ORGANIC LETTERS

2009
Vol. 11, No. 13
2724−2727

Unprecedented Degradation of Nickel(II) 2,3,12,13-Tetrabromo-5,10,15,20-tetraarylporphyrins by the Anion of *E*-Benzaldoxime: A Novel Approach to Nickel(II) Chlorophins and Bacteriophins

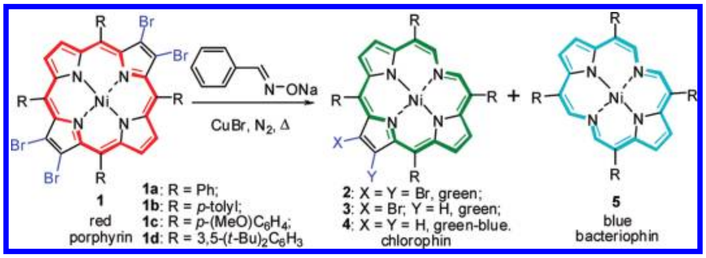
Ke-Lai Li,[†] Can-Cheng Guo,[*,†] and Qing-Yun Chen[*,†,‡]

College of Chemistry and Chemical Engineering, Hunan University,
Changsha 410082, China, and Key Laboratory of Organofluorine Chemistry,
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
345 Lingling Road, Shanghai 200032, China

ccguo@hnu.cn; chenqy@mail.sioc.ac.cn

Received February 10, 2009

ABSTRACT



A novel and convenient approach to chlorophins and bacteriophins has been developed through a degradation of nickel(II) 2,3,12,13-tetrabromo-5,10,15,20-tetraarylporphyrins by the anion of *E*-benzaldoxime. The UV−vis spectra of these chlorophins and bacteriophins are similar to those of metalated chlorin and bacteriochlorin systems but with more intense and bathochromically shifted Q-bands.

Porphyrins and related compounds, especially those possessing intense near-infrared absorption, have received great attention in the last few decades for their potential applications in electro-optical materials and photodynamic therapy (PDT) treatment of cancer.[1] Among them, chlorophins and bacteriophins (porphyrins in which one or two sets of β,β'-carbon atoms have been removed) are of particular interest due to their chlorin and bacteriochlorin-like photophysical properties and their close relationship to various structural models of the porphyrin π-system.[2] While secochlorins (porphyrins in which a β,β'-bond is cleaved) can be prepared by rearrangement of (octadehydrocorrinato)nickel(II) salts[3] or oxidative diol cleavage of 2,3-dihydroxy-2,3-chlorins[4] and tetraphenylchlorophin has also been successfully synthesized by Dolphin et al. via the stepwise decarbonylation of a nickel(II) secochlorin dialdehyde,[2e] reports on bacteriophins are rare. To the best of our knowledge, so far, they can only be obtained by total synthesis. However, this method developed by Flitsch and co-workers[2c,d] was extremely

---

[†] Hunan University.

[‡] Shanghai Institute of Organic Chemistry.

(1) (a) *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000−2003; Vols. 1−20. (b) Jasat, A.; Dolphin, D. *Chem. Rev.* **1997**, *97*, 2267.

(2) (a) Flitsch, W. *Pure Appl. Chem.* **1986**, *58*, 153. (b) Flitsch, W. *Adv. Heterocycl. Chem.* **1988**, *43*, 73. (c) Flitsch, W.; Schulz, D.; Kneip, H.-G. *Liebigs Ann. Chem.* **1985**, 1004. (d) Bohusch, M.; Flitsch, W.; Kneip, H.-G. *Liebigs Ann. Chem.* **1991**, 67. (e) Brückner, C.; Sternberg, E. D.; MacAlpine, J. K.; Rettig, S. J.; Dolphin, D. *J. Am. Chem. Soc.* **1999**, *121*, 2609. (f) Brückner, C.; Hyland, M. A.; Sternberg, E. D.; MacAlpine, J. K.; Rettig, S. J.; Patrick, B. O.; Dolphin, D. *Inorg. Chim. Acta* **2005**, *358*, 2943.

(3) Chang, C. K.; Wu, W.; Chern, S.-S.; Peng, S.-M. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 70.

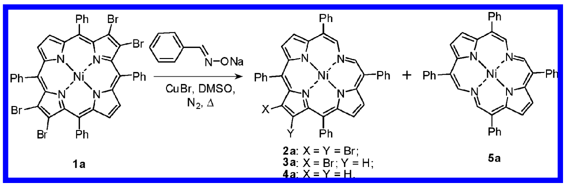
10.1021/ol901052w CCC: $40.75

difficult and very low yielding, and even then no full structural characterization was accomplished. In this communication, we wish to report a novel approach to chlorophins and bacteriophins through a degradation of nickel(II) 2,3,12,13-tetrabromo-5,10,15,20-tetraarylporphyrins by the anion of *E*-benzaldoxime.

During our ongoing efforts in the synthesis and application of perfluoroalkylated porphyrins,[5] a novel synthesis of 20 π-electron nonaromatic isophlorin was achieved by reduction of copper(II) β-tetrakis(trifluoromethyl)-*meso*-tetraphenylporphyrin.[5f] Inspired by this study, we envisioned that a porphyrin system bearing four strongly electron-donating groups instead of four strongly electron-withdrawing trifluoromethyl ones might undergo a two-electron oxidation to afford a 16 π-electron nonaromatic macrocycle.[6]

Initially, we attempted to prepare a porphyrin bearing four hydroxyl groups (which can be converted into alkoxide anions or ether groups) via nucleophilic substitution of bromoporphyrin with the anion of *E*-benzaldoxime by using the method developed by Crossley et al.[7] Thus, **1a** was treated with the sodium salt of *E*-benzaldoxime in DMSO at 60 °C for 3 h. Surprisingly, an unexpected dibromochlorophin **2a** was obtained in 3% yield with no formation of the desired product. When a catalyst CuBr[8] was added, and the reaction temperature was elevated to 100 °C, **2a** was formed in 30% yield (Table 1). It should be noted that the copper(II)-catalyzed reaction is sensitive to temperature. If the reaction temperature is slightly higher than 100 °C, debrominated products of **2a**, namely, **3a** and **4a**, are also produced. The higher the temperature and the longer the reaction time, the more debrominated products there are. Further elevating the reaction temperature to above 120 °C led to the formation of bacteriophin **5a**. Interestingly, the best yield of **5a** is achieved under the conditions that the reaction temperature fluctuates regularly between 80 and 160 °C (Table 1). All of the macrocycles, **2a**, **3a**, **4a**, and **5a**, are much more soluble than nickel(II) tetraphenylporphyrin (NiTPP) in common organic solvents, such as CH_2Cl_2, acetone, and petroleum ether, etc., and form green, green, green−blue, and blue-colored solution in those solvents, respectively.

Table 1. Reaction of **1a** with the Sodium Salt of *E*-Benzaldoxime in the Presence of CuBr[a]



			yields[b] (%)			
entry	temp (°C)	time (h)	**2a**	**3a**	**4a**	**5a**
1[c]	100	4	30	–	–	–
2	110	2	18	13	–	–
3	120	2	7	14	6	3
4	140	1	15	11	–[d]	–[d]
5	160	1	–	8	12	3
6	180	0.5	33	8	–[d]	3
7	180	1	–	6	22	3
8	200	1	–	3	19	3
9	80−160	2	8	7	3	16
10[e]	80−160	2	–	5	3	26

[a] Reaction conditions: **1a** (49 mg, 0.05 mmol), *E*-benzaldoxime (30 equiv), NaH (20 equiv), CuBr (20 equiv), in DMSO (10 mL) under nitrogen. [b] Isolated yields. [c] 12% starting material was recovered. [d] Trace product. [e] CuBr was dried by heating at 200 °C under vacuum for 12 h before use.

The structures of these macrocycles are fully characterized by their spectroscopic and analytical data. Among them, **4a** is a known compound, whose spectral data are identical to those reported by Dolphin et al.[2e] The stepwise loss of a bromine atom from **2a** to **3a** and then to **4a** can be clearly seen from their mass spectra (MALDI$^+$) (**2a**: $m/z = 802.0$; **3a**: $m/z = 724.1$; **4a**: $m/z = 646.2$) and also reflects in the hypsochromic shift of their Soret band from **2a** (λ_{max} [relative intensity] 436 [1.00]) to **3a** (λ_{max} [relative intensity] 430 [1.00]) and to **4a** (λ_{max} [relative intensity] 423 [1.00]). The UV−vis spectra of the three compounds all indicate the presence of metalated chlorin-like systems (λ_{max} [relative intensity] for **2a**: 436 [1.00], 619 [0.13]; for **3a**: 430 [1.00], 613 [0.14]; for **4a**: 423 [1.00], 611 [0.16]), showing more intense and bathochromically shifted Q-bands compared with NiTPP (λ_{max} [relative intensity] 416 [1.00], 492 [0.01], 521 [0.05]) (Figure 1). The ^{1}H NMR spectra of **2a** and **3a** also support their structural alteration from **4a** by replacement of one or two hydrogen atoms with one or two bromine

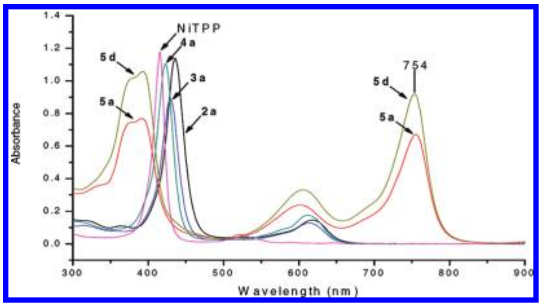


Figure 1. UV−vis spectra of **2a**, **3a**, **4a**, **5a**, **5d**, and NiTPP in CH_2Cl_2.

---

(4) (a) McCarthy, J. R.; Hyland, M. A.; Brückner, C. *Org. Biomol. Chem.* **2004**, *2*, 1484. (b) McCarthy, J. R.; Melfi, P. J.; Capetta, S. H.; Brückner, C. *Tetrahedron* **2003**, *59*, 9137. (c) McCarthy, J. R.; Jenkins, H. A.; Brückner, C. *Org. Lett.* **2003**, *5*, 19. (d) Brückner, C.; Rettig, S.; Dolphin, D. *J. Org. Chem.* **1998**, *63*, 2094. (e) Adams, K. R.; Bonnett, R.; Burke, P. J.; Salgado, A.; Vallés, M. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1769. (f) Adams, K. R.; Bonnett, R.; Burke, P. J.; Salgado, A.; Vallés, M. A. *J. Chem. Soc., Chem. Commun.* **1993**, 1860.

(5) (a) Jin, L. M.; Zeng, Z.; Guo, C. C.; Chen, Q. Y. *J. Org. Chem.* **2003**, *68*, 3912. (b) Liu, C.; Chen, Q. Y. *Eur. J. Org. Chem.* **2005**, 3680. (c) Chen, L.; Jin, L. M.; Guo, C. C.; Chen, Q. Y. *Synlett* **2005**, 963. (d) Jin, L. M.; Yin, J. J.; Chen, L.; Zhou, J. M.; Xiao, J. C.; Guo, C. C.; Chen, Q. Y. *Chem.−Eur. J.* **2006**, *12*, 7935. (e) Liu, C.; Shen, D. M.; Zeng, Z.; Guo, C. C.; Chen, Q. Y. *J. Org. Chem.* **2006**, *71*, 9772. (f) Liu, C.; Shen, D. M.; Chen, Q. Y. *J. Am. Chem. Soc.* **2007**, *129*, 5814.

(6) Yamamoto, Y.; Yamamoto, A.; Furuta, S.; Horie, M.; Kodama, M.; Sato, W.; Akiba, K.; Tsuzuki, S.; Uchimaru, T.; Hashizume, D.; Iwasaki, F. *J. Am. Chem. Soc.* **2005**, *127*, 14540.

atoms. The expected overall symmetry of the dibromochlorophin **2a** (2-fold symmetry) and monobromochlorophin **3a** (no symmetry) can be seen from the coupling patterns of the β-protons locating between 8.0 ppm and 8.5 ppm (**2a**: two doublets $J = 4.5$ Hz, each integrating for 2H; **3a**: four doublets $J = 4.5$ Hz and one singlet, each integrating for 1H). One singlet with an integration corresponding to 2H at 9.53 ppm for **2a** and 9.74 ppm for **3a** is considered in accord with the one at 9.83 ppm (lit.,[2e] 9.80 ppm) for **4a**, which are attributed to the α-protons on the broken pyrrolic unit. The elemental analysis of **2a** and **3a** also corroborates the proposed composition.

A single-crystal X-ray diffraction study was performed on **2a**[9] and **3a**.[10] This provided the ultimate proof of the proposed structure (Figure 2) and allowed us to examine the influence of the bromine atom on the conformation of the chlorophin core. In a manner similar to that of **4a**,[2e] the plane of the metallochlorophin **2a** and **3a**, while retaining a square planar coordination sphere around the central metal, is severely twisted along a N−Ni−N axis resulting in a ruffled[11] conformation of the chlorophin core (rms of the $C_{18}N_4Ni$ mean plane for **2a**, 0.463 Å; for **3a**, 0.443 Å). Compared with **4a** (rms of the $C_{18}N_4Ni$ mean plane, 0.368 Å),[2e] the degree of ruffling of **3a** and **2a** increase with the gradual introduction of the bromo substituent. In the meanwhile, the average Ni−N bond distance is lengthened, from 1.903 Å measured in **2a** to 1.904 Å in **3a** and 1.912 Å reported in **4a**.[2e] The pronounced influence of the bromine atoms on the degree of the ruffling observed here is comparable to those of the formyl substituents in secochlorin aldehydes.[2f] However, the longest bond length found in **2a** and **3a** is not the one between the metal and the nitrogen of the broken pyrrolic unit (Ni−N3) as observed in **4a**, but the one between the metal and the nitrogen of the dibromo pyrrole ring (Ni−N1) for **2a** and the one between the metal and the nitrogen of the pyrrole ring which is furthest away from the bromine atom (Ni−N2) for **3a**. We attribute this to be induced by the presence and position of the bromine atoms.

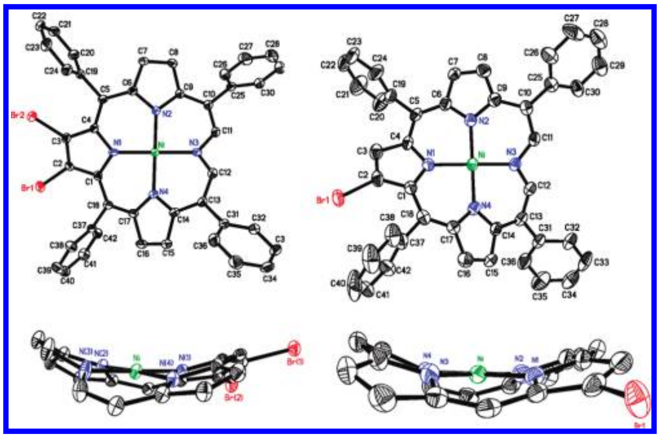
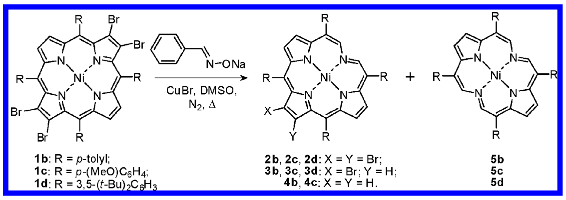


Figure 2. Top view (solvated molecules and hydrogen atoms are omitted for clarity) and side view (solvated molecules, hydrogen atoms, and the *meso*-phenyl substituents have been omitted for clarity) of the X-ray crystal structures of **2a** and **3a**. Thermal ellipsoids are shown at the 70% probability level for **3a**.

The ^1H NMR spectrum of **5a** indicates that the molecule have a high degree of symmetry. There are only two singlets representing the nonphenylic protons, one at 8.20 ppm and another at 9.55 ppm, the integrals of which both correspond to four protons. While the signal at 8.20 ppm is comparable to those measured for β-protons of the other 18 π-electron porphyrinic systems, the one at 9.55 ppm is in accordance with the α-protons measured in chlorophins (for instance, **2a**, **3a**, and **4a**). Analysis of the mass spectrum of **5a** ($m/z = 622.2$) reveals that two carbon atoms are also lost compared with **4a**. The UV−vis spectrum of **5a** (λ_{max} [relative intensity] 392 [1.00], 600 [0.31], 755 [0.87]) is similar to those of metalated bacteriochlorin-like systems but with more intense and bathochromically shifted Q-bands (Figure 1). The elemental analysis of **5a** also corroborates with the assigned structure.

To determine the scope of this novel reaction, some other easily available nickel(II) 2,3,12,13-tetrabromo-5,10,15,20-tetraarylporphyrins were investigated (Scheme 1). Under similar conditions, **1b** and **1c** could also be subjected to smooth degradation to provide the corresponding chlorophins and bacteriophins. The reaction of **1d** was carried out in a sealed tube using DMSO/THF (1:1, v/v) as solvent due to its poor solubility in DMSO. **2d** and **3d** can be obtained from the reaction catalyzed by CuBr, but **5d** was yielded in the absence of CuBr. The various spectra of **5d** are analogous to those of **5a** (Figure 1). Fortunately, single crystals of **5d** were obtained from its acetone/CH_2Cl_2/pyridine (100:10:1,

Scheme 1. Degradation of Other Nickel(II) Tetrabromoporphyrins[a]



[a] For detailed reaction conditions and yields, see Supporting Information.

---

(7) (a) Crossley, M. J.; King, L. G.; Pyke, S. M. *Tetrahedron* **1987**, *43*, 4569. (b) Crossley, M. J.; Burn, P. L.; Langford, S. J.; Pyke, S. M.; Stark, A. G. *J. Chem. Soc., Chem. Commun.* **1991**, 1567.

(8) (a) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. (C)* **1969**, 312. (b) Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34*, 1007.

(9) $C_{42}H_{26}Br_2N_4Ni$ (**2a**) crystallized by diffusion of MeOH into a CH_2Cl_2 solution. Crystal data. $M = 805.20$, triclinic, space group P-1, $a = 9.9480(12)$, $b = 12.8818(15)$, $c = 14.3014(17)$ Å, $\alpha = 70.874(2)$, $\beta = 73.322(2)$, $\gamma = 80.864(2)°$, $V = 1654.4(3)$ Å^3, $T = 293(2)$ K, $Z = 2$, $D_c = 1.616$ g cm^{-3}, μ(Mo Kα) = 3.040 mm^{-1}, 9774 reflections measured, 7009 unique which were used in all calculations. R_1 (all data) = 0.0774. $R_1 = 0.0620$. CCDC 709027.

(10) $C_{42}H_{27}BrN_4Ni{\cdot}0.5C_4H_{10}O$ (**3a**) crystallized by diffusion of MeOH into a CH_2Cl_2 solution. Crystal data. $M = 763.36$, monoclinic, space group $P2(1)/n$, $a = 15.7750(16)$, $b = 12.4675(13)$, $c = 17.5806(18)$ Å, $\alpha = 90.00$, $\beta = 93.757(2)$, $\gamma = 90.00°$, $V = 3450.2(6)$ Å^3, $T = 293(2)$ K, $Z = 4$, $D_c = 1.470$ g/cm^3, μ(Mo Kα) = 1.761 mm^{-1}, 17857 reflections measured, 6405 unique which were used in all calculations. R_1 (all data) = 0.1233. $R_1 = 0.0872$. CCDC 709028 .

v:v:v) solution into which petroleum ether was allowed to slowly diffuse.

A single-crystal X-ray diffraction study of **5d**[12,13] (Figure 3) shows that two opposite pyrrolic units of the parent porphyrin have been degraded to aldimine linkage without any other change in the connectivity of the 18 π aromatic macrocycle, which makes it possible to take some comparative studies between porphyrin and bacteriophin, both experimentally and theoretically, such as their resonance energies.[14] The C−C and C−N bond lengths found in the macrocycle of **5d** are within expectation for a fully conjugated chromophore. Examination of the conformation of **5d** reveals that it deviates to an astonishing degree from planarity. In a manner similar to that of **4a**,[2e] it takes up a ruffled[11] conformation (rms of the $C_{16}N_4Ni$ mean plane, 0.502 Å) but much more pronounced than **4a** (rms of the $C_{18}N_4Ni$ mean plane, 0.368 Å).[2e] The median Ni−N distances have been used to quantify the distortion of nickel(II) porphyrins, and it is commonly considered that the more planar the conformation, the larger the Ni−N bond distances.[2f,15] However, on the contrary, the average Ni−N bond distance found in the strongly ruffled **5d** is 1.933 Å, which is much longer than that in **4a**[2e] (1.912 Å) but quite near that found in the slightly ruffled NiTPP (average Ni−N bond distance, 1.931 Å; rms of the $C_{20}N_4Ni$ mean plane, 0.263 Å).[16] This might be attributed to the extremely increased flexibility of the bacteriphin core compared with that of chlorophin and porphyrin.

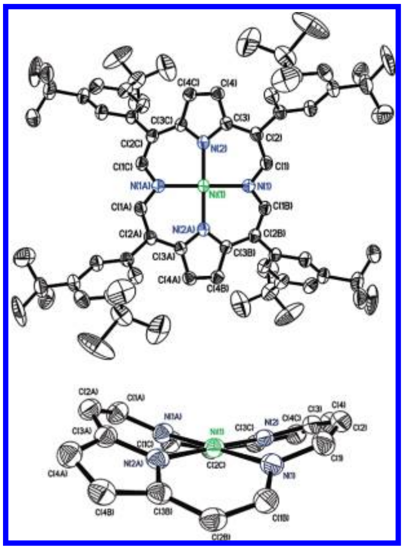


Figure 3. Top view (solvated molecules and hydrogen atoms are omitted for clarity) and side view (solvated molecules, hydrogen atoms, and the *meso*-aryl substituents have been omitted for clarity) of the X-ray crystal structure of **5d**. Thermal ellipsoids are shown at the 50% probability level.

The pursuit for long-wavelength absorbing chromophores has led to the synthesis of porphyrin isomers, expanded porphyrins, and porphyrins containing moieties other than pyrroles as building blocks.[17] The synthesis of bacteriophins with unique spectroscopic properties by degradation of two β,β'-bonds of the parent porphyrins demonstrated here provide an alternative promising possibility toward that aim. We propose that the extremely intense and near-infrared absorption of these bacteriophins results from their lower symmetry and greater deformation of the macrocycle from planarity compared with porphyrins, in a way similar to that of bacteriochlorins.[18] In contrast to the total synthesis of the parent bacteriophin (i.e., the non-*meso*-aryl substituted macrocycle) and isobacteriophin starting from substituted pyrroles over several steps with the best yield, no more than 5%, our facile preparation of bacteriophins is straightforward and comparatively high yielding.

In conclusion, we have shown a novel and convenient approach to chlorophins and bacteriophins starting from the easily available tetrabromoporphyrins. Although the reaction mechanism is not yet clear, degradation of two pyrrolic units and the method using the anion of *E*-benzaldoxime are novel to the field of porphyrin chemistry. Furthermore, the intense near-infrared absorption of bacteriophins shows promise as photosensitizers in PDT and as building blocks in electrooptical materials. Further studies on the reaction mechanism, the extension of this reaction to other metal complexes, and the transformation of the products are now in progress.

Acknowledgment. The authors are grateful to Professor Jia-Bi Chen (Shanghai Institute of Organic Chemistry), Associate Professor Jie Sun (Shanghai Institute of Organic Chemistry), Dr. Zhen-Xia Chen (Fudan University), and Professor Min-Qin Chen (Fudan University) for the resolution of the X-ray crystal structures. We also thank financial support from the National Natural Science Foundation of China (Nos. 20272076, 20772146 and D20032010).

Supporting Information Available: Experimental details, characterization data for all new compounds, and crystallographic data in CIF format for **2a**, **3a**, and **5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901052W

---

(11) (a) Shelnutt, J. A.; Song, X. Z.; Ma, J. G.; Jia, S. L.; Jantzen, W.; Medforth, C. J. *Chem. Soc. Rev.* **1998**, *27*, 31. (b) Ravikanth, M.; Chandrashekar, T. K. *Struct. Bonding (Berlin)* **1995**, *82*, 107. (c) Scheidt, W. R.; Lee, Y. L. *Struct. Bonding (Berlin)* **1987**, *64*, 1.

(12) Crystal data of $C_{72}H_{92}N_4Ni{\cdot}C_5H_5N$ (**5d**). $M = 1151.31$, orthorhombic, space group *Ccca*, $a = 27.770(16)$, $b = 35.78(2)$, $c = 8.445(5)$ Å, $\alpha = 90.00$, $\beta = 90.00$, $\gamma = 90.00°$, $V = 8391(8)$ Å^3, $T = 293(2)$ K, $Z = 4$, $D_c = 0.911$ g/cm^3, μ(Mo Kα) = 0.268 mm^{-1}, 16471 reflections measured, 3692 unique which were used in all calculations. R_1 (all data) = 0.1248. $R_1 = 0.0997$. CCDC 709029.

(13) Although the X-ray crystallographic analysis of **5d** was somewhat less precise due to static and possible dynamic disorders of the *tert*-butyl group and the coordinated solvents, the data of the other atoms are good enough for analysis.

(14) (a) George, P. *Chem. Rev.* **1975**, *75*, 85. (b) Campbell, C. J.; Rusling, J. F.; Brückner, C. *J. Am. Chem. Soc.* **2000**, *122*, 6679.

(15) Barkigia, K. M.; Renner, M. W.; Furenlid, L. R.; Medforth, C. J.; Smith, K. M.; Fajer, J. *J. Am. Chem. Soc.* **1993**, *115*, 3627.

(16) Fleischer, E. B.; Miller, C. K.; Webb, L. E. *J. Am. Chem. Soc.* **1964**, *86*, 2342.

(17) *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vols. 2, pp 1−199 and references therein.

(18) Gouterman, M. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 3, pp 1−156.