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Novel Route to Functionalized Tetraaryltetra[2,3]naphthaloporphyrins via Oxidative Aromatization

Olga S. Finikova,[†] Andrei V. Cheprakov,[‡] Patrick J. Carroll,[§] and Sergei A. Vinogradov*[,†]

Department of Biochemistry and Biophysics, University of Pennsylvania, Philadelphia, Pennsylvania 19104, Department of Chemistry, Moscow State University, Moscow 119899, Russia, and Department of Chemistry, Crystallographic Laboratory, University of Pennsylvania, Philadelphia, Pennsylvania 19104

vinograd@mail.med.upenn.edu

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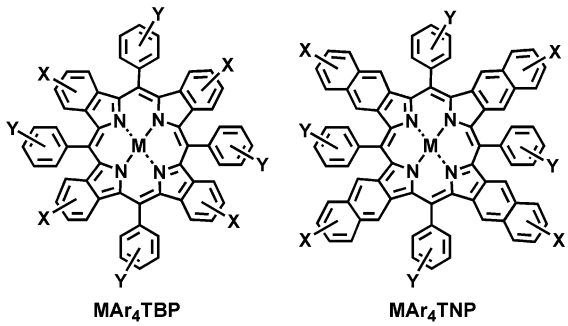
Abstract: A novel general route to substituted *meso*-tetraaryltetra[2,3]naphthaloporphyrins (Ar_4TNP) and *meso*-tetraaryloctamethoxytetra[2,3]naphthaloporphyrins ($Ar_4(MeO)_8$TNP) via oxidative aromatization of nonaromatically fused porphyrin precursors is described. $Ar_4(MeO)_8$TNPs exhibit more red-shifted absorption bands than Ar_4TNPs and differ dramatically in solubility. The first X-ray crystallographic structure of tetranaphthaloporphyrin, i.e., $PdAr_4$TNP (Ar = 4-$MeO_2CC_6H_4$), revealed that the degree of nonplanar distortion of this macrocycle is only slightly higher than that of the homologous tetrabenzoporphyrins (Ar_4TBP).

Porphyrins extended via fusion with external aromatic rings[1] exhibit remarkably red-shifted absorption bands and strong room temperature luminescence. The simplest representatives of laterally extended porphyrins, *meso*-tetraaryltetrabenzoporphyrins (Ar_4TBP), have already been shown to be of interest for biomedical[2] and nonlinear optical applications.[3] At the same time, the next group in the extended porphyrin family, i.e., tetranaphthaloporphyrins, have been explored only minimally,[4] despite their great potential for PDT,[4d] medical oxygen imaging,[4e] and electrooptical[4c] applications.



Naphthalo extension of the core pyrrole moiety leads to an array of isomeric tetranaphthaloporphyrins.[1b] Among them, tetra[2,3]naphthaloporphyrins (TNP) and their more soluble analogues *meso*-tetraaryltetra[2,3]-naphthaloporphyrins (Ar_4TNP)[5] are of particular interest due to their higher molecular symmetry and, consequently, much narrower and stronger spectral transitions.[1] Unfortunately, extremely poor synthetic availability of TNPs and Ar_4TNPs was a serious obstacle on the way to discovery of their practical potential.

The original approach to Ar_4TNPs,[6] based on a high-temperature template condensation of [2,3]naphthalenedicarboximide with arylacetic acids, was of low practicality due to the required severe reaction conditions, extremely low yields (<1%),[4f] and laborious purifications. Recently, a new approach to TNPs has been developed that makes use of the retro-Diels−Alder reaction.[7] This method affords Ar_4TNPs in excellent yields (at the last step of the reaction sequence) but does not permit the introduction of substituents into the fused aromatic rings. In our own effort to develop approaches to aromatically annulated porphyrins, we recently came across a useful strategy based on oxidative aromatization of porphyrins fused with nonaromatic cyclohexene rings.[8] Using this method, a large variety of polyfunctionalized Ar_4TBPs could be obtained in very good yields. Naturally, the question of whether this methodology can be extended to the synthesis of Ar_4TNPs was raised. Oxidative aromatization of nonaromatic precursor porphyrins has been in fact employed in the syntheses of tetra[1,2]naphthaloporphyrins,[9] mono[1,2]-[10,11] and di[1,2]naphthaloporphyrins,[10,12] and a mono[2,3]naphthaloporphyrin.[13]

* To whom correspondence should be addressed. Phone: (215) 898-6382. Fax: (215) 573-3787.

[†] Department of Biochemistry and Biophysics, University of Pennsylvania.

[‡] Department of Chemistry, Moscow State University.

[§] Crystallographic Laboratory, University of Pennsylvania.

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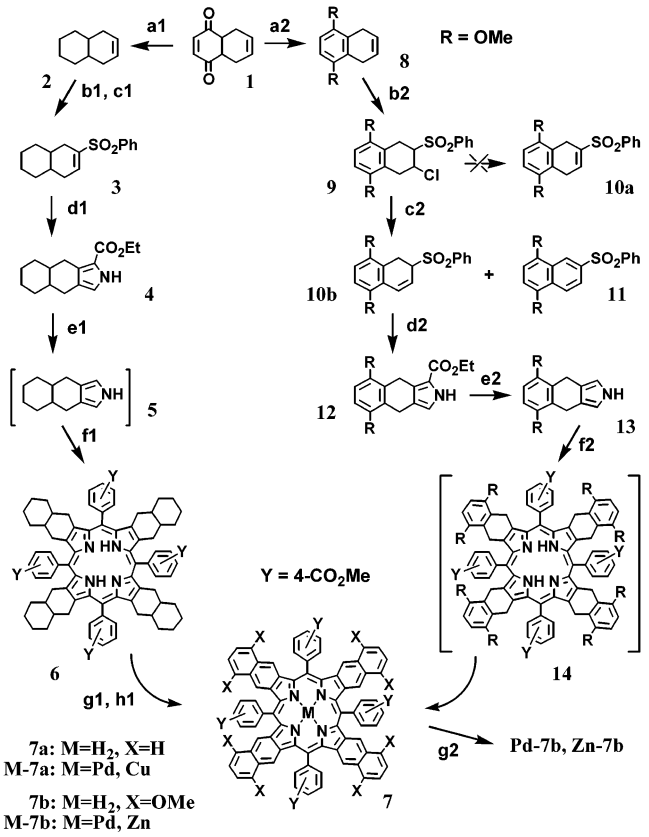
SCHEME 1[a]



[a] Key: (**a1**) (1) sealed tube, C_6H_6, 50 °C, 24 h, (2) Zn dust, AcOH−H_2O, reflux, 30 min, (3) NH_2NH_2·H_2O, KOH, ethylene glycol (40%); (**b1**) (1) PhSCl, CH_2Cl_2, (2) *m*-CPBA; (**c1**) DBU, CH_2Cl_2 (80% for **b1** + **c1**); (**d1**) $CNCH_2CO_2Et$, *t*BuOK, THF, 0 °C to rt (88%); (**e1**) KOH, $(CH_2OH)_2$, reflux, 30 min; (**f1**) (1) ArCHO, BF_3·Et_2O, CH_2Cl_2, 1.5−2 h, rt, (2) DDQ (40% for **e1** + **f1**); (**g1**) $PdCl_2$, MeCN−THF, Et_3N, reflux, 15 min (97%), or $Cu(OAc)_2$·$2H_2O$, CH_2Cl_2−MeOH, reflux, 10 min (99%); (**h1**) DDQ, toluene, reflux, 5 min (46% for **Pd-7a**); or in the presence of $Sc(OTf)_3$ (20% for **Cu-7a**); (**a2**) Me_2SO_4, K_2CO_3, acetone, reflux, 36 h (98%); (**b2**) same as **b1** (97%); (**c2**) same as **c1** (47% for **9b**, 30% for **10**); (**d2**) same as **d1** (33%); (**e2**) same as **e1** (77%); (**f2**) same as **f1** (44% for **14b**); (**g2**) $PdCl_2$ or $Zn(OAc)_2$·$2H_2O$, PhCN/pyridine, reflux, 1 min (80% for **Pd-7b**, 70% for **Zn-7b**).

Surprisingly, synthesis of symmetrical Ar_4TNPs, whose optical properties seem to be much more interesting and practically useful, has never been tackled using this approach. Herein, we report a new route to peripherally substituted Ar_4TNPs based on oxidative aromatization and the first X-ray structure of a novel tetranaphthalo-fused porphyrin.

Two types of cycloalkyl-fused porphyrins were considered as precursors of Ar_4TNP's (Scheme 1). Porphyrin **6** contains fused saturated octahydronaphthalene rings and requires the subtraction of 32 hydrogens for complete aromatization. Tetrahydronaphthalene-fused porphyrin **14**, on the other hand, requires the removal of only eight hydrogens, which places it much closer to the target Ar_4-TNP (**7**) implying easier aromatization. Both routes (Scheme 1) employ the Diels−Alder adduct of butadiene and *p*-benzoquinone (**1**) as the starting material.

In the first route, **1** was converted (**a1**) into *cis*-Δ^2-octaline **2**,[14] which was transformed into vinyl sulfone **3** via the sequence of published reactions (**b1, c1**).[15] Vinyl sulfone **3** reacted with ethyl isocyanoacetate in the modified Barton-Zard synthesis[16,17] (**d1**), giving pyrrole ester **4**, which was converted into pyrrole **5** upon reflux with KOH in ethylene glycol (**e1**). Pyrrole **5** without isolation was introduced into Lindsey-type condensation (**f1**), yielding porphyrin **6** in 44% yield.

Owing to their extremely high basicities, nonplanar *meso*-tetraarylated cycloalkyl-fused porphyrins easily form dications,[18] which are completely inert in oxidative aromatization. Accordingly, aromatization requires conversion of the precursor porphyrins into appropriate metal complexes. The best result was obtained with Pd derivative **Pd-6**, which was oxidized by DDQ (**h1**) into **Pd-7a** in 46% yield. Aromatization of **Cu-6** appeared much less effective (2−3% yield) but was improved considerably in the presence of $Sc(OTf)_3$,[19] affording **Cu-7a** in 20%. By removing Cu from **Cu-7a** using hot phosphoric acid free-base porphyrin **7a** was obtained and characterized by MALDI and optical spectroscopy (see below).

The second route, leading to octamethoxyporphyrin $Ar_4(MeO)_8$TNP **7b**, starts with conversion (**a2**) of **1** into 5,8-dimethoxy-1,4-dihydronaphthalene **8**,[20] followed by the transformation (**b2**) of **8** into α-chlorosulfone **9**.[15] Treatment of **9** with DBU (**c2**) did not, however, give the expected α-vinyl sulfone (**10a**), but instead resulted in the formation of isomeric allyl sulfone **10b** and an undesired byproduct, naphthosulfone **11**. The yield of **11** most likely can be minimized by optimizing the reaction conditions. Nevertheless, allyl sulfone **10b** was found to be active in the Barton−Zard reaction (**d2**),[21] affording pyrrole ester **12** in 33% yield. Compound **12** was further transformed (**e2**) into pyrrole **13**, and **13** was introduced into Lindsey condensation with methyl 4-formylbenzoate (**f2**). The remarkable feature of this synthesis was that instead of the expected porphyrin **14**, the target $Ar_4(MeO)_8$-TNP **7b** was obtained directly as the only product. Apparently, the driving force for aromatization of **14** is so high that removal of all the remaining hydrogens

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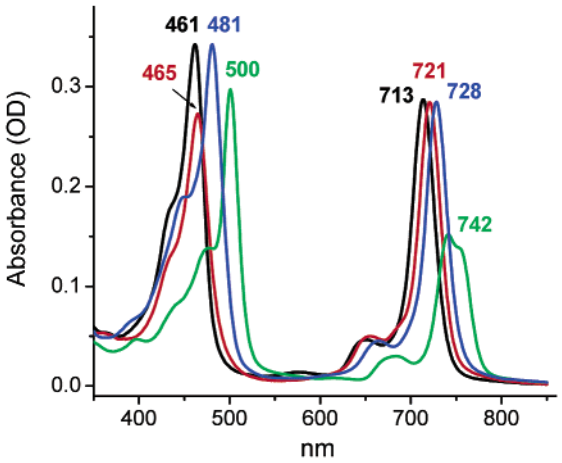

FIGURE 1. Selected optical spectra of Ar_4TNPs. Black line: **Pd-7a** in pyridine. Blue line: **Cu-7a** in THF. Red line: **Pd-7b** in pyridine. Green line: **7b** in THF.

occurred spontaneously even under quite acidic conditions required in the Lindsey reaction. It is possible that oxidation of **14** is additionally favored by the presence of eight electron-donor methoxy groups in **14**, which are likely to decrease its oxidation potential.

Despite their similar molecular structures, Ar_4TNP **7a** and $Ar_4(MeO)_8$TNP **7b** exhibit dramatically different solubility. While **7a** and its metal complexes are well soluble in most organic solvents (e.g., CH_2Cl_2, THF), **7b** is only slightly soluble in hot pyridine, benzonitrile, and nitrobenzene. NMR spectroscopy suggests that both **7a** and **7b** and especially their Pd derivatives tend to aggregate in solutions. The ^{1}H NMR spectra of **7a-Pd** in $CDCl_3$ and **7b-Pd** in nitrobenzene-d_5, however, could be improved by the addition of pyridine and/or DMSO.

Both absorption bands of **Pd-7b** are red-shifted compared to those of **Pd-7a** (e.g., $\lambda_Q^{\mathbf{Pd\text{-}7b}} = 721$ nm vs $\lambda_Q^{\mathbf{Pd\text{-}7a}} = 713$ nm in pyridine) (Figure 1). Electron-donor groups, such as methoxy, are known to result in bathochromic shifts in the spectra of porphyrins, probably via the raising of HOMO energy levels. Interestingly, despite its decreased oxidation potential, porphyrin **Pd-7b** was found to be quite stable with respect to oxidation, even under conditions promoting photosensitization, i.e., in dilute solutions at room light, exposed to air. Both **Pd-7a** and **Pd-7b** exhibit room-temperature phosphorescence (for example, for **Pd-7b**: $\lambda_{max} = 948$ nm, $\tau_0 = 63$ μs, $\phi = 7.9\%$) suggesting suitability as markers for in vivo tissue oxygen imaging, especially considering that their Q-bands fall exactly into the spectral region commonly referred to as "near infra-red window of tissue". On the other hand, complete quenching of phosphorescence in aerated solutions implies that these metalloporphyrins are efficient singlet oxygen sensitizers and perhaps potent chromophors for PDT. Since only trace amounts of fluorescence could be detected from both **Pd-7a** and **Pd-7b**, the triplet states in these molecule are likely to be generated with high efficiencies. High triplet quantum yields combined with the increased gaps between the Q and Soret bands ($\Delta\lambda > 250$ nm) reveals the potential of naphthaloporphyrins as optical limiters.

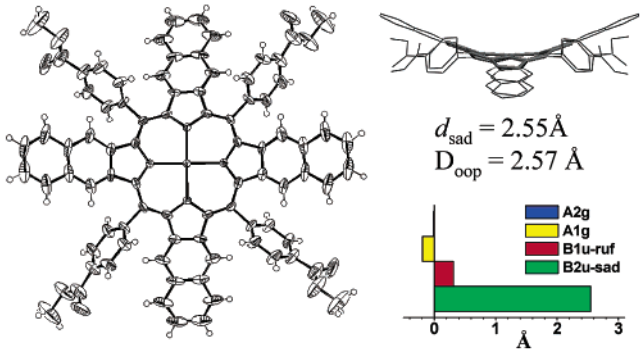

FIGURE 2. Molecular structure of **Pd-7a**. The diagram depicts the results of the NSD analysis.[24]

In comparison with a similar Pd tetraaryltetrabenzoporphyrin ($PdAr_4TBP$, Ar = 4-$BuO_2CC_6H_4$), porphyrin **7a** exhibits more than 70 nm red shift of the absorption Q-band ($\lambda_Q^{\mathbf{PdAr4TBP}} = 632$ nm),[2e] suggesting the dramatic effect of extra π-extension and, possibly, of extra nonplanar distortion, which is known to cause red-shifts in the optical spectra of porphyrins.[22] The ab initio calculations of $ZnPh_4TBP$ and $ZnPh_4TNP$, however, showed nearly identical nonplanarity in these extended macrocycles.[4f] It was, therefore, of interest to compare the experimental crystal structures of Ar_4TBP and Ar_4TNP complexes. The X-ray structure of **Pd-7a**[23] is shown in Figure 2 together with its NSD (normal-coordinate structural decomposition) analysis.[24]

The main distortion in **Pd-7a** is of the saddle type (B2u), combined with a slight ruffling (B1u). The same modes were found to be dominant in the other reported structures of extended porphyrins.[18] Importantly, the degrees of the saddle distortion in **Pd-7a** ($d_{sad} = 2.55$ Å) and of the total out-of-plane distortion ($D_{oop} = 2.57$ Å) are rather close to those observed in the structure of $ZnPh_4TBP$·THF ($d_{sad} = 2.34$ Å, $D_{oop} = 2.35$ Å).[25] Certainly, it is expected that distortions of Ar_4TNPs and Ar_4TBPs are influenced by the metals (Pd vs Zn); however, consistent with computational analysis[4f] it is mainly the lateral [2,3]naphthalo extension in Ar_4TNPs that causes the extra red-shift of its absorption.

In conclusion, a novel method of synthesis of polysubstituted Ar_4TNPs is developed which allows for the introduction of substituents in the *meso*-aryl as well as in the fused rings on the macrocycle. Because of their optical properties Ar_4TNPs are of great interest for PDT, in vivo oxygen imaging, and optical limiting applications.

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(23) Crystal Data. **Pd-7a** [$Pd(MeO_2CC_6H_4)_4TNP$]: $PdC_{86}H_{56}N_4O_6Cl_4$, dark brown prism from PhCN/pyridine, tetragonal, space group I_1/a, with $a = 17.628(3)$ Å, $c = 23.372(5)$ Å, $V = 7262(2)$ Å^3, $Z = 4$ and $d_{calc} = 1.392$ g/cm^3, 4046 reflections (24216 total) with $F > 4\sigma(F)$, $R_1 = 0.0817$, w$R_2 = 0.2561$. CCDC 209497 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information Available: Experimental details, compounds characterization, and spectroscopic data for all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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