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Mendeleev Commun., 2022, **32**, 675–677

Mendeleev Communications

Synthesis of conjugates of 5,15-disubstituted aminoporphyrins and terpyridine derivatives with potential chelating properties

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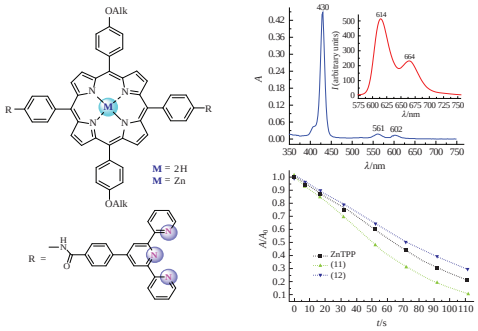
DOI: 10.1016/j.mencom.2022.09.036

***meso*-Arylporphyrin containing two external chelating 2,2′:6′,2′-terpyridine fragments and its zinc complex were synthesized. The key step comprised the amide bond formation between the porphyrin diamine derivative and 4′-(4-carboxyphenyl)-2,2′:6′,2′-terpyridine. The compounds obtained seem to be potent for photodynamic therapy and diagnosis.**



Keywords: porphyrins, terpyridine, Zn complexes of porphyrins, photodiagnostics, photodynamic therapy, chelating groups.

The development of theranostic agents for early tumor detection, imaging and subsequent therapy is an important step towards personalized medicine.[1,2] These compounds provide an opportunity to start therapy immediately after a confirmed successful localization of the drug in the target tissue. In this field the combination of photodynamic therapy (PDT) and magnetic resonance imaging (MRI) is a promising area of research.[3–6] PDT of cancer attracts attention due to low invasiveness, minimal frequency of injuries, simplicity of the method, possibility of combination with traditional methods of therapy and possibility of treatment of the patients for whom standard methods of therapy are contraindicated.[7] Porphyrin-containing compounds are suitable agents for PDT of malignant neoplasms.[8] Synthetic *meso*-arylporphyrins are readily available, chemically stable, possess intense fluorescence and high singlet oxygen quantum yields.[9–12] However, the cavity of the porphyrin macrocycle is known to be limited and does not allow coordination of metals with a large ionic radius. Thus, the possibility of incorporating external chelate-forming fragments into the molecule is of increasing importance.

Among the extensively studied chelators, pyridine-containing compounds are prominent. Moreover, the convenient position of three nitrogen atoms in terpyridine molecule enables the formation of complexes with a large amount of elements.[13–16] These nitrogen-containing heterocycles form stable complexes with paramagnetic metals, independently of their size, since in this case there is no fixed inclusion cavity,[17–19] *e.g.*, a bis-terpyridine complex with ruthenium was documented.[20] The possibility of formation of Eu, Gd, Tb and Sm complexes with 4-carboxyterpyridine *via* additional carboxylate functions has also been shown.[21]

Tetrapyrroles equipped with terpyridine fragments are described scarcely.[22,23] New conjugates with gadolinium for two-photon PDT have been obtained based on cyclen-porphyrins.[24] So, the creation of tetrapyrrole conjugates with chelating terpyridine fragments capable of incorporating metals independently of their ionic radius is an important research in the diagnosis and treatment of malignant neoplasms. In this work, approaches to the synthesis of A2B2-type porphyrins containing an external chelating group based on terpyridine were developed and their photophysical properties were explored. The obtained compounds are promising theranostic agents.

Porphyrins containing an amino group have attracted the attention due to the possibility of their transformation into functionally active derivatives.[25–27] Symmetric amino-substituted *trans*-porphyrins A2B2 can be used as precursors for potential cancer diagnosis and therapy drugs. In addition, symmetrically substituted porphyrins can be further converted to hydrogenated forms such as chlorins and bacteriochlorins without the formation of side products such as isochlorins. Symmetrical amino-substituted *trans*-A2B2 porphyrins can be obtained by the reduction of the nitro groups of the corresponding derivatives. Therefore, in the first step we prepared dinitro-functionalized *trans*-A2B2-tetraphenylporphyrin (*trans* A2B2-TPP). Now, three synthetic strategies can be used to synthesize compounds of this type, namely, mixed-aldehyde condensation,[28] nitration of the phenyl groups of TPP,[29] and the condensation based on dipyrrolylmethanes (DPM).[30,31] We have previously reported the efficiency of monopyrrole condensation in a mixture of organic solvents for the synthesis of asymmetrically substituted A3B-type porphyrins with the active groups and higher alkyl substituents.[11,28] However, this approach is not efficient for the synthesis of disubstituted porphyrins as the theoretical yield of the target compound is about 9–12%. Moreover, mixed-aldehyde condensation affords much *cis*-forms of substituted tetraphenyl-porphyrins with the same number of functional groups, which

requires difficult separation of *trans*-A2B2-TPP from its *cis*-isomer. In this regard, DPM-based condensation is a convenient method for obtaining *trans*-A2B2-TPP. Most DPM-based condensation reactions under the Lindsey[30,31] conditions proceed in organochlorine solvents ($CHCl_3$ or CH_2Cl_2) with the use of Lewis catalysts without heating. However, in our hands this method brought about a complex multicomponent mixture.

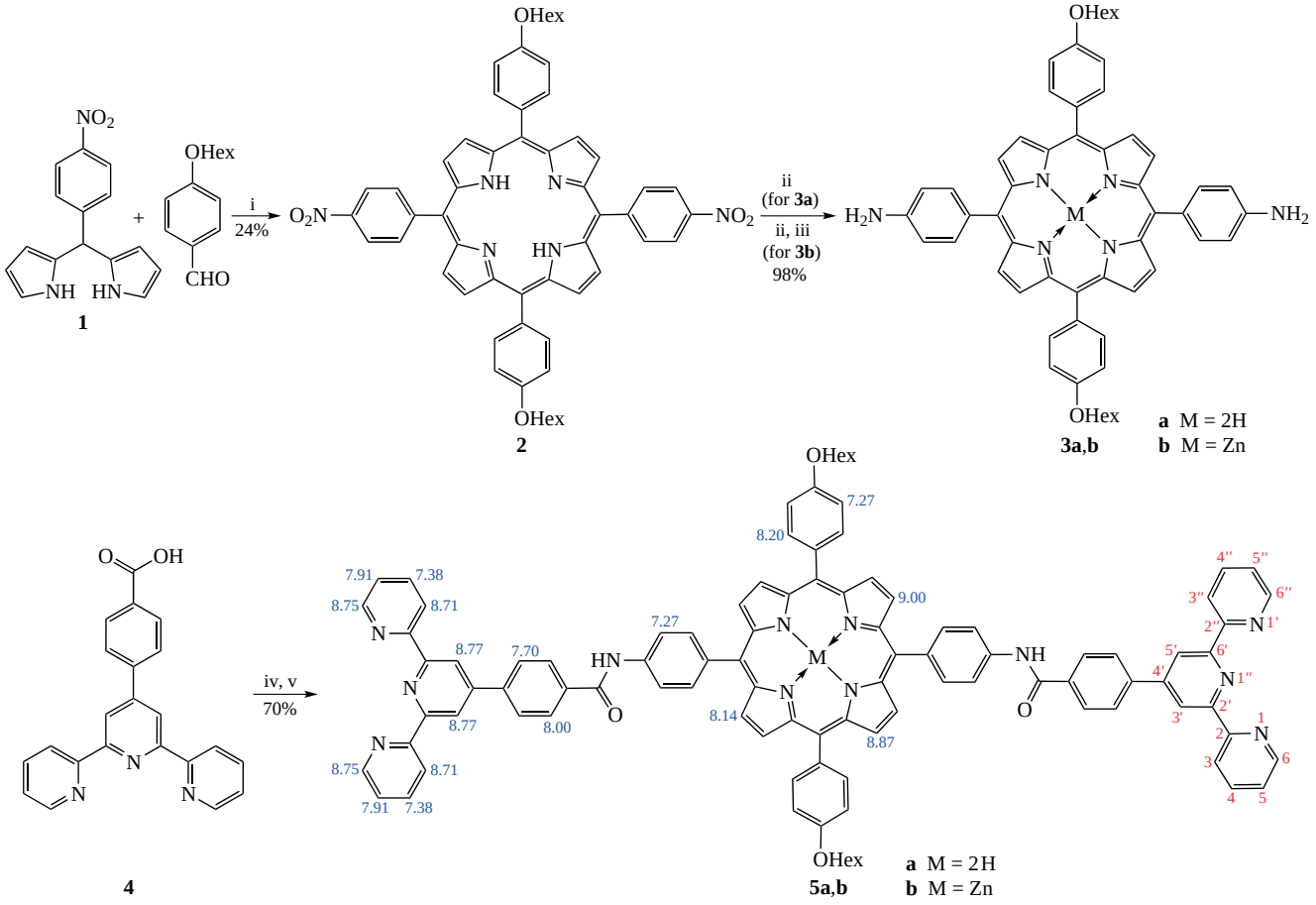
Previously,[32,33] the condensation of 5-(*p*-nitrophenyl)-dipyrromethane with benzaldehyde in boiling propionic acid yielded 5,15-bis(*p*-nitrophenyl)-10,20-diphenylporphyrin in 26% yield. Therefore, we performed the condensation of (*p*-nitrophenyl)dipyrromethane **1** with *p*-hexyloxyphenylbenzaldehyde in the 1:1 ratio followed by reduction of the nitro groups of compound **2** to synthesize amino-*trans*-A2B2 porphyrin **3a** (Scheme 1). The reaction was performed in a mixture of acetic acid and nitrobenzene in a ratio 1:2 at 100 °C with 1 mmol reagent concentration for 1 h. Prolongation of the reaction and increase in the reactant concentration led to the formation of a significant number of polypyrrole side products. In general, the yield of the final nitro-porphyrin **2** depends on several factors: the structure of the benzaldehyde used, the concentration of the reactants, the nitrobenzene/acetic acid ratio (optimally 2:1), and the reaction temperature. The target amino-*trans*-A2B2 porphyrin was obtained upon the reduction with tin dichloride dihydrate in hydrochloric acid in 98% yield. Complex **3b** was prepared by the standard method using excess zinc acetate in methanol. The formation of the metal complex was confirmed using electron absorption spectra (EAS) by the transition of four Q-bands into two bands due to the macrocycle symmetrization typical of Zn^{II} porphyrin complexes.

Synthon (4-carboxyphenyl)terpyridine **4** was synthesized from 2-acetylpyridine and 4-(methoxycarbonyl)benzaldehyde in basic medium as reported.[34,35] The reaction was carried out at 45 °C and a white precipitate, a sodium salt of the resulting terpyridine, appeared within 48 h. For the synthesis of the target products, two methods were tested, *viz.*, the carbodiimide coupling and the Schotten–Baumann procedure. The acylation using carbodiimide gave low yields of compounds, apparently, due to the heterogeneous conditions of the reaction. In the Schotten–Baumann method, carboxylic acid was first converted into its chloride which was further reacted with amino groups of compound **3a** or its Zn^{II} complex **3b** to afford amides **5a** and **5b** in 85–90% yields. The purity and structure of the products were confirmed by TLC, ^{1}H- and ^{13}C-NMR spectroscopy and MALDI-TOF mass spectrometry, HPLC.

In the ^{1}H NMR spectrum of porphyrin **5b**, multiplets from two terpyridine fragments are observed at 8.77 (4H, s, 3′, 5′), 8.75 (4H, dm, 6, 6″), 8.71 (4H, dm, 3′, 3″), 7.90 (4H, m, 5, 5′) and 7.38 ppm (4H, m, 4, 4′). The signals from the β-pyrrole protons are observed as two multiplets (8.84–8.78 and 8.76–8.66 ppm), indicating the presence of a symmetric system (see Online Supplementary Materials, Figure S1).

The main photophysical parameters and photochemical activity in the generation of singlet oxygen were investigated for the obtained compounds (Table 1). The absorption spectra of zinc complexes **3b** and **5b** in DMF are shown in Figure 1. The introduction of terpyridine moiety in the porphyrin *meso*-positions leads to the slight Q bands hypsochromic shift (by 3–5 nm). It is of note that the molar absorption coefficients for both Soret and Q bands of complex **5b** are 1.6 times higher than those of complex **3b** (see Table 1).

The luminescence spectra of both metal complexes differ markedly in the ratio of components and are also characterized by a bathochromic shift of the emission bands relative to ZnTPP



Scheme 1 *Reagents and conditions*: i, AcOH, $PhNO_2$ (1:2, v/v), 100 °C, 1 h, 24%; ii, $SnCl_2 \cdot 2H_2O$, HCl, TFA, $CHCl_3$, reflux, 24 h, 98%; iii, $Zn(OAc)_2$, MeOH, $CHCl_3$, 98%; iv, $SOCl_2$, reflux, 3 h; v, **3a** or **3b**, Et_3N, THF, Ar; 24 h, reflux, 70%.

Table 1 Photophysical properties of compounds **3b** and **5b** in DMF.

Compound	λ_B/nm	log ε	$\Delta\lambda_B$/nm	λ_{em}/nm	I_1/I_2	Φ_F[a]	Φ_Δ[b]
3b	430	5.56	16	623, 667	2.20	0.030	0.72
5b	430	5.77	12	614, 664	2.21	0.036	0.71
ZnTPP[36]	424	5.93	9	605, 658	1.40	0.033	0.74

[a] Fluorescence quantum yield (Φ_F). [b] Singlet oxygen quantum yield (Φ_Δ).

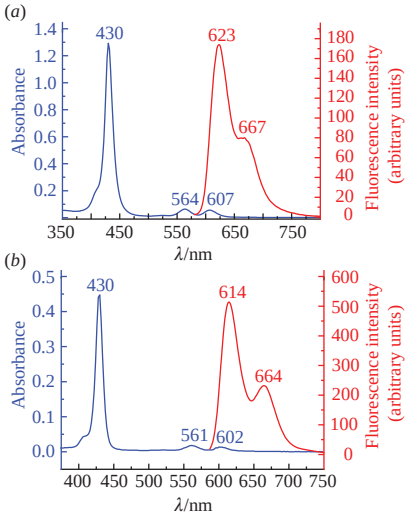


Figure 1 UV-VIS absorption and emission spectra (insert) of (*a*) zinc complex **3b** and (*b*) zinc complex **5b** in DMF at 25 °C.

(see Table 1). Porphyrin-terpyridine conjugate **5b** exhibits a higher fluorescence quantum yield (Φ_F = 0.036) as compared to the initial complex **3b** (Φ_F = 0.030) and the reference compound ZnTPP. The photochemical activity, namely, singlet oxygen quantum yield Φ_Δ for porphyrins **3b** and **5b** in DMF was similar and comparable to that of ZnTPP (see Table 1). For normalized UV-VIS spectra of compounds **3a**,**b** and **5a**,**b**, see Figure S14. Analysis of the kinetic curves of the photosensitized DPBF oxidation with singlet oxygen and the quantum yields of $^1O_2$ generation in DMF indicate type II photodynamic activity in both obtained metal complexes **3b** and **5b**.

In conclusion, we have prepared the novel compounds containing external chelating moieties in high yields. Thus, combination of the maximum values of the absorption coefficient and the singlet oxygen quantum yield allows one to consider the conjugates obtained as promising fluorophores for fluorescence imaging and photosensitizers for photodynamic therapy.

This work was supported by the Russian Science Foundation (grant no. 21-13-00078) and performed using the equipment of the Shared Science and Training Center for Collective Use of RTU MIREA and supported by the Ministry of Science and Higher Education of the Russian Federation. This work is dedicated to the memory of our teacher Prof. Andrey F. Mironov.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.036.

References

1 M. S. Muthu, D. T. Leong, L. Mei and S.-S. Feng, *Theranostics*, 2014, **4**, 660.
2 R. Kojima, D. Aubel and M. Fussenegger, *Curr. Opin. Chem. Biol.*, 2015, **28**, 29.
3 J. Sandland, N. Malatesti and R. Boyle, *Photodiagn. Photodyn. Ther.*, 2018, **23**, 281.
4 N. Rabiee, M. T. Yaraki, S. M. Garakani, S. M. Garakani, S. Ahmadi, A. Lajevardi, M. Bagherzadeh, M. Rabiee, L. Tayebi, M. Tahriri and M. R. Hamblin, *Biomaterials*, 2020, **232**, 119707.
5 P. V. Ostroverkhov, A. S. Semkina, V. A. Naumenko, E. A. Plotnikova, P. A. Melnikov, T. O. Abakumova, R. I. Yakubovskaya, A. F. Mironov, S. S. Vodopyanov, A. M. Abakumov, A. G. Majouga, M. A. Grin, V. P. Chekhonin and M. A. Abakumov, *J. Colloid Interface Sci.*, 2019, **537**, 132.
6 J. Qin, H. Peng, J. Ping and Z. Geng, *Mater. Res. Bull.*, 2019, **114**, 90.
7 S. Kwiatkowski, B. Knap, D. Przystupski, J. Saczko, E. Kędzierska, K. Knap-Czop, J. Kotlińska, O. Michel, K. Kotowski and J. Kulbacka, *Biomed. Pharmacother.*, 2018, **106**, 1098.
8 M. A. Grin, N. V Suvorov and A. F. Mironov, *Mendeleev Commun.*, 2020, **30**, 406.
9 K. A. Zhdanova, I. O. Savelyeva, A. A. Ignatova, M. A. Gradova, O. V. Gradov, A. V. Lobanov, A. V. Feofanov, A. F. Mironov and N. A. Bragina, *Dyes Pigm.*, 2020, **181**, 108561.
10 K. A. D. F. Castro, L. Ramos, M. Mesquita, J. C. Biazzotto, N. M. M. Moura, R. F. Mendes, F. A. Almeida Paz, A. C. Tomé, J. A. S. Cavaleiro, M. M. Q. Simões, M. A. F. Faustino, A. V. Jager, S. Nakagaki, M. G. P. M. S. Neves and R. S. da Silva, *ACS Appl. Bio Mater.*, 2021, **4**, 4925.
11 K. A. Zhdanova, A. V. Ezhov, N. A. Bragina and A. F. Mironov, *Mendeleev Commun.*, 2018, **28**, 626.
12 D. A. Polivanovskaia, K. P. Birin, A. A. Averin, Yu. G. Gorbunova and A. Yu. Tsivadze, *Russ. Chem. Bull.*, 2021, **70**, 2100.
13 C. Bhaumik, S. Das, D. Saha, S. Dutta and S. Baitalik, *Inorg. Chem.*, 2010, **49**, 5049.
14 A. Hussain, K. Somyajit, B. Banik, S. Banerjee, G. Nagaraju and A. R. Chakravarty, *Dalton Trans.*, 2013, **42**, 182.
15 C. Dong, J. Yuan, H. Hoffmann and J. Hao, *New J. Chem.*, 2019, **43**, 19355.
16 D. Patra, S. Mukherjee, I. Chakraborty, T. K. Dash, S. Senapati, R. Bhattacharyya and R. Shunmugam, *ACS Biomater. Sci. Eng.*, 2018, **4**, 1738.
17 E. G. Moore, M. Benaglia, G. Bergamini and P. Ceroni, *Eur. J. Inorg. Chem.*, 2015, 414.
18 A. Hussain, S. Gadadhar, T. K. Goswami, A. A. Karande and A. R. Chakravarty, *Eur. J. Med. Chem.*, 2012, **50**, 319.
19 T. Wieprecht, J. Xia, U. Heinz, J. Dannacher and G. Schlingloff, *J. Mol. Catal. A: Chem.*, 2003, **203**, 113.
20 T. Ezhilarasu, A. Sathiyaseelan, P. T. Kalaichelvan and S. Balasubramanian, *J. Mol. Struct.*, 2017, **1134**, 265.
21 R.-X. Hu, J. Yang, X. Chen, X. Zhang and M.-B. Zhang, *Inorg. Chim. Acta*, 2018, **482**, 702.
22 M. Suzuki, T. Uehara, Y. Arano, T. Hoshino and S. Neya, *Tetrahedron Lett.*, 2011, **52**, 7164.
23 H. Luo, J. Jiang, X. Zhang, C. Li, G. Shen and R. Yu, *Talanta*, 2007, **72**, 575.
24 S. Jenni, F. Bolze, C. S. Bonnet, A. Pallier, A. Sour, É. Tóth, B. Ventura and V. Heitz, *Inorg. Chem.*, 2020, **59**, 14389.
25 Y.-H. Yao, J. Li, L.-F. Yuan, Z.-Q. Zhang and F.-X. Zhang, *RSC Adv.*, 2016, **6**, 45681.
26 A. V. Ezhov, F. Yu. Vyalba, K. A. Zhdanova, A. F. Mironov, K. Yu. Zhizhin and N. A. Bragina, *Tonkie Khim. Tekhnol.*, 2018, **13** (2), 21 (in Russian).
27 V. A. Ol'shevskaya, V. M. Alpatova, A. S. Radchenko, A. A. Ramonova, A. S. Petrova, V. V. Tatarskiy, A. V. Zaitsev, E. G. Kononova, N. S. Ikonnikov, A. A. Kostyukov, A. E. Egorov, M. M. Moisenovich, V. A. Kuzmin, N. A. Bragina and A. A. Shtil, *Dyes Pigm.*, 2019, **171**, 107760.
28 K. A. Zhdanova, A. P. Zhdanov, A. V. Ezhov, N. A. Bragina, K. Yu. Zhizhin, I. P. Ushakova, A. F. Mironov and N. T. Kuznetsov, *Russ. Chem. Bull.*, 2014, **63**, 194.
29 R. Luguya, L. Jaquinod, F. R. Fronczek, M. G. H. Vicente and K. M. Smith, *Tetrahedron*, 2004, **60**, 2757.
30 J. S. Lindsey, *Acc. Chem. Res.*, 2010, **43**, 300.
31 B. J. Littler, Y. Ciringh and J. S. Lindsey, *J. Org. Chem.*, 1999, **64**, 2864.
32 T. Lin, X. S. Shang, J. Adisoejoso, P. N. Liu and N. Lin, *J. Am. Chem. Soc.*, 2013, **135**, 3576.
33 Y.-B. She, H.-Y. Fu, Z.-L. Zhang, X.-F. Song and Z.-C. Sun, *Heterocycles*, 2014, **89**, 503.
34 S. Tu, R. Jia, B. Jiang, J. Zhang, Y. Zhang, C. Yao and S. Ji, *Tetrahedron*, 2007, **63**, 381.
35 A. Stublla and P. G. Potvin, *Eur. J. Inorg. Chem.*, 2010, 3040.
36 M. Taniguchi, J. S. Lindsey, D. F. Bocian and D. Holten, *J. Photochem. Photobiol., C*, 2021, **46**, 100401.

Received: 9th February 2022; Com. 22/6802