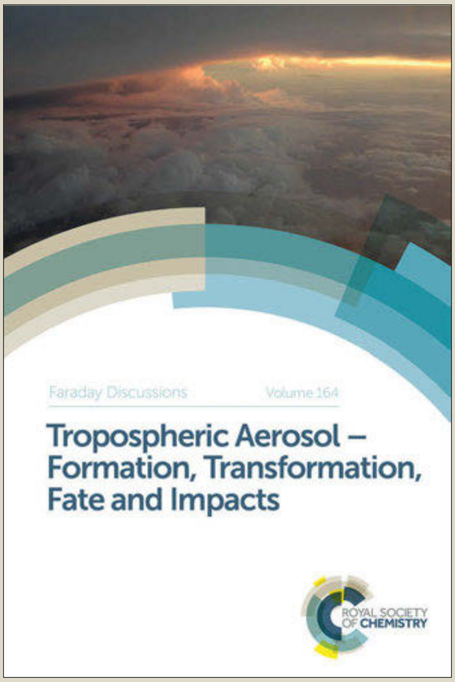
Faraday Discussions

Accepted Manuscript

This manuscript will be presented and discussed at a forthcoming Faraday Discussion meeting. All delegates can contribute to the discussion which will be included in the final volume.

Register now to attend! Full details of all upcoming meetings: http://rsc.li/fd-upcoming-meetings



Faraday Discussions Volume 164

Tropospheric Aerosol – Formation, Transformation, Fate and Impacts

ROYAL SOCIETY OF CHEMISTRY

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/faraday_d

Two-step Mechanochemical Synthesis of Porphyrins

Hannah Shy,[a] Paula Mackin,[a] Andrea S. Orvieto,[a] Deepa Gharbharan,[a] Geneva R. Peterson,[b] Nick Bampos[b] and Tamara D. Hamilton[a]*

DOI: 10.1039/b000000x [DO NOT ALTER/DELETE THIS TEXT]

Porphyrin synthesis under solvent-free conditions represents the "greening" of a traditional synthesis that normally requires large amounts of organic solvent, and has hindered industrial-scale synthesis of this useful class of molecules. We have found that the four-fold acid-catalysed condensation of aldehyde and pyrrole to yield a tetra-substituted porphyrin is possible through mechanochemical techniques, without a solvent present. This represents one of the still-rare examples of carbon-carbon bond formation by mechanochemistry. Specifically, upon grinding equimolar amounts of pyrrole and benzaldehyde in presence of an acid catalyst, cyclization takes place to give reduced porphyrin precursors (reversible), which upon oxidation form tetraphenylporphyrin (TPP). The approach has been found suitable for synthesis of a variety of *meso*-tetrasubstituted porphyrins. Oxidation can occur either by using an oxidizing agent in solution, to give yields comparable to those published for traditional methods of porphyrin synthesis, or through mechanochemical means resulting in a two-step mechanochemical synthesis to give slightly lower yields that are still being optimized. We are also working on "green" methods of porphyrin isolation, including entrainment sublimation, which would hopefully further reduce the need for large amounts of organic solvent. These results hold promise for the development of mechanochemical synthetic protocols for porphyrins and related classes of compounds.

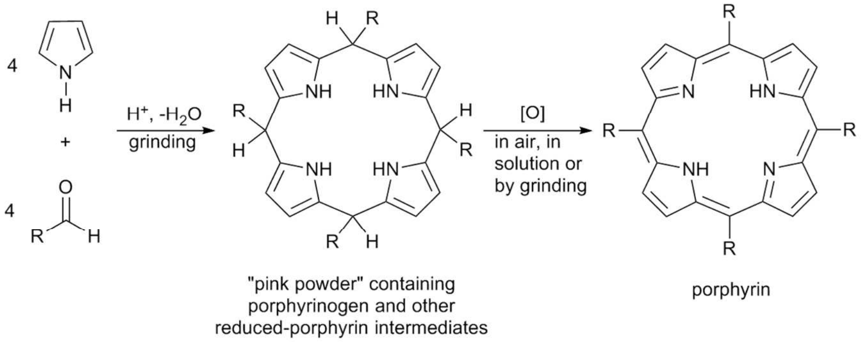
Introduction

Porphyrins and related structures play many roles in systems throughout nature, including light harvesting and metal transport. Of particular synthetic interest are the *meso*-tetrasubstituted porphyrins, since they can serve as a platform for a variety of important applications due to shape, symmetry, and possibility for substitution on the periphery which allows for tailoring of optical, electronic, and biochemical properties.[1] Despite consistent high performance of porphyrin systems in applications like catalysis, industrial use of these species is barred because of the impracticality of scale-up for their syntheses. Established synthetic approaches to *meso*-tetrasubstituted porphyrins involve large amounts of corrosive or toxic organic solvents or high temperature reaction conditions, often followed by extensive chromatographic purification.[2-6]

Mechanochemistry, where chemical reactions are promoted by grinding reagents together either using a mortar and pestle or automated ball mill, is an often-overlooked approach to molecular synthesis that is currently gaining ground due to the relative simplicity of reaction conditions, potential for elimination of solvent, and possibility of generating products not attainable by other methods.[7] In addition, there are growing numbers of examples proving the effectiveness of mechanochemistry for the synthesis of several types of products including co-crystals and metal-organic frameworks, but the extent of applicability of the approach for organic reactions, especially carbon-carbon bond-forming reactions is still emerging.[8] Recent reports have employed sequential mechanochemical steps to reach selected targets.[9]

The first synthesis of *meso*-tetraphenylporphyrin (TPP) was a sealed-tube anaerobic condensation in pyridine at 200°C, resulting in 5% yield.[2] *meso*-Tetrasubstituted porphyrins are now most commonly synthesized in solution using one of two methods. The Adler-Longo reaction produces a porphyrin in one step under aerobic conditions in refluxing acetic or propionic acid solvent (10-30% yield).[3] The Lindsey synthesis[4] requires inert atmosphere and relatively high dilution in chlorinated solvents, and separates the process into two steps – first, equilibrium is established between the starting materials and the porphyrinogen macrocycle (six-electron, six hydrogen reduced porphyrin). This is followed by addition of a gentle oxidizer such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) which, after stirring for several hours, generates the porphyrin (10-60% yield). The latter approach has led to higher yields than the former for several *meso*-tetrasubstituted porphyrins from aldehydes that are sensitive to the harsh conditions of the Adler-Longo synthesis, and also avoids purification problems caused by tar-like by-products for those porphyrins that do not crystallize at the end of the reaction. Two solventless syntheses of *meso*-tetrasubstitued porphyrins have been reported: one involves mixing the two reagents in the gas phase at >200°C (10-23% yield)[5] the other is a microwave synthesis on silica gel support (1-10% yield).[6]

Here we present a mechanochemical synthesis of TPP (Scheme 1) involving the grinding of benzaldehyde and pyrrole in the presence of an acid catalyst to give a solid pink powder. This powder can then be oxidized either in air, in chloroform with an organic oxidizer, or in a second grinding step with an oxidizing agent to produce TPP as the product. We have also expanded the approach to include a series of *meso*-tetrasubstituted porphyrins. The use of mechanochemistry to bring about acid-catalysed condensation between aldehydes and pyrrole, followed by oxidation of the intermediates to produce the porphyrin enables elimination of both solvent and high temperatures from the synthesis of these important compounds, and represents a significant reduction in environmental impact.



Scheme 1 Two-step synthesis of porphyrins involving mechanochemistry. For TPP, R = Ph.

Experimental

Materials and methods

All chemicals used were purchased from Sigma Aldrich and used without further purification, unless otherwise noted. Benzaldehyde and pyrrole were purified by distillation once per week, or whenever discoloration appeared. Automated sample grinding was done using a Retsch Mixer Mill MM200. Electronic spectra were recorded on a Perkin Elmer Lambda 850 UV-Vis spectrophotometer, measured from 200-800 nm at 1nm intervals. The samples were placed in quartz cuvettes with 1-cm path length. ^{1}H NMR spectra were recorded on a Varian 300 MHz nuclear magnetic resonance spectrometer. The MALDI-TOF mass spectrum was collected on an ABI 4700 Proteomics Analyser.

Condensation by manual grinding

Manual grinding was done using an agate mortar and pestle. Pyrrole (0.259g, 3.73mmol) and toluenesulfonic acid (0.026g, 0.151mmol) were added to the mortar and ground together for approximately one minute. Benzaldehyde (0.380g, 3.73mmol) was added and the mixture was ground until a dry pink solid formed (~6 minutes).

Synthesis of *meso*-tetrasubstituted porphyrins - oxidation in chloroform

A 1:1 molar ratio of pyrrole (0.259g, 3.73mmol) and an aldehyde were combined with toluenesulfonic acid (0.026g, 0.151mmol) in a stainless steel grinding jar (10-mL volume) along with two stainless steel balls (5-mm diameter). The mixture was ground in a Retsch MM200 mill at a frequency of 25 Hz. Typical grinding time was 20 minutes until formation of a dry, pink solid. The pink solid was then dissolved in chloroform (*ca*. 50 mL). DDQ (2.54g, 11.19mmol) was added and the mixture was stirred for 2 hours. The mixture was then passed through a 1-cm plug of neutral alumina. Triethylamine (2-3 drops) was added to the resulting filtrate, which was then loaded onto a silica gel column with 9:1 ethylacetate/hexane as the mobile phase. Fractions were collected and assessed using thin-layer chromatography and visible spectroscopy. Those fractions containing porphyrin were combined and solvent was removed using a rotary evaporator. Tetraphenylporphyrin was obtained as a purple powder in 28% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.84 (8H, s), 8.21 (8H, t), 7.76 (12H, d), 7.26 (chloroform), 1.6-0 (solvent residue), -2.79 (2H, s). UV-VIS ($CHCl_3$): λ = 417 (Soret band); λ = 516, 549, 591, 645 (Q-bands).

Mechanochemical oxidation

A pink solid was obtained through either manual or automated grinding of equimolar amounts of benzaldehyde and pyrrole in the presence of an acid, as described above. An oxidizer was then added in a 1:1.5 benzaldehyde:oxidizer molar ratio and the mixture was ground in a Retsch MM200 mill at a frequency of 25 Hz for varying times. In some experiments, a grinding or drying agent was also added. Each resulting dark purple solid was tested for the presence of TPP using visible spectroscopy.

Spectroscopic sample preparation to determine yields from mechanochemical oxidation

A stock solution of pure TPP was prepared by dissolving 30.0 mg TPP in 10.00 mL chloroform. This solution was serially diluted until a solution of concentration 3.00 x 10^{-6} g/mL was obtained. The diluted solution had a measured absorbance of 1.056 (λ = 417 nm). Solutions were then prepared for each oxidized sample in the same way, and the absorbance at 417 nm was measured and compared to that of the pure TPP solution, in order to obtain an approximate yield.

Results and Discussion

Condensation of benzaldehyde and pyrrole

Initial studies promptly showed that simple mortar-and-pestle grinding of two colourless liquids, benzaldehyde and pyrrole, in the presence of an acid catalyst yields first a gummy pink substance which, upon grinding for approximately six minutes becomes a uniform, dry, pink powder. No Soret band (~417 nm), which would be characteristic of TPP, is visible in the electronic spectrum of the freshly-ground powder (Figure 1), rather a broad peak at 500 nm is present. After exposure to air for two weeks however, a black powder is obtained. Electronic spectroscopy of this powder reveals a small Soret band at 417 nm, indicating the presence of TPP (3% yield of porphyrin in the mixture after 15 days). Thin-layer chromatography (TLC; 9:1 ethylacetate:hexanes) and MALDI-TOF mass spectrometry (m/z = 615, $[M + H]^+$) also confirm the presence of TPP in the black powder.

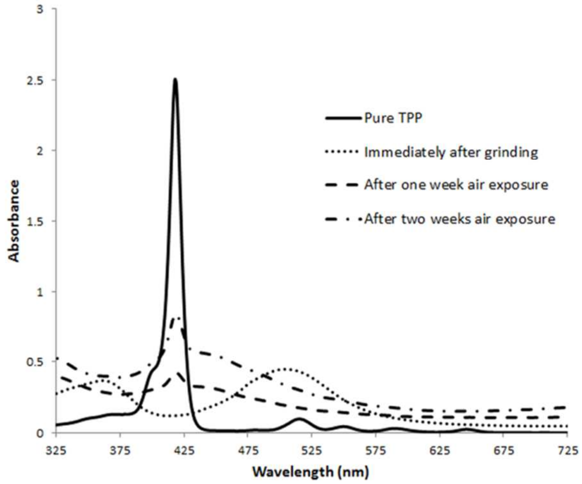


Fig. 1 Electronic spectrum of pure TPP ($CHCl_3$), freshly-ground reaction mixture, and the reaction mixture after having been exposed to air for one, and then two weeks. Pure TPP is shown at one-tenth the concentration of the other samples.

The two broad peaks (~500 nm and ~360 nm) in the UV-Vis spectrum of the freshly-ground pink powder must correspond to a mixture of reduced-porphyrin intermediates (Figure 2), which are able to be oxidised in air to form the porphyrin, since their absorbance decreases over time. Possibilities include dihydroporphyrins (phlorins or chlorins), tetrahydroporphyrins (bacteriochlorin, chlorin-phlorin, or porphomethene) and hexahydroporphyrin (porphyrinogen). All except the porphyrinogen have absorbance in the visible region. Those involving methine-bridge saturation (phlorin and porphomethene) are known to be the least stable to air oxidation.[10] Further studies are required to characterize these products of the mechanochemical condensation, which would help give insight into the mechanism of this process.

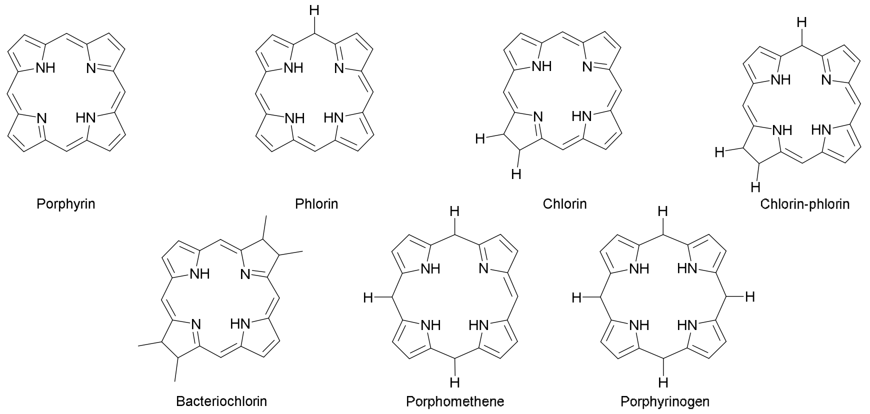


Fig. 2 Some reduced forms of porphyrins.

Mechanochemical synthesis of several *meso*-tetrasubstituted porphyrins

Since the cyclocondensation reaction between an aldehyde and pyrrole is reversible[4], it was hypothesized that letting the ground pink solid stand for several days while undergoing oxidation in air was allowing the cyclized product to revert to starting material before being oxidized to the porphyrin, resulting in low yields. Therefore, in order to evaluate the success of the mechanochemical cyclocondensation reaction, the pink solid was oxidized immediately by stirring for two hours in chloroform with DDQ, followed by column chromatography to isolate the porphyrin and determine the yield. Also, in order to have better control of the mechanochemical reaction conditions, the process was automated using a Retsch MM200 mixer mill. Coupled with these modifications, the scope of the synthesis was expanded to include a series of substituted benzaldehydes. Yields from these reactions are reported in Table 1. Addition of auxiliary grinding agents during the milling process such as magnesium sulfate (to remove water), silica or sodium chloride (to alleviate “stickyness”) did not lead to an increase in yield.

The results show that mechanochemical condensation between an aldehyde and pyrrole to give reduced porphyrin precursors is successful for several aromatic aldehydes, producing yields similar to those reported for solution synthesis. We have also observed Soret bands resulting from reactions of several alkyl adehydes, namely butanal, pentanal, octanal, and trimethyl acetaldehyde. Characterization and determination of yield for these presumable *meso*-alkylsubstituted porphyrin products is ongoing, although preliminary yields are in the 10-20% range.

Table 1 Results from mechanochemical synthesis of tetrasubstituted porphyrins, with oxidation in solution using DDQ.

RCHO; R =	Milling time (min)	Observations	Soret Band (nm)	Yield (%)[a]
Ph	20	Pink powder	417	27.9
2-ClC_6H_4	20	Pink sticky solid	418	32.7
3-ClC_6H_4	30	Pink powder	419	21.9
4-ClC_6H_4	30	Pink sticky solid	419	20.0
2-FC_6H_4	30	Pink powder	416	28.1
3-FC_6H_4	20	Pink powder	417	25.0
4-FC_6H_4	30	Pink powder	418	9.7
α-naphthyl	30	Brown sticky solid	424	2.7
β-naphthyl	40	Brown sticky solid	425	31.3

[a] Yield is based on the average from three trials of dry weight of the fractions displaying a Soret band in the UV-Vis spectrum, with no other major absorbances, after column chromatography.

Mechanochemical Oxidation

Having established the efficacy of a mechanochemical approach for the first step of porphyrin synthesis (Scheme 1) namely, condensation between pyrrole and an aldehyde, we set out to find a way of achieving the second step of the synthesis, oxidation, using mechanochemistry. TPP was used as a model compound for these studies. Various oxidizing agents were chosen, some based on demonstrated success in previous oxidative aromatization reactions[11], and potassium peroxymonosulfate (Oxone; $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) for its proven success in mechanochemical oxidations[12]. Milling time for the oxidation step was varied from twenty minutes to eight hours. In some cases, a grinding agent was added to the reaction to aid with the grinding process by reducing stickiness, increasing friction, and/or removing water from the reaction. We tested three grinding agents: sodium chloride, silica and magnesium sulfate, with the hopes they would help drive the reaction forward by removing the water produced from the reaction between benzaldehyde and pyrrole and alleviate the "stickiness" of the reaction mixture (facilitating grinding). After initial milling of benzaldehyde, pyrrole, and toluenesulfonic acid to produce a powder as described above, the grinding jar was opened and an oxidizing agent (1.5 molar equivalents based on benzaldehyde) was added. The mixture was then further milled. Presence or absence of TPP was confirmed by monitoring absorbance at 417 nm in the UV-Vis spectrum. In order to obtain an approximate yield of porphyrin, a sample of the reaction mixture was weighed and serial dilution was performed in chloroform to obtain a solution with concentration 3.0×10^{-6} g/mL. The absorbance at 417 nm was compared to the absorbance at 417 nm for a pure TPP solution of the same concentration. Results of selected experiments are presented in Table 2.

Table 2 Results from two-step mechanochemical synthesis of TPP (condensation followed by oxidation).

Oxidizing agent	Grinding agent	Milling time (min) for condensation/oxidation	Yield (%)[a]
None	None	20/20	0[b]
DDQ	None	20/20	0[b]
Iodine	None	20/20	1.6
Nitric acid	None	20/20	11.5
Sodium perborate	None	20/20	8.3
Sodium ethoxide	None	20/20	8.2
Sodium ethoxide	None	20/480	6.7
Sodium ethoxide	Silica	20/20	5.2
Sodium ethoxide	Sodium chloride	20/20	0[b]
Sodium ethoxide	Magnesium sulphate	20/20	9.3
Oxone	None	20/20	0[b]
Oxone	None	20/480	8.1
Oxone	Silica	20/20	5.3
Oxone	Sodium chloride	20/20	4.7
Oxone	Magnesium sulphate	20/20	0[b]

[a] Yields determined by absorbance of the reaction mixture at 417 nm, in comparison to pure TPP at the same concentration.

[b] No Soret band detected

Although yields from these experiments are consistently lower than yields of TPP from oxidation in solution using DDQ, milling with some oxidizing agents produces the porphyrin in a shorter time than simple exposure to air. The control experiment with no oxidizing agent added yielded no Soret band after 20 minutes post-condensation milling. Milling with DDQ also produced no result. Molecular iodine produced a low yield of TPP. Nitric acid, while producing the highest yield, is difficult to work with and, and one might expect, caused pitting on the inside of the grinding jars. Sodium perborate, sodium ethoxide, and Oxone were moderately successful, producing yields of just under 10% with the right conditions. Lengthening of grinding times produced different results for sodium ethoxide and oxone – for the former it destroyed the yield completely while for the latter no TPP was observed after 20 minutes but the yield increased with time, reaching a maximum of 8.1%. The two oxidizing agents also behaved differently in the presence of various grinding agents: silica and sodium chloride caused the yield to decrease for sodium ethoxide but increase for Oxone upon 20-minute milling while addition of magnesium sulphate resulted in the best yield for the sodium ethoxide experiments, but did not help in the case of Oxone.

Changes to longer grinding times for the condensation step did not result in significantly different yields of TPP. Manual grinding was also employed for these experiments and consistently resulted in slightly higher yields (1-2% increase) than automated grinding. During automated grinding, the balls may become stuck in the reaction mixture at various times, lowering the efficacy. This problem can be addressed by using larger, heavier grinding balls.

Other methods of oxidation were also tested. Since benzaldehyde itself can be an oxidising agent, synthesis of TPP was attempted in two ways. First, after obtaining the pink solid from the condensation reaction as described above, an additional three molar equivalents of benzaldehyde were introduced as the oxidizing agent and the mixture was milled for a further 20 minutes. Second, instead of beginning with a 1:1 molar ratio of benzaldehyde to pyrrole, a 10:1 molar ratio was used, and the reaction was milled for 60 minutes, while checking for a Soret band at 10-minute intervals to see if TPP could be isolated in a one-step reaction. Neither of these methods resulted in the production of TPP, as evidenced by the absence of absorbance at 417 nm in the electronic spectra. Oxidation of the pink solid by exposure to nitric acid vapours over several hours was also attempted, with no positive results.

Purification by sublimation

While column chromatography has been the method of choice for separating porphyrins from the several by-products that can form during the course of porphyrin synthesis, we have found success by using entrainment sublimation,[13] where a carrier gas such as nitrogen is employed to transport sample vapours away from the heated impure material, so that they may be deposited on a cooler surface. We have isolated pure TPP (as confirmed qualitatively by electronic spectroscopy) from an oxidised reaction mixture using this method, although it was done on a scale too small to allow determination of isolated yield. Experiments are underway to scale up this process using a tube furnace.

Green chemistry impacts

As environmental awareness increases both in industry and academia, incorporation of the 12 Principles of Green Chemistry[14] becomes more and more attractive. Through the elimination of solvent, simplification of technical setup, and reduction of reaction time, the field of mechanochemistry has much to contribute here, however it can sometimes be difficult to determine whether an alternative method is in fact “greener” than the established approach to synthesis. Is it worth it to employ greener methods for a synthesis, when the yield may be lowered as a result? There are several metrics that have been proposed to evaluate how “green” a reaction is in order to compare the “greenness” of various synthetic methodologies. Here we will use two such metrics, E factor[15] and EcoScale[16], to compare three synthetic methodologies to produce TPP: 1) the Lindsey synthesis, 2) mechanochemical condensation followed by oxidation in solution and purification by column chromatography, and 3) two-step mechanochemical synthesis and purification by sublimation. The results are shown in Table 3:

Table 3 Comparison of synthetic methodologies for TPP

	Lindsey synthesis	Mechanochemical condensation step	Two-step Mechanochemical
E factor	2784	1682	19.7
EcoScale[a]	-46	-33.5	6.64

[a] Tables showing the penalty points for each category of the EcoScale calculation can be found in Electronic Supplementary Information.

The E factor is a simple measurement of waste produced for the amount of product obtained:

$$\mathrm{E} = \frac{\text{total waste}}{\text{total product}}$$

Waste includes solvent, by-products, and consumables such as silica or alumina. We can see from Table 3 that elimination of solvent from just one step of the TPP synthesis results in a great reduction in E factor, while complete elimination of solvent results in a huge reduction, even if yield is lowered.

The ideal reaction has an EcoScale value of 100.[16] Starting there, penalty points are deducted based on the requirements of the synthetic procedure in the categories of price of reaction components, safety, technical setup, temperature, time, workup and purification. Percent yield is also taken heavily into consideration; penalty points for the yield are (100-yield)/2. A large, positive EcoScale means a “greener” synthesis. We can see from Table 3 that of the three synthetic methodologies compared, two-step mechanochemical synthesis has the only positive EcoScale score, in spite of the low yield. This can be attributed to both the elimination of solvent and the large amount of DDQ needed for the oxidation, and the elimination of column chromatography as a purification method.

Conclusions

Our results show that the synthetically-important *meso*-tetrasubstitued porphyrins can be synthesized without a solvent, through a two-step mechanochemical process: condensation followed by oxidation. Mechanochemical condensation followed by oxidation in solution leads to yields for a series of *meso*-tetrasubstituted porphyrins that are comparable to those obtained from a Lindsey synthesis. Switching to a mechanochemical oxidation lowers the yield, but elimination of large quantities of hazardous solvents from porphyrin synthesis has important implications for the utilization of porphyrin systems in industrial-scale applications. Two green chemistry metrics, the E factor and the EcoScale show that, even with a lower yield, the mechanochemical process is more efficient from an environmental perspective. Additionally, this is one of the few examples to date of carbon-carbon bond formation *via* mechanochemistry, although examples are growing.[8] Mechanistic studies of this reaction will be important in order to understand reaction intermediates and pathways. Studies of reactions of pyrrole with a mixture of aldehydes are underway, and should shed some light on this.

Acknowledgements

We thank Dr. Tomislav Friščić and Dr. William Jones for use of research facilities. This research was supported by an award from the Research Corporation for Science Advancement Cottrell College Science Award No. 19762 and NIH NIGMS R25 GM059244 to Barry University.

References

[a] *Department of Physical Sciences, Barry University, 11300 NE 2nd Ave. Miami Shores, FL 33161USA. Fax: 305-899-3479; Tel: 305-899-3431; E-mail: thamilton@mail.barry.edu*
[b] *University Chemical Laboratory, University of Cambridge, Lensfield Rd. Cambridge, CB2 1EW United Kingdom. Fax: 44 1223 336017; Tel: 44 01223 336300; E-mail: nb10013@cam.ac.uk*

† Electronic Supplementary Information (ESI) available: ^{1}H NMR spectrum of TPP. MALDI-TOF mass spectrum of TPP. EcoScale calculations tables. See DOI: 10.1039/b000000x/

1 C. M. Drain, A. Varotto and Radivojevic, *Chem. Rev.*2009, **109** 1630-1658; C. J. Medforth, Z. Wang, K. E. Martin, Y. Song, J. L. Jacobsen and J. A. Shelnutt, *Chem. Comm.*, 2009, 7261-

7277; I. Goldberg, *CrystEngComm*, 2008, **6**, 637-645; R. L. Halterman, S.-T. Jan, A. H. Abdulwali and D. J. Standlee, *Tetrahedron*, 1997, **53**, 11277-11296.

2 P. Rothemund, *J. Am. Chem. Soc.* 1935, **57**, 2012-2011; P. Rothemund, *J. Am. Chem. Soc.* 1939*,* **61***,* 2912-2915; R. G. Little, *J. Heterocyc. Chem.*, 1981, **18**, 833-834; G. M. Badger, R. A. Jones and R. L. Laslett, *Aust. J. Chem.* 1964, **17**, 1028-1035.

3 A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour and L. Korsakoff, *J. Org. Chem.,* 1967*,* **32**, 476; A. D. Adler, L. Sklar, F. R. Longo, J. D. Finarelli and M. G. Finarelli, *J. Heterocyc. Chem.* 1968, **5**, 669-678;G. H. Barnett, M. F. Hudson and K. M. Smith, *J. Chem. Soc. Perkin Trans. I*, 1975, 1401-1403.

4 J. S. Lindsey, I. C. Schreiman, H. C. Hsu, P. C. Kearney and A. M. Marguerattaz, *J. Org. Chem.*, 1987, **52**, 827-836; J. S. Lindsey, K. A. MacCrum, J. S. Tyhonas and Y.-Y. Chuang, *J. Org. Chem.*, 1994, **59**, 579-587.

5 C. M. Drain and X. Gong, *Chem. Comm.* 1997, 2117-2118.

6 A. Petit, A Loupy, P. Maillard and M. Momenteau, *Syth. Commun.,* 1992, **22**, 1137-1142.

7 S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.* 2012, **41**, 413-447.

8 G. Kaupp, M. R. Naimi-Jamal and J. Schmeyers, *Tetrahedron*, 2003, **59**, 3753; E. M. C. Gerard, H. Sahin, A. Encinas and S. Bräse, *Synlett*, 2008, 2702-2704; J. Mack and M. Shumba, *Green Chem.* 2007, **9**, 328-330; V. P. Balema, J. W. Wiench, M. Pruski and V. K. Pecharsky, *J. Am. Chem. Soc.* 2002, **124**, 6244-6245; P.-N. Chen, C.-C. Lai and S.-H. Chiu, Org. Lett., 2011, 13, 4660.

9. J. Bonnamour, T.-X. Métro, J. Martinez and F. Lamatay, *Green Chem.*, 2013, **15**, 1116-1120; D. Tan, V. Štrukil; C. Mottillo and T. Friščić *Chem. Commun.*, 2014 Advance Article **DOI:** 10.1039/C3CC47905F

10 G. Peychal-Heiling and G. S. Wilson, *Anal. Chem.*, 1971, **43**, 550-556; D. Dolphin, *J. Heterocyc.Chem.* 1970, **7**, 275-283.

11 S. G. Hegde, A. M. Kassim and A. I. Ingrum, *Tetrahedron Lett.* 1995, **36**, 8395-8398; M. J. Mphalele, *Molecules*, 2009, **14**, 5308-5322.

12 I. Huskić, I Halasz, T. Friščić and H. Vančik, *Green Chem.* 2012, **14**, 1597-1600; R. Thorwirth, F. Bernhardt, A. Stolle, B. Ondruschka and J. Asghari, *Chem.*–*Eur. J.*, 2010, **16**, 13236-13242; G. Cravotto, D. Garella, D. Carnaroglio, E. C. Gaudino and O. Rosai, *Chem. Commun.,* 2012*,* **48**, 11632-11634.

13 H. J. Wagner, R. O. Loutfy and C.-K. Hsiao, *J. Mater. Sci.* 1982, **17**, 2781-2791; P. D. Sattsangi *J. Chem. Ed.*, 1996, **73**, A3.

14 P. T. Anastas and J. C. Warner, in *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998, p.30.

15 R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273-1283.

16 K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**:3. DOI:10.1186/1860-5397-2-3