SYNTHESIS OF NOVEL CARBOXYL PORPHYRINS AND THEIR IRON COMPLEXES : 5,10,15,20-TETRA[α,α,α,α-o-(2,2-DIMETHYL-ω-CARBOXYLALKANAMIDO)PHENYL]PORPHINATO IRON COMPLEXES

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Abstract - Novel porphyrin derivatives having 2,2-dimethyl-ω-carboxylalkyl chains as amphiphilic moieties and their iron complexes are synthesized. The typical compound is bromo-5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-12-carboxyldodecanamido)phenyl]porphinato iron(Ⅲ). The lipophilic-liophilic balance can be controlled by changing the alkyl chain length.

Polyfunctionalized tetraphenylporphyrins are of interest from the standpoint of preparing the models of natural hemoproteins.[1-10] The liposome-bound metalloporphyrins have been reported as a model photosensitizer for chlorophylls[11,12] and of membrane-solubilized hemoproteins.[13-16] Accordingly an amphiphilic property is needed for a porphyrin to be taken better into the model membranes (liposomes). The control of the lipophilic-liophilic balance of a model is expected to be the key to get better model systems. In the present report, we wish to communicate the synthesis of a series of novel amphiphilic porphyrins by introducing four ω-carboxylalkyl groups per porphyrin and the control of the lipophilic-liophilic balance by changing the length of alkyl chains.

The carboxyl group-bearing porphyrins and their iron(Ⅲ) complexes synthesized in the present work are schematically represented in Figure 1 and summarized in Table I. These compounds are 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-ω-carboxylalkanamido)phenyl]porphines and the

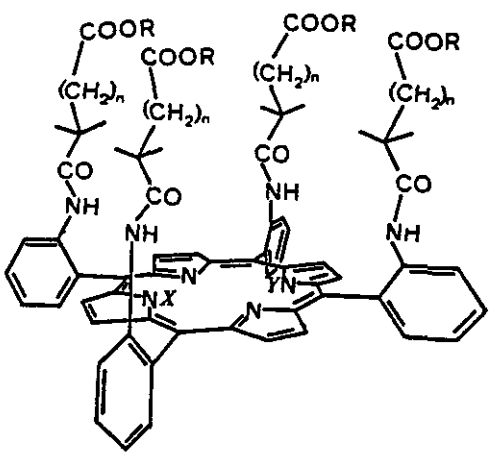


Figure 1. A schematic illustration of the structure of 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-ω-carboxylalkanamido)phenyl]-porphine and its iron complex.

Table I Carboxyl Porphyrins and Iron Complexes

Compound	n	R	X	Y	yield(%)
I	0	methyl	-H	H-	84
II	0	methyl	-Fe(III)Br-		52
III	0	hydrogen	-Fe(III)Cl-		90
IV	1	benzyl	-H	H-	59
V	1	benzyl	-Fe(III)Br-		81
VI	1	hydrogen	-Fe(III)Cl-		72
VII	2	methyl	-H	H-	63
VIII	2	methyl	-Fe(III)Br-		54
IX	2	hydrogen	-Fe(III)Cl-		64
X	10	tert-butyl	-H	H-	8
XI	10	tert-butyl	-Fe(III)Br-		92
XII	10	hydrogen	-Fe(III)Br-		100

corresponding ferric iron complexes.

The porphyrins were synthesized by the reaction of one mole of 5,10,15,20-tetra(α,α,α,α-o-aminophenyl)porphine with excess moles of the corresponding ω-(alkoxycarbonyl)alkanoyl chlorides in the presence of pyridine in dry tetrahydrofuran. The ω-alkoxycarbonylalkanoyl chlorides were prepared by the reaction of the corresponding carboxylic acids with excess moles of thionyl chloride, oxalyl chloride or triphenylphosphine/carbon tetrachloride. The typical synthesis is described on 2,2-dimethyl-12-tert-butoxycarbonyldodecanoyl chloride. Commercial 11-bromo-undodecanoic acid was esterified by 2-butene in the presence of sulfonic acid to give tert-butyl bromoundecanoate (78%). The ester was then reacted with α-lithio isobutylate[17] in a tetrahydro-furan/hexamethylphosphoric triamide mixture at -60°C and then at room temperature. The product was purified by column chromatography on silica gel. The resulted mono ester mono acid compound reacted in dry carbon tetrachloride under reflux with 1.3 equivalent triphenylphosphine[18] to give 2,2-dimethyl-12-tert-butoxycarbonyldodecanoyl chloride quantitatively. The other acid chlorides were prepared by modifying the literautre method.[19] The mono ester mono acid chloride compounds thus prepared were then allowed to react with 5,10,15,20-tetra(α,α,α,α-o-aminophenyl)porphine.[6] Products were purified by chromatography on silica gel or alumina to give the corresponding 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-ω-alkoxycarbonylalkanamido)phenyl]porphines (Compounds I, IV, VII and X). The iron insertion of the porphyrins was carried out in dry tetrahydrofuran with an excess amount of ferrous bromide in the presence of pyridine under nitrogen to give the porphinato iron complexes (Compounds II, V, VIII and XI) and the products were purified by the

literature method.[7,9] The hydrolysis of the iron porphyrins gave the free carboxylic acid porphinato iron complexes (Compounds III, VI, IX and XII). All of these compounds have been characterized by pmr, cmr, ir, and field desorption mass and/or C, H and N analyses. The analytical data are summarized in Table II. The cmr spectrum of X is given in Figure 2. Compounds III, VI and IX are soluble in water as sodium salts, but XII is insoluble. This indicates the possibility of controlling the lipophilic-liophilic balance of the present porphyrin compounds arbitrarily by changing the number of methylene unit (n in Figure 1).

These new carboxylporphyrin derivatives are interesting from not only as amphiphilic compounds as models of membrane-bound hemoproteins but also as the starting compounds of bis macrocyclic compounds like a face-to-face porphyrin[20] and a crowned porphyrin.[21] The distance between the macrocycles may be easily-controllable by changing the methylene number, n, of the bridges.

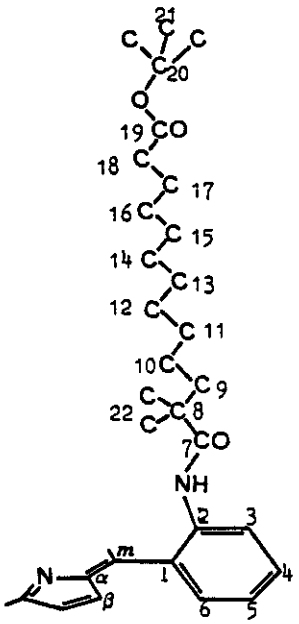
Table II Results of Elemental Analyses

Compound	Formula	C(wt%)		H(wt%)		N(wt%)	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
I	$C_{68}H_{66}N_8O_{12}$	68.79	68.74	5.60	5.75	9.44	9.17
II	$C_{68}H_{64}N_8O_{12}FeBr.1/3CHCl_3$	60.68	60.84	4.79	4.83	8.30	8.27
III	$C_{64}H_{56}N_8O_{12}FeCl.3H_2O$	60.31	60.36	4.90	4.68	8.79	8.67
IV	$C_{96}H_{90}N_8O_{12}$	74.49	74.69	5.86	5.91	7.24	7.28
V	$C_{96}H_{88}N_8O_{12}FeBr1/2CH_2Cl_2$	67.23	67.34	5.20	5.11	6.50	6.28
VI	$C_{68}H_{64}N_8O_{12}FeCl.H_2O$	63.09	63.25	5.14	5.07	8.65	8.63
VII	$C_{76}H_{82}N_8O_{12}.CH_3OH$	69.45	69.34	6.51	6.30	8.42	8.62
VIII	$C_{76}H_{80}N_8O_{12}FeBr$	63.11	63.26	5.78	5.73	7.64	7.73
IX	$C_{72}H_{72}N_8O_{12}FeCl$	64.90	65.19	5.40	5.76	8.40	8.26
X	$C_{120}H_{170}N_8O_{12}$	75.19	74.98	8.94	8.96	5.85	5.78
XI	$C_{120}H_{168}N_8O_{12}FeBr.1/2CH_2Cl_2$	69.15	68.92	8.14	8.08	5.35	5.32
XII	$C_{104}H_{136}N_8O_{12}FeBr$	68.40	68.12	7.51	7.42	6.14	6.24

EXPERIMENTAL SECTION

Apparatus A JEOL JNM-FX100 spectrometer operating at 100MHz was used for measuring nmr spectra. Tetramethylsilane was used as an internal standard. The field desorption mass spectra (FDms) were obtained with a JEOL JMS-01-SG2 mass spectrometer. The electronic absorption spectra were recorded with a Shimadzu UV-240 spectrophotometer. The ir spectra were recorded on a Hitachi 260-50 infrared spectrophotometer.

Reagents Reagents and solvents were purchased commercially and used without purification unless otherwise noted. Tetrahydrofuran was distilled under argon atmosphere from a ketyl solution



Carbon	δ(ppm)
α	146.91
β	131.71
m	114.84
1	130.54
2	138.47
3	120.74
4	130.04
5	122.97
6	134.21
7	174.72
8	42.33
9	41.10
10	24.92
11-16	29.12-30.00
17	25.10
18	35.61
19	173.19
20	79.81
21	28.12
22	24.13

Figure 2. ^{13}C-NMR Spectrum of 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-12-tert-butoxycarbonyldodecanamido)phenyl]porphine (X) in deuteriochloroform.

(sodium and benzophenone). Pyridine was dried over potassium hydroxide pellets and then distilled. Carbon tetrachloride was distilled from anhydrous calcium chloride. Silica gel (Merck Kieselgel-60) and alumina (Merck Alumina 90, Neutral, Activity I) were used for chromatography. TLC measurements were carried out on silica gel (Merck Silica Gel 60).

2,2-Dimethyl-3-benzyloxycarbonylpropanoyl chloride Into an ice-cold solution of 2,2-dimethylsuccinic anhydride (20 g) in 100 ml of benzyl alcohol containing a few drops of phenolphthalein as an indicator, was added dropwise a solution of 20% sodium benzylate in benzyl alcohol to a phenolphthalein end point with stirring. Then benzyl alcohol was distilled off under reduced pressure to give an oily residue, which was dissolved in water. The pH of the solution was adjusted to 4.0 with saturated aqueous sodium phosphate and the solution was extracted with chloroform twice. The chloroform layer was collected and dried with anhydrous sodium sulfate. It was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized twice from benzene/hexane to give 23 g (62%) of 2,2-dimethyl-3-benzyl-oxycarbonyl propionic acid: mp 75.0-76.0°C; ms: 236(M^+); ir (KBr disk): 1730 and 1707 cm^{-1};

pmr ($CDCl_3$): δ 1.30(s,6H), 2.66(s,2H), 5.11(s,2H), 7.35(s, 5H). The acid (6.0 g) was then allowed to react triphenylphosphine (8.0 g) in dry carbon tetrachloride (50 ml) under reflux for 20 h, and cooled. After removing the precipitates by filtration, the filtrate was freed from solvent by evaporation under reduced pressure to give the corresponding acid chloride: ir (KBr disk): 1790 cm^{-1}.

2,2-Dimethyl-12-tert-butoxycarbonyldodecanoyl chloride The lithium diisopropylamide (100 mmole) solution was prepared by the reaction of diisopropylamine in 150 ml of dry tetrahydrofuran with n-butyllithium dissolved in n-hexane at -40°C. To the solution at -40°C was added dropwise 4.7 ml (50 mmole) of isobutyric acid and then 10 ml of hexamethylphosphoric triamide. Then the solution was warmed slowly up to 35°C and allowed to stand at the temperature for 2 h. Then it was cooled to -60°C and ter-butyl 11-bromo-undecanoate (16 g, 50 mmole) was added. It was allowed to be warmed up to room temperature and stirred for further 24 h. The reaction mixture was poured into 300 ml of an ice-water mixture and the pH was adjusted to 2.0 with conc. hycrochloric acid. It was extracted twice with dichloromethane. The organic layer was washed with water and then dried with anhydrous sodium sulfate. It was filtered and the filtrate was evaporated to dryness under reduced pressure. The resulting oily residue was purified by column chromatography on silica gel using a chloroform/diethyl ether (4/1(v/v)) mixture as the eluant to give 3.7 g (11%) of 2,2-dimethyl-12-tert-butoxycarbonyldodecanoic acid: mp 37.0-39.0°C; ms: 329(M+1); ir (CCl_4): 1732 and 1705 cm^{-1}; pmr ($CDCl_3$): δ 1.18(s,6H), 1.26(s,14H), 1.44(s,9H), 2.21(t,2H). Anal. Calcd. for $C_{19}H_{36}O_4$: C 69.47; H 11.05. Found: C 69.32; H 10.89. The free acid (2.2 g) reacted in dry carbon tetrachloride with triphenylphosphine (2.3 g) under reflux for 12 h to give the corresponding acid chroride quantitatively: ir (KBr disk): 1790 cm^{-1}.

Methyl 2,2-dimethylmalonyl chloride This compound was prepared according to the literautre[19]: bp 58-61°C/13 mmHg.

2,2-Dimethyl-4-methoxycarbonylbutanoyl chloride The carboxylic acid (1.4 g) was allowed to react with 1.5 ml of thionyl chloride for 12 h to give an oil of the corresponding acid chloride: ir ($CHCl_3$): 1790 and 1745 cm^{-1}.

5,10,15,20-Tetra[α,α,α,α-o-(2,2-dimethyl-2-methoxycarbonylacetamido)phenyl]porphine (I) To the stirred solution of 5,10,15,20-tetra(α,α,α,α-o-aminophenyl)porphine (500 mg) and dry pyridine (2 ml) dissolved in 50 ml of tetrahydrofuran was added dropwise methyl 2,2-dimethylmalonyl chloride (1.5 g) for 10 min and then reacted for 4 h at room temperature. To the reaction mixture was added 100 ml of 4% aqueous sodium hydrogen carbonate solutoin and then extracted twice with chloroform. The organic layer was washed with 4% aqueous sodium hydrogen carbonate solution and then dried by anhydrous sodium sulfate. It was filtered and the filtrate was evaporated to dryness. The resulting oily residue was purified by column chromatography on

silica gel. The main fraction was collected and recrystallized from chroloform/diethyl ether to afford 740 mg (84%) of the porphyrin (I): mp 251-253°C; FDms: 1187(M+1); ir (KBr disk): 1750, 1695 and 1525 cm^{-1}; pmr ($CDCl_3$): δ -2.54(s,2H), 0.51(s,24H), 2.04(s,12H), 7.4-8.7(m,16H), 8.80 (s,8H); $\lambda_{max}(CHCl_3)$: 418, 512, 544, 586 and 645 nm; R_f of TLC (chloroform/methanol = 20/1): 0.60.

5,10,15,20-Tetra[α,α,α,α-o-(2,2-dimethyl-3-benzyloxycarbonylpropanamido)phenyl]porphine (IV)

2,2-Dimethyl-3-benzyloxycarbonylpropanoyl chloride (2.0 g) was reacted with 5,10,15,20-tetra-(α,α,α,α-o-aminophenyl)porphine (500 mg) by the same procedure described above to give IV (59%): FDms: 1547(M+1); mp 142-143°C; ir(KBr disk): 1730 and 1680 cm^{-1}; pmr ($CDCl_3$): δ -2.63(s,2H), -0.11 (s,24H), 2.09(s,8H), 4.72(s,8H), 7.1-8.7(m,40H), 8.47(s,8H); $\lambda_{max}(CHCl_3)$: 417, 512, 543, 584 and 652 nm; R_f of TLC (chloroform/methanol = 20/1): 0.68.

5,10,15,20-Tetra[α,α,α,α-o-(2,2-dimethyl-4-methoxycarbonylbutanamido)phenyl]porphine (VII)

2,2-Dimethyl-4-methoxycarbonylbutanoyl chloride (1.55 g) was reacted with the aminoporphyrin in the same manner as described above. Purification by silica gel column chromatography using chloroform/methanol (50/1) as the eluant and the subsequent recrystallization from dichloro-methan/methanol gave VII (63%): mp 180-183°C; FDms: 1299(M+1); ir (KBr disk): 1732 and 1690 cm^{-1}; pmr ($CDCl_3$): δ -2.66(s,2H), 0.22(s,24H), 0.6-1.2(m,24H), 1.4-2.0(m,2H), 2.94(s,12H), 7.15-8.97 (m,16H), 8.79(s,8H); $\lambda_{max}(CHCl_3)$: 418, 513, 543, 587 and 644 nm; R_f of TLC (chloroform/methanol = 20/1): 0.53.

5,10,15,20-Tetra[α,α,α,α-o-(2,2-dimethyl-12-tert-butoxycarbonyldodecanamido)phenyl]porphine (X)

2,2-Dimethyl-12-tert-butoxycarbonyldodecanoyl chloride (2.3 g) was reacted with the aminoporphyrin (200 mg) as described above. Column chromatography of the product on silica gel with chloroform and then on alumina with a hexane/diethyl ether mixture (1/1(v/v)) gave 42 mg (7.3 %) of X as an oil: FDms: 1915(M+1); ir (KBr disk): 1735 and 1695 cm^{-1}; pmr ($CDCl_3$): δ -2.60(s,2H), -0.23(s,24H), 1.26(broad,14H), 1.45(s,36H), 2.21(t,8H), 7.12(s,4H), 7.50-8.72(m,16H), 8.82(s,8H); $\lambda_{max}(CHCl_3)$: 417, 510, 543, 585 and 642 nm; R_f of TLC (benzene/diethyl ether = 7/1): 0.39.

Bromo 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-2-methoxycarbonylacetamido)phenyl]porphinato iron(III) (II) The porphyrin I (380 mg) and dry pyridine (0.5 ml) were dissolved in dry tetrahydrofuran (20 ml) and nitrogen gas was then bubbled through the solution. To this was added 1.2 g of ferrous bromide tetrahydrate. It was heated to reflux for 4 h under nitrogen. To this was added 200 ml of chloroform and filtered. The filtrate was washed with water twice and dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated to dryness and the resulting residue was purified by column chromatography on alumina. The first and main fraction was collected, treated with 3 ml of conc. hydrogen bromide and then dried with anhydrous sodium sulfate. It was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from chloroform/diethyl ether/petroleum ether to give

220 mg (52%) of II: mp 234-237°C; FDms: 1321(M+1); ir (KBr disk): 1750 and 1695 cm^{-1}; λ_{max} ($CHCl_3$): 414, 506, 582 and 650 nm; R_f of TLC (chloroform/methanol = 20/1): 0.53.

Bromo 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-3-benzyloxycarbonylpropanamido)phenyl]porphinato iron(III) (V) The same procedure described above was employed to the porphyrin IV and the product was recrystallized from dichloromethane/diethyl ether/petroleum ether to give V (81%): mp 71.5-73.5°C; FDms: 1681(M+1); ir (KBr disk): 1740 and 1690 cm^{-1}; λ_{max}($CHCl_3$): 413, 506 and 650 nm; R_f of TLC (chloroform/methanol = 20/1): 0.65.

Bromo 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-4-methoxycarbonylbutanamido)phenyl]porphinato iron(III) (VIII) The same procedure described above was employed to the porphyrin VI and the product was recrystallized from methanol/water to give VIII (54%): FDms: 1433(M+1); ir (KBr disk): 1730 and 1690 cm^{-1}; λ_{max}($CHCl_3$): 416, 510 and 584 nm; R_f of TLC (chloroform/methanol = 20/1): 0.48.

Bromo 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-12-tert-butoxycarbonyldodecanamido)phenyl]-porphinato iron(III) (XI) The same procedure described above was employed to the porphyrin X and the product was recrystallzied from dichloromethane/diethyl ether/petroleum ether to give XI (92%): FDms: 2049(M+1); ir (KBr disk): 1730 and 1690 cm^{-1}; λ_{max}($CHCl_3$): 415, 507, 580 and 650 nm; R_f of TLC (benzene/diethyl ether = 7/1): 0.37.

Chloro 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-2-carboxylacetamido)phenyl]porphinato iron(III) (III) The porphinato iron II (104 mg) was hydrolyzed with 2N aqueous NaOH solution (3 ml) in 20 ml of methanol at room temperature for 12 h. Solvents were removed by evaporation under reduced pressure. The residue was dissolved in 10 ml of water and the pH of the solution was adjusted to 1.0 by conc. hydrochloric acid. The precipitate formed was collected by centrifugation and dried at 60°C for 7 h to give 86 mg (90%) of III: mp >280°C; ir (KBr disk): 3400, 1695 and 1520 cm^{-1}.

Chloro 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-3-carboxylpropanamido)phenyl]porphinato iron(III) (VI) The same procedure described above was employed to the porphinato iron V to give VI (72%): mp >280°C; ir (KBr disk): 3430, 3400, 1710, 1695 and 1510 cm^{-1}.

Chloro 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-4-carboxylbutanamido)phenyl]porphinato iron(III) (IX) The same procedure described above was employed to the porphinato iron VIII to give IX (64%): mp 183-186°C; ir (KBr disk): 1710 and 1690 cm^{-1}.

Bromo 5,10,15,20-tetra[α,α,α,α-o-(2,2-dimethyl-12-carboxyldodecanamido)phenyl]porphinato iron(III) (XII) The porphinato iron XI (20 mg) was dissolved in 3 ml of trifluoroacetic acid and hydrolyzed for 6 h in an ice-water bath with stirring. Then it was evaporated to dryness under reduced pressure and the resulting product was dried *in vacuo* to give XII quantitatively: mp 110-114°C; ir ($CHCl_3$): 1710 and 1690 cm^{-1}; λ_{max}($CHCl_3$): 415, 507, 580 and 562 nm.

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