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Effect of carbinol group placement on complementary reactions of dipyrromethane+bipyrrole species leading to corrole and/or an octaphyrin

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ABSTRACT

Complementary reactions of a dipyrromethanedicarbinol+2,2′-bipyrrole and a 2,2′-bipyrroledicarbinol+a dipyrromethane were investigated to determine the effect of carbinol group placement on the product distribution and on the broader reaction course. Analytical-scale reactions were performed for both reactions to explore the interplay of acid catalyst, acid concentration, and solvent on the yield of corrole and an octaphyrin. The two reaction routes were further compared under representative conditions by assessing acid-catalyzed decomposition of the dicarbinol species affording benzaldehyde (TLC and GC–MS) and by performing time course experiments monitoring macrocycle yield (UV–vis), presence of benzaldehyde (TLC), and oligomer composition (LD-MS). The complementary reactions were generally found to be quite different. Key to this work was the refinement of a method for the acylation of 2,2′-bipyrrole.

1. Introduction

Porphyrinoids with core structures altered relative to porphyrin are of interest.[1] Such species offer synthetic challenges and display interesting and potentially useful properties. One core alteration of particular note is the presence of one or more direct bipyrrole linkage(s) as exemplified in porphyrinoids such as corrole, sapphyrin, rubyrin, and rosarin (Fig. 1). Within this family of macrocycles, the core dimensions, planarity, and extent of conjugation vary—affording molecules with distinct properties. For example, corrole is known to stabilize metal ions in high oxidation states,[2] and sapphyrin in its diprotonated form binds anions.[3] Continued progress in studies of porphyrinoids with bipyrrole linkages is aided by the further development of synthetic methodology. This effort is in turn assisted by insights into the reactivity of potential building block molecules and a further understanding of the effect of reaction parameters.

Previously, we investigated the reaction of a dipyrromethanedicarbinol **2**-**OH** with a β-unsubstituted 2,2′-bipyrrole **3** leading to *meso*-triphenylcorrole (TPC, **5**) or *meso*-hexaphenyl[34]octaphyrin(1.1.1.0.1.1.1.0) (HPO, **6**) (Scheme 1, reaction of **2**-**OH**+**3**).[4] This work was inspired, in part, by an earlier report by Vogel and coworkers on the reaction of a β-substituted 2,2′-bipyrrole species, which led to a β-substituted octaphyrin rather than corrole.[5] The octaphyrin is an interesting molecule given its chiral, figure eight structure and the presence of two metal binding sites.[6]

The motivations for our prior study were to determine whether reactions involving unsubstituted 2,2′-bipyrrole also predominately afforded the octaphyrin, to examine whether the product distribution could be influenced by the choice of solvent, acid catalyst, catalyst quantity, and reaction time, and to develop a practical method for the preparation of *meso*-substituted corrole and/or the octaphyrin. We found that under nearly all reaction conditions surveyed,

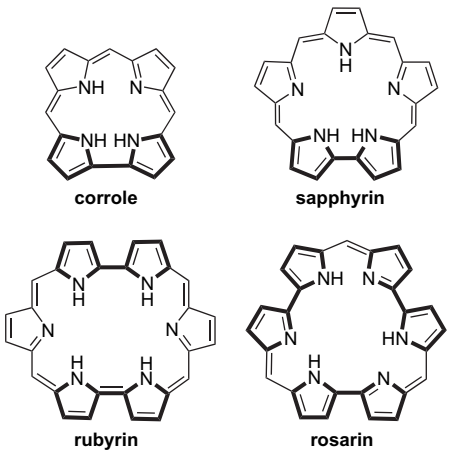

Figure 1. Structures of porphyrinoids bearing bipyrrole linkages.

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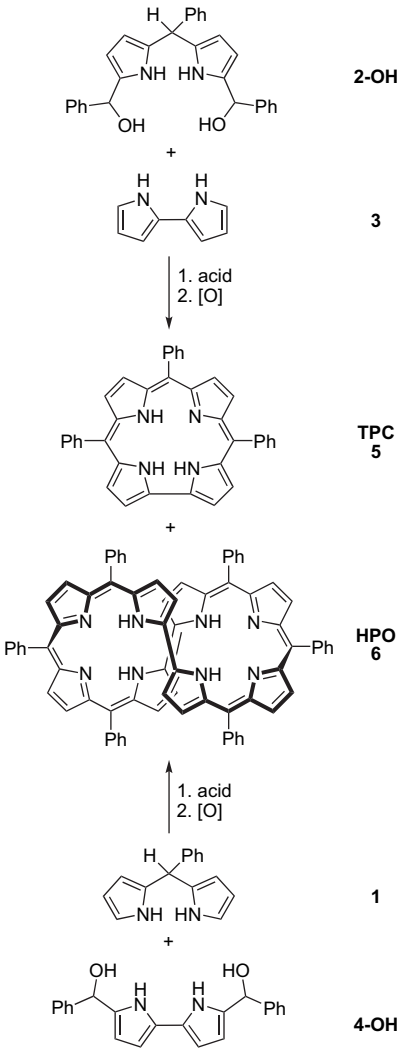


Scheme 1. Complementary reactions of dipyrromethane+bipyrrole species leading to corrole and/or an octaphyrin.

HPO was obtained over TPC. A number of conditions were identified in analytical-scale reactions that afforded HPO in yields of ~20%. The best of these conditions provided an isolated yield of 25% on a preparative scale. The production of the octaphyrin over corrole in the work of Vogel and co-workers and in our own is consistent with the known energetic preference for the *anti* conformation of 2,2′-bipyrrole (Fig. 2).[7] The lower energy *anti* orientation is found in both bipyrrole units of the octaphyrin whereas corrole requires a *syn* orientation about the bipyrrole linkage. Although the *anti* and *syn* conformations of 2,2′-bipyrrole differ in their net dipole moments, we found that the distribution of the corrole and octaphyrin products was not impacted by solvent polarity.

Given the results of our previous study, we wondered how the complementary reaction of a 2,2′-bipyrroledicarbinol **4-OH** with a dipyrromethane **1** might compare to the reaction of **2-OH**+**3** in terms of product distribution and the broader reaction course (Scheme 1, reaction of **4-OH**+**1**). Placement of the polar carbinol groups on the bipyrrole species might perturb the conformation

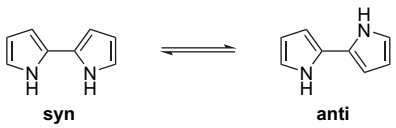


Figure 2. *syn* and *anti* conformations of 2,2′-bipyrrole.

about the bipyrrole linkage in polar solvents. Additionally, investigation of the complementary reactions would provide further insight toward the application of bipyrroledicarbinol species in porphyrinoid synthesis.

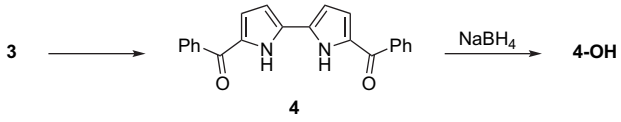
In the present work, we performed a comparative study of the reaction of a dipyrromethanedicarbinol **2-OH**+2,2′-bipyrrole **3** and the complementary reaction of a 2,2′-bipyrroledicarbinol **4-OH**+a dipyrromethane **1**. The interplay of acid catalyst, acid concentration, and solvent was compared in a survey of catalysis conditions. Under representative conditions identified from the survey, the propensity of each dicarbinol species to undergo acid-catalyzed decomposition leading to benzaldehyde was examined. Using the same representative conditions, the two reaction routes were further compared in time course experiments with monitoring for macrocycle yield (UV–vis), presence of benzaldehyde (TLC), and overall oligomer composition (laser desorption mass spectrometry, LD-MS). Taken together, the comparison of the two reaction routes provides insights toward the reactivity of building block molecules with complementary carbinol group placement.

2. Results and discussion

2.1. Preparation of building block molecules

5-Phenyldipyrromethane **1**,[8] 1,9-bis(benzoyl)-5-phenyldipyrromethane **2**,[9] and 2,2′-bipyrrole **3**[9] were prepared in accordance with the literature procedures. Dipyrromethanedicarbinol **2-OH** was prepared freshly via reduction of **2** with $NaBH_4$ and used without purification.[9]

To prepare the required bipyrroledicarbinol **4-OH**, we sought to diacylate **3** to afford the diacylbipyrrole **4**, which would then be reduced with $NaBH_4$ to the dicarbinol (Scheme 2). Key to this approach was the identification of a method for the diacylation of **3**. While there are many examples of the diacylation of 2,2′-bipyrroles bearing β-substituents,[10] there are fewer examples of diacylation of **3**.[11] The acylation of unsubstituted 2,2′-bipyrrole **3** is potentially problematic as acylation may take place at the available α and β positions.



Scheme 2. Synthesis of 2,2′-bipyrroledicarbinol **4-OH**.

Of the various acylation methods previously applied to bipyrroles,[10,11] dipyrromethanes,[12] and/or pyrrole,[13] we explored Friedel–Crafts, Grignard, and Vilsmeier–Haack conditions. Analytical-scale reactions were performed and the crude reaction mixtures were assessed by ^{1}H NMR spectroscopy. Vilsmeier–Haack conditions ($POCl_3$, *N*,*N*-dimethylbenzamide) employed by Vogel and co-workers[11] for the diacetylation of **3** to yield diacetyl, dipropionyl, and dibutyryl 2,2′-bipyrroles gave the best result. Direct application of their method afforded **4** and a monoacyl bipyrrole (5-benzoyl-2,2′-bipyrrole) in a ratio of 1.0:5.7. Further refinement (increase of reaction time and equivalents of $POCl_3$ and amide) improved the ratio to 1.0:0.031 (Supplementary data). ^{1}H NMR analysis of the crude reaction mixture revealed only the presence of a low level of monoacyl bipyrrole and unreacted *N*,*N*-dimethylbenzamide in addition to **4**. Nevertheless, purification of **4** was complicated by its poor solubility in most common organic solvents. Addition of a hot DMSO solution of the crude reaction mixture to hot *i*PrOH was found to precipitate **4** in good purity. ^{1}H NMR analysis of purified **4** revealed only a low level of DMSO and *i*PrOH solvent impurity that could not be removed by prolonged heating under vacuum.

The poor solubility of **4** was expected to complicate the reduction of **4** to **4-OH**. Indeed, **4** was only partially soluble in the

THF/MeOH solvent mixture customarily used in the reduction of diacyl species.[12a] Fortunately, **4-OH** displayed good solubility in the solvent mixture so that by extending the reaction time and providing additional $NaBH_4$ the reduction went to completion as judged by TLC, IR, and ^1H NMR analyses. As is customary in related dipyrromethanedicarbinol chemistry,[12a] **4-OH** was used without extensive purification.

2.2. Solubility of the 2,2′-bipyrroledicarbinol 4-OH

Given the poor solubility of **4**, the solubility of **4-OH** was examined in the solvent systems employed in our prior study of the reaction of **2-OH**+**3** (toluene, CH_2Cl_2, THF, and acetonitrile).[4] Solutions of **4-OH** at the required concentration of 2.5 mM could be obtained from THF and acetonitrile, but not from toluene and CH_2Cl_2. Thus, the solubility of **4-OH** in toluene and CH_2Cl_2 containing a minimal level of THF or acetonitrile was explored. Solutions could be obtained in toluene/THF (4:1) and CH_2Cl_2/THF (9:1) mixtures. A small number of trial reactions of **2-OH**+**3** were carried out in toluene/THF (4:1) and CH_2Cl_2/THF (9:1) mixtures, and meaningful results were obtained in terms of yields of TPC and HPO relative to reactions previously carried out in toluene, CH_2Cl_2, or THF. Thus, for the comparative study of **2-OH**+**3** and **4-OH**+**1**, toluene/THF (4:1), CH_2Cl_2/THF (9:1), THF, and acetonitrile were used.

2.3. Survey of catalysis conditions

The effect of key reaction parameters (acid catalyst, acid concentration, and solvent) on the complementary reactions of **2-OH**+**3** (dipyrromethanedicarbinol route) and **4-OH**+**1** (bipyrroledicarbinol route) was examined in a survey of catalysis conditions. Analytical-scale reactions were performed using five different acid catalysts [TFA, $InCl_3$, $Sc(OTF)_3$, $Yb(OTf)_3$, and $Dy(OTf)_3$], at five different concentrations (0.32, 1.0, 3.2, 10, and 32 mM),[14] in the four different solvents stated above. The acids selected for this study were those examined in our prior investigation of the reaction of **2-OH**+**3**.[4] These acids have also been previously employed in the syntheses of a variety of porphyrinoids from dicarbinol species.[9,15–17] Solvents were selected to afford a range of polarities while considering the solubility of **4-OH**. Each reaction was monitored for the yield of TPC and HPO (UV–vis) at reaction times of 0.25, 1, and 4 h in accordance with our earlier study.[4] In addition, UV–vis analysis was also used to detect tetraphenylporphyrin (TPP), which could arise from reversible processes.

The survey of catalysis conditions revealed sharp differences between the two complementary reactions. Representative data are provided in Table 1 (see Supplementary data for additional results). Generally, the yields of TPC and HPO provided by the complementary reactions under identical conditions were different (the exception being a small number of conditions that failed to provide TPC or HPO from either reaction route). Most commonly, reaction conditions that afforded HPO or HPO and TPC from **2-OH**+**3** failed to provide HPO or TPC from **4-OH**+**1** (e.g., entries 3, 5, and 7). Conditions that did afford HPO from both reaction routes generally provided a lower level of HPO from **4-OH**+**1** (e.g., entries 1, 4, and 6). Interestingly, a subset of conditions afforded HPO from **2-OH**+**3** and TPC from **4-OH**+**1** (e.g., entries 2, 8–10). TPC was most commonly observed from reactions of **4-OH**+**1** carried out in the most polar solvent, acetonitrile. No reaction of **4-OH**+**1** in acetonitrile produced HPO and no reaction of **2-OH**+**3** in acetonitrile produced TPC. Yields of HPO similar to the highest values obtained in CH_2Cl_2 from our previous study of **2-OH**+**3** could be obtained from toluene/THF (4:1) and CH_2Cl_2/THF (9:1) under appropriate catalytic conditions (e.g., entry 1). A number of reaction conditions produced low levels of TPP from both reaction routes, though about twice as many reactions of **4-OH**+**1** provided detectable TPP. TPP was typically observed at the longest time point of 4 h, after HPO and/or TPC had already been observed. Reversible processes leading to the formation of TPP were most prevalent in acetonitrile and least prevalent in THF.

Overall, the survey of catalyst conditions revealed that placement of the carbinol groups on the bipyrrole rather than on the dipyrromethane and choice of solvent have a profound effect on the product distribution. In particular, conditions were identified where the two reaction routes provided entirely different macrocyclic products.

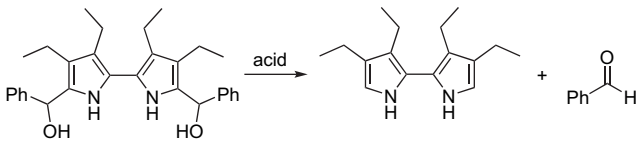
2.4. Acid-catalyzed decomposition of dicarbinol species leading to benzaldehyde

The contrasting yields of HPO and TPC provided by the complementary reactions in the survey of catalysis conditions may have a variety of underlying causes. Previously, Setsune and Maeda reported acid-catalyzed decomposition of a β-substituted bipyrroledicarbinol leading to benzaldehyde (Scheme 3).[18] To the best of our knowledge, such decomposition of dipyrromethanecarbinol species has not been reported. Furthermore, detailed studies of pyrrole+aldehyde reactions leading to tetraarylporphyrins did not detect reversion of oligomeric species to benzaldehyde.[19] Thus, it occurred to us that the contrasting yields of HPO and TPC noted in the survey of catalysis conditions could stem from differential acid-catalyzed decomposition of **2-OH** and **4-OH**. An assessment of acid-catalyzed decomposition of **2-OH** and **4-OH** leading to benzaldehyde would provide insight into the generality of this phenomenon.

Table 1
Comparison of macrocycle yields from the reactions of **2-OH**+**3** (dipyrromethanedicarbinol route) and **4-OH**+**1** (bipyrroledicarbinol route) from representative conditions examined in the survey of catalysis conditions[a]

Entry	Solvent	Acid	[Acid], mM	**2-OH**+**3**			**4-OH**+**1**		
				% Yield of HPO[b]	% Yield of TPC[b]	% Yield of TPP[b]	% Yield of HPO[b]	% Yield of TPC[b]	% Yield of TPP[b]
1	CH_2Cl_2/THF (9:1)	TFA	10	18	—[c]	—	1.8	—	—
2	CH_2Cl_2/THF (9:1)	$Sc(OTf)_3$	1.0	7.4	—	1.4	—	1.8	3.0
3	THF	TFA	1.0	15	8.4	—	—	—	—
4	THF	$Sc(OTf)_3$	1.0	8.6	—	—	2.1	—	—
5	THF	$Dy(OTf)_3$	0.32	8.1	—	—	—	—	—
6	THF	$Dy(OTf)_3$	32	7.0	—	—	2.3	—	—
7	MeCN	TFA	0.32	11	—	—	—	—	—
8	MeCN	$Yb(OTf)_3$	1.0	7.5	—	—	—	8.6	5.2
9	MeCN	$Dy(OTf)_3$	0.32	7.5	—	—	—	4.8	3.2
10	MeCN	$Dy(OTf)_3$	1.0	6.7	—	—	—	8.7	5.7

[a] The reactions were performed with the indicated reactants (2.5 mM each) on a 5–10 mL scale at room temperature. The reactions were monitored at 0.25, 1, and 4 h.
[b] The highest yield (UV–vis) at any of the three time points is reported.
[c] Not detected.



Scheme 3. Acidolysis of a bipyrroledicarbinol leading to benzaldehyde.

To investigate the acid-catalyzed decomposition of **2-OH** or **4-OH**, the dicarbinol species were treated under the conditions of Table 1 and monitored from 5 min to 4 h. This subset of reaction conditions captures the major trends observed from the broader survey of catalysis conditions. At each time point, the level of benzaldehyde was estimated by TLC analysis as described by Lindsey and co-workers.[19] A subset of samples were also assessed by GC–MS. TLC and GC–MS results were generally in good agreement. Control samples of **2-OH** or **4-OH** were monitored in the absence of acid catalyst, and low levels of benzaldehyde ($\leq$5%) were detected by TLC and GC–MS analyses (presumably from decomposition on the silica TLC plate or in the GC injector). Data obtained from the dicarbinol species treated with acid were corrected for the low level of benzaldehyde detected in the control samples.

The results of this study are summarized in Table 2. A low level of benzaldehyde was detected from both dicarbinol species. However, benzaldehyde was detected in larger quantity and under a wider range of reaction conditions from **2-OH**. When observed, acid-catalyzed decomposition occurred rapidly. The maximum level of benzaldehyde was obtained by reaction times of 5–15 min, and there was little additional change at longer time points.

Interpretation of these results is complicated as benzaldehyde generated from acid-catalyzed decomposition may, under some conditions, react further with other species generated during the reaction. Thus, the level of benzaldehyde detected in these experiments may understate the actual level of decomposition of **2-OH** and **4-OH**. Minimally, it is clear that acid-catalyzed decomposition takes place for both dicarbinol species under some reaction conditions. Additionally, differential decomposition does not appear to account for the generally higher macrocycle yields obtained from the reaction of **2-OH**+**3** in the survey of catalysis conditions as **2-OH** rather than **4-OH** was found to be more susceptible to decomposition. The level of dicarbinol decomposition did correlate with some aspects of the macrocycle yield data from the survey of catalysis conditions. Reaction conditions that provided the lowest levels of benzaldehyde from the decomposition of **2-OH** generally afforded the highest yields of HPO in reactions of **2-OH**+**3** (entries 1, 3, and 7). Conditions that gave rise to some decomposition of **4-OH** provided the highest yield of TPC from the reaction of **4-OH**+**1** (entries 8–10).

Table 2
Comparison of the level of benzaldehyde from acidolysis of dipyrromethanedicarbinol **2-OH** and bipyrroledicarbinol **4-OH**[a]

Entry[c]	% Yield of benzaldehyde[b]	
	From **2-OH**	From **4-OH**
1	—[d]	—
2	12	—
3	—	—
4	10	—
5	10	—
6	10	—
7	4	—
8	18	4
9	18	4
10	18	4

[a] The reactions were performed with the indicated dicarbinol species (2.5 mM each) on a 3 mL scale at room temperature. The reactions were monitored at 0.083, 0.25, 0.5, 1, 2, and 4 h.
[b] The reaction conditions for each entry are the same as those found in Table 1.
[c] The highest yield (TLC) at any of the time points is reported. The yield values are corrected for the low level of benzaldehyde observed in control samples not treated with acid catalyst.
[d] The level of benzaldehyde did not exceed the background level detected in the control.

Given the importance of dipyrromethanedicarbinol species in the preparation of a variety of porphyrinoids,[15–17,20] the susceptibility of dipyrromethanedicarbinol **2-OH** to acid-catalyzed decomposition was examined under additional conditions of relevance to porphyrinoid synthesis. Reactions were performed in CH_2Cl_2 with catalysis by $InCl_3$ (0.32 mM), $Sc(OTf)_3$ (0.32, 1.0 mM), $Yb(OTf)_3$ (3.2, 10 mM), or $Dy(OTf)_3$ (1.0, 10 mM), or in acetonitrile with TFA (30 mM). Under all conditions involving CH_2Cl_2, uniformly moderate levels of benzaldehyde (30–40%) were detected. The reaction in acetonitrile provided a lower level of benzaldehyde (8%). It is interesting that a moderate level of decomposition of **2-OH** was observed in the reactions carried out in CH_2Cl_2 as these conditions generally provide good yields of porphyrin when applied to the reactions of a dipyrromethane+a dipyrromethanedicarbinol.[15] A subset of these conditions also provide good yields of HPO from the reaction of **2-OH**+**3**.[4] It is clear that the potential for a reaction condition to facilitate decomposition of the dicarbinol species does not preclude application of the reaction condition toward macrocycle formation. There are likely multiple factors at play such as the relative rate of decomposition compared to the rates of reactions leading to the desired product. Nevertheless, the potential for at least a low level of dicarbinol decomposition should be considered in attempts to more fully understand porphyrin forming reactions that make use of carbinol species—even when mild acid catalysts are employed.

2.5. Reaction time course experiments

To broadly compare the reactions **2-OH**+**3** and **4-OH**+**1** so as to further investigate the contrasting yields of HPO and TPC observed from the complementary reactions in the survey of catalysis conditions, time course experiments were performed under the representative reaction conditions of Table 1. Reactions were monitored from 1 min to 24 h for yield of HPO, TPC, and TPP (UV–vis), yield of benzaldehyde from acid-catalyzed decomposition (TLC), and the overall oligomer composition (LD-MS). Detailed monitoring as a function of time facilitates further examination of conclusions drawn from the more limited sampling utilized in the survey of catalysis conditions. The monitoring of species in addition to HPO, TPC, and TPP allows correlation of macrocycle yields with the presence of other byproducts.

The yield of HPO, TPC, and TPP observed from the time course experiments (Table 3) mirrored results from the survey of catalysis conditions. Thus, trends in macrocycle yields noted from the survey of catalysis conditions were not artifacts of the selection of time points. Again, three general scenarios were observed: (1) reaction of **2-OH**+**3** provided HPO or both HPO and TPC whereas neither were obtained from reaction of **4-OH**+**1** (entries 3, 5, and 7), (2) both reactions provided HPO, albeit at a lower level for reaction of **4-OH**+**1** (entries 1, 4, and 6), and (3) reaction of **2-OH**+**3** provided HPO whereas TPC was obtained from the reaction of **4-OH**+**1** (entries 2, 8–10). It is again interesting that in the most polar solvent, reaction of **2-OH**+**3** provided HPO whereas **4-OH**+**1** provided TPC. This observation is consistent with the polar carbinol groups of the bipyrroledicarbinol impacting the conformation about the bipyrrole linkage in polar solvents.

Representative yield trajectories as a function of time are shown in Figure 3 for a condition that afforded HPO from the reaction of **2-OH**+**3** and TPC from the reaction of **4-OH**+**1** (see Supplementary data for the complete set of plots). In both reactions, the yield of HPO (**2-OH**+**3**) or TPC (**4-OH**+**1**) increased, reached a maximum,

Table 3
Summary of macrocycle yields from the reaction time course experiments of **2-OH**+**3** (dipyrromethanedicarbinol route) and **4-OH**+**1** (bipyrroledicarbinol route)[a]

Entry	Solvent	Acid	[Acid], mM	**2-OH**+**3**			**4-OH**+**1**		
				% Yield of HPO[b]	% Yield of TPC[b]	% Yield of TPP[b]	% Yield of HPO[b]	% Yield of TPC[b]	% Yield of TPP[b]
1	CH_2Cl_2/THF (9:1)	TFA	10	18	—[c]	—	2.1	—	—
2	CH_2Cl_2/THF (9:1)	$Sc(OTf)_3$	1.0	4.9	—	1.8	—	3.1	4.7
3	THF	TFA	1.0	15	7.5	—	—	—	—
4	THF	$Sc(OTf)_3$	1.0	9.2	—	—	1.9	—	—
5	THF	$Dy(OTf)_3$	0.32	8.7	—	—	—	—	—
6	THF	$Dy(OTf)_3$	32	5.7	—	—	1.7	—	—
7	MeCN	TFA	0.32	12	—	—	—	—	—
8	MeCN	$Yb(OTf)_3$	1.0	6.7	—	1.8	—	9.3	5.5
9	MeCN	$Dy(OTf)_3$	0.32	7.3	—	0.7	—	9.8	5.4
10	MeCN	$Dy(OTf)_3$	1.0	6.6	—	1.4	—	8.7	4.9

[a] The reactions were performed with the indicated reactants (2.5 mM each) on a 5–10 mL scale at room temperature. The reactions were monitored from 1 min to 24 h.
[b] The highest yield (UV–vis) at any of the time points is reported.
[c] Not detected.

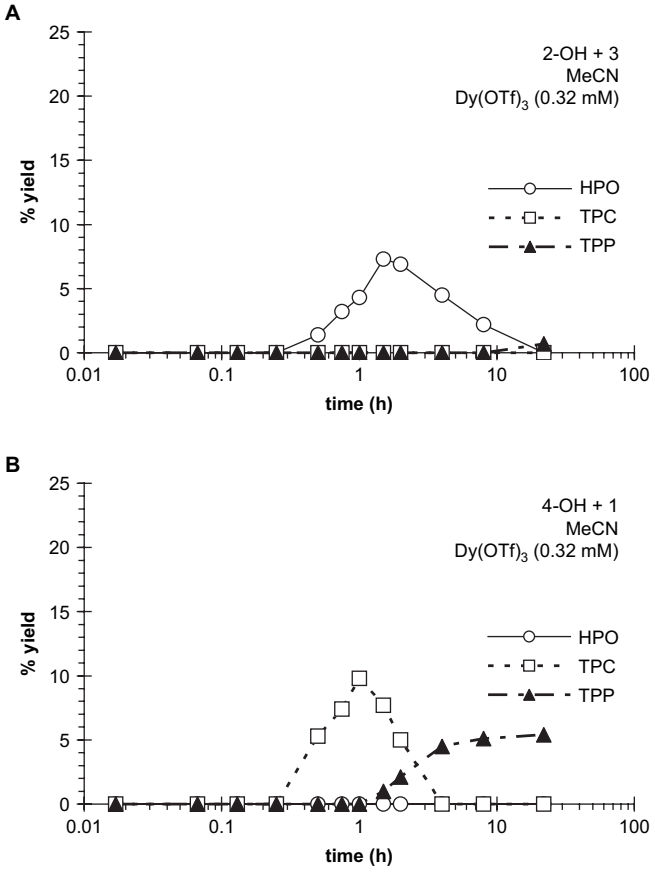


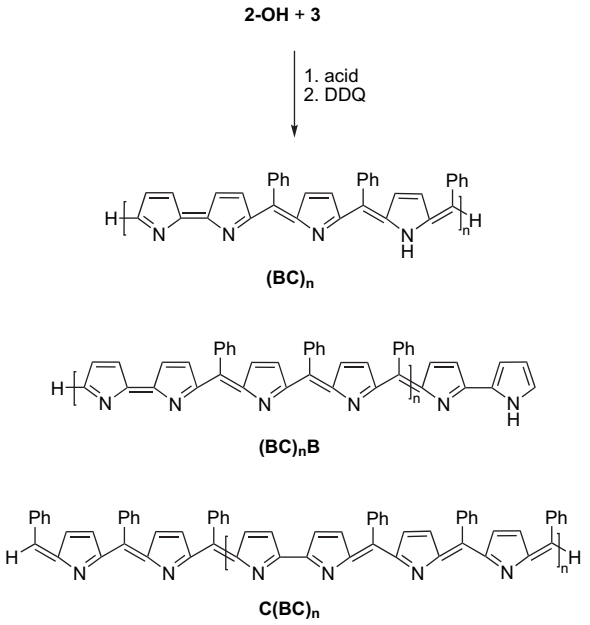
Figure 3. Yield of HPO, TPC, and TPP as a function of condensation time for (A) **2-OH**+**3** and (B) **4-OH**+**1** (2.5 mM each) at room temperature under the indicated conditions. The reactions were monitored spectrophotometrically. Note the log scale for time.

and then declined over time. In both cases TPP was observed late in the reaction, indicating that reversible processes developed over time. A variety of trajectories were observed from the other reaction conditions, but they also generally showed an obtainment of a maximum yield of HPO or TPC followed by a decline in the yield at longer reaction times. In reactions where TPP was observed, it always appeared after the yield of HPO or TPC had substantially declined from its maximum value. Reactions of **2-OH**+**3** carried out in CH_2Cl_2/THF (9:1) were fast, affording the maximum yield of HPO by a reaction time of 1 min followed by a gradual decline in the yield of HPO. The complementary reaction of **4-OH**+**1** under identical conditions was much slower.

The level of benzaldehyde was generally low (4–10%) for both reaction routes under all conditions. The low level of benzaldehyde was typically obtained by 1 min time point and maintained at a similar level throughout the rest of the reaction. There were no sharp differences between the amount of benzaldehyde detected from the reactions of **2-OH**+**3** and **4-OH**+**1** performed under identical conditions. This result contrasts somewhat with observations from the examination of the acid-catalyzed decomposition of **2-OH** and **4-OH**, which found that **2-OH** generally gave higher levels of benzaldehyde (Table 2). It appears that the difference in the propensity of **2-OH** and **4-OH** to undergo acid-catalyzed decomposition is less important when the additional reactant (2,2′-bipyrrole **3** or 5-phenyldipyrromethane **1**) is present. Again, it appears that differential acid-catalyzed decomposition of the dicarbinol species is not an important factor in the obtainment of different macrocycle yields in the reactions of **2-OH**+**3** and **4-OH**+**1**.

The overall oligomer composition from aliquots of crude, oxidized reaction mixtures was assessed at each time point by LD-MS. This methodology has been previously applied to the study of reactions leading to *meso*-tetraarylporphyrins[21] and other porphyrinoids.[22] The assignment of LD-MS spectra obtained from the reactions of **2-OH**+**3** and **4-OH**+**1** was carried out in analogous fashion to previous studies of the reaction of pyrrole+aldehyde.[21a] Sequential condensation of carbinol species with bipyrrole or dipyrromethane followed by oxidation with DDQ would lead to three oligomer series that differ in the nature of the groups terminating the oligomer chain. The oligomer series for the reaction of **2-OH**+**3** is shown in Scheme 4, and the calculated weights for the first four members of each series are shown in Table 4. The calculated weights are for the fully unsaturated form of each open-chain oligomer assuming loss of any terminal carbinol –OH group(s). A peak was considered to be a member of an oligomer series if the m/z value fell within ±2 of the calculated value. TPC belongs to the n=1 member of the $(BC)_n$ series and HPO belongs to the n=2 member of the same series. In some instances, oligomers were detected at m/z values 18 or 36 units higher than the calculated value, indicating the presence of one or two intact –OH groups from terminal carbinol units. Oligomers arising from reversible processes (i.e., scrambling) were recognized by their peaks falling at m/z values correlating with calculated weights of oligomers expected to arise from the reaction of pyrrole+benzaldehyde rather than the calculated weights of Table 4 (see Supplementary data for further discussion). Assignments were made in a similar fashion for **4-OH**+**1** (see Supplementary data).

Trends in oligomer composition provided insight into the general scenarios noted for macrocycle yield. Under conditions where the reaction of **2-OH**+**3** provided HPO, and neither HPO nor TPC were obtained from the reaction of **4-OH**+**1** (Table 3, entries 5 and



Scheme 4. Expected oligomers present in crude, oxidized reaction mixtures from **2-OH**+**3** (B=bipyrrole and C=dipyrromethanedicarbinol).

Table 4
Calculated molecular weights of oligomers from **2-OH**+**3**[a]

n	$(BC)_n$	$(BC)_nB$	$C(BC)_n$
1	526	654	920
2	1050	1178	1440
3	1574	1702	1968
4	2098	2226	2492

[a] The oligomer masses increase with *n* according to (MW_{n+1}=MW_n+524). The oligomers are fully unsaturated.

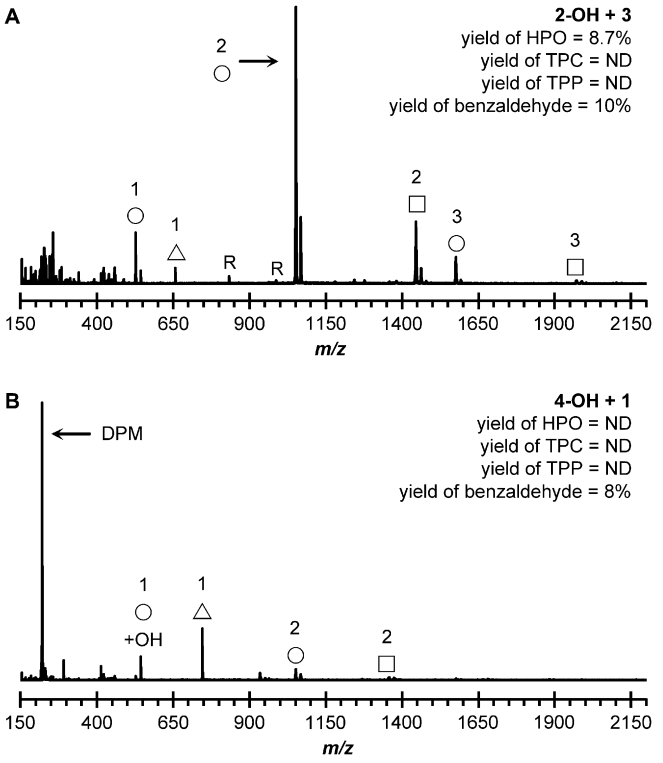


Figure 4. LD-MS spectra of crude, oxidized reaction mixtures from the reaction of (A) **2-OH**+**3** and (B) **4-OH**+**1** (2.5 mM each). The reactions were carried out with $Dy(OTf)_3$ (0.32 mM) in THF at room temperature for 30 min. The yield of HPO, TPC, and TPP (UV–vis) and yield of benzaldehyde (TLC) are shown for each reaction (ND=not detected). ○=$(BC)_n$ or $(DC)_n$ series, △=$(BC)_nB$ or $(DC)_nD$ series, □=$C(BC)_n$ or $C(DC)_n$ series, DPM=dipyrromethene, and R=oligomer from reversible process.

7), **2-OH**+**3** showed much richer oligomer compositions. Representative spectra from the condition of entry 5 are provided in Figure 4 (see Supplementary data for the complete set of spectra for this condition). Compared to the reaction of **2-OH**+**3**, the reaction of **4-OH**+**1** proceeded very sluggishly. Throughout the reaction, **4-OH**+**1** displayed few oligomers, a strong peak corresponding to 5-phenyldipyrromethene (arising from the oxidation of unreacted dipyrromethane upon treatment with DDQ), and oligomers that retained –OH groups from carbinol units. Interestingly, a peak was detected at m/z=544, consistent with an oligomer the size of TPC but still possessing a –OH group. Thus, it appears that the failure of the reaction of **4-OH**+**1** under these conditions to provide detectable levels of HPO or TPC lies in poor oligomer formation and cyclization rather than in other possibilities such as over oligomerization or undesired reversible processes. LD-MS spectra obtained under conditions that afforded both HPO and TPC from the reaction of **2-OH**+**3**, but neither product from the reaction of **4-OH**+**1** (Table 3, entry 3) showed similar trends (see Supplementary data for the complete set of spectra).

Under conditions where both reactions provided HPO albeit at a lower level for **4-OH**+**1** (Table 3, entries 1, 4, and 6), the oligomer compositions were more similar for the two complementary reactions. Representative spectra from the condition of entry 4 are provided in Figure 5 (see Supplementary data for the complete set of spectra for this condition). Although the oligomer compositions were more similar in this scenario, they were not identical. The spectra from the reaction of **4-OH**+**1** still showed a peak corresponding to dipyrromethene at all time points, and the oligomer composition took a longer time to develop. So while it appears that the complementary reactions can follow a similar reaction pathway under some reaction conditions, the reaction of **4-OH**+**1** still proceeded more sluggishly and resulted in a lower yield of HPO.

Under the interesting set of reaction conditions where **2-OH**+**3** provided HPO while **4-OH**+**1** gave TPC (Table 3, entries 2, 8–10), the oligomer compositions were somewhat different from those observed under the other reaction conditions—especially for the reaction of **4-OH**+**1**. Representative spectra from the condition of entry 9 are provided in Figure 6 (see Supplementary data for the complete set of spectra for this condition). Both reactions afforded a number of oligomers, with the oligomer composition from the reaction of **4-OH**+**1** being more complex in this case. Both reactions proceeded slowly at first, with primarily starting materials and short oligomers bearing –OH groups from the carbinol units (including the acyclic precursor to TPC) present at early reaction times. The reaction of **4-OH**+**1** continued to provide a peak corresponding to dipyrromethene at all time points. At long reaction times, both reactions were more subject to reversible processes than was the case under the other reaction conditions. Thus, the conditions that best facilitated oligomerization in the reaction of **4-OH**+**1** were also sufficiently vigorous to increase reversible processes at longer reaction times. However, it is important to note that TPC was detected prior to the detection of oligomers formed by reversible processes. Thus, the production of TPC does not appear to be due to an advantageous recombination of fragments generated from the original building block molecules through reversible processes. In fact, the emergence of oligomers produced through reversible processes correlated with the decline in the yield of TPC at longer reaction times.

The time course experiments along with the results from the survey of catalysis conditions revealed that more exacting conditions are required for the reaction of **4-OH**+**1** than for **2-OH**+**3**. The

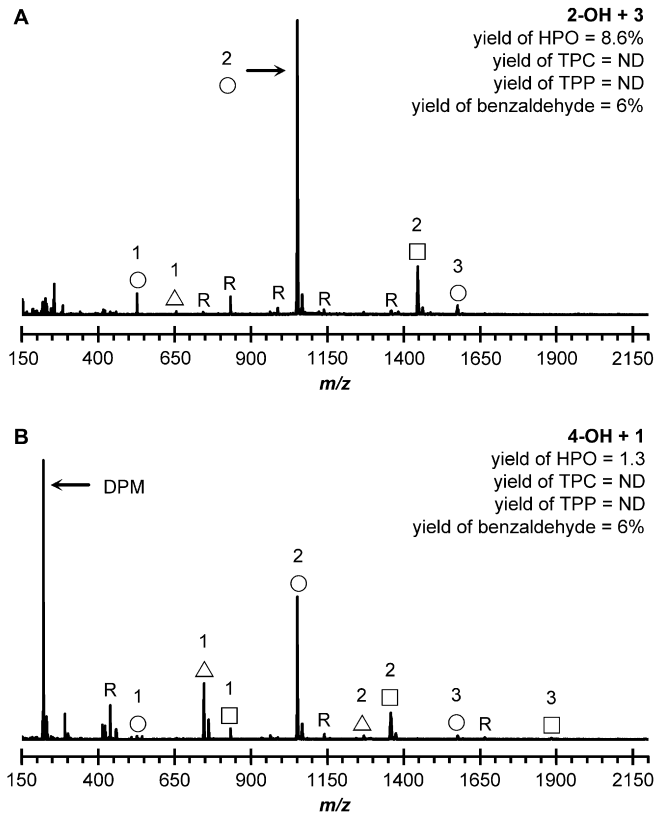


Figure 5. LD-MS spectra of crude, oxidized reaction mixtures from the reaction of (A) **2-OH**+**3** and (B) **4-OH**+**1** (2.5 mM each). The reactions were carried out with $Sc(OTf)_3$ (1.0 mM) in THF at room temperature for 4 h. The yield of HPO, TPC, and TPP (UV–vis) and yield of benzaldehyde (TLC) are shown for each reaction (ND=not detected). ○=$(BC)_n$ or $(DC)_n$ series, △=$(BC)_nB$ or $(DC)_nD$ series, □=$C(BC)_n$ or $C(DC)_n$ series, DPM=dipyrromethene, and R=oligomer from reversible process.

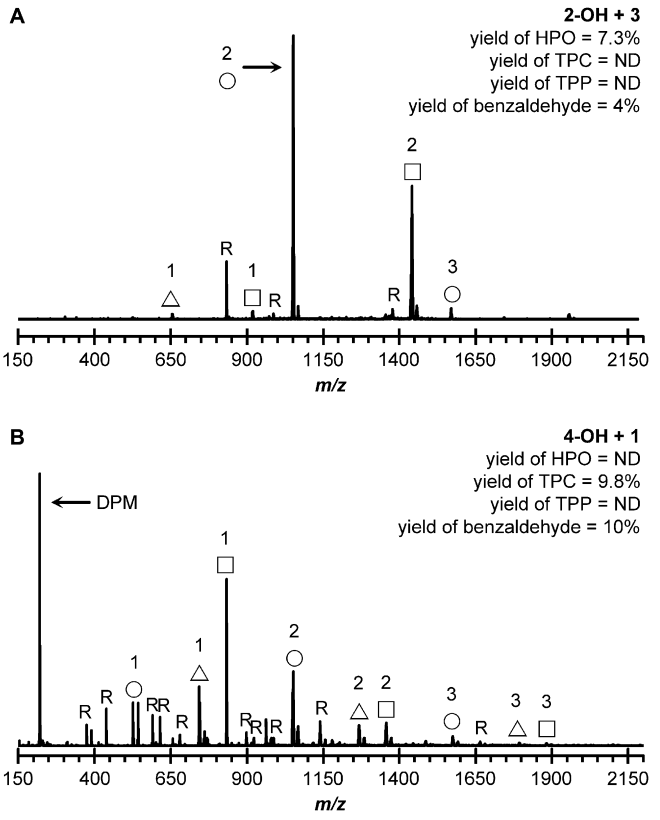


Figure 6. LD-MS spectra from crude, oxidized reaction mixtures from the reaction of (A) **2-OH**+**3** and (B) **4-OH**+**1** (2.5 mM each). The reactions were carried out with $Dy(OTf)_3$ (0.32 mM) in MeCN at room temperature for 1.5 h (**2-OH**+**3**) or 1 h (**4-OH**+**1**). The yield of HPO, TPC, and TPP (UV–vis) and yield of benzaldehyde (TLC) are shown for each reaction (ND=not detected). ○=$(BC)_n$ or $(DC)_n$ series, △=$(BC)_nB$ or $(DC)_nD$ series, □=$C(BC)_n$ or $C(DC)_n$ series, DPM=dipyrromethene, and R=oligomer from reversible process.

reaction of **4-OH**+**1** provided low to modest yields of HPO or TPC under only a subset of reaction conditions. The generally poor macrocycle yields obtained from this reaction route were found to stem from a combination of sluggish oligomer formation, poor cyclization, incomplete utilization of starting material, and/or reversible processes. These issues could not be readily solved through the adjustment of reaction parameters such as acid catalyst concentration, solvent, or reaction time. In contrast, the reaction of **2-OH**+**3** gave modest to moderate levels of HPO across a fairly wide range of reaction conditions. The improved yields of HPO were accompanied by an oligomer distribution centered on the *m*/*z* of HPO and largely devoid of oligomers arising from reversible processes (except at long reaction times).

Given the widespread use of CH_2Cl_2 in porphyrin forming reactions, time course experiments were also carried out for the reaction of **2-OH**+**3** in CH_2Cl_2. The complementary reaction of **4-OH**+**1** could not be compared for these conditions due to the poor solubility of **4-OH** in CH_2Cl_2. The results of these experiments are provided in Supplementary data.

2.6. Practical implications

By investigating the impact of carbinol group placement and the effect of key reaction parameters on the distribution of products and the broader reaction course, observations were made with relevance toward the preparation of porphyrinoids bearing bipyrrole linkages. The reaction of **2-OH**+**3** is the better route to HPO. This route provides good yields of HPO under a variety of reaction conditions. The reaction pathway leading to HPO or TPC can be directed to some extent by the choice of dicarbinol species and solvent. However, there are certainly more efficient routes to the preparation of *meso*-substituted corroles.[9,23] The bipyrroledicarbinol species behaves in distinctive ways relative to the complementary dipyrromethanedicarbinol. In other contexts, bipyrroledicarbinol species may be interesting building block molecules.

3. Conclusions

Complementary reactions of a dipyrromethanedicarbinol+2,2′-bipyrrole (**2-OH**+**3**) and a 2,2′-bipyrroledicarbinol+a dipyrromethane (**4-OH**+**1**) leading to TPC and/or HPO were investigated to establish the impact of carbinol group placement and key reaction parameters on the distribution of products and on the broader reaction course. In addition, we sought to explore the chemistry of a bipyrroledicarbinol species—a building block molecule that has not been as extensively studied as dipyrromethanedicarbinols. The complementary reactions were compared in a survey of catalysis conditions, in an examination of the susceptibility of the dicarbinol species to acid-catalyzed decomposition, and in time course experiments. Supporting the overall study was the refinement of conditions for the acylation of 2,2′-bipyrrole.

Key findings of the work include: (1) The complementary reactions of **2-OH**+**3** and **4-OH**+**1** afforded different quantities of HPO and/or TPC across a range of acid catalysts, acid concentrations, and solvents. (2) Conditions were identified such that the reaction of **2-OH**+**3** provided HPO and the reaction of **4-OH**+**1**

instead provided TPC. This scenario was most commonly observed in the solvent of highest polarity. (3) Both dicarbinol species underwent acid-catalyzed decomposition under some reaction conditions, with the **2**-**OH** being somewhat more susceptible. However, in the presence of the other reactant, the differences in the level of benzaldehyde formation were less pronounced in the reactions of **2**-**OH**+**3** and **4**-**OH**+**1**. Differential extent of acidolysis of **2**-**OH** and **4**-**OH** does not account for the differing yields of macrocycles. (4) Time course experiments supported the trends observed in the survey of catalysis conditions. (5) The examination of oligomer compositions facilitated further comparison of the complementary reactions, providing insight into the contrasting yields of HPO and TPC. In reactions of **4**-**OH**+**1**, oligomer formation proceeded sluggishly and, in some cases, with a good deal of reversibility. Identifying appropriate conditions for the reaction of **4**-**OH**+**1** are more challenging than for the complementary reaction. In summary, the placement of the carbinol groups on the bipyrrole species rather than on the dipyrromethane has a profound effect on the reaction course. Complementary reaction routes can give rise to quite different results, and therefore, may have unique utilities.

4. Experimental section

4.1. General

^{1}H NMR (400 MHz) and absorption spectra were collected routinely. Melting points are uncorrected. Chromatography was performed on silica (Merck, 230–400 mesh, 60 Å). $CHCl_3$ used in the preparation of **4** was distilled from CaH_2. THF used in the reduction of **2** and **4** was stored over 4-Å Linde molecular sieves. CH_2Cl_2 used in analytical-scale reactions of **2**-**OH**+**3** and **4**-**OH**+**1** was distilled from potassium carbonate and stored over 4-Å Linde molecular sieves. THF and toluene used in analytical-scale reactions of **2**-**OH**+**3** and **4**-**OH**+**1** were obtained from a Braun MB-SPS solvent purification system. CH_2Cl_2 used in spectrophotometric determination of the yield of TPC and HPO was passed through a pad of basic alumina prior to use. Dipyrromethane **1**,[8] diacyl dipyrromethane **2**,[9] and 2,2′-bipyrrole **3**[9] were prepared as described in the literature. All other chemicals were reagent grade and were used as received.

4.2. 5,5′-Dibenzoyl-2,2′-bipyrrole (4)

Following a refined published procedure,[11] 2,2′-bipyrrole **3** (250 mg, 1.89 mmol) was combined with *N*,*N*-dimethylbenzamide (3.66 g, 24.5 mmol) in dry $CHCl_3$ (2.3 mL) under argon. The slurry was cooled to 0 °C in an ice bath, and $POCl_3$ (2.28 mL, 24.5 mmol) was added over 30 s. The ice bath was replaced by a water bath heated to 50 °C, and the clear, brown reaction mixture was stirred at 50 °C under argon for 6 h. The reaction mixture was transferred to a solution of sodium acetate (13 g) in water (55 mL). The mixture was heated at 70 °C for ~10 min to drive off the $CHCl_3$. The mixture was further heated at 90 °C for 1 h. The reaction was cooled to room temperature, sonnicated for ~15 min, and placed in a refrigerator overnight. Vacuum filtration, followed by rinsing with water, and drying under vacuum (60 °C for 2 h) afforded crude product as a tan powder (563 mg). The crude product was dissolved in hot DMSO (~7 mL) and then dripped slowly into hot *i*PrOH (~21 mL). A yellow precipitate formed quickly. The mixture was stored in a freezer for 2 h. Vacuum filtration followed by rinsing with *i*PrOH and drying under vacuum (150 °C for 2 h) afforded **4** as a yellow solid (410 mg, 64%). Mp=329–331 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.87 (m, 2H), 6.92 (m, 2H), 7.54 (t, J=7.6 Hz, 4H), 7.63 (t, J=7.1 Hz, 2H), 7.84 (d, J=7.4 Hz, 4H), 12.4 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.4, 121.0, 128.8, 128.9, 131.3, 131.7, 132.1, 138.7, 183.5. IR (thin film): 3273 (NH), 1594 (C=O). HRMS (FAB) m/z calcd for $C_{22}H_{17}N_2O_2$ [MH^+]: 341.1290; found: 341.1303.

4.3. Survey of catalysis conditions

Immediately prior to the condensation reactions, **2** (161 mg, 0.375 mmol) was reduced to the corresponding dicarbinol species **2**-**OH** with $NaBH_4$ (0.71 g, 19 mmol) in THF/methanol (30 mL, 3:1) following a literature procedure.[9,12a] The reduction was monitored by TLC [alumina, EtOAc/hexanes (3:2)]. For reactions involving **4**-**OH**, **4** (128 mg, 0.375 mmol) was reduced in a similar fashion except that three portions of $NaBH_4$ (0.71 g, 19 mmol) were added at reaction times of 0, 30, and 60 min. The reduction of **4** proceeded better if the mixture was sonnicated for ~10 min prior to the first addition of $NaBH_4$ (**4** does not initially dissolve entirely). The reduction was monitored by TLC [alumina, CH_2Cl_2/EtOAc (2:1)]. Crude **4**-**OH** was characterized by ^{1}H NMR and IR. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.63 (m, 4H), 5.76 (s, 2H), 6.07 (t, J=2.8 Hz, 2H), 7.21 (t, J=7.2 Hz, 2H), 7.30 (t, J=7.5 Hz, 4H), 7.39 (d, J=7.7 Hz, 4H), 10.7 (s, 2H). IR (thin film): 3450 (OH), 3264 (NH).

After drying under vacuum for 30 min, the dicarbinol species (**2**-**OH** or **4**-**OH**) was dissolved in the desired solvent and transferred to a 50-mL volumetric flask. A solution of **3** (49.5 mg, 0.375 mmol) or **1** (83.3 mg, 0.375 mmol) was prepared in the desired solvent in a 100-mL volumetric flask. The contents of the two volumetric flasks were mixed, thereby providing a stock solution of **2**-**OH** and **3** or **4**-**OH** and **1** (2.5 mM each). Reactions were performed at room temperature in tightly capped 20-mL vials stirred with a micro stir bar. Solid acids were weighed into all reaction vials prior to beginning the reaction sequence for the day, and each reaction was started by the addition of 5–10 mL of the reactant solution via volumetric pipet. Reactions involving TFA were initiated by the addition of TFA to reaction vials already containing 5 mL of the reactant stock solution. The reactions were monitored spectrophotometrically for yield of HPO, TPC, and TPP at 0.25, 1, and 4 h as described previously.[4] TLC was performed on the crude, oxidized mixture [silica, CH_2Cl_2/ethyl acetate (25:1)].

4.4. Acid-catalyzed decomposition of dicarbinol species leading to benzaldehyde

Immediately prior to the reactions, **2** (16.1 mg, 0.0375 mmol) or **4** (12.8 mg, 0.0375) was reduced to the corresponding dicarbinol species **2**-**OH** or **4**-**OH** as described above in the survey of catalysis conditions. After drying under vacuum for 30 min, the dicarbinol species (**2**-**OH** or **4**-**OH**) was dissolved in the desired solvent to afford a solution of **2**-**OH** or **4**-**OH** (2.5 mM). Reactions were performed at room temperature in tightly capped 20-mL vials stirred with a micro stir bar. Solid acids were weighed into all reaction vials prior to beginning the reaction sequence for the day, and each reaction was started by the addition of 3 mL of the dicarbinol solution via volumetric pipet. Reactions involving TFA were initiated by the addition of TFA to reaction vials already containing 3 mL of the dicarbinol stock solution. The reactions were monitored by TLC and GC/MS analyses at 5 min, 15 min, 30 min, 1 h, 2 h, and 4 h.

TLC analysis: following a published procedure,[19] aliquots (2 μL) of each reaction mixture were spotted using a micropipet on a silica TLC plate alongside spots of aliquots (2 μL) of solutions of benzaldehyde (0.1, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0 mM). Plates were developed in CH_2Cl_2/hexanes (1:1) and visualized by short wavelength UV light. The intensity of spots due to benzaldehyde was visually compared. Control experiments found that residual acid catalyst or other byproducts did not impact the detection of benzaldehyde.

GC–MS analysis: an aliquot (150 μL) of each reaction mixture was transferred to a microfuge tube. Triethylamine (5 equiv relative to acid) was added and the mixture was passed through a filter

pipet into an autosampler vial. The solution (0.5 μL) was analyzed with the following GC conditions: VF-5ms column; 30 m× 0.25 mm×0.25 μm; inlet temperature 260 °C; temperature gradient: temperature 1, 60 °C (2 min); temperature 2, 270 °C (1 min); rate 30 °C/min, total runtime 10 min; helium constant flow of 1.0 mL/min. The retention time for benzaldehyde was 4.4 min. The MS response was calibrated with benzaldehyde solutions of known concentration (0.1, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0 mM) and the response was found to be linear. Control experiments found that the addition of triethylamine and sample filtration did not alter the detection of benzaldehyde. Analysis reproducibility was found to be satisfactory.

4.5. Reaction time course experiments

Immediately prior to the reactions, **2** (37.6 mg, 0.0875 mmol) or **4** (29.8 mg, 0.0875) was reduced to the corresponding dicarbinol species **2**-**OH** or **4**-**OH** as described above in the survey of catalysis conditions. After drying under vacuum for 30 min, the dicarbinol species (**2**-**OH** or **4**-**OH**) was dissolved in the desired solvent and **3** (11.6 mg, 0.0875 mmol) or **1** (19.4 mg, 0.0875 mmol) was added to afford a stock solution of **2**-**OH** and **3** or **4**-**OH** and **1** (2.5 mM each). Reactions were performed at room temperature in tightly capped 20-mL vials stirred with a micro stir bar. Solid acids were weighed into all reaction vials prior to beginning the reaction sequence for the day, and each reaction was started by the addition of 8 mL of the reactant solution via volumetric pipet. Reactions involving TFA were initiated by the addition of TFA to reaction vials already containing 8 mL of the reactant stock solution. The reactions were monitored for yield of HPO, TPC, TPP spectrophotometrically as described previously,[4] for yield of benzaldehyde, and for oligomer composition by LD-MS at 1 min, 4 min, 8 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 4 h, 8 h, and 24 h.

TLC analysis: an aliquot (100 μL) of crude reaction mixture was transferred to a microfuge tube containing DDQ (0.34 mg, 0.0015 mmol). The sample was vortex mixed and allowed to stand for at least 5 min. An aliquot (2 μL) of the crude, oxidized reaction mixture was analyzed by TLC as described above for the acidolysis of dicarbinol species affording benzaldehyde.

LD-MS analysis: following a published procedure,[21a] an aliquot (1 μL) from the same crude, oxidized reaction mixtures used in TLC analysis was spotted onto a MALDI target. The crude, oxidized samples were analyzed in the absence of added matrix. LD-MS spectra were recorded using a TOF instrument in reflector mode equipped with a nitrogen laser (337 nm), 1.2 m flight tube, MCP detector, and a 2 GHz digitizer. Mass accuracy is <100 ppm with external standards. Spectra were averaged over 200–300 shots taken from at least four locations on the target. Samples were analyzed after all reactions for 1 day were completed. Samples spent between 2 and 8 h on the target prior to LD-MS analysis. Control experiments found that samples were stable on the MALDI target while awaiting analysis. LD-MS analysis was found to be insensitive the quantity of DDQ used in the oxidation of the crude reaction mixtures. Very similar spectra were obtained upon oxidizing the reaction aliquot (100 μL) with quantities of DDQ ranging from 0.14 to 2.3 mg.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the oSnline version, at doi:10.1016/j.tet.2008.08.025.

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