Synthesis of *meso*-^{13}C and ^{15}N Labelled Octaethylporphyrin and Optimisation of the "Symmetrical" Route to Octaalkylporphyrins

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A simplified synthesis of octaalkylporphyrins from aldehydes is described and was used to prepare *meso*-^{13}C and ^{15}N labelled octaethylporphyrin.

Octaalkylporphyrins and, in particular, octaethylporphyrin (H_2OEP), and its metal complexes, are widely used as models of the various natural tetrapyrrolic compounds (hemes, chlorophylls, etc). The first target of all syntheses of H_2OEP is a 3,4-disubstituted pyrrole, in general by two ethyl groups. This pyrrole either bears at a position α to nitrogen the precursor of a *meso* bridge, or it is α-unsubstituted and will eventually be treated with formaldehyde.

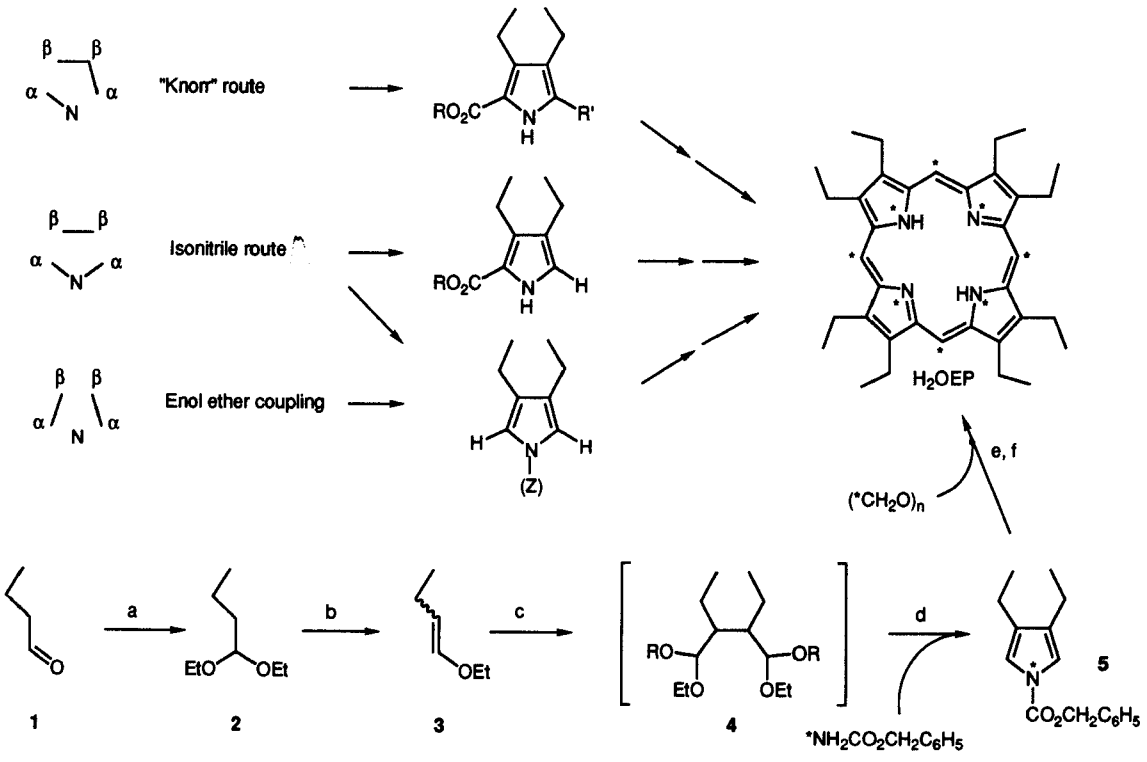
Several synthetic routes (Scheme) have been tested and most are based on strategies where the ββ-bond is preformed: either the initial pyrrole is produced by a Knorr-type condensation of 1,3-dicarbonyl compounds (Nα + αββ),[1-5] or it results from the reaction of an isonitrile with an electron-poor olefin or its precursor (αNα + ββ),[6-10] or it is formed on condensation of a nitrogen compound with a 1,4-dicarbonyl compound. This last synthetic route takes advantage of the high symmetry of the target molecule and exploits an electrochemical coupling of enol ethers[11] to form the precursor of 3,4-dialkylpyrrole (αβ + βα → αββα).[12-14]

We needed samples of H_2OEP labelled at the *meso*- and *N*-positions and had to decide which synthetic route allowed the introduction of the label as late as possible in the synthesis, and preferably using the least elaborate reagent. The *meso*-^{13}C label is easy to introduce during the last step using ^{13}C formaldehyde and diethylpyrrole.

^{15}N labelling of porphyrins is easy as long as pyrrole itself is used, since it is commercially available.[15-16] In one case ^{15}N natural porphyrins could be also biosynthesised from labelled precursors.[17] On the other hand, ^{15}N labelling of polyalkylporphyrins like H_2OEP[18] along the two major synthetic routes (Knorr or isonitriles) requires the preparation of either a labelled isonitrile or an oximino ester, whereas the last (enol ether coupling) allows the use of a simple derivative (benzyl carbamate – easily obtained from a relatively cheap labelled ammonium salt) close to the end of the synthesis (see Scheme,* = label).

For the above reasons we decided to follow the route starting with a butyraldehyde enol ether but realised rapidly that the procedure could be substantially improved as will be described below.

In our initial articles[12] we described the preparation of 1,1-diethoxybutane (**2**) from butyraldehyde and triethyl



a. EtOH, $CaCl_2$, 72 %; b. sulfanilic acid, 140 °C, 60 %; c. electrolysis (conditions see text); d. AcOH, 100 °C, 48h, 28 % from 3; e. H_2, 10 % Pd/C, MeOH; f. AcOH, reflux, O_2, 1h, 40 % from 5. * Labelled positions.

orthoformate under catalysis from ammonium chloride. As this reaction proved to be often erratic, we switched to the much cheaper and simpler ketalisation in the presence of calcium chloride. The next step, *viz.* elimination of ethanol, is better performed on freshly prepared or redistilled ketal using sulfanilic acid as a catalyst.[19]

The electrolysis of 1-ethoxybut-1-ene **(3)** was modified to a large extent and simplified so that it would not need any expensive equipment, as well as any hazardous chemicals. The electrolysis was performed in methanol at room temperature, the current being produced by a battery charger. The electrodes were made of graphite plates. In all cases, the electrolysis was performed until the theoretical amount of current was measured.

In a first set of experiments we used sodium perchlorate as the supporting electrolyte and obtained yields slightly better than in the initial procedure (average yield 33%; all yields expressed as protected pyrrole **5**). We then replaced hazardous sodium perchlorate by potassium hexafluorophosphate and obtained a similar yield (32%). The relative insolubility of the latter salt did not interfere since the increased temperature allowed the use of a smaller concentration of supporting electrolyte (0.05 M). To buffer the mixture we still used 2,6-lutidine but could divide the amount by a factor of 7, without a significant drop in yield (28%).

The workup, as published earlier, required the elimination of most volatiles under vacuum. We found that dilution of the crude electrolysis mixture with diethyl ether followed by a "classical" workup (see experimental section), gave a material suitable for the next step. At this stage, in order to isolate the diketal **4**, we tried a fractionation of the electrolysis mixture. No low molecular weight product distilled and we think that under these modified conditions an oligomer was produced, the protected 1,4-dialdehyde units being attached via C–O–C bridges. However, this did not seem to interfere with the acid-catalysed condensation with benzyl carbamate. The modified electrolysis conditions were also tested with isopentenylethyl ether and gave a 10% yield (measured as protected 3,4-diisopropylpyrrole).

The reaction conditions to form pyrrole **5** were slightly modified: a minimal amount of carbamate (0.35 equivalent) was sufficient to trap all the protected dialdehyde formed in the preceding step, when this step was run under the simplest and safest conditions (see experimental section). The last step (condensation to porphyrin) could be run in the absence of pyridine, and we replaced aqueous formaldehyde by paraformaldehyde.

^{13}C labelled octaethylporphyrin was easily obtained on reaction with commercially available ^{13}C paraformaldehyde. The ^{15}N atoms were introduced as labelled benzyl carbamate, itself obtained from ^{15}N ammonium chloride and benzyl chloroformate under Schotten–Baumann conditions.

Labelled ammonium chloride (98% ^{15}N) and paraformaldehyde (99% ^{13}C) were purchased from Cambridge Isotope Laboratories (Andover, Mass., USA) and CEA (Saclay, France).

1,1-Diethoxybutane (2):
In a round-bottom flask fitted with a mechanical stirrer and a condenser were placed $CaCl_2$ (220 g, 1.98 mol) and EtOH (200 mL). Butyraldehyde (200 mL, 160 g, 2.27 mol) and EtOH (80 mL, total 221 g, 4.8 mol) were added slowly (exothermic reaction) and the mixture stirred for 2–3 h and kept at r.t. overnight. The upper phase organic phase was decanted and the solids washed with CH_2Cl_2 (3 × 100 mL). The organic phases were combined and distilled to give 1,1-diethoxybutane, yield: 290 mL, 239.5 g, 1.64 mol (72%); bp 144 °C, Lit. 143–144 °C.[20]

1-Ethoxybut-1-ene (3):
1,1-Diethoxybutane (100 mL, 82.4 g, 0.565 mol) and sulfanilic acid (750 mg, 4.3 mmol) were heated (oil bath, 150 °C) until EtOH followed by mixture of EtOH and 1-ethoxybut-1-ene (boiling range ca. 95–105 °C; collected on solid K_2CO_3) distilled. This mixture was washed with 5% aq K_2CO_3 (2 × 50 mL), dried over solid K_2CO_3 and distilled to yield pure 1-ethoxybut-1-ene **3**, yield: 35 g (60%, *Z*/*E* ratio ca. 3:2); bp 95 °C, Lit. 94.9–95.3 °C.[19]

Anodic Oxidation of 1-Ethoxybut-1-ene (4):
The following electrolysis procedure is the one we recommend as the simplest and safest. To a stirred solution of KPF_6 (500 mg, 2.7 mmol) and 2,6-lutidine (1 mL, 8 mmol) in MeOH (60 mL) in a 150 mL beaker was added 1-ethoxybut-1-ene **4** (10 mL, 80 mmol). The beaker was fitted with a large rubber stopper pierced by three holes (2 wires + thermometer). Two graphite plates (4 × 3 × 0.5 cm) were dipping in the solution and were connected to a battery charger by platinum wires. The beaker was immersed to 3/4 of its height into a larger beaker containing running water (from tap, 17 °C). The current and the temperature of the solution (0.5 A; ca. 20 °C) were monitored by a transformator connected upstream from the charger. The electrolysis was carried out for 8 h. The crude reaction mixture was diluted with Et_2O (200 mL) and water (200 mL). The organic phase was washed with water (3 × 200 mL), and brine (200 mL), dried (Na_2SO_4), filtered and evaporated. This oily material was used as such in the next step.

1-Benzyloxycarbonyl-3,4-diethylpyrrole (5):
Benzyl carbamate (2.65 g, 17.5 mmol, 0.44 equiv) was added to the reaction product from the preceding step in acetic acid (16 mL). The solution was heated under argon for 48 h at 100 °C. After cooling the solution was diluted with CH_2Cl_2 (100 mL), washed with 0.1 N NaOH (2 × 100 mL), dried (Na_2SO_4) and evaporated. The residue was filtered through an alumina column (250 mL) in toluene. The fractions containing pyrrole **5** were evaporated and the last traces of solvent eliminated under vacuum (0.2–0.3 mbar) (2.23 g, 11.1 mmol, 28%). Oily **5** can be stored at −10 °C and showed NMR and chromatographic data identical to that of previously prepared samples.[12]

^1H NMR ($CDCl_3$): δ = 7.4 (5 H, m, phenyl), 7.00 (2 H, s, pyrrole), 5.33 (2 H, s, benzyl CH_2), 2.38 (4 H, q, J = 7 Hz, ethyl CH_2), 1.18 (6 H, t, J = 7 Hz, ethyl CH_3).

^{15}N Benzyl Carbamate:
^{15}N labelled ammonium chloride (500 mg, 9.3 mmol) was dissolved in an aq solution of NaOH (750 mg, 18.7 mmol). Benzyl chloroformate (1.33 mL, 9.3 mmol) was then added dropwise over 0.5 min and the mixture stirred vigorously overnight. The white solid was filtered, thoroughly washed with water, dissolved in Et_2O and again washed with water (3 × 100 mL), and brine (100 mL), dried (Na_2SO_4), concentrated, and crystallised by addition of hexane, yield: 1.1 g, 7.28 mmol (78%). Mp 91–93 °C (commercial samples: 87–89 °C).

Octaethylporphyrin:
The protected pyrrole **5** (1.35 g) was dissolved in MeOH (20 mL) and hydrogenolysed over 10% Pd/C (55 mg) at atmospheric pressure for 2 h. After filtration of the catalyst, the solvent was evaporated under vacuum (20 mbar, temperature < 30 °C). To the crude product were then added AcOH (40 mL) and paraformaldehyde (100 mg). The reaction mixture was heated under reflux while passing a flux of air through the solution for 1 h. Most H_2OEP crys-

tallised on cooling and the crystals were washed with MeOH. A minor crop was obtained from the mother liquors after evaporation and filtration (eluent CH_2Cl_2–hexane) of the residue on silica gel (total 280 mg; 40% from pyrrole **5**; not optimised).

^{13}C labelled sample: MS indicate 95% ^{13}C at the *meso* bridges. ^1H NMR ($CDCl_3$) identical to literature data[10] except for *meso* bridges: $\delta = 10.11$ (4H, d, $J = 153.7$ Hz, and s, ratio ca. 95:5).

^{15}N labelled sample: MS indicate 98% ^{15}N. ^1H NMR ($CDCl_3$) identical to literature data[10] except for *meso* bridges: $\delta = 10.11$ (4H, t, $J = 4.6$ Hz).

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