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Synthesis of Metal Porphyrins Tailed with Salicylic Acid and their Interaction with Bovine Serum Albumin

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Abstract: A synthetic method of porphyrins tailed with salicylic substituents is described. Reaction of bromoalkoxyphenyl porphyrin **1** with salicylic acid gave porphyrins **2~5**. These new compounds were confirmed by ^{1}H NMR, IR, UV-vis, MS and elemental analysis, and observed their interaction with bovine serum albumin (BSA) in fluorescence spectrum.

Keywords: Metalloporphyrins, salicylic acid, synthesis, bovine serum albumin, fluorescence.

Along with the deep research of porphyrins, people focus on looking for new anticancer drug in the field of medicine. One of the most attractive applications of porphyrins is in treatment of tumors[1]. This treatment is based on the interaction of the porphyrin sensitizer with visible light so as to produce single oxygen, directing to the cancer cells to cause their death[2]. As we know, acetylsalicylic acid (ASA) is widely used as an analgesic, anti-inflammatory and antipyretic drug. In addition, low-dose ASA is employed as an antithrombotic and anticolonic cancer agent[3]. ASA is rapidly hydrolyzed *in vivo* to salicylic acid (SA), which is also active for inhibition of these cancers[4]. In result, SA was linked to porphyrin ring through soft chain and gained new compounds which would be expected to have potential bioactivity. 5-(4-Hydroxy-phenyl)-10,15,20-trisphenyl porphyrin was prepared according to the literatures. The synthetic routes of new salicylic substituted porphyrins and their metal complexes are summarized in **Scheme I**.

Experimental

A mixture of 5-(4-hydroxylphenyl)-10,15,20-trisphenylporphyrin (110 mg, 0.15 mmol), 1,4-dibromobutane (650 mg, 3.12 mmol) and anhydrous K_2CO_3 (500 mg, 3.62 mmol) in DMF (15 mL) was stirred at 60°C for 3 h under N_2. The reaction mixture was poured into saturated water solution of sodium chloride and filtered. The crude product was purified with column chromatography using silica gel as solid support, chloroform as eluent, and the first band was collected. After the product solution was evaporated to **1** was obtained in a yield of 112 mg (84.9 %). ^{1}H NMR ($CDCl_3$, δ，ppm) δ -2.77 (s, 2H,

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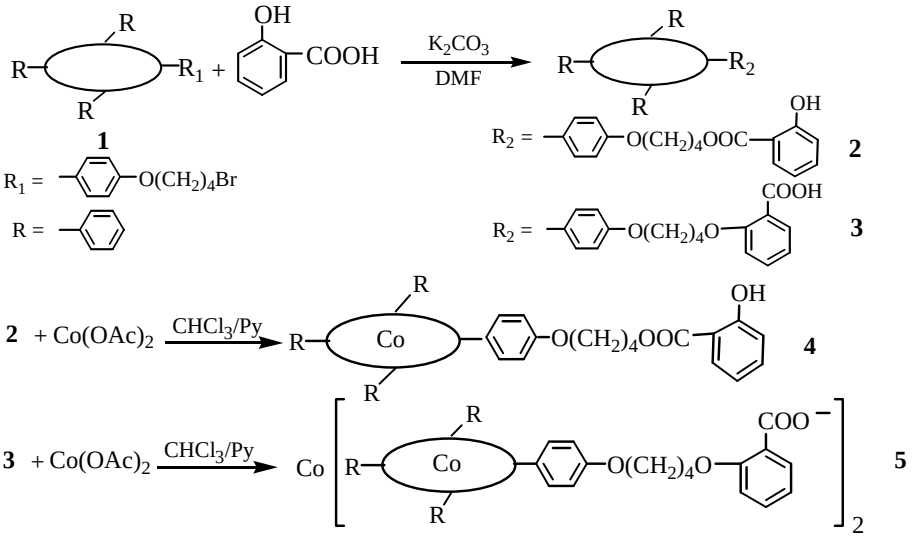
Scheme I



pyrrole N-H), 2.15~2.20 (m, 2H, **-CH$_2$-**CH$_2$-Br), 2.26~2.30 (2H, m, -OCH$_2$-**CH$_2$**), 3.63~3.66 (t, 2H, *J* = 4.8 Hz, Br-**CH$_2$-**), 4.30~4.34 (t, 2H, *J* = 4.8 Hz, **-CH$_2$-**O), 7.75~7.77 (d, 8H, *J* = 4.6 Hz, PhH$_m$), 8.12~8.15 (d, 2H, *J* = 4.6 Hz, O-PhH$_o$), 8.22~8.24 (d, 6H, *J* = 4.5 Hz, PhH$_m$), 8.97 (s, 8H, pyrrol H$_\beta$); UV-vis (λ_{max}, $CHCl_3$): 420, 521, 557, 595, 652 nm; Anal. for $C_{48}H_{37}N_4OBr$ Calcd. C 75.19; H 4.83; N 7.31; Found C 75.17; H 4.82; N 7.29; FAB MS (M^+) *m/z* 766.

To 10 mL of DMF were added 90 mg (0.65 mmol) of salicylic acid and 100 mg (0.13 mmol) of **1**. After stirred at 60^{o}C for 24 h. The reaction mixture was added into saturated water solution of sodium chloride, then was filtrated and washed with 1 mol/L hydrochloric acid, water and methanol in successively. The crude product was chromatographied on a bed of silica gel eluted with chloroform. 45 mg (42.1 %) of the compound **2** was collected from the second band and 38 mg (35.6 %) of compound **3** was collected from the third band, after the solvent was evaporated to dryness under vacuum. Spectrum data of compound **2**: ^{1}H NMR ($CDCl_3$, δ ppm) δ -2.76 (s, 2H, pyrrole NH), 2.10~2.14 (m, 2H, CH_2CH_2-O-Por), 2.25~2.30 (m, 2H, CH_2CH_2OCO-), 4.25~4.26 (t, 2H, *J* = 4.4 Hz, CH_2-O-Por), 4.56~4.59 (t, 2H, *J* = 4.4 Hz, CH_2OCO-), 7.04~7.06 (m, 1H, SalphH$_4$), 7.25~7.28 (m, 2H, SalphH$_{2\sim3}$), 7.64~7.68 (m, 11H, PorphH$_{m,p}$), 7.91~7.93 (m, 1H, SalphH$_1$), 8.15~8.20 (m, 8H, PorphH$_o$), 8.76 (s, 8H, pyrrole H$_\beta$); IR (υ, KBr, cm^{-1}): 3311 (pyrrole N-H), 1719 (ArCOO-CH_2-), 1597, 1501 (ph-H), 1242 (arylaether C-O-C), 1175 (ester C-O); UV-vis (λ_{max}, $CHCl_3$) 419, 516, 551, 590, 646 nm; Anal. for $C_{55}H_{42}N_4O_4$ Calcd. C 80.19; H 5.10; N 6.80. Found C 80.15; H 5.12; N 6.82; FAB MS (M^+) *m/z* 824. Spectrum data of compound **3**: ^{1}H NMR ($CDCl_3$, δ ppm) δ -2.76 (s, 2H, pyrrole N-H), 1.92~1.95 (m, 2H, CH_2CH_2O-Sal), 2.08~2.10 (m, 2H, -OCH_2CH_2-OPor), 3.84~3.86 (t, 2H, *J* = 4.5 Hz, CH_2O-Sal), 4.28~4.30 (t, 2H, *J* = 4.5 Hz, CH_2-O-Por), 7.22~7.25 (m, 3H, SalphH$_{2\text{-}4}$), 7.73~7.82 (m, 11H, PorphH$_{m,p}$), 8.19~8.25 (m, 9H, PorphH$_o$ and SalphH$_1$), 8.80 (s, 8H, pyrrole H$_\beta$); IR

(ν, KBr, cm^{-1}) 3312 (pyrrol N-H), 1634 (ArCOOH), 1603, 1506 (ph-H), 1243 (arylaether C-O-C), 1178 (ester C-O); UV-vis (λ_{max} , $CHCl_3$) 419, 516, 551, 591, 646 nm; Anal. for $C_{55}H_{42}N_4O_4$ Calcd. C 80.19; H5.10; N6.80. Found C 80.17; H 5.09; N 6.79; FAB MS (M^+) *m/z* 824.

2 (50 mg, 0.06 mmol) and 50 mg of Co $(OAc)_2$ in the mixture of chloroform (20 mL) and pyridine (5 mL) were refluxed for 6 h. The solution was cooled, and then filtrated. The product **4** was eluted from the silica gel column using chloroform/methanol (20:1, v/v) as eluent. The yield was 73.5 %. UV-vis (λ_{max} , $CHCl_3$): 411, 529 nm; IR (ν, KBr, cm^{-1}): 1712 (ArCOO-CH_2-), 1599, 1503 (ph-H), 1244 (aryl ether C-O-C), 1168 (ester C=O), 1004 (OSMB); Anal. Calcd. for $C_{55}H_{40}N_4O_4Co$: C 75.08, H 4.55, N 6.37, Found: C 75.14, H 4.50, N 6.38; FAB MS (M^+) *m/z* 879.

The complex **5** was prepared by the same method mentioned above in the yield of 68.8 %. UV-vis (λ_{max} , $CHCl_3$) 412, 526 nm; IR (ν, KBr, cm^{-1}) 1713 (ArCOO-CH_2-), 1608, 1509 (ph-H), 1243 (aryl ether C-O-C), 1175 (ester C=O), 1004 (OSMB); Anal. for $C_{110}H_{78}N_8O_8Co_3$ Calcd. C 72.69; H 4.29; N 6.16. Found C 72.60; H 4.31; N 6.17. FAB MS (M^+) *m/z* 1816.

Interaction with BSA

We used fluorescence spectrum to observe the interaction between BSA and metalloporphyrin of **4** or **5** under different concentration. The condition of the fluorescent tests were in the mixed solution of DMF/water (v/v 9:1) at 25°C. The **Figure 1** and **Figure 2** showed that the fluorescence of BSA was quenched by metalloporphyrins **4** and **5**.

Results and Discussion

The N-H stretching band at 3310 cm^{-1} nearly disappeared in the IR spectrum of **4** and **5**, and a strong and sharp peak at about 1000 cm^{-1} appeared, which is the marked band for oxidation state of metal. The special frequencies of Co^{II} (**4**) or Co^{II} (**5**) is 1004 cm^{-1}. UV-vis. spectrum of metal complexes is distinct from the free-base porphyrins because the Soret band shifts from 419 nm to 411 nm (or 412 nm) and the B band cuts down from four bands to one band.

When the water was alternated with the mixture of DMF and water (v/v 9:1), λ_{ex} (280 nm) and λ_{em} (345 nm) of BSA shifted to 290 nm and 335 nm, respectively, the discrimination of the constant of equation also changed from 1 to 0.875 or 0.981 in this condition.

From **Figure 1**, **Figure 2** and **Figure 3** we can see that the quenching effect of metalloporphyrins **4** and **5** on the BSA's fluorescence is obvious. The slope of linear fit equation of metal porphyrin **5** is steeper than that of metal porphyrin **4**, which might be due to the number of Co in compound **5** is more than that in compound **4**, that is to say, interaction between metal Co^{II} (**4**) and N, O, S of BSA is not so strong as that in metal Co^{II} (**5**). At the same time, we marked value of *F* at 335 nm, then fit line of I_o/I -c (see **Figure 3**).

Figure 1 BSA's fluorescent influenced by **4**[5]

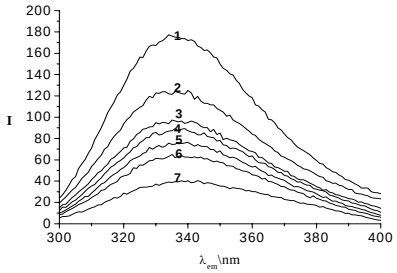


Figure 2 BSA's fluorescent influenced by **5**[5]

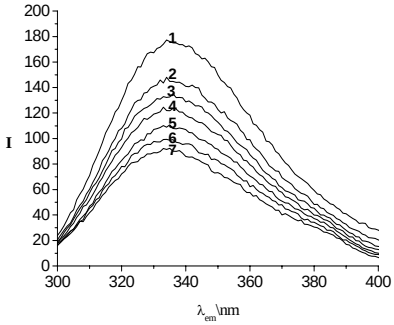
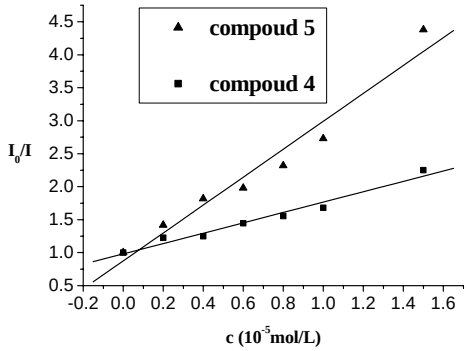


Figure 3 Lineare fit



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References and Note

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5. c (BSA) = 1.0×10^{-5}mol/L, λ_{ex}=290 nm, c (**4**) or (**5**) /10^{5}mol/L, 1 to 7= 0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5×10^{-5} mol/L of **4** or **5**, respectively.

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