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β-Functionalized zinc(II)aminoporphyrins by direct catalytic hydrogenation

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ABSTRACT

We report on a novel synthetic procedure to obtain β-aminoporphyrins with zinc(II) as the metal center by using the catalytic reduction of the parent Zn(II)β-nitroporphyrins with hydrogen in the presence of Pd/C using dimethylformamide as the solvent. This simple method allows the preparation of β-aminoporphyrins with substituents with diverse electronic properties: *meso*-tetraphenylporphyrin (TPP), *meso*-tetrakis(2,6-dichlorophenyl)porphyrin (TDCPP), and *meso*-tetrakis(2,3,4,5,6-pentafluorophenyl)porphyrin (TPFPP).

Porphyrinoid macrocycles are important naturally occurring compounds. They play an essential role in a variety of biological processes, such as photosynthesis, oxygen transport/storage, and oxidative metabolism.[1] Synthetic (metallo)porphyrins have been extensively investigated in biomimetic processes, namely in artificial photosynthesis, photoinduced electron transfer,[2] and as models of monooxygenase and peroxidase enzymes for catalytic oxidation[3] and pollutant degradation.[4] They also find relevant applications in medicine for diagnosis and in photodynamic therapy (PDT)[5] or boron neutron capture therapy (BNCT).[6] The amino-functionalized porphyrins are key precursors for the preparation of dimers,[7] supramolecular systems,[8] and hybrids, in particular, porphyrin structures covalently bonded to fullerenes or carbon nanotubes, affording photoactive nanocomposites for electronic and photonic devices[9,10] and heterogeneous photocatalysis.[11]

The preparation of aminoporphyrins has been mainly achieved through the synthesis of macrocycles with nitrophenyl groups in one or several *meso*-positions, followed by their reduction to aminophenyl derivatives using excess of tin(II) chloride in concentrated hydrochloric acid (Fig. 1a, $R_1 = NH_2$ or Ph-NH_2; R_{2-4} = Ph).[12,13] Alternatively, palladium catalyzed coupling reactions on *meso*-halo(metallo)porphyrins were described to afford the corresponding *meso*-aminoporphyrins.[14,15] However, the preparation of asymmetric porphyrin core structures requires more complex procedures and thus, the introduction of an amino group in the β-positions of a more easily obtainable symmetric porphyrin is preferable. Furthermore, (metallo)porphyrin structures covalently bonded through β-position were shown to have anhanced performance for electron transfer processes relatively to structures bonded through *meso*-phenyl groups.[16]

The preparation of β-amino substituted porphyrins was also reported for Ni(II) and Cu(II) derivatives of TPP (Fig. 1a) using the reduction with tin powder under acidic conditions[17,18] or multistep reactions based on palladium catalyzed couplings.[19] However, these methodologies were not suitable to directly synthesize aminoporphyrins carrying a labile central metal such as zinc or to avoid the conversion of the reactive β-NH_2 group during the multi-step procedures.

The preparation of aminoporphyrin derivatives carrying electron withdrawing substituents can also be significant for a vast range of applications: halogen substituted (metallo)porphyrins are important for photochemical processes based on the generation of triplet states, such as the photosensitized production of singlet oxygen[20] or for the preparation of photonic devices.[21] Furthermore, metalloporphyrins with electron withdrawing groups have been reported as efficient catalysts for several oxidation reactions, and currently their anchoring onto solid supports is of primary importance to allow easy catalyst removal at reaction end and reuse, or to obtain stereo-control during the catalytic reaction.[22] In this context, the synthesis of amino derivatives is very appropriate to establish strong covalent binding to catalyst supports. To the best of our knowledge, β-amino derivatives of TDCPP and TPFPP have not been reported previously in the literature.

Reduction reaction using hydrogen in the presence of heterogeneous Pd/C catalyst is a simple method that proceeds under mild

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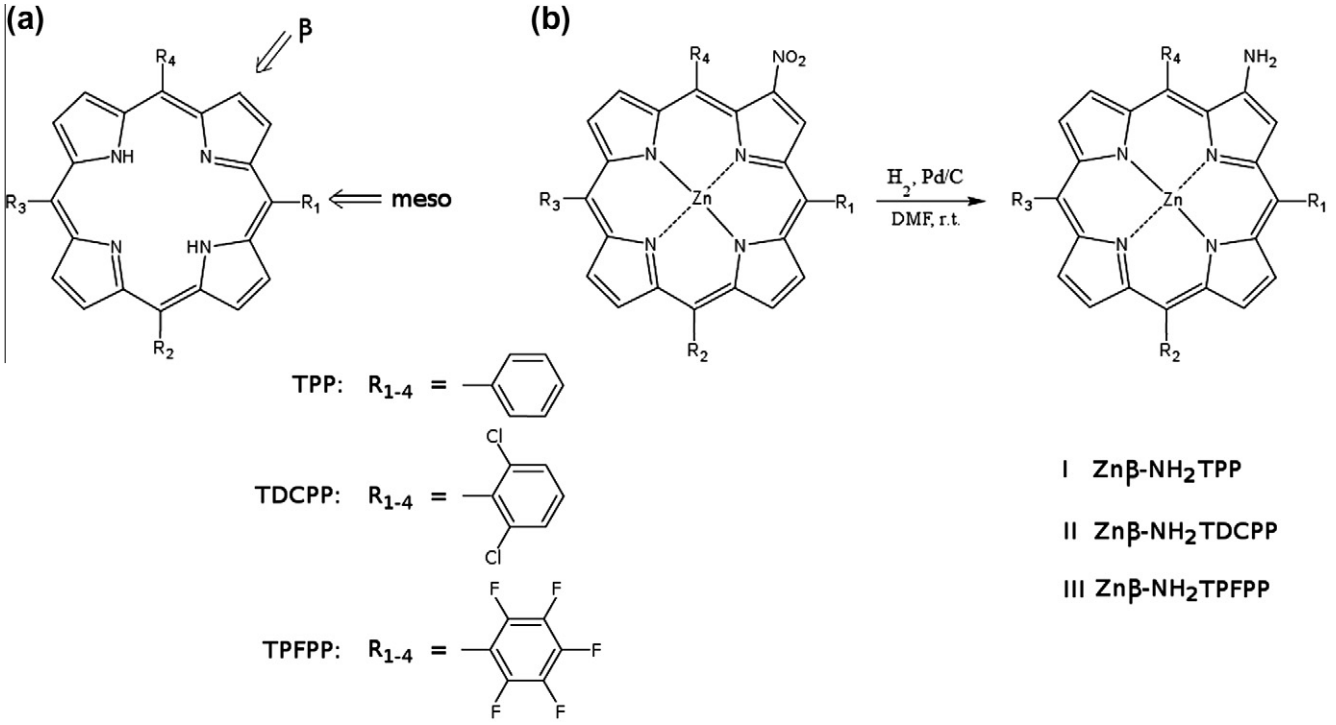


Figure 1. (a) Metalloporphyrin structures. (b) Preparation of the Zn(II)β-aminoporphyrins through catalytic reduction of the corresponding nitro derivatives.

conditions and requires small amount of solvent. This methodology has been previously used for the reduction of porphyrins, namely TPP and uroporphyrin I, to chorins and porphyrinogen derivatives.[23,24] In this Letter, it is described the synthesis of Zn(II)β-aminoporphyrins: zinc(II)β-amino(*meso*-tetraphenyl)porphyrin (Znβ-NH_2TPP) **I**, zinc(II)β-amino(*meso*-tetrakis(2,6-dichlorophenyl))porphyrin (Znβ-NH_2TDCPP) **II**, and zinc(II)β-amino(*meso*-tetrakis(2,3,4,5,6-pentafluorophenyl))porphyrin (Znβ-NH_2TPFPP) **III**, through reduction of zinc(II)β-nitroderivatives using hydrogen as the reductive agent and Pd/C as heterogeneous catalyst. Preparation of the porphyrin free bases and subsequent one-step metallation/nitration affording zinc(II)β-nitroporphyrins were performed following the literature procedures.[25,26] The hydrogenation reaction was tested using several solvents and different reaction times in order to optimize the reaction conditions. The reaction was performed in methanol, anhydrous tetrahydrofuran (THF), anhydrous toluene, 1-methyl-2-pyrrolidone, and in both anhydrous and non-anhydrous dimethylformamide (DMF). Only in the case of the last two solvents, the reaction led to the desired aminoporphyrins. In consequence DMF was chosen as the reaction solvent since no advantage was observed by performing the reaction in the anhydrous solvent. Furthermore, the reaction was also carried out at different reaction times: 30, 60 min, 2, 4, and 16 h. The substrate conversion was complete after 4 h; longer reaction times, for example 16 h, did not change the yields of the aminoporphyrin, originating the amino-product in the same yield. Finally, the reduction reaction in DMF was carried out at room temperature, keeping the reaction mixture protected from light and using Pd/C (10%) catalyst and hydrogen pressure of 4 bar. The reaction was monitored by TLC and at its end the catalyst was filtrated and the metalloporphyrin products were precipitated with *n*-hexane/chloroform mixtures; in-some cases (Znβ-NH_2TPFPP), the DMF was evaporated at low temperature. The total reaction mixture was analyzed by ^{1}H NMR or fractionated by preparative TLC or column chromatography.[27] The observed first red products were isolated and characterized using 1D and 2D ^{1}H and ^{13}C NMR spectroscopies, APT, COSY, HSQC, HMBC; mass spectrometry and elemental analysis (Fig. 1 and Table 1), which confirmed the structures of Zn(II)β-aminoporphyrins **I**,[28] **II**[29] and **III**.[30] Isolated yields were 30%, 23%, and 20%, respectively. The mass spectra (MALDI) for compounds **I**–**III** showed a signal at *m*/*z* corresponding to the $[M+H]^+$ ion and the elemental composition of all compounds was in accordance with theoretical values.[28–30] The ^{1}H NMR spectra of **I**, **II**, and **III** exhibited a broad singlet peak from the –NH_2 group at 4.53, 4.58, and 4.69 ppm, respectively, showing an increase in the chemical shift as the electron withdrawing properties of the porphyrin ring increase. Protons in the aromatic region confirmed the porphyrinic structures in Figure 1b. Moreover, the absence of signals of the internal ring NH protons confirmed that the amino-porphyrin fractions were only present as the Zn(II) complex.

The electronic absorption and fluorescence emission spectra of Zn(II)β-amino compounds are shown in Figure 2. The electronic spectra showed the characteristic Soret band at λ_{max} 423, 426, and 416 nm, respectively, for compounds **I**, **II**, **III** and three Q-bands. The presence of an amino group in one of the β-positions of the metalloporphyrin ring changes the D_{4h} symmetry of the Zn *meso*-tetraphenylporphyrins, (normally showing two Q-bands), to Cs symmetry and consequently, the number of Q bands increased. As can be seen in Table 1, the fluorescence quantum yields of Znβ-NH_2TPP (Φ_F 0.056) decreased relatively to the ZnTPP precursor (Φ_F 0.110), indicating the occurrence of quenching of the excited state in some extend by the amino group through charge transfer complex in the excited-state. The same can be seen with Znβ-NH_2TPFPP (Φ_F 0.018 vs 0.045 for ZnTPFPP). However, an increase of fluorescence quantum yield is observed for Znβ-NH_2TDCPP (Φ_F 0.022) relatively to its ZnTDCPP precursor (Φ_F 0.010). The low ZnTDCPP fluorescence quantum yield is due to the heavy atom effect. By the introduction of an amino group, the balance of excited-state processes (including intersystem crossing) is affected rendering a higher fluorescence.

The control of the reactions by TLC indicated the presence of the other compounds. The isolated green fractions showed characteristic electronic spectra of chlorin compounds, with a relatively intense Q-band at λ_{max} 620 nm and confirmed the occurrence of

Table 1
Selected spectroscopic data and isolated yields for the Zn(II)β-aminoporphyrins

	^{1}H NMR (ppm) (−NH_2)	MS m/z $[M+H]^+$	Soret band (nm)	Φ_f[a]	Yield (%)
Znβ-NH_2TPP (**I**)	4.53 (s, 2H)	692.2[a]	423	0.056 [ZnTPP:0.110]	30
Znβ-NH_2TDCPP (**II**)	4.58 (s, 2H)	963.8[a]	426	0.022 [ZnTDCPP:0.010]	23
Znβ-NH_2TPFPP (**III**)	4.69 (s, 2H)	1051.9[a]	416	0.018 [ZnTPFPP:0.045]	20

[a] λ = 562 nm, standard:TPP Φ_f = 0.11.

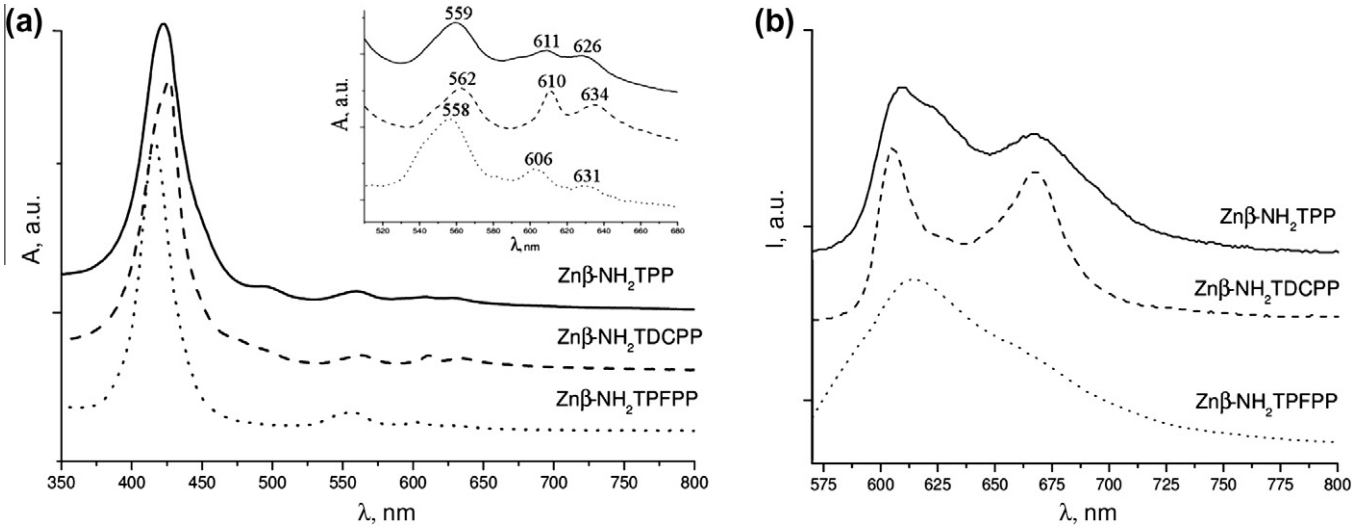
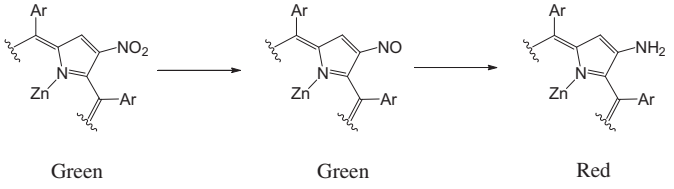


Figure 2. Photophysical data for Znβ-aminoporphyrins: (a) electronic absorption spectra in CH_2Cl_2. (b) Fluorescence spectra in CH_3CN.



Scheme 1. Observed stepwise reduction of nitro to nitroso and amino derivatives.

hydrogenation of the β-positions of porphyrin core as a competing reaction, with formation of β-dihydroporphyrins (chlorin) derivatives.[23] During the reduction of Znβ-NO_2TPFPP the reductive dehalogenation reaction of fluorine substituents was also observed as confirmed by MS analysis of other isolated fractions.[31] In addition, TLC control of the reduction reaction of Znβ-NO_2TPP showed the initial formation of green compounds and only after 2 h it was observed the presence of a red spot, which was assigned to the amino-porphyrin. The green derivative with the highest R_f was isolated and identified by MS (MALDI) analysis showing a molecular ion with m/z 706.2, which matches with the $[M+H]^+$ ion of the β-nitroso derivative. Accordingly, the stepwise reduction pathway shown in Scheme 1 can be proposed. More detailed studies will be presented in a full paper.

The described procedure is an easy and a versatile way to obtain new zinc(II)β-aminoporphyrins with different electron withdrawing properties through direct hydrogenation reaction of the corresponding Zn(II)-nitro precursors that have potential photochemical applications and as precursors to catalytic and photo-active structures.

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References and notes

1. *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 1999.
2. Wasielewski, M. R. *Chem. Rev.* **1992**, *92*, 435–461.
3. Bhyrappa, P.; Purushothaman, B. *J. Chem. Soc., Perkin Trans. 2* **2001**, *2*, 238–242.
4. Rebelo, S. L. H.; Gonçalves, A. R.; Pereira, M. M.; Simões, M. M. Q.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. *J. Mol. Catal. A: Chem.* **2006**, *256*, 321–323.
5. Dougherty, T. J.; Gomer, C. J.; Henderson, B. W.; Jori, G.; Kessel, D.; Korbelik, M.; Moan, J.; Peng, J. *J. Natl. Cancer Inst.* **1998**, *90*, 889–905.
6. Hiramatsu, R.; Kawabata, S.; Miyatake, S.-I.; Kuroiwa, T.; Easson, M. W.; Vicente, M. G. H. *Lasers Surg. Med.* **2011**, *43*, 52–58.
7. Pereira, A. M. V.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S.; Jeandon, C.; Gisselbrecht, J.-P.; Choua, S.; Ruppert, R. *Org. Lett.* **2011**, *13*, 4742–4745.
8. Gomes, A. T. P. C.; Paz, F. A.; Neves, M. G. P. M. S.; Tomé, A. C.; Silva, A. M. S.; de Souza, M. C. B. V.; Ferreira, V. F.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **2011**, *52*, 4741–4744.
9. Jia, F.; Wu, L.; Meng, J.; Yang, M.; Kong, H.; Liu, T.; Xu, H. *J. Mater. Chem.* **2009**, *19*, 8950–8957.
10. Guo, Z.; Du, F.; Ren, D.; Chen, Y.; Zheng, J.; Liu, Z.; Tian, J. *J. Mater. Chem.* **2006**, *16*, 3021–3030.
11. D'Souza, F.; Ito, O. *Chem. Commun.* **2009**, 4913–4928.
12. Kruper, W. J.; Chamberlin, T. A.; Kochanny, M. *J. Org. Chem.* **1989**, *54*, 2753–2756.
13. Luguya, R.; Jaquinod, L.; Fronczek, F. R.; Vicente, M. G. H.; Smith, K. M. *Tetrahedron* **2004**, *60*, 2757–2763.
14. Khan, M. M.; Ali, H.; van Lier, J. E. *Tetrahedron Lett.* **2001**, *42*, 1615–1617.
15. Esdaile, L. J.; Senge, M. O.; Arnold, D. P. *Chem. Commun.* **2006**, 4192–4194.
16. Panda, M. K.; Ladomenou, K.; Coutsolelos, A. G. *Coord. Chem. Rev.* **2012**, *256*, 2601–2627.
17. Tomé, J. P. C.; Pereira, A. M. V. M.; Alonso, C. M. A.; Neves, M. G. P. M. S.; Tomé, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S.; Martinez-Diaz, M. V.; Torres, T.; Rahman, G. M. A.; Ramey, J.; Guldi, D. M. *Eur. J. Org. Chem.* **2006**, 257–267.
18. Alonso, C. M. A.; Neves, M. G. P. M. S.; Tomé, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S. *J. Mex. Chem. Soc.* **2006**, *50*, 100–105.
19. Akita, M.; Hiroto, S.; Shinokubo, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 2894–2897.

20. Azenha, E. G.; Serra, A. C.; Pineiro, M.; Pereira, M. M.; Melo, J. S.; Arnaut, L. G.; Formosinho, S. J.; Gonsalves, A. M. d'A. R. *Chem. Phys.* **2002**, *280*, 177–190.
21. Yang, S. I.; Seth, J.; Strachan, J.-P.; Gentemann, S.; Kim, D.; Holten, D.; Lindsey, J. S.; Bocian, D. F. *J. Porphyrins Phthalocyanines* **1999**, *3*, 117–147.
22. Gaspar, H.; Andrade M.; Pereira C.; Pereira A.M.; Rebelo, S.L.H.; Araújo, J.P.; Pires, J.; Carvalho, A.P.; Freire, C. *Catal. Today* **2012**, http://dx.doi.org/10.1016/j.cattod.2012.04.018.
23. Bergonia, H. A.; Phillips, J. D.; Kushner, J. P. *Anal. Biochem.* **2009**, *384*, 74–78.
24. Brigas, A. F.; Rosa da Costa, A. M.; Serra, A. C.; Pires, C. *J. Pharm. Bioall. Sci.* **2011**, *3*, 294–297.
25. Faustino, M. A. F.; Neves, M. G. P. M. S.; Vicente, M. G. H.; Cavaleiro, J. A. S.; Neumann, M.; Brauer, H.-D.; Jori, G. *Photochem. Photobiol.* **1997**, *66*, 405–412.
26. Watanabe, E.; Nishimura, S.; Ogoshi, H.; Yoshida, Z. *Tetrahedron* **1975**, *31*, 1385–1390.
27. Experimental details: 30 mg of zinc(II)β-nitroporphyrin and 30 mg of Pd/C (10%) were dissolved in 10 mL of DMF (*p.a.* Fisher Chemicals, used without further purification). The reaction mixture was kept stirring in hydrogenator (Framo–Geratetechnik Model M21/1) at the room temperature under hydrogen pressure of 4 bar for 4 h. After that time, the mixture was filtrated to remove the catalyst that was washed with chloroform followed by evaporation of the solvents at a low temperature (<60 °C) or precipitation in *n*-hexane/chloroform mixtures. The product was isolated by preparative thin layer chromatography on silica plates using as the eluent a mixture of chloroform:methanol (99.5:0.5).
28. *Znβ-NH_2TPP*: Violet solid. Isolated yield 30%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.84–8.89 (5H, m, H-β), 8.75 (1H, d, *J* = 4.6 Hz, H-β), 8.63 (1H, d, *J* = 4.6 Hz, H-β), 8.18–8.20 (4H, m, H-Ph_{ortho}); 8.13 (2H, d, *J* = 6.0 Hz, H-Ph_{ortho}), 8.06 (2H, d, *J* = 6.8 Hz, H-Ph_{ortho}), 7.66–7.78 (12H, m, H-$Ph_{meta+para}$), 4.53 (2H, s, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 134.5, 134.4, 134.3, 133.7, 133.0, 132.6, 132.4, 131.8, 131.6, 128.1, 127.2, 126.9, 126.7, 126.7, 126.6 ppm. MS (MALDI) *m*/*z* 692.2 [MH^+]. Vis ($CHCl_3$) λ_{max} 626 (relative absorbance, 0.05), 611 (0.05), 559 (0.07), 423 nm (1.0). Anal. Calcd for $C_{44}H_{29}N_5Zn{\cdot}4H_2O$: C, 69.2; N, 9.2; found: C, 69.1; N, 9.1.
29. *Znβ-NH_2TDCPP*: Violet solid. Isolated yield 23%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.66–8.72 (4H, m, H-β), 8.63 (1H, d, *J* = 4.8 Hz, H-β), 8.52 (1H, d, *J* = 4.8 Hz, H-β), 7.88 (1H, s, H-β), 7.66-7.79 (12H, m, H-$Ph_{meta+para}$), 4.58 (2H, s, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 131.5, 131.3, 131.0, 130.9, 130.7, 130.4, 130.0, 129.0, 128.9, 127.8, 127.7. MS (MALDI) *m*/*z* 963.8 [MH^+]. Vis ($CHCl_3$) λ_{max} 634 (relative absorbance, 0.05), 610 (0.06), 562 (0.06), 426 nm (1.0). Anal. Calcd for $C_{44}H_{21}N_5Cl_8Zn$ $2H_2O{\cdot}CH_3OH$: C, 52.4; N, 6.8; found C, 52.3; N, 6.4.
30. *Znβ-NH_2TPFPP*: Violet solid. Isolated yield 20%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.82–8.90 (6H, m, H-β), 8.70 (1H, d, *J* = 4.8 Hz, H-β), 4.69 (2H, s, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 132.1, 131.8, 131.6, 131.4, 131.0, 130.8, 130.7. MS (MALDI) *m*/*z* 1051.9 [MH^+]. Vis ($CHCl_3$) λ_{max} 631 (relative absorbance, 0.02), 603 (0.03), 558 (0.07), 416 nm (1.0). Anal. Calcd for $C_{44}H_9N_5F_{20}Zn$ $4H_2O{\cdot}CH_3OH$: C, 46.7; N, 6.0; found C, 46.8; N, 5.8.
31. Ramanathan, A.; Jimenez, L. S. *Synthesis* **2010**, *2*, 217–220.