Investigation of porphyrin-forming reactions. Part 3.[1] The origin of scrambling in dipyrromethane + aldehyde condensations yielding *trans*-A_2B_2-tetraarylporphyrins

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The dipyrromethane + aldehyde condensation is a common method for the synthesis of *trans*-A_2B_2-porphyrins, but is often plagued by scrambling processes that lead to a mixture of porphyrins. The problem of scrambling is more pronounced with unhindered dipyrromethanes (*e.g.*, 5-phenyldipyrromethane) than with hindered dipyrromethanes (*e.g.*, 5-mesityldipyrromethane). We have characterized the oligomer composition (by LD-MS), yield of porphyrin (by UV–Vis), yield of N-confused porphyrin (by HPLC), and level of unreacted aldehyde (by TLC) in dipyrromethane + aldehyde condensations leading to *trans*-A_2B_2-porphyrins. Reaction conditions known to suppress scrambling in reactions involving 5-phenyldipyrromethane (PDPM) were compared to conditions known to provide extensive scrambling. The low-scrambling conditions were found to suppress scrambling by inhibiting reaction of oligomer fragments generated by acid-induced cleavage of the dipyrromethane, rather than by inhibiting acidolysis itself. However, such reaction conditions were also found to inhibit the condensation, leading to low yields (<10%) of porphyrin. The condensation of PDPM + aldehyde was also compared to reactions involving 5-mesityldipyrromethane (MDPM) to understand why *trans*-A_2B_2-porphyrins can be prepared in good yield devoid of scrambling from reactions using MDPM. The absence of scrambling in MDPM + aldehyde condensations was due to the resistance of MDPM to acidolysis. Taken together, these studies provide insight into the origin of scrambling with different types of substrates under different reaction conditions in the dipyrromethane + aldehyde route to *trans*-A_2B_2-porphyrins.

Introduction

meso-Substituted porphyrins bearing substituents in a *trans* configuration are versatile building blocks for preparing a wide variety of porphyrin-containing systems.[2] Two major approaches have been taken towards the synthesis of such *trans*-A_2B_2-porphyrins (Scheme 1). A mixed aldehyde condensation of pyrrole and two different aldehydes affords a mixture of up to six porphyrins, from which the desired porphyrin is generally isolated by extensive chromatography.[3,4] A rational approach for the synthesis of *trans*-porphyrins involves the condensation of a dipyrromethane and an aldehyde. The success of this methodology requires reaction conditions that produce only a single porphyrin in good yield. In our studies of two-step, one-flask porphyrin syntheses, all conditions examined that provided good yields of porphyrin also displayed at least some degree of reversibility of oligomer formation.[1] Under conditions providing complete reversibility, a dipyrromethane + aldehyde condensation would give a mixture of porphyrin products identical to that obtained from the corresponding mixed aldehyde condensation. In stepwise, rational porphyrin syntheses such reversibility leads to rearrangement of the substituents, and is referred to as "scrambling".

The problem of scrambling must be overcome to carry out rational syntheses of porphyrins. When 5-substituted dipyrromethanes (lacking β-substituents) first became available,[5] the conditions employed for the dipyrromethane + aldehyde condensation were drawn directly from the analogous pyrrole + aldehyde condensations. These conditions employed TFA,[6] BF_3–Et_2O,[6] or BF_3–Et_2O + ethanol[7] as catalysts in CH_2Cl_2 or $CHCl_3$ (Table 1). With dipyrromethanes containing a sterically hindered aryl substituent (*e.g.*, mesityl), application of these methods resulted in no noticeable scrambling and the desired *trans*-A_2B_2-porphyrin was obtained in a straightforward manner.[5,8] However, application of these methods to dipyrromethanes containing an unhindered aryl substituent (*e.g.*, phenyl) resulted in scrambling, and the desired *trans*-A_2B_2-porphyrin often was quite difficult to isolate.[9]

A lengthy study was undertaken in our laboratory to characterize the effects of various conditions on scrambling in dipyrromethane + aldehyde condensations, and to refine these conditions in order to minimize if not eliminate scrambling.[10] The conditions identified for condensations with dipyrromethanes containing a sterically hindered aryl substituent (*e.g.*, mesityl) closely resembled the TFA catalysis conditions employed in the pyrrole + aldehyde condensation. These conditions are referred to as the "TFA/SH-DPM" conditions (Table 1). Identification of conditions for use with dipyrromethanes containing an unhindered aryl substituent (*e.g.*, phenyl) proved far more difficult. After lengthy empirical experimentation, conditions were identified for such condensations, but scrambling was not entirely eliminated and the porphyrin yield was typically <10%. These conditions employ BF_3–Et_2O + NH_4Cl and are referred to as the "BF_3/UH-DPM" conditions (Table 1). Although developed for dipyrromethane + aldehyde condensations, the BF_3/UH-DPM conditions have been applied to related condensations in porphyrinic chemistry, including the condensations of a dipyrromethane and a thienylpyrromethane-dicarbinol† or a furylpyrromethane-dicarbinol leading to heteroatom-substituted porphyrins.[11]

In this paper, we report our studies of dipyrromethane + aldehyde condensations with the goals of understanding the processes involved in scrambling. A particular concern has been to determine why some reaction conditions

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† The term carbinol has been abandoned by IUPAC; the IUPAC term for carbinol is a substituted methanol.

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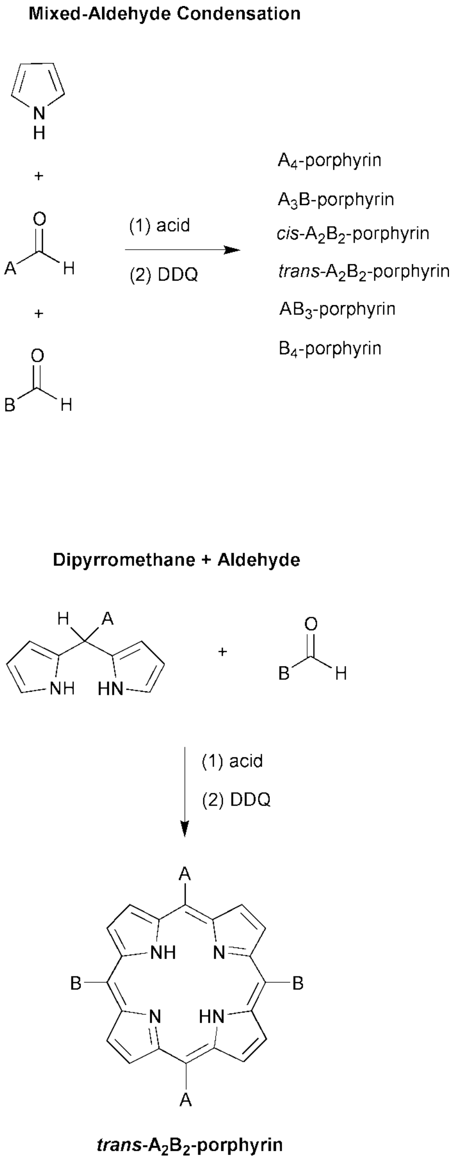


Scheme 1 A statistical approach *versus* a rational approach to the synthesis of *trans*-A_2B_2-porphyrins.

inhibit scrambling while others do not, and to determine the relationship between scrambling and porphyrin yield. Towards that end, we have compared the dipyrromethane + aldehyde condensation under the six reaction conditions summarized in Table 1. In keeping with previous practice, concentrations of 10 mM dipyrromethane and 10 mM aldehyde were employed under the first five reaction conditions listed in Table 1, while concentrations of 90 mM dipyrromethane and 90 mM aldehyde were used in the reaction employing trichloroacetic acid. The latter conditions were originally applied with condensations of a β-substituted dipyrromethane + aldehyde. In all conditions explored in this study, the reactions have been characterized in terms of oligomer content (LD-MS), macrocycle yields (UV–Vis, HPLC), and level of unreacted aldehyde (TLC) over time. The condensations of dipyrromethanes bearing mesityl or phenyl substituents were compared. The results of these experiments provide deeper insight into reaction conditions for dipyrromethane + aldehyde condensations, and provide guidance for further refinements to these types of syntheses.

Results and discussion

Detection of scrambling by LD-MS

We have used LD-MS previously to detect the presence of scrambled porphyrins in dipyrromethane + aldehyde conden-

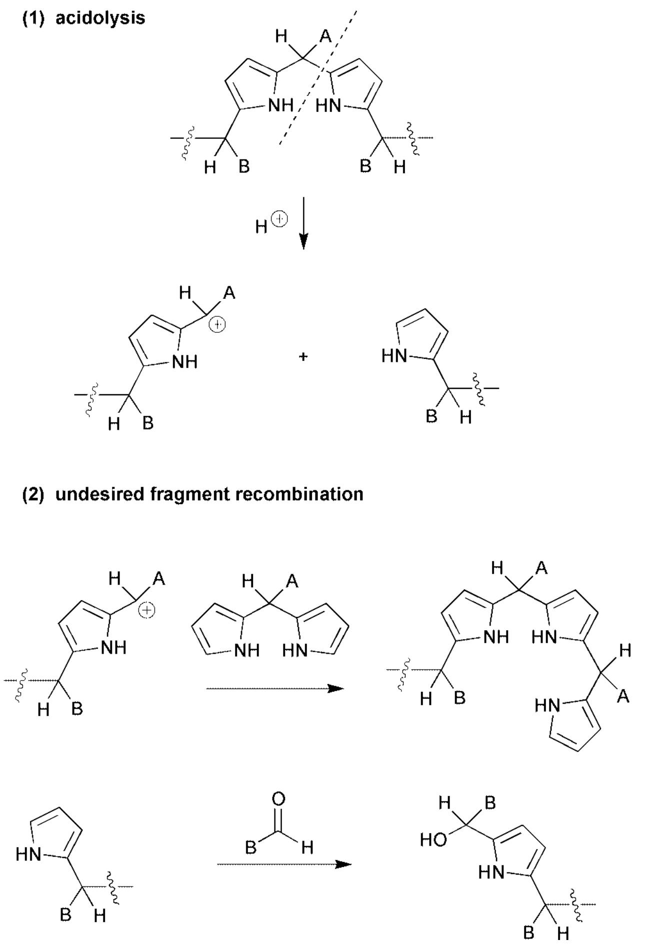
Table 1 Reaction conditions and results from previous porphyrin syntheses

Porphyrin synthesis reactants	Condensation conditions[g]						Results	
	Title	Acid	Conc.[j]	Solvent	T	Time[k]	Yield[l]	Scrambling[n]
Pyrrole + ArCHO[a]	Standard-TFA	TFA, 20 mM	10 mM	CH_2Cl_2	rt	1 h	40%[m]	NA[o]
Pyrrole + ArCHO[a]	Standard-BF_3	BF_3–Et_2O, 1.0 mM	10 mM	CH_2Cl_2	rt	1 h	26%[m]	NA
Pyrrole + ArCHO[b]	BF_3–ethanol	BF_3–Et_2O, 3.3 mM + ethanol, 130 mM	10 mM	$CHCl_3$	rt	1 h	31%[b]	NA
Hindered DPM[c] + ArCHO[d]	TFA/SH-DPM[h]	TFA, 17.8 mM	10 mM	CH_2Cl_2	rt	15 min	14–48%[d]	None
Unhindered DPM + ArCHO[e]	BF_3/UH-DPM[i]	BF_3–Et_2O, 1.0 mM + NH_4Cl, 100 mmol L^{-1}	10 mM	CH_3CN	0 °C	4 h	8%[e]	Low[p]
β-Substituted DPM + ArCHO[f]	TCA/β-DPM	Trichloroacetic acid, 15.3 mM	90 mM	CH_3CN	rt	5 h	52–87%[f]	NR[q]

[a] Ref. 6. [b] Ref. 7. [c] DPM = dipyrromethane. [d] For reaction with hindered dipyrromethanes such as 5-mesityldipyrromethane.[10] [e] For reaction with unhindered dipyrromethanes such as 5-phenyldipyrromethane.[10] [f] Tetrachloro-1,4-benzoquinone was employed as the oxidant rather than DDQ.[15] [g] After the condensation, DDQ was employed as the oxidant. [h] Previously termed "no-scrambling" conditions.[10] [i] Previously termed "low-scrambling" conditions.[10] [j] Concentration of the two reactants (equimolar). [k] Typical condensation period. [l] Isolated yields of porphyrin. [m] Ref. 1. [n] Detected by LD-MS examination of crude, oxidized reaction mixtures prior to workup. [o] NA = not applicable. [p] Level 1 scrambling.[10] [q] Not reported.

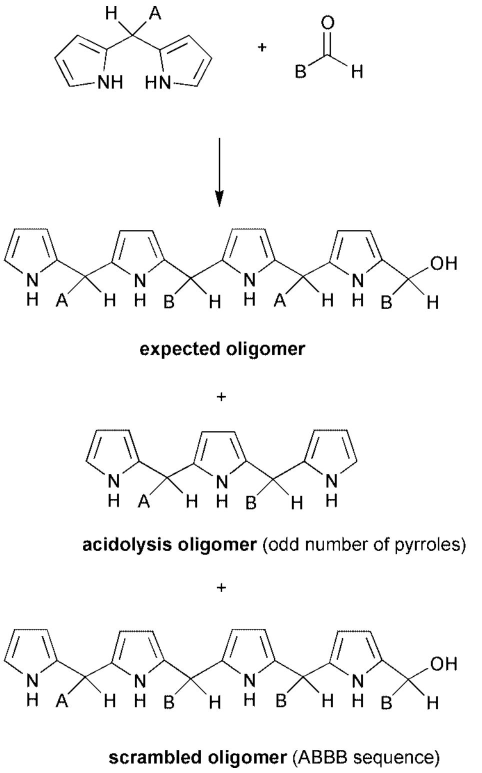
sations.[10] In those studies, the sample was partially purified prior to LD-MS analysis so that only the porphyrin fraction was examined. In the present work, we sought to gain deeper insight concerning the origin of scrambling by examining the entire oligomer composition found in the crude, unpurified reaction mixture derived from the condensation of a dipyrromethane + aldehyde.

Scrambling is the consequence of two processes (Scheme 2).



Scheme 2 Substituent scrambling requires two processes: acidolysis and fragment recombination.

The first step is the acidolysis of the preformed dipyrromethane moiety (either before or after the dipyrromethane has been incorporated into a longer oligomer), yielding two fragments. This cleavage step is a prerequisite for scrambling, but alone does not cause scrambling. Acidolysis merely leads to truncation of the oligomers. The second step is the further reaction (recombination) of the acid-cleaved oligomers with starting materials or other oligomers in such a way as to change the desired order of substituents. Thus, the dipyrromethane + aldehyde condensation can potentially yield three types of oligomeric species: "expected" oligomers arising from the desired condensation, "acidolysis" oligomers arising from acidolytic cleavage only of expected oligomers, and "scrambled" oligomers arising from acidolysis followed by an undesired recombination (Scheme 3).



Scheme 3 The three possible types of oligomers from a dipyrromethane + aldehyde condensation.

The three types of oligomers (expected, acidolysis, scrambled) can be distinguished by LD-MS provided the two substituents are of different molecular weight. Expected oligomers have masses consistent with the sequential addition of dipyrromethane and aldehyde units, giving an even number of pyrrole units and the correct ratio of substituents (the number of "A" substituents must be within ±1 of the number of "B" substituents). Acidolysis oligomers have masses consistent with both an odd number of pyrrole units and a correct ratio of substituents. Scrambled oligomers have masses consistent with an incorrect ratio of substituents (the number of "A" substituents differs from the number of "B" substituents by >±1). The calculated masses for all the possible oligomers of $n \leq 5$ for the reaction of 5-phenyldipyrromethane (PDPM) + *p*-tolualdehyde are shown and assigned in Table 2.[‡]

Condensations of 5-phenyldipyrromethane

We have identified low-scrambling conditions for the reaction of unhindered dipyrromethanes (*e.g.*, 5-phenyldipyrromethane) yielding *trans*-A_2B_2-porphyrins (Table 1).[10][§] We sought to compare the condensation of PDPM + *p*-tolualdehyde (the same model reaction used previously) under these low-

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[‡] There are two minor caveats to this analysis. First, in the higher mass regime there are non-isomeric oligomers of different composition that have coincidentally identical masses; thus, not all of the peaks can be definitively assigned. This is not of major concern as there is an adequate number of unique masses to obtain very good insight into a given reaction. Second, the scrambled oligomers are the only oligomers of the three types that can be definitively assigned. For example, the desired *trans*-A_2B_2-porphyrin has substituents in an A–B–A–B order. Acidolysis and recombination could give rise to a scrambled oligomer with an A–B–B–A order, which has a mass identical to that of the expected oligomer. Thus, a peak assigned as an expected oligomer could actually be derived from a mixture of expected oligomers and scrambled oligomers (as well as expected oligomers that came about through processes of acidolysis and recombination rather than direct condensation of the dipyrromethane and aldehyde). The same is true for the acidolysis oligomers. This uncertainty in the assignment of expected oligomers and acidolysis oligomers is not of grave concern, as we believe it very unlikely that a mass spectrum showing only expected peaks could have arisen from a reaction that involved rampant acidolysis and recombination. Though the absence of acidolysis oligomers and scrambled oligomers does not mean that those processes did not occur, we fully expect peaks that are uniquely assignable to acidolysis oligomers and scrambled oligomers to be present in cases where the expected oligomer peaks are contaminated with scrambled peaks of the same mass.

[§] Such concentrations equal 20 mM pyrrole and aldehyde. Experiments done with 5 mM dipyrromethane + 5 mM aldehyde provided qualitatively identical results.

Table 2 Calculated molecular masses for all possible oligomers ($n \le 5$) belonging to the $(PA)_n$, $(PA)_nP$, $A(PA)_n$, or $P(PA)_nP$ series derived from the condensation of 5-phenyldipyrromethane + *p*-tolualdehyde[a]

Series	*n*	All phenyl	Phenyl and *p*-tolyl mixed oligomers				All *p*-tolyl
$(PA)_n$	1	$\underline{155}$					$\underline{169}$
	2	308	**322**				336
	3	461	$\underline{475}$	$\underline{489}$			503
	4	614	628	**642**	656		670
	5	767	781	$\underline{795}$	$\underline{809}$	823	837
$(PA)_nP$	1	**220**					$\underline{234}$
	2	373	$\underline{387}$				401
	3	526	**540**	$\underline{554}$			568
	4	679	693	$\underline{707}$	721		735
	5	832	846	**860**	$\underline{874}$	888	902
$A(PA)_n$	1	245	$\underline{259}$				273
	2	398	$\underline{412}$	**426**			440
	3	551	565	$\underline{579}$	593		607
	4	704	718	$\underline{732}$	**746**	760	774
	5	858	872	886	$\underline{900}$	914	942
$P(PA)_nP$	1	**285**					299
	2	438	$\underline{452}$				466
	3	592	$\underline{605}$	$\underline{619}$			633
	4	744	**758**	$\underline{772}$	786		800
	5	897	911	$\underline{925}$	$\underline{939}$	953	967

[a] The bold masses can be accounted for without acidolysis or scrambling. Underlined masses can be accounted for by acidolysis without scrambling. All other masses can only be accounted for by scrambling.

scrambling (*i.e.*, BF_3/UH-DPM) conditions with the same reaction under "standard" two-step, one-flask conditions (20 mM TFA or 1.0 mM BF_3–Et_2O in CH_2Cl_2 at room temperature). To illustrate the possible level of scrambling, LD-MS spectra obtained from mixed aldehyde condensations of benzaldehyde, *p*-tolualdehyde, and pyrrole are shown in Fig. 1. In general, the mixed aldehyde condensations provided very complicated mass spectra. The dominant peaks corresponded to $(PA)_n$ series peaks, where P and A correspond to pyrrole and aldehyde, respectively. The peaks appeared as clusters corresponding to the different possible combinations of phenyl and *p*-tolyl groups for each oligomer family (*i.e.*, $(PA)_4$ has five possible peaks each separated by 14 mass units, $(PA)_5$ has six possible peaks, *etc.*). These spectra are representative of statistical scrambling in a dipyrromethane + aldehyde condensation.

(i) Acidolysis and scrambling in PDPM + *p*-tolualdehyde reactions. The condensation of PDPM and *p*-tolualdehyde (10 mM each) was performed under BF_3/UH-DPM conditions (1.0 mM BF_3–Et_2O, 10 equiv. of NH_4Cl, acetonitrile, 0 °C). Samples were removed at 15 min, 2 h, and 24 h and oxidized with DDQ. The resulting crude oxidized samples were then examined by LD-MS. The LD-MS spectra showed a fairly simple oligomer composition in comparison to that of the mixed aldehyde condensation (Fig. 2). Nevertheless, acidolysis oligomers and scrambled oligomers were detected. Peaks assigned to acidolysis oligomers were detected very early in the reaction, even while the yield of porphyrin was <5%. As the reaction proceeded, an increase was observed in the number and intensity of peaks due to acidolysis oligomers. The acidolysis oligomers were observed across the entire mass range that could be detected. Very minor peaks assigned to scrambled oligomers appeared early but remained weak throughout the reaction. Consistent with previous synthetic results, there was little scrambling of the porphyrin-containing oligomers $(PA)_4$ detected at a reaction time of 2 h, which is the usual length of this reaction. Even at 24 h, the level of scrambling was low. Finally, the total porphyrin yield throughout the reaction was low (~10%).

The analysis of the oligomer composition showed that the BF_3/UH-DPM reaction conditions do not avoid acidolysis. Indeed, numerous peaks assigned to acidolysis oligomers were detected throughout the reaction. Thus, the inhibition of scrambling under these conditions must be due to suppression of recombination of the fragments generated by acidolysis. This conclusion is consistent with the low yield of porphyrin obtained in the reaction, as a poor yield of porphyrin reflects sub-optimal condensation conditions. These sub-optimal condensation conditions produce low levels of fragment recombination as well as low yields of porphyrin.

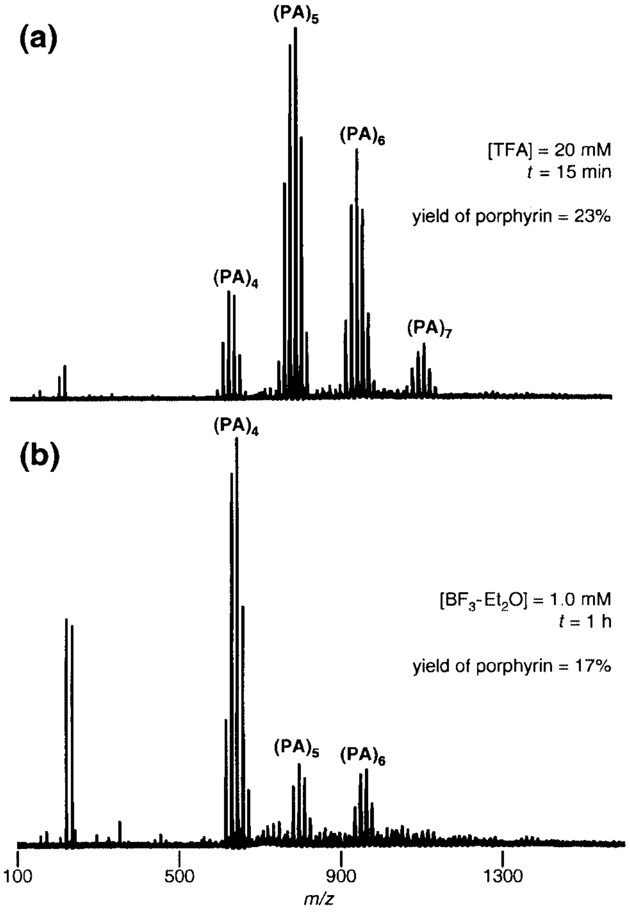


Fig. 1 LD-MS spectra showing oligomer compositions derived from the mixed aldehyde condensation of 20 mM pyrrole, 10 mM benzaldehyde, and 10 mM *p*-tolualdehyde. (a) Catalysis with 20 mM TFA for 15 min; (b) catalysis with 1.0 mM BF_3–Et_2O for 1 h. The reactions were performed in CH_2Cl_2 at room temperature. The total porphyrin yield (UV–Vis) for each reaction is noted.

To explore fragment recombination under more favorable reaction conditions, condensations of PDPM + *p*-tolualdehyde were performed under the conditions of the two-step, one-flask porphyrin reaction. Under conditions of 20 mM TFA in CH_2Cl_2 at room temperature ("standard-TFA"), both acidolysis and scrambling occurred extensively throughout the reaction (Fig. 3). Even at a reaction time of 1 min, when no porphyrin was formed, analysis of the oligomer content showed statistical levels of scrambling. By 30 min, the total yield of porphyrin was 38%, but the oligomer content closely resembled that of the mixed aldehyde condensation. Results obtained with 1.0 mM BF_3–Et_2O in CH_2Cl_2 at room temperature ("standard-BF_3") were very similar. Comparison of the oligomer content and porphyrin yield obtained from the BF_3/UH-DPM and standard-TFA or standard-BF_3 reaction conditions shows a correlation between (1) porphyrin yield and (2) acidolysis and fragment recombination leading to scrambling.

We sought to further explore the relation between porphyrin yield and scrambling by examining two other reaction conditions: (1) the BF_3/UH-DPM conditions with BF_3–Et_2O alone in the absence of NH_4Cl and (2) 200 mM TFA in acetonitrile at

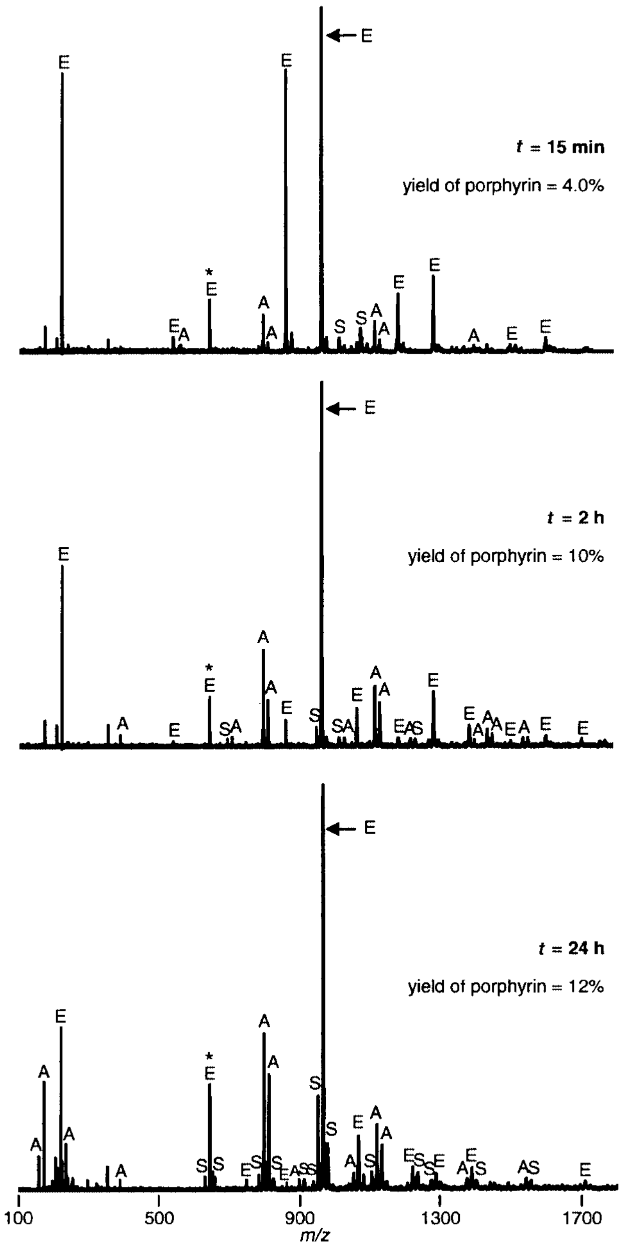


Fig. 2 LD-MS spectra showing the oligomer composition as a function of reaction time obtained under BF_3/UH-DPM conditions in the reaction of 5-phenyldipyrromethane + *p*-tolualdehyde (10 mM each, 1.0 mM BF_3–Et_2O, 10 equiv. of NH_4Cl relative to BF_3–Et_2O, acetonitrile, 0 °C). E = expected oligomers, A = acidolysis oligomers, S = scrambled oligomers. The peak with *m*/*z* corresponding to the desired porphyrin product is marked with an asterisk. The total porphyrin yield (UV–Vis) at each reaction time is noted.

0 °C. The first set of conditions was inspired by a desire to examine the role of NH_4Cl, and the second set was developed to examine catalysis with TFA, the other acid commonly used in porphyrin syntheses.[6] (The concentration of TFA had to be increased under the latter conditions, as a lower concentration of TFA was found to provide very low porphyrin yields.) Examination of a representative LD-MS spectrum from each reaction at 2 h shows that both conditions provided acidolysis and scrambling, and the reaction giving higher yield also gave the greater extent of scrambling (Fig. 4). The absence of NH_4Cl in the BF_3/UH-DPM reaction conditions provided a slightly higher yield of porphyrin as well as a higher level of scrambling. Thus, the presence of NH_4Cl in the reaction appears to inhibit the condensation. TFA at a concentration (200 mM) required to provide good yields of porphyrin (~20%) was found to offer no advantages in the suppression of scrambling compared with BF_3–Et_2O.

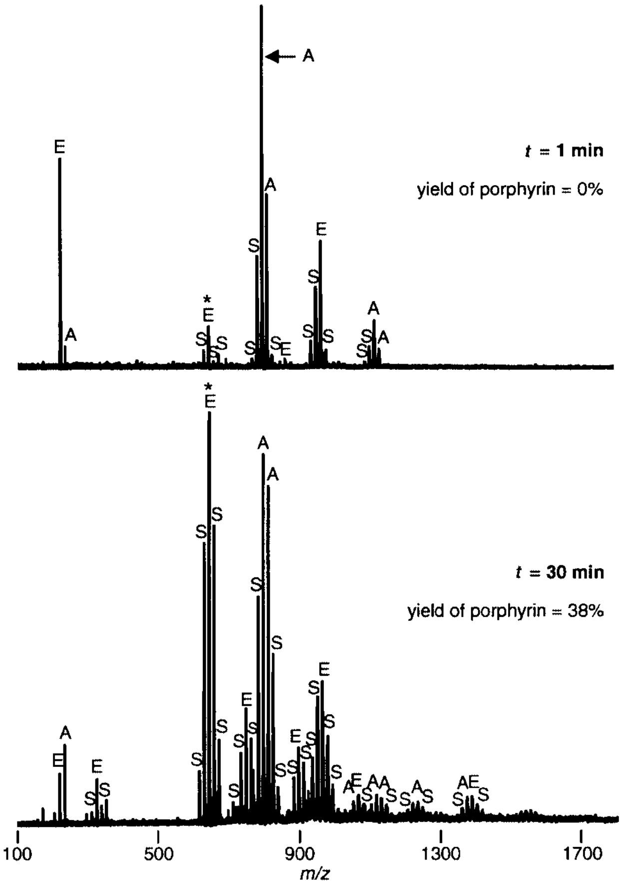


Fig. 3 LD-MS spectra showing the oligomer composition as a function of reaction time obtained under standard-TFA conditions in the reaction of 5-phenyldipyrromethane + *p*-tolualdehyde (10 mM each, 20 mM TFA, CH_2Cl_2, room temperature). E = expected oligomers, A = acidolysis oligomers, S = scrambled oligomers. The asterisk denotes the peak with *m*/*z* equal to the mass of TPP. The total porphyrin yield (UV–Vis) at each reaction time is noted.

We sought to probe the relation between porphyrin yield in the reaction and the level of scrambling observed upon application of these same conditions to the analogous aldehyde + pyrrole reactions. Thus, we examined the yields obtained from the condensation of pyrrole (20 mM), benzaldehyde (10 mM), and *p*-tolualdehyde (10 mM) under each of the previously considered reaction conditions (Fig. 5). Under the BF_3/UH-DPM conditions, the total yield of porphyrin remained ≤3%, whereas under the reaction conditions providing the highest levels of scrambling, porphyrin yields of >25% were obtained. In general, reaction conditions that promote the efficient reaction of pyrrole + aldehyde also give rise to commensurably more scrambling in the analogous dipyrromethane + aldehyde condensation. It appears that the catalytic requirements for the processes leading to scrambling in the dipyrromethane + aldehyde reactions are similar to those required for the reaction of pyrrole + aldehyde. Thus, in order to avoid scrambling in the dipyrromethane + aldehyde reaction, conditions must be employed that are marginal for the pyrrole + aldehyde condensation. Given that the dipyrromethane is only slightly more reactive than pyrrole towards free aldehyde, it is difficult to strike the appropriate balance between poor catalytic conditions that avoid scrambling, and good catalytic conditions that provide a desirable yield of porphyrin.

(ii) Comparison of oligomer composition, N-confused porphyrin yield and unreacted aldehyde. Condensations of PDPM + benzaldehyde (not *p*-tolualdehyde) were performed under the BF_3/UH-DPM, standard-TFA, and standard-BF_3 conditions. In this manner, the oligomer composition (containing all phenyl-substituted oligomers uncomplicated by distinct peaks

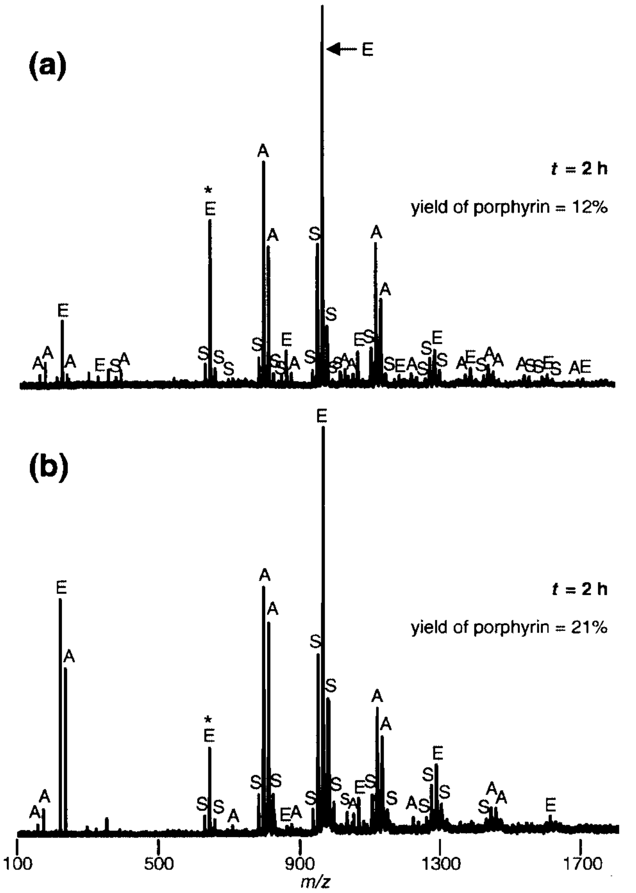


Fig. 4 LD-MS spectra showing the oligomer composition obtained for the reaction of 5-phenyldipyrromethane + *p*-tolualdehyde (10 mM each) in acetonitrile with different acid conditions. (a) 1.0 mM BF_3–Et_2O, 0 °C, 2 h; (b) 200 mM TFA, 0 °C, 2 h. E = expected oligomers, A = acidolysis oligomers, S = scrambled oligomers. The peak with *m*/*z* corresponding to the desired *trans*-A_2B_2-porphyrin product is marked with an asterisk. The total porphyrin yield (UV–Vis) for each reaction is noted.

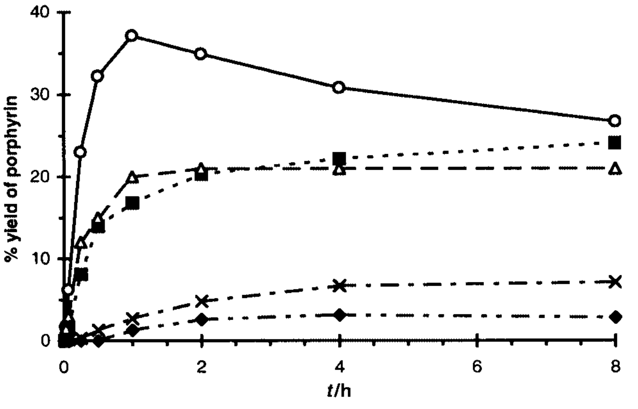


Fig. 5 Effects of five different reaction conditions on the total yield of porphyrin (UV–Vis) obtained from the mixed-aldehyde condensation of 10 mM benzaldehyde, 10 mM *p*-tolualdehyde, and 20 mM pyrrole. Reaction conditions: ○, standard-TFA; ■, standard-BF_3; △, TFA (200 mM) in acetonitrile at 0 °C; ×, BF_3/UH-DPM conditions without NH_4Cl; ◆, BF_3/UH-DPM.

due to scrambled oligomers) could be compared with the yields of porphyrin, N-confused porphyrin, and unreacted aldehyde as a function of different reaction conditions. As expected, the oligomer formation, porphyrin yield, N-confused porphyrin yield,[12] and aldehyde consumption all increased more slowly and to a lower final extent under the BF_3/UH-DPM conditions as compared to the standard-TFA and standard-BF_3 conditions. At 8 h, the yield of N-confused porphyrin was only 0.3% under BF_3/UH-DPM conditions compared to ~6% under the standard-TFA and standard-BF_3 conditions.¶ At 1 h, ~50% of the aldehyde was unreacted under the BF_3/UH-DPM conditions compared to ~20% under standard-BF_3 catalysis and ~0% under standard-TFA catalysis. These data indicate that the BF_3/UH-DPM conditions provide a very sluggish reaction compared to the standard-TFA and standard-BF_3 conditions that lead to high levels of scrambling.

(iii) Acidolysis and recombination in reactions of PDPM alone. The BF_3/UH-DPM conditions *versus* the standard-TFA and standard-BF_3 conditions were contrasted in a final set of experiments examining the reaction of PDPM alone (no added aldehyde). Illustrative LD-MS spectra for 2 h time points for the standard-TFA and standard-BF_3 conditions and an 8 h time point for the BF_3/UH-DPM conditions (all using 10 mM PDPM) were dramatically different (Fig. 6). The standard-TFA and standard-BF_3 conditions showed oligomer compositions and porphyrin yields very similar to those of the reaction of 10 mM benzaldehyde with 20 mM pyrrole, indicating that the dipyrromethane readily underwent acidolysis and fragment recombination under those conditions. In contrast, the reaction under BF_3/UH-DPM conditions showed few oligomers other than a strong peak at *m*/*z* 220 (corresponding to 5-phenyldipyrrin) and no porphyrin at any point in the reaction, indicating that fragment recombination did not occur to a significant extent.

Condensations of 5-mesityldipyrromethane

In contrast to the difficulties encountered while searching for no-scrambling conditions appropriate for dipyrromethanes containing *ortho*-unsubstituted aryl substituents, sterically hindered dipyrromethanes such as 5-mesityldipyrromethane (MDPM)[13] give no-scrambling under conditions very similar to those in the standard two-step, one-flask reaction of an aldehyde and pyrrole involving TFA. The non-scrambling conditions employ 10 mM dipyrromethane + 10 mM aldehyde with 17.8 mM TFA in CH_2Cl_2 at room temperature (*i.e.*, the TFA/SH-DPM conditions). The condensation of MDPM + benzaldehyde was examined as a model reaction and the *trans*-A_2B_2-porphyrin was obtained in yields of ~30% devoid of scrambling. We sought to understand whether the suitability of these conditions for MDPM stems from resistance of MDPM to acidolysis or whether the mesityl-substituted fragments generated by acidolysis are less prone to recombination.

(i) Acidolysis and scrambling in MDPM + benzaldehyde condensations. Reactions of MDPM + benzaldehyde were performed under the TFA/SH-DPM conditions and examined by LD-MS, which showed that the oligomer content of the reaction mixture was simpler than that obtained from condensations with PDPM (Fig. 7). At a reaction time of 4 min, the LD-MS spectrum was almost completely devoid of peaks due to acidolysis oligomers and scrambled oligomers even though the yield of porphyrin upon DDQ oxidation was 18%. At a reaction time of 15 min, the porphyrin yield was near its maximum value of ~30%, and the LD-MS spectrum was still very simple with only a small number of peaks assigned to oligomers derived from acidolysis and scrambling. At a reaction time of 2 h, after the porphyrin yield had begun to decline, the LD-MS spectrum still showed only minor undesired acidolysis peaks and scrambling peaks. Thus, MDPM was significantly more resistant to both acidolysis and scrambling than PDPM under these reaction conditions.

¶ The HPLC assay for NC-TPP also enables quantitation of TPS. In each case where the yield of NC-TPP was examined, no TPS was detected (limits of detection = 0.5%).

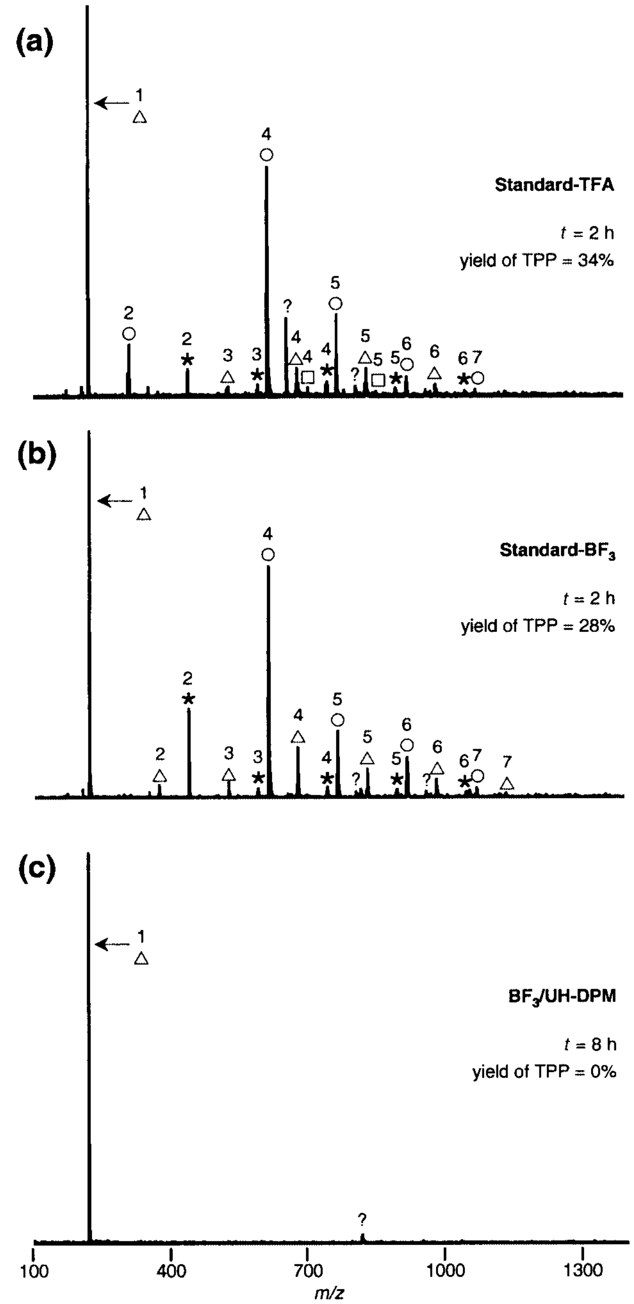


Fig. 6 LD-MS spectra comparing the oligomer composition obtained from the reaction of 10 mM 5-phenyldipyrromethane alone under different acid conditions. (a) Standard-TFA conditions for 2 h; (b) standard-BF$_3$ conditions for 2 h; (c) BF$_3$/UH-DPM conditions for 8 h. The yield of TPP (UV–Vis, HPLC) for each reaction is noted. ○ = (PA)$_n$ series, △ = (PA)$_n$P series, □ = A(PA)$_n$ series, ★ = P(PA)$_n$P series. Significant peaks that could not be assigned to one of the four oligomer series are denoted by a "?". The oligomer length (*n*) is given by the number above the symbol.

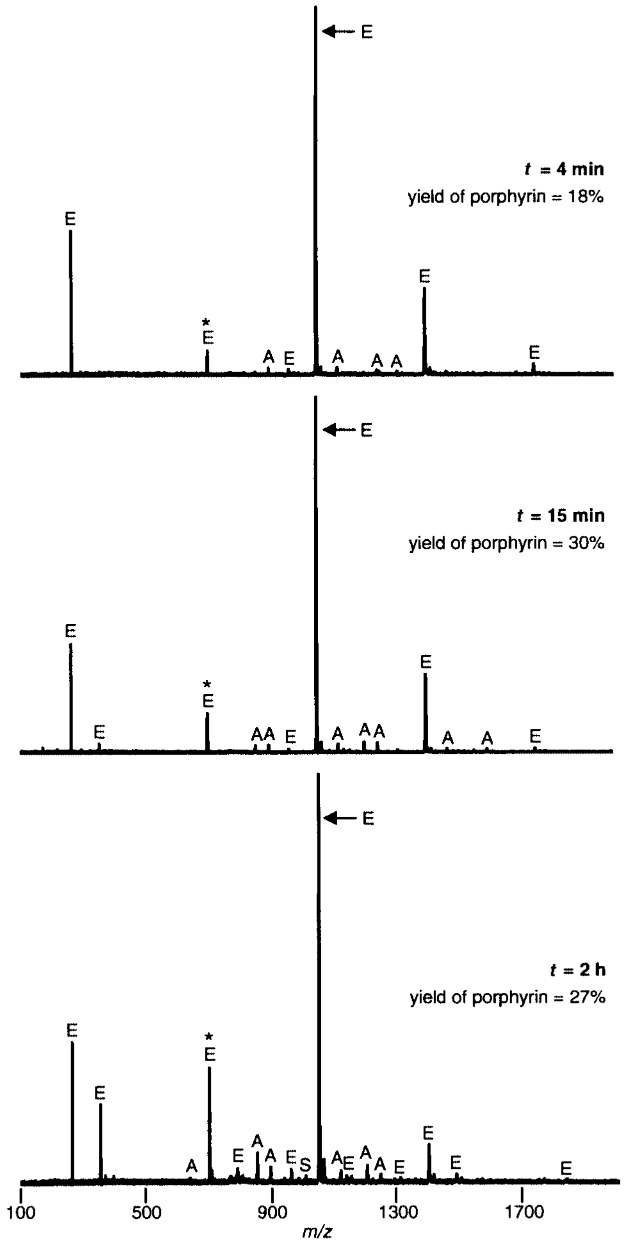


Fig. 7 LD-MS spectra of crude oxidized reaction mixtures from the condensation of 5-mesityldipyrromethane + benzaldehyde (10 mM each) with 17.8 mM TFA in CH$_2$Cl$_2$ at room temperature. The yield of porphyrin (UV–Vis) is noted for each reaction time (4 min, 15 min, and 2 h). E = expected oligomers, A = acidolysis oligomers, S = scrambled oligomers. The peak with *m/z* corresponding to the desired *trans*-A$_2$B$_2$-porphyrin product is marked with an asterisk.

The fact that no scrambling was detected in the condensation of MDPM + benzaldehyde under conditions of 17.8 mM TFA in CH$_2$Cl$_2$ at room temperature was not surprising, given that the reaction of mesitaldehyde + pyrrole does not yield tetramesitylporphyrin (TMP) with the standard-TFA or standard-BF$_3$ conditions.[7] Thus, even if acidolysis of MDPM occurred, further reaction of those fragments should be unlikely under the reaction conditions used in the condensation. (Scrambling in reactions of PDPM was inhibited under reaction conditions not suitable for fragment recombination.) The synthesis of TMP requires modified catalytic conditions involving cocatalysis by BF$_3$–Et$_2$O + ethanol (10 mM mesitaldehyde, 10 mM pyrrole, 3.3 mM BF$_3$–Et$_2$O, and 130 mM ethanol). Thus, condensation of MDPM + benzaldehyde was performed under the BF$_3$–ethanol cocatalytic conditions in order to assess the level of acidolysis and scrambling under conditions favorable for TMP synthesis.

Examination of the oligomer content from the BF$_3$–ethanol cocatalyzed reaction showed that the level of acidolysis and scrambled oligomers was higher than that observed under the TFA/SH-DPM conditions, but the level was still much lower than that observed in reactions of PDPM + *p*-tolualdehyde (Fig. 8). At 15 min, the yield of porphyrin was 57% and low levels of acidolysis and scrambling were observed. The presence of undesired oligomers did increase as shown by the LD-MS spectrum recorded at 8 h, but the oligomer content was generally simpler than that obtained from reactions of PDPM. In addition, reaction of MDPM alone resulted in very little oligomer formation beyond the peak corresponding to

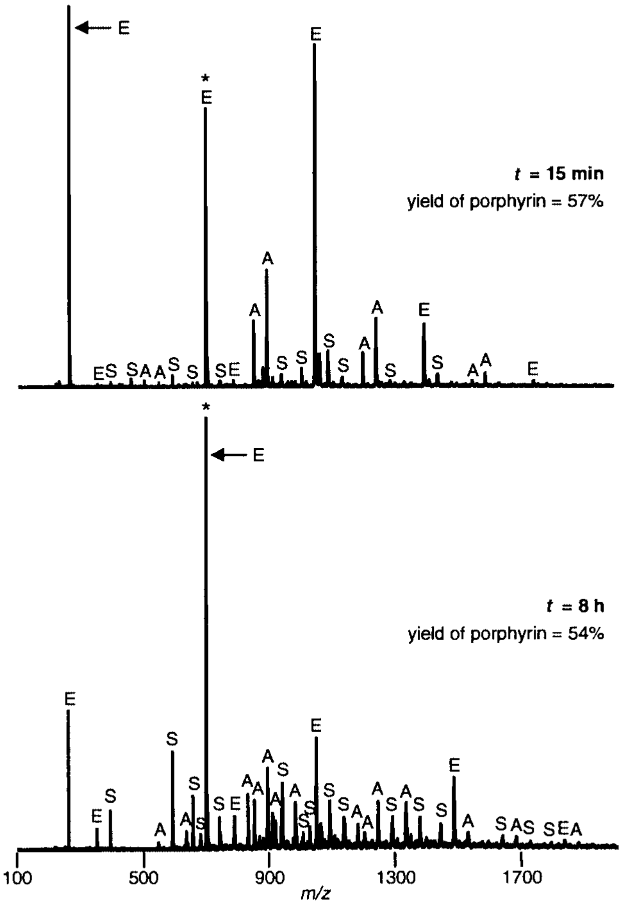


Fig. 8 LD-MS spectra of crude oxidized reaction mixtures from the condensation of 5-mesityldipyrromethane + benzaldehyde (10 mM each) with BF_3–ethanol cocatalysis (3.3 mM, 130 mM, respectively in $CHCl_3$) at room temperature. The yield of porphyrin (UV–Vis) is noted for each reaction time (15 min and 8 h). E = expected oligomers, A = acidolysis oligomers, S = scrambled oligomers. The peak with *m*/*z* corresponding to the desired *trans*-A_2B_2-porphyrin product is marked with an asterisk.

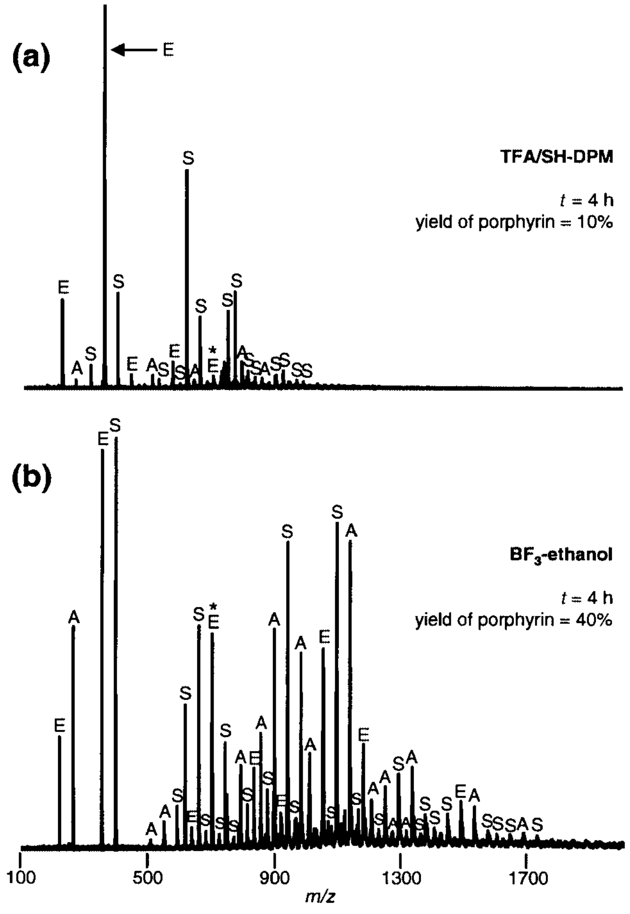


Fig. 9 LD-MS spectra of crude oxidized reaction mixtures from the condensation of 5-phenyldipyrromethane + mesitaldehyde (10 mM each) under different acid conditions. (a) TFA/SH-DPM conditions, 4 h; (b) BF_3–ethanol cocatalysis conditions, room temperature, 4 h. The yield of porphyrin (UV–Vis) is noted for each reaction time. E = expected oligomers, A = acidolysis oligomers, S = scrambled oligomers. The peak with *m*/*z* corresponding to the desired *trans*-A_2B_2-porphyrin product is marked with an asterisk.

5-mesityldipyrrin. These observations indicate that MDPM is fairly stable towards both acidolysis and recombination of oligomer fragments, even under reaction conditions favorable for synthesis of sterically hindered porphyrins.

(ii) Acidolysis and scrambling in PDPM + mesitaldehyde condensations. The complementary condensation of PDPM + mesitaldehyde (2,4,6-trimethylbenzaldehyde) was performed under the TFA/SH-DPM and BF_3–ethanol conditions. In each case, significant levels of acidolysis and scrambling were observed (Fig. 9). At 4 h, both reactions were near their maximum yield and a large number of oligomers were present, particularly under the BF_3–ethanol cocatalytic conditions. Levels of acidolysis and scrambling similar to the 4 h time points were detected much earlier in both reactions, prior to significant porphyrin formation (data not shown). These results further show MDPM to be much more resistant to both acidolysis and scrambling than PDPM.

(iii) Acidolysis and scrambling in MDPM + 2,6-dimethylbenzaldehyde condensations. To examine the resistance of MDPM towards acidolysis and scrambling in the presence of an aldehyde of reactivity similar to that of mesitaldehyde, we studied reactions employing 2,6-dimethylbenzaldehyde. Condensations of MDPM + 2,6-dimethylbenzaldehyde were performed under the BF_3–ethanol cocatalytic conditions. The yield of porphyrin was ~20% and acidolysis and scrambling were modest, even at a reaction time of 24 h (Fig. 10). Under the TFA/SH-DPM conditions, no porphyrin was formed and little formation of oligomers was observed, consistent with the known catalytic requirements for sterically hindered aldehydes. These experiments further show the resistance to acidolysis and scrambling intrinsic to MDPM.

Examination of conditions employed for β-substituted dipyrromethanes

Over the years, dipyrromethanes bearing alkyl substituents at all four β-positions and no substituent at the *meso*-position have been widely used in porphyrin chemistry. Such β-substituted dipyrromethanes have been condensed with an aromatic aldehyde yielding the porphyrin bearing two *meso*-substituents in a *trans* configuration and eight β-substituents (Scheme 4). This transformation was originally performed using methanolic toluene-*p*-sulfonic acid[14] but subsequently has been performed with trichloroacetic acid (15.3 mM) in acetonitrile with the dipyrromethane and aldehyde at 90 mM each.[15] In various applications the concentrations of reactants (β-substituted dipyrromethane, aldehyde) and trichloroacetic acid have varied widely and the duration of reaction has ranged from 5 h to 18 h.[16] The refined conditions that we recently developed for the reaction of an unhindered dipyrromethane + aldehyde (BF_3–Et_2O, NH_4Cl, acetonitrile)[10] or a dipyrromethane-carbinol condensation (TFA, acetonitrile)[17] bear some similarity to the latter conditions. We sought to determine the suitability of the conditions developed for β-substituted (*meso*-

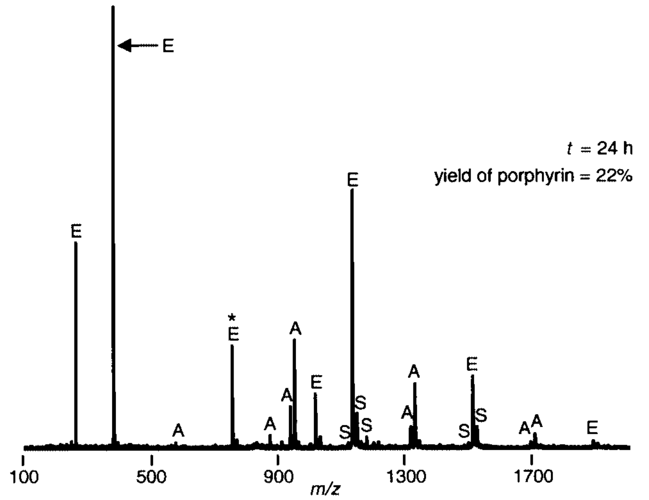
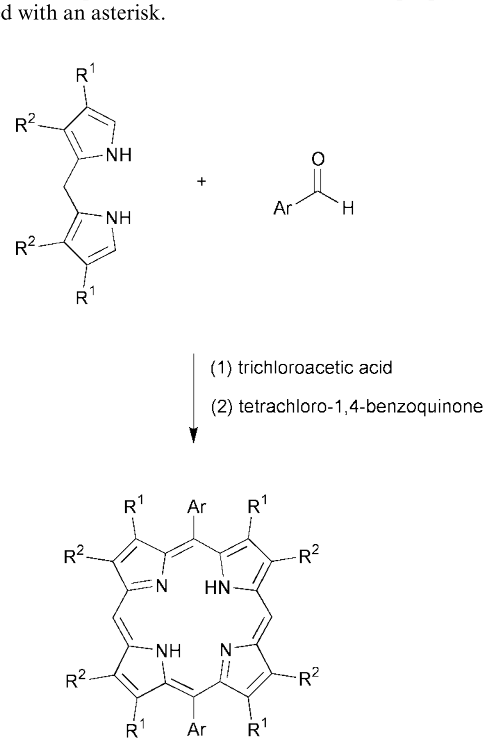


Fig. 10 LD-MS spectrum of a crude oxidized reaction mixture from the condensation of 5-mesityldipyrromethane + 2,6-dimethylbenzaldehyde (10 mM each, BF_3–ethanol cocatalysis conditions, room temperature, 24 h). The yield of porphyrin (UV–Vis) is noted. E = expected oligomers, A = acidolysis oligomers, S = scrambled oligomers. The peak with *m*/*z* corresponding to the desired *trans*-A_2B_2-porphyrin product is marked with an asterisk.



Scheme 4 Synthesis of a porphyrin bearing eight β-substituents and two *meso*-substituents with use of trichloroacetic acid (TCA).

unsubstituted) dipyrromethanes (termed TCA/β-DPM conditions) for reactions with *meso*-substituted, β-unsubstituted dipyrromethanes. Thus, 5-phenyldipyrromethane (90 mM) was condensed with *p*-tolualdehyde (90 mM) in acetonitrile containing 15.3 mM trichloroacetic acid at room temperature (TCA/β-DPM conditions). After 1 h, only 25% of the aldehyde had reacted and no porphyrin was formed upon DDQ oxidation. After 24 h, almost all of the aldehyde had reacted and the yield of porphyrin was 4.0%. The LD-MS spectra showed the presence of unusually long oligomers, though virtually no scrambling was detected. The low porphyrin yields show that the TCA/β-DPM conditions developed for β-substituted (*meso*-unsubstituted) dipyrromethanes are not suitable for *meso*-substituted, β-unsubstituted dipyrromethanes. The low ratio of acid to reactants likely accounts for the slow reaction, which apparently is not a problem with the more electron-rich β-substituted dipyrromethanes.

Conclusions

Understanding the origin of scrambling in reactions with dipyrromethanes is essential for the rational synthesis of porphyrinic macrocycles bearing specific patterns of substituents. From this study of conditions for the reaction of 5-phenyldipyrromethane and benzaldehyde leading to *trans*-A_2B_2-porphyrins, a number of key points have emerged. (1) Scrambling requires two processes: acid-induced cleavage of a dipyrromethane unit and recombination of the fragments in such a way to change the order of substituents. Acidolysis was detected under all reaction conditions examined and appears to be very difficult to suppress. Thus, avoidance of scrambling relies upon prevention of recombination. (2) Recombination of acidolytic fragments was inhibited by reaction conditions that are not optimal for porphyrin formation, resulting in yields of *trans*-A_2B_2-porphyrin that are ~10% or lower. (3) Use of BF_3/UH-DPM reaction conditions causes the overall reaction to be more sluggish in terms of oligomer formation, yield of other macrocyclic products, and consumption of aldehyde. (4) The observation that *trans*-A_2B_2-porphyrins could be prepared in ~10% yield with minimal scrambling indicates that the direct (non-scrambling) pathway for forming the desired porphyrin is slightly more favorable than that yielding scrambled porphyrins, but the differences in the two pathways are insufficient to allow use of reaction conditions that would provide a higher yield of the desired porphyrin. (5) A consistent correlation was found between porphyrin yield and level of scrambling: the higher the yield, the greater the scrambling. Thus, reaction conditions found to suppress scrambling did so at the expense of porphyrin yield. Taken together, these observations suggest that this approach to the synthesis of *trans*-A_2B_2-porphyrins bearing unhindered aryl substituents is unlikely to be both selective and efficient. The presence of hindered *versus* unhindered aryl substituents in a dipyrromethane results in clear reactivity differences. MDPM is adequately stable towards acidolysis and scrambling under a wide range of conditions, allowing reaction conditions to be used that provide good yields of *trans*-A_2B_2-porphyrins while still avoiding scrambling altogether.

From a practical standpoint, these results further demonstrate that the dipyrromethane + aldehyde condensation is a very good synthetic approach for those *trans*-A_2B_2-porphyrins derived from dipyrromethanes bearing *ortho*-disubstituted aryl groups, and a marginal approach for those *trans*-A_2B_2-porphyrins derived from dipyrromethanes bearing *ortho*-unsubstituted aryl groups. These results caused us to turn away from further refinement of reaction conditions for the difficult cases and pursue instead the self-condensation of dipyrromethane-monocarbinols. We recently reported the non-scrambling synthesis of *trans*-A_2B_2-porphyrins from unhindered dipyrromethane-monocarbinols.[17] An examination of the course of dipyrromethanecarbinol reactions is the subject of the fourth paper of this series.[18]

Experimental

Materials

$CHCl_3$ (Aldrich, stabilized with amylenes; ethanol-free) was distilled from potassium carbonate. Mesitaldehyde (Acros, 98%) and acetonitrile (Fisher, ACS grade) were used as received. 5-Phenyldipyrromethane and 5-mesityldipyrromethane were synthesized according to published procedures.[13] 2,6-Dimethylbenzaldehyde was prepared by treating the Grignard reagent of 2,6-dimethylbromobenzene with DMF as described for an analogous compound.[19] Work-up followed by distillation (110 °C, 15 mmHg) afforded a colorless liquid, which gave data consistent with a literature procedure for the synthesis of the same compound *via* a different route.[20] All other materials were obtained and used as described in the preceding papers.[1,21]

General reaction conditions

All condensations were performed with 10 mM dipyrromethane and 10 mM aldehyde. The reaction conditions used are listed in Table 1. The conditions for BF_3–ethanol cocatalysis were obtained by adding BF_3–Et_2O (3.3 mM) and ethanol (130 mM) to distilled $CHCl_3$ (stabilized with amylenes). Reagents and catalysts were dispensed neat or as 1 M CH_2Cl_2 stock solutions depending on the desired final concentration and reaction volume. The reactions were generally performed on a 10 mL scale (assuming additivity of volumes) in a 20 mL scintillation vial. The reaction mixtures were magnetically stirred in tightly capped vials and shielded from light. The PDPM + benzaldehyde reactions that required HPLC analysis were performed on a 45 mL scale in a stoppered 100 mL flask.

Reaction work-up and analyses

The reactions were monitored from 1 min to 24 h. For the 10 mL reactions, at each time point 0.5 mL of the crude unoxidized reaction mixture was transferred from the reaction flask to a 1 dram vial containing solid DDQ (3.4 mg, 0.015 mmol). For the 45 mL reactions, at each time point 2.0 mL of the crude unoxidized reaction mixture was transferred from the reaction flask to a 1 dram vial containing solid DDQ (13.6 mg, 0.060 mmol). The oxidized mixtures were mixed (vortex mixer) for 5 s. An aliquot (1 μL) of the oxidized reaction mixture was spotted onto an LD-MS target.[1] Subsequent work-up of the reaction mixtures, including addition of triethylamine, for determination of the yield of porphyrin (average of UV-vis and HPLC determinations),[12] level of unreacted aldehyde (TLC),[22] and yield of N-confused porphyrin (HPLC)[12] were performed as described previously. The yield determinations by UV–Vis employed $\varepsilon_{\mathrm{Soret}} = 427000\ \mathrm{M^{-1}\ cm^{-1}}$ for tetramesitylporphyrin[7] (and porphyrins bearing *meso*-substituents with a 2,6-dimethylphenyl motif) and $\varepsilon_{\mathrm{Soret}} = 500000\ \mathrm{M^{-1}\ cm^{-1}}$ for all other porphyrins.[6]

LD-MS has been used previously to detect the presence of scrambled porphyrins in dipyrromethane + aldehyde condensations.[10] The analysis involved passage of an aliquot of crude reaction mixture through a short silica column. This purification step was done so that the mass spectrum would not be complicated by the presence of other oligomeric products, thereby providing the highest possible signal-to-noise ratio for the porphyrin component. In the experiments performed in this study, no purification was performed prior to LD-MS analysis. The crude oxidized reaction mixtures were spotted directly onto the LD-MS target so that the entire oligomer composition could be assessed. Although analysis of the entire oligomer composition may lower the signal-to-noise ratio of the porphyrin peaks, more information regarding overall scrambling could be obtained.

Reaction conditions employed for β-substituted dipyrromethanes

The reactions (5.0 mL scale) were monitored by transferring 100 μL of the reaction mixture to a 1 dram vial containing 1.8 mL of 10 mM DDQ in acetonitrile (this dilution during oxidation provided an oxidized mixture of similar concentration to that of the 10 mM pyrrole + 10 mM aldehyde condensations). An aliquot was spotted on an LD-MS target for examination of scrambling and the composition of the oligomers. The yield of porphyrin was determined (UV–Vis) after addition of 2 μL of triethylamine to the oxidized reaction mixture. The quantity of unreacted aldehyde was determined by TLC.

Acknowledgements

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