by rinsing with water, drying, and evaporation, gave a residue, which was crystallized from dichloromethane/*n*-hexane to give 31.6 mg (68%) of the title porphyrin: mp >300 °C; NMR (360 MHz, $CDCl_3$ + Me_2SO-d_6) 11.70 (br s, CO_2H), 10.29, 10.08, 10.07 (each s, 1 H, 2 H, 1 H, *meso*-H), 8.17, 8.12 (each m, 2- and 4-vinyl α-CH), 6.71 (m, C*H*(OH)), 6.25, 6.07 (each m, 2- and 4-vinyl β-CH_2), 4.28 (m, 7a-CH_2), 3.59, 3.57, 3.54, 3.51 (each s, 3 H, 3 H, 6 H, 3 H, four Me and OMe), 3.09 (t, 7b-CH_2), -3.89 (s, two NH). The 6b-CH_2 resonance was obscured. Anal. Calcd for $C_{35}H_{36}N_4O_5$: C, 70.92; H, 6.12; N, 9.45. Found: C, 71.32; H, 6.24; N, 9.13.

6-[1-Hydroxy-2-(methoxycarbonyl)ethyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin (43). 6-[(Methoxycarbonyl)acetyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin **40** (50 mg) in 25 mL of dry dichloromethane was treated at with a solution of 550 mg of sodium borohydride in 25 mL of ice-cold methanol, and the mixture was stirred at room temperature for 7 min before addition of acetone (10 mL), water, and dichloromethane. The organic phase was washed with water, dried, and evaporated to give a residue, which was flash chromatographed on alumina (Brockmann Grade V, elution with dichloromethane). Evaporation of the appropriate eluates gave a residue, which was recrystallized from methanol to give 18.6 mg (37%): mp >300 °C dec; NMR (360 MHz, $CDCl_3$) 10.49, 10.25, 10.22, 10.10 (each s, *meso*-H), 8.30, 8.29 (each m, 2- and 4-vinyl α-CH), 6.85 (m, C*H*(OH)), 6.39, 6.23 (each m, 2- and 4-vinyl β-CH_2), 4.44 (t, 7a-CH_2), 3.82, 3.74, 3.71, 3.70, 3.66, 3.62 (each s, four Me and two OMe), 3.29 (t, 7b-CH_2), -3.65 (s, two NH). The 6b-CH_2 resonance was obscured. Anal. Calcd for $C_{36}H_{38}N_4O_5$: C, 71.27; H, 6.31; N, 9.23. Found: C, 71.37; H, 6.29; N, 9.22.

Magnesium 6-[(Methoxycarbonyl)acetyl]-7-(2-carboxyethyl)-1,3,5,8-tetramethyl-2,4-divinylporphyrin (8). Metal-free porphyrin **41** (4.86 mg) in 3 mL of dry pyridine was treated with 50 mg of anhydrous $Mg(ClO_4)_2$. The solution was heated to 100 °C under Ar in the dark. After 2 h, metalation was still incomplete, so 65 mg more of $Mg(ClO_4)_2$ was added. After 3.5 h further at 100 °C the reaction was filtered hot through a sintered-glass funnel. No solid $Mg(ClO_4)_2$ was collected. The resulting solution was diluted with dichloromethane and rinsed with water. The organic layer was then rinsed with 25 mL of pH 6.8 phosphate buffer, dried, and evaporated. The residue was dissolved in dichloromethane and precipitated with *n*-hexane. Unfortunately, the precipitate was contaminated with $Mg(ClO_4)_2$. Therefore it was redissolved in dichloromethane, rinsed 5 × H_2O, dried, and evaporated to give a green solid. Some of this solid was treated with TFA in the dark for 75 min, followed by the standard basic aqueous workup. The visible spectrum of the demetalated material in dichloromethane was not a perfect "rhodo" type; however, treatment with methanolic potassium hydroxide gave an obvious spectral change to a clean "etio" type spectrum. Thus the 6-β-keto ester side chain of **8** was judged to be intact: UV-vis (of **8**) (CH_2Cl_2, relative absorbance) 596 nm (81.1), 554 (100), (of **8** after treatment with TFA) (CH_2Cl_2) 630 (30.2), 576 (84.3), 548 (97.1), 510 (100), [after addition of methanolic KOH] 628 (28.7), 574 (62.2), 544 (84.0), 508 (100).

Magnesium 6-[1-Hydroxy-2-(methoxycarbonyl)ethyl]-7-(2-carboxyethyl)-1,3,5,8-tetramethyl-2,4-divinylporphyrin (6). To 6-[(methoxycarbonyl)acetyl]-7-(2-carboxyethyl)-1,3,5,8-tetramethyl-2,4-divinylporphyrin **41** (4.82 mg) in 10 mL of dry pyridine was added 72 mg of magnesium(II) perchlorate, and the solution was heated at 100 °C under argon in the dark for 3 h to accomplish metalation as described above. The crude product in 5 mL of dry tetrahydrofuran was then added to a solution of 59 mg of sodium borohydride in 2 mL ice-cold methanol. The mixture was stirred at room temperature for 15 min before addition of acetone (5 mL), dichloromethane, and water. The organic phase was dried and evaporated to give a residue: UV-vis (CH_2Cl_2, relative absorbance) 592 nm (13.2), 554 (15.3), 416 (100). Demetalation of this material with trifluoroacetic acid, followed by an aqueous workup, gave compound **42** in high yield. Further treatment with diazomethane gave the hydroxypropionate dimethyl ester **43** (TLC monitoring).

Magnesium 6-[1-Hydroxy-2-(methoxycarbonyl)ethyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin. 6-[1-Hydroxy-2-(methoxycarbonyl)ethyl]-7-[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethyl-2,4-divinylporphyrin (**43**) (18.6 mg) was dissolved in 4 mL of dry dichloromethane and treated with 4.0 mL of a solution of 175 mg of 2,6-di-*tert*-butyl-4-methylphenol (BHT) in 9 mL of dry dichloromethane and 1.0 mL of 0.080 M ethyl magnesium iodide (freshly prepared and titrated) at room temperature. After 15 min, UV-vis spectrophotometry showed complete metalation [(in CH_2Cl_2, relative absorbance) 592 nm (0.72), 554 (0.912)], so the mixture was poured into water and extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated to give a residue (68 mg) containing excess BHT. This was heated under vacuum at 78 °C to sublime the BHT and afforded 15 mg (77.6%) of the title compound. Treatment of a small amount of this material with trifluoroacetic acid, followed by an aqueous workup, afforded the demetalated starting material (**43**) (TLC analysis) in quantitative yield (spectrophotometry).

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE-81-20891).

Registry No. **6**, 99898-43-8; **6** (methoxy deriv), 99652-11-6; **8**, 100102-34-9; **20a**, 100046-14-8; **20b**, 100046-15-9; **20c**, 100046-16-0; **21**, 100046-10-4; **23**, 52091-21-1; **24**, 51089-82-8; **25**, 51644-01-0; **25** (iodo deriv), 52460-23-8; **26**, 52091-22-2; **27**, 18818-25-2; **28**, 100046-09-1; **28** (base), 100046-08-0; **29**, 100082-67-5; **29** (base), 100082-66-4; **30**, 37059-18-0; **31**, 100082-69-7; **31** (base), 100082-68-6; **32**, 89909-53-5; **33**, 89909-40-0; **33**·HCl (R = CH=NH), 100046-07-9; **34**, 100046-11-5; **35**, 100046-12-6; **36**, 100046-13-7; **37**, 100046-17-1; **38**, 52559-95-2; **39**, 100046-18-2; **40**, 38220-23-4; **41**, 100046-19-3; **42**, 100046-20-6; **43**, 100046-21-7; (*E*)-H_3CCH=$CHCO_2CH_2Ph$, 71338-71-1; $HO_2CCH_2CO_2CH_3$, 16695-14-0.

Methyl Deuteration Reactions in Vinylporphyrins: Protoporphyrins IX, III, and XIII

Kevin M. Smith,* Daniel W. Parish, and Warren S. Inouye

Department of Chemistry, University of California, Davis, California 95616

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Base-catalyzed deuteration of the methyl groups in protoporphyrin IX dimethyl ester (**1**) proceeds with differential deuteration; rate of deuteration, as measured by NMR spectroscopy of reaction products, follows the order 3-Me > 1-Me > 5-Me > 8-Me. A simple qualitative theory to explain the differential deuteration is discussed, based on primary (vinyl group on subunit bearing the deuteriated methyl) and secondary (vinyl group on adjacent subunits) inductive effects, and this is tested by using the symmetrical porphyrins, protoporphyrin III dimethyl ester (**6**) and protoporphyrin XIII dimethyl ester (**7**). Synthesis of **6** and **7**, from monopyrroles via the a,c-biladiene route, are reported.

In early work[1] with deuterium-labeled porphyrins and hemins, it was discovered that generation of vinyl groups by prolonged treatment of (2-chloroethyl)porphyrins with strong base caused a loss of isotopic label from the methyls

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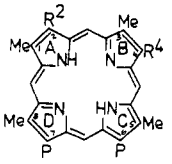
located on the same pyrrole subunits as the 2-chloroethyls. At the same time, no appreciable loss of deuterium was detected from the 5- or 8-methyls which were flanked by propionic side chains.[1a,2] It was theorized that this loss of label took place after dehydrohalogenation to give vinyl had occurred. The vinyl groups were thought to reduce the electron density in the pyrrolic nuclei to which they were attached, rendering the methyl protons more acidic and therefore more susceptible to base-catalyzed exchange. It was reasoned that if deuterium could be exchanged out of the labeled porphyrins under basic conditions, it should be possible to introduce deuterium into unlabeled porphyrins by supplying a suitable deuterium source under basic conditions. This procedure offered a substantial reduction in the overall number of steps required to synthesize porphyrins containing deuterium labeled 1- and/or 3-methyl groups. After treatment of protoporphyrin IX dimethyl ester (PP-IX DME) (1) with sodium methoxide and methanol-*d* in dimethylformamide for 5 days, significant incorporation of deuterium was observed at the 1- and 3-methyls, with little or no incorporation at the 5- or 8-methyls.[1a,3] Similar attempts to incorporate deuterium were unsuccessful using mesoporphyrin IX dimethyl ester (2) and deuteroporphyrin IX dimethyl ester (3), porphyrins with the vinyls replaced by ethyl groups or protons, respectively. Although the propionate methylenes adjacent



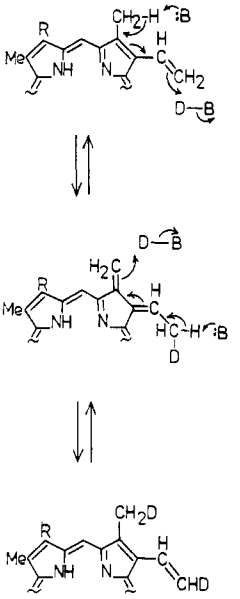
1 $R^2 = R^4 = CH{=}CH_2$
2 $R^2 = R^4 = Et$
3 $R^2 = R^4 = H$
4 $R^2 = R^4 = CO.Me$
5 $R^2 = R^4 = CH{=}CH.CO_2Me$

$P = CH_2CH_2CO_2Me$

to the carbonyl groups were exchanged as in the previous cases, there was no detectable exchange of the methyls.[1c,4] Significant deuteration can be accomplished, however, when a suitably strong electron-withdrawing substituent is located on the same pyrrolic subunit of the porphyrin ring as the methyl group in question. Such a situation exists in diacetyldeuteroporphyrin IX dimethyl ester (4) where a direct enolization pathway from methyl to the acetyl group can be visualized.[1a,3] Likewise, methyls on pyrrole subunits bearing acrylate substituents (e.g., 5) can also be efficiently exchanged using this procedure.[5]

The mechanism in the vinyl-mediated exchange process cannot be totally inductive because the terminal methylenes of the vinyl groups in PP-IX DME (1) also showed some incorporation of deuterium. This would indicate that some resonance contribution must also be operative (Scheme I), as in the case of the acetyl-promoted exchange. Since the extent of incorporation in the vinyl methylenes

Scheme I



was far less than at the methyl groups, the only conclusion was that the resonance pathway depicted in Scheme I is not a major contributor to the overall exchange process occurring in PP-IX DME (1). Further examination of the exchange of PP-IX DME (1), showed that all the methyls can be partially exchanged, and that they incorporate deuterium at different rates. In order of decreasing incorporation, they exchange in the order 3-Me > 1-Me > 5-Me > 8-Me, as interpreted from integration of the NMR spectra.

A simple qualitative explanation for this selectivity can be advanced based on a first-order inductive effect, i.e., whether or not a methyl is situated on a pyrrolic nucleus which also contains an electron-withdrawing substituent, and an additional second-order "fine-tuning" effect based on the distance of the methyl in question from the electron-withdrawing groups on adjacent pyrrolic nuclei. Even this simple approach readily explains the observed incorporation pattern (3-Me > 1-Me > 5-Me > 8-Me) in PP-IX DME (1). Both the 1- and 3-methyls have a first-order effect and hence exhibit far greater incorporation of deuterium than the 5- and 8-methyls which have no such first-order effect. The second-order effect manifests itself in that the 3-methyl incorporates more label than the 1-methyl because of the shorter distance to the electron-withdrawing substituents on the adjacent pyrrolic ring, 3 to 2 vs. 1 to 4. The second-order argument also explains the difference in incorporation between the 5- and 8-methyls, (5 to 4 vs. 8 to 2).

In order to elaborate on the simple exchange theory and to define the second-order effect more clearly, it would be helpful to examine the symmetrical protoporphyrins PP-III DME (6) and PP-XIII DME (7). Due to the fact these compounds possess an α–γ meso axis of symmetry, there will only be one second-order effect occurring in either isomer. The use of these isomers should lead to a better understanding of the role the vinyl substituents are playing in the exchange process.

Syntheses of Protoporphyrins III and XIII

Several papers have appeared recently[6] presenting

(1) (a) Smith, K. M.; Eivazi, F.; Langry, K. C.; Almeida, J. A. P. B.; Kenner, G. W. *Bioorg. Chem.* **1979**, *8*, 485–495. (b) Cavaleiro, J. A. S.; Rocha Gonsalves, A. M. d'A.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1771–1781. (c) Evans, B.; Smith, K. M.; LaMar, G. N.; Viscio, D. B. *J. Am. Chem. Soc.* **1977**, *99*, 7070–7072.

(2) Smith, K. M. *Acc. Chem. Res.* **1979**, *12*, 374–381.

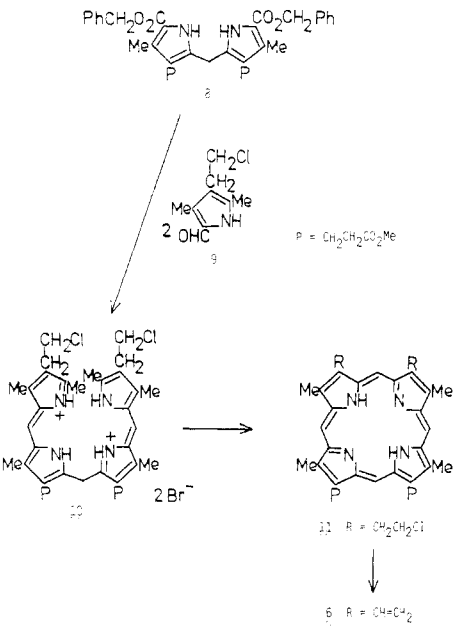
(3) (a) Smith, K. M.; Fujinari, E. M.; Langry, K. C.; Parish, D. W.; Tabba, H. D. *J. Am. Chem. Soc.* **1983**, *105*, 6638–6646.

(4) Evans, B. Ph.D. Dissertation, University of Liverpool, 1977, p 85.

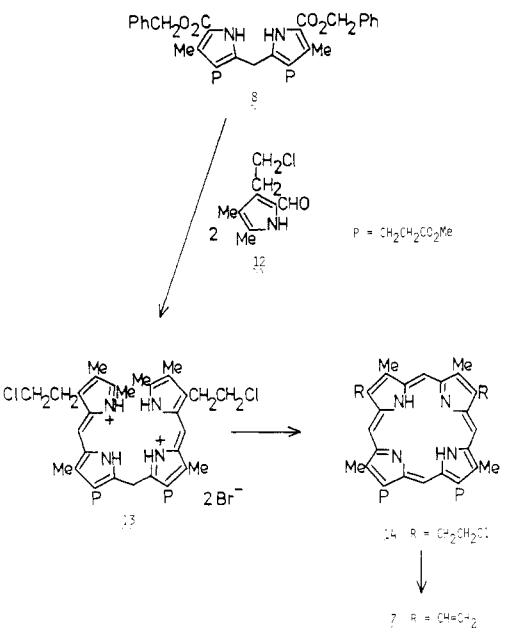
(5) (a) Langry, K. C. Ph.D. Dissertation, University of California, Davis, 1982, p 67. (b) Miura, M. Ph.D. Dissertation, University of California, Davis, 1984, pp 120–124. (c) Fuhrhop, J.-H.; Lehmann, T. *Liebigs Ann. Chem.* **1984**, 1386–1389.

(6) (a) Buldain, G.; Diaz, L.; Frydman, B. *J. Org. Chem.* **1977**, *42*, 2957–2960. (b) Clezy, P. S.; Fookes, C. J. R.; Sternhell, S. *Aust. J. Chem.* **1978**, *31*, 639–648. (c) Battersby, A. R.; Hamilton, A. D.; McDonald, E.; Mombelli, L.; Wong, O.-H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1283–1289.

Scheme II

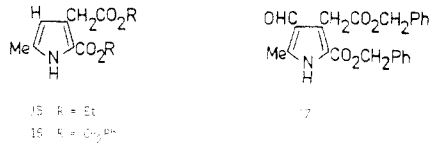


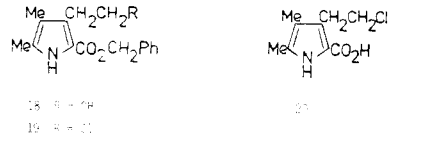
Scheme III



various syntheses of both PP-III DME (**6**) and PP-XIII DME (**7**). A majority of these made use of the MacDonald procedure,[7] in which two pyrromethanes are condensed to yield the desired porphyrin. In our approach to PP-III DME (**6**) we opted for a route involving an intermediate a,c-biladiene.[8] This approach is outlined in Scheme II and proceeded uneventfully.

The method used to prepare PP-XIII DME (**7**) was analogous to that used in the synthesis of **6**. The only difference was in the replacement of readily available formylpyrrole **9** with the formylpyrrole **12**, and the synthesis is outlined in Scheme III. The key formylpyrrole **12** was synthesized as follows. The β-free pyrrole **15** was heated under vacuum in benzyl alcohol containing sodium and gave the desired dibenzyl ester pyrrole **16** in 68% yield. Vilsmeier formylation of the pyrrole **16** gave the formylpyrrole **17** in 66% yield, and reduction with borane–THF[6a] afforded the expected (2-hydroxyethyl)-dimethylpyrrole **18** in 81% yield. Chlorination of this pyrrole with thionyl





chloride in dichloromethane containing pyridine gave the (2-chloroethyl)pyrrole **19** in 65% yield. Hydrogenation over 10% palladium–carbon at atmospheric pressure gave the pyrrole carboxylic acid **20**, which was decarboxylated in trifluoroacetic acid and finally formylated by the Vilsmeier procedure to give the target formylpyrrole **12** in 55% yield. Alternatively, the (2-hydroxyethyl)pyrrole **18** could be hydrogenated, decarboxylated, and formylated by the Vilsmeier procedure (with concomitant converion of the 2-hydroxyethyl into 2-chloroethyl) to give **12**. Attempts to transform the unsubstituted pyrrole **15** into the methylpyrrole **21** using reductive C-alkylation (paraformaldehyde and hydriodic acid) gave only a 44% yield of the required product.

Exchange Studies on Protoporphyrins IX, III, and XIII (Dimethyl Esters)

The initial studies of the base-catalyzed exchange were conducted on PP-IX DME (**1**) because of its availability and ease of preparation. The main purpose of the preliminary investigations was to find the optimum conditions under which the exchange would occur. Solubility problems inherent in porphyrin chemistry had to be overcome, as well as the large amount of decomposition which usually accompanied the exchange process. The solvents that seemed the most promising were tetrahydrofuran and dimethylformamide; they were able to dissolve the porphyrin and sufficient base for the exchange to take place at a reasonable rate. In all cases, the base employed was sodium methoxide and the deuterium source was methanol-*d*. It should be noted that although the solvents were carefully dried before use in these reactions, in all probability there was enough residual water present in the solvents, or eventually absorbed from the atmosphere, so that some hydroxide ion was also present in solution. Once the appropriate solvent system was found (Experimental Section), the concentration of base was varied to find a level which would provide a reasonable compromise between exchange and decomposition. With these parameters known, the exchanges were carried out under identical conditions on all three of the porphyrins, i.e., PP-III DME (**6**), PP-IX DME (**1**), and PP-XIII DME (**7**). After the exchange was complete, it was hoped that comparison of the NMR spectra of these exchanged porphyrins would provide the individual magnitudes of the separate second-order effects. The simple theory for the exchange process predicted that PP-III DME (**6**) would, under identical conditions, exchange at the 5- and 8-methyls to

(7) MacDonald, S. F. *J. Chem. Soc.* **1952**, 4176–4184.
(8) Almeida, J. A. P. B.; Kenner, G. W.; Rimmer, J.; Smith, K. M. *Tetrahedron* **1976**, *32*, 1793–1799.

a lesser extent than the 5- and 8-methyls in PP-XIII DME (7).

Due to the severe overlap of the methyl resonances in the proton NMR spectra of the free-base porphyrins, another transformation was needed before the extent of incorporation could be judged, via NMR spectroscopy, with reasonable accuracy. It was known that in the NMR spectrum of the bis cyano complexes of the low-spin iron(III) porphyrins, the heme methyl resonances are all shifted out of the diamagnetic region and clearly resolved.[2] Iron was therefore inserted into small portions of the exchanged porphyrins to enable the use of NMR to judge the relative levels of deuterium incorporation. Control experiments showed that no deuterium was being lost during any of the procedures subsequent to the exchange experiment. Initially, an attempt was made to develop an HPLC procedure to separate the three protoporphyrin isomers. It was hoped that such a separation could be scaled-up to enable the separation of products from an exchange reaction performed simultaneously on all three isomers. Exchanging all three isomers simultaneously would ensure that all the porphyrins were being subjected to identical reaction conditions. The HPLC separation proved to be unsatisfactory, however, so carefully controlled conditions were used to ensure the exchanges were taking place in environments as equivalent to one another as possible.

In PP-IX DME (1) the lack of symmetry is responsible for the observed differential incorporation of deuterium into the various methyl groups during base-catalyzed exchange. This lack of symmetry makes it difficult to assess individual contributions to the overall extent of exchange being made by the various substituents. The axis of symmetry present in PP-III DME (6) and PP-XIII DME (7) greatly simplifies the problem of separating the mixed secondary effects that occur in the exchange of PP-IX DME (1), since in both cases there is only one type of secondary effect taking place. By a direct comparison of exchanges carried out on these symmetrical porphyrins it should be possible to ascertain if the simple explanation for the observed differential incorporation occurring in PP-IX DME (1) is valid. The qualitative theory readily predicts that the methyl groups located on rings A and B of the porphyrins should incorporate deuterium to a significantly greater extent than the 5- and 8-methyls located on rings C and D. This difference in level of incorporation is due to the first-order effect; i.e., the vinyl groups are attached to the same pyrrolic subunits as the methyl groups in question. Furthermore, the secondary effect predicts that the 1- and 4-methyls of PP-III DME (6) should exchange to the same extent as the 2- and 3-methyls of PP-XIII DME (7) because in both cases the methyl groups in question are two positions removed from the vinyl groups on adjacent pyrrolic subunits. This assumes, of course, that there is no positional-effect, i.e., some additive effect due to the positions of the methyl and vinyl groups relative to each other. This sort of substituent effect would depend on whether or not the methyl groups were between the two vinyl groups, as in PP-XIII DME (7), or on one side of the two vinyl groups, as in PP-III DME (6). The methyl groups on rings C and D of the porphyrins will be the most useful in assessing the sensitivity of the secondary effect to the distance between the groups of interest. The theory predicts that the 5- and 8-methyls of PP-XIII DME (7), which are only one position removed from the vinyl groups on the adjacent pyrrolic rings, will exchange to a greater extent than those of PP-III DME (6), which are two positions removed from

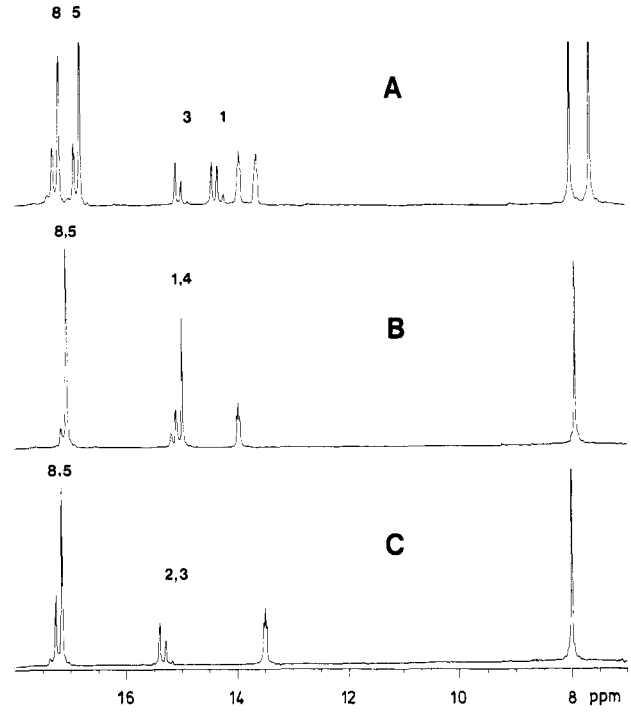


Figure 1. 360-MHz proton NMR spectra (low-field regions) in CD_3OD of the dicyanoferrihemin dimethyl esters obtained by metalation, after being subjected for 30 days to base-catalyzed exchange, of (A) protoporphyrin IX dimethyl ester (1), (B) protoporphyrin III dimethyl ester (6), and (C) protoporphyrin XIII dimethyl ester (7). The numbers above the peaks are the methyl assignments; small peaks to low field of the CH_3 lines are due to CH_2D and CHD_2 components. Also shown, to high field, are the α vinyl CH resonances (13–14 ppm) and the propionate α methylene resonances (7–8 ppm).

the vinyl groups on adjacent rings. This is again assuming that there will be no effect due to the positions of the vinyls relative to each other.

The exchanges were carried out by using rigorously controlled conditions (Experimental Section) on each of the three protoporphyrin isomers. The length of exposure of each of the porphyrins was 30 days. The NMR spectra shown in Figure 1 are of the exchanged porphyrins after conversion to their bis cyano–Fe(III) analogues. Examination of these spectra shows that the major features of the simple theory are valid. As predicted, the methyl groups on rings A and B of the porphyrins exchanged to a significantly greater extent than those on the C and D rings in both PP-III DME (6) and PP-XIII DME (7) due to the primary effect, and the 5- and 8-methyls of PP-XIII DME (7) showed greater incorporation than those of PP-IIIDME (6) due to the closer range of the secondary effect.

Further examination of the spectra shown in Figure 1 shows that the secondary effect did not correctly predict the relative extent of incorporation of the 1- and 4-methyls of PP-III DME (6) compared with the 2- and 3-methyls of PP-XIII DME (7). The theory predicted that these methyls would incorporate deuterium to a similar extent, but examination of the spectra shows this to be incorrect because in PP-XIII DME (7) (where the methyl groups are located between the two vinyl groups), a far greater level of incorporation was achieved than in PP-III DME (6) (where the methyl groups are not located between the two vinyl groups). Obviously, the position of the methyl group in question relative to the positions of the two vinyl groups is of the utmost importance in determining the magnitude of the secondary effect.

These exchange reactions shown that the simple qualitative theory for prediction of relative extents of deu-

terium incorporation during base-catalyzed exchange is correct to the first approximation. The theory does, however, require modification before the secondary effect can be properly correlated with the observed positional effects.

Experimental Section

Melting points were measured on a hot stage apparatus and are uncorrected. Neutral alumina (Merck) or silica gel 60 (70–230 mesh) (Merck) were used for column chromatography, and preparative TLC was carried out on 20 × 20 cm glass plates coated with Merck GF 254 silica gel (1 mm thick). Analytical TLC was performed with Merck silica gel 60 F 254 precoated sheets (0.2 mm). Electronic absorption spectra were measured on a Hewlett-Packard 8450A spectrophotometer (solutions in dichloromethane), and proton NMR spectra were measured at 360 MHz on a Nicolet NT-360 spectrometer (solutions in $CDCl_3$). Elemental analyses were performed at the Berkeley Microchemical Analysis Laboratory, Department of Chemistry, UC Berkeley.

Benzyl 3-[((Benzyloxy)carbonyl)methyl]-5-methylpyrrole-2-carboxylate (16). The pyrrole diethyl ester **15** (20.35 g) was dissolved in benzyl alcohol (200 mL). Once dissolution was complete, freshly cut sodium metal (0.49 g) was added and allowed to dissolve. The resulting mixture was heated at 120 °C under vacuum (45 mmHg) for 20 h. After removal of excess benzyl alcohol under vacuum, the resulting brown oil was chromatographed on either silica gel or neutral alumina (Brockmann Grade III, elution with dichloromethane), and the major fraction was collected and recrystallized from dichloromethane/petroleum ether, yielding 21.1 g (68%) of the title pyrrole: mp 90–91 °C (lit.[6a] mp 92–94 °C); NMR δ 7.71 (10 H, s, 2 × CH_2Ph); 6.30 (1 H, d, 4-H), 5.63, 5.48 (each 2 H, s, 2 × $PhCH_2$), 4.27 (2 H, s, $CH_2CO_2CH_2Ph$), 2.60 (3 H, s, CH_3).

Benzyl 3-[((Benzyloxy)carbonyl)methyl]-4-formyl-5-methylpyrrole-2-carboxylate (17). Phosphorus oxychloride (43.2 mL) was added dropwise to dimethylformamide (52.0 mL), and the mixture was kept at 20 °C for 15 min. A solution of the above dibenzyl ester pyrrole **16** (12.0 g) in dimethylformamide (100 mL) was slowly added while the mixture was kept at 5 °C with continuous stirring under moisture exclusion conditions. The resulting solution was heated at 75 °C for 1 h and cooled back to room temperature, and then a concentrated solution of sodium hydroxide was added to adjust the mixture to pH 8. After being heated to 75 °C for 15 min, the mixture was poured over ice–water (3 L) and filtered. The solid was collected and recrystallized from methanol/water to yield 20.64 g (66%) of the formylpyrrole as a powdery crystalline solid: mp 106.0–107.5 °C; NMR δ 10.01 (1 H, s, CHO), 7.40 (10 H, s, 2 × CH_2Ph), 5.29, 5.13 (each 2 H, s, 2 × CH_2Ph), 4.32 (2 H, s, $CH_2CO_2CH_2Ph$), 2.50 (3 H, s, CH_3).

Anal. Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found: C, 70.55; H, 5.40; N, 3.82.

Benzyl 3-(2-Hydroxyethyl)-4,5-dimethylpyrrole-2-carboxylate (18). The preceding formylpyrrole diester **17** (9.0 g) was dissolved in dry THF (100 mL), and the solution was cooled in an ice–water bath. Borane–THF complex (1 M, 190 mL) was added dropwise to the stirring solution of pyrrole under nitrogen while keeping the temperature below 10 °C. Once the addition was complete, the flask was removed from the ice bath and allowed to warm to room temperature while stirring for 38 h. The reaction was checked by analytical TLC and upon verification of the absence of starting material the remaining borane was neutralized by addition of methanol. The solvents were removed under vacuum and the resulting oily residue was chromatographed on silica gel eluting with 1% methanol/dichloromethane. The major band was collected and recrystallized from benzene/petroleum ether, yielding 5.1 g (81%) of the title pyrrole as a white fluffy solid: mp 82–83 °C; NMR δ 8.82 (1 H, br, NH), 7.3–7.5 (5 H, m, Ph), 5.28 (2 H, s, $PhCH_2$), 3.75, 3.01 (each 2 H, q, CH_2CH_2OH), 2.18, 1.94 (each 3 H, s, 2 × CH_3).

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 69.91; H, 6.99; N, 5.22.

Benzyl 3-(2-Chloroethyl)-4,5-dimethylpyrrole-2-carboxylate (19). Benzyl 3-(2-hydroxyethyl)-4,5-dimethylpyrrole-2-carboxylate (**18**) (3.3 g) was dissolved in dry dichloromethane (50 mL) containing pyridine (1.25 mL). Freshly distilled thionyl chloride (1.2 mL) was added dropwise to the reaction mixture, which was heated to reflux and allowed to stir under nitrogen for 3.5 h. Analytical TLC showed that all starting material had been consumed, so the reaction mixture was diluted with dichloromethane (250 mL), washed with 2 N aqueous hydrochloric acid (1 × 300 mL), saturated aqueous sodium bicarbonate (1 × 300 mL), water (1 × 300 mL), saturated aqueous sodium chloride, (1 × 300), and again with water (2 × 300 mL), and dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. The resulting solid brown residue was chromatographed on silica gel by eluting with dichloromethane, and the running band was collected and recrystallized from dichloromethane/*n*-hexane, yielding 2.3 g (65%) of the title pyrrole as a white chalky solid mp 108–110 °C; NMR δ 8.95 (1 H, br, NH), 7.35–7.50 (5 H, m, Ph), 5.32 (2 H, s, $PhCH_2$), 3.62, 3.20 (each 2 H, q, CH_2CH_2Cl), 3.20, 2.20, 1.98 (each 3 H, s, 2 × CH_3).

Anal. Calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found: C, 66.10; H, 6.27; N, 4.61.

3-(2-Chloroethyl)-2-formyl-4,5-dimethylpyrrole (12). Benzyl 3-(2-hydroxyethyl)-4,5-dimethylpyrrole-2-carboxylate (**18**) (2.3 g) was dissolved in THF (100 mL) followed by the addition of 10% palladium–carbon (298 mg) and triethylamine (4 drops). The resulting solution was hydrogenated at atmospheric pressure and room temperature until hydrogen uptake ceased. The catalyst was removed by filtration and the solvent removed under vacuum. The partially crystalline residue was dissolved in trifluoroacetic acid (15.0 mL) and allowed to stir at room temperature under nitrogen for 1 h. The mixture was then diluted with dichloromethane (200 mL) and washed with dilute aqueous sodium bicarbonate (1 × 250 mL) followed by water (3 × 250 mL), dried over anhydrous sodium sulfate, and then evaporated to a volume of 10–15 mL. This concentrated solution was added to the Vilsmeier complex prepared as follows: dimethylformamide (3.5 mL) was cooled in an ice–water bath, and phosphorus oxychloride (4.2 mL) was added dropwise. The solution started solidifying almost immediately and after 15 min at ice–water temperature and 1 h at room temperature the mixture had completely solidified. This pasty solid was dissolved in dichloromethane (20 mL) and allowed to cool in an ice–water bath. The concentrated eluants of the preceding decarboxylation reaction were added dropwise to the stirred solution of Vilsmeier complex, and after addition was complete the mixture was allowed to stir 1 h while warming up to room temperature. The solution was then heated to reflux for 1 h. After cooling back to room temperature, saturated aqueous sodium acetate (250 mL) was added and the solution allowed to stir overnight. After verification that the pH of the solution was approximately 8, the mixture was extracted with dichloromethane (300 mL), the combined organic layers were washed with water (2 × 300 mL) and dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. The resulting dark brown oil was chromatographed on silica gel (elution with dichloromethane) and the desired band was collected and recrystallized from dichloromethane/petroleum ether, yielding 808 mg (55%) of the formylpyrrole: mp 100–102 °C; NMR δ 10.05 (1 H, br, NH), 9.45 (1 H, s, CHO), 3.62, 3.14 (each 2 H, t, CH_2CH_2Cl), 2.27, 1.97 (each 3 H, s, 2 × CH_3).

Anal. Calcd for $C_9H_{12}ClNO$: C, 58.22; H, 6.52; N, 7.54. Found: C, 58.28; H, 6.52; N, 7.40.

2,7-Bis(2-chloroethyl)-4,5-bis[2-(methoxycarbonyl)ethyl]-1,1′,3,6,8,8′-hexamethyl-a,c-biladiene Dihydrobromide (13). Pyrromethane 8[9] (914.5 mg) was dissolved in tetrahydrofuran (50 mL), and then 10% palladium–carbon (10 mg) and triethylamine (4 drops) were added. Hydrogenation was carried out at atmospheric pressure and room temperature until hydrogen uptake ceased. The catalyst was removed by filtration and evaporation of the solvent at reduced pressure provided 614 mg (95%) of the pyrromethane diacid as a white powdery solid. The pyrromethane diacid was then dissolved in trifluoroacetic acid (6.3 mL) causing the visible evolution of CO_2. When dissolution of the solid was complete and the evolution of gas had ceased, formylpyrrole **12** (526 mg) dissolved in methanol (50 mL) was added followed by a solution of 33% hydrobromic acid/acetic acid (6.8 mL). The solution immediately turned red and was stirred

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at room temperature for an additional 45 min. Diethyl ether (100 mL) was added dropwise slowly to drive the a,c-biladiene salt out of solution. After refrigeration overnight, the solution was filtered and the resultant solid washed with cold ether providing 978 mg (82%) of the title compound as a reddish powdery solid: mp >300 °C; vis λ_{max} 448 nm (ϵ 55 000), 524 (111 000); NMR δ 13.56, 13.46 (each 2 H, br, NH), 7.26, 7.13 (each, 1 H, s, methine H), 5.25 (2 H, br s, methine CH_2), 3.67 (8 H, m, 2 × CH_2CH_2Cl and 2 × $CH_2CH_2CO_2$), 3.45 (6 H, s, 2 × OCH_3), 3.12 (4 H, m, 2 × CH_2CO_2), 2.82 (4 H, m, 2 × CH_2Cl), 2.71, 2.26, 2.10 (each 6 H, s, CH_3).

Anal. Calcd for $C_{37}H_{48}Br_2Cl_2N_4O_4$: C, 52.68; H, 5.74; N, 6.64. Found: C, 52.50; H, 5.62; N, 6.55.

1,8-Bis(2-chloroethyl)-4,5-bis[2-(methoxycarbonyl)ethyl]-1′,2,3,6,7,8′-hexamethyl-a,c-biladiene Dihydrobromide (10). The title compound was prepared in 55% yield (2.54 g) by the same procedure outlined above, except that formylpyrrole **9** (1.02 g) was used in place of formylpyrrole **12**. The product had mp >300 °C: vis λ_{max} 448 nm (ϵ 57 500), 524 (112 500); NMR δ 13.46, 13.42 (each 2 H, br, NH), 7.25, 7.14 (each 1 H, s, methine H), 5.21 (2 H, br s, methine CH_2), 3.70 (8 H, m, 2 × CH_2CH_2Cl and 2 × $CH_2CH_2CO_2$), 3.42 (6 H, s, 2 × OCH_3), 3.10 (4 H, m, 2 × CH_2CO_2), 2.85 (4 H, m, 2 × CH_2Cl), 2.70, 2.22, 2.13 (each 6 H, s, CH_3).

Anal. Calcd for $C_{37}H_{48}Br_2Cl_2N_4O_4$: C, 52.68; H, 5.74; N, 6.64. Found: C, 52.61; H, 5.72; N, 6.65.

1,4-Bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-2,3,5,8-tetramethylporphyrin, (14). The bis(2-chloroethyl)-a,c-biladiene **13** (1.1 g) was added to dry DMF (55 mL) containing copper(II) chloride (4.48 g) stirring at 155 °C under nitrogen and allowed to react for 4 min. The solution was allowed to cool slightly and poured into water (230 mL) containing pyridine (35 mL). The mixture was extracted with dichloromethane (4 × 200 mL), washed with water (5 × 750 mL), and dried over anhydrous sodium sulfate and the solvent removed under vacuum. The resulting residue was dissolved in trifluoroacetic acid (50 mL) containing concentrated sulfuric acid (5 mL) and allowed to stir at room temperature for 1 h before being diluted with dichloromethane (300 mL), washed with water (3 × 250 mL), and dried over anhydrous sodium sulfate. The compound was then treated briefly with excess ethereal alcoholic diazomethane before the solvents were removed under vacuum. Chromatography on neutral alumina (Brockmann Grade III, elution with dichloromethane) followed by recrystallization from dichloromethane/methanol gave the title porphyrin in 57% yield (498 mg): mp 196–198 °C (lit.[6a] mp 201–203 °C); vis λ_{max} 402 nm (ϵ 133 000), 498 (15 370), 532 (10 060), 568 (6910), 622 (4730); NMR δ 10.11, 10.02, (2 H, each s, *meso* H), 9.96 (2 H, s, 2 × *meso* H), 4.40 (8 H, m, 2 × CH_2CH_2Cl and 2 × $CH_2CH_2CO_2$), 4.25 (4 H, m, 2 × CH_2CO_2), 3.72–3.60 (18 H, m, CO_2CH_3 and CH_3), 3.28 (4 H, m, 2 × CH_2Cl), −3.92 (2 H, s, NH).

Anal. Calcd for $C_{36}H_{40}Cl_2N_4O_4$: C, 65.16; H, 6.08; N, 8.44. Found: C, 64.98; H, 6.05; N, 8.29.

2,3-Bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,4,5,8-tetramethylporphyrin (11). The title compound was prepared from the bis(2-chloroethyl)-a,c-biladiene **10** (1.1 g) in a manner analogous to that described above, in a yield of 34% (299 mg). The product had mp 248–250 °C: vis λ_{max} 400 nm (ϵ 152 000), 502 (14 000), 534 (9100), 574 (6000), 622 (2700); NMR δ 9.95–9.82 (4 H, br s, *meso* H), 4.40–4.10 (8 H, m, 2 × CH_2CH_2Cl and 2 × $CH_2CH_2CO_2$), 3.56 (6 H, s, 2 × OCH_3), 3.50–3.35 (12 H, m, CH_3), 3.30–3.00 (8 H, m, 2 × CH_2Cl and 2 × CH_2CO_2).

Anal. Calcd for $C_{36}H_{40}Cl_2N_4O_4$: C, 65.16; H, 6.08; N, 8.44. Found: C, 64.94; H, 5.89; N, 8.48.

6,7-Bis(2-methoxycarbonylethyl)-2,3,5,8-tetramethyl-1,4-divinylporphyrin (7), "Protoporphyrin XIII Dimethyl Ester". Bis(2-chloroethyl)porphyrin **14** (230 mg) was dissolved in deoxygenated, refluxing pyridine (90 mL). Water (17 mL) and 3% aqueous sodium hydroxide (20 mL) were added, and the mixture was refluxed for 2.5 h. The solution was cooled slightly and 25% acetic acid (aqueous) (20 mL) was added. After evaporation of the solvent, water (70 mL) was added to suspend the solid residue, which was collected and washed with additional water. The resulting residue was dissolved in 5% concentrated sulfuric acid/methanol (35 mL) and allowed to stand overnight. The solution was diluted with dichloromethane (175 mL), washed with water (3 × 200 mL), and dried over anhydrous sodium sulfate and the solvent removed under vacuum. Chromatography on neutral alumina (Brockmann Grade III, elution with dichloromethane) and recrystallization from dichloromethane/methanol provided the title compound in 55% yield (113 mg): mp 201–204 °C (lit.[6a] mp 208–210 °C); vis λ_{max} 402 nm (ϵ 140 000), 504 (15 500), 540 (12 530), 576 (7360), 630 (5570); NMR δ 10.11 (2 H, s, 2 × *meso* H), 10.01, 9.98 (2 H, each s, *meso* H), 8.24 (2 H, m, 2 × α-vinyl *CH*), 6.35 (2 H, d, 2 × trans-β-vinyl CH), 6.19 (2 H, d, cis-β-vinyl CH), 4.35 (4 H, m, 2 × $CH_2CH_2CO_2$), 3.70–3.58 (18 H, m, CO_2CH_3 and CH_3), 3.22 (4 H, m, CH_2CO_2), −3.84 (2 H, s, NH).

Anal. Calcd for $C_{36}H_{38}N_4O_4$: C, 73.20; H, 6.48; N, 9.48. Found: C, 73.22; H, 6.44; N, 9.48.

6,7-Bis[2-(methoxycarbonyl)ethyl]-1,4,5,8-tetramethyl-2,3-divinylporphyrin (6), "Protoporphyrin III Dimethyl Ester". The title compound was prepared from the corresponding bis(2-chloroethyl)porphyrin **11** (252 mg) as described above, in a yield of 74% (168 mg): mp 260–263 °C (lit.[6a] mp 262–264 °C); vis λ_{max} 406 nm (ϵ 143 000), 504 (16 000), 540 (13 000), 576 (7500), 630 (6000); NMR δ 9.86 (2 H, s, *meso* H), 9.76, 9.58 (each 1 H, s *meso* H), 8.20 (2 H, m, 2 × α-vinyl CH), 6.18 (4 H, m, 2 × β-vinyl CH), 4.22, 3.12 (8 H, each t, CH_2CH_2), 3.62 (6 H, s, OCH_3), 3.43, 3.35 (12 H, each s, 4 × CH_3), −3.80 (2 H, br, 2 × NH).

Anal. Calcd for $C_{36}H_{38}N_4O_4$: C, 73.20; H, 6.48; N, 9.48. Found: C, 73.02; H, 6.31; N, 9.24.

Typical Exchange Reaction. 1,3-Bis(dideuteriomethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-5,8-dimethyl-2,4-divinylporphyrin. The following reaction is typical of those performed on the various protoporphyrin isomers. PP-IX DME (**1**) (160.7 mg) was completely dissolved in dry dimethylformamide (80 mL) before the addition of sodium methoxide (73.2 mg) in methanol-*d* (15 mL). The homogeneous solution was allowed to stir in the dark at room temperature for 30 days. The solution was then diluted with dichloromethane (200 mL), washed with 2 N aqueous HCl (1 × 250 mL) and water (3 × 250 mL), and dried (Na_2SO_4) and the solvent removed under vacuum. After brief treatment with excess ethereal alcoholic diazomethane, the residue was chromatographed on neutral alumina (Brockmann Grade III, elution with dichloromethane) and recrystallized from dichloromethane/methanol to provide the title compound in 42% yield (67.3 mg): mp 223–225 °C (lit.[10] undeuterated mp 224–226 °C); NMR, same as PP-IX DME (**1**) except for the partial disappearance of the 1- and 3-methyl proton resonances (see text). Similar (40–50%) yields of recovered deuterated porphyrins were also obtained from exchange of PP-III DME (**6**) and PP-XIII DME (**7**).

Typical Iron Insertion. Dry acetonitrile (25 mL) was refluxed under nitrogen for 1 h and then the temperature was allowed to drop to 60 °C. Iron(II) chloride hydrate (160 mg) was added, followed by dropwise addition of a solution of PP-IX DME (**1**) (100 mg) in deoxygenated chloroform (10 mL). The mixture was allowed to continue stirring an additional 10 min after the addition was complete, then diluted with dichloromethane (125 mL), washed with 2 N aqueous HCl (1 × 100 mL) and water (3 × 100 mL), and dried over anhydrous sodium sulfate, and the solvent removed under vacuum. Chromatography on silica gel plates eluting with 5% methanol/dichloromethane followed by recrystallization from dichloromethane/*n*-heptane provided pure protohemin IX dimethyl ester, based on comparison by TLC and NMR spectroscopy (as the dicyanoferrihemin), in a yield of 90% (104 mg), mp <300 °C.

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Registry No. **1**, 5522-66-7; **6**, 7034-33-5; **7**, 59969-40-3; **8**, 992-36-9; **9**, 87434-71-7; **10**, 99885-15-1; **11**, 63089-20-3; **12**, 88055-46-3; **13**, 99885-14-0; **14**, 63089-17-8; **15**, 53700-88-2; **16**, 62562-74-7; **17**, 87308-15-4; **18**, 62562-76-9; **19**, 62562-77-0; $PhCH_2OH$, 100-51-6; $FeCl_2$, 7758-94-3; bis[3-[2-(methoxycarbonyl)ethyl]-4-methyl-5-carboxypyrrol-2-yl]methane, 809-27-8; protohemin IX dimethyl ester, 15741-03-4.

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