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Synthesis of isoxazoline-fused chlorins and bacteriochlorins by 1,3-dipolar cycloaddition reaction of porphyrin with nitrile oxide

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Abstract—The 1,3-dipolar cycloaddition reaction of meso-tetraaryl porphyrin with 2,6-dichlorobenzonitrile oxide yielded novel isoxazoline-fused chlorins and two stereoisometric bacteriochlorins. The crystal structure of bacteriochlorin was characterized by X-ray diffraction.

Chlorins and bacteriochlorins have gained more interests in recent years because of their unique optical and photochemical properties. They can be utilized as second-generation photosensitizers in photodynamic therapy (PDT) of cancer[1] and as models for photosynthetic reaction centers.[2]

Chlorins or bacteriochlorins can be synthesized through the Diels–Alder reaction,[3] reduction by diimide,[4] oxidization by OsO_4[5] and 1,3-dipolar cycloaddition reactions[6] of their peripheral double bonds of porphyrin units. In these reactions, the peripheral double bonds of porphyrin exhibit similar properties to the normal alkenes due to their partial isolation from the macrocyclic conjugation pathway.[3] It is well known that nitrile oxides are reactive 1,3-dipoles to undergo 1,3-dipolar cycloaddition with olefin to furnish isoxazoline derivatives,[7] which serve as useful building blocks in the synthesis of various compounds through chemical modification and ring cleavage. For example, the cleavage of isoxazoline rings provides a variety of acyclic compounds such as α,β-unsaturated ketones, β-hydroxyketones, and γ-amino alcohols.[8]

To the best of our knowledge, there has been no report on the reaction of nitrile oxide with porphyrin although the 1,3-dipolar cycloaddition reactions of azomethine ylides,[9] sugar nitrones,[10] carbonyl ylides,[11] and diazomethane[12] with porphyrin have been reported.

In the present work, the novel isoxazoline-fused chlorins and bacteriochlorins, promising versatile starting materials for further functionalization by chemical transformations of isoxazoline ring, were synthesized by 1,3-dipolar cycloaddition reaction of porphyrin with nitrile oxide. The crystal structure was characterized by X-ray diffraction.

The reaction of meso-tetra (4-chlorophenyl) porphyrin (T(4-Cl)PP, **1b**) with excess of 2,6-dichlorobenzonitrile oxide (**2**)[13] in benzene under refluxing gave a mixture of three kinds of compounds (Scheme 1),[14] which were separated by column chromatography on silica gel and identified by mass, UV–vis and ^1H NMR spectra. The meso-tetra (4-chlorophenyl) chlorin (T(4-Cl)PC, **3b**) was identified as the main product ($R_f = 0.40$, silica gel plate, petroleum ether/CH_2Cl_2 1:1) with yield of 53%. The matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI–TOFMS) gave the molecular ion peak at m/z 940. The ^1H NMR spectrum showed two single signals at δ −1.96 and −1.91 assigned to two unequivalent NH protons due to the asymmetry of the molecule.[15] The UV–vis spectrum of **3b** was shown in Figure 1, which exhibited typical absorption band with a maximum peak at 646 nm. Analysis by MALDI–TOFMS of the following two bands (**4b** and **5b**) gave identical molecular ion peaks at m/z 1128, indicating the addition of two nitrile oxides to the T(4-Cl)PP. They have typical UV–vis spectra similar to that of bacteriochlorin with maximum absorption peaks at

Keywords: Nitrile oxide; Cycloadditions; Porphyrins; Chlorins; Bacteriochlorins.

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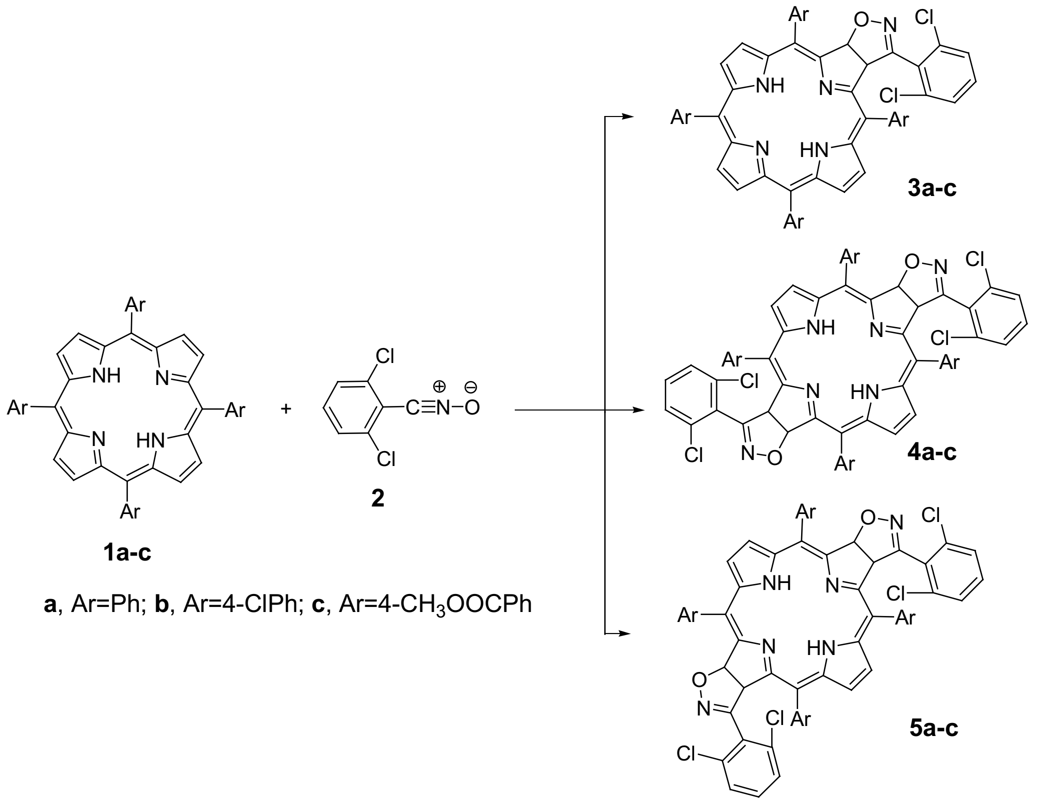


Scheme 1.

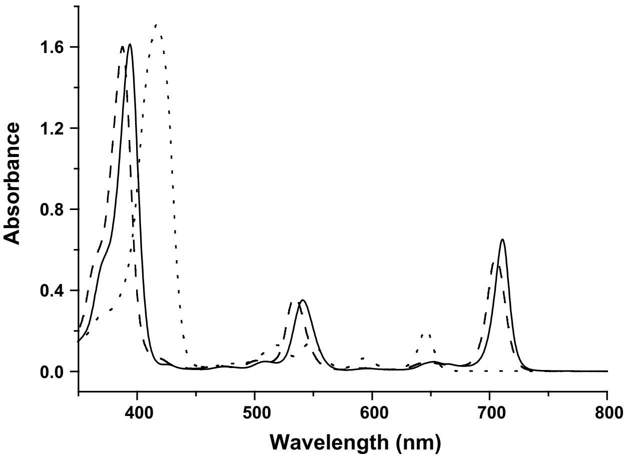
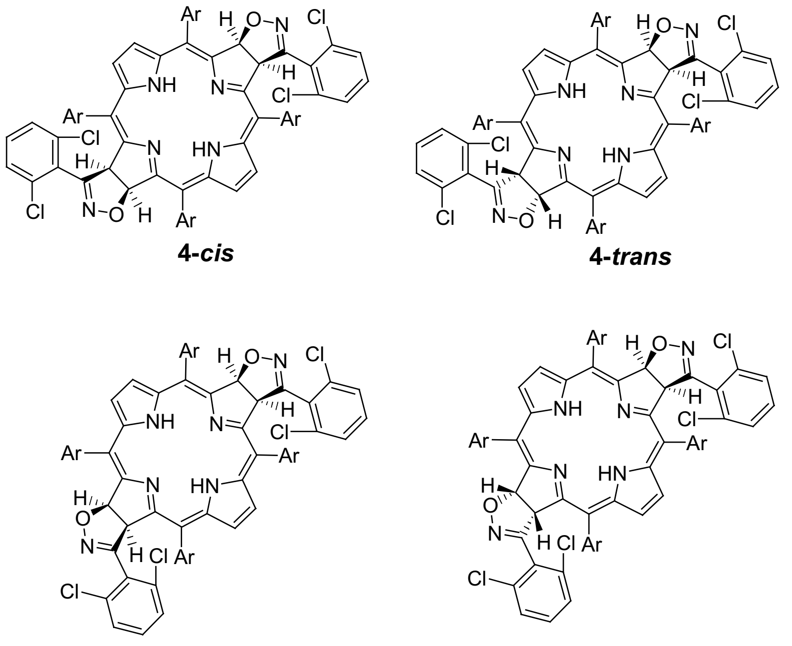


Figure 1. The UV–vis spectra of compound **3b** (···), **4b** (---), and **5b** (—) in the $CHCl_3$ solution.

705 and 711 nm, respectively (Fig. 1). The ^1H NMR spectrum of bacteriochlorin[16] (10% yield) with a higher R_f value ($R_f = 0.17$, silica gel plate, petroleum ether/CH_2Cl_2 1:1) showed one singlet at δ −1.96 (NH protons). This characteristic spectrum is only compatible with structures of **4b**. The ^1H NMR spectrum of the bacteriochlorin[17] (13% yield) with a lower R_f value ($R_f = 0.07$, silica gel plate, petroleum ether/CH_2Cl_2 1:1) showed two singlets at δ −1.96 and −2.00 corresponding to the NH protons. The difference observed in the chemical shift of the two NH protons indicates that the chemical environment of these protons is different,[10] which are consistent with structures **5b**.

The two isoxazoline rings in the bis-adduct of 2,6-dichlorobenzonitrile oxide to the T(4-Cl)PP can be in a '*cis*' or '*trans*' (two isoxazoline rings are on the same or different side of porphyrin macrocycle, respectively) configuration which results in four stereoisometric bacteriochlorins **4**-*cis*, **4**-*trans*, **5**-*cis*, and **5**-*trans* (Fig. 2). To determine the absolute configuration of cycloadduct, a single crystal of **4b** molecule was prepared from chloroform/methanol mixture and subjected to X-ray diffraction analysis.[18] The perspective view of the molecule is shown in Figure 3. The cycloadduct **4b** shows a '*cis*' configuration. The whole molecule exhibits a saddle shape. The two isoxazoline rings are both nearly planar with a mean deviation from plane 0.013(3)′ and 0.043(3)′, respectively, and the dihedral angles between isoxazoline rings and relative pyrrole rings fused with isoxazoline are 118.8(4)° and 115.1(4)°, respectively. The dihedral angles between the substituted phenyl on isoxazoline rings and meso 4-chlorophenyl are 5.0(3)° and 9.5(3)°, respectively, and the average C_α–C_β and C_β–C_β distances of 1.521(4) and 1.514(4)′ in the two pyrroline rings are longer than the analogous distances of 1.421(5) and 1.349(4)′ in two pyrrole rings as expected for a bacteriochlorin.[19]

In order to study the effect of the aryl groups on the cycloaddition reaction, three other porphyrins with different substituted aryl groups were utilized to react with 2,6-dichlorobenzonitrile oxides (**2**) and the reaction



4-*cis* **4-*trans***

5-*cis* **5-*trans***

Figure 2. Four possible isomers of bacteriochlorin.

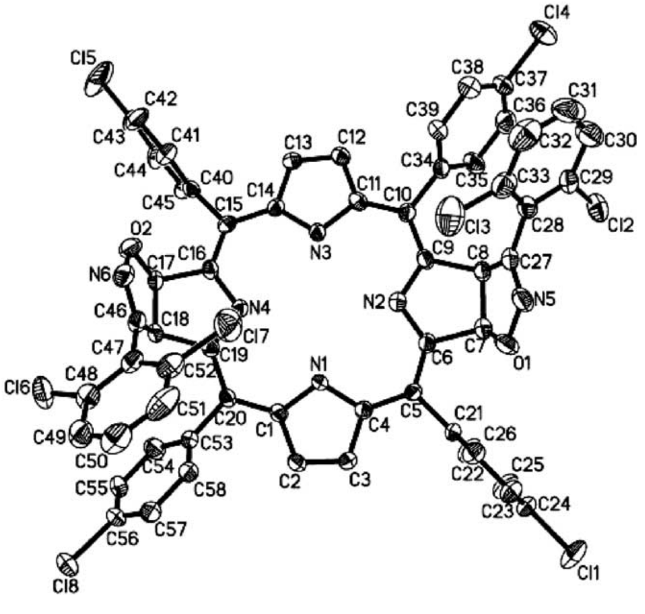


Figure 3. Single crystal X-ray diffraction of **4b**.

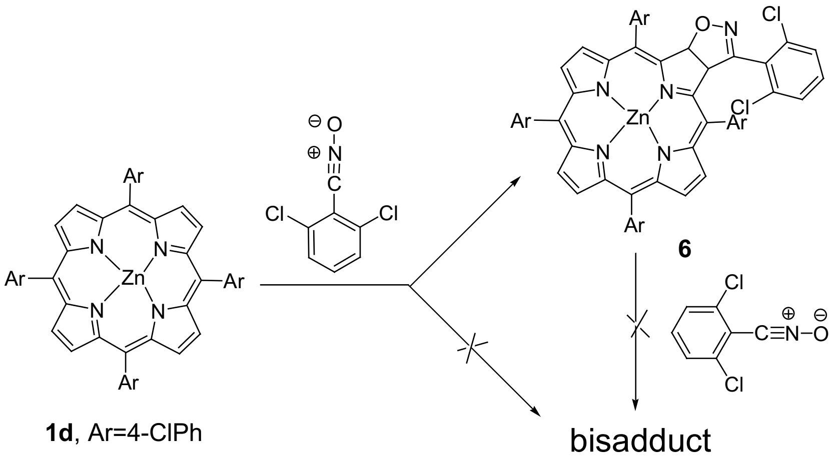
Table 1. Comparative reactivity and product yields of meso-tetraaryl porphyrins with 2,6-dichlorobenzonitrile oxide (reaction time 72 h)

Meso-aryl group	Yield (%)	
	Mono-adduct	Bis-adducts
Ph	44	10
4-ClPh	53	23
4-CH_3OOCPh	51	26
4-CH_3OPh	Not observed	Not observed

results were presented in Table 1. It showed that the electron-withdrawing group in the aryl groups increases the reactivity of the porphyrin as a dipolarphile. On the contrary, for the porphyrin with electron-donating groups, no cycloaddition product was observed. This result is in accord with the reactivity of normal alkenes to nitrile oxide, which the electron withdrawn group of alkenes favors the reaction.[8]

It was reported that the activity of the pyrrole subunit in the chlorin systems is remarkably influenced by the presence of center metal in directing the formation of 2,3,7,8-tetrahydronisobacteriochlorin[4] and β,β-dihydroxyisobacteriochlorin,[5] which are obtained from the diimide reduction and OsO_4 oxidation of the chlorin, respectively. This prompted us to investigate the possible synthesis of isobacteriochlorin from the 1,3-dipolar cycloaddition reaction of zinc meso-tetra (4-chlorophenyl) chlorin (ZnT(4-Cl)PC, **6**)[20] and 2,6-dichlorobenzonitrile oxide. Compound **6** was obtained from the reaction of T(4-Cl)PC and $Zn(OAc)_2$ in refluxing chloroform/methanol with 80% yield. The solution of ZnT(4-Cl)PC (**6**) and 2,6-dichlorobenzonitrile oxide in benzene was refluxed for 48 h, unfortunately, no cycloadduct was detected. This showed that the presence of central metal in chlorin significantly deactivated the reactivity of chlorin dipolarphile. To confirm the negative effect of the central metal on the cycloaddition reaction, the solution of zinc meso-tetra (4-chlorophenyl) porphyrin (ZnT(4-Cl)PP, **1d**) and 2,6-dichlorobenzonitrile oxide in benzene was refluxed for 72 h and ZnT(4-Cl)PC (**6**) was obtained with very low yield (10%) and no bis-adduct product was formed (Scheme 2).

Attempts to use other instable nitrile oxides which generated in situ such as benzonitrile oxide in this reaction were failed due to the liability of the spontaneous



Scheme 2.

dimerization of the instable nitrile oxides under these reaction conditions.

In summary, a new type of isoxazoline-fused chlorins and bacteriochlorins were synthesized and characterized. The substituted aryl group and central metal in porphyrin greatly affect the 1,3-dipolar cycloaddition reaction. The X-ray diffraction showed the bacteriochlorins possess '*cis*' configuration.[21]

Acknowledgements

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14. General procedure for the 1,3-dipolar cycloadditions with 2,6-dichlorobenzonitrile oxide: the meso-tetraaryl porphyrin **1** (10 mmol), 2,6-dichlorobenzonitrile oxide (**2**) (30 mmol) were refluxed in 25 mL dry benzene, 10 mmol of **2** was added for every 24 h to supplement the loss of **2** due to its slight dimerization. After 72 h, the reaction mixture was cooled to rt, the residue was purified by silica gel chromatography. The polarity of the eluant was increased from 3:1 to 2:1 to 1:2 petroleum/CH_2Cl_2 to obtain three products. Further purification of product was achieved by recrystallization from CH_2Cl_2/CH_3OH.
15. Spectroscopic data for chlorin **3b**: ^1H NMR (300 MHz, $CDCl_3$, ppm): δ −1.96 (s, 1H), −1.91 (s, 1H), 6.86–6.89 (m, 1H), 6.97 (s, 2H), 7.15–7.25 (m, 3H), 7.57–7.60 (m, 3H), 7.72 (d, 4H, $J = 9.0$ Hz), 7.81–7.84 (m, 2H), 7.91–8.05 (m, 4H), 8.17 (d, 2H, $J = 6.0$ Hz), 8.38 (d, 1H, $J = 6.0$ Hz), 8.47–8.53 (m, 3H), 8.57 (d, 1H, $J = 6.0$ Hz), 8.68 (d, 1H, $J = 6.0$ Hz); MS (MALDI-TOF): *m/z* 940 (M^+); UV–vis ($CHCl_3$) $\lambda_{max/nm}$: 648, 597, 544, 520, 420, 387.
16. Spectroscopic data for bacteriochlorin **4b**: ^1H NMR (400 MHz, $CDCl_3$, ppm): δ −1.96 (s, 2H), 6.79 (dd, 2H, $J = 2.0$ and 8.0 Hz), 6.85 (dd, 2H, $J = 3.2$ and 6.0 Hz), 6.98–7.02 (m, 4H), 7.18–7.20 (m, 4H), 7.53–7.55 (m, 4H), 7.61 (dd, 2H, $J = 2.0$ and 8.4 Hz), 7.72 (d, 2H, $J = 10.0$ Hz), 7.82 (dd, 2H, $J = 2.0$ and 8.4 Hz), 7.95 (dd, 2H, $J = 2.0$ and 4.8 Hz), 8.05 (dd, 2H, $J = 2.4$ and 8.0 Hz), 8.09 (dd, 2H, $J = 2.0$ and 4.8 Hz), 8.55(dd, 2H, $J = 2.0$ and 8.0 Hz); MS (MALDI-TOF): *m/z* 1128 (M^+); UV–vis ($CHCl_3$) $\lambda_{max/nm}$: 387, 467, 502, 534, 646, 705.

17. Spectroscopic data for bacteriochlorin **5b**: ^{1}H NMR (400 MHz,CDCl$_3$, ppm): δ −1.96 (s, 1H), −2.01 (s, 1H) 6.91–7.03 (m, 8H), 7.22–7.23 (m, 4H), 7.57 (dd, 2H, J = 2.0 and 8.0 Hz), 7.63 (dd, 2H, J = 2.4 and 8.0 Hz), 7.66 (d, 2H, J = 10.0 Hz), 7.74 (dd, 2H, J = 2.0 and 8.0 Hz), 7.78 (dd, 2H, J = 2.0 and 8.0 Hz), 7.81 (d, 2H, J = 1.2 Hz), 7.92 (dd, 2H, J = 1.2 and 8.0 Hz), 8.21 (d, 2H, J = 1.2 Hz), 8.34 (dd, 2H, J = 2.0 and 8.4 Hz); MS (MALDI-TOF): *m*/*z* 1128 (M$^+$); UV–vis (CHCl$_3$) $\lambda_{max/nm}$: 393, 474, 509, 541, 652, 711.
18. The dark purple prismatic crystal of **4b** was subjected to X-ray structural analysis and the monoclinic space group *P*2/*c* with a = 31.029(7) Å, b = 9.1734(15) Å, c = 22.462(5), α= 90.00°, β= 104.025(10)°, γ= 90.00°, V = 6203(2) Å^3, Z = 4, = 1.475 g/cm^3. Final R and wR (on F^2) were 0.110 and 0.288 for 4528 reflections. The crystallographic data will be sent on quoting the CCDC number CCDC 244214 (deposit@ccdc.cam.ac.uk).
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20. Spectroscopic data for **6**: ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 6.91–6.94 (m, 3H), 7.05–7.10 (m, 1H), 7.22–7.24 (m, 4H), 7.48–7.52 (m, 3H), 7.55–7.70 (m, 4H), 7.77–7.79 (m 2H), 7.97–7.99 (m, 2H), 8.03–8.10(m, 3H), 8.32–8.37 (m, 1H), 8.43–8.50 (m, 3H), 8.57–8.59 (m, 1H); MS (MALDI-TOF): *m*/*z* 1003 (M$^+$); UV–vis (CHCl$_3$) $\lambda_{max/nm}$: 416, 465, 564, 593, 614.
21. The heats of formation of compounds **4** and **5** calculated by AM1 semi-empirical methods showed that the '*cis*' configuration is more stable than '*trans*' configuration.