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Synthesis of biomimetic heme precursors

Eric Rose *, Alexandra Lecas, Mélanie Quelquejeu, Alain Kossanyi, Bernard Boitrel

Laboratoire de Synthèse Organique et Organométallique, UMR CNRS 7611, Tour 44, 4 Place Jussieu, 75230 Paris, Cedex 05, France

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* Corresponding author. E-mail: rose@ccr.jussieu.fr

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Abstract

Three kinds of biomimetic heme precursors have been prepared. The first type is based on tetra-aminoporphyrins: either 5,10,15,20-tetrakis (*o*-aminophenyl)porphyrin (various atropoisomers), or 5,15-bis(2′,6′-diaminophenyl)porphyrin. The second type is based on octa-aminoporphyrins: 5,10,15,20-tetrakis (2′,6′-diamino-4′-*tert*-butylphenyl)porphyrin. One example of "basket handle" porphyrin demonstrates selective discrimination between O_2 and CO with an M value [$M=p_{1/2}(O_2)/p_{1/2}(CO)$] of 105. This is similar to values reported for various natural hemoproteins. The third type is based on aminoporphyrin templates [5, 5,10- or 5,15- and 5,10,15-(2′,6′-dinitro,4′-*tert*-butylphenyl)porphyrins] which have been tested in asymmetric epoxidation.

Keywords: Asymmetric oxidation; Hemoprotein model; Metalloporphyrin; Myoglobin; Porphyrins

1. Introduction

There is continuing general interest in models of hemoproteins. Work on synthetic heme complexes began in the 1970s and indeed the construction of sophisticated porphyrins has become a new art. There are still several areas where model complexes can enhance our understanding. Synthetic heme dioxygen complexes, for example, are the subject of many comprehensive reviews [1–16] and, taken together, this work has contributed greatly to our understanding of the biochemistry of oxygen binding. Model complexes are in particular useful for exploring the mechanisms by which structure modulates reactivity. With regard to mechanism there is still great unexplored territory, particularly in the case of hemoglobin, cytochrome P-450 and cytochrome c oxidase.

No one has been able to create a simple model of cytochrome P-450 that can catalyse the asymmetric hydroxylation of unactivated C–H bonds with high turnover and high enantiomeric excess. The catalytic reaction of cyt-P450 involves the cleavage of the O–O bond of molecular oxygen. Two electrons and two protons are consumed such that only one oxygen atom is eliminated as water. The second oxygen atom is introduced into the substrate [Eq. (1)]:

$$RH+O_2+2e^-+2H^+ \rightarrow ROH+H_2O \quad \epsilon^{\circ\prime}=+0.89\ V\ (vs.\ NHE) \qquad (1)$$

The second goal is to understand the "oxygen electrode" of nature's fuel cell. The capture and storage of the free energy released during the reduction of oxygen to water is the basis of respiratory life. Although there is a large thermodynamic driving force for the four-electron reduction of dioxygen to water in the presence of protons, this is kinetically slow [Eq. (2)]:

$$O_2+4H^++4e^- \rightarrow 2H_2O \quad \epsilon^{\circ\prime}=+0.82\ V\ (vs.\ NHE) \qquad (2)$$

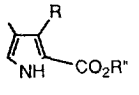
Many chemical model systems based on metalloporphyrin catalysts have been described in the literature. The purpose of this paper is not to give a review of these

results [13,15], but more to give an idea of our own contribution in this field. The strategy we have developed is based on the preparation of porphyrins derivatized on both faces. In the first section, we describe the synthesis of bis-*ansa* compounds: "gyroscope" and "bis-handle" (called also "bis-strapped" or "basket-handle") porphyrins. In the second section, we report some very recent results concerning a new generation of porphyrins: the "double picket fence" porphyrins which seem promising as catalysts in asymmetric oxidation.

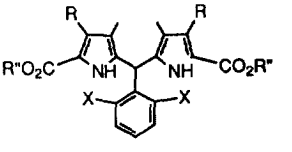
2. *Ansa* porphyrins

2.1. *Preparation of "gyroscope" and "basket handle" porphyrins*

Condensation of 2-ethoxycarbonyl, 3-n-butyl, 4-methyl pyrrole **1a** or 2-benzyloxycarbonyl, 3-n-butyl, 4-methyl pyrrole **1b** with 2,6-dinitrobenzaldehyde in the presence of catalytic amount of CF_3CO_2H in benzene gives aryldipyrrylmethanes **2a** or **2b** [17–19]. In the case of 2,6-diacetamidobenzaldehyde and pyrrole **1b** or 2-benzyloxycarbonyl 3,4-dimethyl pyrrole **1c**, this condensation yields dipyrrylmethanes **2d** and **2c** respectively. However, acidic or basic hydrolysis of **2a** or **2b** gives polymeric material. Hydrogenolysis of dipyrrylmethanes **2c** and **2d** gives the diacids **2e** and **2f**. They react with $HC(OEt)_3$ and CCl_3CO_2H or CF_3CO_2H and after dichlorodicyanobenzoquinone oxidation, give porphyrins **3b** and **3a**. HCl (6 N) hydrolysis of **3a** affords a sparingly soluble porphyrin, **3c**, which we react with pivaloyl chloride to give porphyrin **3e**. Porphyrins **3f**, **3g** and **3h** can be obtained by condensation of **3d** with benzyloxycarbonyl-L-phenylalanine, benzyloxycarbonyl-L-alanine or *tert*-butyloxycarbonyl-L-alanine [20].



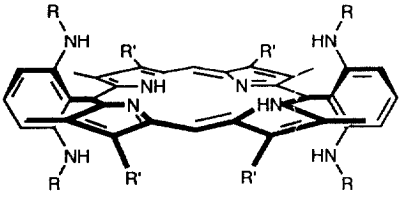
1a R= n-Bu, R"= Et
1b R= n-Bu, R"= CH_2Ph
1c R= Me, R"= CH_2Ph



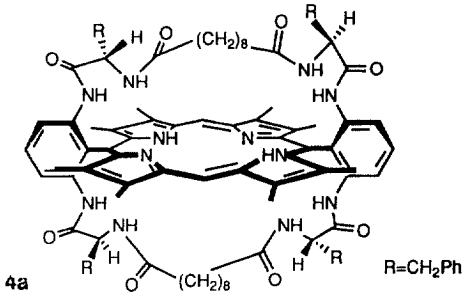
2a R= n-Bu, R" = Et X = NO_2
2b R= n-Bu, R" = CH_2Ph X = NO_2
2c R" = CH_2Ph, X = NHAc, R= Me
2d R" = CH_2Ph, X = NHAc, R= n-Bu
2e R" =H, X = NHAc, R= Me
2f R" = H, X = NHAc, R= n-Bu

Hydrogenolysis of porphyrins **3f** or **3g** or hydrolysis of porphyrin **3h** affords porphyrin **3i** or **3j**. The bis-*ansa* porphyrin **4a** can be obtained, for example, by condensing the four-picket porphyrin **3i** with sebacic acid chloride.

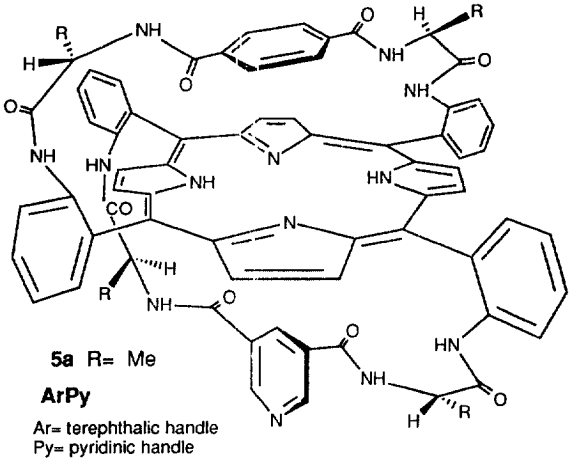
Similarly, porphyrin **5a** can be obtained using the classical α,β,α,β-atropoisomer of *meso*-tetrakis (2-nitrophenyl)porphyrin **6a** [3]. Indeed, reduction of porphyrin **6a** with $SnCl_2$, $2H_2O$ and HCl gives the tetra-aminoporphyrin **6b**. Condensation of **6b** with benzoyloxycarbonyl-L-alanine affords the porphyrin **6c** whose hydrogenolysis affords the porphyrin **6d**.



3a R= Ac R'= n-Bu
3b R= Ac R'= Me
3c R= H R'= n-Bu
3d R= H R'= Me
3e R= $COCMe_3$ R'= n-Bu
3f R= $COCH^*(CH_2Ph)NHCO_2CH_2Ph$ R'= Me
3g R= $COCH^*(Me)NHCO_2CH_2Ph$ R'= Me
3h R= $COCH^*(Me)NHCO_2{}^tBu$ R'= Me
3i R= $COCH^*(CH_2Ph)NH_2$ R'= Me
3j R= $COCH^*(Me)NH_2$ R'= Me



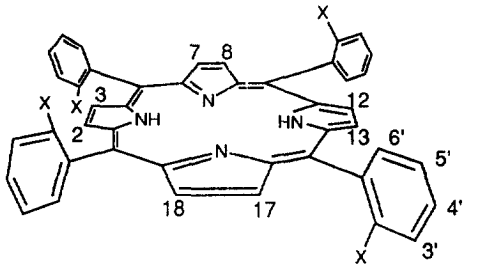
4a R=CH_2Ph



5a R= Me

ArPy

Ar= terephthalic handle
Py= pyridinic handle

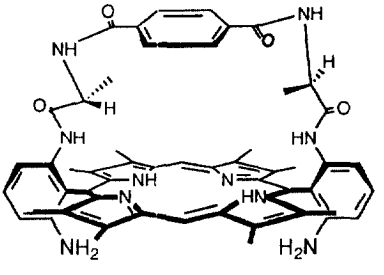


6 a X= NO_2
b X= NH_2
c X= NHCOC*HMeNHCO$_2$R'
d X= NHCOC*HMeNH$_2$
e X= NHCOCHMeNH$_2$ racemic

R'=CH_2Ph, ^tBu

Condensation of **6d** with both terephthaloyl chloride and 3,5-bis (chlorocarbonyl)pyridine afforded inter alia the porphyrins **14**, **5a** and **13** in 11%, 18% and 10% yield respectively. It is worth noting that this atropoisomer can be obtained as the major isomer (72%) on a large scale by heating a mixture of the four atropoisomers α^4, $\alpha^3\beta$, $\alpha^2\beta^2$, $\alpha\beta\alpha\beta$ for 20 min at 130 °C in naphthalene [21]. In a similar manner, the $\alpha^2\beta^2$ atropoisomer can be obtained as the major product (92%) by heating a mixture of the Zn-mixed atropoisomers for four days at 120 °C [22].

Condensation of the porphyrin **3j** (under high dilution conditions) with one equivalent of terephthaloyl chloride afforded the mono-*ansa* porphyrin **7**. This porphyrin can be transformed into the bis-*ansa* porphyrin **8** by condensation with 3,5-bis-(chlorocarbonyl)pyridine. We named porphyrin **8** the "gyroscope" porphyrin [23]. Alternatively, condensation of **3j** with both terephthaloyl chloride and 3,5-bis-(chlorocarbonyl)pyridine gives a mixture of the "gyroscope" porphyrins **8**, **9** and **10**.



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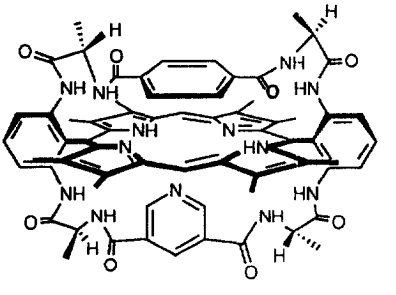

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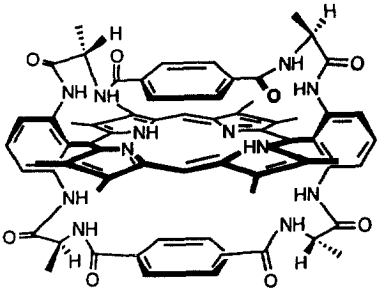
2.2. Unexpected tetracoordinated iron(II) bis-strapped chiral porphyrin bearing a nitrogen base on one handle

Insertion of iron into the bis-strapped porphyrin **5a** with $FeCl_2$ and 2,6-lutidine in refluxing toluene yielded an unexpected square planar iron(II) complex, **11**, which is only soluble in MeOH, pyridine or a mixture of $CHCl_3$ and MeOH. This paramagnetic compound, which demonstrates highly contact shifted signals for the protons



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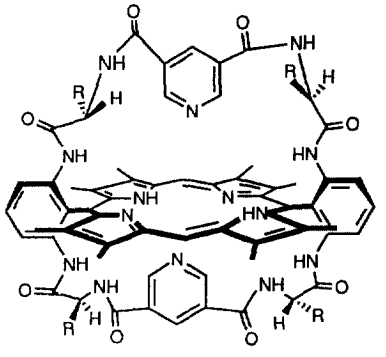
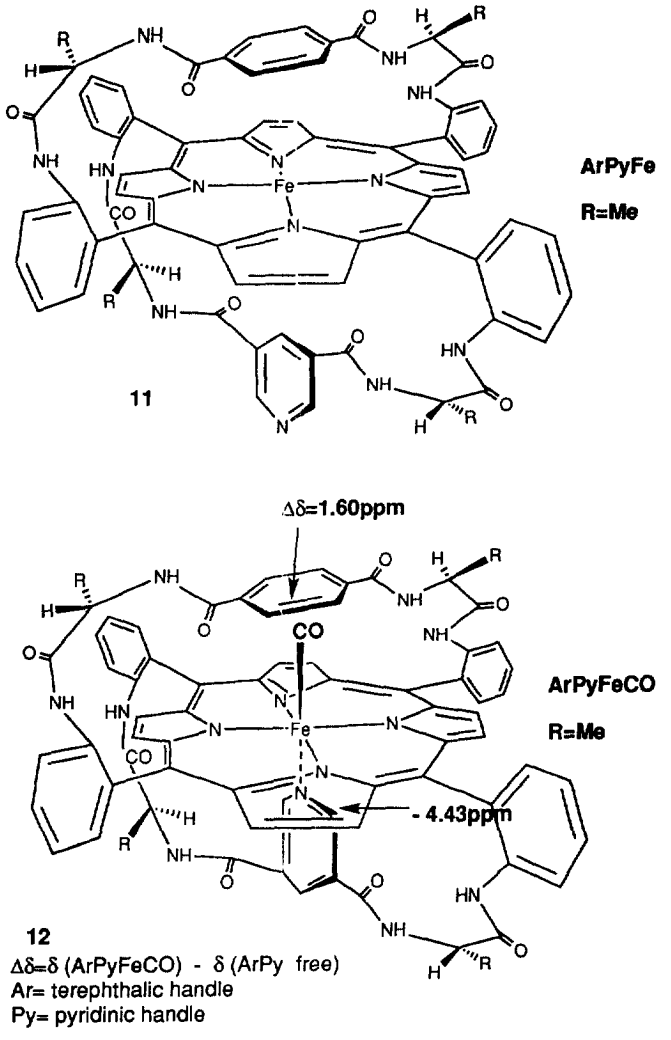


10 R=Me

of the straps, is not able to coordinate the pyridine in the strap. This indicates that the five-coordinated compound, with the iron out of the plane towards the pyridine ligand, cannot be formed [24]. Under a CO atmosphere, the diamagnetic six-coordinated iron(II) derivative, **12**, is obtained [23]. In other words, with CO as ligand, the pyridine strap is now capable of coordinating iron. The ^{1}H NMR spectrum of **11** in CD_3OD shows peaks between +17 and −78 ppm which is typical of an iron(II) ($S=1$) porphyrin. Two high-field resonances at −77.92 and −42.36 ppm reveal small spatial separation between the *para*-pyridine and terephthalic protons from the iron atom [23]. This is in agreement with predictions made using the Abraham et al. ring current model [25, 34]: the terephthalic strap should lie about 3.1 Å from the porphyrin plane.

2.3. Assignments of the chemical shifts of meso-phenyl protons and carbons of tetrakis-α,β,α,β-(2′-amidophenyl)porphyrins

NMR peaks corresponding to the *meso*-phenyl protons of tetrakis (2′-amidophenyl)porphyrins have been assigned in the literature. In four different reports, the H-6′ proton was attributed to the least shielded *meso*-aryl proton [26–29]. In our investigation, using COSY ^{1}H NMR, we established a correlation



between the NH amidophenyl proton and the doublet phenyl proton H-3′ of the hexacoordinated iron porphyrin (see for example **6d**) [20,30–32]. From this we conclude that the H-3′ proton resonates at the lowest field [30]. Similarly, we conclude that the C-3 carbon signals occur at the highest field.

2.4. Simple proof of the absence of racemization of the chiral aminoacid residue of the bis-ansa porphyrins

In order to ascertain that no racemization occurred during the synthesis of porphyrins **6d** and **11**, we compared ^{1}H NMR spectra of the L-alanine derivative **6d** with that of the racemic alanine derivative **6e**. Indeed, the β pyrrolic and the

$-CH(CH_3)-$ protons are privileged spectators vis-à-vis the chirality of the handles (see Fig. 1). As expected, the H-2, H-3, H-12, H-13; and the H-7, H-8, H-17, H-18 pyrrolic protons gave two resonances as singlets in the case of **6d** and as multiplets in the case of **6e**. The same effects have been pointed out for the $-CH(CH_3)-$ protons. This proves definitively that no racemization has occurred during the synthesis of the bis-*ansa* porphyrins even during metallation, which requires the presence of 2,6-lutidine in refluxing toluene [33].

2.5. *Hexacoordinated iron(II) bis-strapped chiral porphyrins*

2.5.1. *Hexacoordinated iron(II) porphyrins with two nitrogen bases*

Condensation of the porphyrin **6d** with 3,5-bis(chlorocarbonyl)pyridine under high dilution conditions (3 h, RT using a syringe pump) gave after flash chromatography the bis-pyridine porphyrin **13** in 45% yield. Iron insertion into the bis-pyridine porphyrin **13** afforded the hexacoordinated iron(II) porphyrin **15**. We have compared the chemical shifts of the protons of the attached handles with those of the unattached handle ($^tBuO_2C$--CHMe--NH--CO)$_2$-*m*-C_5H_5N. The shielding effect δ(handle)$-\delta$(strapped porphyrin) gives an idea of the distance of this handle from the porphyrin plane [34,35]. We have also compared the NMR spectra of the strapped porphyrin with those of the corresponding iron(II) derivative. Thus, in the case of **15**, the differences of chemical shifts is $\Delta\delta = \delta(\mathbf{15}) - \delta(\mathbf{13}) = -4.52$ ppm for the *ortho*-pyridinic proton (*o*-Py) and $+2.14$ ppm for the *para*-pyridinic proton (*p*-Py) [35]. The chemical shifts of the *o*-Py and *p*-Py protons of iron porphyrin **15** are 1.99 and 6.91 ppm and those of the free porphyrin, **13**, are 6.51 and 4.77 ppm. These data clearly give an idea of the orientation of the pyridine plane with respect to the porphyrin plane. Indeed, only a pyridine plane perpendicular to the porphyrin plane can explain the chemical shifts of the *ortho*-pyridinic proton which resonates at 1.99 ppm. This high-field value is due to the anisotropy of the porphyrin ring. In the case of the free bis-pyridine **13**, the *p*-pyridinic proton resonates at a high field

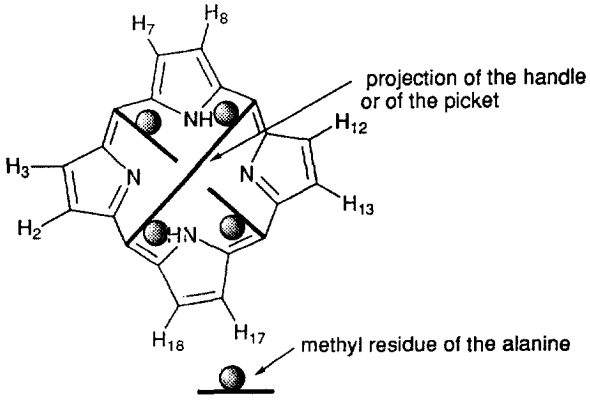
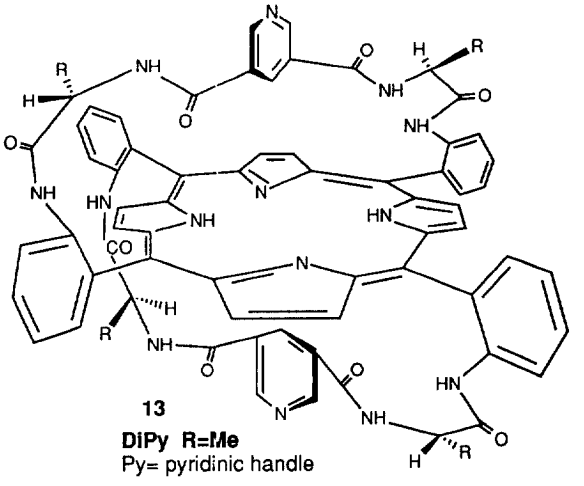
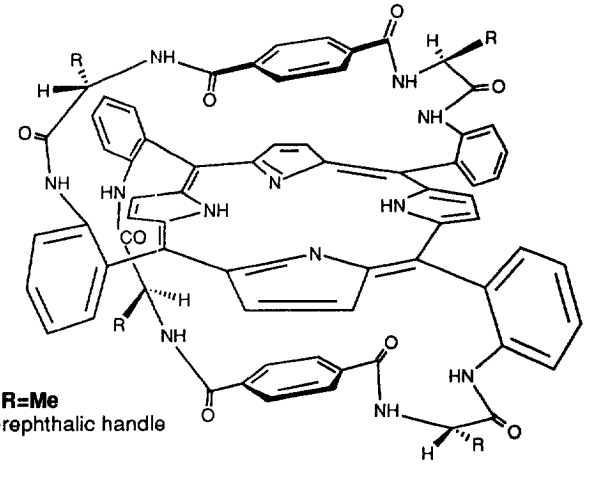


Fig. 1. Two sets of two magnetically equivalent nuclei in the case of two identical handles (H-2, H-12, H-3, H-13 and H-7, H-17, H-8, H-18).

with respect to the *ortho*-pyridinic proton. This is in good agreement with a proton *para* to the pyridinic nitrogen close to the porphyrin ring and with an orientation of the pyridine ring perpendicular to the porphyrin plane.



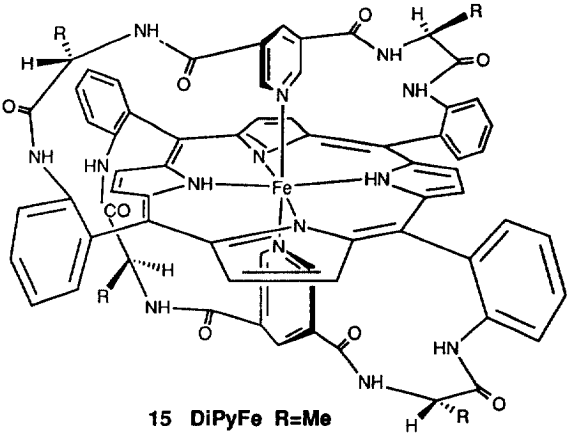
13
DiPy R=Me
Py= pyridinic handle



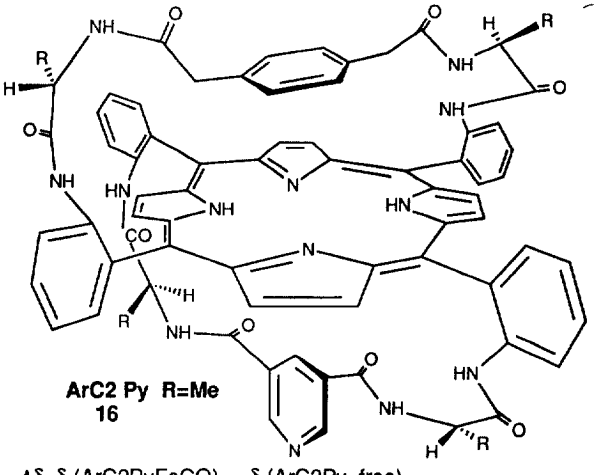
14
DiAr R=Me
Ar= terephthalic handle

2.5.2. Hexacoordinated iron(II)–CO porphyrins

In the case of the porphyrins **12/5a** and **18/16**, with a terephthalic handle and a homoterephthalic handle, the *o*-Py protons are deshielded by −4.43 ppm (1.68−6.11) and −5.31 ppm (1.33−6.64) but the *p*-Py protons are shielded by 2.18 ppm (6.74−4.56) and 1.97 ppm (6.68−4.71). Relative to the corresponding free-base porphyrins **5a** and **16**, the *p*-C_6H_4– protons of both **12** and **18** are deshielded to the same extent: 1.6 ppm. These data are unexpected because the terephthalic handle lies nearer the porphyrin plane than the homoterephthalic handle. The



15 DiPyFe R=Me



ArC2 Py R=Me
16

Δδ=δ (ArC2PyFeCO) - δ (ArC2Py free)
ArC2: homoterephthalic handle
Py: pyridinic handle

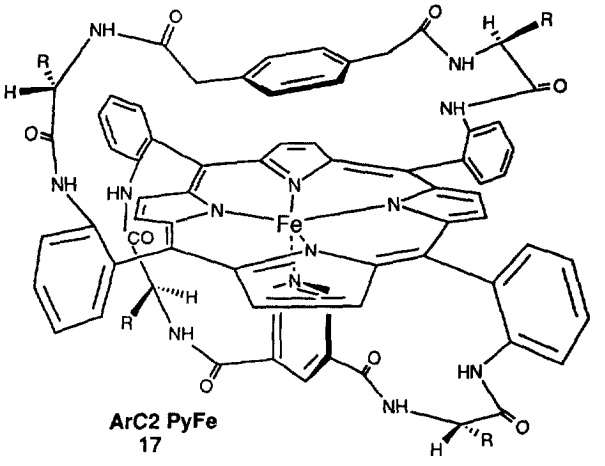
difference in deshielding of the pyridinic protons strongly suggests that *trans* influences of the CO ligand in the case of **12/5a**, and of the axial base in the case of **15/13**, are about the same, whereas the normal *trans* influence of the CO ligand in the case of unconstrained porphyrin **18/16** is different (vide supra). These findings cannot be explained by assuming the same geometry of FeCO relative to the porphyrin ring for both **12** and **18**. Indeed, the shieldings of **15/13** = −4.52 ppm and **12/5a** = −4.43 ppm are about the same.

Moreover, we found that the affinity of **11** for CO is even lower than the affinity of the natural hemoproteins for CO: steric hindrance may play a functional role in lowering the CO affinity, porphyrin **11** represents a good model of myoglobin with respect to CO.

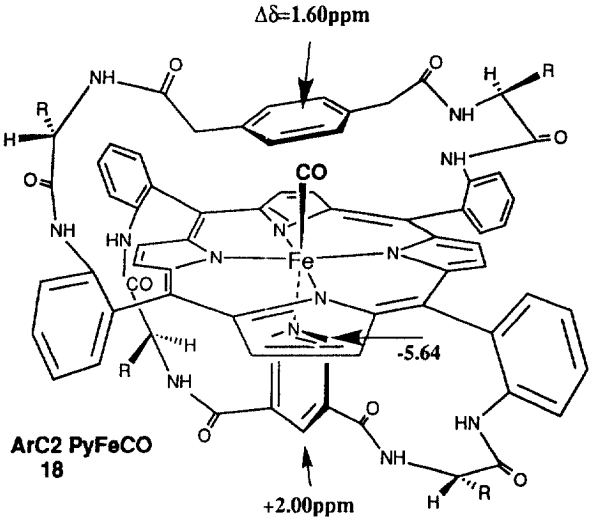
Using ^{13}C-enriched CO, we undertook the ^{13}C NMR of **12** and **18**, which indicated ^{13}CO resonances at 199.4 and 202.7 ppm respectively. These spectra indicate neither shielding nor deshielding effects for the four terephthalic carbons of **5a** relative to **12** (123.6 ppm), but a deshielding effect of 1.2 ppm for the four homoterephthalic carbons in the case of **18** (129.1 ppm) with respect to **16** (127.9 ppm). Again, if a 1.2 ppm deshielding effect is observed in the case of **18**, we would expect a higher deshielding effect going from **5a** to **12**. This is not the case. We observe no effect at all [35].

2.6. Linear free energy relationships in CO and H_2O binding to various amino acid bis-ansa porphyrins

A previous study of CO binding to bis-*ansa* porphyrins containing an internal chelated imidazole as a proximal base, and phenylalanine derived distal handle, revealed the unusual coordination of water as a sixth ligand in the distal cavity [36]. The aquo complex is thought to be stabilized by hydrogen bonds with the amino acid residue. The kinetic rate constants for H_2O binding and dissociation were determined. In our case, the proximal base is a constrained pyridine and the distal handle contains four peptidic bonds (see **12** and **18**).



The comparison of the kinetic data shows that both classes form a homogeneous family with respect to water and presumably CO binding and display linear free energy relationships. The affinities for CO are: $p_{1/2}$(CO) **12** = 5.5 Torr, $p_{1/2}$(CO) **18** = 0.2 Torr. The bimolecular combination rate constant k^+(CO) is 7×10^4 mol^{-1} l s^{-1} and the dissociation rate constant k^-(CO) is 3.5 s^{-1} for **12**. The affinity for O_2 for **17** is 21 Torr. The equilibrium constant $K(H_2O) = 9000$ mol^{-1} l for **17** and the bimolecular combination rate constant $k^+(H_2O) = 1.2 \times 10^{10}$ mol^{-1} l s^{-1} for **17** and the calculated $k^-(H_2O) = 1.3 \times 10^6$ s^{-1}. Linear free energy relationships provide an objective means for comparing the reactivity of whole series of related molecules. In spite of the small number of data, this study suggests that these compounds



Δδ=δ (ArC2PyFeCO) - δ (ArC2Py free)
ArC2: homoterephthalic handle
Py: pyridinic handle

might behave as one reactive family. The transition state is reactant-like, in agreement with the high value of the "on" rate for water, which is close to a diffusion controlled rate. Differences among compounds are seen in the dissociation rate which depends on the local strength of the stabilizing H bonds [37].

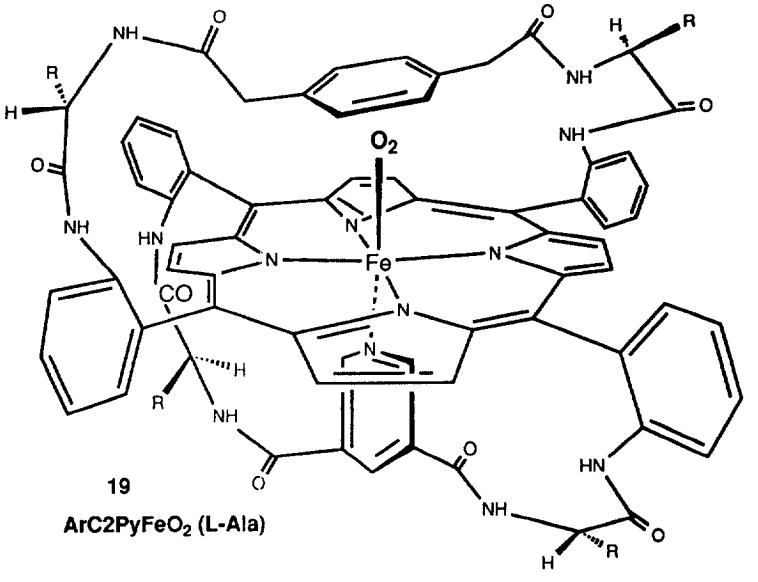
The *ansa*-porphyrin **12** exhibits one of the highest CO dissociation rates and one of the lowest CO affinities ever observed with an Fe^{II} porphyrin [37].

2.7. Partition coefficient $M=p_{1/2}(O_2)/p_{1/2}(CO)=K(CO)/K(O_2)$

Oxygen and carbon monoxide affinities can be obtained by photometry titration. UV–vis spectral changes upon titration of a toluene solution of **11** with CO, and of **17** with O_2, clearly show isobestic points.

It is worth noting that the oxygen complex **19** (**17**+O_2) is stable in toluene for several days at room temperature. The 21 Torr value for the $p_{1/2}(O_2)$ of **17** can be compared with the 0.5 Torr value of myoglobin (Mb). Flushing the Fe–O_2 solution with nitrogen removes the oxygen. Unfortunately, the oxygen adduct of **11** gives an Fe(III) compound. We believed this species to be a hydroxy Fe–OH complex since it is quantitatively reduced by $Na_2S_2O_4$ to the starting tetracoordinated Fe(II) complex, **11**, which has a characteristic intermediate spin ($S=1$) whose UV–vis spectrum shows two classical Soret bonds at 421 and 444 nm [38].

The partition coefficient $M=p_{1/2}(O_2)/p_{1/2}(CO)=K(CO)/K(O_2)$ in heme proteins ranges from 4400 for *glycera* hemoglobin (Hb) to 0.02 in Ascaris Hb. [39–41] and from 50 000 to 5 in model compounds [30–32,42]. The M ratio in heme proteins is



19

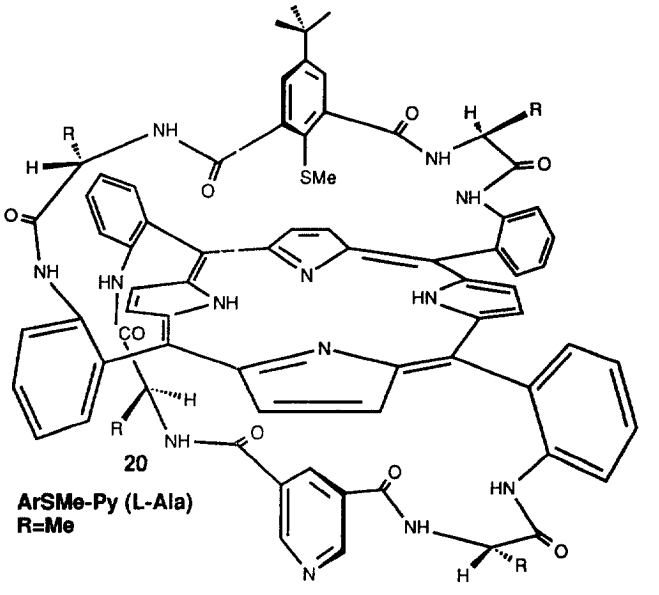
ArC2PyFeO$_2$ (L-Ala)

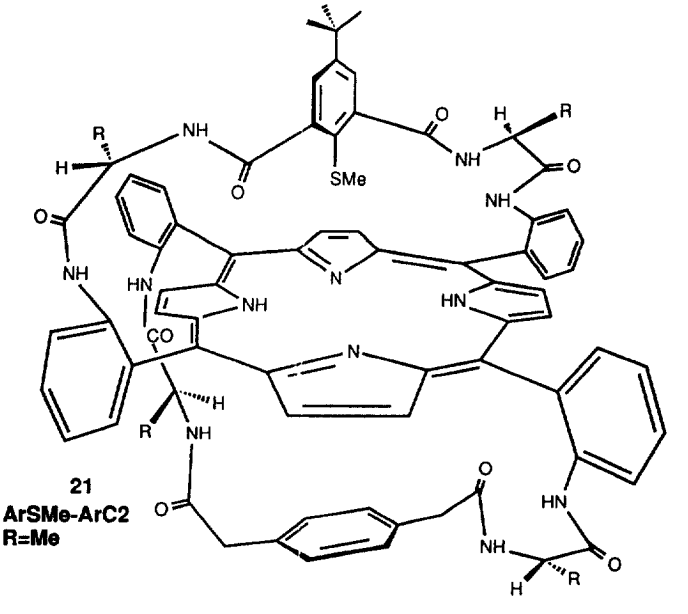
related to the nature of the Fe–CO geometry. In the case of **17**, the *M* ratio is 21/0.2 = 105, which is similar to values for myoglobin and hemoglobin (25 for Mb [39–41], 170 for Hb, Rstate [39]).

We observe for our model **17**, selective discrimination between oxygen and carbon monoxide. This is evidence of distal side interactions which are known to play a role in regulating ligand binding to hemoproteins and which may be the primary factor in their greatly reduced CO affinities [41]. We are currently engaged in further studies of discrimination between O_2 and CO with simpler models whose syntheses, which are simpler, will be described in Section 3.2.

2.8. Model of cytochrome c

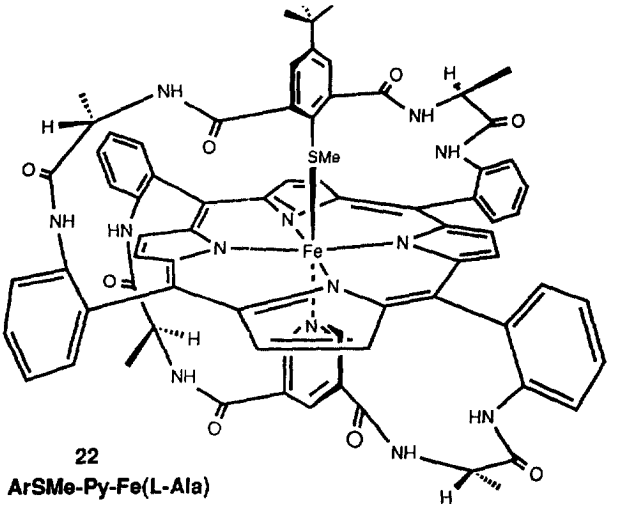
Cytochrome c hemoproteins act as one-electron carriers in the respiratory chain. The heme iron is reversibly oxidizable and can serve as an electron acceptor. The cytochrome c heme is covalently attached to the protein by a thioether bond between its vinyl groups and two cysteine residues of the polypeptide chain. This gives a hydrophilic environment and a more positive reduction potential than it would have in an aqueous medium. The nature of the two axial ligands, Met-80 and His-18, cannot explain the properties of cytochrome c. So, we decided to prepare a bis-*ansa* porphyrin **20**, with a thioether handle and a nitrogen handle. We compared this model, with its two axial ligands forced into coordination by covalent attachments, to another model, **21**, with a thioether handle and a homoterephthalic handle [43]. In the latter case, imidazole can be used to prepare the hexacoordinated Fe(II) porphyrin **23**. Condensation of the chiral tetra-picket porphyrin, **6d**, with dichlorides **24** and **25** affords three porphyrins: **20**, **13** and **26** in 24%, 10% and 9% respectively.



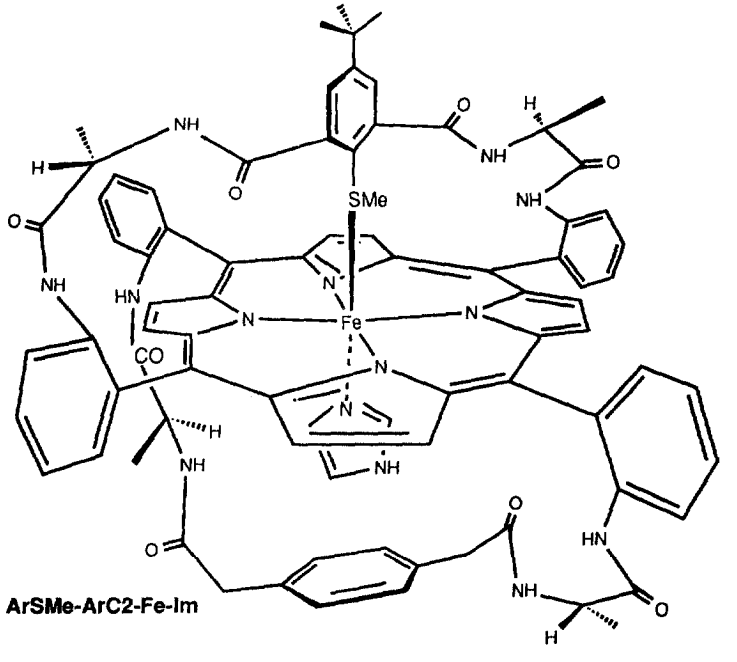


Again, we noticed experimentally that the yield of the porphyrin with two different handles was better using this mixed "one-pot" condensation than the classical two-step method. Incorporation of iron by the usual method ($FeBr_2$, 2,6-lutidine, toluene) yielded, quantitatively, the iron porphyrins **22**, **15** and **27** respectively.

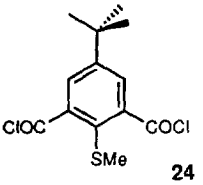
^1H NMR and UV–vis spectroscopies show that the bis-thioether porphyrin **27** is



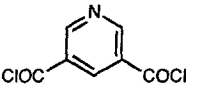
22
ArSMe-Py-Fe(L-Ala)



23
ArSMe-ArC2-Fe-Im



24



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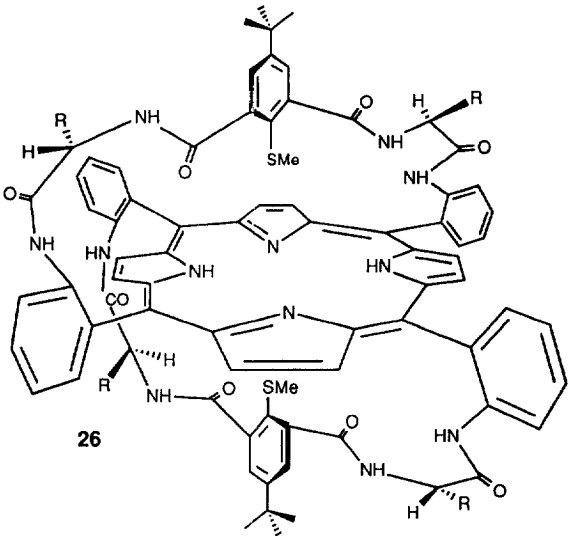
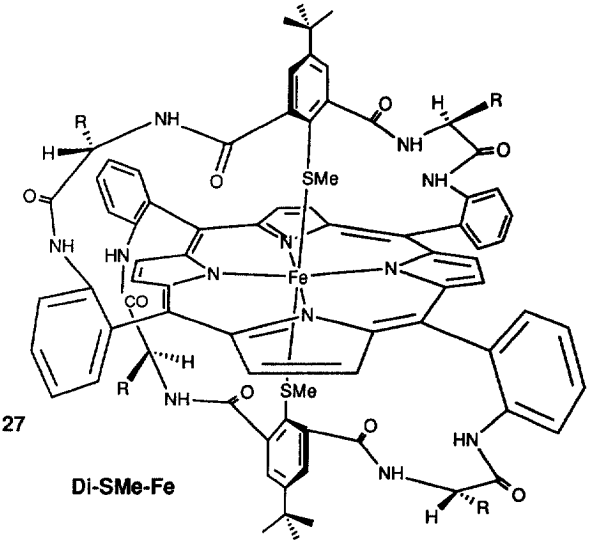




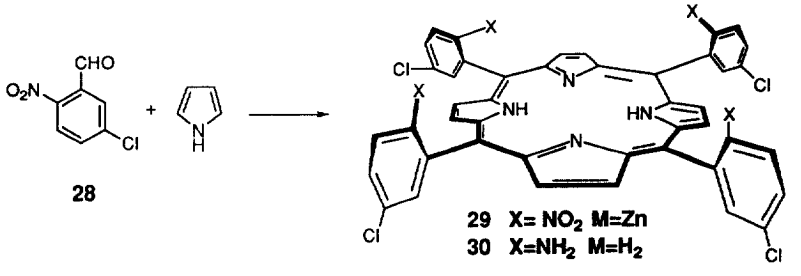
a four-coordinate ($S=1$) complex. The UV–visible spectrum exhibits two Soret bands at 424 and 439 nm. The ^{1}H NMR spectrum shows resonances between 6 and 16 ppm. As expected, porphyrin **22** is a diamagnetic, six-coordinate complex indicating the ligation of two intramolecular ligands (S and N). However, the UV–visible spectrum does not exhibit the well-known α and β absorptions of reduced cytochrome c at 520 and 550 nm, but absorptions at 592 nm and a Soret band at 432 nm [44]. Slow oxidation of the iron atom gives two new absorptions at 421 and 514 nm, which probably account for the iron(III) derivative. So, these results show that the

pyridine is not basic enough to reproduce the UV–visible properties of cytochrome c. For this reason, we prepared the bis-*ansa* porphyrin **23** in 8% yield in order to have a thioether handle and a large homoterephthalic handle using a similar mixed condensation. In this case, the spectrum of **23** looks like the UV–visible spectrum of cytochrome c. This indicates that imidazole is necessary as a nitrogen ligand. Further studies are in progress, in particular potential redox and detailed spectroscopies data will be described in a full paper.

3. Synthesis of eight-picket porphyrins

3.1. Synthesis of 5,10,15,20-tetrakis (2-amino-5-chlorophenyl) porphyrins

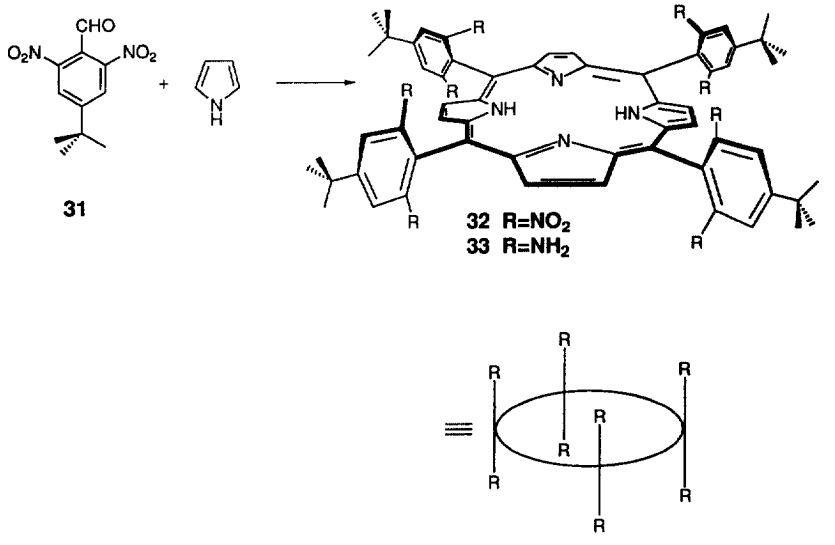
Tetrakis (*o*-substituted phenyl) porphyrins have served as synthons for the creation of many biomimetic hemes [45–64]. We decided to prepare new porphyrins with substitutions on both faces of the porphyrin plane. Thus, condensation of pyrrole with 2-nitro,5-chlorobenzaldehyde **28**, in the presence of $Zn(OAc)_2$, $2H_2O$ in acetic acid, gave nitroporphyrin atropoisomers, **29**. Reduction of the nitro groups and demetallation occurred simultaneously at room temperature with $SnCl_2$, $2H_2O$ and 12 N HCl to give, quantitatively, the aminoporphyrins **30** in 8% yield (four atropoisomers). Silica gel chromatography yielded the four atropoisomers [65]. The yield of each atropoisomer was too low and the separation of these atropoisomers was so difficult that we decided to try to condense dinitrobenzaldehyde.



3.2. Synthesis of "double picket fence" porphyrins

In order to avoid the separation of the atropoisomers, which is expensive and time consuming, we undertook the creation of symmetric porphyrins, simultaneously protected on both faces. Two papers describe the condensation of pyrrole with 2,6-dinitrobenzaldehyde, but we and others were not able to reproduce this synthesis [66,67].

To enhance the solubility of the resulting porphyrin, we used dinitrobenzaldehyde substituted by a *tert*-butyl group. Condensation of pyrrole and 2,6-dinitro-4-*tert*-butyl benzaldehyde, **31**, in CH_2Cl_2 in the presence of $BF_3 \cdot OEt_2$ at room temperature led, after oxidation, to a reproducible yield of a unique porphyrin, **32** (8.5–10.5%), avoiding the problems of separation encountered in Section 3.1 [68,69]. Reduction of the nitro groups with $SnCl_2$, $2H_2O$ and HCl in CH_2Cl_2 at room temperature gives, in reproducible yield, the aminoporphyrin **33** without over-reduction if the reaction is carried out with a stoichiometric amount of HCl [68, 70].



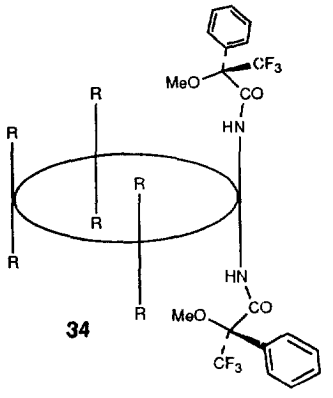
3.3. Synthesis of chiral porphyrins

Treating the octa-aminoporphyrin **33** with excess (R)-Mosher's acid chloride resulted in the formation of the soluble octa-Mosher porphyrin **34** in 45% yield.

Similarly, the octa-aminoporphyrin **33** and (R)-α-methoxyphenyl-acetylchloride gave the soluble chiral porphyrin **35** in 45% yield [68].

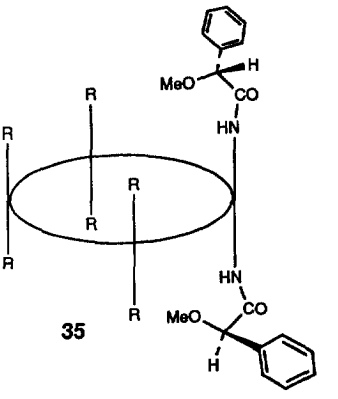
3.4. Synthesis of mono-picket functionalized porphyrin

Condensation of (S)-2-methyl-3-(acetylthio)propanoyl chloride (0.5 equiv) with porphyrin **33** (1 equiv) gave unexpectedly 5,10,15-tris(4′-*tert*-butyl-2′,6′-diaminophenyl)-20-(4″-*tert*-butyl-2″-amino-6″-((S)-(−)-2-methyl-3-(acetylthio)propanamido)phenyl)porphyrin **36** in 49% yield. This porphyrin, when reacted with Mosher's acid chloride, afforded porphyrin **37** which represents a good precursor of cytochrome P-450 [68, 70].



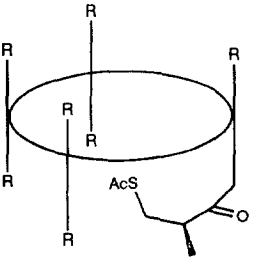
34

R= (R) NHC(O)C(CF_3)(C_6H_5)(OMe)



35

R= (R) NHC(O)CH(C_6H_5)(OMe)



36 R=NH_2

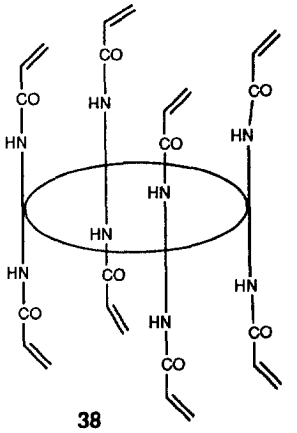
37 R= (R) NHC(O)CH(C_6H_5)(OMe)

3.5. *Synthesis of octa-Michael acceptor porphyrin*

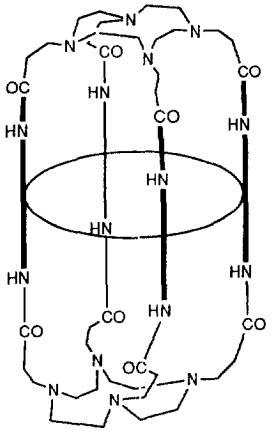
By condensing acryloyl chloride with octa-amino porphyrin **33**, the octa-Michael acceptor **38** was obtained in 25% yield. So, the octa-porphyrin **38** can be derivatized with a wide range of nucleophiles including primary and secondary amines, (chiral) diamines, triamines and tetra-amines [68, 70].

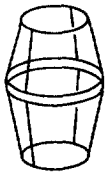
3.6. *Synthesis of a "barrel" porphyrin 39*

The doubly capped porphyrin, that we named "barrel" porphyrin, **39**, was obtained through the reaction of cyclen with the octa-Michael porphyrin **38** [68]. We are preparing other different aza-crown-barrel porphyrins because they can easily be synthesized by reacting cyclam or cyclen. The linkers can be different in order to allow us to control the tightness of the cap of the corresponding bis-capped porphyrins. Indeed, these synthetic models will differ only in their cavity dimensions and will permit us to demonstrate the effects of steric factors on O_2 and CO binding affinities.



38



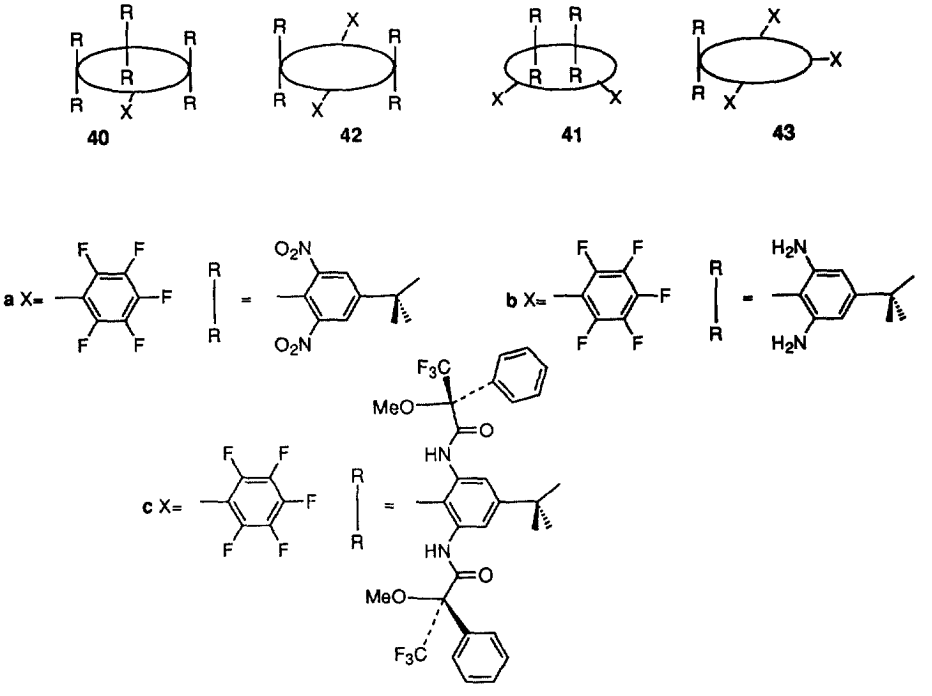


39

4. Bis-faced aminoporphyrin templates

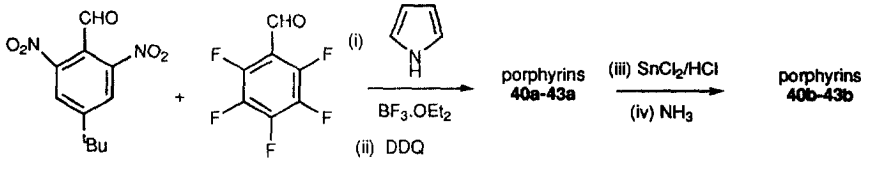
4.1. Synthesis

We decided recently to prepare new porphyrins avoiding not only the problem of the separation of atropoisomers, but also the problems encountered in the case of the sterically demanding "double picket fence" porphyrin. Indeed, our preliminary epoxidation studies using the iron(III)–octa-Mosher's porphyrin **34**-Fe failed to produce enantiomeric excesses [69]. The Mosher's pickets are probably too bulky, inhibiting the approach of the olefin. So, the goal was to obtain new catalysts with an unencumbered approach which could serve as a chiral substrate passage to the metal center. So, instead of preparing an octa-nitroporphyrin **32**, we undertook the synthesis of simple hexa **40a**, tetra-*cis* **41a**, tetra-*trans* **42a** and di-nitro porphyrins **43a** (Scheme 1) [69]. Condensation of pyrrole and a mixture of two aldehydes in the presence of $BF_3 \cdot OEt_2$, followed by reduction of the nitro group to amines,



Scheme 1.

gave porphyrins **40b**, **41b**, **42b** and **43b** for example in the case of pentafluorobenzaldehyde and 2,6-dinitro-4-*tert*-butylbenzaldehyde [Eq. (3)] [69]. Depending on the experimental conditions and the amount of the two aldehydes, a 7.5% yield of porphyrin **40a** for example can be obtained. The condensation reaction showed a preference for *cis* over *trans* arrangement of the aldehyde **31**, indeed geometry **42a** was barely observed (Scheme 1). Reaction of **40b**, **41b** and **43b** with Mosher's acid chloride gave chiral porphyrins **40c**, **41c** and **43c**. Metallation of **41c** and **43c** with $FeBr_2$ afforded iron porphyrins **41c**-Fe and **43c**-Fe. Metallation of **40b** followed by condensation with Mosher's acid chloride yielded iron porphyrin **40c**-Fe (Fig. 2).



(3)

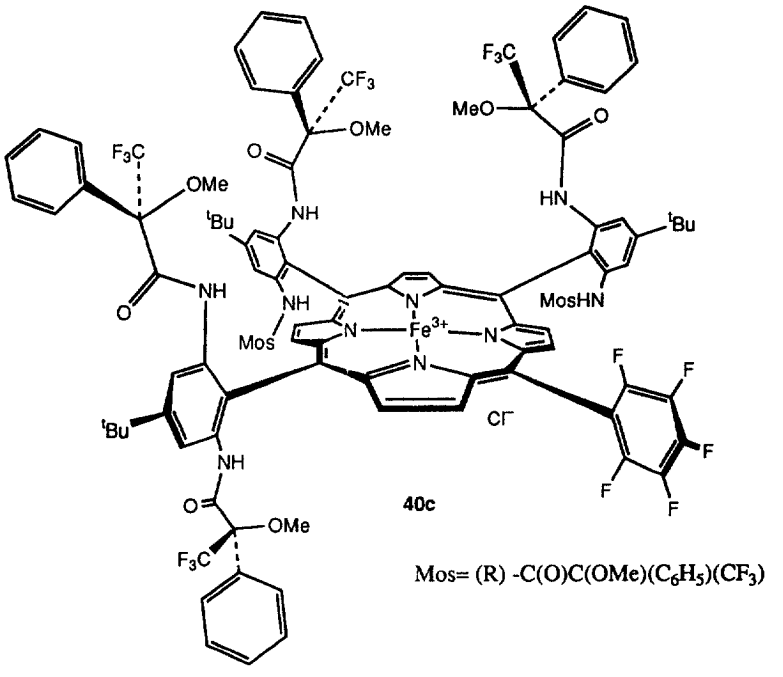


Fig. 2. Hexa-Mosher porphyrin.

4.2. Catalytic oxidation

Catalytic epoxidation of styrene was carried out using PhIO and porphyrins **40c**-Fe, **41c**-Fe and **43c**-Fe. The most bulky analogue **40c**-Fe gave the lowest selectivity (<1% ee), the least bulky porphyrin **43c**-Fe the highest (6% ee) and porphyrin **41c**-Fe halfway between the other two (3% ee) [69]. We have to point out that the selectivities are at the present time very low. However, it is clear that more access to the catalytic metal center will increase the selectivity of the epoxidation reaction and the turnover and that the nature of the chiral picket will play an important role in oxidation. We are presently preparing and exploring "seat" catalysts **44** with new chiral linkages in order to test them in asymmetric oxidation (Fig. 3) [70]. Preliminary results with porphyrins **44** are promising and will be the subject of our next article.

5. Conclusion

We have described the synthesis of three kinds of aminophenylporphyrin.

The first one involved either 5,10,15,20-tetrakis (*o*-aminophenyl)porphyrin (four atropoisomers), or 5,15-(2′,6′-diaminophenyl)porphyrin. These starting porphyrins permitted us to obtain "bis-*ansa*" or "basket handle" porphyrins and "gyroscope" porphyrins. One example of "basket handle" porphyrin demonstrated selective

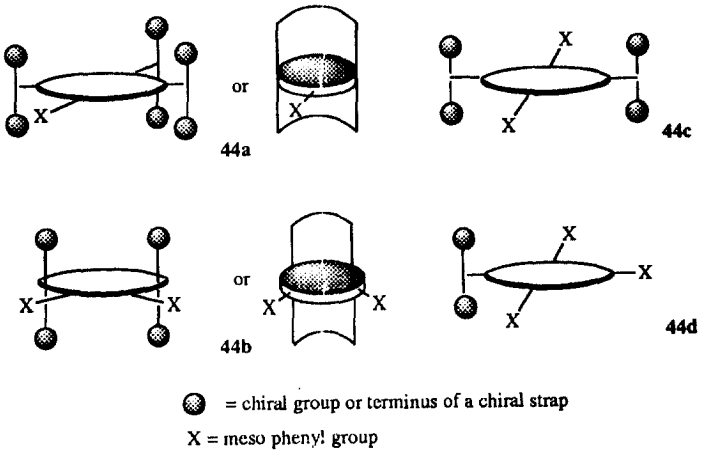


Fig. 3. Chiral "seat" porphyrins (we named porphyrins **44a** and **44b** "seat" porphyrins on the basis of their structural similarity to a seat), some of them appeared to be excellent asymmetric epoxidation catalysts [70].

discrimination between O_2 and CO with an M value $[M=p_{1/2}(O_2)/p_{1/2}(CO)]$ of 105. This is similar to values reported for various natural hemoproteins.

The second case is based on octanitro porphyrin: tetrakis-(2′,6′-dinitro,4′-*tert*-butylphenyl)porphyrin **32**, which is a basic precursor for the synthesis of biomimetic heme models, and of a new generation of chiral porphyrin catalysts for asymmetric oxidation.

The third case involved mono-, bis- and tris-(2′,6′-diamino,4′-*tert*-butylphenyl)porphyrin. In one case, oxidation of styrene has been studied. All these data show that the porphyrin must not be too encumbered in order to give good turnover and very high enantiomeric excesses.

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