Porphyrin Synthesis in Surfactant Solution: Multicomponent Assembly in Micelles

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A synthesis of *meso*-substituted porphyrins in anionic sodium dodecyl sulfate micelles has been developed. Polar, functionalized aromatic aldehydes condense reversibly with pyrrole in the micellar phase. Oxidation of the porphyrinogen then provides functionalized porphyrins in yields of 10−48%. Hydrophobic aldehydes condense irreversibly to give low yields at practical substrate concentrations. Synthesis in D_2O solution results in per-β-deuterated porphyrins. A two-phase model is used to rationalize the dependence of porphyrin yield on reactant and surfactant concentration. Micelles are viewed as potential wells which promote porphyrinogen assembly by binding products more tightly than reactants.

Introduction

Micelles are dynamic clusters of surfactant molecules, able to collect and concentrate species from bulk aqueous solution.[1] Polar solutes tend to reside in the aqueous outer regions of the micelle near the head groups, whereas more hydrophobic molecules prefer the hydrocarbon-like interior.[2] It is this ability to localize and orient substrates according to polarity which is most promising from a synthetic point of view, and micellar solubilization has been exploited to speed up and sometimes change the product distribution of several types of reaction,[3] including some unusual photochemical transformations.[4] Most of the micelle-mediated reactions examined to date are kinetically controlled and irreversible. However, reversible chemistry is also of preparative interest, particularly for one-step assembly of large structures in which many bonds have to be formed, since wrong-way reactions can be corrected under equilibrating conditions.[5]

This paper explores the preparation of symmetrical *meso*-substituted porphyrins in micelles (Scheme 1). The initial stage of porphyrin synthesis is the acid-catalyzed condensation of four aldehydes and four pyrroles to a mixture of linear intermediates which then cyclize to porphyrinogen, a process which can be reversible.[6,7] The porphyrinogen is subsequently irreversibly oxidized to a porphyrin. The idea was that micelles would promote porphyrin synthesis in aqueous solution by (1) collecting and concentrating the reactants and (2) biasing the condensation equilibria in favor of porphyrinogen by binding successive intermediates increasingly tightly; as the aldehyde−pyrrole chain grows, water molecules are eliminated and the hydrophobicity of the chain should increase, pulling it further into the nonpolar interior of the micelle. Previous examples of reversible reactions in micelles include formation of imines,[8] protonation equilibria,[1,9] axial ligation of iron porphyrins,[10] and more recently host−guest type chemistry.[11,12] While the physical properties of micelle-solubilized porphyrins have been widely studied,[9,10,12,13] the use of surfactant aggregates to direct the course of porphyrin synthesis, or any other multiple assembly process, does not appear to have been investigated.

Results

Reconnaissance. Several surfactants were screened for synthesis of tetraphenylporphyrin (TPP). In a typical

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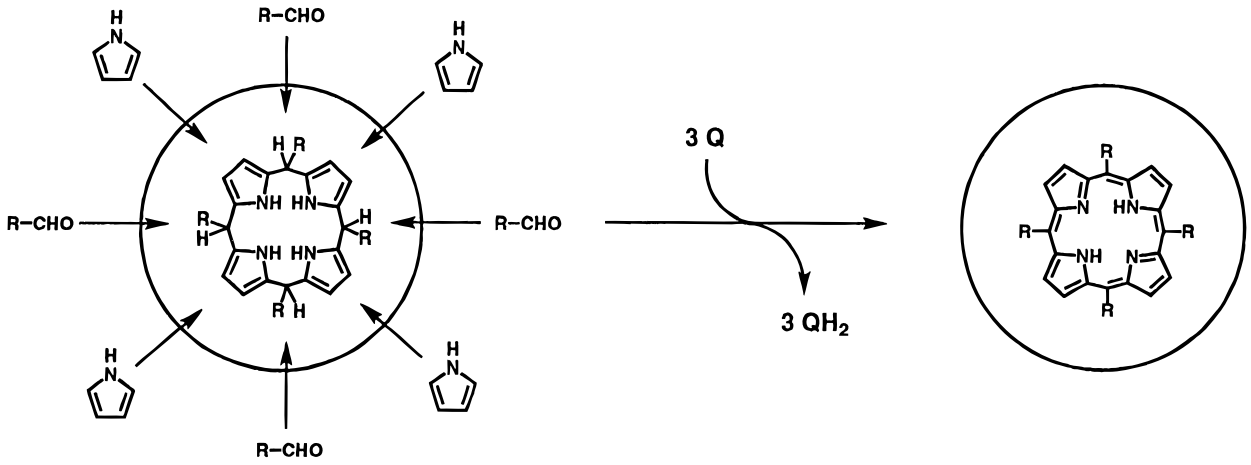
Scheme 1 Porphyrin Synthesis in Surfactant Micelles (Q = quinone oxidant)



trial reaction, 1 equiv of aqueous HCl was added to a solution of benzaldehyde and pyrrole (1:1) in aqueous surfactant, following the concentration of porphyrinogen as a function of time. Porphyrinogen concentrations were estimated by oxidizing samples of reaction mixture with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and measuring by UV−vis absorbance the amount of TPP present.[6c] Anionic surfactants gave the most promising results, as might be expected for an acid-catalyzed reaction involving positively charged intermediates.[1b] Sodium dodecyl sulfate (SDS) was chosen because it is easily removed during workup. Pure SDS gave the same yields as an inexpensive, commercially available mixture containing 72% SDS (the balance being C_{14} and C_{16} homologues), so this commercial mixture was used for all subsequent reactions. Without surfactant, reaction mixtures were heterogeneous and only traces of porphyrin could be detected. The rate of reaction, as judged by the time to reach maximum porphyrinogen concentration, was approximately proportional to the acid concentration, and the maximum yield of TPP was independent of the type or amount of strong acid catalyst employed.

Scope of the Reaction. Results for a variety of aldehydes are summarized in Table 1. All reactions were run under standard conditions: 10 mM aldehyde and 10 mM pyrrole in 0.5 M SDS. These conditions were chosen on the basis of trial experiments to give reasonable yields for polar aldehydes. Aqueous HCl was used to initiate condensations, adding enough acid so that the maximum porphyrinogen concentration was attained on a convenient time scale. Reaction mixtures developed various colors, ranging from light orange to deep burgundy, but remained optically clear throughout. The UV yields in Table 1 show two trends:

(1) There is a broad correlation between porphyrin yield and the water-to-micelle partition coefficient (*P*) of starting aldehydes, Figure 1. In general the more hydrophilic the aldehyde, the higher the yield. In the series of amide-substituted benzaldehydes, *para*-amides **35** and **36** gave higher yields than trichloroacetyl derivative **37** and *meta*-acetamide **33** gave a higher yield than the more lipophilic *meta*-carbamate **34**. Hydroxyl-substituted benzaldehydes behave similarly, free phenols giving higher yields than their methyl ethers and acid **19** giving a higher yield than its methyl ester **20**. If the aldehyde is too water soluble, porphyrinogen formation apparently becomes unfavorable, with low yields for diacid **26** and glucoside **12**.

(2) Some aldehydes gave much lower yields than would be predicted from their partition coefficients. These include electron-rich species with two or more *ortho* or *para* electron-donating groups such as aldehydes **22** and **24** and 2,4,6-trihydroxybenzaldehyde (**30**), some *ortho*-substituted aldehydes such as 2-acetamidobenzaldehyde (**32**) and 2-carboxybenzaldehyde (**7**) (but not its methyl ester **6**), and aldehydes with powerful electron-withdrawing substituents. In these cases brightly colored solutions were produced on addition of acid, and oxidized aliquots displayed intense bands at 450−500 nm, suggesting that the formation of conjugated species such as dipyrrins is competitive with porphyrinogen assembly.[6b]

Small (±10%) deviations from 1:1 aldehyde/pyrrole stoichiometry had little effect on yields. A 10−30% excess of pyrrole increased yields slightly for benzaldehyde and 4-hydroxybenzaldehyde and a 10−30% excess of aldehyde decreased yields. Aliphatic aldehydes gave UV yields of 5−10% under the standard conditions (hexanal, butanal, acetaldehyde dimethyl acetal). 2-(Hydroxymethyl)pyrrole condensed in 0.5 M SDS to give a 2% yield of porphine, the parent heterocycle.

Time Course of Reactions. Some qualitative features of the evolution of porphyrinogen concentration are worth recording. Porphyrinogen from hydrophilic aldehydes built up to a maximum after addition of acid and then began to decline again, resulting in low yields if reaction mixtures were left for long periods before oxidation. In contrast, the porphyrinogen concentration from hydrophobic aldehydes built up and then remained constant. Some aldehydes such as amides **33** and **35** showed intermediate behaviors, porphyrinogen building up rapidly at first and then slowly increasing to a maximum before eventually decreasing.

Preparative Scale Synthesis. The higher yielding porphyrins were isolated from 1 mmol scale reactions under the standard conditions, using the acid concentrations and optimum reaction times from small scale trials. A stoichiometric amount of 2,3,5,6-tetrachloro-1,4-benzoquinone (TCQ), a milder but slower oxidant than DDQ,[6c] gave the best results for porphyrinogen oxidation. Oxidations proceeded smoothly if TCQ, which is only slightly soluble in 0.5 M SDS, was added as a concentrated solution in THF so that the final reaction mixture contained ~5% v/v of THF. Other oxidants such as hydrogen peroxide or ceric ammonium nitrate were also effective for TPP, but gave lower yields for more functionalized porphyrins. Trials of a one-step method in

Table 1. Reaction Conditions and Porphyrin Yields (%)

cmpd	*meso*-phenyl substituent or aldehyde	log P^a	[HCl]^b	reaction time^c	UV yield (DDQ)	isolated yield (TCQ)		lit. yield^d
1	H (benzaldehyde)	2.0	0.3	2 h	18		(TPP)	
2	2-Me		0.3	15 h	14			
3	4-Me	2.4	0.3	1 h	19	15	**P1**	50
4	2,4,6-Me	3.3	0.3	15 min	2			
5	1-naphthaldehyde	3.2	0.3	15 min	10			
6	2-CO_2Me		0.1	2 h	9			
7	2-CO_2H		0.1		0			
8	3-CO_2Me	2.4	0.1	2 h	10			
9	3,5-CO_2Me	2.7	0.3	2 h	7			
10	2-OH	2.0	0.1	25 min	26	20	**P2**	
11	2-OMe		0.05	15 min	15			
12	2-O-β-D-glucoside	1.4	0.1	2 h	5			
13	3-OH	1.8	0.3	1 h	31	26	**P3**	9.7
14	3-OMe	2.3	0.2	1.5 h	10			
15	3-O$(CH_2)_{11}CH_3$	>5	0.3	1 h	11	9^e	**P4**	
16	3-OCH_2CO_2H		0.3	2 h	27			
17	4-OH	1.7	0.1	30 min	42	38	**P5**	11
18	4-OMe	2.3	0.1	15 min	25	18	**P6**	57
19	4-OCH_2CO_2H		0.3	45 min	40	34^f	**P7**	
20	4-OCH_2CO_2Me	2.3	0.3	45 min	22			
21	2,3-OH		0.1	15 min	25			
22	2,4-OH		0.1	15 min	1			
23	2,5-OH		0.1	15 min	10			
24	2,6-OH		0.1	15 min	1			
25	3,4-OH	1.6	0.1	55 min	43	48	**P8**	10
26	3,4-OCH_2CO_2H		0.3	2 h	5			
27	3,5-OH	1.5	0.2	1 h	29	34	**P9**	
28	3-OMe, 4-OH	1.9	0.1	1 h	38	21	**P10**	7.5
29	3,4,5-OH	1.5	0.1	55 min	32	12	**P11**	
30	2,4,6-OH	1.8	0.1		0			
31	2,4,6-OMe	2.6	0.1	2 h	15			
32	2-NHAc	2.1	0.3	45 min	3			
33	3-NHAc	1.9	0.3	8 h	37	23	**P12**	
34	3-N$HCO_2C(CH_3)_3$	3.1	0.3	15 min	15			
35	4-NHAc	2.0	0.3	5 h	36	25	**P13**	10
36	4-N$HCOCF_3$	2.3	0.3	2 h	35	40	**P14**	
37	4-N$HCOCCl_3$	3.0	0.3	2 h	13			
38	2-NO_2 or 3-NO_2 or 4-NO_2		0.1	1 h	1−4			
39	2-furaldehyde	1.3	0.1	5 min	30	10	**P15**	1
40	3-furaldehyde		0.1	20 min	30			
41	2-thiophenecarboxaldehyde	1.7	0.1	1 h	30	24	**P16**	9

^{a} Water−micelle partition coefficient *P*, measured by capillary electrophoresis. ^{b} Concentration of acid catalyst (mol/L). ^{c} Time for maximum porphyrinogen concentration as measured by DDQ oxidation of reaction samples. ^{d} Best recorded yield for direct synthesis from aldehyde and pyrrole, references for individual porphyrins given in Experimental Section. ^{e} DDQ used as oxidant. ^{f} Isolated as the tetramethyl ester.

which solid TCQ was added before the acid produced porphyrin directly, but gave lower yields (75−90% of the two-step yields for **P5** and **P8**).

The best workup procedure was to neutralize reaction mixtures with aqueous KOH and then add enough of an aqueous potassium salt to convert the surfactant into its insoluble potassium salt. Conventional extraction with EtOAc was then possible without producing emulsions. The isolated yields in Table 1 reflect the ease with which pure material could be obtained from a single chromatographic step followed by crystallization. Recoveries were generally good (the isolated yields are occasionally higher than UV yields since TCQ rather than DDQ was used as oxidant), but low in some cases due to borderline stability on silica gel or in solution (**P11** and **P15**) or due to low solubility in organic solvents (**P12** and **P13**). Ester groups hydrolyze slowly under the reaction conditions, but ester-functionalized porphyrins were still isolable in reasonable yields if the reaction mixtures were not left for long periods.

Pyrrole is deuterated rapidly in acidic D_2O,[14] so synthesis in D_2O solutions of SDS results in per-β-deuterated porphyrins. The deuterated versions of **P5** and **P8** were prepared with >97% deuterium incorporation. This represents a simple and economical method of preparing per-β-deuterated porphyrins, compounds of some spectroscopic interest.[15]

Reactant and SDS Concentrations. To investigate partitioning effects in more detail, benzaldehyde derivatives of varying hydrophobicity were condensed with 1 equiv of pyrrole at concentrations between 1 and 100 mM in 0.5 M SDS (Figure 2). The yield of **P5** derived from 4-hydroxybenzaldehyde goes through a well-defined maximum at ~15 mM reactants, whereas the yield of hydrophobic porphyrin **P4** is low at 15 mM and increases with dilution. The curves for the other porphyrins in Figure 2 lie in between these two. Thus hydrophobic substrates give low yields under the standard conditions (Figure 1) because the optimum (bulk) concentration is lower for these than for more water soluble species.

The actual reactant concentration will be higher in micelles than in the bulk solution and can be estimated

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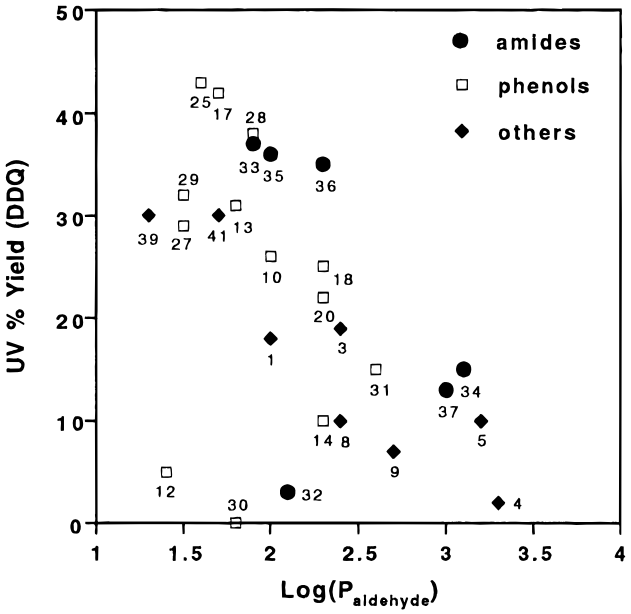

Figure 1. Porphyrin yield versus aldehyde partition coefficient (10 mM aldehyde, 10 mM pyrrole in 0.5 M SDS). "Amides" are amide- or carbamate-substituted benzaldehydes, "phenols" are hydroxy-substituted benzaldehydes, and "others" refer to alkyl or ester-substituted benzaldehydes or other heterocyclic aldehydes in Table 1.

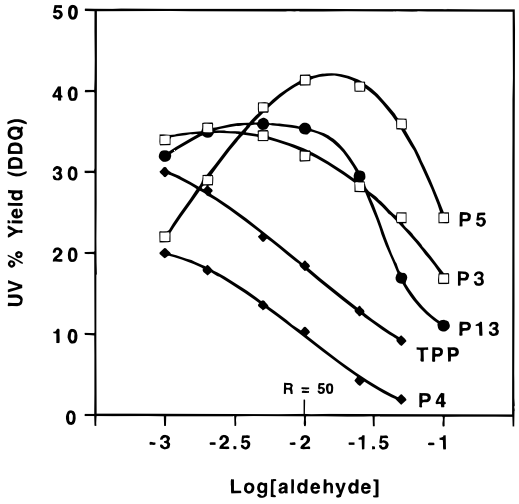

Figure 2. Porphyrin yield versus aldehyde concentration (mol/L) in 0.5 M SDS ([pyrrole] = [aldehyde]).

from the pseudophase model[16] for micellar solubilization:

$$S_m = S_0 P/(1 + \beta(P - 1)) \qquad (1)$$

where S_m is the reactant concentration in micelles, S_0 is the bulk reactant concentration, $\beta = v^m([SDS] - cmc)$ is the volume fraction of solution occupied by the micellar phase, $v^m = 0.25$ L/mol is the partial molar volume of SDS in water, and cmc = 8 mM is the critical micelle concentration of SDS. Under the standard conditions (10 mM reactants, 0.5 M SDS) the concentration of 4-hydroxybenzaldehyde in the micellar phase is estimated from eq 1 as ~70 mM. Pyrrole, the most hydrophilic component of reaction mixtures (log P = 1.2), has a concentration of ~55 mM, and lipophilic aldehydes with log P > 2 all have nominal concentrations of ~80 mM.

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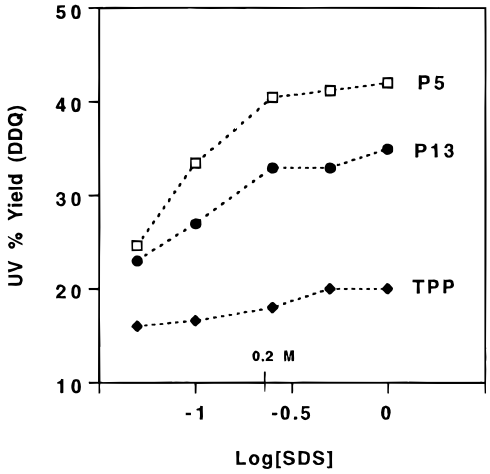


Figure 3. Porphyrin yield versus SDS concentration (mol/L) at a fixed ratio R = [SDS]/[aldehyde] = 50.

A two-phase analysis of this sort is supported by the dependence of porphyrin yield on SDS concentration at a fixed ratio R = [SDS]/[aldehyde] = 50 (Figure 3). Solute concentrations calculated from eq 1 are almost constant above ~0.2 M SDS, so yields should vary little, as observed. Below ~0.2 M SDS, the mole fraction of aldehyde (and pyrrole) in the micellar phase begins to decrease, so yields should decrease. The decrease is rapid for **P5** since S_m also moves away from its optimum value (Figure 2). The decrease is less marked for TPP since yields increase with decreasing S_m for more hydrophobic aldehydes.

Reversibility of the Reaction. Thermodynamic versus Kinetic Control. The shapes of the curves in Figure 2 and the qualitative kinetic observations suggested that porphyrinogen assembly might be irreversible for hydrophobic aldehydes. Two types of experiment were performed to examine reversibility:

(1) Slow Addition. Concentrated solutions of 3-(dodecyloxy)benzaldehyde (**15**) or 3-hydroxybenzaldehyde (**13**) and pyrrole (1:1) in 0.5 M SDS were added at various rates to a larger volume of acidified 0.5 M SDS solution so that the final reactant concentration was 10 mM (Figure 4). Slow addition of lipophilic aldehyde **15** gave higher yields of porphyrin **P4**, indicative of an irreversible reaction in which reactants are effectively maintained at high dilution in the micellar phase. Slow addition of **13** had a much smaller effect on the yield of **P3**, consistent with a reversible reaction in which the yield of porphyrin is determined by the final concentration of reactants.

(2) Porphyrinogen Exchange.[6c] Two aldehydes were condensed separately with pyrrole, and when the porphyrinogen concentrations had reached a maximum (time = t_{max}), the solutions were mixed. At a common time $5t_{max}$ after mixing, the distribution of crossover products was analyzed. Three pairs of aldehydes were chosen which reacted at similar rates and gave similar yields of porphyrin: two pairs of hydroxybenzaldehydes (**13**/**27** and **17**/**28**) and one pair of hydrophobic aldehydes (**15**/**37**). Little or no unreacted aldehyde monomer remained before mixing, as judged by TLC of oxidized samples. The two pairs of hydroxybenzaldehydes gave between 31 and 38% exchange, and the pair of hydro-

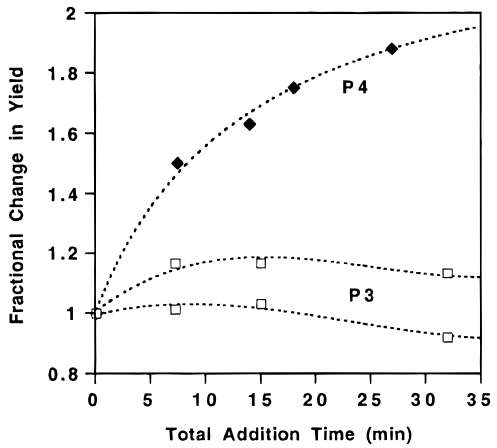


Figure 4. Porphyrin yield versus total addition time of a 1:1 mixture of aldehyde and pyrrole to acidified 0.5 M SDS. For **P4** the yields measured at 15 min and 5 h after the end of additions were the same, but absolute and relative yields for **P3** after 15 min (upper curve) were higher than those after 5 h (lower curve).

phobic aldehydes gave <10% exchange (see Experimental Section for details). In further experiments a mixture of unreacted aldehyde and pyrrole was added directly to the porphyrinogen derived from the other aldehyde. Under these conditions, scrambling was about twice as fast (54% for **13**/**27** and 62% for **17**/**28**) since only one porphyrinogen has to dissociate, at least in the early stages of the reaction. Control experiments showed that if SDS solutions of the aldehydes were mixed before addition of acid, near-statistical mixtures (100% exchange) of porphyrins resulted after oxidation at t_{max}.

The slow addition and mixing experiments confirm that porphyrinogen assembly is under kinetic control for hydrophobic aldehydes. For the more hydrophilic aldehydes, assembly is clearly reversible, but the slow exchange rates suggest that equilibrium may not always be achieved at t_{max}, therefore the reactions are not completely under thermodynamic control. The slight increase in yield of **P3** measured after short total addition times (Figure 4), which disappears if the reaction mixtures are left to stand, is also consistent with fairly slow kinetics. In principle, irreversible condensation should lead to quantitative yields of porphyrinogen at sufficiently high dilution. In practice, yields are probably limited by the accompanying side reactions, which would also be irreversible. Side reactions certainly occur in micellar synthesis as seen by the steady decline with time of porphyrinogen generated from hydrophilic aldehydes and the failure of certain classes of aldehyde.

Control Reactions in Organic Solvents. Aromatic solutes experience polar environments in micelles,[2,17] so the best control for micellar porphyrin synthesis is synthesis in a polar solvent at micelle-like reactant concentrations. Accordingly, benzaldehyde and 4-hydroxybenzaldehyde were condensed with pyrrole in methanol, ethanol, THF, and DMF at reactant concentrations between 50 and 500 mM, using 1 equiv of aqueous 10 M HCl as catalyst. The higher concentration was included to allow for the fact that micelles are not isotropic, so concentrations from the two-phase analysis are lower limits. Reactions were generally slow and heterogeneous,

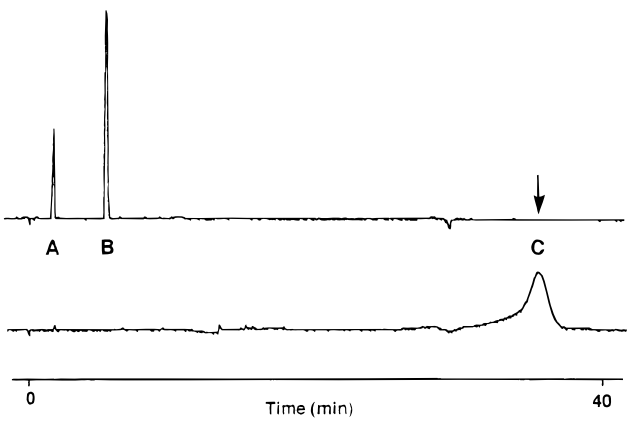


Figure 5. Capillary electrophoretograms before (upper trace) and after (lower trace) reaction between 4-hydroxybenzaldehyde (1 mM) and pyrrole (1 mM) in 0.1 M SDS (A = pyrrole, B = aldehyde). The arrow shows the retention time of micelles.

and while some porphyrin was formed in all solvents, yields were less than 5%.

Literature yields are low for direct condensation of pyrrole with aldehydes bearing unprotected functional groups (Table 1). For completeness, the synthesis of the phenolic porphyrins in Table 1 was also briefly investigated using Lindsey's conditions (10 mM reactants in CH_2Cl_2 or $CHCl_3$ with $BF_3{\cdot}Et_2O$ or TFA catalysis).[6b,c] UV yields from DDQ oxidation of reaction samples were as follows: **P2** (<1%), **P3** and **P5** (~22%), **P8** (~10%), **P9** (~5%), and **P11** (<1%). While useful amounts of **P3** and **P5** were formed, reactions were heterogeneous, confirming the finding by Lindsey et al. that this method gives low yields if reactants or products are sparingly soluble in CH_2Cl_2 or $CHCl_3$.[6c] The *ortho*-amide **32** also failed to give significant amounts of porphyrin under these conditions.

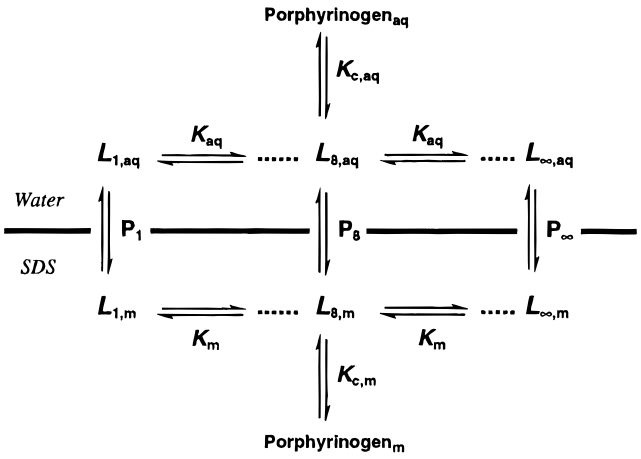
Partitioning of Reaction Products. To determine the relative affinity of micelles for reactants and products, the reaction between 4-hydroxybenzaldehyde and pyrrole in SDS was examined in more detail. Micellar capillary electrophoresis is a useful technique for measuring water−micelle partition coefficients—the more hydrophobic a solute is, the longer its retention time, with very hydrophobic species coeluting with the micelles.[18] As shown in Figure 5, the reactants transform into species which coelute with the micelles and thus have high partition coefficients with log $P \geq 5$.

The same reaction was also followed by ^{1}H NMR in a D_2O solution of SDS. Upon addition of acid, the pair of aromatic doublets from the aldehyde was gradually replaced with an upfield-shifted pair of multiplets and the aldehyde singlet at 9.7 ppm was replaced by a multiplet at 5.3 ppm. Longitudinal relaxation rates and self-diffusion coefficients were measured for aldehyde, products, and micelles. Products were found to relax about twice as fast as the starting aldehyde and to diffuse at a rate intermediate between starting aldehyde and micelles. These findings are also consistent with the reaction products being more strongly bound to the micelle than the reactants.

(17) Abraham, M. H.; Chadha, H. S.; Dixon, J. P.; Rafols, C.; Treiner, C. *J. Chem. Soc., Perkin Trans. 2* **1995**, 887.

(18) (a) *Capillary Electrophoresis: theory and practice;* Camilleri, P., Ed.; CRC Press: Boca Raton, FL, 1993. (b) Terabe, S.; Otsuka, K.; Ando, T. *Anal. Chem.* **1985**, *57*, 834.

Scheme 2. Model for Reversible Porphyrinogen Assembly in a Two-Phase System (L_i = Linear Intermediate Composed of *i* Monomer Units, Distributed with Partition Coefficient P_i between Micellar (Subscript m) and Aqueous (Subscript aq) Phases)



Discussion

In the classical Adler−Longo porphyrin synthesis, a solution of aldehyde and pyrrole in a high-boiling acid solvent is refluxed in air so that condensation and oxidation occur simultaneously.[19] This simple reaction is still the best way of making large quantities of robust porphyrins, particularly those which crystallize cleanly from the reaction mixture. A major improvement in the scope of aldehyde−pyrrole condensations was the introduction of a two-step method in which aldehyde and pyrrole are allowed to condense in a nonpolar solvent with exclusion of air, followed by oxidation of the porphyrinogen.[6,20a] The procedure optimized by Lindsey et al. in chlorinated solvents is currently the most useful one for organic soluble porphyrins, with yields of 20−40%, rising to ~50% in a few instances.[6,21] Recent improvements in the synthesis of tetraarylporphyrins include the use of an oxidizing cosolvent,[20b] oxidizing Lewis acids,[22a] and various clays as catalysts.[22b−d]

Adler−Longo synthesis gives low yields of sensitive porphyrins, reflecting the rather vigorous conditions, and the Lindsey method gives low yields of polar porphyrins, due to solubility problems. Micellar synthesis is thus complementary to these procedures, giving good yields of sensitive, polar porphyrins. The major practical limitation is that relatively large quantities of surfactant are required.

Role of the Micellar Phase. Cyclocondensation of four aldehydes and four pyrroles is calculated to be a favorable process in the gas phase.[23] Since the Adler−Longo synthesis is performed in polar solvents, and β-substituted pyrroles condense quite readily in polar solvents at room temperature,[24] porphyrinogen synthesis is also likely to be energetically downhill in polar media. The failure of control reactions in solvents with micelle-like polarity can therefore be ascribed to kinetic barriers, implying that one function of the surfactant phase is to provide a kinetically viable route to porphyrinogen. Simply keeping reaction mixtures homogeneous may be sufficient.

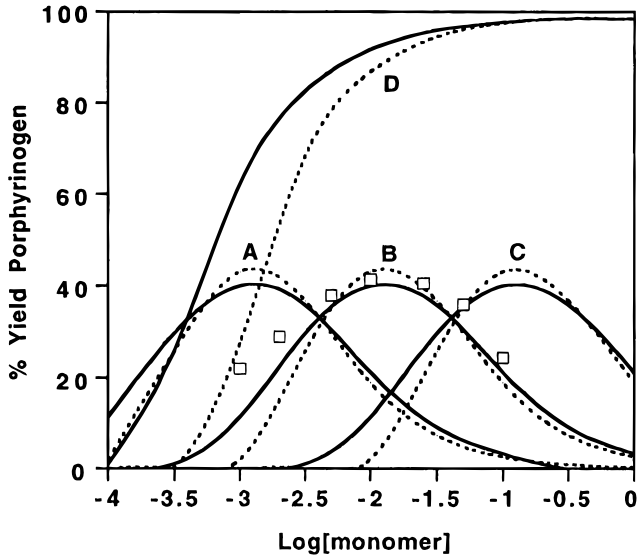


Figure 6. Simulation of porphyrinogen assembly in a single phase (solid curves) and in two phases (dotted curves). Equilibrium constants for single phase assembly: **A**, $K_m = 2 \times 10^4$, $K_c = 10$; **B**, $K_m = 2 \times 10^3$, $K_c = 10$; **C**, $K_m = 200$, $K_c = 10$; **D**, $K_m = 2 \times 10^3$, $K_c = 1 \times 10^3$. Equilibrium constants for assembly in 0.5 M SDS ($\beta = 0.125$), assuming an average reactant partition coefficient log $P_1 = 1.5$: **A**, $K_m = 5 \times 10^3$, $K_c = 15$; **B**, $K_m = 500$, $K_c = 15$; **C**, $K_m = 50$, $K_c = 15$; **D**, $K_m = 500$, $K_c = 1.5 \times 10^3$. The squares are UV yields of **P5** (DDQ oxidation), representing experimental values for the 4-hydroxybenzaldehyde−pyrrole equilibrium.

To provide further insight into the role of the surfactant, reversible porphyrinogen assembly was modeled according to Scheme 2. In this model porphyrinogen is produced by cyclization of octamer L_8, which is one of a series of linear intermediates present at equilibrium in both phases. Details of the model are discussed in the Experimental Section. Most of the reaction occurs inside micelles under the standard conditions, so simulations were initially confined to a single phase. Porphyrinogen yield as a function of reactant concentration is shown in Figure 6 (solid curves) for various values of the inter- and intramolecular equilibrium constants K_m and K_c. These were initially chosen to roughly reproduce experimental data for the 4-hydroxybenzaldehyde−pyrrole equilibrium (curve B) and then varied independently. The simulations illustrate three general points:

(1) An optimum reactant concentration arises naturally for porphyrinogen assembly, as noted by Lindsey et al. for TPP synthesis in CH_2Cl_2.[6c] If the reactants are too dilute, the linear species will consist largely of monomer and the concentration of $L_{8,m}$ will be low. If the reactants

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(20) (a) Rocha Gonsalves, A. M. d'A.; Pereira, M. M. *J. Heterocycl. Chem.* **1985**, *22*, 931. (b) Rocha Gonsalves, A. M. d'A.; Varejão, J. M. T. B.; Pereira, M. M. *J. Heterocycl. Chem.* **1991**, *28*, 635.

(21) (a) Quast, H.; Dietz, T.; Witzel, A. *Liebigs Ann. Chem.* **1995**, 1495. (b) Wagner, R. W.; Ruffing, J.; Breakwell, B. V.; Lindsey, J. S. *Tetrahedron Lett.* **1991**, *32*, 1703.

(22) (a) Gradillas, A.; del Campo, C.; Sinisterra, J. V.; Llama, E. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2611. (b) Shinoda, T.; Izumi, Y.; Onaka, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1805. (c) Onaka, M.; Shinoda, T.; Izumi, Y.; Nolen, E. *Tetrahedron Lett.* **1993**, *34*, 2625. (d) Laszlo, P.; Luchetti, J. *Chem. Lett.* **1993**, 449.

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(24) Tietze, L. F.; Geissler, H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1038 and references therein.

are too concentrated, $[L_{8,m}]$ will again be low, as the equilibrium overshoots to polymer.

(2) For a fixed value of K_c, the optimum reactant concentration is inversely proportional to K_m, as illustrated by the shift of curve C to curve A when log K_m is increased by a factor of 2. An increase in K_m may account for the higher yields from hydrophobic aldehydes at low reactant concentrations (Figure 2), although an equilibrium treatment eventually becomes inappropriate when condensation is irreversible.

(3) The maximum yield for a fixed K_m depends only on K_c. Curve D shows that if K_c is large enough, the entire equilibrium is pulled over to porphyrinogen, as expected.

In reality the aqueous phase is also present, tending to extract the more polar species out of micelles. For assembly to be favorable under these conditions, K_m should remain approximately constant for each step, as in homogeneous solution, and simulations with this assumption (dotted curves in Figure 6) are qualitatively similar to the single-phase results. If K_m is constant, then Scheme 2 requires that the binding energies of successive intermediates to the micelle increase in an additive fashion. In fact this is a reasonable expectation since group additivity schemes are well established for partitioning processes.[25] Experimental support comes from the finding that the products of the 4-hydroxybenzaldehyde−pyrrole equilibrium do indeed bind to micelles much more strongly than the reactants. In addition Martinek et al. found that the product from condensation of benzaldehyde and aniline in SDS solution is bound about twice as well as the reactants.[8b]

Micelles can thus be said to fulfill the basic thermodynamic requirements for efficient assembly, acting as potential wells for porphyrinogen. An inevitable consequence of the progressive solubilization mechanism is that if species sink too far into the potential well, the rate of dissociation back to reactants will start to decrease, and this provides a qualitative explanation of why hydrophobic aldehydes condense under kinetic control. The very slow rate of monomer exchange between hydrophobic porphyrinogens clearly shows that porphyrinogens can become trapped in micelles; a similar observation was made for clay-mediated porphyrin synthesis, in which products are compartmentalized within the pores of the mineral.[22c]

Summary and Concluding Remarks

Porphyrins have been prepared from a range of aldehydes in anionic micelles. Porphyrinogen assembly was found to be reversible for polar aromatic aldehydes but irreversible for hydrophobic ones. Moderate to good yields of sensitive functionalized porphyrins, and also their β-deuterated versions, could be obtained directly from the corresponding aldehydes without the need for protecting groups. The reactions are simple to perform, and the conditions are mild,[26] although large quantities of surfactant are required. The present work is unusual among micelle-mediated reactions in that it is preparatively unique—many of the more highly functionalized porphyrins in Table 1 are difficult to make by direct aldehyde−pyrrole condensation under conventional conditions. SDS was used exclusively, but other surfactants with different local microenvironments and partitioning properties would be expected to have their own particular selectivities.

The variation of porphyrin yield with substrate partition coefficient, reactant concentration, and surfactant concentration was rationalized within a two-phase scheme and supported by numerical simulations. It was concluded that micelles act as potential wells, binding products more tightly than reactants, and may also catalyze condensation reactions. Multiple assembly within micelles is an interesting strategy which may be extendible to other reactions and other phases.[27]

Experimental Section

General. Pyrrole was distilled and stored under argon. One liter stock solutions of 0.5 M SDS were prepared by stirring 150 g of "95% lauryl sulfate" (Aldrich, SDS content 72%) in MilliQ water under a flow of argon. SDS solutions were sealed with rubber septa and used within a few months of preparation. Reactions were run under argon, transferring surfactant solutions with plastic syringes. Silica gel 60 (Merck 9385, 230−400 mesh) was employed for flash chromatography. FAB mass spectra were obtained using a *m*-nitrobenzyl alcohol matrix. NMR spectra are referenced to $CHCl_3$ (7.25 ppm) or acetone (2.05 ppm). Extinction coefficients and λ_{max} values were measured in "solvent A" which refers to a mixture of CH_2Cl_2 and MeOH (4:1) containing 1% v/v pyridine. Capillary electrophoresis was performed on an Applied Biosystems 270-HT instrument.

Small Scale Trials (R = [SDS]/[aldehyde] = 50). Aldehyde (0.1 mmol) was stirred with aqueous SDS (10 mL, 0.5 M) until a clear solution was obtained, and then pyrrole (7 μL, 0.1 mmol) was added. Hydrochloric acid (25−300 μl, 10 M, plastic syringe and needle) was injected to initiate reaction, and samples (0.5 mL) were withdrawn at intervals. The samples were quenched by addition to 100 μL portions of a 10 mg/mL solution of DDQ in THF in 5 mL volumetric flasks (stock solutions of DDQ in THF were prepared in dry THF, shielded from light, and used within 1 day). After allowing the solution to stand for ~30 min, the flasks were filled up to the mark with THF, and 50 or 100 μL of this solution was added to 2.0 mL of solvent A in a cuvette. The difference in absorbance was measured between the top of the Soret band and the inflection between the Soret and the peak due to DDQ reduction products at ~350 nm. An operational extinction coefficient (ϵ_{exp}) measured between 350 nm and the top of the Soret for pure porphyrin in solvent A was used to calculate porphyrin concentrations (generally $\epsilon_{exp} \sim 0.95\epsilon$ where ϵ is the true extinction coefficient). This method underestimates the concentration of porphyrin slightly, particularly for low-yielding reactions due to band overlap. In those cases where the porphyrin was not isolated on a preparative scale, the ϵ_{exp} value measured for a similarly substituted porphyrin was used to estimate the yield. For alkyl- and ester-substituted tetraarylporphyrins, the extinction coefficient for TPP was used (log $\epsilon_{exp} = 5.69$). For tetraalkylporphyrins an extinction coefficient of log $\epsilon_{exp} = 5.30$[28] was assumed.

Representative Procedure for Preparative Scale Synthesis: *meso*-Tetrakis(4-hydroxyphenyl)porphyrin (P5).[22a] Hydrochloric acid (1.0 mL, 10 M) was added to a rapidly stirring solution of 4-hydroxybenzaldehyde (122 mg, 1.0 mmol) and pyrrole (70 μL, 1.0 mmol) in aqueous SDS (100

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(26) The ease with which porphyrinogens can be assembled in a micelles hints at a role for such supramolecular aggregates in the prebiotic synthesis of porphyrins. For prebiotic type mineral-catalyzed porphyrin synthesis, see: Cady, S. S.; Pinnavaia, T. J. *Inorg. Chem.* **1978**, *17*, 1501.

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(28) Albers, V. M.; Knorr, H. V. *J. Chem. Phys.* **1936**, *4*, 422.

mL, 0.5 M) under a slow flow of argon. The initial straw-colored solution quickly turned orange and then orange-brown but remained clear. A solution of TCQ (220 mg, 0.89 mmol) in THF (5 mL, warmed briefly to dissolve the TCQ) was added after 30 min, and the mixture was stirred overnight open to the air. The dark suspension was poured into a separatory funnel containing a mixture of EtOAc (100 mL), aqueous potassium hydroxide (5 mL, 2 M), potassium phosphate pH 7 buffer (10 mL, 1 M), and aqueous potassium chloride (10 mL, 3 M), rinsing out the reaction flask with water (50 mL). Phase separation after shaking was rapid to give a dark organic layer. The aqueous layer was extracted with a further portion of EtOAc (50 mL), and the combined organic extracts were washed with water (2 × 100 mL; a little brine was added after the initial water shake to induce rapid phase separation) and dried (Na_2SO_4). The desiccant was filtered off through a coarse glass frit, which also removed some insoluble black material, and the filtrate rotary evaporated with the addition of ~5 g of flash silica gel to give a friable brown-black solid. This was tipped onto a prepacked (5% THF in CH_2Cl_2) silica gel column (2.2 × 25 cm), and the column was eluted with 5−12% THF in CH_2Cl_2, collecting the main purple band. The crude porphyrin was dissolved in warm THF (~5 mL), filtered through a plug of cotton wool, and then diluted with hot cyclohexane (10−15 mL) until crystallization started. After allowing the solution to stand overnight, the crystals that formed were filtered, washed with cyclohexane, and dried at 180 °C (0.1 mmHg) for 12 h to give porphyrin **P5** (65 mg, 38%) as fine purple needles: ^{1}H NMR (d_6-acetone, 250 MHz) δ −2.71 (br s, 2H), 7.30 (d, J = 8.5 Hz, 8H), 8.07 (d, J = 8.5 Hz, 8H), 8.89 (br s, 4H, OH), 8.93 (s, 8H); λ_{max} (solvent A) 421 (log ϵ = 5.66), 518, 556, 591, 650 nm; HRFABMS m/z 679.2327 (MH^+), $C_{44}H_{31}N_4O_4$ requires 679.2341.

Other porphyrins were prepared on the same scale from the appropriate aldehydes using the acid concentrations and reaction times listed in Table 1. The solvents for extraction (if different solvents or solvent volumes were used), chromatography, and crystallization are summarized for each porphyrin, along with any other differences in procedure. Unless indicated otherwise, reaction mixtures were neutralized with aqueous KOH, adding enough of an aqueous potassium salt before extraction to convert the surfactant into its potassium salt. This material is only slightly soluble in water and most organic solvents and remains largely suspended in the aqueous layer (magnesium or calcium salts were also effective). EtOAc was found to be the best solvent for extractions because it is a good solvent for polar porphyrins and has little tendency to form emulsions. Chlorinated solvents could also be employed, but generally give slower phase separations.

The progress of DDQ or TCQ oxidations was conveniently followed by injecting 5 μL of reaction mixture directly into solvent A in a cuvette. Porphyrin concentrations were usually monitored by UV at various stages during purification to check for material recovery. Porphyrins bearing polar functionality frequently crystallize with solvent or water of crystallization,[29] and prolonged drying at high temperatures was sometimes necessary to produce material of constant weight. All isolated porphyrins were pure by ^{1}H NMR with no residual organic solvent.

***meso*-Tetrakis(4-methylphenyl)porphyrin (P1).**[22a] Extraction: 100 mL and then 2 × 50 mL of CH_2Cl_2 (slight emulsion formation). Chromatography: 50% hexane in CH_2Cl_2. The crude porphyrin was refluxed briefly in methanol, and the crystals were washed well with methanol and dried at 200 °C (0.1 mmHg) for 12 h to give **P1** (25 mg, 15%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ −2.79 (br s, 2H), 2.70 (s, 12H), 7.54 (d, J = 8.5 Hz, 8H), 8.09 (d, J = 8.5 Hz, 8H), 8.84 (s, 8H); λ_{max} (solvent A) 417 (log ϵ = 5.69), 515, 551, 589, 645 nm; FABMS m/z 671.4 (MH^+).

***meso*-Tetrakis(2-hydroxyphenyl)porphyrin (P2).**[30] Chromatography: 2−10% THF in CH_2Cl_2, collecting four red bands. Part of the slowest moving α,α,α,α-atropisomer band was contaminated with brown material and was discarded. The combined red fractions were crystallized from THF/cyclohexane and then recrystallized from MeOH/cyclohexane. The mixture of crystals and amorphous purple powder was dried at 150 °C (0.1 mmHg) for 12 h to give **P2** (35 mg, 20%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ −2.75 (br s, 2H), 5.0 (br s, 4H, OH), 7.32 (m, 8H), 7.72 (m, 4H), 7.97 (m, 4H), 8.9 (m, 4H); λ_{max} (solvent A) 417 (log ϵ = 5.65), 511, 545, 586, 642 nm; FABMS m/z 679.4 (MH^+).

***meso*-Tetrakis(3-hydroxyphenyl)porphyrin (P3).**[19d] Chromatography: 3−12% THF in CH_2Cl_2. The crude porphyrin was washed with methanol, then dissolved in hot reagent-grade chloroform, and left to evaporate to a small volume over several days. The small purple-black prisms were dried at 150 °C (0.1 mmHg) for 12 h to give **P3** (44 mg, 26%): ^{1}H NMR (d_6-acetone, 250 MHz) δ −2.77 (br s, 2H), 7.33 (d, J = 7.3 Hz, 4H), 7.63 (t, J = 7.3 Hz, 4H), 7.73 (d, J = 7.3 Hz, 4H), 7.74 (s, 4H), 8.83 (br s, 4H), 8.95 (s, 8H); λ_{max} (solvent A) 417 (log ϵ = 5.67), 514, 548, 587, 643 nm; FABMS m/z 679.4 (MH^+).

***meso*-Tetrakis(3-(dodecyloxy)phenyl)porphyrin (P4).** Extraction: 2 × 100 mL and then 50 mL of EtOAc (phase separation was best seen with the help of a hand-held UV lamp since both aqueous and organic layers were very dark). Chromatography: 25−35% CH_2Cl_2 in hexane. The crude porphyrin was dissolved in warm MeOH with the minimum volume of CH_2Cl_2. On standing, a slowly solidifying shiny purple oil was deposited. This was washed with MeOH and dried at 150 °C (0.1 mmHg) for 12 h to give porphyrin **P4** (33 mg, 9%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ −2.80 (br s, 2H), 0.84 (br t, 12 H), 1.12−1.55 (m, 72H), 1.86 (m, 8H), 4.13 (br t, 8H), 7.31(d, J = 7.3 Hz, 4H), 7.61 (t, J = 7.3 Hz, 4H), 7.77 (s, 4H), 7.78 (d, J = 7.3 Hz, 4H), 8.88 (s, 8H); λ_{max} (solvent A) 418 (log ϵ = 5.73), 514, 547, 587, 643 nm; HRFABMS m/z 1351.9851 (MH^+), $C_{92}H_{127}N_4O_4$ requires 1351.9857. Anal. Calcd for $C_{92}H_{126}N_4O_4$: C, 81.73; H 9.39; N, 4.14. Found: C, 81.72; H, 9.45; N, 4.02.

***meso*-Tetrakis(4-methoxyphenyl)porphyrin (P6).**[20b,22a] Chromatography: 5% THF in CH_2Cl_2. The crude porphyrin was refluxed briefly in methanol, and the crystals were washed well with methanol and dried at 200 °C (0.1 mmHg) for 12 h to give porphyrin **P6** (34 mg, 18%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ −2.75 (br s, 2H), 4.09 (s, 12H), 7.28 (d, J = 8.5 Hz, 8H), 8.11 (d, J = 8.5 Hz, 8H), 8.65 (s, 8H); λ_{max} (solvent A) 420 (log ϵ = 5.66), 516, 554, 591, 649 nm; FABMS m/z 635.7 (MH^+).

***meso*-Tetrakis(4-(2-(methoxycarbonyl)ethoxy)phenyl)-porphyrin (P7).** Aqueous potassium hydroxide (15 mL, 2 M), aqueous potassium chloride (15 mL, 3 M), and water (100 mL) were added after TCQ oxidation, and the precipitated potassium dodecyl sulfate was filtered from the basic reaction mixture using a coarse glass frit and washed with water. The filtrate was acidified with aqueous HCl until the porphyrin precipitated (pH ~ 5), filtered through a 3 × 3 cm plug of flash silica gel, and washed with water. The porphyrin-containing silica gel was partially dried under aspirator pressure, and then porphyrin was eluted with 10% MeOH in THF and the filtrate evaporated. The crude porphyrin tetraacid was stirred overnight in a mixture of 10% w/w HCl in MeOH (50 mL) and CH_2Cl_2 (30 mL). The volatiles were evaporated, and a solution of the crude porphyrin tetraester in CH_2Cl_2 was washed with pH 7 buffer, concentrated to a small volume, and applied directly to a silica gel column, eluting with 1−2% THF in CH_2Cl_2. The product was washed with a little THF and then MeOH and dried at 100 °C (0.1 mmHg) for 12 h to give **P7** (82 mg, 34%) as a purple powder: ^{1}H NMR ($CDCl_3$, 250 MHz) δ −2.81 (br s, 2H), 3.94 (s, 12H), 4.93 (s, 8H), 7.28 (d, J = 8.5 Hz, 8H), 8.12 (d, J = 8.5 Hz, 8H), 8.84 (s, 8H); λ_{max} (solvent A) 419 (log ϵ = 5.72), 516, 552, 590, 647 nm; FABMS m/z 967.9 (MH^+).

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(30) Stäubli, B.; Fretz, H.; Piantini, U.; Woggon, W.-D. *Helv. Chim. Acta* **1987**, *70*, 1173.

***meso*-Tetrakis(3,4-dihydroxyphenyl)porphyrin (P8).**[31] Extraction: 200 mL and then 150 mL of EtOAc. Chromatography: 30% THF in CH_2Cl_2 containing 0.01% v/v AcOH. The crude porphyrin was crystallized from THF/cyclohexane and dried at 100 °C (0.1 mmHg) for 24 h to give **P8** (89 mg, 48%) as a purple-black microcrystalline powder: ^{1}H NMR (d_6-acetone, 250 MHz) δ −2.73 (br s, 2H), 7.27 (d, J = 8.3 Hz, 4H), 7.57 (dd, J = 8.3, 2.2 Hz, 4H), 7.73 (d, J = 2.2 Hz, 4H), 8.39 (br s, 8H), 8.97 (s, 8H); λ_{max} (solvent A) 423 (log ϵ = 5.51), 518, 556, 591, 648 nm; HRFABMS m/z 743.2138 (MH^+), $C_{44}H_{31}N_4O_8$ requires 743.2142.

***meso*-Tetrakis(3,5-dihydroxyphenyl)porphyrin (P9).** Extraction: 200 mL and then 100 mL of EtOAc. Chromatography: 30% THF in CH_2Cl_2 containing 0.01% v/v AcOH. The crude porphyrin was washed twice with CH_2Cl_2, and the purple flakes were recrystallized from THF/cyclohexane and dried at 150 °C (0.1 mmHg) for 24 h to give **P9** (65 mg, 34%) as a purple powder: ^{1}H NMR (d_6-acetone, 250 MHz) δ −2.81 (br s, 2H) 6.85 (t, J = 2.1 Hz, 4H), 7.25 (d, J = 2.1 Hz, 8H), 8.71 (br s, 8H), 9.03 (s, 8H); λ_{max} (solvent A) 419 (log ϵ = 5.47), 514, 548, 587, 642 nm; HRFABMS m/z 743.2200 (MH^+), $C_{44}H_{31}N_4O_8$ requires 743.2142.

***meso*-Tetrakis(4-hydroxy-3-methoxyphenyl)porphyrin (P10).**[19d] Extraction: 2 × 100 mL of EtOAc. Chromatography: 1−5% THF in CH_2Cl_2. The crude porphyrin was crystallized from THF/MeOH, washed thoroughly with MeOH, and dried at 180 °C (0.1 mmHg) for 12 h to give **P10** (42 mg, 21%) as a purple powder: ^{1}H NMR (d_6-acetone, 250 MHz) δ −2.72 (br s, 2H), 4.02 (s, 12H), 7.28 (d, J = 8.3 Hz, 4H), 7.68 (br d, J = 8.3 Hz, 4H), 7.85 (s, 4H), 8.14 (br s, 4H), 8.96 (s, 8H); λ_{max} (solvent A) 423 (log ϵ = 5.61), 518, 555, 590, 650 nm; FABMS m/z 799.8 (MH^+).

***meso*-Tetrakis(3,4,5-trihydroxyphenyl)porphyrin (P11).**[32] The starting aldehyde required ∼45 min of stirring to dissolve completely. Extraction: 2 × 100 mL and then 50 mL of EtOAc. Chromatography: 0.2% v/v AcOH in EtOAc (41% porphyrin recovery as measured by UV). The crude porphyrin was crystallized under argon from THF/cyclohexane and dried at 100 °C (0.1 mmHg) for 12 h to give **P11** (24 mg, 12%) as a black powder: ^{1}H NMR (d_6-DMSO, 250 MHz) δ −2.96 (br s, 2H), 7.11 (s, 4H), 8.60 (br s, 4H), 8.93 (s, 8H), 9.31 (br s, 8H); λ_{max} (solvent A) 421 (log ϵ = 5.32), 517, 555, 591, 649 nm; HRFABMS m/z 807.1955 (MH^+), $C_{44}H_{31}N_4O_{12}$ requires 807.1938.

The absorbance of this porphyrin decreases slowly on being allowed to stand in solvent A. **P11**, previously prepared by demethylation of its permethyl ether, showed the same changes in UV−vis spectra on addition of base and acid as reported by Milgrom et al.[32]

***meso*-Tetrakis(3-acetamidophenyl)porphyrin (P12).** The starting aldehyde required 1 h of stirring to dissolve completely. DDQ (200 mg) in THF (5 mL) was used as the oxidant. Extraction: 200, 150, and then 100 mL of EtOAc. Chromatography: 30% THF in CH_2Cl_2, discarding some greenish forerun and contaminated tailings. The crude porphyrin was crystallized from MeOH/trichloroethylene, washed well with trichloroethylene, and dried at 180 °C (0.1 mmHg) for 12 h to give **P12** (50 mg, 23%) as purple crystals: ^{1}H NMR (d_6-acetone, 250 MHz) δ −2.76 (br s, 2H), 2.16 (s, 12H), 7.75 (br t, 4H), 7.95 (br d, 4H), 8.17 (br d, 4H), 8.56 (br s, 4H), 8.94 (s, 8H), 9.54 (br s, 4H); λ_{max} (solvent A) 418 (log ϵ = 5.65), 513, 548, 587, 643 nm; HRFABMS m/z 843.3401 (MH^+), $C_{52}H_{43}N_8O_4$ requires 843.3407.

***meso*-Tetrakis(4-acetamidophenyl)porphyrin (P13).**[19d] Extraction: 150, 100, and then 50 mL of EtOAc. Chromatography: 1−10% MeOH in 1:1 THF/CH_2Cl_2, discarding fast running yellow and brown bands and contaminated tailings. The crude product was dissolved in a small volume of hot pyridine and hot trichloroethylene added until crystals began to separate. This process was repeated, and the product washed was well with methanol and dried at 180 °C (0.1 mmHg) for 12 h to give **P13** (52 mg, 25%) as purple crystals: ^{1}H NMR (d_6-acetone, 250 MHz) δ −2.73 (br s, 2H), 2.26 (s, 12H), 8.10, 8.18 (ABq, J = 8.8 Hz, 16H), 8.92 (s, 8H), 9.64 (br s, 4H); λ_{max} (solvent A) 421 (log ϵ = 5.67), 517, 554, 591, 648 nm; FABMS m/z 843.7 (MH^+).

***meso*-Tetrakis(4-(trifluoroacetamido)phenyl)porphyrin (P14).** The starting aldehyde was not completely soluble in 0.5 M SDS, but a clear solution was formed ∼30 min after the addition of acid. Extraction: 150 mL and then 50 mL of EtOAc. Chromatography: 3−7.5% THF in CH_2Cl_2, discarding contaminated tailings. The crude product was crystallized twice from THF/cyclohexane and dried at 180 °C 0.1 mm Hg for 12 h to give **P14** (107 mg, 40%) as a purple powder: ^{1}H NMR (d_6-acetone, 400 MHz) δ −2.75 (br s, 2H), 8.23, 8.31 (ABq, J = 8.5 Hz, 16H), 8.94 (s, 8H), 10.74 (br s, 4H); λ_{max} (solvent A) 419 (log ϵ = 5.71), 515, 552, 590, 646 nm; HRFABMS m/z 1059.2247 (MH^+), $C_{52}H_{31}N_8O_4F_{12}$ requires 1059.2276.

***meso*-Tetrakis(furan-2-yl)porphyrin (P15).**[19d] Extraction: 150 mL and then 100 mL of EtOAc. Chromatography: 1−5% THF in CH_2Cl_2. The crude porphyrin, which contained some coeluted SDS, was slurried with MeOH, filtered, and washed well with MeOH. Crystallization from THF/cyclohexane gave **P15** (15 mg, 10%) as small purple crystals after being dried at rt 0.1 mmHg for 2 days. ^{1}H NMR (d_6-acetone, 400 MHz) δ −2.70 (br s, 2H), 7.50 (dd, J = 3.3, 2 Hz, 4H), 7.48 (d, J = 3.3 Hz, 4H), 8.32 (d, J = 2 Hz, 4H), 9.23 (s, 8H); λ_{max} (solvent A) 430 (log ϵ = 5.37), 525, 572, 670 nm; HRFABMS m/z 575.1702 (MH^+), $C_{36}H_{23}N_4O_4$ requires 575.1719.

This porphyrin was previously prepared in trace amounts by Triebs and Haberle.[19d] **P15** decomposes slowly in solution, coating glassware with a yellow film, but appears to be quite stable when crystalline.

***meso*-Tetrakis(thien-2-yl)porphyrin (P16).**[19d] Extraction: 150 mL and then 50 mL of EtOAc. Chromatography: 0.01% pyridine in CH_2Cl_2. The crude porphyrin was slurried with MeOH, filtered, washed well with MeOH, and dried at 100 °C 0.1 mm Hg for 12 h to give **P16** (39 mg, 24%) as purple crystals: ^{1}H NMR ($CDCl_3$, 400 MHz) δ −2.66 (br s, 2H), 7.50 (dd, J = 5.3, 3.4 Hz, 4H), 7.85 (dd, J = 5.3, 1.3 Hz, 4H), 7.91 (dd, J = 3.4, 1.3 Hz, 4H), 9.03 (s, 8H); λ_{max} (solvent A) 430 (log ϵ = 5.56), 525, 572, 670 nm; HRFABMS m/z 639.0785 (MH^+), $C_{36}H_{23}N_4S_4$ requires 639.0806.

Porphine.[33] Hydrochloric acid (0.25 mL, sp gr 1.16) was added to a stirred solution of 2-(hydroxymethyl)pyrrole (97 mg, 1.0 mmol) in aqueous SDS (100 mL, 0.5 M). The solution rapidly turned bright orange. DDQ (200 mg) in THF (5 mL) was added after 10 min, and after a further 30 min the reaction mixture was worked up in the usual manner. Extraction: 3 × 100 mL of EtOAc (the aqueous layer was filtered after the first extraction to remove finely divided black material). Volatiles were evaporated, and a solution of the crude material in CH_2Cl_2 was eluted through a short column of silica gel. The crude porphin thus obtained (∼2 mg, 2% UV yield assuming logϵ = 5.26[28]) was not purified further.

Per-β-deuterated *meso*-Tetrakis(4-hydroxyphenyl)porphyrin (d_8-P5). This reaction was run with a low surfactant/substrate ratio (R = 13) to maximize the amount of porphyrin produced per mL of D_2O rather than the chemical yield. A mixture of 4-hydroxybenzaldehyde (50 mg, 0.41 mmol), pyrrole (28.5 μL, 0.41 mmol), and SDS (1.5 g, 5.2 mmol) was stirred in D_2O (5 g) under argon until a clear solution was obtained. Deuteriotrifluoroacetic acid (32 μL, 0.41 mmol) was added, followed after 15 min by a suspension of TCQ (100 mg, 0.39 mmol) in dry THF (1 mL). After overnight stirring, workup as for **P5** and crystallization from THF/cyclohexane gave ***d*$_8$-P5** (8.5 mg, 12%). ^{1}H NMR (20% d_6-acetone in $CDCl_3$) integration of the residual β-pyrrole resonance indicated 97.5% deuterium incorporation: FABMS m/z 687.5 (MH^+).

Per-β-deuterated *meso*-Tetrakis(3,4-dihydroxyphenyl)porphyrin (d_8-P8). The same procedure as for ***d*$_8$-P5** was followed starting from 3,4-dihydroxybenzaldehyde (50 mg, 0.36

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Table 2. Relative Percent Yields of Porphyrins from Porphyrinogen Mixing Experiments

	statistical distribution	A = **17**, B = **28**			A = **13**, B = **27**		
		λ_{max} (nm)	[A + B][a]	[A] + [B][b]	λ_{max} (nm)	[A + B]	[A] + [B]
A_4	6.25	417.0	8[c]	37	422.9	7	34
A_3B	25	417.6	28	13	422.5	19	11
A_2B_2	37.5	418.2	37	9	422.0	41	14
AB_3	25	418.8	23	5	421.4	27	8
B_4	6.25	419.2	4	36	421.0	6	33

[a] SDS solutions of A and B mixed before addition of acid. DDQ oxidation at t_{max}. [b] SDS solutions of A and B condensed separately with pyrrole and then mixed at t_{max}. DDQ oxidation at $5t_{max}$. [c] Relative yields reproducible to within a few percent.

mmol) to give ***d*$_8$-P8** (10.5 mg, 15%). ^{1}H NMR (d_6-acetone) indicated >98% deuterium incorporation: FABMS *m*/*z* 751.3 (MH^+).

Porphyrinogen Exchange Experiments. The procedure is illustrated for the pair of aldehydes 3-hydroxybenzaldehyde (**13**) and 3,5-dihydroxybenzaldehyde (**27**). Three solutions were prepared. Solution A contained aldehyde **13** (0.1 mmol) and pyrrole (0.1 mmol) in aqueous SDS (10 mL, 0.5 M). Solution B was the same except with aldehyde **27**. Solution C was prepared by mixing 3.33 mL of A and 3.33 mL of B in a separate flask so that A, B, and C were all of a volume of 6.66 mL. Reaction was initiated by addition of aqueous HCl (200 μL, 10 M) to A, B, and C. After 1 h, DDQ (15 mg) in THF (0.5 mL) was added to C, and solutions A and B were mixed. Samples (2 mL) of the A/B mixture were then withdrawn at various times and added to DDQ (4 mg) in THF (0.5 mL). After the solution was allowed to stand for 1 h, sufficient potassium phosphate buffer (pH 7, 1 M) was added to the oxidized samples to precipitate surfactant and the crude porphyrins were isolated by extraction with EtOAc. Preparative TLC (15% MeOH in CH_2Cl_2) of a portion of the 5 h ($5t_{max}$) sample from the A/B mixture gave **P3**, **P9**, and three mixed porphyrins of intermediate polarity. A portion of the reaction mixture from C was also chromatographed. The relative yields given in Table 2 were calculated from absorbance measurements, assuming that extinction coefficients for mixed porphyrins were weighted linear combinations of extinction coefficients for **P3** and **P9**. The A_2B_2 fraction was assumed to be an unresolved mixture of the two possible isomeric porphyrins. The remaining portions of the 5 h sample and the C reaction mixture were eluted separately through short columns of silica gel to remove base line material and analyzed by FABMS. The relative intensities of the five MH^+ peaks (679 (A_4 = **P3**), 695 (A_3B), 711 (A_2B_2), 727 (AB_3), and 743 (B_4 = **P9**)) were in qualitative agreement with chromatographically isolated porphyrin yields.

In similar experiments, solid aldehyde **13** or **27** (0.1 mmol) along with an equivalent of pyrrole was added separately to solutions of porphyrinogen derived from the other aldehyde 1 h after the reaction had been initiated, and the products were analyzed as above. Adding aldehyde **13** to the porphyrinogen formed from **27** gave 54% exchange after $5t_{max}$, and the opposite order of addition gave 63% exchange after the same time.

For aldehydes **17** and **28** (Table 2), the reaction was initiated with aqueous HCl (100 μL, 10 M), solutions were mixed after 0.5 h, and mixtures were chromatographed with 7% MeOH in CH_2Cl_2. For aldehydes **15** and **37**, the reaction was initiated with aqueous HCl (200 μl, 10 M), and the solutions were mixed after 1 h. For this pair of aldehydes only three fractions were isolated by chromatography (CH_2Cl_2): **P4**, a mixed fraction of all four resolvable crossover products, and *meso*-tetrakis(4-(trichloroacetamido)phenyl)porphyrin (FABMS *m*/*z* 1256.6 (MH^+)).

Slow Addition Experiments. A mixture of 3-(dodecyloxy)benzaldehyde (**15**) (1.0 mmol) and pyrrole (1.0 mmol) was stirred in aqueous SDS (10 mL, 0.5 M) until a clear solution was obtained. Portions (1.0 mL) of this solution were added by syringe pump at different rates to separate flasks containing aqueous SDS (9.0 mL, 0.5 M) and aqueous HCl (0.3 mL, 10 M). Samples were withdrawn at 15 min, 1 h, and 5 h after completion of addition, and the porphyrin concentration was assayed in the usual manner. Slow addition of 3-hydroxybenzaldehyde (**13**) was performed in exactly the same fashion. After the additions had been completed, yields from **15** stayed constant, but yields from **13** declined slowly. Yields measured 5 h after completion of addition were ~65% of those after 15 min.

Control Reactions in Organic Solvents. Aqueous HCl (20 μL, 10 M) was added to a solution of benzaldehyde or 4-hydroxybenzaldehyde (0.2 mmol) and pyrrole (0.2 mmol) in a solvent (0.4, 2, or 4 mL) and the mixture stirred under argon. Aliquots of reaction mixture were withdrawn periodically and oxidized with DDQ, measuring the porphyrin content by UV absorbance as described above. Solvents used were MeOH, EtOH, THF, and DMF. Trifluoroacetic acid (1 equiv) was also employed as catalyst for the reaction of benzaldehyde and pyrrole in MeOH, THF, and DMF at 10 mM reactants. Yields in all cases were less than 5%.

UV yields and conditions for synthesis under Lindsey's conditions (10 mM reactants in anhydrous chlorinated solvent)[6c] are summarized in the format porphyrin {aldehyde, solvent, catalyst, maximum yield, time}: **P2** {2-hydroxybenzaldehyde, CH_2Cl_2 or $CHCl_3$ (with or without EtOH), 20 mM TFA or 3.3 mM $BF_3{\cdot}Et_2O$, <1%}, **P3** {3-hydroxybenzaldehyde, CH_2Cl_2, 20 mM TFA, 22%, 2 h}, **P5** {4-hydroxybenzaldehyde, CH_2Cl_2, 20 mM TFA, 22%, 1 h}, **P8** {3,4-dihydroxybenzaldehyde, CH_2Cl_2, 33 mM TFA, 10%, 3 h}, **P9** {3,5-dihydroxybenzaldehyde, CH_2Cl_2, 33 mM TFA, 5%, 6 h}, **P11** {3,4,5-trihydroxybenzaldehyde, CH_2Cl_2, 20 mM TFA, <1%}, **P32** {2-acetamidobenzaldehyde, CH_2Cl_2, 3.3 mM $BF_3{\cdot}Et_2O$, 3%, 8 h}. $BF_3{\cdot}Et_2O$ (8 mM) in place of TFA gave much lower yields for **P3** and **P5**.

^{1}H NMR Study of the Reaction between 4-Hydroxybenzaldehyde and Pyrrole. 4-Hydroxybenzaldehyde (12.2 mg, 0.1 mmol) and pyrrole (7 μL, 0.1 mmol) were stirred under argon in 0.825 M SDS in D_2O (1.0 mL) until a clear solution was obtained. A portion of this solution (25 μL) was injected into 0.14 M SDS in D_2O (0.575 mL) in an argon-filled NMR tube, and deuteriotrifluoroacetic acid (5 μL, 65 μmol) was added to initiate reaction. The pyrrole resonances disappeared immediately, and the aromatic resonances from the starting aldehyde {9.69 (s, 1H, CHO), 7.83 (d, 2H), and 7.0 (d, 2H) ppm} began to reduce in intensity with the appearance of another set of resonances {7.1 (m, 2H), 6.8 (m, 2H), and 5.3 (m, 1H) ppm}. After 15 min, the reaction had reached ~50% conversion and was stopped at this stage by addition of 60 μL of buffered aqueous NaOH (0.725 M Na_2HPO_4/NaH_2PO_4 pH 6.5 buffer which had been made 1.05 M in NaOH). The final mixture of species was of approximate composition: 1.9 mM aldehyde, 1.9 mM pyrrole, 1.9 mM product(s), 160 mM SDS, 96 mM sodium trifluoroacetate, and 65 mM buffer salts. The intensities of the reactant and product peaks did not change further during subsequent measurements. Longitudinal relaxation rates (R_1) were measured by inversion recovery in standard fashion. R_1 values for aldehyde, product(s), and the main SDS peak at 1.3 ppm were 0.4, 0.8, and 1.5 s^{-1}, respectively. Self-diffusion coefficients (D) were measured with a pulsed-gradient spin−echo (PGSE) sequence[34a] which minimized transverse relaxation effects.[34b] The diffusion coefficient (corrected for R_1 weighting) for the product(s) was 0.6 relative to aldehyde (i.e. $D_{aldehyde} = 1$) and for SDS was 0.4 relative to aldehyde. Similar results were obtained from experiments in which R_1 rates and relative D values were

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measured before reaction and after complete disappearance of starting material. Less acid was added in these experiments so that condensation proceeded more slowly and the porphyrinogen concentration did not decrease significantly during the final measurements.

Partition Coefficients. The partition coefficients in Table 1 were measured in 100 mM SDS containing 50 mM pH 7 buffer by micellar capillary electrophoresis[18] using an uncoated 75 μm, 70 cm long silica gel capillary. The column temperature was 27 °C voltage 25 kV, current ~50 μA, and detection by UV at 200 or 250 nm. One to five microliters of ligand solutions (2−10 mg/mL in the mobile phase or saturated solutions for the less soluble aldehydes) were added successively to 200 μL of the mobile phase in the source vial, running a chromatogram after each addition to identify the peaks. (Dodecyloxy)benzene or TPP was used as markers to measure the micelle retention time (t_m). After the ligands and the micelle marker had been added, the solvent front time (t_0) was obtained by adding enough methanol to the mixture (1−2% v/v) to produce a detectable inflection in the base line. Provided the amount of methanol added was small, the retention times of ligands and marker were not significantly affected. P values were calculated from $P = (t_r/t_0 - 1)/\{(1 - t_r/t_m)([SDS] - cmc)v^m\}$, where t_r is the solute retention time.

The reaction between 4-hydroxybenzaldehyde and pyrrole was monitored by micellar capillary electrophoresis in the following manner. A portion (200 μL) of a solution of the reactants in 100 mM SDS (1 mM in both aldehyde and pyrrole) was placed in the source vial, and a chromatogram was run using 100 mM SDS containing 100 mM pH 7 buffer as the mobile phase (detection at 200 nm). Aqueous HCl (20 μL, 1.0 M) was then added to the source vial, and chromatograms were run after various times. After the starting materials had disappeared, (decyloxy)benzene was added to mark the micelles (arrow in Figure 5). Adding the marker before the addition of acid gave the same results. Transient broad peaks appeared with retention times between reactants and product(s) during the course of reaction, but were not well resolved.

The reaction was also run on a larger scale, analyzing aliquots by electrophoresis and UV absorbance in parallel with the same results as the above in situ method.

Simulation of Porphyrinogen Assembly. The following assumptions were made to simplify numerical treatment of Scheme 2: (1) aldehyde and pyrrole can be treated as equivalent monomer units, (2) a single equilibrium constant can be used to describe stepwise chain growth,[35a] (3) water activity is constant and the same in both phases, and (4) equilibrium constants in water and micelles are equal ($K_m = K_{aq} = K$). The last assumption requires that the linear i-mer L_i has the partition coefficient P^i, where $P = [L_{1,m}]/[L_{1,aq}]$ is the partition coefficient of monomer L_1. As discussed in the main text, micellar binding energies ($\Delta G = -RT \ln P^i = -iRT \ln P$) are in fact likely to be roughly additive. Assumption 3 is harder to justify, since there is presumably a gradient of water concentration from the surface to the center of the micelle. However, the reversible reactions involve polar reactants that are likely to prefer the wet outer regions of micelles, which may be quite extensive,[1f,36] so constant water activity seems reasonable. With assumptions 1−4, mass balance on Scheme 2 gives

$$[L_0] = (z/K)\{(1 - \beta)/(1 - z/P)^2 + \beta/(1 - z)^2\} + \alpha;$$
$$\alpha = n(K_c/K)z^n\{\beta + (1 - \beta)/P^n\} \quad (2)$$

where $[L_0]$ is the bulk concentration of monomer units, $z = K[L_{1,m}]$ and is the degree of polymerization of the chain fraction in the micellar phase, β is the phase ratio defined in the main text, and n is the number of monomer units in the ring in equilibrium with linear polymer ($n = 8$ for a porphyrinogen). The percentage yield of cyclic n-mer ($100\alpha/[L_0]$) was obtained by solving for z with various values of $[L_0]$, K, K_c, P, and β. For assembly in a single phase, $P = 1$ and eq 2 reduces to a special case of ring−chain equilibrium in homogeneous solution.[35b] Given the simplicity of the model, the numerical values of K_m and K_c necessarily reflect the various approximations made, and so it is the relative valves rather than the absolute values of these parameters which are of significance. More elaborate schemes can be constructed at the expense of extra parameters, but the qualitative conclusion that there is an optimum reactant concentration for reversible assembly in a two-phase system provided binding energies that are approximately additive remains unchanged.

Aldehydes. Commercially available aldehydes were used as received. 4-Acetamidobenzaldehyde and 4-hydroxybenzaldehyde were recrystallized from water.

Methyl 2-formylbenzoate (**6**)[37] was prepared from 2-formylbenzoic acid by alkylation with methyl iodide. Methyl 3-formylbenzoate (**8**)[38] was prepared by chromium trioxide−acetic anhydride oxidation[39] of 3-methylbenzoic acid and treatment of the resulting 3-bis(acetoxymethyl)benzoic acid with HCl in anhydrous MeOH followed by aqueous workup.

2-(Hydroxymethyl)pyrrole was obtained as a yellow oil by reduction of 2-formylpyrrole following the literature method,[40] but using 1 equiv of $NaBH_4$. The crude material was pure by ^{1}H NMR and was used directly.

5-Formylbenzene-1,3-dicarboxylic acid dimethyl ester (9) was prepared in the same manner as **8** from 5-methylbenzene-1,3-dicarboxylic acid.[41] For **9**: mp 86−88 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.98 (s, 6H), 8.71 (d, J = 1.5 Hz, 2H), 8.91 (t, J = 1.5 Hz, 1H), 10.12 (s, 1H); EI m/z 222.1 (M^+, 50%), 191 (100), 163 (10).

3-(Dodecyloxy)benzaldehyde (15).[42] A mixture of 3-hydroxybenzaldehyde (1.22 g, 10 mmol), 1-bromododecane (2.24 g, 9 mmol), and K_2CO_3 (1.5 g) in DMF (5 mL) was stirred under argon at 80 °C. After 30 min the mixture was cooled and partitioned between EtOAc and water. The organic layer was washed successively with 1 M aqueous NaOH, water, and pH 7 buffer and then dried and evaporated to a yellow oil. This was eluted through a short plug of silica gel to give **15** (2.3 g, 80%) as a colorless slowly crystallizing oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (br t, 3H), 1.2−1.5 (m, 18H), 1.80 (m, 2H), 4.0 (t, J = 6.5 Hz, 2H), 7.16 (m, 1H), 7.36 (m, 1H), 7.42 (m, 2H), 9.96 (s, 1H). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.67; H, 10.19.

The acids **16**,[43] **19**,[43] and **26**[44] were obtained by addition of a slight excess of aqueous 2 M KOH to solutions of their methyl esters (prepared in near-quantitative yields by alkylation of the corresponding phenols with a slight excess of methyl bromoacetate using the procedure given above for **15**) in MeOH/THF and crystallization from hot water as needles.

3,4-Bis(2-carboxyethoxy)benzaldehyde (26):[44] mp 244−246 °C; ^{1}H NMR (d_6-DMSO, 250 MHz) δ 4.68 (s, 2H), 4.71 (s, 2H), 7.04 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 1.5 Hz, 1H), 7.51 (dd, J = 8.4, 1.5 Hz, 1H), 9.80 (s, 1H); EI m/z (254, M^+).

2-Acetamidobenzaldehyde (32)[45] was prepared in an analogous fashion to **36** by acetylation of 2-aminobenzyl alcohol with acetic anhydride (1 h, rt). The intermediate *N*-acetylated benzyl alcohol was crystallized from THF/cyclohexane before oxidation. Crude **32** was purified by crystallization from cyclohexane (31% overall).

3-Acetamidobenzaldehyde (33)[46] was prepared from

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3-aminobenzyl alcohol in the same way as **32**. Crude **33** was purified by crystallization from toluene (37% overall).

3-((*tert*-Butoxycarbonyl)amino)benzaldehyde (34) was obtained from 3-aminobenzyl alcohol following the literature procedure for 4-((*tert*-butoxycarbonyl)amino)benzaldehyde[47] and crystallized as needles from hexane, mp 93 °C. For **34**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.52 (s, 9H), 6.65 (br s, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.91 (s, 1H), 9.97 (s, 1H). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.82; N, 6.33. Found: C, 64.83; H, 6.71; N, 6.09.

4-(Trifluoroacetamido)benzaldehyde (36).[48,49] Trifluoroacetic anhydride (0.75 mL, 5.1 mmol) was added dropwise to a stirred solution of 4-aminobenzyl alcohol (0.5 g, 4.07 mmol) in THF (3 mL) at ice-bath temperature. After 15 min, aqueous NaOH (2.0 mL, 2.5 M) was added followed by saturated aqueous $NaHCO_3$ (2.0 mL) and MeOH (5 mL), and the suspension was stirred at rt for 15 min to selectively hydrolyze *O*-trifluoroacetates (TLC, 1:1 hexane/EtOAc). The reaction mixture was partitioned between EtOAc and brine, and the organic layer was dried and evaporated. Pyridinium chlorochromate (1.3 g, 6.0 mmol) was added to a solution of the crude 4-(trifluoroacetamido)benzyl alcohol in a mixture of CH_2Cl_2 (4 mL) and THF (4 mL), and the brown suspension was stirred rapidly at rt. After 2.5 h, the reaction mixture was diluted with EtOAc and filtered into a separating funnel. The tarry residue was extracted several times with EtOAc, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine and evaporated. Crystallization from MeOH/water (decolorizing charcoal) gave **36** as white crystals (600 mg, 68%): mp 185 (softens)−200 °C; ^{1}H NMR (d_6-acetone, 250 MHz) δ 7.98 (narrow ABq, 4H), 10.01 (s, 1H), 10.58 (br s, 1H). Anal. Calcd for $C_9H_6NO_2F_3$: C, 49.78; H, 2.79; N, 6.45. Found: C, 49.86; H, 2.86; N, 6.31.

4-(Trichloroacetamido)benzaldehyde (37)[50] was prepared in an analogous fashion to **36** by acetylation of 4-aminobenzyl alcohol with trichloroacetic anhydride and crystallized as yellow needles from MeOH/water (71%), mp 121 (softens)−129 °C. For **37**: ^{1}H NMR (d_6-acetone, 200 MHz) δ 7.98 (s, 4H), 10.01 (s, 1H), 10.26 (br s, 1H). Anal. Calcd for $C_9H_6NO_2Cl_3$: C, 40.56; H, 2.27; N, 5.26. Found: C, 40.36; H, 2.34; N, 5.07.

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