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FEATURE ARTICLE

The porphyrinogen–porphyrin relationship: the discovery of artificial porphyrins

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The oxidation of *meso*-tetrahydrotetraalkylporphyrinogen, which is the chemical and biochemical precursor of porphyrins, has been reexamined using *meso*-octaalkylporphyrinogen as a model compound. This investigation has led to the discovery of oxidized forms of porphyrinogen other than porphyrins, which we call artificial porphyrins. They contain cyclopropane moieties which function as two-electron shuttles *via* the formation and cleavage of a C–C bond. The metal-assisted modifications of the porphyrinogen skeleton, namely the homologation of a pyrrole to a pyridine ring using carbon monoxide and the functionalization of the aliphatic periphery, are the consequences of the bifunctional acid–base carrier properties of these metal–porphyrinogen complexes. This observation allowed us to establish general synthetic methodologies in the fields of metal-assisted C–H bond activation and C–C bond formation.

Introduction

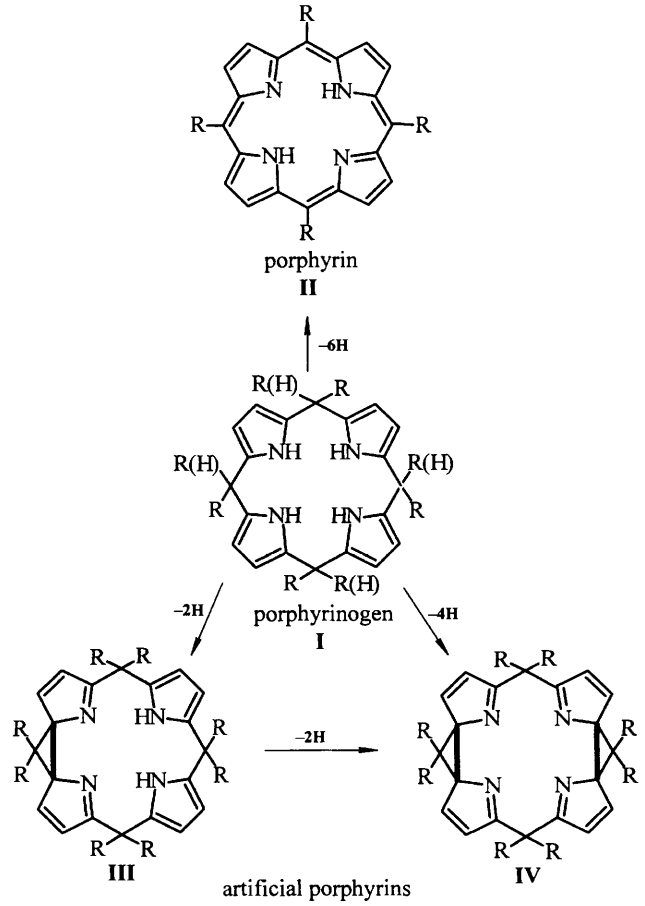
The popularity of the porphyrinogen molecular skeleton (Scheme 1) is based upon its use as a chemical and biochemical precursor of porphyrins.[1] This notwithstanding, its chemistry is almost unexplored, except for the spontaneous, six-electron oxidation leading to the corresponding porphyrin (Scheme 1). This is due to the fact that the *meso*-tetrahydrotetraalkylporphyrinogen is not available in a stable form, *i.e.* one which does not convert into a porphyrin. However, the prototype of a stable form of porphyrinogen, the *meso*-octamethylporphyrinogen, was discovered back in 1886 by Baeyer,[2] and it is abbreviated as $[R_8N_4H_4]$ (Scheme 1, R = Me). Until now, the molecule and its homologues have been almost totally ignored by chemists.[3]

The present report deals with: (*i*) an overview of the very recent metal-assisted redox chemistry of *meso*-octaalkylporphyrinogen.[4] This investigation has also led to the discovery of oxidized forms of porphyrinogen other than porphyrins, the so-called 'artificial porphyrins';[4c–e] (*ii*) the potential applications of such a skeleton to coordination and organometallic chemistry with an emphasis on its very recent metal-assisted transformations.[5–7]

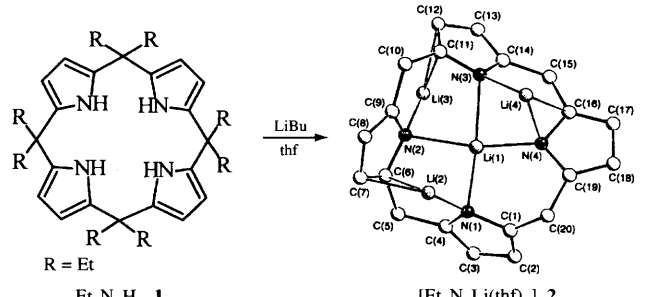
meso-Octaalkylporphyrinogen and its Deprotonated Form

The syntheses of *meso*-octaalkylporphyrinogens are quite straightforward, and follow a slight modification of the original method of Baeyer, which involves the acid catalysed condensation of pyrrole and the relevant ketone.[3] Considerable amounts of linear by-products and/or polymers form, depending on the reaction conditions and the substituent at the ketone functionality.

The presence of *meso* sp^3 carbons in **1** (Scheme 2) allows the coexistence of a number of conformations which have been observed both in solution[8] and in the solid state,[4e] as in the case of calix[4]arenes.[9] In the case of porphyrinogen, however, the R substituents play a significant role in the choice of the preferred conformation. Unlike its deprotonated forms, which have been obtained as alkali-metal derivatives, *meso*-octaalkylporphyrinogen is a very poor ligand for metals. The former compounds have different synthetic uses depending on the alkali-metal cation. The full deprotonation of **1** in the case of the *meso*-octaethyl derivative (Scheme 2) occurs as a result of the formation of a very tight ion-pair complex between lithium and



Scheme 1



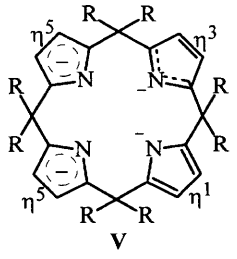
Scheme 2

the tetraanion, in which the lithium binding modes emphasize the polyfunctionality of the ligand.[10] A further solvated form $[Et_8N_4Li_4(thf)_4]$ **3** is currently used in our laboratories in metal complexation.[10]

We should comment briefly on the very peculiar bonding mode of the porphyrinogen tetraanion.[11] The four independent and conformationally flexible pyrrolyl anions can bind the metal in an η^1, η^3 or η^5 fashion providing $4(n + 2)$ electrons ($0 \leqslant n \leqslant 4$) to the metal (considering the following contribution for each pyrrolyl anion: η^1, $n = 0$; η^3, $n = 0.5$; η^5, $n = 1$) (Scheme 3) depending on its needs along the reaction pathway.[6,7,11] In addition, the pyrrolyl anions σ-bonded to the central metal atom maintain the ability to bind η^3 or η^5 to another metal ion on the periphery of ligand **V**.[4,6,7,11a,12] This peculiarity allows the *meso*-octaalkylporphyrinogen complexes to display an acid–base, bifunctional behaviour.[11a,13] We should also mention that the orientation of metal π-bonded pyrrolyl anions along with the *meso*-substituents provides a protected cavity for the metal.

The properties of the porphyrinogen ligand mentioned above are illustrated (Scheme 4) in the complexation of an electron-rich metal, *e.g.* Ni^{II} (see complex **4**),[12] and an electron-poor metal, *e.g.* Zr^{IV} (see complex **5**).[11a] The structure of **4**, which is quite similar to those of several other metal(II) ion–porphyrinogen complexes,[4,12] emphasizes the binding ability of the electron-rich porphyrinogen towards alkali cations along with the σ-bonding mode of the pyrrolyl anions. In complex **5**, the electron poor, d^0 zirconium(IV) forces some of the pyrrolyl anions to bind η^5 to the metal. The fluxionality of this molecule over a very small range of temperature (290–330 K) is in agreement with the electronic and steric flexibility of the tetraanion.[11a] The addition of electron-rich substrates to zirconium forces one of the π-bonded pyrrolyl anions to change to a σ-bonding mode.[6,7,11a]

Complexes **4** and **5** represent the two prototypes for metal–porphyrinogen chemistry.



V

4(2+*n*) electron donor ligand

$0<n<4$

8 24 electrons

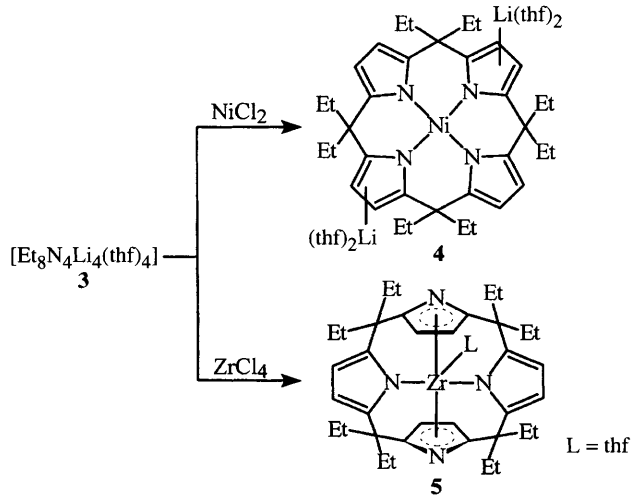
$n = 1$ for η^5

$n = 1/2$ for η^3

$n = 0$ for η^1

} pyrrolyl anion

Scheme 3



Scheme 4

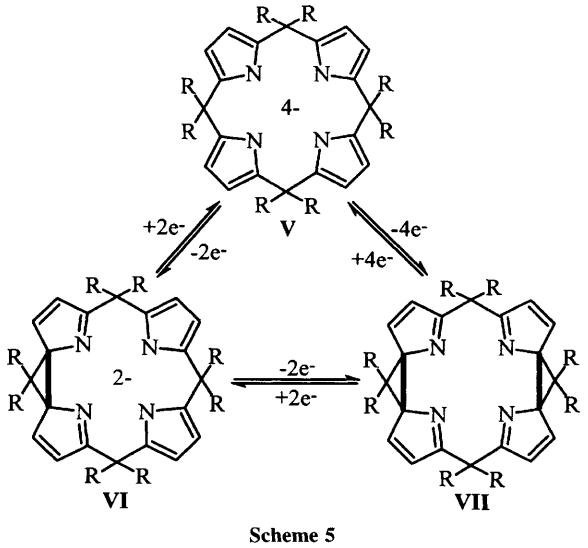
(*a*) Artificial Porphyrins: Oxidized Forms of Porphyrinogen other than Porphyrins

It is very difficult to understand the so-called oxidative aromatization of the porphyrinogen to the porphyrin skeleton (see Scheme 1), because such a process can be formally viewed as the result of two molecular actions, namely, the removal of six electrons followed by the removal of six protons. The key part of this process is the removal of four hydrogens from the *meso* positions. We were interested in answering the following questions in order to understand the porphyrinogen–porphyrin transformations: 'what happens when there are only alkyl groups in the *meso*-positions?', 'can we identify partially or fully oxidized forms other than porphyrins?', and 'is it possible to follow the pathway leading to these species?' Our results are shown in Scheme 1 and displayed using the standard convention for illustrating the oxidation of the porphyrinogen skeleton. They show the formation of a conventional porphyrin, **II**, from the six-electron oxidation of the *meso*-tetraalkyltetrahydroporphyrinogen and the formation of artificial porphyrins, **III** and **IV**, from the two- and four-electron oxidation of the *meso*-octaalkylporphyrinogen.

Two- and four-electron oxidized forms of porphyrinogen, like those shown in Scheme 1, would have no chance of being trapped in the case of *meso*-tetrahydrotetraalkylporphyrinogen, although they may be eventually identified in the *meso*-octaalkyl form. Scheme 5 gives a more clear picture of the oxidation of *meso*-octaalkylporphyrinogen tetraanion by two and four electrons in which no removal of atoms is required.

Such a redox scheme is correct if one assumes that the tetraanion is bound to the transition metal, which should assist the oxidation (*vide infra*) of the porphyrinogen skeleton. We anticipated that oxidation by two electrons leads to the formation of a cyclopropane unit, which can undergo the reverse reduction with the cleavage of the same C–C bond. Therefore each cyclopropane unit within the artificial porphyrin acts as a two-electron shuttle. Let us first discuss the overall metal-assisted pathway and the reaction conditions leading to the generation of 'artificial porphyrins'.[4c–e]

Scheme 6 shows the stepwise oxidation of a parent porphyrinogen–metal complex to an artificial porphyrin. Such an oxidation allows, depending on the nature of the metal and the oxidation agent, the isolation of all the reported species.



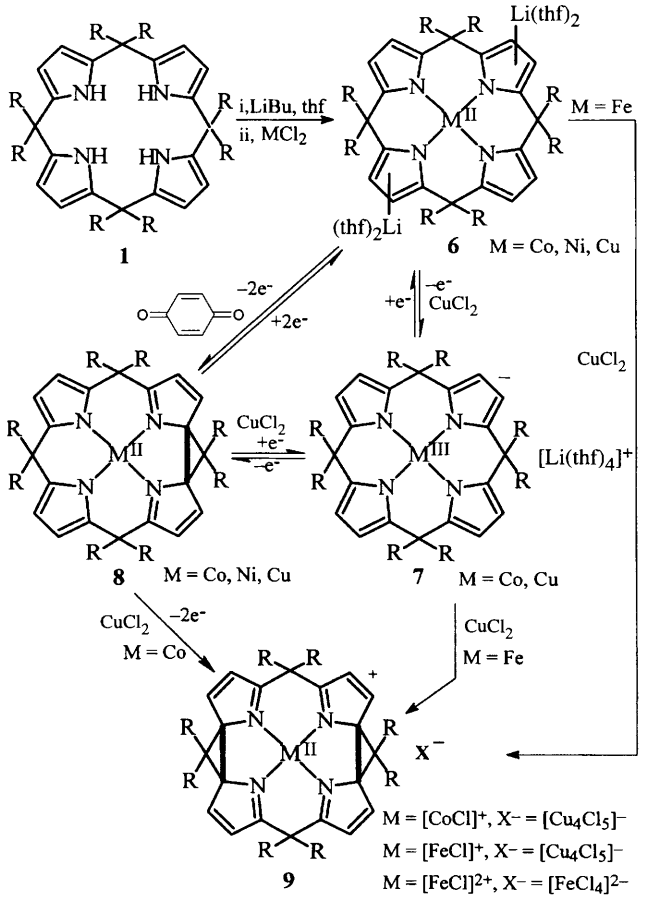
Scheme 5

Although the formation of a cyclopropane unit is an overall two-electron oxidation (see Scheme 5), it proceeds *via* two monoelectronic steps, the first being the metal(II) to metal(III) oxidation followed by the formation of a cyclopropane unit and the concomitant reduction of M^{III} to M^{II}.[4c] The monoelectronic pathway has been elucidated by using $CuCl_2$ as oxidizing agent in the case of Cu^{II} and Co^{II}, which have an accessible +3 oxidation state. The use of *para*-benzoquinone as oxidant led to the two-electron oxidation product, that is the cyclopropane, regardless of the transition metal, and it works only in case of the formation of the first cyclopropane. The monoelectronic pathway emphasizes the effectiveness of the metal-to-ligand intramolecular electron transfer. In addition, we can reasonably assume that the cyclopropane unit is masking a +2 oxidation state for the bound metal.[4c,d]

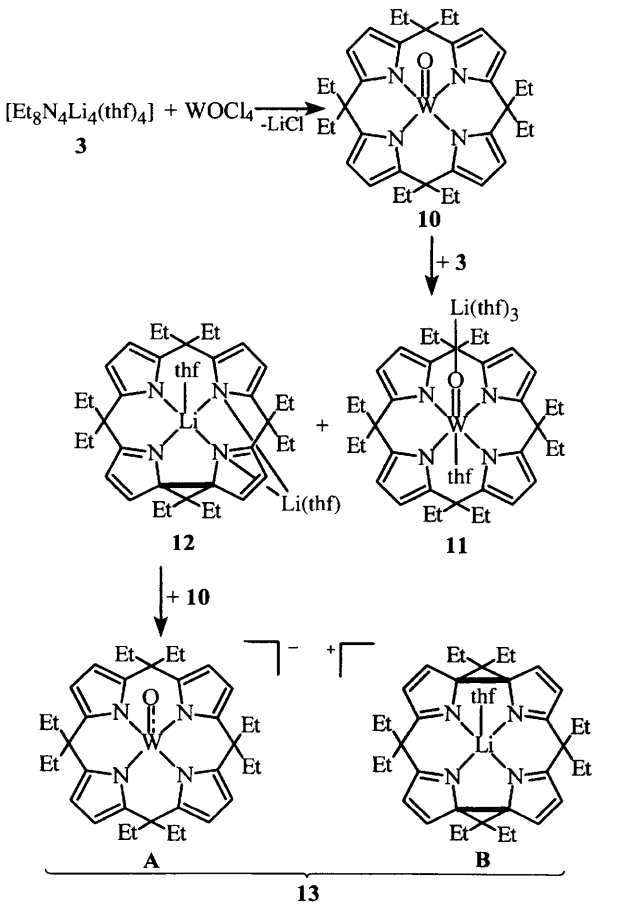
The disproportionation of **7** to **8** and **6**, or the reaction of **8** with **6** leading to **7**,[4c] both being solvent-dependent reactions, emphasize how the formation and cleavage of a cyclopropane unit can occur as a result of an intermolecular electron transfer process. The fully oxidized form of *meso*-octaalkylporphyrinogen containing two cyclopropane units and obtained using $CuCl_2$ as oxidant, has only been obtained for Co,[4d] Fe[4d] and Mn.[14] The use of $CuCl_2$ gives the inconvenient cluster $[Cu_4Cl_5]^-$ as a counter anion for **9** bonded to the four pyrrolic C=C double bonds. However, $[Cu_4Cl_5]^-$ does not impart any extra stabilization to the biscyclopropane form, as evidenced by the isolation of **9**·$[FeCl_4]^{2-}$.[4d] Reduction of the cyclopropane forms **8** and **9** with lithium metal reverses this process to give the parent porphyrinogen–metal complexes *via* the same monoelectronic pathway.[4c–e] Therefore, when complexes **8** are reacted with 1 equiv. of a reducing agent, **7** is formed. A variety of reducing agents can cleave the cyclopropane unit and restore the porphyrinogen skeleton, the mildest ones being S^{2-} and RS^-.[14] Scheme 6 may be extremely suggestive of a possible stepwise aromatization pathway of the porphyrinogen leading to porphyrins. In this case, the formation of the cyclopropane derivative would not be restricted to the oxidation of *meso*-octaalkylporphyrinogen, but may be a fundamental intermediate in the formation of porphyrins preceding the removal of the four *meso*-hydrogens.

One question which arises at this point is: can we provide these artificial porphyrins as metal-free ligands? As for many of the metal–porphyrin complexes, the synthesis is better achieved *via* the oxidation of the corresponding metal–porphyrinogen precursor. However, quite recently we were able to study the redox chemistry of high valent, early transition metal–porphyrinogen complexes, thus making available **III** and **IV** (Scheme 1) as free ligands. The reactions in Scheme 7 have been converted into synthetic methods for **12** and **13B**.[15]

Although their exploitation is at an early stage, these preliminary accounts on the discovery of 'artificial porphyrins' allow one to catch a glimpse of the potential of such molecules in electron-transfer processes. A few facts should be emphasized: (*i*) unlike the porphyrinogen–porphyrin couple, in the *meso*-octaalkylporphyrinogen–artificial porphyrin couple the redox interconversion between the two forms is energetically quite easy. It is particularly attractive to follow the small conformational changes which parallel the conversion of porphyrinogen into artificial porphyrins, as shown in Scheme 8 for the case of a cobalt–porphyrinogen complex. Such small conformational changes may be one of the reasons for the easy porphyrinogen–artificial porphyrin interconversion; (*ii*) the cyclopropane unit functions as a two-electron shuttle, thus the C–C bond formation and breakage behaves as a molecular battery; (*iii*) the metal-to-ligand synergism allows one to use the cyclopropane to mask high oxidation states of the metal, each cyclopropane unit having a contribution of +2 per metal; (*iv*) the redox processes can be tailored to occur exclusively at the



Scheme 6 Reductions carried out with Li; R = Et



Scheme 7

metal, at the ligand, or at the metal–ligand sites; (*v*) the cleavage and formation of cyclopropane can be used for planning long-range electron-transfer processes; (*vi*) the appropriate site opening of the cyclopropane may lead to a ring-contracted corrinoid-type skeleton, or to other modifications of the porphyrinogen frame.

(*b*) Modifying the Porphyrinogen Skeleton using Organometallic Methodologies

In the context of the porphyrinogen–artificial porphyrin relationship, modification of the porphyrinogen skeleton may shed more light on the mechanism of this transformation and make available other types of artificial porphyrins. Traditionally, such modifications of the porphyrinogen skeleton may be achieved using conventional organic assembly methods, but we will approach this problem using organometallic methodologies applied directly to the porphyrinogen skeleton.[1] These have been essentially based on the discovery that *meso*-octaalkylporphyrinogen–metal complexes behave as carriers for polar organometallics.[5,11a,13] As a result, we have been able to: (*i*) functionalize the *meso*-octaalkylporphyrinogen at the aliphatic periphery, or, in more general terms, to establish a novel entry into intra- and inter-molecular C–H bond activation;[5,6] (*ii*) change the redox properties of the porphyrinogen skeleton by replacing pyrrole rings with pyridine ones.[7,13c] This was carried out *via* a direct homologation of a pyrrole to pyridine within the porphyrinogen structure using carbon monoxide under mild conditions (Scheme 9).

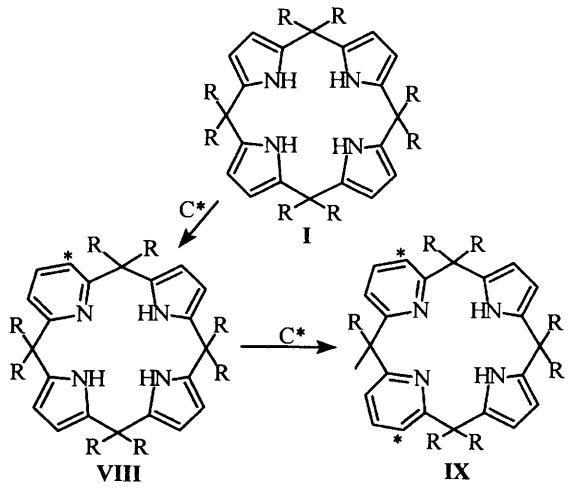
(*i*) **Regiochemically controlled mono- and bis-homologation of porphyrinogen using carbon monoxide.** The homologation[16] of porphyrinogen involves the introduction of one carbon atom into one or two pyrrole rings, as depicted in Scheme 9. Such a homologation of pyrrole to pyridine leads to the otherwise barely accessible trispyrrole–monopyridine and bispyrrole–bispyridine porphyrinogen-based macrocycles.[7,13c]

The homologation of pyrrole to pyridine has been successfully achieved by exploiting some well known organometallic reactions, such as the insertion of carbon monoxide into Zr–H and Zr–C bonds *via* the migration of the hydride and alkyl ligands.[17] This often studied reaction produces η^2-formyl and η^2-acyl carbenium ions.[18] When sterically protected towards dimerization (which would yield an enediolato complex)[17] or reduction, a carbenium ion will react as such.

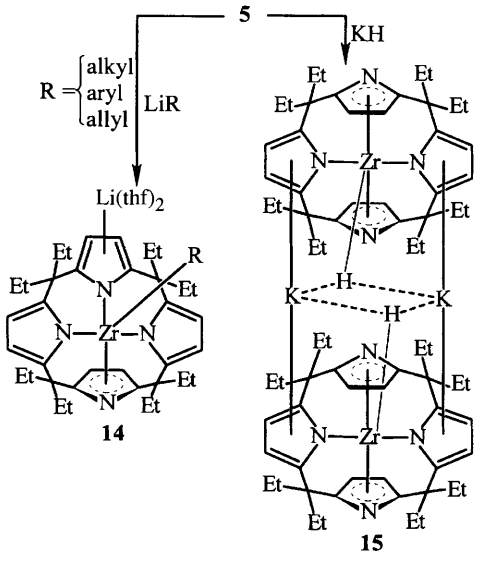
The *meso*-octaethylporphyrinogen ligand exhibits some interesting characteristics which assist the transformations mentioned above. Specifically, the conformations derived from the sp^3 carbons in the *meso*-positions and the porphyrinogen to zirconium bonding modes create cavities, thus to assure the stabilization of reactive intermediates at the metal and the geometrical proximity of reactive sites (pyrroles).[7] Further, the electron-rich periphery of porphyrinogen is capable of binding an alkali-metal cation[4,6,7,11a,12] and this property is of major assistance in the homologation reaction pathway. This property makes the early transition metal–porphyrinogen complexes particularly novel carriers for polar substrates, such as metal hydrides and alkali-metal organometallics,[11a,13] as exemplified in Scheme 10.

The addition of a carbenium η^2-formyl or η^2-acyl unit to a pyrrole ring, followed by the complete cleavage of a C–O multiple[19] bond due to the presence of very oxophilic metal centres such as zirconium and potassium, led to the homologation of a pyrrole to a pyridine ring (Scheme 11).

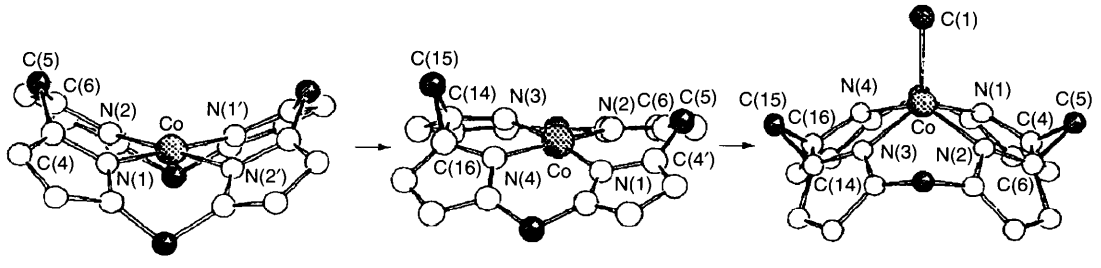
It is the reaction of these metal hydride bridged dimers with carbon monoxide which paves the way for the pyrrole to



Scheme 9



Scheme 10

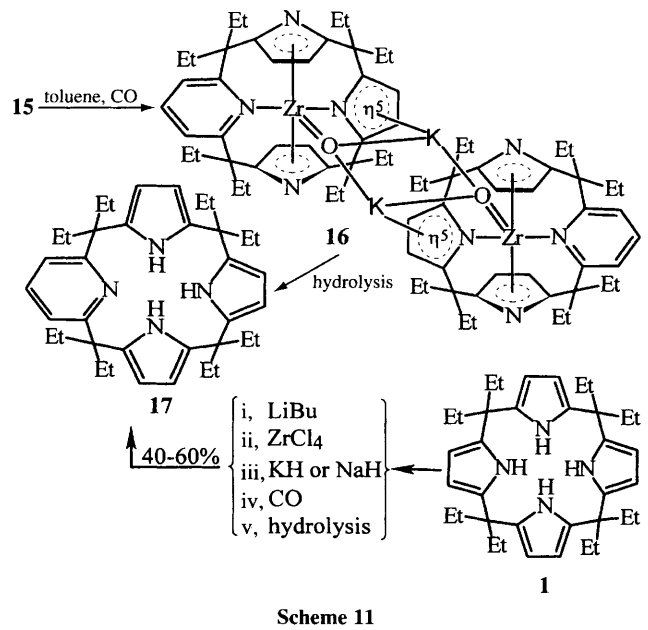


Scheme 8

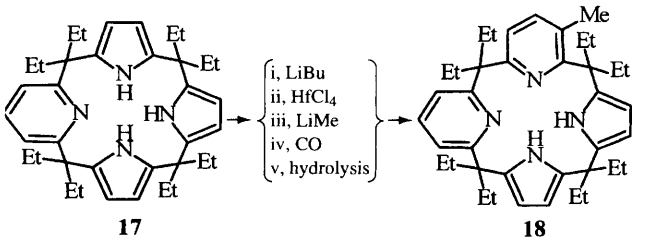
pyridine transformation. Migratory insertion reactions of carbon monoxide with Zr–H (and Zr–C) bonds have mainly focused on cyclopentadienyl- and alkoxo-based systems.[17] The analogous reaction performed with **15** emphasizes the unusual role that porphyrinogen can play as an auxiliary ligand. Indeed, the ability to bind alkali-metal cations has already been alluded to. Furthermore, the considerable three-dimensional bulk of the ligand provides the necessary steric protection for the organometallic functionality. We have investigated the large-scale synthesis of **17** as either a multiple step or a one-pot preparation. Both strategies gave comparable yields (40–60%)[7] and we are now able to produce **17** in quantities of up to 50 g following the sequence shown in Scheme 11.

One major stereochemical consideration which should be addressed in the pyrrole to pyridine conversion is the regiochemistry of the homologation reaction. As a result of the attack of a carbenium ion on the pyrrole ring, the formyl carbon should be in the *meta* position of the final pyridine fragment. This regiochemistry is observed in the ring expansion of pyrrole to pyridine when using carbenes.[20] This regiochemistry has been found in the reaction of Zr–alkyl derivatives **14** with carbon monoxide leading exclusively to *meta*-substituted pyridines. Attempts to modify the regiochemistry of the homologation of the *meso*-octaethylporphyrinogen [$Et_8N_4H_4$], and to proceed further with the homologation of a second pyrrole ring have been successfully negotiated using metals other than zirconium. For instance, the use of niobium[7] and titanium[13c] allowed the preparation of *para*-substituted pyridine rings.

For the second homologation, the sequence followed is shown in Scheme 12.[7] The reasons for the compulsory use of Hf instead of Zr is still obscure. The organometallic pathway leading from **17** to **18** is quite similar to that clarified for the homologation of **1** to **17** in Scheme 11.



Scheme 11



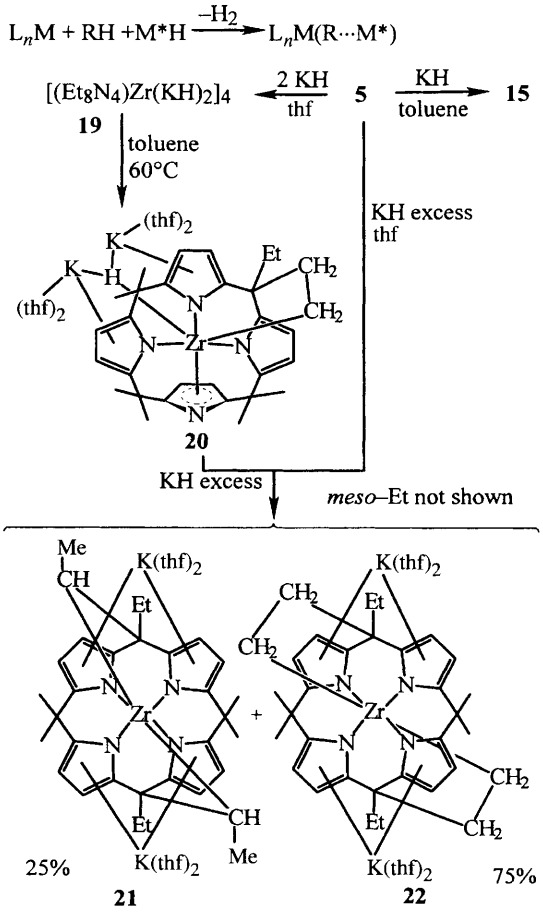
Scheme 12

Between the two possible positional isomers (consider the two non-equivalent *meta* positions), **18** is the only one we have identified.[7]

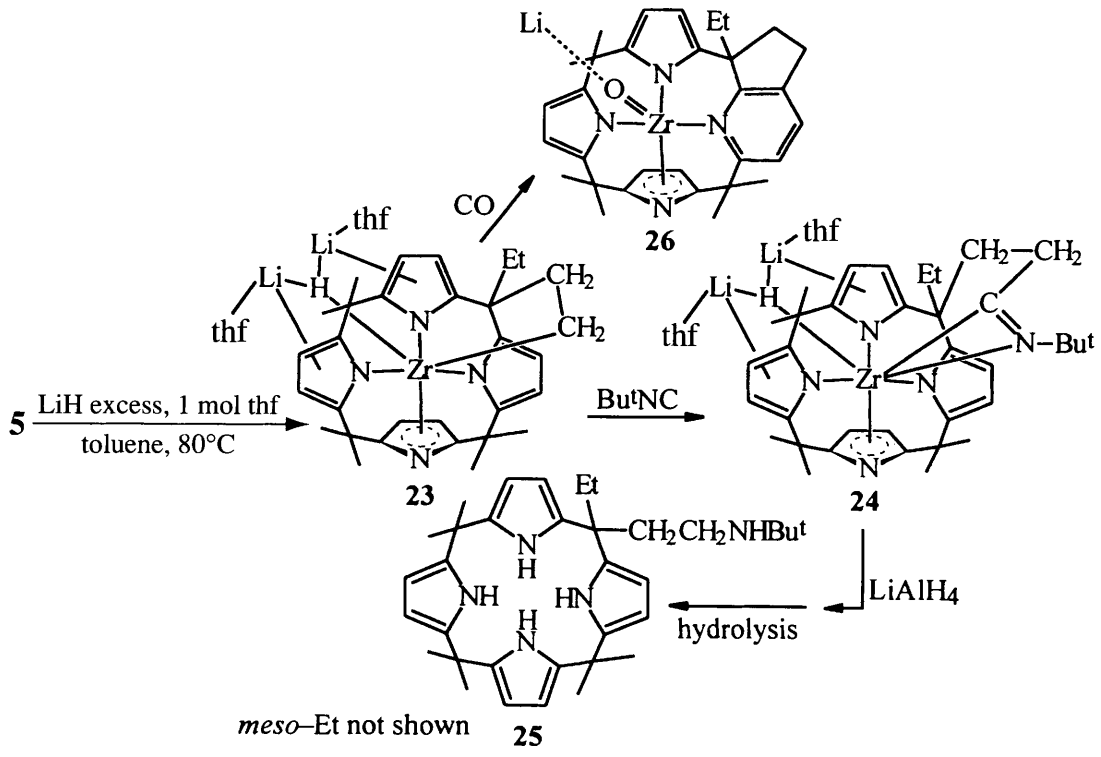
The results reported emphasize how we can modify the skeleton and control the related regiochemistry of rather complex structures, like those of macrocyclic polypyrroles, using organometallic methodologies. In addition, this process does not remain just a chemical curiosity, since we can use this transformation as a good preparative method for a novel class of macrocycles. The introduction of one or two pyridines into a tetrapyrrolic macrocycle greatly modifies the geometric and electronic properties of this very important class of compounds, and could lead to porphyrins other than those shown in Scheme 1.

(*ii*) **The functionalization of aliphatic chains at the porphyrinogen periphery**. Although electrophilic, metal-mediated aliphatic C–H cleavage is precedented in the literature,[21] its application to the functionalization of complex substrates is almost unknown. We review here a novel electrophilic C–H bond activation and its application to the functionalization of the porphyrinogen skeleton (see Scheme 13). Unlike the usual approach, in which a metal-bonded alkyl or hydride is employed to remove an aliphatic hydrogen in intra- or inter-molecular processes,[21] the following strategy has been explored. The removal of an aliphatic hydrogen by an alkali-metal hydride M*H, assisted by an electrophilic metal, leads to the formation of a polar alkali metal···alkyl species complexed by L_nM (Scheme 13).[11a,13]

Therefore, the process depicted at the top of Scheme 13 is achieved intra-molecularly using alkali-metal hydrides. This type of reaction is particularly intriguing and very dependent on factors such as the MH : Zr ratio, the nature of the solvent, and the nature of the alkali-metal cation.[13b] The reaction of **5** with



Scheme 13



Scheme 14

KH exemplifies the complexity of this chemistry (Scheme 13). The mixture of **21** and **22** obtained from **20** is accounted for by the facile σ-bond metathesis of Zr–C and Zr–H bonds and is also the entry into the intermolecular C–H bond activation.[5,6]

The alkali-metal ion plays a major role in the metallation reaction. Using LiH and NaH, instead of KH, even under very drastic conditions and in a large excess, a single ethyl group undergoes metallation, **23**.

The Zr–C bonds formed *via* the intramolecular metallation of the porphyrinogen periphery should readily allow its functionalization using conventional organometallic methodologies.[5,6a] Among the reactions that have been explored, the insertions of isocyanides and carbon monoxide are summarized in Scheme 14.[6a]

In conclusion, the metallation of aliphatic chains at the periphery of *meso*-octaethylporphyrinogen has been achieved *via* the electrophilic activation of the C–H bond followed by the removal of the β-proton using alkali-metal hydrides. The success of this class of reactions depends on two important features. First, the bifunctional nature of metal–porphyrinogen complexes allows the binding of cations at the electron-rich periphery and, as a consequence, their ability to function as polar organometallic carriers. Secondly, their reactivity is very dependent on the conformation of the porphyrinogen, which allows the C–H bond of the periphery to come in close proximity to the central electrophilic metal. Finally, an intramolecular σ-bond metathesis between Zr–C and C–H bonds was observed in the conversion of the ethyl groups of porphyrinogen from the β- to the α-metallated forms.

The results we have reported emphasize how appropriate organometallic methodologies (bifunctional complexes, conformational effects, polar organometallic carriers) allow the activation and functionalization of aliphatic substituents in large organic molecules.

Future Prospects

In this brief survey, I have been able to give an exhaustive account of all of our recent results in the field of porphyrinogen–transition-metal chemistry. Furthermore, the work that is described has only been briefly outlined. The future prospects for this field are quite exciting, and some of major directions may be: (*i*) the exploitation of the artificial porphyrins; (*ii*) the chemistry of the porphyrinogen–metal complexes allowing the development of systems whose redox chemistry is associated with the formation and cleavage of C–C bonds, as in the artificial porphyrins; (*iii*) the use of transition metal–porphyrinogen complexes as carriers for polar organometallics, ion-pairs and salts leading to the development of novel synthetic methodologies in organic chemistry.

Acknowledgments

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Carlo Floriani's research interest is in molecular design to target specific functions. After obtaining his doctoral degree in organic chemistry (Milano, Italy), he went to CERI (Geneva) for a post-doctoral training in organometallic chemistry. He returned to Italy and became a Professor of Inorganic Chemistry at the University of Pisa. He then moved to Columbia University (New York, USA) as a Professor of Chemistry, followed by his return to Europe at the University of Lausanne (Switzerland). He has been honoured, among other things, by the award of the Centenary Lecture and the silver medal by the Royal Society of Chemistry.

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