disorder and may be used to estimate microcrystallite size, L_a.[17,18] The 1360-cm^{-1} mode has been attributed to disorder induced breakdown of Raman selection rules near graphitic edges and perhaps the presence of a vibration with A_{1g} symmetry.[18] The improved resolution of the disorder and E_{2g} modes on further heat treatment of **1c** at 400 and 600 °C indicates an increase in the crystallite dimensions (L_a and L_c) by an annealing process. The Raman spectra of the parent system (**1c**) thermally treated at 600 °C is remarkably similar to that of GC. *Clearly, an sp^2-hybridized carbon lattice is formed at 200–600 °C, as opposed to 1000–3000 °C when conventional GC is prepared from materials such as polyacrylonitrile.*

The density, elastic modulus, shear modulus, and Poisson's ratio of the solid prepared from poly(phenylenediacetylene) (**1c**) are strikingly similar to GC (Table I).[19] It is important to note that the Young's moduli of **2c**–**4c** (~12 000 MN/m^2) are less than half that found for **1c** (28 500 MN/m^2). The incorporation of dopants dramatically affected the elasticity of the organic solid.

Thermal treatment of **1c**–**4c** at 200 °C for 6 h gave only electrically insulating materials. However, the electrical conductivity of the organic solids increased with final heat treatment temperature (Table I).[20] With the exception of the silicon-doped solids, further heat treatment of these same solids at 400 °C for 6 h resulted in conductivities of approximately 10^{-8} S/cm. Further heat treatment at 600 °C for 6 h gave **1c**–**3c** with conductivities of approximately 1 S/cm. *Note that this conductivity is achieved even with **2c** which contains >30 wt % fluorine.*

These DGC materials function as practical electrodes. The voltammetry of the ferri/ferrocyanide [$Fe(CN_6)^{3-/4-}$] couple on GC prepared at 2000 °C (ΔE_p = 74 mV, $k°$ = 0.017 cm/s) and that of **1c** prepared at 600 °C (ΔE_p = 91 mV, $k°$ = 0.0075 cm/s) are remarkably similar.[22] With our approach, we have synthesized a homogeneously doped material which has catalytic properties similar to those of superficially modified electrodes.[23] Figure 2 shows the current vs potential curves for the reduction of proton to dihydrogen on glassy carbon (**1c**), platinum, and two platinum DGC (0.25 and 1 atom %) electrodes. These platinum DGC electrodes also exhibit excellent stability. *We have found no evidence for degradation of the electrode or loss of catalytic activity over several thousand reduction cycles.*

The elastic modulus, electrical conductivity, and Raman spectroscopy of these materials provide convincing evidence for a low-temperature synthesis of doped glassy carbon. This method of synthesis provides a new vehicle for the homogeneous immobilization of precious catalyst microparticles in a stable, conductive environment. We have also imparted catalytic electrochemical behavior to glassy carbon with our methodology. We are continuing to explore the preparation and electrochemical activity of these materials and also the preparation of thin films of these materials on various substrates.

Acknowledgment. We are grateful to Dr. Robert Haddon (AT&T Bell Laboratories, Murray Hill, NJ) for the electrical resistivity measurements, Bonnie J. Bachman (AT&T Bell Laboratories, Murray Hill, NJ) for the thermal analyses, and Howard Hutton (The Ohio State University) for the preparation of glassy carbon samples. We thank Professor Richard R. Schrock, Gui Bazan, and Steven A. Krouse (Massachusetts Institute of Technology, Cambridge, MA) for the donation of their gel permeation chromatography computer programs. We also thank Professor George Whitesides (Harvard University, Cambridge, MA) for useful discussions and encouragement and for the use of his ultrasonic measurement instrumentation.

---

(19) Modulus measurements were made by an ultrasonic method; see: McSkimin, H. J. In *Physical Acoustics, Principles and Methods*; Mason, W. P., Ed.; Academic: New York, 1964; p 271. Papadakis, E. P. In *Physical Acoustics, Principles and Methods*; Mason, W. P., Thurston, R. N., Eds.; Academic: New York, 1976; p 277. Krautkramer, J.; Krautkramer, H. *Ultrasonic Testing of Materials*; Springer-Verlag: New York, 1977. Fitting, D. W.; Adler, L. *Ultrasonic Spectral Analysis for Nondestructive Evaluation*; Plenum: New York, 1981. McMaster, R. C., Ed. *Nondestructive Testing Handbook*; The Ronald Press Company: New York, 1959.

(20) Electrical resistivity measurements were made with a four-point probe. The resistivity of a film prepared from **1a** at ~500 °C has been reported; see: Newkirk, A. E.; Hay, A. S.; McDonald, R. S. *J. Polym. Sci., Part A* **1964**, *2*, 2217.

(21) Field, J. E., Ed. *The Properties of Diamond*; Academic Press: New York, 1979.

(22) The electrode surfaces were prepared by sequential polishing with 1.0 μ, 0.3 μ, and 0.05 μ alumina paste. The scan rate was 100 mV/s with 1 M potassium chloride as the supporting electrolyte.

(23) For reviews of superficially modified glassy carbon electrodes, see: Snell, K. D.; Keenan, A. G. *Chem. Soc. Rev.* **1979**, *8*, 259. Murray, R. W. *Acc. Chem. Res.* **1980**, *13*, 135. Murray, R. W. In *Electroanalytical Chemistry*; Bard, A. J., Ed.; Dekker: New York, 1984; p 192. Miller, J. S., Ed. *Chemically Modified Surfaces in Catalysis and Electrocatalysis*; ACS Symposium Series 192; American Chemical Society: Washington, DC, 1982. Zak, J.; Kuwana, T. *J. Electroanal. Chem. Interfacial Electrochem.* **1983**, *150*, 645.

Studies on Tumor Promoters. 9. A Second-Generation Synthesis of Phorbol[1]

Paul A. Wender* and Frank E. McDonald

Department of Chemistry, Stanford University
Stanford, California 94305

Received February 23, 1990
Revised Manuscript Received April 11, 1990

Phorbol myristate acetate (PMA, **1a**) has long been recognized for its extraordinary ability to enhance the effect of various carcinogens in animal studies. The phorbol esters also elicit a wide variety of other biological responses, providing new opportunities for research on cancer, inflammation, cardiovascular disease, cystic fibrosis, AIDS, and memory development.[2,3] Our interest in the basic biochemistry of these compounds and their chemotherapeutic potential has recently led to the first synthesis of phorbol (**1b**).[4] We describe here a new route to phorbol and its analogues that features an unprecedented silicon transfer induced oxidopyrylium cycloaddition and transition metal mediated A ring synthesis.

The previous synthesis of phorbol was based on the potentially general tigliane, ingenane, and daphnane precursor **2**,[5] which was obtained by A ring annelation of the cycloadduct of zwitterion **3a** (Scheme I). Since this annelation was found to require a C4 ketone, a more direct route to **2** was envisaged through the oxidopyrylium–alkene cycloaddition of **3b**, a precursor incorporating a latent C4 ketone and potentially derivable from kojic acid.[6] To test this strategy, attachment of a secondary carbon of a tethered alkene to the C9 position (phorbol numbering) of kojic acid with provision for oxidation at C12 was required and was concisely accomplished by O-allylation and Claisen rearrangement.[7] Thus, addition of allylic bromide **5**,[8,9] prepared in three steps (62%) from

---

(1) This work was presented in part at the 197th National Meeting of the American Chemcial Society, Dallas, TX, 1989; ORGN 61.

(2) (a) Alkon, D. L. *Scientific American* **1989**, July, 42–50. (b) Poli, G.; Orenstein, J. M.; Kinter, A.; Folks, T. M.; Fauci, A. S. *Science* **1989**, *244*, 575. (c) Harada, S.; Yamamoto, N.; Fujiki, H. *AIDS Res. Hum. Retroviruses* **1988**, *4*, 99.

(3) For reviews of the phorbol esters and their role in tumor promotion, see: (a) *Naturally Occurring Phorbol Esters*; Evans, F. J., Ed.; CRC Press: Boca Raton, FL, 1986. (b) *Mechanism of Tumor Promotion*; Slaga, T. J., Ed.; CRC Press: Boca Raton, FL, 1984; Vol. I–IV.

(4) (a) Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954. (b) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957.

(5) This compound corresponds to structure **5** in ref 4b.

(6) For a review of oxidopyrylium cycloadditions, see: (a) Sammes, P. G. *Gazz. Chim. Ital.* **1986**, *119*, 109. (b) Footnote 12 in ref 4a.

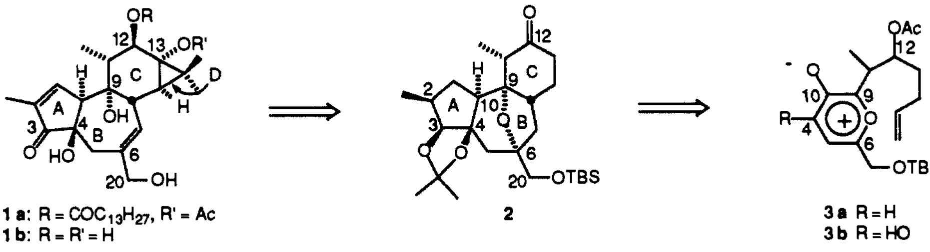
(7) McLamore, W. M.; Gelblum, E.; Bavley, A. *J. Am. Chem. Soc.* **1956**, *78*, 2816.

(8) (a) Marvel, C. S.; Hager, F. D. *Org. Synth.* **1941**, *Collect. Vol. I*, 248. (b) Marshall, J. A.; Andersen, N. H.; Hochstetler, A. R. *J. Org. Chem.* **1967**, *32*, 113.

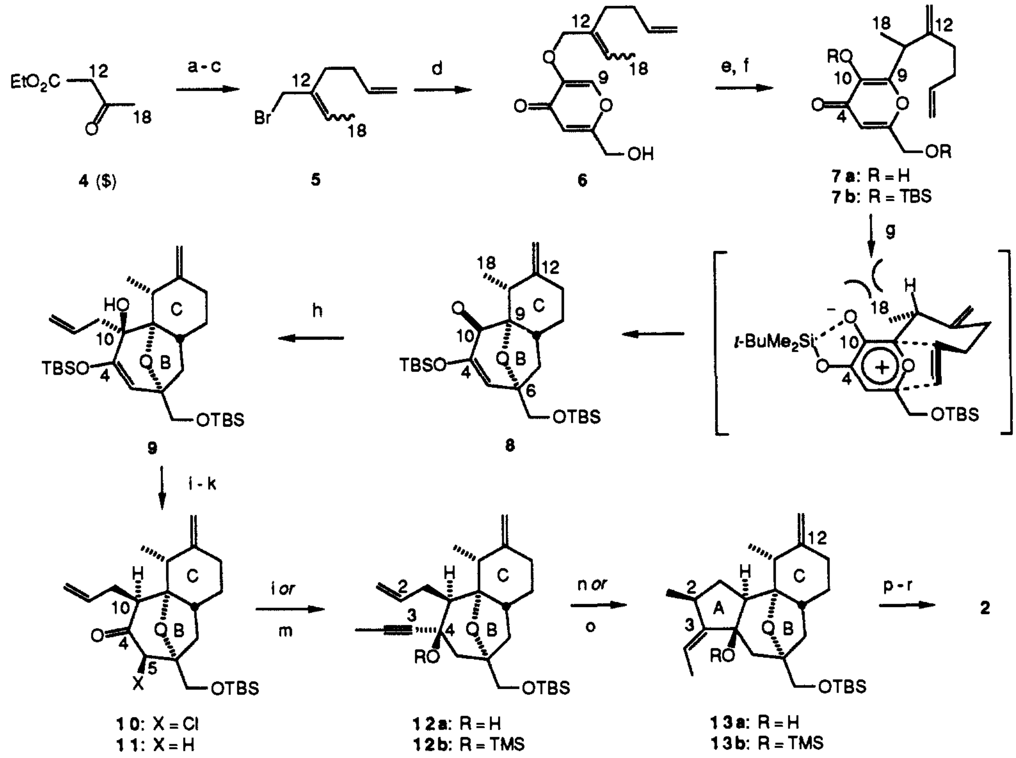
(9) Satisfactory NMR, IR, and mass spectra and combustion analyses were obtained for all new compounds.

0002-7863/90/1512-4956$02.50/0

Scheme I



Scheme II^a



^{a}(a) NaOEt, EtOH, reflux; 4-bromo-1-butene, reflux. (b) NaH, THF; then $LiAlH_4$, THF, reflux. (c) PBr_3, ether; then 48% aqueous HBr, 0 °C. (d) Kojic acid cesium salt, MeOH. (e) EtOH, 78 °C, 4 h. (f) TBSCl, imidazole, DMF. (g) 200 °C, toluene, sealed tube, 48 h. (h) $CH_2{=}CHCH_2MgBr$, THF. (i) $SOCl_2$, pyridine, Et_2O, 0 °C. (j) TBAF, THF, 0 °C. (k) Bu_3SnH, catalyst AIBN, toluene, 80 °C. (l) 1-Lithio-1-propyne, 4 equiv of LiBr, THF, −78 to 20 °C. (m) 1-Lithio-1-propyne, 4 equiv of LiBr, THF, −78 to 20 °C; then TMSCl. (n) 0.1 equiv of $Pd_2(dba)_3{\cdot}CHCl_3$, 0.2 equiv of tri(*o*-tolyl)phosphine, 2 equiv of HOAc, 2 equiv of $[(CH_3)_2SiH]_2O$, toluene. (o) Cp_2ZrBu_2, THF, −78 to 20 °C; then HOAc quench. (p) O_3, CH_2Cl_2, MeOH, −78 °C; $NaBH_4$, −78 to 20 °C. (q) 2-Methoxypropene, catalyst PPTS, CH_2Cl_2. (r) PCC, NaOAc, CH_2Cl_2.

ethyl acetoacetate (**4**) and 4-bromo-1-butene, to a methanolic solution of cesium kojate[10] gave allylic ether **6** (Scheme II). When heated at 78 °C in ethanol for 4 h, this ether smoothly rearranged to pyronealkene **7a** (62% yield for two steps). Protection of both hydroxyl groups of **7a** as *tert*-butyldimethylsilyl (TBS) ethers established efficient access to the key cycloaddition precursor (**7b**, 100%).

When a toluene solution of **7b** in a base-washed sealed tube was heated at 200 °C for 48 h, cycloadduct **8** was obtained as a single isomer (71% isolated, 77% yield based on recovered **7b**). The impressive stereoselectivity of this reaction is consistent with the involvement of a transition state in which the tether between the pyrone and alkene assumes a chair-like conformation, with the C18 methyl oriented equatorially in order to minimize 1,3 interaction with the C10 substituent. While efforts to determine the involvement of a pentacoordinate silicate or an oxidopyrylium intermediate in this cycloaddition are in progress, it is clear that the nature and transferability of the migrating group (R) are important. When this group is methyl, no reaction occurs. With acyl groups, the cycloaddition occurs, although higher temperatures are required to achieve reasonable rates. Our use of the TBS group represents the best compromise found between reaction efficacy and protecting group versatility. It is of further significance that a cyclohexane solution of **7b** also provides **8** when irradiated *at room temperature* (15 min, 350 nm lamp-Rayonet photoreactor), albeit in only 15% yield.

The availability of a cycloadduct incorporating a latent C4 ketone allowed for the implementation of a new A ring annelation, involving stereocontrolled attachment of allyl and propynyl groups to C10 and C4, respectively, followed by their metal-mediated closure. Toward this end, allylmagnesium bromide was added to ketone **8** to provide, in accord with the facial bias of the C10 carbonyl, only the alcohol **9** (72% yield). Conversion of the allylic alcohol moiety of **9** to the allylic chloride[11] and selective desilylation of the enol ether with stereoelectronically controlled protonation at C10 gave chloro ketone **10**. Tin hydride[12] reduction provided ketone **11** (56%, three steps). Reaction of this ketone with 1-lithio-1-propyne in the presence of lithium bromide[13] proceeded with convex face addition to afford the axial alcohol **12a** (48% yield, 88% isomeric purity) or, upon treatment with trimethylsilyl

---

[10] Van Keulen, B. J.; Kellogg, R. M.; Piepers, O. *J. Chem. Soc., Chem. Commun.* **1979**, 285.

[11] Georgoulis, C.; Ville, G. *Bull. Soc. Chim. Fr.* **1975**, *42*, 607.

[12] Kuivila, H. G.; Menapace, L. W. *J. Org. Chem.* **1963**, *28*, 2165.

[13] Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes, and Cumulenes: A Laboratory Manual*; Elsevier: Amsterdam, Oxford, New York, 1981; pp 75–76.

(TMS) chloride, the silyl ether **12b** (55% yield).

Cyclization of enyne **12a** with catalytic palladium dibenzylideneacetone complex $(Pd_2(dba)_3)$[14] in the presence of tri-*o*-tolylphosphine, dimethylhydrosiloxane, and acetic acid completed the phorbol A ring, giving with impressive 1,3-stereocontrol only diene **13a** (58%). Enyne **12b** exhibited similar behavior with palladium catalysis affording **13b**, and it also reacted with dibutylzirconocene[15] followed by acetic acid quench of the zirconacyclopentene intermediate to give a 69% yield of **13b**. Despite the different mechanisms operative for these cyclizations the stereochemistry at C2 and of the ethylidene group is the same for both processes.

With the assembly of the tricyclic ABC core of phorbol completed, the latent oxidation at C3 and C12 was unveiled by ozonolysis of both exocyclic alkenes followed by reductive workup with sodium borohydride to afford a triol, again as a single isomer. Selective protection of the C3–C4 *cis*-diol as the acetonide followed by oxidation of the C-12 alcohol to the ketone yielded **2** (24% for three steps), thereby completing a formal synthesis of phorbol.[4b]

In summary, the synthesis of phorbol precursor **2**, possessing all of the putative pharmacophore heteroatoms of the natural products, has been achieved in 16 steps from commercial materials ($) by a novel group transfer induced cycloaddition and a transition metal mediated cyclization. This shortened route offers improved access to racemic phorbol esters as well as unnatural analogues that are needed to establish the structural requirements for tumor promotion. These studies and the extension of this strategy to ingenane and daphnane diterpenes are in progress.

Acknowledgment. Support of this research by the National Cancer Institute through Grant CA31841 is gratefully acknowledged.

Supplementary Material Available: NMR, IR, MS, and elemental analysis data for compounds **7b**, **8**, **11**, and **2** (4 pages). Ordering information is given on any current masthead page.

---

(14) (a) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161. (b) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1988**, *29*, 1231.

(15) (a) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336. (b) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128.

Geometry Dependence of Intramolecular Photoinduced Electron Transfer in Synthetic Zinc–Ferric Hybrid Diporphyrins

Atsuhiro Osuka,[†] Kazuhiro Maruyama,[*,†] Noboru Mataga,[*,‡] Tsuyoshi Asahi,[‡] Iwao Yamazaki,[§] and Naoto Tamai[§]

Department of Chemistry, Faculty of Science
Kyoto University, Kyoto 606, Japan
Department of Chemistry
Faculty of Engineering Science
Osaka University, Toyonaka, Osaka 560, Japan
Department of Chemical Process Engineering
Faculty of Engineering, Hokkaido University
Sapporo 060, Japan

Received November 7, 1989

Despite the crucial role of photoinduced electron transfer (ET) reactions in photosynthetic energy conversion, the factors that control this reactivity remain poorly understood. Among these, the geometrical factors such as distance and mutual orientation offer important effects in the photoinduced ET reaction. Recent theoretical work indicates the importance of orientation effects on the rates of the nonadiabatic ET process between diporphyrin pairs.[1] Synthetic model compounds with well-defined geometries are particularly effective in probing this problem.[2] Recently McLendon et al. reported the occurrence of intramolecular ET reaction in aryl-linked diporphyrin hybrid complexes.[3] This paper reports more comprehensive geometric effects in an extensive array[4] of hybrid metal complexes consisting of zinc porphyrin (ZnP) and ferric porphyrin chloride ($Fe^{III}PCl$) (Figure 1).[5] Diporphyrin models studied here include a variety of mutual orientations and different kinds of aromatic spacers such as benzene, naphthalene, and spirobiindan.

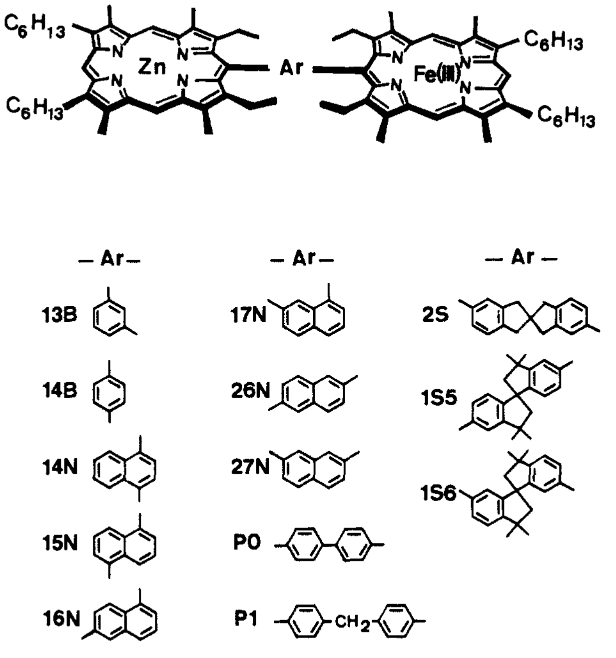


Figure 1. Structure of ZnP–Fe^{III}P hybrid diporphyrins used in this study. Abbreviations are indicated at the left side of the aromatic spacer.

The ground-state absorption spectra of the hybrid diporphyrins ZnP–$Fe^{III}PCl$ in the Q-band region can be adequately described in terms of a superposition of the spectra of the individual chromophores, but those at the B-band displayed slight broadening, indicating very weak interaction in the S_1 states and excitonic interaction in the S_2 states. The fluorescence spectra are that of the unperturbed ZnP alone,[6] but the fluorescence quantum yields for the ZnP in these hybrid diporphyrins decreased dramatically. This decrease in the fluorescence quantum yield can be ascribed to the intramolecular ET from the $^1(ZnP)^*$ to the $Fe^{III}PCl$ on the basis of the picosecond transient absorption measurements.[7] As an example, the transient absorption spectra of 4,4′-diphenylmethylene-bridged diporphyrin **P1** in DMF are shown in Figure 2. The spectrum at the delay time of 26 ps was almost due to

---

[†] Kyoto University.
[‡] Osaka University.
[§] Hokkaido University.

(1) (a) Cave, R. J.; Siders, P.; Marcus, R. A. *J. Phys. Chem.* **1986**, *90*, 1436–1444. (b) Siders, P.; Cave, R. J.; Marcus, R. A. *J. Chem. Phys.* **1984**, *81*, 5613–5624. (c) Petke, J. D.; Maggiora, G. M. *J. Chem. Phys.* **1986**, *84*, 1640–1652.

(2) Wasielewski, M. R. Distance Dependencies of Electron Transfer Reactions. In *Photoinduced Electron Transfer*; Fox, M. A., Chanon, M., Eds.; Elsevier: Amsterdam, 1988; Part A, pp 161–206.

(3) Heiler, D.; McLendon, G.; Rogalskj, P. *J. Am. Chem. Soc.* **1987**, *109*, 604–606.

(4) (a) Osuka, A.; Maruyama, K. *J. Am. Chem. Soc.* **1988**, *110*, 4454–4456. (b) Osuka, A.; Maruyama, K.; Yamazaki, I.; Tamai, N. *J. Chem. Soc., Chem. Commun.* **1988**, 1243–1245.

(5) For intramolecular electron transfer from $^1(ZnP)^*$ to $Fe^{III}P$, see: (a) Fujita, I.; Netzel, T. L.; Chang, C. K.; Wang, C.-B. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 413–417. (b) Brookfield, R. L.; Ellul, H.; Harriman, A. *J. Chem. Soc., Faraday Trans. 2* **1985**, *81*, 1837–1848. (c) Mataga, N.; Yao, H.; Okada, T.; Kanda, Y.; Harriman, A. *Chem. Phys.* **1989**, *131*, 473–480.

(6) It is well-known that $Fe^{III}Cl$ porphyrins are d-type hyperporphyrins and their excited states are very short lived and nonfluorescent: Irrine, M. P.; Harrison, R. J.; Strahand, M. A.; Beddard, G. S. *Ber. Bunsenges. Phys. Chem.* **1985**, *89*, 226–232.

(7) The measurements were done by means of a microcomputer-controlled double-beam ps spectrometer with a repetitive mode-locked Nd^{3+}/YAG laser as the excitation source. Miyasaka, H.; Masuhara, H.; Mataga, N. *Laser Chem.* **1983**, *1*, 357–386.

0002-7863/90/1512-4958$02.50/0