

A Facile Synthesis of [$^{15}\text{N}_4$]-Octamethylporphyrin

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SUMMARY

In order to obtain an efficient and reproducible synthesis of [$^{15}\text{N}_4$]-octamethyl porphyrin for solid state CP-MAS NMR studies, a synthesis of the outlined compound was achieved. Thus, by condensation of [$^{15}\text{N}_2$]-5,5'-dicarboxy-3,4,3',4'-tetramethyldipyrromethane with [$^{15}\text{N}_2$]-5,5'-diformyl-3,4,3',4'-tetramethyldipyrromethane in ethanol-hydrochloric acid, pure [$^{15}\text{N}_4$]-octamethylporphyrin was obtained in 46% yield.

Key Words: [$^{15}\text{N}_4$]-octamethylporphyrin, synthesis.

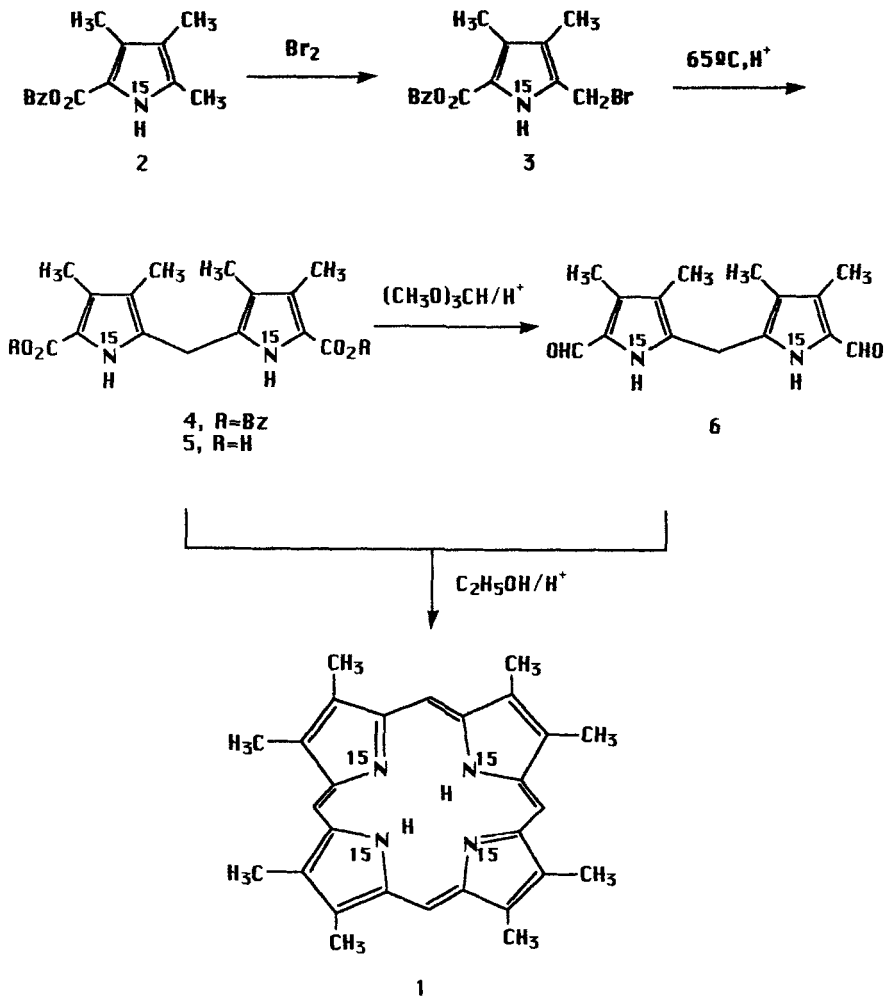
INTRODUCTION

Porphyrins are formally derived by substitution of some or all of the peripheral positions of porphine, the basic cyclic tetrapyrrole nucleus. In addition to their widespread distribution in biological systems, the particular electronic properties of porphyrins and porphyrinoid derivatives make these compounds useful as building blocks in the construction of molecular metals¹.

In order to be used in these conductors, molecules have to fulfill not only a number of electronic, but also a series of stringent steric conditions. Among the latter the most important one is the need of an efficient stacking of the macrocycles in the solid, an efficiency which can exclusively be achieved if planar porphyrins are used. Thus, chelates of porphine and meso-tetramethylporphyrin can be successfully used to build organic conductors although NMR studies have shown that as free bases the solid-state properties of these compounds differ considerably²⁻⁴. Octamethylporphyrin **1** also fulfills the steric and electronic requirements necessary for participating in this kind of conductive systems; its use has not been explored however, probably due to the lack of a simple and clean way of synthesizing it. Porphine can be obtained in low yields by polymerization of 2-hydroxymethylpyrrole^{3,4} and is commercially available⁵. While the synthesis and purification of higher porphyrin homologues can be achieved due to the fact that these are soluble in most organic solvents, octamethylporphyrin on the other hand is not; this complicates the preparation of large amounts of the pure compound. To explore the properties of octamethylporphyrin **1** in the crystalline state a convenient synthesis of [$^{15}\text{N}_4$]-octamethylporphyrin **1** was needed which should allow us to obtain it in good yields, minimizing the required purification procedure.

DISCUSSION

Octamethylporphyrin **1** was prepared for the first time by Fisher and Walach by heating either 5-bromo-pentamethyldipyrrylmethene hydrobromide⁶, or 5-bromo 5'-bromomethyl-3,3',4,4'-tetramethyldipyrrylmethene hydrobromide in acids at high temperatures. The last procedure was again used in later years⁷. Fisher and Walach also reported that prolonged heating of the diacid **5** (Scheme 1) in acids afforded **1**. In every case extensive purifications using serial extractions with solvents were needed to obtain pure **1**. Siedel and Winkler⁸ heated 2-hydroxymethyl-5-carboxy-3,4-dimethylpyrrole in vacuo; dry fusion of 2-acetoxy-methyl derivative was also attempted. In every case low yields of **1** were obtained after extensive purifications. Condensation of 3,4-dimethylpyrrole with formaldehyde⁹ gave, in our hands, reproducible 5% yield of **1**.



Scheme 1

An alternative preparative synthesis of [$^{15}\text{N}_4$]-octamethylporphyrin **1** is outlined in Scheme 1; it follows MacDonald's synthetic procedure¹⁰. The starting material is [^{15}N]-pyrrole **2**, a precursor that can easily be obtained¹¹. The Knorr synthesis was convenient for the preparation of [^{15}N]-pyrrole **2** in good yields. By treatment with bromine, [^{15}N]-pyrrole **2** was converted into its [^{15}N]-2-bromomethyl derivative **3**, which was then dimerized in good yields by heating in methanol-acid to give the [$^{15}\text{N}_2$]-5,5'-di-benzyloxycarbonyltetramethyldipyrrylmethane **4**. The latter was reduced with hydrogen over 10% Pd/C to give the [$^{15}\text{N}_2$]-diacid **5** in 83% yield. The latter was dissolved in trifluoroacetic acid and was transformed into the [$^{15}\text{N}_2$]-dialdehyde **6** (83%) by reaction with trimethylorthoformate. The condensation of [$^{15}\text{N}_2$]-dicarboxydipyrrylmethane **5** and [$^{15}\text{N}_2$]-dialdehyde **6** in 95% ethanol in the presence of hydrochloric acid afforded [$^{15}\text{N}_4$]-octamethylporphyrin **1** in 46% yield. Noteworthy, we found that the reaction yield of the condensation of **5** and **6** increases as the reaction scales up.

EXPERIMENTAL

General procedures. Melting points were determined on a Kofler melting point apparatus and are uncorrected. ^1H NMR spectra routinely recorded in CDCl_3 on a Varian FT-80 A spectrometer. Mass spectra were obtained on a QPGS-MS 1000 Shimadzu spectrometer. The silica gel used in column chromatography was TLC Kieselgel (Riedel-de Haen). TLC was performed on precoated silica gel F-254 plates (Merck, 0.25 mm layer thickness).

Benzyl [^{15}N]-3,4,5-trimethylpyrrol-2-carboxylate **2**

A solution of 4 g of [^{15}N]-sodium nitrite (MSD Isotopes) in 15 mL of water was added with stirring to a solution of benzyl acetoacetate (4 g, 21 mM) in 35 mL of acetic acid at 10°C. The resulting solution was further kept at 5°C during 18 h; it was then added slowly to a stirred mixture of 2.25 g (20 mM) of 3-methyl-2,4-pentanedione, 10 g of sodium acetate, and 10 g of powdered zinc in 20 mL of acetic acid. The suspension was heated at 65°C during 1 h, poured over a large volume of ice-water, cooled at 5°C during 18 h, filtered, and the precipitate was crystallized twice from methanol-water. 1.9 g (38%) of **2** were obtained; mp 120°C (lit.¹¹, mp 119-120°C); ^1H NMR (CDCl_3), δ : 8.6 ppm (d, $J=100\text{ Hz}$, 1H, ^{15}NH); 2.0(s, 3H, CH_3); 1.95(d, $J=2.6\text{ Hz}$, 3H, $^{15}\text{N}-\text{C}_5-\text{CH}_3$); 1.7(s, 3H, CH_3).

Dibenzyl [$^{15}\text{N}_2$]-3,3',4,4'-tetramethyldipyrrylmethane-5,5'-dicarboxylate **4**

Bromine (0.8 mL) dissolved in ethyl ether (40 mL) was added to a solution of [^{15}N]-pyrrole **2** (3.6 g) in 40 mL of ethyl ether. The mixture was heated under reflux for 1 h, cooled and filtered. The solid [^{15}N]-2-bromomethylpyrrole **3** (3.5 g), ^1H NMR (CDCl_3) 8.8(d, $J=108\text{ Hz}$, 1H, ^{15}NH); 4.25(d, $J=2.6\text{ Hz}$, 2H, $^{15}\text{N}-\text{C}_5-\text{CH}_2\text{Br}$) was dissolved in 80 mL of dry methanol, 80 mg of p-toluensulfonic acid were added, the mixture was heated under reflux for 3 h, cooled, filtered, and the dried precipitate was recrystallized from petroleum ether; 1.8 g (70%); mp 180°C (lit.¹¹ mp 179°C); mass spectrum, m/z (relative

intensity) 472 (M^+ , 16); 1H NMR ($CDCl_3$) δ : 8.90(d, $J=100$ Hz, 2H, ^{15}NH); 3.60(t, $J=2.5$ Hz, 2H, $^{15}N-C_2-CH_2$); 1.9(s, 6H, 2CH₃); 1.7(s, 6H, 2CH₃).

5,5'-Diformyl [$^{15}N_2$]-3,3',4,4'-tetramethyldipyrrylmethane **6**

[$^{15}N_2$]-Dipyrrylmethane **4** (4g) was dissolved in 300 mL of tetrahydrofuran, 2 mL of triethylamine were added, and the solution was reduced with hydrogen over 1.5 g of 10% palladized charcoal at 50 psi during 2 h. The catalyst was filtered, the solvent was evaporated to dryness in vacuo, and the resulting diacid **5** (2 g, 83%) was dissolved in 35 mL of trifluoroacetic acid at 5°C by stirring with nitrogen during 10 min.

Trimethylorthoformate (13 mL) was added at 5°C under nitrogen and the solution was stirred during 15 min. An excess of ice-water was then added, and the stirring was maintained for additional 30 min. The precipitated dialdehyde **6** was filtered, dried, and crystallized from methanol-water; 1.5g (87%); mp 297°C (lit. 12 mp 294-295°C); mass spectrum, m/z (relative intensity) 260(M^+ , 100); 1H NMR ($DMSO-d_6$) δ : 9.60(d, $J=2.6$ Hz, 2H, $^{15}N-C_5-CHO$), 3.80(t, $J=2.5$ Hz, 2H, $^{15}N-C_2-CH_2$), 2.10(s, 6H, 2 CH₃), 1.8(s, 6H, 2 CH₃).

[$^{15}N_4$]-Octamethylporphyrin **1**

[$^{15}N_2$]-Dicarboxydipyrrylmethane **5** (1.5 g, 5.2 mMol) and [$^{15}N_2$]-dialdehyde **6** (1.35 g, 5.2 mMol) were suspended in 600 mL of 95% ethanol and stirred under a stream of nitrogen during 10 min. Hydrochloric acid (1N, 15 mL) was then added and the mixture was heated and stirred under nitrogen at 55°C during 1 h. It was then kept at 25°C in the dark in contact with air during 3 days, when [$^{15}N_4$]-octamethylporphyrin **1** slowly precipitated. The suspension was then cooled, filtered, and washed exhaustively with methanol (0.6 g). The filtrates were evaporated to dryness, and the residue was suspended in methanol, filtered, and washed several times with methanol (0.42 g). Both crystalline residues were pooled and washed repeatedly with glacial acetic acid. The [$^{15}N_4$]-octamethylporphyrin **1** thus obtained (1 g, 46%) had mass spectrum, m/z (relative intensity) 427(M^++1 , 100); 214($M^++1/2$, 14); 1H NMR ($CDCl_3/TFA$) δ : 10.6(t, $J=5.2$ Hz; 4H, $^{15}N-C=CH$); 3.62(s, 24H, -CH₃). Anal. Calcd. for $C_{28}H_{30}^{15}N_4$: C, 78.87; H, 7.04; N, 14.08. Found: C, 78.90; H, 7.10; N, 13.98.

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