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A Survey of Acid Catalysts for Use in Two-Step, One-Flask Syntheses of Meso-Substituted Porphyrinic Macrocycles

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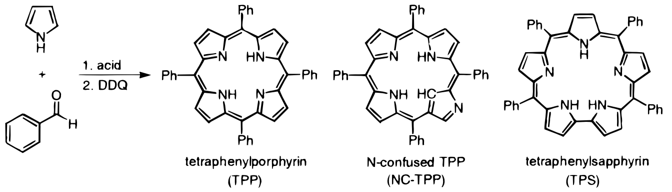
ABSTRACT



Diverse Lewis acids and Brønsted acids were examined in the two-step, one-flask synthesis of *meso*-tetraphenylporphyrin, N-confused tetraphenylporphyrin, and tetraphenylsapphyrin. The scope of acid catalysis was found to be very broad, with 35 of 45 acids providing TPP in yields ranging from 5% to 58%. NC-TPP was also widely observed in yields of 1–40%, and TPS was infrequently observed in yields of <1%. Additionally, conditions were found for direct preparation of magnesium TPP and copper TPP.

The acid-catalyzed condensation of pyrrole + aldehyde followed by oxidation provides a convenient synthesis of meso-substituted porphyrins.[1] The dominant acid catalysts for this reaction have been TFA and BF_3-etherate, with only a few additional acid catalysts having been examined.[2] The absence of studies examining diverse acid catalysts for use in porphyrin synthesis contrasts with the active study of acid catalysis in other key areas of organic and polymer synthesis. The critical role of the acid in porphyrin synthesis has prompted us to examine a much broader selection of acid catalysts. Further encouragement for this examination has come from the recent observations of additional meso-substituted porphyrinic macrocycles (N-confused porphyrin, sapphyrin, and corrole) formed under standard[3] or related[4] two-step, one-flask reaction conditions. Such conditions provide only modest yields of N-confused porphyrin (<8%), sapphyrin (<2%), and corrole (<12%) macrocycles. Thus, we undertook a survey of acid catalysts to examine the scope of acid catalysis in porphyrin synthesis and to potentially identify reaction conditions for efficient synthesis of other porphyrinic macrocycles.

The condensation of pyrrole + benzaldehyde leading to tetraphenylporphyrin (TPP) served as our model reaction. One exciting discovery from this study has already been reported: the efficient synthesis of N-confused TPP (NC-TPP) in ~40% yield using methanesulfonic acid.[5] In this

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Table 1. Rank Ordering of Acids Providing the Highest Yield of TPP[a]

entry	acid	[acid], mM[b]	solubility[c]	time, h	% TPP	% NC-TPP[d]
1	BF_3-etherate/NaCl	1.0[e]	yes	1	58	2.7
2	TFA/BF_3-etherate	15/0.32	yes	1	53	5.5
3	*p*-$CH_3C_6H_4SO_3H·H_2O$	0.32	no	1	50	9.2
4	CH_3SO_3H	0.32	yes	1	46	8.3
5	K10[f]	20 g/L	no	1	43	1.8
6	$MgBr_2$	32	no	2	43	5.8
7	SbF_5	0.32	yes	2	43	5.1
8	$GeBr_4$	10	yes	4	43	5.0
9	PBr_5	0.10	yes	0.25	41	4.5
10	BBr_3	0.10	yes	1	41	4.3
11	$TiBr_4$	0.70	no	1 min	40	2.9
12	CCl_3CO_2H	32	yes	1	39	2.3
13	TFA	20	yes	1	38	3.0
14	$CuCl_2$	32	no	0.5	37	0
15	$AlCl_3$	3.2	no	0.25	36	0.6
16	$MgBr_2$-etherate	32	no	0.5	34	0.9
17	$TiCl_4$	1.0	yes	1	34	1.0
18	$GaCl_3$	1.0	yes	2	34	5.5
19	$SnCl_4$	1.0	yes	2	34	4.8
20	$FeCl_3$	1.0	no	4	34	4.4
21	HCl(g)[g]	32% satd	yes	1	31	0.6
22	$SiCl_4$	0.32	yes	1	31	1.0
23	BCl_3	1.0	yes	0.5	30	0.7
24	$TeCl_4$	1.0	no	1	30	0.6
25	BF_3-etherate	1.0	yes	4	26	7.7
26	$C_6F_5CO_2H$	1000	no	4	26	0.9
27	GeI_4	32	yes	2	23	0.8
28	BEt_3	100	yes	8	23	0
29	HCl(aq)[h]	10	no	24	21	5.3
30	Nafion[i]	100 g/L	no	4	19	5.0
31	TiF_4	3.2	no	8	17	6.8
32	CF_3SO_3H	1.0	yes	2	10	8.4
33	$Yb(OTf)_3$	100	no	4	9.6	5.2
34	$Sc(OTf)_3$	3.2	no	8	9.5	6.7
35	SnF_4	32	no	8	5.0	2.3

[a] Reactions were performed with 10 mM pyrrole and 10 mM benzaldehyde in CH_2Cl_2 at room temperature. [b] Acid concentration affording the highest yield of TPP. [c] Acid solubility was assessed visually with "yes" meaning that all acid dissolved and "no" meaning that at least some solid acid was observed. [d] NC-TPP yield at the identical reaction time. [e] 25 equiv of NaCl relative to pyrrole was used. [f] Montmorillonite K10 was activated for 3 h at 120 °C and <1 Torr. [g] HCl gas was bubbled through CH_2Cl_2 for 15 min followed by dilution with fresh CH_2Cl_2. [h] Aqueous concentrated HCl. In this case the reaction solvent was 3:1 toluene/EtOH. See ref 1. [i] Nafion SAC-13 (Aldrich, 47,454-1).

letter, we now report a summary of the entire study, including a further set of conditions providing NC-TPP in ~25% yield and conditions that provide direct access to selected metalloporphyrins. A comprehensive description of this study will be reported elsewhere.

For this study, efforts were made to select a diverse set of acids.[6] Lewis acids and Brønsted acids were chosen from four general categories, including (1) acids previously used in porphyrin synthesis, (2) acids commonly used in other organic reactions involving condensations of carbonyl containing compounds (e.g., aldol condensation, Friedel−Crafts acylation), (3) recently reported acids with novel properties (e.g., rare earth triflates and lanthanide triflates that are water-stable),[7] and (4) novel acids with no known previous application in organic synthesis. In all, 45 acids (or combinations of acids) were examined.

The acids were initially screened to determine whether TPP was formed and the approximate concentration of acid required for the maximum yield of TPP (see Supporting Information).[8] Of the 45 acids examined, only 10 provided no detectable TPP (<1%). Those acids were AlF_3, CrF_3, $Dy(OTf)_3$, $InCl_3$, oxalic acid, phosphotungstic acid hydrate, $SmCl_3·6H_2O$, tungstic acid, $ZnCl_2$, and $Zn(OAc)_2$.

The 35 acids found to provide TPP were examined in greater detail. Reactions were performed using the approximately optimal acid concentration determined from the screening experiments. The reactions were monitored from 1 min to 24 h by DDQ oxidation of aliquots from the reaction mixture. The crude, oxidized samples were analyzed for the yields of TPP (UV−vis and HPLC), NC-TPP (HPLC), and tetraphenylsapphyrin (TPS) (HPLC).[9]

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The highest yields of TPP for each acid were found to range from 5.0% to 58% (Table 1).[10] The highest yield was obtained with the previously reported cocatalytic system of BF_3-etherate/NaCl.[11] In second place was a TFA/BF_3-etherate cocatalytic system discovered during our recent studies on the reaction course of TPP synthesis.[12] Acids that have been previously examined for use in porphyrin syntheses (*p*-toluenesulfonic acid,[13] methanesulfonic acid,[14] Montmorillonite K10,[15] trichloroacetic acid,[16] and $SnCl_4$[17]) were also found to be suitable catalysts.

In general, there was tremendous diversity among the acids found to provide TPP. Polymeric acids, mineral acids, Lewis acid complexes involving diverse metals, and Brønsted acids with a wide range of pK_a values were found to be active. The effective acid concentrations spanned a 10,000-fold range from 0.1 mM (PBr_5 and BBr_3) to 1 M ($C_6F_5CO_2H$). Both homogeneous and heterogeneous catalyst systems were found to provide good yields of TPP, though the soluble catalysts generally provided better day-to-day consistency. At the reaction time of highest TPP yield, all acids but BEt_3 and $CuCl_2$ were found to provide at least some NC-TPP (<10%). TPS was rarely observed (detection limit of ~0.3%) and was never detected at >1% yield. Under the reaction conditions reported in Table 1, the highest yields of NC-TPP observed at any time were also generally <10% and typically occurred after the maximum yield of TPP had been obtained (Table 2). Although there was no clear correlation between TPP and NC-TPP formation, the three acids giving the highest yields of NC-TPP all were sulfonic acids.

The three sulfonic acids were examined further for NC-TPP production. The results for methanesulfonic acid have already been reported (~40% yield using 7 mM acid).[5] *p*-Toluenesulfonic acid provided NC-TPP in a maximum yield of 25% (20 mM acid, 30 min), and trifluoromethanesulfonic acid provided only 9.0% (1.0 mM acid, 1 h; see Supporting Information). The origin of the anomalously high levels of NC-TPP with sulfonic acids remains to be determined, but this observation provides further direction for studies of catalysts for NC-TPP synthesis.

Table 2. Rank Ordering of Acids Providing the Highest Yield of NC-TPP at Any Time from Optimal Conditions for TPP Synthesis[a]

entry[b]	acid	[acid], mM	time, h	% NC-TPP	% TPP[c]
3	p-$CH_3C_6H_4SO_3H\cdot H_2O$	0.32	4	10.3	46
4	CH_3SO_3H	0.32	8	10.0	43
32	CF_3SO_3H	1.0	4	8.5	10
25	BF_3-etherate	1.0	4	7.7	26
6	$MgBr_2$	32	24	7.1	30
31	TiF_4	3.2	8	6.8	17
34	$Sc(OTf)_3$	3.2	8	6.7	9.5
8	$GeBr_4$	10	24	6.2	26
33	$Yb(OTf)_3$	100	24	6.2	7.5
30	Nafion	100 g/L	24	6.1	17
11	$TiBr_4$	0.7	0.5	6.0	20
9	PBr_5	0.10	8	5.8	41
18	$GaCl_3$	1.0	2	5.5	34
2	TFA/BF_3-etherate	15/0.32	1	5.5	53
19	$SnCl_4$	1.0	4	5.4	34
29	HCl(aq)	10	24	5.3	21
7	SbF_5	0.32	0.5	5.2	39

[a] Only acids providing >5% NC-TPP are listed. Reactions were performed with 10 mM pyrrole and 10 mM benzaldehyde in CH_2Cl_2 at room temperature. [b] The entry number for each acid is the same as that in Table 1. [c] TPP yield at the identical reaction time.

Finally, the Lewis acid catalysts $MgBr_2$-etherate and $CuCl_2$ were found to metalate the free base porphyrin following DDQ oxidation and treatment with triethylamine. These provide the first examples of the direct one-flask preparation of metalloporphyrins in which the metal complex serves to both catalyze porphyrinogen formation and insert into the free base porphyrin. The case of $MgBr_2$-etherate is particularly significant given the importance of porphyrinic magnesium chelates in nature. These present results extend a previously reported method for magnesium insertion[18] to the direct preparation of MgTPP from pyrrole and benzaldehyde. Note that $MgBr_2$ does not result in metalation under the conditions of the oxidation, consistent with previous observations of slow metalation from $MgBr_2$ compared to $MgBr_2$-etherate.[18] Also, as previously reported triethylamine was required for magnesium insertion. With 150 mM triethylamine, the insertion was quantitative by approximately 2−4 h according to UV−vis, TLC, and HPLC analysis. Larger scale preparations were performed allowing isolation of both metalloporphyrins and conclusive identification by absorption

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[8] The preliminary acid screening experiments also allowed identification of acids providing high yields of other porphyrinic products. At appropriate concentration, methanesulfonic acid and *p*-toluenesulfonic acid gave rise to a strong peak at 438 nm (characteristic of the NC-TPP Soret band) in the UV−vis spectrum of the crude, oxidized reaction mixture (see Supporting Information). Thus, prior to more detailed experiments, it was clear that those acids were good catalysts for NC-TPP formation. No other acids provided clear evidence for NC-TPP, and no acids showed peaks associated with tetraphenylsapphyrin (TPS) in these screening experiments.

[9] Triphenylcorrole (TPC) could not be reliably detected in these experiments. Control experiments with authentic TPC showed that TPC was retained by the pre-HPLC sample cleanup column for removal of polar impurities. The retention was exacerbated by the presence of triethylamine (required for accurate detection of NC-TPP), which deprotonates the acidic corrole leading to a polar ionic species.[4e] Furthermore, the Soret band of TPC is almost identical to that of TPP, making UV−vis detection of small quantities impossible. LD-MS analysis of crude reaction mixtures provided our only means to qualitatively address TPC formation. No peak or a minor peak at $m/z = 526$ (mass of TPC) was observed, indicating that TPC is probably a minor product or absent under the conditions found to be optimal for TPP formation for each acid.

[10] The analytically determined yields of TPP, NC-TPP, and TPS reported here compare well with isolated yields in all cases where preparative scale synthesis has been performed.

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spectroscopy, fluorescence spectroscopy, and mass spectrometry.

In conclusion, we have examined 45 diverse acid catalysts in the two-step, one-flask reaction of pyrrole + benzaldehyde leading to TPP. The scope of acid catalysis is very broad, and the effective acid concentration varies widely from acid to acid (0.1 mM to 1 M). Under the best conditions identified for each acid for producing TPP, NC-TPP was found to be a widespread but minor byproduct ($<$10% yield). However, conditions optimized for NC-TPP formation were found to provide NC-TPP in yields of up to 40%. An apparent trend of anomalously high yields of NC-TPP from catalysis by sulfonic acids was uncovered. Conditions for efficient synthesis of TPS were not found from this survey. Finally, the direct synthesis of metalloporphyrins from the two-step, one-flask reaction of pyrrole + benzaldehyde was demonstrated for the first time.

The success of the two-step, one-flask porphyrin synthesis has relied in part on finding effective catalysts for the pyrrole−aldehyde condensation. The large scope of effective acids identified here should encourage further examination of potential catalysts, especially newly developed acid catalysts, for use in this versatile reaction. Also, the discovery of a wide array of catalysts provides much more latitude in identifying effective catalysts for recalcitrant aldehydes and pyrroles, for use with even milder reaction conditions or different solvents, and for reactions with dipyrromethane species in which irreversibility (no acid-promoted scrambling) is imperative.

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Supporting Information Available: A description of experimental methods, illustrative UV−vis spectra showing detection of NC-TPP in acid screening experiments, and plots showing yields of TPP and NC-TPP under *p*-toluenesulfonic acid and trifluoromethanesulfonic acid catalysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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