(m, 4); IR (neat) 3440, 2920, 1290, 1100, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 166 (M - 1, 8.07), 151 (5.80), 134 (4.54), 81 (8.11), 61 (13.8), 43 (base).

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Rothemund and Adler–Longo Reactions Revisited: Synthesis of Tetraphenylporphyrins under Equilibrium Conditions

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We present a new synthetic strategy for preparing tetraphenylporphyrins that should greatly expand synthetic entries into porphyrin containing model systems. Pyrrole and the desired benzaldehyde react reversibly at room temperature with trace acid catalysis to form the cyclic tetraphenylporphyrinogen at thermodynamic equilibrium. An oxidant is then added to irreversibly convert the porphyrinogen to the porphyrin. The greater stability of the cyclic porphyrinogen over the open-chain polypyrrylmethanes occurs when the reaction is performed at moderate dilution (10^{-2} M). The reaction at high dilution or high concentration affords a negligible yield of the cyclic porphyrinogen. Porphyrinogen exchange reactions provide proof of equilibrium. This methodology is complementary to the Adler–Longo procedure, allowing small quantities of porphyrins to be prepared from sensitive aldehydes in 30–40% yield without difficult purification problems. This methodology is also extended to the preparation of *meso*-tetraalkylporphyrins and one hybrid porphyrin containing both aryl and alkyl substituents. The mild reaction conditions and convenience of this method permit consideration of new design strategies in preparing complex porphyrins.

The porphyrins lie at the focal point formed from divergent fields of research, including solar energy conversion, catalysis, spectroscopy, and the development of organic metals. A constant theme among these diverse areas is the creation of structured assemblies containing porphyrins located in well-defined chemical environments. The precise sculpturing of the porphyrin environment requires the synthesis of porphyrin derivatives carrying functional groups attached at the periphery of the macrocycle. The *meso*-tetraphenylporphyrins offer attractive features in this context and have been used in a wide variety of model studies.[1,2]

Tetraphenylporphyrin was first synthesized 50 years ago by Rothemund, who caused benzaldehyde and pyrrole in pyridine to react in a sealed bomb at 150 °C for 24 h.[3] The yields were low and the conditions so severe that few substituted benzaldehydes could be converted to the corresponding porphyrin. The Rothemund conditions were obviously based on the premise that the porphyrin is aromatic, aromatic compounds are stable, and therefore merely cracking the initially formed adducts of benzaldehyde and pyrrole at high temperatures should give the porphyrin. Adler and Longo modified the Rothemund reaction by allowing benzaldehyde and pyrrole to react for 30 min in refluxing propionic acid (141 °C) open to the air.[4] These comparatively milder reaction conditions have allowed a wider selection of substituted benzaldehydes to be converted to the corresponding porphyrins in yields of up to 20%.[5-7] The reaction is also amenable to large-scale syntheses and multigram quantities of many porphyrins have been prepared.

Nonetheless, the Adler–Longo methodology is beset with certain vexing problems. First, the harsh reaction conditions result in complete failure with benzaldehydes bearing sensitive functional groups. Second, the high level of tar produced presents purification problems in many instances, especially with those porphyrins that do not crystallize or precipitate at the end of the reaction. Third, the batch-to-batch reproducibility of the reaction is often rather poor.

The current synthetic needs of porphyrin chemistry are thus only partially satisfied by this methodology. Of at least comparable necessity is the ability to prepare small quantities of porphyrins from sensitive aldehydes in high yield without encountering difficult purification problems. This paper describes in detail a procedure that achieves the latter goals and is therefore complementary in nature to the Adler–Longo procedure.[8]

The development of our procedure began from a vantage point fundamentally different from that of Rothemund, Adler, and Longo. Our strategy, based on studies of

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(2) Bogatskii, A. V.; Zhilina, Z. I. *Russ. Chem. Rev.* **1982**, *51*, 592.

(3) Rothemund, P. *J. Am. Chem. Soc.* **1936**, *58*, 625. Rothemund, P. *J. Am. Chem. Soc.* **1939**, *61*, 2912.

(4) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476. Kim, J. B.; Adler, A. D.; Longo, F. R. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 1, pp 85–100.

(5) For reports of yields greater than 20% in the Adler–Longo procedure, see ref 6 and 7. The frequent absence of yield data in the tetraphenylporphyrin literature suggests that for a variety of benzaldehydes the actual yields are in fact much less than 20%.

(6) Dolphin, D. *J. Heterocycl. Chem.* **1970**, *7*, 275.

(7) Adler, A.; Longo, F. R.; Shergalis, W. *J. Am. Chem. Soc.* **1964**, *86*, 3145.

(8) Presented in part at the 20th Meeting of the American Chemical Society, Great Lakes Region, Milwaukee, June, 1986, and the 192nd National Meeting of the American Chemical Society, Anaheim, CA, Sept. 1986. Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C. *Tetrahedron Lett.* **1986**, *27*, 4969.

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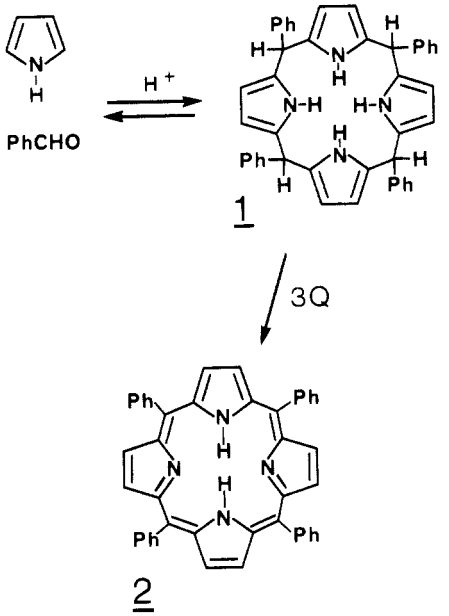

Figure 1. Pyrrole and benzaldehyde react reversibly at room temperature to form an equilibrium distribution of tetraphenylporphyrinogen (1) and polypyrrylmethanes (not shown). The addition of an oxidant irreversibly converts porphyrinogen (1) to the aromatic porphyrin (2).

equilibrium cyclizations[9] and biomimetic studies of porphyrin biosynthesis,[10] is centered around the following hypotheses. First, tetraphenylporphyrinogen 1 should be the thermodynamically favored product when benzaldehyde and pyrrole are condensed under appropriate conditions (Figure 1). Reaction conditions that facilitate the attainment of equilibria prior to oxidation should therefore favor high yields of the porphyrin. Second, benzaldehyde and pyrrole are reactive molecules and high temperatures are not necessary for their reaction. Third and of equal importance, synthetic conditions sufficiently mild for equilibrium to be achieved should also be compatible with an unprecedented variety of substituted benzaldehydes, thereby allowing the corresponding porphyrins to be obtained in good yield. Although the intermediacy of porphyrinogens in the synthesis and biosynthesis of porphyrins has been recognized for many years,[6,10,11] knowledge of the thermodynamic stability of porphyrinogen structures and their ease of formation has not been widely exploited in the design of synthetic strategies for preparing porphyrins.

These hypotheses generally appear to be valid. The gentle room-temperature reaction conditions of our procedure are compatible with a wide scope of substituted benzaldehydes, permitting the corresponding substituted porphyrins to be routinely prepared in yields of 30–40%. *The appropriate sphere of application of our new procedure is not in the preparation of tetraphenylporphyrin in high yield but rather in the synthesis of those substituted porphyrins that are inaccessible via alternate routes.* The detailed synthetic conditions, however, have been delineated by using the synthesis of tetraphenylporphyrin as a model.

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(10) Mauzerall, D. *J. Am. Chem. Soc.* **1960**, *82*, 2601. Mauzerall, D. *J. Am. Chem. Soc.* **1960**, *82*, 2605. Mauzerall, D. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. II, Part B, pp 91–101.
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Table I. Reaction Conditions and Porphyrin Yields

oxidant	water scavenger	catalyst[a]	yield (%)
p-chloranil	TEOA[b]	BF_3	50–55
p-chloranil		BF_3 or TFA	45–50
DDQ	TEOA	BF_3	45–50
DDQ		BF_3 or TFA	35–40

[a] Acid catalysts and concentrations were BF_3 (1 mM) and TFA (10 mM). Yields were obtained by adding the oxidant after 1 h of reaction. Porphyrin yield refers to *meso*-tetraphenylporphyrin. [b] Triethyl orthoacetate (TEOA) is not effective with TFA catalysis.

Results

Synthetic Method. The maximum yield of tetraphenylporphyrin is obtained when a solution of dry methylene chloride under N_2 is charged with benzaldehyde, pyrrole, and triethyl orthoacetate at equimolar concentrations of 10^{-2} M. To this is added an aliquot of boron trifluoride etherate (10^{-3} M), and the reaction is allowed to proceed at room temperature. After 1 h the oxidant 2,3,5,6-tetrachlorobenzoquinone (*p*-chloranil) is added and the solution is refluxed (39 °C) for 1 h. Removal of aliquots and analysis by absorption spectroscopy indicate the tetraphenylporphyrin to be present in yields which typically range around 50%. Evaporation of the solvent followed by flash chromatography affords tetraphenylporphyrin that is virtually pure in yields of 45–50%. The yields scale linearly throughout the 25 mL to 1 L range.

The yield of porphyrin is dependent on a variety of factors, including choice of oxidant and acid catalyst, duration of condensation period, concentrations of acid, pyrrole, and benzaldehyde, and the presence of water in the solvent. These factors have been systematically examined by performing trial condensations from which aliquots are removed periodically and oxidized at room temperature with excess 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[12] and the yield of porphyrin is determined by absorption spectroscopy.

The oxidation of porphyrinogen to porphyrin can be performed with either *p*-chloranil or DDQ (Table I). The addition of DDQ at room temperature gives a nearly instantaneous conversion of porphyrinogen to porphyrin and of pyrrylmethanes to pyrrylmethenes. *p*-Chloranil is a much milder oxidant, requires an exposure time of 1 h for complete reaction, and affords yields uniformly higher than those obtained with DDQ. Neutralization of the acid catalyst (by addition of K_2CO_3 or triethylamine) prior to the addition of *p*-chloranil caused no effect on the porphyrin yield. *p*-Chloranil was used in preparative work when a maximal yield was the chief objective. DDQ was employed to provide rapid quenching during exploratory studies of reaction conditions, and all reported yield data were obtained with DDQ unless noted otherwise.

The optimal duration of the condensation period was determined by reacting benzaldehyde and pyrrole at equimolar concentrations of 10^{-2} M. Consistent yields of tetraphenylporphyrin in the 35–40% range were obtained with several acid catalysts, including BF_3 (10^{-3} M, 1 h), trifluoroacetic acid (TFA, 1–2.5 × 10^{-2} M, 1-2 h), and BCl_3 (3 × 10^{-3} M, 30 min). The rate of porphyrinogen formation is proportional to the acid concentration. Higher or lower acid concentrations significantly change the rate of reaction but result in only slightly altered yields. For example, BF_3 at 3.3 × 10^{-3} M results in a 30% yield after 40 min, but at 3.3 × 10^{-4} M the yield is 35% after 75 min. A broader range of reaction conditions that have been explored are listed in the Experimental Section.

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Table II. Dipyrrylmethene Formation

benzaldehyde and pyrrole concn (M)	% yield of dipyrrylmethenes[a]	
	BF_3 (1 mM)	TFA (10 mM)
10^{-3}	0.36	6.5
10^{-2}	0.25	3.9
10^{-1}	0.09	0.38

[a] Yield of dipyrrylmethenes after 1 h was determined by the absorbance of the unquenched reaction (λ_{max} 483, ϵ 60 000 M^{-1} cm^{-1}).[13]

The high yield of porphyrinogen is contingent on minimizing oxidation until the condensing system closely approaches thermodynamic equilibrium. Oxidative formation of a dipyrrylmethene moiety within a polypyrrylmethane chain can produce chain configurations unable to cyclize. The formation of dipyrrylmethenes in yields of 0.25% (BF_3) and 3.9% (TFA) after 1 h results in pale orange and brilliant burgundy solutions, respectively (Table II). The dipyrrylmethenes were identified by their characteristic absorption spectra and discharge of color upon exposure to $NaBH_4$.[13] The colored solutions were not due to formation of the polymer "pyrrole red"[14] because pyrrole alone subjected to these acid conditions resulted in colorless solutions. The disparity in oxidation in the BF_3- and TFA-catalyzed reactions is also reflected in the adventitious formation of tetraphenylporphyrin, though the total amount is less than 0.01% with BF_3 and around 0.1% with TFA catalysis.

The presence of water in the solution causes a shift in the polypyrrylmethane chain distribution at equilibrium. The addition of as little as 0.18 μL of H_2O per mL of CH_2Cl_2 after 1 h of reaction displaces the equilibrium and causes a one-third decline in yield, while the addition of larger quantities (5 μL per mL of CH_2Cl_2) buffers the acid and terminates the reaction. Triethyl orthoacetate was found to be moderately effective as a water scavenger, since the addition of both water (10^{-2} M) and triethyl orthoacetate (10^{-2} M) left the porphyrin yield unchanged. Attempts were only partially successful to exploit the dehydrating effect of triethyl orthoacetate and increase the extent of benzaldehyde–pyrrole bond formation with the reaction performed in dilute solution (Table I). When triethyl orthoacetate was added after 1 h to the reaction at 10^{-3} M, the yield of porphyrin increased by 1.5-fold. The full magnitude of these effects was observed when a booster of BF_3 (10^{-3} M) was added, indicating that the effectiveness of the acid catalyst diminishes as the reaction proceeds. The effects of triethyl orthoacetate were not transferrable to the TFA-catalyzed reaction, which is quenched by the addition of both ethanol and water.

Equilibrium Studies. The concentrations of benzaldehyde and pyrrole are critical determinants of the ultimate yield of porphyrin. The maximum yield of porphyrin is observed at equimolar benzaldehyde and pyrrole concentrations of 10^{-2} M (Figure 2). The yield declines markedly at concentrations 10-fold higher and 10-fold lower. High dilution in this case does not afford increased yields of the cyclic vs. polymeric products. Though the yield at 10^{-3} M exhibited the greatest experimental variability, the yield generally fell within the range of 10–20%. At each concentration the reported yield is believed to closely approximate the true equilibrium yield.

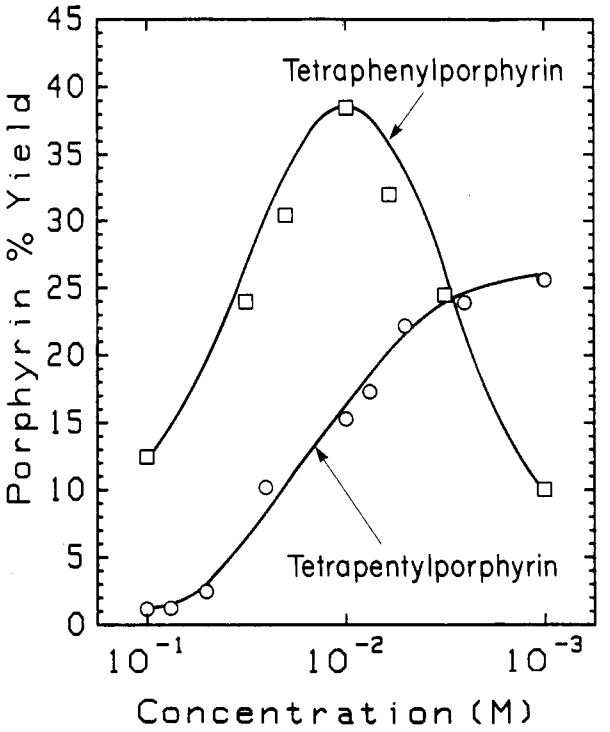

Figure 2. Yields were obtained with DDQ oxidation. The tetraphenylporphyrin curve is the average from both BF_3 and TFA catalysis. The tetrapentylporphryin yield was obtained with TFA only.

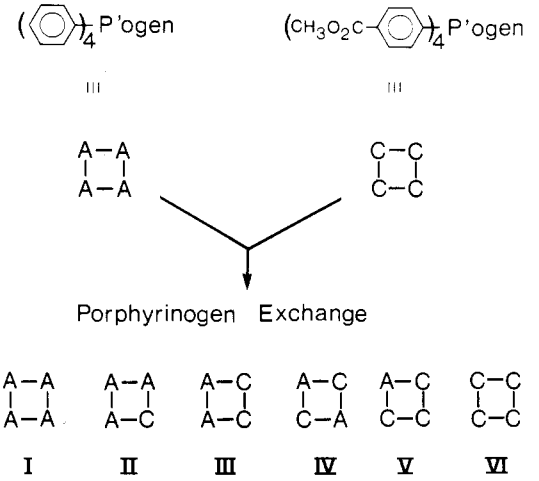

Figure 3. Six porphyrin products observed after mixing preformed solutions of tetraphenylporphyrinogen and tetrakis[4-(methoxycarbonyl)phenyl]porphyrinogen. Porphyrins II–V constitute the new products formed via exchange (see Table III). (P'ogen ≡ porphyrinogen).

Gel permeation chromatography of the crude oxidized reaction mixtures showed a broad distribution of polypyrrylmethene species across a molecular weight range of 100–5000 amu with the upper mass range defined by monodisperse polystyrene mass markers. The ratio of the integrated areas given by the components preceding the porphyrin to those eluting after the porphyrin for each sample is (given as components before:components after, reaction concentration) 90:10, 10^{-1} M; 63:37, 10^{-2} M; 50:50, 10^{-3} M, showing an unmistakable shift to higher molecular weight as the reaction concentration is increased.

The reversibility of porphyrinogen formation was examined through a simple exchange experiment (Figure 3). Simultaneous reactions of benzaldehyde and pyrrole, and methyl 4-formylbenzoate and pyrrole, were allowed to

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(14) Schofield, K. In *Hetero-Aromatic Nitrogen Compounds*; Plenum Press: New York, 1967; p 87.

Table III. Porphyrinogen Distribution upon Exchange (see Figure 3)[a]

	% yield of porphyrinogens					
	I	II	III	IV	V	VI
before exchange	42.0					48.8
after exchange	7.3	24.6	23.2	11.6	20.5	12.8
mixed condensation	6.8	22.4	24.6	13.0	25.8	7.4
statistical expectation	6.25	25	25	12.5	25	6.25

[a] I and VI are the homosubstituted tetraphenylporphyrinogen and tetrakis[4-(methoxycarbonyl)phenyl]porphyrinogen, respectively. II–V are hybrid porphyrinogens composed of both phenyl and 4-(methoxycarbonyl)phenyl substituents. The porphyrinogen distributions were determined by HPLC of the oxidized solutions (see Experimental Section). "After exchange" is the distribution obtained 2 h after combining *preformed* and *separate* solutions of the porphyrinogens I and VI. "Mixed condensation" is the porphyrinogen distribution obtained when equimolar benzaldehyde and methyl 4-formylbenzoate were *simultaneously* condensed with a stoichiometric amount of pyrrole. "Statistical expectation" derives from the ratio of total permutations of the respective isomers. The latter assumes a 1:1 ratio of aldehydes and therefore an equal probability for incorporation of each aldehyde. The yields "before exchange" are actual yields. All other yields in each row are relative percent yields.

proceed in separate vessels. After 1 h only residual amounts of benzaldehyde and methyl 4-formylbenzoate remained, and the yield of porphyrin corresponded to at least a 42% yield of porphyrinogen in the respective reactions. The solutions were then combined and allowed to react further under acid catalysis for 2 h, followed by oxidation and analysis by TLC and HPLC. The distribution of porphyrin products consisted of small amounts of the two parent homosubstituted porphyrins and a larger amount of the hybrid porphyrins (Table III). The profile of porphyrins resembles that obtained when the condensation is performed with an equimolar mixture of the two aldehydes. The occurrence of exchange illustrates the reversibility of the reactions and the drive toward equilibrium.

The exchange reaction was also examined with the combinations of *p*-nitrobenzaldehyde and *p*-tolualdehyde (reaction 2), *p*-cyanobenzaldehyde and benzaldehyde (reaction 3), and *p*-chlorobenzaldehyde and methyl 4-formylbenzoate (reaction 4). In each case porphyrinogen exchange occurred. Visual inspection of thin layer chromatograms provided an estimate of the extent of exchange. In both reactions 2 and 3, four new porphyrin products were formed and the ratio of new porphyrins to starting porphyrins was 2:1. In reaction 4 only three new porphyrins were observed and the ratio of new porphyrins to starting porphyrins was 1:2.

Synthetic Applications. Over 30 substituted porphyrins have been prepared in a straightforward manner in typical yields of 30–40%. The chlorin content of the crude reaction mixtures averaged around 6% within a range of less than 1% to as much as 12%. The yields after chromatographic workup were generally 60–95% of the spectroscopically determined yield. The porphyrins shown in Table IV were fully characterized by NMR, IR, and UV–vis spectroscopy and ^{252}Cf fission fragment mass spectrometry.[15]

This synthetic methodology was then extended to the preparation of *meso*-tetraalkylporphyrins. Hexanal, undecylic aldehyde, and hydrocinnamaldehyde were converted to *meso*-tetrapentylporphyrin (**24**), *meso*-tetradecylporphyrin (**25**), and *meso*-tetraphenethylporphyrin (**26**), respectively. Further experimentation, however, unveiled substantial differences between the course of reaction of aromatic and alkyl aldehydes. First, the tetraalkylporphyrin yield increases steadily upon reactant dilution and levels off at 10^{-3} M (Figure 2). Second, the exchange reaction performed between the phenethylporphyrinogen and the decylporphyrinogen failed completely. The addition of three times the normal amount of acid still produced hybrid porphyrin products accounting for less than 3% of the total porphyrin yield. These results indicate that the alkyl aldehyde–pyrrole condensation is irreversible under these conditions, and the yield of tetraalkylporphyrins is thus under kinetic rather than thermodynamic control.

Table IV. Synthesis of Complex Porphyrins

		% yield[a]	
porphyrin	*meso*-phenyl substituent	BF_3	TFA
3	4-$O(CH_2)_7CH_3$	4 (9)[b]	30
4	4-$OCH_2C_6H_5$	8 (24)[b]	40
5	4-$O(CH_2)_2OH$	8 (17)[c]	14
6	4-$O(CH_2)_2Cl$	11	36
7	4-CN	38	18
8	4-$CO_2CH_2COC_6H_5$	36	14
9	3-$CO_2CH_2COC_6H_5$	37	23
10		34	35
11		14	33
12		0[d]	21
13	4-$OCH_2CH{=}CH_2$	34	10
14	4-$CO_2(CH_2)_3CH_3$	41	17
15	4-CO_2CH_3	41	26

[a] Benzaldehyde and pyrrole concentrations were 1.5×10^{-2} M, and oxidation was performed with DDQ. Yields shown were obtained without triethyl orthoacetate (TEOA) unless noted otherwise. [b] BF_3 and TEOA (10^{-2} M each). [c] TEOA (10^{-2} M). [d] Gave 30% hydrolysis to terephthalaldehyde.

The synthetic reaction conditions for preparing tetraalkylporphyrins were explored by using the preparation of tetrapentylporphyrin from hexanal as an exemplary case. Using DDQ as an oxidant gave only slightly higher yields at reflux (39 °C) than at room temperature. The optimal concentrations of TFA and BF_3 were found to be 5×10^{-3} M and 10^{-3} M, respectively, with peak yields attained in 30–90 min in each case. The yield of dipyrrylmethenes (λ_{max} 500 nm, assuming ϵ 60 000 M^{-1} cm^{-1}) remained below 1% with both acids throughout the 10^{-1} to 10^{-3} M aldehyde–pyrrole concentration range. Omission experiments demonstrated further the mildness of the reaction conditions. Exposure of hexanal to acid for 1 h followed by the addition of pyrrole led to the same yield as occurred when the two reagents were added simultaneously, indicating the absence of decomposition under these conditions.

One hybrid porphyrin bearing three *meso*-alkyl and one *meso*-aryl substituents was prepared via a simultaneous mixed condensation of undecylic aldehyde and phenacyl 4-formylbenzoate in a 3:1 ratio. The desired 5,10,15-tridecyl-20-[4-((phenacyloxy)carbonyl)phenyl]porphyrin (**27**) was isolated after chromatography in 14.2% overall yield.

Discussion

Exchange and Equilibrium. High yields of porphyrins are obtained when the formation of tetraphenylporphyrinogen is allowed to reach equilibrium prior to oxidative quenching. The thermodynamic stability of tetraphenylporphyrinogen and the reversibility of bond

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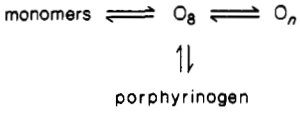
Scheme I



formation are unequivocally demonstrated by the exchange experiments. When solutions of tetraphenylporphyrinogen and tetrakis[4-(methoxycarbonyl)phenyl]porphyrinogen were performed in separate vessels and then combined in the presence of acid, the dynamic nature of the equilibrium state was easily observed (Figure 3). The distribution of porphyrin products after 2 h consisted predominantly of the hybrid porphyrins containing both phenyl and 4-(methoxycarbonyl)phenyl groups (Table III). The distribution of scrambled products deviated only slightly from statistical expectations for a 1:1 binary condensation. The distribution observed upon exchange was almost identical with that obtained when a simultaneous mixed condensation of methyl 4-formylbenzoate and benzaldehyde with pyrrole was performed. The high yield of the separate porphyrinogens and the low yield of unreacted aldehyde prior to mixing, and the high extent of exchange after mixing, combine to rule out residual unreacted aldehyde as the sole source of hybrid porphyrin products. The product distribution obtained after mixing can only result from iteration of the process of porphyrinogen ring opening, depolymerization, repolymerization with uptake of the alternate aldehyde, and ring closure to reform the porphyrinogen.

The exchange phenomenon was observed with each aromatic aldehyde examined. The selection criteria for aldehydes to study in exchange reactions were that each give comparable yields of porphyrin and that the hybrid porphyrins formed in mixed condensations be easily separable via chromatography for quantification purposes.

One striking feature in the tetraphenylporphyrin reaction is the decline in yield upon dilution (Figure 2). The observed decrease in yield upon dilution is in sharp contrast with the normally observed behavior of high dilution giving an increased yield of cyclic vs. polymeric components.[16] "High dilution" represents a viable methodology for irreversible intramolecular cyclizations, exemplified by the formation of lactones from ω-haloalkanoic acids. High dilution, however, does not necessarily afford higher yields of the desired cyclic compound when the cyclization step is preceded by a reversible association step.[17] Though dilution to 10^{-3} M favors cyclization in the porphyrinogen reaction, it also deters the polymerization process necessary to arrive at the octamer stage. Formation of the octamer is a prerequisite for cyclization to the porphyrinogen.

The observed concentration dependence can be better understood by consideration of the overall anatomy of the porphyrinogen reaction (Scheme I). The benzaldehyde and pyrrole monomers undergo indefinite self-association to form a distribution of pyrrylmethane oligomers having n components (O_n), where n is the total number of benzaldehyde and pyrrole units in each chain. All reactions are assumed to be reversible and the concentrations of all components are thereby coupled via mass action at equilibrium. The degree of polymerization is proportional to the starting concentration of monomers.[18] The octamer (O_8, containing 4 benzaldehyde and 4 pyrrole components) can cyclize to form the porphyrinogen, and the yield of porphyrinogen is therefore linked to the yield of the octamer. A change in the starting monomer concentrations changes the equilibrium distribution profile of oligomers, and the yield of porphyrinogen is altered through its dependence on the equilibrium octamer concentration.

An appealing explanation of the yield–concentration curve based on this reaction format is that at 10^{-2} M the competing cyclization and polymerization processes are in balance. At high concentration (10^{-1} M) the oligomer equilibrium distribution is shifted predominantly to higher molecular weight components. At low concentration (10^{-3}M) the distribution is shifted predominantly toward shorter oligomers. In each case the yield of the octamer (O_8) is decreased relative to that at 10^{-2} M, resulting in a concomitant decrease in the yield of porphyrinogen. The concentration-dependent yield of porphyrinogen merely reflects the sensitivity of the distribution profile of oligomers to a 100-fold change in the starting monomer concentrations.

This intuitive picture is supported by theoretical mass action calculations[19] and experimental results. Gel permeation studies were performed of polypyrrylmethene fractions obtained from different concentration reaction mixtures. A clear shift to higher molecular weight components was observed as the concentration was increased, though a detailed analysis of the product profile was not possible. The equilibrium distribution of polypyrrylmethanes can also be displaced by irreversible removal of water. In the limit of total dehydration at sufficient dilution the yield of porphyrinogen should become quantitative.[20] Though this theoretical ideal was not attained, slight increases in yield (1.5–2-fold) at dilute solution (10^{-3} M) were obtained when the reaction was carried out in the presence of triethyl orthoacetate, a water scavenger. Finally, deliberate attempts by Franck to form the 10-, 12-, and 14-membered cycles resulted in the 8-membered porphyrinogen as the sole cyclic product in each case.[21] The failure to form cyclic products other than the porphyrinogen supports the reaction format shown in Scheme I.

Synthetic Applications. The synthetic procedure is mild, clean, and convenient. The polypyrrylmethenes formed upon oxidation exhibit no properties characteristic of tars and are easily separated from the porphyrin. The product workup involves passage of the concentrated crude reaction mixture over a short chromatography column. The quinone and polypyrrylmethene components usually bind near the top of the column. The porphyrin, residual unreacted benzaldehyde, and a very small amount of uncharacterized pigments pass through the column. The porphyrin obtained in this manner is typically of high purity. Quantities of porphyrins up to 1 g can be easily prepared from sensitive aldehydes without encountering difficult separation problems. In contrast to the Adler–Longo procedure, the yield of porphyrin is not contingent on the precipitation or crystallization of the product at the end of the reaction.

The reaction conditions are compatible with a wide variety of functional groups and protecting groups, including phenacyl and alkyl esters, dithiolanes, dioxanes, benzyl and allyl ethers, and alcohols. The yields shown in Table IV are intentionally conservative. Even higher

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yields can be achieved in almost all cases by working at 10^{-2} M, examining both BF_3 and TFA for optimal catalytic conditions, and utilizing *p*-chloranil as the oxidant. For example, the yields observed for alkoxybenzaldehydes with BF_3 catalysis were rather low but could be increased by 2–3-fold through the use of a higher BF_3 concentration (Table IV). Though the addition of triethyl orthoacetate affords slightly higher yields of tetraphenylporphyrin, we have generally not included it in preparative synthetic applications. Porphyrins **8** and **9** illustrate the chemoselective reaction at the aldehyde in the presence of hindered ketones and labile esters. The differential selectivity observed with acetal protecting groups is of particular note. Exposure of aldehyde **22** (monoacetal of terephthalaldehyde with 2,2-dimethylpropanediol) to 10^{-3} M BF_3 afforded 30% conversion to deprotected terephthalaldehyde. The acetal was stable for at least 1 h to 10^{-2} M TFA, however, and the corresponding porphyrin **12** was readily prepared with TFA catalysis. Benzaldehyde dimethyl acetal underwent hydrolysis with both BF_3 and TFA, therefore, dimethyl acetals are ineffective protecting groups in these conditions but can be directly utilized in the preparation of porphyrins.

The reaction of alkyl aldehydes resulted in moderate yields of *meso*-tetraalkylporphyrins. The yield of porphyrin increased steadily as the concentration was decreased, in contrast to the behavior observed with aromatic aldehydes (Figure 2). The steady increase in yield upon dilution in conjunction with the absence of porphyrinogen exchange indicated the alkylporphyrinogen formation to be irreversible under these conditions. Dilution beyond 10^{-3} M gave no further increases in yield, though in theory the yield should reach 100% in the absence of side reactions. The presence of a high level of side reactions was not discernible, since omission experiments with hexanal showed the absence of decomposition and the total yield of dipyrrylmethenes remained below 1%. The yields of tetraalkylporphyrins are comparable to those obtained by a more elaborate procedure recently reported by Rocha Gonsalves.[22] The tetraalkylporphyrins have appreciable solubilities in decane, reaching at least 1 mM for **24** and **25**. The ready availability of these porphyrins and their high solubility in aliphatic hydrocarbon solvents now (see Experimental Section) permits a host of physical and biomimetic studies to be undertaken.

The trialkyl monoaryl porphyrin **27** represented approximately half of the total porphyrin products from a binary mixed aldehyde condensation of undecylic aldehyde and phenacyl 4-formylbenzoate in a 3:1 ratio, respectively. Whereas a 1:1 ratio of aldehydes A and B should afford a product distribution containing the A_3B-porphyrin in 25% statistical abundance, a 3:1 ratio should afford a 42% relative yield. This one-step synthesis of asymmetrically substituted porphyrins compares favorably with the ring transplantation technique recently reported by Eschenmoser.[23] Enrichment of the product distribution of other hybrid porphyrins is also feasible by judicious selection of the reactant concentrations.[24]

Aldehydes that failed to give good yields of porphyrins generally fell into the classes of sterically hindered aldehydes (mesitaldehyde, 9-anthraldehyde, pivalaldehyde, 2-norbornenecarboxaldehyde), α,β-unsaturated alkyl aldehydes (cinnamaldehyde, phenylpropargylaldehyde, *trans*-2-octenal), aldehydes insoluble in CH_2Cl_2 (4-carboxybenzaldehyde), and aldehydes giving rise to products with limited solubility (acetaldehyde, paraformaldehyde). One example of the latter is *p*-acetamidobenzaldehyde, which gave rise to precipitates during the course of the reaction and afforded a 15% yield of the corresponding porphyrin.

Outlook. Tetraphenylporphyrinogen may now be added to a collection of other porphyrinogens that have been shown to be easily formed, including uroporphyrinogen (85% yield at thermodynamic equilibrium),[10] octamethylporphyrinogen from acetone and pyrrole (88%),[25] and *meso*-tetramethyl-*meso*-tetraphenylporphyrinogen.[26] The related reversible condensation of resorcinol and benzaldehyde under acid catalysis results in cyclic octamers which are stable at equilibrium. The yield also declines upon dilution in analogy with tetraphenylporphyrinogen.[27] Formation of the tetraphenylporphyrinogen prior to oxidation to give the porphyrin recapitulates the initial stages of heme and chlorophyll biosynthesis.[28]

Several attempts have been made to use metal salts to facilitate porphyrin macrocycle formation in the Adler–Longo and Rothemund reactions.[7,29] However, *porphyrinogen and pyrrole do not ligate to metals.* A higher isolated yield of metalloporphyrin can result from different mechanisms but does not alone implicate either a kinetic or thermodynamic template effect in the cyclization process. In cases such as the formation of acetone–furan where metal templating is possible, increased yields have been shown to result from acidity effects of the added metal salts rather than template effects.[30] A large body of data indicates that templating agents are not necessary to form porphyrinogens in high yield.

New Design Strategies. The ability to convert complex substituted benzaldehydes to porphyrins in good yield suggests new design strategies in the preparation of porphyrin model systems. Due to the idiosyncracies of porphyrin chemistry (difficulty with purification, low solubilities, susceptibility to oxidation and reduction, lability to base, demetalation with acid, photosensitivity, etc.), it is generally desirable to perform as many synthetic transformations as possible prior to forming the porphyrin. This heuristic was partially thwarted with the Adler–Longo reaction as the only means of preparing tetraphenylporphyrins, since only a fraction of common protecting agents and functional groups could survive the harsh reaction conditions. *Now many synthetic transformations can be performed to prefunctionalize the aldehyde, minimizing porphyrin manipulations by delaying conversion to the porphyrin until later stages of the synthesis.* The feasibility of incorporating any synthetic moiety can be assessed by separate exposure of model compounds to the acid catalyst and to the oxidant in CH_2Cl_2 at room temperature. This equilibrium strategy should be especially useful in the synthesis of complex

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porphyrin model systems where design requirements mandate the porphyrin environment be sculptured with precision and detail.

Experimental Section

General. Methylene chloride (Fisher certified A.C.S.) was distilled from potassium carbonate and stored over 4-Å molecular sieves. Column chromatography of porphyrins was performed on Florisil (magnesia–silica gel, 100–200 mesh) obtained from Fisher. Stock solutions (2.5 M) of BF_3 etherate (Aldrich) were prepared in CH_2Cl_2 and were used for approximately 1 week. Pyrrole was distilled from calcium hydride and stored samples were discarded when discoloration occurred. Benzaldehyde was distilled under reduced pressure. Substituted benzaldehydes obtained from commercial sources (Aldrich, Frinton, Fluka) were used as received. Dialdehydes monoprotected with dithiolane protecting groups were prepared from the corresponding cyanobenzaldehyde.[31]

Melting points are uncorrected. All reported ^1H NMR spectra were obtained at 80 MHz (IBM NR80) unless indicated at 300 MHz (General Electric GN300NB). IR spectra were recorded on a Nicolet 5DXB spectrometer, and UV–vis absorption spectra were obtained with a HP 8451A photodiode array spectrometer. HPLC analyses were performed on a HP-1090 liquid chromatograph equipped with a UV–vis diode array detector and a DPU multichannel integrator. TLC densitometry was performed with a Shimadzu CS-930 dual-wavelength scanning densitometer. Fluorescence analysis was performed with a Gilford Fluoro IV scanning spectrofluorometer. Preparative centrifugal TLC was performed with a Harrison Research Chromatotron Model 7924T.

Mass spectral analyses of the porphyrins were performed by ^{252}Cf fission fragment mass spectrometry.[15] Samples of approximately 20 μg of porphyrin in acetone or chloroform–methanol solution were electrosprayed onto aluminized polyester. Positive ion spectra were obtained in 1–35 min. The porphyrin parent molecular ion (MH^+ or $M^{\bullet+}$) invariably formed the most intense peak in the mass spectrum above 100 mass units. Mass spectra of the aldehydes were obtained with a VG 70G high resolution electron impact spectrometer by using direct probe insertion.

General Procedure for *meso*-Tetraphenylporphyrins. The general procedure is described for the preparation of tetraphenylporphyrin. Standard reactions were performed in a 50-mL, three-necked, round-bottomed flask fitted with a septum port, a reflux condenser, and a gas inlet port. The inlet port consisted of a fritted glass disk immersed in the solution, with nitrogen or argon flow rates maintained at about 2 mL per min. The flask was charged with 25 mL of distilled CH_2Cl_2, benzaldehyde (25.4 μL, 0.25 mmol, 10^{-2} M), and pyrrole (17.3 μL, 0.25 mmol, 10^{-2} M). The resulting solution was magnetically stirred at room temperature. After purging the solution for 5–10 min, the appropriate amount of BF_3 etherate (10 μL of a 2.5 M solution in CH_2Cl_2, 0.025 mmol, 10^{-3} M) or anhydrous trifluoroacetic acid (19.3 μL, 0.25 mmol, 10^{-2} M) was added via syringe. The reaction vessel was shielded from ambient lighting.

To monitor the progress of the reaction, aliquots were periodically removed from the reaction vessel via syringe and injected into an oxidizing solution. With an oxidizing solution of DDQ, the oxidation of porphyrinogen to porphyrin and pyrrylmethanes to pyrrylmethenes occurs almost instantaneously. The yield of porphyrinogen at any point in the condensation is taken to be equal to the yield of porphyrin formed upon oxidation.[32] In particular, 50-μL aliquots were removed from the reaction vessel and injected into 300 μL of a 10^{-2} M solution of DDQ in toluene. This solution was diluted in CH_2Cl_2/EtOH (3:1) and the visible absorption spectra were recorded. The yield of tetraphenylporphyrin was determined by the intensity of the Soret band (420 nm, ε 500 000 M^{-1} cm^{-1}) measured from the apex to the inflection point at the base of the red edge of the band. This eliminated the contribution of the pyrrylmethene and quinone components which exhibit a broad absorption in the 400–450-nm region.

The yield of porphyrin is found to level off between 1 and 2 h, and the entire solution may be converted to porphyrin during this period. A sample of *p*-chloranil (46.1 mg, 0.188 mmol, 3 equiv per porphyrinogen, $^3/_4$ equiv per pyrrole) in powder form is added all at once and the flask is immersed in a water bath preheated to 45 °C. The solution is refluxed for 1 h and then concentrated by rotary evaporation to a volume of approximately 5–10 mL. At this point the solution can be extracted with aqueous alkaline dithionite to remove quinone components. Alternatively, the concentrated solution is chromatographed on Florisil to separate the porphyrin and the polypyrrylmethenes. In the chromatography procedure the quinone and polypyrrylmethene components usually bind near the top of the column.

We found that flash chromatography could best be performed by adding several grams of Florisil to the concentrated porphyrin solution obtained during the rotary evaporation process. The slurry so formed was further dried by rotary evaporation to yield a damp powder, which could be poured on top of the chromatography column dry-packed with Florisil. The column was washed with CH_2Cl_2/petroleum ether (1:1) to remove small amounts of fast moving pigments (uncharacterized) followed by either CH_2Cl_2 or mixtures of CH_2Cl_2 containing 10–20% ethyl acetate to elute the porphyrin. The porphyrin fraction was of high purity and could either be evaporated to dryness or crystallized by addition of petroleum ether or methanol. With the application of modest pressures, the entire chromatography operation requires only 30 min. This procedure eliminates the solubility problems arising when flash chromatography is initiated with porphyrins in a solid form, as well as the large load volumes often required during normal adsorption chromatography.

The reaction is readily scaled-up to afford 1-g quantities of the porphyrin. A 2-L, three-necked, round-bottomed flask fitted with a reflux condenser and nitrogen inlet port was filled with 1 L of distilled CH_2Cl_2. Samples of benzaldehyde (1.525 mL, 0.015 mol, 1.5×10^{-2} M) and pyrrole (1.04 mL, 0.015 mol, 1.5×10^{-2} M) were added and the solution was stirred magnetically at room temperature under a slow steady stream of nitrogen. After 15 min, BF_3 etherate (0.4 mL of a 2.5 M solution in CH_2Cl_2, 10^{-3} M) was added and the reaction vessel was shielded from ambient lighting. After 1 h, *p*-chloranil (2.77 g, 0.011 mol, 3 equiv per porphyrinogen) in powder form was added all at once to the reaction vessel. The flask was immersed in a water bath preheated to 45 °C and the solution was refluxed for 1 h. The solution was then concentrated to about 50 mL by rotary evaporation, and 10–12 g of Florisil was added. The slurry was further dried to afford a damp dark powder, which was poured onto the top of a chromatography column (2.5-cm diameter) filled with Florisil (38 cm in height). The column was washed with about 500 mL of CH_2Cl_2/petroleum ether (3:1) to elute several small bands of fast moving pigments, followed by 300–400 mL of CH_2Cl_2 to elute the porphyrin. The first two porphyrin fractions contained 10% impurities while the third and final fraction appeared pure. These three porphyrin fractions were combined and concentrated to afford a crude product weighing 1.254 g (54%), which upon recrystallization gave 1.033 g of tetraphenylporphyrin (45% yield overall). The product was pure as determined by absorption spectroscopy, TLC (silica gel, CH_2Cl_2/petroleum ether, 1:1), and ^1H NMR spectroscopy.

General Procedure for *meso*-Tetraalkylporphyrins. These compounds were prepared in analogy with the tetraphenylporphyrins with only several minor differences. Pyrrole and the alkyl aldehyde were reacted at 10^{-2} M for convenience, though lower concentrations afford higher yields. TFA was used at 5×10^{-3} M. Chromatography of the crude reaction mixture on Florisil was performed initially with petroleum ether before enriching with CH_2Cl_2 or ethyl acetate. All of the other parameters were unchanged from those employed in the tetraphenylporphyrin procedure.

Exemplary Procedure for Substituted Porphyrins. Porphyrin **12** was prepared by adding aldehyde **22** (110 mg, 0.5 mmol) and pyrrole (34.8 μL, 0.5 mmol) in 50 mL of dry CH_2Cl_2 in a 100-mL, three-necked, round-bottomed flask. The solution

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(32) Though we have no evidence that porphyrinogen is quantitatively converted to porphyrin, the yield must be quite high. An 80% overall yield was reported for the series of manipulations including catalytic reduction of a porphyrin to form the porphyrinogen, DDQ oxidation to give the porphyrin, chromatography, and crystallization. See: Cavaleiro, J. A. S.; Rocha Gonsalves, A. M.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1771.

was stirred magnetically at room temperature under nitrogen. Trifluoroacetic acid (38.6 μL, 0.5 mmol, 10^{-2} M) was added, and the reaction was monitored by removing aliquots as previously described. The spectrophotometric yield was 21% after 75 min (DDQ oxidation). A sample of *p*-chloranil (92 mg, 0.375 mmol) was added and the flask was immersed in a water bath preheated to 45 °C. After a 1-h reflux the spectrophotometric yield was 25%. The solution was poured into a 250-mL, round-bottomed flask containing 10 g of Florisil and the resulting slurry was evaporated to dryness. The powder was poured on top of a column (2-cm diameter) packed with a bed of Florisil 25 cm in height. Flash chromatography with CH_2Cl_2/petroleum ether (9:1) eluted both porphyrin and polypyrrylmethenes. The eluant was concentrated, diethyl ether was added, and the solution was slowly concentrated again. Filtration afforded crystals (30 mg, 0.028 mmol) of the desired porphyrin **12** in 22% overall yield.

Exchange Experiment. The reactions of pyrrole with benzaldehyde, and pyrrole with methyl 4-formylbenzoate, were performed simultaneously in separate vessels. After 1 h, 12.5-mL samples were withdrawn from each solution via syringe and combined in a 50-mL round-bottomed flask. A booster of acid (10 μL of 2.5 M BF_3 in CH_2Cl_2) was added and the reaction was allowed to proceed. The extent of porphyrinogen exchange was monitored by periodic removal of reaction aliquots and oxidation with DDQ, followed by both TLC and HPLC analysis.

An aliquot removed 2 h after combining the solutions was subjected to TLC analysis following oxidation. Visual inspection showed four new porphyrin products bracketed by the fast moving tetraphenylporphyrin and the slow moving tetrakis[4-(methoxycarbonyl)phenyl]porphyrin. The four new products accounted for an estimated three-fourths of the total porphyrin products. For comparative purposes, a mixed condensation was performed with 0.125 mmol of benzaldehyde, 0.125 mmol of methyl 4-formylbenzoate, and 0.250 mmol of pyrrole. An aliquot was oxidized after 1 h, and TLC analysis showed the distribution of porphyrin products to be nearly identical with that obtained after 2 h of exchange.

To obtain more precise quantification concerning the porphyrin product distribution, aliquots from the exchange reaction and the mixed condensation were purified to remove quinone and polypyrrylmethene components, followed by TLC densitometry and HPLC analysis. Reaction aliquots (5 mL) were passed over a short column of silica gel (Fisher PrepSep-Si) and were slowly eluted with CH_2Cl_2 until no porphyrin remained on the column, as determined by the absence of porphyrin fluorescence. The chromatographed samples were concentrated by rotary evaporation to 5-mL volumes and then passed through a 0.22-μm nylon-66 filter (MSI). TLC examination of the chromatographed and crude samples showed that the selective removal of particular porphyrin products did not occur. The four hybrid porphyrins were bracketed on both TLC and HPLC by the fast-moving tetraphenylporphyrin and the slow-moving tetrakis[4-(methoxycarbonyl)phenyl]porphyrin. The two porphyrin bands chromatographing closely to the respective homosubstituted parent porphyrins were assigned to the two trisubstituted hybrid products. The two porphyrin bands that exhibited intermediate retention times were provisionally assigned to the two disubstituted hybrid products.

The porphyrin products from both the exchange reaction and the mixed aldehyde condensation were separated by TLC (silica gel, CH_2Cl_2) and the relative peak areas determined by densitometry using a Shimadzu dual-wavelength scanning densitometer. Reflection absorption chromatograms of the TLC plates were obtained at 420 nm by using a beam aperture of 1.2 × 1.2 mm^2 and 0.5–1.0-mm scanning intervals. A zig–zag scanning mode was employed with a 6-mm width centered around the spot.

HPLC analysis was done with a 300 × 3.9 mm Waters μ-Porasil column and isocratic (hexane containing 10% ethyl acetate) elution at a flow rate of 1.0 mL/min. Integration was performed at 420 ± 5 nm (reference 475 ± 5 nm), and each peak was identified as a porphyrin due to its characteristic visible absorption spectra by using a flow-thru diode array detector. Peak areas were normalized and area percents were used in the quantification.

Gel Permeation Chromatography. The tetraphenylporphyrin synthesis was conducted with benzaldehyde and pyrrole concentrations of 10^{-1}, 10^{-2}, and 10^{-3} M. The reactions were subjected to oxidation with DDQ and were washed with an aqueous alkaline dithionite solution (5% NaOH, 5% $Na_2S_2O_4$) to remove excess quinone components. The porphyrin and polypyrrylmethenes were unaffected by this procedure. The reaction products were dried (Na_2SO_4) and concentrated by rotary evaporation. Then CH_2Cl_2 was added to give solutions approximately 0.05% by weight on the basis of the original benzaldehyde and pyrrole concentrations. Gel permeation chromatography was performed with a HP-PLgel 100 A column (size exclusion < 4000 mol wt) and elution with CH_2Cl_2 at 1 mL/min. The concentration of eluting polypyrrylmethenes was monitored by absorption at 325 nm. These components exhibit broad absorption curves in the 300–350-nm region. The apparent molecular weight range was spanned by the elution points of toluene (8.8 min) and monodisperse polystyrene (mol wts 10 300 (4.7 min) and 900 (6.0 min)). Tetraphenylporphyrin eluted at 7.4 min. The integrated areas given by the components preceding the porphyrin and those eluting after the porphyrin were used to reflect high and low molecular weight portions of the polypyrrylmethene distribution.

***meso*-Tetrakis[4-(1-octyloxy)phenyl]porphyrin (3)**: $C_{76}H_{94}N_4O_4$ 1126.7 calcd mass (M), 1128.0 ($M + H^+$); ^1H NMR ($CDCl_3$) δ −2.8 (s, 2 H, NH), 0.9 (m, 12 H, CH_3), 1.3 (m, 48 H, $(CH_2)_6$), 4.25 (t, J = 5.9 Hz, 8 H, OCH_2), 7.25, 8.1 (dd, J = 7.9 Hz, 16 H, C_6H_4), 8.9 (s, 8 H, β-pyrrole); IR (KBr) 1250 (PhOC) cm^{-1}.

***meso*-Tetrakis[4-(benzyloxy)phenyl]porphyrin (4)**: $C_{72}H_{54}N_4O_4$ 1038.4 calcd mass (M), 1039.6 ($M + H^+$); ^1H NMR ($CDCl_3$) δ −2.7 (br s, NH), 5.35 (s, 8 H, OCH_2), 7.7 (m, 36 H, C_6H_4 and C_6H_5), 8.5 (s, 8 H, β-pyrrole); IR (KBr) 1250 (PhOC) cm^{-1}.

***meso*-Tetrakis[4-(2-hydroxyethoxy)phenyl]porphyrin (5)**: $C_{52}H_{46}N_4O_4$ 854.3 calcd mass (M), 855.5 ($M + H^+$); 837.5 ($M + H^+ - H_2O$); ^1H NMR ($CDCl_3$) δ −2.9 (s, br, NH), 3.4 (m, 8 H, CH_2OH), 4.4 (m, 8 H, CH_2OPh), 5.3 (s, 4 H, OH), 7.55 (m, 16 H, C_6H_4), 8.9 (s, 8 H, β-pyrrole); IR (KBr) 3400 (OH), 1210 (PhOC) cm^{-1}.

***meso*-Tetrakis[4-(2-chloroethoxy)phenyl]porphyrin (6)**: $C_{52}H_{42}N_4O_4Cl_4$ 926.2 calcd mass (M), 928.4 ($M + H^+$), 866.3 ($M + H^+ - CH_2CH_2Cl$), 803.3 ($M + H^+ - 2(CH_2CH_2Cl)$), 741.3 ($M + H^+ - 3(CH_2CH_2Cl)$); ^1H NMR ($CDCl_3$) δ −2.8 (s, 2 H, NH), 4.0 (t, J = 5.5 Hz, 8 H, CH_2Cl), 4.55 (t, J = 5.5 Hz, 8 H, OCH_2), 7.7 (m, 16 H, C_6H_4), 8.85 (s, 8 H, β-pyrrole); IR (KBr) 1280 (PhOC), 1225 (CH_2Cl) cm^{-1}.

***meso*-Tetrakis(4-cyanophenyl)porphyrin (7)**: $C_{48}H_{26}N_8$ 714.2 calcd mass (M), 714.3 ($MH^{+\bullet}$); ^1H NMR ($CDCl_3$) δ −2.87 (s, 2 H, NH), 8.05, 8.32 (dd, J = 8.4 Hz, 16 H, C_6H_4), 8.8 (s, 8 H, β-pyrrole); IR (KBr) 2210 (C≡N) cm^{-1}.

***meso*-Tetrakis[4-((phenacyloxy)carbonyl)phenyl]porphyrin (8)**: prepared from aldehyde **16**; $C_{80}H_{54}N_4O_{12}$ 1262.3 calcd mass (M), 1264.7 ($M + H^+$); ^1H NMR ($CDCl_3$) δ −2.72 (br s, 2 H, NH), 5.8 (s, 8 H, CH_2), 8.0 (m, 36 H, C_6H_4 and C_6H_5), 8.9 (s, 8 H, β-pyrrole); IR (KBr) 1725 (C=O), 1700 (CO_2R), 1290 (COC) cm^{-1}.

***meso*-Tetrakis[3-((phenacyloxy)carbonyl)phenyl]porphyrin (9)**: prepared from aldehyde **17**; $C_{80}H_{54}N_4O_{12}$ 1262.3 calcd mass (M), 1262.8 ($MH^{+\bullet}$); ^1H NMR ($CDCl_3$) δ −2.8 (br s, 2 H, NH), 5.62 (s, 8 H, CH_2), 8.1 (m, 36 H, C_6H_4 and C_6H_5), 8.83 (s, 8 H, β-pyrrole); IR (KBr) 1725 (CO_2R), 1700 (C=O), 1230 (COC) cm^{-1}.

***meso*-Tetrakis[4-(1,3-dithiacyclopent-2-yl)phenyl]porphyrin (10)**: prepared from aldehyde **19**; $C_{56}H_{46}N_4S_8$ 1030.1 calcd mass (M), 1031.4 ($M + H^+$); ^1H NMR ($CDCl_3$) δ −2.8 (s, 2 H, NH), 3.5 (m, 16 H, SCH_2CH_2S), 6.0 (s, 4 H, CHS_2), 7.9, 8.18 (dd, J = 8.0 Hz, 16 H, C_6H_4), 8.9 (s, 8 H, β-pyrrole); IR (KBr) 1450 (CH_2S), 700 (CS) cm^{-1}.

***meso*-Tetrakis[3-(1,3-dithiacyclopent-2-yl)phenyl]porphyrin (11)**: prepared from aldehyde **21**; $C_{56}H_{46}N_4S_8$ 1030.1 calcd mass (M), 1031.4 ($M + H^+$); ^1H NMR ($CDCl_3$) δ −2.86 (br s, NH), 4.65 (m, 16 H, SCH_2CH_2S), 6.0 (s, 4 H, CHS_2), 8.0 (m, 16 H, C_6H_4), 8.85 (s, 8 H, β-pyrrole); IR (KBr) 1410 (CH_2S), 640 (CS) cm^{-1}.

***meso*-Tetrakis[4-(1,3-dioxa-5,5-dimethylcyclohex-2-yl)phenyl]porphyrin (12)**: prepared from aldehyde **22**; $C_{68}H_{70}N_4O_8$ 1070.5 calcd mass (M), 1070.9 ($M^{+\bullet}$); ^1H NMR ($CDCl_3$) δ −2.84 (br s, 2 H, NH), 0.91 (s, 12 H, CH_3), 1.46 (s, 12 H, CH_3), 3.9 (m, 16 H, CH_2), 5.97 (s, 4 H, CH), 7.9, 8.25 (dd, J = 8.2 Hz, 16 H, C_6H_4), 8.8 (s, 8 H, β-pyrrole); IR (KBr) 1120 (COC) cm^{-1}.

***meso*-Tetrakis[4-(allyloxy)phenyl]porphyrin (13)**: $C_{56}H_{46}N_4O_4$ 838.3 calcd mass (M), 839.5 (M + H$^+$); ^{1}H NMR ($CDCl_3$) δ −2.5 (br s, 2 H, NH), 4.82 (m, 8 H, C=CH_2), 5.5 (m, 8 H, OCH_2), 6.25 (m, 4 H, C=CH), 7.3, 8.1 (dd, J = 7.9 Hz, 16 H, C_6H_4), 8.85 (s, 8 H, β-pyrrole); IR (KBr) 1250 (PhOC), 1000 (CH=CH_2) cm^{-1}.

***meso*-Tetrakis[4-((butyloxy)carbonyl)phenyl]porphyrin (14)**: prepared from aldehyde **23**; $C_{64}H_{62}N_4O_8$ 1014.4 calcd mass (M), 1015.6 (M + H$^+$); ^{1}H NMR ($CDCl_3$) δ −2.79 (s, 2 H, NH), 1.07 (t, J = 6.8 Hz, 12 H, CH_3), 1.80 (m, 16 H, CH_2CH_2), 4.40 (m, 8 H, OCH_2), 8.25, 8.4 (dd, J = 8.1 Hz, 16 H, C_6H_4), 8.87 (s, 8 H, β-pyrrole); IR (KBr) 1720 (C=O), 1270 (COC) cm^{-1}.

***meso*-Tetrakis[4-(methoxycarbonyl)phenyl]porphyrin (15)**: $C_{52}H_{38}N_4O_8$ 846.3 calcd mass (M), 847.3 (M + H$^+$); ^{1}H NMR ($CDCl_3$) δ −3.0 (br s, 2 H, NH), 4.1 (s, 12 H, CH_3), 8.28, 8.45 (dd, J = 8.7 Hz, 16 H, C_6H_4), 8.8 (s, 8 H, β-pyrrole); IR (KBr) 1720 (C=O), 1278 (COC) cm^{-1}.

Phenacyl 4-Formylbenzoate (16). Samples of *p*-carboxybenzaldehyde (1.5 g, 0.01 mol) and phenacyl bromide (1.99 g, 0.01 mol) were dissolved in DMF (10–15 mL) in a 25-mL, round-bottomed flask. Pulverized KF (1.28 g, 0.02 mol) was added,[33] and after 3 h at room temperature with magnetic stirring the reaction was complete. The mixture was poured into water and extracted with ethyl acetate. The ethyl acetate phase was washed with aqueous $NaHCO_3$ and saturated brine, dried (Na_2SO_4), and concentrated. Recrystallization from ethanol–water afforded 2.37 g, 88% yield: mp 112–115 °C; mass spectrum, m/e 238, 133, 105, 107; ^{1}H NMR ($CDCl_3$) δ 5.6 (s, 2 H, CH_2), 7.9 (m, 9 H, Ar H), 10.1 (s, 1 H, CHO); IR (KBr) 1740 (C=O), 1710 (CO_2R), 1700 (CHO), 1225 (COC) cm^{-1}.

Phenacyl 3-Formylbenzoate (17). Samples of isophthalaldehydic acid (0.75 g, 0.005 mol) and phenacyl bromide (1.0 g, 0.005 mol) were dissolved in 10 mL of tetrahydrofuran in a 25-mL, round-bottomed flask. Pulverized KF (0.64 g, 0.01 mol) was added and the flask was immersed in an oil bath at 75 °C. After 3.5 h ethyl acetate and water were added. The organic layer was washed with 5% aqueous $NaHCO_3$, dried (Na_2SO_4), treated with charcoal, and concentrated. Crystals were obtained on cooling: 1.075 g, 80% yield; mp 106–109 °C; mass spectrum, m/e 238, 133, 105, 77; ^{1}H NMR ($CDCl_3$) δ 5.6 (s, 2 H, CH_2), 8.05 (m, 9 H, Ar H), 10.08 (s, 1 H, CHO); IR (KBr) 1730 (C=O), 1705 (CO_2R), 1680 (CHO), 1230 (COC) cm^{-1}.

2-(4-Cyanophenyl)-1,3-dithiolane (18). Samples of *p*-cyanobenzaldehyde (4.5 g, 0.034 mol) and 1,2-ethanedithiol (4.85 mL, 0.058 mol) were placed in a 250-mL flask containing 130 mL of dry CH_2Cl_2. Boron trifluoride etherate (0.8 mL) was added and the mixture was stirred overnight at room temperature. The mixture was extracted with 35 mL of 5% NaOH, washed with water, and dried (Na_2SO_4). Two crops of crystals were obtained which appeared pure by TLC analysis (silica gel, CH_2Cl_2): 6.57 g (92.5% yield); mp 71 °C; mass spectrum, m/e 207 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 3.36 (s, 4 H), 5.5 (s, 1 H), 7.46 (s, 4 H).

2-(4-Formylphenyl)-1,3-dithiolane (19). A sample of nitrile **18** (3 g, 0.0145 mol) was dissolved in 9 mL of dry benzene in a 25-mL, three-necked, round-bottomed flask purged with nitrogen. The flask was immersed in an ice bath and diisobutylaluminum hydride (17.8 mL of a 1 M solution in hexane) was added dropwise over 30 min. After an additional 30 min, TLC analysis (CH_2Cl_2/petroleum ether, 2:1) indicated that the reaction was complete. The contents of the reaction vessel were poured into a 250-mL separatory funnel containing 40 mL of 2.5 N HCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 until all organic materials had been removed. The organic phases were combined, dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil. After overnight refrigeration a crystalline solid was obtained: 2.8 g (92% yield); mp 38–40 °C; mass spectrum, m/e 210 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 3.40 (m, 4 H), 5.51 (s, 1 H), 7.7 (m, 4 H), 9.9 (s, 1 H); IR (film) 2828, 2746, 1696 (CHO), 1425 (CH_2S), 621 (CS) cm^{-1}; oxime mp 115–116 °C.

2-(3-Cyanophenyl)-1,3-dithiolane (20). A 250-mL, round-bottomed flask was charged with samples of 3-cyanobenzaldehyde (2.6 g, 0.02 mol), 1,2-ethanedithiol (2.5 mL, 0.03 mol), and 114 mL of distilled CH_2Cl_2. Boron trifluoride etherate (0.7 mL, 0.006 mol) was added and the solution was stirred overnight at room temperature. The solution was then poured into a separatory funnel and washed with 30–50 mL of 5% aqueous NaOH. The organic layer was washed with water, dried (Na_2SO_4), and concentrated to yield a pale yellow oil weighing 4.02 g (97% yield): mass spectrum, m/e 207 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 3.4 (m, 4 H, SCH_2CH_2S), 5.6 (s, 1 H, HCS_2), 7.6 (m, 4 H, C_6H_4); IR (film) 2210 (C≡N), 1420 (CH_2S), 610 (CS) cm^{-1}.

2-(3-Formylphenyl)-1,3-dithiolane (21). A sample of nitrile **20** (4.15 g, 0.02 mol) was dissolved in benzene (6–10 mL) in a 50-mL, three-necked, round-bottomed flask. The flask was immersed in an ice bath and diisobutylaluminum hydride (24 mL of a 1 M solution in hexane) was added dropwise under nitrogen. After 1 h the mixture was poured into a separatory funnel and carefully washed twice with 10% aqueous HCl, followed by two aqueous washes. The combined aqueous washes were extracted (5 × 25 mL) with CH_2Cl_2. The organic solutions were combined, dried (Na_2SO_4), and concentrated to afford a yellow oil weighing 3.98 g (95% yield): mass spectrum, m/e 207 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 3.4 (m, 4 H, SCH_2CH_2S), 5.65 (s, 1 H, HCS_2), 7.7 (m, 4 H, C_6H_4), 10.0 (s, 1 H, HC=O); IR (film) 2810, 2710 (CHO), 1700 (C=O), 1430 (CH_2S), 640 (CS) cm^{-1}.

2-(4-Formylphenyl)-5,5-dimethyl-1,3-dioxane (22). Samples of *p*-cyanobenzaldehyde (5.25 g, 0.04 mol) and 2,2-dimethyl-1,3-propanediol (4.17 g, 0.04 mol) were placed in a 250-mL flask containing 60 mL of $CHCl_3$ and 60 mL of cyclohexane. Toluenesulfonic acid monohydrate (0.76 g, 0.004 mol) and 5-Å molecular sieves (8 g) were added to the solution.[34] The flask was immersed in an ice bath and stirred overnight. The reaction was quenched with triethylamine (1.2 mL) and filtered, and the filtrate was concentrated by rotary evaporation. Additional $CHCl_3$ was added and the organic solution was washed with water. Unreacted aldehyde was removed by vigorously stirring the $CHCl_3$ solution with an equal volume of 15% aqueous $Na_2S_2O_4$ for 90 min. The organic layer was separated, washed with water, and worked up to afford the desired product: 7.1 g, 82% yield; mp 106–109 °C (softened 98 °C); ^{1}H NMR ($CDCl_3$) δ 0.8 (s, 3 H), 1.25 (s, 3 H), 3.65 (m, 4 H), 5.38 (s, 1 H), 7.56 (s, 4 H). A sample of the nitrile (2.25 g, 0.01 mol) was dissolved in 75 mL of dry benzene and the reaction vessel was cooled in an ice bath. To this solution was added diisobutylaluminum hydride (12.5 mL of a 1 M solution in hexane) dropwise with stirring under argon. After 4 h the contents of the reaction vessel were poured into a separatory funnel and 20 mL of 3.7% aqueous HCl was carefully added. The organic phase was separated, washed with water, dried (Na_2SO_4), and concentrated to afford an oil which solidified on standing: 1.71 g, 75% yield; mp 59–62 °C; mass spectrum, m/e 220 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 0.8 (s, 3 H), 1.25 (s, 3 H), 3.71 (s, 4 H), 5.42 (s, 1 H), 7.3–8.1 (m, 4 H), 10.0 (s, 1 H); IR (KBr) 1700 (CHO), 1110, 1100 (COC) cm^{-1}.

***n*-Butyl 4-Formylbenzoate (23).** To a suspension of 4-carboxybenzaldehyde (1.5 g, 0.01 mol) in 20 mL of absolute ethanol was added potassium *tert*-butoxide (1.12 g, 0.01 mol). The mixture was refluxed for 3 h and the solvent was stripped off by rotary evaporation. The solid residue was taken up in 20 mL of DMF and the flask immersed in an oil bath at 160 °C. Excess *n*-bromobutane (3.2 mL, 0.03 mol) was added dropwise over 1 h to the refluxing DMF solution. After an additional 2-h reflux period, the reaction mixture was cooled and poured into 150 mL of ice water, and the resulting slurry was extracted five times with ether. The ether phase was washed with water, dried (Na_2SO_4), and concentrated to afford a pale yellow oil. The oil was chromatographed on Florisil with anhydrous diethyl ether and concentrated to afford an oil weighing 1.78 g (87% yield): mass spectrum, m/e 205 (M$^+$ − H); ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 8.0 Hz, 3 H, CH_3), 1.55 (m, 4 H, CH_2CH_2), 4.32 (t, J = 6.9 Hz, 2 H, OCH_2), 8.08 (m, 4 H, Ar H), 10.09 (s, 1 H, CHO); IR (film) 1725 (CO_2R), 1700 (CHO), 1275 (COC) cm^{-1}.

***meso*-Tetrapentylporphyrin (24)**: $C_{40}H_{54}N_4$ 590.4 calcd mass (M), 591.5 (M + H$^+$); ^{1}H NMR (300 MHz) ($CDCl_3$) δ −2.62 (br s, 2 H, NH) 0.97, 1.02 (t, J = 7.2 Hz, 14.4 Hz, 12 H, $C_\epsilon H_3$), 1.50, 1.60 (m, 8 H, $C_\delta H_2$), 1.75, 1.85 (m, 8 H, $C_\gamma H_2$), 2.48, 2.58 (m, 8 H, $C_\beta H_2$), 4.92, 4.97 (t, J = 7.95 Hz, 15.9 Hz, 8 H, $C_\alpha H_2$), 9.5 (s,

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8 H, β-pyrrole); UV-vis 418, 520, 554, 600, 658 nm.

***meso*-Tetradecylporphyrin (25)**: $C_{60}H_{94}N_4$ 870.7 calcd mass (M), 871.8 (M + H^+); ^1H NMR ($CDCl_3$) δ −2.62 (br s, 2 H, NH), 0.91 (s, 12 H, CH_3), 1.00, 1.45 (m, 56 H, $(CH_2)_7$), 2.31, 2.72 (m, 8 H, $C_\beta H_2$), 4.82, 5.02 (t, J = 8.0 Hz, 16.0 Hz, 8 H, $C_\alpha H_2$), 9.48 (s, 8 H, β-pyrrole); UV-vis 418, 520, 554, 600, 658 nm.

***meso*-Tetraphenethylporphyrin (26)**: $C_{52}H_{46}N_4$ 726.4 calcd mass (M), 727.5 (M + H^+); ^1H NMR (300 MHz) ($CDCl_3$) δ −2.62 (br s, 2 H, NH), 3.83, 3.88 (t, J = 8.1 Hz, 16.2 Hz, 8 H, $C_\alpha H_2$), 5.25, 5.30 (t, J = 8.4 Hz, 16.8 Hz, 8 H, $C_\beta H_2$), 7.33, 7.52 (m, 20 H, C_6H_5), 9.50 (s, 8 H, β-pyrrole); UV-vis 420, 520, 556, 600, 658 nm.

Solubility Studies. The concentration range which brackets the solubility limit was estimated by visual examination for precipitate formation of several samples prepared at different concentrations. The samples were briefly sonicated and allowed to stand at room temperature for at least 6 h. Results listed as compound, solvent (concentration range which brackets the solubility limit): **24**, CH_2Cl_2 (0.070–0.099 M), decane (0.0016–0.0022 M); Zn chelate of **24**, CH_2Cl_2 (0.019–0.038 M), decane (0.0026–0.0032 M); **25**, CH_2Cl_2 (0.047–0.052 M), decane (0.006–0.012 M); Zn chelate of **25**, CH_2Cl_2 (0.014–0.035 M), decane (0.0008–0.0015 M); **26**, CH_2Cl_2 (0.016–0.027 M), decane (<3.8 × 10^{-6} M).

5,10,15-Tridecyl-20-[(4-(phenacyloxy)carbonyl)phenyl]-porphyrin (27). Into a 500-mL, three-necked, round-bottomed flask equipped with nitrogen purge was placed 250 mL of CH_2Cl_2. Samples of pyrrole (17.4 μL, 2.5 mmol, 10^{-3} M), undecylic aldehyde (38.7 μL, 0.188 mmol, 7.5 × 10^{-4} M), and phenacyl 4-formylbenzoate (**16**) (16.7 mg, 0.062 mmol, 2.5 × 10^{-4} M) were added with magnetic stirring at room temperature. The reaction was initiated by addition of TFA (97 μL, 5 × 10^{-3} M) and allowed to proceed for 2–2.5 h. Aliquots were removed and oxidized by DDQ in the standard manner to monitor the progress of the reaction. The reaction was terminated by addition of DDQ (42.5 mg, 0.187 mmol) in solid form. After 30 min at room temperature the overall yield of porphyrins was 27.3% (assuming ϵ_{420} = 500 000 M^{-1} cm^{-1} for all porphyrin species). TLC analysis (silica gel, CH_2Cl_2/petroleum ether, 3:2) showed the presence of at least five porphyrin species. The fastest moving component was determined by cochromatography to be tetradecylporphyrin **25**. The next porphyrin was assigned as the tridecylmonoarylporphyrin **27**. The crude reaction mixture was concentrated and chromatographed on silica gel to remove quinone and polypyrrylmethene species. The porphyrins were eluted with CH_2Cl_2 steadily enriched with ethyl acetate. Further purification was achieved by preparative centrifugal TLC. The porphyrins were chromatographed on a 1-mm-thick silica gel rotor by using CH_2Cl_2–ethyl acetate, affording a fraction enriched with **25** and **27**. Rechromatography via centrifugal TLC of this fraction using CH_2Cl_2/petroleum ether (3:2) afforded **27** in 14.2% overall yield. The structural assignment of the title compound was verified by ^1H NMR spectroscopy and ^{252}Cf fission fragment mass spectrometry. The NMR assignments were confirmed by standard decoupling experiments. **27**: $C_{65}H_{82}N_4O_3$ 968.6 calcd mass (M), 969.7 (M + H^+); ^1H NMR (300 MHz) ($CDCl_3$) δ −2.65 (s, 2 H, NH), 0.80, 0.91 (m, 9 H, CH_3), 1.13, 1.45 (m, 36 H, $(CH_2)_6$), 1.75, 1.90 (m, 6 H, $C_\gamma H_2$), 2.45, 2.52 (m, 6 H, $C_\beta H_2$), 4.90, 5.05 (m, 6 H, $C_\alpha H_2$), 5.80 (s, 2 H, OCH_2), 7.51, 7.56 (m, 2 H, phenacyl C_3H, C_5H), 7.62, 7.65 (m, 1 H, phenacyl C_4H), 8.02, 8.05 (d, J = 4.3 Hz, 2 H, phenacyl C_2H, C_6H), 8.25, 8.53 (dd, J = 9.1 Hz, 73.4 Hz, 4 H, phenacyl C_6H_4), 8.74, 8.76 (d, J = 4.8 Hz, 2 H, C_2H, $C_{18}H$), 9.37, 9.38 (d, J = 4.8 Hz, 2 H, C_3H, $C_{17}H$), 9.45, 9.50 (dd, J = 4.8 Hz, 9.0 Hz, 4 H, C_7H, C_8H, $C_{12}H$, $C_{13}H$); IR (KBr) 2955, 2924, 2853 ($C_{10}H_{21}$), 1731 ($PhCO_2$), 1702 (PhC=O), 1275 (COC).

Other Reaction Conditions. The following notes refer to modification of one variable in the standard room temperature reaction described in general conditions for porphyrin synthesis.

Solvents: Chloroform in place of methylene chloride gave 40% yields. Toluene/ethanol (3:1) with 10^{-2} M HCl gave about 20% yields over the course of 24 h. No reaction occurred in tetrahydrofuran.

Catalysts: $ZnCl_2$ in methanolic THF gave no reaction. CH_2Cl_2 saturated with gaseous HCl gave low yields (≤10%) in 30 s. BCl_3 (10^{-3} M) in place of BF_3 gave good yields (40%) in 30 min. $HClO_4$ in glacial acetic acid gave low yields (<5%).

Oxidants: I_2 was found ineffective in oxidizing the porphyrinogens under these conditions, in contrast to its utility in the oxidation of uroporphyrinogen.[10]

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Synthesis and Cation-Extraction Study of Lithium-Selective Chromogenic 14-Crown-4 Derivatives

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Various proton-dissociable chromogenic crown ethers have been synthesized, which possess a 14-crown-4 ring and a nitrophenol or azophenol chromophore. Proton-dissociation of the chromogenic crown ethers and extraction equilibria between the crown ether dichloroethane solutions and basic aqueous solutions of alkali and alkaline-earth metal ions have been investigated spectrophotometrically. Most of the chromogenic 14-crown-4 derivatives extract Li^+ selectively and efficiently into the organic phase, thus showing marked spectral changes of the chromophores. Slight and no extractions of Na^+ and the other alkali and alkaline-earth metal ions, respectively, were found with the 14-crown-4 derivatives. Replacement of the 14-crown-4 cycle by other crown rings and a noncyclic analogue resulted in drastic decrease of the Li^+ extractability and selectivity. The high Li^+ extractability is lost even in the corresponding 13-crown-4 derivative. The location of the phenoxide anion in the chromophores attached to the 14-crown-4 ring is also important for the effective Li^+ extraction. Excellent Li^+/Na^+ selectivity ratios in the extraction equilibrium constant, which range from 45 to 240, were attained with most of the chromogenic 14-crown-4 derivatives.

Crown ether derivatives bearing chromophores in the periphery of the crown ring, which are referred to as chromogenic crown ethers or crown ether dyes, are great candidates for cation-detecting and -determining reagents.

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