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Synthesis of electron-deficient fluorinated porphyrins through scrambling: Characterization and quantitative crystal structure analysis

Fasalu Rahman Kooriyaden [a,1], Subramaniam Sujatha [a,1], Babu Varghese [b], Chellaiah Arunkumar [a,*]

[a] Bioinorganic Materials Research Laboratory, Department of Chemistry, National Institute of Technology Calicut, Kozhikode, Kerala 673 601, India
[b] SAIF, Indian Institute of Technology Madras, Chennai, Tamilnadu 600 036, India

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ABSTRACT

MacDonald type 2 + 2 condensation of 5-(4-cyanophenyl)dipyrromethane with pentafluorobenzaldehyde in presence of $BF_3 \cdot OEt_2$ results in unexpected formation of fluorinated porphyrins namely, B_4, H_2T(PFP)P, **1**; AB_3, H_2T(PFP)(CP)P, **2**; *cis*-A_2B_2, *cis*-H_2B(PFP)B(CP)P, **3** and A_3B, H_2(PFP)T(CP)P, **5** in addition to the expected *trans*-A_2B_2, *trans*-H_2B(PFP)B(CP)P, **4** porphyrin through scrambling of the 4-cyano/pentafluoro phenyl substituents. The same reaction in TFA catalyst leads to non-scrambling condition and yields *trans*-A_2B_2 porphyrin. The complementary reactions were also performed using 5-(pentafluorophenyl)dipyrromethane to analyze the level of scrambling. The copper complexes of **3** and **5** have been structurally characterized by single crystal X-ray diffraction analysis and the role of weak intermolecular interactions in their crystal packing has been analyzed and quantified using Hirshfeld surface analysis.

1. Introduction

Porphyrins are very attractive molecules because of their unique structure of altering the central metal atom, large extended π-system, high thermal stability, synthetic versatility, physicochemical properties and biological activities [1,2]. *Meso*-substituted porphyrins are important building blocks in biomimetic and material chemistry [1,3]. In particular, meso-substituted electron deficient iron (III) porphyrins are versatile catalyst for the oxidation of organic substrates [4]. It is well-known that fluorinated porphyrinoids show promising potential for photodynamic therapy, imaging, pharmaceutical research and as synthetic models of natural compounds [5]. Synthetic porphyrin chemistry is a rapidly changing area of research starting from Rothemund method, Adler–Longo method and finally many of the harsh conditions associated with the above two methods were overcome by following Lindsey method [6]. *Meso*-substituted porphyrins are mainly synthesized by the condensation of appropriate aldehyde with either pyrrole or dipyrromethane and its related analogs [7,8]. *Trans*-A_2B_2 porphyrins can be effectively synthesized by acid-catalyzed two-step one pot reaction of dipyrromethane with an aldehyde. Instead of an expected *trans*-A_2B_2 porphyrin, the scrambled products were also isolated in these reactions. Hence, porphyrin synthesis under these conditions without scrambling is a difficult task for synthetic chemists. Lindsey et al. first investigated the scrambling in several aryldipyrromethane with aldehyde condensation reaction and found that scrambling occurs before the formation of porphyrinogen [9,10].

In this line, we are motivated to investigate the scrambling involving electron deficient aldehydes (pentafluorophenyl and *p*-cyanophenyl) with its dipyrromethane under Lindsey conditions for the formation of porphyrins (Fig. 1). In addition to this, the quantitative crystal structure analysis of the copper derivatives of the scrambled products such as Cu-*cis*-A_2B_2 and Cu-A_3B porphyrins have been performed using Hirshfeld surface analysis with Crystal Explorer 3.1.

2. Results and discussion

Synthesis of electron deficient fluorinated porphyrins, B_4, H_2T(PFP)P, **1**; AB_3, H_2T(PFP)(CP)P, **2**; *cis*-A_2B_2, *cis*-H_2B(PFP)B(CP)P,

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[*] Corresponding author. Tel.: +91 9746244507; fax: +91 495 228 7250.
E-mail address: arunkumarc@nitc.ac.in (C. Arunkumar).

[1] Equally contributed to this work.

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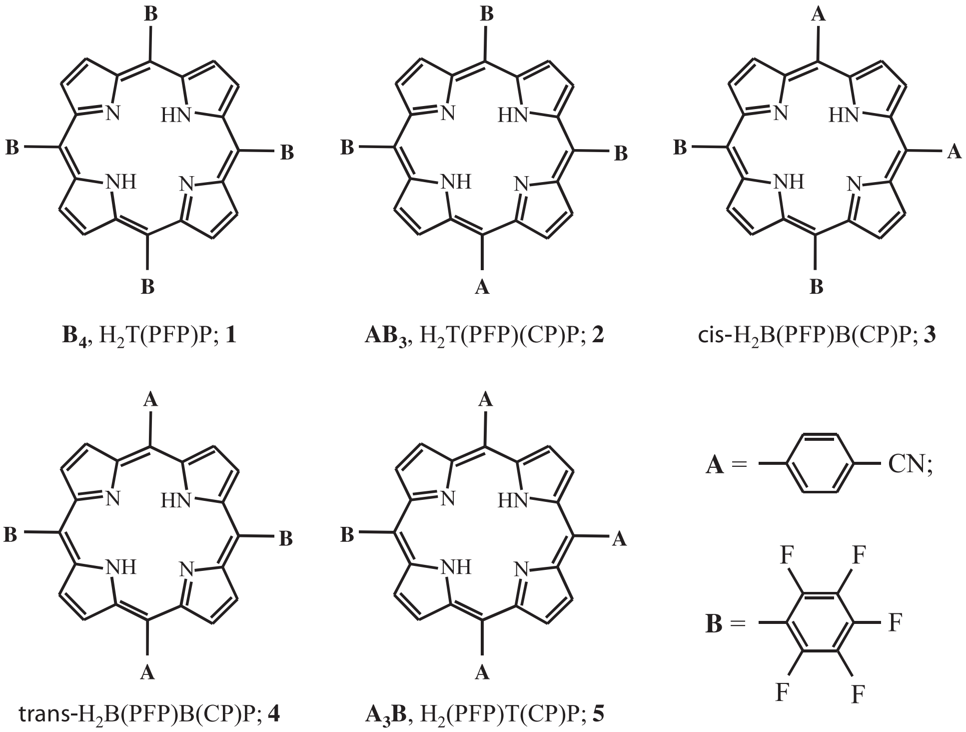

Fig. 1. Porphyrins formed during scrambling in MacDonald type 2 + 2 condensation of dipyrromethane and an aldehyde.

3; *trans*-A_2B_2, *trans*-$H_2B(PFP)B(CP)P$, **4** and A_3B, $H_2(PFP)T(CP)P$, **5** have been carried out by MacDonald type 2 + 2 condensation of 5-(4-cyanophenyl)dipyrromethane with pentafluorobenzaldehyde in presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (Scheme 1).

After stirring the reaction mixture for 50 min at room temperature under nitrogen atmosphere, DDQ was added to oxidize the porphyrinogen to form the porphyrins. The TLC analysis showed the formation of five different porphyrins **1–5** in which the AB_3, **2** and *cis*-A_2B_2, **3** porphyrins were obtained as major fractions through scrambling and all the porphyrins were isolated, purified by column chromatography.

The scrambling process is initiated by the acidolysis of dipyrromethane and recombination of the fragments with the starting materials or other oligomers [10]. Acidolysis of simple 5-(4-cyanophenyl)dipyrromethane or its oligomer yields two fragments which undergo further reaction with pentafluorobenzaldehyde or other oligomers, yielding the major scrambled products such as AB_3 (**2**) and *cis*-A_2B_2 (**3**) porphyrins in 8 and 12% yield respectively. In order to analyze the level of scrambling, the same reaction was carried out in presence of trifluoro acetic acid (TFA) which remarkably yields only the expected *trans*-A_2B_2 (**4**) porphyrin with very low yield (12%). This indicates that the level acidolysis and scrambled oligomers are lower in TFA catalyzed reaction compared to that of $BF_3{\cdot}OEt_2$. The low yield of scrambled porphyrin may be attributed to the suppression of recombination of the fragments generated by acidolysis which results in low level of fragment recombination as well as low yields of porphyrin. Note that, scrambling in MacDonald-type condensation with sterically unhindered dipyrromethanes is very difficult to suppress [9]. Moreover, the complementary reaction of condensing 5-(pentafluorophenyl)dipyrromethane and 4-cyanobenzaldehyde in presence of $BF_3{\cdot}OEt_2$ leads to the formation of both *cis*-A_2B_2 (**3**) and AB_3 (**2**) porphyrins in reasonable yield (12 and 18% respectively) which indicates that the extent of scrambled products are very limited in this reaction. Interestingly, there is no porphyrin formation when the same reaction is carried out in presence of TFA as acid catalyst (Scheme 1). Also, the yield of porphyrin is more in the condensation reaction involving 5-(4-cyanophenyl)dipyrromethane compared to its complementary TFA catalyzed reaction in which no scrambling occurred. Overall, the obtained results show that the non-scrambling occurs only in TFA catalyzed reaction involving 5-(4-cyanophenyl) dipyrromethane.

All the synthesized porphyrins were characterized by UV–vis, ^1H NMR spectroscopic methods and mass spectrometry. Freebase porphyrins exhibited an intense Soret (B) and four visible (Q) bands and these absorption spectral features are similar to that of the corresponding H_2TPP. The main absorption bands in **1–5** are gradually shifted bathochromically with decreasing number of pentafluorophenyl groups in the porphyrin periphery. However, the copper(II) complexes show a blue shifted Soret (B) and two Q bands and is similar to that reported for MTPPs [11].

A representative overlayed ^1H NMR spectrum of *cis*-A_2B_2 and *trans*-A_2B_2 porphyrins are shown in Fig. 2 with the aromatic and negative regions and they feature resonances arising from meso-phenyl-H, β-pyrrole-H and imino hydrogens. The presence of spilt up in the β-pyrrole proton resonances around 8.90 ppm suggests that all the β-pyrrole protons are not in the same chemical environment which is due to the lower symmetry in *cis*-A_2B_2 isomer than that of *trans*-A_2B_2. The same effect is found in the imino hydrogen resonances around −2.90 ppm, appeared as a doublet in *cis*-A_2B_2 isomer and a singlet in *trans*-A_2B_2 isomer. And, the observed integrated intensities of the proton NMR data are in good agreement with the proposed structures. The FAB mass spectrum of **2** (AB_3) and **3** (*cis*-A_2B_2) show peaks at m/z values 911 and 845 which correspond to $[M{+}1]^+$ and $[M]^+$ respectively.

Attempts to get the single crystals of free base porphyrins, **2–5** with suitable size for the X-ray diffraction analysis were unsuccessful. However, we successfully characterized the copper complexes of **3** (Cu-*cis*-A_2B_2) and **5** (Cu-A_3B) by single crystal XRD analysis. Both the complexes are crystallized in monoclinic system with space groups, $P2_1/n$ and Cc respectively (Table 1).