

# ChemComm

Accepted Manuscript



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.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

**Size and ability do matter!****Influence of acidity and pore size on the synthesis of hindered halogenated *meso*-phenyl porphyrins catalysed by porous solid oxides**Mónica Silva,<sup>a</sup> Auguste Fernandes,<sup>b</sup> Suse S. Bebiano,<sup>b</sup> Mário J. F. Calvete,<sup>a\*</sup> M. Filipa Ribeiro,<sup>b</sup> Hugh D. Burrows<sup>a</sup> and Mariette M. Pereira<sup>a\*</sup>

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

**Abstract** The rationalisation of the influence of acidity and pore size of several solid oxides in order to selectively act as support for preparation of encapsulated porphyrin hybrid materials or as catalyst for synthesis of porphyrins in solution is here discussed. Encapsulated porphyrin yields are dependent on both the acidity and the material pore size, being Al-MCM-41 the best fitting solid, with Lewis acidity of 120  $\mu\text{mol Py/g}$  and pore size 30 Å. On the other hand, when the goal is the synthesis of hindered mesoarylporphyrins in solution, the best solid porous catalyst is NaY, with Lewis acidity of 510  $\mu\text{mol Py/g}$  and pore size 14 Å. This method provides an appealing efficient, reusable and scalable catalyst alternative for one-pot synthesis of meso-arylporphyrins in high yields.

Porphyrins are ubiquitous in nature, and have even been considered the crucial elements for the continuity of life on our planet.<sup>1</sup> These intriguing molecules have attracted the allure of chemists since the pioneering work of Fischer on isolation of natural porphyrins.<sup>2</sup> The limited number of natural porphyrins compared with their multitude of applications (medicine, catalysis, materials, energy, environment, etc) has stimulated the development of new synthetic methodologies for both the natural type  $\beta$ -substituted porphyrins and non-natural *meso*-substituted ones. Since the preparation of beta-substituted porphyrins requires many steps, the most useful compounds for large scale applications are undoubtedly the *meso*-substituted ones. Following from the ground-breaking work of Rothemund in 1935,<sup>3</sup> two main routes to the synthesis of *meso*-substituted porphyrins have been followed: i) one-pot synthesis involving acid catalysed condensation/cyclisation of pyrrol with the desired aldehydes into the porphyrinogen followed by direct oxidation into the porphyrin, either by air (Adler-Longo method)<sup>4</sup> or nitrobenzene<sup>5</sup>; ii) two step synthesis, involving acid catalysed condensation/cyclisation into porphyrinogen, followed by oxidation with high potential quinones, in a separate step.<sup>6</sup> Despite the higher yields obtained by the latter approach, the high dilutions (~0.01 M) and expensive oxidants required hamper the use of this methodology in large scale implementation. Thus, for both industry and fundamental studies, the one-pot approach to porphyrin synthesis is normally the method of choice (~0.1 M),

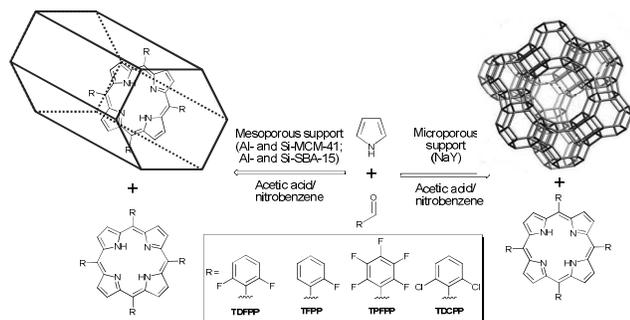
with the nitrobenzene route being that most used for obtaining pure crystals of *meso*-2,6-disubstituted phenyl halogenated porphyrins, directly from reaction mixture (negligible chlorine contamination). Since *meso*-(2,6-difluorophenyl)porphyrin and *meso*-(2,6-dichlorophenyl)porphyrin show extraordinary properties, for instance as precursor for near infrared sensitizers for photodynamic therapy (PDT)<sup>7</sup> and catalytic oxidations,<sup>8</sup> there is still the need for alternative synthetic methodologies.

Solid catalysts show considerable potential in this area. It is well established that the  $\text{pK}_a$  and type of acid (organic<sup>3-6</sup> or solid<sup>9</sup>-Lewis or Brønsted) are determining factors for efficient pyrrole and aldehyde condensation. Additionally, there are also examples of the use of solid acids to promote ship-in-a-bottle porphyrin synthesis and of the use of these porous materials in photocatalysis.<sup>10-12</sup> However, quantitative data is lacking, and, to the best of our knowledge, no attempts have been made to correlate overall meso-arylporphyrin yields with parameters such as pore size/acidity.

In this communication, we establish the correlation between influence of acidity and pore size of several solid oxides and the yields of encapsulated porphyrin hybrid materials or hindered *meso*-arylporphyrins prepared from one-pot synthesis. In a typical experiment, equimolar amounts of pyrrole and 2,6-difluorobenzaldehyde (model compound) were mixed in glacial acetic acid and nitrobenzene (7:5) at 130 °C for *ca.* 2 hours, in 0.1 molar concentration, using selected porous material as catalysts (NaY, Si-MCM-41, Al-MCM-41, Si-SBA-15 and Al-SBA-15) (Scheme 1). Isolated yields of *meso*-tetra-2,6-difluorophenylporphyrin (TDFPP) in both solution and encapsulated are presented in Table 1. Remarkably, we found that isolated product yields are strongly dependent on: i) presence of aluminium in solid material (acidity); ii) material pore size. The adsorption of pyridine (Py) followed by infrared spectroscopy (see ESI) was used to correlate the isolated porphyrin yield with the acidity of the porous materials (essentially Lewis acid sites), and the results are presented on Table 1. A broad range of acidity values was obtained from 510  $\mu\text{mol Py/g}$  for NaY, to 0  $\mu\text{mol Py/g}$  for both Si-MCM-41 and Si-SBA-15.

Additionally, we determined the quantity of encapsulated TDFPP using thermogravimetry–differential scanning calorimetry (TG-

DSC), where samples were heated from 25-800 °C (heating rate 10 °C/min) and the weight losses recorded. The values for yields of encapsulated porphyrin were then calculated based on the amount of organic material decomposed (Table 1 and ESI).



Scheme 1

Table 1 Parameters of the different catalytic supports and porphyrin yields.

Support	Pore size (Å)	Lewis acidity ( $\mu\text{mol Py/g}$ )	Yield TDFPP (%)		Yield TFPP (%)	Yield TPFPF (%)	Yield TDCPP (%)	
			In solution <sup>b</sup>	Encapsulated <sup>c</sup>	In solution <sup>b</sup>	In solution <sup>b</sup>	In solution <sup>b</sup>	
1	NaY	14 (7.4) <sup>a</sup>	510	23±2.0	~0	30±2.0	17±1.0	6±0.7
2	Al-MCM-41	30	120	5.2±1.0	54	--	--	--
3	Si-MCM-41	30	0	1.8±0.4	29	--	--	--
4	Al-SBA-15	80	105	3.6±0.4	46	--	--	--
5	Si-SBA-15	80	0	1.0±0.3	17	--	--	--
6	nitrobenzene method	--	--	9 <sup>13</sup>	18 <sup>14</sup>	8 <sup>15</sup>	3 <sup>14</sup>	--

<sup>a</sup>Window opening; <sup>b</sup>Calculated based on the initial amount (mmol) of pyrrole used and the obtained amount (mmol) of purified porphyrin. (each experiment was repeated 5 times); <sup>c</sup>Calculated based on the amount of organic material decomposed between 250 and 800°C, as determined by thermogravimetric analysis (see ESI) and initial amount of pyrrole used.

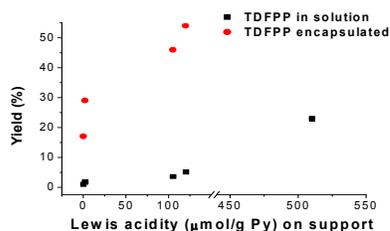


Fig. 1 TDFPP yields against support Lewis acidity.

The diffuse reflectance (DRS)-UV-vis and luminescence spectra of all the solids were also recorded, and selected results for TDFPP-Al-MCM-41 and TDFPP-NaY are presented in Fig. 2a and 2b, respectively.<sup>16</sup>

A significant effect of the Lewis acidity of the solid oxides on porphyrin yield isolated from the solution was observed, with NaY (510  $\mu\text{mol Py/g}$ ) being the best solid porous oxide (entry 1, Table 1 and Fig. 1). Moreover, we found that encapsulated porphyrin yields were dependent on both the Lewis acidity and also the material pore size (Table 1 and Fig 1) where the best yields were obtained with Al-MCM-41 (higher Lewis acidity among mesoporous solids- 120  $\mu\text{mol Py/g}$ ), which has the best porphyrin fitting pore size (30 Å). This could be probably due to the fact that a material with larger pores (SBA-15 – 80 Å) might allow outside porphyrin migration through the channels, while a smaller pore material (MCM-41 – 30 Å) would better limit porphyrin diffusion within the channels.

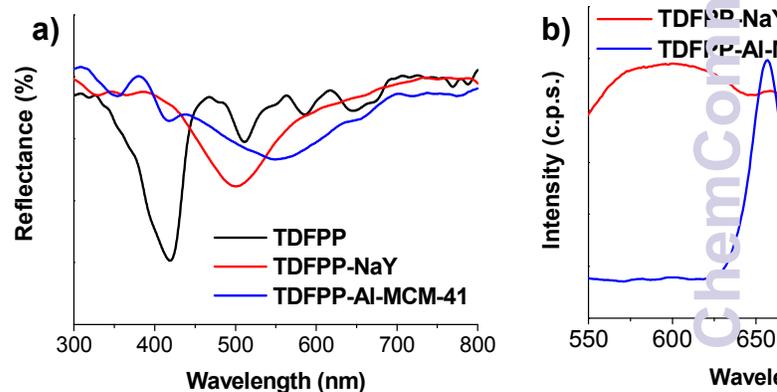


Fig. 2 DRS-UV-vis reflectance spectra (a) and solid-state emission spectra ( $\lambda_{\text{exc}}=415$  nm) (b) of TDFPP (inset - black line), TDFPP-NaY and TDFPP-Al-MCM-41.

The DRS-UV-vis absorption spectrum of TDFPP-Al-MCM-41 shows the characteristic Soret band at  $\lambda_{\text{max}}=427$  nm together with other bands at  $\lambda_{\text{max}}=550$  and 659 nm, and show a 7 nm red shift when compared with TDFPP in solid state (Fig. 2a). Although this may partially be affected by the refractive index of the porous host, this is probably mainly due to the fact that the

porphyrins are inside the mesoporous structure and subject to some constraints/interactions with support cavity. This may lead to some distortion of the macrocycle compared with its behaviour in solution, favouring a lower energy configuration of the arylporphyrins.<sup>10a</sup> In contrast, DRS-UV-Vis absorption spectrum of TDFPP-NaY did not show either the characteristic Soret band of the porphyrins or the typical Q-bands. Only a band at  $\lambda_{\text{max}} = 502$  nm was observed, typical of a dipyrromethene, as previously been reported by us and by Corma.<sup>10a,11</sup> This may be attributed to the small size of the cavities of zeolite NaY (14 Å), which precludes the formation of the porphyrin macrocycle. In addition, the luminescence spectra of immobilised TDFPP-Al-MCM-41 and TDFPP-NaY were recorded with excitation at 415 nm (Fig. 2b). The emission spectra observed for TDFPP-Al-MCM-41 presents the typical bands at 660 nm and 720 nm, very similar (662 and 715 nm) to the TDFPP in solid state (Fig. 2b inset), which indicates the presence of TDFPP inside the pores of Al-MCM-41. The yield of TDFPP was calculated based on the amount of organic material decomposed between 250 and 800°C (Table 1), which could also include acyclic oligomeric materials, typical from porphyrin synthesis. We assume the sole presence of TDFPP inside the pores, based on the emission spectra similarity for TDFPP and TDFPP-Al-MCM-41 (Fig. 2b); however, this does not exclude the minor presence of encapsulated oligopyrroles. Further studies are currently underway to clarify this issue. Since NaY is the best performing Lewis acid as catalyst in the condensation of pyrrol with 2,6-difluorobenzaldehyde, the study was extended to the synthesis of the other sterically hindered *meso*-arylporphyrins, namely *meso*-tetrakis(2-fluorophenyl)porphyrin (TFPP), *meso*-tetrakis(2,3,4,5,6-pentafluorophenyl)porphyrin (TPFPP) and *meso*-tetrakis(2,6-dichlorophenyl)porphyrin (TDCPP) under similar reaction conditions. Results are also presented on Table 1. As previously observed with other catalysts<sup>4-6</sup> the isolated yields are strongly dependent on the aldehyde structure (TFPP-30 %, TPFPP-17 % and TDCPP-6 %). It should be noted that this new approach for one pot *meso*-halogenated substituted porphyrin synthesis gave a twofold increase in yields, compared with the original nitrobenzene method<sup>14-16</sup> (Table 1). The scalability of this approach is also an important matter, and all experiments were repeated using 60 mmol benzaldehyde (~50 x higher scale) with similar yields obtained. Application of this method as a real practical alternative to synthesis of hindered porphyrins requires the validation of NaY as a potential green catalyst: This was achieved by evaluating its reutilization in the synthesis of TDFPP; and after the first cycle, the NaY was recovered by filtration and washed with chloroform and tetrahydrofuran, following by solid drying overnight, at 150 °C, under vacuum. The reactivated solid was used in second, third, fourth and fifth cycles, following the same reactivation procedure in-between cycles and similar isolated yields have been obtained (Fig. 3).

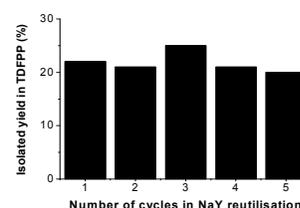


Fig. 3 Reutilisation of NaY on the synthesis of TDFPP.

It is worth mentioning that a reutilisation experiment, in which the catalyst was used without reactivation, gave just 12 % yield, similar to that obtained using the nitrobenzene method alone,<sup>14</sup> suggesting that the NaY voids were mostly occupied by organic materials, blocking the catalyst acid sites.

To conclude, the tested solid porous oxides act as supports for preparation of encapsulated porphyrin hybrid materials or as catalysts for synthesis of porphyrins in solution, rationalised by the influence of acidity and pore size of the solid oxides in selective use of their ability. An MCM-41 type material (Lewis acidity of 120  $\mu\text{mol Py/g}$  and pore size 30 Å) was found to be the best solid to promote the synthesis of encapsulated porphyrins, while NaY (Lewis acidity of 510  $\mu\text{mol Py/g}$  and pore size 14 Å) was the best one to act as an efficient reusable catalyst for one-pot synthesis of *meso*-porphyrins, with potential for scaling up for large scale preparation of these important compounds. It should be noted that yields typically have a twofold increase when compared with literature methods.

This “NaY method” can be recognised as a real practical alternative to synthesis of porphyrins since, after washing, full catalytic ability is regained by the porous solid oxide NaY, confirming its reusability. Further analysis of the scope of this reaction is underway.

We thank FCT-Portugal and QREN/FEDER (COMPETE-Programa Operacional Factores de Competitividade) for funding (PTDC/QUI-QUI/112913/2009). NMR data was obtained at the Nuclear Magnetic Resonance Laboratory of Coimbra Chemistry Centre (www.nmrccc.uc.pt), Universidade de Coimbra, (REEQ/481/QUI/2006 and POCI-2010). MS thanks for a post-doc grant SFRH/BPD/34372/2007.

## Notes and references

- <sup>a</sup> Centro de Química de Coimbra, Departamento de Química, Universidade de Coimbra, Rua Larga, 3004-535 Coimbra, Portugal Fax: +351 239827703; Tel: +351 239854474; E-mail: mcalvete@qui.uc.pt and mmpereira@qui.uc.pt.
- <sup>b</sup> Instituto de Biotecnologia e Bioengenharia, Centro de Engenharia Biológica e Química, Instituto Superior Técnico – Universidade Técnica de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal †Electronic Supplementary Information (ESI) available: [Synthesis, acid and thermal analysis; infra-red and photophysical properties of used solids and synthesised porphyrins]. See DOI: 10.1039/b000000x/
- L. R. Milgrom in *The Colours of Life: An Introduction to the Chemistry of Porphyrins and Related Compounds*, Oxford University Press, New York, 1997
- H. Fischer, H. Orth. *Die Chemie des Pyrrols*, Akademische Verlagsgesellschaft: Leipzig, 1934, Vol. 1..
- P. Rothmund, *J. Am. Chem. Soc.*, 1935, **57**, 2010.
- A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour, L. Korsakoff, *J. Org. Chem.*, 1967, **32**, 476. (ca 2100 citations: source Web of Knowledge®)

- 5 M. D. R. Gonsalves, J. M. T. B. Varejão, M. M. Pereira, *J. Heterocyclic Chem.*, 1991, **28**, 635. (ca 170 citations: source Web of Knowledge®)
- 6 J. S. Lindsey, I. C. Schreiman, H. C. Hsu, P. C. Kearney, A. M. Marguerettaz, *J. Org. Chem.*, 1987, **52**, 827. (ca 1050 citations: source Web of Knowledge®)
- 7 (a) M. M. Pereira, A. R. Abreu, N. P. F. Goncalves, M. J. F. Calvete, A. V. C. Simões, C. J. P. Monteiro, L. G. Arnaut, M. E. S. Eusébio, J. Canotilho, *Green Chem.*, 2012, **14**, 1666; (b) M. M. Pereira, L. G. Arnaut, S. J. Formosinho and C. J. P. Monteiro, *WO Patent* 053707, 2006; (c) M. M. Pereira, C. J. P. Monteiro, A. V. C. Simões, S. M. A. Pinto, A. R. Abreu, G. F. F. Sá, E. F. F. Silva, L. B. Rocha, J. M. Dabrowski, S. J. Formosinho, S. Simões, L. G. Arnaut, *Tetrahedron*, 2010, **66**, 9545; (d) J. M. Dabrowski, L. G. Arnaut, M. M. Pereira, K. Urbanska, G. Stochel, *MedChemComm*, 2012, **3**, 502.
- 8 (a) S. L. H. Rebelo, A. R. Gonçalves, M. M. Pereira, M. M. Q. Simões, M. G. P. M. S. Neves, J. A. S. Cavaleiro, *J. Mol. Catal. A: Chem.*, 2006, **256**, 321; (c) D. Mansuy, *Compt. Rendus Chim.*, 2007, **10**, 392.
- 9 T. Shinoda, Y. Izumi, M. Onaka, *J. Chem. Soc. Chem. Commun.*, 1995, 1801; (b) M. R. Kishan, V. R. Rani, M. R. V. S. Murty, P. S. Devi, S. J. Kulkarni, K. V. Raghavan, *J. Mol. Catal. A: Chem.* 2004, **223**, 263.
- 10 (a) M. Silva, M. E. Azenha, M. M. Pereira, H. D. Burrows, M. Sarakha, M. F. Ribeiro, A. Fernandes, P. Monsanto, F. Castanheira, *Pure Appl. Chem.*, 2009, **81**, 2025; (b) M. Silva, M. E. Azenha, M. M. Pereira, H. D. Burrows, M. Sarakha, C. Forano, M. F. Ribeiro, A. Fernandes, *Appl. Catal., B*, 2010, **100**, 1; (c) M. Silva, M. J. F. Calvete, N. P. F. Gonçalves, M. E. Azenha, H. D. Burrows, M. Sarakha, M. F. Ribeiro, A. Fernandes, M. M. Pereira *J. Hazard. Mater.*, 2012, **233-234**, 79 (d) M. J. F. Calvete, M. Silva, M. M. Pereira, H. D. Burrows *RSC Adv.*, 2013, **3**, 22774.
- 11 (b) F. Algarra, M. A. Esteves, V. Fornés, H. Garcia, J. Primo *New J. Chem.*, 1998, 333; A. Corma, H. Garcia, *J. Chem. Soc., Dalton Trans.* 2000, 1381.
- 12 V. R. Rani, M. R. Kishan, S. J. Kulkarni, K. V. Raghavan, *Catal. Commun.* 2005, **6**, 531.
- 13 R. A. W. Johnstone, M. L. P. G. Nunes, M. M. Pereira, A. M. d'A. R. Gonsalves, A. C. Serra, *Heterocycles*, 1996, **43**, 1423.
- 14 C. J. P. Monteiro, M. M. Pereira, S. M. A. Pinto, A. V. C. Simões, G. F. F. Sá, L. G. Arnaut, S. J. Formosinho, S. Simões, M. F. Wyatt *Tetrahedron*, 2008, **64**, 5132.
- 15 J. C. P. Grancho, M. M. Pereira, M. G. Miguel, A. M. R. Gonsalves, H. D. Burrows, *Photochem. Photobiol.*, 2002, **75**, 249.
- 16 The  $\lambda_{\text{max}}$  of TDFPP absorption spectra in solid state and those obtained by DRS-UV-Vis for all the porous materials are presented as ESI.