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Quinoline-Annulated Porphyrins

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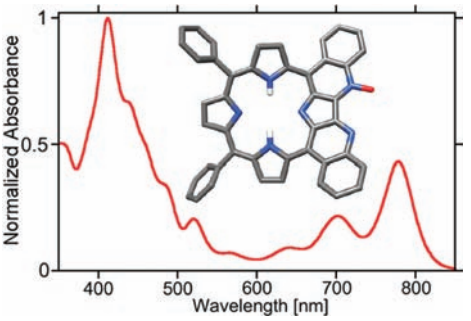
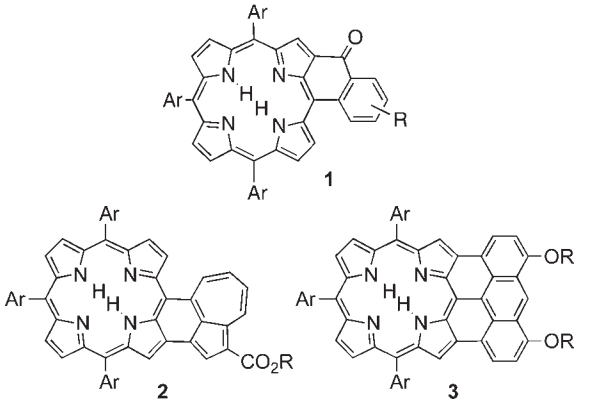
ABSTRACT



Porphyrin-2,3-dione mono- and dioximes were used as starting materials for the efficient syntheses of mono- and bis-quinoline-annulated porphyrins and their corresponding *N*-oxides. Owing to an extended π-system, these novel porphyrinoid chromophores show significantly red-shifted UV−vis spectra compared to the parent porphyrins. A crystal structure exemplifies the nonplanar conformation of the macrocycle.

The maximum wavelength of absorbance (λ_{max}) for the prototypical and most readily synthesized porphyrin *meso*-tetraphenylporphyrin is 648 nm. This is outside the 'optical window' of tissue.[1] Therefore, unmodified porphyrins can find only limited use as spectroscopic labels, photosensitizers, or imaging agents in tissue. Porphyrin reduction or ring expansion may generate red-shifted chromophores.[2] The establishment of a covalent linkage between the β-position and a flanking phenyl group, such as in **1**, has also shown to be a viable route toward bathochromically shifted *meso*-tetraarylporphyrin-based chromophores, as long as the linkage forces the phenyl group into (idealized) coplanarity with the porphyrinic chromophore, thus extending the π-conjugation pathway.[3,4]



In general, the strategy to expand the porphyrinic π-conjugated electronic system by direct fusion of a coplanar aromatic segment onto the periphery of the

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(1) Generally speaking, the wavelength between 600 and 1300 nm. Anderson, R. R.; Parrish, J. A. *J. Invest. Dermatol.* **1981**, *77*, 13–19. For instance, the wavelengths of maximum penetration of breast tissue are ~725 nm.Cerussi, A. E.; Berger, A. J.; Bevilacqua, F.; Shah, N.; Jakubowski, D.; Butler, J.; Holcombe, R. F.; Tromberg, B. J. *Acad. Radiol.* **2001**, *8*, 211–218.

(2) (a) Sessler, J. L.; Weghorn, S. *Expanded, Contracted & Isomeric Porphyrins*; Pergamon Press: New York, NY, 1997. (b) *The Porphyrin Handbook, Vol. 2 - Heteroporphyrins, Expanded Porphyrins and Related Macrocycles*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 2. (c) Flitsch, W. *Adv. Heterocycl. Chem.* **1988**, *43*, 73–126.

(3) (a) Fox, S.; Boyle, R. W. *Tetrahedron* **2006**, *62*, 10039–10054. (b) Daniell, H. W.; Brückner, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1688–1691.

(4) McCarthy, J. R.; Hyland, M. A.; Brückner, C. *Org. Biomol. Chem.* **2004**, *2*, 1484–1491.

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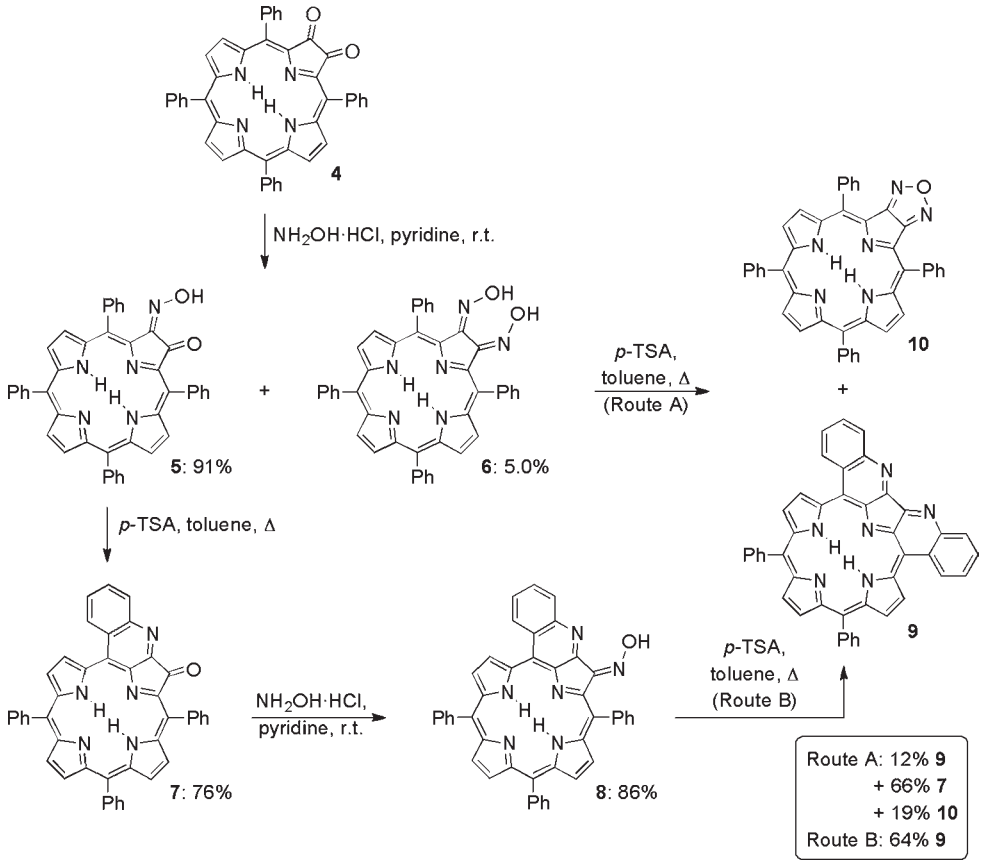
Scheme 1. Synthesis and Acid-Induced Reactions of Porphyrin-2,3-dione Mono- and Dioximes



porphyrin has been shown to be quite versatile, whereby the largest spectral shifts are achieved by annulation of (multiple) polycyclic aromatic moieties (including other porphyrins).[5,6] Recent examples, such as the azulene- and anthracene-fused porphyrins **2** and **3**, introduced by Osuka, Kim, and Anderson, respectively, are representative examples for such annulated porphyrins.[6]

Porphyrin-2,3-dione **4**, introduced by the group of Crossley,[7] was shown to be a versatile molecule for the generation of a structurally diverse family of β,β-annulated systems by reaction of **4** with diamines.[8] We report here the formation and reactivity of the mono- and dioximes of **4** (Scheme 1) and their conversion to mono- and bis-quinoline-annulated chromophores that are also characterized by bathochromically shifted optical spectra when compared to the parent *meso*-tetraphenylporphyrin or dione **4**. We also report the formation and X-ray crystal structure of a bis-quinoline-fused porphyrin quinoline-*N*-oxide **12**.

Reaction of dione **4** with an ~100-fold excess of $NH_2OH \cdot HCl$ in pyridine at ambient temperature over 24 h forms one major product and a minor product (91% and 5% isolated yields, respectively) that are identified as the corresponding monooxime **5** (HR-MS ESI+, 100% CH_3CN, suggests a composition of $C_{44}H_{30}N_5O_2$ for MH^+) and bisoxime **6**, respectively. A diagnostic signal in the ^1H NMR spectrum ($CDCl_3$, 400 MHz) for **5** is a

(5) For recent select examples of aromatic systems fused to porphyrins, see: (a) Lash, T. D.; Werner, T. M.; Thompson, M. L.; Manley, J. M. *J. Org. Chem.* **2001**, *66*, 3152–3159. (b) Gill, H. S.; Harmjanz, M.; Santamaría, J.; Finger, I.; Scott, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 485–490. (c) Nakamura, N.; Aratani, N.; Shinokubo, H.; Takagi, A.; Kawai, T.; Matsumoto, T.; Yoon, Z. S.; Kim, D. Y.; Ahn, T. K.; Kim, D.; Muranaka, A.; Kobayashi, N.; Osuka, A. *J. Am. Chem. Soc.* **2006**, *128*, 4119–4127. (d) Hayashi, S.; Tanaka, M.; Hayashi, H.; Eu, S.; Umeyama, T.; Matano, Y.; Araki, Y.; Imahori, H. *J. Phys. Chem. C* **2008**, *112*, 15576–15585. (e) Sooambar, C.; Troiani, V.; Bruno, C.; Marcaccio, M.; Paolucci, F.; Listorti, A.; Belbakra, A.; Armaroli, N.; Magistrato, A.; De Zorzi, R.; Geremia, S.; Bonifazi, D. *Org. Biomol. Chem.* **2009**, *7*, 2402–2413. (f) Jiao, C. J.; Huang, K. W.; Guan, Z. P.; Xu, Q. H.; Wu, J. S. *Org. Lett.* **2010**, *12*, 4046–4049. (g) Diev, V. V.; Hanson, K.; Zimmerman, J. D.; Forrest, S. R.; Thompson, M. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5523–5526 and references therein.

(6) (a) Kurotobi, K.; Kim, K. S.; Noh, S. B.; Kim, D.; Osuka, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 3944–3947. (b) Davis, N. K. S.; Pawlicki, M.; Anderson, H. L. *Org. Lett.* **2008**, *10*, 3945–3947. (c) Davis, N. K. S.; Thompson, A. L.; Anderson, H. L. *J. Am. Chem. Soc.* **2011**, *133*, 30–31. (d) Davis, N. K. S.; Thompson, A. L.; Anderson, H. L. *Org. Lett.* **2010**, *12*, 2124–2127.

(7) First report: (a) Crossley, M. J.; Burn, P. L. *J. Chem. Soc., Chem. Commun.* **1987**, 39–40. Alternative syntheses: (b) Crossley, M. J.; Harding, M. M.; Sternhell, S. *J. Org. Chem.* **1988**, *53*, 1132–1137. (c) Daniell, H. W.; Williams, S. C.; Jenkins, H. A.; Brückner, C. *Tetrahedron Lett.* **2003**, *44*, 4045–4049. (d) Starnes, S. D.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 4659–4669.

(8) For recent examples, see: (a) Khoury, T.; Crossley, M. J. *Chem. Commun.* **2007**, 4851–4853. (b) Khoury, T.; Crossley, M. J. *New J. Chem.* **2009**, *33*, 1076–1086. (c) Crossley, M. J.; Sintic, P. J.; Walton, R.; Reimers, J. R. *Org. Biomol. Chem.* **2003**, *1*, 2777–2782.

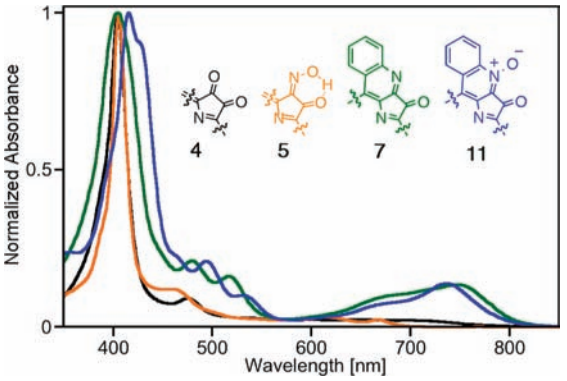


Figure 1. UV−vis spectra (CH_2Cl_2) of dione **4** (black trace), monooxime **5** (tangerine trace), monoquinoline-fused **7** (green trace), and quinoline *N*-oxide **11** (blue trace).

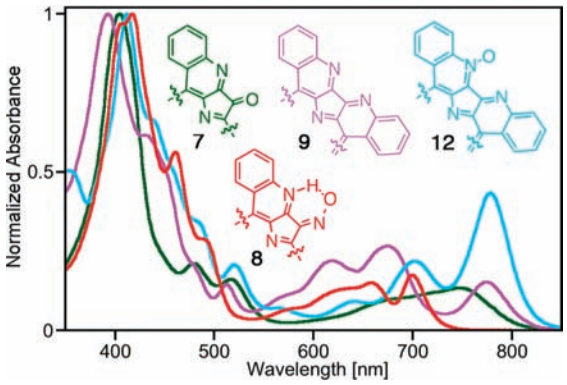


Figure 2. UV−vis spectra (CH_2Cl_2) of monoquinoline-fused **7** (green trace), monoquinoline-oxime **8** (red trace), bis-quinoline-fused **9** (violet trace), and bis-quinoline-fused *N*-oxide **12** (turquoise trace).

broadened peak at 15.7 ppm that is exchangeable with D_2O, assigned to the oxime hydrogen that is H-bonded to the neighboring carbonyl group. Of note is that reaction of **5** over extended periods of time with excess $NH_2OH \cdot HCl$ in pyridine yields only small (< 20% yield) quantities of bisoxime **6**.

The UV−vis spectrum of the monooxime **5** and the starting material **4** are similar in that both have a much broadened Q-band region (Figure 1). The bisoxime **6** possesses a much sharpened UV−vis spectrum (see Supporting Information).

Treatment of olive-colored monooxime **5** with a strong acid (*p*-TSA) under enforcing conditions (toluene, reflux) converts it into a light brown product with a mass indicating the loss of H_2O (HR-MS ESI+, 100% CH_3CN, suggests a composition of $C_{44}H_{28}N_5O$ for MH^+). The ^1H NMR spectrum of this product shows the hallmarks of the presence of an *o*-fused phenyl group (also confirmed by 2D NMR spectroscopy, see ESI).[4] The ^{13}C NMR and IR (neat) spectra indicate the preservation of the one β-imine and one β-ketone (at 151 and 196 ppm, respectively). Taken together, the spectroscopic evidence suggests quinoline-fused structure **7**. This structure could be indirectly confirmed by the X-ray crystal analysis of a downstream product (see below).

The quinoline moiety fused to an oxochlorin framework represents a novel motif in annulated porphyrins. The steric requirements of this all-sp^2-atom fusion imply, first, an idealized coplanarity of the porphyrinoid chromophore with the quinoline and, second, a steric clash between the *o*′-hydrogen of the fused phenyl group with the neighboring β-hydrogen. The latter may be alleviated by a distortion of the chromophore from planarity. The UV−vis spectrum of **7** is much different from that of the starting material and shows an overall broadened Soret band and an intensified, broadened, and red-shifted Q-band region (Figure 1).

The β-keto functionality of **7** is susceptible to conversion to the corresponding oxime **8**. Diagnostic peaks for resulting oxime **8** in the ^1H NMR spectrum are, analogous to oxime **5**, the signal for the strongly H-bonded oxime hydrogen (at 15.9 ppm). The ketone-to-oxime conversion of **7** to **8** perturbs the UV−vis spectrum much more than the corresponding conversion of dione **3** to oxime **5** (cf. Figures 1 and 2). Oxime **8** lends itself to the formation of the bisquinoline-fused system **9**. The conversion generates a molecule with 2-fold symmetry in its NMR spectra and only one imine stretching frequency in its IR spectrum.[9] Owing to the presence of the two annulated quinoline systems forming a pyrrolo-[3,2-*b*:4,5-*b*′]diquinoline moiety, a dramatically bathochromic UV−vis spectrum (λ_{max} = 775 nm) is observed (Figure 2), complementing the results obtained for other annulated systems, such as **2** and **3**.[6]

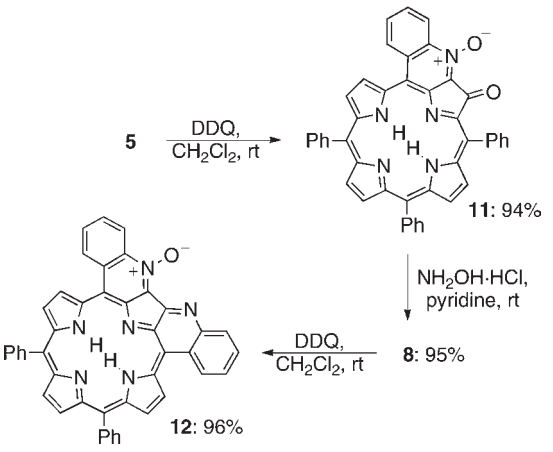
Bisoxime **6** can also be directly converted to bisquinoline **9**, albeit at significantly lower yield (12%) compared to the stepwise approach (**5**→**7**→**8**→**9**, overall yield ~40%).[10] Upon treatment of bisoxime **6** with acid, the majority of the starting material ring-fuses only once and hydrolyzes to monofused ketone **7**. The next common product is the dehydration product 1,2,5-oxadiazole-fused porphyrin **10**. The latter is a novel porphyrin-fused system, but since its UV−vis spectrum is very regular porphyrin-like, compound **10** will not be discussed any further.

Serendipitously we found that oxidation of monooxime **5** with DDQ also establishes a quinoline-fused porphyrin, albeit as the quinoline-*N*-oxide **11** (Scheme 2). $NaBH_4$ reduction of **11** regenerates **7**, though a DDQ oxidation of **7** does not lead to **11**. Quinoline-fused system **7** and its *N*-oxide analogue **11** show very similar NMR spectroscopic properties, and the presence of the oxygen is only clearly demonstrated by MS. The presence of the *N*-oxide has, however, an influence on the UV−vis

(9) Solubility problems prevented the recording of ^{13}C NMR of **9**, but its Ni(II) complex is soluble and characterized, including ^{13}C NMR spectrum; see Supporting Information.

(10) Also considering the inefficient synthesis of bisoxime **6**, the direct synthesis of bisquinoline **9** is not at all advantageous.

Scheme 2. Oxidation-Induced Reactions of Oximes **5** and **8**



spectrum of the chromophore, highlighting the direct conjugation of the quinoline with the porphyrinic chromophore (Figure 1).

Reaction of β-keto *N*-oxide **11** with hydroxylamine converts it to quinoline oxime **8**; i.e., the *N*-oxide moiety is lost in the process (Scheme 2). Oxidation of this oxime establishes once again a fused quinoline *N*-oxide moiety, thus forming the mono-*N*-oxide of the bis-quinoline-fused compound **9**, *N*-oxide **12**. Again, the *N*-oxidation of **9** has a surprisingly strong effect on the UV−vis spectrum of **12**.

Crystals of **12** suitable for investigation by single crystal X-ray diffractometry could be grown by diffusion of MeOH into a solution of **12** in $CHCl_3$ (Figure 3). The structure confirms the deduced connectivity of **12** and, by inference, confirms also the structure of the mono- and bis-quinoline fused systems **7**−**9** and **11**. Most noticeable, the pentacyclic pyrrole-fused bis-quinoline moiety is nearly planar, while the porphyrinic macrocycle is significantly nonplanar. Most likely, the steric interactions between the β-hydrogens on the pyrrole and the hydrogens on the neighboring quinoline force the macrocycle into the observed conformation.

The quinoline-annulated porphyrins possess low (0.1 to 10^{-3} %) fluorescence and singlet oxygen quantum yields, an effect likely due to the interaction of the porphyrinic π−system with the imine/ketone functionalities. A detailed study of the ground and excited state photophysical parameters of these chromophores is currenly ongoing.

In conclusion, we have shown that porphyrin-2,3-dione mono- and bisoximes can be utilized in the generation of

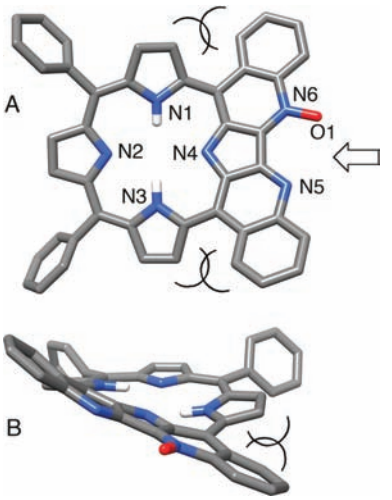


Figure 3. Single crystal X-ray structure of bis-quinoline-fused *N*-oxide system **12**. (A) Top view. (B) View along axis indicated in A by arrow. Disorder or hydrogens attached to sp^2-carbons not shown for clarity. Steric interaction between the β-hydrogens and the neighboring quinoline hydrogens is indicated. For full crystallographic information, see Supporting Information.

quinoline-annulated porphyrin chromophores with significantly bathochromic spectra compared to regular porphyrins. The red shift is rationalized by the presence of an extended porphyrinic π-system. Thus, we have merged Crossley's β,β'-annulation strategies with *meso*-β-fusions to generate a novel *meso*-β,β'-*meso*-annulated system. We have also shown a further modulation of the chromophore by *N*-oxidation of the annulated heterocycle.

Studies investigating the metal complexes, particularly those of group 10 metal ions, and a detailed photophysical characterization of the novel chromophores are ongoing.

Acknowledgment. This work was supported by the U.S. National Science Foundation under Grant Number CHEM-0517782 (to C.B.). The diffractometer was funded by NSF Grant 0087210, by Ohio Board of Regents Grant CAP-491, and by YSU.

Supporting Information Available. Experimental procedures and characterization data of new compounds, including representative reproductions of ^1H, ^{13}C NMR and IR spectra. X-ray crystallographic data of compound **13** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.