Synthesis, Structure, and Reactivity of Copper Dioxygen Complexes Derived from Molecular Receptor Ligands

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Three novel bis{(2-pyridyl)ethyl}amine (PY2) containing ligands and their corresponding Cu(I) complexes have been synthesized. The effect of varying Cu−Cu distances in these complexes on their ability to bind dioxygen was investigated, as was the reactivity of the resulting O_2 complexes. Ligand **2**, based on a diphenylglycoluril derived molecular receptor, was designed to bind dihydroxybenzenes in close proximity to a dinuclear metal center. To facilitate the identification of the chemistry of **2**, the ligands **3** and **4**, based on crown ethers, were also studied. Ligands **2**−**4** gave the air sensitive Cu(I) complexes **5**−**7**. At −85 °C these formed the meta-stable O_2 complexes **8**−**10** upon introduction of O_2 into their solutions (**8** = [**2**$(Cu^{II})_2(O_2)$]$(ClO_4)_2$, **9** = [{**3**(Cu^{II})}$_2(O_2)$]-$(ClO_4)_2$, **10** = [**4**$(Cu^{II})_2(O_2)$]$(ClO_4)_2$). Spectroscopic studies showed that **8**−**10** are best described as peroxo-copper(II) species, most likely with a (bent) side-on μ-η^2:η^2-peroxo bridging ligand. A solvent dependence was found for the absorption spectra of **8** and **9**, which is explained by geometric changes in the Cu_2O_2 core. XAS studies on complex **7** and **10** revealed a change in valence from Cu(I) to Cu(II) upon oxygenation of **7** and a change in the copper coordination sphere from 2 coordinating pyridines and 1 coordinating amine nitrogen in **7** to a coordination sphere that additionally includes 2 oxygens per copper in **10**. Upon heating of **8** and **10**, an oxidative N-dealkylation reaction was found to take place on the ligand. Oxidation of exogenous phenol substrates by **8** led mainly to polymeric products.

Introduction

The current interest in copper dioxygen chemistry stems from the need to develop more efficient catalysts for oxidation reactions and to further understand the role that copper enzymes play in biological dioxygen chemistry.[1,2] Several copper proteins are known to interact with molecular oxygen. Examples include the O_2 transporting protein hemocyanin (Hc) found in molluscs and arthropods,[3] and the enzyme tyrosinase (Tyr) which catalyses the *ortho* hydroxylation of phenols to catechols and the further oxidation of these molecules to *o*-quinones.[4] The active sites of these biomolecules contain two copper ions, which are each held by three histidyl ligands from the peptide backbone. Between the two copper centers one molecule of dioxygen is bound in a planar side-on μ-η^2:η^2 mode, as was proven for oxy-Hc.[3b−d] Copper enzymes that display dioxygen chemistry and which are believed to bind the dioxygen ligand to one Cu ion only, include dopamine-β-hydroxylase (DβH), which stereospecifically hydroxylates dopamine to noradrenaline, the peptidylglycine α-amidating enzyme (PAM), which catalyzes the fission of terminal glycine residues from peptides,[5] and possibly the copper amine oxidases.[6] Active sites with a higher nuclearity are found in e.g. ascorbate oxidase where the dioxygen molecule is believed to bind to a trinuclear copper site.[4,7]

Recent modeling studies on synthetic copper dioxygen complexes have provided insight into the way in which dicopper

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(1) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981.

(2) *Bioinorganic Chemistry of Copper*; Karlin, K. D., Tyeklár, Z., Eds.; Chapman & Hall: New York, 1993.

(3) (a) Volbeda, A.; Hol, W. G. J. *J. Mol. Biol.* **1989**, *209*, 249−279. (b) Magnus, K. A.; Hazes, B.; Thon-Tat, H.; Bonaventura, C.; Bonaventura, J.; Hol, W. G. J. *Proteins: Struct. Funct. Genet.* **1994**, *19*, 302−309. (c) Magnus, K. A.; Ton-That, H.; Carpenter, J. E. *Chem. Rev.* **1994**, *94*, 727−735. (d) Cuff, M. E.; Miller, K. I.; van Holde, K. E.; Hendrickson, W. A. *J. Mol. Biol.* **1998**, *278*, 855−870.

(4) (a) Solomon, E. I.; Sundaram, U. M.; Machonkin, T. E. *Chem. Rev.* **1996**, *96*, 2563−2603. (b) Solomon, E. I. In *Copper Coordination Chemistry, Biochemical and Inorganic Perspectives*; Karlin, K. D., Zubieta, J., Eds.; Adenine Press: Guilderland, NY, 1983, pp 1−22.

(5) Prigge, S. T.; Kolkehar, A.; Eipper, B. A.; Mains, R. E.; Amzel, M. *Science* **1997**, *278*, 1300−1305.

(6) Klinman, J. P. *Chem. Rev.* **1996**, *96*, 2541−2561 and references cited therein.

(7) Messerschmidt, A.; Lücke, H.; Huber, R. *J. Mol. Biol.* **1993**, *230*, 997−1014.

(8) For selected reviews, see: (a) Sorrell, T. N. *Tetrahedron* **1989**, *45*, 3−68. (b) Kitajima, N.; Moro-oka, Y. *Chem. Rev.* **1994**, *94*, 737−757. (c) Karlin, K. D.; Tyeklár, Z.; Zuberbühler, A. D. In *Bioinorganic Catalysis*; Reedijk, J., Ed.; Marcel Dekker: New York, 1993; pp 261−315.

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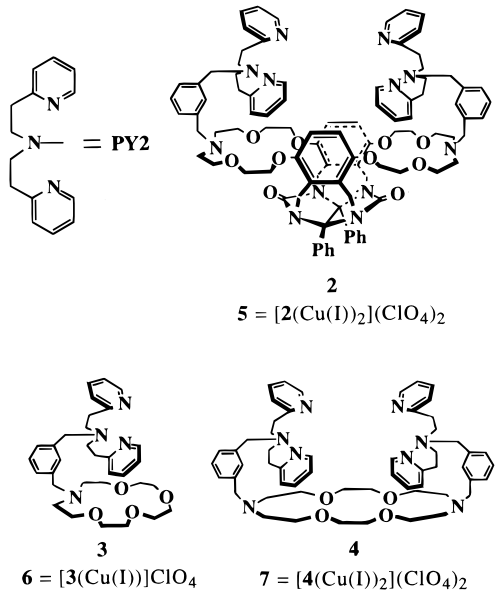
Chart 1



2

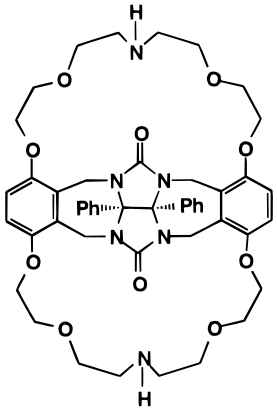
5 = [**2**(Cu(I))$_2$](ClO$_4$)$_2$

3 **4**

6 = [**3**(Cu(I))]ClO$_4$ **7** = [**4**(Cu(I))$_2$](ClO$_4$)$_2$

proteins interact and react with dioxygen.[8] Karlin and co-workers suggested, on the basis of EXAFS experiments on model compounds, that a side-on μ-η^2:η^2 peroxo coordination mode of the dioxygen ligand is present in oxy-Hc.[9] In later studies, before the X-ray structure of the oxygenated protein was known, Kitajima and co-workers presented compelling evidence that the dioxygen ligand in oxy-Hc is bound as a planar side-on μ-η^2:η^2 peroxo ligand. Their complex, [Cu(HB(3,5-*i*-Pr$_2$pz)$_3$)]$_2$(O$_2$) (HB(3,5-*i*-Pr$_2$pz)$_3$) = hydrotris(3,5-diisopropylpyrazolyl)borate anion), was the first crystallographically characterized copper dioxygen complex of this type.[10] Recently several other discrete Cu_2O_2 complexes have been inferred from crystallographic and/or spectroscopic studies. These include the complexes [{(TMPA)Cu}$_2$(O$_2$)]$^{2+}$ (TMPA = tris(2-pyridylmethyl)amine)[11] and [Cu$_2$(N*n*PY2)(O$_2$)]$^{2+}$ (where N*n* stands for $-(CH_2)_n-$ (n = 3−5) connecting two PY2 ligands, PY2 = bis-[2-(2-pyridyl)ethyl]amine, see Chart 1),[12] two closely related, trisimidazolylphosphine-based complexes,[13,14] and the complexes [(LCu)$_2$(O$_2$)] (L = various amines).[15] In these complexes the coordination mode of the dioxygen ligand varies from end-on μ-1,2 peroxo to bent side-on peroxo, and further to planar side-on peroxo and bis-μ-oxodicopper(III).[16] Recently, two Cu_2O_2 complexes with stability at room temperature have been reported.[17] Both have structural and spectroscopic characteristics very similar to that of [{(TMPA)Cu}$_2$(O$_2$)]$^{2+}$. One uses a dinucleating analogue of TMPA,[17a] while the other employs a macrocyclic ligand.[17b]

Although the structural and spectroscopic properties of dicopper complexes are now reasonably well documented, their reactivity toward substrates is still not well understood. Most of the dioxygen complexes reported so far are only stable at low temperatures and either liberate dioxygen upon warming or give rise to oxidative ligand degradation. Few complexes have been shown to be able to oxidize exogenous substrates. We have started a program aimed at modeling the oxidation chemistry displayed by enzymes like Tyr and DβH with the ultimate goal of developing a biomimetic catalyst that can oxidize such substrates. As a starting point, the relative similarities and differences of the active sites of Hc and Tyr were considered. Whereas the copper coordination sites of these proteins are believed to be closely related, their functions are different, i.e. dioxygen transport vs dioxygen activation. One of the major reasons for this difference is probably the presence of a binding site for substrates or in general the accessibility of the active site of Tyr for substrates, whereas in Hc the active site is not accessible for these molecules.[18] Our objectives, therefore, were (i) to prepare Cu_2O_2 complexes that have a binding site for substrates, (ii) to study the spectroscopic features of these complexes, and (iii) to investigate in which way their oxidation chemistry is affected by the presence of the binding site. We decided to make use of molecular receptors that had been previously developed by us, viz. those based on diphenylglycoluril (**1**).[19] One of the properties of these receptors is that they selectively bind dihydroxybenzenes. Binding of the guest molecules is based on hydrogen bonding and $\pi-\pi$ interactions.



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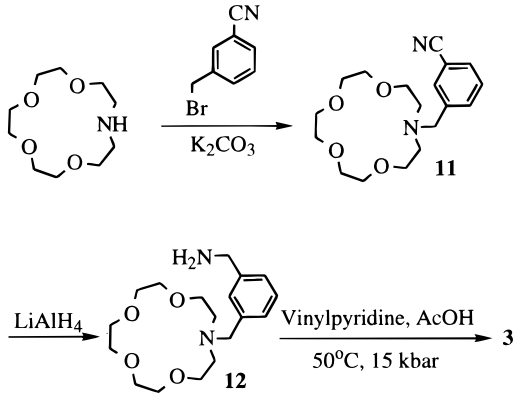
With the help of molecular modeling and CPK models, we designed the ligand **2** (see Chart 1) in which two PY2 units are

(9) Blackburn, N. J.; Strange, R. W.; Farooq, A.; Haka, M. S.; Karlin, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 4263−4272.
(10) Kitajima, N.; Fujisawa, K.; Fujimoto, C.; Moro-oka, Y.; Hashimoto, S.; Kitagawa, T.; Toriumi, K.; Tatsumi, K.; Nakamura, A. *J. Am. Chem. Soc.* **1992**, *114*, 1277−1291.
(11) Tyeklár, Z.; Jacobson, J. J.; Wei, N.; Murthy, N. N.; Zubieta, J.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2677−2689.
(12) (a) Karlin, K. D.; Haka, M. S.; Cruse, R. W.; Meyer, G. J.; Farooq, A.; Gultneh, Y.; Hayes, J. C.; Zubieta, J. *J. Am. Chem. Soc.* **1988**, *110*, 1196−1207. (b) Karlin, K. D.; Tyeklár, Z.; Farooq, A.; Haka, M. S.; Ghosh, P.; Cruse, R. W.; Gultneh, Y.; Hayes, J. C.; Toscano, P. J.; Zubieta, J. *Inorg. Chem.* **1992**, *31*, 1436−1451. (c) Sanyal, I.; Mahroof-Tahir, M.; Nasir, M. S.; Ghosh, P.; Cohen, B. I.; Gultneh, Y.; Cruse, R. W.; Farooq, A.; Karlin, K. D.; Lin, S.; Zubieta, J. *Inorg. Chem.* **1992**, *31*, 4322−4332. (d) Karlin, K. D.; Kaderli, S.; Zuberbühler, A. D. *Acc. Chem. Res.* **1997**, *30*, 139−147. (e) Lee, D.-H.; Wei, N.; Murthy, N. N.; Tyeklár, Z.; Karlin, K. D.; Kaderli, S.; Jung, B.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1995**, *117*, 12498−12513.
(13) Lynch, W. E.; Kurtz, Jr., D. M.; Wang, S.; Scott, R. A. *J. Am. Chem. Soc.* **1994**, *116*, 11030−11038.
(14) Sorrell, T. N.; Allen, W. E.; White, P. S. *Inorg. Chem.* **1995**, *34*, 952−960.
(15) (a) Mahapatra, S.; Halfen, J. A.; Wilkinson, E. C.; Pan, G.; Wang, X.; Young, V. G., Jr.; Cramer, C. J.; Que, L., Jr.; Tolman, W. B. *J. Am. Chem. Soc.* **1996**, *118*, 11555−11574. (b) Mahadevan, V.; Hou, Z.; Cole, A. P.; Root, D. E.; Lal, T. K.; Solomon, E. I.; Stack, T. D. P. *J. Am. Chem. Soc.* **1997**, *119*, 11996−11997.
(16) An unusual trinuclear copper complex in which the dioxygen ligand is bound as a bis μ_3-oxo ligand and a tetranuclear copper complex featuring a μ_4-oxo and a μ_4-peroxo ligand have been reported: (a) Cole, A. P.; Root, D. E.; Mukherjee, P.; Solomon, E. I.; Stack, T. D. P. *Science* **1996**, *273*, 1848−1850. (b) Reim, J.; Werner, R.; Haase, W.; Krebs, B. *Chem. Eur. J.* **1998**, *4*, 289−298.
(17) (a) Karlin, K. D.; Lee, D.-H.; Kaderli, S.; Zuberbühler, A. D. *Chem. Commun.* **1997**, 475−476. (b) Bol, J. E.; Driessen, W. L.; Ho, R. Y. N.; Maase, B.; Que, L., Jr.; Reedijk, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 998−1000.

Scheme 1. Synthesis of Ligand **3**



connected to the molecular receptor. In addition, we decided to study also the chemistry of the related aza crown ether ligands **3** and **4** for comparison. Copper complexes of PY2-derived ligands have been previously investigated by one of us and were shown to form dioxygen complexes.[12] In one case an arene ring, which is part of a binucleating ligand, was found to be rapidly hydroxylated due to its close proximity to a Cu_2O_2 site.[20] A similar reaction can be foreseen to take place in the case of a substrate that is bound in the novel ligand **2**. In a previous paper we reported that a synthetic host compound with a dinuclear copper complex related to **2** can display highly selective oxidation of substrates, albeit in a stoichiometric fashion.[21]

A set of Cu(I) complexes, which have similar ligand backbones and are therefore expected to have close to identical anion association and intrinsic polarity, as is described here, allows a comparison of the dioxygen binding in mononuclear and dinuclear complexes, as well as the effect of Cu−Cu distance in the latter. The synthesis and spectroscopy of Cu(I) complexes **5**−**7** is described here, along with the investigations of the formation kinetics and spectroscopy of O2 complexes **8**−**10**.[22] In addition, reactivity studies of the novel O_2 complexes will be discussed.

Results and Discussion

Synthesis. The aza crown ether based ligands **3** and **4** were synthesized following the route depicted in Scheme 1 for **3**. Reaction of the commercially available monoaza-15-crown-5 and 1,10-diaza-18-crown-6 with α-bromo-*m*-tolunitrile gave compounds **11** and **13**, respectively. After reduction of the cyano function with $LiAlH_4$, the resulting primary amines **12** and **14** were reacted with vinylpyridine. Under the circumstances normally used for this type of reaction, i.e. refluxing in methanol for several days in the presence of acetic acid as a catalyst, the yield of PY2 functionalized crown was very low. We, therefore, used a procedure that was recently developed in our laboratory for the synthesis of pyridine functionalized aza crown ethers.[23] Leaving the reaction mixture at 50 °C under a high pressure of 15 kbar for 8−16 h yielded the desired products **3** and **4** in good to excellent yield after purification. The high-pressure method may be a good alternative for the literature procedure: several PY2 derivatives, including dendritic compounds,[24] could be prepared in excellent yields and in relatively short reaction times.

The route of Scheme 1 was also used for the preparation of receptor molecule **2**. Protected diamine **17** was synthesized from the tetrachloro compound **15** and mono Boc-protected diamino-*m*-xylene (**16**) using a standard procedure previously developed by our group for the synthesis of this type of molecular receptors (Scheme 2).[19a] After deprotection with TFA, diamine **18** was obtained in excellent yield. The final step to **2** proceeded smoothly and in good yields under high-pressure conditions.

The air-sensitive complexes **5**−**7** were isolated as golden-brown oils or solids after treatment of the appropriate amount of solid $Cu^{I}(CH_3CN)_4(ClO_4)$ with dichloromethane solutions of the individual ligands **2**−**4** and after several precipitations using diethyl ether.[25] Isolation from acetonitrile solutions yielded Cu(I) compounds which were not reactive toward O_2 (vide infra). ^{1}H NMR and UV−vis spectra of the isolated materials were in accordance with their formulations as Cu(I) complexes. The line widths observed in the ^{1}H NMR spectra were somewhat broader than expected for purely diamagnetic species. This is possibly due to the dynamic behaviour of the ligand complexes.[11] Small downfield shifts for the signals of the pyridine protons and the protons close to the tertiary amine of the PY2 unit were observed relative to the free ligand, indicating the coordination of these groups to the copper centers. UV−vis spectra lacked the presence of a d−d transition band, which is indicative of the presence of a d^{10} species in solution. In addition, metal to ligand charge transfer (MLCT) bands were observed around 340 nm. X-ray absorption spectra confirmed that the metal centers were in the Cu(I) oxidation state and that the Cu-ions were coordinated by 3 nitrogen ligands (vide infra). These observations are in line with the spectral properties of related Cu(I) complexes.[12,20]

Binding of O_2 by Complexes 5−7. The ability of Cu(I) complexes **5**−**7** to bind molecular oxygen was initially studied in solvent mixtures containing acetonitrile. At −80 °C, precooled O_2 was bubbled through solutions of these complexes and the spectral features were followed by UV−vis spectroscopy, but no changes were observed. This result, together with the observation that the Cu(I) complexes isolated from acetonitrile solution did not bind O_2 in other solvents, strongly suggests that acetonitrile is coordinated to the copper centers, which stabilizes the +1 oxidation state of these metals, even under conditions of exposure to pure O_2. Acetonitrile coordination in these complexes was further indicated by EXAFS experiments (vide infra).

(18) (a) Himmelwright, R. S.; Eichman, N. C.; LuBien, C. D.; Lerch, K.; Solomon, E. I. *J. Am Chem. Soc.* **1980**, *102*, 7339−7344. (b) Hepp, A. F.; Himmelwright, R. S.; Eichman, N. C.; Solomon, E. I. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 1050−1057.

(19) (a) Smeets, J. W. H.; Sybesma, R. P.; Niele, F. G. M.; Spek, A. L.; Smeets, W. J. J.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1987**, *109*, 928−929. (b) Sijbesma, R. P.; Kentgens, A. P. M.; Lutz, E. T. G.; Van der Maas, J. H.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1993**, *115*, 8999−9005. (c) Reek, J. N. H.; Priem, A. H.; Engelkamp, H.; Rowan, A. E.; Elemans, J. A. A. W.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1997**, *119*, 9956-9964.

(20) (a) Karlin, K. D.; Nasir, M. S.; Cohen, B. I.; Cruse, R. W.; Kaderli, S.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1994**, 116, 1324−1336. (b) Nasir, M. S.; Cohen, B. I.; Karlin, K. D. *J. Am. Chem. Soc.* **1992**, *114*, 2482−2494. (c) Karlin, K. D.; Hayes, J.; Gultneh, Y.; Cruse, R. W.; McKnown, J. W.; Hutchinson, J. P.; Zubieta, J. *J. Am. Chem. Soc.* **1984**, *106*, 2121−2128.

(21) Martens, C. F., Klein Gebbink, R. J. M.; Feiters, M. C.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1994**, *116*, 5667−5670.

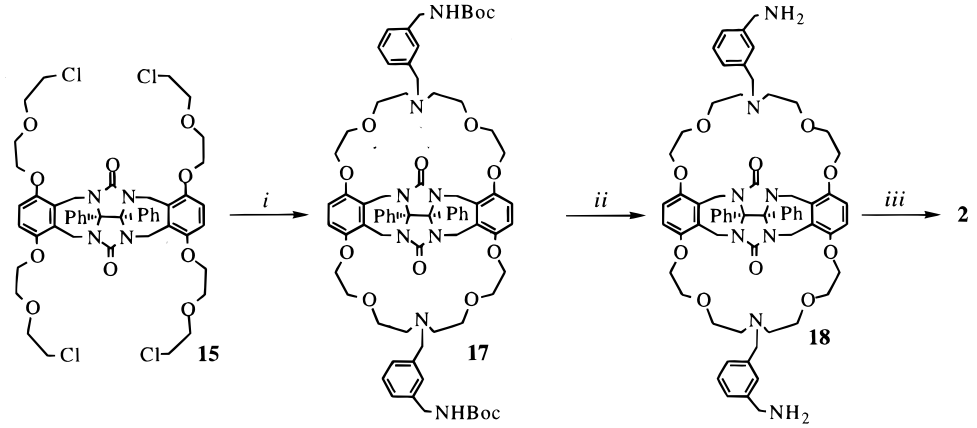
(22) Part of this work has been described in a preliminary communication, cf.: Klein Gebbink, R. J. M.; Martens, C. F.; Feiters, M. C.; Karlin, K. D.; Nolte, R. J. M. *Chem. Commun.* **1997**, 389−390.

(23) Martens, C. F.; Klein Gebbink, R. J. M.; Feiters, M.C.; Kooijman, H.; Smeets, W. J. J.; Spek, A.L.; Nolte, R. J. M. *Inorg. Chem.* **1994**, *33*, 5541−5546.

(24) Klein Gebbink, R. J. M.; Bosman, A. W.; Feiters, M. C.; Meijer, E. W.; Nolte, R. J. M. *Chem. Eur. J.* **1999**, *5*, 65−69.

(25) Karlin, K. D.; Haka, M. S.; Cruse, R. W.; Meyer, G. J.; Farooq, A.; Gultneh, Y.; Hayes, J. C.; Zubieta, J. *J. Am. Chem. Soc.* **1988**, *110*, 1196−1207.

Scheme 2. Synthesis of Receptor Ligand **2**[a]



[a] (i) **16**, Na_2CO_3, NaI; (ii) TFA; (iii) vinylpyridine, acetic acid, 15 kbar

Table 1. UV−Vis Spectra of Copper Complexes **5**−**10** in CH_2Cl_2 and of oxy-Hc[a]

ligand	Cu(I)	Cu_2:O_2	Cu(II)
2	340 (5000)	364 (13100)	358 (3400)
		418 (2900)	630 (500)
		524 (150)	
		650 (100)	
3	340 (2150)	364 (4900)	346 (3900)
		428 (1000)	616 (600)
		656 (450)	
4	344 (5800)	364 (11100)	344 (4000)
		526 (1000)	628 (300)
		642 (800)	768 (100)
hemocyanin[b]		345 (20000)	700 (200)
		570 (1000)	

[a] Wavelengths are given in nm. The extinction coefficients (M^{-1} cm^{-1}) are given in parentheses. They were calculated by assuming complete formation of the O_2 complexes. [b] Taken from ref 4b.

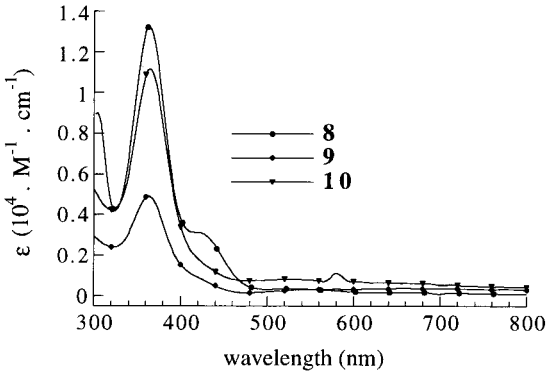


Figure 1. Spectral characteristics of complexes **8**−**10** in CH_2Cl_2 at -85 °C. (The features around 580 nm in spectrum of **10** are artefacts due to background substraction.)

The O_2 affinity of the complexes was subsequently studied in CH_2Cl_2, in a similar way as described above. For complexes **5** and **6** a color change from slightly yellow to bright orange was observed, whereas for complex **7** a dark purplish-green color appeared upon oxygenation of their CH_2Cl_2 solutions at low temperature. The difference in color is reflected in the spectral characteristics of the solutions, as shown in Table 1. The O_2 complexes formed in CH_2Cl_2 all showed a distinct absorption at 364 nm (see Figure 1), whereas the wavelength positions of the other absorption bands differed. In addition to these observations, in each case a low intensity absorption band around 650 nm appeared, indicating the formation of Cu(II) complexes. These observations are similar to the results obtained with related PY2-based dicopper complexes.[12] In these complexes each of the Cu-centers are thought to have donated one electron to the O_2 ligand, resulting in the formation of an $(O_2)^{2-}$ or peroxo ligand and a decrease in O−O bond order. The observed instability of the complexes and the 364 nm absorption band[26] are indicative of the formation of peroxo complexes in which the peroxide dianion is bound in a (putative) bent μ-η^2:η^2 mode between two Cu(II) centers. Changes in the other absorption bands are believed to arise from small changes in the ligand geometry around the metal centers and in the geometry of the Cu_2O_2 core (vide infra). On the basis of the above-described observations, the O_2 complexes can be formulated as [**2**$(Cu^{II})_2(O_2)$]$(ClO_4)_2$ (**8**), [{**3**(Cu^{II})}$_2(O_2)$]$(ClO_4)_2$ (**9**), and [**4**$(Cu^{II})_2(O_2)$]$(ClO_4)_2$ (**10**), respectively. Attempts to prove the diamagnetic nature of these complexes by EPR spectroscopy failed, due to their thermal instability.

The molar extinction coefficients of the UV−vis absorption bands of complexes **8** and **10** are of the same order of magnitude as those observed for oxy-Hc and structurally related synthetic Cu_2:O_2 complexes. The fact that these extinction coefficients, overall, are a factor of 2 lower than those of oxy-Hc (Table 1), is a phenomenon that is not unprecedented for synthetic complexes.[12a,b] The values of the extinction coefficients were rather small in the case of **9**, which is probably due to the simultaneous formation and degradation of this complex over prolonged reaction times.

Attempts to determine the stoichiometry of O_2 uptake by **7** by a UV titration, as described by Gultneh et al. for dinuclear Mn complexes, failed.[27] The stoichiometry, therefore, was determined by manometric O_2 uptake measurements at low temperature, even though this method has the disadvantage of requiring large quantities of material. The Cu:O_2 ratio was calculated to be 2.1(±0.1):1 (average of two trials). This value for **7** corresponds well with the above given description of the O_2 complexes as being Cu_2:O_2 species.

Although complexes **8**−**10** showed similar spectroscopic characteristics, their rates of formation were significantly different, see Figure 2 and Table 2. Whereas the formation of **10** in CH_2Cl_2 at −85 °C was completed within a few minutes and the formation of **8** within 20 min after O_2 bubbling, the formation of **9** at −85 °C took about 3−5 h. Pseudo-first-order rate contants were calculated using the data in Figure 2 by

(26) Baldwin, M. J.; Root, D. E.; Pate, J. E.; Fujisawa, K.; Kitajima, N.; Solomon, E. I. *J. Am. Chem. Soc.* **1992**, *114*, 10421−10431.
(27) Gultneh, Y.; Ahvazi, B.; Khan, A. R.; Butcher, R. J.; Tuchagues, J. P. *Inorg. Chem.* **1995**, *34*, 3633−3645.

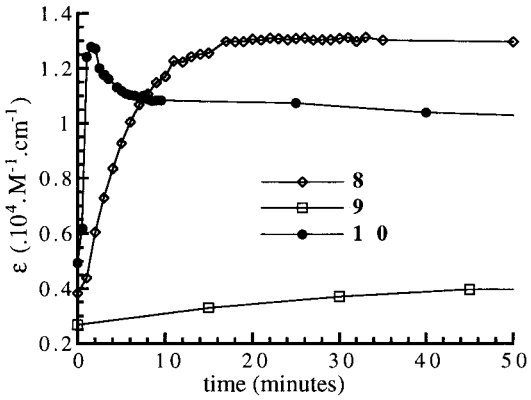


Figure 2. Time dependence of the formation of the O_2 complexes **8**−**10** in CH_2Cl_2 at -85 °C and (0.4−1.3) × 10^{-4} M concentration of Cu(I) complex. The extinction coefficient at 362−364 nm is recorded as a function of time.

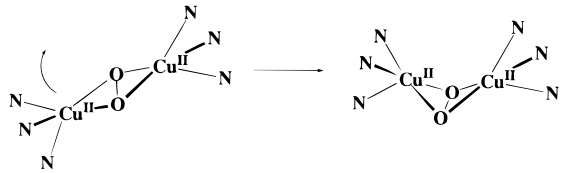
Table 2. Apparent Rate Constants of Formation and Half-Life of Formation of the O_2 Complexes **8**−**10** in CH_2Cl_2[a]

complex	k_{form} (×10^3 s)	$t_{1/2,form}$ (min)
8	3.41	3.39
9	0.256	45.1
10[b]	23	0.5

[a] $T = -85$ °C; concentration of Cu(I) complex - (0.4−1.3) × 10^{-4} M. [b] Estimated from $t_{1/2,form}$.

assuming that the formation of these complexes goes to completion, and that the reaction is first order in copper complex and zero order in oxygen (Table 2). Plots of ln([Cu^I complex]$_0$/{[Cu^I complex]$_0$ − [O_2 complex]}) versus time for **8** and **9** gave straight lines, from which the rate constants and half-lifes of formation were obtained. This procedure could not be applied to **10** (vide infra). The large $t_{1/2}$ value measured for **9** is in line with the fact that in this complex dioxygen is bound in an inter- rather than an intramolecular fashion. Similar low formation rates of O_2 adducts have been reported for other mononuclear PY2 complexes.[12c] The distinct difference in the formation rate of **8** and **10** as compared to **9** is a very strong indication that in the former two complexes intramolecular O_2 binding is favored over intermolecular O_2 binding. In addition, no concentration dependence was observed for the UV−vis characteristics of complexes **8** and **10**, which also strongly suggest intramolecular O_2 binding. The difference in formation rate between **8** and **10** most probably derives from differences in reorganization energy in the respective Cu(I) complexes upon binding of O_2.

Closer examination of the formation curve of **10** in Figure 2 reveals an initially steep rise in absorbance at 364 nm, followed by a small loss in intensity. Stabilization of the absorption intensity of this band occurred within a few minutes. Comparison of the change in intensity at 364 nm with changes at 526 and 642 nm revealed that these two latter absorbances showed a normal, exponential formation curve. A similar formation behaviour of **10** was found in acetone solution. These observations are indicative of an intermediate species in the formation of **10**. We propose that in the reaction of Cu(I) complex **7** and O_2, a planar side-on peroxo species is initially generated which slowly converts to a bent side-on peroxo species.[28,29] A simple conversion from a planar to a bent Cu_2O_2 unit without further rearrangements is expected to be very fast. This stepwise formation may thus be connected to a conformational change in the ligand backbone, which eventually converts a kinetic reaction product into a thermodynamic one.



Dioxygen complexes **8**−**10**, once formed, are stable for several hours at −85 °C. Per hour, a decrease of approximately 3% in absorption intensity for **10** is observed. At temperatures above −60 to −40 °C these complexes rapidly decompose to give green solutions (vide infra). The binding of O_2 by **8**−**10** appears to be irreversible; attempts to detect reversibility in the case of **10**, either by rapid heating under vacuum or by purging the sample with argon, failed.

The UV−vis spectrum of a CH_2Cl_2 solution of complex **8** clearly shows two bands in the 350−450 nm region, viz. at 364 and at 418 nm. The relative intensities of these bands changed upon diluting the solutions with THF (not shown).[31] In acetone solution no absorption band around 420 nm was observed (see Figure 3). Similar solvent dependent observations were made for complex **9**. The relative intensity of the 420 nm band in each solvent tested (dichloromethane, acetone, and THF) was different from that in the case of complex **8** (see Supporting Information). In contrast, no changes in spectral characteristics were observed upon generating complex **10** in different solvents (vide infra).

As no proof was found for intermolecular O_2 binding[32] by complexes **5** and **7**, the spectral solvent dependences of the above O_2 complexes are governed by different factors than intra- vs intermolecular O_2 binding. The most plausible factor to induce an additional electronic transition is a geometric perturbation of the Cu_2O_2 core. This could either involve the partial formation of Cu(III) bis-μ-oxo complexes or a perturbation of the bending angle ($\angle$Cu−O−Cu) of the Cu(II) peroxo butterfly core. Copper dioxygen complexes containing the [$Cu^{III}_2(\mu$−$O)_2$]$^{2+}$ core have recently been reported.[15] These complexes are characterized by intense absorption features around 320 ($\epsilon \sim$ 12 000 M^{-1} cm^{-1}) and 430 nm ($\epsilon \sim$ 14 000 M^{-1} cm^{-1}). It was shown that this core can be interconverted to a [$Cu^{II}_2(\mu$-η^2:η^2)-(O_2)]$^{2+}$ core by solvent[33] and ligand substituent[34] variation.

(28) The expression "slowly" is used in here a relative sense. Other stepwise mechanisms are proposed for the formation of Cu_2O_2 complexes that involve intermediates which convert much faster as the one discussed here: Jung, B.; Karlin, K. D.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 3763−3764.

(29) The formation of other possible intermediates, e.g. end-on peroxo or bis side-on superoxo complexes, was ruled out on the basis of their spectral characteristics (see refs 11 and 30). The presence of a 420−490 nm band in the optical spectrum of **10**, indicative of a bent side-on coordination of the peroxo ligand, is not obvious from Figure 1. The spectral features of **10** were, however, equally well fit with as without the presence of such a band at 390−425 nm (see Supporting Information).

(30) Fujisawa, K.; Tanaka, M.; Moro-oka, Y.; Kitajima, N. *J. Am. Chem. Soc.* **1994**, *116*, 12079−12080.

(31) Compound **5** and related receptor molecules are not soluble in pure THF. As a result the spectra that were obtained on CH_2Cl_2/THF solutions of **8** suffered from a low signal/noise ratio at higher THF ratios.

(32) See for example: Lee, D.-H.; Wei, N.; Murthy, N. N.; Tyeklár, Z.; Karlin, K. D.; Kaderli, S.; Jung, B.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1995**, *117*, 12498−12513.

(33) Halfen, J. A.; Mahapatra, S.; Wilkinson, E. C.; Kaderli, S.; Young, V. G., Jr.; Que, L., Jr.; Zuberbühler, A. D.; Tolman, W. B. *Science*, **1996**, *271*, 1397−1400.

(34) Mahapatra, S.; Halfen, J. A.; Wilinson, E. C.; Pan, G.; Cramer, C. J.; Que, L., Jr.; Tolman, W. B. *J. Am. Chem. Soc.* **1995**, *117*, 8865−8866.

Table 3. Parameters Used for the Simulation of Cu EXAFS Spectra of Various Cu Complexes **5**−**7**[a]

complex	solvent[b]	range (eV)	ΔE_0	pyridines[c]	amine N[c]	Cu[c]	fit index
5	AN	2.44−550.00	24.15	2.1 (1.947)	1.1 (2.000)	−	0.00048
6	AN	2.37−500.00	23.84	2.3 (1.950)	0.8 (2.089)	−	0.00058
7	AN	2.40−597.00	23.66	2.4 (1.942)	1.2 (2.027)	−	0.00092
7	DC	2.24−545.00	17.09	1.8 (1.941)	0.9 (2.077)	−	0.00150
7	AC	2.37−550.00	22.83	2.2 (1.952)	0.8 (2.122)	−	0.00064
7[d]	AC + O_2	2.17−460.00	17.50	2.0 (2.070)	1.4 N (2.272) 1.1 O (1.913, 1.918)	1.1 (3.313)	0.00010
7	THF	2.30−550.00	26.74	3.1 (1.939)	0.1 (2.165)	−	0.00087
7[d]	THF + O_2	2.28−460.00	18.05	2.1 (2.066)	1.1 N (2.267) 1.0 O (1.929, 1.929)	1.0 (2.788)	0.00034

[a] Restrained refinement (see Experimental Section) and one multiple scattering unit (pyridine) were used in the simulations. [b] AN = acetonitrile, DC = dichloromethane, AC = acetone, THF = tetrahydrofuran. [c] Number of donors or other ligands as indicated; distance to Cu (Å) in parentheses. [d] Two multiple scattering units used (pyridine and Cu_2O_2 unit).

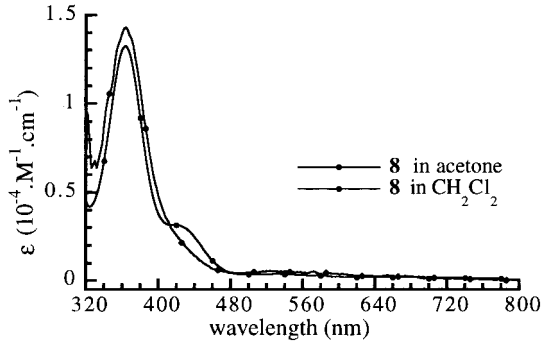


Figure 3. UV−vis spectra of complex **8** in acetone and CH_2Cl_2 solution at -85 °C.

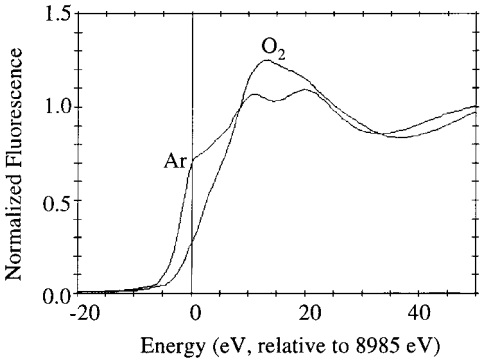


Figure 4. X-ray absorption near-edge spectra of the Cu(I) complex **7** (deoxy) and the corresponding O_2 complex **10** (oxy) in acetone, E_0 is 8985 eV.

Recent Raman studies on PY2-derived Cu_2:O_2 complexes related to complexes **8**−**10** have shown that care must be taken in the asignment of a 420−490 nm band in their absorption spectra. For the series $[Cu_2(NnPY2)(O_2)]^{2+}$, where N*n* stands for $-(CH_2)_n-$ (n = 3−5) connecting two PY2 ligands, it was established that this band significantly shifts to lower energy and, in addition, gains intensity with increased bending of the dinuclear side-on peroxide-bridged core.[35] No proof was found for the presence of Cu(III) bis-μ-oxo complexes in this series. In contrast, the complex $[\{Cu(MePY2)\}_2O_2]^{2+}$ was shown to consist of a mixture of side-on peroxo and bis-μ-oxo adducts in solution (1−10% bis-μ-oxo)[36] as well as in the solid state (5−20% bis-μ-oxo).[37] In terms of structural degrees of freedom, complexes **8** and **9** are closer related to the dimeric complex $[\{Cu(MePY2)\}_2O_2]^{2+}$ than to the structurally more constrained $[Cu_2(NnPY2)(O_2)]^{2+}$ complexes. Complexes **8** and **9**, therefore, are believed to be composed of mixtures of side-on peroxo and bis-μ-oxo adducts. Complex **10**, in contrast, solely contains (bent) side-on peroxo adducts.

EXAFS Characterization. The structures of the novel Cu(I) complexes **5**−**7** in frozen dichloromethane/acetonitrile and, additionally, for **7**, the structures in frozen acetone, dichloromethane, and THF solution were studied by X-ray absorption spectroscopic techniques. Details of the spectra and their analysis are described elsewhere.[38] The edge positions (shown for **7** in acetone in Figure 4) confirm that the copper ion is Cu(I) in all cases. The edges of **7** in acetone, THF, and dichloromethane showed a pronounced shoulder, which was blurred, however, in the spectra taken in dichloromethane/acetonitrile.[38] This blurring could point to a different coordination in acetonitrile, involving a solvent molecule. Analysis of the Fourier-filtered main shells pointed to coordination by 3 nitrogen (or other low-Z) ligands in complex **7** in all solvents. The fact that the exact occupancy in mixtures containing acetonitrile was slightly higher than that in the other solvents may be taken as an additional indication that coordination of one solvent molecule takes place in acetonitrile. Similar observations were made for complexes **5** and **6** in frozen acetonitrile solution.

Simulations of the raw data on complexes **5**−**7** with multiple scattering contributions for the pyridine rings gave optimum agreement with 2 pyridine rings and 1 amine nitrogen, confirming the proposed coordination sphere for Cu, see Table 3. In our preliminary account[39] of the analysis of the EXAFS of a sample of **7** in dichloromethane, which, unlike the present samples, was generated in situ, we proposed that the copper centers were at a distance of 4.3 Å. This would have meant that in this complex the copper ions are preorganized for binding of dioxygen. With the results of the recent, more detailed analysis,[38] including simulation of the contributions of the pyridine rings by multiple scattering, of a complex that was isolated after preparation, we find that the complete (i.e. non-

(35) Pidcock, E.; Obias, H. V.; Abe, M.; Liang, H.-C.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1999**, *121*, 1299−1308.
(36) Obias, H. V.; Lin, Y.; Murthy, N. N.; Pidcock, E.; Solomon, E. I.; Ralle, M.; Blackburn, N. J.; Neuhold, Y.-M.; Zuberbühler, A. D.; Karlin, K. D. *J. Am. Chem. Soc.* **1998**, *120*, 12960−12961.
(37) Pidcock, E.; DeBeer, S.; Obias, H. V.; Hedman, B.; Hodgson, K. O.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1999**, *121*, 1870−1878.
(38) (a) Feiters, M. C.; Klein Gebbink, R. J. M.; Martens, C. F.; Nolte, R. J. M.; Karlin, K. D.; Solé, V. A.; Nolting, H.-F.; Hermes, C.; Hazes, B.; Magnus, K. A.; Godette, G.; Bonaventura, C. In *Proceedings of 3rd European Conference on Bio-inorganic Chemistry (EUROBIC 3)*; Feiters, M. C., Hagen, W. R., Veeger, C., Eds.; NSR Center: Nijmegen, **1996**; F5. (b) Feiters, M. C.; Klein Gebbink, R. J. M.; Solé, V. A.; Nolting, H.-F.; Karlin, K. D.; Nolte, R. J. M. *Inorg. Chem.*, in press.
(39) Martens, C. F.; Klein Gebbink, R. J. M.; Kenis, P. J. A.; Schenning, A. P. H. J.; Feiters, M. C.; Karlin, K. D.; Nolte, R. J. M. In *Bioinorganic Chemistry of Copper*; Karlin, K. D., Tyeklar, Z., Eds.; Chapman & Hall: New York, **1993**; pp 374−381.

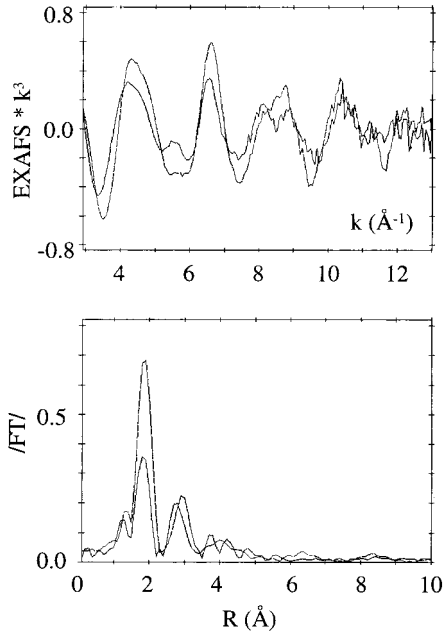


Figure 5. EXAFS (k^3-weighted, upper panel) and corresponding Fourier transforms (bottom panel) of the Cu(I) complex **7** (deoxy, solid traces) and the corresponding O_2 complex **10** (oxy, dashed traces) in acetone.

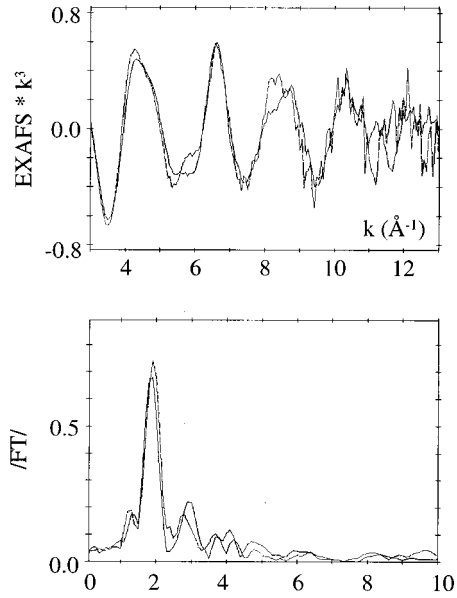


Figure 6. EXAFS (k^3-weighted, upper panel) and corresponding Fourier transforms (bottom panel) of the O_2 complex **10** in acetone (solid traces) and THF (dashed traces).

Fourier filtered) spectra of complex **7**, as well as complexes of **5** and **6**, can be satisfactorily fitted without any additional Cu−Cu contribution.

Structural changes upon O_2 binding were studied in the case of O_2 binding for complex **7**. Drastic changes in edge (Figure 4), EXAFS, and Fourier transform (Figure 5) were observed upon oxygenation of **7** in acetone and THF at −85 °C to give **10**. The effect on the edge is similar to that observed upon oxygenation of the oxygen transport protein, hemocyanin,[40] and is strong evidence for a change in valence from Cu(I) to Cu(II).[41] In the Fourier transform of **7** dissolved in acetone and THF, almost a doubling of the intensity of the main shell of low-Z atoms at approximately 2 Å is noted upon oxygenation, similar to the effect in hemocyanin.[42] This allows the conclusion that each Cu in complex **10** must coordinate both oxygen atoms of the bound molecular oxygen, corroborating our proposal that the oxygen is coordinated in the $\mu-\eta^2:\eta^2$ mode. Single scattering analysis of the Fourier-filtered main shell showed an increase from an occupancy of 3 ± 1 per Cu ion in the Cu(I) complex **7** to an occupancy of 4 ± 1 per Cu ion in the dioxygen complex **10**. We note that the result for the dioxygen complex is the same as the expected coordination number of 5, within the experimental error typically quoted for determination of the coordination number by EXAFS (20%),[43] and that the edge spectrum of this complex is consistent with 5-coordination. The results of detailed simulations of the full EXAFS including multiple scattering contributions for the pyridine and Cu_2O_2 units[38] also point to coordination by 2 pyridines, 1 (amine) nitrogen, and 2 oxygen atoms per copper (see Table 4).

A subtle but significant effect of the solvent (acetone or THF) on the XAS characteristics of complex **10** was observed, in particular in the region around 3 Å in the Fourier transform, and 6−8 $Å^{-1}$ in the EXAFS (Figure 6). The changes in the Fourier transform in particular are best fit by different Cu−Cu distances. In a detailed analysis of the spectra[38] the best fits were obtained with values of 3.3 and 2.9 Å for the Cu−Cu distance in acetone and THF, respectively. Formation of Cu(III) bis-μ-oxo cores in **10**, which would be compatible with a shortening of the Cu−Cu distance to ∼2.9 Å,[34] in THF is ruled out by UV−vis data (vide supra) and by the fact that no shift to higher energy in the X-ray absorption edge spectrum[44] was observed. Assuming, therefore, that the O−O bond is not affected by the solvent, the Cu−Cu distances of 3.3 and 2.9 Å point to a bending of the Cu_2O_2 unit by 140 and 112° in acetone and THF, respectively. In addition to these considerations, fits of the optical spectra of **10** in dichloromethane and acetone solutions also point to the possibility that bending of the butterfly core could vary with solvent (see Supporting Information). These spectra could equally well be fitted with an additional band at 391 and 423 nm, for dichloromethane and acetone respectively, as without this band. The combined UV−vis and XAS data, therefore, indicate that the degree of Cu_2O_2 core bending in **10** increases from dichloromethane to acetone to THF solution.

Reaction Products of O_2 Complexes. Upon warming the solutions containing the O_2 complexes **8**−**10** to ambient temperature, a color change from orange/purple to green was observed. Light green solids can be isolated from the green solutions via repeated precipitations. UV−vis and IR analyses suggested that Cu(II)-hydroxide complexes had been formed. FAB-MS analyses were in agreement with such complexes. It should be noted, however, that the parent peaks for the monocharged cations had very low intensities, probably due to the lability of the hydroxo ligands. Powder EPR spectra of the complexes display broadened $g = 2$ signals, see Figure 7. In dichloromethane or methanol solution the observation of "half-field" lines indicates the presence of exchange-coupled, dimeric Cu(II) complexes. It was concluded, therefore, that the bulk of the isolated green materials contained dimeric Cu(II) complexes

(40) Volbeda, A.; Feiters, M. C.; Vincent, M. G.; Bouwman, E.; Dobson, B.; Kalk, K. H.; Reedijk, J.; Hol, W. G. J. *Eur. J. Biochem.* **1989**, *181*, 669−673.
(41) Kau, L.-S.; Spira-Solomon, D. J.; Penner-Hahn, J. E.; Hodgson, K. O.; Solomon, E. I. *J. Am. Chem. Soc.* **1987**, *109*, 6433−6442.
(42) Feiters, M. C. *Comm. Inorg. Chem.* **1990**, *11*, 131−174.
(43) Teo, B. K. In *EXAFS Spectroscopy, Techniques and Applications*; Teo, B. K., Joy, D. C., Eds.; Plenum Press: New York, 1980.
(44) DuBois, J. L.; Mukherjee, P.; Collier, A. M.; Mayer, J. M.; Solomon, E. I.; Hedman, B.; Stack, T. D. P.; Hodgson, K. O. *J. Am. Chem. Soc.* **1997**, *119*, 8578−8579.

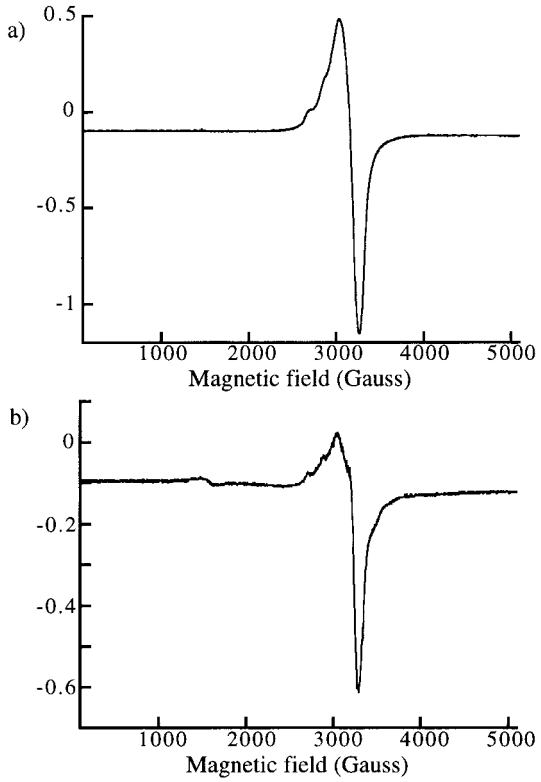


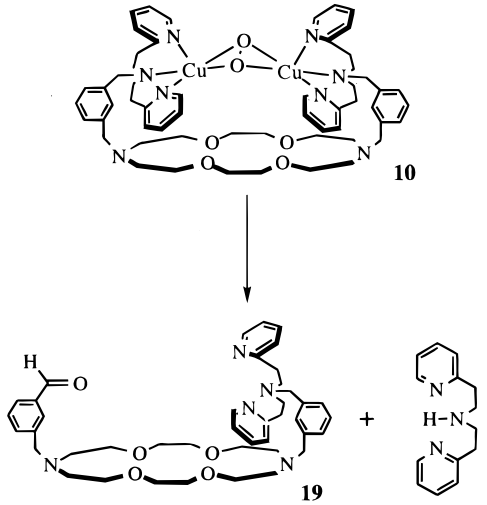
Figure 7. EPR spectra (X-band) of the product obtained from **10** after warming: (a) solid (11 K, 2 mW, 9.230 GHz); (b) CH_2Cl_2 solution (10 K, 100 mW, 9.321 GHz).

in addition to monomeric impurities.[45] All together these analyses are in close agreement with the results reported for dinuclear Cu(II) hydroxide complexes obtained from mononuclear Cu(I) PY2 complexes.[12c] Further attempts to isolate the main compounds from the product mixtures by precipitation or crystallization failed.

In order to obtain insight into the fate of the ligands during the oxygenation and warming processes, the organic parts of the complexes were extracted by washing with aqueous ammonia. TLC analysis of the organic fractions clearly revealed the presence of more than one compound, while NMR analysis showed that aldehydes were present. Isolation of the reaction products in the case of **10** yielded intact ligand **4** and aldehyde **19** (see Scheme 3, products were isolated in 40 and 60% yield, respectively). In addition, NMR analysis of the reaction mixture after work-up showed PY2 (yield not determined). A ligand oxidation product similar to **19**, i.e. **20** (25−50%), was observed after warming of complex **8** to ambient temperature. When complex **9** was treated as described above the only reaction product was the intact ligand **3** (>90%).

The oxidative N-dealkylation reaction shown in Scheme 3 is not unprecedented for PY2 ligand systems. For a related ligand it was shown by labelling studies that the oxygen atom which is incorporated at the benzylic position is derived from the molecular oxygen that is used in the preparation of the initial O_2 complex.[12c] It is proposed that initially an amino alcohol is formed which further rearranges to an aldehyde and a secondary amine. Both processes are probably mediated by copper. Hydrolysis of an intermediate Schiff base species, which would also yield the observed products, can be ruled out on the basis

Scheme 3. Ligand Degradation after Warming of **10**



of the above-mentioned labeling study. The fact that for **10** only the monoaldehyde **19** is found, suggests that only one of the oxygen atoms of the peroxo ligand is transferred to the ligand. The other oxygen atom probably ends up as one of the hydroxo bridges in the initially isolated Cu(II) complexes or is reduced to water. Complexes **8** and **10**, therefore, seem to behave as mono-oxygenases: one oxygen atom is used in substrate oxidation, and the other one is reduced to water. The mono-oxygenases dopamine-β-hydroxylase and the peptidylglycine α-amidating enzyme (PAM, see Introduction) operate by a similar mechanism. The difference between the synthetic adducts **8** and **10** and those of the enzymes is that dioxygen is bound to only one of the copper centers in the latter. The formation of monoaldehydes also suggests that the oxidation chemistry in **8** and **10** takes place intramolecularly, i.e. the oxygen atom transferred to the ligand originates from a peroxo species that is coordinated to the ligand itself. An intermolecular oxidation probably would have led to the formation of dialdehydes, which were not observed.

The type of oxidation chemistry described above requires that considerable orbital overlap[20] or strong hydrogen bonding interactions[46] are present between the ligand and the Cu_2O_2 unit in the complexes. From the torsion-minimalized structure of **10** (Figure 8) it can be concluded that the xylylene groups (and therefore the reacting benzylic positions) are close to the Cu_2O_2 unit in this complex (shortest distance approximately 2.3 Å), showing that such interactions are indeed possible. The yield of aldehyde in the case of **10** (60%) is higher than in the case of **8** (25−50%), which has a more open structure (not shown). As a consequence of the conformational freedom of the two ligands in **9** the oxidative N-dealkylation pathway can be expected to be suppressed. This result was indeed found (yield of aldehyde <10%). It has previously been reported that mononuclear PY2-based systems have a diminished tendency to be oxygenated at the benzylic ligand site.[12c] In contrast to these observations, Itoh and co-workers[47] have described a dopamine-β-hydroxylase model system wherein efficient benzylic hydroxylation occurs on the β-carbon of a phenylethyl appended PY2 ligand. Apparently the xylylene groups in **9** tend

(45) Similar spectral characteristics were obtained for other exchange coupled dimers, c.f.: Martens, C. F.; Schenning, A. P. H. J.; Feiters, M. C.; Heck, J.; Beurskens, G.; Beurskens, P. T.; Steinwender, E.; Nolte, R. J. M. *Inorg. Chem.* **1993**, *32*, 3029−3033.

(46) Mahapatra, S.; Halfen, J. A.; Tolman, W. B. *J. Am. Chem. Soc.* **1996**, *118*, 11575−11586.

(47) (a) Itoh, S.; Kondo, T.; Komatsu, M.; Ohshiro, Y.; Li, C.; Kanehisa, N.; Kai, Y.; Fuzuzumi, S. *J. Am. Chem. Soc.* **1995**, *117*, 4174−4715. (b) Itoh, S.; Nakao, H.; Berreau, L. M.; Kondo, T.; Komatsu, M.; Fukuzumi, S. *J. Am. Chem. Soc.* **1998**, *120*, 2890−2899.

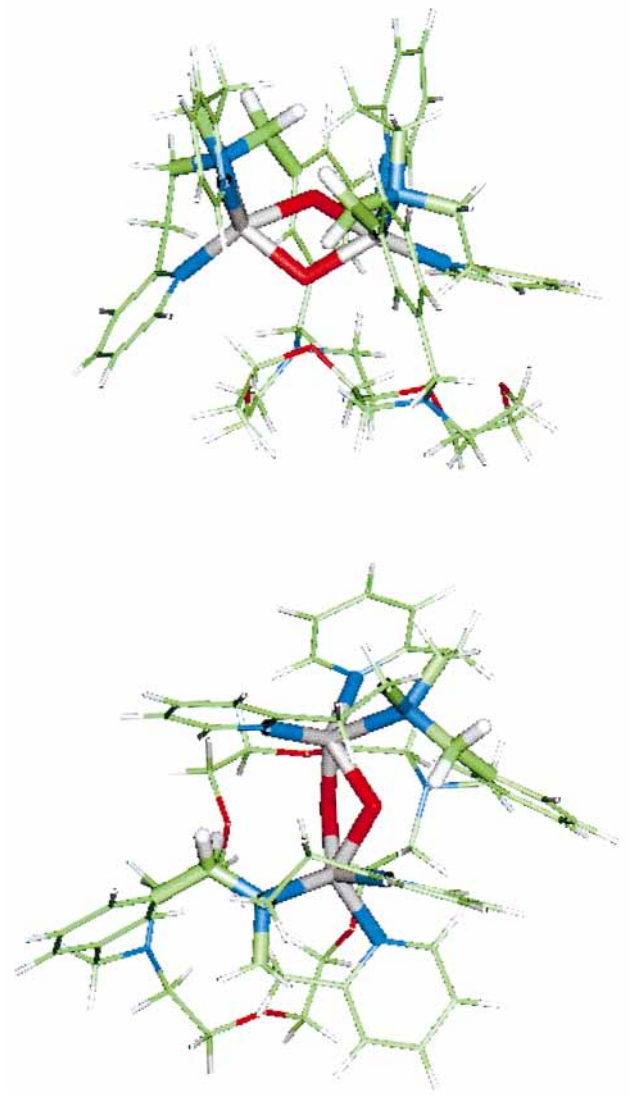


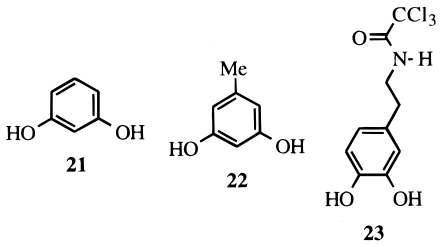
Figure 8. Torsion-minimized structure of complex **10**.

to point away from the reaction center and consequently do not suffer from oxidative degradation.

Reactivity Towards Exogenous Substrates. Several experiments were performed to investigate the ability of metallo-host **8** to oxidize substrates bound in its cavity. For these reactions the dihydroxybenzenes depicted in Chart 2 were used. By analogy with the xylyl-bridged PY2 copper complexes studied in the literature,[20] oxidation of resorcinol is expected to yield phloroglucinol (or another trihydroxybenzene). Orcinol (**22**) could undergo hydroxylation of the aromatic ring and in addition oxidation at the benzylic position, which in principle should be more facile than the former oxidation. Dopamine analogue **23** could show a reaction very similar to the mono-oxygenase reaction performed by dopamine-β-hydroxylase, i.e. benzylic hydroxylation to an adrenalin analogue.

The oxidation experiments were performed as follows. Complex **8** was prepared in situ by bubbling O_2 gas through a freshly prepared solution of **5** at low temperature. The excess O_2 was removed by repeated vacuum$-N_2$ purges. Substrates were added at low temperature either before or after O_2 introduction. After workup, the organic fractions were analyzed by GC, GC/MS, and/or NMR. When 1 equiv of substrate was used, identification of product or starting material was difficult in most cases. This feature has been observed before in related

Chart 2



systems and may be due to the fact that in order to be detectable the product must be driven out of the cavity of **8** by a second substrate.[48] When more than 1 equiv of substrate was applied, however, the starting compound was recovered. Other (polymeric) reaction products were isolated but could not be identified. Unfortunately, in none of the experiments was a product detected or isolated that could be assigned as being the result of an oxidation reaction involving the substrate.[49]

The fact that no oxygenated reaction products could be detected from the reaction between **8** and dihydroxybenzene derivates, may be the result of the formation of polymeric reaction products. It was found that the reaction between 2,4-bis(tert-butyl)phenol and complex **10** gave 2,2′,4,4′-tetra-tert-butyl-*o*,*o*′-biphenol. This type of radical coupling product is frequently observed when Cu_2O_2 complexes are treated with phenols. Formation of polymeric materials upon reaction of **8** with substrates **21**−**23** can therefore not be excluded. Substrates **21**−**23** are known to bind in the cavity of **1** and **2**,[19,50] but it is questionable whether they are held firmly enough at the binding site throughout the course of the reaction. Although the reactions were performed at −80 °C, which would strengthen the binding interaction, the exchange rate of bound and unbound substrate may still be considerable.[51]

Conclusions

By combining two building blocks that have been studied intensively in terms of their chemistry and physical properties, i.e. diphenylglycoluril-based molecular receptors and PY2-based copper complexes, we have developed a set of novel metallo-hosts. These hosts were all shown to bind molecular oxygen at low temperature (−85 °C). Although the Cu(I) complexes presented in this paper are closely related with regard to their composition, they display structural differences such as nuclearity, metal-to-metal distance, and ligand fluxionality. These differences strongly affect the behavior of these complexes in terms of O_2 binding and reactivity.

Complex **10** displays the most straightforward chemistry, i.e., a fast rate of formation and a high yield of aldehyde formation as the result of an internal N-dealkylation reaction during warming. Combined UV−vis and EXAFS experiments showed that the μ-η^2:η^2-peroxo binding mode of the O_2 ligand in this

(48) Coolen, H. K. A. C.; Meeuwis, J. A. M.; van Leeuwen, P. W. N. M.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1995**, *117*, 11906−11913.

(49) Only once a trace of 1,3,5-trihydroxybenzene was detected as a product in the reaction of resorcinol with **9**. This result could, however, not be reproduced.

(50) Martens, C. F. Supramolecular Bio-inorganic Chemistry. Ph.D. Thesis, University of Nijmegen, 1993.

(51) Mixtures of dihydroxybenzenes and diphenylglycoluril-based receptors showed averaged signals for the protons of complexed and uncomplexed guest and host molecules in the NMR spectra. Recently the binding of guest molecules in these host systems was shown to be enthalpy driven. See ref 19 and: (a) Sijbesma, R. P.; Kentgens, A. P. M.; Nolte, R. J. M. *J. Org. Chem.* **1991**, *56*, 3122−3201. (b) Reek, J. N. H. Synthesis, Binding Properties and Reactivity of Molecular Clips. Ph.D. Thesis, University of Nijmegen, 1996.

complex is nondependent on solvent. In addition, these experiments provided strong indications for the degree of bending of the Cu_2O_2 butterfly core in **10** to significantly vary with solvent. This observation could have implications for the understanding of Cu_2O_2 cores in reactive chemical systems or possibly Cu enzymes in terms of active site polarity and solvent accessibility, and ultimately reactivity towards exogenous substrates. In contrast to complex **10**, the behavior of complexes **8** and **9** is less well defined. The formation of these complexes is significantly slower than in the case of **10**, and complex **9** does not seem to form completely without degradation taking place. Large differences in UV−vis spectra were observed upon the generation of complexes **8** and **9** in different solvents. Although their origin is not completely understood, these observations are believed to be induced by geometric modulations in the Cu_2O_2 core.

Our objective to realize substrate selective oxidation utilizing complex **8** as outlined in the Introduction has not yet been achieved. Although this complex is reactive toward phenols, mainly undesired radical coupling reactions were observed. To circumvent the shortcomings of the present system, current investigations focus on the modification of the copper complexing ligand system in **2** in such a way that oxidation of exogenous substrates is more likely to take place.

Experimental Section

Materials and Methods. $Cu(I)(CH_3CN)_4ClO_4$ was synthesized by a method published by Kubas.[52] 2-Vinylpyridine was purified before use by flash chromatography over Silica 60 using diethyl ether as the eluent. All other chemicals were purchased commercially and used as received.

Solvents were dried and distilled prior to their use, except methanol which was of HPLC-grade and used as received. Diethyl ether, tetrahydrofuran, dioxane, and *n*-hexane were distilled from sodium/benzophenone, ethyl acetate and acetone were distilled from potassium carbonate, and dichloromethane and acetonitrile were distilled from calcium hydride. Dichloromethane used in the handling of the Cu(I) complexes was stirred with concentrated sulfuric acid for 2 days, and neutralized by washings with ammonia and water prior to distillation. Preparation of the air-sensitive Cu(I) samples was carried out using standard Schlenk techniques. Solvents were deoxygenated by repeated freeze/thaw cycles or by bubbling dinitrogen through them (20 min).

TLC analyses were performed on precoated silica gel 60 F_{254} plates or on aluminium oxide 150 F_{254} (type T) plates (Merck). Flash chromatography was carried out using Silica 60H (Merck) or neutral aluminium oxide 70−200 mesh (Across) brought to activity III.[53] GC analyses were performed on a Varian 3700GC equipped with a Chrompack WCOT CP-SIL 5 CB column (diameter = 0.25 μm). Calculations were performed on Silicon Graphics Challenge and Silicon Graphics Indigo II work stations, using the QUANTA molecular modeling package, with the CHARMM 3.3 force field.

Syntheses. 1-(*m*-Cyanobenzyl)-1-aza-4,7,10,13-tetraoxacyclopentadecane (11). To a solution of 10 mL of acetone were added 517 mg (2.36 mmol) of 1-aza-4,7,10,13-tetraoxacyclopentadecane, 463 mg (2.52 mmol) of α-bromo-*m*-tolunitrile, and 330 mg (2.39 mmol) of K_2CO_3. The mixture was refluxed for 16 h. After the formed KBr was filtered off, the solution was concentrated in vacuo and the resulting material was further purified using column chromatography (silica 60H, 4% MeOH in $CHCl_3$). Yield: 709 mg (90%) of yellow oil **11**. ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.80 (t, 4H, CH_2CH_2N), 3.60 (S, 2H, NCH_2Ar), 3.60−3.80 (m, 16H, CH_2O), 7.3−7.8 (m, 4H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.39 (NCH_2CH_2), 59.81 (NCH_2Ar), 69.81, 70.17, 70.48, 70.96 (CH_2OCH_2), 112.17 (Ar*C*−CN), 119.04 (Ar−*C*≡N), 128.86, 130.54, 132.14, 132.99 (Ar*C*−H), 141.68 (Ar*C*−CH_2). IR (KBr, cm^{-1}): 3061 (ArH); 2862 (CH_2); 2228 (C≡N); 1601, 1583, 1479, 1471, 1450 (C═C); 1357, 1297, 1252 (CH_2); 1126 (C−O−C). FAB-MS: *m*/*z* 335 $(M + H)^+$. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.95: H, 7.95; N, 7.96. Found: C, 64.65; H, 7.84; N, 8.38.

1-(α-Amino-*m*-xylylyl)-1-aza-4,7,10,13-tetraoxacyclopentadecane (12). To a suspension of 100 mg (2.63 mmol) of $LiAlH_4$ in 30 mL of dry THF was added dropwise a solution of 619 mg (1.85 mmol) of **11** in 7 mL of dry THF. The solution turned purple-red. After the addition was complete, the reaction mixture was refluxed for 3 h and subsequently stirred for 16 h at ambient temperature. Thereafter 20 mL of an aqueous 1 N NH_4Cl solution was added. The mixture was extracted with dichloromethane and brine. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo. Yield: 610 mg (100%) of oil **12**. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.9 (br, 2H, NH_2), 2.80 (t, 4H, CH_2CH_2N, J = 6 Hz), 3.60−3.80 (m, 18H, CH_2O, NCH_2Ar), 3.86 (s, 2H, CH_2NH_2), 7.10−7.14 (m, 4H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.38 (CH_2NH_2), 54.26 (NCH_2CH_2), 60.67 (NCH_2Ar), 69.85, 70.14, 70.42, 70.93 (CH_2OCH_2), 125.69, 127.43, 127.65, 128.33 (Ar*C*−H), 139.83, 143.01 (Ar*C*−CH_2). IR (KBr, cm^{-1}): 3372 (NH_2); 3065, 3026 (ArH); 2866 (CH_2); 1607, 1589, 1451 (C═C); 1356, 1300, 1252 (CH_2); 1121 (C−O−C). No reproducible elemental or mass-analysis could be obtained for this compound.

1-{α-[Bis(2-(2-pyridyl)ethyl)amino)]-*m*-xylylyl}-1-aza-4,7,10,13-tetraoxacyclo pentadecane (3). A solution containing 600 mg (1.8 mmol) of **12**, 1.38 g (13 mmol) of 2-vinylpyridine, and 470 mg (7.8 mmol) of acetic acid in 7.5 mL of methanol was transferred to a Teflon high-pressure capsule. The solution was kept at a pressure of 15 kbar and a temperature of 50 °C for 16 h. The red reaction mixture was subsequently extracted with dichloromethane and aqueous 15% NaOH. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo. The obtained oil was further purified by column chromatography (neutral alumina (activity III), first eluent 100% Et_2O, second eluent 2% MeOH in $CHCl_3$). Yield: 581 mg (60%) of **3** as a straw yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.78 (t, 4H, CH_2CH_2N, J = 6 Hz); 2.93 (s, 8H, NCH_2CH_2Py), 3.59−3.69 (m, 20H, CH_2O, NCH_2Ar), 7.02−7.18 (m, 8H, Ar*H*, Py$H_{3,5}$), 7.53 (m, 2H, PyH_4, J = 7.7, 1.8 Hz), 8.48 (m, 2H, PyH_6, J = 3.9 Hz). IR (KBr, cm^{-1}): 3059, 3007 (ArH); 2926, 2861 (CH_2), 1591, 1569, 1475, 1435 (C═C, C═N); 1356, 1298, 1250 (CH_2); 1124 (C−O−C). FAB-MS: *m*/*z* 549 $(M + H)^+$. No reproducible elemental analysis could be obtained for this compound.

1,10-Bis(*m*-cyanobenzyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (13). A procedure identical to that described for **11** was followed for the preparation of this compound. The following amounts were used: 40 mL of acetone, 960 mg (3.66 mmol) of 2,2′-Kryptofix (**10**), 1.44 g (3.66 mmol) of α-bromo-*m*-tolunitrile, and 1.06 g (7.68 mmol) of K_2CO_3. The obtained material was purified by column chromatography (silica 60H, eluent 3% MeOH in $CHCl_3$). Yield: 1.8 g (100%) of white crystalline **13**. Mp = 89.5 °C. ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.82 (t, 8H, CH_2CH_2N, J = 6 Hz), 3.62 (t, 16H, CH_2O), 3.74 (s, 4H, NCH_2Ar), 7.4−7.8 (m, 8H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.93 (NCH_2CH_2), 59.05 (NCH_2Ar), 69.92, 70.79 (CH_2O), 119.08 (*C*≡N), 128.85, 130.51, 132.12, 132.96 (Ar*C*H), 141.79 (Ar*C*−CH_2). IR (KBr, cm^{-1}): 2999 (ArH), 2822−2944 (CH_2), 2224 (CN), 1603−1586 (C═C), 1482−1431 (CH_2), 1174−1046 (C−O−C). FAB-MS: *m*/*z* 493 $(M + H)^+$. Anal. Calcd for $C_{28}H_{36}N_4O_4$: C, 68.27; H, 7.37; N, 11.09. Found: C, 68.06; H, 7.22; N, 11.09.

1,10-Bis(α-amino-*m*-xylylyl)-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (14). A procedure identical to that described for **12** was followed for the preparation of this compound. The following amounts were used: 400 mg (10.5 mmol) of $LiAlH_4$ in 70 mL of dry THF and 1.35 g (2.74 mmol) of **13** in 40 mL of THF. The color of the reaction mixture was green-yellow. The work-up was the same as for **12**. Yield: 861 mg (63%) of oily **14**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s (br), 4H, NH_2), 2.82 (t, 8H, CH_2CH_2N, J = 6 Hz), 3.84−3.60 (m, 20H, CH_2NH2, CH_2O), 7.28−7.16 (m, 8H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.40 (CH_2NH_2), 53.72 (NCH_2CH_2), 59.85 (NCH_2Ar), 69.90, 70.63 (CH_2O), 125.62, 127.39, 127.56, 128.35 (Ar*C*−H), 139.84, 143.10 (Ar*C*−CH_2). IR (KBr, cm^{-1}): 3364 (NH_2); 3025 (ArH); 2865 (CH_2); 1607, 1589 (C═C); 1110 (C−O−C). FAB-MS: *m*/*z* 501 $(M + H)^+$. No reproducible elemental analysis of oily **14** could be obtained.

(52) Kubas, G. *J. Inorg. Synth.* **19**, *1979*, 90.
(53) Brockmann, H.; Schodder, H. *Ber.* **1941**, *74B*, 73.

1,10-Bis(α-[bis(2-(2-pyridyl)ethyl)amino)]-*m*-xylylyl}-1,10-diaza-4,7,13,16-tetra oxacyclooctadecane (4). For the preparation of this compound a procedure identical to the one described for **3** was followed. The following amounts of compound were used: 10 mL of methanol, 861 mg (1.7 mmol) of **14**, 2.53 g (24.1 mmol) of 2-vinylpyridine, and 720 mg (12 mmol) of acetic acid. The color of the reaction mixture was purple. The workup procedure was as follows: dichloromethane was added, and the organic layer was washed with a saturated $NaHCO_3$ solution. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting red-brown oil was further purified by column chromatography (neutral alumina (activity III), eluent 2% EtOH in CH_2Cl_2). Yield: 1.4 g (92%) of oily **4**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.80 (t, 8H, CH_2CH_2N, J = 6.2 Hz), 2.94 (s, 16H, $PyCH_2CH_2$), 3.55−3.70 (m, 24H, CH_2O, NCH_2Ar), 7.01−7.18 (m, 16H, Ar*H*, Py$H_{3,5}$), 7.52 (m, 4H, PyH_4, J = 7.6, 1.8 Hz), 8.48 (m, 4H, PyH_6, J = 4.7, 0.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.6, 52.7 (NCH_2CH_2, NCH_2CH_2Py), 57.4, 58.9 (NCH_2Ar), 69.0, 69.9 (CH_2O), 126.3, 126.4, 127.0, 128.2 (Ar*C*−H), 120, 122.3, 135.1, 148.0 (Py*C*−H), 138.1, 138.6 (Xy*C*), 159.6 (Py*C*) IR (KBr, cm^{-1}): 3058, 3007 (ArH), 2819−2931 (CH_2), 1591 (C═C), 1065−1119 (C−O−C). FAB-MS: *m*/*z* 921 $(M + H)^+$. Anal. Calcd for $C_{56}H_{72}N_8O_4 \cdot 0.5\ CH_2Cl_2$: C, 70.42; H, 7.63; N, 11.63. Found: C, 69.99; H, 7.59; N, 11.02.

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetrakis[2-(2-chloroethoxy)-ethoxy]-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]-azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione (15). This compound was prepared following a procedure previously described by us.[19]

α-Amino-α′-[(*tert*-butyloxycarboxy)amido]-*m*-xylene (16). To a stirred solution of 4 g (29.4 mmol) of α,α′-*m*-diaminoxylene in 40 mL of water was added 3 g (21 mmol) of *tert*-butyloxycarboxy azide in 40 mL of dioxane through a dropping funnel. The mixture was stirred overnight at ambient temperature. The volume of the solvent was reduced to one third in vacuo. A white precipitate (di-substituted product) was formed which was filtered off. The filtrate was washed three times with 50 mL of diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on neutral alumina using 100% diethyl ether as the first eluent. The di-substituted product was collected. The eluent was subsequently changed to methanol and **16** was obtained as a yellow oil. Yield: 1.24 g (26%). ^{1}H NMR ($CDCl_3$, 90 MHz): δ 3.68 (2 × s, 11H, NH_2, $C(CH_3)_3$), 4.27 (d, 2H, CH_2−NH), 4.93 (s br, N*H*−C(O)), 7.18 (m, 4H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 (CH_3), 44.5 (CH_2NH_2), 46.2 (CH_2NHCO), 79.3 ($C(CH_3)_3$), 125.8, 126.0, 126.1, 128.7 (Ar*C*), 139.2 (Ar*C*−CH_2NHCO), 143.4 (Ar*C*−CH_2NH_2), 155.9 (*C*ONH). MS (CI): *m*/*z* 237 $(M + H)^+$.

2a,8,9,12,13,14,15,17,18,25,26,29,30,31,32,34,35,38b-Octadecahydro-2a,38b-diphenyl-13,30-bis(α-[(*tert*-butyloxycarboxy)amido]-*m*-xylylyl)-1H,4*H*-6,37:20,23-dietheno-2,22:3,21-dimethano-5*H*,11*H*,28*H*,38*H*-7,10,16,19,24,27,33,36-octaoxa-2,3,4a,13,30,38a-hexaazacyclopenta[*cd*]cyclotetratriacont[*g*]azulene-1,4-dione (17). Under a nitrogen atmosphere, 7.0 g (66.0 mmol) of Na_2CO_3, 7.0 g (46.7 mmol) of NaI, and 2.0 g (2.03 mmol) of **15** were suspended in 250 mL of acetonitrile. While the mixture was refluxed, a solution of 1.02 g (4.32 mmol) of **16** in 100 mL of acetonitrile was added over a period of 2 days. After the addition of **16** was complete, the mixture was refluxed for an additional 2 days. Subsequently, the mixture was filtered and concentrated in vacuo. The resulting material was redissolved in dichloromethane and washed with brine. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated. The solid material was subjected to column chromatography (silica 60 H, eluent $CHCl_3$/MeOH/triethylamine, 94/5/1 v/v/v) to yield 2.75 g (95%) of white solid **17**. Mp > 300 °C (dec). ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.48 (s, 18H, CH_3), 2.91 (t, 8H, CH_2CH_2N, J = 5 Hz), 3.6−4.2 (m, 32H, NCH*H*Ar, OCH_2, NCH_2Xy(Boc)), 4.23 (d, 4H, CH_2NH, J = 6 Hz), 4.93 (s (br), 2H, N*H*CO), 5.70 (d, 4H, NC*H*HAr, J = 16 Hz), 6.76 (s, 4H, Ar*H*), 7.0−7.4 (m, 18H, Xy*H*, Ph*H*). IR (KBr, cm^{-1}): 2869, 2926 (CH_2); 1713 (C═O); 1506 (NH−CO); 1482, 1459, 1427 (C═C); 1354, 1307, 1258 (CH_2O), 1365, 1390 (^{t}Bu); 1128, 1070 (COC). FAB-MS: *m*/*z* 1338 $(M + Na^+)$, 1316 (M + H+). Anal. Calcd for $C_{74}H_{90}N_8O_{14}$: C, 67.56; H, 6.90; N, 8.52. Found: C, 67.63; H, 7.08; N, 8.26.

2a,8,9,12,13,14,15,17,18,25,26,29,30,31,32,34,35,38b-Octadecahydro-2a,38b-diphenyl-13,30-bis(α-amino-*m*-xylylyl)-1*H*,4*H*-6,37:20,23-dietheno-2,22:3,21-dimethano-5*H*,11*H*,28*H*,38*H*-7,10,16,19,24,27,33,36-octaoxa-2,3,4a,13,30,38a-hexaazacyclopenta[*cd*]cyclotetratriacont[*g*]azulene-1,4-dione (18). A mixture of 10 mL of trifluoroacetic acid and 10 mL of CH_2Cl_2 was cooled to 0 °C. To this mixture was added a solution of 660 mg (0.502 mmol) of **17** in 10 mL of CH_2Cl_2. Gas evolution started immediately. After stirring for 1 h at 0 °C, 50 mL of dichloromethane was added. The solution was washed (3×) with 50 mL of an aqueous 15% NaOH solution, the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo yielding a white solid. Yield: 400 mg (72%) of **18**. Mp > 300 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (t, 8H, CH_2CH_2N, J = 5 Hz), 3.36 (s (br), 4H, NH_2), 3.7−4.0 (m, 28H, CH_2O, NCH_2Xy, NC*H*H), 4.17 (m, 4H, CH_2NH_2), 5.67 (d, 4H, NCH*H*Ar, J = 16 Hz), 6.56 (s, 4H, Ar*H*), 7.0−7.3 (m, 18H, Ph*H*, Xy*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.01 (NCH_2Ar), 45.05 (CH_2NH_2), 54.09 (NCH_2CH_2), 58.31 (NCH_2Xy), 69.31, 69.45, 69.72 (CH_2O), 85.68 (N*C*N), 113.45 (Ar*C*), 125.86, 128.04, 128.32 (Ph*C*, Xy*C*), 128.40 (Ar*C*), 133.78 (Ar*C*), 139.24 (Xy*C*), 150.38 (Ar*C*), 158.38 (*C*O). IR (KBr, cm^{-1}): 3433 (NH_2); 2921, 2870 (CH_2); 1710 (C═O); 1461, 1427 (C═C), 1353, 1307, 1258 (CH_2O); 1126, 1069 (COC). FAB MS: *m*/*z* 1137 $(M + Na^+)$, 1115 $(M + H^+)$. Anal. Calcd for $C_{64}H_{74}N_8O_{10} \cdot CHCl_3$: C, 63.23; H, 6.12; N, 9.08. Found: C, 63.81; H, 5.96; N, 8.65.

2a,8,9,12,13,14,15,17,18,25,26,29,30,31,32,34,35,38b-Octadecahydro-2a,38b-diphenyl-13,30-bis(α-[bis(2-(2-pyridyl)ethyl)amino)]-*m*-xylylyl)-1*H*,4*H*-6,37:20, 23-dietheno-2,22:3,21-dimethano-5*H*,11*H*,28*H*,38*H*-7,10,16,19,24,27,33,36-octaoxa-2,3,4a,13,30,38a-hexaazacyclopenta[*cd*]cyclotetratriacont[*g*]azulene-1,4-dione (2). To a mixture of 2-vinylpyridine (263 mg, 2.5 mmol), 346 mg (0.313 mmol) of **18**, and 75 mg (1.25 mmol) of acetic acid was added a 1:1 mixture (v/v) of methanol and dichloromethane so that the total volume amounted to 7.5 mL. The light yellow solution was transferred to a high-pressure Teflon capsule and kept under a constant pressure of 15 kbar at a temperature of 50 °C for 16 h. The dark red reaction mixture was concentrated in vacuo and the resulting oil was further purified by column chromatography (neutral alumina (activity III), eluent 2% MeOH in $CHCl_3$). Yield: 450 mg (95%) of **2** as an yellow-orange solid. Mp: dec at $T \geq 40$ °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85−2.89 (m, 24 H, NCH_2CH_2Py, OCH_2CH_2N), 3.63−4.15 (m, 36H, CH_2O, NC*H*HAr, NCH_2Xy), 5.59 (d, 4H, NCH*H*Ar, J = 16.0 Hz), 6.55 (s, 4H, Ar*H*), 7.04−7.19 (m, 26H, Ph*H*, Xy*H*, Py$H_{3,5}$), 7.43 (m, 4H, PyH_4, J = 7.0, 1.9 Hz), 8.40 (m, 4H, PyH_6, J = 3.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.05 ($PyCH_2$), 36.96 (NCH_2Ar), 53.77, 53.89 (NCH_2CH_2), 58.42, 59.93 (NCH_2Xy), 69.40, 69.84, 70.17 (CH_2O), 85.03 (N*C*N), 114.11 (Ar*C*), 120.03, 123.34, 136.08, 149.10 (Py*C*−H), 127.22−129.31 (m, Ph*C*−H, Xy*C*−H, Ar*C*−H), 134.23 (Ar*C*), 139.46, 139.69 (Xy*C*), 150.89 (Ph*C*), 157.38 (*C*O). IR (KBr, cm^{-1}): 3058, 3005 (ArH); 2924, 2866 (CH_2); 1710 (C═O); 1591, 1568, 1459, 1437 (C═C, C═N); 1125 (C−O−C). FAB-MS: *m*/*z* 1535 $(M + H)^+$. Anal. Calcd for $C_{92}H_{102}N_{12}O_{10}$: C, 71.95; H, 6.69; N, 10.94. Found: C, 72.25; H, 6.69; N, 10.64.

$[(2)(Cu^{I})_2](ClO_4)_2 \cdot CH_2Cl_2 \cdot Et_2O$ (5). Upon dissolving of 100 mg (6.52×10^{-5} mol) of ligand **2** and 68 mg (0.208 mmol) of $Cu(CH_3CN)_4ClO_4$ in 25 mL of CH_2Cl_2, a yellow-orange solution was obtained. This solution was stirred for 3 h and subsequently concentrated to 5 mL. After addition of 10 mL of Et_2O the flask was placed in a refrigerator at −20 °C overnight. The supernatant was decanted, and the remainders were dried in vacuo. Another reprecipitation was performed, yielding a yellow powder. Yield: 103 mg (85%) of a pale yellow solid. Anal. Calcd for $C_{92}H_{102}N_{12}O_{18}Cl_2Cu_2 \cdot CH_2Cl_2 \cdot Et_2O$: C, 57.65; H, 5.69; N, 8.32. Found: C, 57.67; H, 5.52; N, 8.17. ^{1}H NMR (300 MHz, CD_3NO_2): δ 2.93 (s, 8H, NCH_2CH_2), 3.26 (s, 16H, CH_2CH_2-Py), 3.89 (m, 36H, OCH_2, NCH_2Ar, NCH*H*Ar), 5.65 (d, 4H, NCH*H*Ar, J = 15.8 Hz), 6.70 (s, 4H, Ar*H*), 7.06−7.47 (m. 26H, Ph*H*, Ar*H*, Py$H_{3,5}$), 7.89 (s, 4H, PyH_4), 8.63 (s, 4H, PyH_6). UV (CH_2Cl_2): 340 nm (ϵ 5000 M^{-1} cm^{-1}).

$[(3)Cu^{I}]ClO_4$ (6). A solution of 86 mg (0.157 mmol) of ligand **3** in 10 mL of CH_2Cl_2 was added at once to 51 mg (0.156 mmol) of $Cu(CH_3CN)_4ClO_4$. The resulting yellow solution was stirred for 30 min and subsequently concentrated to 5 mL. Addition of 20 mL of Et_2O yielded a cloudy solution, which was placed in a refrigerator at −20 °C overnight. The supernatant was decanted, and the remaining golden

yellow oil was dried in vacuo. Yield: 100 mg (90%) of a golden yellow foam. ^{1}H NMR (300 MHz, CD_3NO_2): δ 2.61 (s, 4H, NCH_2CH$_2$), 3.24 (s, 8H, CH_2CH_2Py), 3.61 (s, 22H, OCH_2 + NCH_2Ar), 4.08 (s, 2H, NCH_2Ar), 7.21−7.47 (m, 8H, Ar*H*, Py$H_{3,5}$), 7.92 (dt, 2H, PyH_4, J = 7.8, resp. 1.7 Hz), 8.56 (d, 2H, PyH_6, J = 5.2 Hz). UV (CH_2Cl_2): 340 nm (ϵ 1900 M^{-1} cm^{-1}). Anal. Calcd for $C_{32}H_{44}N_4O_8ClCu$: C, 54.07; H, 6.2; N, 7.89. Found: C, 53.39; H, 5.98; N, 7.47.

[(4)(Cu^I)$_2$](ClO$_4$)$_2$·1.5CH$_2$Cl$_2$·Et$_2$O (7). A solution of 293 mg (0.318 mmol) of ligand **4** in 15 mL of CH_2Cl_2 was added at once to 208 mg (0.636 mmol) of Cu(CH_3CN)$_4$ClO$_4$. The resulting orange solution was stirred for 3 h and then concentrated to 7 mL, after which 15 mL of Et_2O was added whereupon a brownish solid was formed. The vessel was placed in a refrigerator at −20 °C overnight. The supernatant was decanted and the remainders were dried in vacuo. Another reprecipitation was performed yielding 360 mg (78%) of a yellow-brownish powder. ^{1}H NMR (300 MHz, CD_3NO_2): δ 2.80 (s, 8H, NCH_2CH$_2$), 3.20 (s, 16H, CH_2CH_2Py), 3.61 (m, 24H, OCH_2, NCH_2Ar), 7.22−7.44 (m, 16H, Ar*H*, Py$H_{3,5}$), 7.88 (dt, 4H, PyH_4, J = 7.7, resp. 1.4 Hz), 8.52 (s, 4H, PyH_6). Signals are somewhat broadened, probably due to partial oxidation during sample handling. UV (CH_2Cl_2): 344 nm (ϵ 5800 M^{-1} cm^{-1}). Anal. Calcd for $C_{56}H_{72}N_8O_{12}Cl_2Cu$·1.5$CH_2Cl_2$·$Et_2O$: C, 50.99; H, 5.91; N, 7.73. Found: C, 50.61; H, 5.87; N, 7.55.

1,2-Dimethoxy-4-((2-trichloroacetamide)ethyl)benzene (24). To a solution of 2.34 g (12.9 mmol) of homoveratrylamine in 50 mL of dichloromethane was added 1.31 g (12.9 mmol) of dry triethylamine, and subsequently 4.1 g (25.8 mmol) of trichloroacetyl chloride was added dropwise. The mixture was stirred for 3 h at room temperature. The organic layer was washed (2×) with aqueous 6 N HCl, separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting oil was further purified by column chromatography (silica 60 H, eluent $CHCl_3$) to yield 2.7 g (63%) of **24** as a white solid. Mp = 107 °C. IR (KBr, cm^{-1}): 3362 (N−H), 2944 (C−H), 1709 (amide I), 1515 (amide II), 1459 (OMe), 858, 825 (1,2,4 subst. Ar). ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.85 (t, 2H, ArCH_2CH$_2$), 3.62 (q, 2H, ArCH$_2$CH_2), 3.87 (s, 6H, OCH_3), 6.62−6.91 (m, 3H, Ar*H*). MS (EI): *m*/*z* 326 (M^+).

1,2-Dihydroxy-4-((2-trichloroacetamide)ethyl)benzene (23). Under a dinitrogen atmosphere, a solution of 25 mL of dichloromethane containing 2.7 g (8.16 mmol) of **24** was cooled to −78 °C by immersion in an isopropyl/CO_2 bath. To this solution was added 32.6 mL of a 1 M BBr_3 solution in dichloromethane (4 equiv) via syringe. The solution turned deep red and was maintained at − 78 °C for 30 min, after which it was allowed to warm up to ambient temperature. After stirring for 10 h a yellowish brown solution was obtained to which 100 mL of brine was added. After the gas evolution had ceased, the mixture was concentrated and the resulting solid material was extracted with ethyl acetate. The organic layer was washed with brine, separated, dried over $MgSO_4$, filtered, and concentrated in vacuo. The solid material was further purified by column chromatography (silica 60 H, eluent 5% MeOH in $CHCl_3$). Yield: 1.79 g (74%) of **23** as an off-white solid. Mp = 115 °C. The product is easily identified by dipping the TLC plate in a $FeCl_3$ solution showing the product as a purple spot. IR (KBr, cm^{-1}): 3314 (N−H), 1717 (amide I), 1523 (amide II), 1191 (Ar−OH), 879 + 823 (1, 2, 4 subst. Ar). ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.80 (t, 2H, ArCH_2CH$_2$), 3.60 (q, 2H, ArCH$_2$CH_2), 5.39 (br, 2H, OH), 6.50−6.88 (m, 3H, Ar*H*). Anal. Calcd for $C_{10}H_{10}NO_3Cl_3$: C, 40.23; H, 3.38; N, 4.69. Found: C, 40.03; H, 3.37; N, 4.63. MS-EI: *m*/*z* 297 $(M)^+$.

Low-Temperature UV−vis Spectroscopy. The low-temperature UV−vis spectra were obtained on a Hewlett-Packard 8452A diode array spectrophotometer driven by a Compaq Deskpro 386S computer using a software system writen by On-Line Instrument Systems Inc. The spectrophotometer was equipped with a Kontes KM-611772 variable-temperature UV−vis Dewar cell with quartz windows. The low temperature inside the Dewar assembly was achieved by putting a copper tubing coil inside the methanol-filled Dewar cell. Through the coil cold methanol was circulated by an external cooling unit (Neslab CC-100II cryocool immersion cooler, in Agitainer A with circulation pump). The cuvette assembly consisted of a quartz cuvette fused to one end of a glass tube. The other end was attached to a high-vacuum-stopcock and a 14/20 ground glass joint. The temperature inside the Dewar assembly was monitored by an Omega model 651 resistance thermometer probe.

Solid Cu(I) samples were weighted in a drybox and transferred to the cuvette assembly. Freshly distilled solvent was added after it had been saturated with argon. After placing the cuvette into the Dewar assembly, the temperature was allowed to equilibrate for 10 min and the spectrum was subsequently recorded. The cuvette assembly had been previously calibrated for volume vs height in the tube, and the height of the solution in the cuvette assembly at low temperature was noted for the purposes of concentration determination. Oxygenation of the chilled solutions was effected by direct bubbling of dry, precooled dioxygen using a syringe needle. The spectra were recorded at set intervals. After the solution had warmed to room temperature, the spectra were recorded again.

Manometric O_2 Uptake Measurements on Complex 7. O_2 uptake by **7** at −80 °C was monitored under constant pressure in a glass buret as described previously.[12] A calibrated 10 mL side-arm Schlenk flask containing a dichloromethane solution of **7** was attached to the manometer setup and cooled to −80 °C under an inert nitrogen atmosphere. After temperature equilibration the flask was evacuated for 30 min while stirring, the stopcock leading to the flask was closed, and the buret assembly was equilibrated to 1 atm of O_2. The stopcock to the flask was then opened, causing an immediate color change of the solution to dark-purplish green. The volume of consumed O_2 was recorded after equilibration and after taking into account the amount of O_2 taken up by the solvent. Two independent runs were performed on 170 mg (0.135 mmol) and 108 mg (0.0854 mmol) of **7**, respectively. The volumes of O_2 taken up were 3.1 and 2.1 mL, respectively, corresponding to an average Cu/O_2 ratio of 2.1(±0.1):1.

Reaction of [4(Cu^{II})$_2$](ClO$_4$)$_2$ (7) with O_2 at −80 °C: Identification of the Cu(II) Complexes. Cu(I) complex **7** was synthesized in situ in CH_2Cl_2 solution as described above using 244 mg (0.265 mmol) of **4** and 175 mg (0.535 mmol) of Cu^I(CH_3CN)$_4$ClO$_4$ in 30 mL of solvent. The resulting solution was cooled to −78 °C, after which predried O_2 was bubbled through for several min, resulting in a color change from golden yellow to dark green. After this mixture had been stirred for 2 h at −78 °C, it was allowed to warm up to ambient temperature. After concentrating the solution in vacuo, the concentrated solution was layered with a large volume of Et_2O. The resulting precipitate was filtered off and repeatedly washed with EtOAc and *n*-hexane to yield 171 mg of a green powder. IR (KBr pellet, cm^{-1}): 3550, 3450 (br) OH/H_2O, 3071 (ArH), 2936, 2868 (CH_2), 1608, 1571 (Ar), 1485, 1445 (CH_2), 1094, 623 (ClO_4), 769 (ArH). UV (CH_3CN, nm): 257, 310 (sh), 490, 652. FAB-MS: *m*/*z* 1177 (**4** + 2Cu + 2OH + ClO_4)$^+$, 1153 (**4** + 2Cu + OH + ClO_4)$^+$, 1147 (**4** + 2Cu + ClO_4)$^+$, very low intensities. Anal. Calcd for $C_{56}H_{72}N_8O_{14}Cu_2Cl_2$: C, 52.58; H, 5.67; N, 8.76. Found: C, 52.03; H, 5.60; N, 9.38.

Formation of Aldehyde 19 from [4(Cu^{II})$_2$(O$_2$)](ClO$_4$)$_2$ (10). A similar procedure as described for the identification of the Cu(II) complex of **7** (see above) was used to generate the O_2 complex, either at low or at ambient temperature, using 65 mg (0.071 mmol) of **7** and 46.3 mg (0.142 mmol) of Cu^I(CH_3CN)$_4$ClO$_4$. After the reaction mixture had warmed up, the clear reaction mixture was washed with a mixture of brine and aqueous 30% ammonia (3×) and dried over $MgSO_4$. After removal of the solvent in vacuo 75 mg of an orange oil was obtained. By flash chromatography (alumina (activity III), eluent 2% EtOH in CH_2Cl_2) two fractions were obtained, viz. 10 mg of the starting ligand and 15 mg of the mono aldehyde **19**. ^{1}H NMR ($CDCl_3$, 90 MHz): δ 2.83 (t, 8H, NCH_2CH$_2$, J = 6 Hz), 2.95 (s, 8H, CH_2CH_2Py), 3.60−3.78 (m, 22H, NCH_2Ar, CH_2O), 7.0−7.87 (m, 14 H, Ar*H*, Py$H_{3,4,5}$), 8.49 (qd, 2H, PyH_6), 10.02 (s, 1H, C*H*O). FAB-MS: *m*/*z* 748 (M + K)$^+$, 732 (M + Na)$^+$, 710 (M + 1)$^+$.

Reaction of [2(Cu^{II})$_2$](ClO$_4$)$_2$ (5) with O_2 at −80 °C: Identification of the Cu(II) Complexes. A similar procedure as described for **7** was followed. Starting from 63 mg (0.041 mmol) of **2** and 27.5 mg (0.084 mmol) of Cu^I(CH_3CN)$_4$(ClO_4), 30 mg of a moss-green powder was obtained after several precipitations with Et_2O. IR (KBr pellet, cm^{-1}): 3443 (br, OH/H_2O), 3080 (ArH), 2925, 2873 (CH_2), 1709 (C=O), 1608, 1571 (Ar), 1463,1450 (CH_2), 1094, 623 (ClO_4), 770 (ArH). UV (DMF, nm): λ_{max} 267, 293, 678.

Formation of Aldehyde 20 from [2(Cu^{II})$_2$(O$_2$)](ClO$_4$)$_2$ (8). In a similar manner as described for **7**, the O_2 complex was prepared and treated in CH_2Cl_2 solution with 80.6 mg (0.052 mmol) of **2** and 34.1

mg (0.104 mmol) of $Cu^I(CH_3CN)_4ClO_4$. The color of the reaction mixture turned green after 30 min and changed to grenish-blue after warming. Washing with aqueous 30% ammonia (3×), drying over $MgSO_4$ and evaporation of the solvent in vacuo yielded 75 mg of an off-white residue. Yield of aldehyde **20** was 25−50% (based on integration of NMR signals). Attempts to purify **20** by flash chromatography failed. ^{1}H NMR ($CDCl_3$, 90 MHz): δ 2.82−3.03 (m, NCH_2-CH_2, CH_2CH_2Py), 3.60−4.14 (m, NCHHAr, OCH_2, NCH_2Xy), 5.68 (d, NCHHAr, J = 16.2 Hz), 6.52, 6.65 (2 s, ArH), 6.90−7.21 (m, PhH, XyH, Py$H_{3,5}$), 7.38−7.62 (m, PyH_4), 8.47 (m, PyH_6), 9.98 (s, CHO). FAB-MS: m/z 1537 (**2** + H)$^+$, 1324 (**20** + H)$^+$.

Reaction of [3(Cu^I)](ClO$_4$) (6) with O$_2$ at −80 °C: Identification of the Cu(II) Complexes. A similar procedure as described for **7** was used. Starting from 205 mg (0.374 mmol) of **3** and 123 mg (0.376 mmol) of $Cu^I(CH_3CN)_4ClO_4$, 103 mg of a moss-green powder was isolated. IR (KBr pellet, cm^{-1}): 3525, 3450 (br) OH/H_2O, 3084 ArH, 2924, 2873 CH_2, 1609, 1571 Ar, 1485, 1447 CH_2, 1095, 623 ClO4, 771 ArH. UV (CH_3CN, nm): 260, 310 (sh), 637. FAB-MS: m/z 942 (**3** + PY2 + 2Cu + 2OH)$^+$, 711 (**3** + Cu + ClO_4)$^+$, 627 (**3** + Cu + OH)$^+$, 611 (**3** + Cu)$^+$. Anal. Calcd for $C_{64}H_{90}N_8O_{18}Cu_2Cl_2$: C, 52.74; H, 6.22; N, 7.69 . Found: C, 52.12; H, 6.06; N, 8.47.

Formation of Aldehydes from [{3(Cu^{II})}$_2$(O$_2$)](ClO$_4$)$_2$ (9). A procedure similar to the one described for **7** was applied. Using 26 mg (0.047 mmol) of **3** and 15.3 mg (0.047 mmol) of $Cu^I(CH_3CN)_4ClO_4$, 30 mg of an orange-yellow oil was obtained. Yield of aldehyde was <10% (based on integration of NMR signals). The ^{1}H NMR spectrum of the product was identical to the spectrum of **3**. Only one additional peak (low intensity) at 10.0 ppm (CHO) was observed. FAB-MS: m/z 549 (**3** + H)$^+$ (no 336 peak observed).

Reaction of [4(Cu^{II})$_2$(O$_2$)](ClO$_4$)$_2$ (10) with 2,4-Di-*tert*-butyl Phenol. Complex **7** was prepared in situ in CH_2Cl_2 solution, as described above, using 68 mg (0.074 mmol) of **4** and 48.4 mg (0.148 mmol) of $Cu^I(CH_3CN)_4ClO_4$. Predried O_2 was bubbled through the solution at −80 °C until a purplish-green color appeared. Excess O_2 was then removed by two vacuum−N_2 purge cycles. The color of the solution did not change during these manipulations. Stirring was continued for 1−2 h after which 15.2 mg (0.076 mmol) of 2,4-di-*tert*-butyl phenol was added. The color of the reaction mixture changed to deep blue/green upon addition of the substrate. Within 1−2 min it changed again to aqua. After warming the mixture was washed with 10 mL of aqueous 1 N H_2SO_4, yielding a colorless organic layer that was dried over $MgSO_4$. Removal of the solvent in vacuo yielded 5−15 mg of a slightly yellow oil/solid. TLC analysis showed the presence of two components; one was identified as 2,2′,4,4′-tetra-*tert*-butyl-*o*,*o*′-biphenol, the other one could not be identified. MS (EI): m/z 410 (M^+).

Reaction of [2(Cu^{II})$_2$(O$_2$)](ClO$_4$)$_2$ (8) with Exogenous Substrates. (a) Resorcinol (20). Complex **5** was generated in situ by using 25.6 mg (0.017 mmol) of **2** and 10.8 mg (0.034 mmol) of $Cu^I(CH_3CN)_4ClO_4$. The resulting golden yellow solution was stirred for 5 min after which it was added via syringe to 1.81 mg (0.017 mmol) of resorcinol. The color of the reaction mixture turned slightly brown within seconds. After cooling to −78 °C, predried O_2 was bubbled through the solution for 10 min. The resulting brownish solution was allowed to warm up to ambient temperature, yielding a clear, dark brown solution. This solution was treated with a silylating reagent (a combination of TMSCl and $(TMS)_2NH$) and worked up according to a procedure published by Stewart et al.[54] Aliquots of the product mixture were analyzed by GC and GC−MS. Several unidentified products were detected in this manner.

In a similar procedure complex **5** was allowed to react with 3 equiv of resorcinol instead of one. GC−MS analysis clearly showed the presence of disilylated resorcinol; the presence of a trisilylated trihydroxybenzene or another low molecular weight reaction product, however, could not be detected. Workup of the reaction mixture by using an acetylating reagent gave identical results.

(b) Orcinol (21). The procedure as described for the reaction with resorcinol was followed. Amounts used: 56.5 mg (0.037 mmol) of **2**, 24 mg (0.074 mmol) of $Cu^I(CH_3CN)_4(ClO_4)$ and 5.5 mg (0.039 mmol, 1 equiv) of orcinol. After stirring for 1 h an excess Ac_2O was added together with two drops of concentrated H_2SO_4.[55] The reaction mixture was stirred overnight, after which it was poured on ice. CH_2Cl_2 was added, and the water layer was made basic by the addition of a saturated Na_2SO_4 solution. The greenish-blue aqueous layer was extracted twice with CH_2Cl_2, and the organic layers were combined, washed once with water, and dried over $MgSO_4$. Yield: 62 mg of a brown powder. GC analysis revealed the presence of three major components: mono- and di-acetylated orcinol and an unidentified product.

(c) 1,2-Dihydroxy-4-((2-trichloroacetylamide)ethyl)benzene (23). In a similar manner as described for resorcinol, 1.5 mg (0.005 mmol) of **23** was reacted with O_2 and **8**, prepared from 8.8 mg (0.0051 mmol) of **2** and 33.5 mg (0.010 mmol) of $Cu^I(CH_3CN)_4PF_6$ in dichloromethane. After workup by treatment with TMSCl and $(TMS)_2NH$, the aqueous layers were analyzed by GC and GC−MS. No hydroxylated or related products were detected.

Preparation of EXAFS Samples. Solution samples for EXAFS measurements were prepared in an inert glovebox. Typically, 100 μL of an approximately 1 mM solution of Cu(I) complex was transferred via syringe to a sample holder. The sample holder was then cooled at −78 °C in a thermally isolated acetone bath that was cooled by an external cryostat. After temperature equilibration for 5−10 min, 100 μL of O_2-saturated solvent (precooled in the same acetone bath) was added via a precooled syringe and care was taken that mixing occurred homogeneously. The brightly colored samples were stored in liquid nitrogen before use. Aluminum cells with Kapton windows and rectangular apertures (10 × 15 mm) and a sample thickness of 1 mm were used.

EXAFS Experiments. EXAFS measurements were carried out in the European Molecular Biology Laboratoy (EMBL) Outstation in the Hamburg Synchrotron Laboratory (HASYLAB) at the Deutsches Elektronen-Synchrotron (DESY) in Hamburg, Germany. The EXAFS station features a gold-coated segmented toroidal focusing mirror, an order sorting monochromator (Si 111 crystals), which was set at 50% of peak intensity to suppress harmonics, a CANBERRA 13 element solid-state fluorescence detector, and an energy calibration device.[56] Typically 4−10 scans per sample were taken. During the measurements, the samples were kept at 20 K in the He exchange gas atmosphere of a closed-cycle cryostat and moved in between scans so that the part of the sample that was exposed to the beam was varied as much as possible in order to prevent radiation-induced artefacts. No spectroscopic differences between the scans were observed.

Data reduction was carried out on VAX computers at the Bijvoet Center, University of Utrecht, and on the CAOS-CAMM Center, University of Nijmegen, with the EMBL Outstation data reduction package EXPROG (H.-F. Nolting, C. Hermes, and R. F. Pettifer, unpublished). The energy of some of the X-ray fluorescence spectra of our complexes with dichloromethane as the solvent could not be properly calibrated due to the relatively high absorption by this solvent. Simulations of the calibrated, averaged, and background-substracted EXAFS were carried out on the Daresbury Laboratory (UK) dedicated X-ray absorption spectroscopy UNIX computer with the programm EXCURVE92,[57] including the programm MUFPOT for the ab initio calculation of phase shifts and back-scattering factors.

The approach for the analysis of the EXAFS is described in detail elsewhere.[38b] The principle is as follows: multiple scattering simulations were carried out for both the pyridine[58] and Cu_2:O_2[38b] moieties, where applicable, and the difference between experimental and theoretical

(54) Stewart, R. F.; Miller, L. L. *J. Am. Chem. Soc*. **1980**, *102*, 4999−5004.

(55) Prichard, W. W. In *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 452.

(56) Hermes, C.; Gilberg, E.; Koch, M. H. *J. Nucl. Instr. Methods* **1984**, *222*, 207−214.

(57) (a) Binsted, N.; Campbell, J. W.; Gurman, S. J.; Stephenson, P. C. *EXCURVE92*; SERC Daresbury Laboratory: Daresbury, U.K., 1991. (b) Gurman, S. J.; Binsted, N.; Ross, I. *J. Phys. C: Solid State Phys.* **1984**, *17*, 143−151. (c) Gurman, S. J.; Binsted, N.; Ross, I. *J. Phys. C: Solid State Phys.* **1986**, *19*, 1845−1861.

(58) Blackburn, N. J.; Strange, R. W.; Farooq, A.; Haka, M. S.; Karlin, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 4263−4272.

(59) Binsted, N.; Strange, R. W.; Hasnain, S. S. *Biochemistry* **1992**, *31*, 12117−12125.

spectrum, as expressed in a fit index, was minimized by the restrained refinement approach described earlier for imidazoles and polypyrroles.[59]

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Supporting Information Available: Fitting procedure for UV−vis data, overlays of fitted and experimental spectra of **8**, a figure showing the compostion of the fitted spectrum of **8**, and tabulated fitted spectral data for complexes **8**−**10**; structural parameters and examplified extreme structures of the Cu_2O_2 core used in the EXAFS analysis of **10**; and EPR spectrum of an intermediate species observed during thermal degradation of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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