Preparation of Stable 5,15-Dihydroporphyrin

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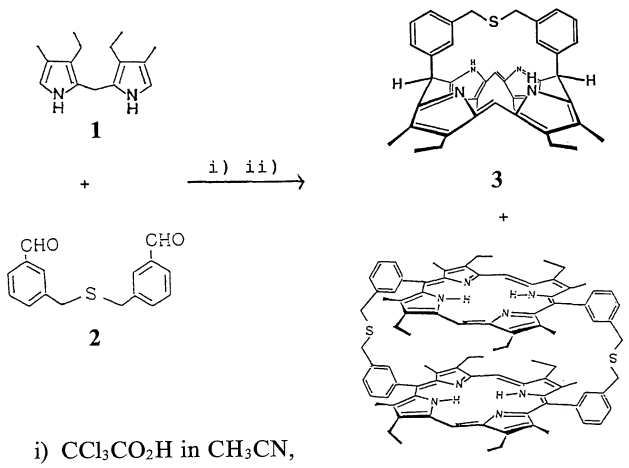
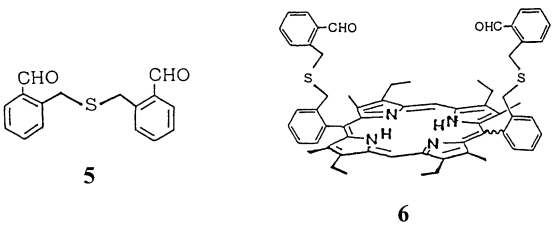
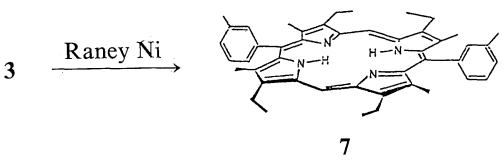
Synopsis. Very stable 5,15-dihydroporphyrin was perpared by the acid catalyzed reaction of dipyrromethane with two benzaldehyde molecules which were linked by an appropriate linkage.

Porphyrin macrocycles constitute an important class of compounds of particular interest owing to their role in biological systems.[1] Recent work has been devoted to the design of new porphyrin ligands with specific properties, or new structural analogues of porphyrins.[2] Dihydroporphyrins, which have two additional hydrogen atoms on the porphyrin nucleus, have also been the subjects of intense study.[3] 5,15-Dihydroporphyrins are intermediates in the formation of porphyrins, but they have not been isolated in the preparation of porphyrins, for they are readily oxidized to porphyrins. The most general synthetic procedure for stable 5,15-dihydroporphyrins is the reductive alkylation of metalloporphyrins. Various 5,15-dihydroporphyrins have been prepared by this method, and they have been used as effective ligands for various metals.[4] In this paper we wish to report a novel method for the preparation of a very stable strapped 5,15-dihydroporphyrin which was not oxidized to the corresponding porphyrins by strong oxidizing agents such as *p*-chloranil. Such strapped 5,15-dihydroporphyrins can not be prepared by the alkylation of an anion of metalloporphyrin with a dihalide.[4]





The acid-catalyzed reaction of dipyrromethane (**1**) with a dialdehyde linked by a thioether group was carried out in order to generate thioether strapped porphyrins or face-to-face dimeric porphyrins bridged by a thioether linkage. The thioether linkage is important, because the sulfur atom may be removed by the procedure established in cyclophane chemistry.[5] Thioether strapped porphyrin can also be regarded as a model of the active electron transporting site of cytochrome c.[6] The two benzaldehyde molecules are linked by CH_2SCH_2 at the *o*- or *m*-position. Such aldehydes were prepared by the reaction of the corresponding bromethylbenzaldehydes with sodium sulfide. The reaction of **1** with dialdehyde (**2**) linked at the *m*-position gave strapped 5,15-dihydroporphyrin (**3**) and face-to-face dimeric porphyrin (**4**) in 65% and 3% yields, respectively. The high yield of **3** was remarkable. On the other hand, the reaction of **1** with dialdehyde (**5**), in which two aldehyde moieties were linked at the *o*-position, gave a complex set of products. It was impossible to isolate any pure products. The mass spectra of the products suggested the formation of porphyrin **6**, but further characterization was very difficult due to the instability and complexity of the products. However, the mass spectra of the corresponding 5,15-dihydroporphyrin and porphirin dimers were not detected. Compound **3** was extremely stable to oxidizing agents, and it was not oxidized to the corresponding porphyrins by chloranil or oxygen. Thus, the formation of stable 5,15-dihydroporphyrins depended on the linkage which connected the two aldehyde moieties. When a longer linkage was used, the strapped porphyrin and face-to-face porphyrin dimers were formed by the similar reaction.[7] The CPK model of **3** showed that the bond angles around the 5 and 15 positions of the tetrapyrrole macrocycle were ideal for the formation of stable 5,15-dihydroporphyrins. The bond angles of the tetrapyrrole which may be obtained from 5 were unfavorable for the formation of 5,15-dihydroporphyrin. 5,15-Dihydroporphyrins were not isolated from the reaction of dialdehydes linked by longer linkages, for they were readily oxidized to the corresponding porphyrins. When the thioether linkage of **3** was cleaved, tetrapyrrole should have been readily oxidized to porphyrins. In fact, treatment of **3** with Raney Ni gave porphyrin **7** in a good yield, which may provide a useful method for the stereoselective synthesis of 5,15-diarylporphyrins.



Compound **3** was an orange solid (λ_{max} 427.5 nm) and has a strong affinity to various metals like porphyrins. Preliminary experiments using an ion selective electrode showed a strong affinity to Ni or Cu. The use of **3** as a ligand is now being studied.

Experimental

Mass spectra were recorded on a JEOL DX-300 spectrometer using the FAB method; the FAB matrix was $CHCl_3$+trifluoroacetic acid/*m*-nitrobenzyl alcohol/glycerol.

Bis(3-formylbenzyl) Sulfide (2). A mixture of *m*-bromomethylbenzadehyde[8] (1.25 g, 6.3 mmol) and $Na_2S \cdot 9H_2O$ (0.87 g, 7.5 mmol) in *N*,*N*-dimethylformamide (80 ml) was stirred for 30 h under Ar at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave crude **2**, which was purified by column chromatography (silica gel/hexane–ethyl acetate 3:1) to give pure **2** as a white solid, mp 74—76 °C, 0.64 g (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.68 (s, 4H). 7.48 (t, J=4 Hz, 2H), 7.54 (d, J=4 Hz, 2H), 7.75 (s, 2H), 7.76 (d, J=4 Hz, 2H), and 10.0 (s, 2H). Found: C, 71.05; H, 5.90%. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.96%.

Bis(2-formylbenzyl) Sulfide (5). This compound was prepared from *o*-bromomethylbenzaldehyde by the same procedure as the preparation of **2**, mp 60—62 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.15 (s, 4H), 7.36 (d, J=4 Hz, 2H), 7.45 (t, J=4 Hz, 2H), 7.52 (t, J=4 Hz, 2H), 7.83 (d, J=4 Hz, 2H), and 10.2 (s, 2H). Found: C, 71.12; H, 5.88%. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.96%.

Preparation of 5,15-Dihydroporphyrin (3) and Porphyrin (4). A solution of trichloroacetic acid (10 mg) in dry acetonitrile (30 ml) was added to a stirred solution of bis(3-ethyl-4-methyl-2-pyrrolyl)methane[9] (**1**, 0.65 mmol) and dialdehyde (**2**, 0.32 mmol) in dry acetonitrile (30 ml) under N_2 in the dark. After stirring the solution at room temperature for 12 h, *p*-chloranil (0.45 g) in dry tetrahydrofuran (10 ml) was added and the resulting mixture was stirred for 12 h at room temperature. After removing the solvent, the residue was subjected to column chromatography (alumina Woelm N-I/CH_2Cl_2) to give **3** and **4**, respectively. Recrystallization from CH_2Cl_2–CH_3OH gave pure **3** as an orange solid in a 65% yield. Mp 250 °C (decomp), UV-vis (CH_2Cl_2) 427.5 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.11 (t, J=7 Hz, 12H), 2.11 (s, 12H), 2.53 (q, J=7 Hz, 8H), 3.35 (s, 4H), 5.46 (s, 2H), 6.99 (s, 2H), 7.26—7.36 (m, 8H), and 9.20 (br, 2H, NH). MS (FAB) m/z 691 ($M+H^+$). Found: C, 79.84; H, 7.36; N, 8.02%. Calcd for $C_{46}H_{50}N_4S$: C, 79.96; H, 7.29; N, 8.11%. Porphyrin **4**: 3% yield as a purple solid, UV-vis (CH_2Cl_2) 395, 507, 540, 578, and 627 nm. MS (FAB) m/z 1377 ($M+H^+$). NMR spectra were too complicated to be characterized. The absorption spectra indicated interaction between two chromopheres; the soret band is blue-shifted and the Q bands are red-shifted compared to the monomeric 5,15-diarylporphyrin.

The reaction of **5** with **1** was carried out in the same way as described above. Several unstable products were detected by TLC. All attempts to isolate pure compounds by column chromatography or recrystallization were unsuccessful. MS (FAB) m/z 959, which suggested that porphyrin **6** may have been involved in a complex set of products. However, further charaterization of the products was impossible due to instability of the products.

Preparation of 5,15-Di-*m*-tolyl-2,8,12,18-tetraethyl-3,7-13,17-tetramethylporphyrin (7). A mixture of **3** (30 mg) and Raney Ni W-7 (500 mg) in ethanol (1 ml) and CH_2Cl_2 (15 ml) was heated at reflux temperature for 24 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with water and dried with anhydrous magnesium sulfate. After the removal of the solvent, the residue was subjected to column chromatography (silica gel/CH_2Cl_2) to give **7** (20 mg, 80% yield). Uv-vis (CH_2Cl_2) λ_{max} 408, 506, 538, 571, and 625 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.24 (br, 2H, NH), 1.76 (t, J=7 Hz, 12H), 2.20 (s, 6H), 2.43 (s, 12H), 4.00 (m, 8H), 7.8—8.2 (m, 8H), and 10.18 (s, 2H). MS (FAB) m/z 657 ($M+H^+$).

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