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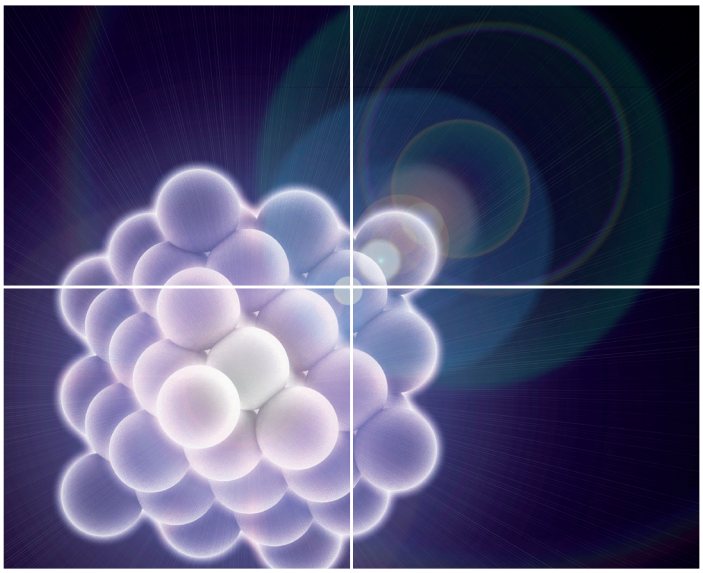

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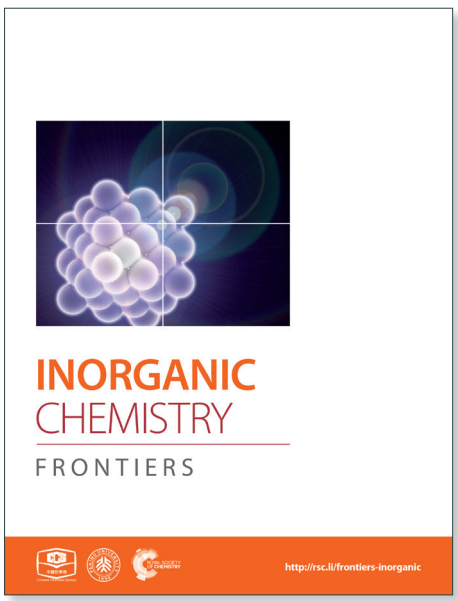

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ARTICLE

A Stable *iso*-Bacteriochlorin Mimics from Porpholactone: Effect of *β*-oxazolone Moiety on the Frontier π-Molecular Orbitals

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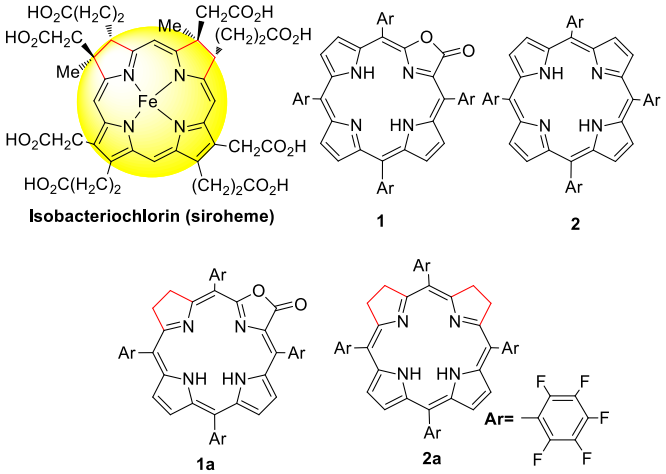
Iso-bacteriochlorins known as siroheme in some reductases, featured with two *adjacent reduced* pyrrole rings, have distinctive electronic structures from porphyrin, chlorin and bacteriochlorin analogues. However, synthesis of such cofactor mimics from hydrogenation of chlorin or porphyrin suffers from the uncertain regioselectivity and stability. In this work, we present the first example that *selective hydrogenation* of *the adjacent pyrroles* in porphyrin or porpholactone free bases assisted by Woollins reagent (WR). More importantly, *adjacent*-dihydroporpholactone (**1a**) display *iso*-bacteriochlorin type spectral features and much higher stability under oxidative condition, compared to the tetrahydroporphyrin analogue (**2a**). Analysis of magnetic circular dichroism (MCD) spectra and DFT calculations for the frontier π-molecular orbitals for **1a** and **2a** reveals the significant effect of an β-oxazolone moiety replacement on lowering the HOMO energy level and enhancing the stability resistant to oxidative condition.

Introduction

Tetrapyrroles are distributed as biological cofactors with diverse biochemical roles such as light absorption characteristics, redox and catalytic reactivity, etc.[1] Significant diversity in biological functions suggests the importance of electronic differences, arising from the saturation levels of tetrapyrrole rings with their broad structural similarity.[2] To decipher the chemical basis, the development of synthetic hydroporphyrins to mimic the electronic structures of natural tetrapyrroles becomes one of the key areas in current synthetic porphyrin chemistry.[3] An *iso*-bacteriochlorin, featured with two adjacent reduced pyrrole rings, plays important role in sulfite and nitrite reductases as prosthetic groups[4] (known as siroheme, scheme 1) and key intermediates in the biosynthetic pathway to vitamin B12.[5] However, synthesis of such mimics is challenging and fraught with a number of problems such as 1) stability, suffering from easily oxidation back to a porphyrin (or other products); and 2) uncertain regioselectivity, lack of methodology to selective hydrogenation of *adjacent* pyrroles from chlorin or porphyrin free bases. Although total synthesis or semisynthesis by the joining of eastern and western dipyrrolic components have been reported,[6] multiple synthetic steps with small scales thus diminish practical value. Thus, new approach to stable *iso-ba*cteriochlorin mimics is highly desirable to expand the scope of hydroporphyrins,[2a, 7] in a manner that should facilitate the fundamental understanding of the electronic structures and further applications.

As our continued interest in porpholactone,[8] in which one pyrrole of porphyrin is replaced by an oxazolone (or lactone) moiety (Scheme 1), we envisioned that this replacement might facilitate to stabilize the hydroporphyrins by lowering HOMO energy level. Moreover, for the partial saturated oxazolone replacement, selective hydrogenation of the *adjacent pyrroles* of oxazolone moiety might achieve *iso*-bacteriochlorin mimics. This would circumvent the regioselectivity issue by tuning the electronic effect of substituents on porphyrin periphery, according to theoretical study by Bruhn and Brückner.[9] In this work, we reported the first example that *selective hydrogenation* of *the adjacent pyrroles* in porphyrin or porpholactone free bases assisted by Woollins reagent $(PhPSe_2)_2$. More importantly, *adjacent*-dihydroporpholactone (**1a**) display *iso*-bacteriochlorin like spectral features and much higher stability under oxidative condition, compared to tetrahydroporphyrin analogue (**2a**). To decipher the effect of *β*-oxazolone on the electronic structures, we performed magnetic circular dichroism (MCD) spectroscopy and DFT calculation to analyze the relative energies of the frontier π-molecular orbitals and hence on the optical properties. These results suggested that higher stability of **1a** is due to the decreased HOMO energy level after replacing *β*-oxazolone moiety. Furthermore, we applied **1a** as a cell imaging agent by encapsulating into



Scheme 1. Structural formulae of siroheme, porphyrin and porpholactone and hydrogenated analogues.

poly(lactide-co-glycolide) nanoparticles and demonstrated its good stability and luminescence. Thus, this work provides an access to stable *iso*-bacteriochlorin like analogue and highlights the importance of *β*-oxazolone moiety replacement on further studying natural tetrapyrrole mimics.

Results and discussions

To evaluate the effect of β-oxazolone moiety on the stability of hydroporphyrins, we firstly estimated the molecular structures and molecular orbital (MO) diagrams of *adjacent*-dihydro-porpholactones (**1a**) and tetrahydroporphyrin analogue (**2a**) derivatized from tetrapentafluorophenylporpholactone (H_2F_{20}TPPL, **1**) and tetrapentafluorophenylporphyrin (H_2F_{20}TPP, **2**), at B3LYP/6-31G* level using Gaussian 09 package, on the basis of Gourterman's four orbital model. As shown in Fig. 1, for **1a** and **2a**, the hydrogenation of tetrapyrrole rings leads to less degenerated MOs, which is in accordance with those for previously reported *iso*-bacteriochlorin analogues.[2c] For *β*-oxazolone moiety participated into the π-conjugation, the energies of four frontier orbitals of **1a** is evidently lowered than those of **2a**, especially for HOMO and LUMO levels (ca. 0.46 and 0.50 eV, respectively). Thus, on the basis of DFT calculation, the replacement of β-oxazolone moiety renders *iso-ba*cteriochlorin mimics **1a** more resistant to oxidative condition.

Synthesis of *iso*-bacteriochlorin mimics 1a and 2a

Regioselectivity is another important issue yet to be addressed in synthesis of *iso*-bacteriochlorin mimics. Generally, the reactions of diimide based reductants,[7j, 10] or electrophlic agents such as OsO_4,[8h, 11] ozone[12] or dienes[13] or 1,3-dipoles such as azomethine ylides, nitrones, or nitrile oxides[14], with chlorin or porphyrin free bases afforded bacteriochlorin type hydroporphyrin (the *opposite* pyrroles were hydrogenated), while with metallochlorin or porphyrin lead to metallo*iso*-bacteriochlorins. In this work, attempts to hydrogenation of **1** to **1a** using previous methods such as photoreduction[7i] or reducing with diimide[7j] were failed. We then turned our

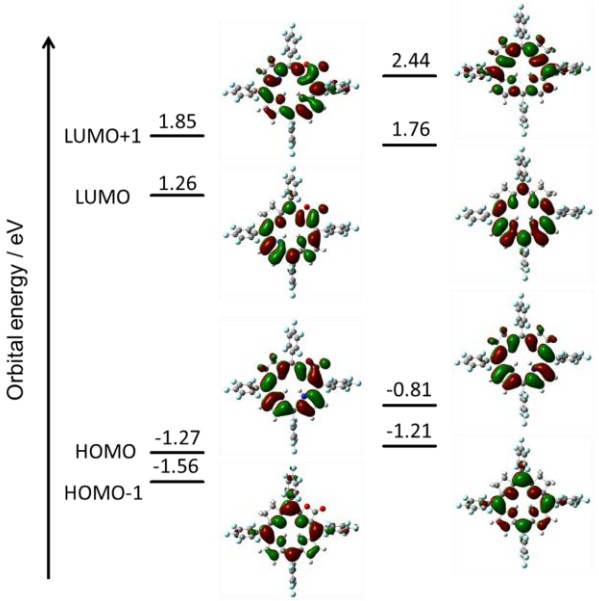
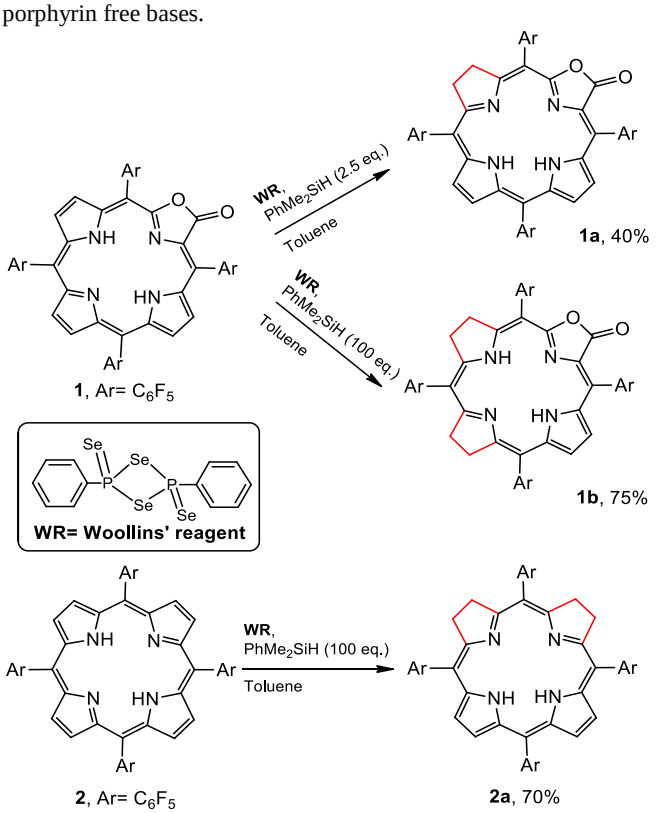


Figure 1. Molecular orbital diagrams of **1a** (left) and **2a** (right), optimized at B3LYP/6-31 G* level using the Gaussian 09 software package.

attention to selenium-assisted reduction system based on Woollins' reagent (WR).[15] Since Jaisankar et al. demonstrated the effectiveness in hydrogenation of aromatic ketones,[16] WR based reduction procedures had been extended to selective hydrogenation of C=C bond in *α,β*-unsaturated carbonyl compounds, despite the mechanisms were still unclear.[17] As shown in Scheme 2, the reaction of 1 eq. WR, **1** and 4 eq. $PhMe_2SiH$ in refluxed toluene gave the *adjacent*-dihydroporpholactone **1a** in an isolated yield of 40%. We did not observe the product that Se replaces O atom of carbonyl group. ESI-MS showed a molecular ion peak at m/z=995.0543 (cal. 995.0557), consistent to the dihydrogenation of one pyrrole in **1a**. ^{1}H NMR spectrum ($CDCl_3$) displayed three sets of peaks at 7.28, 7.54 and 7.74 ppm (*β*-H, 4H), two sets of multiple peaks at 3.86 and 3.82 ppm (C-H at reduced pyrrole, 4H) and two broad protons at 3.97 and 4.86 ppm (N-H, 2H) which would disappear after coordination with Zn^{2+} ion (supporting information). The splitting of ^{19}F signals at -138, -153 and -162 ppm illustrated lower symmetry than that of porpholactone **1**. The vibration of C=O at 1780 cm^{-1} on IR spectrum showed the lactone moiety kept intact (1766 cm^{-1} for **1**). UV-vis spectrum of **1a** (will discuss in next section) displays *iso*-bacteriochlorin type absorption. Similarly, tetrahydroporphyrin **2a** was obtained using **2** as precursor in the isolated yield of 70% (supporting information). Large excess amount of silane (100 equiv.) in synthesis of **2a** was used, probably due to two adjacent pyrroles need to be hydrogenated other than one pyrrole in **1a**. To confirm this, we increased the amount of silane to 100 equiv. in the reaction of **1** with WR, and found that tetrahydroporpholactone **1b** was obtained in the yield of 75% (characterization in supporting information). **1b** and **2a** also exhibits *iso*-bacteriochlorin type spectra as previously reported tetraphenylporphyrin analogues.[2a, 18] It is worthy to note that, in absence of WR or $PhMe_2SiH$, the formation of **1a, 1b** or **2a** was not observed. Interestingly, no reaction was observed using metalloporpholactone **Zn1** or metalloporphyrin **Zn2** as starting material under the same conditions. Metalation of **1a**, **1b**

and **2a** with $Zn(OAc)_2$ in methanol produced **Zn1a**, **Zn1b** and **Zn2a** (the details listed in supporting information). These results demonstrated that the protocol containing WR and silane is effective to directly reduce the *adjacent* double bond of porpholactone and porphyrin free bases.



Scheme 2. Synthetic routes for **1a**, **1b** and **2a**.

To clarify where hydrogenation takes place, we tried to grow the single crystals of **1a** and, however, could not get the plausible data due to the disorder of lactone moiety. Metalation of **1a** with Zn^{2+} ion produced **Zn1a** and the single crystal suitable for X-ray diffraction could be obtained in presence of pyridine (CCDC: 1047515). In Fig. 2, the ORETP structure shows the additional hydrogens are located on the pyrrole adjacent to the oxazolone ring (oxa-atom side). It is reflected by the elongated C6–C7 bond length (1.473 Å) relative to the other pyrroles (C11-C12 and C16-C17: 1.365 and 1.407 Å), which is comparable to 1.479 and 1.497 Å in previously reported *adjacent*-(tetrahydrotetraphenylporphinato)(pyridine)zinc(II).[19] Similar 1.481Å and 1.498 Å are also observed in C5-C6 and C7-C8 bond distances (1.472Å to 1.508 Å in the case of (*adjacent*-tetrahydrotetraphenylporphinato)(pyridine)zinc(II)). Zn–N2 distance is 2.122 (5) Å, which is longer than the other three Zn–N distances (2.023 (4) Å, 2.075 (4) Å and 2.100 (5) Å). The torsion angle of $C_\alpha C_\beta C_\beta C_\alpha$ of the reduced pyrrole ring is 4.23 °, indicating the twist (0.86 °and 2.40 ° for the other two conjugated pyrrole rings) in porphyrin ring.

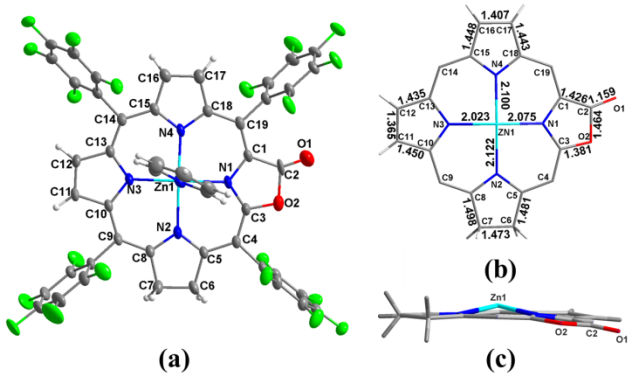


Figure 2. (a) ORTEP diagram of **Zn1a** (thermal ellipsoids at 30% probability level); (b) Selected bond distances (Å) for the core of **Zn1a**; (c) Edge-on-views of the core of **Zn1a** along the N2-N3-N4 planes.

Photophysical properties

To better demonstrate the effect of the replacement of β-oxazolone moiety, we discuss the photophysical properties of **1**a and **2a** in the context. The electronic absorptions of **1a**, **2a** and their zinc complexes in CH_2Cl_2, as shown in Fig. 3(a), display *iso*-bacteriochlorin type spectra with broader, split, and blue-shifted Soret bands.[2d, 4f, 18a] Compared to **1** and **2**, **1a** and **2a** also exhibit broad, intense and blue-shifted Q bands at 500-610 nm, indicating the degeneracy of molecular orbitals and slightly increasing HOMO-LUMO gaps due to lower molecular symmetry after hydrogenation. For **1a**, there is small absorption with maxima at 636 nm, which disappears after metallation with Zn^{2+} ion (Fig. 3a). Thus, this absorption is assumed to be partial protonation of pyrroles, further verified by acid titration experiment as shown in Fig S7. However, for **2a**, the absorption at ca. 750 nm does not disappear even in **Zn2a**, which might be due to the contamination of trace bacteriochlorin for less selective reduction of porphyrin **2**. Compared with the free bases, Zn complexes show red shifts of the absorption bands. In particularly, the difference of Q(0,0) bands between **1a** and **Zn1a** is 43 nm, which is larger than those between **2a** and **Zn2a** (14 nm), respectively. The red shifts of absorption bands indicate less macrocycle distortion of Zn complexes and enhancing π-conjugation.

The fluorescence spectra of **1a** and **2a** in Fig. 3(b) display peak maxima (λ_{max}) at 583 nm and 603 nm with a shoulder at 625 and 654 nm, respectively. The fluorescence quantum yields and fluorescence lifetimes were determined to be 0.47 and 3.88 ns for **1a**, 0.55 and 5.63 ns for **2a**, respectively. After metallization, the quantum yield and lifetime of **Zn1a** were 0.13 and 0.70 ns, while 0.08 and 1.08 ns for **Zn2a**. Thus, radiative and nonradiative decay rates were calculated to be k_r=1.2×10^8 and k_{nr}=1.4×10^8 s^{-1} for **1a**, k_r= 9.8×10^7 and k_{nr}=9.8×10^7 s^{-1} for **2a**, k_r=1.9×10^8 and k_{nr}=1.2×10^9 s^{-1} for **Zn1a**, k_r= 7.4×10^7 and k_{nr}=8.5×10^8 s^{-1} for **Zn2a**, respectively.

The electrochemical properties were studied by cyclic voltammetry in CH_2Cl_2 (*vs.* ferrocene 0.45 V as standard, Table

2, Fig. S13-14). Compared with **1** and **2**, **1a** and **2a** display anthodic shifts of ca. 0.37 and 0.61 V, respectively, for the first oxidation potentials; and ca. 0.21-0.33V for the first reduction potentials. The first oxidation potential of **1a** ((1.33 V) is more positive than **2a** (0.92 V) whereas less difference of the first reduction potentials between **1a** (-0.78 V) and **2a** (-1.13 V). Similar trend was observed for **Zn1a** and **Zn2a**, in which the first oxidation potential of **Zn1a** (0.99 V) is 0.37 V higher than that of **Zn2a** (0.62 V). Again, these electrochemical studies clearly showed that the replacement of *β*-oxazolone moiety lowers the first oxidative potentials of hydroporphyrins more than the first reduction potentials, given that the similar HOMO−LUMO gaps obtained from UV-vis absorptions for **1a** and **2a**, **Zn1a** and **Zn2a**. This is consistent to the trend of energies of four frontier orbitals and HOMO−LUMO gaps for **1a** and **2a** based on DFT calculation

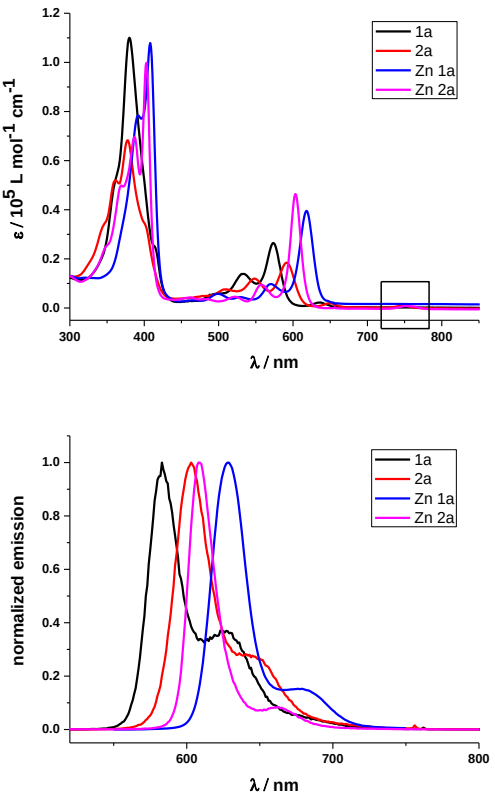


Figure 3. (top) Absorption spectra of **1a** (black), **2a** (red), **Zn1a** (blue) and **Zn2a** (purple) in CH_2Cl_2; (bottom) normalized emission spectra of **1a** (black), **2a** (red), **Zn1a** (blue) and **Zn2a** (purple) in CH_2Cl_2. Concentrations are all 5.0×10^{-6} M, and all excited at maximum absorptions.

Stability

Stabilities of **1a**, **2a**, **Zn1a** and **Zn2a** were examined under oxidative conditions using *m*-CPBA, DDQ and light irradiation (supporting information). We used UV-*vis* absorption and ^{1}H NMR spectroscopy to monitor the reaction process. **1a** and **Zn1a** exhibited high stability and kept intact when treated with 10 eq. *m*-CPBA for 1 day or irradiated with the light at 365 nm for 2 h. **2a** decomposed upon addition of *m*-CPBA in 2h or light irradiation for 90 mins (88%, calculated based on ^{1}H NMR integration). **Zn2a** was very unstable toward oxidation or UV irradiation, and even decomposition was observed on silica gel column. These results clearly demonstrated that the oxazolone replacement indeed stabilized the reduced porphyrinoid structures, in line with electrochemical and theoretical studies.

MCD spectroscopy and DFT calculation

To further demonstrate the advantage of porpholactone, we used **1a**, **Zn1a**, **2a** and **Zn2a** to discuss the effect of oxazolone replacement on the photophysical properties and electronic structures. The electronic absorption and MCD spectra of these complexes in CH_2Cl_2 are shown in Fig. 4. Compared with normal porphyrins which have four unsaturated pyrrole rings, the intensity of the Q band is much stronger, so that the Q/Soret intensity ratio is stronger than in normal porphyrins. According to the Gouterman's four orbital theory that has been applied in understanding spectra of porphyrinoids,[20] this indicates that the energy difference between the HOMO and HOMO-1 (ΔHOMO) is larger than that in normal porphyrins. Due to the uncertainty of the position of two pyrrole protons and the presence of several isomers, the spectra of metal-free **1a** and **2a** are more complex than those of the **Zn1a** and **Zn2a**. For **1a**, there is a small absorption with maximum at 636 nm. This absorption is ascribed to the partial protonation of pyrroles, which is verified by acid titration experiment, and which disappears after metallation with Zn^{2+} ion. The Zn complexes show red-shifted absorption compared with those of metal-free species. In particular, the difference of the Q_{00} bands between **1a** and **Zn1a** is 43 nm, which is larger than that between **2a** and **Zn2a** (14 nm). The spectra of **1a** and **Zn1a** are broadly similar to those of *iso*-bacteriochlorin whose two pyrrole rings at adjacent positions are reduced.[18a, 21] The splitting of the Q band is theoretically not large, different from that of bachteriochlorin which has saturated pyrrole rings at opposite positions.[22]

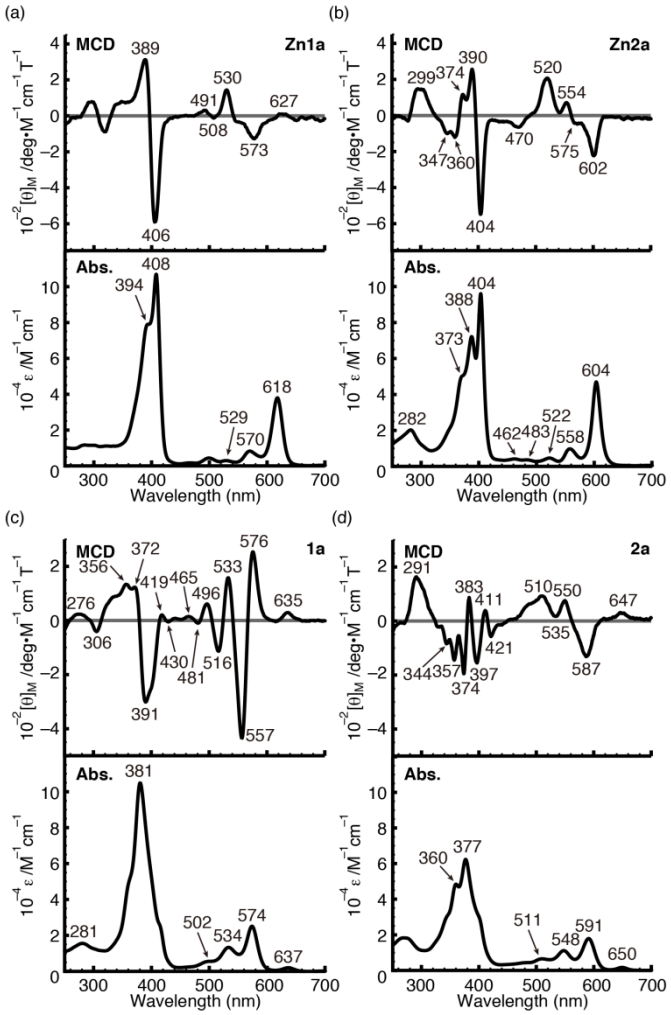


Figure 4. MCD (top) and UV/Vis (bottom) absorption spectra of **Zn1a** (a), **Zn2a** (b), **1a** (c) and **2a** (d) in CH_2Cl_2.

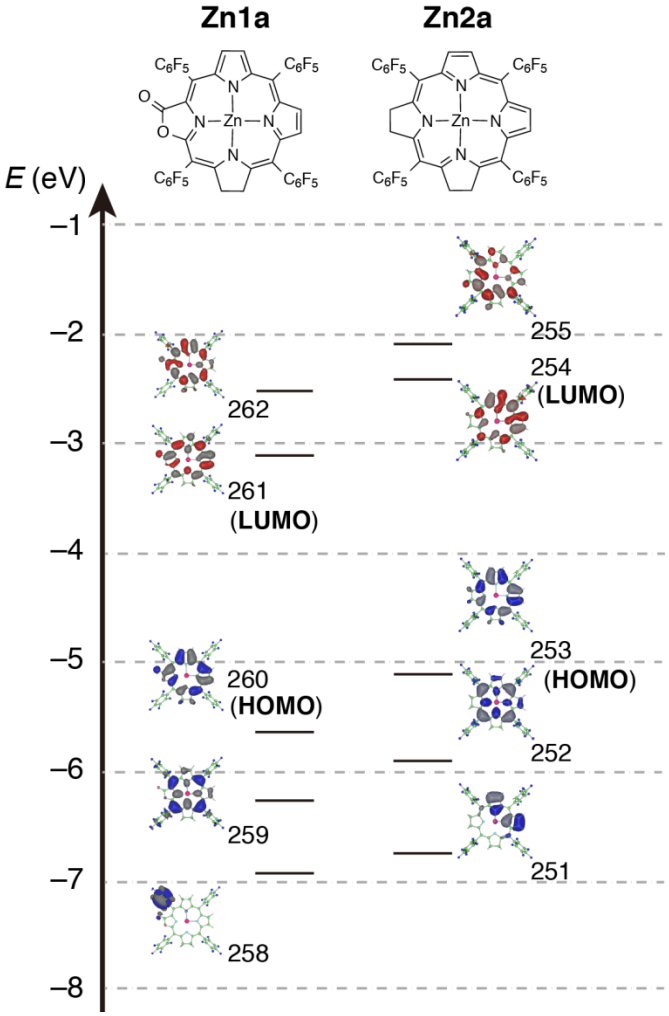


Figure 5. Calculated fronteir orbitals of **Zn1a** (left) and **Zn2a** (right).

For complexes in this study, the MCD spectra are all contribution of Faraday *B* terms.[23] The observed spectra were interpreted in consideration of the results of MO calculations. Although the MCD spectra are complex for meta-free species, the most decisive difference between **1a** and **2a** is that the MCD sign for the Q_{00} band is positive for **1a** and negative for **2a** in ascending energy, experimentally suggesting that the ΔHOMO is smaller than ΔLUMO (the energy difference between the LUMO and LUMO+1) for **1a** and opposite for **2a**.[23] The MCD spectra of **Zn1a** and **Zn2a** appear similar at a glance, but there is a decisive difference in the Q band region. Namely, for **Zn2a**, a clear negative MCD envelope was observed corresponding to the Q_{00} absorption peak at 604 nm, indicating that ΔHOMO is obviously larger than ΔLUMO.[23] Meanwhile for **Zn1a**, no (or very small positive) MCD intensity was observed associated with Q_{00} band at 616 nm, indicating experimentally that ΔHOMO is nearly equal to ΔLUMO. Judging from the MCD sign, another important information is that the peak at 570 nm for **Zn1a** and 558 nm for **Zn2a** correspond to the split components of the Q band, since the interacting MCD *B*-terms give signals of opposite sign.[23-24] Taken all the MCD data of **1a**, **2a**, **Zn1a**, and **Zn2a** into account, it is experimentally concluded that ΔHOMO is much larger than ΔLUMO for **2a** and **Zn2a**, while that the ΔHOMO is similar to or very slightly smaller than ΔLUMO for **1a** and **Zn1a**. We have calculated molecular orbitals (MOs) of **Zn1a**and **Zn2a**, since then we don't need to consider the position of pyrrole protons that occurred for metal-free **1a** and **2a**. The data are shown in Fig. 5. Compared with the MOs of **Zn2a**, those of **Zn1a** are all From the calculation, the above relationship on the size of ΔHOMO and ΔLUMO was nicely reproduced, i.e. they are 0.61 and 0.60 eV for **Zn1a** and 0.79 and 0.32 eV for **Zn2a**, respectively.

Fluorescence and cell imaging

Since *β*-lactonization of pyrrole ring renders hydroporphyrins higher stability, we used **1a** as an example to demonstrate their potential application in cellular imaging. To make it water-soluble, we used the modified solvent extraction/evaporation single-emulsion method to prepare **1a**-loaded poly(lactide-co-glycolide) nanoparticles (PLGA NPs) as reported.[25] The intracellular luminescence and subcellular distribution of **1a-NPs** were investigated using LysoTracker® Green DND-26 by confocal laser scanning microscopy (CLSM). HeLa cells were co-incubated with **1a-NPs**

with a final concentration of 10 μM in complete culture medium for 24 h at 37°C. As shown in Fig. 6, **1a-NPs** possesses good cell membrane permeability and leads to the perinuclear punctate red fluorescence in HeLa cells. It mainly distributes in lysosomal/endosomal compartments and exhibits a co-localization level of approximately 0.92 with LysoTracker® Green DND-26. Thus, preliminary imaging results show **1a-NPs** can be internalized into living cells and detected by confocal imaging, which offers the prerequisite and convenience for further biological applications.

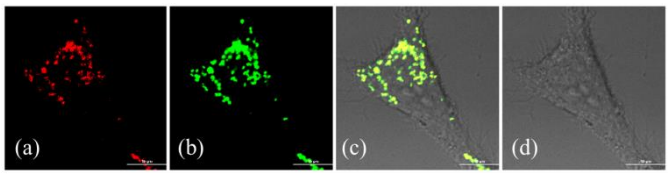


Figure 6. Co-localization of **1a-NPs** (10 μM) with LysoTracker® Green DND-26in HeLa cells. (a) fluorescence image of **1a-NPs**; (b) fluorescence image of LysoTracker® Green DND-26; (c) the merge of (a), (b) and (d); (d) differential interference contrast (DIC) image. Scale bar: 10 μm.

Conclusions

Taken together, we developed a new approach based on Woollins reagent to prepare *iso*-bacterochlorin mimics from porpholactone or porphyrin free bases. More importantly, with an oxazolone moiety replacement, *β-adjacent* dihydroporpholactone (**1a**) exhibits high stability toward oxidative condition and photo-irradiation. A detailed analysis of optical spectra and TD-DFT calculations reveal that **1a** and **2a** possess electronic structures similar to *iso*-bacteriochlorins and the significant effect of oxazolone moiety on lowering the HOMO energy level. Furthermore, cellular uptake and subcellular localization investigations have demonstrated the potential utility of these compounds in the biological studies. The application of such *iso*-bacterochlorin analogue as ligand to mimic the reactivity of sulfite and nitrite reductases is currently under investigation.

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Notes and references

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†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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