Synthesis and Reactivity of a Family of Copper Monooxygenase Model Systems[1]

Luigi Casella,* Michele Gullotti, Gianfranco Pallanza, and Luigi Rigoni

Contribution from the Dipartimento di Chimica Inorganica e Metallorganica, Centro CNR, Università di Milano, 20133 Milano, Italy. *Received June 1, 1987*

Abstract: A series of binuclear copper(I) complexes with the bis(imines) derived from the condensation of benzene-1,3-dicarboxaldehyde and two molecules of histamine (**1**), L-histidine methyl ester (**2**), N^{τ}-methylhistamine (**3**), and N^{τ}-methyl-L-histidine methyl ester (**4**) have been synthesized and characterized. The ligands provide two nitrogen donors, from an imine and an imidazole group, to each copper(I) center, but a molecule of solvent is additionally coordinated to the metal in solution. The complexes **3** and **4** undergo ready aromatic hydroxylation at position 2 of the phenyl nucleus when reacted with molecular oxygen in solution. The stoichiometry of the reaction is 1:2 O_2/Cu, and the products formed are the corresponding binuclear, four-coordinate μ-phenoxo and μ-hydroxo copper(II) complexes. This reaction mimics the reactivity of the copper monooxygenase tyrosinase. For complexes **1** and **2** such a hydroxylation reaction can be observed only in protic solvents and is in competition with simple copper(I) oxidation. When **1** and **2** are reacted with O_2 in nonprotic solvents, only copper(I) oxidation occurs, to form μ-imidazolato copper(II) compounds, with a stoichiometry of 1:4 O_2/Cu. The ratio between hydroxylation and oxidation can be shifted in favor of the former reaction by addition of small amounts of acid. The products resulting from the oxygenation of **1**–**4** have also been isolated and characterized. The copper(I) complexes form weak three-coordinate adducts when reacted with CO (ν(CO) at 2088–2096 cm^{-1}) and four-coordinate adducts when the carbonylation reaction is carried out in the presence of excess imidazole (ν(CO) at 2069–2073 cm^{-1}). These ν(CO) data are discussed in relation to those of other Cu(I) systems and carbonyl hemocyanin.

The attempt to gain a better understanding of the factors that rule the binding and activation of molecular oxygen by the type 3 active sites of copper proteins, hemocyanin, tyrosinase, and the copper oxidases, is a main current research topic in bioinorganic chemistry. Although the crystal structure determination of *Panulirus interruptus* hemocyanin has revealed some basic features of the dinuclear copper site,[2] other important details, like the eventual presence of a bridging group between the copper units, their coordination geometry, and even the actual oxidation state of the species analyzed (reduced or met form of the protein), remain unclear. Also, some structural differences among the binuclear sites of arthropod and molluscan hemocyanins,[3,4] tyrosinase,[5] and especially the blue copper oxidases[3,6] may or even are likely to occur, in view of the different functions performed by these proteins. Model studies on the interaction of copper(I) complexes with dioxygen can be very important for the understanding of the factors that rule the modulation of the reactivity of dioxygen moieties bound to copper centers. Thus, several studies have appeared recently on model copper(I) systems exhibiting different types of dioxygen activation[7,8] or various degrees of reversible dioxygen binding,[8b,c,9] including reports on almost fully reversible binding in solution at low temperature (−80 °C).[10]

We have been involved for some time in studies on binuclear copper complexes[1,11] and on the interaction of copper(I) complexes with dioxygen.[9d] Recently, our interest was stimulated by the proposal made by Solomon et al.[5] of a binuclear, two-coordinate copper(I) site for the deoxy form of tyrosinase in which the donor ligands are provided by imidazole groups of histidine residues. Although the subsequent EXAFS studies[12] and crystal structure determination[2] of hemocyanin have somewhat attenuated such a possibility, it is true that the chemistry of two-coordinate copper(I) systems with ligands of potential biological relevance has been little developed,[13] particularly their reactivity with dioxygen.

(1) Binuclear Complexes. 3. Part 2: Casella, L.; Gullotti, M.; Pessina, C.; Pintar, A. *Gazz. Chim. Ital.* **1986**, *116*, 41–49.

(2) (a) Gaykema, W. P. J.; Hol, W. G. J.; Vereijken, J. M.; Soeter, N. M.; Bak, H. J.; Beintema, J. J. *Nature (London)* **1984**, *309*, 23–29. (b) Gaykema, W. P. J.; Volbeda, A.; Hol, W. G. J. *J. Mol. Biol.* **1985**, *187*, 255–275.

(3) Solomon, E. I.; Penfield, K. W.; Wilcox, D. E. *Struct. Bonding* (Berlin) **1983**, *53*, 1–57.

(4) (a) Linzen, B.; Soeter, N. M.; Riggs, A. F.; Schneider, H.-J.; Schartan, W.; Moore, M. D.; Yokota, E.; Behrens, P. Q.; Nakashima, H.; Takagi, T.; Nemoto, T.; Vereijken, J. M.; Bak, H. J.; Beintema, J. J.; Volbeda, A.; Gaykema, W. P. J.; Hol, W. G. J. *Science (Washington D.C.)* **1985**, *229*, 519–524. (b) Himmelwright, R. S.; Eickman, N. C.; LuBien, C. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1980**, *102*, 5378–5388. (c) Wilcox, D. E.; Long, J. R.; Solomon, E. I. *Ibid.* **1984**, *106*, 2186–2194.

(5) (a) Himmelwright, R. S.; Eickman, N. C.; LuBien, C. D.; Lerch, K.; Solomon, E. I. *J. Am. Chem. Soc.* **1980**, *102*, 7339–7344. (b) Winkler, M. E.; Lerch, K.; Solomon, E. I. *Ibid.* **1981**, *103*, 7001–7003. (c) Wilcox, D. E.; Porras, A. G.; Hwang, Y. T.; Lerch, K.; Winkler, M. E.; Solomon, E. I. *J. Am. Chem. Soc.* **1985**, *107*, 4015–4027.

(6) (a) Malmström, B. G. *Annu. Rev. Biochem.* **1982**, *51*, 21–59. (b) Cohen, I. A. *Struct. Bonding (Berlin)* **1980**, *40*, 1–37. (c) Farver, O.; Pecht, I. *FEBS Lett.* **1979**, *108*, 436–438. (d) LuBien, C. D.; Winkler, M. E.; Thamann, T. J.; Scott, R. A.; Co, M. S.; Hodgson, K. O.; Solomon, E. I. *J. Am. Chem. Soc.* **1981**, *103*, 7014–7016. (e) Spira-Solomon, D. J.; Allendorf, M. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1986**, *108*, 5318–5328.

(7) (a) Karlin, K. D.; Dahlstrom, P. L.; Cozzette, S. N.; Scensny, P. M.; Zubieta, J. *J. Chem. Soc., Chem. Commun.* **1981**, 881–882. (b) Blackburn, N. J.; Karlin, K. D.; Concannon, M.; Hayes, J. C.; Gultneh, Y.; Zubieta, J. *Ibid.* **1984**, 939–940. (c) Karlin, K. D.; Gultneh, Y.; Hutchinson, J. P.; Zubieta, J. *J. Am. Chem. Soc.* **1982**, *104*, 5240–5242. (d) Karlin, K. D.; Hayes, J. C.; Gultneh, Y.; Cruse, R. W.; McKown, J. W.; Hutchinson, J. P.; Zubieta, J. *Ibid.* **1984**, *106*, 2121–2128. (e) Karlin, K. D.; Gultneh, J.; Hayes, J. C.; Zubieta, J. *Inorg. Chem.* **1984**, *23*, 519–521. (f) Karlin, K. D.; Shi, J.; Hayes, J. C.; McKown, J. W.; Hutchinson, J. P.; Zubieta, J. *Inorg. Chim. Acta* **1984**, *91*, L3–L7.

(8) (a) Karlin, K. D.; Cruse, R. W.; Gultneh, Y.; Hayes, J. C.; Zubieta, J. *J. Am. Chem. Soc.* **1984**, *106*, 3372–3374. (b) Thompson, J. S. *Ibid.* **1984**, *106*, 4057–4059. (c) Thompson, J. S. *Ibid.* **1984**, *106*, 8308–8309. (d) Sorrell, T. N.; Malachowski, M. R.; Jameson, D. L. *Inorg. Chem.* **1982**, *21*, 3250–3252. (e) Sorrell, T. N.; Borovik, A. S. *J. Chem. Soc., Chem. Commun.* **1984**, 1489–1490. (f) Bhaduri, S.; Sapre, N. Y.; Basu, A. *Ibid.* **1986**, 197–198. (g) Nelson, S. M.; Esho, F.; Lavery, A.; Drew, M. G. B. *J. Am. Chem. Soc.* **1983**, *105*, 5693–5695. (h) Nelson, S. M.; Lavery, A.; Drew, M. G. B. *J. Chem. Soc., Dalton Trans.* **1986**, 911–920.

(9) (a) Simmons, M. G.; Wilson, L. J. *J. Chem. Soc., Chem. Commun.* **1978**, 634–636. (b) Simmons, M. G.; Merrill, C. L.; Wilson, L. G.; Bottomley, L. A.; Kadish, K. M. *J. Chem. Soc., Dalton Trans.* **1980**, 1827–1837. (c) Merrill, C. L.; Wilson, L. J.; Thamann, T. J.; Loehr, T. M.; Ferris, N. S.; Woodruff, W. H. *Ibid.* **1984**, 2207–2221. (d) Casella, L.; Silver, M. E.; Ibers, J. A. *Inorg. Chem.* **1984**, *23*, 1409–1418. (e) Bulkowski, J. E.; Burk, P. L.; Ludmann, M. F.; Osborn, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 498–499. (f) Nishida, Y.; Takahashi, K.; Kuramoto, H.; Kida, S. *Inorg. Chim. Acta* **1981**, *548*, L103–L104.

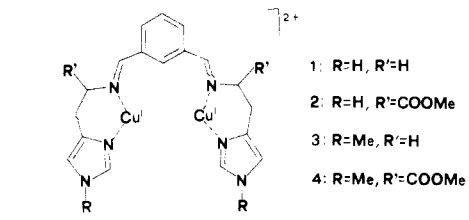
(10) (a) Karlin, K. D.; Hata, M. S.; Cruse, R. W.; Gultneh, Y. *J. Am. Chem. Soc.* **1985**, *107*, 5828–5829. (b) Karlin, K. D.; Cruse, R. W.; Gultneh, Y.; Farooq, A.; Hayes, J. C.; Zubieta, J. *Ibid.* **1987**, *109*, 2668–2679.

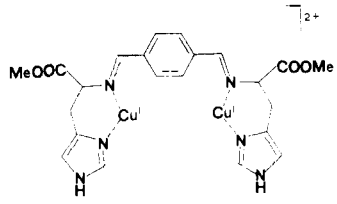
(11) Casella, L.; Ghelli, S. *Inorg. Chem.* **1983**, *22*, 2458–2463.

(12) Woolery, G. L.; Powers, L.; Winkler, M.; Solomon, E. I.; Spiro, T. G. *J. Am. Chem. Soc.* **1984**, *106*, 86–92.

0002-7863/88/1510-4221$01.50/0

In this paper we report the synthesis and reactivity toward dioxygen and carbon monoxide of the binuclear copper(I) complexes **1**–**5**[14] with bis(imines) of derivatives of histidine, which provide





5

two nitrogen donors to each copper(I) center. Although additional solvent coordination to these copper(I) centers occurs in solution, they share with two-coordinate Cu(I) the typical low affinity for carbon monoxide. The characterization of the products resulting from the oxygenation of these complexes is also given.

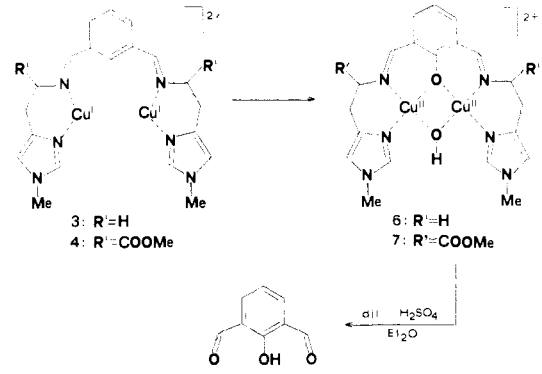
Experimental Section

Reagents and Solvents. All reagents were of the highest grade commercially available. Tetrakis(acetonitrile)copper(I) perchlorate,[15] N^{τ}-methylhistamine dihydrochloride,[16] and N^{τ}-methyl-L-histidine methyl ester dihydrochloride[17] were prepared according to published procedures. Acetonitrile (spectral grade) was distilled from potassium permanganate and dry potassium carbonate; then it was stored over calcium hydride and distilled immediately prior to use under a nitrogen atmosphere. Dimethylformamide was refluxed under vacuum over barium oxide to remove dimethylamine, stored over calcium hydride, and distilled under reduced pressure before use. Purified nitrogen gas was carefully deoxygenated with hot BASF R3-11 catalysts.

Physical Measurements. Elemental analyses were from the microanalytical laboratory of the University of Milano. Infrared spectra of solid compounds were obtained as Nujol mulls with a Nicolet MX-1E FT-IR instrument; a standard resolution of 2 cm^{-1} was used in the measurements. Electronic spectra were recorded on a Perkin-Elmer Lambda-5 spectrophotometer. Circular dichroism spectra were recorded on a Jasco J-500 C dichrograph. The optical and CD spectra of air-sensitive solutions were obtained in 1-cm and 1-mm quartz cells fitted with Schlenk connections. ^1H NMR spectra were recorded at 80 or 200 MHz on Bruker WP-80 or Bruker AC-200 FT spectrometers, respectively. Magnetic susceptibilities of solid samples were measured at 295 K by the Faraday technique on a Cahn 1000 electrobalance.

Manometric measurements of oxygen uptake were performed at constant pressure with a modified Warburg apparatus. A solution or suspension of the copper(I) complex (50–100 mg) in freshly distilled, dry solvent (30–50 mL) was prepared under a nitrogen atmosphere. The flask was attached to the microburet apparatus, and the system was thermostated at 15 °C. Nitrogen was removed from the solution under reduced pressure, but care was taken that a minimum of solvent loss occurred in this operation. After the system was allowed to equilibrate at 15 °C, stirring of the mixture was stopped. The flask was then rapidly

Scheme I



filled with dioxygen at atmospheric pressure and immediately connected with the gas buret, which was also filled with dioxygen (5 cm^3) previously. Vigorous stirring of the solution was accompanied by dioxygen uptake; readings were taken at atmospheric pressure from time to time, during several hours, until no further changes were apparent, by means of a Mariotte connected to the gas buret. A blank was taken after every experiment with pure solvent to correct the readings for the solubility of dioxygen in the solvent. Duplicate experiments showed a reproducibility in the measurements within ±10%.

Preparation of Copper(I) Complexes.[18] The synthesis and manipulation of all the copper(I) complexes were carried out in Schlenk glassware, under an atmosphere of purified nitrogen, according to the following general procedure. The amine or L-amino acid ester (5 mmol) was freed from its dihydrochloride salt as described previously[9d] and treated in degassed, dry methanol (50 mL) with benzene-1,3-dicarboxaldehyde or benzene-1,4-dicarboxaldehyde (2.5 mmol). Solid $Cu(MeCN)_4ClO_4$ (5.5 mmol) was then quickly added, and the mixture was stirred for about 1 h at room temperature and for a few hours at reflux temperature. After cooling, the crude product was collected by filtration and washed several times with carefully degassed absolute methanol. The materials were usually crystallized from methanol; however, since the solubility of $[Cu_2(pb\text{-}L\text{-}his)][ClO_4]_2$ is very low, this compound was simply washed with methanol at reflux temperature. Yields were in the range 30–50%.

$[Cu_2(mb\text{-}him)][ClO_4]_2$ (**1**). Anal. Calcd for $C_{18}H_{20}N_6Cl_2Cu_2O_8$: C, 33.44; H, 3.12; N, 13.00; Cu, 19.66. Found: C, 33.29; H, 3.28; N, 12.95; Cu, 19.5. IR (cm^{-1}): 3250 br [ν(NH)]; 3130 vw [Im ν(CH)]; 1624 m [ν(C=N)]; 1596 w, 1575 w, 1496 vw [ν(ring)]; 1100 vs br, 620 s [ν(ClO_4)]; 790 m, 723 w, 689 w [δ(CH)]. Electronic spectrum [CH_3CN; λ_{max}, nm (ϵ, M^{-1} cm^{-1})]: 290 sh (2700), 250 sh (17000). Λ_M (acetonitrile): 250 S cm^2 mol^{-1}, concentration 10^{-3} M.

$[Cu_2(mb\text{-}L\text{-}his)][ClO_4]_2$ (**2**). Anal. Calcd for $C_{22}H_{24}N_6Cl_2Cu_2O_{12}$·$CH_3OH$: C, 34.77; H, 3.55; N, 10.58; Cu, 16.00. Found: C, 34.58; H, 3.55; N, 10.56; Cu, 15.7. IR (cm^{-1}): 3250 br [ν(NH)]; 3127 w [Im ν(CH)]; 1710 s [ν(C=O)]; 1628 m [ν(C=N)]; 1596 w, 1574 vw, 1496 vw [ν(ring)]; 1100 vs br, 621 s [ν(ClO_4)]; 805 w, 721 m, 681 w [δ(CH)]. Electronic spectrum [CH_3CN; λ_{max}, nm (ϵ, M^{-1} cm^{-1})]: 290 sh (3200), 250 sh (24000). CD [CH_3CN; λ_{max}, nm ($\Delta\epsilon$, M^{-1} cm^{-1})]: 285 sh (−5.55), 248 (−10.33). Λ_M (acetonitrile): 235 S cm^2 mol^{-1}, concentration 10^{-3} M.

$[Cu_2(mb\text{-}Mehim)][ClO_4]_2$ (**3**). Anal. Calcd for $C_{20}H_{24}N_6Cl_2Cu_2O_8$: C, 35.62; H, 3.59; N, 12.46; Cu, 18.84. Found: C, 35.44; H, 3.59; N, 12.25; Cu, 18.6. IR (cm^{-1}): 3123 w [Im ν(CH)]; 1640 m, 1619 m [ν(C=N)]; 1596 w, 1576 w, 1526 m [ν(ring)]; 1095 vs br, 624 s [ν(ClO_4)]; 793 w, 721 m, 688 m [δ(CH)]. Electronic spectrum [CH_3CN; λ_{max}, nm (ϵ, M^{-1} cm^{-1})]: 300 sh (2900), 250 sh (20800). Λ_M (acetonitrile): 240 S cm^{-2} mol^{-1}, concentration 10^{-3} M.

$[Cu_2(mb\text{-}L\text{-}Mehis)][ClO_4]_2$ (**4**). Anal. Calcd for $C_{24}H_{28}N_6Cl_2Cu_2O_{12}$: C, 36.47; H, 3.54; N, 10.64; Cu, 16.08. Found:

(13) (a) Birker, J. J. M. W. L.; Hendriks, H. M. J.; Reedijk, J. *Inorg. Chim. Acta* **1981**, *55*, L17–L18. (b) Hendriks, H. M. J.; Birker, P. J. M. W. L.; Van Rijn, J.; Verschoor, G. C.; Reedijk, J. *J. Am. Chem. Soc.* **1982**, *104*, 3607–3617. (c) Sorrell, T. N.; Jameson, D. L. *Ibid.* **1982**, *104*, 2053–2054. (d) Sorrell, T. N.; Jameson, D. L. *Ibid.* **1983**, *105*, 6013–6018. (e) Villacorta, G. M.; Gibson, D.; Williams, I. D.; Lippard, S. J. *Ibid.* **1985**, *107*, 6732–6734. (f) Sorrell, T. N.; Borovik, A. S.; Caswell, D. S.; Grygon, C.; Spiro, T. G. *Ibid.* **1986**, *108*, 5636–5637.

(14) For a preliminary report on some of these systems, see: Casella, L.; Rigoni, L. *J. Chem. Soc., Chem. Commun.* **1985**, 1668–1669.

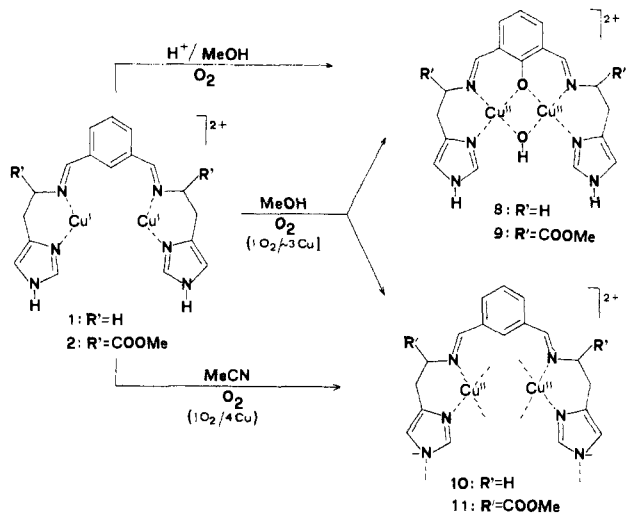
(15) Hemmerich, P.; Sigwart, C. *Experientia* **1963**, *19*, 488–489.

(16) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Roe, A. M.; Slater, R. A. *J. Med. Chem.* **1976**, *19*, 923–928.

(17) (a) Noordam, A.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 293–298. (b) Casella, L.; Gullotti, M. *Inorg. Chem.* **1983**, *22*, 242–249.

(18) Abbreviations used for the ligands are as follows. The condensation products between benzene-1,3-dicarboxaldehyde and two molecules of amine or amino ester are mb-him for histamine, mb-L-his for L-histidine methyl ester, mb-Mehim for N^{τ}-methylhistamine, and mb-L-Mehis for N^{τ}-methyl-L-histidine methyl ester. The bis(imine) obtained from benzene-1,4-dicarboxaldehyde and two molecules of L-histidine methyl ester is abbreviated as pb-L-his. The bis(imine) ligands of 2-hydroxy-5-methylbenzene-1,3-dicarboxaldehyde resulting from hydroxylation of complexes **1**–**4** are abbreviated as mbOH-him, mbOH-L-his, mbOH-Mehim, and mbOH-L-Mehis, respectively. The bis(imine) ligand anions resulting from loss of one or two imidazole protons in the oxidation of complexes **1** and **2** are indicated as (mb-him,–H) or (mb-him,–2H) and (mb-L-his,–H) or (mb-L-his,–2H), respectively. Other abbreviations are imidazole = Im, phenyl = Ph, and methyl = Me.

Scheme II



C, 36.82; H, 3.65; N, 10.92; Cu, 15.8. IR (cm^{-1}): 3130 m [Im ν(CH)]; 1713 s [ν(C=O)]; 1627 m [ν(C=N)]; 1597 w, 1580 w, 1526 m [ν(ring)]; 1095 vs br, 623 s [$\nu(ClO_4)$]; 800 w, 722 w, 683 w [δ(CH)]. Electronic spectrum [CH_3CN; λ_{max}, nm (ϵ, M^{-1} cm^{-1})]: 290 sh (2700), 250 sh (22 000). CD [CH_3CN; λ_{max}, nm ($\Delta\epsilon$, M^{-1} cm^{-1})]: 295 (−2.20), 250 (−3.14). Λ_M (acetonitrile): 232 S cm^2 mol^{-1}, concentration 10^{-3} M.

$[Cu_2$(pb-L-his)$][ClO_4]_2$ (**5**). Anal. Calcd for $C_{22}H_{24}N_6Cl_2Cu_2O_{12}$: C, 34.65; H, 3.18; N, 11.02. Found: C, 34.28; H, 3.30; N, 11.08. IR (cm^{-1}): 3300 br [ν(NH)]; 3140 w [Im ν(CH)]; 1723 s [ν(C=O)]; 1622 s [ν(C=N)]; 1600 sh, 1500 w [ν(ring)]; 1100 vs br, 623 s [$\nu(ClO_4)$]; 823 m, 721 m, 655 w [δ(CH)]. This compound is almost insoluble in common solvents.

Isolation of the Oxygenation Products.[18] The phenolate, hydroxy-bridged copper(II) complexes $[Cu_2$(mbO-Mehim)(OH)$][ClO_4]_2$ (**6**) and $[Cu_2$(mbO-L-Mehis)(OH)$][ClO_4]_2$ (**7**) (see Scheme I) were isolated by exposing solutions of **3** and **4** (~50 mg), respectively, in dry and deoxygenated acetonitrile (50 mL) to dry oxygen for 3 h under stirring. The resulting green solutions were concentrated to a small volume and the products precipitated by adding dry diethyl ether. Yields were above 90%.

$[Cu_2$(mbO-Mehim)(OH)$][ClO_4]_2$ (**6**). Anal. Calcd for $C_{20}H_{24}N_6Cl_2Cu_2O_{10}$: C, 34.00; H, 3.42; N, 11.90. Found: C, 33.68; H, 3.42; N, 11.60. IR (cm^{-1}): 3570 m [ν(OH)]; 3136 w [Im ν(CH)]; 1642 s [ν(C=N)]; 1572 s, 1530 m [ν(ring)]; 1095 vs br, 624 s [$\nu(ClO_4)$]; 759 w [δ(CH)]. Electronic spectrum [CH_3CN; λ_{max}, nm (ϵ, M^{-1} cm^{-1})]: 600 (140), 370 sh (4600), 350 (6300), 250 (29 800). Magnetic moment: 1.15 μ_B.

$[Cu_2$(mbO-L-Mehis)(OH)$][ClO_4]_2$ (**7**). Anal. Calcd for $C_{24}H_{28}N_6Cl_2O_4$: C, 35.04; H, 3.43; N, 10.22. Found: C, 35.42; H, 3.44; N, 10.48. IR (cm^{-1}): 3525 m [ν(OH)]; 3126 w [Im ν(CH)]; 1733 s [ν(C=O)]; 1637 s [ν(C=N)]; 1567 m, 1528 m [ν(ring)]; 1085 vs br, 621 s [$\nu(ClO_4)$]; 756 m, 721 m [δ(CH)]. Electronic spectrum [CH_3CN, λ_{max}, nm [ϵ, M^{-1} cm^{-1})]: 620 (110), 370 sh (4000), 353 (5000), 330 sh (3800), 251 (29 000). CD [CH_3CN; λ_{max}, nm ($\Delta\epsilon$, M^{-1} cm^{-1})]: 650 sh (+0.19), 575 (+0.28), 498 (−0.05), 369 (+4.95), 322 (−0.94), 300 sh (+0.24), 265 (+8.50), 237 (+7.30). Magnetic moment: 1.13 μ_B.

The phenolate, hydroxo-bridged complex $[Cu_2$(mb-L-his)(OH)$][ClO_4]_2$ (**9**) and the μ-imidazolato complex $[Cu_2$(mb-L-his,−2H)$][ClO_4]_2$ (**11**) (see Scheme II) were obtained by exposure of a solution of **2** (75 mg) in degassed absolute methanol (80 mL) to dry nitrogen for 3 h under stirring. The green solution produced was concentrated to about 30 mL under vacuum. Then 5 mL of dry diethyl ether was added, and the precipitate of **11** was quickly collected by filtration (35 mg). Evaporation almost to dryness of the filtrate followed by addition of dry diethyl ether (20 mL) yielded complex **9** (30 mg).

$[Cu_2$(mbO-L-his)(OH)$][ClO_4]_2 \cdot 2CH_3OH$ (**9**). Anal. Calcd for $C_{22}H_{24}N_6Cl_2Cu_2O_{14} \cdot 2CH_3OH$: C, 33.57; H, 3.75; N, 9.79. Found: C, 33.25; H, 3.79; N, 9.72. IR (cm^{-1}): 3550 br [ν(OH)]; 3300 br [ν(NH)]; 3130 w [Im ν(CH)]; 1733 s [ν(C=O)]; 1636 s [ν(C=N)]; 1592 vw, 1568 m, 1505 w [ν(ring)]; 1090 vs br, 622 s [$\nu(ClO_4)$]; 757 w, 721 m [δ(CH)]. Electronic spectrum [DMF; λ_{max}, nm (ϵ, M^{-1} cm^{-1})]: 614 (120), 358 (5700). CD [DMF; λ_{max}, nm ($\Delta\epsilon$, M^{-1} cm^{-1})]: 706 (−0.13), 610 (+0.17), 525 (−0.14), 374 (+4.41), 324 (−2.86), 290 sh (−0.50). Magnetic moment: 0.70 μ_B.

$[Cu_2$(mb-L-his,−2H)$][ClO_4]_2 \cdot 2CH_3OH$ (**11**). Anal. Calcd for $C_{22}H_{22}N_6Cl_2Cu_2O_{12} \cdot 2CH_3OH$: C, 34.96; H, 3.67; N, 10.20. Found: C, 34.83; H, 3.64; N, 10.59. IR (cm^{-1}): 3550 br [ν(OH)]; 3250 br [ν(NH)]; 3140 w [Im ν(CH)]; 1710 s [ν(C=O)]; 1625 m [ν(C=N)]; 1595 w, 1505 vw [ν(ring)]; 1095 vs br, 622 [$\nu(ClO_4)$]; 800 w, 722 w, 683 vw [δ(CH)]. Electronic spectrum [DMF; λ_{max}, nm (ϵ, M^{-1} cm^{-1})]: 600 (150), 360 sh (1800), 300 sh (3000).

The phenolate, hydroxy-bridged complex $[Cu_2$(mbO-him)(OH)$][ClO_4]_2$ (**8**) was obtained from oxygenation of **1** (70 mg) in absolute methanol (80 mL) as described above for **9** (yield 38 mg), while the corresponding μ-imidazolato complex **10** was not obtained in acceptable purity.

$[Cu_2$(mbO-him)(OH)$][ClO_4]_2 \cdot CH_3OH$ (**8**). Anal. Calcd for $C_{18}H_{20}N_6Cl_2Cu_2O_{10} \cdot CH_3OH$: C, 32.12; H, 3.41; N, 11.83. Found: C, 32.50; H, 3.44; N, 12.03. IR (cm^{-1}): 3550 m [ν(OH)]; 3320 m br [ν(NH)]; 3143 w [Im ν(CH)]; 1639 s [ν(C=N)]; 1590 sh, 1571 s, 1505 w [ν(ring)]; 1090 vs, 622 s [$\nu(ClO_4)$]; 758 m, 721 w [δ(CH)]. Electronic spectrum [DMF; λ_{max}, nm (ϵ, M^{-1} cm^{-1})]: 615 (140), 370 sh (5300), 354 (6100), 263 (23 000). Magnetic moment: 0.71 μ_B.

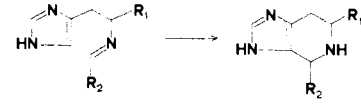
Isolation of 2-Hydroxy-5-methylbenzene-1,3-dicarboxaldehyde. This product was obtained upon oxygenation of a solution of **4** (73 mg) in dry, degassed acetonitrile (75 mL) for 3 h under stirring. The resulting solution was then evaporated to dryness. The green residue was treated with dilute sulfuric acid (20 mL) and extracted three times with diethyl ether (20 mL). The organic phase was washed with water, dried ($MgSO_4$), and evaporated to dryness to give a white solid residue (yield 95%). The spectral properties of this compound have been reported in ref 14.

The ^{18}O-labeled 2-hydroxy-5-methylbenzene-1,3-dicarboxaldehyde was prepared as above by exposing the acetonitrile solution of **4** to 90% $^{18}O_2$-enriched dioxygen. Mass spectrometric analysis of the resulting hydroxy dicarboxaldehyde shows the parent peak at m/z 152, indicating incorporation of one ^{18}O atom into the product.

Caution! Although the compounds reported in this paper seem to be stable to shock and heat, extreme care should be used in handling them for the potential explosive nature of perchlorate salts. We worked with no problems on 50–100 mg of the compounds.

Results and Discussion

Synthesis and Characterization. The preparation of the complexes was carried out by template synthesis in the presence of an excess of the copper(I) salt. In the absence of such an excess we found in some instances that the products were contaminated by the mononuclear, presumably four-coordinate copper(I) complexes of the bis(imine) ligands, as revealed by higher C, H, and N and lower Cu analyses. We did not attempt to isolate the free ligands since it is known that histidine or histamine Schiff bases readily undergo cyclization reactions to tetrahydropyrido[3,4-*d*]imidazole compounds according to reaction[19] 1. Formation



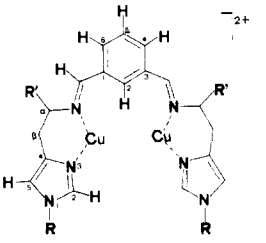
(1)

of these cyclic derivatives can be easily monitored by IR and especially ^1H NMR spectroscopies through the replacement of the features associated with the imine group (e.g. δ(CH=N) at δ 8.0–8.5) by those of the cyclic saturated amine compound (δ-(CH–R') at δ 5.7–6.0).[19] By contrast, the IR and NMR spectra of the copper(I) complexes display well-resolved ν(C=N) stretching bands (in the range 1620–1640 cm^{-1}) and azomethine proton signals, respectively.

The chemical shift data for the various aromatic, imine, and imidazole proton signals of the complexes **1–4** show some interesting regularity (Table I). The imine and imidazole 2-H protons undergo increasing downfield shift in the series $[Cu_2$(mb-L-his)$]^{2+}$ (**2**) < $[Cu_2$(mb-him)$]^{2+}$ (**1**) < $[Cu_2$(mb-L-Mehis)$]^{2+}$ (**4**) < $[Cu_2$(mb-Mehim $]^{2+}$ (**3**), i.e. with increase in the overall basicity of the ligands. Since these protons are on carbons directly attached to the nitrogen donor atoms, their shifts reflect the degree of σ-bonding interaction between the donor atoms and the metal centers. By contrast, the aromatic protons undergo an opposite trend, i.e. increasing upfield shift, in the above series, except for a reversal between **1** and **4**. Qualitatively, this effect may be accounted for by an enhancement of charge density on the carbon atoms of the aromatic nucleus, by bond back-donation from Cu(I) into the conjugated π^* system, since the aromatic protons are too

(19) Casella, L.; Gullotti, M. *J. Am. Chem. Soc.* **1981**, *103*, 6338–6347.

Table I. ^{1}H NMR Data for the Binuclear Copper(I) Complexes in CD_3CN[a]



complex	CH=N	Im 2-H	Im 5-H	Ph (4-H + 6-H)	Ph 2-H	Ph 5-H	α-CH	β-CH	OCH_3	NCH_3	Im NH
1	8.45 ~s	8.29 ~s	6.95 s	7.82 d (J_o = 7.5 Hz)	7.57 ~s	7.38 ~t	3.97 br	2.95 br			10.4 br
2	8.22 ~s	8.18 ~s	6.98 s	7.88 d (J_o = 7.3 Hz)	7.74 ~s	7.56 ~t	4.5 m	3.1–3.5 m	3.70 s		10.6 br
3	8.74 ~s	8.38 s	6.95 s	7.77 dd (J_o = 7.7 Hz; J_m = 1.4 Hz)	7.46 d	7.40 t	4.07 ~t ($J_{\alpha\beta}$ = 5.2 Hz)	3.00 ~t		3.68 s	
4	8.56 ~s	8.32 ~s	6.96 s	7.86 d (J_o = 7.5 Hz)	7.69 s	7.53 t	4.5 m	3.1–3.5 m	3.70 s	3.66 s	

[a] Spectra recorded under nitrogen: singlet = s, doublet = d, doublet of doublets = dd, triplet = t, multiplet = m, broad = br.

far from the metal sites to experience any direct bonding effects. This interpretation seems confirmed by the finding that the chemical shift of the imidazole 5-H proton, which is certainly closer to the copper(I) center than the aromatic protons, is practically unchanged in the spectra of the complexes **1–4**.

The ligands in $[Cu_2(mb\text{-}him)][ClO_4]_2$ and $[Cu_2(mb\text{-}Me\text{-}him)][ClO_4]_2$ have available for coordination only two nitrogen donors for each copper(I). Since the IR spectra of the complexes do not exhibit the characteristic pattern of IR bands for coordinated perchlorate groups, it may seem straightforward to assume two-coordinate structures for these copper(I) centers in the solid state. However, molecular models show that the fragments N–Cu–N cannot achieve a perfectly linear arrangement; therefore, it is likely that some intra- or intermolecular Cu^I–Cu^I bonding occurs in these complexes, as is often the case with Cu(I) systems with few donors,[20,23] and gives rise to three-coordinate structures. In the complexes containing histidine or *N*-methylhistidine residues, the ester groups of the ligands can additionally be involved in metal binding. Actually, the somewhat low ester ν(C=O) stretching frequency found in the IR spectra of $[Cu_2(mb\text{-L-}his)][ClO_4]_2$ and $[Cu_2(mb\text{-L-}Mehis)][ClO_4]_2$ in the solid state (but not in solution) may indicate an interaction of these groups with the metals. Unfortunately, all the attempts to grow crystals suitable for X-ray analysis and thus fully characterize these compounds in the solid state have been unsuccessful so far.

In solution the situation appears much simpler. Conductivity measurements show that the complexes behave as uni-divalent electrolytes and rule out the existence of polynuclear clusters. It is thus very likely that molecules of solvent coordinate to the copper(I) centers. A recent analysis of the electronic spectra of copper(I) complexes with pyrazole and imidazole ligands allows us to discriminate between two-, three-, or four-coordinate structures on the basis of the position and intensity of MLCT transitions.[13f] The bands in the range 285–300 nm observed in the spectra of the present complexes agree, in both position and intensity, with those associated with three-coordinate structures. This apparently confirms that a solvent molecule binds to each copper(I) center in solution. The CD spectra of the complexes containing histidine residues exhibit rather intense Cotton effects within the MLCT bands and corroborate the $d\sigma^* \rightarrow \pi^*$ assignment given for such transitions,[13f] since they imply a rotation of electronic charge.

Oxygenation. It is useful to describe the oxygenation behavior of the complexes starting from $[Cu_2(mb\text{-}Mehim)]^{2+}$ (**3**) and $[Cu_2(mb\text{-L-}Mehis)]^{2+}$ (**4**). Solutions of these compounds in any solvent react with dioxygen to give the corresponding μ-phenoxo, binuclear copper(II) complexes **6**, $[Cu_2(mbO\text{-}Mehim)(OH)]^{2+}$, and **7**, $[Cu_2(mbO\text{-L-}Mehis)(OH)]^{2+}$, respectively, according to the reaction depicted in Scheme I. The products **6** and **7** have an additional μ-hydroxo bridge when the reaction is carried out in nonprotic solvents, but this bridge may be replaced by a μ-alkoxo bridge when the reaction is performed in alcohol. The course of the oxygenation reaction can be conveniently monitored by UV–vis spectroscopy following the growth of a rather intense absorption band near 350 nm ($\epsilon \sim 6000\ M^{-1}\ cm^{-1}$) or that of a weaker visible band near 600 nm ($\epsilon \sim 100$) due to the product. The ~350-nm band is mostly associated with the (2-hydroxyphenyl)imino chromophore of the ligand in **6** and **7**,[19,24] with additional small contributions ($\epsilon \sim 500\ M^{-1}\ cm^{-1}$) by LMCT transitions from the phenolate group to Cu(II).[25] The stoichiometry of the reaction has been established by manometric measurements of dioxygen uptake and corresponds to 1 mol of O_2/mol of binuclear complex **3** or **4** (1:2 O_2/Cu). The reaction can thus be described schematically as in eq 2. The phenolic nature of the ligand in the products **6** and **7** can be probed simply by treating the sample

$$[Cu^I_2(LH)]^{2+} + O_2 \rightarrow [Cu^{II}_2(LO^-)(OH^-)]^{2+} \quad (2)$$

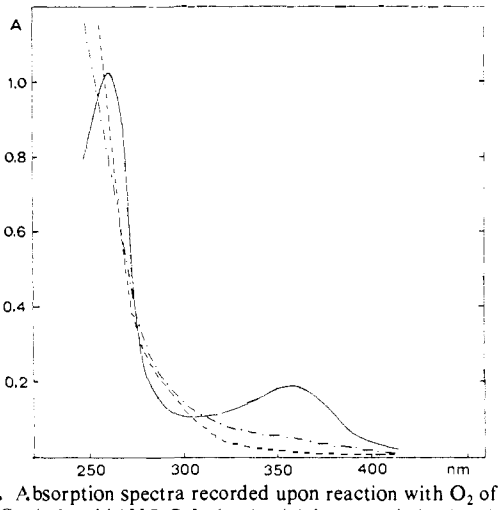


Figure 1. Absorption spectra recorded upon reaction with O_2 of a solution of $[Cu_2(mb\text{-L-}his)][ClO_4]_2$ (---): (a) in acetonitrile (–·–), (b) in methanol (—). The concentration of the copper(I) complex was about 6.0×10^{-4} M, and the optical path length was 0.1 cm in both cases.

(20) (a) Pasquali, M.; Floriani, C.; Gaetani-Manfredotti, A.; Guastini, C. *J. Am. Chem. Soc.* **1981**, *103*, 185–186. (b) Mealli, C.; Arcus, C. S.; Wilkinson, J. L.; Marks, T. J.; Ibers, J. A. *Ibid.* **1976**, *98*, 711–718.
(21) Do, Y.; Knobler, C. B.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1987**, *109*, 1853–1854, and references cited therein.
(22) Mehrotra, P. K.; Hoffmann, R. *Inorg. Chem.* **1978**, *17*, 2187–2189.
(23) Drew, M. G. B.; Lavery, A.; McKee, V.; Nelson, S. M. *J. Chem. Soc., Dalton Trans.* **1985**, 1771–1774.
(24) Smith, H. E. *Chem. Rev.* **1983**, *83*, 359–377.
(25) (a) Amundsen, A. R.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6730–6739. (b) Letter, J. E.; Baumann, J. E., Jr. *Ibid.* **1970**, *92*, 443–447. (c) Ainscogh, E. W.; Bingham, A. G.; Brodie, A. M.; Husbands, J. M.; Plowman, J. E. *J. Am. Chem. Soc., Dalton Trans.* **1981**, 1701–1707. (d) Hefford, R. J. W.; Pettit, L. D. *Ibid.* **1981**, 1331–1335. (e) Garnier-Suillerot, A.; Albertini, J. P.; Collet, A.; Faury, L.; Pastor, J. M.; Tosi, L. *Ibid.* **1981**, 2544–2549. (f) Kiss, T.; Gergely, A. *Ibid.* **1984**, 1951–1957.

with mineral acid and extracting with ether or chloroform 2-hydroxy-5-methylbenzene-1,3-dicarboxaldehyde.[14] A labeling experiment with $^{18}O_2$ unequivocally confirmed the incorporation of one ^{18}O atom into this product.

The reaction with dioxygen of the complexes $[Cu_2(mb\text{-}him)]^{2+}$ (**1**) or $[Cu_2(mb\text{-}L\text{-}his)]^{2+}$ (**2**) is markedly affected by the medium. In dry, nonprotic solvents like acetonitrile (10^{-3}–10^{-4} M) simple oxidation of copper(I) to copper(II) occurs, with concomitant reduction of O_2 to H_2O, as shown in Scheme II. The electronic spectra of the oxygenated solutions do not show the intense band near 350 nm that characterizes the hydroxylation products **6** and **7** but only a modest and featureless increase of absorption in the range 300–400 nm (Figure 1). The stoichiometry of the reaction, determined by the amount of O_2 absorbed by the solution, corresponds to 1 mol of O_2/2 mol of binuclear copper(I) complex (1:4 O_2/Cu) and can be described as in eq 3. The weak absorption

$$2[Cu^{I}_2(H_2L)]^{2+} + O_2 \rightarrow 2[Cu^{II}_2(L^{2-})]^{2+} + 2H_2O \quad (3)$$

of the products in the 300–400-nm region arises from charge-transfer transitions from the imine and imidazole or imidazolate groups to Cu(II).[26] Thus, the protons necessary for the reduction of O_2 come from the imidazole NH groups of the ligands. Deprotonation of amine NH groups by Cu(I)/O_2 systems, usually to form H_2O, has often been observed,[27] and it is likely that a similar mechanism is operative here. We can formulate the oxidation products **10** and **11** as the bis(imidazolate)-bridged copper(II) complexes $[Cu_2(mb\text{-}him,-2H)]^{2+}$ and $[Cu_2(mb\text{-}L\text{-}his,-2H)]^{2+}$, respectively, formed according to reaction 3 or the mono(imidazolate)-bridged, hydroxocopper(II) complexes $[Cu_2(mb\text{-}him,-H)(OH)]^{2+}$ and $[Cu_2(mb\text{-}L\text{-}his,-H)(OH)]^{2+}$, respectively, formed according to the equivalent oxidation reaction (4).

$$2[Cu^{I}_2(H_2L)]^{2+} + O_2 \rightarrow 2[Cu^{II}_2(HL^{-})(OH^{-})]^{2+} \quad (4)$$

When the reaction between O_2 and the complexes $[Cu_2(mb\text{-}him)]^{2+}$ or $[Cu_2(mb\text{-}L\text{-}his)]^{2+}$ is carried out in protic solvents like methanol (10^{-3}–10^{-4} M), the optical spectra show the appearance of the 350-nm band that characterizes the hydroxylation products **6** and **7**, but its intensity is only about half of that observed in the oxygenation of **3** and **4** (Figure 1). Also, the amount of dioxygen absorbed in these conditions is higher than in nonprotic medium and corresponds to about 1:3 O_2/Cu. We thus conclude that in this case the reaction of **1** and **2** with O_2 leads to mixtures of the hydroxylation products **8**, $[Cu_2(mbO\text{-}him)(OH)]^{2+}$, and **9**, $[Cu_2(mbO\text{-}L\text{-}his)(OH)]^{2+}$, respectively, and the oxidation products **10** and **11**, respectively, in approximately a 1:1 ratio (Scheme II). Unlike **1**–**4** the oxygenation of $[Cu_2(pb\text{-}L\text{-}his)][ClO_4]_2$ in any solvent provides simple oxidation products, which we formulated as the analogues of **11** but did not characterize further.

The solvent dependence of the oxygenation of **1** and **2** suggests that we may be able to shift the ratio between the hydroxylation (**8** and **9**) and the oxidation products (**10** and **11**) in favor of the former product by increasing the proton donor ability of the medium. This was proved by carrying out the oxygenation of $[Cu_2(mb\text{-}him)]^{2+}$ and $[Cu_2(mb\text{-}L\text{-}his)]^{2+}$ in alcoholic medium containing small amounts of acid. As is shown in Figure 2 for the oxygenation of **2**, the 350-nm absorption band associated with **9** increases markedly in the presence of acetic acid. Yields of **9** above 90% are estimated for reactions carried out with 0.5–1.0% (v/v) concentration of acetic acid in methanol. Larger amounts of acetic acid lead to a decrease in the yield of **9**, probably because the starting copper(I) complex is cleaved when the medium becomes too acidic. It is also expected that in the presence of acetic acid the μ-hydroxo bridge of the hydroxylation products **8** and **9** will be replaced by an acetate bridge. Results similar to those displayed in Figure 2 were obtained using perchloric acid instead of acetic acid. In this case the highest amounts of **8** and **9** were obtained when the acid was only slightly more than in stoichiometric amount with respect to copper(I).

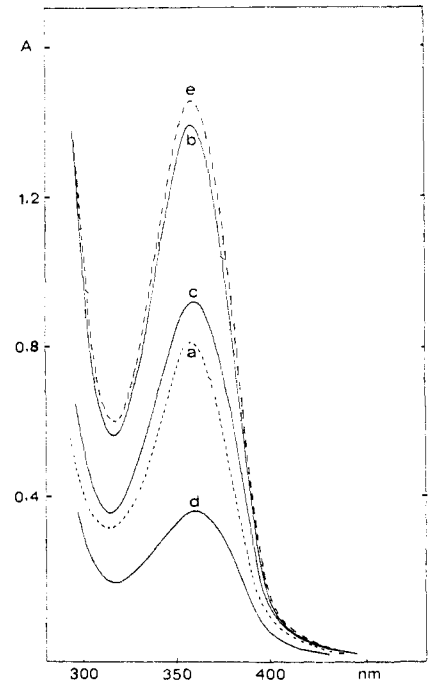


Figure 2. Absorption spectra recorded on oxygenated solutions of $[Cu_2(mb\text{-}L\text{-}his)][ClO_4]_2$ in methanol (a) and in methanol containing 1% (b), 5% (c), and 20% (d) (v/v) acetic acid, respectively. The concentration of the complex was 2.7×10^{-4} M, and the optical path length was 1 cm in all cases. Spectrum e represents the hypothetical 100% conversion to $[Cu_2(mbO\text{-}L\text{-}his)(OH)][ClO_4]_2$.

Characterization of the Oxygenation Products. The phenolate and hydroxy-bridged binuclear Cu(II) complexes $[Cu_2(mbO\text{-}Mehim)(OH)][ClO_4]_2$ (**6**) and $[Cu_2(mbO\text{-}L\text{-}Mehis)(OH)][ClO_4]_2$ (**7**) were isolated in high yields by oxygenating acetonitrile or methanol solutions of **3** and **4**, respectively, for several hours and adding diethyl ether to the resulting green solutions. The μ-phenoxo, $[Cu_2(mbO\text{-}L\text{-}his)(OH)][ClO_4]_2$ (**9**), and the μ-imidazolato, $[Cu_2(mb\text{-}L\text{-}his,-2H)][ClO_4]_2$ (**11**), binuclear complexes resulting from oxygenation of solutions of **2** in methanol could be conveniently separated on the basis of their different solubility, since the μ-imidazolato complex is much less soluble than the μ-phenoxo derivative. Both these products strongly retain molecules of methanol, suggesting that methoxo groups may replace the μ-hydroxo group in **9** and the μ-imidazolato group in **11**. However, the product **11** obtained when the oxygenation reaction was carried out in isopropyl alcohol contains no molecules of solvent, and it is thus a true bis(μ-imidazolato)-bridged compound.[28] From the oxygenation of **1** in methanol, carried out as for **2**, we could obtain only the μ-phenoxo derivative $[Cu_2(mbO\text{-}him)(OH)][ClO_4]_2$ (**8**) in reasonable purity, while the elemental analyses of the μ-imidazolato compound (higher C, H, and N values and lower Cu content) revealed some loss of copper

(26) (a) Schugar, H. J. In *Copper Coordination Chemistry: Biochemical and Inorganic Perspectives*; Karlin, K. D., Zubieta, J., Eds.; Adenine: Guilderland, NY, 1983; pp 43–74. (b) Bernaducci, E. E.; Bharadwaj, P. K.; Lalancette, R. A.; Krogh-Jespersen, K.; Potenza, J. A.; Schugar, H. J. *Inorg. Chem.* **1983**, *22*, 3911–3920. (c) Casella, L.; Gullotti, M. *J. Inorg. Biochem.* **1983**, *18*, 19–31; *Inorg. Chem.* **1983**, *22*, 242–249, 2259–2266.

(27) (a) Burnett, M. G.; Mckee, V.; Nelson, S. M.; Drew, M. G. B. *J. Chem. Soc., Chem. Commun.* **1980**, 829–831. (b) Cabral, J. d. O.; Cabral, M. F.; Drew, M. G. B.; Esho, F. S.; Nelson, S. M. *Ibid.* **1982**, 1068–1069. (c) Nelson, S. M. *Inorg. Chim. Acta* **1982**, *62*, 39–50. (d) Hoedt, R. W. M. T.; Hulsbergen, F. B.; Verschoor, G. C.; Reedijk, J. *Inorg. Chem.* **1982**, *21*, 2369–2373. (e) Kajimoto, T.; Takahashi, H.; Tsuji, J. *J. Org. Chem.* **1976**, *41*, 1389–1393. (f) Kametani, T.; Takahashi, K.; Ohsawa, T.; Ihara, M. *Synthesis* **1977**, 245.

(28) $[Cu_2(mb\text{-}L\text{-}his,-2H)][ClO_4]_2$. Anal. Calcd for $C_{22}H_{22}N_6Cl_2Cu_2O_{12}$: C, 34.75; H, 2.92; N, 11.05. Found: C, 35.00; H, 2.71; N, 10.93. IR (cm^{-1}): 3130 w [Im ν(CH)]; 1708 s [ν(C=O)]; 1628 m [ν(C=N)]; 1596 w, 1505 vw [ν(ring)]; 1095 vs br, 621 s [$\nu(ClO_4)$]; 721 w, 681 w [δ(CH)]. Electronic spectrum [DMF, λ_{max}, nm (ϵ, M^{-1} cm^{-1})]: 627 (160), 420 sh (300), 380 sh (1000), 340 sh (2400). CD [DMF; λ_{max}, nm ($\Delta\epsilon$, M^{-1} cm^{-1})]: 610 (+0.24), 420 (−0.52), 326 (−2.15), 265 (−6.20).

(approximately 2:3 ligands/Cu), a predictable result in view of the low denticity of the ligand.

The products **7**, **9**, and **11**, obtained from copper(I) complexes containing chiral ligands, appear reasonably optically stable, although we noted slow racemization processes upon standing of their solutions. In repeated preparations of **7**, **9**, and **11**, we never observed byproducts resulting from decarboxylation at the amino acid residue, a process that has been occasionally observed for metal complexes of histidine imines when the amino acid residue is bound, as it is here, in a histamine-like fashion.[9d,29] We did obtain, however, oxygenation and oxidation products that underwent some degree of hydrolysis of the ester groups when we used undried solvents. These byproducts can be easily recognized by IR spectra displaying broad carboxylate bands near 1600 cm^{-1}.

The spectral properties of the μ-phenoxo complexes **6–9** are very similar to those of binuclear copper(II) complexes of the bis(imines) derived from 2-hydroxy-5-methylisophthalaldehyde,[30,31] substantiating the structural analogy between the two groups of complexes. Besides the intense electronic absorption near 350 nm, the (2-hydroxyphenyl)imino chromophore is characterized by a medium to strong IR band near 1570 cm^{-1} (replacing the much weaker aromatic ring vibrations of **1–4** in the same range); this is associated with the ν(CO) vibration of the phenolic residue, which assumes partial double-bond character by conjugation with the imine groups.[31] The presence of equatorial double bridges between tetragonal copper(II) centers establishes an efficient pathway for spin coupling of the unpaired electrons, as shown by the reduced values of the magnetic moments found for **6–9** (μ_{eff} 0.7–1.2 μ_B at room temperature). These μ_{eff} values are similar to those of the related complexes derived from 2-hydroxy-5-methylisophthalaldehyde.[30,31]

It is interesting to note that the CD range spanned by the near-UV absorption of the μ-phenoxo complexes **7** and **9** (300–400 nm) contains two bands of opposite sign: a prominent, positive band near 370 nm, due to the imine $\pi \rightarrow \pi^*$ transition and, possibly, to O(phenolate) $\rightarrow$ Cu(II) LMCT,[25] and a weaker negative band near 320 nm, probably associated with $HO^- \rightarrow$ or $RO^- \rightarrow$ Cu(II) LMCT.[3,7d,32] Reduction of these complexes with ascorbate under anaerobic conditions supports the above assignments, since the negative CD peak is absent in the spectra of the resulting copper(I) solutions and a single positive band remains in the CD spectrum, with the maximum at ~365 nm almost coincident with the absorption maximum. The copper(I) solutions display also a new absorption band near 500 nm, which is responsible for their purple color, and by analogy with the spectra of other aromatic bis(imine)–copper(I) complexes,[9,23] is attributed to charge-transfer transitions from the filled copper(I) d orbitals to low-energy π^* orbitals of the conjugated imine system.

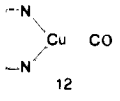
Although the characterization of the μ-imidazolate complexes **11** obtained in the various conditions is still incomplete, it is likely that in the bis(μ-imidazolato)-bridged complex $[Cu_2(mb\text{-}L\text{-}his,-2H)][ClO_4]_2$ each copper(II) center achieves four-coordination by binding intra- or intermolecularly to the oxygen atom of a carbonyl group, as shown by the markedly reduced position of the ester ν(C=O) stretch in the IR spectrum of the complex.[28] The complicated polymeric structure of this compound resulting from the double μ-imidazolate bridging is reflected by its very low solubility even in polar solvents. The most notable signature of the imidazolate–Cu^{II} interaction appears in the CD spectrum of the complex, where the two bands near 325 and 420 nm can be associated with LMCT transitions from π(imidazolate), and possibly also from π(imine), to Cu(II).[26] The corresponding low-intensity and broad optical absorption in the 300–400-nm range is in favor of such an assignment.

Table II. Carbonyl Stretching Frequencies for the Adducts of the Copper(I) Complexes in Methanol Solution[a]

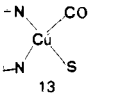
complex	ν(CO), cm^{-1}	
	$n = 0$	$n = 5$
$[Cu_2(mb\text{-}him)][ClO_4]_2$	2088	2071
$[Cu_2(mb\text{-}L\text{-}his)][ClO_4]_2$	2095	2073
$[Cu_2(mb\text{-}Mehim)][ClO_4]_2$	2096	2073
$[Cu_2(mb\text{-}L\text{-}Mehis)][ClO_4]_2$	2093	2072
$[Cu_2(pb\text{-}L\text{-}his)][ClO_4]_2$	2091	2069

[a] The number n refers to the moles of imidazole added per mole of copper(I) to the solution. Higher amounts of imidazole did not affect the spectra.

Reaction with Carbon Monoxide. The copper(I) complexes **1–5** react reversibly with carbon monoxide in solution to form weak adducts. These adducts lose CO by simple treatment under vacuum of the solution. The position of ν(CO) occurs in the range 2088–2096 cm^{-1} (Table II) and is thus indicative of terminally bound CO, since bridging CO exhibits a much lower stretching frequency.[33] The rather low affinity of the present complexes for CO[34] is reminiscent of the behavior of two-coordinate Cu(I) complexes with nitrogen donors,[13c,d] which often exhibit even complete lack of reactivity toward CO. In those systems the almost perfectly linear arrangement of the N–Cu–N fragment is probably responsible for the inertness to CO, whereas here such a linear arrangement cannot be achieved. This conclusion is supported by the behavior of the dicopper(I) complexes of tropocoronands, which do form trigonal CO adducts but where the N–Cu–N fragment is necessarily bent.[13e] The very similar position of ν(CO) observed for the carbonyl adducts of **3** and **4** in solution and in the solid state[34] indicates that trigonal, **12**, rather than tetragonal coordination, **13** (S = solvent), occurs also in the adducts of **1–5**.



12



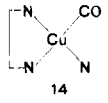
13

The position of ν(CO) for the carbonyl adducts of **1–5** is intermediate between those reported for other trigonal N_2CuCO complexes. The adducts of bis(pyrazole)- or bis(picoline)copper(I) complexes display the ν(CO) stretch at 2112–2117 cm^{-1},[13d] while for those of the dicopper(I) tropocoronands ν(CO) occurs at 2070 cm^{-1}.[13e] These differences can be accounted for qualitatively in terms of the basicity of the nitrogen ligands, since it is to be expected that an increase of electron density on copper(I) will stabilize the binding of a π-acid ligand such as CO and correspondingly decrease ν(CO) for the adduct. The basicity of picoline or pyrazole is lower than that of imidazole, and this is reflected by the higher frequency of ν(CO) in the carbonyl complexes of the former ligands. On the other hand, the nitrogen donors of the tropocoronands carry negative charge that concentrates considerable electron density on copper(I) and lowers remarkably ν(CO) in the carbonyl complexes. On the basis of the data in Table II, quite certainly the carbonyl adduct of the copper(I)–histamine complex, $[Cu(him)(CO)]^+$, exhibiting ν(CO) at 2091 cm^{-1},[35] has been incorrectly formulated and contains a trigonal N_2CuCO fragment. The ligand basicity criterion, however, cannot be taken too strictly, since other factors can be operative. For instance, it has been found that a slight perturbation of the basically trigonal N_2CuCO unit even by an extremely weakly coordinating anion such as ClO_4^- is able to raise ν(CO) above the

(29) Casella, L.; Gullotti, M.; Pacchioni, G. *J. Am. Chem. Soc.* **1982**, *104*, 2386–2396.
(30) Grzybowski, J. J.; Merrell, P. H.; Urbach, F. L. *Inorg. Chem.* **1978**, *17*, 3078–3802.
(31) Mandal, S. K.; Nag, K. J. *J. Chem. Soc., Dalton Trans.* **1984**, 2141–2149.
(32) (a) Arcus, C.; Fivizzani, K. P.; Pankovic, S. F. *J. Inorg. Nucl. Chem.* **1977**, *39*, 285–287. (b) Ishimura, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3728–3733.
(33) (a) Pasquali, M.; Floriani, C.; Venturi, G.; Gaetani-Manfredotti, A. G.; Chiesi-Villa, A. *J. Am. Chem. Soc.* **1982**, *104*, 4092–4099. (b) Doyle, G.; Eriksen, K. A.; Modrick, M.; Ansell, G. *Organometallics* **1982**, *1*, 1613–1618.
(34) We were able to isolate carbonyl adducts in the solid state only for the complexes **3** and **4**, containing N-methylated imidazole nuclei, by evaporating to dryness the carbonylated solutions under a stream of CO. For the other complexes this treatment afforded the unreacted Cu(I) complexes. The solid-state IR spectra of the CO adducts of **3** and **4** displayed single ν(CO) bands at 2095–2098 cm^{-1}, very close to the values observed in solution.
(35) Pasquali, M.; Marini, G.; Floriani, C.; Gaetani-Manfredotti, A.; Guastini, C. *Inorg. Chem.* **1980**, *19*, 2525-2531.

position expected on the basis of the ligand basicity alone.[36]

The addition of an excess donor base to solutions of **1–5** promotes formation of a different carbonyl adduct, which we formulate e.g. as N_3CuCO (**14**) on the basis of ν(CO). The carbonyl



14

stretching frequencies observed in the presence of an excess imidazole occur near 2070 cm^{-1} (Table II). These ν(CO) values are in the range observed for other N_3CuCO complexes containing ligands with comparable basicity,[13a,d,35,37] while similar complexes with ligands of lower basicity display ν(CO) at higher energies.[11,38] The data obtained for the present complexes support the view[13c] that the carbonyl adduct of mollusc hemocyanins (ν(CO) at 2054–2063 cm^{-1})[39] contains N_3CuCO sites, where the nitrogen donors are quite certainly provided by histidine imidazoles. The somewhat higher values of ν(CO) found here for the adducts of type **14** are due to the presence of an imine instead of a third imidazole group. As a matter of fact, the closest ν(CO) values to the protein data are provided by copper(I) carbonyl complexes with N_3CuCO cores containing two imidazoles, or benzimidazoles, and a third nitrogen ligand with basicity higher than that of the imine group.[13a,c,35] Hemocyanins from crustaceans form carbonyl adducts with lower CO stretching frequencies (2043–2045 cm^{-1}).[39b] This may suggest either a different ligand environment for copper(I) or the existence of some perturbation on the CO fragment, such as that (H bonding) found recently for the CO adducts of horseradish peroxidase[40] and cytochrome *c* peroxidase.[41]

Biological Relevance. The present investigation has explored the chemistry of a new family of binuclear and formally two-coordinate copper(I) complexes with ligands of potential biological interest. The copper-mediated hydroxylation of the phenyl nucleus of **1–4** is reminiscent of that effected by copper monooxygenases.[42] Although this reaction has precedent in synthetic copper systems,[7ad,43] the particular ligand type of the complexes reported here bears on the feasibility of the reaction scheme proposed by Solomon et al. for the mechanism of tyrosinase, where a binuclear, two-coordinate copper(I) site, with imidazole ligands, was involved for the deoxy form of the protein.[5] While we have no evidence at the present time for the possible intermediates of the reaction, a copper–dioxygen adduct is obviously the attractive candidate on the basis of the stoichiometry of the oxygenation reaction.

Two other aspects of the reactivity of these copper(I) systems with O_2 may have biological relevance with respect to (i) medium effects and (ii) substrate activation. As evidenced by the behavior of $[Cu_2(mb\text{-}him)]^{2+}$ and $[Cu_2(mb\text{-}L\text{-}his)]^{2+}$, the competition between aromatic hydroxylation and simple copper(I) oxidation is controlled by subtle acidity requirements of the medium. The effect of enhancement of the hydroxylation reaction in acidic medium may actually indicate the involvement of a protonated dioxygen species, but we emphasize that a similar control can be operative in the enzymic reactions, where often changes in the local availability of protons are induced by group transfer or conformational modifications in the neighborhood of the active site. On the other hand, the failure by the complex $[Cu_2(pb\text{-}L\text{-}his)]^{2+}$ (**5**) to undergo aromatic hydroxylation is associated with lack of activation of the appropriate position of the phenyl nucleus of the ligand. Here, the larger separation between the two copper(I) centers may actually render more difficult, if not impossible, the formation of an intramolecular $Cu\text{–}O_2\text{–}Cu$ bridge as that hypothesized in the Solomon's reaction scheme for tyrosinase.[5]

Finally, the picture emerging from the studies on CO binding by copper(I) complexes indicates that ν(CO) may become a useful probe for investigating the ligand environment of the copper(I) sites in the proteins.[44] The currently available protein data are practically limited to that of carbonyl hemocyanin, but it should not be too difficult to obtain this type of information for other copper proteins. As shown by the variability of ν(CO) to the Cu(I) environment, it is important that model studies aimed at mimicking the spectral behavior of the protein derivatives contain ligand types as close as possible to the amino acid residues that are possible candidates for the metal sites in the biological systems. This has been our effort here and in other work currently in progress on related systems.

Acknowledgment. This work was supported by the Italian MPI and the Italian CNR. We thank M. Bonfà for recording the NMR spectra, M. S. Franzoni for the magnetic susceptibility measurements, and P. Russo for the MS spectra.

(36) (a) Pasquali, M.; Floriani, C.; Gaetani-Manfredotti, A. *J. Chem. Soc., Chem. Commun.* **1987**, 921–922. (b) Pasquali, M.; Floriani, C.; Gaetani-Manfredotti, A. *Inorg. Chem.* **1980**, *19*, 1191–1197. (c) Thompson, J. S.; Whitney, J. F. *Ibid.* **1984**, *23*, 2813–2819. (d) Thompson, J. S.; Świątek, R. M. *Ibid.* **1985**, *24*, 110–113.

(37) (a) Bruce, M. I. *J. Organomet. Chem.* **1972**, *44*, 209–226. (b) Gagnē, R. R.; Gall, R. S.; Lisensky, G. C.; Marsh, R. E.; Spelz, L. M. *Inorg. Chem.* **1979**, *18*, 771–781. (c) Pasquali, M.; Marchetti, F.; Floriani, C. *Ibid.* **1978**, *17*, 1684–1688.

(38) Gagnē, R. R.; Kreh, R. P.; Dodge, J. A.; Marsh, R. E.; McCool, M. *Inorg. Chem.* **1982**, *21*, 254–261.

(39) (a) Alben, J. O.; Yen, L.; Farrier, N. J. *J. Am. Chem. Soc.* **1970**, *92*, 4475–4476. (b) Yen-Fager, L.; Alben, J. O. *Biochemistry* **1972**, *11*, 4786–4792.

(40) Evangelista-Kirkup, R.; Smulevich, G.; Spiro, T. G. *Biochemistry* **1986**, *25*, 4420–4425.

(41) Smulevich, G.; Evangelista-Kirkup, R.; English, A.; Spiro, T. G. *Biochemistry* **1986**, *25*, 4426–4430.

(42) Spiro, T. G., Ed. *Copper Proteins*; Wiley: New York, 1981.

(43) (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic: New York, 1981. (b) Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1982**, 1573–1576, 1577–1580. (c) Rogic, M. M.; Swerdloff, M. D.; Demmin, T. R. In Reference 22a, pp 259–279. (d) Kinoshita, T.; Harada, J.; Ito, S.; Sasaki, K. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 502.

(44) For instance, see: Sorrell, T. N.; Borovik, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 2479–2481.