Synthesis of Ferrocene−Modified Porphyrins by the Reductive Amination Reaction

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Ferrocene-modified porphyrins were synthesized via the reductive amination reaction of ferrocenylpyrazole-carboxaldehydes and tetraphenylporphyrinamine. The steric hindrance of the ferrocene moiety was found to play the key role in this reaction.

Keywords: Porphyrin, ferrocene, reductive amination reaction.

Introduction

For many years, porphyrins has been used in photodynamic tumor therapy.[1] They can act as radiosensitizers in thick tumors.[2] At the same time, bioconjugates containing ferrocene represent a new class of biomaterials, with the organometallic unit serving as a molecular scaffold, a sensitive probe, a catalytic or redox-active site and so forth.[3] Ferrocenyl heterocyclic compounds have been found to exhibit biological activities (*e.g.* antitumor[4] and antimicrobial[5]). Noteworthy, pyrazole motif makes up the core structure of numerous biologically active compounds.[6] Some pyrazole compounds have affinity for the human CRF-1 receptor,[7] exhibit anti-viral/anti-tumor,[8] antibacterial,[9] anti-parasitic,[10] antipyretic,[11] anty-flammatory,[9,11,12] analgesic,[12] fungistatic,[13] fungicidal,[14] and anti-hyperglycemic activity.[15]

Ferrocene and porphyrins have already been associated by means of various methods. These include direct connection,[16,17] linkage through conjugated spacers,[18] linkage through saturated spacers.[19] Besides, there are *β*-pyrrole-linked ferrocene-porphyrins[20,21,22] and ferrocene-porphyrin analogues.[23]

The difference of bounding ways in the ferrocene-porphyrin assemblies suggests the variety of application. Their donor-acceptor properties have been employed to study photoinduced electron transfer processes and to simulate photosynthesis active sites.[24,25] Thus, such structures have been employed as molecular sensors[26] and for an increase of memory density that allowed multibit information storage.[27]

In our work we aimed to obtain ferrocene-porphyrins, containing pyrazole moiety.

Previously, we have studied the reductive amination reaction of ferrocenylpyrazolecarboxaldehydes with primary and secondary aliphatic and aromatic amines. Therefore, we used this reaction to produce ferrocene-porphyrins.

Experimental

The solvents were dehydrated by conventional methods directly before use. Mass spectra (MS) were obtained on a "FINNIGAN POLARIS" Q spectrometer using electron ionization method and on a "LCQ Advantage" spectrometer using electro spray ionization. NMR spectra were registered on an "AVANCE" spectrometer with operational frequency 300 MHz and on a "Bruker DRX-500" spectrometer with operational frequencies 500.13 MHz and 125.76 MHz for protons and ^{13}C nuclei respectively, in $CDCl_3$ and DMSO-d_6. Two-dimensional spectra COSY, HSQC and HMBC were registered using the gradient method. The UV-vis spectral measurements were carried out with a "Carl Zeiss Jena" model Specord M40 spectrometer in 200-1000 nm region.

Starting ferrocenyl-(1-phenyl-5-ferrocenyl-3-formylpyrazole[28] **2a**, 1-phenyl-5-ferrocenyl-4-formylpyrazole[29] **2b**, 1-phenyl-3-ferrocenyl-4-formylpyrazole[30,31] **2c**, formylferrocene[32] **2d**) and phenylformylpyrazoles (1-phenyl-5-ferrocenyl-4-pyrazolecarboxaldehyde[33] **4a**, and 1-phenyl-3-ferrocenyl-4-pyrazolecarboxaldehyde[34] **4b**) were obtained by methods described in literature.

3-(5-(p-Aminophenyl)-10,15,20-triphenylporphyrin)-5-ferrocenyl-1-phenylpyrazole, ***3a.*** Violet powder. Yield 63% (0.03 g). ^1H NMR, 500 MHz ($CDCl_3$) δ ppm: 4.14 (s, 5H, Cp), 4.23 (s, 4H, Cp), 4.70 (s, 2H), 6.68 (s, 1H, Pz), 7.14 – 7.16 (d, 2H, *o*-Ph-NH, *J* = 10 Hz), 7.76 – 7.80 (s, 9H, Ph, *J* = 20 Hz), 8.09 – 8.11 (d, 2H, *m*-Ph-NH, *J* = 10 Hz), 8.26 – 8.27 (d, 6H, Ph, *J* = 5 Hz), 8.88 (s, 6H,), 9.02 (d, 2H, *J* = 5 Hz). ^{13}C NMR, 126 MHz ($CDCl_3$) δ, ppm: 42.5, 68.7, 69.9, 75.0, 105.4, 111.5, 119.6, 119.9, 121.3, 126.6, 127.6, 128.1, 128.9, 131.5, 134.6, 135.8, 140.4, 142.3, 142.4, 142.9, 147.8, 150.9. ESI/MS (*m/z*): 969.3154 $[M+H]^+$. Calculated: M = 969.3242.

1,5-Diphenyl-4-(5-(p-aminophenyl)-10,15,20-triphenylporphyrin)pyrazole, ***5a***. Yield 40% (0.017 g). UV-vis (CH_2Cl_2) λ_{max} nm: 278, 420, 516, 556, 648. ^1H NMR, 300 MHz ($CDCl_3$) δ ppm: 4.47 (s, 1H, CH_2), 6.99 (d, 2H, 2CH, *o*-Ph – NH, *J* = 3 Hz), 7.34 – 7.48 (m, 10H, 10CH, Ph) 7.83 (m, 9H, 9CH, Ph), 8.07 (d, 2H, 2CH, *m*-Ph-NH, *J* = 3 Hz), 8.09 (c, 1H, Pz), 8.27 (d, 2H, 2CH, Ph, *J* = 3 Hz), 8.89 (s, 6H, 6CH), 9.01 (d, 2H, 2CH, *J* = 3 Hz). ^{13}C NMR, 126 MHz ($CDCl_3$) δ ppm: 34.6, 112.1, 117.2, 119.8,

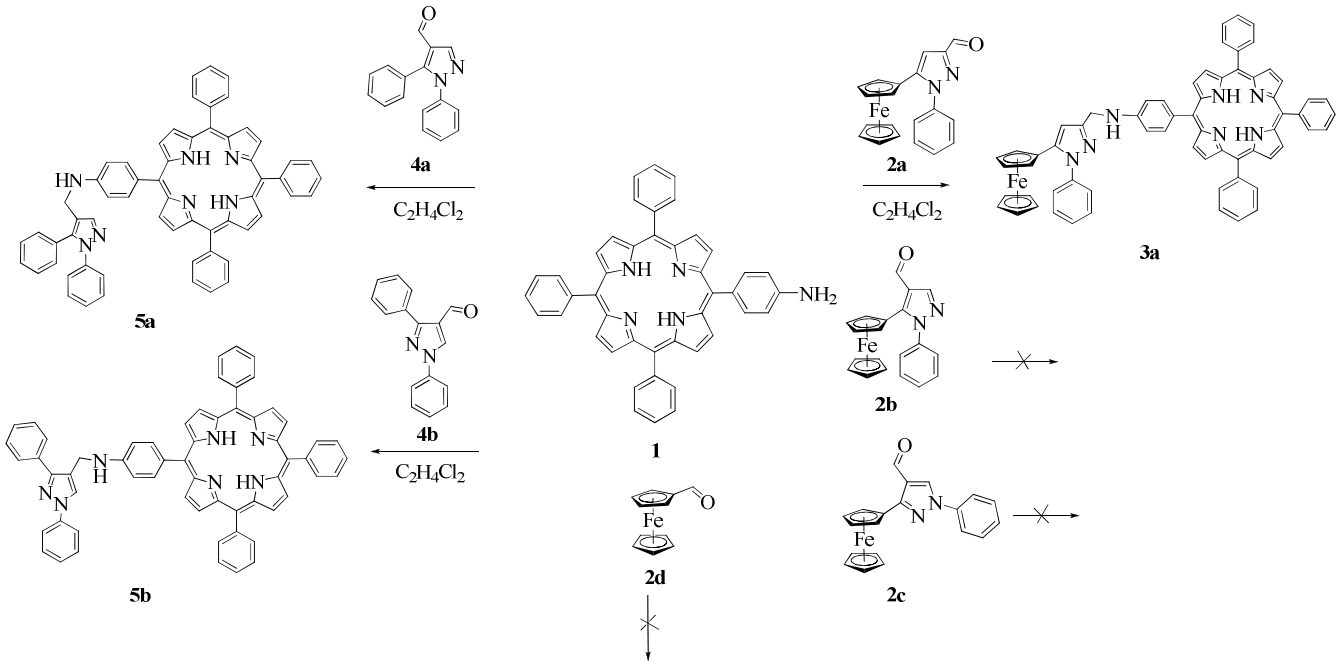

Figure 1. The preparation of ferrocenylheterocyclyc porphyrins and their phenyl analogues.

120.0, 124.5, 126.0, 127.3, 127.9, 128.7, 129.2, 130.2, 130.7, 131.0, 133.0, 134.4, 135.6, 139.7, 141.0, 142.3, 146.6, 148.5, 149.7. ESI/MS (*m/z*) (I_{re} %): 862.5 (100) $[M+H]^+$.

1,3-Diphenyl-4-(5-(p-aminophenyl)-10,15,20-triphenylporphyrin)pyrazole, ***5b***. Yield 44% (0.019 g). UV-vis (CH_2Cl_2) λ_{max} nm: 279, 420, 515, 556, 649. ^{1}H NMR, 500 MHz ($CDCl_3$) δ ppm: 4.64 (s, 2H, CH_2), 6.99 (d, 2H, *o*-Ph – NH, *J* = 5 Hz), 7.34 (t,1H, *p*-Ph, *J* = 10 Hz) 7.46 (t, 1H, *p*-Ph, *J* = 10 Hz), 7.51 (t, 2H, *m*-Ph, *J* = 5 Hz), 7.55 (t, 2H, *m*-Ph, *J* = 5 Hz), 7.73 (s, 9H, Ph), 7.84 (d, 2H, *o*-Ph, *J* = 5 Hz), 7.94 (d, 2H, *o*-Ph, *J* = 5 Hz), 8.05 (d, 2H, *m*-Ph-NH, *J* = 10 Hz), 8.17 (s, 1H, Pz), 8.23 (d, 6H, *o*-Ph, *J* = 10 Hz), 8.85 (s, 6H, 6CH), 8.97 (d, 2H, 2CH, *J* = 5 Hz). ^{13}C NMR, 126 MHz ($CDCl_3$) δ, ppm: 30.0, 111.5, 119.0, 126.5, 126.7, 127.6, 127.7, 127.8, 128.2, 128.8, 129.5, 130.8, 134.0, 135.9, 142.4 ESI/MS (*m/z*) (I_{re} %): 862.5 (100) $[M+H]^+$.

Results and Discussion

The reductive amination reaction was carried out in 1,2-dichloroethane using $NaB(OAc)_3H$ as a reductive reagent. In the interactions of ferrocenylpyrazolecarboxaldehydes with 5-(*p*-aminophenyl)-10,15,20-triphenylporphyrin **1** the product, **3a**, was obtained only from the reaction with 1-phenyl-5-ferrocenyl-3-formylpyrazole **2a**.

The variation of the reaction time and conditions for 1-phenyl-5-ferrocenyl-4-formylpyrazole **2b** and 1-phenyl-3-ferrocenyl-4-formylpyrazole **2c** didn't lead to the target products. We assumed that the bulky ferrocene moiety near carbonyl group played the key role preventing the attack of reducing agent. The same effect was observed in the case of reaction with formylferrocene **2d**, and the Shiff base was the mostly formed.

To confirm our suggestion about the steric hindrance caused by the ferrocenyl group, we carried out the reaction of aminoporphyrin with 1-phenyl-5-ferrocenyl-4-pyrazolecarboxaldehyde **4a**, and 1-phenyl-3-ferrocenyl-4-pyrazolecarboxaldehyde **4b**.

In contrast to the ferrocene analogues, phenylaldehydes entered into this reaction. Noteworthy, in the absence of the ferrocene moety the reaction proceeded more easily. Thus we isolated corresponding amines **5a**,**b** in 40 and 44% yields, respectively.

Conclusions

We have first obtained the ferrocenylheterocyclic porphyrin by means of the reductive amination reaction and optimized the reaction conditions. It was revealed that the reaction proceeded only with those ferrocenylformaldehydes, that lacked steric hindrances between substituents in the pyrazole unit. Biological tests of obtained ferrocene-porphyrin **3a** are carrying out.

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