Porphyrins with Exocyclic Rings. Part 8 [1]. Synthesis of Nitrogen-15 and Carbon-13 Labeled 2,3:7,8:12,13:17,18-Tetrabutanoporphyrin [2,3]

Shaohua Chen and Timothy D. Lash*

Department of Chemistry, Illinois State University,
Normal, Illinois 61790-4160, U.S.A.

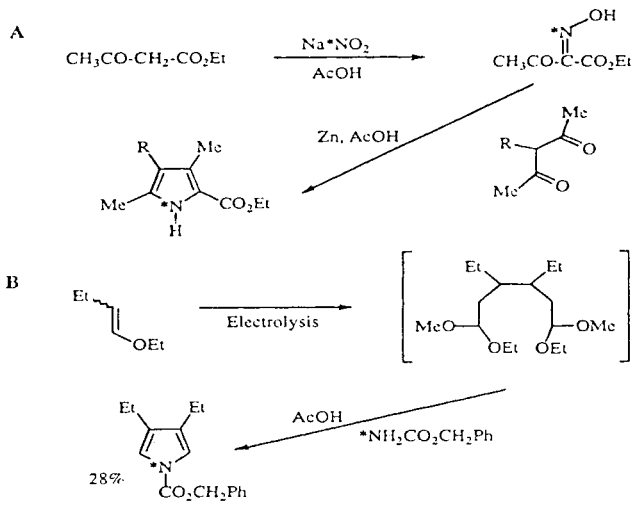
Received March 13, 1996
Revised September 16, 1996

Nitrogen-15 labeled butyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate was prepared *via* butyl isocyanoacetate from ^{15}N-glycine in an overall 46% yield. This bicyclic intermediate was converted into nitrogen-15 and carbon-13 labeled 2,3:7,8:12,13:17,18-tetrabutanoporphyrin, a useful model system for the sedimentary tetrahydrobenzoporphyrins.

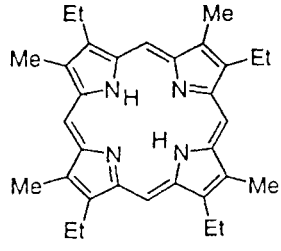
J. Heterocyclic Chem., **34**, 273 (1997).

Nitrogen-15 and carbon-13 labeled porphyrins are of value in the assignment of nmr, ms and vibrational spectra [4], as well as in mechanistic and biochemical studies [5]. In order to synthesize ^{15}N labeled porphyrin structures, efficient routes to suitably substituted ^{15}N-pyrroles are required. In most of the previous studies, these pyrroles were prepared from ^{15}N labeled sodium nitrite *via* the nitrosation of a β-keto ester (usually ethyl acetoacetate) followed by Knorr-type condensation with a β-diketone (Scheme 1A) [4-7]. A more efficient route to per-^{15}N labeled 2,3:7,8:12,13:17,18-octaethylporphyrin was recently reported where the key pyrrolic intermediate was prepared (Scheme 1B) by the condensation of an electrochemically generated (and hence symmetrical) γ-diketone (in the form of a bisacetal) with ^{15}N-labeled benzyl carbamate (Paal-Knorr condensation) [8].

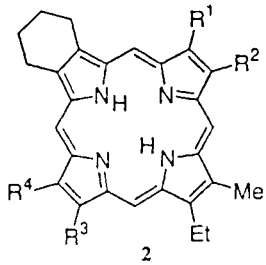
Scheme 1



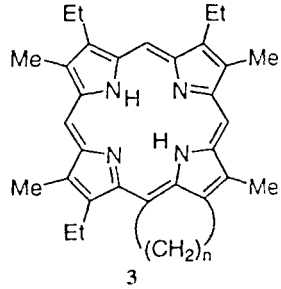
In collaborative studies, we have been examining the vibrational spectra of geochemically significant metalloporphyrins [9-12]. The long term goal of this research is to develop resonance Raman spectroscopy as a tool for the analysis of metalloporphyrins from oil shales and petroleum [10]. Petroporphyrins are valuable chemical markers that provide indications of thermal maturity [13] and are diagnostically useful in that each organic-rich sediment has a unique fingerprint of metalloporphyrin components [14]. The latter may be useful in tracking the source of oil spills, as petroporphyrins, unlike other chemical markers, undergo little chemical weathering or biological degradation and can be correlated with the original petroleum source. Detailed resonance Raman studies have been carried out on nickel(II) etioporphyrins, *e.g.* structure **1**, [9,10], tetrahydrobenzoetioporphyrins **2** [11] and cycloalkanoporphyrins **3** [12], and this technique has been



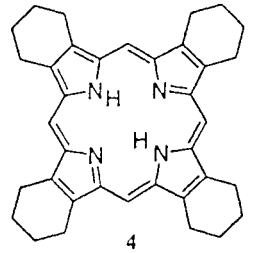
1
Etioporphyrin-III



2
Tetrahydrobenzoetioporphyrins
a. $R^1 = R^4 = Me$; $R^2 = R^3 = Et$
b. $R^2 = R^4 = Me$; $R^1 = R^3 = Et$
c. $R^2 = R^3 = Me$; $R^1 = R^4 = Et$
d. $R^1 = R^3 = Me$; $R^2 = R^4 = Et$



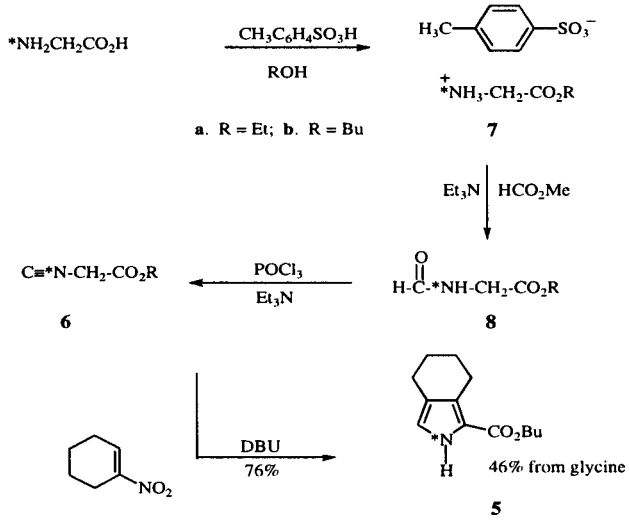
3
Cycloalkanoporphyrins
n = 2-4



4

shown to be very sensitive to minor structural variations. For instance, all four tetrahydrobenzoetioporphyrin isomers **2a-d** are easily distinguishable in this way [11]. Tetrabutanoporphyrin **4a** has proven to be a useful spectroscopic model for the asymmetrical porphyrins **2a-d** and has aided in the assignment of their vibrational spectra. In order to more rigorously assign these spectra, ^{15}N and ^{13}C labeled samples of tetrabutanoporphyrin **4** were required. The ^{15}N labeled tetrahydroisoindole intermediate **5** (Scheme 2) that was needed for this study could not be easily obtained by the procedures outlined in Scheme 1. Instead, it was necessary to adapt the methodology introduced by Barton and Zard, where the pyrrolic structures are generated by the base catalyzed condensation of isocyanoacetate esters **6** with nitroalkenes [15-19]. This approach had been utilized in our earlier syntheses of tetrahydrobenzoetioporphyrins **2a-d** [18-20], as well as for the preparation of unlabeled **4** [18,19].

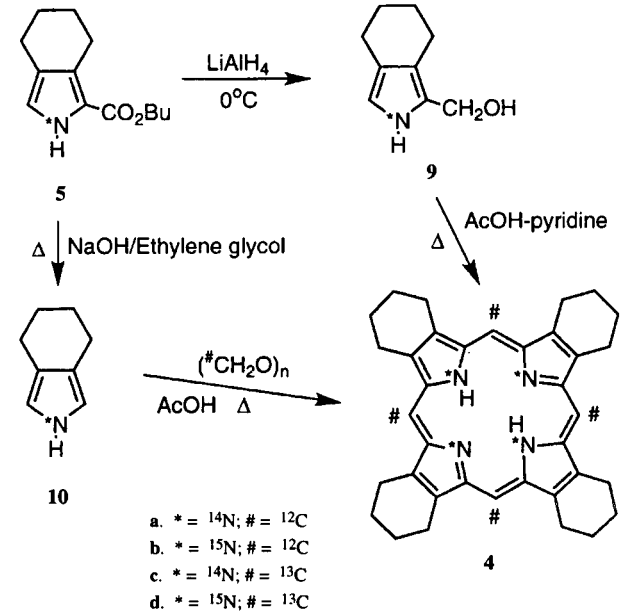
Scheme 2



Isocyanoacetate esters **6** can be generated in three steps from commercially available ^{15}N-labeled glycine[16,21,-22]. Initially, glycine was esterified with ethanol in the presence of one equivalent of *p*-toluenesulfonic acid to give the corresponding *p*-toluenesulfonate salt **7a**. However, formylation with methyl formate-triethylamine afforded the required *N*-formylglycinate **8a** in low yield, especially when the reaction was carried out on a small scale with 1.00 g of glycine. An extraction step was necessary in this procedure and the low yields were almost certainly due to losses due to the water solubility of **8a**. The use of saturated sodium chloride solutions was helpful but this did not give sufficiently improved yields for this approach to be viable. It should be noted that the ethyl ester is simply a protective grouping and since it is cleaved (or reduced) at a later stage, a different, less polar ester moiety could be used and this should facilitate extraction of the labeled product. The *n*-butyl ester of glycine was prepared, again as the *p*-toluenesulfonate salt **7b**, and this was treated with refluxing triethylamine-methyl formate. Following workup, the *N*-formylglycinate **8b** was isolated in good yield. The crude oil was dehydrated by treatment with phosphorus oxychloride-*N*,*N*-dimethylformamide at 0° to give the isocyanoacetate **6b**. No attempt was made to purify these intermediates, as this led to unacceptable losses of labeled material. Butyl isocyanoacetate (**6b**) condensed with 1-nitrocyclohexene in the presence of one equivalent of 1,8-diazabicyclo-[5.4.0]undec-7-ene to give the required tetrahydroindole **5** (Scheme 2). An overall yield of 46% from nitrogen-15 labeled glycine was obtained [23].

Tetrahydroisoindole **5** was converted into porphyrin **4a** under standard conditions (Scheme 3) [19]. Reduction with lithium aluminum hydride afforded the unstable carbinol **9**, and subsequent cyclotetramerization in refluxing acetic acid-pyridine gave the symmetrical porphyrin **4** in approximately 25% yield (slightly higher yields are obtained for larger scale reactions [19]). Alternatively, cleavage of the ester moiety with sodium hydroxide in refluxing ethylene glycol afforded the α,α'-diunsubstituted pyrrole **10** and subsequent reaction with paraformaldehyde in refluxing acetic acid yielded the required porphyrin **4a**. ^{15}N-labeled **5** afforded the per-^{15}N labeled tetrabutanoporphyrin **4b**. Similarly, the use of carbon-13 labeled paraformaldehyde allowed the synthesis of meso-$^{13}C_4$-labeled tetrabutanoporphyrin **4c** and the doubly labeled porphyrin **4d**. These compounds were fully characterized by nmr spectroscopy and mass spectrometry.

Scheme 3



The 70 eV electron impact mass spectra for porphyrins **4a-d** are worthy of note (Figure 1). Most porphyrins exhibit benzylic-type fragmentations in mass spectrometry [24], although this is not possible for the tetrabutanoporphyrin system **4**. A strong molecular ion is observed, together with daughter ions corresponding to losses of m/z of 28, 56 and 74. This corresponds to a series of retro-Diels-Alder fragmentations (Scheme 4), with losses of 1-3 units of ethylene and this presumably leads to the formation of species such as **11** and **12**. As expected, the nature of these fragmentations is not influenced by isotopic substitution. Interestingly, the EI mass spectra of tetrahydrobenzoetioporphyrins **2a-d** only showed benzylic fragmentation (M-15 peaks), and no retro-Diels-Alder processes could be observed for these compounds.

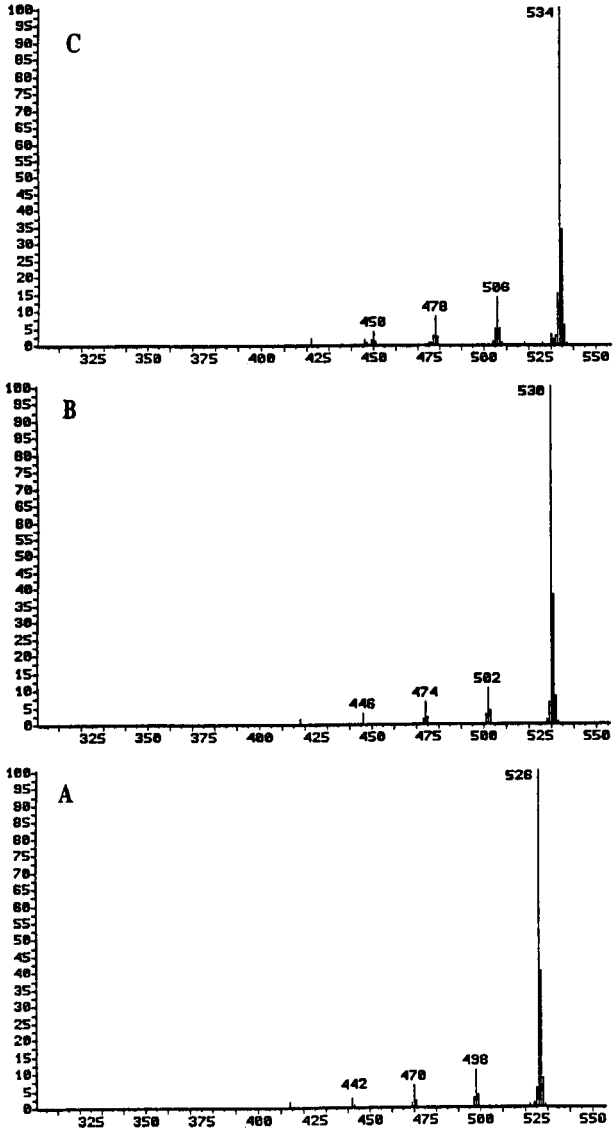
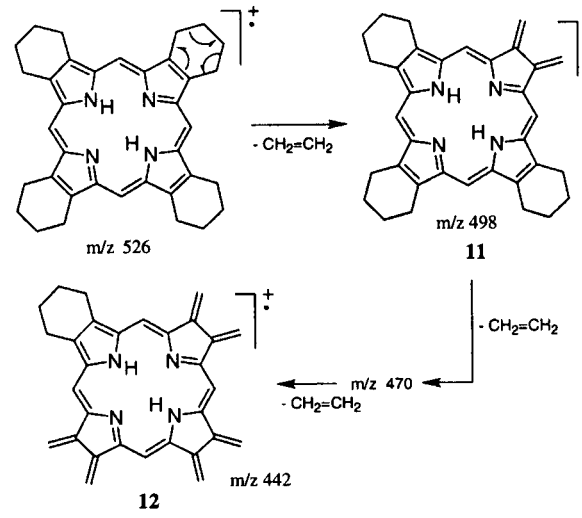


Figure 1. 70 eV electron impact mass spectra of tetrabutanoporphyrins **4a** (A), **4b** (B) and **4d** (C).

Scheme 4



In conclusion, we have demonstrated that the isocyanoacetate methodology can be used in the preparation of nitrogen-15 labeled pyrroles and this approach provides a practical alternative for the synthesis of labeled porphyrins. The isotopically labeled porphyrins **4b-d** will be particularly useful in assigning the vibrational spectra of sedimentary porphyrins [9-12].

EXPERIMENTAL

Nitrogen-15 labeled glycine (99%) and carbon-13 labeled paraformaldehyde (98%) were purchased from Cambridge Isotope Laboratories, Inc. All other reagents were purchased from Aldrich Chemical Co. and were used without further purification. Silica gel (70-230 mesh, 60 A) for column chromatography was obtained from Aldrich Chemical Co., and columns were prepared by slurry packing. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1600 Series FT-IR Spectrometer and only selected absorptions (in reciprocal centimeters) are listed. Proton and carbon-13 nmr spectra were obtained on a Varian Gemini-300 nmr spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (ppm) downfield (δ) from TMS. Mass spectral data were obtained from the Mass Spectral Laboratory, School of Chemical Sciences, University of Illinois at Urbana-Champaign, supported in part by a grant from the National Institute of General Medical Sciences (GM 27029). Elemental analyses were obtained from the School of Chemical Sciences Microanalysis Laboratory at the University of Illinois.

Butyl Glycinate *p*-Toluenesulfonate (**7b**).

Glycine (1.00 g) and *p*-toluenesulfonic acid monohydrate (2.534 g) were dissolved in 1-butanol (10 ml) and heated under reflux for 3 hours. Most of the 1-butanol was removed on a rotary evaporator, and the residue was diluted with diethyl ether

(20 ml) and cooled in an ice/water bath to aid crystallization. The product was filtered and washed with diethyl ether to give the salt (3.652 g, 90%) as white crystals, mp 78°.

Unlabeled **7b** had ^{1}H-nmr (deuteriochloroform): δ 0.86 (t, 3H, $CH_2CH_2CH_2CH_3$), 1.30 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.50 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.34 (s, 3H, C_6H_4-CH_3), 3.71 (b, 2H, $CH_2NH_3^+$), 4.03 (t, 2H, $CH_2CH_2CH_2CH_3$), 7.12-7.73 (AB quartet, 4H, C_6H_4), 8.08 (br s, 3H, NH_3^+).

Anal. Calcd. for $C_{13}H_{21}NO_5S$ (303.37): C, 51.47; H, 6.98; N, 4.62. Found: C, 51.25; H, 6.74; N, 4.73.

Nitrogen-15 labeled **7b** had ^{1}H-nmr (deuteriochloroform): δ 0.86 (t, 3H, $CH_2CH_2CH_2CH_3$), 1.30 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.50 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.34 (s, 3H, $C_6H_4CH_3$), 3.71 (b, 2H, $CH_2NH_3^+$), 4.03 (t, 2H, $CH_2CH_2CH_2CH_3$), 7.12-7.73 (AB quartet, 4H, C_6H_4), 8.06 (dt, J_{NH} = 78 Hz, $^3J_{HH}$ = 4 Hz, 3H, NH_3).

Butyl *N*-Formylglycinate (**8b**) [25].

In a 25 ml three necked round-bottom flask fitted with a magnetic stirrer, a thermometer, a pressure-equalizing addition funnel, and an efficient reflux condenser with a cold finger were placed butyl glycinate *p*-toluenesulfonate (**7b**) (3.597 g) and methyl formate (8 ml). The suspension was stirred under reflux, while triethylamine (1.8 ml) was added over a period of 10 minutes and the resulting mixture was stirred under reflux for 20 hours. After the mixture had cooled to room temperature, water was added and the mixture extracted with chloroform (3 x 10 ml). The extracts were combined, and washed with 5% aqueous sodium bicarbonate solution (20 ml), and water (20 ml). The aqueous layers were back extracted with chloroform (3 x 10 ml) after every wash. The organic layers were combined, dried over sodium sulfate and the solvent evaporated under reduced pressure to yield the crude amide (1.325 g, 70%) as a yellow oil.

Unlabeled **8b** had ^{1}H-nmr (deuteriochloroform): δ 0.97 (t, J = 7 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.40 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.62 (m, 2H, $CH_2CH_2CH_2CH_3$), 4.10 (d, J = 5 Hz, 2H, CH_2-NH), 4.19 (t, J = 7 Hz, 2H, $CH_2CH_2CH_2CH_3$), 6.51 (br s, 1H, NH), 8.29 (s, 1H, CHO).

Nitrogen-15 labeled **8b** had ^{1}H-nmr (deuteriochloroform): δ 0.97 (t, J = 7 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.40 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.62 (m, 2H, $CH_2CH_2CH_2CH_3$), 4.10 (d, J = 5 Hz, 2H, CH_2-NH), 4.19 (t, J = 7 Hz, 2H, $CH_2CH_2CH_2CH_3$), 6.24 (dt, $^1J_{NH}$ = 93 Hz, $^3J_{HH}$ = 5 Hz, 1H, NH), 8.31 (d, $^2J_{NH}$ = 17 Hz, 1H, CHO).

Butyl Isocyanoacetate (**6b**) [25].

The crude butyl *N*-formylglycinate (1.220 g), triethylamine (5.0 ml) and dichloromethane (23 ml) were placed in a three-necked round-bottom flask fitted with a pressure equalizing addition funnel, a reflux condenser with a calcium chloride drying tube, and a thermometer. The resulting solution was cooled to 0° and phosphorus oxychloride (1.4 ml) was added dropwise, maintaining the temperature between 0° and 2°. Once the addition was complete, the solution was allowed to stir at 0° for 1 hour. A solution of sodium carbonate (3.00 g) in water (14 ml) was added dropwise to the mixture while maintaining the temperature below 30°. The biphasic mixture was stirred for 30 minutes at room temperature, after which water was added to bring the total volume to 45 ml. The aqueous layer was separated and extracted with dichloromethane (3 x 10 ml). The organic solutions were combined, washed with water, dried over potassium carbonate, filtered through Celite, and the solvent evaporated under reduced pressure to yield crude *n*-butyl isocyanoacetate (1.10 g, quantitative) as a pale yellow oil. The product was used without further purification; ^{1}H-nmr (deuteriochloroform): δ 0.95 (t, J = 7 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.39 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.64 (m, 2H, $CH_2CH_2CH_2CH_3$), 4.23 (m, 4H, $CH_2CO_2CH_2$).

Butyl 4,5,6,7-Tetrahydro-2*H*-isoindole-1-carboxylate (**5**).

1,8-Diazabicyclo[5.4.0]undec-7-ene (3.550 g) was added dropwise to a stirred solution of 1-nitrocyclohexene (1.257 g) and butyl isocyanoacetate (**6b**) (1.10 g) in tetrahydrofuran (8 ml), maintaining the temperature of the reaction mixture between 20° and 30° throughout. The reaction mixture was stirred under reflux for 16 hours. The mixture was diluted with chloroform and washed with 5% hydrochloric acid (25 ml). The aqueous phase was extracted with 20 ml of chloroform, the combined organic phases evaporated under reduced pressure, and the residue chromatographed on silica gel eluting with toluene. The product fractions were crystallized form hexane to yield the tetrahydroisoindole (1.25 g, 74% from butyl isocyanoacetate, 46% from glycine) as white crystals, mp 79-80°. Unlabeled **5** had ir (Nujol mull): ν 3291 (st, sh, NH), 1667 (st, sh, C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.96 (t, 3H, CH_2CH_2-CH_2CH_3), 1.44 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.75 (m, 6H, $CH_2(CH_2)_2CH_2$ and $CH_2CH_2CH_2CH_3$), 2.53 (t, 2H), 2.80 (t, 2H) ($CH_2(CH_2)_2CH_2$), 4.23 (t, 2H, $CO_2CH_2CH_2CH_2CH_3$), 6.64 (d, $^3J_{HH}$ = 3 Hz, 1H, pyrrole-H), 8.73 (br s, 1H, NH); ^{13}C-nmr (deuteriochloroform): δ 13.8, 19.4, 21.9, 22.0, 23.3, 23.5, 31.1, 63.8, 118.1, 119.1, 122.3, 128.2, 162.3.

Anal. Calcd. for $C_{13}H_{19}NO_2$ (221.30): C, 70.56; H, 8.65; N, 6.33. Found: C, 70.25; H, 8.46; N, 6.42.

Nitrogen-15 labeled **5** had ir (Nujol mull): ν 3283 (st, sh, NH), 1668 (st, sh, C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.96 (t, 3H, $CH_2CH_2CH_2CH_3$), 1.44 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.75 (m, 6H, overlap of $CH_2(CH_2)_2CH_2$ and $CO_2CH_2CH_2CH_2$-CH_3), 2.53 (t, 2H), 2.80 (t, 2H) ($CH_2(CH_2)_2CH_2$), 4.23 (t, 2H, $CO_2CH_2CH_2CH_2CH_3$), 6.64 ("t", $^2J_{NH}$ = $^3J_{HH}$ = 3 Hz, 1H, pyrrole-H), 8.75 (dd, $^1J_{NH}$ = 96 Hz, $^3J_{HH}$ = 3 Hz, 1H, NH); ^{13}C-nmr (deuteriochloroform): δ 13.8, 19.4, 22.0, 22.0, 23.3 (d, $^3J_{NC}$ = 1 Hz), 23.5 (d, $^3J_{NC}$ = 2 Hz), 31.1, 63.8, 118.1 (d, $^1J_{NC}$ = 15 Hz), 118.9 (d, $^1J_{NC}$ = 14 Hz), 122.4 (d, $^2J_{NC}$ = 3 Hz), 128.3 (d, $^2J_{NC}$ = 5 Hz), 162.2 (d, $^2J_{NC}$ = 2 Hz).

2,3:7,8:12,13:17,18-Tetrabutanoporphyrin (**4a**).

Method A.

Lithium aluminum hydride (0.35 g) and anhydrous ether (20 ml) were placed in a 100 ml round bottom flask equipped with an addition funnel, a condenser and a magnetic stirrer. Butyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (**5**) (375 mg) dissolved in 10 ml of anhydrous ether was added dropwise to the stirred mixture over 30 minutes while the reaction vessel was cooled in an ice bath. The reaction mixture was stirred for 1 hour after the addition was complete. Water (20 ml) was added cautiously dropwise to destroy the excess lithium aluminum hydride. The brown organic phase was separated and the aqueous layer extracted with ether (2 x 10 ml). The organic solutions were combined and the solvent removed on a rotatory evaporator while maintaining the temperature of water bath at 25-30°. The residue was taken up in pyridine (5 ml) and acetic acid (20 ml) and immediately heated under reflux for 1 hour. The result-

ing mixture was allowed to stand at room temperature for several days, suction filtered, and washed with methanol. The crude porphyrin was chromatographed on Grade III alumina using dichloromethane as the eluent. The red fractions were evaporated and recrystallized from dichloromethane/methanol to give the title porphyrin (49 mg, 22%) as a dark purple solid, mp >300° (lit mp >300° [19], lit mp 320-325° [26], lit mp 295-300° [17a]); ^{1}H-nmr (deuteriochloroform): δ -3.90 (br s, 2H, 2 x NH), 2.51 (m, 16H, 4 x $CH_2(CH_2)_2CH_2$), 4.12 (m, 16H, 4 x $CH_2(CH_2)_2CH_2$), 9.88 (s, 4H, 4 x *meso*-H); ^{13}C-nmr (deuteriochloroform): δ 23.1, 23.9 (16 x CH_2), 96.0 (4 x *meso*-carbons), 138.6 (8 x β-carbons), 142.0 (8 x α–carbons) (very broad due to NH proton exchange); ms: (electron impact) m/z (relative intensity) 528 (7), 527 (40), 526 (100) (M^+), 525 (6), 498 (11), 470 (7), 442 (3), 263 (22) (M^{2+}), 249 (6).

Method B.

Butyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (**3**) (222 mg, 0.10 mmole) was heated with sodium hydroxide (1.00 g) and ethylene glycol (10 ml) under reflux conditions for 30 minutes. The mixture was diluted with water and extracted with hexane (3 x 20 ml). The combined hexane solutions were dried over sodium sulfate and the solvent evaporated under reduced pressure to give a dark oil. Acetic acid (8 ml) and paraformaldehyde (20 mg) were added, and the mixture was refluxed while air was bubbled through it for 1 hour. The mixture was cooled and the resulting precipitate filtered and recrystallized from chloroform/methanol to give porphyrin **4a** (33 mg, 25%) as a purple solid, mp >300°.

per-Nitrogen-15 Labeled 2,3:7,8:12,13:17,18-Tetrabutanoporphyrin (**4b**).

Using method A, 375 mg of nitrogen-15 labeled butyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (**5**) gave the title porphyrin (52 mg, 23%) as a purple solid; ^{1}H-nmr (deuteriochloroform): δ -3.9 (br s, 2H, 2 x NH), 2.51 (m, 16H, 4 x $CH_2(CH_2)_2CH_2$), 4.12 (m, 16H, 4 x $CH_2(CH_2)_2CH_2$), 9.89 (t, $^3J_{NH}$ = 3 Hz, 4H, 4 x *meso*-H); ms: (electron impact) m/z (relative intensity) 532 (8), 531 (38), 530 (100) (M^+), 529 (7), 502 (11), 474 (7), 446 (3.5), 265 (24) (M^{2+}), 251 (5).

5,10,15,20-$^{13}C_4$-2,3:7,8:12,13:17,18-Tetrabutanoporphyrin (**4c**).

Using method B, carbon-13 labeled paraformaldehyde (20 mg) and butyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (**5**) (222 mg) gave the title porphyrin (35 mg, 26%) as a purple solid; ^{1}H-nmr (deuteriochloroform): δ -3.90 (br s, 2H, 2 x NH), 2.51 (m, 16H, 4 x $CH_2(CH_2)_2CH_2$), 4.12 (m, 16H, 4 x $CH_2(CH_2)_2CH_2$) 9.87 (d, J_{CH} = 154 Hz, 4H, 4 x *meso*-H); ms: (electron impact) m/z (relative intensity) 532 (7), 531 (36), 530 (100) (M^+), 529 (16), 502 (12), 474 (7), 446 (4), 265 (23) (M^{2+}), 251 (5).

5,10,15,20-$^{13}C_4$-21,22,23,24-$^{15}N_4$-2,3:7,8:12,13:17,18-Tetrabutanoporphyrin (**4d**).

Using method B, nitrogen-15 labeled butyl-4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (**5**) (221 mg) and carbon-13 labeled paraformaldehyde (20 mg) gave the title porphyrin (30 mg, 24%) as a purple solid; ^{1}H-nmr (deuteriochloroform): δ -3.9 (br s, 2H, 2 x NH), 2.51 (m, 16H, 4 x $CH_2(CH_2)_2CH_2$), 4.12 (m, 16H, 4 x $CH_2(CH_2)_2CH_2$), 9.87 (dt, J_{CH} = 154 Hz, $^3J_{NH}$ = 3 Hz, 4H, 4 x *meso*-H); ms: (electron impact) m/z (relative intensity) 536 (6), 535 (34), 534 (100) (M^+), 533 (15), 506 (14), 505 (5), 478 (9), 450 (4), 267 (22) (M^{2+}), 253 (6).

Acknowledgements.

This material is based upon work supported by the National Science Foundation under Grant No. CHE-9500630 and the University Research Fund of Illinois State University. We also thank the National Science Foundation (Grant Numbers CHE-9001175 and DUE-9452437) for providing partial funding for two 300 MHz NMR spectrometers.

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