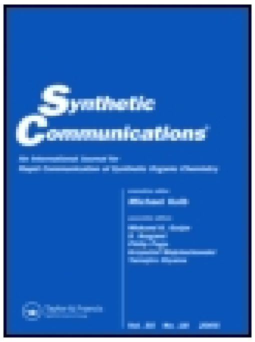

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A NEW SYNTHESIS OF MESO-TETRA[4-(CARBOXYMETHYLENOXY)PHENYL]PORPHYRIN

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Abstract: A new convenient synthetic method is reported for *meso*-tetra[4-(carboxymethylenoxy)phenyl]-porphyrin ($TCMOPPH_2$) comprising two steps from meso-tetra(4-hydroxyphenyl)porphyrin nickel (THPPNi) and monochloroacetic acid. The product was characterized by Uv-Vis, IR, and ^{1}HNMR spectra.

Introduction

Porphyrins and metalloporphyrins are essential to the life of bacteria, fungi, plants and animals, and have already received considerable attention from many investigators in various fields. Synthetic porphyrins, especially, meso-tetraphenylporphine derivatives substituted in the para-positions with soluble acidic, basic and neutral groups, are of potential interest in medicinal chemistry because they can form chelates either with some toxic heavy metals or with a gamma-ray emitting radioisotopes[1-4]. They are also used as fluorescent indicators for the delineation of neoplastic tisssue in cancer patients. In past years it was found that

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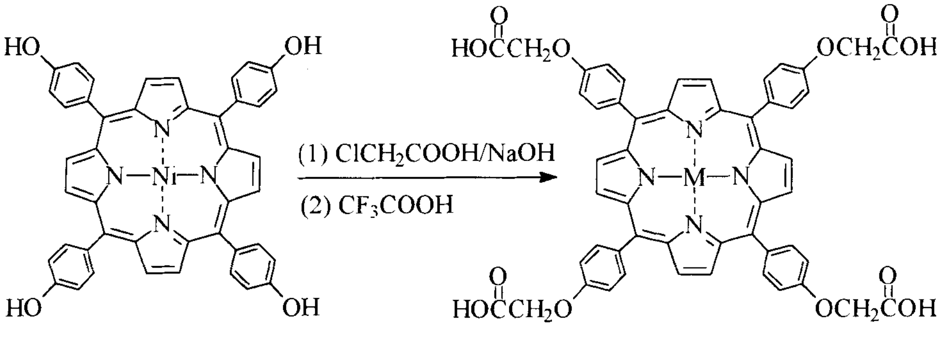
such compounds may be used as tumor-selective radiation sensitizers and are used in cancer therapy[4-8]. Harada[9] reviewed the development of functionalized antibodies of tetra(carboxyphenyl)porphyrin.

In general, there are two typical methods for synthesizing the meso-tetrakis[4-(carboxymethylenoxy)porphyrin[10-13]. One is by hydrolysis of the corresponding esters in aqueous KOH containing pyridine, and the corresponding esters were obtained by alkylation of tetrakis(hydroxyphenyl)-porphyrins with $ClCH_2COOC_2H_5$. The other is by condensation of pyrrole with $CH_3CH_2OCOCH_2OC_6H_4CHO$. However, both of them are inconvenient and complicated, products are difficult to isolate and purify. In the present paper, a new convenient synthesis of meso-tetra[4-(carboxymethylenoxy)phenyl]-porphyrin is reported (scheme 1).



THPPNi TCMOPPM [(1) M=Ni; (2) M=H2]

Scheme 1

Experimental

The pyrrole and propanonic acid were distilled before use. The meso-tetra(4-hydroxylphenyl)porphyrin($THPPH_2$) was prepared according to the improved method of literature[14]. Anal Found(Calcd. for $C_{44}H_{30}N_4O_4 \cdot 4H_2O$): C,70.30(70.04); H,5.03(5.06); N,7.19(7.46).

The electronic absorption spectra were recorded on Hitachi U-3400 Spectrophotometer. The infrared spectra were measured by Alpha Centauri FT-IR. The proton magnetic resonance spectrometry was detected with Brucke AC-400 FT-NMR. The elementary analysis data were obtained on Vario EL 1106 elemental analyzer.

1). Synthesis of meso-tetra(4-hydroxyphenyl)porphyrin nickel (THPPNi)

15 mL hot alcohol solution containing 0.06 g nickel acetate was added into 30 mL dimethylformamide (DMF) dissolving 0.1337 g THPPH$_2$. After refluxing and stirring at 80 °C for 2h, the mixture is poured into equal volume cold distilled water. The solution was acidified with 2 $mol \cdot L^{-1}$ hydrochloric acid while stirring until pH=2.0, and the brownish-red precipitation appeared. The mixture was allowed to stand for 3h, then the product was filtered, and washed with distilled water until the filtrate became neutral. Drying over P_2O_5 under vacuum, got violet crystal, yield 98%. mp>300 °C. Anal.Found(Calcd. for $C_{44}H_{28}N_4O_4Ni \cdot 4H_2O$): C,65.60(65.45); H,4.52(4.46); N,6.74(6.94).

2). Synthesis of meso-tetra[4-(carboxymethylenoxy)phenyl]porphyrin nickel (TCMOPPNi)

The THPPNi was added into 20 mL of aqueous solution of sodium hydroxide(containing 0.7454 g of NaOH). The mixture was stirred until THPPNi was dissolved. Accompanying with stirring, the 0.7441 g monochloroacetic acid was added slowly. After stirring at 90 ℃ for 2 h, the reaction mixture was acidified to pH=5.0 with 2 mol·L^{-1} hydrochloric acid, and brownish black precipitation appeared. Standing for several hours, the product was filtered and washed with distilled water until the filtrate became neutral. Drying over phosphorous pentoxide under vacuum, the violet black crystal was obtained, yield 60%. mp>300 ℃. Anal.Found(Calcd. for $C_{52}H_{36}N_4O_{12}Ni \cdot 4H_2O$): C,60.21(60.08); H,4.35(4.24); N,5.28(5.39)

3). Synthesis of *meso*-tetra[4-(carboxymethylenoxy)phenyl]porphyrin (TCMOPPH$_2$)

The above product (TCMOPPNi) was dissolved into 10 mL of chloroform and added trifluoroacetic acid 7 mL gradually at room temperature. After stirring 3h, the reaction mixture was poured into 500 mL mixture of alcohol and water (V/V=1:1), and then neutralized with anhydrous sodium carbonate. The resulting green compound in the solution is filtered and sample is recrystallized from a mixture of methanol-chloroform and is dried over phosphorous pentoxide under vacuum at room temperature for about 8h , yield 80%. mp>300 ℃. Anal.Found(Calcd. for $C_{52}H_{38}N_4O_{12}H_2 \cdot 4H_2O$): C,63.42(63.54); H,4.65(4.68); N,5.82(5.70).

Results and discussion

The *meso*-tetra[4-(carboxymethylenoxy)phenyl]porphyrin (TCMOPPH$_2$) and intermediates in preparation are characterized by electronic absorption spectra, vibrational spectra, and ^{1}HNMR. The data of visible spectra of $TCMOPPH_2$ and $THPPH_2$ were recorded in DMF(Table 1). Comparison of both spectra shows that the $TCMOPPH_2$ is different from $THPPH_2$.

Table 1 The UV-Vis spectra data of $TCMOPPH_2$ and $THPPH_2$

Compound	Solvent	Soret Band	$Q_y(1\text{-}0)$	$Q_y(0\text{-}0)$	$Q_x(1\text{-}0)$	$Q_x(0\text{-}0)$
$TCMOPPH_2$	DMF	415.7	520.5	558.7	590.0	620.0
$THPPH_2$	DMF	415.0	513.0	549.4	589.4	648.3
TCMOPPNi	DMF	419.0		531.0		

Infared spectroscopic data ascertain some functional groups to exist, for example, $\nu_{N\text{-}N}$ absorption band of porphyrin is about 3312 cm^{-1} , $\delta_{N\text{-}H}$(in planarity) and $\delta_{N\text{-}H}$ (out of planarity) absorption band is about 967 cm^{-1} and 732 cm^{-1}, respectively. In the nickel complex of porphyrin, these three bands disappear, and a strong absorption band appears near 1000 cm^{-1} according to skeletal ring of metalloporphyrin[15].

Table 2 The IR spectra data(cm^{-1}) of TCMOPPNi , $TCMOPPH_2$, and $THPPH_2$

$THPPH_2$	TCMOPPNi	$TCMOPPH_2$	Assignment
800.4	797.0	820.7	$\delta_{c\text{-}H}$ (phenyl)
983.6		984-6	$\delta_{N\text{-}H}$
1078.1	1074.0	1067.5	ν_{C-C} (phenyl)
1101.3		1118.7	
1170.7	1169.0	1176.5	
1265.2	1260.0	1258.5	$\delta_{O\text{-}H}$
1349.1	1350.0	1383.8	$\nu_{=C\text{-}N}$
1508.3	1505.0	1507.3	$C=N$ $C=C$
1605.6	1607.0	1599.9	
	1724.0	1731.0	$\nu_{C=O}$
3378.2	3369.0	3370.4	$\nu_{N\text{-}H}$
	3460.0	3529.5	$\nu_{COO\text{-}H}$

Table 3 The Chemical shifts of porphyrins(δ ppm)

Compound	-COOH	Pyrrole-H	Phenyl-H	$-OCH_2-$	O-H	N-H
TCMOPPNi	9.92(4H)	8.77 (8H)	7.77~7.92(8H) 7.11~7.28(8H)	4.92 (8H)	__	__
$TCMOPPH_2$	9.91(4H)	8.84 (8H)	8.10~8.16(8H) 7.33~7.35(8H)	4.93 (8H)	__	-2.94 (2H)
$THPPH_2$	__	8.85(8H)	7.98~8.00(8H) 7.18~7.20(8H)	__	3.02(4H)	-2.91(2H)

The ^{1}HNMR data of TCMOPPNi, $TCMOPPH_2$, and $THPPH_2$ (Table 3) show that the peak at -2.91 ppm is the N-H at the center of porphyrin ligand, this peak disappears after porphyrin complexes with metal because the two H atoms are replaced by metal ion. There is a great movement to high field on the basis of strong shield effect of porphine ring. Peaks of H atoms in OH and OCH_2 appear in low field because of the induce effect of oxygen atom.

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