# A Route to Bis(benzimidazole) Ligands with Built-In Asymmetry: Potential Models of Protein Binding Sites Having Histidines of Different Basicity

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A synthetic strategy has been developed for bis(benzimidazole) ligands in which the two halves are different (**4**−**11**), and consequently of different basicity, which could be important for biomimicry and metal ion transport. Their coordination chemistry toward copper(II) has been studied in the solid state via X-ray crystallography. The ligands were complexed with copper(II) bromide and perchlorate salts to yield complexes of a 1:1 stoichiometry. Crystal structures have been determined and compared for [Cu(**4**)(NCCH$_3$)(OH$_2$)](ClO$_4$)$_2$ (complex **A**, [$C_{20}H_{23}$-$CuN_5O_2$](ClO$_4$)$_2$, monoclinic, space group $P2_1/c$, $a$ = 10.2168(7) Å, $b$ = 30.740(2) Å, $c$ = 8.3403(6) Å, $\beta$ = 105.960(2)°, $V$ = 2518.4(3) Å$^3$, $Z$ = 4), [Cu(**6**)Br$_2$]·DMF (complex **B**, [$C_{17}H_{16}Br_2CuN_4O$]·$C_3H_7NO$, monoclinic, space group $P2_1/c$, $a$ = 8.3348(11) Å, $b$ = 18.165(2) Å, $c$ = 14.140(2) Å, $\beta$ = 91.646(3)°, $V$ = 2140.0(5) Å$^3$, $Z$ = 4), [Cu(**8**)Br$_2$]·DMF·H$_2$O (complex **C**, [$C_{16}H_{13}Br_2CuN_5O_3$]·$C_3H_7NO$·$H_2O$, monoclinic, space group $P2_1/c$, $a$ = 8.7241(10) Å, $b$ = 18.172(2) Å, $c$ = 14.506(2) Å, $\beta$ = 97.376(2)°, $V$ = 2280.7(4) Å$^3$, $Z$ = 4), [Cu(**3**)Br$_2$]·MeOH (complex **D**, [$C_{16}H_{14}Br_2CuN_4O$]·$CH_4O$, orthorhombic, space group *Pbca*, $a$ = 14.325(2) Å, $b$ = 13.919(2) Å, $c$ = 18.837(2) Å, $V$ = 3756.0(9) Å$^3$, $Z$ = 8), [Cu(**4**)Br$_2$]·MeOH (complex **E**, [$C_{18}H_{18}Br_2CuN_4O$]·$CH_4O$, triclinic, space group $P\bar{1}$, $a$ = 7.3120(11) Å, $b$ = 9.9460(15) Å, $c$ = 15.189(2) Å, $\alpha$ = 87.476(4)°, $\beta$ = 89.093(4)°, $\gamma$ = 68.673(3)°, $V$ = 1028.0(3) Å$^3$, $Z$ = 2), and Cu(**10**)Br$_2$ (complex **F**, $C_{16}H_{13}Br_2CuN_3OS$, monoclinic, space group $P2_1/c$, $a$ = 7.3130(9) Å, $b$ = 15.861(2) Å, $c$ = 14.846(2) Å, $\beta$ = 98.318(2)°, $V$ = 1704.0(4) Å$^3$, $Z$ = 4). The Cu(II) complexes were found to be five coordinate, lying between perfect square-based-pyramidal (SBP) and trigonal-bipyramidal (TBP) extremes; in each case the ligands act as tridentate donors coordinating through the pyridine-like nitrogens of the benzimidazole moieties and the ether donor atom of the linking bridge. Use of the structural index parameter ($\tau$) for five-coordinate metal complexes indicated that all the copper(II) complexes exhibit a greater tendency toward square-based-pyramidal geometry (i.e. $\tau < 0.5$). Comparison of the symmetrical bis(benzimidazole) complex with the other, asymmetric, complexes revealed no significant change in the geometrical parameters around the copper(II) ion consequent on introduction of asymmetry and a change of pKa within the bis(benzimidazole) fragment. The degree of hydrogen bonding, solvent of crystallization, and the nature of the anion have a greater impact on the geometrical parameters and coordination environment of the copper(II) ion. The import for biological metal coordination is considered.

## Introduction

In many catalytic sites of enzymes are found histidines arranged to have different basicities,[1] which can either donate or accept protons and/or coordinate metal ions to facilitate relevant reactions under catalysis,[2] for example zinc carbonic anhydrase or superoxide dismutase. In biomimicry model enzymes (e.g. cyclodextrins[3] with two imidazoles in the cavity), and poly(benzimidazoles)[4] have been favorite targets to simulate the imidazoles of catalytic enzymes. Many bis- and poly-(benzimidazoles) with two or more equivalent imidazole rings have been synthesized and examined in this context.[5] We have now developed a synthetic strategy to form bis(benzimidazoles) in which the two halves are different, and consequently of different basicity, which could be important for biomimicry. We have also synthesized mono-N-alkylated bis(benzimidazoles) (R = alkyl, R′ = H), again having the two halves of different basicity but lacking the prototropy on one subunit. The new synthetic route also led to ligands which have a benzimidazole fragment on one side and the much less basic 5-nitrobenzimidazole or benzothiazole fragment on the other side. These ligands (Table 1) are described in this paper. The potential for asymmetry in the interaction of these new ligands with copper(II) has been examined by X-ray crystallography and by UV−vis spectrometry in solution, and the importance of the results to interpretation of biological metal sites is discussed.

## Experimental Section

Reagents and solvents used were of commercially available reagent grade quality. ***Caution***! Shock sensitivity of the perchlorate complexes synthesized has not been observed, but care should be taken to prevent explosion. $^1$H and $^{13}$C NMR spectra were obtained on a Bruker WP200 spectrometer ($^1$H at 200.13 MHz; $^{13}$C at 50.32 MHz). Elemental analysis was performed on a Carlo Erba 1106 elemental analyzer; fast atom bombardment and electron impact mass spectrometry were run on a KRATOS MS80 RF instrument. UV−vis solution spectra were recorded in methanol with a Perkin-Elmer 550S instrument and IR spectra were run (KBr disk) on a Nicolet 20 PC-IR spectrometer.

Labeling for the $^1$H and $^{13}$C NMR assignments is shown in Figure 1.

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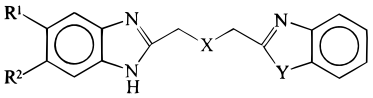
**Table 1.** Ligands **1**−**11**

| ligand | X | Y | $R^1$ | $R^2$ |
|---|---|---|---|---|
| **1a**[a] | S | | | |
| **1b** | S | | | |
| **2**[a] | O | | | |
| **3**[b] | O | NH | H | H |
| **4** | O | NH | $CH_3$ | $CH_3$ |
| **5** | S | NH | $CH_3$ | $CH_3$ |
| **6** | O | N-$CH_3$ | H | H |
| **7** | S | N-$CH_3$ | H | H |
| **8** | O | NH | $NO_2$ | H |
| **9** | O | NH | $CF_3$ | H |
| **10** | O | S | H | H |
| **11** | S | S | H | H |

[a] As hydrochloride. [b] The symmetrical bis(benzimidazole) was prepared as previously described



**Preparation of Ligands 1−11. 4-(2-Benzimidazolyl)-3-thiabutanoic Acid (1a).** The benzimidazole acids were prepared by a modified literature method.[6] To a refluxing solution of 6 M HCl (350 mL) containing thiodiglycolic acid (62.25 g, 0.414 mol) was added *o*-phenylenediamine (22.91 g, 0.212 mol) in a solution of 4 M HCl (140 mL) dropwise. [Half the volume (70 mL) was added immediately over a period of 90 min and the remainder 16 h later in the same fashion.] The green acidic solution was allowed to reflux for a total of 72 h and allowed to cool to room temperature. A green precipitate (A) formed overnight at room temperature and was filtered and dried. The remaining filtrate was reduced in volume (*ca.* 300 mL) and cooled to −20 °C overnight; the resulting precipitate (B) was filtered and dried. Precipitate A was dissolved using the residual filtrate and made up to a total volume of *ca.* 400 mL with distilled water. The solution was stirred at 5 °C and basified with 0.880 ammonia solution slowly until the pH of the solution was strongly alkaline, pH 9, when a fawn-colored precipitate formed, which was filtered and dried. This step removed the unwanted fully condensed bis(benzimidazole) byproduct. The temperature of the filtrate was maintained at 5 °C and concentrated HCl was added slowly until pH 7. The solution was stirred rapidly at this stage and after 20 min a white precipitate formed (if no precipitate formed at this stage the volume was reduced until the first signs of precipitation). The solution was left at −20 °C overnight and filtered, then washed with cold water and finally diethyl ether to yield the zwitterion as a pure white solid. Overall yield: 44%, see **1b**. Mp: 186 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta_H$ 3.50 (s, 2H, C$H_2$COO), 4.14 (s, 2H, Bzm−C$H_2$), 6.78 (br s, N*H* in exchange with solvent), 7.21−7.29 [m, 2H, Ar (5/6, half of AA′BB′)], 7.56−7.66 [m, 2H, Ar (4/7, half of AA′BB′)]. $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta_C$ 171.6 (C═O), 152.0 (2), 138.8 (8/9), 122.1 (5/6), 115.1 (4/7), 34.1 (Bzm−*C*$H_2$), 28.9 (*C*$H_2$COO). $\upsilon_{max}$/cm$^{-1}$ (KBr disk): broad absorption 3200−2800, 1670 s. FAB-MS: *m/z* (assignment, relative intensity): 223 ($MH^+$, 70%). Anal. Calcd for $C_{10}H_{10}N_2O_2S\cdot 1H_2O$: C, 50.0; H, 5.0; N, 11.7. Found: C, 50.2; H, 4.9; N, 11.5.

**4-(2-Benzimidazolyl)-3-thiabutanoic Acid Hydrochloride (1b).** The pure hydrochloride was obtained by recrystallizing the Precipitate B obtained as above from 6 M HCl to give a pale green powder. Yield: 20.56 g, 44%. Mp: 177 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta_H$ 3.71 (s, 2H, C$H_2$COO), 4.50 (s, 2H, Bzm−C$H_2$), 7.58−7.66 [m, 2H, Ar (5/6, half of AA′BB′)], 7.81−7.92 [m, 2H, Ar (4/7, half of AA′BB′)]. $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta_C$ 171.1 (C═O), 151.9 (2), 131.1 (8/9), 126.1 (5/6), 114.3 (4/7), 34.7 (Bzm−*C*$H_2$), 26.4 (*C*$H_2$-COO). $\upsilon_{max}$/cm$^{-1}$ (KBr dis;): 3441 s (br), 1776 s (sh). FAB-MS: *m/z* (assignment, relative intensity) 223 ($MH^+$ − HCl, 90%). Anal. Calcd for $C_{10}H_{10}N_2O_2S_1\cdot$HCl: C, 46.4; H, 4.1; N, 10.8. Found: C, 46.7; H, 4.1; N, 10.8.

**4-(2-Benzimidazolyl)-3-oxabutanoic Acid Hydrochloride (2).** The pure hydrochloride was obtained as above to yield a green crystalline material. Yield: 22.67 g, 44%. Mp: 203 °C. $^1$H NMR (200 MHz, $D_2O$): $\delta_H$ 4.35 (s, 2H, C$H_2$COO), 5.00 (s, 2H, Bzm−C$H_2$), 7.32−7.40 [m, 2H, Ar (5/6, half of AA′BB′)], 7.43−7.51 [m, 2H, Ar (4/7, half of AA′BB′)]. $^{13}$C NMR (50 MHz, $D_2O$): $\delta_C$ 174.9 (C═O), 150.6 (2), 131.5 (8/9), 127.7 (5/6), 115.0 (4/7), 69.7 (Bzm−*C*$H_2$), 64.8 (*C*$H_2$-COO). $\upsilon_{max}$/cm$^{-1}$ (KBr disk): 3441 s (br), 1769 s (sh). FAB-MS: *m/z* (assignment, relative intensity) 206 ($MH^+$ − HCl, 90%). Anal. Calcd for $C_{10}H_{10}N_2O_3\cdot$HCl$\cdot H_2O$: C, 46.1; H, 5.0; N, 10.8. Found: C, 45.8; H, 5.1; N, 10.7.

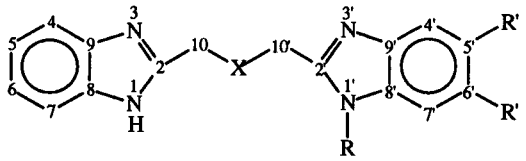


**Figure 1.** Labeling for the $^1$H and $^{13}$C NMR assignments.

Ligand **3** was prepared as previously described.[7]

Ligands **4**−**9** were synthesized via the Phillips[8] condensation reaction from the appropriate benzimidazole monoacid, **1**, **1b**, or **2** and the required *o*-phenylenediamine. The final products were recrystallized from ethanol after treatment with charcoal and addition of water to the cold filtered ethanolic solution.

**Preparation of 1-(5,6-Dimethylbenzimidazolyl)-3-benzimidazolyl-2-oxapropane (4).** The preparation from 4-(2-benzimidazolyl)-3-oxabutanoic acid hydrochloride (**2**) (5.29 g, 21.86 mmol) with added 4,5 dimethyl-*o*-phenylenediamine (2.98 g, 21.86 mmol) gave a white powder. Yield: 4.20 g, 63%. Mp: 207 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta_H$ 2.39 [s, 6H, 2 × C$H_3$ (R′)], 4.97 (s, 2H, C$H_2$−O), 4.98 (s, 2H, C$H_2$-O), 5.93 (br s, N*H* in exchange with solvent), 7.28−7.32 [m, 2H, Ar (5/6, half of AA′BB′)], 7.46 [s, 2H, Ar (4′/7′)], 7.65−7.70 [m, 2H, Ar (4/7, half of AA′BB′)]. $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta_C$ 151.3 (2), 150.2 (2′), 138.7 (8/9), 136.8 (8′/9′), 130.9 (5/6), 122.2 (5′/6′), 115.4 (4/7), 115.3 (4′/7′), 66.3 (O−*C*$H_2$), 66.2 (*C*$H_2$−O), 20.3 [*C*$H_3$ (R′)]. FAB-MS: *m/z* (assignment, relative intensity) 307 ($MH^+$, 30%). Anal. Calcd for $C_{18}H_{18}N_4O_1\cdot 1H_2O$: C, 66.7; H, 6.2; N, 17.3. Found: C, 66.5; H, 6.0; N, 17.2.

**Preparation of 1-(5,6-Dimethylbenzimidazolyl)-3-benzimidazolyl-2-thiapropane (5).** The preparation from 4-(2-benzimidazolyl)-3-thiabutanoic acid hydrochloride (**1b**) (5.01 g, 19.41 mmol) with added 4,5-dimethyl-*o*-phenylenediamine (2.64 g, 19.38 mmol) gave a white powder. Yield: 4.56 g, 73%. Mp: 254 °C;.$^1$H NMR (200 MHz, DMSO-$d_6$): $\delta_H$ 2.39 [s, 6H, 2 × C$H_3$ (R′)], 4.14 (s, 2H, C$H_2$−S), 4.15 (s, 2H, C$H_2$−S), 6.50 (br s, N*H* in exchange with solvent), 7.23−7.31 [m, 2H, Ar (5/6, half of AA′BB′)], 7.40 [s, 2H, Ar (4′/7′)], 7.60−7.68 [m, 2H, Ar (4/7, half of AA′BB′)]. $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta_C$ 152.0 (2), 150.9 (2′), 139.0 (8/9), 137.5 (8′/9′), 130.4 (5/6), 122.0 (5′/6′); 115.3 (4/7), 115.2 (4′/7′), 29.1 (S−*C*$H_2$), 29.0 (*C*$H_2$−S), 20.3 [*C*$H_3$ (R′)]. FAB-MS: *m/z* (assignment, relative intensity) 323 ($MH^+$, 30%). Anal. Calcd for $C_{18}H_{18}N_4S_1$: C, 67.1; H, 5.6; N, 17.4. Found: C, 67.0; H, 5.5; N, 17.5.

**Preparation of 1-(*N*-Methylbenzimidazolyl)-3-benzimidazolyl-2-oxapropane (6).** The preparation from 4-(2-benzimidazolyl)-3-oxabutanoic acid hydrochloride (**2**) (3.16 g, 13.09 mmol) with added *N*-methyl-*o*-phenylenediamine (1.60 g, 13.09 mmol) gave a white powder. Yield: 4.28 g, 89%. Mp: 258 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta_H$ 3.95 [s, 3H, C$H_3$ (R)], 4.92 (s, 2H, C$H_2$−O), 5.02 (s, 2H, O−C$H_2$), 7.24−7.43 [m, 4H, Ar (5/5′/6/6′)], 7.62−7.77 [m, 4H, Ar (4/4′/7/7′)]. $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta_C$ 151.1 (2), 150.8 (2′), 142.1 (9′),† (9),† (8), 136.4 (8′), 122.9 (5/6), 122.1 (5′), 121.9 (6′), 119.6 (4′),† (4),† (7), 110.6 (7′), 66.0 (O-*C*$H_2$), 64.9 (*C*$H_2$-O), 30.2 [*C*$H_3$ (R)]. FAB-MS: *m/z* (assignment, relative intensity) 293 ($MH^+$, 30%). Anal. Calcd for $C_{17}H_{16}N_4O\cdot H_2O$: C, 65.8; H, 5.9; N, 18.1. Found: C, 66.1; H, 5.8; N, 18.0

**Preparation of 1-(*N*-Methylbenzimidazolyl)-3-benzimidazole-2-thiapropane (7).** The preparation from 4-(2-benzimidazolyl)-3-thiabutanoic acid hydrochloride (**1b**) (2.00 g, 7.73 mmol) with added *N*-methyl-*o*-phenylenediamine (0.94 g, 7.73 mmol) gave a white powder. Yield: 2.05 g, 86%. Mp: 201 °C. $^1$H NMR (200 MHz,

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DMSO-$d_6$): $\delta_H$ 3.89 [s, 3H, C$H_3$ (R)], 4.12 (s, 2H, C$H_2$−S), 4.31 (s, 2H, S−C$H_2$), 7.29−7.33 [m, 4H, Ar (5/5′/6/6′)], 7.62−7.70 [m, 3H, Ar (4/4′/7)], 7.80−7.85 [m, 1H, Ar (7′)]. $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta_C$ 151.8 (2), 151.4 (2′), 142.2 (9′),† (9),† (8), 136.2 (8′), 122.4 (5/6), 121.8 (5′), 121.8 (6′), 118.9 (4′),† (4),† (7), 110.1 (7′), 30.1 (S−*C*$H_2$), 27.4 (S−*C*$H_2$), 20.6 [*C*$H_3$ (R)]. FAB-MS: *m/z* (assignment, relative intensity) 309 ($MH^+$, 25%). Anal. Calcd for $C_{17}H_{16}N_4S\cdot H_2O$: C, 62.6; H, 5.6; N, 17.2. Found: C, 62.6; H, 5.4; N, 17.5.

**Preparation of 1-(5-Nitrobenzimidazolyl)-3-benzimidazolyl-2-oxapropane (8).** The preparation from 4-(2-benzimidazolyl)-3-oxabutanoic acid hydrochloride (**2**) (2.55 g, 10.54 mmol) with added 4-nitro-*o*-phenylenediamine (1.61 g, 10.54 mmol) gave a cream-colored powder. Yield: 2.20 g, 65%. Mp: 106 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta_H$ 3.55 (br s, N*H* in exchange with solvent), 5.01 (s, 2H, C$H_2$−O), 5.05 (s, 2H, O−C$H_2$), 7.25−7.30 [m, 2H, Ar (5/6, half of AA′BB′)], 7.64−7.68 [m, 2H, Ar (4/7, half of AA′BB′)], 7.80−7.84 [d, 1H, (4′)], 8.19−8.25 [d, 1H, (5′)], 8.55 [s, 1H, (7′)]. $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta_C$ 158.6 (2/2′), 151.1 (9/9′), 142.9 (8/8′), 122.2 (5/6), 118.05 (5′/6′), 115.4 [4/4′/7/7′ (in slow exchange)], 66.6 (O−*C*$H_2$), 66.2 (*C*$H_2$−O); FAB-MS: *m/z* (assignment, relative intensity) 324 ($MH^+$, 95%). Anal. Calcd for $C_{16}H_{13}N_5O_3\cdot 2H_2O$: C, 53.5; H, 4.8; N, 19.5. Found: C, 53.6; H, 4.5; N, 19.4.

**Preparation of 1-((5-trifluoromethyl)benzimidazolyl)-3-benzimidazolyl-2-oxapropane (9).** The preparation from 4-(2-benzimidazolyl)-3-oxabutanoic acid hydrochloride (**2**) (2.54 g, 10.50 mmol) with added 3,4-diaminobenzotrifluoride (1.85 g, 10.50 mmol) gave a white powder. Yield: 0.31 g, 10%. Mp: 230 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta_H$ 5.00 (s, 2H, C$H_2$−O), 5.03 (s, 2H, O−C$H_2$), 6.30 (br s, N*H* in exchange with solvent), 7.27−7.34 [m, 2H, Ar (5/6, half of AA′BB′)], 7.59−7.70 [m, 3H, Ar (4/4′/7),], 7.83−7.87 [d, 1H, (5′)], 8.02 [s, 1H, (7′)]. $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta_C$ 154.6 (2/2′), 151.1 (9/9′), 138.6 (8/8′), 122.3 (5/6), 118.9 (5′/6′), 115.3 (*C*$F_3$), 113.5 [(4/4′/7/7′)], 66.4 (O−*C*$H_2$), 66.3 (*C*$H_2$−O). FAB-MS: *m/z* (assignment, relative intensity) 347 ($MH^+$, 20%). Anal. Calcd for $C_{17}H_{13}F_3N_4O\cdot H_2O$: C, 56.0; H, 4.2; N, 15.4. Found: C, 56.0; H, 4.2; N, 15.6.

Ligands **10** and **11** were synthesized via the method of Rai and Braunwarth.[9]

**Preparation of Benzimidazolyl-3-benzothiazolyl-2-oxapropane (10).** Poly(phosphoric acid) (25 mL) was heated with efficient stirring (*ca.* 100 °C). 4-(2-Benzimidazole)-3-oxabutanoic acid hydrochloride (**2**) (4.846 g, 20.02 mmol) and *o*-aminothiophenol (2.521 g, 20.02 mmol) were mixed and added to the polyphosphoric acid. The temperature was raised to 140 °C and maintained, with efficient stirring for 4 h, or until the reaction ceased. The reaction mixture was allowed to cool to room temperature and poured onto vigorously stirred water (200 mL). A pale blue precipitate formed which was filtered and dried. The pale blue solid was slurried with dilute sodium carbonate solution for 3 h (or until pH was neutral) resulting in a pale pink precipitate which was filtered and dried. The crude product was recrystallized from ethanol to yield fine colorless needles (3.689 g, 63%). Mp: 164 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta_H$ 4.94 (s, 2H, C$H_2$−O), 5.10 (s, 2H, C$H_2$−O), 7.19−7.22 (m, 2H, Ar), 7.42−7.61 (m, 4H, Ar), 7.98−8.03 (m, 1H, Ar), 8.11−8.16 (m, 1H, Ar), 12.7 (br s, N*H* in exchange with solvent). $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta_C$ 169.7 (2′), 153.0 (9′), 150.8 (2/2′), 138.5 (8/9), 134.8 (8′), 126.6 (5′), 125.6 (6′), 123.0 (4′), 122.7 (7′), 122.5 (5/6), 115.5 (4/7), 69.8 (O−*C*$H_2$), 66.5 (C$H_2$−O). FAB-MS: *m/z* (assignment, relative intensity) 296 ($MH^+$, 50%). Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.1; H, 4.4; N, 14.2. Found: C, 65.0; H, 4.2; N, 14.0.

**Preparation of Benzimidazolyl-3-benzothiazolyl-2-thiapropane (11).** The preparation from 4-(2-benzimidazolyl)-3-thiabutanoic acid hydrochloride (**1b**) (4.80 g, 18.59 mmol) with added *o*-aminothiophenol (2.33 g, 18.59 mmol) gave a white powder. Yield: 3.927 g, 68%. Mp: 171 °C. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta_H$ 4.11 (s, 2H, C$H_2$−O),4.40 (s, 2H, C$H_2$−O), 7.17−7.24 (m, 2H, Ar), 7.43−7.59 (m, 4H, Ar), 7.94−8.03 (m, 1H, Ar), 8.09−8.14 (m, 1H, Ar), 12.4 (br s, N*H* in exchange with solvent). $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta_C$ 170.1 (2′), 153.2 (9′), 151.5 (2/2′), 138.5 [(8/9), in slow exchange], 135.6 (8′), 126.5 (5′), 125.5 (6′), 123.8 (4′), 122.6 (7′), 122.0 (5/6), 115.5 [(4/7), in slow exchange], 33.4 (S−*C*$H_2$), 29.0 (C$H_2$−S). FAB-MS: *m/z* (assignment, relative intensity) 312 ($MH^+$, 50%). Anal. Calcd for $C_{16}H_{13}N_3S_2$: C, 61.7; H, 4.2; N, 13.5. Found: C, 61.8; H, 4.1; N, 13.5.

Due to the prototropy of the unalkylated benzimidazole unit carbons 4,7 and 5,6 are in a state of fast exchange and their signals are not observed separately at room temperature on this NMR time scale.

**Preparation of Copper Complexes.** All copper(II) complexes were prepared by equimolar addition of ligand (0.50 mmol) to the corresponding copper(II) salt in methanol (25 mL). The benzimidazole ligands immediately gave a green solution on addition of the copper(II) salt. The methanolic solution was heated for 30 min after which time the complex usually precipitated; in the absence of a precipitate the solution was reduced in volume while hot until the first sign of precipitation and allowed to cool gradually to room temperature. The precipitates were collected by miniature filtration apparatus and washed with diethyl ether and finally dried in a vacuum desiccator over $P_2O_5$. Crystals suitable for X-ray diffraction were obtained by the methods described herein. Yields (30−60%).

**[Cu(3)Br$_2$]·MeOH, Complex D.**[10] Orange crystals suitable for X-ray diffraction were produced from slow evaporation of a methanolic solution.

**Cu(4)Br$_2$.** An orange powder was obtained. Mp = 216 °C. Anal. Calcd for $C_{18}H_{18}N_4O\cdot CuBr_2$: C, 40.8; H, 3.4; N, 10.6. Found: C, 40.7; H, 3.5; N, 10.5. FAB-MS: *m/z* = 448 [Cu(**4**)Br]$^+$.

**[Cu(4)Br$_2$]·MeOH, Complex E.** Orange crystals suitable for X-ray diffraction were produced from slow evaporation of a methanolic solution. Mp = 187 °C. Anal. Calcd for $C_{18}H_{18}N_4O\cdot CuBr_2\cdot CH_3OH$: C, 40.6; H, 4.0; N, 10.0. Found: C, 40.7; H, 3.9; N, 10.1.

**Cu(4)(ClO$_4$)$_2$·H$_2$O.** A green powder was obtained. Mp = 265 °C. Anal. Calcd for $C_{18}H_{18}N_4O\cdot Cu(ClO_4)_2\cdot H_2O$: C, 36.8; H, 3.4; N, 9.6. Found: C, 36.7; H, 3.4; N, 9.6. FAB-MS: *m/z* = 468 [Cu(**4**)(ClO$_4$)]$^+$.

**[Cu(4)(NCCH$_3$)(OH$_2$)](ClO$_4$)$_2$, Complex A.** Yellow/green crystals suitable for X-ray diffraction were produced by vapor diffusion of diethyl ether into a saturated solution of Cu(**4**)(ClO$_4$)$_2$·H$_2$O in acetonitrile. Mp = 257 °C. Anal. Calcd for $C_{18}H_{18}N_4O\cdot Cu(ClO_4)_2\cdot H_2O\cdot CH_3CN$: C, 38.3; H, 3.7; N, 11.2. Found: C, 38.5; H, 3.2; N, 11.0.

**Cu(5)Br$_2$.** A green powder was obtained. Mp = 223 °C. Anal. Calcd for $C_{18}H_{18}N_4S\cdot CuBr_2$: C, 39.6; H, 3.3; N, 10.3. Found: C, 39.4; H, 3.1; N, 10.0. FAB-MS: *m/z* = 385 [Cu(**5**)]$^+$.

**Cu(5)(ClO$_4$)$_2$·H$_2$O.** A green powder was obtained. Mp = 254 °C. Anal. Calcd for $C_{18}H_{18}N_4S\cdot Cu(ClO_4)_2\cdot H_2O$: C, 35.9; H, 3.3; N, 9.3. Found: C, 35.6; H, 3.5; N, 9.5. FAB-MS: *m/z* = 484 [Cu(**5**)(ClO$_4$)]$^+$.

**Cu(6)Br$_2$.** A yellow powder was obtained. Mp = 214 °C. Anal. Calcd for $C_{17}H_{16}N_4O\cdot CuBr_2$: C, 39.6; H, 3.1; N, 10.9. Found: C, 39.4; H, 2.9; N, 10.6. FAB-MS: *m/z* = 355 [Cu(**6**)]$^+$.

**[Cu(6)Br$_2$]·DMF, Complex B.** Cu(**6**)Br$_2$ was recrystallized from DMF to yield orange crystals suitable for X-ray diffraction. Mp = 197 °C. Anal. Calcd for $C_{17}H_{16}N_4O\cdot CuBr_2\cdot C_3H_7N_1O$: C, 40.8; H, 3.9; N, 11.9. Found: C, 40.7; H, 3.9; N, 11.7.

**Cu(6)(ClO$_4$)$_2$·H$_2$O.** A green powder was obtained. Mp = 285 °C. Anal. Calcd for $C_{17}H_{16}N_4O\cdot Cu(ClO_4)_2\cdot H_2O$: C, 35.7; H, 3.2; N, 9.8. Found: C, 35.7; H, 3.1; N, 10.0. FAB-MS: *m/z* = 355 [Cu(**6**)]$^+$.

**Cu(7)Br$_2$.** A green powder was obtained. Mp = 227 °C. Anal. Calcd for $C_{17}H_{16}N_4S\cdot CuBr_2$: C, 38.4; H, 3.0; N, 10.5. Found: C, 38.1; H, 2.7; N, 10.4. FAB-MS: *m/z* = 371 [Cu(**7**)]$^+$.

**Cu(7)(ClO$_4$)$_2$·H$_2$O.** A green powder was obtained. Mp = 289 °C. Anal. Calcd for $C_{17}H_{16}N_4S\cdot Cu(ClO_4)_2\cdot H_2O$: C, 34.7; H, 3.1; N, 9.5. Found: C, 34.5; H, 2.9; N, 9.4. FAB-MS: *m/z* = 371 [Cu(**7**)]$^+$.

**Cu(8)Br$_2$.** An orange powder was obtained. Mp = 222 °C. Anal. Calcd for $C_{16}H_{13}N_5O_3\cdot CuBr_2$: C, 35.2; H, 2.4; N, 12.8. Found: C, 35.0; H, 2.1; N, 12.7. FAB-MS: *m/z* = 386 [Cu(**8**)]$^+$.

**[Cu(8)Br$_2$]·DMF·H$_2$O, Complex C.** Cu(**8**)Br$_2$ was recrystallized from DMF:MeCN (1:1) to yield orange crystals suitable for X-ray diffraction. Mp = 197 °C. Anal. Calcd for $C_{16}H_{13}N_5O_3\cdot CuBr_2\cdot C_3H_7N_1O\cdot H_2O$: C, 35.8; H, 3.5; N, 13.2. Found: C, 35.7; H, 3.4; N, 13.2.

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**Table 2.** Crystallographic Data

| complex | **A** | **B** | **C** | **D** | **E** | **F** |
|---|---|---|---|---|---|---|
| chem formula | $[C_{20}H_{23}CuN_5O_2](ClO_4)_2$ | $[C_{17}H_{16}Br_2CuN_4O]\cdot C_3H_7NO$ | $[C_{16}H_{13}Br_2CuN_5O_3]\cdot C_3H_7NO\cdot H_2O$ | $[C_{16}H_{14}Br_2CuN_4O]\cdot CH_4O$ | $[C_{18}H_{18}Br_2CuN_4O]\cdot CH_4O$ | $[C_{16}H_{13}Br_2CuN_3OS]$ |
| fw | 627.9 | 588.8 | 637.8 | 533.7 | 561.8 | 518.7 |
| space group | $P2_1/c$ (No. 14) | $P2_1/c$ (No. 14) | $P2_1/c$ (No. 14) | *Pbca* (No. 61) | $P\bar{1}$ (No. 2) | $P2_1/c$ (No. 14) |
| *a*, Å | 10.2168(7) | 8.3348(11) | 8.7241(10) | 14.325(2) | 7.3120(11) | 7.3130(9) |
| *b*, Å | 30.740(2) | 18.165(2) | 18.172(2) | 13.919(2) | 9.9460(15) | 15.861(2) |
| *c*, Å | 8.3403(6) | 14.140(2) | 14.506(2) | 18.837(2) | 15.189(2) | 14.846(2) |
| $\alpha$, deg | | | | | 87.476(4) | |
| $\beta$, deg | 105.960(2) | 91.646(3) | 97.376(2) | | 89.093(4) | 98.318(3) |
| $\gamma$, deg | | | | | 68.673(3) | |
| *V*, Å$^3$ | 2518.4(3) | 2140.0(5) | 2280.7(4) | 3756.0(9) | 1028.0(3) | 1704.0(4) |
| *Z* | 4 | 4 | 4 | 8 | 2 | 4 |
| $\rho_{obsd}$, g cm$^{-3}$ | 1.656 | 1.828 | 1.857 | 1.888 | 1.815 | 2.022 |
| $\mu$, cm$^{-1}$ | 11.4 | 47.8 | 45.1 | 54.4 | 49.7 | 61.0 |
| $R^a$ | 0.0528 | 0.0375 | 0.0438 | 0.0402 | 0.0514 | 0.0386 |
| $R_w{}^b$ | 0.1360 | 0.0869 | 0.1060 | 0.0933 | 0.1184 | 0.0826 |

[a] Conventional $R = \sum||F_o| - |F_c||/\sum|F_o|$ for "observed" reflections having $F_o^2 > 2\sigma(F_o^2)$. [b] $R_w = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$ for all data.

**Cu(9)Br$_2$.** An orange powder was obtained. Mp = 292 °C. Anal. Calcd for $C_{17}H_{13}N_4F_3O\cdot CuBr_2$: C, 35.8; H, 2.3; N, 9.8. Found: C, 35.6; H, 2.0; N, 9.8. FAB-MS: *m/z* = 409 [Cu(**9**)]$^+$.

**Cu(10)Br$_2$, Complex F.** Orange crystals suitable for X-ray diffraction were produced from slow evaporation of a methanolic solution. Mp = 189 °C. Anal. Calcd for $C_{16}H_{13}N_3O_1S\cdot CuBr_2$: C, 37.1; H, 2.5; N, 8.1. Found: C, 37.4; H, 2.2; N, 7.9. FAB-MS: *m/z* = 437 [Cu(**10**)(Br)]$^+$.

**Cu(10)(ClO$_4$)$_2$·H$_2$O.** A green powder was obtained. Mp = 248 °C. Anal. Calcd for $C_{16}H_{13}N_3OS\cdot Cu(ClO_4)_2\cdot H_2O$: C, 33.4; H, 2.6; N, 7.3. Found: C, 33.4; H, 2.5; N, 7.2. FAB-MS: *m/z* = 457 [Cu(**10**)(ClO$_4$)]$^+$.

**Cu(11)Br·H$_2$O.** A gray powder was obtained. Mp = 198 °C. Anal. Calcd for $C_{16}H_{13}N_3S_2\cdot CuBr\cdot H_2O$: C, 40.6; H, 3.2; N, 8.9. Found: C, 40.4; H, 3.0; N, 8.7. FAB-MS: *m/z* = 374 [Cu(**11**)]$^+$.

**Cu(11)(ClO$_4$)·H$_2$O.** A white powder was obtained. Mp = 279 °C. Anal. Calcd for $C_{16}H_{13}N_3S_2\cdot Cu(ClO_4)\cdot H_2O$: C, 39.0; H, 3.1; N, 8.5. Found: C, 38.6; H, 3.0; N, 8.2. FAB-MS: *m/z* = 374 [Cu(**11**)]$^+$.

**X-ray Crystallography.** Crystal data for complexes **A**−**F** are listed in Table 2, and further details of the experiment and calculations are in the Supporting Information. A crystal of complex **D** was examined on a Stoe-Siemens four-circle diffractometer; cell parameters were refined from 2$\theta$ values of 44 reflections measured at $\pm\omega$ to reduce systematic errors, and intensities were collected with $\omega/\theta$ scans and an on-line profile-fitting procedure, to $2\theta_{max} = 50°$.[11] Crystals of the other complexes were examined on a Siemens SMART CCD area-detector diffractometer; cell parameters were refined from the observed rotation angles for all strong reflections in the complete data set in each case, and intensities were integrated from more than a hemisphere of data recorded on 0.3° frames by $\omega$ rotation, with unique data essentially complete to about 50° in 2$\theta$. Graphite-monochromated Mo K$\alpha$ radiation ($\lambda$ = 0.710 73 Å) was used for all measurements, and all samples were cooled to 160 K. No significant intensity decay was observed. Semiempirical absorption corrections were applied, based on symmetry-equivalent, repeated, and azimuthal-scan data.

The structures were determined by direct methods and refined by full-matrix least-squares on $F^2$ for all data. Anisotropic displacement parameters were refined for all non-H atoms, and isotropic H atoms were included with appropriate riding model constraints. Programs were standard Siemens control (SMART) and integration (SAINT) software, Stoe control software (DIF4), SHELXTL,[12] and local programs. Selected bond lengths (Å) and angles (deg) for complexes **A**−**F** are listed in Table 3. Complete tables of coordinates, geometry, and displacement parameters can be found in the Supporting Information.

## Results

**Synthesis**. The new ligands **1**−**2** and **4**−**10** have been prepared by the route shown in Scheme 1. The route has exploited the conventional Phillips condensation reaction by using a 2:1 ratio of the dicarboxylic acid to diamine to produce a half-condensed benzimidazole carboxylic acid as the desired product together with symmetrical fully condensed bis(benzimidazole) as side product. This strategy was first adopted by Reedijk *et al.*[6] to synthesize 4-(2-benzimidazolyl)-3-azabutanoic acid. We are the first to demonstrate the versatility of such mono benzimidazole carboxylic acid precursors in the synthesis of asymmetric bis(benzimidazoles). Purification of the benzimidazole carboxylic acids has proved difficult, but a successful separation technique has been established via successive recrystallization, taking advantage of the notorious insolubility of bis(benzimidazoles) in water. The mono(benzimidazole)-carboxylic acid precursors display a unique kind of coordination chemistry which is currently under review; the current synthesis will be adapted to other diacids with the ultimate aim of exploring the coordination chemistry of such benzimidazole carboxylic acids. Such ligands possess an imidazole and a carboxylic acid functionality within the same ligand which could be important in mimicking the histidine and glutamate/aspartate residues in metalloproteins[13] such as carbonic anhydrase. The carboxylic acid residue was subsequently condensed with a different *o*-phenylenediamine or aminothiophenol to produce the asymmetric ligands **4**−**10**. To discover the effect of differences in the two donor halves of the asymmetric ligands, they were complexed with copper(II) bromide and perchlorate salts to give complexes of a 1:1 stoichiometry. Crystal structures were obtained for the copper(II) bromide complexes of **3**, **4**, **6**, **8, 10** and the copper perchlorate complex of **4**, in all of which the donor atom of the linking chain is ether oxygen.

The benzimidazole ligands immediately gave a green colored solution on addition of the copper(II) salt; however, the mixed heterocyclic ligand (**11**) when complexed with copper(II) rapidly turned from a green solution to afford a white precipitate in a clear solution. This observation suggests the copper(II) may have been reduced to copper(I). The ligand (**11**) possesses thioether sulfur in the linking bridge and sulfur is also present from the benzothiazole unit of the mixed heterocycle. Reduction to copper(I) by similar bis(benzimidazoles) with thioether bridges has been observed previously.[14] The colorless copper compound when dried appeared stable in air, but in deuterated dimethyl sulfoxide solution a rapid change from colorless to green indicated a rapid re-oxidation of Cu(I) to Cu(II). No alternative deuterated solvent to solubilize the complex was

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**Table 3.** Selected Bond Lengths (Å) and Angles (deg)

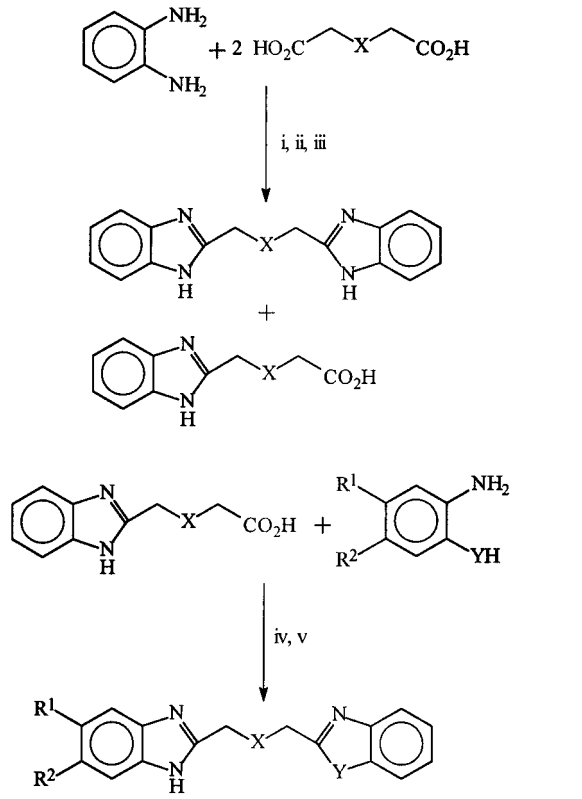
| | | | |
|---|---|---|---|
| | Complex **A** | | |
| Cu−N(3) | 1.930(4) | Cu−N(1) | 1.940(3) |
| Cu−O(2) | 2.019(3) | Cu−O(1) | 2.093(3) |
| Cu−N(5) | 2.118(4) | | |
| N(3)−Cu−N(1) | 156.71(14) | N(3)−Cu−O(2) | 94.09(14) |
| N(1)−Cu−O(2) | 97.70(14) | N(3)−Cu−O(1) | 79.53(12) |
| N(1)−Cu−O(1) | 79.83(12) | O(2)−Cu−O(1) | 147.96(12) |
| N(3)−Cu−N(5) | 99.82(14) | N(1)−Cu−N(5) | 99.77(14) |
| O(2)−Cu−N(5) | 91.97(14) | O(1)−Cu−N(5) | 120.02(13) |
| | Complex **B** | | |
| Cu−N(1) | 1.978(3) | Cu−N(3) | 1.981(3) |
| Cu−O(1) | 2.219(2) | Cu−Br(1) | 2.3940(6) |
| Cu−Br(2) | 2.5795(6) | | |
| N(1)−Cu−N(3) | 153.91(12) | N(1)−Cu−O(1) | 77.37(10) |
| N(3)−Cu−O(1) | 77.38(10) | N(1)−Cu−Br(1) | 98.48(9) |
| N(3)−Cu−Br(1) | 98.19(8) | O(1)−Cu−Br(1) | 144.36(6) |
| N(1)−Cu−Br(2) | 93.40(8) | N(3)−Cu−Br(2) | 92.58(8) |
| O(1)−Cu−Br(2) | 88.96(6) | Br(1)−Cu−Br(2) | 126.68(2) |
| | Complex **C** | | |
| Cu−N(3) | 1.988(4) | Cu−N(1) | 1.991(4) |
| Cu−O(1) | 2.243(3) | Cu−Br(1) | 2.4100(8) |
| Cu−Br(2) | 2.5219(9) | | |
| N(3)−Cu−N(1) | 152.1(2) | N(3)−Cu−O(1) | 76.51(14) |
| N(1)−Cu−O(1) | 76.20(14) | N(3)−Cu−Br(1) | 99.85(11) |
| N(1)−Cu−Br(1) | 98.28(13) | O(1)−Cu−Br(1) | 142.57(10) |
| N(3)−Cu−Br(2) | 96.05(12) | N(1)−Cu−Br(2) | 92.22(13) |
| O(1)−Cu−Br(2) | 95.65(10) | Br(1)−Cu−Br(2) | 121.70(3) |
| | Complex **D** | | |
| Cu−N(3) | 1.979(4) | Cu−N(1) | 1.981(4) |
| Cu−O(1) | 2.242(3) | Cu−Br(2) | 2.4133(8) |
| Cu−Br(1) | 2.4938(9) | | |
| N(3)−Cu−N(1) | 152.6(2) | N(3)−Cu−O(1) | 75.97(14) |
| N(1)−Cu−O(1) | 76.93(14) | N(3)−Cu−Br(2) | 98.55(12) |
| N(1)−Cu−Br(2) | 99.03(12) | O(1)−Cu−Br(2) | 138.54(9) |
| N(3)−Cu−Br(1) | 90.89(13) | N(1)−Cu−Br(1) | 96.43(12) |
| O(1)−Cu−Br(1) | 97.28(9) | Br(2)−Cu−Br(1) | 124.09(3) |
| | Complex **E** | | |
| Cu−N(3) | 1.963(5) | Cu−N(1) | 1.969(5) |
| Cu−O(1) | 2.226(5) | Cu−Br(2) | 2.4011(11) |
| Cu−Br(1) | 2.5201(11) | | |
| N(3)−Cu−N(1) | 153.7(2) | N(3)−Cu−O(1) | 77.1(2) |
| N(1)−Cu−O(1) | 76.7(2) | N(3)−Cu−Br(2) | 95.2(2) |
| N(1)−Cu−Br(2) | 98.5(2) | O(1)−Cu−Br(2) | 124.48(12) |
| N(3)−Cu−Br(1) | 93.5(2) | N(1)−Cu−Br(1) | 93.3(2) |
| O(1)−Cu−Br(1) | 102.09(12) | Br(2)−Cu−Br(1) | 133.40(4) |
| | Complex **F** | | |
| Cu−N(2) | 1.967(3) | Cu−N(1) | 1.992(3) |
| Cu−O(1) | 2.216(3) | Cu−Br(2) | 2.4178(7) |
| Cu−Br(1) | 2.4513(7) | | |
| N(2)−Cu−N(1) | 150.63(14) | N(2)−Cu−O(1) | 75.26(12) |
| N(1)−Cu−O(1) | 75.38(12) | N(2)−Cu−Br(2) | 98.71(11) |
| N(1)−Cu−Br(2) | 96.20(10) | O(1)−Cu−Br(2) | 121.73(10) |
| N(2)−Cu−Br(1) | 97.65(10) | N(1)−Cu−Br(1) | 96.82(10) |
| O(1)−Cu−Br(1) | 118.84(10) | Br(2)−Cu−Br(1) | 119.40(3) |

found. The FAB mass spectra contained peaks corresponding to $(ML)^+$ and $[ML(X)]^+$ (L = **4**−**11**, X = Br, $ClO_4$) for the 1:1 complexes.

**Crystal Structures.** In each case the ligands are tridentate with an $N_2O$ donor set. This coordination gives two linked five-membered chelate rings which are approximately in the same plane. Table 3 summarizes the coordination geometry of the copper(II) ion in each structure.

The domed square pyramidal complex cation $[Cu(\mathbf{4})(NCCH_3)(OH_2)]^{2+}$ in **A** (Figure 2) has an acetonitrile ligand in the apical site, the basal sites being occupied by the tridentate ligand and a water molecule. One perchlorate anion forms what may be

**Scheme 1.** Synthesis of Asymmetric Bis(Benzimidazoles)[a]




[a] Reagents and conditions: (i) 6 M HCl, reflux 72 h; (ii) 0.880 $NH_3$ (pH ∼ 9); (iii) concentrated HCl (to pH ∼ 7); (iv) 4 M HCl, refluxed 17 h, 0.880 $NH_3$ (pH ∼ 9 0); (v) recrystallized from ethanol/charcoal and water.

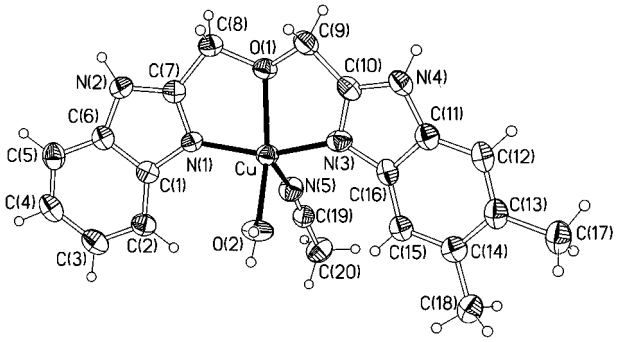



**Figure 2.** Structure of the cation of complex **A**. In Figures 2−7, non-H atoms are shown as 50% probability ellipsoids and H atoms as spheres of arbitary radius; uncoordinated solvent molecules and counterions are not shown.

considered a sixth, weaker interaction with the central $Cu^{2+}$ at 2.917 Å, opposite the acetonitrile ligand and is also hydrogen bonded through a different oxygen atom to the aqua ligand (O···O 2.781 Å). The second perchlorate anion is also hydrogen bonded to $H_2O$ (O···O 2.837 Å). Further hydrogen bonding occurs between each benzimidazole N−H and a perchlorate anion (N···O 2.917 and 2.936 Å), to give a three-dimensional hydrogen bonding network. This perchlorate structure has shorter Cu−N and Cu−O bonds and a larger N−Cu−N angle than all the bromide structures (Table 3). In particular, complex **E**, which has the same tridentate ligand but with two coordinated large bromide anions, shows an increase of *ca.* 0.03 Å in Cu−N and of 0.13 Å in Cu−O bond lengths, and a decrease of 3° in the N−Cu−N angle.

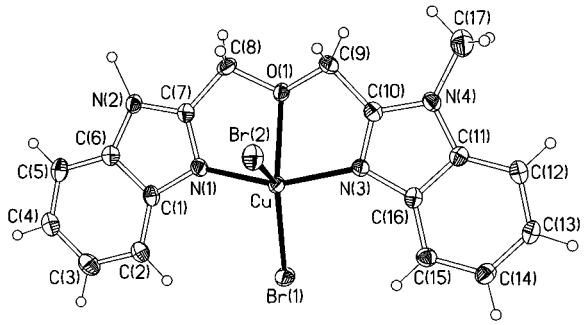



**Figure 3.** Structure of complex **B**.

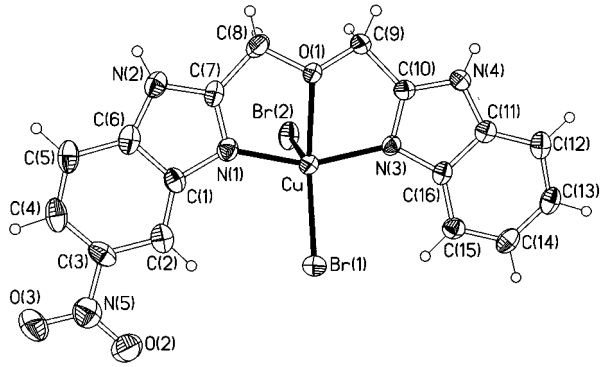



**Figure 4.** Structure of complex **C**.

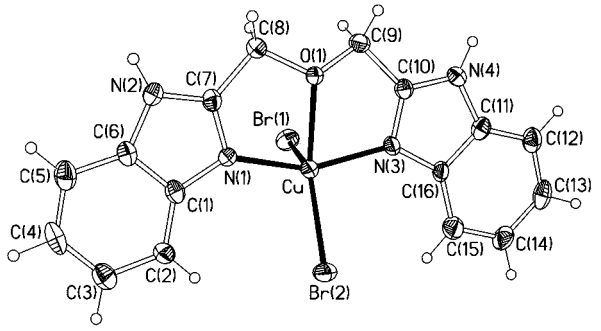



**Figure 5.** Structure of complex **D**.

Molecules of complex **B** (Figure 3) are associated in loose centrosymmetric dimers, with the oxygen atom of each molecule 3.315 Å from the copper(II) ion of the other, opposite the apical bromide ligand. This Cu···O distance is beyond the typical van der Waals distance and is considerably larger than the Cu···O distance of 2.743 Å, found within a single complex of a bis(benzimidazole) ether,[15] and 3.08 and 3.14 Å, for the peptide oxygen of a glycine residue in azurin.[16] The tridentate ligand in complex **B** has one *N*-alkyl group; the single N−H is hydrogen bonded to DMF (N···O 2.665 Å), so that two DMF molecules are associated with each pair of complex molecules in the crystal structure. There are no other significant intermolecular interactions.

Complex **C** (Figure 4) is also loosely associated as centrosymmetric dimers, with even longer Cu···O distances of 3.399 Å. The crystal structure contains DMF and water molecules producing an extensive hydrogen bonding network, in which benzimidazole N−H groups act as donors to DMF (N···O 2.746 Å) and to $H_2O$ (N···O 2.762 Å), and $H_2O$ acts as a donor to both DMF (O···O 2.789 Å) and bromide (O···Br 3.383 Å).

Complexes **D** (Figure 5) and **E** (Figure 6) have qualitatively very similar hydrogen-bonding arrangements. In each of them,

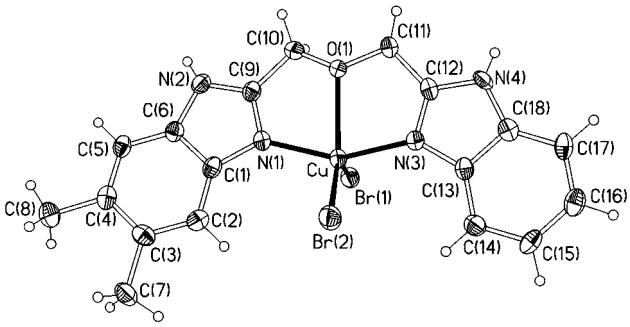



**Figure 6.** Structure of complex **E**.

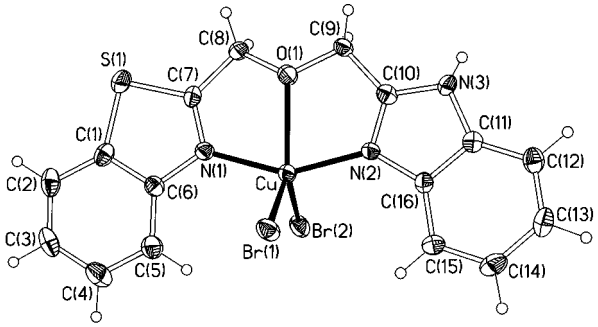



**Figure 7.** Structure of complex **F**.

one N−H interacts with oxygen of methanol (N−H = 2.717 and 2.764 Å for **D** and **E** respectively), the other with bromide (N···Br = 3.383 and 3.335 Å), and methanol O−H is hydrogen bonded to bromide (O···Br = 3.257 and 3.258 Å), so that each bromide ligand forms one hydrogen bond.

The bromide ligands in complex **F** (Figure 7) also form one hydrogen bond each, but this structure contains no solvent and the tridentate ligand has only one N−H group, so this is involved in a bifurcated interaction (N···Br 3.498 and 3.322 Å). This results in hydrogen-bonded chains of molecules. There are no significant S···S interactions, such as have been noted as dominant in the packing of free ligands containing benzothiazole units.[5]

**UV−vis.** Electronic spectra of the copper(II) complexes in methanol solution in the UV and visible regions are shown in Table 4. The UV spectra are consistent with what has been observed previously[17] with an absorption pattern similar to that of a substituted benzene derivative, the short- and long-wavelength absorptions corresponding to transitions made in the imidazole and aryl rings, respectively. Ligand to metal charge transfer bands (LMCT) at *ca.* $28.6-23.8 \times 10^3$ cm$^{-1}$, $\epsilon$ *ca.* 190−700 dm$^3$ mol$^{-1}$ cm$^{-1}$ were observed for all the copper complexes, the perchlorate complexes showing considerably smaller extinction coefficients compared to their bromide analogs, and ligands containing a thioether donor having larger extinction coefficients compared to their ether analogs. This observation is carried through to the visible region with d−d transitions at *ca.* $15.3-13.2 \times 10^3$ cm$^{-1}$, $\epsilon$ *ca.* 20−250 dm$^3$ mol$^{-1}$ cm$^{-1}$; complexes of ligands containing thioether donors showed a maximum absorption at *ca.* 650 nm ($15.3 \times 10^3$ cm$^{-1}$), while the ether donors displayed a maximum absorption over a broad range typically from 710 nm ($14.1 \times 10^3$ cm$^{-1}$) to the maximum wavelength of (800 nm, $12.5 \times 10^3$ cm$^{-1}$) of the spectrometer.

## Discussion

Syntheses of symmetrical N-alkylated bis(benzimidazoles) and those bearing varied ring substitution patterns of a sym-

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**Table 4.** UV−vis Data for the Copper(II) Complexes of Ligands **4**−**11**

| complex | $\lambda_{max}$/nm ($\epsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$) |
|---|---|
| [Cu(**3**)$Br_2$]·MeOH[a] | 238 (15 130), 271 (17 000), 279 (17 600), 380 (430), 665−714 (140) |
| [Cu(**4**)$Br_2$]·MeOH | 246 (14 700), 274 (19 500), 280 (18 900), 380 (sh, 430), 675−800[b] (br, 130) |
| Cu(**4**)$(ClO_4)_2$·$H_2O$ | 238 (12 000), 272 (16 900), 278 (17 200), 350 (190), 675−800[b] (br, 60) |
| Cu(**5**)$Br_2$ | 232 (13 600), 278 (18 500), 280 (18 100), 410 (sh, 685), 654 (145) |
| Cu(**5**)$(ClO_4)_2$·$H_2O$ | 244 (12 610), 274 (17 030), 280 (16 900), 370 (210), 750 (85) |
| Cu(**6**)$Br_2$ | 244 (12 400), 272 (18 200), 278 (18 020), 385 (sh, 670), 675−800 (br, 220) |
| Cu(**6**)$(ClO_4)_2$·$H_2O$ | 250 (13 010), 270 (16 220), 278 (17 180), 360 (200), 700−800[b] (br, 75) |
| Cu(**7**)$Br_2$ | 246 (14 700), 274 (19 500), 280 (18 500), 410 (sh, 700), 630 (250) |
| Cu(**7**)$(ClO_4)_2$·$H_2O$ | 234 (14 500), 270 (18 000), 280 (19 075), 375 (200), 720 (100) |
| Cu(**8**)$Br_2$ | 244 (14 000), 278 (18 180), 294 (17 100), 390 (sh, 452), 700−800[b] (br, 140) |
| Cu(**9**)$Br_2$ | 240 (9800), 272 (12 660), 278 (15 130), 420 (sh, 380), 700−800[b] (br, 190) |
| Cu(**10**)$Br_2$ | 232 (24 500), 248 (21 660), 252 (22 300), 256 (22 100), 410 (270), 710−800[b] (110) |
| Cu(**10**)$(ClO_4)_2$·$H_2O$ | 234 (26 000), 244 (22 300), 252 (23 100), 254 (23 000), 380 (380), 760 (20) |

[a] Data taken from ref 10. [b] Spectrophotometer maximum wavelength.

metrical nature are known,[18] giving a range of compounds having a convenient gradation of solubilities. Such substituted bis(benzimidazoles) provide steric bulk and sufficient rigidity in order to control the stereochemistry of the metal complex and the ligand alone. These features are important when designing models for metalloprotein sites since both the complexed and free ligand environments affect the metalloprotein's ability to complex metals and release them with sufficient efficacy within the protein environment. Changes to the biological system can be, and usually are, very small in order to effect the coordination with, and release of, a metal ion. The coordinating atoms within the biological system are held in very precisely defined geometries in relation to the protein, but they still retain a degree of mobility. Within the biomimetic ligand the steric properties are determined by the rigidity of the molecule. An important feature is that there should be sufficient flexibility within the rigid model molecule to optimize the coordinating properties of its donor atoms when associating with, and dissociating from, the metal ion of interest. By incorporation of a small chain linker group between the benzimidazole fragments, a degree of change can be brought about. In addition, the incorporation of a potential donor atom within this chain gives the option for benefits derived from additional coordination through the linker atom (which can then result in additional benefits to the complex by affecting the normal electronic "pattern" making it easier to mimic the biological asymmetry and charge density patterns), and it may also give rise to unusual coordination geometries for the metal of interest. It can also bring about some interesting arrangements of molecular fragments, forcing the asymmetric units together by introducing torsional twists etc. These features can all lead to improvements on design for models as metalloprotein sites.

Benzimidazoles bearing varied ring substitution also provide useful diagnostics for the interpretation of $^1$H N. M. R spectra; this has been exploited[19] to investigate the rates and mechanisms of exchange with cadmium(II) salts. With this in mind the asymmetric bis(benzimidazole) ligands of the type described in Table 1 will allow the exploration of the rates at which the metal enters or leaves the coordinating environment of a biomimetic ligand possessing structural asymmetry; changes in basicity can also be investigated to study the effect on rates within the series of ligands. These studies on the series of asymmetric ligands complement work undertaken within this group on the symmetric ligands. One of the major advantages of a synthetic route which offers a clean reaction product is that these studies can be undertaken without excessive rework

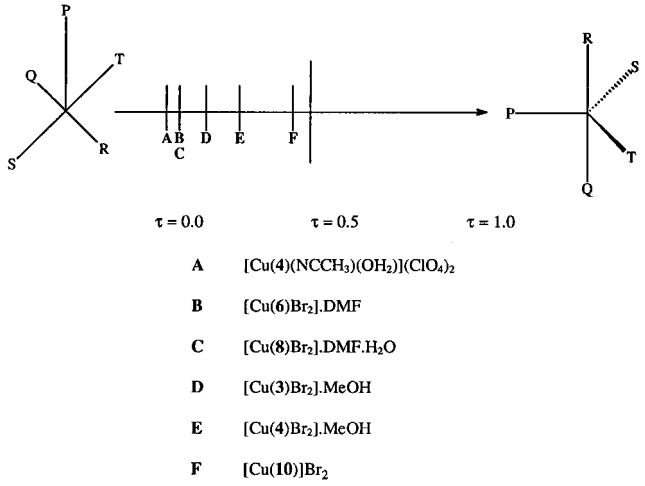


**Figure 8.** Structures **A**−**F** lying between SBP ($\tau = 0$) and TBP ($\tau = 1.0$) extremes.

of mixtures. The asymmetric ligands (Table 1) can be synthesized cleanly from the synthetic route shown in Scheme 1. The ligands **6**, **7**, **10**, and **11** possess only one free NH per ligand which is an exception amongst bis(benzimidazole) ligands; thus they lack prototropy on one half of the ligand. Poly(imidazole) ligands with the ability to provide at least one NH per molecule are of current interest[20] in studies of new platinum antitumoral compounds. The requirement of ligands to possess an NH moiety to hydrogen bond to DNA for antitumor activity is of debate, since some platinum complexes that contain no NH moiety display antitumoral activity and form an exception. One argument could be extended whereby the NH moiety is not critical but that the asymmetry which results from this feature can affect the electronic properties of the molecule such that there is an electronic gradient which will exhibit a certain matrix effect. The variations in charge distribution which are brought about could mimic the situation within a metalloprotein which enables a metal complex to be stabilized and destabilized as required, more closely than otherwise. Changes in the steric arrangements of the donor atoms will affect the charge densities and facilitate either complexation and/or decomplexation.

Each of the Cu(II) complexes **A**−**F** (Figure 8) studied in the solid state by X-ray crystallography was five coordinate with Cu−N distances for the series lying within a range of 1.930−1.992 Å (mean 1.972, sample $\sigma = 0.006$ Å) with N−Cu−N angles of 150.63−156.71° as shown in Table 3; these are essentially invariant within the series of structures presented,

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**Table 5.** Atom Labeling and $\tau$ Values for Five-Coordinate Copper(II) Crystal Structures **A**−**F**

| complex | P | Q/R | S/T | α, deg | $\beta$, deg | $\tau$ |
|---|---|---|---|---|---|---|
| [Cu(**4**)(NCCH$_3$)(OH$_2$)](ClO$_4$)$_2$ (**A**) | N5 | N3, N1 | O1, O2 | 147.96 | 156.71 | 0.146 |
| [Cu(**6**)Br$_2$]·DMF (**B**) | Br2 | N3, N1 | O1, Br1 | 144.36 | 153.91 | 0.159 |
| [Cu(**8**)Br$_2$]·DMF·H$_2$O (**C**) | Br2 | N3, N1 | O1, Br1 | 142.57 | 152.10 | 0.159 |
| [Cu(**3**)Br$_2$]·MeOH (**D**) | Br1 | N3, N1 | O1, Br2 | 138.54 | 152.60 | 0.234 |
| [Cu(**4**)Br$_2$]·MeOH (**E**) | O1 | N3, N1 | Br1, Br2 | 133.40 | 153.70 | 0.338 |
| Cu(**10**)Br$_2$ (**F**) | Br1 | N1, N2 | O1, O2 | 121.73 | 150.63 | 0.482 |

with no discernible pattern. A search of the Cambridge Structural Database[21] revealed 36 related crystal structures of copper(II) complexes containing a bis(benzimidazole) fragment, and with an *R* factor of ≤10%. Statistical analysis of this set of structures gave the mean Cu−N bond distance as 1.964 Å (sample $\sigma = 0.034$, minimum 1.890 and maximum 2.005 Å). The Cu−N bond distances of the structures presented in this work show no marked deviation from the mean values calculated from the related structures. However, the structure **A** with neutral ligands in the coordination sphere had the shortest Cu−N bonds.

In geometry, the structures lie between perfect square-based-pyramidal (SBP) and trigonal-bipyramidal (TBP) extremes (Figure 8), and can be systematized using a structural index parameter ($\tau$).[18] This is used as a measure of the trigonality of the structure within the structural continuum between trigonal bipyramidal and rectangular pyramidal. One ligand P is regarded as the apical donor site of the square based pyramid and is chosen by the criterion that it should not be any of the four atoms which define the two largest angles (α, $\beta$) around the metal center. Donor atoms Q/R (these are the benzimidazole nitrogens in the present structures) are associated with the greater basal angle $\beta$ and donor atoms S/T are related to the second largest basal angle α (Table 5). The parameter $\tau = (\beta - \alpha)/60$. The structure of complex **A** lies closest to SBP ($\tau = 0.146$) and is unlike the others in the series, having noncoordinating perchlorate anions whereas the remaining complexes (**B**−**F**) have the bromide anions in the coordination sphere of the Cu(II). The donor groups S/T are neutral ligands in the complex **A** while for the remaining structures (**B**−**F**) S and T are bromide anions and/or neutral ether donor atoms. The analogous bromide complex **E** is more TBP in nature ($\tau = 0.338$) but still lies in the SBP range ($\tau < 0.50$). The complexes **B** and **C** are near to SBP ($\tau = 0.159$) in character with the symmetrical complex **D** occupying the middle point of the series ($\tau = 0.234$); the apical donor site of **E** however is now occupied by the ether donor atom from the linking bridge rather than a bromide anion. The complex **D** has been prepared previously[10] but not characterized by X-ray crystallography; the perchlorate complex of the ligand has also been prepared[22] and its UV−vis, ESR and magnetochemistry studied, showing an $N_2O$ donor set from the bis(benzimidazole) surrounding the central copper(II) ion with a single perchlorate and water molecule as the remaining donors to give a severely distorted tetragonal geometry surrounding the copper. The mixed heterocyclic complex **F** is the closest to TBP in geometry ($\tau = 0.482$) with the smallest N−Cu−N angle of 150.63° but the complex revealed no striking differences in structure when compared to the rest of the series. The coordination chemistry of benzimidazoles is well documented in comparison to that of benzothiazoles, there being few benzothiazole copper(II) complexes in the literature.[23] A search of the Cambridge Structural Database[21] revealed a lack of known

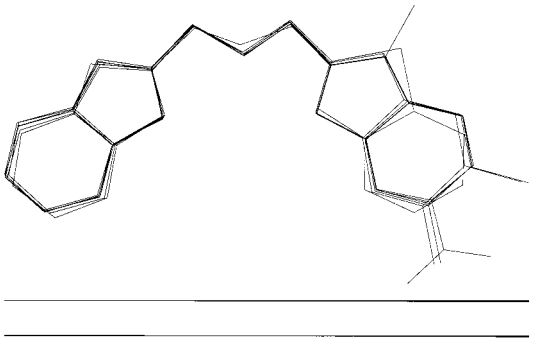

**Figure 9.** Superposition and rigid-body-fit of the copper(II) complexes **A**, **B**, **C**, **E** and **F** to the target molecule, complex **D**.

bis(benzimidazole) copper(II) structures containing ether bridges; much solid state study has centered on the thioether analogs in attempts to mimic copper(II) type proteins.[24] The search revealed only one analogous copper(II) bromide structure[15] where X = $OCH_2CH_2O$. The central copper atom is in a pseudooctahedral environment coordinated by the benzimidazole pyridine-like nitrogens with a Cu−N distance of 1.987 Å, N−Cu−N angle of 168.9°, and a Cu−O distance of 2.743 Å.

The series of copper complexes of the new asymmetric bis(benzimidazole) ligands also raised the possibility of investigating the effect on crystal structure geometry of the asymmetry and other features. The principal variants of the compounds investigated were as follows: (a) differential basicity of benzimidazole/benzothiazole fragments of each half, (b) asymmetry of ligand, (c) loss of prototropy on one half, (d) solvent contribution to prototropy, (e) the presence of a coordinating versus a noncoordinating anion. Comparison of the geometry of the symmetrical bis(benzimidazole) complex **D** with the asymmetric complexes **A**, **B**, **C**, **E**, and **F** revealed no significant change in the geometrical parameters around the copper(II) ion consequent on a change of p$K_a$[25,26] or induced asymmetry within the bis(benzimidazole) fragment. The coordination geometries of the Bzm−$CH_2$−O−$CH_2$−Bzm (Bzm = benzimidazole) segments provided by the heterocycles and ether donor atom of the linking bridge are superposable. Superposition of the coordination geometries of the Bzm−$CH_2$−O−$CH_2$−Bzm (Bzm = benzimidazole) segments (Figure 9) provided by the heterocycles and ether donor atom of the linking bridge was performed using a rigid-body fit to a target molecule (the symmetrical bis(benzimidazole) complex **D**) as described in the QUANTA[27] manual. The variation is slight [total root mean square (rms) 0.115] with individual complexes deviating from the target molecule **D** in the following order **F** (0.194) > **A** (0.122) > **E** (0.084) > **C** (0.060) > **B** (0.054); the complex **F**, deviating to a greater extent, contained the benzothiazole heterocycle (ligand

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**Table 6.** Comparison of Cu−N Bond Distances of the Copper(II) Complexes **A**−**F** with pK Values[a]

| ligand | complex | p$K^b$ | Cu−N[b] | Cu−N[c] | p$K^c$ |
|---|---|---|---|---|---|
| **10** | **F** | 1.5 | 1.992 | 1.967 | 5.5 |
| **8** | **C** | 3.0 | 1.991 | 1.989 | 5.5 |
| **6** | **B** | | 1.981 | 1.978 | 5.5 |
| **3** | **D** | 5.5 | 1.979 | 1.981 | 5.5 |
| **4** | **E** | 6.5 | 1.969 | 1.963 | 5.5 |
| **4**[b] | **A** | 6.5 | 1.940 | 1.930 | 5.5 |

[a] Quoted literature values from ref 26. [b] Substituted ring. [c] Unsubstituted ring.

**10**) while the complex **B**, deviating the least, contained the ligand **6.** Geometrical features relating to the attached monodentate donors (Br, $H_2O$ and $CH_3CN$) are much more variable. Approximate pKs have been estimated[25,26] for the basic benzimidazole/thiazole fragments of the ligands **3**, **4**, **6**, **8**, and **10** as indicated in Table 6, and described in the supporting information. These cover a range of *ca.* 5 p*K* units. In Table 6, comparison of the five structures **B**−**F** which all had two bromide ions in the coordination sphere indicates very slightly longer bonds to tertiary nitrogens of the two least basic residues (benzothiazole, and 5-nitrobenzimidazole) in this series. However, the Cu−N distances to the unsubstituted benzimidazole fragment are generally almost the same as for the more/less basic substituted fragment *in the same molecule*. It would seem that other factors in the crystal have more influence on the bond length. The loss of prototropy consequent on change of basicity merely reduces the degree of hydrogen bonding observed in the solid state structures within the series of complexes but this has little effect on the coordination environment of the central metal atom. The implication of these two studies is that change of basicity and asymmetry of ligand have virtually no effect on coordination geometry of the metal−donor environment. From the failure to induce a structural effect in the coordinating environment despite the altered basicity in the series of model benzimidazole ligands, we suggest that biological provision of HIS of different basicity likewise carries no structural implication. Rather the differential basicity may assist pH-switchable control of HIS coordination in appropriate environments. The effect of differential basicity may well be more important in a mechanistic context. Subtle alteration of the bis(benzimidazole) ligand to induce asymmetry must affect the rate at which the metal enters or leaves its coordinating environment. The degree of hydrogen bonding, the solvent of crystallization, and the nature of the metal anion have a greater impact on the geometrical parameters and coordination environment of the copper(II) ion in the series **A**−**F** examined here than the asymmetry and differential basicity. The way in which solvation occurs in our complexes is also seen to contribute more to gross structural variation; hydrogen bonding to donor nitrogen atoms or associated NH creates additional asymmetric interaction and can have a serious effect on geometry. Likewise a change from coordinating bromide anion to noncoordinating perchlorate changes the geometry substantially.

The electronic spectra of the Cu(II) complexes showed typical LMCT bands; the broadness of these bands observed in the bromide complexes could possibly be attributed the Cu−Br charge transfer together with $\pi-\pi^*$ transitions of the benzimidazoles which result in a broad band displaying shoulders. The perchlorate complexes show no shoulders and have smaller extinction coefficients which could be attributed to the noncoordinating behavior of the perchlorate anions in solution and replacement with a solvent molecule such as methanol. Thioether ligation also causes an increase in $\epsilon$; the increase in extinction coefficients from thioether chelation is attributed to the ligand field strength of thioether which is intermediate between that of ether and heterocyclic nitrogen; this effect has been observed previously.[28] Copper(II) compounds with five-coordinate geometry often show one broad absorption band in the visible region with a shoulder on the high energy slope of the band; this phenomenon[24e] is seen in all the complexes, suggesting the Cu(II) retains a five-coordinate geometry in solution as well as in the solid state observations. The increase in $\epsilon$ due to bromide and thioether ligation is also observed in the visible region. In earlier work, Duggan *et al.*[29] characterized crystallographically the $[Cu(tren)(NH_3)]^{2+}$ and $[Cu(NH_3)_5]^{2+}$ cations as trigonal-bipyramidal ($\tau = 1.0$) and square pyramidal ($\tau = 0.0$) respectively. They also interpreted single crystal spectra to suggest that the TBP molecule absorbed at 11 400 $cm^{-1}$, while the SBP absorbed at 15 300 $cm^{-1}$. Although our series with a range of values looked useful to test any relation between $\tau$ value and absorption maxima, our solution spectral data were inconclusive.

**Acknowledgment.** We wish to thank E. P. S. R. C. and Zeneca Specialties (CASE award to Mr. C. J. Matthews) for financial support. We thank a reviewer for suggesting a possible relationship between $\tau$ values and absorption maxima.

**Supporting Information Available:** Tables and drawings of intermolecular interactions for complexes **A**−**F**, drawings of crystal packing for complexes **B**−**F**, and tables of crystallographic data, atomic parameters, bond lengths and angles, anisotropic displacement parameters and hydrogen atom parameters (48 pages). Ordering information is given on any current masthead page.

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