Investigation of porphyrin-forming reactions. Part 2.[1] Examination of the reaction course in two-step, one-flask syntheses of *meso*-substituted porphyrins †

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Received (in Cambridge, UK) 13th November 2000, Accepted 14th March 2001
First published as an Advance Article on the web 20th April 2001

The reaction course leading to *meso*-substituted porphyrins was examined for reversibility (formation of oligomers, formation of α- and β-pyrrole linkages), inactivation of the acid catalyst, homogeneity of the reaction medium, and the pathway of oligomer formation. The methodology employed enabled characterization of the oligomer composition (LD-MS), yield of porphyrin (UV–Vis), yield of N-confused porphyrin (HPLC), and level of unreacted aldehyde (TLC). Experiments were performed with benzaldehyde and pyrrole with catalysis by TFA or BF_3–Et_2O. Key observations include the following. (1) Reactions with BF_3–Et_2O exhibited reversible exchange of oligomers throughout the reaction. With TFA, the oligomer exchange processes were reversible at short reaction times, but became largely irreversible over the course of several hours. (2) The BF_3–Et_2O activity declined during the course of the reaction, whereas that of TFA was little changed. (3) The reaction medium remained homogeneous at 10 mM pyrrole + aldehyde. (4) Dipyrromethanes comprised of α- but not β-linkages underwent cleavage with either TFA or BF_3–Et_2O. (5) Condensations with carbinol intermediates (pyrrole-carbinol, dipyrromethane-monocarbinol, dipyrromethane-dicarbinol) provided rapid reactions, lower yields of porphyrin, and longer oligomers than typical in reactions of pyrrole + benzaldehyde. Higher porphyrin yields were obtained with BF_3–Et_2O than TFA, which is attributed to the more facile recovery from longer oligomers with the former *versus* the latter catalyst. Collectively, these and other observations lead to a model for the aldehyde + pyrrole condensation comprised of a combination of irreversible and reversible reactions in oligomer formation, irreversible side reactions (formation of dipyrrins, β-linkages), and slow inactivation of the catalyst (BF_3–Et_2O).

Introduction

Studies of the two-step, one-flask porphyrin synthesis have yielded a sizable body of data concerning the effects of various reaction conditions and substituents on the yield of porphyrin. However, such yield data only describe the outcome of the reaction and are rather uninformative about the efficacy of the individual steps leading to the porphyrin. Indeed, a fundamental understanding of how various factors affect the course of the reaction has remained rather obscure. Acquiring a thorough understanding of the processes supporting porphyrin formation is important for guiding the design of improved reaction conditions, providing insight into the origin of failure with selected substrates, and developing conditions for extensions of this general reaction strategy to more elaborate starting materials such as dipyrromethane derivatives.

A key issue in porphyrin-forming reactions is the extent to which the reactions are reversible. From a fundamental perspective, studies of reversibility are central to the discussion of whether porphyrinogen formation is under thermodynamic or kinetic control.[2] From a practical perspective, understanding the factors that affect reaction reversibility is important for the development of stepwise syntheses of porphyrins bearing different *meso*-substituents. In these cases the reactions must be irreversible in order to avoid scrambling leading to mixtures of porphyrinogens.[3,4] The initial condensation of a molecule of aldehyde with pyrrole was found to be irreversible by experiments using isotopically labeled aldehyde.[5] However, double-label crossover experiments showed that porphyrinogens derived from unhindered aryl aldehydes undergo exchange under optimal reaction conditions. Thus, these studies revealed reversible and irreversible facets of the pyrrole–aldehyde reaction. Further insight into these processes was precluded by an inability to examine the broader oligomer composition derived from the condensations. In the previous paper, we described the use of laser desorption mass spectrometry (LD-MS) to examine the oligomers derived from the condensation of pyrrole + benzaldehyde followed by DDQ oxidation.[1] Examination of the crude reaction mixtures by additional techniques (UV–Vis and TLC) allowed the relationship among porphyrin yield, oligomer composition, and concentration of unreacted aldehyde to be probed. One significant finding was that the decline in yield over time is accompanied by truncation processes yielding shortened oligomers.

In this paper, the methodology developed in the previous paper was employed to probe the diverse facets of the porphyrin-forming reaction. A major focus concerns the reversibility of the reaction course. Other facets investigated include the reversible formation of β-pyrrole linkages (now known to form under conditions optimal for porphyrin formation, as N-confused porphyrin is present in such reactions),[6] the effect of the changing reaction medium on the acid activity (particularly the generation of water), the homogeneity of the reaction

† Electronic supplementary information (ESI) available: discussion of peak assignments for phenyl- and *p*-tolyl-containing oligomers; illustrative LD-MS and yield data for condensations of PDPM alone, N-confused PDPM alone, and N-confused PDPM + benzaldehyde; light-scattering data; LD-MS and yield data for condensations involving pyrrole-carbinol, PDPM, dipyrromethane-monocarbinol, and dipyrromethane-dicarbinol; and control experiments examining the effect of residual THF and methanol in pyrrole-carbinol condensations. See http://www.rsc.org/suppdata/p2/b0/b009092l/

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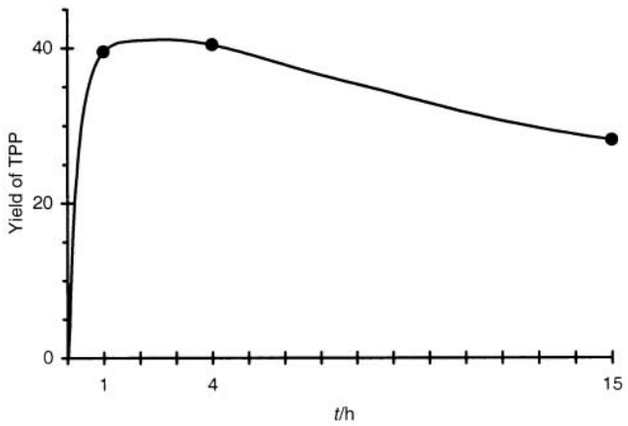


Fig. 1 Yield of porphyrin as a function of time (10 mM reactants, 20 mM TFA, CH_2Cl_2, room temperature). The three data points indicate the reaction times selected for exchange experiments.

medium, the pathway of oligomer formation from starting materials to porphyrinogen, and the generality of the reaction course mediated by the two acids (TFA and BF_3–Et_2O) most commonly employed to catalyze the aldehyde–pyrrole condensation. Taken together, these studies further our understanding of porphyrin syntheses, illustrate the utility of multiple analytical techniques for probing the reaction course, and provide data of practical relevance for developing refined conditions for porphyrin syntheses.

Results

Reversible exchange of oligomers

We previously performed double-label crossover experiments, and found that porphyrinogens derived from unhindered aryl aldehydes undergo exchange under optimal reaction conditions.[2] The mixture of porphyrins derived from the exchange process was monitored by TLC, which only allows detection of exchange affecting the porphyrinogen species. Moreover, TLC analysis requires the use of substituents of different polarity to achieve separation of the porphyrins; such substituents typically also lead to quite different reactivities of the corresponding aldehydes. We now have employed LD-MS to examine reversibility in the broader oligomer composition of porphyrin-forming reactions. With LD-MS analysis, substituents of nearly identical polarity and reactivity, but distinct masses, can be employed in exchange experiments.

(i) Exchange experiments. The exchange experiments were performed as follows. A reaction of pyrrole + benzaldehyde and a reaction of pyrrole + *p*-tolualdehyde were performed side-by-side. After a defined "premixing time", an aliquot from each reaction was transferred to a common flask and the exchange process was allowed to occur. The premixing times correspond to the time when the maximum yield of porphyrin is initially attained (1 h), a later time point when porphyrin yield was still high (4 h), and a long time point (15 h) when the porphyrin yield had declined (Fig. 1). At all premixing times examined, the level of unreacted aldehyde was low (except with BF_3–Et_2O at 1 h). 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. Because the phenyl and *p*-tolyl groups are of different mass, oligomers containing the two different substituents could be distinguished by LD-MS (see supplementary information for discussion of peak assignments). In the limit of no reversibility, the oligomer composition of the mixed reaction is restricted to oligomers containing all phenyl or all *p*-tolyl groups, and the LD-MS spectrum would be identical to 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 + benzaldehyde + *p*-tolualdehyde.

An exchange experiment was performed with reactions of pyrrole + aldehyde (10 mM each) in the presence of 1.0 mM BF_3–Et_2O in CH_2Cl_2. The results are summarized in Fig. 2. With a premixing time of 1 h, significant exchange (though lower than statistical) of phenyl and *p*-tolyl groups gradually occurred. The results of exchange processes were noted not only in the *m*/*z* region corresponding to porphyrinogen exchange [various $(PA)_4$ have *m*/*z* ranging from 614 to 670], but also in all the other oligomers detected by LD-MS.[1] For example, the $(PA)_5$ and $(PA)_6$ series displayed all the expected peaks due to exchange. However, as the premixing time was increased to 4 h and 15 h, the level of exchange decreased dramatically. These results show that (1) reversible processes involve oligomers of different lengths and are not restricted to the porphyrinogen, (2) the exchange processes are sluggish, and (3) the reversible processes leading to exchange diminish with time.

A similar exchange experiment was performed under 20 mM TFA catalysis in CH_2Cl_2 (Fig. 3). Exchange was again observed in multiple series of oligomers, though the level was low even at the earliest premixing time. The level of exchange decreased as the premixing time was lengthened. Analogous experiments under high concentration conditions known to provide good yields of porphyrin (100 mM pyrrole and benzaldehyde, 64 mM TFA or 10 mM BF_3–Et_2O)[7] gave features identical to those of the 10 mM reactions (data not shown). Thus, for all reactions examined, TFA provided less exchange than BF_3–Et_2O catalysis after the maximum yield of porphyrinogen was obtained.

(ii) Exchange experiments with an acid pulse. A plausible explanation for the decline in exchange as a function of reaction time is that the acid is gradually inactivated. Thus, experiments were performed to examine the role of acid inactivation in the decline of oligomer exchange. The exchange experiments described in the previous section were repeated and at the time of mixing, a fresh quantity of acid was added (equal to the amount of acid initially used). With reactions of 10 mM pyrrole + aldehyde under BF_3–Et_2O catalysis or TFA catalysis (Fig. 4), the acid pulse provided an increased level of exchange without significantly altering the porphyrin yield. The increased exchange was greatest with BF_3–Et_2O. In spite of the added acid, the exchange decreased to lower levels as the premixing period increased. Analogous experiments with reactions of 100 mM pyrrole + aldehyde provided similar results (data not shown). Thus, inactivation of the acid was not the primary cause of the loss of exchange at long reaction times under TFA catalysis or BF_3–Et_2O catalysis (otherwise statistical exchange would have been observed upon addition of fresh acid).

(iii) Reaction dilution experiments. In order to assess whether long oligomers (*m*/*z* > 700) can revert to short oligomers and to the porphyrinogen, reaction dilution experiments were performed. In these experiments, pyrrole + benzaldehyde condensations were carried out at 1 M in CH_2Cl_2 with a suitable concentration of acid (50 mM TFA or 70 mM BF_3–Et_2O) so that <1% of the aldehyde remained unreacted, little porphyrinogen was formed, and long oligomers were predominantly obtained. At various reaction times (15 min, 1 h, and 4 h), an aliquot of the concentrated reaction mixture was diluted 100-fold into CH_2Cl_2 so that the effective concentration of "pyrrole" and "benzaldehyde" units was 10 mM. The acid concentration was also adjusted to an optimal level (20 mM TFA or 1.0 mM BF_3–Et_2O). The diluted reactions were monitored (15 min, 1 h, and 4 h) for tetraphenylporphyrin (TPP) and

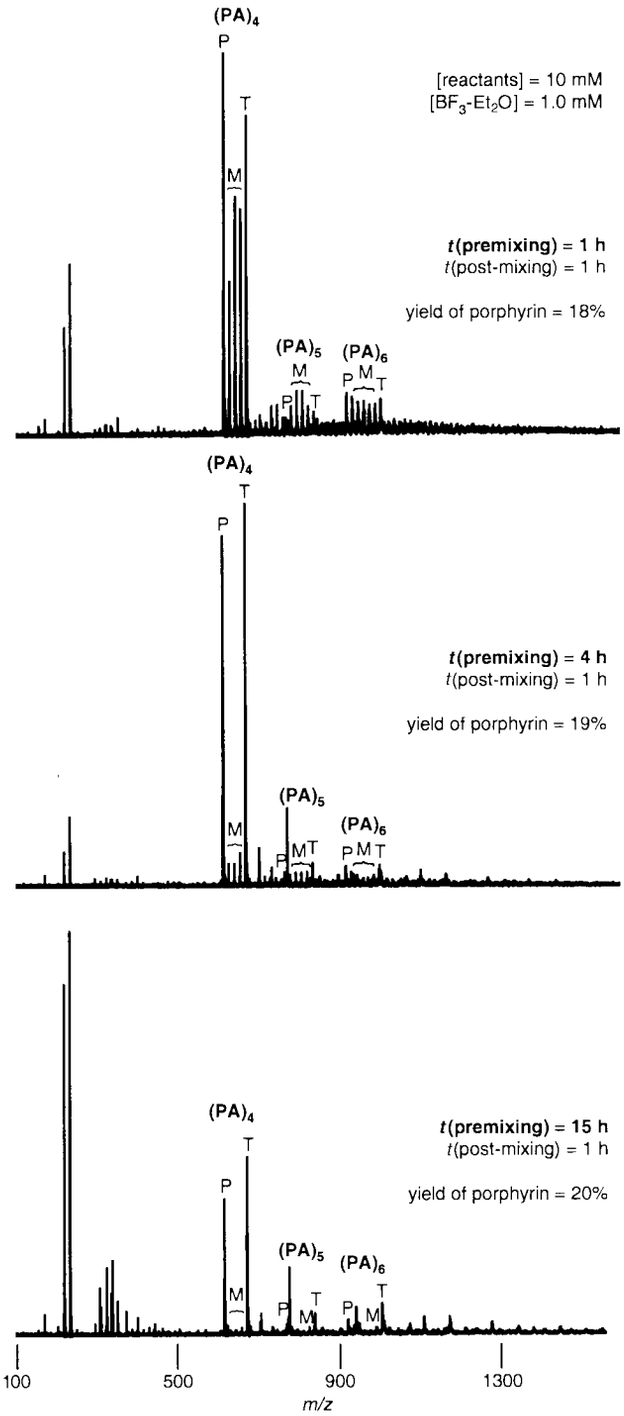


Fig. 2 LD-MS spectra showing the extent of oligomer exchange with BF_3–Et_2O catalysis and premixing times of 1, 4, or 15 h (1.0 mM BF_3–Et_2O, CH_2Cl_2, room temperature, 10 mM pyrrole + benzaldehyde or *p*-tolualdehyde). In all cases, the post-mixing reaction time was 1 h. P = oligomers with all phenyl substituents, T = oligomers with all *p*-tolyl substituents, M = oligomers with a mixture of phenyl and *p*-tolyl substituents. The total porphyrin yield (UV–Vis) is provided for each experiment.

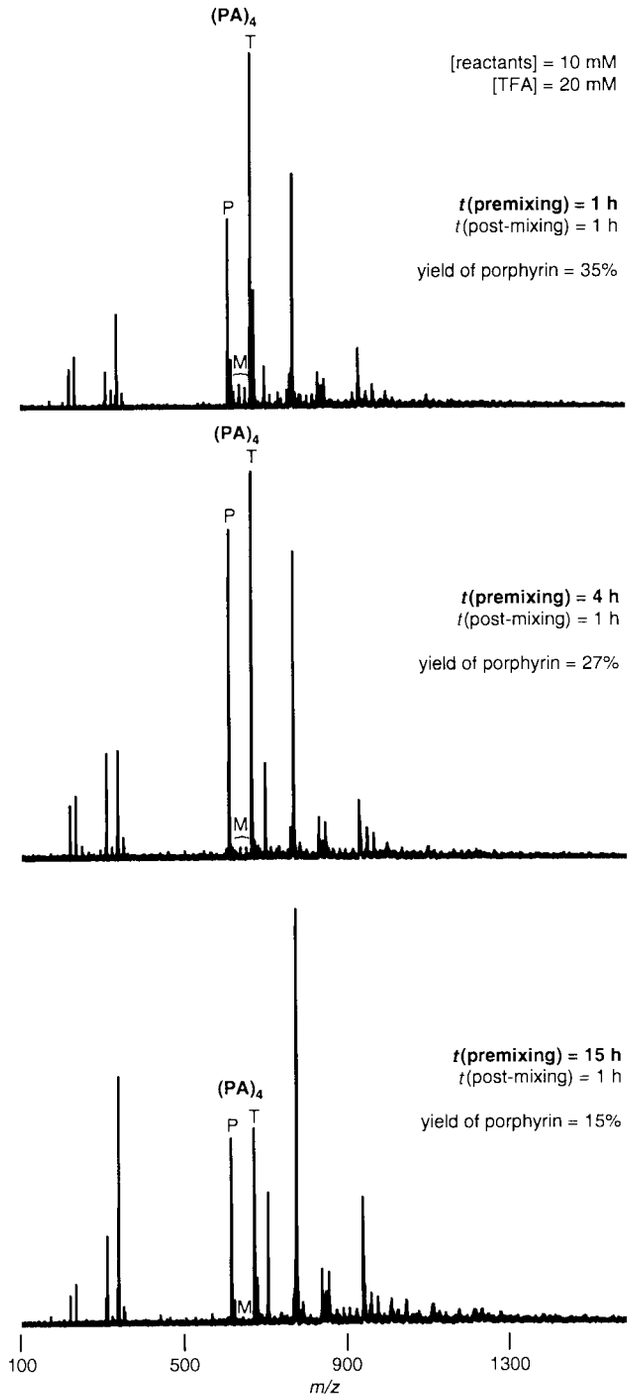


Fig. 3 LD-MS spectra showing the extent of oligomer exchange with TFA catalysis and premixing times of 1, 4, or 15 h (20 mM TFA, CH_2Cl_2, room temperature, 10 mM pyrrole + benzaldehyde or *p*-tolualdehyde). In all cases, the post-mixing reaction time was 1 h. P = oligomers with all phenyl substituents, T = oligomers with all *p*-tolyl substituents, M = oligomers with a mixture of phenyl and *p*-tolyl substituents. Labels are only provided for the $(PA)_4$ series due to overlap of peaks in other series of larger oligomers. The total porphyrin yield (UV–Vis) is provided for each experiment.

N-confused TPP (NC-TPP) (analysis by UV–Vis[2] and HPLC[6]), benzaldehyde (analysis by TLC),[5] and oligomer composition (analysis by LD-MS). In the limit of no reversibility, the oligomer composition and product yields would remain unchanged upon dilution. In the limit of total reversibility, the oligomer composition and product yields would be identical to those from condensations of 10 mM pyrrole + benzaldehyde.

Under TFA catalysis, dilution resulted in a sharp shift to shorter oligomers and an increase in the yields of TPP and NC-TPP [Fig. 5(a)]. The changes observed upon dilution were similar regardless of the reaction time prior to dilution, and were intermediate to the limiting cases of no reversibility and complete reversibility. For example, in each case the maximum yield of TPP or NC-TPP obtained after dilution was 19–20% or 6–7%, respectively, to be compared with 35–40% or ~4% typically obtained from a 10 mM reaction. No free benzaldehyde was detected after dilution. The most significant changes in oligomer composition and product yields occurred by 15 min after dilution, with only minor additional changes observed

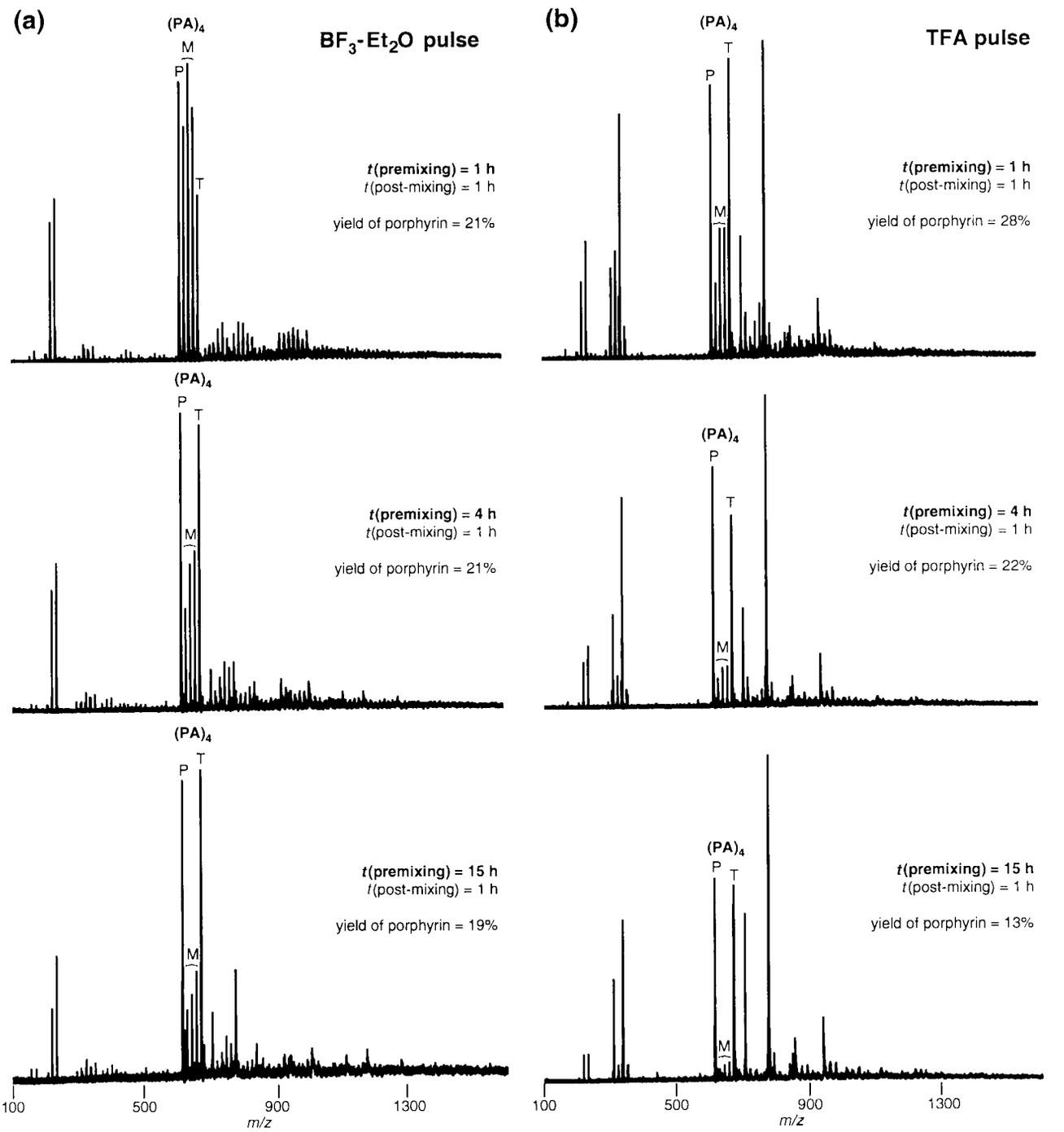


Fig. 4 LD-MS spectra showing the extent of oligomer exchange with a pulse of acid upon mixing. Premixing times were 1, 4, or 15 h. (a) 10 mM pyrrole + benzaldehyde or *p*-tolualdehyde, 1.0 mM BF_3–Et_2O, CH_2Cl_2, room temperature. At the time of mixing, 1.0 mM fresh BF_3–Et_2O was added. (b) 10 mM pyrrole + benzaldehyde or *p*-tolualdehyde, 20 mM TFA, CH_2Cl_2, room temperature. At the time of mixing, 20 mM fresh TFA was added. In all cases, the post-mixing reaction time was 1 h. P = oligomers with all phenyl substituents, T = oligomers with all *p*-tolyl substituents, M = oligomers with a mixture of phenyl and *p*-tolyl substituents. Labels are only provided for the $(PA)_4$ series due to overlap of peaks in other series of larger oligomers. The total porphyrin yield (UV–Vis) is provided for each experiment.

at the 1 h and 4 h post-dilution time points. Experiments with BF_3–Et_2O catalysis provided results very similar to those with TFA [Fig. 5(b)]. These experiments show that an oligomer composition skewed toward long oligomers and low porphyrinogen yield (due to the high concentration of reactants) undergoes significant but incomplete redistribution upon dilution to provide shorter oligomers and a higher yield of porphyrinogen (implied by the yield of TPP).

(iv) Reversible formation of α-pyrrole and β-pyrrole linkages. Pyrrole undergoes electrophilic aromatic substitution at both the α- and β-positions. In the condensation of an aldehyde with pyrrole, the reaction occurs predominantly, but not exclusively, at the α-pyrrole positions, as evidenced by the formation of N-confused porphyrin (which contains one β-linkage).[6,8] The α-linkage is known to form reversibly as illustrated by the propensity of dipyrromethanes bearing unhindered aryl substituents to undergo scrambling upon exposure to diverse acidic conditions.[3] We compared the reversibility of the formation of α- and β-linkages in the following experiments.

Treatment of 5-phenyldipyrromethane (**1**, 5 mM) alone in the presence of TFA (20 mM) or BF_3–Et_2O (1.0 mM) in CH_2Cl_2 provided >30% yields of TPP and extensive formation of oligomers (see supplementary information). In contrast, N-confused phenyldipyrromethane (**2**) alone under identical

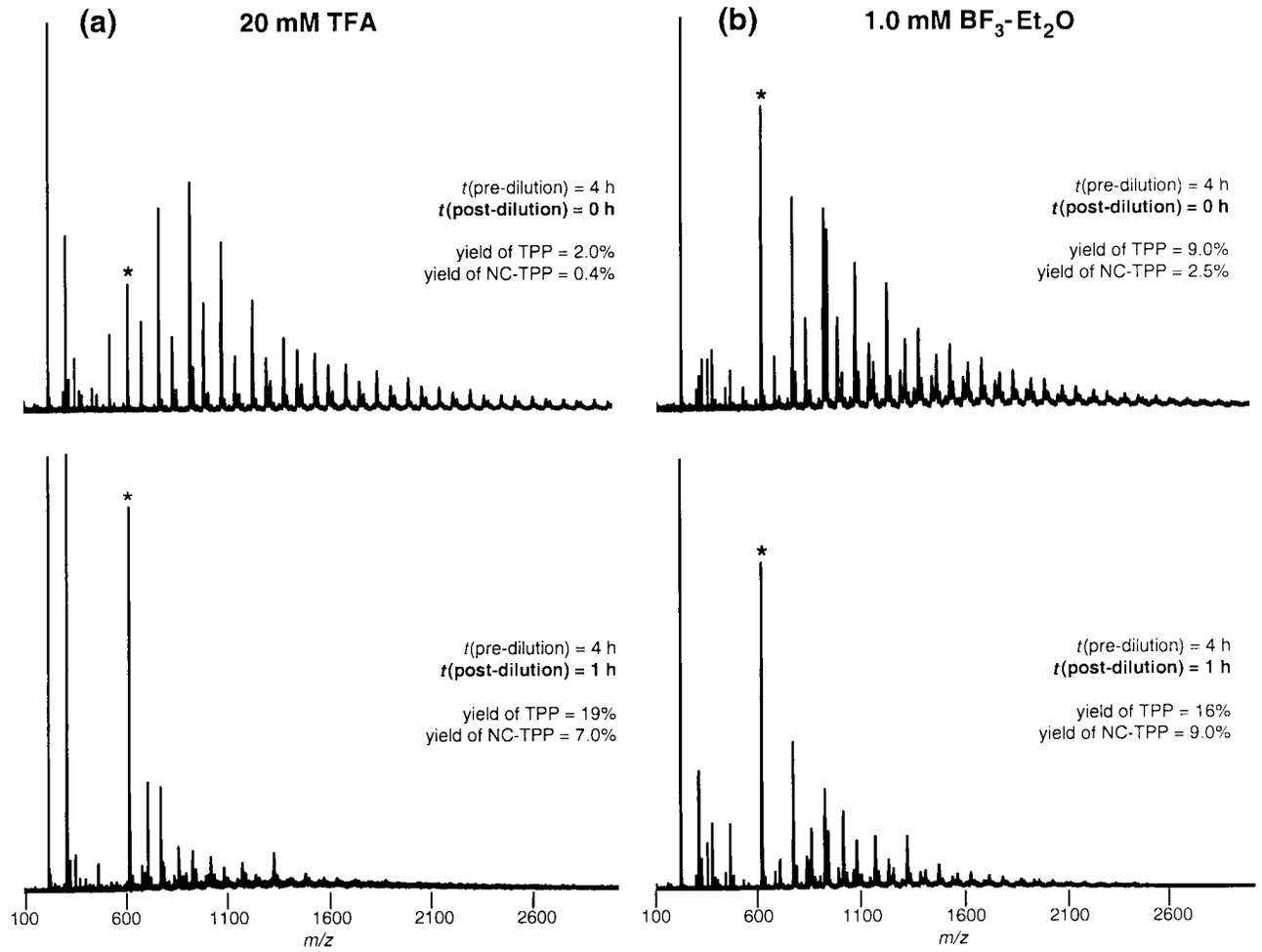
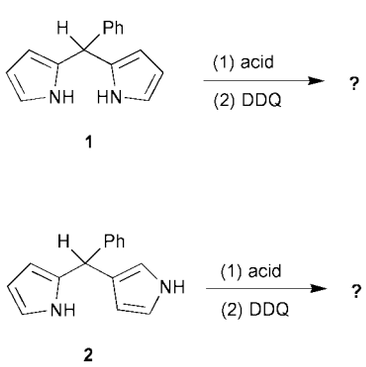


Fig. 5 LD-MS spectra showing the effect of diluting a concentrated reaction mixture on the oligomer composition. (a) The pre-dilution conditions were 1 M reactants, 50 mM TFA, CH_2Cl_2, room temperature; the post-dilution conditions were 10 mM reactants, 20 mM TFA, CH_2Cl_2, room temperature. (b) The pre-dilution conditions were 1 M reactants, 70 mM BF_3–Et_2O, CH_2Cl_2, room temperature; the post-dilution conditions were 10 mM reactants, 1.0 mM BF_3–Et_2O, CH_2Cl_2, room temperature. For each acid the top spectrum was obtained immediately after dilution and the bottom spectrum was obtained 1 h after dilution. The pre-dilution reaction time was 4 h. The peak with correct *m/z* for TPP is marked with an asterisk. The yields of TPP (UV–Vis and HPLC) and NC-TPP (UV–Vis) are provided for each post-dilution reaction time.



Scheme 1 Comparison of acidolysis of dipyrromethane **1** (PDPM) and N-confused dipyrromethane **2**.

conditions (Scheme 1) gave no TPP or NC-TPP by 8 h, though oligomers larger than the dipyrromethane were observed in modest amounts (see supplementary information). The condensation of N-confused dipyrromethane + benzaldehyde also provided little TPP (<1%) or NC-TPP (<2%) despite detection by LD-MS of significant levels of oligomers (see supplementary information). These results show that the N-confused dipyrromethane can react further with benzaldehyde, but without cleavage of the β-linkage, while the α-linkage is readily cleaved. In fact, the formation of β-linkages constitutes an irreversible shunt under these conditions.

Acid activity during the condensation

The reaction medium changes during the course of the reaction due to the consumption of starting materials, formation of oligomeric species, the generation of water, and in some cases precipitate formation.[5] One particular concern is whether such changes, particularly those stemming from the generation of water, cause inactivation of the acid (*vide supra*). We performed two types of pulse experiments to examine the effect of the changing reaction medium on the acid activity. Pulse experiments with pyrrole + benzaldehyde addressed whether the reaction medium remained sufficiently active to support further formation of porphyrinogen. Pulse experiments with pyrrole + benzaldehyde + acid addressed whether components of the reaction medium interfere with porphyrinogen formation, even when fresh acid is provided.

(i) Pulse experiments with benzaldehyde. Six identical reactions of pyrrole + benzaldehyde (10 mM each) were performed side-by-side. At the time when the maximum yield of porphyrinogen was obtained (Fig. 1), one reaction was pulsed with a fresh quantity of pyrrole and benzaldehyde (equal to the amount originally used), and a second reaction was pulsed with pyrrole, benzaldehyde, and acid. At a later time when the yield of porphyrinogen was still high and at a long time when the yield had begun to decline, the remaining four reactions were pulsed in the same fashion. Changes in the yield of porphyrinogen after addition of the fresh reagent pulse were monitored

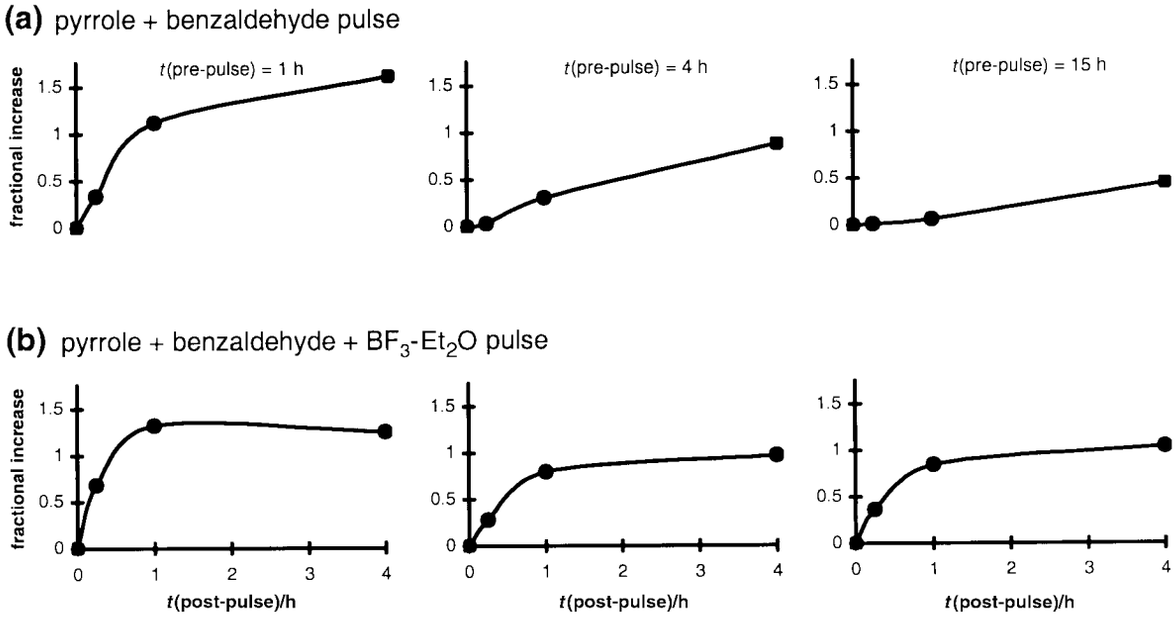


Fig. 6 Summary of the fractional increase in the yield of TPP as a function of time upon (a) a pulse of additional 10 mM reactants or (b) a pulse of additional 10 mM reactants and 1.0 mM BF_3–Et_2O. [The fractional increase = $(A_{post\text{-}pulse} - A_{pre\text{-}pulse})/A_{pre\text{-}pulse}$, where A is the baseline-corrected absorbance at 417 nm. A fractional increase of 1.0 means the quantity of porphyrin doubled upon addition of the reactant pulse.] The pre-pulse reaction times were 1, 4, or 15 h. The pre-pulse reaction conditions were 10 mM reactants, 1.0 mM BF_3–Et_2O, CH_2Cl_2, room temperature.

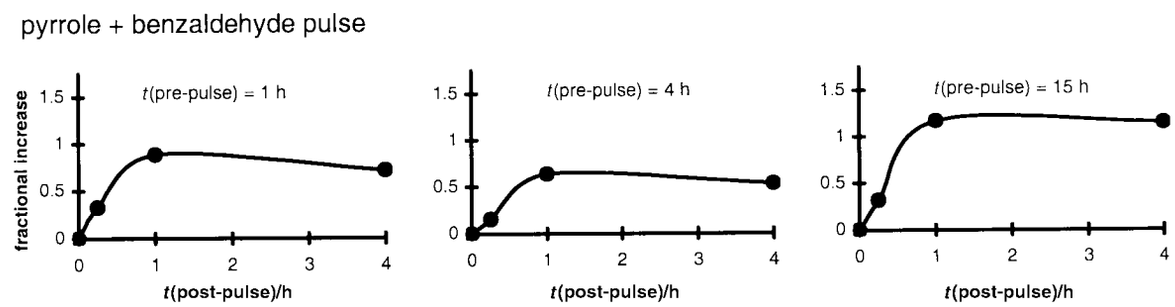


Fig. 7 Summary of the fractional increase in yield of TPP as a function of time upon a pulse of additional 10 mM reactants (no additional TFA). [The fractional increase = $(A_{post\text{-}pulse} - A_{pre\text{-}pulse})/A_{pre\text{-}pulse}$, where A is the baseline-corrected absorbance at 417 nm. A fractional increase of 1.0 means the quantity of porphyrin doubled upon addition of the reactant pulse.] The pre-pulse reaction times were 1, 4, or 15 h. The pre-pulse reaction conditions were 10 mM reactants, 20 mM TFA, CH_2Cl_2, room temperature.

by DDQ oxidation of small reaction aliquots (converting porphyrinogen to porphyrin) followed by UV–Vis analysis.

The pyrrole + benzaldehyde pulse experiments in the presence of BF_3–Et_2O (1.0 mM) revealed declining activity during the course of the reaction (*i.e.*, the formation of further porphyrinogen diminished as the pre-pulse period lengthened) [Fig. 6(a)]. However, the inclusion of acid in conjunction with pyrrole and benzaldehyde compensated for lost activity and the further increase in yield of porphyrinogen was roughly independent of the pre-pulse reaction time [Fig. 6(b)]. Thus, inactivation of BF_3–Et_2O appeared to be the primary explanation for the low additional production of porphyrinogen after the pyrrole + benzaldehyde pulse at long reaction times. The acid inactivation is a gradual process, and changes in the reaction medium that inactivated the original acid did not instantly inactivate the pulse of fresh acid. Finally, at the pre-pulse reaction time when the maximum yield of porphyrinogen is initially attained (~1 h), the BF_3–Et_2O was still very active. Thus, the maximum yield of porphyrin and the corresponding oligomer composition were reached prior to the inactivation of the acid. Analogous pulse experiments performed with 100 mM pyrrole + benzaldehyde and 10 mM BF_3–Et_2O provided similar results.

Similar pulse experiments were performed with 10 mM (Fig. 7) and 100 mM reactions catalyzed by TFA. The increase in porphyrinogen yield after the pyrrole and benzaldehyde pulse was largely unaffected by the pre-pulse reaction time. Thus, the acidic medium in the TFA-catalyzed reaction retained the ability to support further porphyrinogen formation even at long reaction times.

(ii) Pulse experiments with *p*-tolualdehyde. To clearly identify whether the additional reaction in the pulse experiments was due to reaction of the added pyrrole with the added benzaldehyde or due to overall redistribution of the pre-existing oligomers, the pulse experiments were repeated using *p*-tolualdehyde in place of benzaldehyde followed by LD-MS analysis of the oligomers.

In reactions catalyzed by BF_3–Et_2O, LD-MS spectra recorded after the pulse of pyrrole + *p*-tolualdehyde showed the presence of diverse oligomers of almost statistical composition [Fig. 8(a)]. Such a composition is consistent with oligomer rearrangement during further reaction of the added pyrrole and *p*-tolualdehyde. The level of rearrangement declined slightly at the longest pre-pulse reaction time, where the increase of porphyrinogen yield was modest. Similar observations were made in reactions pulsed with pyrrole, *p*-tolualdehyde, and BF_3–Et_2O (data not shown). In reactions catalyzed by TFA, some incorporation of *p*-tolualdehyde into the phenyl substituted oligomers was observed. However, the level of mixing of the two substituents was much lower than observed under BF_3–Et_2O catalysis, and the level declined

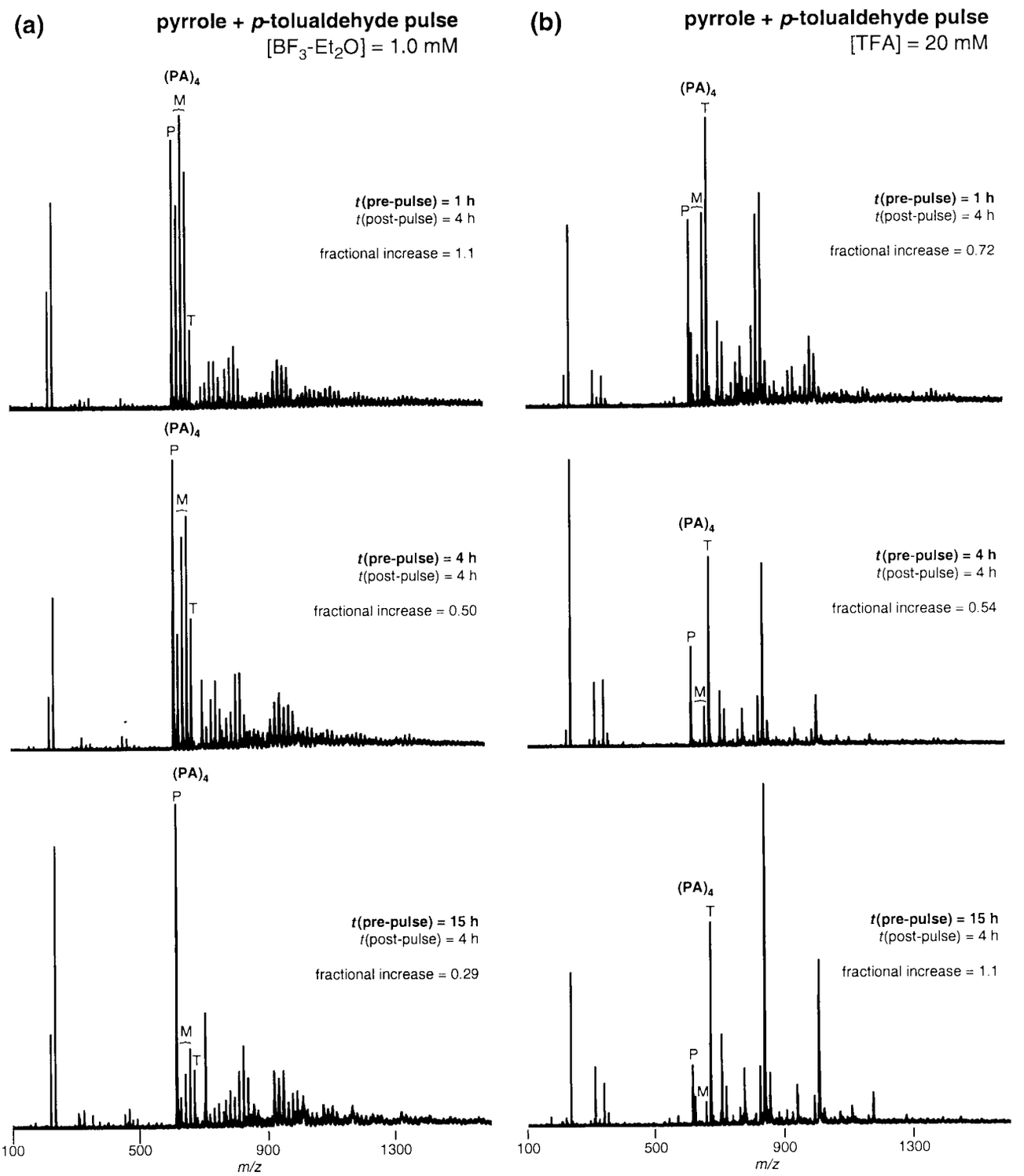


Fig. 8 Summary of the oligomer composition after a pulse of reactants (10 mM pyrrole and 10 mM *p*-tolualdehyde) at pre-pulse reaction times of 1, 4, or 15 h and a post-pulse reaction time of 4 h. (a) Pre-pulse reaction conditions were 10 mM reactants, 1.0 mM BF_3–Et_2O, CH_2Cl_2, room temperature. (b) Pre-pulse reaction conditions were 10 mM reactants, 20 mM TFA, CH_2Cl_2, room temperature. P = oligomers with all phenyl substituents, T = oligomers with all *p*-tolyl substituents, M = oligomers with a mixture of phenyl and *p*-tolyl substituents. The fractional increase in yield of porphyrin (UV–Vis) is provided for each experiment.

sharply with increased pre-pulse reaction time [Fig. 8(b)]. Including fresh TFA along with the pulse of pyrrole + *p*-tolualdehyde only modestly increased the level of substituent mixing (data not shown). These observations indicate that BF_3–Et_2O catalysis provides a more dynamic reaction mixture with greater reversibility than that obtained with TFA (at least after the maximum yield of porphyrinogen has been obtained). The less dynamic nature of the TFA reactions and the apparent low degree of incorporation of *p*-tolualdehyde into the pre-formed oligomers are consistent with the occurrence of irreversible damage to the oligomers in the presence of TFA.

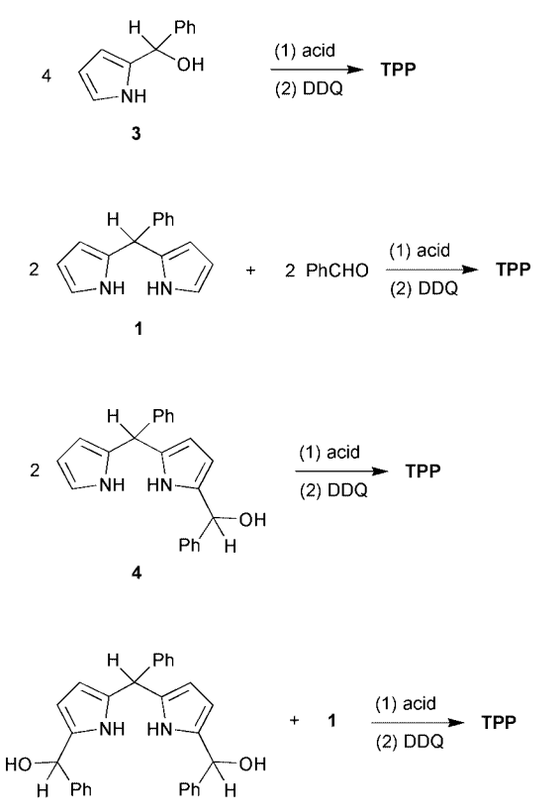
Homogeneity of the reaction medium

The pyrrole + aldehyde reaction under some conditions (*e.g.*, 100 mM reactants, BF_3–Et_2O catalysis) results in precipitates as determined by light-scattering measurements.[5] In this study, the generality of precipitate formation was determined *via* further light-scattering experiments. Small-scale reactions

were performed directly in cuvettes and monitored for scattered light (indicative of precipitates) until the maximum yield of porphyrin was reached. Neither of the commonly used 10 mM reaction conditions for pyrrole + benzaldehyde (20 mM TFA or 1 mM BF_3–Et_2O) provided any detectable light scattering. Precipitate formation was observed with pyrrole + benzaldehyde at 100 mM with BF_3–Et_2O catalysis (10 mM), as observed previously (see supplementary information for graphical data). Thus, precipitate formation occurs in more concentrated reactions but is not a general phenomenon in pyrrole + aldehyde reactions at 10 mM. In the few cases in which precipitation occurred, porphyrinogen formation was little affected as the maximum yield was obtained well after the onset of precipitation. The nature of the precipitate remains to be determined.

Pathway of oligomer formation

Relatively little information has been obtained regarding the pathway of oligomer formation. In a stepwise growth process, the pyrrole-capped oligomer reacts with an aldehyde forming a pyrrole-carbinol‡ capped oligomer. The latter then reacts with pyrrole to form a pyrrole-capped oligomer that has been elongated by one pyrromethane unit. In this study, we compared the reaction products obtained from condensations of all of the possible types of linear, α-linked phenyl-substituted components from pyrrole-carbinol **3** to dipyrromethane-dicarbinol **5** (Scheme 2). These species are putative intermedi-



Scheme 2 Condensations leading to TPP from intermediates ranging from a pyrrole-carbinol to a dipyrromethane-dicarbinol.

ates in the pathway of oligomer formation. This study provides useful data comparing the reactivity of the different components commonly used in rational syntheses of porphyrins bearing different *meso*-substituents.[3,4,9] It is noteworthy that carbinol derivatives of pyrroles, dipyrromethanes, and related compounds have been used by a number of groups in the synthesis of various *meso*-substituted porphyrinic compounds.[10–23]

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

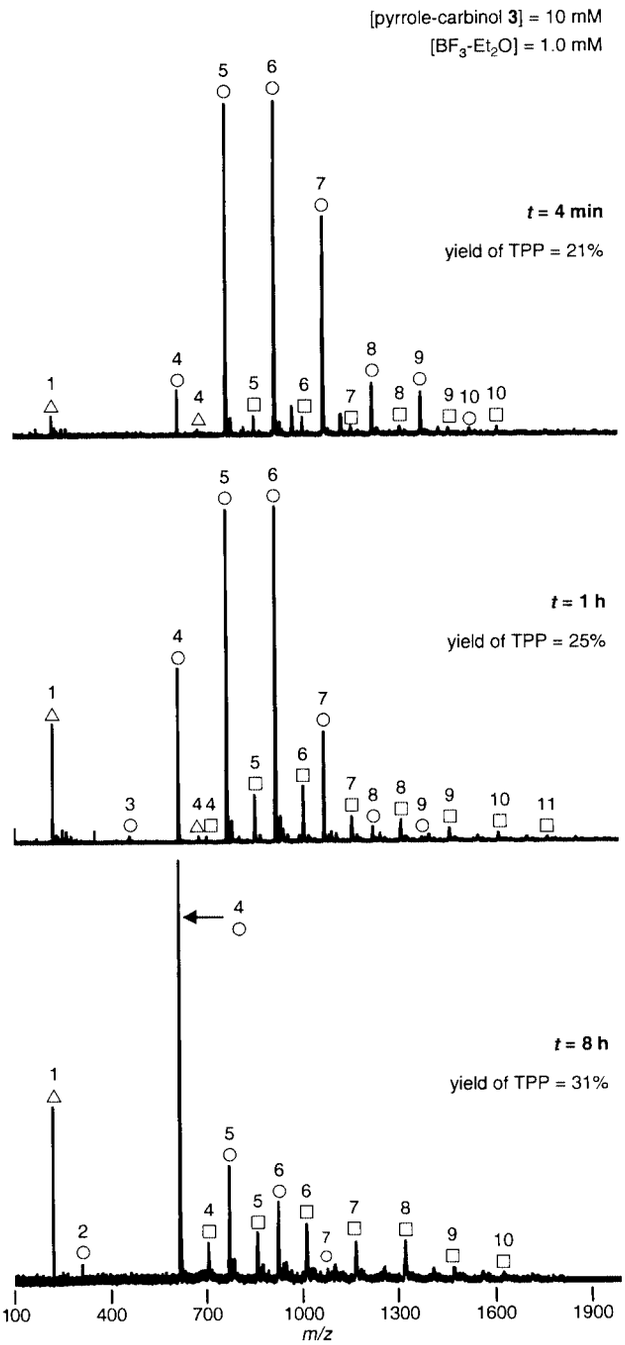


Fig. 9 LD-MS spectra showing the oligomer composition derived from the condensation of pyrrole-carbinol **3** at reaction times of 4 min, 1 h, and 8 h (10 mM **3**, 1.0 mM BF_3–Et_2O, CH_2Cl_2, room temperature). The yield of TPP (UV–Vis) is noted for each reaction time. ○ = $(PA)_n$ series, △ = $(PA)_nP$ series, □ = $A(PA)_n$ series, ★ = $P(PA)_nP$ series. The oligomer length (*n*) is given by the number above the symbol.

(i) Self-condensation of a pyrrole-carbinol. The condensation of pyrrole-carbinol **3** (10 mM) in the presence of 1.0 mM BF_3–Et_2O provided a 20% yield of TPP by 1 min, compared to 0% in the reaction of pyrrole + benzaldehyde.[24] Though the reaction was rapid, the maximum yields of TPP and NC-TPP (31% and 10%, respectively) were very similar to the 32% and 8% yields obtained from the reaction of pyrrole + benzaldehyde (see supplementary information). The oligomer composition obtained at short reaction times from the reaction of **3** under BF_3–Et_2O catalysis showed a greater contribution from oligomers having *m*/*z* 700–1500 (Fig. 9) compared with that from condensations of pyrrole + benzaldehyde. Gradually, the oligomer composition contracted to shorter oligomers, and by 8 h the LD-MS spectra resembled those typical from reactions of pyrrole + benzaldehyde.

Under 20 mM TFA catalysis, the product yields and oligomer composition from the self-condensation of pyrrole-carbinol **3** deviated significantly from those obtained from the pyrrole + benzaldehyde condensation (see supplementary information).[24] Again, the reaction was fast providing a 15% yield of TPP by 1 min, but the maximum never rose above 21% compared to ~40% yields obtained with pyrrole + benzaldehyde. The NC-TPP yields in the two reactions showed better agreement, with the pyrrole-carbinol providing 3% compared to 4% with pyrrole + benzaldehyde. The oligomer distribution was dominated by peaks from the oligomers $(PA)_{5–7,9}$ throughout the reaction, and a slight contraction of oligomer size was observed at longer reaction times. These results show that the pyrrole-carbinol (**3**) is a very reactive species, but the high reactivity only translates into faster reactions, not higher yields. The absence of higher yields is due in part to the rapid formation of long oligomers, from which recovery is incomplete.

(ii) Condensation of 5-phenyldipyrromethane + benzaldehyde. The condensation of 5-phenyldipyrromethane (**1**, PDPM) and benzaldehyde (5 mM each, effective concentration of "pyrrole" or "aldehyde" = 10 mM) under 1.0 mM BF_3–Et_2O catalysis provided results very similar to those from the condensation of pyrrole + benzaldehyde under identical conditions, with two exceptions (see supplementary information). The maximum yield of TPP was 45% (obtained at 1 h), compared to 32% from pyrrole + benzaldehyde. The level of unreacted benzaldehyde was 20% after 1 h, mirroring that of the pyrrole + benzaldehyde condensation. The reaction of PDPM + benzaldehyde provided longer oligomers earlier in the reaction, though by 1 h the oligomer compositions were very similar. The oligomer composition was also very similar to that from the condensation of pyrrole + benzaldehyde throughout the duration of the reaction. There appeared to be no preference for the even-numbered peaks in the $(PA)_n$ series. The successive condensation of PDPM and aldehyde units without scrambling of the dipyrromethane would result in oligomer growth in steps of 2 (PA) units. The absence of such a preference indicates that the dipyrromethane (PDPM) undergoes cleavage under these conditions. No detectable benzaldehyde remained after 1 h, mirroring the outcome of the pyrrole + benzaldehyde condensation.

The analogous reaction with 20 mM TFA also gave results similar to those of the corresponding pyrrole + benzaldehyde reaction (see supplementary information). The maximum yields of TPP and NC-TPP were 42% and 5%, respectively. At long reaction times (>4 h) the yield of porphyrin declined. The oligomer composition was also very similar to that from the condensation of pyrrole + benzaldehyde throughout the duration of the reaction. Again, there was no preference for even-numbered $(PA)_n$ series oligomers, indicating that scrambling of the dipyrromethane units occurred. No detectable benzaldehyde remained after 1 h, mirroring the outcome of the pyrrole + benzaldehyde condensation.

(iii) Self-condensation of a PDPM-monocarbinol. The self-condensation of PDPM-monocarbinol **4** (5 mM) under BF_3–Et_2O catalysis provided results similar to those obtained with pyrrole-carbinol **3** and the condensation of pyrrole + benzaldehyde (see supplementary information). The reaction was rapid, with a 26% yield of TPP obtained at 1 min. LD-MS analysis detected oligomeric species in the typical mass range (though longer species were initially present). The $(PA)_n$ series dominated the oligomer composition, particularly $n = 6$. The oligomer composition contracted to shorter species over time, accompanied by an increase in yield of TPP. Overall, the oligomer composition resembled that of the pyrrole-carbinol reaction more than that of the pyrrole + benzaldehyde reaction.

The analogous reaction under TFA catalysis again compared very well with that of the self-condensation of pyrrole-carbinol **3** (see supplementary information). The reaction was rapid, with a 20% yield of TPP by 1 min. The highest yield of TPP (27% at 1 h) was again lower than that obtained from the pyrrole + benzaldehyde condensation. The formation of β-linkages was evidenced by the 4% yield of NC-TPP. As in the previous reactions, the oligomer composition was restricted to *m*/*z* up to ~1500. In this reaction the predominant peaks were $(PA)_{4–7}$, and the oligomer composition was not skewed toward the anticipated even-numbered $(PA)_n$ peaks. Again, the reaction displayed reversible formation of oligomers at least early in the reaction. The low yield of TPP is attributed to the rapid formation of longer oligomers, from which full recovery yielding shorter oligomers does not occur.

(iv) Condensation of a PDPM-dicarbinol + PDPM. The condensation of PDPM-dicarbinol (**5**) + PDPM (2.5 mM each) under 1.0 mM BF_3–Et_2O catalysis afforded a rapid reaction with a 35% yield of TPP in 1 min (see supplementary information). The maximum yield of TPP (41%) was higher than that of the other carbinol reactions and closer to the yield obtained from the condensation of PDPM + benzaldehyde. NC-TPP was formed in 10% yield. The oligomer composition was initially dominated by species of *m*/*z* 700–2000. The oligomer size gradually contracted (accompanied by an increase in yield of TPP) until the oligomer composition resembled that of the pyrrole + benzaldehyde condensation (~4 h). The oligomer composition was not skewed toward species formed from the direct condensation of PDPM-carbinol + PDPM, indicating the reversible reaction and cleavage of the dipyrromethane species.

The analogous reaction under 20 mM TFA catalysis provided results similar to those of the other carbinols (see supplementary information for complete data). A rapid reaction gave a 31% yield of TPP, compared to ~40% from pyrrole + benzaldehyde, and NC-TPP was formed in 3% yield. The oligomer composition showed little preference for the peaks anticipated from the condensation without scrambling. Thus, the formation of oligomers was reversible at least in the early stages of the reaction. Again, the formation of long oligomers (*i.e.*, $(PA)_n$ where $n > 4$) appeared to limit the yield of porphyrin. As the oligomer size contracted at long reaction times, a diverse set of new oligomers belonging to the $A(PA)_n$ series was formed. This observation is consistent with truncation of oligomers *via* irreversible side reactions rather than reversible shortening of the oligomer distribution.

Discussion

The criteria sought in developing the two-step, one-flask synthesis of porphyrins were to utilize mild conditions, to perform the condensation and oxidation processes sequentially, and to achieve equilibrium in porphyrinogen formation.[2,23] The motivation for mild conditions was to broaden the scope of substituents that could be incorporated into the aldehyde unit for conversion to the porphyrin. The rationale for temporally separate condensation and oxidation steps was to mimic the biosynthesis of naturally occurring porphyrins[25] and to achieve formation of the porphyrinogen prior to any oxidation processes that might thwart cyclization. The desire to achieve equilibrium in the aldehyde–pyrrole condensation leading to the porphyrinogen was prompted by (1) the prior demonstration of the thermodynamic stability of the porphyrinogen macrocycle,[26] and (2) the Jacobson–Stockmayer reaction model for equilibrium condensations involving cyclization and polymerization.[27] One of the major conclusions of the Jacobson–Stockmayer theory is that the yield of cyclic species can reach 100% at thermodynamic equilibrium if the reaction is performed in dilute solution and bond formation is driven to completion.

The mild room-temperature conditions for the separate con-

Table 1 Summary of features observed in the TPP-forming reaction

Feature of reaction	TFA	BF_3–Et_2O
Pyrrole + benzaldehyde reaction[a]		
Unreacted benzaldehyde	<1%[d]	20–40%
Yield of TPP, NC-TPP (1 h)	40%, 4%	22–32%,[e] 8%
Oligomer exchange (early/late)	Partial/very little	Extensive/partial
Effect of added acid on exchange	Little change	Significant increase
Activity of acid	1 h: active	1 h: active
	4 h: active	4 h: partially active
	15 h: active	15 h: inactive
Oligomer recovery upon dilution (15 min)	Partial	Partial
Oligomer truncation from 1–15 h[b]	Extensive	Very limited
Turnover in porphyrin yield	Large decline	Very small
Yield of dipyrrins at 1 h[c]	3.9%	0.25%
Homogeneous medium	Yes	Yes
Other experiments	Yield of TPP/NC-TPP	Yield of TPP/NC-TPP
Acidolysis of PDPM (**1**) (α-linkage reversibility)	39%/4%	34%/7%
Acidolysis of N-confused PDPM (**2**) (β-linkage reversibility)	<0.1%[d]/<0.2%[d]	<0.1%[d]/<0.2%[d]
PDPM (**1**) + benzaldehyde	42%/5%	45%/7%
Pyrrole-carbinol **3** self-condensation	21%/3%	31%/10%
PDPM-monocarbinol **4** self-condensation	27%/4%	34%/9%
PDPM (**1**) + PDPM-dicarbinol (**5**)	31%/3%	41%/10%

[a] 10 mM reactants. [b] Ref. 1. [c] Ref. 2. [d] Below the limit of detection. [e] The range is 22–32% and the typical value is 26%.

densation and oxidation processes have enabled the synthesis of a wide variety of porphyrins.[23] However, quantitative formation of the porphyrinogen has remained an unrealized theoretical ideal. Moreover, some questions have arisen as to the reversibility of the pyrrole–aldehyde condensation. We showed by isotope-labeling experiments that the aldehyde consumed upon reaction with pyrrole is not reformed.[5] In this sense the aldehyde–pyrrole condensation is irreversible, but the irreversibility of this first step does not imply that porphyrinogen formation is under kinetic control. Double-label crossover experiments have revealed that the oligomers and/or porphyrinogens formed upon aldehyde–pyrrole condensation undergo exchange, indicating the reversibility of the oligomerization processes involving pyrromethane species.[2] Moreover, exchange has proved to be a pervasive phenomenon in condensations with dipyrromethanes.[3] Indeed, identifying catalysis conditions for the aldehyde + dipyrromethane condensation without acidolytic scrambling (leading to a mixture of porphyrins) has been extremely difficult; in the most challenging cases (sterically unhindered dipyrromethanes) yields of ~10% are the norm under low-scrambling conditions.[3] Thus, these limited experiments show that the pyrrole–aldehyde condensation leading to the porphyrinogen proceeds *via* a combination of irreversible and reversible processes.

In the following sections, we develop a more comprehensive view of the benzaldehyde–pyrrole condensation based on the results obtained herein. A reaction model is presented that encompasses the reversibility of oligomer formation, the integrity of the acidic medium during the condensation, and the reactivity of putative intermediates for catalysis by TFA or BF_3–Et_2O, the two most commonly used acids in porphyrin syntheses.

Comparison of TFA and BF_3–Et_2O

(i) Pyrrole + benzaldehyde reaction. The results obtained with TFA and with BF_3–Et_2O showed broad similarities and a number of key differences. The results for the pyrrole + benzaldehyde reaction at 10 mM are summarized in Table 1.

TFA provides rapid reaction with very little of the benzaldehyde remaining after 1 h of condensation. The yield of TPP is consistently near 40%. Three experiments addressed reversibility in the formation of the oligomers: a double-labeling crossover experiment, a dilution experiment, and a pulse experiment with *p*-tolualdehyde. Examination of oligomer exchange (double-labeling crossover and pulse experiments) showed only limited exchange early in the reaction and very little exchange after 4 h. The addition of fresh acid only slightly increased the exchange. In contrast, the dilution of the reaction contents containing a composition of long oligomers (formed at high concentrations) resulted in partial recovery, affording shorter oligomers and a higher yield of porphyrin. The recovery displayed by the TFA-catalyzed reactions was greater than anticipated based upon the results of the exchange experiments.§ The integrity of the acid catalyst remains high during the course of the condensation, as demonstrated by the additional condensation that occurred upon adding a pulse of fresh aldehyde and pyrrole to the reaction medium. During the condensation the oligomer composition increased in length, passed through a regime of maximum diversity near 1 h, and then shortened over the course of 15 h.[1] The truncation in oligomer length was accompanied by a decline in yield of porphyrin from 40% to <20%. In addition, the yield of dipyrrin chromophores was quite high (3.9% after 1 h).[2,28] The extensive truncation in oligomer length and the decrease in exchange over time are not due to inactivation of the TFA and must stem from side reactions that affect the integrity of the oligomers.

BF_3–Et_2O provides a comparatively slow reaction of the aldehyde, with 20–40% remaining after 1 h of condensation (though little remained after 15 h of reaction). The yield of porphyrin is variable and ranges from 22–32%. The experiments to address reversibility showed extensive exchange of oligomers early in the reaction and partial exchange later in the reaction. The addition of fresh acid increased the exchange. The dilution experiment showed partial but incomplete

§ A possible explanation for the discrepancy lies in the ratio of acid to reactants (pyrrole and benzaldehyde) in the two experiments. During the premixing reactions of the exchange experiments, the acid : reactant ratio was 1.0. During the pre-dilution reactions of the dilution experiments, the acid : reactant ratio was 0.025. Because acid-mediated irreversible reactions are not expected to be as important in the dilution experiments (prior to dilution), reversibility could occur to a greater extent in the dilution experiments (the extent of reversibility was not dependent on the pre-dilution reaction time). These results suggest that TFA-catalyzed reactions may be very reversible at the earliest stages of the condensation, consistent with the significant yield of TPP obtained from the reaction of PDPM alone under TFA catalysis.

recovery to give shorter oligomers and an increased yield of porphyrin. (The oligomer composition continued to include atypically long oligomers, and no free benzaldehyde was observed.) This observation is particularly noteworthy as 20–40% unreacted benzaldehyde is typically present with BF_3–Et_2O catalysis at the point of maximum yield of TPP. The integrity of the acid catalyst declines substantially during the course of the condensation, as evidenced by the lack of additional condensation upon adding a pulse of fresh aldehyde and pyrrole to the reaction medium. However, the loss of activity is a slow process, as a fresh BF_3–Et_2O pulse was not instantly inactivated. Moreover, the oligomer composition providing the maximum yield of porphyrin was reached prior to inactivation of acid, indicating the maximum yield obtained is not affected by the acid inactivation processes. Very little truncation in the length of the oligomers was observed, and the turnover in the yield of porphyrin also was quite small.[1] The yield of dipyrrin chromophores is quite low (0.25% after 1 h).[2,28] The decline in exchange over time (and perhaps the absence of oligomer truncation and turnover in yield) can be largely, but not completely, attributed to the loss of activity of BF_3–Et_2O over time.

(ii) Reactions of intermediates. A variety of experiments were performed to investigate the reactivity of putative intermediates in the pyrrole + benzaldehyde reaction. Exposure of 5-phenyldipyrromethane alone to either TFA or BF_3–Et_2O resulted in extensive acidolysis, as measured by the >30% yield of TPP obtained with each acid. In contrast, the N-confused 5-phenyldipyrromethane gave at most trace quantities of TPP or NC-TPP upon exposure to TFA or BF_3–Et_2O. These experiments highlight the facile reversibility in the formation of the α-linked pyrromethane unit and the essentially irreversible formation of the β-linked pyrromethane unit. Thus, the formation of a β-linkage constitutes an irreversible side reaction along the path toward the normal all α-linked porphyrinogen. The only other side reaction that has been identified is the formation of dipyrrin chromophores. A dipyrrin unit at the terminus of a chain will cause cessation of chain growth, while a dipyrrin at the interior of a chain may or may not preclude subsequent cyclization.¶

One major difference between TFA and BF_3–Et_2O was revealed upon studying reactions of 5-phenyldipyrromethane + benzaldehyde. Under BF_3–Et_2O catalysis, the yield of TPP from the PDPM + benzaldehyde condensation was ~2-fold higher than that obtained from pyrrole + benzaldehyde. In contrast, under TFA catalysis the yields from both reactions were similar. These observations indicate that BF_3–Et_2O is a poor catalyst for the initial reaction of pyrrole + aldehyde, but a good catalyst for subsequent steps. Thus, the initial condensation of pyrrole + aldehyde appears to be a kinetically limiting step with BF_3–Et_2O catalysis. In contrast, TFA was found to be a good catalyst for all steps.

The carbinol-derivatized compounds exhibited very rapid reactions under the conditions for the pyrrole + aldehyde condensation. However, the high reactivity only translated into faster reactions, not higher yields. Part of the absence of enhanced yields appears to stem from the formation of longer oligomers, from which the TFA reaction in particular was unable to recover. The BF_3–Et_2O-catalyzed condensations with carbinols eventually resembled the pyrrole + benzaldehyde condensation whereas the TFA-catalyzed reactions did not. This result again is consistent with oligomer formation being more reversible under BF_3–Et_2O catalysis. Comparable quantities of NC-TPP were formed in condensations of the pyrrole-carbinol and the analogous condensations of pyrrole + aldehyde, indicating that β-pyrrole linkages do not occur solely during the initial pyrrole + aldehyde condensation.

¶ A porphyrinogen in which a dipyrrin is formed constitutes a tetrahydroporphyrin and can proceed to the porphyrin upon oxidation.

Reaction model

There is no simple reaction model that can describe the pyrrole–aldehyde condensation leading to the porphyrinogen. The overall reaction proceeds *via* a combination of irreversible and reversible processes. The aldehyde + pyrrole addition forming a pyrromethane species is irreversible, but the reactions involving α-linkage formation among pyrromethane species exhibit a high level of reversibility. The reversible exchange processes involve oligomers of the various series and of widely varying length. The absence of rapid, statistical exchange at even the shortest premixing time, however, indicates that the reversible processes are in general slow. At longer reaction times, the reaction mixture becomes increasingly static. Thus, superimposed on these largely reversible processes involving pyrromethane components are processes that irreversibly alter some oligomers by side reactions and/or alter the acid catalyst activity. Such irreversible processes depend on the nature of the acid catalyst.

With BF_3–Et_2O the activity of the acid catalyst declines gradually during the condensation.‖ With TFA the presence of significant side reactions leads to eventual truncation of the oligomers. The decline in yield of the porphyrin obtained at long reaction times (particularly with TFA) is attributed to reversible ring-opening and closing of the porphyrinogen to which are coupled irreversible side reactions that damage the oligomers. Eventually these side reactions (with TFA) cause pronounced shortening of the oligomer composition. The nature of the damaged oligomers is not known, but the side reactions that have been identified to date include formation of dipyrrin chromophores and β-linkages. Dipyrrins can form by oxidation or tautomerization processes, though the latter is a more likely source because (1) the reactions are not particularly sensitive to molecular oxygen,[2] and (2) the oxidation would be expected to be rather indifferent to the two acid catalysts. Neither dipyrrins nor β-linkages can be selectively detected by the LD-MS methodology.** The nearly equivalent production of NC-TPP in each type of reaction examined makes it clear that β-linkages do not form exclusively in early stages of oligomer growth. Indeed, the nearly identical amounts of NC-TPP obtained despite the variable number of pre-formed α-linkages suggest that β-linkages occur predominantly later in the reaction pathway. Given the 5–10% yields of N-confused porphyrin commonly observed, the overall presence of β-linkages likely has significant impact on the overall yield of porphyrin.

The porphyrin-forming reaction is known to be sensitive to the initial concentration of reactants. The effects of concentration on the yields of competing cyclization and polymerization processes have been studied in detail for a wide variety of reactions.[29] In an early study of polyesterification, Spanagel and Carothers described the case of competitive cyclization and polymerization in which a pre-polymerization must occur to form an oligomer of sufficient length, whereupon cyclization or continued polymerization can occur.[30] In such a case, the traditional approach of high dilution to favor cyclization over polymerization is generally ineffective (unless bond formation can be driven to completion) as the dilute solution also suppresses the polymerization needed to form the acyclic precursor

‖ The acid inactivation with BF_3–Et_2O likely stems from interaction with water (present in the solvent and generated during the condensation). The absence of decreased activity with TFA may be due to intrinsic differences of the two catalysts, or due to the 20-fold higher concentration of TFA employed (20 mM TFA *vs.* 1.0 mM BF_3–Et_2O for the reaction of 10 mM pyrrole + aldehyde) which would be less affected by the low level of water.

** The presence of β-linkages results in no mass difference compared with α-linkages. Oligomers containing dipyrrin units are not distinguished from fully saturated oligomers in the LD-MS method we have employed (the oligomers are oxidized with DDQ prior to analysis).

to the macrocycle. The formation of the porphyrinogen involves the same scenario described by Spanagel and Carothers, in which pyrrole + benzaldehyde undergo oligomerization to form a linear tetramer, which can undergo intramolecular cyclization to form the porphyrinogen or intermolecular reaction (with pyrrole or aldehyde components) to form the longer oligomer. A graph of yield *versus* concentration for such reactions typically shows a maximum at intermediate concentration, with lower yields at higher concentration (due to a shift in the oligomer composition to longer species) and at lower concentration (due to insufficient oligomerization to reach the stage at which cyclization can occur). For the reactions at 10 mM pyrrole + aldehyde, the oligomers generally have molecular weight <1000, and the LD-MS data are in accord with our prior (limited and low-resolution) data obtained by size exclusion chromatography.[2] The oligomer compositions are shifted to longer or shorter oligomers according to the high or low concentration, respectively, of the initial reactants. Furthermore, the dilution experiments show that the oligomer composition is redistributed (and the porphyrinogen yield increases commensurably) to reflect the effective concentration of reactants, but the redistribution is sluggish and incomplete. Taken together, the pyrrole–aldehyde condensation forming the porphyrinogen exhibits a number of the broad features expected for an equilibrium condensate with competition between polymerization and cyclization.

The porphyrin-forming reaction also is sensitive to the concentration of the acid catalyst. In principle, the concentration of the acid catalyst should alter only the rate of reaction. In many respects, this situation holds true in the pyrrole + benzaldehyde reaction. The gradual inactivation of the acid (BF_3–Et_2O) and the side reactions (with BF_3–Et_2O and particularly with TFA) cause deviation from ideal behavior. Thus, with neither acid catalyst is the true equilibrium position attained in which (1) oligomer exchange is completely reversible, (2) the acid is active, and (3) the oligomer composition remains unchanged (and is independent of the initial starting position). Instead each porphyrin-forming reaction exhibits a trajectory which depends on the concentration of the reactants and the concentration of the acid for a given acid catalyst. The oligomer composition and yield of porphyrinogen pass through a maximum at different times depending on the concentrations of reactants and acid. The existence of these yield trajectories constitutes a significant deviation from a simple equilibrium model, in which an endpoint (thermodynamic equilibrium) of unvarying composition for a given initial concentration of reactants is expected.

Practical implications

The conditions employed for the pyrrole + aldehyde reaction have often served as the starting point for analogous reactions with higher-ordered substrates such as pyrrole-carbinols or dipyrromethanes. The results obtained herein show that the direct extension of the acid catalysis conditions from the former to the latter cases is fraught with problems. The oligomer growth processes in the reaction of pyrrole + benzaldehyde proceed in a largely reversible manner (following pyrrole + aldehyde addition), at least early in the reaction. The direct application of these conditions to stepwise syntheses (*e.g.*, sterically unhindered dipyrromethane + aldehyde) generally yields extensive substituent scrambling. Similarly, the reaction course in condensations of carbinol-derivatized compounds is very different to that in reactions of pyrrole + aldehyde. The carbinol reactions are very fast and are susceptible to forming a composition of oligomers comprised of longer species than would occur with the corresponding reaction of pyrrole + aldehyde. Recovery to form a shorter oligomer distribution is slow and incomplete, and when occurs results in scrambling. Thus, the optimal conditions for one-flask reactions of pyrrole + benzaldehyde should not be expected to provide optimal results with carbinol-containing components.

Conclusions

The examination of the two-step, one-flask porphyrin synthesis by LD-MS characterization of the oligomer composition has revealed new facets of the reaction course. Experiments involved examination of reaction reversibility, acid inactivation, reversible formation of α-linkages and β-linkages, and the pathway of reaction. The irreversibility of the pyrrole–aldehyde addition step (the aldehyde is not regenerated) does not imply that the formation of the porphyrinogen is under kinetic control. Indeed, the pyrrole–aldehyde condensation exhibits the broad features expected for an equilibrium condensate with competition between polymerization and cyclization. The gradual inactivation of the acid (BF_3–Et_2O) and the side reactions (with BF_3–Et_2O and particularly with TFA) cause deviation from ideal equilibrium behavior. The side reactions identified thus far include the formation of dipyrrin structures and β-linked dipyrromethanes. The β-linked species are formed irreversibly in sharp contrast to the reversible formation of α-linked pyrromethane species. The reaction conditions developed for one-flask syntheses of porphyrin from aldehyde + pyrrole are unsuited for reactions of sterically unhindered dipyrromethanes and dipyrromethanecarbinols due to (1) acidolytic scrambling of the dipyrromethanes and (2) production of an oligomer composition shifted to undesirably long species. The study of the origins of scrambling in dipyrromethane + aldehyde reactions and the reactions of dipyrromethanecarbinols form the subjects of the following papers in this series.[31,32]

Experimental

Materials

5-Phenyldipyrromethane,[33,34] N-confused 5-phenyldipyrromethane,[34] 1,9-dibenzoyl-5-phenyldipyrromethane,[35] *S*-2-pyridyl benzenethioate,[9] and 2-benzoylpyrrole[36] were synthesized according to published procedures. The reduction of the acyl compounds to the corresponding carbinols was performed using $NaBH_4$ in THF–methanol as described previously.[4,9] *p*-Tolualdehyde (99%) was obtained from Acros. All other materials and solvents were obtained and used as described in the preceding paper.[1]

Analyses

LD-MS Analysis of the oligomer composition was in all cases performed on crude, oxidized reaction mixtures in the absence of added matrix as described in the preceding paper.[1] Analyses were performed to determine the yield of porphyrin (average of the result of UV–Vis and HPLC determinations),[6] yield of N-confused porphyrin (HPLC),[6] and level of unreacted aldehyde (TLC).[5] Light-scattering experiments were performed as described previously[5] (see supplementary information for illustrative data).

Oligomer exchange experiments

An illustrative procedure is given for the reaction using 10 mM reactants and 20 mM TFA. In vial A, 80 μL of a 1 M solution of pyrrole and 80 μL of a 1 M solution of benzaldehyde (in CH_2Cl_2) were added to 7.84 mL of CH_2Cl_2 (giving a total volume of 8 mL assuming additivity of volumes). In vial B, 80 μL of a 1 M stock solution of pyrrole and 80 μL of a 1 M stock solution of *p*-tolualdehyde were added to 7.84 mL of CH_2Cl_2. Both reactions were started at the same time by the addition of TFA (12.3 μL, 0.160 mmol). The reactions were stirred at room temperature in tightly capped vials shielded from light for the

desired premixing time (1, 4, or 15 h). At the end of the premixing time, a 0.5 mL aliquot was removed from vial A and from vial B and transferred to separate vials containing DDQ (1.7 mg, 7.5 μmol). Then, the remaining 7.5 mL of vial B were poured into vial A. Aliquots (0.5 mL) were removed from the mixed reaction immediately after mixing and at post-mixing times of 4 min, 15 min, 1 h, and 4 h. The aliquots were transferred to vials containing DDQ (1.7 mg, 7.5 μmol). All oxidized aliquots were spotted directly onto an LD-MS target for LD-MS analysis, then treated with triethylamine (TEA, 8-fold relative to acid) and analyzed by UV–Vis spectroscopy to determine the yield of porphyrin. In exchange experiments involving an acid pulse at the time of mixing, a suitable quantity of acid was added so that the concentration of acid was doubled. In the example stated above, at the time of mixing, TFA (23.1 μL, 0.300 mmol) was added to the 15 mL of combined reaction volume giving a total [TFA] = 40 mM. In exchange experiments involving 100 mM reactants, pyrrole and aldehyde were dispensed as the neat reagents and the 0.5 mL aliquots were transferred to vials containing DDQ (17 mg, 75 μmol).

Reaction dilution experiments

In a 20 mL vial, benzaldehyde (1.02 mL, 10.0 mmol) and pyrrole (0.690 mL, 10.0 mmol) were added to 8.3 mL of CH_2Cl_2 to give a total volume of 10 mL assuming additivity of volumes. The reaction was initiated by addition of TFA (38.5 μL, 0.500 mmol) or BF_3–Et_2O (89.0 μL, 0.700 mmol). The reaction was stirred in a tightly capped vial shielded from light at room temperature. At dilution times of 15 min, 1 h, and 4 h, 100 μL of the reaction mixture were transferred to a vial with 9.9 mL of CH_2Cl_2; fresh acid was added so that the total acid concentration would be 20 mM TFA or 1.0 mM BF_3–Et_2O (15.0 μL TFA or 3.0 μL of a 1 M BF_3–Et_2O solution). Also, at the time of dilution, a 20 μL aliquot was removed from the concentrated reaction and transferred to a vial containing DDQ (5.0 mg, 22 μmol) and 2.0 mL of CH_2Cl_2. After dilution, the diluted reactions were monitored at 15 min, 1 h, and 4 h by transferring a 2 mL aliquot to a vial containing DDQ (5.0 mg, 22 μmol). All crude oxidized reaction mixtures were spotted on LD-MS targets. TEA (8-fold relative to acid) was added to the crude oxidized reaction mixtures followed by analysis by UV–Vis, HPLC, and TLC.

Reagent pulse experiments

An illustrative procedure is given for the reaction using 10 mM reactants and 20 mM TFA. In a 20 mL vial, 80 μL of a 1 M solution of pyrrole and 80 μL of a 1 M solution of benzaldehyde (in CH_2Cl_2) were added to 7.84 mL of CH_2Cl_2 (giving a total volume of 8 mL assuming additivity of volumes). The reaction was started by the addition of TFA (12.3 μL, 0.160 mmol). The reaction mixture was stirred at room temperature in the vial, which was tightly capped and shielded from light for the desired pre-pulse time (1, 4, or 15 h). At the end of the pre-pulse time, a 0.5 mL aliquot was removed and transferred to a vial containing DDQ (1.7 mg, 7.5 μmol). Then, to the remaining reaction mixture a fresh volume of pyrrole (75 μL, 75 μmol), aldehyde (75 μL, 75 μmol), and if desired, TFA (11.5 μL, 0.150 mmol) was added. The "pulse" reagents equal the concentration of the reagents originally used. Aliquots (0.5 mL) were removed from the mixed reaction immediately after pulsing and at post-pulse times of 4 min, 15 min, 1 h, and 4 h. The aliquots were transferred to vials containing DDQ (3.5 mg, 15 μmol). All oxidized aliquots were spotted directly onto an LD-MS target for LD-MS analysis, then treated with triethylamine (TEA, 8-fold relative to acid) and analyzed by UV–Vis spectroscopy to determine the yield of porphyrin. In pulse experiments involving 100 mM reactants, pyrrole and aldehyde were dispensed as the neat reagents and the 0.5 mL aliquots were transferred to vials containing DDQ (35 mg, 0.15 mmol).

1-Benzoyl-5-phenyldipyrromethane

The reaction of 5-phenyldipyrromethane (2.22 g, 10 mmol) and *S*-2-pyridyl benzenethioate (2.15 g, 10 mmol) was performed following the published procedure for 1-(*p*-toluoyl)-5-phenyldipyrromethane.[9] A bright-yellow foam was obtained that was ground to a powder (1.9 g, 59%): mp 60–63 °C (darkens); δ_H(300 MHz; $CDCl_3$; Me_4Si) 5.60 (1H, s, 5-H), 6.00 (1H, s, 9-H), 6.14 (2H, m, pyrrole-H), 6.62 (1H, m, pyrrole-H), 6.82 (1H, m, pyrrole-H), 7.18–7.29 (5H, m, ArH), 7.43–7.59 (3H, m, ArH), 7.78 (2H, d, J = 7.5 Hz, ArH), 8.57 (1H, br, NH), 10.49 (1H, br, NH); δ_C(75 MHz; $CDCl_3$) 44.7, 108.4, 108.9, 111.4, 118.5, 122.0, 127.8, 128.9, 129.0, 129.3, 129.7, 131.3, 131.7, 132.4, 139.0, 141.5, 142.9, 185.5. Found: C, 80.60; H, 5.76; N, 8.42. Calcd for $C_{22}H_{18}N_2$: C, 80.96; H, 5.56; N, 8.58%.

Condensations

Dipyrromethane and N-confused dipyrromethane condensations. To a 100 mL round-bottom flask, 5-phenyldipyrromethane (**1**) or N-confused 5-phenyldipyrromethane (**2**) (44.4 mg, 200 μmol) was added to 40 mL of CH_2Cl_2. For reactions in which benzaldehyde was also present, benzaldehyde (20.3 μL, 200 μmol) was also added. The reactions were started by addition of TFA (61.6 μL, 800 μmol) or BF_3–Et_2O (40.0 μL of a 1 M solution in CH_2Cl_2, 40.0 μmol). The reactions were stirred in tightly capped vials shielded from light at room temperature. The reactions were monitored from 1 min to 8 h by transferring a 2 mL aliquot to a vial containing DDQ (5.0 mg, 22 μmol). The crude, oxidized samples were analyzed by LD-MS, UV–Vis, HPLC, and TLC.[1]

Pyrrole-carbinol condensations. The reduction of 2-benzoylpyrrole to the corresponding carbinol was performed using $NaBH_4$ in THF–methanol using the method for acyl dipyrromethanes.[4,9] The reduction was performed in one batch and the carbinol was divided into equal portions for reaction under the different condensation conditions (thus, the carbinol was identical in all reactions). The carbinol (51.9 mg, 0.100 mmol) was added to a 50 mL flask containing 30 mL of CH_2Cl_2. Reactions were initiated by addition of TFA (46.2 μL, 0.600 mmol) or BF_3–Et_2O (30.0 μL of a 1 M solution in CH_2Cl_2, 30.0 μmol). The reactions were monitored from 1 min to 8 h by transferring a 2 mL aliquot to a vial containing DDQ (5 mg, 22 μmol). LD-MS, UV–Vis, and HPLC were performed as described previously.[1]

Condensations of PDPM (1) + benzaldehyde. Condensation reactions were performed on a 30 mL reaction volume as described for the pyrrole-carbinol condensations. TLC analysis was also performed as described previously.[5]

Self-condensation of PDPM-carbinol (4). Condensation reactions were performed on a 30 mL reaction volume as described for the pyrrole-carbinol condensations.

Condensations of PDPM-dicarbinol (5) + PDPM (1). Condensation reactions were performed on a 30 mL reaction volume as described for the pyrrole-carbinol condensations.

Acknowledgements

This work was funded by the NIH (GM36238). Mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology. Partial funding for the Facility was obtained from the North Carolina Biotechnology Center and the National Science Foundation.

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