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Fast and Robust Route to Hydroporphyrin−Chalcones with Extended Red or Near-Infrared Absorption

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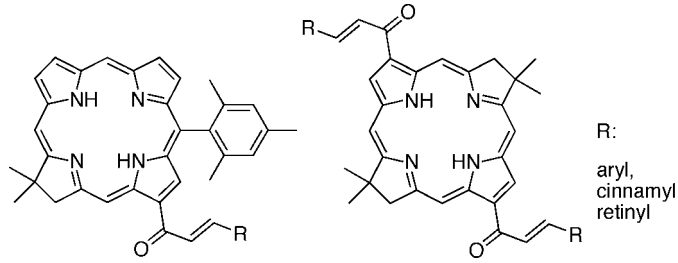
ABSTRACT



The reaction of an acetylchlorin or diacetylbacteriochlorin with an aldehyde under microwave conditions readily affords the corresponding hydroporphyrin−chalcone. The aldehydes include aryl aldehydes, cinnamaldehyde, and *all-trans*-retinal. The chalcone causes a bathochromic shift of the long-wavelength absorption band of the hydroporphyrin by up to 24 nm. The facile conjugation and wavelength tunability should make such constructs valuable for fundamental spectroscopic studies as well as diverse photochemical applications in the relatively unexplored red and near-infrared spectral regions.

The development of chromophores that absorb in the red and near-infrared (NIR) spectral regions is essential for diverse applications. For photodynamic therapy or in vivo optical imaging, red and NIR light affords deep penetration in soft tissue.[1] For flow cytometry, fluorophores that function in the red and NIR regions would complement UV- and visible-region fluorophores and thereby increase the range of multicolor applications.[2] For artificial photosynthesis, the ability to capture sunlight in the red and NIR regions is essential for high solar-conversion efficiency.[3]

Chlorophylls and bacteriochlorophylls, nature's chief chromophores, display strong absorbances in the red and NIR regions. Semisynthetic modification of chlorophylls and bacteriochlorophylls has been widely used but exhibits limitations due to a nearly full complement of substituents about the perimeter of the macrocycle[4] and, in the case of bacteriochlorophylls, susceptibility to adventitious dehydrogenation.[5] A synthetically intensive yet ultimately more versatile alternative relies on de novo synthesis, which has afforded chlorins[6] and bacteriochlorins[7] that are stable by virtue of a geminal dimethyl group in each pyrroline ring.

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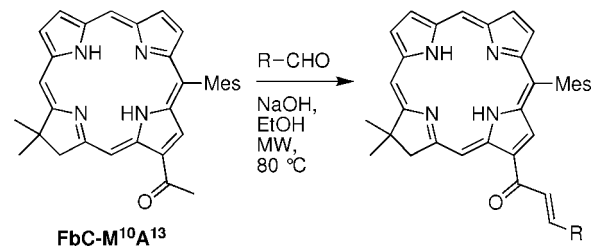
Numerous chlorin[8,9] and bacteriochlorin[10,11] analogues have been prepared bearing substituents at designated sites. Functionalization of the 3- and 13-positions by Pd-mediated (Sonogashira, Stille, and Suzuki) coupling reactions provided a means to tune the position of the long-wavelength absorption band. Of particular interest are 3/13-acetylhydroporphyrins, which display strong red or NIR absorption.[8−10]

The availability of acetyl substituents suggested elaboration into chalcones. Chalcones are readily derived by aldol condensation and have found use in medical therapy,[12] as optical materials,[13] and as polymeric UV-absorption filters.[14] However, most studies concerning the spectroscopic properties of chalcones have focused on carbocycles and heterocycles,[15] and the few known examples of chalcone analogues of tetrapyrrole macrocycles result from the use of a formylporphyrin[16] rather than acetylhydroporphyrins. The aldol condensation has recently been performed under microwave irradiation.[17,18] Microwave irradiation also has been used with (hydro)porphyrins for the formation of the macrocycle,[19] metal insertion,[20] and functionalization.[19,21]

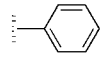
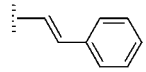
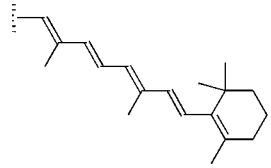
This report describes the condensation of an acetylchlorin (**FbC-M^{10}A^{13}**; derived from the zinc chelate,[9] see the Supporting Information) and a diacetylbacteriochlorin (**BC-A^{3}A^{13}**)[10] with a variety of aldehydes. The aldol condensation was carried out using **FbC-M^{10}A^{13}** or **BC-A^{3}A^{13}** with 4 equiv of the aldehyde and 20 equiv of NaOH in absolute ethanol at 80 °C under microwave irradiation for 40 min in a sealed microwave tube.

Under these conditions, the 13-acetylchlorin **FbC-M^{10}A^{13}** was treated with benzaldehyde, *trans*-cinnamaldehyde, and *all-trans*-retinal, affording **FbC-1**, **FbC-2**, and **FbC-3**, respectively (Table 1). The reaction with benzaldehyde and *trans*-cinnamaldehyde gave excellent yields (92% and 90%, respectively). The reaction with *all-trans*-retinal afforded the retinyl-chlorin conjugate **FbC-3** in 53% yield.

Table 1. Chalcone Formation with **FbC-M^{10}A^{13}**



FbC-M^{10}A^{13}

aldehyde (R)	product	yield (%)
	**FbC-1**	92
	**FbC-2**	90
	**FbC-3**	53

The same reaction was conducted on 3,13-diacetylbacteriochlorin **BC-A^{3}A^{13}**. The aldol condensations with benzaldehyde and *trans*-cinnamaldehyde afforded the disubstituted bacteriochlorins **BC-1** (58%) and **BC-2** (57%), respectively, in good yield. On the other hand, the *all-trans*-retinal afforded a mixture of the monosubstituted and the disubstituted (**BC-3**) bacteriochlorins in lower yield (17% and 9%, respectively). The lower yields with **BC-A^{3}A^{13}** versus **FbC-M^{10}A^{13}** may stem from the following: (1) only one condensation is required with the chlorin, and (2) **FbC-M^{10}A^{13}** is completely soluble in EtOH at room temperature, whereas **BC-A^{3}A^{13}** is not completely soluble in ethanol at room temperature (although the final reaction mixture appeared homogeneous). The influence of substitution on the phenyl ring was studied by the reaction of 3,5-bis(methoxymethoxy)benzaldehyde[22] and 4-(dimethylamino)benzaldehyde to afford **BC-4** (24%) and **BC-5** (17%), respectively (Table 2).

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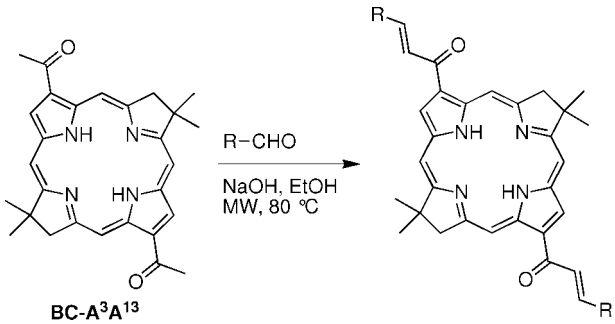
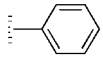
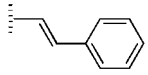
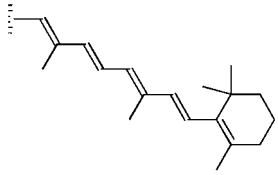
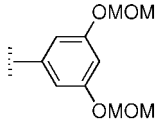
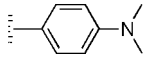
Table 2. Chalcone Formation with **BC-A^{3}A^{13}**



BC-A^{3}A^{13}

aldehyde (R)	product	yield (%)
	**BC-1**	58
	**BC-2**	57
	**BC-3**	9[a]
	**BC-4**	24[a]
	**BC-5**	17

[a] The monosubstituted bacteriochlorin also was isolated.

Further functionalization was carried out on one chlorin and one bacteriochlorin. For spectroscopic studies, **FbC-1** was converted to the zinc chelate **ZnC-1** by the reaction with $Zn(OAc)_2$. For application in photodynamic therapy, the MOM groups in **BC-4** were cleaved in a mixture of 10% aqueous HCl in MeOH[11] to afford **BC-6**, which bears four phenolic −OH groups.

Each chalcone−hydroporphyrin was characterized by ^{1}H NMR, absorption, and fluorescence spectroscopy, as well as LD-MS and ESI-MS. Protons of the double bond gave two doublets in the ^{1}H NMR spectra with a coupling constant of 15.6 Hz, consistent with exclusive presence of the (*E*) configuration. Each construct exhibited expected spectral properties, with the exception of **BC-3**, which did not give a peak for the molecule ion regardless of mass spectrometric method.

Each microwave-assisted condensation was carried out at an exploratory scale (0.010 mmol). The condensations of **FbC-M^{10}A^{13}** with benzaldehyde, **BC-A^{3}A^{13}** with benzaldehyde, and **BC-A^{3}A^{13}** with 3,5-bis(methoxymethoxy)benzaldehyde were subsequently conducted on a 0.10 mmol scale. The latter afforded **FbC-1** (54 mg), **BC-1** (37 mg), and **BC-4** (20 mg) in quantities sufficient for a range of studies, and the yields corresponded well to those obtained in the exploratory reactions. Examination of reactions under conventional heating generally gave poor results with low or no yield of the desired product (see the Supporting Information).

The absorption and emission spectra for the chlorin−chalcones and bacteriochlorin−chalcones are shown in Figures 1 and 2, respectively. The spectral properties of the

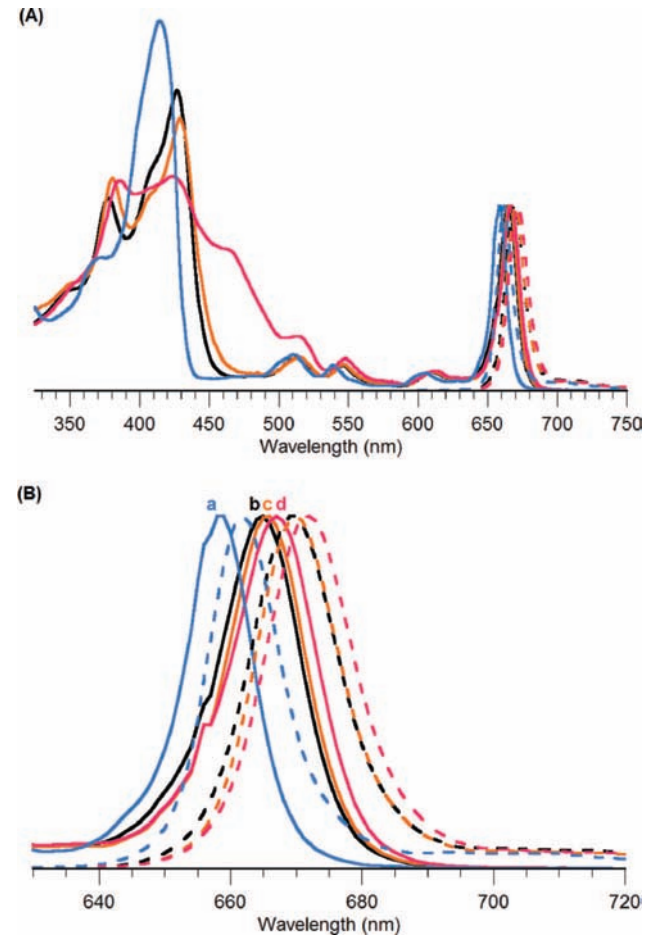


Figure 1. Absorption (—) and emission (---) spectra in toluene at room temperature of chlorins (normalized at the Q_y bands). (A) Entire spectra and (B) expansion of the Q_y region. The labels and colors in the graph are as follows: **FbC-M^{10}A^{13}** (a, blue), **FbC-1** (b, black), **FbC-2** (c, orange), and **FbC-3** (d, magenta).

hydroporphyrin−chalcones and the benchmark compounds **FbC-M^{10}A^{13}** and **BC-A^{3}A^{13}** are listed in Table 3.

Several general observations are noteworthy: (1) The spectral range covered by the long-wavelength $Q_y(0,0)$ band of the chalcone−chlorins (λ = 640−667 nm) and chalcone−bacteriochlorins (λ = 782−792 nm) extended further into the red or near-infrared region than the previously described chlorin or bacteriochlorin analogues.[9,10] The bathochromic shift of the $Q_y(0,0)$ band was 160−205 cm^{-1} for the chlorin−chalcones and 233−395 cm^{-1} for the bacteriochlorin−chalcones versus their respective acetyl−hydroporphyrin benchmark compounds. (2) The $Q_y(0,0)$ band remains relatively sharp with a fwhm of 13−16 nm for the chlorins and 26−36 nm for the bacteriochlorins. (3) The bathochromic

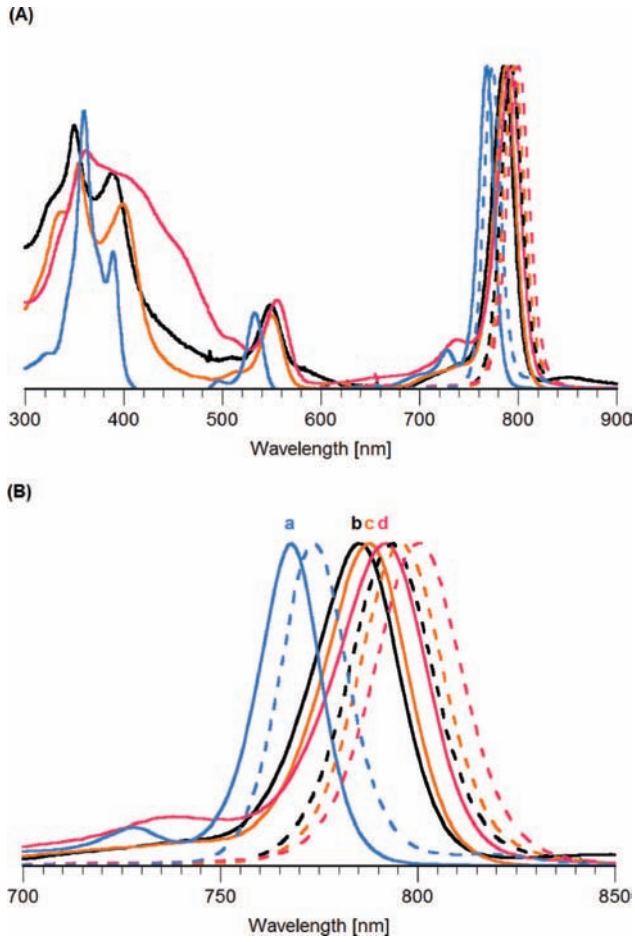


Figure 2. Absorption (—) and emission (---) spectra in toluene at room temperature of bacteriochlorins (normalized at the Q_y bands). (A) Entire spectra and (B) expansion of the Q_y region. The labels and colors in the graph are as follows: **BC-A^{3}A^{13}** (a, blue), **BC-1** (b, black), **BC-2** (c, orange), and **BC-3** (d, magenta).

shift is accompanied by a relative increase of the intensity of the $Q_y(0,0)$ band versus the B band in both chlorins and bacteriochlorins. (4) The fluorescence spectra mirror the long-wavelength absorption band, exhibiting a strong $Q_y(0,0)$ transition and a much weaker, almost negligible $Q_y(0,1)$ transition. The width of the $Q_y(0,0)$ emission transition remains relatively sharp with a fwhm of 14−18 nm in the chlorins and 24−26 nm for the bacteriochlorins. The Stokes shift ranges from 90 to 145 cm^{-1} for the chlorins and from 80 to 144 cm^{-1} for the bacteriochlorins.

The results described herein show that acetyl-substituted hydroporphyrins provide a versatile scaffold for synthetic

Table 3. Absorption and Fluorescence Spectral Properties of Chlorins and Bacteriochlorins[a]

compd	$\lambda Q_y(0,0)$ (fwhm)/nm	I_{Qy}/I_{Bmax}[b]	λ_{em} (fwhm)/nm
FbC-M^{10}A^{13}	658 (11)	0.50	662 (12)
FbC-1	665 (13)	0.61	670 (15)
FbC-2	666 (13)	0.68	670 (14)
FbC-3	667 (15)	0.86	672 (15)
ZnC-1	640 (16)	0.71	646 (18)
BC-A^{3}A^{13}	768 (21)	1.16	774 (20)
BC-1	785 (26)	1.22	794 (25)
BC-2	788 (26)	1.43	796 (24)
BC-3	792 (28)	1.35	801 (26)
BC-4	786 (26)	1.73	795 (25)
BC-5	782 (29)	1.31	790 (25)
BC-6[c]	787 (36)	1.33	792 (24)

[a] In toluene at room temperature unless noted otherwise. [b] Ratio of the intensities of the $Q_y(0,0)$ and B_{max} bands. [c] Absorption and emission in toluene/MeOH.

elaboration into hydroporphyrin−chalcone analogues. The derivatization of acetyl groups proceeds in a facile manner and good yields under basic conditions in alcoholic media with microwave irradiation. The reaction scope encompasses different hydroporphyrins (chlorins and bacteriochlorins) and a variety of aldehydes. While alternative routes to hydroporphyrin−chalcones can be envisaged (e.g., Pd-mediated coupling of a bromohydroporphyrin, carbon monoxide, and an alkene), the ability to employ diverse aldehydes (including polyene-carboxaldehydes) makes this simple route especially attractive. Indeed, the facile synthesis of retinyl−hydroporphyrin **FbC-3** and **BC-3** suggests extension to longer polyenes of interest in artificial photosynthetic systems. The compounds prepared herein extend the absorption maxima into the red and NIR regions. The sharp absorption and emission bands, intensified long-wavelength absorption, and wavelength tunability are attractive for applications such as polychromatic flow cytometry and light-harvesting energy-cascade schemes.

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Supporting Information Available: Experimental section and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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