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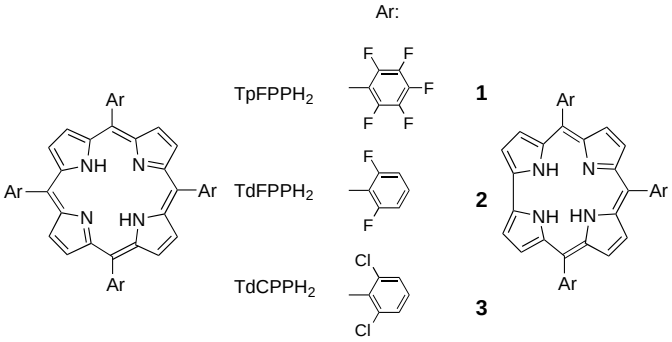
The First Direct Synthesis of Corroles from Pyrrole**

Zeev Gross,* Nitsa Galili, and Irena Saltsman

Core-modified porphyrins have been receiving increased attention in recent years,[1] mainly because of their superiority over porphyrins in many applications, most notably as agents for photodynamic therapy.[2] Some of these macrocycles form complexes with transition metals, which due to the alteration of the ligand structure have very different properties than the analogous metalloporphyrins. The most interesting compounds in this regard are corroles, whose skeletons are contracted by one carbon atom with respect to porphyrins (Scheme 1).[3] In contrast to the diprotonic porphyrins, corroles act as tetradentate trianionic ligands toward metal ions. The most remarkable feature of corroles is the stabilization of unusually high oxidation states, such as iron(IV), cobalt(IV), and cobalt(V).[4] Surprisingly, however, there is no reported application in any field for either corroles or their metal complexes. The reason for that is almost certainly the lack of obvious procedures for their preparation. Thus, in spite of the significant progress in corrole synthesis, even the most simple procedures reported to date require starting materials that are not commercially available.[5] Similarly, the first synthesis of a *meso*-substituted corrole—*meso*-aryl substitution is most likely a prerequisite for the utilization of metallocorroles in catalysis—appeared only in 1993.[6]



Scheme 1. Schematic representation of tetraarylporphyrins $TpFPPH_2$, $TdFPPH_2$, and $TdCPPH_2$ (left) and the corresponding triarylcorroles **1**–**3** (right).

Owing to our ongoing interest in the synthesis of porphyrins and their core-modified analogues,[7] we explored a new approach, the solvent-free condensation of pyrrole and aldehydes. The research goal was the development of a simple synthetic methodology for the preparation of porphyrins, driven by the anticipation that the rather unusual reaction conditions might also lead to the formation of some porphyrin isomers. We have focused on two aldehydes: benzaldehyde, as the prototype of other *meso*-aryl-substituted porphyrins, and perfluorobenzaldehyde, because the metal complexes of the corresponding porphyrin ($TpFPPH_2$, Scheme 1) are among the most efficient oxygenation catalysts. The reaction conditions were very simple indeed, consisting of mixing pyrrole and the aldehyde in equimolar quantities on a solid support, heating to 100 °C for four hours, oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and chromatographic separation. The reaction vessel was open to air, which not only simplifies the procedure but was also found to be required. With benzaldehyde as reactant, tetraphenylporphyrin ($TPPH_2$) was obtained in 5–8% yield, depending on the solid support (see Experimental Section).

When the same reaction conditions (best with basic alumina as solid support) were applied for perfluorobenzaldehyde, very different results were observed. Only traces of the corresponding porphyrin ($TpFPPH_2$) were obtained, accompanied by a compound (**1**, isolated in 11% yield) which showed a strong porphyrin-like fluorescence and an electronic spectrum similar to that of $TpFPPH_2$ (Figure 1). However, while the ^1H NMR spectrum of $TpFPPH_2$ consists of two singlets in a ratio of 8:2 at $\delta = 8.91$ (sharp) and -2.93 (broad) for the β-pyrrole and the inner nitrogen hydrogen atoms, respectively, in the spectrum of **1** three doublets ($J \approx 4.5$ Hz) in the ratio of 1:1:2 were obtained in the pyrrole hydrogen region ($\delta = 9.10$, 8.75, and 8.57) together with an extremely broad resonance at $\delta = -2.25$ (Figure 1, inset). Similarly, the

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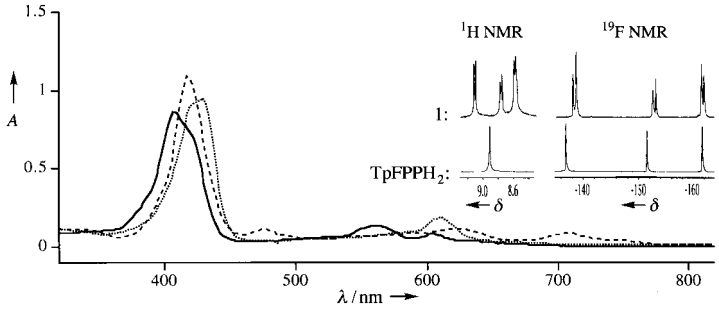
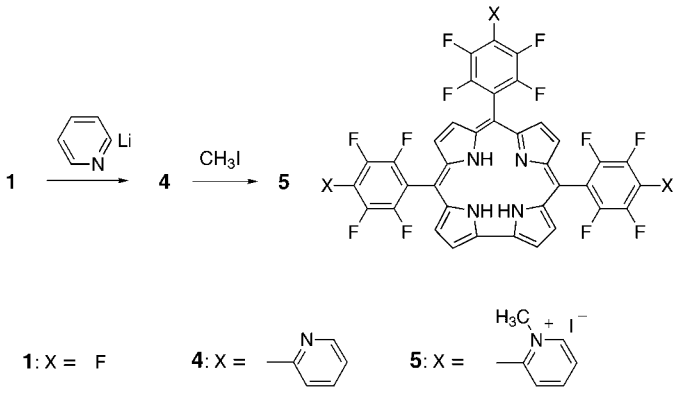


Figure 1. UV/Vis spectra of **1** (——), and its protonated (- - - -); reaction with CF_3CO_2H) and deprotonated forms (••••; reaction with Et_3N). The spectra were measured in CH_2Cl_2 at identical concentrations. Inset: The ^{1}H and ^{19}F NMR spectra of **1** and $TpFPPH_2$ in $CDCl_3$.

signal for only one type of pentafluorophenyl group is present in the ^{19}F NMR of $TpFPPH_2$, but two such groups in the ratio of 2:1 are evident for **1**. This data, together with the mass spectrum of the compound (*m*/*z* 796) allowed the identification of **1** as 5,10,15-tri(2,3,4,5,6-pentafluorophenyl)corrole, the first β-pyrrole-unsubstituted corrole.

Because of the difference in reactivity between benzaldehyde and pentaflurobenzaldehyde—formation of porphyrin and corrole, respectively—we turned our attention to other halogeno-substituted benzaldehydes, namely, the 3,5-dichloro, 2,6-dichloro, and 2,6-difluoro derivatives. Traces of porphyrin and 6% of 5,10,15-tri(2,6-difluorophenyl)corrole (**2**) were formed in the reaction of pyrrole and 2,6-difluorobenzaldehyde (equimolar amounts). However, no corrole was formed with the two chlorinated aldehydes, and only trace amounts of porphyrin appeared with 3,5-dichlorobenzaldehyde. The only isolated product (7%) from the reaction of 2,6-dichlorobenzaldehyde was the *meso*-aryl-α-benzyldipyrromethene.[8, 9] Reexamination of the reactions with pentafluoro- and 2,6-difluorobenzaldehyde revealed that analogous compounds were also obtained as minor components. As dipyrromethenes are the H_2O elimination products of the chain-growing polypyrroles which lead to both porphyrin and corrole,[10] we anticipate that further optimization of the synthetic procedure will allow the successful preparation of additional triarylcorroles. Indeed, a simple change of the pyrrole:aldehyde ratio to 2:1 allowed the isolation of 5,10,15-tri(2,6-dichlorophenyl)corrole (**3**) in 1% yield.

The absence of electron-donating alkyl groups in the β-pyrrole positions and the presence of the electron-withdrawing pentafluorophenyl groups at the *meso*-carbon atoms in corrole **1** lead to some unique properties. For example, the known larger NH acidity of corroles relative to porphyrins is brought to quite an extreme in **1**. In ethanolic solutions the dominant species is the monoanion of **1**, and in organic solvents **1** is deprotonated by weak bases. This is demonstrated in Figure 1, which shows the changes in the electronic spectrum of **1** upon its deprotonation by triethylamine. Interestingly, the single imine-like nitrogen atom of **1** remains basic; that is, it is protonated by a sufficiently strong acid (Figure 1). These spectral changes are accompanied in both cases by a color change from violet to green. Finally, another peculiarity of **1** is that it may serve as the precursor of many other corroles, since its *para*-fluoro substituents can easily be replaced by nucleophilic substitution. This is demonstrated by the reaction of **1** with *ortho*-pyridyllithium to provide 5,10,15-tris[4-(2-pyridyl)-2,3,5,6-tetrafluorophenyl]corrole (**4**; Scheme 2; see Experimental Section). The reaction of **4** with iodomethane leads to **5**, which to our knowledge is the first ever reported ionic corrole. The solubility of **5** in water is about 2 mg mL^{-1}, and at least in the range determinable by UV/Vis spectroscopy there is no sign of aggregation.



Scheme 2. Synthesis of **4** and water-soluble **5** from **1**.

To summarize, we report the first corrole synthesis to start with commercially available reactants (pyrrole and aldehyde), the first corroles without substituents at the β-pyrrole positions, and the first water-soluble corrole. We have already prepared the iron, cobalt, rhodium, and copper complexes of **1**, whose full characterization and examination in various applications is currently in progress. We also trust that the facile synthesis described herein will soon make corrole derivatives commercially available.[11]

Experimental Section

General procedure described for the synthesis of $TPPH_2$: The solid absorbant (florisil, silica, or alumina; 1 g) was mixed in a 50-mL flask with a solution of benzaldehyde (1.06 g, 10 mmol) and pyrrole (0.67 g, 10 mmol) in CH_2Cl_2 (2 mL), and the solvent was distilled at normal pressure. The condenser was removed, and the solid mixture was heated to 100 °C, upon which the color changed to black in 5–10 min. After heating of the mixture for 4 h, the solid support was washed with CH_2Cl_2 (50 mL), DDQ (1.13 mg, 5 mmol) was added, and the product was obtained by chromatography on basic alumina with hexane/CH_2Cl_2 (2.5/1) as eluent. With florisil, silica, neutral alumina, and basic alumina as solid supports the isolated chemical yields of $TPPH_2$ were 5, 5, 7, and 8%, respectively. When the first step of the reaction was carried out under an inert atmosphere, neither porphyrins or corroles were obtained.

1: Under the same reaction conditions as for $TPPH_2$, with the solid absorbant (0.5 g), pentafluorobenzaldehyde (0.49 g, 2.5 mmol), and pyrrole (0.17 g, 2.5 mmol), traces of $TpFPPH_2$ and significant amounts of **1** were obtained (R_f (hexane/CH_2Cl_2 3/1) = 0.52 and 0.34, respectively). The yields of isolated **1** (after crystallization from CH_2Cl_2/hexane) were 4%, traces, 11%, and 11%, with florisil, silica, neutral alumina, and basic alumina as solid support, respectively. Identical chemical yields were obtained in a reaction with half the amount of solid support; that is, 55 mg of **1** were isolated from the reaction supported by 0.25 g of basic alumina. UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$) = 408 (114.0), 560 (17.6), 602 nm (9.3); ^{1}H NMR ($CDCl_3$): δ = 9.10 (d, J = 4.4 Hz, 2H), 8.75 (d, J = 4.4 Hz, 2H), 8.57 (d, J = 4.4 Hz, 4H), −2.25 (br s, 3H); ^{19}F NMR ($CDCl_3$): δ = −137.55 (dd, ^1J = 24.2, ^2J = 8.1 Hz, 2F), −138.14 (dd, ^1J = 23.03, ^2J = 6.9 Hz, 4F), −152.52 (t, J = 19.6 Hz, 2F), −153.10 (t, J = 20.7 Hz, 1F), −161.78 (dt, ^1J = 24.2, ^2J =

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8.1 Hz, 4F), −162.35 (dt, ^1J = 23.03, ^2J = 6.9 Hz, 2F); HR-MS: *m/z*: 797.0854 (calcd for $C_{37}H_{12}N_4F_{15}$: 797.0822).

2: UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$): 406 (118.6), 562 (20.3), 602 nm (11.9); ^{1}H NMR ($CDCl_3$): δ = 8.99 (d, J = 4.3 Hz, 2H), 8.71 (d, J = 4.3 Hz, 2H), 8.52 (t, J = 4.3 Hz, 4H), 7.72 (m, 3H), 7.33 (m, 6H), −2.1 (br s, 3H); ^{19}F NMR ($CDCl_3$): δ = −109.32 (t, J = 6.4 Hz, 2F), −109.75 (t, J = 6.4 Hz, 4F); HR-MS: *m/z*: 635.1660 (calcd for $C_{37}H_{21}N_4F_6$: 635.1670).

3: UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$): 408 (106.1), 422 (86.6), 560 (16.7), 604 nm (9.3); ^{1}H NMR ($CDCl_3$): δ = 8.91 (d, J = 4.2 Hz, 2H), 8.49 (d, J = 4.8 Hz, 2H), 8.35 (d J = 4.6 Hz, 4H), 7.72 (m, 3H), 7.33 (m, 6H), −1.7 (br s, 3H); HR-MS: *m/z*: 729.9810 (calcd for $C_{37}H_{20}N_4Cl_6$: 729.9819).

4: A 1.6 M *n*BuLi solution (0.42 mL, 0.7 mmol) was added to a stirred solution of 2-bromopyridine (0.054 mL, 0.56 mmol) in dry THF (6 mL) under an argon atmosphere at −78 °C, at such a rate that the temperature of the reaction mixture did not exceed −70 °C. After the addition was complete, the reaction mixture was stirred for 1 h at −78 °C, resulting an a clear yellow solution. Next, a solution of **1** (0.03 g, 0.038 mmol) in dry THF (6 mL) was added dropwise. The mixture was stirred for 1 h at −78 °C and then hydrolyzed with saturated aqueous bicarbonate solution. The layers were separated, the aqueous layer was washed with diethyl ether, and the combined diethyl ether extracts were dried and evaporated to yield a solid residue. The product was purified by column chromatography on silica gel (EtOAc/hexane 1/1) and recrystallized from CH_2Cl_2/hexane to provide 13 mg (35 % yield) of pure **4** as a violet solid. UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon \times 10^{-3}$): 414 (111.6), 564 (18.4), 606 nm (sh); ^{1}H NMR ($CDCl_3$): δ = 9.12 (d, J = 3.9 Hz, 2H), 8.93 (m, 5H), 8.73 (d, J = 4.88 Hz, 2H), 8.66 (d, J = 3.91 Hz, 2H), 8.00 (dt, ^1J = 7.81, ^2J = 1.95 Hz, 3H), 7.84 (br d, J = 7.81 Hz, 3H), 7.51 (dt, ^1J = 6.84, ^2J = 1.95 Hz, 3H), −2.02 (br s, 3H); ^{19}F NMR ($CDCl_3$): δ = −138.19 (q, J = 23.79 Hz, 2F), −138.81 (q, J = 23.79 Hz, 4F), −144.11 (q, J = 23.79 Hz, 4F), −144.57 (q, J = 23.79 Hz, 2F); HR-MS: *m/z*: 973.1910 (calcd for $C_{52}H_{23}N_7F_{12}$: 973.1823).

5: A mixture of **4** (11 mg, 11 μmol) and CH_3I (0.8 mL, 13 mmol) in freshly distilled DMF (2 mL) was heated to 70 °C for 3 h. After evaporation of the solvent, the product was recrystallized from MeOH/diethyl ether to provide 15.5 mg (98 % yield) of **5** as a green solid. UV/Vis (MeOH): λ_{max} ($\varepsilon \times 10^{-3}$): 430 (76.2), 576 (10.9), 622 nm (17.8); ^{1}H NMR ([D$_6$]DMSO): δ = 9.49 (d, J = 5.98 Hz, 3H), 9.16 (br m, 8H), 9.00 (t, J = 8.54 Hz, 3H), 8.75 (t, J = 7.68 Hz, 3H), 8.51 (t, J = 7.68 Hz, 3H), 4.68 (s, 3H), 4.65 (s, 6H); ^{19}F NMR ([D$_6$]DMSO): δ = −137.26 (br m, 4F), −138.04 (br m, 6F), −138.60 (br m, 2F); electron spray MS: *m/z*: 339.9 ([M^+ − 3I]/3, 100 %).

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Regioselective Reduction of NAD$^+$ Models with [Cp*Rh(bpy)H]$^+$: Structure – Activity Relationships and Mechanistic Aspects in the Formation of the 1,4-NADH Derivatives**

H. Christine Lo, Olivier Buriez, John B. Kerr, and Richard H. Fish*

The interest in practical methods for the regeneration of the co-enzyme 1,4-NADH, the reduced form of nicotinamide adenine dinucleotide (NAD$^+$), has continued to be high in the field of biocatalysis, where enzymatic reduction reactions are important for the synthesis of chiral organic compounds.[1a, b] Conversion of NAD$^+$ into 1,4-NADH by enzymatic, chemical, photochemical, and electrochemical methods has been studied extensively in order to increase the rate of the regeneration, while maintaining the necessary high regioselectivity. The regeneration is frequently the limiting step in the eventual use of 1,4-NADH in enzymatic synthesis, particularly for higher volume and more energy intensive processes.[1a, b]

In the search for higher rates and a more economical regeneration process various transition metal hydrides have been studied as catalysts for the regioselective reduction of NAD$^+$ and NAD$^+$ models to their corresponding 1,4-NADH derivatives.[2a–g] In the most successful example, Steckhan and co-workers have described the use of [Cp*Rh(bpy)(H)]$^+$ (Cp* = pentamethylcyclopentadienyl, bpy = 2,2′-bipyridyl), generated in situ, for the regiospecific reduction of NAD$^+$ to 1,4-NADH,[2b] and then demonstrated the cofactor regeneration process in enzymatic, chiral reduction reactions.[3, 4]

While the above mentioned reduction of NAD$^+$ by [Cp*Rh(bpy)H]$^+$ was shown to be regiospecific for 1,4-NADH,[2b, 5a] the full mechanistic details of this important

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