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β-Octamethoxyporphycenes

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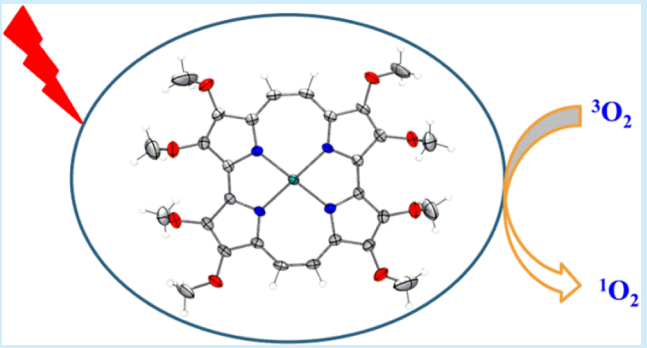
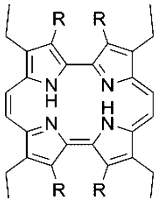
Supporting Information

ABSTRACT: Porphycene with eight methoxy substituents at its β-positions was synthesized for the first time in three steps from 3,4-dimethoxypyrrole. The presence of methoxy groups increases its hydrophilicity as evident from their increased solubility in methanol. Among its metallo-derivatives, the Pd(II)-complex displays efficient singlet oxygen quantum yield (73%) and hence can be a potentially good photosensitizer for photo-oxidation, DNA cleavage, and photodynamic therapy (PDT).

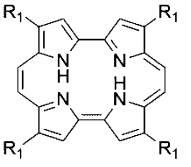


Porphycene is the first constitutional isomer of porphyrin to be synthesized.[1] This is achieved by rearranging the *meso*-methines of the porphyrin moiety, where two bipyrrolic moieties are linked through two *meso*-like carbons on either side through their α-positions. This rezigging of the *meso*-methines led to a rectangular shaped macrocyclic core with reduced molecular symmetry compared to porphyrin. Owing to its unique structural feature, porphycene displays NH···N hydrogen bonding stronger than that of its parent isomer. Because of the structural similarities, both isomers display similar photophysical properties and coordination behavior; however, few subtle differences were also noticed.[2] An important attribute, in which porphycene scores over porphyrin, is their relatively stronger absorption in the red region, thereby making them a better candidate for PDT application.[3] In addition, porphycenes have also been explored for possible applications in material chemistry,[4] catalysis,[5] photoinactivation of viruses and bacteria,[6] protein mimicry,[7] and nonlinear optical study.[8]

A general synthetic approach toward porphycenes includes the McMurry coupling of diformyl-2,2′-bipyrroles employed first by Vogel.[1] However, owing to recent developments in organic synthesis, the synthesis of the bipyrrole building block has undergone several optimizations.[9] Despite these developments, the functionalization of porphycene is mostly limited to alkyl or aryl substituents at the periphery.[10] In this regard, we found that the presence of methoxy groups (**3b**) has significant advantages over the nonmethoxylated analogues such as **3a**; first, it enhances cell localization, probably owing to the greater hydrophilicity it imparts, and second, it can be subsequently deprotected to hydroxy and further substituted with long alkyl, alkoxy, or sugar moieties or different salts in order to modulate the lipophilicity of the resultant macrocycle.[11]



2a; R= Et
2b; R= Me



3a; R_1 = Propyl
3b; R_1 = 1-methoxy ethyl

Since Merz reported the synthesis of octamethoxyporphyrin in 1993, 3,4-dimethoxypyrrole finds very little application in the synthesis of porphyrinoids.[12] This is ascribed to the difficulties associated with this chemistry including a relatively less stable nature, which was described in detail later by Merz himself.[13] However, our recent interest in this chemistry[14] led us to explore the possible synthesis of β-octamethoxyporphycene, which has potential application as a photosensitizer (PS) in PDT. Another aspect of our interest is to see if the introduction of oxygen atoms at the 3,6- and 13,16-positions can reduce the nonbonding interaction and their consequence on its structure and photophysical properties.

The key to our target was the precursor diformyl derivative of tetramethoxy-2,2′-bipyrrole **5**. Iodination of 2-formyl-3,4-dimethoxypyrrole **A1** using *N*-iodosuccinimide led to the desired 5-iodo compound **A2** (68%); however, subsequent Ullmann coupling led to the formation of deiodinated compound **A1** (Supporting Information). Modified Pd-catalyzed Ullmann coupling of **A2**, following Smith's strategy, led to desired bipyrrole **5** in poor yield (14%) (Supporting Information).[9c] Therefore, we decided to explore the synthesis

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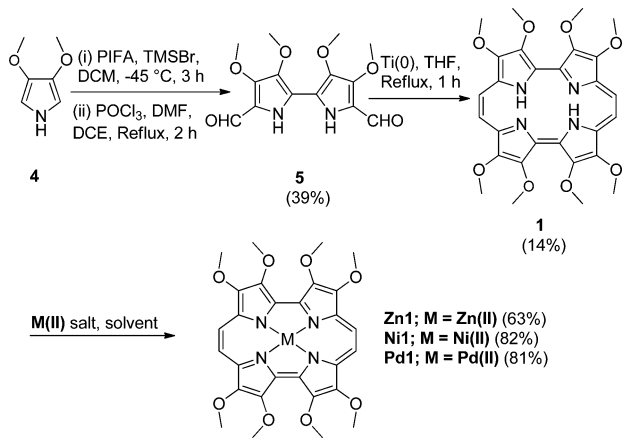
of bipyrrole directly from the pyrrole itself using hypervalent iodine mediated Lewis acid catalyzed coupling reactions with [bis(trifluoroacetoxy)iodo]-benzene (PIFA) as an oxidant and trimethylsilyl bromide (TMSBr) as a Lewis acid reported by Kita's group.[9d] Owing to the high reactivity of the 3,4-dimethoxypyrrole **4**,[12b] initially we used the corresponding *N*-benzyl derivative **A3** (which happens to be the precursor for pyrrole **4**), as our starting material. This led to the successful isolation of the doubly N-protected 2,2′-bipyrrole **A4** in good yield (71%), whose structure was further confirmed by X-ray diffraction (XRD) analysis (Supporting Information). Subsequent debenzylation using Na/liq NH_3, however, led to decomposition of the desired product (Supporting Information). Therefore, we decided to explore the PIFA-TMSBr coupling of 3,4-dimethoxypyrrole **4** itself. As expected, we could notice the formation of the product at −45 °C; however, the compound undergoes decomposition during the purification. In order to avoid this, we subjected the reaction mixture to Vilsmeier−Haack formylation, immediately after the workup process. Finally this led us to the desired product **5** (two-step yield 39%; Scheme 1), whose structure was confirmed by XRD

Scheme 1. Synthesis of *β*-Octamethoxyporphycene and Its M(II) Derivatives



analysis (Supporting Information). McMurry coupling of the dialdehyde **5** using $TiCl_4$/Zn finally resulted in the formation of the desired octamethoxyporphycene **1** in 14% yield (Scheme 1). Here the porphycene could be synthesized in only three steps from the constituent pyrrole derivative, making it the shortest route to *β*-substituted porphycenes. Further, this strategy emerged as more efficient compared to the traditional iodination and Ulmann coupling route (also not possible in this case) to bipyrrole synthesis (where in many occasions BOC protection is essential for enhanced yield). The freebase porphycene could be further converted to its Zn(II)-, Ni(II)- and Pd(II)-complexes. All of the porphycene derivatives were characterized following standard spectroscopic techniques. Further, the solid state structures of the freebase **1**, **Zn1**, and **Pd1** could be ascertained by XRD analyses. All of these porphycenes show good lipophilicity and hydrophilicity, displaying good solubility in all organic solvents ranging from hexane to methanol (Supporting Information).

The ^{1}H NMR spectrum of **1** reveals the *meso* protons and imino protons resonating at 9.66 and 0.36 ppm. In comparison to analogous octaethylporphycene **2a**, the *meso* protons (9.48 ppm) are shifted 0.18 ppm downfield, whereas the NH signal (0.65 ppm) is shifted upfield by about 0.3 ppm,[10b] which may be attributed to the presence of eight electron-donating methoxy groups at the porphycene periphery.

The UV−vis spectra of porphycene **1** and its metallo-derivatives were recorded in chloroform (Figure 1). Porphycene **1** shows one characteristic intense Soret band at 382 nm and three weaker Q-bands at 557, 599, and 636 nm. The lowest energy band is 29 and 21 nm blue-shifted compared to octaethylporphycene **2a** and etioporphycene **2b**, respectively,[10b] which may be attributed to an increase in HOMO−LUMO energy difference due to the presence of electron-rich methoxy groups at its periphery. The UV−vis spectra of metalloporphycenes **Zn1**, **Ni1**, and **Pd1** show red-shifted Soret bands at 388−390 nm compared to freebase porphycene **1** and also display one Q-band between 590 and 618 nm. Further, compound **1** displays very weak emission ($\phi_f < 10^{-4}$), whereas insertion of zinc led to a substantial enhancement in the emission (ϕ_f of **Zn1** 0.025; Supporting Information) with an intense band at 632 nm accompanied by a weaker lower energy band (689 nm). Both porphycene **1** and its Zn(II)-derivative show relatively weaker emission compared to **2a** and its Zn(II)-complex (**Zn2a**), with **Zn1** possessing a shorter fluorescence lifetime (0.6 ns; Supporting Information) compared to analogous **Zn2a** (3.2 ns).[15a]

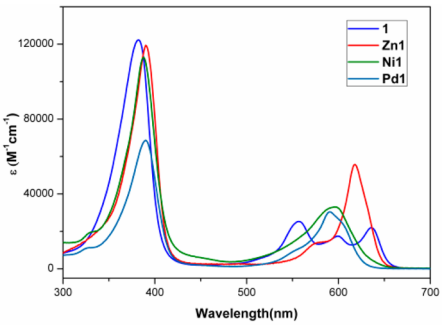


Figure 1. UV−vis spectra of **1**, **Zn1**, **Ni1**, and **Pd1** in chloroform at 25 °C.

Molecular structure of porphycenes **1**, **Pd1** and **Zn1** were unequivocally characterized in the solid state by X-ray crystallographic analysis (Figure 2). All porphycenes display planar macrocyclic core, and the observed planarity is more compared to **2a**. For example, the mean deviation of nitrogen atoms from the mean plane of porphycene **1** (excluding the methoxy substituents) is only ±0.021 Å (±0.27 Å for **2a**).[10b] This probably resulted from the reduced van der Waals repulsion between 3,6- and 13,16-substituents, by replacing the

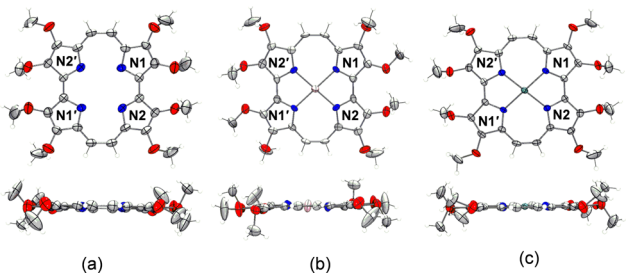


Figure 2. X-ray crystal structure of (a) **1**, (b) **Zn1**, and (c) **Pd1** (above front view and below side view) drawn in 35% probability level. Color code: C, gray; N, blue; O, red; H, white; Zn, pink; Pd, green.

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ethyl groups with less bulky methoxy groups in **2a**. However, these repulsive interactions are still strong enough to enforce a square -type core for porphycene **1** (N1···N2 2.741 Å and N1···N2′ 2.758 Å), as observed in case of **2a,b**.[10b]

Among the metalloporphycenes, the deviation is relatively more in the case of **Zn1** (±0.083 Å) than **Pd1** (±0.034 Å). As expected, metal insertion led to a change in the macrocyclic core geometry from square to rectangular type (**Pd1** N1···N2 2.575 Å, N1···N2′ 3.009 Å and **Zn1** N1···N2 2.613 Å, N1···N2′ 3.024 Å).

Redox potentials of porphycene **1** and its metallo-derivatives were determined by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) in dichloromethane (Figure 3 and Supporting Information). These porphycenes display typical two ring oxidation and two ring reduction potentials, except for **Pd1**, which shows an additional reduction potential (confirmed by DPV; the reason is not known at this stage). A closer inspection of the voltammogram of **1** reveals reversibility for the second ring reduction potential only, and further the absence of the clear reduction waves in the oxidation half indicates the unstable nature of both the cation radical and the dication of porphycene **1**. Oxidation and reduction potentials of **1** and its M(II) complexes are summarized vs SCE in Table 1.

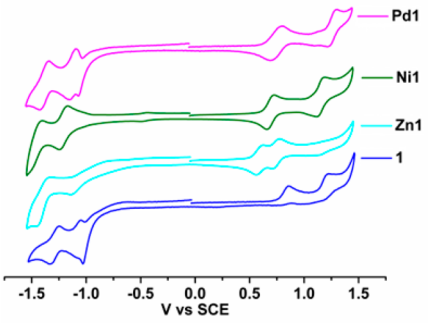

Figure 3. Cyclic voltammograms of **1**, **Zn1**, **Ni1**, and **Pd1** in dichloromethane at 25 °C (scan rate 50 mV/s).

Table 1. Comparative Oxidation and Reduction Potentials (in V vs SCE) for Porphycenes and Their M(II) Complexes

porphycenes	reduction	oxidation
1	−1.29, −1.11[a]	+0.78,[a] +1.15[a]
Zn1	−1.38, −1.13[a]	+0.60, +0.75
Ni1	−1.45, −1.19	+0.71, +1.17
Pd1	−1.36, −1.13,[a] −1.03[a]	+0.77, +1.28
2a[b]	−1.26, −0.94	+0.87, +1.10
Zn2a[b]	−1.38, −1.09	+0.64, +0.78
Ni2a[b]	−1.46, −1.06	+0.81, +1.12

[a]Measured by DPV. [b]Taken from ref 16.

All of the metallo-porphycenes show two reversible ring oxidation potentials (stabilized by the presence of Lewis acidic metal ions) and two reduction potentials. The relatively electron-rich character of the octamethoxyporphycene **1** and its metal complexes, in comparison to their octaethyl analogue **2a** and its metal complexes, is clearly reflected in their redox potentials (Table 1), in particular in their corresponding first oxidation (less positive potential) and reduction (more negative potential) potentials.[16] In addition, the evaluated HOMO−LUMO energy gap of **1** and its M(II)-derivatives from the difference between the first oxidation and first reduction potentials. The energy gap of **1** ($\Delta E = E_{ox1} - E_{red1}$ = 1.89 V) is slightly higher than that of **2a** (1.81 V), which is increased due to the presence of strong electron-donating methoxy groups and again clearly reflected in the blue shift of Q-bands in the absorption spectrum.

In photodynamic therapy, an efficient photosensitizer is one that converts molecular oxygen to singlet oxygen ($^1O_2$) most effectively, in the presence of light, which is responsible for subsequent death of the cancerous cells. So keeping this in mind, we have measured steady state luminescence spectra of singlet oxygen for **1** and its metallo-derivatives in aerated toluene. Among them, **Zn1** and **Pd1** show emission bands ranging from 1240 to 1320 nm with maxima at about 1274 nm, when excited at 600 nm (Supporting Information). Singlet oxygen quantum yield of **Zn1** and **Pd1** was evaluated by comparative actinometry method by using tetraphenylporphyrin (**H_2TPP**) as reference (ϕ_Δ 0.7) in aerated toluene.[17] The singlet oxygen quantum yields obtained for **Zn1** and **Pd1** are 0.12 and 0.73, respectively. Although not very high (up to 0.95) as noticed in case of bromo-substituted porphycenes (owing to expected heavy atom effect of bromine),[17a] still it is comparable to that observed (0.78) in the case of 2,7,12,17-tetraphenylporphycenato palladium(II).[17c] Analogous measurement for **Zn2a** and **Pd2a**, synthesized following Kita's procedure (for bipyrrole)[9d] and subsequently the route of their methoxy counterparts (Supporting Information), display singlet oxygen quantum yields of 0.68 and 0.89, respectively. Interestingly, in case of octaethylporphycene, the effect of the heavy atom is marginal (Zn vs Pd), whereas that in case of their methoxy analogues is quite substantial. This indicates the higher intersystem crossing (ISC) noticed in the case of **Zn2a**[15a] is not a general phenomenon in porphycenes. Further, like its strong dependence on nature of substituents at the periphery,[15b] it also depends on the nature of the metal ion at the core, and further detailed photophysical study may elaborate on this aspect. Free base **1** didn't show any singlet oxygen emission like **2a**, probably due to lack of efficient ISC.[15a]

In conclusion, PIFA-TMSBr coupling of 3,4-dimethoxypyrrole to corresponding bipyrrole enabled us to synthesize octamethoxyporphycene **1** for the first time, which happens to be the most efficient route toward the synthesis of β-substituted porphycenes. Further, the presence of methoxy groups led to an increase in their hydrophilicity (these porphycenes display good solubility in methanol). Photosensitizers based on the Pd(II)-porphyrinoids display promising results in clinical trials.[3c] In this regard, the Pd(II)-complex of porphycene **1** possesses efficient singlet oxygen quantum yield (73%), along with its expected higher cell viability (owing to the presence of eight methoxy groups), may emerge as a promising photosensitizer for photo-oxidation, DNA cleavage, and PDT.

■ ASSOCIATED CONTENT

Supporting Information

Reaction scheme, detailed experimental procedures, NMR spectra, electrochemical data, singlet oxygen luminiscence spectra and crystal data CCDC 950087−950091. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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