UiT
THE ARCTIC UNIVERSITY OF NORWAY

Faculty of Science and Technology

Department of Chemistry

Synthesis of Sterically Hindered Macrocyclic Ligands via Demetalation of Metallocorroles

Jan Capar

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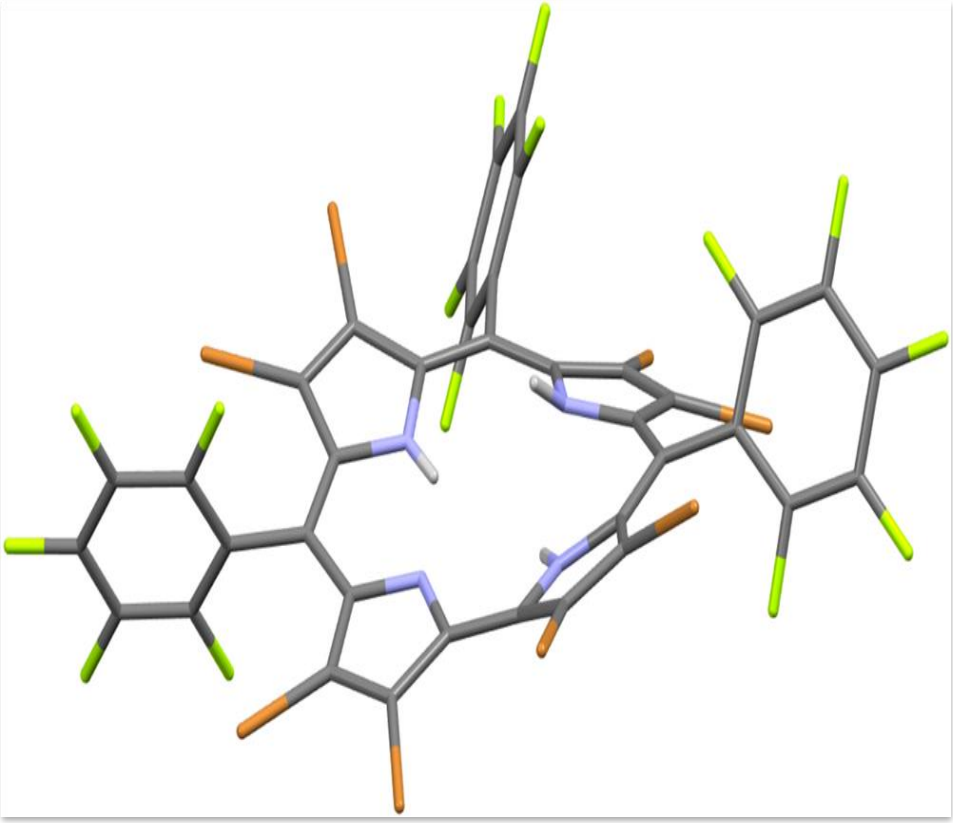

UNIVERSITY OF TROMSØ

Abstract

Despite important developments in synthetic corrole chemistry, the field has long been handicapped by the lack of procedures for demetalation of metallocorroles. This thesis presents general demetalation methods for metallocorroles. A reductive demetalation method was developed using concentrated H_2SO_4 with 5-200 equivalent of $FeCl_2$ or $SnCl_2$ as a reducing agent. The method proved to be quite general in that, by adjusting the amount of the reducing agent, various electron-rich and -deficient copper corroles could be demetalated in good yields. This discovery is described in Paper I.

The reductive demetalation method was also applicable for manganese corroles by tuning the temperature. In this way, the highly electron-deficient and sterically crowded *β*-octabromo-*meso*-tris(pentafluorophenyl)corrole ligand was synthesized, as described in Paper II. Low resolution X-ray data and DFT calculations demonstrated that the unusual nonplanar distortion of the free-base corrole is a direct result of the repulsion among the inner core hydrogens.

High-resolution X-ray analysis of the free-base corrole finally proved possible (Paper III), allowing the assignment of the inner hydrogens corresponding to a specific tautomer. However, DFT calculations revealed no significant energy difference between the two possible tautomers.

Sterically hindered free-base octabromocorrole ligands obtained by the above demetalation methods were utilized to synthesize iron octabromocorrole complexes, two of which were characterized by single-crystal X-ray diffraction analyses. These are presented in Papers IV and V.

Isocorroles are new members of the porphyrinoid family, about which little is known. They are nevertheless of great interest as reagents in photodynamic therapy on account of their strong absorption in the near-infrared. I developed a general method for synthesizing undecaarylisocorroles and this is the subject of Paper VI.

Acknowledgements

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List of Publications and Contributions

1) Capar, J.; Thomas, K. E.; Ghosh, A. "Reductive Demetallation of Copper Corroles: First Simple Route to Free-Base *β*-Octabromocorroles", *J. Porphyrins Phthalocyanines,* **2008**, 12, 964–967.

My contribution to this work was the development of the demetalation method and the syntheses of several compounds.

2) Capar, J.; Hansen, L.-K.; Conradie, J.; Ghosh, A. "*β*-octabromo-*meso*-tris(pentafluorophenyl)corrole: Reductive demetalation-based synthesis of a heretofore inaccessible, perhalogenated free-base corrole", *J. Porphyrins Phthalocyanines,* **2010**, 14, 509–512.

My contribution was the synthesis of the free-base *β*-octabromo-*meso*-tris(pentafluorophenyl)corrole, and crystallization of said compound for X-ray diffraction analysis.

3) Capar, J.; Conradie, J.; Beavers, C. M.; Ghosh A. "Molecular Structures of Free-Base Corroles: Nonplanarity, Chirality, and Enantiomerization", *J. Phys. Chem. A,* **2015**, 119, 3452–3457.

My contribution was numerous crystallization attempts of free-base *β*-octabromo-*meso*-tris(pentafluorophenyl)corrole, which ultimately led to a successful high-resolution X-ray structure.

4) Capar, J.; Berg, S.; Thomas, K. E.; Beavers, C. M.; Gagnon, K. J.; Ghosh, A. "Improved syntheses of *β*-octabromo-*meso*-triarylcorrole derivatives", *J. Inorg. Biochem.* **2015**, 153, 162–166.

My contribution was the syntheses of the new *β*-octabromo-*meso*-tris(2,6-dichlorophenyl)-corrole (H_3[Br_8TDCPC]) ligand, and its iron complexes Fe[Br_8TDCPC](py)$_2$ and Fe[Br_8TDCPC]Cl, as well as the crystallization of Fe[Br_8TDCPC](py)$_2$ for the X-ray diffraction analysis.

5) Norheim, H.-K.; Capar, J.; Einrem R. F.; Gagnon, K. J.; Beavers, C. M.; Vazquez-Lima, H.; Ghosh A. "Ligand noninnocence in FeNO corroles: insights from *β*-octabromocorrole complexes", *Dalton Trans.* **2016**, 45, 681–689.

My contribution was the syntheses of Fe[Br_8TPFPC](NO) and Fe[Br_8TPFPC]Cl, and the crystallization of Fe[Br_8TPFPC](NO) for the X-ray structure determination.

6) Capar, J.; Zonneveld, J.; Berg, S.; Isaksson, J.; Gagnon, K. J.; Thomas, K. E.; Ghosh, A. "Demetalation of Copper Undecaarylcorroles: Molecular Structures of a Free-Base Undecaarylisocorrole and a Gold Undecaarylcorrole", Submitted to *J. Inorg. Biochem.*

My contribution was the development of the method for synthesizing the undecaaryl-isocorroles, the syntheses of the three new copper undecaarylcorroles and the four undecaarylisocorrole ligands, and crystallization of the H_2[$(CF_3)_8$$Me_3$(5-OH)] for the X-ray diffraction analysis.

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1. Introduction to Corroles

1.1 Introduction

Porphyrins are ubiquitous in nature. They are present as prosthetic groups of hemoproteins such as myoglobin, hemoglobin, various cytochromes, and peroxidases. Their general role in biology is to accommodate a metal ion, which has a key catalytic or other important role. Reduced porphyrins such as chlorin and bacteriochlorin also occur widely of which the most notable example is the magnesium-containing pigment chlorophyll. The highly saturated macrocycle corrin has a unique structure with a direct pyrrole-pyrrole linkage and is only found as part of the structure of vitamin B_{12}.

Unlike porphyrins and corrins, corroles are synthetic substances and are not known to occur in nature. They share the skeleton of corrins and the aromaticity of porphyrins (Figure 1.1). As trianionic ligands with a contracted N_4 core, they exhibit a wide range of unique properties.

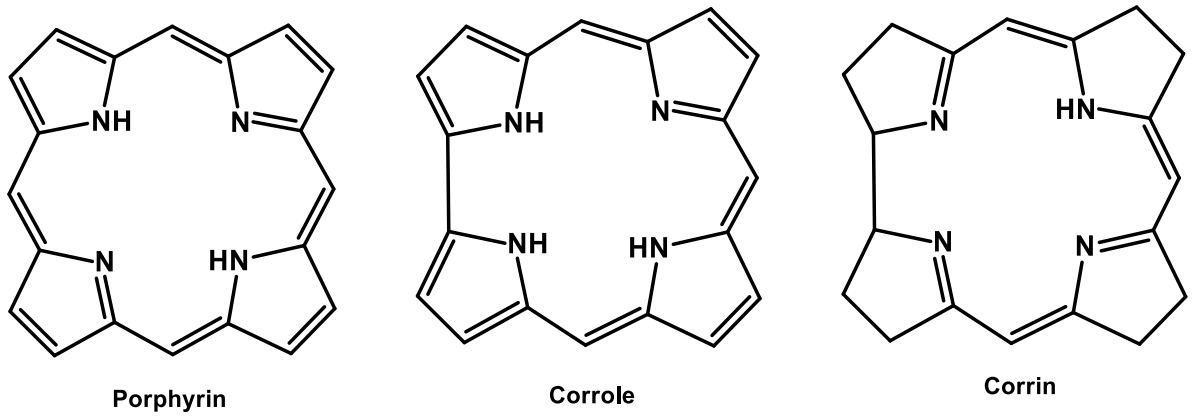


Figure 1.1. Skeletal structures of porphyrin, corrole, and corrin.

Corroles were discovered in 1965 by Johnson and Kay[1] during attempts to synthesize vitamin B_{12}. Their idea was to use corrole as precursor to the corrin ring. Although these attempts at corrin synthesis were not successful, corroles were recognized as interesting ligands. Various metallocorroles were prepared right after their first synthesis.[1,2] The first synthesis of corroles required difficult syntheses of pyrrole intermediates, which proceeded with poor yields. Unfortunately, the difficulty of corrole syntheses made them unpopular as ligands relative to

other macrocycles in the porphyrin family. For about 40 years the chemistry of corroles remained very limited.

In 1994, particular attention was directed towards corroles when Vogel and coworkers[3] discovered that corroles stabilize high-valent Fe(IV) ions. Metals, especially iron in high-valent states serve as reactive intermediates in numerous biological and biomimetic oxidation processes. Fe(IV) porphyrins are highly reactive and isolated intermediates are generally only stable at low temperatures. Thus, this finding came as a breakthrough for these long wanted molecules by the porphyrin scientists. Soon thereafter, a number of other *formally* high-valent Co(IV),[4] Cu(III)[5] and Ni(III)[5] metallocorroles were successfully prepared (even though recent research has shown that many of these complexes are not truly high-valent, but noninnocent).[6] In 1999, two research groups independently discovered one-pot synthesis of corroles from commercially available starting materials.[7,8] After the discovery of its facile synthesis, corrole chemistry started to develop almost exponentially.

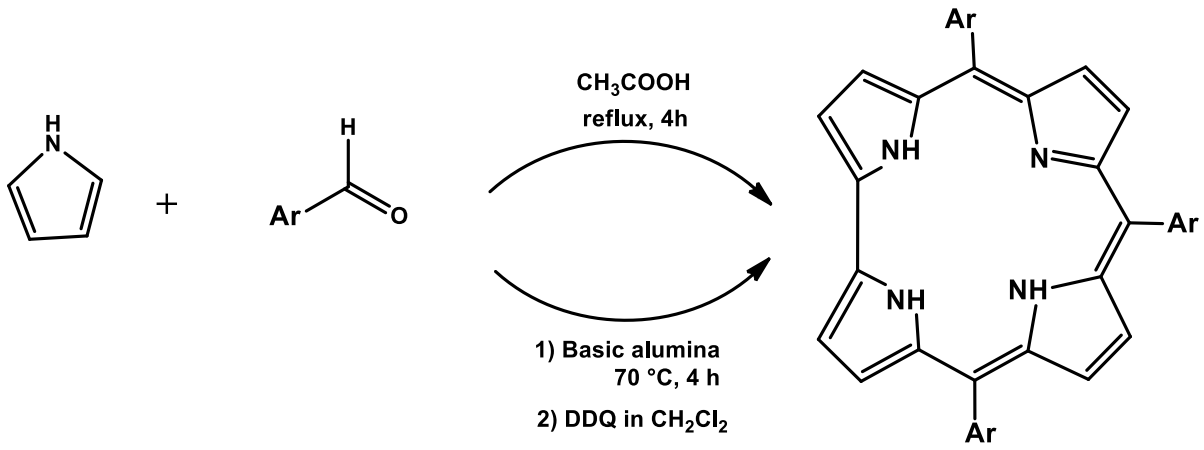
1.2 One-Pot Synthesis of Corroles

The multistep syntheses of corroles were difficult and tedious. One-pot synthesis of corroles from commercially available starting materials was therefore important. The synthesis and functionalization of corroles have been reviewed extensively.[9,10,11] Thanks to the all these great efforts, a wide library of synthetic procedures are now available for corroles.

Particularly, one-pot synthesis of *meso*-triarylcorroles played a major role in the development of corrole chemistry. Like porphyrins, *meso*-carbon atoms of corroles are very reactive and most prone to oxidation. Hence, *meso*-substituted porphyrins and corroles are the most stable derivatives. Since corroles are more electron-rich than porphyrins, and much more sensitive to oxidation, *meso*-substitutions are particularly useful for corroles. In addition, *meso*-aryl substitution enables diverse functionalization, both at *meso*-aryl and *β*-pyrrolic positions.

Two research groups working independently reported the first one-pot synthesis of *meso*-triarylcorroles.[7,8] The research group of Paolesse reported modified Rothemund procedure with 3:1 pyrrole to aldehyde ratio and obtained 5,10,15-triphenylcorrole (Scheme 1.1, top).[7] Gross and coworkers reported solvent-free synthesis with equimolar mixture of the aldehyde

and pyrrole on a solid support and obtained 5,10,15-tris(pentafluorophenyl)corrole (Scheme 1.1, bottom).[8]



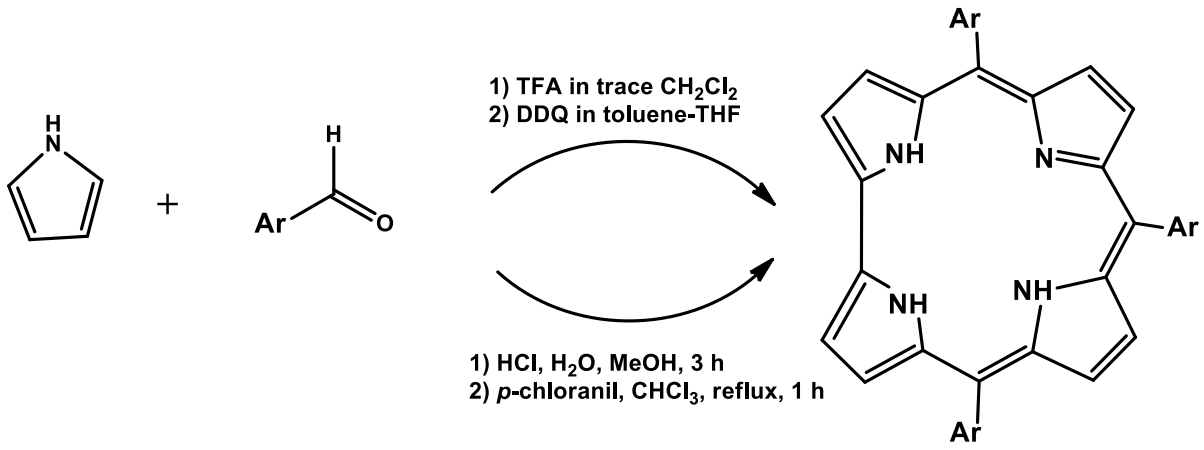
Scheme 1.1. The first one-pot synthesis of corroles reported by research groups of Paolesse[7] (top, Ar= -Ph) and Gross[8] (bottom, Ar= -PhF_5).

The solvent-free procedure was initially limited to electron-deficient corroles. Ghosh and coworkers proved that the method was more general and reported a variety of both electron-rich and-deficient corroles.[12] They also reported the synthesis of *β*-octafluorinated *meso*-triarylcorroles using the same method, starting with 3,4-difluoropyrrole and aryl aldehydes.[13] The research group of Paolesse also showed that their modified Rothemund procedure was applicable to a large variety of aryl aldehydes.[14] However a significant drawback of this procedure was the simultaneous formation of the corresponding porphyrin, with the only exception being 5,10,15-tris(4-nitrophenyl)corrole which was isolated in good yield without a porphyrin byproduct. With similar chromatographic retention factors, the separation of corrole from porphyrin was relatively tedious and accordingly nowadays alternative synthetic approaches are preferred.

In search of a better method, Paolesse and coworkers modified the Lindsey porphyrin synthesis which involved condensation of pyrrole and aldehyde in dichloromethane using trifluoroacetic acid (TFA) as a catalyst, followed by oxidation with *p*-chloranil.[15] A large excess of pyrrole was necessary in order to drive the reaction towards the formation of corrole precursor bilane, instead of the porphyrin precursor porphyrinogen. In this way, without the porphyrin byproduct, a large variety of *meso*-triarylcorroles were synthesized

including the use of sterically hindered aldehydes which were not possible in the previous synthesis.

The research group of Gryko developed pyrrole-aldehyde condensation, using TFA as a catalyst, and adjusting pyrrole-aldehyde ratio according to the reactivity of the aromatic aldehydes.[16] The method was applied to a large variety of aromatic aldehydes (Scheme 1.2, top). The *trans*-A_2B-corroles could also be synthesized with the same procedures if the synthesis was started from dipyrromethanes instead of pyrrole.



Scheme 1.2. The synthesis of *meso*-triaryl corroles reported by Gryko and coworkers (Ar= Aryl).[16,17]

A breakthrough in corrole synthesis came when Gryko and coworkers reported a two-pot synthesis of corrole using 2:1 pyrrole/aldehyde, in a mixture of MeOH and H_2O, catalyzed by HCl, following with oxidation by *p*-chloranil (Scheme 1.2, bottom).[17] The reaction conditions were carefully optimized to favor bilane formation. In addition, due to lower solubility of the bilane in water, an optimum ratio of 1:1 H_2O/MeOH was adjusted to favor the precipitation of bilane before the formation of higher oligocondensates. The method was general for many types of aldehydes and the yields were among the highest reported yields (14-27%). The same procedure was also optimized to synthesize *trans*-A_2B-corroles in high yields. This procedure has become the preferred method for corrole synthesis today. Interestingly, although this method was the most general and successful for corrole synthesis, it did not work for the preparation of 5,10,15-tris(pentafluorophenyl)corrole. The solvent-free method is still used to synthesize this particular corrole.[8,18]

1.3 Applications of Corroles

The availability as well as special features have led corroles to enjoy high popularity in terms of applications. Corroles have been utilized as catalysts, sensors, solar cells and anticancer drugs. The applications of corroles have been summarized in two detailed reviews written in 2007[19] and 2009.[20]. Fe and Mn corroles have been leading corroles in terms of applications in catalysis.[20] Other metals such as Cr and Co are also continuously being incorporated.[19]

Especially in medicinal applications, water-soluble metallocorroles have exhibited remarkable successes in recent years. A water-soluble sulfonated gallium(III) corrole has been shown to have significant *in vivo* anti-tumor activity in photodynamic therapy (PDT) experiments.[21] Moreover, the strong fluorescence of gallium(III) corrole enables efficient tumor detection, safe targeting and in vivo visualization of the therapeutic effect. Various water-soluble metallocorroles with different functional groups have been tested, among all, bis-sulfonated Al(III), Mn(III), and particularly Ga(III) corroles have been shown strong cytostatic and cytotoxic action against several human cancer cell lines.[22] Phosphorus(V) 5,10,15-tris(4-methoxycarbonylphenyl)corrole (Figure 1.2) has been demonstrated to be a potential bioimaging agent, more effectively than phosphorus(V) tetraphenylporphyrin counterparts.[23]

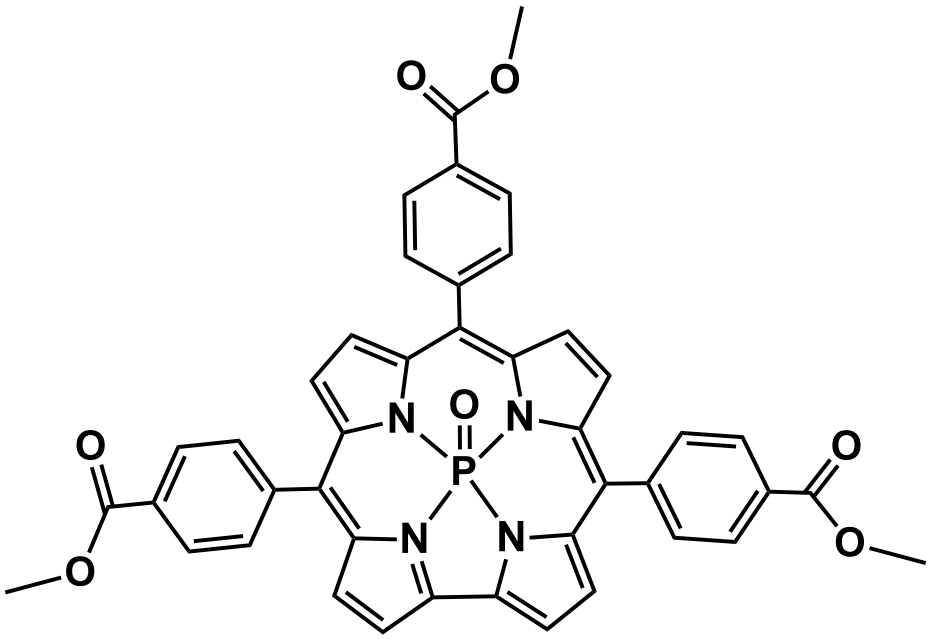


Figure 1.2. Phosphorus(V) 5,10,15-tris(4-methoxycarbonylphenyl)corrole.[23]

In efforts aimed at developing diabetes drugs, a positively charged Mn(III) corrole (Figure 1.3) has been shown to prevent intracellular nitration and protect rat pancreatic *beta* cells.[24] Another water-soluble negatively charged sulfonated Fe(III) corrole significantly reduced cataract incidents in diabetic rats, and also led to improved kidney function and lipid profile.[25] The mechanisms were thought to function by disarming reactive oxygen and nitrogen species (ROS/RNS).

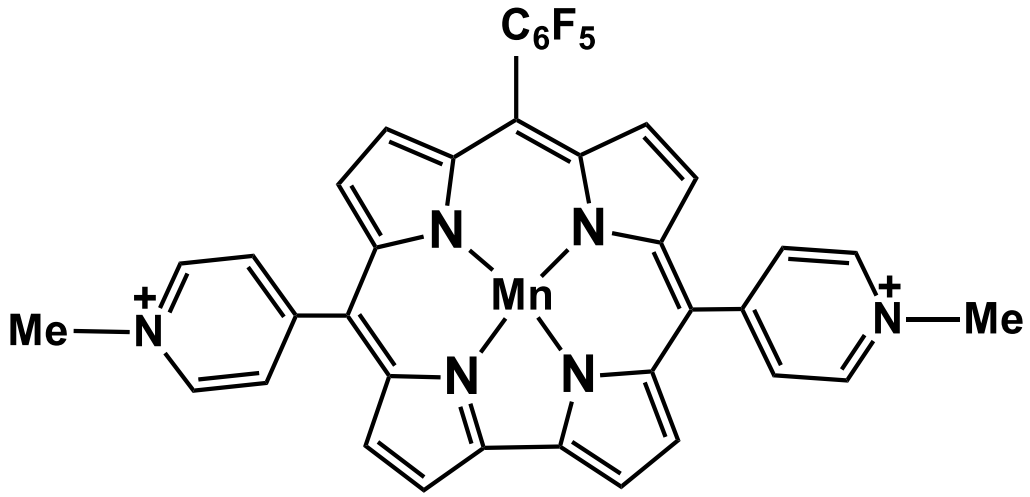


Figure 1.3. Positively charged Mn(III) corrole which prevented intracellular nitration.[24]

Numerous nonmedical applications have emerged as well. Co(III) hangman β-octafluoro corrole was found to be an active water splitting catalyst.[26] The effectiveness of the reported corrole was the highest among other molecular cobalt-based water oxidation catalysts. Au(III) corroles have been used for high performance organic solar cells (OSC).[27] Carbomethoxyphenyl substituted free-base corroles have been shown to be efficient basic anion detectors.[28] Positively charged Sb(III) and P(V) corroles have been found to severely damage fungal spores and inhibit their growth *via* photodynamic inactivation, thus potentially promising new antifungal agents.[29]

1.4 Properties of free-base corroles

The most characteristic feature of the corrole is the contracted core owing to the direct pyrrole-pyrrole link. A free-base corrole has three inner N-H protons and hence gives rise to a trianionic ligand. Recall that porphyrin and corrin are respectively dianionic and monoionic ligands. The smaller cavity and trianionic nature make corroles tightly binding ligands, and enable them to form stable, high-valent metal complexes. Corroles are more electron-rich

than porphyrins. The 18 π-aromatic electrons are shared among fewer atoms in corroles than in porphyrins. The UV-vis spectra of corroles are qualitatively similar to those of analogous porphyrins which display an intense Soret band at around 400 nm and several Q-bands at 500-650 nm.

Like typical aromatic compounds unsubstituted free-base corroles may be naively expected to be planar. But crystallographic studies have revealed significant distortions from planarity regardless of the peripheral substitution.[18,15,30,31] The non-planarity is caused by steric crowding of the three N-H protons in the rather small corrole cavity (Figure 1.4).

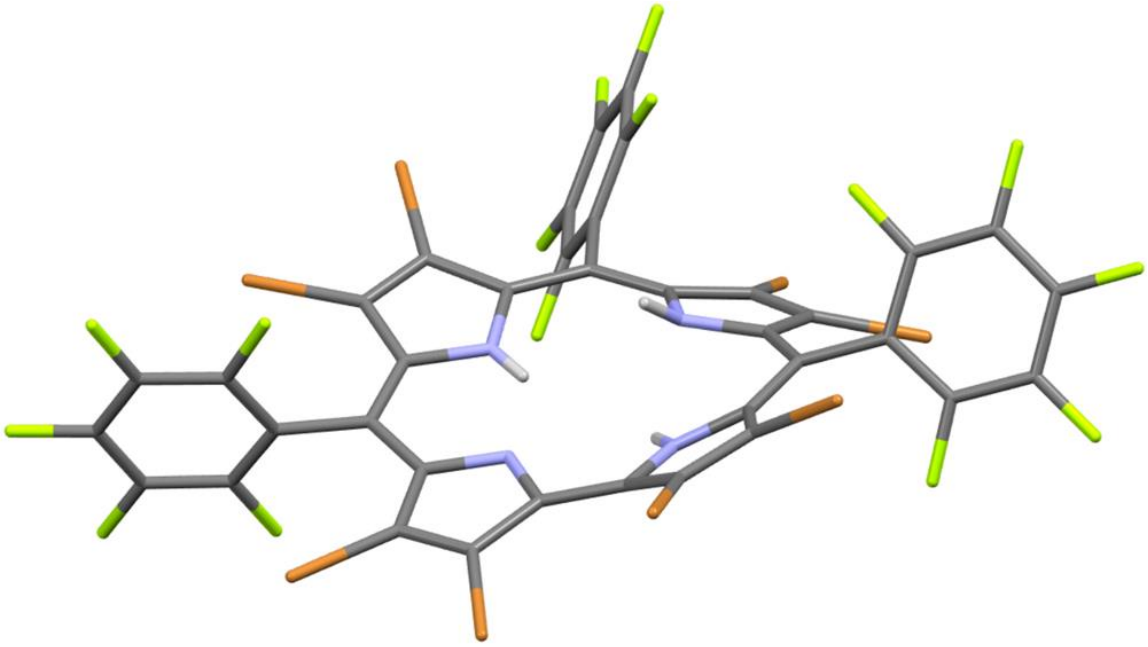


Figure 1.4. The X-ray structure of *β*-octabromo-meso-tris(pentafluorophenyl)corrole.[31]

As shown in paper II, the DFT calculations also suggest that the main reason for nonplanarity is the steric interactions among the three central hydrogens, and that the steric crowding on the corrole periphery has only a small effect.[30] The crystal structures of *meso*-tris(penta-fluorophenyl)corrole, H_3[TPFPC][18] and *β*-octabromo-*meso*-tris(pentafluorophenyl)corrole, H_3[Br_8TPFPC][30,31] (Figure 1.4) are both nonplanar, but the latter is only slightly more nonplanar than the former. In contrast and not surprisingly, sterically unhindered free-base porphyrins have a planar structure.[32]

The porphyrin analog of the above-mentioned corrole, *meso*-tetrakis(pentafluorophenyl)-porphyrin (H_2TFPP) is completely planar, whereas *β*-octabromo-*meso*-tetrakis(pentafluoro-

phenyl)porphyrin (H_2Br_8TFPP) is severely distorted.[32] On the other hand, *β*-octafluoro-*meso*-tetrakis-(pentafluorophenyl)porphyrin (H_2F_8TFPP) is essentially planar, suggesting that peripheral crowding with small fluorine atoms do not cause steric strain on the porphyrin ring.[33]

Corroles have a much more rigid structure than porphyrins due to the direct pyrrole-pyrrole linkage. Thus, metalloporphyrin structures with ruffled and saddled conformations are quite common. In contrast, a great majority of metallocorroles are planar.[34] Even peripherally crowded, sterically strained metallocorroles such as *β*-octabromo-*meso*-tris(pentafluoro-phenyl)corrolato-iridium(III)[35] (Figure 1.5) and *β*-octabromo-*meso*-tris(2,6-dichlorophenyl)-corrolato-manganese(III)[36] have planar structures.

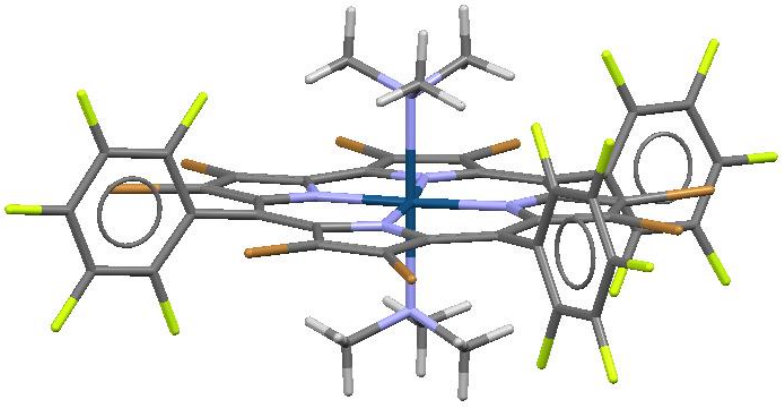


Figure 1.5. The crystal structure of *β*-octabromo-*meso*-tris(pentafluorophenyl)corrolato-iridium(III).[35]

Copper corroles are a key exception in this regard; they are relatively strongly saddled even in sterically unhindered complexes as a result of a specific Cu(d)–corrole(π) orbital interaction (Figure 1.6).[37]

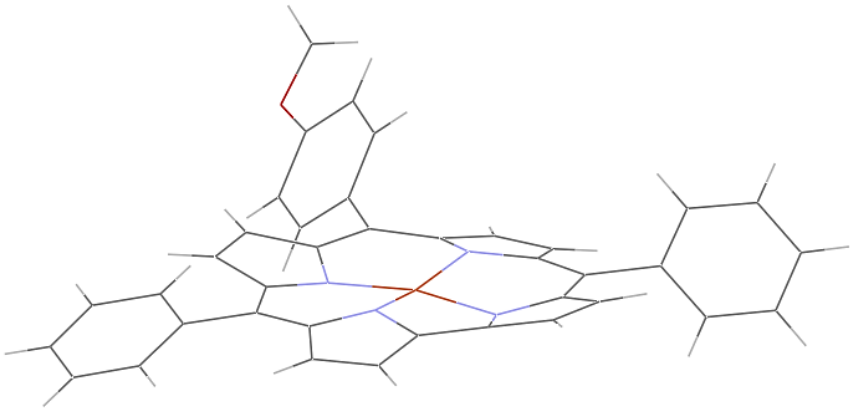
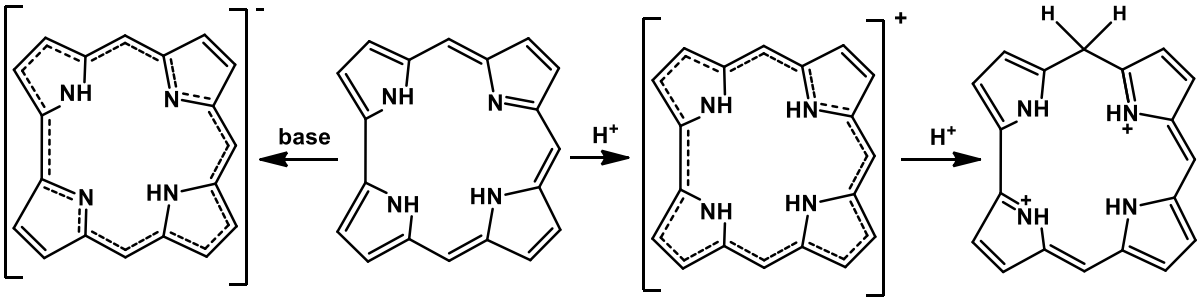


Figure 1.6. The crystal structure of a sterically unhindered copper *meso*-triarylcorrole displaying the saddled conformation.[37]

Corroles are more acidic than porphyrins, in fact they are among the most acidic free-base tetrapyrrolic macrocycles. Free-base corroles [(Cor)H_3] readily form monoanionic species [(Cor)H_2]$^-$ even in weakly basic solvents such as DMF. The strongly acidic nature of corrole is attributed to the steric relief upon loss of one of the three N-H protons. The monoanionic corrole is still aromatic and retains an intense Soret band. Acidic solvents can generate monocationic corroles [(Cor)H_4]$^+$ which also retains their aromaticity (Scheme 1.3). In addition, both monoanionic and monocationic free-base corroles have much stronger Q bands than the neutral corrole.[38] The easy generation of [(Cor)H_4]$^+$ arises from the fact that once the inner core contains three N-H protons, adding the forth proton causes relatively little additional steric strain.[20] Strongly acidic conditions can however disrupt the aromaticity by protonation at *meso*-5 position (Scheme 1.3).[39]



Scheme 1.3. Structural changes of the corrole ring in basic and acidic conditions.[38,39]

Basic peripheral substituents on free-base corroles tend to protonate before the inner core nitrogens. For example, in the case of the *meso*-pyridyl substituted corrole, only after the protonation of all *meso*-pyridyl nitrogens the protonation of the forth central nitrogen commences.[40] As expected, electron-withdrawing substituents decrease the basicity of the inner core nitrogens, or increase the acidity of the corrole. Thus, corroles with electron deficient substituents such as H_3[Br_8TPFPC] display one of the strongest acidic character among all other tetrapyrrolic macrocycles.

Monoprotonated and monoanionic corroles also form during oxidation and reduction reactions[41]. After the first one-electron reduction, [(Cor)H_3] rapidly converts to [(Cor)H_2]$^-$. The first oxidation of [(Cor)H_3] generates a mixture of ($^\bullet$Cor)H_2 and [(Cor)H_4]$^+$. Oxidation potentials of protonated corroles display two distinct characters, one for corroles with sterically hindered *meso*-substituents, and the other for non-sterically hindered *meso*-substituents.[41]

1.5 Corrole NH Tautomerism

The inner core hydrogens of the corrole are not localized on three nitrogens but rather move rapidly between them to give NH tautomers.[42] According to the calculations done by Ghosh and Jynge,[43] there is no significant energy difference between the two possible tautomers, which differ only by a couple of kcal mol^{-1}. Crystal structures of free-base corroles also confirm this, since both tautomers have been experimentally observed.[18,15,31,44,45]

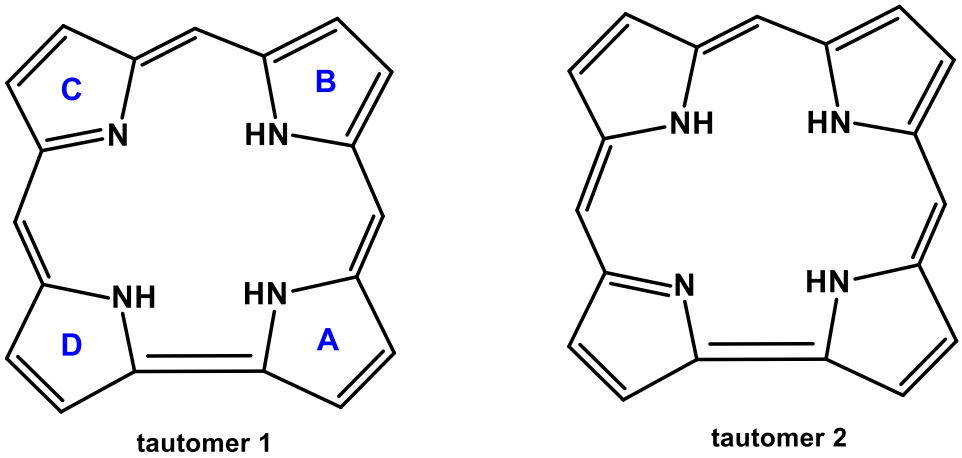
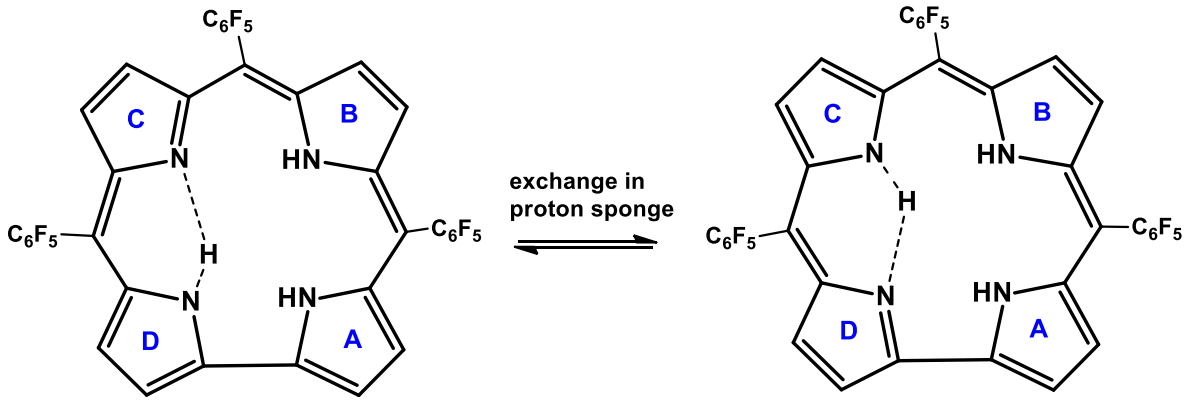


Figure 1.7. The two possible tautomers of the free-base corrole and the marking of the rings.

According to DFT calculations, the two tautomers of H_3[Br_8TPFPC] are almost perfectly equienergetic.[30,31] In the crystal structure of H_3[Br_8TPFPC], the imine nitrogen is in ring D which corresponds to tautomer 2 (Figure 1.7).[31] In this structure, pyrrole rings A and B are found to be strongly tilted, whereas rings C and D are roughly in the mean plane of the macrocycle (Figure 1.4). These structural details and DFT calculations were presented in paper III. The observed "half-saddling" is also present in the other free-base corrole crystal structures but is somewhat more pronounced in this particular case due to peripheral steric crowding. In the crystal structure of H_3[TPFPC], the imine nitrogen was located at ring C which corresponds to tautomer 1.[18]

Gross and coworkers[46] investigated in detail the low temperature NMR of ^{15}N labeled H_3[TPFPC]. Based on the data gathered, it was possible to locate the inner hydrogens at -72 °C in which the imine nitrogen was proposed to be at ring C. An extensive NMR study of ^{15}N-enriched H_3[TPFPC] was also carried by Szymanski *et al*.[47] According to their results it was not possible to locate the imine nitrogen. The two tautomers were found to be in rapid dynamic equilibrium (Scheme 1.4).[47] Even at the lowest measured temperature -88 °C, the rapid interconversion of tautomers 1 and 2 was observed, but with a strong shift towards tautomer 1 by a factor of about 4.



Scheme 1.4. The tautomerization process of H_3[TPFPC] was assessed to remain very fast even at the lowest temperatures.[47]

Szymanski *et al.*[47] proposed that when the proton is located at ring D, it engages in a strong hydrogen bond with the nitrogen atom at ring C, and a similar interaction occurs vice versa. The process was described with a sponge proton which is rapidly exchanging between the pyrrole rings C and D (Scheme 1.4). They also suggested that these interactions are likely responsible for the perfect coplanar alignment of ring C and D.

During the stepwise protonation studies of *meso*-pyrimidinyl-substituted free-base corrole, it was discovered that the formation of protonated species was highly temperature dependent. Two steps in the titration curve were observed at lower temperatures, whereas one-step formation of protonated species was found at higher temperatures. The two steps in protonation rate at lower temperatures were attributed to individual tautomers.[48]

Recently it was discovered that individual tautomers display different fluorescence spectra.[49] Furthermore, the rapid NH tautomerism equilibrium directly influences the fluorescence. Thus, fluorescence emission was found to be highly temperature dependent due to the alteration in the tautomer equilibrium. The individual absorption spectra of the two NH tautomers were assigned with a combined experimental and theoretical study. Overall, tautomer 1 exhibited blue-shifted absorption spectra, relative to tautomer 2.[50]

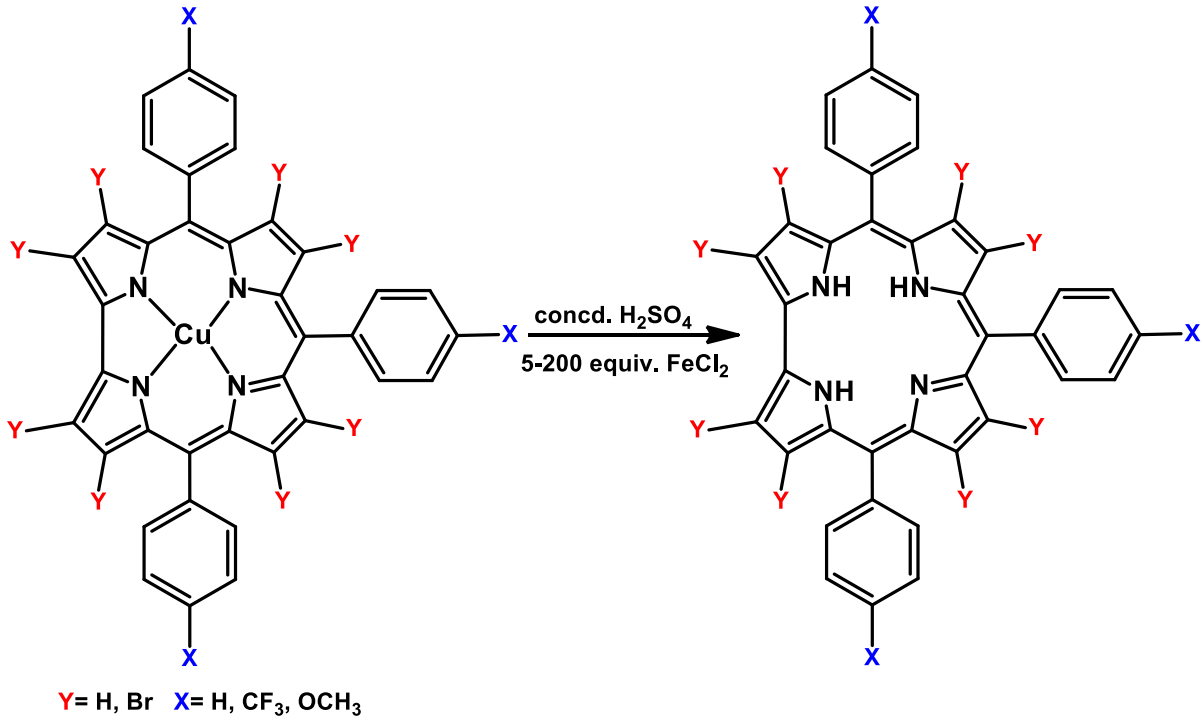
2. Demetalation of Corrole Complexes

Despite the important developments in synthetic corrole chemistry, the field has long been handicapped by the lack of procedures for demetalation of metallocorroles. In porphyrin chemistry, metalation/demetalation protocols are relatively routine.[51] In a few cases, metals are used as a template for the cyclization reaction that leads to porphyrins. Functionalization reactions of porphyrins are often performed on metalloporphyrins. Metal coordination exerts a variety of activating and directing effects on the different functionalization processes. Metal coordination is also necessary to protect the inner core nitrogens from electrophilic reagents. In some cases, the free-bases are quite unstable and decompose rapidly whereas the corresponding metal complexes are quite stable. After functionalization, derivatized free-base porphyrins may be obtained by well-established demetalation procedures.[51] Demetalation is often performed under acidic conditions, the strength of the acid or acid mixtures are prepared depending upon the particular metal complex. Although not common, reductive demetalation with using $NaBH_4$ is also known.[52]

Until recently, no procedure was available for demetalation of metallocorroles. This was considered an unfortunate obstacle for the syntheses of new functionalized corroles. Unlike porphyrins, demetalation of corroles is much more challenging. The difficulty of demetalating corroles can be attributed to several features: shorter and stronger metal-nitrogen bonds due to the smaller core, lower stability hence easy decomposition, and the higher acidity of corroles relative to porphyrins. As a consequence, more acidic and rigorous conditions are necessary for corrole demetalation. Since corroles are reactive macrocycles, increased rigorous conditions often result in undesired corrole modifications or in the decomposition of the macrocycle. Thus, until recently, only two demetalation procedures were reported for corroles, one for Mn[OEC] (OEC=octaethylcorrole), using HBr in acetic acid,[53] and the other for Ag(III) triarylcorroles with aqueous HCl in a biphasic system using $CHCl_3$ or CH_2Cl_2.[54] However, neither the experimental details nor the yields of these reactions were reported. In addition, the reactions were very specific and could not be extended to other metallocorroles.

The situation started to change in 2008 when Paolesse and coworkers reported a general demetalation procedure, with an added title of “an old dream turning into reality”.[55] The procedure involved using the $CHCl_3/H_2SO_4$ acidic mixture. In my own study I have

developed a reductive demetalation method using concentrated H_2SO_4 with 5-200 equivalent of $FeCl_2$ or $SnCl_2$ as a reducing agent.[56,57] The reaction was general and various electron-rich and deficient copper corroles could be demetalated in good yields (Scheme 2.1).



Scheme 2.1. Reductive demetalation of copper corroles.[56,57]

Before the publication of Paolesse's $CHCl_3/H_2SO_4$ method, I was also studying similar mixtures with various organic solvents. I found that the yields obtained with the reductive demetalation were considerably better than with $CHCl_3/H_2SO_4$, CH_2Cl_2/H_2SO_4, or H_2SO_4 alone. As shown in Table 2.1, particularly with electron-rich oxidation-prone metallocorroles the reductive protocol was essential. The experimental procedures are presented in Paper I.

Table 2.1. Comparison of demetalation yields (%) under different reaction conditions.[56,57]

Complex	H_2SO_4, $CHCl_3$	H_2SO_4, CH_2Cl_2	H_2SO_4 only	H_2SO_4 + $FeCl_2$	H_2SO_4 + $SnCl_2$
Cu[TPC]	18	18	-	68	77
Cu[T(*p*-OMeP)C]	-	-	-	75	77
Cu[T(*p*-CF_3P)C]	Not attempted	26	37	74	Inseparable mixture
Cu[Br_8TPC]	Inseparable impurities	Inseparable impurities	Inseparable impurities	79	Inseparable mixture
Cu[Br_8T(*p*-CF_3P)C]	10	22	33	82	85
Cu[Br_8T(*p*-OCH_3P)C]	35	79	-	81	85

Subsequently, Dehaen and coworkers also reported the reductive demetalation of copper corroles.[58] The procedure involved using HCl and $SnCl_2$ in acetonitrile/dichloromethane (2:1) solution to ensure sufficient solubility of both the tin salt and the Cu corrole. Chang and coworkers developed a similar procedure for reductive demetalation of manganese corroles in CH_2Cl_2/HCl by using $SnCl_2$ as a reducing agent.[59] However as for electron deficient Mn(III)-5,10,15-tris(pentafluorophenyl)corrole acid-induced demetalation in HOAc–H_2SO_4 (V/V = 3:1) was used.[59] Later on, Paolesse *et al* reported a list of procedures for the demetalation of silver corroles, including a reductive method using $NaBH_4$.[60] Very recently, tin corroles were demetalated using the Grignard reagent methylmagnesium chloride.[61]

Thanks to all the joined efforts by different research groups, the demetalation procedures have started to enrich the corrole synthetic and functionalization chemistry. The first gold corroles were synthesized from *β*-octabromo corroles obtained *via* demetalation of the corresponding metal complexes.[62,63] The structure of *β*-octabrominated Au(III) corrole is shown in Figure 2.1.[63]

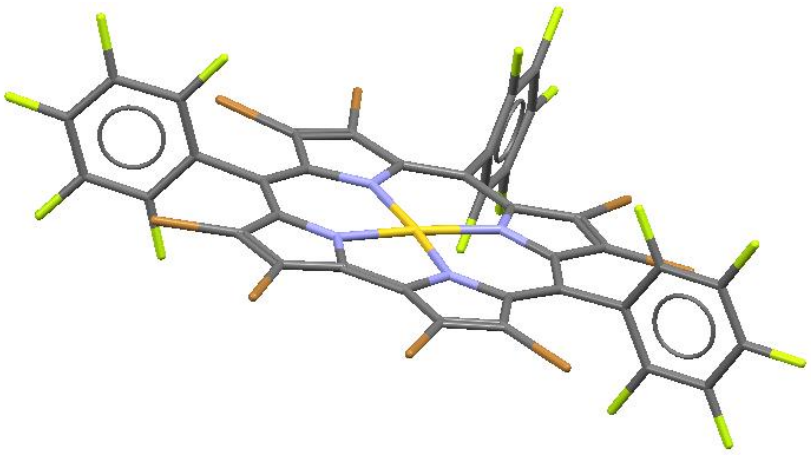


Figure 2.1. The crystal structure of an *β*-octabrominated Au(III) corrole.[63]

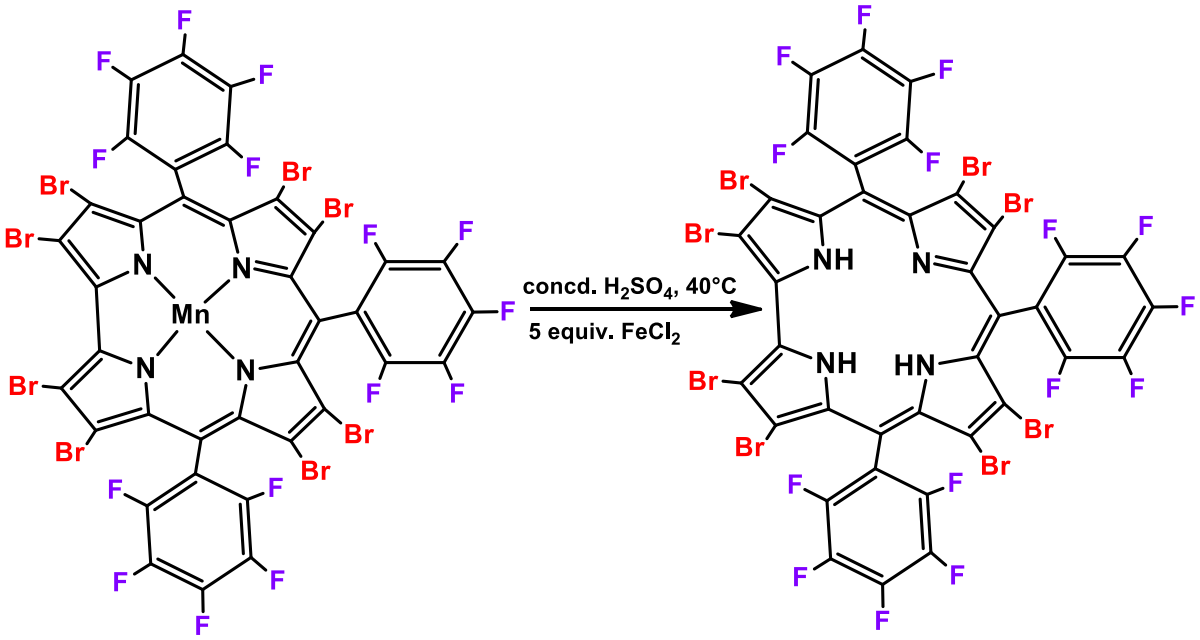
Corrole–porphyrin conjugates were also synthesized and functionalized by applying demetalation methods.[64] New corrole ligands were prepared by functionalizing bismuth corroles in various Pd-catalyzed coupling reactions, followed by successful demetalations.[65]

2.1 Synthesis of free-base *β*-octabromo-*meso*-tris(pentafluorophenyl)corrole

One of my main goal during demetalation studies was to obtain free-base *β*-octabromo-*meso*-tris(pentafluorophenyl)corrole, H_3[Br_8TPFPC]. Various metal complexes of this corrole were previously obtained and exploited for applications.[66,35] In fact, the metal complexes of H_3[Br_8TPFPC] were among the most popular complexes in terms of applications.[19] The electron-deficiency created by the three pentafluorophenyl and eight bromine atoms gives superior stability to the corrole. Unfortunately, full bromination of free-base H_3[Br_8TPFPC] is not possible. Therefore, bromination reactions were performed on metallo-[TPFPC] derivatives. However, not all metallo-[TPFPC] can be fully brominated. Hence, it was important to develop a synthesis for octabrominated free-base corrole ligands, particularly H_3[Br_8TPFPC].

Using previously reported demetalation procedures[55,57,58] on copper corroles it was not possible to demetalate Cu[Br_8TPFPC]. Therefore, I turned my attention to other metal complexes. When I applied my own H_2SO_4/$FeCl_2$ method to Mn[Br_8TPFPC][66] at room temperature, the free-base H_3[Br_8TPFPC] was isolated in about 50% yield. An additional

finding was the effect of temperature. The demetalation was performed at 40 °C under the same conditions and the yield increased to 86% relative to room temperature. At 45 °C the purity of the product and the yield decreased slightly. The temperature was optimized at 40 °C. Using $SnCl_2$ instead of $FeCl_2$ did not affect the yields. The reaction with optimized conditions is shown in Scheme 2.2.



Scheme 2.2. The synthesis of $H_3[Br_8TPFPC]$ *via* reductive demetalation of $Mn[Br_8TPFPC]$.

X-ray quality crystals of $H_3[Br_8TPFPC]$ were grown in CH_2Cl_2/*n*-hexane solution by slow evaporation.[30] The experimental details are given in Paper II. Unfortunately, the crystals were of poor quality and the inner hydrogens could not be located. Nevertheless, it revealed a pronounced saddled conformation which was the strongest nonplanar distortions observed for any free-base corrole. After multiple attempts, it was possible to obtain a high-resolution X-ray structure of $H_3[Br_8TPFPC]$, where the inner hydrogens could be located.[31] The structure is shown in chapter 1, Figure 1.4, and the structural details are presented in Paper III.

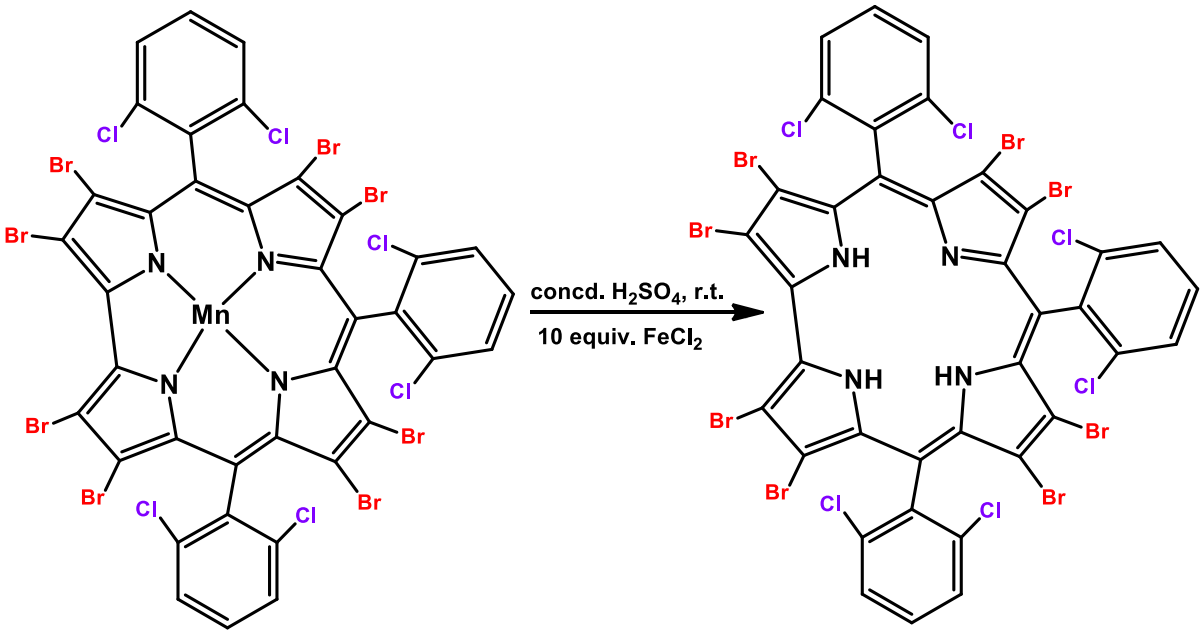
2.2 Synthesis of free-base *β*-octabromo-*meso*-tris(2,6-dichlorophenyl)corrole

Another important corrole ligand in terms of applications is *β*-octabromo-*meso*-tris(2,6-dichlorophenyl)corrole (H_3[Br_8TDCPC]) shown in Scheme 2.3. The manganese complex Mn[Br_8TDCPC] (Scheme 2.3) was recently prepared and showed superior stability during application reactions.[36] The free-base derivative of the octabrominated corrole H_3[Br_8TDCPC] was not available, and I turned my attention towards synthesizing the free-base H_3[Br_8TDCPC] *via* demetalation reactions. Since the *β*-octabromination of the corrole ring is typically easiest with copper complexes, my first demetalation attempt was performed on copper *β*-octabromo-*meso*-tris(2,6-dichlorophenyl)corrole, Cu[Br_8TDCPC]. When Dehaen and coworkers[58] reported the synthesis of [Cu(Br_8TDCPC] using a similar procedure reported by the Ghosh group,[12] their goal was to obtain the free-base H_3[Br_8TDCPC] by applying the demetalation procedure described in the same study, viz. HCl/$SnCl_2$ in acetonitrile/dichloro-methane (2:1). The procedure worked well in demetalating the unbrominated derivative Cu[TDCPC], but failed to demetalate Cu[Br_8TDCPC] to the desired octabromo free-base. Thereafter, they synthesized Cu[Cl_8TDCPC], and reported the demetalation of Cu[Cl_8TDCPC] in 20% yield by applying the same method.

I tried the same procedure with [CuBr_8TDCPC] by substituting $SnCl_2$ with $FeCl_2$, bearing in mind that $FeCl_2$ gave better results in our previous study.[57] The reaction caused complete decomposition of the starting material. The partial or the complete decomposition of the corrole macrocycle in demetalation reactions using organic solvents had been observed earlier.[56,57] Therefore, I performed the same reaction by eliminating the organic solvent. The procedure still resulted in complete decomposition. According to Dehaen and coworkers, the decomposition products are partially debrominated (mostly tetra- and pentabromo) free-base corroles.[58] My own procedure[57], concentrated H_2SO_4 together with $FeCl_2$ for 2 hours, at room temperature demetalated Cu[Br_8TDCPC] in 8% yield with 79% of recovered Cu[Br_8TDCPC]. Applying higher temperature at 50 °C for 4 hours increased the yield to 14%. Longer reaction times did not improve the yield.

The low yield of the reaction led me to use the manganese complex Mn[Br_8TDCPC] as the starting metallocorrole. Initially, a reported synthetic procedure for Mn[Br_8TDCPC] was not available. While I was working on the synthesis, Gross and coworkers reported a method to obtain Mn[Br_8TDCPC].[36] With the starting material available, I tried to obtain

H_3[Br_8TDCPC] *via* demetalation reactions. Demetalation of Mn[Br_8TDCPC] was achieved using the same procedure as I developed for Mn[Br_8TPFPC],[30] but with the following slight adjustments to optimize the yields: (a) using 10 equivalents of $FeCl_2$ instead of 5, which increased the yield about 15% and (b) carrying out the reaction at room temperature rather than 40 °C. Ultimately, H_3[Br_8TDCPC] was obtained with 75% yield in 1.5 h of reaction time.[67] The reaction is shown in Scheme 2.3.



Scheme 2.3. The synthesis of H_3[Br_8TDCPC] *via* reductive demetalation of Mn[Br_8TDCPC].

The above experimental procedures are described in Paper IV.[67] In addition, improved syntheses of *β*-octabromo-*meso*-triarylcorrole derivatives are also presented. The purifications of the compounds *via* tedious column chromatographic separations were replaced by simple recrystallization, saving both time and solvents.[67]

3. Synthesis of Sterically Hindered Metallocorroles

Sterically hindered metallocorroles are of interest as potential shape-selective catalyts[19,68,69] and also as highly targeted reagents in medicinal applications.[70] In addition, peripheral steric crowding of the corrole macrocycle is also expected to prevent the formation of μ-oxo-bridged dimerization in iron corroles[71] and metal−metal-bonded dimer formation from ruthenium[72] corroles. My main contribution in this area has been the use of new sterically hindered ligands that I have developed (out of demetalation experiments) to synthesize some of the first sterically hindered iron corroles.

3.1 Iron Corroles

Iron has important functions in all living organisms. In heme proteins such as myoglobin, hemoglobin, peroxidases, and cytochromes P450, iron is coordinated at the center of a porphyrin ring. They are responsible for diverse biological functions such as transportation of diatomic gases, electron transfer and chemical catalysis. A great deal of research has been done both experimentally and computationally on characterization of reactive intermediates in all these processes.[73,74]

Cytochrome P450s are heme enzymes that catalyze the oxidation of organic substances. The most common reaction catalyzed by P450s is hydroxylation of C-H bonds which are otherwise inactive organic groups. Cytochrome P450 enzymes are found both in animals and plants, and even in bacteria and viruses. Cytochrome P450 enzymes are involved in the drug metabolism of approximately 75% of pharmaceuticals.[75] In the catalytic cycle, the highly reactive intermediate termed as compound I is thought be a high-valent iron complex (Figure 3.1).[76]

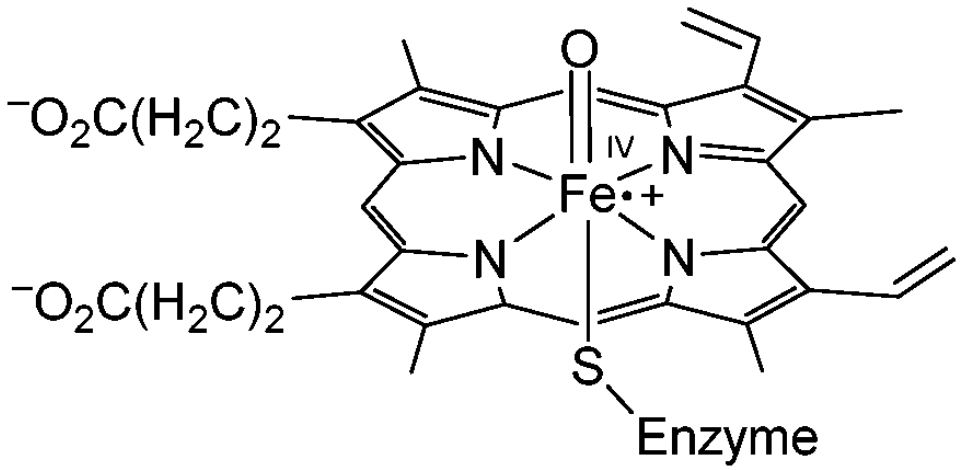


Figure 3.1. Compound I, an iron(IV)oxo porphyrin radical.[77]

Compound I has been studied theoretically for many years[78] but it was not captured and properly characterized until 2010.[79] It was generally concluded that this intermediate was too reactive to be trapped. Latest research suggest that P450 Compound I should be an iron(IV)oxo porphyrin radical species which abstracts hydrogen from substrate, forming an iron(IV)hydroxide that rapidly recombines with substrate to yield hydroxylated product.[79,80] An alternative reactive intermediate, perferryl iron(V)oxo was suggested but there was no substantial evidence to prove it.[81] Since complexes of iron porphyrins containing tetravalent iron occur as reactive intermediates in living systems, and isolated stable Fe(IV) porphyrins are quite rare,[82] corroles have emerged as promising compounds to understand the functions of heme enzymes in biological systems.

Iron corroles are most commonly *formally* at the Fe(IV) oxidation state.[3,71,83] However, many iron corroles also have noninnocent character.[83] For example, chloroiron corroles (Figure 3.2) were initially believed to be a high-valent Fe(IV)-Cl complexes,[3,71,84] but have later been formulated as intermediate-spin (S = 3/2) Fe(III) antiferromagnetically coupled to a corrole radical, as shown in Scheme 3.1.[6,83,85,86]

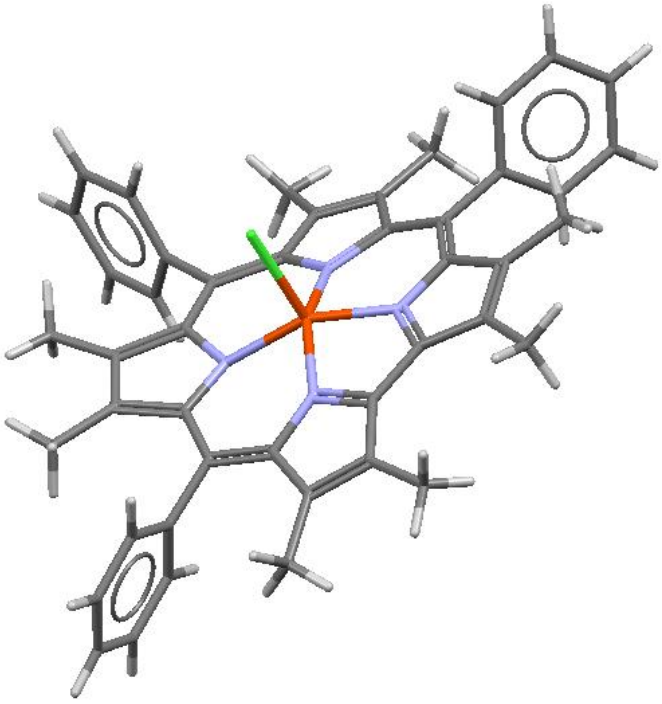
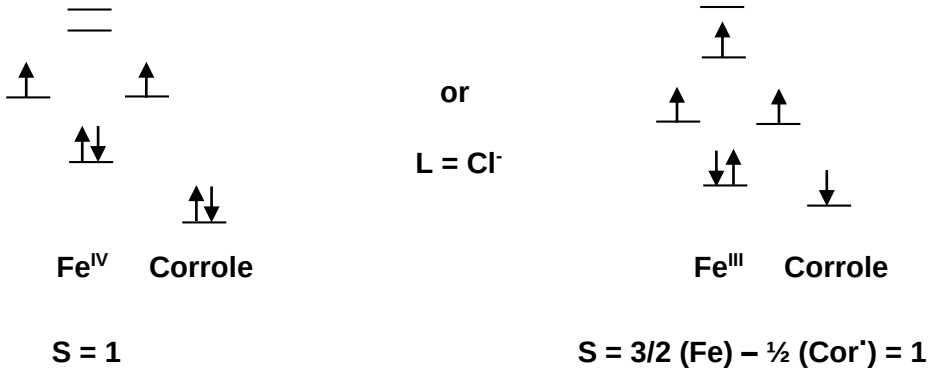


Figure 3.2. The X-ray structure of a chloroiron corrole, namely octamethyltriphenyl-corrolatoiron chloride (Fe(OMTPCorr)Cl).[85]



Scheme 3.1. The two potentials electronic configurations of chloroiron corrole. Left: Low spin d^4 S = 1 Fe(IV) coordinated to a $(corrolate)^{3-}$ anion. Right: Intermediate-spin d^5 S = 3/2 Fe(III) coordinated to a $(corrolate)^{2-}$ π-cation radical.[87]

Walker and coworkers suggested that based on NMR results, intermediate-spin Fe(III) π-cation radical was a more accurate description of the electronic configuration of chloroiron corroles.[83,85,88] Ghosh and coworkers also favored the intermediate-spin Fe(III) π-cation radical formulation for chloroiron corroles with combined electrochemical and DFT computational studies. [6,13,86] Recently, based on the Ab initio complete active space self-consistent field (CASSCF) calculations Ghosh and coworkers provided unambiguous support for the Fe(III) configuration for the chloroiron corroles.[89]

Walker and coworkers, analyzed all the experimental and computational data in a detailed review article, and concluded that the chloroiron complexes are best assigned as intermediate-spin Fe(III) π-cation radical configurations.[88] Gross, Neese and coworkers also reported that chloroiron corroles are best formulated as Fe(III) π-cation radicals based on combined experimental (Mossbauer spectroscopy) and computational (DFT) results in a recent study.[90] Nevertheless, Fe corrole in "true" high-valent form is also known, such as phenyliron corrole[3] (Figure 3.3), which is best formulated as low-spin Fe(IV)-Ph complex.[3,83,88]

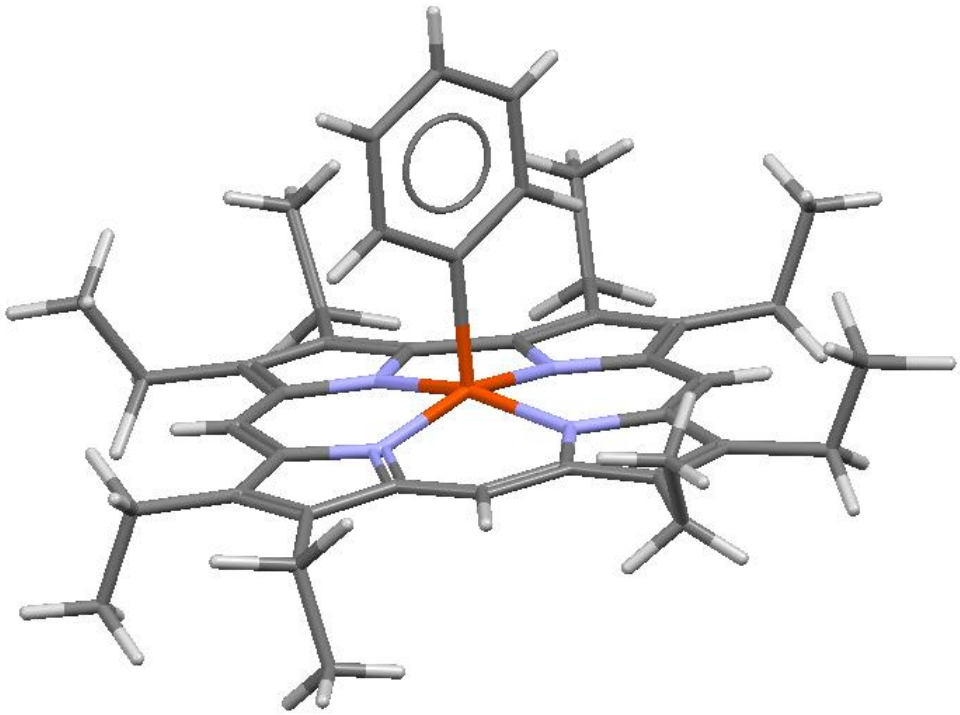
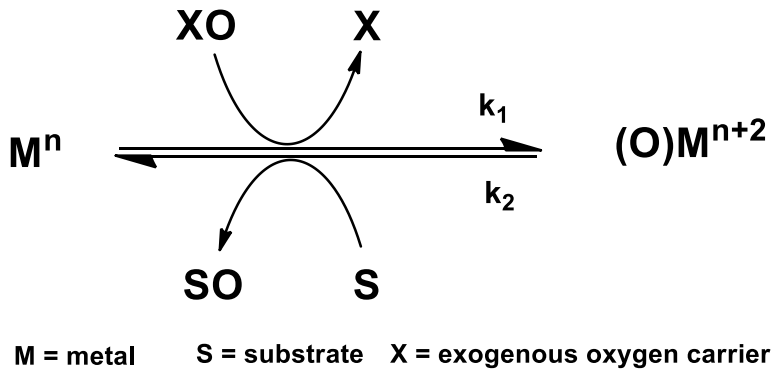


Figure 3.3. The crystal structure of a phenyliron corrole Fe(OECorr)Ph.[3]

Similar to porphyrins, the properties of corroles have enabled them to be used in numerous applications such as in catalysis and pharmaceutical drug development.[19] Iron corroles are among the leading metallocorroles in terms of applications.[20] Iron corroles have been utilized as a catalyst for aziridination of olefins *via* metal catalyzed nitrene-transfer,[91] epoxidation of olefins[92] and hydroxylation of alkanes[92] *via* oxygen-atom transfer (Scheme 3.2).



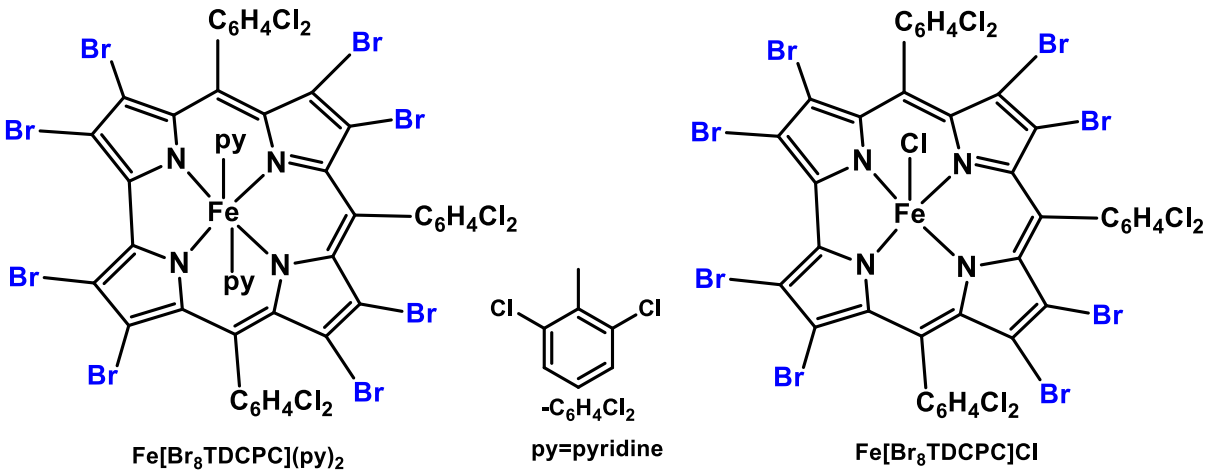
Scheme 3.2. Oxygen-atom transfer from exogenous oxygen carrier (XO) to metal catalyst (M^n), and from oxidized metal catalyst ($(O)M^{n+2}$) to substrate (S) to form oxidized substrate (SO), $k_2 >> k_1$.[93]

3.2 Synthesis of Iron Octabromocorroles

Electron-deficient corroles have been proven to be advantageous for catalysis.[36,66,94] It was proposed that electron-withdrawing groups may increase the dioxygen-binding ability.[94] It was also suggested that electron-withdrawing substituents increase the stability of the corrole macrocycle towards oxidative decomposition.[36,66]

Octabrominated iron corroles with these desirable properties have not been prepared until now. On the other hand, octabrominated manganese[36,66,95] and chromium[96] corroles had long been available. Therefore, highly electron-deficient and sterically crowded free-base octabromocorrole ligands obtained by the newly developed demetalation methods (see section 2.1 and 2.2) were utilized to synthesize the corresponding iron octabromocorroles. Molecular structures of the new iron corroles synthesized are shown in Schemes 3.3 and 3.4. The experimental and the structural details of $Fe[Br_8TDCPC](py)_2$ and $Fe[Br_8TDCPC]Cl$ are

presented in Paper IV. Fe[Br_8TDCPC](py)$_2$ was also characterized by X-ray diffraction analysis which is shown in Figure 3.4.



Scheme 3.3. Molecular structures of the newly synthesized complexes Fe[Br_8TDCPC](py)$_2$ and Fe[Br_8TDCPC]Cl.

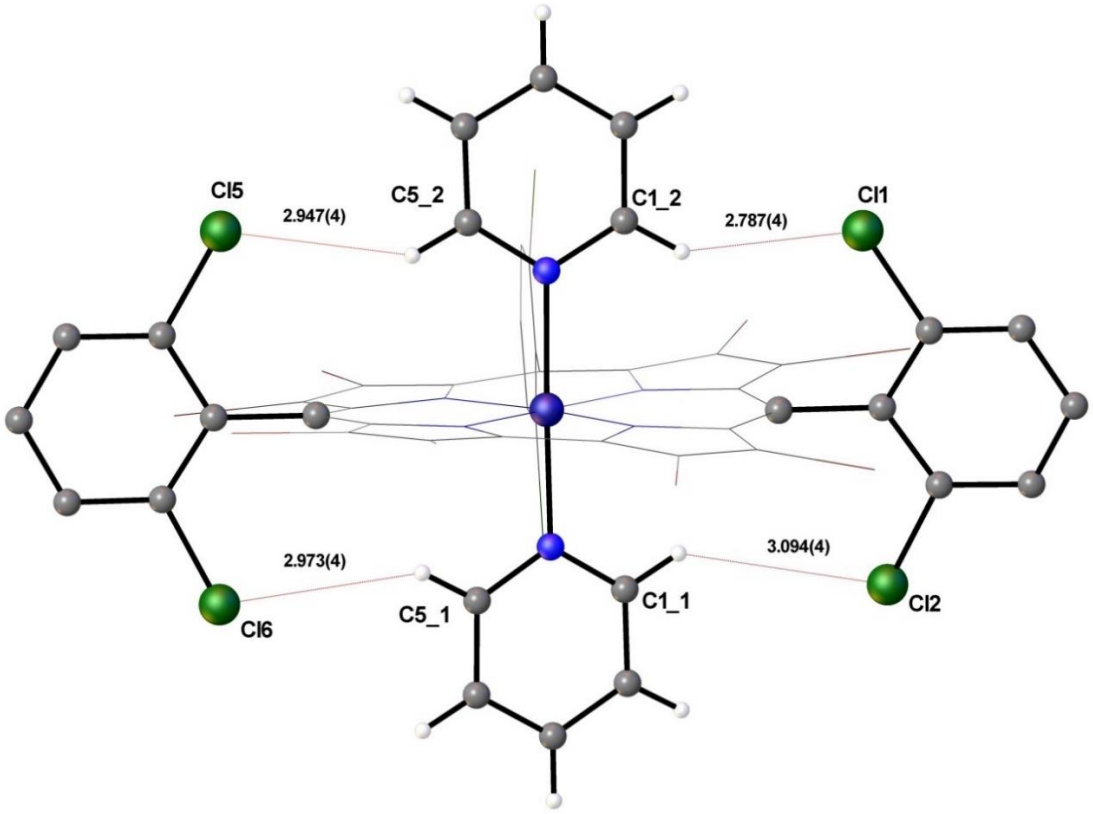
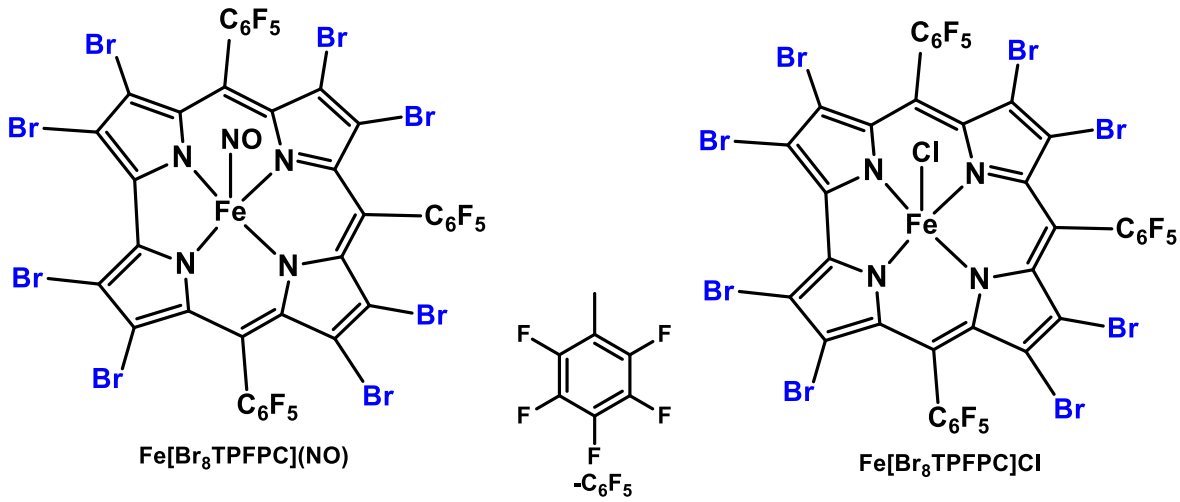


Figure 3.4. The X-ray structure of Fe[Br_8TDCPC](py)$_2$ showing C–H···Cl hydrogen bonding interactions.[67]



Scheme 3.4. The molecular structures of the newly synthesized complexes Fe[Br_8TPFPC](NO) and Fe[Br_8TPFPC]Cl.

The synthesis of Fe[Br_8TPFPC](NO) and Fe[Br_8TPFPC]Cl are described in Paper V. The structural details and DFT calculations are also given. X-ray structure of Fe[Br_8TPFPC](NO) is shown in Figure 3.5.[97] My contribution in Paper V has been the synthesis and spectroscopic characterization of Fe[Br_8TPFPC](NO) and Fe[Br_8TPFPC]Cl, and the crystallization of Fe[Br_8TPFPC](NO) for X-ray diffraction analysis. My ability to crystallize the unstable Fe[Br_8TPFPC](NO) under an NO atmosphere was considered an experimental tour de force by the referees of Paper V. See paper V for a detailed explanation for the instability of this compound. Note, however, that the theoretical analysis of the complex electronic structures of FeNO corroles was not my work, but that of my laboratory colleagues.

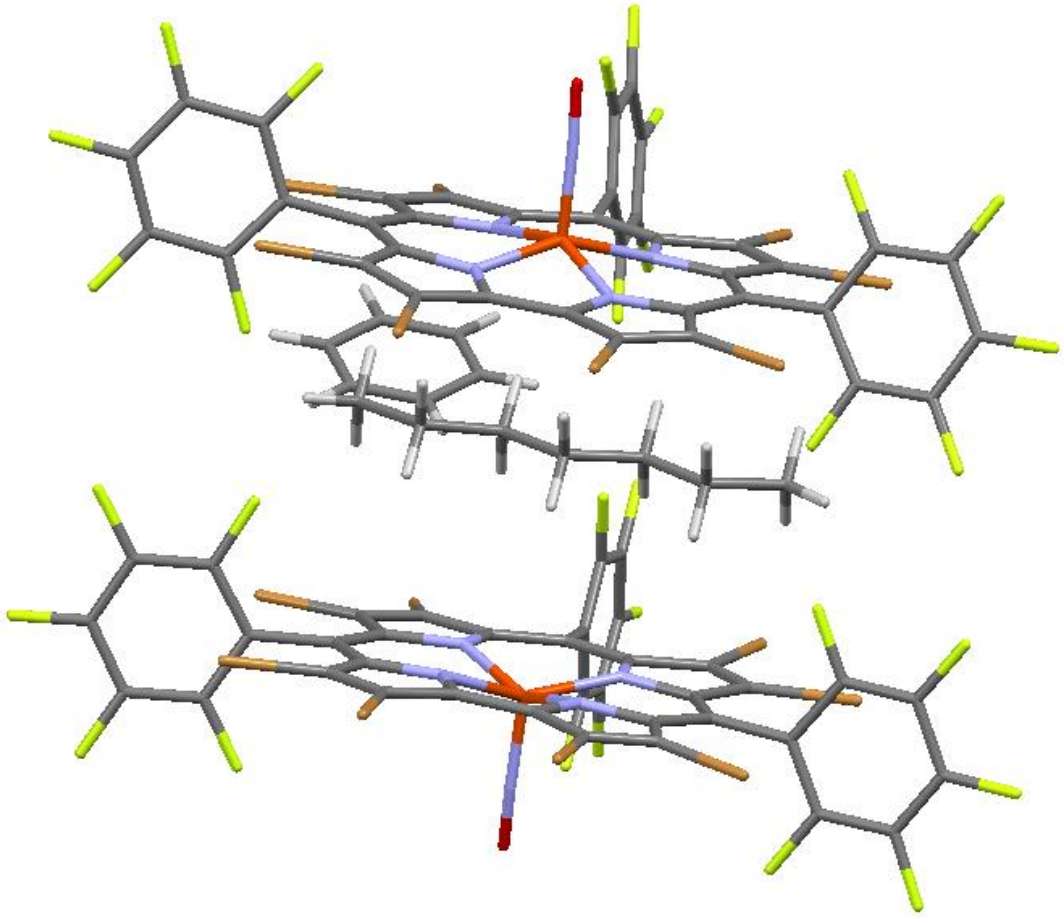


Figure 3.5. The X-ray structure of Fe[Br_8TPFPC](NO).

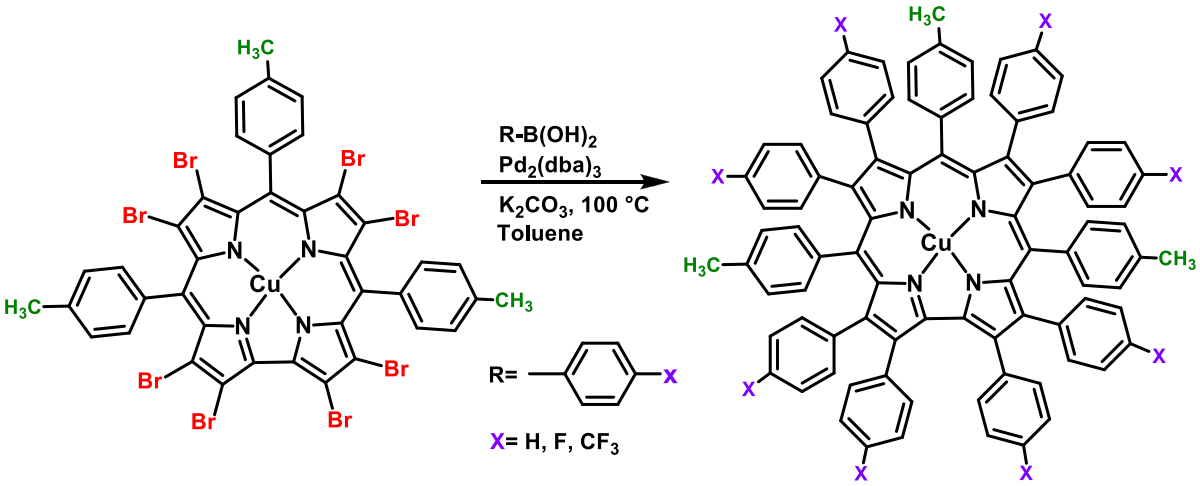
3.3 Synthesis of Copper Undecaarylcorroles

In recent years, various sterically hindered copper undecaarylcorroles have been prepared using Suzuki−Miyaura cross-coupling reactions.[98,99,100] Various copper *β*-octabromo-*meso*-triarylcorroles were used as starting materials and were reacted with different arylboronic acids. Most recently, a free-base undecaarylcorrole was also synthesized by reductive demetalation of the copper undecaarylcorrole, and subsequently, the cobalt complex was prepared from the obtained free-base undecaarylcorrole.[101]

In my attempts to synthesize new undecaarylcorrole ligands *via* the Suzuki-Miyaura reaction, rather than copper complexes, I tried to use free-base *β*-octabromo-*meso*-triarylcorroles as starting materials. But these attempts were unsuccessful. Applying much longer reaction times than previous procedures[99] and an excess of arylboronic acids did not make any difference. In all cases, partially arylated products were obtained i.e. tetra-, penta- and hexa-arylated products. Similar unsatisfactory results were obtained with a wide range of free-base *β*-octabromo-*meso*-triarylcorroles.

In the same vein, the syntheses of undecaarylcorroles from manganese *β*-octabromo-*meso*-triarylcorroles were unsuccessful. Penta- and hexa-arylated products dominated, only trace amounts of hepta- and octa-arylated products could be isolated.

Thus, as in the earlier reported procedures, copper *β*-octabromo-*meso*-triarylcorroles were found to be the most convenient starting materials for Suzuki−Miyaura cross-coupling reactions. Three new copper undecaarylcorroles were synthesized, copper *β*-octakis(*p*-X-phenyl)-*meso*-tris(*p*-methylphenyl)corrole, where X = H, F, and CF_3. For brevity, the complexes will be referred as Cu[X_8Me_3] (Scheme 3.5).



Scheme 3.5. The synthesis of copper undecaarylcorroles.

The reaction times and the yields of the reactions depended on the nature of starting copper corrole and the particular arylboronic acid. In one case where electron-deficient copper *β*-octa-bromo-*meso*-tris(*p*-trifluoromethylphenyl)corrole was reacted with phenylboronic acid, the corresponding Cu[H_8(*p*-CF_3)$_3$] could not be obtained in reasonable yields. Prolonged reaction times and excess phenylboronic acid yielded mostly *β*-hepta-phenylated product.

On the other hand, using electron-deficient arylboronic acid led to increased yields and shorter reaction times. However, in all cases hexa- and hepta-arylated products were still present, necessitating careful preparative thin-layer chromatographic (PLC) purification. A photograph of Cu[H_8Me_3] during the PLC purification is shown in Figure 3.6. The experimental details of synthesized copper undecaarylcorroles are given in Paper VI.

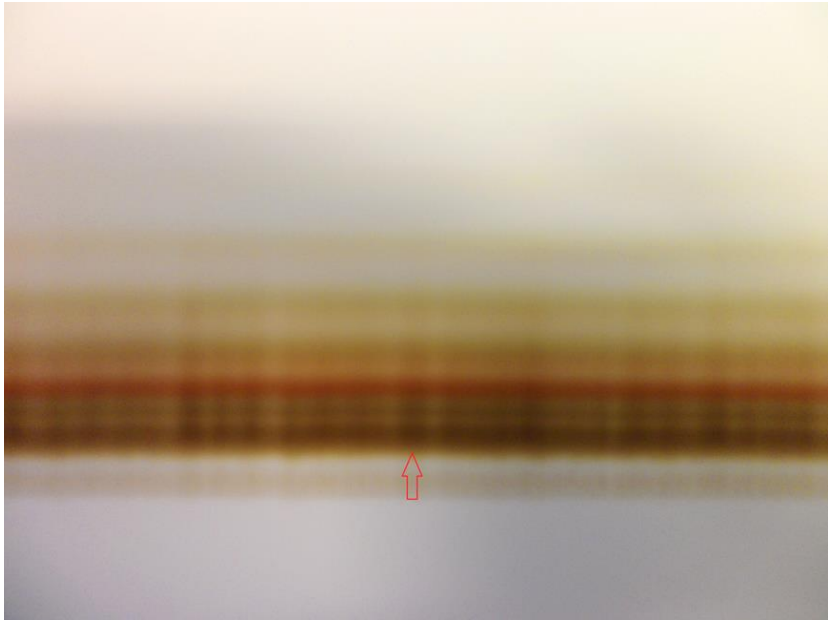


Figure 3.6. PLC of Cu[H_8Me_3].

4. Isocorroles

Isocorroles are new members of the porphyrinoid family. Isocorroles are isomers of corroles where one of the three *meso*-carbons of the aromatic macrocycle is sp^3 hybridized. The sp^3 hybridized carbon atom is either at the 5- or 10-position of the corrole macrocycle (5- or 10-isocorrole, respectively) (Figure 4.1). Isocorroles have two inner N-H protons instead of three as in the case of corroles.

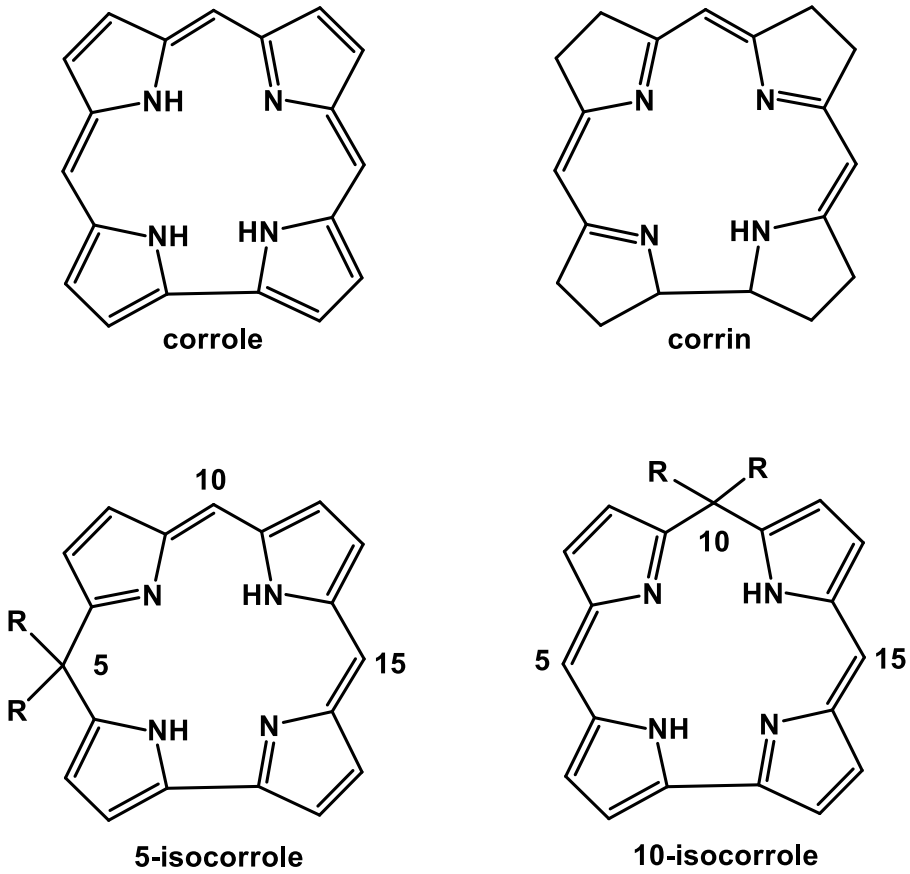


Figure 4.1. The structures of the corrole, corrin, 5-isocorrole and 10-isocorrole.

The name isocorrole was first used for a quite different ring system, viz., the (2.0.1.0) isomer of corrole (Figure 4.2).[43,102,103,104] To avoid confusion, it has been suggested that corrole-(2.0.1.0) should be given the trivial name "corrolene".[105] For the sake of consistency with porphyrin chemistry, the name isocorrole is nowadays generally used to describe the 5/10-sp^3 hybridized isomers of (1.1.1.0)-type corroles as shown in Figure 4.1.[106]

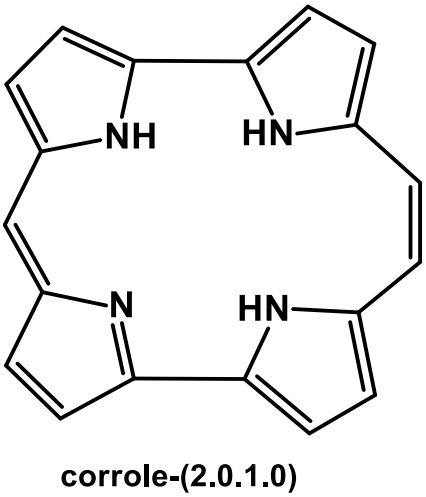


Figure 4.2. The (2.0.1.0) isomer of corrole.

Isocorroles can be considered as intermediate between naturally occurring corrins and synthetic corroles. Thus, like corrin, isocorroles have interrupted conjugation on the macrocycle, but they have the same number of π-electrons as corroles. Isocorroles form dianionic ligands, and are thus intermediate between monoanionic corrin and trianionic corrole. Isocorroles are also intermediate between corrin and corrole in terms of flexibility and structure with sp^3 hybridized carbon atom. The structural comparison between corroles and isocorroles, closely resemble to the comparison between porphyrins and isoporphyrins, namely phlorins (Figure 4.3). Other hybrid molecules such as porphyrinogens and chlorins are widespread in the nature. Many types of these molecules also exist as intermediates in the biosynthetic pathways of porphyrins.[107]

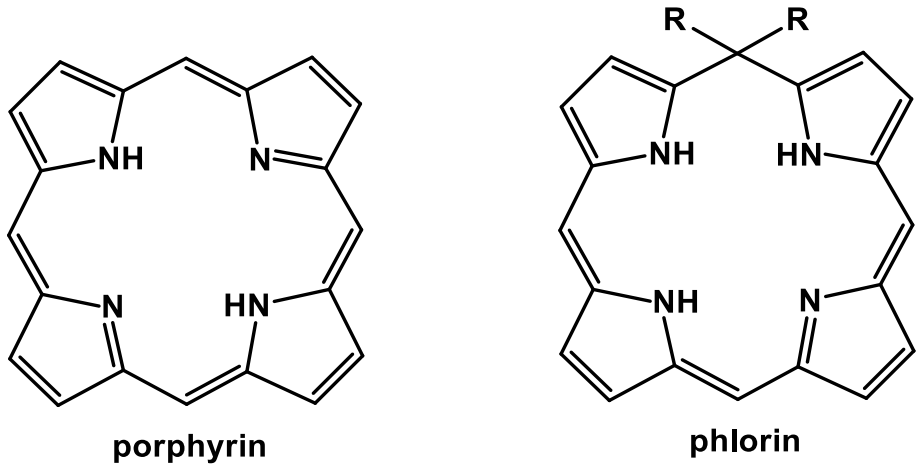
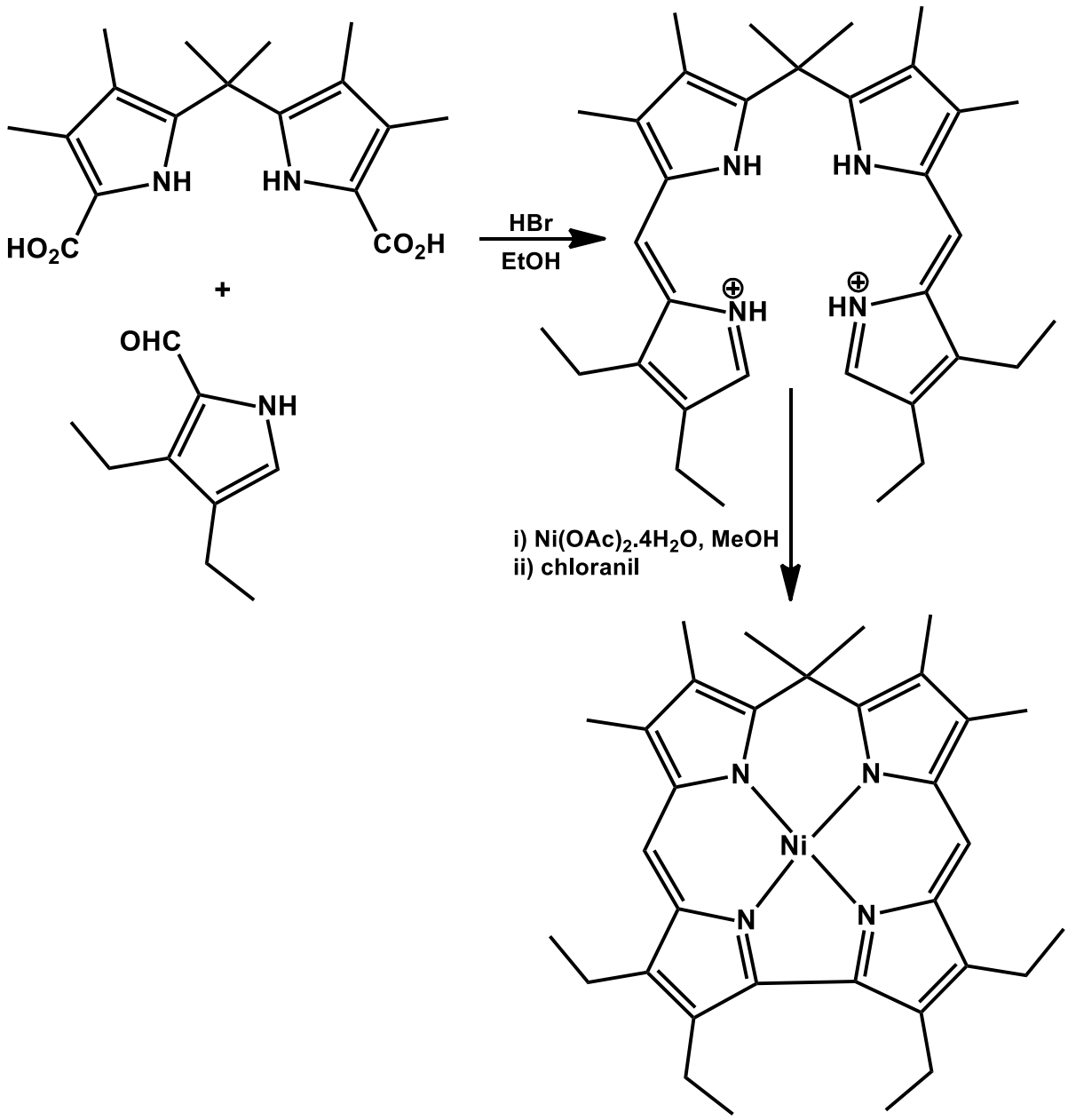


Figure 4.3. The structures of porphyrin and phlorin.

The chemistries of these hybrid molecules are complementary to each other in many ways such as metal or anion binding abilities, stabilities in varying media and structural features. Many of these molecules were synthesized and investigated for their applications in different fields, such as receptors[108] and photodynamic therapy.[70] In contrast to extensively studied modified porphyrins, little is known about modified corroles. The investigation of similar hybrid molecules for corroles and corrins could also be worthy. In addition, the challenges in corrole chemistry lead to a search of new corrole analogs. For these reasons, isocorroles, which were seen as undesired byproducts up until now, have started to attract particular attention.[109]

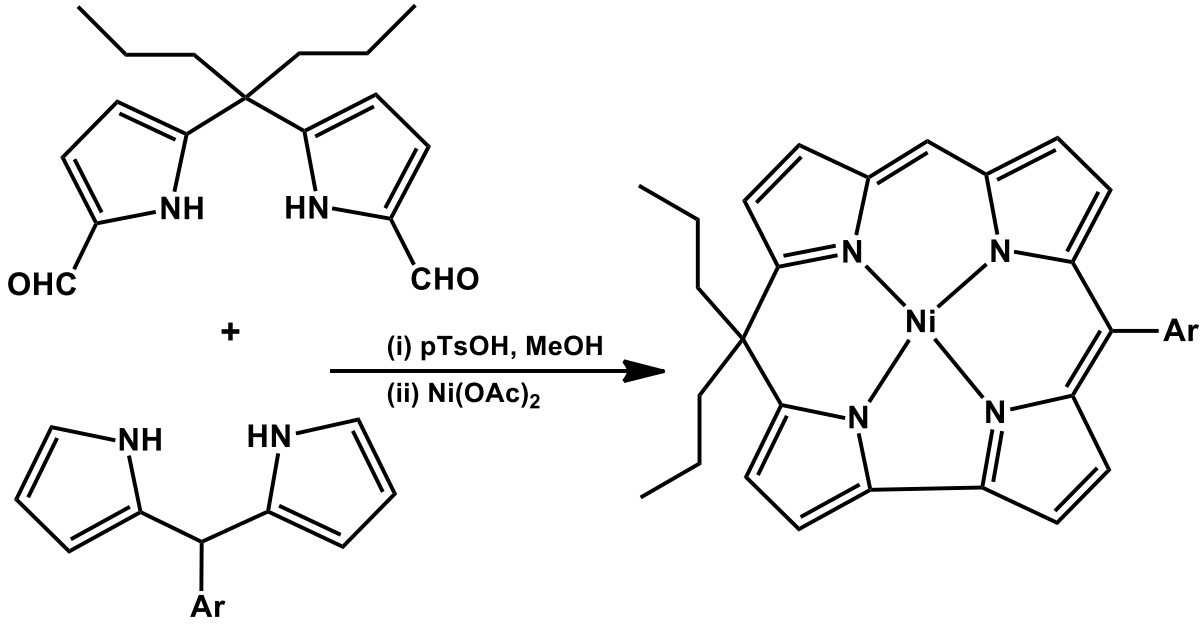
4.1 Synthesis of isocorroles

There are two major ways of synthesizing isocorroles: the first is through a condensation reaction of *meso*-disubstituted dipyrromethanes, and the second is a direct one-step oxidation of a corrole. The first reported syntheses were through condensation reaction of dipyrromethane derivatives. Vogel and coworkers synthesized a 10-isocorrole Ni(II) complex, by condensing 2 equiv. of 3,4-diethyl-2-formylpyrrole with *gem*-dimethyl-3,3′,4,4′-tetramethyldipyrryl-methane-5,5′-dicarboxylic acid, following the addition of a nickel salt and chloranil to induce cyclization of the resulting *a,c*-biladiene (Scheme 4.1).[105,110]



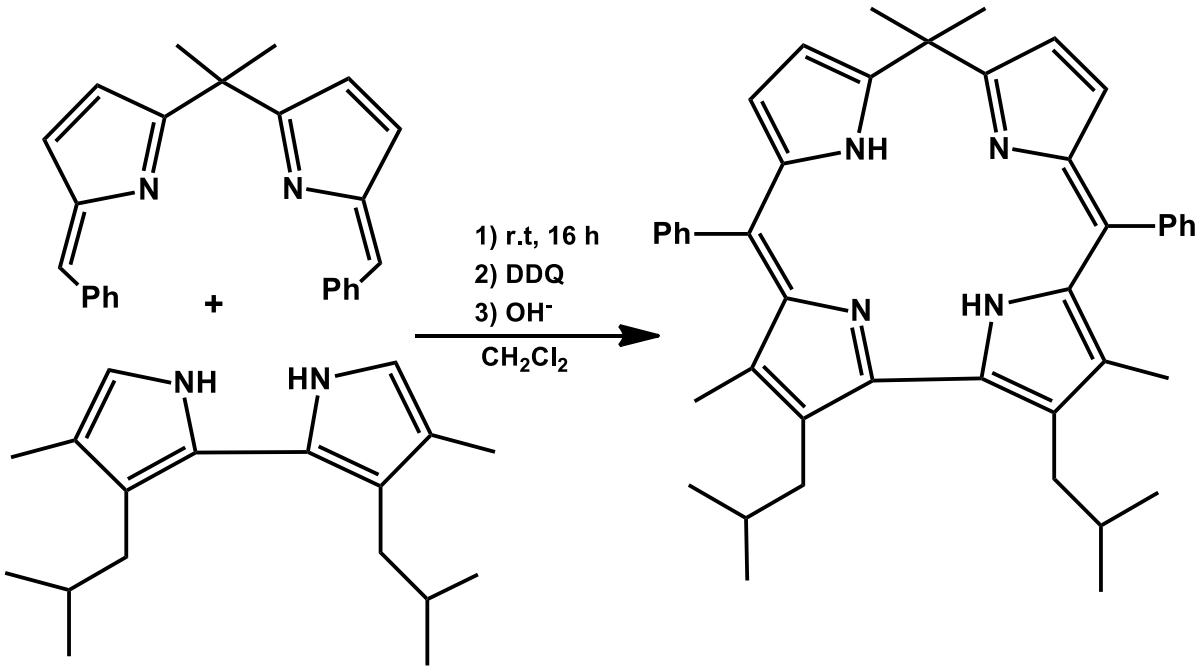
Scheme 4.1. The synthesis of a 10-isocorrole Ni(II) complex reported by Vogel coworkers.[105]

Another Ni isocorrole was formed unexpectedly when a double bond at the 5-*meso* position was reduced upon nickel insertion into a biphenylenyl bridged biscorrole. The resulting biscorrole Ni(II) complex had 5-isocorrole in one of the biscorrole rings, and 5-oxocorrole on the other.[111] Dehaen and coworkers synthesized a 5-isocorrole Ni(II) complex *via* the MacDonald [2+2] condensation of formylated dialkyldipyrromethanes with 5-aryldipyrro-methanes (Scheme 4.2).[112]



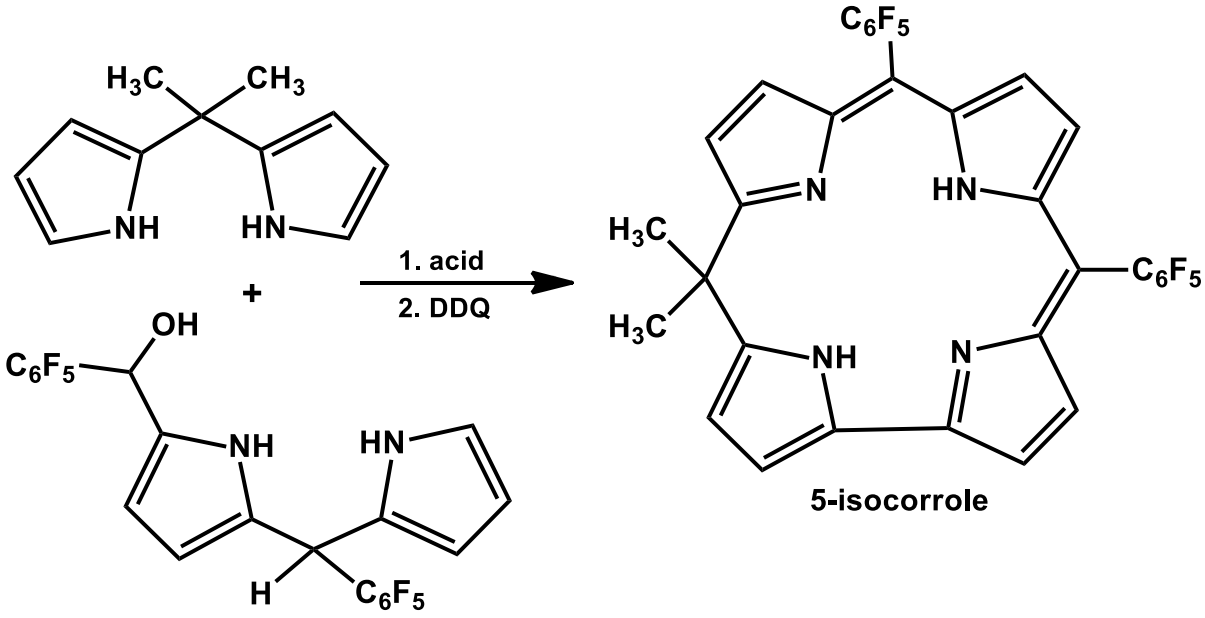
Scheme 4.2. The synthesis of a 5-isocorrole Ni(II) complex reported by Dehaen and coworkers.[112]

The first free-base isocorrole was also reported through condensation reactions of dipyrromethane derivatives. Setsune *et al* prepared a free-base 10-isocorrole from a bis(azafulvene) derivatized dipyrromethane and 2,2′-bipyrrole without using any catalyst, the resulting *gem*-dimethylisocorrole was isolated from a mixture of expanded isocorroles (Scheme 4.3).[113] The same authors later presented various metal complexes of *gem*-dimethylisocorrole with Ni(II), Cu(II), Fe(III)-Cl, Mn(III)-Cl and the six-coordinate Rh(III)-Py-Cl metal centers.[114]



Scheme 4.3. The synthesis of a *gem*-dimethylisocorrole reported by Setsune and coworkers.[113]

Geier and coworkers reported the synthesis of the first free-base 5-isocorrole bearing alkyl substituents at the sp^3 hybridized position (R, R′= -CH_3) by condensing dipyrromethane-monocarbinol with a dipyrromethane in the presence of an acid catalyst (Scheme 4.4).[115]

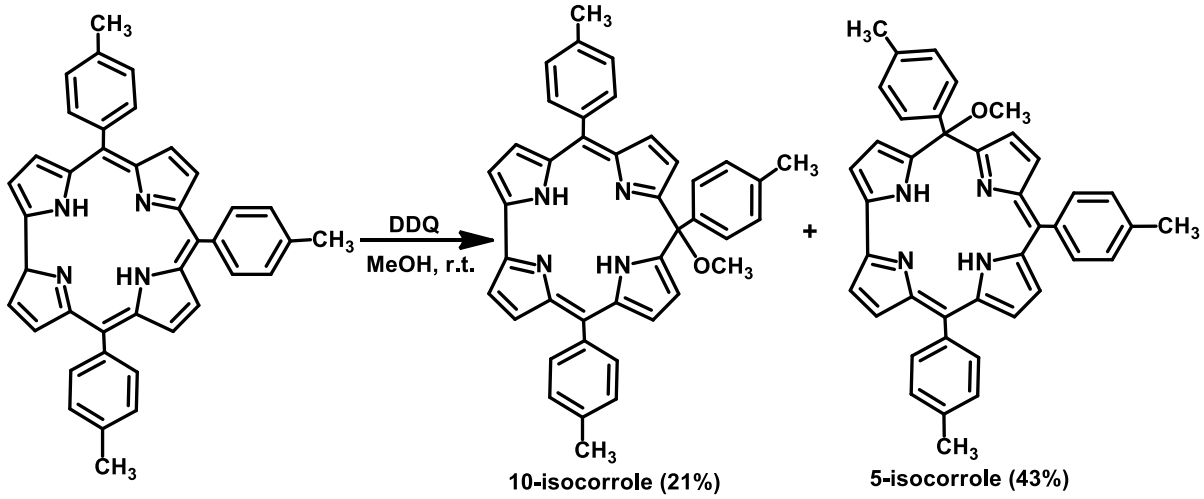


Scheme 4.4. The synthesis of 5-isocorrole (R, R′= -CH_3) *via* condensation of dipyrromethane derivatives.[115]

Crystal structures of the free-base along with Cu and Zn complexes were published in a separate study.[116] The zinc complex was the first example of a zinc isocorrole and the second example in the whole corrole family aside from a *N*-alkylated corrole zinc complex.[117]

The above mentioned isocorrole syntheses *via* condensations of dipyrromethane derivatives require somewhat laborious preparations of the functionalized precursors. The condensation reactions produce multiple types of porphyrinic macrocycles of which only small fractions are isocorroles. Moreover, the reactions require careful adjustment of reaction conditions and subsequently tedious purifications. In addition, in many cases, nickel is necessary to induce cyclization.

The second approach for synthesizing of isocorroles is *via* direct one-step oxidation of corrole. This method is more straightforward. Recent advances in the synthesis of free-base corroles also provide relative advantages. Inspired by the isolation of the first isoporphyrin from the oxidized zinc tetraphenylporphyrin (ZnTPP) in methanol, Paolesse's research group accomplished the first synthesis of isocorroles by the oxidation of a free-base triarylcorrole using DDQ in methanol.[106] The reaction produced 5- and 10-isocorroles (43% and 21%, respectively) and both had a methoxy group (R= -OMe) at the sp^3 hybridized positions (Scheme 4.5). In addition, with an electron donating *meso*-aryl substituted corrole a much higher yield (75%) was obtained compared with corroles with electron-withdrawing *meso* groups (only traces).



Scheme 4.5. The synthesis of isocorroles *via* direct one-step oxidation of readily available corrole.[106]

Isocorroles bearing hydroxyl (-OH) group at the sp^3 hybridized position were first isolated as byproducts of acid induced demetalation reaction of copper corroles.[55] Both 5- and 10-OH free-base isocorroles were formed in the same reaction. Interestingly in the case of *β*-octabromo-*meso*-triphenylcorrole, Br_8TPC, exclusively 10-OH isocorrole was formed, presumably due to steric factors. Both 5- and 10-isocorrols (R = -OH) were also isolated as byproducts during acid induced demetalation of silver(III) corrolates.[60] Remarkably, demetalation of a *β*-3-NO_2 substituted silver(III) triarylcorrole solely led to a (3-NO_2, 5-OH)-isocorrole (Figure 4.4) instead of a mixture of 5- and 10-substituted isocorroles.

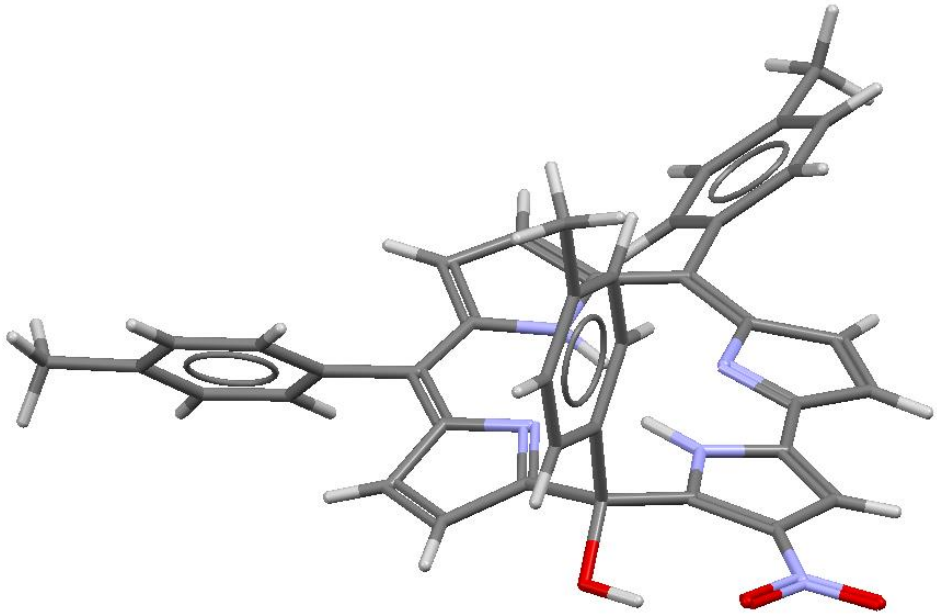


Figure 4.4. The X-ray structure of the (3-NO_2, 5-OH)-isocorrole.[60]

This phenomenon was explained by X-ray analysis which showed that the favored structure was the result of intramolecular hydrogen bond between the hydroxyl and nitro groups (Figure 4.4). However, purification details and yields of isocorroles were not reported in both Cu(III) and Ag(III) corrole demetalation reactions. Thus, isocorroles formed *via* demetalation reactions were solely considered as byproducts rather than actual syntheses.

Isocorrole synthesis *via* direct one-step oxidation of readily available corroles was extended to the synthesis of isocorroles bearing (R, R′= -CH_2CH_3) at the sp^3 hybridized *meso* position.[118] Paolesse *et al* used DDQ oxidation of the 5,10,15-tritolylcorrole followed by addition of a Grignard reagent (EtMgBr) and obtained 5- and 10-alkyl substituted isocorroles in good yields.[118]

One-step oxidation of readily available triarylcorroles using DDQ in methanol also led to isocorrole metal complexes with an -OMe group at the sp^3 hybridized *meso* position.[119] Ni and Cu complexes of both 5- and 10-OMe isocorroles were prepared, whereas insertion of Co(II), Mn(II) and Zn(II) were unsuccessful.[119] Unlike the Zn(II) isocorrole bearing R, R′= -CH_3 at the sp^3 hybridized *meso* position,[116] Zn isocorrole (R= -OMe) could not be isolated due to rapid decomposition during the reaction work up.[119] An interesting finding on metalation of isocorroles (R= -OMe) with Co(II) and Mn(II) was that the metalations induced rearomatization of the macrocycle and converted the isocorrole to the corresponding metallocorrole.[119] This phenomenon was only observed with isocorroles with R = -OMe. In the case of Setsune's *gem*-dimethylisocorrole (see Scheme 4.3, p. 39), an Mn(III)-Cl isocorrole complex was successfully prepared.[114] Paolesse *et al* suggested that metals capable of achieving higher oxidation can induce metal-to-ligand electron transfer, causing loss of methoxide, accompanied by rearomatization to the corresponding corrole.[119] The presence of a methoxy group instead of an alkyl group at the sp^3 hybridized *meso* position may enable rearomatization through easy loss of the methoxy group.

Isocorrole to corrole conversion was also achieved by direct reduction of a free-base isocorrole (R= -OH) using $NaBH_4$ as a reducing agent to obtain the corresponding free-base corrole, albeit in low yield (35%).[109] The specific isocorrole in this reaction was a result of an unexpected formation of 2-Br-15-OH-17-NO_2-isocorrole during the bromination of a *β*-3-NO_2 substituted free-base corrole.[109] The importance of this reaction was a demonstration of how isocorrole formation could provide regioselectivity during functionalization of a corrole. The research group of Paolesse successfully proved that the bromination occurred at the 2- instead of the usually more reactive 3-position as a result of the isocorrole formation.[109]

4.2 Structural and spectroscopic properties of isocorroles

The sp^3 hybridized carbon atom of the isocorrole introduces flexibility and impairs the flatness of the molecular structure at that position. In addition, the presence of the sp^3 hybridized carbon allows tilting of the pyrrole rings to adapt various metal coordination geometries.[114]

Like sterically unhindered free-base porphyrins but unlike free-base corroles, free-base isocorroles are nearly planar.[106,116] However, peripheral substituents can change the structural confirmation, such as in the case of the *β*-3-NO_2 substituted free-base (3-NO_2, 5-OH)-isocorrole (see Figure 4.4, p. 41) which displays a flattened saddle confirmation.[60]

Similar to Cu porphyrins, Cu isocorroles exhibit relatively planar structures,[114,116,119] in contrast to Cu corroles which have saddled structures due to specific metal–corrole orbital interactions.[37] The X-ray structures of Cu(II) and Zn(II) 5-isocorroles (R, R′= -CH_3)[116] are shown in Figure 4.5. The structural alignments of isocorrole metal complexes with Ni, Fe, Mn and Rh also show very close resemblance to the metalloporphyrin counterparts.[114]

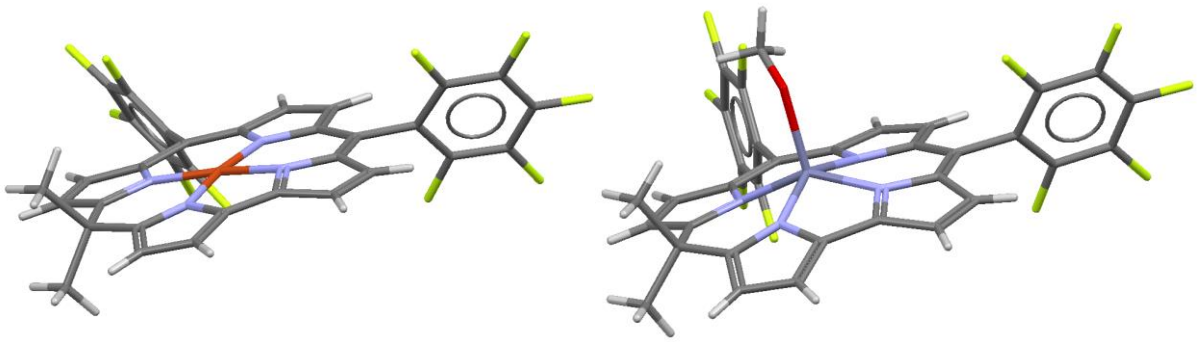


Figure 4.5. The X-ray structures of a Cu(II) (left) and Zn(II) (right) 5-isocorroles (R, R′= -CH_3) (see Scheme 4.4 p. 39 for the molecular structure of the free-base ligand).[116]

The ^{1}H NMR spectra of free-base isocorroles display characteristic shifts below 7 ppm for *β*-pyrrolic protons and about 15 ppm for the inner N-H protons. The resonances for N-H protons are consistent with the absence of overall aromaticity.[106,115,60] The appearance of different resonances for the inner N-H protons suggests slow tautomerism.[115] Due to lower symmetry than 10-isocorrole, the ^{1}H NMR spectrum of free-base 5-isocorrole displays two distinct peaks for the N-H protons and an increased number of peaks for *β*-pyrrolic protons.[106]

The UV-vis spectra of isocorroles exhibit a characteristic pattern which clearly distinguishes them from corroles and porphyrins. In a way, they are similar to the phlorins. For example, the UV-vis spectrum of a free-base 5-isocorrole is quite similar to that of the corresponding phlorin.[120] Relative to the free-base corroles, the UV-vis spectra of free-base isocorroles exhibit a blue-shifted Soret band around 400 nm and two more intense red-shifted Q bands above 600 nm.[109,115] The UV-vis spectra of metal isocorrole complexes display remarkable low energy absorptions above 800 nm with intense Q-like bands (Figure 4.6). Both 5- and 10-

isocorrole metal complexes of Zn, Cu, Fe, Mn and Rh show intense absorption bands above 750 nm.[114,116,119] One of the key desirable features of photosensitizers used in photodynamic therapy (PDT) is the absorption at long wavelengths (700-850 nm). Hence, isocorroles appear attractive molecules in terms of applications in PDT.[70]

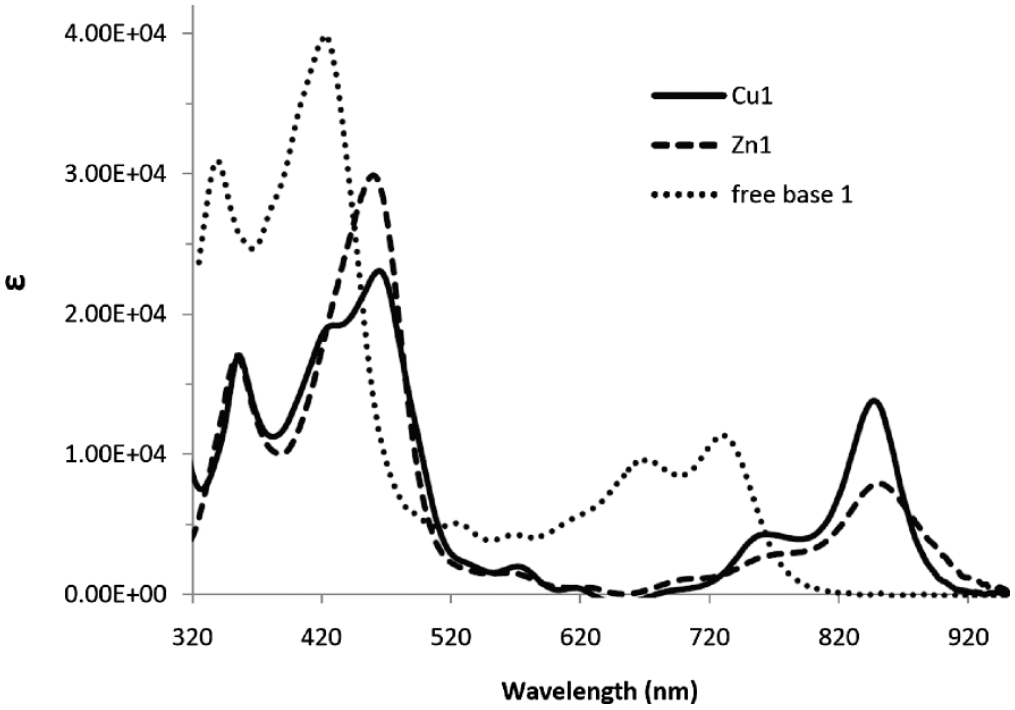


Figure 4.6. The UV-visible spectra of free-base 5-isocorrole (R,R'= -CH_3) and its Cu and Zn complexes.[116] (See Scheme 4.4 p. 39 for the molecular structure of "**free-base 1**", and Figure 4.5 p. 43 for the X-ray structures of "**Cu1**" and "**Zn1**"). (The figure is taken from reference 116).[116]

The free-base 5-isocorrole with R,R′= -CH_3 was monitored for a period of 14 days under light and air by UV-vis spectroscopy and HPLC, and proved to be very stable with no change in the spectra.[115] The stability of free-base isocorroles toward light and air is particularly important in terms of applications and would be complementary to free-base corroles which are unstable under the light and air.[121] Interestingly, most free-base phlorins are also reported to be unstable toward light and air.[122]

4.3 Spontaneous formation of isocorroles by the decomposition of free-base corroles

Isocorroles are also formed spontaneously during the decomposition of free-base corroles in the presence of air and light. The isocorroles formed in this way bear hydroxyl group (R= -OH) at the sp^3 carbon at the 5- or 10-*meso* position. However, isocorroles are isolated only as a small fraction of the decomposition products (~10%). The major isolated decomposition products are oxidized open-chain tetrapyrroles (biliverdin species).[121,123]

The instability of free-base corroles was observed as early as 1998 when Guilard *et al* reported the air sensitivity of a free-base octaalkylcorrole and identified the decomposition product (24% yield) as an open-chain tetrapyrrole.[124] Paolesse *et al* reported that the octamethylcorrole moiety in a porphyrin-corrole dyad underwent photo-oxidation induced ring opening and gave the corresponding porphyrin-biliverdin dyad species.[125]

The instability of free-base corroles 5,10,15-triphenylcorrole, H_3[TPC], and 5,10,15-tris (pentafluorophenyl)corrole, H_3[TPFPC], towards air and light were studied by observing the changes in the absorbance of the Soret band as a function of time.[126] The electron-deficient H_3[TPFPC] was found to be fairly stable in contrast to relatively electron-rich H_3[TPC], which underwent ~50% decomposition in 2 h. In addition, light was found necessary for the decomposition. The researchers did not identify the decomposition products.

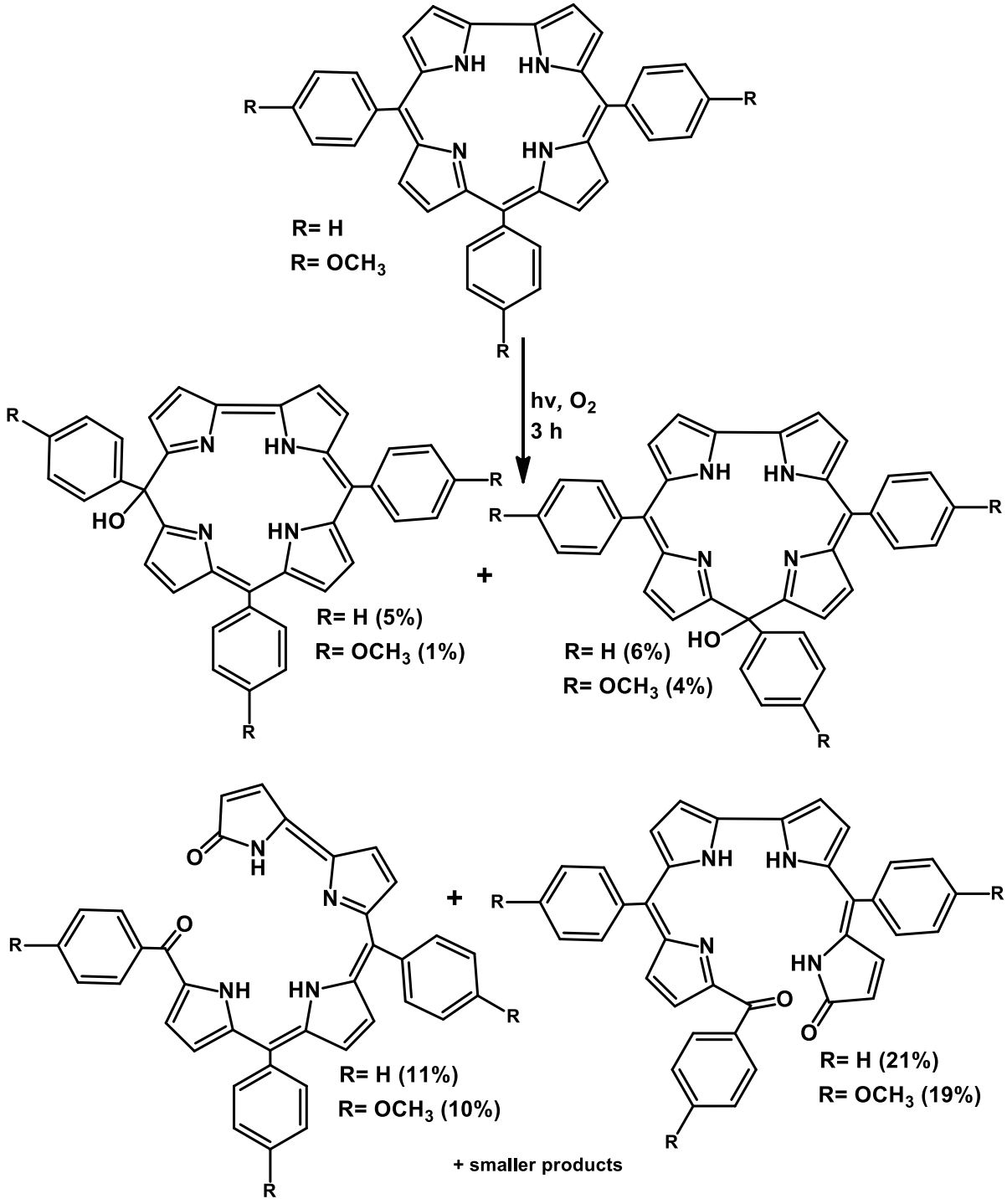
In a surprising study, free-base A_2B-type 5,15-dimesityl-10-nitrophenylcorrole was found to convert to a *trans*-AB_2C-porphyrin.[127] After 48 h of exposure to air and light in benzene/methanol at room temperature, the porphyrin was isolated in 19% yield. The researchers used $^{13}CH_3OH$ but did not detect a ^{13}C-*meso*-carbon atom in the ^{13}C NMR spectrum of the isolated porphyrin. The other isolated decomposition product was a biliverdin species, whose yield was not reported. The suggested mechanism for the porphyrin formation was through the cycloaddition of the two corrole macrocycles to form a dyad, then splitting upon oxidation to give biliverdin and porphyrin. In this process, the extra *meso*-carbon needed for porphyrin comes from the corrole which forms the biliverdin.[127]

Cavaleiro and coworkers studied the stability of free-base H_3[TPFPC] in various solvents.[128] After 30 days of exposure to air and light in chloroform solution, H_3[TPFPC] was converted to *β–β* linked corrole dimer in 28% yield. A trace amount of trimer was also isolated in 4% yield. The yields were different in varied solvents, but in all cases, the free-base H_3[TPFPC]

was recovered as the major product despite the 30 days of exposure. In a control experiment in the dark, free-base H_3[TPFPC] remained unchanged, which made the authors believe that the mechanism of the oligomerization involved radical reactions. This reported oxidative dimerization was an exception in the sense that all the other free-base corroles mainly decompose to biliverdin-type compounds.

A detailed study was carried out to investigate the stability and the decomposition products of various free-base *meso*-triarylcorroles.[121] Electron-withdrawing, electron-donating and sterically hindered *meso*-aryl substituents were evaluated. As previously observed,[126,129] corroles with electron-withdrawing substituents were found to be more stable towards air and light and decomposed at a slower rate. Numerous decomposition products were detected, but mainly open-chain compounds. In order to isolate the major products on a preparative scale, A_2B-type corrole bearing sterically hindered aryl groups at 5- and 15- positions were exposed to air and light for 60 h. After this time all the corrole disappeared completely and three major products were isolated: 10-isocorrole (R-OH) in 8% yield, and two isomeric biliverdin species in 79% total yield. In addition, 15 other open-chain products were detected but could not be isolated in sufficient quantities for the structural identifications. As a consequence of the sterically hindered substituents at positions 5 and 15, only 10-isocorrole was formed instead of a mixture of 5- and 10-isocorroles. The authors also proposed a mechanism for the decomposition and showed that both isocorrole formation and ring opening were the result of attack by O_2 at the 10-*meso* position. Similar to other observations, the decomposition did not take place in the absence of light. The solvent choice also had a pronounced effect on the decomposition rate.

The stability and the decomposition products of sterically unhindered free-base *meso*-triarylcorroles were recently studied by Latos-Grazyński and coworkers.[123] The research group investigated the photooxidation of 5,10,15-triphenylcorrole and 5,10,15- tris(4-methoxyphenyl)corrole (Scheme 4.6).[123] The reaction time was optimized to 3 h in order to prevent the formation of multiple photochemical reaction products. As a result, 10-15% of corroles were recovered. The dichloromethane solution of corroles were exposed to air and light for 3 h. Decomposition products 5- and 10-isocorroles (R-OH) were isolated in ~10% total yield, and two isomeric biliverdin species were isolated in 30% combined yield (Scheme 4.6).



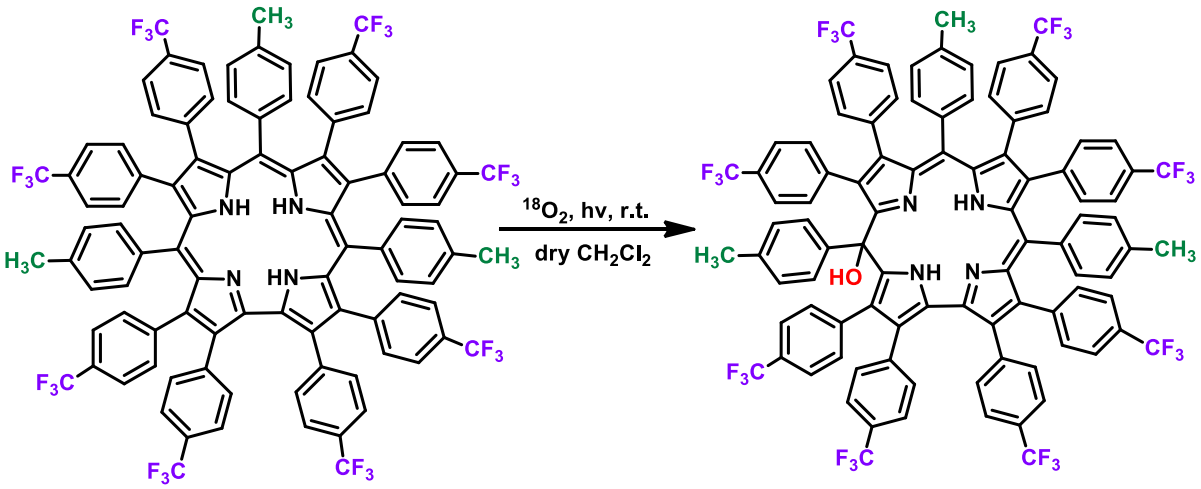
Scheme 4.6. The decomposition products of sterically unhindered free-base *meso*-triarylcorroles.[123]

In summary, isocorroles can also be obtained from readily available corroles *via* photooxidation. The decomposition rate varies depending on the substituents. The main decomposition products are the two isomeric 5/10-hydroxyisocorroles, and two isomeric biliverdin species in approximately 10% and 30% overall yields, respectively.

4.4 $H_2{}^{18}O$ and $^{18}O_2$ experiments for the detection of the oxygen source

None of the reported stability and decomposition studies of free-base corroles were carried out under moisture-free conditions. In all cases, corrole solutions were exposed to air and the possibility of ambient moisture was not taken into account. In some cases, the dryness of the solvents was also uncertain.[123,126] That said, the source of the oxygen in the 5/10-hydroxyisocorrole products has been claimed to be air rather than water.[121,123] In order to be sure of this claim, a better option would be to run the reactions in dry solvents under argon and bubble reagent-grade O_2, instead of exposing the solutions to open air for long hours.

In order to identify the source of the oxygen in the 5/10-hydroxyisocorrole product, I conducted corrole decomposition experiments using isotopically labeled $H_2{}^{18}O$ and $^{18}O_2$. Free-base undecaarylcorrole $H_3[(CF_3)_8Me_3]$ was used for this experiment (Scheme 4.7). Since free-base undecaarylcorroles are among the most electron-rich corroles, rapid oxidation and almost instantaneous formation of isocorrole was observed. This makes undecaarylcorroles particularly suitable for studies with expensive $^{18}O_2$ reagent, since we would not need to bubble large amounts of the expensive gas over long reaction times.



Scheme 4.7. The isocorrole ($H_2[(CF_3)_8Me_3(5\text{-}OH)]$) formation using isotopically labeled $^{18}O_2$.

The decomposition experiment using isotopically labeled $H_2{}^{18}O$ and $^{18}O_2$. PLC-purified free-base $H_3[(CF_3)_8Me_3]$ (3 mg, 0.0017 mmol) was placed in a 50 mL round-bottom flask, along with a magnetic stirrer, and the flask was sealed with a rubber septum. The flask was then connected to a Schlenk line with a needle and the sample was dried under vacuum at 50 °C for 4 hours. Dry CH_2Cl_2 (10 mL) was then added under argon, and the solution was magnetically stirred. No attempt was made to exclude light in this experiment. Electrospray ionization (ESI) mass spectrum taken at this moment indicated the presence of pure corrole (M^+= 1721.42) with a trace amount of isocorrole (M^+= 1738.42). Subsequently, $H_2{}^{18}O$ (100 µL, 97% enriched, 5 mmol, 2870-fold excess) was added and the solution was stirred under Ar. After 40 minutes, an ESI measurement did not indicate any difference in composition. The solution was left to stir overnight under Ar, without an outlet from the sealed flask to prevent the evaporation of $H_2{}^{18}O$ and CH_2Cl_2. Even after 24 hours, an ESI measurement indicated no difference in composition. The argon line was disconnected, and 100 µL of $H_2{}^{18}O$ was added and the solution was stirred in an open flask overnight. An ESI measurement then indicated around 30% conversion to isocorrole, with ^{16}O incorporation, as well as to other biliverdin species with ^{16}O. Based on these results, the conclusion was that free-base undecaarylcorrole is air-sensitive, and not moisture-sensitive. The oxygen source for isocorrole formation is air rather than water.

In order to confirm this conclusion, a similar experiment (again in the presence of ambient light) was carried out with $^{18}O_2$ gas (95% enriched) as the potential oxygen source. PLC-purified free-base corrole $H_3[(CF_3)_8Me_3]$ was dried under high vacuum at 50 °C for 4 hours. The high vacuum pump was stopped and the vacuum line was switched to an argon line. Under Ar, dry CH_2Cl_2 was added. After thorough degassing with Ar, an ESI measurement indicated the presence of pure corrole (M^+= 1721.42) with a trace amount of isocorrole (M^+= 1738.42). $^{18}O_2$ was then bubbled for 20 minutes; however, an ESI measurement indicated isocorrole formation with ^{16}O! Bubbling was continued for another 20 minutes. An ESI measurement displayed slight addition of ^{18}O to corrole to form ^{18}O-labelled isocorrole. But this change was too small to confirm. $^{18}O_2$ bubbling was continued for a further 30 minutes. Even so, an ESI measurement indicated the incorporation of ^{16}O to form the ^{16}O-isotope of isocorrole but not the ^{18}O.

A plausible explanation for the above observations is that the mass spectrometer is not air-free and during the measurements ^{18}O atoms might exchange with ^{16}O. We also found that under different instrumental settings the ratio of corrole/isocorrole and biliverdin species

changes. When air flow in the instrument is high, the ratio of isocorrole and biliverdin species increases. It was previously observed that mass spectroscopy measurement with ESI induces oxidation that results in the detection of the [M+15] signal (isocorrole), even if a corrole sample is pure.[121]

Our observations were in agreement and we decided to connect an $^{18}O_2$ cylinder to the ESI instrument. Upon flushing the instrument with $^{18}O_2$, an ESI$^+$ spectrum showed the immediate formation of ^{18}O-labelled isocorrole and biliverdin species. Figure 4.7 shows the HR-ESI spectrum (in positive ion mode) of pure $H_3[(CF_3)_8Me_3]$ immediately before flushing with $^{18}O_2$. Figure 4.8 shows the HR-ESI spectra (in positive ion mode) immediately after $^{18}O_2$ flushing into the ESI instrument.

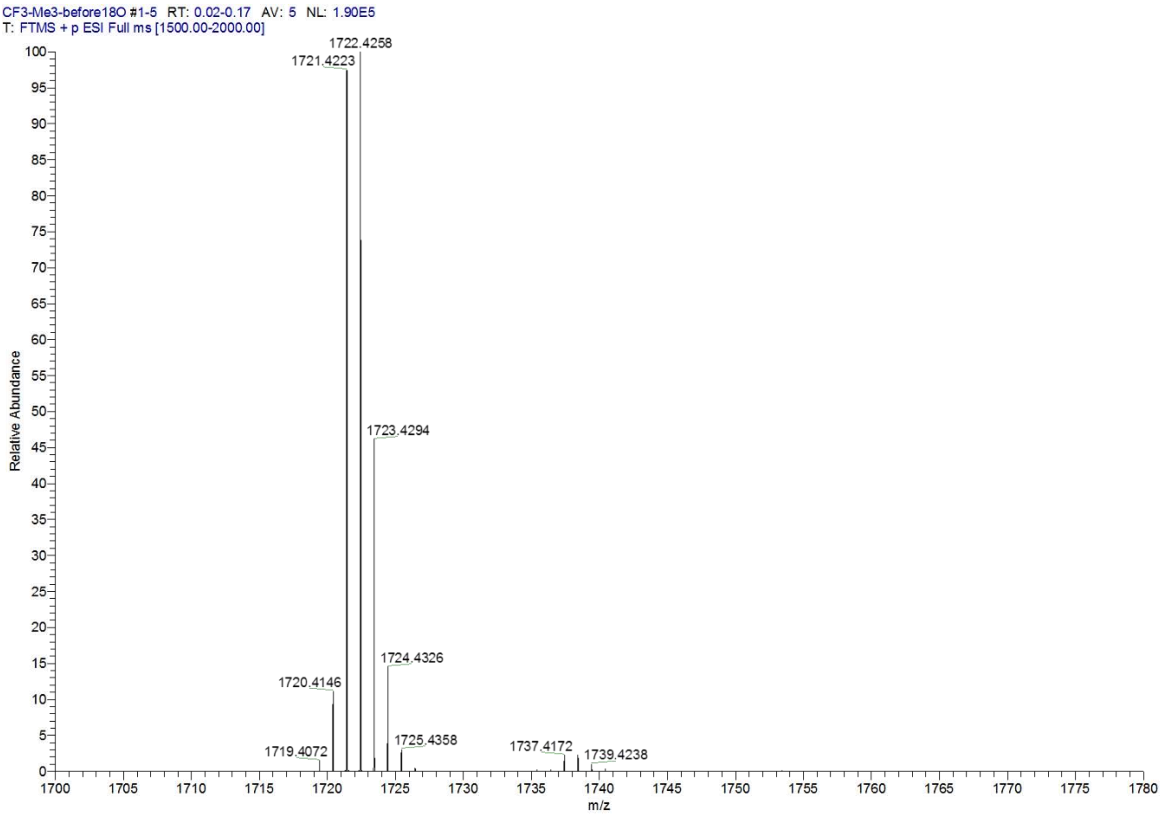


Figure 4.7. The HR-ESI spectrum (in positive ion mode) of pure $H_3[(CF_3)_8Me_3]$ (M^+= 1721.4) immediately before $^{18}O_2$ flushing.

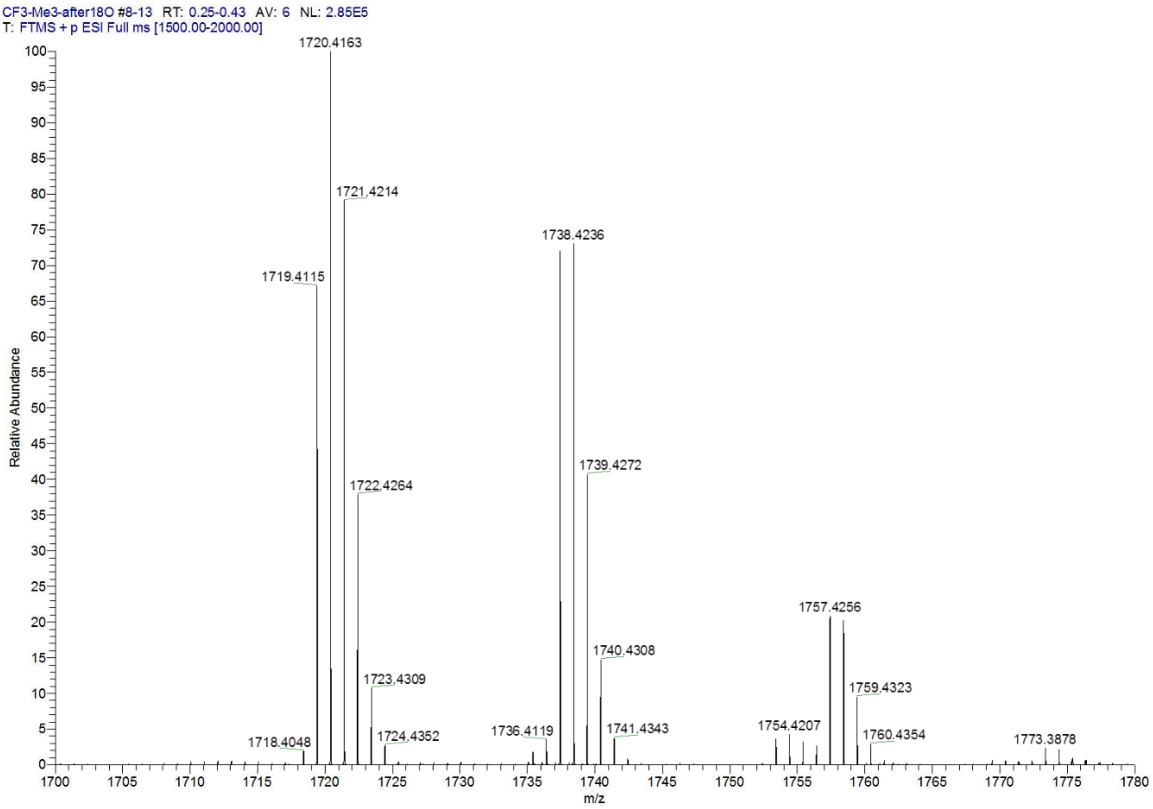


Figure 4.8. The HR-ESI spectrum (in positive ion mode) immediately after $^{18}O_2$ flushing into the ESI instrument. M^+= 1738.4 is ^{18}O-labelled isocorrole, M^+= 1757.4 is ^{18}O-labelled biliverdin species (See text, p. 50).

The above experiment was repeated by flushing the mass spectrometer with normal air, leading to immediate formation of isocorrole and biliverdin species. This result is shown in Figure 4.9.

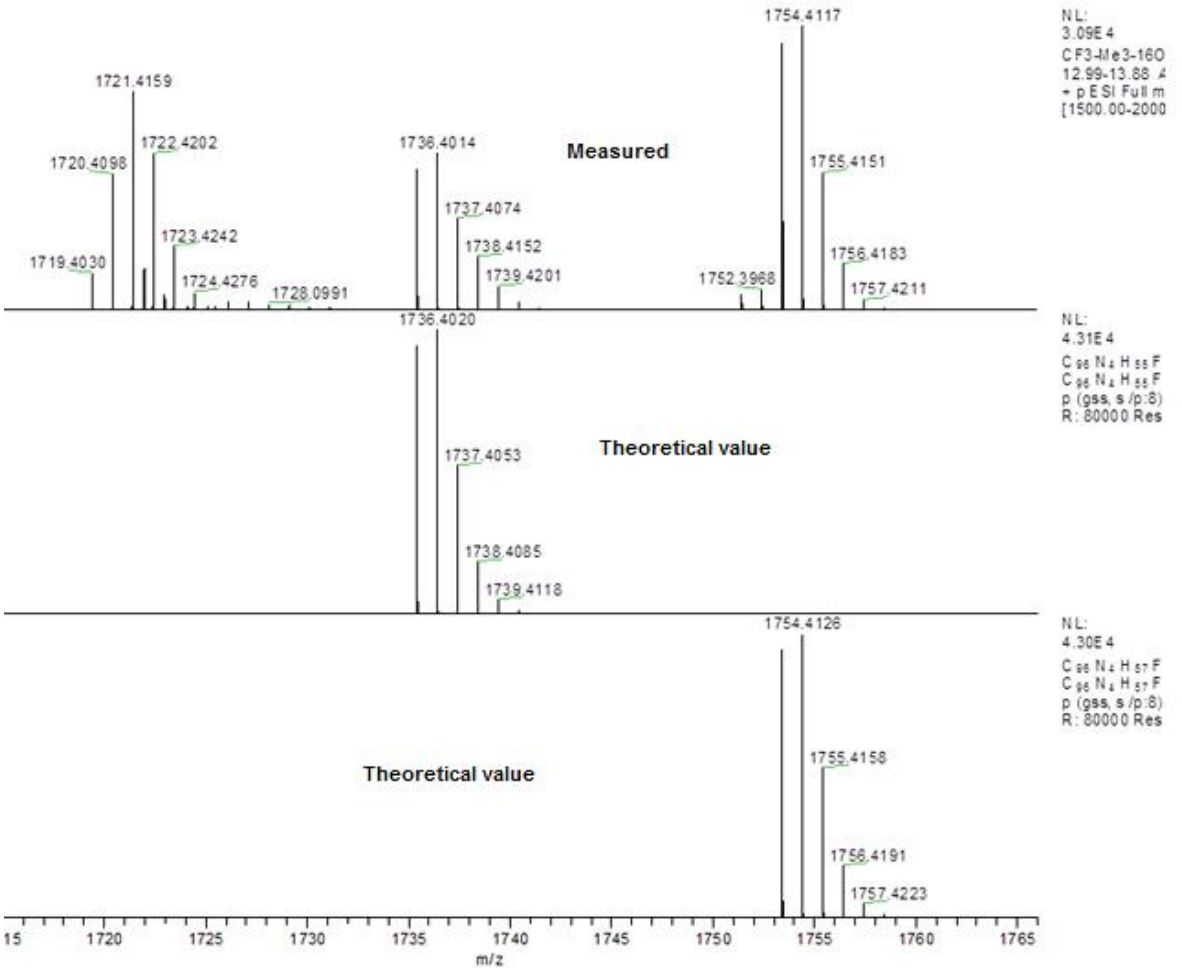


Figure 4.9. The HR-ESI spectrum (in positive ion mode) immediately after $^{16}O_2$ flushing into the ESI instrument. M^+= 1736.4 is isocorrole, M^+= 1754.4 is biliverdin species (See text, p. 51).

Thus, the final conclusion was that the free-base undecaarylcorrole studied is air-sensitive rather than moisture-sensitive. $H_2{}^{18}O$ experiments under Ar and in an open flask, as well as $^{18}O_2$ and $^{16}O_2$ experiments, all give the same conclusion. The oxygen source for isocorrole formation is air, rather than water. This was the first experiment to truly identify the oxygen source during the decomposition of free-base corroles. The results also provide strong experimental evidence in favor of previously proposed mechanisms.[121,123] A reaction mechanism for photooxidative degradation of free-base undecaarylcorroles to form isocorroles and biliverdin species is presented in Paper VI.

5. Undecaarylisocorroles

My original goal in this area was to synthesize free-base undecaarylcorroles using demetalation procedures. Free-base undecaarylcorroles were indeed obtained in good yields using a previously reported demetalation procedure with $H_2SO_4/FeCl_2$.[57] However the new free-base corroles proved to be unstable in solution and quickly decomposed to biliverdin and isocorrole species. As a result, proper spectroscopic analysis could not be made. Rapid photo-oxidation of electron-rich free-base corroles has been observed earlier.[126,129] Free-base undecaarylcorroles are among the most electron-rich corroles; in addition have steric strain due to the peripheral crowding. As a result, the rapid decomposition observed was not surprising. In contrast to free-base undecaarylcorroles, the isocorrole derivatives are very stable. Since isocorroles also have several interesting features (as discussed on p. 44), we turned our attention to investigate the free-base undecaarylisocorroles. This study, as well as all experimental procedures are presented in Paper VI.

Four undecaarylisocorroles were synthesized from the three new copper undecaarylcorroles that were described in Chapter 3.3: copper *β*-octakis(*p*-X-phenyl)-*meso*-tris(*p*-methylphenyl)-corrole, where X = H, F, and CF_3. These complexes are referred to $Cu[X_8Me_3]$. The corresponding isocorroles will be referred to by a notation such as $H_2[X_8Me_3(5\text{-OH})]$ (Scheme 5.1) and $H_2[X_8Me_3(10\text{-OH})]$. A single-crystal X-ray structure was successfully obtained for $H_2[(CF_3)_8Me_3(5\text{-OH})]$ and is shown in Figure 5.1.

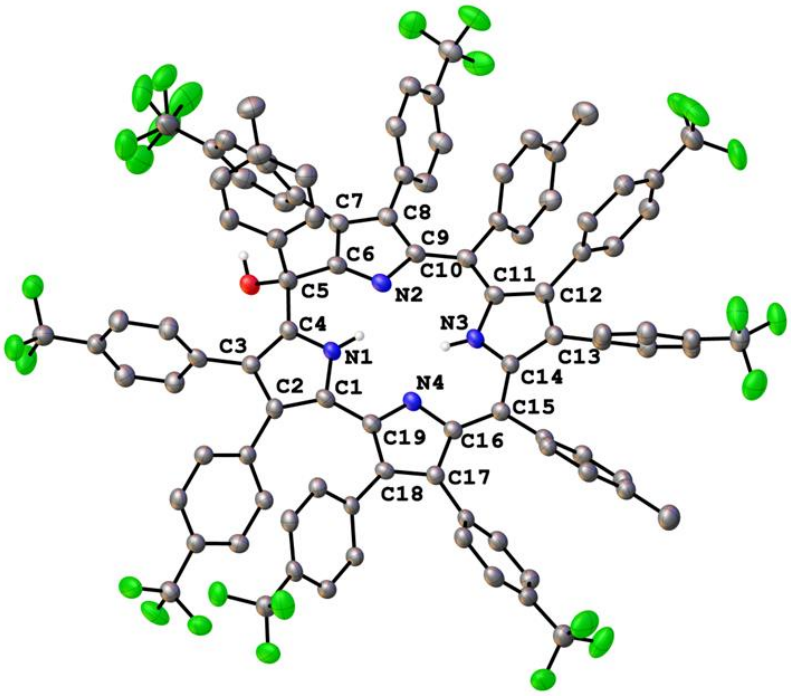
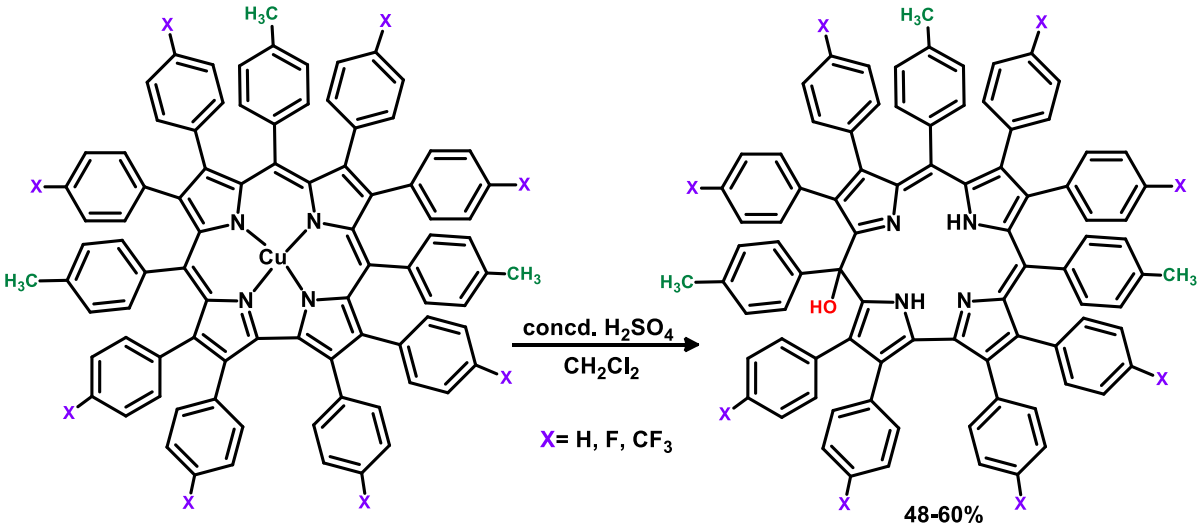


Figure 5.1. The X-ray structure of $H_2[(CF_3)_8Me_3(5\text{-}OH)]$.

The standard reductive demetalation procedure applied to copper undecaarylcorroles led rapidly to free-base corroles as the main product (in about 70% yields), along with small amounts of free-base isocorroles. Under light and air, the free-base corroles however quickly decomposed to biliverdin species and small amounts of isocorroles. Attention was therefore turned to optimize the isocorrole yield during the demetalation reaction. In the absence of $FeCl_2$, the isocorrole amount increased and the free-base yield decreased. Further, adding an organic solvent considerably increased the isocorrole yield and decreased the free-base corrole yield. The best method turned out to involve concentrated H_2SO_4 with CH_2Cl_2, which gave free-base isocorroles as the main product, and negligible amounts of free-base corrole (Scheme 5.1).



Scheme 5.1. The Synthesis of undecaarylisocorroles.

Both 5- and 10-OH isomers were obtained, with the former predominating. The 10-OH isomer could not be isolated in sufficient quantities, except in one case where $H_2[(CF_3)_8Me_3(10\text{-}OH)]$ was obtained in sufficient yield. Column chromatography could not separate the 5- and the 10-OH isomers; thus PLC was invariably required for the isolation of these compounds. A photograph of the preparative thin-layer chromatogram is shown in Figure 5.2.

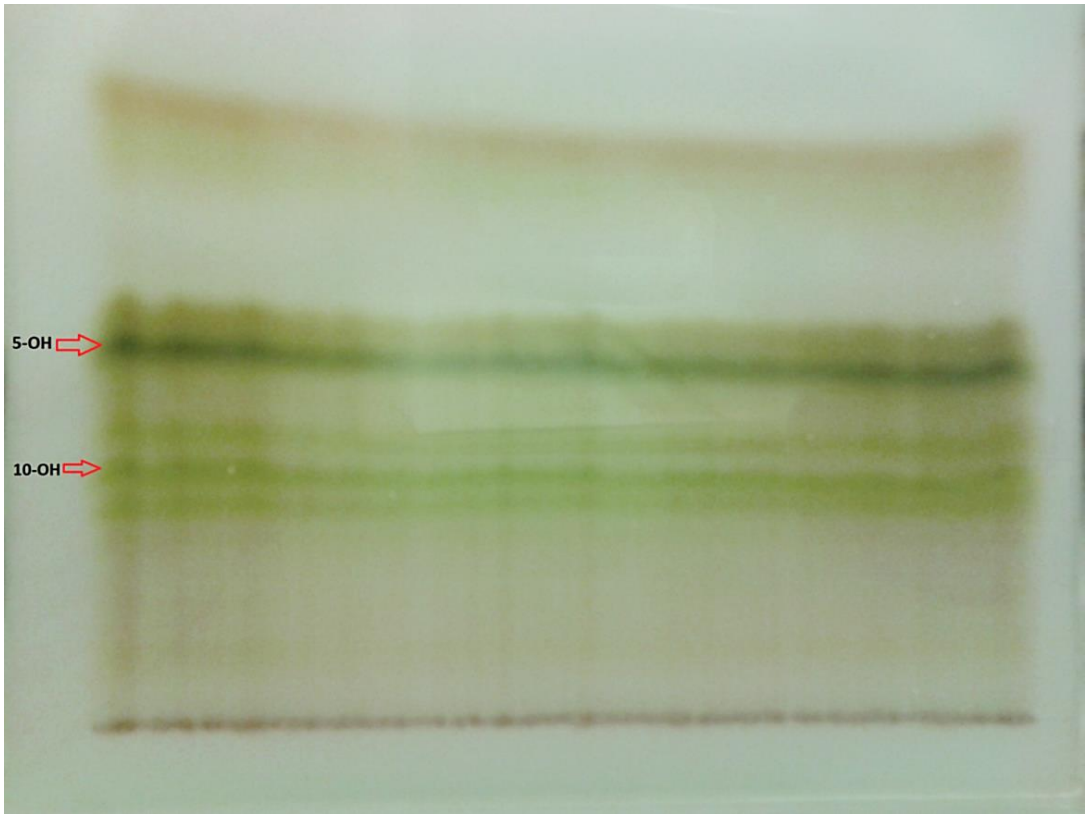
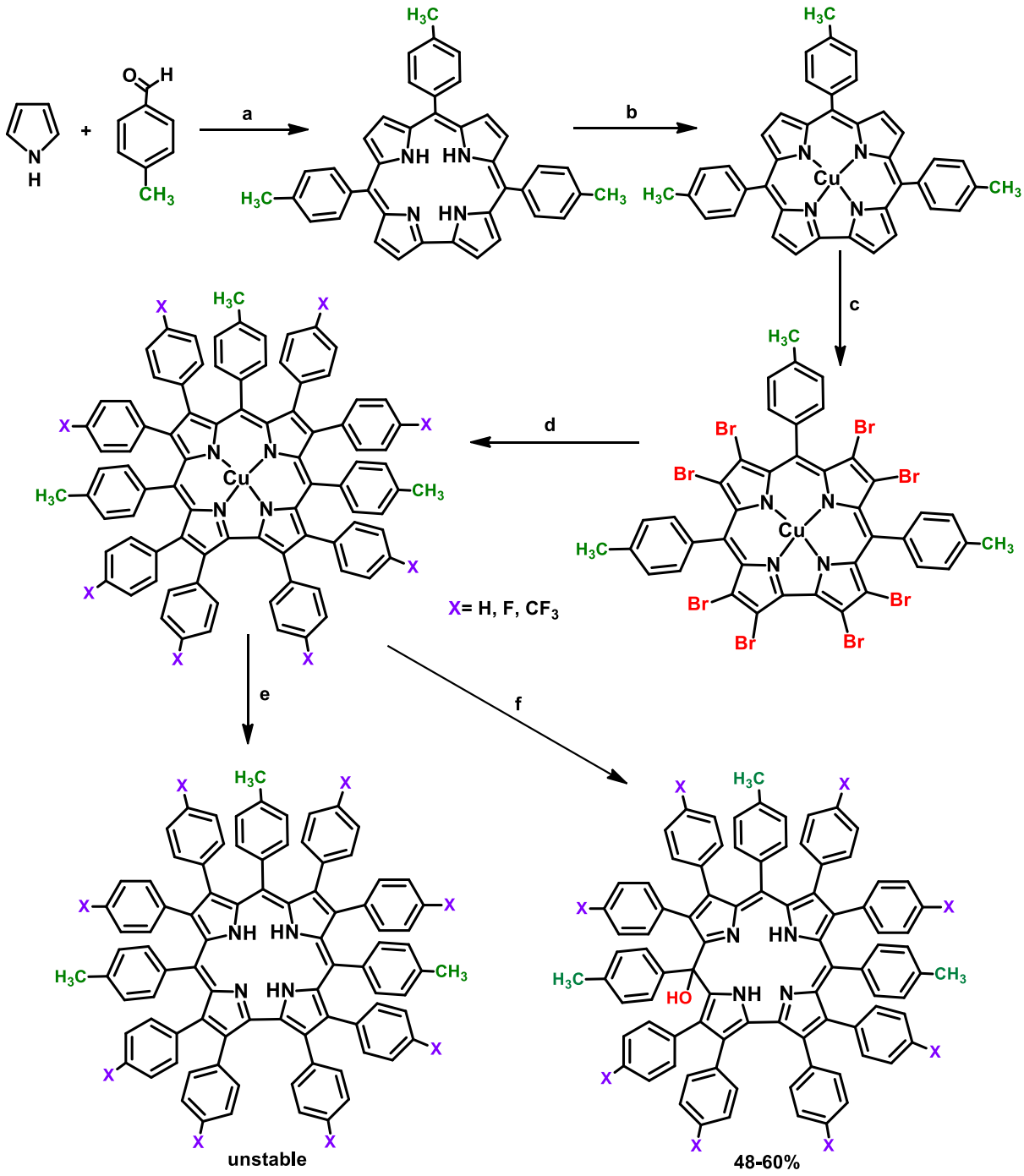


Figure 5.2. PLC of $H_2[(CF_3)_8Me_3(5\text{-}OH)]$ and $H_2[(CF_3)_8Me_3(10\text{-}OH)]$.

Until now, isocorrole formations *via* metallocorrole demetalation has only been viewed as a side-reaction rather than an actual synthesis. This work constitutes the first systematic synthesis of isocorroles *via* metallocorrole demetalation. Scheme 5.2 summarizes the complete synthetic scheme for undecaarylisocorroles.



Scheme 5.2. The synthesis of undecaarylisocorroles. **a)** (i) HCl, H_2O, MeOH, 3 h, (ii) *p*-chloranil, $CHCl_3$, reflux, 1 h. **b)** $Cu(OAc)_2.H_2O$, pyridine, 15 min. **c)** (i) Br_2, $CHCl_3$, 1 h (ii) pyridine 1 h. **d)** R-$B(OH)_2$, (R= 4-XPh, X= H, F, CF_3), $Pd_2(dba)_3$, K_2CO_3, 100 °C, toluene, under Argon, 1-2 days. **e)** Concd. H_2SO_4, $FeCl_2$, 15 min. **f)** Concd. H_2SO_4, CH_2Cl_2, 2-4 h.

Although both 5- and 10-OH isocorroles were observed in earlier demetalation reactions,[55,60] the proportion of these isomers was not specified. It was reported that in the demetalation of Cu[Br_8TPC], exclusively 10-OH isocorrole was formed, which the authors ascribed to steric reasons.[55] In this study, demetalation of copper undecaarylcorroles mainly produced the 5-OH isocorrole. The dominance of the 5-OH isomer is also in line with the synthesis of isocorroles (R= -OMe) by oxidation, where the authors noted higher reactivity of the 5-*meso* position towards oxidation.[106] Finally, the "probability factor" may also partly explain the dominance of 5-OH isomer. Oxygen attack on both the 5- and 15-*meso* positions produces a 5-OH isocorrole. Hence, formation of the 5-OH isocorrole is statistically twice as likely as formation of the 10-OH isomer.

An attempt at metalation of an undecaarylisocorrole with gold(III) acetate induced rearomatization of the macrocycle and produced the fully aromatized gold undecaarylcorrole complex Au[$(CF_3)_8H_3$]. A single-crystal X-ray structure of Au[$(CF_3)_8H_3$] was also obtained and is shown in Figure 5.3. The experimental and structural details of the complex is presented in paper VI.

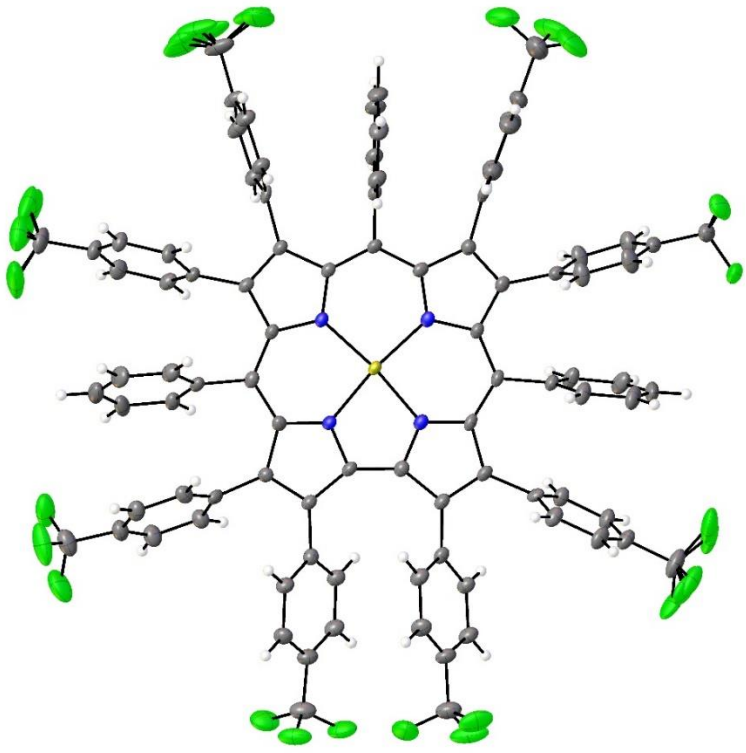


Figure 5.3. The X-ray structure of Au[$(CF_3)_8H_3$].

6. Concluding Remarks

The main accomplishments of my PhD research may be listed as follows:

1. The lack of demetalation procedures has long limited the corrole synthetic chemistry. Toward the end of my master's degree and in the early months of my PhD, I developed the reductive demetalation reaction for metallocorroles. During the remainder of my PhD, I investigated the full scope of the method as well as applications of the method to synthesize new complexes. Highly electron-deficient and sterically crowded corrole ligands were synthesized by applying newly developed demetalation procedures.

2. X-ray data and DFT calculations on a sterically crowded free-base corrole demonstrated that the unusual nonplanar distortion of free-base corroles is a direct result of the repulsion among the inner core hydrogens. High-resolution X-ray analysis enabled to locate the inner hydrogens corresponding to a specific tautomer. However, DFT calculations revealed no significant energy difference between the possible tautomers, explaining the varied locations of the inner hydrogens in the reported crystal structures to date.

3. Iron corroles are among the leading metallocorroles in terms of applications. Electron-deficient iron corroles have proven to be more robust and advantageous for several applications. Sterically hindered iron corroles are also expected to lead to improved shape-selectivity in catalysis and more effectively targeted drugs. Therefore, I used new free-base octabromocorrole ligands to synthesize iron octabromocorrole complexes, two of which were also characterized by single-crystal X-ray diffraction analysis.

4. Isotopically labeled $H_2{}^{18}O$ and ${}^{18}O_2$ experiments were conducted in order to identify the source of oxygen during the photodecomposition of the free-base corroles. The results showed that the oxygen source during the decomposition is air, rather than water.

5. A general method for synthesizing undecaarylisocorroles was developed and new highly sterically hindered ligands were prepared, one of which was identified through X-ray structural analysis. In contrast to free-base corroles, free-base isocorroles are fairly stable and can be complementary to corroles in terms of applications, such as photodynamic therapy which is mainly performed with free-base analogs of porphyrins.

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