meso-Dichloropyrimidinyl substituted expanded porphyrins†

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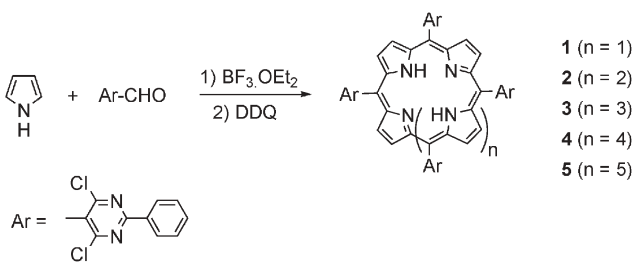
Condensation of 4,6-dichloro-2-phenylpyrimidine-5-carbaldehyde with pyrrole enables the synthesis of a number of expanded porphyrins of which the [26]hexaphyrin was easily isolated and successfully converted into the decasubstituted doubly N-fused hexaphyrin variant.

Inspired by the versatility of porphyrin chemistry, a great interest has recently developed in the synthesis of non-porphyrin polypyrrole macrocycles. Three classes of porphyrin analogues, *in casu* isomeric, expanded and contracted porphyrinoids, are studied because of their chemical resemblance to porphyrins while adding some particular non-porphyrin features.[1] *meso*-Aryl substituted [(1.1.1.1…)] expanded porphyrins have become synthetically accessible by a simple modified Rothemund–Lindsey condensation of pyrrole and electron deficient *o,o′*-disubstituted arylaldehydes and the best results so far have been achieved with pentafluorobenzaldehyde.[2] Osuka *et al*. further explored the use of pentafluorobenzaldehyde in the synthesis of a diversity of expanded porphyrinoids.[3] "Confusion", "inversion" and "fusion" of individual pyrrole units has been observed in some expanded porphyrins, creating novel porphyrinoids showing unprecedented properties.[1–3] Here, we report the use of a heteroaromatic electron deficient arylaldehyde, 4,6-dichloro-2-phenylpyrimidine-5-carbaldehyde,[4] for the creation of expanded porphyrins with an increased reactivity towards synthetic modifications of the macrocyclic system.

Our recent research was focused on the synthesis of *meso*-pyrimidinyl substituted porphyrins and their use in dendrimer chemistry.[5] However, by a slight modification of the synthetic conditions, as optimized for porphyrins,[5b] expanded porphyrin analogues were synthetically accessible. A tenfold increase in concentration (4,6-dichloro-2-phenylpyrimidine-5-carbaldehyde and pyrrole under Lindsey conditions) afforded, besides the expected porphyrin **1**, a number of expanded porphyrins, ranging from penta- to octaphyrin (Scheme 1, Fig. 1).



Scheme 1 *meso*-Dichloropyrimidinyl expanded porphyrins **1–5**.

† Electronic supplementary information (ESI) available: synthetic procedures, characterization data and spectra [MS (ESI), NMR (^{1}H, ^{13}C and 2D-NMR)] for hexaphyrin **3** and the doubly N-fused isomers **6** and **7**; additional information regarding porphyrin **1** and pentaphyrin **2**. See http://www.rsc.org/suppdata/cc/b5/b501089f/

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Using the conditions optimized by Osuka *et al*. for pentafluorobenzaldehyde,[2b,c] we were able to isolate porphyrin **1** (10%), pentaphyrin **2** (11%) and hexaphyrin **3** (11%) from the reaction mixture in acceptable yields. An excess of oxidant (DDQ) was used to avoid the presence of any partially oxidized species. The consecutive expanded porphyrins were purified by column chromatography but their full characterization was hampered by their low solubility. The hexaphyrin homologue **3** showed the highest solubility in common organic solvents and was characterized completely by NMR spectroscopy.† The obtained [26]hexaphyrin **3** displayed a partially inverted structure, similar to the *meso*-hexakis(pentafluorophenyl) substituted hexaphyrin.[2a,b] The inner, strongly shielded *β*-hydrogen atoms (4H, $\delta = -2.5$ ppm) correlate, in the HMQC (2D-NMR) spectrum, with a carbon signal at 123 ppm.

The UV/Vis absorption spectrum confirms the aromaticity of the hexaphyrin by the presence of an intense Soret-band and Q-bands into the near IR region (Fig. 2). A low-wavelength absorption is observed around 270 nm and can be assigned to the 2-phenylpyrimidine substituent.

Porphyrin **1** was found to be very insoluble but could be characterized by MS and UV/Vis spectroscopy (Fig. 2) as well as by its reactivity to form soluble octaphenoxy-substituted porphyrins (by substitution of all eight chlorine groups with 4-*tert*-butylphenol).† The structure of pentaphyrin **2** could not be established unambiguously by NMR techniques due to overlapping proton signals and low solubility, but its ^{1}H NMR and UV/Vis spectra (Fig. 2) strongly point in the direction of the expected N-fused [22]pentaphyrin, as earlier observed for Osuka's pentafluorophenyl based system.[2c]†

The unique properties of the hexaphyrin chromophore enable its use in different modern applications such as photodynamic

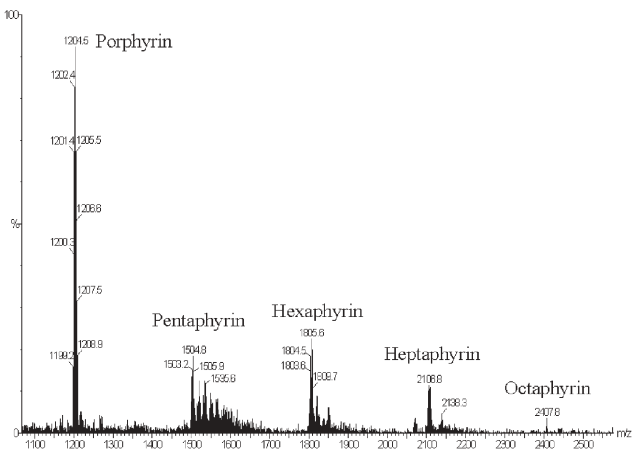


Fig. 1 ESI-MS spectrum of the crude reaction mixture containing the consecutive expanded porphyrin homologues.

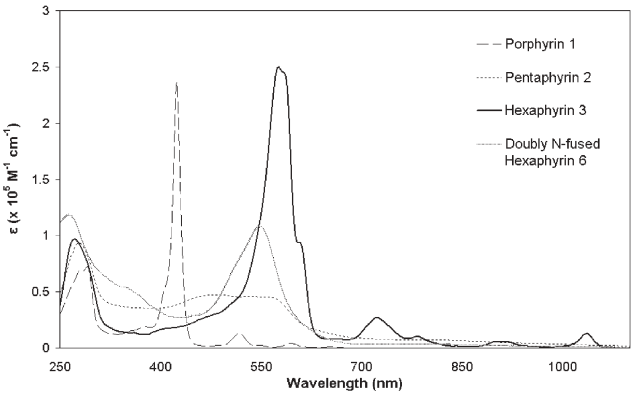
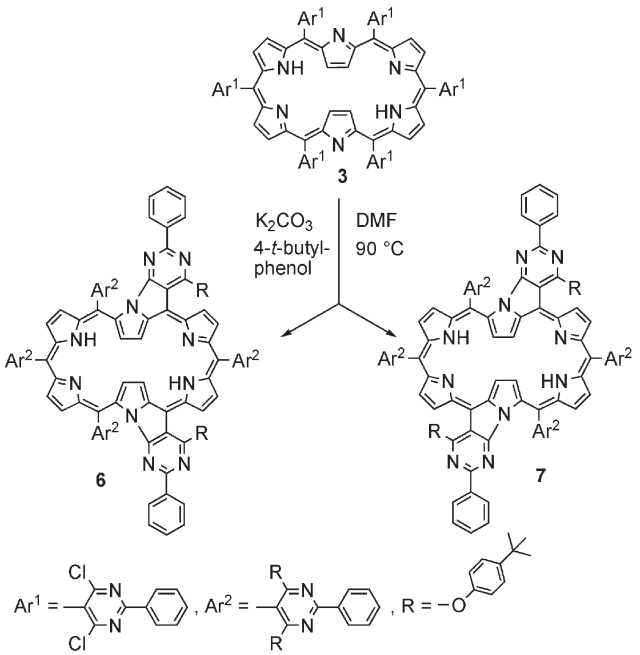


Fig. 2 UV/Vis absorption spectra of porphyrin homologues.

therapy, as an NMR contrast agent or as a DVD recording dye.[1] In order to explore its potential use in such applications, it is essential to be able to tune the chromophores absorption characteristics and solubility (in a wide range of solvents) towards the application needs. However, very few reports have been published focusing on synthetic modifications of polyphyrin macrocycles. Osuka *et al.* earlier reported on the regioselective (*para*-F) nucleophilic substitution reaction on their [26]hexaphyrin system,[3d] and very recently the same group was also able to perform regioselective Diels–Alder reactions on the inverted pyrrole moiety of the same hexaphyrin.[3h] The main advantage of our new route towards expanded porphyrins based on 4,6-dichloropyrimidine-5-carbaldehydes, is the ease and broad scope of the post-macrocyclization synthetic modifications that are possible on this system. The substituents are introduced on the *o*,*o*′-positions of the *meso*-aryl ring close to the centre of the expanded porphyrin, allowing tuning of the microenvironment of the macrocycle. The electron deficient pyrimidine moiety (in contrast to the dichlorophenyl moiety) allows easy substitution of the chlorine groups by nucleophilic aromatic substitution (NAS) or transition metal catalyzed cross-coupling reactions. High-yielding NAS reactions have already been performed on analogous porphyrins[5a,b] and even dendrimers[5c] have been built based on this reaction by multiple dendron substitution on a *meso*-dichloropyrimidine A_2B_2-porphyrin core. Recently we also reported on the high synthetic accessibility of highly sterically encumbered porphyrins through Suzuki reactions on the same bis(pyrimidinyl)-porphyrin.[5d] Hence it seems likely that these reactions may be extended to the expanded porphyrin analogues.

As a proof of principle, nucleophilic aromatic substitution of the chlorine groups of [26]hexaphyrin **3** with 4-*tert*-butylphenol was carried out. After reaction for 48 h under basic conditions (K_2CO_3) in DMF at 90 °C, the reaction mixture was subjected to chromatographic purification which afforded two (very soluble) tenfold substituted, isomeric, doubly N-fused hexaphyrins **6** and **7** (65% yield, 1:3 ratio) in which the two "flipped" pyrrole units have substituted their neighbouring dichloropyrimidines to form 5,5,6-tricyclic systems (Scheme 2).[3g,6] The two red-purple isomers showed similar MS (ESI) spectra and were differentiated on the base of symmetry by NMR spectroscopy. Such N-fusion is known for pentaphyrins[2c] and was very recently shown on Osuka's pentafluorophenyl hexaphyrin.[3g] The 2,6-dichlorophenyl derivative however seemed practically unreactive under the applied



Scheme 2 Synthesis of doubly N-fused hexaphyrin isomers **6** and **7**.

conditions. The *anti*-doubly (two tricyclic systems at opposite sides) N-fused *meso*-pentafluorophenyl substituted hexaphyrin was isolated in an optimized yield of 55%, while *syn*-double N-fusion could only be achieved in a low yield when *anti*-fusion was blocked through insertion of an unreactive *meso*-aryl substituent. In our case yields are obviously superior while both isomers are obtained in one reaction and are easily separated by column chromatography. While considering the yield, one should take into account that twelve substitution reactions have been carried out to obtain the N-fused isomers (a tenfold phenoxy substitution and two internal N-fusion reactions), what amounts to a spectacular and unprecedented yield of over 95% for each substitution reaction. The NMR and UV/Vis data (Fig. 2) of the doubly N-fused hexaphyrins **6** and **7** point to the formation of a reduced [28]hexaphyrin chromophore and resemble Osuka's data.[3g]†

The presented route represents pronounced advantages and extensions to the work conducted by Osuka *et al.* on related pentafluorophenyl substituted hexaphyrins and other expanded porphyrins.[2,3] The increased sensitivity towards substitution of the expanded macrocycle was shown by applying standard nucleophilic aromatic substitution reaction conditions on the [26]hexaphyrin derivative **3**, resulting not only in complete substitution but also generating a doubly N-fused hexaphyrin variant. In future work, we will extend the applied principle to other substitutions (and potentially also to Pd catalyzed cross couplings) on the hexaphyrin as well as on the related polyphyrins (pentaphyrin **2** *etc.*). The encountered solubility problems for the other homologues may be solved by introducing other substituents at the 2-position of the pyrimidine (for instance *tert*-butyl groups) or by subjecting these homologues to similar substitution reactions (as proven for porphyrin **1** and hexaphyrin **3**).

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Notes and references

1 (*a*) *Expanded, Contracted and Isomeric Porphyrins*, ed. J. L. Sessler and S. J. Weghorn, Elsevier, Oxford, 1997; (*b*) J. L. Sessler, A. Gebauer and S. J. Weghorn, in *The Porphyrin Handbook*, ed. K. M. Kadish, K. M. Smith and R. Guilard, Academic Press, San Diego, 2000, vol. 2, ch. 9, pp. 55–124; (*c*) J. L. Sessler and D. Seidel, *Angew. Chem. Int. Ed.*, 2003, **42**, 5134–5175.

2 (*a*) M. G. P. M. S. Neves, R. M. Martins, A. C. Tome, A. J. D. Silvestre, A. M. S. Silva, V. Felix, M. G. B. Drew and J. A. S. Cavaleiro, *Chem. Commun.*, 1999, 385–386; (*b*) J.-Y. Shin, H. Furuta, K. Yoza, S. Igarashi and A. Osuka, *J. Am. Chem. Soc.*, 2001, **123**, 7190–7191; (*c*) J.-Y. Shin, H. Furuta and A. Osuka, *Angew. Chem. Int. Ed.*, 2001, **40**, 619–621.

3 Some examples: (*a*) H. Furuta, H. Maeda and A. Osuka, *Chem. Commun.*, 2002, 1795–1804; (*b*) S. Shimizu, J.-Y. Shin, H. Furuta, R. Ismael and A. Osuka, *Angew. Chem. Int. Ed.*, 2003, **42**, 78–82; (*c*) M. Suzuki and A. Osuka, *Org. Lett.*, 2003, **5**, 3943–3946; (*d*) M. Suzuki, S. Shimizu, J.-Y. Shin and A. Osuka, *Tetrahedron Lett.*, 2003, **44**, 4597–4601; (*e*) S. Shimizu, V. G. Anand, R. Taniguchi, K. Furukawa, T. Kato, T. Yokoyama and A. Osuka, *J. Am. Chem. Soc.*, 2004, **126**, 12280–12281; (*f*) Y. Inokuma and A. Osuka, *Org. Lett.*, 2004, **6**, 3663–3666; (*g*) M. Suzuki, R. Taniguchi and A. Osuka, *Chem. Commun.*, 2004, 2682–2683; (*h*) H. Hata, H. Shinokubo and A. Osuka, *Angew. Chem. Int. Ed.*, 2005, **44**, 932–935.

4 (*a*) J. A. Hendry and R. F. Homer, *J. Chem. Soc.*, 1952, 328–333; (*b*) D. H. Kim, W. A. Santilli and A. A. Santilli, *US 3631045*, 1971.

5 (*a*) F. Motmans, E. Ceulemans, S. Smeets and W. Dehaen, *Tetrahedron Lett.*, 1999, **40**, 7545–7548; (*b*) S. Smeets, C. V. Asokan, F. Motmans and W. Dehaen, *J. Org. Chem.*, 2000, **65**, 5882–5885; (*c*) W. Maes, D. B. Amabilino and W. Dehaen, *Tetrahedron*, 2003, **59**, 3937–3943; (*d*) W. Maes and W. Dehaen, *Synlett*, 2003, **1**, 79–82.

6 C. H. Hung, J. P. Jong, M. Y. Ho, G. H. Lee and S. M. Peng, *Chem. Eur. J.*, 2002, **8**, 4542–4548.

