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Effects of aldehyde or dipyrromethane substituents on the reaction course leading to *meso*-substituted porphyrins

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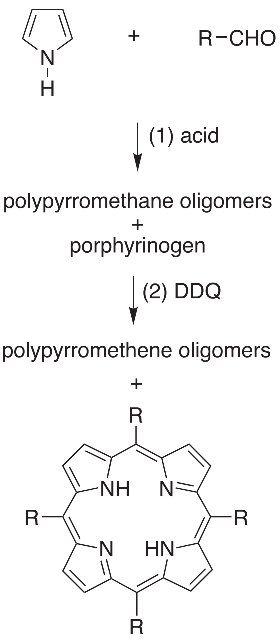
Abstract—To better understand the effects of diverse substituents on reactions leading to porphyrins, pyrrole + aldehyde condensations and related reactions of dipyrromethanes were examined. The course of pyrrole + aldehyde condensations was investigated by monitoring the yield of porphyrin (by UV–Vis spectroscopy), reaction of aldehyde (by TLC), and changes in the composition of oligomers (by laser desorption mass spectrometry). Reaction reversibility was examined via exchange experiments. Reversibility of reactions leading to porphyrin was further probed with studies of dipyrromethanes. The reaction course was found to depend on the nature of the substituent and the acid catalyst. Alkyl or electron-donating substituents displayed levels of reversibility (exchange/scrambling) on par or greater than that of the phenyl substituent, whereas electron-withdrawing or sterically bulky substituents exhibited little to no reversibility. The results obtained provide insight into the electronic and steric effects of different substituents and should facilitate the design of synthetic plans for preparing porphyrinic macrocycles.

1. Introduction

The one-flask reaction of pyrrole and an aldehyde provides a direct approach for the synthesis of *meso*-substituted porphyrins.[1] The reaction is performed in two stages: (1) acid catalyzed condensation of pyrrole + aldehyde forming predominantly polypyrromethane oligomers and the cyclic porphyrinogen; (2) addition of an oxidant (e.g., DDQ or *p*-chloranil) to give the corresponding polypyrromethenes and porphyrin (Scheme 1). We previously carried out a series of experiments to gain insight into the course of the condensation.[2–5] A battery of analytical techniques was employed, which allowed determination of the yields of porphyrinic macrocycles such as the porphyrin, *N*-confused porphyrin and sapphyrin (by UV–Vis and HPLC),[6] consumption of the aldehyde (by TLC),[7] change in the composition of the mixture of oligomers (by laser desorption mass spectrometry, LD-MS),[2,3] and formation of dipyrrin chromophores (by UV–Vis).[8] These studies, performed with the benchmark reaction of benzaldehyde and pyrrole under a variety of conditions, revealed the complexity of the overall reaction. A key finding was that the condensation entails a combination of reversible and irreversible reactions, thereby often causing the yield of porphyrinogen to pass through a maximum and then decline. The overall rate of reaction and



Scheme 1.

Keywords: Porphyrin; Porphyrinogen; Dipyrromethane; Polypyrromethane; Pyrrole; Laser desorption mass spectrometry.

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ultimate yield of porphyrin is dependent on the concentration of the reactants, the nature of the acid catalyst, and on the concentration of the acid. Obtaining a maximal yield of porphyrin requires careful monitoring of the reaction 'trajectory' so that oxidation, the second step of the porphyrin-forming process (which terminates all condensation processes), can be initiated at the appropriate time. The decline in porphyrinogen yield that occurs under some conditions is accompanied by a shift of the oligomer composition to shorter species ('oligomer truncation').

In related experiments, we examined the reversibility of dipyrromethane + aldehyde condensations leading to *trans*-A_2B_2-porphyrins. Dipyrromethanes are valuable building blocks in diverse routes to porphyrins.[9–13] However, the successful use of dipyrromethanes requires the reaction to proceed without acidolysis of the dipyrromethane and recombination of the resulting dipyrromethane fragments yielding undesired porphyrin products (i.e., scrambling).[14] Again, the phenyl group was the predominant substituent employed.[4,5]

A present objective has been to determine the generality of the observations for substituents that differ markedly from that of the phenyl group. Of particular interest are the effects of electron-withdrawing, electron-releasing, sterically bulky, and non-aryl groups on the catalytic requirements, the trajectory of the reaction, the oligomer composition and its change over time, and the reversibility of the reaction. Improved understanding of these issues is important for the rational refinement of reaction conditions, for suppressing undesired reversible processes, and for the design of synthetic plans so as to avoid potentially problematic reactions.

In this paper, we report studies of condensations of a representative set of aldehydes with pyrrole, and condensations involving dipyrromethanes. Diverse aryl substituents were employed (electron donating, electron withdrawing, and sterically bulky) as well as alkyl groups. The studies first identified appropriate catalytic conditions with TFA or BF_3-etherate for reaction with 10 mM each of aldehyde and pyrrole in CH_2Cl_2 at room temperature. Under refined conditions, the consumption of aldehyde, changes in the oligomer composition, and the yield of porphyrin were investigated as a function of time for each aldehyde. The reversibility of the condensation was investigated via exchange experiments. Studies of a set of dipyrromethanes examined the propensity for reversible processes leading to scrambling. Taken together, these studies provide a foundation for understanding the effects of structural and electronic changes in the aldehyde or dipyrromethane moiety on the course of reaction leading to porphyrins.

2. Results and discussion

2.1. Reactions of aldehydes

Two specific aldehydes of a given type were selected for comparison to benzaldehyde in reactions leading to *meso*-substituted porphyrins. In each case, the two aldehydes that comprise a pair have similar structures but different molecular weights in anticipation of the exchange experiments. The selected aldehydes are as follows: benzaldehyde and *p*-tolualdehyde (benchmark case), *p*-anisaldehyde and 4-ethoxybenzaldehyde (electron donating), pentafluorobenzaldehyde and 2,3,5,6-tetrafluorobenzaldehyde (electron withdrawing), mesitaldehyde and 2,6-dimethylbenzaldehyde (sterically bulky), and hexanal and heptanal (alkyl). Three general types of experiments were performed: investigation of acid catalyst requirements, reaction time course studies, and examination of reaction reversibility.

2.1.1. Acid catalysis requirements. The catalytic requirements for each aldehyde were examined by reacting an aldehyde and pyrrole (10 mM each) at room temperature in CH_2Cl_2 over a range of concentrations of TFA or BF_3-etherate. After condensation for 15 min, 1 h, or 4 h, an aliquot of the reaction mixture was oxidized with DDQ and the yield of porphyrin was determined

Table 1. The acid catalysis conditions identified for each aldehyde[a]

Entry	Substituent type	R group in RCHO	Acid	[Acid], mM[b]	% Yield of porphyrin[c]
1	Benchmark	Phenyl	TFA	22	41
2	Benchmark	Phenyl	BF_3-etherate	1.0	23
3	Benchmark	*p*-Tolyl	TFA	22	41
4	Benchmark	*p*-Tolyl	BF_3-etherate	1.0	17
5	e-rich	4-MeO-phenyl	TFA	22	29
6	e-rich	4-MeO-phenyl	BF_3-etherate	—[d]	ND[d]
7	e-rich	4-EtO-phenyl	TFA	22	28
8	e-rich	4-EtO-phenyl	BF_3-etherate	—[d]	ND[d]
9	e-deficient	C_6F_5	TFA	215	11
10	e-deficient	C_6F_5	BF_3-etherate	10	23
11	e-deficient	2,3,5,6-F_4-phenyl	TFA	215	13
12	e-deficient	2,3,5,6-F_4-phenyl	BF_3-etherate	10	22
13	Alkyl	Pentyl	TFA	10	14
14	Alkyl	Pentyl	BF_3-etherate	1.0	8
15	Alkyl	Hexyl	TFA	10	16
16	Alkyl	Hexyl	BF_3-etherate	1.0	12

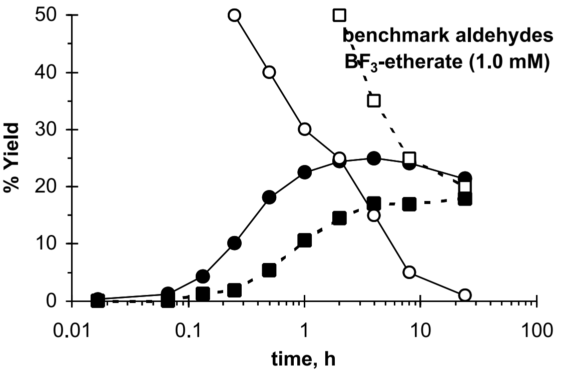
[a] The reactions were performed with 10 mM each of pyrrole and aldehyde at a 10 ml scale in CH_2Cl_2 at room temperature. The reactions were monitored at 15 min, 1 h, and 4 h.

[b] The optimal acid concentration in terms of yield of porphyrin and reaction time.

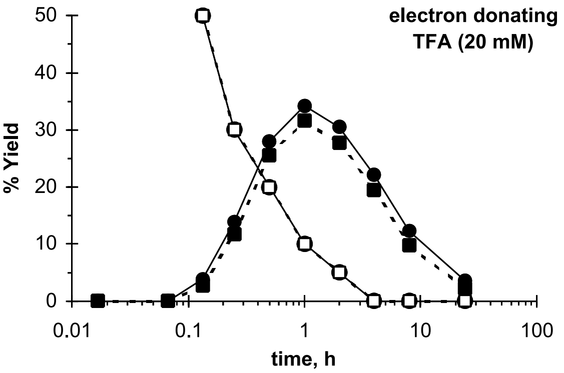
[c] The highest yield (UV–Vis) at any of the three timepoints is reported.

[d] No porphyrin was detected at any concentration of BF_3-etherate (limit of detection is 0.5%).

A benzaldehyde (circle) and *p*-tolualdehyde (square)



B *p*-anisaldehyde (circle) and 4-ethoxybenzaldehyde (square)



C pentafluorobenzaldehyde (circle) and 2,3,5,6-tetrafluorobenzaldehyde (square)

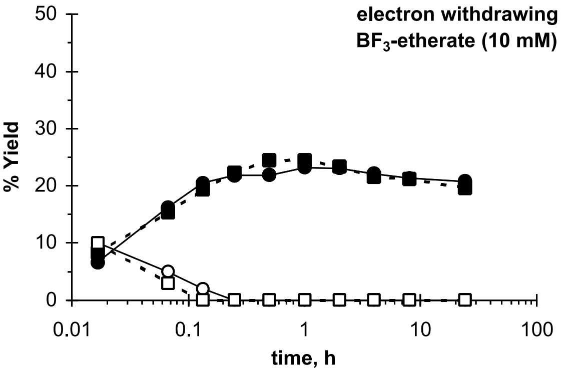


Figure 1. Percent yield of porphyrin (filled symbols) and percent unreacted aldehyde (open symbols) as a function of condensation time for reactions of pyrrole + aldehyde (10 mM each) in CH_2Cl_2 at room temperature. Reactions were monitored by removing an aliquot of the reaction mixture, oxidizing with DDQ, and analyzing spectrophotometrically for yield of porphyrin and by TLC for unreacted aldehyde. Note the log scale for time.

spectrophotometrically. All aldehydes were examined in this manner with the exception of mesitaldehyde and 2,6-dimethylbenzaldehyde, which are known not to react under these conditions and were instead condensed with pyrrole using the established conditions of BF_3-etherate/ethanol cocatalysis.[15]

The rate of formation (and possible decay) of the porphyrinogen is dependent on the concentration of a

***p*-anisaldehyde, TFA (20 mM)**

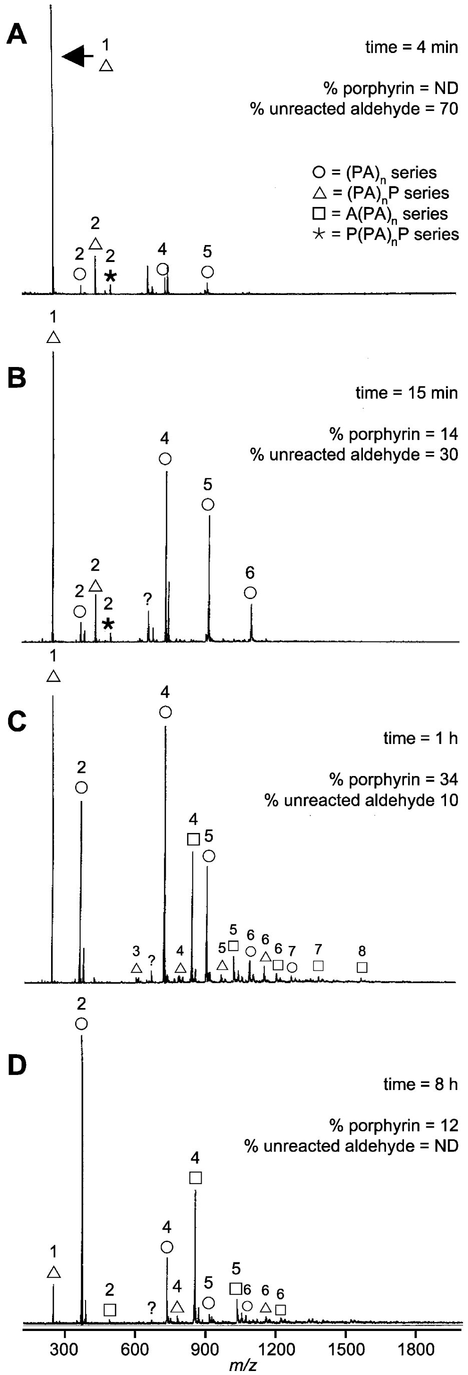


Figure 2. LD-MS spectra showing the oligomer composition at selected timepoints for the reaction of pyrrole + *p*-anisaldehyde (10 mM each) under TFA catalysis (20 mM) in CH_2Cl_2 at room temperature. Reactions were monitored by removing an aliquot of the reaction mixture, oxidizing with DDQ, and directly analyzing the crude, oxidized reaction mixture. The percent yield of porphyrin (UV–Vis) and percent unreacted aldehyde (TLC) are reported for each timepoint. Three oligomer series are defined based on the groups present at the oligomer chain termini: (1) a pyrrole and an aldehyde terminus, $(PA)_n$ series, ○; (2) pyrrole units at both termini, $(PA)_nP$ series, △; and (3) aldehyde units at both termini, $A(PA)_n$ series, □. A fourth oligomer series has an internal bipyrrole group, and pyrrole groups at both termini, $P(PA)_nP$ series, ★. Significant peaks that could not be assigned to one of the four oligomer series are denoted with a '?'. The number (n) of repeating pyrrole-aldehyde (PA) units is given by the number above the symbol.

given type of acid. Such a phenomenon, which is well documented for the reaction of benzaldehyde and pyrrole, was observed to varying degrees with the aldehydes examined herein (see the Supplementary data for plots of the yield of porphyrin as a function of acid concentration). For example, for *p*-anisaldehyde, the reaction with 46 mM TFA afforded a yield of 26% at 15 min, 5% after 1 h, and 0% after 4 h. However, the reaction with 22 mM TFA provided a yield of 29% after 1 h and ∼17% after 4 h. For the reaction at 10 mM TFA, the reaction at 4 h afforded the highest yield (24%), with less than a 10% yield obtained at the earlier timepoints.

These results concerning the interplay of acid concentration and reaction rate illustrate the complexity of identifying a single best set of conditions for a given aldehyde. A range of acid concentration afforded a good yield of porphyrin at one of the three timepoints for each type of aldehyde. This range varied from the extremes of ∼50-fold for reactions of aldehydes with electron-withdrawing groups under BF_3-etherate catalysis to ∼5-fold for aldehydes with electron-donating groups under TFA catalysis. In addition, aldehydes bearing electron-withdrawing groups required ∼10 times higher acid concentration to obtain the maximum yield of porphyrin than the other aldehydes examined herein. It is noteworthy that despite the subtleties of the conditions affording the highest yield of porphyrin, application of one or both of the standard reaction conditions [20 mM TFA or 1.0 mM BF_3-etherate] to all aldehydes (except those bearing bulky substituents in the 2- and 6-positions) provided a yield of porphyrin at some point in the reaction that was close to the maximum yield of porphyrin obtained under any acid concentration. Nearly identical yields of porphyrin were obtained from each member of a pair of aldehydes under a given reaction condition. The lone exception involved benzaldehyde and *p*-tolualdehyde. Under BF_3-etherate catalysis, *p*-tolualdehyde provided less porphyrin (1.4 to five times lower) than did benzaldehyde at equivalent reaction times. The acid catalyst concentrations identified for subsequent use herein are summarized in Table 1. Note that the yields obtained are not fully optimized. Investigation of other reaction conditions known to give improved yields in some cases such as use of clays,[16–20] cocatalysis (BF_3-etherate + salt,[7] BF_3-etherate + TFA[21]), or other catalysts,[22–24] as well as variation in the concentration of the aldehyde and pyrrole were not within the scope of the present study.

2.1.2. Reaction time course. The time course for the pyrrole + aldehyde reactions was examined in greater detail by following the formation of the porphyrin (UV–Vis), disappearance of the aldehyde (TLC), and change in oligomer composition (LD-MS) as a function of time from 1 min to 24 h. The reactions were performed under the catalytic conditions identified from the acid catalysis examination, as well as BF_3-ethanol cocatalysis conditions previously reported for mesitaldehyde.[15] The latter conditions also were employed for *p*-anisaldehyde, as *p*-alkoxybenzaldehydes are known to condense poorly with pyrrole in the presence of BF_3-etherate alone.[8] Representative plots of the percent yield of porphyrin and percent unreacted aldehyde as a function of condensation

Table 2. Effects of aldehyde structure on the reaction course leading to porphyrin[a]

Entry	R in RCHO	Acid	[Acid], mM	Time[b]	% Porphyrin[c]	% Unreacted aldehyde[d]	Yield turnover[e]	Oligomer truncation[f]
1	Phenyl	TFA	20	1–4 h	40	<5	High	High
2	Phenyl	BF_3-etherate	1.0	1–8 h	25	30	Low	Trace
3	*p*-Tolyl	TFA	20	30 min–1 h	39	15	High	High
4	*p*-Tolyl	BF_3-etherate	1.0	4–24 h	17	35	None	None
5	4-MeO-phenyl	TFA	20	1 h	34	10	Near total	High
6	4-MeO-phenyl	BF_3/EtOH	3.3/130	15 min–1 h	38	<5	Near total	Low
7	4-EtO-phenyl	TFA	20	1 h	32	10	Near total	High
8	4-EtO-phenyl	BF_3/EtOH	3.3/130	15 min–1 h	36	ND[g]	Near total	Low
9	C_6F_5	TFA	215	8 min–4 h	12	5	Low	Low[h]
10	C_6F_5	BF_3-etherate	10	8 min–24 h	23	<5	Low	None
11	2,3,5,6-F_4-phenyl	TFA	215	4 min–8 h	13	10	Low	Low[h]
12	2,3,5,6-F_4-phenyl	BF_3-etherate	10	15 min–8 h	25	ND[g]	Low	Trace
13	2,4,6-Me_3-phenyl	BF_3/EtOH	3.3/130	1–4 h	19	10	Low	Low[h]
14	2,6-Me_2-phenyl	BF_3/EtOH	3.3/130	1–8 h	19	10	Low	Low[h]
15	Pentyl	TFA	10	15 min–8 h	16	—[i]	Low	None[i]
16	Pentyl	BF_3-etherate	1.0	8 min–24 h	9	—[i]	None	None[j]
17	Hexyl	TFA	10	15 min–8 h	16	—[i]	Low	None[j]
18	Hexyl	BF_3-etherate	1.0	8 min–24 h	9	—[i]	None	None[j]

[a] The reactions were performed with 10 mM each of pyrrole and aldehyde at a 15 ml scale at room temperature in CH_2Cl_2 (for mesitaldehyde and 2,6-dimethylbenzaldehyde, ethanol cocatalysis was carried out in $CHCl_3$ stabilized with amylenes or in CH_2Cl_2). The reactions were monitored at 1 min, 4 min, 8 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, and 24 h.

[b] The range of time during the condensation reaction where the yield of porphyrinogen was maximal (as inferred from the yield of porphyrin in aliquots of the oxidized reaction mixture).

[c] The maximum yield of porphyrin (UV–Vis).

[d] The level of unreacted aldehyde at the time that the maximum yield of porphyrin was first obtained.

[e] Yield turnover refers to a decline in the yield of porphyrin after the maximum has been obtained.

[f] Oligomer truncation refers to disappearance of larger oligomers, and appearance of shorter oligomers that were not present at early reaction times.

[g] Below the limits of detection (<1%).

[h] The changes in oligomer composition occurred between the 8 h and 24 h timepoints.

[i] Alkyl aldehydes could not be detected readily by TLC analysis.

[j] The intensity and resolution of peaks of higher *m/z* than the porphyrin were poor for all spectra; nevertheless, the appearance of the spectra remained consistent once the maximum yield of porphyrin was obtained.

time are provided in Figure 1 (see the Supplementary data for the complete set of plots for all aldehydes). The quantity of unreacted aldehyde was not determined for the alkyl aldehydes, which are poorly detected upon TLC analysis. A representative set of LD-MS spectra showing changes in the oligomer composition as a function of time are shown in Figure 2 (see the Supplementary data for the complete set of spectra). Observations from the time course experiments are summarized in Table 2.

Two key features concerning the trajectory of the pyrrole + aldehyde reaction are (1) the extent to which the yield of porphyrinogen declines after reaching a maximum, and (2) the extent to which the oligomers undergo truncation. The turnover in porphyrinogen yield is readily established by monitoring the condensation over time. In some cases, the turnover was near total while in other cases the porphyrinogen yield reached a maximum and then plateaued. Reactions of aldehydes with electron-donating substituents showed a substantial turnover in the yield of porphyrinogen under TFA or BF_3-etherate/EtOH catalysis (Fig. 1B), much more than previously observed with benzaldehyde under TFA or BF_3-etherate catalysis. Examination of crude, oxidized reaction samples by LD-MS reveals the composition of the oligomers.[2] Studies of the reaction with benzaldehyde + pyrrole under TFA catalysis showed that the oligomeric composition continues changing over a period well beyond the peak in porphyrinogen yield. The composition becomes enriched in shorter oligomers that were not originally present in the LD-MS spectra, a phenomenon we have referred to as oligomer truncation.[2] Oligomer truncation can result from reactions giving reversible formation/disassembly of polypyrromethanes in conjunction with irreversible side reactions, and/or irreversible side reactions that cause fragmentation of polypyrromethanes. In the present work, reactions of aldehydes with electron-donating substituents showed significant levels of oligomer truncation (Fig. 2), while other reactions provided little to no truncation. It is noteworthy that continued formation of long oligomers at prolonged reaction times was not observed, even for aldehydes that react poorly or in a non-reversible manner.

The two members of a given pair of aldehydes generally provided identical results. The lone exception was the benchmark pair of benzaldehyde and *p*-tolualdehyde. Benzaldehyde was consumed faster under BF_3-etherate or TFA catalysis and provided a higher yield of porphyrin under BF_3-etherate than *p*-tolualdehyde (Fig. 1A). There were no sharp differences in the oligomer compositions provided by the two aldehydes. The disparities are not due to inappropriate acid concentrations, as the acid catalysis study found both aldehydes to require similar acid concentrations.

2.1.3. Reaction reversibility.

The reversibility of the condensations was examined by double-labeling crossover (i.e., 'exchange') studies.[7,8] Reactions of two aldehydes of a given type (e.g., *p*-anisaldehyde and 4-ethoxybenzaldehyde) were performed side-by-side under the conditions used in the reaction course studies. After a defined 'premixing time', an aliquot from each reaction was transferred to a common flask and the exchange processes were allowed to occur. Three premixing times were examined: a time close to when the maximum yield of porphyrinogen is initially attained and the concentration of unreacted aldehyde is $<10\%$ of the original concentration, a later timepoint when porphyrinogen yield was still high, and a long timepoint when the porphyrinogen yield had in some cases declined. (The objective of $<10\%$ unreacted aldehyde was achieved in every case with the exception of *p*-tolualdehyde under BF_3-etherate catalysis.) Duplicate mixtures were prepared at each premixing time. One mixture was allowed to react with no additional acid catalyst, and the second mixture was

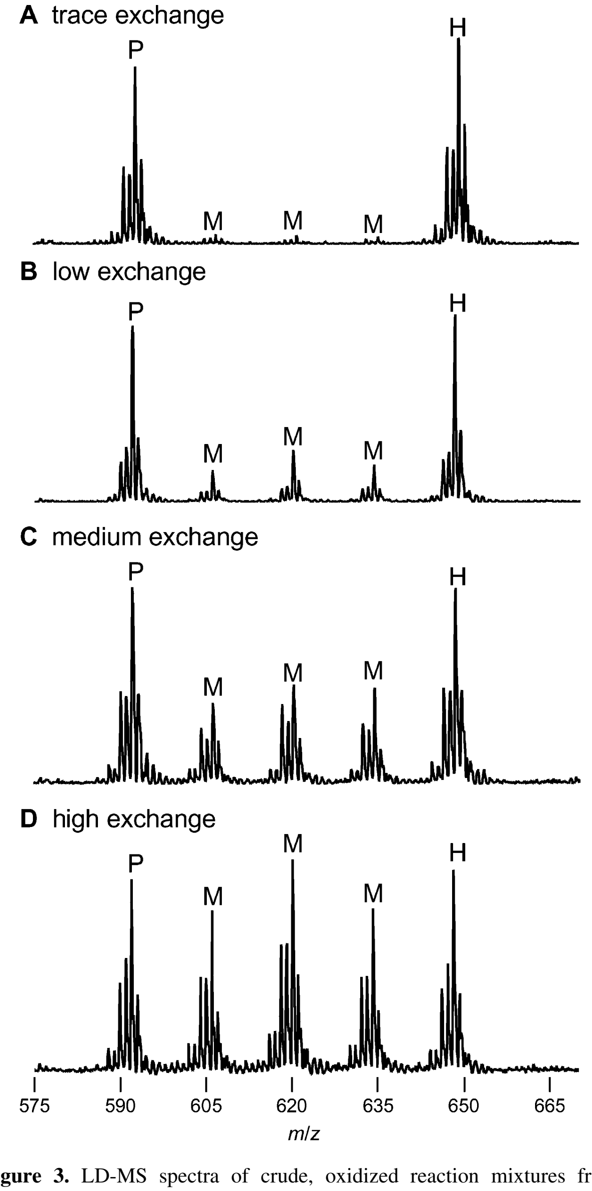


Figure 3. LD-MS spectra of crude, oxidized reaction mixtures from exchange experiments involving hexanal (R = pentyl) and heptanal (R = hexyl) that illustrate the assignment of the level of exchange. The region corresponding to the *m/z* ratio of the possible porphyrin products is shown. The peaks are labeled as follows: P = oligomer containing only pentyl substituents, H = oligomer containing only hexyl substituents, and M = oligomers containing a mixture of pentyl and hexyl substituents. The conditions that provide each spectrum are as follows: (A) BF_3-etherate (1.0 mM), no acid pulse, premixing = 15 h, postmixing = 4 h; (B) BF_3-etherate (1.0 mM), no acid pulse, premixing = 15 min, postmixing = 1 h; (C) BF_3-etherate (1.0 mM), acid pulse, premixing = 4 h, postmixing = 4 h; (D) BF_3-etherate (1.0 mM), acid pulse, premixing = 15 min, postmixing = 4 h.

treated with fresh acid catalyst (acid pulse) at the time of mixing. At the time of mixing, the oligomer composition (LD-MS) and the level of unreacted aldehyde (TLC analysis) were examined. After mixing, the porphyrin yield and oligomer composition of the combined reactions were monitored from 4 min to 4 h. As the two aldehydes of a given pair are of different mass, oligomers containing the two different substituents could be distinguished by LD-MS. The peak assignments were made as described previously.[2] In the limit of no reversibility, the LD-MS spectrum would be identical to the superimposed spectra of separate reactions of pyrrole with each aldehyde. In the limit of total reversibility, the oligomer composition (and thus the LD-MS spectrum) would be identical to that obtained from a mixed condensation of pyrrole and the two aldehydes. Illustrative LD-MS spectra for the case of hexanal and heptanal are shown in Figure 3. The results of all of the exchange experiments are summarized in Table 3.

The results led to an approximate rank ordering of aldehyde substituents in terms of reversibility in the pyrrole + aldehyde condensation: phenyl/*p*-tolyl $\geq$ 4-alkoxyphenyl $>$ alkyl $\gg$ pentafluorophenyl/tetrafluorophenyl $>$ mesityl/2,6-dimethylphenyl. The rank order is somewhat dependent on the conditions of the exchange experiment as evidenced by entries 1–4 in Table 3 that pertain to the benchmark aldehydes. Previously, we reported observing a low level of exchange in reactions involving alkyl aldehydes and concluded that reactions involving such aldehydes are largely irreversible.[8] Those previous experiments were restricted to a single reaction condition and premixing period, and only exchange manifested in the distribution of porphyrins upon oxidation and TLC analysis was detected. The present experiments investigated wider reaction conditions and mixing times, and the LD-MS analysis allows detection of exchange in all oligomer species produced in the reaction. Thus, it is now clear that at least some aspects of condensations of alkyl aldehydes exhibit reversibility under some reaction conditions.

There was no strong correlation between yield of porphyrin and extent of exchange, indicating that porphyrinogen formation does not depend on reaction reversibility (recovery from unproductive oligomers). The extent of exchange was greatest at the shortest premixing times, regardless of the addition of an acid pulse. Thus, in all cases there appears to be gradual, irreversible damage to the oligomers that prevents exchange processes. In all cases where exchange was detected, the exchange occurred gradually upon mixing the individual reactions and did not reach a statistical level. These results indicate that while initial oligomer formation is reversible to varying degrees depending on the aldehyde and acid, the reversibility is sluggish, declines over time, and cannot be overcome by adding fresh acid catalyst.

2.2. Reactions of dipyrromethanes

5-Substituted dipyrromethanes possessing substituents analogous to those employed in the reactions of aldehydes were selected: phenyl (benchmark case), 4-methoxyphenyl (electron donating), pentafluorophenyl (electron withdrawing), mesityl (sterically hindered), and pentyl (alkyl). Two general types of experiments were performed: acidolysis and oligomerization of the dipyrromethane in the absence of

Table 3. Results of porphyrinogen exchange experiments[a]

Entry	Substituent type	Acid[b]	Premixing times[c]	Acid pulse[d]	Level of exchange[e]		
					Short premixing time	Intermediate premixing time	Long premixing time
1	Benchmark	TFA	1, 4, 15 h	No	Trace-low	Trace	Trace
2	Benchmark	TFA	1, 4, 15 h	Yes	Medium-high	Low-medium	Trace
3	Benchmark	BF_3-etherate	1, 4, 15 h	No	High	Low	Trace-low
4	Benchmark	BF_3-etherate	1, 4, 15 h	Yes	High-statistical	Medium-high	Medium
5	e-rich	TFA	1, 2, 6 h	No	Medium	Low	Trace
6	e-rich	TFA	1, 2, 6 h	Yes	High-statistical	Medium-high	Trace
7	e-rich	BF_3/EtOH	0.5, 2, 6 h	No	Medium	Low	Trace
8	e-rich	BF_3/EtOH	0.5, 2, 6 h	Yes	Medium-high	Medium	Trace
9	e-deficient	TFA	0.25, 2, 15 h	No	Trace	Not detected	Not detected
10	e-deficient	TFA	0.25, 2, 15 h	Yes	Trace	Trace	Not detected
11	e-deficient	BF_3-etherate	0.25, 2, 15 h	No	Low	Trace	Not detected
12	e-deficient	BF_3-etherate	0.25, 2, 15 h	Yes	Low	Trace	Not detected
13	Bulky	BF_3/EtOH	2, 4, 24 h	No	Trace	Not detected	Not detected
14	Bulky	BF_3/EtOH	2, 4, 24 h	Yes	Low	Trace-low	Not detected
15	Alkyl	TFA	0.5, 4, 15 h	No	Low	Trace	Trace
16	Alkyl	TFA	0.5, 4, 15 h	Yes	Medium	Trace	Trace
17	Alkyl	BF_3-etherate	0.25, 4, 15 h	No	Medium	Trace-low	Trace
18	Alkyl	BF_3-etherate	0.25, 4, 15 h	Yes	High	Medium	Low

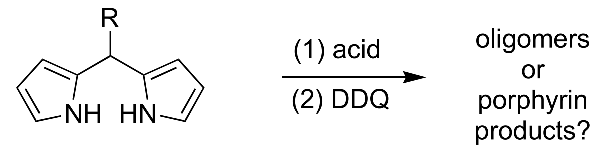
[a] The reactions were performed with 10 mM each of pyrrole and aldehyde at room temperature in CH_2Cl_2 (for mesitaldehyde and 2,6-dimethylbenzaldehyde, $CHCl_3$ stabilized with amylenes was used instead of CH_2Cl_2). At the conclusion of the premixing time, an equal volume (7.5 mL) of each pair of reaction mixtures was mixed in a common flask. The combined mixture was monitored for exchange at 4 min, 15 min, 1 h, and 4 h by LD-MS.

[b] Refer to Table 2 for acid concentrations.

[c] The three values refer to the short, intermediate, and long premixing times listed in the final three columns of this table. A level of unreacted aldehyde of $<10\%$ was present in each exchange experiment except with benzaldehyde and *p*-tolualdehyde under BF_3-etherate (1.0 mM) catalysis. Both aldehydes react slowly under BF_3-etherate catalysis. The level of unreacted aldehyde at the three premixing times are as follows: 1 h: $\sim 30\%$ benzaldehyde and $\sim 70\%$ *p*-tolualdehyde, 4 h: $\sim 15\%$ benzaldehyde and $\sim 35\%$ *p*-tolualdehyde, and 15 h: $<5\%$ benzaldehyde and $\sim 20\%$ *p*-tolualdehyde.

[d] The acid pulse provided a quantity of fresh acid catalyst equal to that initially present (i.e., the overall acid concentration is doubled).

[e] The level of exchange by 4 h after mixing ranges from not detected/trace/low/medium/high/statistical.



Scheme 2.

added aldehyde, and reaction of a dipyrromethane and an aldehyde.

2.2.1. Acidolysis and oligomerization. Each dipyrromethane (10 mM) was treated with acid catalysis conditions in the absence of any added aldehyde (Scheme 2). The acid catalysis conditions include (a) those identified herein for porphyrin formation in the corresponding pyrrole + aldehyde reaction, (b) the standard condition of TFA (20 mM), (c) the standard condition of BF_3-etherate (1.0 mM), and (d) our previously reported ‘low scrambling’ condition for the condensation of sterically unhindered dipyrromethanes and an aldehyde leading to *trans*-A_2B_2-porphyrins (1.0 mM BF_3-etherate, 100 mM NH_4Cl, in MeCN at 0 °C).[14] The latter condition was employed to better discriminate among those dipyrromethanes that are particularly susceptible toward acidolysis. The reactions were monitored from 4 min to 4 h for yield of porphyrin (UV–Vis) and oligomer composition (LD-MS). Observation of peaks in the LD-MS spectrum due to the porphyrin and to oligomers of mass greater than the dipyrromethane imply scrambling processes, as their formation requires acidolysis of the dipyrromethane and further reaction of the resulting fragments. The results of the experiments are summarized in Table 4, and representative LD-MS spectra are provided in the Supplementary data.

5-Mesityldipyrromethane was found to be stable towards all conditions investigated (Table 4, entries 13–15), and 5-pentafluorophenyldipyrromethane only underwent significant, albeit slow reaction under BF_3-etherate catalysis (entries 9 and 12). The other dipyrromethanes generally underwent rapid reaction (except under the low scrambling conditions). Interestingly, 5-(4-methoxyphenyl)dipyrromethane underwent significant reaction in the presence of 1.0 mM BF_3-etherate (entry 5) even though the same condition fails to cause pyrrole + *p*-anisaldehyde to produce detectable porphyrin. Accordingly, the failure of the *p*-anisaldehyde + pyrrole reaction with 1.0 mM BF_3-etherate to give porphyrin must originate in the initial condensation rather than subsequent steps of oligomer or porphyrinogen formation. With the exception of 5-mesityldipyrromethane, each dipyrromethane provided a yield of porphyrin and oligomer composition similar to the reaction of pyrrole + aldehyde under at least one of the conditions investigated. Thus, the extent of reversibility from the starting point of pure dipyrromethane is greater than that obtained from the mixing of diverse species in the exchange experiments (where statistical exchange was not observed).

2.2.2. Reaction of a dipyrromethane and an aldehyde. Reactions of a dipyrromethane with an aldehyde bearing a complementary substituent (e.g., 5-pentafluorophenyldipyrromethane + 2,3,5,6-tetrafluorobenzaldehyde; 5 mM each; Scheme 3) were performed under conditions identified for the corresponding pyrrole + aldehyde reaction. The

Table 4. Results upon treatment of dipyrromethanes with acid (in the absence of added aldehyde)

Entry	R in R-dipyrromethane	Reaction condition[a]	Detection of porphyrin[b]	Maximum porphyrin[c]	% Porphyrin[d]	Oligomer formation[e]
1	Phenyl	TFA, 20 mM	15 min	1 h	35	Yes
2	Phenyl	BF_3-etherate, 1.0 mM	30 min	4 h	33	Yes
3	Phenyl	Low scrambling	ND[f]	ND[f]	ND[f]	Trace
4	4-MeO-phenyl	TFA, 20 mM	<4 min	15 min	36	Yes
5	4-MeO-phenyl	BF_3-etherate, 1.0 mM	15 min	1 h	41	Yes
6	4-MeO-phenyl	Low scrambling	4 h	4 h	6	Yes
7	4-MeO-phenyl	BF_3-etherate/EtOH, 3.3/130 mM	<4 min	15 min	38	Yes
8	C_6F_5	TFA, 20 mM	ND[f]	ND[f]	ND[f]	Trace
9	C_6F_5	BF_3-etherate, 1.0 mM	1 h	4 h	15	Yes
10	C_6F_5	Low scrambling	ND[f]	ND[f]	ND[f]	Yes
11	C_6F_5	TFA, 215 mM	30 min	4 h	3	Yes
12	C_6F_5	BF_3-etherate, 10 mM	30 min	4 h	13	Yes
13	Mesityl	TFA, 20 mM	ND[f]	ND[f]	ND[f]	Trace
14	Mesityl	BF_3-etherate, 1.0 mM	ND[f]	ND[f]	ND[f]	Trace
15	Mesityl	BF_3-etherate/EtOH, 3.3/130 mM	ND[f]	ND[f]	ND[f]	Trace
16	Pentyl	TFA, 20 mM	<4 min	15 min	23	Yes
17	Pentyl	BF_3-etherate, 1.0 mM	<4 min	4 h	25	Yes
18	Pentyl	TFA, 10 mM	<4 min	30 min	25	Yes
19	Pentyl	Low scrambling	1 h	4 h	10	Yes

[a] The reactions were performed with 10 mM of dipyrromethane. With the exception of the low scrambling condition, reactions were performed at room temperature in CH_2Cl_2 (for mesitaldehyde and 2,6-dimethylbenzaldehyde, $CHCl_3$ stabilized with amylenes was used instead of CH_2Cl_2). The low scrambling conditions are as follows: BF_3-etherate (1.0 mM), NH_4Cl (100 mmol l^{-1}), in MeCN at 0 °C. The reactions were monitored at 4 min, 15 min, 30 min, 1 h, and 4 h.

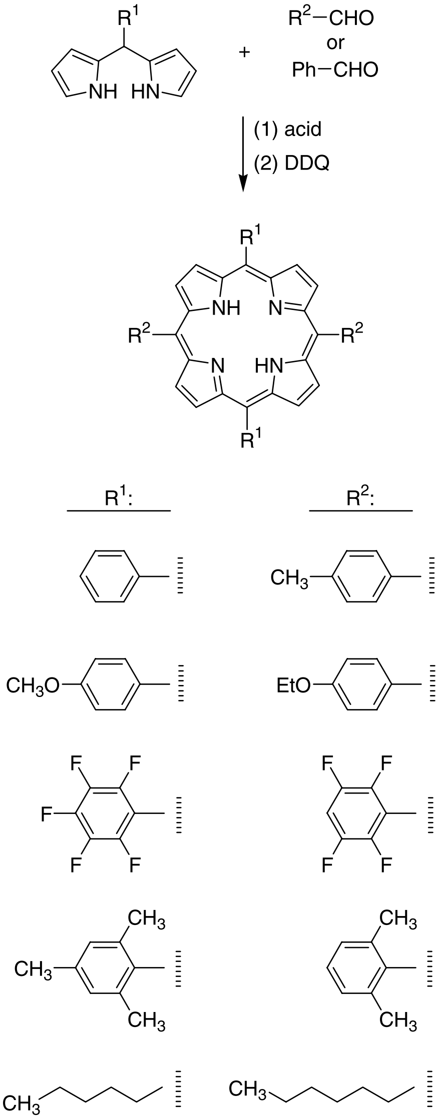
[b] The time at which porphyrin was first detected (UV–Vis) in an oxidized aliquot of the reaction mixture (limit of detection is 0.5%).

[c] The time at which the highest yield of porphyrin was observed.

[d] The highest yield of porphyrin observed. The yield is based on the stoichiometry of 1 equiv of porphyrinogen per 4 equiv of dipyrromethane.

[e] Detection of oligomers (LD-MS) of *m*/*z* greater than that of the dipyrromethane. ‘Trace’ means that only a small number of peaks of intensity close to the limit of detection were observed.

[f] No porphyrin was detected at any timepoint (limit of detection is 0.5%).



Scheme 3.

reactions were monitored from 4 min to 8 h for yield of porphyrin (UV–Vis) and oligomer composition (LD-MS). Acidolysis and scrambling were assessed by examination of the LD-MS spectra,[4] where peaks due to expected oligomers, oligomers formed by acidolysis, and oligomers produced by scrambling are readily identified. The results of these experiments are summarized in Table 5, and illustrative LD-MS spectra are provided in Figure 4. Similar reactions and analyses were performed for the reaction of each dipyrromethane + benzaldehyde (see Supplementary data).

With the exception of 5-mesityldipyrromethane and 5-pentafluorophenyldipyrromethane, condensations performed in the presence of a complementary aldehyde or benzaldehyde generally exhibited scrambling very early in the reaction and the level of scrambling reached statistical levels by the time the maximum yield of porphyrinogen was obtained. 5-(4-Methylphenyl)dipyrromethane was found to undergo scrambling more rapidly than 5-phenyldipyrromethane, even under the 'low scrambling' conditions (see Supplementary data for LD-MS spectra). Thus, differences between benzaldehyde and *p*-tolualdehyde observed during the studies of pyrrole + aldehyde condensations may also stem from different stability of oligomers bearing phenyl vs. *p*-tolyl substituents. Although in this study aldehydes of related structure generally behaved similarly, the contrasting behavior of benzaldehyde and *p*-tolualdehyde does show that small electronic differences can alter the course and outcome of the reaction.

3. Outlook

The ability to prepare porphyrinic macrocycles bearing diverse substituents is essential for a broad range of applications. The objectives of this study were to examine the catalytic requirements of a range of aldehydes, to better understand the effects of diverse substituents on the reaction course in terms of yield of porphyrin, reaction of aldehyde, composition of the oligomers, and reversibility of polypyrromethane and porphyrinogen formation, and to better

Table 5. Results of reactions of dipyrromethanes with their partner aldehydes[a]

Entry	R in R-dipyrromethane	Aldehyde substituent	Reaction condition	Time[b]	% Porphyrin	Scrambling[c]	Onset of scrambling[d]
1	Phenyl	*p*-Tolyl	TFA, 20 mM	15 min	45	Statistical	<4 min
2	Phenyl	*p*-Tolyl	BF_3-etherate, 1.0 mM	30 min	33	Statistical	15 min
3	4-MeO-phenyl	4-EtO-phenyl	TFA, 20 mM	15 min	34	Statistical	<4 min
4	4-MeO-phenyl	4-EtO-phenyl	BF_3-etherate/EtOH, 3.3/130 mM	4 min	38	Statistical	<4 min
5	C_6F_5	2,3,5,6-F_4-phenyl	TFA, 215 mM	4 min	15	Low level	<4 min
6	C_6F_5	2,3,5,6-F_4-phenyl	BF_3-etherate, 10 mM	15 min	20	Statistical	<4 min
7	Mesityl	2,6-Me_2-phenyl	BF_3-etherate/EtOH, 3.3/130 mM	4 h	35	None[e]	NA
8	Pentyl	Hexyl	TFA, 10 mM	4 min	22	Statistical	<4 min
9	Pentyl	Hexyl	BF_3-etherate, 1.0 mM	15 min	31	Statistical	<4 min

[a] The reactions were performed with 5 mM each of dipyrromethane and aldehyde at the 15 ml scale at room temperature in CH_2Cl_2 (for 5-mesityldipyrromethane and 2,6-dimethylbenzaldehyde, $CHCl_3$ stabilized with amylenes was used instead of CH_2Cl_2). The reactions were monitored at 4 min, 15 min, 30 min, 1 h, 4 h, and 8 h.

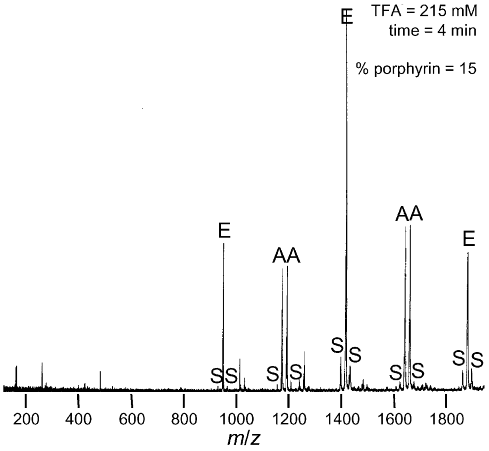
[b] The time at which the yield of porphyrin reached its maximum value.

[c] Level of scrambling (LD-MS) at the time of maximum yield of porphyrin. Refer to Figure 4 for representative LD-MS spectra.

[d] The time at which scrambling was first detected (LD-MS).

[e] Peaks were observed that may be assigned to oligomers produced by acidolysis, but no scrambling was detected.

A 5-pentafluorophenyldipyrromethane + 2,3,5,6-tetrafluorobenzaldehyde



B 5-(4-methoxyphenyl)dipyrromethane + 4-ethoxybenzaldehyde

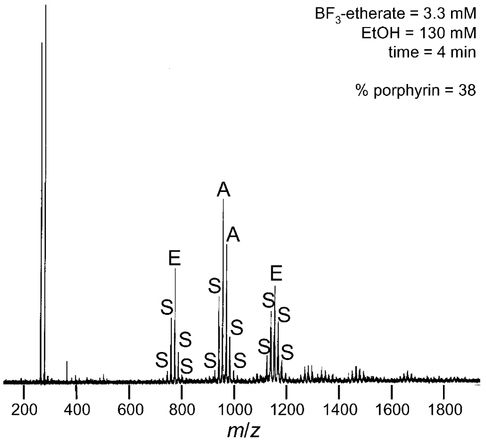


Figure 4. LD-MS spectra of crude, oxidized reaction mixtures from condensation of a dipyrromethane (R^1-DPM) with an aldehyde bearing a complementary substituent (R^2-CHO). The yield of porphyrin was determined by UV–Vis analysis. The panels illustrate the following: (A) a low level of scrambling, and (B) statistical scrambling. The peaks are labeled as follows: E = expected oligomers, A = oligomers formed by acidolysis, and S = oligomers produced by scrambling. The peaks were assigned as described previously.[4]

delineate the propensity for reversible processes leading to scrambling in reactions of dipyrromethanes.

Examination of the catalytic requirements of the pyrrole + aldehyde condensations revealed that quite a broad range of acid concentrations can be employed as long as the differing reaction trajectories resulting from the various aldehydes are taken into account. Application of one or both of the standard catalysis conditions [TFA (20 mM) or BF_3-etherate (1.0 mM)] results in reasonable yields of porphyrin for most aldehydes (except sterically bulky aldehydes such as mesitaldehyde) provided that the condensation is monitored so that the oxidant is added at the time of maximum yield of porphyrinogen.

The reaction course of the pyrrole + aldehyde condensations showed dependence on reaction conditions and aldehyde substituent. The reactions of the phenyl, *p*-tolyl, and alkyl aldehydes using BF_3-etherate generally afforded little turnover in porphyrinogen, little oligomer truncation, and a medium to high level of reversibility. The same aldehydes with TFA catalysis generated a higher level of turnover in porphyrinogen with a commensurate increase in level of oligomer truncation. Turnover in porphyrinogen level and extent of oligomer truncation were not always correlated. For example, the reaction of *p*-anisaldehyde gave near-total turnover (~35% yield of porphyrin at 1 h; <4% at 24 h) with both TFA and BF_3-ethanol catalysis, but the oligomer truncation was pronounced in the former yet low in the latter. The condensations with mesitaldehyde and pentafluorobenzaldehyde were generally irreversible, as evidenced by the lack of porphyrinogen and oligomer exchange. This finding illustrates that reversibility is not a prerequisite for achieving a good yield of the porphyrin.

The level of scrambling observed with various 5-substituted dipyrromethanes is somewhat dependent on the reaction conditions. Nevertheless, dipyrromethanes bearing phenyl, alkyl, and electron-donating aryl groups were generally prone to scrambling, while 5-pentafluorophenyldipyrromethane was very insensitive and 5-mesityldipyrromethane was essentially inert toward scrambling. This order is largely in agreement with the results of the porphyrinogen exchange experiments, although the extent of scrambling was often much greater than the level of exchange produced in the corresponding pyrrole + aldehyde reaction. These observations provide guidance for the design of synthetic plans that minimize the potential for undesired scrambling.

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Supplementary data

Complete experimental section, plots of the yield of porphyrin as a function of acid concentration, and plots of the yield of porphyrin and the percent unreacted aldehyde as a function of condensation time for all aldehydes examined; LD-MS spectra showing the oligomer composition at each timepoint for all reactions of pyrrole + aldehyde examined; data pertaining to studies of 5-substituted dipyrromethanes bearing diverse substituents.

Supplementary data associated with this article can be found at doi:10.1016/j.tet.2004.09.081

References and notes

1. Lindsey, J. S. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, CA, 2000; Vol. 1, pp 45–118.

2. Geier, G. R., III; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 677–686.
3. Geier, G. R., III; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 687–700.
4. Geier, G. R., III; Littler, B. J.; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 701–711.
5. Geier, G. R., III; Littler, B. J.; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 712–718.
6. Geier, G. R., III; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1596–1603.
7. Li, F.; Yang, K.; Tyhonas, J. S.; MacCrum, K. A.; Lindsey, J. S. *Tetrahedron* **1997**, *53*, 12339–12360.
8. Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827–836.
9. Arsenault, G. P.; Bullock, E.; MacDonald, S. F. *J. Am. Chem. Soc.* **1960**, *82*, 4384–4389.
10. Paine, J. B., III In *The Porphyrins*; Dolphin, D., Ed.; Academic: New York, 1979; Vol. I, pp 101–234.
11. Clezy, P. S. *Aust. J. Chem.* **1991**, *44*, 1163–1193.
12. Mamardashvili, N. Z.; Golubchikov, O. A. *Russ. Chem. Rev.* **2000**, *69*, 307–323.
13. Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323–7344.
14. Littler, B. J.; Ciringh, Y.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 2864–2872.
15. Lindsey, J. S.; Wagner, R. W. *J. Org. Chem.* **1989**, *54*, 828–836.
16. Onaka, M.; Shinoda, T.; Izumi, Y.; Nolen, E. *Tetrahedron Lett.* **1993**, *34*, 2625–2628.
17. Onaka, M.; Shinoda, T.; Izumi, Y.; Nolen, E. *Chem. Lett.* **1993**, 117–120.
18. Laszlo, P.; Luchetti *J. Chem. Lett.* **1993**, 449–452.
19. Shinoda, T.; Onaka, M.; Izumi, Y. *Chem. Lett.* **1995**, 493–494.
20. Shinoda, T.; Izumi, Y.; Onaka, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1801–1802.
21. Geier, G. R., III; Riggs, J. A.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2001**, *5*, 681–690.
22. Geier, G. R., III; Ciringh, Y.; Li, F.; Haynes, D. M.; Lindsey, J. S. *Org. Lett.* **2000**, *2*, 1745–1748.
23. Geier, G. R., III; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2002**, *6*, 159–185.
24. Sharghi, H.; Nejad, A. H. *Tetrahedron* **2004**, *60*, 1863–1868.