

An Efficient One-Flask Synthesis of N-Confused Tetraphenylporphyrin

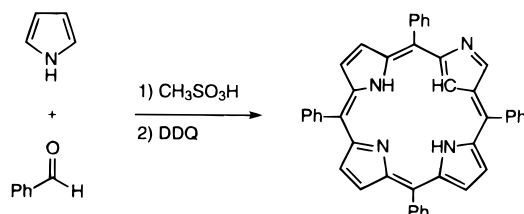
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ABSTRACT



N-Confused *meso*-substituted porphyrin is a porphyrin isomer previously available from one-flask porphyrin syntheses as a low-yield byproduct (<7.5%). We have found that methanesulfonic acid catalyzed condensation of pyrrole and benzaldehyde followed by DDQ oxidation provides N-confused tetraphenylporphyrin (NC-TPP) in up to 39% yield in analytical scale experiments. Preparative synthesis provided an isolated yield of 35% (800 mg). This represents a >5-fold yield improvement and makes significant quantities of NC-TPP readily available.

In 1994, the groups of Latos-Grazynski¹ and Furuta² independently reported the isolation of a *meso*-substituted porphyrin isomer in ~5% yield from the acid-catalyzed condensation of pyrrole and an aryl aldehyde followed by oxidation. This intriguing isomer, 2-aza-21-carba-5,10,15,20-tetraarylporphyrin (also called carbaporphyrin, N-confused or N-inverted porphyrin), has distinctive coordination properties and reactivity.³ The condensation conditions reported to lead to N-confused porphyrin were somewhat unusual. Latos-Grazynski used 70 mM pyrrole and 40 mM *p*-tolualdehyde in CH₂Cl₂ at room temperature with 8 mM BF₃–etherate catalysis, whereas Furuta used equimolar pyrrole and benzaldehyde in *tert*-butyl alcohol/CH₂Cl₂ (1:1) at room temperature with HBr catalysis. Although these conditions led to the discovery of N-confused porphyrin, this

isomer was only available in marginal yield (~5%) as a byproduct accompanying the porphyrin (~20%).

To explore the generality of N-confused porphyrin formation, we examined a much broader range of condensation conditions for pyrrole + benzaldehyde using BF₃–etherate and TFA,⁴ the most commonly employed acids in two-step, one-flask syntheses of *meso*-substituted porphyrins (Scheme 1).⁵ We found N-confused tetraphenylporphyrin (NC-TPP) to be a ubiquitous reaction byproduct under virtually any condition providing at least ~10% yield of tetraphenylporphyrin (TPP). NC-TPP yields were generally less than 5%, with 7.5% being the highest yield observed. In addition, changes in the yield of NC-TPP as a function of reaction parameters were found to mirror those of TPP.

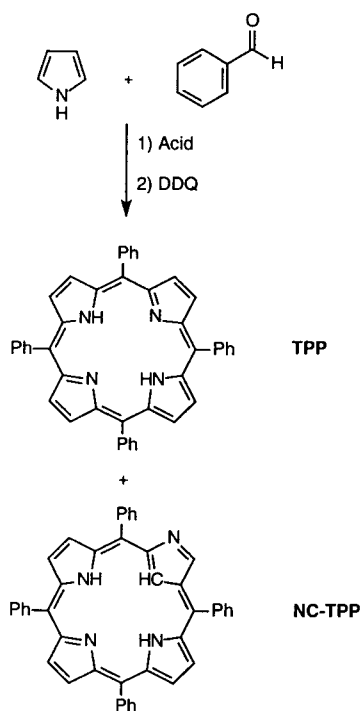
Recently, we examined the effects of a broad range of acids on the products formed in one-flask porphyrin syntheses. Analytical scale reactions (10 mL reaction volume) have been performed with pyrrole and benzaldehyde (reactants) at 10 mM or 100 mM in CH₂Cl₂ at room temperature followed by oxidation with DDQ. Acid concentrations ranging from 0.1 to 1000 mM were examined. The yield of TPP was determined spectrophotometrically and by HPLC, and the yield of NC-TPP was determined by HPLC using established methodology.^{4,5} The full details of this study will

(1) Chmielewski, P. J.; Latos-Grazynski, L.; Rachlewicz, K.; Glowiac, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 779–781.

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(3) (a) Latos-Grazynski, L.; Chmielewski, P. J. *New. J. Chem.* **1997**, *27*, 691–700. (b) Chmielewski, P. J.; Latos-Grazynski, L. *Inorg. Chem.* **1997**, *36*, 840–845. (c) Chmielewski, P. J.; Latos-Grazynski, L.; Glowiac, T. *J. Am. Chem. Soc.* **1996**, *118*, 5690–5701. (d) Chmielewski, P. J.; Latos-Grazynski, L. *J. Chem. Soc., Perkin Trans. 2* **1995**, 503–509. (e) Ishikawa, Y.; Yoshida, I.; Akaiwa, K.; Koguchi, E.; Sasaki, T.; Furuta, H. *Chem. Lett.* **1997**, 453–454. (f) Ariga, K.; Kunitake, T.; Furuta, H. *J. Chem. Soc., Perkin Trans. 2* **1996**, 667–672. (g) Ghosh, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1028–1030.

Scheme 1



be reported elsewhere, but of immediate interest is the finding of reaction conditions providing unusually high yields of NC-TPP.

During the course of examining diverse acid catalysts, we found that methanesulfonic acid (MSA) efficiently produces NC-TPP. This finding was surprising, as lower concentrations of MSA had previously been used to prepare TPP.⁶ The effect of MSA concentration on the yield of NC-TPP was investigated (Figure 1). Reactions of pyrrole and benzaldehyde

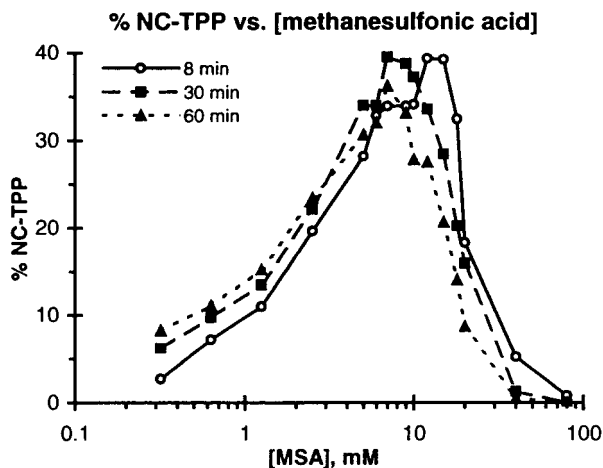


Figure 1. NC-TPP yield as a function of MSA concentration. Reactions were performed using 10 mM reactants in CH_2Cl_2 at room temperature, and yields were determined by HPLC analysis of DDQ-oxidized reaction samples taken at the times indicated.

(10 mM each) were monitored at 8 min, 30 min, and 1 h after addition of acid. The optimal range of MSA was found to be 5–15 mM, providing NC-TPP in yields of close to 40%.

The effects of MSA concentration on yields of TPP and NC-TPP were examined and found to be very different (Figure 2). By changing the MSA concentration, the yields

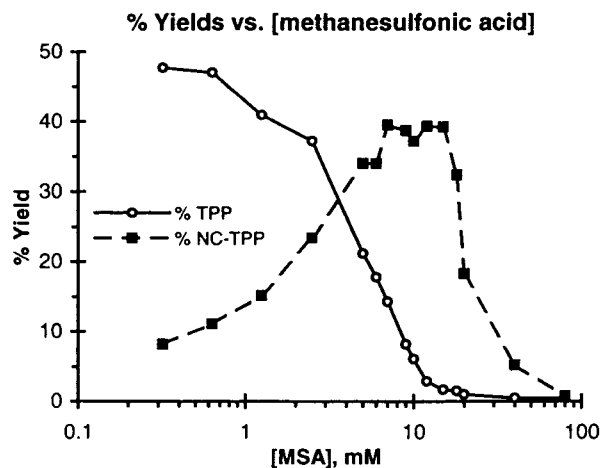


Figure 2. NC-TPP and TPP yields as a function of MSA concentration. Reactions were performed using 10 mM reactants in CH_2Cl_2 at room temperature. Yields from DDQ-oxidized reaction samples were determined by HPLC. The highest yield obtained at 8 min, 30 min, or 1 h is plotted.

of TPP and NC-TPP were inverted. Optimal conditions for TPP (~40%) provided a yield of <10% for NC-TPP, while optimal conditions for NC-TPP (~40%) provided TPP in <10% yield. The maximum yield of TPP was obtained at 30-fold lower MSA concentration than the maximum yield of NC-TPP. These findings are in sharp contrast to the results obtained with BF_3 -etherate and TFA catalysis, where the yields of TPP and NC-TPP responded similarly to changes in acid concentration.⁴

Because the maximal NC-TPP yield was obtained with MSA concentrations higher than required for maximal TPP yield, we examined whether exposure of pyrrole to MSA prior to benzaldehyde addition might further increase the yield of NC-TPP. Pyrrole (10 mM) was treated with MSA (7 mM) for 0, 5, 15, or 30 min prior to benzaldehyde addition. Reactions carried out in this way showed a significant decrease in NC-TPP (to <5%) with increasing time prior to benzaldehyde addition (see Supporting Information). Interestingly, very little decrease in TPP yield was observed. The decreased yield of NC-TPP but not TPP was unexpected and indicates the presence of processes involving pyrrole and MSA that selectively affect the pathway leading

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 (5) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827–836.
 (6) Lindsey, J. S.; MacCrum, K. A.; Tyhonas, J. S.; Chuang, Y. Y. *J. Org. Chem.* **1994**, *59*, 579–587.

to NC-TPP. The reverse experiment with benzaldehyde and MSA revealed no change in yield of NC-TPP or TPP.

One set of conditions leading to the discovery of N-confused porphyrin employed excess pyrrole;¹ thus, we examined the effect of various ratios of pyrrole and benzaldehyde on NC-TPP yield. The ratios examined ranged from a 3-fold excess of benzaldehyde to a 4.5-fold excess of pyrrole (the limiting reactant was 10 mM) with a MSA concentration of 9 mM. The maximum yield of NC-TPP was found to occur at equimolar concentrations pyrrole and benzaldehyde, indicating that excess pyrrole is not required for optimal NC-TPP production.

The yields of TPP and NC-TPP from a reaction of 10 mM reactants and 7 mM MSA were followed as a function of time (Figure 3). The maximum TPP yield (32%) occurred

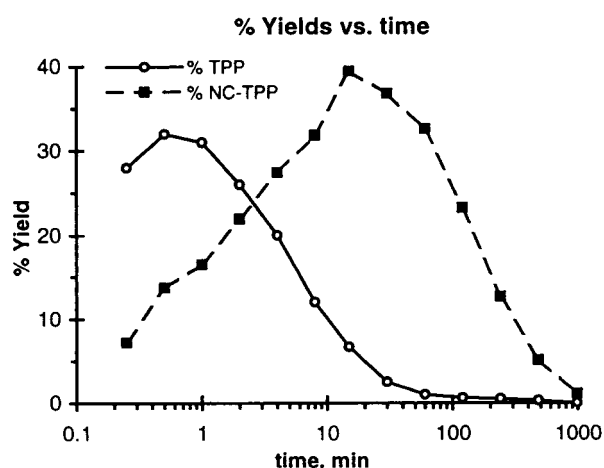


Figure 3. NC-TPP and TPP yields as a function of time (note the log scale). The reaction was performed using 10 mM reactants, 7 mM MSA in CH_2Cl_2 at room temperature. Yields from DDQ-oxidized reaction samples were determined by HPLC.

at 30 s after addition of acid, but the yield was only 10% after 10 min. The maximum NC-TPP yield (39%) occurred 15 min after addition of acid. Again, this difference in rate of reaction leading to TPP and NC-TPP sharply contrasts with observations under BF_3 -etherate and TFA catalysis where the reaction rates are comparable. The difference in yields of TPP and NC-TPP as a function of time under MSA catalysis is of practical utility, as <5% TPP was present at reaction times affording >35% NC-TPP (30 min), simplifying preparative isolation of NC-TPP.

The results of the analytical scale experiments were extended to a 1.5-L preparative scale reaction employing 10 mM reactants and 7 mM MSA. After condensation for 30 min, DDQ was added. HPLC analysis of an aliquot obtained after DDQ oxidation revealed NC-TPP and TPP yields of 37% and 5%, respectively. Filtration of the crude reaction mixture through a pad of basic alumina (CH_2Cl_2) followed by column chromatography on basic alumina (hexanes/ CH_2Cl_2) afforded NC-TPP and TPP in yields of 35% (800 mg) and 6% (140 mg), respectively. The relatively high yield

of NC-TPP and low yield of TPP rendered the overall synthesis and isolation straightforward, readily affording substantial quantities of NC-TPP.

To further refine the preparative scale synthesis to require less solvent, we examined the formation of NC-TPP at higher reaction concentrations (20, 50, and 100 mM). At each concentration, a range of MSA concentrations was examined (2.5–320 mM). For each concentration of reactants, the MSA concentration and time affording the highest yield of NC-TPP have been determined (Table 1). In general, maximum

Table 1. Optimal Conditions for Synthesis of NC-TPP at Different Reactant Concentrations^a

[reactants], mM	[MSA], mM	time, min	% NC-TPP	%TPP
10	7	30	39	5
20	20	8	29	2
50	40	8	20	6
100	50	8	12	12

^a See Supporting Information for complete data.

yields of NC-TPP were found to decline with increasing reactant concentration consistent with previous findings of high concentration porphyrin syntheses.⁶ Nevertheless, the 29% yield of NC-TPP obtained with 20 mM reactants offers a reasonable compromise between yield and solvent requirement for the preparative scale synthesis of NC-TPP.

The efficient synthesis of NC-TPP under MSA catalysis is not only of clear practical value for the preparation of this intriguing porphyrin isomer but this finding also reveals additional mechanistic complexity and richness of chemistry possible in two-step, one-flask porphyrin syntheses. With BF_3 -etherate or TFA catalysis, the formation of NC-TPP in low levels under conditions producing significant quantities of TPP could be explained by the expected low level of β -pyrrolic substitution. The ubiquitous presence of NC-TPP and the similar changes in yield of NC-TPP and TPP as a function of reaction parameters suggested that both share a common reaction pathway. The anomalously high production of NC-TPP under MSA catalysis and the divergence of TPP and NC-TPP yields as a function of MSA concentration or time raise a number of questions. (1) Why do appropriate concentrations of TFA, BF_3 -etherate, and MSA provide good yields of TPP, while only MSA provides good yields of NC-TPP? (2) Why does a change in MSA concentration alone invert the quantities of TPP and NC-TPP produced? (3) How is the course of reaction—rates, equilibrium, porphyrinogen and N-confused porphyrinogen stabilities, reactivity of intermediates, oligomer distribution, etc.—altered with TFA, BF_3 -etherate, or MSA catalysis? (4) Can conditions be found that provide efficient one-flask syntheses of other porphyrinic macrocycles (corrole, sapphyrin, penta-pyrin, etc.)? The resolution of such questions awaits further experimentation.

In summary, we have reported an efficient, one-flask synthesis of NC-TPP utilizing MSA catalysis. The isolated yield of 35% (800 mg) represents a >5-fold improvement

over previously reported conditions. The inversion of TPP and NC-TPP yields obtained with these reaction conditions (making TPP a low-yield byproduct and NC-TPP the dominant product) provides ready access to significant quantities of NC-TPP. This methodology should open the door to the preparation of a wide variety of NC-TPP derivatives, facilitate further studies of metal coordination, organometallic reactivity, and fundamental physical properties, and stimulate continued investigation of methods for one-flask porphyrin syntheses.

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Supporting Information Available: Experimental procedures and additional data of NC-TPP and TPP yields. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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