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Original article

Metalloporphyrin receptors for histidine-containing peptides

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ABSTRACT

Two new ditopic metalloporphyrin receptors constructed by combining metalloporphyrin with crown ethers have been prepared and characterized. ^{1}H NMR and MS spectra confirmed the complexation of receptor with peptide driven by coordination interaction and hydrogen bonding. UV/vis experiments revealed that the receptors exhibited high binding affinity to histidine-containing peptides. These receptors could differentiate short peptides of C-terminal histidine and N-terminal histidine and formed the most stable complexes with tripeptide.

1. Introduction

Selective recognition of short peptides by synthetic receptors has attracted a great deal of interest in past decade because of their important roles in nature [1–5]. The intrinsic properties of short peptides originated from flexible conformation and irregular topology placed a number of challenges in the design of receptors [6]. In the recently reported examples, one strategy has been proved to be effective for selective recognition of peptides, this is, the binding of peptide N terminus and side chain of peptide in ditopic fashion [7–10].

Crown ethers are ideal binding units for ammonium ions in amino acids [11–14]. On the other hand, metalloporphyrins have been documented to coordinate the nitrogen atom of imidazole [15–18]. Porphyrin platform can further provide a large molecular surface for dispersive interaction with peptide backbone [19–21]. In this context, the aim of this letter is to develop new receptors by combining crown ethers with metalloporphyrin and to investigate their recognition behavior toward histidine-containing short peptides.

The strapped porphyrin developed by our group was served as a scaffold to align peptide backbone in one direction from the N to C terminus [22,23]. The metal cation Zn(II) in the center of porphyrin could provide additional coordination site to bind nitrogen atom of histidine. Aza-crown ethers of varied size were incorporated to porphyrin *via* amide linkage as recognition site of ammonium ion, which allowed the receptor preorganized as the distance between N terminus and side chain of peptides (Scheme 1).

2. Experimental

NMR spectra were recorded on a Varian spectrometer operating at 300 and 400 MHz for ^{1}H and ^{13}C respectively in the indicated solvents. Chemical shifts were expressed in parts per million (δ) using residual solvent protons as internal standards. MALDI-TOF mass spectra were recorded on a Voyager-DE STR mass spectrometer (AB SCIEX, USA). UV/vis absorption spectra were measured with a Cary 100 UV/vis spectrophotometer (Varian, USA). Elemental analysis was carried out at the SIOC analytical center. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. All solvents were dried before use following standard procedures. All reactions were performed under an atmosphere of dry nitrogen. Compound **5** was prepared following our previous method [24,25]. Column chromatography was carried out using silica gel (300–400 mesh). All of the modified peptides were prepared following standard procedures in the solution (see Supporting information).

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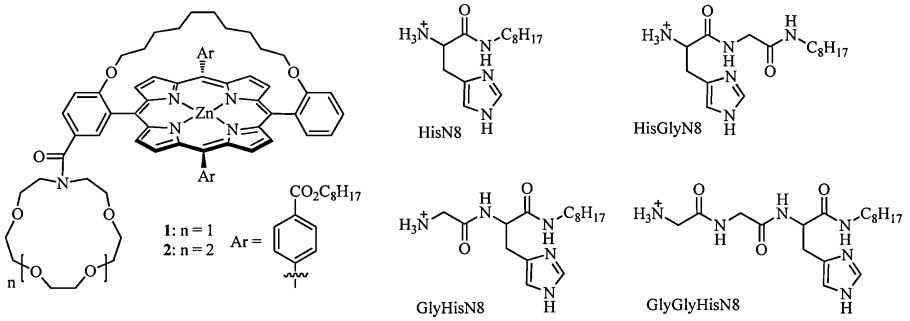


Scheme 1. Metalloporphyrin receptors and modified peptides.

The UV/vis titration experiments were performed according to the following procedure. A solution of receptor (2.0 mL, 1.1×10^{-6} mol/L) in chloroform was titrated with 10 μL of histidine-containing peptide (2.0×10^{-5} mol/L to 5.0×10^{-5} mol/L in chloroform, adjusted with 10 fold HCl). After each addition the solution was allowed to equilibrate for 5 min and the absorption intensity was recorded in the wavelength region of 350–600 nm at 25 °C.

2.1. General procedure for the synthesis of metalloporphyrin receptors

To a solution of porphyrin acid **5** in dichloromethane oxalyl chloride and several drops of DMF were added. The mixture was stirred at room temperature for 5 h. After evaporating the solvents under vacuum, the residue was dissolved in dichloromethane and then aza-crown ether and triethyl amine were added and stirred overnight at room temperature. After removal of solvent, the resulting residue was purified by column chromatography to afford aza-crown ether porphyrin. The free base porphyrin was dissolved in dichloromethane/methanol (3:1) and zinc acetate was added with stirring. The mixture was stirred under reflux overnight. The solvent was removed *in vacuo* and the resulting residue was subjected to column chromatography to afford metalloporphyrin receptor as a purple solid in high yield (Scheme 2).

Compound **1**: Purple solid (68%). Mp > 250 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ −1.39 (m, 2H), −1.21 (m, 2H), −1.00 (m, 2H), −0.80 (m, 2H), −0.60 (br, 4H), 0.65 (br, 4H), 0.90 (t, 6H), 1.25–1.56 (m, 20H), 1.89 (p, 4H), 3.35–3.86 (m, 20H), 4.49 (t, 4H, *J* = 6.75 Hz), 7.28 (m, 2H), 7.46 (d-t, 1H, *J* = 0.9, 7.5 Hz), 7.76 (d-t, 1H, *J* = 1.8, 5.1 Hz), 7.86 (d-d, 1H, *J* = 2.25, 8.55 Hz), 8.19 (d-d, 2H, *J* = 1.05, 7.95 Hz), 8.32 (d-d, 1H, *J* = 7.5, 1.8 Hz), 8.37–8.48 (m, 7H), 8.81 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.1, 26.1, 27.7, 28.3, 28.9, 29.1, 29.3, 29.4, 31.9, 65.5, 70.1, 112.9, 113.8, 116.4, 117.8, 119.5, 120.0, 127.7, 128.0, 129.1, 129.6, 129.8, 131.6, 131.7, 131.9, 132.2, 132.8, 134.4, 134.7, 147.7, 149.5, 150.4, 150.7, 159.8, 160.6, 167.0, 172.0, 172.3. MS (MALDI-TOF) (*m*/*z*): 1407 ($M+H^+$). Anal. Calcd. for $C_{83}H_{97}N_5O_{11}Zn$: C, 70.90; H, 6.95; N, 4.98. Found: C, 70.39; H, 7.04; N, 4.91.

Compound **2**: Purple solid (71%). Mp > 250 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ −1.39 (br, 2H), −1.26 (br, 2H), −1.00 (br, 2H), −0.85 (br, 2H), −0.69 (br, 4H), 0.61 (br, 4H), 0.90 (t, 6H), 1.25–1.55 (m, 20H), 1.88 (p, 4H), 2.29–3.06 (m, 20H), 3.67 (m, 4H), 4.42 (t, 4H, *J* = 6.75 Hz), 7.09 (d, 1H, *J* = 9.0 Hz), 7.29 (s, 1H), 7.46 (t, 1H, *J* = 7.5 Hz), 7.56 (d, 1H, *J* = 5.4 Hz), 7.76 (t, 1H, *J* = 5.1 Hz), 7.99 (s, 1H), 8.22–8.45 (m, 9H), 8.75–8.88 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.1, 26.2, 29.1, 29.3, 29.4, 29.7, 31.9, 65.4, 70.4, 112.8, 113.8, 116.3, 117.7, 119.4, 119.9, 127.6, 128.9, 129.5, 129.8, 131.4, 131.6, 131.8, 132.1, 134.3, 134.7, 147.8, 149.5, 150.5, 150.9, 159.8, 160.5, 167.0, 171.8, 172.0. MS (MALDI-TOF) (*m*/*z*): 1451 ($M+H^+$). Anal. Calcd. for $C_{85}H_{101}N_5O_{12}Zn$: C, 70.40; H, 7.02; N, 4.83. Found: C, 70.61; H, 7.02; N, 4.64.

3. Results and discussion

To investigate the binding modes of the metalloporphyrin receptor and the histidine-containing peptides, ^{1}H NMR experiments were firstly carried out. When 5 equiv. of HisN8 was added to a solution of metalloporphyrin **1** or **2** in $CD_3OD/CDCl_3$ (1/1), the signals of the protons of the imidazole group shifted upfield (*ca.* 0.17 ppm) as a result of the coordination interaction between the imidazole nitrogen atom and the zinc cation (Fig. 1). The strong

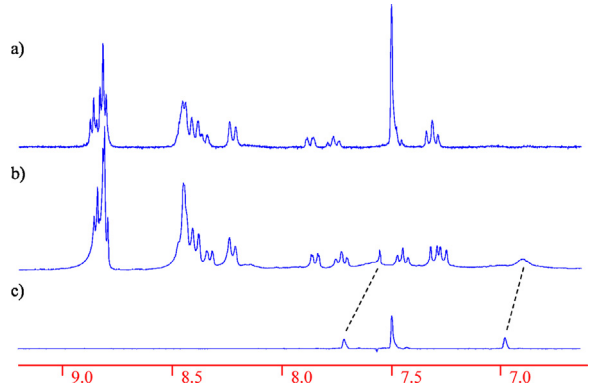
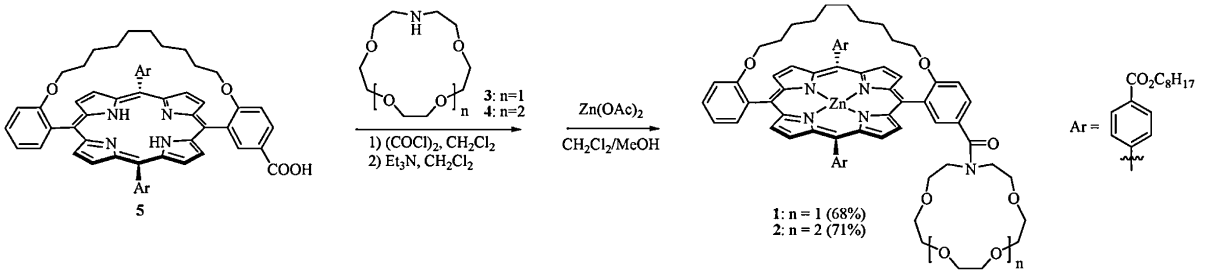


Fig. 1. Partial ^{1}H NMR spectra (300 MHz) in $CD_3OD/CDCl_3$ (1/1) at 25 °C: (a) Receptor **1**; (b) Receptor **1** + **5** equiv. HisN8; (c) HisN8.



Scheme 2. Synthetic route of metalloporphyrin receptors **1** and **2**.