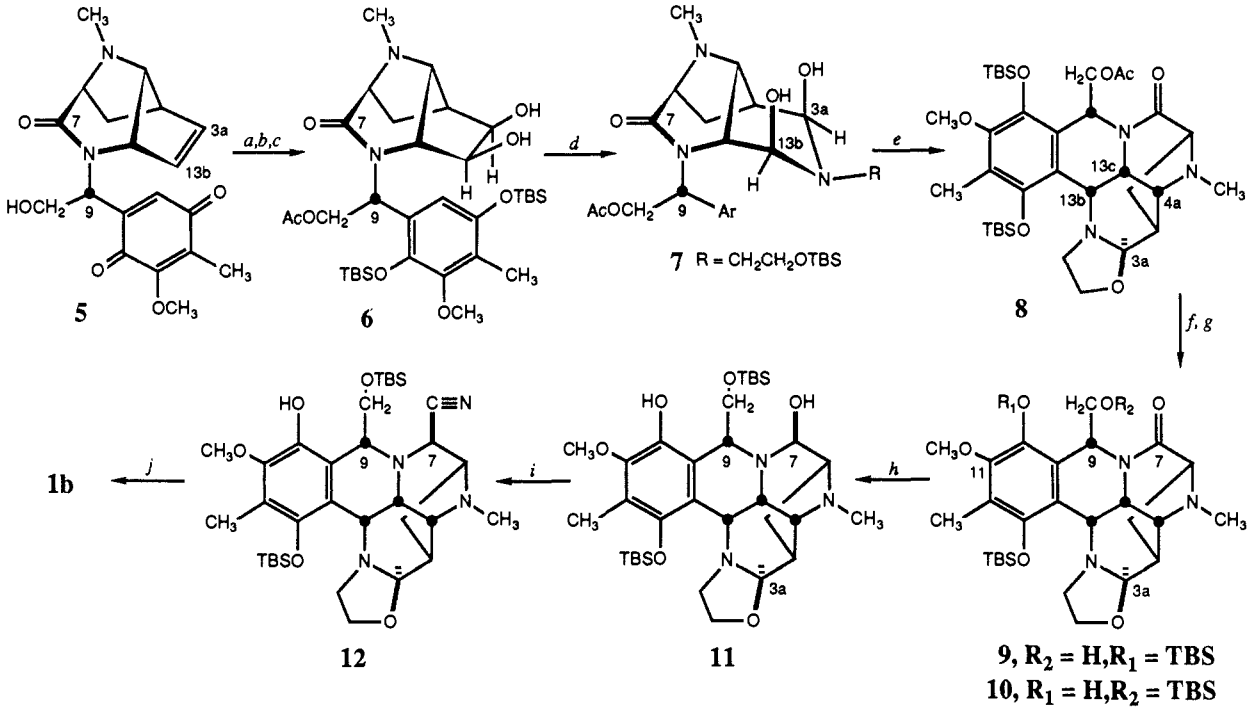
Scheme II



[a] Ac_2O, pyr, DMAP, CH_2Cl_2, 0 °C, 30 min. [b] Zn dust, TBSCl, DMAP, *i*-Pr_2NEt, CH_2Cl_2, 0.13 M concentration, 0–25 °C, 1 h. [c] OsO_4, *N*-methylmorpholine *N*-oxide, acetone, 25 °C, 30 min. [d] Et_4NIO_4, $TBSOCH_2CH_2NH_2$, CH_2Cl_2, 25 °C, 16–24 h. [e] Neat TFA, 25 °C, 24–30 h. [f] $LiBEt_3H$, THF, 25 °C, 3 h. [g] $KN(Me_3Si)_2$, THF, 0 °C, 45 min. [h] Li, NH_3-THF, −33 °C, 10 min, then EtOH over 45 min; NH_4Cl; aqueous $NaHCO_3$ wash. [i] NaCN, 0.2 M pH 8.0 Tris buffer, CH_3CN, 25 °C, 2 h. [j] $(HF)_x$·pyr(xs), CH_3CN, 50 °C, 3.0 h; then aqueous Na_2CO_3 to pH 10, O_2, 25 °C.

the forcing conditions required for reduction, the oxazolidine ring was unexpectedly labile toward reduction at C(3a).[12] Efforts to obtain a selective reduction of **8** via the derived thioamide were also unsuccessful. The use of dissolving metal reduction conditions provided the eventual solution to this problem. Although amide reduction under these conditions is precedented,[13] competitive reduction of the aromatic remains as a potential complication. Preliminary dissolving metal reduction studies carried out with lactam **9** indicated that aromatic ring reduction preempted C(7) carbonyl reduction, the principal product being that derived from loss of the C(11) methoxyl group. To suppress this process, silyl transfer from the C(10) oxygen moiety was effected. Treatment of **9** with potassium hexamethyldisilylamide (1.1 equiv, 45 min, 0 °C, 90%) resulted in the efficient silylatropic isomerization to phenol **10** which was anticipated to be more resistant to aromatic ring reduction. The successful reduction of **10** was achieved by treatment with excess lithium (100 equiv) in NH_3–THF at reflux followed by the slow addition of ethanol (120 equiv, 45–50 min). The unstable carbinolamine **11**, which could be isolated in 67% yield, was best directly transformed to the derived α-amino nitrile **12** under conditions similar to those employed in the conversion of **1a** to **1b** (1.2 equiv, NaCN, MeCN–H_2O, pH 8.0 Tris buffer, 30 min, 25 °C, 41% from **10**).[3] The final steps of the cyanocycline synthesis were accomplished by treatment of **12** with pyridine hydrofluoride (excess, 3 h, 50 °C) followed by careful adjustment of the reaction to pH 10 with aqueous sodium carbonate in the presence of molecular oxygen. These conditions afforded synthetic cyanocycline (**1b**) in 84% yield. The material thus obtained proved to be identical with a sample of (+)-cyanocycline (**1b**) via all spectroscopic and chromatographic comparisons.[14]

Acknowledgment. This research was supported by the National Institutes of Health (GM 33328-03). The NIH BRS Shared Instrumentation Grant Program 1 S10RR0148-01A1 is also acknowledged for providing NMR facilities. The structures in this manuscript were prepared by ChemDraw developed by S. Rubenstein of Harvard University.

Supplementary Material Available: Physical data and selected experimental procedures for **1b**, **5**, **6**, **8–12**, and **14–16** (16 pages). Ordering information is given on any current masthead page.

(12) Danishefsky has fully reduced a similar lactam in the synthesis of quinocarcinol methyl ester but has failed to achieve partial reduction in attempts with either DIBAL or diborane. Danishefsky, S.; Harrison, P. J.; Webb, R. R., II; O'Neill, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421–1423 and private communication.

(13) Dissolving metal reduction of amides is precedented; however, yields are generally very poor except in the cases of aromatic and *N*-aryl amides. (a) Birch, A. J.; Cymerman-Craig, J.; Slaytor, M. *Aust. J. Chem.* **1955**, *8*, 512–518. (b) Clemo, G. R.; King, T. J. *J. Chem. Soc.* **1948**, 1661–1666. (c) Benkeser, R. A.; Watanabe, H.; Mels, S. J.; Sabol, M. A. *J. Org. Chem.* **1970**, *35*, 1210–1211. (d) Kaiser, E. M. *Synthesis* **1972**, 391–415.

(14) The authors thank Professor S. Gould, Department of Chemistry, Oregon State University, for providing us with an authentic sample of (+)-**1b**.

Luminescence Behavior of Copper(I)–Imidazole Complexes. A Spectroscopic Model for the Carbonyl Derivative of Hemocyanin

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Many derivatives of hemocyanin have been investigated in the attempt to define the molecular structure of its binuclear-copper active site.[2] These include the deoxy, carbonyl, oxy, half-met (mixed valence), and met (oxidized) forms of the protein. Until

(1) Fellow of the Alfred P. Sloan Foundation, 1985–1987.

(2) (a) Solomon, E. I. In *Copper Proteins*; Spiro, T. G., Ed.; Wiley: New York, 1981; Chapter 2. (b) Solomon, E. I.; Penfield, K. W.; Wilcox, D. E. *Struct. Bonding (Berlin)* **1983**, *53*, 1–57.

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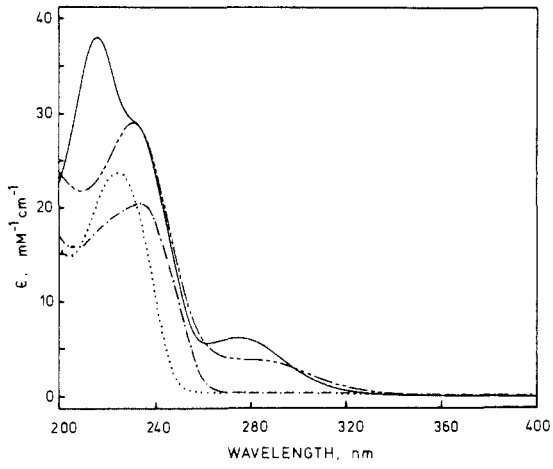
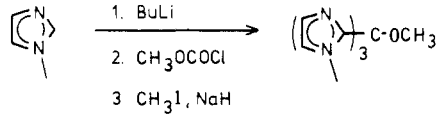


Figure 1. Absorption spectra in methanol for timm (•••), Cu(timm)BF_4 (– – –), Cu(timm)(CO)BF_4 (—), and Ag(timm)BF_4 (– –).

recently, the deoxy form of the protein has received the least attention because the Cu(I) ion lacks any notable spectroscopic features. However, a crystal structure of this derivative grown at low pH has now focused attention on the deoxy form by showing the copper atoms to be ligated by three histidyl imidazoles.[3]

The form of the protein most closely associated with the deoxy derivative is the carbonyl (HcCO)[4] which does show two unique spectroscopic properties relative to deoxy: an increase in absorption at 310 nm[5] and an emission signal centered at 550 nm.[6] Only 1 equiv of CO binds per active site, and the carbon monoxide binds to only one Cu(I) ion in a terminal manner.[7] We anticipated that by modeling the luminescence of HcCO, we might be able to probe the nature of the ligands at the active site.[8] We report here the synthesis of a new imidazole-containing tridentate ligand and its Ag(I) and Cu(I) derivatives, the reaction of the Cu(I) complex with CO, and the electronic and luminescent properties of these complexes.

The ligand tris[2-(1-methylimidazolyl)]methoxymethane (timm) was prepared from 1-methylimidazole and methyl chloroformate as shown in eq 1. The Ag(I) and Cu(I) complexes



(1)

were obtained by allowing the corresponding tetrafluoroborate salts to react with timm in methanol followed by crystallization from methanol.[9]

The electronic spectrum for Cu(timm)$^+$ is shown in Figure 1 and is dominated by two transitions centered at 232 and 285 nm. These are Cu(I) → imidazole charge-transfer transitions corresponding to $d\pi \rightarrow \pi^*$ and $d\sigma^* \rightarrow \pi^*$ transitions, respectively.[10]

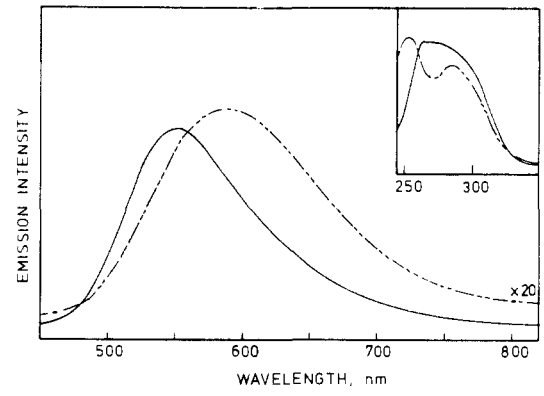


Figure 2. Corrected emission spectra for Cu(timm)BF_4, (– – –) and Cu(timm)(CO)BF_4 (—) in a methanol–ethanol glass at 77 K with excitation at 280 nm. The inset shows the excitation spectra for the same two species.

The absorption spectrum of Ag(timm)$^+$ supports these assignments since the MLCT bands have been shifted to higher energy.[11] Cu(timm)$^+$ reacts with CO in methanol as shown by the appearance of a strong CO stretch at 2080 cm^{-1} in the infrared region. Binding of CO shifts the MLCT transitions to higher energy with the position of the $d\pi \rightarrow \pi^*$ band being shifted to a greater extent (232 → 216 nm; ΔE = 3200 cm^{-1}) than that for the $d\sigma^* \rightarrow \pi^*$ transition (285 → 276 nm; ΔE = 1100 cm^{-1}). This is expected since binding of a π-acid-like CO should stabilize the $d\pi$ orbitals to a greater extent by back-bonding.[12]

The corrected emission and excitation spectra for Cu(timm)$^+$ and Cu(timm)CO$^+$ at 77 K are shown in Figure 2.[13] Both complexes show broad structureless bands which are characteristic of emission from MLCT states of Cu(I) complexes.[14] The emission from Cu(timm)CO$^+$ shifts 1300 cm^{-1} to higher energy relative to that for Cu(timm)$^+$ (550 vs. 592 nm). This corresponds to the energy difference seen for the corresponding transition in the absorption spectrum. Hence, we associate the emission from both complexes as originating from a Cu → imidazole charge-transfer state. Particularly noteworthy is that the luminescence at 550 nm observed for Cu(timm)CO$^+$ occurs at the same energy as that for HcCO.

These results complement the crystallographic results by showing that three imidazoles bound as ancillary ligands to the Cu(I)–CO center in HcCO can create conditions leading to the observed luminescence at 550 nm. Thus, there are now *two separate pieces of evidence* that the active site in *two different*

(3) Linzen, B.; Soeter, N. M.; Riggs, A. F.; Schneider, H.-J.; Schartau, W.; Moore, M. D.; Yokota, E.; Behrens, P. Q.; Nakashima, H.; Takagi, T.; Nemoto, T.; Vereijken, J. M.; Bak, H. J.; Beintema, J. J.; Volbeda, A.; Gaykema, W. P. J.; Hol. W. G. J. *Science (Washington, D.C.)* **1985**, *229*, 519–524.

(4) Abbreviations used in this paper: HcCO, carbonyl derivative of hemocyanin; timm, tris[2-(1-methylimidazolyl)]methoxymethane.

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(7) Fager, L. Y.; Alben, J. O. *Biochemistry* **1972**, *11*, 4786.

(8) Sorrell, T. N.; Borovik, A. S.; Shen, C.-C. *Inorg. Chem.* **1986**, *25*, 589–590.

(9) Analytical data: Cu(timm)BF_4 ($C_{14}H_{18}BCuF_4N_6O$), Calcd.: C, 38.51; H, 4.16; N, 19.24. Found: C, 38.55; H, 4.09; N, 19.29. Ag(timm)BF_4, Calcd: C, 34.95; H, 3.76; N, 17.46. Found: C, 34.91; H, 3.78; N, 17.29. We have recently completed the crystal structure of Cu(timm)BF_4 which shows it to be a dimer in the solid state. However, conductivity measurements *in methanol* under N_2 and CO indicate that the species is a 1:1 electrolyte, hence monomeric.

(10) We see similar transitions in related Cu(I) complexes with pyrazole ligands.

(11) We think that the peak at about 240 nm for the metal complexes is predominantly a ligand $\pi \rightarrow \pi^*$ transition on the basis of the appearance of the spectrum for the silver complex which apparently shows no MLCT bands in the region above 230 nm. This is expected because of the higher oxidation potential for Ag(I) relative to Cu(I) and mirrors results for several two-, three-, and four-coordinate pyrazole complexes that we have examined (unpublished results). Because the absorption band at 240 nm is clearly unsymmetrical, it is possible that at least one MLCT band occurs in this region. However, without additional evidence, we cannot assign the MLCT transitions for Ag(timm)$^+$ with any certainty.

(12) When the Cu(I) complex is treated with CO, then the MLCT band at 240 nm shifts to higher energy (216 nm), and the shoulder observed in the spectrum for that compound is the isolated imidazole $\pi \rightarrow \pi^*$ transition. It is known that the back-bonding ability of Cu(I) is relatively poor (cf.: Thompson, J. S.; Whitney, J. F. *Inorg. Chem.* **1984**, *23*, 2813–2819); however, the CO stretching frequency of Cu(timm)(CO)$^+$ relative to that for free carbon monoxide suggests that back-bonding does occur, at least to an extent that should affect the energies of the $d\pi$ orbitals. We are currently examining other π-acid ligands such as isonitriles and CN^- to see if similar behavior is observed. In the latter context, however, Zolla has reported that CN^- causes quenching of the luminescence in HcCO: Zolla, L.; Kuiper, H. A.; Finazzi Agro, A.; Brunori, M. *J. Inorg. Biochem.* **1984**, *22*, 143–153.

(13) Corrected emission and excitation spectra were recorded on an SLM Smart 8000 spectrofluorimeter at 77 K in a methanol–ethanol glass. For the emission spectra, excitation was carried out at 280 nm. Excitation spectra were corrected ratiometrically with Rhodamine 6G as a standard.

(14) McMillian, D. R.; Kirchoff, J. R.; Goodwin, K. V. *Coord. Chem. Rev.* **1985**, *64*, 83–92.

derivatives of hemocyanin has copper(I) ions ligated by three imidazole ligands.[15] While the role of an endogenous ligand in the binding of molecular oxygen to hemocyanin is still uncertain, it appears certain that the binding of CO requires no other ligands in addition to imidazole to reproduce the spectroscopic properties for HcCO. We are currently examining the reaction of Cu(timm)$^+$ with other biologically important small molecules, including O_2.

Acknowledgment is made to the National Science Foundation and to the University of North Carolina for support of this research.

(15) It should be noted that Zolla has reported that the carbonyl derivative of the half-apo form of hemocyanin [one Cu(I)] does *not* show any luminescence, even though the remaining single copper ion should still be bound by three imidazoles ligands and CO: Zolla, L.; Calabrese, L.; Brunori, M. *Biochim. Biophys. Acta* **1984**, *788*, 206–213. It may be that the absence of the second copper results in a conformational change that allows the active site to be exposed to solvent, quenching the luminescence. The monomeric imidazole complexes reported here only show luminescence *when isolated in a glass*; in solution, the emission is quenched. Solvent quenching of emission has been observed for a number of Cu(I) complexes when the solvent can coordinate to the metal (see ref 14).

2,3-Bis(trimethylsilyl)- and 2,3,8,9-Tetrakis(trimethylsilyl)[4]phenylene

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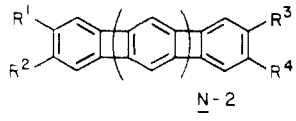
The linear phenylenes **1** are of great theoretical importance as



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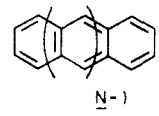

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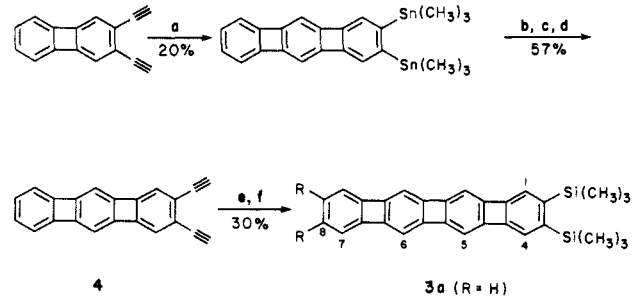
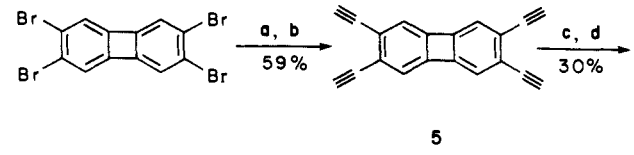
novel synthetic oligomers on which to probe the aromaticity criterion. These substances are unusual because the aromatic benzene ring is juxtaposed to the antiaromatic cyclobutadiene nucleus in an alternating manner, giving rise to new electronic, perhaps conducting, properties.[1] In contrast to the acenes **2**,[2] the series is alternating between a $4n$ (N even) and $4n + 2$ (N odd) π-electron count. We recently described the synthesis of [3]phenylene **1** ($N = 3$, $R^1 = R^2 = R^3 = R^4 = H$),[1] and the unusual reactivity and spectral properties of this system raised several questions: (a) Is the next higher benzocyclobutadienolog, [4]phenylene, capable of existence? (b) If it is, will it be paratropic? (c) How will such a polycycle accommodate unfavorable cyclobutadienoid[3] character? We now report the synthesis of the [4]phenylene nucleus **3**,[4] crucial in order to understand the basic electronic features associated with this novel class of compounds, and as another step to the higher members of the series. The approach to **3a** also incorporates a novel cobalt-catalyzed alkyne cyclization[5] involving bis(trimethylstannyl)acetylene.

Scheme I[a]



[a] (a) $(CH_3)_3SnC{\equiv}CSn(CH_3)_3$, $CpCo(CO)_2$, xylenes, Δ, $h\nu$, 3.5 h; (b) I_2, $CHCl_3$, 1 h, 80%; (c) $(CH_3)_3SiC{\equiv}CH$, $PdCl_2(PPh_3)_2$, Et_3N, 23 °C, 20 h, 75%; (d) KOH, CH_3OH, 1 h, 95%; (e) $(CH_3)_3SiC{\equiv}CSi(CH_3)_3$, $CpCo(CO)_2$, THF, Δ, $h\nu$, 9 h, 30%; (f) CO (1 atm), 90 °C, 16 h, 100%.

Scheme II[a]



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3b [R = $(CH_3)_3Si$]

[a] (a) $(CH_3)_3SiC{\equiv}CH$, $PdCl_2(PPh_3)_2$, piperidine, 24 h, 90–100 °C, 60%; (b) KOH, ether, CH_3OH, 2 h, 98%; (c) $(CH_3)_3SiC{\equiv}CSi(CH_3)_3$, $CpCo(CO)_2$, THF, Δ, $h\nu$, 13 h, 30%; (d) CO (1 atm), 120 °C, 72 h, 99%.

The original strategy involved an extension of our cyclobutabenzoannelation scheme[1] employing 2,3-bis(trimethylsilyl)[3]phenylene **1** [$N = 3$, $R^1 = R^2 = Si(CH_3)_3$, $R^3 = R^4 = H$] as a starting point. However, iododesilylation of this system proved impossible, electrophilic attack occurring at the reactive central ring.[6] Therefore, the synthetic plan was revised to (a) explore the utility of the trimethylstannyl group as a masked halogen[7] in cobalt-catalyzed [2 + 2 + 2] cycloadditions, starting from 2,3-diethynylbiphenylene[1] (Scheme I) or (b) to employ the new tetrayne **5**, thought to be accessible from 2,3,6,7-tetrabromobiphenylene[8] (Scheme II).[9] Gratifyingly, both strategies were successful, Scheme I in particular demonstrating the feasibility of trimethylstannyl alkyne cyclizations and the stability of the [3]phenylene nucleus in the presence of Pd^{2+}. Minor byproducts in the cyclization of **4** were **6** (one stereoisomer) and in that of **5** they were **7** (one stereoisomer) and **8** (stereochemistry tentative).

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(2) Clar, E. *Polycyclic* Hydrocarbons; Academic Press: New York, 1964; Vol. 1.
(3) Vollhardt, K. P. C. *Top. Curr. Chem.* **1975**, *59*, 113.
(4) An attempt to synthesize [4]phenylene by dimerization of 2,3-didehydrobiphenylene failed: Losey, E. N.; LeGoff, E. *J. Org. Chem.* **1972**, *37*, 3812.
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(9) All new compounds gave satisfactory analytical and/or spectral data. For selected data, **3a**–CpCo: ^1H NMR (C_6D_6) δ 0.32 (s, 18 H), 4.54 (s, 5 H), 6.57 (s, 2 H), 6.72 (s, 2 H), 6.75 (m, 4 H), 7.44 (s, 2 H). **3a**: HRMS m/e (relative intensity) 444.1735 (M^+, 100), calcd for $C_{30}H_{28}Si_2$ 444.1722; ^1H NMR (C_6D_6) δ 0.31 (s, 18 H), 5.73 (s, 2 H, H_6), 5.89 (s, 2 H, H_5), 6.17 (dd, $J = 4.97$, 2.84 Hz, 2 H, H_7), 6.44 (dd, $J = 4.97$, 2.84 Hz, 2 H, H_8), 6.81 (s, 2 H, H_1); ^{13}C NMR (C_6D_6) δ 2.23, 109.31, 109.50, 115.04, 120.35, 128.30, 147.53, 150.14, 150.84, 151.16, 151.21, 152.10, 153.46; UV (THF) λ_{max} (log ϵ) 247 (3.60), 253 (3.80), 259 (4.00), 300 (4.20), 316 (4.13), 364 (3.20), 377 (3.20), 458 (3.50), 488 nm (3.64). **3b**–CpCo: ^1H NMR (C_6D_6) δ 0.32 (s, 36 H), 4.59 (s, 5 H) 6.72 (s, 4 H), 7.45 (s, 4 H); ^{13}C NMR (C_6D_6) δ 2.23, 74.05, 80.09, 114.90, 125.21, 143.24, 147.99, 148.96. **3b**: MS, m/e (relative intensity) 588 (M^+, 100), 573 (2.5), 516 (9.8), 294 (21), 207 (75); ^1H NMR (C_6D_6) δ 0.31 (s, 36 H), 5.89 (s, 4 H, H_5), 6.81 (s, 4 H, H_1); ^{13}C NMR (C_6D_6) δ 2.20, 109.6, 120.4, 147.5, 150.1, 151.3, 153.5. **8**: MS, m/e (relative intensity) 1006 (M^+, 0.4), 836 (8.8), 712 (7.1), 369 (15), 57 (100); ^1H NMR (C_6D_6) δ 0.29 (s, 18 H), 0.34 (s, 18 H), 0.40 (s, 18 H), 4.37 (s, 2 H), 4.69 (s, 10 H), 6.25 (s, 2 H), 7.10 (s, 2 H), 7.57 (s, 2 H).
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