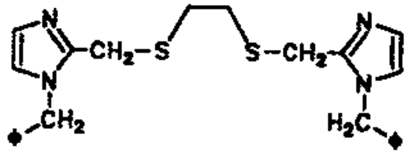
Summarizing, with the $N_2S$ ligands, five-coordinate copper compounds were encountered, with geometries varying from trigonal bipyramidal to square pyramidal. The fact that with $N_2S$ ligands and an extra sulphur donor atom the desired $N_2SS^*$ chromophore could be obtained is proven by the compound $[Cu(2Bz38)(2Bz39)](ClO_4)$.

4-Imidazolyl



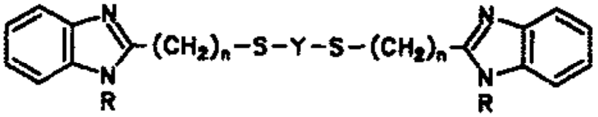
| Code | $n$ | $m$ | R | Ref. |
|---|---|---|---|---|
| 4Im12 | 1 | 2 | H | 17, 33, 38, 64, 65, 66, 83 |
| 4Im13 | 1 | 2 | $CH_3$ | 17, 64, 66 67, 68, 84 |
| 4Im14 | 1 | 3 | $CH_3$ | 16, 63, 85 |
| 4Im15 | 2 | 2 | H | 94 |

2-Imidazolyl



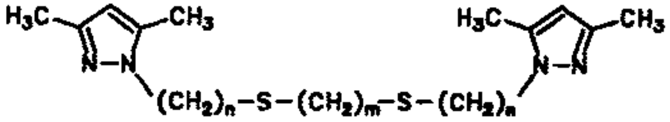
Code 2Im24 [19]

2-Benzimidazolyl*



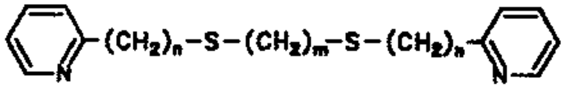
| Code | $n$ | R | Y | Ref. |
|---|---|---|---|---|
| 2Bz40 | 1 | H | $C_2H_4$ | 71, 86, 87, 88 |
| 2Bz41 | 1 | $CH_3$ | $C_3H_6$ | 63, 69 |
| 2Bz42 | 1 | H | $C_3H_6$ | 70, 87 |
| 2Bz43 | 1 | H | $o$-$C_6H_4$ | 72 |
| 2Bz44 | 2 | H | $C_2H_4$ | 89 |

1-Pyrazolyl

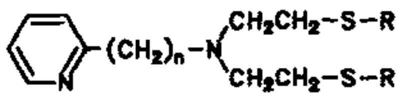


| Code | $n$ | $m$ | Ref. |
|---|---|---|---|
| 1Pz55 | 1 | 2 | 51 |
| 1Pz56 | 2 | 2 | 29, 76 |
| 1Pz57 | 2 | 3 | 73 |

2-Pyridyl



| Code | $n$ | $m$ | Ref. |
|---|---|---|---|
| 2Py69 | 1 | 2 | 33, 90 |
| 2Py70 | 1 | 3 | 33, 90 |
| 2Py71 | 2 | 2 | 82, 91, 95 |
| 2Py72 | 2 | 3 | 33, 90 |



| Code | $n$ | R | Ref. |
|---|---|---|---|
| 2Py73 | 1 | $CH_3$ | 77, 93 |
| 2Py74 | 1 | $CH_2CH_3$ | 78, 79, 95 |
| 2Py75 | 2 | $CH_2CH_3$ | 79, 80, 81 |

Fig. 9. Schematic drawing of the tetradentate chelating $N_2S_2$ ligands.

*Note: One tripod benzimidazole ligand has been presented [92,93], but no copper structure has been described.

## E. COMPLEXES CONTAINING TETRADENTATE $N_2S_2$ LIGANDS

As already stated, the main difficulty in modelling the active site of Type I copper proteins lies in incorporating the thiol group. In low molecular weight copper(II) compounds, a thiolate anion is rapidly oxidized to disulphide. Therefore, instead of a thiol group, a second thioether function is often introduced. A series of $N_2S_2$ ligands is shown in Fig. 9. Coordination distances of reported copper complexes with these ligands are given in Table 3.

A remarkable feature, when comparing Table 3 with Table 2, is the appearance of many compounds with trigonal bipyramidal geometry in this class of compounds, in contrast with the square pyramids encountered with the $N_2S$ ligands.

In our study on the 4-imidazolyl ligands 4Im12, 4Im13 and 4Im14 a surprising number of 'compressed' structures with inverted axial EPR spectra were obtained. The compound [Cu(4Im14)$Cl_2$] [16,63] is illustrative of this compressed octahedral series. In this compound the copper ion is coordinated to two imidazole nitrogen atoms at relatively short distances in the axial positions; the equatorial plane is formed by the two thioether sulphur atoms and the chloride ions at very long distances. In fact both the short Cu–N distances and the long equatorial Cu–S distances are the extremes in Table 3. A similar compressed octahedral geometry has been observed with the compound [Cu(4Im13)$Cl_2$] [64]. A projection of the structure of this compound is given in Fig. 10. A less-pronounced compression is observed in [Cu(4Im12)$(NO_3)_2$] [65].

Another geometry rendering inverted axial EPR spectra is the trigonal bipyramid. This geometry has been observed for [Cu(4Im13)Cl]Cl·$2H_2O$ [64]. In this structure the copper(II) ion is coordinated by the two imidazole nitrogen atoms in the axial positions. The trigonal plane is formed by the two thioether sulphur atoms and one of the chloride ions. The other chloride ion is involved in an extended hydrogen-bond network with the water molecules and the imidazole N–H hydrogen atoms. The projection of the cation $[Cu(4Im13)Cl]^+$ is redrawn in Fig. 11.

Interestingly, the ligand 4Im13 forms two different copper chloride compounds, each being very stable. The non-hydrated one forms a compressed octahedron with two coordinating chloride ions, which even crystallizes from 96% aqueous ethanol. The hydrated compound forms in aqueous ethanol when some water is added.

The trigonal bipyramidal geometry would be expected when a chloride–tetrafluoroborate mixed-anion compound is used. In the case of the ligand 4Im12 this indeed yields the compound [Cu(4Im12)Cl]$BF_4$ [66] in which the copper ion is in a geometry very much like the one shown in Fig. 11. However, with the ligand 4Im13, a third geometry has been found. In the

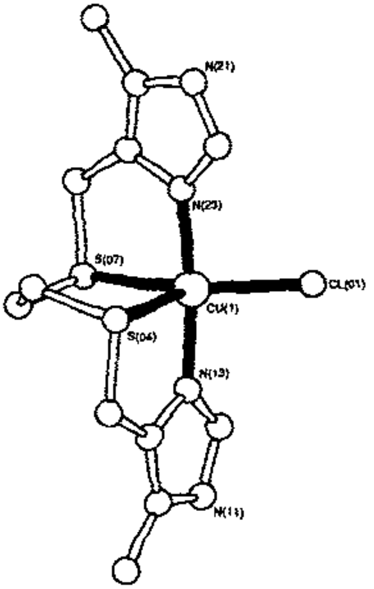


Fig. 11. Pluto projection of $[Cu(4Im13)Cl]^+$.

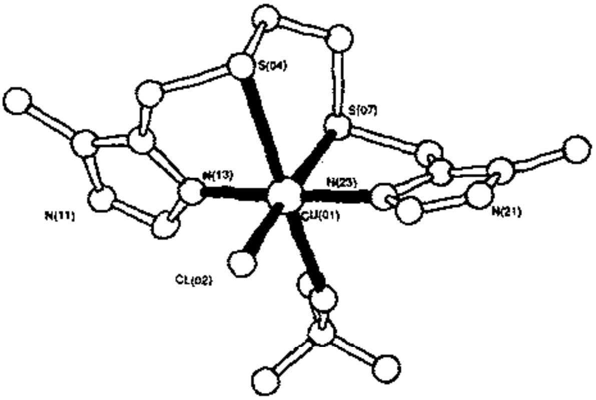


Fig. 12. Pluto projection of $[Cu(4Im13)Cl(BF_4)]$.

so far, the azole nitrogen atoms are coordinated in mutual trans positions. In $[Cu(2Bz41)(H_2O)](ClO_4)_2$ the trigonal plane is formed by one benzimidazole nitrogen, one thioether sulphur and the oxygen atom of the water molecule; the other benzimidazole nitrogen and thioether sulphur occupy the axial positions. The copper-to-sulphur distances are relatively short, although not the shortest reported in this table. A similar coordination geometry is found in $[Cu(1Pz57)(H_2O)](BF_4)_2$ [73].

With the ligand 2Bz42 a copper(I) complex has been structurally characterized [70]. The copper(I) ion is linearly coordinated by the two azole nitrogen atoms. The thioether sulphur atoms are regarded as non-bonding, not only because of the long Cu–S distances (which could still be regarded as bonding), but more because of the small Cu–S–C angles (which are 73.2° and 87.5°). This fact indicates that the lone pair of the thioether sulphur is not directed towards the copper ion. Cu–S–C angles in the range 90°–106°, being considerably larger than those in the present compound, have been reported for a complex structure in which the thioether sulphur atom is coordinating [74,75]. For instance, in $[Cu(4Im12)(NO_3)_2]$ the Cu–S–C angles are 97° [65], whereas our other compounds generally show values of $97° \pm 4°$, with almost no exceptions.

The ligand 1Pz56 forms two isomeric copper chloride compounds with formula $[Cu(1Pz56)Cl_2]$ [76]. In both isomeric forms the thioether sulphur atoms are non-coordinating, resulting in $CuN_2Cl_2$ chromophores, the one isomer being a distorted tetrahedron, the other having a distorted square planar geometry. The non-coordination of the thioether sulphur atoms was attributed to the larger chelate rings in this ligand, offering the sulphur atoms an "escape" from coordination.

In the pyridine $N_2S_2$ ligand series, tripod $NN^*S_2$ ligands were also designed for modelling the blue-copper site. These tripod ligands have been designed to impart pseudotetrahedral geometry upon metal ions. The tripod ligands shown in Fig. 9 demonstrate the influence of chelate ring size on the preference of the copper(II) ion for a certain five coordination. In those cases where a five-membered chelate ring is formed, as in $[Cu(2Py73)Br](ClO_4)$ [77] and in $[Cu(2Py74)(SO_4)]\cdot 7H_2O$ [78,79], trigonal bipyramidal geometry is obtained with the addition of a fifth ligand to the apical site trans to the amine nitrogen of the tripodal ligand. The trigonal plane is formed by the three pendent arms, i.e. the pyridine nitrogen and the two thioether sulphur atoms. When the chelate ring size increases to a six-membered chelate ring as in the ligand 2Py75, a square pyramidal geometry results as in $[Cu(2Py75)(NO_3)](NO_3)$ [79,80]. Once again, the fifth ligand is found trans to the amine nitrogen. The equatorial plane is now formed by the amine nitrogen, the pyridine nitrogen, the anion and one of the thioether sulphur atoms; the other sulphur atom occupies the apical position.

The copper(I) complexes of these tripod ligands are essentially geometrically identical and unaffected by ligand constraints. Both in $[Cu(2Py74)](BPh_4)$ [78,79] and in $[Cu(2Py75)](ClO_4)$ [81] the copper(I) ion is coordinated in a trigonal pyramidal geometry; the apical position is occupied by the amine nitrogen, and the trigonal plane is formed by the pendent arms.

With the open-chain $N_2S_2$ ligand 2Py71 both a copper(I) and a copper(II) complex have been reported. The structure of $[Cu(2Py71)(ClO_4)](ClO_4)$ [82] is essentially square pyramidal with the nitrogen and the sulphur donors of

TABLE 3

Relevant distances (Å) in copper complexes with the $N_2S_2$ ligands

| Compound | Ref. | Cu–N | Cu–S | Cu–X | Geometry |
|---|---|---|---|---|---|
| $[\mathrm{Cu(4Im12)(NO_3)_2}]$ | 65 | 1.933(4) | 2.495(1) | 2.280(3) | Octahedral |
| $[\mathrm{Cu(4Im13)Cl_2}]$ | 64 | 1.980(7) | 2.623(3) | 2.388(3) | Octahedral |
| | | 1.962(6) | 2.805(3) | 2.562(3) | |
| $[\mathrm{Cu(4Im13)Cl(BF_4)}]$ | 66 | 1.952(3) | 2.747(1) | 2.299(1) | Octahedral |
| | | 1.939(3) | 2.436(1) | 2.592(2) | |
| $[\mathrm{Cu(4Im13)(NCS)(NO_3)}]$ | 66 | 1.968(9) | 2.370(4) | 1.968(9) | Octahedral |
| | | 1.969(8) | 2.746(4) | 2.70(1) | |
| $[\mathrm{Cu_2(4Im13)(NCS)_3}]$[a] | 67, 68 | 1.968(3) | 2.426(1) | 2.002(4) | Octahedral |
| | | 1.972(3) | 2.814(1) | 2.395(4) | |
| $[\mathrm{Cu(4Im14)Cl_2}]$ | 16, 63 | 1.949(2) | 2.886(1) | 2.395(1) | Octahedral |
| | | 1.955(2) | 2.970(1) | 2.457(1) | |
| $[\mathrm{Cu(1Pz56)Cl_2}]$ | 76 | 2.002(9) | | 2.235(3) | Square planar |
| | | 2.026(9) | | 2.240(3) | |
| $[\mathrm{Cu(2Py71)(ClO_4)](ClO_4)}$ | 82 | 2.011(5) | 2.311(2) | 2.264(5) | Square pyramid |
| | | 2.008(5) | 2.316(2) | | |
| $[\mathrm{Cu(2Py75)(NO_3)](NO_3)}$ | 79, 80 | 2.031(5) | 2.334(2) | 1.991(4) | Square pyramid |
| | | 2.078(5) | 2.564(?) | | |
| $[\mathrm{Cu(4Im12)Cl](BF_4)}$ | 66 | 1.944(3) | 2.488(1) | 2.266(1) | Trigonal bipyramid |
| | | 1.956(3) | 2.534(1) | | |
| $[\mathrm{Cu(4Im13)Cl]Cl(H_2O)_2}$ | 64 | 1.945(2) | 2.5287(7) | 2.2864(7) | Trigonal bipyramid |
| | | 1.939(2) | 2.4621(7) | | |
| $[\mathrm{Cu(2Im24)Br]Br \cdot solvent}$ | 19 | 1.94(2) | 2.565(6) | 2.417(3) | Trigonal bipyramid |
| | | 1.93(2) | 2.470(6) | | |
| $[\mathrm{Cu(2Bz40)Cl]Cl.2EtOH}$ | 71 | 1.961(6) | 2.434(2) | 2.241(2) | Trigonal bipyramid |
| | | 1.968(6) | 2.561(2) | | |
| $[\mathrm{Cu(2Bz41)(H_2O)](ClO_4)_2}$ | 63, 69 | 1.997(4) | 2.328(1) | 2.225(4) | Trigonal bipyramid |
| | | 1.950(4) | 2.337(1) | | |
| $[\mathrm{Cu(2Bz43)(H_2O)](ClO_4)_2 \cdot 5EtOH}$ | 72 | 1.951(9) | 2.477(4) | 1.968(8) | Trigonal bipyramid |
| | | 1.945(9) | 2.450(4) | | |
| $[\mathrm{Cu(1Pz57)(H_2O)](BF_4)_2}$ | 73 | 2.00(1) | 2.366(6) | 2.17(1) | Trigonal bipyramid |
| | | 1.99(1) | 2.363(5) | | |
| $[\mathrm{Cu(2Py73)Br](ClO_4)}$ | 77 | 2.058(7) | 2.357(3) | 2.393(1) | Trigonal bipyramid |
| | | 2.037(6) | 2.473(3) | | |
| $[\mathrm{Cu(2Py73)I](ClO_4)}$ | 93 | 2.053(8) | 2.340(4) | 2.604(1) | Trigonal bipyramid |
| | | 2.052(9) | 2.452(4) | | |
| $[\mathrm{Cu(2Py74)](BPh_4)}$ | 78, 79 | 2.035(10) | 2.230(5) | | Trigonal pyramid[b] |
| | | 2.158(8) | 2.275(5) | | |
| $[\mathrm{Cu(2Py74)(SO_4)] \cdot 7H_2O}$ | 78, 79 | 2.021(5) | 2.385(1) | 1.909(4) | Trigonal bipyramid |
| | | 2.033(4) | 2.461(2) | | |
| $[\mathrm{Cu(1Pz56)Cl_2}]$ | 76 | 1.985(9) | | 2.228(3) | Distorted tetrahedral |
| $[\mathrm{Cu(2Bz42)](PF_6)_{0.66}(BF_4)_{0.33}}$ | 70 | 1.918(4) | 2.867(2) | | Linear[b] |
| $[\mathrm{Cu(2Py75)](ClO_4)}$ | 79, 81 | 2.000 | 2.247 | | Trigonal pyramid[b] |
| | | 2.192 | 2.343 | | |
| $[\mathrm{Cu(2Py71)](ClO_4)}$ | 82 | 2.042(5) | 2.345(1) | | Tetrahedral[b] |

[a] Mixed-valence compound, distances are only given for the copper(II) coordination sphere.
[b] Copper(I) compound.

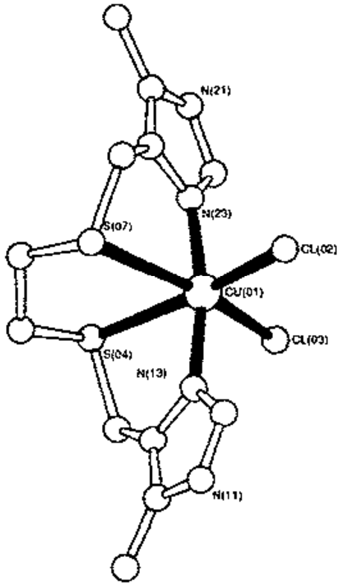


Fig. 10. Pluto projection of [Cu(4Im13)$Cl_2$].

compound [Cu(4Im13)Cl($BF_4$)] [66] the tetrafluoroborate anion is also coordinated to the copper ion. The copper ion has an elongated octahedral geometry, with the imidazole nitrogen atoms, the chloride ion and one of the thioether sulphur atoms in the equatorial plane at relatively short distances. The axial positions of the octahedron are occupied by the other thioether sulphur and the tetrafluoroborate anion at relatively long distances. A projection of the compound is redrawn in Fig. 12.

Especially noteworthy is the fact that the very symmetric ligand is coordinated in an asymmetric fashion in this compound, with one thioether at a short distance, the other at a rather long coordinating distance. Such an asymmetric binding mode of the ligand was also observed in the other elongated octahedral complexes, namely [Cu(4Im13)NCS($NO_3$)] [66] and the mixed-valence compound [$Cu_2$(4Im13)$(NCS)_3$] [67,68]. The origin for this asymmetry seems to be related to the fact that the two additional ligands have quite different donor properties. As a result the ligands trans to these ligands also "behave" asymmetrically (trans effect), which apparently is allowed by the flexibility of the copper(II) coordination sphere.

With the 2-imidazolyl ligand 2Im24 [19], the benzimidazolyl ligands 2Bz40, 2Bz41 and 2Bz43 [69,71,72], copper(II) also forms trigonal bipyramidal structures. In this series the compound [Cu(2Bz41)($H_2O$)]$(ClO_4)_2$ [63,69] is unusual, because here the benzimidazole nitrogen atoms are coordinated in cis positions relative to each other. In all structures discussed

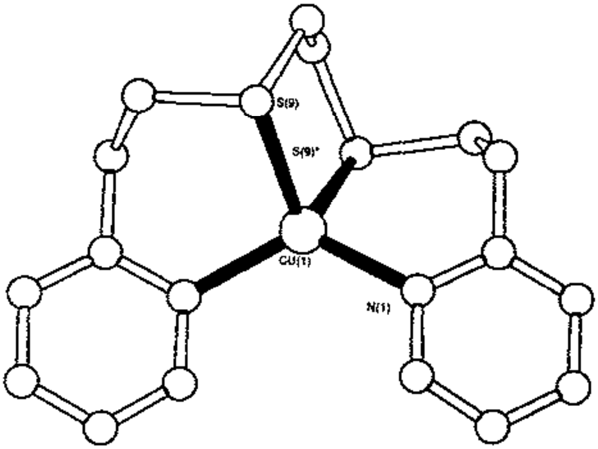


Fig. 13. Pluto projection of $[Cu(2Py71)]^+$ based on the atomic coordinates as determined by Brubaker et al. [82].

the ligand occupying the basal plane and a perchlorate oxygen bound to the apex. The copper(I) ion in $[Cu(2Py71)](ClO_4)$ [82] shown in Fig. 13 is tetrahedrally (distorted) coordinated by the ligand with average Cu–N and Cu–S distances. The coordination angles vary between 92.4° and 121.6° causing the main distortion from tetrahedral. This is due to the limited bite between the two sulphur atoms which form a five-membered chelate ring.

In summary, mainly pentacoordinate or hexacoordinate copper compounds are formed with the tetradentate $N_2S_2$ ligands. For these ligands which can only form five-membered chelate rings, this is not surprising, because of the large constraints within the ligand. However, with the ligands which can form six-membered chelate rings, five-coordinate compounds are also observed [82]. In the few four-coordinate copper(II) complexes (distorted square planar and distorted tetrahedral [76]), the sulphur atoms are not coordinated to the copper ion, resulting in $CuN_2Cl_2$ chromophores.

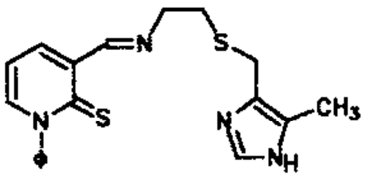
## F. COMPLEXES CONTAINING NN*SS⁻ LIGANDS

For the design of model compounds for blue-copper proteins, ideally one should use two imidazole nitrogen atoms, a thioether sulphur and a thiolate sulphur. The ligands discussed so far only contain thioether sulphur: it has already been stated that the incorporation of a thiolate sulphur is rather difficult, because of its easy oxidation to disulphide particularly in the presence of copper(II) species. For the modelling strategy, the $N_2S$ ligands in combination with a thiol group as anion could be the best hit. To prevent oxidation of the thiol group to disuphide, either the ligand should contain some bulky groups protecting the thiol function, or the thiol function must be electronically constrained. Some groups have succeeded in designing asymmetric tetradentate ligands with a thiolate function incorporated in the ligand. Some of these ligands are included in Fig. 14.

Casella et al. [96] have prepared a series of benzimidazole-containing ligands; these ligands contain a pyridine–thione functional group as the thiolate donor (2Bz45). The second imidazole nitrogen, needed for the blue-copper models, had to be replaced with an imino group. Unfortunately, no crystal structures are described with these ligands. The copper(II) compounds with these ligands are not very stable, at best they are stable in non-aqueous solvents for a few minutes in cyclic voltammetric measurements [8]. Spectroscopy showed that these copper compounds in solution adopted square planar or five-coordinate geometry.

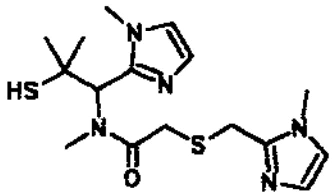
With the ligand 4Im11 (see Section D, $N_2S$ ligands) a similar ligand, also containing a pyridine–thione group, was prepared [97]. While the free

4-Imidazolyl



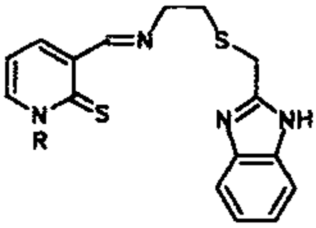
4Im16

2-Imidazolyl



2Im25

2-Benzimidazolyl



2Bz45

Fig. 14. Schematic drawing of the ligands discussed in Section F. R in ligand 2Bz45 denotes various substituents. Similar ligands with varying chain lengths have been described [96].

ligand 4Im16 exhibits typical thione character, it is bound to copper in its tautomeric thiolate form. The spectroscopic properties of [Cu(4Im16)] ($ClO_4$) indicate an approximate tetragonal stereochemistry. The stability of this copper(II) thiolate system is very high: solutions of [Cu(4Im16)]($ClO_4$) gave unchanged spectra after having been stored for one week. Unfortunately, no single crystals could be obtained with this type of ligand. These pyridine–thione ligands provide a useful source of thiolate ligands to form rather stable copper(II) thiolate complexes.

An extremely interesting $N_2SS^*$ ligand is 2Im25, as shown in Fig. 14 [98]. The potentially tetradentate ligand contains two 2-imidazolyl groups, one thioether and a thiolate group. The thiol sulphur atom is sterically hindered by two methyl groups to reduce the rate of disulphide formation when copper(II) is coordinated. With copper(II) a blue–green solid could be obtained. In this compound the copper ion is not in (distorted) tetrahedral coordination, but has a tetragonal geometry in a polymeric structure. The compound was not very stable in solution: even at −60°C in acetonitrile the copper ion is reduced, so that extinction coefficients were not obtained. Unfortunately, the copper(I) coordination complexes with this ligand are ill-defined oligomeric compounds. Cobalt(II) complexes with this ligand, however, showed similar spectroscopic features as the cobalt-substituted plastocyanin. Unfortunately no suitable crystals for X-ray crystallography, not even for the cobalt compound, could be obtained. Groups bulkier than methyl groups seem to be needed to slow down further the oxidation of the thiol group in this (and similar) ligands.

## G. PHYSICAL STUDIES

The Type I copper ions which occur in the so-called "blue-copper proteins" have unique spectroscopic properties. Most striking is the intense blue colour: the molar extinction may exceed 3000 L $mol^{-1}$ $cm^{-1}$ near 600 nm, which is at least ten times the extinction of a *d–d* transition in a normal copper coordination compound. This transition is ascribed to a thiolate sulphur-to-copper charge transfer transition [99]. Another characteristic feature is encountered in the EPR spectra: an extraordinarily small hyperfine splitting constant ($A_\parallel$) of $(50–90) \times 10^{-4}$ $cm^{-1}$ is observed. The third unique feature of these proteins is the rather high Cu(II)/Cu(I) reduction potential (from 0 to +0.6 V vs. standard calomel electrode (SCE) [100]). If one considers that the aqua copper(II/I) couple is located at −0.08 V(SCE), it can be deduced that in the blue-copper proteins the access to the copper(I) state is markedly facilitated.

An extended account of the redox changes in copper complexes with $N_2S_2$

donor sets has been given by Zanello [8]. Zanello states that many $CuN_2S_2$ complexes constitute valid models of blue-copper proteins because they display high reduction potentials. The high reduction potentials appear to originate from the thioether sulphur atoms. However, Karlsson et al. recently established that replacing the methionine by leucine in azurin, the typical blue-copper spectroscopic features were not altered [101].

Nickles et al. [90] compared the redox potentials of some $Cu(Py)_2N_2$ complexes with the analogous $Cu(Py)_2S_2$ compounds (with $Py_2S_2$ =2Py69–2Py72, see Fig. 9). The redox potentials for the $Py_2S_2$ series spanned a range ($E^{0\prime} = +400$ to $+600$ mV vs. normal hydrogen electrode (NHE) substantially higher than those exhibited by the $Py_2N_2$ series ($E^{0\prime} = -170$ to $+320$ mV(NHE)). The substitution of two thioether donors for two amine donors produced an increase in $E^{0\prime}$ of 300–700 mV in pairs of $Py_2S_2$ and $Py_2N_2$ complexes with the same chelate ring sizes. The reduction potentials for both series increase with increasing chelate ring size, suggesting that the larger chelate rings can more readily accommodate a pseudotetrahedral copper(I) form.

Similar results were obtained with benzimidazole–thioether ligands [102].

$Cu(2Py71)(ClO_4)_2$ exhibits a rather high redox potential (+557 mV (NHE)) and a rather small hyperfine splitting constant ($A_{\parallel} = 67 \times 10^{-4}$ cm$^{-1}$) in a frozen solution [82], but the extinction coefficient at $\lambda_{max} = 605$ nm is only 510 L mol$^{-1}$ cm$^{-1}$.

The spectroscopic properties of most of the low molecular weight model compounds described here are comparable to those of the so-called normal copper species. The sulphur-to-copper charge transfer transition only appears at higher energies (below 380 nm). Azole-to-copper charge transfer transitions also appear in this region. Around 600 nm normal *d–d* transitions are observed, although some complexes have rather high extinction coefficients ($\varepsilon$ in the range of 800 L mol$^{-1}$ cm$^{-1}$) [22].

The EPR spectra of most compounds are typical of tetragonal copper complexes ($g_{\parallel} > g_{\perp} > 2.0$, $A_{\parallel} = 110$–$200$ G). Some of the imidazole–thioether ligands enforce a compressed geometry upon the copper ions, resulting in inversed axial EPR spectra [63–65,71]. "Not surprisingly, the majority of these approaches failed to produce electronic properties remotely comparable to the unique properties of the biological system." [103].

## H. CONCLUSIONS

The structures described in this review give a clear demonstration of the flexibility of the geometries around the copper ion (the so-called plasticity). The copper(II) ion in compounds with azole–thioether ligands is either five-or six-coordinate. Square pyramidal, trigonal bipyramidal and intermediate five coordination is encountered. In the six-coordinate compounds one observes compressed octahedral geometry with four soft donor atoms in the equatorial plane and two strong axial donors, as well as elongated octahedral geometry with four strong donor atoms in the equatorial plane and two weak axial donors.

The $N_xS_y$ ligands described in this review have many common characteristics. In all these ligands the hard nitrogen donor atoms and the soft sulphur donor atoms are arranged in such a way that the sulphur atom is forced towards the copper ion, in spite of the weaker coordinating ability of sulphur to copper(II). Owing to the chelating effect the sulphur atom is sometimes coordinated at a rather short distance. Remarkable in this respect is the tight coordination of the thioether sulphur atom in the bidentate NS ligands.

With the ligand 1Pz56 (Fig. 9), the sulphur atoms were not coordinated to the copper ion, resulting in $CuN_2Cl_2$ chromophores [76]. This phenomenon was attributed to the larger chelate rings in this ligand, the flexibility offering the sulphur atoms an "escape" from coordination to the copper(II) ion. However, the ligand 2Py71, which has a flexibility similar to that of the ligand 1Pz56, nevertheless coordinates with the sulphur atoms to the copper(II) ion at rather short distances [82].

A complete model system for a blue-copper protein has not yet been prepared, and most probably is still far away. It has been shown that the high redox potential of the blue-copper site is not the biggest problem to model [8]. This high redox potential is easily obtained when sulphur donor atoms are inserted into the ligand. The small hyperfine splitting constant and the intense absorption in the visible region are more difficult to obtain in low molecular weight model compounds. Some groups claim to have obtained such spectroscopic features on model systems in solution, but those observations were described only for extremely low temperatures: at higher temperatures reduction of the copper(II) ion occurs.

For the ideal model system for Type I proteins, more effort should be put in the design and synthesis of chelating ligands with a severely protected thiol group.

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